Ion-Pairing Catalysis in the Enantioselective Addition of Hydrazones to *N*-Acyldihydropyrrole Derivatives

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Contents

1. General Methods.[1]

NMR: Monodimensional nuclear magnetic resonance experiments, proton, carbon and fluorine spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR), were acquired on a Bruker AC-300 spectrometer (300 MHz for ^{1}H, 75.5 MHz for ^{13}C and 282 MHz for ^{19}F) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz ^{13}C) at the indicated temperature in each case. Chemical shifts (δ) are reported in ppm relative to residual solvent signals;[2] and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal; appt t, apparent triplet. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT (Distortionless Enhancement by Polarization Transfer) experiments and/or HSQC (Heteronuclear Single Quantum Correlation) and HMBC (Heternuclear Multiple Bond Correlation) experiments for assigning different types of carbon environment. Correlation Spectroscopy (^{1}H-^{1}H COSY) experiments were acquired to confirm precise molecular connectivity and to assist in deconvoluting complex multiplet signals.[3]

IR: Infrared spectra were measured in a Jasco FT/IR 4100 apparatus in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution, using Attenuated Total Reflection (ATR) technique. Only characteristic bands are given in each case.

MS: Mass spectra were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 mass spectrometer under electronic impact (EI) conditions at 70 eV. The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%).

HRMS: High-resolution mass spectra were recorded on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI$^+$ or ESI$^-$).

M.p.: Melting points were measured in a Büchi B-540 apparatus in open capillary tubes and are uncorrected.

HPLC: High performance liquid chromatography traces were recorded on a chiral stationary phase was performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector or Waters 600 chromatograph coupled to a Waters 996 photodiode array detector. Daicel Chiralpak AD-H, AS-H, IA, IC, ID-3, IE-3, AY-3 and Chiralcel OD-3, OZ-3 columns (0.46 cm × 25 cm) were used. Specific conditions are indicated for each case.

X-ray data collections were performed in an Agilent Supernova diffractometer equipped with an Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184Å, 250µm FWHM beam size). The sample was kept at 120 K with an Oxford Cryosystems Cryostream 700 cooler. The quality of the crystals was checked under a polarizing microscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount^{T}M using Paratone N inert oil and transferred to the diffractometer.

Miscellaneous: Analytical grade solvents and commercially available reagents were used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use[4] or using standard procedures described in the literature.[5] For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140ºC, and allowed to cool under a dehumidified atmosphere.[6] Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kieselgel 60 F254). These were visualized by ultraviolet irradiation and *p*-anisaldehyde dips.[7] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[8] For the removal of solvents under reduced pressure Büchi series R-2 rotary evaporators were used. Reaction at reduces temperatures were carried out using a Termo Haake EK90 refrigerator.

The racemic standards for HPLC separation of stereoisomers were prepared using diphenyl phosphate as catalyst.

[1] SGIker technical support (MEC, GV/EJ and European Social Fund) is gratefully acknowledged (NMR and X-ray analysis).

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[6] G. W. Kramer, A. B. Levy, M. M. Midland, *Organic Synthesis via Boranes*; John Wiley & Sons: New York, 1975.

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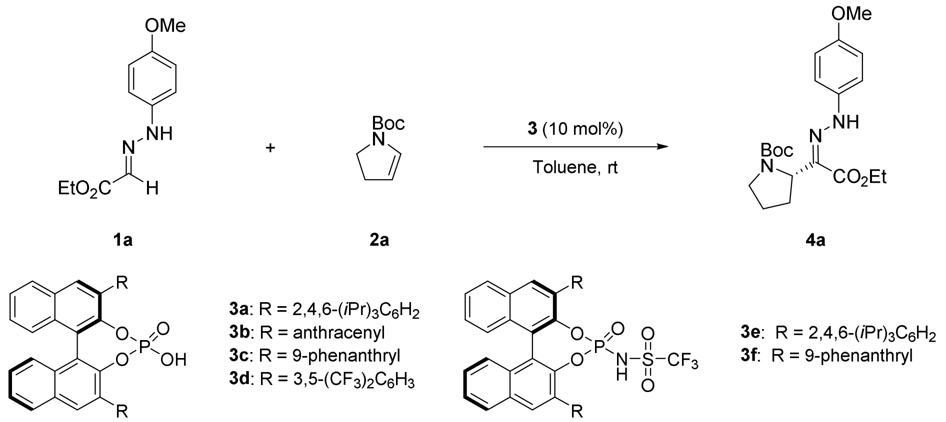
2. Optimization of Reaction Conditions

Optimization of reactions conditions with different BINOL-based chiral phosphoric acids and *N*-triflylphosphoramides are presented in table SI-1, screening of different solvents are presented in table SI-2 and screening of temperature and drying agents are summarized in table SI-3.

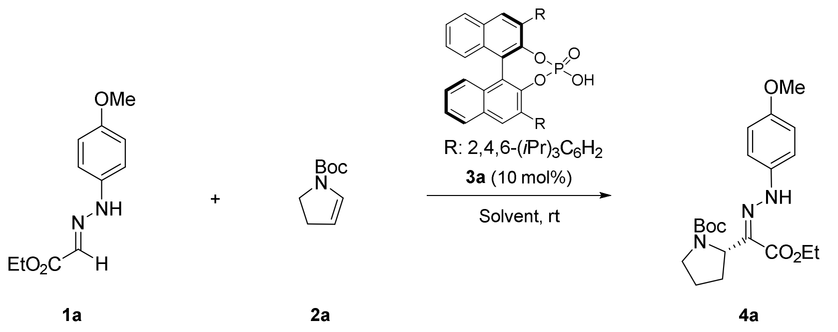
Table SI-1. Chiral BINOL-derived Brønsted acid catalyst survey [a]



Entry	Catalyst	Yield[b]	e.e.[c]
1	**3a**	**54**	**68**
2	**3b**	52	23
3	**3c**	53	25
4	**3d**	53	15
5	**3e**	61	8
6	**3f**	74	0
7[d]	**3f**	48	2

[a] The reaction was performed in 0.26 mL of toluene and 0.13 mmol of **2a**, using 1.2 eq. of **1a** at rt. [b] Yield of pure product isolated after flash chromatography. [c] Determined by HPLC analysis of the pure product. [d] Reaction carried out at -78ºC.

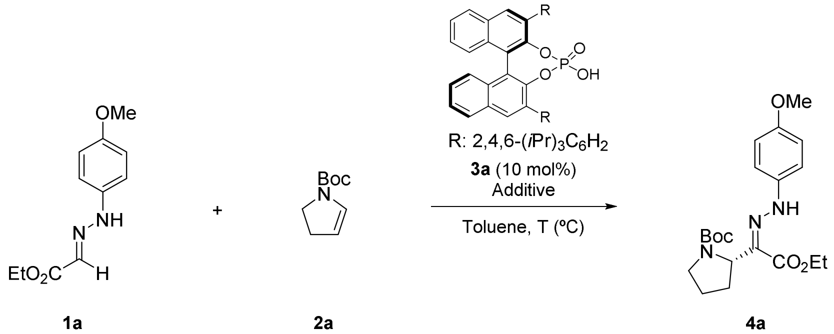
Table SI-2. Screening of different solvents [a]



Entry	Solvent	Yield[b]	e.e.[c]
1	**Toluene**	**54**	**68**
2	**Benzene**	53	65
3	***o*-Xylene**	43	67
4	**CH_2Cl_2**	52	49
5	**$CHCl_3$**	27	26
6	**EtOAc**	83	57

[a] The reaction was performed in 0.26 mL of toluene and 0.13 mmol of **2a**, using 1.2 eq. of **1a** at rt. [b] Yield of pure product isolated after flash chromatography. [c] Determined by HPLC analysis of the pure product.

Table SI-3. Influence of temperature and drying agents in the reaction [a]

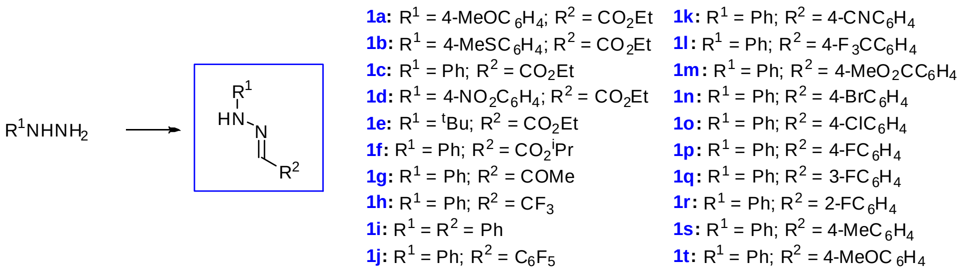


Entry	T (ºC)	Additive	Yield[b]	e.e.[c]
1	**rt**	**-**	54	68
2	**-5**	**-**	43	74
3	**-15**	**-**	30	71
4	**-20**	**-**	-	-
5[d]	**-5**	**$MgSO_4$**	45	76
6[d]	**-5**	**4 Å MS**	40	82
7[d,e]	**-5**	**4 Å MS**	42	86
8[d,e,f]	**-5**	**4 Å MS**	**60**	**86**

[a] The reaction was performed in 0.26 mL of toluene and 0.13 mmol scale of **2a**, using 1.2 eq. of **1a** for 14h. [b] Yield of pure product isolated after flash chromatography. [c] Determined by HPLC analysis of the pure product. [d] 27 mg of additive was added. [e] Reaction carried out with dry toluene. [f] Reaction carried out for 24h.

3. Experimental Procedures and Characterizations

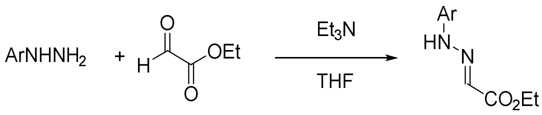
3.1. General structures of Hydrazones 1a-t



Scheme SI-1. Structure of hydrazones **1a-t**

Hydrazone **1g** is commercially available. Hydrazones **1a**,[9] **1c**,9 **1d**,9 **1h**[10], **1j**[11] and **1s**[12] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature.

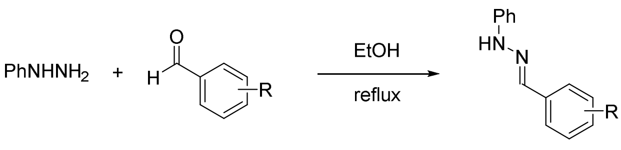
General Procedures for the Synthesis of Hydrazones 1b, 1e-f, 1j-r and 1t



1b, 1e

Scheme SI-2. Synthesis of hydrazones **1b, 1e**

General Procedure A (GP-A). Hydrazone derivatives **1b** and **1e** were prepared according to literature procedure9 as followed. A suspension of the corresponding hydrazine hydrochloride (28.65 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (40 mL) was treated with triethylamine (28.65 mmol, 1.0 eq.) before the corresponding aldehyde (28.65 mmol, 1.0 eq.) was added dropwise to the reaction mixture at 0 ºC. The mixture was stirred at this temperature for 30 minutes and then for 12 h at room temperature. The crude was filtered under vacuum and the filtrates were concentrated *in vacuo*. The resulting solids were dissolved in dichloromethane (~30 mL) and washed with HCl 1*M* (2 × 20 mL) and water (2 × 20 mL). The resulting organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting solids were triturated with diethyl ether or purified by flash column chromatography to obtain the desired hydrazone.



1j-q, 1t

Scheme SI-3. Synthesis of hydrazones **1j-q, 1t**

General Procedure B (GP-B). Hydrazone derivatives **1j-r** and **1t** were prepared according to literature procedure with some modifications.[13] The corresponding aldehyde (9.25 mmol, 1.0 eq.) was added to a solution of hydrazine (9.25 mmol, 1.0 eq.) in ethanol (9.25 mL). The mixture was stirred and heated to reflux for 3 hours. The precipitated hydrazone was filtered, washed with EtOH, dried and used without further purification.

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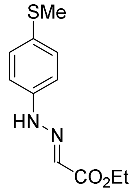
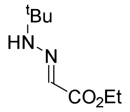
[13] Chen, Z.; Li, H.; Dong, W.; Miao, M.; Ren, H. *Org. Lett.* **2016**, *18*, 1334.

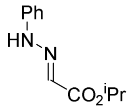
*Procedures for the synthesis of hydrazones **1f** and **1i.*** Individual procedures are indicated in each case.



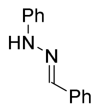
Ethyl (*E*)-2-{2-[4-(methylthio)phenyl]hydrazono}acetate (1b). Following *GP-A*, **1b** (936 mg, 3.9 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) in 75% yield as a yellow solid starting from ethyl glyoxylate (50% *w/v* solution in toluene, 1.04 mL, 5.24 mmol), triethylamine (0.73 mL, 5.24 mmol) and 4-(methylthio)phenylhydrazine hydrochloride (1.0 g, 5.24 mmol) in anhydrous tetrahydrofuran (10 mL). R_f: 0.59 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (bs, 1H, NH), 7.24 (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 7.11 (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 7.06 (s, 1H, CH), 4.31 (q, *J* = 7.1 Hz, 2H, CH_2), 2.45 (s, 3H, SCH_3), 1.35 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (COO), 140.8 (C_{Ar}-C), 131.2 (C_{Ar}-C), 129.4 (C_{Ar}-H), 126.0 (CH), 114.8 (C_{Ar}-H), 61.1 (CH_2), 17.6 (SCH_3), 14.5 (CH_3). IR (ATR) cm^{-1}: 3253 (NH), 2959 (C-H), 1692 (C=O), 1537 (C=N). MS (EI) m/z (%): 238 (M^+, 61), 164 (22), 138 (100), 122 (12). HRMS: Calculated for $[C_{11}H_{15}N_2O_2S]^+$: 239.0854 $[(M+H)^+]$; found: 239.0853. M.p. (CH_2Cl_2): 130-132 ºC.



Ethyl (*E*)-2-[2-(*tert*-butyl)hydrazono]acetate (1e). Following *GP-B*, **1e** (315 mg, 1.83 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) in 81% yield as a yellow solid starting from ethyl glyoxylate (50% *w/v* solution in toluene, 0.445 mL, 2.25 mmol), triethylamine (0.314 mL, 2.25 mmol) and *tert*-butylhydrazine hydrochloride (380 mg, 2.25 mmol) in anhydrous tetrahydrofuran (10 mL). R_f: 0.77 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H, CH), 6.29 (s, 1H, NH), 4.24 (q, *J* = 7.1 Hz, 2H, CH_2), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3), 1.27 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6 (COO), 123.3 (CH), 60.3 (CH_2), 54.9 ($\mathbf{C}(CH_3)_3$), 28.8 ($C(\mathbf{C}H_3)_3$), 14.4 (CH_3). IR (ATR) cm^{-1}: 3264 (NH), 2977 (C-H), 1691 (C=O), 1533 (C=N). MS (EI) m/z (%): 172 (M^+, 29), 157 (100), 115 (94), 87 (81), 83 (46), 72 (12), 57 (67). HRMS: Calculated for $[C_8H_{17}N_2O_2]^+$: 173.1290 $[(M+H)^+]$; found: 173.1286. M.p. (CH_2Cl_2): 60-62 ºC.



Isopropyl-(*E*)-2-(2-phenylhydrazono)acetate (1f).[9] To a suspension of phenylhydrazine (1.4 g, 12.9 mmol) in anhydrous tetrahydrofuran (12.9 mL) isopropyl glyoxylate (1.5 g, 12.9 mmol) was added dropwise at 0 ºC. The mixture was stirred at this temperature for 30 minutes and then for 12 hours at room temperature. Solvents were removed *in vacuo* and the resulting solid was purified by flash column chromatography (hexanes/EtOAc gradient from 19:1 to 7:3) to afford **1f** (1.4 g, 6.8 mmol, 53%) as a light brown solid. R_f: 0.55 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): (8:1 *E*/*Z* ratio, *denotes minor isomer resonances) δ 8.61 (bs, 1H, NH), 7.32-7.23 (m, 2H, C_{Ar}-H), 7.22-7.11 (m, 2H, C_{Ar}-H), 7.07 (s, 1H, NCH), 6.97 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 5.30-5.02 (m, 1H, $C\mathbf{H}(CH_3)_2$), 1.32 (d, *J* = 6.3 Hz, 6H, $CH(C\mathbf{H}_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6 (COO), 143.1 (C_{Ar}-C), 142.7* (C_{Ar}-C), 129.5 (C_{Ar}-H), 126.4* (NCH), 122.7 (C_{Ar}-H), 122.5* (C_{Ar}-H), 119.1 (NCH), 114.1* (C_{Ar}-H), 114.0 (C_{Ar}-H), 68.5* ($\mathbf{C}H(CH_3)_2$), 68.3 ($\mathbf{C}H(CH_3)_2$), 22.1* ($CH(\mathbf{C}H_3)_2$), 22.0 ($CH(\mathbf{C}H_3)_2$). IR (ATR) cm^{-1}: 3255 (NH), 3052 (C-H), 1689 (C=O), 1539 (C=N). MS (EI) m/z (%): 206 (M^+, 54), 164 (56), 118 (100), 91 (94), 77 (22), 65 (43), 51 (9). HRMS: Calculated for $[C_{11}H_{15}N_2O_2]^+$: 207.1134 $[(M+H)^+]$; found: 207.1136. M.p. (EtOH): 124-126 ºC.



(*E*)-1-benzylidene-2-phenylhydrazine (1i).[14] To a solution of phenylhydrazine (0.91 mL, 9.25 mmol) in MeOH (8 mL) was added benzaldehyde (0.9 mL, 8.8 mmol) slowly. The mixture was stirred at room temperature for 6h. MeOH was evaporated *in vacuo,* and the residue was recristallized from MeOH to afford (*E*)-1-benzylidene-2-phenylhydrazine **1i** (1.36 g, 6.9 mmol) in 79% yield as a light yellow solid. R_f: 0.9 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73-7.64 (m, 3H, CH + C_{Ar}-H), 7.59 (bs, 1H, NH),7.44-7.25 (m, 5H, C_{Ar}-H), 7.14 (d, *J* = 7.7 Hz, 2H, C_{Ar}-H), 6.90 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8 (C_{Ar}-C), 137.4 (CH), 135.4 (C_{Ar}-C), 129.4 (C_{Ar}-H), 128.7 (C_{Ar}-H), 128.6 (C_{Ar}-H), 126.3 (C_{Ar}-H), 120.2 (C_{Ar}-H), 112.9 (C_{Ar}-H). IR (ATR) cm^{-1}: 3313 (NH), 2924 (C-H), 1592 (CN). MS (EI) m/z (%): 196 (M^+, 100), 103 (51), 92 (43), 77 (41), 65 (30), 51 (24). HRMS: Calculated for $[C_{13}H_{13}N_2]^+$: 197.1079 $[(M+H)^+]$; found: 197.1078. M.p. (EtOH): 155-157 ºC.

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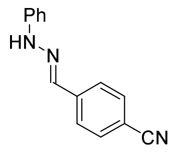
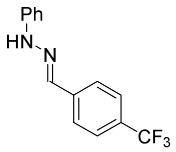
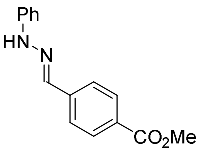


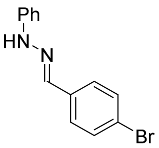
(*E*)-4-[(2-phenylhydrazono)methyl]benzonitrile (1k). Following *GP-B*, **1k** (1.7 g, 7.7 mmol) was isolated in 83% yield as a yellow solid starting from 4-formylbenzonitrile (1.27 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). R_f: 0.36 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (bs, 1H, NH), 7.77-7.69 (m, 2H, C_{Ar}-H), 7.68-7.59 (m, 3H, CH + C_{Ar}-H), 7.31 (ddd, *J* = 8.5, 5.5, 1.7 Hz, 2H, C_{Ar}-H), 7.18-7.10 (m, 2H, C_{Ar}-H), 6.99-6.90 (m, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9 (C_{Ar}-C), 139.9 (C_{Ar}-C), 134.4 (CH), 132.5 (C_{Ar}-H), 129.5 (C_{Ar}-H), 126.4 (C_{Ar}-H), 121.2 (C_{Ar}-H), 119.2 (CN), 113.2 (C_{Ar}-H), 111.1 (C_{Ar}-C). IR (ATR) cm^{-1}: 3273 (NH), 3038 (C-H), 2221 (*p*-CN), 1577 (C=N). MS (EI) m/z (%): 221 (M^+, 66), 207 (38), 128 (100), 102 (13), 92 (66), 77 (13), 65 (27), 51 (14). HRMS: Calculated for $[C_{14}H_{12}N_3]^+$: 222.1031 [$(M+H)^+$]; found: 222.1021. M.p. (EtOH): 151-153 ºC.



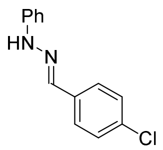
(*E*)-1-phenyl-2-[4-(trifluoromethyl)benzylidene]hydrazine (1l). Following *GP-B*, **1l** (1.35 g, 5.1 mmol) was isolated in 55% yield as a light yellow solid starting from 4-(trifluoromethyl)benzaldehyde (1.3 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). R_f: 0.68 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.70 (m, 3H, NH + C_{Ar}-H), 7.67-7.57 (m, 3H, CH + C_{Ar}-H), 7.32 (ddd, *J* = 8.6, 5.7, 2.2 Hz, 2H, C_{Ar}-H), 7.18-7.10 (m, 2H, C_{Ar}-H), 6.94 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.2 (C_{Ar}-C), 138.9 (C_{Ar}-C), 135.3 (CH), 129.9 (q, $^2J_{C-F}$ = 32.1 Hz, **C**CF_3), 129.5 (C_{Ar}-H), 126.2 (C_{Ar}-H), 125.7 (q, $^3J_{C-F}$ = 3.9 Hz, C_{Ar}-H), 122.9 (q, $^1J_{C-F}$ = 272.5 Hz, CF_3), 120.9 (C_{Ar}-H), 113.1 (C_{Ar}-H). ^{19}F NMR (300 MHz, $CDCl_3$): δ -62.5 (CF_3). IR (ATR) cm^{-1}: 3292 (NH), 1594 (C=N). MS (EI) m/z (%): 264 (M^+, 100), 207 (13), 171 (78), 152 (36), 121 (44), 92 (88), 75 (20), 65 (37), 51 (17). HRMS: Calculated for $[C_{14}H_{12}N_2F_3]^+$: 265.0953 [$(M+H)^+$]; found: 265.0948. M.p. (EtOH): 132-134 ºC.



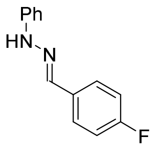
Methyl (*E*)-4-[(2-phenylhydrazono)methyl]benzoate (1m). Following *GP-B*, **1m** (1.9 g, 7.5 mmol) was isolated in 80% yield as a yellow solid starting from methyl 4-formylbenzoate (1.53 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). R_f: 0.42 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 2H, C_{Ar}-H), 7.82 (bs, 1H, NH), 7.78-7.63 (m, 3H, CH + C_{Ar}-H), 7.36-7.24 (m, 2H, C_{Ar}-H), 7.19-7.09 (m, 2H, C_{Ar}-H), 6.91 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 3.93 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0 (COO), 144.2 (C_{Ar}-C), 139.9 (C_{Ar}-C), 135.7 (CH), 130.0 (C_{Ar}-H), 129.5 (C_{Ar}-H), 125.9 (C_{Ar}-H), 120.7 (C_{Ar}-H), 113.0 (C_{Ar}-H), 52.2 (CH_3). IR (ATR) cm^{-1}: 3288 (NH), 3042 (C-H), 1690 (C=O), 1578 (C=N). MS (EI) m/z (%): 254 (M^+, 83), 207 (28), 161 (26), 130 (100), 102 (40), 92 (57), 77 (19), 65 (26), 51 (18). HRMS: Calculated for $[C_{15}H_{15}N_2O_2]^+$: 255.1134 [$(M+H)^+$]; found: 255.1132. M.p. (EtOH): 142-144 ºC.



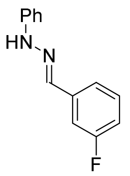
(*E*)-1-(4-bromobenzylidene)-2-phenylhydrazine (1n). Following *GP-B*, **1n** (1.1 g, 3.99 mmol) was isolated in 49% yield as a light yellow solid starting from 4-bromobenzaldehyde (1.52 g, 8.1 mmol) and phenylhydrazine (0.8 mL, 8.1 mmol) in ethanol (8.1 mL). R_f: 0.56 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (s, 1H, NH), 7.60 (s, 1H, CH), 7.56-7.46 (m, 4H, C_{Ar}-H), 7.33-7.24 (m, 2H, C_{Ar}-H), 7.11 (d, *J* = 8.5 Hz, 2H, C_{Ar}-H), 6.95-6.86 (m, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5 (C_{Ar}-C), 136.0 (CH), 134.4 (C_{Ar}-C), 131.9 (C_{Ar}-H), 129.5 (C_{Ar}-H), 127.7 (C_{Ar}-H), 122.3 (C_{Ar}-C), 120.5 (C_{Ar}-H), 113.0 (C_{Ar}-H). IR (ATR) cm^{-1}: 3308 (NH), 3051 (C-H), 1591 (C=N). MS (EI) m/z (%): 274 (M^+, 91), 207 (93), 183 (100), 102 (69), 92 (95), 75 (37), 65 (47), 51 (27). HRMS: Calculated for $[C_{13}H_{12}N_2Br]^+$: 275.0184 [$(M+H)^+$]; found: 275.0185. M.p. (EtOH): 120-122 ºC.



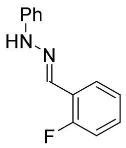
(*E*)-1-(4-chlorobenzylidene)-2-phenylhydrazine (1o). Following *GP-B*, **1o** (1.35 g, 5.9 mmol) was isolated in 63% yield as a white solid starting from 4-chlorobenzaldehyde (1.32 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). R_f: 0.64 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.54 (m, 4H, NH + CH + C_{Ar}-H), 7.38-7.24 (m, 4H, C_{Ar}-H), 7.11 (d, *J* = 7.6 Hz, 2H, C_{Ar}-H), 6.90 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5 (C_{Ar}-C), 135.9 (CH), 134.1 (C_{Ar}-C), 134.0 (C_{Ar}-C), 129.5 (C_{Ar}-H), 129.0 (C_{Ar}-H), 127.4 (C_{Ar}-H), 120.5 (C_{Ar}-H), 112.9 (C_{Ar}-H). IR (ATR) cm^{-1}: 3312 (NH), 3055 (C-H), 1598 (C=N), 747 (CCl). MS (EI) m/z (%): 230 (M^+, 66), 207 (57), 137 (100), 102 (30), 92 (54), 65 (24). HRMS: Calculated for $[C_{13}H_{12}N_2Cl]^+$: 231.0689 [$(M+H)^+$]; found: 231.0689. M.p. (EtOH): 126-128 ºC.



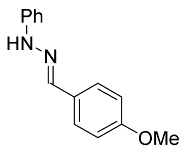
(*E*)-1-(4-fluorobenzylidene)-2-phenylhydrazine (1p). Following *GP-B*, **1p** (1.28 g, 5.97 mmol) was isolated in 65% yield as a white solid starting from 4-fluorobenzaldehyde (1.32 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). R_f: 0.64 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.49 (m, 4H, NH + CH + C_{Ar}-H), 7.29 (t, J = 7.9 Hz, 2H, C_{Ar}-H), 7.16-7.00 (m, 4H, C_{Ar}-H), 6.89 (t, J = 6.8 Hz, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (d, $^1J_{C-F}$ = 248.2 Hz, CF), 144.7 (C_{Ar}-C), 136.3 (CH), 131.7 (d, $^4J_{C-F}$ = 3.2 Hz, C_{Ar}-C), 129.5 (C_{Ar}-H), 127.9 (d, $^3J_{C-F}$ = 8.1 Hz, C_{Ar}-H), 120.4 (C_{Ar}-H), 116.0 (d, $^2J_{C-F}$ = 21.9 Hz, C_{Ar}-H), 112.9 (C_{Ar}-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -112.7 (CF). IR (ATR) cm^{-1}: 3311 (NH), 3053 (C-H), 1597 (C=N), 1230 (CF). MS (EI) m/z (%): 214 (M^+, 87), 121 (100), 92 (52), 77 (11), 65 (27), 51 (9). HRMS: Calculated for $[C_{13}H_{12}N_2F]^+$: 215.0985 [$(M+H)^+$]; found: 215.0988. M.p. (EtOH): 145-147 ºC.



(*E*)-1-(3-fluorobenzylidene)-2-phenylhydrazine (1q). Following *GP-B*, **1q** (1.4 g, 6.5 mmol) was isolated in 81% yield as a light yellow solid starting from 3-fluorobenzaldehyde (0.88 mL, 8.1 mmol) and phenylhydrazine (0.8 mL, 8.1 mmol) in ethanol (8.1 mL). R_f: 0.86 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (bs, 1H, NH), 7.63 (s, 1H, CH), 7.49-7.25 (m, 5H, C_{Ar}-H), 7.20-7.08 (m, 2H, C_{Ar}-H), 7.04-7.95 (m, 1H, C_{Ar}-H), 6.91 (t, J = 7.3 Hz, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3 (d, $^1J_{C-F}$ = 245.3 Hz, CF), 144.4 (C_{Ar}-C), 137.8 (d, $^3J_{C-F}$ = 8.0 Hz, C_{Ar}-C), 135.8 (d, $^4J_{C-F}$ = 3.2 Hz, CH), 130.2 (d, $^3J_{C-F}$ = 8.4 Hz, C_{Ar}-H), 129.5 (C_{Ar}-H), 122.3 (d, $^4J_{C-F}$ = 2.7 Hz, C_{Ar}-H), 120.6 (C_{Ar}-H), 115.3 (d, $^2J_{C-F}$ = 21.7 Hz, C_{Ar}-H), 113.0 (C_{Ar}-H), 112.4 (d, $^2J_{C-F}$ = 22.8 Hz, C_{Ar}-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -113.2 (CF). IR (ATR) cm^{-1}: 3311 (NH), 3008 (C-H), 1594 (C=N), 1262 (CF). MS (EI) m/z (%): 214 (M^+, 100), 121 (88), 107 (11), 92 (75), 75 (18), 65 (37), 51 (14). HRMS: Calculated for $[C_{13}H_{12}N_2F]^+$: 215.0985 [$(M+H)^+$]; found: 215.0981. M.p. (EtOH): 115-117 ºC.



(*E*)-1-(2-fluorobenzylidene)-2-phenylhydrazine (1r). Following *GP-B*, **1r** (1.7 g, 7.9 mmol) was isolated in 98% yield as an orange solid starting from 2-fluorobenzaldehyde (0.88 mL, 8.1 mmol) and phenylhydrazine (0.8 mL, 8.1 mmol) in ethanol (8.1 mL). R_f: 0.78 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (td, J = 7.6, 1.8 Hz, 1H, C_{Ar}-H), 7.94 (s, 1H, CH), 7.77 (bs, 1H, NH), 7.36-7.22 (m, 3H, C_{Ar}-H), 7.20-7.10 (m, 3H, C_{Ar}-H), 7.10-7.00 (m, 1H, C_{Ar}-H), 6.89 (t, J = 7.3 Hz, 1H, C_{Ar}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6 (d, $^1J_{C-F}$ = 249.5 Hz, CF), 114.5 (C_{Ar}-C), 130.2 (d, $^3J_{C-F}$ = 4.9 Hz, CH), 129.7 (d, $^3J_{C-F}$ = 8.2 Hz, C_{Ar}-H), 129.5 (C_{Ar}-H), 126.3 (d, $^4J_{C-F}$ = 3.1 Hz, C_{Ar}-H), 124.4 (d, $^3J_{C-F}$ = 3.4 Hz, C_{Ar}-H), 123.3 (d, $^2J_{C-F}$ = 10.2 Hz, C_{Ar}-C), 120.5 (C_{Ar}-H), 115.7 (d, $^2J_{C-F}$ = 21.0 Hz, C_{Ar}-H), 112.9 (C_{Ar}-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -122.5 (CF). IR (ATR) cm^{-1}: 3307 (NH), 3055 (C-H), 1598 (C=N), 1258 (CF). MS (EI) m/z (%): 214 (M^+, 99), 121 (100), 107 (11), 92 (65), 75 (21), 65 (35), 51 (13). HRMS: Calculated for $[C_{13}H_{12}N_2F]^+$: 215.0985 [$(M+H)^+$]; found: 215.0982. M.p. (EtOH): 86-88 ºC.

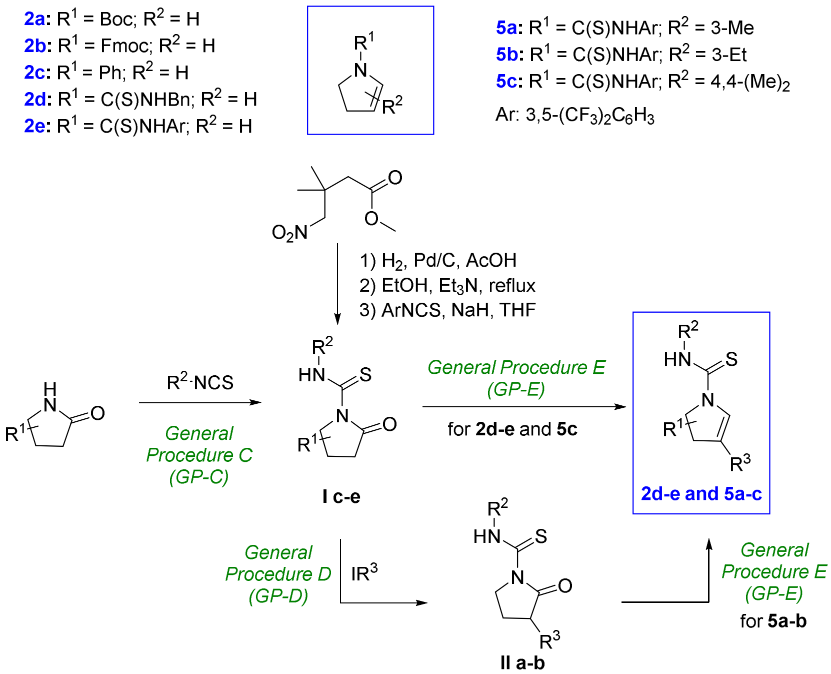


(*E*)-1-(4-methoxybenzylidene)-2-phenylhydrazine (1t). Following *GP-B*, **1t** (2.05 g, 8.0 mmol) was isolated in 99% yield as a white solid starting from 4-methoxybenzaldehyde (0.99 mL, 8.1 mmol) and phenylhydrazine (0.88 mL, 8.1 mmol) in ethanol (8.1 mL). R_f: 0.64 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.56 (m, 3H, C_{Ar}-H), 7.48 (bs, 1H, NH), 7.33-7.23 (m, 2H, C_{Ar}-H), 7.10 (d, J = 7.6 Hz, 2H, C_{Ar}-H), 6.98-6.81 (m, 3H, CH + C_{Ar}-H), 3.84 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1 (C_{Ar}-C), 145.1 (C_{Ar}-C), 137.5 (CH), 129.4 (C_{Ar}-H), 128.3 (C_{Ar}-C), 127.7 (C_{Ar}-H), 119.9 (C_{Ar}-H), 114.3 (C_{Ar}-H), 112.8 (C_{Ar}-H), 55.5 (OCH_3). IR (ATR) cm^{-1}: 3314 (NH), 3024 (C-H), 1594 (C=N). MS (EI) m/z (%): 226 (M^+, 100), 207 (41), 133 (58), 107 (11), 92 (37), 77 (31), 65 (24), 51 (13). HRMS: Calculated for $[C_{14}H_{15}N_2O]^+$: 227.1184 [$(M+H)^+$]; found: 227.1188. M.p. (EtOH): 145-147 ºC.

3.2. General structures of Dihydropyrroles 2a-e and 5a-c

Cyclic enecarbamate **2a** is commercially available. Cyclic enamide **2b**[15] and cyclic enamine **2c**[16] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature.

[15] Gerard, B.; O´shea, M. W.; Donckele, E.; Kesavan, S.; Akella, L. B.; Xu, H.; Jacobsen, E. N.; Marcaurelle, L. A. *ACS Comb. Sci*. **2012**, *14*, 621.



Scheme SI-4. General Overview of the Synthesis of **2d-e** and **5a-c**

General Procedure C (GP-C). Lactams **Ic-e** were prepared according to literature procedure[17] as followed. To a stirred solution of pyrrolidin-2-one (13.4 mmol, 1.0 eq.) in THF (60 mL) at 0 °C, was added portionwise NaH (60%, 20.1 mmol, 1.5 eq.). After stirring at 0 °C for 30 min, the corresponding isothiocyanate (20.1 mmol, 1.5 eq.) was slowly added at -78 °C and the reaction was stirred and allowed to warm to room temperature overnight. Then a solution of saturated NH_4Cl was added to quench the reaction, and the mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by flash column chromatography on silica gel. Spectroscopic data for lactam **Id**[17] was in agreement with the literature.

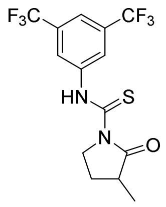
General Procedure D (GP-D). 3-substituted lactams **IIa-b** were prepared according to an adapted literature procedure[18] as followed. To a stirred solution of *N*-substituted-pyrroldin-2-one (9.82 mmol, 1.0 eq.) in THF (47 mL) at -78 °C, was added dropwise a solution of lithium bis(trimethylsilyl)amide (LHMDS) (20.6 mmol, 2.1 eq.), followed by stirring for 1 hour. Then, iodomethane or iodoethane (9.82 mmol, 1.0 eq.) was dropwise added. Thereafter, the temperature was gradually raised to -30 ºC for 2 hours. 50 mL of EtOAc was added to the solution, and the reaction solution was washed with aqueous NH_4Cl, and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, then the residue was purified by flash column chromatography on silica gel.

General Procedure E (GP-E). Cyclic enethioureas **2d-e** and **5a-c** were prepared in two steps according to an addapted literature procedure[17] as followed. 1st step: A solution of *N*-substituted-lactams (6.4 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) was cooled to –78 °C under argon atmosphere. Then super-hydride (1*M* in THF, 14.1 mmol, 1.1 eq.) was slowly added and the reaction was stirred for 30 min at –78 °C and 2 hours at room temperature. Then, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude pyrrolidinol derivative which was purified by column chromatography (hexanes/EtOAc gradient from 19:1 to 7:3). 2nd step: To a solution of previously synthesized intermediates (3.33 mmol, 1.0 eq.) in a mixture of tetrahydrofuran/toluene (8 mL/16 mL) and cooled to -78 ºC. Then, DMAP (0.128 mmol, 0.02 eq.), and trifluoroacetic anhydride (7.7 mmol, 1.2 eq.) were added. After 5 minutes Et_3N (35.2 mmol, 5.5 eq.) was slowly added during 30 minutes and the reaction mixture was

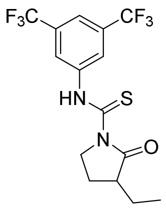
[16] For the synthesis, see: Hyeok, S.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160; For the spectroscopic data, see: Seto, Y.; Guengerich, F. P. *J. Biol. Chem.* **1993**, *268*, 9986.
[17] Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. *Chem. Eur. J.* **2012**, *18*, 5869.
[18] Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180.

allowed to warm to room temperature for 2 hours. Then, water was added, and the organic layer was dried over Na_2SO4 and concentrated *in vacuo*. The crude product was then purified by flash column chromatography on silica gel. Spectroscopic data for lactam **2d**[17] was in agreement with the literature.

*Procedure for the synthesis of lactam **Ic*** is indicated.

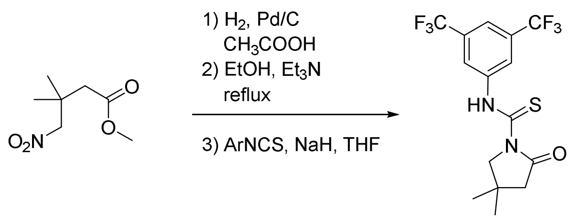


***N*-[3,5-bis(trifluoromethyl)phenyl]-3-methyl-2-oxopyrrolidine-1-carbothioamide (Ia).** Following *GP-D*, **Ia** (3.5 g, 9.45 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) in 96% yield as a colorless oil starting from *N*-3,5-bis(trifluoromethyl)phenylpyrroldin-2-one (3.5 g, 9.82 mmol), lithium bis(trimethylsilyl)amide (20.6 mL, 20.6 mmol) and iodomethane (0.62 mL, 9.82 mmol) in THF (47 mL). R_f: 0.78 (hexanes/EtOAc 7:3). ^1H NMR (300 MHz, $CDCl_3$): δ 12.92 (bs, 1H, NH), 8.20 (s, 2H, C_{Ar}-H), 7.72 (s, 1H, C_{Ar}-H), 4.39 (ddd, J = 11.5, 8.9, 2.5 Hz, 1H, C_5-H_a), 3.99 (ddd, J = 11.5, 9.5, 7.5 Hz, 1H, C_5-H_b), 3.03-2.79 (m, 1H, C_4-H_a), 2.41-2.16 (m, 1H, C_4-H_b), 1.81-1.64 (m, 1H, C_3-H), 1.32 (d, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.9 (CS), 179.5 (C_2), 139.8 (C_{Ar}-C), 132.2 (q, $^2J_{C-F}$ = 33.7 Hz, **C**CF_3), 124.2 (q, $^3J_{C-F}$ = 2.9 Hz, C_{Ar}-H), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 119.7 (q, $^3J_{C-F}$ = 3.6 Hz, C_{Ar}-H), 49.2 (C_5), 40.6 (C_3), 25.6 (C_4), 15.5 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.0 (CF_3). IR (ATR) cm^{-1}: 2978 (NH), 2925 (C-H), 1703 (C=O), 1276 (C=S), 1126 (C-N). MS (EI) m/z (%): 271 (100), 252 (23), 213 (24), 202 (10), 163 (11), 143 (7), 99 (13), 56 (8). HRMS: Calculated for $[C_{14}H_{13}N_2OSF_6]^+$: 371.0653 [$(M+H)^+$]; found: 371.0649.



***N*-[3,5-bis(trifluoromethyl)phenyl]-3-ethyl-2-oxopyrrolidine-1-carbothioamide (Ib).** Following *GP-D*, **Ib** (0.84 g, 2.19 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 52% yield as a white solid starting from *N*-3,5-bis(trifluoromethyl)phenylpyrroldin-2-one (1.5 g, 4.22 mmol), lithium bis(trimethylsilyl)amide (8.84 mL, 8.84 mmol) and iodoethane (0.342 mL, 4.22 mmol) in THF (20 mL). R_f: 0.83 (hexanes/EtOAc 8:2). ^1H NMR (300 MHz, $CDCl_3$): δ 12.94 (bs, 1H, NH), 8.20 (s, 2H, C_{Ar}-H), 7.72 (s, 1H, C_{Ar}-H), 4.39 (ddd, J = 11.8, 8.9, 3.1 Hz, 1H, C_5-H_a), 4.02 (ddd, J = 11.7, 9.0, 7.6 Hz, 1H, C_5-H_b), 2.79 (ddd, J = 18.5, 8.8, 4.8 Hz, 1H, C_4-H_a), 2.45-2.15 (m, 1H, C_3-H), 2.11-1.87 (m, 1H, C_4-H_b), 1.87-1.68 (m, 1H, $C\mathbf{H}_aH_bCH_3$), 1.68-1.47 (m, 1H, $CH_a\mathbf{H}_bCH_3$), 1.05 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.5 (C_2), 179.3 (CS), 139.8 (C_{Ar}-C), 132.2 (q, $^2J_{C-F}$ = 33.5 Hz, **C**CF_3), 124.3 (C_{Ar}-H), 123.1 (q, $^1J_{C-F}$ = 272.7 Hz, CF_3), 119.7 (q, J = 3.2 Hz, C_{Ar}-H), 49.4 (C_5), 47.0 (C_3), 23.8 (C_4), 22.9 ($\mathbf{C}H_2CH_3$), 11.4 ($CH_2\mathbf{C}H_3$). ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.0 (CF_3). IR (ATR) cm^{-1}: 2977 (NH), 2877 (C-H), 1699 (C=O), 1274 (C=S), 1125 (C-N). MS (EI) m/z (%): 271 (100), 252 (25), 213 (26), 202 (12), 163 (13), 83 (35), 69 (10). HRMS: Calculated for $[C_{15}H_{15}N_2OSF_6]^+$: 385.0809 [$(M+H)^+$]; found: 385.0808. M.p. (CH_2Cl_2): 77-79 ºC.

***N*-[3,5-bis(trifluoromethyl)phenyl]-4,4-dimethyl-2-oxopyrrolidine-1-carbothioamide (Ic).**

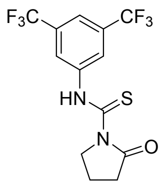


Scheme SI-5. Synthesis of **Ic**

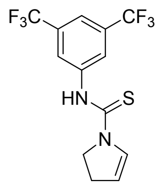
Pd/C (53.2 mg, 10wt%) was added to a solution of methyl 3,3-dimethyl-4-nitrobutanoate[19] (1.86 g, 10.6 mmol) in acetic acid (26.5 mL) and the mixture was stirred under a hydrogen atmosphere at room temperature for 12 hours. After that, the mixture was filtered through celite and the solvent was evaporated. Then, the crude product was dissolved in EtOH (20 mL) and Et_3N was added to maintain basic pH. The solution was stirred at reflux overnight. Then, solvent was evaporated and the crude mixture was dissolved in Et_2O and 1*M* HCl was added. Aqueous phase was extracted with Et_2O (2 × 20 mL), organic phases were

[19] Bunce, R. A.; Drumright, R. E. *The New Journal for Organic Synthesis*, **1987**, *19*, 471.

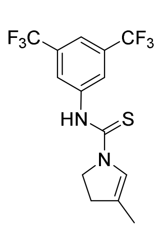
collected, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Then, to a stirred solution of the crude product in THF (48 mL) at 0 °C, NaH (0.64 g, 60%, 15.9 mmol) was added portionwise. After stirring at 0 °C for 30 min, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (3.0 mL, 15.9 mmol) was slowly added at -78 °C and the reaction was stirred and allowed to warm to room temperature overnight. Then a solution of saturated NH_4Cl was added to quench the reaction, and the mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel (Hexanes/EtOAc) to afford 2.7 g of **Ic** (7.0 mmol, 66%) as a white solid. R_f: 0.88 (hexanes/EtOAc 8:2). ^1H NMR (300 MHz, $CDCl_3$): δ 12.79 (s, 1H, NH), 8.18 (s, 2H, C_{Ar}-H), 7.72 (s, 1H, C_{Ar}-H), 4.01 (s, 2H, C_5-H), 2.62 (s, 2H, C_3-H), 1.23 (s, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.7 (CS), 176.7 (C_2), 139.8 (C_{Ar}-C), 132.2 (q, $^2J_{C-F}$ = 33.7 Hz, 2 × **C**CF_3), 123.2 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF_3), 124.5 (C_{Ar}-H), 124.4 (C_{Ar}-H), 119.8 (q, $^3J_{C-F}$ = 3.8 Hz, C_{Ar}-H), 63.6 (C_5), 49.1 (C_3), 31.2 (C_4), 27.2 (2 × CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.0 (2 × CF_3). IR (ATR) cm^{-1}: 2960 (NH), 1709 (C=O), 1276 (C=S), 1127 (C-N). MS (EI) m/z (%): 271 (100), 252 (24), 213 (25), 202 (13), 163 (15), 143 (8), 113 (10), 69 (10). HRMS: Calculated for $[C_{15}H_{15}N_2OSF_6]^+$: 385.0809 $[(M+H)^+]$; found: 385.0808. M.p. (CH_2Cl_2): 93-95 ºC.



***N*-[3,5-bis(trifluoromethyl)phenyl]-2-oxopyrrolidine-1-carbothioamide (Ie).** Following *GP-C*, **Ie** (2.15 g, 6.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 98% yield as colorless cristals starting from pyrrolidin-2-one (0.47 mL, 6.15 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.68 mL, 9.2 mmol) and NaH (0.37 g, 9.2 mmol) in tetrahydrofuran (28 mL). R_f: 0.53 (hexanes/EtOAc 7:3). ^1H NMR (300 MHz, $CDCl_3$): δ 12.86 (bs, 1H, NH), 8.18 (s, 2H, C_{Ar}-H), 7.72 (s, 1H, C_{Ar}-H), 4.35-4.20 (m, 2H, C_5), 2.83 (t, *J* = 8.1 Hz, 2H, C_3-H), 2.18-2.04 (m, 2H, C_4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.5 (CS), 177.3 (C_2), 139.7 (C_{Ar}-C), 132.2 (q, $^2J_{C-F}$ = 33.7 Hz, **C**CF_3), 124.4 (q, $^3J_{C-F}$ = 3.8 Hz, C_{Ar}-H), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 119.8 (q, $^3J_{C-F}$ = 3.9 Hz, C_{Ar}-H), 51.4 (C_5), 34.7 (C_3), 16.6 (C_4). ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.0 (CF_3). IR (ATR) cm^{-1}: 2992 (NH), 1704 (C=O), 1276 (C=S), 1120 (C-N). MS (EI) m/z (%): 271 (100), 252 (24), 213 (25), 202 (13), 163 (15), 144 (8), 85 (13), 69 (9). HRMS: Calculated for $[C_{13}H_{11}N_2OSF_6]^+$: 357.0496 $[(M+H)^+]$; found: 357.0500. M.p. (CH_2Cl_2): 101-103 ºC.

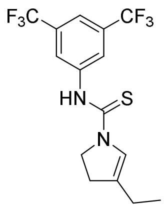


***N*-[3,5-bis(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-pyrrole-1-carbothioamide (2e).** Following *GP-E*, **2e** (862 mg, 2.53 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 76% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2-oxopyrrolidine-1-carbothioamide **Ie** (1.19 g, 3.3 mmol) and $LiEt_3BH$ (7.0 mL, 7.0 mmol) in tetrahydrofuran (7 mL), and then, using DMAP (8.2 mg, 0.067 mmol), TFAA (0.57 mL, 4.0 mmol) and Et_3N (2.57 mL, 18.4 mmol) in tetrahydrofuran/toluene mixture (4 mL/8 mL). R_f: 0.46 (hexanes/EtOAc 7:3). ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 7.13 (s, 1H, C_2-H), 5.53 (s, 1H, C_3-H), 4.14-3.99 (m, 2H, C_5-H), 2.93-2.78 (m, 2H, C_4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (CS), 140.5 (C_{Ar}-C), 131.2 (C_2), 131.9 (q, $^2J_{C-F}$ = 33.6 Hz, **C**CF_3), 124.4 (C_{Ar}-H), 123.2 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 118.7 (C_{Ar}-H), 115.2 (C_3), 53.6 (C_5), 29.8 (C_4). ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.0 (CF_3). IR (ATR) cm^{-1}: 3197 (NH), 2910 (C-H), 1537 (C=C), 1277 (C=S), 1125 (C-N). MS (EI) m/z (%): 271 (100), 252 (26), 213 (24), 202 (12), 163 (16), 143 (9), 83 (34), 69 (10). HRMS: Calculated for $[C_{13}H_{11}N_2SF_6]^+$: 341.0547 $[(M+H)^+]$; found: 341.0554. M.p. (CH_2Cl_2): 142-144 ºC.

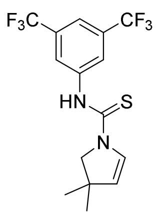


***N*-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide (5a).** Following *GP-E*, **5a** (868 mg, 2.45 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 57% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-2-oxopyrrolidine-1-carbothioamide **IIa** (1.6 g, 4.3 mmol) and $LiEt_3BH$ (9.0 mL, 9.0 mmol) in tetrahydrofuran (10 mL), and then, using DMAP (10.5 mg, 0.086 mmol), TFAA (0.73 mL, 5.17 mmol) and Et_3N (3.3 mL, 23.7 mmol) in tetrahydrofuran/toluene mixture (5.5 mL/11 mL). R_f: 0.69 (hexanes/EtOAc 7:3). ^1H NMR (500 MHz, DMSO-d_6, 100 ºC): δ 9.36 (bs, 1H, NH), 8.24 (s, 2H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 7.08 (s, 1H, C_2-H), 4.23-4.05 (m, 2H, C_5-H), 2.73-2.65 (m, 2H, C_4-H), 1.82 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 172.3 (CS), 142.3 (C_{Ar}-C), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, **C**CF_3), 125.2 (C_2), 123.2 (C_{Ar}-H), 122.9 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 115.6 (q, $^3J_{C-F}$ = 4.1 Hz, C_{Ar}-H), 49.7 (C_5), 32.7 (C_3), 13.0 (CH_3). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 2930 (NH), 2820 (C-H), 1540 (C=C), 1274 (C=S), 1123 (C-

N). MS (EI) m/z (%): 271 (100), 252 (22), 213 (22), 202 (10), 163 (12), 143 (7), 83 (31), 69 (6). HRMS: Calculated for $[C_{14}H_{13}N_2SF_6]^+$: 355.0704 $[(M+H)^+]$; found: 355.0712. M.p. (CH_2Cl_2): 144-146 ºC.



***N*-[3,5-bis(trifluoromethyl)phenyl]-4-ethyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide (5b).** Following *GP-E*, **5b** (244 mg, 0.66 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 51% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-ethyl-2-oxopyrrolidine-1-carbothioamide **IIb** (500 mg, 1.3 mmol) and $LiEt_3BH$ (2.7 mL, 2.7 mmol) in tetrahydrofuran (3.0 mL), and then, using DMAP (3.2 mg, 0.026 mmol), TFAA (0.219 mL, 1.55 mmol) and Et_3N (0.99 mL, 7.12 mmol) in tetrahydrofuran/toluene mixture (1.7 mL/3.4 mL). R_f: 0.58 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): δ 9.38 (bs, 1H, NH), 8.24 (s, 2H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 7.08 (s, 1H, C_2-H), 4.16-4.09 (m, 2H, C_5-H), 2.75-2.64 (m, 2H, C_4-H), 2.19 (q, *J* = 7.4 Hz, 2H, C**H**$_2$CH$_3$), 1.10 (t, *J* = 7.4 Hz, 3H, CH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 172.4 (CS), 142.3 (C_{Ar}-C), 131.4 (C_3), 129.5 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, **C**CF$_3$), 124.4 (C_2), 123.2 (C_{Ar}-H), 122.9 (q, $^1J_{C\text{-}F}$ = 272.6 Hz, CF_3), 115.6 (C_{Ar}-H), 49.6 (C_5), 30.8 (C_4), 20.9 (**C**H$_2$CH$_3$), 11.5 (CH$_2$**C**H$_3$). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (CF_3). IR (ATR) cm^{-1}: 2971 (NH), 1537 (C=C), 1274 (C=S), 1126 (C-H). MS (EI) m/z (%): 271 (100), 252 (25), 213 (26), 202 (10), 163 (11), 83 (10), 69 (12). HRMS: Calculated for $[C_{15}H_{15}N_2SF_6]^+$: 369.0860 $[(M+H)^+]$; found: 369.0863. M.p. (CH_2Cl_2): 133-135 ºC.



***N*-[3,5-bis(trifluoromethyl)phenyl]-3,3-dimethyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide (5c).** Following *GP-E*, **5c** (465 mg, 1.26 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 92% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-4,4-dimethyl-2-oxopyrrolidine-1-carbothioamide **Ic** (530 mg, 1.372 mmol) and $LiEt_3BH$ (2.88 mL, 2.88 mmol) in tetrahydrofuran (3 mL), and then, using DMAP (3.4 mg, 0.0274 mmol), TFAA (0.23 mL, 1.65 mmol) and Et_3N (1.05 mL, 7.55 mmol) in tetrahydrofuran/toluene mixture (1.5 mL/3.5 mL). R_f: 0.80 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.53 (s, 1H, NH), 8.26 (s, 2H, C_{Ar}-H), 7.69 (s, 1H, C_{Ar}-H), 7.21 (d, *J* = 4.2 Hz, 1H, C_2-H), 5.46 (d, *J* = 4.6 Hz, 1H, C_3-H), 3.86 (s, 2H, C_5-H), 1.21 (s, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 174.2 (CS), 142.0 (C_{Ar}-C), 129.5 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, **C**CF$_3$), 128.4 (C_2), 124.1 (C_3), 123.6 (C_{Ar}-H), 122.8 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, CF_3), 116.0 (C_{Ar}-H), 62.9 (C_5), 42.0 (C_4), 27.5 (C(**C**H$_3$)$_2$). ^{19}F NMR (282 MHz, DMSO-d_6): δ -63.0 (CF_3). IR (ATR) cm^{-1}: 2960 (NH), 2931 (C-H), 1534 (C=C), 1274 (C=S), 1125 (C-N). MS (EI) m/z (%): 271 (100), 252 (23), 213 (23), 202 (12), 163 (14), 143 (7), 83 (35), 69 (8). HRMS: Calculated for $[C_{15}H_{15}N_2SF_6]^+$: 369.0860 $[(M+H)^+]$; found: 369.0866. M.p. (CH_2Cl_2): 123-125 ºC.

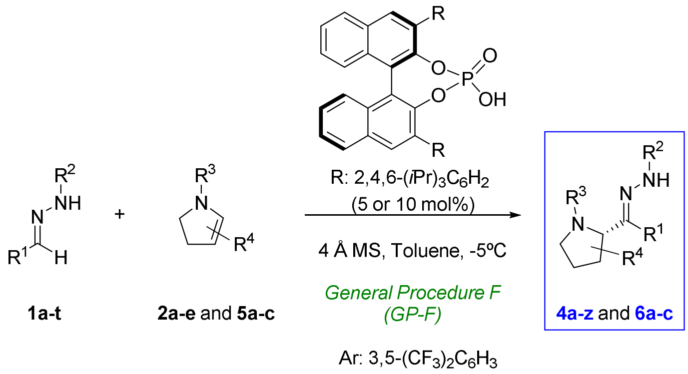
3.3. Preparation of catalysts 3

Catalyst **3a**, **3b**, **3c** and **3d** are commercially available. Catalysts **3e**[20] and **3f**[21] have been previously synthesized and used in the literature.

[20] D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626.

[21] M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Ieawsuwan, *Chem. Eur. J.* **2010**, *16*, 13116.

3.4. Preparation of hydrazono pyrrolidines 4a-z and 6a-c (Table 1, 2 and Scheme 2)

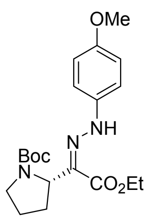


4a: R^1 = CO_2Et; R^2 = 4-OMeC_6H_4; R^3 = Boc; R^4 = H
4b: R^1 = CO_2Et; R^2 = 4-SMeC_6H_4; R^3 = Boc; R^4 = H
4c: R^1 = CO_2Et; R^2 = Ph; R^3 = Boc; R^4 = H
4d: R^1 = CO_2Et; R^2 = 4-$NO_2C_6H_4$; R^3 = Boc; R^4 = H
4e: R^1 = CO_2Et; R^2 = ^{t}Bu; R^3 = Boc; R^4 = H
4f: R^1 = CO_2Et; R^2 = Ph; R^3 = Fmoc; R^4 = H
4g: R^1 = CO_2Et; R^2 = Ph; R^3 = Ph; R^4 = H
4h: R^1 = CO_2Et; R^2 = Ph; R^3 = C(S)NHBn; R^4 = H
4i: R^1 = CO_2Et; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4j: R^1 = CO_2Et; R^2 = 4-OMeC_6H_4; R^3 = C(S)NHAr; R^4 = H
4k: R^1 = CO_2Et; R^2 = ^{t}Bu; R^3 = C(S)NHAr; R^4 = H
4l: R^1 = $CO_2{}^iPr$; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4m: R^1 = Ac; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4n: R^1 = CF_3; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4o: R^1 = Ph; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4p: R^1 = C_6F_5; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4q: R^1 = 4-CNC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4r: R^1 = 4-$CF_3C_6H_4$; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4s: R^1 = 4-$MeO_2CC_6H_4$; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4t: R^1 = 4-BrC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4u: R^1 = 4-ClC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4v: R^1 = 4-FC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4w: R^1 = 3-FC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4x: R^1 = 2-FC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4y: R^1 = 4-MeC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
4z: R^1 = 4-OMeC_6H_4; R^2 = Ph; R^3 = C(S)NHAr; R^4 = H
6a: R^1 = CO_2Et; R^2 = Ph; R^3 = C(S)NHAr; R^4 = 3-Me
6b: R^1 = CO_2Et; R^2 = Ph; R^3 = C(S)NHAr; R^4 = 3-Et
6c: R^1 = CO_2Et; R^2 = Ph; R^3 = C(S)NHAr; R^4 = 4,4-$(Me)_2$

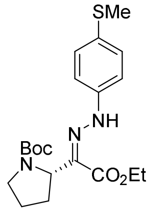
Scheme SI-6. 1,2-Addition reaction of hydrazones to enamides

General procedure F (GP-F). An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **(*R*)-TRIP (**0.009 mmol, 0.01 eq.), dry toluene (0.18 mL) and smashed molecular sieves (4Å, 27 mg). The reaction was cooled to -5 ºC and the corresponding enecarbamte/enethiourea (0.135 mmol, 1.5 eq.) and the corresponding hydrazone (0.09 mmol, 1.0 eq.) were added. The reaction mixture was stirred at -5 ºC until completion of reaction. The crude reaction mixture was directly charged onto silica gel and subjected to flash chromatography, affording the corresponding adducts **4a-z** and **6a-c**.

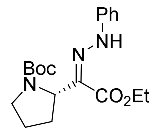
The ^{1}H NMR and ^{13}C NMR spectra of products **4h-z** and **6a-c** were performed in DMSO-d_6 and at 100 ºC to get rid of rotamers and simplified the spectra. It should be pointed out that ^{13}C NMR for these compounds were assigned by 2D NMR experiments (HSQC, HMBC), due to the low signal intensities in the ^{13}C NMR spectra.



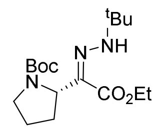
(*S*)-*N*-Boc-(*Z*)-2-{2-ethoxy-1-[2-(4-(methoxyphenyl))hydrazono]-2-oxoethyl}pyrrolidine (4a). Following slight modification, **4a** (30.8 mg, 0.079 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 24h in 60% yield as a yellow oil starting from ethyl (*E*)-2-(2-(4-(methoxy)phenyl)hydrazono)acetate **1a** (34.4 mg, 0.156 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole **2a** (23.2 mg, 0.13 mmol) in the presence of catalyst (*R*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent. R_f: 0.72 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): (1.45:1 rotamer ratio, *denotes minor rotamer resonances, $^\#$denotes overlapped signals) δ 12.01$^\#$ (bs, 1H, NH), 11.98*$^\#$ (bs, 1H, NH), 7.08 (d, J = 8.5 Hz, 2H, C_{Ar}-H), 6.84 (d, J = 8.5 Hz, 2H, C_{Ar}-H), 5.03-4.90* (m, 1H, C_2-H), 4.81 (dd, J = 7.8, 3.2 Hz, 1H, C_2-H), 4.27 (q, J = 7.2 Hz, 2H, C**H**$_2CH_3$), 3.77 (s, 3H, OCH_3), 3.68-3.33 (m, 2H, C_5-H), 2.30-1.68 (m, 4H, C_3-H + C_4-H), 1.58-1.23 (m, 12H, CH_2C**H**$_3$ + $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1 (COO), 155.2 (C_{Ar}-C), 154.4 (NCOO), 137.4 (CN), 127.7 (C_{Ar}-C), 114.8 (C_{Ar}-H), 114.8 (C_{Ar}-H), 79.1 (**C**$(CH_3)_3$), 60.6 (**C**H_2CH_3), 58.0 (C_2), 55.7 (OCH_3), 46.6 (C_5), 32.5 (C_3), 28.6 (C(**C**$H_3)_3$), 22.8 (C_4), 14.4 (CH_2**C**H_3). IR (ATR) cm^{-1}: 2977 (NH), 2930 (C-H), 1691 (C=O), 1548 (C=N). MS (EI) m/z (%): 281 (16), 207 (57), 149 (100), 134 (62), 108 (50), 93 (14), 78 (52), 52 (40). HRMS: Calculated for $[C_{20}H_{30}N_3O_5]^+$: 392.2185 $[(M+H)^+]$; found: 392.2188. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 5.295 min, τ_{minor} = 6.207 min (86% ee). $[\alpha]_D^{20}$: -88.5 (c = 1.0, CH_2Cl_2).



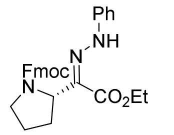
(*S*)-*N*-Boc-(*Z*)-2-{2-ethoxy-1-[2-(4-(methylthio)phenyl)hydrazono]-2-oxoethyl}pyrrolidine (4b). Following *GP-F* with slight modification, **4b** (28.1 mg, 0.069 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 24h in 53% yield as a yellow oil starting from ethyl (*E*)-2-(2-(4-(methylthio)phenyl)hydrazono)acetate **1b** (37.2 mg, 0.156 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole **2a** (23.2 mg, 0.13 mmol) in the presence of catalyst (*R*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent. R_f: 0.52 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): (1.25:1 rotamer ratio, *denotes minor rotamer resonances) δ 12.02 (bs, 1H, NH), 7.24 (d, J = 8.5 Hz, 2H, C_{Ar}-H), 7.09 (d, J = 8.5 Hz, 2H, C_{Ar}-H), 5.01-4.92* (m, 1H, C_2-H), 4.86-4.77 (m, 1H, C_2-H), 4.29 (q, J = 7.1 Hz, 2H, C**H**$_2$CH$_3$), 3.68-3.35 (m, 2H, C_5-H), 2.45 (s, 3H, SCH_3), 2.25-2.07 (m, 1H, C_3-H_a), 2.02-1.77 (m, 3H, C_3-H_b + C_4-H), 1.52-1.27 (m, 12H, CH$_2$C**H**$_3$ + C(CH$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (COO), 163.0* (COO), 154.3 (NCO), 142.1* (C_{Ar}-C), 141.6 (C_{Ar}-C), 130.5* (C_{Ar}-C), 129.7* (C_{Ar}-H), 129.6 (C_{Ar}-H), 129.0 (C_{Ar}-C), 127.9 (CN), 114.4 (C_{Ar}-H), 114.4* (C_{Ar}-H), 79.2* (**C**(CH$_3$)$_3$), 79.1 (**C**(CH$_3$)$_3$), 60.8 (**C**H$_2$CH$_3$), 58.1 (C_2), 57.7* (C_2), 47.0* (C_5), 46.6 (C_5), 32.4 (C_3), 31.3* (C_3), 28.8* (C(**C**H$_3$)$_3$), 28.5 (C(**C**H$_3$)$_3$), 22.9* (C_4), 22.8 (C_4), 17.9* (SCH_3), 17.7 (SCH_3), 14.4 (CH$_2$**C**H$_3$), 14.3* (CH$_2$**C**H$_3$). IR (ATR) cm^{-1}: 2976 (NH), 2820 (C-H), 1693 (C=O), 1551 (C=N). MS (EI) *m/z* (%): 281 (20), 238 (16), 207 (89), 191 (11), 165 (100), 150 (61), 138 (37), 124 (53), 106 (27), 78 (29), 69 (33), 56 (28). HRMS: Calculated for $[C_{20}H_{30}N_3O_4S]^+$: 408.1957 $[(M+H)^+]$; found: 408.1938; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 5.036 min, τ_{minor} = 5.915 min (92% ee). $[\alpha]_D^{20}$: -158.7 (*c* = 1.0, CH_2Cl_2).



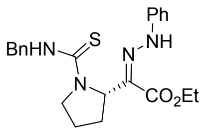
***(S)-N*-Boc-(*Z*)-2-[2-ethoxy-1-(2-(phenyl)hydrazono)-2-oxoethyl]pyrrolidine (4c).** Following *GP-F* with slight modification, **4c** (45.1 mg, 0.125 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 24h in 96% yield as an orange oil starting from ethyl (*E*)-2-(2-phenylhydrazono)acetate **1c** (25.0 mg, 0.13 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole **2a** (6 × 5.9 µL every 1h 30 min, 0.195 mmol) added in portions in the presence of catalyst (*R*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent. R_f: 0.79 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): (1.5:1 rotamer ratio, *denotes minor rotamer resonances, #overlapped signals) δ 12.02 (s, 1H, NH), 11.99* (s, 1H, NH), 7.43-7.22 (m, 2H, C_{Ar}-H), 7.22-7.07 (m, 2H, C_{Ar}-H), 7.05-6.83 (m, 1H, C_{Ar}-H), 5.02-4.94* (m, 1H, C_2-H), 4.82 (dd, J = 7.5, 3.3 Hz, 1H, C_2-H), 4.29 (q, J = 6.9 Hz, 2H, CH$_2$CH$_3$), 3.72-3.30 (m, 2H, C_5-H), 2.30-1.73 (m, 4H, C_3-H + C_4-H), 1.45* (s, 9H, C(CH$_3$)$_3$), 1.40-1.19# (m, 12H, CH$_2$C**H**$_3$ + C(CH$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (COO), 154.3 (NCO), 143.7* (CN), 143.4 (CN), 129.4 (C_{Ar}-H), 129.2* (C_{Ar}-H), 128.8 (C_{Ar}-C), 127.6* (C_{Ar}-C), 122.1 (C_{Ar}-H), 121.9* (C_{Ar}-H), 113.8 (C_{Ar}-H), 79.2* (**C**(CH$_3$)$_3$), 79.1 (**C**(CH$_3$)$_3$), 60.8 (**C**H$_2$CH$_3$), 58.1 (C_2), 57.6* (C_2), 46.6 (C_5), 32.4 (C_3), 31.3* (C_3), 28.7* (C(**C**H$_3$)$_3$), 28.4 (C(**C**H$_3$)$_3$), 22.9* (C_4), 22.7 (C_4), 14.3 (CH$_2$**C**H$_3$), 14.3* (CH$_2$**C**H$_3$). IR (ATR) cm^{-1}: 2976 (NH), 2920 (C-H), 1694 (C=O),1550 (C=N). MS (EI) *m/z* (%): 281 (16), 207 (57), 149 (100), 134 (62), 108 (50), 93 (14), 78 (52), 52 (40). HRMS: Calculated for $[C_{19}H_{28}N_3O_4]^+$: 362.2080 $[(M-H)^+]$; found: 362.2081. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 4.754 min, τ_{minor} = 3.825 min (93% ee). $[\alpha]_D^{20}$: -177.8 (*c* = 1.0, CH_2Cl_2).



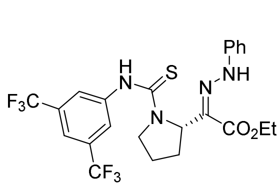
(*S*)-*tert*-Butyl-(*Z*)-2-[1-(2-(*tert*-butyl)hydrazono)-2-ethoxy-2-oxoethyl]pyrrolidine-1-carboxylate (4e). Following *GP-F* with slight modification, **4e** (38.6 mg, 0.113 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 5h in 87% yield as a light yellow oil starting from ethyl (*E*)-2-(2-(*tert*-butyl)hydrazono)acetate **1e** (26.9 mg, 0.156 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole **2a** (23.6 µL, 0.13 mmol) in the presence of catalyst (*R*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent. R_f: 0.70 (hexanes/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): (1.3:1 rotamer ratio, *denotes minor rotamer resonances) δ 9.99 (s, 1H, NH), 9.92* (s, 1H, NH), 4.88* (d, J = 7.1 Hz, 1H, C_2-H), 4.75 (dd, J = 7.5, 2.9 Hz, 1H, C_2-H), 4.19 (q, J = 7.2 Hz, 2H, C**H**$_2$CH$_3$), 3.58-3.22 (m, 2H, C_5-H), 2.16-1.73 (m, 4H, C_3-H + C_4-H), 1.43* (s, 9H, OC(CH$_3$)$_3$), 1.33 (s, 9H, OC(CH$_3$)$_3$), 1.31-1.24 (m, 3H, CH$_2$CH$_3$), 1.20 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9 (COO), 162.8* (COO), 154.3 (NCO), 154.1* (NCO), 125.4 (CN), 124.0* (CN), 78.6 (O**C**(CH$_3$)$_3$), 59.9* (**C**H$_2$CH$_3$), 59.8 (**C**H$_2$CH$_3$), 57.5 (C_2), 57.2* (C_2), 54.5 (**C**(CH$_3$)$_3$), 54.4* (**C**(CH$_3$)$_3$), 46.5 (C_5), 32.7 (C_3), 31.5* (C_3), 28.9 (OC(**C**H$_3$)$_3$), 28.8* (OC(**C**H$_3$)$_3$), 28.7* (C(**C**H$_3$)$_3$), 28.6 (C(**C**H$_3$)$_3$), 22.8* (C_4), 22.6 (C_4), 14.5 (CH$_2$**C**H$_3$), 14.4* (CH$_2$**C**H$_3$). IR (ATR) cm^{-1}: 2977 (NH), 2876 (C-H), 1695 (C=O), 1537 (C=N). MS (EI) *m/z* (%): 341 (M^+, 8), 184 (40), 169 (38), 156 (30), 114 (47), 95 (17), 70 (38), 57 (100). HRMS: Calculated for $[C_{17}H_{32}N_3O_4]^+$: 342.2393 $[(M+H)^+]$; found: 342.2394. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 5.957 min, τ_{minor} = 7.067 min (72% ee). $[\alpha]_D^{20}$: -42.5 (*c* = 1.0, CH_2Cl_2).



(*S*)-(9*H*-Fluoren-9-yl)methyl-(*Z*)-2-[2-ethoxy-2-oxo-1-(2-phenylhydrazono)ethyl]pyrrolidine-1-carboxylate (4f). Following the *GP-F* with slight modification, **4f** (58.2 mg, 0.120 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 72h in 93% yield as an orange oil starting from ethyl (*E*)-2-(2-phenyl)hydrazono)acetate **1c** (24.9 mg, 0.13 mmol) and *N*-Fmoc-2,3-dihydro-1*H*-pyrrole **2b** (5 × 9.5 mg + 1 × 9.3 mg every 1h 30 min, 0.195 mmol) added in portions in the presence of catalyst (*R*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent at 10 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): (1.2:1 rotamer ratio, *denotes minor rotamer resonances) δ 12.05* (s, 1H, NH), 11.93 (s, 1H, NH), 7.78 (d, *J* = 7.5 Hz, 1H, C_{Ar}-H), 7.72-7.61 (m, 2H, C_{Ar}-H), 7.50-7.27 (m, 5H, C_{Ar}-H), 7.23-7.06 (m, 4H, C_{Ar}-H), 7.01-6.85 (m, 1H, C_{Ar}-H), 5.09* (dd, *J* = 7.5, 2.3 Hz, 1H, C_2-H), 4.89-4.77 (m, 1H, C_2-H), 4.58-4.44 (m, 1H, C**H**CH_2O), 4.40-4.00 (m, 4H, CHC**H**$_2$O + C**H**$_2CH_3$), 3.85-3.44 (m, 2H, C_5-H), 2.30-1.80 (m, 4H, C_3-H + C_4-H), 1.38-1.32 (m, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4 (**C**OO), 162.9* (NCO), 162.6 (NCO), 154.9 (CN), 154.7* (CN), 144.5* (C_{Ar}-C), 144.2 (C_{Ar}-C), 144.2 (C_{Ar}-C), 144.2* (C_{Ar}-C), 143.5* (C_{Ar}-C), 143.3 (C_{Ar}-C), 142.8* (C_{Ar}-C), 141.4 (C_{Ar}-C), 141.2 (C_{Ar}-C), 129.5 (C_{Ar}-H), 129.4 (C_{Ar}-H), 129.3* (C_{Ar}-H), 127.7 (C_{Ar}-H), 127.5 (C_{Ar}-H), 127.5* (C_{Ar}-H), 127.1* (C_{Ar}-H), 127.1 (C_{Ar}-H), 127.0 (C_{Ar}-H), 126.9* (C_{Ar}-H), 125.8 (C_{Ar}-H), 125.3 (C_{Ar}-H), 124.8* (C_{Ar}-H), 122.3* (C_{Ar}-H), 122.2 (C_{Ar}-H), 122.1 (C_{Ar}-H), 120.1 (C_{Ar}-H), 120.0* (C_{Ar}-H), 119.8 (C_{Ar}-H), 114.0 (C_{Ar}-H), 113.8 (C_{Ar}-H), 113.7* (C_{Ar}-H), 67.3* (CH**C**H_2O), 66.6 (CH**C**H_2O), 60.9 (**C**H_2CH_3), 60.8* (**C**H_2CH_3), 58.0* (C_2), 57.7 (C_2), 47.6* (**C**HCH_2O), 47.4 (**C**HCH_2O), 47.0 (C_5), 46.6* (C_5), 32.2 (C_3), 31.4* (C_3), 23.2* (C_4), 22.0 (C_4), 14.4* (CH_2**C**H_3), 14.3 (CH_2**C**H_3); R_f: 0.54 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2980 (NH), 2810 (C-H), 1695 (C=O), 1551 (C=N); MS (EI) *m/z* (%): 178 (100), 152 (12), 88 (9), 76 (13); HRMS: Calculated for $[C_{29}H_{30}N_3O_4]^+$: 484.2236 $[(M+H)^+]$; found: 484.2238; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (80:20)]; flow rate 1.00 mL/min; τ_{major} = 21.319 min, τ_{minor} = 61.500 min (92% ee); $[\alpha]_D^{20}$: -5.5 (*c* = 1.0, CH_2Cl_2).



(*S*)-Ethyl-(*Z*)-2-[1-(benzylcarbamothioyl)pyrrolidin-2-yl]-2-(2-phenylhydrazono)acetate (4h). Following *GP-F*, **4h** (35.3 mg, 0.086 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 95% yield as a yellow solid starting from ethyl (*E*)-2-(2-phenylhydrazono)acetate **1c** (17.2 mg, 0.09 mmol) and *N*-benzyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2d** (29.5 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.35 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: 5.8:1, *denotes *E* diastereoisomer resonances) δ 11.68 (s, 1H, NNH), 9.70* (s, 1H, NNH), 7.56* (s, 1H, CSNH), 7.48 (s, 1H, CSNH), 7.35-7.13 (m, 7H, C_{Ar}-H + C_{Ar}-H*), 7.13-7.01 (m, 2H, C_{Ar}-H + C_{Ar}-H*), 6.95 (dd, *J* = 6.5, 1.2 Hz, 1H, C_{Ar}-H), 6.90-6.85* (m, 1H, C_{Ar}-H), 5.49* (dd, *J* = 8.2, 5.8 Hz, 1H, C_2-H), 5.45-5.38 (m, 1H, C_2-H), 4.88-4.66 (m, 2H, NHC**H**$_2$ + NHC**H**$_2$*), 4.38-4.20 (m, 2H, C**H**$_2CH_3$), 4.15* (q, *J* = 7.1 Hz, 2H, C**H**$_2CH_3$), 3.81 (ddd, *J* = 11.8, 8.7, 3.3 Hz, 1H, C_5-H_a), 3.85-3.61 (m, 1H, C_5-H_a* + C_5-H_b + C_5-H_b*), 2.37-2.27* (m, 1H, C_3-H_a), 2.27-2.18 (m, 1H, C_3-H_a), 2.18-2.12* (m, 1H, C_3-H_b), 2.12-1.92 (m, 3H, C_3-H_b + C_4-H + C_4-H_a*), 1.92-1.81* (m, 2H, C_4-H_b), 1.33 (t, *J* = 7.1 Hz, 3H, CH_3), 1.24* (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 179.0 (CS), 178.5* (CS), 162.8* (CO), 161.4 (CO), 144.2 (CN), 143.1 (C_{Ar}-C), 139.4 (C_{Ar}-C), 139.4* (C_{Ar}-C), 128.6 (C_{Ar}-H), 128.3* (C_{Ar}-H), 127.3* (C_{Ar}-H), 127.3 (C_{Ar}-H), 126.5* (C_{Ar}-H), 126.4 (C_{Ar}-H), 125.8* (C_{Ar}-H), 125.7 (C_{Ar}-H), 121.1 (C_{Ar}-H), 120.2* (C_{Ar}-H), 113.3* (C_{Ar}-H), 113.2 (C_{Ar}-H), 60.3 (C_2), 60.1 (**C**H_2CH_3), 59.2* (**C**H_2CH_3), 57.5* (C_2), 48.9 (C_5), 48.4* (C_5), 47.5 ($NHCH_2$), 30.4 (C_3), 28.4* (C_3), 23.9* (C_4), 22.0 (C_4), 13.6* (CH_2**C**H_3), 13.4 (CH_2**C**H_3). IR (ATR) cm^{-1}: 3264 (NH), 2977 (NH), 2820 (C-H), 1679 (C=O), 1530 (C=N), 1236 (C=S), 1149 (C-N). MS (EI) *m/z* (%): 149 (17), 91 (100), 83 (10), 65 (16), 51 (5). HRMS: Calculated for $[C_{22}H_{27}N_4O_2S]^+$: 411.1855 $[(M+H)^+]$; found: 411.1858; The ee was determined by HPLC using a Chiralpak IC column [*n-hexane*/*i*PrOH (85:15)]; flow rate 1.00 mL/min; τ_{major} = 18.766 min, τ_{minor} = 27.998 min (92% ee). $[\alpha]_D^{20}$: -119.9 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 124-126 ºC.

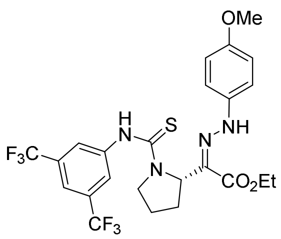


(*S*)-Ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate (4i). Following *GP-F*, **4i** (47 mg, 0.088 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 98%

yield as a light yellow solid starting from ethyl (*E*)-2-(2-phenyl)hydrazono)acetate **1c** (17.2 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.67 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: 5.0:1, *denotes *E* diastereoisomer resonances) δ 11.68 (s, 1H, NNH), 9.83* (s, 1H, NNH), 9.31* (s, 1H, CSNH), 9.20 (s, 1H, CSNH), 8.18* (s, 2H, C_{Ar}-H), 8.13 (s, 2H, C_{Ar}-H), 7.64* (s, 1H, C_{Ar}-H), 7.63 (s, 1H, C_{Ar}-H), 7.30-7.20 (m, 4H, C_{Ar}-H), 6.97-6.92 (m, 1H, C_{Ar}-H), 6.91-6.86* (m, 1H, C_{Ar}-H), 5.58-5.50 (m, C_2-H), 4.41-4.25 (m, 2H, C**H**$_2$CH$_3$), 4.18* (q, *J* = 7.1 Hz, 2H, C**H**$_2$CH$_3$), 4.02-3.92 (m, 1H, C_5-H_a), 3.92-3.82 (m, 1H, C_5-H_b), 2.45-2.37* (m, 1H, C_3-H_a), 2.37-2.27 (m, 1H, C_3-H_a), 2.27-2.17* (m, 1H, C_3-H_b), 2.17-2.00 (m, 3H, C_3-H_b + C_4-H), 2.00-1.90* (m, 2H, C_4-H), 1.35 (t, *J* = 7.1 Hz, 3H, CH$_3$), 1.26* (t, *J* = 7.1 Hz, 3H, CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 177.7 (CS), 176.7* (CS), 162.7* (CO), 161.3 (CO), 144.1 (C_{Ar}-C), 143.0 (CN), 142.5 (C_{Ar}-C), 142.4* (C_{Ar}-C), 129.4 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, **C**CF$_3$), 128.6 (C_{Ar}-H), 128.4* (C_{Ar}-H), 124.0 (q, $^3J_{C\text{-}F}$ = 3.9 Hz, C_{Ar}-H), 123.3* (C_{Ar}-H), 122.8 (q, $^1J_{C\text{-}F}$ = 272.7 Hz, CF$_3$), 121.3 (C_{Ar}-H), 120.5* (C_{Ar}-H), 115.9 (q, $^3J_{C\text{-}F}$ = 3.9 Hz, C_{Ar}-H), 115.7* (C_{Ar}-H), 113.5* (C_{Ar}-H), 113.2 (C_{Ar}-H), 61.1 (C_2), 60.2 (**C**H$_2$CH$_3$), 59.3* (**C**H$_2$CH$_3$), 57.8* (C_2), 50.1 (C_5), 30.6 (C_3), 28.5* (C_3), 24.0* (C_4), 22.2 (C_4), 13.5* (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.3* (CF$_3$), -61.7 (CF$_3$). IR (ATR) cm^{-1}: 3262 (NH), 2983 (NH), 2830 (C-H), 1683 (C=O), 1550 (C=N), 1277 (C=S), 1132 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (25), 213 (24), 202 (13), 163 (16), 143 (9), 83 (29), 69 (10); HRMS: Calculated for $[C_{23}H_{23}N_4O_2SF_6]^+$: 533.1446 $[(M+H)^+]$; found: 533.1451. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 15.395 min, τ_{minor} = 5.896 min (>99% ee). $[\alpha]_D^{20}$: -157.6 (*c* = 1.0, CH$_2$Cl$_2$). M.p. (CH$_2$Cl$_2$): 127-129 ºC.

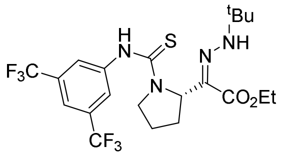
The reaction was carried out with 1 mol% of catalyst loading: Following *GP-F*, **4i** (41 mg, 0.077 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 86% yield (>99% ee) as a light yellow solid starting from ethyl (*E*)-2-(2-phenyl)hydrazono)acetate **1c** (17.2 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (0.68 mg, 0.0009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.67 (hexanes/EtOAc 7:3).

The reaction was carried out in a bigger scale: Following *GP-F*, **4i** (199 mg, 0.37 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 93% yield (>99% ee) as a light yellow solid starting from ethyl (*E*)-2-(2-phenyl)hydrazono)acetate **1c** (76.4 mg, 0.40 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (204 mg, 0.60 mmol) in the presence of catalyst (*R*)-TRIP (15.1 mg, 0.002 mmol), MS (4Å, 120 mg) and using dry toluene (0.82 mL) as solvent.

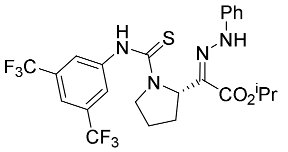


(*S*)-Ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-[2-(4-methoxyphenyl)hydrazono]acetate (4j). Following *GP-F*, **4j** (43.1 mg, 0.0766 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 85% yield as a yellow solid starting from ethyl (*E*)-2-(2-(4-(methoxy)phenyl)hydrazono)acetate **1a** (20.0 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.59 (hexanes/EtOAc 7:3); ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: 6.7:1, *denotes *E* diastereoisomer resonances) δ 11.67 (s, 1H, NNH), 9.71* (s, 1H, NNH), 9.28* (s, 1H, CSNH), 9.17 (s, 1H, CSNH), 8.18* (s, 2H, C_{Ar}-H), 8.13 (s, 2H, C_{Ar}-H), 7.63 (s, 1H, C_{Ar}-H), 7.18 (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 6.88 (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 5.55-5.49 (m, 1H, C_2-H), 4.39-4.22 (m, 2H, **C**H$_2$CH$_3$), 4.16* (q, *J* = 7.1 Hz, 2H, **C**H$_2$CH$_3$), 4.00-3.81 (m, 2H, C_5-H), 3.73 (s, 3H, OCH$_3$), 2.44-2.26 (m, 1H, C_3-H_a), 2.26-1.91 (m, 3H, C_3-H_b + C_4-H), 1.34 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$), 1.25* (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 177.7 (CS), 176.7* (CS), 162.8* (CO), 161.4 (CO), 154.7 (C_{Ar}-C), 154.0* (C_{Ar}-C), 142.5 (CN), 142.4* (CN), 138.0* (C_{Ar}-C), 136.9 (C_{Ar}-C), 132.5 (C_{Ar}-C), 129.4 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, **C**CF$_3$), 124.0 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C_{Ar}-H), 123.9* (C_{Ar}-H), 122.8 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, CF$_3$), 115.9 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C_{Ar}-H), 115.6* (C_{Ar}-H), 114.6* (C_{Ar}-H), 114.5 (C_{Ar}-H), 114.4 (C_{Ar}-H), 114.2* (C_{Ar}-H), 61.1 (C_2), 60.0 (**C**H$_2$CH$_3$), 59.2* (**C**H$_2$CH$_3$), 57.7* (C_2), 55.1 (OCH$_3$), 50.1 (C_5), 30.7 (C_3), 28.5* (C_3), 24.0* (C_4), 22.1 (C_4), 13.5* (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (CF$_3$). IR (ATR) cm^{-1}: 3231 (NH), 2955 (NH), 2830 (C-H), 1679 (C=O), 1550 (C=N), 1275 (C=S), 1131 (C-N). MS (EI) *m/z* (%): 149 (17), 91 (100), 83 (10), 65 (16). HRMS: Calculated for $[C_{23}H_{25}N_4O_3SF_6]^+$:

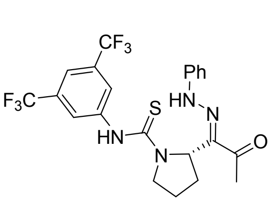
563.1552 [(M+H)$^+$]; found: 563.1566. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 14.567 min, τ_{minor} = 9.426 min (98% ee). $[\alpha]_D^{20}$: -96.0 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 128-130 ºC.



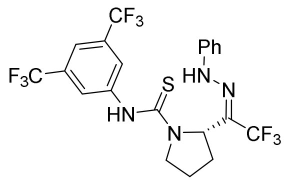
(*S*)-Ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-[2-(*tert*-butyl)hydrazono]acetate (4k). Following *GP-F*, **4k** (36.9 mg, 0.072 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 80% yield as a white solid starting from ethyl (*E*)-2-(2-(*tert*-butyl) hydrazono)acetate **1e** (15.5 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.69 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: >20:1) δ 9.75 (bs, 1H, NH), 9.03 (bs, 1H, CSNH), 8.12 (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 5.44-5.37 (m, 1H, C_2-H), 4.30-4.13 (m, 2H, **C**H_2CH_3), 3.88-3.73 (m, 2H, C_5-H), 2.29-2.17 (m, 1H, C_3-H_a), 2.05-1.92 (m, 3H, C_3-H_b + C_4-H), 1.29 (t, *J* = 7.1 Hz, 3H, CH_2**C**H_3), 1.19 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 177.4 (CS), 161.2 (CO), 142.6 (CN), 130.5 (C_{Ar}-C), 129.3 (q, $^2J_{C-F}$ = 33.0 Hz, **C**CF_3), 123.9 (C_{Ar}-H), 122.9 (q, $^1J_{C-F}$ = 272.1 Hz, CF_3), 115.7 (C_{Ar}-H), 60.8 (C_2), 59.3 (**C**H_2CH_3), 53.6 (**C**$(CH_3)_3$), 50.2 (C_5), 30.8 (C_3), 27.8 (C(**C**$H_3)_3$), 21.8 (C_4), 13.5 (CH_2**C**H_3). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (CF_3). IR (ATR) cm^{-1}: 3266 (NH), 2976 (NH), 2850 (C-H), 1678 (C=O), 1537 (C=N), 1275 (C=S), 1126 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (23), 202 (9), 163 (12), 83 (13). HRMS: Calculated for $[C_{21}H_{27}N_4O_2SF_6]^+$: 513.1759 [(M+H)$^+$]; found: 513.1779. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ_{major} = 3.761 min, τ_{minor} = 4.230 min (91% ee). $[\alpha]_D^{20}$: -46.9 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 76-78 ºC.



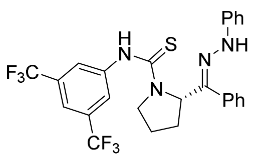
(*S*)-Isopropyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate (4l). Following *GP-F*, **4l** (42.8 mg, 0.078 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 87% yield as a light yellow solid starting from isopropyl (*E*)-2-(2-phenylhydrazono)acetate **1f** (18.6 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.67 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: 7.8:1, *denotes *E* diastereoisomer resonances) δ 11.72 (s, 1H, NNH), 9.77* (s, 1H, NNH), 9.20 (s, 1H, CSNH), 8.18* (s, 2H, C_{Ar}-H), 8.14 (s, 2H, C_{Ar}-H), 7.65* (s, 1H, C_{Ar}-H), 7.63 (s, 1H, C_{Ar}-H), 7.34-7.13 (m, 4H, C_{Ar}-H), 6.98-6.92 (m, 1H, C_{Ar}-H), 6.91-6.86* (m, 1H, C_{Ar}-H), 5.56-5.49 (m, 1H, C_2-H), 5.19-5.09 (m, 1H, C**H**$(CH_3)_2$), 5.04-4.96* (m, 1H, C**H**$(CH_3)_2$), 4.05-3.77 (m, 2H, C_5-H), 2.46-2.38* (m, 1H, C_3-H_a), 2.38-2.27 (m, 1H, C_3-H_a), 2.26-2.18* (m, 1H, C_3-H_b), 2.18-1.90 (m, 3H, C_3-H_b + C_4-H), 1.35 (d, *J* = 6.1 Hz, 6H, CH(C**H**$_3)_2$), 1.27* (d, *J* = 6.3 Hz, 3H, CH(C**H**$_3$)), 1.25* (d, *J* = 6.3 Hz, 3H, CH(C**H**$_3$)). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 177.7 (CS), 176.6* (CS), 162.2* (COO), 160.9 (COO), 144.2* (C_{Ar}-C), 143.0 (C_{Ar}-C), 142.5 (CN), 142.3* (CN), 134.5 (C_{Ar}-C), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, **C**CF_3), 128.6 (C_{Ar}-H), 128.3* (C_{Ar}-H), 124.0 (C_{Ar}-H), 123.4* (C_{Ar}-H), 123.9 (CF_3), 121.3 (C_{Ar}-H), 120.3* (C_{Ar}-H), 115.9 (tt, *J* = 6.9, 3.3 Hz, C_{Ar}-H), 113.4* (C_{Ar}-H), 113.2 (C_{Ar}-H), 68.3 (**C**$H(CH_3)_2$), 66.7* (**C**$H(CH_3)_2$), 61.3 (C_2), 57.9* (C_2), 50.0 (C_5), 30.6 (C_3), 28.4* (C_3), 24.0* (C_4), 22.3 (C_4), 21.0 (CH(**C**$H_3)_2$), 21.0 (CH(**C**$H_3)_2$). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (CF_3). IR (ATR) cm^{-1}: 3227 (NH), 2985 (NH), 2924 (C-H), 1676 (C=O), 1551 (C=N), 1273 (C=S), 1133 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (22), 202 (10), 163 (12), 83 (20). HRMS: Calculated for $[C_{24}H_{25}N_4O_2SF_6]^+$: 547.1602 [(M+H)$^+$]; found: 547.1588. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 9.683 min, τ_{minor} = 5.086 min (99% ee). $[\alpha]_D^{20}$: -84.3 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 139-141 ºC.



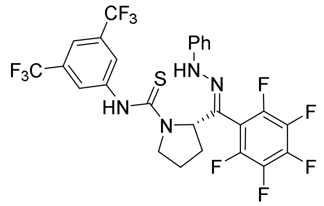
(*S,E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[2-oxo-1-(2-phenylhydrazono)propyl]pyrrolidine-1-carbothioamide (4m). Following *GP-F*, **4m** (39.4 mg, 0.078 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 1h in 87% yield as a yellow solid starting from pyruvic aldehyde 1-phenylhydrazone **1g** (14.6 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.49 (hexanes/EtOAc 6:4). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: 1:10, *denotes *Z* diastereoisomer resonances) δ 13.24* (s, 1H, NNH), 9.98 (s, 1H, NNH), 9.27 (s, 1H, CSNH), 8.20 (s, 2H, C_{Ar}-H), 8.15* (s, 2H, C_{Ar}-H), 7.64* (s, 1H, C_{Ar}-H), 7.62 (s, 1H, C_{Ar}-H), 7.36-7.22 (m, 4H, C_{Ar}-H), 7.02-6.96* (m, 1H, C_{Ar}-H), 6.96-6.85 (m, 1.6 Hz, 1H, C_{Ar}-H), 5.61-5.56* (m, 1H, C_2-H), 5.49-5.41 (m, 1H, C_2-H), 3.99-3.76 (m, 2H, C_5-H), 2.40-2.29 (m, 4H, C_3-H_a + CH_3), 2.24-2.14 (m, 1H, C_4-H_a), 2.06-1.95 (m, 1H, C_4-H_b), 1.92-1.83 (m, 1H, C_3-H_b). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 194.8 (CO), 176.1 (CS), 143.9 (C_{Ar}-C), 142.4 (C_{Ar}-C), 141.1 (CN), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, **C**CF_3), 128.7* (C_{Ar}-H), 128.6* (C_{Ar}-H), 128.5 (C_{Ar}-H), 123.0 (q, $^3J_{C-F}$ = 3.5 Hz, C_{Ar}-H), 122.9 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 121.1* (C_{Ar}-H), 120.9 (C_{Ar}-H), 115.5 (q, $^3J_{C-F}$ = 3.9 Hz, C_{Ar}-H), 113.7* (C_{Ar}-H), 113.6 (C_{Ar}-H), 57.3 (C_2), 57.1* (C_2), 51.7* (C_5), 50.0 (C_5), 28.3 (C_3), 24.6 (CH_3), 24.2 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (CF_3). IR (ATR) cm^{-1}: 3296 (NH), 2968 (NH), 2850 (C-H), 1645 (C=O), 1559 (C=N), 1269 (C=S), 1127 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (21), 202 (11), 163 (12), 83 (25). HRMS: Calculated for $[C_{22}H_{21}N_4OSF_6]^+$: 503.1340 [$(M+H)^+$]; found: 503.1341. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ_{major} = 4.522 min, τ_{minor} = 14.340 min (>99% ee). $[\alpha]_D^{20}$: +287.1 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 190-192 ºC.



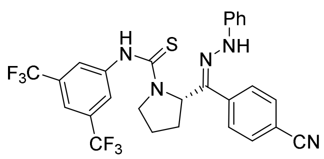
(*S,E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[2,2,2-trifluoro-1-(2-phenylhydrazono)ethyl]pyrrolidine-1-carbothioamide (4n). Following *GP-F*, **4n** (34.9 mg, 0.066 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 73% yield as a white solid starting from (*E*)-1-phenyl-2-(2,2,2-trifluoroethylidene)hydrazine **1h** (16.9 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.37 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: 1:16, *denotes *Z* diastereoisomer resonances) δ 9.86 (s, 1H, NNH), 9.70* (s, 1H, NNH), 9.53 (s, 1H, CSNH), 9.37* (s, 1H, CSNH), 8.22 (s, 2H, C_{Ar}-H), 8.16* (s, 2H, C_{Ar}-H), 7.69 (s, 1H, C_{Ar}-H), 7.66* (s, 1H, C_{Ar}-H), 7.27 (appt t, *J* = 7.8 Hz, 2H, C_{Ar}-H), 7.21 (d, *J* = 7.8 Hz, 2H, C_{Ar}-H), 6.90 (appt t, *J* = 7.2 Hz, 1H, C_{Ar}-H), 5.83-5.70 (m, 1H, C_2-H), 5.51-5.44* (m, 1H, C_2-H), 4.00-3.90 (m, 1H, C_5-H_a), 3.83-3.70 (m, 1H, C_5-H_b), 2.51-2.39 (m, 1H, C_3-H_a), 2.23-2.12 (m, 1H, C_4-H_a), 2.11-2.01 (m, 1H, C_4-H_b), 2.00-1.92 (m, 1H, C_3-H_b). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.8 (CS), 143.9 (C_{Ar}-C), 142.2 (CN), 129.6 (q, $^2J_{C-F}$ = 33.0 Hz, **C**CF_3), 128.4 (C_{Ar}-H), 123.6 (C_{Ar}-H), 122.8 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 122.1 (q, $^1J_{C-F}$ = 274.1 Hz, CF_3), 120.5 (C_{Ar}-H), 116.1 (q, $^3J_{C-F}$ = 3.5 Hz, C_{Ar}-H), 113.2 (C_{Ar}-H), 57.1 (C_2), 49.9 (C_5), 28.3 (C_3), 23.8 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (CF_3). IR (ATR) cm^{-1}: 3285 (NH), 2924 (NH), 2853 (C-H), 1536 (C=N), 1276 (C=S), 1175 (C-F), 1124 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (24), 213 (24), 202 (10), 163 (12), 83 (29). HRMS: Calculated for $[C_{21}H_{18}N_4OSF_9]^+$: 529.1108 [$(M+H)^+$]; found: 529.1119. The ee was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 59.265 min, τ_{minor} = 15.983 min (99% ee). $[\alpha]_D^{20}$: +125.7 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 129-131 ºC.



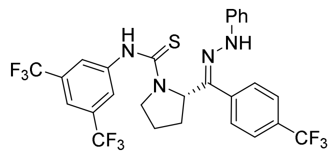
(*S,E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[phenyl(2-phenylhydrazono)methyl]pyrrolidine-1-carbothipamide (4o). Following *GP-F*, **4o** (45.6 mg, 0.085 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 94% yield as a white solid starting from (*E*)-1-benzylidene-2-phenylhydrazine **1i** (17.7 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.58 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 4.3:1, *denotes *Z* diastereoisomer resonances) δ 9.28 (s, 1H, CSNH), 9.11* (s, 1H, NNH), 8.27 (s, 1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 7.98-7.89* (m, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 7.63* (s, 1H, C_{Ar}-H), 7.58-7.50 (m, 2H, C_{Ar}-H), 7.51-7.45 (m, 3H, C_{Ar}-H), 7.35-7.28* (m, 2H, C_{Ar}-H), 7.24-7.15* (m, 3H, C_{Ar}-H), 7.14-7.08 (m, 2H, C_{Ar}-H), 7.08-7.03 (m, 2H, C_{Ar}-H), 6.81-6.76* (m, 1H, C_{Ar}-H), 6.75-6.69 (m, 1H, C_{Ar}-H), 5.76-5.72* (m, 1H, C_2-H), 5.51-5.43 (m, 1H, C_2-H), 3.98-3.88 (m, 1H, C_5-H_a), 3.88-3.75 (m, 1H, C_5-H_b), 2.66-2.55* (C_3-H), 2.23-2.12 (m, 1H, C_3-H_a), 2.12-1.94 (m, 3H, C_3-H_b + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.2* (CS), 178.0 (CS), 145.6* (CN), 145.2 (CN), 143.7 (C_{Ar}-C), 142.4 (C_{Ar}-C), 142.2* (C_{Ar}-C), 132.4 (C_{Ar}-C), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, **C**CF_3), 128.7 (C_{Ar}-H), 128.5* (C_{Ar}-H), 128.2* (C_{Ar}-H), 128.1 (C_{Ar}-H), 127.6 (C_{Ar}-H), 127.2* (C_{Ar}-H), 126.8* (C_{Ar}-H), 126.7 (C_{Ar}-H), 123.7 (C_{Ar}-H), 123.5* (C_{Ar}-H), 122.8 (q, $^1J_{C-F}$ = 272.7 Hz, CF_3), 118.8* (C_{Ar}-H), 118.6 (C_{Ar}-H), 116.1* (C_{Ar}-H), 115.8 (q, $^3J_{C-F}$ = 4.0 Hz, C_{Ar}-H), 112.7* (C_{Ar}-H), 112.4 (C_{Ar}-H), 65.3 (C_2), 50.0 (C_5), 29.2 (C_3), 28.9* (C_3), 22.9* (C_4), 22.1 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 3335 (NH), 2924 (NH), 2810 (C-H), 1602 (C=N), 1275 (C=S), 1126 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (22), 202 (10), 163 (12), 83 (11). HRMS: Calculated for $[C_{26}H_{23}N_4SF_6]^+$: 537.1548 $[(M+H)^+]$; found: 537.1543. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ_{major} = 4.825 min, τ_{minor} = 5.576 min (90% ee). $[\alpha]_D^{20}$: +158.0 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 56-58 ºC.



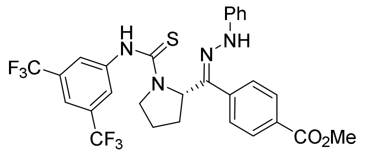
(*S*,*Z*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(perfluorophenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4p). Following *GP-F*, **4p** (44.0 mg, 0.070 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 78% yield as a white foam starting from (*E*)-1-((perfluorophenyl)methylene)-2-phenylhydrazine **1j** (25.8 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.49 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: >20:1, *denotes *E* diastereoisomer resonances) δ 9.66* (s, 1H, NNH), 9.43* (s, 1H, CSNH), 9.31 (s, 1H, CSNH), 9.12 (s, 1H, NNH), 8.21* (s, 2H, C_{Ar}-H), 8.13 (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 7.23-7.16 (m, 2H, C_{Ar}-H), 7.11 (d, *J* = 7.9 Hz, 2H, C_{Ar}-H), 6.86-6.79 (m, 1H, C_{Ar}-H), 5.88-5.82* (m, 1H, C_2-H), 5.73-5.66 (m, 1H, C_2-H), 3.98-3.75 (m, 2H, C_5-H), 2.37-2.30 (m, 1H, C_3-H_a), 2.26-2.08 (m, 3H, C_3-H_b + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.6 (CS), 144.4 (C_{Ar}-C), 143.4 (dm, $J_{C\text{-}F}$ = 245.9 Hz, C_6-F_5), 142.4 (CN), 142.3 (C_{Ar}-C), 137.1 (dm, $J_{C\text{-}F}$ = 249.8 Hz, C_6-F_5), 129.5 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, **C**CF_3), 128.3 (C_{Ar}-H), 123.1 (C_{Ar}-H), 123.1 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, CF_3), 119.7 (C_{Ar}-H), 115.7 (C_{Ar}-H), 112.7 (C_{Ar}-H), 107.3 (dm, C_{Ar}-C), 63.8 (C_2), 49.4 (C_5), 28.4 (C_3), 22.4 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (CF_3), -137.4 (m, C_6F_5 *m*-F), -154.3 (m, C_6F_5 *p*-F), -162.1 (m, C_6F_5 *o*-F). IR (ATR) cm^{-1}: 3269 (NH), 2926 (NH), 1520 (C=N), 1277 (C=S), 1171 (C-F), 1132 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (22), 202 (10), 163 (11). HRMS: Calculated for $[C_{26}H_{18}N_4SF_{11}]^+$: 627.1077 $[(M+H)^+]$; found: 627.1086. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/min; τ_{major} = 47.899 min, τ_{minor} = 57.949 min (97% ee). $[\alpha]_D^{20}$: +15.7 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 157-159 ºC.



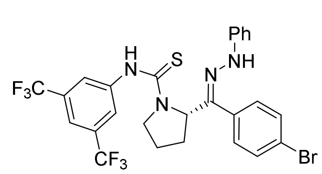
(*S*,*E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(4-cyanophenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4q). Following *GP-F*, **4q** (45.6 mg, 0.081 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 90% yield as a yellow solid starting from (*E*)-4-((2-phenylhydrazono)methyl)benzonitrile **1k** (19.9 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.43 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 1.3:1, *denotes *Z* diastereoisomer resonances) δ 9.37* (s, 2H, NNH + CSNH), 9.31 (s, 1H, CSNH), 8.60 (s, 1H, NNH), 8.19 (s, 2H, C_{Ar}-H), 7.99-7.86 (m, 2H, C_{Ar}-H), 7.74-7.59 (m, 2H, C_{Ar}-H), 7.26-7.20* (m, 4H, C_{Ar}-H), 7.16-7.10 (m, 2H, C_{Ar}-H), 7.10-7.06 (m, 2H, C_{Ar}-H), 6.87-6.79* (m, 1H, C_{Ar}-H), 6.77-6.70 (m, 1H, C_{Ar}-H), 5.72-5.66* (m, 1H, C_2-H), 5.48-5.42 (m, 1H, C_2-H), 4.05-3.78 (m, 2H, C_5-H), 2.69-2.60* (m, 1H, C_3-H_a), 2.27-1.90 (m, 3H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.4* (CS), 178.0 (CS), 145.2* (C_{Ar}-C), 145.1 (C_{Ar}-C), 142.4 (CNNH), 142.1* (CNNH), 141.8 (C_{Ar}-C), 141.3* (C_{Ar}-C), 137.8 (C_{Ar}-C), 132.4 (C_{Ar}-H), 131.0* (C_{Ar}-H), 129.4 (q, $^2J_{C\text{-}F}$ = 32.5Hz, **C**CF_3), 128.9 (C_{Ar}-H), 128.3* (C_{Ar}-H), 128.1 (C_{Ar}-H), 127.0* (C_{Ar}-H), 123.9 (C_{Ar}-H), 123.5* (C_{Ar}-H), 119.4* (C_{Ar}-H), 118.8 (C_{Ar}-H), 118.2* (CN), 117.9 (CN), 116.0 (C_{Ar}-H), 112.9* (C_{Ar}-H), 112.5 (C_{Ar}-H), 111.3 (C_{Ar}-C), 111.2* (C_{Ar}-C), 65.2 (C_2), 59.4* (C_2), 50.9 (C_5), 49.8* (C_5), 29.2 (C_3), 28.6* (C_3), 23.9* (C_4), 22.2 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 3308 (NH), 2928 (NH), 2231 (*p*-CN), 1600 (C=N), 1276 (C=S), 1128 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (22), 213 (22), 202 (11), 163 (12), 83 (17). HRMS: Calculated for $[C_{27}H_{22}N_5SF_6]^+$: 562.1500 $[(M+H)^+]$; found: 562.1495. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 17.194 min, τ_{minor} = 11.594 min (88% ee). $[\alpha]_D^{20}$: +47.0 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 97-99 ºC.



