Quinine as Highly Responsive Chiral Sensor for the ^{1}H and ^{19}F NMR Enantiodiscrimination of *N*-Trifluoroacetyl Amino Acids with Free Carboxyl Functions

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Supplementary Information

Table S1. Nonequivalence ($\Delta\Delta\delta=|\Delta\delta_R-\Delta\delta_S|$, ppm) data of **1**-**10** at 60 mM and 5 mM (in parenthesis) in the presence of one equivalent (for **1**-**7**, **9**, **10**) or two equivalents (for **8**) of **Qui** in $CDCl_3$ or C_6D_6.

	$\Delta\Delta\delta$ (ppm)			
substrate	NH	CHα	CH_3	CF_3
1*	0.038 (0.013)	0.020 (0.011)	0.015 (0.008)	0.015 (0.006)
2*	0.020 (0.015)	0.004 (0.006)	0.010/0.022 (0.013/0.018)	0.033 (0.011)
3	0.210 (0.058)	0.007 (0.004)	0.026/0.011 (0.0027/0.020)	0.089 (0.009)
3*	0.041	0.008	0.016/0.023	0.032
4	0.183 (0.088)	0.028 (-)	0.036 (0.034)	0.082 (0.040)
4*	0.035	0.008	0.017	0.023
5	0.964 (1.230)	0.329 (0.374)		0.065 (0.103)
5*	0.533	0.267		0.057
6	0.201 (0.056)	0.084 (0.010)		0.052 (-)
6*	0.032	0.001	-	0.008
7	0.169 (0.070)	0.006 (0.005)	0.029 (0.030)	0.090 (0.025)
7*	0.034	0.011	0.004	0.032
8*	1.302 (1.090)	0.012 (0.024)		0.156 (0.114)
9		0.108/0.066 (0.037/0.038)		0.047/0.057 (0.037/0.081)
9*		0.029/0.032		0.037/0.064
10*	0.025 (0.081)	0.047 (0.004)		- (0.004)

*NMR analysis carried out in $CDCl_3$

Table S2. Comparison of ee (%) of (*R*)-**3** determined by gravimetric data and by integration of ^{1}H and ^{19}F NMR signals of **3** (60 mM) in equimolar mixtures **3**/**Qui** in C_6D_6. The corresponding absolute error is also reported.

ee by gravimetric data (%)	ee by NMR integration (%)	absolute error
98.94	99.26	0.32
89.86	89.3	0.56
80.30	79.64	0.66
59.86	59.5	0.36
40.42	40.72	0.30
19.94	20.16	0.22
0.38	0.92	0.54
-20.16	-19.76	0.40
-39.92	-39.54	0.38
-60.18	-60.64	0.46
-79.94	-80.44	0.50
-89.8	-90.36	0.56
-99.8	-99.24	0.56

