Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

A Compact, Practical Photoreactor for Multi-Reaction Arrays

Gregory D. Brown*, Daniel Batalla, Cullen L. Cavallaro, Heidi L. Perez, Stephen T. Wrobleski, Trevor C. Sherwood*

Research and Development, Bristol Myers Squibb Company, Route 206 and Province Line Road, Princeton, NJ 08543-4000

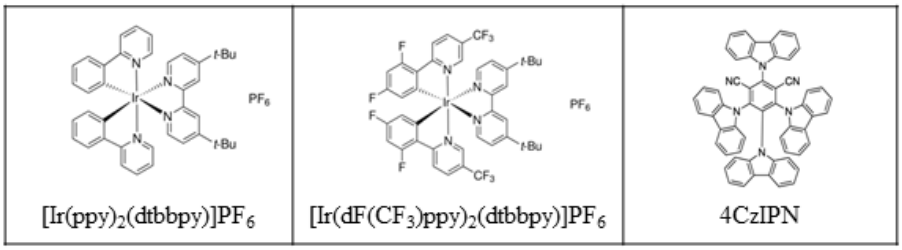
Supplemental Information

Table of Contents

Table S1. Abbreviations/Reagent information

Abbreviation	Name
BMS-PR460	Bristol Myers Squibb Photoreactor with blue LEDs (460 nm)
LED	light-emitting diode
UHPLC-MS	ultra-high performance liquid chromatography-mass spectrometry
Cs_2CO_3	cesium carbonate
DIC	*N,N'*-diisopropylcarbodiimide
DMAP	*N,N*-dimethylaminopyridine
TFA	trifluoroacetic acid
DMA	*N,N*-dimethylacetamide
DMSO	dimethyl sulfoxide
$Ni(dtbbpy)Br_2$	[4,4'-di-tert-butyl-2,2'-bipyridine] nickel (II) bromide
4CzIPN	1,2,3,5-Tetrakis (carbazol-9-yl)-4,6-dicyanobenzene
$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	[4,4′-Bis (1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]bis [3,5-difluoro-2- [5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium (III) hexafluorophosphate
$[Ir(ppy)_2(dtbbpy)]PF_6$	[4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]bis[2-(2-pyridinyl-*N*)phenyl-C]iridium(III) hexafluorophosphate

Figure S1. Photocatalyst Structures



$[Ir(ppy)_2(dtbbpy)]PF_6$ | $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ | 4CzIPN

Safety

The LEDs used during reactions in this publication generate light at wavelengths that are potentially harmful if exposed to the unprotected eye. For safety purposes, a light filtering shield was used during all reactions. If a shield is not available, the appropriate eyewear is strongly recommended. For the blue LEDs (wavelength = 460 nm), orange tinted glasses are appropriate.

Irradiance Measurements

Irradiance measurements were performed using a StellarNet Black-Comet-SR Concave Grating Spectrometer, model C-SR50 with UV-VIS-NIR wavelength range covering 200-1080 nm

(https://www.stellarnet.us/spectrometers/black-comet-sr/). Spectral irradiances of the LEDs were measured inside the reactor by placing the detector probe inside near the vial holder. Average irradiance (W/m^2) was calculated. To measure the light filtering shield effectiveness, the intensity was measured above the reactor with and without the shield. An internal irradiance measurement showed max emission wavelength of the SMD 5050 blue LEDs described in Table S2 to be 455 nm, see Figure S2. As the manufacturer has rated emission at 460 – 465 nm, 460 nm was selected as the number to use for reactor naming and description purposes for the BMS-PR460.

Figure S2. SMD 5050 Blue LED irradiance measurement

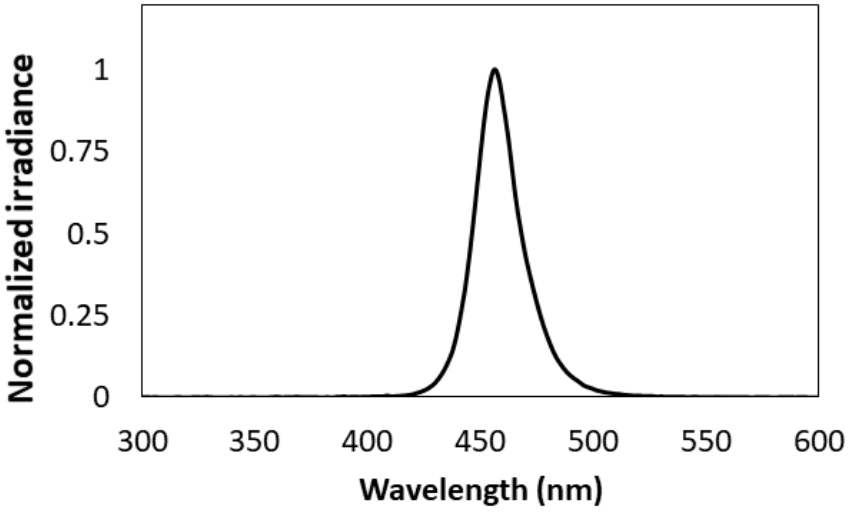


Figure S3. BMS-PR460 Dimensions

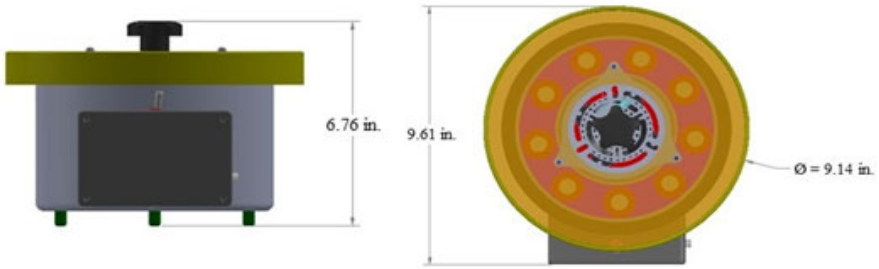


Table S2. BMS-PR460 Parts List

Name	Description	Qty	Cost (Each)	Source
Non-waterproof Blue LED light strips	Type: SMD 5050, 460-465nm, 300 LEDs/5m	2	$15.00	Amazon
Non-waterproof Purple LED light strips for BMS-PR400	Type: SMD 5050, 385-400nm, 300 LEDs/5m	2	$12.99	Amazon
Stainless Steel Beaker	Modified: 6 L Beaker # 5MZFO	1	$77.00	Grainger # 5MZFO
Edge Trim	Plastic Trim	2 ft	$5.00	McMaster-Carr # 86875K94
Cooling Fan	FP-108 F/DC 24V DC Axial fan S-3	1	$23.75	McMaster- Carr Part# 1939K59
Cooling Fan Mount	3d printed White Natural Versatile Plastic	1	$25.00	Shapeways 3D Printing
Safety Switch	Orion Air Flo Switch #AFM-01NO	1	$46.00	Digi-Key #1053-1579-ND
Control Enclosure	Modified: Hammond Manufacturing #1591TBK	1	$8.33	Digi-Key # HM122-ND
*Control Relay	TE Connectivity P&B Relay #RT214012	1	$3.50	Digi-Key # PB1690-ND
*PCB Board	Modified: Uxcell 3x7cm Printed Circuit Board	1	$1.00	Amazon
*6 Position Term Blk	Amphenol Fixed Terminal Blk#VI062155000G	1	$1.40	Mouser# 649-220316-H061B01LF
*4 Position Term Blk	Amphenol Fixed Terminal Blk#VI042155000G	1	$1.30	Mouser# 649-220316-H041B01LF
*Toggle Switch	2 position SPST-NO 15A	1	$5.50	McMaster-Carr # 7343K711
*Power Jack	Ayecehi 5 pack 5.5x2.1mm 10 amps DC-099	1	$2.50	Amazon
Power Supply	Alitove 12 VDC 10 Amp	1	$20.00	Amazon
Air Flow Tube	Modified: 3.75" OD x 3.5" ID 6061 Aluminum Tube	1	$21.00	Metals Depot # T3R334125
Air Flow Tube Mount	Modified: .5" x 1.0 "x 3.50" 6061 Aluminum Bar	1	$3.50	McMaster-Carr # 8975K11
Light Filtering Shield	Modified: .125" Clear Cast Acrylic Fluorescent Amber	1	$15.50	McMaster-Carr # 85635K522
*Shield Skirt	3d printed White Natural Versatile Plastic	1	$34.00	Shapeways 3D Printing
Vial Insert Rack	Modified: .125" Clear Cast Acrylic sheet	2	$9.50	McMaster-Carr # 8560K239
*Knob	Plastic Five Arm Knob with 1/4-20 Threaded Hole	1	$1.10	McMaster-Carr # 59625K31
* Standoff	Aluminum threaded Standoff 1/4" OD x 1-1/2"	3	$1.12	McMaster-Carr # 93330A462
* Standoff	Aluminum threaded Standoff 1/4" OD x 2-1/4"	3	$0.63	McMaster-Carr # 91780A041
*Vial Insert Mount	Modified: Clear Polycarbonate 3/8" x 6" x 6"	1	$7.88	McMaster-Carr # 8574K311

General Reaction and Analytical Information

The reactions were run in 8-mL Chemglass vials with pressure relief septum caps. The products were purified via Purification Method 1, except where otherwise indicated.

Purification Method 1: Flash column chromatography on a Teledyne Isco instrument using RediSep Rf silica columns and 40−63 μm silica gel from Fluka Analytical. Fractions containing the desired product were combined and dried under reduced pressure. Hexanes, ethyl acetate, and dichloromethane used for purification were purchased as HPLC grade from Sigma-Aldrich.

Purification Method 2: The crude material was purified via preparative Reverse Phase chromatography with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5 μm particles; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and

dried via centrifugal evaporation. A mobile phase buffered with ammonium acetate was used except where otherwise noted.

Purification Method 3: The crude material was purified via preparative Reverse Phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 100 mm, 5 μm particles; Flow Rate: 17 mL/min. Fraction collection was triggered by peaks UV (200-300 nm). Fractions containing the desired product were combined and dried via centrifugal evaporation (Biotage V-10 Touch).

The purified products were analyzed by liquid chromatography/mass spectrometry (LCMS) on a Waters Acquity UPLC BEH C18 column (1.7 μm particles, 4.6 mm × 50 mm); using Method A, except where otherwise noted.

Method A: Column: Waters Acquity UPLC BEH C18, 4.6 x 50 mm, 1.7 μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1 % trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1 % trifluoroacetic acid; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1 mL/min; Detection: UV (220 nm and 254 nm) and low-resolution mass spectrometry detection with Waters SPD 30AM Detector with dual electrospray ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI).

Method B: Column: Waters Acquity BEH C18, 2.1 x 50mm, 1.7 μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1 mL/min; Detection: UV (220 nm and 254 nm) and low-resolution mass spectrometry detection with Waters SPD 30AM Detector with dual electrospray ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI).

Method C: Column: XBridge C18, 2.1 mm x 50 mm, 1.7 μm particles; Mobile Phase A: ACN/H2O (5:95) with 10 mM AA; Mobile Phase B: ACN/H2O (95:5) with 10 mM AA; Temperature: 50 °C; Gradient: 0-100 %B (0.0-3.0 min), 100 %B (3.0-3.5 min); Flow: 1.0 mL/min; Detection: UV (220 nm and 254 nm) and MS (ESI +).

Method D: Column: XBridge C18, 2.1 mm x 50 mm, 1.7 μm particles; Mobile Phase A: ACN/H2O (5:95) with 0.05 % TFA; Mobile Phase B: ACN/H2O (95:5) with 0.05 % TFA;
Temperature: 50 °C; Gradient: 0-100 %B (0.0-3.0 min), 100 %B (3.0-3.5 min); Flow: 1.0 mL/min; Detection: UV (220 nm) and MS (ESI +).

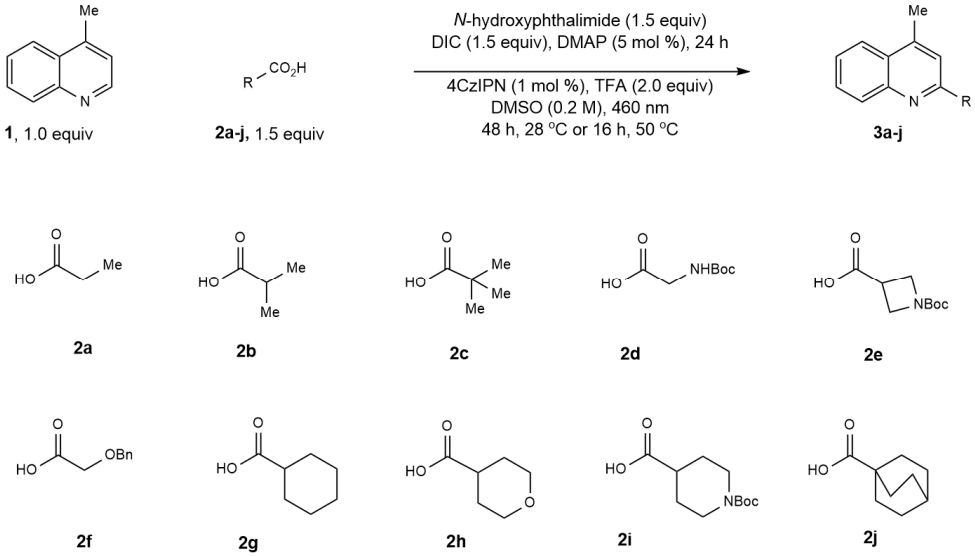
All reagents were purchased from commercial suppliers and used without further purification. All reactions were conducted in the standard, ambient temperature BMS-PR460 with single setting full speed fan except where indicated.

All NMR spectra were obtained at room temperature unless otherwise stated. NMR spectra were internally referenced to the solvent peak according to the following reference: *J. Org. Chem.* 1997, **62**, 7512-7515.

Reaction Experimentals

1. Minisci-Type C-H Alkylation Reaction.

Scheme S1. One-pot Minisci-type C-H alkylation between lepidine (**1**) and carboxylic acids **2a-j**



General Procedure 1 – NAP formation

To a DMSO (700 µl) solution of the desired acid (210 µmol) in a pressure relief vial, *N*-hydroxyphthalimide (34.2 mg, 210 µmol), DMAP (0.9 mg, 6.98 µmol), and DIC (32.4 µl, 210

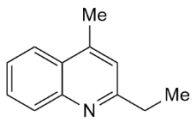
μmol) were added. The reaction was stirred at ambient temperature for 24 hours, forming the intermediate *N*-(acyloxy)phthalimides (NAP).

General Conditions A (ambient temperature, 28 °C). To the reaction vial containing the NAP intermediate, 4-methylquinoline (18.5 μl, 140 μmol), 4CzIPN (1.1 mg, 1.40 μmol), and TFA (21.5 μl, 279 μmol) were added to each reaction vial. Each solution was purged with nitrogen for 2 minutes. The reaction was sealed and stirred at 28 °C in the BMS-PR460 with fan cooling for 48 hours. The reaction was diluted with ethyl acetate. The solution was washed successively with 10% LiCl, water, 1.5 N K_2HPO_4, and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The collected fractions containing the desired product were isolated and concentrated to dryness under reduced pressure.

General Conditions B (50 °C). The NAP intermediate was formed in situ as described in **General Procedure 1**. Using the procedure described in **General Conditions A**, the reactions were conducted at 50 °C using the variable temperature BMS-PR460 for 16 hours.

Products **3a-3j** from General Conditions A and B were characterized by ^{1}H NMR and LCMS. Purity for compounds **3a-j** was judged by LCMS Method A at 254 nm except where otherwise indicated. Purity for compounds **3a-j** was also assessed by ^{1}H NMR, and all compounds were judged to be >95% pure unless otherwise stated. Full characterization data (^{1}H NMR, ^{13}C NMR, HRMS) for these materials can be found in our previous manuscript: *J. Org. Chem.* 2018, **83**, 3000-3012.

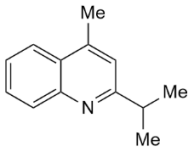
3a. **2-ethyl-4-methylquinoline**



3a was prepared from 4-methylquinoline (**1**) and **2a** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding 2-ethyl-4-methylquinoline (General Conditions A, 7.3 mg, 31% yield; General

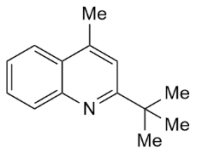
Conditions B, 18.2 mg, 76% yield) as a white solid. **General Condition A** for substrate **3a** had to be re-run as a single reaction due to purification issues encountered with reaction **3a** in the 10-reaction array run for **General Condition A**. Product **3a** was found to undergo sublimation while drying under vacuum, complicating isolation during **General Condition A** and resulting in decreased yield for this single reaction run. **3a** in **General Condition A** from this single reaction run was isolated with residual solvent, and the weight of the residual solvent was subtracted by NMR integration to arrive at the reported yield for **General Condition A**. LC-MS Anal.Calc'd for $C_{12}H_{13}N$ 171.2, found (General Condition A) [M+H] 171.8, Tr = 0.627 min., Purity = 100.0% as judged by ^{1}H NMR after accounting for contained residual solvent; (General Condition B) [M+H] 171.9, Tr = 0.640 min., Purity >95% as judged by ^{1}H NMR. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.41 - 8.33 (m, 1H), 8.15 - 8.11 (m, 1H), 8.09 - 8.04 (m, 1H), 7.90 (ddd, *J*=8.4, 7.0, 1.2 Hz, 1H), 7.82 (s, 1H), 3.19 (q, *J*=7.6 Hz, 2H), 2.97 (d, *J*=0.8 Hz, 3H), 1.50 (t, *J*=7.6 Hz, 3H).

3b. **2-isopropyl -4-methylquinoline**



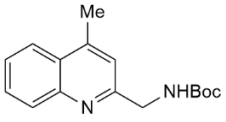
3b was prepared from 4-methylquinoline (**1**) and **2b** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding 2-isopropyl -4-methylquinoline (General Conditions A, 15.1 mg, 58% yield; General Conditions B, 16.5 mg, 64% yield) as a white solid. LC-MS Anal.Calc'd for $C_{13}H_{15}N$ 185.3, found (General Condition A) [M+H] 186.1, Tr = 0.663 min., Purity > 95%; (General Condition B) [M+H] 186.0, Tr = 0.658 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.04 - 8.00 (m, 1H), 8.00 - 7.96 (m, 1H), 7.69 (ddd, *J*=8.5, 6.9, 1.4 Hz, 1H), 7.53 (ddd, *J*=8.3, 6.9, 1.2 Hz, 1H), 7.32 (app d, *J*=0.8 Hz, 1H), 3.18 (spt, *J*=7.0 Hz, 1H), 2.69 (d, *J*=1.0 Hz, 3H), 1.37 (d, *J*=6.9 Hz, 6H).

3c. **2-(tert-butyl)-4-methylquinoline**



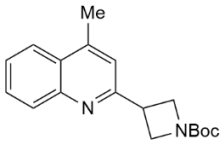
3c was prepared from 4-methylquinoline (**1**) and **2c** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding 2-(tert-butyl)-4-methylquinoline (General Conditions A, 18.9 mg, 68% yield; General Conditions B, 20.5 mg, 74% yield) as a white solid. LC-MS Anal.Calc'd for $C_{14}H_{17}N$ 199.3, found (General Condition A) [M+H] 200.3, Tr = 0.677 min., Purity = 100.0%; (General Condition B) [M+H] 199.8, Tr = 0.657 min., Purity = 100.0%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.05 - 7.99 (m, 2H), 7.68 (ddd, *J*=8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J*=8.3, 7.0, 1.2 Hz, 1H), 7.49 (app d, *J*=0.8 Hz, 1H), 2.71 (d, *J*=1.0 Hz, 3H), 1.46 (s, 9H).

3d. **tert-butyl ((4-methylquinolin-2-yl)methyl)carbamate**



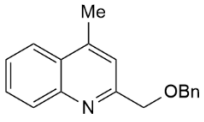
3d was prepared from 4-methylquinoline (**1**) and **2d** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding tert-butyl ((4-methylquinolin-2-yl)methyl)carbamate (General Conditions A, 22.8 mg, 60% yield; General Conditions B, 23.5 mg, 62% yield) as a white solid. Purification Method 2 buffered with trifluoroacetic acid was used. LC-MS Anal.Calc'd for $C_{16}H_{20}N_2O_2$ 272.3, found (General Condition A) [M+H] 273.0, Tr = 0.700 min., Purity > 95%; (General Condition B) [M+H] 272.9, Tr = 0.677 min., Purity = 100.0%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.09 (d, *J*=8.4 Hz, 1H), 7.99 (d, *J*=8.4 Hz, 1H), 7.77 - 7.71 (m, 1H), 7.60 (t, *J*=7.5 Hz, 1H), 7.37 (s, 1H), rotameric singlets: (4.48 (s) and 4.45 (br s), 2H), 2.74 (s, 3H), rotameric BOC singlets: (1.49 (s) and 1.32 (s), 9H). Water signal suppression was applied to this ^{1}H NMR.

3e. **tert-butyl 3-(4-methylquinolin-2-yl)azetidine-1-carboxylate**



3e was prepared from 4-methylquinoline (**1**) and **2e** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding tert-butyl 3-(4-methylquinolin-2-yl)azetidine-1-carboxylate (General Conditions A, 18.1 mg, 43% yield; General Conditions B, 17.6 mg, 42% yield) as a white solid. LC-MS Anal.Calc'd for $C_{18}H_{22}N_2O_2$ 298.4, found (General Condition A) [M+H] 299.0, Tr = 0.788 min., Purity > 95%; as determined by LC-MS analysis at 220 nm; (General Condition B) [M+H] 298.9, Tr = 0.710 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.11 - 8.06 (m, 1H), 8.05 - 8.02 (m, 1H), 7.74 (ddd, *J*=8.4, 7.0, 1.4 Hz, 1H), 7.59 (ddd, *J*=8.3, 6.9, 1.2 Hz, 1H), 7.37 (app d, *J*=0.8 Hz, 1H), 4.41 - 4.33 (m, 2H), 4.29 - 4.19 (m, 2H), 4.08 (tt, *J*=8.8, 6.1 Hz 1H), 2.74 (d, *J*=1.0 Hz, 3H), 1.48 (s, 9H).

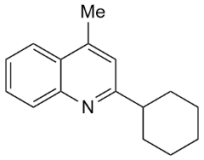
3f. **2-((benzyloxy)methyl)-4-methylquinoline**



3f was prepared from 4-methylquinoline (**1**) and **2f** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding 2-((benzyloxy)methyl)-4-methylquinoline (General Conditions A, 22.9 mg, 62% yield; General Conditions B, 26.1 mg, 71% yield) as a white solid. **General Conditions B** for substrate **3f** had to be re-run as a single reaction due to purification issues encountered with reaction **3f** in the 10-reaction array run for **General Conditions B**. The reported yield for **General Conditions B 3f** is from this single reaction run. LC-MS Anal.Calc'd for $C_{18}H_{17}NO$ 263.4, found (General Condition A) [M+H] 264.2, Tr = 0.735 min., Purity > 95%. (General Condition B) [M+H] 263.8, Tr = 0.715 min., Purity > 95%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.10 (dd, *J*=8.4, 0.8 Hz, 1H), 7.99 (d, *J*=8.6 Hz, 1H), 7.74 (ddd, *J*=8.4, 7.0, 1.4 Hz, 1H), 7.61 (ddd, *J*=8.3, 6.9, 1.2 Hz, 1H), 7.55

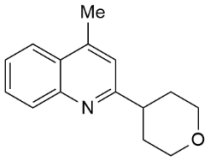
(s, 1H), 7.44 - 7.39 (m, 2H), 7.39 - 7.32 (m, 2H), 7.32 - 7.26 (m, 1H), 4.77 (s, 2H), 4.68 (s, 2H), 2.75 (d, *J*=0.8 Hz, 3H). Proton NMR obtained in $CDCl_3$ is consistent with the spectrum reported in our previous manuscript: *J. Org. Chem.* 2018, **83**, 3000-3012.

3g. **2-cyclohexyl-4-methylquinoline**



3g was prepared from 4-methylquinoline (**1**) and **2g** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding 2-cyclohexyl-4-methylquinoline (General Conditions A, 20.8 mg, 66% yield; General Conditions B, 22.6 mg, 72% yield) as a white solid. LC-MS Anal.Calc'd for $C_{16}H_{19}N$ 225.3, found (General Condition A) [M+H] 226.2, Tr = 0.722 min., Purity > 95%. General Condition B) [M+H] 225.9, Tr = 0.702 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.03 (app dd, *J*=8.3, 0.8 Hz, 1H), 8.00 - 7.96 (m, 1H), 7.69 (ddd, *J*=8.4, 7.0, 1.4 Hz, 1H), 7.54 (ddd, *J*=8.3, 6.9, 1.2 Hz, 1H), 7.31 (app d, *J*=0.7 Hz, 1H), 2.85 (tt, *J*=12.1, 3.3 Hz, 1H), 2.71 (d, *J*=0.8 Hz, 3H), 1.97 - 1.88 (m, 4H), 1.84 - 1.77 (m, 1H), 1.72 - 1.61 (m, 2H), 1.54 - 1.44 (m, 2H), 1.43 - 1.32 (m, 1H).

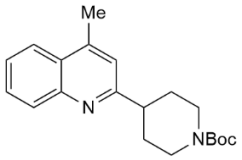
3h. 4-methyl-2-(tetrahydro-2H-pyran-4-yl)quinoline



3h was prepared from 4-methylquinoline (**1**) and **2h** following the procedure described for the synthesis of **General Procedure 1, Conditions A and General Procedure 1, Conditions B**, yielding 4-methyl-2-(tetrahydro-2H-pyran-4-yl)quinoline (General Conditions A, 18.1 mg, 57% yield; General Conditions B, 20.7 mg, 65% yield) as a white solid. LC-MS Anal.Calc'd for

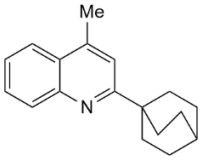
$C_{15}H_{17}NO$ 227.3, found (General Condition A) [M+H] 228.0, Tr = 0.645 min., Purity > 95% as judged by ^{1}H NMR; General Condition B) [M+H] 227.8, Tr = 0.618 min., Purity > 95% as judged by ^{1}H NMR. ^{1}H NMR (500 MHz, MeOH-d4) δ 8.08 - 8.05 (m, 1H), 8.02 - 7.98 (m, 1H), 7.72 (ddd, *J*=8.4, 7.0, 1.4 Hz, 1H), 7.57 (ddd, *J*=8.3, 6.9, 1.2 Hz, 1H), 7.36 (app d, *J*=0.8 Hz, 1H), 4.14 - 4.06 (m, 2H), 3.62 (td, *J*=11.8, 2.0 Hz, 2H), 3.13 (tt, *J*=12.1, 3.9 Hz, 1H), 2.74 (d, *J*=1.0 Hz, 3H), 2.08 - 1.97 (m, 2H), 1.92 - 1.84 (m, 2H).

3i. tert-butyl 4-(4-methylquinolin-2-yl)piperidine-1-carboxylate



3i was prepared from 4-methylquinoline (**1**) and **2i** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding tert-butyl 4-(4-methylquinolin-2-yl)piperidine-1-carboxylate (General Conditions A, 26.7 mg, 59% yield; General Conditions B, 29.8 mg, 65% yield) as a white solid. LC-MS Anal.Calc'd for $C_{18}H_{26}N_2O_2$ 326.4, found (General Condition A) [M+H] 327.2, Tr = 0.798 min., Purity = 100.0%; (General Condition B) [M+H] 326.9, Tr = 0.730 min., Purity = 100.0%. ^{1}H NMR (500 MHz, MeOH-d4) δ 8.06 (dd, *J*=8.4, 0.9 Hz, 1H), 8.01 - 7.98 (m, 1H),7.71 (ddd, *J*=8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J*=8.3, 6.9, 1.2 Hz, 1H), 7.33 (app d, *J*=0.7 Hz, 1H), 4.33 - 4.20 (m, 2H), 3.05 (tt, *J*=12.1, 3.8 Hz 1H), 2.98 - 2.82 (m, 2H), 2.72 (d, *J*=0.8 Hz, 3H), 1.98 - 1.90 (m, 2H), 1.89 - 1.78 (m, 2H), 1.50 (s, 9H).

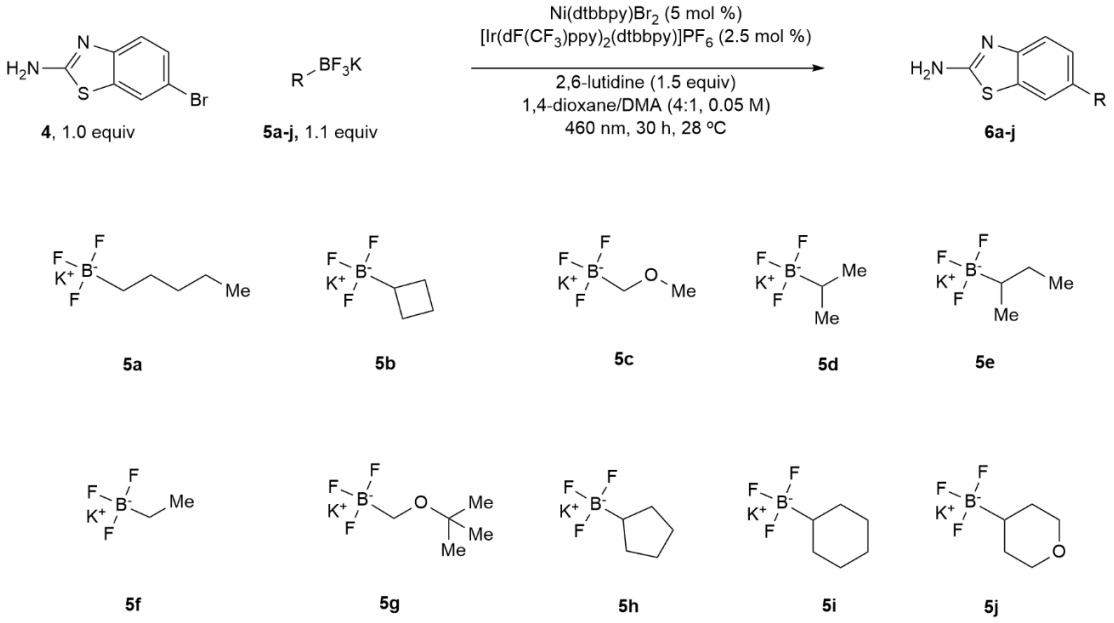
3j. 2-(bicyclo[2.2.2]octan-1-yl)-4-methylquinoline



3j was prepared from 4-methylquinoline (**1**) and **2j** following the procedure described for the synthesis of **General Procedure 1, Conditions A** and **General Procedure 1, Conditions B**, yielding 2-(bicyclo[2.2.2]octan-1-yl)-4-methylquinoline (General Conditions A, 15.8 mg, 45% yield; General Conditions B, 18.4 mg, 52% yield) as a white solid. LC-MS Anal.Calc'd for $C_{18}H_{21}N$ 251.4, found (General Condition A) [M+H] 252.3, Tr = 0.757 min., Purity = 100.0%; (General Condition B) [M+H] 251.9, Tr = 0.730 min., Purity = 100.0%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.03 – 7.98 (m, 2H), 7.66 (ddd, *J*=8.5, 6.9, 1.4 Hz, 1H), 7.51 (ddd, *J*=8.3, 7.0, 1.2 Hz, 1H), 7.38 (app d, *J*=0.8 Hz, 1H), 2.69 (d, *J*=1.0 Hz, 3H), 2.02 - 1.96 (m, 6H), 1.80 - 1.74 (m, 6H), 1.74 - 1.68 (m, 1H).