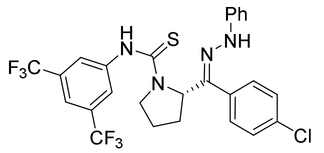
(*S*,*E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-{(2-phenylhydrazono)[4-(trifluoromethyl)phenyl]methyl}pyrrolidine-1-carbothioamide (4r). Following *GP-F*, **4r** (32.7 mg, 0.054 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 60% yield as a white solid starting from (*E*)-1-phenyl-2-(4-(trifluoromethyl)benzylidene)hydrazine **1l** (23.8 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.56 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 2.0:1, *denotes *Z* diastereoisomer resonances) δ 9.33* (s, 1H, NNH), 9.30 (s, 1H, CSNH + CSNH*), 8.58 (s, 1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 7.89* (s, 2H, C_{Ar}-H), 7.86 (d, *J* = 8.0 Hz, 2H, C_{Ar}-H), 7.75-7.68 (m, 2H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 7.63* (s, 2H, C_{Ar}-H), 7.26-7.17* (m, 4H, C_{Ar}-H), 7.17-7.03 (m, 4H, C_{Ar}-H), 6.86-6.77* (m, 1H, C_{Ar}-H), 6.77-6.70 (m, 1H, C_{Ar}-H), 5.76-5.68* (m, 1H, C_2-H), 5.51-5.44 (m, 1H, C_2-H), 4.05-3.73 (m, 2H, C_5-H), 2.75-2.59* (m, 1H, C_3-H_a), 2.29-1.94 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.4* (CS), 178.0 (CS), 145.2 (C_{Ar}-C), 142.4* (C_{Ar}-C), 142.1 (CN), 141.3 (CN), 137.1 (C_{Ar}-C), 129.6 (q, $^2J_{C-F}$ = 32.9 Hz, **C**CF_3 + *p*-**C**CF_3), 128.7 (C_{Ar}-H), 128.3* (C_{Ar}-H), 128.0 (C_{Ar}-H), 127.1* (C_{Ar}-H), 125.4 (q, $^3J_{C-F}$ = 3.9 Hz, C_{Ar}-H), 123.9* (C_{Ar}-H), 123.8 (C_{Ar}-H), 123.6* (C_{Ar}-H), 123.7 (q, $^1J_{C-F}$ = 272.2 Hz, CF_3), 122.9 (q, $^1J_{C-F}$ = 272.2 Hz, CF_3), 121.7 (C_{Ar}-C), 121.6* (C_{Ar}-C), 119.2* (C_{Ar}-H), 118.7 (C_{Ar}-H), 115.9 (C_{Ar}-H), 112.8* (C_{Ar}-H), 112.6 (C_{Ar}-H), 65.2 (C_2), 59.4* (C_2), 50.8* (C_5), 49.9 (C_5), 29.2 (C_3), 28.7* (C_3), 23.9* (C_4), 22.2 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.2 (CF_3), -61.6 (CF_3). IR (ATR) cm^{-1}: 3340 (NH), 2981 (NH), 1601 (C=N), 1276 (C=S), 1169 (C-F), 1124 (C-N). MS (EI) *m*/*z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (12), 83 (6). HRMS: Calculated for $[C_{27}H_{22}N_4SF_9]^+$: 605.1421 $[(M+H)^+]$; found: 605.1434. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 6.290 min, τ_{minor} = 6.940 min (86% ee). $[\alpha]_D^{20}$: +125.9 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 81-83 ºC.



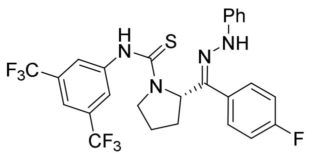
(*S*)-Methyl-(*E*)-4-{{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}(2-phenylhydrazono)methyl}benzoate (4s). Following *GP-F*, **4s** (34.7 mg, 0.058 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 65% yield as a light yellow solid starting from methyl (*E*)-4-((2-phenylhydrazono)methyl)benzoate **1m** (22.9 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.45 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 2.1:1, *denotes minor *Z* resonances, # overlapped signals) δ 9.32* (s, 1H, NNH), 9.30 (bs, 1H, CSNH), 8.48 (s, 1H, NNH), 8.19 (s, 2H, C_{Ar}-H), 8.08 (d, *J* = 8.0 Hz, 2H, C_{Ar}-H), 7.90 (d, *J* = 8.3 Hz, 1H, C_{Ar}-H), 7.66-7.56 (m, 2H, C_{Ar}-H), 7.25-7.18* (m, 4H, C_{Ar}-H), 7.16-7.03 (m, 4H, C_{Ar}-H), 6.85-6.78* (m, 1H, C_{Ar}-H), 6.75-6.71 (m, 1H, C_{Ar}-H), 5.75-5.68* (m, 1H, C_2-H), 5.49 (dd, *J* = 7.8, 2.0 Hz, 1H, C_2-H), 4.05-3.82# (m, 5H, C_5-H + OCH_3), 2.71-2.59* (m, 1H, C_3-H_a), 2.26-1.97 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.3* (CS), 178.0 (CS), 165.6* (COO), 165.5 (COO), 145.2* (C_{Ar}-C), 145.1 (C_{Ar}-C), 142.4 (CN), 137.5 (C_{Ar}-C), 129.8 (C_{Ar}-C), 129.6 (q, $^2J_{C-F}$ = 33.0 Hz, **C**CF_3), 129.4 (C_{Ar}-H), 128.3* (C_{Ar}-H), 128.1 (C_{Ar}-H), 128.1* (C_{Ar}-H), 128.0 (C_{Ar}-H), 126.5* (C_{Ar}-H), 123.8 (q, $^3J_{C-F}$ = 3.3 Hz, C_{Ar}-H), 123.5* (C_{Ar}-H), 122.8 (q, $^1J_{C-F}$ = 273.1 Hz, CF_3), 119.2* (C_{Ar}-H), 118.7 (C_{Ar}-H), 115.9 (q, $^3J_{C-F}$ = 2.9 Hz, C_{Ar}-H), 112.8* (C_{Ar}-H), 112.5 (C_{Ar}-H), 65.0 (C_2), 59.5* (C_2), 51.5 (OCH_3), 51.2* (OCH_3), 50.9* (C_5), 50.0 (C_5), 29.2 (C_3), 28.7* (C_3), 23.9* (C_4), 22.2 (C_4). ^{19}F NMR (300 MHz, DMSO-d_6): δ -61.6 (CF_3). IR (ATR) cm^{-1}: 3308 (NH), 2959 (NH), 1717 (C=O), 1601 (C=N), 1275 (C=S), 1129 (C-N). MS (EI) *m*/*z* (%): 271 (100), 252 (23), 213 (24), 202 (11), 163 (13), 83 (25). HRMS: Calculated for $[C_{28}H_{25}N_4O_2SF_6]^+$: 595.1602 $[(M+H)^+]$; found: 595.1607. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 10.350 min, τ_{minor} = 12.245 min (83% ee). $[\alpha]_D^{20}$: +102.4 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 77-79 ºC.



(*S*,*E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(4-bromophenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4t). Following *GP-F*, **4t** (43.9 mg, 0.071 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 79% yield as a light yellow solid starting from (*E*)-1-(4-bromobenzylidene)-2-phenylhydrazine **1n** (24.8 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.58 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 3.2:1, *denotes *Z* diastereoisomer resonances) δ 9.32* (s, 1H, CSNH), 9.28 (s, 1H, CSNH), 9.18* (s, 1H, NNH), 8.47 (s, 1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 7.96* (s, 2H, C_{Ar}-H), 7.71 (d, *J* = 8.4 Hz, 2H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 7.52-7.47* (m, 2H, C_{Ar}-H), 7.47-7.40 (m, 2H, C_{Ar}-H), 7.25-7.17* (m, 4H, C_{Ar}-H), 7.16-7.05 (m, 4H, C_{Ar}-H), 6.82-6.77* (m, 1H, C_{Ar}-H), 6.75-6.69 (m, 1H, C_{Ar}-H), 5.74-5.66* (m, 1H, C_2-H), 5.47-5.40 (m, 1H, C_2-H), 4.01-3.76 (m, 2H, C_5-H), 2.66-2.56* (C_3-H_a), 2.27-1.93 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.3* (CS), 178.0 (CS), 145.4* (CN), 145.2 (CN), 142.4 (C_{Ar}-C), 142.1* (C_{Ar}-C), 136.6 (C_{Ar}-C), 131.8 (C_{Ar}-C), 131.7 (C_{Ar}-H), 130.1* (C_{Ar}-H), 129.9 (C_{Ar}-H), 129.4 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, **C**CF_3), 128.6* (C_{Ar}-H), 128.3* (C_{Ar}-H), 128.0 (C_{Ar}-H), 123.8 (C_{Ar}-H), 123.6* (C_{Ar}-H), 123.0 (q, $^1J_{C\text{-}F}$ = 272.3 Hz, CF_3), 123.8 (C_{Ar}-H), 121.7 (C_{Ar}-C), 119.0* (C_{Ar}-H), 118.6 (C_{Ar}-H), 115.9 (q, $^3J_{C\text{-}F}$ = 4.3 Hz, C_{Ar}-H), 112.7* (C_{Ar}-H), 112.5 (C_{Ar}-H), 65.3 (C_2), 59.5* (C_2), 49.9 (C_5), 29.2 (C_3), 28.7* (C_3), 23.9* (C_4), 22.1 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 3341 (NH), 2971 (NH), 2930 (C-H), 1591 (C=N), 1276 (C=S), 1129 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (27), 213 (24), 202 (10), 163 (13), 83 (25), 69 (9). HRMS: Calculated for $[C_{26}H_{22}N_4SF_6Br]^+$: 615.0653 [$(M+H)^+$]; found: 615.0647. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ_{major} = 4.597 min, τ_{minor} = 4.956 min (92% ee). $[\alpha]_D^{20}$: +114.7 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 88-90 ºC.

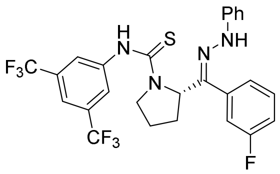


(*S*,*E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(4-chlorophenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4u). Following *GP-F*, **4u** (42.3 mg, 0.074 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 82% yield as a yellow solid starting from (*E*)-1-(4-chlorobenzylidene)-2-phenylhydrazine **1o** (20.8 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.55 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 3:1, *denotes *Z* diastereoisomer resonances) δ 9.32* (s, 1H, CSNH), 9.29 (s, 1H, CSNH), 9.17* (s, 1H, NNH), 8.46 (s, 1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 7.96* (s, 2H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 7.57 (d, *J* = 8.5 Hz, 2H, C_{Ar}-H), 7.52-7.47 (m, 2H, C_{Ar}-H), 7.34* (d, *J* = 8.5 Hz, 2H, C_{Ar}-H), 7.25-.716 (m, 1H, C_{Ar}-H), 7.15-7.02 (m, 3H, C_{Ar}-H), 6.82-6.77* (m, 1H, C_{Ar}-H), 6.75-6.70 (m, 1H, C_{Ar}-H), 5.74-5.69* (m, 1H, C_2-H), 5.47-5.39 (m, 1H, C_2-H), 4.02-3.74 (m, 2H, C_5-H), 2.65-2.57* (C_3-H_a), 2.28-1.94 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.3* (CS), 178.0 (CS), 145.4* (C_{Ar}-C), 145.2 (C_{Ar}-C), 142.4 (CN), 142.2* (CN), 136.2 (C_{Ar}-C), 133.4 (C_{Ar}-C), 131.4 (C_{Ar}-C), 129.6 (C_{Ar}-H), 129.4 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, **C**CF_3), 128.7 (C_{Ar}-H), 128.3* (C_{Ar}-H), 128.0 (C_{Ar}-H), 127.2* (C_{Ar}-H), 123.8 (C_{Ar}-H), 123.5* (C_{Ar}-H), 122.8 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, CF_3), 119.0* (C_{Ar}-H), 118.6 (C_{Ar}-H), 115.9 (q, $^3J_{C\text{-}F}$ = 3.3 Hz, C_{Ar}-H), 112.7* (C_{Ar}-H), 112.5 (C_{Ar}-H), 65.3 (C_2), 59.5* (C_2), 50.7* (C_5), 50.0 (C_5), 29.2 (C_3), 28.7* (C_3), 23.9* (C_4), 22.1 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 2984 (NH), 1601 (C=N), 1278 (C=S), 1134 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (24), 213 (23), 202 (11), 163 (14), 143 (9), 83 (34), 69 (9). HRMS: Calculated for $[C_{26}H_{22}N_4SF_6Cl]^+$: 571.1158 [$(M+H)^+$]; found: 571.1157. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 9.354 min, τ_{minor} = 11.676 min (90% ee). $[\alpha]_D^{20}$: +145.3 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 81-83 ºC.

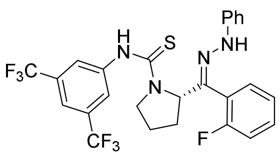


(*S*,*E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(4-fluorophenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4v). Following *GP-F*, **4v** (47.8 mg, 0.086 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 95% yield as a white solid starting from (*E*)-1-(4-fluorobenzylidene)-2-phenylhydrazine **1p** (19.3 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.52 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 3.7:1, *denotes *Z* diastereoisomer resonances) δ 9.30* (s, 1H, CSNH*), 9.28 (s, 1H, CSNH), 9.12* (s, 1H, NNH), 8.37 (s, 1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 7.95* (s, 2H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 7.57-7.48 (m, 2H, C_{Ar}-H), 7.36-7.29 (m, 2H, C_{Ar}-H), 7.25-7.15 (m, 1H, C_{Ar}-H), 7.15-7.02 (m, 3H, C_{Ar}-H), 6.81-6.76* (m, 1H, C_{Ar}-H), 6.75-6.69 (m, 1H, C_{Ar}-H), 5.75-5.68* (m, 1H, C_2-H), 5.47-5.40 (m, 1H, C_2-H), 4.01-3.72 (m, 2H, C_5-H), 2.67-2.57* (C_3-H), 2.26-1.95 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.2* (CS), 178.0 (CS), 161.9 (d, $^1J_{C\text{-}F}$ = 246.4 Hz, CF), 145.5* (C_{Ar}-C), 145.2 (C_{Ar}-C), 142.4 (CN), 142.2* (CN), 130.0 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, C_{Ar}-H), 129.4 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, **C**CF_3), 128.6 (C_{Ar}-C), 128.2* (C_{Ar}-H), 128.0 (C_{Ar}-H), 123.8 (C_{Ar}-H), 123.5* (C_{Ar}-H), 122.8 (q, $^1J_{C\text{-}F}$ = 272.6 Hz, CF_3), 118.8* (C_{Ar}-H), 118.6 (C_{Ar}-H), 115.9 (C_{Ar}-H), 115.6 (d, $^2J_{C-F}$ = 21.6 Hz, C_{Ar}-H), 113.9* (d, $^2J_{C-F}$ = 21.2 Hz, C_{Ar}-H), 112.7* (C_{Ar}-H), 112.5 (C_{Ar}-H), 65.3 (C_2), 59.5* (C_2), 50.7* (C_5), 49.9 (C_5), 29.1 (C_3), 28.7* (C_3), 22.1 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3), -112.4 (CF). IR (ATR) cm^{-1}: 2930 (NH), 1600 (C=N), 1276 (C=S), 1172 (C-F), 1128 (C-N). MS (EI) *m*/*z* (%): 271 (100), 252 (24), 213 (22), 202 (10), 163 (11), 83 (33). HRMS: Calculated for $[C_{26}H_{22}N_4SF_7]^+$: 555.1453 [(M+H)$^+$]; found: 555.1453. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ_{major} = 4.716 min, τ_{minor} = 5.079 min (94% ee). $[\alpha]_D^{20}$: +169.4 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 77-79 ºC.

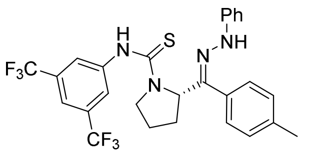
The reaction was carried out in a one-pot procedure starting from phenylhydrazine and p-fluorobenzaldehyde:
Phenylhydrazine (8.9 µL, 0.09 mmol) and *p*-fluorobenzaldehyde (9.9 µL, 0.09 mmol) were heated in dry toluene (0.18 mL) at 55ºC for 3h. After cooling the reaction to -5ºC, *N*-[3,5-bis(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) was added to the mixture together with catalyst **3a** (6.8 mg, 0.009 mmol) and 4Å MS and the mixture was allowed to stir at this temperature for 20h. The crude reaction mixture was directly charged onto silica gel and subjected to flash chromatography (petroleum ether/EtOAc gradient from 19:1 to 7:3) to afford **4v** (45.5 mg, 0.082 mmol, 91%, 94% ee) as a white solid.



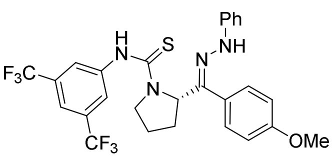
(*S,E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(3-fluorophenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4w). Following *GP-F*, **4w** (39.8 mg, 0.072 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 80% yield as a light yellow solid starting from (*E*)-1-(3-fluorobenzylidene)-2-phenylhydrazine **1q** (19.3 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.58 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 2.7:1, *denotes *Z* diastereoisomer resonances) δ 9.36* (s, 1H, CSNH), 9.29 (s, 1H, CSNH), 9.20* (s, 1H, NNH), 8.47 (s, 1H, NNH), 8.19 (s, 2H, C_{Ar}-H), 7.96* (s, 2H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 7.61-7.51 (m, 1H, C_{Ar}-H), 7.39-7.15 (m, 3H, C_{Ar}-H), 7.15-7.04 (m, 4H, C_{Ar}-H), 6.84-6.77* (m, 1H, C_{Ar}-H), 6.77-6.69 (m, 1H, C_{Ar}-H), 5.75-5.68* (m, 1H, C_2-H), 5.48-5.41 (m, 1H, C_2-H), 4.02-3.73 (m, 2H, C_5-H), 2.66-2.55* (m, 1H, C_3-H_a), 2.27-1.96 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.3* (CS), 178.0 (CS), 162.1 (d, $^1J_{C-F}$ = 245.6 Hz, CF), 145.3* (C_{Ar}-C), 145.2 (C_{Ar}-C), 142.4 (CN), 142.2* (CN), 134.8 (C_{Ar}-C), 130.7 (d, $^3J_{C-F}$ = 8.5 Hz, C_{Ar}-H), 129.4 (q, $^2J_{C-F}$ = 33.2 Hz, **C**CF_3), 128.3* (C_{Ar}-H), 128.0 (C_{Ar}-H), 123.8 (C_{Ar}-H), 123.6* (C_{Ar}-H), 122.5 (d, $^4J_{C-F}$ = 2.5 Hz, C_{Ar}-H), 122.9 (q, $^1J_{C-F}$ = 272.7 Hz, CF_3), 119.6 (d, $^3J_{C-F}$ = 5.5 Hz, C_{Ar}-C), 119.1* (C_{Ar}-H), 118.7 (C_{Ar}-H), 116.0* (C_{Ar}-H), 115.9 (C_{Ar}-H), 115.4 (d, $^2J_{C-F}$ = 20.9 Hz, C_{Ar}-H), 114.7 (d, $^2J_{C-F}$ = 22.0 Hz, C_{Ar}-H), 113.5* (d, $^2J_{C-F}$ = 21.1 Hz, C_{Ar}-H), 113.2* (d, $^2J_{C-F}$ = 22.4 Hz, C_{Ar}-H), 112.8* (C_{Ar}-H), 112.5 (C_{Ar}-H), 65.2 (C_2), 59.5* (C_2), 50.7* (C_5), 49.9 (C_5), 29.2 (C_3), 28.7* (C_3), 23.8* (C_4), 22.1 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3), -112.0 (CF). IR (ATR) cm^{-1}: 3335 (NH), 2974 (NH), 1601 (C=N), 1275 (C=S), 1170 (C-F), 1126 (C-N). MS (EI) *m*/*z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (13), 83 (7); HRMS: Calculated for $[C_{26}H_{22}N_4SF_7]^+$: 555.1453 [(M+H)$^+$]; found: 555.1459. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 20.990 min, τ_{minor} = 6.946 min (84% ee). $[\alpha]_D^{20}$: +124.6 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 73-75 ºC.



(*S,E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(2-fluorophenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4x). Following *GP-F*, **4x** (47.2 mg, 0.085 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 94% yield as a yellow solid starting from (*E*)-1-(2-fluorobenzylidene)-2-phenylhydrazine **1r** (19.3 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.54 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 9.1:1, *denotes *Z* diastereoisomer resonances) δ 9.28 (s, 1H, CSNH), 8.48 (s ,1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 8.01* (s, 1H, CSNH), 7.64 (s, 1H, C_{Ar}-H), 7.59-7.47 (m, 2H, C_{Ar}-H), 7.35 (t, *J* = 7.5 Hz, 1H, C_{Ar}-H), 7.30 (t, *J* = 9.0 Hz, 1H, C_{Ar}-H), 7.17-7.05 (m, 4H, C_{Ar}-H), 6.80-6.76* (m, 1H, C_{Ar}-H), 6.76-6.71 (m, 1H, C_{Ar}-H), 5.88-5.77* (m, 1H, C_2-H), 5.52-5.45 (m, 1H, C_2-H), 3.99-3.77 (m, 2H, C_5-H), 3.58-3.51* (m, 1H, C_5-H_a), 3.42-3.35* (m, 1H, C_5-H_b), 2.67-2.59* (m, 1H, C_3-H_a), 2.24-1.91 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.3* (CS), 178.1 (CS), 158.7 (d, $^{1}J_{C\text{-}F}$ = 246.6 Hz, CF), 145.0 (C_{Ar}-C), 142.4 (CN), 137.3 (C_{Ar}-C), 130.9 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz, C_{Ar}-H), 129.8 (d, $^{3}J_{C\text{-}F}$ = 4.3 Hz, C_{Ar}-H), 129.4 (q, $^{2}J_{C\text{-}F}$ = 33.1 Hz, **C**CF_3), 128.2* (C_{Ar}-H), 128.1 (C_{Ar}-H), 124.6 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz, C_{Ar}-H), 123.6 (C_{Ar}-H), 122.8 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz, CF_3), 119.9 (d, $^{2}J_{C\text{-}F}$ = 19.3 Hz, C_{Ar}-C), 119.0* (C_{Ar}-H), 118.7 (C_{Ar}-H), 115.8 (C_{Ar}-H), 115.7 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz, C_{Ar}-H), 112.7* (C_{Ar}-H), 112.5 (C_{Ar}-H), 65.1 (C_2), 50.0 (C_5), 28.9 (C_3), 22.0 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3), -112.2 (CF). IR (ATR) cm^{-1}: 3331 (NH), 2963 (NH), 1601 (C=N), 1276 (C=S), 1172 (C-F), 1128 (C-N). MS (EI) *m*/*z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (12), 83 (8). HRMS: Calculated for $[C_{26}H_{22}N_4SF_7]^+$: 555.1453 $[(M+H)^+]$; found: 555.1467. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 11.820 min, τ_{minor} = 7.849 min (82% ee). $[\alpha]_D^{20}$: +100.7 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 73-75 ºC.

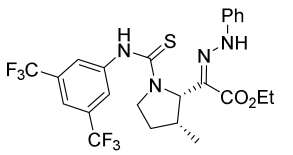


(*S*,*E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(2-phenylhydrazono)(*p*-tolyl)methyl]pyrrolidine-1-carbothioamide (4y). Following *GP-F*, **4y** (41.2 mg, 0.075 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 83% yield as a yellow solid starting from (*E*)-1-(4-methylbenzylidene)-2-phenylhydrazine **1s** (18.9 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.70 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 5.2:1, *denotes *Z* diastereoisomer resonances) δ 9.27 (s, 1H, CSNH), 9.06* (s, 1H, NNH), 8.24 (s, 1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 7.93* (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 7.40-7.29 (m, 4H, C_{Ar}-H), 7.23-7.14* (m, 4H, C_{Ar}-H), 7.14-7.01 (m, 4H, C_{Ar}-H), 6.81-6.75* (m, 1H, C_{Ar}-H), 6.74-6.68 (m, 1H, C_{Ar}-H), 5.75-5.68* (m, 1H, C_2-H), 5.50-542 (m, 1H, C_2-H), 3.98-3.79 (m, 2H, C_5-H), 2.64-2.55* (m, 1H, C_3-H_a), 2.39 (s, 3H, CH_3), 2.32* (s, 3H, CH_3), 2.23-2.12 (m, 1H, C_3-H_a), 2.11-1.95 (m, 3H, C_3-H_b + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.2* (CS), 178.0 (CS), 145.7* (C_{Ar}-C), 145.2 (C_{Ar}-C), 143.8 (C_{Ar}-C), 142.5 (CN), 142.2* (CN), 138.0 (C_{Ar}-C), 136.2 (C_{Ar}-C), 129.3 (q, $^{2}J_{C\text{-}F}$ = 33.2 Hz, **C**CF_3), 129.3 (C_{Ar}-H), 128.2* (C_{Ar}-H), 128.0 (C_{Ar}-H), 127.8* (C_{Ar}-H), 127.4 (C_{Ar}-H), 126.5* (C_{Ar}-H), 123.6 (C_{Ar}-H), 123.6* (C_{Ar}-H), 122.8 (q, $^{1}J_{C\text{-}F}$ = 272.9 Hz, CF_3), 118.7* (C_{Ar}-H), 118.5 (C_{Ar}-H), 115.8 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, C_{Ar}-H), 112.7* (C_{Ar}-H), 112.4 (C_{Ar}-H), 65.2 (C_2), 59.4* (C_2), 50.9* (C_5), 50.0 (C_5), 29.2 (C_3), 28.9* (C_3), 23.7* (C_4), 22.0 (C_4), 20.3 (CH_3), 20.0* (CH_3). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 3336 (NH), 2972 (NH), 2830 (C-H), 1602 (C=N), 1275 (C=S), 1127 (C-N). MS (EI) *m*/*z* (%): 271 (100), 252 (23), 213 (22), 202 (11), 163 (12), 83 (16). HRMS: Calculated for $[C_{27}H_{25}N_4SF_6]^+$: 551.1704 $[(M+H)^+]$; found: 551.1698. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (97:03)]; flow rate 1.00 mL/min; τ_{major} = 19.741 min, τ_{minor} = 22.974 min (91% ee). $[\alpha]_D^{20}$: +163.7 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 68-70 ºC.

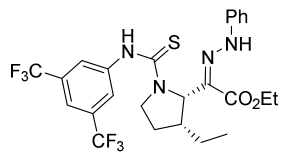


(*S*,*E*)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-2-[(4-methoxyphenyl)(2-phenylhydrazono)methyl]pyrrolidine-1-carbothioamide (4z). Following *GP-F*, **4z** (31.0 mg, 0.055 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 60% yield as a yellow solid starting from (*E*)-1-(4-methoxybenzylidene)-2-phenylhydrazine **1t** (20.4 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **2e** (45.9 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.40 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*E:Z* ratio: 6.2:1, *denotes *Z* diastereoisomer resonances, #overlapped signals) δ 9.26 (s, 1H, CSNH), 9.01* (s, 1H, NNH), 8.25 (s, 1H, NNH), 8.20 (s, 2H, C_{Ar}-H), 7.97* (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 7.47-7.35 (m, 2H, C_{Ar}-H), 7.23-7.14* (m, 4H, C_{Ar}-H), 7.14-7.02 (m, 6H, C_{Ar}-H), 6.89* (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 6.80-6.74* (m, 1H, C_{Ar}-H), 6.74-6.68 (m, 1H, C_{Ar}-H), 5.74-5.67* (m, 1H, C_2-H), 5.47-5.42 (m, 1H, C_2-H), 4.00-3.88 (m, 1H, C_5-H_a), 3.88-3.80# (m, 4H, C_5-H_b + OCH_3), 3.79* (s, 4H, C_5-H_b + OCH_3), 2.66-2.56* (m, 1H, C_3-H_a), 2.24-1.90 (m, 4H, C_3-H + C_4-H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.2* (CS), 177.9 (CS), 159.4 (C_{Ar}-C), 158.6* (C_{Ar}-C), 145.8* (C_{Ar}-C), 145.2 (C_{Ar}-C), 143.7 (C_{Ar}-C), 142.4 (CN), 142.2* (CN), 129.4 (q, $^{2}J_{C\text{-}F}$ = 33.3 Hz, **C**CF_3), 129.0 (C_{Ar}-H), 128.2* (C_{Ar}-H), 128.0 (C_{Ar}-H), 127.9* (C_{Ar}-H), 124.4 (C_{Ar}-C), 123.7 (C_{Ar}-H), 123.5* (C_{Ar}-H), 122.9 (q, $^{1}J_{C\text{-}F}$ = 273.3 Hz, CF_3), 118.6* (C_{Ar}-H), 118.5 (C_{Ar}-H), 115.8 (q, $^{3}J_{C\text{-}F}$ = 4.0 Hz, C_{Ar}-H), 114.4 (C_{Ar}-H), 112.9* (C_{Ar}-H), 112.6* (C_{Ar}-H), 112.4 (C_{Ar}-H), 65.3 (C_2), 58.9* (C_2), 54.8 (OCH_3), 54.7* (OCH_3), 50.8* (C_5), 50.1 (C_5), 29.2 (C_3), 28.8* (C_3), 22.0 (C_4). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 3334 (NH), 2973 (NH), 2820 (C-H), 1602 (C=N), 1278 (C=S), 1134 (C-N). MS (EI) *m*/*z* (%): 271 (100), 252 (23), 213 (22), 202 (11), 163 (12), 83 (6), 69 (7). HRMS: Calculated for $[C_{27}H_{25}N_4OSF_6]^+$: 567.1653 $[(M+H)^+]$; found: 567.1668. The ee was determined by HPLC using a Chiralpak

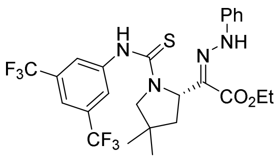
AD-H column [n-hexane/iPrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 12.553 min, τ_{minor} = 9.783 min (83% ee). $[\alpha]_D^{20}$: +135.3 (c = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 76-78 ºC.



(2*S*/3*R*)-Ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]-3-methylpyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate (6a). Following *GP-F* with slight modification, **6a** (29.8 mg, 0.054 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 72h in 60% yield as a light yellow solid starting from ethyl (*E*)-2-(2-phenylhydrazono)acetate **1c** (17.2 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-4-methyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **5a** (5 × 7.9 mg + 1 × 8.3 mg every 14 h, 0.135 mmol) added in portions and in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.81 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (3.2:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.82 (s, 1H, NNH), 11.67* (s, 1H, NNH), 9.16 (bs, 1H, CSNH), 8.18 (s, 2H, C_{Ar}-H), 8.13* (s, 2H, C_{Ar}-H), 7.65* (s, 1H, C_{Ar}-H), 7.63 (s, 1H, C_{Ar}-H), 7.34-7.24 (m, 2H, C_{Ar}-H), 7.24-7.13 (m, 2H, C_{Ar}-H), 6.99-6.91 (m, 1H, C_{Ar}-H), 5.72-5.63 (m, 1H, C_2-H), 5.13-5.07* (m, 1H, C_2-H), 4.39-4.24 (m, 2H, C**H**$_2$CH$_3$), 4.07-3.99 (m, 1H, C_5-H_a), 3.97-3.92* (C_5-H), 3.85-3.70 (m, 1H, C_5-H_b), 2.72-2.54 (m, 1H, C_3-H), 2.30-2.13 (m, 1H, C_4-H_a), 2.13-1.90 (m, 1H, C_4-H_b), 1.77-1.66* (m, 1H, C_4-H_b), 1.34 (t, J = 7.0 Hz, 3H, CH$_2$C**H**$_3$), 1.19* (d, J = 6.8 Hz, 3H, CHC**H**$_3$), 0.98 (d, J = 6.8 Hz, CHC**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ CS not detected 161.8 (CO), 161.4* (CO), 143.0 (CN), 142.4 (C_{Ar}-C), 129.3 (q, $^2J_{C-F}$ = 33.1 Hz, **C**CF$_3$), 128.7 (C_{Ar}-H), 128.6* (C_{Ar}-H), 128.4 (C_{Ar}-C), 122.8 (q, $^1J_{C-F}$ = 272.6 Hz, CF_3), 123.8 (C_{Ar}-H), 121.4 (C_{Ar}-H), 121.3* (C_{Ar}-H), 115.8 (q, $^3J_{C-F}$ = 4.0 Hz, C_{Ar}-H), 113.2* (C_{Ar}-H), 113.2 (C_{Ar}-H), 68.4 (C_2), 64.0* (C_2), 60.1 (**C**H$_2$CH$_3$), 49.1 (C_5), 36.2 (C_3), 30.6 (C_4), 18.0* (CH**C**H$_3$), 13.6 (CH**C**H$_3$), 13.4 (CH$_2$**C**H$_3$), 13.4* (CH$_2$**C**H$_3$). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 3253 (NH), 2966 (NH), 2830 (C-H), 1681 (C=O), 1603 (C=N), 1277 (C=S), 1132 (C-N). MS (EI) m/z (%): 271 (100), 252 (26), 213 (26), 202 (11), 163 (13), 83 (84), 69 (16). HRMS: Calculated for $[C_{24}H_{25}N_4O_2SF_6]^+$: 547.1602 $[(M+H)^+]$; found: 547.1613. The ee was determined by HPLC using a Chiralpak IA column [n-hexane/iPrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 11.179 min, τ_{minor} = 8.525 min (For the major diastereisomer: 97% ee). $[\alpha]_D^{20}$: -87.7 (c = 0.75, CH_2Cl_2). M.p. (CH_2Cl_2): 190-192 ºC.

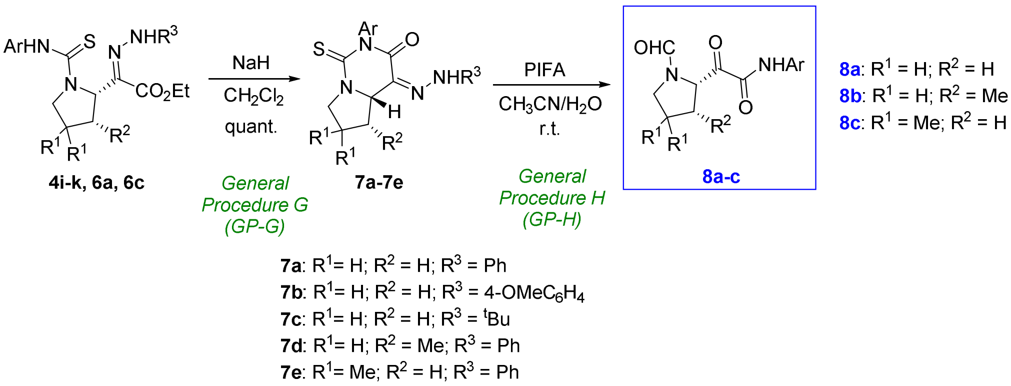


(2*S*/3*R*)-Ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]-3-ethylpyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate (6b). Following *GP-F*, **6b** (44.8 mg, 0.080 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 68h in 89% yield as a light yellow solid starting from ethyl (*E*)-2-(2-phenylhydrazono)acetate **1c** (17.2 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-4-ethyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **5b** (49.7 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.59 (hexanes/EtOAc 8:2). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (2.5:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.81 (s, 1H, NNH), 11.70* (s, 1H, NNH), 9.20* (s, 1H, CSNH), 9.14 (s, 1H, CSNH), 8.20 (s, 2H, C_{Ar}-H), 8.13* (s, 2H, C_{Ar}-H), 7.63 (s, 1H, C_{Ar}-H), 7.32-7.23 (m, 2H, C_{Ar}-H), 7.22* (d, J = 7.9 Hz, 2H, C_{Ar}-H), 7.18 (d, J = 7.9 Hz, 2H, C_{Ar}-H), 6.98-6.92 (m, C_{Ar}-H), 5.76-5.68 (m, 1H, C_2-H), 5.30-5.22* (m, 1H, C_2-H), 4.33 (q, J = 7.3 Hz, 2H, OC**H**$_2$CH$_3$), 4.23-4.12* (m, 2H, OC**H**$_2$CH$_3$), 4.08-4.02 (m, 1H, C_5-H_a), 3.97-3.88* (m, 2H, C_5-H), 3.83-3.73 (m, 1H, C_5-H_b), 2.46-2.37 (m, 1H, C_3-H), 2.32-2.21 (m, 1H, C_4-H_a), 2.12-1.97 (m, 1H, C_4-H_b), 1.85-1.74* (m, 1H, C_4-H_b), 1.66-1.43 (m, 1H, CHC**H**$_a$H$_b$CH$_3$), 1.33 (t, J = 7.3 Hz, 3H, OCH$_2$C**H**$_3$), 1.21-1.07 (m, 1H, CHCH$_a$**H**$_b$CH$_3$), 1.03* (t, J = 7.3 Hz, 3H, CHCH$_2$C**H**$_3$), 0.95 (t, J = 7.3 Hz, 3H, CHCH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 177.1 (CS), 161.8 (COO), 142.9 (C_{Ar}-C), 142.4 (CN), 129.3 (q, $^2J_{C-F}$ = 29.7 Hz, **C**CF$_3$), 128.7 (C_{Ar}-H), 128.6* (C_{Ar}-H), 128.4 (C_{Ar}-C), 122.7 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 123.8 (C_{Ar}-H), 121.4 (C_{Ar}-H), 121.3* (C_{Ar}-H), 115.8 (C_{Ar}-H), 113.2 (C_{Ar}-H), 66.3* (C_2), 63.3 (C_2), 60.1 (O**C**H$_2$CH$_3$), 59.3* (O**C**H$_2$CH$_3$), 49.0* (C_5), 48.5 (C_5), 45.2* (C_3), 44.0 (C_3), 28.3 (C_4), 21.7 (CH**C**H$_2$CH$_3$), 13.4 (OCH$_2$**C**H$_3$), 11.7 (CHCH$_2$**C**H$_3$), 11.1* (CHCH$_2$**C**H$_3$). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (CF_3). IR (ATR) cm^{-1}: 3257 (NH), 2966 (NH), 2872 (C-H), 1682 (C=O), 1603 (C=N), 1276 (C=S), 1129 (C-N). MS (EI) m/z (%): 271 (100), 252 (23), 213 (27), 163 (12), 83 (63), 69 (11). HRMS: Calculated for $[C_{25}H_{27}N_4O_2SF_6]^+$: 561.1759 $[(M+H)^+]$; found: 561.1769. The ee was determined by HPLC using a Chiralpak AD-H column [n-hexane/iPrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 20.686 min, τ_{minor} = 4.110 min (For the major diastereoisomer: >99% ee). $[\alpha]_D^{20}$: -254.2 (c = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 185-187 ºC.



(*S*)-Ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]-4,4-dimethylpyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate (6c). Following *GP-F*, **6c** (45.0 mg, 0.080 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 89% yield as a light yellow solid starting from ethyl (*E*)-2-(2-phenylhydrazono)acetate **1c** (17.2 mg, 0.09 mmol) and *N*-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **5c** (49.7 mg, 0.135 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. R_f: 0.67 (hexanes/EtOAc 7:3). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC): (*Z:E* ratio: 3.1:1, *denotes *E* diastereoisomer resonances) δ 11.63 (s, 1H, NNH), 9.97* (s, 1H, NNH), 9.37* (s, 1H, CSNH), 9.27 (s, 1H, CSNH), 8.19* (s, 2H, C_{Ar}-H), 8.11 (s, 2H, C_{Ar}-H), 7.62* (s, 1H, C_{Ar}-H), 7.59 (s, 1H, C_{Ar}-H), 7.29-7.17 (m, 4H, C_{Ar}-H), 6.97-6.84 (m, 1H, C_{Ar}-H), 5.73-5.62* (m, 1H, C_2-H), 5.50-5.40 (m, 1H, C_2-H), 4.34-4.26 (m, 2H, C**H**$_2$CH$_3$), 4.22-4.12* (m, 2H, C**H**$_2$CH$_3$), 3.93-3.82 (m, 1H, C_5-H_a), 3.74-3.62* (m, 2H, C_5-H), 3.62-3.54 (m, 1H, C_5-H_b), 2.27 (dd, *J* = 12.3, 8.2 Hz, 1H, C_3-H_a), 2.22-2.15* (m, 1H, C_3-H_a), 1.95 (dd, *J* = 12.5, 8.1 Hz, 1H, C_3-H_b), 1.91-1.84* (m, 1H, C_3-H_b), 1.34 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$), 1.25* (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$), 1.21* (s, 3H, CH$_3$), 1.19 (s, 3H, CH$_3$), 1.15* (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC): δ 178.4 (CS), 161.3 (COO), 144.1 (C_{Ar}-C), 142.9 (C_{Ar}-C), 142.4 (CN), 129.4 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, **C**CF$_3$), 128.6 (C_{Ar}-H), 128.3* (C_{Ar}-H), 123.0 (C_{Ar}-H), 122.7 (q, $^1J_{C\text{-}F}$ = 271.5 Hz, CF$_3$), 122.6* (C_{Ar}-H), 121.4 (C_{Ar}-H), 120.5* (C_{Ar}-H), 115.5 (C_{Ar}-H), 113.5* (C_{Ar}-H), 113.3 (C_{Ar}-H), 63.4 (C_5), 61.3 (C_2), 60.2 (**C**H$_2$CH$_3$), 59.3* (**C**H$_2$CH$_3$), 45.4 (C_3), 36.5 (C_4), 26.2 (CH$_3$), 25.8* (CH$_3$), 25.5 (CH$_3$), 25.0* (CH$_3$), 13.6* (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$). ^{19}F NMR (282MHz, DMSO-d_6): δ -61.6 (CF$_3$). IR (ATR) cm^{-1}: 3248 (NH), 2962 (NH), 2820 (C-H), 1681 (C=O), 1603 (C=N), 1276 (C=S), 1127 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (12), 83 (8). HRMS: Calculated for $[C_{25}H_{27}N_4O_2SF_6]^+$: 561.1759 $[(M+H)^+]$; found: 561.1769. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 4.858 min, τ_{minor} = 10.813 min (>99% ee). $[\alpha]_D^{20}$: +258.3 (*c* = 1.0, CH$_2$Cl$_2$). M.p. (CH$_2$Cl$_2$): 110-112 ºC.

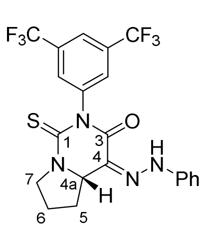
3.5. Oxidative cleavage of hydrazone moiety (Scheme 3)



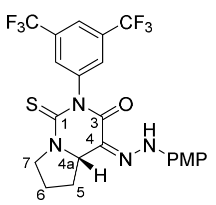
Scheme SI-7. Synthesis of α-ketoamides **8a-c**

General Procedure G (GP-G). Under inert atmosphere, to a stirred solution of hydrazone (0.38 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (4.2 mL), sodium hydride (0.46 mmol, 1.2 eq.) was added. The reaction mixture was allowed to stir at room temperature until completion of the reaction. Then, water was added and the mixture was extracted with CH$_2$Cl$_2$, washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo* and was used for the next step without further purification.

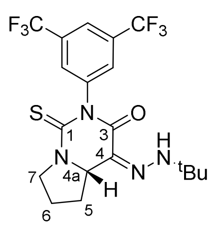
General Procedure H (GP-H). PIFA (0.696 mmol, 3 eq.) was added to a cooled solution (0 ºC) of **7a-e** (0.232 mmol, 1 eq.) in CH$_3$CN/H$_2$O (5/1). The reaction was allowed to stir at room temperature for 10 min and then the mixture was diluted with CH$_2$Cl$_2$, washed with saturated NaHCO$_3$ solution and water, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude mixture (**7a`-e`**) was redissolved in CH$_3$CN/H$_2$O (5/1) and cooled to 0 ºC. PIFA (0.27 mmol, 1.2 eq.) was added and the reaction was allowed to stir at room temperature for 10 min and then the mixture was diluted with CH$_2$Cl$_2$, washed with saturated NaHCO$_3$ solution and water, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel. After purification, the product racemizes with time.



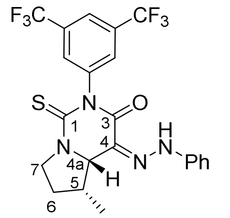
(*S*,*Z*)-2-[3,5-Bis(trifluoromethyl)phenyl]-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (7a). Following *GP-G*, **7a** (116 mg, 0.238 mmol) was isolated after 30 min in >99% yield as a yellow solid starting from (*S*)-ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate **4i** (129 mg, 0.24 mmol, >99% ee) and NaH (11.6 mg, 0.29 mmol, 60% in mineral oil) in CH_2Cl_2 (3.0 mL). R_f: 0.8 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.56 (s, 1H, NH), 7.94 (s, 1H, C_{Ar}-H), 7.73 (s, 2H, C_{Ar}-H), 7.34 (appt t, *J* = 7.7 Hz, 2H, C_{Ar}-H), 7.20 (d, *J* = 8.0 Hz, 2H, C_{Ar}-H), 7.07 (appt t, *J* = 7.2 Hz, 1H, C_{Ar}-H), 4.71 (dd, *J* = 9.8, 5.9 Hz, 1H, C_{4a}-H), 4.15-4.02 (m, 1H, C_7-H_a), 3.99-3.82 (m, 1H, C_7-H_b), 2.80-2.68 (m, 1H, C_5-H_a), 2.45-2.06 (m, 3H, C_5-H_b + C_6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5 (C_1), 158.5 (C_3), 142.3 (C_{Ar}-C), 139.5 (C_4), 132.3 (q, $^2J_{C-F}$ = 34.0 Hz, **C**CF_3), 131.0 (C_{Ar}-H), 129.7 (C_{Ar}-H), 124.0 (C_{Ar}-H), 123.1 (q, $^1J_{C-F}$ = 272.6 Hz, CF_3), 122.7 (q, $^3J_{C-F}$ = 3.5 Hz, C_{Ar}-H), 120.8 (C_{Ar}-C), 114.6 (C_{Ar}-H), 61.1 (C_{4a}), 53.5 (C_7), 31.1 (C_5), 22.6 (C_6). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.7 (CF_3). IR (ATR) cm^{-1}: 2930 (NH), 1660 (C=O), 1548 (C=N), 1277 (C=S), 1122 (C-N). MS (EI) *m/z* (%): 486 (M^+, 100), 381 (19), 252 (11), 207 (16), 77 (45), 69 (11). HRMS: Calculated for $[C_{21}H_{17}N_4OSF_6]^+$: 487.1027 [$(M+H)^+$]; found: 487.1026. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/min; τ_{major} = 6.439 min, τ_{minor} = 7.654 min (>99% ee). $[\alpha]_D^{20}$: -186.5 (*c* = 0.8, CH_2Cl_2). M.p. (CH_2Cl_2): 176-178 ºC.



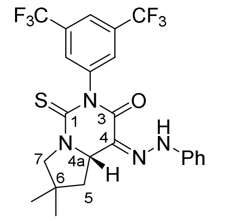
(*S*,*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-4-[2-(4-methoxyphenyl)hydrazono]-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (7b). Following *GP-G*, **7b** (91.7 mg, 0.177 mmol) was isolated after 30 min in >99% yield as a yellow solid starting from (*S*)-ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-[2-(4-methoxyphenyl)hydrazono]acetate **4j** (100 mg, 0.177 mmol, 98% ee) and NaH (8.5 mg, 0.21 mmol, 60% in mineral oil) in CH_2Cl_2 (2.0 mL). R_f: 0.51 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.63 (s, 1H, NH), 7.93 (s, 1H, C_{Ar}-H), 7.73 (s, 2H, C_{Ar}-H), 7.15 (d, *J* = 9.0 Hz, 2H, C_{Ar}-H), 6.89 (d, *J* = 9.0 Hz, 2H, C_{Ar}-H), 4.70 (dd, *J* = 9.9, 5.9 Hz, 1H, C_{4a}-H), 4.14-4.02 (m, 1H, C_7-H_a), 3.98-3.78 (m, 4H, C_7-H_b + OCH_3), 2.79-2.66 (m, 1H, C_5-H_a), 2.42-2.05 (m, 3H, C_5-H_b + C_6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5 (C_1), 158.6 (C_3), 156.6 (C_{Ar}-C), 139.6 (C_4), 136.1 (C_{Ar}-C), 132.3 (q, $^2J_{C-F}$ = 33.9 Hz, **C**CF_3), 131.0 (C_{Ar}-H), 123.1 (q, $^1J_{C-F}$ = 271.9 Hz, CF_3), 122.6 (q, $^3J_{C-F}$ = 3.8 Hz, C_{Ar}-H), 119.5 (C_{Ar}-C), 115.9 (C_{Ar}-H), 115.0 (C_{Ar}-H), 61.0 (C_{4a}), 55.7 (OCH_3), 53.5 (C_7), 31.2 (C_5), 22.6 (C_6). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.7 (CF_3). IR (ATR) cm^{-1}: 2917 (NH), 2847 (C-H), 1741 (C=O), 1514 (C=N), 1279 (C=S), 1124 (C-N). MS (EI) *m/z* (%): 271 (100), 252 (31), 213 (27), 202 (14), 163 (16), 108 (10), 83 (100), 69 (15). HRMS: Calculated for $[C_{22}H_{19}N_4O_2SF_6]^+$: 517.1133 [$(M+H)^+$]; found: 517.1122. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 6.642 min, τ_{minor} = 7.732 min (96% ee). $[\alpha]_D^{20}$: -191.3 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 178-180 ºC.



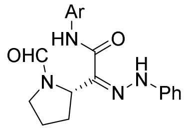
(*S*,*Z*)-2-[3,5-Bis(trifluoromethyl)phenyl]-4-[2-(*tert*-butyl)hydrazono]-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (7c). Following *GP-G*, **7c** (121 mg, 0.261 mmol) was isolated after 30 min in 91% yield as a light yellow solid starting from (*S*)-ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-[2-(*tert*-butyl)hydrazono]acetate **4k** (147 mg, 0.287 mmol, 91% ee) and NaH (13.8 mg, 0.43 mmol, 60% in mineral oil) in CH_2Cl_2 (1.8 mL). R_f: 0.68 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.88 (s, 1H, NH), 7.90 (s, 1H, C_{Ar}-H), 7.71 (s, 2H, C_{Ar}-H), 4.59 (dd, *J* = 9.2, 6.1 Hz, 1H, C_{4a}-H), 4.08-3.96 (m, 1H, C_7-H_a), 3.94-3.78 (m, 1H, C_7-H_b), 2.66-2.52 (m, 1H, C_5-H_a), 2.29-1.97 (m, 3H, C_5-H_b + C_6-H), 1.28 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7 (C_1), 158.3 (C_3), 139.9 (C_4), 132.1 (q, $^2J_{C-F}$ = 33.7 Hz, **C**CF_3), 131.2 (C_{Ar}-H), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 122.4 (q, $^3J_{C-F}$ = 3.7 Hz, C_{Ar}-H), 116.6 (C_{Ar}-C), 61.0 (C_{4a}), 56.0 (**C**$(CH_3)_3$), 53.3 (C_7), 31.1 (C_5), 28.7 (C(**C**$H_3)_3$), 22.6 (C_6). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.7 (CF_3). IR (ATR) cm^{-1}: 2925 (NH), 2883 (C-H), 1658 (C=O), 1538 (C=N), 1274 (C=S), 1120 (C-N). MS (EI) *m/z* (%): 466 (M^+, 100), 451 (45), 381 (22), 252 (12), 213 (12), 152 (16), 82 (17), 69 (12), 57 (35). HRMS: Calculated for $[C_{19}H_{21}N_4OSF_6]^+$: 467.1340 [$(M+H)^+$]; found: 467.1348. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*PrOH (95:05)]; flow rate 0.70 mL/min; τ_{major} = 5.416 min, τ_{minor} = 4.948 min (87% ee). $[\alpha]_D^{20}$: -20.8 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 197-199 ºC.



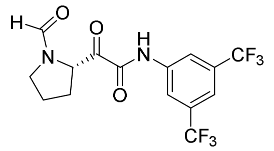
(4a*S*,5*R*,*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-5-methyl-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (7d). Following *GP-G*, **7d** (46.7 mg, 0.093 mmol) was isolated after 30 min in >99% yield as an orange solid starting from a mixture of diastereoisomers 3.2:1 of (2*S*,3*R*)-ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]-3-methylpyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate **6a** (51.2 mg, 0.094 mmol, 97% ee) and NaH (5.6 mg, 0.14 mmol, 60% in mineral oil) in CH_2Cl_2 (0.6 mL). ^{1}H NMR (300 MHz, $CDCl_3$): (3.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 12.90 (s, 1H, NH), 12.57* (s, 1H, NH), 7.94 (s, 1H, C_{Ar}-H), 7.73 (s, 2H, C_{Ar}-H), 7.34 (appt t, *J* = 7.8 Hz, 2H, C_{Ar}-H), 7.20 (d, *J* = 8.0 Hz, 2H, C_{Ar}-H), 7.08 (appt t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 4.78 (d, *J* = 4.6 Hz, 1H, C_{4a}-H), 4.69* (d, *J* = 4.2 Hz, 1H, C_{4a}-H), 4.17-4.08* (m, 1H, C_7-H), 4.01 (dd, *J* = 10.5, 4.4 Hz, 1H, C_7-H), 3.25-3.12* (m, 1H, C_5-H), 3.10-2.98 (m, 1H, C_5-H), 2.34-2.17 (m, 1H, C_6-H_a), 2.01-1.90 (m, 1H, C_6-H_b), 1.13 (d, *J* = 6.9 Hz, 3H, CH_3), 1.02* (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8 (C_1), 158.7 (C_3), 142.3 (C_{Ar}-C), 139.7 (C_4), 132.4 (q, $^2J_{C\text{-}F}$ = 33.4 Hz, **C**CF_3), 130.9 (C_{Ar}-H), 129.7 (C_{Ar}-H), 124.1 (C_{Ar}-H), 123.1 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, CF_3), 122.7 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, C_{Ar}-H), 118.6 (C_{Ar}-C), 114.7 (C_{Ar}-H), 114.6* (C_{Ar}-H), 65.5* (C_{4a}), 64.5 (C_{4a}), 51.8 (C_7), 36.4 (C_5), 29.8 (C_6), 14.3* (CH_3), 14.0 (CH_3). ^{19}F NMR (282MHz, $CDCl_3$): δ -62.8* (CF_3), -62.7 (2 × CF_3). IR (ATR) cm^{-1}: 2973 (NH), 2876 (C-H), 1665 (C=O), 1552 (C=N), 1275 (C=S), 1124 (C-N). MS (EI) *m*/*z* (%): 500 (M^+, 100), 395 (10), 252 (15), 207 (31), 92 (22), 77 (39), 65 (17). HRMS: Calculated for $[C_{22}H_{19}N_4OSF_6]^+$: 501.1184 $[(M+H)^+]$; found: 501.1186. The ee was determined by HPLC using a Chiralpak IE-3 column [*n*-hexane/*i*PrOH (95:05)]; flow rate 0.70 mL/min; τ_{major} = 6.953 min, τ_{minor} = 7.400 min (For the major diastereoisomer: 96% ee). $[\alpha]_D^{20}$: -55.7 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): Decomposition before melting.



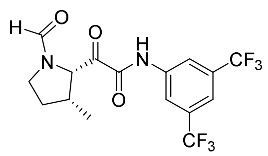
(*S*,*Z*)-2-[3,5-Bis(trifluoromethyl)phenyl]-6,6-dimethyl-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (7e). Following *GP-G*, **7e** (104 mg, 0.20 mmol) was isolated after 30 min in >99% yield as an orange solid starting from (*S*)-ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]-4,4-dimethylpyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate **6c** (114 mg, 0.20 mmol, >99% ee) and NaH (9.8 mg, 0.24 mmol, 60% in mineral oil) in CH_2Cl_2 (1.4 mL). R_f: 0.67 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): (*Z:E* ratio: 8.9:1, *denotes *E* diastereoisomer resonances) δ 12.52 (s, 1H, NH), 8.47* (s, 1H, NH), 7.95 (s, 1H, C_{Ar}-H), 7.92* (s, 1H, C_{Ar}-H), 7.76 (s, 2H, C_{Ar}-H), 7.72* (s, 2H, C_{Ar}-H), 7.40-7.30 (m, 2H, C_{Ar}-H), 7.24-7.17 (m, 2H, C_{Ar}-H), 7.07 (appt t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 4.92 (dd, *J* = 10.2, 6.1 Hz, 1H, C_{4a}-H), 3.86 (d, *J* = 12.9 Hz, 1H, C_7-H_a), 3.70 (d, *J* = 12.9 Hz, C_7-H_b), 2.46 (dd, *J* = 12.8, 6.1 Hz, C_5-H_a), 2.30 (dd, *J* = 12.8, 10.2 Hz, C_5-H_b), 1.31 (s, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5 (C_1), 158.5 (C_3), 142.3 (C_{Ar}-C), 139.4 (C_4), 132.3 (q, $^2J_{C\text{-}F}$ = 34.0 Hz, **C**CF_3), 131.0 (C_{Ar}-H), 129.6 (C_{Ar}-H), 123.9 (C_{Ar}-H), 123.1 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, CF_3), 122.6 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, C_{Ar}-H), 120.9 (C_{Ar}-C), 114.5 (C_{Ar}-H), 66.1 (C_7), 60.0 (C_{4a}), 44.4 (C_5), 36.4 (C_6), 27.7 (CH_3), 27.5 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.7 (CF_3). IR (ATR) cm^{-1}: 2962 (NH), 2872 (C-H), 1659 (C=O), 1543 (C=N), 1275 (C=S), 1127 (C-N). MS (EI) *m*/*z* (%): 514 (M^+, 100), 409 (52), 252 (13), 207 (15), 135 (19), 123 (37), 92 (33), 77 (64), 65 (27). HRMS: Calculated for $[C_{23}H_{21}N_4OSF_6]^+$: 515.1340 $[(M+H)^+]$; found: 515.1348. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (95:05)]; flow rate 0.70 mL/min; τ_{major} = 6.344 min, τ_{minor} = 15.231 min (>99% ee). $[\alpha]_D^{20}$: -63.6 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 184-186 ºC.



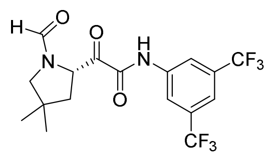
(*S*,*Z*)-*N*-[3,5-bis(trifluromethyl)phenyl]-2-(1-formylpyrrolidin-2-yl)-2-(2-phenylhydrazono)acetamide (7a'). PIFA (309 mg, 0.696 mmol) was added to a cooled (0 ºC) solution of (*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **7a** (113 mg, 0.232 mmol, >99% ee) in CH_3CN/H_2O (0.9/0.2 mL). The reaction was allowed to stir at room temperature for 10 min and then the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was used for the next step without further purification, in this case affording 108 mg of **7a'** (0.23 mmol, 99%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.84 (s, 1H, NNH), 11.74 (s, 1H, NHAr), 8.27 (s, 3H, C_{Ar}-H + CHO), 7.64 (s, 1H, C_{Ar}-H), 7.35 (appt t, *J* = 7.5 Hz, 2H, C_{Ar}-H), 7.20 (d, *J* = 7.5 Hz, 2H, C_{Ar}-H), 7.03 (appt t, *J* = 7.5 Hz, 1H, C_{Ar}-H), 5.23 (dd, *J* = 8.3, 2.7 Hz, 1H, C_2-H), 3.85-3.63 (m, 2H, C_5-H), 2.70-2.61 (m, 1H, C_3-H_a), 2.54-2.42 (m, 1H, C_4-H_a), 2.25-2.14 (m, 1H, C_3-H_b), 2.14-2.04 (m, 1H, C_4-H_b). ^{13}C NMR (75 MHz, CDCl3): δ 163.6 (CO), 162.7 (CHO), 143.3 (CN), 140.1 (C_{Ar}-C), 132.3 (q, $^2J_{C\text{-}F}$ = 33.4 Hz, **C**CF_3), 129.6 (C_{Ar}-H), 128.1 (C_{Ar}-C), 123.2 (q, $^1J_{C\text{-}F}$ = 272.7 Hz, CF_3), 122.7 (C_{Ar}-H), 120.3 (C_{Ar}-H), 117.5 (C_{Ar}-H), 114.0 (C_{Ar}-H), 55.0 (C_2), 46.5 (C_5), 30.4 (C_3), 24.0 (C_4). ^{19}F NMR (282MHz, $CDCl_3$): δ -62.9 (CF_3). IR (ATR) cm^{-1}: 2962 (NH), 1635 (C=O), 1534 (C=N), 1123 (C-N). HRMS: Calculated for $[C_{21}H_{19}N_4O_2F_6]^+$: 473.1412 [$(M+H)^+$]; found: 473.1411. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 5.106 min, τ_{minor} = 5.663 min (>99% ee). $[\alpha]_D^{20}$: -261.9 (*c* = 0.57, CH_2Cl_2). M.p. (CH_2Cl_2): 140-142 ºC.



(*S*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-2-(1-formylpyrrolidin-2-yl)-2-oxoacetamide (8a). Following *GP-H*, **8a** (43.2 mg, 0.11 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 67% yield as a white foam starting from (*S*,*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **7a** (80 mg, 0.164 mmol, >99% ee) and PIFA (218 mg, 0.492 mmol + 87.5 mg, 0.197 mmol) in CH_3CN/H_2O (0.7/0.2 mL). ^{1}H NMR (300 MHz, $CDCl_3$): (3.7:1 rotamer ratio, *denotes minor rotamer resonances) δ 9.36* (bs,1H, NH), 9.21 (bs, 1H, NH), 8.28 (s, 1H, NCHO), 8.21* (s, 2H, C_{Ar}-H), 8.16 (s, 2H, C_{Ar}-H), 8.13* (s, 1H, NCHO), 7.69* (s, 1H, C_{Ar}-H), 7.65 (s, 1H, C_{Ar}-H), 5.42* (dd, *J* = 9.2, 4.2 Hz, 1H, C_2-H), 5.33-5.23 (m, 1H, C_2-H), 3.78-3.69 (m, 2H, C_5-H), 2.64-2.56* (m, 1H, C_3-H_a), 2.55-2.40 (m, 1H, C_3-H_a), 2.15-1.95 (m, 3H, C_3-H_b + C_4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8* (CO), 194.1 (CO), 161.9* (NCHO), 160.7 (NCHO), 157.8 (CONH), 157.3* (CONH), 138.0 (C_{Ar}-C), 137.8* (C_{Ar}-C), 133.6* (q, $^2J_{C-F}$ = 33.4 Hz, **C**CF_3), 132.7 (q, $^2J_{C-F}$ = 33.8 Hz, 2 × **C**CF_3), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 119.9 (q, $^3J_{C-F}$ = 3.8 Hz, C_{Ar}-H), 118.7 (q, $^3J_{C-F}$ = 3.8 Hz, C_{Ar}-H), 61.0* (C_2), 58.5 (C_2), 46.7 (C_5), 44.4* (C_5), 29.3* (C_3), 28.9 (C_3), 24.7 (C_4), 22.8* (C_4). ^{19}F NMR (282MHz, $CDCl_3$): δ -63.1 (CF_3). IR (ATR) cm^{-1}: 2961 (NH), 2886 (C-H), 1653 (C=O), 1126 (C-N). MS (EI) *m*/*z* (%): 255 (56), 207 (17), 98 (100), 83 (12), 69 (31). HRMS: Calculated for $[C_{15}H_{13}N_2O_3F_6]^+$: 383.0830 [$(M+H)^+$]; found: 383.0833. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 6.548 min, τ_{minor} = 5.993 min (99% ee). $[\alpha]_D^{20}$: -40.7 (*c* = 1.0, CH_2Cl_2).



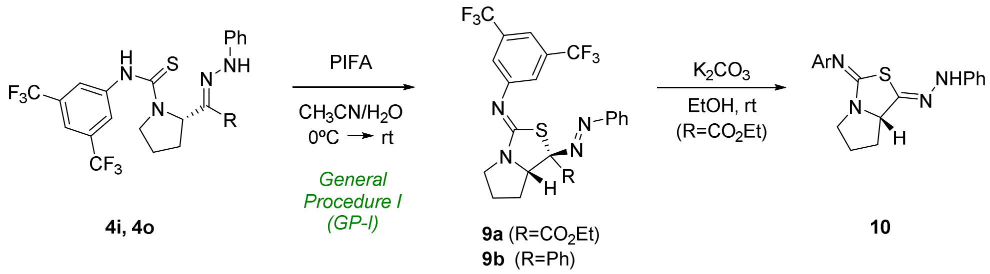
(*S*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-2-[(2*S*,3*R*)-1-formyl-3-methylpyrrolidin-2-yl]-2-oxoacetamide (8b). Following *GP-H*, **8b** (17.2 mg, 0.043 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 60% yield as a yellow foam starting from (4a*S*,5*R*,*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-5-methyl-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **7d** (36.3 mg, 0.073 mmol, 96% ee) and PIFA (96.4 mg, 0.22 mmol + 38.6 mg, 0.087 mmol) in CH_3CN/H_2O (0.4/0.1 mL). ^{1}H NMR (300 MHz, $CDCl_3$): (7.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.17 (bs, 1H, NH), 8.20 (s, 1H, NCHO), 8.15 (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 4.75 (d, *J* = 7.0 Hz, 1H, C_2-H), 3.82-3.70 (m, 2H, C_5-H), 2.58-2.42 (m, 1H, C_3-H), 2.28-2.13 (m, 1H, C_4-H_a), 1.82-1.65 (m, 1H, C_4-H_b), 1.33* (d, *J* = 7.0 Hz, 3H, CH_3), 1.27 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (CO), 160.8 (NCHO), 158.1 (CONH), 138.1 (C_{Ar}-C), 137.7* (C_{Ar}-C), 132.7 (q, $^2J_{C-F}$ = 33.6 Hz, **C**CF_3), 123.0 (q, $^1J_{C-F}$ = 273.1 Hz, CF_3), 119.9 (C_{Ar}-H), 118.7 (q, $^3J_{C-F}$ = 3.6 Hz, C_{Ar}-H), 62.9* (C_2), 60.6 (C_2), 45.7 (C_5), 43.7* (C_5), 38.1* (C_3), 36.7 (C_3), 32.4 (C_4), 30.8* (C_4), 15.2* (CH_3), 14.9 (CH_3). ^{19}F NMR (282MHz, $CDCl_3$): δ -63.1 (CF_3). IR (ATR) cm^{-1}: 2973 (NH), 2887 (C-H), 1652 (C=O), 1126 (C-N). MS (EI) *m*/*z* (%): 255 (68), 236 (30), 207 (29), 112 (100), 83 (39), 69 (37). HRMS: Calculated for $[C_{16}H_{15}N_2O_3F_6]^+$: 397.0987 [$(M+H)^+$]; found: 397.0988; The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 10.119 min, τ_{minor} = 9.370 min (For the major diastereisomer: 96% ee). $[\alpha]_D^{20}$: -15.7 (*c* = 0.85, CH_2Cl_2).



(*S*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-2-(1-formyl-4,4-dimethylpyrrolidin-2-yl)-2-oxoacetamide (8c). Following *GP-H*, **8c** (50.1 mg, 0.122 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 63% yield as a yellow foam starting from (*S*,*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-6,6-dimethyl-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **7e** (100 mg, 0.194 mmol, >99% ee) and PIFA (258 mg, 0.582 mmol + 103 mg, 0.233 mmol) in CH_3CN/H_2O (0.8/0.2 mL). ^{1}H NMR (300 MHz, $CDCl_3$): (3.0:1 rotamer ratio, *denotes minor rotamer resonances) δ 9.21 (bs, 1H, NH), 9.11* (bs, 1H, NH), 8.27 (s, 1H, NCHO), 8.22* (s, 1H, NCHO), 8.21* (s, 2H, C_{Ar}-H), 8.17 (s, 2H, C_{Ar}-H), 7.70* (s, 1H, C_{Ar}-H), 7.66 (s, 1H, C_{Ar}-H), 5.46-5.38* (m, 1H, C_2-H), 5.33-5.24 (m, 1H, C_2-H), 3.78-3.68 (m, 2H, C_5-H), 2.52-2.41 (m, 1H, C_3-H_a), 2.07-2.04 (m, 1H, C_3-H_b), 1.91* (s, 6H, $C(CH_3)_2$), 1.34 (s, 6H, $C(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8* (CO), 194.0 (CO), 169.9* (NCHO), 161.7* (CONH), 160.7 (NCHO), 157.7 (CONH), 138.0 (C_{Ar}-C), 137.7* (C_{Ar}-C), 132.7 (q, $^2J_{C-F}$ = 33.7 Hz, **C**CF_3), 123.1 (q, $^1J_{C-F}$ =

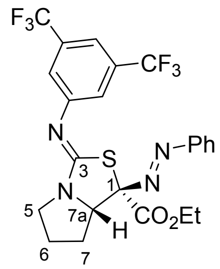
272.7 Hz, CF_3), 119.9 (q, $^3J_{C\text{-}F}$ = 3.3 Hz, C_{Ar}-H), 118.7 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C_{Ar}-H), 60.9* (C_2), 58.5 (C_2), 51.5 (C_4), 46.7 (C_5), 44.4* (C_5), 28.9 ($C(CH_3)_2$), 24.7 (C_3), 24.6* ($C(CH_3)_2$), 22.8* (C_3). ^{19}F NMR (282MHz, $CDCl_3$): δ -63.1 (CF_3). IR (ATR) cm^{-1}: 2965 (NH), 2877 (C-H), 1658 (C=O), 1128 (C-N). MS (EI) *m/z* (%): 380 (17), 281 (16), 255 (72), 236 (41), 207 (31), 186 (15), 152 (57), 108 (100), 81 (23), 69 (25). The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 6.502 min, τ_{minor} = 5.960 min (90% ee). $[\alpha]_D^{20}$: -27.5 (*c* = 1.0, CH_2Cl_2).

3.6. Chemical manipulation of adducts 4 (Scheme 4)

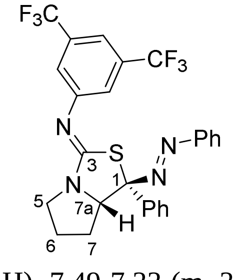


Scheme SI-8. Derivatization of adducts **4i** and **4o**

General Procedure I (GP-I). To a stirred solution of hydrazone (0.43 mmol, 1.0 eq.) in CH_3CN/H_2O (1.4/0.25 mL) at 0 °C, was added [bis(trifluoroacetoxy)iodo]benzene (0.86 mmol, 2.0 eq.). The reaction mixture was allowed to stir at room temperature for 15 min. Then, the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ aqueous solution and water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

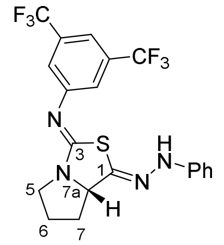


Ethyl (1*S*,7*aS*,*Z*)-3-{[3,5-bis(trifluoromethyl)phenyl]imino}-1-[(*E*)-phenyldiazenyl]tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-1-carboxylate (9a). Following *GP-I*, **9a** (72.8 mg, 0.137 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 15min in 73% yield as an orange solid starting from (*S*)-ethyl-(*Z*)-2-{1-[(3,5-bis(trifluoromethyl)phenyl)carbamothioyl]pyrrolidin-2-yl}-2-(2-phenylhydrazono)acetate **4i** (100 mg, 0.188 mmol, >99% ee) and PIFA (166.5 mg, 0.376 mmol) in CH_3CN/H_2O (0.7/0.12 mL). R_f: 0.7 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82-7.69 (m, 2H, C_{Ar}-H), 7.60-7.50 (m, 4H, C_{Ar}-H), 7.46 (s, 2H, C_{Ar}-H), 5.04 (appt t, *J* = 6.8 Hz, 1H, C_2-H), 4.43-4.16 (m, 2H, C**H**$_2$CH$_3$), 3.77-3.58 (m, 1H, C_5-H_a), 3.56-3.36 (m, 1H, C_5-H_b), 2.26-1.88 (m, 4H, C_3-H + C_4-H), 1.28 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7 (COO), 155.1 (C_{Ar}-C), 152.5 (C_{Ar}-C), 150.8 (CN), 132.6 (C_{Ar}-H), 132.2 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, **C**CF$_3$), 129.5 (C_{Ar}-H), 123.6 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, CF_3), 123.3 (C_{Ar}-H), 122.7 (q, $^3J_{C\text{-}F}$ = 3.4 Hz, C_{Ar}-H), 116.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C_{Ar}-H), 88.5 (**C**COO), 70.2 (C_2), 63.0 (**C**H$_2$CH$_3$), 46.1 (C_5), 27.6 (C_4), 24.5 (C_3), 14.2 (CH$_2$**C**H$_3$). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.9 (CF_3). IR (ATR) cm^{-1}: 2887 (C-H), 1737 (C=O), 1602 (C=N), 1125 (C-N). MS (EI) *m/z* (%): 502 (29), 429 (58), 387 (10), 194 (26), 158 (17), 121 (100), 77 (6). HRMS: Calculated for $[C_{23}H_{21}N_4O_2SF_6]^+$: 531.1289 [$(M+H)^+$]; found: 531.1312. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/min; τ_{major} = 5.707 min, τ_{minor} = 5.306 min (>99% ee). $[\alpha]_D^{20}$: -275.9 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 127-129 ºC.

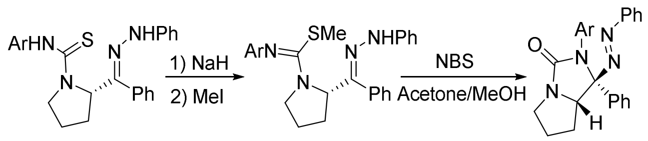


(1*R*,7a*S*,*Z*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-1-phenyl-1-[(*E*)-phenyldiazenyl]tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-3-imine (9b). Following *GP-I*, **9b** (37.6 mg, 0.07 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 15min in 90% yield as an orange solid starting from (*S*)-(*Z*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-2-[phenyl(2-phenylhydrazono)pyrrolidine]-1-carbothioamide **4o** (41.8 mg, 0.078 mmol, 90% ee) and PIFA (69.1 mg, 0.156 mmol) in CH_3CN/H_2O (1.2/0.24 mL). R_f: 0.57 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7.80 (m, 2H, C_{Ar}-H), 7.69-7.60 (m, 4H, C_{Ar}-H), 7.60-7.50 (m, 4H, C_{Ar}-H), 7.49-7.33 (m, 3H, C_{Ar}-H), 5.04 (appt t, *J* = 7.1 Hz, 1H, C_{7a}-H), 3.63-3.49 (m, 1H, C_5-H_a), 3.49-3.34 (m, 1H, C_5-H_b), 2.48-2.29 (m, 1H, C_6-H_a), 2.26-1.85 (m, 3H, C_6-H_b + C_7-H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8 (C_{Ar}-C), 152.7 (C_{Ar}-C), 151.0 (C_3), 136.8 (C_{Ar}-H), 132.0 (C_{Ar}-H), 131.9 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, **C**CF$_3$), 129.4 (C_{Ar}-H), 128.9 (C_{Ar}-H), 127.5 (C_{Ar}-H), 123.6 (q, $^1J_{C\text{-}F}$ = 272.7 Hz, CF_3), 123.2 (C_{Ar}-H), 122.8 (q, $^3J_{C\text{-}F}$ = 2.9 Hz, C_{Ar}-H), 116.3-115.9 (m, C_{Ar}-H), 91.4 (C_1), 74.5 (C_{7a}), 45.7 (C_5), 27.2 (C_6), 23.8 (C_7). ^{19}F NMR (282

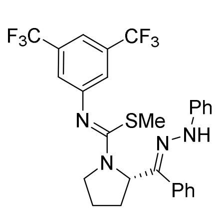
MHz, $CDCl_3$): δ -62.8 (CF_3). IR (ATR) cm^{-1}: 2877 (C-H), 1595 (C=N), 1125 (C-N). MS (EI) *m/z* (%): 502 (73), 398 (24), 330 (100), 213 (12), 115 (24), 77 (85), 69 (24). HRMS: Calculated for $[C_{26}H_{21}N_4SF_6]^+$: 535.1391 $[(M+H)^+]$; found: 535.1400. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 4.544 min, τ_{minor} = 5.694 min (90% ee). $[\alpha]_D^{20}$: -193.9 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 50-52 ºC.



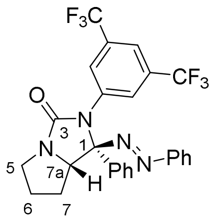
(*S*,1*Z*,3*Z*)-*N*-[3,5-bis(trofluoromethyl)phenyl]-1-(2-phenylhydrazono)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-imine (10). K_2CO_3 (14.7 mg, 0.107 mmol) is added to a cooled solution (0 ºC) of ethyl (1*S*,7*aS*,*E*/*Z*)-3-{[3,5-bis(trifluoromethyl)phenyl]imino}-1-[(*E*)-phenyldiazenyl]tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-1-carboxylate **9a** (56.5 mg, 0.107 mmol, >99% ee) in ethanol (0.9 mL). The reaction was allowed to stir at room temperature for 6 hours and then quenched with NH_4Cl. The crude product was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel to afford 43.4 mg of **10** (0.095 mmol, 88%) as an orange solid. R_f: 0.81 (hexanes/EtOAc 8:2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (s, 1H, C_{Ar}-H), 7.41 (s, 2H, C_{Ar}-H), 7.31-7.19 (m, 2H, C_{Ar}-H), 6.99 (d, *J* = 7.7 Hz, 2H, C_{Ar}-H), 6.91 (appt t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 6.45 (bs, 1H, NH), 4.85 (dd, *J* = 9.9, 5.9 Hz, 1H, C_{7a}-H), 3.98-3.83 (m, 1H, C_5-H_a), 3.60-3.46 (m, 1H, C_5-H_b), 2.46-2.14 (m, 3H, C_6-H_a + C_7-H), 1.98-1.80 (m, 1H, C_6-H_b). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8 (C_3), 152.2 (C_1), 144.7 (C_{Ar}-C), 137.6 (C_{Ar}-C), 132.5 (q, $^2J_{C\text{-}F}$ = 33.2 Hz, **C**CF_3), 129.4 (C_{Ar}-H), 123.4 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, CF_3), 122.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C_{Ar}-H), 121.2 (C_{Ar}-H), 117.1 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C_{Ar}-H), 113.5 (C_{Ar}-H), 69.1 (C_{7a}), 47.9 (C_5), 30.4 (C_7), 26.4 (C_6). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.9 (CF_3). IR (ATR) cm^{-1}: 2989 (NH), 1601 (C=N), 1121 (C-N). MS (EI) *m/z* (%): 458 (96), 353 (10), 271 (100), 252 (30), 213 (35), 202 (10), 163 (19), 143 (11), 93 (47), 77 (52), 69 (22). HRMS: Calculated for $[C_{20}H_{17}N_4SF_6]^+$: 459.1078 $[(M+H)^+]$; found: 459.1088. The ee was determined by HPLC using a Chiralpak ID-3 column [*n*-hexane/*i*PrOH (98:02)]; flow rate 0.70 mL/min; τ_{major} = 8.310 min, τ_{minor} = 11.439 min (>99% ee). $[\alpha]_D^{20}$: +253.5 (*c* = 0.46, CH_2Cl_2). M.p. (CH_2Cl_2): 86-88 ºC.



Scheme SI-9. Derivatization of adducts **4o**



Methyl-(*S*,*Z*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-2-[(*E*)-phenyl(2-phenylhydrazineylidine)methyl]pyrrolidine-1-carbimidothioate (11). To a solution of **4o** (100 mg, 0.186 mmol, 90% ee) in CH_2Cl_2 (2.0 mL) at 0 ºC, sodium hydride (9.0 mg, 0.224 mmol, 60% in mineral oil) was added. After being stirred for 30 min at 0 ºC, methyl iodide (12.8 µL, 0.205 mmol) was added and the reaction was stirred 3 hours at room temperature. Then, the reaction mixture was washed with water and brine, and extracted with EtOAc (3 x 2 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 76.3 mg of **11** (0.139 mmol, 75%) as a yellow solid. R_f: 0.89 (hexanes/EtOAc 8:2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.59-7.44 (m, 3H, C_{Ar}-H), 7.44-7.34 (m, 6H, C_{Ar}-H + NH), 7.32-7.20 (m, 2H, C_{Ar}-H), 7.05-6.99 (m, 2H, C_{Ar}-H), 6.86 (appt t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 5.23-5.14 (m, 1H, C_2-H), 3.97-3.85 (m, 1H, C_5-H_a), 3.81-3.67 (m, 1H, C_5-H_b), 2.25-1.98 (m, 4H, C_3-H + C_4-H), 1.89 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5 (NCN), 151.4 (C_{Ar}-C), 145.2 (C_{Ar}-C), 145.0 (CNN), 132.6 (C_{Ar}-C), 131.9 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, **C**CF_3), 129.8 (C_{Ar}-H), 129.6 (C_{Ar}-H), 129.3 (C_{Ar}-H), 128.0 (C_{Ar}-H), 123.7 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, CF_3), 121.9 (C_{Ar}-H), 120.1 (C_{Ar}-H), 114.1 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C_{Ar}-H), 112.7 (C_{Ar}-H), 64.9 (C_2), 49.9 (C_5), 30.2 (C_3), 22.8 (C_4), 16.0 (SCH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.9 (CF_3). IR (ATR) cm^{-1}: 2976 (NH), 2875 (C-H), 1601 (C=N), 1124 (C-N). MS (EI) *m/z* (%): 502 (71), 398 (25), 330 (100), 207 (15), 215 (24), 77 (81), 69 (23). HRMS: Calculated for $[C_{27}H_{25}N_4SF_6]^+$: 551.1704 $[(M+H)^+]$; found: 551.1711. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*PrOH (99:01)]; flow rate 0.70 mL/min; τ_{major} = 10.461 min, τ_{minor} = 11.362 min (88% ee). $[\alpha]_D^{20}$: -93.3 (*c* = 1.0, CH_2Cl_2). M.p. (CH_2Cl_2): 82-84 ºC.



(1*S*,7a*S*,*E*)-2-[3,5-bis(trifluoromethyl)phenyl]-1-phenyl-1-(phenyldiazenyl)hexahydro-3*H*-pyrrolo[1,2-*c*]imidazol-3-one (12). Powered *N*-bromosuccinimide (52.3 mg, 0.291 mmol) was added at 0 ºC to an stirred 50% acetone-MeOH (0.2 mL-0.2 mL) solution of **11** (40.0 mg, 0.073 mmol, 88% ee). The reaction mixture was allowed to stir at room temperature for 30 min and water was added. The crude product was extracted with CH_2Cl_2 (3 x 1 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 22.0 mg of **12** (0.042 mmol, 58%) as an orange oil. R_f: 0.43 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.79 (m, 2H, C_{Ar}-H), 7.79-7.73 (m, 2H, C_{Ar}-H), 7.56-7.49 (m, 3H, C_{Ar}-H), 7.48-7.38 (m, 3H, C_{Ar}-H), 7.35 (bs, 3H, C_{Ar}-H), 4.43 (appt t, J = 6.8 Hz, 1H, C_{7a}-H), 3.66 (ddd, J = 11.0, 7.8, 5.1 Hz, 1H, C_5-H_a), 3.23-3.10 (m, 1H, C_5-H_b), 1.90-1.70 (m, 3H, C_6-H_a + C_7-H), 1.59-1.47 (m, 1H, C_6-H_b). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2 (C_3), 151.0 (C_{Ar}-C), 139.2 (C_{Ar}-C), 132.3 (C_{Ar}-H), 131.2 (q, $^2J_{C-F}$ = 33.3 Hz, **C**CF_3), 129.5 (C_{Ar}-H), 129.5 (C_{Ar}-H), 129.1 (C_{Ar}-H), 127.1 (C_{Ar}-H), 123.2 (q, $^1J_{C-F}$ = 273.2 Hz, CF_3), 123.1 (C_{Ar}-H), 122.5 (C_{Ar}-H), 116.4 (q, $^3J_{C-F}$ = 4.0 Hz, C_{Ar}-H), 91.2 (C_1), 71.0 (C_{7a}), 45.4 (C_5), 25.9 (C_7), 24.2 (C_6). ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.2 (CF_3). IR (ATR) cm^{-1}: 1722 (C=O), 1128 (C-N). MS (EI) *m*/*z* (%): 412 (100), 316 (28), 253 (14). HRMS: Calculated for $[C_{26}H_{21}N_4OF_6]^+$: 519.1620 [$(M+H)^+$]; found: 519.1612. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/min; τ_{major} = 7.107 min, τ_{minor} = 7.926 min (88% ee). $[\alpha]_D^{20}$: -113.7 (c = 0.66, CH_2Cl_2).

4.1. X-Ray Analysis of Compound 4m

Crystal Data for C22H20F_6N_4OS (*M* =502.48 g/mol) (**4m**): triclinic, space group P1 (no. 1), *a* = 12.62193(18) Å, *b* = 13.55916(19) Å, *c* = 20.6596(3) Å, *α* = 92.8838(11)°, *β* = 91.5768(11)º, *γ* = 94.1281(11)°, *V* = 3520.38(8) $Å^3$, *Z* = 6, *T* = 149.99 (10) K, μ(Cu Kα) = 1.866 mm^{-1}, *Dcalc* = 1.422 g/cm^3, 72604 reflections measured (6.544° ≤ 2Θ ≤ 139.998°), 25823 unique (R_{int} = 0.0426, R_{sigma} = 0.0555) which were used in all calculations. The final R_1 was 0.0550 (I>=2u(I)) and wR_2 was 0.1532 (all data).

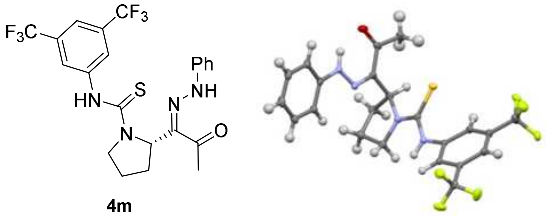


Figure SI-1. ORTEP diagram for compound **(*S*,*Z*)-4m**

Table SI-4 Crystal data and structure refinement for **4m**.

Identification code	**NZ906**
Empirical formula	$C_{22}H_{20}F_6N_4OS$
Formula weight	502.48
Temperature/K	149.99(10)
Crystal system	triclinic
Space group	P1
a/Å	12.62193(18)
b/Å	13.55916(19)
c/Å	20.6596(3)
α/°	92.8838(11)
β/°	91.5768(11)
γ/°	94.1281(11)
Volume/$Å^3$	3520.38(8)
Z	6
ρ_{calc}g/cm^3	1.422
μ/mm^{-1}	1.866
F(000)	1548.0
Crystal size/mm^3	0.699 × 0.186 × 0.058
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.544 to 139.998
Index ranges	-15 ≤ h ≤ 15, -16 ≤ k ≤ 16, -25 ≤ l ≤ 24
Reflections collected	72604
Independent reflections	25823 [R_{int} = 0.0426, R_{sigma} = 0.0555]
Data/restraints/parameters	25823/363/2075
Goodness-of-fit on F^2	1.066
Final R indexes [I>=2σ (I)]	R_1 = 0.0550, wR_2 = 0.1507
Final R indexes [all data]	R_1 = 0.0567, wR_2 = 0.1532
Largest diff. peak/hole / e $Å^{-3}$	0.41/-0.36
Flack parameter	-0.013(13)

Table SI-5 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **4m**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1A	12961.8(9)	8792.0(8)	-785.2(6)	38.0(2)
F10A	11100(3)	8889(3)	2370(2)	60.2(9)
F11A	11321(4)	7339(3)	2373.7(19)	64.5(10)
F12A	12434(3)	8386(4)	2873.0(18)	73.7(12)
O1A	11075(4)	9497(3)	-2561(2)	52.9(10)
N1A	11895(3)	7073(3)	-1066(2)	34.0(8)
N2A	12208(3)	7412(3)	23(2)	33.6(8)
N3A	10335(3)	8049(3)	-1691(2)	37.0(8)
N4A	9649(3)	8719(3)	-1813(2)	38.2(9)
C1A	11975(4)	7286(4)	-1763(2)	39(1)
C2A	11650(5)	6281(4)	-2100(3)	47.9(12)
C3A	10876(5)	5786(4)	-1649(3)	49.1(12)
C4A	11315(4)	6117(4)	-973(3)	41.2(11)
C5A	12321(4)	7698(3)	-605(2)	32.7(9)
C6A	12632(4)	7926(3)	593(2)	33.5(9)
C7A	13620(4)	8450(4)	622(3)	43.9(12)
C8A	13996(5)	8925(5)	1195(3)	53.4(14)
C9A	13418(5)	8864(4)	1760(3)	48.4(12)
C10A	12454(4)	8310(3)	1736(2)	36.6(10)
C11A	12049(4)	7849(3)	1154(2)	31.8(9)
C12A	15036(6)	9509(6)	1229(3)	80(3)
C13A	11828(4)	8228(4)	2332(3)	42.9(11)
C14A	11278(4)	8103(4)	-1942(2)	35.8(10)
C15A	11662(5)	8870(4)	-2380(3)	44.3(12)
C16A	12788(5)	8906(6)	-2591(3)	59.0(16)
C17A	8659(4)	8659(4)	-1526(3)	39(1)
C18A	8039(5)	9465(4)	-1582(3)	46.6(12)
C19A	7054(5)	9431(5)	-1318(4)	55.8(15)
C20A	6666(5)	8626(5)	-995(4)	57.0(15)
C21A	7282(5)	7824(4)	-944(3)	49.3(13)
C22A	8282(4)	7836(4)	-1199(3)	41.9(11)
F1A	15006(15)	10435(11)	1524(13)	90(5)
F4A	15456(12)	9669(15)	641(6)	63(3)
F7A	15791(8)	9048(10)	1570(8)	56(3)
F3A	15114(15)	10157(15)	753(9)	79(4)
F6A	15860(14)	8908(15)	1148(16)	114(6)
F9A	15181(14)	10120(14)	1788(7)	76(4)
F2A	14910(14)	10461(13)	1083(13)	88(4)
F5A	15684(12)	9197(15)	724(9)	76(4)
F8A	15572(12)	9508(15)	1754(8)	72(4)
S1F	-330.2(8)	1773.9(8)	9084.1(6)	32.7(2)
O1F	-1810(3)	2664(3)	11000(2)	47.7(9)
N1F	-117(3)	207(3)	9773.0(19)	32.1(8)

N2F	1269(3)	560(3)	9119(2)	32.9(8)
N3F	-170(3)	1343(3)	10919.7(19)	34.1(8)
N4F	15(3)	2087(3)	11359(2)	37.1(8)
C1F	-1139(4)	383(4)	10075(2)	35.4(10)
C2F	-1406(4)	-604(4)	10395(3)	44.4(12)
C3F	-327(4)	-974(4)	10572(3)	45.6(12)
C4F	377(4)	-658(4)	10018(3)	40.0(11)
C5F	307(3)	802(3)	9335(2)	29.9(8)
C6F	1968(4)	1121(3)	8731(2)	30.4(9)
C7F	3041(4)	1173(3)	8913(2)	34.3(9)
C8F	3785(4)	1678(4)	8546(3)	42.1(11)
C9F	3467(5)	2151(4)	8007(3)	46.7(12)
C10F	2401(4)	2102(4)	7833(3)	40.6(11)
C11F	1640(4)	1570(3)	8181(2)	34.4(9)
C12F	4942(5)	1748(5)	8762(4)	60.8(17)
C13F	2031(6)	2630(5)	7258(3)	54.6(14)
C14F	-1034(4)	1270(3)	10550(2)	32.1(9)
C15F	-1881(4)	1966(4)	10599(3)	40.1(11)
C16F	-2841(5)	1803(5)	10146(4)	58.5(15)
C17F	928(4)	2132(4)	11762(2)	39.1(10)
C18F	1185(5)	2991(5)	12141(3)	47.9(13)
C19F	2076(6)	3047(6)	12557(3)	61.9(19)
C20F	2713(5)	2268(6)	12587(3)	57.8(17)
C21F	2461(5)	1422(5)	12208(3)	55.2(15)
C22F	1571(4)	1331(4)	11790(3)	43.1(11)
F7F	1850(50)	3470(40)	7370(30)	95(17)
F11F	2570(30)	2460(40)	6693(18)	91(11)
F9F	1030(30)	2150(30)	6920(20)	54(8)
F6F	5250(4)	2647(4)	9051(4)	78(2)
F2F	5166(4)	1097(7)	9202(4)	71.3(18)
F4F	5582(4)	1613(7)	8287(3)	83(2)
F8F	1511(8)	3432(6)	7445(4)	60.4(18)
F10F	1406(12)	2071(8)	6874(5)	79(3)
F12F	2858(6)	2990(7)	6923(4)	75(3)
F5F	5390(30)	2540(30)	8570(30)	91(13)
F1F	5100(40)	1560(40)	9300(20)	76(12)
F3F	5300(30)	960(30)	8215(19)	79(11)
S1C	-1131.4(8)	4740.3(8)	5793.3(5)	32.7(2)
O1C	-4779(3)	3487(3)	5325.4(18)	39.8(7)
N1C	-2116(3)	6169(3)	5244.4(19)	31.1(7)
N2C	-375(3)	6109(3)	4986.1(19)	32.1(8)
N3C	-3669(3)	4911(3)	4591.7(19)	32.5(8)
N4C	-4178(3)	4162(3)	4239(2)	34.4(8)
C1C	-3100(3)	5844(3)	5564(2)	31.9(9)
C2C	-3742(4)	6757(4)	5534(3)	40.8(11)
C3C	-3417(4)	7221(4)	4907(3)	42.5(11)

C4C	-2237(4)	7047(4)	4865(3)	38.5(10)
C5C	-1212(3)	5721(3)	5320(2)	29.2(8)
C6C	669(4)	5791(3)	4971(2)	30.0(9)
C7C	1162(4)	5803(3)	4374(2)	35.2(9)
C8C	2219(4)	5577(3)	4340(3)	39.7(11)
C9C	2784(4)	5336(4)	4882(3)	41.1(11)
C10C	2286(4)	5337(3)	5473(3)	36.6(10)
C11C	1231(4)	5561(3)	5525(2)	31.6(9)
C12C	2751(5)	5624(4)	3707(3)	59.5(17)
C13C	2920(4)	5137(4)	6059(3)	49.1(13)
C14C	-3666(3)	4932(3)	5223(2)	29.7(8)
C15C	-4226(3)	4178(3)	5605(2)	31.6(9)
C16C	-4092(4)	4231(4)	6327(2)	40.3(10)
C17C	-4165(3)	4141(4)	3565(2)	33.9(9)
C18C	-4492(4)	3245(4)	3226(3)	41.5(11)
C19C	-4495(4)	3181(5)	2559(3)	50.2(13)
C20C	-4183(4)	4005(5)	2216(3)	50.1(13)
C21C	-3872(5)	4882(5)	2549(3)	48.1(12)
C22C	-3855(4)	4971(4)	3225(3)	42.4(11)
F1C	1987(7)	5372(9)	3189(4)	58(2)
F3C	3039(10)	6551(6)	3566(4)	80(3)
F5C	3479(9)	5038(10)	3588(6)	65(3)
F8C	2409(14)	5186(17)	6615(7)	46(3)
F10C	3811(9)	5733(13)	6130(8)	60(4)
F12C	3269(19)	4215(11)	5965(11)	65(4)
F2C	2199(12)	5783(13)	3204(6)	69(4)
F4C	3677(12)	6276(10)	3783(7)	83(4)
F6C	3273(10)	4748(8)	3619(7)	42(3)
F7C	2280(20)	4929(19)	6560(11)	49(5)
F9C	3578(17)	5980(12)	6285(10)	65(4)
F11C	3527(18)	4367(15)	6049(15)	61(5)
S1D	-2937.6(9)	1154.8(8)	4181.7(6)	34.5(2)
F00I	-2037(3)	1846(3)	7830.7(16)	62.3(10)
F00O	-841(3)	2676(3)	7323.6(19)	65.4(10)
F007	-942(3)	1093(3)	7251.7(17)	53.0(8)
O1D	-571(3)	306(2)	2521.1(17)	37.2(7)
N1D	-1828(3)	2823(3)	3947.3(18)	28.5(7)
N2D	-2197(3)	2649(3)	5015.9(19)	30.4(7)
N3D	-156(3)	1824(3)	3520.3(18)	30.0(7)
N4D	604(3)	1198(3)	3464.8(19)	30.2(7)
C1D	-1810(3)	2485(3)	3261(2)	29.9(9)
C2D	-1516(4)	3454(4)	2928(2)	35.0(9)
C3D	-778(4)	4047(4)	3429(2)	36.6(10)
C4D	-1247(4)	3800(3)	4081(2)	32.9(9)
C5D	-2292(3)	2268(3)	4394(2)	27.5(8)
C6D	-2574(3)	2199(3)	5579(2)	29.6(8)

C7D	-1908(4)	2257(3)	6127(2)	31.1(9)
C8D	-2274(4)	1873(3)	6697(2)	34.1(9)
C9D	-3287(4)	1439(4)	6736(2)	39.2(10)
C10D	-3951(4)	1384(4)	6186(3)	39.9(10)
C11D	-3602(4)	1756(4)	5606(2)	34.6(9)
C12D	-1525(4)	1881(4)	7275(3)	41.6(11)
C13D	-5057(5)	967(4)	6214(3)	54.5(14)
C14D	-1018(3)	1707(3)	3149(2)	28.1(8)
C15D	-1230(4)	911(3)	2639(2)	31.4(9)
C16D	-2273(4)	852(4)	2262(3)	44.0(11)
C17D	1558(3)	1390(3)	3828(2)	31.8(9)
C18D	2289(4)	670(4)	3807(2)	37.5(10)
C19D	3268(4)	856(5)	4129(3)	46.1(12)
C20D	3521(4)	1744(4)	4469(3)	47.6(13)
C21D	2784(4)	2452(4)	4503(3)	44.1(12)
C22D	1798(4)	2286(4)	4182(3)	36.6(10)
F212	-5804(9)	1579(14)	6062(14)	85(4)
F213	-5257(16)	216(16)	5764(11)	87(5)
F214	-5274(13)	608(17)	6791(6)	70(4)
F215	-5717(13)	1698(11)	6357(16)	72(5)
F216	-5460(16)	527(19)	5657(6)	67(5)
F217	-5213(17)	250(20)	6641(14)	77(6)
S1B	10322.0(9)	8055.6(8)	4116.1(6)	35.0(2)
F7B	4918(3)	8200(4)	3871(2)	83.5(15)
F8B	4627(3)	7733(3)	2868(2)	68.2(11)
F9B	4895(3)	9265(3)	3153(2)	68(1)
O1B	11468(4)	7487(3)	6306(2)	54.2(10)
N1B	10142(3)	9727(3)	4811.7(18)	28.1(7)
N2B	8810(3)	9358(3)	4052.0(19)	32.2(8)
N3B	9871(3)	8697(3)	5894.2(19)	37.2(9)
N4B	9540(4)	8055(3)	6327(2)	44.9(10)
C1B	11093(4)	9519(3)	5196(2)	31.5(9)
C2B	11416(4)	10539(3)	5537(2)	35.3(9)
C3B	10358(4)	10993(4)	5643(2)	36.9(10)
C4B	9669(4)	10631(3)	5048(2)	31.5(9)
C5B	9729(3)	9096(3)	4337(2)	29.4(8)
C6B	8157(4)	8802(3)	3571(2)	32.2(9)
C7B	8559(4)	8340(4)	3031(2)	38.3(10)
C8B	7846(5)	7846(4)	2571(3)	44.6(12)
C9B	6756(5)	7829(4)	2644(3)	45.9(12)
C10B	6380(4)	8311(4)	3178(3)	41.2(11)
C11B	7072(4)	8793(3)	3649(2)	35.7(10)
C12B	8275(5)	7329(5)	1998(3)	61.2(17)
C13B	5207(5)	8359(5)	3269(3)	51.5(13)
C14B	10828(4)	8725(3)	5678(2)	37.1(10)
C15B	11645(5)	8085(4)	5881(3)	44.3(12)

C16B	12705(5)	8160(5)	5568(4)	59.5(15)
C17B	8519(5)	8089(4)	6565(2)	45.6(12)
C18B	7886(6)	8846(4)	6436(3)	57.1(16)
C19B	6864(6)	8856(5)	6688(4)	62.6(18)
C20B	6495(6)	8126(5)	7081(3)	59.7(16)
C21B	7147(6)	7382(5)	7220(3)	58.7(17)
C22B	8146(6)	7346(5)	6960(3)	54.8(15)
F2B	8730(30)	6483(16)	2170(20)	84(3)
F4B	8990(20)	7979(18)	1750(13)	73(2)
F6B	7469(16)	6910(20)	1604(11)	86(2)
F1B	8391(9)	6365(6)	2087(7)	84(3)
F3B	9262(7)	7660(8)	1823(4)	73(2)
F5B	7669(7)	7370(9)	1449(4)	86(2)
S1E	769.6(8)	5404.7(8)	10750.5(6)	34.6(2)
F1E	-2897(3)	5148(3)	11056.7(18)	64.2(10)
F2E	-3555(3)	6064(3)	10343(2)	61.3(9)
F3E	-4164(3)	4553(3)	10408(2)	61.5(9)
O1E	4402(3)	6456(2)	11034.5(18)	39.4(7)
N1E	1783(3)	3802(3)	10444.2(18)	28.1(7)
N2E	211(3)	3885(3)	9891(2)	31.8(8)
N3E	3447(3)	5038(3)	10084.2(19)	29.3(7)
N4E	4044(3)	5763(3)	9838.0(19)	31.6(8)
C1E	2006(4)	2876(3)	10096(2)	34.1(9)
C2E	3147(4)	2716(4)	10308(2)	35.8(10)
C3E	3268(4)	3230(3)	10981(2)	34.2(9)
C4E	2629(3)	4150(3)	10925(2)	28.2(8)
C5E	925(3)	4310(3)	10345(2)	29.2(8)
C6E	-789(3)	4240(3)	9709(2)	30.8(9)
C7E	-1496(4)	4538(3)	10171(2)	33.9(9)
C8E	-2479(4)	4822(4)	9961(3)	37.3(10)
C9E	-2765(4)	4828(4)	9313(3)	40.3(11)
C10E	-2057(4)	4514(3)	8860(3)	38(1)
C11E	-1066(4)	4210(3)	9053(2)	34.3(9)
C12E	-3264(4)	5146(5)	10445(3)	46.9(12)
C13E	-2366(4)	4521(4)	8160(3)	50.6(13)
C14E	3305(3)	5031(3)	10702(2)	27.3(8)
C15E	3792(3)	5774(3)	11193(2)	30.3(9)
C16E	3515(4)	5682(4)	11889(2)	41.7(11)
C17E	4218(3)	5751(3)	9173(2)	31.5(9)
C18E	3982(5)	4920(4)	8759(3)	44.5(12)
C19E	4180(5)	4970(5)	8108(3)	52.3(13)
C20E	4601(5)	5838(5)	7860(3)	50.0(13)
C21E	4831(4)	6652(4)	8270(3)	46.3(12)
C22E	4647(4)	6619(4)	8924(3)	40.2(11)
F5E	-3057(14)	5206(11)	8043(5)	69(4)
F7E	-2887(13)	3666(8)	7933(7)	68(3)

F9E	-1529(9)	4666(15)	7777(6)	69(3)
F4E	-2530(30)	5461(10)	7982(7)	66(6)
F6E	-3199(18)	3880(20)	7980(14)	79(6)
F8E	-1585(16)	4270(20)	7757(9)	58(5)

4.2. X-Ray Analysis of Compound 7a’

Crystal structure determination of **7a’**

Crystal Data for $C_{21}H_{18}F_6N_4O_2$ (M =472.39 g/mol) (**7a’**): monoclinic, space group I2/a (no. 15), a = 23.7773(15) Å, b = 5.4608(4) Å, c = 31.7244(19) Å, β = 92.002(6)°, V = 4116.7(5) Å^3, Z = 8, T = 150.01(10) K, μ(CuKα) = 1.202 mm^{-1}, $Dcalc$ = 1.524 g/cm^3, 15208 reflections measured (7.44° ≤ 2Θ ≤ 139.94°), 3904 unique (R_{int} = 0.0508, R_{sigma} = 0.0374) which were used in all calculations. The final R_1 was 0.0572 (> 2σ(I)) and wR_2 was 0.1679 (all data).

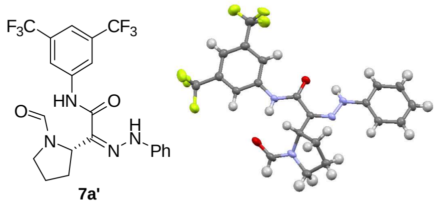


Figure SI-2. ORTEP diagram for compound **(*S*,*Z*)-7a’**

Table SI-6 Crystal data and structure refinement for **7a’**.