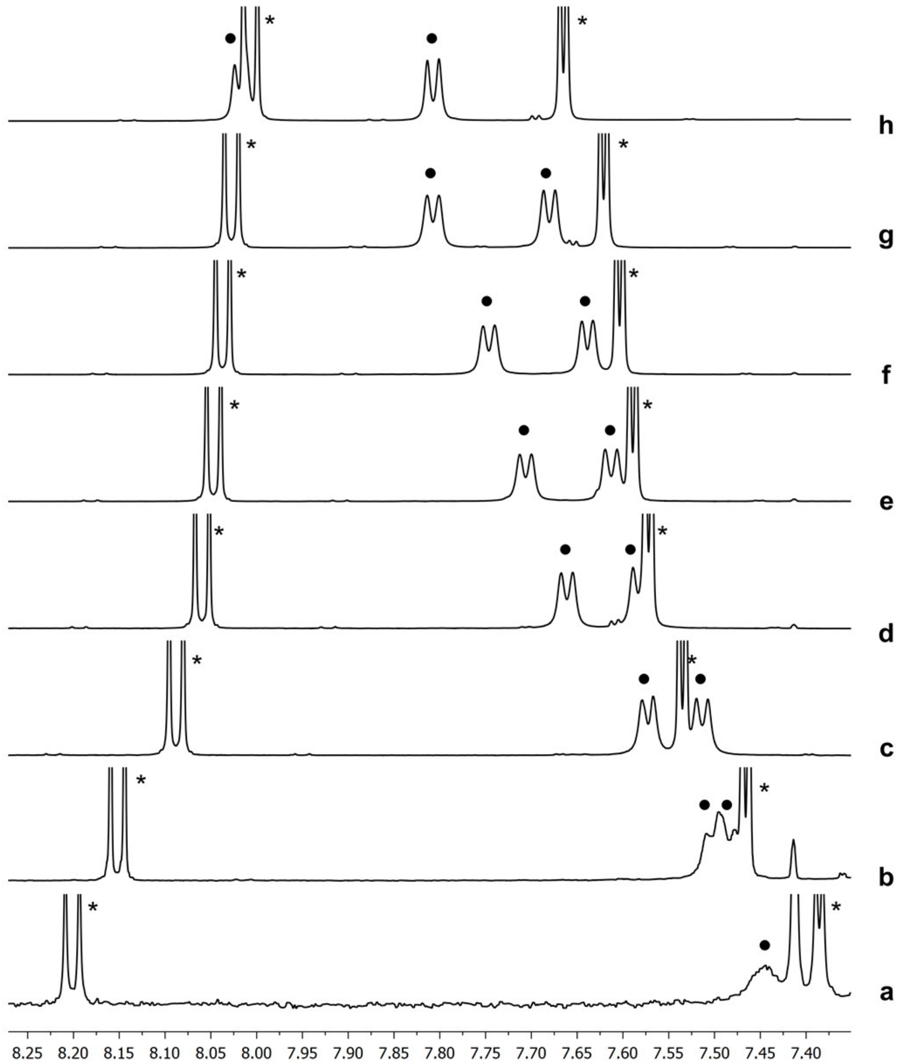

Figure S1. Comparison of ^{1}H NMR (600 MHz, 25 °C, C_6D_6) spectral regions corresponding to *NH* proton (●) of racemic **3** in equimolar **3**/**Qui** mixture at: a) 0.1 mM; b) 1 mM; c) 5 mM; d) 10 mM; e) 15 mM; f) 20 mM; g) 30 mM; h) 60 mM; ***Qui** resonance.

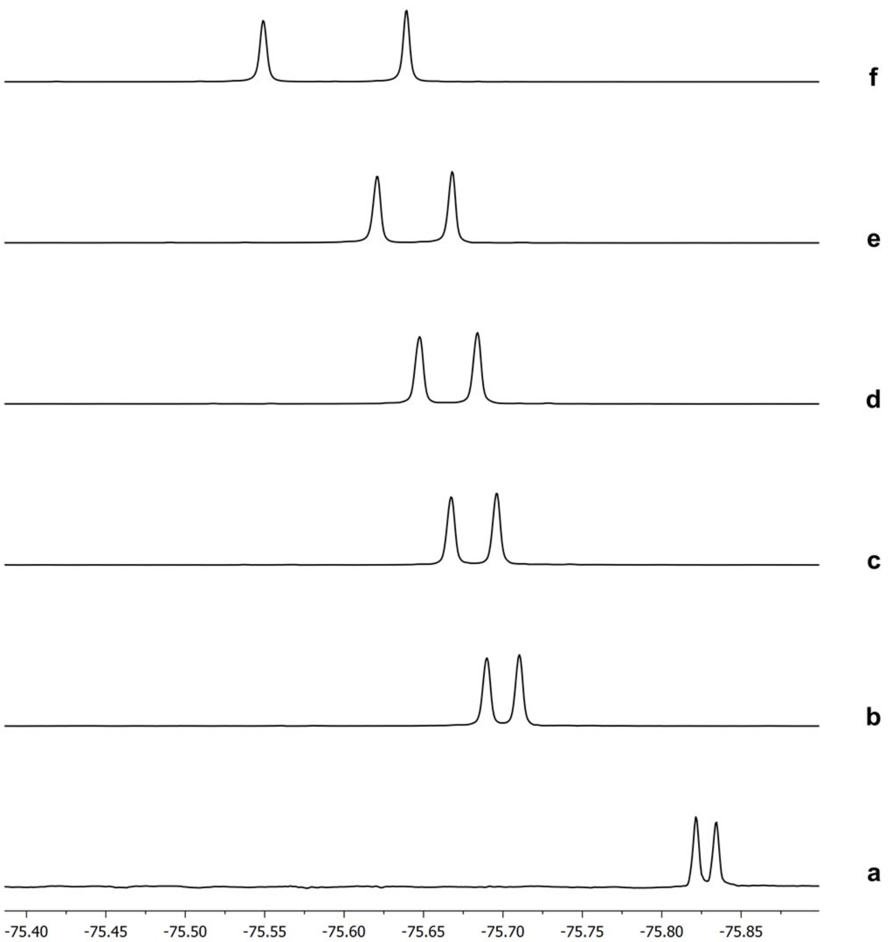

Figure S2. Comparison of ^{19}F NMR (564 MHz, 25 °C, C_6D_6) spectra of racemic **3** in equimolar **3**/**Qui** mixture at: a) 0.1 mM; b) 10 mM; c) 15 mM; d) 20 mM; e) 30 mM; f) 60 mM.

