

Supporting Information

Ni-catalyzed Reductive Liebeskind-Srogl Alkylation of Heterocycles

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1. General Information

Unless otherwise stated, all manipulations were performed using standard Schlenk techniques under dry argon. Flash chromatography: Merck silica gel 60 (40-63 μm). GC-MS (FID): GC-MS-QP2010 equipped (Shimadzu Europe Analytical Instruments). MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ 3000 (Bruker). Accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or MAT 95 (Finnigan). NMR spectra were recorded using a Bruker Avance VIII-300 or Bruker Avance III HD 400 MHz spectrometer. The ^1H NMR (400 MHz) chemical shifts were measured relative to tetramethylsilane as an internal standard (TMS: $\delta = 0$ ppm). The ^{13}C NMR (101 MHz) chemical shifts were given using CDCl_3 as the internal standard (CDCl_3 : $\delta = 77.16$ ppm). Anhydrous THF, toluene (Na/K) and DMPU (CaH_2) were distilled and were transferred under argon. Anhydrous Et_3N , DMF, DMSO, Dioxane and CH_3CN were taken from solvent purification system. Anhydrous NMP, DMAc, $\text{NiBr}_2 \cdot \text{diglyme}$, 1,1'-Ferrocenediyl-bis(diphenylphosphine) (dppf), zinc dust ($< 10 \mu\text{m}$) and K_2HPO_4 purchased from Millipore-Sigma and stored in an argon-filled glove box. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Most heterocyclic sulfides and alkyl bromides were purchased from TCI and Millipore-Sigma in Germany.

2. Preparation of Substrates

(A) Sequence of cyclization and methylation from corresponding anilines according to literature procedure¹:

6-Fluoro-2-(methylthio)benzo[*d*]thiazole, 2-(Methylthio)benzo[*d*]thiazole-6-carbonitrile, 6-Methyl-2-(methylthio)benzo[*d*]thiazole, Methyl 2-(methylthio)benzo[*d*]thiazole-6-carboxylate, 2-(Methylthio)-6-(thiophen-2-yl)benzo[*d*]thiazole, 6-(4-Methoxyphenyl)-2-(methylthio)benzo[*d*]thiazole, and 2-(Methylthio)-5-(trifluoromethyl)benzo[*d*]thiazole.

(B) Alkylation from corresponding thiols according to literature procedure or modified procedures:

5-Methoxy-2-(methylthio)benzo[*d*]thiazole,¹ 2-(Butylthio)benzo[*d*]thiazole,¹ 2-(Dodecylthio)benzo[*d*]thiazole,¹ 2-(Methylthio)pyrimidine²

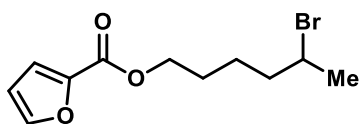
(C) Methylthiolation from corresponding chloride or bromide according to literature procedure^{3,4}:

2-(Methylthio)nicotinonitrile,³ 4-Methyl-2-(methylthio)quinolone,³ 1-(Methylthio)isoquinoline,³ 3-(Methylthio)-6-phenylpyridazine,³ 5-Methyl-2-(methylthio)pyridine⁴.

(D) Secondary alkyl bromides were prepared according to previous procedure⁵⁻¹⁰:

Benzyl 4-bromopiperidine-1-carboxylate,⁵ 4-Bromo-1-tosylpiperidine,⁶ 3-Bromobutyl benzoate,⁷ Methyl 5-bromohexanoate,⁸ ((5-Bromohexyl)oxy)(tert-butyl)dimethylsilane,⁹ 5-Bromo-1-phthalimidohexane,^{8,10}.

Synthesis and Characterization of compounds



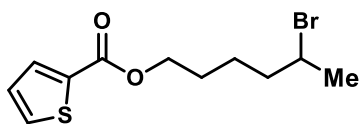
5-Bromohexyl furan-2-carboxylate, S1

Furan-2-carbonyl chloride (507 mg, 3.9 mmol) was added to a stirred solution of 5-bromohexan-1-ol⁸ (540 mg, 3.0 mmol) in pyridine (10 mL). The resulting mixture was stirred for 15 h, and then pyridine solvent was removed under reduced pressure. Water was added to mixture, and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic layers were over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography, furnishing the product **S1** as colorless oil (731 mg, 89%).

¹H NMR (400 MHz, CDCl₃): δ 1.51–1.69 (m, 2H), 1.72 (d, *J* = 6.4 Hz, 3H), 1.75–1.94 (m, 4H), 4.10–4.18 (m, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 6.51–6.52 (m, 1H), 7.18 (dd, *J* = 3.2 Hz, 0.8 Hz, 1H), 7.58–7.59 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 24.4, 26.6, 28.2, 40.7, 51.4, 64.7, 111.9, 117.9, 144.9, 146.4, 158.9.

HRMS (EI): calc'd for C₁₁H₁₅BrO₃⁺ [M]⁺ 274.019920; found 274.019760.



5-Bromohexyl thiophene-2-carboxylate, **S2**

Thiophene-2-carbonyl chloride (569.4 mg, 3.9 mmol) was added to a stirred solution of 5-bromohexan-1-ol⁸ (540 mg, 3.0 mmol) in pyridine (10 mL). The resulting mixture was stirred for 15 h, and then pyridine solvent was removed under reduced pressure. Water was added to mixture, and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic layers were over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography, furnishing the product **S2** as colorless oil (740 mg, 85%).

¹H NMR (400 MHz, CDCl₃): δ 1.52–1.91 (m, 9H), 4.10–4.19 (m, 1H), 4.31 (t, *J* = 6.8 Hz, 2H), 7.09–7.11 (m, 1H), 7.55 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 7.80 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 24.4, 26.6, 28.2, 40.7, 51.4, 65.0, 127.8, 132.4, 133.5, 134.0, 162.4.

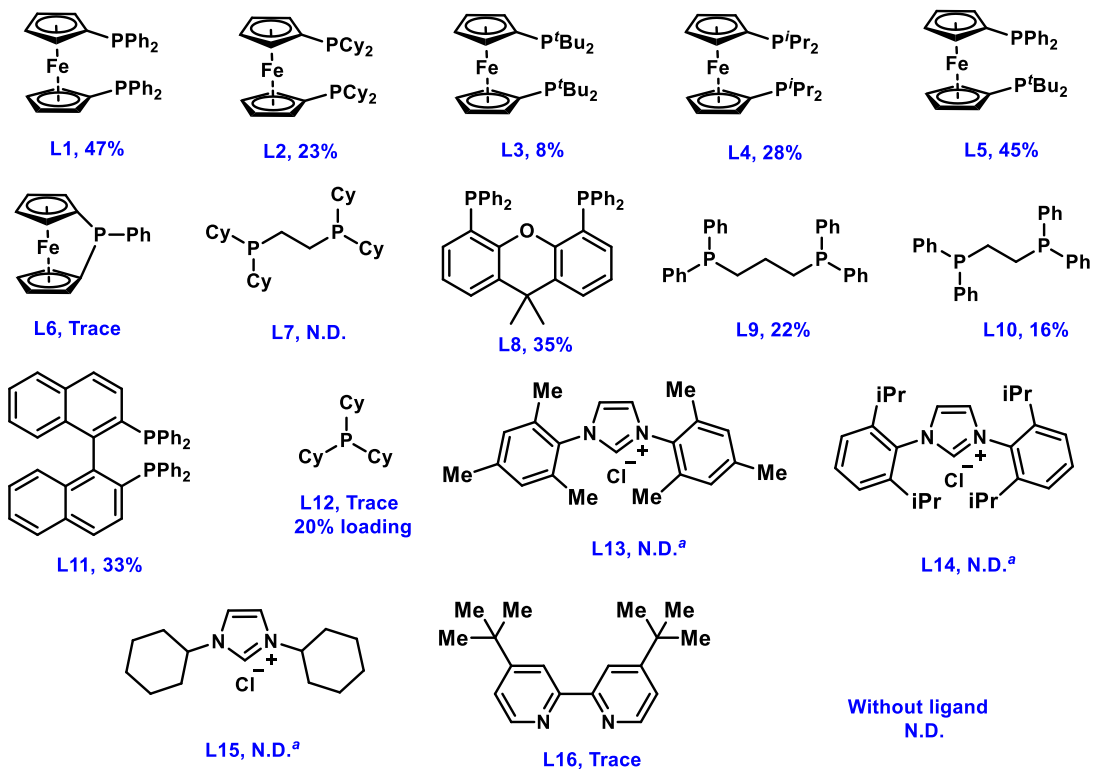
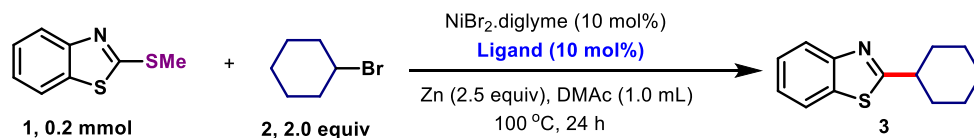
HRMS (EI): calc'd for C₁₁H₁₅BrO₂S⁺ [M]⁺ 289.997078; found 289.997060.

3. Optimization Studies

General Procedure for Optimization

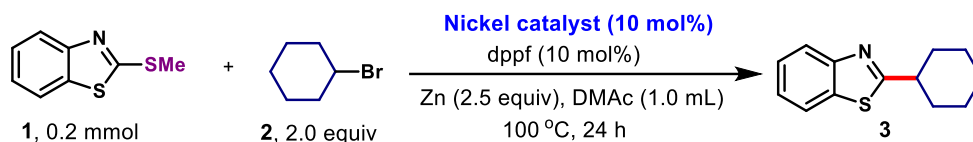
A dry reaction vial (10 mL) equipped with a stir bar was charged with 2-(methylthio)benzo[*d*]thiazole (**1**) (36.2 mg, 0.2 mmol), and then transferred to a glove box. Nickel catalyst (0.02 mmol), ligand (0.02 mmol), reductant (0.5 mmol) and corresponding additives (if required) were added. The vial was taken out of the glovebox and connected to a Schlenk line. Solvent (1.0 mL) and bromocyclohexane (50 μL, 0.4 mmol) were added to the vial via a microsyringe under an argon atmosphere. Finally, the vial was sealed and the resulting mixture was stirred at 100 °C for 24 h. After completion of the reaction, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~10 mL). The yield was confirmed by GC-FID using dodecane as an internal standard.

Ligand Screening



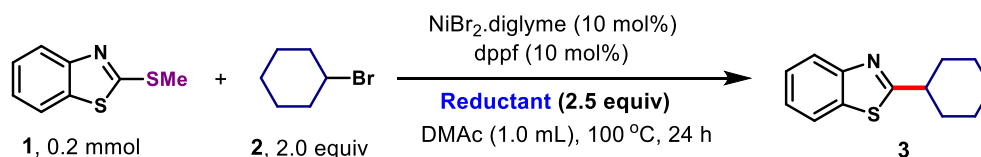
^a 20% ligand together with *N,N*-dimethylpyridin-4-amine (DMAP, 1.0 equiv, 0.2 mmol) was used.

Catalyst Screening



NiBr ₂ .diglyme	NiBr ₂ .glyme	NiCl ₂ .glyme	Ni(acac) ₂	Ni(COD) ₂	without catalyst
47%	37%	41%	27%	38%	0%

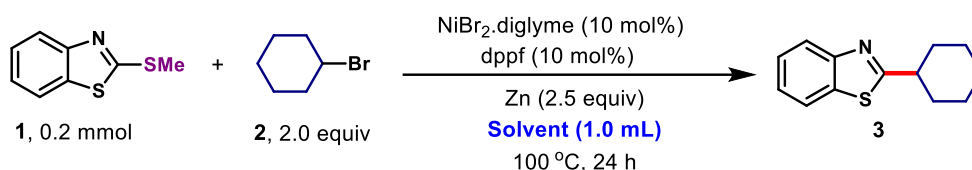
Reductant Screening



Zn, 47% **Mn, N.D.** **TDAE, N.D.** **Without reductant, N.D.**

TDAE = Tetrakis(dimethylamino)ethylene N.D. = Not detected

Solvent Screening

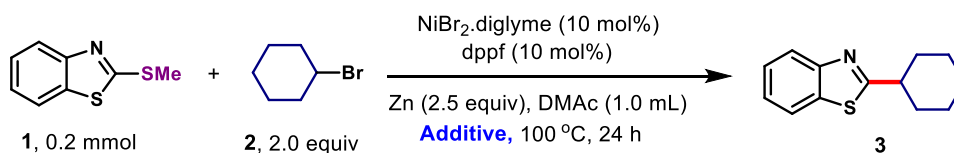


Toluene N.D.	Dioxane N.D.	THF, at 80 °C N.D.	CH₃CN, at 80 °C N.D.
DMSO 42%	DMF 40%	DMAc 47%	NMP 36%
			DMPU N.D.

DMSO = Dimethyl sulfoxide DMF = *N,N*-Dimethylformamide DMAc = *N,N*-Dimethylacetamide

NMP = 1-Methyl-2-pyrrolidinone DMPU = *N,N'*-dimethylpropylene urea N.D. = Not detected

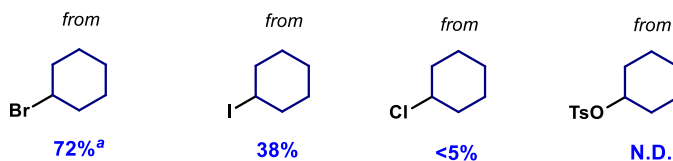
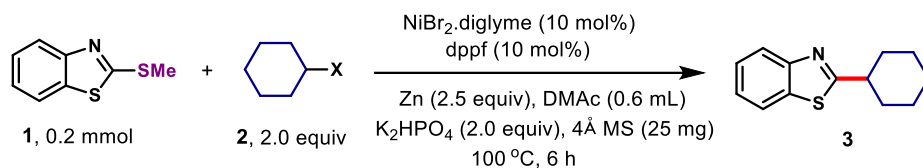
Additive Screening



NaI (1.0 equiv), 24%	Pyridine (1.0 equiv), 26%	CuTc (1.0 equiv), 11%	KF (1.0 equiv), 55%
K₃PO₄ (1.0 equiv), 44%	K₂HPO₄ (1.0 equiv), 60%	K₂HPO₄ (2.0 equiv), 65%	Na₂HPO₄ (2.0 equiv), N.D.
NaOAc (2.0 equiv), Trace	NaHCO₃ (2.0 equiv), <10%	KOAc (2.0 equiv), N.D.	K₂CO₃ (2.0 equiv), <10%
	KH₂PO₄ (2.0 equiv), 62%		K₂HPO₄ (2.0 equiv)+4Å MS (25 mg), 77%
	K₂HPO₄ (2.0 equiv)+4Å MS (25 mg) at 80 °C, 42%		K₂HPO₄ (2.0 equiv)+4Å MS (25 mg), 83%^a (72%)^b

^a DMAc (0.6 mL) was used and 6 h reaction time. ^b Isolated yield.

Evaluation of Alkyl Electrophiles



^aIsolated yield. N.D. = Not detected

4. General Procedure for Reductive Cross-Coupling

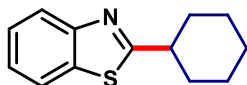
A dry 10 mL-reaction vial equipped with a round-edged stir bar (7 mm × 0.5 mm) was charged with heterocyclic sulfides (0.2 mmol) and alkyl bromides (if solid) (0.4 or 0.6 mmol), and then transferred to an argon-filled glove box. NiBr₂·diglyme (7.0 mg, 10 mol%), dppf (11.0 mg, 10 mol%), activated Zn dust (32.6 mg, 0.5 mmol), K₂HPO₄ (69 mg, 2.0 equiv), 4Å MS (25 mg) and DMAc (0.6 mL) were added successively. The vial was sealed and taken out of the glovebox. The alkyl bromide (if liquid) was added under Ar with a microsyringe. The resulting mixture was stirred (average speed= 600 rpm) at 100 °C (temperature of oil bath) for 6 h. After this time, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~10 mL) and filtered through a sintered funnel with a thin layer of celite, and the filtrate was evaporated to dryness. The crude mixture was then purified by column chromatography on silica gel (Hexane/EtOAc, Pentane/Et₂O, or Hexane/DCM, 1% Et₃N was added to eluent) to afford the desired coupled product. Importantly, at the beginning of isolation, hexane or pentane (50-100 mL) was used as eluent to remove high boiling-point DMAc on the column.

Note: In the case of products 13-19, zinc dust (< 10 μm, from Millipore-Sigma) was used directly.

Zinc activation with acid according to Weix's method.¹¹ Zinc dust (10 g) was washed with 2% aqueous HCl (25 mL) for 1 min in a 50 mL beaker. It is important that the zinc not to be exposed to the acidic solution for more than ~1 min under argon. The zinc was collected by vacuum filtration and washed with water (3 ×20 mL), ethanol

(20 mL), and ether (20 mL). The zinc was dried under high vacuum for 4 h at 150 °C and then it was stored in the argon-filled glove box.

5. Characterization Data

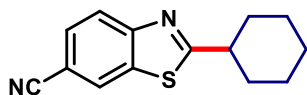


2-Cyclohexylbenzo[d]thiazole¹², **3**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **3** as colorless oil (31.3 mg, 0.144 mmol, 72% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.29–1.50 (m, 3H), 1.59–1.70 (m, 2H), 1.74–1.79 (m, 1H), 1.86–1.91 (m, 2H), 2.18–2.23 (m, 2H), 3.07–3.14 (m, 1H), 7.31–7.35 (m, 1H), 7.42–7.46 (m, 1H), 7.83–7.86 (m, 1H), 7.96–7.98 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.2, 33.6, 43.6, 121.7, 122.7, 124.6, 125.9, 134.7, 153.2, 177.7.



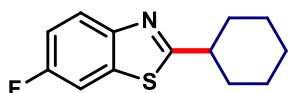
2-Cyclohexylbenzo[d]thiazole-6-carbonitrile, **4**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **4** as colorless oil (29.3 mg, 0.121 mmol, 61% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.22–1.31 (m, 1H), 1.34–1.45 (m, 2H), 1.53–1.63 (m, 2H), 1.69–1.74 (m, 1H), 1.81–1.86 (m, 2H), 2.13–2.17 (m, 2H), 3.04–3.11 (m, 1H), 7.63 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.96 (dd, *J* = 8.8 Hz, 0.8 Hz, 1H), 8.12 (dd, *J* = 1.6 Hz, 0.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.8, 26.1, 33.4, 43.8, 108.2, 119.0, 123.5, 126.5, 129.3, 135.3, 155.8, 182.4.

HRMS (ESI): calc'd for C₁₄H₁₅N₂S⁺ [M+H]⁺ 243.095045; found 243.095020.



2-Cyclohexyl-6-fluorobenzo[d]thiazole, **5**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **5** as a pale solid (41.2 mg, 0.175 mmol, 88% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.22–1.29 (m, 1H), 1.32–1.43 (m, 2H), 1.50–1.60 (m, 2H), 1.67–1.72 (m, 1H), 1.79–1.84 (m, 2H), 2.10–2.15 (m, 2H), 2.97–3.05 (m, 1H), 7.10 (td, *J* = 8.8 Hz, 2.8 Hz, 1H), 7.45 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.81–7.84 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.2, 33.5, 43.5, 107.9 (d, *J* = 26.7 Hz, 1C), 114.5 (d, *J* = 24.7 Hz, 1C), 123.5 (d, *J* = 9.3 Hz, 1C), 135.6 (d, *J* = 11.1 Hz, 1C), 149.8, 160.2 (d, *J* = 245.3 Hz, 1C), 177.4 (d, *J* = 3.2 Hz, 1C).

¹⁹F NMR (282 MHz, CDCl₃): δ -117.2 (1F).

HRMS (ESI): calc'd for C₁₃H₁₅FNS⁺ [M+H]⁺ 236.090375; found 236.090350.

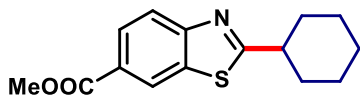


2-Cyclohexyl-6-methylbenzo[d]thiazole¹³, **6**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **6** as yellow oil (28.5 mg, 0.123 mmol, 62% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.18–1.42 (m, 3H), 1.50–1.60 (m, 2H), 1.66–1.71 (m, 1H), 1.78–1.83 (m, 2H), 2.09–2.14 (m, 2H), 2.39 (s, 3H), 2.97–3.04 (m, 1H), 7.16–7.19 (m, 1H), 7.55–7.56 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 21.6, 25.9, 26.2, 33.6, 43.5, 121.4, 122.1, 127.5, 134.6, 134.8, 151.3, 176.7.



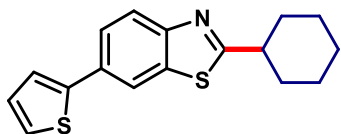
Methyl 2-cyclohexylbenzo[d]thiazole-6-carboxylate, **7**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **7** as a yellow solid (38.3 mg, 0.140 mmol, 70% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.20–1.31 (m, 1H), 1.33–1.44 (m, 2H), 1.53–1.63 (m, 2H), 1.68–1.73 (m, 1H), 1.80–1.85 (m, 2H), 2.12–2.17 (m, 2H), 3.02–3.10 (m, 1H), 3.88 (s, 3H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.05 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 8.50 (dd, *J* = 2.0 Hz, 0.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.1, 33.5, 43.8, 52.4, 122.4, 124.0, 126.5, 127.2, 134.7, 156.2, 166.9, 181.6.

HRMS (ESI): calc'd for C₁₅H₁₈NO₂S⁺ [M+H]⁺ 276.105276; found 276.105340.



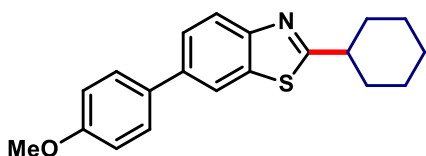
2-Cyclohexyl-6-(thiophen-2-yl)benzo[d]thiazole, **8**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **8** as a pale solid (33.4 mg, 0.112 mmol, 56% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.23–1.43 (m, 3H), 1.53–1.63 (m, 2H), 1.67–1.72 (m, 1H), 1.81–1.85 (m, 2H), 2.12–2.16 (m, 2H), 2.99–3.07 (m, 1H), 7.01–7.03 (m, 1H), 7.22 (dd, *J* = 4.8 Hz, 0.8 Hz, 1H), 7.27 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.63 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.88 (dd, *J* = 8.8 Hz, 0.8 Hz, 1H), 7.99 (dd, *J* = 2.0 Hz, 0.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.2, 33.5, 43.6, 118.7, 122.8, 123.6, 124.6, 125.2, 128.3, 131.3, 135.6, 144.1, 152.6, 178.1 .

HRMS (EI): calc'd for C₁₇H₁₇NS₂⁺ [M]⁺ 299.079694; found 299.079700.



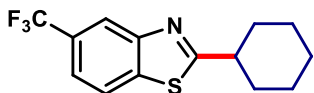
2-Cyclohexyl-6-(4-methoxyphenyl)benzo[d]thiazole, **9**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 10/1, v/v) afforded **9** as a light yellow solid (38.7 mg, 0.120 mmol, 60% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.21–1.42 (m, 3H), 1.52–1.62 (m, 2H), 1.66–1.71 (m, 1H), 1.78–1.83 (m, 2H), 2.11–2.15 (m, 2H), 2.99–3.06 (m, 1H), 3.77 (s, 3H), 6.89–6.92 (m, 2H), 7.45–7.49 (m, 2H), 7.54 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.89–7.92 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.2, 33.5, 43.6, 55.5, 114.4, 119.4, 122.6, 125.3, 128.5, 133.4, 135.4, 137.8, 152.1, 159.3, 177.6.

HRMS (EI): calc'd for C₂₀H₂₁NOS⁺ [M]⁺ 323.133836; found 323.133800.



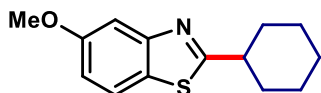
2-Cyclohexyl-5-(trifluoromethyl)benzo[d]thiazole¹⁴, **10**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **10** as yellow oil (37.5 mg, 0.132 mmol, 66% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.30–1.52 (m, 3H), 1.60–1.70 (m, 2H), 1.76–1.80 (m, 1H), 1.88–1.93 (m, 2H), 2.19–2.23 (m, 2H), 3.09–3.17 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 8.24 (s, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.1, 33.5, 43.6, 119.9 (q, *J* = 4.1 Hz, 1C), 121.1 (q, *J* = 3.6 Hz, 1C), 122.3, 124.4 (d, *J* = 273.1 Hz, 1C), 128.6 (q, *J* = 32.7 Hz, 1C), 138.3, 152.9, 179.9.

¹⁹F NMR (282 MHz, CDCl₃): δ -61.7.



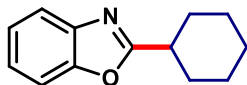
2-Cyclohexyl-5-methoxybenzo[*d*]thiazole, **11**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **11** as yellow oil (32.2 mg, 0.130 mmol, 65% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.27–1.50 (m, 3H), 1.58–1.68 (m, 2H), 1.73–1.79 (m, 1H), 1.86–1.91 (m, 2H), 2.17–2.22 (m, 2H), 3.03–3.11 (m, 1H), 3.87 (s, 3H), 6.98 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.2, 33.5, 43.6, 55.7, 105.3, 114.7, 121.9, 126.4, 154.5, 158.9, 179.1 .

HRMS (EI): calc'd for C₁₄H₁₇NOS⁺ [*M*]⁺ 247.102536; found 247.102660.

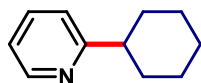


2-Cyclohexylbenzo[*d*]oxazole¹³, **12**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **12** as colorless oil (25.2 mg, 0.125 mmol, 63% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.30–1.49 (m, 3H), 1.66–1.79 (m, 3H), 1.84–1.89 (m, 2H), 2.15–2.20 (m, 2H), 2.92–2.99 (m, 1H), 7.26–7.31 (m, 2H), 7.45–7.49 (m, 1H), 7.66–7.70 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.8, 25.9, 30.6, 38.1, 110.4, 119.7, 124.1, 124.4, 141.4, 150.7, 170.5.