Identification code	a20170014_NZ1259
Empirical formula	$C_{21}H_{18}F_6N_4O_2$
Formula weight	472.39
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	I2/a
a/Å	23.7773(15)
b/Å	5.4608(4)
c/Å	31.7244(19)
α/°	90.00
β/°	92.002(6)
γ/°	90.00
Volume/Å^3	4116.7(5)
Z	8
ρ_{calc}g/cm^3	1.524
μ/mm^{-1}	1.202
F(000)	1936.0
Crystal size/mm^3	0.51 × 0.047 × 0.044
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.44 to 139.94
Index ranges	-28 ≤ h ≤ 28, -6 ≤ k ≤ 3, -36 ≤ l ≤ 38
Reflections collected	15208
Independent reflections	3904 [R_{int} = 0.0508, R_{sigma} = 0.0374]
Data/restraints/parameters	3904/72/354
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0572, wR_2 = 0.1565
Final R indexes [all data]	R_1 = 0.0717, wR_2 = 0.1679
Largest diff. peak/hole / e Å^{-3}	0.70/-0.29

Table SI-7 Fractional Atomic Coordinates (×10[4]) and Equivalent Isotropic Displacement Parameters ($Å^2$×10[3]) for **7a'**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O001	-3369.3(8)	-7638(4)	-5948.6(6)	31.6(4)
F002	-3504(7)	2600(20)	-7513(4)	51(2)
F003	-2937(4)	70(20)	-7788(4)	44(2)
O004	-4698.5(10)	-6591(5)	-7088.4(6)	48.7(6)
F005	-2287(7)	-350(30)	-5832(6)	47(3)
F006	-3806(6)	-860(30)	-7764(3)	52(2)
N007	-3886.0(9)	-5717(4)	-6468.4(7)	27.9(5)
N008	-4291.5(9)	-10807(4)	-5808.5(6)	25.6(5)
N009	-3818.3(9)	-11392(4)	-5598.6(7)	29.3(5)
N00A	-5032.6(9)	-9600(4)	-6668.8(7)	31.0(5)
F00B	-1857(6)	840(30)	-6400(4)	68(3)
C00C	-3813.3(11)	-7414(5)	-6154.3(8)	25.2(5)
C00D	-3498.6(11)	-3951(5)	-6592.1(8)	26.9(5)
C00E	-4311.5(10)	-8987(5)	-6071.4(8)	25.1(5)
C00F	-3807.9(11)	-13351(5)	-5314.9(8)	27.1(5)
C00G	-4895.8(10)	-8387(5)	-6259.6(8)	25.6(5)
C00H	-3624.1(11)	-2753(5)	-6975.1(8)	28.2(6)
F00I	-1774(5)	-2820(30)	-6226(4)	60(3)
C00J	-3273.3(11)	-945(5)	-7115.9(8)	30.1(6)
C00K	-3017.9(11)	-3293(5)	-6356.8(8)	31.2(6)
C00L	-4267.9(11)	-14863(5)	-5255.0(8)	29.9(6)
C00M	-2681.1(12)	-1422(6)	-6502.7(9)	34.4(6)
C00N	-3302.0(12)	-13806(6)	-5091.7(9)	35.0(6)
C00O	-2795.9(12)	-240(5)	-6880.1(9)	34.0(6)
C00P	-4216.2(12)	-16829(6)	-4984.7(9)	35.7(6)
C00Q	-5381.2(11)	-9261(5)	-5992.7(9)	31.2(6)
C00R	-3253.8(13)	-15793(6)	-4824.2(9)	39.4(7)
C00S	-3711.0(13)	-17327(6)	-4768.7(9)	38.2(7)
C00T	-3391.1(13)	236(6)	-7535.7(9)	36.2(6)
C00U	-5510.1(12)	-11841(6)	-6153.3(10)	36.8(7)
C00V	-4953.9(12)	-8529(6)	-7038.2(9)	38.2(7)
C00W	-5430.0(14)	-11664(6)	-6623.5(10)	41.8(7)
C00X	-2167.0(14)	-732(7)	-6243.8(12)	49.1(9)
F2	-3043(8)	-500(30)	-7818(4)	58(3)
F4	-3911(4)	-230(30)	-7690(5)	49(2)
F5	-3341(7)	2690(30)	-7515(5)	51(2)
F0AA	-1733(2)	-1930(17)	-6338(3)	78.3(19)
F1AA	-2229(4)	-1016(16)	-5834(3)	60.8(19)

5. NMR Spectra

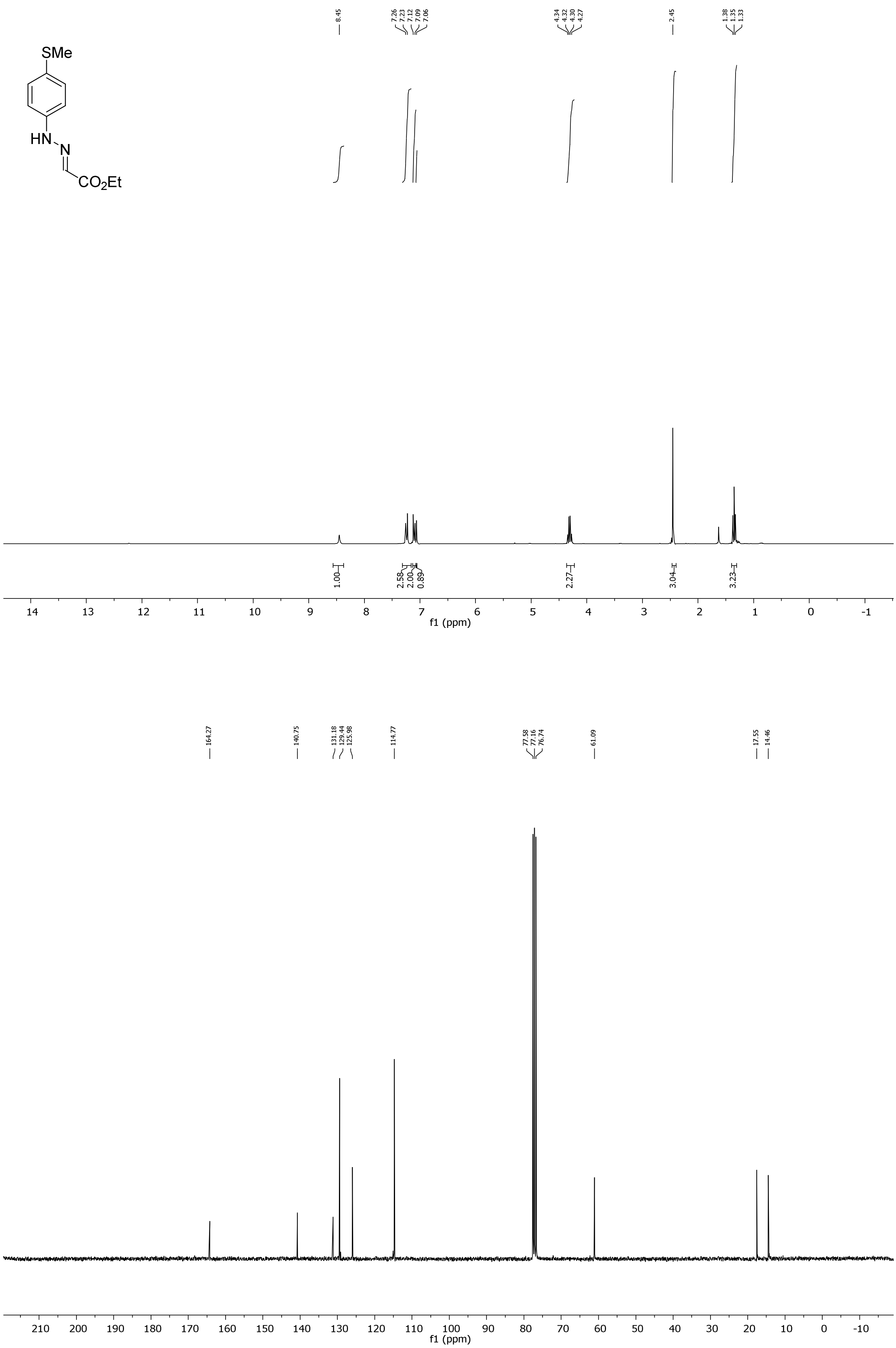
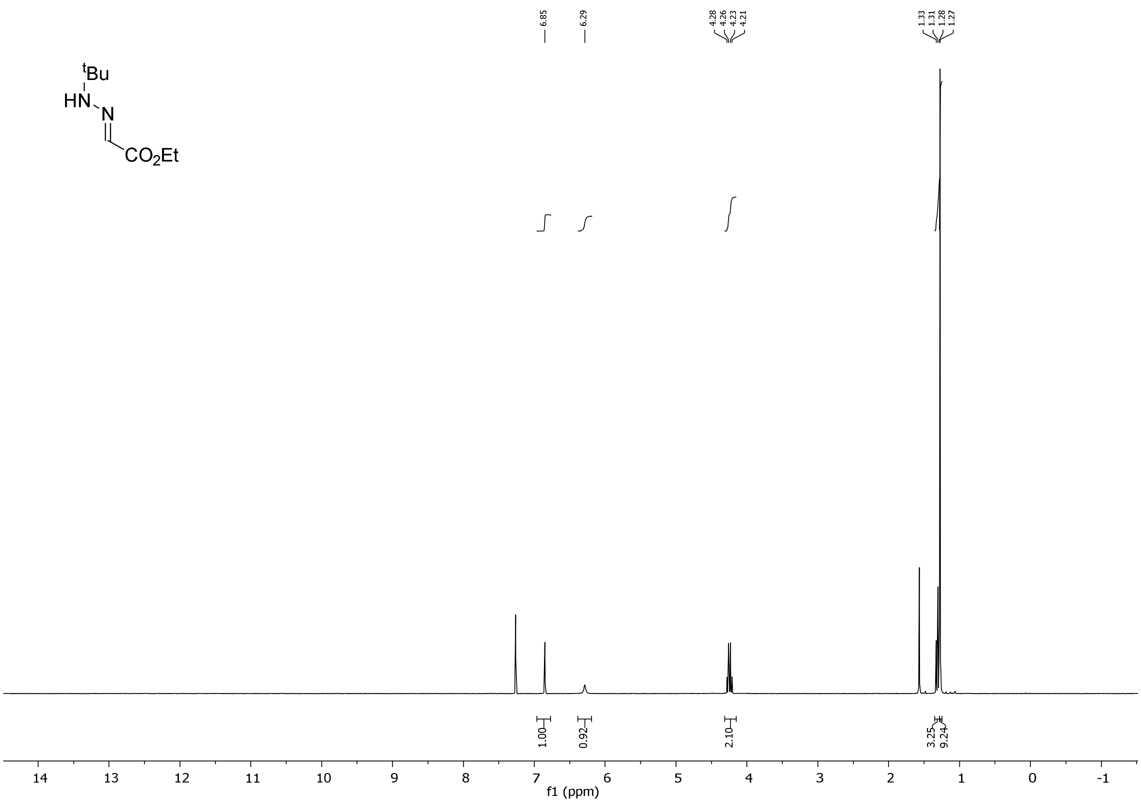


Figure SI-3. NMR spectra for compound **1b**



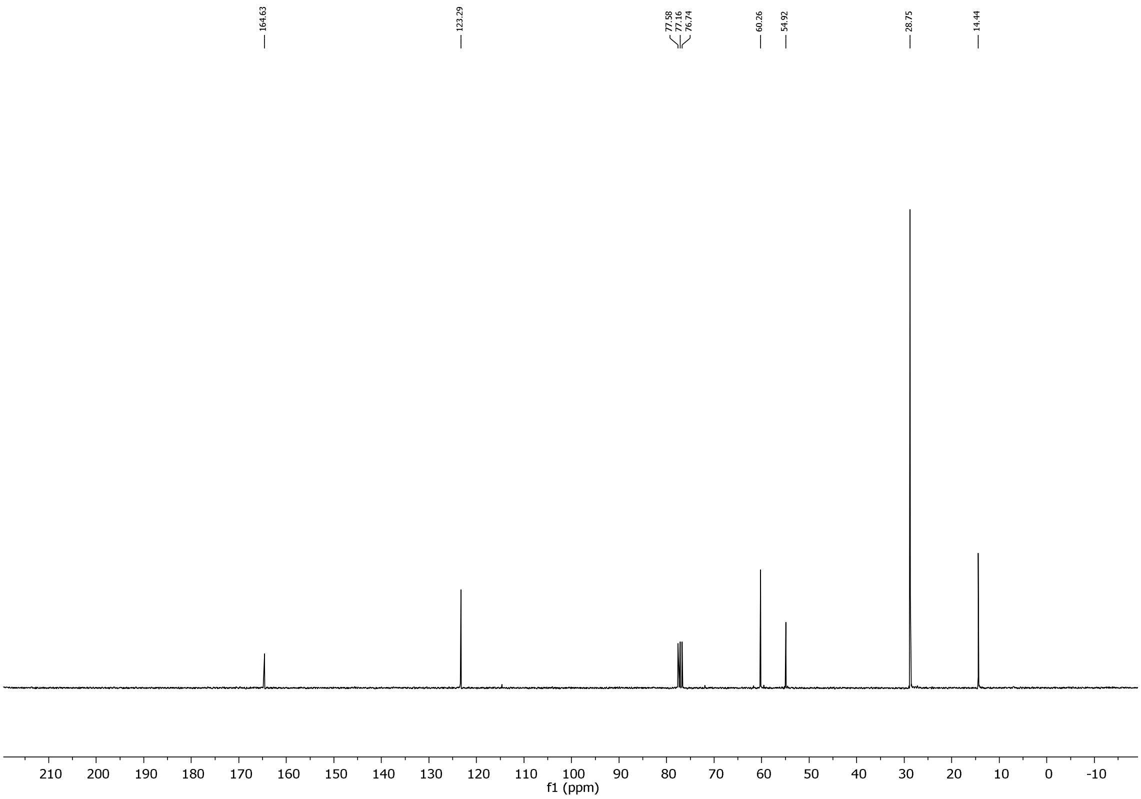
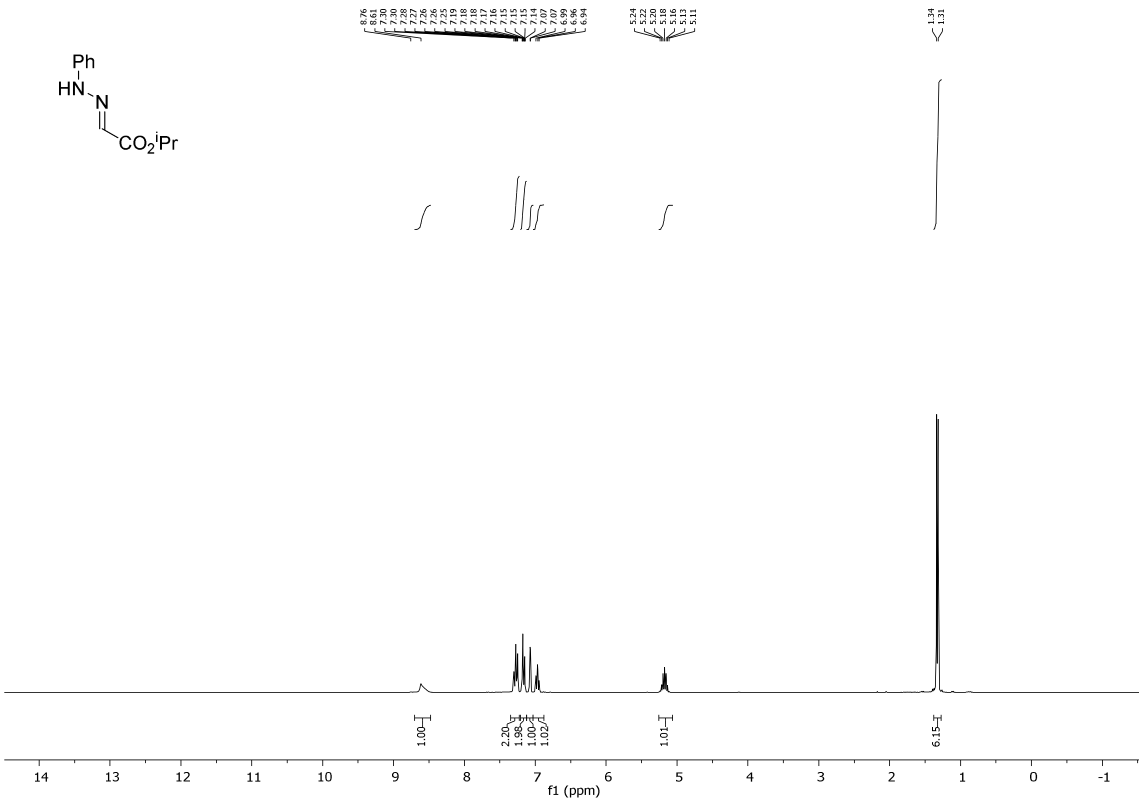


Figure SI-4. NMR spectra for compound **1e**



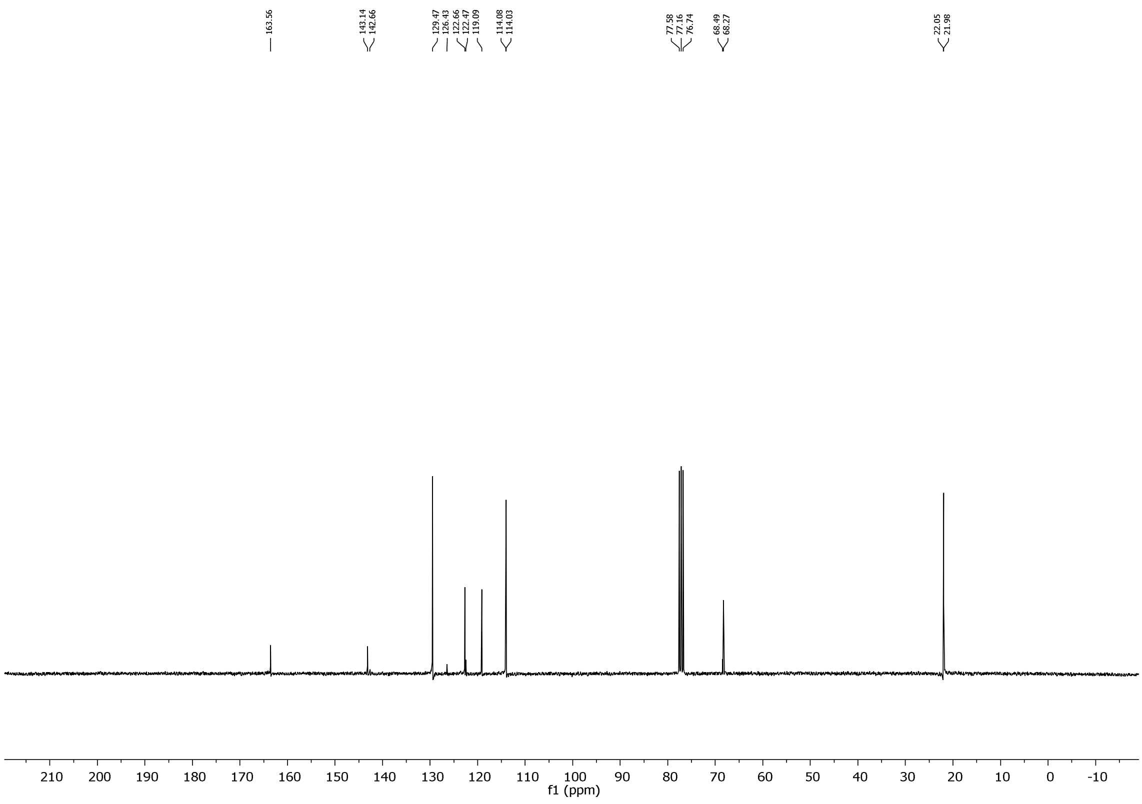
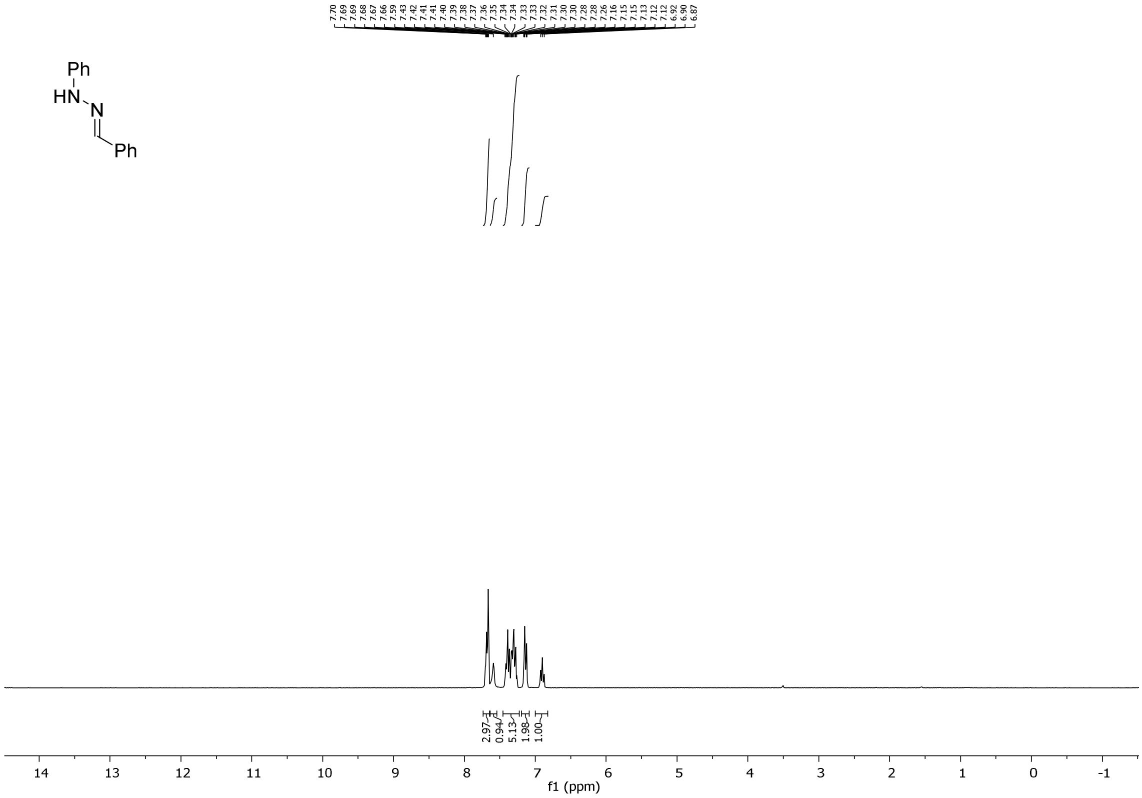


Figure SI-5. NMR spectra for compound **1f**



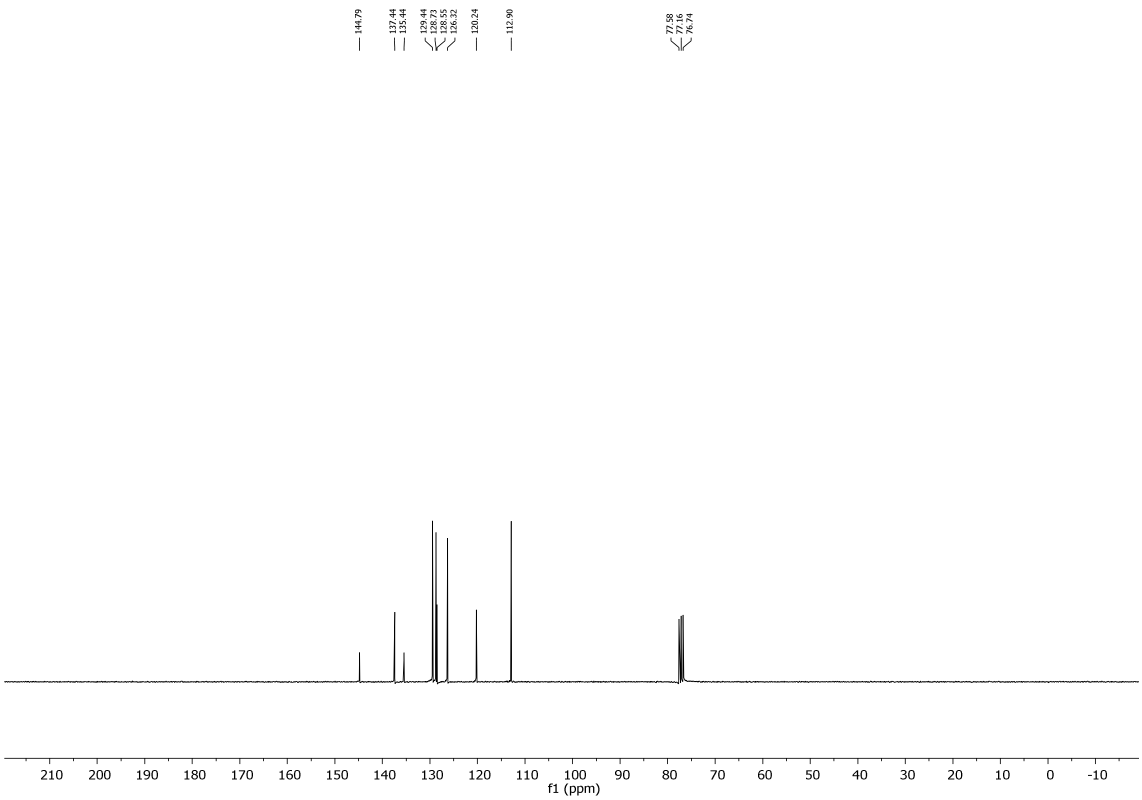


Figure SI-6. NMR spectra for compound **1i**

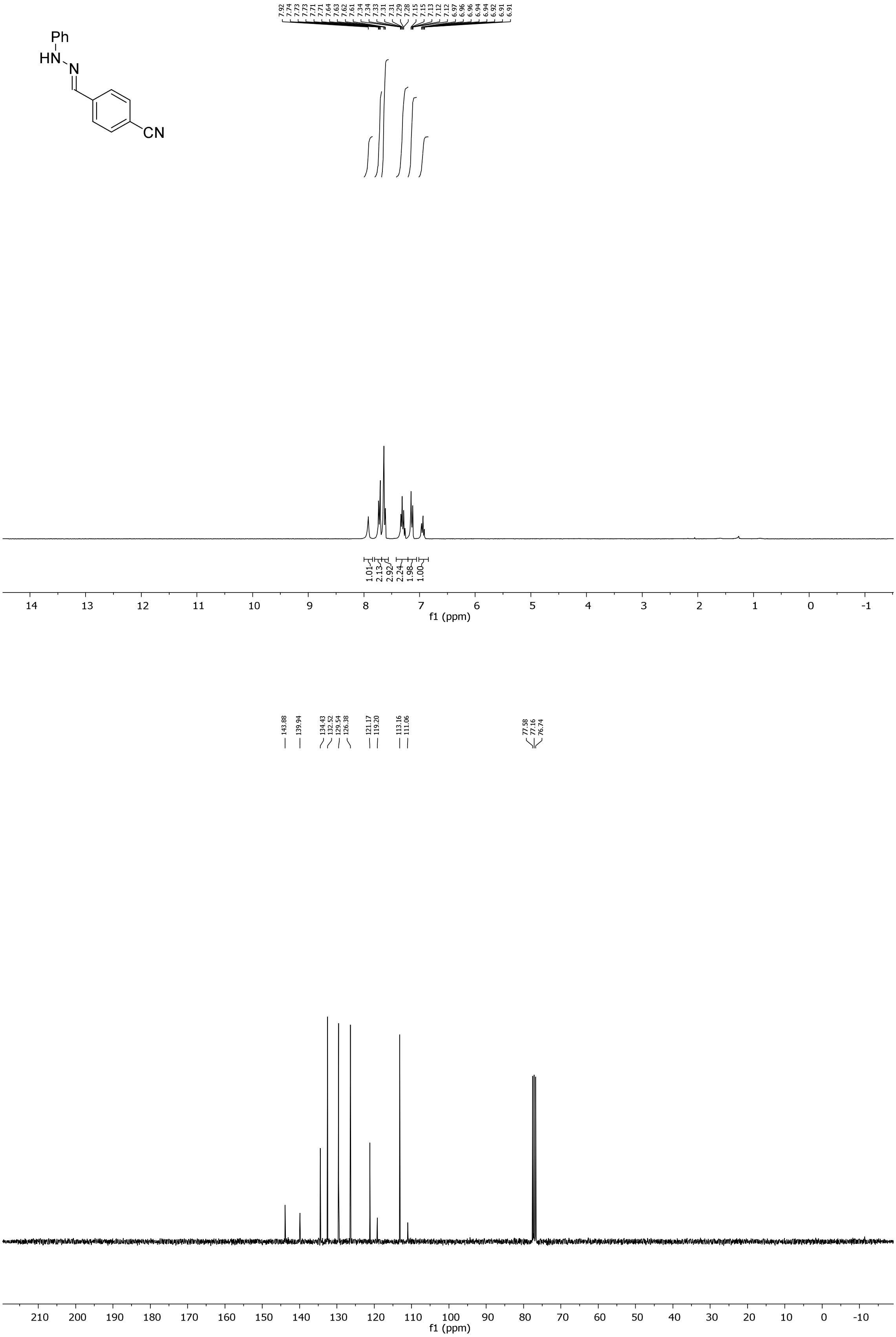
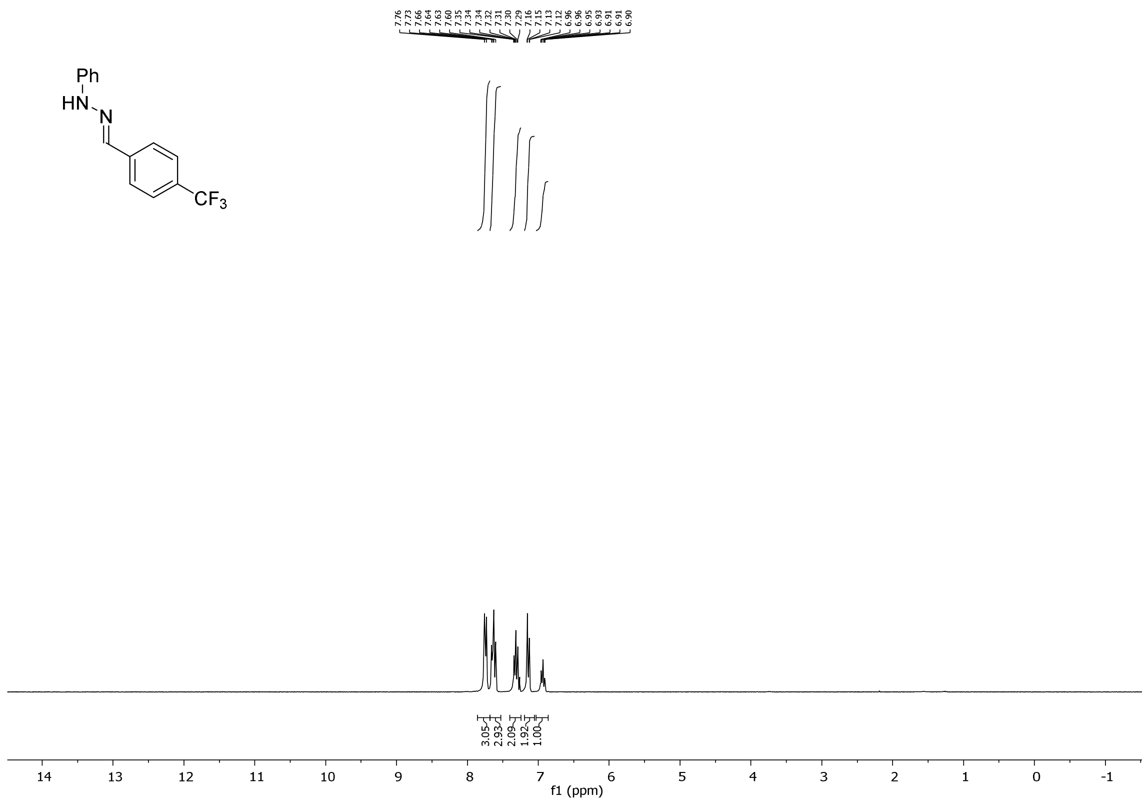


Figure SI-7. NMR spectra for compound **1k**



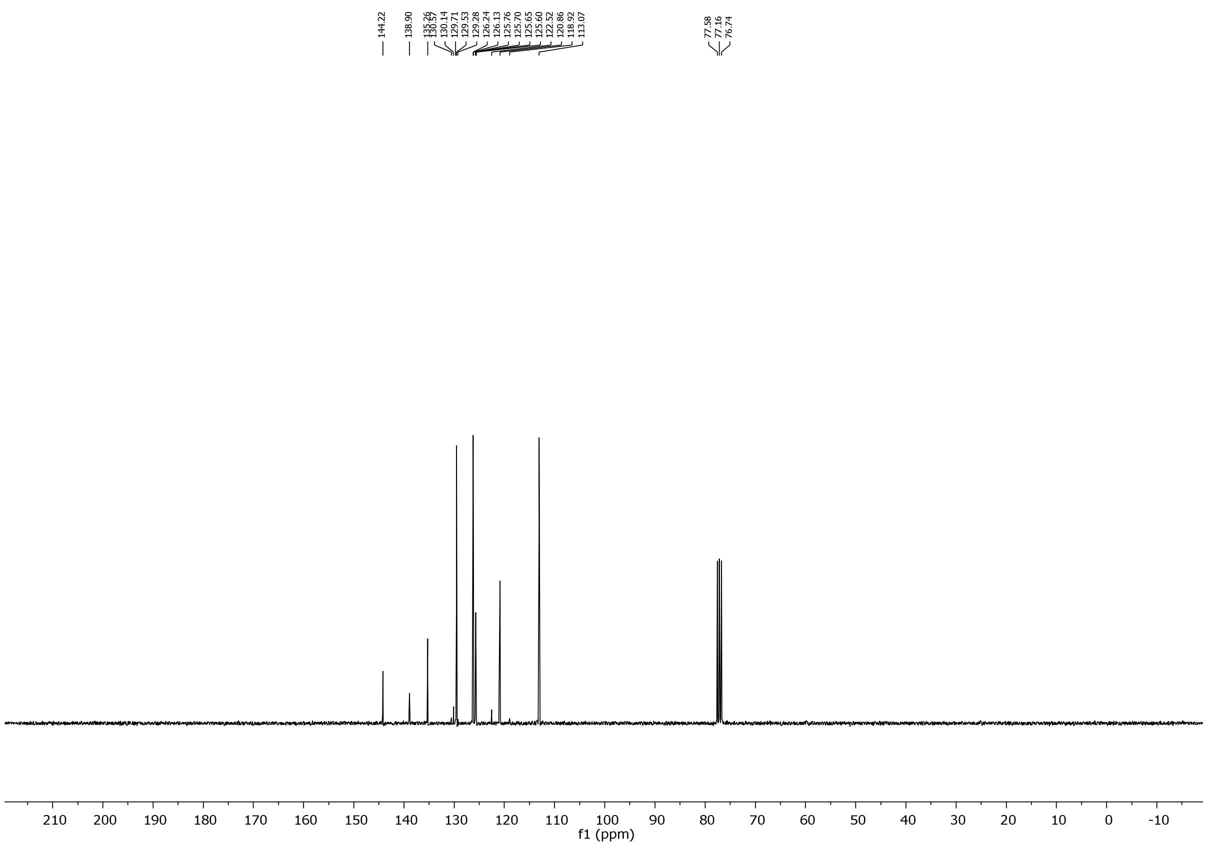
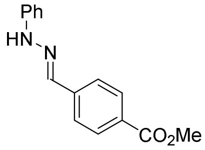
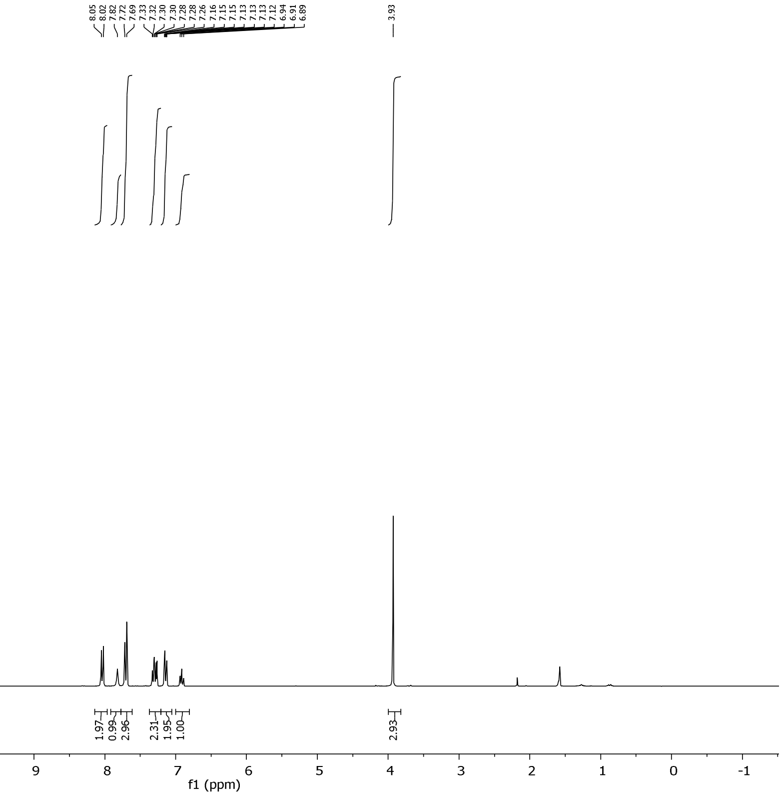


Figure SI-8. NMR spectra for compound **1l**





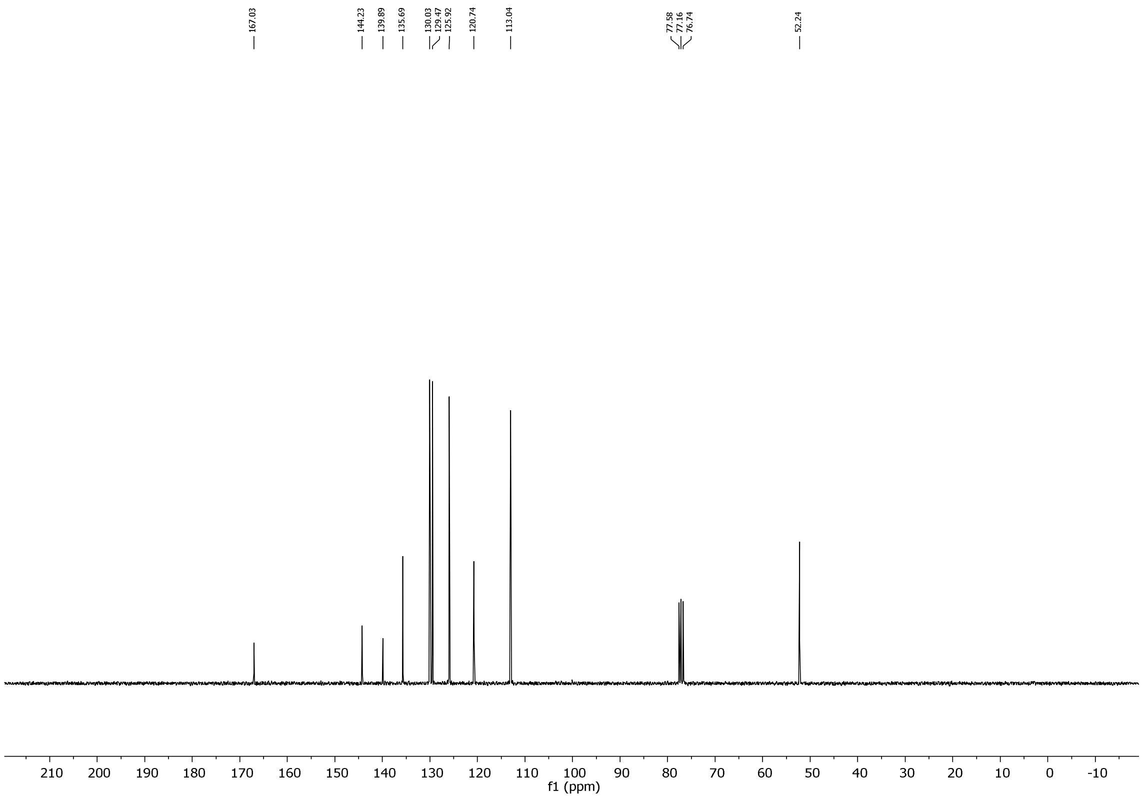


Figure SI-9. NMR spectra for compound **1m**

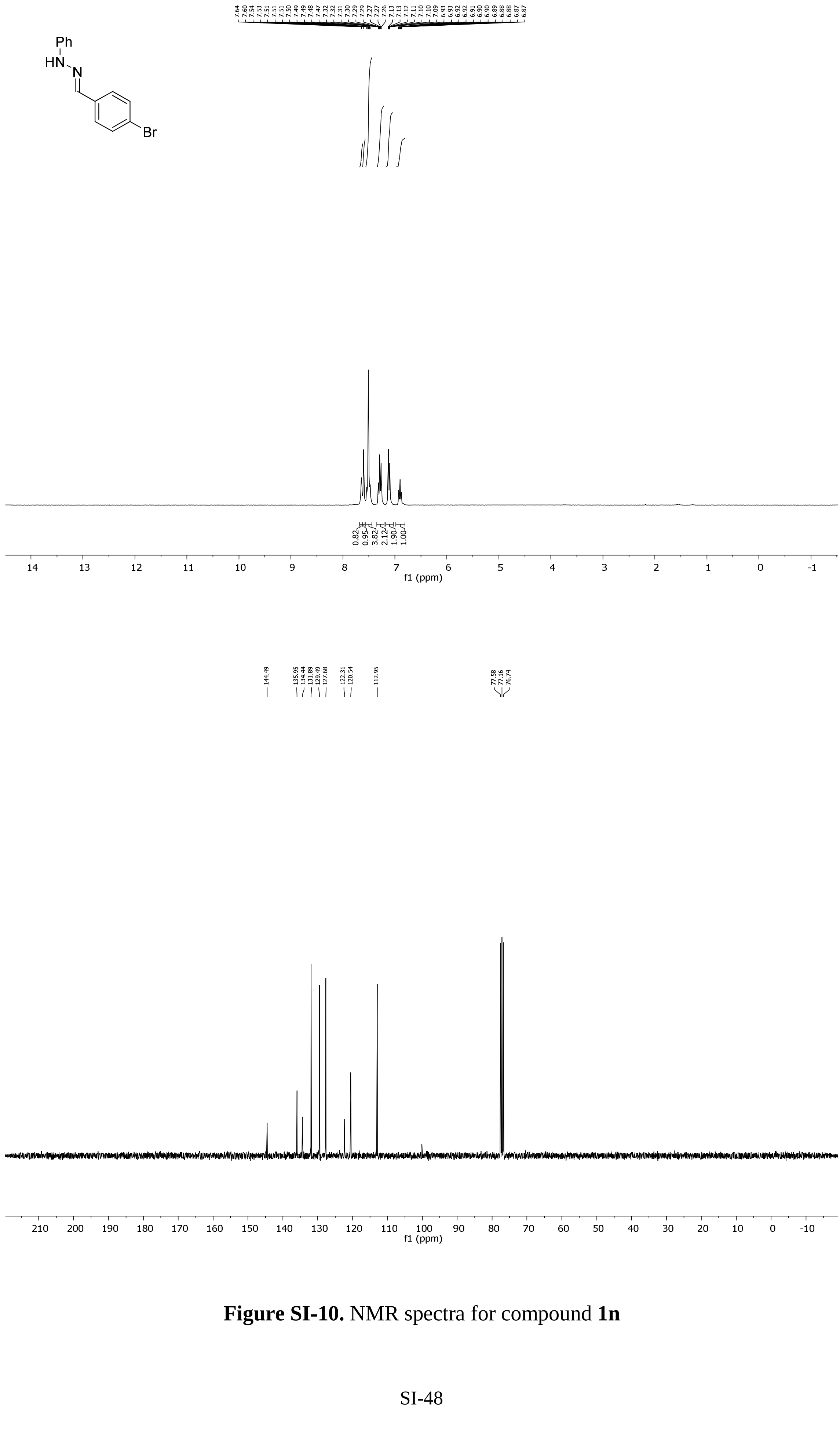


Figure SI-10. NMR spectra for compound **1n**

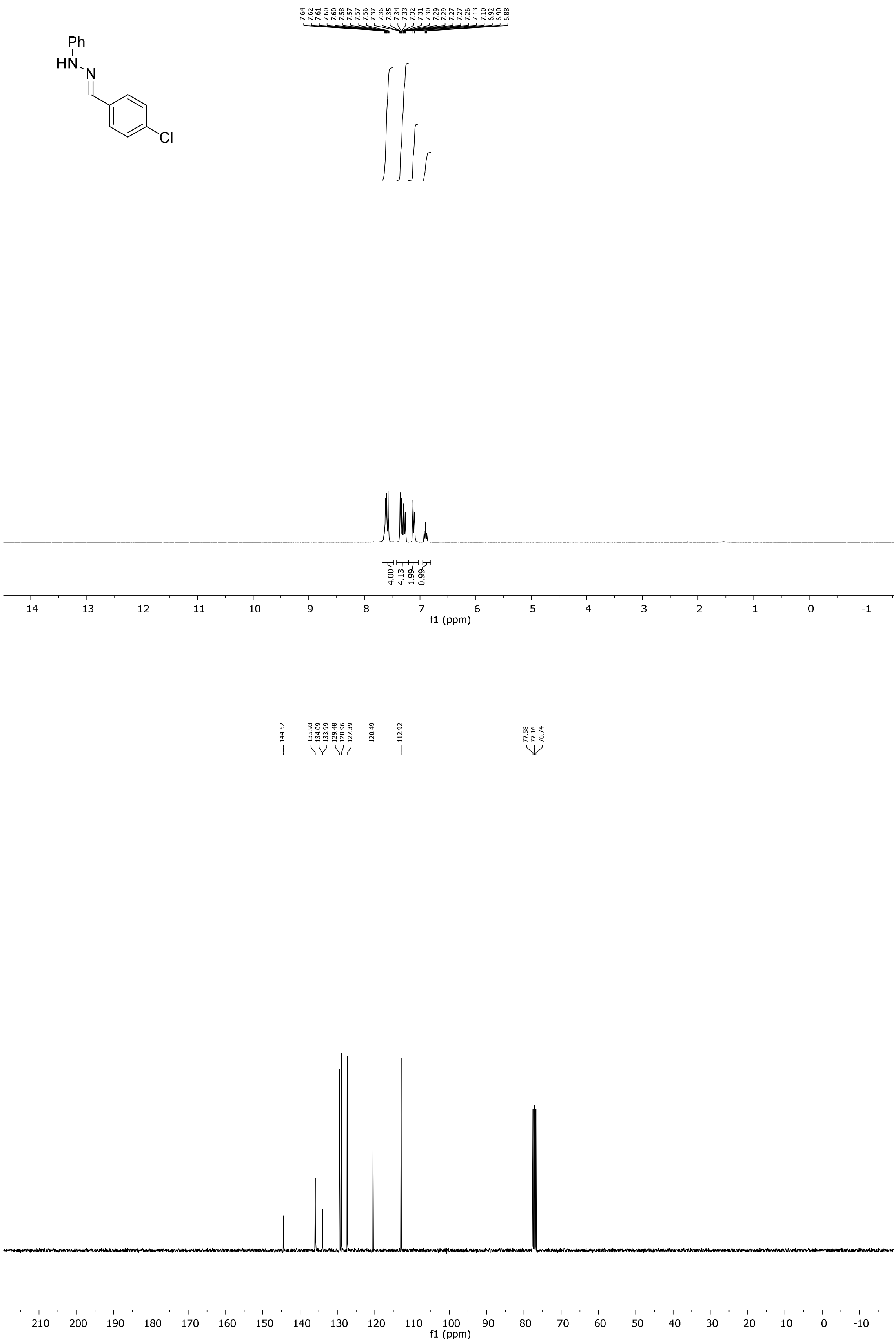
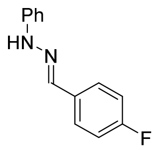
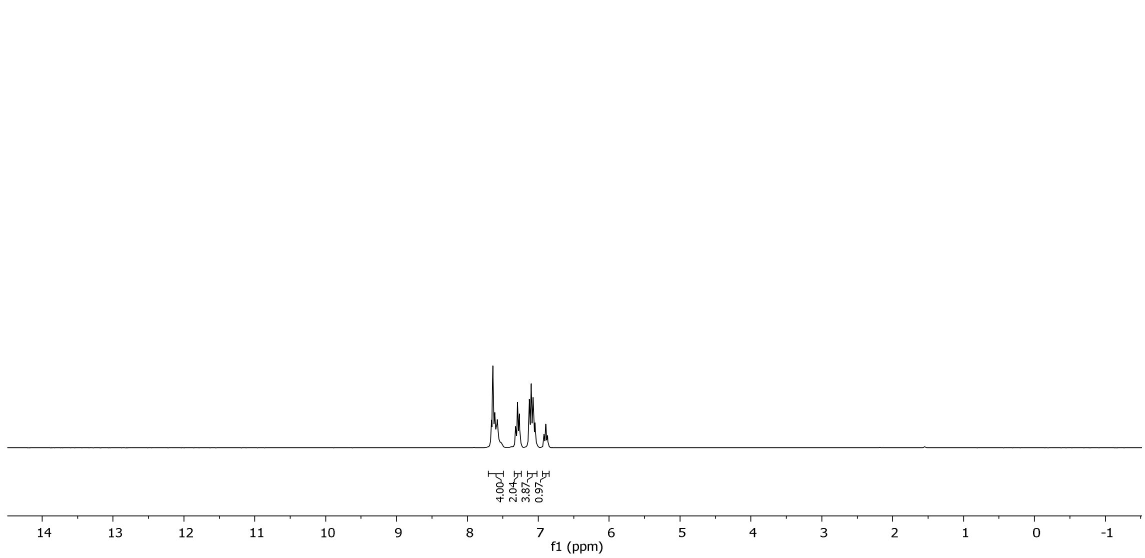


Figure SI-11. NMR spectra for compound **1o**





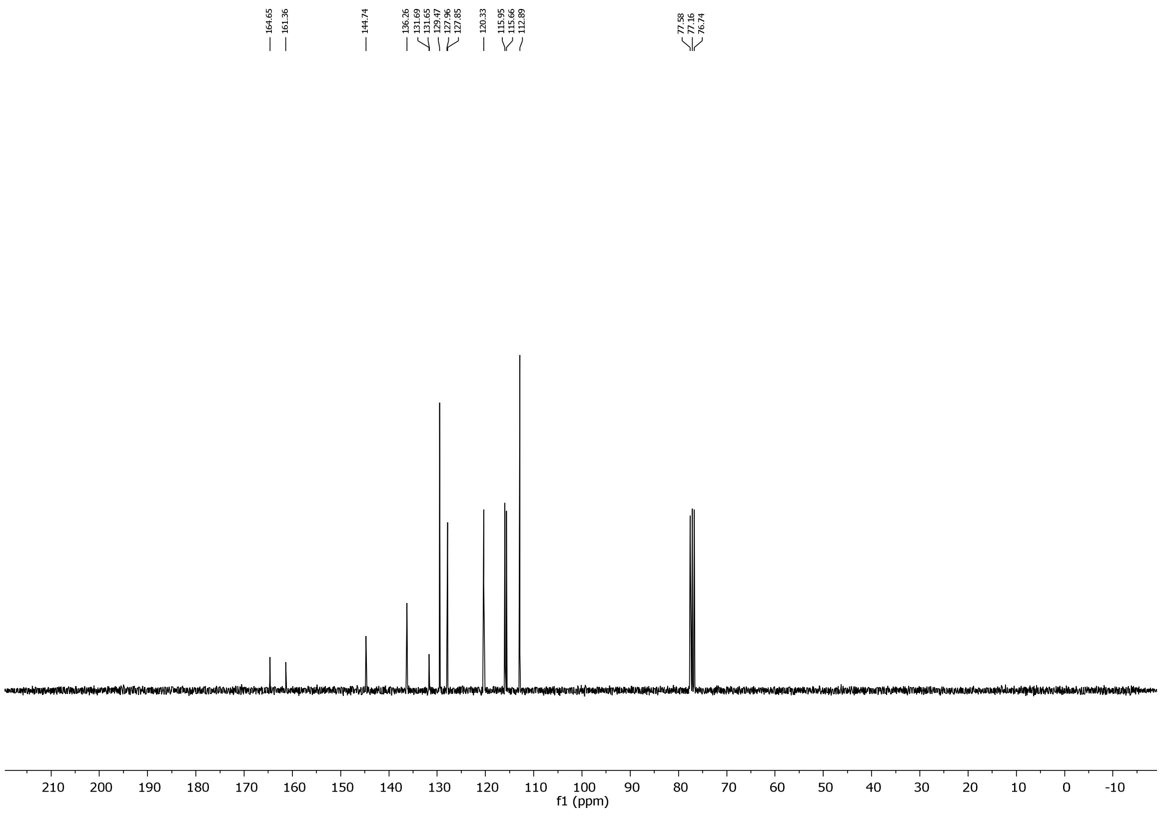


Figure SI-12. NMR spectra for compound **1p**

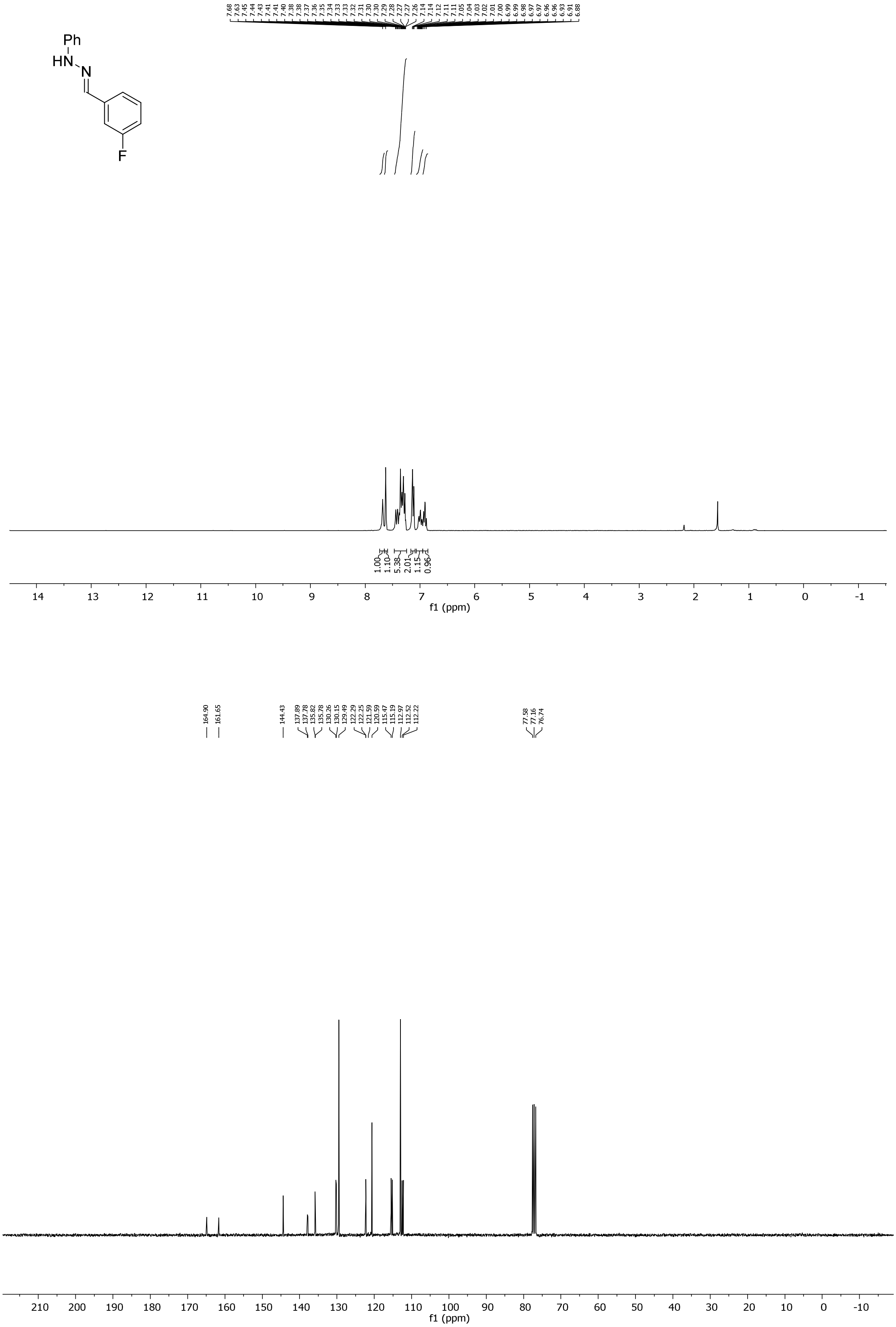
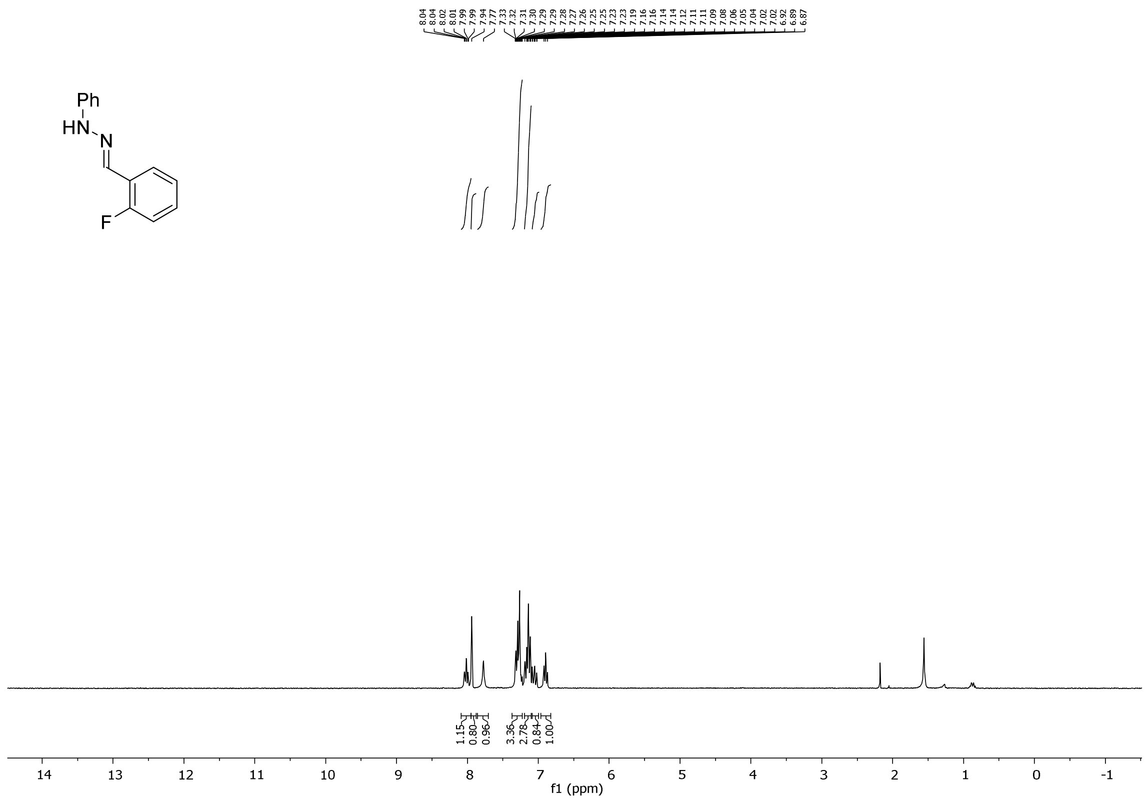


Figure SI-13. NMR spectra for compound **1q**



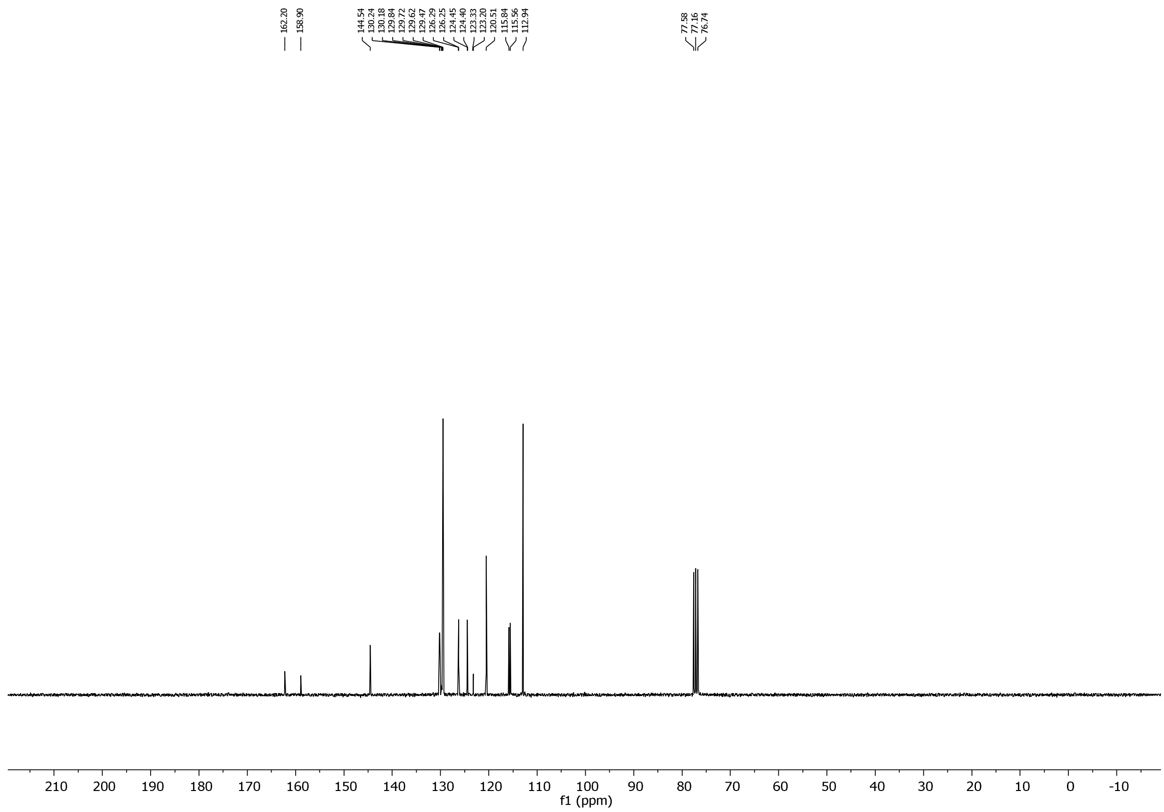


Figure SI-14. NMR spectra for compound **1r**

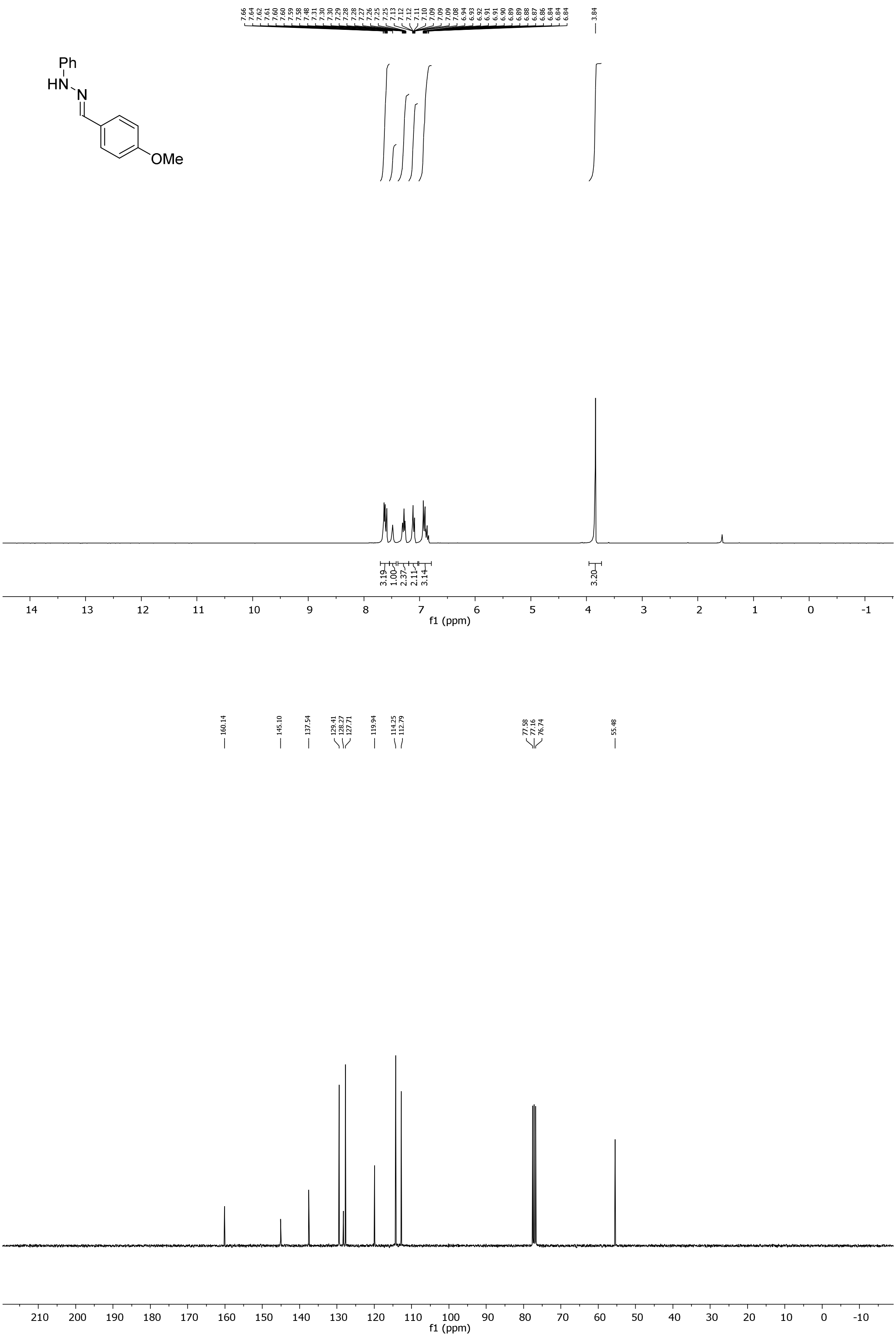


Figure SI-15. NMR spectra for compound **1t**

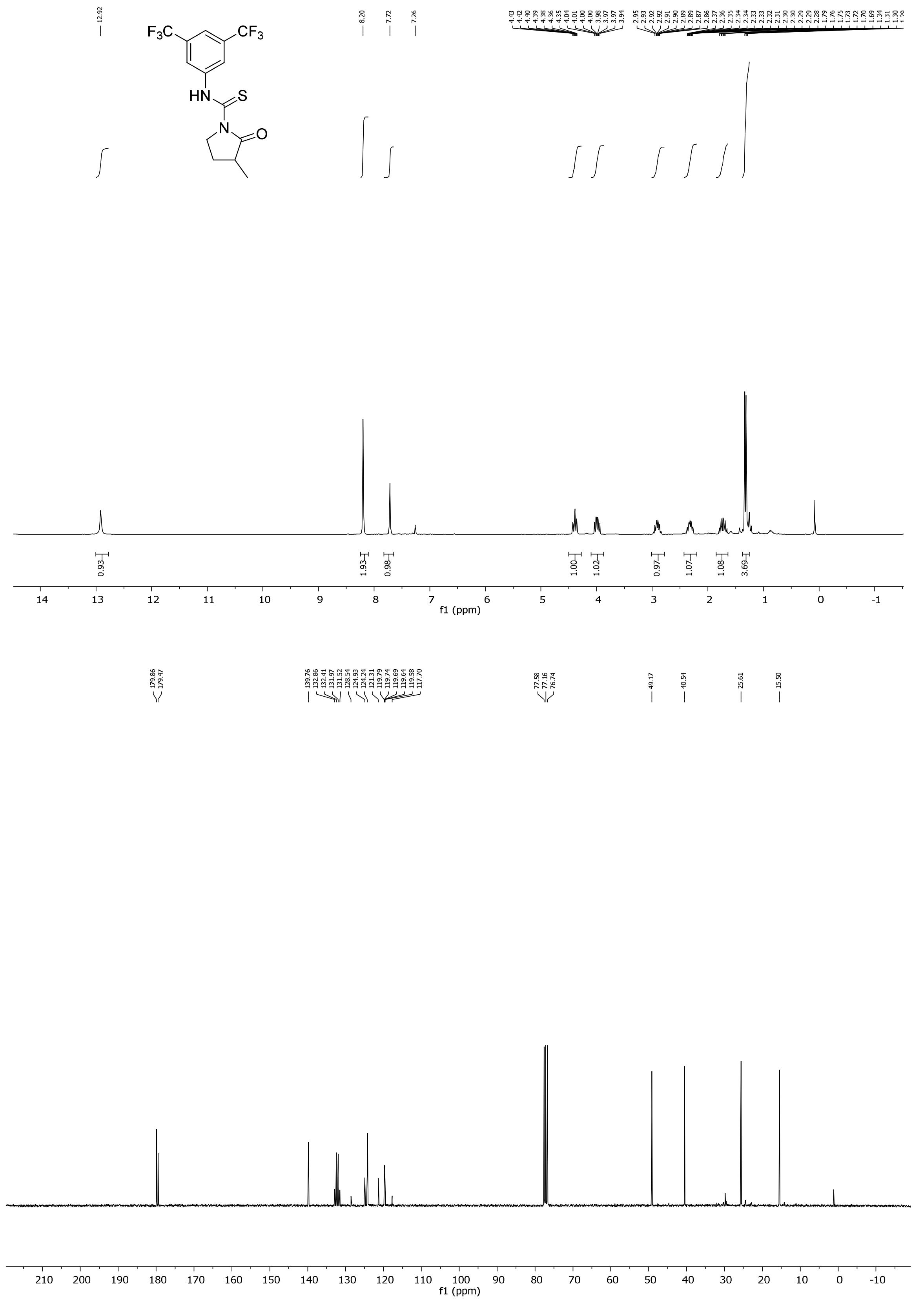


Figure SI-16. NMR spectra for compound **Ia**

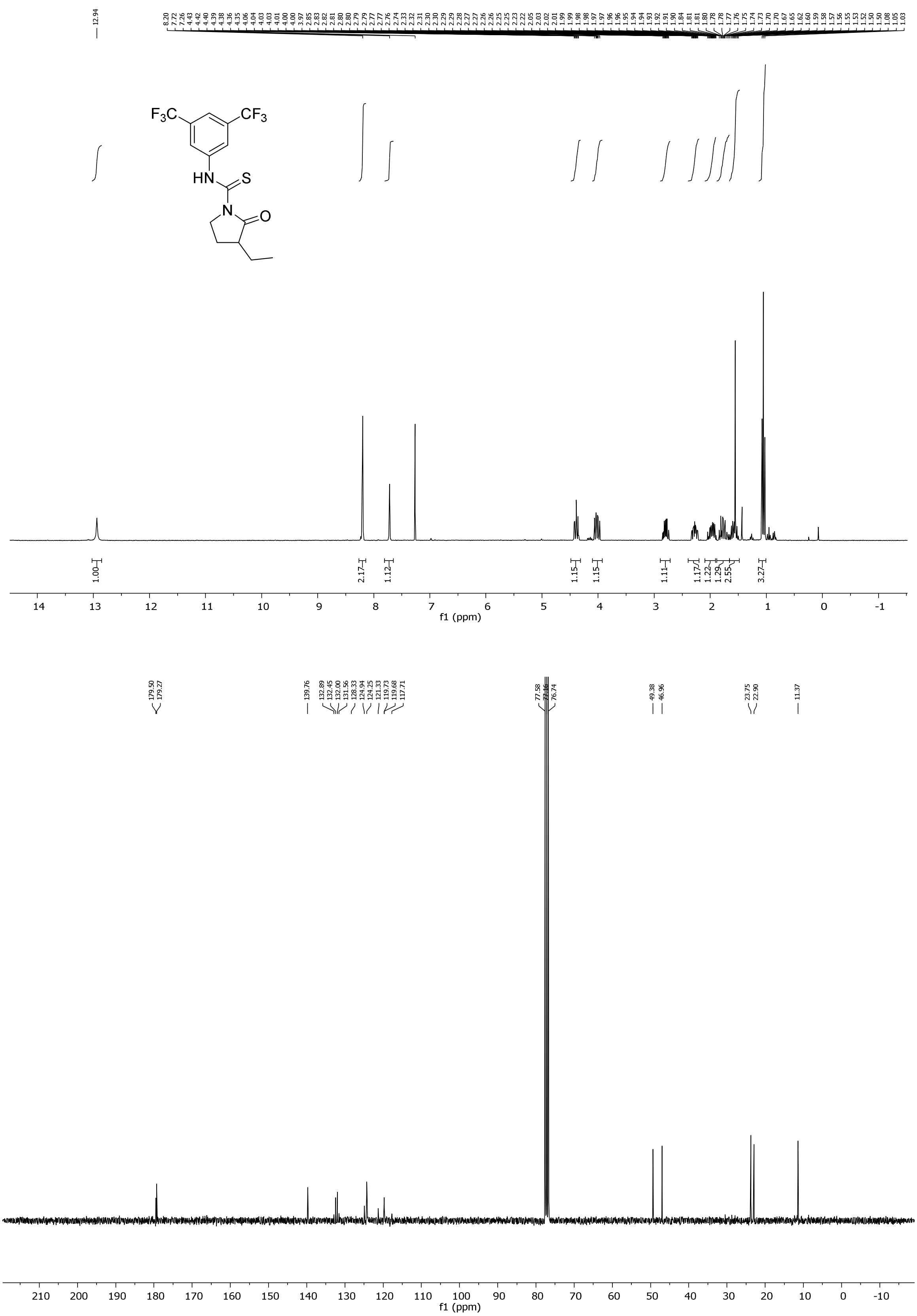
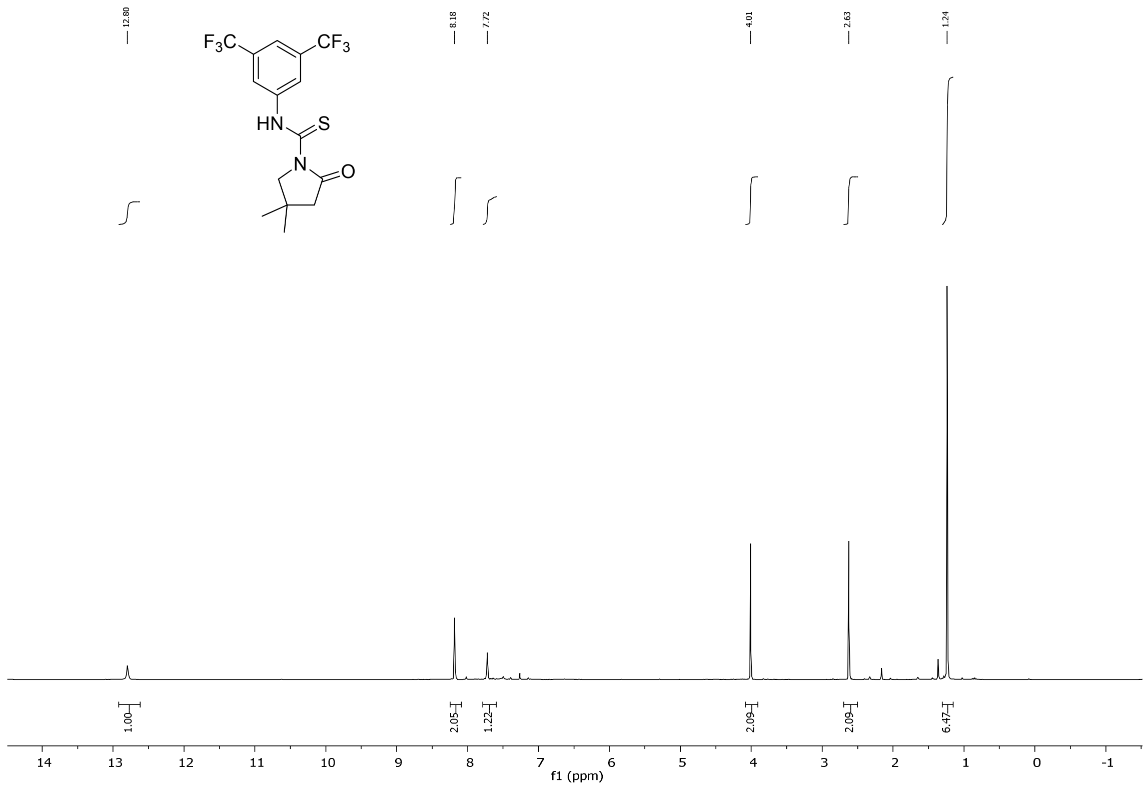


Figure SI-17. NMR spectra for compound **Ib**



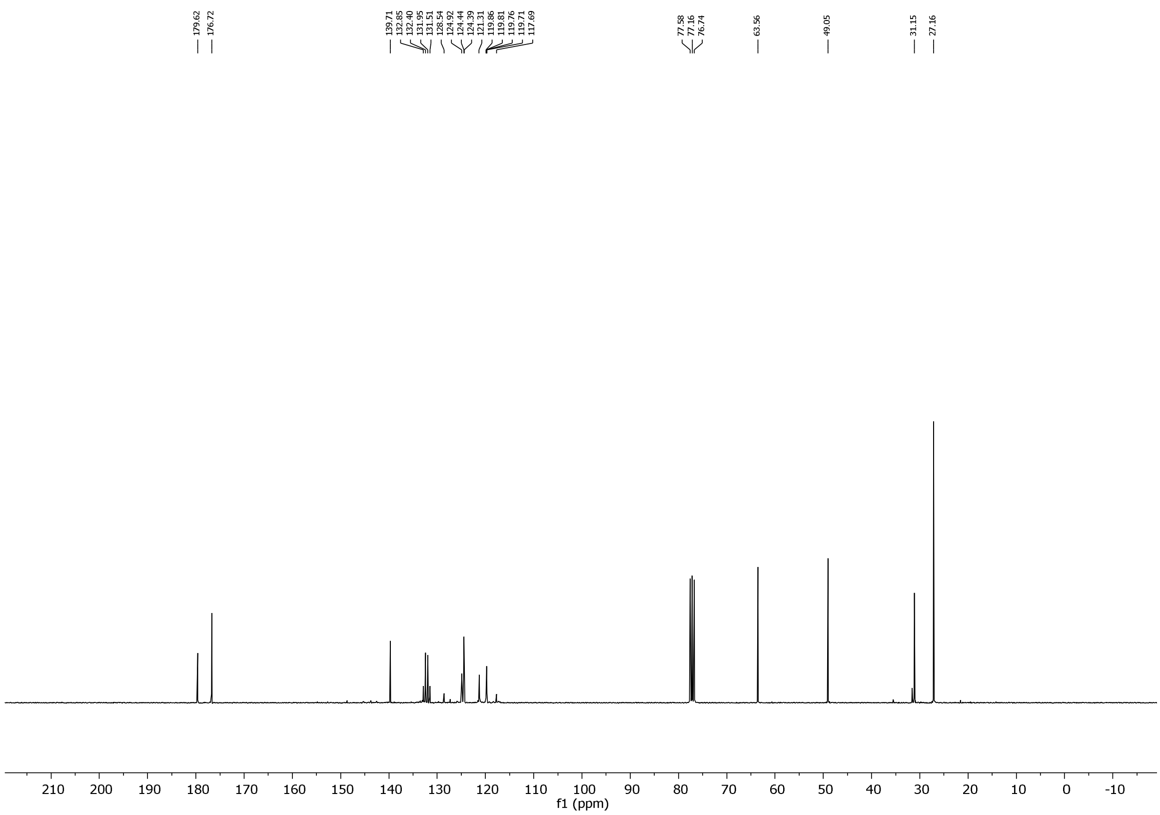
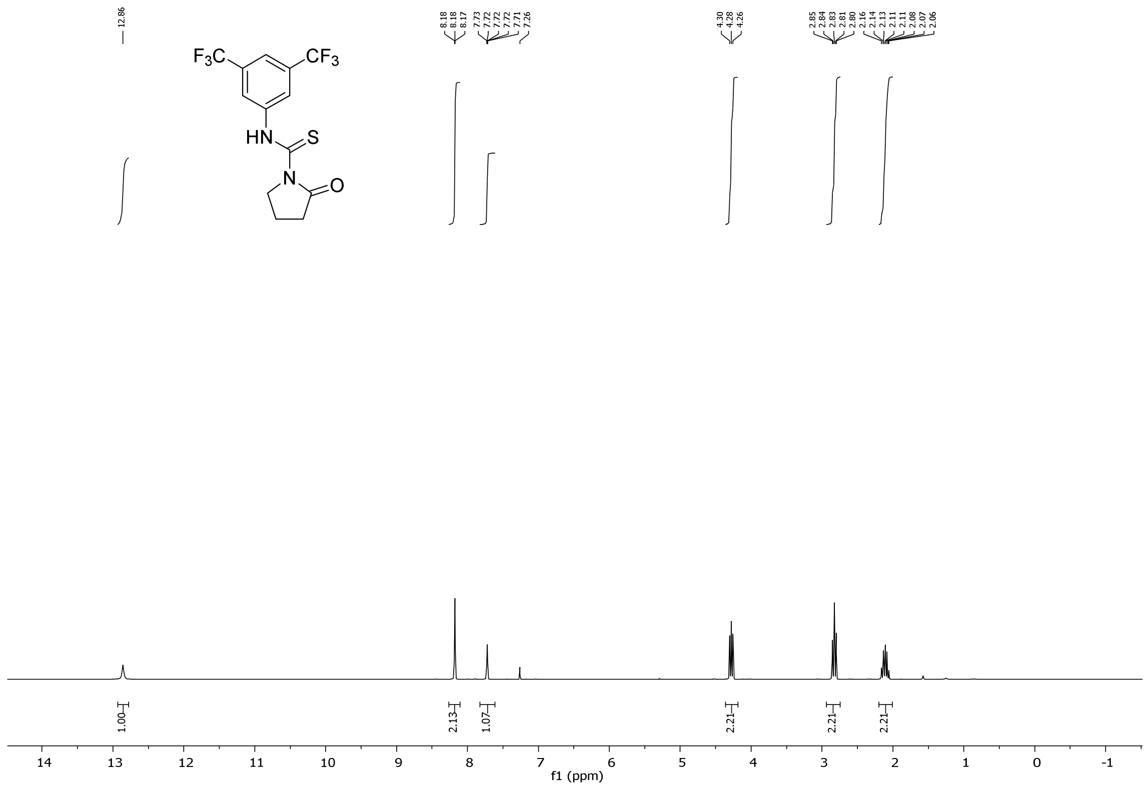


Figure SI-18. NMR spectra for compound **Ic**



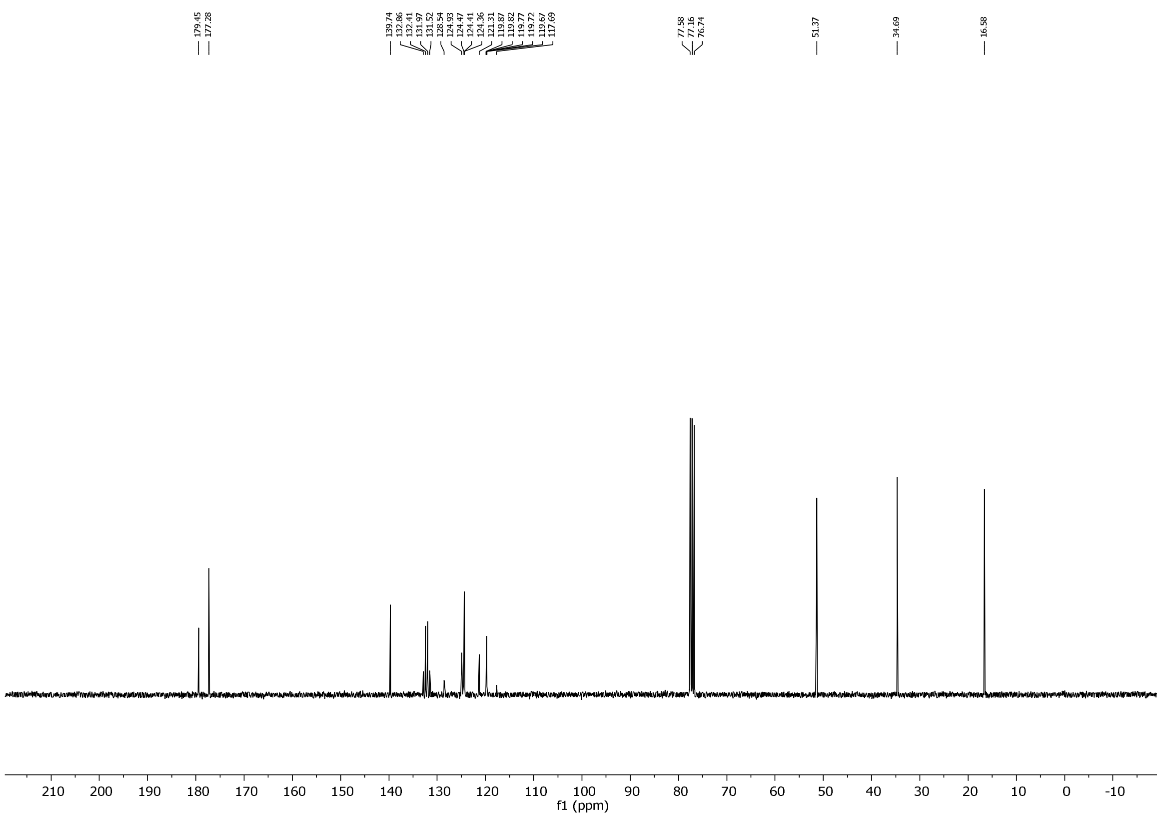


Figure SI-19. NMR spectra for compound **Ie**

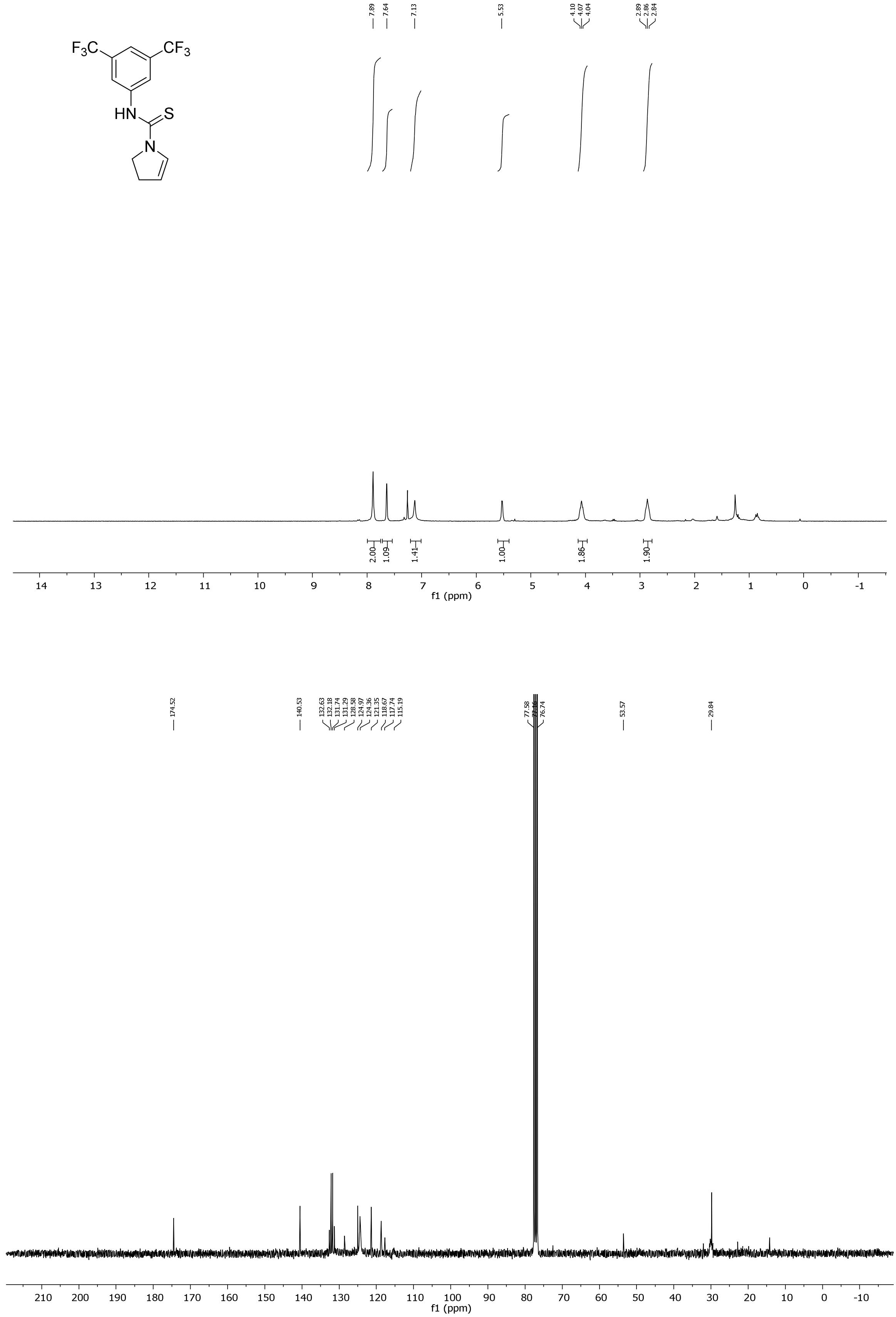
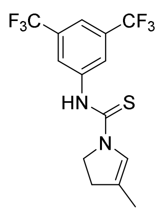
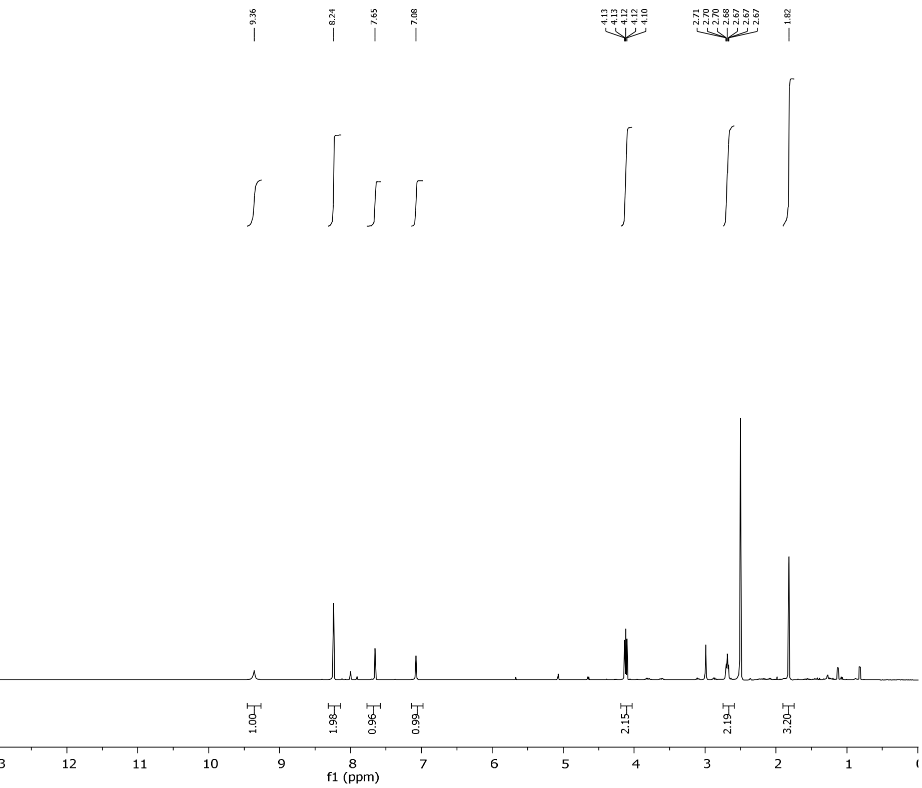


Figure SI-20. NMR spectra for compound **2e**





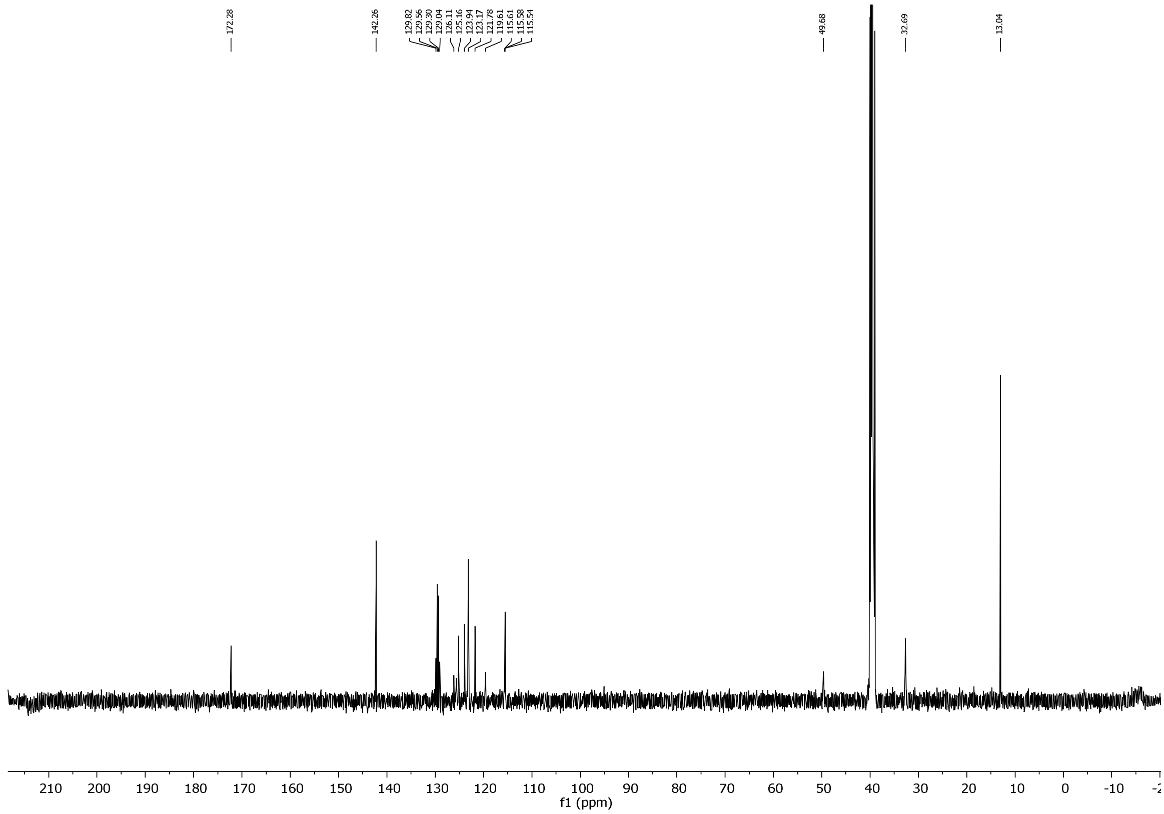
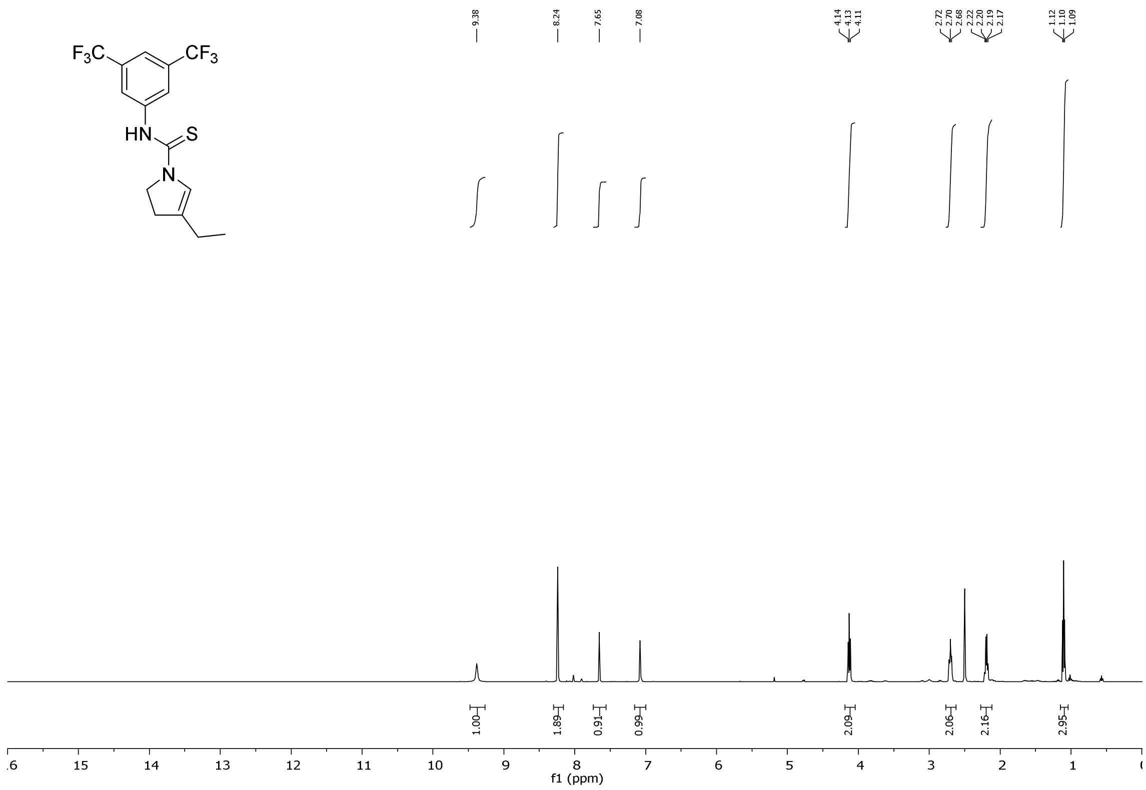


Figure SI-21. NMR spectra for compound **5a** (DMSO-d_6, 100ºC)



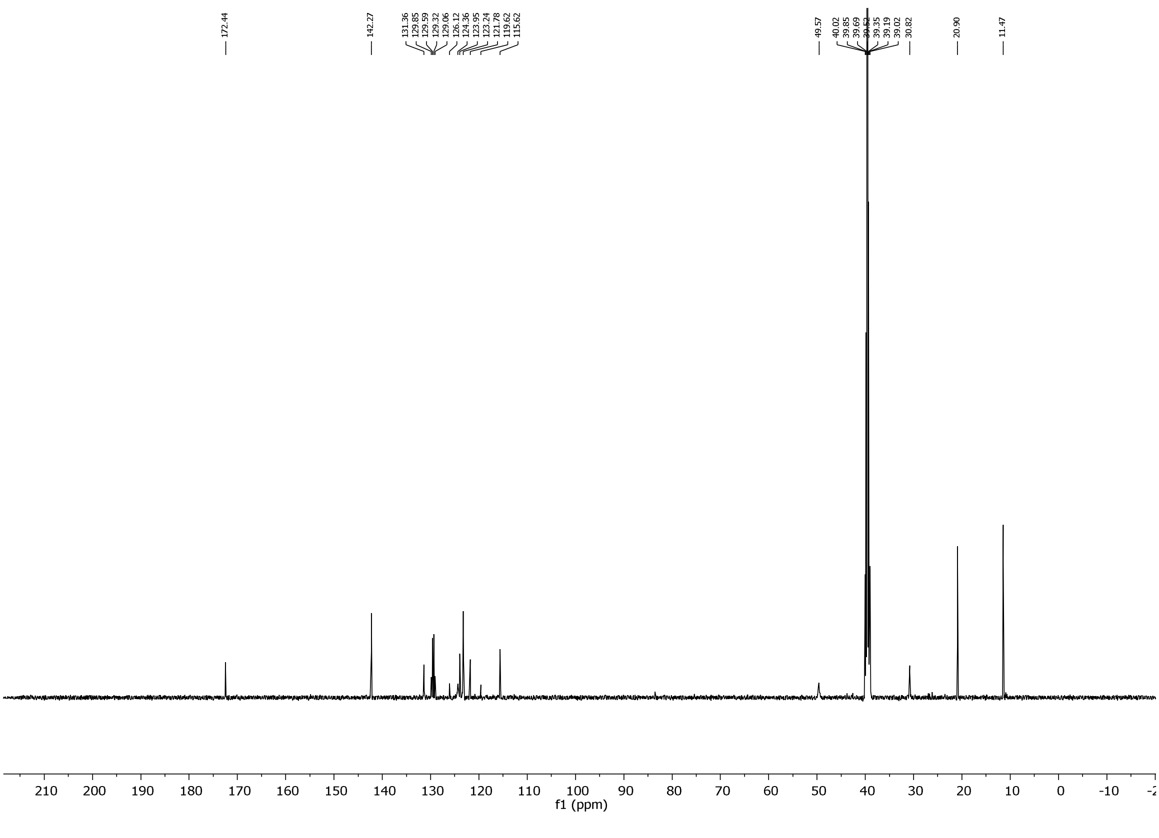


Figure SI-22. NMR spectra for compound **5b** (DMSO-d_6, 100ºC)

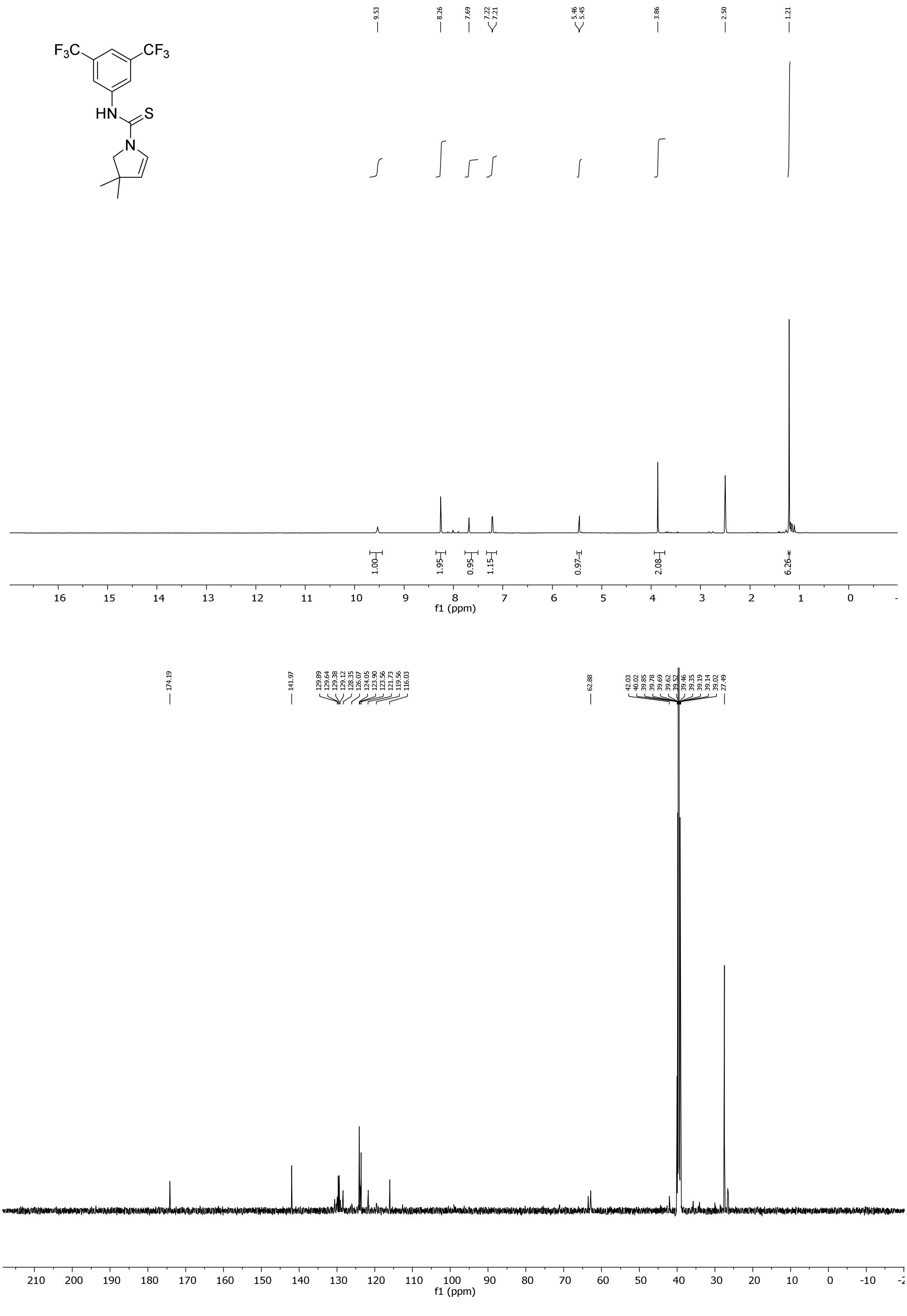


Figure SI-23. NMR spectra for compound **5c** (DMSO-d_6)

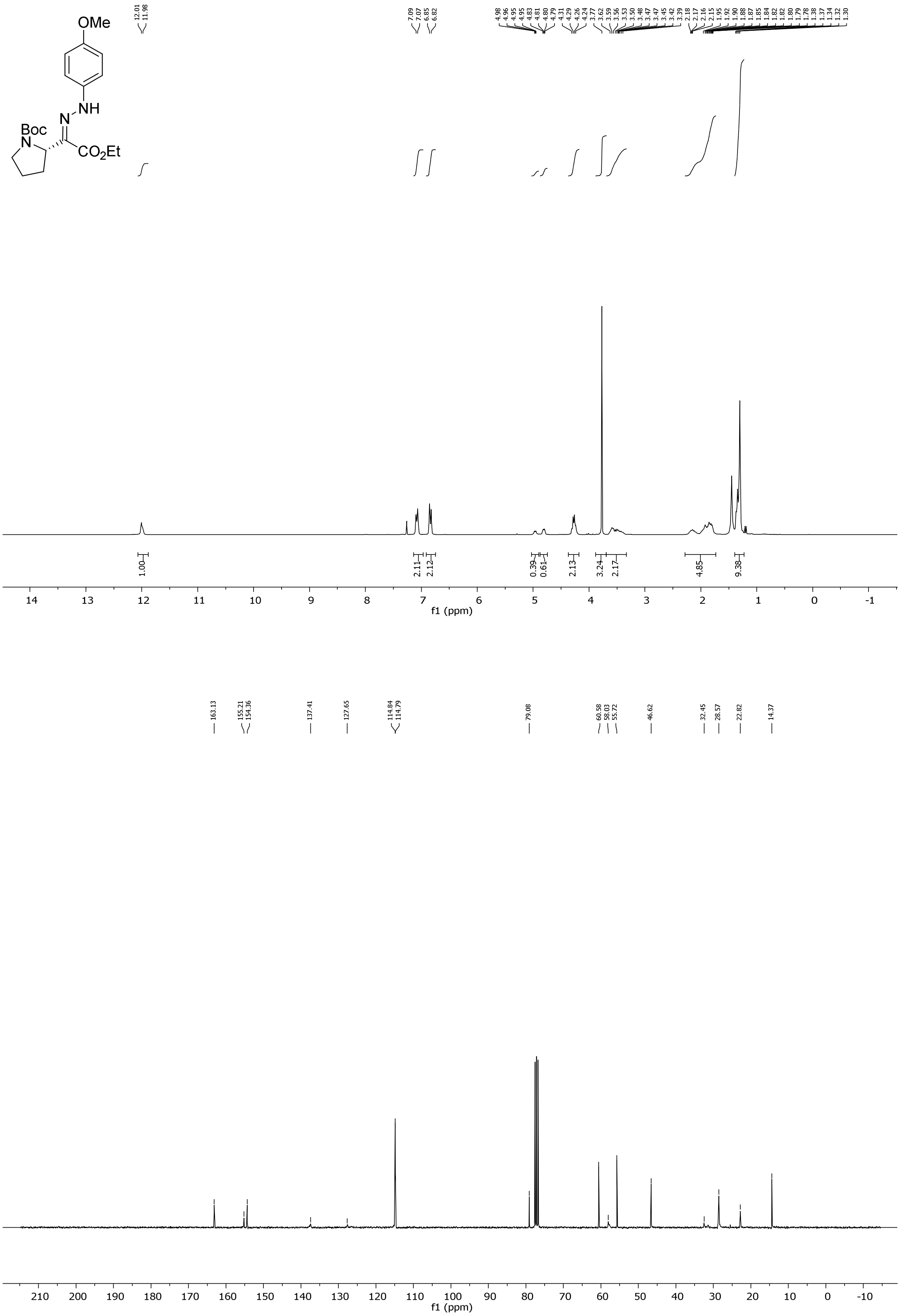
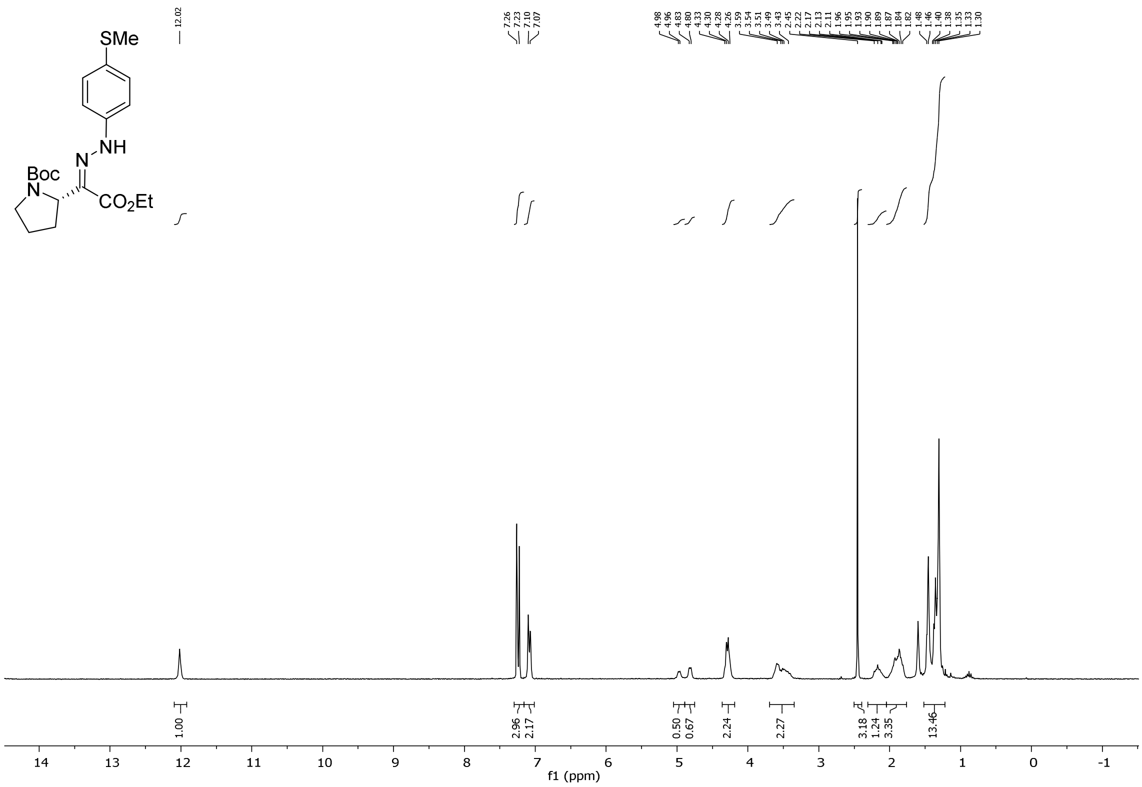


