

Supporting Information

Benzylic C–H Isocyanation/Amine Coupling Sequence Enabling High-Throughput Access to Pharmaceutically Relevant Ureas

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1. General Information

Materials and spectroscopic methods. Cu salts were purchased from Sigma Aldrich. Benzylic C–H substrates and the reagents for the syntheses were purchased from Oakwood Chemicals, Combi-Blocks, Chem-Impex, Alfa Aesar, TCI America, Ark Pharm, Enamine, AstaTech or Sigma Aldrich, and were used without further purification. TMSNCO was purchased from TCI America. Ligands were purchased from Aldrich or TCI America. *N*-fluorobenzenesulfonimide (NFSI) was purchased from Ark Pharm. The solvents were purchased from Fisher Scientific or Sigma Aldrich. The silica gel (particle size 40-63 μm , 230-400 mesh) that was used for flash column chromatography and thin layer chromatography plates (250 μm thickness) were purchased from SiliCycle. Chromatography was conducted using Biotage Isolera One® with reusable 60 or 120 g SNAP Ultra® C18 cartridges. The ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker 400, 500, or 600 MHz spectrometer. High-resolution mass spectra were obtained using a Thermo Q Exactive™ Plus by the mass spectrometry facility at the University of Wisconsin–Madison. IR spectra were recorded on a Bruker Platinum-ATR ALPHA spectrometer. Melting points were determined using a DigiMelt MPA160 SRS melting point apparatus. Enantioselectivities were determined by SFC/MS analyses on a Waters TharInvestigator equipped with a Daicel CHIRALCEL® OD-H HPLC analytical column (particle size 5 μm , ID 4.6 mm x L 250 mm).

2. General Procedure for Cu-Catalyzed Benzylic C–H Isocyanation

Procedure A: A 4 mL borosilicate glass vial was charged with benzylic substrate (0.4 mmol), 2.0 mol% of copper(I) acetate (1.0 mg, 8.0 μmol), 2.0 mol% of 2,2'-bis(2-oxazoline) (1.1 mg, 8.0 μmol), 2.5 equivalents of *N*-fluorobenzenesulfonimide (315 mg, 1.00 mmol), and a magnetic stir bar outside a glovebox. The vial was capped with an open-top cap installed with a PTFE lined silicone septum. The septum cap was pierced by a needle and the vial was moved into the glovebox and underwent four cycles of vacuum-nitrogen-backfill over 40 minutes. After removal of the needle, the vial was removed from the glovebox. The vial was charged with acetonitrile (3.3 mL, 0.12 M), 3.0 equivalents of (trimethylsilyl)isocyanate (160 μL , 1.2 mmol), 0.5 equivalents of diisopropyl phosphite (33 μL , 0.2 mmol) sequentially, stirred, and heated to 30 $^\circ\text{C}$ (inner temperature) in a heating block on a hot plate. After 20 hours, the vial was cooled to room temperature (25 $^\circ\text{C}$) for urea formation reaction without any workup.

Procedure B: Adopting Procedure A, the reaction was performed for 2 hours.

Procedure C: Adopting Procedure A, the reaction was performed at 25 $^\circ\text{C}$ for 2 hours.

Procedure D: Adopting Procedure A, the reaction was performed at 40 $^\circ\text{C}$ for 20 hours. Deviation from Procedure A was 6.0 mol% of copper(I) acetate (2.9 mg, 24 μmol), 6.0 mol% of 2,2'-bis(2-oxazoline) (3.4 mg, 24 μmol).

Procedure E: Adopting Procedure D, the reaction was performed at 30 $^\circ\text{C}$ for 20 hours.

Procedure F: Adopting Procedure A, the reaction was performed at 30 $^\circ\text{C}$ for 20 hours. Deviation from Procedure A was 10 mol% of copper(I) acetate (4.9 mg, 40 μmol), 10 mol% of 2,2'-bis(2-oxazoline) (5.6 mg, 40 μmol).

Notes:

- (1) Calibration of hot plate is highly recommended to maintain inner reaction temperature because performance of this reaction is sensitive to temperature.
- (2) Liquid benzylic C–H substrates were added between addition of acetonitrile and (trimethylsilyl)isocyanate.
- (3) Hamilton glass syringe was used for the addition of (trimethylsilyl)isocyanate which is sensitive to plastics.
- (4) Diisopropyl phosphite was stored in glovebox.

3. General Procedure for Urea Formation

Following isocyanation, an 8 mL borosilicate glass vial was equipped with a magnetic stir bar and capped with an open-top cap containing a PTFE-lined silicone septum. The septum was then pierced with a needle before moving the vial into the small antechamber of the glovebox. Three cycles of vacuum-nitrogen backfill were performed and the vial was placed inside the glovebox. The needle was then detached from the cap and the sealed vial was subsequently removed from the glovebox. Afterwards, the vial was charged with 5 equivalents of *m*-anisidine (225 μ L, 2 mmol) and placed on a heating block set at 50°C and stirring. The 4 mL vial containing the isocyanate crude mixture was pierced with a needle attached to a nitrogen-filled balloon. Then, a syringe was used to draw the isocyanate crude mixture. Following this, a needle connected to a nitrogen-filled balloon was used to puncture the 8 mL reaction vial charged with *m*-anisidine before the slow addition of the isocyanate crude mixture. The 4 mL vial containing the isocyanate crude mixture was rinsed three times with 300 μ L of acetonitrile, and each rinse was added to the 8mL vial. After 20 hours of urea formation, the reaction mixture was cooled to room temperature and the purification procedure involved direct subjection to a reverse-phase column on Biotage, which used a gradient deionized H₂O:CH₃CN (2:3) elution.

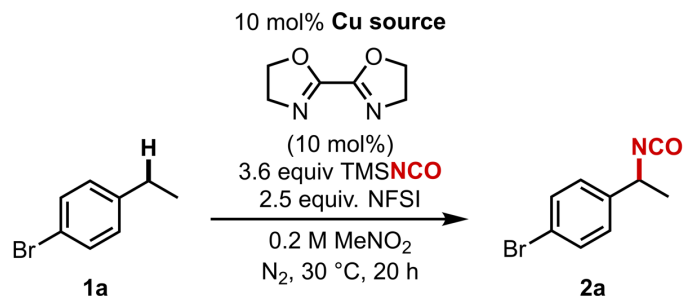
4. Computational Methods for Calculation of Molecular Properties

The calculations of the physicochemical properties were performed using the method described by Tan *et al.*¹ The SMILES code of all coupling amines and corresponding ureas were generated from the structures drawn in ChemDraw. The SMILES codes were copied into an MS Excel document before saving the file as a tab delimited .txt file. The text file containing the codes was imported into Instant JChem and the physicochemical properties (clogP, hydrogen bond donors, hydrogen bond acceptors, number of rotatable bonds, molecular weight, and topological polar surface area) were calculated using the New Chemical Term Field function. Following the calculations, the structures and physicochemical properties were exported from Instant JChem as the Excel spreadsheet (.XLSX).

5. Screening Tables for Reaction Optimization

Note: Reaction protocol for screening was adopted from General Procedure A.

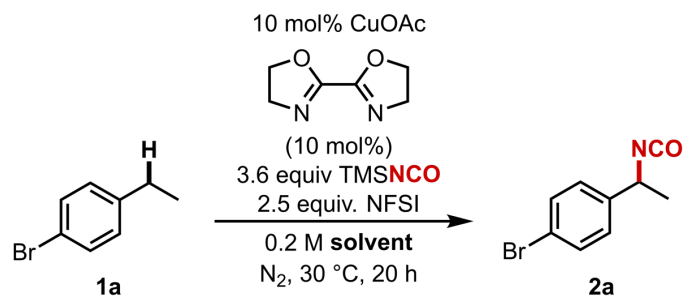
Table S1. Optimization of the Reaction Conditions with Various Copper Salts^a



entry	Cu source	conv. of 1a (%)	yield of 2a (%)
1	CuCl	32	12
2	CuBr	0	0
3	CuBr SMe ₂	36	12
4	CuBr ₂	7	0
5	CuI	0	0
6	CuOAc	22	15
7	Cu(OAc) ₂	20	11
8	Cu(CH ₃ CN) ₄ BF ₄	15	9
9	Cu(IMes) ₂ BF ₄	13	13
10	Cu(acac) ₂	19	8
11	CuSO ₄	4	4
12	Cu(OTf) ₂	0	0
13	CuO	0	0
14	Cu ₂ O	0	0

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. IMes, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; acac, acetylacetonate.

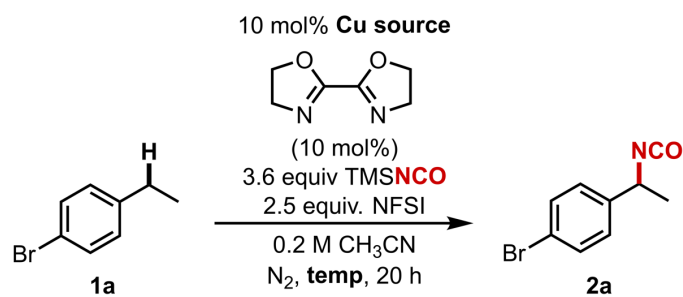
Table S2. Optimization of Reaction Conditions with Various Solvents^a



entry	solvent	conv. of 1a (%)	yield of 2a (%)
1	MeNO ₂	22	15
2	CHCl ₃	32	6.9
3	CH ₂ Cl ₂	13	7.2
4	DCE	0	0
5	benzene	0	0
6	PhCF ₃	0	0
7	PhNO ₂	0	0
8	PhCl	0	0
9	Et ₂ O	0	0
10	Ph ₂ O	0	0
11	THF	0	0
12	1,4-dioxane	0	0
13	DME	0	0
14	Acetone	23	14
15	EtOAc	5.7	3.3
16	DMF	0	0
17	DMA	0	0
18	HFIP	17	0
19	CH₃CN	78	36

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. DCE, 1,2-dichloroethane; THF, tetrahydrofuran; DME, 1,2-dimethoxyethane; EtOAc, ethyl acetate; DMF, *N,N*-dimethylformamide; DMA, *N,N*-dimethylacetamide; HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol.

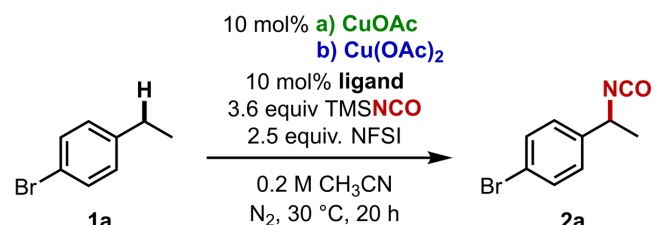
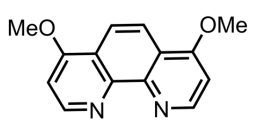
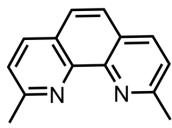
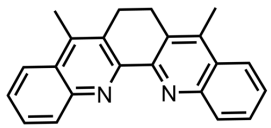
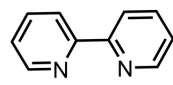
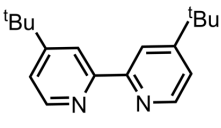
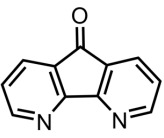
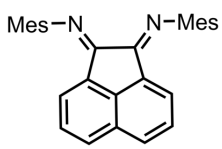
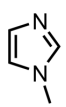
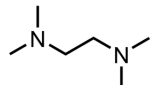
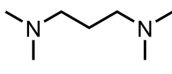
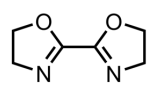
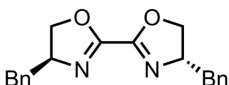
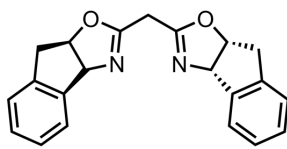
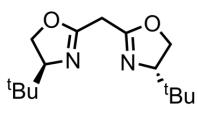
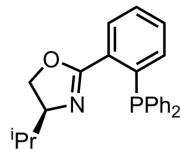
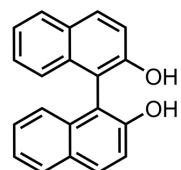
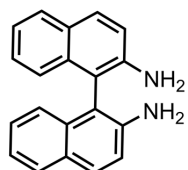
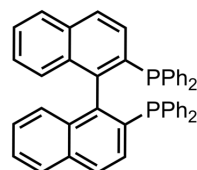
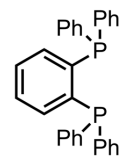
Table S3. Optimization of Reaction Conditions with Selected Copper Salts at 30 and 40 °C^a



entry	[Cu]	temp (°C)	conv. of 1a (%)	yield of 2a (%)
1	None	30	0	0
2	Cu(OAc) ₂	30	74	34
3	CuOAc	30	78	36
4	CuCl	30	79	30
5	CuCN	30	83	33
6	Cu(OAc)₂	40	88	36
7	CuOAc	40	85	36
8	CuCl	40	83	32
9	CuCN	40	86	36

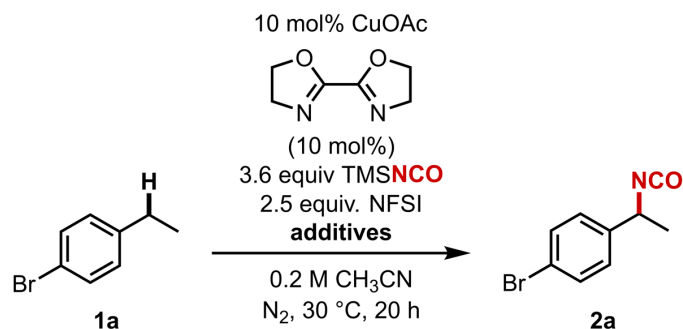
^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard.

Table S4. Optimization of Reaction Conditions with Various Ligands and Copper Salts^a

			
			
73% conv, 25% yield 0% conv, 0% yield	73% conv, 27% yield 66% conv, 20% yield	67% conv, 25% yield 8% conv, 0% yield	78% conv, 20% yield 9% conv, 0% yield
			
65% conv, 20% yield 12% conv, 4% yield	70% conv, 33% yield 71% conv, 31% yield	0% conv, 0% yield 9% conv, 0% yield	85% conv, 25% yield 89% conv, 16% yield
			
91% conv, 28% yield 86% conv, 27% yield	80% conv, 23% yield 83% conv, 19% yield	78% conv, 36% yield 12% conv, 0% yield	59% conv, 30% yield 14% conv, 0% yield
			
68% conv, 26% yield 36% conv, 14% yield	91% conv, 29% yield 94% conv, 8% yield	84% conv, 35% yield 83% conv, 30% yield	
			
0% conv, 0% yield 10% conv, 0% yield	0% conv, 0% yield 0% conv, 0% yield	62% conv, 26% yield 1% conv, 0% yield	88% conv, 30% yield 91% conv, 24% yield

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard.

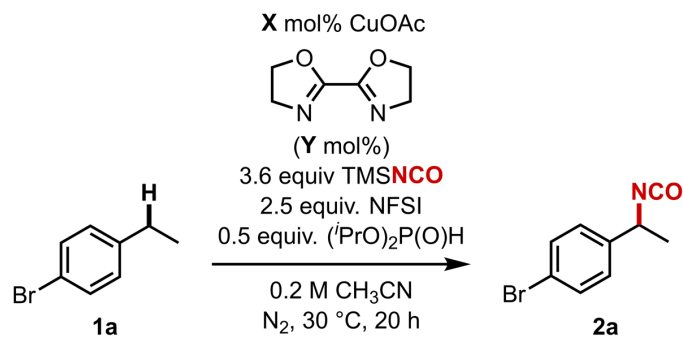
Table S5. Optimization of Reaction Conditions with Various Additives^a



entry	solvent	additives	conv. of 1a (%)	yield of 2a (%)
1	CH ₃ CN	none	78	36
2	CH₃CN	(^tPrO)₂P(O)H (0.5 equiv.)	90	42
3	PhCN	None	4	4
4	PhCN	(^t PrO) ₂ P(O)H (0.5 equiv.)	87	41
5	HFIP:CH ₃ CN (1:4)	None	70	0
6	HFIP:CH ₃ CN (1:4)	(^t PrO) ₂ P(O)H (0.5 equiv.)	100	0
7	CH ₃ CN	Li ₂ CO ₃ (2.0 equiv.)	70	32
8	CH ₃ CN	Li ₂ CO ₃ (2.0 equiv.) (^t PrO) ₂ P(O)H (0.5 equiv.)	94	30
9	PhCN	Li ₂ CO ₃ (2.0 equiv.)	2.4	2.4
10	PhCN	Li ₂ CO ₃ (2.0 equiv.) (^t PrO) ₂ P(O)H (0.5 equiv.)	88	28
11	HFIP:CH ₃ CN (1:4)	Li ₂ CO ₃ (2.0 equiv.)	85	0
12	HFIP:CH ₃ CN (1:4)	Li ₂ CO ₃ (2.0 equiv.) (^t PrO) ₂ P(O)H (0.5 equiv.)	100	0

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard.

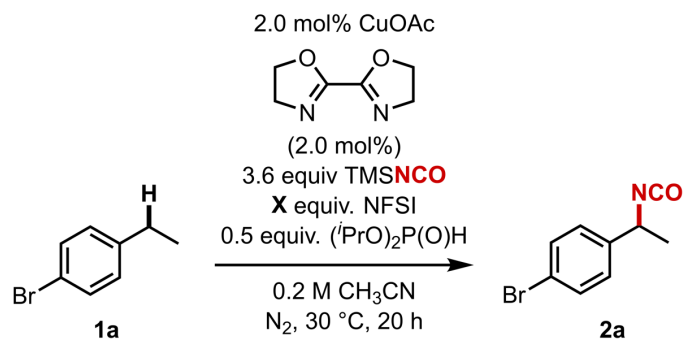
Table S6. Optimization of Reaction Conditions with Various Equivalents of Catalyst and Ligand^a



entry	X (mol%)	Y (mol%)	conv. of 1a (%)	yield of 2a (%)
1	1.0	1.0	73	44
2	2.0	2.0	81	43
3	5.0	5.0	79	44
4	10	10	90	42
5	15	15	89	37
6	20	20	91	33

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard.

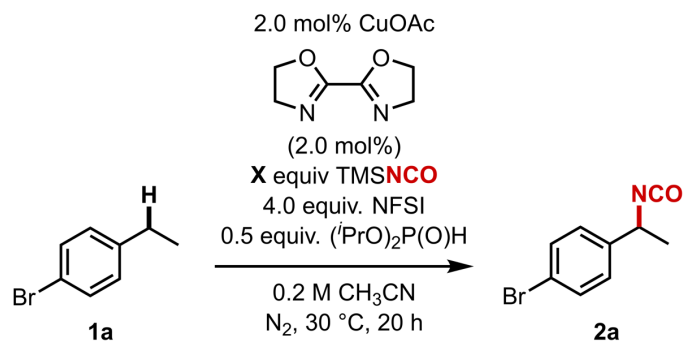
Table S7. Optimization of Reaction Conditions with Various Equivalents of NFSI^a



entry	X (equiv.)	conv. of 1a (%)	yield of 2a (%)
1	0	0	0
2	0.5	22	17
3	1	52	34
4	1.5	66	40
5	2	74	42
6	2.5	76	45
7	3	80	45
8	3.5	82	45
9	4	82	47
10	5	86	47

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard.

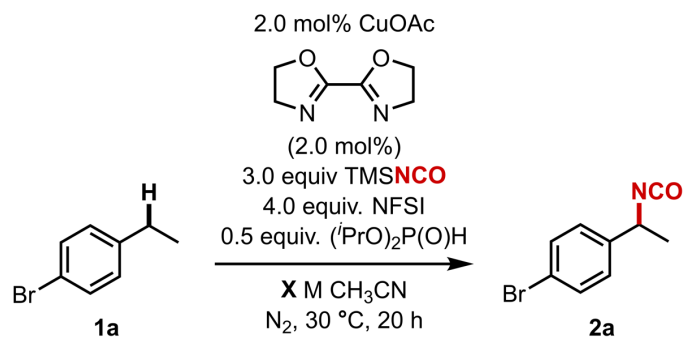
Table S8. Optimization of Reaction Conditions with Various Equivalents of TMSNCO^a



entry	X (equiv.)	conv. of 1a (%)	yield of 2a (%)
1	1	86	41
2	1.5	83	43
3	2	82	46
4	2.5	86	45
5	3	80	47
6	3.5	78	45
7	4	80	46
8	5	82	46
9	6	78	45
10	10	76	41

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard.

Table S9. Optimization of Reaction Conditions with Various Concentrations^a

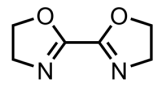


entry	X (M)	conv. of 1a (%)	yield of 2a (%)
1	1.00	83	36
2	0.80	84	40
3	0.50	84	44
4	0.40	90	46
5	0.30	89	46
6	0.25	90	48
7	0.20	90	48
8	0.16	90	48
9	0.12	90	52
10	0.10	88	51

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard

Table S10. Optimization of Reaction Conditions with Various Reaction Times^a

2.0 mol% CuOAc



(2.0 mol%)

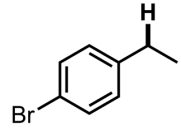
3.0 equiv TMSNCO

4.0 equiv. NFSI

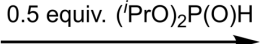
0.5 equiv. (iPrO)₂P(O)H

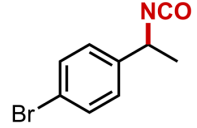
0.12 M CH₃CN

N₂, 30 °C, **time**



1a





2a

entry	Time (h)	conv. of 1a (%)	yield of 2a (%)
1	0.5	6.6	4
2	1	45	39
3	2	75	52
4	4	76	52
5	6	81	52
6	16	87	52
7	20	90	52 (56^b)
8	22	91	50
9	28	93	50
10	48	93	48

^aReaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. ^b2.5 equiv. of NFSI was used.

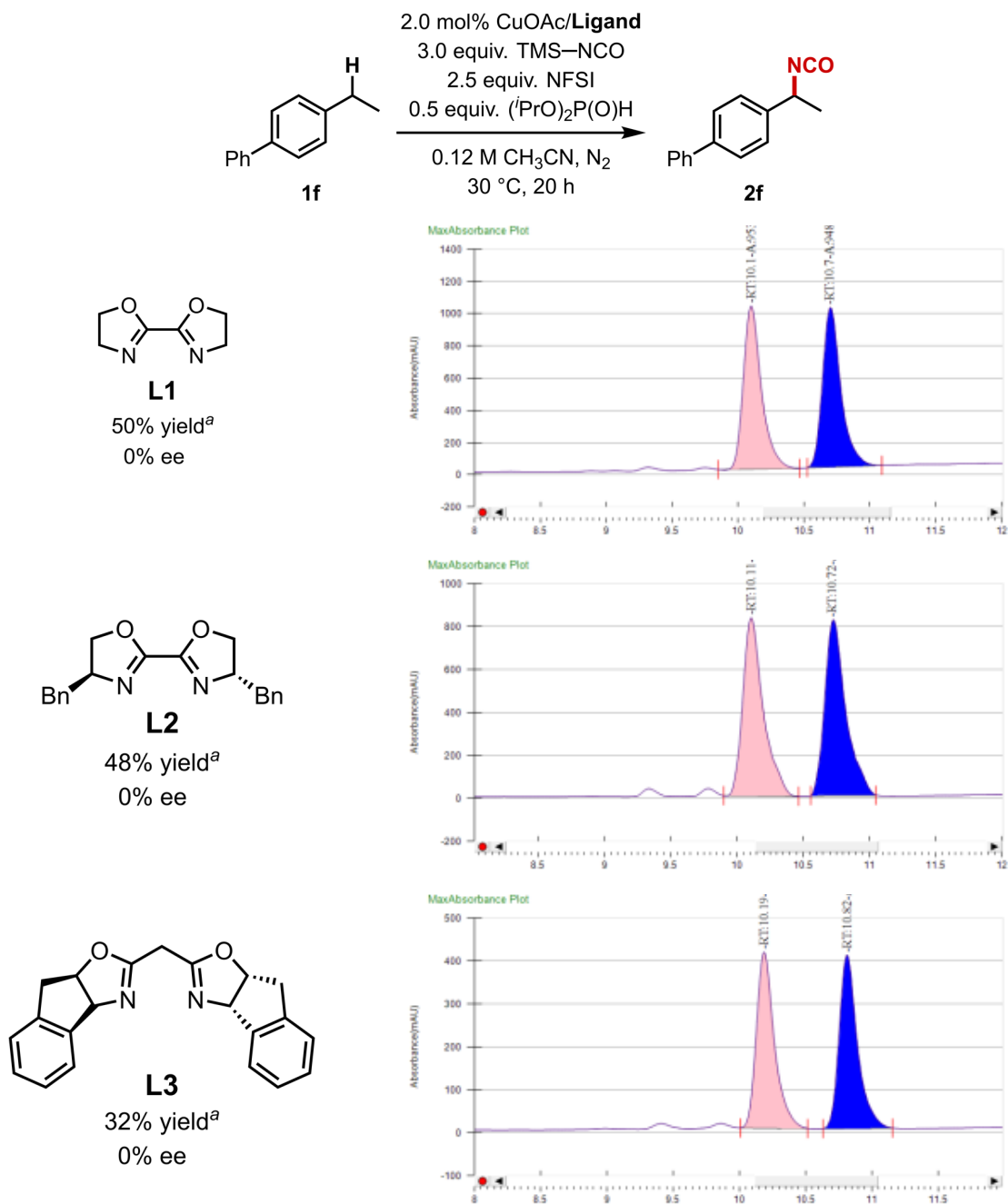
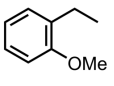
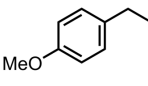
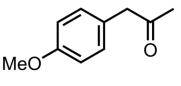
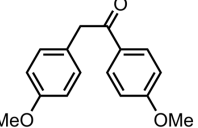
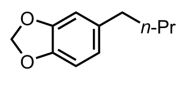
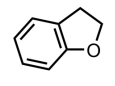
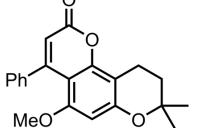
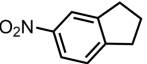
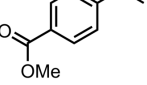
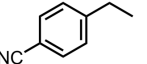
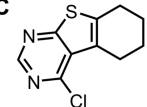
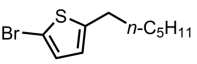
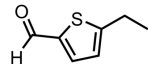
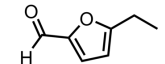
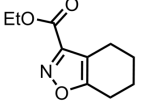
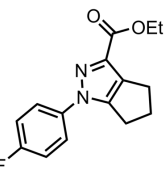
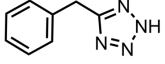
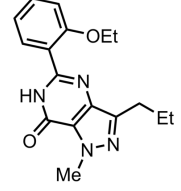
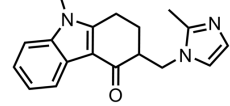


Fig. S1 Enantioselectivity survey. Reaction yields were monitored by ¹H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. Enantioselectivities for isolated analytes (**2f**) were determined by supercritical fluid chromatography (SFC) analysis. SFC/MS analyses were conducted on a Waters TharInvestigator equipped with a Daicel CHIRALCEL[®] OD-H HPLC analytical column (particle size 5 μm, ID 4.6 mm x L 250 mm) was used for separations of enantiomers. The samples were eluted with MeOH 20% with CO₂ at a flow rate of 3 mL/min at 35 °C with an automated backpressure regulator at 100 bar. Injection volume for each sample was 5.0 μL of a 10-30 μM solution in acetonitrile and the detection wavelength was 273 nm.