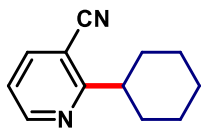


2-Cyclohexylpyridine¹⁵, **13**

Following the general procedure, bromocyclohexane (3.0 equiv) was used. Purification via column chromatography on silica gel (Pentane/Et₂O = 2/1, v/v) afforded **13** as colorless oil (19.2 mg, 0.119 mmol, 60% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.17–1.50 (m, 5H), 1.64–1.69 (m, 1H), 1.75–1.80 (m, 2H), 1.84–1.89 (m, 2H), 2.57–2.65 (m, 1H), 6.97–7.01 (m, 1H), 7.05 (dt, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.50 (td, *J* = 7.6 Hz, 2.0 Hz, 1H), 8.43–8.45 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 26.1, 26.7, 33.0, 46.6, 121.0, 136.4, 149.1, 166.5. (1 C is not observable)



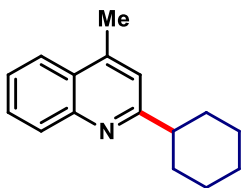
2-Cyclohexylnicotinonitrile, **14**

Following the general procedure, bromocyclohexane (3.0 equiv) was used. Purification via column chromatography on silica gel (Pentane/Et₂O = 8/1, v/v) afforded **14** as colorless oil (17.2 mg, 0.0923 mmol, 46% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.27–1.37 (m, 1H), 1.41–1.52 (m, 2H), 1.65–1.81 (m, 3H), 1.86–1.90 (m, 4H), 3.13–3.19 (m, 1H), 7.21–7.24 (m, 1H), 7.89 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 8.73 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.4, 32.1, 44.9, 108.3, 117.1, 120.9, 140.6, 152.6, 169.3.

HRMS (ESI): calc'd for C₁₂H₁₅N₂⁺ [M+H]⁺ 187.122972; found 187.122960.

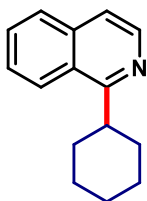


2-Cyclohexyl-4-methylquinoline¹⁶, **15**

Following the general procedure, bromocyclohexane (3.0 equiv) was used. Purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **15** as yellow oil (21.5 mg, 0.0956 mmol, 48% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.31–1.52 (m, 3H), 1.57–1.68 (m, 2H), 1.76–1.81 (m, 1H), 1.87–1.92 (m, 2H), 1.99–2.03 (m, 2H), 2.68 (d, *J* = 0.8 Hz, 3H), 2.83–2.91 (m, 1H), 7.16 (d, *J* = 1.2 Hz, 1H), 7.47–7.51 (m, 1H), 7.64–7.68 (m, 1H), 7.93–7.95 (m, 1H), 8.03–8.06 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 19.0, 26.3, 26.7, 33.0, 47.8, 120.4, 123.7, 125.5, 127.2, 129.1, 129.6, 144.4, 147.8, 166.7.

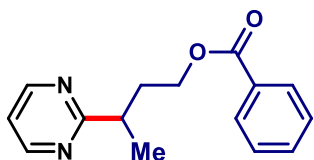


1-Cyclohexylisoquinoline¹⁷, **16**

Following the general procedure, bromocyclohexane (3.0 equiv) was used. Purification via column chromatography on silica gel (Hexane/EtOAc = 10/1, v/v) afforded **16** as colorless oil (18.9 mg, 0.0896 mmol, 45% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.30–1.37 (m, 1H), 1.41–1.51 (m, 2H), 1.72–1.81 (m, 3H), 1.84–1.94 (m, 4H), 3.45–3.53 (m, 1H), 7.41 (d, *J* = 5.6 Hz, 1H), 7.49–7.53 (m, 1H), 7.56–7.60 (m, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 5.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 26.4, 27.0, 32.7, 41.7, 119.0, 124.9, 126.4, 126.9, 127.7, 129.7, 136.5, 142.0, 165.8.



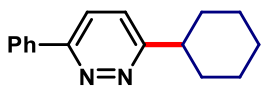
3-(Pyrimidin-2-yl)butyl benzoate, **17**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 2/1, v/v) afforded **17** as colorless oil (24.2 mg, 0.094 mmol, 47% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.41 (d, *J* = 6.8 Hz, 3H), 2.08–2.16 (m, 1H), 2.38–2.47 (m, 1H), 3.29–3.36 (m, 1H), 4.28–4.39 (m, 2H), 7.10 (t, *J* = 4.8 Hz, 1H), 7.39–7.43 (m, 2H), 7.51–7.56 (m, 1H), 7.95–7.97 (m, 2H), 8.67 (d, *J* = 4.8 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 20.5, 34.7, 40.4, 63.5, 118.8, 128.4, 129.7, 130.5, 132.9, 157.2, 174.2. (1 C is not observable)

HRMS (ESI): calc'd for C₁₅H₁₆N₂NaO⁺ [M+Na]⁺ 279.110396; found 279.110610.

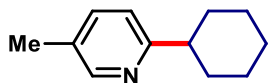


3-Cyclohexyl-6-phenylpyridazine¹⁸, **18**

Following the general procedure, bromocyclohexane (3.0 equiv) was used and the reaction was performed at 50 °C for 24 h. Purification via column chromatography on silica gel (Hexane/EtOAc = 8/1, v/v) afforded **18** as a light yellow solid (25.3 mg, 0.106 mmol, 53% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.30–1.38 (m, 1H), 1.42–1.54 (m, 2H), 1.59–1.69 (m, 2H), 1.78–1.83 (m, 1H), 1.89–1.94 (m, 2H), 2.03–2.07 (m, 2H), 2.97–3.05 (m, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.47–7.54 (m, 3H), 7.79 (d, *J* = 8.8 Hz, 1H), 8.07–8.10 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 26.1, 26.6, 32.8, 44.6, 124.2, 125.4, 127.0, 129.1, 129.8, 136.7, 157.5, 166.2.

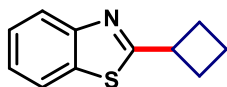


2-Cyclohexyl-5-methylpyridine¹⁷, **19**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 2/1, v/v) afforded **19** as colorless oil (18.3 mg, 0.104 mmol, 52% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.25–1.55 (m, 5H), 1.71–1.77 (m, 1H), 1.82–1.87 (m, 2H), 1.91–1.95 (m, 2H), 2.28 (s, 3H), 2.62–2.70 (m, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.39–7.41 (m, 1H), 8.35–8.36 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 18.1, 26.2, 26.8, 33.1, 46.2, 120.5, 130.2, 137.1, 149.5, 163.7.

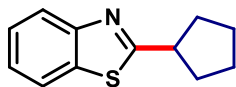


2-Cyclobutylbenzo[d]thiazole¹⁹, **20**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **20** as yellow oil (25.6 mg, 0.135 mmol, 68% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.91–2.13 (m, 2H), 2.39–2.49 (m, 4H), 3.86–3.95 (m, 1H), 7.25–7.29 (m, 1H), 7.36–7.40 (m, 1H), 7.77–7.79 (m, 1H), 7.90–7.93 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 18.7, 29.8, 39.1, 121.7, 122.7, 124.8, 126.1, 135.0, 153.4, 176.3.

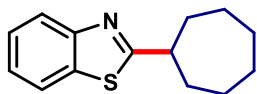


2-Cyclopentylbenzo[d]thiazole¹², **21**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **21** as yellow oil (29.6 mg, 0.146 mmol, 73% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.72–1.77 (m, 2H), 1.84–2.00 (m, 4H), 2.22–2.30 (m, 2H), 3.52–3.60 (m, 1H), 7.31–7.35 (m, 1H), 7.42–7.46 (m, 1H), 7.82–7.85 (m, 1H), 7.95–7.98 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 25.7, 34.2, 44.9, 121.6, 122.6, 124.7, 126.0, 134.9, 153.3, 177.3.

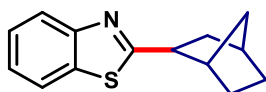


2-Cycloheptylbenzo[*d*]thiazole¹³, **22**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **22** as yellow oil (27.5 mg, 0.119 mmol, 60% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.52–1.65 (m, 6H), 1.75–1.86 (m, 4H), 2.13–2.19 (m, 2H), 3.20–3.27 (m, 1H), 7.24–7.28 (m, 1H), 7.35–7.39 (m, 1H), 7.76–7.78 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 26.7, 28.2, 35.5, 45.6, 121.7, 122.6, 124.7, 126.0, 134.8, 153.0, 178.9.



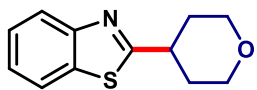
2-((*1S,4R*)-Bicyclo[2.2.1]heptan-2-yl)benzo[*d*]thiazole, **23**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **23** as a pale solid (39.5 mg, 0.172 mmol, 86% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.26–1.35 (m, 2H), 1.42–1.48 (m, 1H), 1.58–1.71 (m, 3H), 1.86–1.92 (m, 1H), 2.10–2.16 (m, 1H), 2.43–2.45 (m, 1H), 2.63–2.64 (m, 1H), 7.31–7.35 (m, 1H), 7.41–7.46 (m, 1H), 7.82–7.84 (m, 1H), 7.95–7.98 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 28.9, 29.9, 36.6, 36.7, 38.4, 44.5, 47.3, 121.6, 122.7, 124.6, 126.0, 135.0, 153.2, 177.9.

HRMS (EI): calc'd for C₁₄H₁₅NS⁺ [*M*]⁺ 229.091971; found 229.092180.



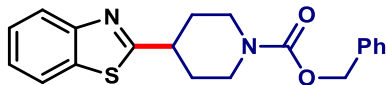
2-(Tetrahydro-2*H*-pyran-4-yl)benzo[*d*]thiazole, **24**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **24** as a light yellow solid (30.8 mg, 0.140 mmol, 70% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.90–2.07 (m, 4H), 3.25–3.33 (m, 1H), 3.51 (td, *J* = 11.6 Hz, 2.4 Hz, 2H), 4.01–4.05 (m, 2H), 7.27–7.31 (m, 1H), 7.37–7.41 (m, 1H), 7.78–7.80 (m, 1H), 7.90–7.93 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 33.0, 40.6, 67.6, 121.8, 122.8, 125.0, 126.2, 134.6, 153.1, 175.5.

HRMS (EI): calc'd for C₁₂H₁₃NOS⁺ [M]⁺ 219.071236; found 219.071240.



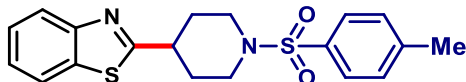
Benzyl 4-(benzo[*d*]thiazol-2-yl)piperidine-1-carboxylate, **25**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 2/1, v/v) afforded **25** as a yellow solid (40.7 mg, 0.116 mmol, 58% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.72–1.85 (m, 2H), 2.08–2.12 (m, 2H), 2.90–2.96 (m, 2H), 3.16–3.24 (m, 1H), 4.23 (br, 2H), 5.08 (s, 2H), 7.24–7.30 (m, 6H), 7.36–7.40 (m, 1H), 7.76–7.79 (m, 1H), 7.88–7.91 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 32.1, 41.4, 43.9, 67.3, 121.7, 122.8, 125.0, 126.2, 128.0, 128.1, 128.6, 134.6, 136.8, 153.1, 155.3, 174.9.

HRMS (ESI): calc'd for C₂₀H₂₀NNaO₂S⁺ [M+Na]⁺ 375.113769; found 375.113760.



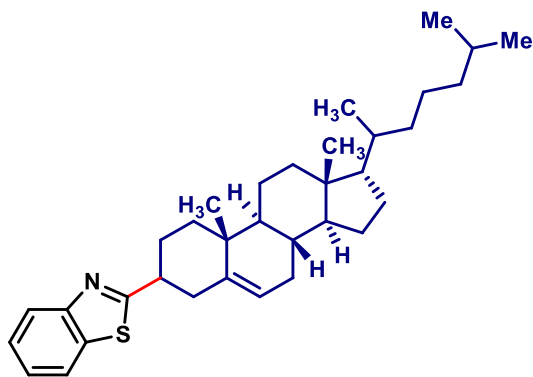
2-(1-Tosylpiperidin-4-yl)benzo[*d*]thiazole, **26**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 3/1, v/v) afforded **26** as a light yellow solid (56.3 mg, 0.152 mmol, 76% yield).

¹H NMR (400 MHz, CDCl₃): δ 2.00–2.09 (m, 2H), 2.21–2.27 (m, 2H), 2.44 (s, 3H), 2.50 (td, *J* = 12.0 Hz, 2.8 Hz, 2H), 3.01–3.08 (m, 1H), 3.86–3.90 (m, 2H), 7.27–7.37 (m, 3H), 7.43–7.47 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 21.7, 31.6, 40.5, 46.0, 121.7, 122.8, 125.1, 126.2, 127.8, 129.8, 133.3, 134.6, 143.8, 153.0, 174.2.

HRMS (ESI): calc'd for C₁₉H₂₀N₂NaO₂S₂⁺ [M+Na]⁺ 395.085842; found 395.086080.



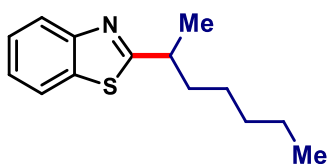
2-((8S,9S,10R,13R,14S,17S)-10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)benzo[*d*]thiazole, 27

Following the general procedure, purification via column chromatography on silica gel (Hexane/CH₂Cl₂ = 1/1, v/v) afforded **27** as a light yellow solid (51.2 mg, 0.102 mmol, 51% yield).

¹H NMR (400 MHz, CDCl₃): δ 0.63 (s, 3H), 0.79–0.81 (m, 6H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.96–1.09 (m, 10H), 1.16–1.33 (m, 6H), 1.41–1.56 (m, 7H), 1.73–1.88 (m, 2H), 1.90–1.99 (m, 3H), 2.02–2.07 (m, 1H), 2.43–2.48 (m, 1H), 2.54–2.62 (m, 1H), 2.98–3.06 (m, 1H), 5.37–5.38 (m, 1H), 7.25–7.29 (m, 1H), 7.36–7.40 (m, 1H), 7.77–7.80 (m, 1H), 7.92 (d, *J* = 8.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 12.0, 18.9, 19.6, 21.1, 22.7, 23.0, 24.0, 24.5, 28.2, 28.4, 29.7, 32.0, 32.1, 36.0, 36.4, 37.2, 39.3, 39.4, 39.7, 39.9, 42.5, 44.9, 50.4, 56.3, 56.9, 121.6, 121.7, 122.7, 124.7, 126.0, 134.6, 141.3, 153.2, 177.0.

HRMS (ESI): calc'd for C₃₄H₅₀NS⁺ [M+H]⁺ 504.365846; found 504.365726.

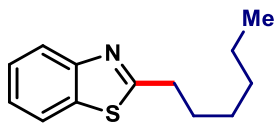


2-(Heptan-2-yl)benzo[*d*]thiazole²⁰, 28

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **28** as yellow oil (35.3 mg, 0.151 mmol, 76% yield).

¹H NMR (400 MHz, CDCl₃): δ 0.77–0.81 (m, 3H), 1.21–1.24 (m, 6H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.61–1.68 (m, 1H), 1.76–1.84 (m, 1H), 3.18–3.26 (m, 1H), 7.25–7.29 (m, 1H), 7.36–7.40 (m, 1H), 7.77–7.79 (m, 1H), 7.90–7.92 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 14.2, 21.4, 22.7, 27.2, 31.9, 37.8, 39.7, 121.7, 122.7, 124.7, 126.0, 134.8, 153.1, 178.4.

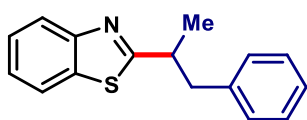


2-(Heptan-2-yl)benzo[*d*]thiazole²¹, **29**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **29** as yellow oil (15.3 mg, 0.070 mmol, 35% yield).

¹H NMR (400 MHz, CDCl₃): δ 0.87–0.91 (m, 3H), 1.31–1.37 (m, 4H), 1.41–1.47 (m, 2H), 1.84–1.92 (m, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 7.32–7.36 (m, 1H), 7.43–7.47 (m, 1H), 7.83–7.85 (m, 1H), 7.96–7.98 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 14.2, 22.6, 29.0, 29.8, 31.6, 34.5, 121.6, 122.6, 124.7, 126.0, 135.3, 153.4, 172.6.



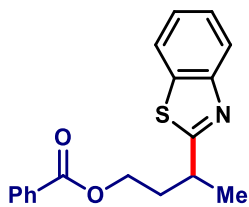
2-(1-Phenylpropan-2-yl)benzo[*d*]thiazole, **30**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **30** as light yellow oil (25.1 mg, 0.0992 mmol, 50% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.43 (d, *J* = 6.8 Hz, 3H), 2.92–2.97 (m, 1H), 3.30–3.35 (m, 1H), 3.54–3.63 (m, 1H), 7.18–7.22 (m, 3H), 7.25–7.29 (m, 2H), 7.33–7.37 (m, 1H), 7.44–7.48 (m, 1H), 7.83–7.85 (m, 1H), 7.98–8.01 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 20.5, 41.2, 43.6, 121.7, 122.8, 124.8, 126.0, 126.5, 128.5, 129.3, 134.8, 139.4, 153.3, 177.0.

HRMS (EI): calc'd for C₁₆H₁₅NS⁺ [M]⁺ 253.091972; found 253.092250.



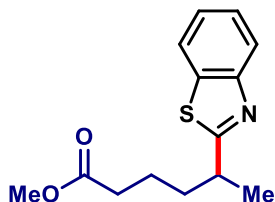
3-(Benzo[*d*]thiazol-2-yl)butyl benzoate, **31**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 12/1, v/v) afforded **31** as light yellow oil (35.1 mg, 0.112 mmol, 56% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.55 (d, *J* = 6.8 Hz, 3H), 2.18–2.27 (m, 1H), 2.41–2.49 (m, 1H), 3.50–3.59 (m, 1H), 4.38–4.49 (m, 2H), 7.33–7.38 (m, 3H), 7.43–7.47 (m, 1H), 7.49–7.54 (m, 1H), 7.82–7.85 (m, 1H), 7.92–7.99 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 21.5, 36.1, 36.7, 62.9, 121.7, 122.9, 124.9, 126.1, 128.4, 129.6, 130.2, 133.0, 134.8, 153.3, 166.6, 176.4.

HRMS (EI): calc'd for C₁₈H₁₇NO₂S⁺ [M]⁺ 311.097451; found 311.097250.



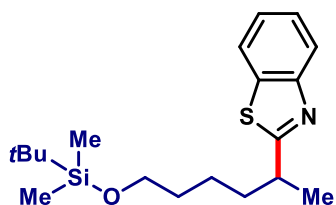
Methyl-5-(benzo[d]thiazol-2-yl)hexanoate, **32**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 12/1, v/v) afforded **32** as light yellow oil (27.3 mg, 0.104 mmol, 52% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.47 (d, *J* = 6.8 Hz, 3H), 1.65–1.83 (m, 3H), 1.88–1.97 (m, 1H), 2.34 (t, *J* = 7.2 Hz, 2H), 3.26–3.36 (m, 1H), 3.65 (s, 3H), 7.33–7.37 (m, 1H), 7.43–7.47 (m, 1H), 7.84–7.86 (m, 1H), 7.96–7.98 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 21.3, 22.9, 34.0, 37.0, 39.4, 51.7, 121.7, 122.8, 124.8, 126.0, 134.8, 153.2, 173.9, 177.4.

HRMS (EI): calc'd for C₁₄H₁₇NO₂S⁺ [M]⁺ 263.097451; found 263.097420.



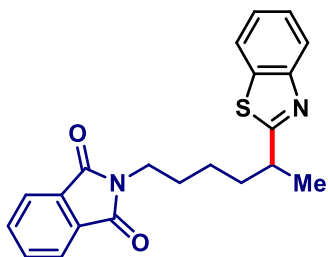
2-(6-((*tert*-Butyldimethylsilyl)oxy)hexan-2-yl)benzo[d]thiazole, **33**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 15/1, v/v) afforded **33** as light yellow oil (43.8 mg, 0.126 mmol, 63% yield).

¹H NMR (400 MHz, CDCl₃): δ 0.01 (s, 6H), 0.85 (s, 9H), 1.32–1.46 (m, 5H), 1.49–1.58 (m, 2H), 1.73–1.80 (m, 1H), 1.85–1.94 (m, 1H), 3.25–3.34 (m, 1H), 3.58 (t, *J* = 6.8 Hz, 2H), 7.32–7.36 (m, 1H), 7.42–7.46 (m, 1H), 7.83–7.86 (m, 1H), 7.96–7.98 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ -5.1, 18.5, 21.3, 23.8, 26.1, 32.8, 37.6, 39.7, 63.1, 121.7, 122.7, 124.7, 125.9, 134.8, 153.2, 178.1.

HRMS (EI): calc'd for $\text{C}_{19}\text{H}_{31}\text{NOSSi}^+$ $[\text{M}]^+$ 349.189015; found 349.188830.



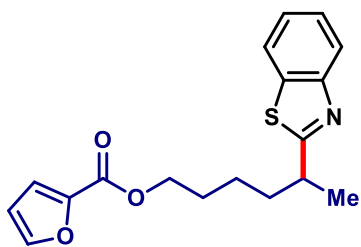
2-(5-(Benzo[d]thiazol-2-yl)hexyl)isoindoline-1,3-dione, **34**

Following the general procedure, purification via column chromatography on silica gel (Hexane/EtOAc = 5/1, v/v) afforded **34** as light yellow oil (45.3 mg, 0.124 mmol, 62% yield).

^1H NMR (400 MHz, CDCl_3): δ 1.37–1.46 (m, 5H), 1.68–1.82 (m, 3H), 1.89–1.98 (m, 1H), 3.26–3.31 (m, 1H), 3.66 (t, J = 7.2 Hz, 2H), 7.31–7.35 (m, 1H), 7.41–7.45 (m, 1H), 7.68–7.70 (m, 2H), 7.80–7.84 (m, 3H), 7.94–7.96 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 21.3, 24.7, 28.6, 37.1, 37.9, 39.5, 121.7, 122.7, 123.3, 124.7, 125.9, 132.2, 134.0, 134.7, 153.2, 168.5, 177.6.

HRMS (ESI): calc'd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]^+$ 365.131825; found 365.132090.



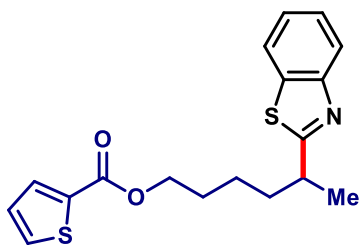
5-(Benzo[d]thiazol-2-yl)hexyl furan-2-carboxylate, **35**

Following the general procedure with 12 h as reaction time, purification via column chromatography on silica gel (Hexane/EtOAc = 6/1, v/v) afforded **35** as yellow oil (42.5 mg, 0.130 mmol, 65% yield).

^1H NMR (400 MHz, CDCl_3): δ 1.46–1.58 (m, 5H), 1.74–1.84 (m, 3H), 1.91–2.01 (m, 1H), 3.27–3.36 (m, 1H), 4.28 (td, J = 6.4 Hz, 1.2 Hz, 2H), 6.46–6.47 (m, 1H), 7.10 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.33–7.37 (m, 1H), 7.43–7.47 (m, 1H), 7.54–7.55 (m, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 21.4, 23.8, 28.7, 37.2, 39.5, 64.8, 111.9, 117.7, 121.7, 122.8, 124.8, 126.0, 134.7, 144.9, 146.3, 153.2, 158.9, 177.6.

HRMS (EI): calc'd for C₁₈H₁₉NO₃S⁺ [M]⁺ 329.108016; found 329.108170.



5-(Benzo[d]thiazol-2-yl)hexyl thiophene-2-carboxylate, **36**

Following the general procedure with 12 h as reaction time, purification via column chromatography on silica gel (Hexane/EtOAc = 8/1, v/v) afforded **36** as yellow oil (40.6 mg, 0.118 mmol, 59% yield).

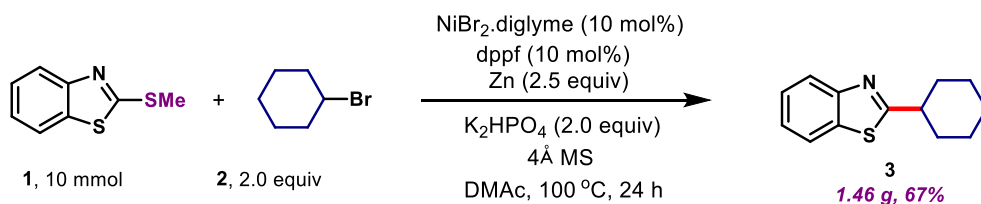
¹H NMR (400 MHz, CDCl₃): δ 1.42–1.59 (m, 5H), 1.74–1.85 (m, 3H), 1.91–2.00 (m, 1H), 3.28–3.36 (m, 1H), 4.27 (t, *J* = 6.4 Hz, 2H), 7.05–7.07 (m, 1H), 7.32–7.36 (m, 1H), 7.43–7.47 (m, 1H), 7.50 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.74 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.83–7.85 (m, 1H), 7.96–7.98 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 21.4, 23.9, 28.7, 37.2, 39.5, 64.9, 121.7, 122.8, 124.8, 126.0, 127.8, 132.3, 133.4, 134.1, 134.8, 153.2, 162.4, 177.7.

HRMS (ESI): calc'd for C₁₈H₁₉NNaO₂S₂⁺ [M+Na]⁺ 368.074943; found 368.074930.

