

SUPPLEMENTARY INFORMATION

Fluorine containing amino acids: Synthesis and peptide coupling of amino acids containing the all-*cis* tetrafluorocyclohexyl motif

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1. General Experimental

All reactions were carried out in oven-dried glassware under an argon atmosphere using a double vacuum manifold with the inert gas passing through a bed of silica gel and molecular sieves. Petrol refers to the petroleum ether fraction with a boiling point between 40-60 °C. All chemicals were used as supplied. All NMR spectra were recorded using a Bruker Avance III 500, Bruker Avance II 400, Bruker Avance 300 or 500 spectrometers. The deuterated solvent was used for an internal deuterium lock. ^1H NMR spectra were recorded at either 300, 400 or 500 MHz. ^{13}C NMR spectra were recorded using UDEFT pulse sequence and broadband proton decoupling at either 75, 100 or 126 MHz. ^{19}F NMR spectra were recorded at 282, 376 or 470 MHz. All chemical shifts, δ , are stated in units of parts per million (ppm), relative to a standard, for ^1H NMR and ^{13}C NMR the reference point is TMS (δ_{H} and δ_{C} : 0.00 ppm). For ^{19}F NMR the reference point is CCl_3F (δ_{F} : 0.00 ppm). Melting points were determined using a Griffin MPA350 or a Electrothermal 9100 melting point apparatus and are uncorrected. High and low resolution mass spectra were obtained by atmospheric pressure chemical ionisation (APCI), electrospray ionization (ESI) and electron ionization (EI). ESI-MS spectra were recorded on a Waters Micromass LCT spectrometer in positive mode or negative mode. EI-MS spectra were recorded on a Waters Micromass GCT spectrometer. Values are reported as a ratio of mass to charge (m/z).

2. Experimental Details and Analytical Data

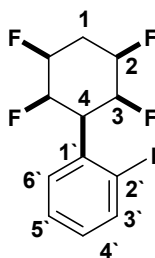
1- Iodination of *cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane 3

Iodine (600 mg, 2.36 mmol) was added to a solution of all *cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane **3** (500 mg, 2.15 mmol) in acetic acid (50 ml), periodic acid 50 % (w/w) (0.123 mL, 0.43 mmol), conc. H_2SO_4 95 % (0.28 mL, 5.4 mmol), and water (10 mL). The solution was heated for 16h at 70 °C and then the mixture was left to cool to room temperature. The reaction was quenched by a adding of solution of saturated sodium bisulfite (30 mL), then the mixture was washed with ethyl acetate (3 × 50 mL). The organic layers were combined and dried over sodium sulfate, filtered and the solvent evaporated

under reduced pressure (710 mg 92 % overall yield). The product was purified by flash column chromatography using diethyl ether / petrol (1:2), as an eluent.

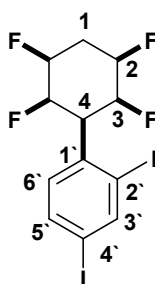
This gave **4:5:6:7** in a ratio of 1:5:15:4 respectively.

All *cis* -1,2,4,5-tetrafluoro-3-(2-iodophenyl)-cyclohexane (**4**)



Colorless solid (28 mg, 3.6 %). **mp** 169 - 170 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.96 (1H, dd, J 7.9, 1.6 Hz, **CH-6'**), 7.90 (1H, dd, J 8.0, 1.3 Hz, **CH-3'**), 7.41 (1H, td, J 7.6, 1.3 Hz **CH-5'**), 7.05 (1H, td, J 7.6, 1.6 Hz, **CH-4'**), 5.11 - 4.91 (2H, m, **CHF-3**), 4.82 - 4.57 (2H, m, **CHF-2**), 3.13 (1H, tt, J 36.8, 1.6 Hz, **CH-4**), 2.84 - 2.69 (1H, m, **CH_AH_B-1**), 2.55 - 2.46 (1H, m, **CH_AH_B-1**); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 139.7, 137.9, 131.1 (t, J 6.6 Hz), 130.1, 129.2, 101.3 (**C-2'**), 89.6 - 87.7 (m, **CHF-3**), 88.7 - 85.9 (m, **CHF-2**), 47.4 (m, **CH-4**), 27.3 (tt, J 22.1, 2.4 Hz, **CH₂-1**); $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ_{F} -189.9 (2F, dd, J 7.7, 5.6 Hz, **CHF-2**), -210.9 (2F, dd, J 7.7, 5.5 Hz, **CHF-3**); (**ESI**⁺) [2M+6H]⁺ calcd for $\text{C}_{12}\text{H}_{11}\text{IF}_4$ ⁺: 721.9684 found: 722.2411

All *cis* -1,2,4,5-tetrafluoro-3-(2, 4-diiodophenyl)-cyclohexane (**7**)



Colorless solid (122 mg, 15.8 %). **mp** 203 - 204 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 8.24 (1H, d, J 2.2 Hz, **CH-3'**), 7.59 (1H, d, J 8.4, **CH-6'**), 7.38 (1H, dd, J 8.4, 2.2 Hz **CH-5'**), 5.10 - 4.84 (2H, m, **CHF-3**), 4.87 - 4.55 (2H, m, **CHF-2**), 3.04 (1H, tt, J 36.2, 1.6 Hz, **CH-4**), 2.82 - 2.68 (1H, m, **CH_AH_B-1**), 2.54 - 2.46 (1H, m, **CH_AH_B-1**); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 140.9, 139.8, 139.8, 139.2, 100.5, 99.9, 89.3 - 87.6 (m, **CHF-3**), 87.6 - 85.7 (m, **CHF-2**), 47.1 (m, **CH-4**),

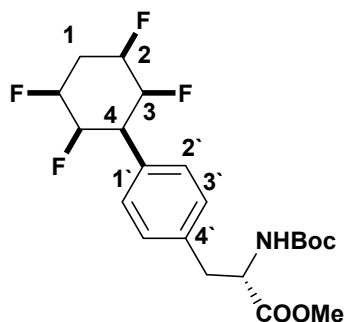
27.2 (tt, *J* 22.2, 2.3 Hz, CH₂-1); ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ_F -189.9 (2F, dd, *J* 7.9, 5.5 Hz, CHF-2), -210.6 (2F, dd, *J* 8.0, 4.9 Hz, CHF-3); (ESI⁺) [M+Na]⁺ calcd for C₁₂H₁₀I₂F₄⁺: 506.8706 found: 506.2082.

All *cis* -1,2,4,5-tetrafluoro-3-(3'-iodophenyl)-cyclohexane **5**, all *cis* -1,2,4,5-tetrafluoro-3-(4'-iodophenyl)-cyclohexane **6** (560 mg 72 %) were isolated as an inseparable mixture, and were not fully characterized at this stage, in ratio (1:3) respectively.

General Procedure for the preparation of 9 and 10.

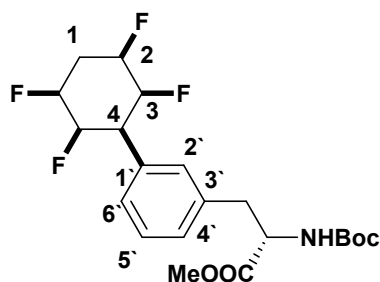
A flame dried, three-necked, round bottomed flask (25 mL) equipped with an argon inlet adapter, reflux condenser, rubber septum, and magnetic stir bar was charged with zinc dust (190 mg, 3.0 mmol) and iodine (38 mg, 0.15 mmol). The flask is evacuated and flushed with argon three times and then DMF (1mL) a solution of iodoalanine (330 mg, 1.00 mmol) in DMF (1mL) was added dropwise *via* syringe at 0 °C. The reaction was kept stirred at 0 °C for 30 min to generate a solution of the zinc reagent. The ice bath is removed and the aryl iodide (300 mg, 0.84 mmol), tris(dibenzylideneacetone)dipalladium (11 mg, 0.0125 mmol), and Sphos (11 mg, 0.025 mmol) were added and the reaction mixture stirred at 60 °C for 16 h. The resulting mixture was poured into a conical flask containing water (10 mL). Citric acid solution (5ml of 10 %) was added in order to break up the black emulsion. The aqueous mixture was extracted into DCM (2 × 60 mL), and the combined organic layers are washed with of water (30 mL) and of brine (30 mL). The organic fractions were dried and filtered. Concentration under vacuum gave the product which was purified over silica gel using petrol /ethyl acetate/DCM, (7:2:1) as an eluent

Methyl -2S-2-(*tert*-Butoxycarbonylamino)-3-(4-(all-*cis*-2,3,5,6-tetrafluoro cyclohex-1-yl) phenyl)propanoate (9)



Colorless solid (216 mg, 59 %). **mp** 186 - 187 °C; $[\alpha]_D^{20} + 22.0$ ($c = 1 \times 10^{-3}$, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ_{H} 7.39 (2H, d, J 7.6 Hz, **CH-2'**), 7.13 (2H, d, J 8.0, **CH-3'**), 5.02 - 4.82 (3H, m, **CHF-3**, **NHBoc**), 4.780 - 4.46 (3H, m, **CHF-2**, **CHNHBoc**), 3.71 (3H, s, COOCH_3), 3.17-2.97 (2H, m, PhCH_2), 2.79 - 2.38 (3H, m, **CH-4**, CH_AH_B -1), 1.39 (9H, s, $\text{C}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 172.3, 155.1, 136.0, 134.3, 129.7, 129.4, 90.1 - 88.0 (m, **CHF-3**), 88.0 - 86.1 (m, **CHF-2**), 80.0, 54.3, 52.3, 43.7, 38.0, 28.2, 27.1 (tt, J 22.3, 2.2 Hz, CH_2 -1); $^{19}\text{F}\{^1\text{H}\}$ NMR (282 MHz, CDCl_3) δ_{F} -190.7 (2F, dd, J 7.7, 5.5 Hz, **CHF-2**), -210.3 (2F, dd, J 8.0, 5.1 Hz, **CHF-3**); (**ESI+**) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{F}_4\text{NO}_4$: 456.1774 found: 456.1762

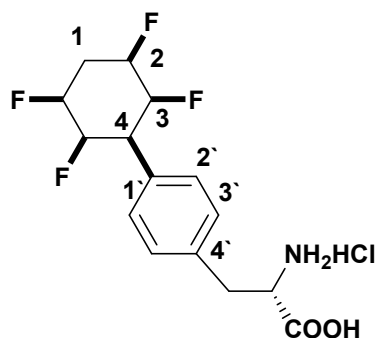
Methyl -2S-(tert-Butoxycarbonylamino)-3-(3-(all-cis-2,3,5,6-tetrafluorocyclohex-1-yl) phenyl) propanoate. (10)



Colorless solid (88 mg, 24 %). **mp** 164 - 165 °C; $[\alpha]_D^{20} + 35.0$ ($c = 1 \times 10^{-3}$, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ_{H} 7.33 - 7.27 (3H, m, **CH-2'**, **CH-4'**, **CH-6'**), 7.16 - 7.09 (1H, m, **CH-5'**), 5.10 - 4.87 (3H, m, **CHF-3**, **NHBoc**), 4.78 - 4.47 (3H, m, **CHF-2**, **CHNHBoc**), 3.72 (3H, s, COOCH_3), 3.19 - 3.02 (2H, m, PhCH_2), 2.83 - 2.40 (3H, m, **CH-4**, CH_AH_B -1), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} 172.1, 155.0, 136.7, 135.8, 130.2, 129.2, 128.9, 127.8, 89.8 - 88.2 (m, 2C, **CHF-3**), 87.8 - 86.3 (m, 2C, **CHF-2**), 79.9, 54.3, 52.3, 43.8 (tt, 1 C J 17.5, 5.8 Hz **CH-4**), 38.3), 28.2, 27.1 (tt, J 22.3, 2.2 Hz, CH_2 -1); $^{19}\text{F}\{^1\text{H}\}$ NMR (282 MHz,