6. Limitation of C–H Isocyanation

Table S11. Unsuccessful C–H Substrates

A						
						
34% yield 89% conv.	32% yield 96% conv.	4% yield 32% conv.	12% yield 36% conv.	7% yield 100% conv.	NDP 100% conv.	NDP 34% conv.
B			C			
						
trace yield 23% conv.	29% yield 49% conv.	24% yield 30% conv.	NDP 100% conv.	trace yield 98% conv.	21% yield 97% conv.	14% yield 100% conv.
D						
						
25% yield 51% conv.	NDP 100% conv.	trace yield 53% conv.	NDP 0% conv.	NDP 100% conv.		

Isocyanation of some substrates were not successful. Electron-rich (Table S11A) and electron-deficient (Table S11B) gave low yields. Even though the reactions with both thiophene and furan substrates showed excellent conversion, but the yields were low-to-no yield (Table S11C). The *N*-heterobenzyl substrates embedding isoxazole, pyrazole, tetrazole, pyrazolopyrimidine, and benzopyrrole rings afforded low-to-no yield (Table S11D).

7. Experimental Details for High Throughput Synthesis of Benzylic Ureas

High-Throughput Experiment Procedure of Isocyanation/Urea Formation

All reagents were used as purchased from commercial suppliers. Solvents were purchased from Sigma-Aldrich, anhydrous, sure-seal quality, and used with no further purification. The reagents and catalysts were purchased from commercial sources and stored in the glovebox. All reactions were performed inside an MBraun glovebox operating with a constant nitrogen purge (oxygen typically < 5 ppm) unless otherwise noted. Liquid handling was done using single and multi-channel Eppendorf pipettors (10, 100, 200, and 1000 μL).

A 24 mL borosilicate glass vial was charged with benzylic substrate (1.3 mmol for **1s** and **1t**), 2.0 mol% of copper(I) acetate (3.2 mg, 26 μmol), 2.0 mol% of 2,2'-bis(2-oxazoline) (3.6 mg, 26 μmol), 2.5 equivalents of *N*-fluorobenzenesulfonimide (0.103 g, 3.25 mmol), and a magnetic stir bar outside a glovebox. [For the substrate **1u**, 10 mol% of copper(I) acetate (15.9 mg, 0.13 mmol), 10 mol% of 4,4',5,5'-tetrahydro-2,2'-bi-1,3-oxazole (18.2 mg, 0.13 mmol) were used.] The vial was capped with an open-top cap installed with a PTFE lined silicone SURE-LINK™ septum. The septum cap was pierced by a needle (22 gauge - 1 1/2", 0.7 mm x 40 mm). The vial (having the needle on top) was moved into the glovebox antechamber and underwent four cycles of vacuum-nitrogen-backfill over 20 minutes, and then the vial is moved into the glovebox. After removal of the needle and cap, the vial was charged with acetonitrile (12.5 mL), diisopropyl phosphite (33 μL , 0.2 mmol), and 3.0 equivalents of (trimethylsilyl)isocyanate (160 μL , 1.2 mmol) sequentially, stirred, and heated to 30 °C (for the substrates **1u**) for 20 hours in a heating block on a hot plate. For the substrates **1s** and **1t**, the reaction was conducted at 25 °C for 2 h. [**Note:** Glass pipette or glass syringe/plunger should be used to transfer (trimethylsilyl)isocyanate. (trimethylsilyl)isocyanate reacts with plastics, forms a white powder (maybe polymer), and drops the reaction yield.]

2.0 mL of acetonitrile was added to each vial having 2.0 mmol of amine. All vials were sonicated vigorously at an acceleration of 10G (G is the acceleration of gravity; 9.81 m/s²) for 2 hours in Resodyn acoustic mixing LabRam (PharmaRAM II Mixer). 0.05 mL of each 1.0 M amine in acetonitrile was dispensed to 250 μL microvials (Analytical Sales, Cat. No. 10421) containing a stir bar in 96-well reaction microplates (Analytical-Sales, Cat. No. 24250). Using a multichannel pipette, 0.1 mL of the crude isocyanate solution (0.01 mmol) was added to each vial containing amine outside the glove box (**Note:** The exposure of the crude isocyanate solution to moisture should be minimized). On completion of solution dosing, the plates were covered by a perfluoroalkoxy alkane (PFA) mat (Analytical-Sales, Cat. No. 96967 and 24261), followed by two silicon rubber mats (Analytical-Sales, Cat. No. 96965 and 24262), and an aluminum cover which was tightly and evenly sealed by 9 screws. The sealed plates were put inside the glovebox, opened, purged with N₂ for 30 seconds, covered again, and stirred at 35 °C.

After 20 hours, the plate was removed from the glovebox. 0.2 mL of DMSO was added to each well and mixed on the plate. 0.02 mL of each reaction mixture was taken and filtered through a Millipore multiscreen-solvinert filter plate (0.45 μM low binding hydrophilic PTFE MSRLN0450) to a shallow 96-well storage plate (Corning) and rinsed the filter twice with 0.09 mL of DMSO. The 96-well storage plate having the analytes was sealed and injected to Waters UPLC-MS instrument.

Table S12. 96-Well Plates Display of Selected Amines for High-Throughput Experiments

	1	2	3	4	5	6	7	8	9	10	11	12	
a													
b													
c													
d													
e													
f													
g													
h													

Theoretical molecular properties of amines (**a-1** to **h-12**) can be accessed from the Excel spreadsheet (.XLSX).

UPLC-MS Analysis of HTE Results

Reactions were monitored using a Waters Acquity UPLC I-Class system (Waters Corp., Milford, MA, USA) equipped with a binary pump, a FTN sampler, column manager, a photodiode array detector, SQD detector 2 with electrospray ionization (ESI) source in the positive mode and MassLynx® software. Waters CORTECS UPLC C18+ column (30 × 2.1mm, 1.6µm) was used for peak separation.

Conditions: mobile phase A = 0.1% TFA in H₂O and B = 0.1% TFA in CH₃CN.

Gradient:

Time (min)	Flow (mL/min)	% A	% B
0.00	0.700	95	5
1.70	0.700	0	100
1.95	0.700	0	100
1.96	0.700	95	5
2.00	0.700	95	5

Flow rate 0.7 mL/min; column temperature = 45 °C; injection volume = 1µL; UV scan = 210 – 500 nm. 0.1% TFA in H₂O and 0.1% TFA in CH₃CN (LC/MS grade) were purchased from Fisher Scientific. High throughput data analysis was done with Virscidian Analytical Studio™ software. Conversion to product was analyzed by UPLC-UV. Area percents of product, remaining starting material and side product peaks at 210 nm were calculated. The reactions were analyzed by molecular weights of products, anticipated side products, and reactants. The protocol for this analysis was shown with an example in Figure S2 and S3. The desired products (blue shading) and all known/unknown byproducts (grey and orange shading) except irrelevant compounds to C–H substrates were taken into account for determining total UPLC area percentage of components.

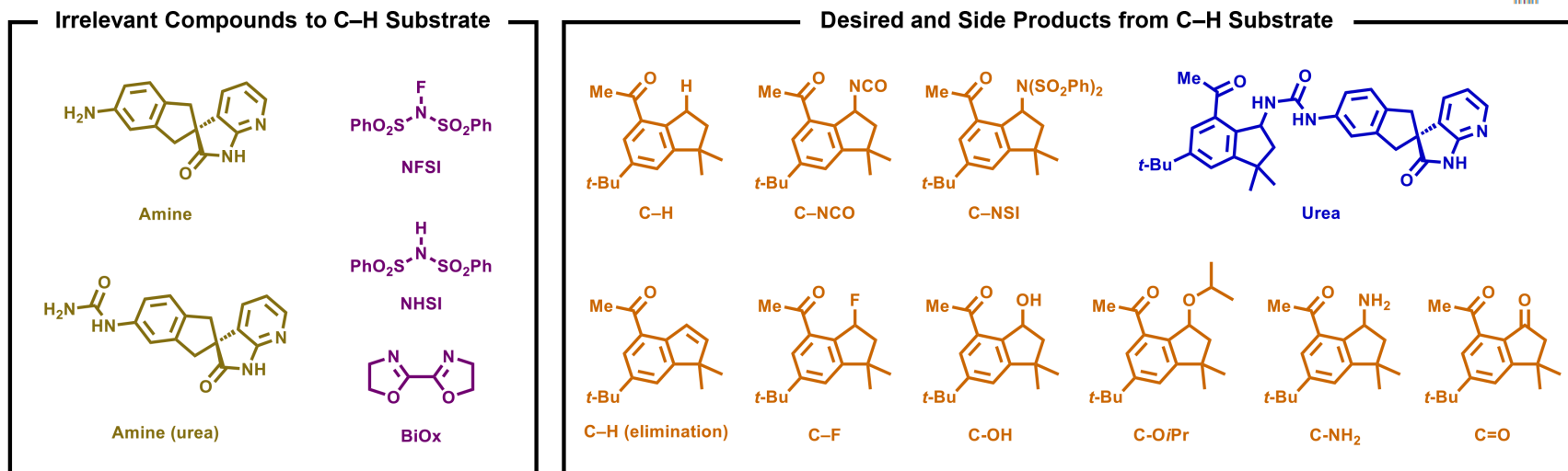
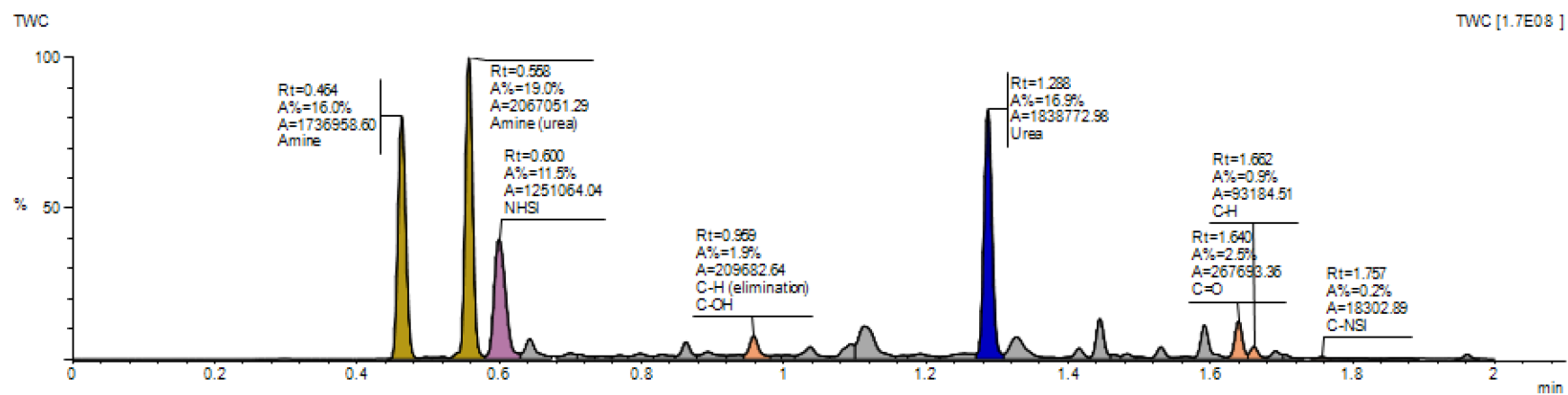


Fig. S2 UPLC chromatogram of crude mixture from the reaction of **1t** and amine (**a-1**) and the list of possible compounds.

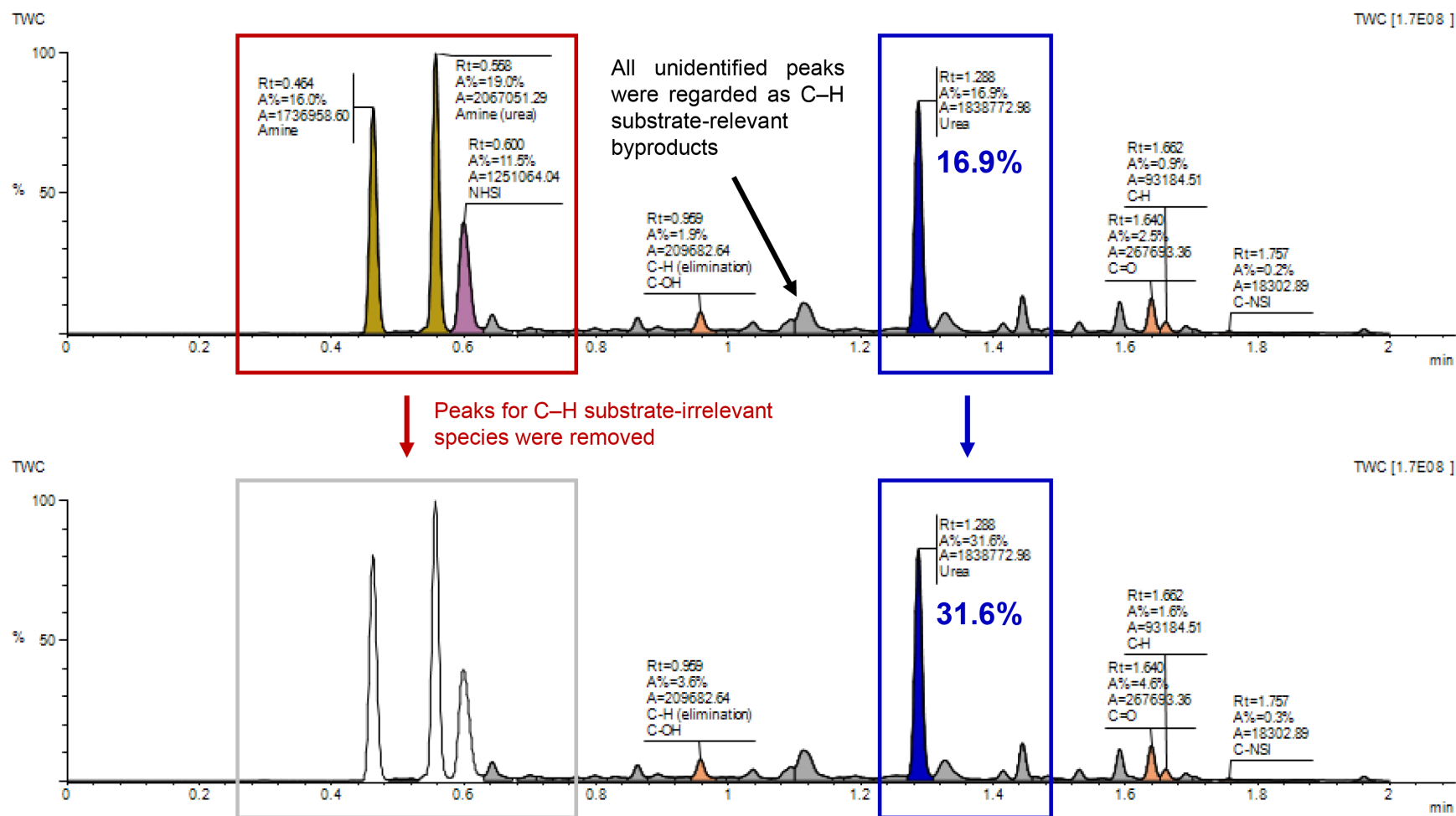


Fig. S3 Determination of UPLC area percentage of urea.

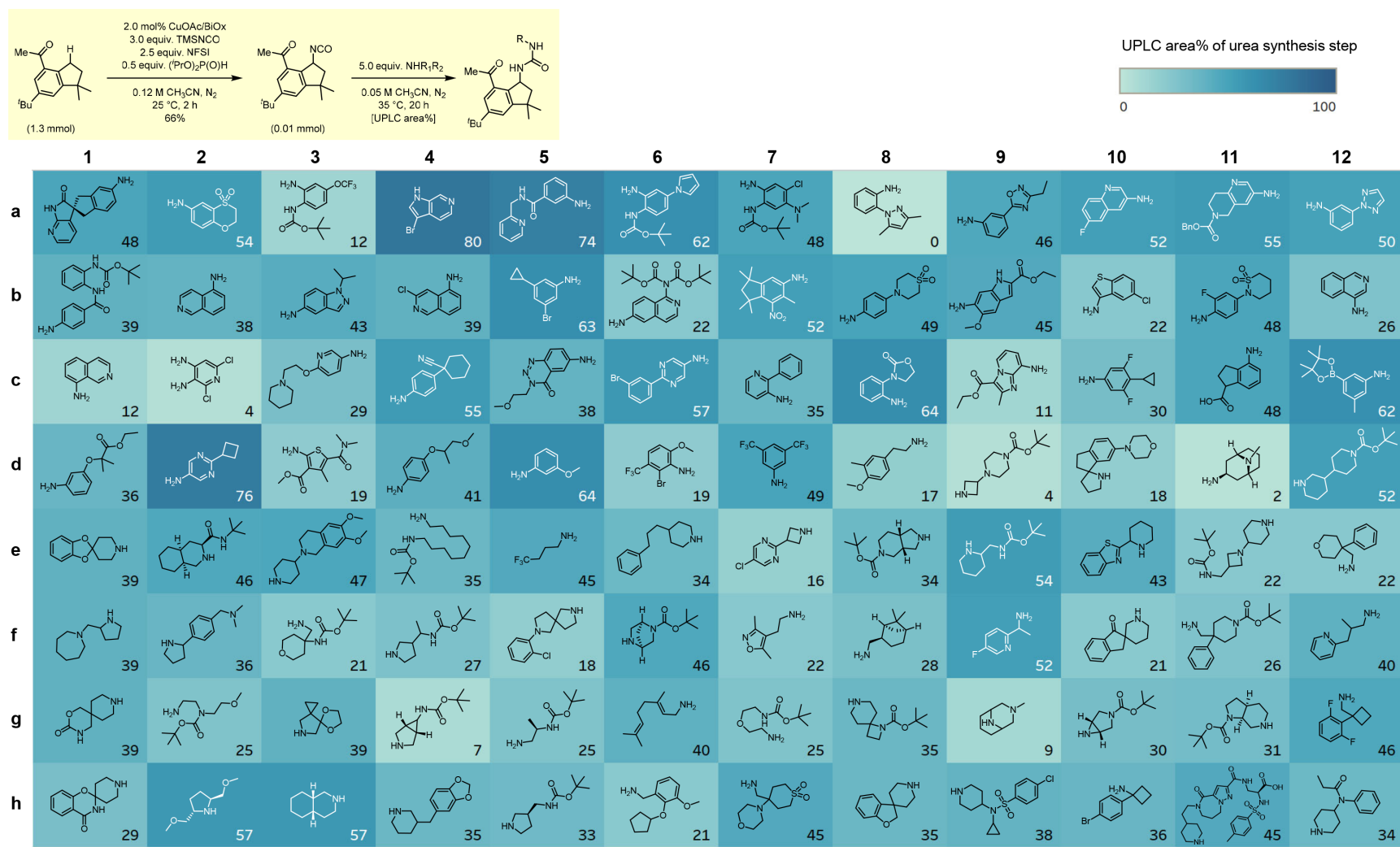


Fig. S4 UPLC analysis results of coupling of **1t** with amines. Actual structures of ureas were not depicted due to the limited space.

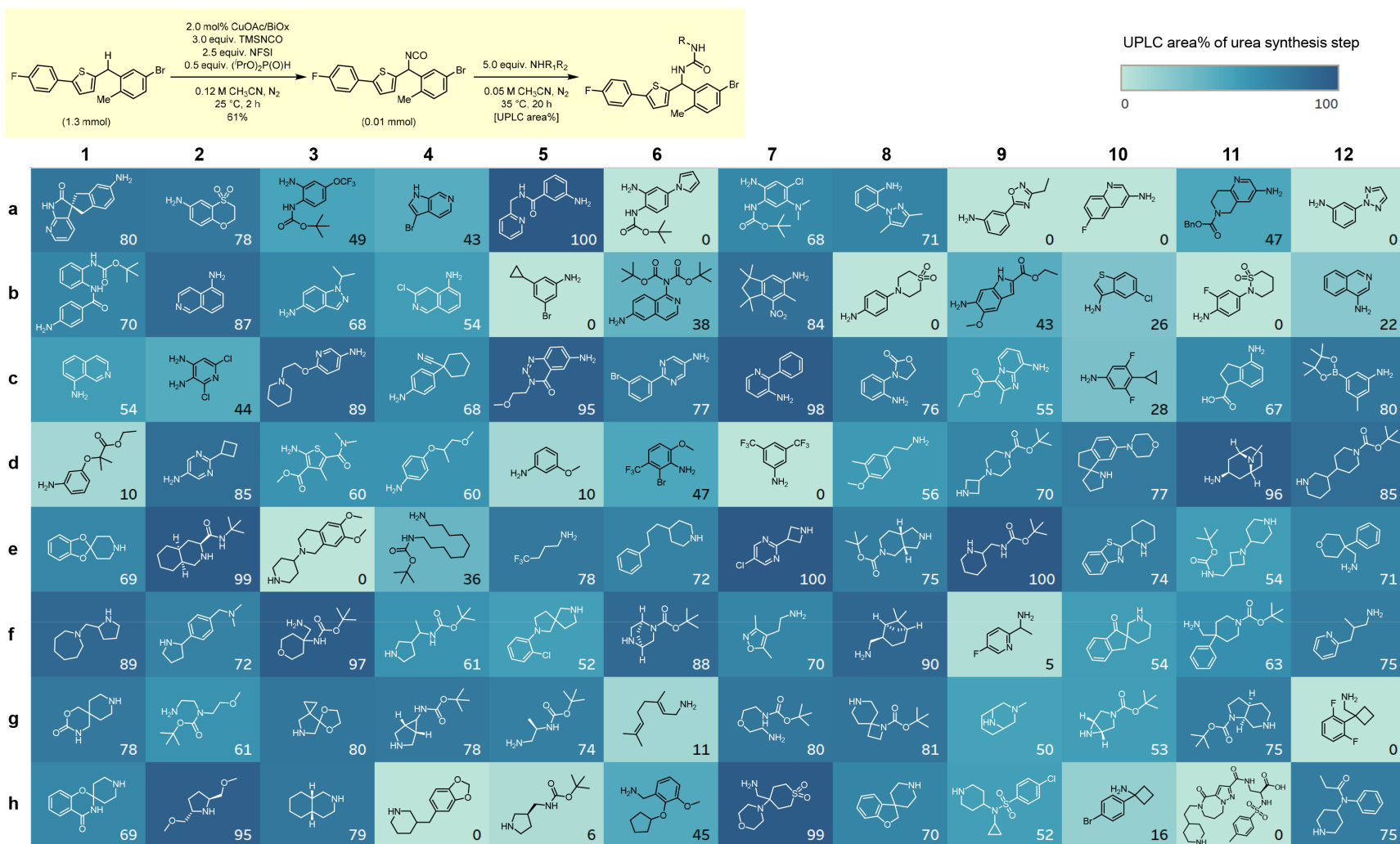


Fig. S5 UPLC analysis results of coupling of **1s** with amines. Actual structures of ureas were not depicted due to the limited space.