2. Aryl Bromide and Potassium Alkyl Trifluoroborate Coupling: C(sp^2)−C(sp^3) cross-coupling

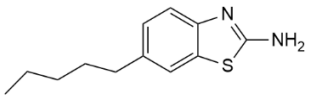
Scheme S2. Cross-coupling of heteroaryl bromide **4** and alkyl trifluoroborates **5a-j**



General Procedure 2

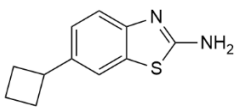
To an 8-mL pressure relief vial charged with 6-bromobenzo[*d*]thiazol-2-amine (20 mg, 87 µmol), the desired potassium trifluoroborate salt (96 µmol), Ni(dtbbpy)Br_2 precomplex (2.1 mg, 4.37 µmol), and Ir(dF(CF_3)ppy)$_2$(dtbbpy)PF_6 (2.4 mg, 2.18 µmol), 1,4-dioxane (1.4 ml), DMA (349 µl), and 2,6-lutidine (15.3 µl, 131 µmol) were added. The solution was purged with nitrogen for 5 minutes. The reaction was sealed and stirred in the BMS-PR460 with fan cooling for 30 hours. The reaction was diluted with ethyl acetate. The solution was washed successively with 10% LiCl, water, 1.5M K_2HPO_4, and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The compounds were purified using Purification Method 3. The collected fractions containing the desired product were isolated and concentrated to dryness under reduced pressure. Purity for compounds **6a-j** was judged by LCMS Method A at 254 nm except where otherwise indicated.

6a. 6-pentylbenzo[*d*]thiazol-2-amine



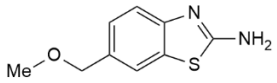
6a was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5a** following the procedure described in **General Procedure 2**, yielding 6-pentylbenzo[*d*]thiazol-2-amine (8.6 mg, 45% yield) as a white solid. LC-MS Anal.Calc'd for $C_{12}H_{16}N_2S$, 220.3, found [M+H] 220.8, Tr = 0.785 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.39 (d, *J*=1.2 Hz, 1H), 7.28 (d, *J*=8.2 Hz, 1H), 7.07 (dd, *J*=8.3, 1.7 Hz, 1H), 2.65 - 2.60 (m, 2H), 1.67 - 1.58 (m, 2H), 1.41 - 1.27 (m, 4H), 0.91 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 169.2, 151.0, 138.0, 132.0, 127.4, 121.3, 118.5, 36.6, 32.8, 32.6, 23.6, 14.4.

6b. 6-cyclobutylbenzo[*d*]thiazol-2-amine



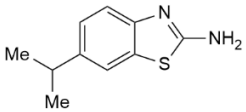
6b was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5b** following the procedure described in **General Procedure 2**, yielding 6-cyclobutylbenzo[*d*]thiazol-2-amine (8.0 mg, 45% yield) as a white solid. LC-MS Anal.Calc'd for $C_{11}H_{12}N_2S$, 204.3, found [M+H] 204.8, Tr = 0.707 min., Purity = 100.0%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.44 (d, *J*=1.1 Hz, 1H), 7.29 (d, *J*=8.3 Hz, 1H), 7.12 (ddd, *J*=8.3, 1.8, 0.6 Hz, 1H), 3.57 (quin, *J*=8.8 Hz, 1H), 2.39 - 2.30 (m, 2H), 2.20 - 2.10 (m, 2H), 2.08 – 1.98 (m, 1H), 1.90 - 1.82 (m, 1H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 169.3, 151.1, 141.4, 132.0, 125.3, 119.3, 118.5, 41.7, 31.2, 18.9.

6c. 6-(methoxymethyl)benzo[*d*]thiazol-2-amine



6c was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5c** following the procedure described in **General Procedure 2**, yielding 6-(methoxymethyl)benzo[*d*]thiazol-2-amine (7.8 mg, 46% yield) as a white solid. LC-MS Anal.Calc'd for $C_9H_{10}N_2OS$, 194.3, found [M+H] 194.9, Tr = 0.707 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.57 (d, *J*=1.2 Hz, 1H), 7.35 (d, *J*=8.2 Hz, 1H), 7.23 (dd, *J*=8.2, 1.7 Hz, 1H), 4.47 (s, 2H), 3.36 (s, 3H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 170.0, 152.8, 133.1, 132.1, 127.2, 121.7, 118.5, 75.6, 58.1.

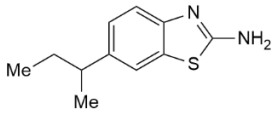
6d. 6-isopropylbenzo[*d*]thiazol-2-amine



6d was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5d** following the procedure described in **General Procedure 2**, yielding 5-isopropylbenzo[*d*]thiazol-2-amine (3.6 mg, 21% yield) as a white solid. Purification Method 2 was used. LC-MS Anal.Calc'd for $C_{10}H_{12}N_2S$, 192.2, found [M+H] 192.9, Tr = 1.267 min., Purity = 100.0%. Method D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 (d, *J*=1.5 Hz, 1H), 7.38 (br s, 1H), 7.24 (d, *J*=8.2 Hz, 1H), 7.08 (dd, *J*=8.2, 1.6

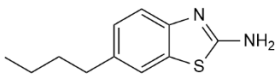
Hz, 1H), 2.89 (spt, *J*=7.0 Hz, 1H), 1.20 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.8, 150.9, 141.3, 131.0, 123.9, 118.2, 117.4, 33.2, 24.3. Water signal suppression was applied to the ^{1}H proton NMR acquisition of **6d**.

6e. 6-(sec-butyl)benzo [*d*]thiazol-2-amine



6e was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5e** following the procedure described in **General Procedure 2**, yielding 6-(sec-butyl)benzo [*d*]thiazol-2-amine (6.9 mg, 38% yield) as a white solid. (A structurally related coeluting byproduct, assigned as **6e-2**, was observed in the NMR, ~3.3:1 ratio of desired product **6e** to co-eluting **6e-2**.) For characterization, this material was further resolved by Purification Method 2 optimized for high purity with TFA-buffered mobile phase to provide samples of **6e** and **6e-2**, allowing for tentative assignment of **6e-2** as the corresponding n-butyl isomer of **6e**. Building block **5e** was determined to be a single component by ^{1}H NMR analysis. We propose that **6e-2** forms in the reaction via migration from the secondary position to the primary position of the butyl chain of a reactive intermediate species prior to final C-C bond formation. **6e**: LC-MS Anal.Calc'd for $C_{11}H_{14}N_2S$, 206.3, found [M+H] 207.0, Tr = 1.365 min., Purity > 95%. Method D. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.61 (d, *J*=1.7 Hz, 1H), 7.41 (d, *J*=8.3 Hz, 1H), 7.32 (dd, *J*=8.4, 1.6 Hz, 1H), 2.75 - 2.67 (m, 1H), 1.72 - 1.57 (m, 2H), 1.27 (d, *J*=6.9 Hz, 3H), 0.83 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 171.2, 146.2, 139.3, 128.2, 125.9, 121.8, 115.4, 42.9, 32.3, 22.5, 12.5.

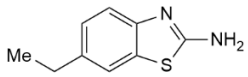
6e-2. 6-butylbenzo[d]thiazol-2-amine



6e-2: LC-MS Anal.Calc'd for $C_{11}H_{14}N_2S$, 206.3, found [M+H] 207.0, Tr = 1.428 min., Purity = 100.0%. Method D. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.59 (d, *J*=1.1 Hz, 1H), 7.38 (d, *J*=8.3 Hz, 1H), 7.30 (dd, *J*=8.3, 1.7 Hz, 1H), 2.73 - 2.67 (m, 2H), 1.67 - 1.59 (m, 2H), 1.41 - 1.32 (m, 2H),

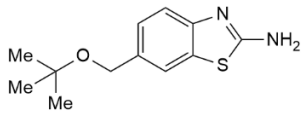
0.95 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (126 MHz, METHANOL-d$_4$) δ 171.0, 141.2, 139.9 (br), 129.3, 126.2, 123.0, 115.5, 36.3, 35.0, 23.2, 14.2.

6f. 6-ethylbenzo[*d*]thiazol-2-amine



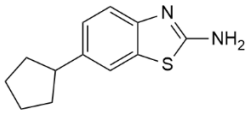
6f was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5f** following the procedure described in **General Procedure 2**, yielding 6-ethylbenzo[d]thiazol-2-amine (4.3 mg, 28% yield) as a white solid. Purification Method 2 buffered with trifluoroacetic acid was used. LC-MS Anal.Calc'd for $C_9H_{10}N_2S$, 178.3, found [M+H] 178.8, Tr = 1.141 min., Purity = 100.0%. Method D. ^{1}H NMR (500 MHz, MeOH-d$_4$) δ 7.57 (app d, *J*=1.1 Hz, 1H), 7.37 (d, *J*=8.3 Hz, 1H), 7.28 (dd, *J*=8.3, 1.7 Hz, 1H), 2.72 (q, *J*=7.6 Hz, 2H), 1.26 (t, *J*=7.6 Hz, 3H). ^{13}C NMR (126 MHz, MeOH-d$_4$) δ 170.7, 142.1, 141.7 (br), 128.5, 127.2, 122.1, 116.1, 29.6, 16.3.

6g. 6-(tert-butoxymethyl)benzo[*d*]thiazol-2-amine



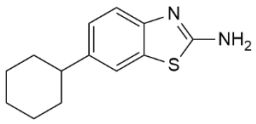
6g was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5g** following the procedure described in **General Procedure 2**, yielding 6-(tert-butoxymethyl)benzo[*d*]thiazol-2-amine (7.9 mg, 38% yield) as a white solid. LC-MS Anal.Calc'd for $C_{12}H_{16}N_2OS$, 236.3, found [M+H] 236.9, Tr = 0.698 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d$_4$) δ 7.57 (d, *J*=1.2 Hz, 1H), 7.33 (d, *J*=8.2 Hz, 1H), 7.22 (dd, *J*=8.3, 1.7 Hz, 1H), 4.48 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, MeOH-d$_4$) δ 169.8, 152.4, 134.6, 131.9, 127.0, 121.3, 118.5, 75.0, 65.3, 28.0.

6h. 6-cyclopentylbenzo[*d*]thiazol-2-amine



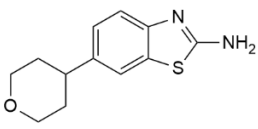
6h was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5h** following the procedure described in **General Procedure 2**, yielding 6-cyclopentylbenzo[*d*]thiazol-2-amine (10.0 mg, 53% yield) as a white solid. LC-MS Anal.Calc'd for $C_{12}H_{14}N_2S$, 218.3, found [M+H] 218.8, Tr = 0.740 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d$_4$) δ 7.45 (d, *J*=1.7 Hz, 1H), 7.28 (d, *J*=8.2 Hz, 1H), 7.14 (dd, *J*=8.3, 1.7 Hz, 1H), 3.09 - 2.96 (m, 1H), 2.12 - 2.00 (m, 2H), 1.88 - 1.78 (m, 2H), 1.76 - 1.66 (m, 2H), 1.65 - 1.54 (m, 2H). ^{13}C NMR (126 MHz, MeOH-d$_4$) δ 169.2, 151.1, 141.5, 132.0, 126.1, 120.0, 118.5, 47.1, 36.0, 26.4.

6i. 6-cyclohexylbenzo[*d*]thiazol-2-amine



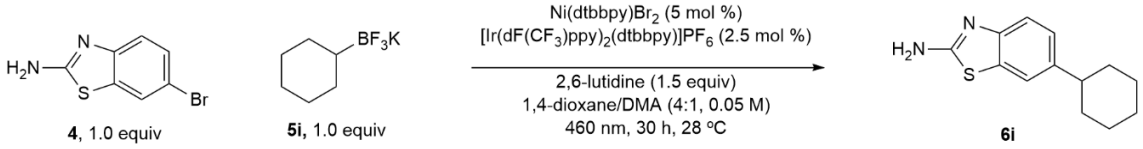
6i was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5i** following the procedure described in **General Procedure 2**, yielding 6-cyclohexylbenzo[*d*]thiazol-2-amine (9.7 mg, 48% yield) as a white solid. LC-MS Anal.Calc'd for $C_{13}H_{16}N_2S$, 232.3, found [M+H] 233.0, Tr = 0.838 min., Purity > 95% as judged by ^{1}H NMR. ^{1}H NMR (500 MHz, MeOH-d$_4$) δ 7.42 (d, *J*=1.8 Hz, 1H), 7.28 (d, *J*=8.3 Hz, 1H), 7.11 (dd, *J*=8.3, 1.7 Hz, 1H), 2.58 - 2.48 (m, 1H), 1.91 - 1.80 (m, 4H), 1.79 - 1.72 (m, 1H), 1.52 - 1.38 (m, 4H), 1.36 - 1.24 (m, 1H). ^{13}C NMR (126 MHz, MeOH-d$_4$) δ 169.3, 151.1, 143.4, 132.0, 125.9, 119.7, 118.5, 45.8, 36.0, 28.1, 27.3.

6j. 6-(tetrahydro-2H-pyran-4-yl)benzo[*d*]thiazol-2-amine



6j was prepared from 6-bromobenzo[*d*]thiazol-2-amine (**4**) and **5j** following the procedure described in **General Procedure 2**, yielding 6-(tetrahydro-2H-pyran-4-yl)benzo[*d*]thiazol-2-amine (6.3 mg, 31% yield) as a white solid. LC-MS Anal.Calc'd for $C_{12}H_{14}N_2OS$, 234.3, found [M+H] 234.9, Tr = 0.650 min., Purity > 95%. ^{1}H NMR (500 MHz, MeOH-d$_4$) δ 7.48 (d, *J*=1.8 Hz, 1H), 7.31 (d, *J*=8.3 Hz, 1H), 7.15 (dd, *J*=8.4, 1.7 Hz, 1H), 4.07 - 4.01 (m, 2H), 3.60 - 3.52 (m, 2H), 2.82 (tt, *J*=10.5, 5.3 Hz, 1H), 1.85 - 1.73 (m, 4H). ^{13}C NMR (126 MHz, MeOH-d$_4$) δ 169.5, 151.5, 141.2, 132.2, 125.8, 119.8, 118.7, 69.4, 42.5, 35.5.

Scheme S2-b. 21-Reaction Parallel Synthesis Array: Cross-coupling of bromide **4** and potassium cyclohexyltrifluoroborate **5i**



A 1,4-dioxane (22.0 ml) solution of 6-bromobenzo[*d*]thiazol-2-amine (315 mg, 1.38 mmol), potassium cyclohexyltrifluoroborate **5i** (261 mg, 1.38 mmol), Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (38.6 mg, 0.034 mmol) and 2,6-lutidine (0.240 ml, 2.06 mmol) was purged with nitrogen for 5 minutes. A DMA (5.5 ml) solution of Ni(dtbbpy)Br$_2$ precomplex (33.5 mg, 0.069 mmol) was purged with nitrogen for 5 minutes.

The 1,4-dioxane and DMA solutions were combined and evenly dispensed to 21 – 8 mL pressure relief vials while under a gentle stream of nitrogen. The reaction vials were sealed and stirred in the BMS-PR460 with fan cooling for 30 hours. The reactions were removed from the reactor and 0.25M biphenyl (25 μL) in acetonitrile were added to each reaction. The reactions were analyzed via LC-MS. The ratios of observed area percentages of the Product and Internal Standard (IS) were calculated.

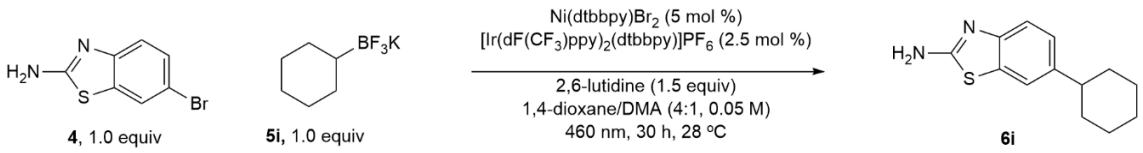
Table S3: Product to SI Ratio

Vial #	1	2	3	4	5	6	7
Product : IS	1.75	1.79	2.19	1.94	1.97	1.95	1.95
Vial #	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Product : IS	2.15	2.10	1.53	1.91	2.03	1.83	1.38
Vial #	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Product : IS	1.98	2.09	2.21	2.09	1.99	2.23	2.20

Individual reaction scale: 1,4-dioxane (1.05 ml), DMA (262 µL), 6-bromobenzo[*d*]thiazol-2-amine (15 mg, 65 µmol), potassium cyclohexyltrifluoroborate **5i** (12.4 mg, 65 µmol), 2,6-lutidine (11.44 µl, 98 µmol), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (1.84 mg, 1.64 µmol), and $Ni(dtbbpy)Br_2$ precomplex (1.6 mg, 3.29 µmol).

Select vials of this reaction to form **6i** were purified to obtain isolated yields (**Vial 1**, 8.5 mg, 56% yield, LC-MS Anal.Calc'd for $C_{13}H_{16}N_2S$, 232.3, found [M+H] 232.8, Tr = 0.805 min., Purity = 100.0%; **Vial 14**, 7.8 mg, 52% yield, [M+H] 232.8, Tr = 0.778 min., Purity = 100.0%; **Vial 21**, 9.1 mg, 60% yield, [M+H] 232.8, Tr = 0.775 min., Purity = 100.0%)

Scheme S2-c. Large Scale Cross-coupling of bromide **4** and potassium cyclohexyltrifluoroborate **5i**

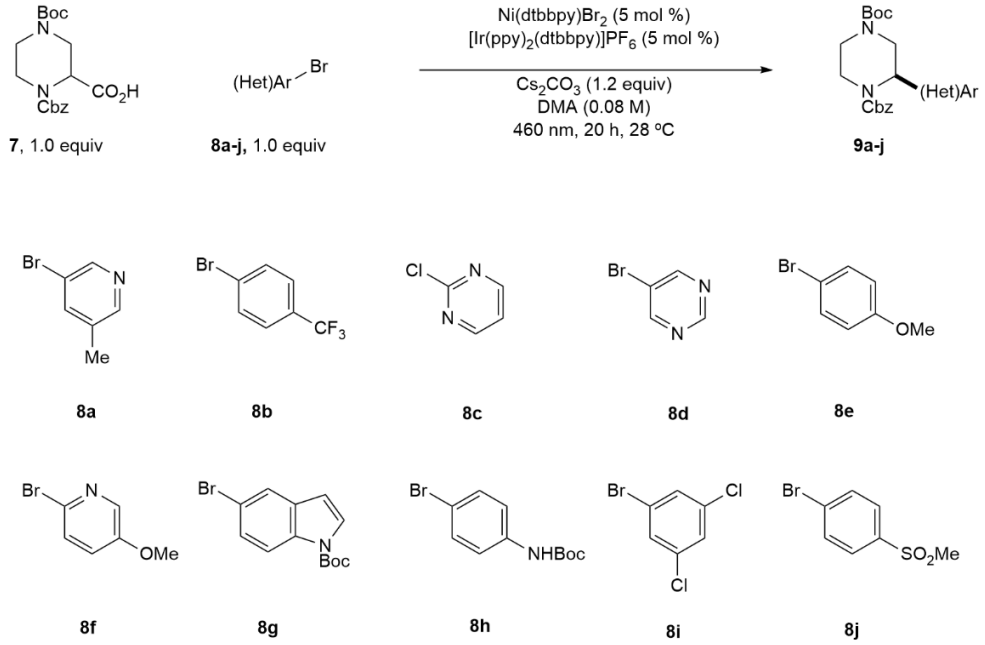


To a 40-mL pressure relief vial charged with 6-bromobenzo[*d*]thiazol-2-amine (210 mg, 0.917 mmol), the potassium cyclohexyltrifluoroborate **5i** (174 mg, 0.917 mmol), $Ni(dtbbpy)Br_2$ precomplex (22.3 mg, 0.046 mmol), and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (25.7 mg, 0.023 mmol), 1,4-dioxane (14.4 ml), DMA (3.6 ml), and 2,6-lutidine (160 µl, 1.38 mmol) were added. The solution was purged with nitrogen for 5 minutes. The reaction was sealed and stirred in the BMS-PR460

with fan cooling for 30 hours. The reaction was diluted with ethyl acetate. The solution was washed successively with 10% LiCl, water, 1.5 N K_2HPO_4, and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified via silica gel chromatography. The collected fractions containing the desired product were isolated and concentrated to dryness under reduced pressure, yielding 6-cyclohexylbenzo[*d*]thiazol-2-amine (91.0 mg, 43% yield) as a white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.42 (d, *J*=1.4 Hz, 1H), 7.28 (d, *J*=8.2 Hz, 1H), 7.11 (dd, *J*=8.3, 1.5 Hz, 1H), 2.58 - 2.46 (m, 1H), 1.93 - 1.83 (m, 4H), 1.81 – 1.75 (m, 1H), 1.52 - 1.43 (m, 4H), 1.35 - 1.25 (m, 1H). LC-MS Anal.Calc'd for $C_{13}H_{16}N_2S$, 232.3, found [M+H] 232.9, Tr = 0.800 min., Purity = 100.0%.

3. Decarboxylative Arylation: C(sp^2)−C(sp^3) Cross-Coupling

Scheme S3. Decarboxylative arylation with carboxylic acid **7** and (hetero)aryl halides **8a-j**

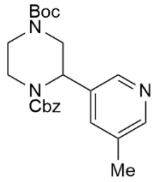


General Procedure 3

To an 8-mL pressure relief vial charged with 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl) piperazine-2-carboxylic acid (20 mg, 55.0 µmol), the desired halide (55.0 µmol), cesium carbonate (21.5 mg, 66.0 µmol), $[Ir(dtbbpy)(ppy)_2]PF_6$ (2.5 mg, 2.74 µmol), $Ni(dtbbpy)Br_2$ precomplex (1.3

mg, 2.74 μmol), and DMA (686 μl) were added. The solution was purged with nitrogen for 5 minutes. The reaction was sealed and stirred in the BMS-PR460 with fan cooling for 20 hours. The reaction was diluted with ethyl acetate. The solution was washed successively with 10% LiCl, water, 1.5 N K_2HPO_4, and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude products were purified using Purification Method 2. Purity for compounds **9a-j** was judged by both LCMS Methods C and D at 220 nm. Room temperature ^{1}H NMR characterization was performed in CD_3OD or DMSO-d_6 with water signal suppression applied. Room temperature ^{1}H NMR showed broad signals, assumed to be due to the presence of rotamers. Additional ^{1}H NMR, ^{13}C NMR, and HSQC spectra for all products was acquired in DMSO-d_6 at 100 °C in order to provide better resolved, sharper signals. Water signal suppression was not applied to 100 °C DMSO-d_6 NMR spectra.

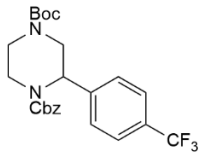
9a. 1-benzyl 4-(tert-butyl) 2-(5-methylpyridin-3-yl)piperazine-1,4-dicarboxylate



9a was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8a** following the procedure described in **General Procedure 3**, yielding 1-benzyl 4-(tert-butyl) 2-(5-methylpyridin-3-yl)piperazine-1,4-dicarboxylate (18.2 mg, 81% yield) as a white solid. LC-MS Anal.Calc'd for $C_{23}H_{29}N_3O_4$, 411.5, found [M+H] 412.3, Tr = 1.953 min., (**Method C**), LCMS Purity = 96.2%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.36 - 8.21 (m, 2H), 7.65 - 7.41 (m, 1H), 7.41 - 7.18 (m, 5H), 5.40 - 5.29 (m, 1H), 5.21 (d, *J*=12.2 Hz, 1H), 5.14 (br d, *J*=12.2 Hz, 1H), 4.55 - 4.34 (m, 1H), 4.10 - 3.98 (m, 1H), 3.97 - 3.77 (m, 1H), 3.56 - 3.38 (m, 1H), 3.25 - 2.94 (m, 2H), 2.31 (s, 3H), 1.38 (br s, 9H). 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (s, 2H), 7.43 (s, 1H), 7.38 - 7.23 (m, 5H), 5.26 (t, *J*=3.4 Hz, 1H), 5.16 (d, *J*=12.8 Hz, 1H), 5.13 (d, *J*=12.8 Hz, 1H), 4.33 - 4.22 (m, 1H), 3.95 (dt, *J*=13.5, 3.6 Hz, 1H), 3.79 (dt, *J*=12.7, 3.3 Hz, 1H), 3.44 (dd, *J*=14.0, 4.4 Hz, 1H), 3.22 - 3.14 (m, 1H), 3.12 - 3.04 (m, 1H), 2.27 (s, 3H), 1.35 (s, 9H). ^{13}C

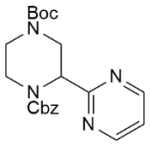
NMR (126 MHz, DMSO-d_6) δ 154.5, 153.3, 148.1, 144.8, 136.2, 134.0, 133.8, 131.8, 127.8, 127.2, 126.9, 78.8, 66.2, 52.4, 44.8 (br), 42.4, 39.1, 27.4, 17.2.

9b. 1-benzyl 4-(tert-butyl) 2-(4-(trifluoromethyl)phenyl)piperazine-1,4-dicarboxylate



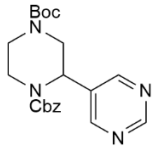
9b was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8b** following the procedure described in **General Procedure 3** with TFA-buffered mobile phase, yielding 1-benzyl 4-(tert-butyl) 2-(4-(trifluoromethyl)phenyl)piperazine-1,4-dicarboxylate (4.8 mg, 19% yield) as a white solid. LC-MS Anal.Calc'd for $C_{24}H_{27}F_3N_2O_4$, 464.49, found [M+Na] 487.0, Tr = 2.506 min., (**Method D**), Purity = 100.0%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.62 (br d, *J*=6.6 Hz, 2H), 7.46 (d, *J*=8.0 Hz, 2H), 7.38 - 7.11 (m, 5H), 5.35 (br s, 1H), 5.19 (d, *J*=12.2 Hz, 1H), 5.12 (br d, *J*=12.4 Hz, 1H), 4.54 - 4.30 (m, 1H), 4.04 (br d, *J*=13.4 Hz, 1H), 3.96 - 3.74 (m, 1H), 3.62 - 3.40 (m, 1H), 3.39 - 2.93 (m, 2H), 1.47 - 1.16 (m, 9H). 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (d, *J*=8.0 Hz, 2H), 7.49 (d, *J*=8.0 Hz, 2H), 7.37 - 7.18 (m, 5H), 5.32 - 5.27 (m, 1H), 5.15 (d, *J*=12.8 Hz, 1H), 5.11 (d, *J*=12.8 Hz, 1H), 4.25 (dd, *J*=14.1, 3.2 Hz, 1H), 3.96 (dt, *J*=13.7, 3.9 Hz, 1H), 3.76 (dt, *J*=12.8, 3.8 Hz, 1H), 3.50 (dd, *J*=14.1, 4.3 Hz, 1H), 3.27 (ddd, *J*=13.8, 10.2, 4.0 Hz, 1H), 3.16 - 3.06 (m, 1H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.6, 153.3, 144.0, 136.1, 127.7, 127.5 (q, *J* = 31.5 Hz), 127.2, 126.8, 126.7, 124.6 (q, *J*=3.8 Hz), 123.7 (q, *J* = 272 Hz), 78.7, 66.2, 54.3, 45.1 (br), 42.4, 39.3 (resolved by HSQC), 27.4.

9c. 1-benzyl 4-(tert-butyl) 2-(pyrimidin-2-yl)piperazine-1,4-dicarboxylate



9c was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8c** following the procedure described in **General Procedure 3**, yielding 1-benzyl 4-(tert-butyl) 2-(pyrimidin-2-yl)piperazine-1,4-dicarboxylate (2.2 mg, 10% yield) as a white solid. LC-MS Anal.Calc'd for $C_{21}H_{26}N_4O_4$, 398.5, found [M+H] 399.0, Tr = 1.890 min., (**Method C**) Purity = 100.0%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 - 8.67 (m, 2H), 7.49 - 7.15 (m, 5H), 7.08 - 6.95 (m, 1H), 5.24 - 5.15 (m, 1H), 5.14 - 5.08 (m, 1H), 5.08 - 4.89 (m, 1H), 4.67 - 4.38 (m, 1H), 4.04 - 3.71 (m, 2H), 3.52 - 3.31 (m, 1H), 3.11 - 2.72 (m, 1H), 1.34 - 0.83 (m, 9H). One piperazine ring proton was unobserved due to broadening and/or suppression due to water signal suppression in NMR acquisition. 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (d, *J*=4.8 Hz, 2H), 7.35 (t, *J*=4.9 Hz, 1H), 7.33 - 7.09 (m, 5H), 5.22 (dd, *J*=4.8, 2.0 Hz, 1H), 5.09 (br d, *J*=12.8 Hz, 1H), 5.07 (br d, *J*=13.0 Hz, 1H), 4.57 - 4.50 (m, 1H), 3.93 - 3.86 (m, 2H), 3.65 - 3.56 (m, 1H), 3.46 (dd, *J*=13.7, 4.8 Hz, 1H), 3.05 - 2.98 (m, 1H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.3, 156.5, 155.2, 153.0, 136.3, 127.6, 127.0, 126.6, 119.0, 78.3, 65.8, 56.4, 45.5 (br), 42.1 (br), 40.2 (resolved by HSQC), 27.3.