6. Gram-scale Synthesis and Synthetic Applications

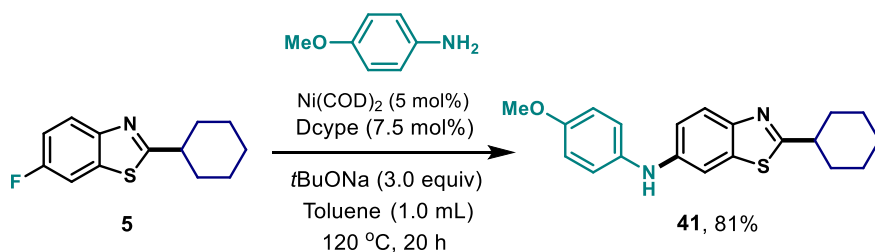
6.1 Gram-scale synthesis



A dry 100-mL Schlenk tube equipped with a stir bar was charged with 2-(methylthio)benzo[d]thiazole (1.81 g, 10 mmol), and then transferred to an argon-filled glove box. NiBr₂·diglyme (350 mg, 10 mol%), dppf (550 mg, 10 mol%), activated Zn dust (1.63 mg, 25 mmol), K₂HPO₄ (3.45 g, 20 mmol), 4Å MS (1.25 g) and DMAc (30 mL) were added in sequence. The vial was taken out of the glovebox and connected to a Schlenk line. Bromocyclohexane (2.5 mL, 20 mmol) were added to vial via a syringe under an argon atmosphere. The vial was

sealed and the resulting mixture was stirred at 100 °C for 24 h. After this time, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~30 mL), filtered through a glass funnel with a thin layer of celite and washed with ethyl acetate (~50 mL). The filtrate was washed with brine water (3 ×30 mL). The organic phase was over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The mixture was then purified by column chromatography on silica gel (Hexane-Hexane/EtOAc(15/1), 1% Et₃N was added to eluent) to afford the desired coupled product as yellow oil (1.46 g, 67%).

6.2 C–F Amination with 4-Methoxyaniline via Ni Catalysis²²



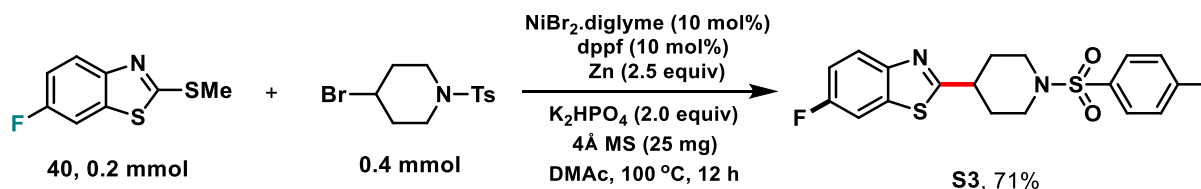
A dry 10 mL-reaction vial equipped with a stir bar was charged with **5** (47.1 mg, 0.2 mmol) and 4-methoxyaniline (73.9 mg, 0.6 mmol), and then transferred to an argon-filled glove box. [Ni(cod)₂] (2.8 mg, 0.01 mmol, 5 mol%), 1,2-bis(dicyclohexylphosphino)ethane (6.3 mg, 0.015 mmol, 7.5 mol%), tBuONa (57.7 mg, 0.6 mmol) and toluene (1.0 mL) were added successively. The tube was sealed with a screw cap and was removed from the glove box. The mixture was stirred at 120 °C for 20 h. After this time, the vial was cooled to rt and the mixture diluted with ethyl acetate (~10 mL), filtered through a glass funnel with a thin layer of celite and washed with ethyl acetate (~10 mL). The volatiles were removed under reduced pressure. The crude product was purified by silica gel column chromatography (Hexane/EtOAc, 5/1) to give product **41** as pale yellow oil (54.5 mg, 0.161 mmol, 81% yield).

¹H NMR (400 MHz, CDCl₃): δ 1.26–1.46 (m, 3H), 1.55–1.65 (m, 2H), 1.71–1.76 (m, 1H), 1.83–1.88 (m, 2H), 2.14–2.18 (m, 2H), 2.98–3.06 (m, 1H), 3.79 (m, 3H), 5.66 (br, 1H), 6.86–6.89 (m, 2H), 6.97 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 25.9, 26.2, 33.5, 43.3, 55.7, 106.5, 114.9, 116.3, 122.4, 123.0, 135.8, 136.2, 142.9, 147.1, 155.6, 174.1 ppm.

HRMS (ESI): calc'd for C₂₀H₂₃N₂OS⁺ [M+H]⁺ 339.152560; found 339.152490.

6.3 C–F Amination with 2-Phenylethan-1-amine via Ni Catalysis²²



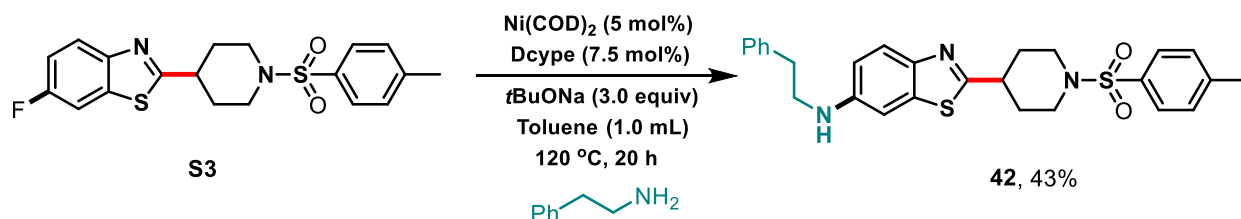
Following the general procedure (0.2 mmol scale), reaction time is 12 h. Purification via column chromatography on silica gel (Hexane/EtOAc = 2/1, v/v) afforded alkylated product **S3** as a light yellow solid (55.3 mg, 0.142 mmol, 71% yield).

¹H NMR (400 MHz, CDCl_3): δ 1.98-2.08 (m, 2H), 2.20-2.26 (m, 2H), 2.45-2.53 (m, 5H), 2.98-3.06 (m, 1H), 3.86-3.91 (m, 2H), 0.86 (td, $J = 8.8$ Hz, 2.4 Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.34 (dd, $J = 8.0$ Hz, 2.4 Hz, 1H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.86-7.89 (m, 1H).

¹³C NMR (101 MHz, CDCl_3): δ 21.7, 31.5, 40.5, 46.0, 107.9 (d, $J = 26.8$ Hz, 1C), 114.8 (d, $J = 24.7$ Hz, 1C), 123.8 (d, $J = 9.4$ Hz, 1C), 127.8, 129.8, 133.2, 135.6 (d, $J = 11.1$ Hz, 1C), 143.8, 149.7 (d, $J = 1.9$ Hz, 1C), 160.4 (d, $J = 246.3$ Hz, 1C), 173.8 (d, $J = 3.2$ Hz, 1C).

¹⁹F NMR (282 MHz, CDCl_3): δ -116.3.

HRMS (ESI): calc'd for $\text{C}_{19}\text{H}_{20}\text{FN}_2\text{O}_2\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 391.094471; found 391.094580.



A dry 10 mL-reaction vial equipped with a stir bar was charged with 6-fluoro-2-(1-tosylpiperidin-4-yl)benzo[*d*]thiazole **S3** (39.0 mg, 0.1 mmol), and then transferred to an argon-filled glove box. $[\text{Ni}(\text{COD})_2]$ (1.4 mg, 0.005 mmol, 5 mol%), 1,2-bis(dicyclohexylphosphino)ethane (3.2 mg, 0.0075 mmol, 7.5 mol%), $t\text{BuONa}$ (29 mg, 0.3 mmol) were added successively. The vial was taken out of the glovebox and connected to a Schlenk line. Toluene (0.5 mL) and 2-phenylethan-1-amine (38 μL , 0.3 mmol) were added to vial via a syringe under an argon atmosphere. The vial was sealed and the resulting mixture was stirred at 120 °C for 20 h. After being cooled to r.t., the mixture was diluted with ethyl acetate (~10 mL), filtered through a glass funnel with a thin layer of celite and washed with ethyl acetate (~10 mL). The volatiles were removed under reduced pressure. The crude product was purified by silica gel column chromatography (Hexane/EtOAc, 2/1) to give product **42** as colorless oil (21.2 mg, 0.043 mmol, 43% yield).

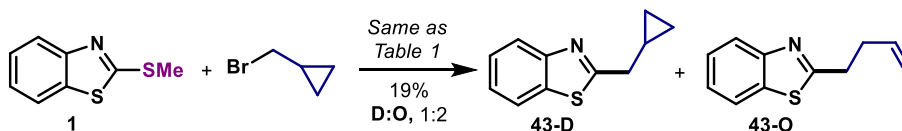
¹H NMR (400 MHz, CDCl₃): δ 1.95-2.05 (m, 2H), 2.16-2.21 (m, 2H), 2.44-2.51 (m, 5H), 2.92-3.00 (m, 3H), 3.43 (t, *J* = 6.8 Hz, 2H), 3.83-3.88 (m, 2H), 6.71 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 7.20-7.26 (m, 3H), 7.30-7.34 (m, 4H), 7.66-7.70 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 21.7, 31.6, 35.4, 40.3, 45.4, 46.0, 102.6, 114.5, 123.1, 126.7, 127.8, 128.8, 128.9, 129.8, 133.3, 136.6, 139.1, 143.7, 145.5, 146.0, 169.2.

HRMS (ESI): calc'd for C₂₇H₂₉N₃O₂S₂⁺ [M+H]⁺ 492.177396; found 492.177490.

7. Mechanistic Studies

7.1 Radical Ring-opening



A dry reaction vial (10 mL) equipped with a stir bar was charged with 2-(methylthio)benzo[d]thiazole **1** (36.2 mg, 0.2 mmol), and then transferred to a glove box. NiBr₂·diglyme (7.0 mg, 10 mol%), dppf (11.0 mg, 10 mol%), activated Zn dust (32.6 mg, 0.5 mmol), K₂HPO₄ (69 mg, 2.0 equiv), 4Å MS (25 mg) and DMAc (0.6 mL) were added successively. The vial was taken out of the glovebox and connected to a Schlenk line. (Bromomethyl)cyclopropane (39 μL, 0.4 mmol) was added to the vial via a microsyringe under an argon atmosphere. Finally, the vial was sealed and the resulting mixture was stirred at 100 °C for 6 h. After this time, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~10 mL) and filtered through a glass funnel with a thin layer of celite, and concentrated in vacuo. The mixture was subjected to short silica gel column (hexane as eluent) to remove DMAc. The yield and ratio was confirmed by ¹H NMR using mesitylene as an internal standard.

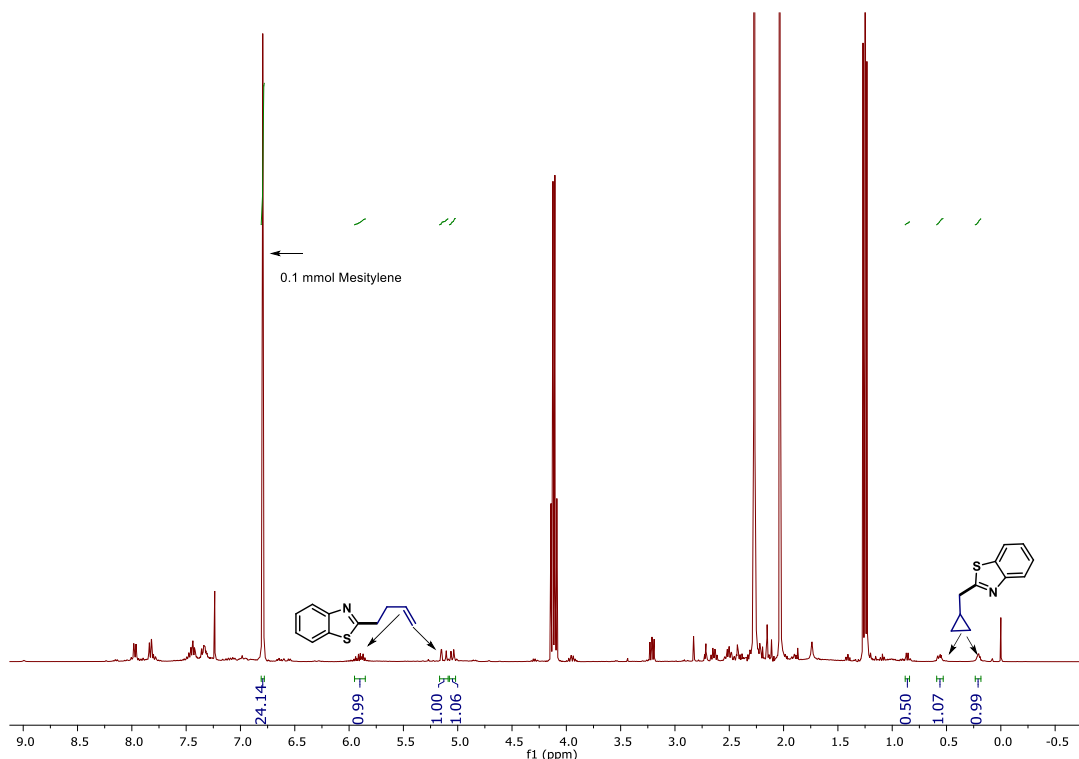
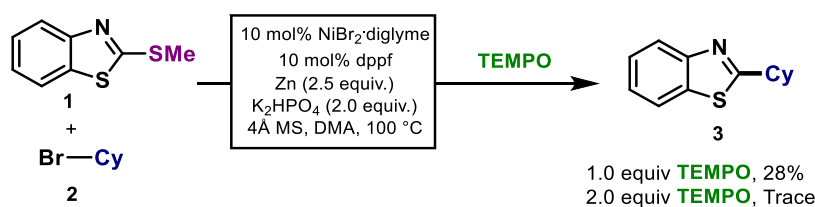
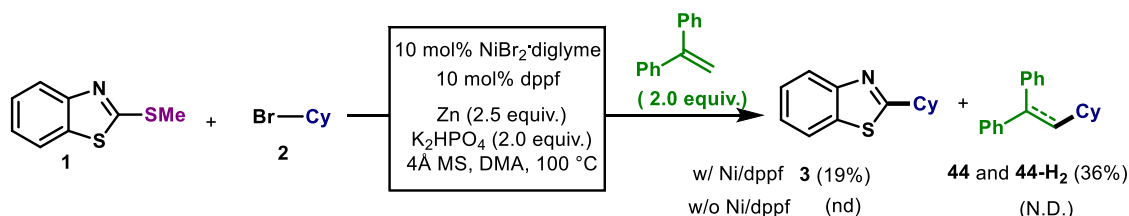


Figure S1. Ratio confirmed by ^1H NMR.

7.2 Radical Scavengers

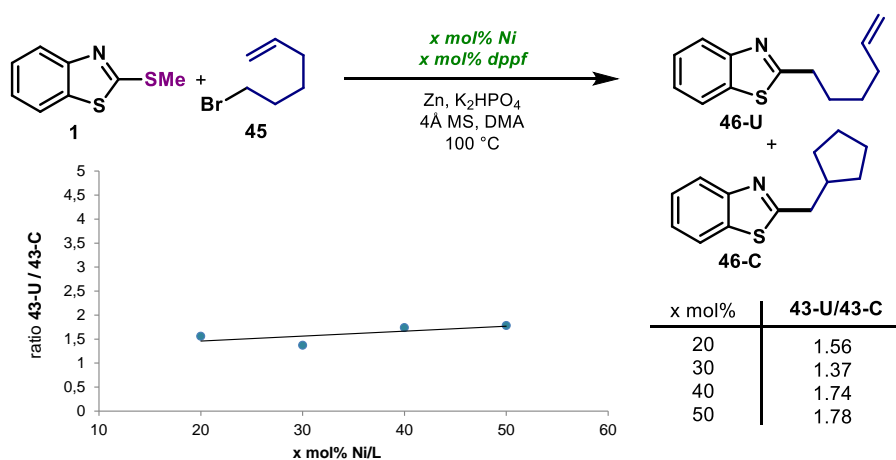


A dry reaction vial (10 mL) equipped with a stir bar was charged with 2-(methylthio)benzo[*d*]thiazole **1** (36.2 mg, 0.2 mmol) and TEMPO (1.0 or 2.0 equiv), and then transferred to a glove box. $\text{NiBr}_2 \cdot \text{diglyme}$ (7.0 mg, 10 mol%), dppf (11.0 mg, 10 mol%), activated Zn dust (32.6 mg, 0.5 mmol), K_2HPO_4 (69 mg, 2.0 equiv), 4Å MS (25 mg) and DMAc (0.6 mL) were added successively. The vial was taken out of the glovebox and connected to a Schlenk line. Bromocyclohexane (50 μL , 0.4 mmol) was added to the vial via a microsyringe under an argon atmosphere. Finally, the vial was sealed and the resulting mixture was stirred at 100 °C for 6 h. After this time, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~10 mL). The yield was confirmed by GC-FID using dodecane as an internal standard.



A dry reaction vial (10 mL) equipped with a stir bar was charged with 2-(methylthio)benzo[*d*]thiazole **1** (36.2 mg, 0.2 mmol), and then transferred to a glove box. NiBr₂·diglyme (7.0 mg, 10 mol%), dppf (11.0 mg, 10 mol%), activated Zn dust (32.6 mg, 0.5 mmol), K₂HPO₄ (69 mg, 2.0 equiv), 4Å MS (25 mg) and DMAc (0.6 mL) were added successively. The vial was taken out of the glovebox and connected to a Schlenk line. Bromocyclohexane (50 µL, 0.4 mmol) and 1,1-diphenylethylene (70 µL, 0.4 mmol) were added to the vial via a microsyringe under an argon atmosphere. Finally, the vial was sealed and the resulting mixture was stirred at 100 °C for 6 h. After this time, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~10 mL). The yield (19%) of product was confirmed by GC-FID using dodecane as an internal standard. The yield (36%) of product **44** and **44-H₂** (inseparable) was confirmed by ¹H NMR using mesitylene as internal standard after isolation by silica gel column chromatography.

7.3 Radical 5-*exo-trig* Cyclization

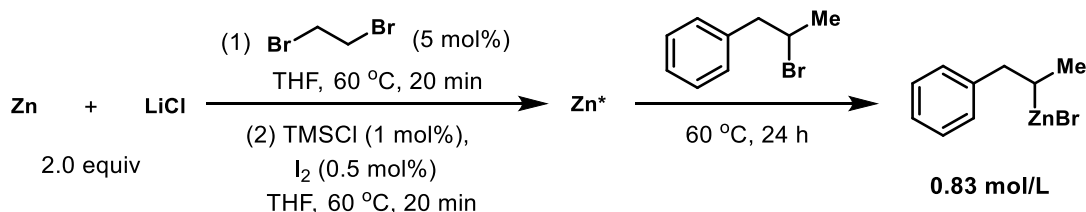


A dry reaction vial (10 mL) equipped with a stir bar was charged with 2-(methylthio)benzo[*d*]thiazole **1** (36.2 mg, 0.2 mmol), and then transferred to a glove box. NiBr₂·diglyme, dppf, activated Zn dust (32.6 mg, 0.5 mmol), K₂HPO₄ (69 mg, 2.0 equiv), 4Å MS (25 mg) and DMAc (0.6 mL) were added successively. The vial was taken out of the glovebox and connected to a Schlenk line. 6-Bromohex-1-ene (53 µL, 0.4 mmol) was added to the vial

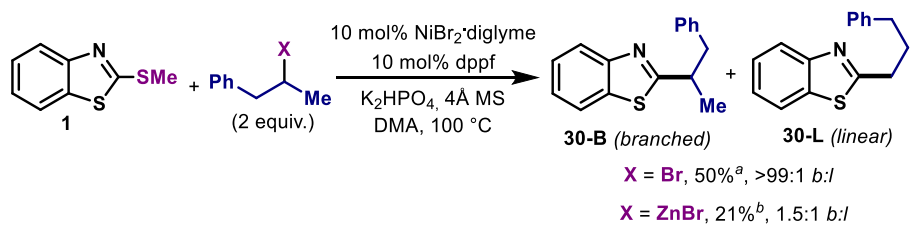
via a microsyringe under an argon atmosphere. Finally, the vial was sealed and the resulting mixture was stirred at 100 °C for 6 h. After this time, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~10 mL). The ratio of two isomers was confirmed by GC-FID.

7.4 Formation of Organozinc Species

Preparation of Secondary Alkylzinc Reagent²³,



In a glovebox, a 50 mL round-bottom flask equipped with a magnetic stir bar was charged with LiCl (0.848 g, 20 mmol) and zinc dust (1.3 g, 20 mmol) then sealed with a rubber septum and moved outside the glovebox. Under high vacuum, the flask was heated with a heat gun for 15 min with occasional stirring then cooled to r.t. and carefully backfilled with argon. After repeating this process once more, THF (10 mL) and 1,2-dibromoethane (43 μL , 0.5 mmol) were added via syringe and the reaction mixture was heated at 60 °C for 20 min. After cooling to rt, TMSCl (13 μL , 0.1 mmol) and a solution of iodine (10 mg, 0.04 mmol) were added to reaction system. The reaction mixture was heated at 60 °C for 20 min and then cooled to rt. The (2-bromopropyl)benzene (1.54 mL, 10 mmol) was added dropwise over 5 min after which the flask was sealed and allowed to stir at 60 °C for 24 h. After that, it was cooled to r.t. and allowed to stand for 3 h. The concentration (0.83 mol/L) of the organozinc solution was determined by iodometric titration of the resulting supernatant using Knochel's procedure.²⁴

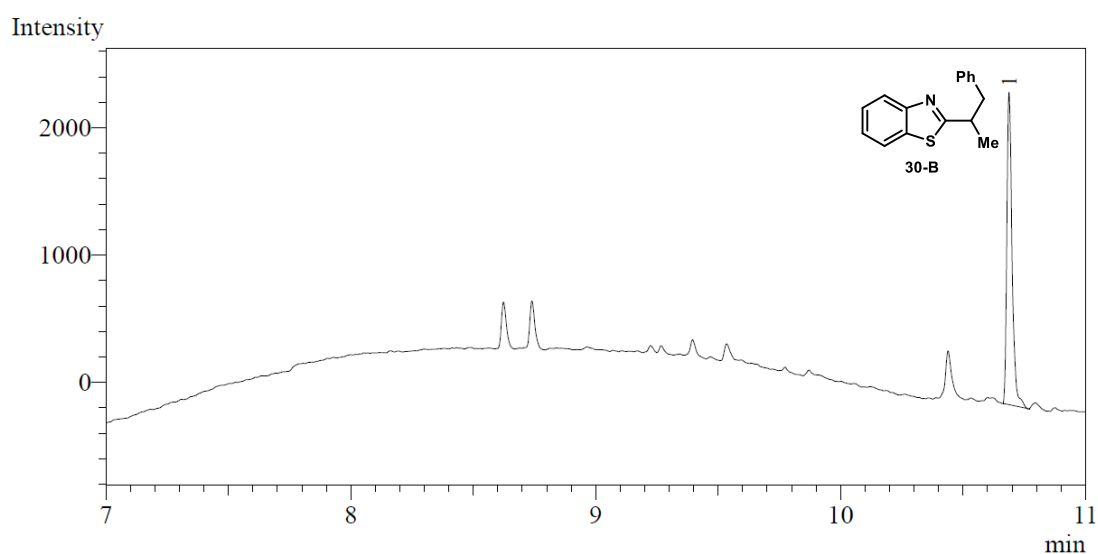


^a2.5 equiv. of Zn was added. ^bGC Yield.

Reaction of 1 with (2-Bromopropyl)benzene: Following General Procedure.

Procedure for Reaction of 1 with Alkylzinc Reagent:

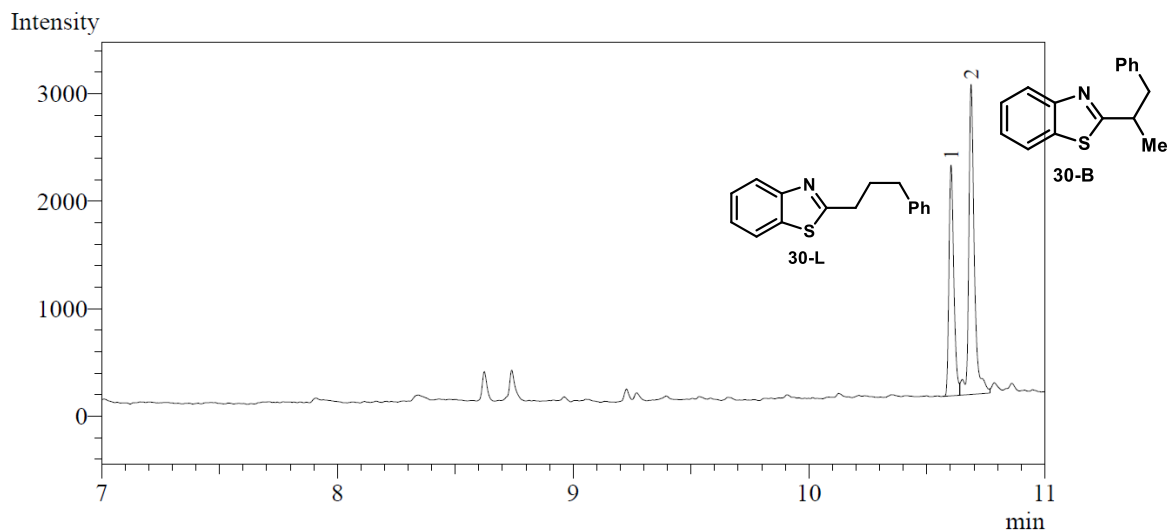
A dry reaction vial (10 mL) equipped with a stir bar was charged with 2-(methylthio)benzo[*d*]thiazole **1** (36.2 mg, 0.2 mmol), and then transferred to a glove box. NiBr₂·diglyme (7.0 mg, 10 mol%), dppf (11.0 mg, 10 mol%), K₂HPO₄ (69 mg, 2.0 equiv), 4Å MS (25 mg) and DMAc (0.6 mL) were added successively. The vial was taken out of the glovebox and connected to a Schlenk line. The solution of (1-Phenylpropan-2-yl)zinc(II) bromide in THF (0.83 M) (0.48 mL, 0.4 mmol) was added added to the vial via syringe under an argon atmosphere. Finally, the vial was sealed and the resulting mixture was stirred at 100 °C for 6 h. After this time, the vial was cooled to room temperature. The solution was diluted with ethyl acetate (~5 mL) and quenched by water (~2 mL). The crude yield and ratio of isomers were confirmed by GC-FID using dodecane as an internal standard.



Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Name
1	10,69	3625	2367	100,0	
Total		3625	2367	100,0	

Figure S1. GC-FID for reaction with alkyl bromide



Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Name
1	10,60	3089	2092	39,6	
2	10,69	4714	2780	60,4	
Total		7803	4872	100,0	

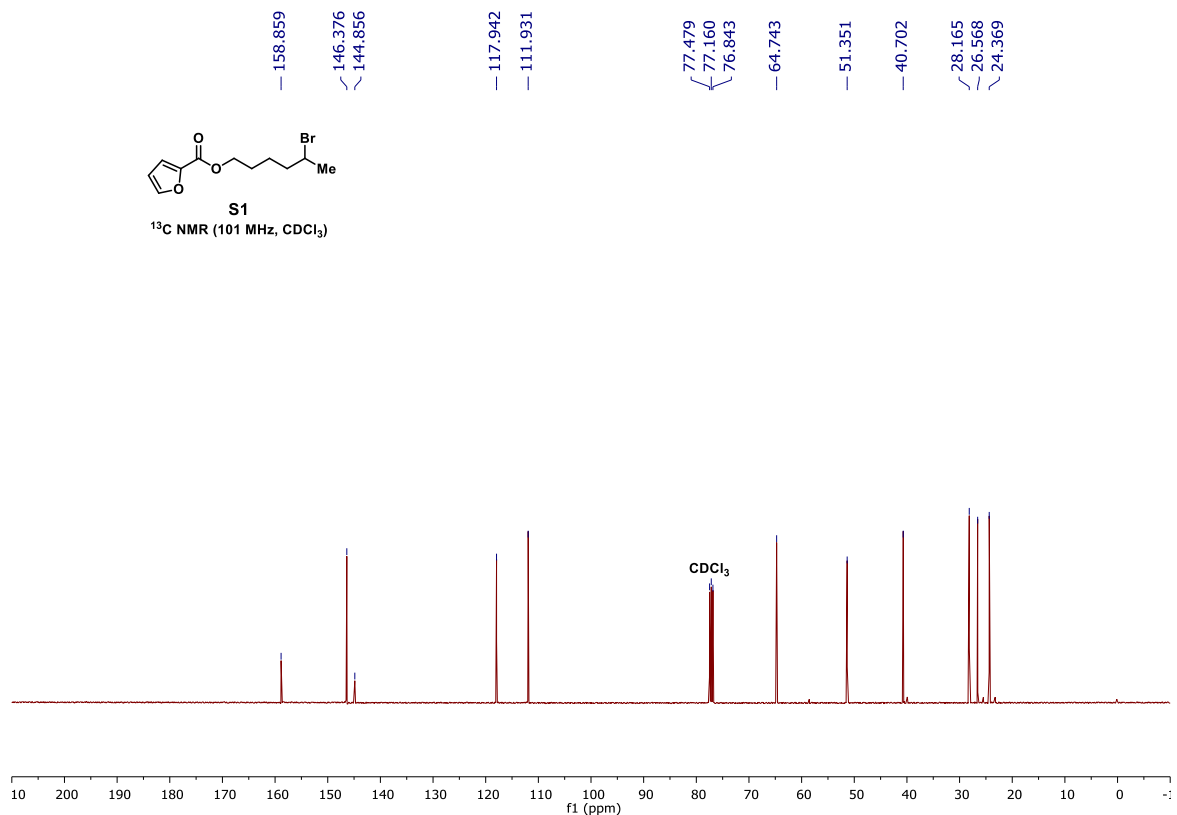
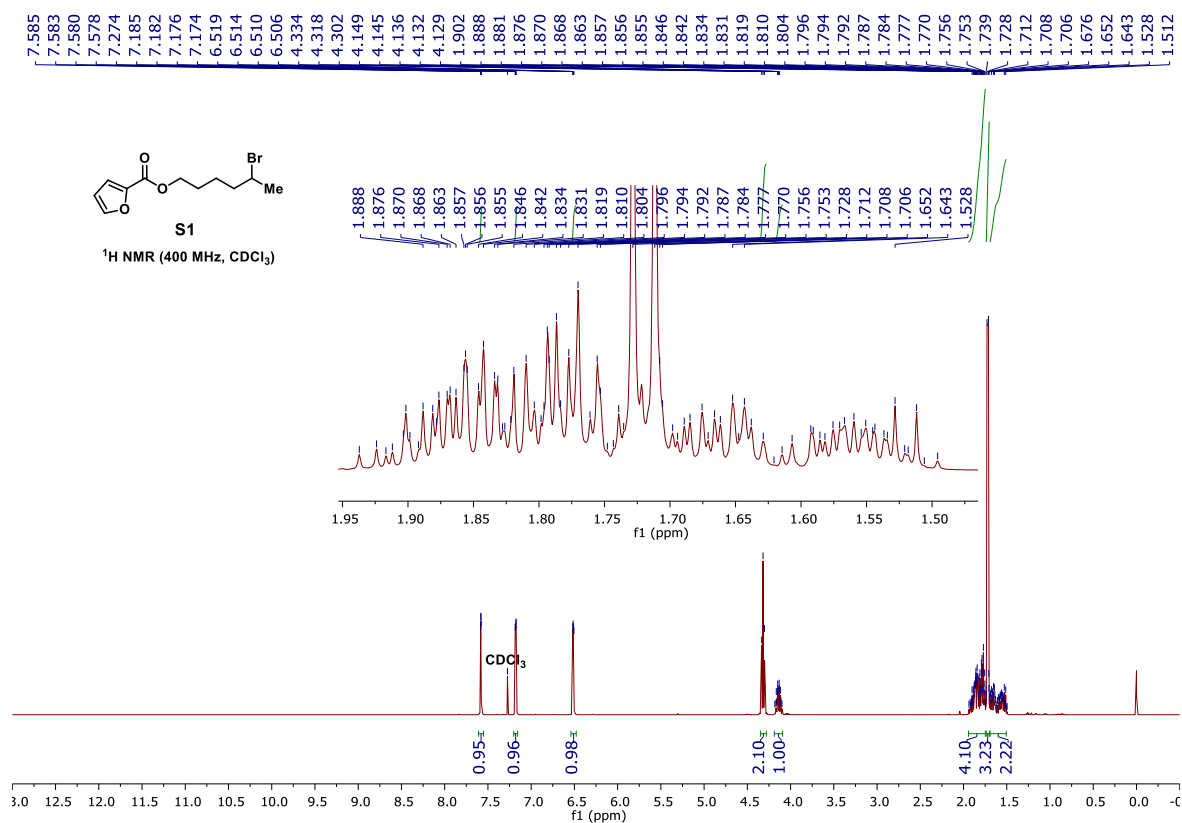
Figure S2. GC-FID for reaction with alkyl zinc reagent

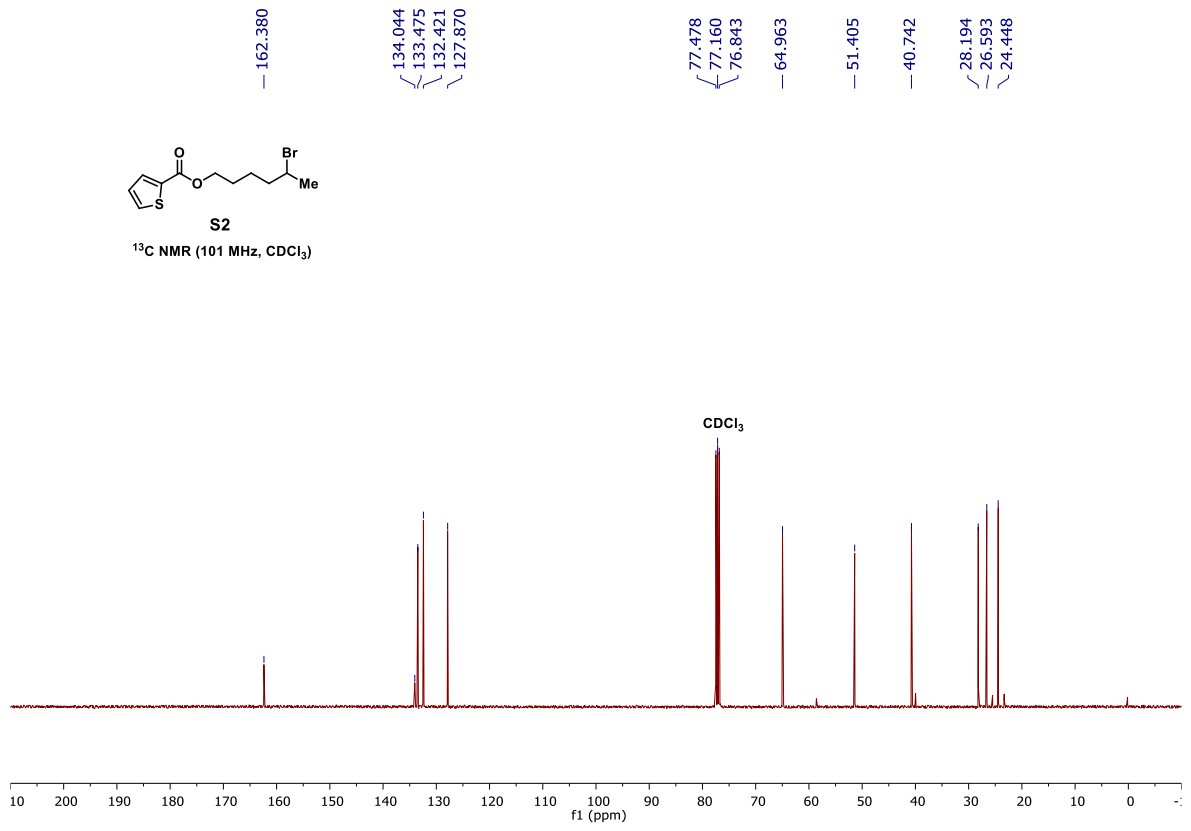
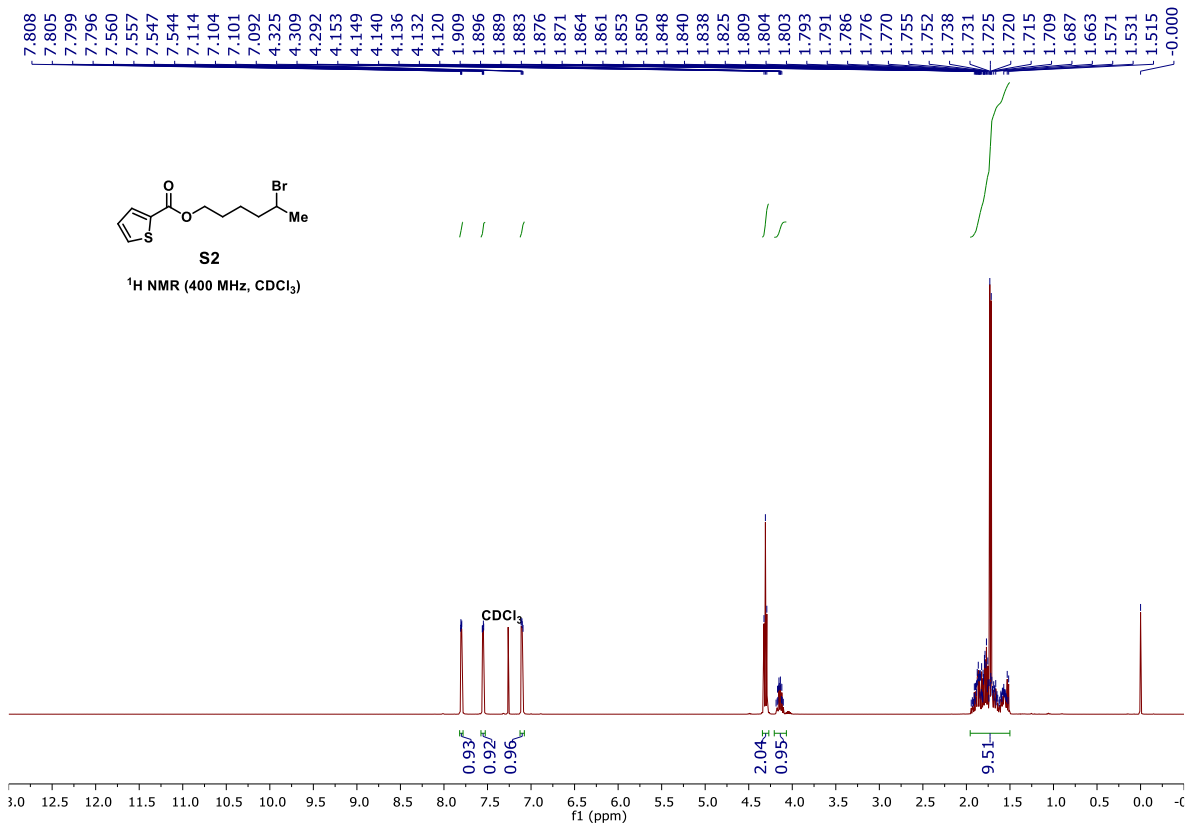
8. References

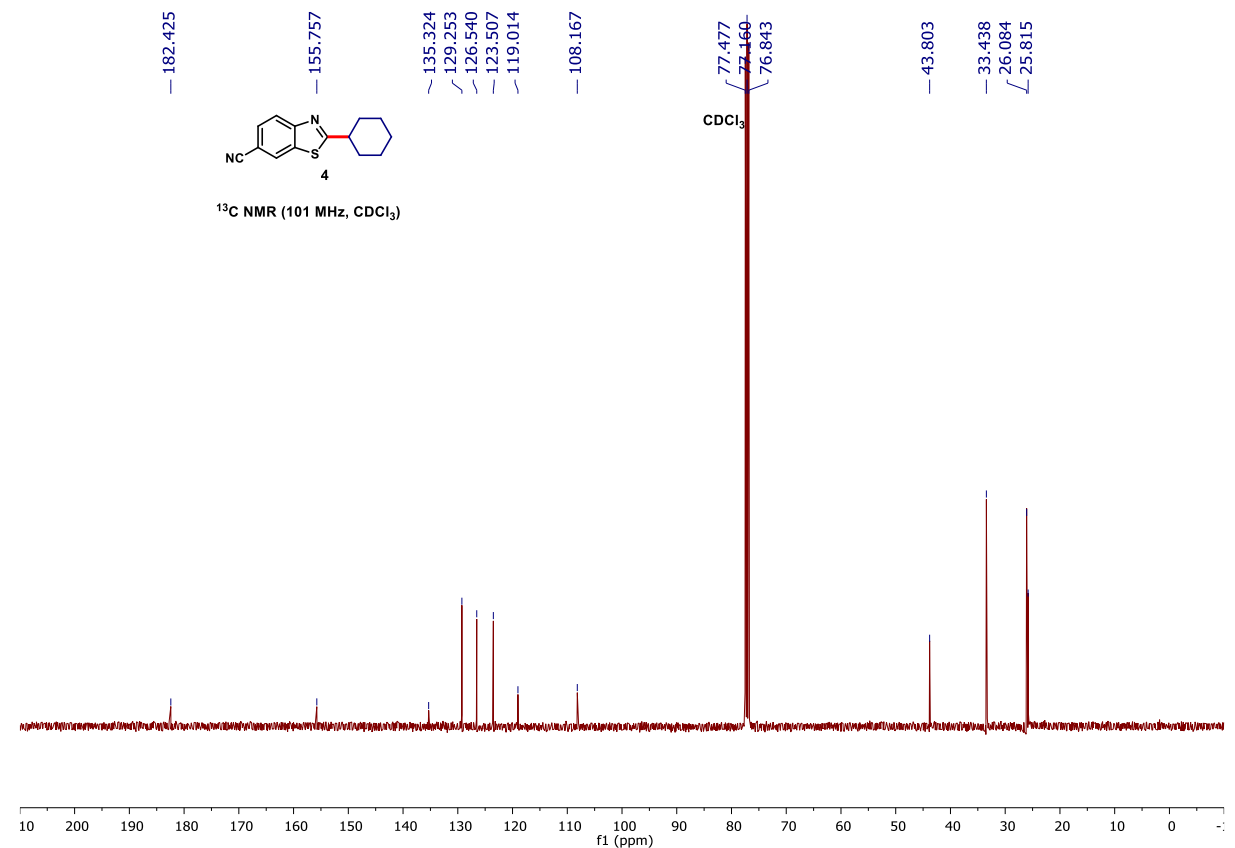
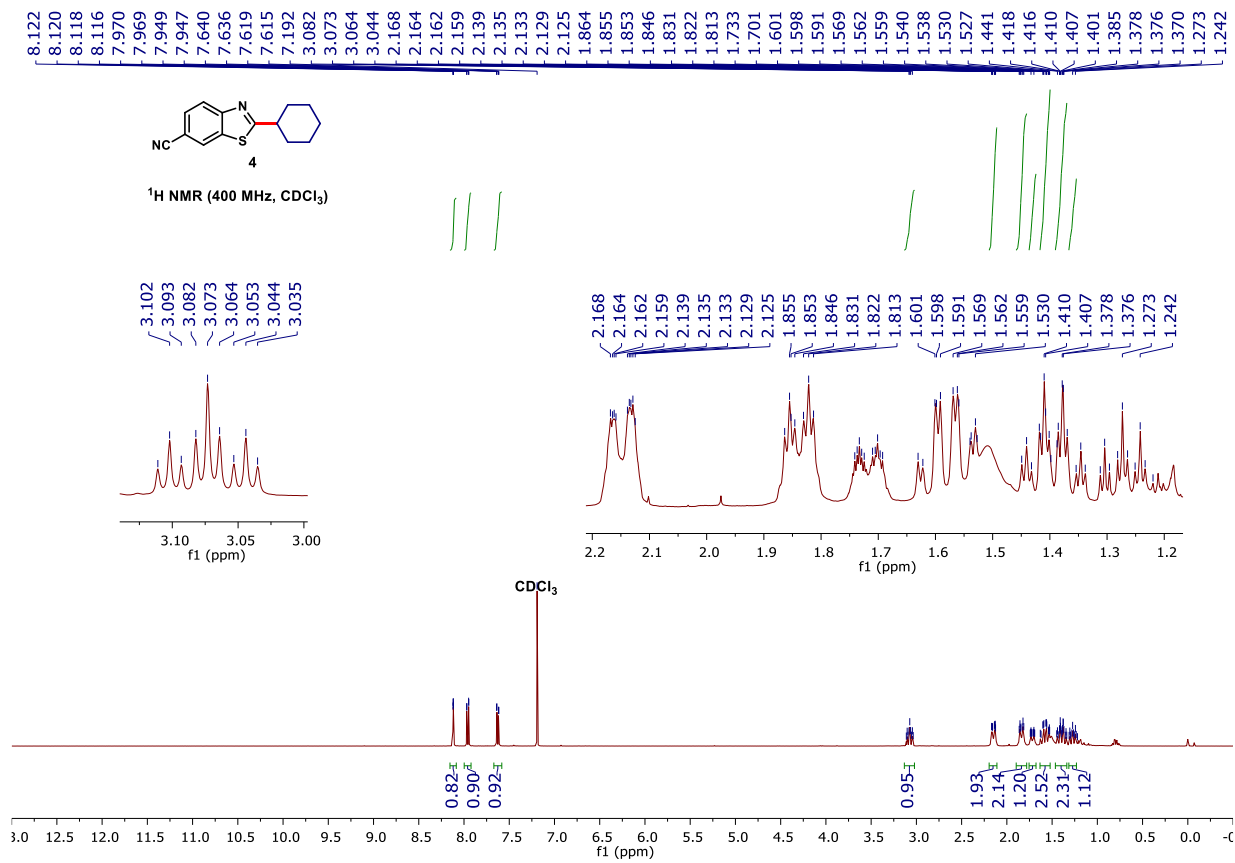
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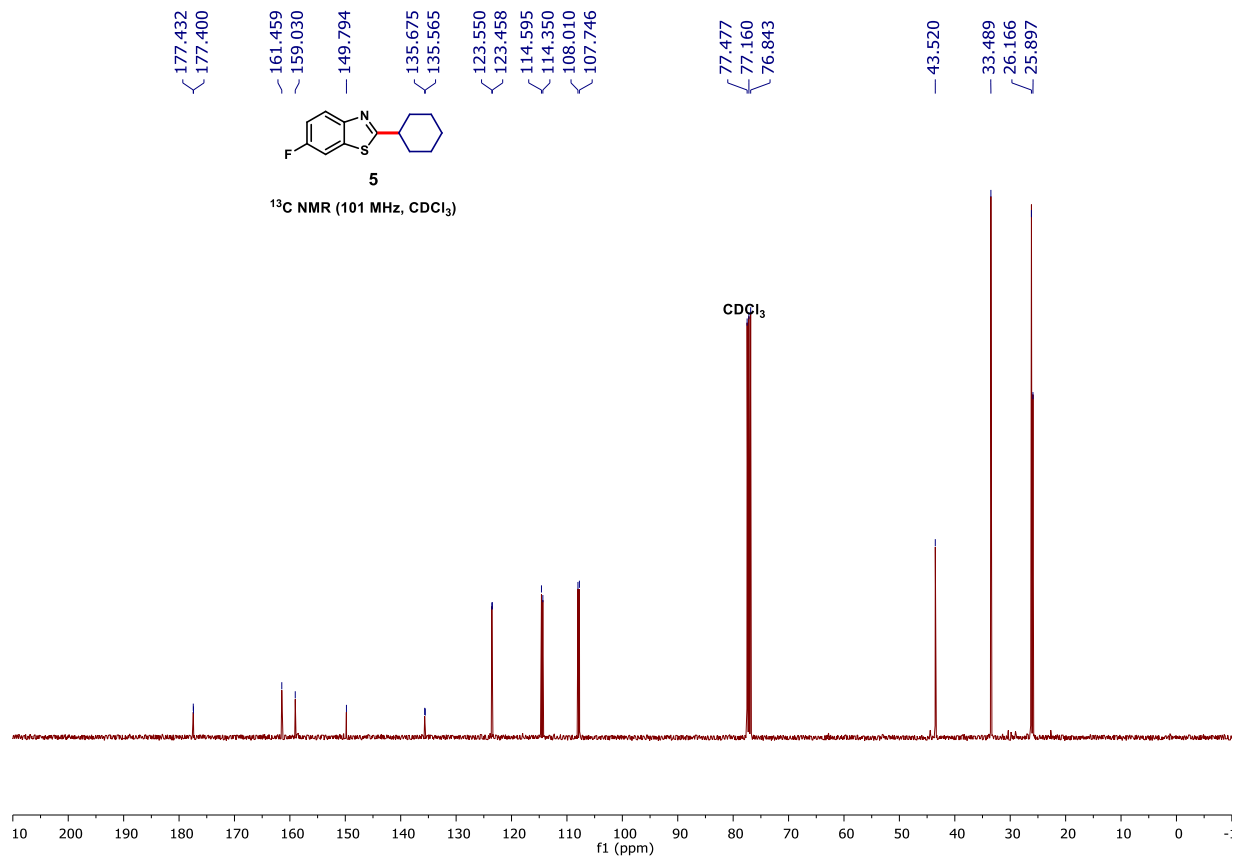
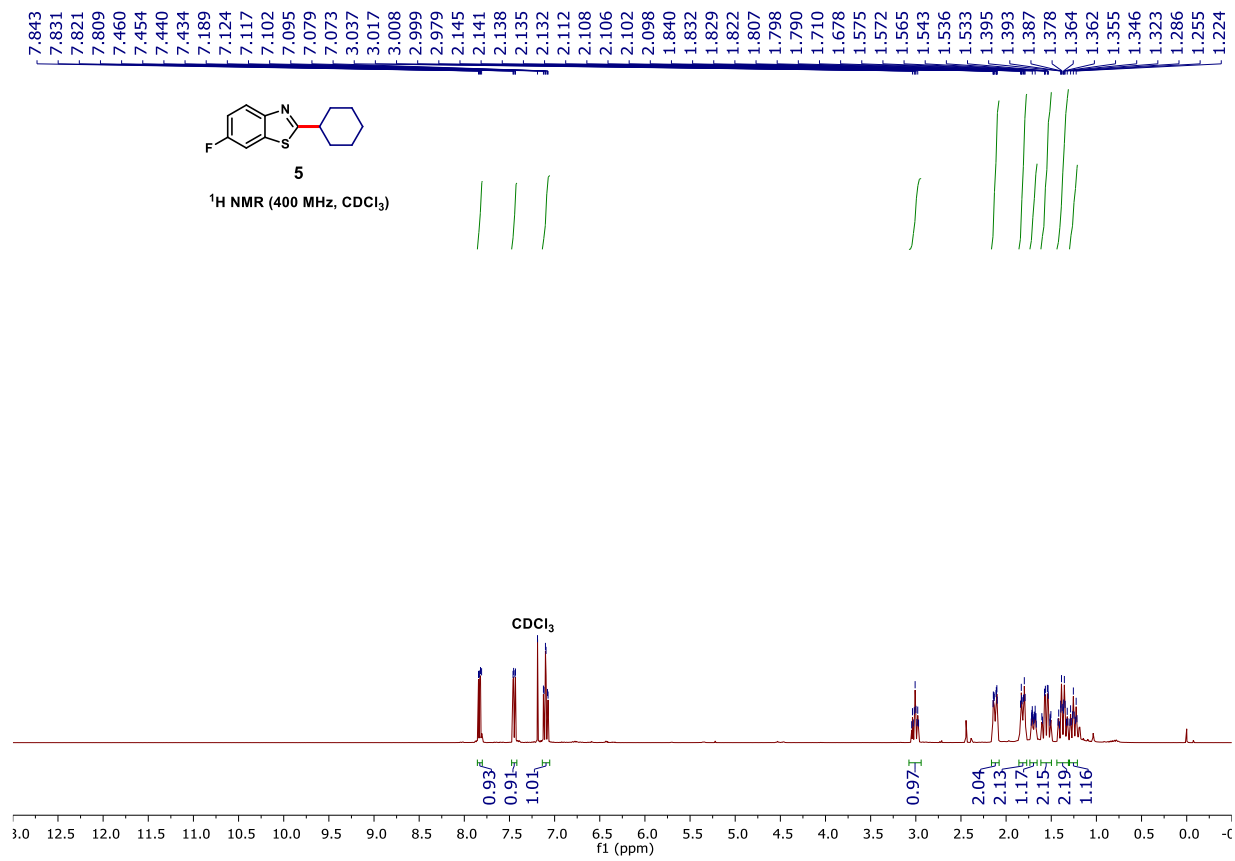
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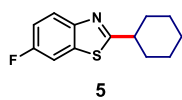
9. NMR spectra