Table S3. ^{1}H NMR chemical shifts (δ, ppm) of H1 and H2 protons of **Qui** at variable concentration in the presence of **3** (15 mM) in C_6D_6.

	δ (ppm)	
Qui [mM]	H1	H2
1.5	7.54	8.74
4.5	7.51	8.73
7.5	7.53	8.76
15	7.61	8.80
30	7.47	8.71
45	7.44	8.63

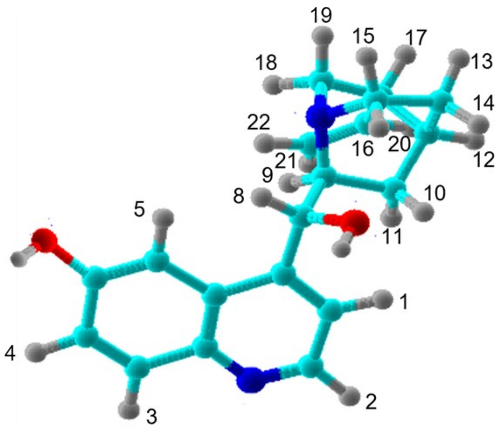

Figure S3. Schematic representation of **Qui** (with numbered protons) in the open-like conformation, obtained by detection of ROE effects.

Table S4. Comparison of ee (%) determined by gravimetric data and by integration of ^{19}F NMR signals of the two amino acids mixtures analysed in C_6D_6 and $CDCl_3$ and the corresponding absolute error.

N-TFA amino acid	ee by gravimetric data (%)	ee by NMR integration (%)	absolute error
1[a]	20.18	19.45	0.73
2[a]	19.96	19.58	0.38
3[b]	-19.92	-20.72	0.80
4[b]	-19.70	-19.36	0.34
5[b]	19.76	20.42	0.66
6[b]	19.90	19.20	0.70
7[b]	19.22	19.50	0.28
8[a]	20.12	20.68	0.56
9[b]	-19.22	-19.42	0.20
10[a]	20.12	19.40	0.72

[a]*N*-TFA amino acid derivatives (total concentration 60 mM) and Qui (66 mM) mixture in $CDCl_3$.
[b]*N*-TFA amino acid derivatives (total concentration 40 mM) and Qui (20 mM) mixture in C_6D_6.

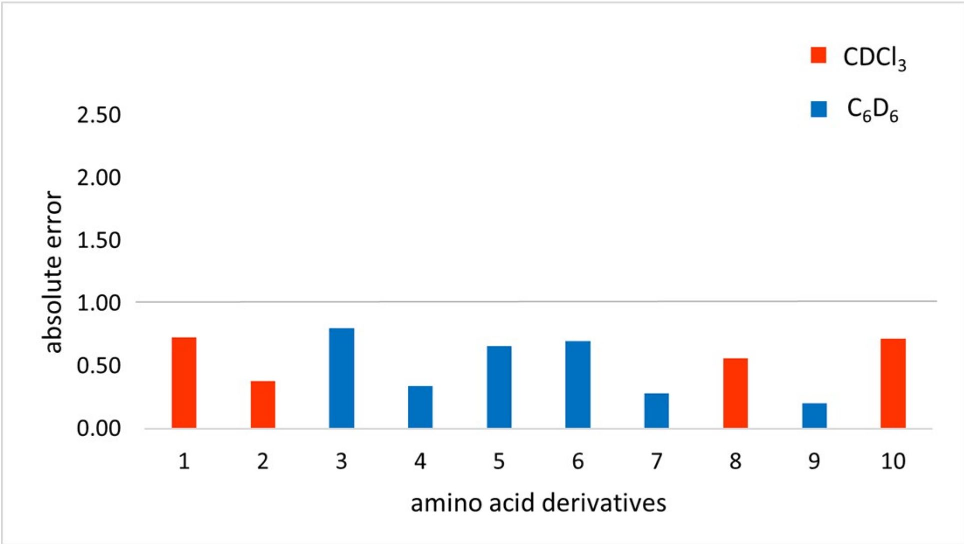

Figure S4. Absolute errors of ee in the determination of ee by NMR integration of *N*-TFA-amino acid derivatives in mixtures.