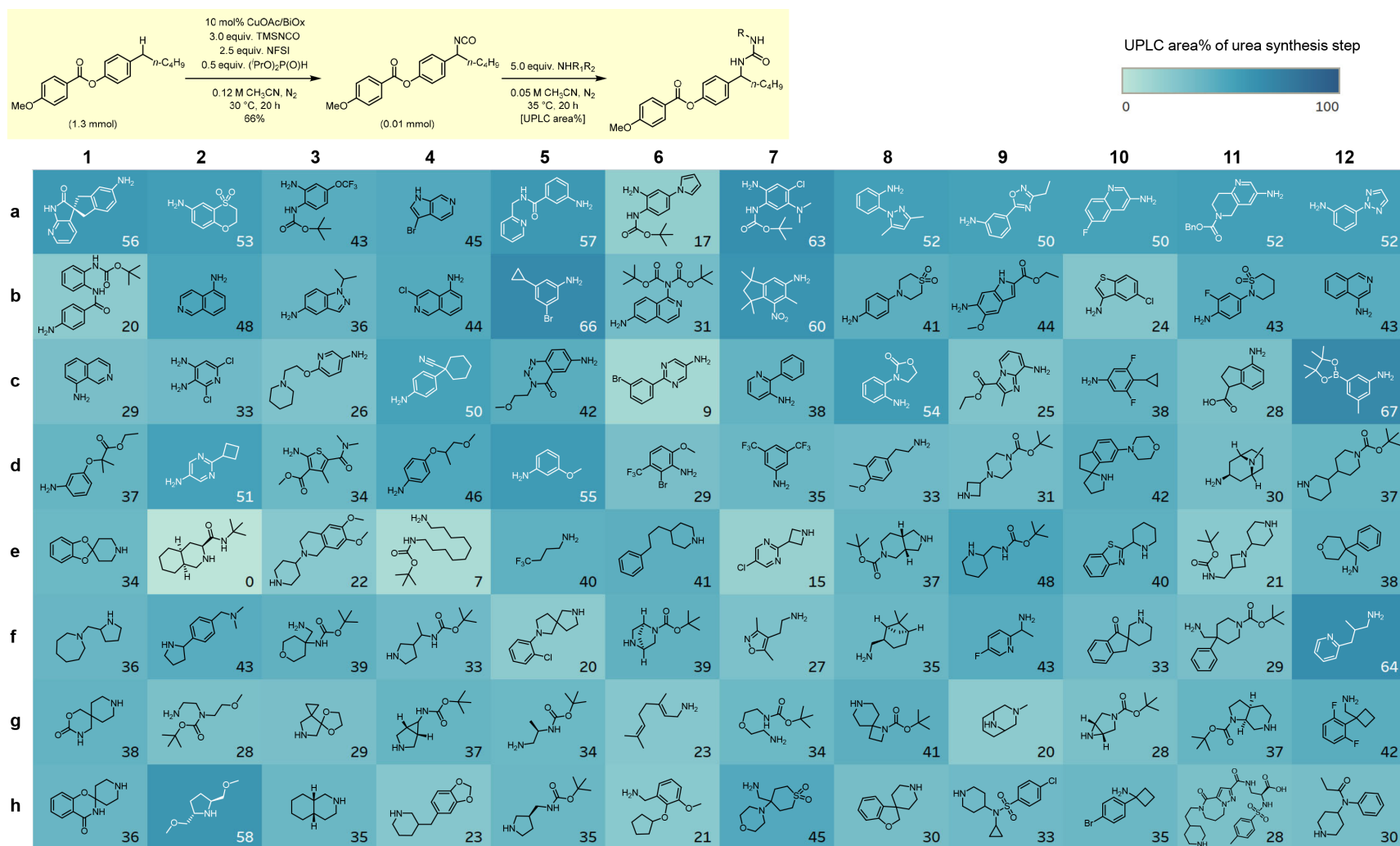


Fig. S6 UPLC analysis results of coupling of 1u with amines. Actual structures of ureas were not depicted due to the limited space.

8. Theoretical Molecular Properties of Amines and Protected/Deprotected Ureas

Table S13. Molecular Information of Amines

Compound ID (Row-Column)	MFCD	cLogP	Number of H-Bond Donors	Number of H-Bond Acceptors	Number of Rotatable Bonds	Molecular Weight (Da)	Topological Polar Surface Area (Å ²)
a-1	MFCD18251611	1.90	2	3	0	251.29	68.01
a-2	MFCD20702077	-0.19	1	4	0	199.22	69.39
a-3	MFCD27992364	3.49	2	4	5	292.26	73.58
a-4	MFCD06738910	1.62	1	1	0	197.04	28.68
a-5	MFCD09734296	0.81	2	3	3	227.27	68.01
a-6	MFCD24469761	3.02	2	3	4	273.34	69.28
a-7	MFCD27992395	2.77	2	4	4	285.77	67.59
a-8	MFCD08696361	1.56	1	2	1	187.25	43.84
a-9	MFCD09971308	2.23	1	3	2	189.22	64.94
a-10	MFCD11917896	1.44	1	2	0	162.17	38.91
a-11	MFCD19689174	1.51	1	3	3	283.33	68.45
a-12	MFCD20921922	0.42	1	3	1	160.18	56.73
b-1	MFCD26392734	3.15	3	4	5	327.38	93.45
b-2	MFCD00006907	0.92	1	2	0	144.18	38.91
b-3	MFCD09026344	1.36	1	2	1	175.24	43.84
b-4	MFCD09999240	1.74	1	2	0	178.62	38.91
b-5	MFCD21099990	2.69	1	1	1	212.09	26.02
b-6	MFCD26401900	3.72	1	5	5	359.43	94.75
b-7	MFCD03783538	3.78	1	3	1	248.33	69.16
b-8	MFCD06797046	-0.09	1	4	1	226.29	63.40
b-9	MFCD10039825	1.37	2	3	4	234.26	77.34

b-10	MFCD12407368	2.62	1	1	0	183.65	26.02
b-11	MFCD20485524	0.44	1	3	1	244.28	63.40
b-12	MFCD00034752	0.92	1	2	0	144.18	38.91
c-1	MFCD00179553	0.92	1	2	0	144.18	38.91
c-2	MFCD10697689	0.75	2	3	0	178.02	64.93
c-3	MFCD12786502	1.23	1	4	4	221.30	51.38
c-4	MFCD20528291	2.81	1	2	1	200.29	49.81
c-5	MFCD26523098	1.14	1	5	3	220.23	80.28
c-6	MFCD11180854	2.39	1	3	1	250.10	51.80
c-7	MFCD04114113	1.96	1	2	1	170.22	38.91
c-8	MFCD09055390	0.69	1	3	1	178.19	55.56
c-9	MFCD10758082	0.34	1	3	3	219.24	69.62
c-10	MFCD14585542	2.21	1	1	1	169.18	26.02
c-11	MFCD20651334	0.97	2	3	1	177.20	63.32
c-12	MFCD22207064	3.58	1	3	1	233.12	44.48
d-1	MFCD26783748	1.97	1	3	5	223.27	61.55
d-2	MFCD16618895	0.91	1	3	1	149.20	51.80
d-3	MFCD01827720	1.69	1	3	3	242.29	72.63
d-4	MFCD08144821	1.36	1	3	4	181.24	44.48
d-5	MFCD00007783	0.99	1	2	1	123.16	35.25
d-6	MFCD28741782	2.63	1	2	2	270.05	35.25
d-7	MFCD00000394	2.90	1	1	2	229.13	26.02
d-8	MFCD06212661	1.74	1	2	3	165.24	35.25
d-9	MFCD09264437	0.46	1	3	3	241.34	44.81
d-10	MFCD11616037	2.29	1	3	1	258.37	24.50
d-11	MFCD12198832	0.37	1	2	0	154.26	29.26
d-12	MFCD10700117	1.90	1	2	3	268.40	41.57
e-1	MFCD01646389	2.05	1	3	0	191.23	30.49

e-2	MFCD01313226	1.90	2	2	2	238.38	41.13
e-3	MFCD05864538	1.28	1	4	3	276.38	33.73
e-4	MFCD02094501	3.31	2	2	12	272.43	64.35
e-5	MFCD06213030	0.89	1	1	3	127.11	26.02
e-6	MFCD00023152	3.41	1	1	4	203.33	12.03
e-7	MFCD20527357	0.59	1	3	1	169.61	37.81
e-8	MFCD22035710	0.68	1	2	2	226.32	41.57
e-9	MFCD02181068	1.41	2	2	4	214.31	50.36
e-10	MFCD05190089	2.81	1	2	1	218.32	24.92
e-11	MFCD08275919	0.41	2	3	5	269.39	53.60
e-12	MFCD02946795	1.31	1	2	2	191.27	35.25
f-1	MFCD06653331	1.59	1	2	2	182.31	15.27
f-2	MFCD09864209	1.94	1	2	3	204.32	15.27
f-3	MFCD12408610	-0.05	2	3	4	230.31	73.58
f-4	MFCD18073167	0.98	2	2	4	214.31	50.36
f-5	MFCD22083491	2.41	1	2	1	236.74	15.27
f-6	MFCD01569250	0.56	1	2	2	198.27	41.57
f-7	MFCD03043478	0.08	1	2	2	140.19	52.05
f-8	MFCD00001349	1.74	1	1	1	153.27	26.02
f-9	MFCD18260255	0.67	1	2	1	140.16	38.91
f-10	MFCD22393927	1.95	1	2	0	201.27	29.10
f-11	MFCD07779083	2.27	1	2	4	290.41	55.56
f-12	MFCD09894554	0.85	1	2	3	150.23	38.91
g-1	MFCD20684482	-0.47	2	2	0	170.21	50.36
g-2	MFCD23144009	0.25	1	3	7	218.30	64.79
g-3	MFCD18375098	0.50	1	3	0	155.20	30.49
g-4	MFCD21099540	0.12	2	2	3	198.27	50.36
g-5	MFCD11112229	0.49	2	2	4	174.24	64.35

g-6	MFCD00192193	2.40	1	1	4	153.27	26.02
g-7	MFCD12031501	0.02	2	3	7	204.27	73.58
g-8	MFCD14581196	0.55	1	2	2	226.32	41.57
g-9	MFCD19221442	0.62	1	2	0	140.23	15.27
g-10	MFCD21332851	0.50	1	2	2	184.24	51.48
g-11	MFCD25509361	1.08	1	2	2	226.32	41.57
g-12	MFCD11100031	2.40	1	1	2	197.23	26.02
h-1	MFCD02182967	1.28	2	3	0	218.26	50.36
h-2	MFCD00210016	0.24	1	3	4	159.23	30.49
h-3	MFCD00137757	1.73	1	1	0	139.24	12.03
h-4	MFCD05863607	2.22	1	3	2	219.28	30.49
h-5	MFCD11101394	0.57	2	2	4	200.28	50.36
h-6	MFCD12177214	2.14	1	3	4	221.30	44.48
h-7	MFCD16045661	-2.06	1	5	2	248.34	72.63
h-8	MFCD20488777	1.46	1	2	0	189.26	21.26
h-9	MFCD01567991	1.74	1	3	3	314.83	49.41
h-10	MFCD09910041	2.70	1	1	1	226.12	26.02
h-11	MFCD00932349	-2.20	4	8	9	546.64	162.73
h-12	MFCD00145005	1.42	1	2	3	232.33	32.34

Table S14. Molecular Information of Protected Ureas

Compound ID (Substrate-Row- Column)	cLogP	Number of H-Bond Donors	Number of H-Bond Acceptors	Number of Rotatable Bonds	Molecular Weight (Da)	Topological Polar Surface Area (Å ²)
A-a-1	5.82	3	4	4	536.68	100.19
A-a-2	3.72	2	5	4	484.61	101.57
A-a-3	7.40	3	5	9	577.65	105.76
A-a-4	4.79	1	3	3	482.42	63.99
A-a-5	4.72	3	4	7	512.65	100.19
A-a-6	6.93	3	4	8	558.72	101.46
A-a-7	6.68	3	5	8	571.16	99.77
A-a-8	5.48	2	3	5	472.63	76.02
A-a-9	6.27	2	4	6	474.61	97.12
A-a-10	5.36	2	3	4	447.55	71.09
A-a-11	5.42	2	4	7	568.72	100.63
A-a-12	4.43	2	4	5	445.57	88.91
A-b-1	7.06	4	5	9	612.77	125.63
A-b-2	4.83	2	3	4	429.56	71.09
A-b-3	5.28	2	3	5	460.62	76.02
A-b-4	5.66	2	3	4	464.01	71.09
A-b-5	6.61	2	2	5	497.48	58.20
A-b-6	7.64	2	6	9	644.81	126.93
A-b-7	7.69	2	4	5	533.71	101.34
A-b-8	3.83	2	5	5	511.68	95.58
A-b-9	5.28	3	4	8	519.64	109.52
A-b-10	6.54	2	2	4	469.04	58.20
A-b-11	4.36	2	4	5	529.67	95.58

A-b-12	4.83	2	3	4	429.56	71.09
A-c-1	4.83	2	3	4	429.56	71.09
A-c-2	4.66	3	4	4	463.40	97.11
A-c-3	5.15	2	5	8	506.69	83.56
A-c-4	6.72	2	3	5	485.67	81.99
A-c-5	5.05	2	6	7	505.62	112.46
A-c-6	6.43	2	4	5	535.49	83.98
A-c-7	5.87	2	3	5	455.60	71.09
A-c-8	4.61	2	4	5	463.58	87.74
A-c-9	4.26	2	4	7	504.63	101.80
A-c-10	6.13	2	2	5	454.56	58.20
A-c-11	5.29	3	4	5	462.59	95.50
A-c-12	7.59	2	4	5	518.51	76.66
A-d-1	5.88	2	4	9	508.66	93.73
A-d-2	4.95	2	4	5	434.58	83.98
A-d-3	5.60	2	4	7	527.68	104.81
A-d-4	5.27	2	4	8	466.62	76.66
A-d-5	4.90	2	3	5	408.54	67.43
A-d-6	6.55	2	3	6	555.44	67.43
A-d-7	6.82	2	2	6	514.51	58.20
A-d-8	5.41	2	3	7	450.62	67.43
A-d-9	3.92	1	4	6	526.72	82.19
A-d-10	5.75	1	4	4	543.75	61.88
A-d-11	4.04	2	3	4	439.64	61.44
A-d-12	5.36	1	3	6	553.79	78.95
A-e-1	5.51	1	4	3	476.62	67.87
A-e-2	5.35	2	3	5	523.76	78.51
A-e-3	4.74	1	5	6	561.77	71.11

A-e-4	6.98	3	3	16	557.82	96.53
A-e-5	4.56	2	2	7	412.50	58.20
A-e-6	6.87	1	2	7	488.72	49.41
A-e-7	4.24	1	4	4	455.00	75.19
A-e-8	4.14	1	3	5	511.71	78.95
A-e-9	4.87	2	3	7	499.70	87.74
A-e-10	6.27	1	3	4	503.71	62.30
A-e-11	3.87	2	4	8	554.78	90.98
A-e-12	4.98	2	3	6	476.66	67.43
A-f-1	5.04	1	3	5	467.70	52.65
A-f-2	5.40	1	3	6	489.70	52.65
A-f-3	3.62	3	4	8	515.70	105.76
A-f-4	4.44	2	3	7	499.70	87.74
A-f-5	5.86	1	3	4	522.13	52.65
A-f-6	4.02	1	3	5	483.65	78.95
A-f-7	3.75	2	3	6	425.57	84.23
A-f-8	5.41	2	2	5	438.66	58.20
A-f-9	4.34	2	3	5	425.55	71.09
A-f-10	5.41	1	3	3	486.66	66.48
A-f-11	5.94	2	3	8	575.79	87.74
A-f-12	4.52	2	3	7	435.61	71.09
A-g-1	2.99	2	3	3	455.60	87.74
A-g-2	3.91	2	4	11	503.68	96.97
A-g-3	3.96	1	4	3	440.58	67.87
A-g-4	3.57	2	3	6	483.65	87.74
A-g-5	4.15	3	3	8	459.63	96.53
A-g-6	6.06	2	2	8	438.66	58.20
A-g-7	3.69	3	4	11	489.66	105.76

A-g-8	4.00	1	3	5	511.71	78.95
A-g-9	4.08	1	3	3	425.62	52.65
A-g-10	3.96	1	3	5	469.63	78.72
A-g-11	4.54	1	3	5	511.71	78.95
A-g-12	6.06	2	2	6	482.62	58.20
A-h-1	4.74	2	4	3	503.64	87.74
A-h-2	3.70	1	4	7	444.62	67.87
A-h-3	5.19	1	2	3	424.63	49.41
A-h-4	5.68	1	4	5	504.67	67.87
A-h-5	4.03	2	3	7	485.67	87.74
A-h-6	5.81	2	4	8	506.69	76.66
A-h-7	1.61	2	6	6	533.73	104.81
A-h-8	4.92	1	3	3	474.65	58.64
A-h-9	5.20	1	4	6	600.22	86.79
A-h-10	6.37	2	2	5	511.50	58.20
A-h-11	3.73	4	9	12	832.03	200.11
A-h-12	4.88	1	3	6	517.71	69.72
B-a-1	8.35	3	3	5	653.57	83.12
B-a-2	6.25	2	4	5	601.51	84.5
B-a-3	9.93	3	4	10	694.54	88.69
B-a-4	7.32	1	2	4	599.32	46.92
B-a-5	7.25	3	3	8	629.55	83.12
B-a-6	9.46	3	3	9	675.62	84.39
B-a-7	9.21	3	4	9	688.05	82.7
B-a-8	8.01	2	2	6	589.53	58.95
B-a-9	8.70	2	3	7	591.50	80.05
B-a-10	7.89	2	2	5	564.45	54.02
B-a-11	7.96	2	3	8	685.61	83.56

B-a-12	6.78	2	3	6	562.46	71.84
B-b-1	9.59	4	4	10	729.67	108.56
B-b-2	7.36	2	2	5	546.46	54.02
B-b-3	7.81	2	2	6	577.52	58.95
B-b-4	8.19	2	2	5	580.90	54.02
B-b-5	9.14	2	1	6	614.37	41.13
B-b-6	10.17	2	5	10	761.71	109.86
B-b-7	10.23	2	3	6	650.61	84.27
B-b-8	6.36	2	4	6	628.58	78.51
B-b-9	7.81	3	3	9	636.54	92.45
B-b-10	9.07	2	1	5	585.93	41.13
B-b-11	6.89	2	3	6	646.57	78.51
B-b-12	7.36	2	2	5	546.46	54.02
B-c-1	7.36	2	2	5	546.46	54.02
B-c-2	7.19	3	3	5	580.30	80.04
B-c-3	7.68	2	4	9	623.59	66.49
B-c-4	9.26	2	2	6	602.57	64.92
B-c-5	7.58	2	5	8	622.51	95.39
B-c-6	8.87	2	3	6	652.38	66.91
B-c-7	8.41	2	2	6	572.50	54.02
B-c-8	7.14	2	3	6	580.47	70.67
B-c-9	6.79	2	3	8	621.53	84.73
B-c-10	8.66	2	1	6	571.46	41.13
B-c-11	7.82	3	3	6	579.48	78.43
B-c-12	9.94	2	3	6	635.40	59.59
B-d-1	8.42	2	3	10	625.55	76.66
B-d-2	7.39	2	3	6	551.48	66.91
B-d-3	8.14	2	3	8	644.57	87.74

B-d-4	7.80	2	3	9	583.52	59.59
B-d-5	7.43	2	2	6	525.44	50.36
B-d-6	9.08	2	2	7	672.33	50.36
B-d-7	9.35	2	1	7	631.41	41.13
B-d-8	7.94	2	2	8	567.52	50.36
B-d-9	6.45	1	3	7	643.62	65.12
B-d-10	8.29	1	3	5	660.65	44.81
B-d-11	6.57	2	2	5	556.54	44.37
B-d-12	7.89	1	2	7	670.68	61.88
B-e-1	8.04	1	3	4	593.51	50.8
B-e-2	7.89	2	2	6	640.66	61.44
B-e-3	7.27	1	4	7	678.66	54.04
B-e-4	9.51	3	2	17	674.71	79.46
B-e-5	7.09	2	1	8	529.39	41.13
B-e-6	9.40	1	1	8	605.61	32.34
B-e-7	6.67	1	3	5	571.89	58.12
B-e-8	6.67	1	2	6	628.60	61.88
B-e-9	7.40	2	2	8	616.59	70.67
B-e-10	8.80	1	2	5	620.60	45.23
B-e-11	6.40	2	3	9	671.67	73.91
B-e-12	7.51	2	2	7	593.56	50.36
B-f-1	7.58	1	2	6	584.59	35.58
B-f-2	7.93	1	2	7	606.60	35.58
B-f-3	6.15	3	3	9	632.59	88.69
B-f-4	6.98	2	2	8	616.59	70.67
B-f-5	8.40	1	2	5	639.02	35.58
B-f-6	6.55	1	2	6	600.55	61.88
B-f-7	6.28	2	2	7	542.47	67.16

B-f-8	7.94	2	1	6	555.55	41.13
B-f-9	6.87	2	2	6	542.44	54.02
B-f-10	7.94	1	2	4	603.55	49.41
B-f-11	8.47	2	2	9	692.69	70.67
B-f-12	7.05	2	2	8	552.51	54.02
B-g-1	5.52	2	2	4	572.49	70.67
B-g-2	6.45	2	3	12	620.58	79.9
B-g-3	6.49	1	3	4	557.48	50.8
B-g-4	6.11	2	2	7	600.55	70.67
B-g-5	6.69	3	2	9	576.53	79.46
B-g-6	8.59	2	1	9	555.55	41.13
B-g-7	6.22	3	3	12	606.55	88.69
B-g-8	6.54	1	2	6	628.60	61.88
B-g-9	6.61	1	2	4	542.51	35.58
B-g-10	6.49	1	2	6	586.52	61.65
B-g-11	7.07	1	2	6	628.60	61.88
B-g-12	8.60	2	1	7	599.51	41.13
B-h-1	7.27	2	3	4	620.54	70.67
B-h-2	6.23	1	3	8	561.51	50.8
B-h-3	7.73	1	1	4	541.52	32.34
B-h-4	8.21	1	3	6	621.57	50.8
B-h-5	6.56	2	2	8	602.56	70.67
B-h-6	8.34	2	3	9	623.58	59.59
B-h-7	4.14	2	5	7	650.62	87.74
B-h-8	7.45	1	2	4	591.54	41.57
B-h-9	7.73	1	3	7	717.11	69.72
B-h-10	8.90	2	1	6	628.40	41.13
B-h-11	6.26	4	8	13	948.92	183.04

B-h-12	7.41	1	2	7	634.61	52.65
C-a-1	6.92	3	5	10	590.68	118.65
C-a-2	4.82	2	6	10	538.62	120.03
C-a-3	8.50	3	6	15	631.65	124.22
C-a-4	5.89	1	4	9	536.43	82.45
C-a-5	5.82	3	5	13	566.66	118.65
C-a-6	8.03	3	5	14	612.73	119.92
C-a-7	7.78	3	6	14	625.16	118.23
C-a-8	6.57	2	4	11	526.64	94.48
C-a-9	7.28	2	5	12	528.61	115.58
C-a-10	6.46	2	4	10	501.56	89.55
C-a-11	6.52	2	5	13	622.72	119.09
C-a-12	5.53	2	5	11	499.57	107.37
C-b-1	8.16	4	6	15	666.78	144.09
C-b-2	5.93	2	4	10	483.57	89.55
C-b-3	6.38	2	4	11	514.63	94.48
C-b-4	6.75	2	4	10	518.01	89.55
C-b-5	7.71	2	3	11	551.48	76.66
C-b-6	8.74	2	7	15	698.82	145.39
C-b-7	8.79	2	5	11	587.72	119.8
C-b-8	4.93	2	6	11	565.69	114.04
C-b-9	6.38	3	5	14	573.65	127.98
C-b-10	7.64	2	3	10	523.04	76.66
C-b-11	5.46	2	5	11	583.68	114.04
C-b-12	5.93	2	4	10	483.57	89.55
C-c-1	5.93	2	4	10	483.57	89.55
C-c-2	5.76	3	5	10	517.41	115.57
C-c-3	6.25	2	6	14	560.70	102.02

C-c-4	7.82	2	4	11	539.68	100.45
C-c-5	6.15	2	7	13	559.62	130.92
C-c-6	7.45	2	5	11	589.49	102.44
C-c-7	6.97	2	4	11	509.61	89.55
C-c-8	5.71	2	5	11	517.58	106.2
C-c-9	5.36	2	5	13	558.64	120.26
C-c-10	7.22	2	3	11	508.57	76.66
C-c-11	6.39	3	5	11	516.59	113.96
C-c-12	8.70	2	5	11	572.51	95.12
C-d-1	6.98	2	5	15	562.66	112.19
C-d-2	5.97	2	5	11	488.59	102.44
C-d-3	6.70	2	5	13	581.68	123.27
C-d-4	6.37	2	5	14	520.63	95.12
C-d-5	6.00	2	4	11	462.55	85.89
C-d-6	7.65	2	4	12	609.44	85.89
C-d-7	7.91	2	3	12	568.52	76.66
C-d-8	6.51	2	4	13	504.63	85.89
C-d-9	5.02	1	5	12	580.73	100.65
C-d-10	6.85	1	5	10	597.76	80.34
C-d-11	5.14	2	4	10	493.65	79.9
C-d-12	6.45	1	4	12	607.79	97.41
C-e-1	6.61	1	5	9	530.62	86.33
C-e-2	6.45	2	4	11	577.77	96.97
C-e-3	5.84	1	6	12	615.77	89.57
C-e-4	8.08	3	4	22	611.82	114.99
C-e-5	5.65	2	3	13	466.50	76.66
C-e-6	7.97	1	3	13	542.72	67.87
C-e-7	5.25	1	5	10	509.00	93.65