Figure SI-24. NMR spectra for compound **4a**



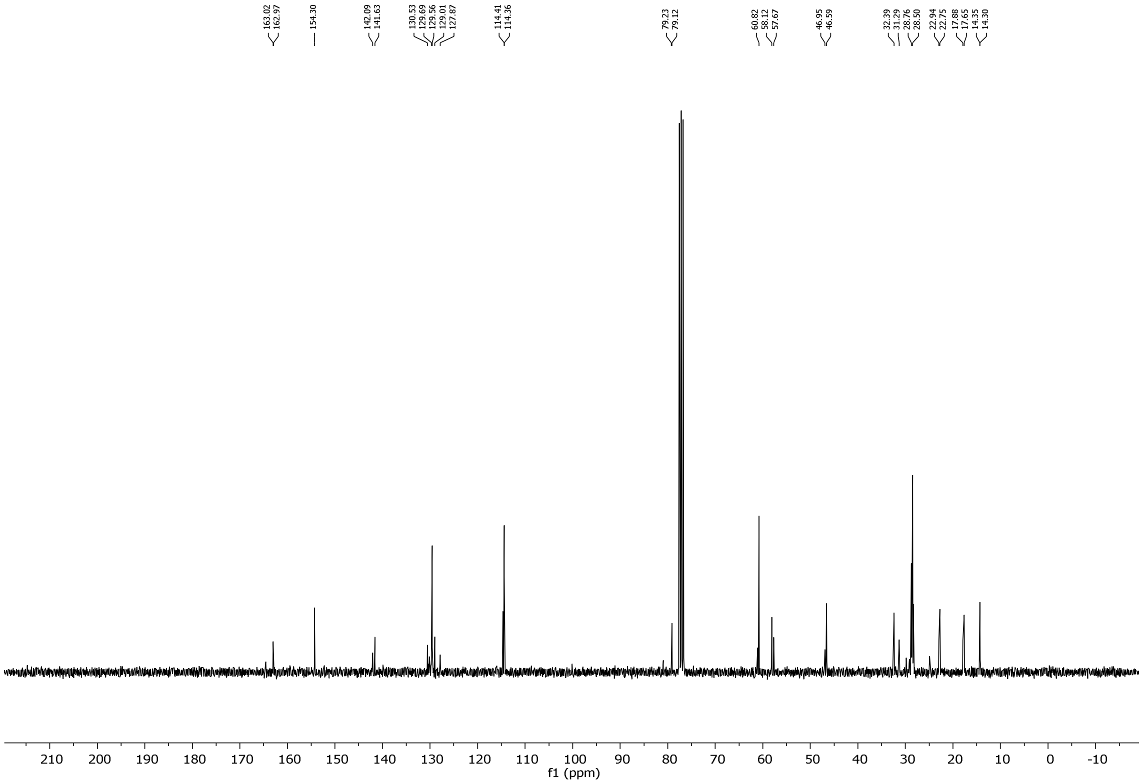
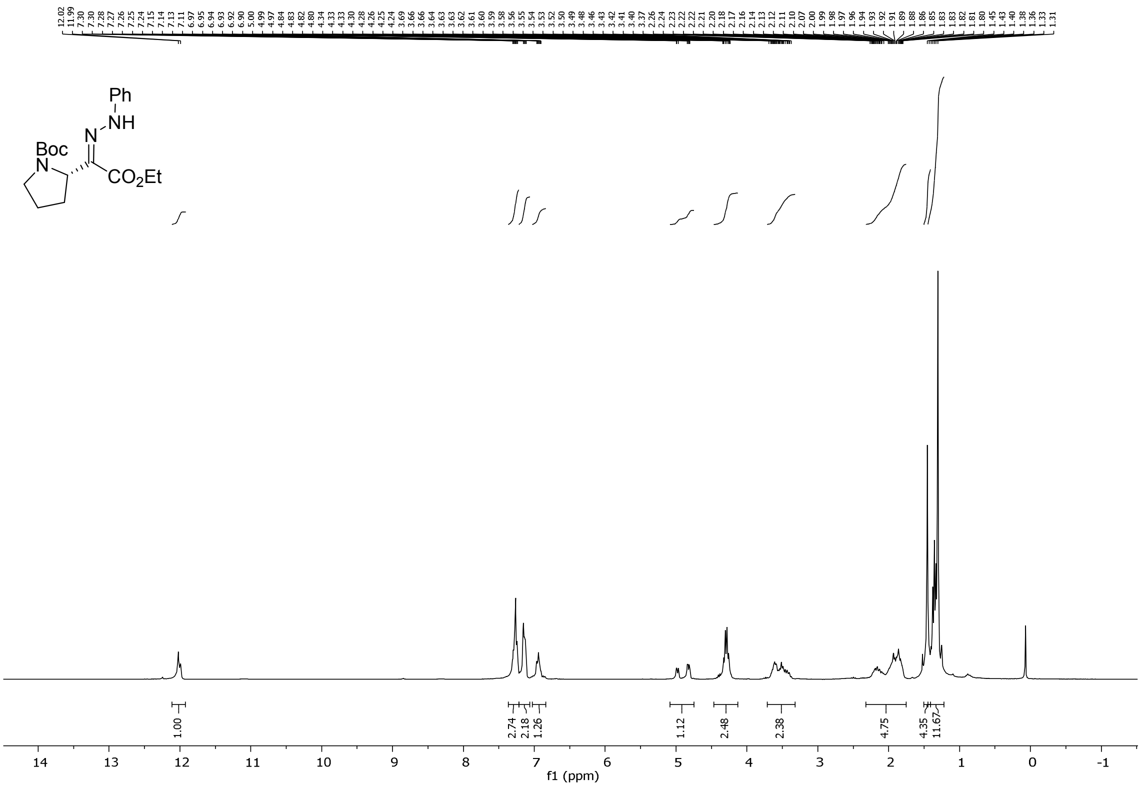


Figure SI-25. NMR spectra for compound **4b**



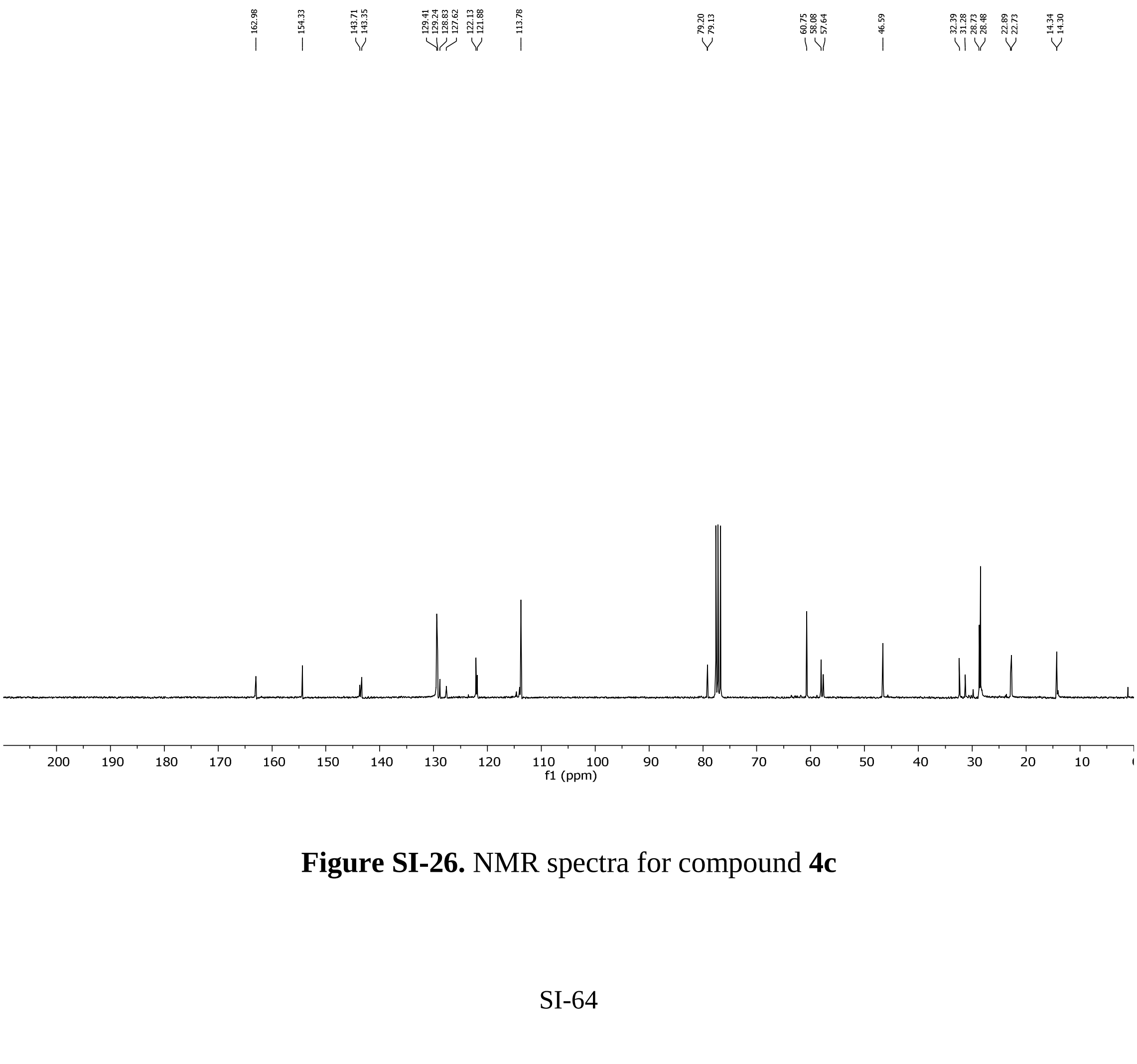


Figure SI-26. NMR spectra for compound **4c**

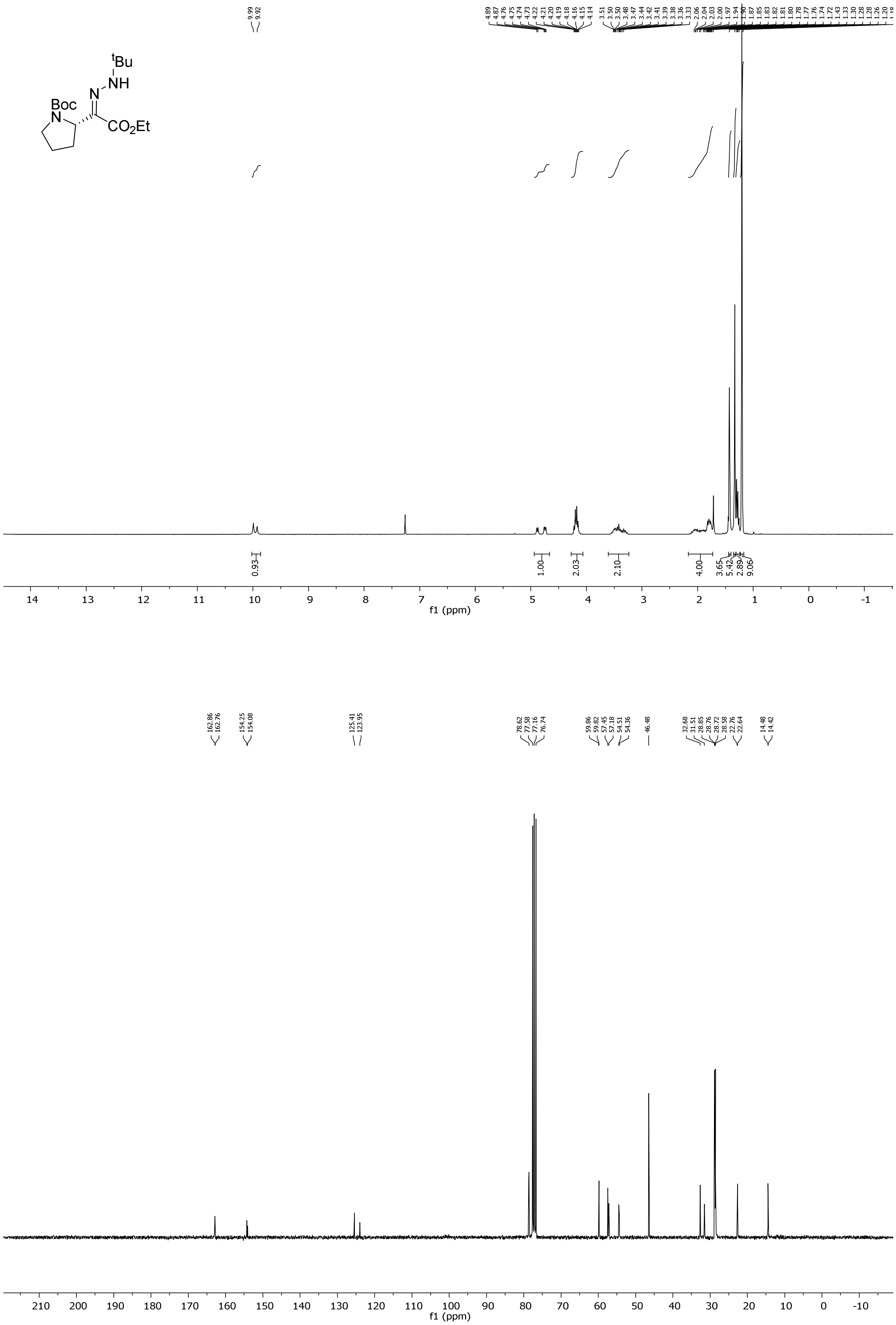


Figure SI-27. NMR spectra for compound **4e**

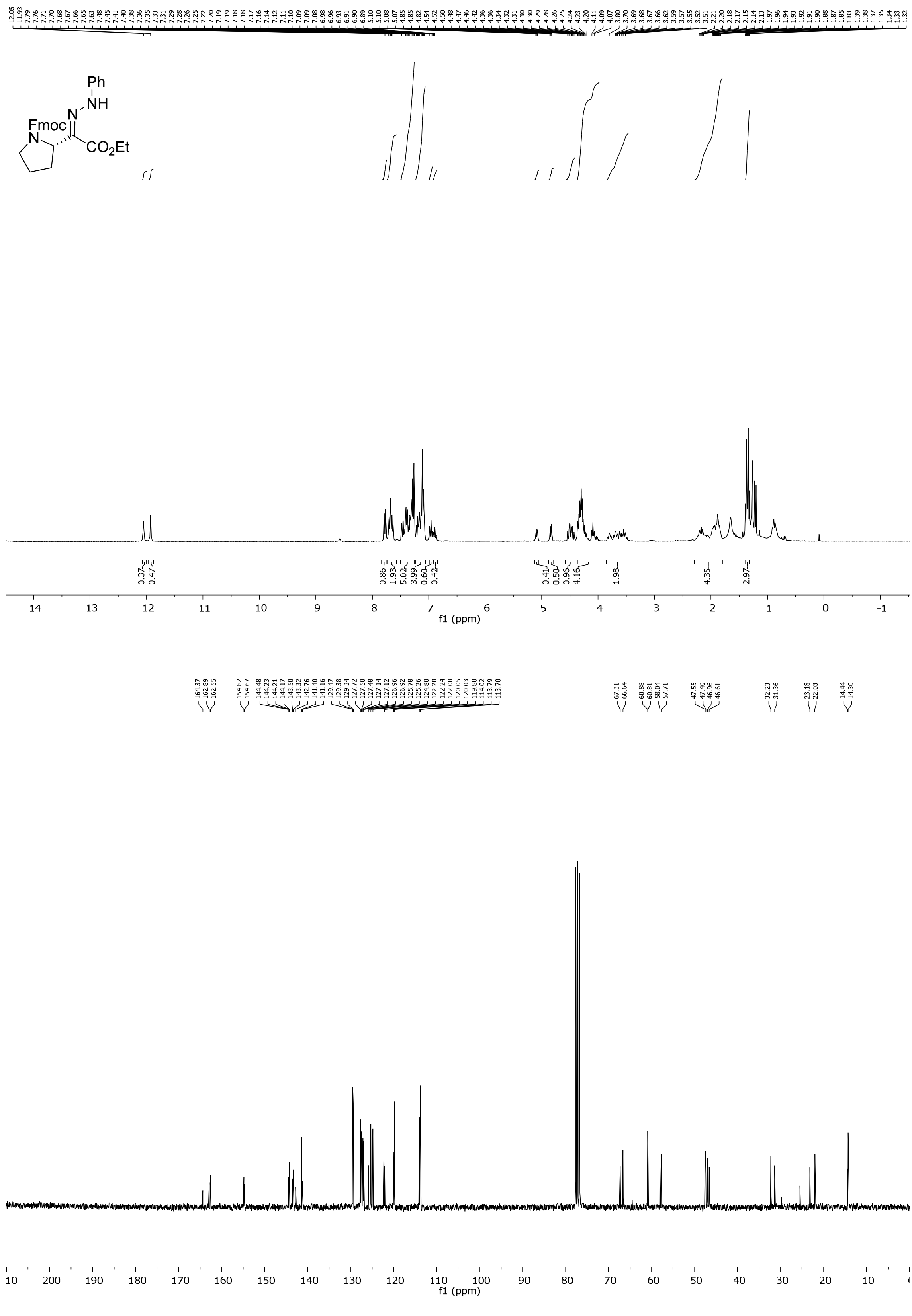


Figure SI-28. NMR spectra for compound **4f**

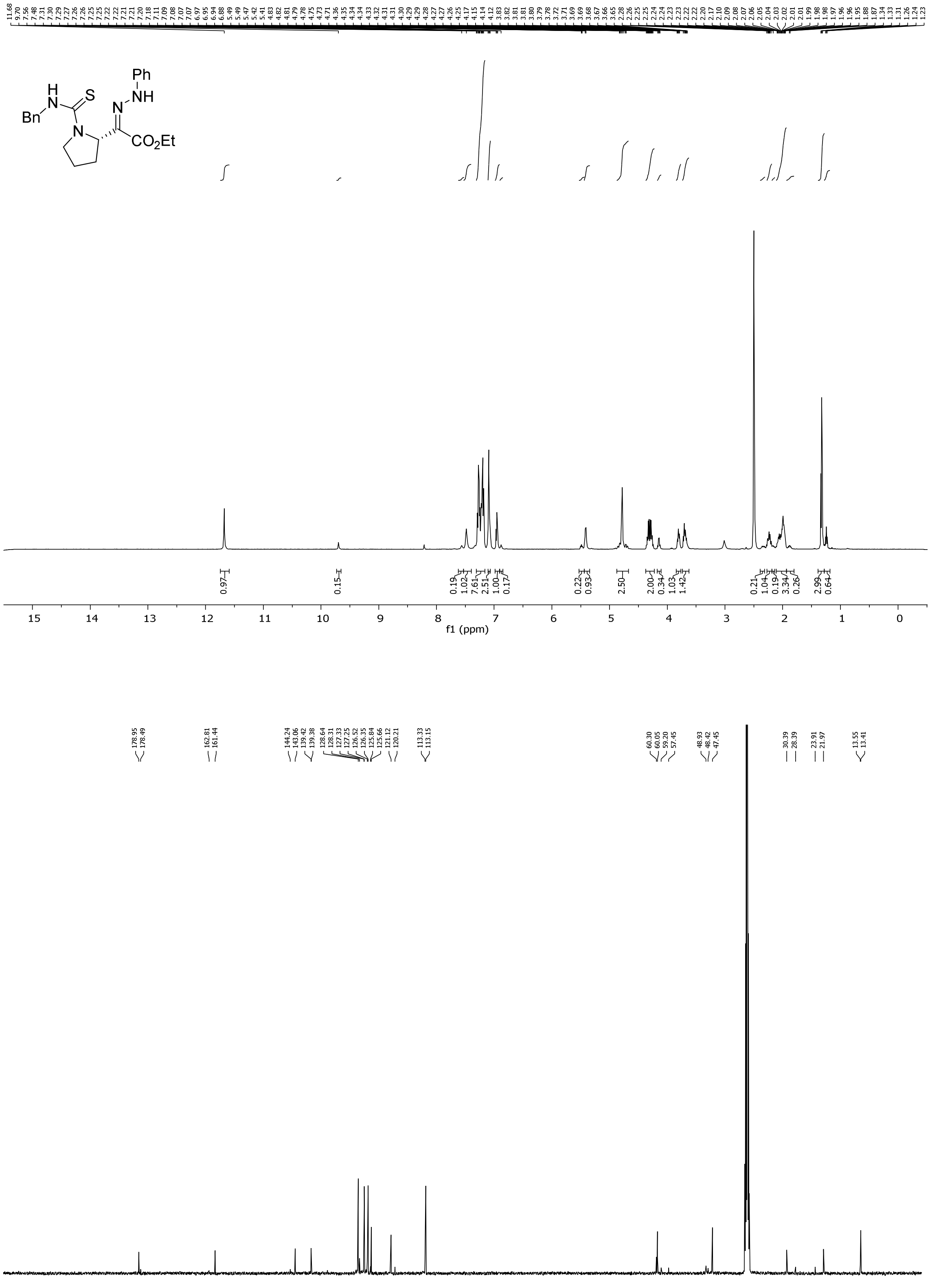
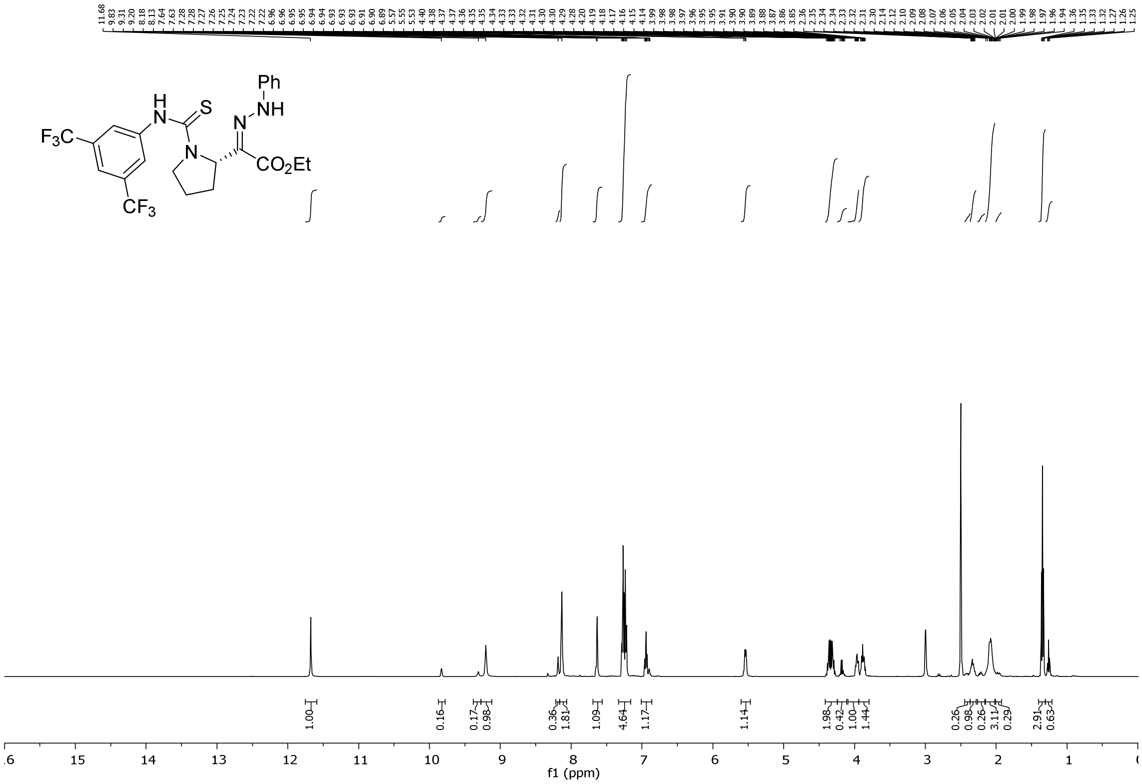
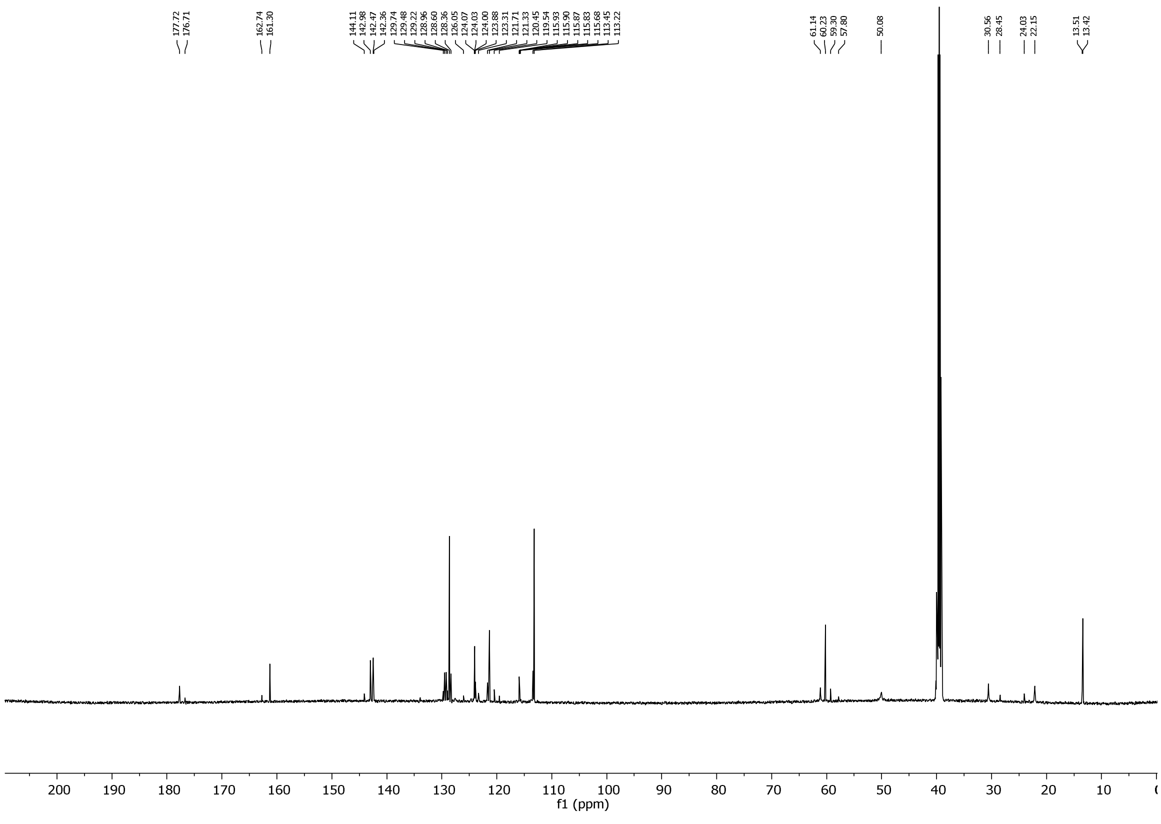
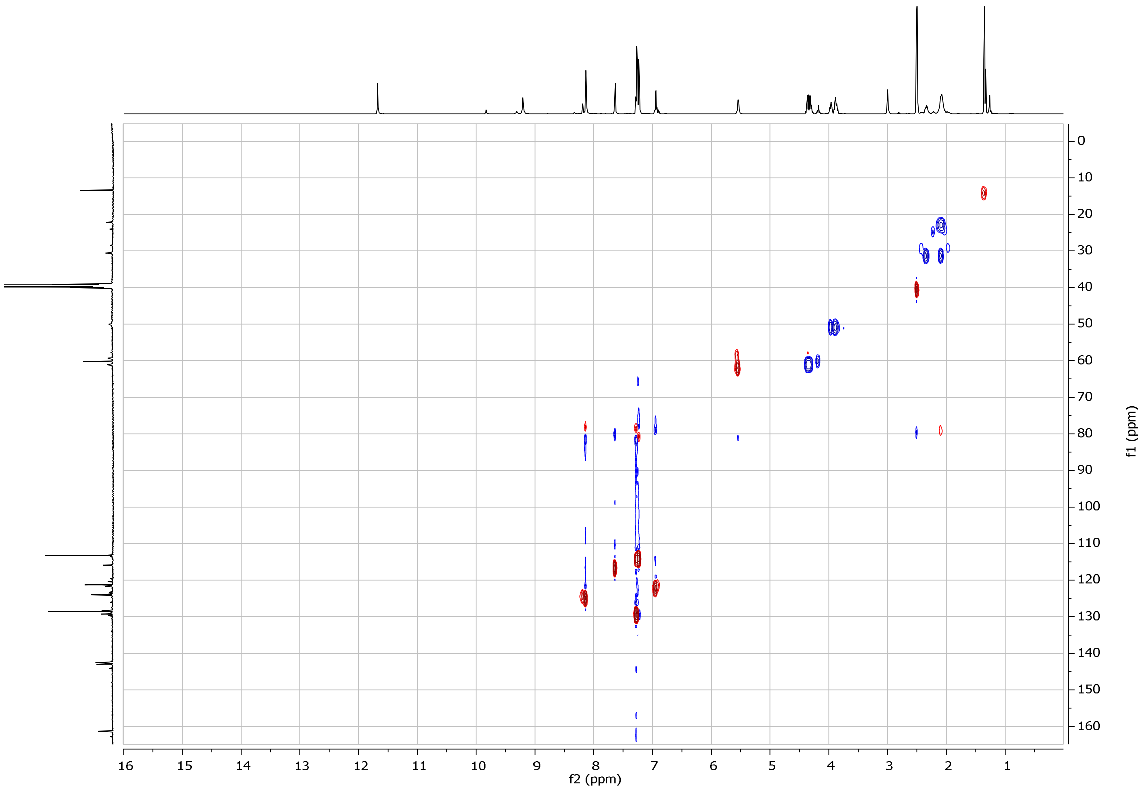


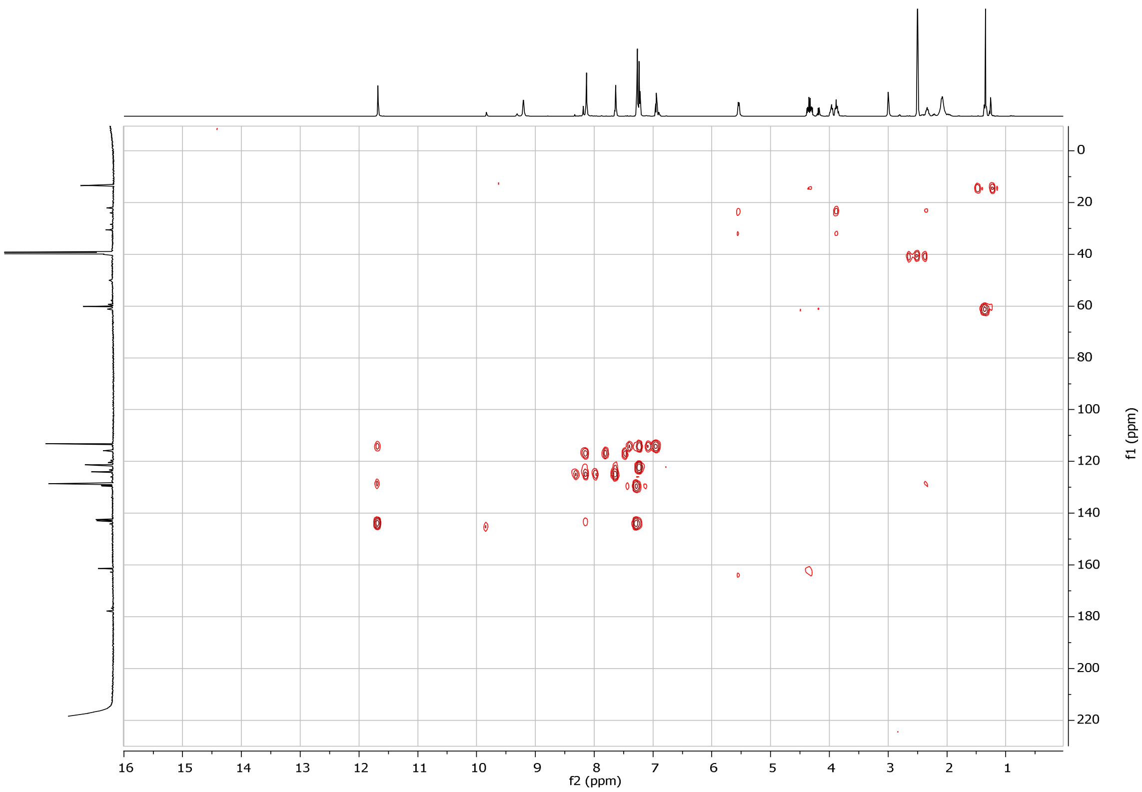
Figure SI-29. NMR spectra for compound **4h** (DMSO-d_6, 100ºC)


f1 (ppm)


f1 (ppm)

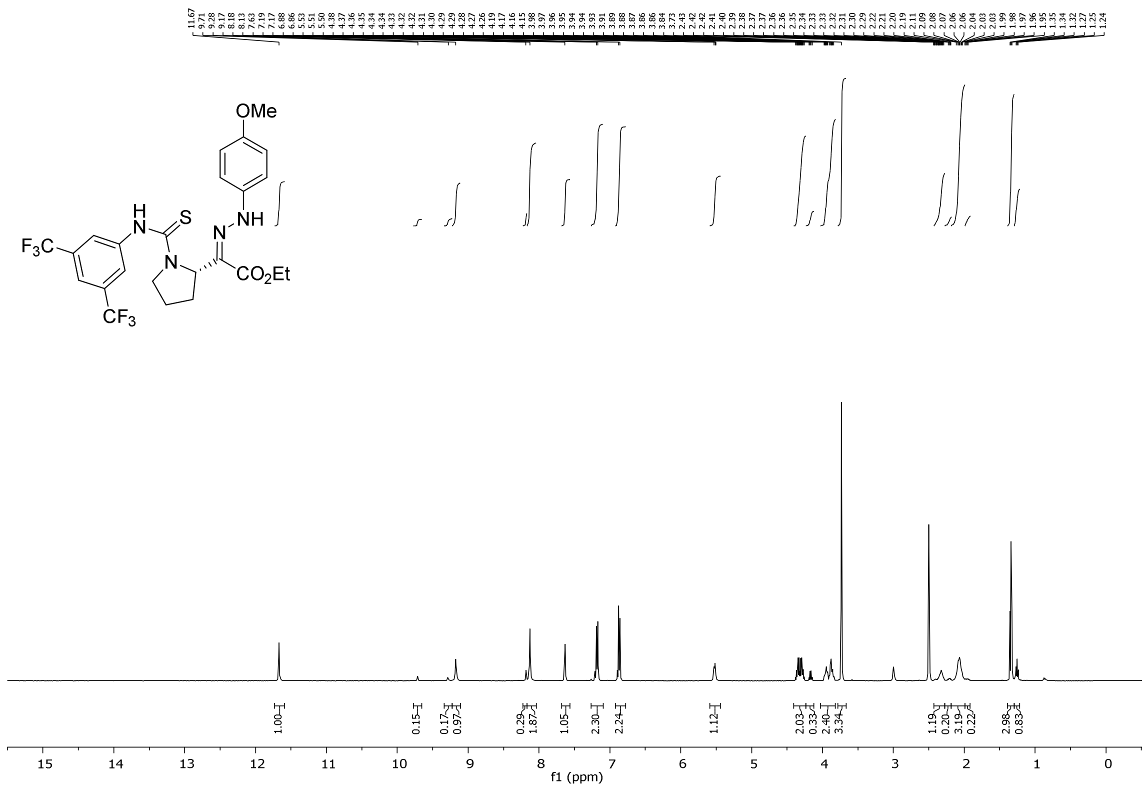


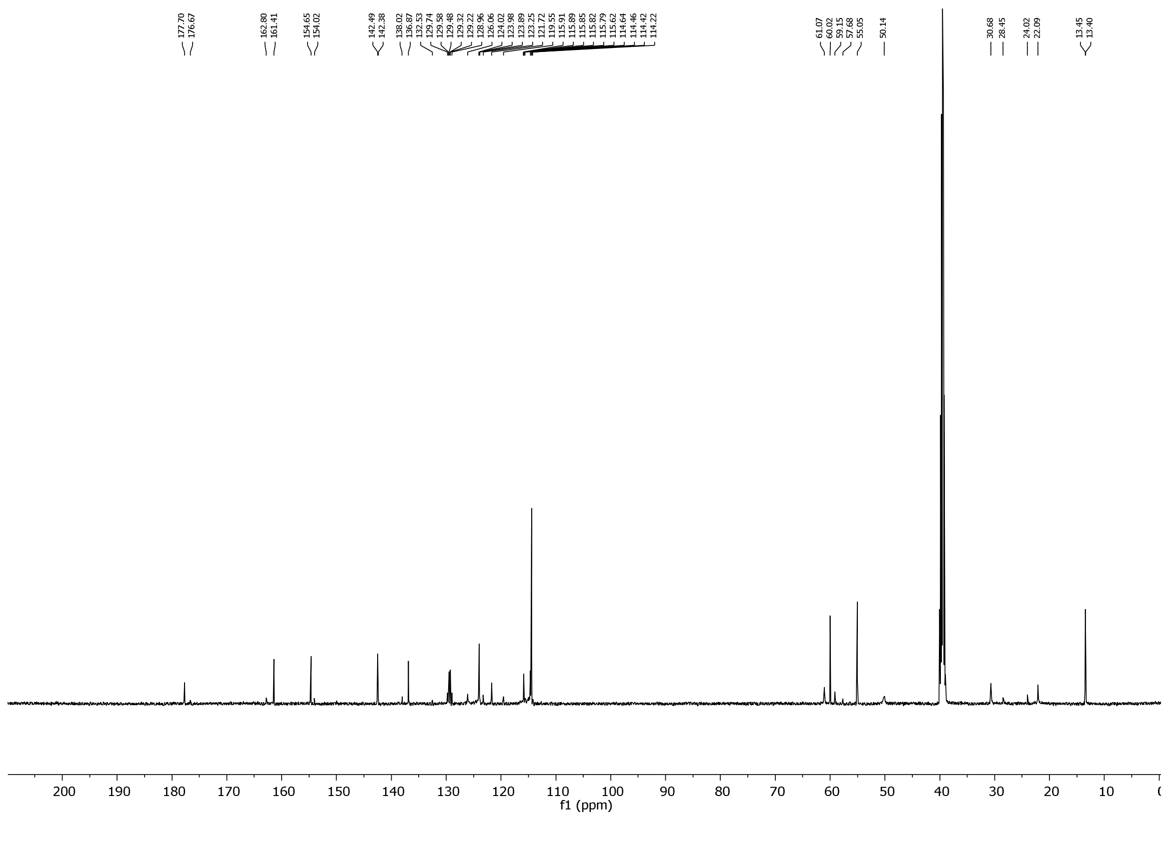
HSQC **4i**

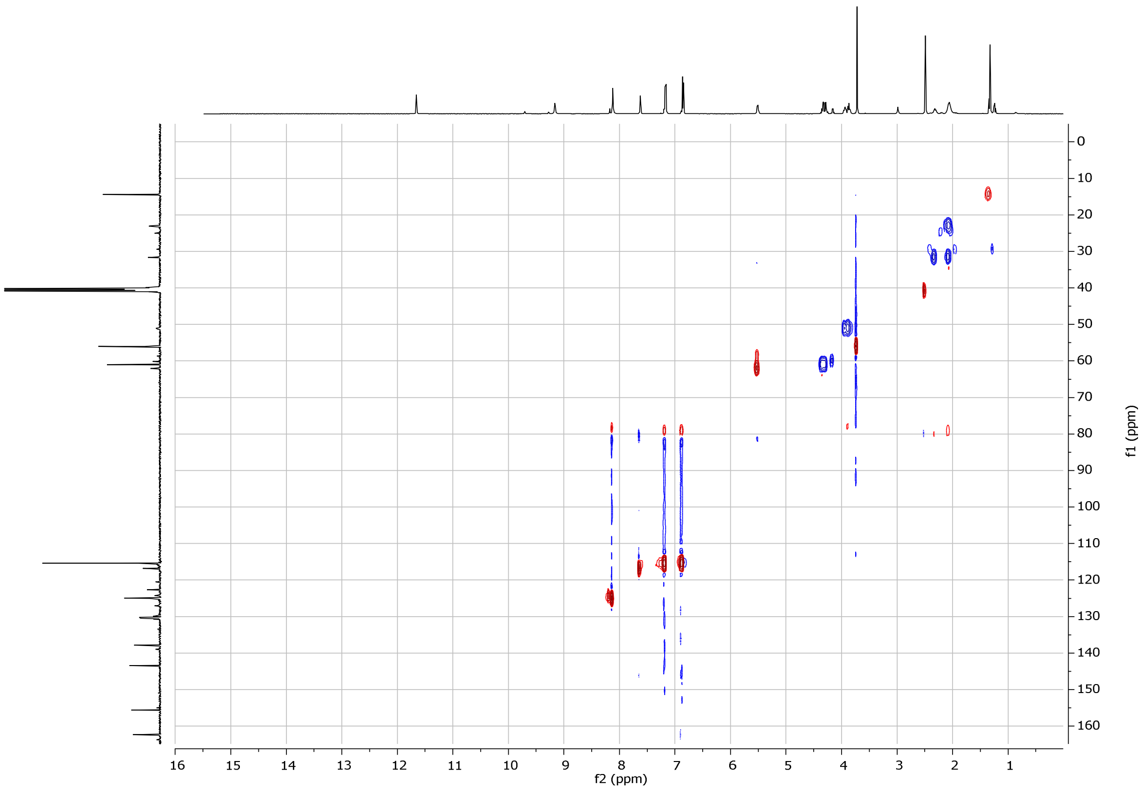


HMBC **4i**

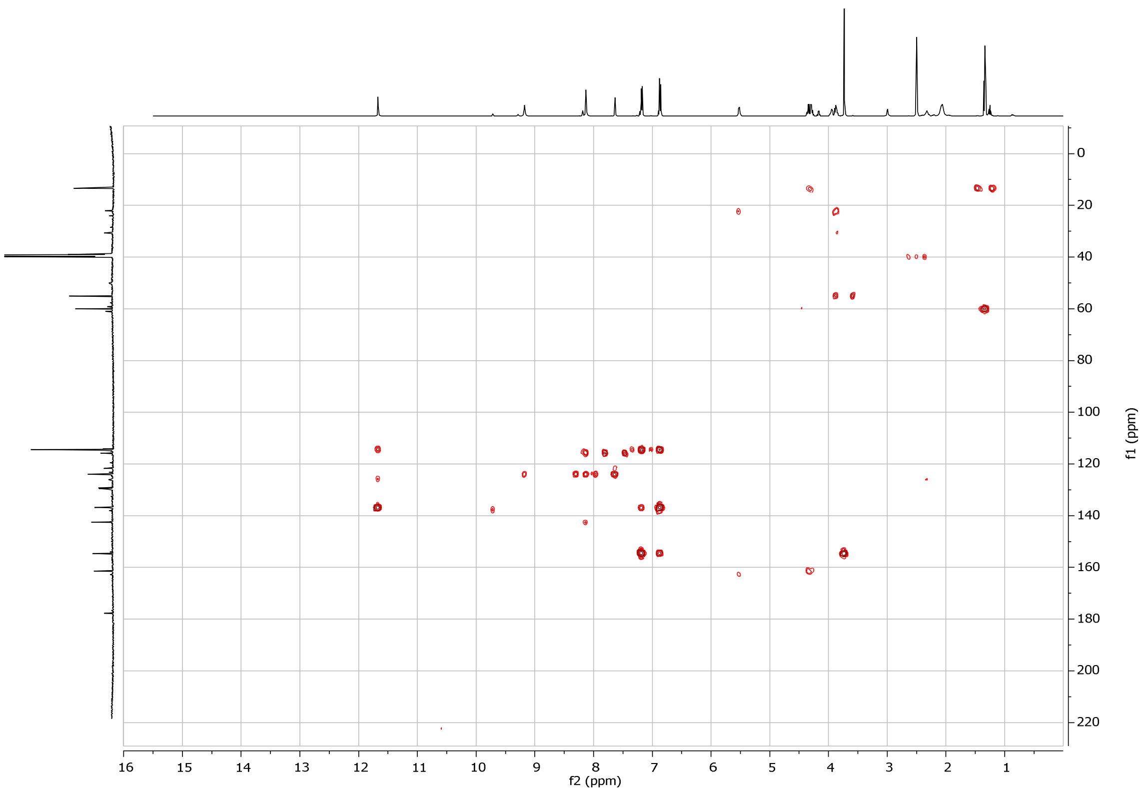
Figure SI-30. NMR spectra for compound **4i** (DMSO-d_6, 100°C)


OMe
NH
H
N
S
N
F3C
CO2Et
CF3
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

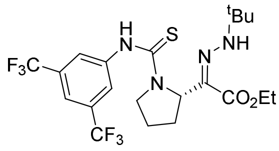


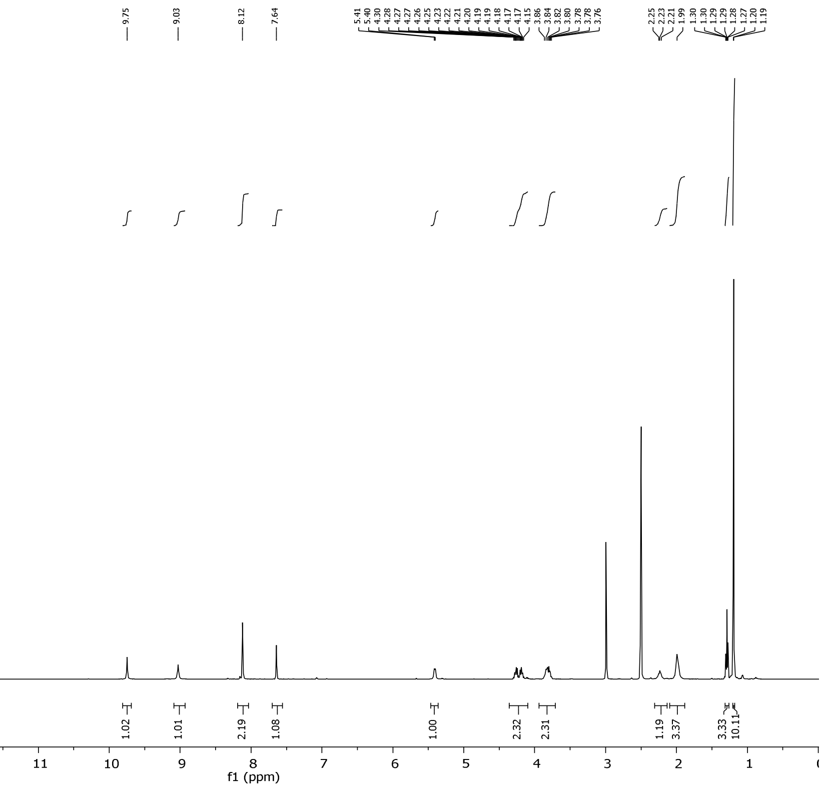
HSQC **4j**

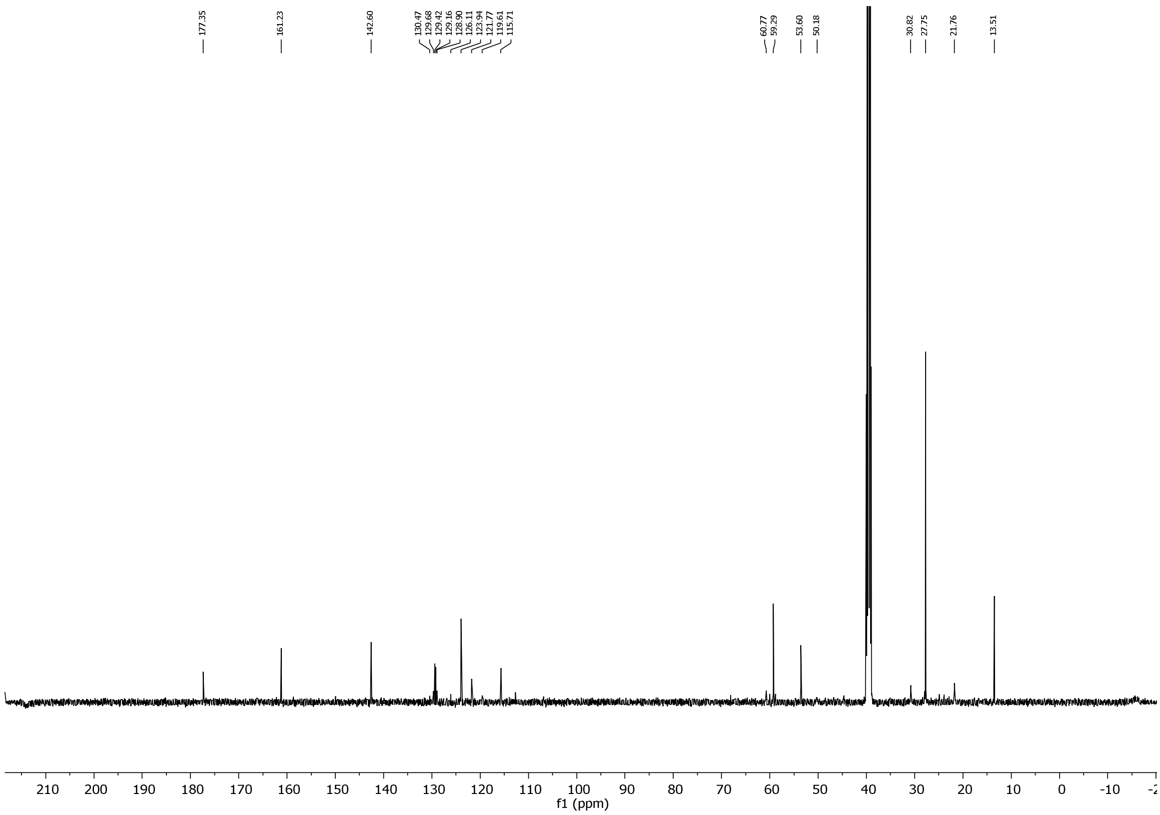


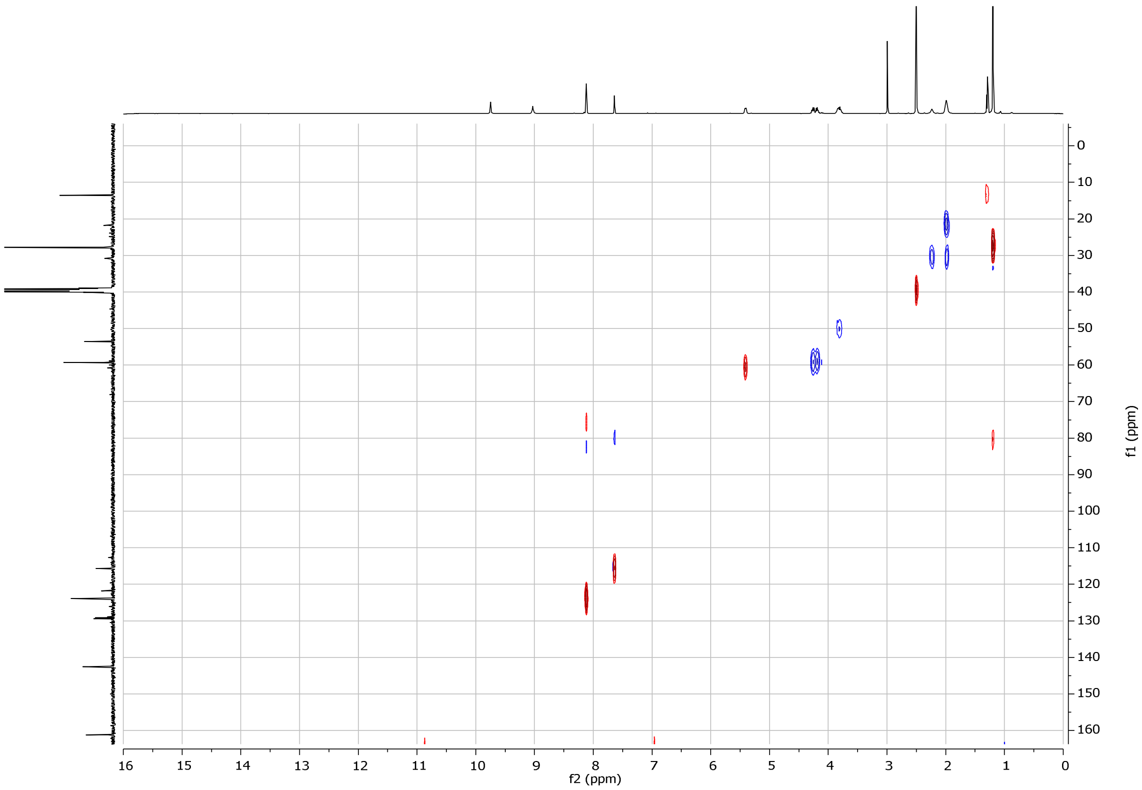
HMBC **4j**

Figure SI-31. NMR spectra for compound **4j** (DMSO-d_6, 100ºC)

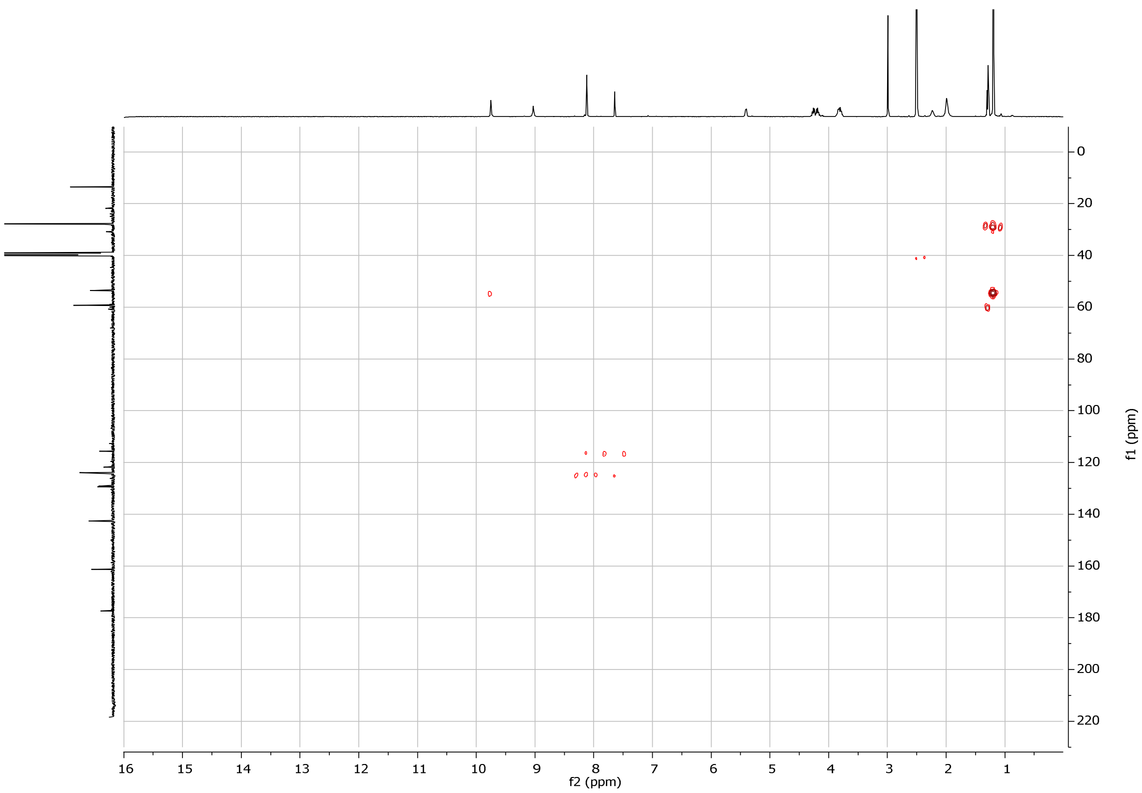






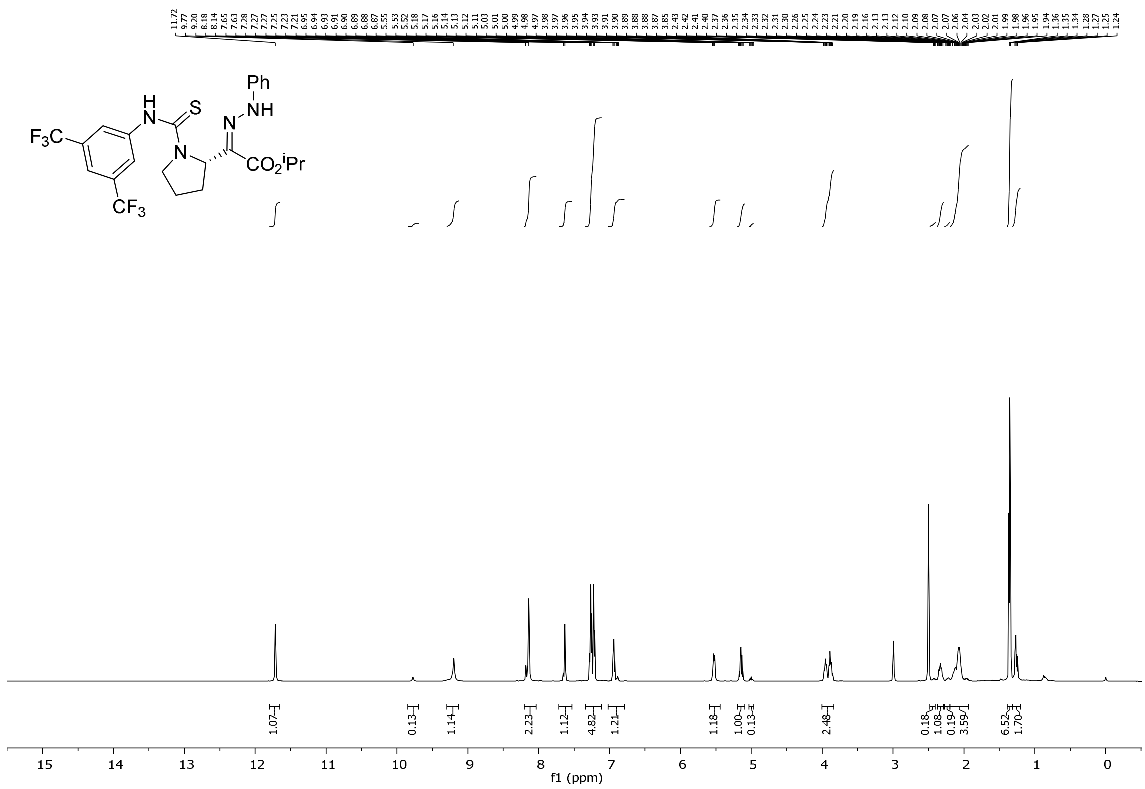


HSQC **4k**

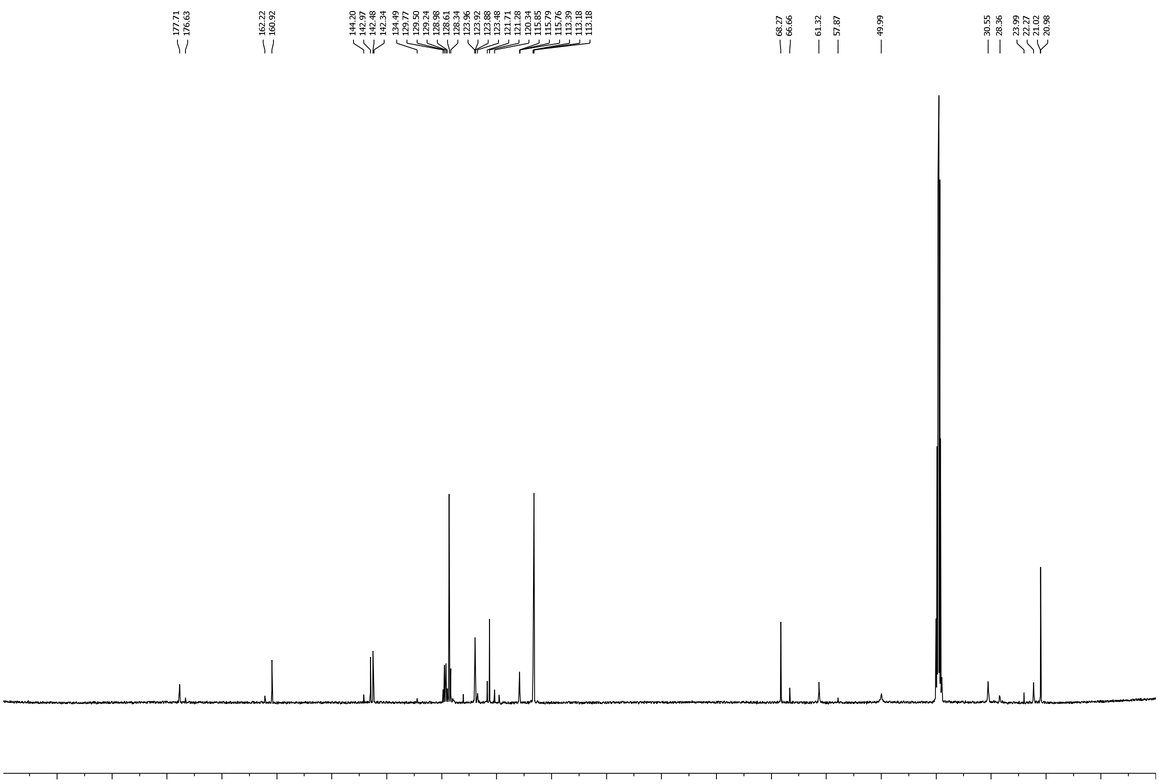


HMBC **4k**

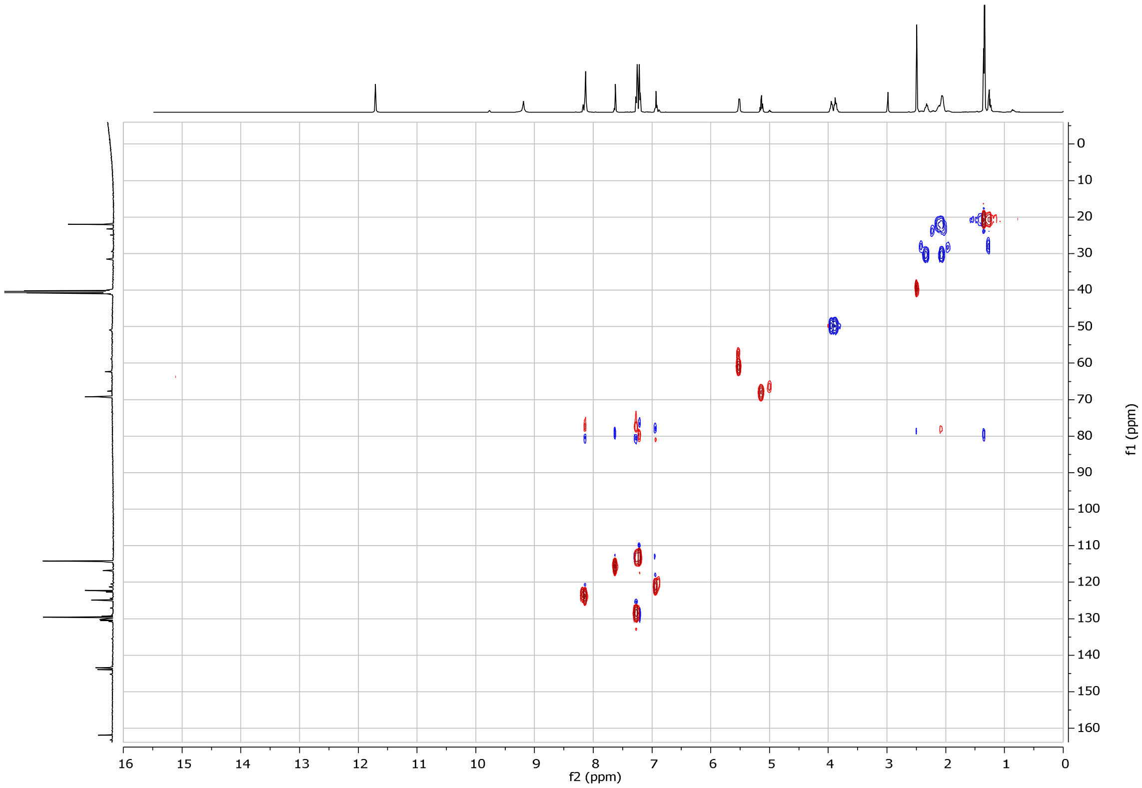
Figure SI-32. NMR spectra for compound **4k** (DMSO-d_6, 100ºC)



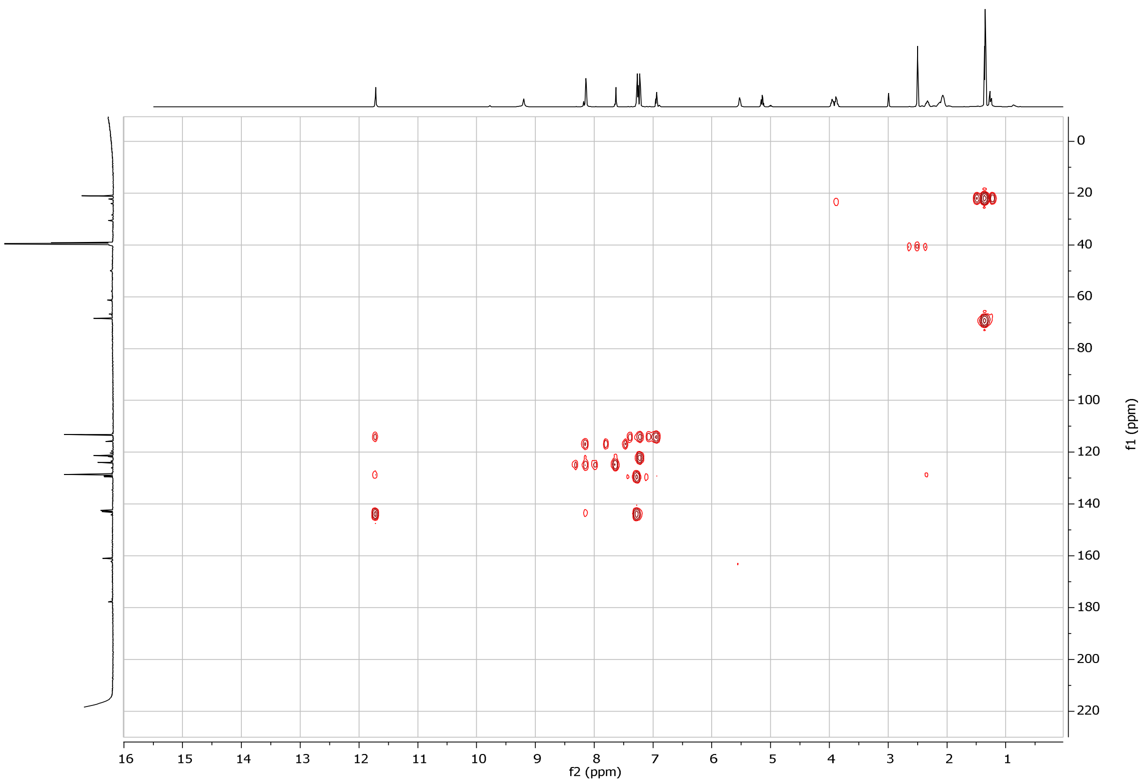
Ph
NH
N
H
N
S
F3C
N
CO2iPr
CF3
f1 (ppm)



f1 (ppm)

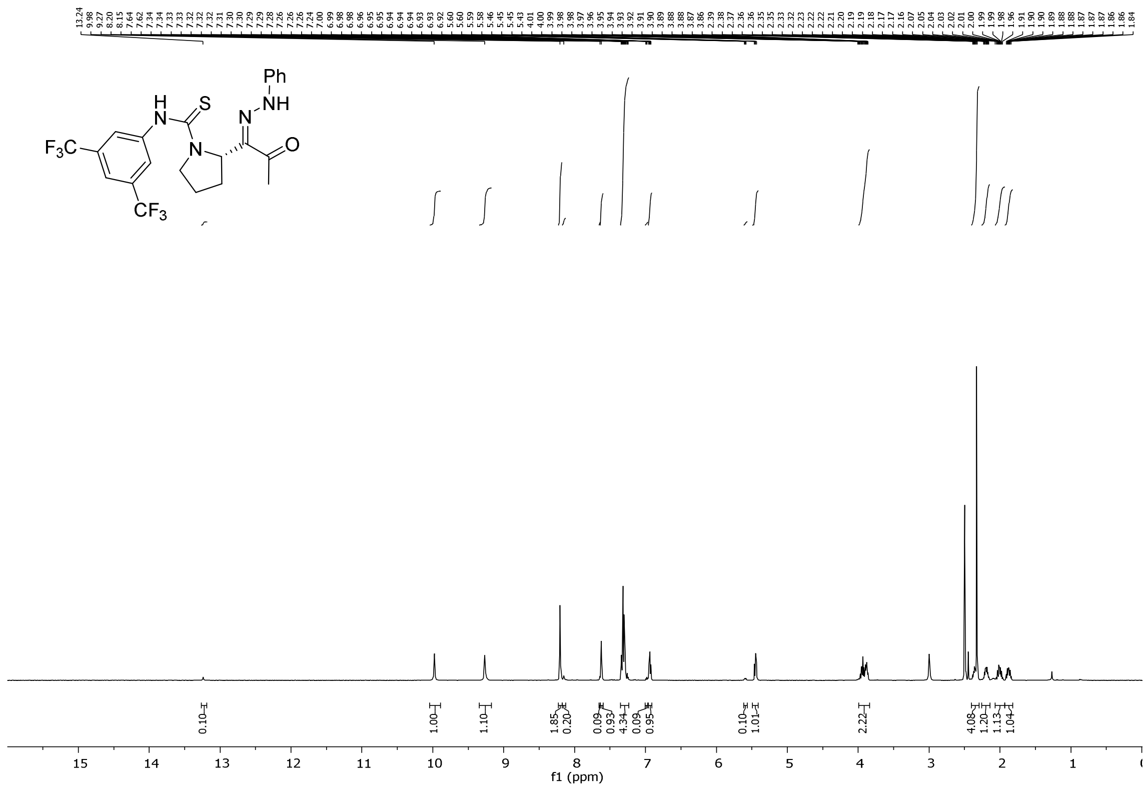


HSQC **4l**

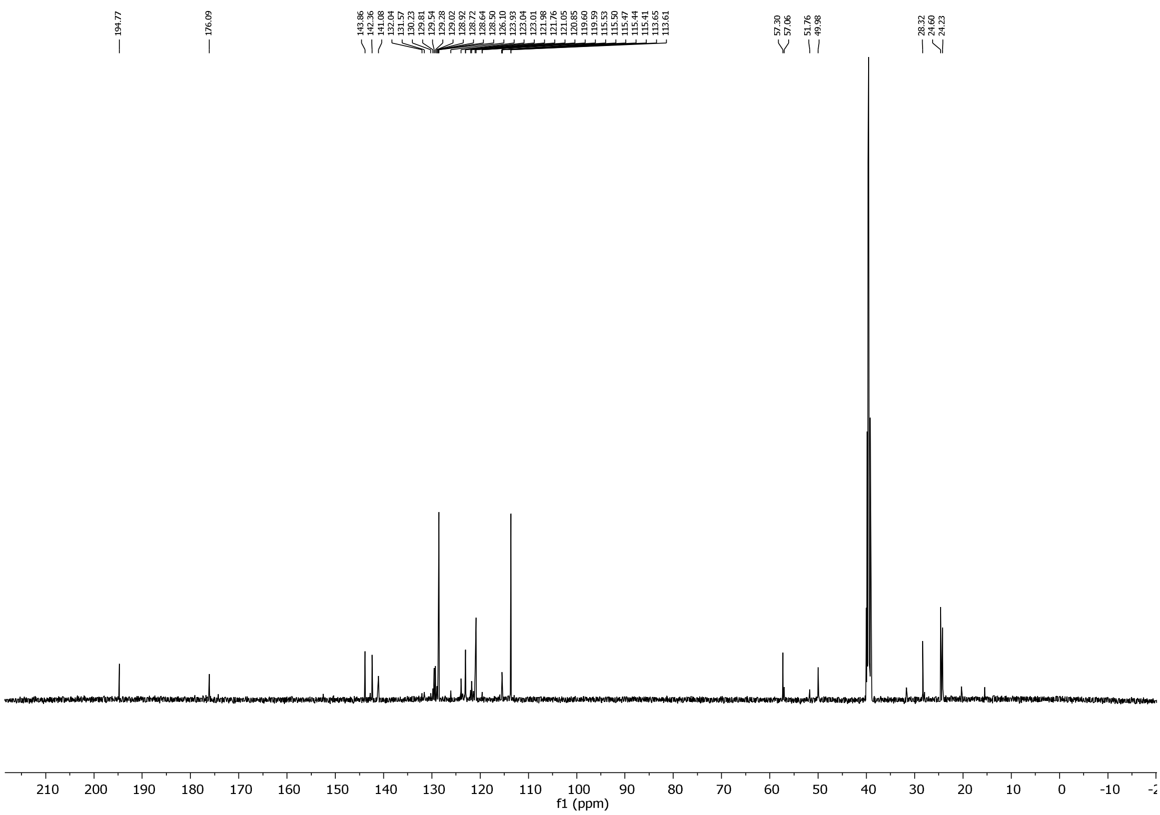


HMBC **4l**

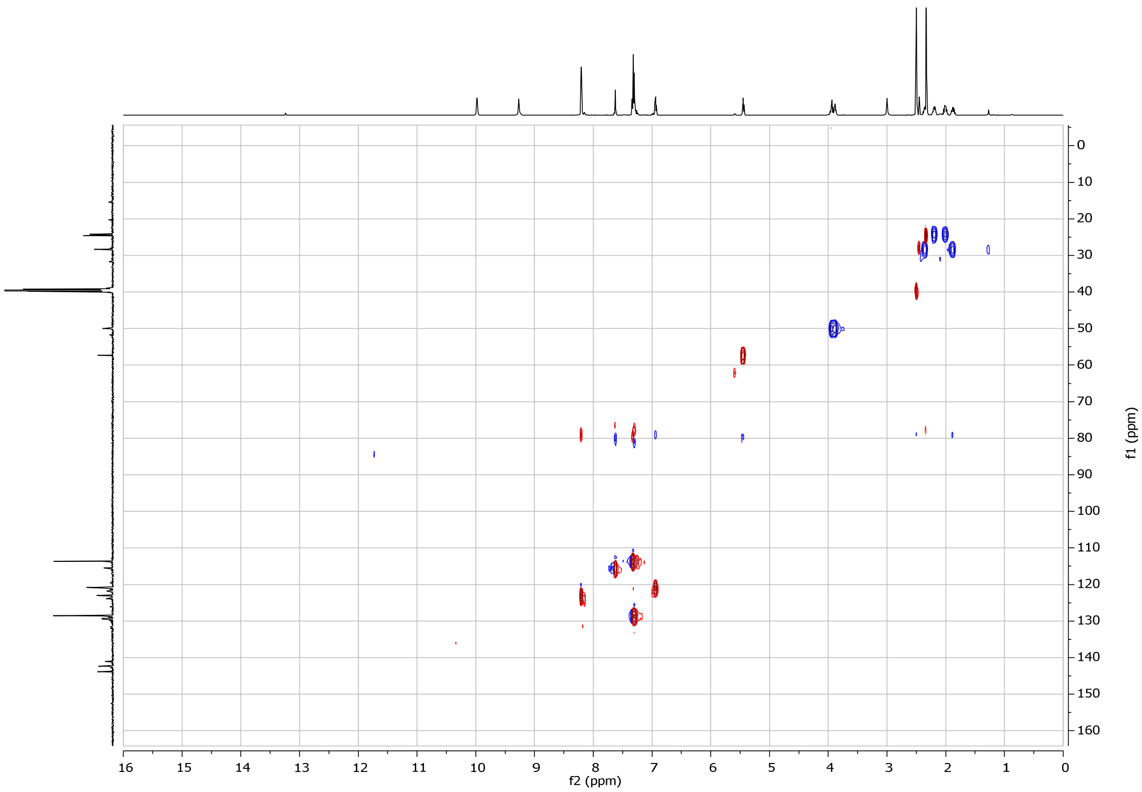
Figure SI-33. NMR spectra for compound **4l** (DMSO-d_6, 100ºC)



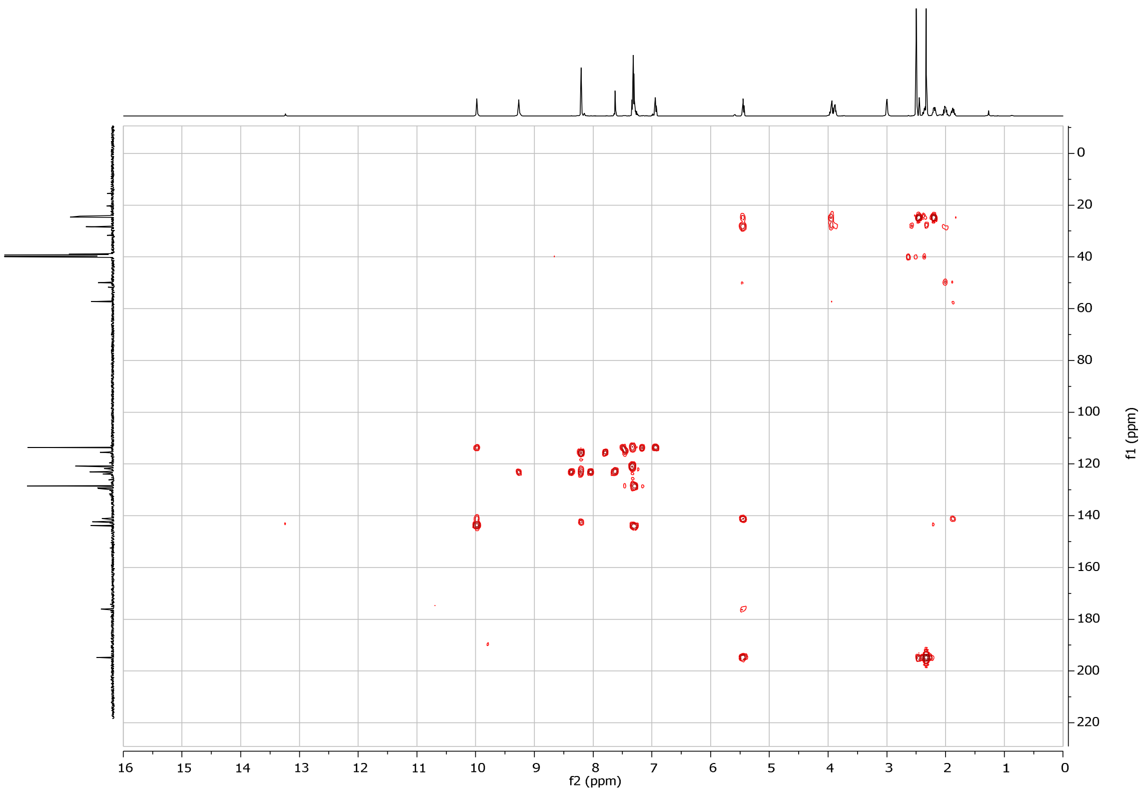
Ph
NH
N
H
N
S
O
N
F3C
CF3
f1 (ppm)



f1 (ppm)

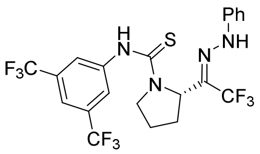


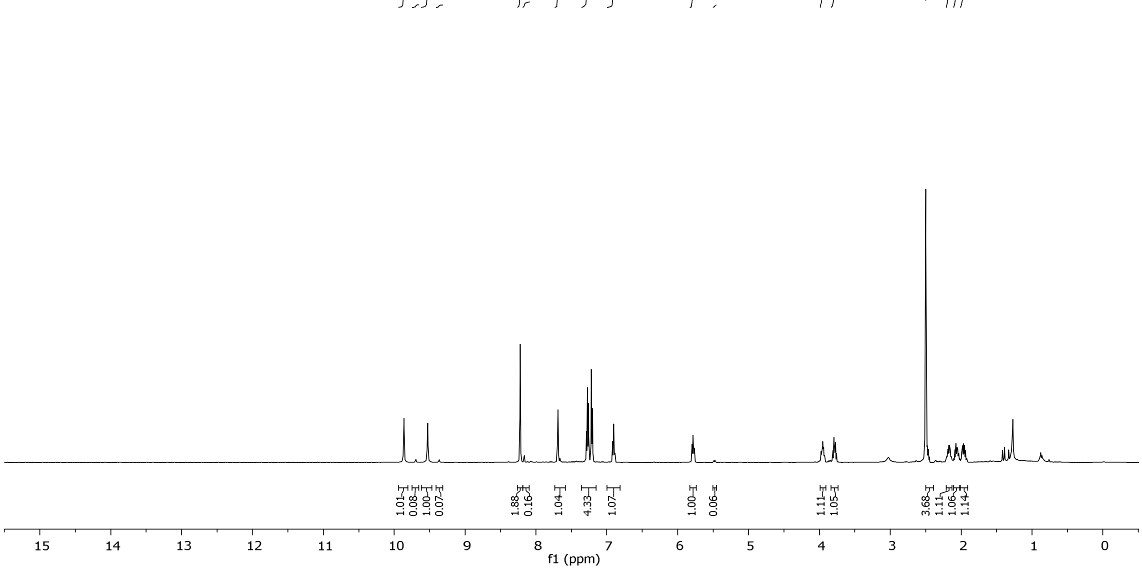
HSQC **4m**

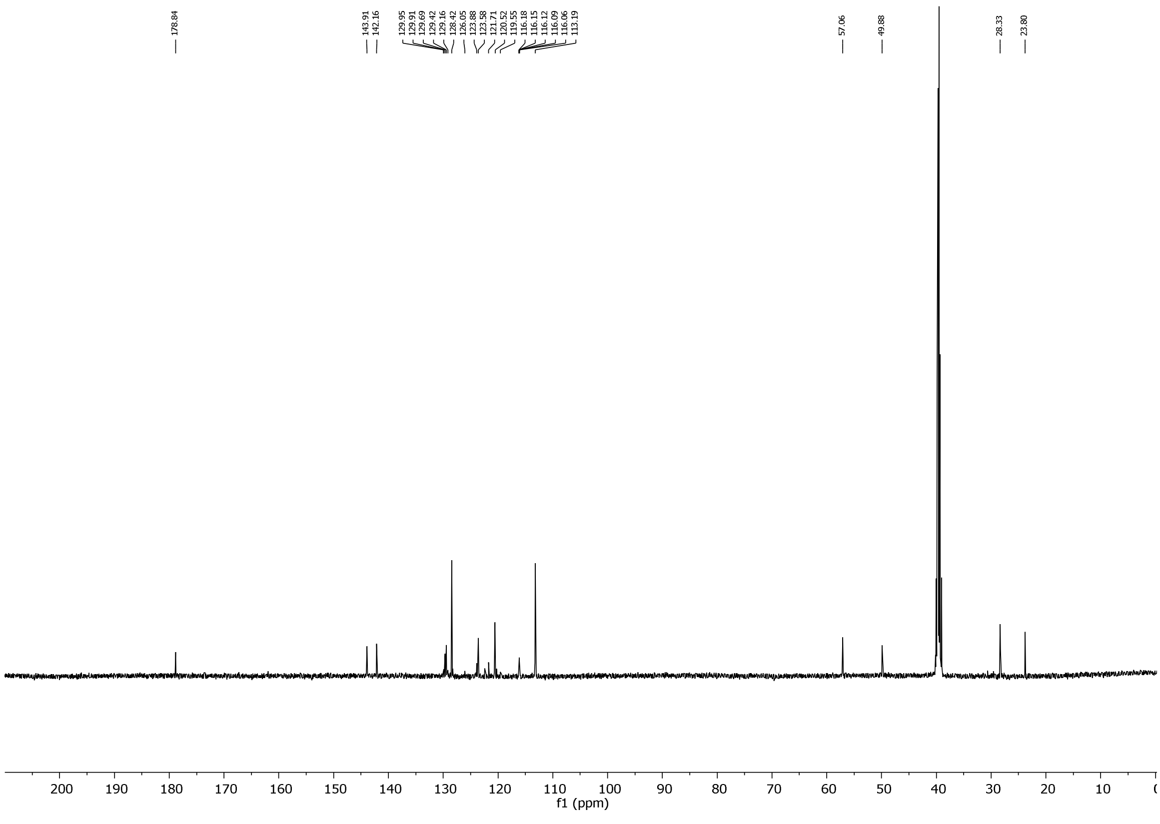


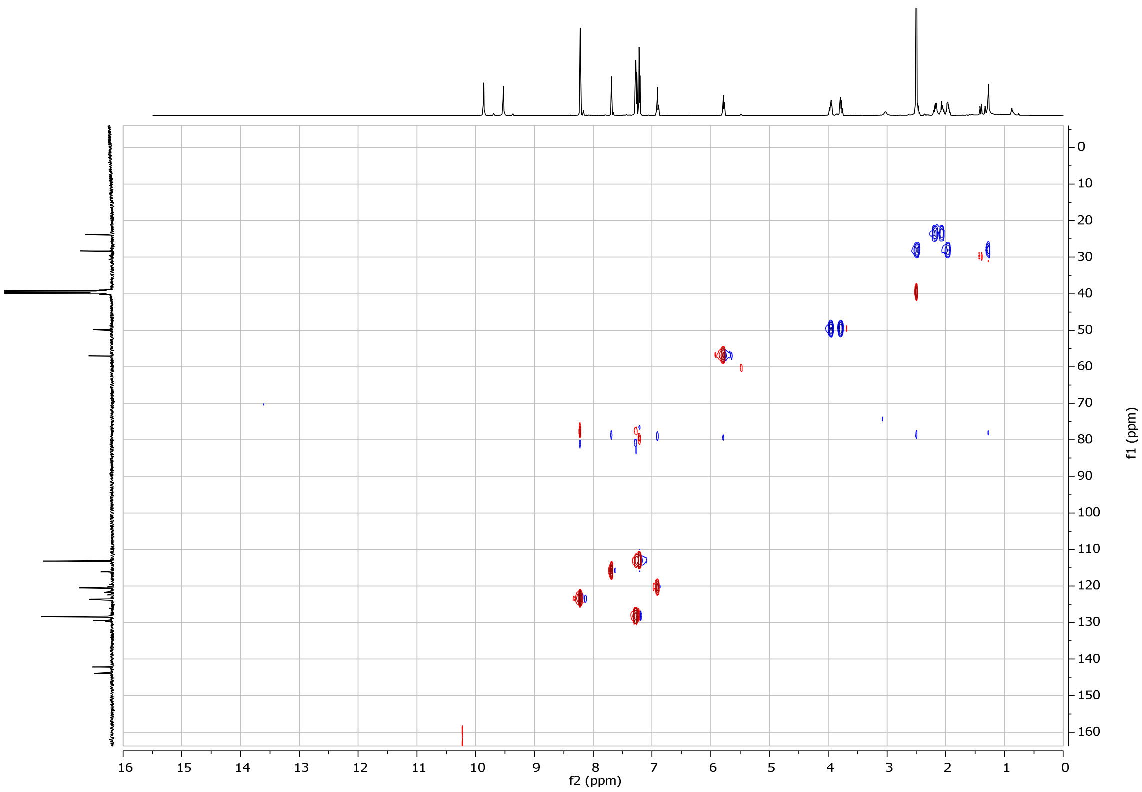
HMBC **4m**

Figure SI-34. NMR spectra for compound **4m** (DMSO-d_6, 100ºC)

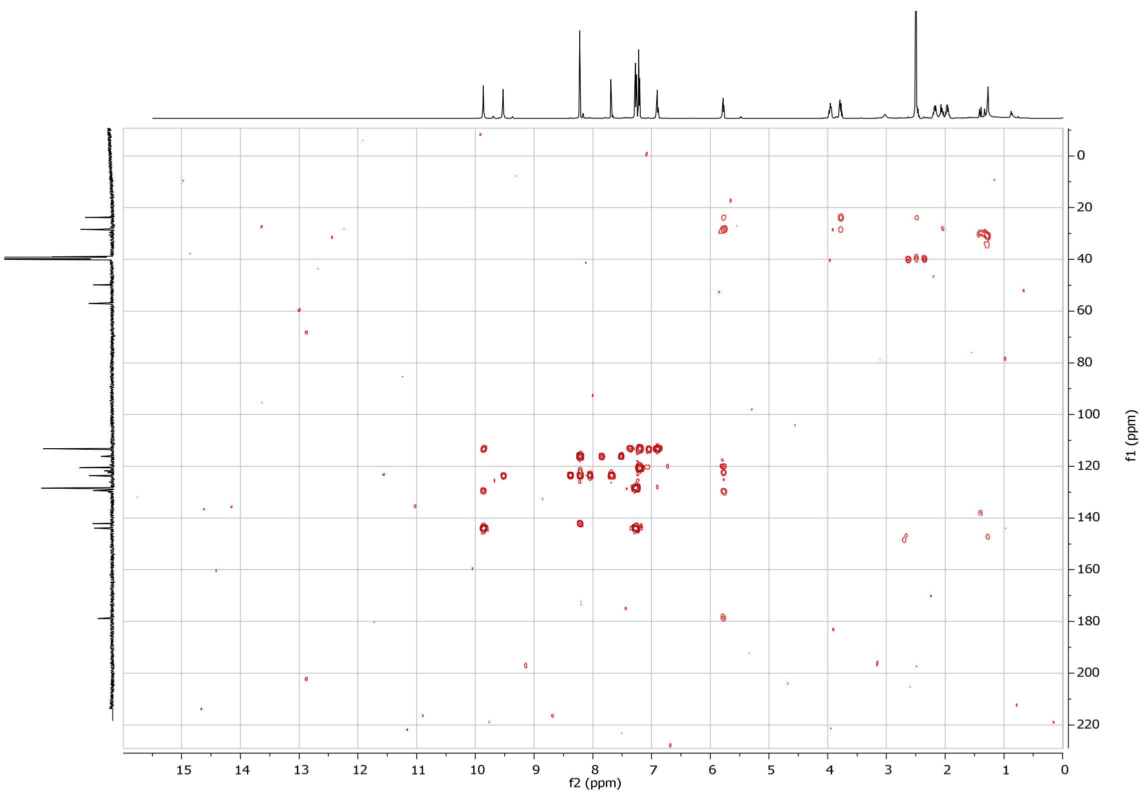

Ph
NH
N
H
N
S
N
CF3
F3C
CF3


15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.84
143.91
142.16
57.06
49.88
28.33
23.80
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

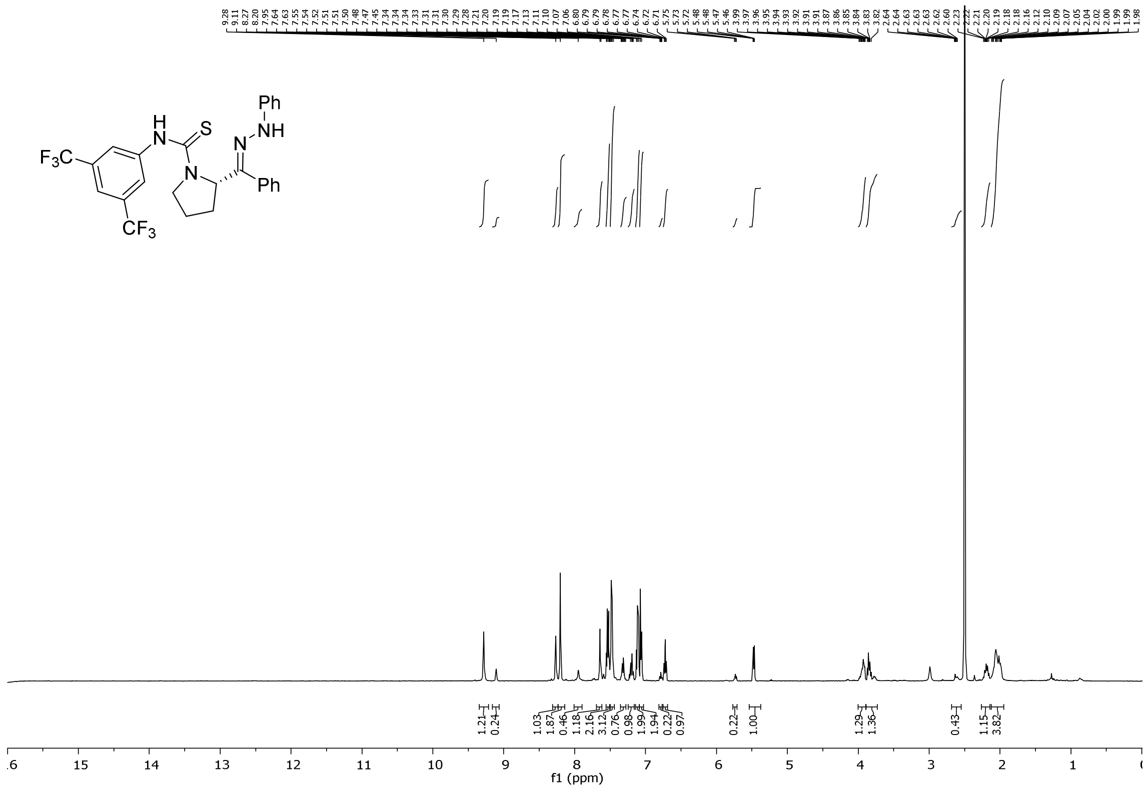


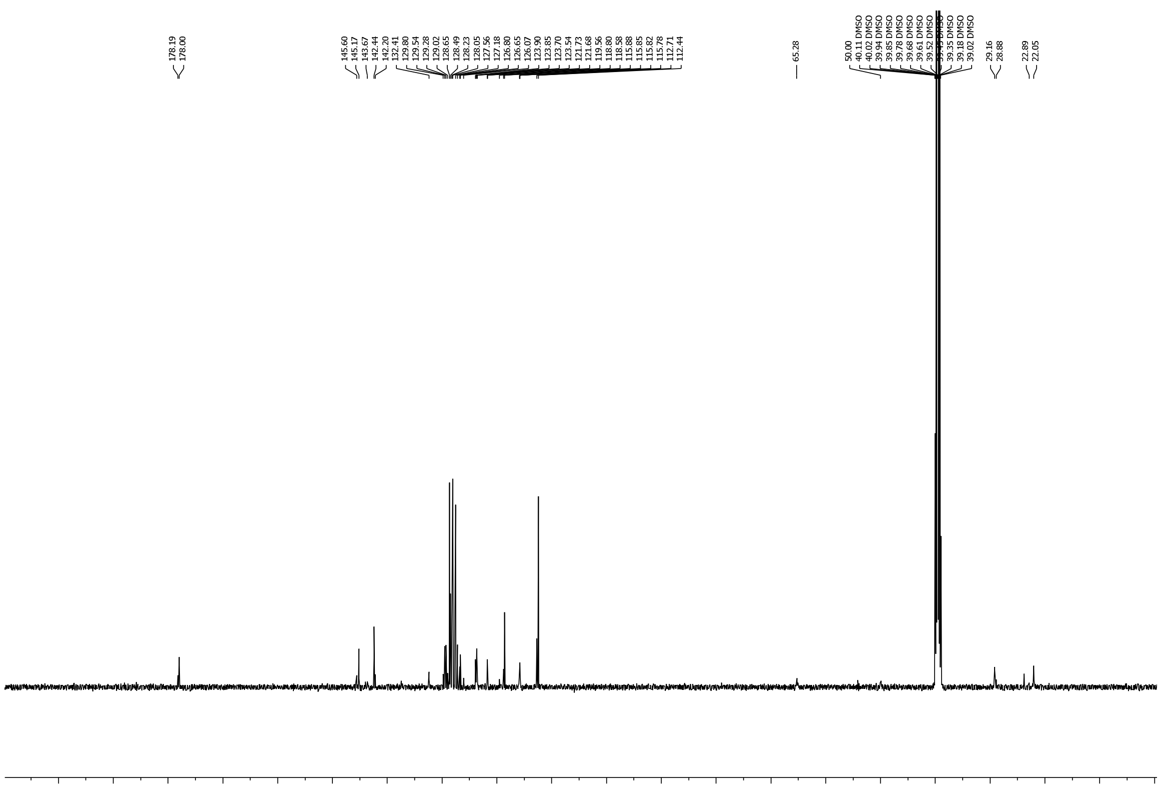
HSQC **4n**

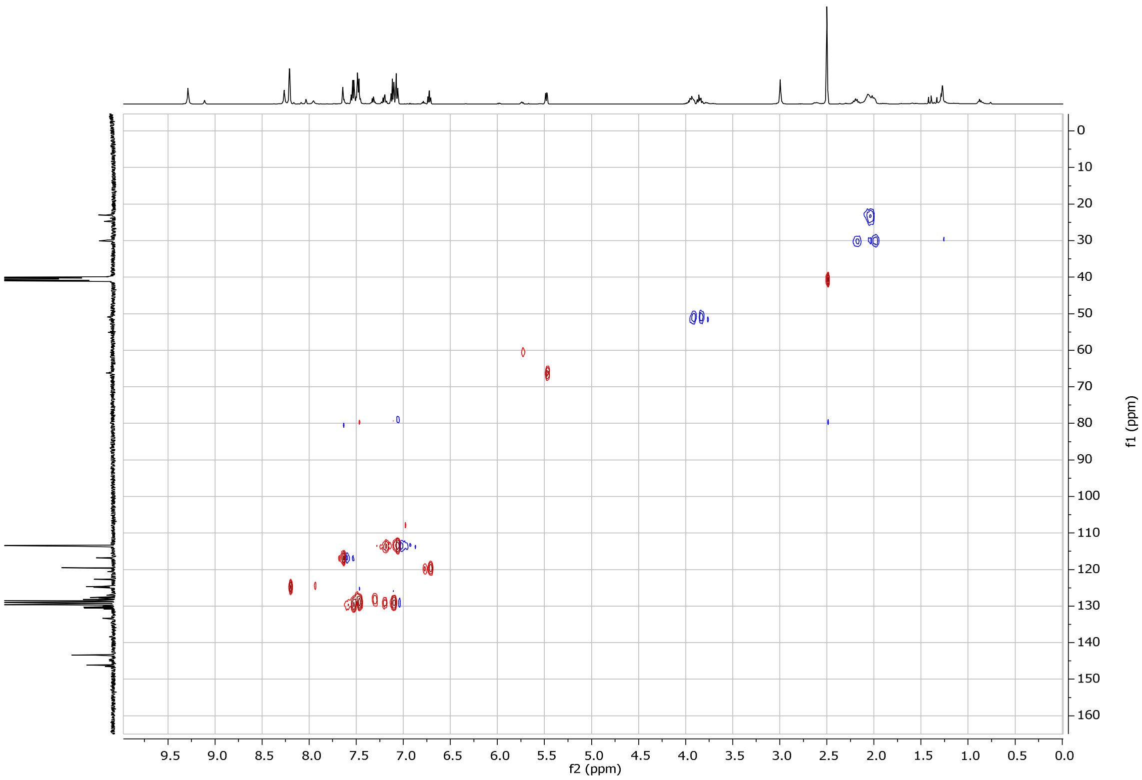


HMBC **4n**

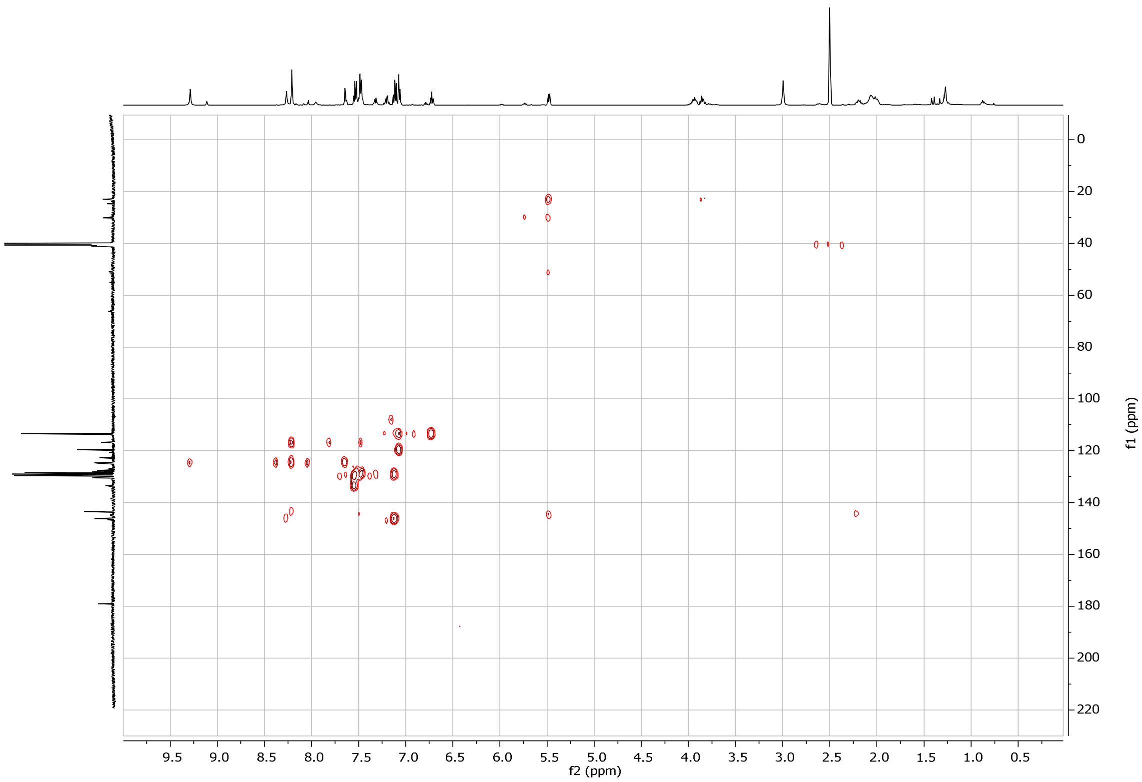
Figure SI-35. NMR spectra for compound **4n** (DMSO-d_6, 100ºC)





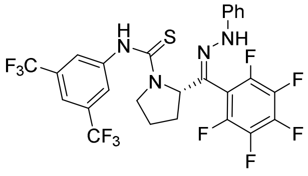


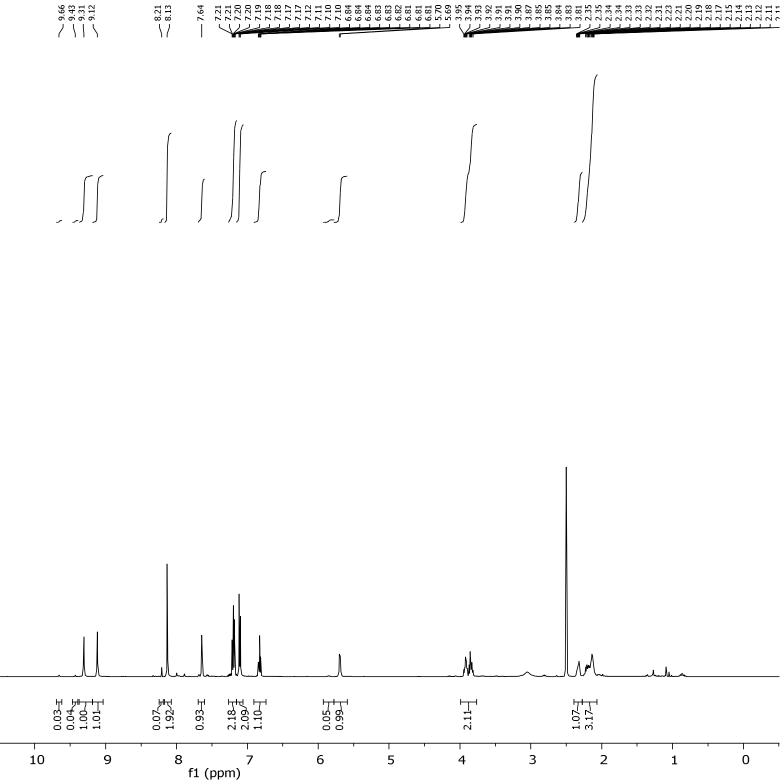
HSQC **4o**

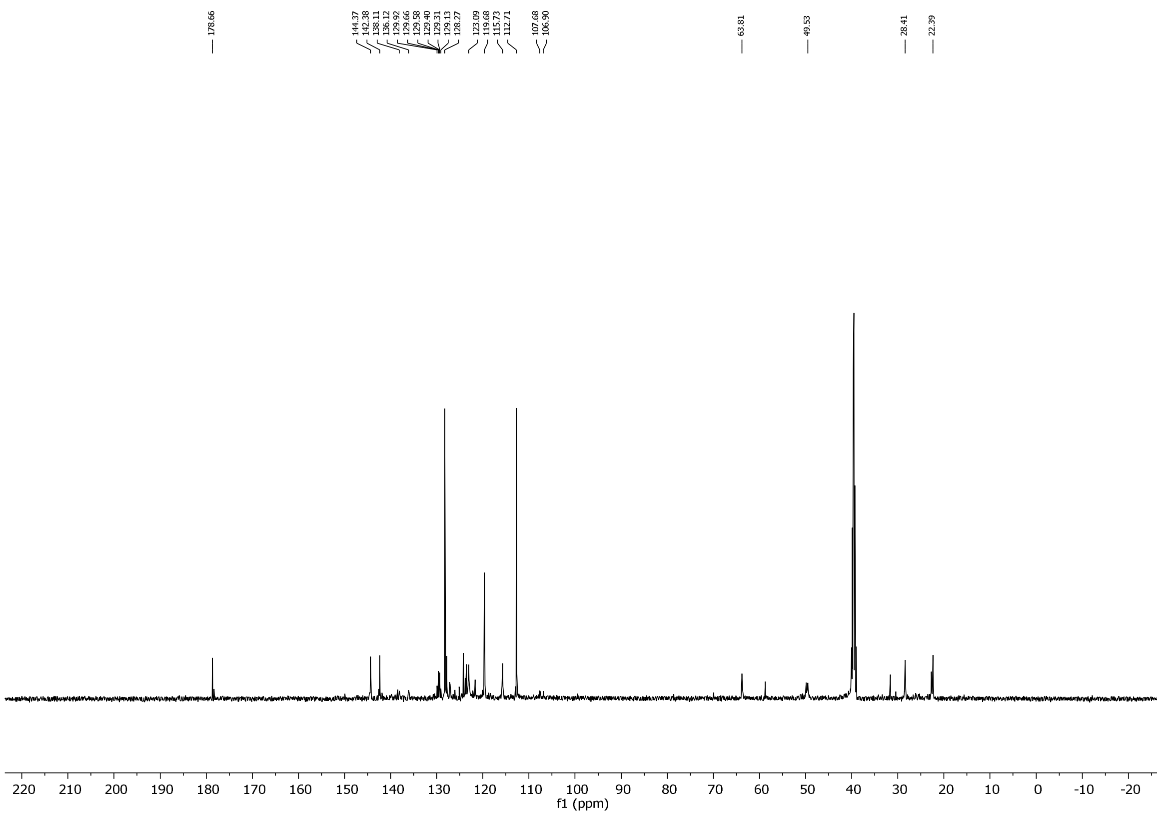


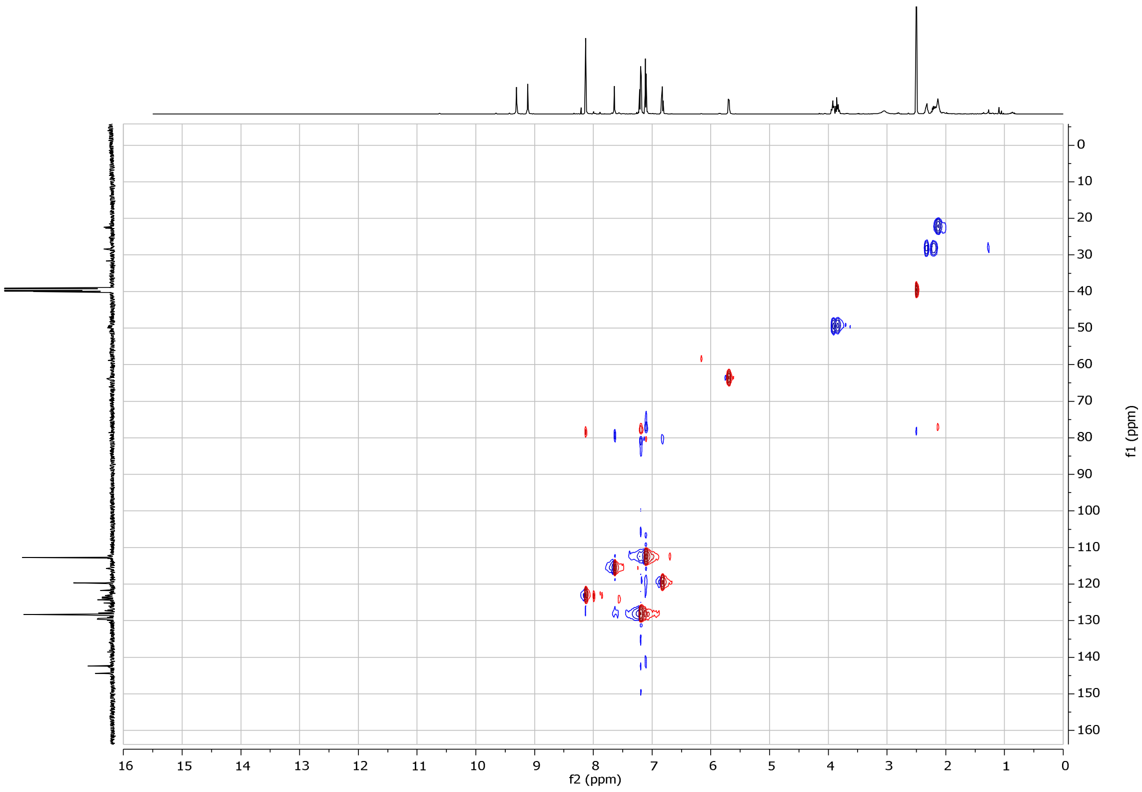
HMBC **4o**

Figure SI-36. NMR spectra for compound **4o** (DMSO-d_6, 100ºC)