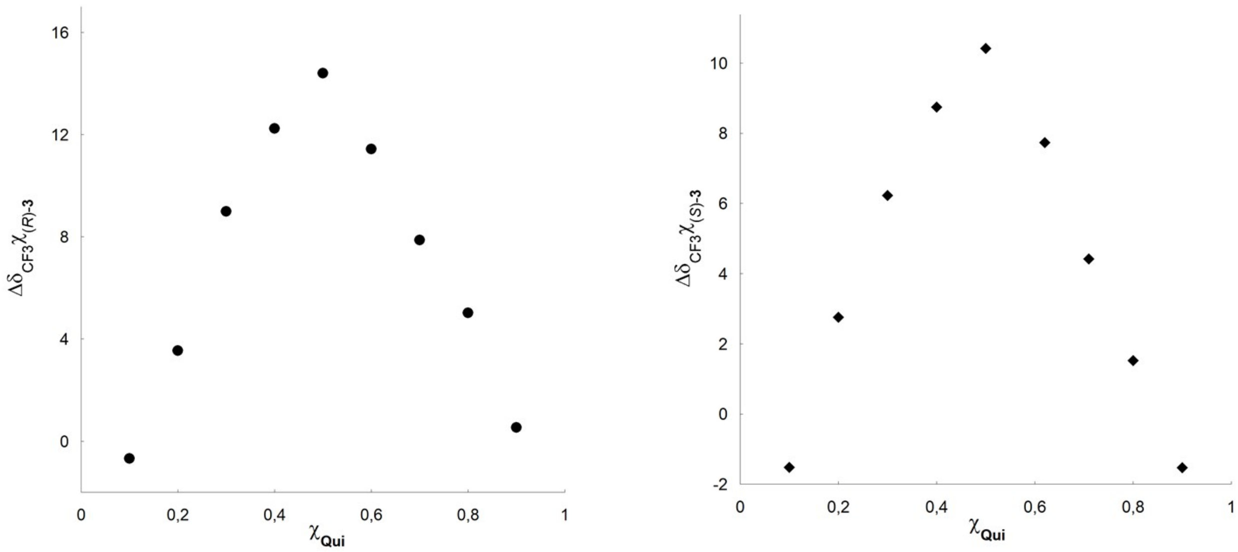

Figure S5. Stoichiometry determination based on CF_3 group for (*R*)-**3**/**Qui** (•) and (*S*)-**3**/**Qui** (♦) complexes.

$$C = \frac{(\delta_{obs} - \delta_f)\,(\delta_b - \delta_f)}{K(\delta_b - \delta_{obs})^2}$$

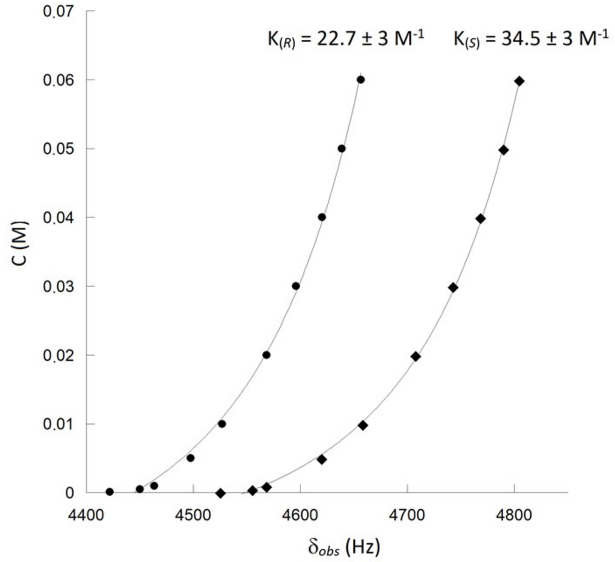

Figure S6. Non-linear fitting of dilution data: dependence of NH proton chemical shift (δ_{obs}, Hz) of **3** on the concentration (C) in equimolar mixtures (*R*)-**3**/**Qui** (ꝏ) and (*S*)-**3**/**Qui** (✹): δ_b and δ_f in equation are the chemical shift in the bound and in the free state, respectively.