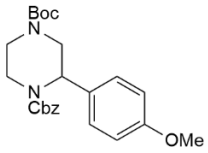
9d. 1-benzyl 4-(tert-butyl) 2-(pyrimidin-5-yl)piperazine-1,4-dicarboxylate



9d was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8d** following the procedure described in **General Procedure 3** with TFA-buffered mobile phase, yielding 1-benzyl 4-(tert-butyl) 2-(pyrimidin-5-yl)piperazine-1,4-dicarboxylate (3.0 mg, 14% yield) as a white solid. LC-MS Anal.Calc'd for $C_{21}H_{26}N_4O_4$, 398.5, found [M+H] 399.0, Tr = 1.750 min., (**Method C**), Purity = 96.2%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 9.07 (s, 1H), 8.72 (s, 2H), 7.40 - 7.24 (m, 5H), 5.47 - 5.38 (m, 1H), 5.21 (d, *J*=12.2 Hz, 1H), 5.15 (br d, *J*=12.2 Hz, 1H), 4.48 (br d, *J*=13.4 Hz, 1H), 4.14 - 3.99 (m, 1H), 3.98 - 3.81 (m, 1H), 3.61 - 3.37 (m, 1H), 3.23 - 2.94 (m, 2H), 1.39 (s, 9H). 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.68 (d, *J*=0.7 Hz, 2H), 7.39 - 7.25 (m, 5H), 5.33 (t, *J*=3.6 Hz, 1H), 5.15 (d, *J*=12.8 Hz, 1H), 5.14 (d, *J*=12.8 Hz, 1H), 4.28 (ddd, *J*=14.2, 3.1, 1.4 Hz, 1H), 3.96 (dt, *J*=13.7, 3.9 Hz, 1H), 3.80 (dtd,

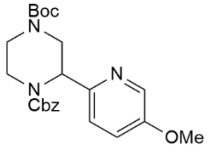
J=12.8, 3.9, 1.3 Hz, 1H), 3.49 (dd, *J*=14.1, 4.3 Hz, 1H), 3.28 - 3.20 (m, 1H), 3.15 - 3.08 (m, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.7, 154.8, 154.4, 153.3, 136.0, 132.4, 127.8, 127.3, 126.9, 79.0, 66.4, 51.1, 44.6 (br), 42.4, 39.1 (resolved by HSQC), 27.4.

9e. 1-benzyl 4-(tert-butyl) 2-(4-methoxyphenyl)piperazine-1,4-dicarboxylate



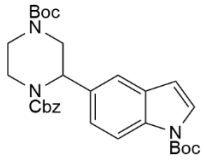
9e was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8e** following the procedure described in **General Procedure 3**, yielding 1-benzyl 4-(tert-butyl) 2-(4-methoxyphenyl)piperazine-1,4-dicarboxylate (6.9 mg, 30% yield) as a white solid. LC-MS Anal.Calc'd for $C_{24}H_{30}N_2O_5$, 426.5, found [M+Na] 449.1, Tr = 2.275 min., (**Method C**), Purity = 97.5%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.38 - 7.23 (m, 5H), 7.18 (d, *J*=8.5 Hz, 2H), 6.87 (br d, *J*=7.0 Hz, 2H), 5.31 - 5.22 (m, 1H), 5.19 (d, *J*=12.4 Hz, 1H), 5.14 (br d, *J*=12.4 Hz, 1H), 4.50 - 4.31 (m, 1H), 4.07 - 3.94 (m, 1H), 3.94 - 3.80 (m, 1H), 3.78 (s, 3H), 3.47 - 3.32 (m, 1H), 3.26 - 2.90 (m, 2H), 1.39 (br s, 9H). 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 - 7.22 (m, 5H), 7.18 (br d, *J*=8.7 Hz, 2H), 6.88 (br d, *J*=8.7 Hz, 2H), 5.22 - 5.03 (m, 3H), 4.25 (br d, *J*=13.0 Hz, 1H), 3.97 - 3.84 (m, 1H), 3.75 (s, 3H), 3.80 - 3.70 (m, 1H), 3.38 (br dd, *J*=13.9, 4.3 Hz, 1H), 3.16 - 3.08 (m, 1H), 3.07 - 3.01 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.1, 154.5, 153.4, 136.3, 130.7, 127.8, 127.2, 127.1, 126.9, 113.5, 78.7, 66.1, 54.8, 53.4, 45.1 (br), 42.4 (br), 38.9 (br, resolved by HSQC), 27.5.

9f. 1-benzyl 4-(tert-butyl) 2-(5-methoxypyridin-2-yl)piperazine-1,4-dicarboxylate



9f was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8f** following the procedure described in **General Procedure 3** with TFA-buffered mobile phase, yielding 1-benzyl 4-(tert-butyl) 2-(5-methoxypyridin-2-yl)piperazine-1,4-dicarboxylate (11.6 mg, 49% yield) as a white solid. Contains a small amount of a co-eluting impurity as judged by proton NMR. LC-MS Anal.Calc'd for $C_{23}H_{29}N_3O_5$, 427.5, found [M+H] 428.4, Tr = 2.044 min., (**Method C**), Purity = 95.6%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (br s, 1H), 7.53 - 7.00 (m, 7H), 5.20 - 4.98 (m, 3H), 4.53 - 4.22 (m, 1H), 3.92 - 3.71 (m, 2H), 3.80 (s, 3H), 3.47 - 3.25 (m, 1H), 3.13 - 2.82 (m, 1H), 1.35 - 1.02 (m, 9H). One piperazine ring proton was unobserved due to broadening and/or suppression due to water signal suppression in NMR acquisition. 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (d, *J*=2.7 Hz, 1H), 7.41 - 7.24 (m, 6H), 7.22 (d, *J*=8.7 Hz, 1H), 5.16 (t, *J*=3.6 Hz, 1H), 5.11 (d, *J*=12.8 Hz, 1H), 5.09 (d, *J*=13.0 Hz, 1H), 4.37 (dd, *J*=13.7, 1.6 Hz, 1H), 3.91 (dt, *J*=13.2, 3.8 Hz, 1H), 3.83 (s, 3H), 3.82 - 3.75 (m, 1H), 3.47 - 3.38 (m, 2H), 3.10 - 3.01 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.9, 154.0, 153.3, 150.1, 136.4, 136.0, 127.7, 127.1, 126.7, 120.9, 120.8, 78.3, 65.9, 55.3, 55.1, 45.2 (br), 42.2 (br), 39.6 (resolved by HSQC), 27.4.

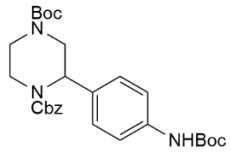
9g. 1-benzyl 4-(tert-butyl) 2-(1-(tert-butoxycarbonyl)-1H-indol-5-yl)piperazine-1,4-dicarboxylate



9g was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8g** following the procedure described in **General Procedure 3**, yielding 1-benzyl 4-(tert-butyl) 2-(1-(tert-butoxycarbonyl)-1H-indol-5-yl)piperazine-1,4-dicarboxylate (1.1 mg, 4% yield) as a white solid. LC-MS Anal.Calc'd for $C_{30}H_{37}N_3O_6$, 535.6, found [M+Na] 558.3, Tr = 2.702 min., (**Method C**), Purity = 100.0%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.05 (br d, *J*=5.7 Hz, 1H), 7.62 (br d, *J*=3.2 Hz, 1H), 7.47 (br s, 1H), 7.37 - 7.23 (m, 5H), 7.20 (d, *J*=8.6 Hz, 1H), 6.55 (br d, *J*=2.6 Hz, 1H), 5.45 - 5.35 (m, 1H), 5.21 (d, *J*=12.3 Hz, 1H), 5.15 (br d, *J*=12.4 Hz, 1H), 4.60 - 4.37 (m, 1H), 4.13 - 3.98 (m, 1H), 3.97 - 3.79 (m, 1H), 3.54 - 3.38 (m, 1H), 3.28 - 2.93

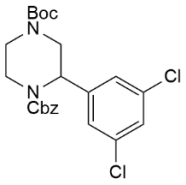
(m, 2H), 1.68 (s, 9H), 1.49 - 1.26 (m, 9H). 100 °C NMR: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J*=8.7 Hz, 1H), 7.63 (dd, *J*=3.6, 1.1 Hz, 1H), 7.50 (s, 1H), 7.40 - 7.25 (m, 5H), 7.23 (d, *J*=8.7 Hz, 1H), 6.62 (d, *J*=3.6 Hz, 1H), 5.33 (br s, 1H), 5.16 (d, *J*=12.8 Hz, 1H), 5.14 (d, *J*=12.5 Hz, 1H), 4.38 - 4.28 (m, 1H), 4.00 - 3.92 (m, 1H), 3.82 - 3.74 (m, 1H), 3.46 (ddd, *J*=14.0, 4.4, 0.9 Hz, 1H), 3.23 - 3.15 (m, 1H), 3.08 (td, *J*=11.9, 3.8 Hz, 1H), 1.69 - 1.61 (m, 9H), 1.38 - 1.30 (m, 9H). Sample decomposition was observed after extended heating at 100 °C for ^{13}C NMR and HSQC, preventing accurate reporting of ^{13}C signals for **9g**.

9h. 1-benzyl 4-(tert-butyl) 2-(4-((tert-butoxycarbonyl)amino)phenyl)piperazine-1,4-dicarboxylate



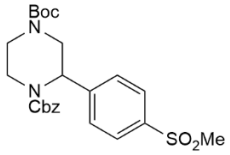
9h was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8h** following the procedure described in **General Procedure 3**, yielding 1-benzyl 4-(tert-butyl) 2-(4-((tert-butoxycarbonyl)amino)phenyl)piperazine-1,4-dicarboxylate (10.8 mg, 39% yield) as a white solid. LC-MS Anal.Calc'd for $C_{28}H_{37}N_3O_6$, 511.6, found [M+Na] 534.2, Tr = 2.401 min., (**Method C**), Purity = 95.5%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (br s, 1H), 7.43 - 7.22 (m, 7H), 7.10 (d, *J*=8.5 Hz, 2H), 5.20 - 5.15 (m, 1H), 5.13 (d, *J*=12.9 Hz, 1H), 5.11 (br d, *J*=12.7 Hz, 1H), 4.45 - 4.17 (m, 1H), 3.95 - 3.83 (m, 1H), 3.83 - 3.62 (m, 1H), 3.45 - 3.20 (m, 1H), 3.18 - 2.78 (m, 2H), 1.46 (s, 9H), 1.32 (br s, 9H). 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.41 - 7.37 (m, 2H), 7.37 - 7.26 (m, 5H), 7.16 - 7.11 (m, 2H), 5.18 (t, *J*=3.6 Hz, 1H), 5.14 (d, *J*=13.0 Hz, 1H), 5.13 (d, *J*=12.8 Hz, 1H), 4.25 (ddd, *J*=13.9, 3.0, 1.1 Hz, 1H), 3.92 (dt, *J*=13.2, 3.2 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.37 (dd, *J*=13.9, 4.6 Hz, 1H), 3.16 - 3.08 (m, 1H), 3.07 - 3.00 (m, 1H), 1.49 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.5, 153.4, 152.3, 138.0, 136.3, 132.3, 127.7, 127.2, 126.9, 126.1, 118.0, 78.7, 78.5, 66.1, 53.5, 44.9 (br), 42.4, 38.9, 27.7, 27.5.

9i. 1-benzyl 4-(tert-butyl) 2-(3,5-dichlorophenyl)piperazine-1,4-dicarboxylate



9i was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8i** following the procedure described in **General Procedure 3**, yielding 1-benzyl 4-(tert-butyl) 2-(3,5-dichlorophenyl)piperazine-1,4-dicarboxylate (4.2 mg, 16% yield) as a white solid. LC-MS Anal.Calc'd for $C_{23}H_{26}Cl_2N_2O_4$, 465.4, found [M-tert butyl+H] 408.9, Tr = 2.632 min., (**Method C**), Purity = 98.7% . ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.41 - 7.27 (m, 6H), 7.24 (br s, 2H), 5.32 - 5.26 (m, 1H), 5.22 (d, *J*=12.3 Hz, 1H), 5.19 - 5.09 (m, 1H), 4.57 - 4.24 (m, 1H), 4.10 - 3.96 (m, 1H), 3.96 - 3.78 (m, 1H), 3.47 - 3.36 (m, 1H), 3.25 - 2.89 (m, 2H), 1.41 (br s, 9H). 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.45 - 7.42 (m, 1H), 7.38 - 7.28 (m, 5H), 7.28 - 7.25 (m, 2H), 5.25 - 5.21 (m, 1H), 5.17 (d, *J*=12.8 Hz, 1H), 5.13 (d, *J*=12.8 Hz, 1H), 4.26 (br d, *J*=14.1 Hz, 1H), 3.93 (dt, *J*=13.6, 3.2 Hz, 1H), 3.80 - 3.74 (m, 1H), 3.43 (ddd, *J*=14.1, 4.3, 1.1 Hz, 1H), 3.22 - 3.13 (m, 1H), 3.12 - 3.02 (m, 1H), 1.40 - 1.31 (m, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.4, 153.2, 143.5, 136.1, 133.8, 127.8, 127.3, 126.8, 126.3, 124.9, 78.9, 66.3, 53.7, 44.7 (br), 42.3 (br), 39.2 (resolved by HSQC), 27.4.

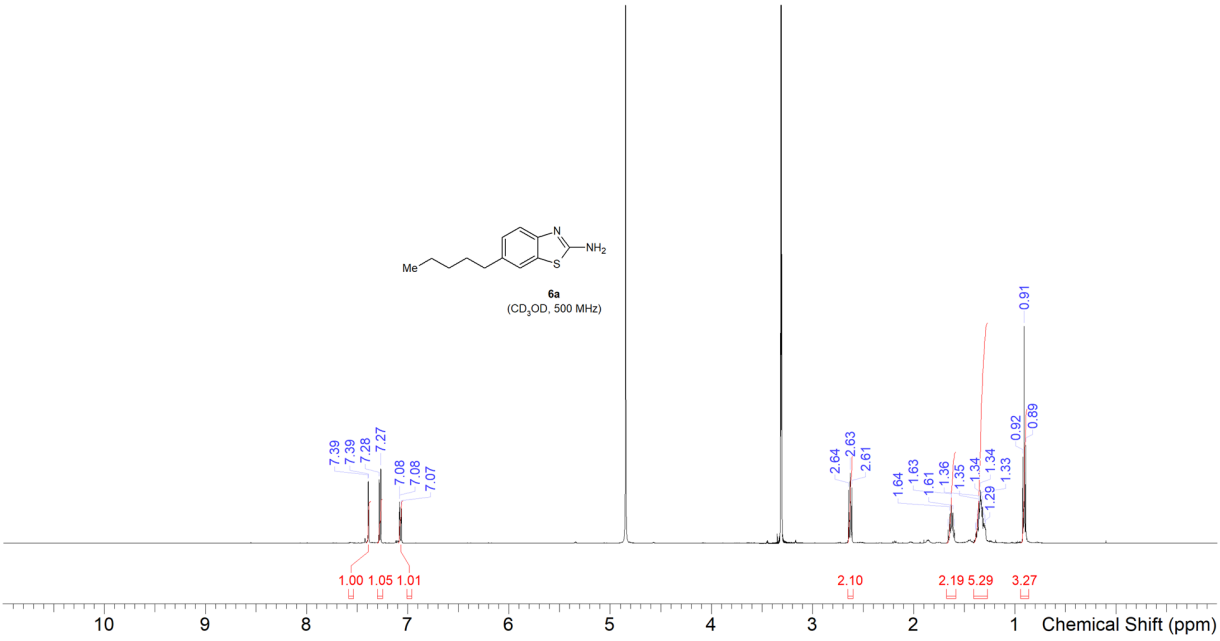
9j. 1-benzyl 4-(tert-butyl) 2-(4-(methylsulfonyl)phenyl)piperazine-1,4-dicarboxylate

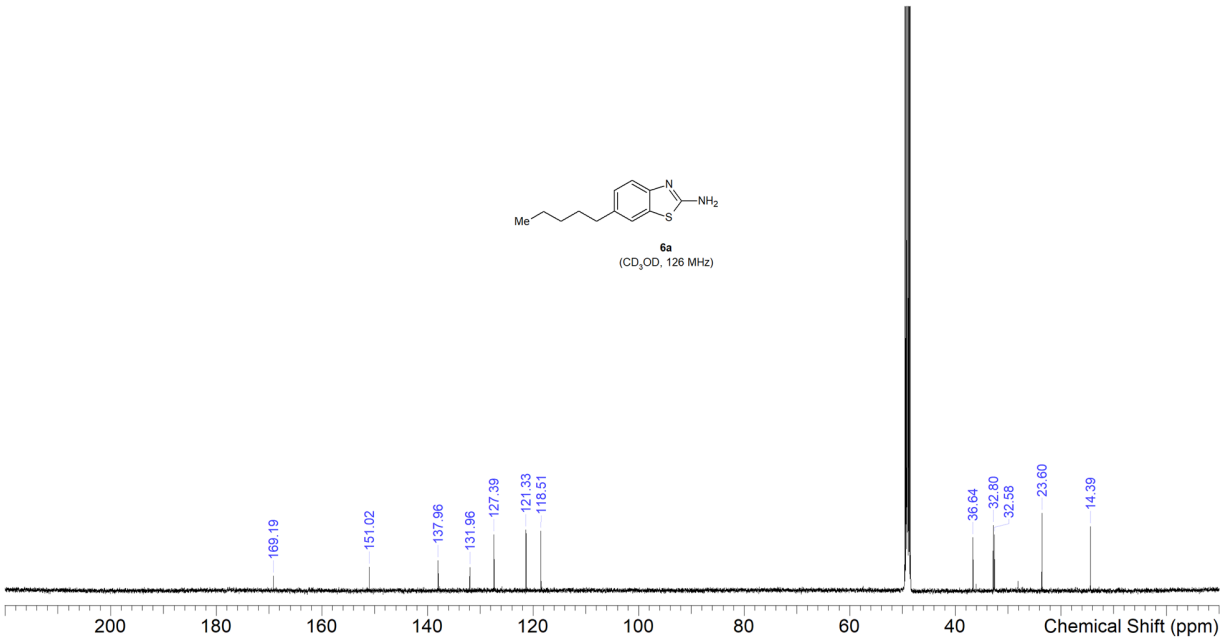


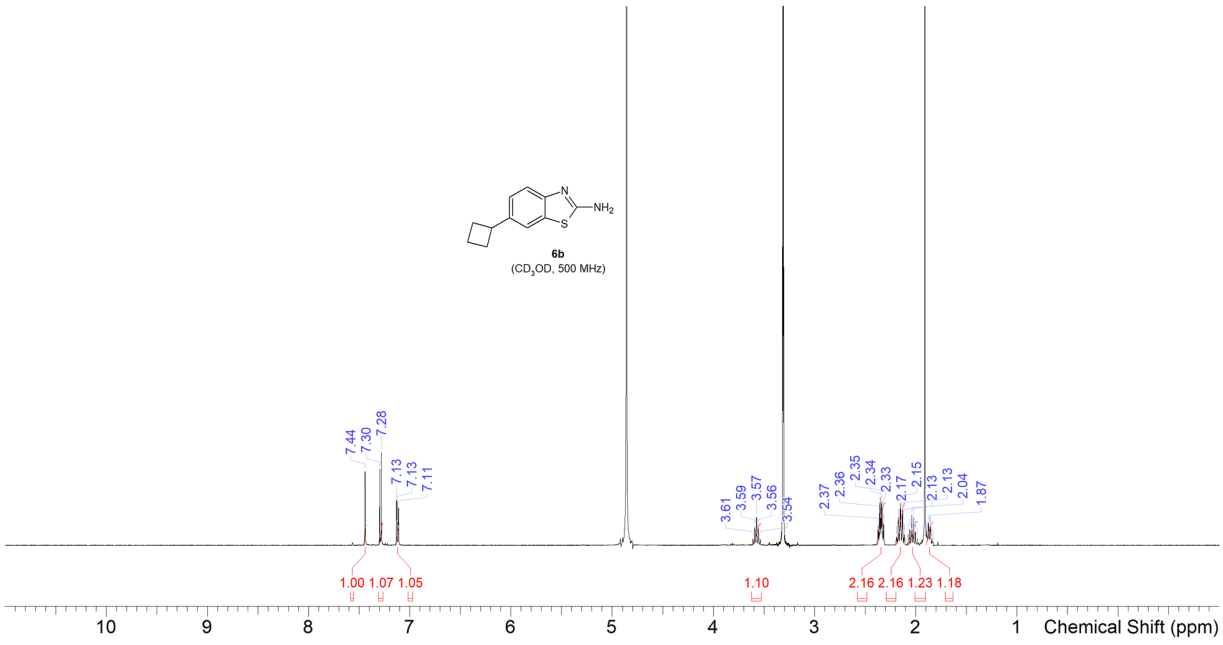
9j was prepared from 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**7**) and **8j** following the procedure described in **General Procedure 3** with TFA-buffered mobile phase, yielding 1-benzyl 4-(tert-butyl) 2-(4-(methylsulfonyl)phenyl)piperazine-1,4-dicarboxylate (2.7 mg, 10% yield) as a white solid. LC-MS Anal.Calc'd for $C_{24}H_{30}N_2O_6S$, 474.6, found [M+Na] 497.0, Tr = 1.988 min., (**Method D**), Purity = 100.0%. ^{1}H NMR (500 MHz,

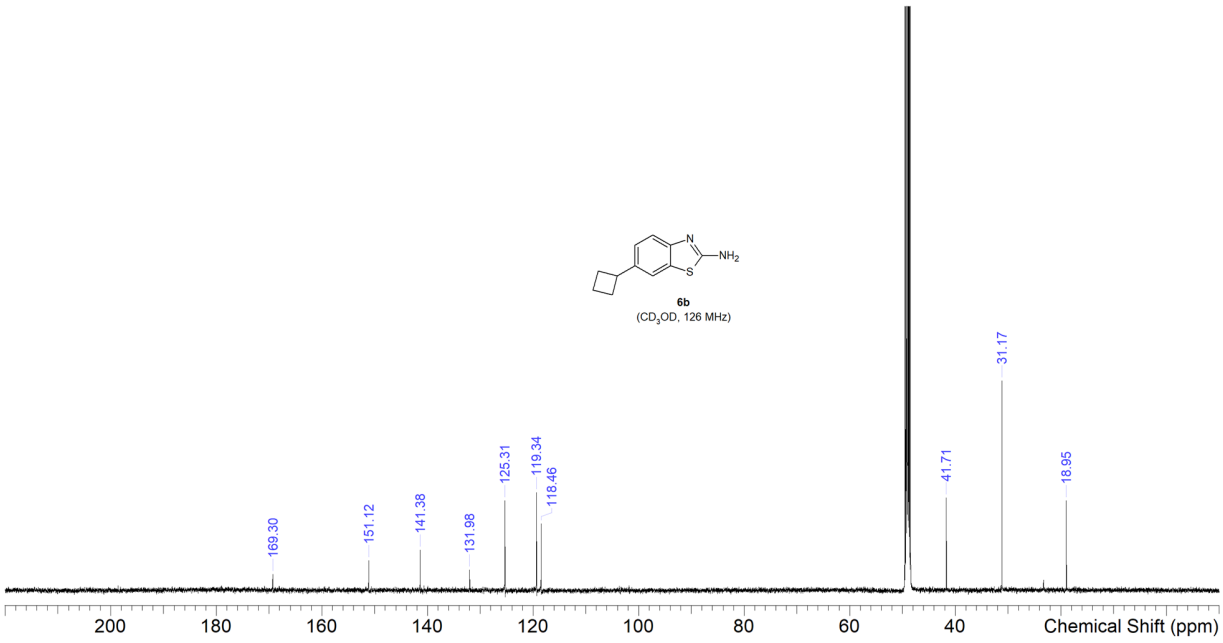
MeOH-d_4) δ 7.91 (br d, *J*=7.3 Hz, 2H), 7.54 (d, *J*=8.1 Hz, 2H), 7.40 - 7.12 (m, 5H), 5.43 - 5.32 (m, 1H), 5.19 (d, *J*=12.2 Hz, 1H), 5.12 (br d, *J*=12.0 Hz, 1H), 4.54 - 4.27 (m, 1H), 4.12 - 3.99 (m, 1H), 3.97 - 3.74 (m, 1H), 3.60 - 3.43 (m, 1H), 3.38 - 2.97 (m, 2H), 3.11 (s, 3H), 1.53 - 1.15 (m, 9H). 100 °C NMRs: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 - 7.83 (m, 2H), 7.53 (d, *J*=8.2 Hz, 2H), 7.39 - 7.21 (m, 5H), 5.33 - 5.29 (m, 1H), 5.15 (d, *J*=12.5 Hz, 1H), 5.12 (d, *J*=12.5 Hz, 1H), 4.31 - 4.21 (m, 1H), 3.97 (dt, *J*=13.6, 3.8 Hz, 1H), 3.80 - 3.72 (m, 1H), 3.51 (dd, *J*=14.1, 4.3 Hz, 1H), 3.26 (ddd, *J*=13.7, 10.4, 3.9 Hz, 1H), 3.15 (s, 3H), 3.14 - 3.08 (m, 1H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.5, 153.3, 145.2, 139.6, 136.1, 127.7, 127.2, 126.9 (2 overlapping signals by HSQC), 126.4, 78.8, 66.3, 54.3, 45.1 (br), 43.2, 42.4, 39.3 (resolved by HSQC), 27.4.