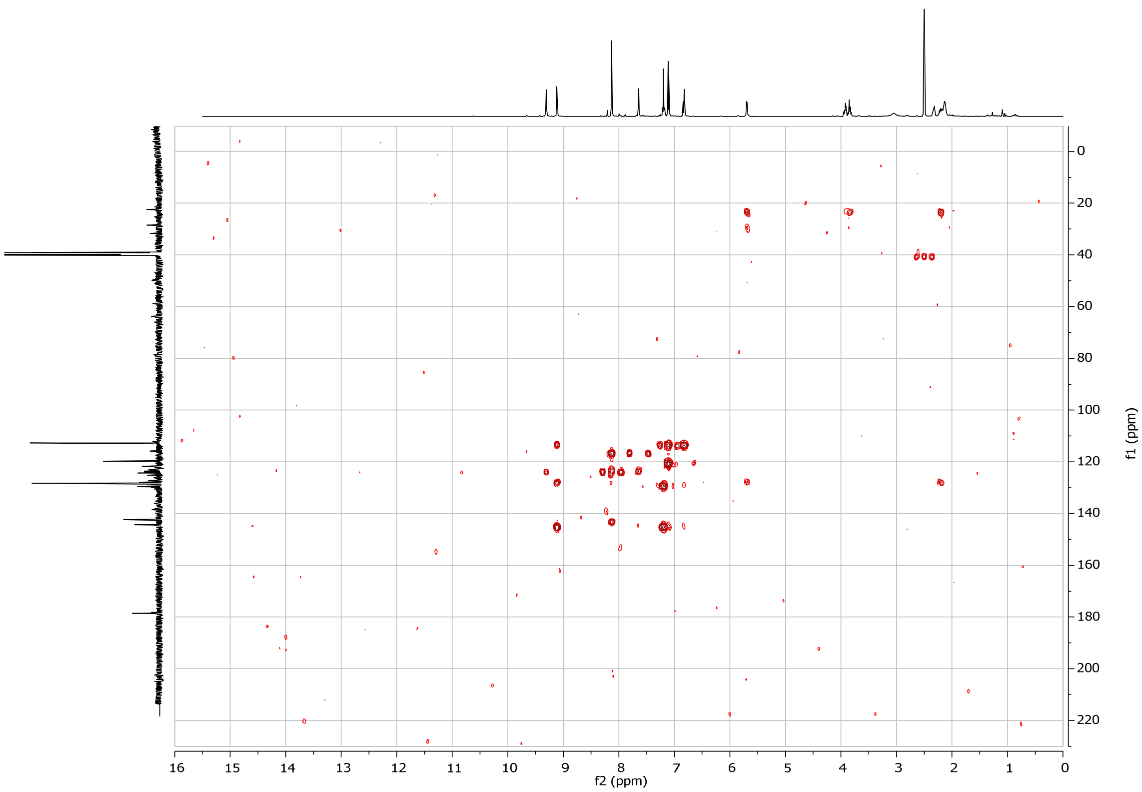






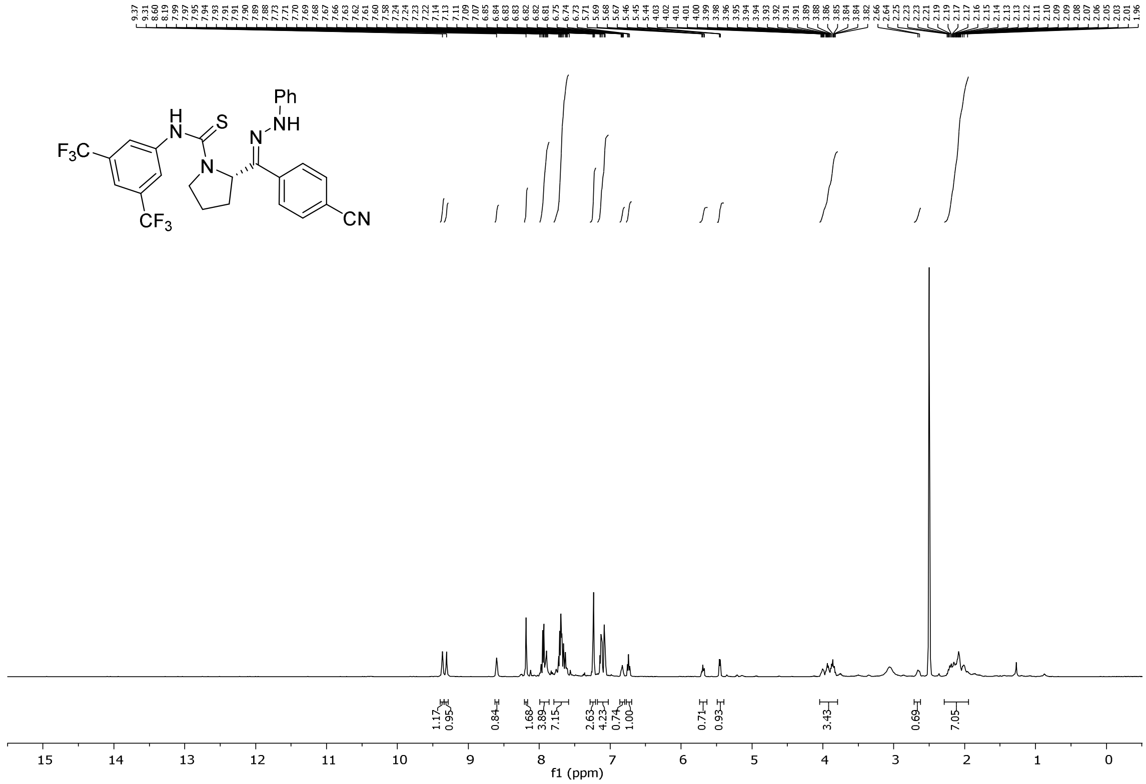


HSQC **4p**

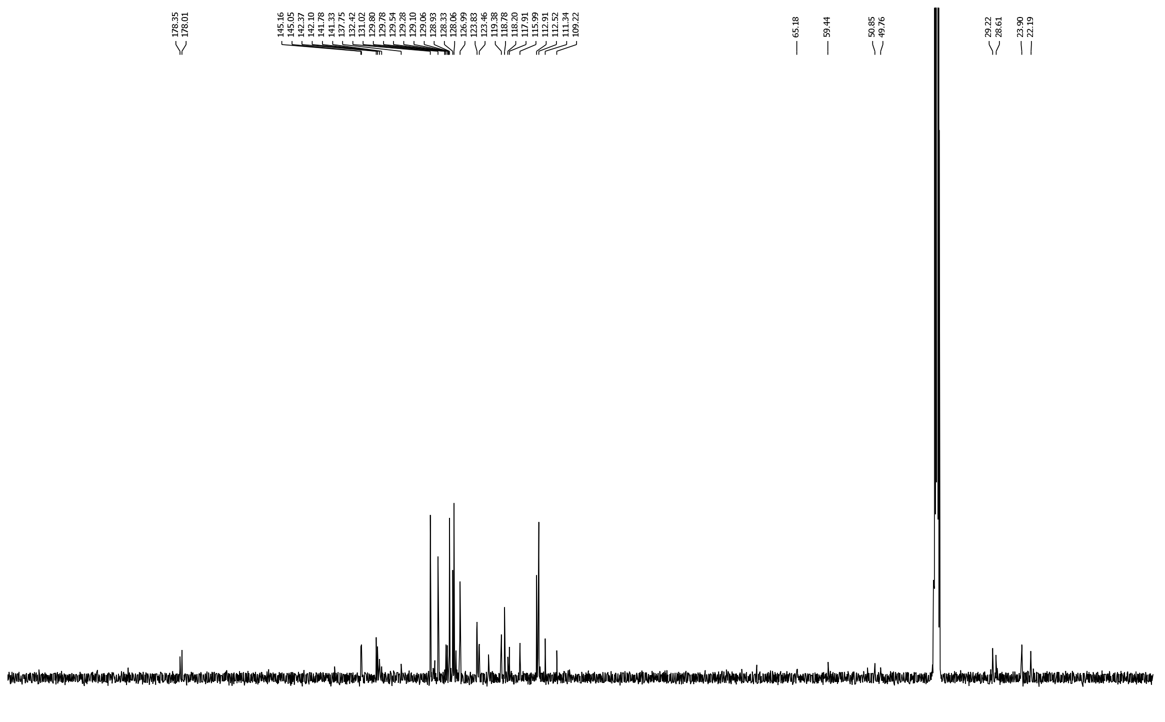


HMBC **4p**

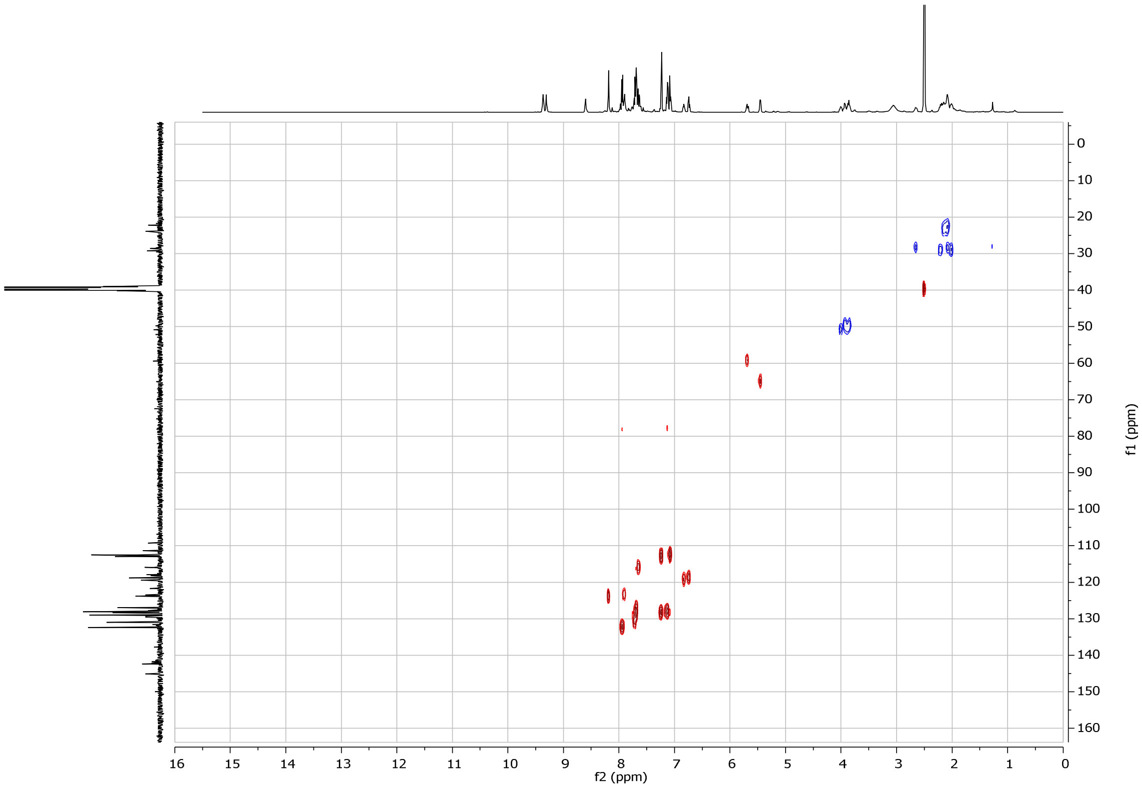
Figure SI-37. NMR spectra for compound **4p** (DMSO-d_6, 100ºC)



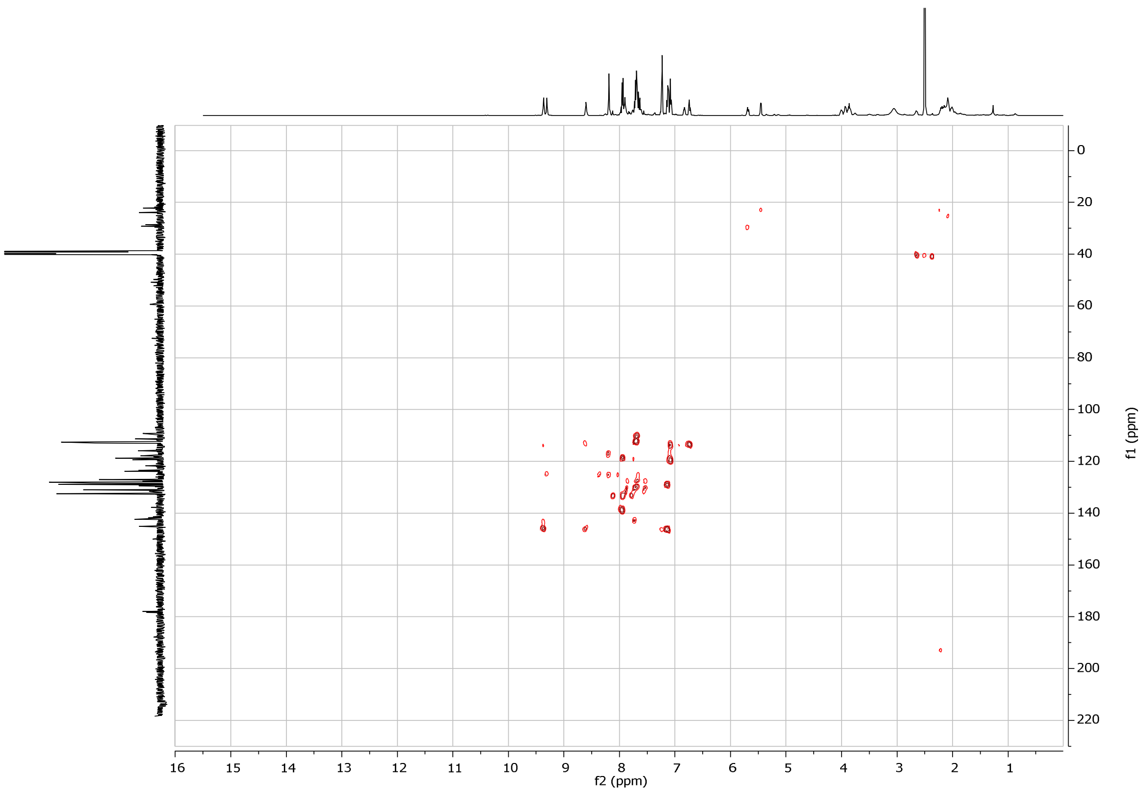
Ph
NH
N
H
N
S
F_3C
CF_3
N
CN
f1 (ppm)



f1 (ppm)

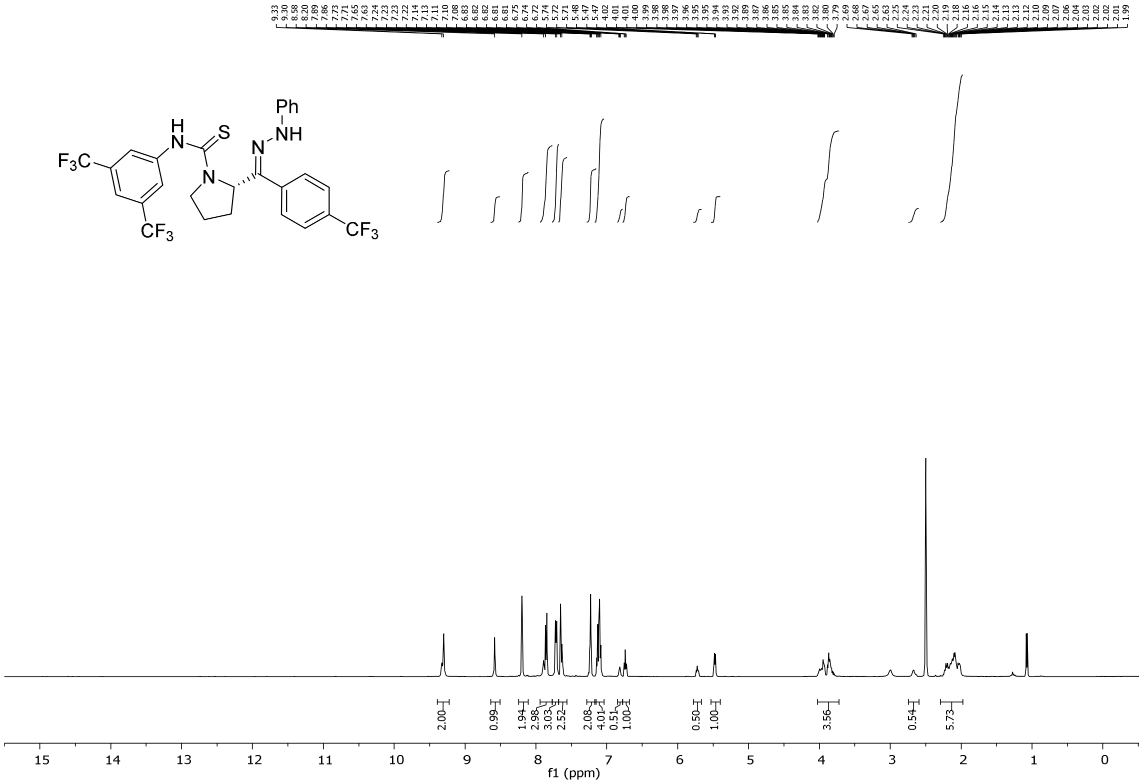


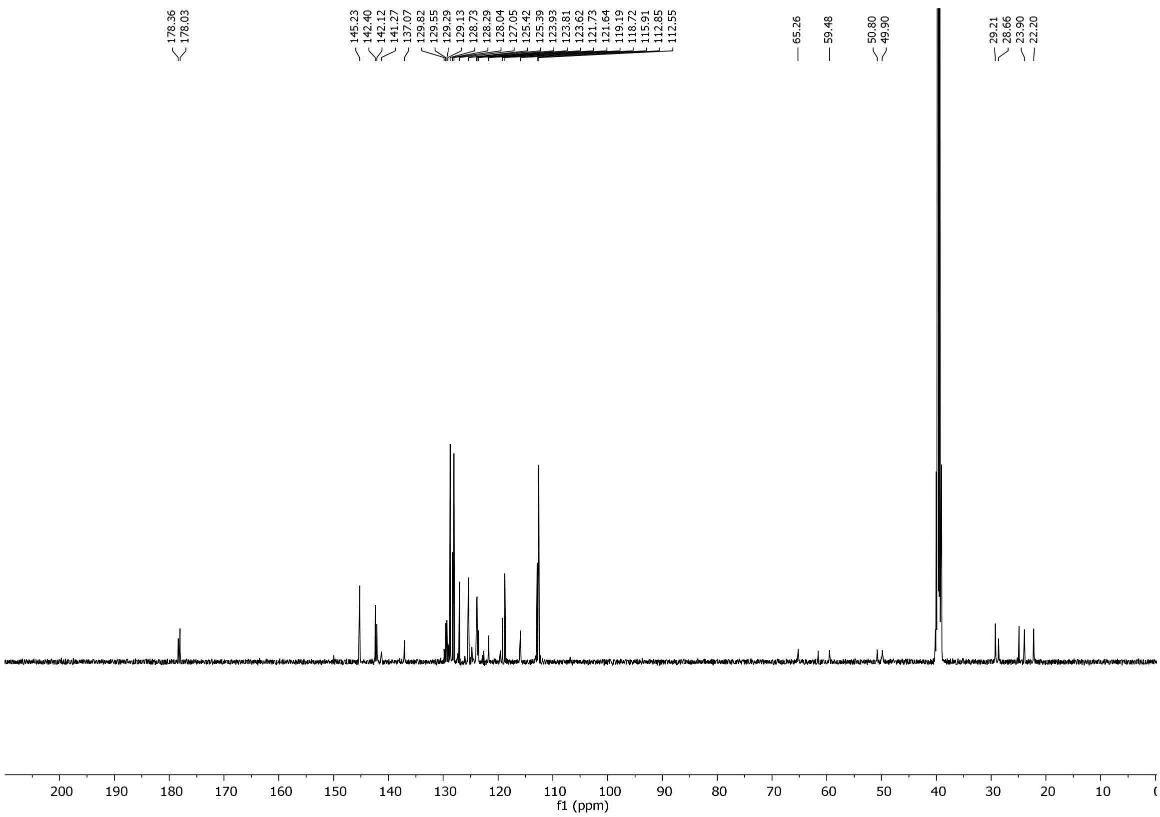
HSQC **4q**

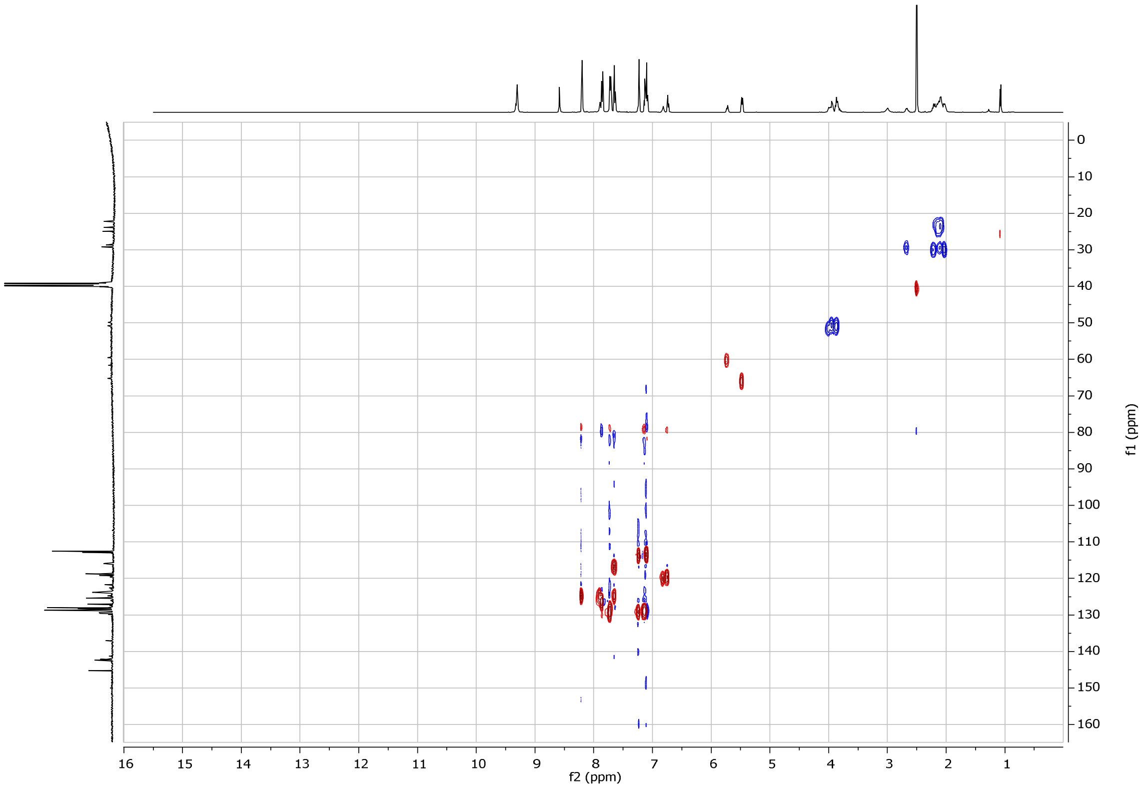


HMBC **4q**

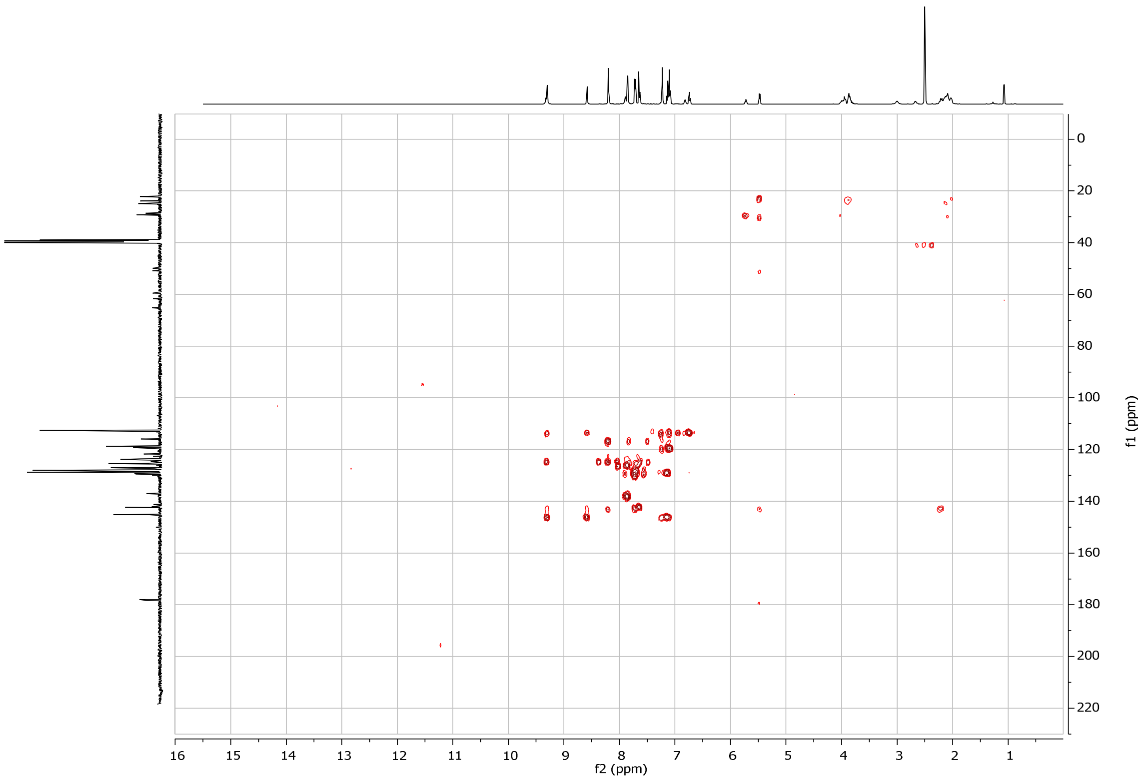
Figure SI-38. NMR spectra for compound **4q** (DMSO-d_6, 100ºC)


f1 (ppm)


f1 (ppm)

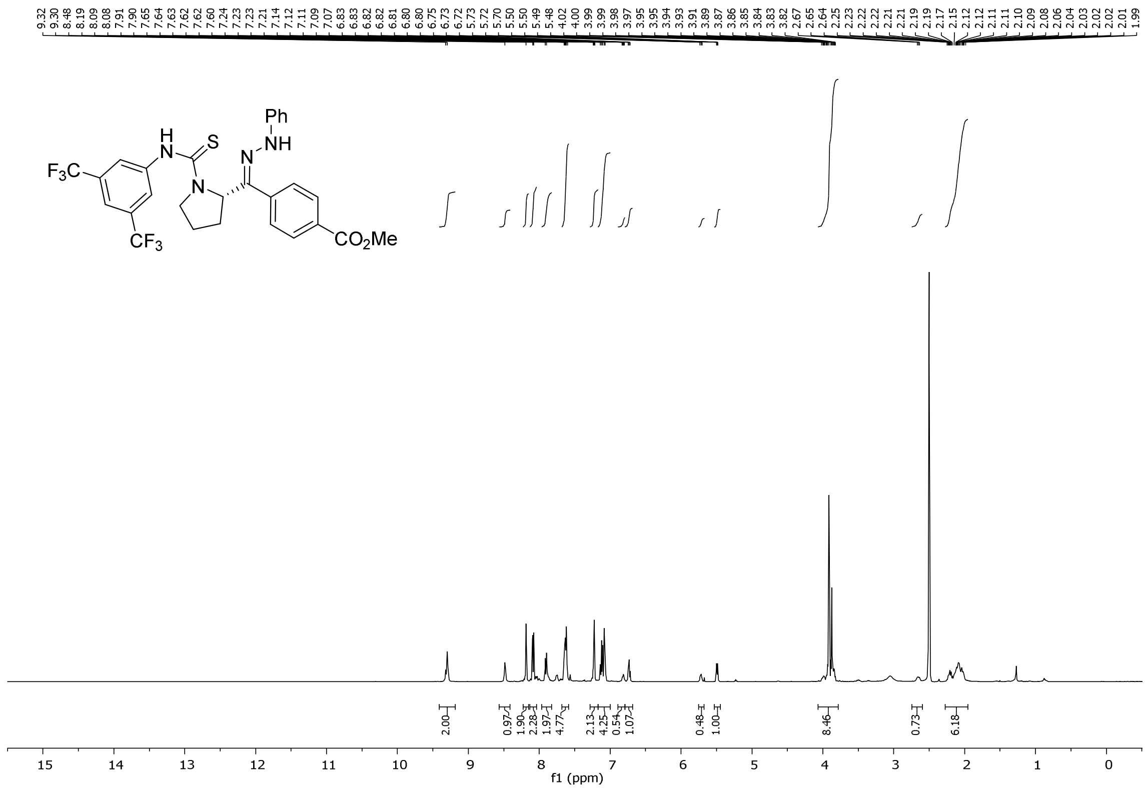


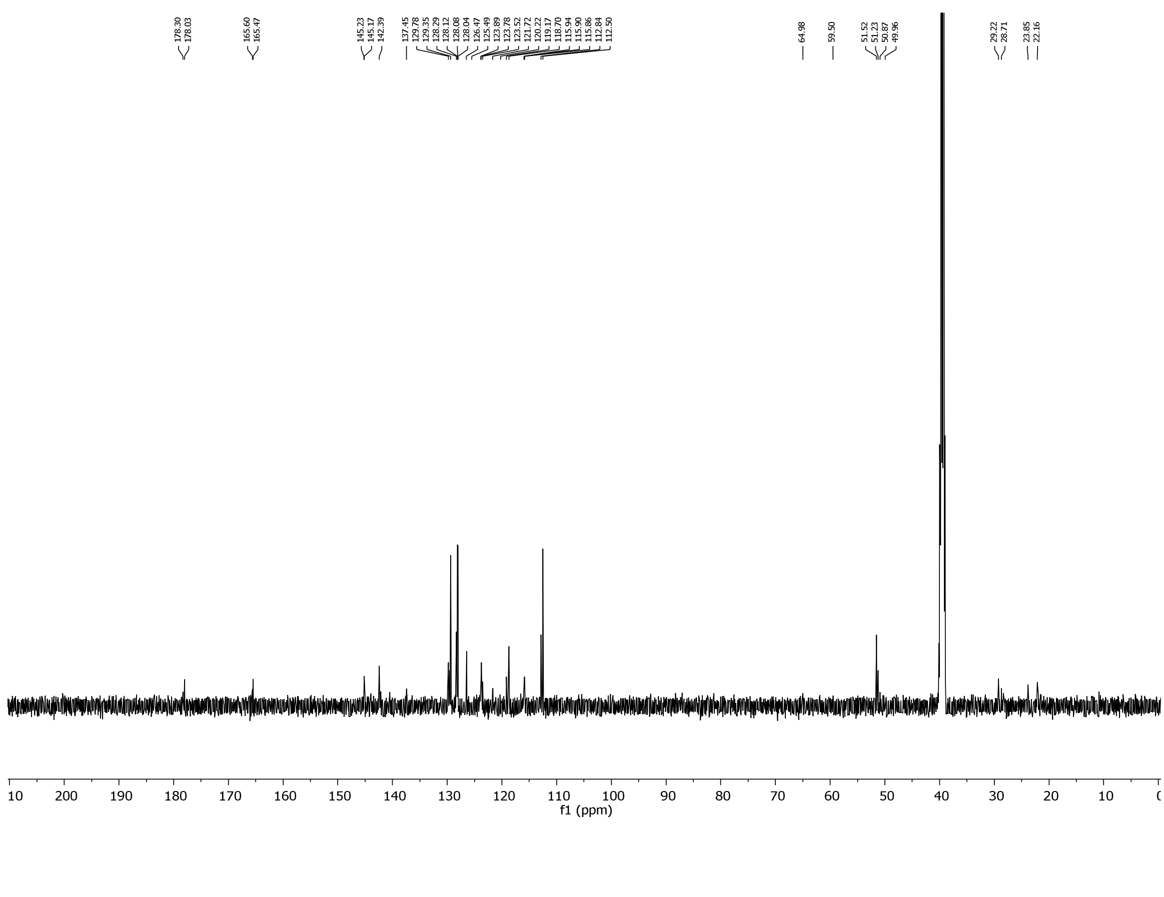
HSQC **4r**

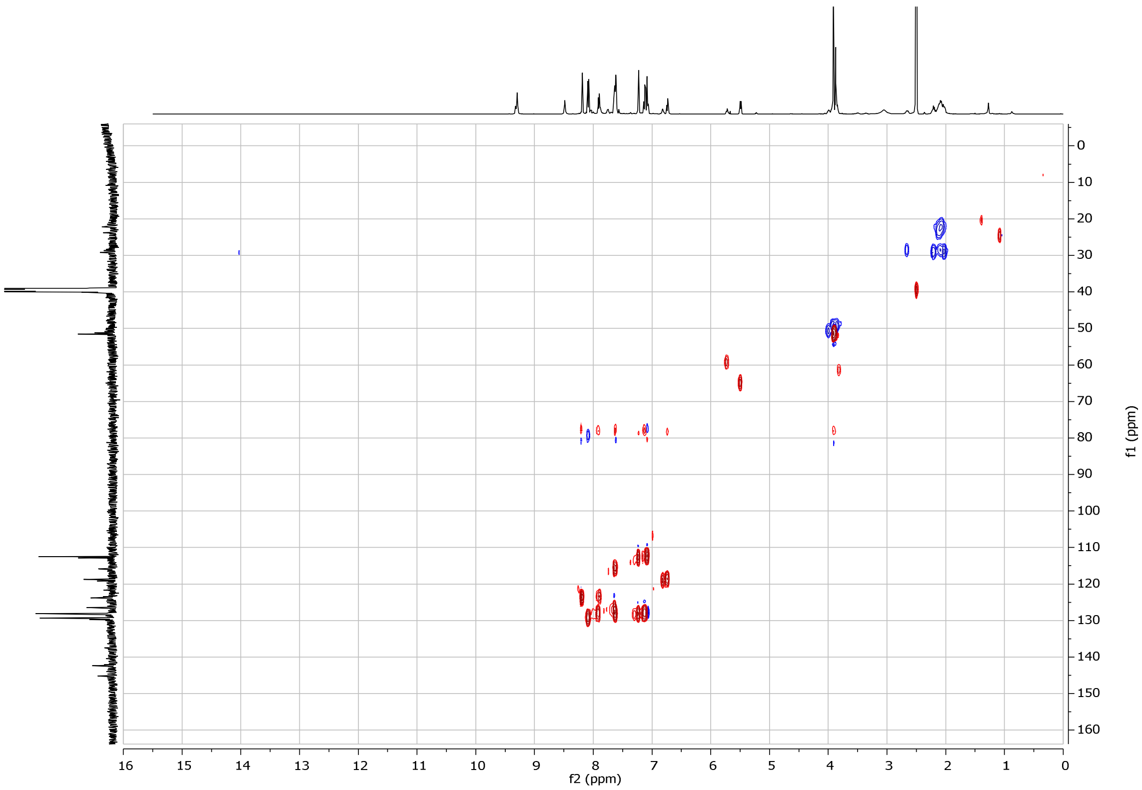


HMBC **4r**

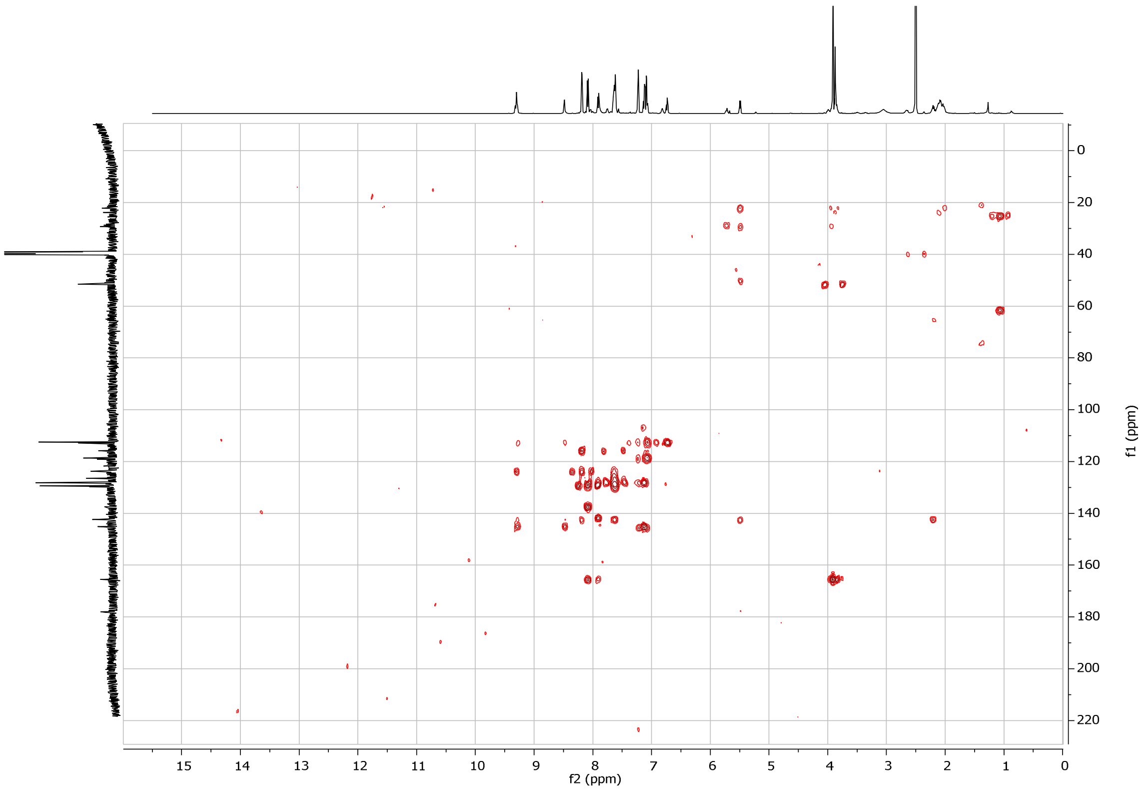
Figure SI-39. NMR spectra for compound **4r** (DMSO-d_6, 100ºC)


9.32 9.30 8.48 8.19 8.09 8.08 7.91 7.90 7.65 7.64 7.63 7.62 7.62 7.60 7.24 7.23 7.23 7.21 7.14 7.12 7.11 7.09 7.07 6.83 6.83 6.82 6.81 6.80 6.80 6.75 6.73 6.72 5.73 5.72 5.70 5.50 5.49 5.48 4.02 4.00 3.99 3.98 3.97 3.95 3.95 3.94 3.93 3.91 3.89 3.87 3.86 3.85 3.84 3.83 3.82 2.67 2.65 2.64 2.25 2.23 2.22 2.22 2.21 2.19 2.17 2.15 2.12 2.11 2.10 2.09 2.08 2.06 2.04 2.03 2.02 2.02 2.01 1.99
Ph
H
N
S
N
NH
F_3C
N
CF_3
CO_2Me
2.00 0.97 1.90 2.28 1.97 4.77 2.13 4.25 0.54 1.07 0.48 1.00 8.46 0.73 6.18
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)


178.30 178.03 165.60 165.47 145.23 145.17 142.39 137.45 129.78 129.35 128.29 128.12 128.08 128.04 126.47 125.49 123.89 123.78 123.52 121.72 120.22 119.17 118.70 115.94 115.90 115.86 112.84 112.50 64.98 59.50 51.52 51.23 50.87 49.96 29.22 28.71 23.85 22.16
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

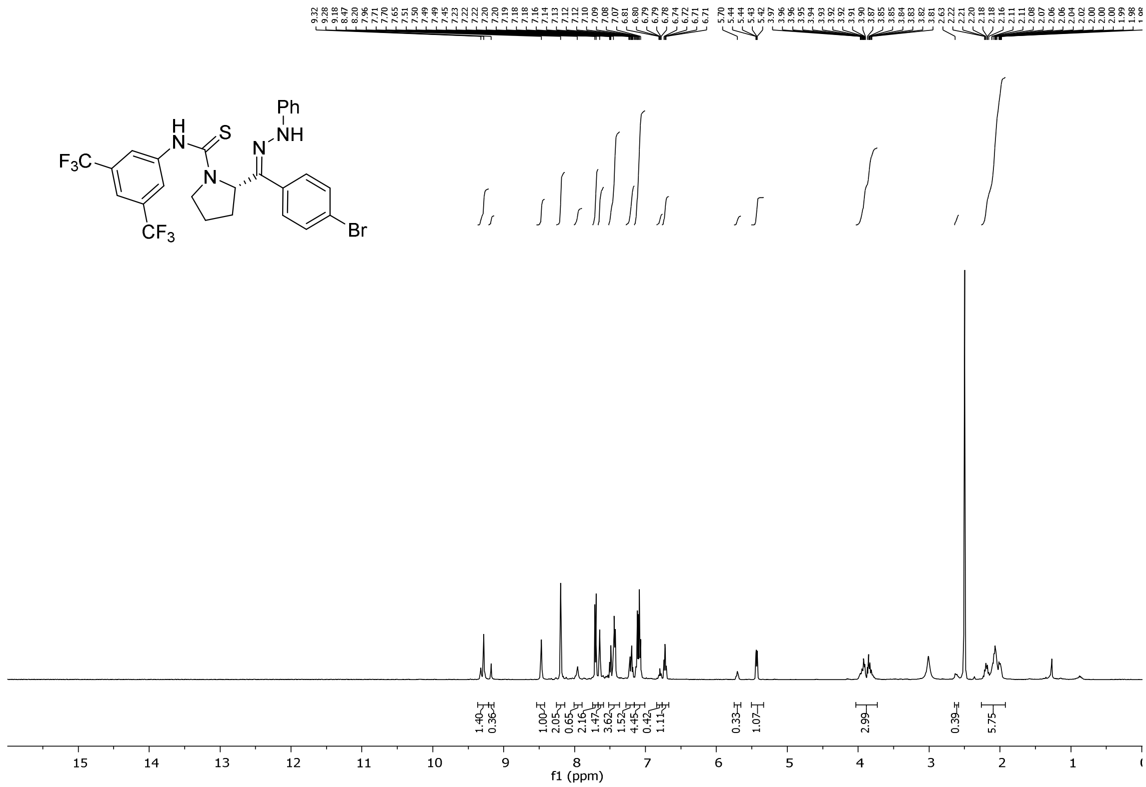


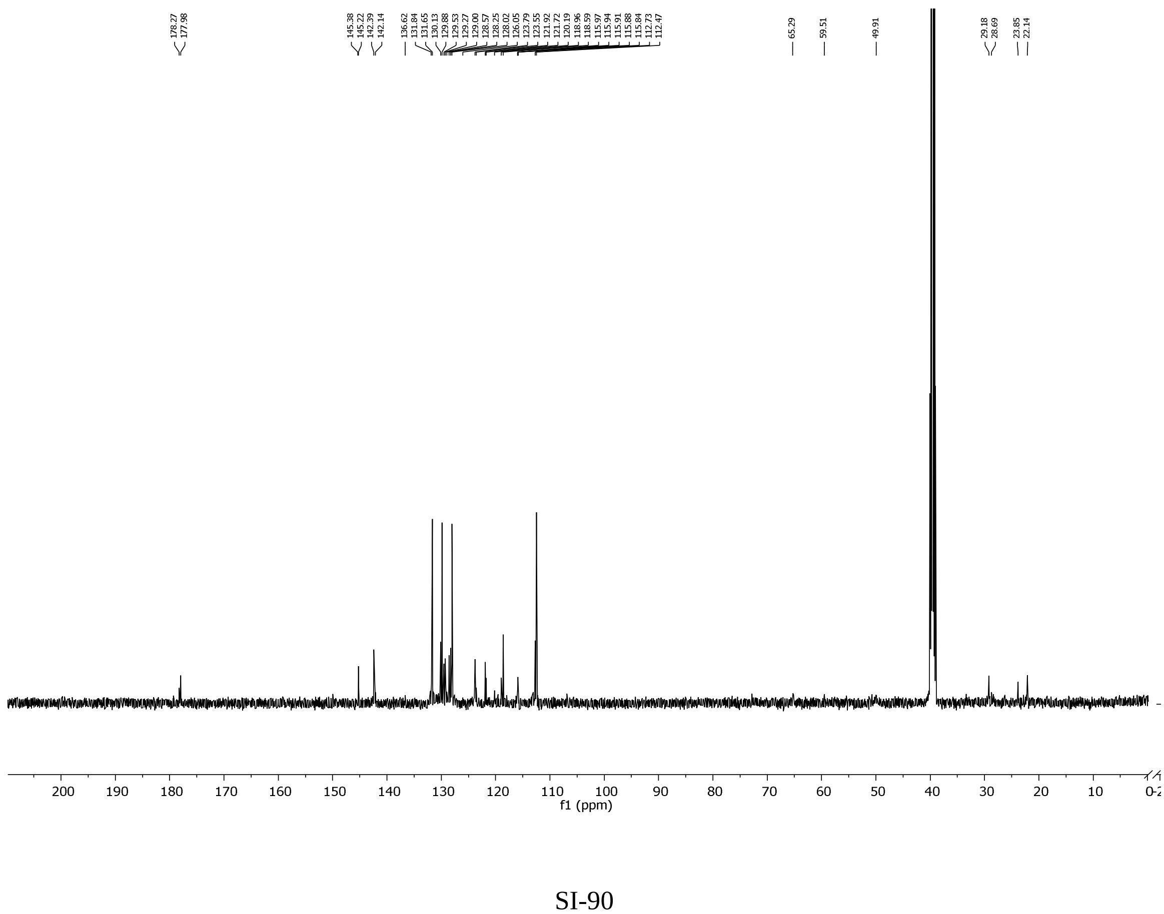
HSQC **4s**

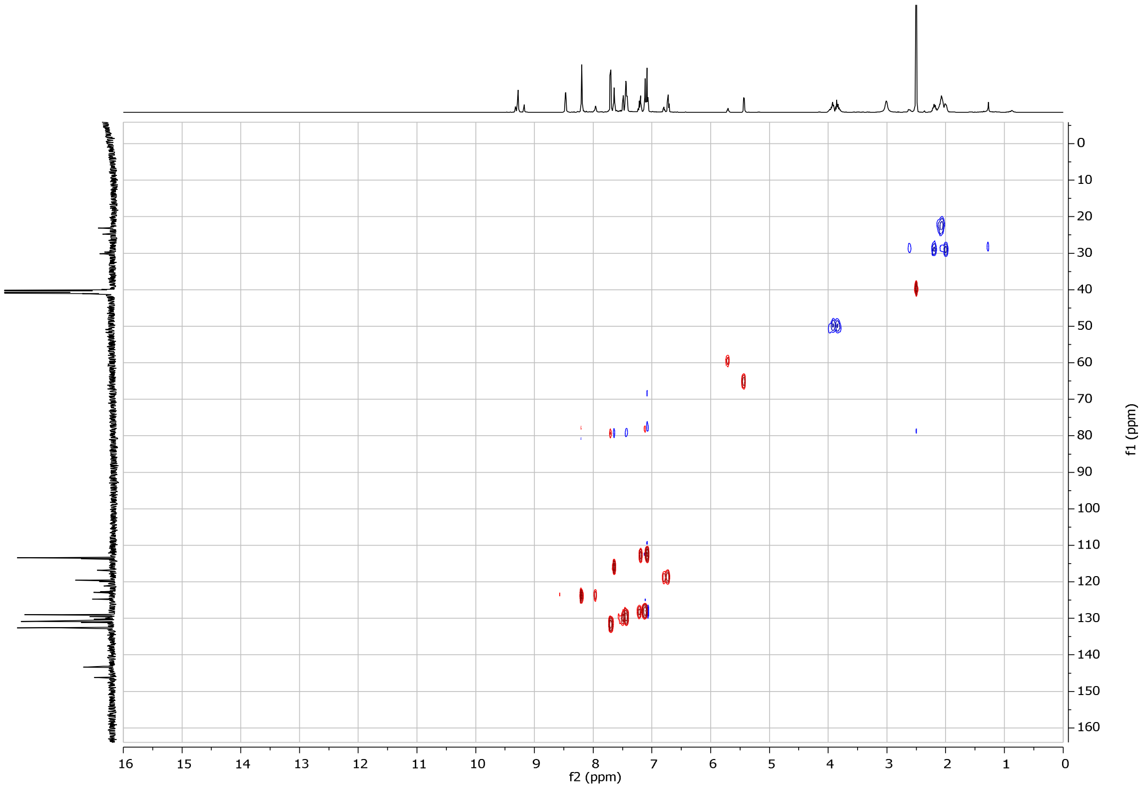


HMBC **4s**

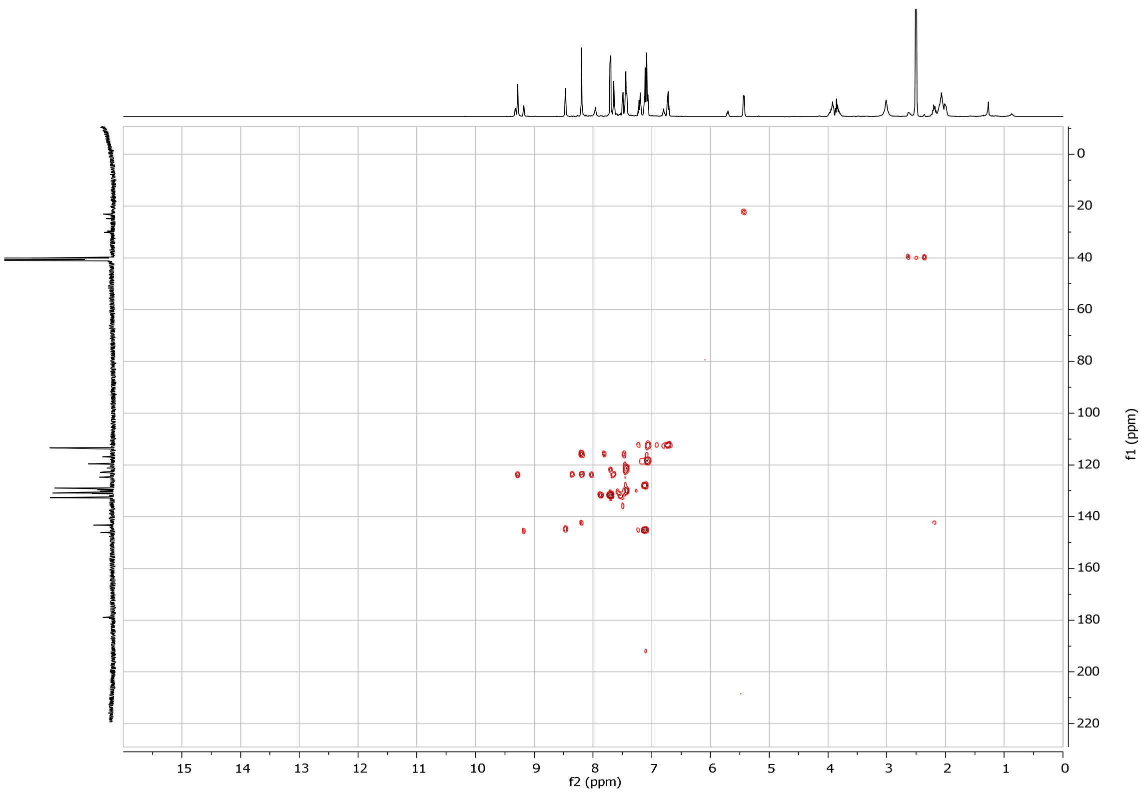
Figure SI-40. NMR spectra for compound **4s** (DMSO-d_6, 100ºC)





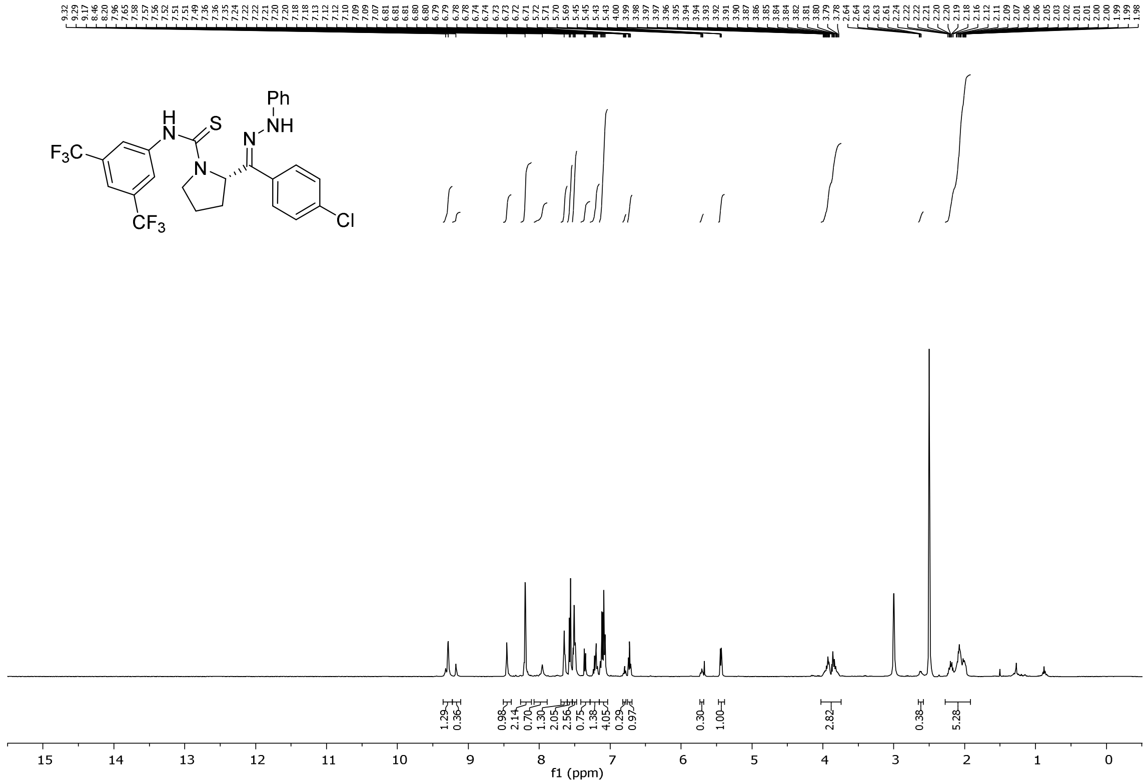


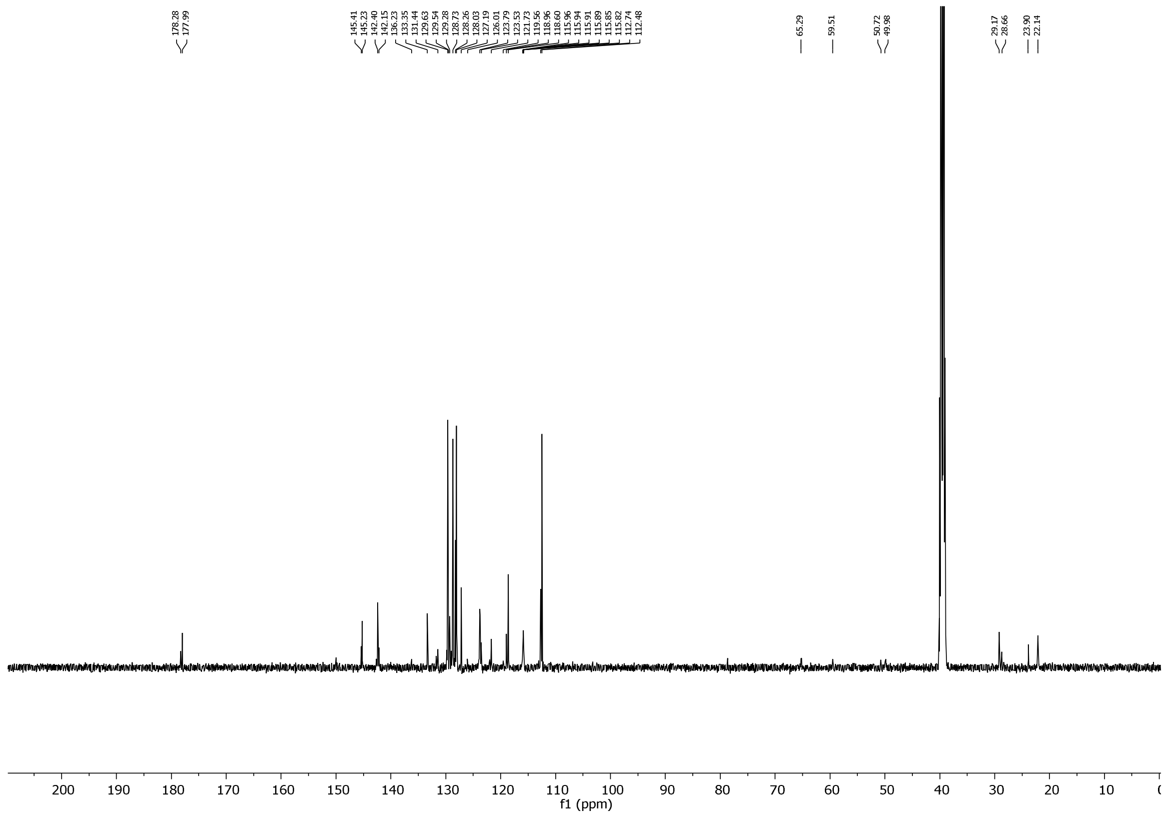
HSQC **4t**

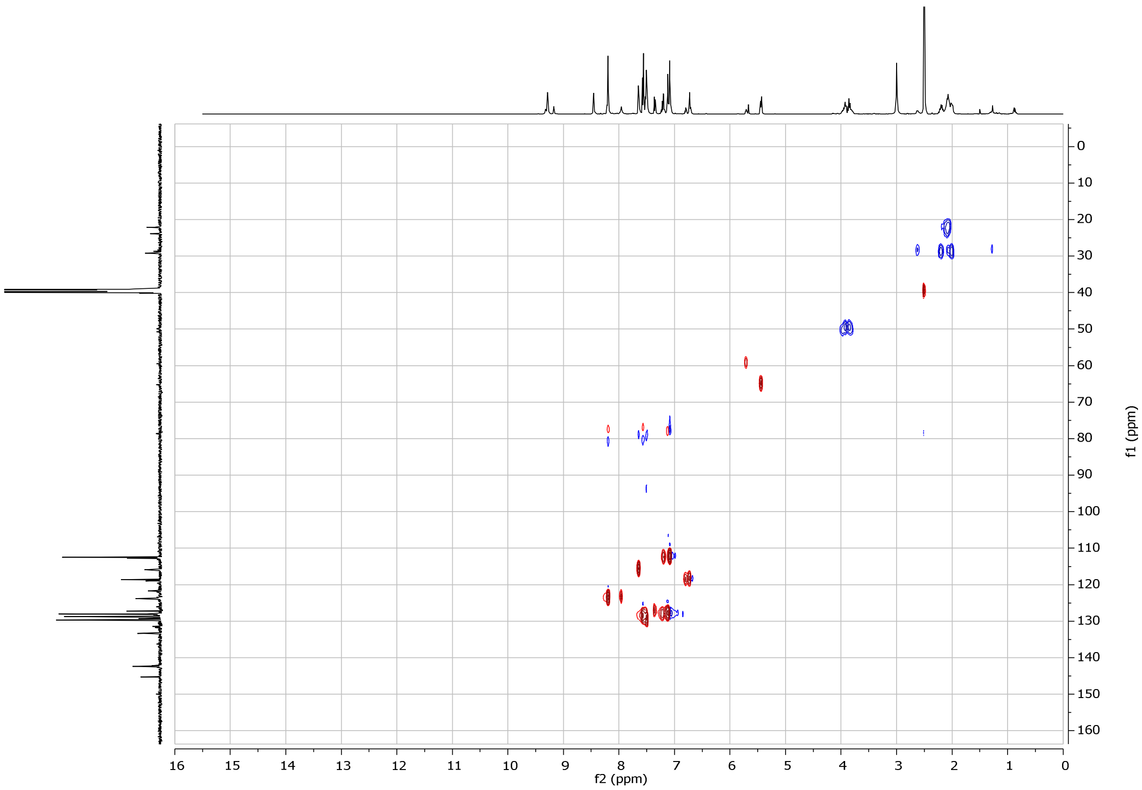


HMBC **4t**

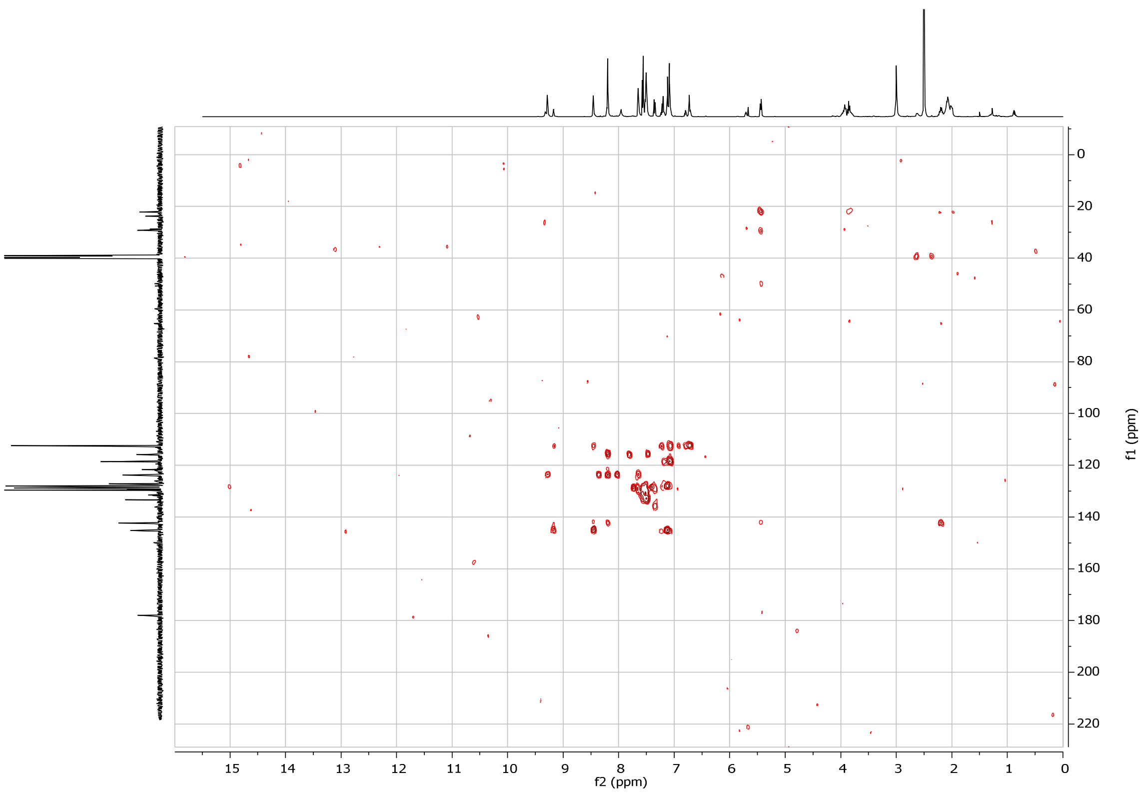
Figure SI-41. NMR spectra for compound **4t** (DMSO-d_6, 100ºC)


Ph
NH
N
H
N
S
N
F3C
CF3
Cl
f1 (ppm)


f1 (ppm)

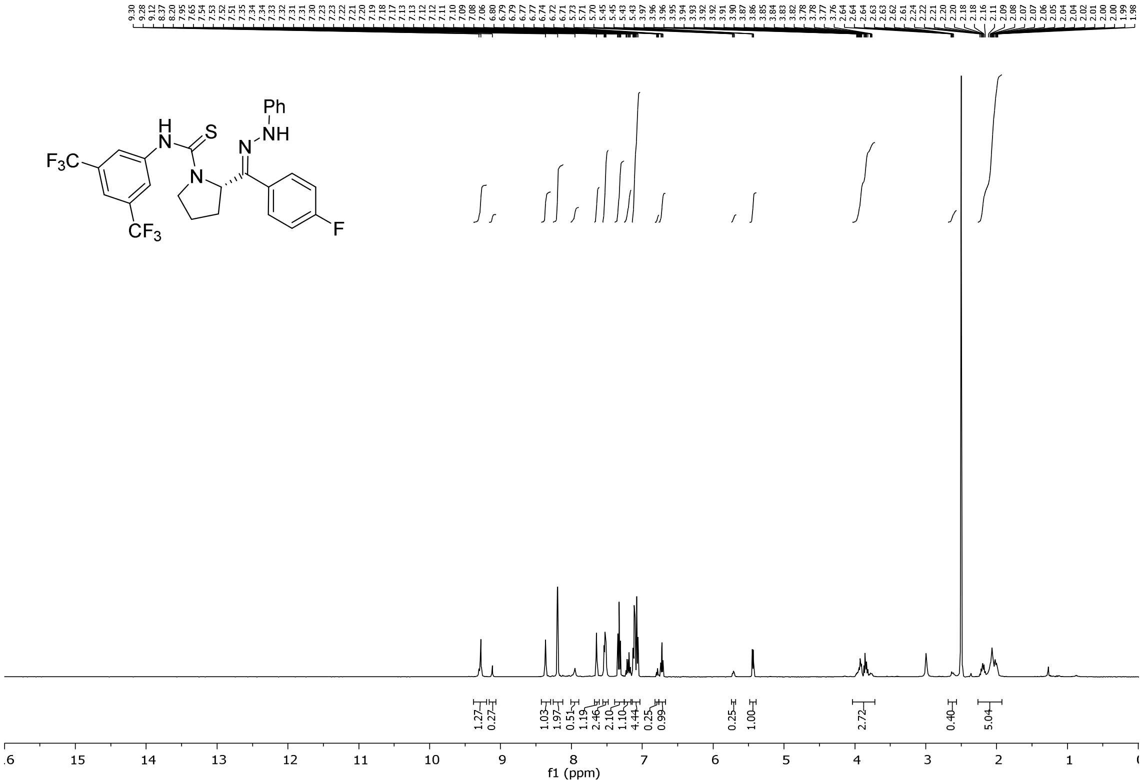


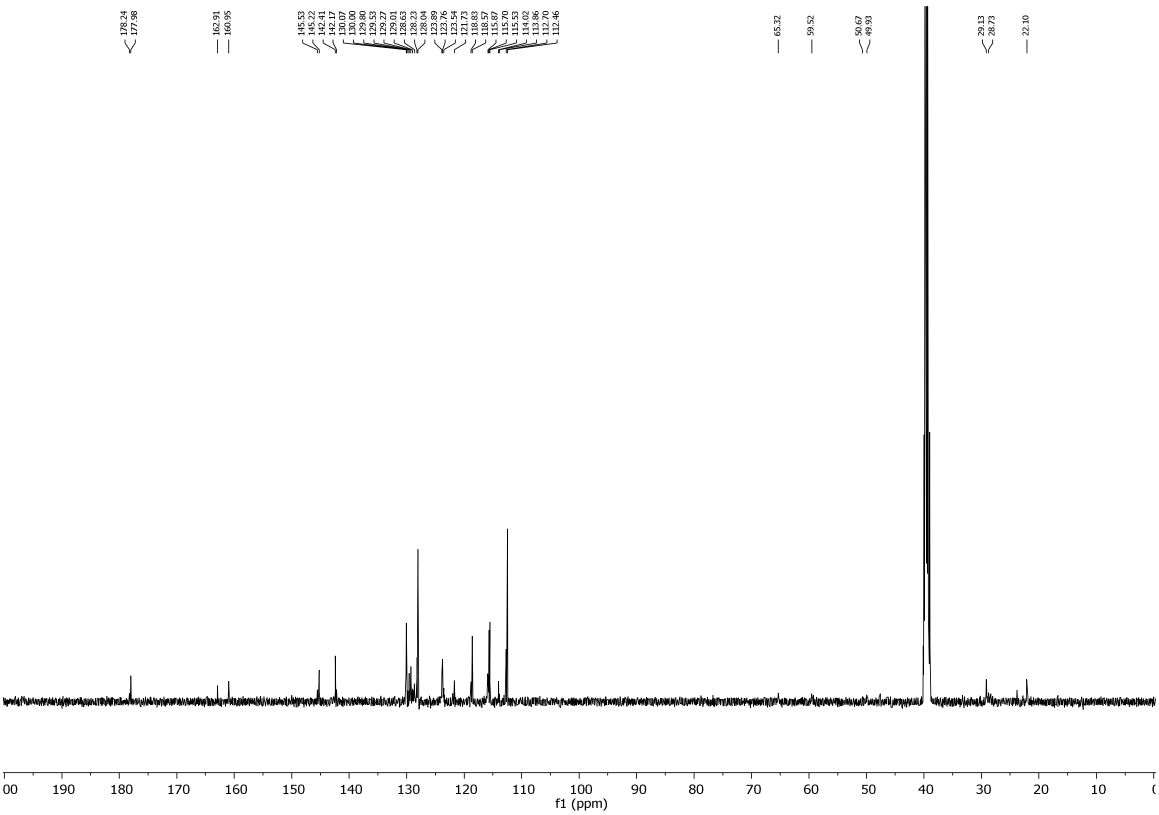
HSQC **4u**

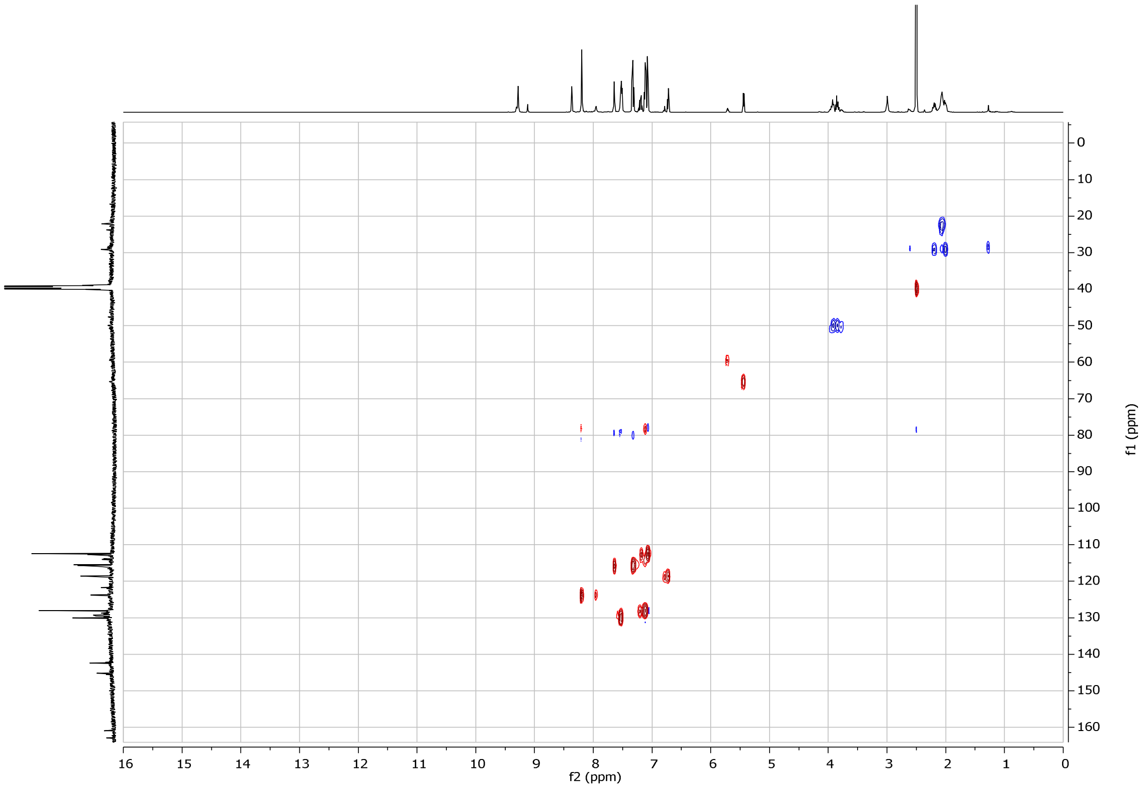


HMBC **4u**

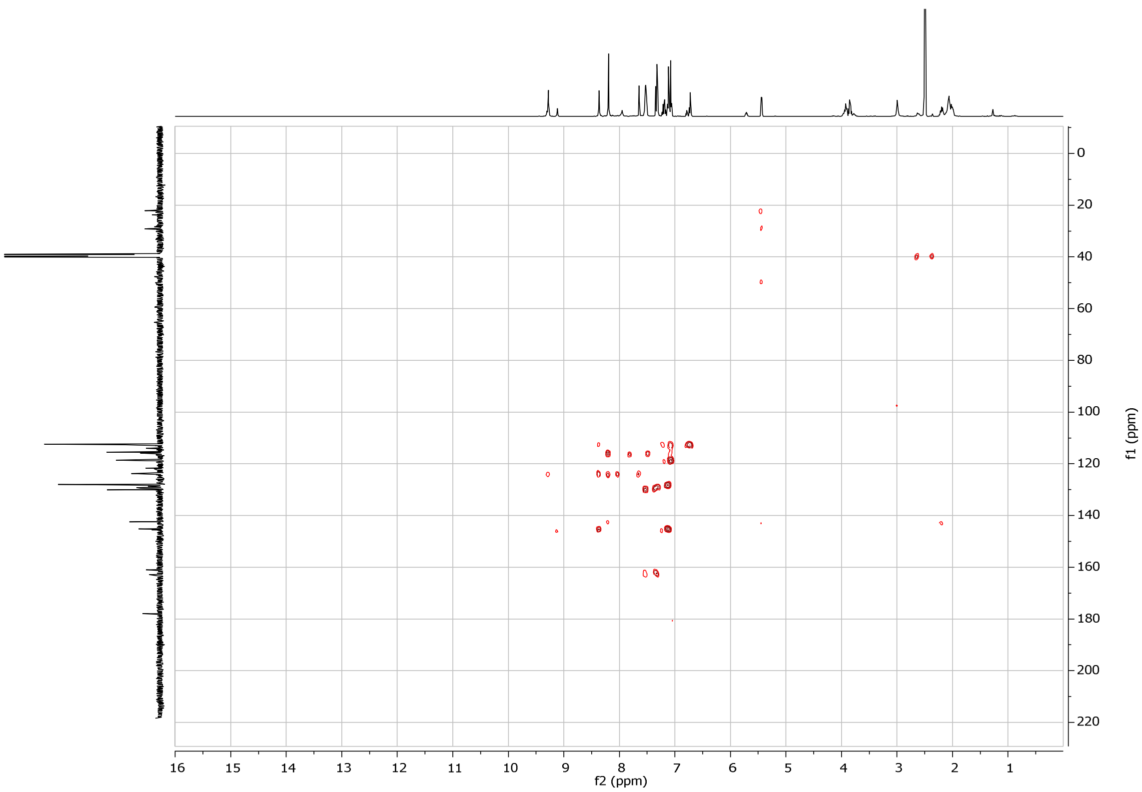
Figure SI-42. NMR spectra for compound **4u** (DMSO-d_6, 100ºC)





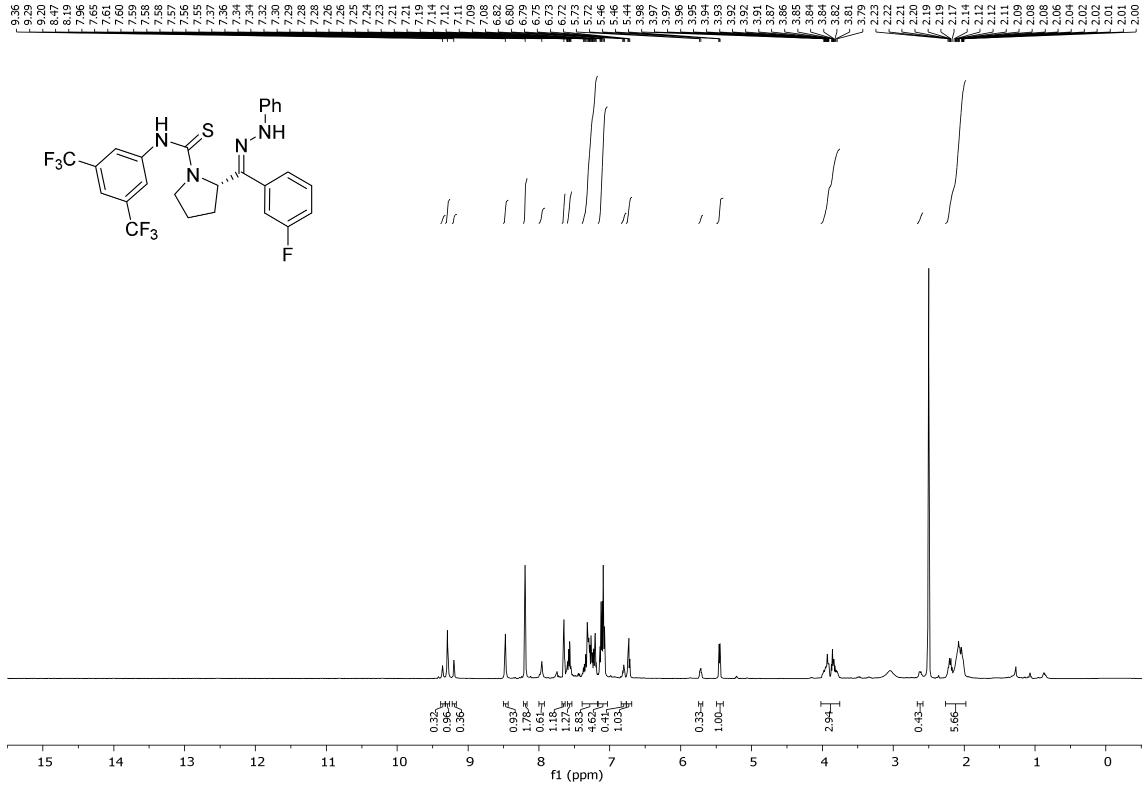


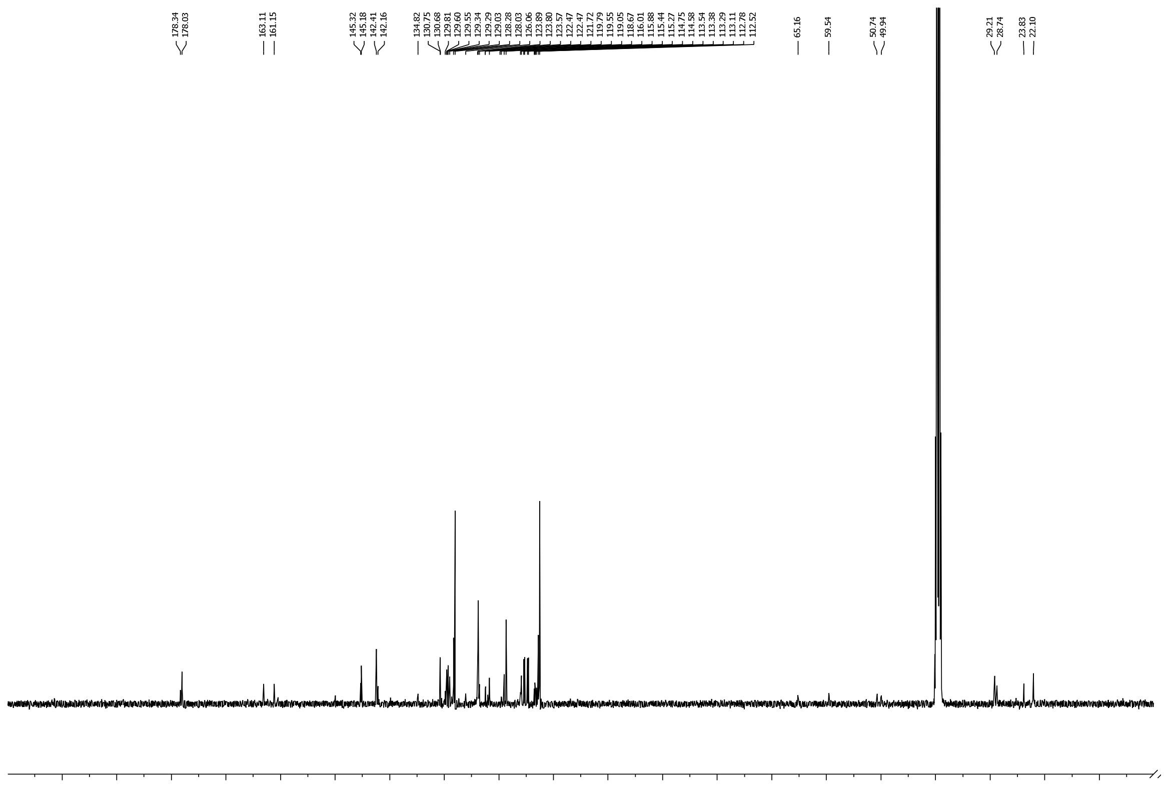
HSQC **4v**

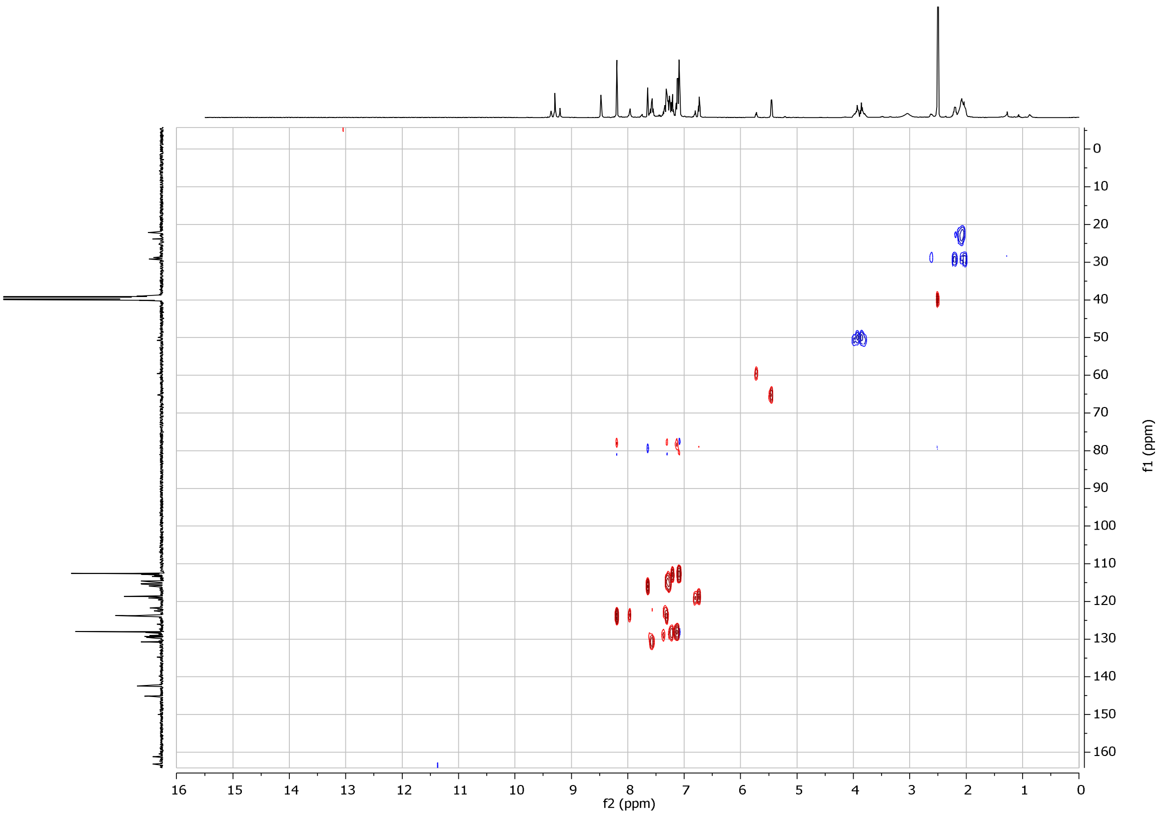


HMBC **4v**

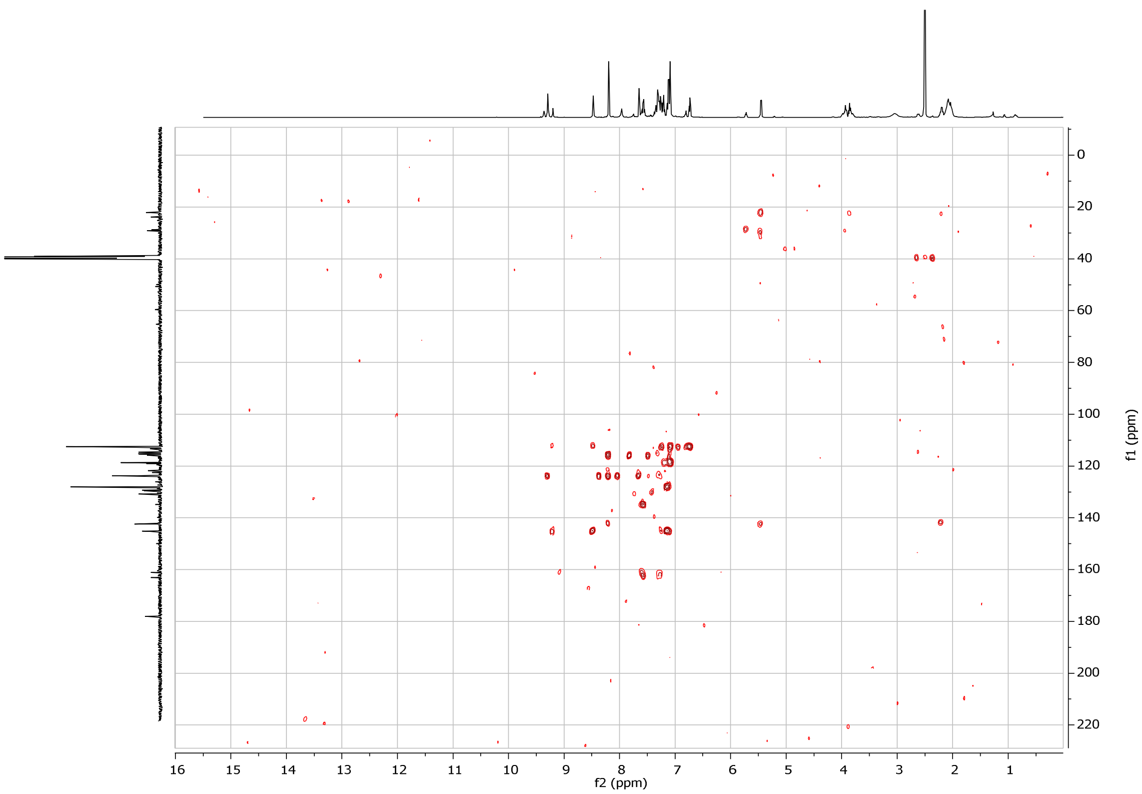
Figure SI-43. NMR spectra for compound **4v** (DMSO-d_6, 100ºC)


Ph
NH
N
H
N
S
N
F3C
CF3
F
f1 (ppm)


f1 (ppm)

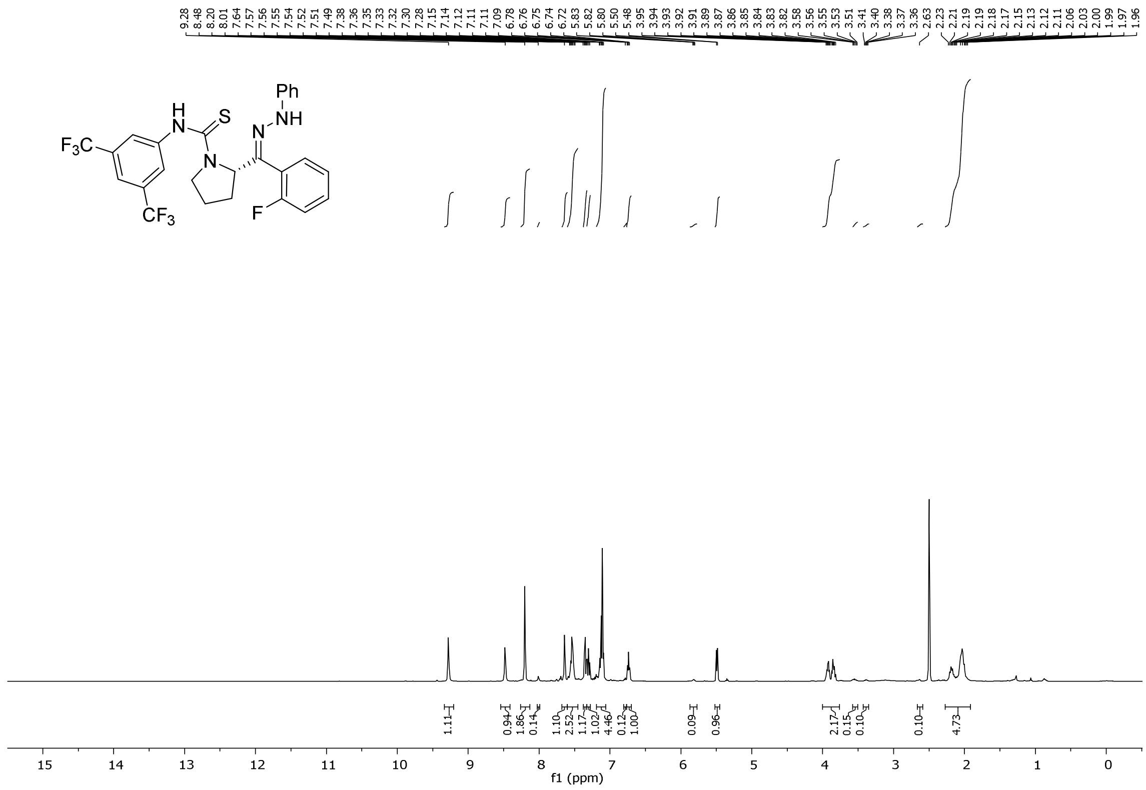


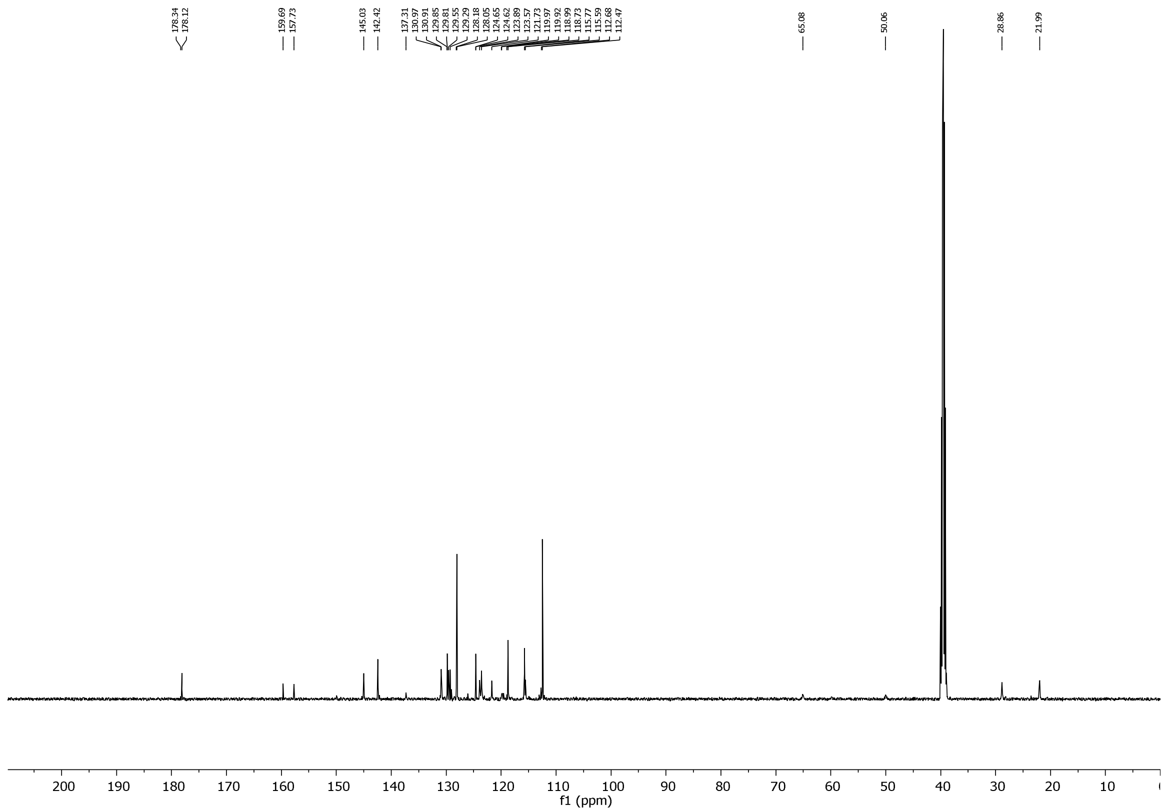
HSQC **4w**

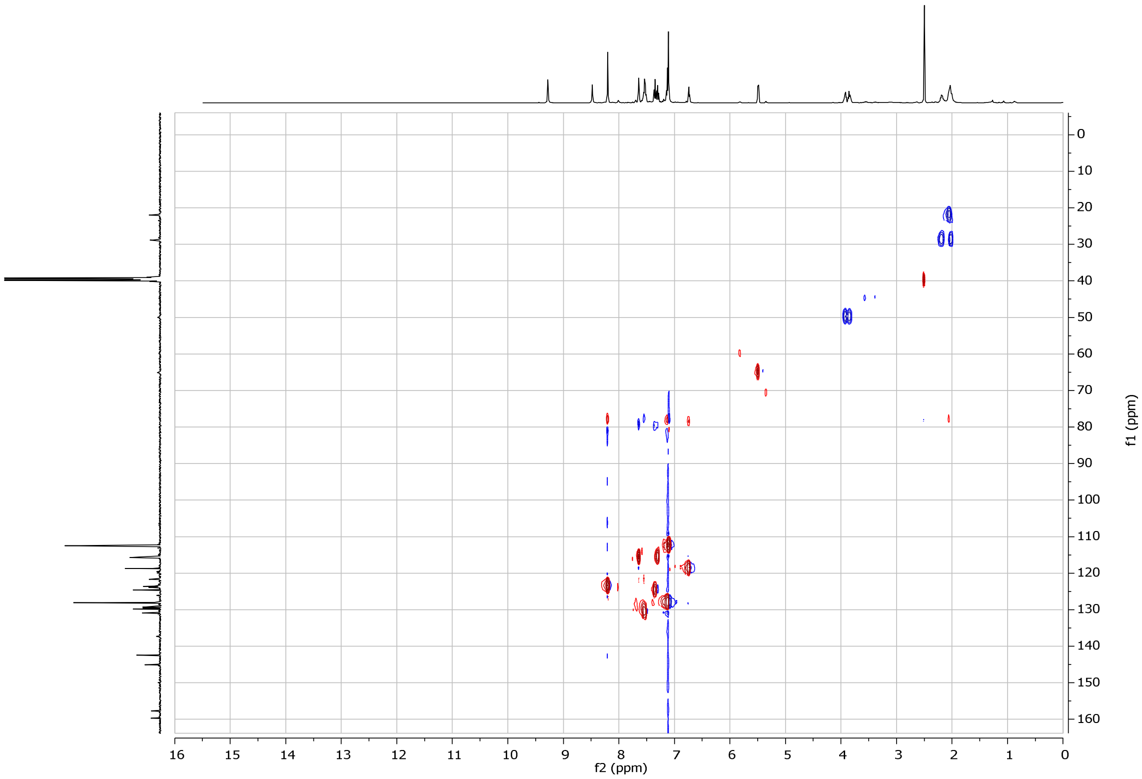


HSQC **4w**

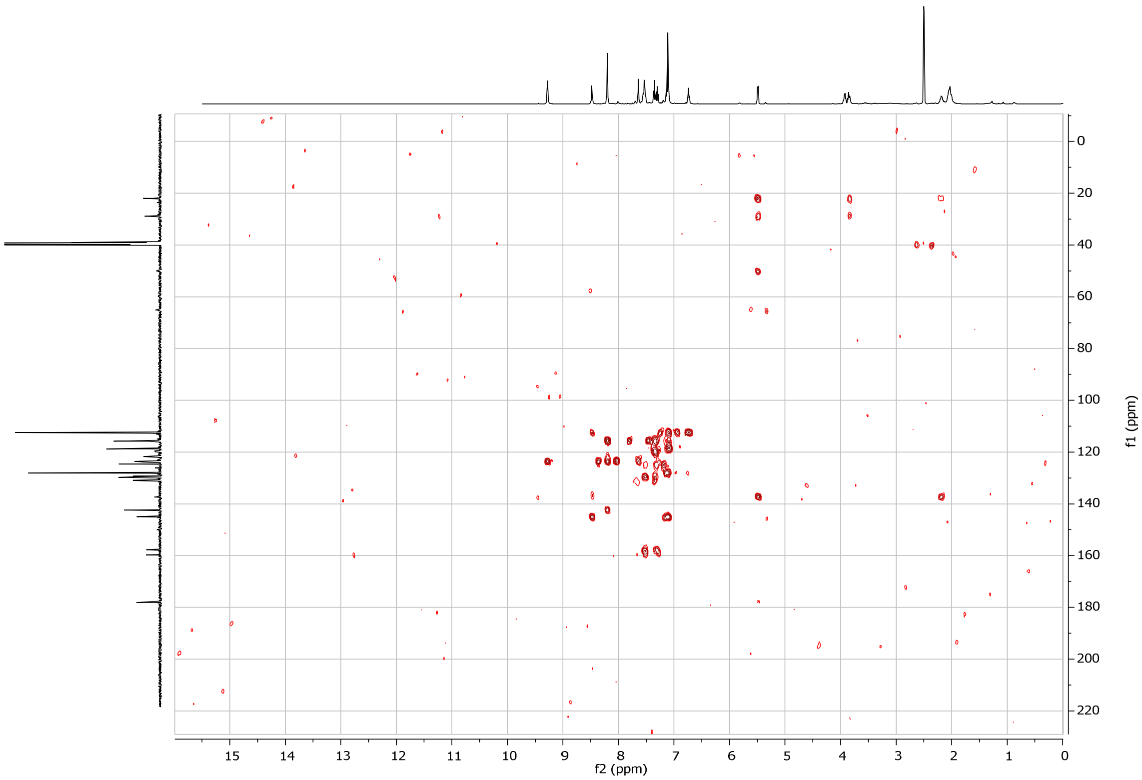
Figure SI-44. NMR spectra for compound **4w** (DMSO-d_6, 100ºC)





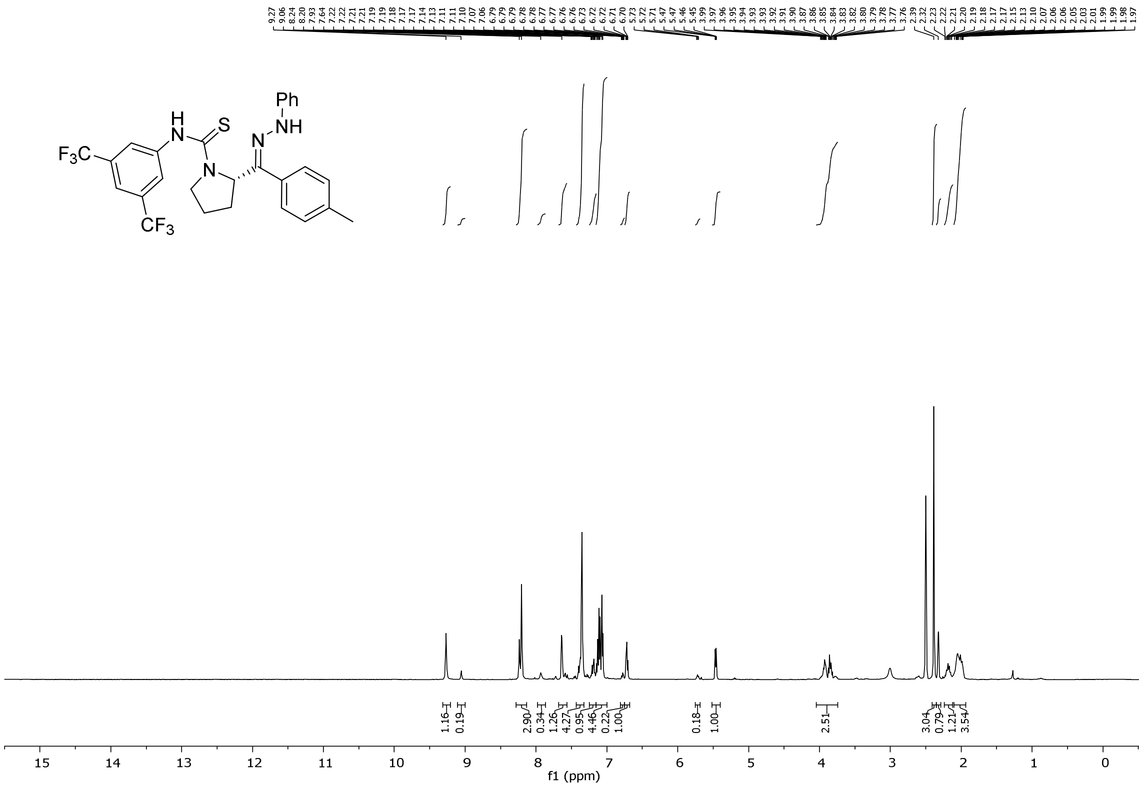


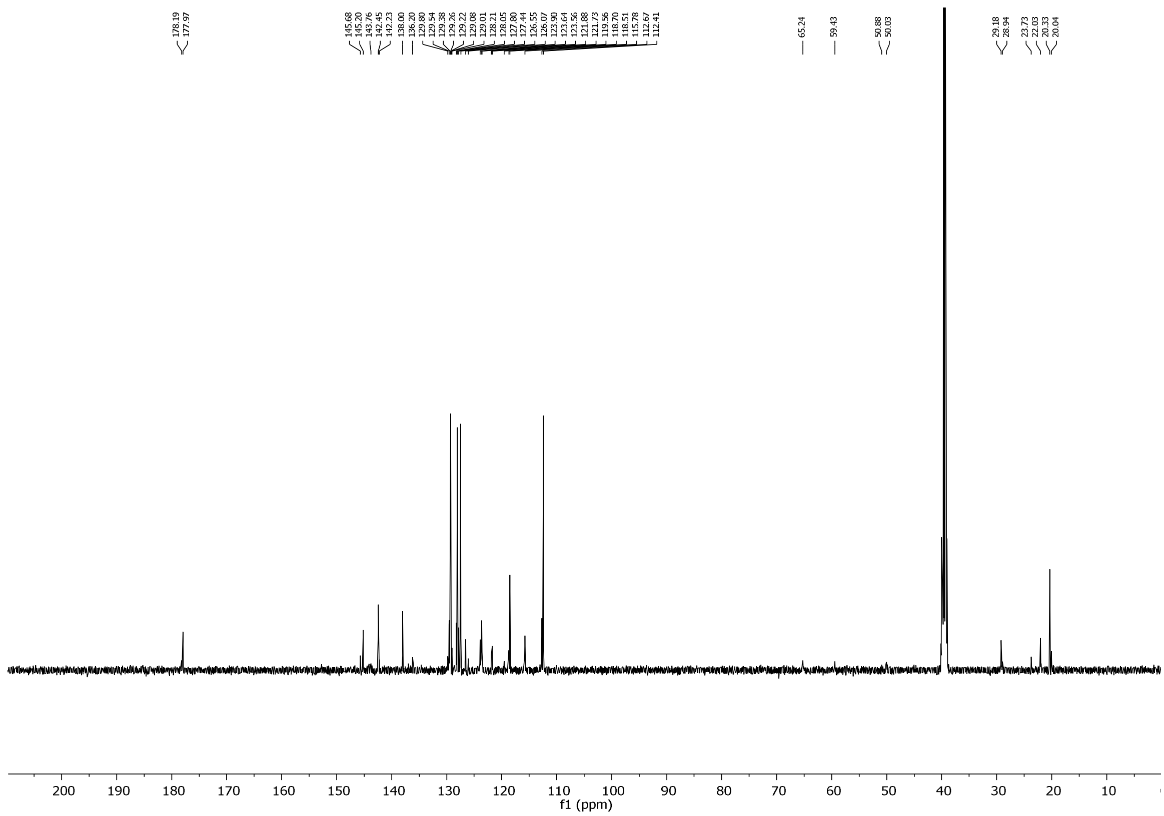
HSQC **4x**

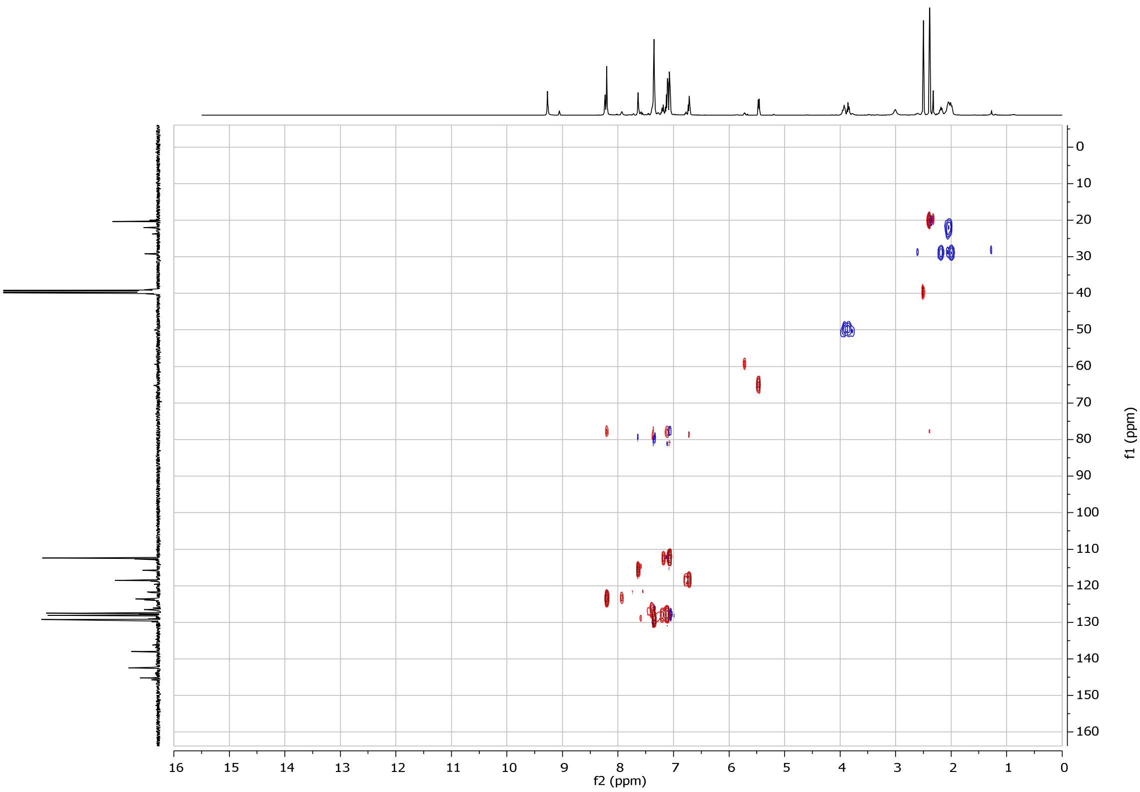


HMBC **4x**

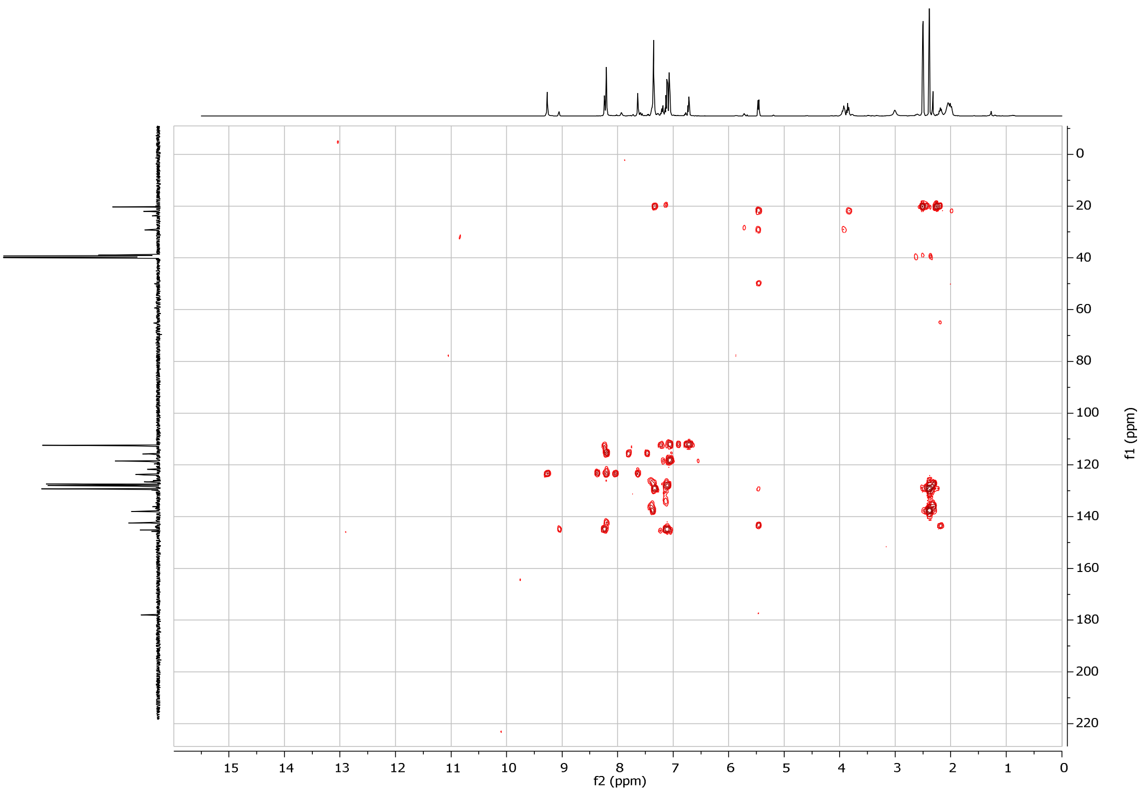
Figure SI-45. NMR spectra for compound **4x** (DMSO-d_6, 100°C)