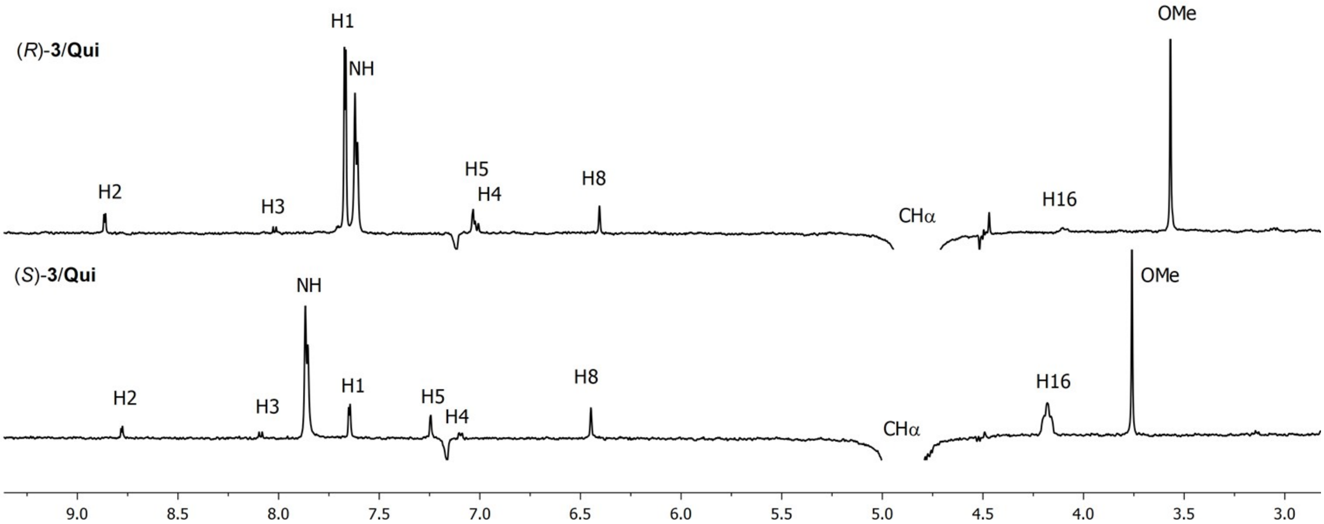

Figure S7. Comparison of 1D ROESY spectra of methine proton at the chiral center (CHα) of **3** (30 mM) in the equimolar mixtures (*R*)-**3**/**Qui** (top) and (*S*)-**3**/**Qui** (bottom).

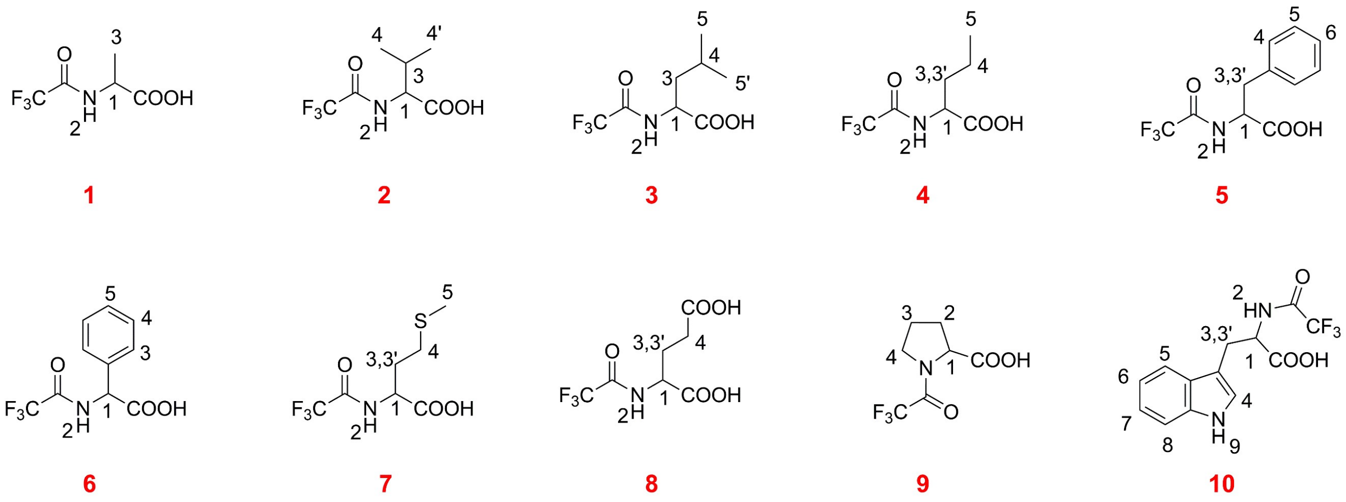

Figure S8. *N*-TFA-amino acid derivatives **1**-**10** with numbered protons.

NMR characterization of 1-10 and Quinine

N-Trifluoroacetylalanine (**1**) (white crystalline solid, 0.879 g, 95%).