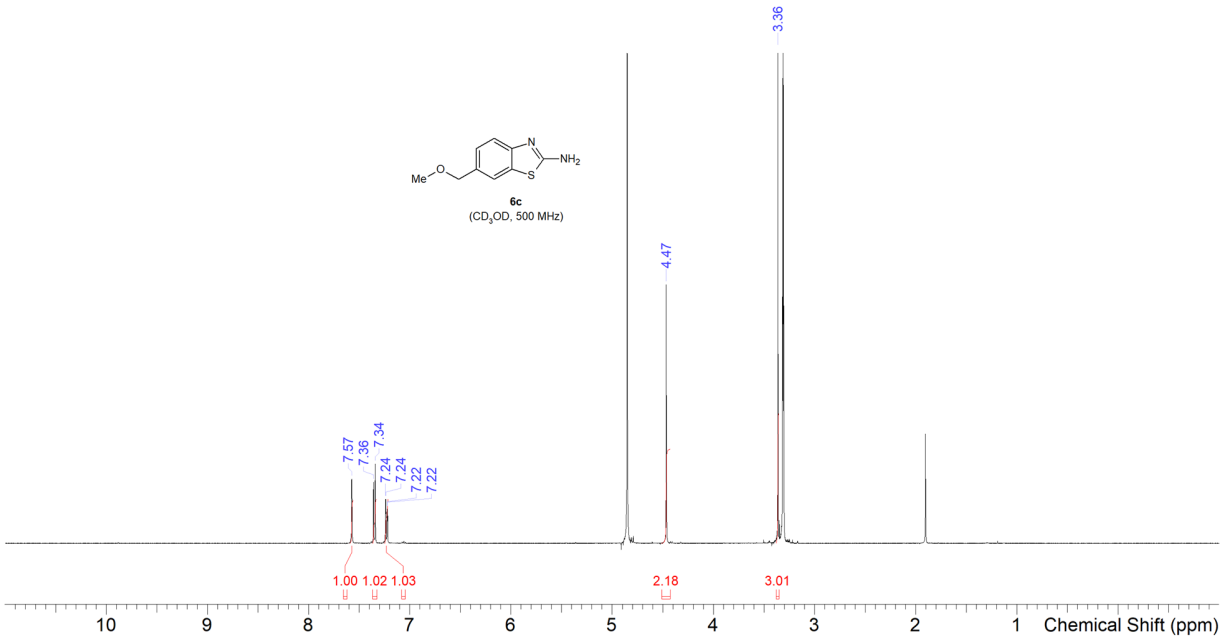
^{1}H and ^{13}C NMR Spectra: Scheme 2. Aryl Bromide and Potassium Alkyl Trifluoroborate Coupling

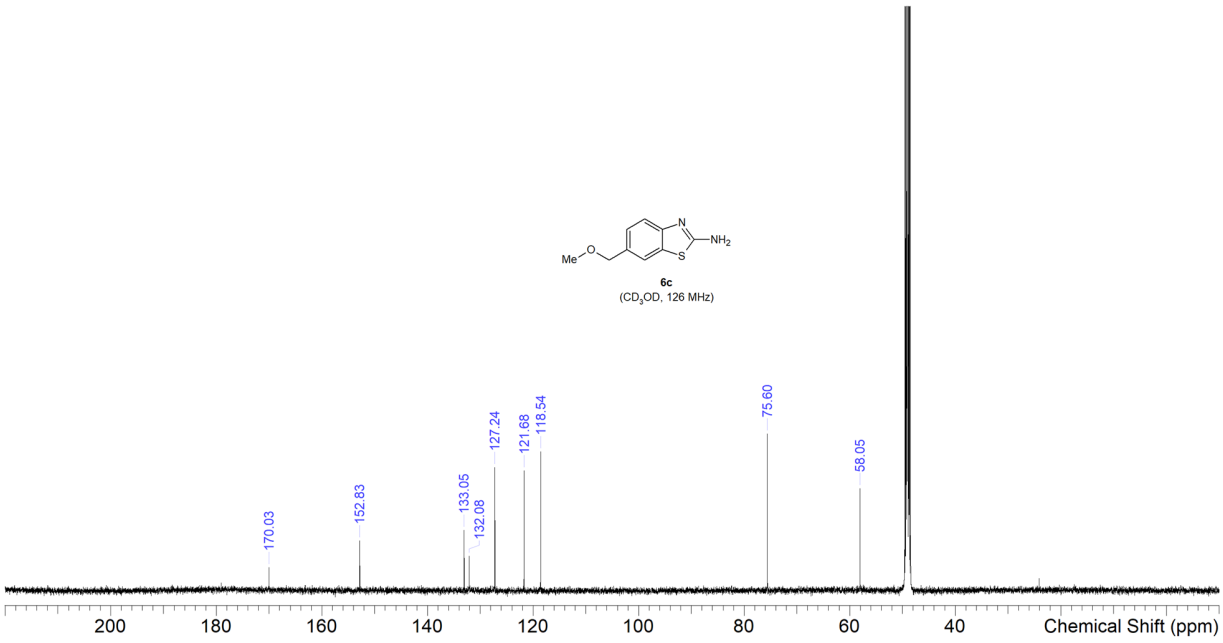


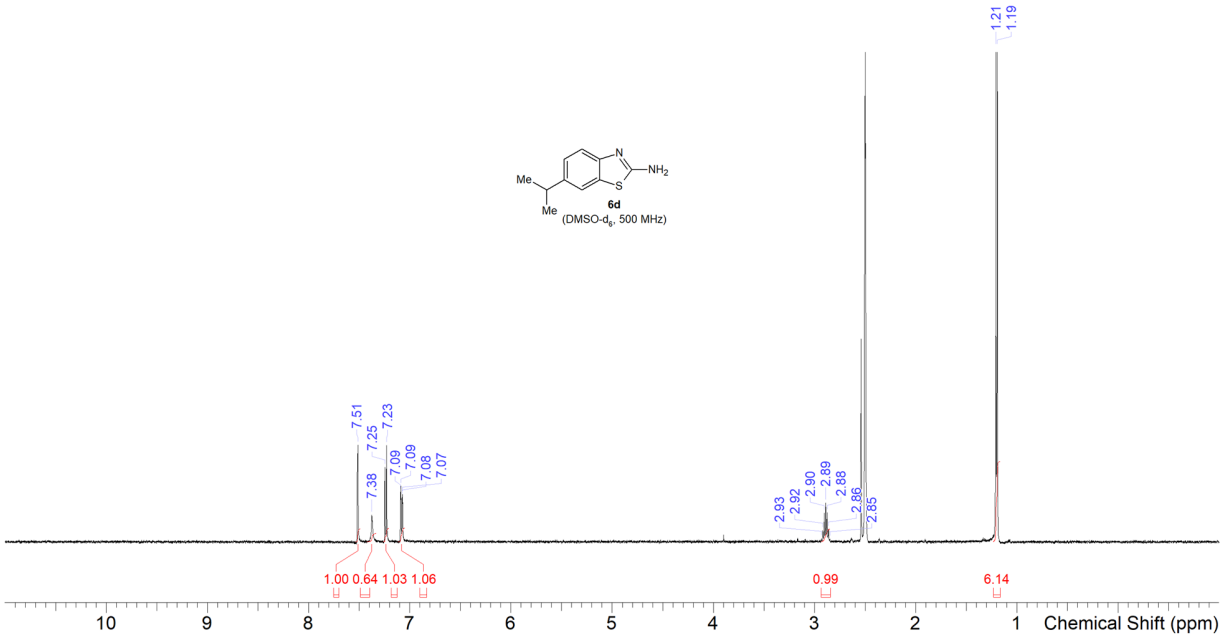

Me
N
S
NH2
6a
(CD3OD, 126 MHz)
169.19
151.02
137.96
131.96
127.39
121.33
118.51
36.64
32.80
32.58
23.60
14.39
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

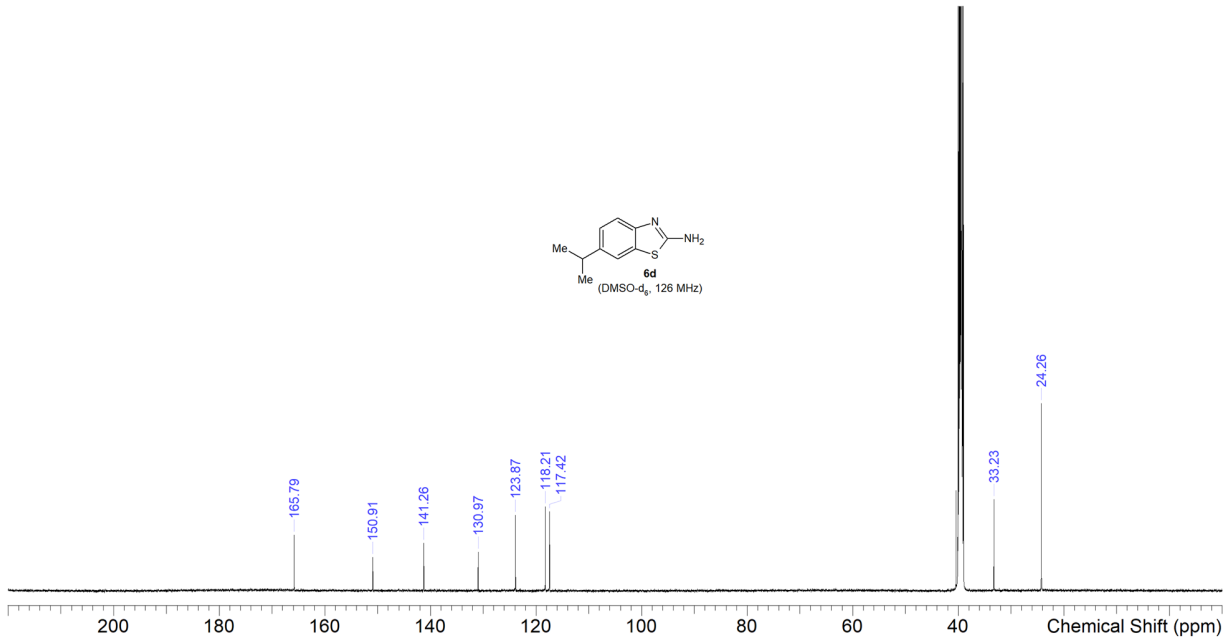

N
S
NH2
6b
(CD3OD, 500 MHz)
7.44
7.30
7.28
7.13
7.13
7.11
3.61
3.59
3.57
3.56
3.54
2.37
2.36
2.35
2.34
2.33
2.17
2.15
2.13
2.13
2.04
1.87
1.00
1.07
1.05
1.10
2.16
2.16
1.23
1.18
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

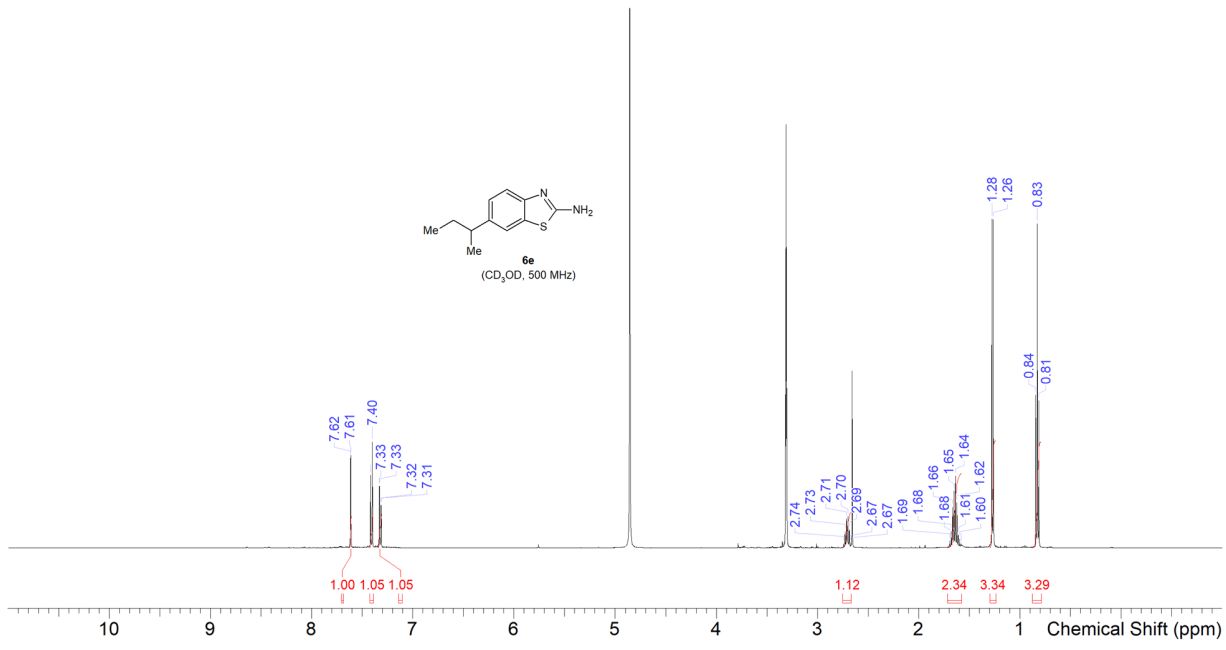

N
NH2
S
6b
(CD3OD, 126 MHz)
169.30
151.12
141.38
131.98
125.31
119.34
118.46
41.71
31.17
18.95
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

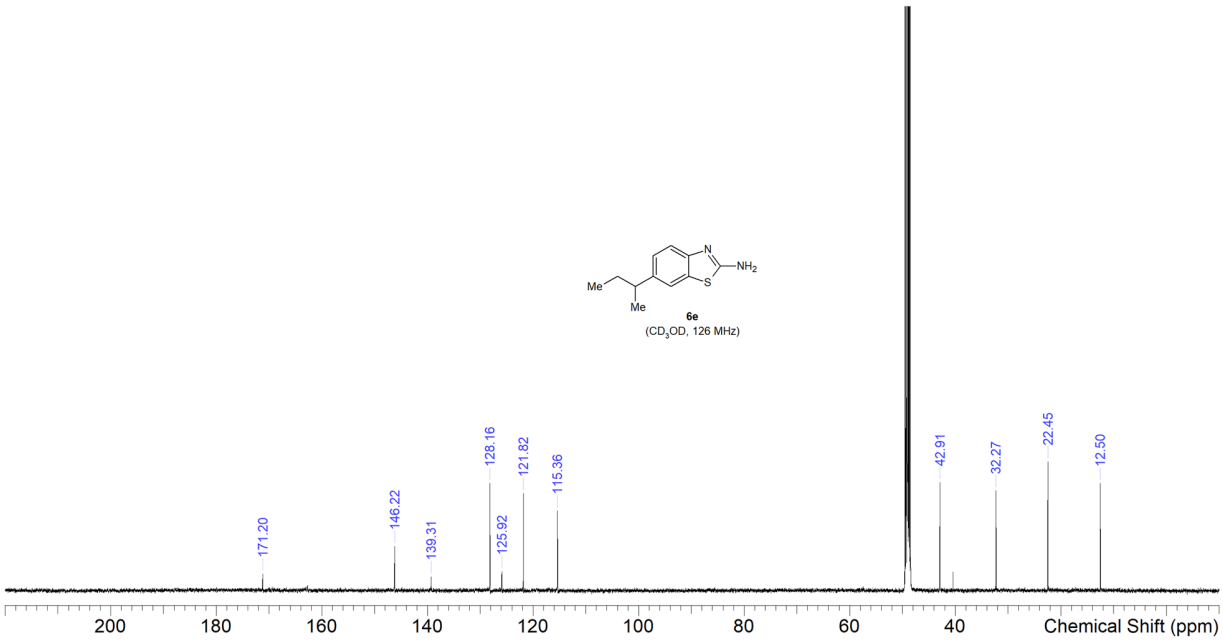

N
NH2
Me
O
S
6c
(CD3OD, 500 MHz)
3.36
4.47
7.57
7.36
7.34
7.24
7.24
7.22
7.22
1.00
1.02
1.03
2.18
3.01
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

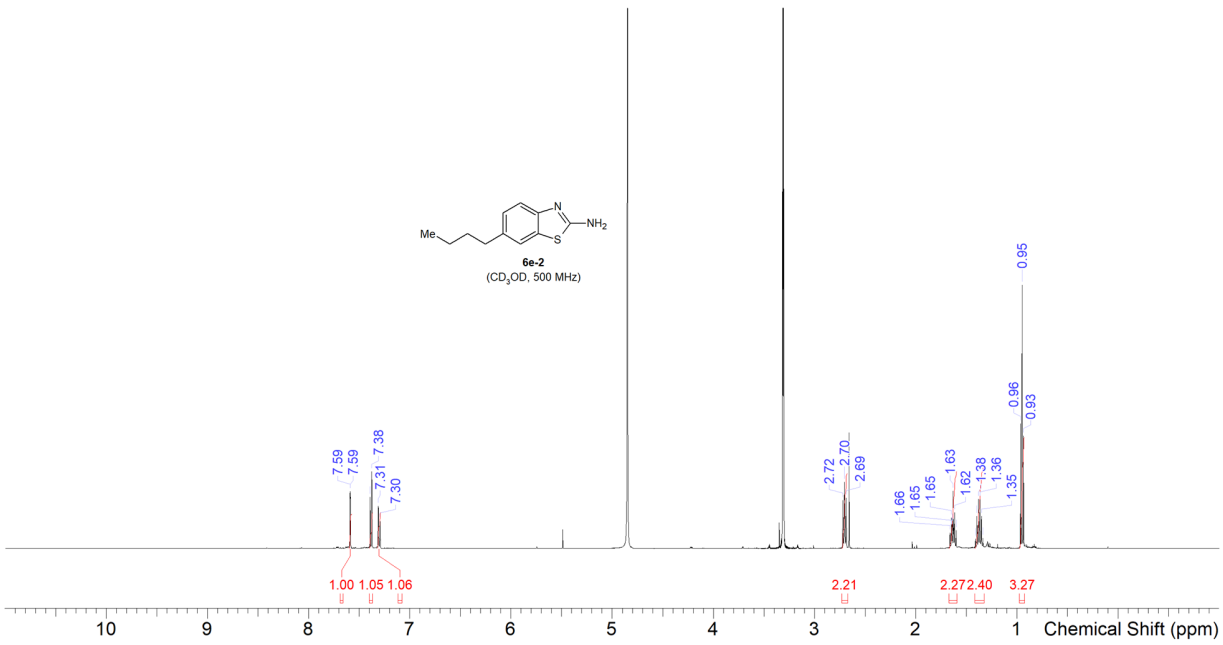

Me
O
N
S
NH2
6c
(CD3OD, 126 MHz)
170.03
152.83
133.05
132.08
127.24
121.68
118.54
75.60
58.05
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

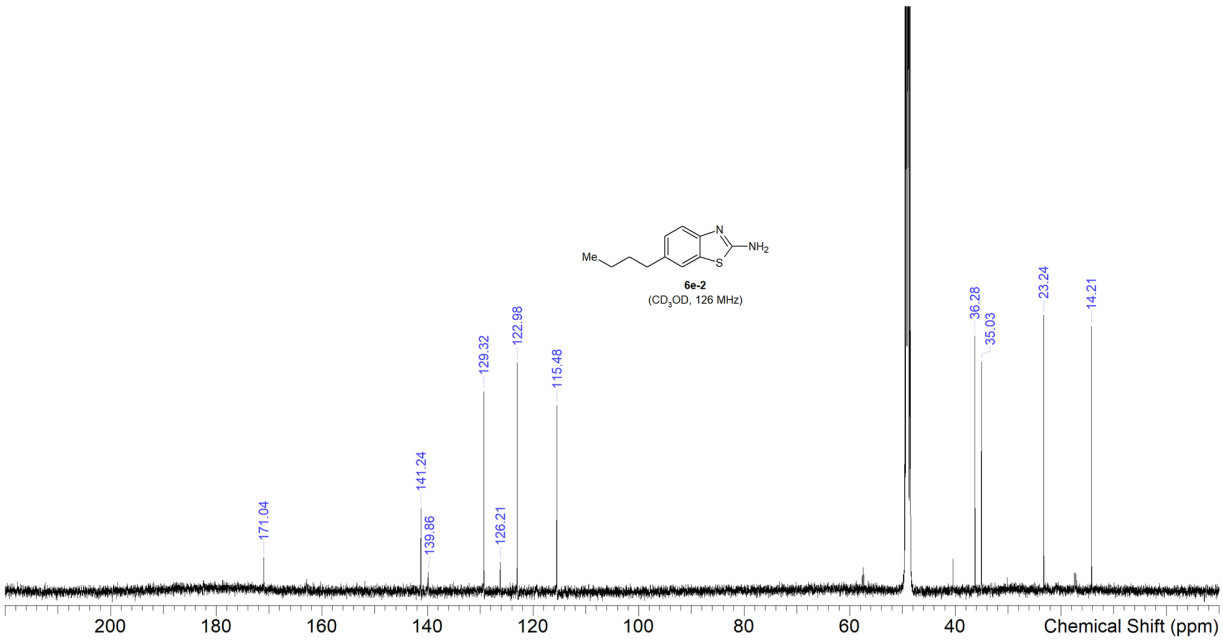

Me
Me
N
S
NH2
6d
(DMSO-d6, 500 MHz)
7.51
7.25
7.23
7.38
7.09
7.09
7.08
7.07
2.93
2.92
2.90
2.89
2.88
2.86
2.85
1.21
1.19
1.00
0.64
1.03
1.06
0.99
6.14
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

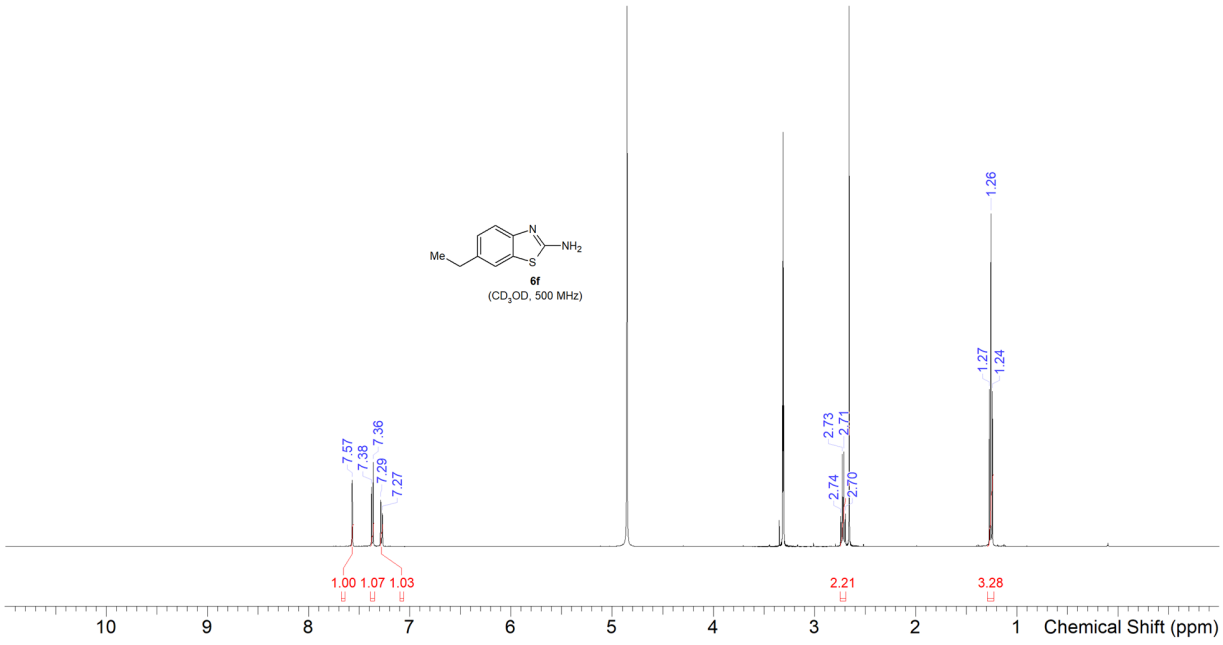

Me
Me
N
NH2
S
6d
(DMSO-d6, 126 MHz)
165.79
150.91
141.26
130.97
123.87
118.21
117.42
33.23
24.26
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

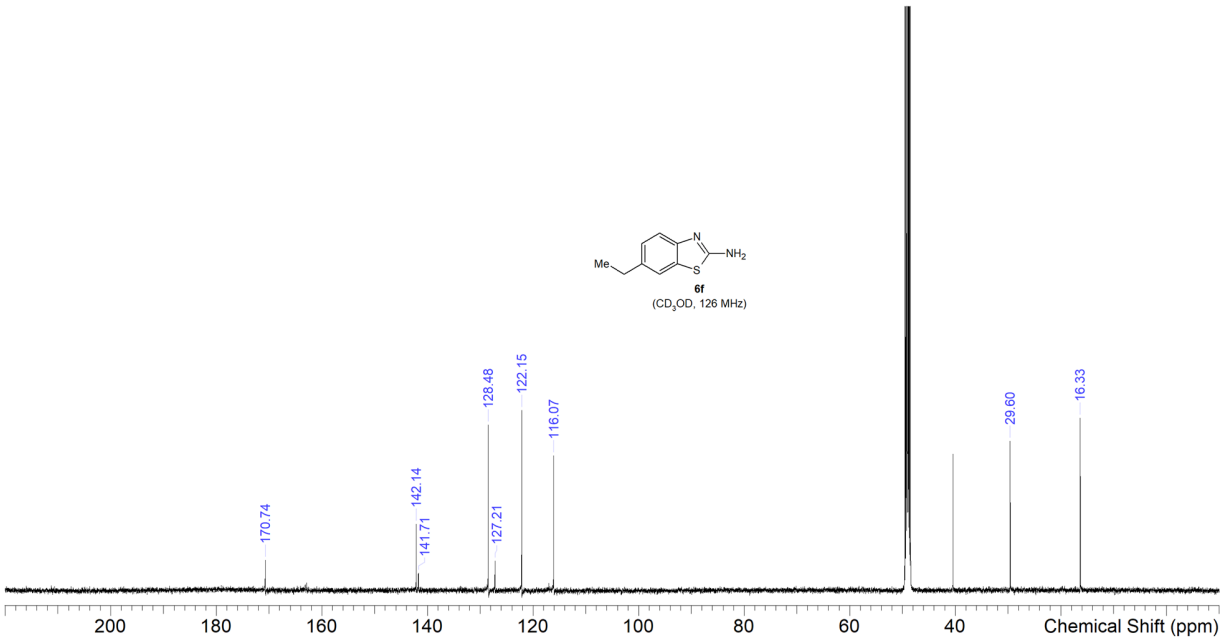

Me
Me
N
NH2
S
6e
(CD3OD, 500 MHz)
7.62
7.61
7.40
7.33
7.33
7.32
7.31
2.74
2.73
2.71
2.70
2.69
2.67
2.67
1.69
1.68
1.66
1.65
1.64
1.62
1.61
1.60
1.28
1.26
0.84
0.81
0.83
1.00
1.05
1.05
1.12
2.34
3.34
3.29
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

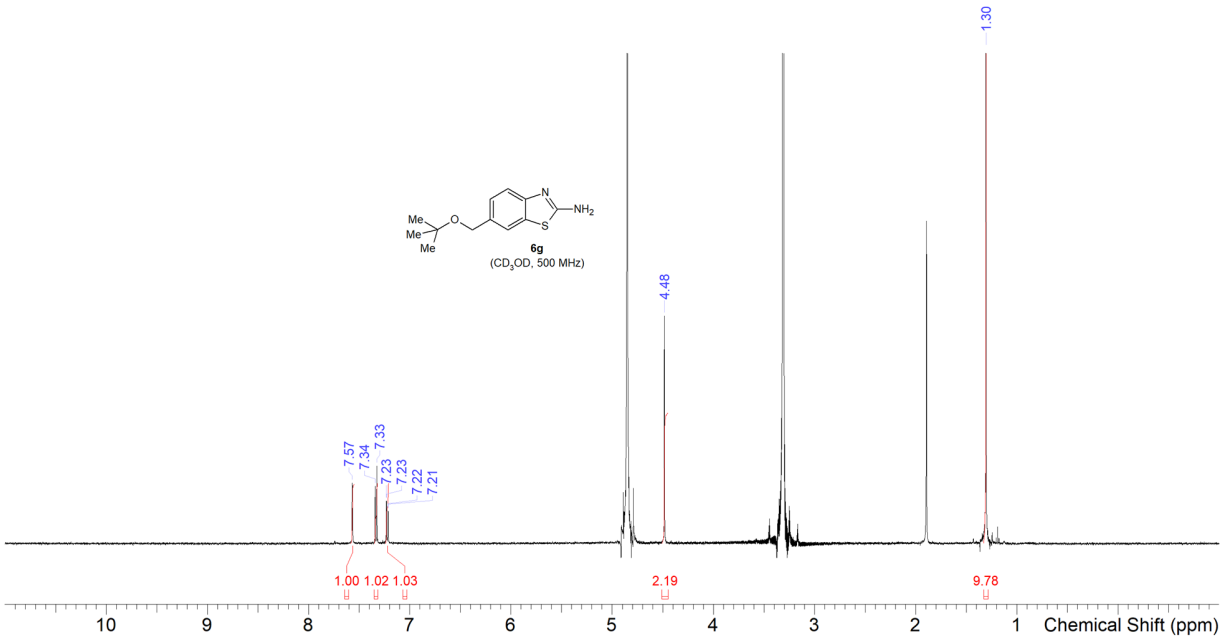

Me
Me
N
NH2
S
6e
(CD3OD, 126 MHz)
171.20
146.22
139.31
128.16
125.92
121.82
115.36
42.91
32.27
22.45
12.50
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

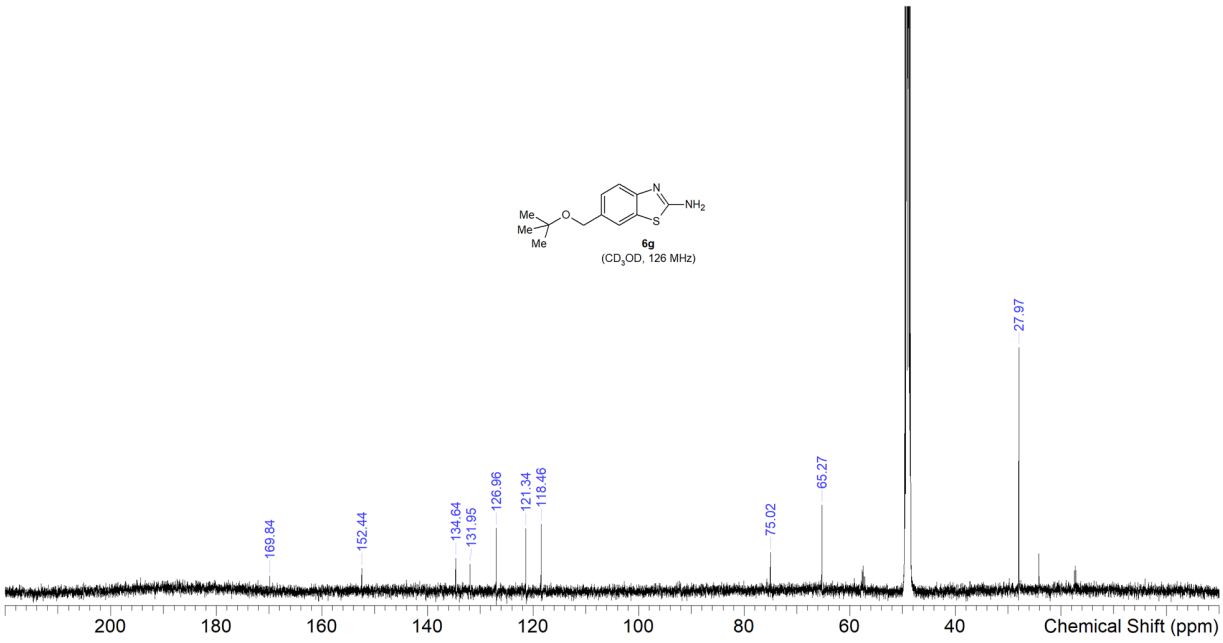

Me
N
NH2
S
6e-2
(CD3OD, 500 MHz)
7.59
7.59
7.38
7.31
7.30
2.72
2.70
2.69
1.66
1.65
1.65
1.63
1.62
1.38
1.36
1.35
0.95
0.96
0.93
1.00
1.05
1.06
2.21
2.27
2.40
3.27
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

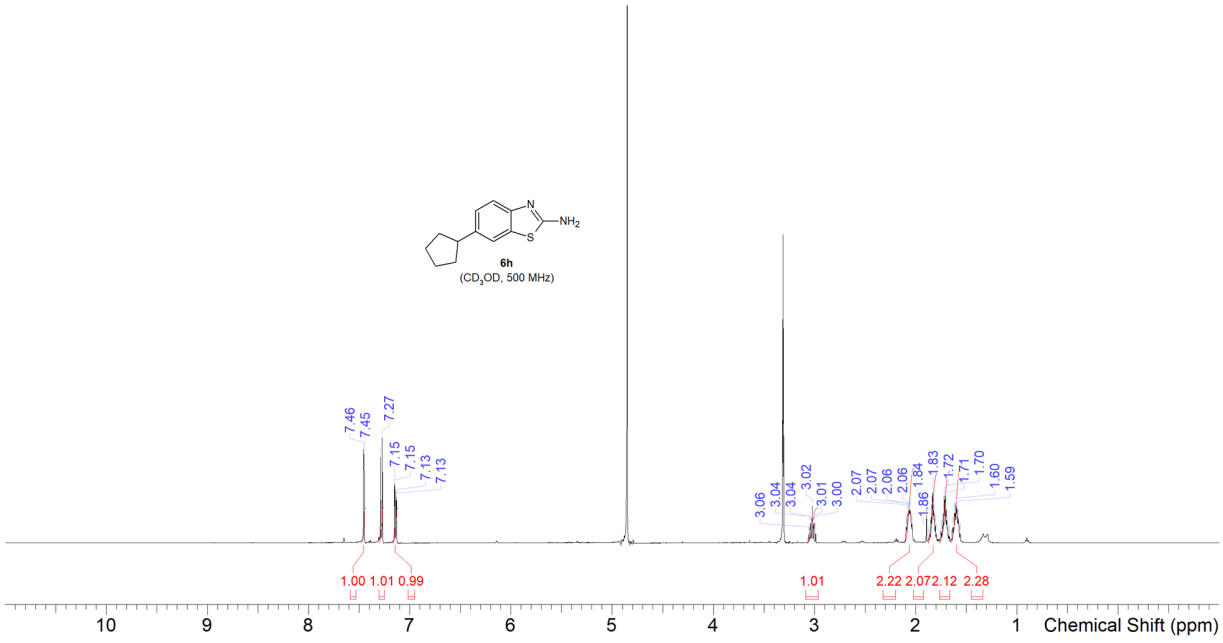

Me
N
NH2
S
6e-2
(CD3OD, 126 MHz)
171.04
141.24
139.86
129.32
126.21
122.98
115.48
36.28
35.03
23.24
14.21
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