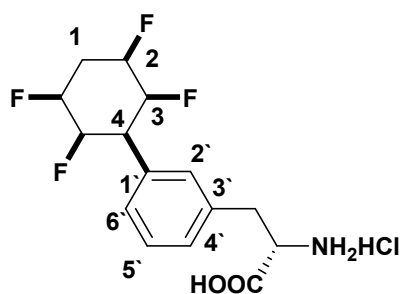
CDCl₃) δ_F -190.7 (2F, dd, *J* 7.1, 5.1 Hz, CHF-2), -210.0 (2F, dd, *J* 7.2, 5.0 Hz, CHF-3); (ESI+) *m/z* [M+Na]⁺ calcd for C₂₁H₂₇F₄NO₄⁺: 456.1774 found: 456.1759

(2S)-2-(aminohydrochloride)-3-(4-(all- cis -2,3,4,5-tetrafluorocyclohex-1-yl)phenyl)propanoic (11)



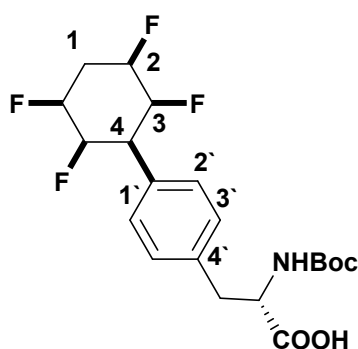
A solution of **9** (70 mg, 0.161 mmol) in HCl 6 M :1,4-dioxane (1:1) (4 mL) and anisole (26 mg, 0.24 mmol) was stirred at 70 °C for 48 h, until TLC showed that the substrate had been consumed. The reaction mixture was diluted with water (10 mL) and the aqueous washed with ethyl acetate (2 × 15 ml). The aqueous was the evaporated under reduced pressure, to afford the hydrochloride salt **11** (52 mg, 91 %) as colorless needles. **mp** 273 - 274 °C; $[\alpha]_D^{20} + 60.0$ (*c* = 2 × 10⁻⁴, DMSO); ¹H NMR (400 MHz, d₆-DMSO) δ_H 8.36 (3H, bs, NH₃Cl), 7.45 (2H, d, *J* 7.8 Hz, CH-2'), 7.29 (2H, d, *J* 7.9 Hz, CH-3'), 5.19 – 4.83 (4H, m, CHF-3, CHF-2), 4.17 (1H, t, *J* 6.0 Hz, CHNH₃Cl), 3.25- 3.5 (3H, m, PhCH₂, CH-4), 2.46 – 2.29 (2H, m, CH_AH_B-1); ¹³C NMR (126 MHz, d₆-DMSO) δ_C 170.8, 136.1, 134.5, 130.0, 129.4, 90.8 – 89.1 (m, CHF-3), 88.7 – 88.3 (m, CHF-2), 53.7, 35.8, 42.0, 27.4 (tt, *J* 22.1, 3.0 Hz, CH₂-1); ¹⁹F{¹H} NMR (376 MHz, d₆-DMSO) δ_F -189.4 (2F, dd, *J* 8.1, 4.6 Hz, CHF-2), -209.7 (2F, dd, *J* 8.1, 5.8 Hz, CHF-3); (ESI+) *m/z* [M-HCl + H]⁺ calcd for C₁₅H₁₈ClF₄NO₂⁺: 320.1273 found 320.1263;

(2S)- 2-(Aminohydrochloride)-3-(3-(all- cis -2,3,5,6-tetrafluorocyclohex-1-yl)phenyl)propanoic (12)



A solution of **10** (50 mg, 0.115 mmol) HCl 6 M :1,4-dioxane (1:1) (4 mL) and anisole (21 mg, 0.20 mmol) was stirred at 70 °C for 48 hr, until TLC showed that the substrate was consumed. The reaction mixture was diluted with water (10 mL) and washed with ethyl acetate (2 × 15 ml). The aqueous was collected and evaporated under vacuum, to afford the hydrochloride salt **12** (38 mg, 92 %) as colorless solid. **mp** 223 - 224 °C; $[\alpha]_D^{20} + 42.0$ ($c = 2 \times 10^{-4}$, DMSO); **¹H NMR** (500 MHz, d_6 -DMSO) δ_H 8.41 (3H, bs, NH_3Cl), 7.24 - 7.17 (4H, m, $CH-2'$, $CH-4'$, $CH-5'$, $CH-6'$), 5.19 - 4.87 (4H, m, $CHF-3$, $CHF-2$), 4.13 (1H, bs, $CHNH_3Cl$), 3.14 (2H, m, $PhCH_2$), 2.44 - 2.36 (3H, m, $CH-4$, CH_AH_B-1); **¹³C NMR** (126 MHz, $CDCl_3$) δ_C 170.8, 137.5, 135.6, 130.5, 129.1, 128.8, 128.1, 90.9 - 89.2 (m, 2C, $CHF-3$), 88.1 - 86.7 (m, 2C, $CHF-2$), 67.7, 53.7, 36.3.0, 27.5 (bt, CH_2-1); **¹⁹F{¹H} NMR** (470 MHz, d_6 -DMSO) δ_F -189.4 (2F, bs, $CHF-2$), -209.4 (2F, m, $CHF-3$); **(ESI+)** m/z $[M-HCl + H]^+$ calcd for $C_{15}H_{18}ClF_4NO_2^+$: 320.1273 found 320.1266; **(ESI-)** m/z $[M-H]^+$ calcd for $C_{15}H_{18}ClF_4NO_2^+$: 354.0962 found 354.0890;

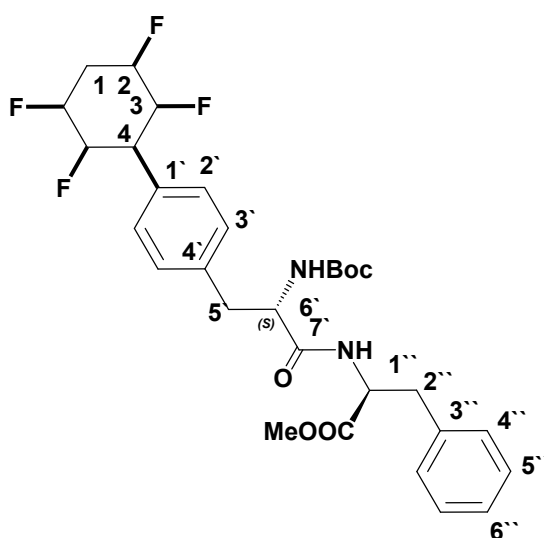
(2S)- 2-(tert-Butoxycarbonylamino)-3-(4-(all cis-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl)propanoic. (13)



Di-*tert*-butyl dicarbonate (45 mg, 0.2 mmol), and sodium bicarbonate (46 mg, 0.54 mmol) was added to a solution of **11** (60 mg, 0.17 mmol) in mixture of water and THF 1:1 (3mL). The reaction was stirred at 0 °C for 1 h then left to come to ambient over 16h. The reaction

mixture was then extracted into diethyl ether (2 × 20 mL) and the aqueous layer was acidified to pH 2 with HCl 1 M, and then extracted into ethyl acetate (2 × 30). The organic layers was dried over sodium sulfate, filtered and evaporated under vacuum to afford *N*-*boc* amino acid **13** (66 mg, 93 %). **mp** 189 - 190 °C. $[\alpha]_D^{20} + 50$ (c= 2 × 10⁻⁴, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 7.45 (2H, d, *J* 7.7 Hz, CH-2'), 7.20 (2H, d, *J* 8.0, CH-3'), 5.09 – 4.88 (3H, m, CHF-3, NH*Boc*), 4.74 – 4.48 (3H, m, CHF-2, CHNH*Boc*), 3.23-3.05 (2H, m, PhCH₂), 2.78 – 2.49 (3H, m, CH-4, CH_AH_B-1), 1.42 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 175.8, 155.3, 135.7, 134.5, 129.9, 129.4, 90.2 – 88.1 (m, CHF-3), 88.1 – 86.1 (m, CHF-2), 85.3, 54.3, 43.6, 37.2, 28.3, 27.1 (tt, *J* 22.3, 2.2 Hz, CH₂-1); ¹⁹F{¹H} NMR (470 MHz, CDCl₃) δ_F -190.1 (2F, bt, CHF-2), -209.4 (2F, bt, CHF-3); (ESI⁺) *m/z* [M+Na]⁺ calcd for C₂₀H₂₅F₄NO₄⁺: 442.1618 found 442.1605;

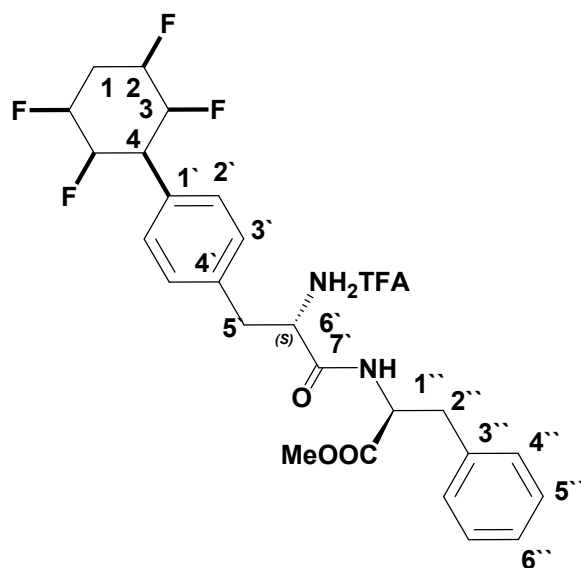
Methyl-(2*S*)-2 [N-((2*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-(all *cis*-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl)propanoyl]-2-amino-3-phenylpropanoate. (14**)**



EDCI hydrochloride (30 mg, 0.15 mmol) and NMM (mg, 0.48 mmol) were added to a solution of *N*-*Boc* amino acid **13** (50 mg, 0.119 mmol) (1mL) and HOBT (20 mg, 0.148 mmol) in dry DMF and the solution was stirred for 5 min at 0 °C. *L*-Phenylalanine OMe hydrochloride **14** (31 mg, 0.144 mmol) was added and the solution was stirred at room temperature for 16h. The reaction was diluted by sat ammonium chloride solution (10 mL), stirred for 1 h and then extracted into ethyl acetate (2 × 30 mL). The organic layer was washed with NaHCO₃ 10 % (20 mL), and brine (10 mL), dried and then the organic

solvent was evaporated under reduced pressure. The product was purified over silica gel using by ethyl acetate / petrol (1:1) as an eluent, to afford peptide **14** as a white solid (60 mg, 87 %). **mp** 136 - 137 °C. $[\alpha]_D^{20} + 20$ ($c = 2 \times 10^{-4}$, CHCl_3); **$^1\text{H NMR}$** (500 MHz, CDCl_3) δ_{H} 7.39 (2H, d, J 7.7 Hz, $\text{CH-2}'$), , 7.26-7.18 (5H, m, CH, CH''), 6.98 (2H, d, J 8.0 Hz, CH, CH''), 6.26 (1H, bd, C-1''- NH), 5.02 – 4.89 (3H, m, CHF-3 , NH Boc), 4.78 (1H, bs, $\text{H-1}''$), 4.70 – 4.52 (2H, m, CHF-2), 4.34 (1H, bs, $\text{H-6}''$), 3.68 (3H, s, COOMe), 3.11 - 3.00 (4H, m, $\text{CH}_2\text{-5}'$, $\text{CH}_2\text{-2}''$), 2.80–2.70 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{-1}$), 2.56 (1H, t, J 37.1 Hz, H-4), 2.48–2.43 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{-1}$), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$); **$^{13}\text{C NMR}$** (126 MHz, CDCl_3) δ_{C} 171.3, 170.5, 155.2, 136.5, 135.5, 134.3, 129.7, 129.5, 129.2, 128.5, 127.1, 89.7 – 88.2 (m, CHF-3), 87.8 – 86.2 (m, CHF-2), 55.7, 53.2, 52.3, 43.8, 37.9, 29.7, 28.2, 27.1 (t, J 22.0 Hz, $\text{CH}_2\text{-1}$); **$^{19}\text{F}\{^1\text{H}\}$ NMR** (470 MHz, CDCl_3) δ_{F} -190.2 (2F, m, CHF-2), -209.7 (2F, m, CHF-3); (**ESI+**) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{36}\text{F}_4\text{N}_2\text{O}_5^+$: 603.2458 found 603.2440.