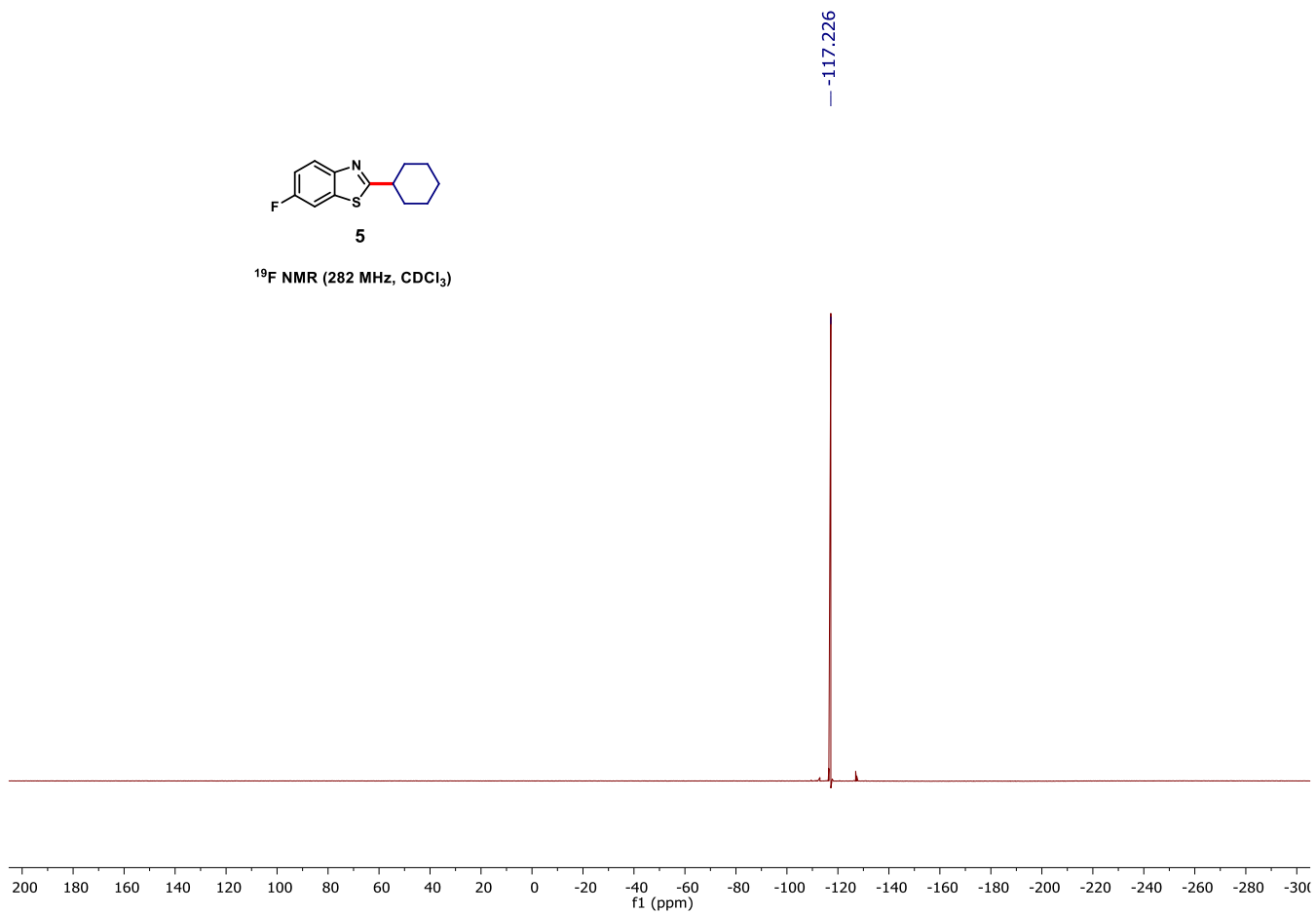


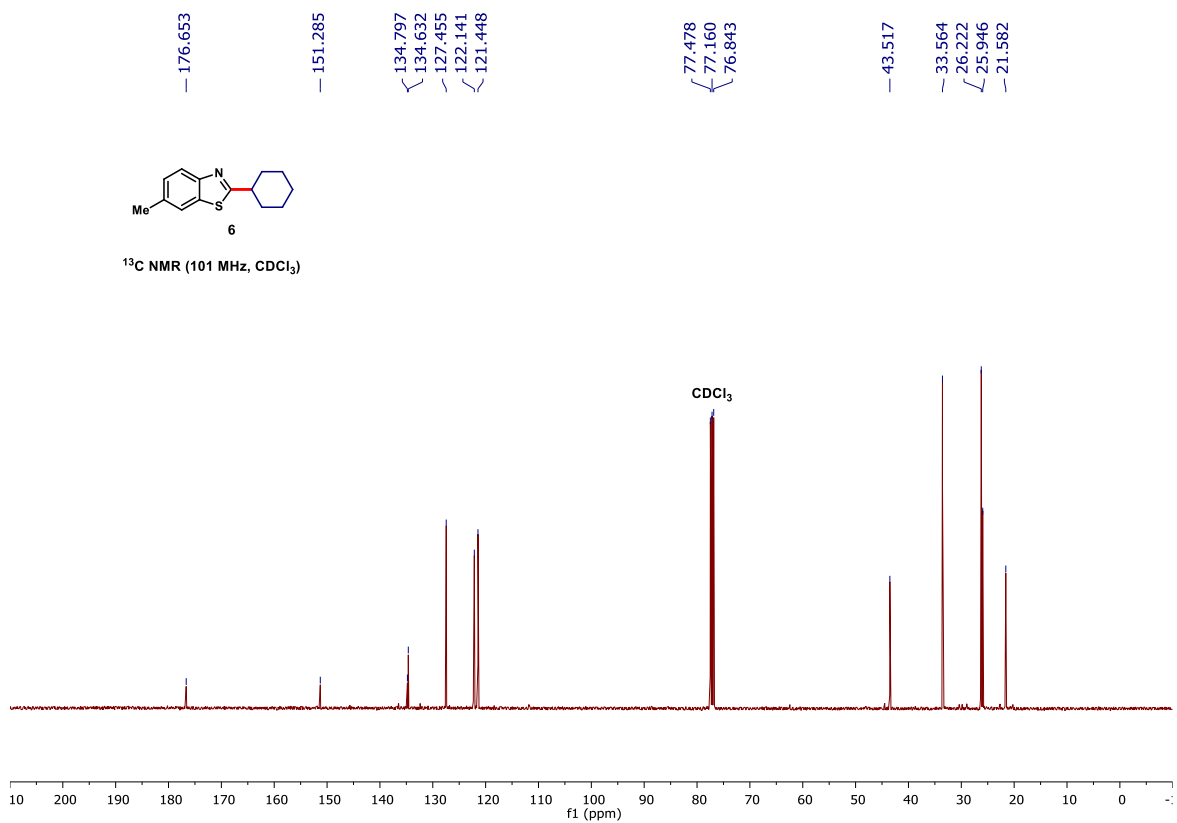
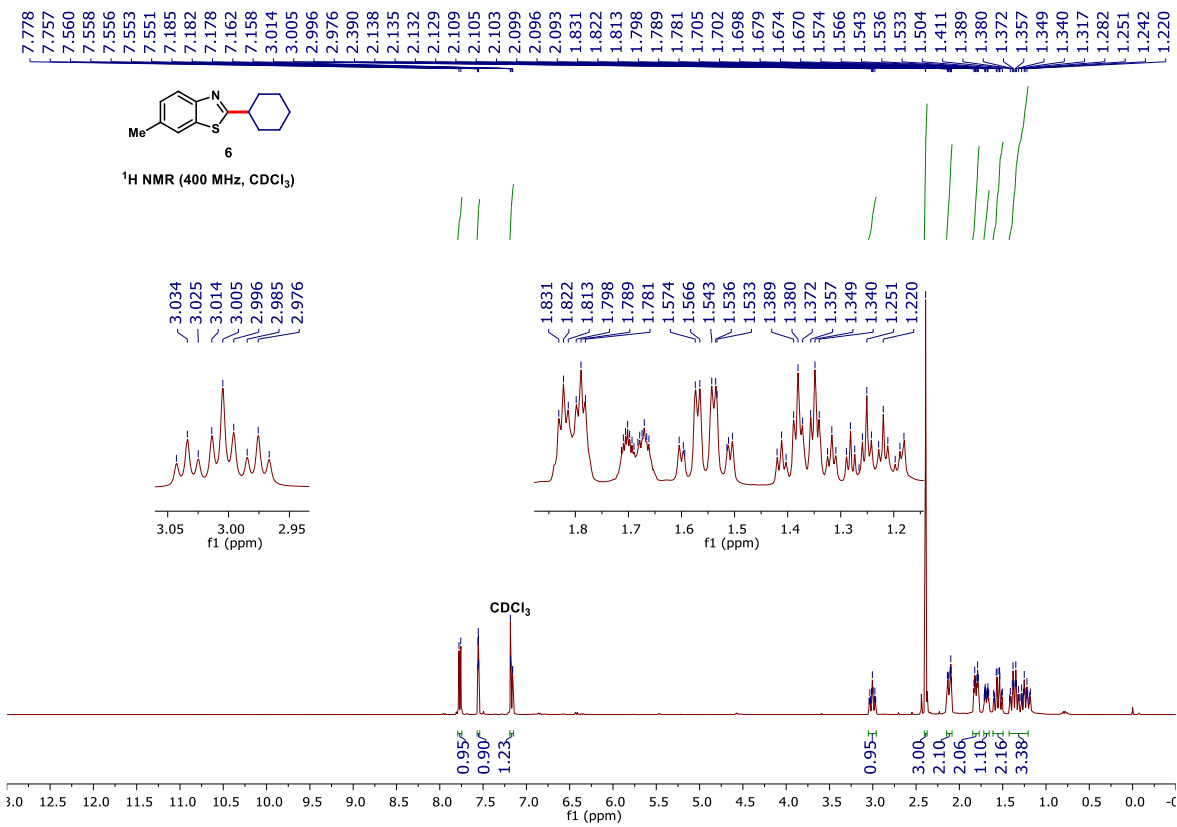


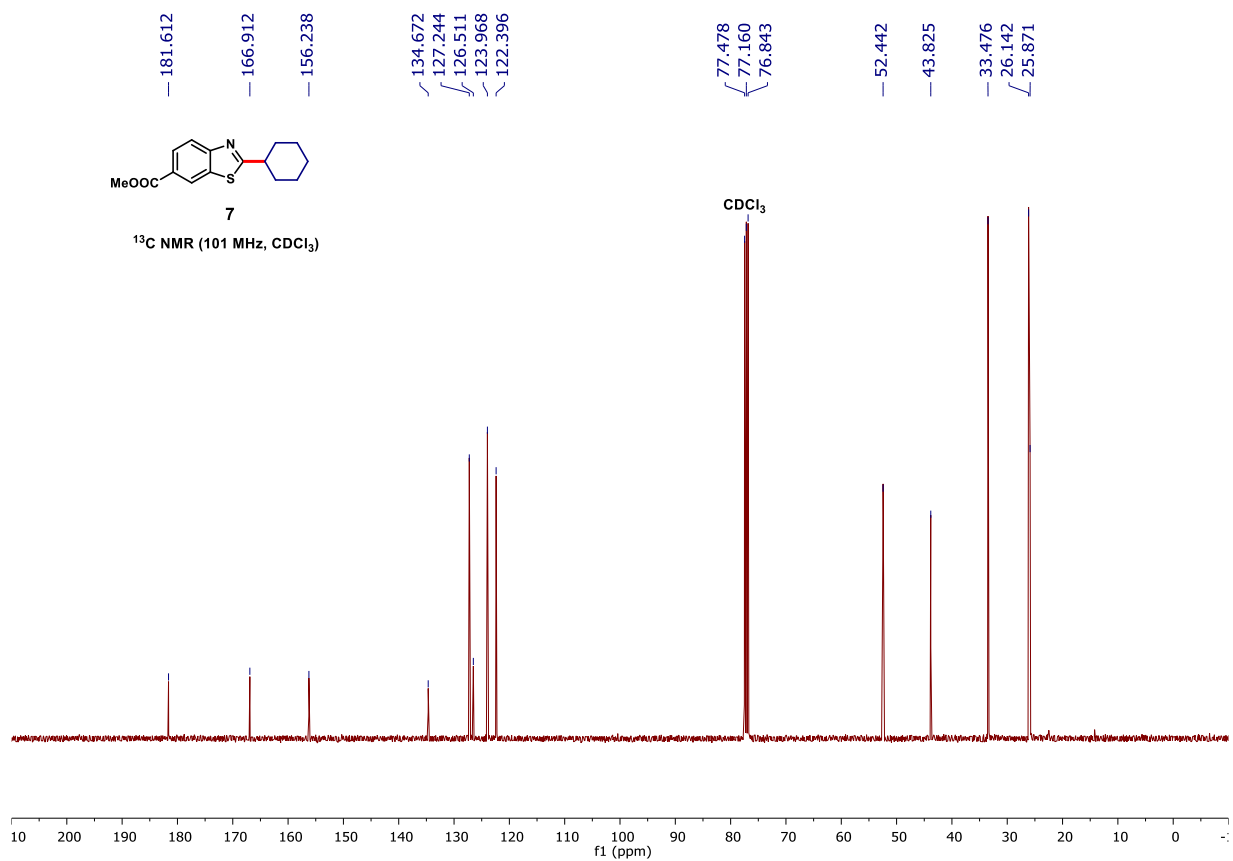
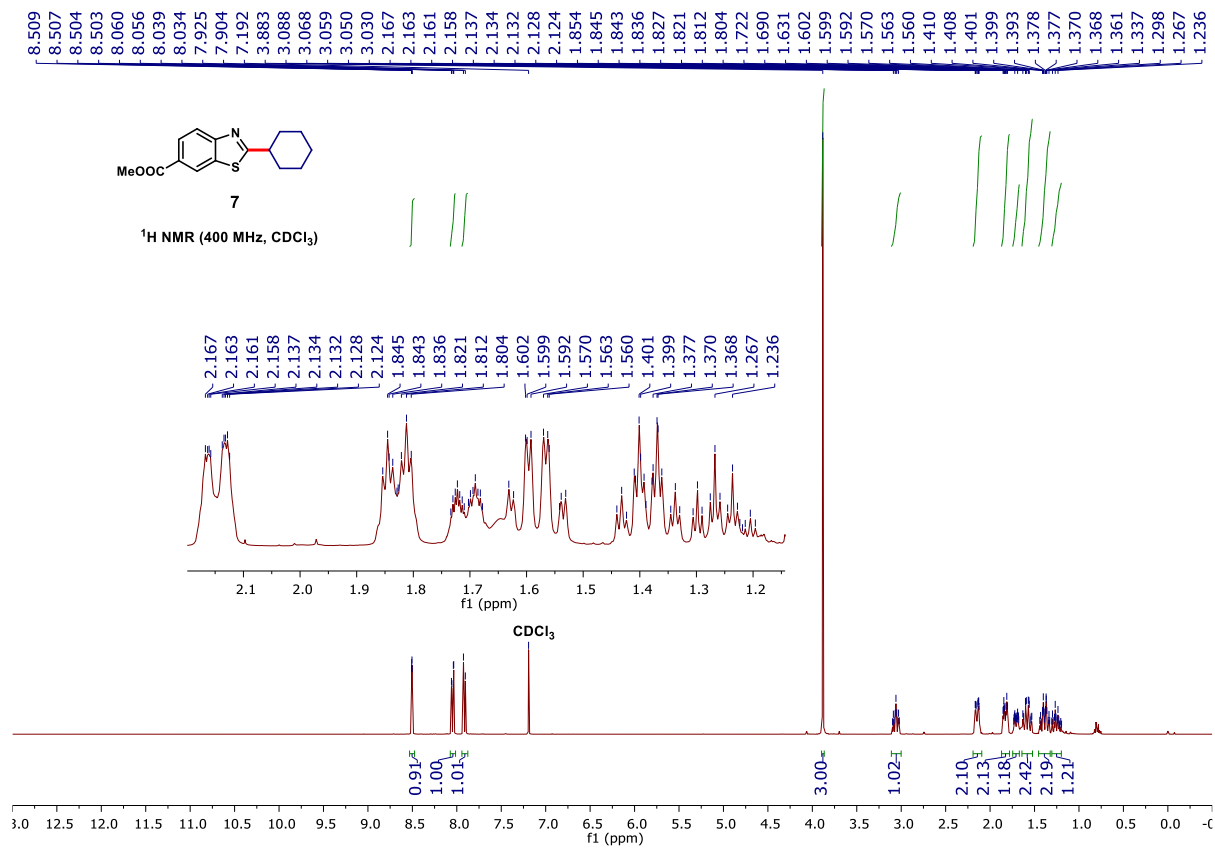


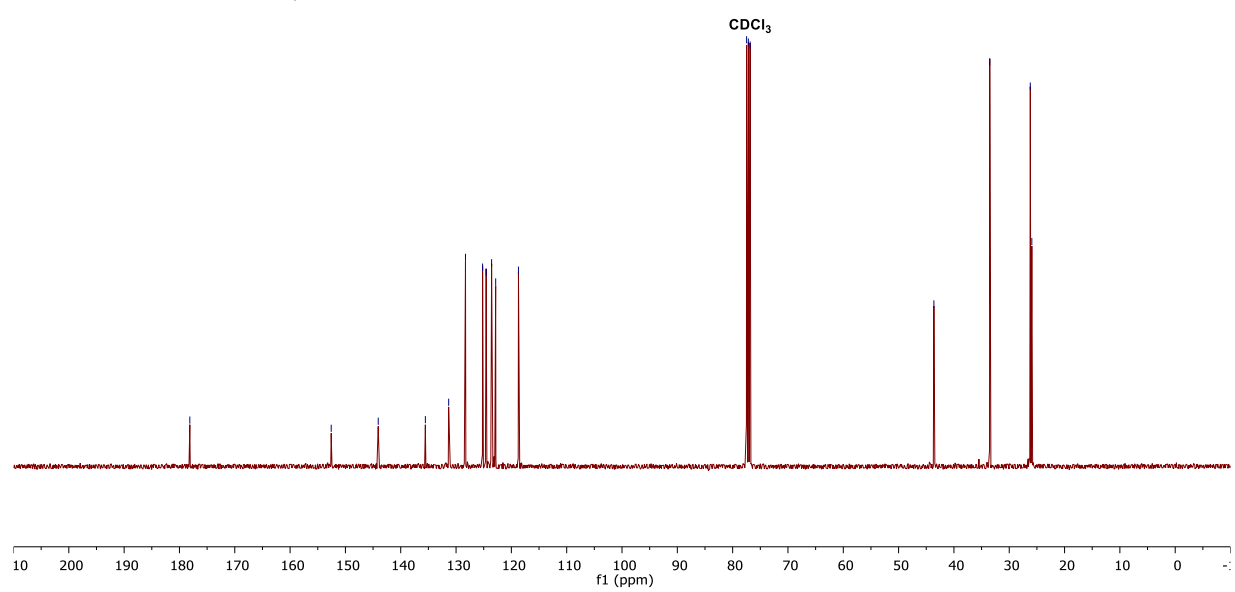
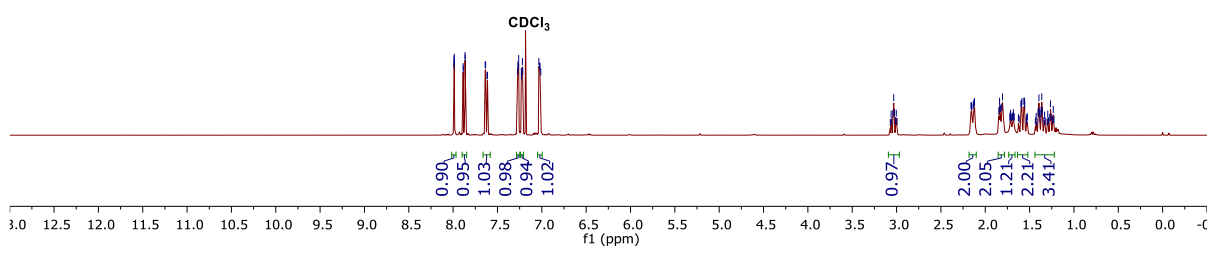
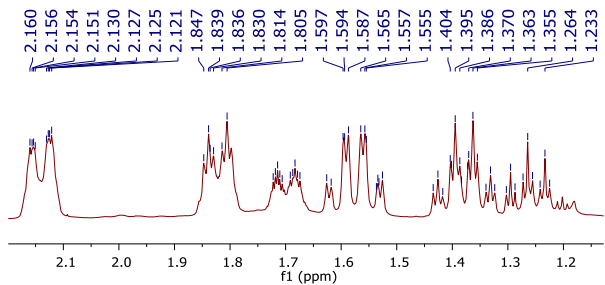
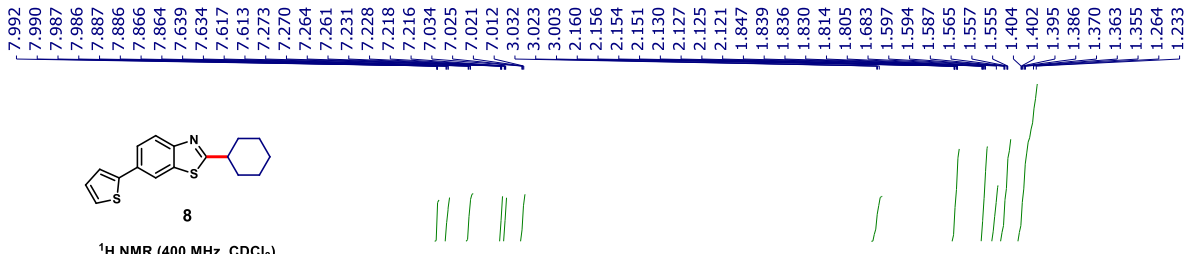