C-e-8	5.24	1	4	11	565.71	97.41
C-e-9	5.97	2	4	13	553.70	106.2
C-e-10	7.36	1	4	10	557.71	80.76
C-e-11	4.97	2	5	14	608.78	109.44
C-e-12	6.07	2	4	12	530.67	85.89
C-f-1	6.14	1	4	11	521.70	71.11
C-f-2	6.50	1	4	12	543.71	71.11
C-f-3	4.72	3	5	14	569.70	124.22
C-f-4	5.54	2	4	13	553.70	106.2
C-f-5	6.96	1	4	10	576.13	71.11
C-f-6	5.12	1	4	11	537.66	97.41
C-f-7	4.85	2	4	12	479.58	102.69
C-f-8	6.51	2	3	11	492.66	76.66
C-f-9	5.44	2	4	11	479.55	89.55
C-f-10	6.51	1	4	9	540.66	84.94
C-f-11	7.04	2	4	14	629.80	106.2
C-f-12	5.62	2	4	13	489.62	89.55
C-g-1	4.09	2	4	9	509.60	106.2
C-g-2	5.01	2	5	17	557.69	115.43
C-g-3	5.05	1	5	9	494.59	86.33
C-g-4	4.67	2	4	12	537.66	106.2
C-g-5	5.25	3	4	14	513.64	114.99
C-g-6	7.16	2	3	14	492.66	76.66
C-g-7	4.79	3	5	17	543.66	124.22
C-g-8	5.10	1	4	11	565.71	97.41
C-g-9	5.18	1	4	9	479.62	71.11
C-g-10	5.06	1	4	11	523.63	97.18
C-g-11	5.64	1	4	11	565.71	97.41

C-g-12	7.16	2	3	12	536.62	76.66
C-h-1	5.84	2	5	9	557.65	106.2
C-h-2	4.80	1	5	13	498.62	86.33
C-h-3	6.29	1	3	9	478.63	67.87
C-h-4	6.78	1	5	11	558.68	86.33
C-h-5	5.12	2	4	13	539.67	106.2
C-h-6	6.90	2	5	14	560.69	95.12
C-h-7	2.70	2	7	12	587.73	123.27
C-h-8	6.02	1	4	9	528.65	77.1
C-h-9	6.30	1	5	12	654.22	105.25
C-h-10	7.47	2	3	11	565.51	76.66
C-h-11	4.83	4	10	18	886.03	218.57
C-h-12	5.98	1	4	12	571.72	88.18

Table S15. Molecular Information of Deprotected Ureas

Compound ID (Substrate-Row- Column)	cLogP	Number of H-Bond Donors	Number of H-Bond Acceptors	Number of Rotatable Bonds	Molecular Weight (Da)	Topological Polar Surface Area (Å²)
De-A-a-1	5.82	3	4	4	536.676	100.19
De-A-a-2	3.72	2	5	4	484.61	101.57
De-A-a-3	5.66	3	4	6	477.528	93.45
De-A-a-4	4.79	1	3	3	482.422	63.99
De-A-a-5	4.72	3	4	7	512.654	100.19
De-A-a-6	5.19	3	3	5	458.606	89.15
De-A-a-7	4.94	3	4	5	471.04	87.46
De-A-a-8	5.48	2	3	5	472.633	76.02
De-A-a-9	6.27	2	4	6	474.605	97.12
De-A-a-10	5.36	2	3	4	447.554	71.09
De-A-a-11	3.47	3	4	4	434.584	83.12
De-A-a-12	4.43	2	4	5	445.567	88.91
De-A-b-1	5.32	4	4	6	512.654	113.32
De-A-b-2	4.83	2	3	4	429.564	71.09
De-A-b-3	5.28	2	3	5	460.622	76.02
De-A-b-4	5.66	2	3	4	464.01	71.09
De-A-b-5	6.61	2	2	5	497.477	58.20
De-A-b-6	4.60	3	4	4	444.579	97.11
De-A-b-7	7.69	2	4	5	533.713	101.34
De-A-b-8	3.83	2	5	5	511.68	95.58
De-A-b-9	5.28	3	4	8	519.642	109.52
De-A-b-10	6.54	2	2	4	469.04	58.20
De-A-b-11	4.36	2	4	5	529.67	95.58

De-A-b-12	4.83	2	3	4	429.564	71.09
De-A-c-1	4.83	2	3	4	429.564	71.09
De-A-c-2	4.66	3	4	4	463.4	97.11
De-A-c-3	5.15	2	5	8	506.691	83.56
De-A-c-4	6.72	2	3	5	485.672	81.99
De-A-c-5	5.05	2	6	7	505.619	112.46
De-A-c-6	6.43	2	4	5	535.486	83.98
De-A-c-7	5.87	2	3	5	455.602	71.09
De-A-c-8	4.61	2	4	5	463.578	87.74
De-A-c-9	4.26	2	4	7	504.631	101.80
De-A-c-10	6.13	2	2	5	454.562	58.20
De-A-c-11	5.29	3	4	5	462.59	95.50
De-A-c-12	7.59	2	4	5	518.51	76.66
De-A-d-1	5.88	2	4	9	508.659	93.73
De-A-d-2	4.95	2	4	5	434.584	83.98
De-A-d-3	5.60	2	4	7	527.68	104.81
De-A-d-4	5.27	2	4	8	466.622	76.66
De-A-d-5	4.90	2	3	5	408.542	67.43
De-A-d-6	6.55	2	3	6	555.436	67.43
De-A-d-7	6.82	2	2	6	514.512	58.20
De-A-d-8	5.41	2	3	7	450.623	67.43
De-A-d-9	2.64	2	4	4	426.605	64.68
De-A-d-10	5.75	1	4	4	543.752	61.88
De-A-d-11	4.04	2	3	4	439.644	61.44
De-A-d-12	4.07	2	3	4	453.671	61.44
De-A-e-1	5.51	1	4	3	476.617	67.87
De-A-e-2	5.35	2	3	5	523.762	78.51
De-A-e-3	4.74	1	5	6	561.767	71.11

De-A-e-4	5.49	3	3	13	457.703	84.22
De-A-e-5	4.56	2	2	7	412.497	58.20
De-A-e-6	6.87	1	2	7	488.716	49.41
De-A-e-7	4.24	1	4	4	455	75.19
De-A-e-8	2.86	2	3	3	411.59	61.44
De-A-e-9	3.38	2	3	4	399.579	75.43
De-A-e-10	6.27	1	3	4	503.71	62.30
De-A-e-11	2.38	2	4	5	454.659	78.67
De-A-e-12	4.98	2	3	6	476.661	67.43
De-A-f-1	5.04	1	3	5	467.698	52.65
De-A-f-2	5.40	1	3	6	489.704	52.65
De-A-f-3	2.13	3	4	5	415.578	93.45
De-A-f-4	2.95	2	3	4	399.579	75.43
De-A-f-5	5.86	1	3	4	522.13	52.65
De-A-f-6	2.74	2	3	3	383.536	61.44
De-A-f-7	3.75	2	3	6	425.573	84.23
De-A-f-8	5.41	2	2	5	438.656	58.20
De-A-f-9	4.34	2	3	5	425.548	71.09
De-A-f-10	5.41	1	3	3	486.656	66.48
De-A-f-11	4.66	3	3	6	475.677	70.23
De-A-f-12	4.52	2	3	7	435.612	71.09
De-A-g-1	2.99	2	3	3	455.599	87.74
De-A-g-2	2.63	3	4	9	403.567	79.46
De-A-g-3	3.96	1	4	3	440.584	67.87
De-A-g-4	2.08	2	3	3	383.536	75.43
De-A-g-5	2.66	3	3	5	359.514	84.22
De-A-g-6	6.06	2	2	8	438.656	58.20
De-A-g-7	2.20	3	4	8	389.54	93.45

De-A-g-8	2.72	2	3	3	411.59	61.44
De-A-g-9	4.08	1	3	3	425.617	52.65
De-A-g-10	2.68	2	3	3	369.509	61.21
De-A-g-11	3.26	2	3	3	411.59	61.44
De-A-g-12	6.06	2	2	6	482.616	58.20
De-A-h-1	4.74	2	4	3	503.643	87.74
De-A-h-2	3.70	1	4	7	444.616	67.87
De-A-h-3	5.19	1	2	3	424.629	49.41
De-A-h-4	5.68	1	4	5	504.671	67.87
De-A-h-5	2.53	2	3	4	385.552	75.43
De-A-h-6	5.81	2	4	8	506.687	76.66
De-A-h-7	1.61	2	6	6	533.73	104.81
De-A-h-8	4.92	1	3	3	474.645	58.64
De-A-h-9	5.20	1	4	6	600.22	86.79
De-A-h-10	6.37	2	2	5	511.504	58.20
De-A-h-11	3.73	4	9	12	832.03	200.11
De-A-h-12	4.88	1	3	6	517.714	69.72
De-B-a-1	8.35	3	3	5	653.57	83.12
De-B-a-2	6.25	2	4	5	601.51	84.50
De-B-a-3	8.19	3	3	7	594.42	76.38
De-B-a-4	7.32	1	2	4	599.32	46.92
De-B-a-5	7.25	3	3	8	629.55	83.12
De-B-a-6	7.72	3	2	6	575.5	72.08
De-B-a-7	7.47	3	3	6	587.94	70.39
De-B-a-8	8.01	2	2	6	589.53	58.95
De-B-a-9	8.70	2	3	7	591.5	80.05
De-B-a-10	7.89	2	2	5	564.45	54.02
De-B-a-11	6.00	3	3	5	551.48	66.05

De-B-a-12	6.78	2	3	6	562.46	71.84
De-B-b-1	7.85	4	3	7	629.55	96.25
De-B-b-2	7.36	2	2	5	546.46	54.02
De-B-b-3	7.81	2	2	6	577.52	58.95
De-B-b-4	8.19	2	2	5	580.9	54.02
De-B-b-5	9.14	2	1	6	614.37	41.13
De-B-b-6	7.13	3	3	5	561.47	80.04
De-B-b-7	10.23	2	3	6	650.61	84.27
De-B-b-8	6.36	2	4	6	628.58	78.51
De-B-b-9	7.81	3	3	9	636.54	92.45
De-B-b-10	9.07	2	1	5	585.93	41.13
De-B-b-11	6.89	2	3	6	646.57	78.51
De-B-b-12	7.36	2	2	5	546.46	54.02
De-B-c-1	7.36	2	2	5	546.46	54.02
De-B-c-2	7.19	3	3	5	580.3	80.04
De-B-c-3	7.68	2	4	9	623.59	66.49
De-B-c-4	9.26	2	2	6	602.57	64.92
De-B-c-5	7.58	2	5	8	622.51	95.39
De-B-c-6	8.87	2	3	6	652.38	66.91
De-B-c-7	8.41	2	2	6	572.5	54.02
De-B-c-8	7.14	2	3	6	580.47	70.67
De-B-c-9	6.79	2	3	8	621.53	84.73
De-B-c-10	8.66	2	1	6	571.46	41.13
De-B-c-11	7.82	3	3	6	579.48	78.43
De-B-c-12	9.94	2	3	6	635.4	59.59
De-B-d-1	8.42	2	3	10	625.55	76.66
De-B-d-2	7.39	2	3	6	551.48	66.91
De-B-d-3	8.14	2	3	8	644.57	87.74

De-B-d-4	7.80	2	3	9	583.52	59.59
De-B-d-5	7.43	2	2	6	525.44	50.36
De-B-d-6	9.08	2	2	7	672.33	50.36
De-B-d-7	9.35	2	1	7	631.41	41.13
De-B-d-8	7.94	2	2	8	567.52	50.36
De-B-d-9	5.17	2	3	5	543.5	47.61
De-B-d-10	8.29	1	3	5	660.65	44.81
De-B-d-11	6.57	2	2	5	556.54	44.37
De-B-d-12	6.60	2	2	5	570.57	44.37
De-B-e-1	8.04	1	3	4	593.51	50.80
De-B-e-2	7.89	2	2	6	640.66	61.44
De-B-e-3	7.27	1	4	7	678.66	54.04
De-B-e-4	8.02	3	2	14	574.6	67.15
De-B-e-5	7.09	2	1	8	529.39	41.13
De-B-e-6	9.40	1	1	8	605.61	32.34
De-B-e-7	6.67	1	3	5	571.89	58.12
De-B-e-8	5.39	2	2	4	528.48	44.37
De-B-e-9	5.91	2	2	5	516.47	58.36
De-B-e-10	8.80	1	2	5	620.6	45.23
De-B-e-11	4.91	2	3	6	571.55	61.60
De-B-e-12	7.51	2	2	7	593.56	50.36
De-B-f-1	7.58	1	2	6	584.59	35.58
De-B-f-2	7.93	1	2	7	606.6	35.58
De-B-f-3	4.66	3	3	6	532.47	76.38
De-B-f-4	5.48	2	2	5	516.47	58.36
De-B-f-5	8.40	1	2	5	639.02	35.58
De-B-f-6	5.27	2	2	4	500.43	44.37
De-B-f-7	6.28	2	2	7	542.47	67.16

De-B-f-8	7.94	2	1	6	555.55	41.13
De-B-f-9	6.87	2	2	6	542.44	54.02
De-B-f-10	7.94	1	2	4	603.55	49.41
De-B-f-11	7.19	3	2	7	592.57	53.16
De-B-f-12	7.05	2	2	8	552.51	54.02
De-B-g-1	5.52	2	2	4	572.49	70.67
De-B-g-2	5.16	3	3	10	520.46	62.39
De-B-g-3	6.49	1	3	4	557.48	50.80
De-B-g-4	4.61	2	2	4	500.43	58.36
De-B-g-5	5.19	3	2	6	476.41	67.15
De-B-g-6	8.59	2	1	9	555.55	41.13
De-B-g-7	4.73	3	3	9	506.43	76.38
De-B-g-8	5.25	2	2	4	528.48	44.37
De-B-g-9	6.61	1	2	4	542.51	35.58
De-B-g-10	5.21	2	2	4	486.4	44.14
De-B-g-11	5.79	2	2	4	528.48	44.37
De-B-g-12	8.60	2	1	7	599.51	41.13
De-B-h-1	7.27	2	3	4	620.54	70.67
De-B-h-2	6.23	1	3	8	561.51	50.80
De-B-h-3	7.73	1	1	4	541.52	32.34
De-B-h-4	8.21	1	3	6	621.57	50.80
De-B-h-5	5.07	2	2	5	502.45	58.36
De-B-h-6	8.34	2	3	9	623.58	59.59
De-B-h-7	4.14	2	5	7	650.62	87.74
De-B-h-8	7.45	1	2	4	591.54	41.57
De-B-h-9	7.73	1	3	7	717.11	69.72
De-B-h-10	8.90	2	1	6	628.4	41.13
De-B-h-11	6.26	4	8	13	948.92	183.04

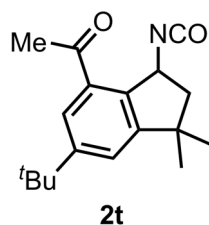
De-B-h-12	7.41	1	2	7	634.61	52.65
De-C-a-1	6.92	3	5	10	590.68	118.65
De-C-a-2	4.82	2	6	10	538.62	120.03
De-C-a-3	6.76	3	5	12	531.532	111.91
De-C-a-4	5.89	1	4	9	536.426	82.45
De-C-a-5	5.82	3	5	13	566.658	118.65
De-C-a-6	6.29	3	4	11	512.61	107.61
De-C-a-7	6.04	3	5	11	525.05	105.92
De-C-a-8	6.57	2	4	11	526.637	94.48
De-C-a-9	7.28	2	5	12	528.609	115.58
De-C-a-10	6.46	2	4	10	501.558	89.55
De-C-a-11	4.57	3	5	10	488.588	101.58
De-C-a-12	5.53	2	5	11	499.571	107.37
De-C-b-1	6.42	4	5	12	566.658	131.78
De-C-b-2	5.93	2	4	10	483.568	89.55
De-C-b-3	6.38	2	4	11	514.626	94.48
De-C-b-4	6.75	2	4	10	518.01	89.55
De-C-b-5	7.71	2	3	11	551.481	76.66
De-C-b-6	5.69	3	5	10	498.583	115.57
De-C-b-7	8.79	2	5	11	587.717	119.80
De-C-b-8	4.93	2	6	11	565.69	114.04
De-C-b-9	6.38	3	5	14	573.646	127.98
De-C-b-10	7.64	2	3	10	523.04	76.66
De-C-b-11	5.46	2	5	11	583.68	114.04
De-C-b-12	5.93	2	4	10	483.568	89.55
De-C-c-1	5.93	2	4	10	483.568	89.55
De-C-c-2	5.76	3	5	10	517.41	115.57
De-C-c-3	6.25	2	6	14	560.695	102.02

De-C-c-4	7.82	2	4	11	539.676	100.45
De-C-c-5	6.15	2	7	13	559.623	130.92
De-C-c-6	7.45	2	5	11	589.49	102.44
De-C-c-7	6.97	2	4	11	509.606	89.55
De-C-c-8	5.71	2	5	11	517.582	106.20
De-C-c-9	5.36	2	5	13	558.635	120.26
De-C-c-10	7.22	2	3	11	508.566	76.66
De-C-c-11	6.39	3	5	11	516.594	113.96
De-C-c-12	8.70	2	5	11	572.51	95.12
De-C-d-1	6.98	2	5	15	562.663	112.19
De-C-d-2	5.97	2	5	11	488.588	102.44
De-C-d-3	6.70	2	5	13	581.68	123.27
De-C-d-4	6.37	2	5	14	520.626	95.12
De-C-d-5	6.00	2	4	11	462.546	85.89
De-C-d-6	7.65	2	4	12	609.44	85.89
De-C-d-7	7.91	2	3	12	568.516	76.66
De-C-d-8	6.51	2	4	13	504.627	85.89
De-C-d-9	3.73	2	5	10	480.609	83.14
De-C-d-10	6.85	1	5	10	597.756	80.34
De-C-d-11	5.14	2	4	10	493.648	79.90
De-C-d-12	5.17	2	4	10	507.675	79.90
De-C-e-1	6.61	1	5	9	530.621	86.33
De-C-e-2	6.45	2	4	11	577.766	96.97
De-C-e-3	5.84	1	6	12	615.771	89.57
De-C-e-4	6.59	3	4	19	511.707	102.68
De-C-e-5	5.65	2	3	13	466.501	76.66
De-C-e-6	7.97	1	3	13	542.72	67.87
De-C-e-7	5.25	1	5	10	509	93.65

De-C-e-8	3.96	2	4	9	465.594	79.90
De-C-e-9	4.48	2	4	10	453.583	93.89
De-C-e-10	7.36	1	4	10	557.71	80.76
De-C-e-11	3.48	2	5	11	508.663	97.13
De-C-e-12	6.07	2	4	12	530.665	85.89
De-C-f-1	6.14	1	4	11	521.702	71.11
De-C-f-2	6.50	1	4	12	543.708	71.11
De-C-f-3	3.23	3	5	11	469.582	111.91
De-C-f-4	4.05	2	4	10	453.583	93.89
De-C-f-5	6.96	1	4	10	576.13	71.11
De-C-f-6	3.84	2	4	9	437.54	79.90
De-C-f-7	4.85	2	4	12	479.577	102.69
De-C-f-8	6.51	2	3	11	492.66	76.66
De-C-f-9	5.44	2	4	11	479.552	89.55
De-C-f-10	6.51	1	4	9	540.66	84.94
De-C-f-11	5.76	3	4	12	529.681	88.69
De-C-f-12	5.62	2	4	13	489.616	89.55
De-C-g-1	4.09	2	4	9	509.603	106.20
De-C-g-2	3.73	3	5	15	457.571	97.92
De-C-g-3	5.05	1	5	9	494.588	86.33
De-C-g-4	3.18	2	4	9	437.54	93.89
De-C-g-5	3.76	3	4	11	413.518	102.68
De-C-g-6	7.16	2	3	14	492.66	76.66
De-C-g-7	3.30	3	5	14	443.544	111.91
De-C-g-8	3.82	2	4	9	465.594	79.90
De-C-g-9	5.18	1	4	9	479.621	71.11
De-C-g-10	3.78	2	4	9	423.513	79.67
De-C-g-11	4.36	2	4	9	465.594	79.90

De-C-g-12	7.16	2	3	12	536.62	76.66
De-C-h-1	5.84	2	5	9	557.647	106.20
De-C-h-2	4.80	1	5	13	498.62	86.33
De-C-h-3	6.29	1	3	9	478.633	67.87
De-C-h-4	6.78	1	5	11	558.675	86.33
De-C-h-5	3.63	2	4	10	439.556	93.89
De-C-h-6	6.90	2	5	14	560.691	95.12
De-C-h-7	2.70	2	7	12	587.73	123.27
De-C-h-8	6.02	1	4	9	528.649	77.10
De-C-h-9	6.30	1	5	12	654.22	105.25
De-C-h-10	7.47	2	3	11	565.508	76.66
De-C-h-11	4.83	4	10	18	886.03	218.57
De-C-h-12	5.98	1	4	12	571.718	88.18

9. Characterization Data



1-(6-(*tert*-butyl)-3-isocyanato-1,1-dimethyl-2,3-dihydro-1*H*-inden-4-yl)ethan-1-one (2t): Prepared from celestolide (**1t**) according to Procedure C. The reaction mixture was purified by flash column chromatography (ethyl acetate:pentane = 1:20) to afford **2t**.

Note: (1) Flash column chromatography was performed within 15 minutes since the isocyanate reacts with silica gels and it could lead to low isolated yield. (2) Evaporation of solvents on rotovap was carefully conducted due to the volatility of **2t**. To measure the exact isolated yield, rigorous repeating distillations are recommended. In this experiment, further distillation was not performed, but the mass of **2t** was calibrated by offsetting that of remaining ethyl acetate on ^1H NMR spectrum.

NMR Yield: 66%

Isolated Yield: 51% (58.0 mg)

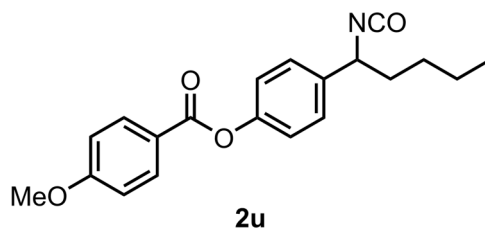
Physical Property: Colorless oil.

^1H NMR (500 MHz, methylene chloride- d_2) δ 7.80 (d, $J = 1.8$ Hz, 1H), 7.44 (d, $J = 1.8$ Hz, 1H), 5.54 (dd, $J = 7.4, 1.8$ Hz, 1H), 2.64 (s, 3H), 2.15 – 2.01 (m, 2H), 1.38 (s, 9H), 1.36 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (126 MHz, methylene chloride- d_2) δ 200.1, 154.6, 153.7, 138.7, 133.4, 126.7, 124.9, 124.5, 56.7, 49.2, 43.3, 35.3, 31.5, 30.9, 29.1, 28.3.

IR (neat): 2956, 2921, 2854, 2250, 1682, 1467, 1366, 1257, 1239 cm^{-1} .

HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{23}\text{NO}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 308.1621, found 308.1613.



4-(1-isocyanatopentyl)phenyl 4-methoxybenzoate (2u): Prepared from nematal 105 (**1u**) according to Procedure F. The reaction mixture was purified by flash column chromatography (ethyl acetate:pentane = 1:10) to afford **2u**.

Note: The isocyanate **2u** is sensitive to silica gels. See the note for the preparation of **2t**.

NMR Yield: 66%

Isolated Yield: 58% (78.8 mg)

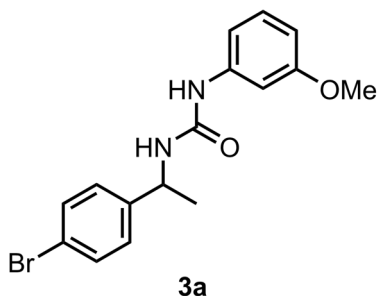
Physical Property: Colorless oil.

^1H NMR (600 MHz, methylene chloride- d_2) δ 8.15 – 8.10 (m, 2H), 7.38 – 7.34 (m, 2H), 7.22 – 7.17 (m, 2H), 7.02 – 6.97 (m, 2H), 4.64 (dd, $J = 8.2, 5.6$ Hz, 1H), 3.88 (s, 3H), 1.90 – 1.77 (m, 2H), 1.46 – 1.30 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (151 MHz, methylene chloride- d_2) δ 165.1, 164.4, 150.9, 139.6, 132.5, 127.3, 123.5, 122.4, 122.1, 114.3, 59.4, 56.0, 39.9, 28.7, 22.6, 14.1.

IR (neat): 2963, 2938, 2868, 2250, 1738, 1611, 1510 cm^{-1} .

HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 340.1543, found 340.1537.



1-(1-(4-bromophenyl)ethyl)-3-(3-methoxyphenyl)urea (3a): Prepared from 1-bromo-4-ethylbenzene (**1a**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2a** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2a**): 95% (74.1 mg)

NMR Yield (Isocyanation Step): 56%

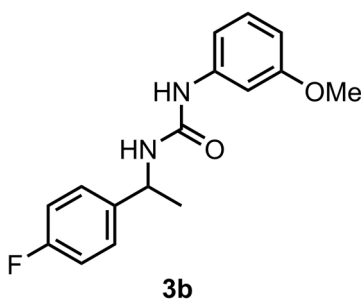
Physical Property: White solid. m.p. = 177 – 179 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.12 – 7.07 (m, 2H), 6.81 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.46 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.77 (p, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.7, 154.4, 144.9, 141.6, 131.3, 129.5, 128.2, 119.6, 110.1, 106.8, 103.5, 54.9, 48.3, 22.9.

IR (neat): 3339, 2945, 1654, 1601, 1529, 1489, 1450 cm⁻¹.

HRMS (ESI) calculated for C₁₆H₁₇BrN₂O₂Na⁺ [M+Na]⁺ 371.0366, found 371.0366.