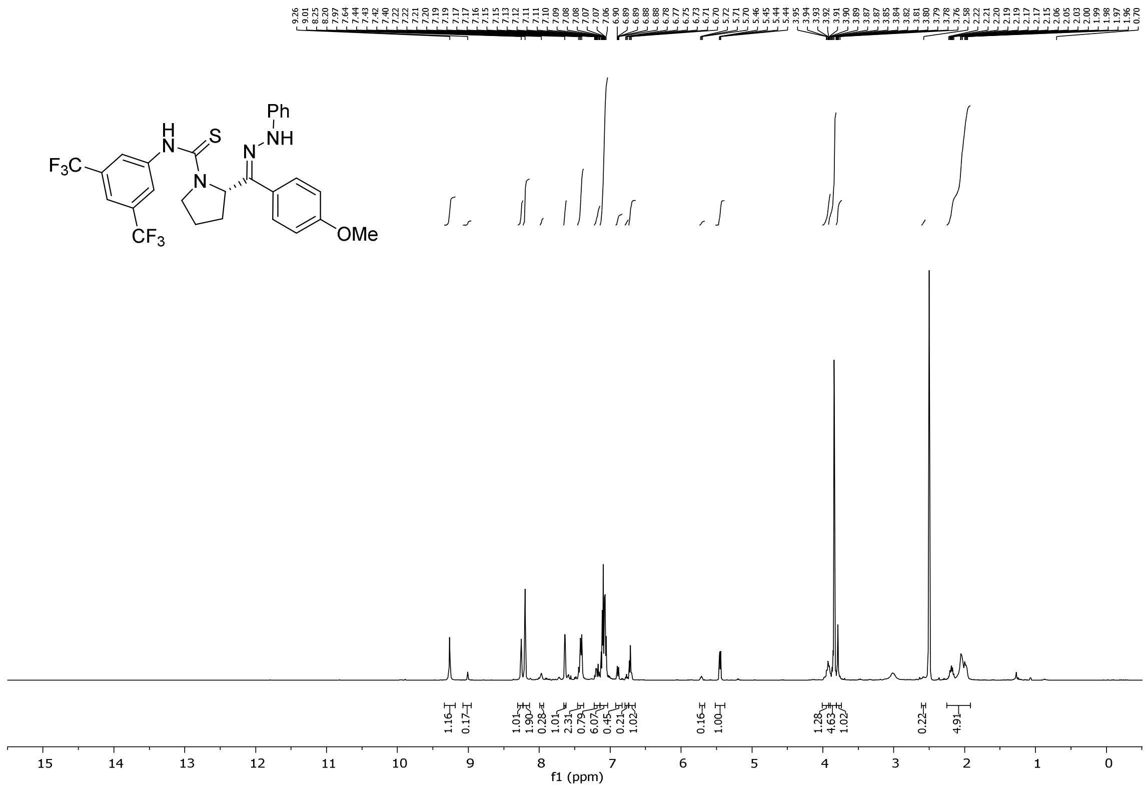


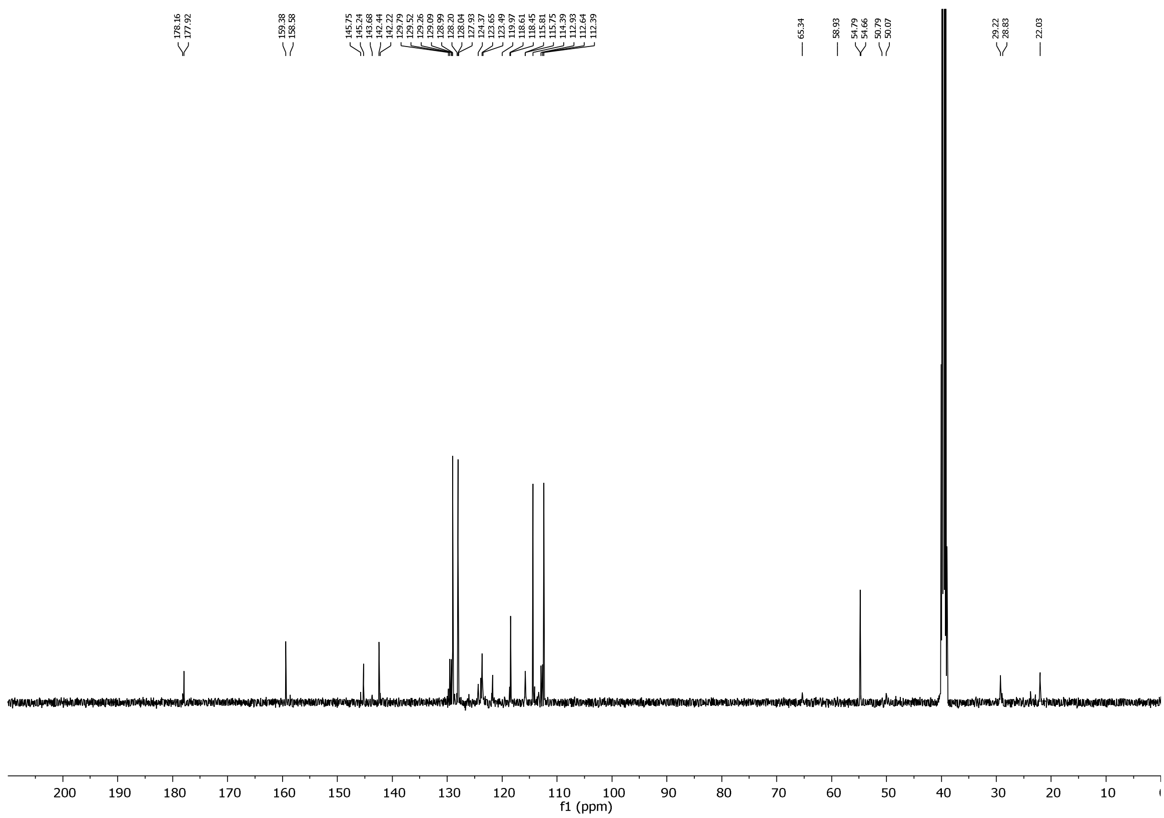
HSQC **4y**

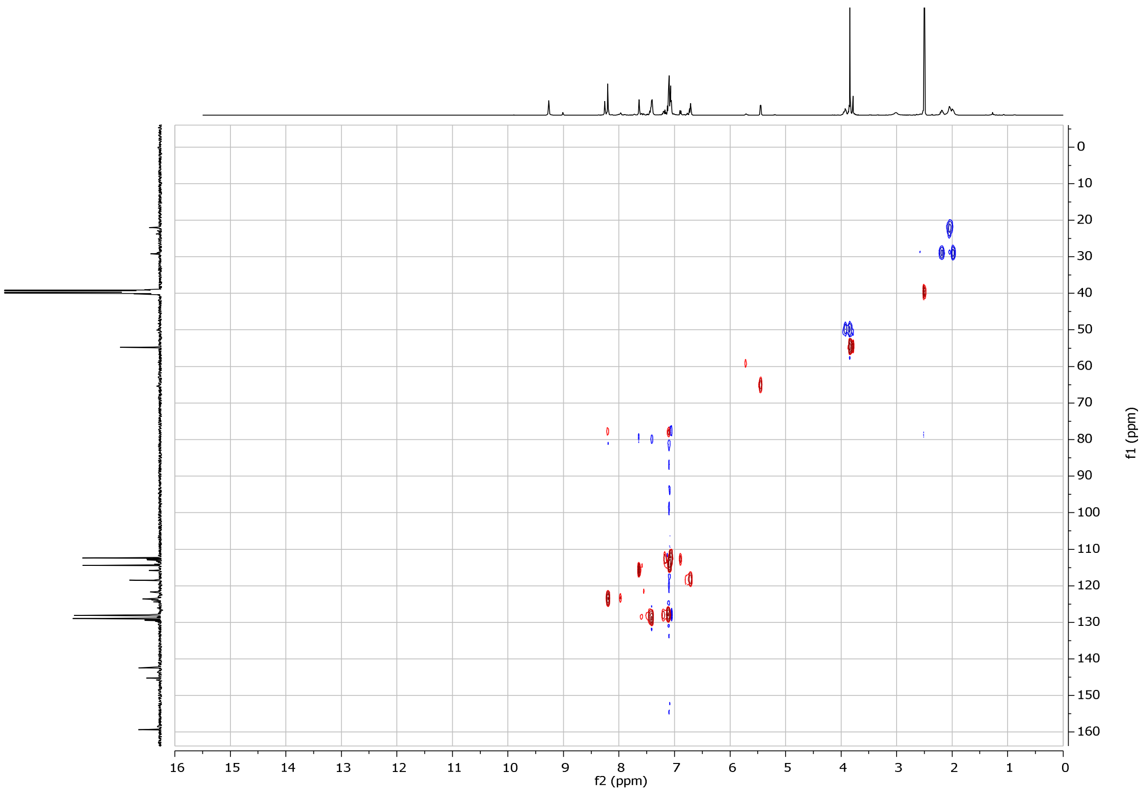


HMBC **4y**

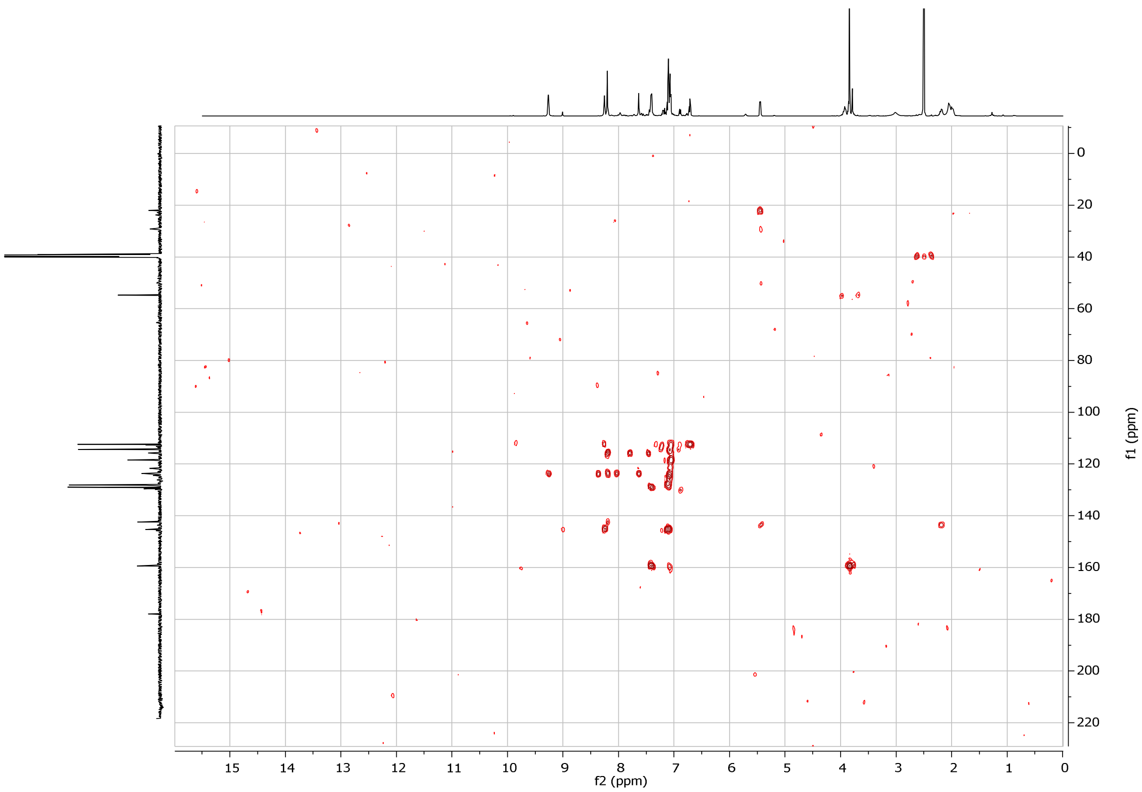
Figure SI-46. NMR spectra for compound **4y** (DMSO-d_6, 100ºC)





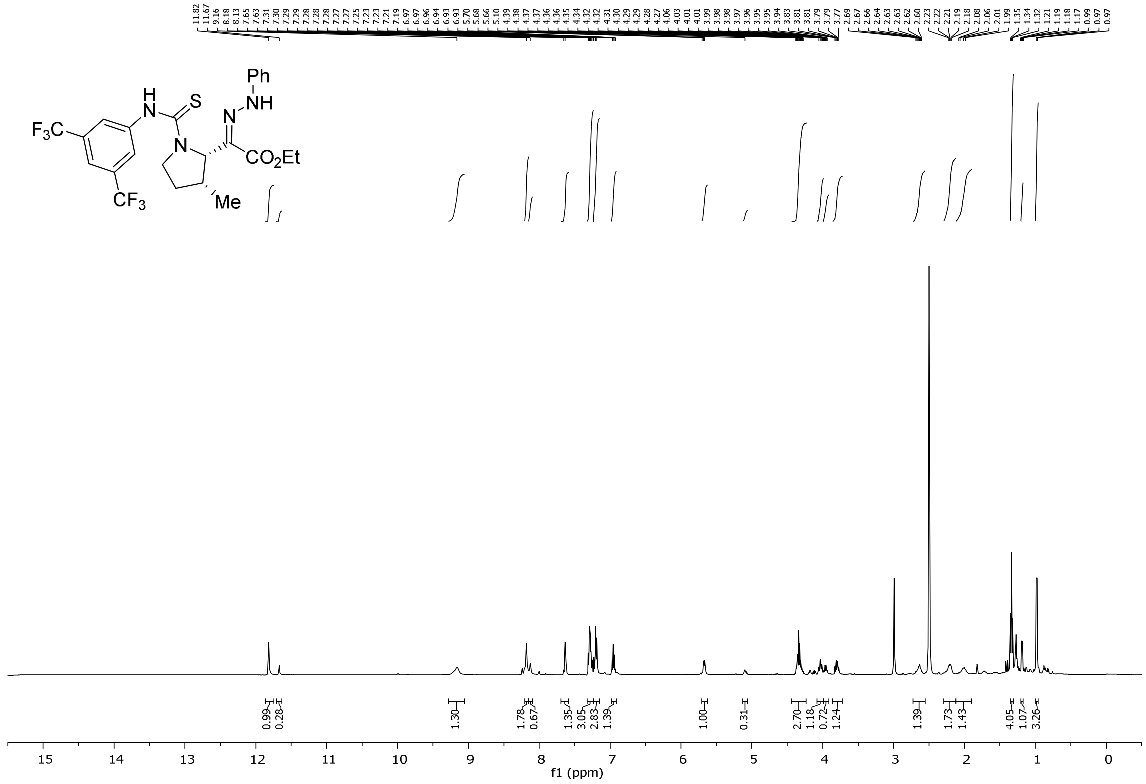


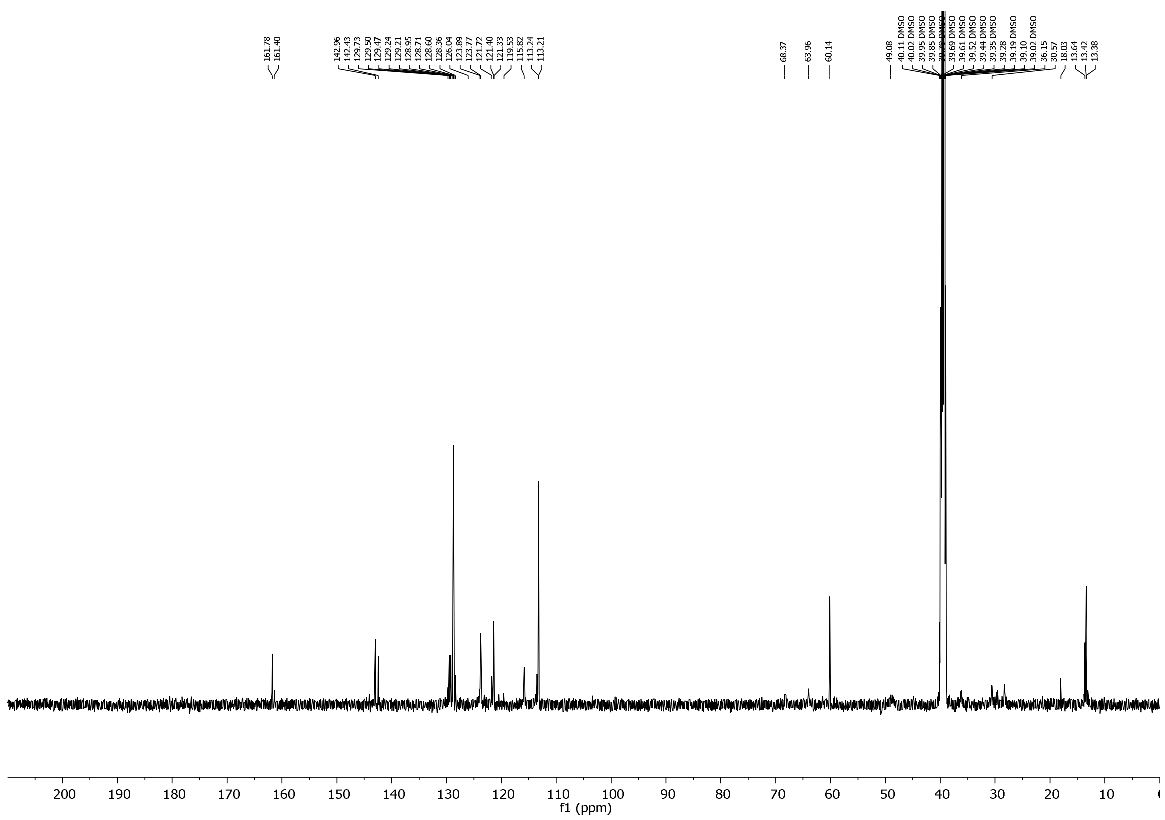
HSQC **4z**

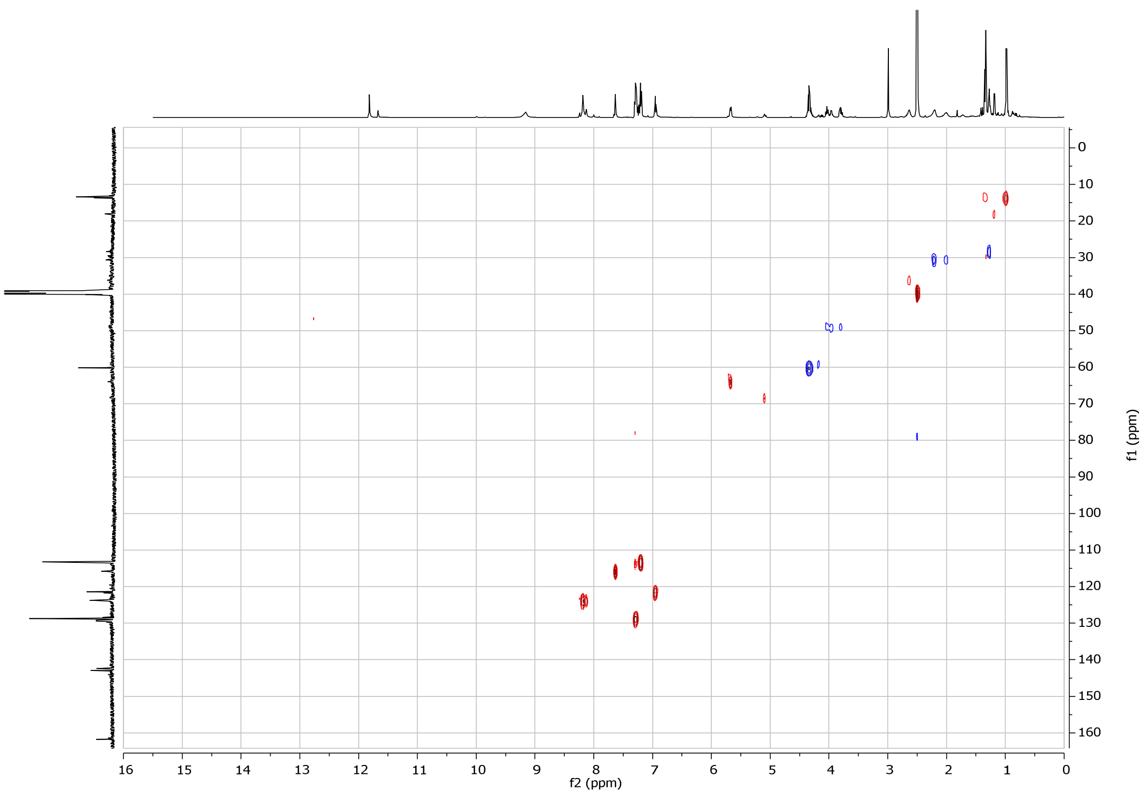


HMBC **4z**

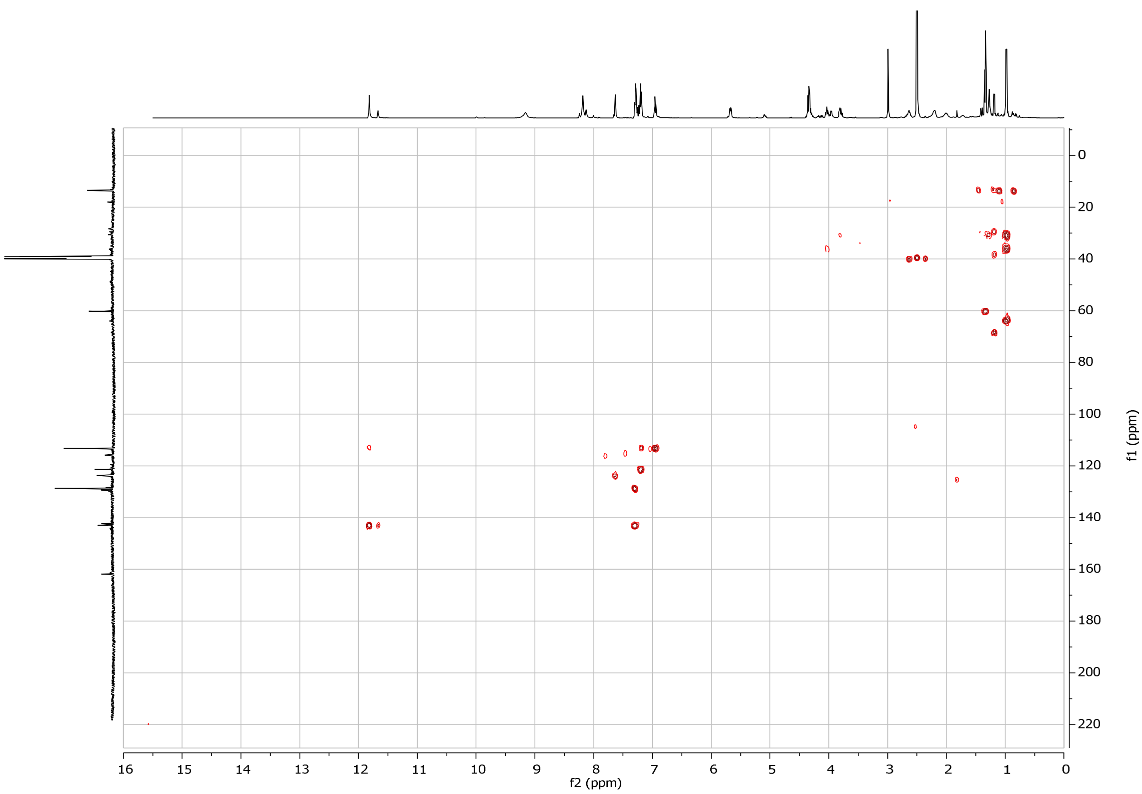
Figure SI-47. NMR spectra for compound **4z** (DMSO-d_6, 100ºC)


Ph
NH
N
H
N
S
F3C
N
CO2Et
Me
CF3
f1 (ppm)

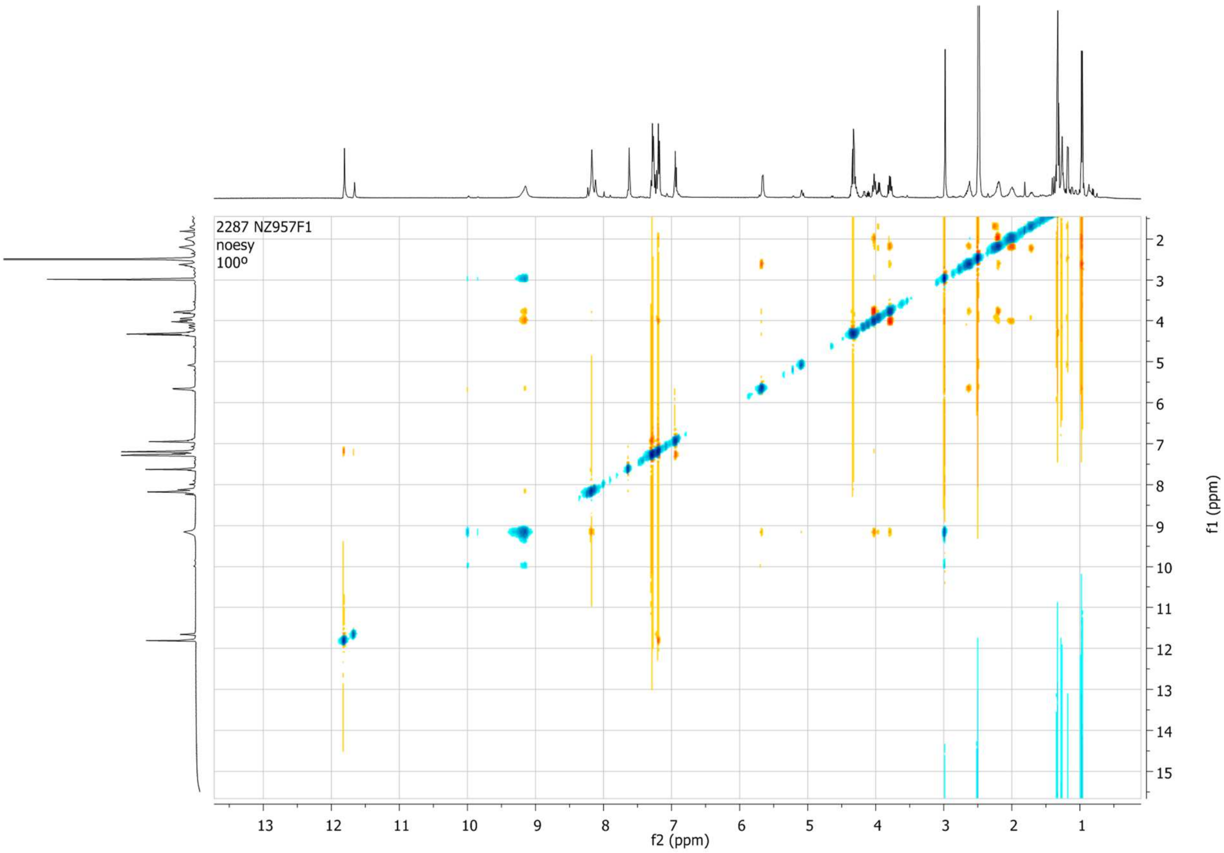

f1 (ppm)



HSQC **6a**

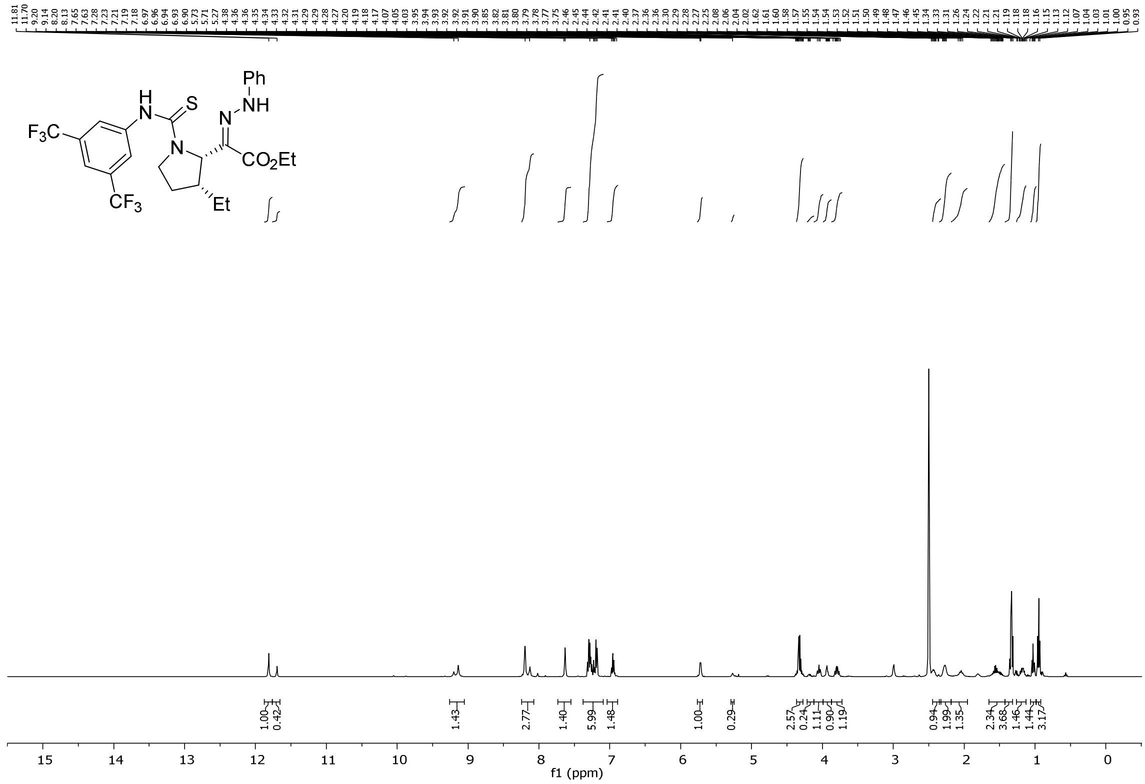


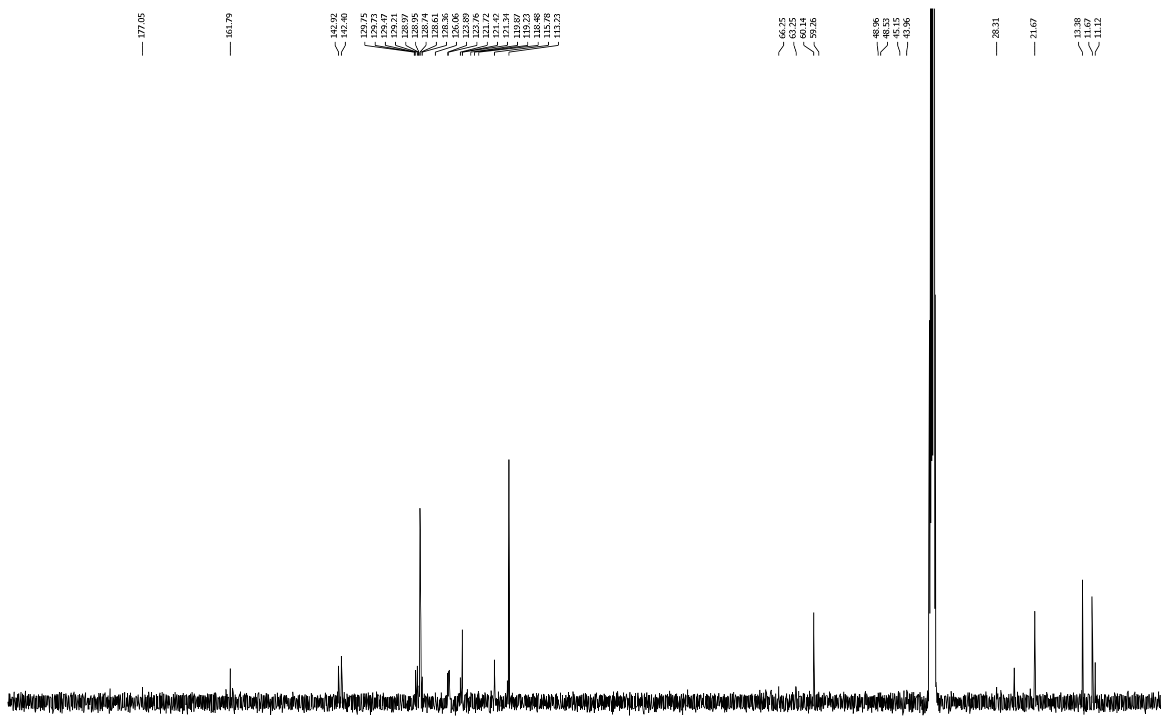
HMBC **6a**

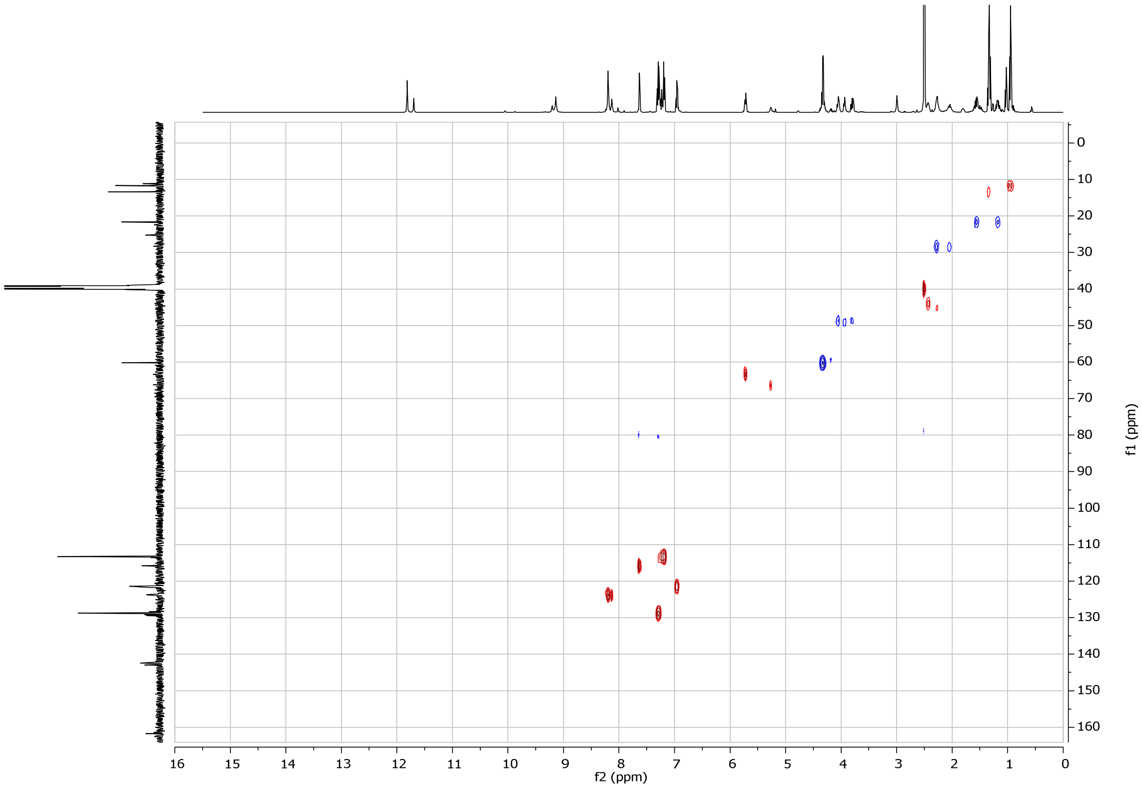


NOESY **6a**

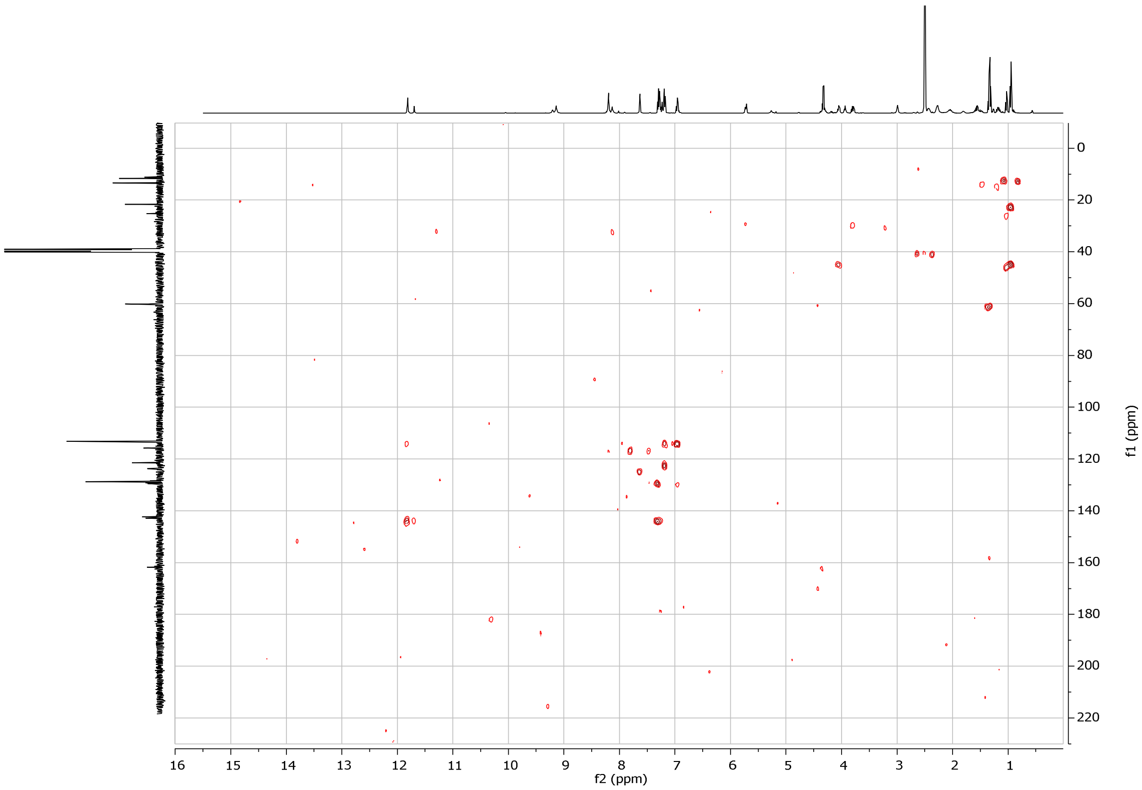
Figure SI-48. NMR spectra for compound **6a** (DMSO-d_6, 100ºC)


Ph
NH
N
H
N
S
F3C
N
CO2Et
CF3
Et
f1 (ppm)

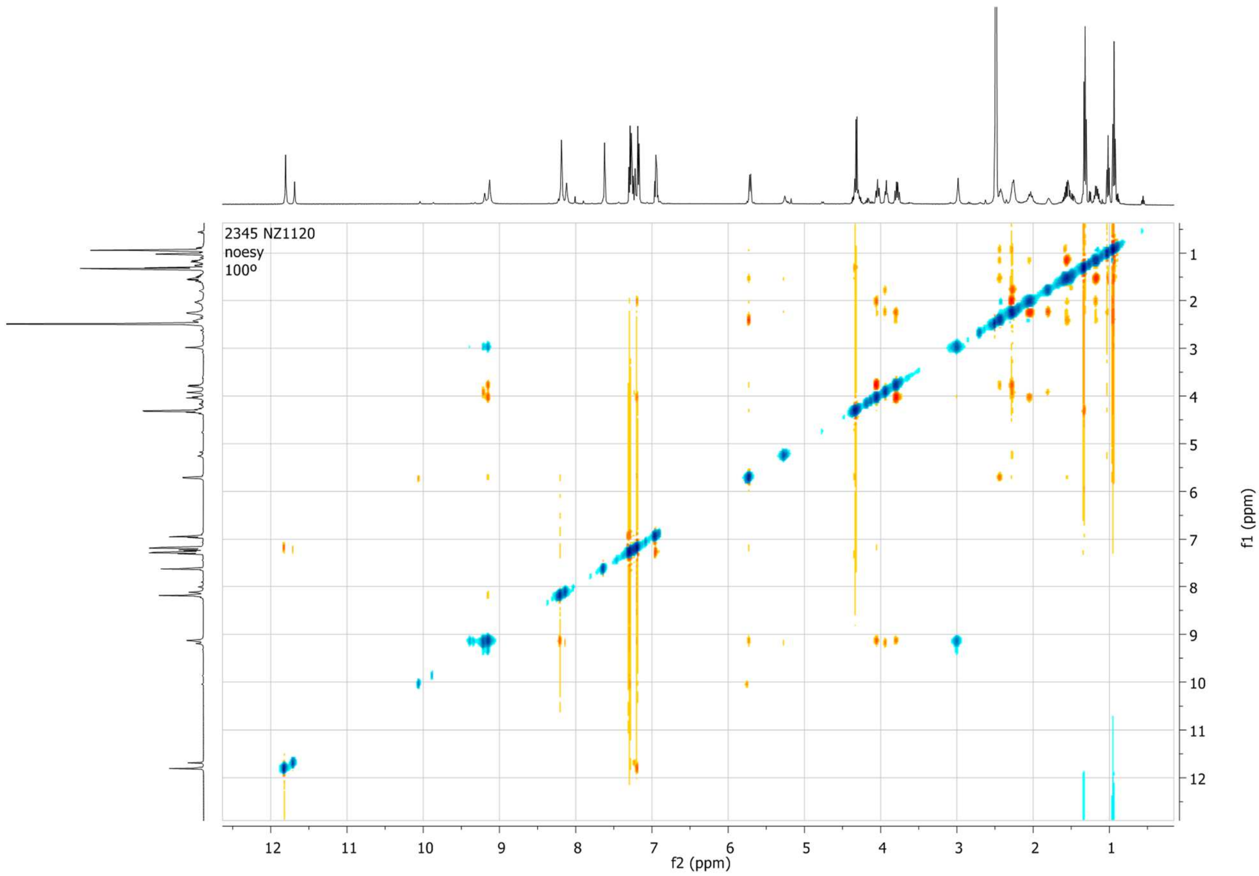

f1 (ppm)



HSQC **6b**

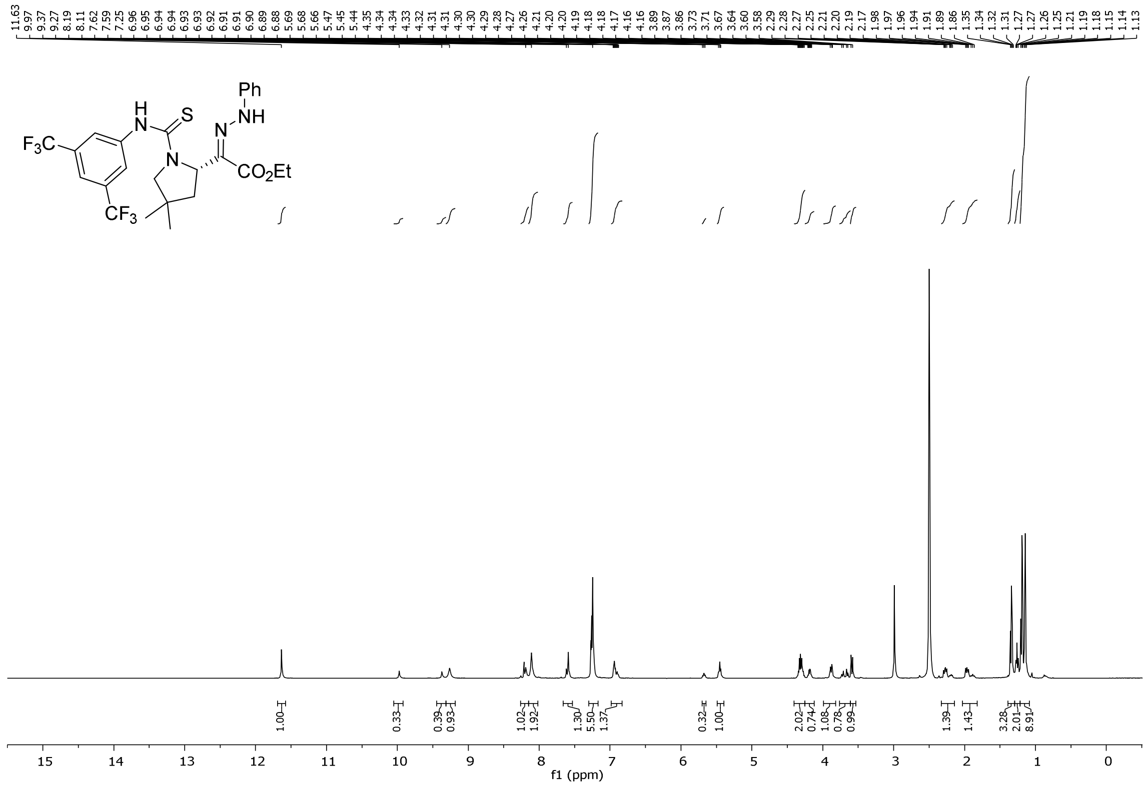


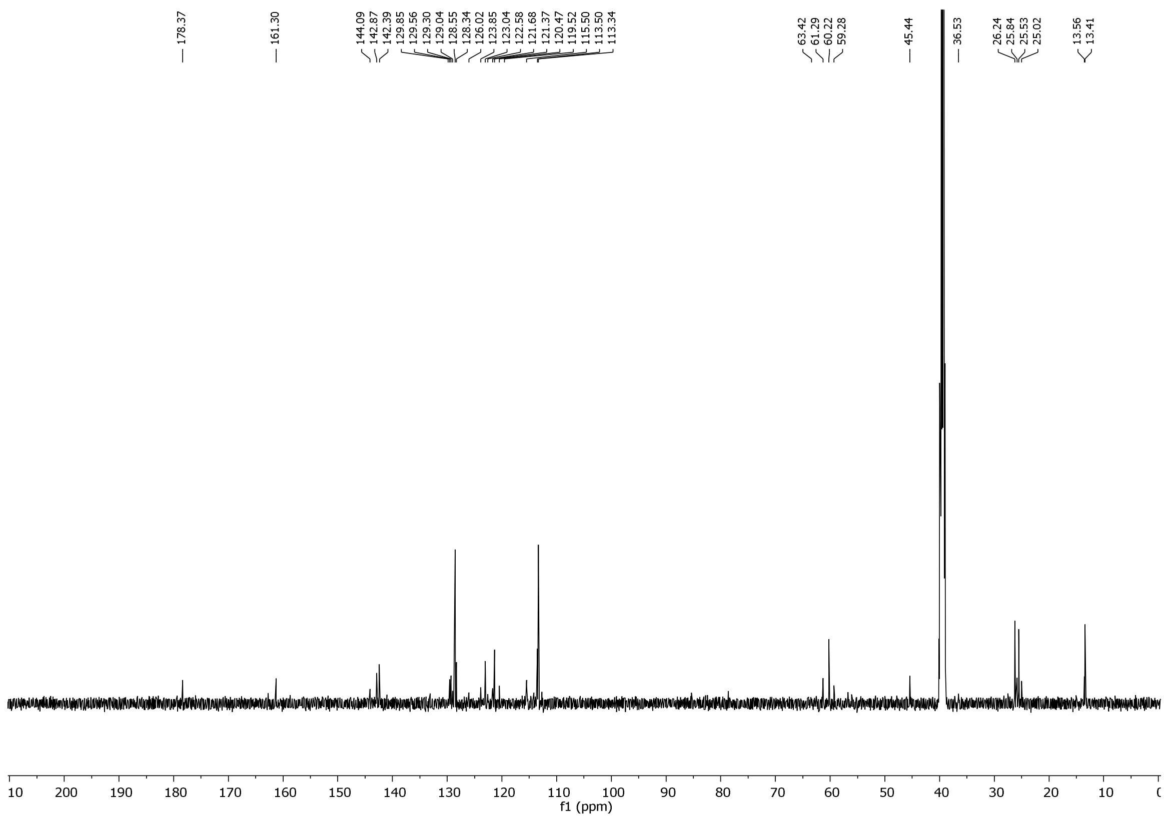
HMBC **6b**

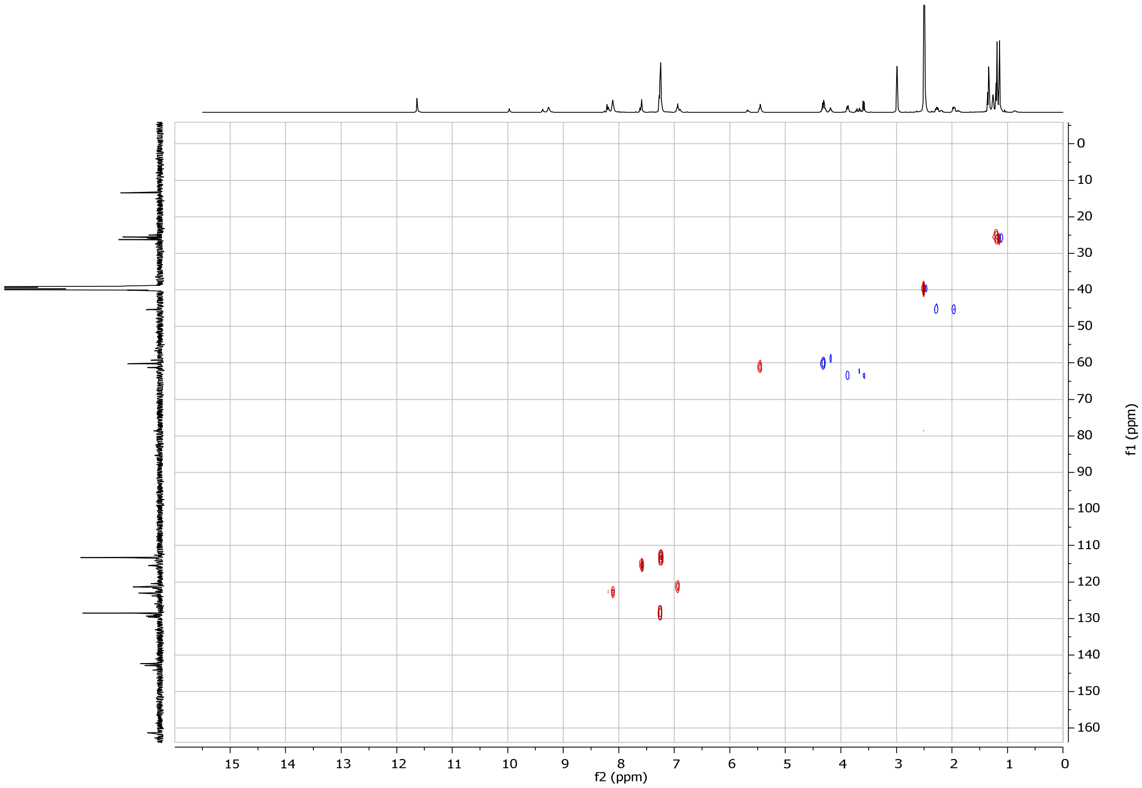


NOESY **6b**

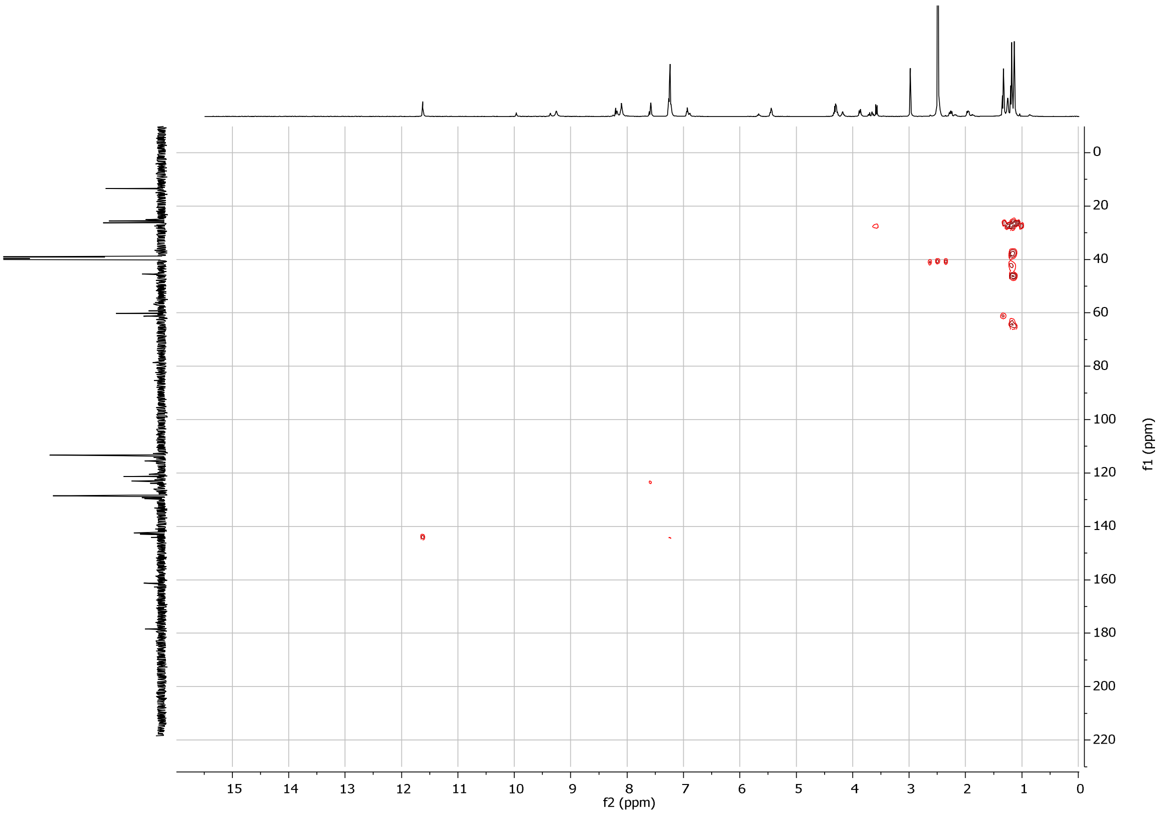
Figure SI-49. NMR spectra for compound **6b** (DMSO-d_6, 100ºC)


Ph
NH
N
H
N
S
F3C
CF3
CO2Et
f1 (ppm)


f1 (ppm)



HSQC **6c**



HMBC **6c**

Figure SI-50. NMR spectra for compound **6c** (DMSO-d_6, 100ºC)

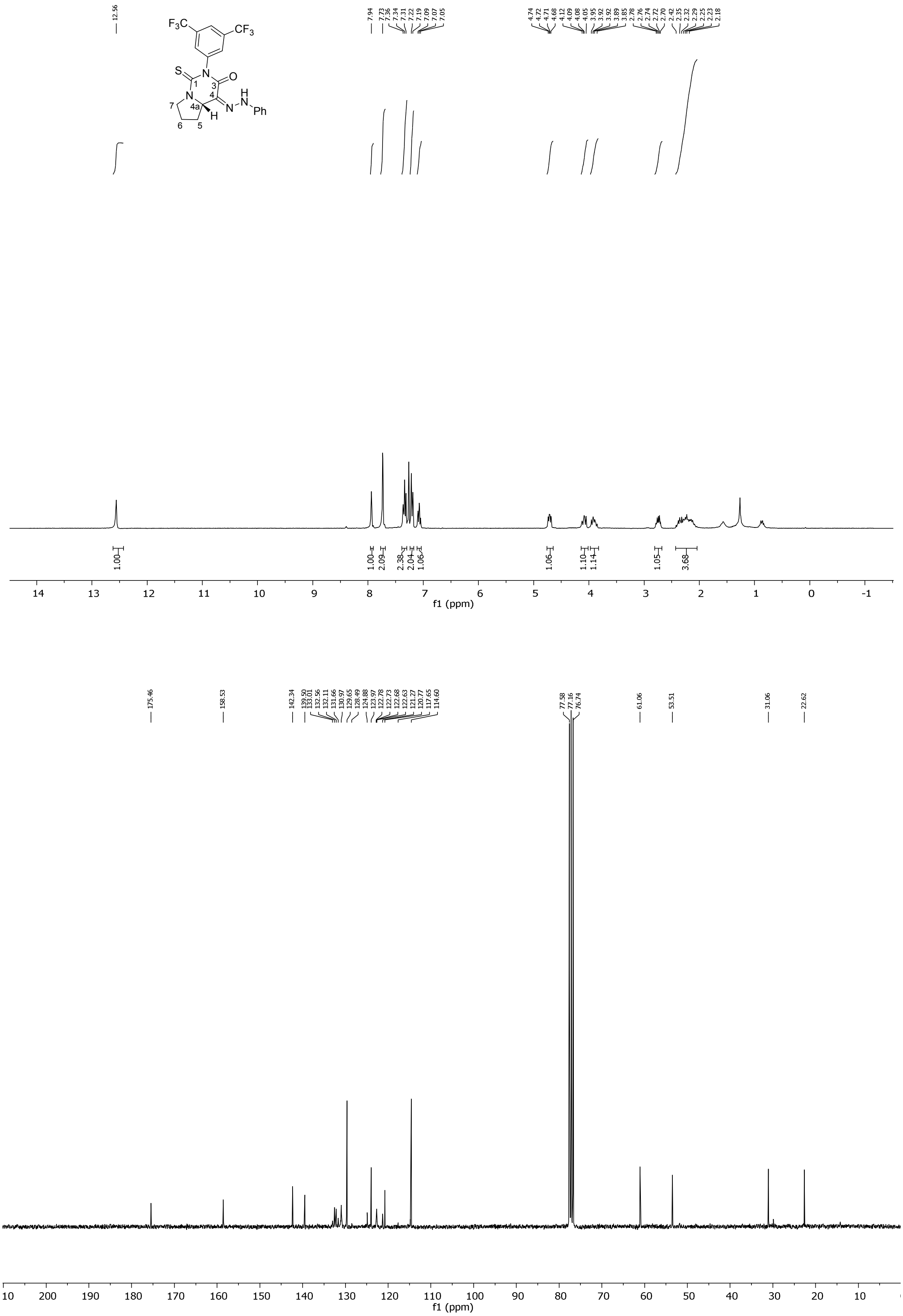


Figure SI-51. NMR spectra for compound **7a**

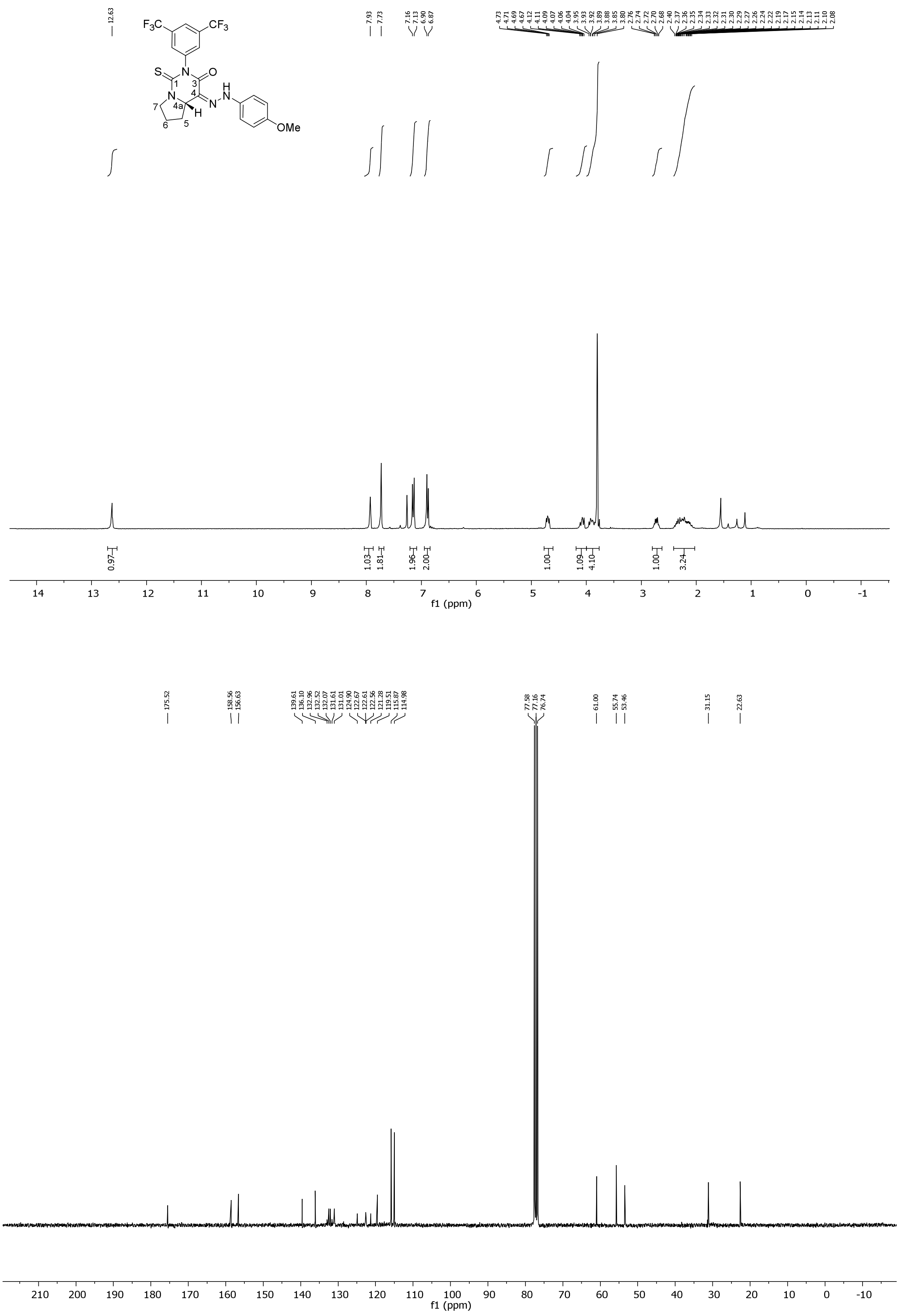


Figure SI-52. NMR spectra for compound **7b**

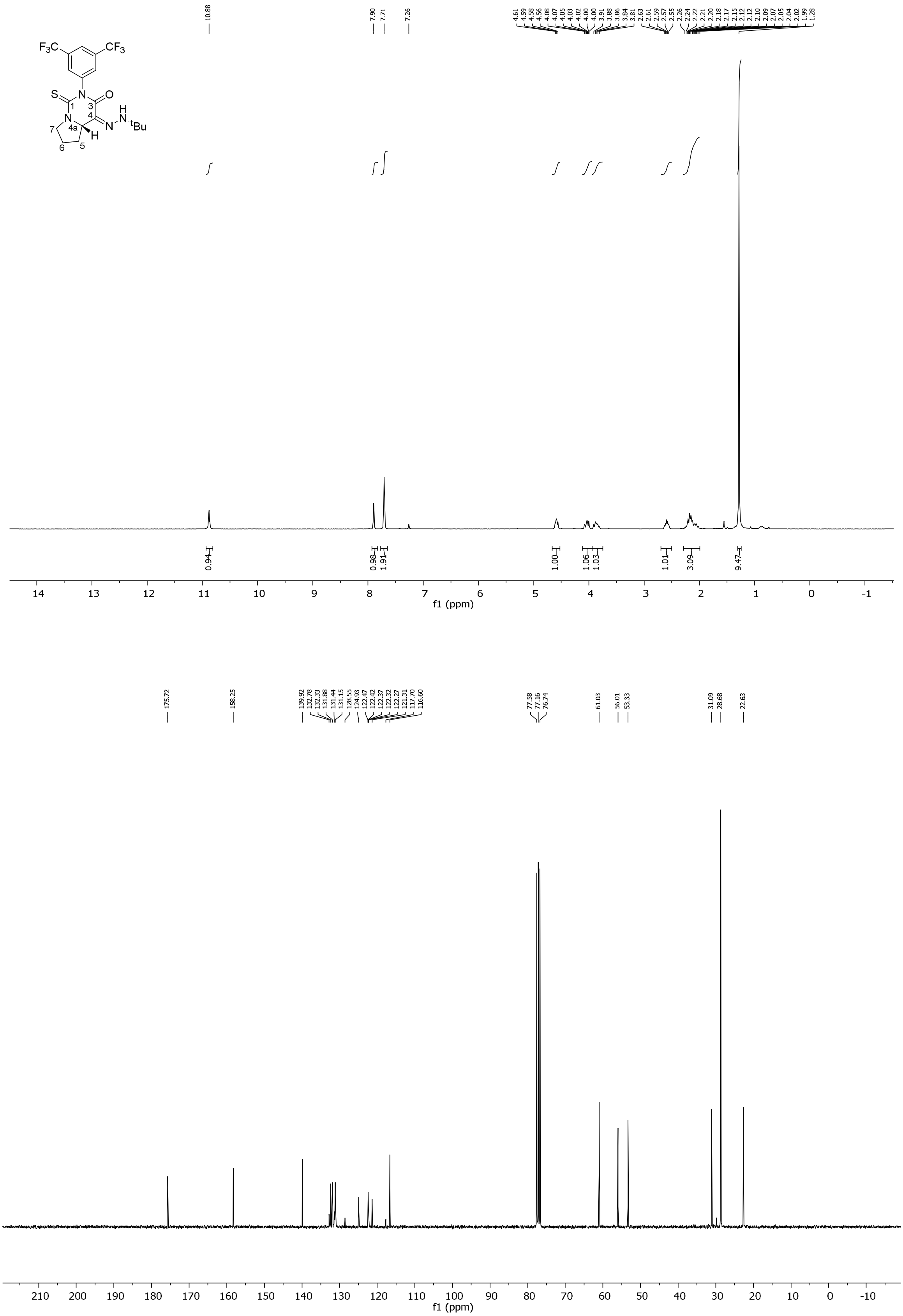
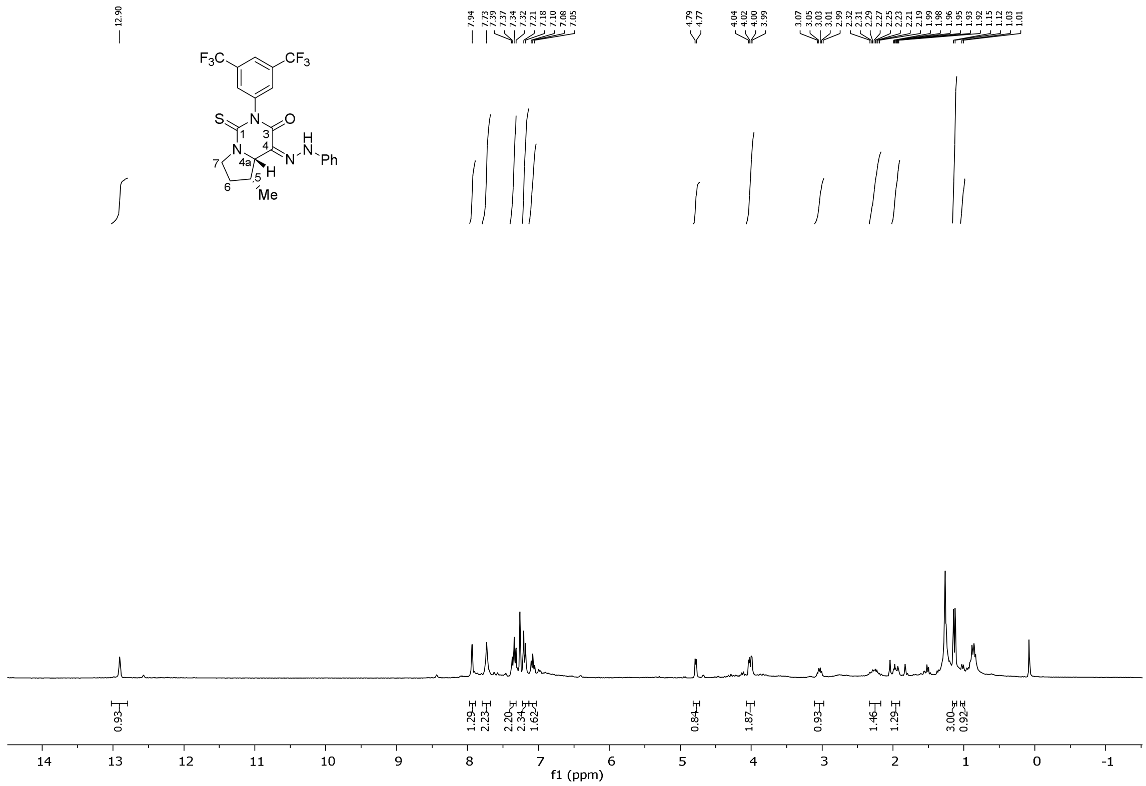


Figure SI-53. NMR spectra for compound **7c**



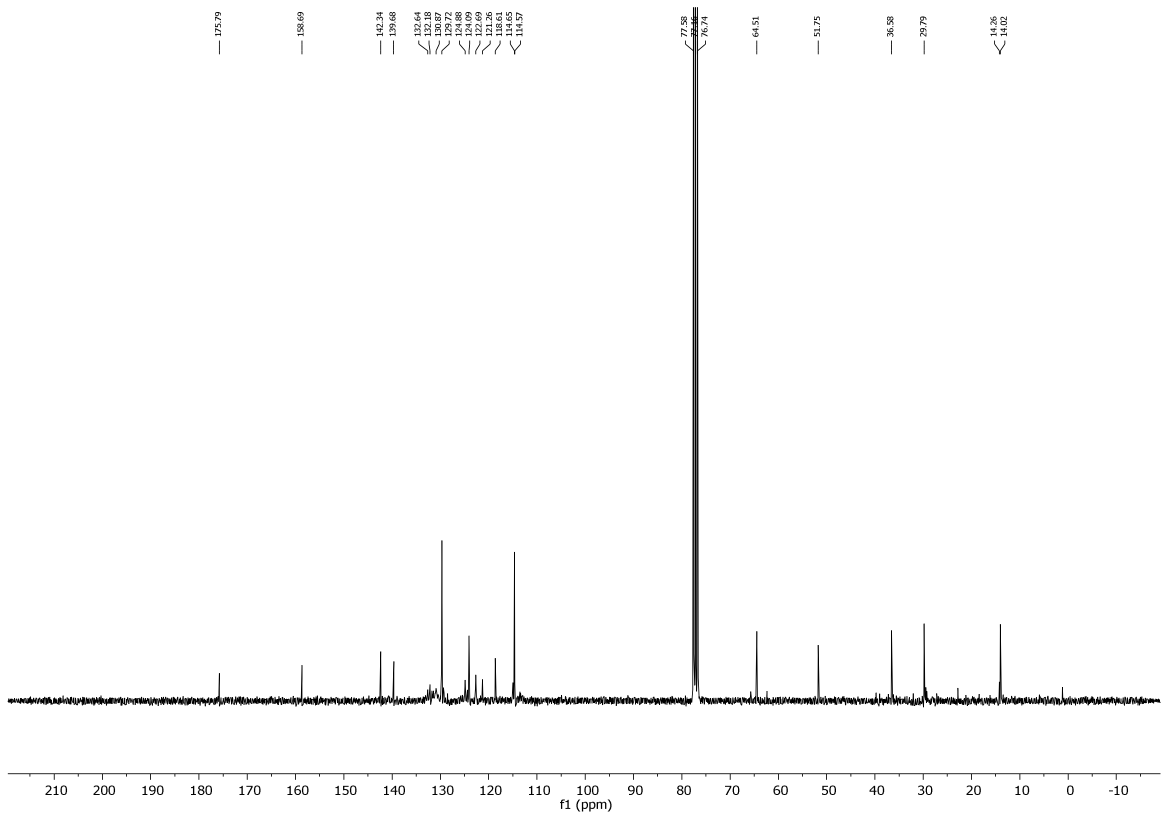
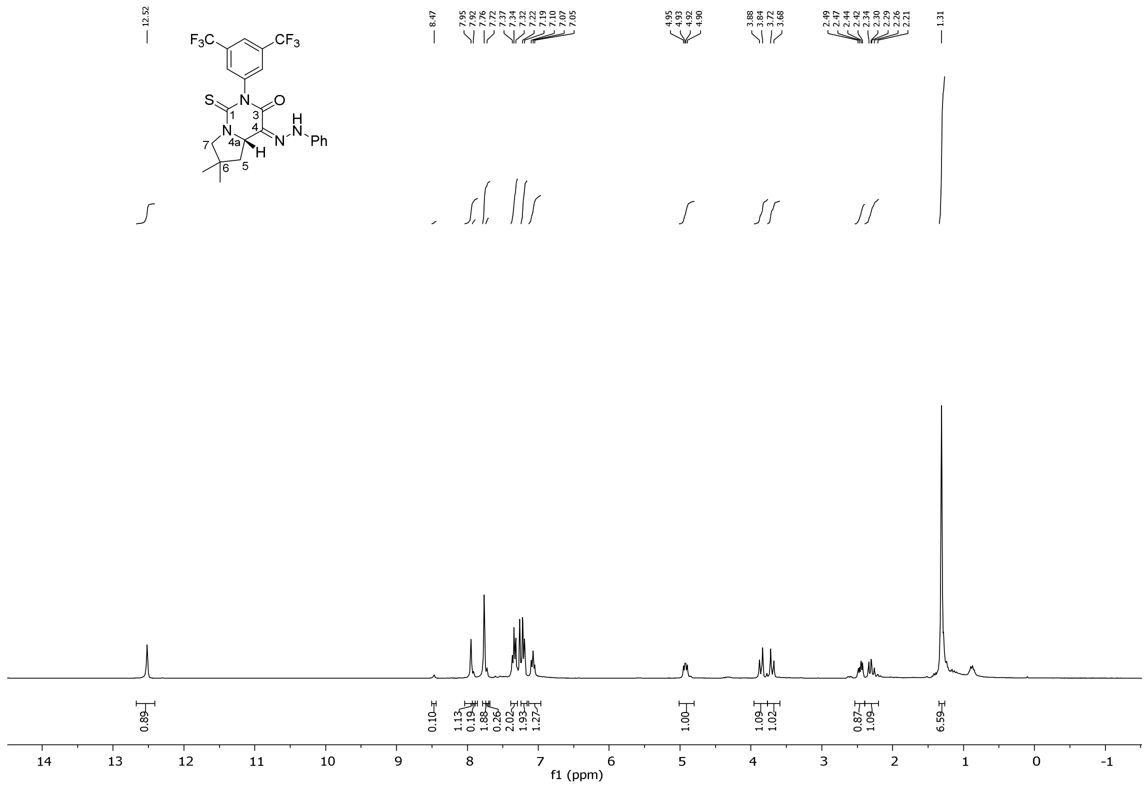


Figure SI-54. NMR spectra for compound **7d**



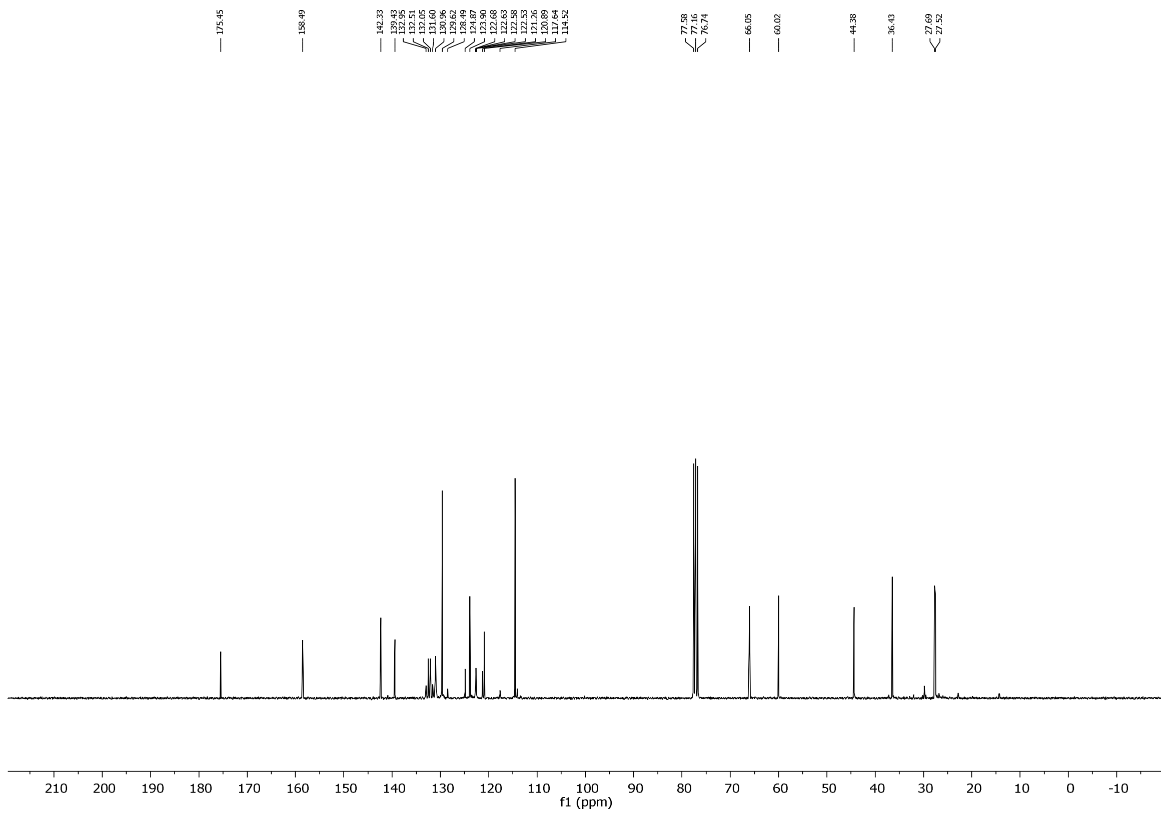
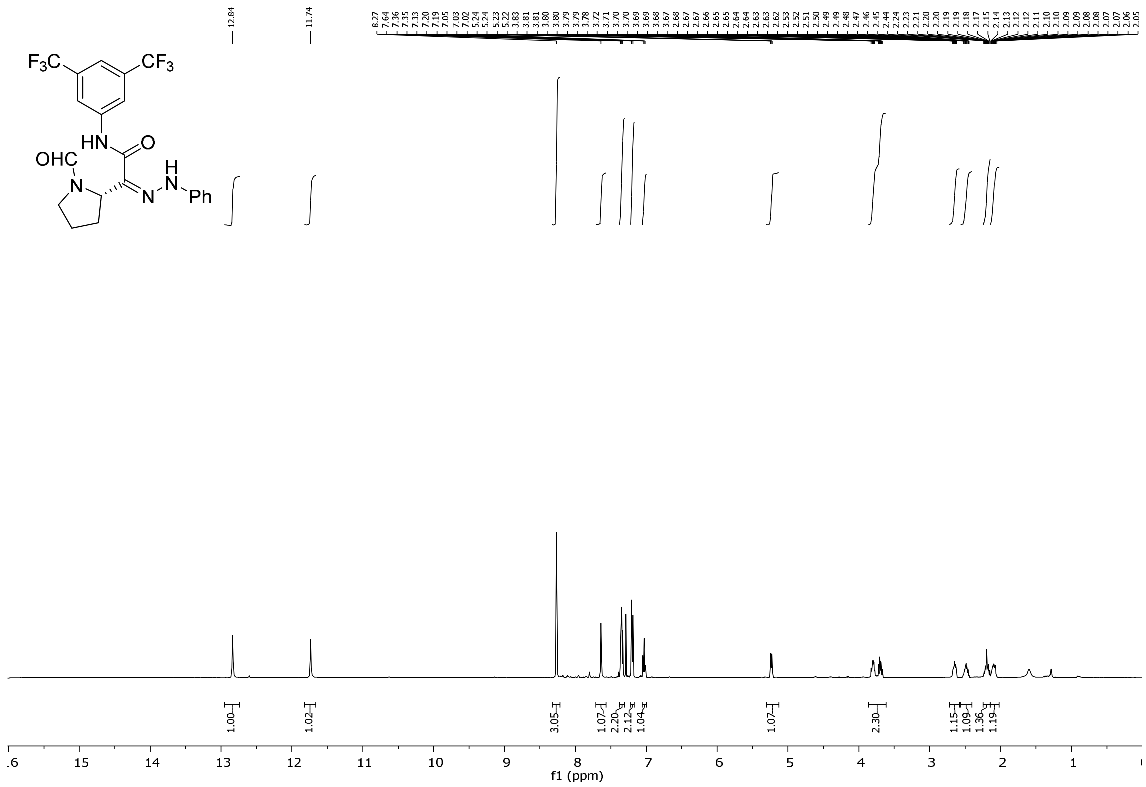


Figure SI-55. NMR spectra for compound **7e**



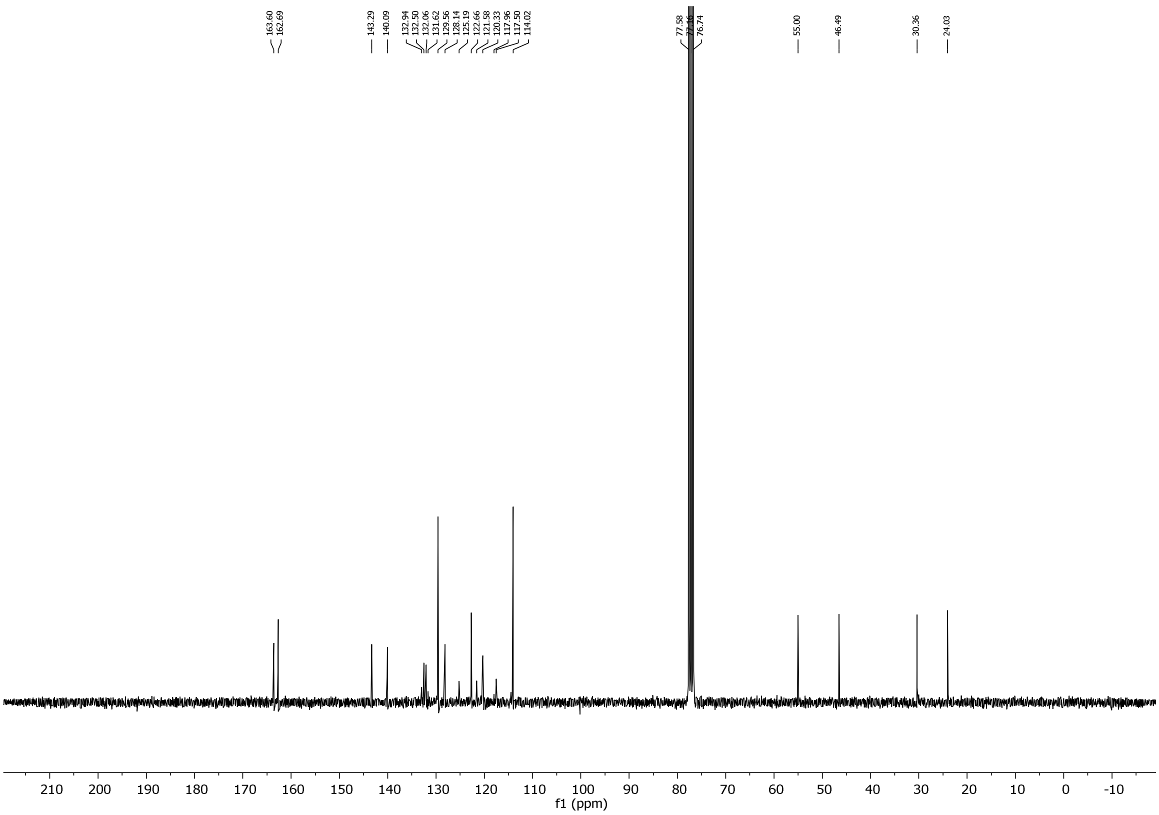


Figure SI-56. NMR spectra for compound **7a’**

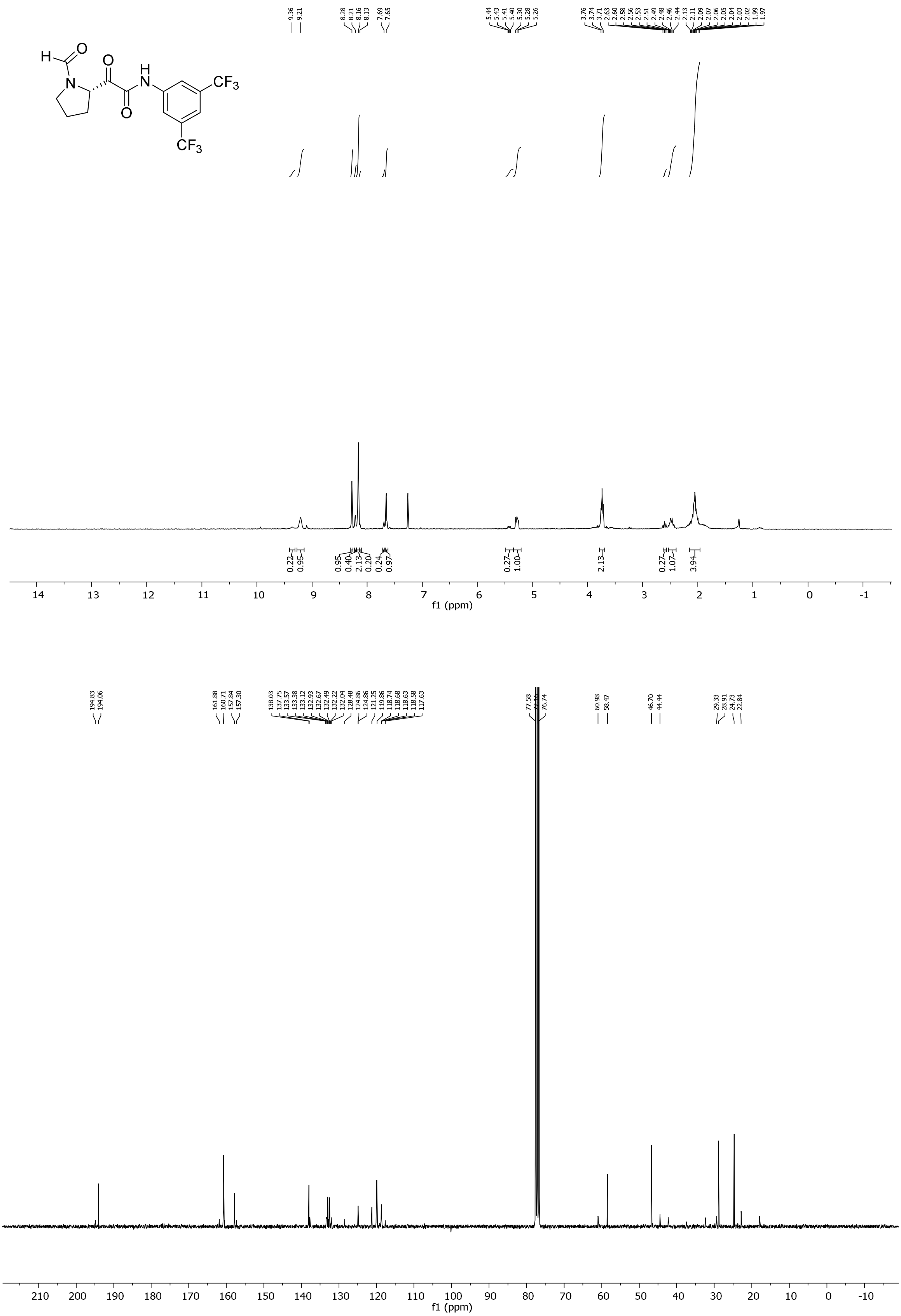
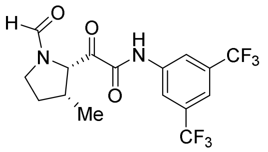
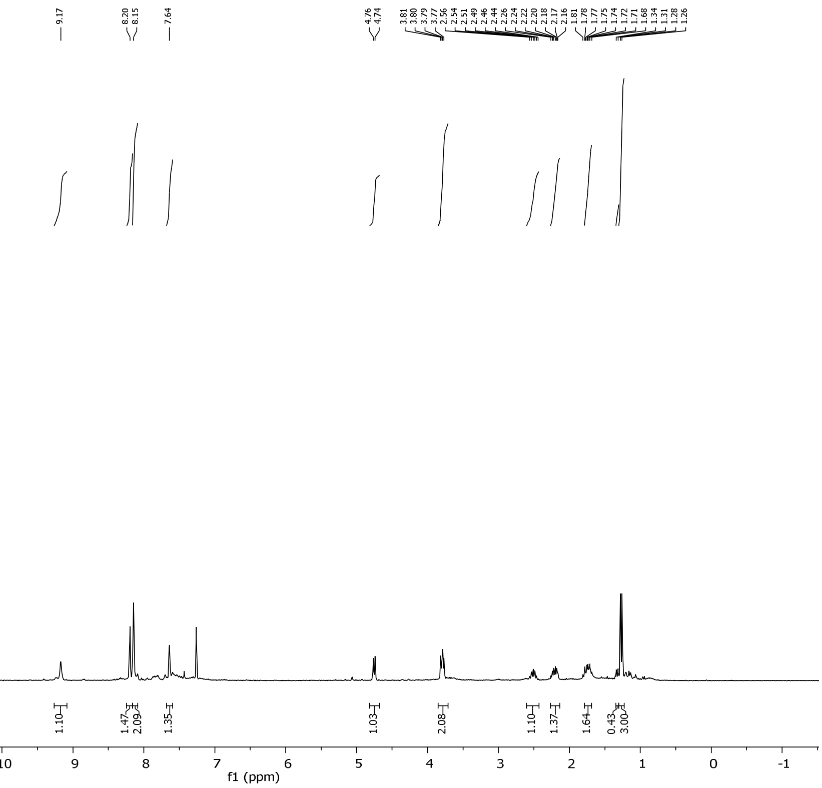


Figure SI-57. NMR spectra for compound **8a**





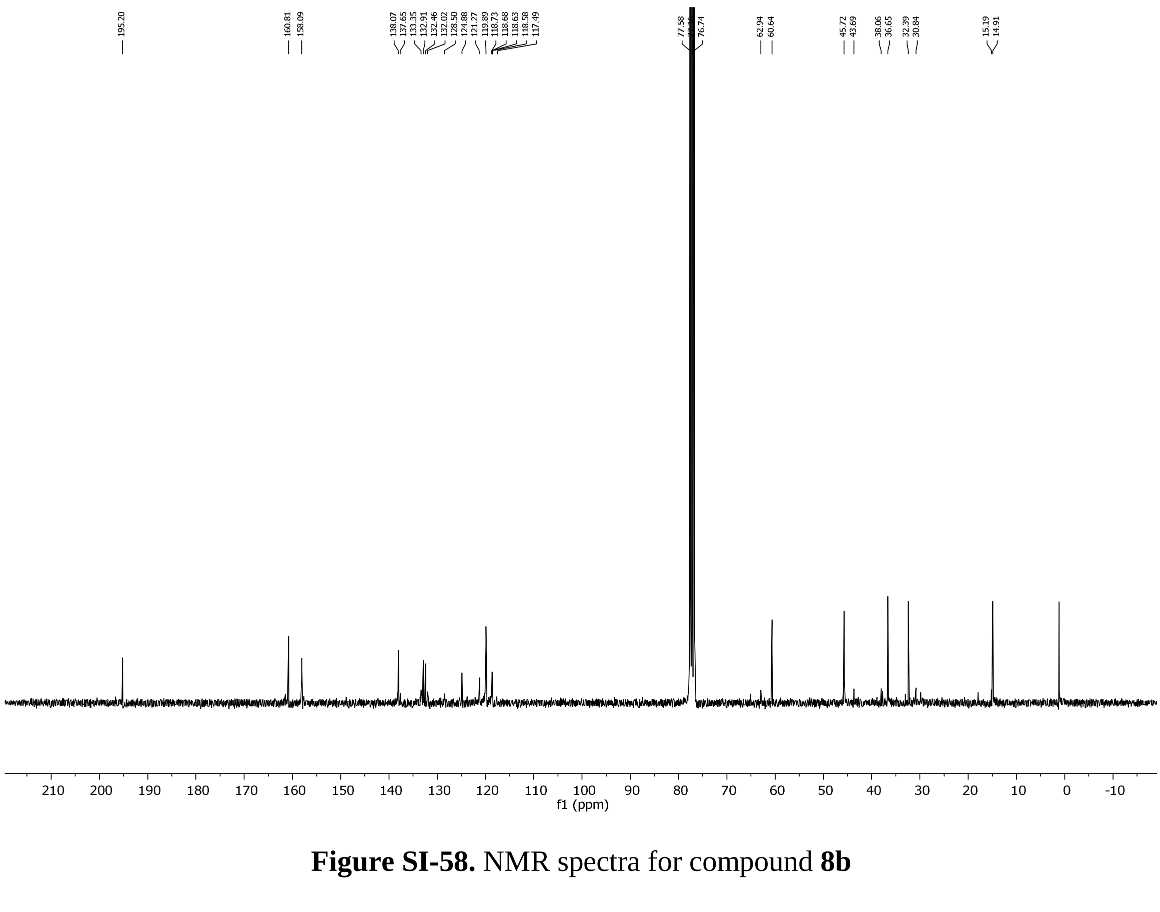


Figure SI-58. NMR spectra for compound **8b**

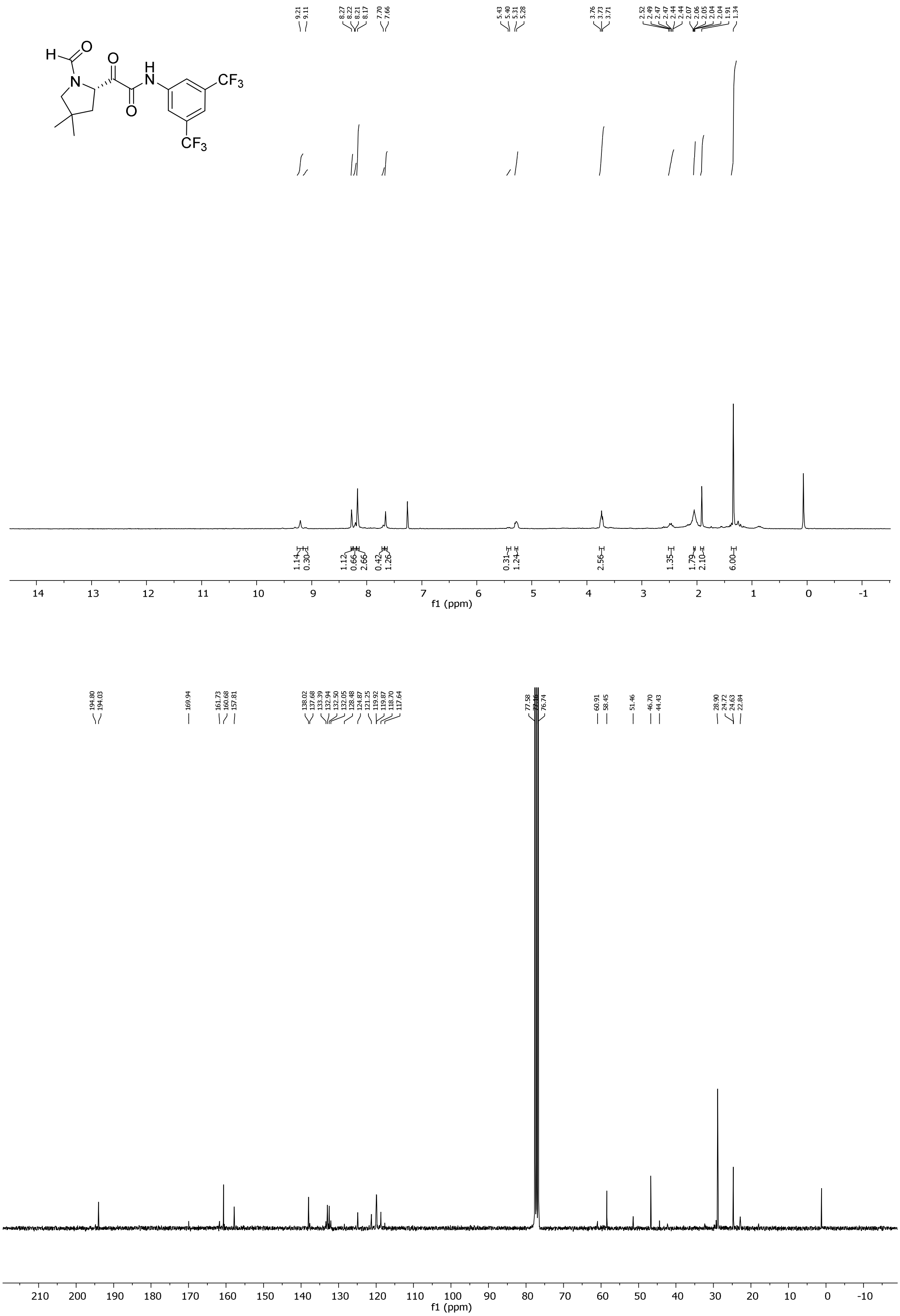


Figure SI-59. NMR spectra for compound **8c**

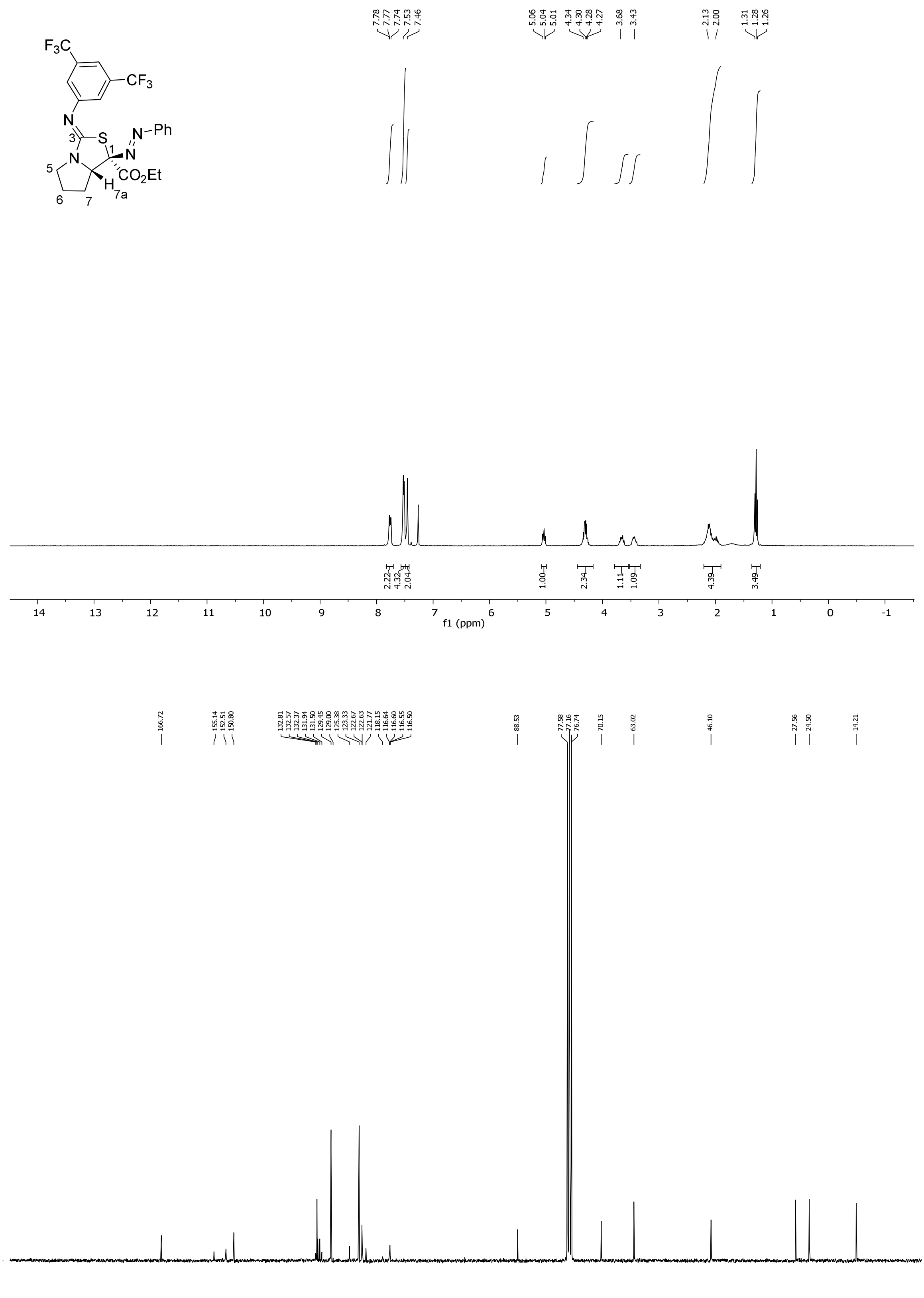
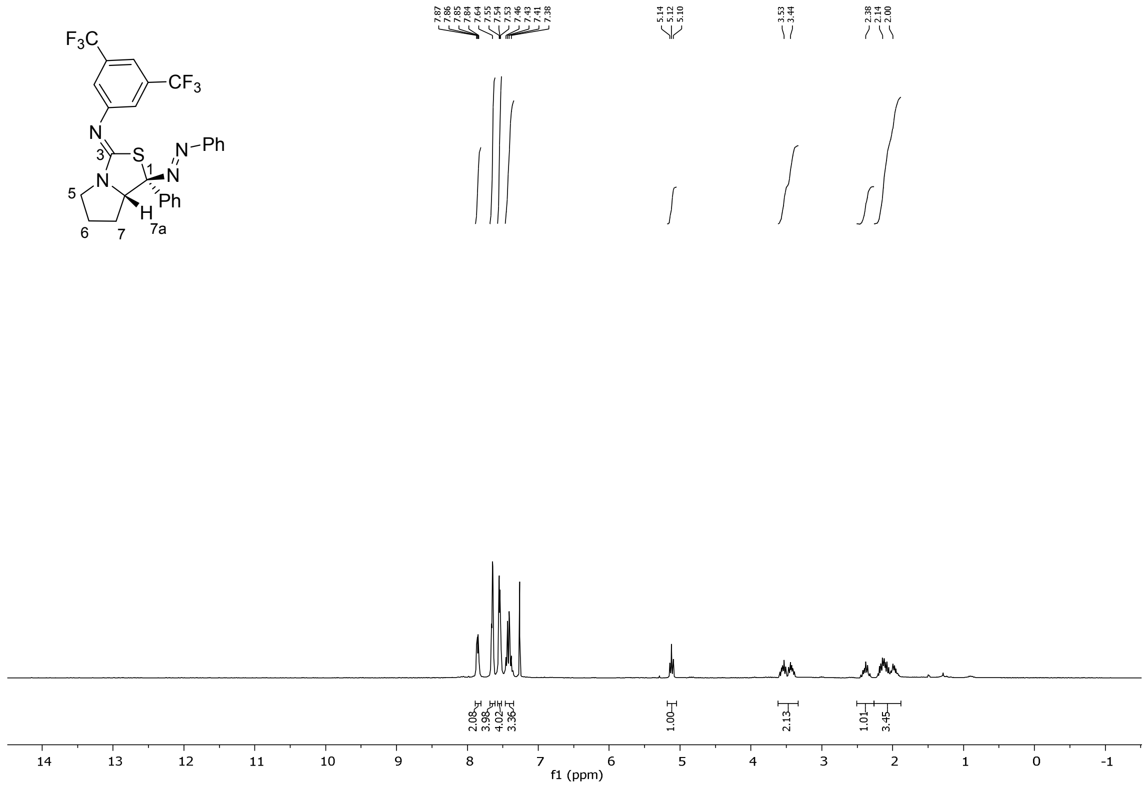