δH (600 MHz, DMSO, Me_4Si, 25 °C): 12.89 (1H, br s, COOH); 9.70 (1H, d, H2, $J_{H2\text{-}H1}$ = 6.7 Hz); 4.29 (1H, dq, H1, $J_{H1\text{-}H3}$ = 7.2 Hz, $J_{H1\text{-}H2}$ = 6.7 Hz); 1.33 (3H, d, H3, $J_{H3\text{-}H1}$ = 7.2 Hz).

δC (150 MHz, DMSO, Me_4Si, 25 °C): 172.9 (COOH); 156.6 (CONH, q, $J_{C\text{-}F}$ = 37.2 Hz); 116.2 (CF_3, q, $J_{C\text{-}F}$ = 282.9 Hz); 48.6 (C1); 16.7 (C3).

N-Trifluoroacetylvaline (**2**) (pink pearl crystalline solid, 1.04 g, 97%).

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 6.75 (1H, d, H2, $J_{H2\text{-}H1}$ = 8.4 Hz); 4.65 (1H, dd, H1, $J_{H1\text{-}H2}$ = 8.4 Hz, $J_{H1\text{-}H3}$ = 4.6 Hz); 2.35 (1H, m, H-3); 1.02 (3H, d, H4, $J_{H4\text{-}H3}$ = 6.9 Hz); 1.00 (3H, d, H4', $J_{H4'\text{-}H3}$ = 6.9 Hz).

δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 174.9 (COOH); 157.2 (CONH, q, $J_{C\text{-}F}$ = 37.6 Hz); 115.7 (CF_3, q, $J_{C\text{-}F}$ = 288.6 Hz); 57.1 (C1); 31.2 (C3); 18.8 (C4); 17.0 (C4').

N-Trifluoroacetylleucine (**3**) (white crystalline solid, 1.01 g, 89%).

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 6.64 (1H, d, H2, $J_{H2\text{-}H1}$ = 8.0 Hz); 4.71 (1H, m, H1); 1.70 (2H, m, H3/H3'); 1.82 (1H, m, H4); 0.99 (6H, d, H5/H5', $J_{H5/5'\text{-}H4}$ = 6.3 Hz).

δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 174.8 (COOH); 156.9 (CONH, q, $J_{C\text{-}F}$ = 37.5 Hz); 115.6 (CF_3, q, $J_{C\text{-}F}$ = 288.9 Hz); 50.9 (C1); 41.1 (C3); 24.9 (C4); 22.6 (C5); 21.8 (C5').

N-Trifluoroacetylnorvaline (**4**) (white crystalline solid, 0.905 g, 85%).

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 6.75 (1H, d, H2, $J_{H2\text{-}H1}$ = 7.6 Hz); 4.69 (1H, dt, H1, $J_{H1\text{-}H2}$ = 7.6 Hz; $J_{H1\text{-}H3}$ = $J_{H1\text{-}H3'}$ = 5.4 Hz); 1.98 (1H, m, H3); 1.80 (1H, m, H3'); 1.41 (2H, m, H4); 0.97 (3H, t, H5, $J_{H5\text{-}H4}$ = 7.4 Hz).

δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 175.4 (COOH); 156.9 (CONH, q, $J_{C\text{-}F}$ = 38.0 Hz); 115.6 (CF_3, q, $J_{C\text{-}F}$ = 286.7 Hz); 52.7 (C1); 33.8 (C3); 18.1 (C4); 13.5 (C5).

N-Trifluoroacetylphenylalanine (**5**) (white crystalline solid, 0.992 g, 76%).

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 7.33 (2H, t, H5, J_{H5-H6} = J_{H5-H4} = 7.0 Hz); 7.30 (1H, t, H6, J_{H6-H5} = 7.0 Hz); 7.14 (2H, d, H4, J_{H4-H5} = 7.0 Hz); 6.71 (1H, d, H2, J_{H2-H1} = 6.9 Hz); 4.94 (1H, dt, H1, J_{H1-H2} = 6.9 Hz, J_{H1-H3} = $J_{H1-H3'}$ = 5.6 Hz); 3.30 (1H, dd, H3, $J_{H3-H3'}$ = 14.2 Hz, J_{H3-H1} = 5.6 Hz); 3.21 (1H, dd, H3', $J_{H3'-H3}$ = 14.2 Hz, $J_{H3'-H1}$ = 5.6 Hz).

δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 174.1 (COOH); 156.7 (CONH, q, J_{C-F} = 38.2 Hz); 134.2 ($\underline{C}$-C4); 129.2 (C4); 129.0 (C5); 127.8 (C6); 115.5 (CF_3, q, J_{C-F} = 287.6 Hz); 53.2 (C1); 36.9 (C3).

N-Trifluoroacetylphenylglycine (**6**) (white crystalline solid, 1.20 g, 97%).

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 7.33 (5H, m, H3, H4, H5); 7.23 (1H, d, H2, J_{H2-H1} = 7.0 Hz); 5.59 (1H, d, H1, J_{H1-H2} = 7.0 Hz).

δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 173.1 (COOH); 156.4 (CONH, q, J_{C-F} = 38.1 Hz); 133.8 ($\underline{C}$-C3); 129.6/129.3/127.2 (C3, C4, C5); 115. 5 (CF_3, q, J_{C-F} = 279.5 Hz); 56.4 (C1).

N-Trifluoroacetylmethionine (**7**) (white crystalline solid, 0.981 g, 80 %).

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 7.23 (1H, d, H2, J_{H2-H1}= 7.5 Hz); 4.82 (1H, dt, H1, J_{H1-H2} = 7.5 Hz, J_{H1-H3} = $J_{H1-H3'}$ = 5.4 Hz); 2.60 (2H, m, H4); 2.29 (1H, m, H3); 2.20 (1H, m, H3'); 2.12 (3H, s, H5). δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 174.2 (COOH); 157.1 (CONH, q, J_{C-F} = 38.2 Hz); 115.5 (CF_3, q, J_{C-F} = 288.8 Hz); 51.9 (C1); 30.2 (C3); 29.8 (C4); 15.5 (C5).

N-Trifluoroacetylglutamic acid (**8**) (white crystalline solid, 0.827 g, 68%).

δH (600 MHz, DMSO, Me_4Si, 25 °C): 12.60 (2H, br s, COOH); 9.67 (1H, d, H2, J_{H2-H1} = 7.9 Hz); 4.27 (1H, m, H1); 2.27 (2H, t, H-4, J_{H4-H3} = $J_{H4-H3'}$ = 7.3 Hz); 2.06 (1H, m, H3); 1.87 (1H, m, H3').

δC (150 MHz, DMSO, Me_4Si, 25 °C): 174.0 (C1-$\underline{C}$OOH); 172.1 (C4-$\underline{C}$OOH); 157.0 (CONH, q, J_{C-F} = 36.4 Hz); 116.2 (CF_3, q, J_{C-F} = 289.0 Hz); 52.3 (C1); 30.4 (C4); 25.6 (C3).

N- Trifluoroacetylproline (**9**) (white crystalline solid, 0.897 g, 85%).

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 4.72 (1H, br d, $H1_{syn}$, J = 8.0 Hz); 4.59 (1H, dd, $H1_{anti}$, J = 8.0 Hz, J = 2.9 Hz); 3.89-3.62 (2H, m, H4); 2.40-1.90 (4H, m, H2/H3).

δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 176.2 and 175.8 (COOH); 156.2 and 155.7 (CONH, q, J_{C-F} = 37.9 Hz); 116.0 (CF_3, q, J_{C-F} = 287.0 Hz); 60.1 and 59.0 (C1); 48.0 and 47.3 (C4); 31.6, 28.6, 25.0, and 21.1 (C3 and C2).

N-Trifluoroacetyltryptophan (**10**) (light brown crystalline solid, 1.30 g, 87%).

δH (600 MHz, DMSO, Me_4Si, 25 °C): 13.06 (1H, s, H9); 10.83 (1H, s, COOH); 9.73 (1H, d, H2, J_{H2-H1} = 8.0 Hz); 7.53 (1H, d, H8, J_{H8-H7} = 7.6 Hz); 7.32 (1H, d, H5, J_{H5-H6} = 7.6 Hz); 7.12 (1H, s, H4); 7.05 (1H, t, H-7, J_{H7-H8} = J_{H7-H6} = 7.6 Hz); 6.97 (1H, t, H6, J_{H6-H7} = J_{H6-H5} = 7.6 Hz); 4.49 (1H, dt, H1, J_{H1-H2} = 8.0 Hz, J_{H1-H3} = $J_{H1-H3'}$ = 4.2 Hz); 3.29 (1H, dd, H3, $J_{H3-H3'}$ = 14.9 Hz; J_{H3-H1} = 4.2 Hz); 3.15 (1H, dd, H3', $J_{H3'-H3}$ = 14.9 Hz; $J_{H3'-H1}$ = 4.2 Hz). δC (150 MHz, DMSO, Me_4Si, 25 °C): 172.2 (COOH); 156.8 (CONH, q, J_{C-F} = 36.1 Hz); 136.5 ($\underline{C}$-C8); 127.3 ($\underline{C}$-C5); 124.0 (C4); 121.5 (C7); 118.9 (C6); 118. 5 (C8); 116.2 (CF_3, q, J_{C-F} = 288.9 Hz); 111.9 (C5); 110.1 (C4-C); 54.1 (C1); 26.5 (C3/C3').