1-(1-(4-fluorophenyl)ethyl)-3-(3-methoxyphenyl)urea (3b): Prepared from 1-ethyl-4-fluorobenzene (**1b**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2b** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2b**): 100% (60.0 mg)

NMR Yield (Isocyanation Step): 52%

Physical Property: White solid. m.p. = 115 – 117 °C

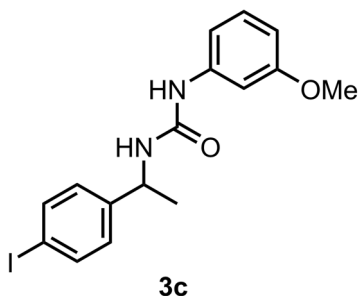
¹H NMR (500 MHz, DMSO-*d*₆) δ 8.37 (s, 1H), 7.37 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.15 (t, *J* = 8.9 Hz, 2H), 7.12 – 7.07 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.46 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.81 (p, *J* = 7.0 Hz, 1H), 3.69 (s, 3H), 1.37 (d, *J* = 7.0 Hz, 3H).

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -116.5.

¹³C NMR (126 MHz, DMSO) δ 161.0 (d, *J* = 242.0 Hz), 159.6, 154.2, 141.5, 141.4 (d, *J* = 3.0 Hz), 129.4, 127.7 (d, *J* = 8.0 Hz), 114.9 (d, *J* = 21.1 Hz), 109.9, 106.6, 103.3, 54.8, 48.0, 23.0.

IR (neat): 3342, 2956, 1647, 1611, 1555, 1510, 1496, 1460, 1432 cm⁻¹.

HRMS (ESI) calculated for C₁₆H₁₇FN₂O₂Na⁺ [M+Na]⁺ 311.1166, found 311.1163.



1-(1-(4-iodophenyl)ethyl)-3-(3-methoxyphenyl)urea (3c): Prepared from 1-ethyl-4-iodobenzene (**1c**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2c** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2c**): 60% (48.4 mg)

NMR Yield (Isocyanation Step): 51%

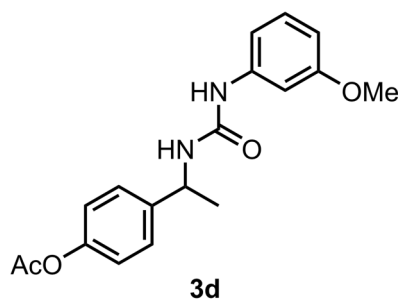
Physical Property: White solid. m.p. = 162 – 164 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.38 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.12 – 7.07 (m, 2H), 6.83 – 6.78 (m, 1H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.46 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.75 (p, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.6, 154.2, 145.2, 141.5, 137.0, 129.4, 128.3, 109.9, 106.6, 103.3, 92.2, 54.8, 48.2, 22.8.

IR (neat): 3339, 2928, 1654, 1597, 1559, 1478, 1453 cm⁻¹.

HRMS (ESI) calculated for C₁₆H₁₇IN₂O₂Na⁺ [M+Na]⁺ 419.0227, found 419.0225.



4-(1-(3-(3-methoxyphenyl)ureido)ethyl)phenyl acetate (3d): Prepared from 4-ethylphenyl acetate (**1d**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2d** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2d**): 90% (49.7 mg)

NMR Yield (Isocyanation Step): 42%

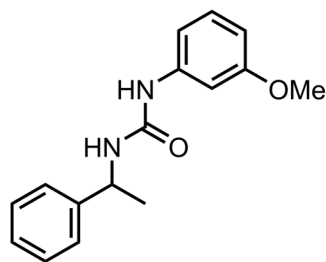
Physical Property: White solid. m.p. = 128 – 130 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.13 – 7.05 (m, 4H), 6.83 – 6.79 (m, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 6.46 (dd, *J* = 8.1, 2.2 Hz, 1H), 4.81 (p, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 2.25 (s, 3H), 1.38 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 169.4, 159.7, 154.4, 149.2, 142.8, 141.6, 129.5, 126.9, 121.7, 110.1, 106.7, 103.4, 54.9, 48.2, 23.0, 20.9.

IR (neat): 3346, 2963, 2931, 1773, 1654, 1611, 1559, 1496 cm⁻¹.

HRMS (ESI) calculated for C₁₈H₂₀N₂O₃Na⁺ [M+Na]⁺ 351.1315, found 351.1311.



3e

1-(3-methoxyphenyl)-3-(1-phenylethyl)urea (3e): Prepared from ethylbenzene (**1e**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2e** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2e**): 98% (47.6 mg)

NMR Yield (Isocyanation Step): 45%

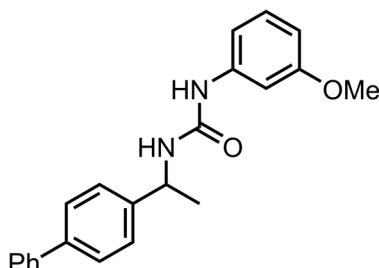
Physical Property: Colorless oil.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (s, 1H), 7.34 (d, *J* = 4.4 Hz, 4H), 7.23 (dt, *J* = 8.7, 4.2 Hz, 1H), 7.13 (t, *J* = 2.2 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.85 – 6.80 (m, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.46 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.81 (p, *J* = 7.0 Hz, 1H), 3.69 (s, 3H), 1.38 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.7, 154.3, 145.2, 141.6, 129.4, 128.3, 126.6, 125.8, 109.9, 106.5, 103.3, 54.8, 48.6, 23.1.

IR (neat): 3339, 2963, 2931, 1654, 1604, 1552, 1499, 1450 cm⁻¹.

HRMS (ESI) calculated for C₁₆H₁₈N₂O₂Na⁺ [M+Na]⁺ 293.1261, found 293.1257.



3f

1-(1-([1,1'-biphenyl]-4-yl)ethyl)-3-(3-methoxyphenyl)urea (3f): Prepared from 4-ethyl-1,1'-biphenyl (**1f**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2f** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2f**): 93% (61.9 mg)

NMR Yield (Isocyanation Step): 48%

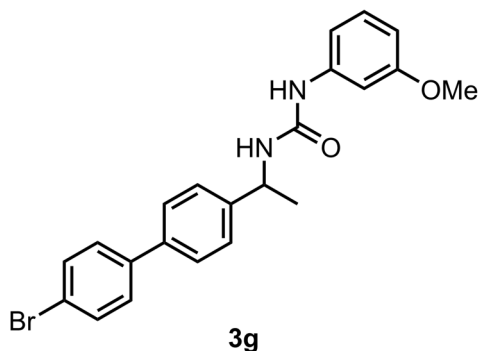
Physical Property: White solid. m.p. = 145 – 147 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.40 (s, 1H), 7.63 (t, *J* = 7.7 Hz, 4H), 7.48 – 7.40 (m, 4H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 2.3 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.82 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.46 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.85 (p, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 1.42 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.6, 154.3, 144.5, 141.6, 140.0, 138.6, 129.4, 128.9, 127.3, 126.7, 126.6, 126.4, 109.9, 106.5, 103.3, 54.8, 48.3, 23.0.

IR (neat): 3325, 3037, 2970, 2924, 1643, 1608, 1562, 1492, 1460, 1422 cm⁻¹.

HRMS (ESI) calculated for C₂₂H₂₂N₂O₂Na⁺ [M+Na]⁺ 369.1574, found 369.1569.



1-(1-(4'-bromo-[1,1'-biphenyl]-4-yl)ethyl)-3-(3-methoxyphenyl)urea (3g): Prepared from 4-bromo-4'-ethyl-1,1'-biphenyl (**1g**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2g** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2g**): 71% (55.5 mg)

NMR Yield (Isocyanation Step): 46%

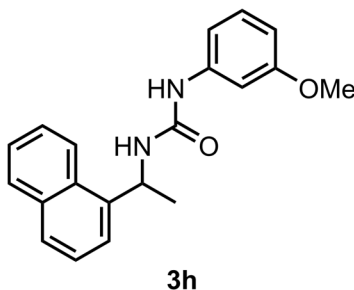
Physical Property: White solid. m.p. = 179 – 181 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.40 (s, 1H), 7.66 – 7.59 (m, 6H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.12 (t, *J* = 2.1 Hz, 1H), 7.10 (t, *J* = 8.2 Hz, 1H), 6.84 – 6.80 (m, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.46 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.84 (p, *J* = 7.0 Hz, 1H), 3.69 (s, 3H), 1.41 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.6, 154.3, 145.0, 141.6, 139.2, 137.3, 131.8, 129.4, 128.7, 126.6, 126.5, 120.7, 109.9, 106.6, 103.3, 54.8, 48.3, 22.9.

IR (neat): 3314, 2938, 1643, 1615, 1597, 1573, 1482 cm⁻¹.

HRMS (ESI) calculated for C₂₂H₂₁BrN₂O₂Na⁺ [M+Na]⁺ 447.0679, found 447.0676.



1-(3-methoxyphenyl)-3-(1-(naphthalen-1-yl)ethyl)urea (3h): Prepared from 1-ethylnaphthalene (**1h**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2h** was measured from an identical reaction in parallel. NMR spectra of **S1** was matched with the literature.²

Isolated Yield (Urea Formation Step from Isocyanate **2h**): 90% (62.5 mg)

NMR Yield (Isocyanation Step): 54%

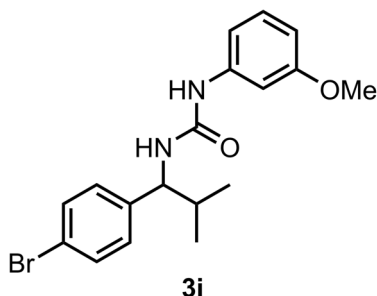
Physical Property: Yellowish white solid. m.p. = 140 – 142 °C

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.40 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.50 (m, 4H), 7.13 (t, *J* = 2.2 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.80 (ddd, *J* = 8.1, 1.9, 0.7 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.46 (ddd, *J* = 8.2, 2.5, 0.7 Hz, 1H), 5.62 (p, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 1.53 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 159.7, 154.2, 141.6, 140.7, 133.4, 130.3, 129.4, 128.7, 127.3, 126.2, 125.6, 125.5, 123.1, 122.0, 109.8, 106.6, 103.2, 54.8, 44.6, 22.2.

IR (neat): 3325, 3058, 2981, 1636, 1601, 1559, 1492, 1453 cm⁻¹.

HRMS (ESI) calculated for C₂₀H₂₀N₂O₂Na⁺ [M+Na]⁺ 343.1417, found 343.1413.



1-(1-(4-bromophenyl)-2-methylpropyl)-3-(3-methoxyphenyl)urea (3i): Prepared from 1-bromo-4-isobutylbenzene (**1i**) according to Procedure F followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2i** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2i**): 76% (49.1 mg)

NMR Yield (Isocyanation Step): 43%

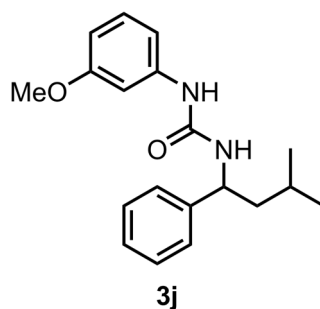
Physical Property: Amorphous solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.12 – 7.07 (m, 2H), 6.83 – 6.77 (m, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.46 (dd, *J* = 8.1, 2.2 Hz, 1H), 4.52 – 4.47 (m, 1H), 3.68 (s, 3H), 1.95 (h, *J* = 6.7 Hz, 1H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.6, 154.6, 142.7, 141.5, 130.9, 129.4, 129.0, 119.5, 109.8, 106.6, 103.1, 58.0, 54.8, 33.0, 19.6, 17.9.

IR (neat): 3314, 2970, 2924, 2872, 2191, 2008, 1643, 1601, 1555, 1492, 1464 cm⁻¹.

HRMS (ESI) calculated for C₁₈H₂₁BrN₂O₂Na⁺ [M+Na]⁺ 399.0679, found 399.0676.



1-(3-methoxyphenyl)-3-(3-methyl-1-phenylbutyl)urea (3j): Prepared from isopentylbenzene (**1j**) according to Procedure A followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2j** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2j**): 62% (46.3 mg)

NMR Yield (Isocyanation Step): 60%

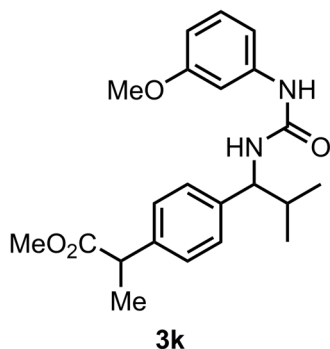
Physical Property: White solid. m.p. = 125 – 127 °C.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.34 (s, 1H), 7.36 – 7.27 (m, 4H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.12 (t, *J* = 2.3 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 6.45 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.77 – 4.69 (m, 1H), 3.68 (s, 3H), 1.64 – 1.53 (m, 2H), 1.49 (dq, *J* = 12.7, 7.1 Hz, 1H), 0.92 (d, *J* = 2.7 Hz, 3H), 0.90 (d, *J* = 2.7 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.6, 154.4, 144.7, 141.6, 129.4, 128.3, 126.6, 126.1, 109.8, 106.6, 103.1, 54.8, 51.2, 46.2, 24.6, 22.7, 22.0.

IR (neat): 3339, 2956, 1650, 1608, 1559, 1496, 1450, 1432, 1285 cm⁻¹.

HRMS (ESI) calculated for C₁₉H₂₄N₂O₂Na⁺ [M+Na]⁺ 335.1730, found 335.1728.



methyl 2-(4-(1-(3-(3-methoxyphenyl)ureido)-2-methylpropyl)phenyl)propanoate (3k): Prepared from ibuprofen methyl ester (**1k**) according to Procedure D followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2k** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2k**): 82% (59.3 mg)

NMR Yield (Isocyanation Step): 47%

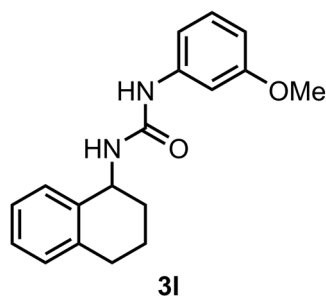
Physical Property: Colorless oil.

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.42 (s, 1H), 7.22 (q, *J* = 8.2 Hz, 4H), 7.12 (t, *J* = 2.2 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.81 – 6.78 (m, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.45 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.50 (dd, *J* = 8.6, 6.7 Hz, 1H), 3.77 (q, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.57 (s, 3H), 1.95 (h, *J* = 6.7 Hz, 1H), 1.37 (d, *J* = 7.1 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 174.3, 159.7, 154.6, 142.00, 141.98, 141.6, 138.8, 138.7, 129.4, 127.1, 126.9, 109.7, 106.6, 103.0, 58.2, 54.8, 51.8, 44.04, 44.03, 33.2, 19.8, 18.6, 18.5, 18.0.

IR (neat): 2967, 2924, 2865, 1745, 1661, 1618, 1555, 1460 cm⁻¹.

HRMS (ESI) calculated for C₂₂H₂₈N₂O₄Na⁺ [M+Na]⁺ 407.1941, found 407.1940.



1-(3-methoxyphenyl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea (3l): Prepared from tetralin (**1l**) according to Procedure B followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2l** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2l**): 95% (55.0 mg)

NMR Yield (Isocyanation Step): 49%

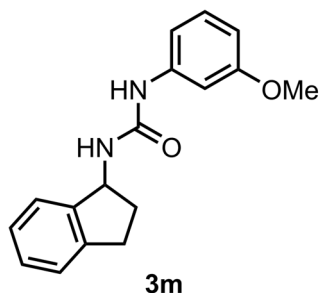
Physical Property: White solid. m.p. = 137 – 139 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.31 (s, 1H), 7.30 – 7.26 (m, 1H), 7.20 – 7.08 (m, 5H), 6.85 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.50 – 6.44 (m, 2H), 4.87 – 4.81 (m, 1H), 3.71 (s, 3H), 2.78 (dt, *J* = 16.6, 5.8 Hz, 1H), 2.70 (dt, *J* = 16.8, 5.7 Hz, 1H), 1.93 (ddt, *J* = 11.3, 8.9, 4.3 Hz, 1H), 1.86 – 1.70 (m, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.7, 154.6, 141.6, 138.0, 136.9, 129.4, 128.8, 128.3, 126.8, 125.9, 109.9, 106.5, 103.3, 54.8, 46.8, 30.2, 28.7, 19.7.

IR (neat): 3332, 2942, 2854, 1647, 1604, 1559, 1496, 1460, 1436 cm⁻¹.

HRMS (ESI) calculated for C₁₈H₂₀N₂O₂Na⁺ [M+Na]⁺ 319.1417, found 319.1415.



1-(2,3-dihydro-1H-inden-1-yl)-3-(3-methoxyphenyl)urea (3m): Prepared from indan (**1m**) according to Procedure C followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2m** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2m**): 89% (45.0 mg)

NMR Yield (Isocyanation Step): 45%

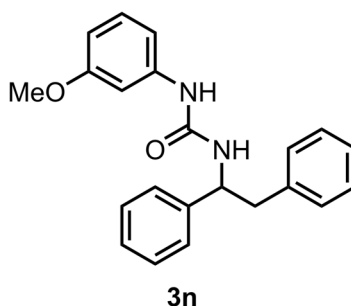
Physical Property: White solid. m.p. = 111 – 113 °C.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.38 (s, 1H), 7.30 – 7.24 (m, 2H), 7.21 (td, *J* = 4.6, 4.2, 1.9 Hz, 2H), 7.17 (t, *J* = 2.2 Hz, 1H), 7.12 (t, *J* = 8.1 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.51 – 6.44 (m, 2H), 5.16 (q, *J* = 7.7 Hz, 1H), 3.71 (s, 3H), 2.92 (ddd, *J* = 15.8, 8.6, 3.5 Hz, 1H), 2.80 (dt, *J* = 16.0, 8.3 Hz, 1H), 2.45 (dtd, *J* = 11.3, 7.8, 3.6 Hz, 1H), 1.76 (dq, *J* = 12.6, 8.5 Hz, 1H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.7, 154.9, 144.3, 142.8, 141.6, 129.4, 127.4, 126.4, 124.6, 123.8, 110.0, 106.5, 103.4, 54.9, 54.4, 33.9, 29.6.

IR (neat): 3307, 2956, 2837, 1640, 1608, 1545, 1496, 1453 cm⁻¹.

HRMS (ESI) calculated for C₁₇H₁₈N₂O₂Na⁺ [M+Na]⁺ 305.1261, found 305.1257.



1-(1,2-diphenylethyl)-3-(3-methoxyphenyl)urea (3n): Prepared from bibenzyl (**1n**) according to Procedure D followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2n** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2n**): 100% (45.7 mg)

NMR Yield (Isocyanation Step): 33%

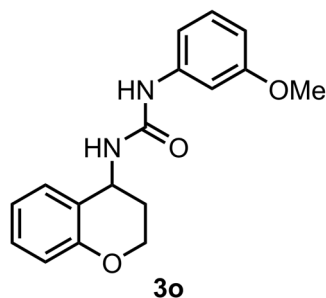
Physical Property: Colorless oil.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.42 (s, 1H), 7.31 (d, *J* = 4.4 Hz, 4H), 7.27 – 7.21 (m, 3H), 7.18 (d, *J* = 7.5 Hz, 3H), 7.10 – 7.04 (m, 2H), 6.78 (d, *J* = 7.0 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.44 (dd, *J* = 8.1, 2.2 Hz, 1H), 4.97 (q, *J* = 8.1 Hz, 1H), 3.67 (s, 3H), 3.03 – 2.97 (m, 2H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.6, 154.3, 143.7, 141.5, 138.4, 129.3, 129.2, 128.2, 128.1, 126.7, 126.4, 126.1, 109.8, 106.6, 103.1, 54.8, 54.6, 42.7,

IR (neat): 3346, 3016, 2945, 1636, 1604, 1545, 1496, 1460, 1278 cm⁻¹.

HRMS (ESI) calculated for C₂₂H₂₂N₂O₂Na⁺ [M+Na]⁺ 369.1574, found 369.1570.



1-(chroman-4-yl)-3-(3-methoxyphenyl)urea (3o): Prepared from chromane (**1o**) according to Procedure B followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2o** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2o**): 96% (40.0 mg)

NMR Yield (Isocyanation Step): 35%

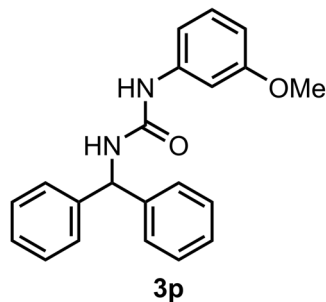
Physical Property: White solid. m.p. = 208 – 210 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.15 – 7.10 (m, 1H), 6.91 – 6.85 (m, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.50 (dd, *J* = 8.1, 2.2 Hz, 1H), 4.87 (q, *J* = 5.7 Hz, 1H), 4.25 (ddd, *J* = 10.0, 6.5, 3.1 Hz, 1H), 4.14 (ddd, *J* = 11.3, 8.7, 2.7 Hz, 1H), 3.71 (s, 3H), 2.10 (ddt, *J* = 13.6, 8.3, 3.5 Hz, 1H), 1.96 (dtd, *J* = 13.6, 6.3, 2.8 Hz, 1H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.7, 154.6, 154.5, 141.5, 129.43, 129.35, 128.6, 123.7, 120.3, 116.5, 110.1, 106.6, 103.5, 63.0, 54.9, 43.0, 29.1.

IR (neat): 3307, 2945, 16899, 1636, 1608, 1555, 1513, 1489 cm⁻¹.

HRMS (ESI) calculated for C₁₇H₁₈N₂O₃Na⁺ [M+Na]⁺ 321.1210, found 321.1207.



1-benzhydryl-3-(3-methoxyphenyl)urea (3p): Prepared from diphenylmethane (**1p**) according to Procedure E followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2p** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2p**): 75% (39.9 mg)

NMR Yield (Isocyanation Step): 40%

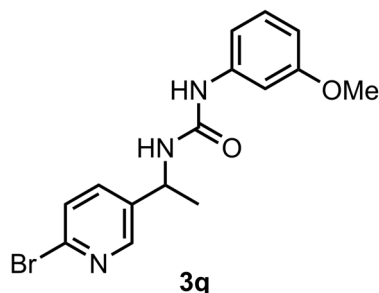
Physical Property: White solid. m.p. = 174 – 176 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 4H), 7.30 (d, *J* = 7.1 Hz, 4H), 7.25 (t, *J* = 7.1 Hz, 2H), 7.16 – 7.08 (m, 3H), 6.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.48 (dd, *J* = 8.2, 2.5 Hz, 1H), 5.95 (d, *J* = 8.0 Hz, 1H), 3.69 (s, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.7, 154.2, 143.1, 141.4, 129.4, 128.5, 126.92, 126.87, 109.8, 106.7, 103.2, 56.8, 54.8.

IR (neat): 3346, 3321, 1647, 1608, 1552, 1499, 1450 cm⁻¹.

HRMS (ESI) calculated for C₂₁H₂₀N₂O₂Na⁺ [M+Na]⁺ 355.1417, found 355.1412.



1-(1-(6-bromopyridin-3-yl)ethyl)-3-(3-methoxyphenyl)urea (3q): Prepared from 2-bromo-5-ethylpyridine (**1q**) according to Procedure E followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2q** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2q**): 99% (27.6 mg)

NMR Yield (Isocyanation Step): 20%

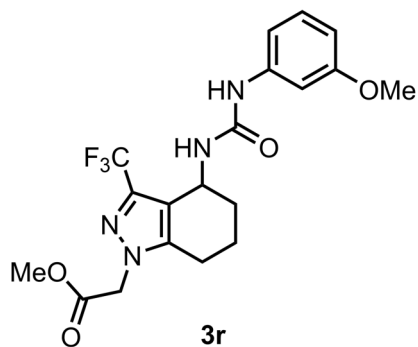
Physical Property: Colorless oil

¹H NMR (¹H NMR (500 MHz, methylene chloride-*d*₂) δ 8.34 (d, *J* = 2.5 Hz, 1H), 7.52 (ddd, *J* = 8.2, 2.5, 0.5 Hz, 1H), 7.43 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 2.3 Hz, 1H), 6.79 (ddd, *J* = 8.0, 2.1, 0.9 Hz, 1H), 6.61 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 6.46 (s, 1H), 5.05 (d, *J* = 7.0 Hz, 1H), 4.96 (p, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, methylene chloride-*d*₂) δ 160.4, 154.2, 148.3, 140.5, 139.8, 139.3, 136.6, 129.8, 127.8, 112.3, 109.0, 106.0, 55.2, 47.2, 21.9.

IR (neat): 3346, 2970, 2931, 2833, 1647, 1601, 1548, 1492, 1453, 1429, 1383 cm⁻¹.

HRMS (ESI) calculated for C₁₅H₁₆BrN₃O₂Na⁺ [M+Na]⁺ 372.0318, found 372.0314.



methyl 2-(4-(3-(3-methoxyphenyl)ureido)-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (3r): Prepared from methyl 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**1r**) according to Procedure E followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2r** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2r**): 82% (43.5 mg)

NMR Yield (Isocyanation Step): 31%

Physical Property: White solid. m.p. = 194 – 196 °C

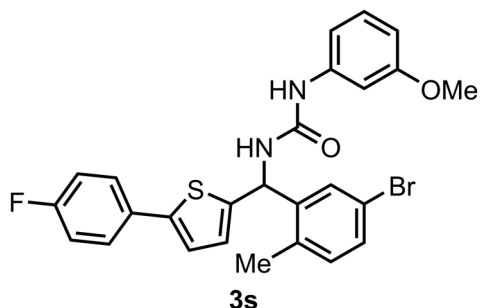
¹H NMR (600 MHz, DMSO-*d*₆) δ 8.19 (s, 1H), 7.15 (t, *J* = 2.3 Hz, 1H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.81 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H), 6.51 – 6.44 (m, 2H), 5.21 – 5.12 (m, 2H), 4.94 – 4.88 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.75 – 2.67 (m, 1H), 2.50 – 2.42 (m, 1H), 1.89 – 1.79 (m, 2H), 1.76 – 1.63 (m, 2H).