Figure SI-60. NMR spectra for compound **9a**



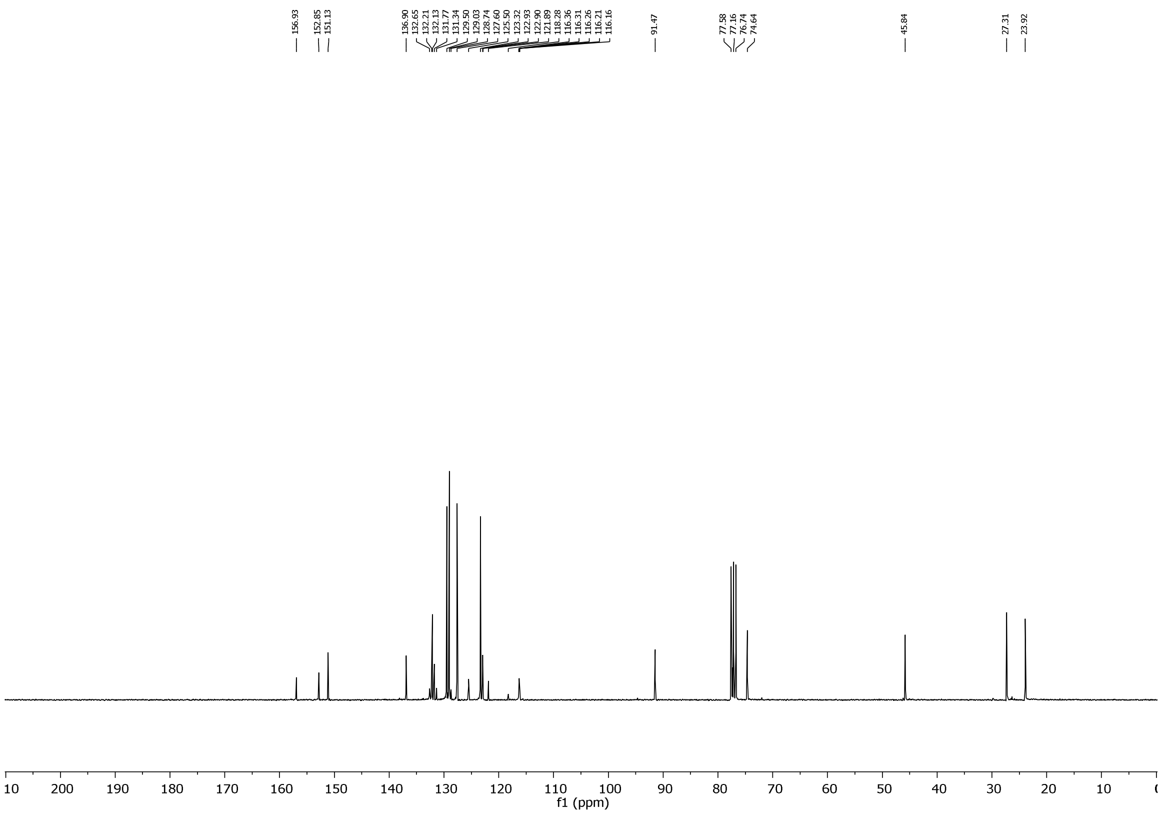
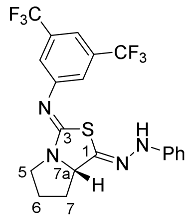
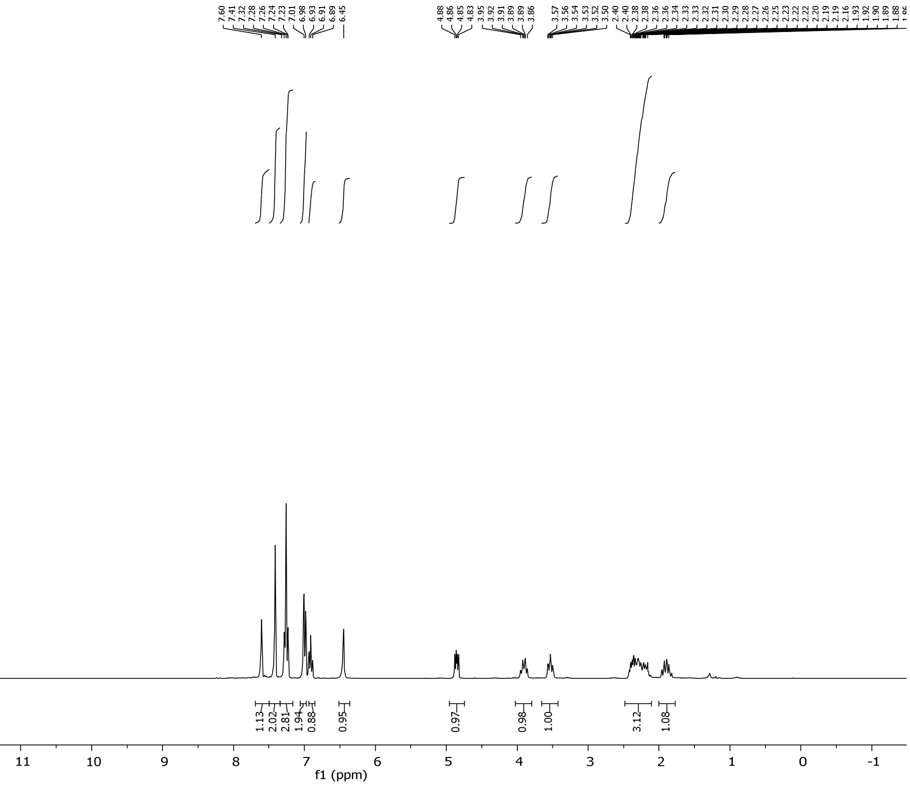


Figure SI-61. NMR spectra for compound **9b**





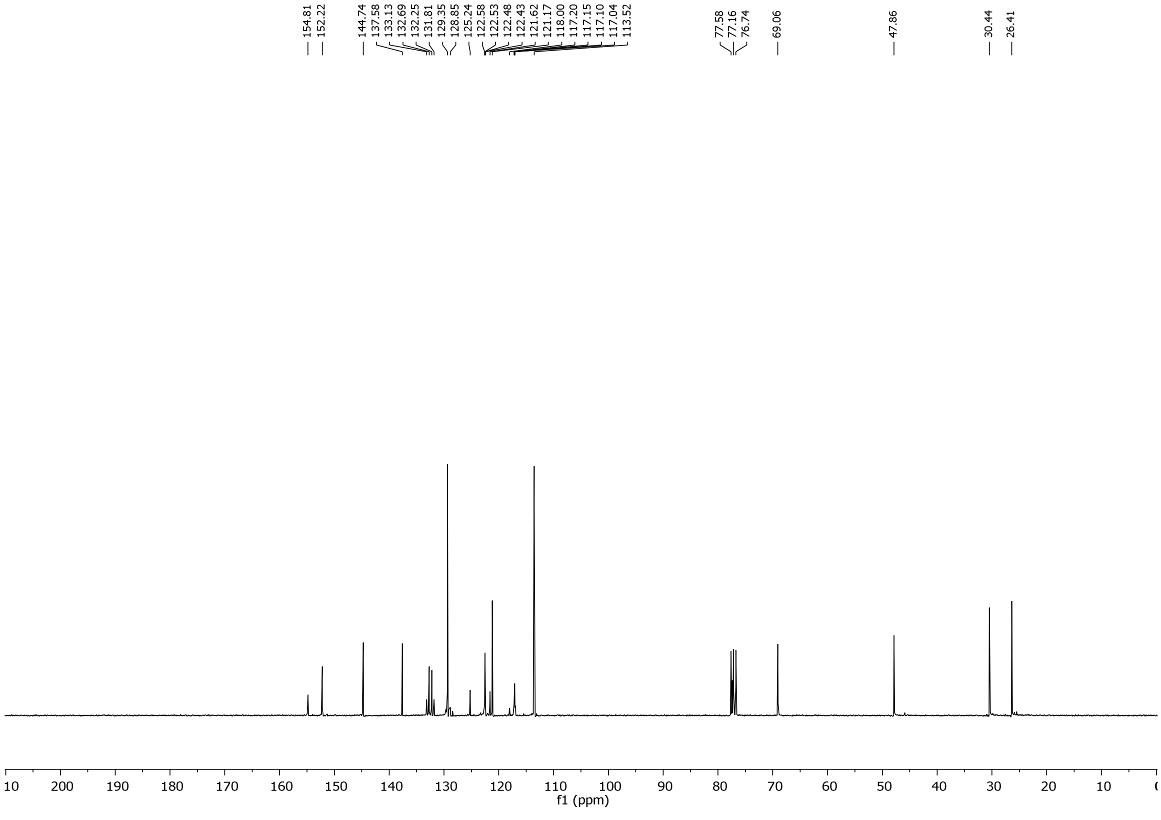
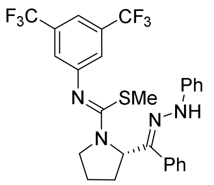
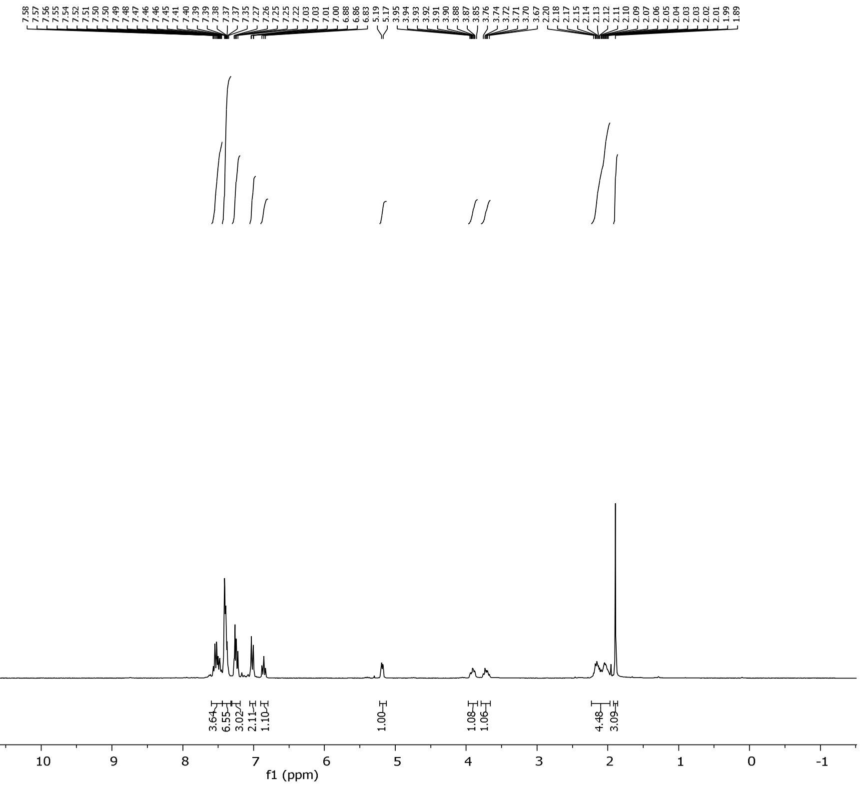


Figure SI-62. NMR spectra for compound **10**





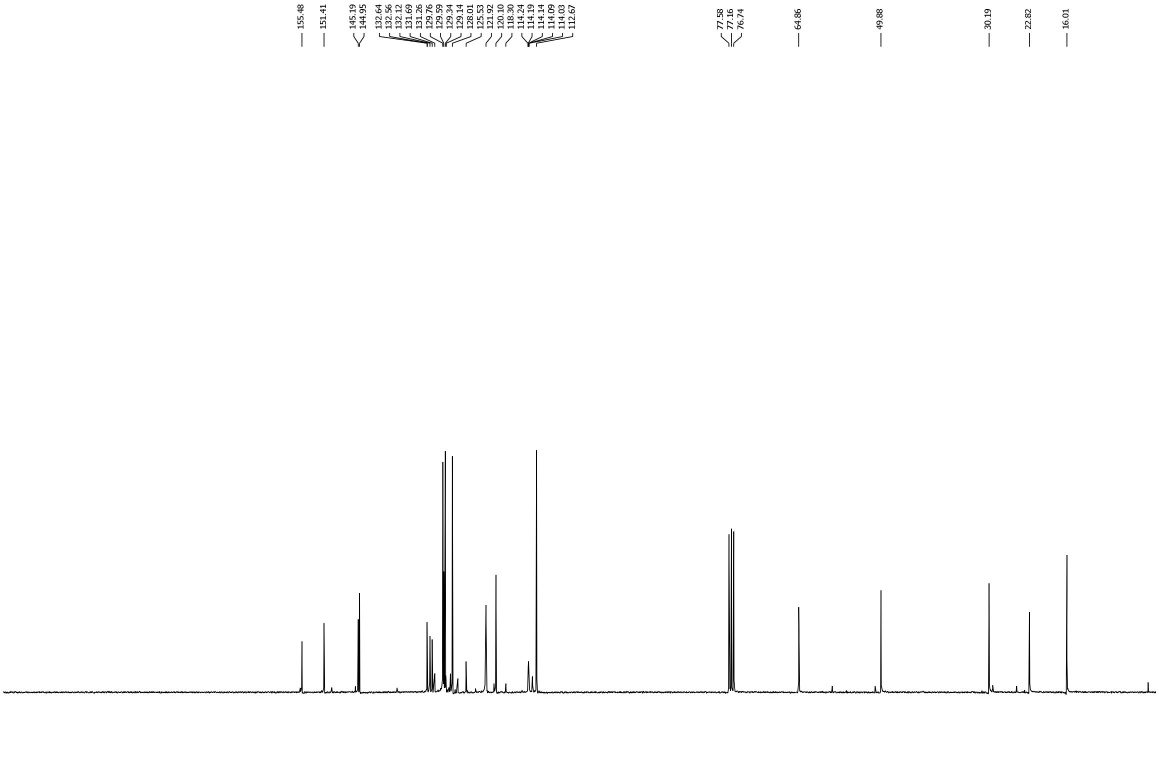
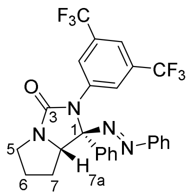
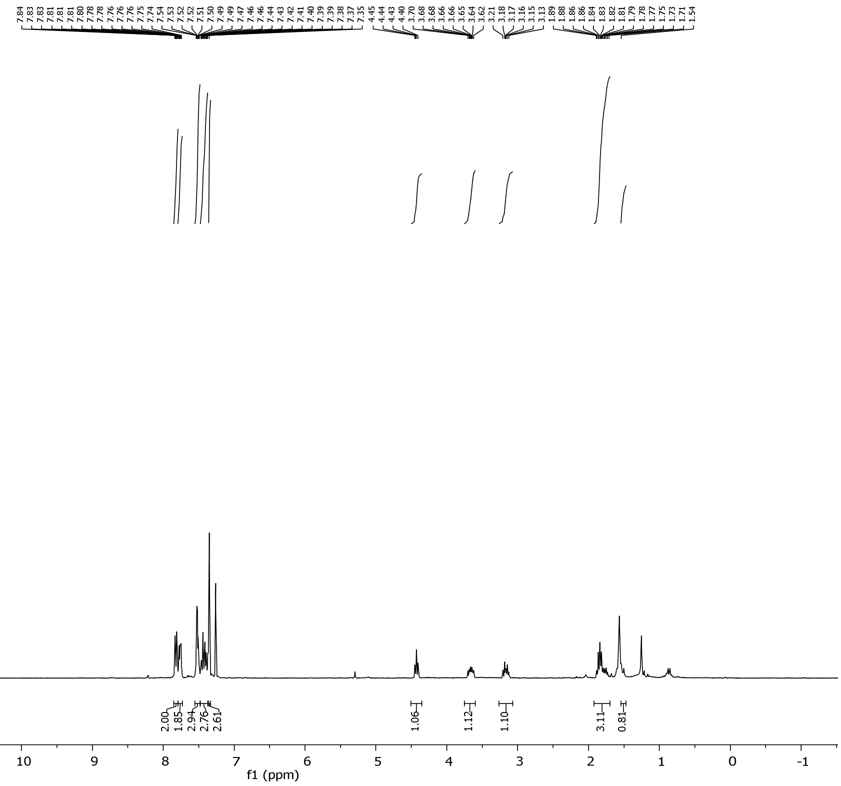


Figure SI-63. NMR spectra for compound **11**





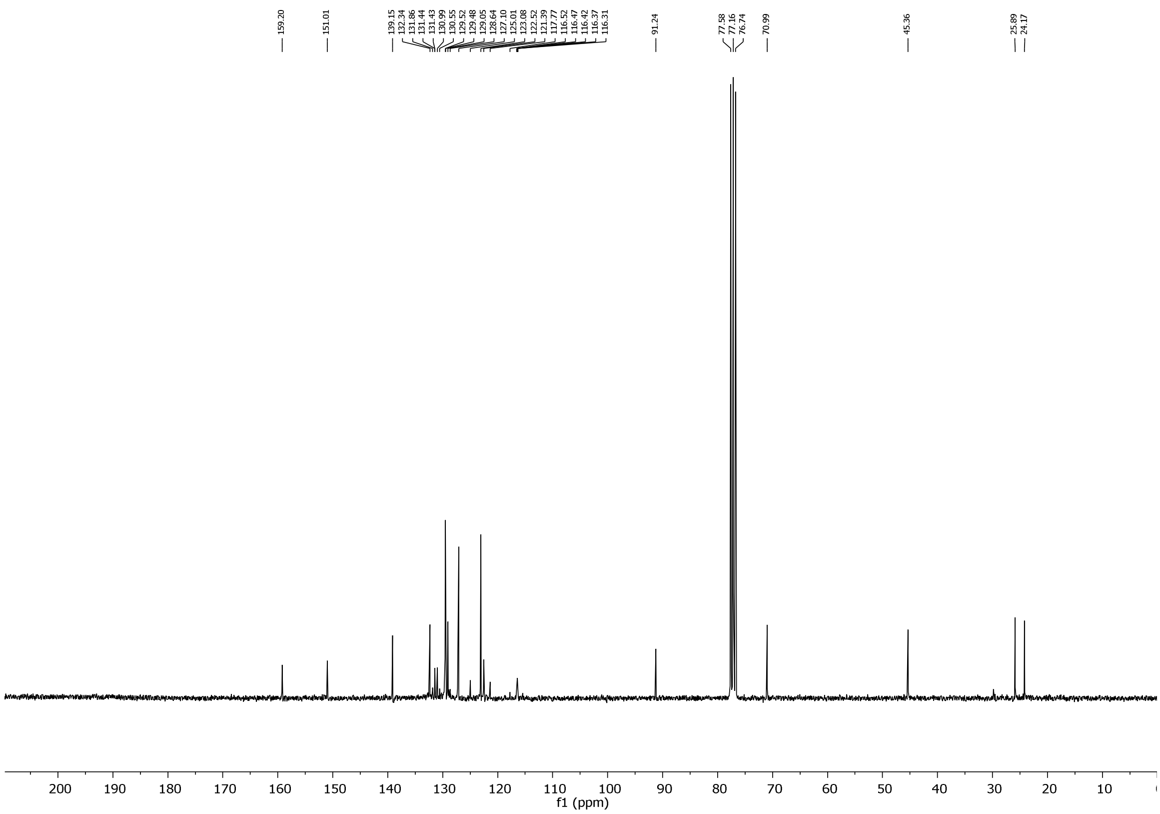
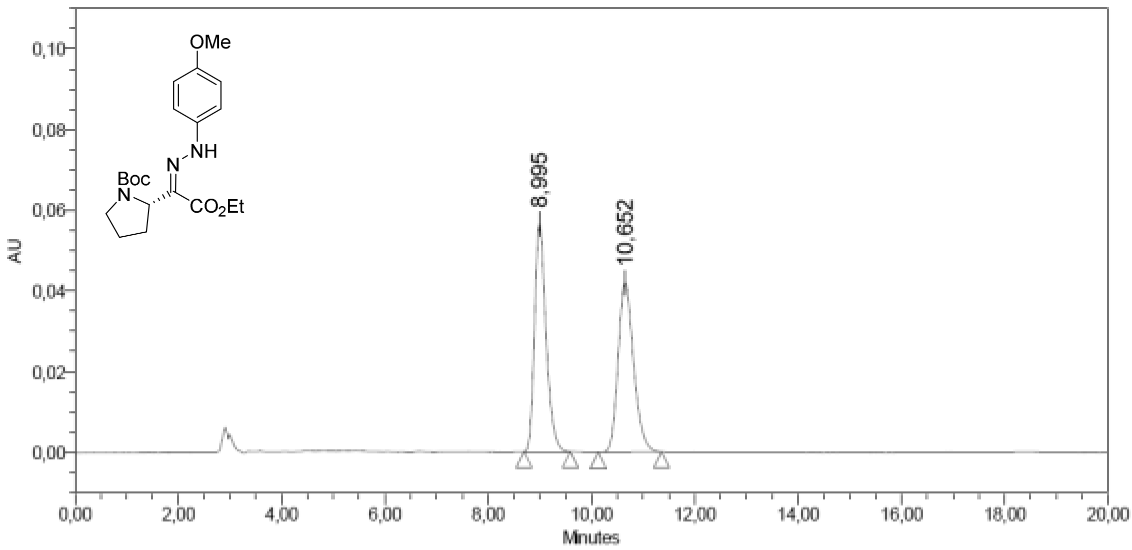
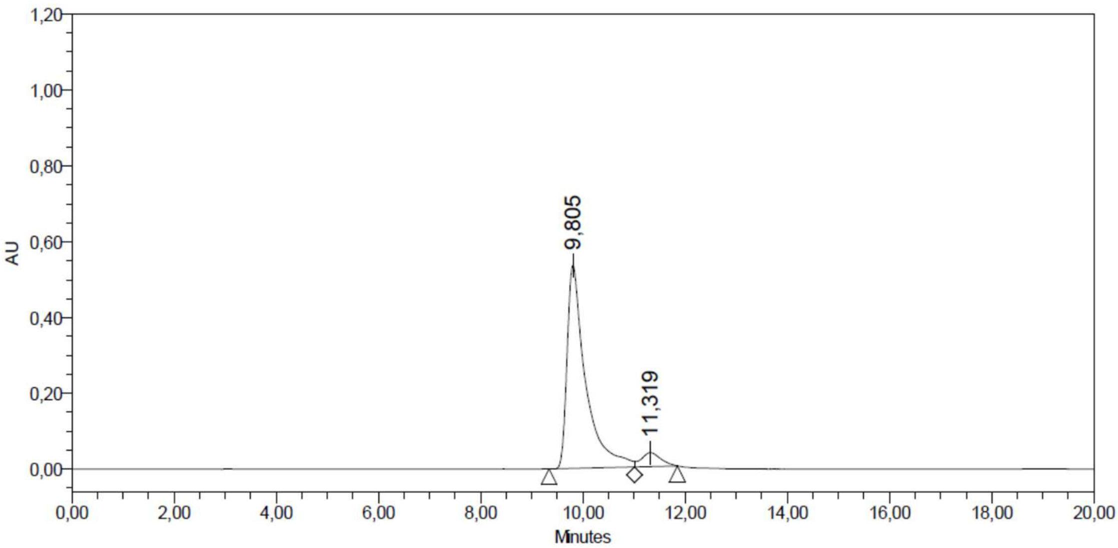


Figure SI-64. NMR spectra for compound **12**

6. HPLC traces





Peak Results

	RT	Area	Height	% Area
1	9,805	13465931	536636	93,29
2	11,319	968813	36598	6,71

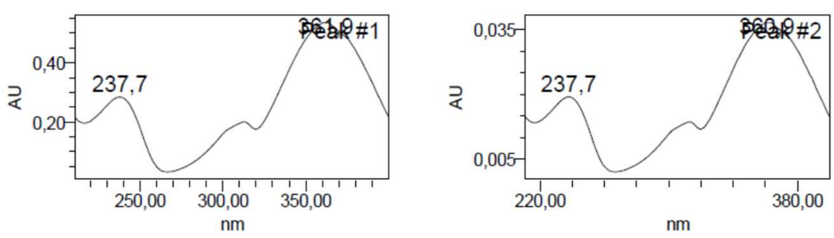
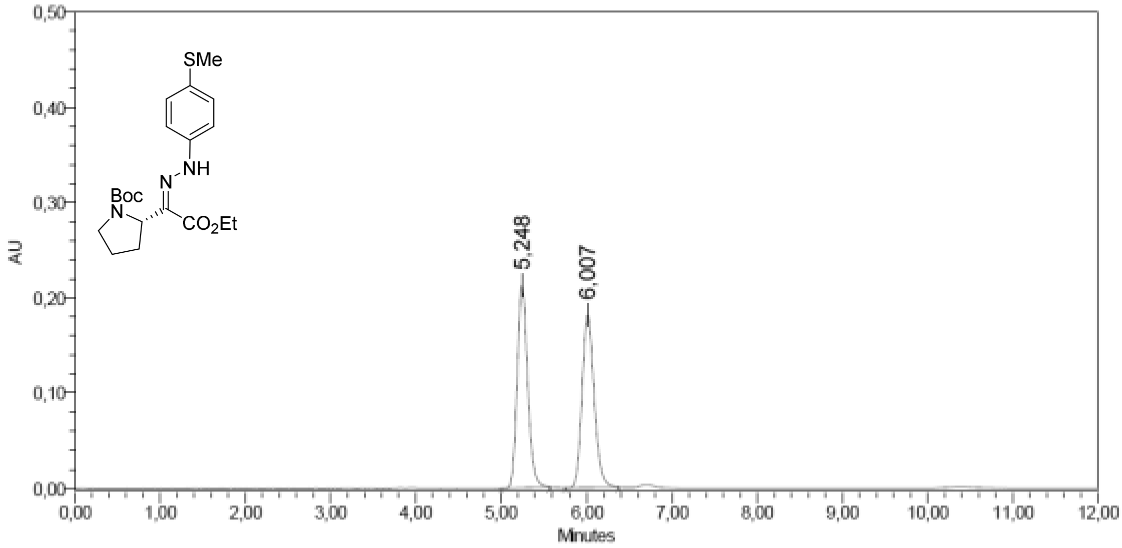
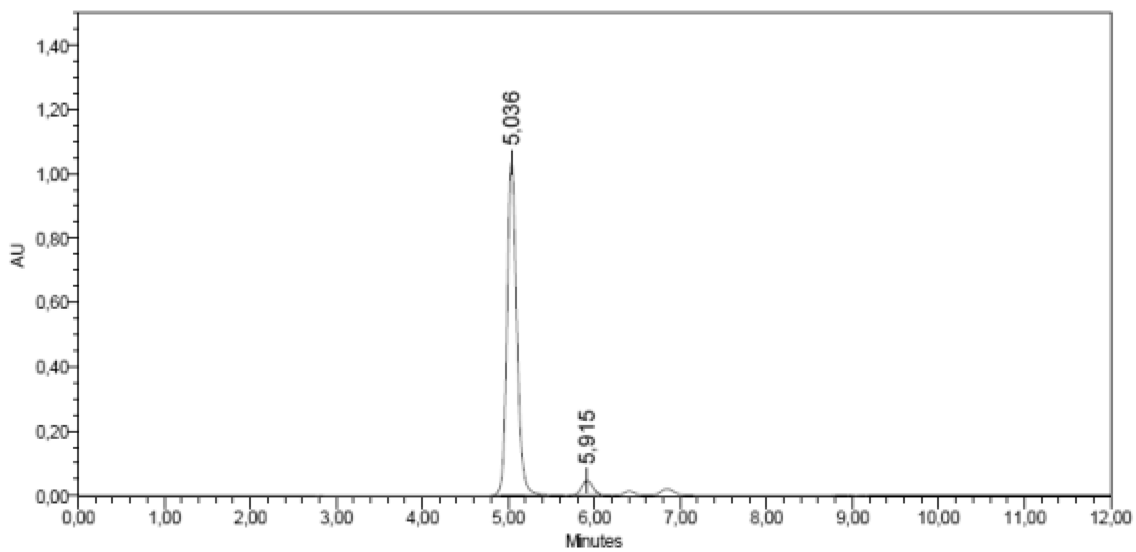


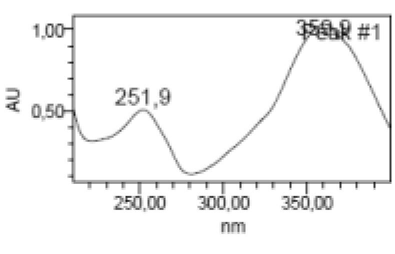
Figure SI-65. HPLC traces of compound **4a**





Peak Results

	RT	Area	Height	% Area
1	5,036	8161609	1035446	95,78
2	5,915	359474	42078	4,22



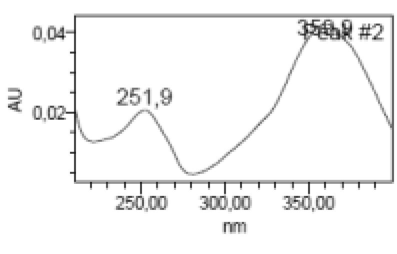
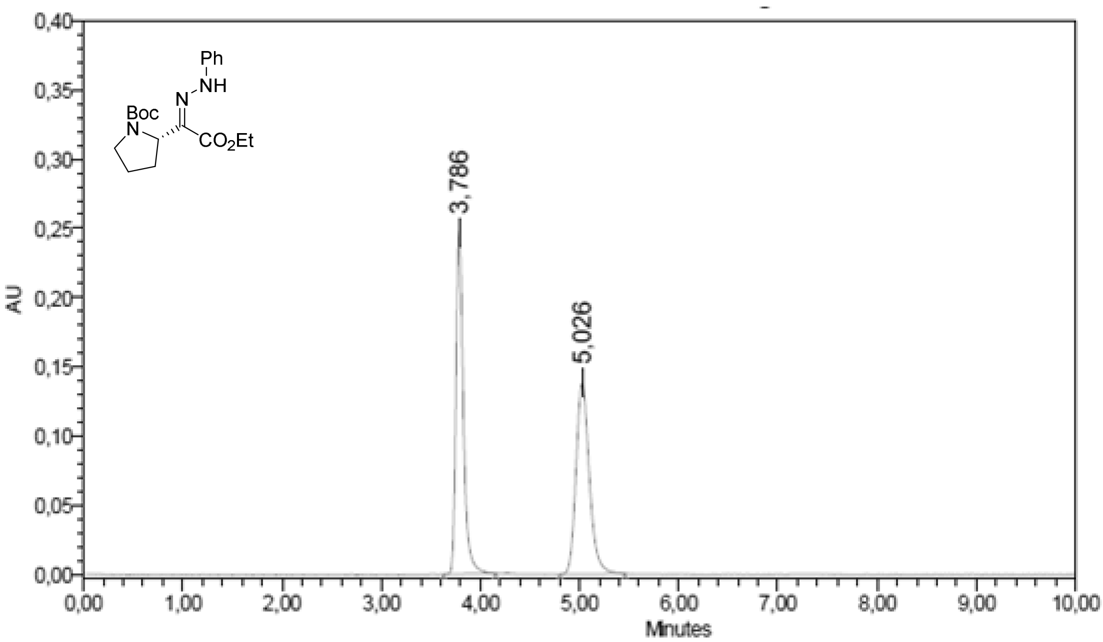
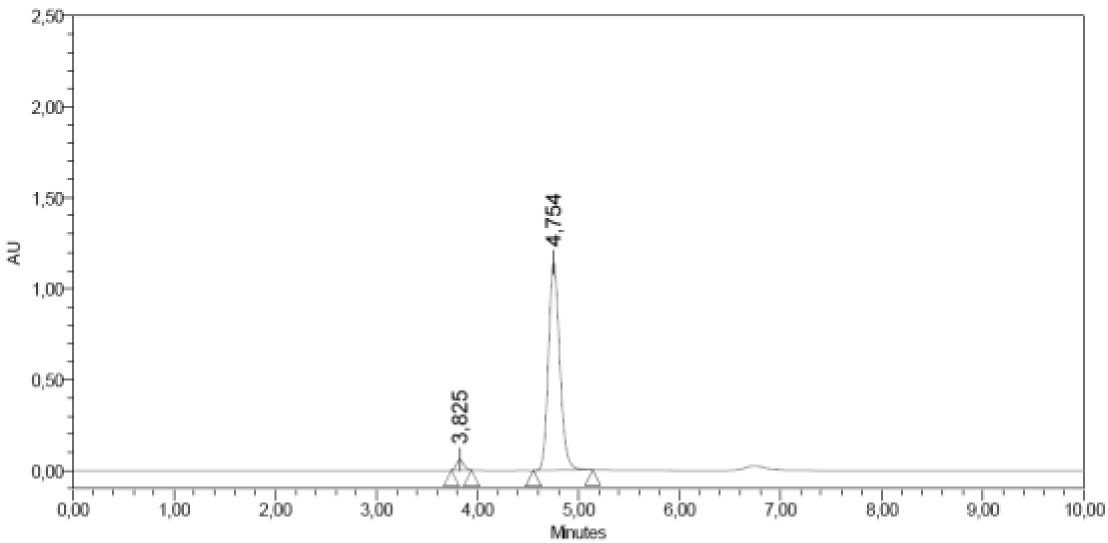


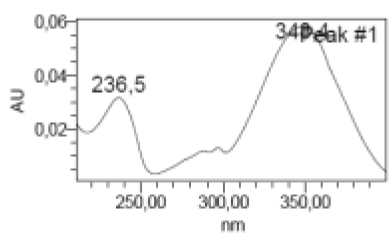
Figure SI-66. HPLC traces of compound **4b**





Peak Results

	RT	Area	Height	% Area
1	3,825	291093	57952	3,16
2	4,754	8915927	1143319	96,84



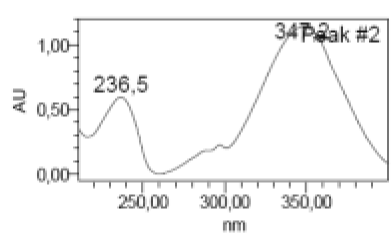
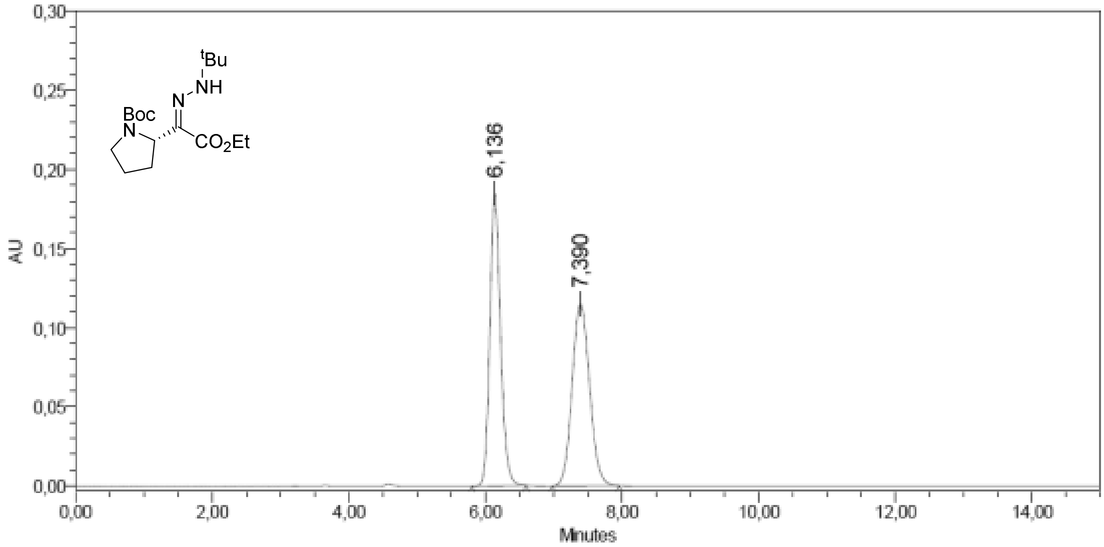
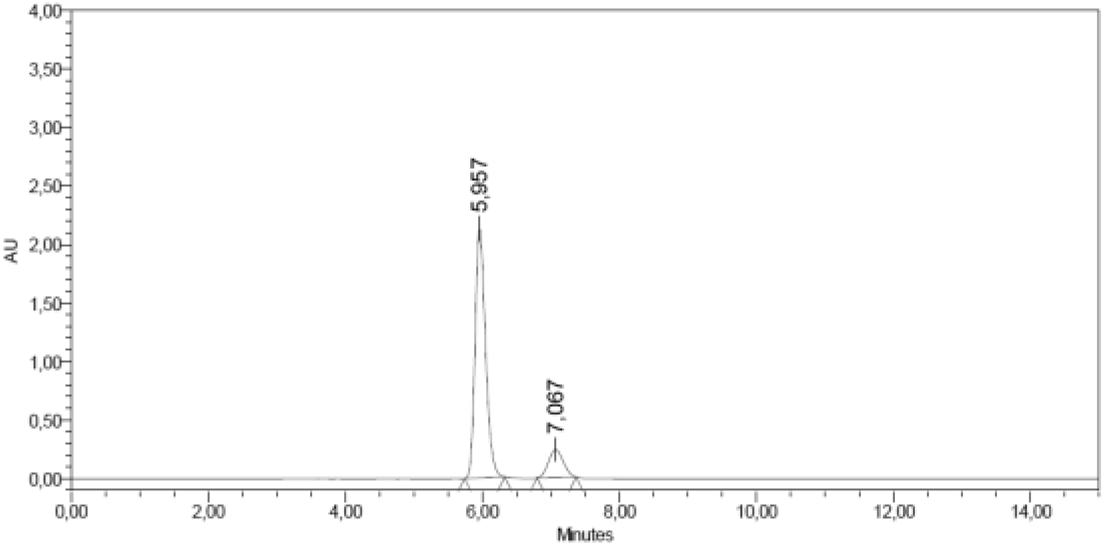


Figure SI-67. HPLC traces of compound **4c**





Peak Results

	RT	Area	Height	% Area
1	5,957	22493123	2131286	86,26
2	7,067	3582735	238327	13,74

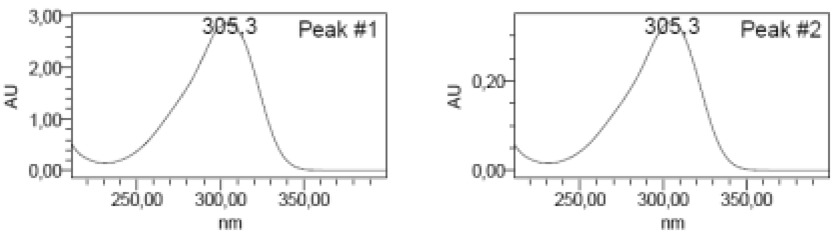
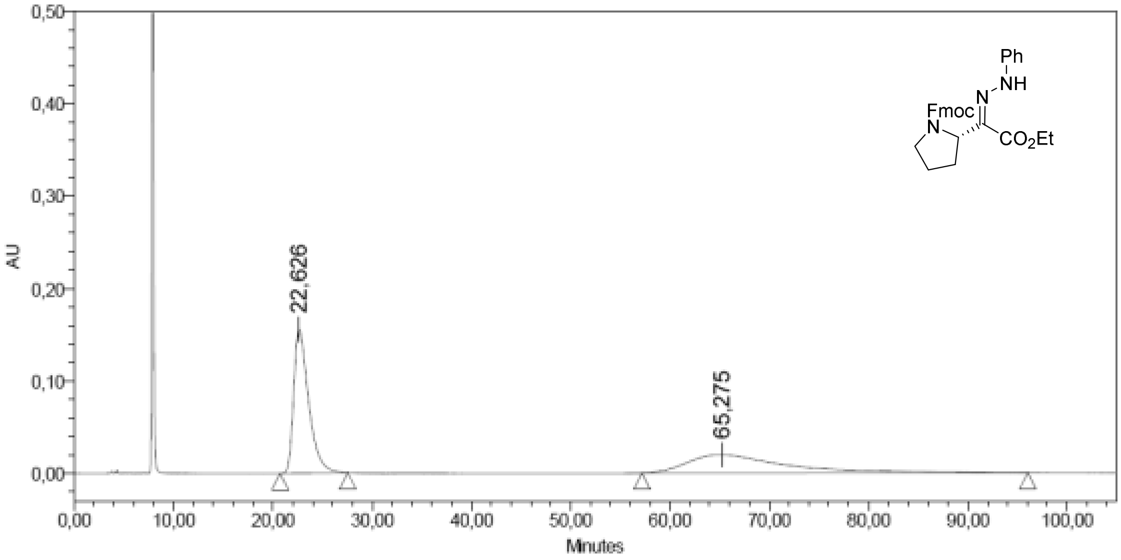
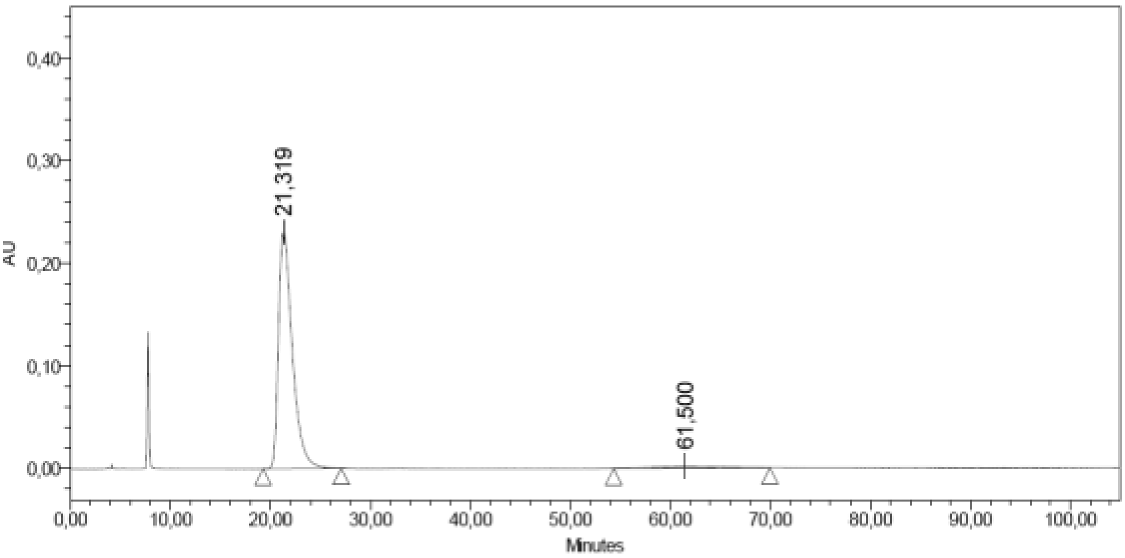


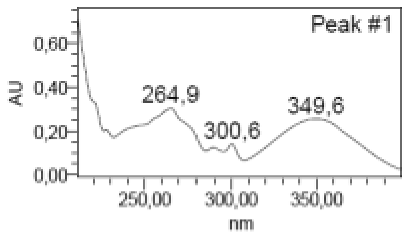
Figure SI-68. HPLC traces of compound **4e**





Peak Results

	RT	Area	Height	% Area
1	21,319	21471387	230252	96,18
2	61,500	851754	1843	3,82



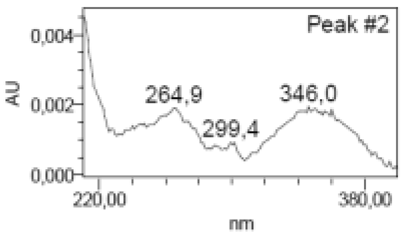
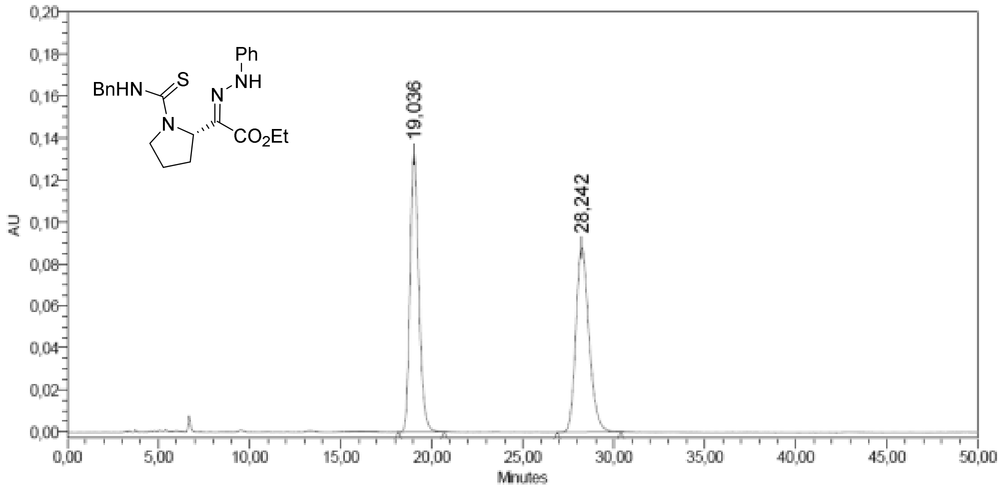
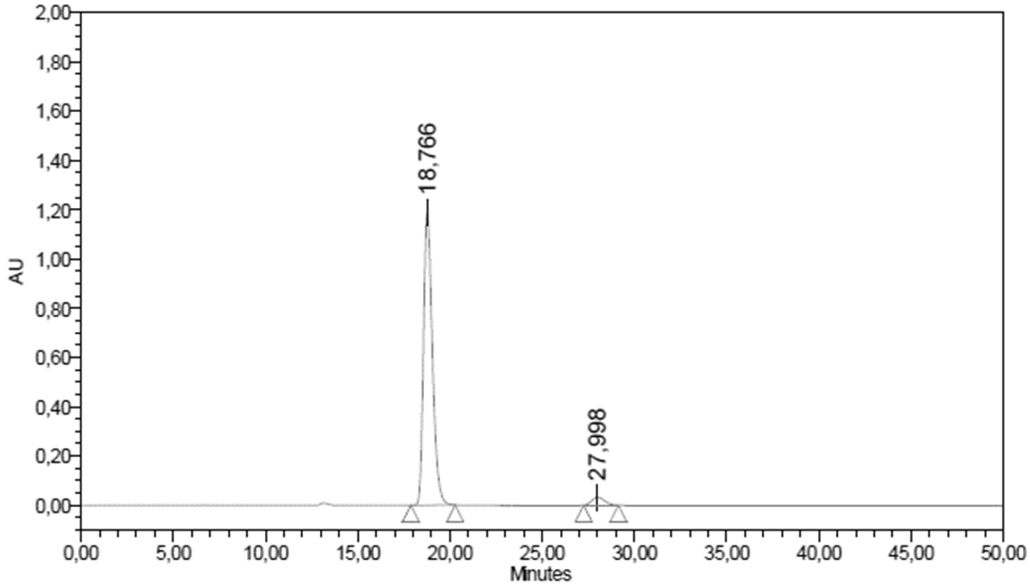


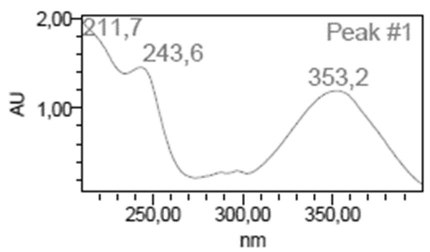
Figure SI-69. HPLC traces of compound **4f**





Peak Results

	RT	Area	Height	% Area
1	18,766	39714030	1190283	96,24
2	27,998	1550351	32656	3,76



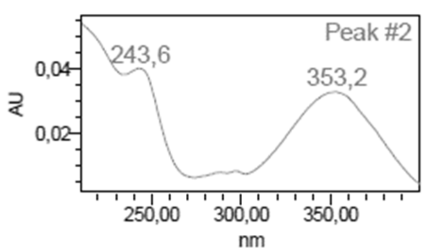
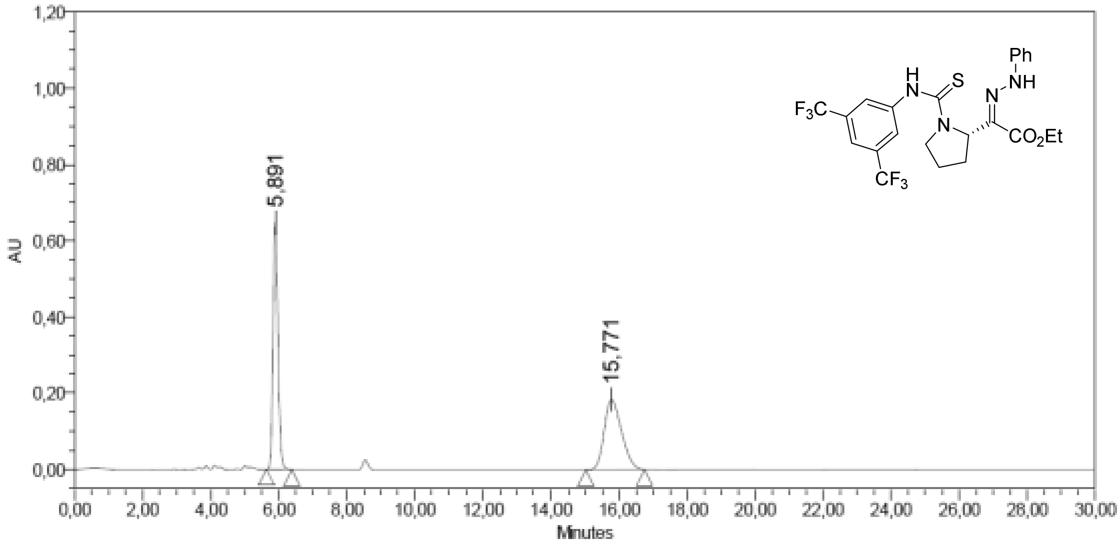
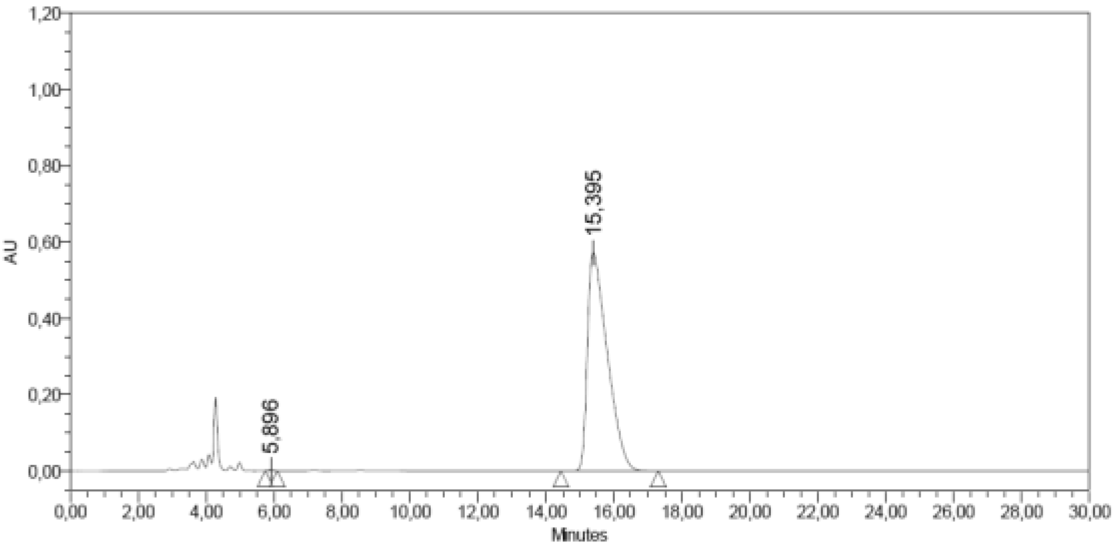


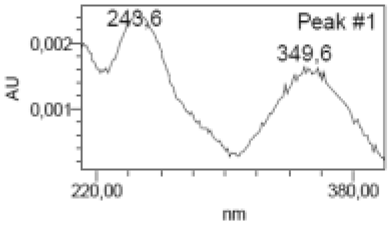
Figure SI-70. HPLC traces of compound **4h**





Peak Results

	RT	Area	Height	% Area
1	5,896	22847	2405	0,10
2	15,395	23210614	572070	99,90



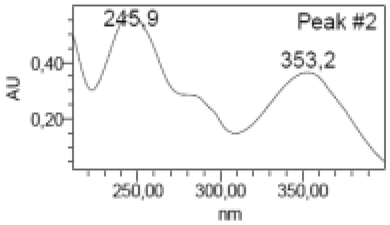
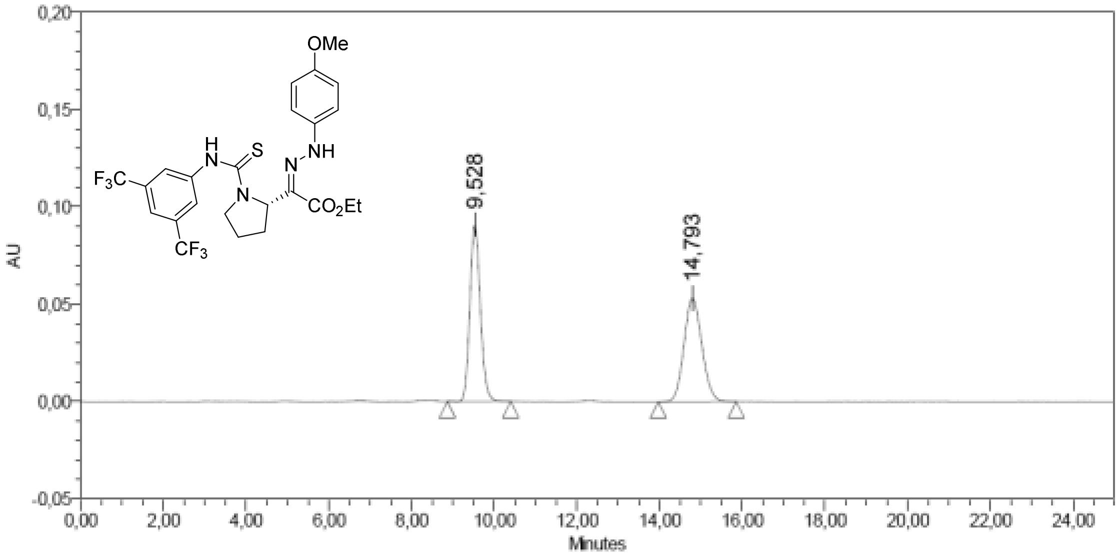
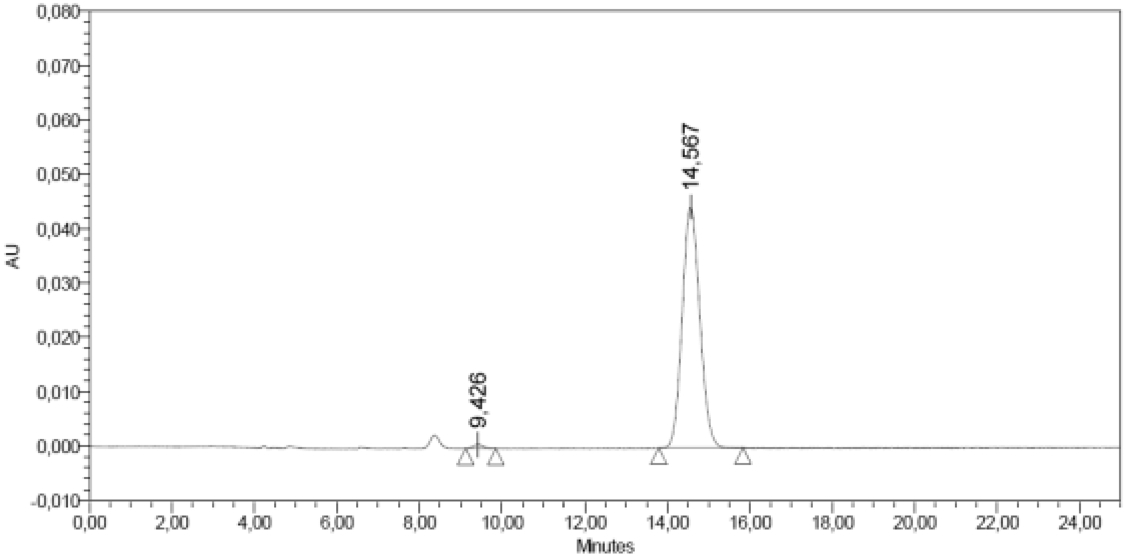


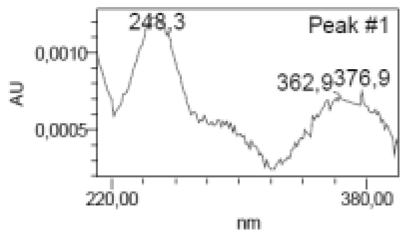
Figure SI-71. HPLC traces of compound **4i**





Peak Results

	RT	Area	Height	% Area
1	9,426	11569	699	0,87
2	14,567	1313243	44259	99,13



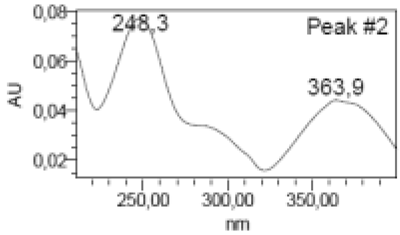
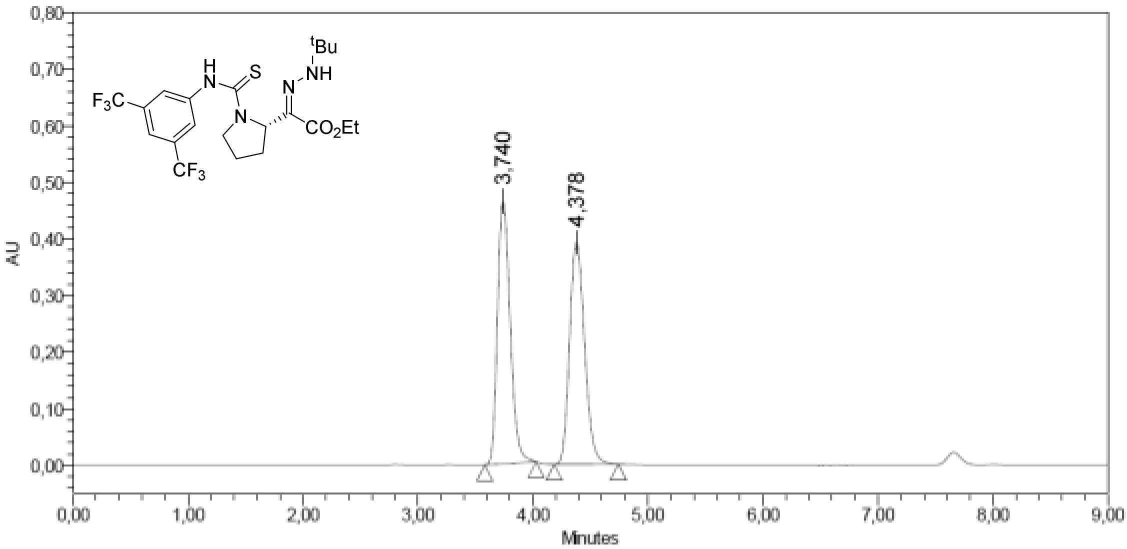
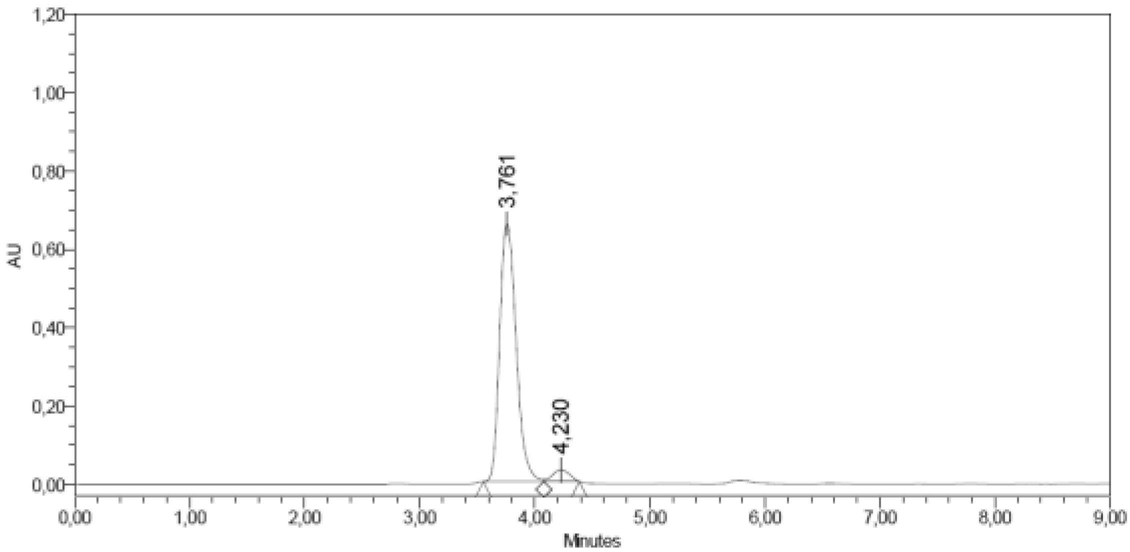


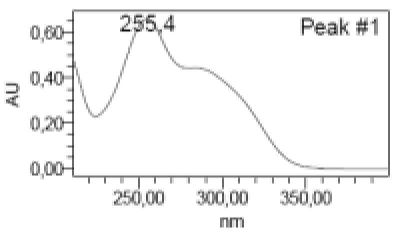
Figure SI-72. HPLC traces of compound **4j**





Peak Results

	RT	Area	Height	% Area
1	3,761	6535916	657448	95,64
2	4,230	298065	29708	4,36



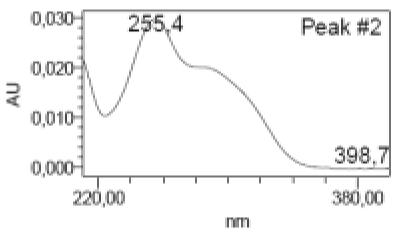
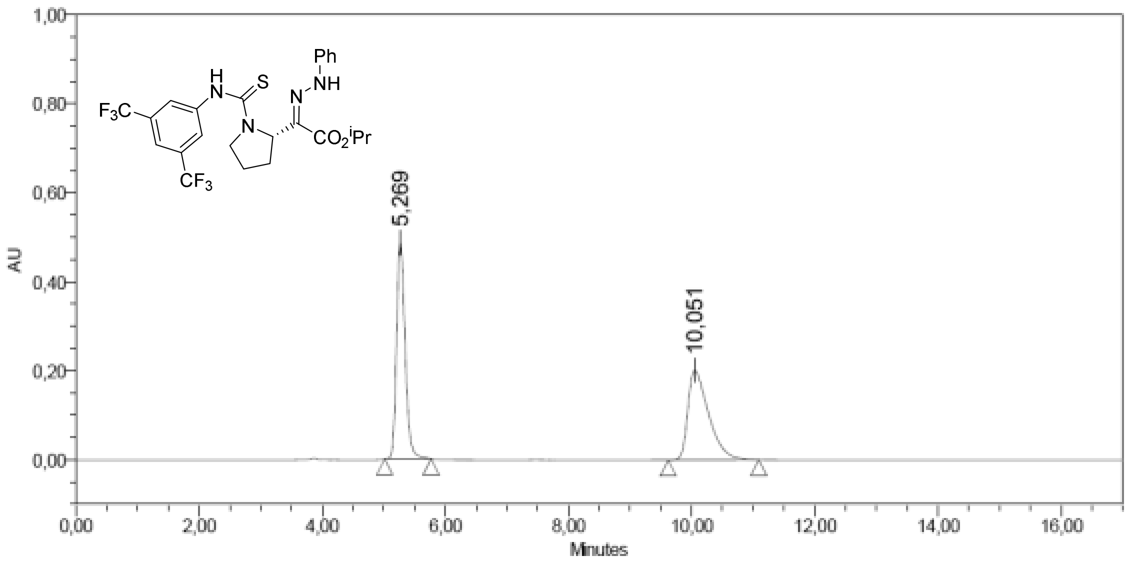
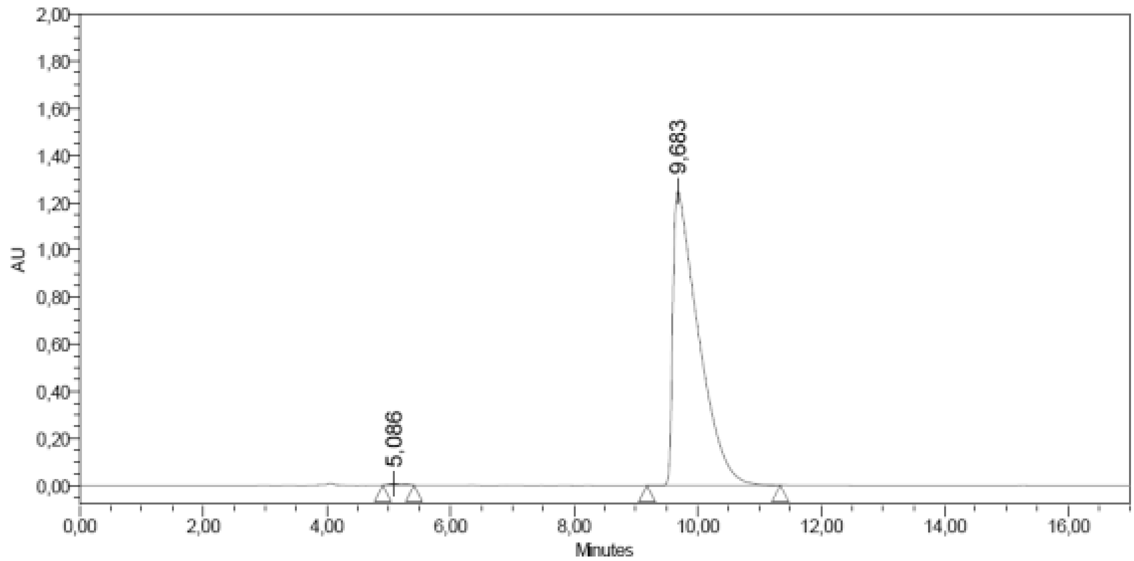


Figure SI-73. HPLC traces of compound **4k**





Peak Results

	RT	Area	Height	% Area
1	5,086	134125	6996	0,37
2	9,683	35695952	1249599	99,63

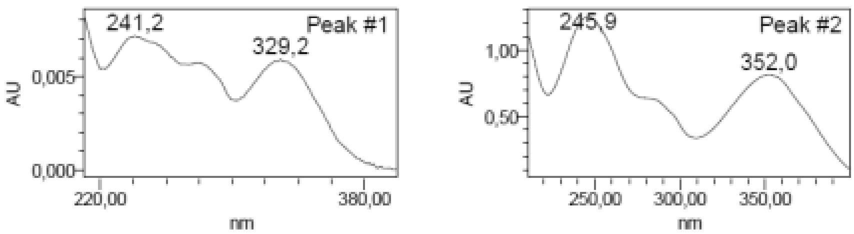
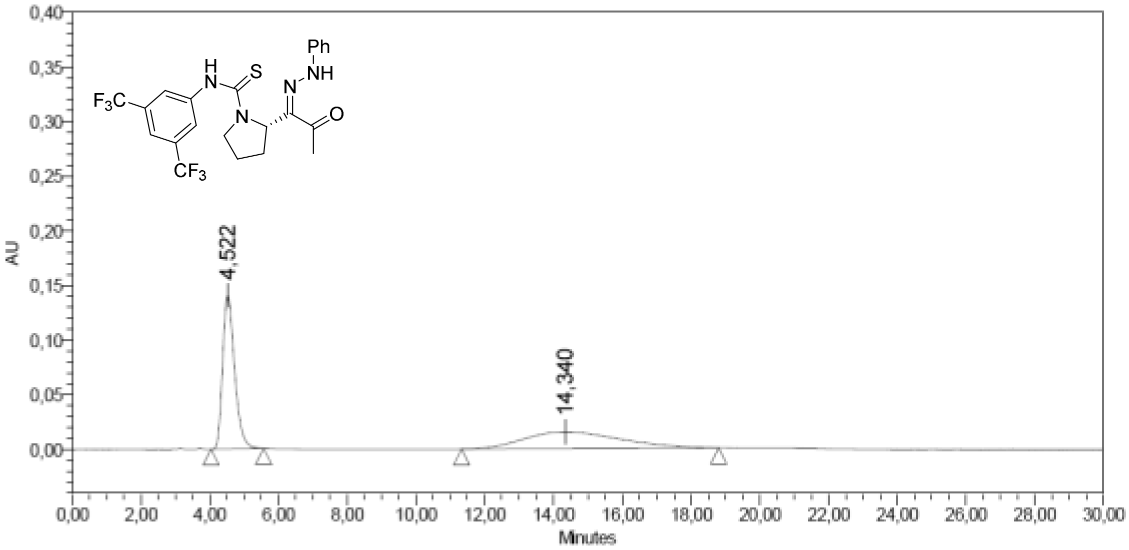
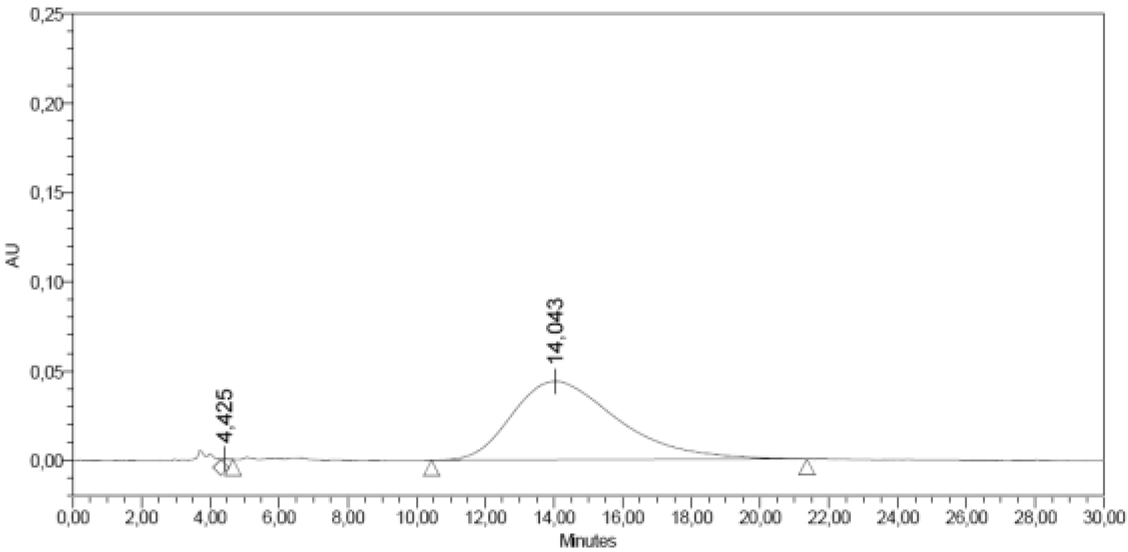


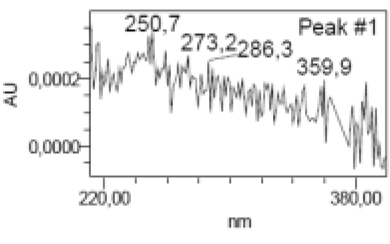
Figure SI-74. HPLC traces of compound **4l**





Peak Results

	RT	Area	Height	% Area
1	4,425	2522	228	0,03
2	14,043	9385019	43899	99,97



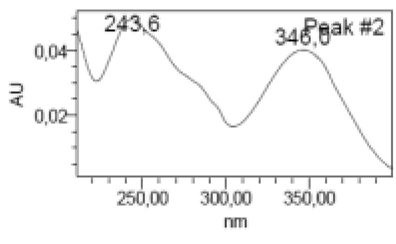
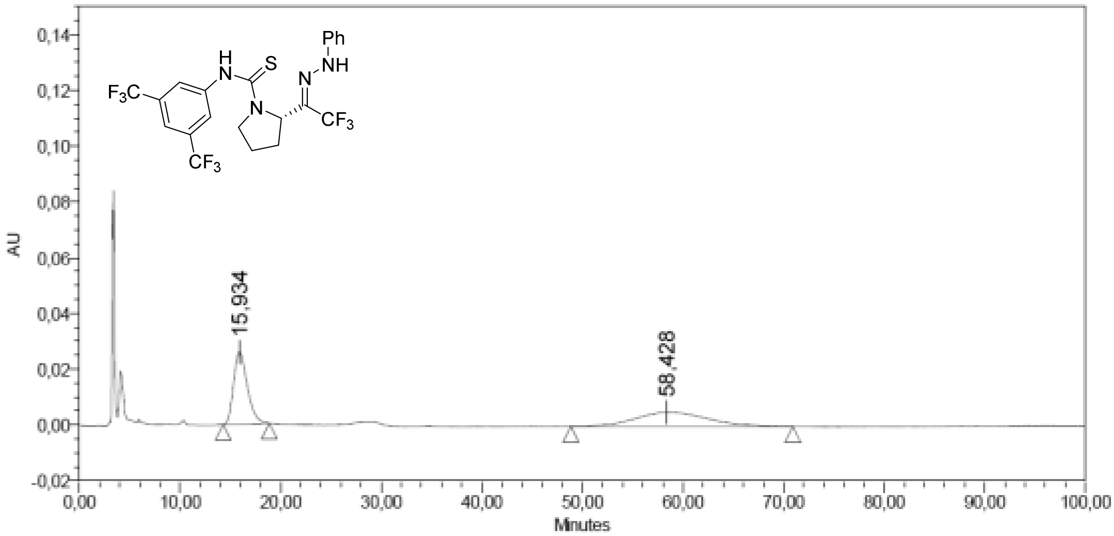
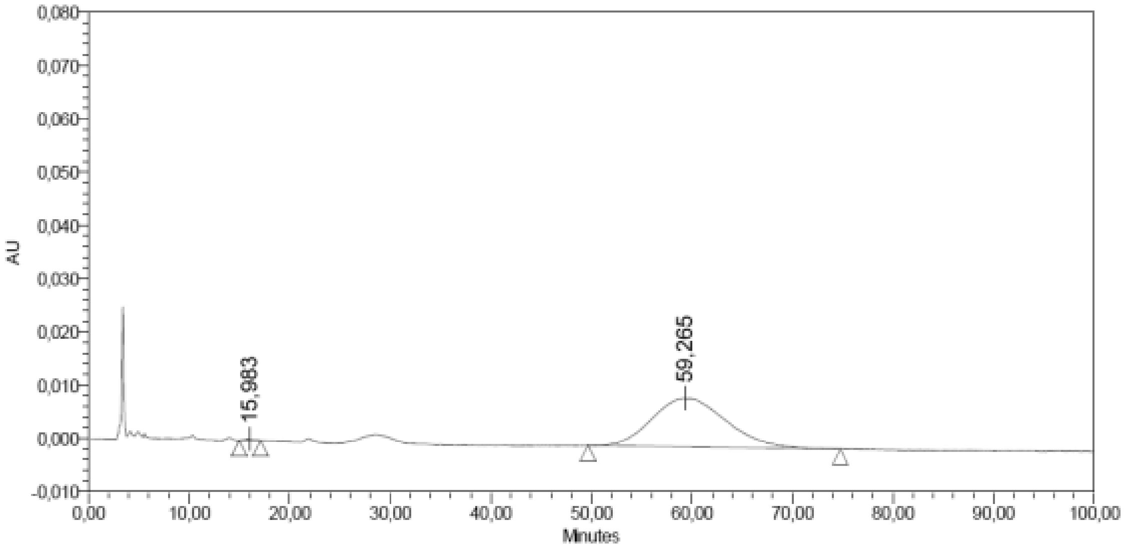


Figure SI-75. HPLC traces of compound **4m**





Peak Results

	RT	Area	Height	% Area
1	15,983	16770	283	0,36
2	59,265	4664337	9161	99,64

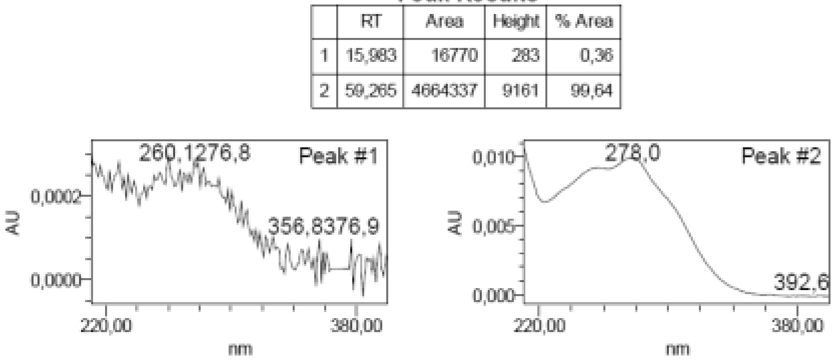
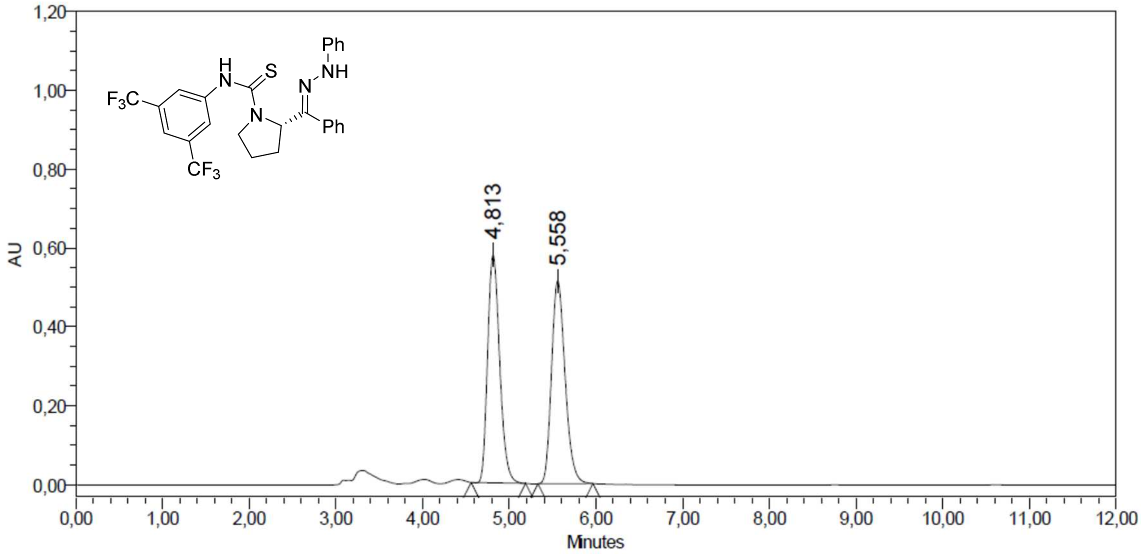
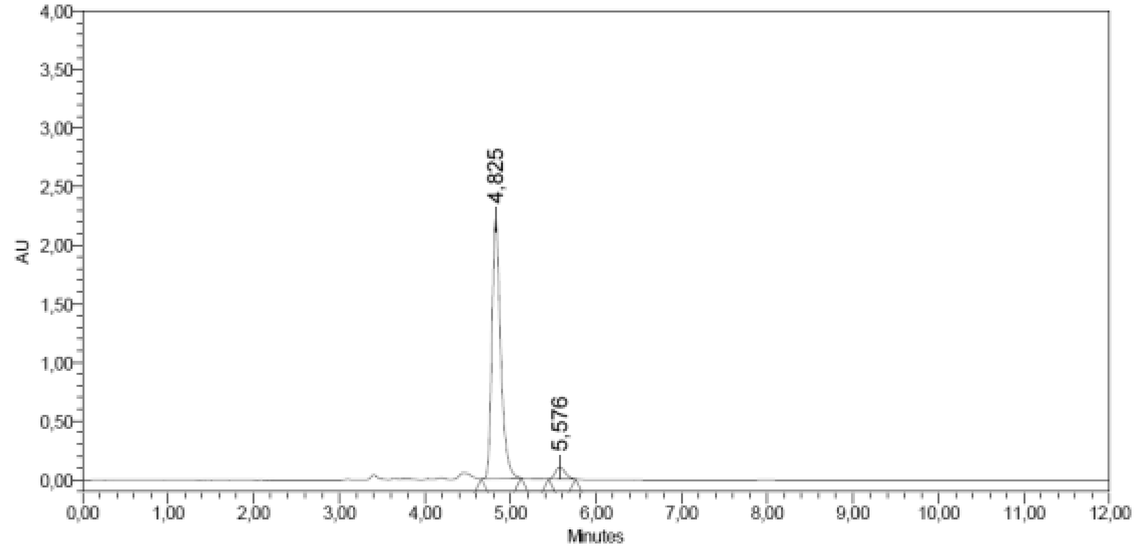


Figure SI-76. HPLC traces of compound **4n**





Peak Results

	RT	Area	Height	% Area
1	4,825	15633380	2212083	95,25
2	5,576	779737	97311	4,75

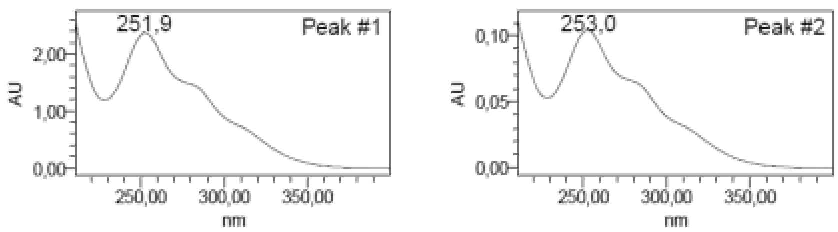
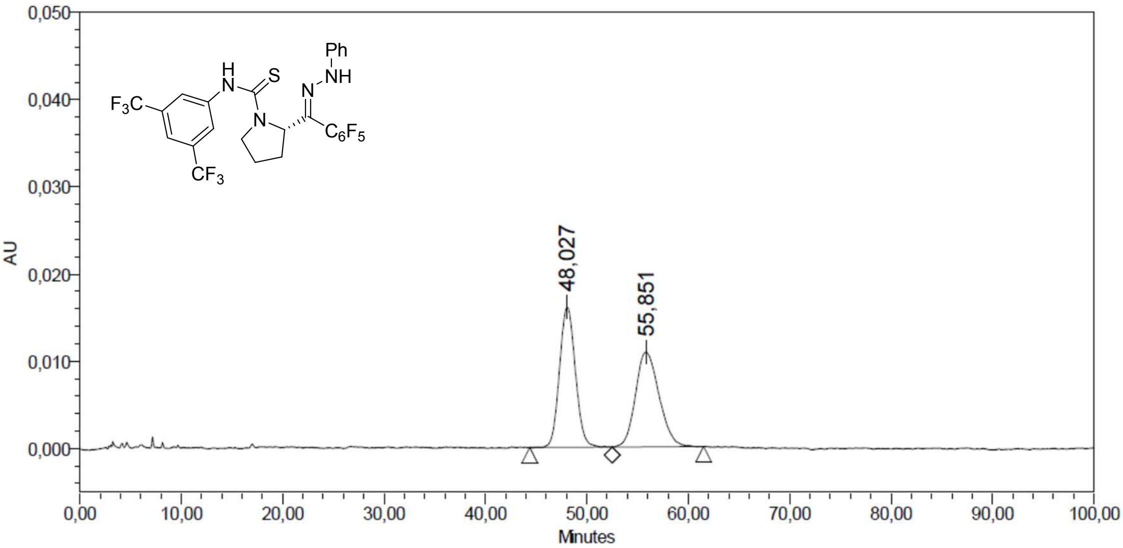
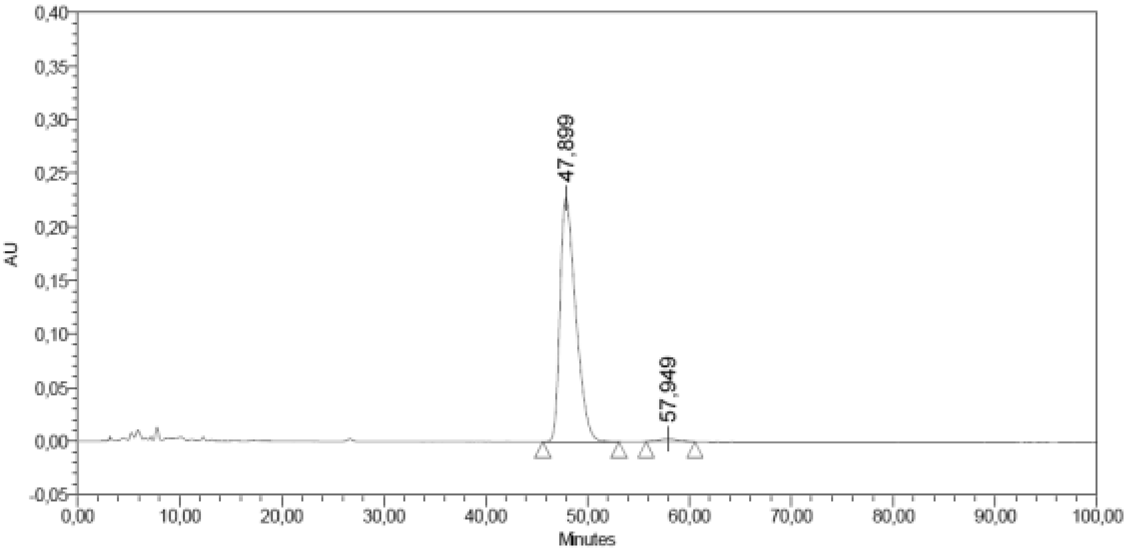


Figure SI-77. HPLC traces of compound **4o**





Peak Results

	RT	Area	Height	% Area
1	47,899	24421675	227126	98,57
2	57,949	354859	2454	1,43

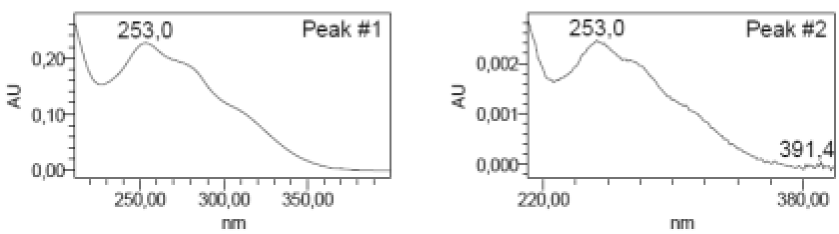
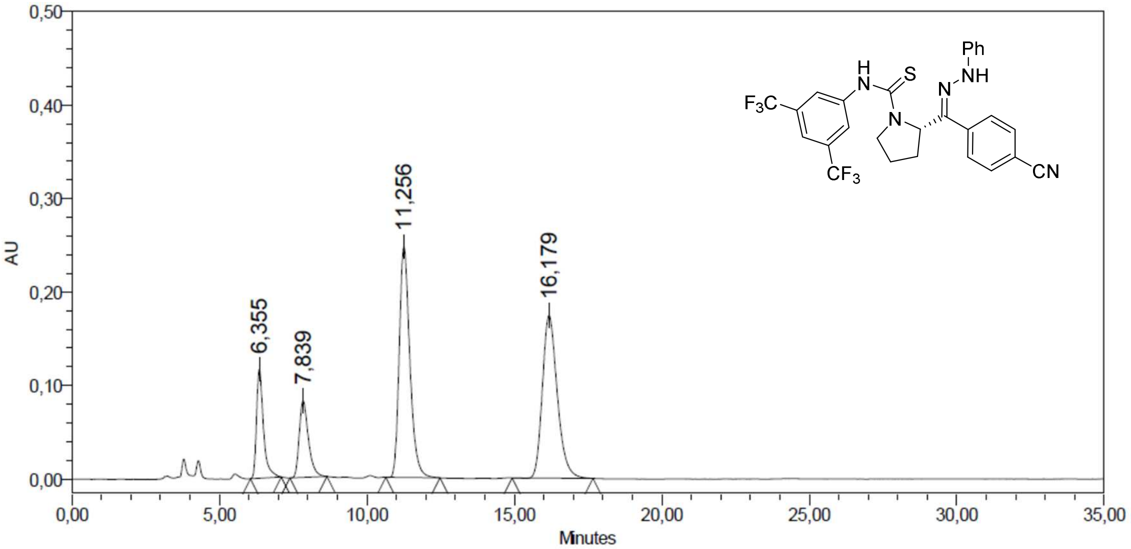
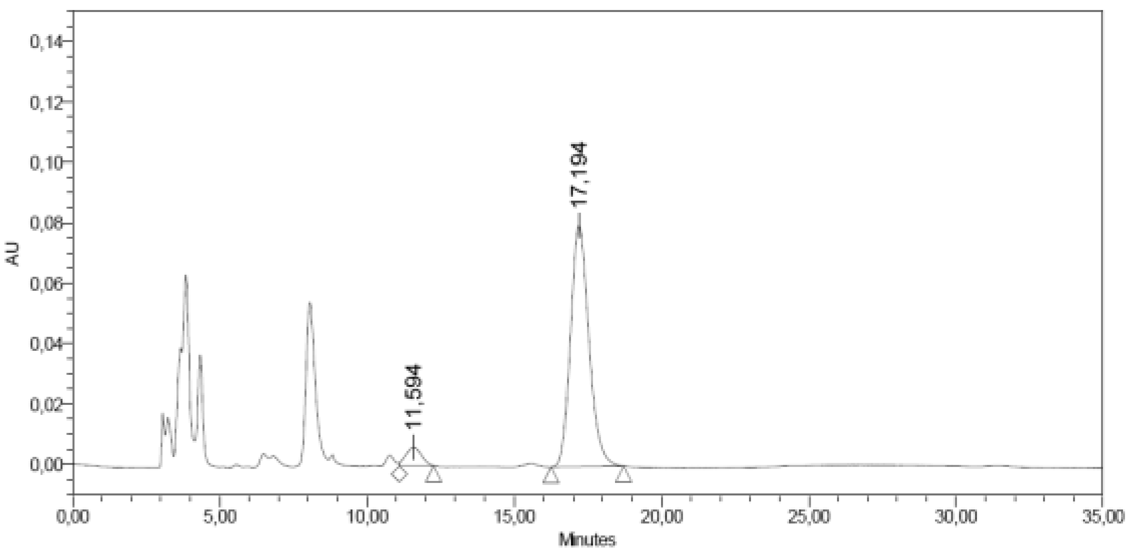


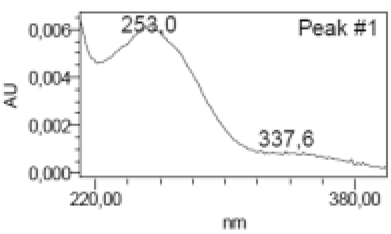
Figure SI-78. HPLC traces of compound **4p**





Peak Results

	RT	Area	Height	% Area
1	11,594	226725	6186	6,16
2	17,194	3455871	79882	93,84



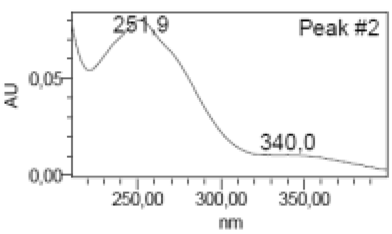
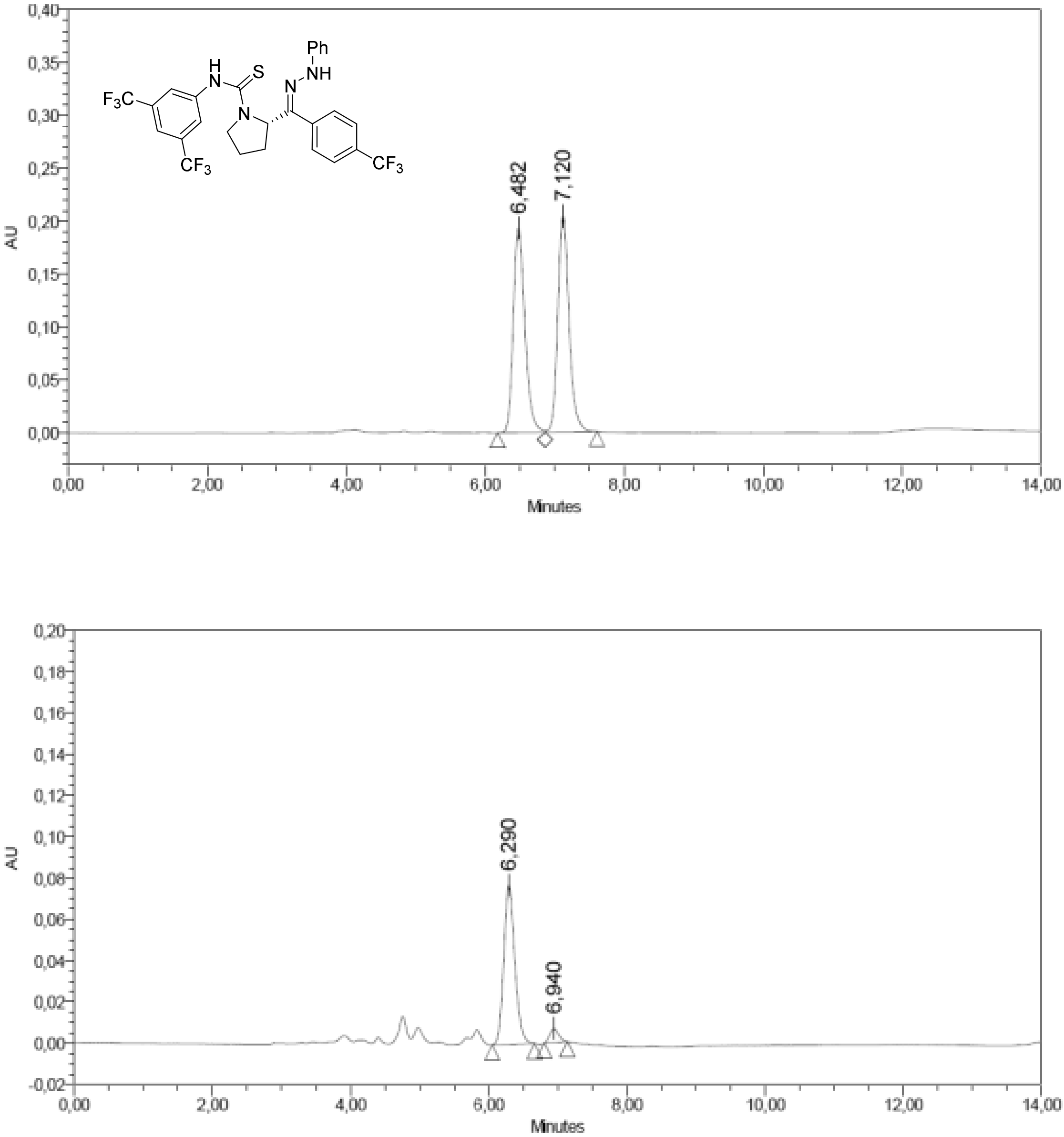


Figure SI-79. HPLC traces of compound **4q**



Peak Results

	RT	Area	Height	% Area
1	6,290	866498	77159	93,14
2	6,940	63852	6938	6,86

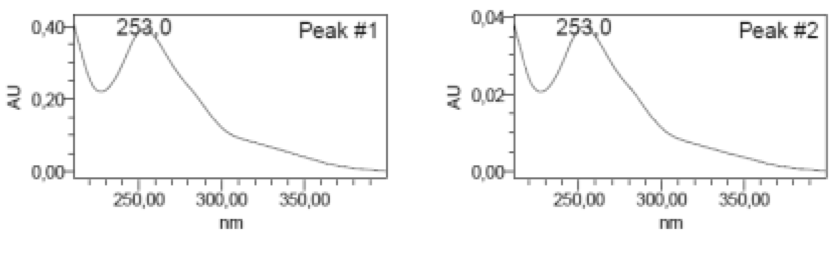
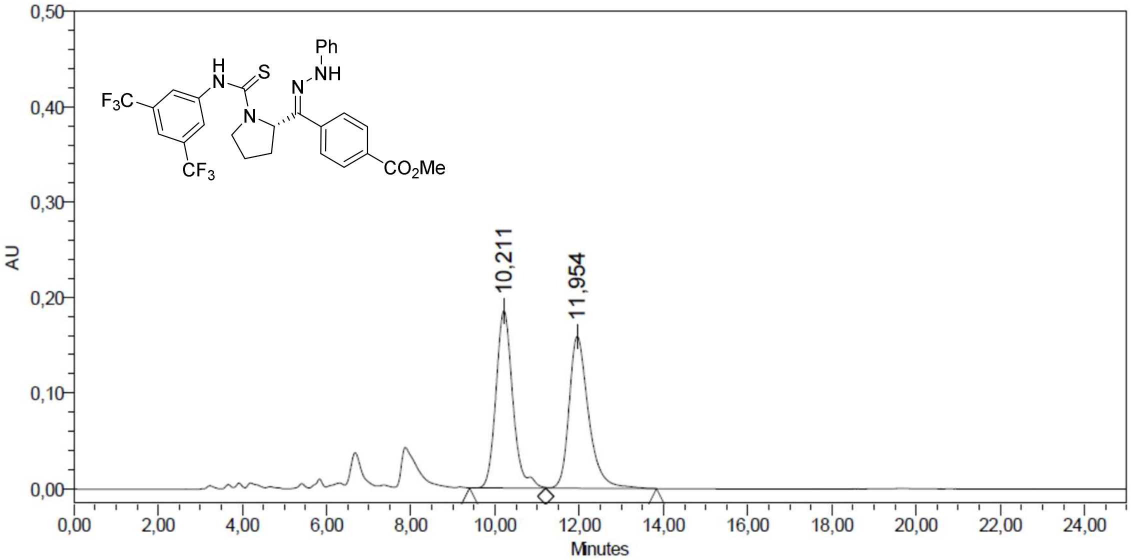
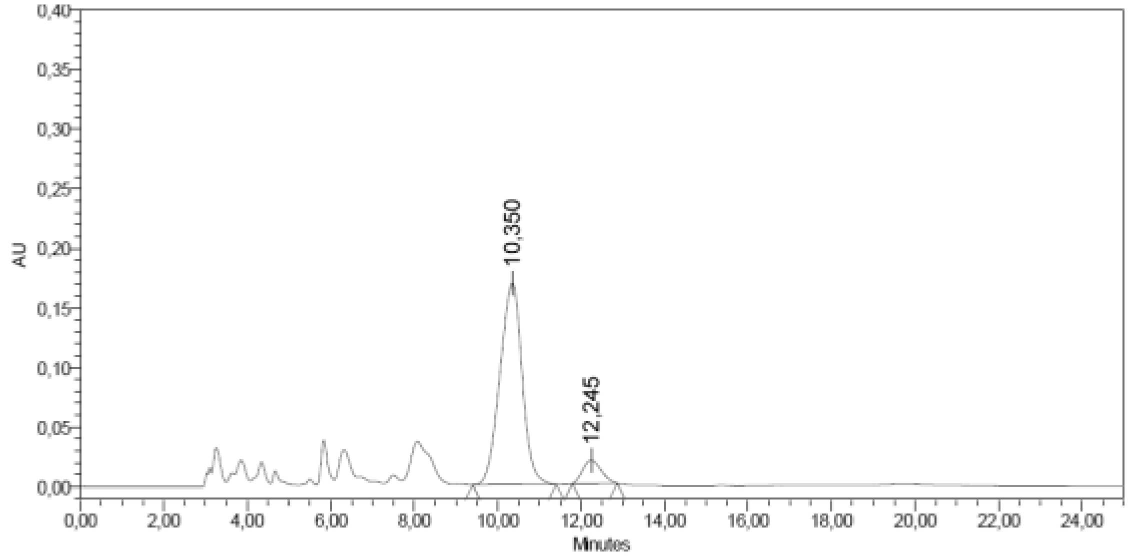


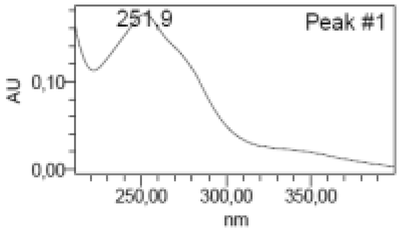
Figure SI-80. HPLC traces of compound **4r**





Peak Results

	RT	Area	Height	% Area
1	10,350	6267059	169203	91,36
2	12,245	592725	19365	8,64



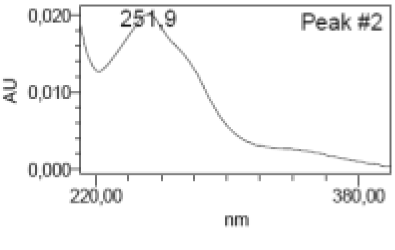
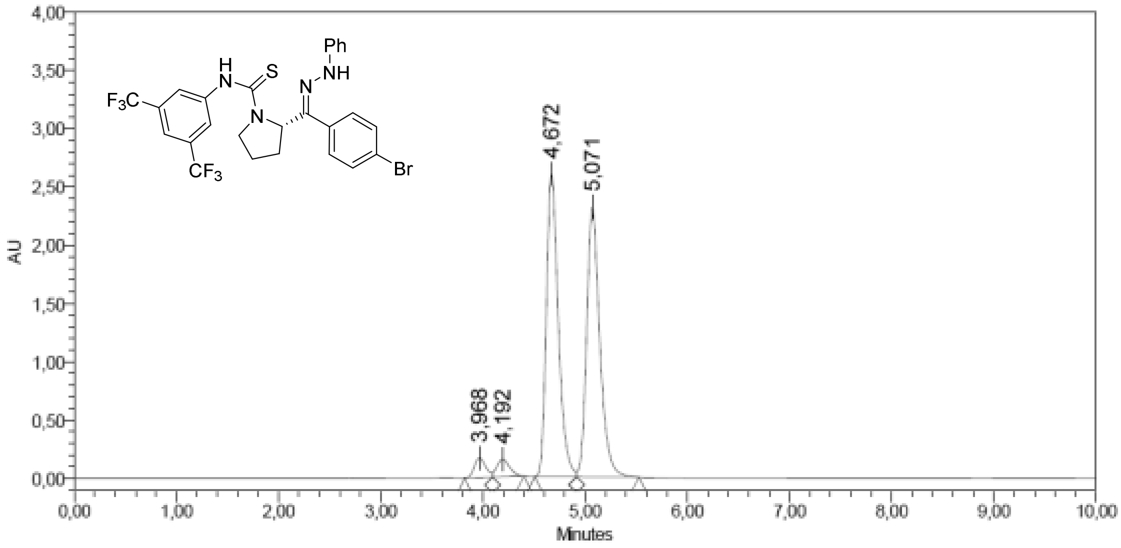
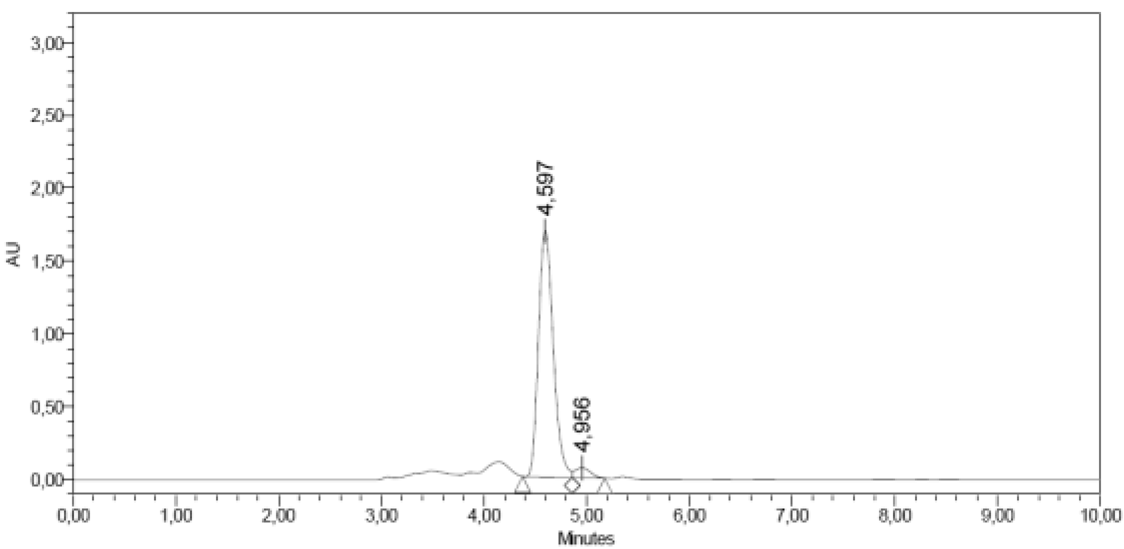


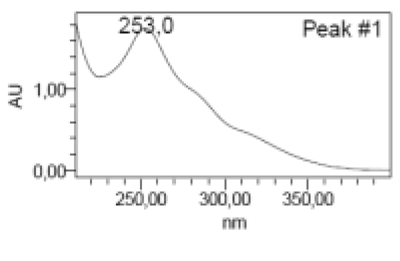
Figure SI-81. HPLC traces of compound **4s**





Peak Results

	RT	Area	Height	% Area
1	4,597	16912977	1687122	95,97
2	4,956	710811	67405	4,03



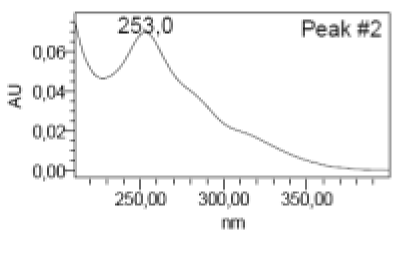
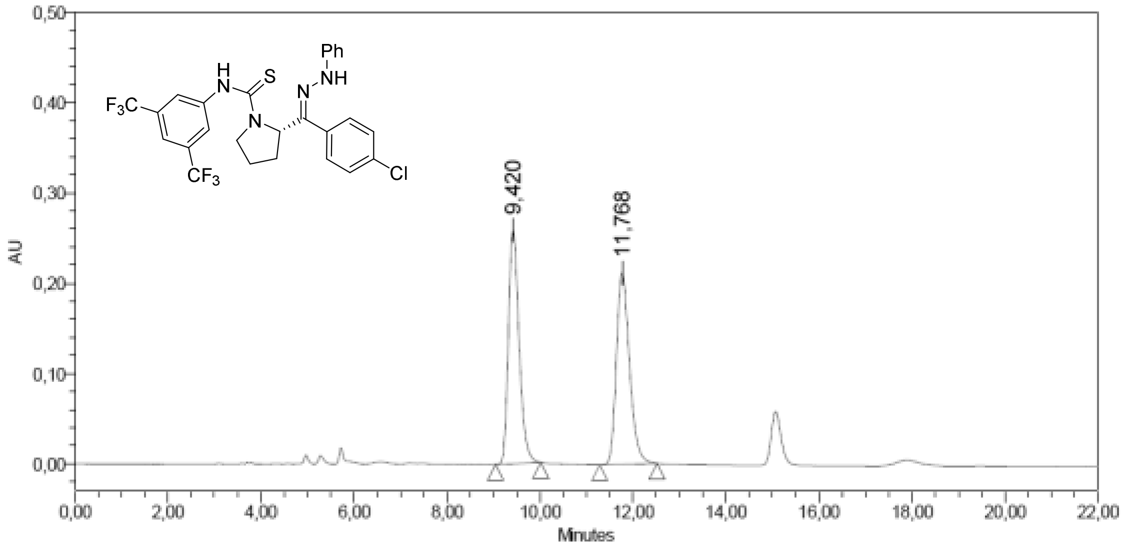
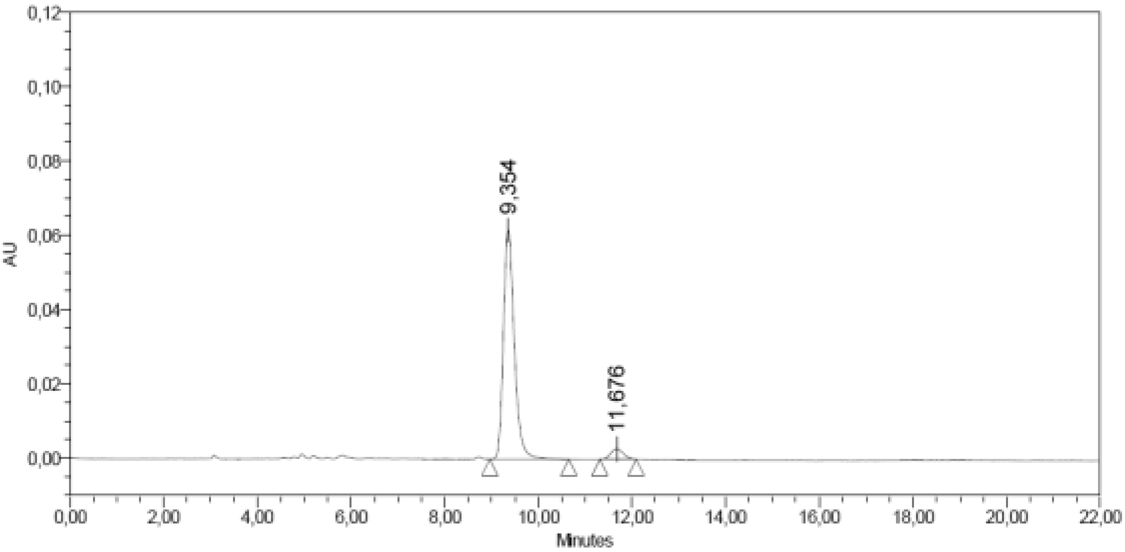