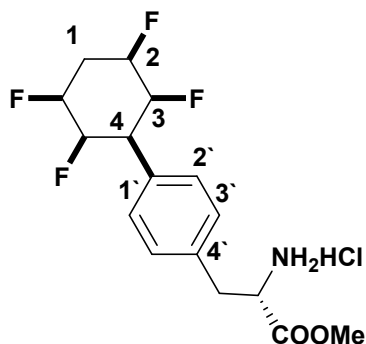
Methyl-2S-2 [N-((S)-2-(aminotrifluoroacetic)-3-(4-(all *cis*-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl)propanoyl)-2-amino-3-phenylpropanoate (15**)**



A solution of **14** (20 mg, 0.034 mmol) in a mixture of DCM and TFA (4 : 1) (2 mL) was stirred at RT for 4 h, until TLC showed the consumption of starting. The reaction mixture was then diluted with water (10 mL) and extracted into diethyl ether (2×15 ml), and the organic layer was washed with water (20 mL). The aqueous layers were collected and evaporated under vacuum and the product was purified using a C-18 coated silica cartridge

with water/methanol (1:1) as the eluent to afford trifluoroacetate salt **15** (18 mg, 94 %) as colorless solid. **mp** 240 °C. $[\alpha]_D^{20} + 45$ ($c = 2 \times 10^{-4}$, DMSO); $^1\text{H NMR}$ (300 MHz, CD_3COCD_3) δ_{H} 7.46 – 7.15 (9H, m, **CH-2'**, **CH-3'**, **H-5''**, **H-6''**, **H-7''**), 5.21 – 4.79 (6H, m, **CHF-2**, **CHF-3**, **H-6'**, **NH**), 4.68 (1H, m, **H-1''**), 3.69 (3H, s, **COOMe**), 3.40 - 3.15 (4H, m, **CH₂-5'**, **CH₂-2''**), 3.12 – 2.99 (1H, m, **CH_AH_B-1**), 2.59 – 2.41 (2H, m, **H-4**, **CH_AH_B-1**); $^{13}\text{C NMR}$ (100 MHz, CD_3COCD_3) δ_{C} 170.2, 167.0, 159.9, 138.5, 137.3, 134.6, 129.8, 129.6, 129.4, 129.3, 129.1, 128.3, 126.7, 126.7, 126.6, 115.7, 91.0 – 88.6 (m, 2C, **CHF-3**), 88.2 – 86.0 (m, 2C, **CHF-2**), 65.3, 57.1, 51.6, 42.6, 36.3, 36.1, 27.3 – 26.8 (m, **CH₂-1**); $^{19}\text{F}\{^1\text{H}\}$ **NMR** (470 MHz, CD_3COCD_3) δ_{F} -76.3 (3F, s, **CF₃COO**), -191.3 (2F, **CHF-2**), -210.8 (2F, m, **CHF-3**); **(ESI+)** m/z $[\text{M-TFA+H}]^+$ calcd for $\text{C}_{27}\text{H}_{29}\text{F}_7\text{N}_2\text{O}_5^+$: 481.2036 found 481.2094

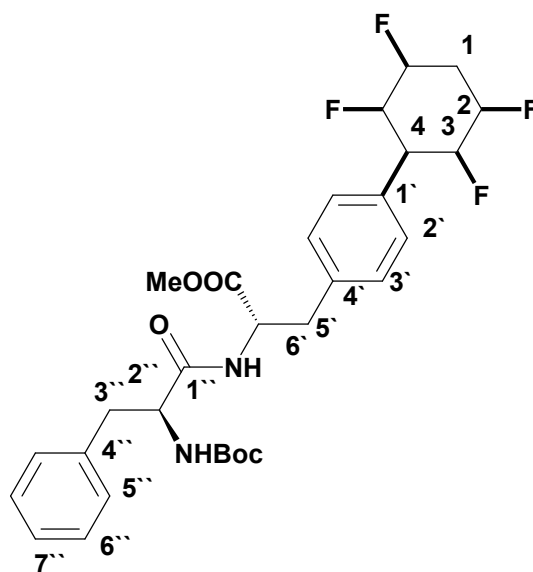
Methyl -2S-2- (aminohydrochloride)-3-(4-(all *cis*-2,3,5,6-tetrafluorocyclohex-1-yl))phenylpropanoate. (16)



A solution of protected amino acid **9** (90 mg, 0.208 mmol) in mixture of HCl 4 M and ethyl acetate (1:1) (3mL) was stirred for 24 hr at room temperature, until the starting material was consumed. The reaction mixture was extracted into ethyl acetate (2 × 30 ml), and the organic layers washed with water (20 mL). The aqueous layers were collected and evaporated at reduced pressure, to afford hydrochloride salt **16** without further purification (74 mg, 96 %) as colorless solid **mp** 240 - 241 °C $[\alpha]_D^{20} +70.0$ ($c = 2 \times 10^{-4}$, DMSO); $^1\text{H NMR}$ (300 MHz, D_2O) δ_{H} 7.45 (2H, d, J 8.1 Hz, **CH-2'**), 7.21 (2H, d, J 8.2, **CH-3'**), 5.25 – 5.03 (2H, m, **CHF-3**), 4.97 – 4.77 (2H, m, **CHF-2**), 4.33 (1H, dd, J 7.2, 6.0 Hz **CHNH₃Cl**), 3.71 (3H, s, **COOCH₃**), 3.28 – 3.04 (3H, m, **PhCH₂**, **CH_AH_B-1**), 2.49-2.35 (2H, m, **CH-4**,

CH_AH_B-1); ¹³C NMR (100 MHz, d₆-DMSO) δ_C 169.8, 136.2, 134.2, 129.9, 129.5, 90.9 – 89.1 (m, CHF-3), 88.5 – 86.3 (m, CHF-2), 53.5, 53.0 41.9, 35.8, 27.3 (t, *J* 21.3, Hz, CH₂-1); ¹⁹F{¹H} NMR (282 MHz, D₂O) δ_F –190.9 (2F, dd, *J* 7.7, 5.5 Hz, CHF-2), –210.4 (2F, dd, *J* 8.3, 4.4 Hz, CHF-3); (ESI+) *m/z* [M-HCl+Na]⁺ calcd for C₁₆H₂₀ClF₄NO₂⁺: 356.1250 found 356.1237

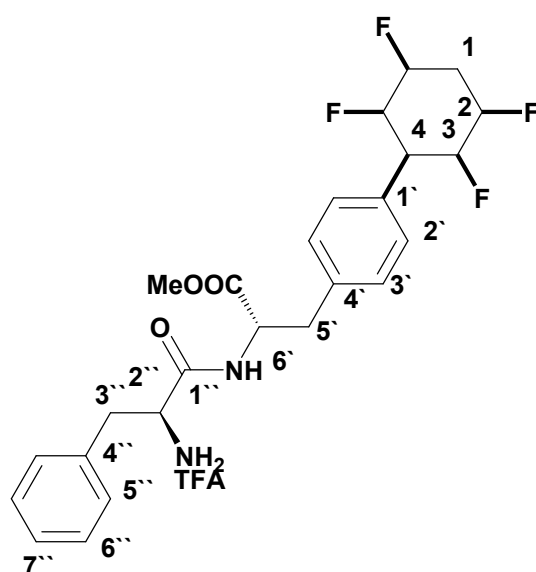
Methyl-2S-2N [(S-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoyl]-3-(4-(all *cis*-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl)-2-amino-propanoate (17)



HOBt (19 mg, 0.14 mmol), EDCI hydrochloride (34 mg, 0.14 mmol) and DIPEA (63 mg, 0.48 mmol) were added to a solution of N-Boc-L-phenylalanine acid (34 mg, 0.128 mmol) in dry DMF (1mL) and the solution was stirred for 5 min at 0 °C. Amino acid hydrochloride **16** (40 mg, 0.108 mmol) was then added and the solution was stirred at room temperature for 12 h. The reaction was then quenched by the addition of sat. ammonium chloride (10 mL), stirred for a further 1 h and was then extracted into ethyl acetate (2 × 30 mL). The organic layer was washed with NaHCO₃ 10 % (20 mL) and brine (20 mL), dried and the solvent evaporated under reduced pressure. The product was purified over silica gel using ethyl acetate / petrol (1:2) as an eluent to afford the target peptide as a white solid (58 mg, 92 %). **mp** 194 - 195 °C [α]_D²⁰ + 25.0 (*c* = 2 × 10⁻⁴, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ_H 7.35 (2H, d, *J* 7.7 Hz, CH-2'), 7.27 (2H, d, *J* 7.0, CH-3'), 7.26-7.18 (3H, m, CH''), 7.0 (2H, d, *J* 8.0 Hz, CH''), 6.38 (1H, d, *J* 7.7 Hz, C1''-NH), 5.02 – 4.90 (3H, m, CHF-3, NHBoc), 4.77 (1H, bs, H-6'),

4.71 – 4.53 (2H, m, CHF-2), 4.34 (1H, bs, H-2''), 3.67 (3H, s, COOMe), 3.11 - 2.99 (4H, m, CH₂-5', CH₂-3''), 2.78–2.68 (1H, m, CH_AH_B-1), 2.56 (1H, t, *J* 37.1 Hz, H-4), 2.48–2.42 (1H, m, CH_AH_B-1), 1.40 (9H, s, C(CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ_C 171.2, 170.9, 155.4, 136.4, 135.6, 134.4, 129.7, 129.4, 128.7, 127.0, 89.8 – 88.1 (m, CHF-3), 87.7 – 86.3 (m, CHF-2), 55.8, 53.2, 52.3 43.6, 38.2, 37.5, 37.0, 28.2, 27.1 (tt, *J* 22.0, 2.3 Hz, CH₂-1); ¹⁹F{¹H} NMR (470 MHz, CDCl₃) δ_F -190.2 (2F, m, CHF-2), -209.7 (2F, m, CHF-3); (ESI+) *m/z* [M+Na]⁺ calcd for C₃₀H₃₆F₄N₂O₅⁺: 603.2458 found 603.2444.