¹⁹F NMR (564 MHz, DMSO-*d*₆) δ -60.1.

¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.0, 159.7, 153.8, 143.5, 141.5, 137.4 (q, *J* = 36.6 Hz), 129.4, 121.6 (q, *J* = 269.0 Hz), 115.1, 109.8, 106.6, 103.2, 54.9, 52.5, 50.4, 29.8, 20.3, 17.2.

IR (neat): 3332, 2945, 1755, 1654, 1611, 1552, 1517, 1492 cm⁻¹.

HRMS (ESI) calculated for C₁₉H₂₁F₃N₄O₄Na⁺ [M+Na]⁺ 449.1407, found 449.1403.



1-((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methyl)-3-(3-methoxyphenyl)urea (3s): Prepared from 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (**1s**) according to Procedure C followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2s** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2s**): 97% (124.5 mg)

NMR Yield (Isocyanation Step): 61%

Physical Property: Yellowish solid. m.p. = 185 – 187 °C

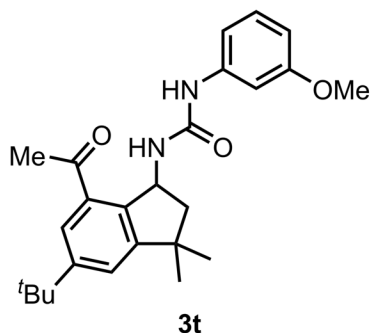
¹H NMR (500 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 7.64 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 3.7 Hz, 1H), 7.24 – 7.18 (m, 3H), 7.16 (t, *J* = 2.2 Hz, 1H), 7.13 (t, *J* = 8.2 Hz, 1H), 6.88 – 6.84 (m, 1H), 6.83 – 6.80 (m, 1H), 6.50 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 2.29 (s, 3H).

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.4.

¹³C NMR (126 MHz, DMSO) δ 161.6 (d, *J* = 245 Hz), 159.7, 153.9, 144.9, 143.1, 141.7, 141.1, 134.7, 132.7, 130.3, 130.1 (d, *J* = 3.2 Hz), 129.5, 128.5, 127.2 (d, *J* = 8.2 Hz), 126.8, 123.5, 119.2, 116.0 (d, *J* = 21.8 Hz), 110.07, 107.05, 103.4, 54.9, 49.5, 18.3.

IR (neat): 3335, 2342, 2096, 1647, 1608, 1552, 1510, 1499, 1467, 1432 cm⁻¹.

HRMS (ESI) calculated for C₂₆H₂₂BrFN₂O₂SN⁺ [M+Na]⁺ 547.0462, found 547.0460.



1-(7-acetyl-5-(*tert*-butyl)-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl)-3-(3-methoxyphenyl)urea (3t): Prepared from celestolide (**1t**) according to Procedure C followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2t** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2t**): 94% (101.5 mg)

NMR Yield (Isocyanation Step): 66%

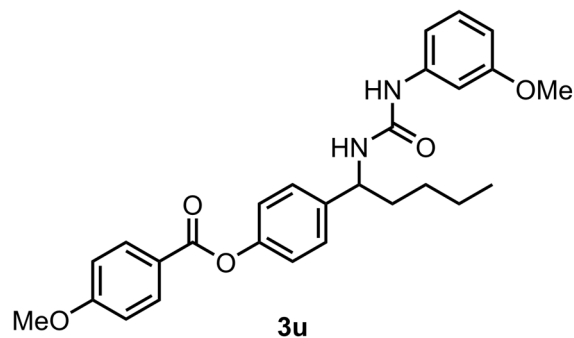
Physical Property: White solid. m.p. = 116 – 118 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.04 (s, 1H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.15 (t, *J* = 2.2 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.81 – 6.76 (m, 1H), 6.47 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.34 (d, *J* = 7.1 Hz, 1H), 5.44 (td, *J* = 7.2, 3.0 Hz, 1H), 3.71 (s, 3H), 2.55 (s, 3H), 2.19 (dd, *J* = 13.2, 7.5 Hz, 1H), 1.91 (dd, *J* = 13.2, 3.1 Hz, 1H), 1.33 (s, 9H), 1.32 (s, 3H), 1.28 (s, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 200.3, 159.7, 154.4, 154.2, 151.9, 141.6, 137.7, 135.3, 129.4, 125.9, 124.5, 124.2, 122.8, 109.7, 106.4, 103.1, 54.8, 52.0, 49.3, 42.1, 34.7, 31.2, 31.0, 29.4, 29.0.

IR (neat): 3342, 2960, 2861, 1682, 1643, 1601, 1548, 1517 cm⁻¹.

HRMS (ESI) calculated for C₂₅H₃₂N₂O₃Na⁺ [M+Na]⁺ 431.2305, found 431.2301.



4-(1-(3-(3-methoxyphenyl)ureido)pentyl)phenyl 4-methoxybenzoate (3u): Prepared from nematal 105 (**1u**) according to Procedure F followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2u** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2u**): 69% (84.7 mg)

NMR Yield (Isocyanation Step): 66%

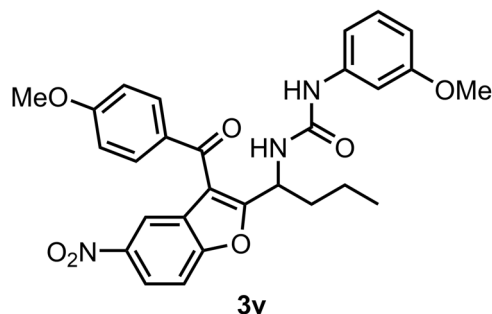
Physical Property: White solid. m.p. = 77 – 79 °C

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (s, 1H), 8.08 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.15 – 7.07 (m, 4H), 6.85 – 6.80 (m, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.46 (dd, *J* = 8.1, 2.2 Hz, 1H), 4.70 (q, *J* = 7.4 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 1.71 (q, *J* = 5.9, 5.3 Hz, 2H), 1.36 – 1.19 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 164.3, 163.7, 159.6, 154.5, 149.3, 142.0, 141.6, 132.0, 129.4, 127.2, 121.7, 121.0, 114.3, 109.9, 106.6, 103.2, 55.6, 54.8, 52.6, 36.4, 28.0, 21.9, 13.9.

IR (neat): 3356, 2956, 2924, 2861, 1745, 1650, 1604, 1562, 15200, 1496 cm⁻¹.

HRMS (ESI) calculated for C₂₇H₃₀N₂O₅Na⁺ [M+Na]⁺ 485.2047, found 485.2042.



1-(1-(3-(4-methoxybenzoyl)-5-nitrobenzofuran-2-yl)butyl)-3-(3-methoxyphenyl)urea (3v): Prepared from (2-butyl-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone (**1v**) according to Procedure E followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2v** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2v**): 72% (55.3 mg)

NMR Yield (Isocyanation Step): 37%

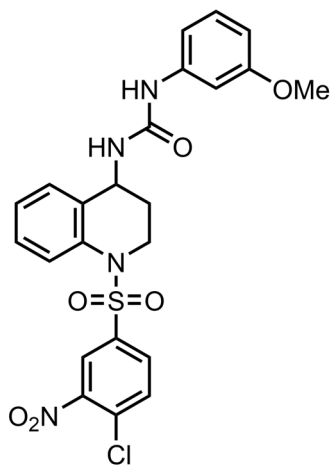
Physical Property: Amorphous solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.44 (s, 1H), 8.27 (dd, *J* = 9.1, 2.4 Hz, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 7.96 (d, *J* = 9.1 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 2H), 7.10 – 7.05 (m, 3H), 6.98 (t, *J* = 2.2 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.74 (ddd, *J* = 8.1, 1.9, 0.7 Hz, 1H), 6.45 (ddd, *J* = 8.2, 2.5, 0.7 Hz, 1H), 5.04 (q, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 1.87 (q, *J* = 7.5 Hz, 2H), 1.38 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.26 (dq, *J* = 14.7, 7.4 Hz, 1H), 0.85 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 188.1, 165.0, 163.6, 159.6, 155.7, 154.2, 144.2, 141.1, 131.7, 130.4, 129.4, 127.2, 120.8, 117.1, 116.6, 114.2, 112.6, 110.0, 106.7, 103.5, 55.6, 54.8, 46.5, 35.3, 18.7, 13.3.

IR (neat): 3353, 2956, 2938, 2847, 1650, 1601, 1559, 1531, 1460 cm⁻¹.

HRMS (ESI) calculated for C₂₈H₂₇N₃O₇Na⁺ [M+Na]⁺ 540.1741, found 540.1739.



3w

1-(1-((4-chloro-3-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(3-methoxyphenyl)urea

(3w): Prepared from 1-((4-chloro-3-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline (**1w**) according to Procedure B followed by General Procedure for Urea Formation. The NMR yield of the isocyanate intermediate **2w** was measured from an identical reaction in parallel.

Isolated Yield (Urea Formation Step from Isocyanate **2w**): 68% (46.4 mg)

NMR Yield (Isocyanation Step): 33%

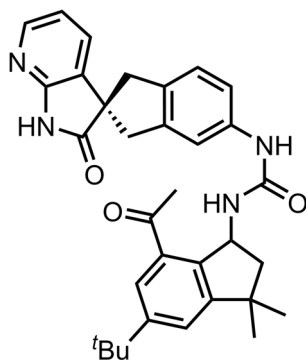
Physical Property: White solid. m.p. = 81 – 83 °C

¹H NMR (500 MHz, methylene chloride-*d*₂) δ 8.12 (d, *J* = 2.2 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.30 (ddd, *J* = 8.5, 7.3, 1.7 Hz, 1H), 7.23 – 7.14 (m, 2H), 6.97 (t, *J* = 2.3 Hz, 1H), 6.79 (ddd, *J* = 8.0, 2.1, 0.9 Hz, 1H), 6.61 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 6.30 (s, 1H), 4.84 – 4.74 (m, 2H), 4.03 (ddd, *J* = 13.9, 7.5, 3.8 Hz, 1H), 3.83 (ddd, *J* = 13.9, 8.5, 3.6 Hz, 1H), 3.76 (s, 3H), 1.94 (dddd, *J* = 13.6, 8.8, 5.4, 3.8 Hz, 1H), 1.82 (dddd, *J* = 13.6, 7.5, 6.0, 3.6 Hz, 1H).

¹³C NMR (126 MHz, methylene chloride-*d*₂) δ 160.8, 154.5, 148.2, 140.10, 140.05, 136.4, 133.6, 132.4, 131.4, 130.6, 130.3, 129.6, 128.9, 126.4, 124.7, 124.0, 112.8, 109.5, 106.6, 55.64, 46.3, 44.8, 29.4.

IR (neat): 3363, 2917, 2847, 2356, 1657, 1604, 1555, 1492, 1453, 1352 cm⁻¹.

HRMS (ESI) calculated for C₂₃H₂₁ClN₄O₆SNa⁺ [M+Na]⁺ 539.0763, found 539.0759.



A-a-1

1-(7-acetyl-5-(tert-butyl)-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl)-3-((*S*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl)urea (A-a-1): Prepared from celestolide (**1t**) and (*S*)-5-amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (**a-1**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1t** in 0.2 mmol scale according to Procedure C followed by General Procedure for Urea Formation using **a-1**. The NMR yield of the isocyanate intermediate **2t** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2t):** 48%

Isolated Yield (Urea Formation Step from Isocyanate **2t):** 46%, d.r. = 1:1 (32.6 mg)

NMR Yield (Isocyanation Step): 66%

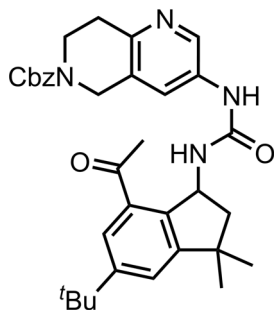
Physical Property: Light yellow solid. m.p. = 130 – 132 °C

¹H NMR (500 MHz, methylene chloride-*d*₂) δ 9.05 (s, 1H), 8.07 (d, *J* = 5.1 Hz, 1H), 7.58 (d, *J* = 1.4 Hz, 1H), 7.39 (s, 1H), 7.33 (d, *J* = 16.8 Hz, 1H), 7.19 – 7.07 (m, 2H), 6.86 (d, *J* = 11.5 Hz, 1H), 6.81 (ddd, *J* = 7.1, 5.3, 1.4 Hz, 1H), 5.53 (td, *J* = 7.3, 4.5 Hz, 1H), 5.19 – 5.09 (m, 1H), 3.51 (dd, *J* = 15.6, 11.0 Hz, 2H), 3.08 – 2.97 (m, 2H), 2.57 (s, 3H), 2.38 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.03 (dt, *J* = 13.2, 4.5 Hz, 1H), 1.38 – 1.24 (m, 15H).

¹³C NMR (126 MHz, methylene chloride-*d*₂) δ 201.91, 201.86, 180.3, 155.4, 155.2, 154.58, 154.57, 152.5, 146.5, 141.87, 141.85, 138.4, 137.6, 135.66, 135.64, 135.4, 130.4, 129.6, 124.9, 124.8, 124.7, 123.14, 123.13, 119.4, 118.3, 116.7, 54.8, 49.80, 49.78, 43.5, 43.0, 42.4, 34.8, 31.1, 30.5, 30.4, 29.5, 28.9, 28.8.

IR (neat): 3340, 2970, 2931, 2879, 1724, 1703, 1661, 1615, 1548, 1432, 1243 cm⁻¹.

HRMS (ESI) calculated for C₃₃H₃₆N₄O₃Na⁺ [M+Na]⁺ 559.2680, found 559.2673.



A-a-11

benzyl 3-(3-(7-acetyl-5-(*tert*-butyl)-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl)ureido)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (A-a-11): Prepared from celestolide (**1t**) and benzyl 3-amino-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (**a-11**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1t** in 0.2 mmol scale according to Procedure C followed by General Procedure for Urea Formation using **a-11**. The NMR yield of the isocyanate intermediate **2t** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2t**): 55%

Isolated Yield (Urea Formation Step from Isocyanate **2t**): 62% (46.5 mg)

NMR Yield (Isocyanation Step): 66%

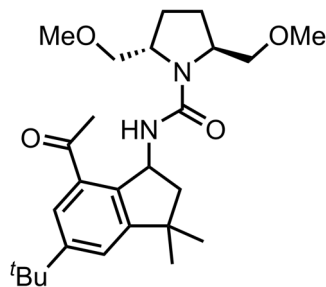
Physical Property: White solid. m.p. = 113 – 115 °C

¹H NMR (500 MHz, methylene chloride-*d*₂) δ 8.37 – 8.00 (m, 1H), 7.84 – 7.62 (m, 1H), 7.58 (d, *J* = 1.4 Hz, 1H), 7.42 – 7.29 (m, 6H), 7.23 (s, 1H), 5.48 (td, *J* = 7.2, 4.1 Hz, 1H), 5.33 – 5.28 (m, 1H), 5.15 – 5.08 (m, 2H), 4.68 – 4.49 (m, 2H), 3.76 – 3.68 (m, 2H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.52 (s, 3H), 2.32 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.01 (dd, *J* = 13.3, 4.1 Hz, 1H), 1.35 – 1.25 (m, 15H).

¹³C NMR (126 MHz, methylene chloride-*d*₂) δ 202.1, 155.6, 155.5, 155.1, 153.0, 148.6, 148.5, 139.4, 137.9, 137.3, 135.8, 134.8, 128.9, 128.4, 128.2, 125.5, 124.8, 123.7, 67.5, 50.0, 45.5, 42.8, 42.1, 41.9, 35.2, 31.8, 31.5, 31.0, 29.9, 29.1.

IR (neat): 3342, 2956, 2865, 1689, 1657, 1548, 1471, 1425, 1404 cm⁻¹.

HRMS (ESI) calculated for C₃₄H₄₀N₄O₄Na⁺ [M+Na]⁺ 591.2942, found 591.2934.



A-h-2

(2*S*,5*S*)-*N*-(7-acetyl-5-(*tert*-butyl)-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl)-2,5-bis(methoxymethyl)pyrrolidine-1-carboxamide (A-h-2): Prepared from celestolide (**1t**) and (2*S*,5*S*)-2,5-bis(methoxymethyl)pyrrolidine (**h-2**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1t** in 0.2 mmol scale according to Procedure C followed by General Procedure for Urea Formation using **h-2**. The NMR yield of the isocyanate intermediate **2t** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2t**): 57%

Isolated Yield (Urea Formation Step from Isocyanate **2t**): 76%, d.r. = 1:1 (44.6 mg)

NMR Yield (Isocyanation Step): 66%

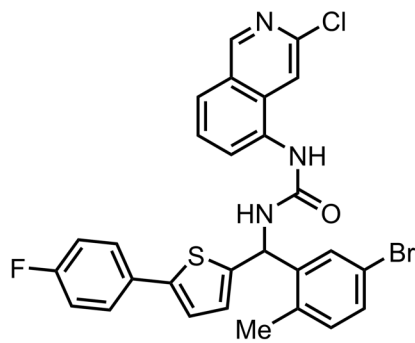
Physical Property: Colorless oil.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.47 – 7.40 (m, 2H), 6.48 (dd, *J* = 38.9, 7.9 Hz, 1H), 5.61 – 5.48 (m, 1H), 3.96 – 3.78 (m, 2H), 3.41 – 3.30 (m, 2H), 3.24 – 3.06 (m, 8H), 2.46 (d, *J* = 6.2 Hz, 3H), 2.24 (ddd, *J* = 44.3, 12.6, 7.6 Hz, 1H), 1.91 (td, *J* = 9.1, 7.8, 2.8 Hz, 2H), 1.83 – 1.62 (m, 3H), 1.37 – 1.29 (m, 12H), 1.22 (d, *J* = 14.2 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 201.9, 201.5, 155.3, 153.49, 153.48, 150.93, 150.89, 138.3, 138.0, 136.61, 136.58, 123.2, 123.1, 122.0, 121.9, 72.7, 71.9, 58.3, 58.2, 55.7, 52.6, 52.2, 50.2, 49.9, 41.7, 41.6, 34.6, 31.2, 30.0, 29.9, 29.48, 29.45, 29.2, 29.1, 25.9.

IR (neat): 3304, 2963, 2935, 2872, 2826, 1689, 1654, 1520 cm⁻¹.

HRMS (ESI) calculated for C₂₆H₄₀N₂O₄Na⁺ [M+Na]⁺ 467.2880, found 467.2874.



B-b-4

1-((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methyl)-3-(3-chloroisoquinolin-5-yl)urea (B-b-4): Prepared from 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (**1s**) and 3-chloroisoquinolin-5-amine (**b-4**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1s** in 0.2 mmol scale according to Procedure C followed by General Procedure for Urea Formation using **b-4**. The NMR yield of the isocyanate intermediate **2s** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2s):** 54%

Isolated Yield (Urea Formation Step from Isocyanate **2s):** 70% (49.5 mg)

NMR Yield (Isocyanation Step): 61%

Physical Property: Brown solid. m.p. = 200 – 202 °C

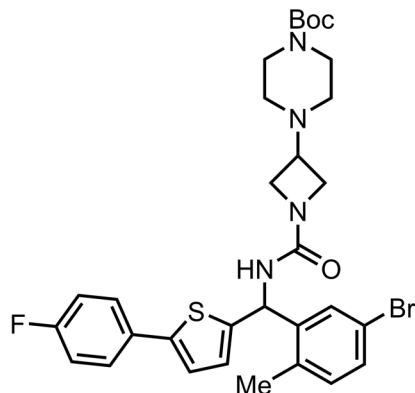
¹H NMR (400 MHz, DMSO-*d*₆) δ 9.19 (s, 1H), 8.78 (s, 1H), 8.34 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.07 (s, 1H), 7.79 (dd, *J* = 19.1, 8.0 Hz, 2H), 7.70 – 7.56 (m, 4H), 7.45 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.38 (d, *J* = 3.7 Hz, 1H), 7.28 – 7.17 (m, 3H), 6.92 (dd, *J* = 3.7, 1.0 Hz, 1H), 6.35 (d, *J* = 7.7 Hz, 1H), 2.31 (s, 3H).

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.4.

¹³C NMR (126 MHz, DMSO-*d*₆) δ 161.7 (d, *J* = 245.4 Hz), 154.1, 153.5, 144.6, 143.0, 141.9, 134.8, 133.8, 132.8, 130.4, 130.1 (d, *J* = 3.2 Hz), 129.6, 128.4, 128.1, 127.7, 127.3 (d, *J* = 8.1 Hz), 127.1, 123.6, 121.7, 120.2, 119.2, 116.0 (d, *J* = 21.8 Hz), 113.9, 49.8, 18.3.

IR (neat): 3321, 3065, 1436, 1548, 1510, 1467, 1436 cm⁻¹.

HRMS (ESI) calculated for C₂₈H₂₀BrClFN₃OSNa⁺ [M+Na]⁺ 602.0075, found 602.0074.



B-d-9

tert-butyl 4-(1-(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methyl)carbamoyl)azetidin-3-yl)piperazine-1-carboxylate (**B-d-9**): Prepared from 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (**1s**) and *tert*-butyl 4-(azetidin-3-yl)piperazine-1-carboxylate (**d-9**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1s** in 0.2 mmol scale according to Procedure C followed by General Procedure for Urea Formation using **d-9**. The NMR yield of the isocyanate intermediate **2s** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2s**): 70%

Isolated Yield (Urea Formation Step from Isocyanate **2s**): 91% (71.4 mg)

NMR Yield (Isocyanation Step): 61%

Physical Property: White solid. m.p. = 179 – 181 °C

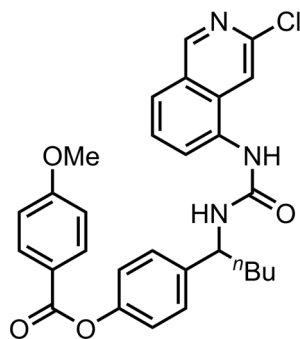
¹H NMR (500 MHz, methylene chloride-*d*₂) δ 7.55 – 7.50 (m, 2H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.36 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.11 – 7.04 (m, 4H), 6.68 (d, *J* = 3.7 Hz, 1H), 6.34 (d, *J* = 7.5 Hz, 1H), 4.83 (d, *J* = 7.6 Hz, 1H), 3.96 (q, *J* = 7.9 Hz, 2H), 3.82 (dt, *J* = 7.8, 5.1 Hz, 2H), 3.41 (t, *J* = 5.0 Hz, 4H), 3.19 – 3.11 (m, 1H), 2.29 (d, *J* = 14.2 Hz, 7H), 1.43 (s, 9H).

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.6.

¹³C NMR (126 MHz, Methylene Chloride-*d*₂) δ 162.8 (d, *J* = 246.7 Hz), 158.0, 154.9, 145.2, 143.5, 143.0, 135.6, 132.8, 131.0, 130.9 (d, *J* = 3.3 Hz), 129.3, 127.7 (d, *J* = 8.0 Hz), 127.3, 123.2, 120.2, 116.2 (d, *J* = 21.9 Hz), 79.8, 53.5, 50.97, 49.76, 28.50, 18.99.

IR (neat): 3297, 2988, 2875, 2809, 1692, 1636, 1524, 1510, 1482, 1457 cm⁻¹.

HRMS (ESI) calculated for C₃₁H₃₆BrFN₄O₃SN⁺ [M+Na]⁺ 665.1568, found 665.1565.



C-b-4

4-(1-(3-(3-chloroisoquinolin-5-yl)ureido)pentyl)phenyl 4-methoxybenzoate (C-b-4): Prepared from nematal 105 (**1u**) and 3-chloroisoquinolin-5-amine (**b-4**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1u** in 0.2 mmol scale according to Procedure F followed by General Procedure for Urea Formation using **b-4**. The NMR yield of the isocyanate intermediate **2u** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2u**): 44%

Isolated Yield (Urea Formation Step from Isocyanate **2u**): 60% (40.8 mg)

NMR Yield (Isocyanation Step): 66%

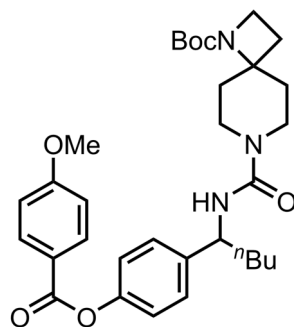
Physical Property: Brown oil.

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.17 (s, 1H), 8.69 (s, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.12 – 8.04 (m, 3H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.27 – 7.22 (m, 2H), 7.12 (dd, *J* = 8.4, 3.9 Hz, 3H), 4.78 (q, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 1.78 (p, *J* = 7.8, 6.6 Hz, 2H), 1.43 – 1.27 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 164.2, 163.7, 154.5, 153.4, 149.4, 144.4, 141.6, 134.2, 132.0, 129.3, 128.1, 127.7, 127.3, 121.8, 121.1, 121.0, 119.6, 114.3, 113.8, 55.6, 52.8, 36.4, 28.0, 21.9, 13.9.

IR (neat): 2924, 2861, 2500, 2166, 2036, 1966, 1734, 1647, 1601, 1545 cm⁻¹.

HRMS (ESI) calculated for C₂₉H₂₈ClN₃O₄Na⁺ [M+Na]⁺ 540.1661, found 540.1656.