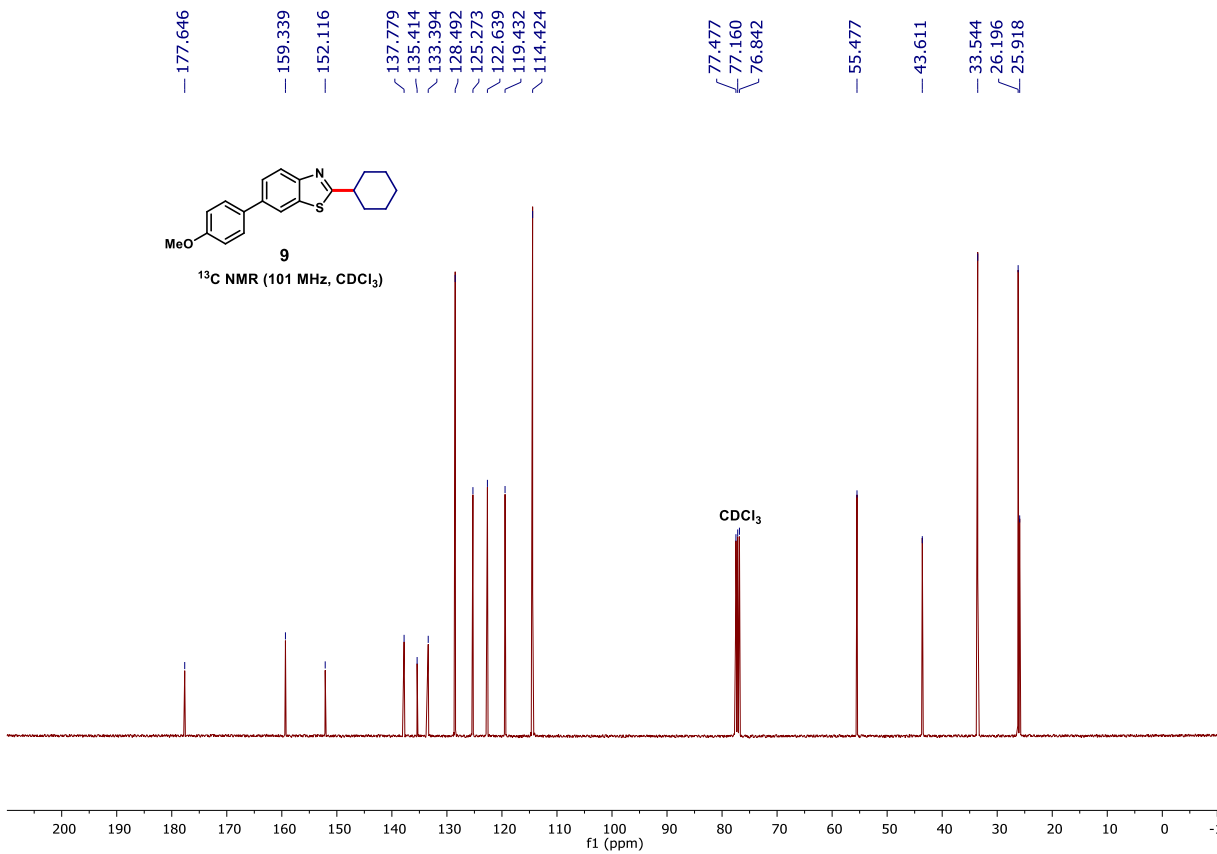
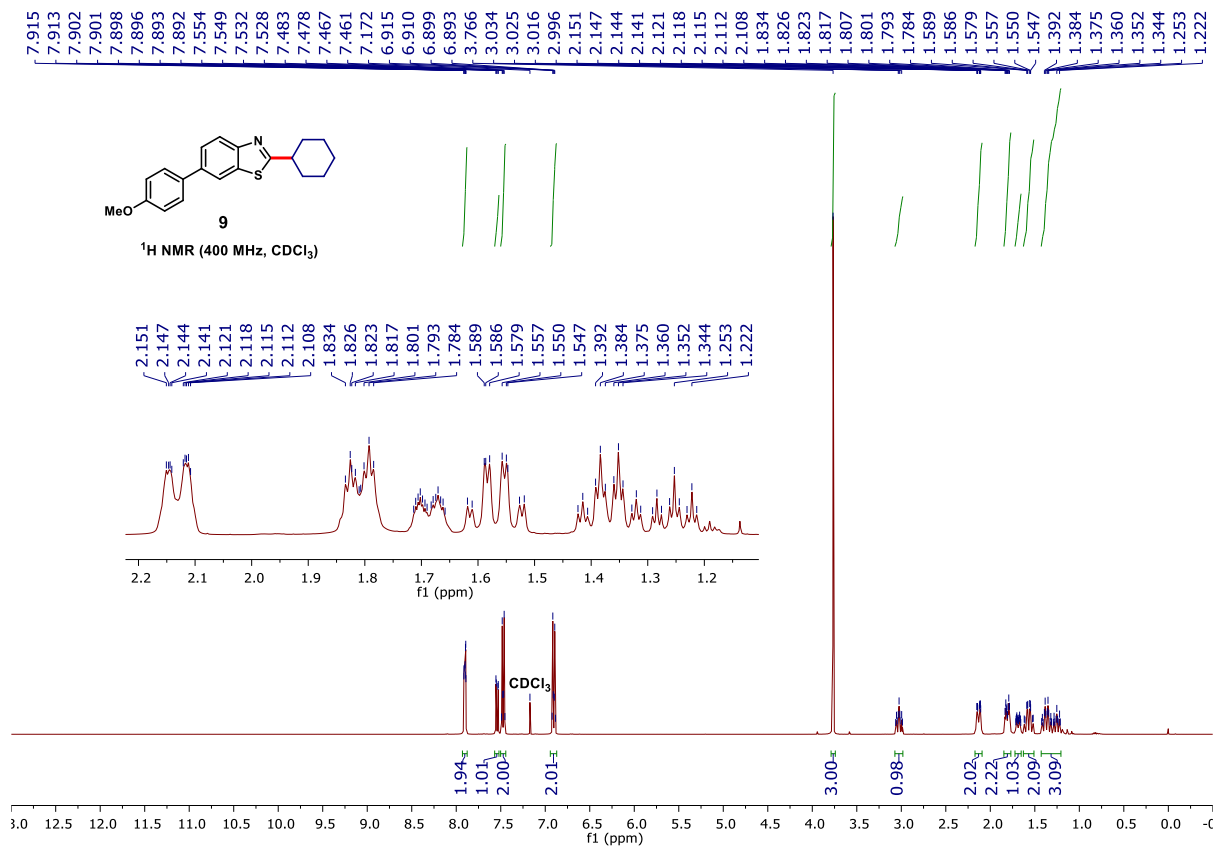
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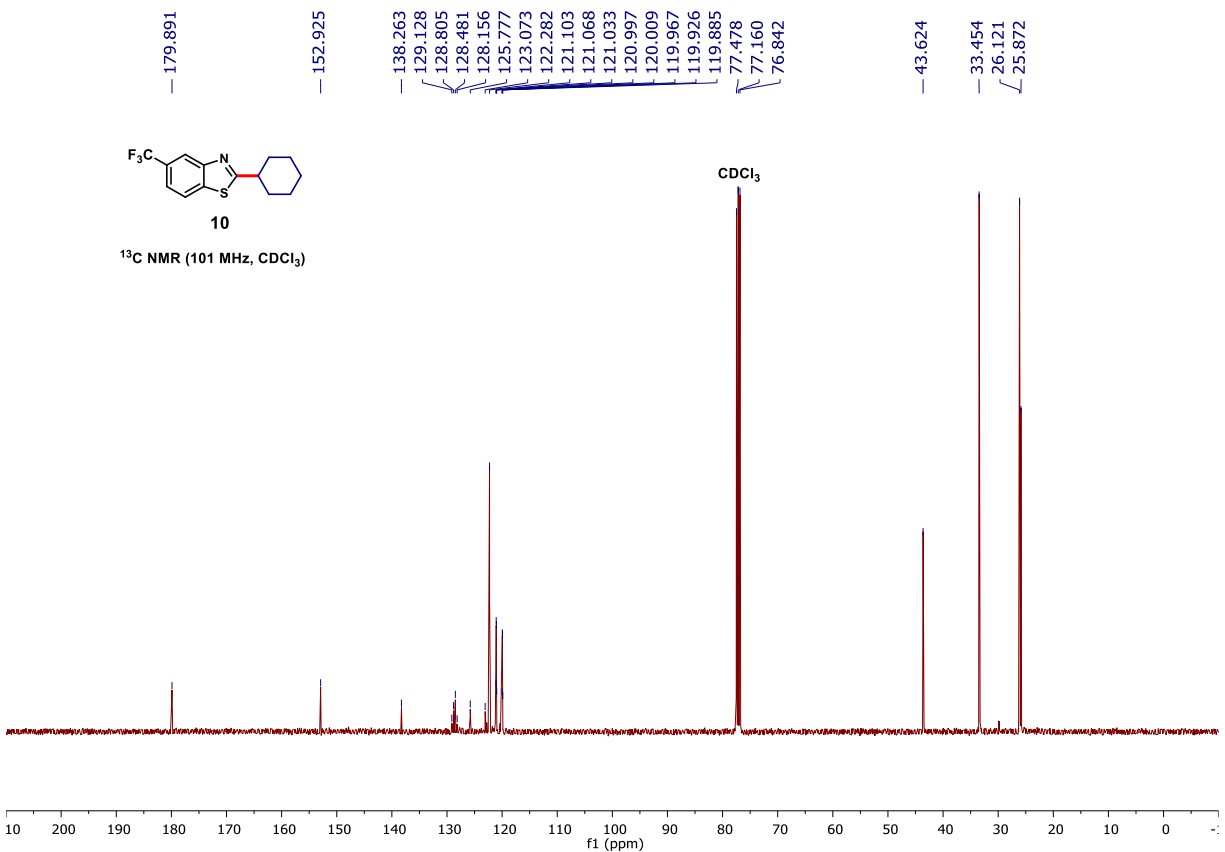
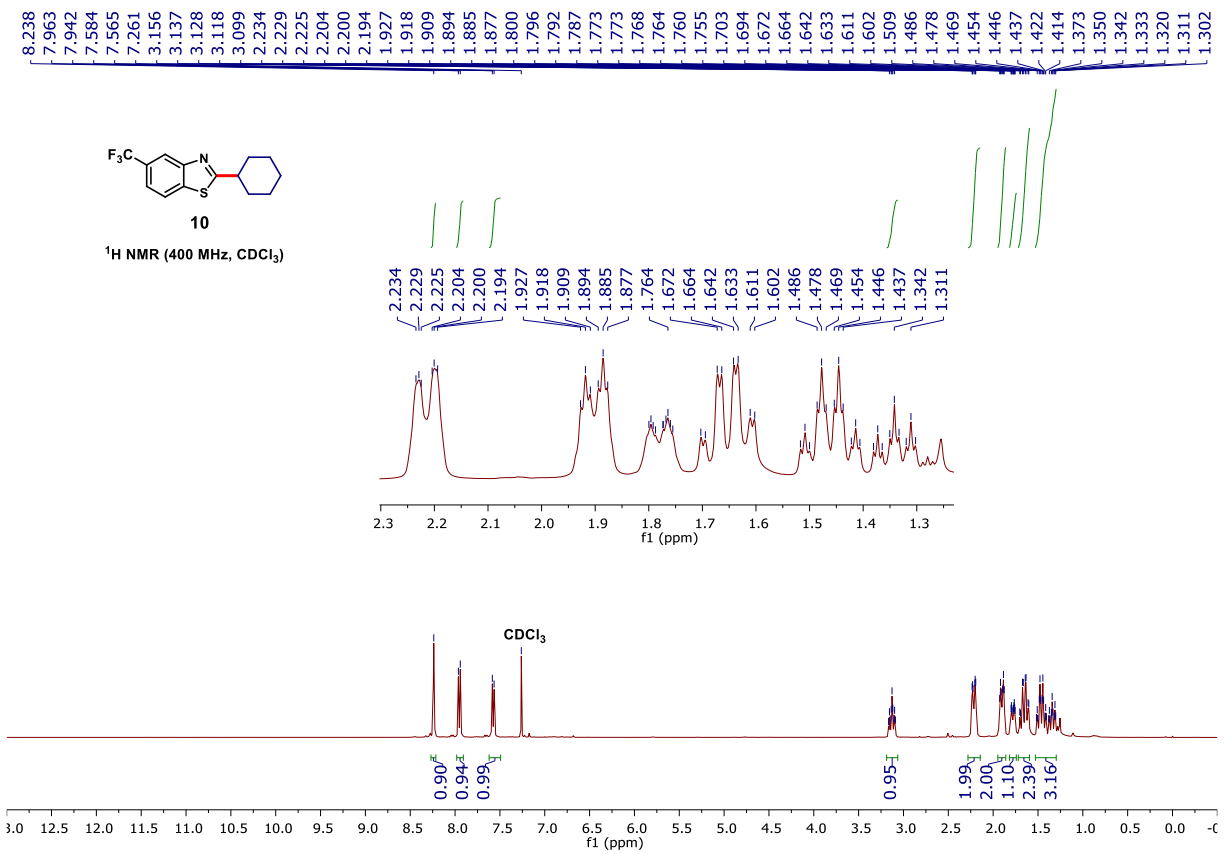


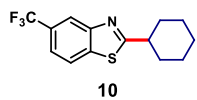






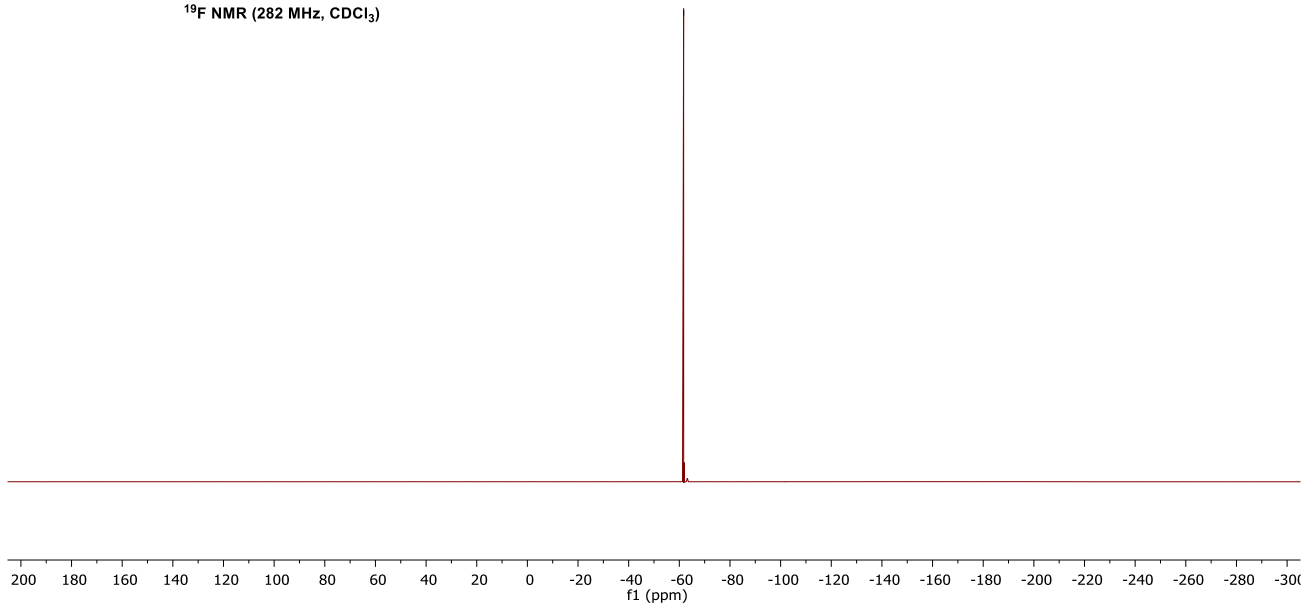


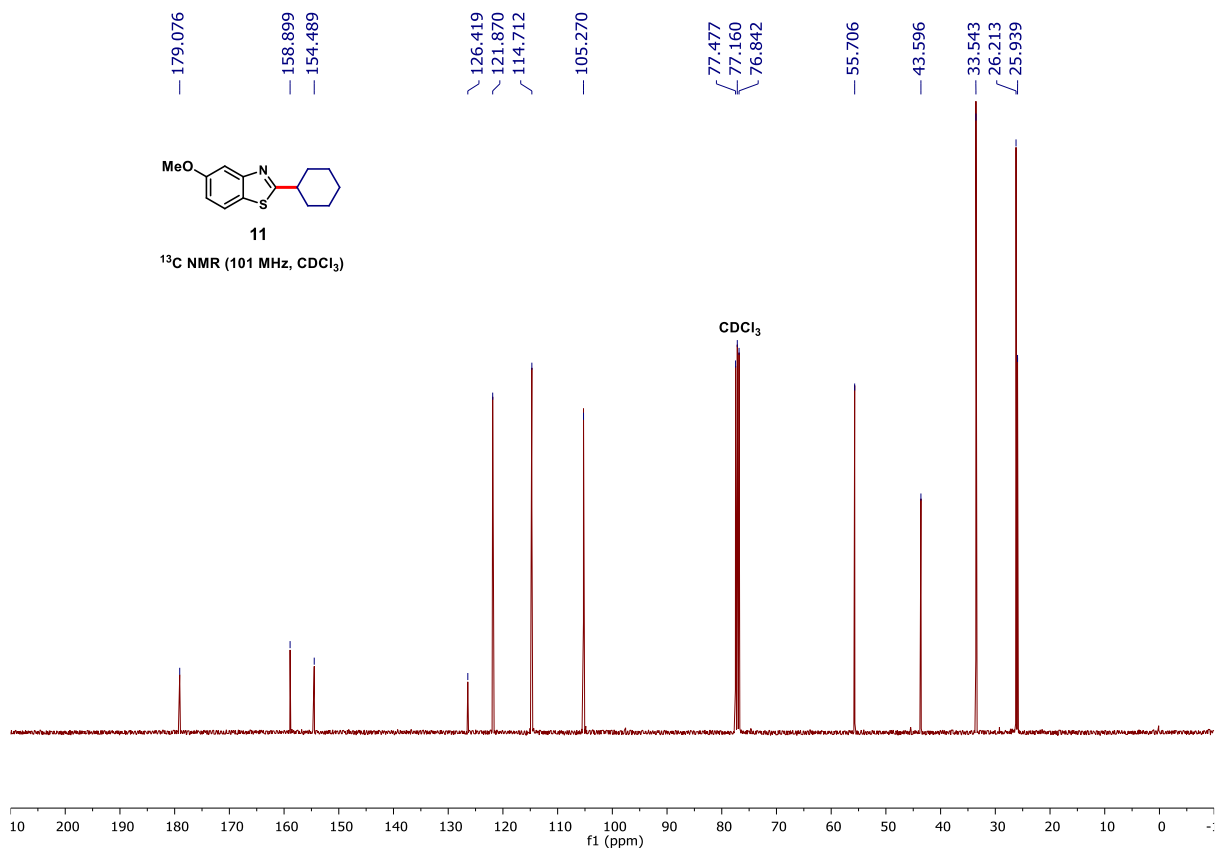
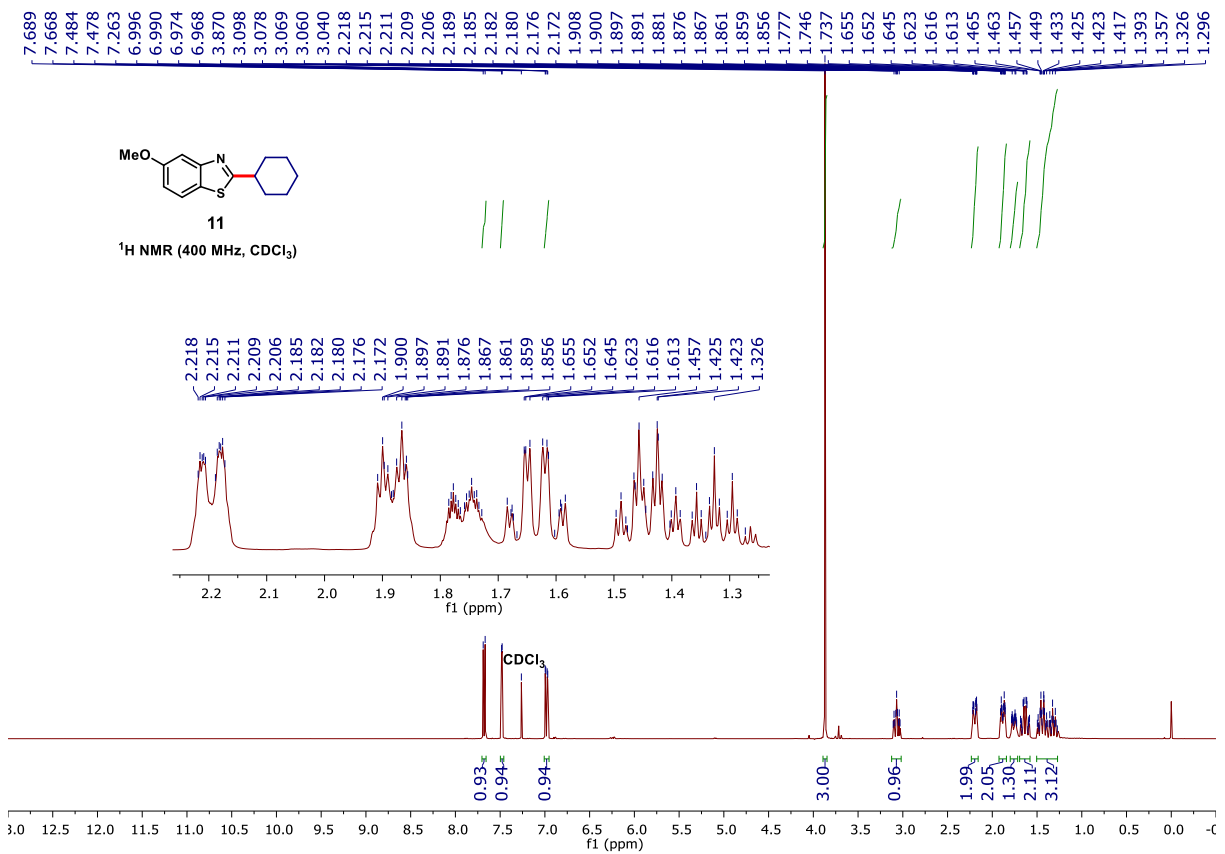


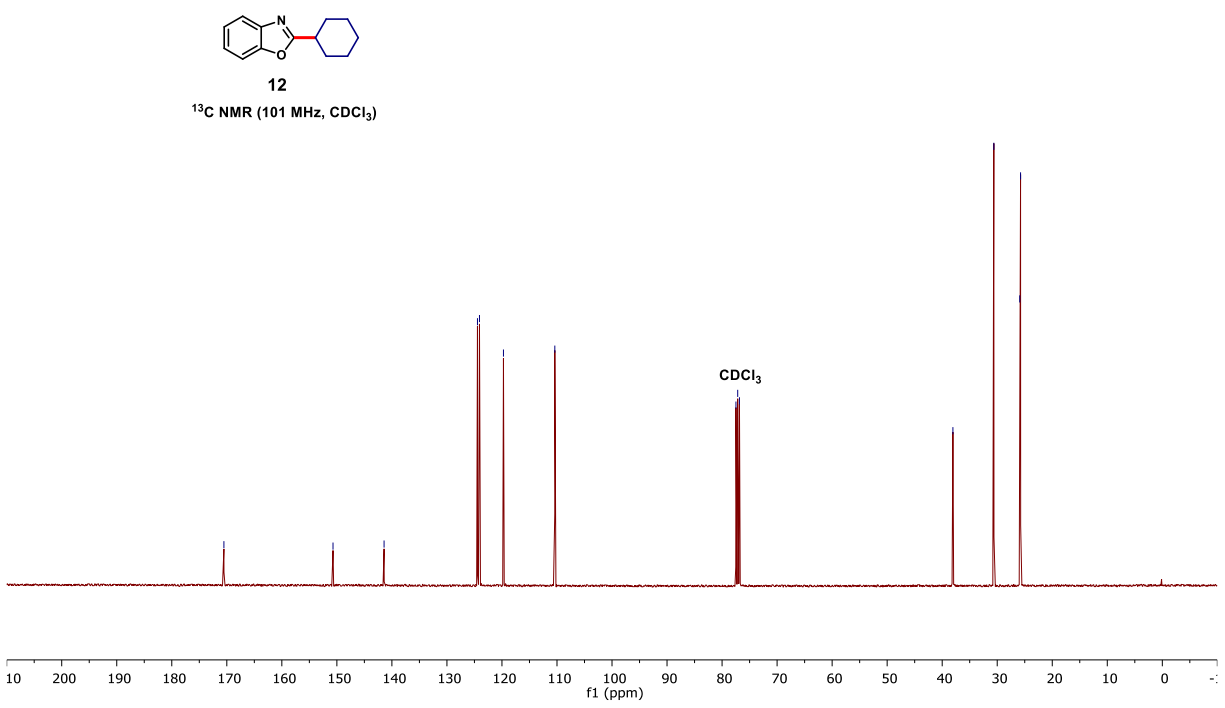
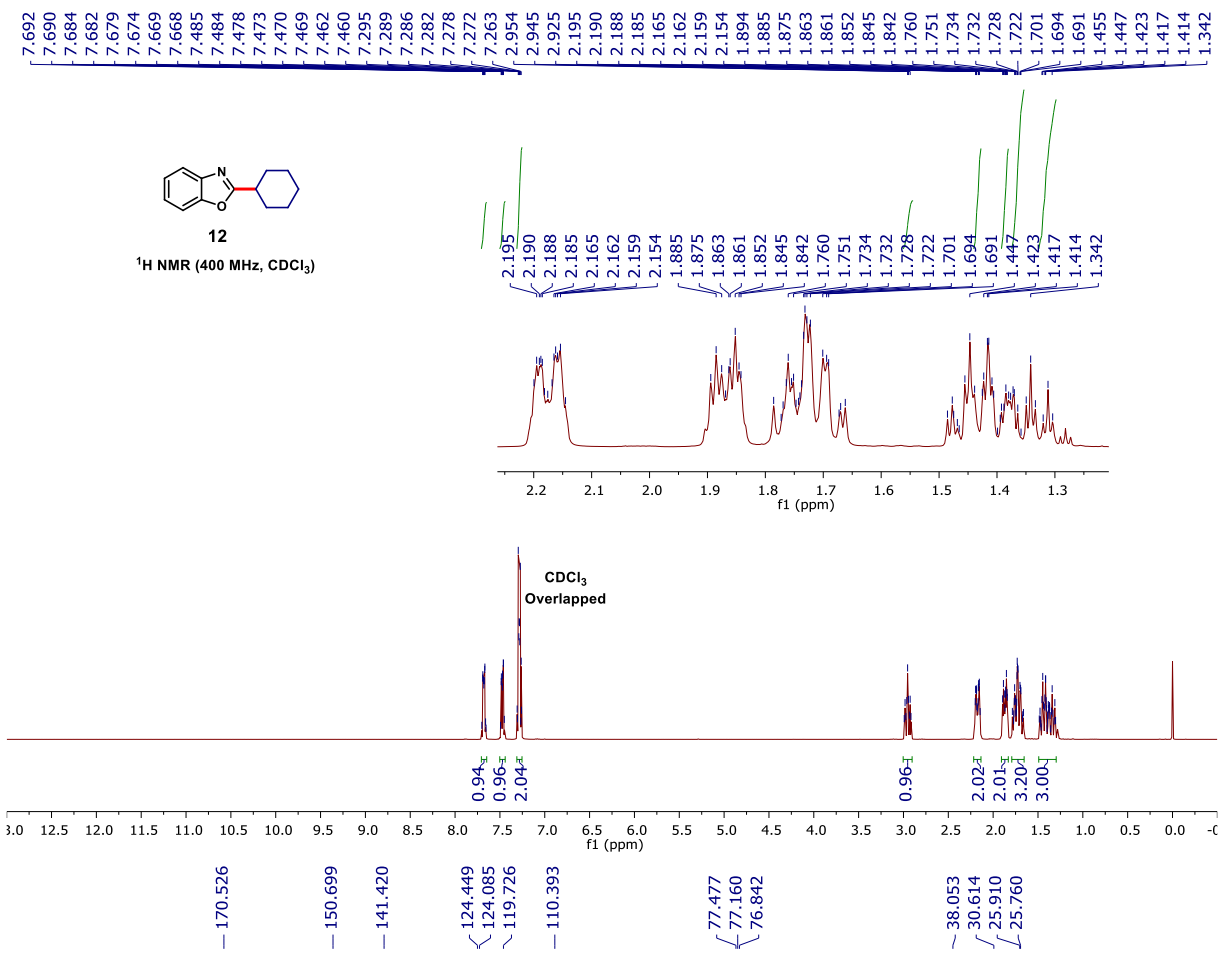