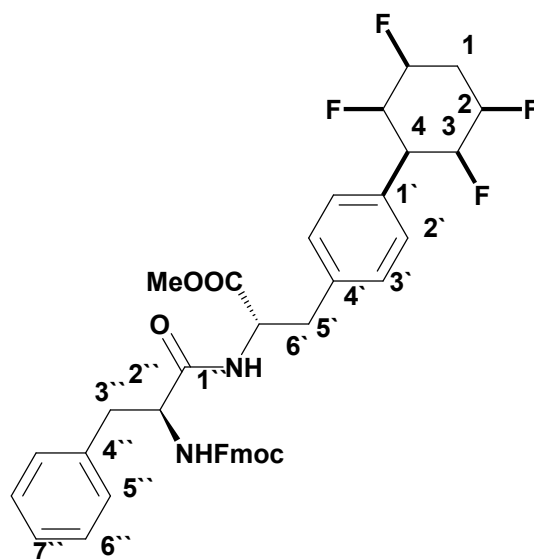
Methyl-2S-2N [(S-2-(ammoniumtrifluoroacetate)-3-phenylpropanoyl]-3-(4-(all cis-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl)-2-amino-propanoate (19a)



A solution of **17** (15 mg, 0.025 mmol) in a mixture of DCM and TFA (4 : 1) (2 mL) was stirred at room temperature and then the reaction mixture was diluted by water (10 mL) and extracted into diethyl ether (2 × 15 ml). The organic layer was then washed with water (20 mL) the aqueous layer collected and evaporated under vacuum, to afford the trifluoroacetate salt **19a** (13 mg, 89 %) as a colorless solid. **mp** decompose at 230 °C, [α]_D²⁰ + 40.0 (c= 2 × 10⁻⁴, DMSO); ¹H NMR (300 MHz, CD₃COCD₃) δ_H 7.50 (2H, d, *J* 7.6 Hz, CH-2'), 7.35 (2H, d, *J* 8.6, CH-3'), 7.30-7.10 (5H, m, H-5'', H-6'', H-7''), 5.22 – 4.77 (6H, m, CHF-2, CHF-3, H-2'', C1''-NH), 4.68 (1H, dd, *J* 9.8, 4.7 Hz, H-6'), 3.70 (3H, s, COOMe), 3.37 - 3.14 (4H, m, CH₂-5', CH₂-3''), 3.09 – 3.01 (1H, m, CH_AH_B-1), 2.55 – 2.40 (2H, m, H-4, CH_AH_B-1),

^{13}C NMR (126 MHz, CD_3COCD_3) δ_{C} 171.2, 166.6, 159.4 (1C, q, J 36.0, Hz, CF_3COO), 136.4, 135.6, 135.1, 129.4, 129.4, 129.2, 128.6, 127.3, 116.2 (q, 1C, J 288.9 Hz, CF_3COO), (90.6 – 89.0 (m, 2C, CHF-3), 87.8 – 86.3 (m, 2C, CHF-2), 63.9, 54.0, 51.7, 42.7, 37.0, 36.1, 27.0 (tt, J 21.7, 3.5 Hz, CH_2 -1); $^{19}\text{F}\{^1\text{H}\}$ NMR (282 MHz, CD_3COCD_3) δ_{F} -76.3 (3F, s, CF_3COO), -191.3 (2F, dd, J 6.9, 1.8 Hz, CHF-2), -210.7 (2F, dd, J 8.7, 2.6 Hz, CHF-3); (ESI+) m/z $[\text{M-TFA+H}]^+$ calcd for $\text{C}_{27}\text{H}_{29}\text{F}_7\text{N}_2\text{O}_5^+$: 481.2036 found 481.2095.

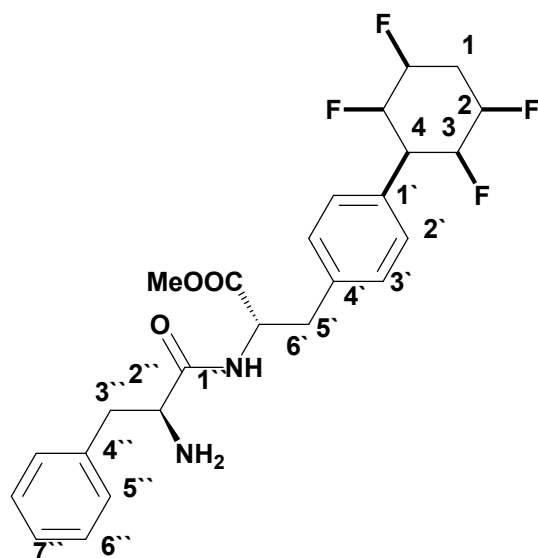
Methyl-2S-2N[[(2S)-2-(9-Fluorenylmethoxycarbonylamino)-3-phenylpropanoyl]-3-(4-(all cis-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl propanoate (18).



HBTU (27 mg, 0.071 mmol), NMM (11 mg, 0.10 mmol) and HOBT (10 mg, 0.074 mmol) were added to a solution of N-Fmoc-phenylalanine (25 mg, 0.064 mmol) **X** in dry DMF (1mL) and the solution was stirred for 5 min at 0 °C. Amino acid hydrochloride **16** (20 mg, 0.054 mmol) was added and the solution was stirred at room temperature for 6 h when a saturated solution of ammonium chloride (10 mL) was added and the reaction mixture was stirred for a further 10 min. The product was extracted into ethyl acetate (2 × 30 mL) and the organic layer was washed with NaHCO_3 10 % (20 mL) and brine (10 mL) and dried over MgSO_4 . The product was purified by over silica gel using ethyl acetate / petrol (2:1) as an eluent to afford dipeptide **18** as white solid (31 mg, 81 %). **mp** 210-212 °C. $[\alpha]_{\text{D}}^{20} + 40.0$ ($c = 2 \times 10^{-4}$, DMSO); ^1H NMR (300 MHz, CD_3COCD_3) δ_{H} 7.84 (2H, d, J 7.6 Hz, Ar-H),

7.61 (3H, bd, **Ar-H**, **NHFmoc**), 7.43-7.17 (13H, m, **Ar-H**), 6.67 (1H, d, *J* 8.6 Hz, **NHCO**), 5.17 – 4.70 (5H, m, **CHF-3**, **CHF-2**, **CH-2''**), 4.54 – 4.46 (1H, m, **H-6'**), 4.32 – 4.24 (1H, m, **CH-9Fmoc**), 4.20 – 4.10 (2H, m, **CH₂-Fmoc**), 3.67 (3H, s, **COOMe**), 3.20 - 3.00 (4H, m, **CH₂-5'**, **CH₂-3''**), 2.95–2.88 (1H, m, **CH_AH_B-1**), 2.57 – 2.38 (2H, m, **H-4**, **CH_AH_B-1**); ¹³C NMR (126 MHz, CD₃COCD₃) δ_C 171.4, 171.2, 155.9, 144.1, 141.1, 137.7, 136.1, 135.4, 129.4, 129.3, 129.2, 128.2, 127.6, 127.0, 126.3, 125.3, 125.2, 119.9, 90.5 – 89.0 (2C, m, **CHF-3**), 87.8 – 86.4, 66.3, 56.1, 53.6, 51.5, 47.0, 42.6, 37.7, 36.8, 27.0 (tt, *J* 22.2, 2.7 Hz, **CH₂-1**); ¹⁹F{¹H} NMR (282 MHz, CD₃COCD₃) δ_F -191.3 (2F, dd, *J* 6.3, 4.8 Hz **CHF-2**), -210.7 (2F, dd, *J* 7.7, 5.3 Hz, **CHF-3**); (**ESI+**) *m/z* [M+Na]⁺ calcd for C₄₀H₃₈F₄N₂O₅⁺: 725.2615 found 725.2603.

Methyl-2S-2N [((2S)-2-(amino)-3-phenylpropanoyl]-3-(4-(all-syn-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl-2-aminopropanoate (19b)



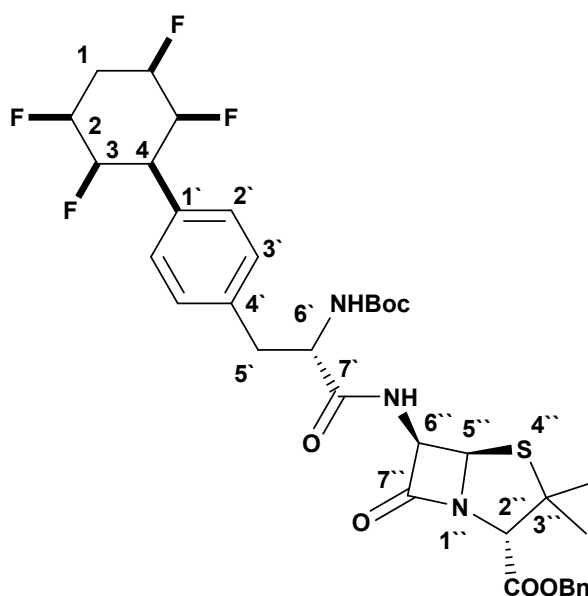
Diethylamine was added via syringe (0.012 mL, 0.11 mmol) to a solution of Fmoc-dipeptide **18** (28 mg, 0.039 mmol) in DMF (0.5 mL). The reaction was stirred for 2 hr at room temperature and then the solvent was evaporated under reduced pressure. The residue was washed with diethyl ether (3 × 10 ml) and the insoluble product was collected and dried under vacuum, to afford free amine **19b** without further purification (18 mg, 94 %) as colorless solid. **mp** decompose 270 °C. $[\alpha]_D^{20} + 55.0$ ($c = 2 \times 10^{-4}$, DMSO)

Alternative method:

A solution of piperidine in DMF (20 %, 0.5 mL) was added to Fmoc-dipeptide **18** (15 mg, 0.021 mmol) at 0 °C and the reaction was stirred for 2 h at room temperature. The reaction mixture was diluted with water and evaporated under reduced pressure. The insoluble residue was washed with diethyl ether (3 × 10 ml) and the product dried under vacuum, to afford the free amine **19b** without further purification (10 mg, 97 %) as colorless solid. **mp** decompose 270 °C. $[\alpha]_D^{20} + 55.0$ ($c = 2 \times 10^{-4}$, DMSO); $^1\text{H NMR}$ (500 MHz, d_6 -DMSO) δ_{H} 7.95 (2H, d, J 11.6 Hz, NH_2), 7.39 – 7.01 (9H, m, **Ar-H**), 5.76 (1H, s, **NHCO**), 5.07 – 4.80 (4H, m, **CHF-3**, **CHF-2**), 4.05 – 3.95 (2H, m, **H-6'**, **H-2''**), 3.40 (3H, s, **COOMe**), 3.10 – 2.88 (4H, m, **CH₂-5'**, **CH₂-3''**), 2.67–2.62 (1H, m, **CH_AH_B-1**), 2.39 – 2.34 (1H, m, **H-4**), 2.18 – 2.12 (1H, m, **CH_AH_B-1**); $^{13}\text{C NMR}$ (126 MHz, d_6 -DMSO) δ_{C} 166.8, 137.0, 136.1, 135.4, 130.4, 130.2, 129.2, 128.6, 127.0, 90.7 – 89.2 (2C, m, **CHF-3**), 88.0 – 86.6 (2C, m, **CHF-2**), 66.3, 60.2, 55.9, 55.7, 55.3, 42.0, 27.3 (m, **CH₂-1**); $^{19}\text{F}\{^1\text{H}\}$ NMR (470 MHz, d_6 -DMSO) δ_{F} -189.4 (2F, m, **CHF-2**), –

209.7 (2F, m, CHF-3); (ESI+) m/z $[M+Na]^+$ calcd for $C_{25}H_{28}F_4N_2O_3^+$: 503.1934 found 503.1916.