C-g-8

tert-butyl 7-((1-(4-((4-methoxybenzoyl)oxy)phenyl)pentyl)carbamoyl)-1,7-diazaspiro[3.5]nonane-1-carboxylate (C-g-8): Prepared from nematal 105 (**1u**) and tert-butyl 7-carbamoyl-1,7-diazaspiro[3.5]nonane-1-carboxylate (**g-8**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1u** in 0.2 mmol scale according to Procedure F followed by General Procedure for Urea Formation using **g-8**. The NMR yield of the isocyanate intermediate **2u** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2u):** 41%

Isolated Yield (Urea Formation Step from Isocyanate **2u):** 73% (54.6 mg)

NMR Yield (Isocyanation Step): 66%

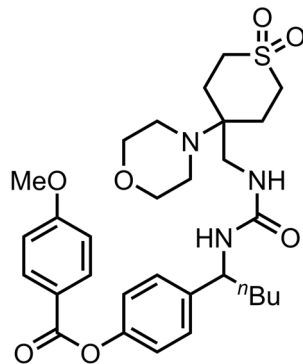
Physical Property: White solid. m.p. = 86 – 88 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.12 – 8.03 (m, 2H), 7.41 – 7.31 (m, 2H), 7.19 – 7.09 (m, 4H), 6.82 – 6.74 (m, 1H), 4.68 (q, *J* = 8.0 Hz, 1H), 3.99 (d, *J* = 13.5 Hz, 2H), 3.87 (s, 3H), 3.78 – 3.59 (m, 2H), 2.70 – 2.53 (m, 2H), 2.07 – 1.58 (m, 8H), 1.41 – 1.25 (m, 13H), 0.86 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 164.3, 163.7, 156.7, 154.3, 149.0, 143.1, 131.9, 127.3, 121.4, 121.0, 114.3, 78.2, 67.1, 55.6, 53.6, 42.5, 40.6, 36.1, 34.4, 28.6, 28.2, 26.5, 21.9, 13.9.

IR (neat): 2974, 2935, 2847, 1734, 1703, 1625, 1608, 1590, 1531, 1520 cm⁻¹.

HRMS (ESI) calculated for C₃₂H₄₃N₃O₆Na⁺ [M+Na]⁺ 588.3044, found 588.3037.



C-h-6

4-(1-(3-((4-morpholino-1,1-dioxido-2H-thiopyran-4-yl)methyl)ureido)pentyl)phenyl 4-methoxybenzoate (C-h-6): Prepared from nematal 105 (**1u**) and 4-(aminomethyl)-4-morpholinotetrahydro-2H-thiopyran 1,1-dioxide (**h-6**) according to High-Throughput Experiment Procedure.

For a single pot reaction, the reaction was carried out from **1u** in 0.2 mmol scale according to Procedure F followed by General Procedure for Urea Formation using **h-6**. The NMR yield of the isocyanate intermediate **2u** was measured from an identical reaction in parallel.

UPLC Area Percentage (Urea Formation Step from Isocyanate **2u):** 45%

Isolated Yield (Urea Formation Step from Isocyanate **2u):** 98% (75.8 mg)

NMR Yield (Isocyanation Step): 66%

Physical Property: Amorphous solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.9 Hz, 2H), 6.40 (d, *J* = 8.5 Hz, 1H), 5.88 (t, *J* = 6.4 Hz, 1H), 4.63 (q, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 3.55 (s, 4H), 3.19 – 3.00 (m, 4H), 2.58 – 2.49 (m, 4H), 2.16 – 2.02 (m, 2H), 1.89 – 1.74 (m, 2H), 1.70 – 1.58 (m, 2H), 1.35 – 1.16 (m, 4H), 0.85 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 164.3, 163.7, 157.4, 149.1, 142.5, 131.9, 127.1, 121.6, 121.0, 114.3, 67.2, 56.1, 55.6, 52.7, 46.3, 45.0, 41.0, 36.6, 28.2, 28.0, 21.9, 13.9.

IR (neat): 3363, 2970, 2931, 2851, 1738, 1654, 1608, 1562, 1520, 1460, 1457 cm⁻¹.

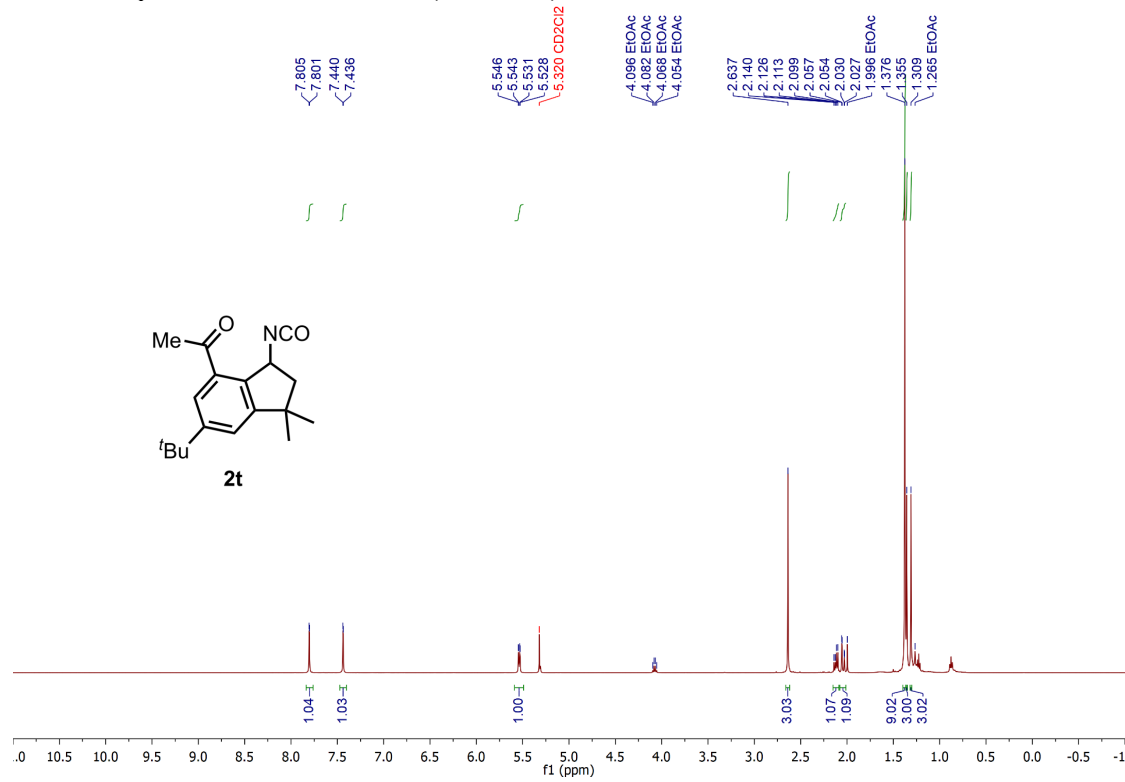
HRMS (ESI) calculated for C₃₀H₄₁N₃O₇SNa⁺ [M+Na]⁺ 610.2557, found 610.2552.

10. References

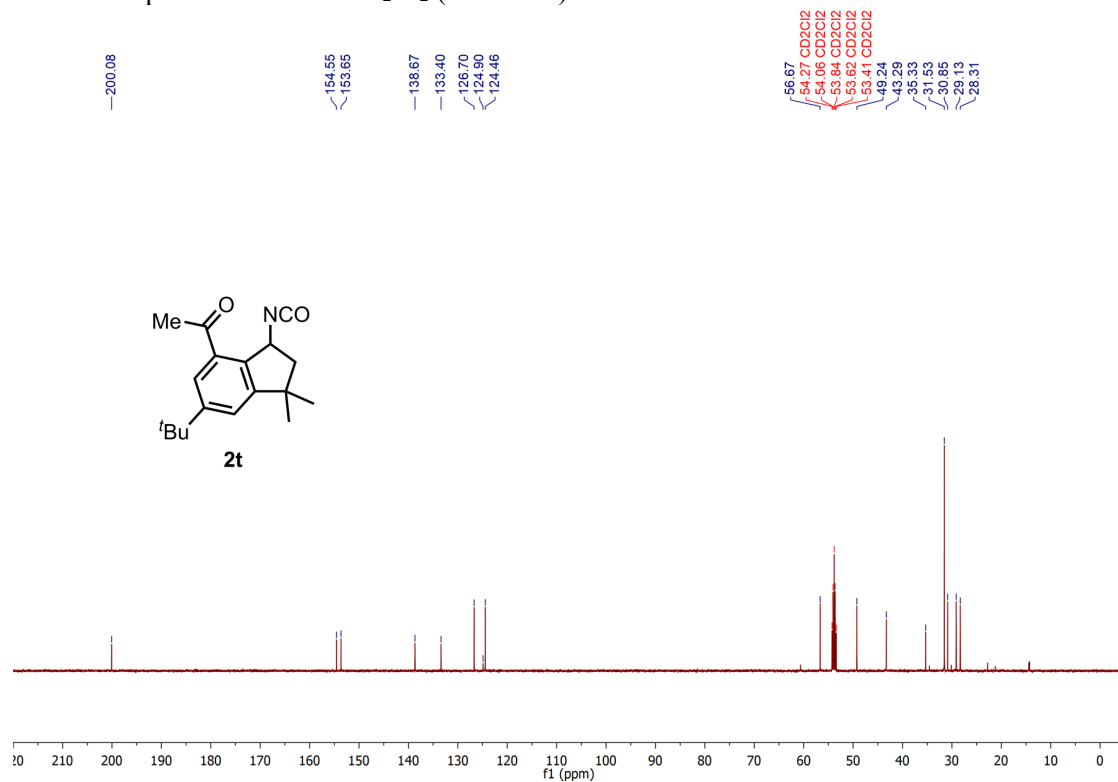
1. T. A. Wenderski, C. F. Stratton, R. A. Bauer, F. Kopp and D. S. Tan, In *Chemical Biology. Methods and Protocols*; eds. J. E. Hempel, C. H. Williams and C. C. Hong, Humana Press, New York, 2015, Vol. 1263, Chapter 18, p. 225–242.
2. T. Nakagawa, M. Amakatsu, K. Munenobu, H. Fujii and M. Yamanaka, *Chem. Lett.* 2013, **42**, 229–231.

11. NMR Spectra of Characterized Compounds

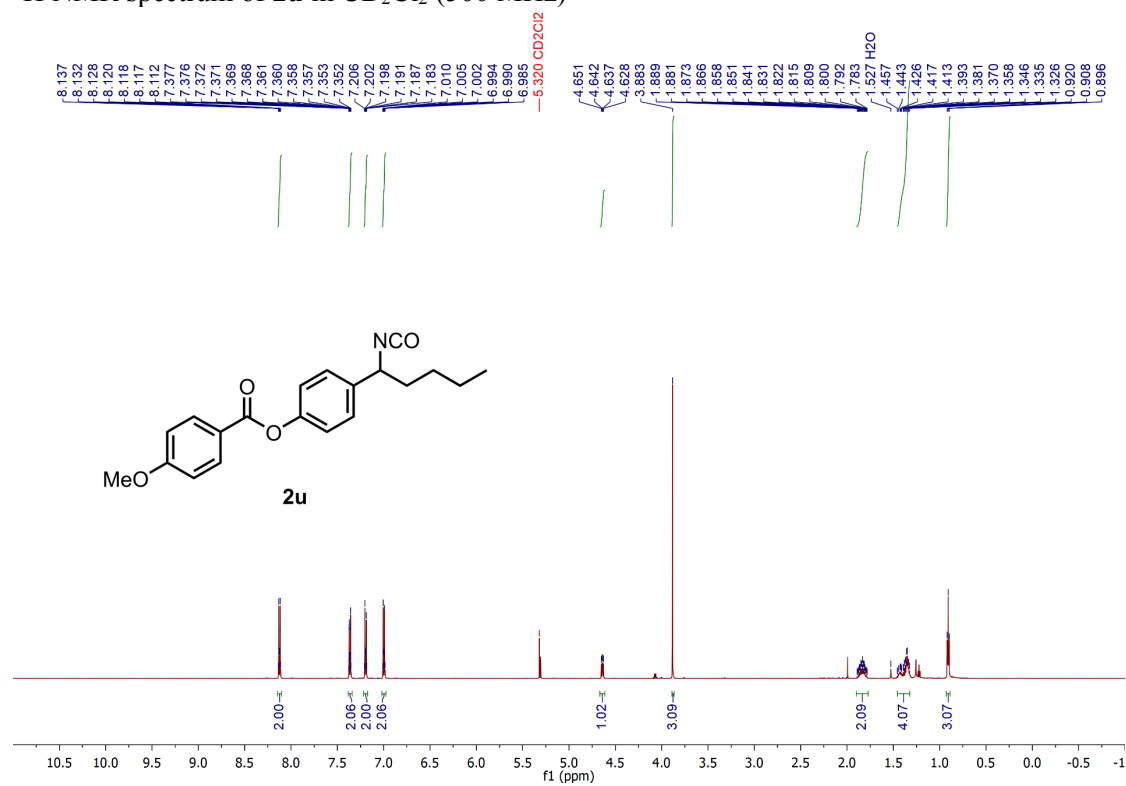
^1H NMR spectrum of **2t** in CD_2Cl_2 (500 MHz)



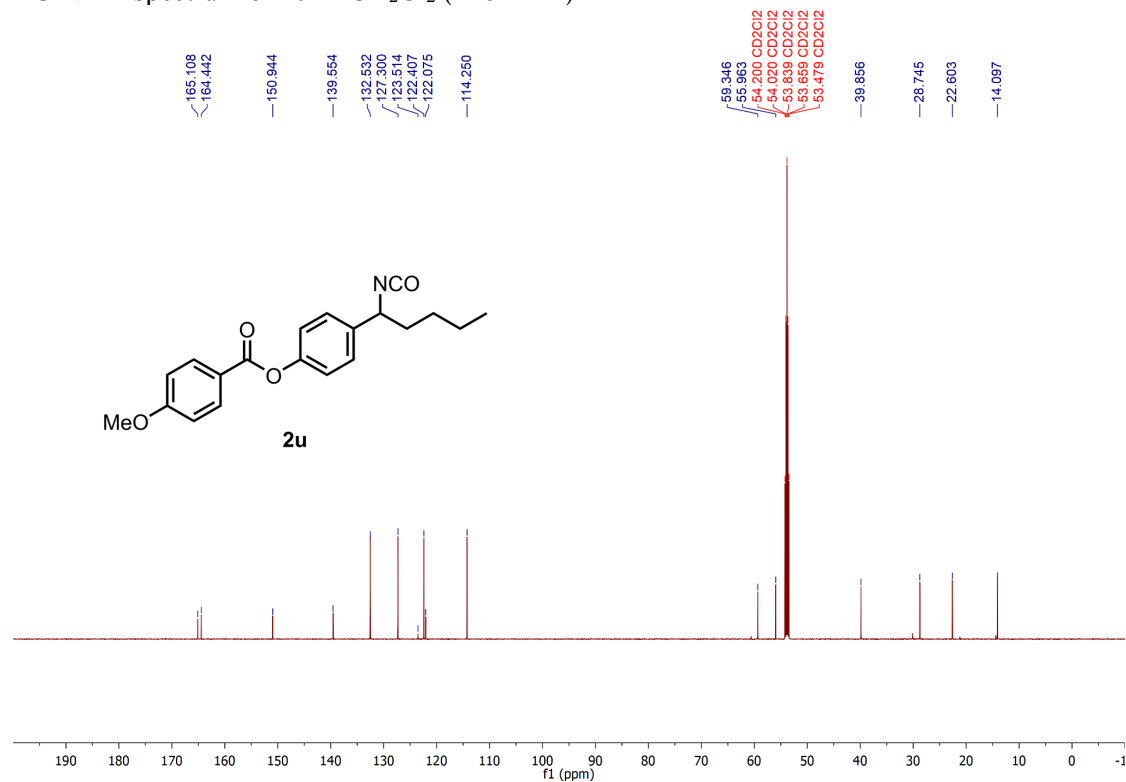
^{13}C NMR spectrum of **2t** in CD_2Cl_2 (126 MHz)



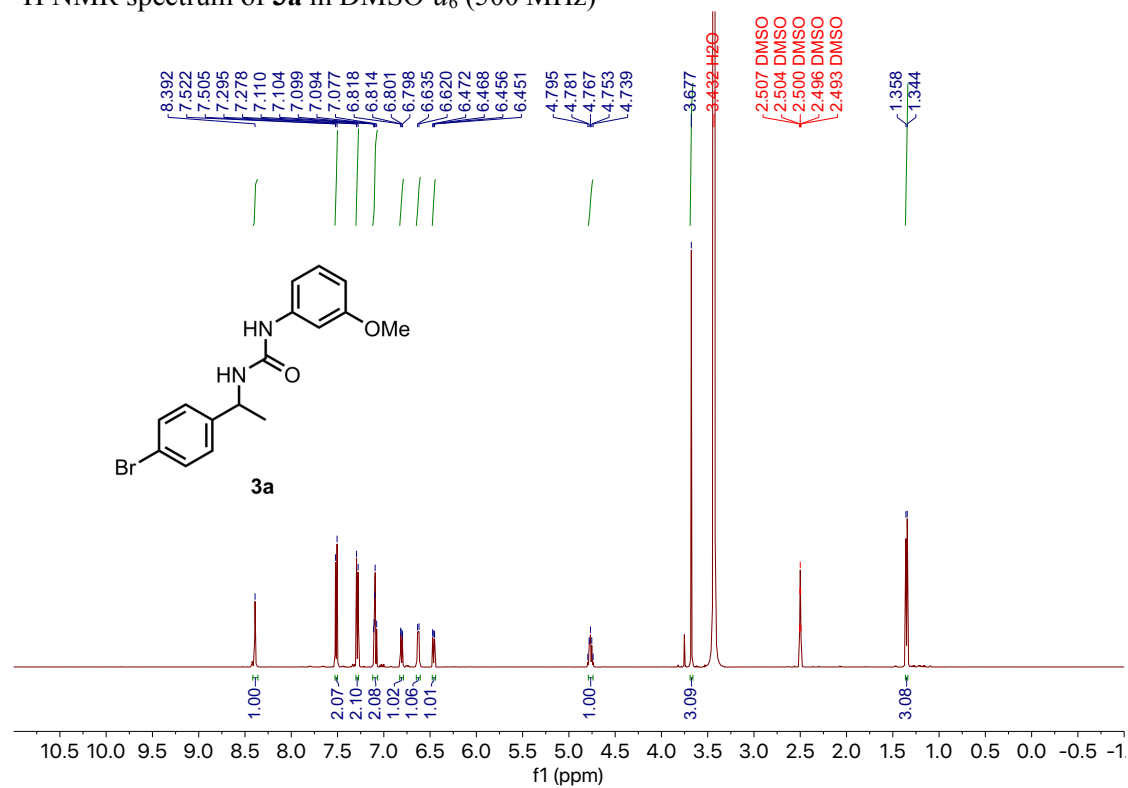
^1H NMR spectrum of **2u** in CD_2Cl_2 (500 MHz)



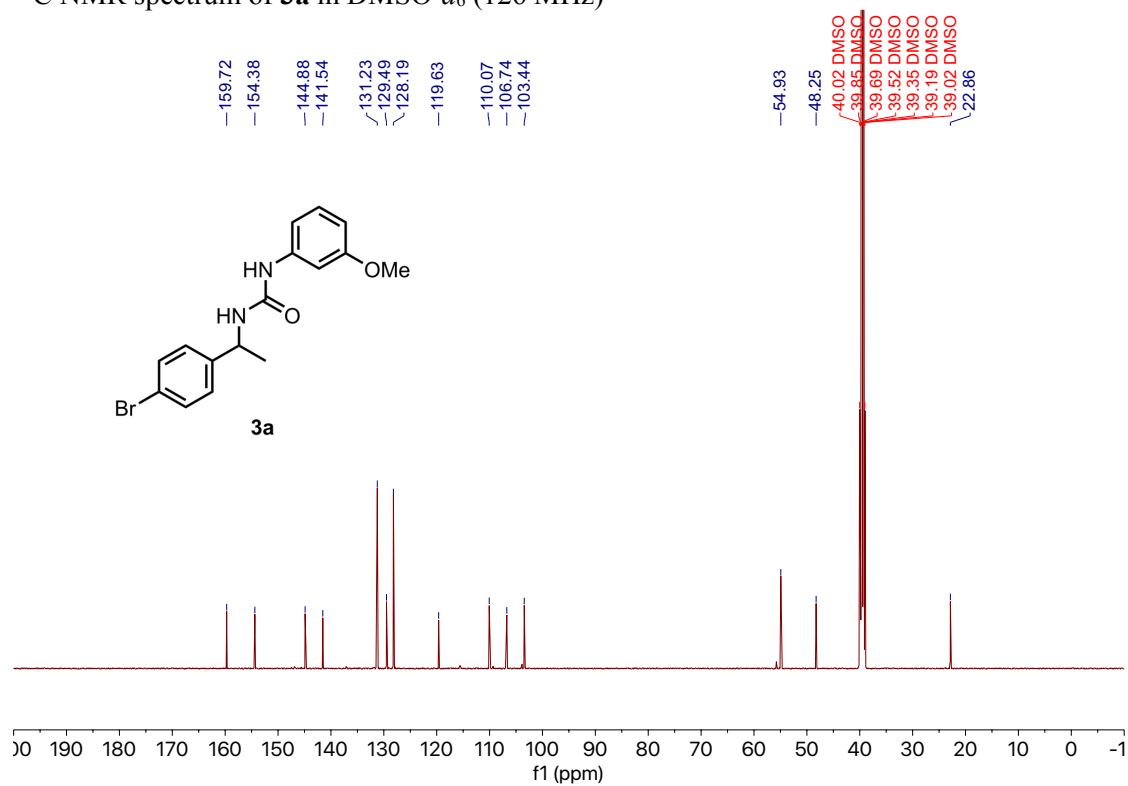
^{13}C NMR spectrum of **2u** in CD_2Cl_2 (126 MHz)



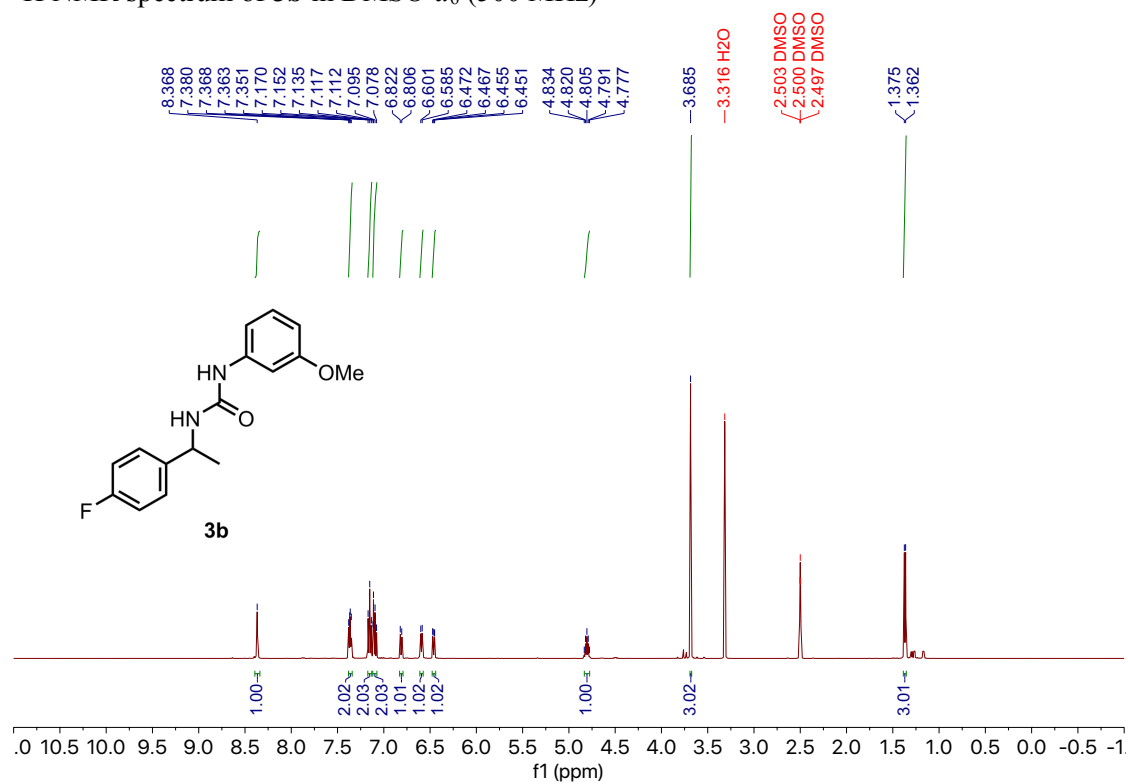
^1H NMR spectrum of **3a** in $\text{DMSO-}d_6$ (500 MHz)