Qui

δH (600 MHz, $CDCl_3$, Me_4Si, 25 °C): 8.68 (1H, d, H2, J_{H2-H1} = 4.5 Hz); 7.97 (1H, d, H3, J_{H3-H4} = 8.5 Hz); 7.51 (1H, d, H1, J_{H1-H2} = 4.5 Hz); 7.31 (1H, dd, H4, J_{H4-H3} = 8.5 Hz, J_{H4-H5} = 2.7 Hz,); 7.22 (1H, d, H5, J_{H5-H4} = 2.7 Hz,); 5.73 (1H, ddd, H20, $J_{H20-H22}$ = 17.1 Hz, $J_{H20-H21}$ = 10.4 Hz, $J_{H20-H17}$ = 7.5 Hz); 5.61 (1H, br s, H8); 4.96 (1H, dt, H22, $J_{H22-H20}$ = 17.1 Hz, $J_{H22-H21}$ = $J_{H22-H17}$ = 1.1 Hz); 4.92 (1H, dt, H21, $J_{H21-H20}$ = 10.4 Hz, $J_{H21-H22}$ = $J_{H21-H17}$ = 1.1 Hz); 3.87 (3H, s, OMe); 3.50 (1H, m, H16); 3.30 (1H, s, OH); 3.16 (1H, m, H9); 3.11 (1H, dd, H19, $J_{H19-H18}$ = 14.0 Hz, $J_{H19-H17}$ = 10.0 Hz); 2.71 (1H, m, H18); 2.69 (1H, m, H15); 2.30 (1H, m, H17); 1.84 (1H, m, H12); 1.76 (1H, m, H10); 1.75 (1H, m, H14); 1.56 (1H, m, H13); 1.53 (1H, m, H11).

δC (150 MHz, $CDCl_3$, Me_4Si, 25 °C): 157.7 (COMe); 147.6 (<u>C</u>-C8); 147.0 (C2); 144.3 (<u>C</u>-C3); 141.4 (C20); 131.6 (C3); 126.5 (<u>C</u>-C5); 121.6 (C4); 118.5 (C1); 114.5 (C22/21); 101.4 (C5); 71.9 (C8); 60.4 (C9); 56.8 (C18/19); 56.0 (OMe); 43.3 (C15/16); 39.9 (C17); 27.8 (C12); 27.4 (C10/11); 21.7 (C13/14).

δH (600 MHz, C_6D_6, Me_4Si, 25 °C): 8.58 (1H, d, H2, J_{H2-H1} = 4.3 Hz); 8.15 (1H, d, H3, J_{H3-H4} = 9.3 Hz); 7.39 (1H, d, H5, J_{H5-H4} = 2.9 Hz); 7.28 (1H, d, H-1, J_{H1-H2} = 4.3 Hz); 7.15 (1H, dd, H4, J_{H4-H3} = 9.3 Hz, J_{H4-H5} = 2.9 Hz); 5.49 (1H, ddd, H20, $J_{H20-H22}$ = 17.2 Hz, $J_{H20-H21}$ = 10.5 Hz, $J_{H20-H17}$ = 8 Hz); 5.35 (1H, br s, H8); 4.82 (1H, dt, H22, $J_{H22-H20}$ = 17.2 Hz, $J_{H22-H21}$ = $J_{H22-H17}$ =1.5 Hz); 4.77 (1H, dt, H21, $J_{H21-H20}$ = 10.5 Hz, $J_{H21-H22}$ = $J_{H21-H17}$ = 1.5 Hz); 3.48 (3H, s, OMe); 3.40 (1H, m, H16); 3.09 (1H, m, H9); 2.84 (1H, dd, H19, $J_{H19-H18}$ = 13.8 Hz, $J_{H19-H17}$ = 10.1 Hz); 2.50 (1H, m, H18); 2.45 (1H, m, H15); 1.94 (1H, m, H17); 1.77 (1H, m, H11); 1.58 (1H, m, H12); 1.58 (1H, m, H14); 1.46 (1H, m, H10); 1.17 (1H, m, H13).