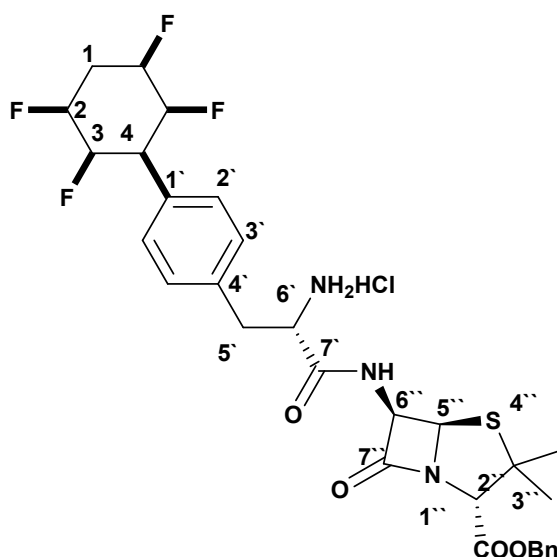
Benzyl (2*S*, 5*R*, 6*R*)-6- [(N-((2*S*)-2-(tert-Butoxycarbonylamino)-3-(4-(all *cis*-2,3,5,6-tetrafluorocyclohex-1-yl)phenyl)propanoyl)amino)]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (21).



HOBt (40 mg, 0.3 mmol), EDCI hydrochloride (73 mg, 0.38 mmol) and N-methylmorpholine (58 mg, 0.57 mmol) were added to a solution of N-Boc amino acid **13** (80 mg, 0.191 mmol) in dry DMF (1mL). The solution was stirred for 5 min at 0 °C, and then 6-APA p-toluenesulfonate (100 mg, 0.21 mmol) was added and the solution stirred at room temperature 12 h. The reaction was diluted with sat. ammonium chloride solution (10 mL) and the stirred for 1 h. The product was extracted into ethyl acetate (2 × 30 mL) and the organic layer washed with NaHCO₃ 10 % (20 mL) and brine (20 mL) and then dried over MgSO₄. Solvent removal gave the product which was purified over silica gel using ethyl acetate / petrol (1:1) as an eluent. This gave peptide **18** as a white solid (81 mg, 60 %). **mp** 153 - 154 °C. $[\alpha]_D^{20} + 140.0$ ($c = 2 \times 10^{-4}$, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ_H 7.41 (2H, d, J 7.8 Hz, CH-2'), 7.38 - 7.34 (5H, m, CH₂Ph), 7.21 (2H, d, J 7.6 Hz CH-3'), 6.74 (1H, d, J 7.6 Hz, C-6''-NH), 5.59 (1H, dd, J 6.6, 3.9 Hz, H-6''), 5.49 (1H, d, J 4.3 Hz, H-5''), 5.20 - 5.14 (2H, m, PhCH₂), 5.08 - 4.90 (3H, m, CHF-3, NHBoc), 4.78 (1H, bs, H-1''), 4.71 - 4.53 (2H, m, CHF-2), 4.41 (2H, bs, H-6', H-3''), 3.13 - 2.99 (2H, m, CH₂-5''), 2.79-2.68 (1H, m, CH_AH_B-1), 2.59 (1H,

t, J 37.3 Hz, **H-4**), 2.49–2.42 (1H, m, $\text{CH}_A\text{H}_B\text{-1}$), 1.53 (3H, s, $\text{C3}''\text{-CH}_3\text{A}$), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.38 (3H, s, $\text{C3}''\text{-CH}_3\text{B}$); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 173.1, 170.9, 167.5, 155.4, 136.2, 134.6, 134.3, 129.7, 129.6, 128.79, 128.74, 128.71, 89.9 – 88.1 (m, **CHF-3**), 87.9 – 86.1 (m, **CHF-2**), 70.4, 67.7, 67.5, 64.8, 58.5, 55.7, 43.6, 37.6, 31.5, 29.7, 28.8, 28.4, 27.1 (tt, J 22.0, 2.8 Hz, **CH₂-1**), 26.8 ; $^{19}\text{F}\{^1\text{H}\}$ NMR (470 MHz, CDCl_3) δ_{F} -190.2 (2F, m, **CHF-2**), -209.7 (2F, m, **CHF-3**); (**ESI+**) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{35}\text{H}_{41}\text{F}_4\text{N}_3\text{O}_6\text{S}^+$: 730.2550 found 730.2531.

Benzyl (2S, 5R, 6R)-6- [(N-((S)-2-(ammonium hydrochloride)-3-(4-(all *cis*-2,3,5,6 tetrafluorocyclohex-1-yl)phenyl)propanoyl)amino)]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. (22).



Boc-dipeptide **18** (20 mg, 0.028 mmol) was added to mixture of HCl 4M and 1,4-dioxane (1:1) (2 mL) at 0°C and then the mixture was stirred at room temperature for 1 h. The reaction was diluted with water (10 mL) and extracted into diethyl ether (2 × 15 mL). The organic layer was washed with water (20 mL) and the aqueous collected and evaporated under vacuum. The product was purified using a C-18 coated silica cartridge using methanol-water as the eluent (1:1) to afford hydrochloride salt **19** (15 mg, 83 %) as a colourless solid. **mp** decompose at 130 °C; $[\alpha]_{\text{D}}^{20}$ +95.0 ($c = 2 \times 10^{-4}$, DMSO); ^1H NMR (500 MHz, CD_3COCD_3) δ_{H} 7.47 - 7.28 (8H, m **Ar-H**), 7.15 (1H, dd, J 8.1, 1.6 Hz, **Ar-H**), 5.27 – 5.16 (3H, m, **PhCH₂, NH**), 5.27 – 4.82 (4H, m, **CHF-2, CHF-3**), 4.75 – 4.70 (1H, m, **H-6'**), 4.14 – 4.03 (1H, m, **H - 6''**), 3.83 - 3.64 (3H, m, **NH₃**), 3.43 – 3.34 (1H, m, **H-5''**), 3.30 (2H, bs,

PhCH₂-5`), 3.14 (1H, s, H-3``) 2.68 - 2.33 (3H, m, CH_AH_B-1, CH_AH_B-1, H-4), 1.57 (3H, s, C3``-CH₃A), 1.18 - 1.14 (3H, m, C3``-CH₃B); ¹³C NMR (126 MHz, CD₃COCD₃) δ_C 172.2, 169.0, 168.7, 137.6, 136.8, 135.1, 129.9, 128.9, 128.7, 128.4, 128.3, 90.7 – 89.0 (m, CHF-3), 88.1 – 86.3 (m, CHF-2), 74.1, 67.0, 66.5, 65.6, 44.8, 42.6, 41.5, 40.1, 29.4 – 28.4 (3C, CH₂-1, CH₃A, CH₃B under the solvent peak) ; ¹⁹F{¹H} NMR (282 MHz, d6-Acetone) δ_F -191.3 (2F, m, CHF-2), -210.9 (2F, m, CHF-3); HRMS (ESI+) *m/z* [M+H]⁺ calcd for C₃₀H₃₄ClF₄N₃O₄S⁺: 644.1895found 644.2524.

Crystallographic Details for single X-ray structure of 11

Data Collection

A colorless needle crystal of $C_{15}H_{18}ClF_4NO_2$ having approximate dimensions of 0.300 x 0.030 x 0.010 mm was mounted in a loop. All measurements were made on a Rigaku XtaLAB P100 diffractometer using multi-layer mirror monochromated Cu-K α radiation.

The crystal-to-detector distance was 30.10 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

$$\begin{aligned} a &= 5.3827(19) \text{ \AA} \\ b &= 7.108(2) \text{ \AA} \quad \beta = 97.301(6)^\circ \\ c &= 20.990(7) \text{ \AA} \\ V &= 796.6(4) \text{ \AA}^3 \end{aligned}$$

For $Z = 2$ and F.W. = 355.76, the calculated density is 1.483 g/cm³. Based on the reflection conditions of:

$$0k0: k = 2n$$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P2_1 (\#4)$$

The data were collected at a temperature of $-100 \pm 1^\circ\text{C}$ to a maximum 2θ value of 136.4° . A total of 3983 oscillation images were collected. A sweep of data was done using ϕ scans from 0.0 to 200.0° in 0.50° step, at $\omega=0.0^\circ$ and $\chi = 0.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -30.73° . A second sweep was performed using ω scans from -72.0 to 1.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -90.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -30.73° . Another sweep was performed using ω scans from -113.0 to -71.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -45.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -30.73° . Another sweep was performed using ϕ scans from 0.0 to 200.0° in 0.50° step, at $\omega=0.0^\circ$ and $\chi = 0.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle

was -67.73° . Another sweep was performed using ω scans from -85.0 to -13.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 90.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -67.73° . Another sweep was performed using ω scans from -133.0 to -93.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 0.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -67.73° . Another sweep was performed using ω scans from -85.0 to -12.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -90.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -67.73° . Another sweep was performed using ω scans from -126.0 to -86.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -180.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -67.73° . Another sweep was performed using ϕ scans from 0.0 to 200.0° in 0.50° step, at $\omega=-25.0^\circ$ and $\chi = 0.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -128.0 to -20.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -135.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -128.0 to -20.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 45.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -115.0 to -20.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -45.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -113.0 to -23.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 135.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -141.0 to -46.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -90.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -141.0 to -46.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -180.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -141.0 to -59.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 90.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -141.0 to -55.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 0.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -141.0 to -59.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 45.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -141.0 to -78.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -45.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -140.0 to -77.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = -135.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Another sweep was performed using ω scans from -140.0 to -56.0° in 0.50° step, at $\chi=0.0^\circ$ and $\phi = 135.0^\circ$. The exposure rate was 40.0 [sec./ $^\circ$]. The detector swing angle was -110.73° . Readout was performed in the 0.172 mm pixel mode.

Data Reduction

Of the 7844 reflections were collected, where 2667 were unique ($R_{\text{int}} = 0.1436$); equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku).¹

The linear absorption coefficient, μ , for Cu-K α radiation is 26.058 cm⁻¹. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.214 to 0.974. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction² was applied (coefficient = 0.038050).

Structure Solution and Refinement

The structure was solved by direct methods³ and expanded using Fourier techniques.

The crystal is a non-merohedral twin with twin law:

$$\begin{array}{ccc} -1.00000 & 0.00000 & 0.00000 \\ 0.00000 & -1.00000 & 0.00000 \\ 0.99100 & 0.00000 & 1.00000 \end{array}$$

Twin component #1 comprises 28.50% of the crystal.

The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically, and the rest were refined using the riding model. The final cycle of full-matrix least-squares refinement⁴ on F^2 was based on 2667 observed reflections and 222 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.0966$$

$$wR2 = [\sum (w (F_o^2 - F_c^2)^2) / \sum w(F_o^2)^2]^{1/2} = 0.2711$$

The goodness of fit⁵ was 0.98. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.59 and -0.33 e⁻/Å³, respectively. The final Flack parameter⁶ was -0.03(6), indicating that the present absolute structure is correct.⁷

Neutral atom scattering factors were taken from International Tables for Crystallography (IT), Vol. C, Table 6.1.1.4⁸. Anomalous dispersion effects were

included in F_{calc}^9 ; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley¹⁰. The values for the mass attenuation coefficients are those of Creagh and Hubbell¹¹. All calculations were performed using the CrystalStructure¹² crystallographic software package except for refinement, which was performed using SHELXL2013¹³.