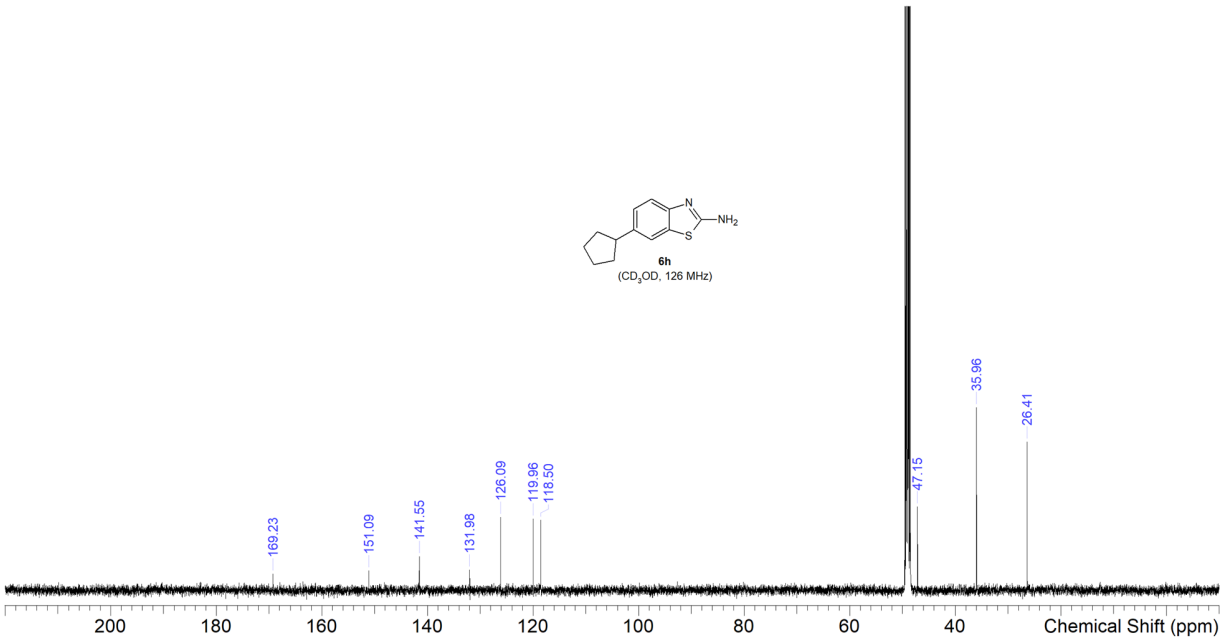

Me
N
NH2
S
6f
(CD3OD, 500 MHz)
7.57
7.38
7.36
7.29
7.27
2.73
2.71
2.74
2.70
1.26
1.27
1.24
1.00
1.07
1.03
2.21
3.28
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

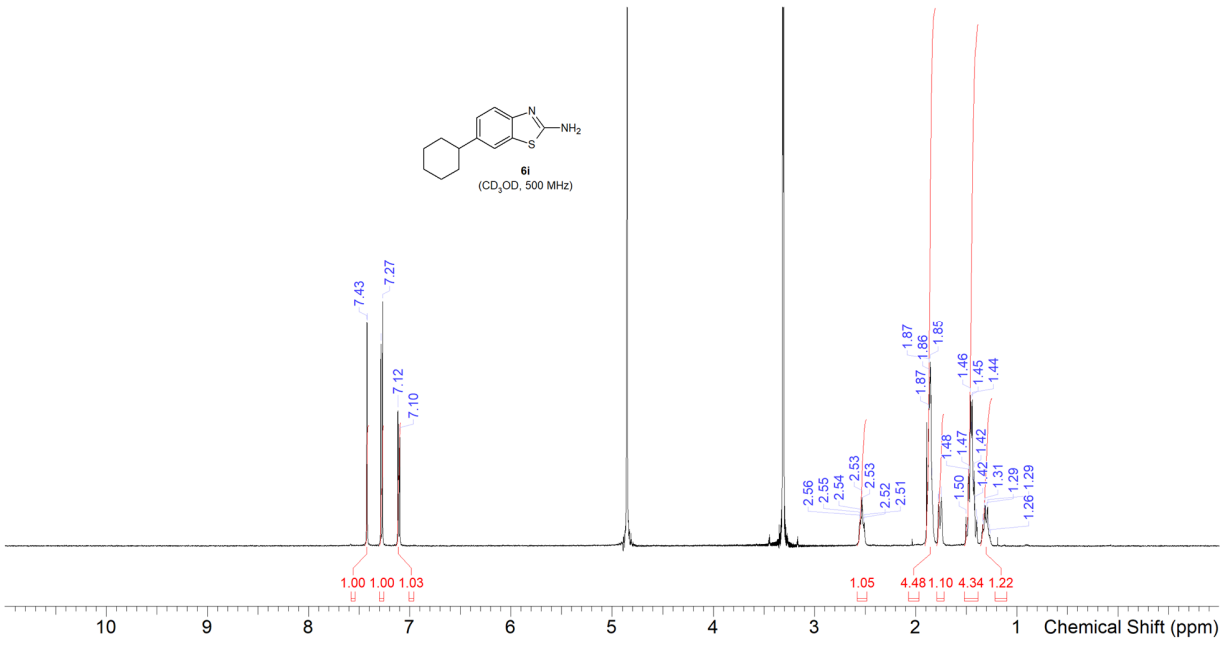

Me
N
S
NH2
6f
(CD3OD, 126 MHz)
170.74
142.14
141.71
128.48
127.21
122.15
116.07
29.60
16.33
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

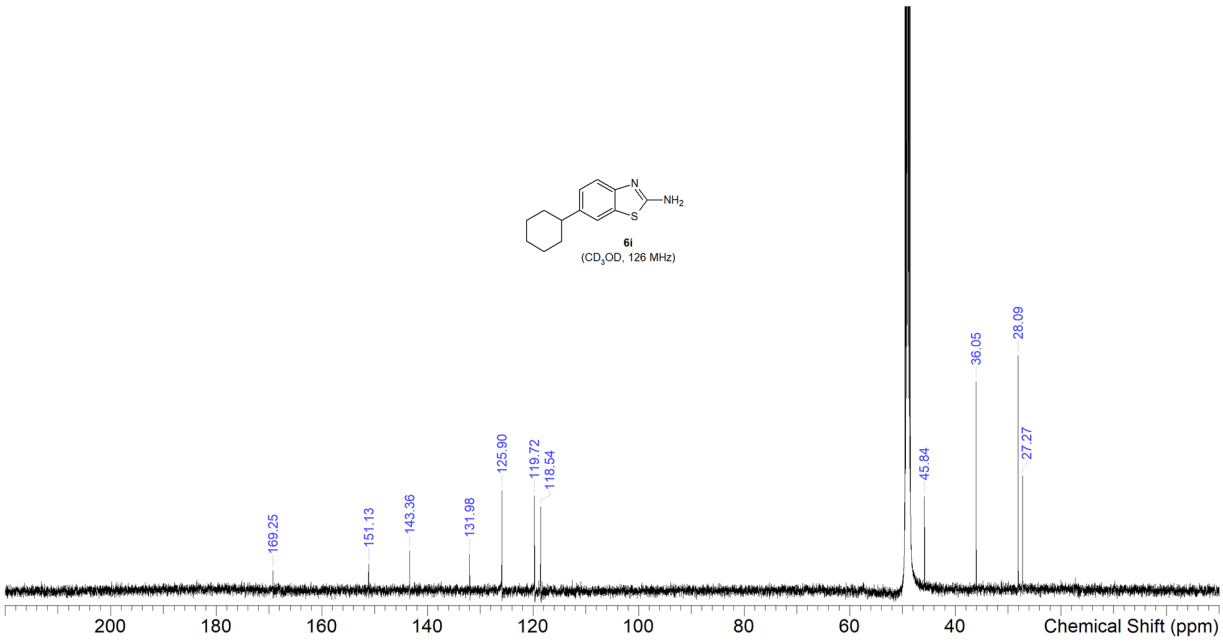

Me
Me
Me
O
N
S
NH2
6g
(CD3OD, 500 MHz)
1.30
4.48
7.57
7.34
7.33
7.23
7.23
7.22
7.21
1.00
1.02
1.03
2.19
9.78
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

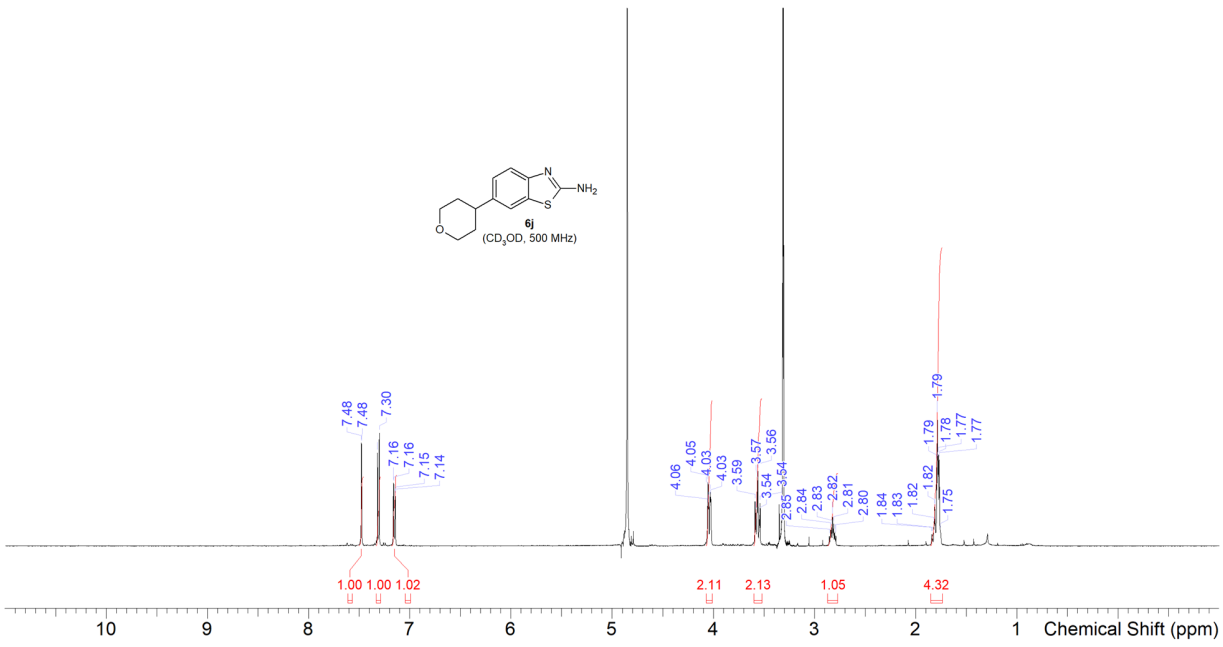

Me
Me
Me
O
N
S
NH2
6g
(CD3OD, 126 MHz)
169.84
152.44
134.64
131.95
126.96
121.34
118.46
75.02
65.27
27.97
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

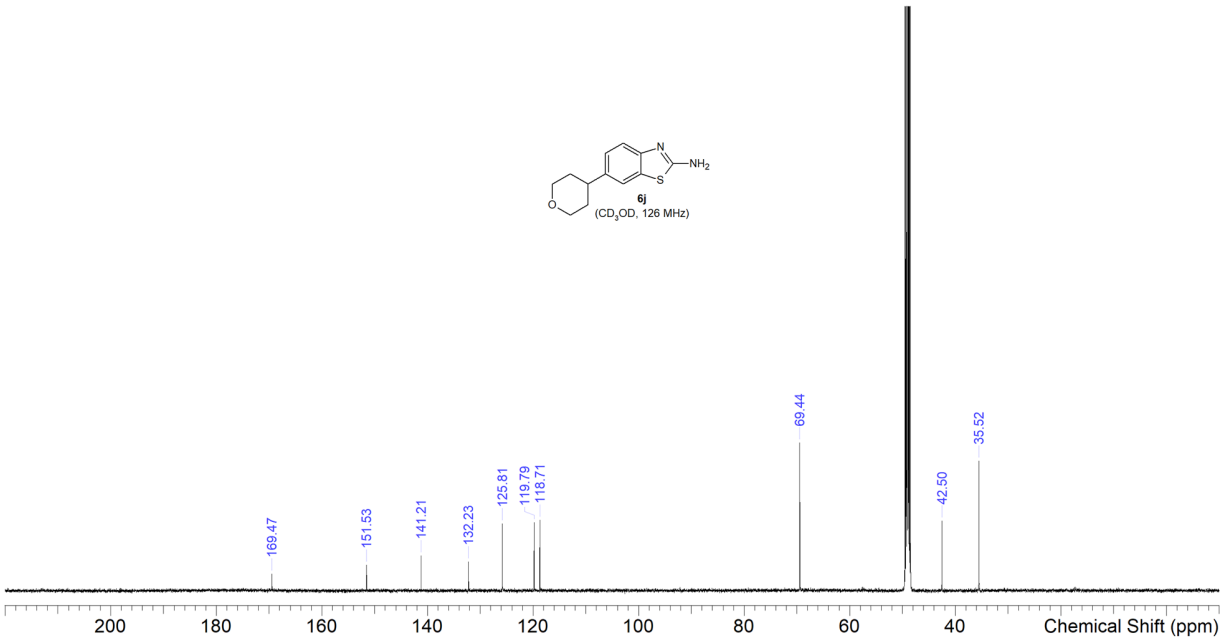

N
S
NH2
6h
(CD3OD, 500 MHz)
7.46
7.45
7.27
7.15
7.15
7.13
7.13
3.06
3.04
3.04
3.02
3.01
3.00
2.07
2.07
2.06
2.06
1.84
1.86
1.83
1.72
1.71
1.70
1.60
1.59
1.00 1.01 0.99
1.01
2.22 2.07 2.12 2.28
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


6h
(CD3OD, 126 MHz)
169.23
151.09
141.55
131.98
126.09
119.96
118.50
47.15
35.96
26.41
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

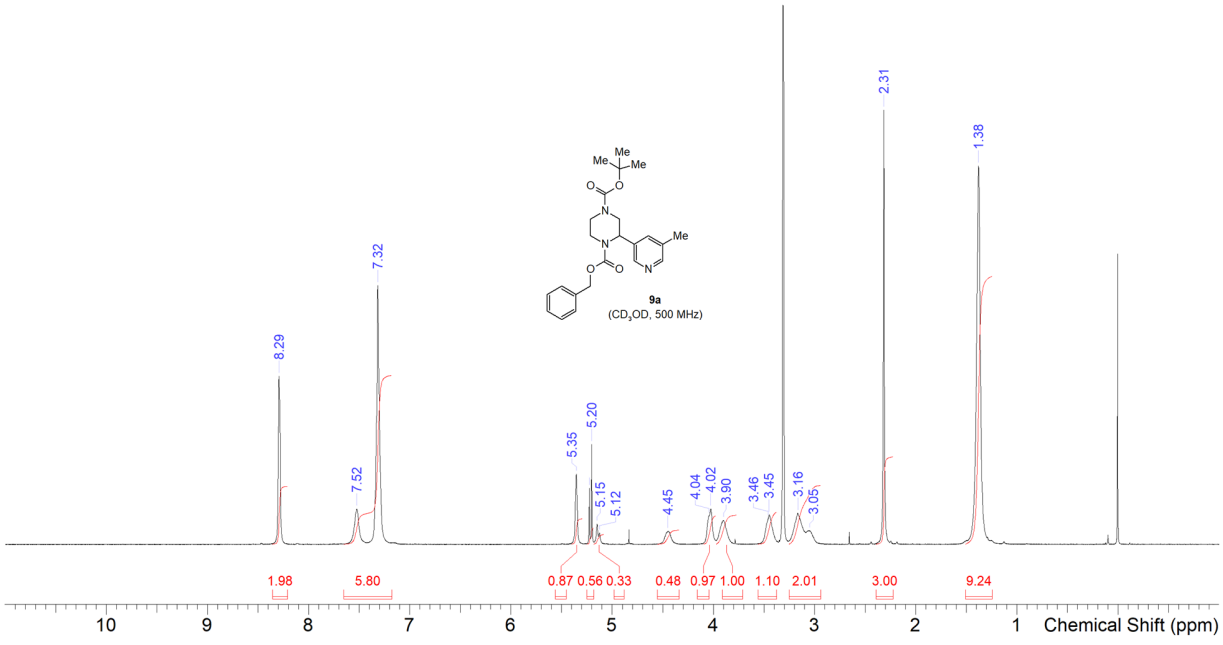

6i
(CD3OD, 500 MHz)
7.43
7.27
7.12
7.10
2.56
2.55
2.54
2.53
2.53
2.52
2.51
1.87
1.86
1.87
1.85
1.48
1.47
1.50
1.46
1.45
1.44
1.42
1.42
1.31
1.29
1.29
1.26
1.00 1.00 1.03
1.05
4.48 1.10 4.34 1.22
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

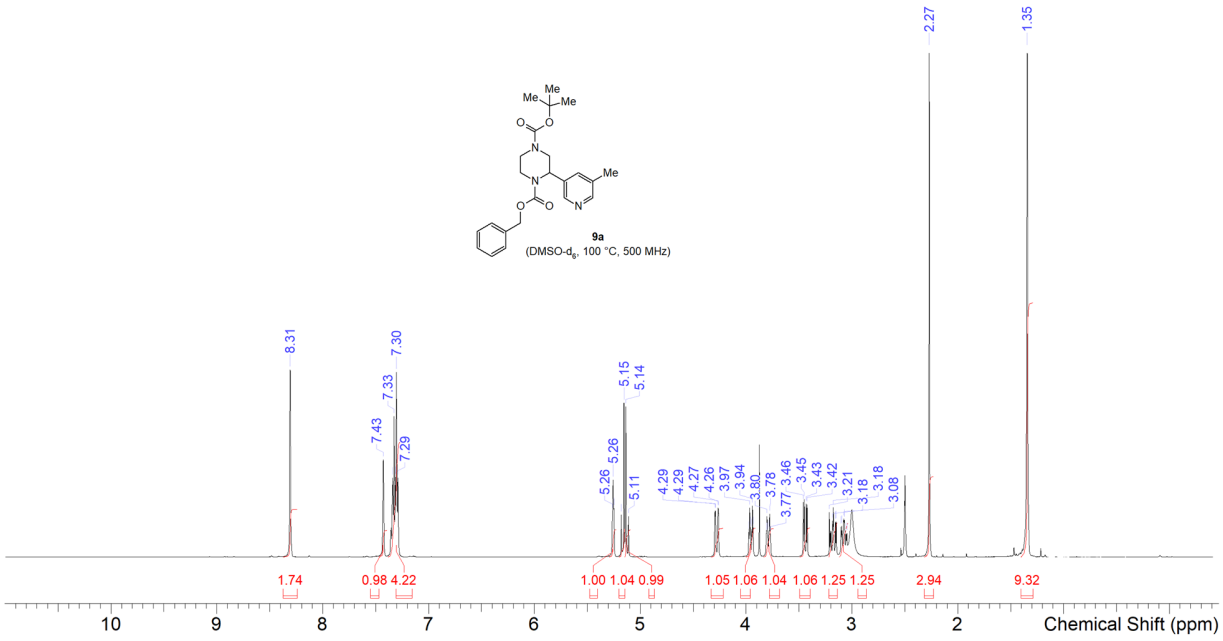

6i
(CD3OD, 126 MHz)
169.25
151.13
143.36
131.98
125.90
119.72
118.54
45.84
36.05
28.09
27.27
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

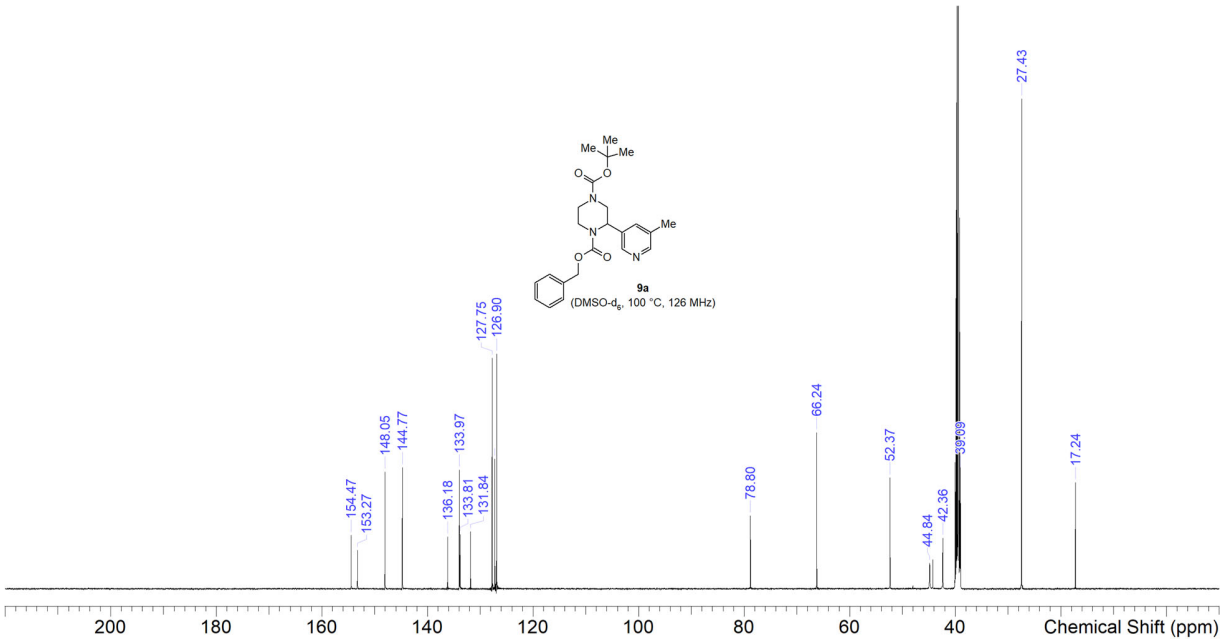

6j
(CD3OD, 500 MHz)
7.48
7.48
7.30
7.16
7.16
7.15
7.14
4.06
4.05
4.03
4.03
3.59
3.57
3.56
3.54
3.54
2.85
2.84
2.83
2.82
2.81
2.80
1.84
1.83
1.82
1.82
1.79
1.79
1.78
1.77
1.77
1.75
1.00
1.00
1.02
2.11
2.13
1.05
4.32
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

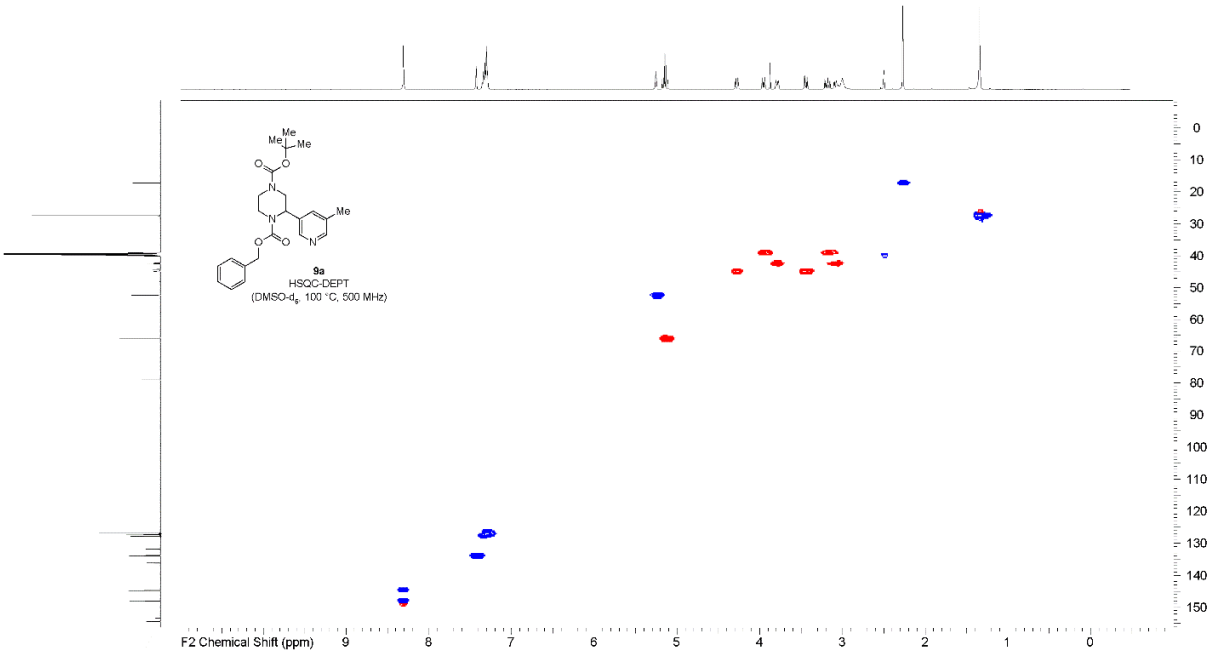


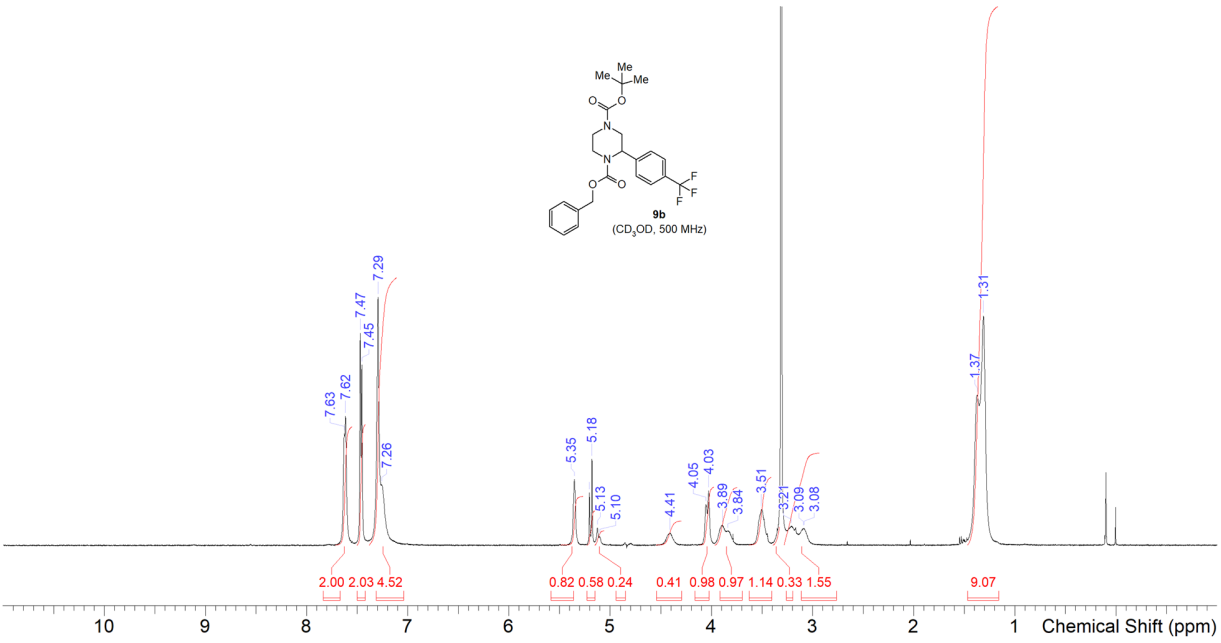
^{1}H and ^{13}C NMR Spectra: Scheme 3. Decarboxylative arylation