Figure SI-82. HPLC traces of compound **4t**





Peak Results

	RT	Area	Height	% Area
1	9,354	1002201	61783	94,95
2	11,676	53338	2820	5,05

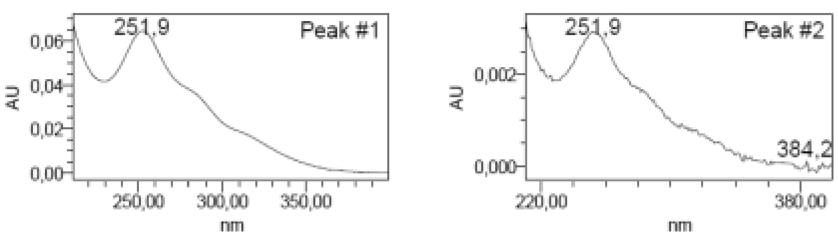
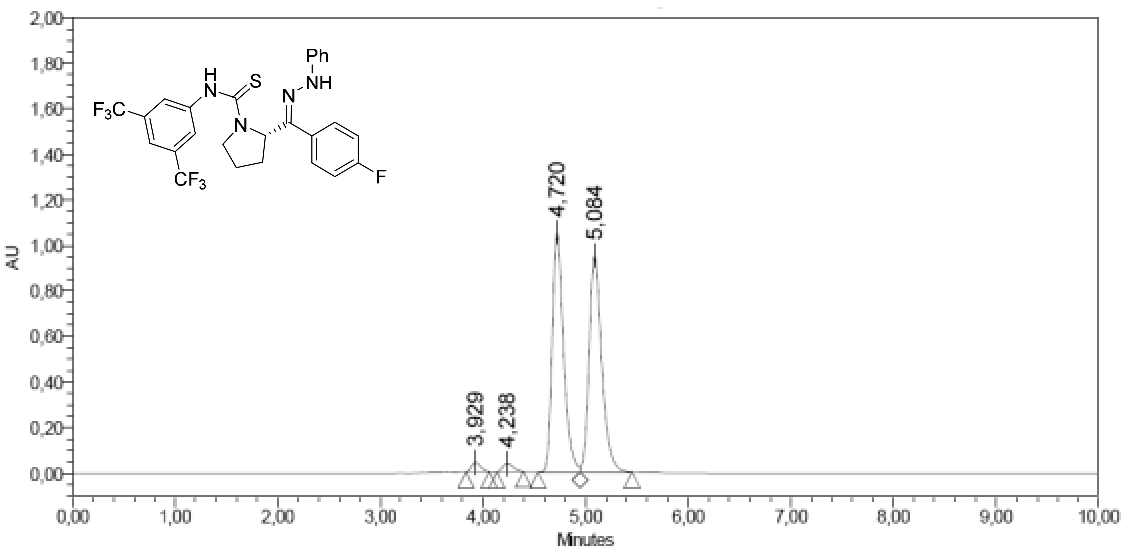
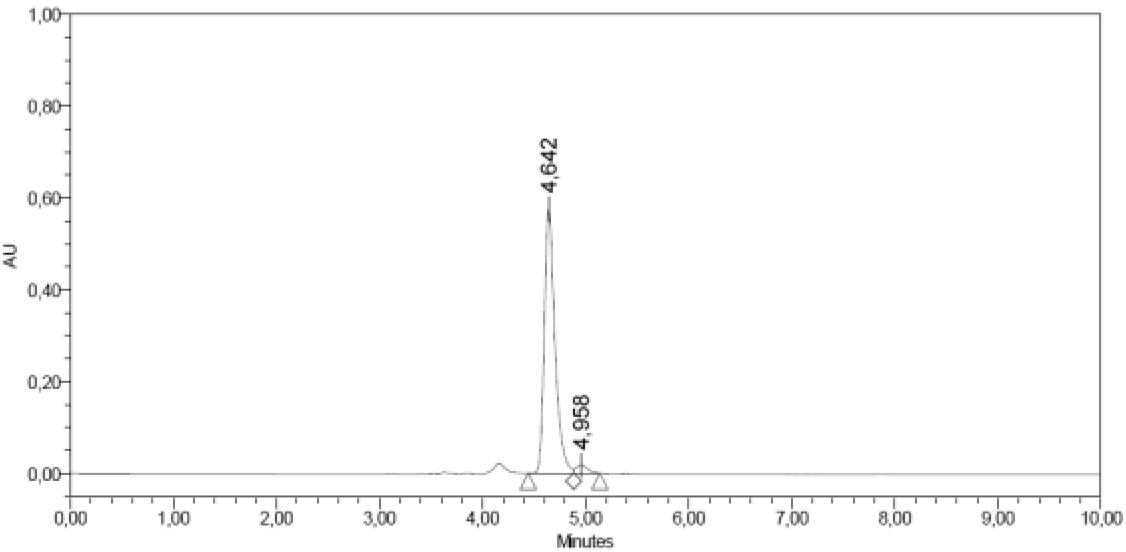


Figure SI-83. HPLC traces of compound **4u**





Peak Results

	RT	Area	Height	% Area
1	4,642	4126235	576195	96,82
2	4,958	135313	17570	3,18

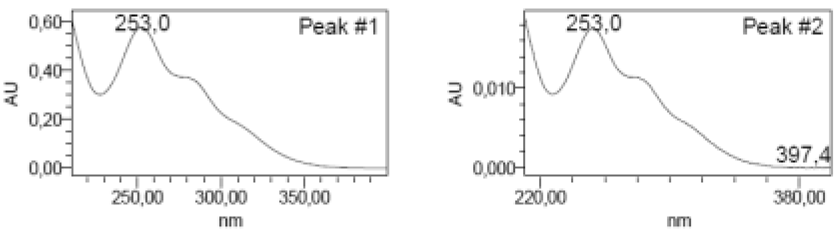
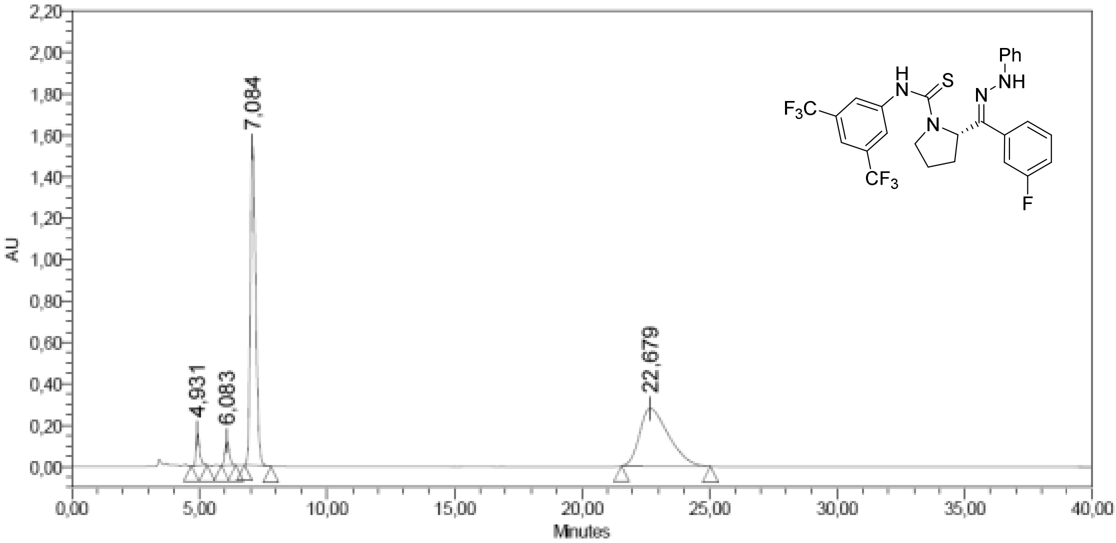
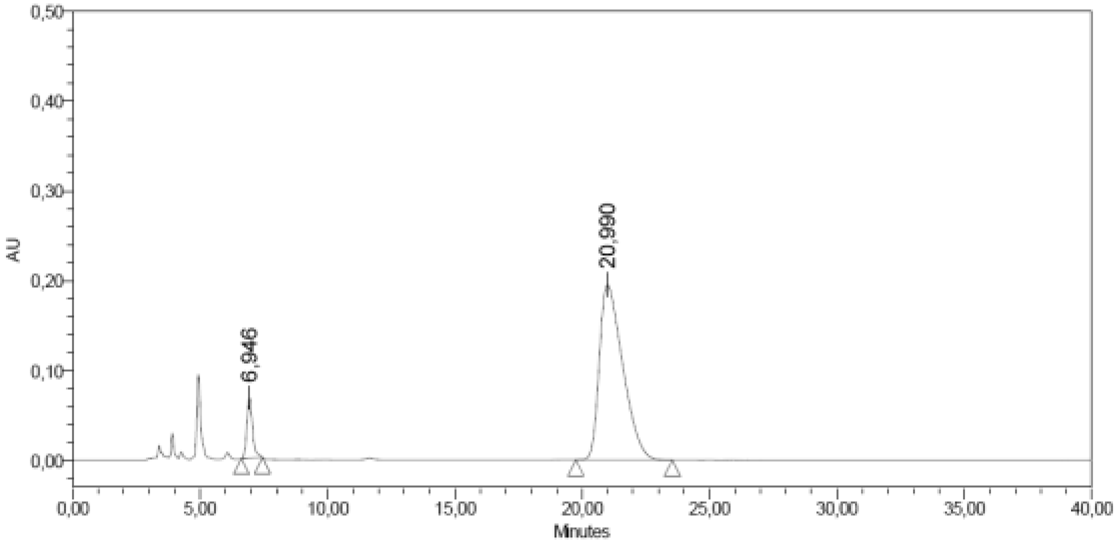


Figure SI-84. HPLC traces of compound **4v**





Peak Results

	RT	Area	Height	% Area
1	6,946	1054068	67571	7,79
2	20,990	12476842	195009	92,21

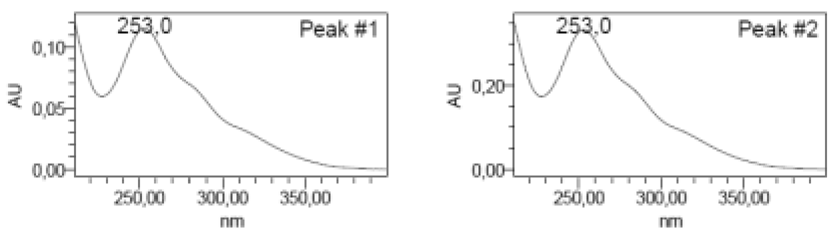
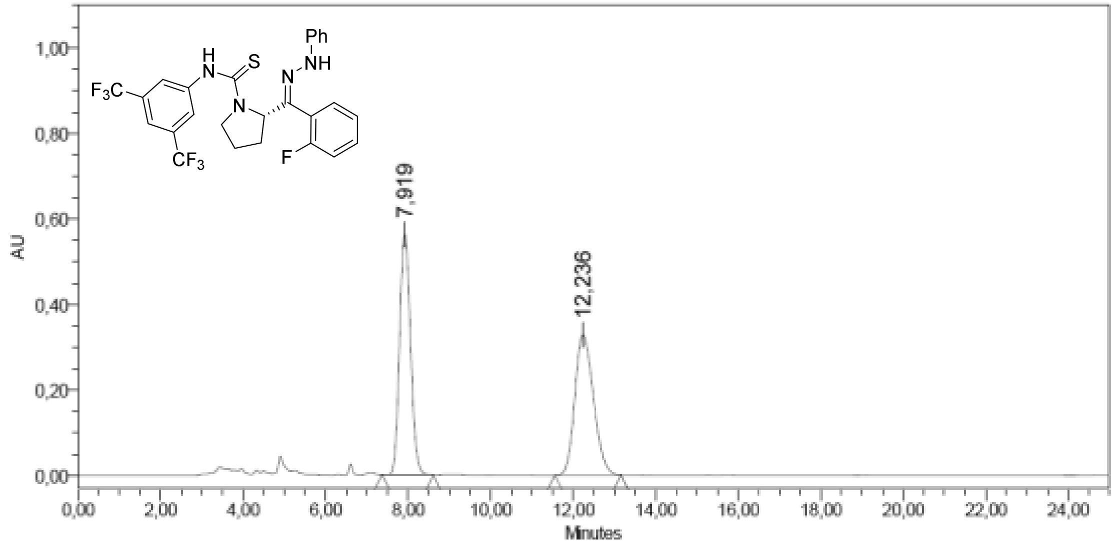
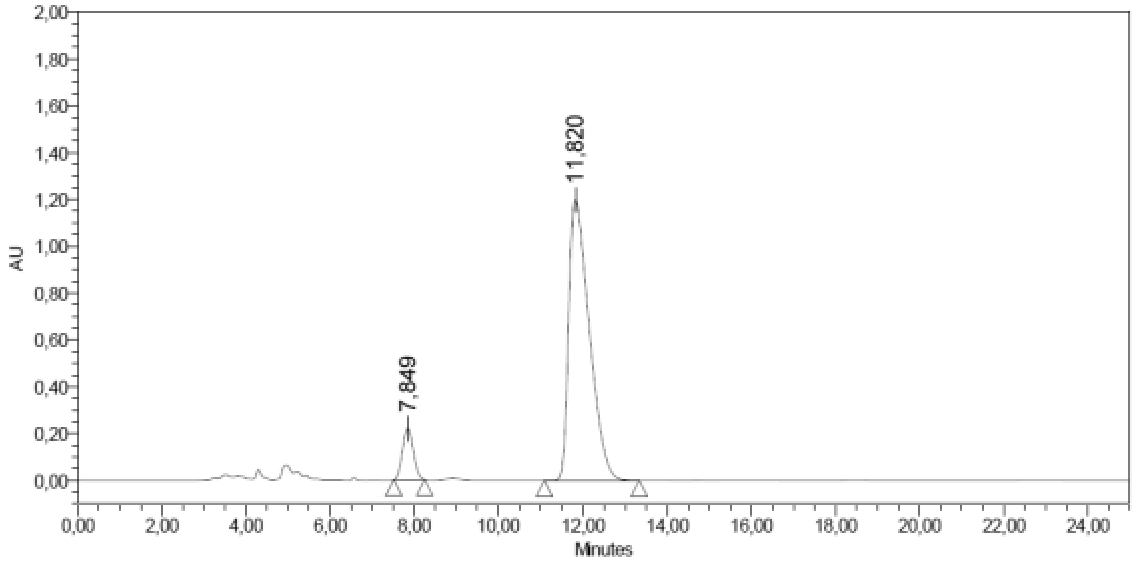


Figure SI-85. HPLC traces of compound **4w**





Peak Results

	RT	Area	Height	% Area
1	7,849	3913407	218472	9,09
2	11,820	39142274	1198064	90,91

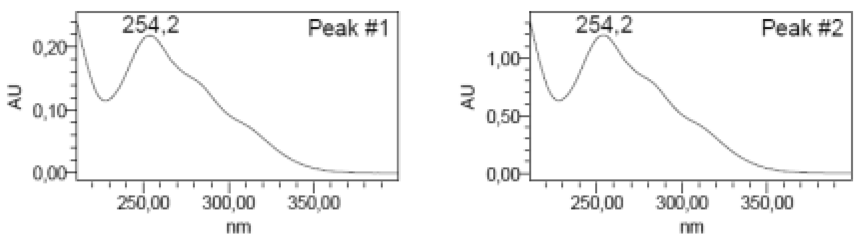
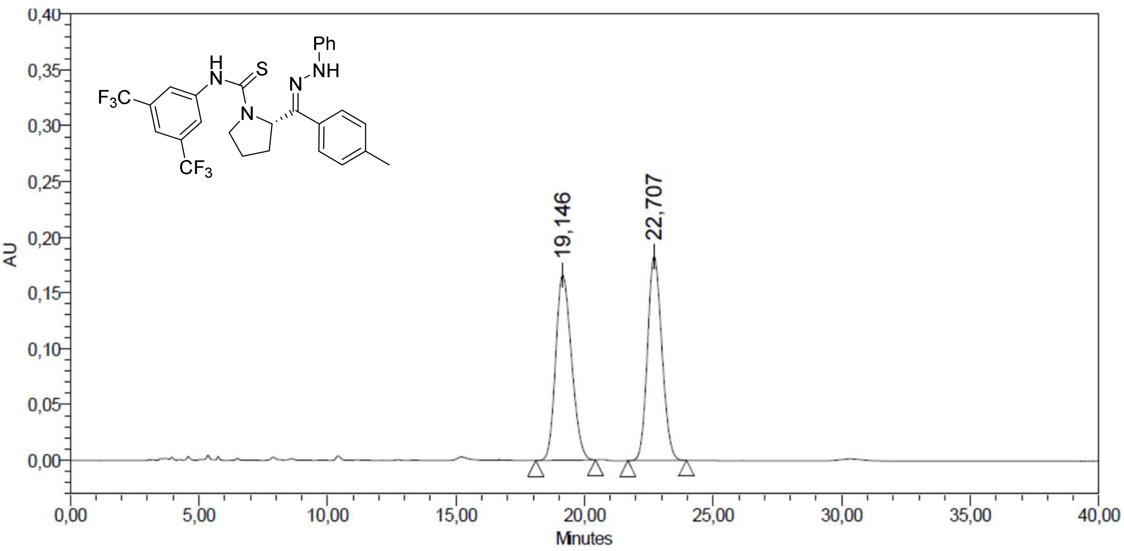
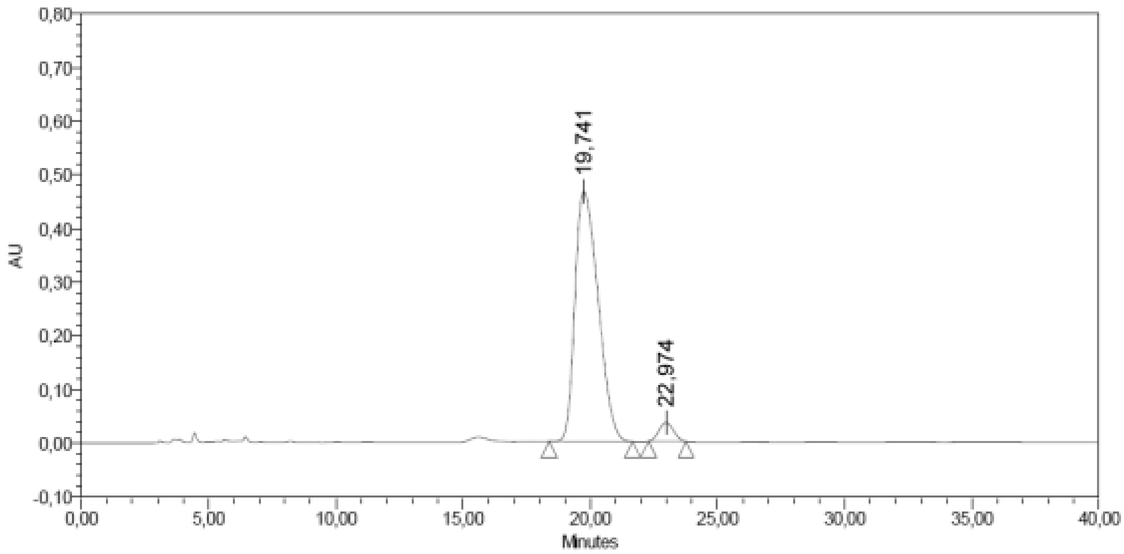


Figure SI-86. HPLC traces of compound **4x**





Peak Results

	RT	Area	Height	% Area
1	19,741	29578742	465790	95,45
2	22,974	1411372	35383	4,55

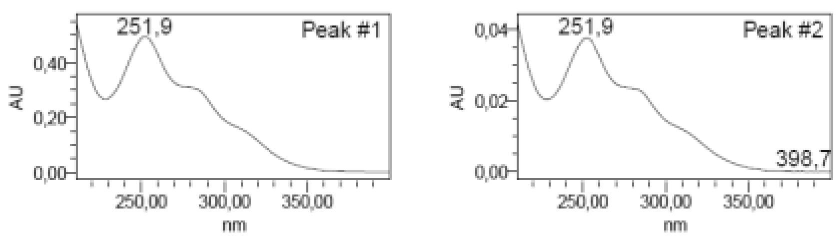
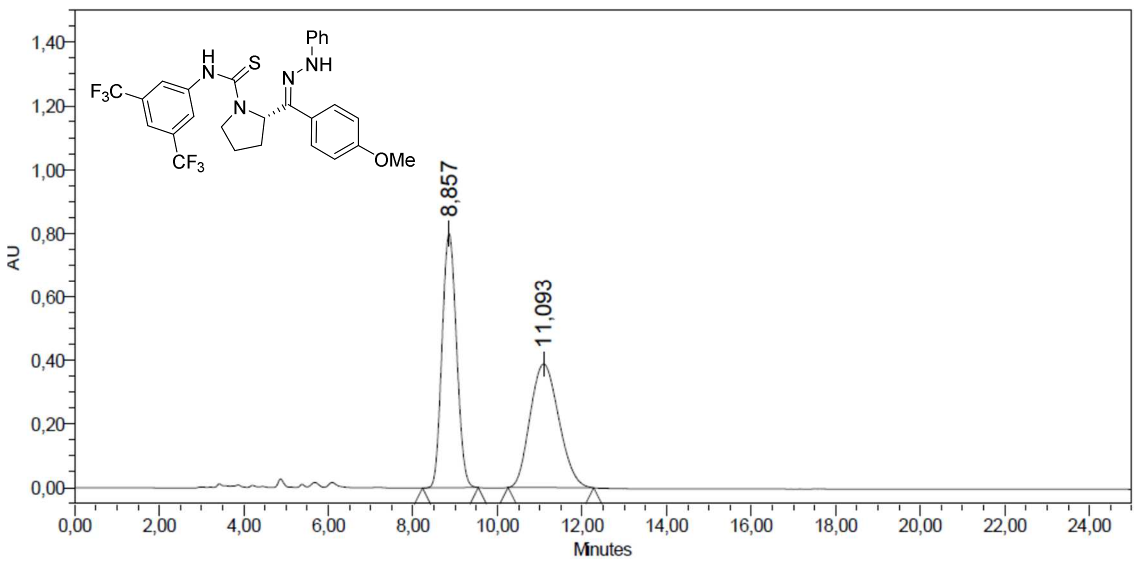
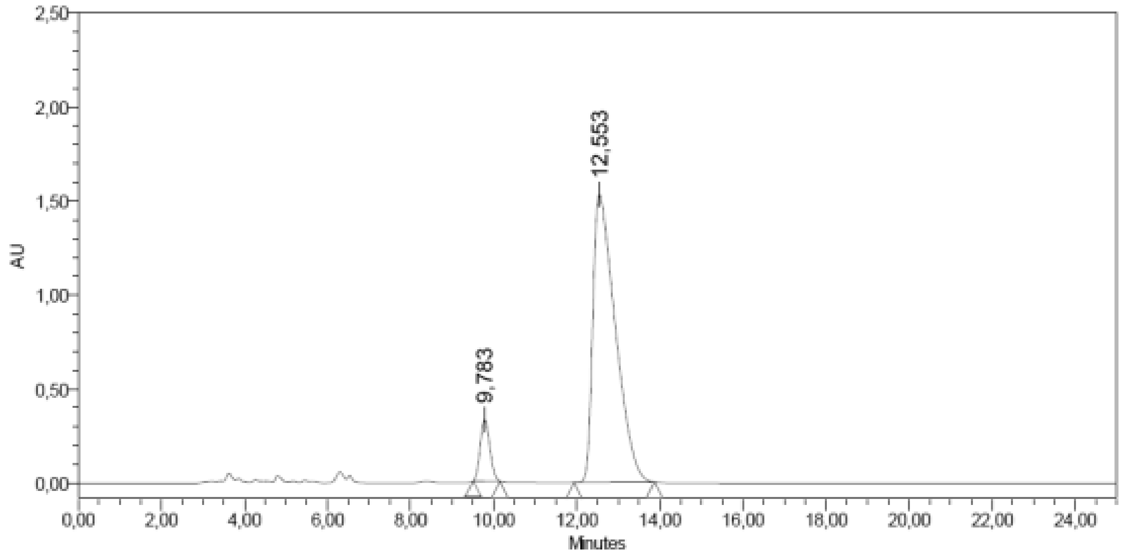


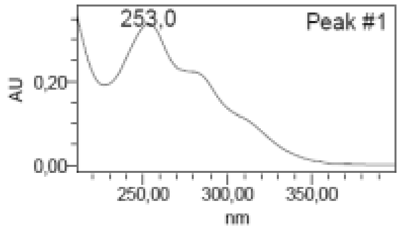
Figure SI-87. HPLC traces of compound **4y**





Peak Results

	RT	Area	Height	% Area
1	9,783	5326867	328323	8,53
2	12,553	57090742	1531667	91,47



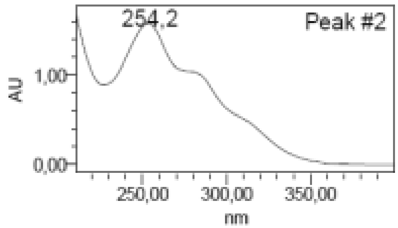
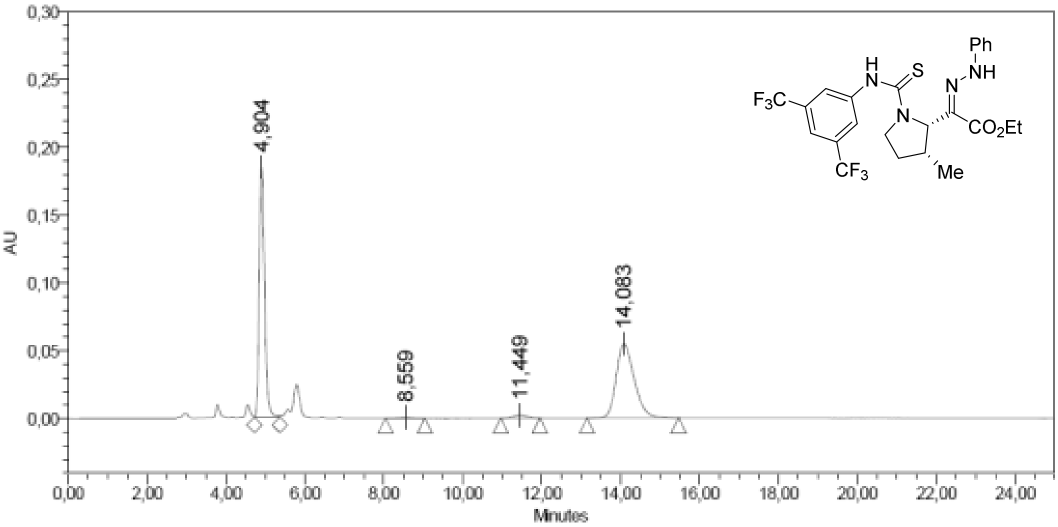
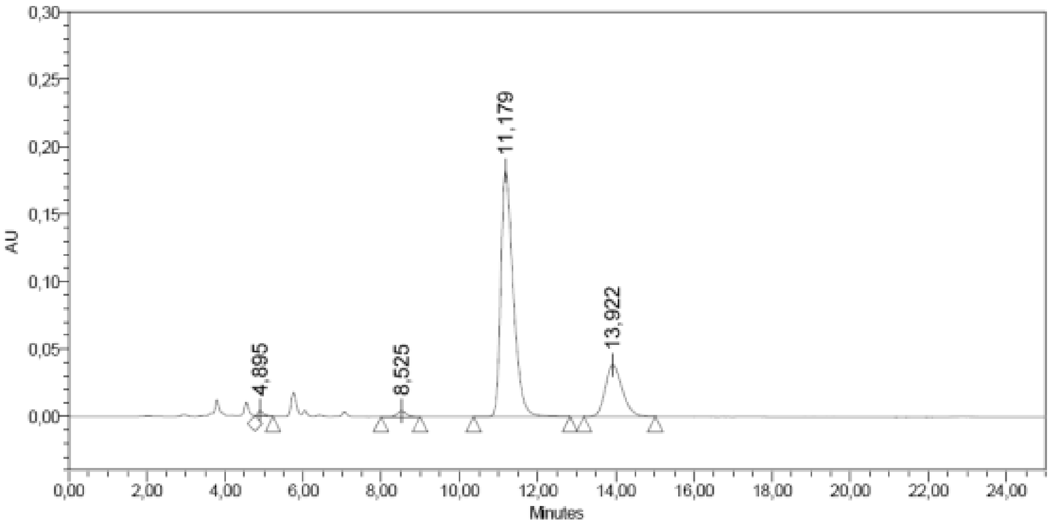


Figure SI-88. HPLC traces of compound **4z**





Peak Results

	RT	Area	Height	% Area
1	4,895	41589	4106	0,79
2	8,525	65461	4226	1,24
3	11,179	4025307	182616	76,08
4	13,922	1158358	38262	21,89

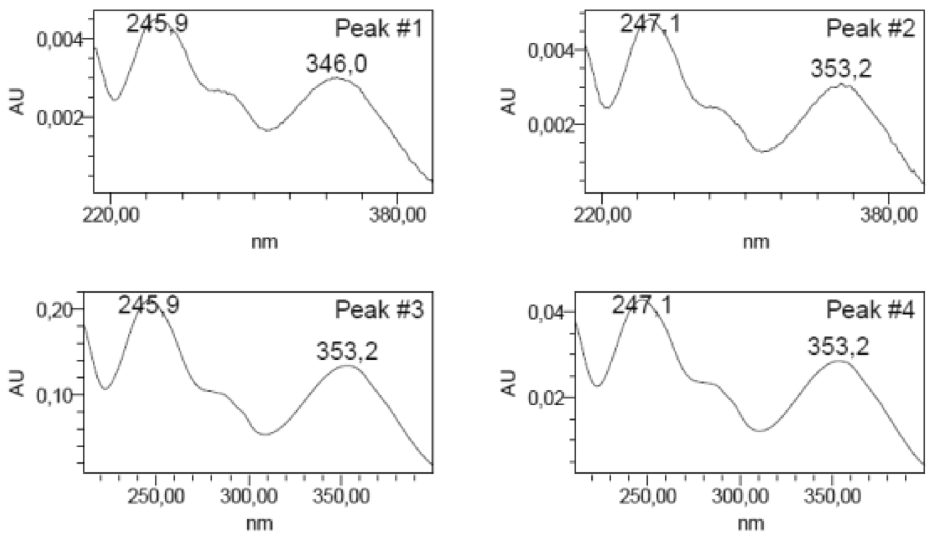
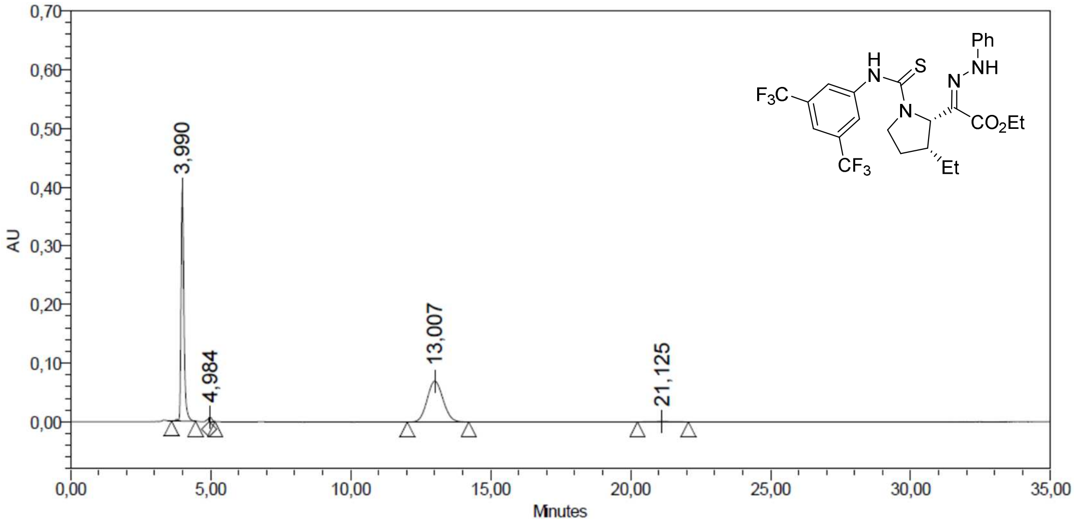
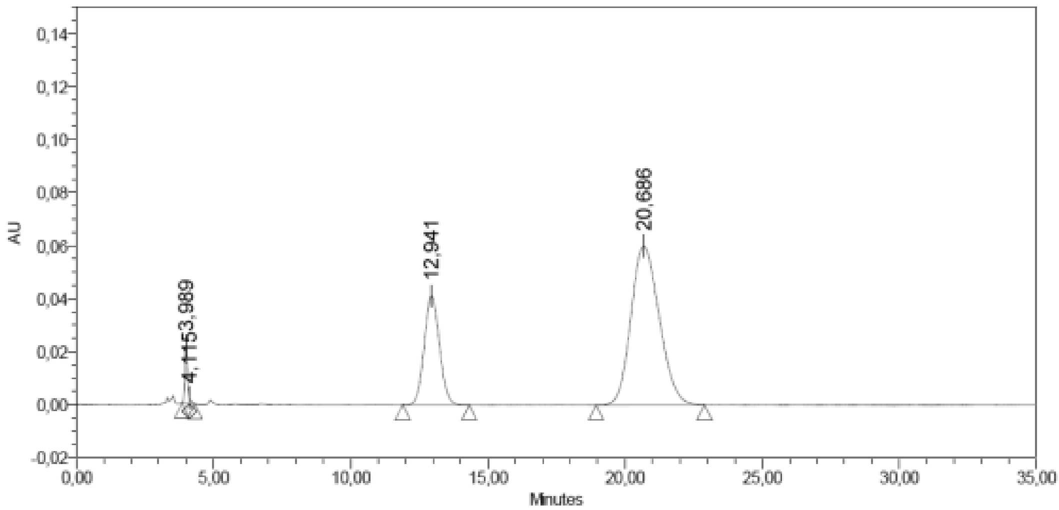


Figure SI-89. HPLC traces of compound **6a**





Peak Results

	RT	Area	Height	% Area
1	3,989	145267	21810	2,40
2	4,115	8980	2160	0,15
3	12,941	1600727	41101	26,39
4	20,686	4310147	60026	71,06

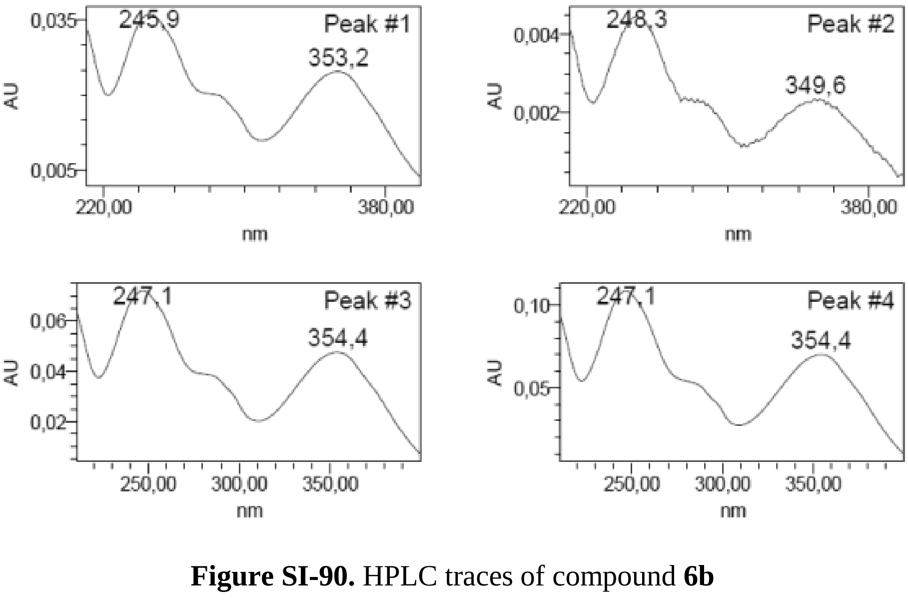
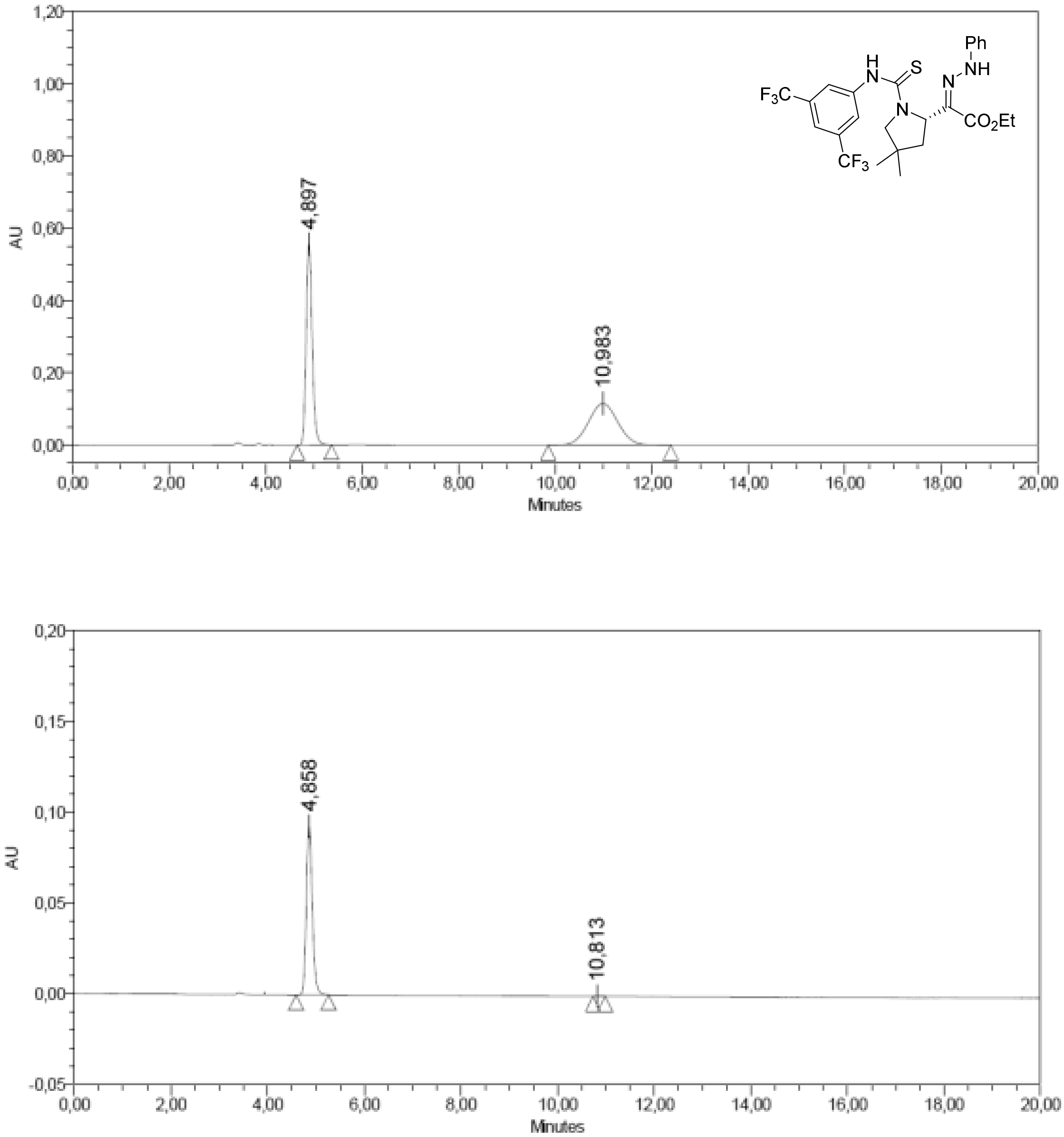


Figure SI-90. HPLC traces of compound **6b**



Peak Results

	RT	Area	Height	% Area
1	4,858	803114	93054	99,94
2	10,813	510	83	0,06

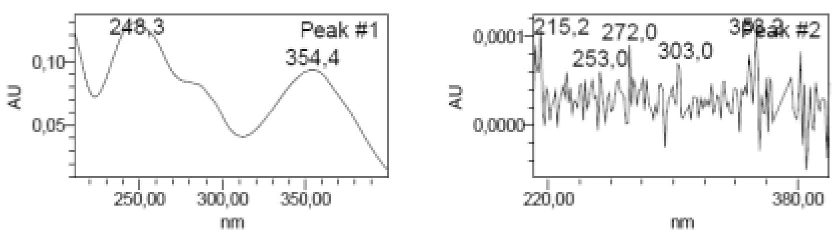
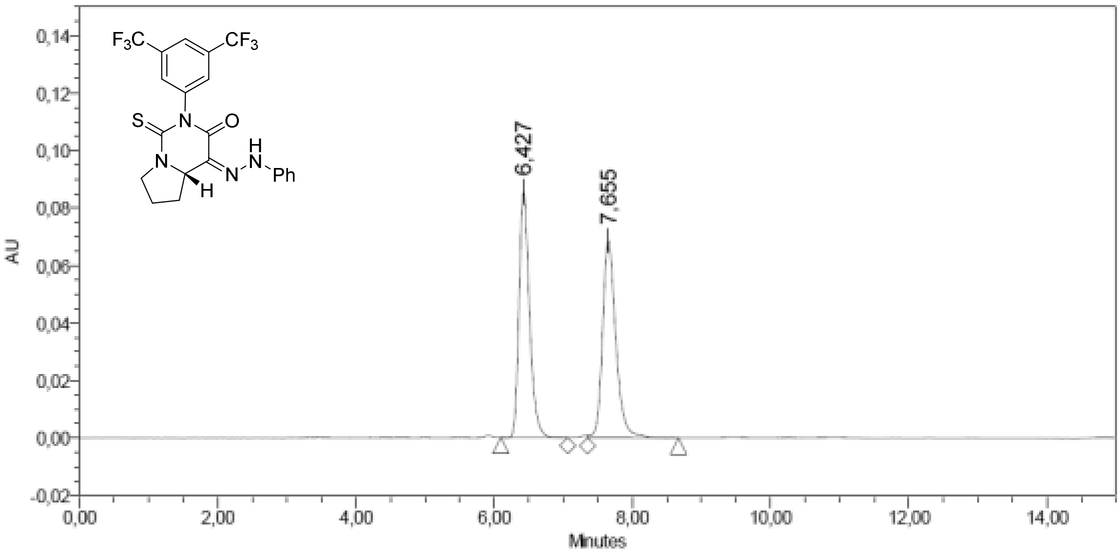
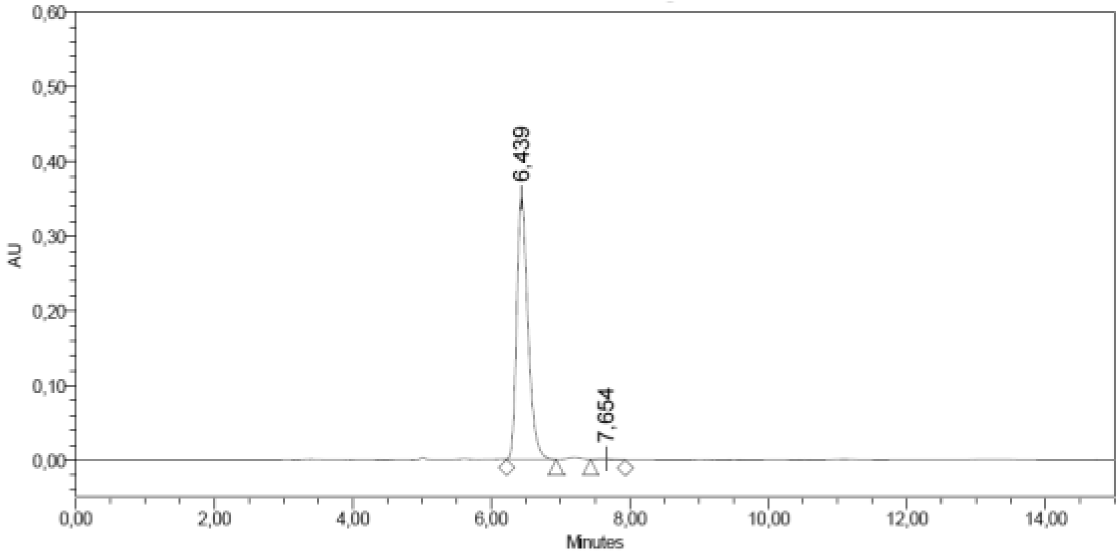


Figure SI-91. HPLC traces of compound **6c**





Peak Results

	RT	Area	Height	% Area
1	6,439	3949431	350288	99,61
2	7,654	15509	993	0,39

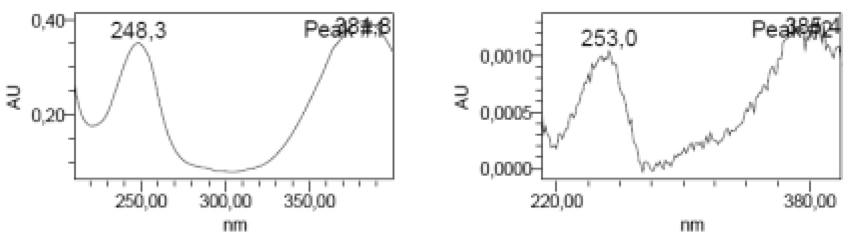
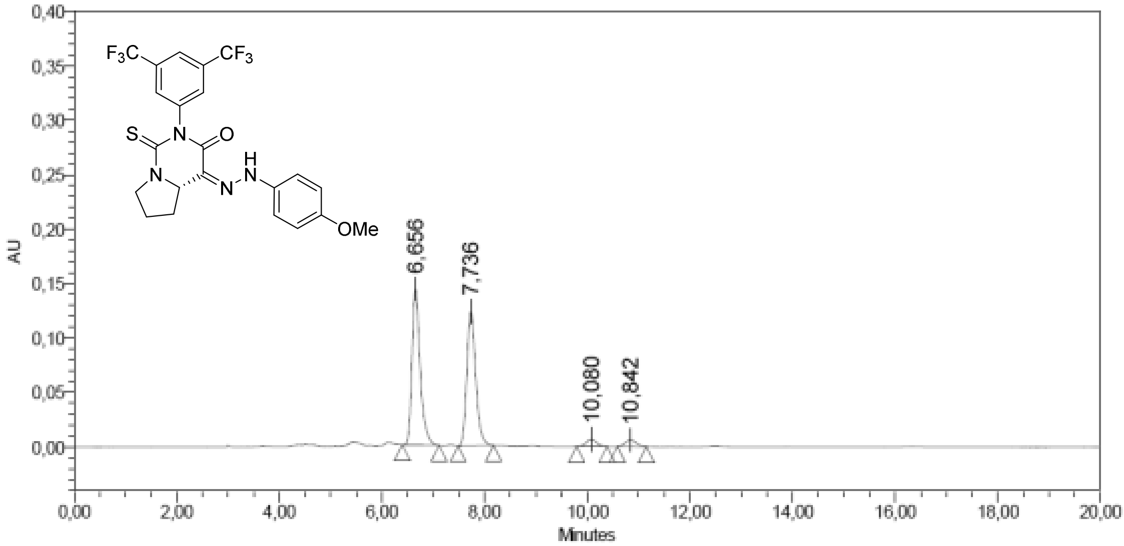
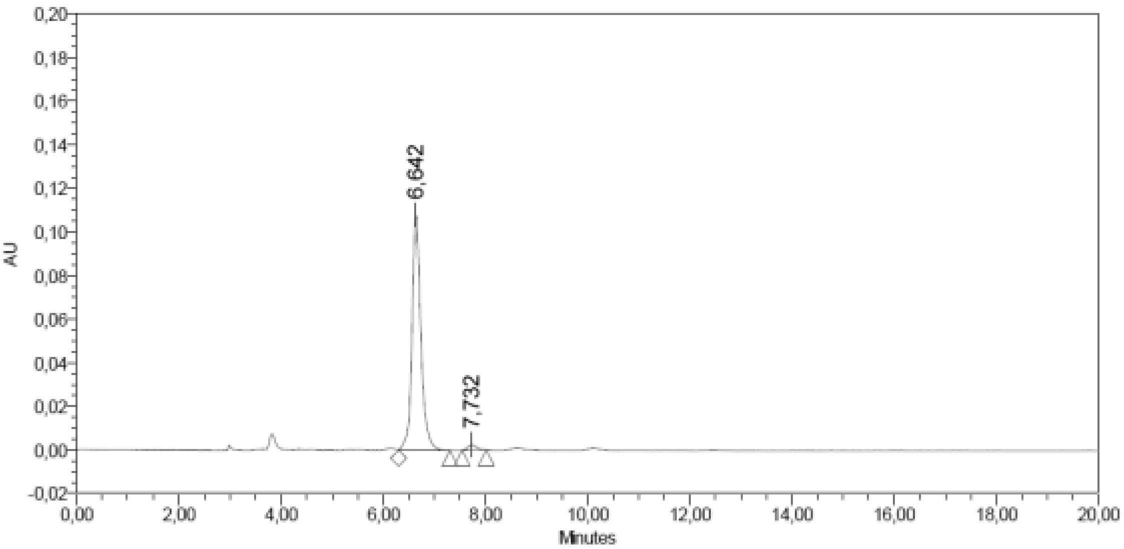


Figure SI-92. HPLC traces of compound **7a**





Peak Results

	RT	Area	Height	% Area
1	6,642	1305558	107907	97,86
2	7,732	28535	2449	2,14

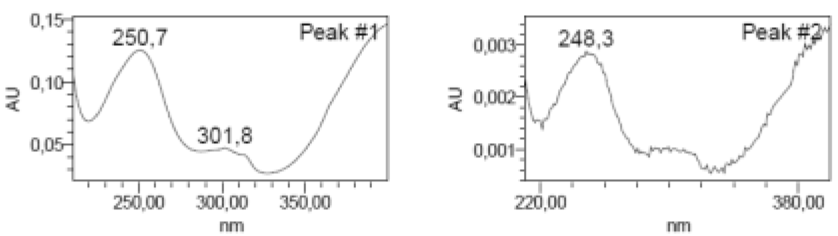
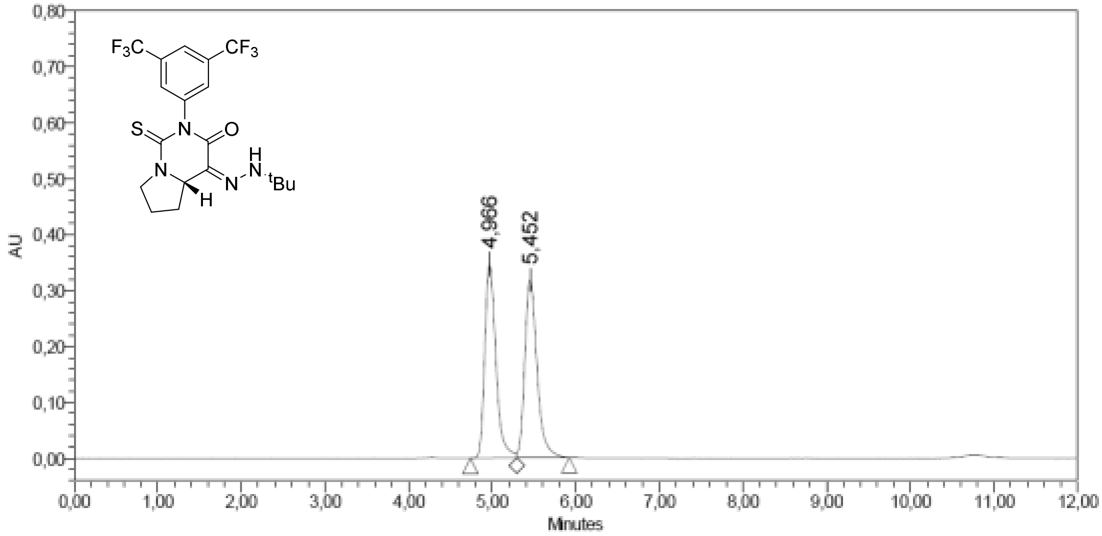
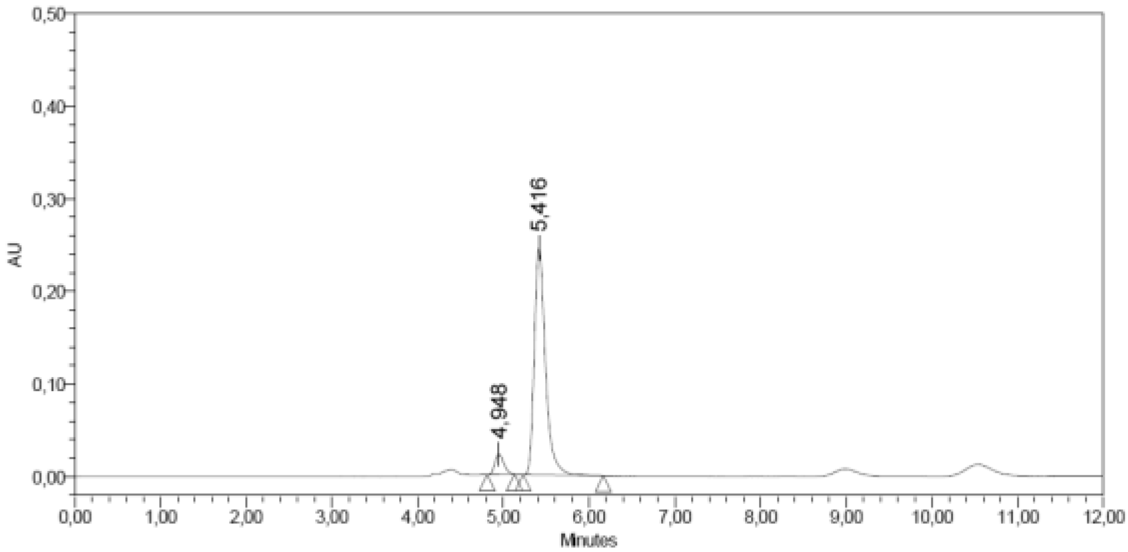


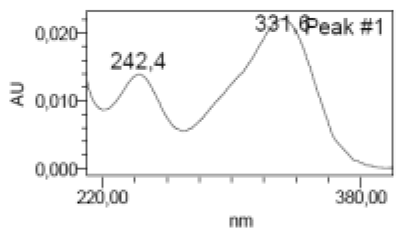
Figure SI-93. HPLC traces of compound **7b**





Peak Results

	RT	Area	Height	% Area
1	4,948	159819	22040	6,71
2	5,416	2220751	244989	93,29



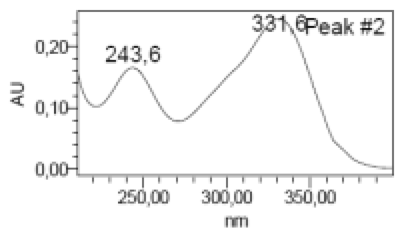
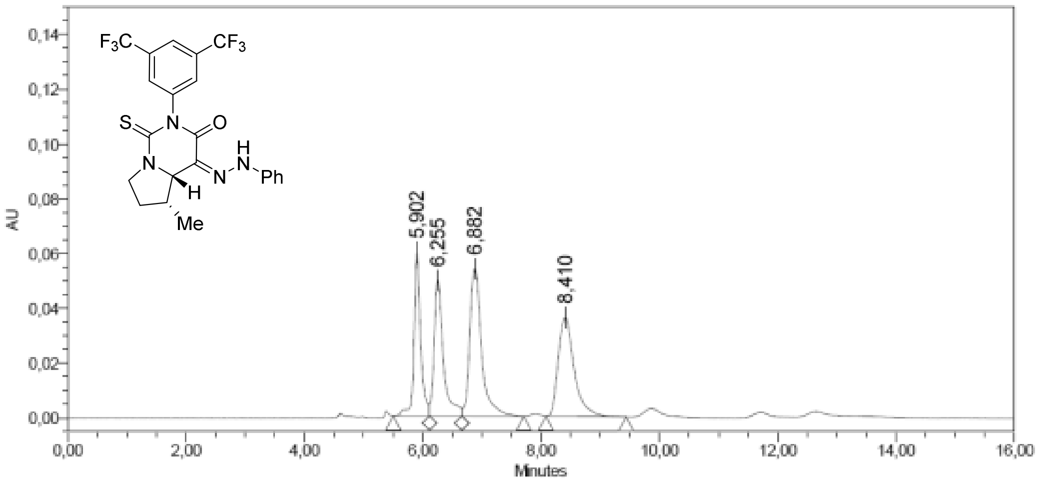
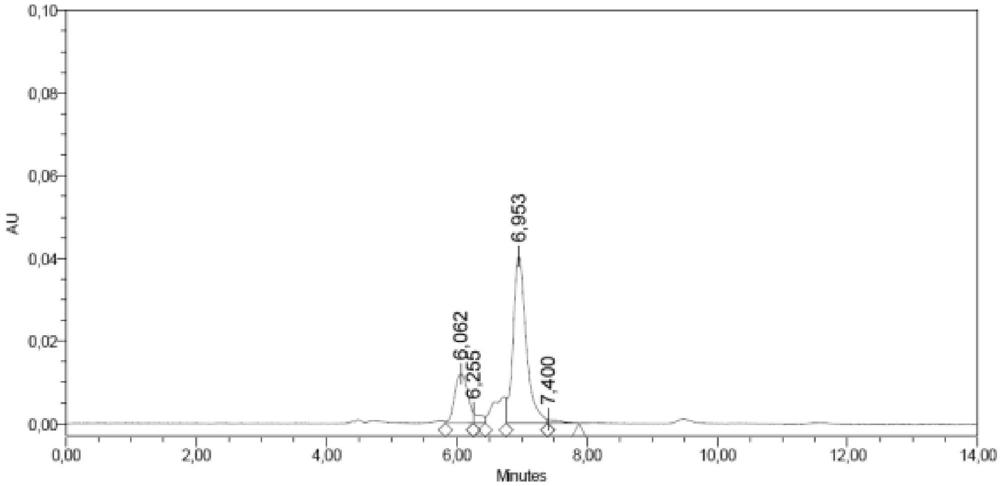


Figure SI-94. HPLC traces of compound **7c**





Peak Results

	RT	Area	Height	% Area
1	6,062	165339	11866	22,00
2	6,255	19897	2501	2,65
3	6,953	555296	40305	73,90
4	7,400	10868	935	1,45

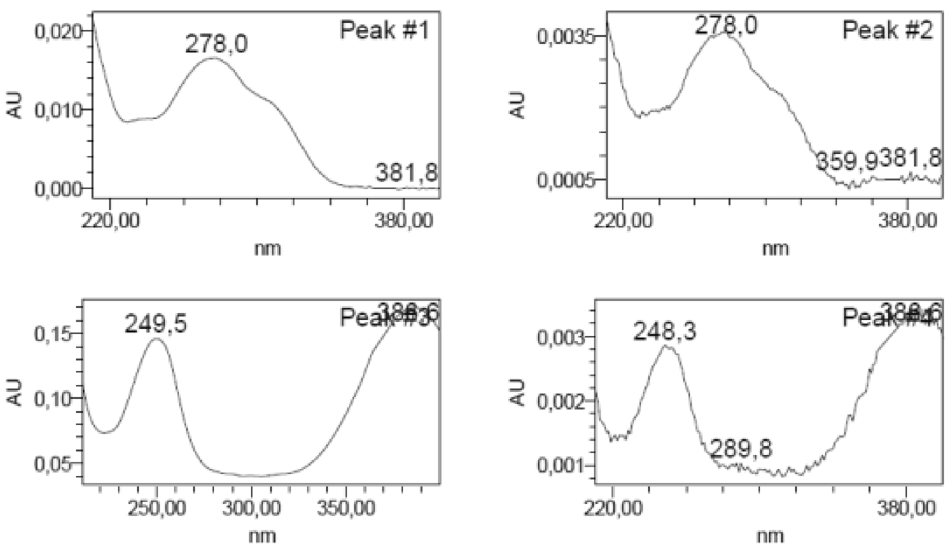
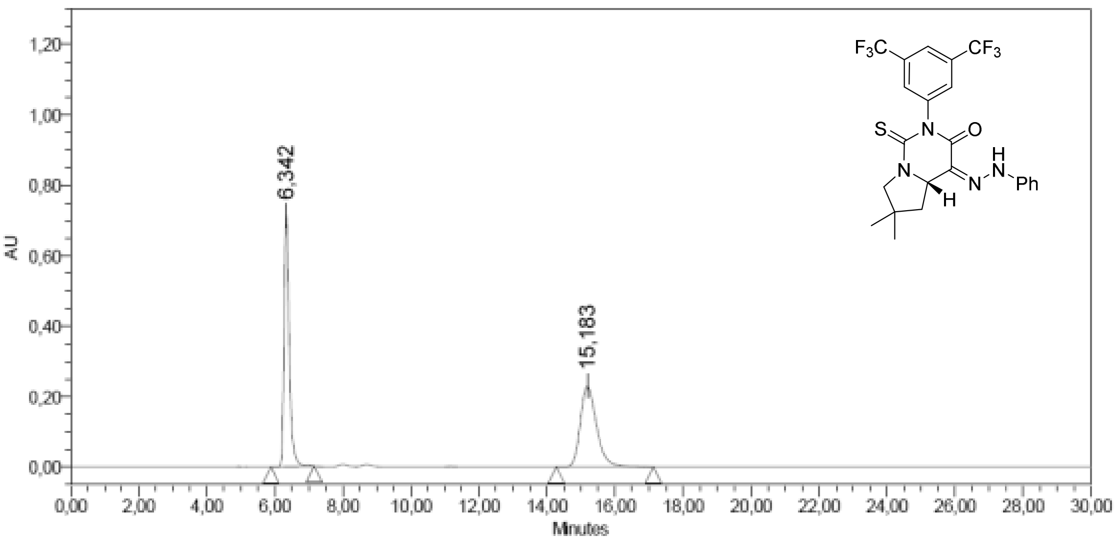
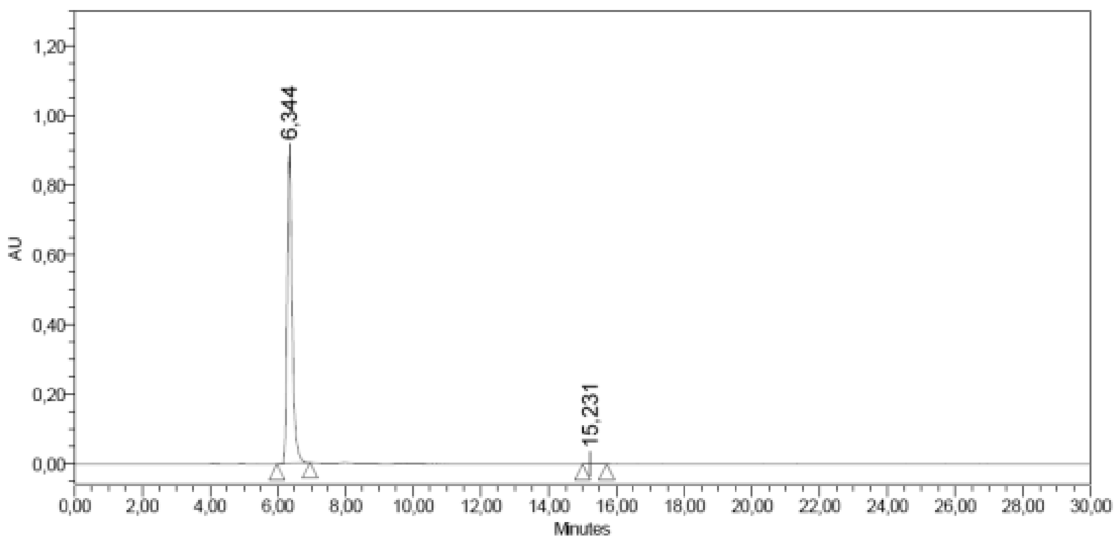


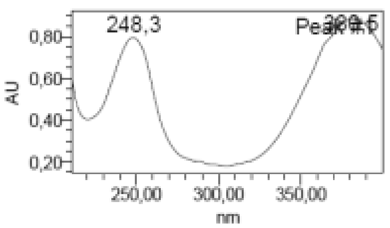
Figure SI-95. HPLC traces of compound **7d**





Peak Results

	RT	Area	Height	% Area
1	6,344	9130700	883608	99,81
2	15,231	17605	769	0,19



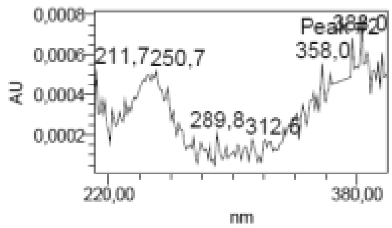
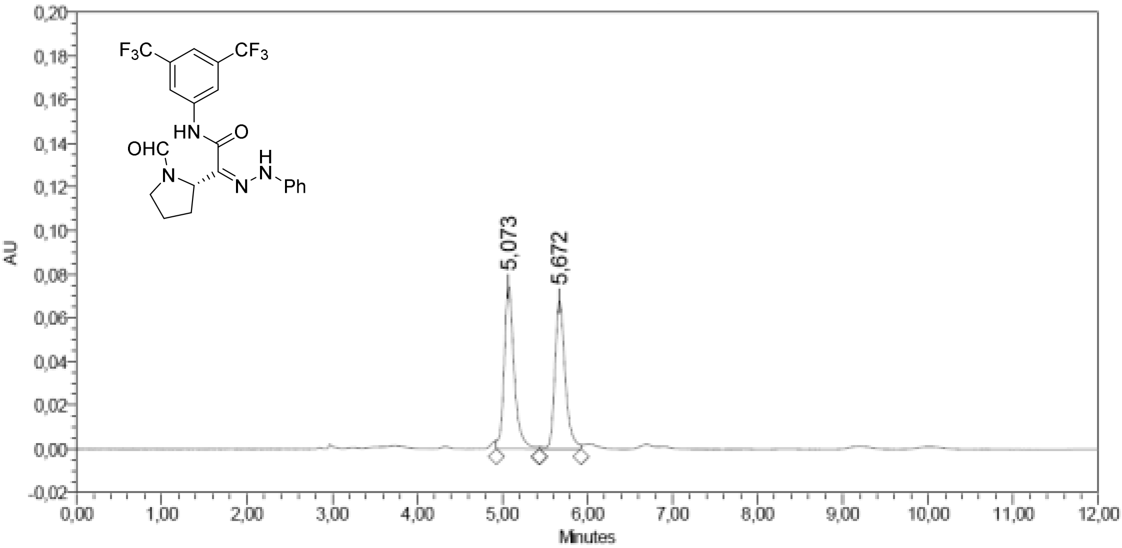
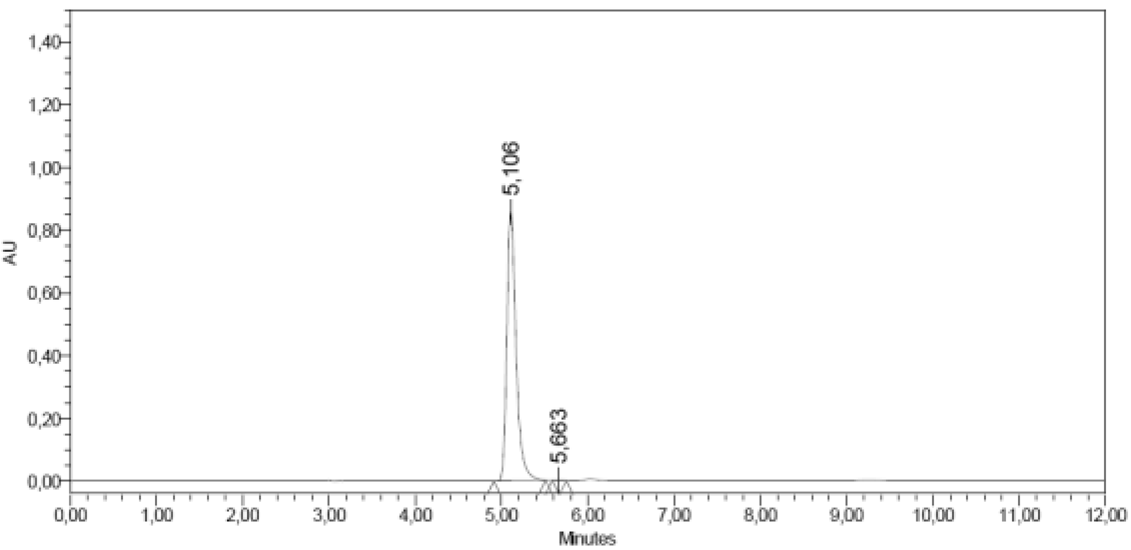


Figure SI-96. HPLC traces of compound **7e**





Peak Results

	RT	Area	Height	% Area
1	5,106	6372139	855498	99,84
2	5,663	10146	1902	0,16

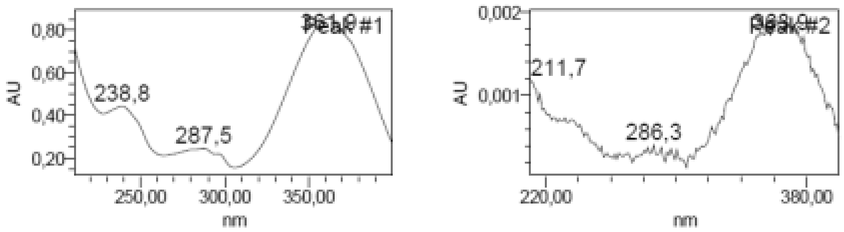
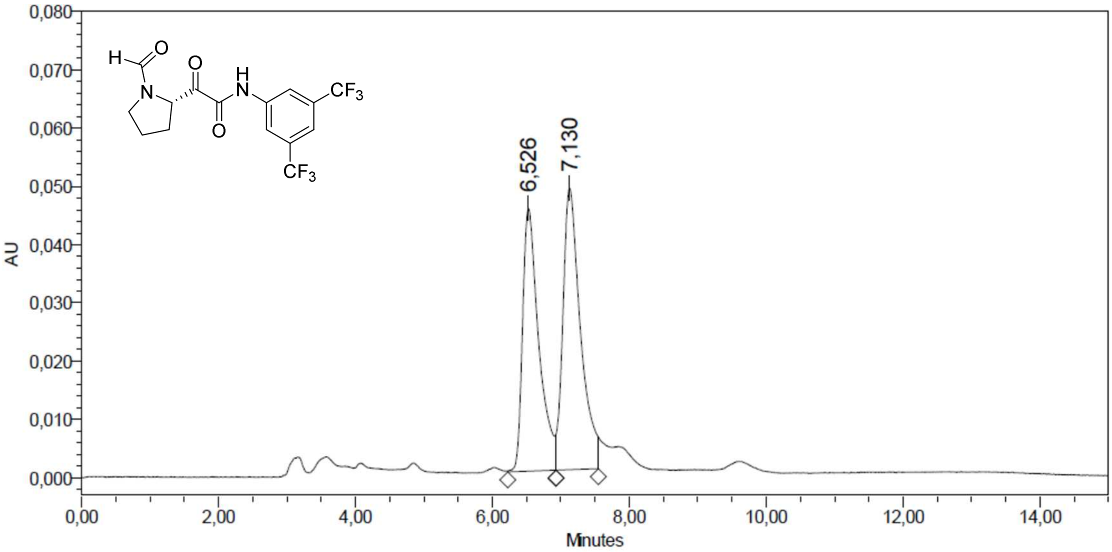
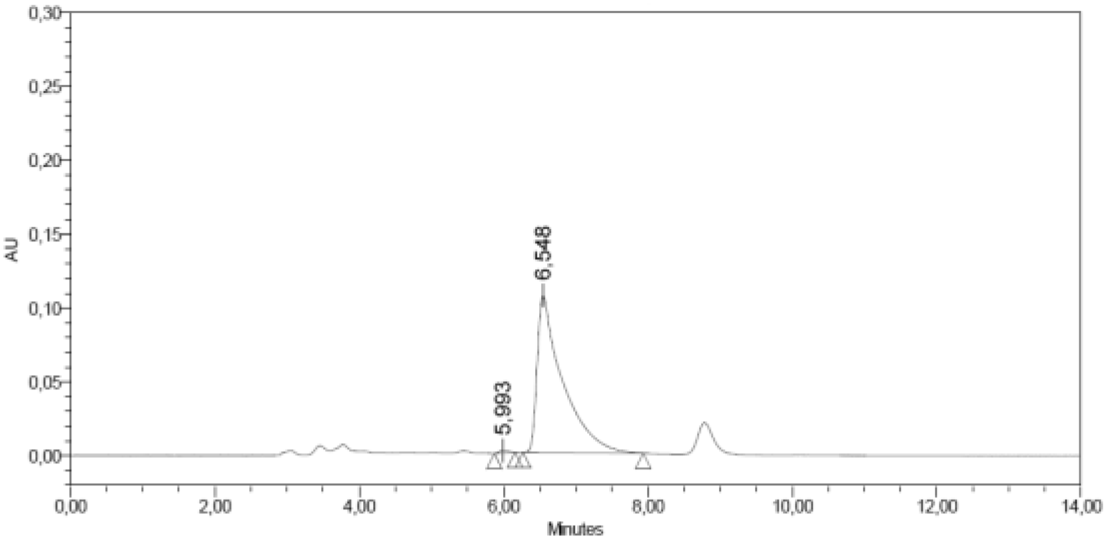


Figure SI-97. HPLC traces of compound **7a’**





Peak Results

	RT	Area	Height	% Area
1	5,993	14086	1651	0,54
2	6,548	2596747	106187	99,46

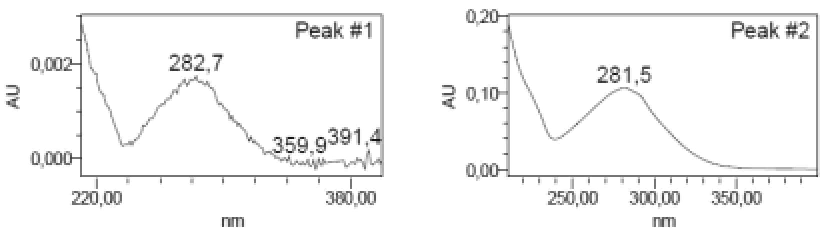
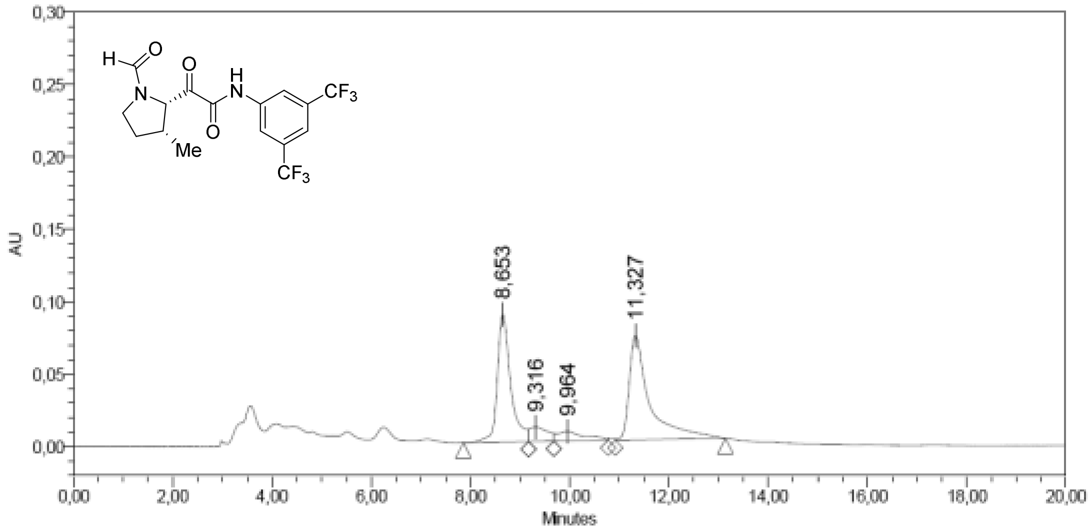
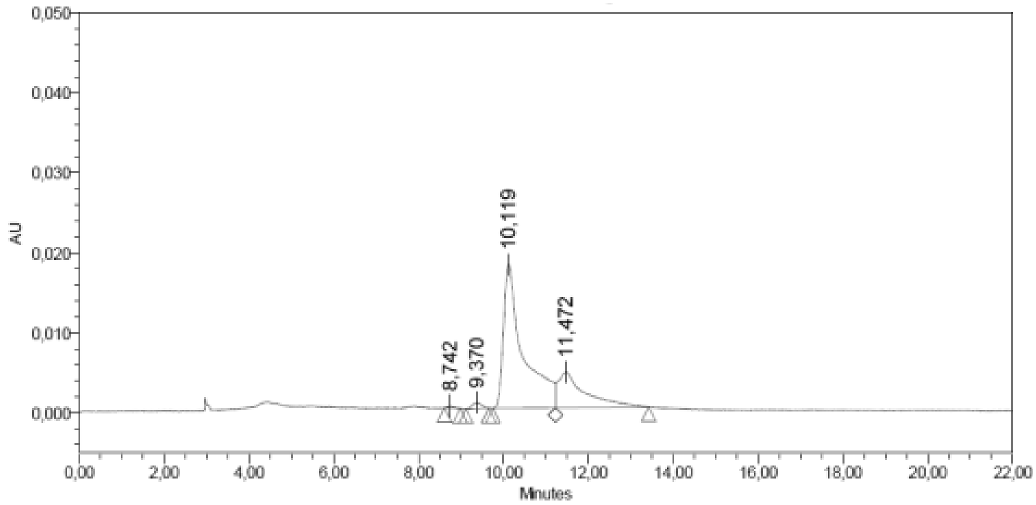


Figure SI-98. HPLC traces of compound **8a**





Peak Results

	RT	Area	Height	% Area
1	8,742	2537	279	0,32
2	9,370	11476	773	1,45
3	10,119	576480	17941	73,02
4	11,472	198984	4451	25,20

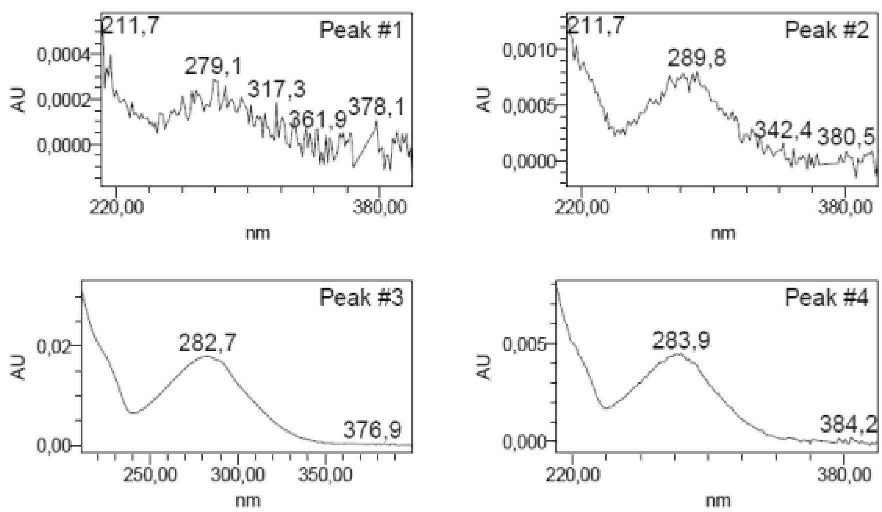
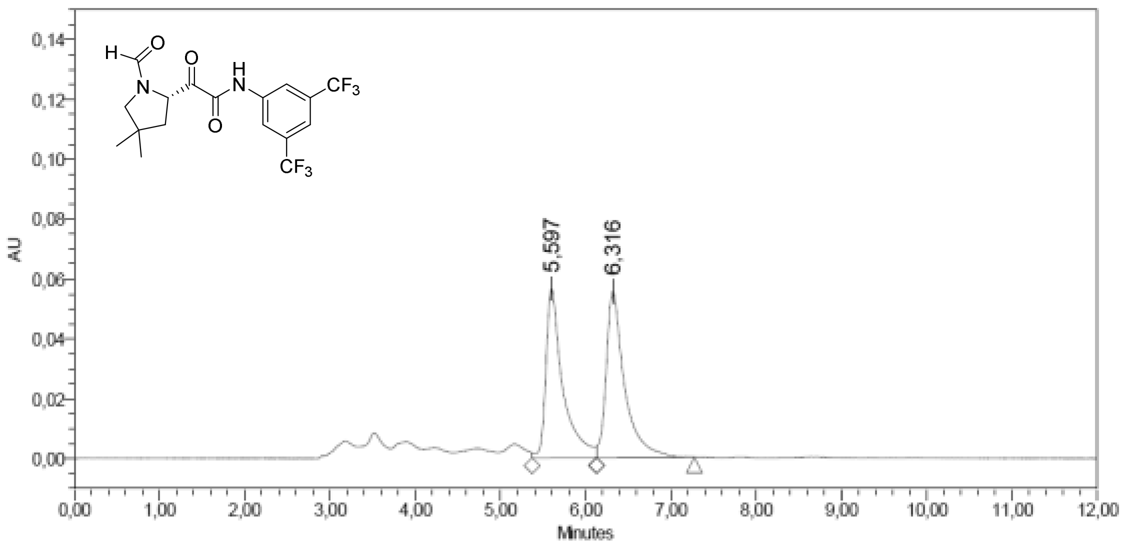
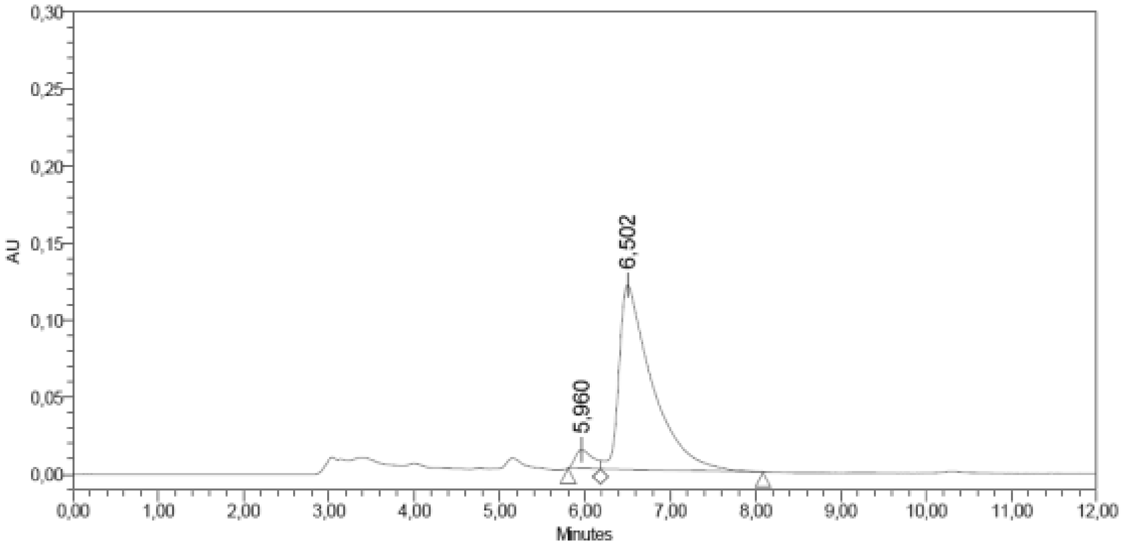


Figure SI-99. HPLC traces of compound **8b**





Peak Results

	RT	Area	Height	% Area
1	5,960	169687	11977	5,03
2	6,502	3201397	119566	94,97

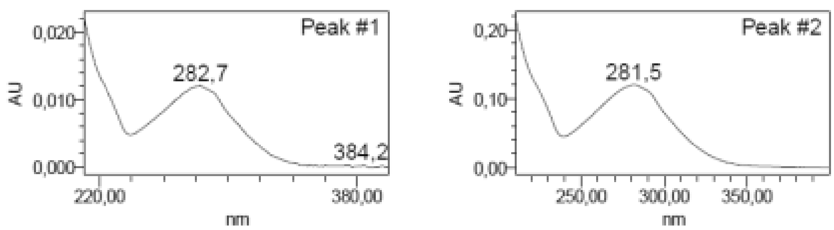
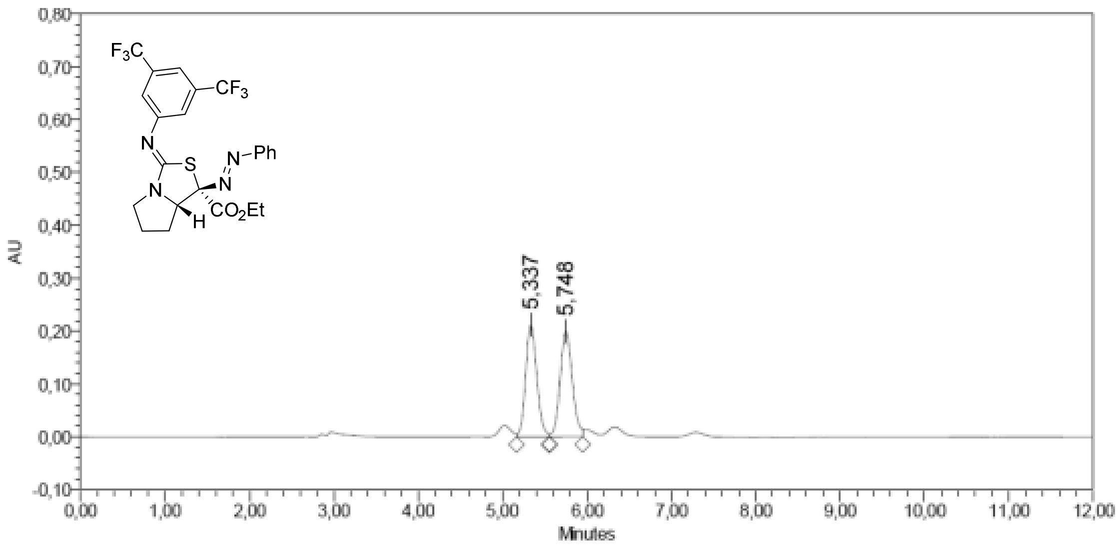
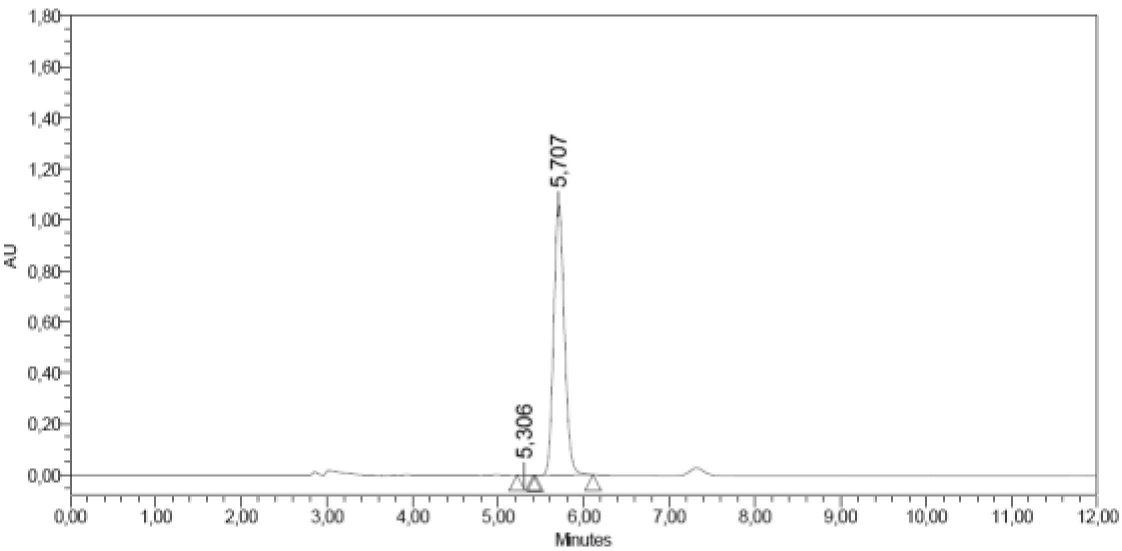


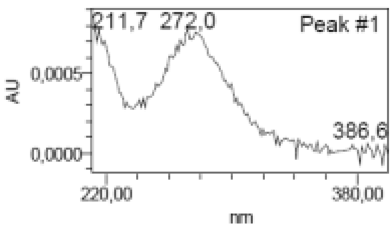
Figure SI-100. HPLC traces of compound **8c**





Peak Results

	RT	Area	Height	% Area
1	5,306	5131	842	0,06
2	5,707	9242299	1061838	99,94



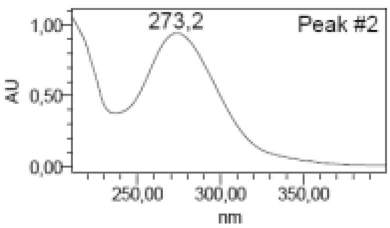
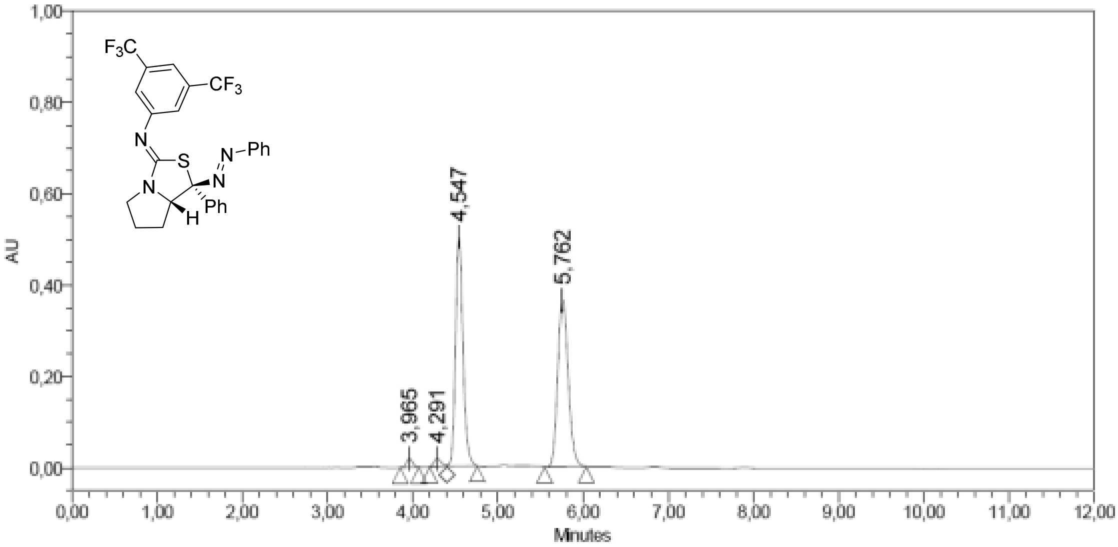
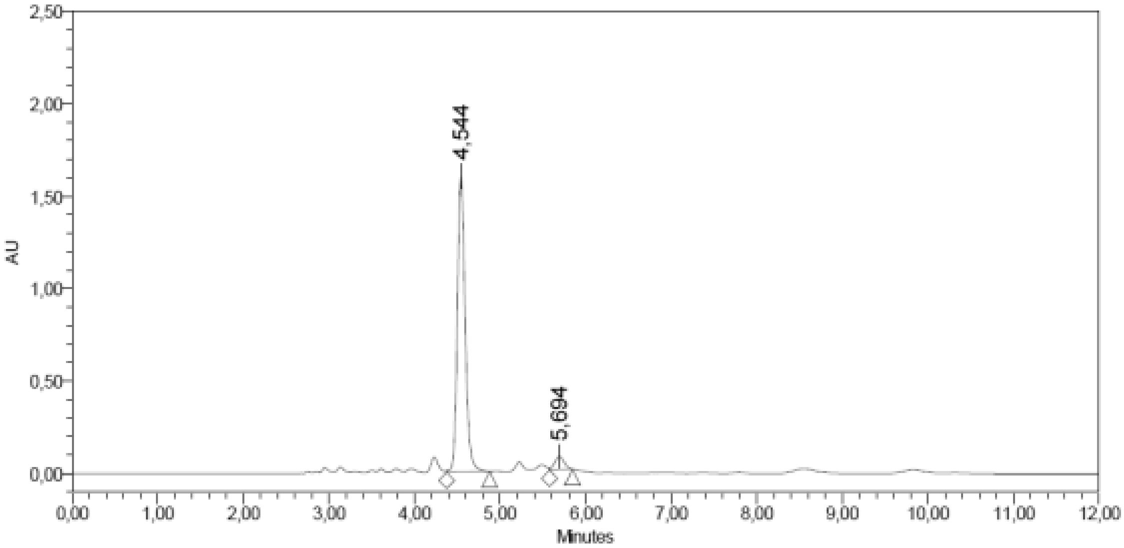


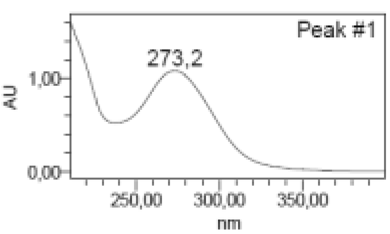
Figure SI-101. HPLC traces of compound **9a**





Peak Results

	RT	Area	Height	% Area
1	4,544	10123017	1605123	94,93
2	5,694	540965	71689	5,07



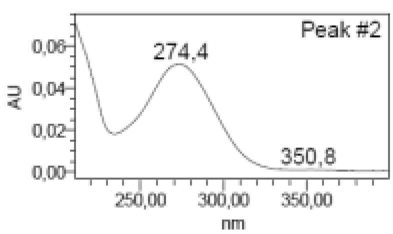
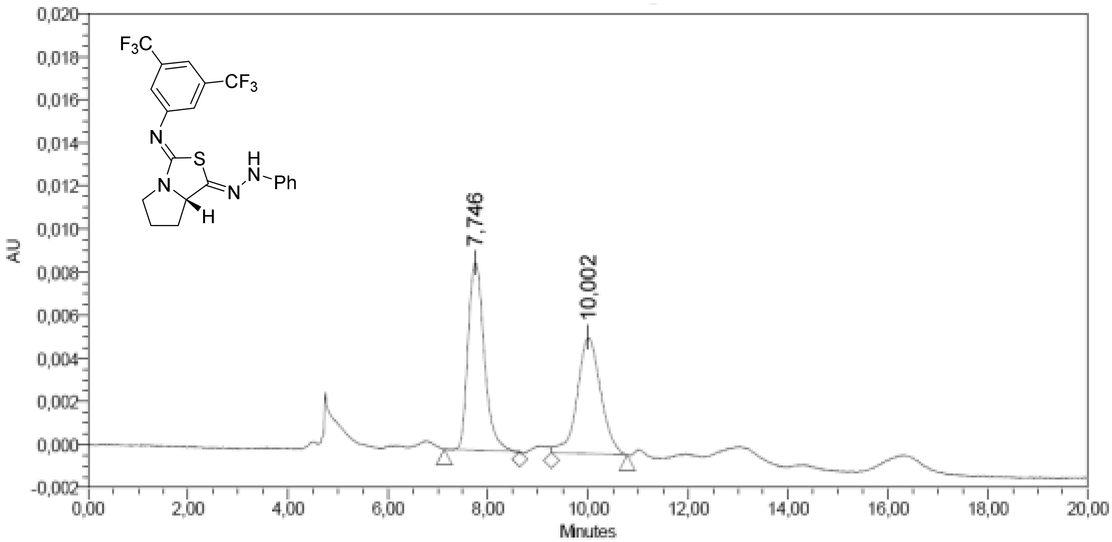
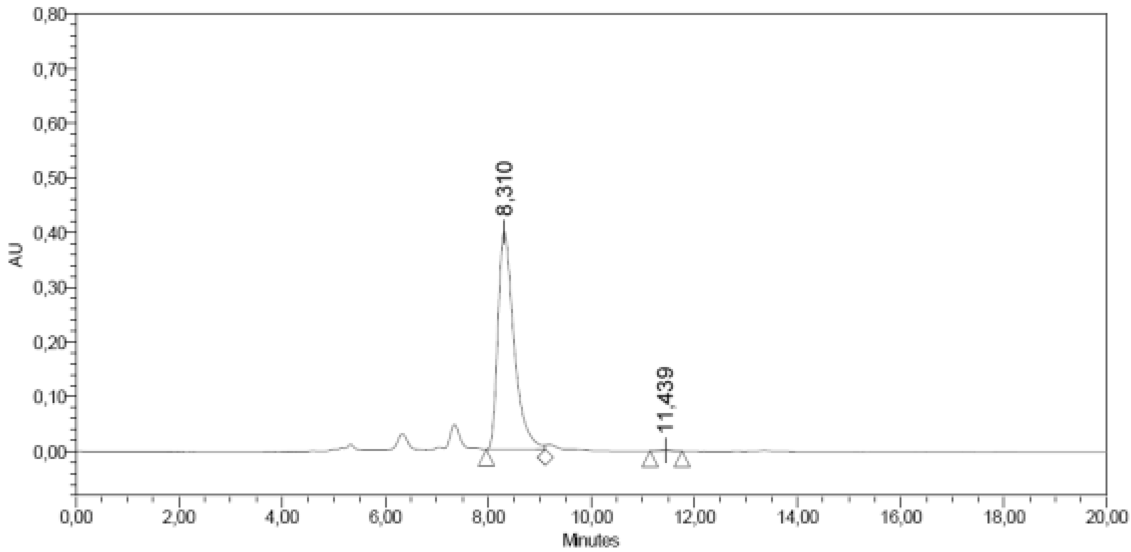


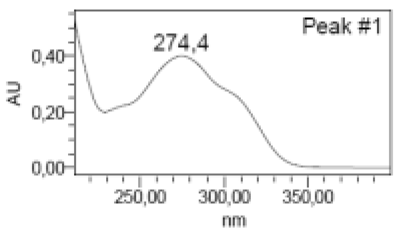
Figure SI-102. HPLC traces of compound **9b**





Peak Results

	RT	Area	Height	% Area
1	8,310	8650302	398324	99,73
2	11,439	23074	1116	0,27



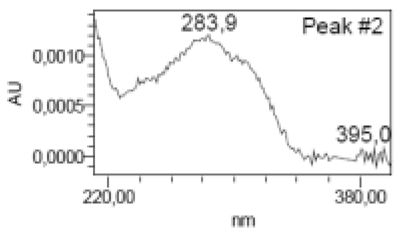
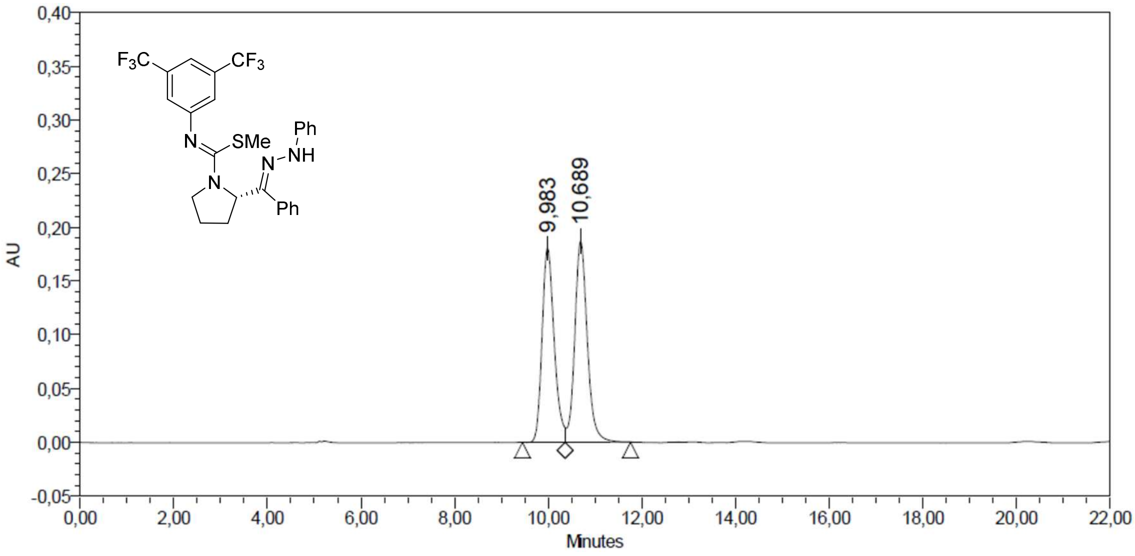
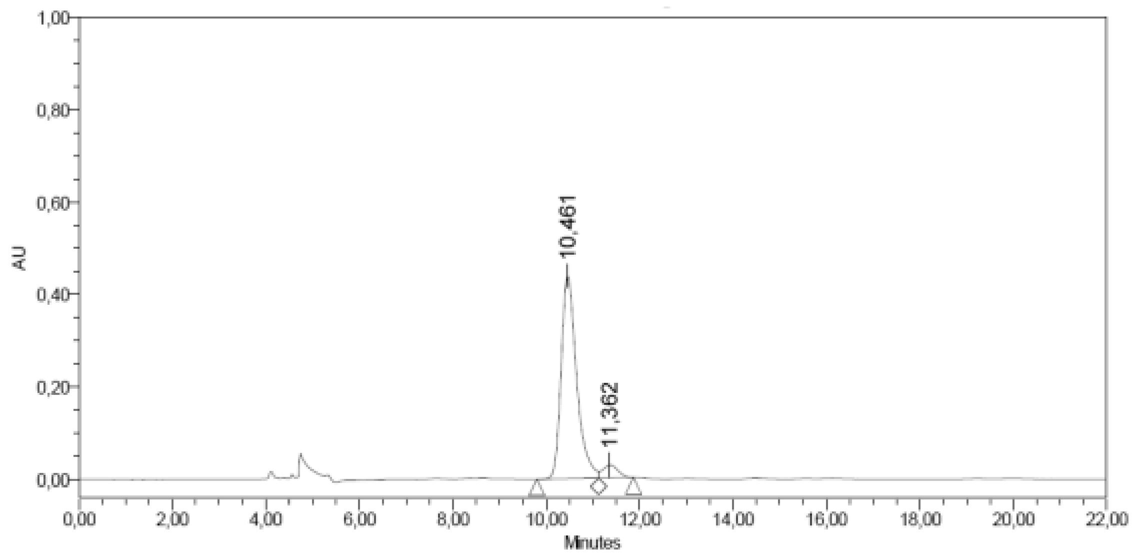


Figure SI-103. HPLC traces of compound **10**





Peak Results

	RT	Area	Height	% Area
1	10,461	10105834	438968	93,99
2	11,362	646645	28138	6,01

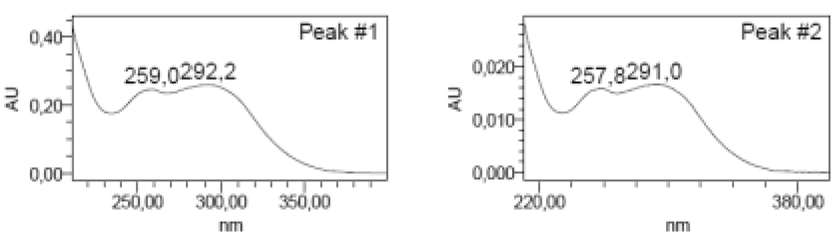
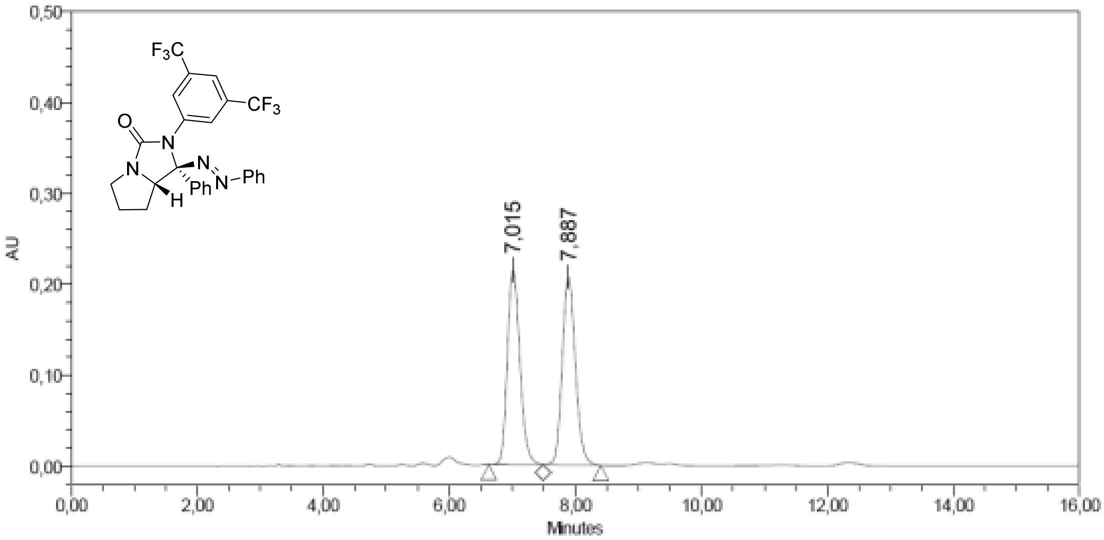
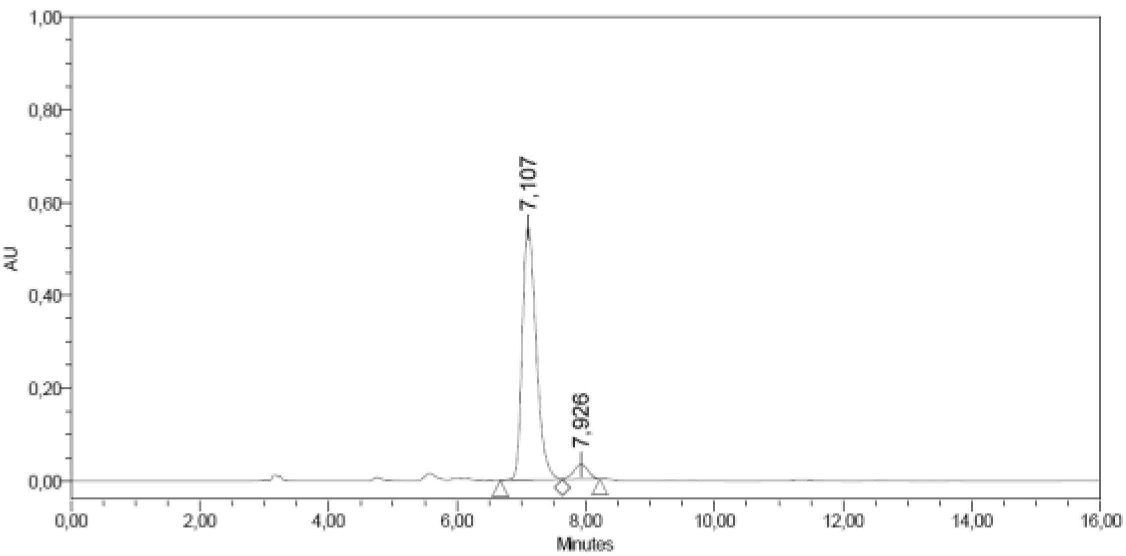


Figure SI-104. HPLC traces of compound **11**





Peak Results

	RT	Area	Height	% Area
1	7,107	8192095	545097	94,22
2	7,926	502868	32115	5,78

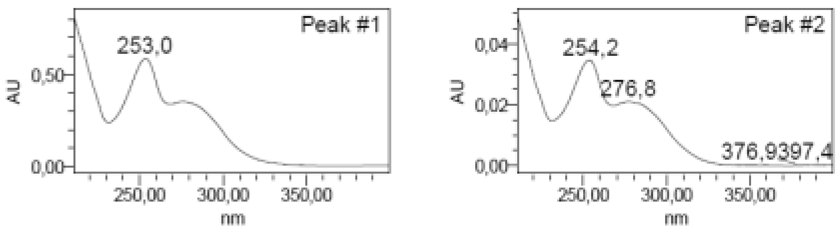


Figure SI-105. HPLC traces of compound **12**