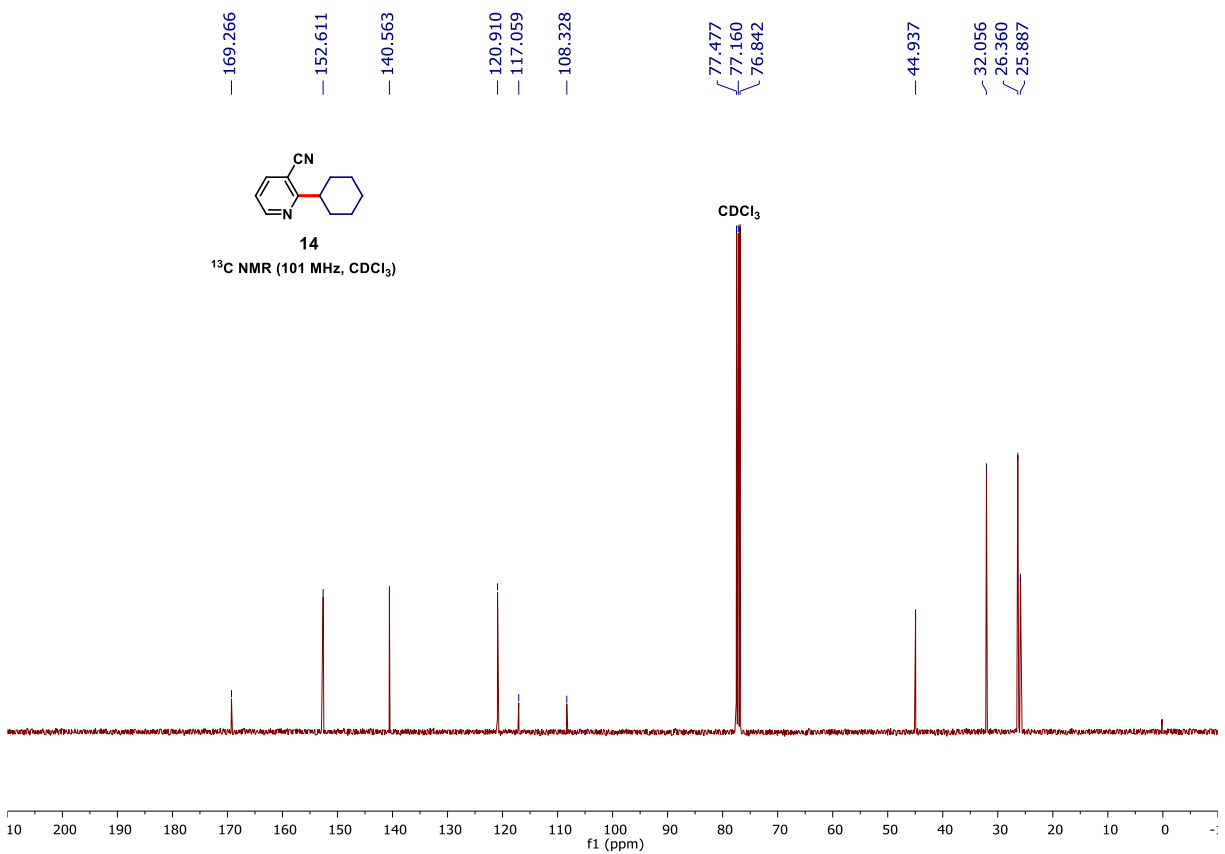
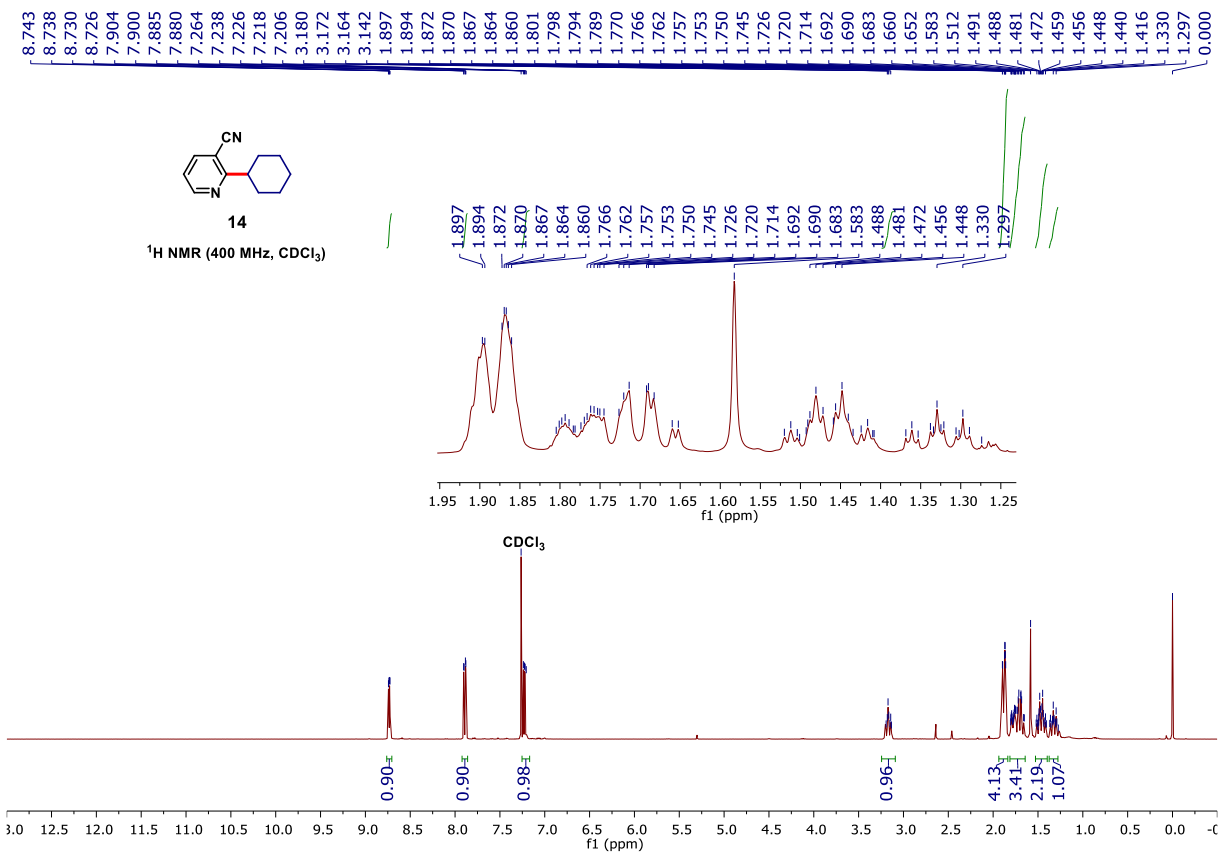
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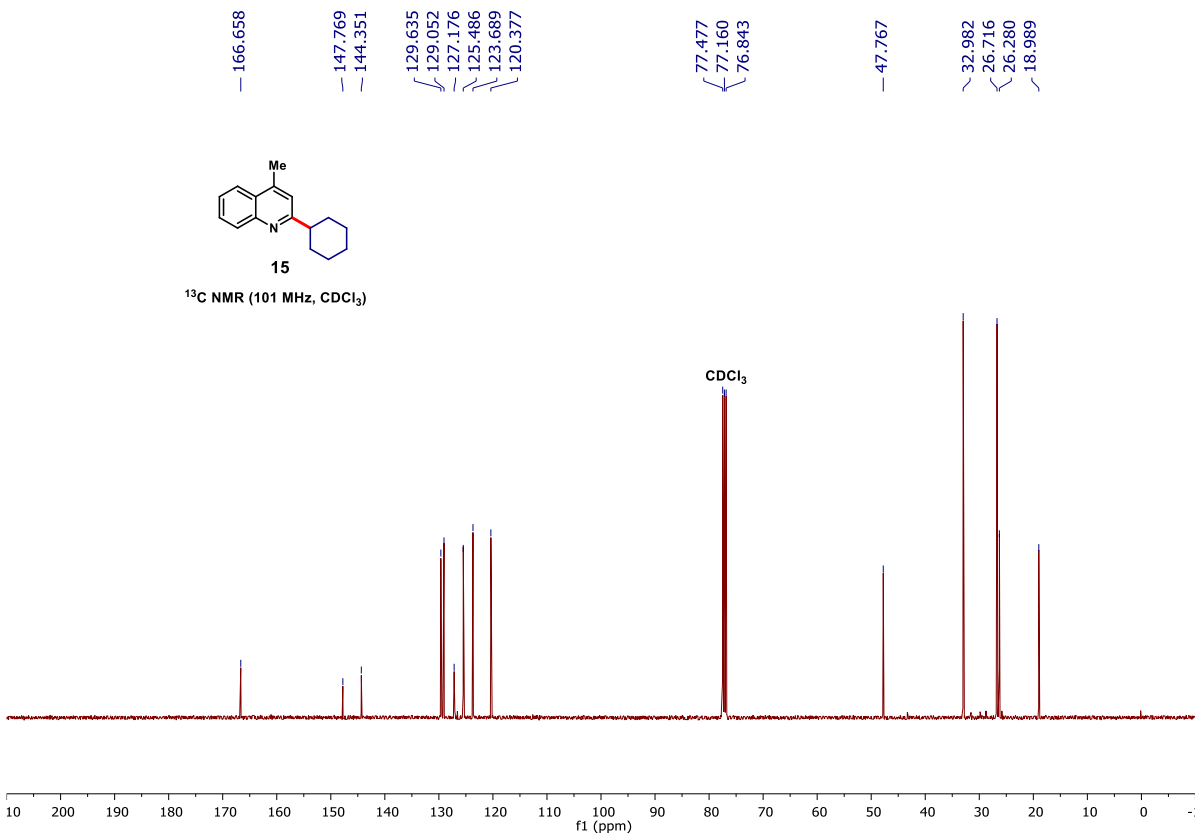
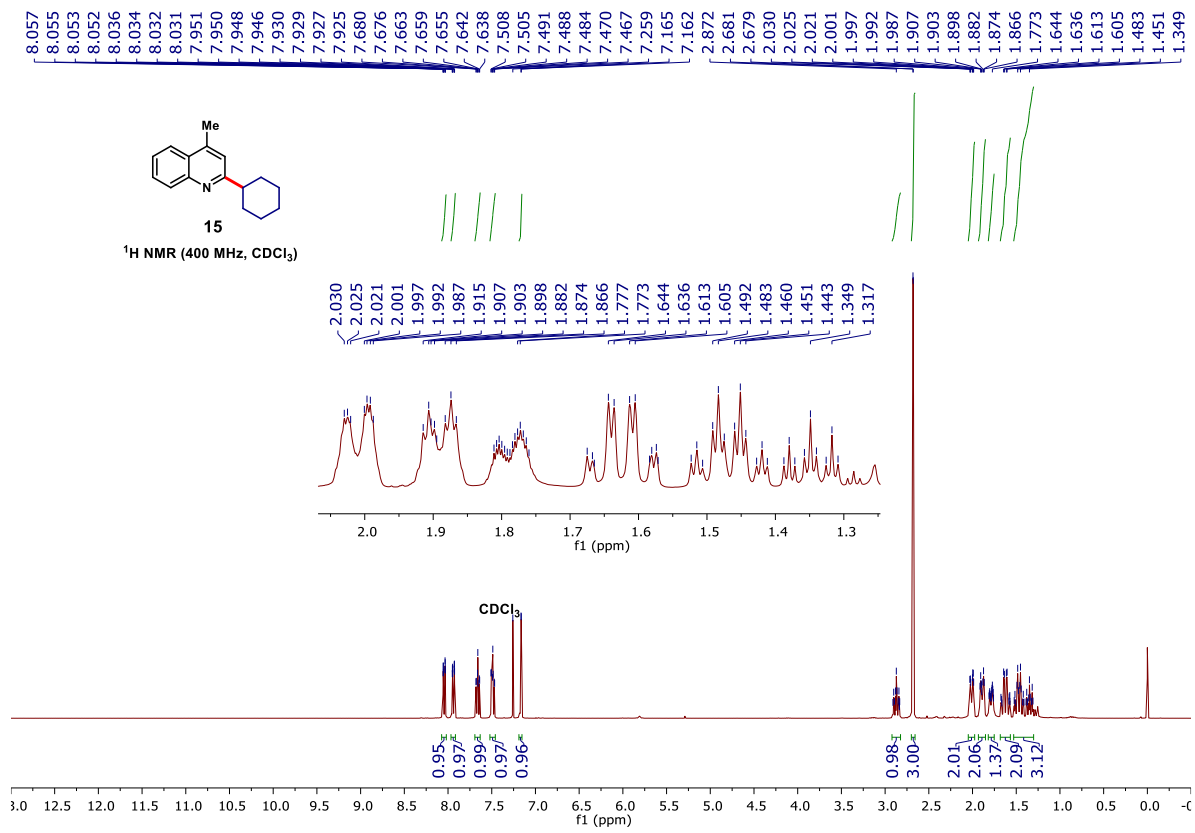
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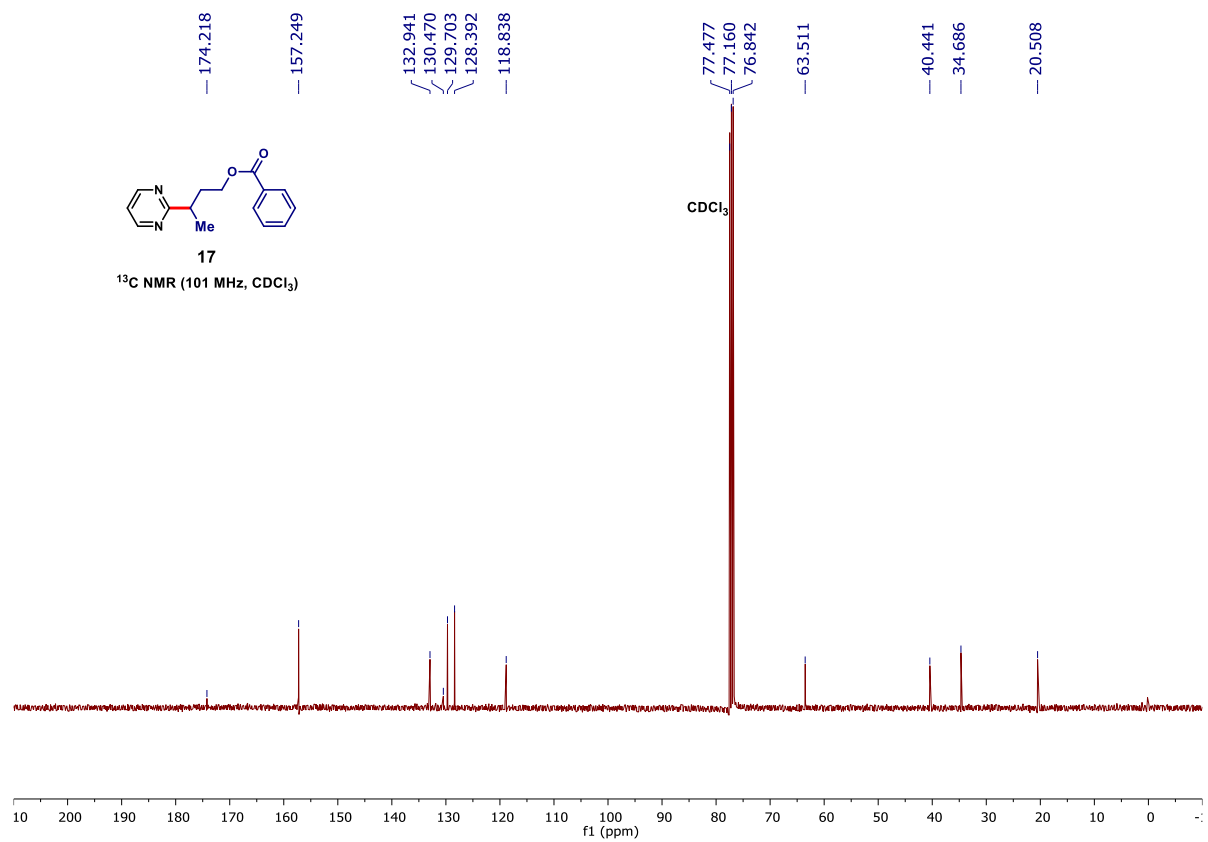
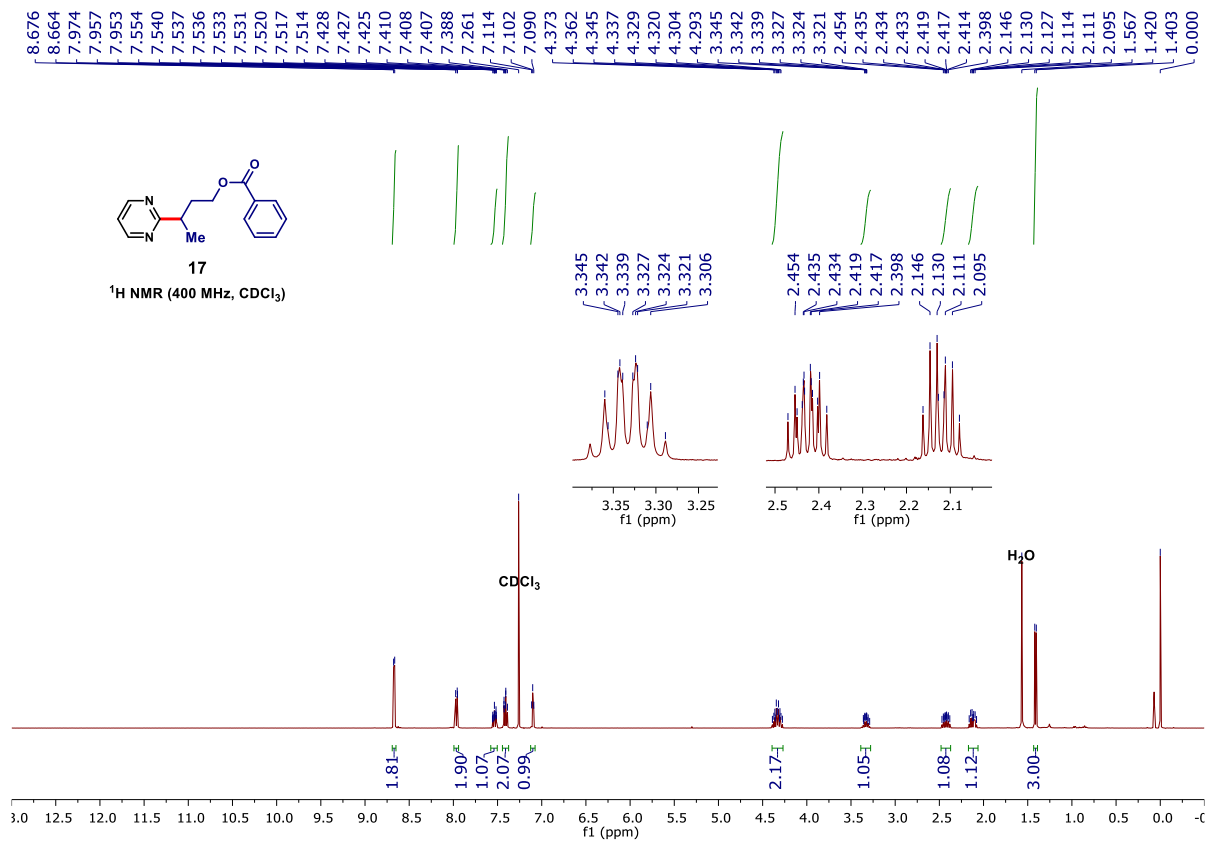


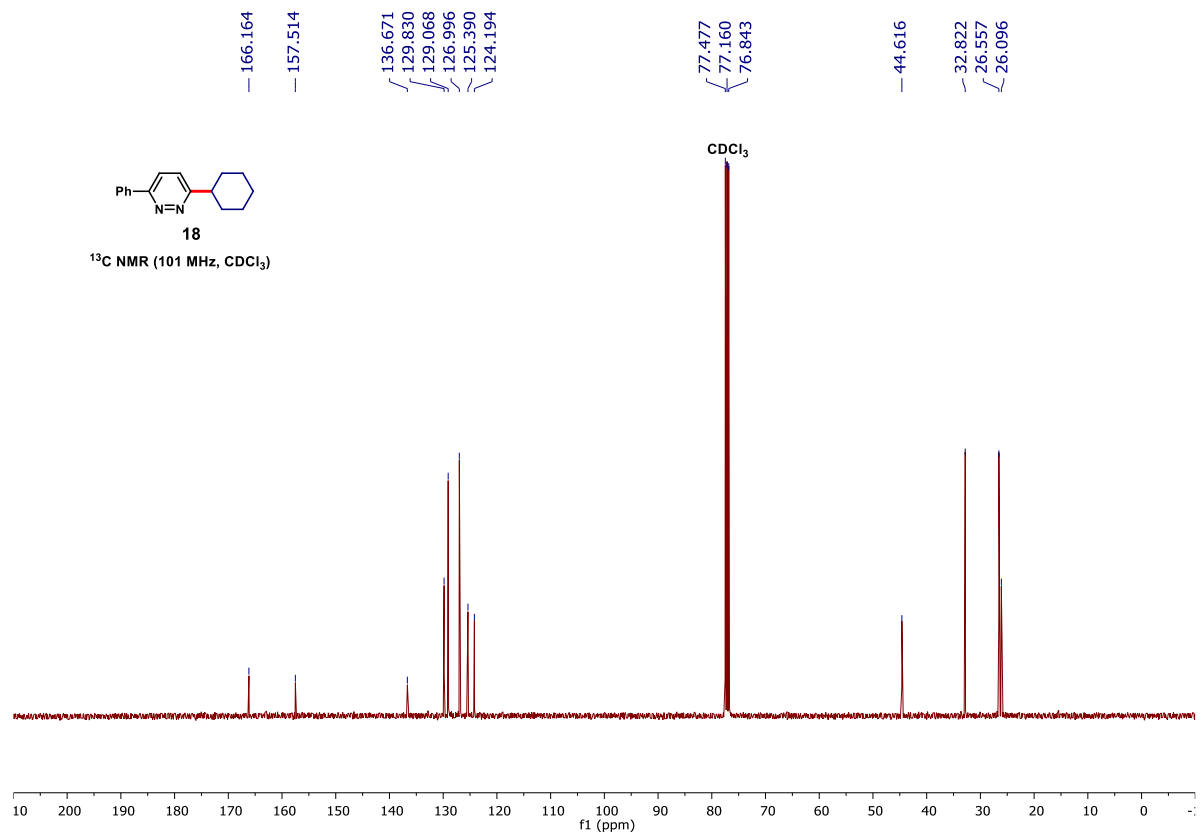
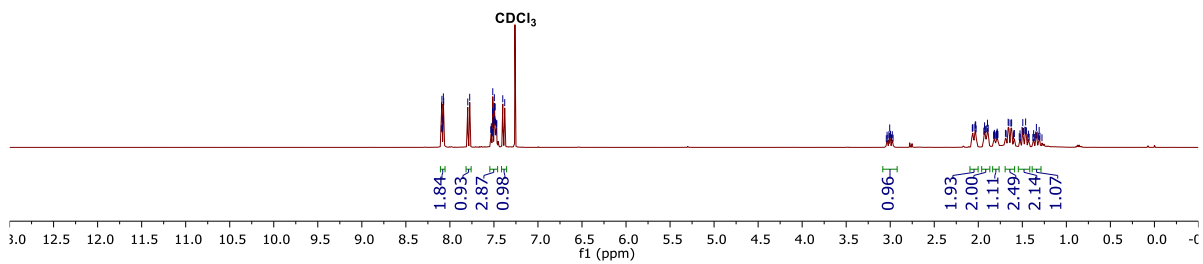
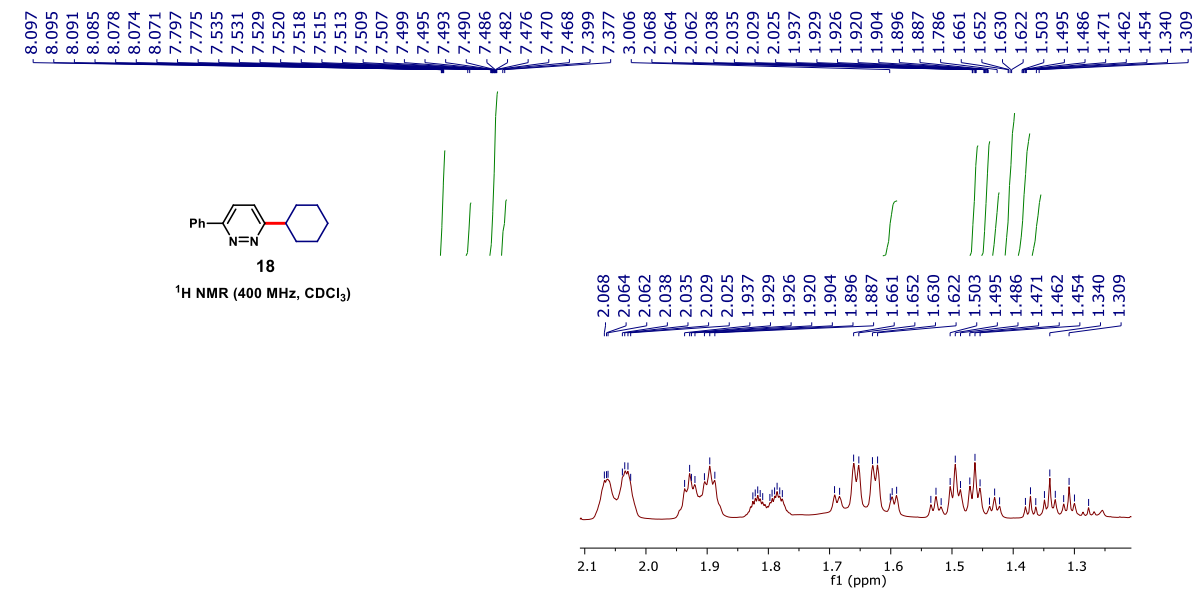