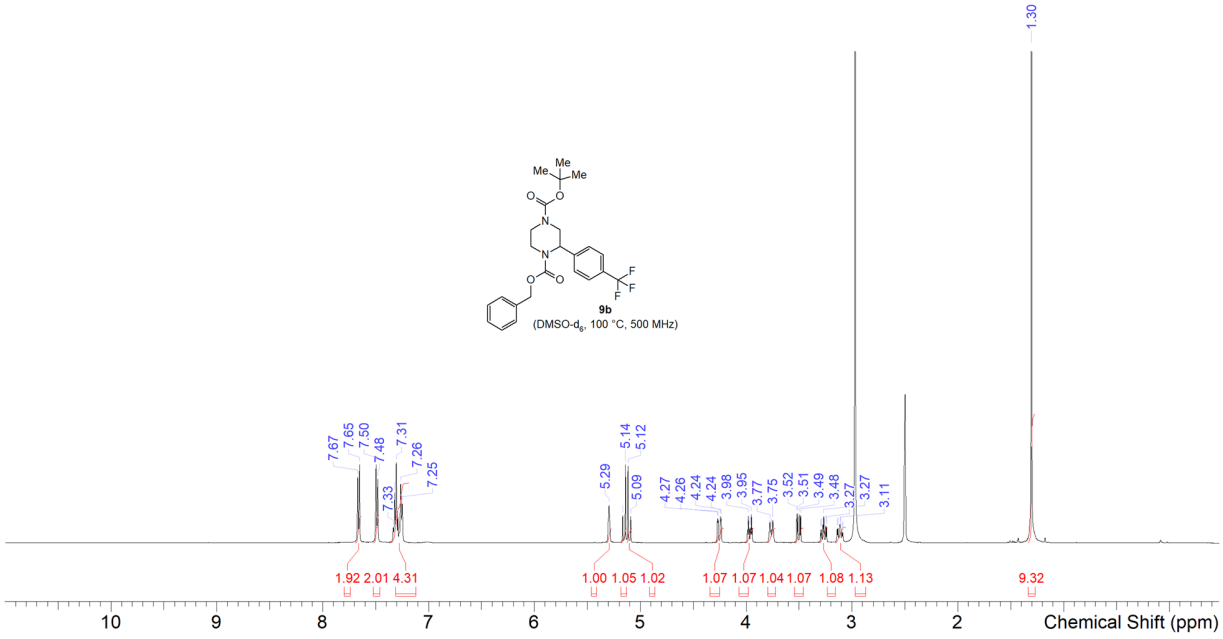


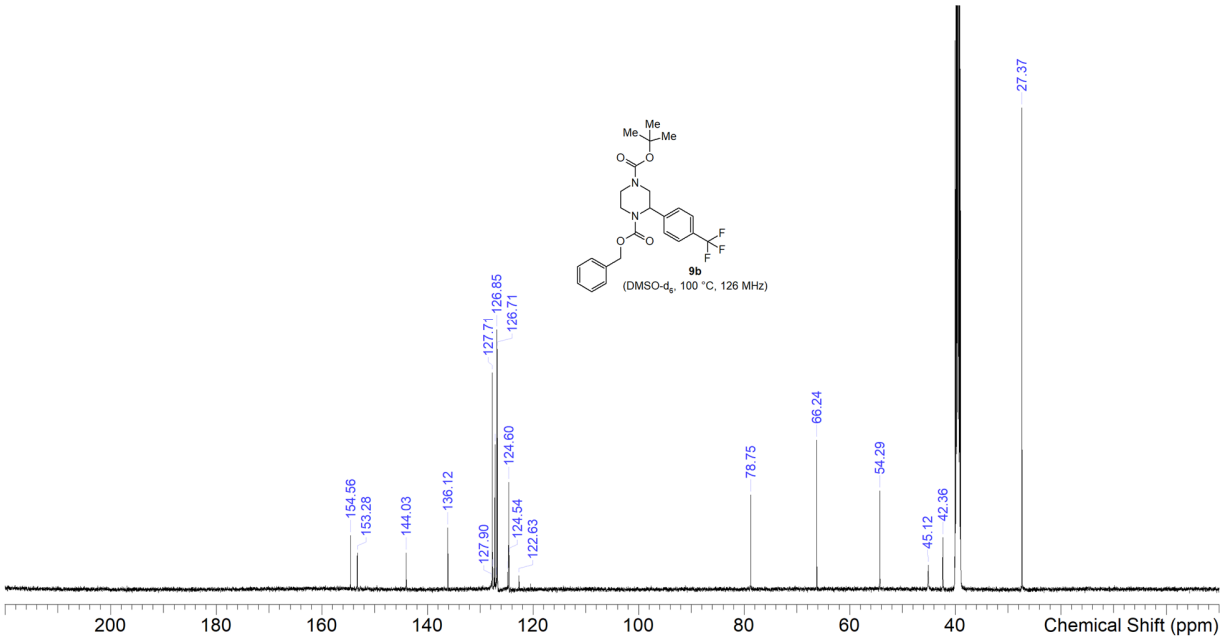

9a
(DMSO-d6, 100 °C, 500 MHz)
8.31
7.43
7.33
7.30
7.29
5.26
5.26
5.15
5.14
5.11
4.29
4.29
4.27
4.26
3.97
3.94
3.80
3.78
3.77
3.46
3.45
3.43
3.42
3.21
3.18
3.18
3.08
2.27
1.35
1.74
0.98
4.22
1.00
1.04
0.99
1.05
1.06
1.04
1.06
1.25
1.25
2.94
9.32
Chemical Shift (ppm)

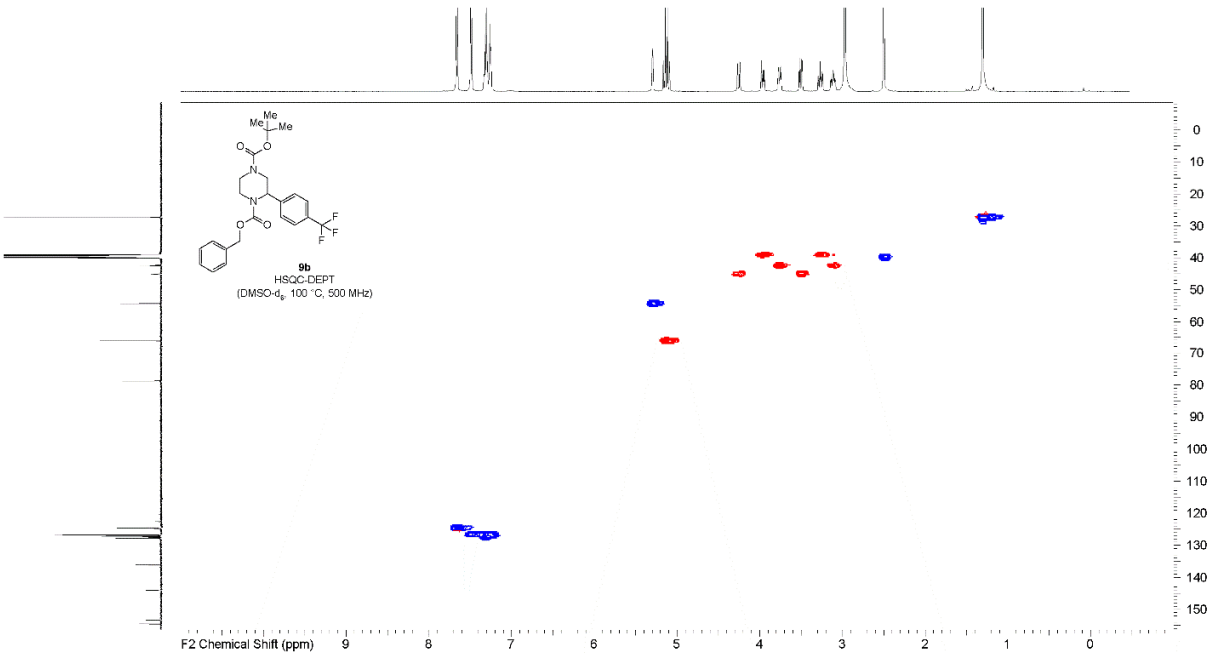

9a
(DMSO-d6, 100 °C, 126 MHz)
154.47
153.27
148.05
144.77
136.18
133.97
133.81
131.84
127.75
126.90
78.80
66.24
52.37
44.84
42.36
39.09
27.43
17.24
Chemical Shift (ppm)

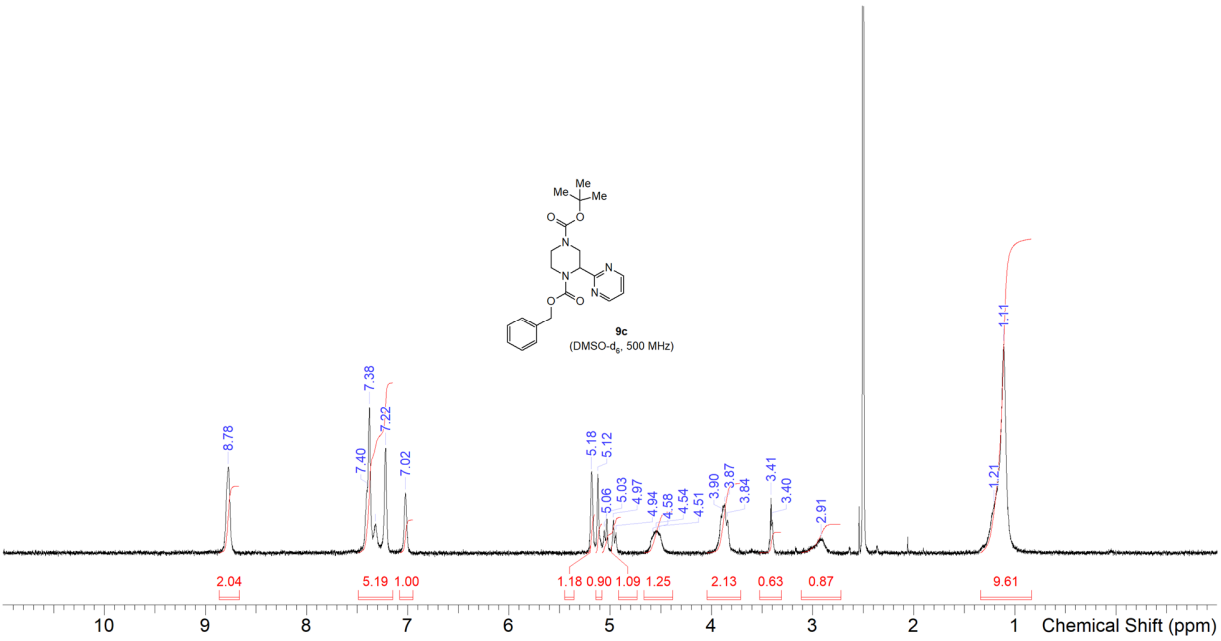

9a
HSQC-DEPT
(DMSO-d6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)

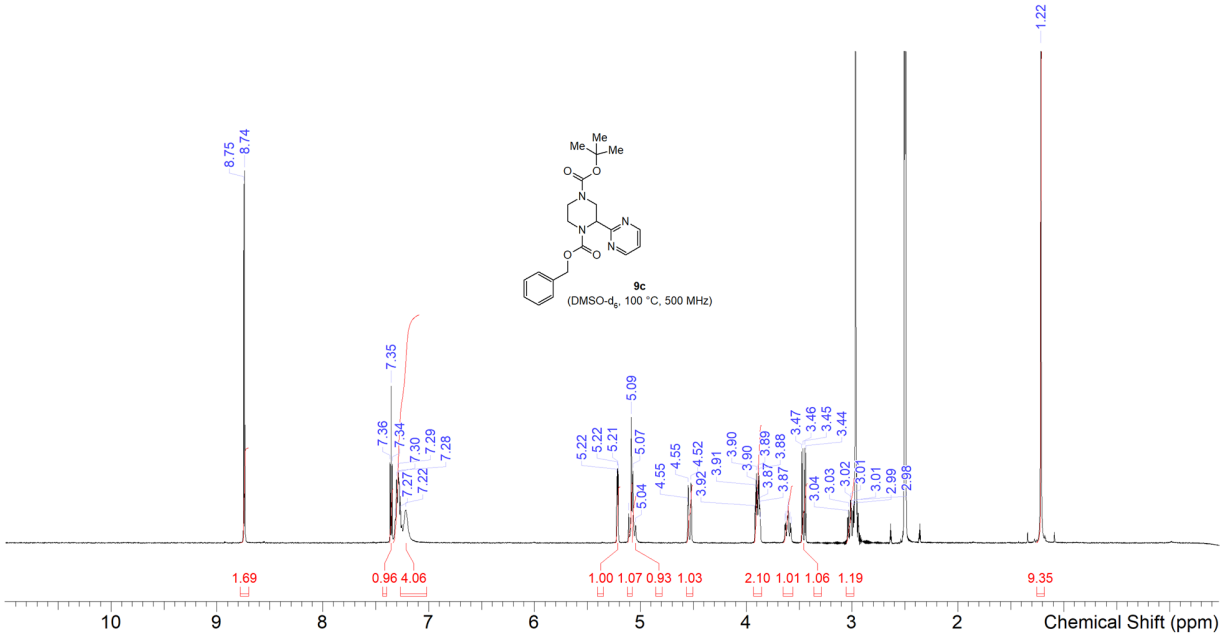

9b
(CD3OD, 500 MHz)
7.63
7.62
7.47
7.45
7.29
7.26
5.35
5.18
5.13
5.10
4.41
4.05
4.03
3.89
3.84
3.51
3.21
3.09
3.08
1.37
1.31
2.00 2.03 4.52
0.82 0.58 0.24
0.41 0.98 0.97 1.14 0.33 1.55
9.07
Chemical Shift (ppm)

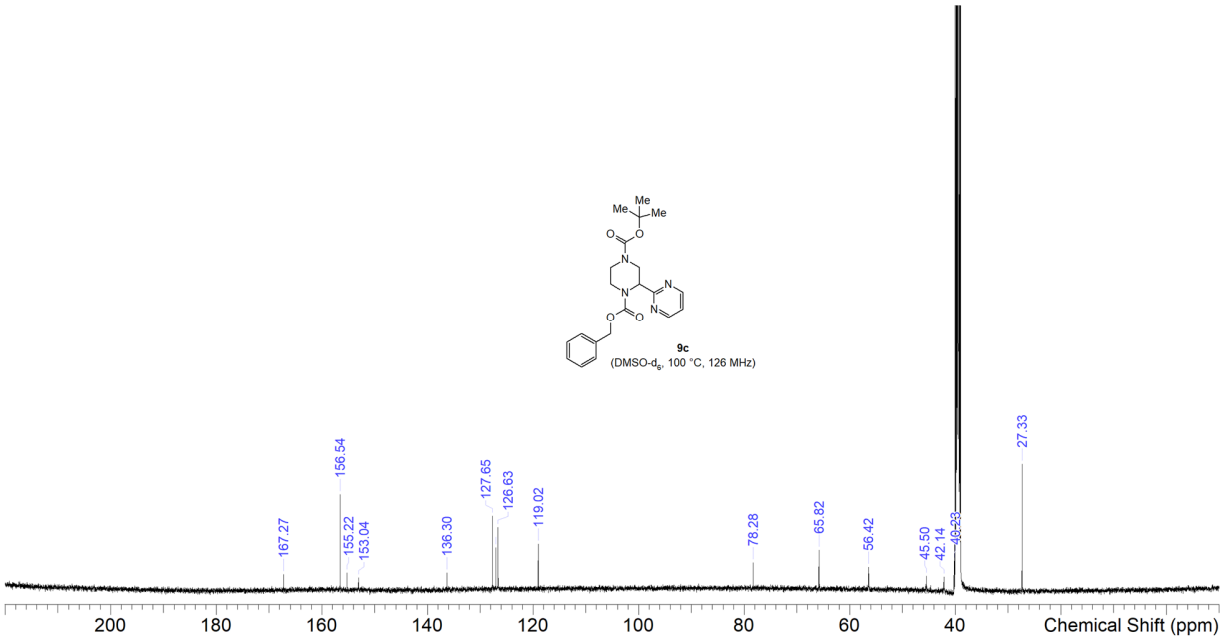

9b
(DMSO-d6, 100 °C, 500 MHz)
7.67
7.65
7.50
7.48
7.33
7.31
7.26
7.25
5.29
5.14
5.12
5.09
4.27
4.26
4.24
4.24
3.98
3.95
3.77
3.75
3.52
3.51
3.49
3.48
3.27
3.27
3.11
1.30
1.92 2.01 4.31
1.00 1.05 1.02
1.07 1.07 1.04 1.07 1.08 1.13
9.32
Chemical Shift (ppm)

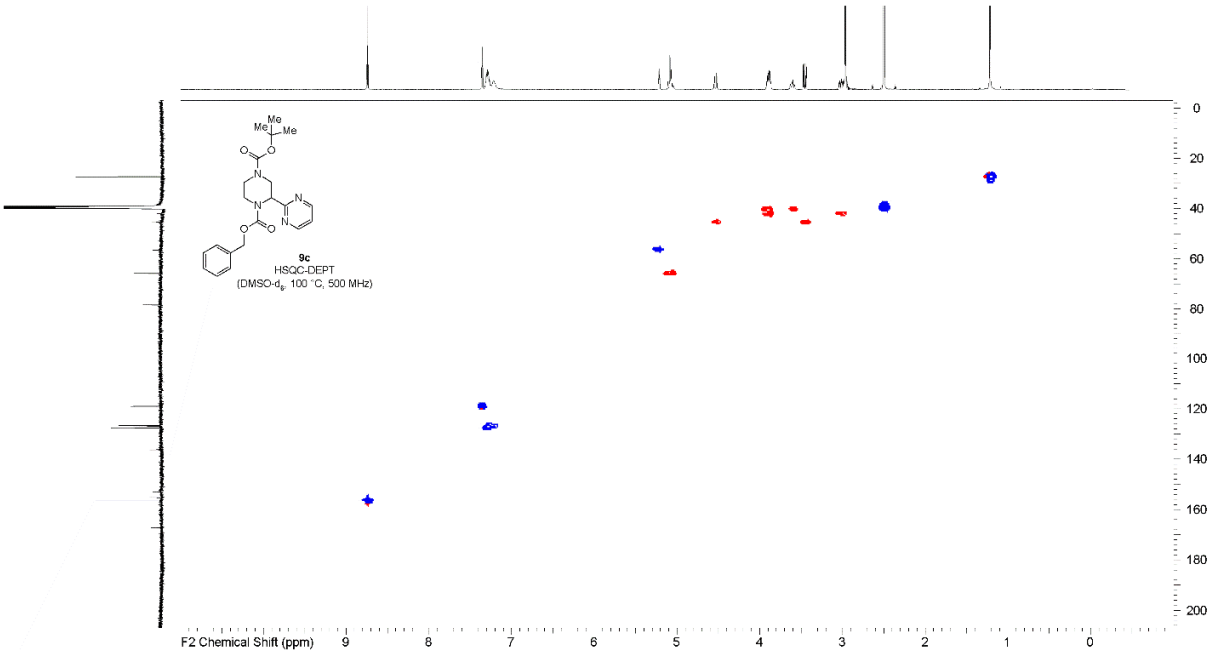

9b
(DMSO-d6, 100 °C, 126 MHz)
154.56
153.28
144.03
136.12
127.90
127.71
126.85
126.71
124.60
124.54
122.63
78.75
66.24
54.29
45.12
42.36
27.37
Chemical Shift (ppm)

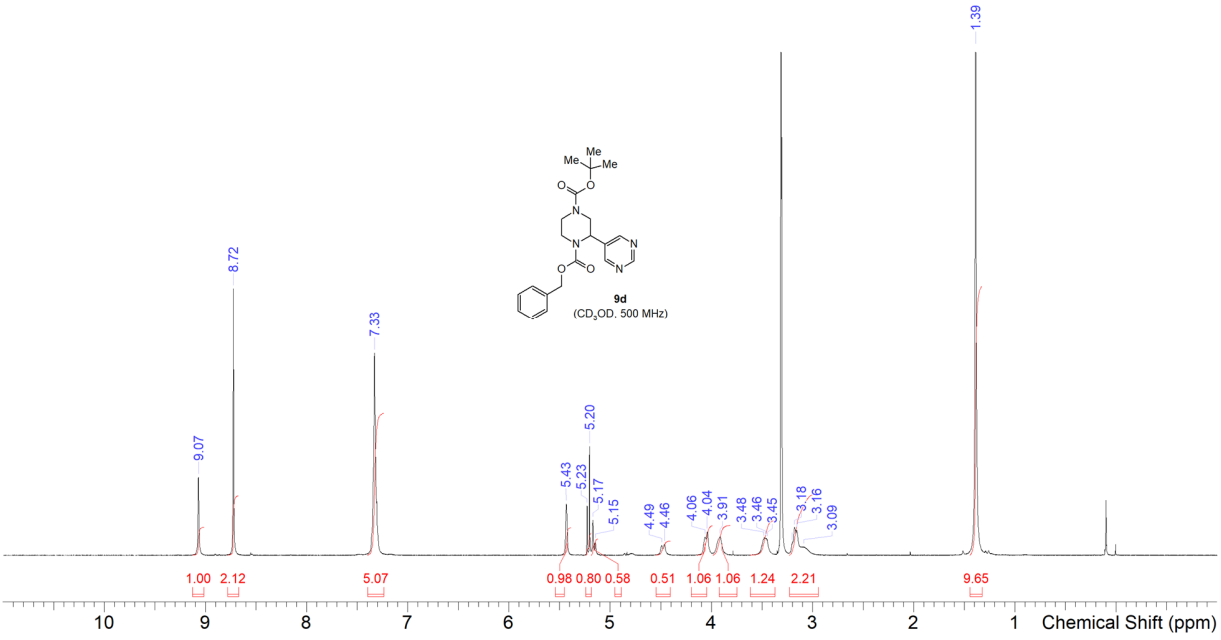

9b
HSQC-DEPT
(DMSO-d6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)

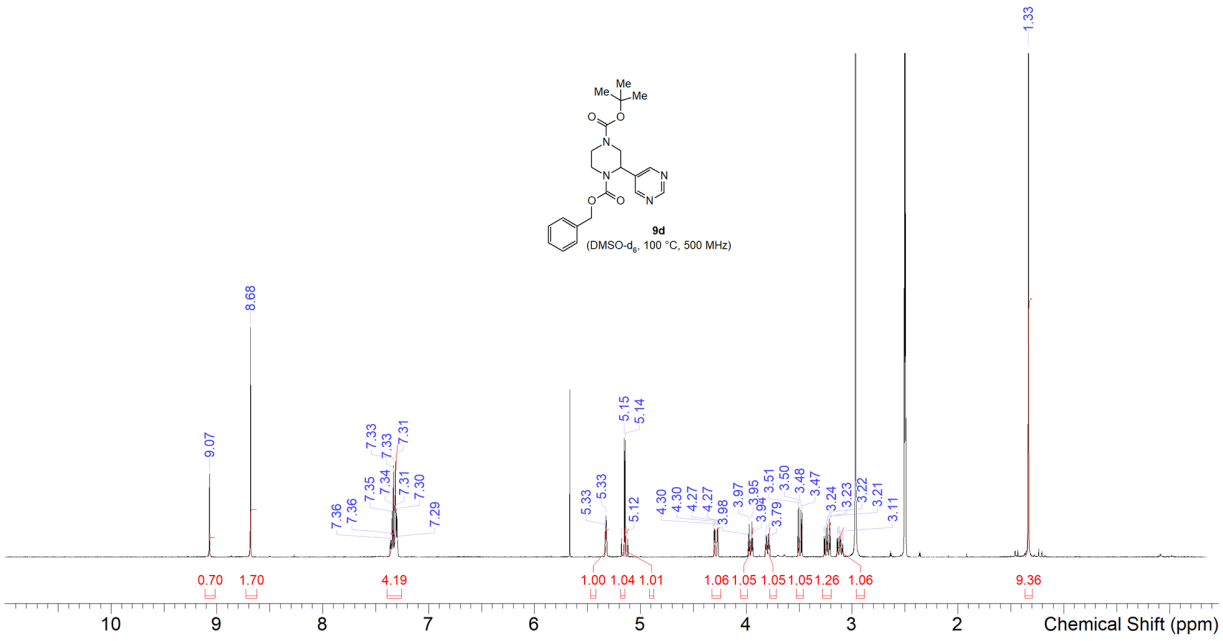

9c
(DMSO-d6, 500 MHz)
8.78
7.40
7.38
7.22
7.02
5.18
5.12
5.06
5.03
4.97
4.94
4.58
4.54
4.51
3.90
3.87
3.84
3.41
3.40
2.91
1.21
1.11
2.04
5.19
1.00
1.18
0.90
1.09
1.25
2.13
0.63
0.87
9.61
Chemical Shift (ppm)

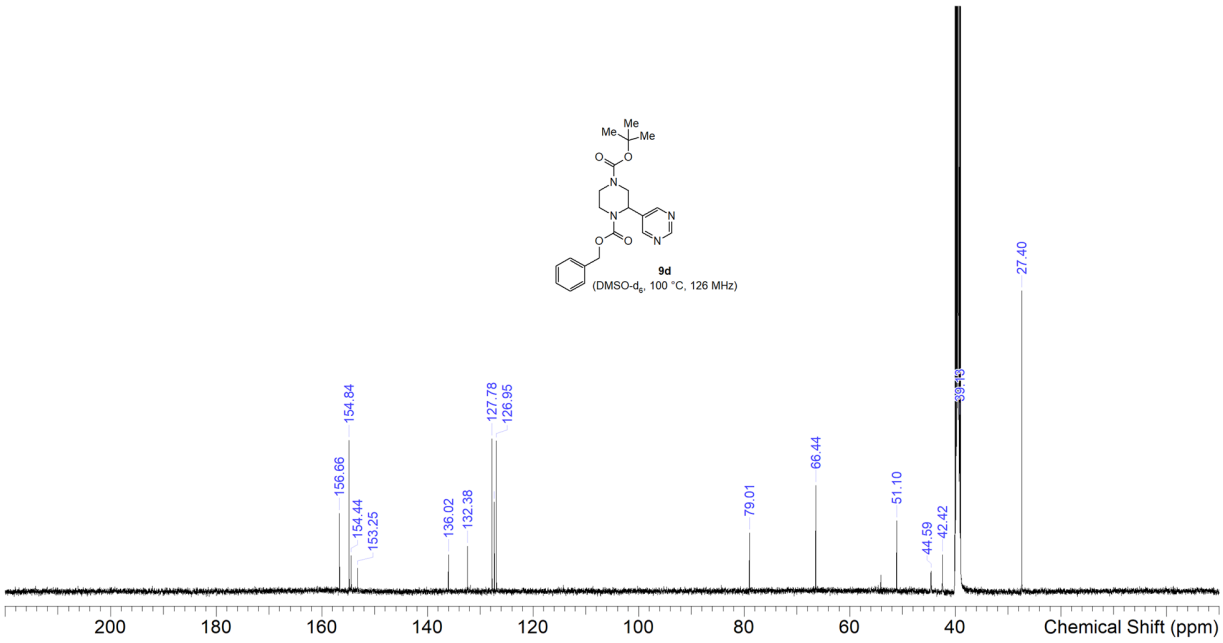

9c
(DMSO-d6, 100 °C, 500 MHz)
8.75
8.74
7.36
7.35
7.34
7.30
7.29
7.28
7.27
7.22
5.22
5.22
5.21
5.09
5.07
5.04
4.55
4.55
4.52
3.92
3.91
3.90
3.90
3.89
3.88
3.87
3.47
3.46
3.45
3.44
3.04
3.03
3.02
3.01
3.01
2.99
2.98
1.22
1.69
0.96
4.06
1.00
1.07
0.93
1.03
2.10
1.01
1.06
1.19
9.35
Chemical Shift (ppm)

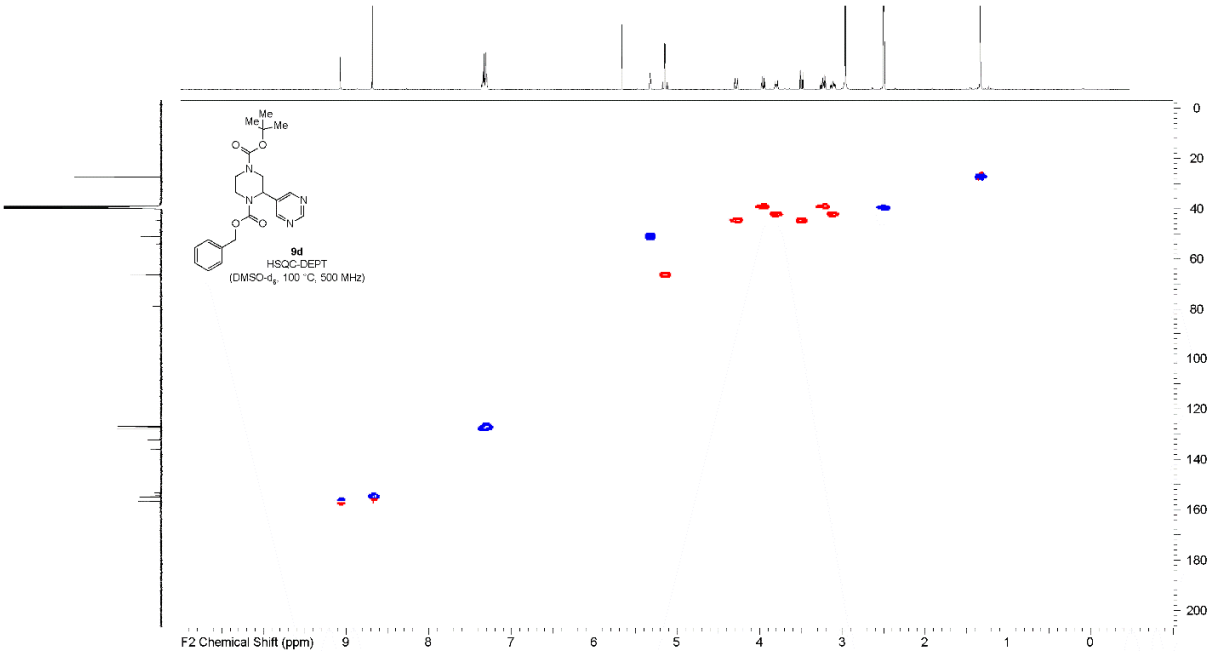

9c
(DMSO-d6, 100 °C, 126 MHz)
167.27
156.54
155.22
153.04
136.30
127.65
126.63
119.02
78.28
65.82
56.42
45.50
42.14
40.23
27.33
Chemical Shift (ppm)