References for the above paragraph

- (1) CrystalClear: Data Collection and Processing Software, Rigaku Corporation (1998-2014). Tokyo 196-8666, Japan.
- (2) Larson, A.C. (1970), Crystallographic Computing, 291-294. F.R. Ahmed, ed. Munksgaard, Copenhagen (equation 22, with V replaced by the cell volume).
- (3) SIR2011: Burla, M. C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G. L., Giacovazzo, C., Mallamo, M., Mazzone, A., Polidori, G. and Spagna, R. (2012). J. Appl. Cryst. 45, 357-361.
- (4) Least Squares function minimized: (SHELXL2013)
$$\sum w(F_o^2 - F_c^2)^2 \quad \text{where } w = \text{Least Squares weights.}$$
- (5) Goodness of fit is defined as:
$$[\sum w(F_o^2 - F_c^2)^2 / (N_o - N_v)]^{1/2}$$

where: N_o = number of observations
 N_v = number of variables
- (6) Parsons, S. and Flack, H. (2004), Acta Cryst. A60, s61.
- (7) Flack, H.D. and Bernardinelli (2000), J. Appl. Cryst. 33, 114-1148.
- (8) International Tables for Crystallography, Vol.C (1992). Ed. A.J.C. Wilson, Kluwer Academic Publishers, Dordrecht, Netherlands, Table 6.1.1.4, pp. 572.
- (9) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).
- (10) Creagh, D. C. & McAuley, W.J. ; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).
- (11) Creagh, D. C. & Hubbell, J.H.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages

200-206 (1992).

- (12) CrystalStructure 4.1: Crystal Structure Analysis Package, Rigaku Corporation (2000-2014). Tokyo 196-8666, Japan.
- (13) SHELXL2013: Sheldrick, G. M. (2008). Acta Cryst. A64, 112-122.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	C ₁₅ H ₁₈ ClF ₄ NO ₂
Formula Weight	355.76
Crystal Color, Habit	colorless, needle
Crystal Dimensions	0.300 X 0.030 X 0.010 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 5.3827(19) Å b = 7.108(2) Å c = 20.990(7) Å β = 97.301(6) ° V = 796.6(4) Å ³
Space Group	P2 ₁ (#4)
Z value	2
D _{calc}	1.483 g/cm ³
F ₀₀₀	368.00
μ(CuKα)	26.058 cm ⁻¹

B. Intensity Measurements

Diffractometer	XtaLAB P100
Radiation	CuK α ($\lambda = 1.54187 \text{ \AA}$) multi-layer mirror monochromated
Voltage, Current	40kV, 30mA
Temperature	-100.0 $^{\circ}$ C
Detector Aperture	83.8 x 33.5 mm
Data Images	3983 exposures
ϕ oscillation Range ($\omega=0.0, \chi=0.0$)	0.0 - 200.0 $^{\circ}$
Exposure Rate	40.0 sec./ $^{\circ}$
Detector Swing Angle	-30.73 $^{\circ}$
ω oscillation Range ($\chi=0.0, \phi=-90.0$)	-72.0 - 1.0 $^{\circ}$
Exposure Rate	40.0 sec./ $^{\circ}$
Detector Swing Angle	-30.73 $^{\circ}$
ω oscillation Range ($\chi=0.0, \phi=-45.0$)	-113.0 - -71.0 $^{\circ}$
Exposure Rate	40.0 sec./ $^{\circ}$
Detector Swing Angle	-30.73 $^{\circ}$
ϕ oscillation Range ($\omega=0.0, \chi=0.0$)	0.0 - 200.0 $^{\circ}$
Exposure Rate	40.0 sec./ $^{\circ}$
Detector Swing Angle	-67.73 $^{\circ}$
ω oscillation Range ($\chi=0.0, \phi=90.0$)	-85.0 - -13.0 $^{\circ}$
Exposure Rate	40.0 sec./ $^{\circ}$

Detector Swing Angle	-67.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=0.0$)	-133.0 - -93.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-67.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=-90.0$)	-85.0 - -12.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-67.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=-180.0$)	-126.0 - -86.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-67.73 ⁰
ϕ oscillation Range ($\omega=-25.0, \chi=0.0$)	0.0 - 200.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=-135.0$)	-128.0 - -20.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=45.0$)	-128.0 - -20.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=-45.0$)	-115.0 - -20.0 ⁰
Exposure Rate	40.0 sec./ ⁰

Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=135.0$)	-113.0 - -23.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=-90.0$)	-141.0 - -46.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=-180.0$)	-141.0 - -46.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=90.0$)	-141.0 - -59.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=0.0$)	-141.0 - -55.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=45.0$)	-141.0 - -59.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰
ω oscillation Range ($\chi=0.0, \phi=-45.0$)	-141.0 - -78.0 ⁰
Exposure Rate	40.0 sec./ ⁰
Detector Swing Angle	-110.73 ⁰

ω oscillation Range ($\chi=0.0, \phi=-135.0$)	-140.0 - -77.0 $^{\circ}$
Exposure Rate	40.0 sec./ $^{\circ}$
Detector Swing Angle	-110.73 $^{\circ}$
ω oscillation Range ($\chi=0.0, \phi=135.0$)	-140.0 - -56.0 $^{\circ}$
Exposure Rate	40.0 sec./ $^{\circ}$
Detector Swing Angle	-110.73 $^{\circ}$
ω oscillation Range ($\chi=0.0, \phi=0.0$)	-91.0 - -90.5 $^{\circ}$
Exposure Rate	4.0 sec./ $^{\circ}$
Detector Swing Angle	-30.73 $^{\circ}$
Detector Position	90.10 mm
Pixel Size	0.172 mm
$2\theta_{\max}$	136.4 $^{\circ}$
No. of Reflections Measured	Total: 7844 Unique: 2667 ($R_{\text{int}} = 0.1436$)
Parsons quotients (Flack x parameter):	359
Corrections	Lorentz-polarization Absorption (trans. factors: 0.214 - 0.974) Secondary Extinction (coefficient: 3.80500e-002)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR2011)
Refinement	Full-matrix least-squares on F ²
Function Minimized	$\Sigma w (F_o^2 - F_c^2)^2$
Least Squares Weights	$w = 1 / [\sigma^2(F_o^2) + (0.1611 \cdot P)^2 + 0.0000 \cdot P]$ where $P = (Max(F_o^2, 0) + 2F_c^2) / 3$
$2\theta_{max}$ cutoff	136.4°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	2667
No. Variables	222
Reflection/Parameter Ratio	12.01
Residuals: R1 ($I > 2.00\sigma(I)$)	0.0966
Residuals: R (All reflections)	0.1193
Residuals: wR2 (All reflections)	0.2711
Goodness of Fit Indicator	0.978
Flack parameter (Parsons' quotients = 359)	-0.03(6)
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.59 e ⁻ /Å ³
Minimum peak in Final Diff. Map	-0.33 e ⁻ /Å ³

Table 1. Atomic coordinates and $B_{\text{iso}}/B_{\text{eq}}$

atom	x	y	z	B_{eq}
Cl1	0.7416(7)	0.4443(6)	0.9258(2)	6.55(9)
F8	0.5256(17)	0.6947(12)	0.6644(5)	6.09(18)
F9	0.9512(19)	0.8566(13)	0.6395(6)	7.4(2)
F11	0.6905(19)	0.3659(16)	0.4920(5)	7.2(2)
F12	0.3734(15)	0.4077(15)	0.5814(4)	6.3(2)
O15	0.5873(19)	-0.0674(18)	0.9385(6)	6.9(2)
O16	0.336(2)	-0.2767(19)	0.8827(7)	7.2(3)
N17	0.228(2)	0.1933(18)	0.9441(7)	5.9(2)
C1	0.522(2)	0.303(2)	0.7156(9)	5.5(3)
C2	0.398(3)	0.415(2)	0.7561(8)	6.1(3)
C3	0.228(3)	0.332(2)	0.7949(7)	5.6(3)
C4	0.203(3)	0.138(2)	0.7964(8)	5.6(3)
C5	0.333(3)	0.029(2)	0.7567(10)	6.9(4)
C6	0.488(3)	0.110(2)	0.7161(10)	6.2(3)
C7	0.697(3)	0.3812(19)	0.6689(8)	5.3(3)
C8	0.743(3)	0.593(2)	0.6780(8)	5.5(3)
C9	0.921(3)	0.660(2)	0.6314(9)	6.0(3)
C10	0.830(3)	0.614(3)	0.5623(10)	6.9(4)
C11	0.788(3)	0.404(2)	0.5560(8)	5.5(3)
C12	0.611(3)	0.331(2)	0.6011(8)	6.0(3)
C13	0.028(3)	0.052(2)	0.8403(7)	5.5(3)
C14	0.154(3)	0.010(2)	0.9093(8)	5.7(3)
C15	0.389(3)	-0.1135(19)	0.9114(9)	6.2(3)

$$B_{\text{eq}} = 8/3 \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos \gamma + 2U_{13}(aa^*cc^*)\cos \beta + 2U_{23}(bb^*cc^*)\cos \alpha)$$

Table 2. Atomic coordinates and B_{iso} involving hydrogen atoms

atom	x	y	z	B_{iso}
H16	0.46(4)	-0.38(3)	0.888(12)	10.8258
H17A	0.27(5)	0.15(3)	0.988(4)	8.8163
H17B	0.11(3)	0.30(2)	0.933(10)	8.8163
H17C	0.38(2)	0.24(3)	0.930(10)	8.8163
H2	0.42637	0.54665	0.75783	7.368
H3	0.13214	0.40909	0.81956	6.691
H5	0.31536	-0.10441	0.75724	8.291
H6	0.57142	0.03250	0.68854	7.398
H7	0.86264	0.31831	0.68033	6.404
H8	0.81885	0.61802	0.72320	6.588
H9	1.08745	0.59851	0.64333	7.177
H10A	0.95597	0.65384	0.53453	8.330
H10B	0.67170	0.68107	0.54833	8.330
H11	0.95327	0.33873	0.56586	6.642
H12	0.60066	0.19090	0.59731	7.220
H13A	-0.04170	-0.06680	0.82080	6.658
H13B	-0.11395	0.13911	0.84285	6.658
H14	0.03015	-0.05643	0.93298	6.786

Table 3. Anisotropic displacement parameters

atom	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
Cl1	0.071(2)	0.0630(18)	0.115(3)	0.0164(17)	0.0100(18)	-0.000(2)
F8	0.060(5)	0.056(5)	0.117(6)	0.004(4)	0.021(4)	0.001(4)
F9	0.076(6)	0.070(6)	0.135(8)	-0.020(5)	0.021(5)	-0.010(5)
F11	0.073(6)	0.109(8)	0.095(6)	-0.011(5)	0.017(5)	-0.008(5)
F12	0.054(4)	0.087(6)	0.100(6)	-0.004(4)	0.011(4)	-0.013(5)
O15	0.057(6)	0.060(5)	0.148(9)	-0.005(6)	0.023(6)	0.002(7)
O16	0.072(7)	0.069(7)	0.130(9)	0.009(6)	0.002(6)	-0.001(6)
N17	0.067(7)	0.058(6)	0.096(8)	0.007(6)	0.004(7)	-0.010(6)
C1	0.046(7)	0.050(7)	0.114(11)	0.001(5)	0.010(7)	0.000(7)
C2	0.072(9)	0.049(8)	0.112(11)	0.009(7)	0.011(8)	0.002(7)
C3	0.063(8)	0.058(8)	0.092(9)	-0.005(6)	0.013(7)	0.002(7)
C4	0.057(8)	0.055(7)	0.103(10)	0.011(7)	0.015(7)	0.004(7)
C5	0.062(9)	0.049(8)	0.153(16)	-0.011(7)	0.019(9)	-0.001(9)
C6	0.062(8)	0.058(8)	0.116(12)	0.001(7)	0.017(8)	-0.014(8)
C7	0.054(8)	0.049(7)	0.101(10)	0.004(6)	0.010(6)	-0.003(6)
C8	0.060(8)	0.066(9)	0.083(9)	-0.006(7)	0.010(6)	-0.012(6)
C9	0.059(8)	0.058(8)	0.112(11)	-0.008(6)	0.019(8)	-0.010(7)
C10	0.040(8)	0.086(12)	0.138(15)	0.004(7)	0.017(8)	0.007(10)
C11	0.064(8)	0.058(9)	0.091(8)	-0.002(7)	0.020(6)	-0.005(6)
C12	0.057(8)	0.075(10)	0.099(10)	0.008(7)	0.019(7)	-0.007(8)
C13	0.061(8)	0.066(9)	0.082(9)	-0.003(6)	0.003(7)	0.001(7)
C14	0.064(8)	0.063(7)	0.089(8)	-0.002(7)	0.011(7)	-0.003(7)
C15	0.051(8)	0.047(7)	0.141(13)	-0.010(6)	0.018(8)	0.005(7)