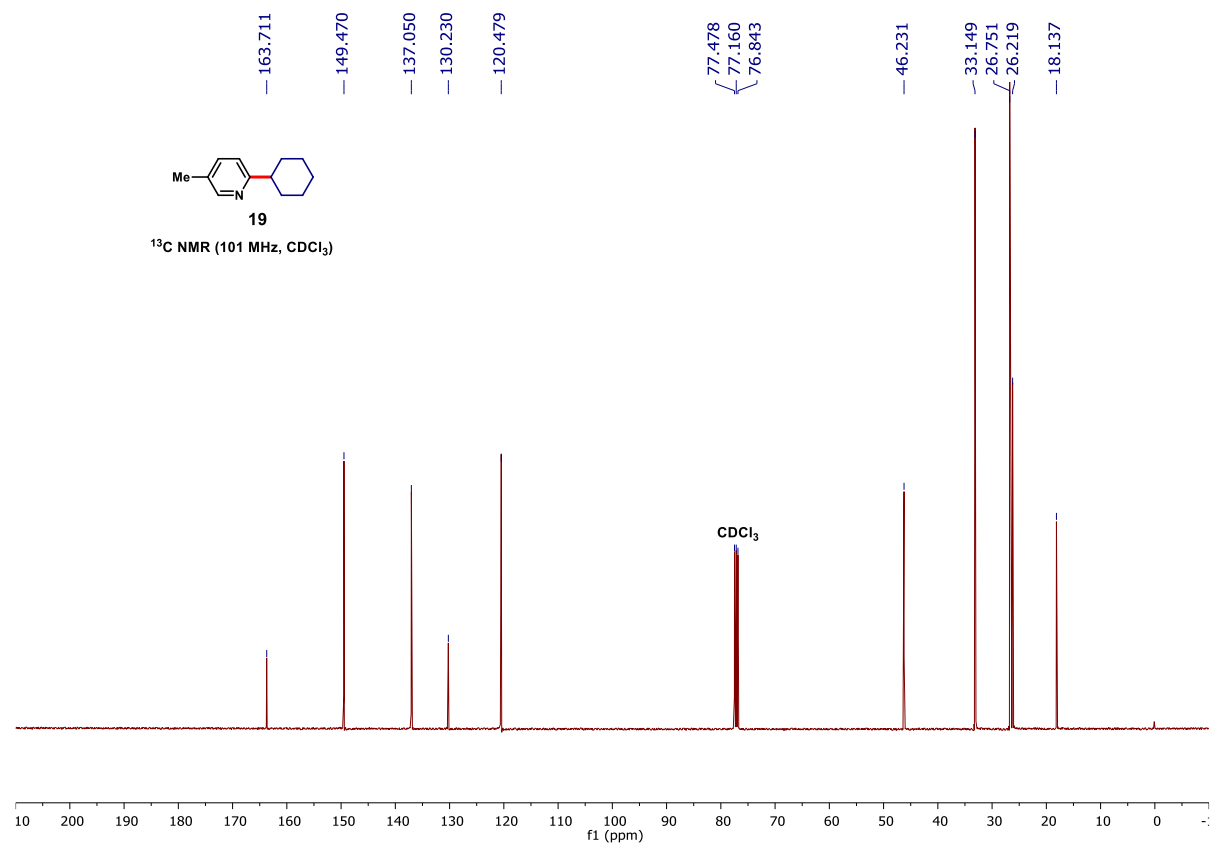
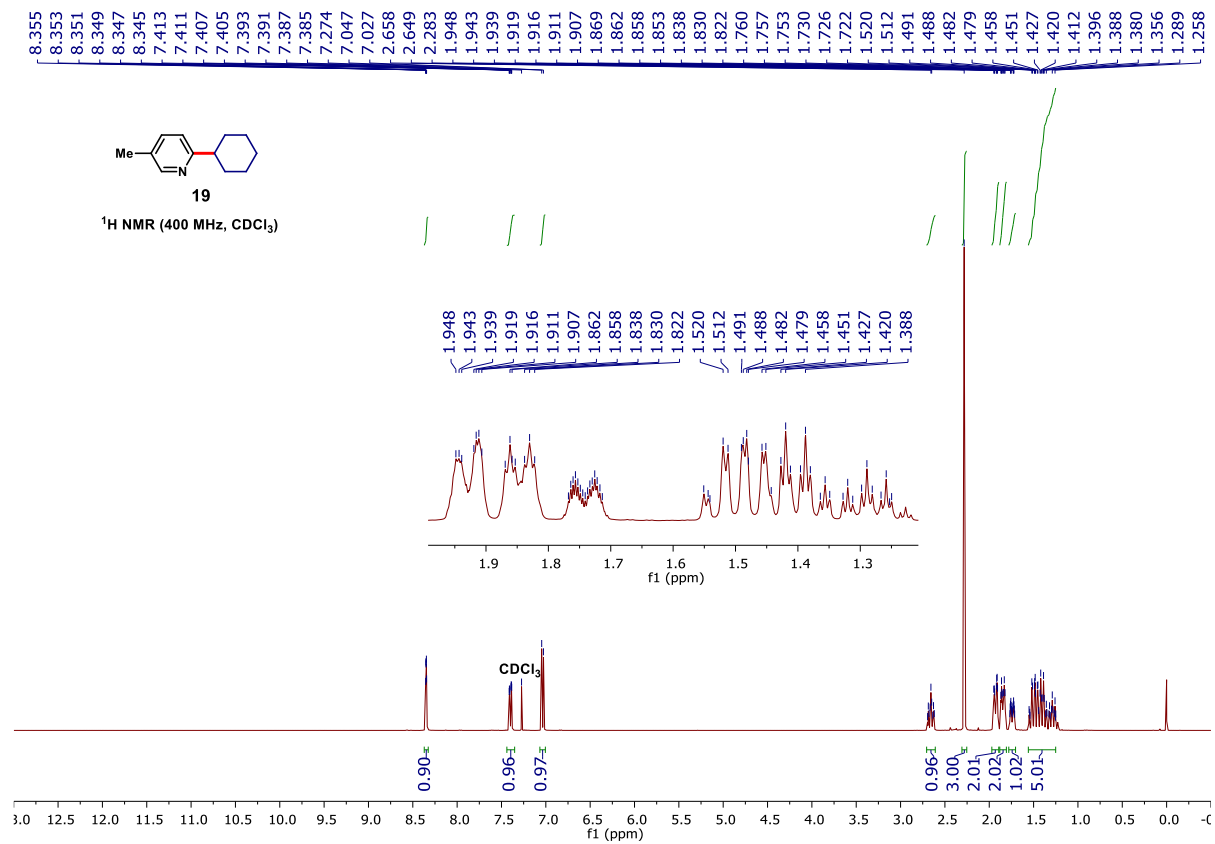


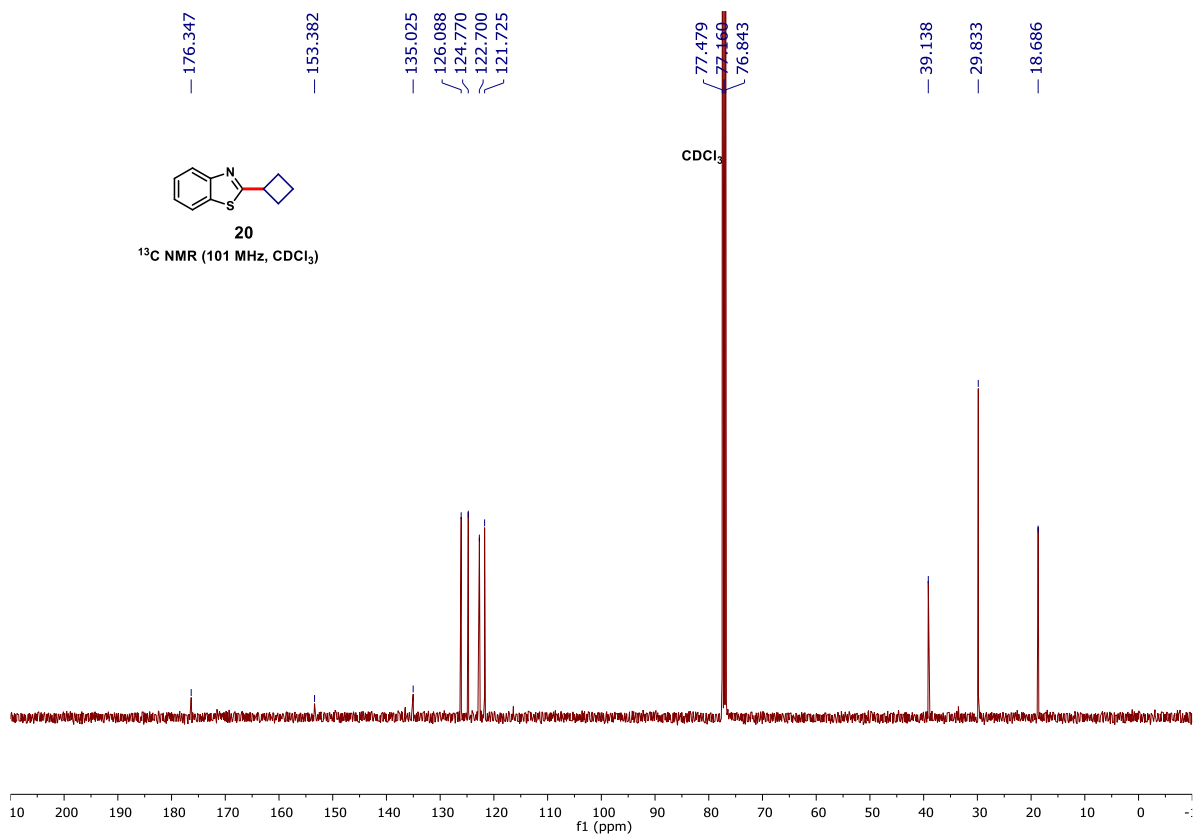
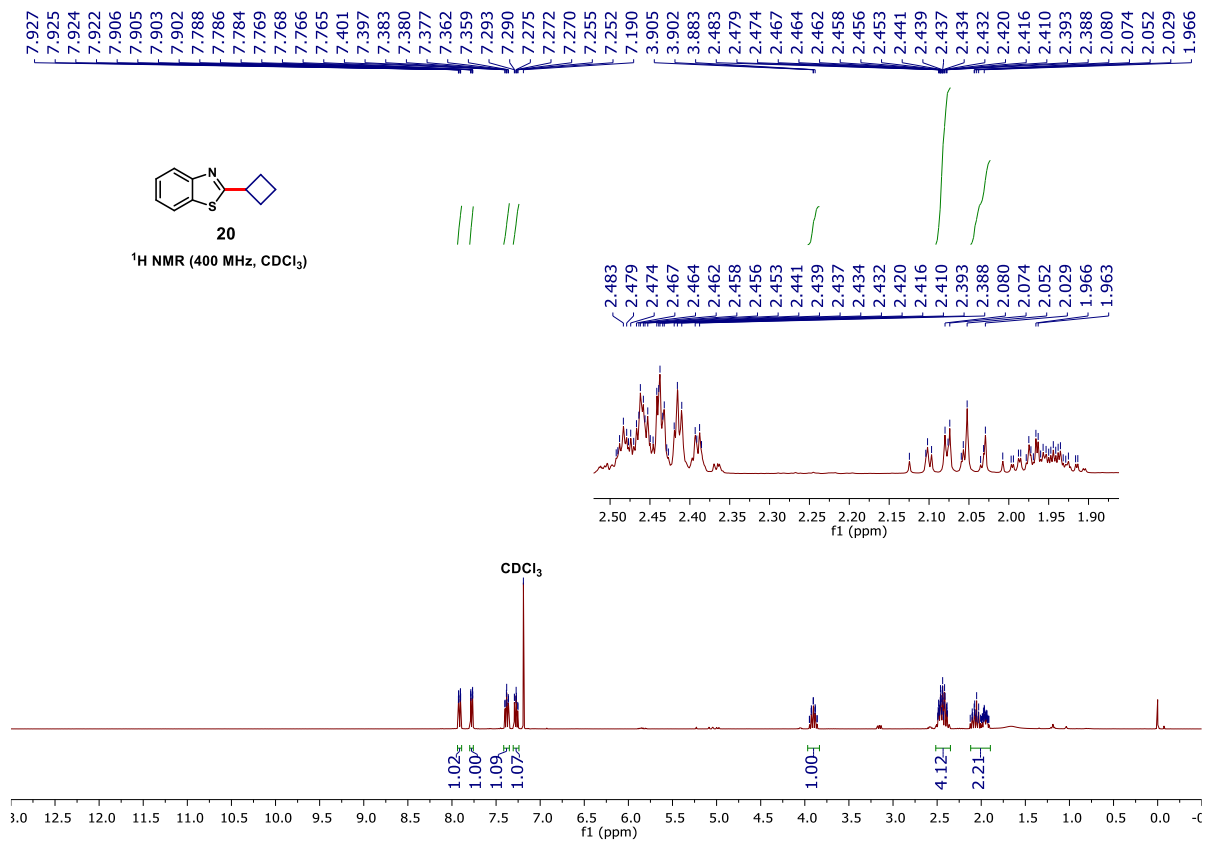


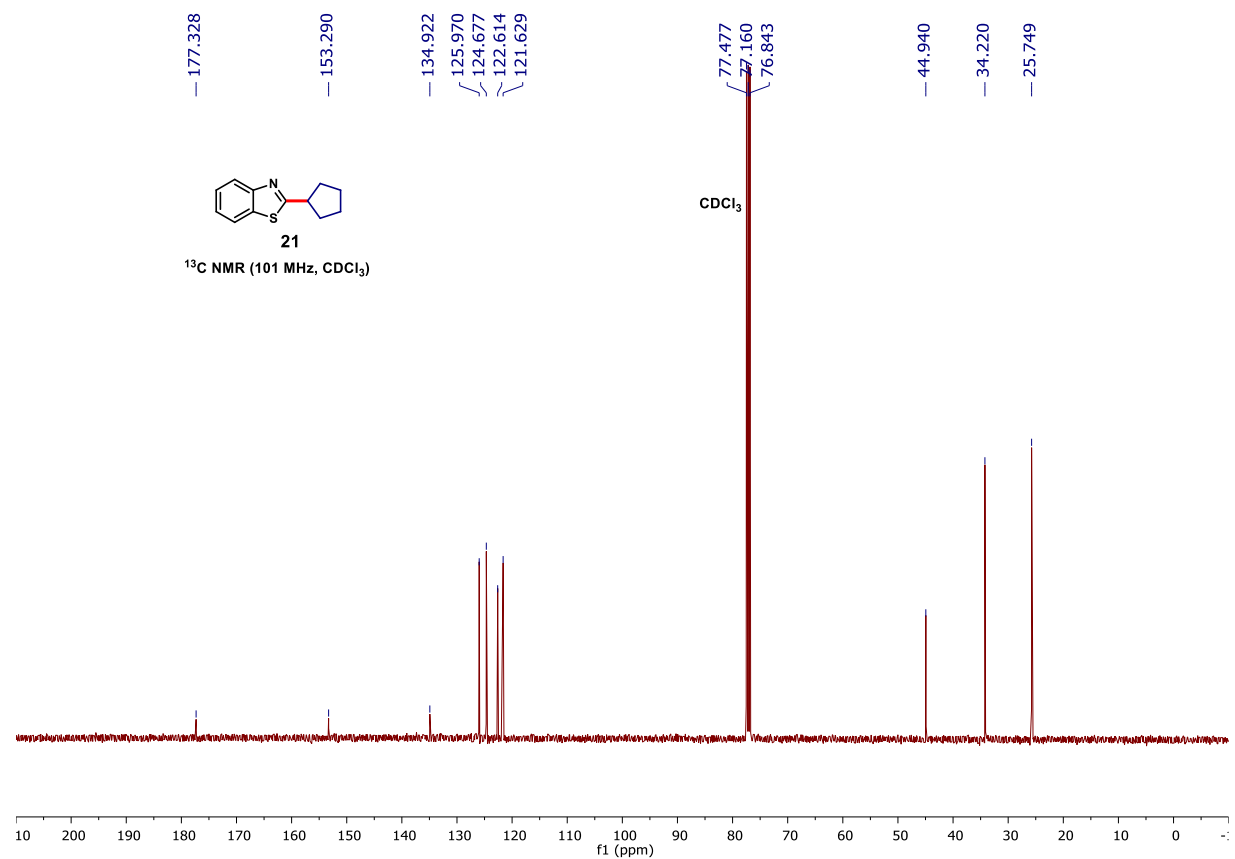
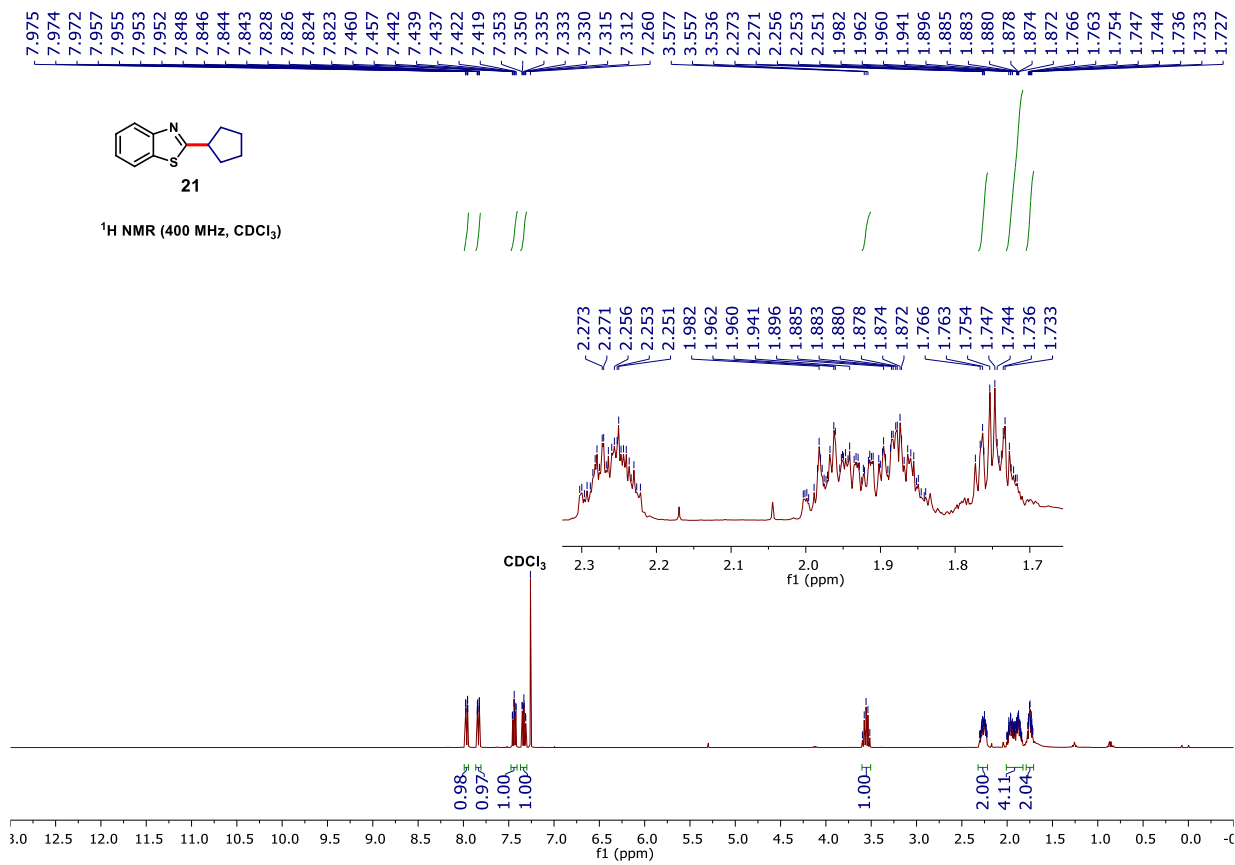




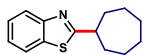






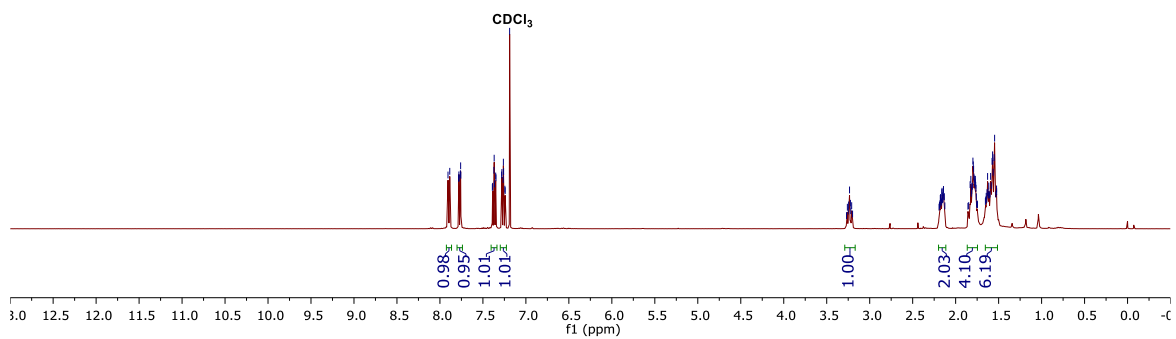


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7.782
7.780
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7.757
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7.372
7.387
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7.366
7.351
7.348
7.282
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7.264
7.262
7.259
7.244
7.241
7.189
3.235
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2.158
2.144
2.142
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1.823
1.814
1.810
1.807
1.799
1.795
1.791
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1.782
1.778
1.774
1.771
1.767
1.763
1.634
1.629
1.624
1.615
1.593
1.586
1.576
1.570
1.568
1.564
1.553
1.547
1.524
1.523



22

¹H NMR (400 MHz, CDCl₃)



178.942

153.043

134.773

125.953

124.655

122.649

121.661

77.478

77.160

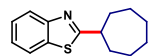
76.842

45.649

35.523

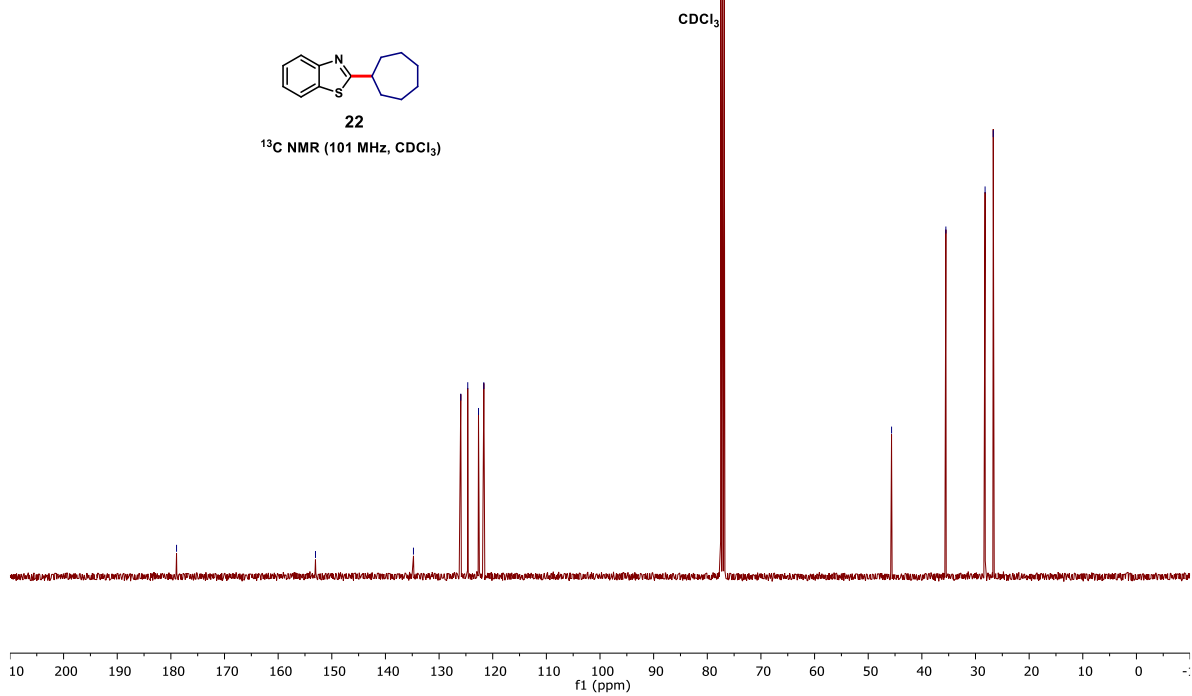
28.213

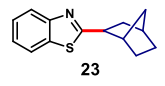
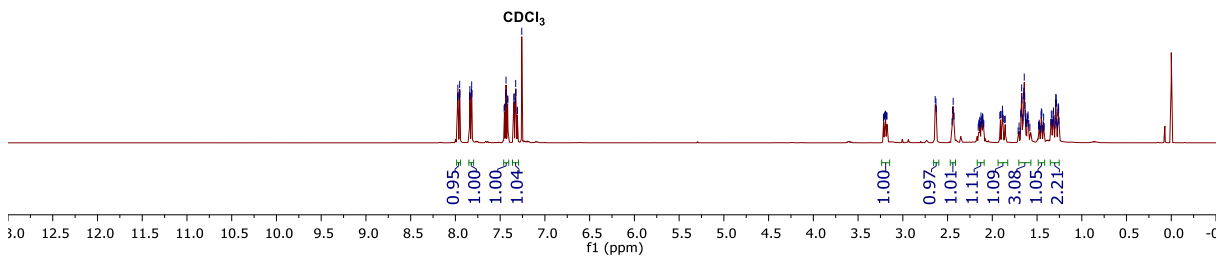
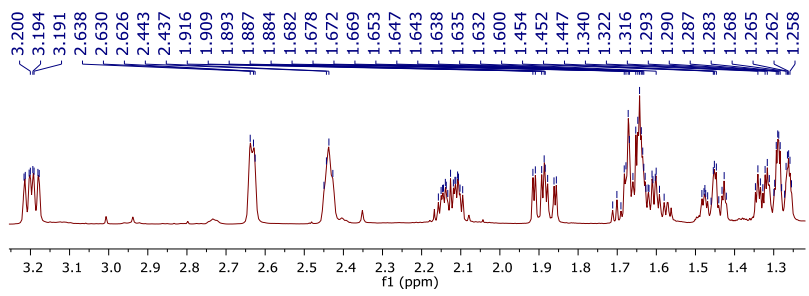
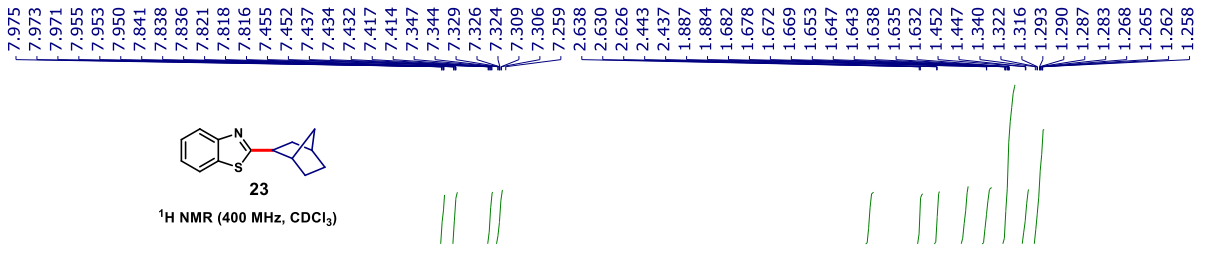
26.690



22

¹³C NMR (101 MHz, CDCl₃)





¹³C NMR (101 MHz, CDCl₃)