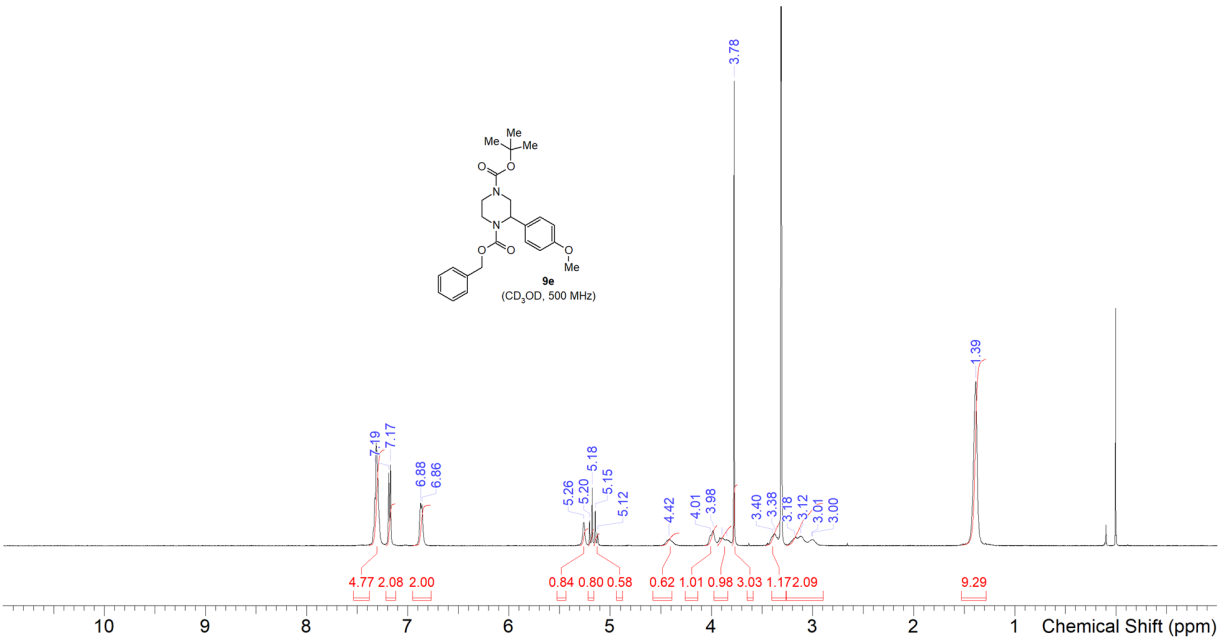

9c
HSQC-DEPT
(DMSO-d_6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)

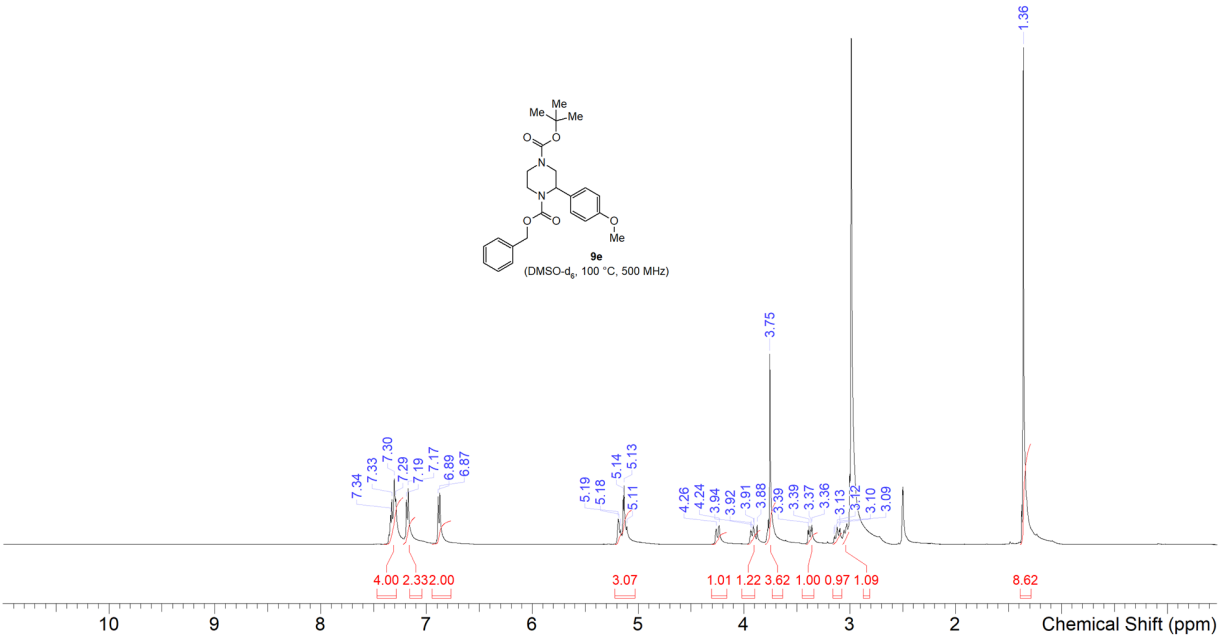

9d
(CD_3OD, 500 MHz)
9.07
8.72
7.33
5.43
5.23
5.20
5.17
5.15
4.49
4.46
4.06
4.04
3.91
3.48
3.46
3.45
3.18
3.16
3.09
1.39
1.00
2.12
5.07
0.98
0.80
0.58
0.51
1.06
1.06
1.24
2.21
9.65
Chemical Shift (ppm)

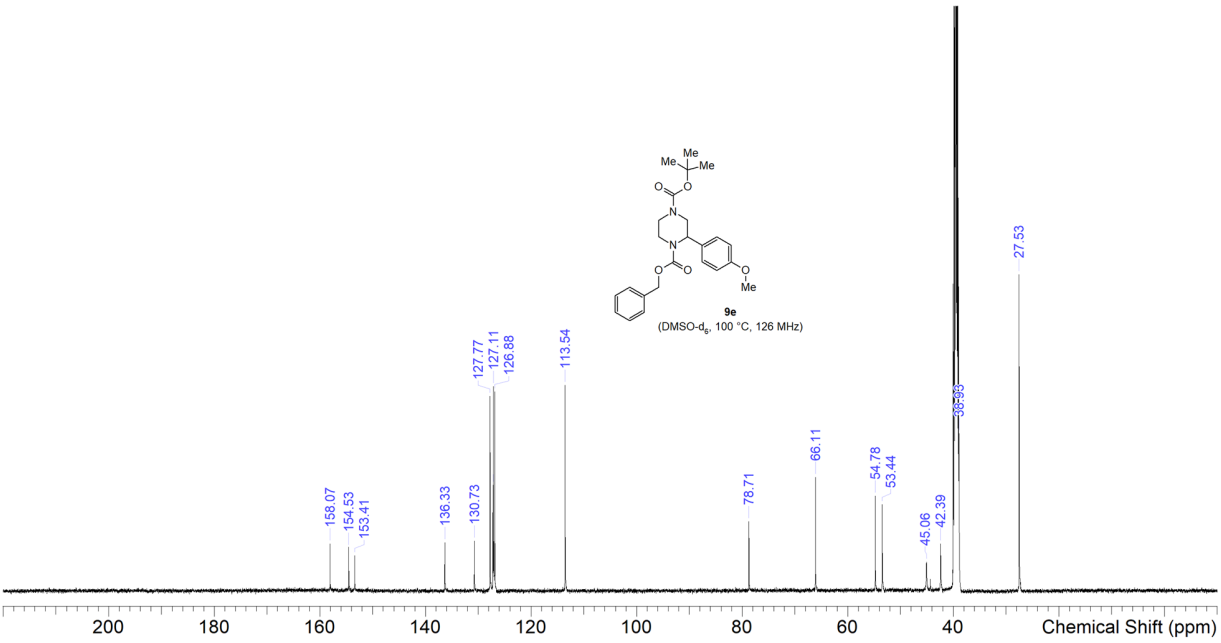

9d
(DMSO-d6, 100 °C, 500 MHz)
9.07
8.68
7.36
7.35
7.34
7.33
7.31
7.30
7.29
5.33
5.15
5.14
5.12
4.30
4.27
3.98
3.97
3.95
3.94
3.51
3.50
3.48
3.47
3.24
3.23
3.22
3.21
3.11
1.33
0.70
1.70
4.19
1.00
1.04
1.01
1.06
1.05
1.05
1.05
1.26
1.06
9.36
Chemical Shift (ppm)

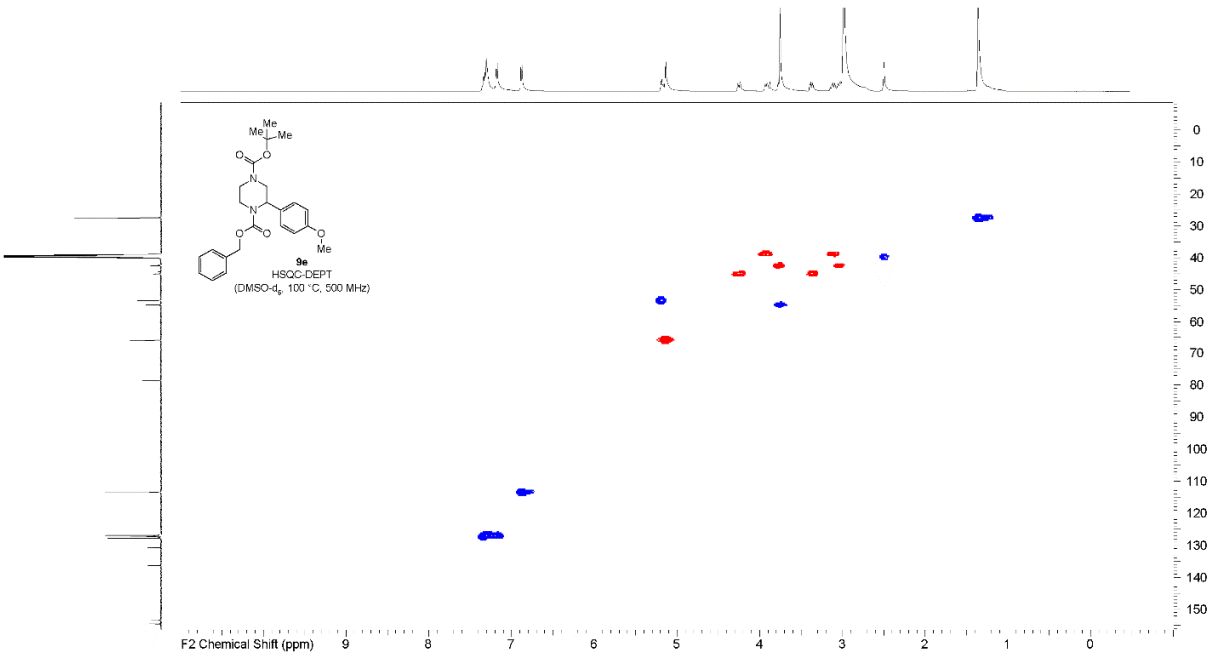

9d
(DMSO-d6, 100 °C, 126 MHz)
156.66
154.84
154.44
153.25
136.02
132.38
127.78
126.95
79.01
66.44
51.10
44.59
42.42
27.40
Chemical Shift (ppm)

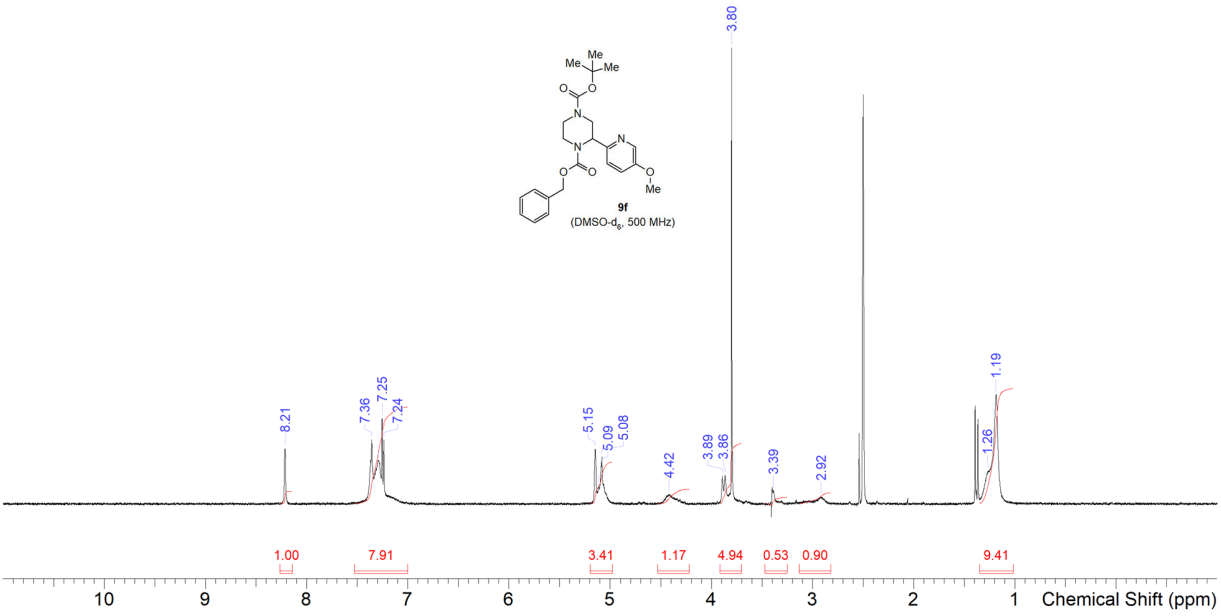

9d
HSQC-DEPT
(DMSO-d6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)

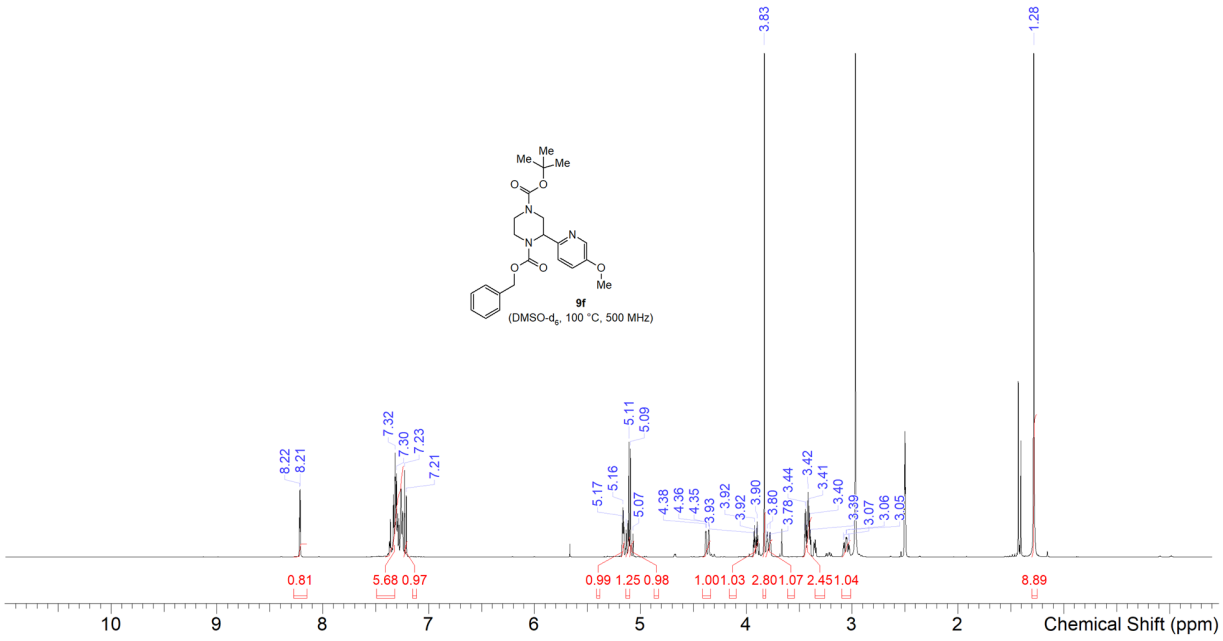

9e
(CD3OD, 500 MHz)
7.19
7.17
6.88
6.86
5.26
5.20
5.18
5.15
5.12
4.42
4.01
3.98
3.78
3.40
3.38
3.18
3.12
3.01
3.00
1.39
4.77 2.08 2.00
0.84 0.80 0.58
0.62 1.01 0.98 3.03 1.17 2.09
9.29
Chemical Shift (ppm)

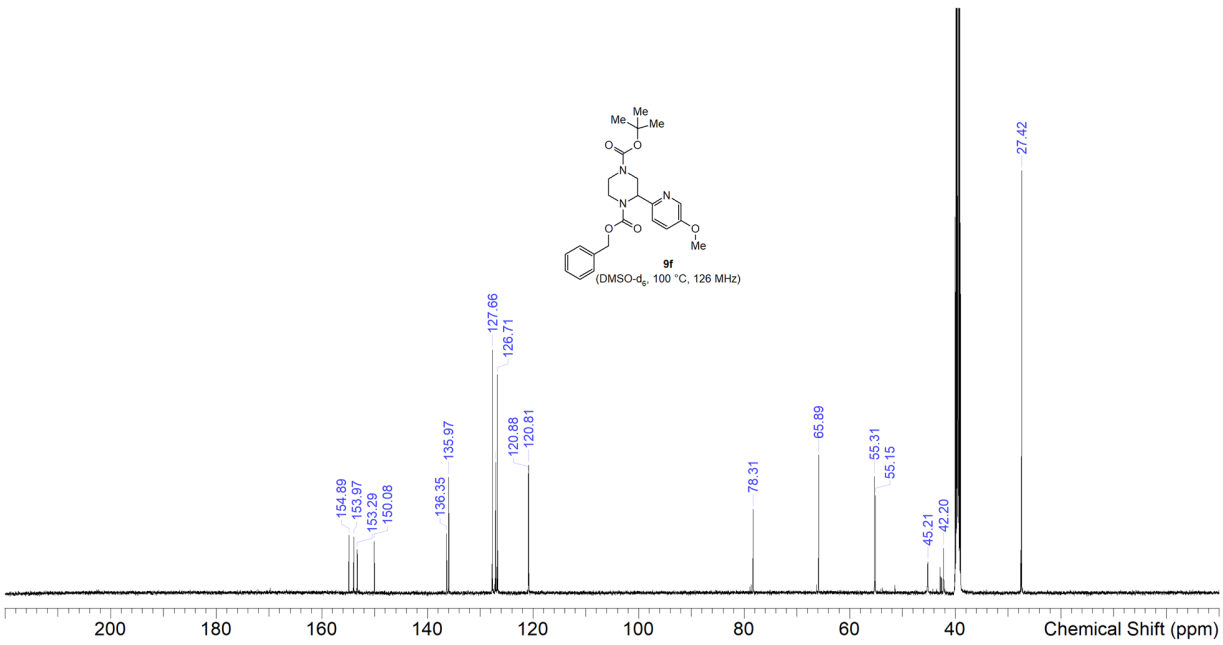

9e
(DMSO-d6, 100 °C, 500 MHz)
1.36
3.75
7.34
7.33
7.30
7.29
7.19
7.17
6.89
6.87
5.19
5.18
5.14
5.13
5.11
4.26
4.24
3.94
3.92
3.91
3.88
3.39
3.39
3.37
3.36
3.13
3.12
3.10
3.09
4.00 2.33 2.00
3.07
1.01 1.22 3.62 1.00 0.97 1.09
8.62
Chemical Shift (ppm)

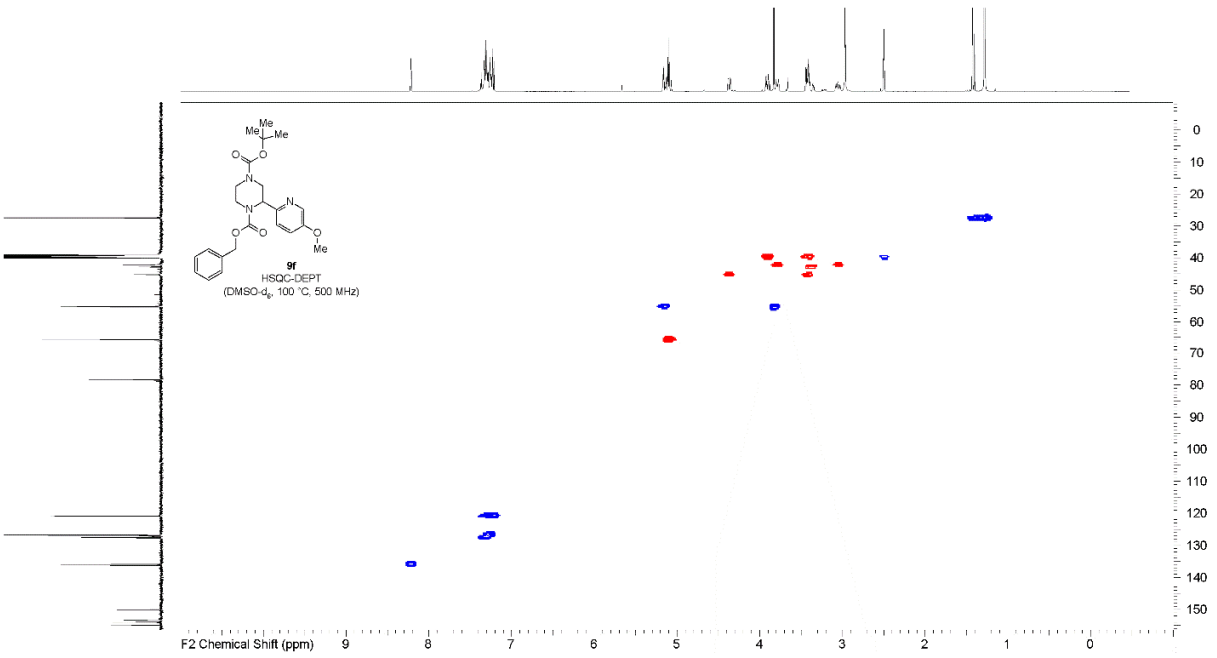

9e
(DMSO-d6, 100 °C, 126 MHz)
158.07
154.53
153.41
136.33
130.73
127.77
127.11
126.88
113.54
78.71
66.11
54.78
53.44
45.06
42.39
39.93
27.53
Chemical Shift (ppm)

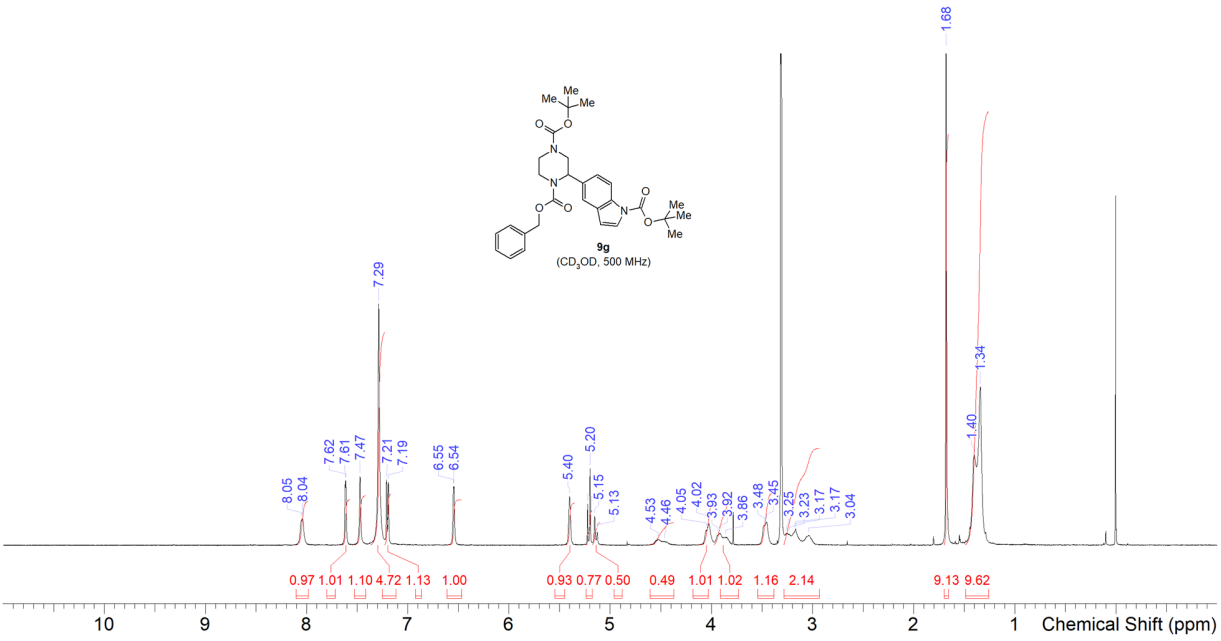

9e
HSQC-DEPT
(DMSO-d6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)

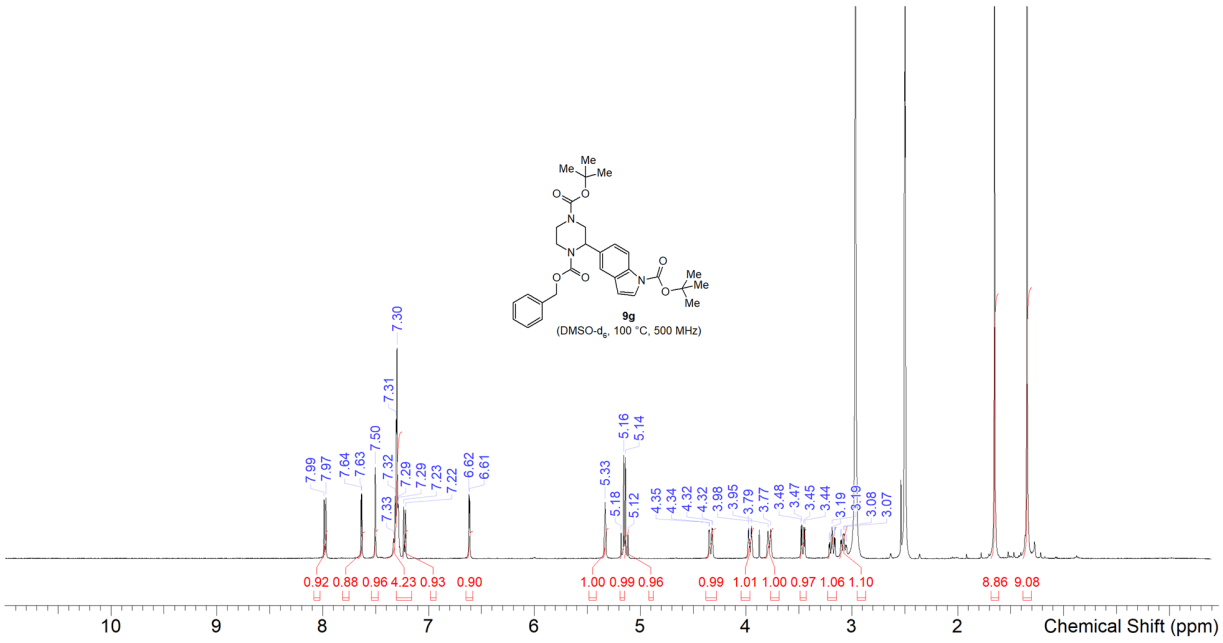

9f
(DMSO-d6, 500 MHz)
8.21
7.36
7.25
7.24
5.15
5.09
5.08
4.42
3.89
3.86
3.80
3.39
2.92
1.26
1.19
1.00
7.91
3.41
1.17
4.94
0.53
0.90
9.41
Chemical Shift (ppm)

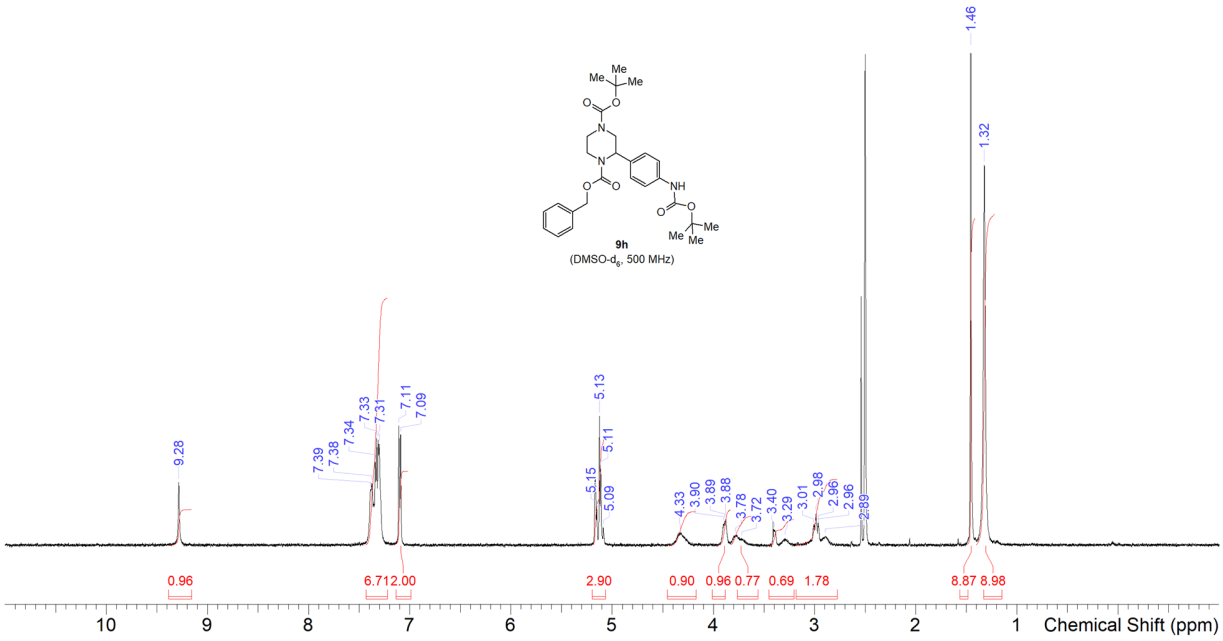

9f
(DMSO-d6, 100 °C, 500 MHz)
3.83
1.28
8.22
8.21
7.32
7.30
7.23
7.21
5.11
5.09
5.17
5.16
5.07
4.38
4.36
4.35
3.93
3.92
3.92
3.90
3.80
3.78
3.44
3.42
3.41
3.40
3.39
3.07
3.06
3.05
0.81
5.68
0.97
0.99
1.25
0.98
1.00
1.03
2.80
1.07
2.45
1.04
8.89
10
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