The general temperature factor expression: $\exp(-2\pi^2(a^2U_{11}h^2 + b^2U_{22}k^2 + c^2U_{33}l^2 + 2a*b*U_{12}hk + 2a*c*U_{13}hl + 2b*c*U_{23}kl))$

Table 4. Fragment Analysis

fragment: 1
Cl(1)

fragment: 2

F(8)	F(9)	F(11)	F(12)	O(15)
O(16)	N(17)	C(1)	C(2)	C(3)
C(4)	C(5)	C(6)	C(7)	C(8)
C(9)	C(10)	C(11)	C(12)	C(13)
C(14)	C(15)			

Table 5. Bond lengths (Å)

atom	atom	distance	atom	atom	distance
F8	C8	1.376(18)	F9	C9	1.415(18)
F11	C11	1.406(18)	F12	C12	1.404(17)
O15	C15	1.191(19)	O16	C15	1.32(2)
N17	C14	1.52(2)	C1	C2	1.39(2)
C1	C6	1.38(2)	C1	C7	1.55(2)
C2	C3	1.43(2)	C3	C4	1.39(2)
C4	C5	1.39(3)	C4	C13	1.53(2)
C5	C6	1.39(3)	C7	C8	1.53(2)
C7	C12	1.48(2)	C8	C9	1.53(2)
C9	C10	1.51(3)	C10	C11	1.51(3)
C11	C12	1.52(2)	C13	C14	1.55(2)
C14	C15	1.53(2)			

Table 6. Bond lengths involving hydrogens (Å)

atom	atom	distance	atom	atom	distance
O16	H16	1.0(2)	N17	H17A	0.99(11)
N17	H17B	0.98(16)	N17	H17C	0.98(17)
C2	H2	0.950	C3	H3	0.950
C5	H5	0.950	C6	H6	0.950
C7	H7	1.000	C8	H8	1.000
C9	H9	1.000	C10	H10A	0.990
C10	H10B	0.990	C11	H11	1.000
C12	H12	1.000	C13	H13A	0.990
C13	H13B	0.990	C14	H14	1.000

Table 7. Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C2	C1	C6	119.1(16)	C2	C1	C7	124.0(13)
C6	C1	C7	116.9(15)	C1	C2	C3	120.3(14)
C2	C3	C4	119.7(15)	C3	C4	C5	118.9(15)
C3	C4	C13	118.7(14)	C5	C4	C13	122.3(14)
C4	C5	C6	121.5(15)	C1	C6	C5	120.4(17)
C1	C7	C8	112.1(13)	C1	C7	C12	112.5(12)
C8	C7	C12	112.5(13)	F8	C8	C7	111.8(12)
F8	C8	C9	106.6(12)	C7	C8	C9	109.4(13)
F9	C9	C8	107.7(13)	F9	C9	C10	110.6(14)
C8	C9	C10	113.2(13)	C9	C10	C11	109.1(16)
F11	C11	C10	107.9(13)	F11	C11	C12	109.9(12)
C10	C11	C12	112.4(14)	F12	C12	C7	110.5(13)
F12	C12	C11	107.8(12)	C7	C12	C11	111.8(13)
C4	C13	C14	114.2(13)	N17	C14	C13	110.0(12)
N17	C14	C15	108.1(12)	C13	C14	C15	113.6(14)
O15	C15	O16	126.1(15)	O15	C15	C14	122.8(14)
O16	C15	C14	111.0(13)				

Table 8. Bond angles involving hydrogens (°)

atom	atom	atom	angle	atom	atom	atom	angle
H16	O16	C15	118(13)	H17A	N17	H17B	123(18)
H17A	N17	H17C	109(18)	H17A	N17	C14	100(12)
H17B	N17	H17C	99(17)	H17B	N17	C14	115(10)
H17C	N17	C14	110(13)	C1	C2	H2	119.9
C3	C2	H2	119.9	C2	C3	H3	120.2
C4	C3	H3	120.2	C4	C5	H5	119.3
C6	C5	H5	119.3	C1	C6	H6	119.8
C5	C6	H6	119.8	C1	C7	H7	106.4
C8	C7	H7	106.4	C12	C7	H7	106.4
F8	C8	H8	109.7	C7	C8	H8	109.7
C9	C8	H8	109.7	F9	C9	H9	108.4
C8	C9	H9	108.4	C10	C9	H9	108.4
C9	C10	H10A	109.9	C9	C10	H10B	109.9
C11	C10	H10A	109.9	C11	C10	H10B	109.9
H10A	C10	H10B	108.3	F11	C11	H11	108.8
C10	C11	H11	108.8	C12	C11	H11	108.8
F12	C12	H12	108.9	C7	C12	H12	108.9
C11	C12	H12	108.9	C4	C13	H13A	108.7
C4	C13	H13B	108.7	C14	C13	H13A	108.7
C14	C13	H13B	108.7	H13A	C13	H13B	107.6
N17	C14	H14	108.4	C13	C14	H14	108.4
C15	C14	H14	108.4				

Table 9. Torsion Angles($^{\circ}$)(Those having bond angles > 160 or < 20 degrees are excluded.)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C2	C1	C6	C5	-0(2)	C6	C1	C2	C3	-3(2)
C2	C1	C7	C8	7.1(19)	C2	C1	C7	C12	-120.8(14)
C7	C1	C2	C3	176.1(12)	C6	C1	C7	C8	-173.6(12)
C6	C1	C7	C12	58.5(16)	C7	C1	C6	C5	-179.7(12)
C1	C2	C3	C4	6(2)	C2	C3	C4	C5	-4(2)
C2	C3	C4	C13	177.5(12)	C3	C4	C5	C6	0(2)
C3	C4	C13	C14	-88.8(15)	C5	C4	C13	C14	92.8(17)
C13	C4	C5	C6	178.9(12)	C4	C5	C6	C1	2(2)
C1	C7	C8	F8	-63.3(15)	C1	C7	C8	C9	178.8(10)
C1	C7	C12	F12	61.6(16)	C1	C7	C12	C11	-178.4(10)
C8	C7	C12	F12	-66.1(16)	C8	C7	C12	C11	53.9(16)
C12	C7	C8	F8	64.6(17)	C12	C7	C8	C9	-53.3(15)
F8	C8	C9	F9	56.7(14)	F8	C8	C9	C10	-65.8(15)
C7	C8	C9	F9	177.8(11)	C7	C8	C9	C10	55.2(15)
F9	C9	C10	C11	-177.3(11)	C8	C9	C10	C11	-56.5(16)
C9	C10	C11	F11	176.7(12)	C9	C10	C11	C12	55.3(15)
F11	C11	C12	F12	-54.0(16)	F11	C11	C12	C7	-175.6(11)
C10	C11	C12	F12	66.3(15)	C10	C11	C12	C7	-55.3(16)
C4	C13	C14	N17	66.9(16)	C4	C13	C14	C15	-54.4(16)
N17	C14	C15	O15	2(2)	N17	C14	C15	O16	179.0(12)
C13	C14	C15	O15	124.6(17)	C13	C14	C15	O16	-58.7(18)

Table 10. Possible hydrogen bonds

Donor	H	Acceptor	D...A	D-H	H...A	D-H...A
O16	H16	Cl1 ¹	3.004(13)	1.0(2)	2.1(2)	163(21)
N17	H17A	Cl1 ²	3.240(15)	0.99(11)	2.31(15)	158(17)
N17	H17A	O15	2.690(18)	0.99(11)	2.6(2)	84(12) intramol.
N17	H17B	Cl1 ³	3.153(14)	0.98(16)	2.25(18)	154(15)
N17	H17C	O15	2.690(18)	0.98(17)	2.5(2)	92(15) intramol.

Symmetry Operators:

- (1) X,Y-1,Z
 (2) -X+1,Y+1/2-1,-Z+2
 (3) X-1,Y,Z

Table 11. Intramolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
F8	F9	2.673(14)	F8	F12	2.739(13)
F8	C1	2.986(17)	F8	C2	2.912(19)
F8	C10	2.92(2)	F8	C11	3.501(19)
F8	C12	2.969(19)	F11	F12	2.710(14)
F12	C1	2.925(19)	F12	C6	3.52(2)
F12	C8	2.962(17)	F12	C9	3.495(18)
F12	C10	2.932(19)	O15	N17	2.690(18)
O15	C13	3.530(18)	O16	C4	3.49(2)
O16	C5	3.42(2)	O16	C13	2.94(2)
N17	C3	3.28(2)	N17	C4	3.11(2)
C1	C4	2.82(2)	C2	C5	2.77(2)
C2	C8	2.92(2)	C3	C6	2.79(2)
C3	C14	3.38(2)	C4	C15	3.07(2)
C5	C14	3.46(3)	C5	C15	3.38(3)
C6	C12	3.02(3)	C7	C10	2.94(3)
C8	C11	2.93(2)	C9	C12	2.90(2)

Table 12. Intramolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
F8	H2	2.347	F8	H7	3.226
F8	H9	3.186	F8	H10B	2.654
F9	H8	2.605	F9	H10A	2.636
F9	H10B	2.598	F11	H10A	2.589
F11	H10B	2.541	F11	H12	2.635
F12	H6	3.563	F12	H7	3.203
F12	H10B	2.668	F12	H11	3.217
O15	H16	2.5(2)	O15	H17A	2.6(2)
O15	H17C	2.5(2)	O15	H14	2.987
O16	H5	2.894	O16	H13A	2.714
O16	H14	2.590	H16	C14	3.3(2)
H16	H5	3.368	H16	H14	3.471
N17	H3	3.019	N17	H13A	3.358
N17	H13B	2.658	H17A	C13	3.28(11)
H17A	C15	2.58(18)	H17A	H13B	3.460
H17A	H14	2.163	H17B	C3	3.0(2)
H17B	C4	3.2(2)	H17B	C13	2.62(18)
H17B	C15	3.34(16)	H17B	H3	2.520
H17B	H13A	3.538	H17B	H13B	2.408
H17B	H14	2.568	H17C	C3	2.9(2)
H17C	C4	2.9(2)	H17C	C13	2.85(18)
H17C	C15	2.6(2)	H17C	H3	2.775

H17C	H13B	3.121	H17C	H14	2.861
C1	H3	3.302	C1	H5	3.261
C1	H8	2.743	C1	H12	2.692
C2	H6	3.256	C2	H7	3.204
C2	H8	2.846	C3	H5	3.248
C3	H13A	3.259	C3	H13B	2.596
C4	H2	3.286	C4	H6	3.281
C4	H14	3.415	C5	H3	3.254
C5	H13A	2.651	C5	H13B	3.283
C6	H2	3.254	C6	H7	2.683
C6	H12	2.701	C7	H2	2.771
C7	H6	2.615	C7	H9	2.717
C7	H10B	3.298	C7	H11	2.726
C8	H2	2.558	C8	H10A	3.384
C8	H10B	2.773	C8	H11	3.280