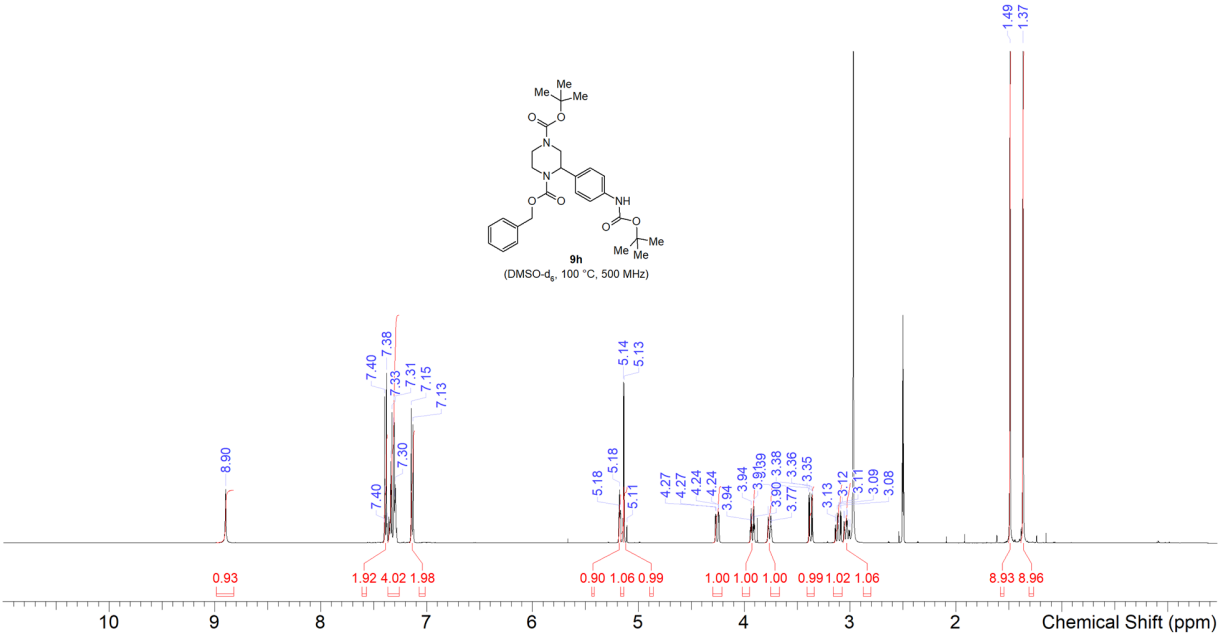

9f
(DMSO-d6, 100 °C, 126 MHz)
27.42
127.66
126.71
120.88
120.81
135.97
154.89
153.97
153.29
150.08
136.35
78.31
65.89
55.31
55.15
45.21
42.20
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

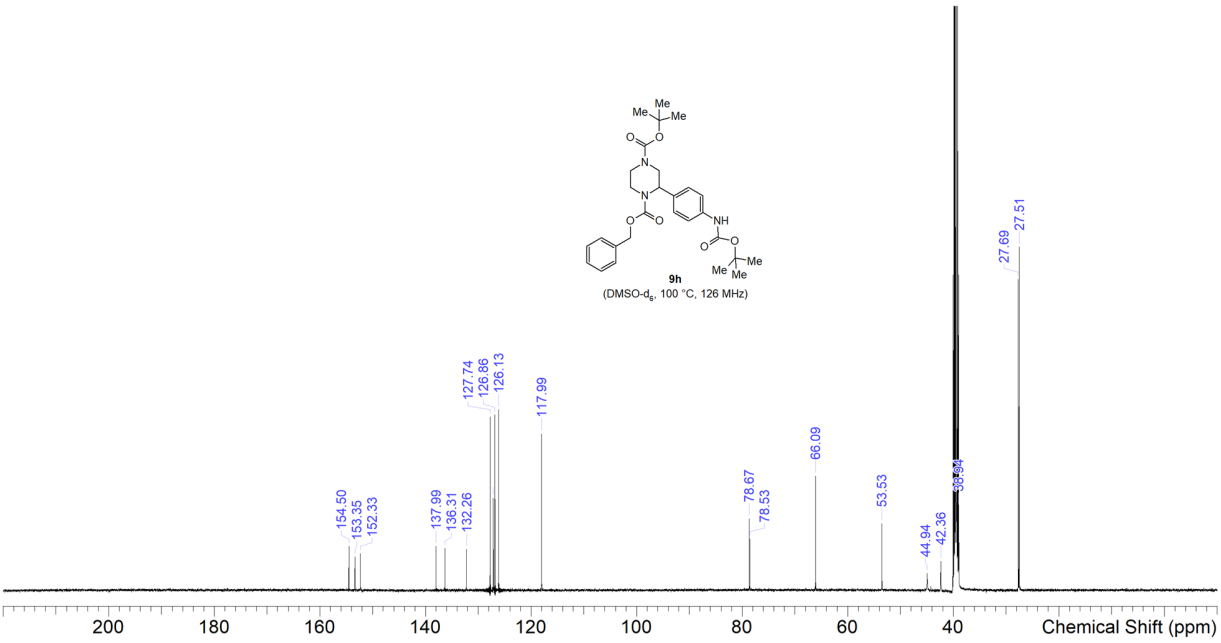

9f
HSQC-DEPT
(DMSO-d_6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)

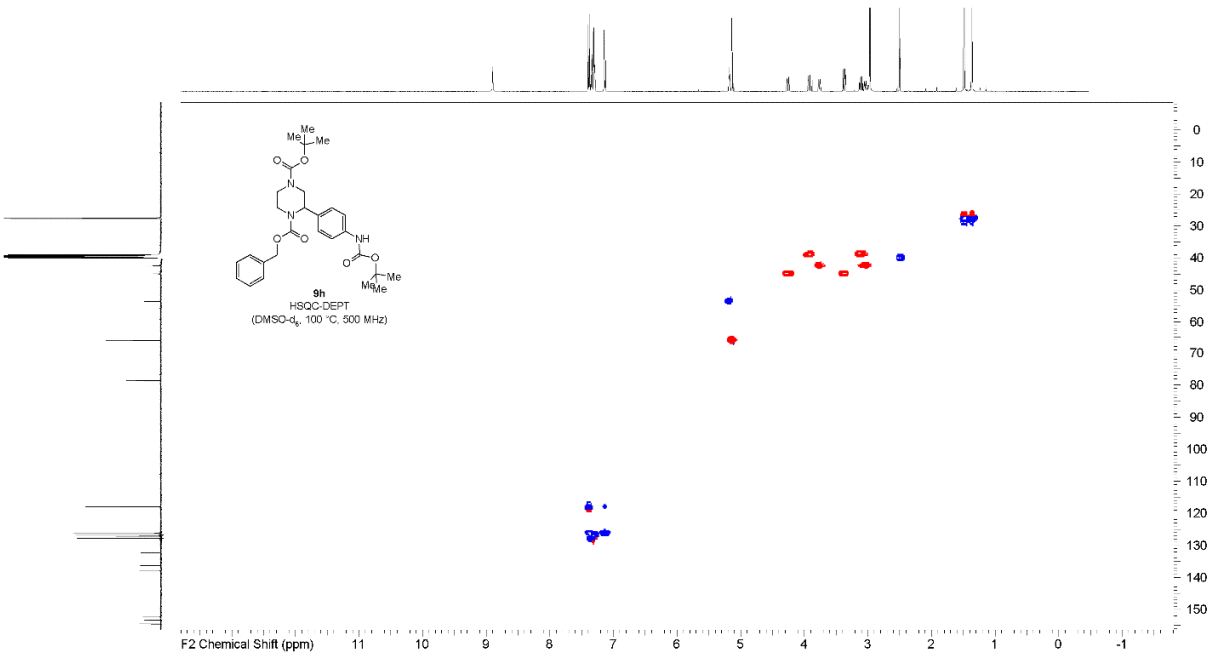

9g
(CD_3OD, 500 MHz)
Chemical Shift (ppm)

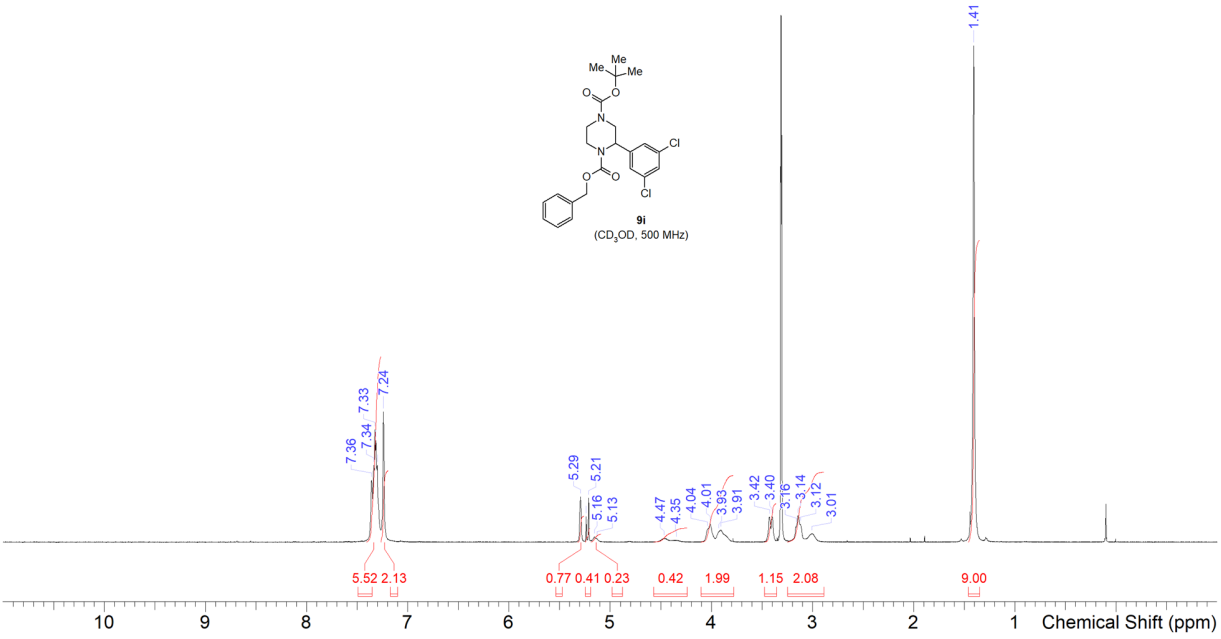

9g
(DMSO-d6, 100 °C, 500 MHz)
Chemical Shift (ppm)

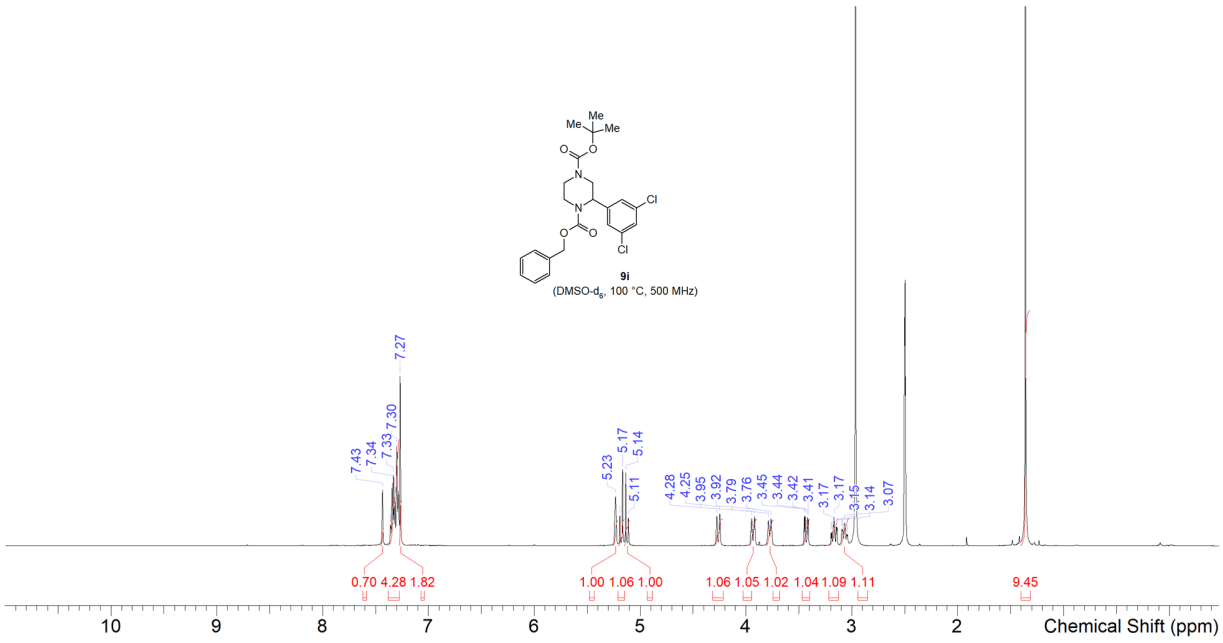

9h
(DMSO-d6, 500 MHz)
Chemical Shift (ppm)

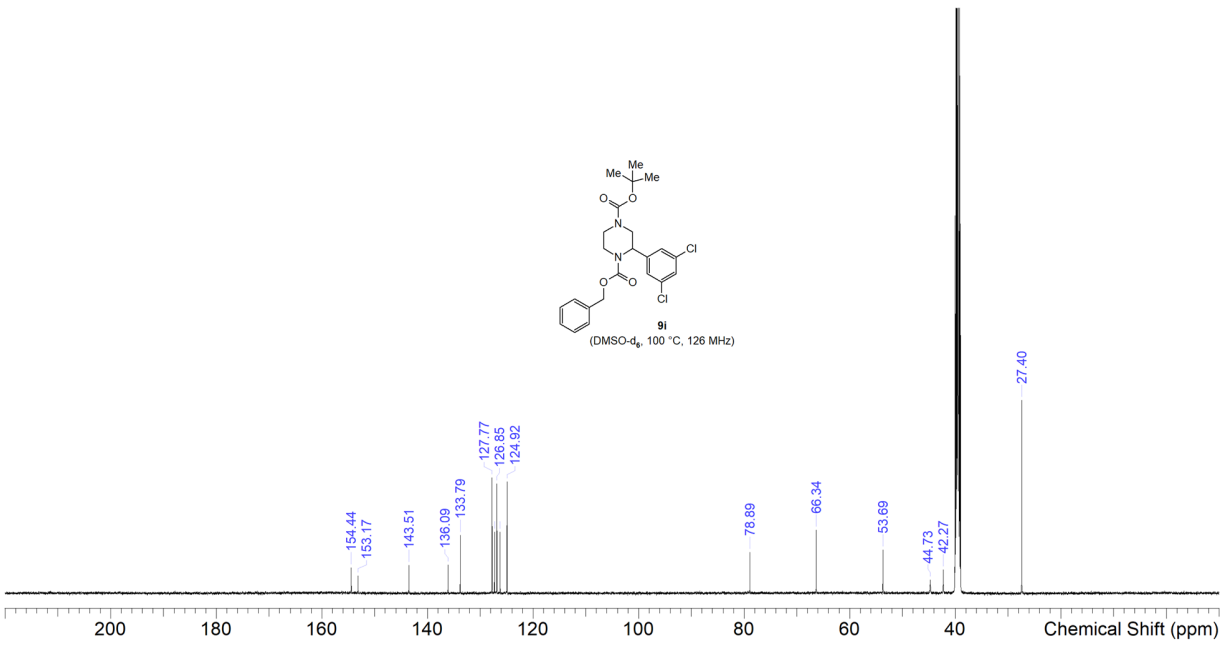

9h
(DMSO-d6, 100 °C, 500 MHz)
Chemical Shift (ppm)

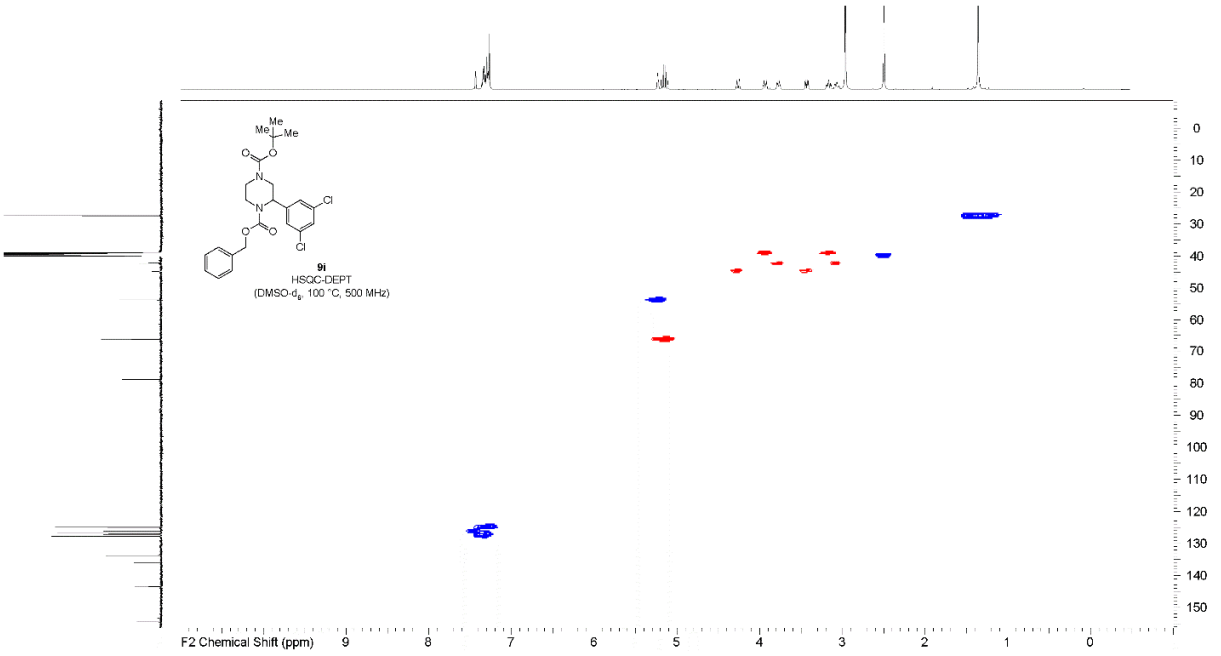

9h
(DMSO-d6, 100 °C, 126 MHz)
Chemical Shift (ppm)

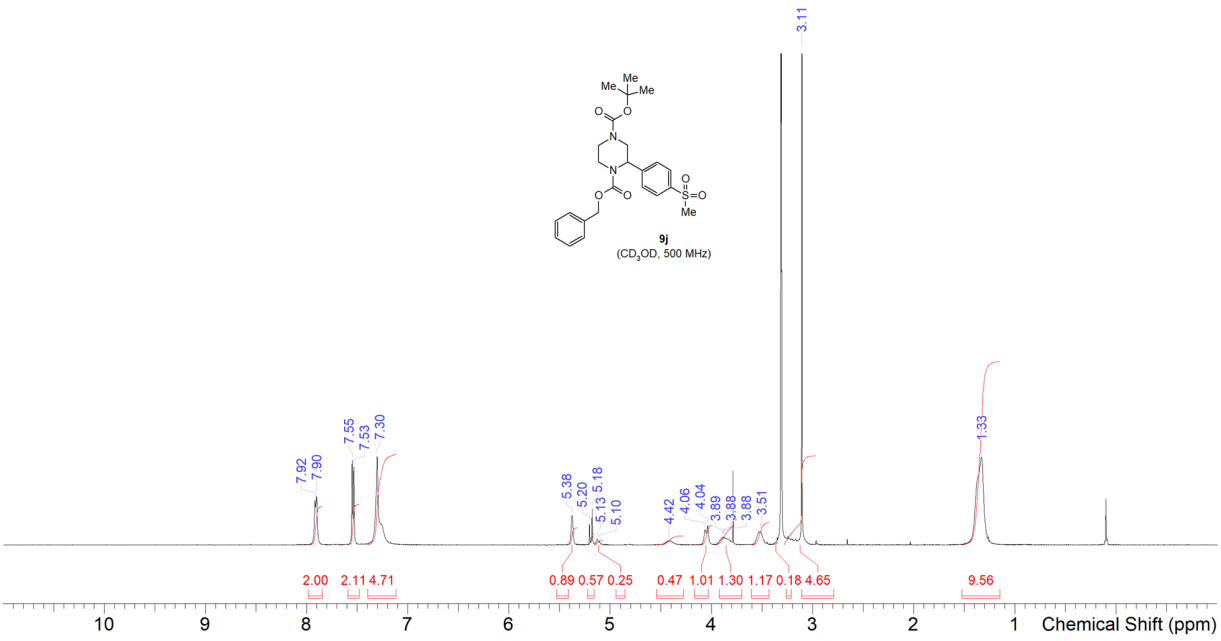

9h
HSQC-DEPT
(DMSO-d6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)

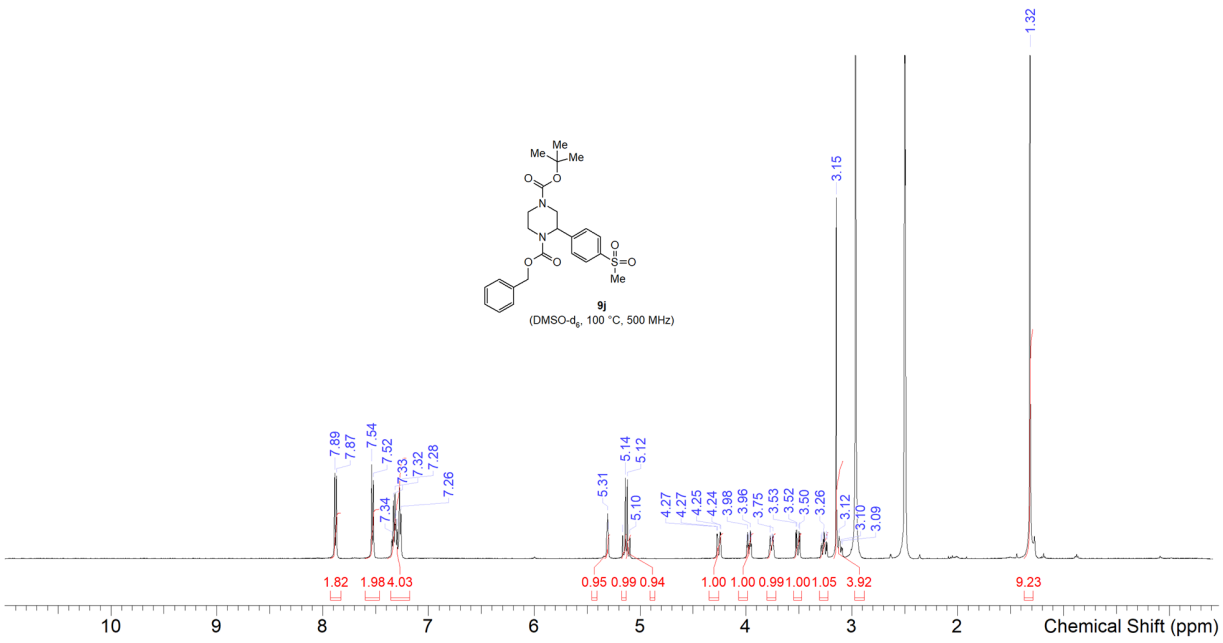

9i
(CD3OD, 500 MHz)
Chemical Shift (ppm)

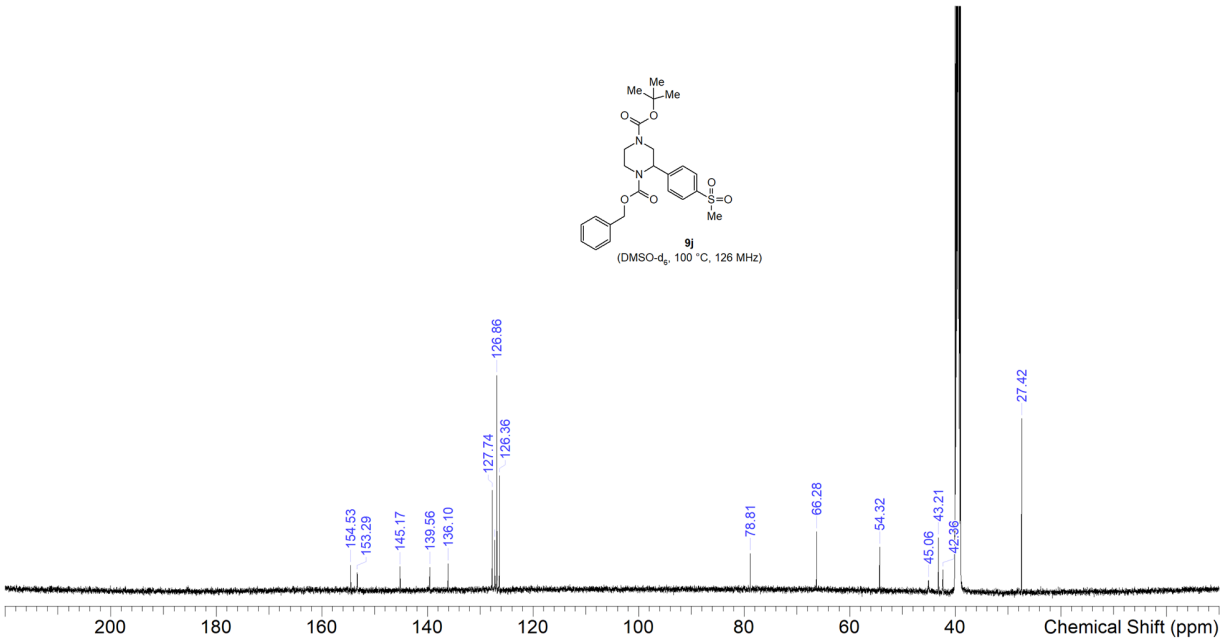

9i
(DMSO-d6, 100 °C, 500 MHz)
7.43
7.34
7.33
7.30
7.27
5.23
5.17
5.14
5.11
4.28
4.25
3.95
3.92
3.79
3.76
3.45
3.44
3.42
3.41
3.17
3.17
3.15
3.14
3.07
0.70 4.28 1.82
1.00 1.06 1.00
1.06 1.05 1.02 1.04 1.09 1.11
9.45
10
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

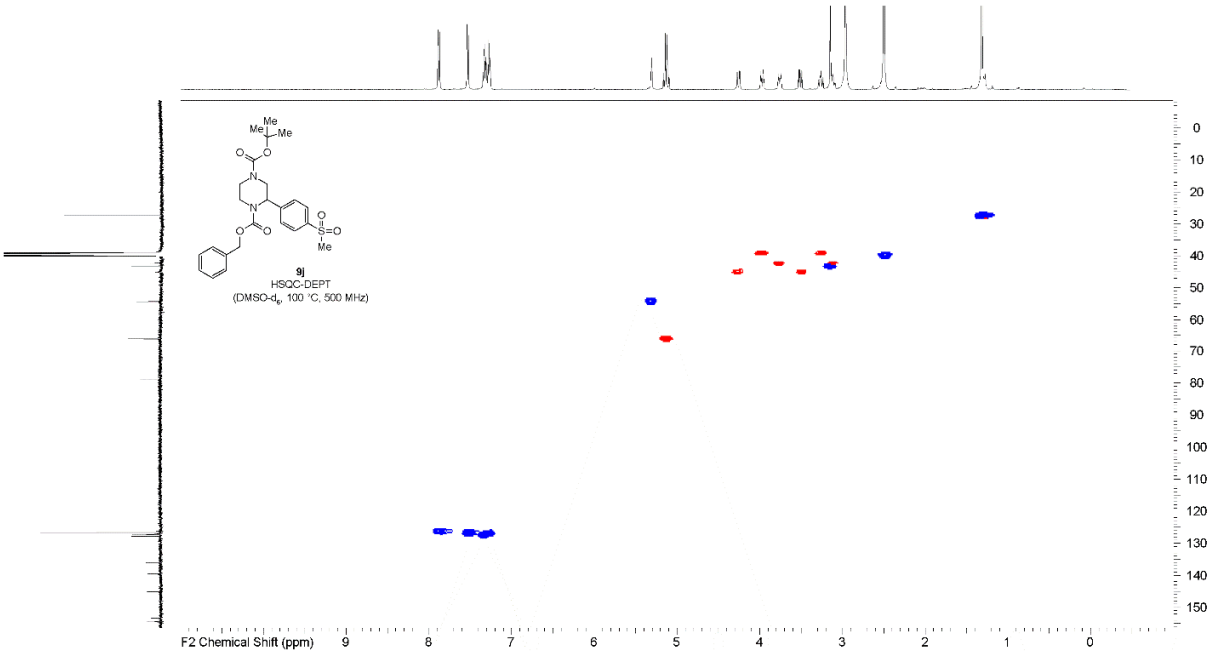

9i
(DMSO-d6, 100 °C, 126 MHz)
154.44
153.17
143.51
136.09
133.79
127.77
126.85
124.92
78.89
66.34
53.69
44.73
42.27
27.40
200
180
160
140
120
100
80
60
40
Chemical Shift (ppm)


9i
HSQC-DEPT
(DMSO-d6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)


9j
(CD3OD, 500 MHz)
7.92
7.90
7.55
7.53
7.30
5.38
5.20
5.18
5.13
5.10
4.42
4.06
4.04
3.89
3.88
3.88
3.51
3.11
1.33
2.00
2.11
4.71
0.89
0.57
0.25
0.47
1.01
1.30
1.17
0.18
4.65
9.56
Chemical Shift (ppm)


9j
(DMSO-d6, 100 °C, 500 MHz)
7.89
7.87
7.54
7.52
7.34
7.33
7.32
7.28
7.26
5.31
5.14
5.12
5.10
4.27
4.27
4.25
4.24
3.98
3.96
3.75
3.53
3.52
3.50
3.26
3.15
3.12
3.10
3.09
1.32
1.82
1.98
4.03
0.95
0.99
0.94
1.00
1.00
0.99
1.00
1.05
3.92
9.23
Chemical Shift (ppm)


9j
(DMSO-d6, 100 °C, 126 MHz)
154.53
153.29
145.17
139.56
136.10
128.86
127.74
126.36
78.81
66.28
54.32
45.06
43.21
42.36
27.42
Chemical Shift (ppm)


9j
HSQC-DEPT
(DMSO-d6, 100 °C, 500 MHz)
F2 Chemical Shift (ppm)
9
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150