Table 12. Intramolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
C8	H12	3.359	C9	H7	2.671
C9	H11	2.683	C10	H7	3.235
C10	H8	3.386	C10	H12	3.365
C11	H7	2.661	C11	H9	2.666
C12	H6	2.831	C12	H8	3.354
C12	H9	3.225	C12	H10A	3.366
C12	H10B	2.760	C13	H3	2.649
C13	H5	2.712	C14	H3	3.399
C14	H5	3.507	C15	H5	3.211
C15	H13A	2.825	C15	H13B	3.410
H2	H3	2.380	H2	H7	3.430
H2	H8	2.375	H3	H13A	3.511
H3	H13B	2.417	H5	H6	2.331
H5	H13A	2.489	H5	H13B	3.553
H6	H7	2.585	H6	H12	2.244
H7	H8	2.336	H7	H9	2.505
H7	H11	2.516	H7	H12	2.285
H8	H9	2.353	H9	H10A	2.337
H9	H10B	2.863	H9	H11	2.505
H10A	H11	2.335	H10B	H11	2.866
H11	H12	2.337	H13A	H14	2.338
H13B	H14	2.396			

Table 13. Intermolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
Cl1	O15 ¹	3.586(13)	Cl1	O15 ²	3.539(14)
Cl1	O16 ¹	3.004(13)	Cl1	N17	3.351(14)
Cl1	N17 ³	3.153(14)	Cl1	N17 ²	3.240(15)
Cl1	C14 ²	3.467(16)	Cl1	C15 ²	3.60(2)
F8	F9 ⁴	3.278(13)	F8	F11 ⁵	3.554(13)
F8	C5 ¹	3.31(2)	F8	C6 ¹	3.159(18)
F8	C9 ⁴	3.250(18)	F9	F8 ³	3.278(13)
F9	F11 ⁶	3.563(16)	F9	C5 ⁷	3.24(2)
F11	F8 ⁸	3.554(13)	F11	F9 ⁹	3.563(16)
F11	C10 ⁸	3.40(2)	F11	C10 ⁹	3.45(2)
F12	C9 ⁴	3.300(19)	F12	C10 ⁴	3.248(18)
F12	C11 ⁴	3.126(17)	O15	Cl1 ¹⁰	3.586(13)
O15	Cl1 ¹¹	3.539(14)	O15	N17 ¹¹	3.053(18)
O15	C13 ³	3.44(2)	O15	C14 ³	3.24(2)
O16	Cl1 ¹⁰	3.004(13)	O16	C2 ¹⁰	3.49(2)
O16	C3 ¹⁰	3.35(2)	N17	Cl1 ⁴	3.153(14)
N17	Cl1	3.351(14)	N17	Cl1 ¹¹	3.240(15)
N17	O15 ²	3.053(18)	C2	O16 ¹	3.49(2)
C3	O16 ¹	3.35(2)	C5	F8 ¹⁰	3.31(2)
C5	F9 ¹²	3.24(2)	C6	F8 ¹⁰	3.159(18)
C9	F8 ³	3.250(18)	C9	F12 ³	3.300(19)
C10	F11 ⁵	3.40(2)	C10	F11 ⁶	3.45(2)

C10	F12 ³	3.248(18)	C11	F12 ³	3.126(17)
C13	O15 ⁴	3.44(2)	C14	CI1 ¹¹	3.467(16)
C14	O15 ⁴	3.24(2)	C15	CI1 ¹¹	3.60(2)

Symmetry Operators:

- | | |
|------------------------|-----------------------|
| (1) X,Y+1,Z | (2) -X+1,Y+1/2,-Z+2 |
| (3) X+1,Y,Z | (4) X-1,Y,Z |
| (5) -X+1,Y+1/2,-Z+1 | (6) -X+2,Y+1/2,-Z+1 |
| (7) X+1,Y+1,Z | (8) -X+1,Y+1/2-1,-Z+1 |
| (9) -X+2,Y+1/2-1,-Z+1 | (10) X,Y-1,Z |
| (11) -X+1,Y+1/2-1,-Z+2 | (12) X-1,Y-1,Z |

Table 14. Intermolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
Cl1	H16 ¹	2.1(2)	Cl1	H17A ²	2.31(15)
Cl1	H17B	3.55(19)	Cl1	H17B ³	2.25(18)
Cl1	H17C	2.41(18)	Cl1	H3 ³	3.264
Cl1	H13B ³	2.948	Cl1	H14 ²	3.060
F8	H5 ¹	2.771	F8	H6 ¹	2.460
F8	H9 ⁴	2.441	F9	H5 ⁵	2.966
F9	H6 ¹	2.708	F9	H6 ⁵	3.591
F9	H7 ¹	3.440	F9	H12 ¹	3.093
F11	H10A ⁶	2.544	F11	H10B ⁷	2.413
F11	H12 ⁸	3.250	F12	H9 ⁴	2.530
F12	H10A ⁴	2.918	F12	H10A ⁷	3.351
F12	H10B ⁷	3.147	F12	H11 ⁴	2.296
O15	H17A ⁹	2.61(18)	O15	H17B ⁹	3.11(19)
O15	H17C ⁹	3.1(2)	O15	H13A ³	3.369
O15	H13B ³	3.098	O15	H14 ³	2.403
O16	H17A ⁹	3.27(15)	O16	H17B ¹⁰	3.46(17)
O16	H17C ¹⁰	3.5(2)	O16	H2 ¹⁰	3.002
O16	H3 ¹⁰	2.752	H16	Cl1 ¹⁰	2.1(2)
H16	N17 ¹⁰	3.6(2)	H16	H17A ⁹	2.8(3)
H16	H17B ¹⁰	3.2(3)	H16	H17C ¹⁰	2.9(3)
H16	C2 ¹⁰	3.1(2)	H16	C3 ¹⁰	3.0(2)
H16	H2 ¹⁰	2.767	H16	H3 ¹⁰	2.626

N17	H16 ¹	3.6(2)	N17	H14 ¹¹	3.560
H17A	Cl1 ⁹	2.31(15)	H17A	O15 ²	2.61(18)
H17A	O16 ²	3.27(15)	H17A	H16 ²	2.8(3)
H17A	C15 ²	3.13(18)	H17A	H14 ¹¹	3.238
H17B	Cl1 ⁴	2.25(18)	H17B	Cl1	3.55(19)
H17B	O15 ²	3.11(19)	H17B	O16 ¹	3.46(17)
H17B	H16 ¹	3.2(3)	H17B	H14 ¹¹	3.182
H17C	Cl1	2.41(18)	H17C	O15 ²	3.1(2)
H17C	O16 ¹	3.5(2)	H17C	H16 ¹	2.9(3)
H17C	C15 ²	3.6(2)	H17C	H13B ³	3.539
C1	H7 ⁴	3.535	C1	H9 ⁴	3.360
C1	H13B ³	3.316	C2	H16 ¹	3.1(2)
C2	H5 ¹	3.447	C2	H7 ⁴	3.183
C2	H8 ⁴	3.425	C2	H9 ⁴	3.015
C2	H13B ³	3.584	C3	H16 ¹	3.0(2)

Table 14. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
C3	H7 ⁴	2.907	C3	H8 ⁴	3.226
C4	H7 ⁴	3.130	C5	H2 ¹⁰	3.462
C5	H7 ⁴	3.491	C5	H13A ³	3.529
C5	H13B ³	3.375	C6	H13A ³	3.376
C6	H13B ³	3.203	C8	H6 ¹	3.276
C8	H9 ⁴	3.511	C9	H5 ⁵	3.587
C9	H6 ¹	3.544	C10	H11 ¹²	3.457
C11	H10A ⁶	3.055	C11	H10B ⁷	3.474
C12	H10B ⁷	3.475	C12	H11 ⁴	3.524
C15	H17A ⁹	3.13(18)	C15	H17C ⁹	3.6(2)
C15	H14 ³	3.448	H2	O16 ¹	3.002
H2	H16 ¹	2.767	H2	C5 ¹	3.462
H2	H5 ¹	2.551	H2	H8 ⁴	3.298
H2	H9 ⁴	2.851	H3	Cl1 ⁴	3.264
H3	O16 ¹	2.752	H3	H16 ¹	2.626
H3	H7 ⁴	3.160	H3	H8 ⁴	2.876
H5	F8 ¹⁰	2.771	H5	F9 ¹³	2.966
H5	C2 ¹⁰	3.447	H5	C9 ¹³	3.587
H5	H2 ¹⁰	2.551	H5	H8 ¹³	3.326
H5	H8 ¹⁰	3.499	H5	H9 ¹³	3.307
H5	H13A ³	3.557	H6	F8 ¹⁰	2.460
H6	F9 ¹³	3.591	H6	F9 ¹⁰	2.708

H6	C8 ¹⁰	3.276	H6	C9 ¹⁰	3.544
H6	H8 ¹⁰	3.277	H6	H13A ³	3.328
H6	H13B ³	3.541	H7	F9 ¹⁰	3.440
H7	C1 ³	3.535	H7	C2 ³	3.183
H7	C3 ³	2.907	H7	C4 ³	3.130
H7	C5 ³	3.491	H7	H3 ³	3.160
H8	C2 ³	3.425	H8	C3 ³	3.226
H8	H2 ³	3.298	H8	H3 ³	2.876
H8	H5 ¹	3.499	H8	H5 ⁵	3.326
H8	H6 ¹	3.277	H8	H13A ⁵	3.064
H9	F8 ³	2.441	H9	F12 ³	2.530
H9	C1 ³	3.360	H9	C2 ³	3.015
H9	C8 ³	3.511	H9	H2 ³	2.851
H9	H5 ⁵	3.307	H10A	F11 ¹²	2.544
H10A	F12 ³	2.918	H10A	F12 ⁸	3.351

Table 14. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H10A	C11 ¹²	3.055	H10A	H11 ¹²	2.582
H10B	F11 ⁸	2.413	H10B	F12 ⁸	3.147
H10B	C11 ⁸	3.474	H10B	C12 ⁸	3.475
H10B	H11 ¹²	3.508	H10B	H12 ⁸	3.219
H11	F12 ³	2.296	H11	C10 ⁶	3.457
H11	C12 ³	3.524	H11	H10A ⁶	2.582
H11	H10B ⁶	3.508	H12	F9 ¹⁰	3.093
H12	F11 ⁷	3.250	H12	H10B ⁷	3.219
H13A	O15 ⁴	3.369	H13A	C5 ⁴	3.529
H13A	C6 ⁴	3.376	H13A	H5 ⁴	3.557
H13A	H6 ⁴	3.328	H13A	H8 ¹³	3.064
H13B	Cl1 ⁴	2.948	H13B	O15 ⁴	3.098
H13B	H17C ⁴	3.539	H13B	C1 ⁴	3.316
H13B	C2 ⁴	3.584	H13B	C5 ⁴	3.375
H13B	C6 ⁴	3.203	H13B	H6 ⁴	3.541
H14	Cl1 ⁹	3.060	H14	O15 ⁴	2.403
H14	N17 ¹⁴	3.560	H14	H17A ¹⁴	3.238
H14	H17B ¹⁴	3.182	H14	C15 ⁴	3.448

Symmetry Operators:

(1) X,Y+1,Z

(3) X+1,Y,Z

(5) X+1,Y+1,Z

(2) -X+1,Y+1/2,-Z+2

(4) X-1,Y,Z

(6) -X+2,Y+1/2-1,-Z+1

- (7) $-X+1, Y+1/2-1, -Z+1$
- (9) $-X+1, Y+1/2-1, -Z+2$
- (11) $-X, Y+1/2, -Z+2$
- (13) $X-1, Y-1, Z$

- (8) $-X+1, Y+1/2, -Z+1$
- (10) $X, Y-1, Z$
- (12) $-X+2, Y+1/2, -Z+1$
- (14) $-X, Y+1/2-1, -Z+2$