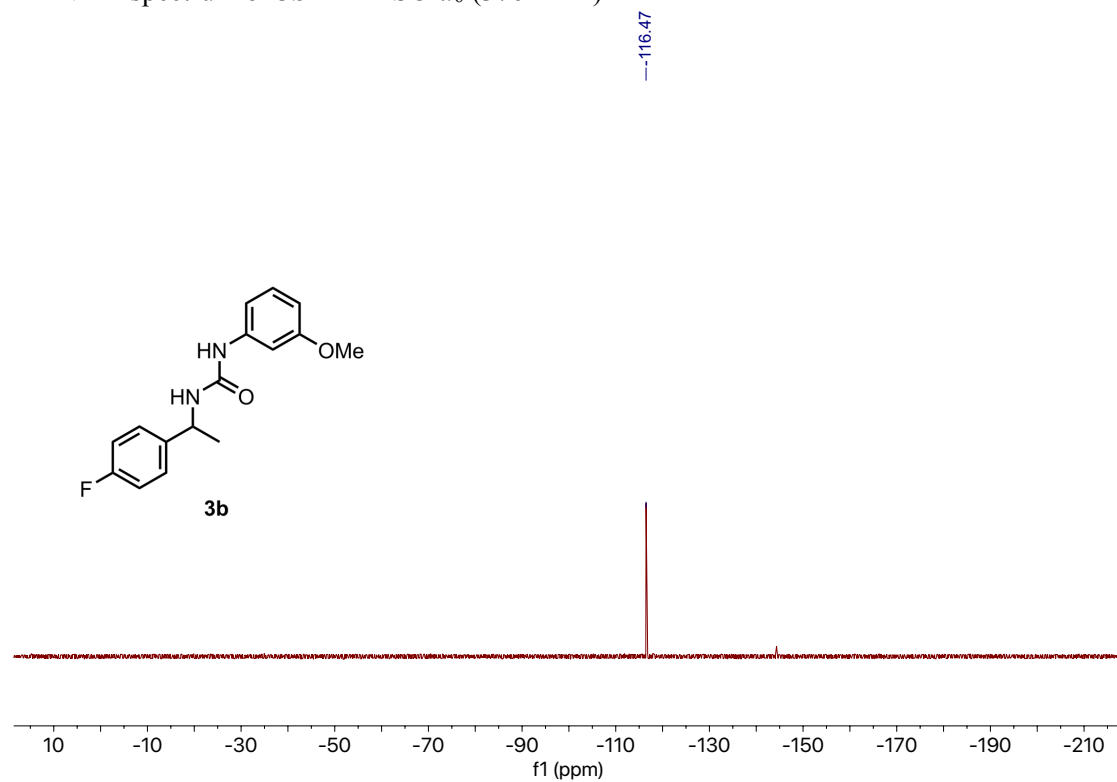
^{13}C NMR spectrum of **3a** in $\text{DMSO-}d_6$ (126 MHz)



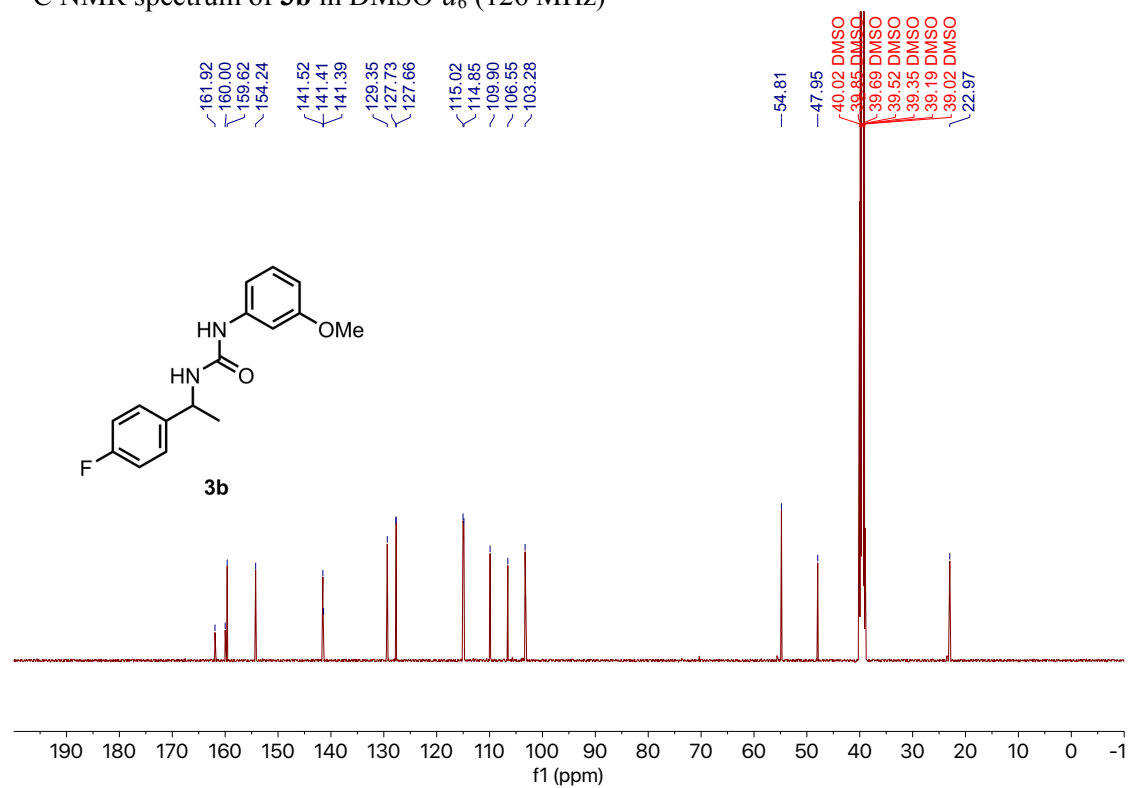
^1H NMR spectrum of **3b** in $\text{DMSO-}d_6$ (500 MHz)



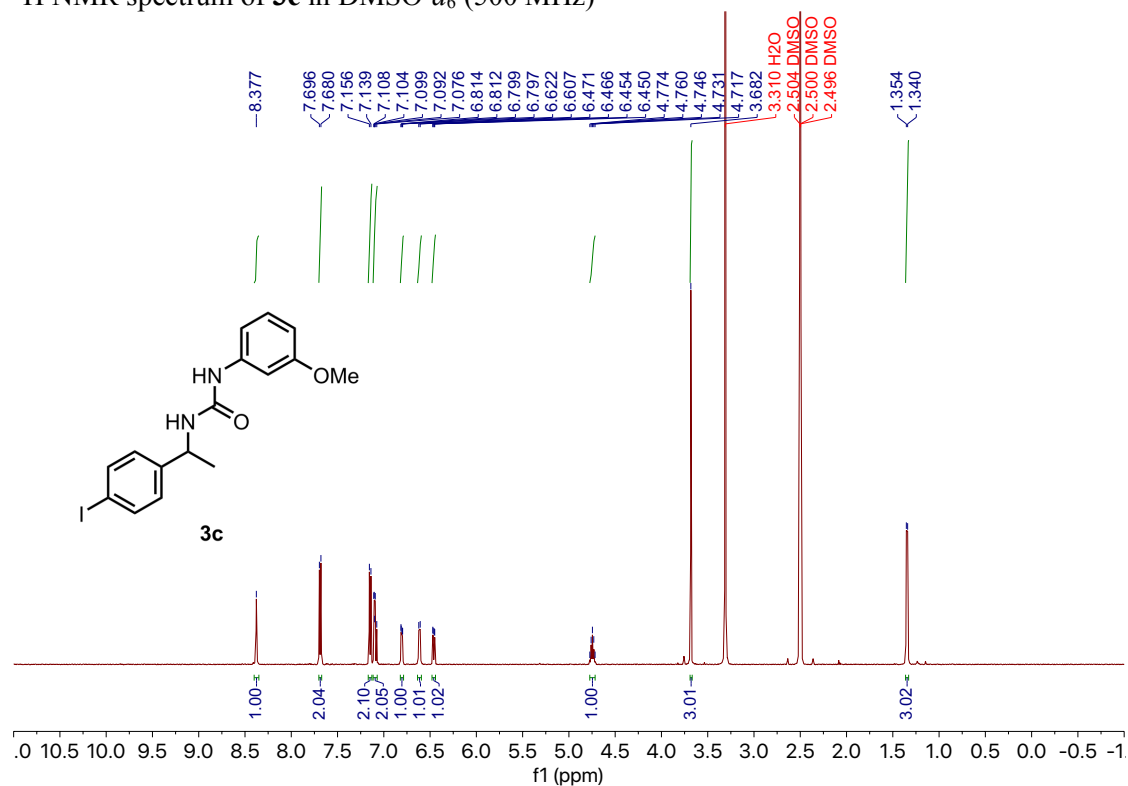
^{19}F NMR spectrum of **3b** in $\text{DMSO-}d_6$ (376 MHz)



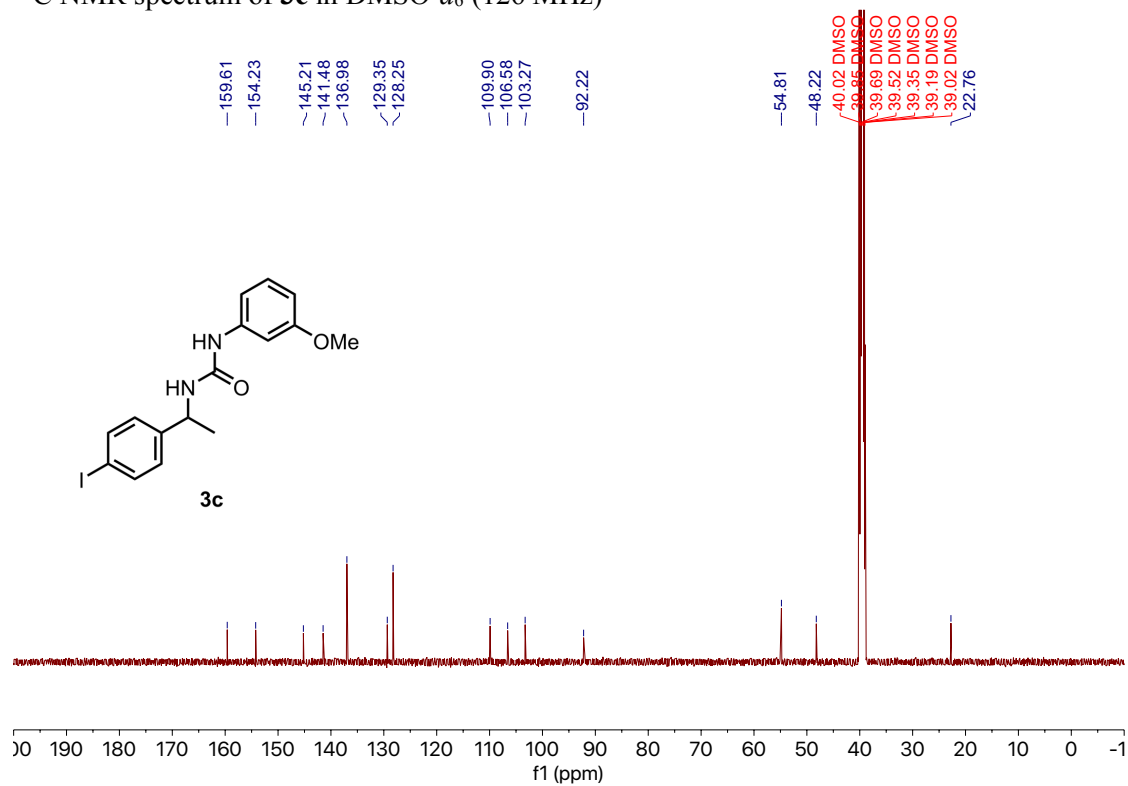
^{13}C NMR spectrum of **3b** in $\text{DMSO-}d_6$ (126 MHz)



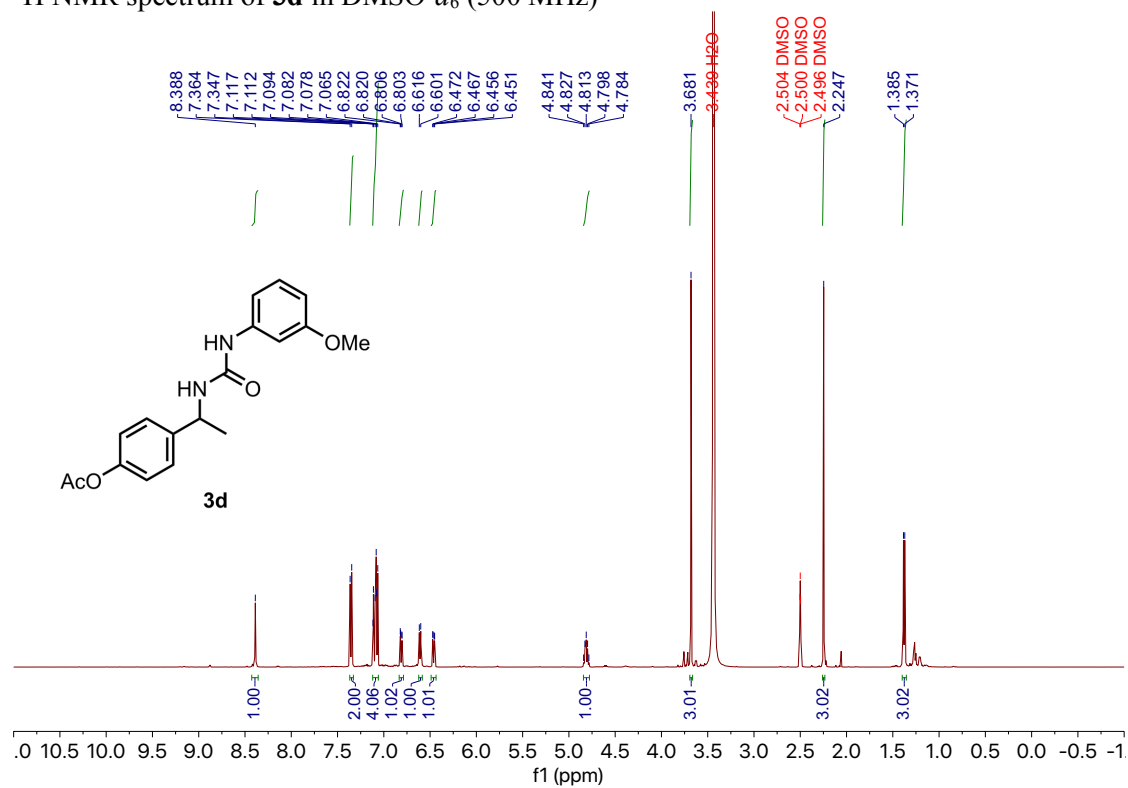
¹H NMR spectrum of **3c** in DMSO-*d*₆ (500 MHz)



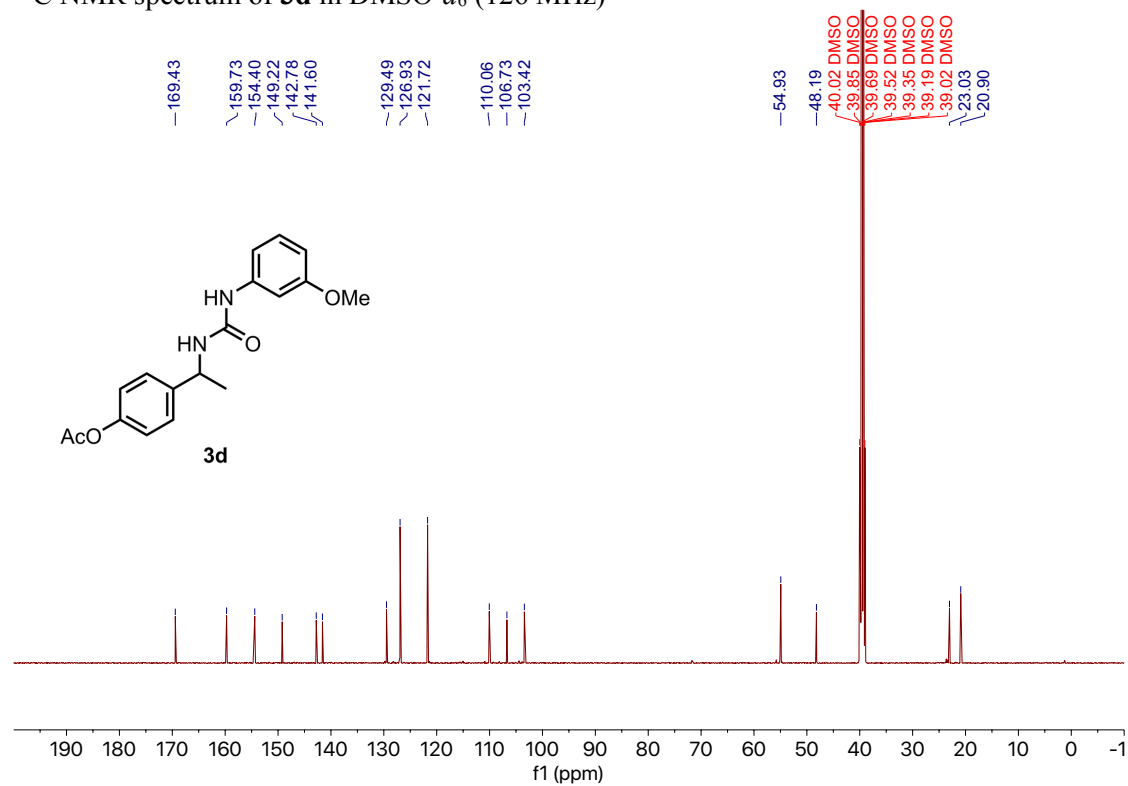
¹³C NMR spectrum of **3c** in DMSO-*d*₆ (126 MHz)



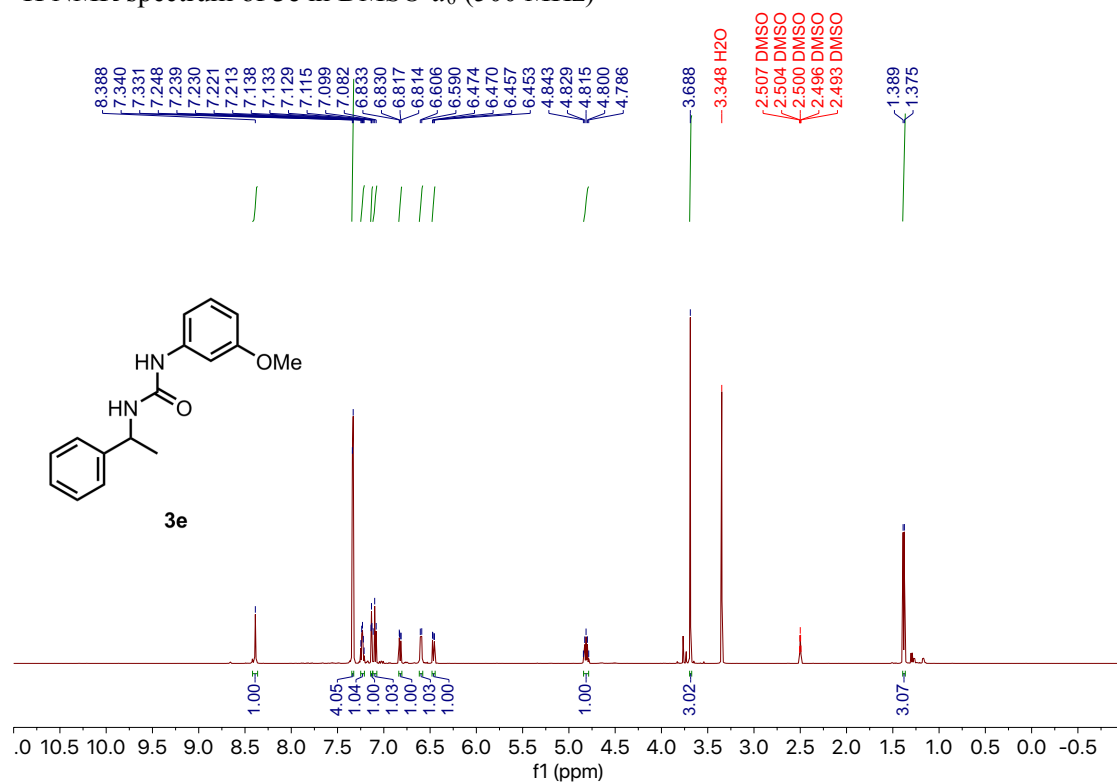
^1H NMR spectrum of **3d** in $\text{DMSO-}d_6$ (500 MHz)



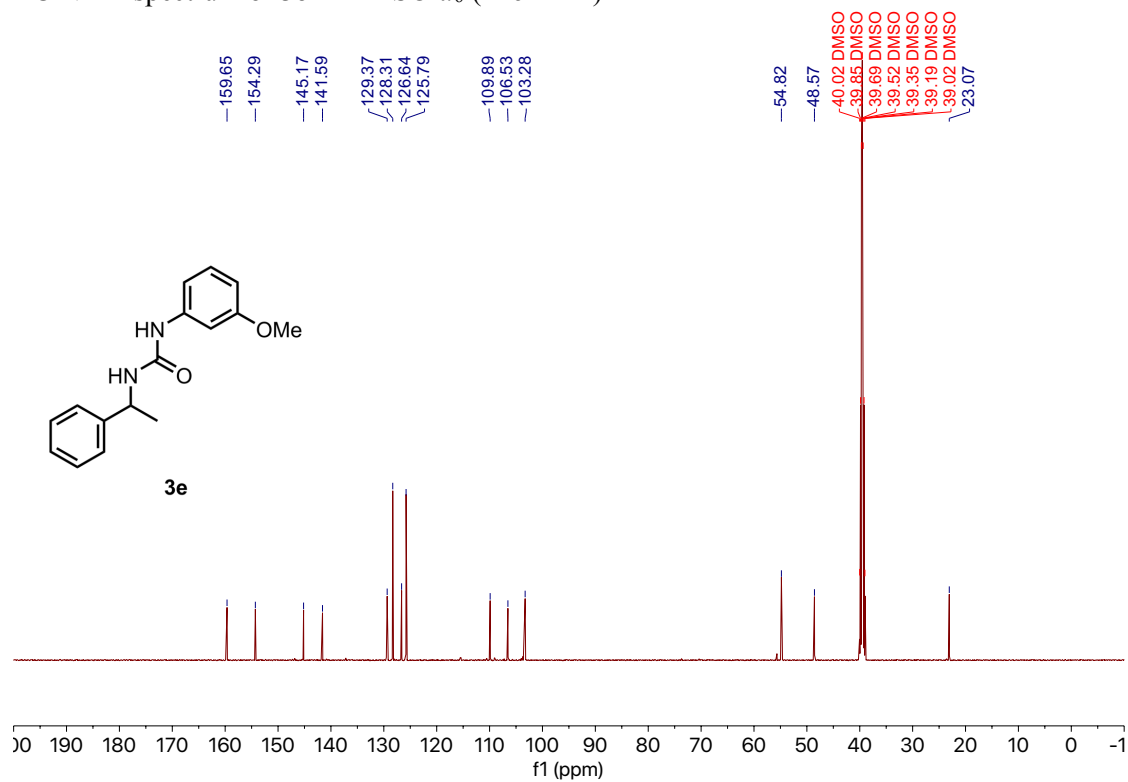
^{13}C NMR spectrum of **3d** in $\text{DMSO-}d_6$ (126 MHz)



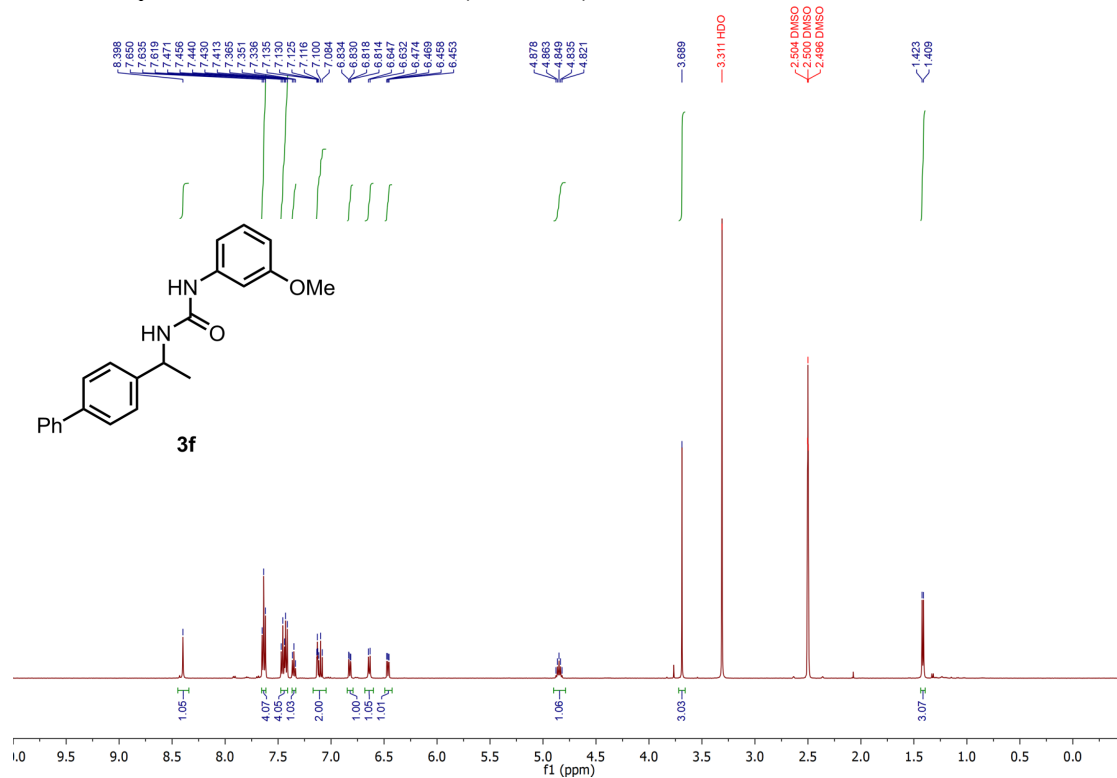
^1H NMR spectrum of **3e** in $\text{DMSO-}d_6$ (500 MHz)



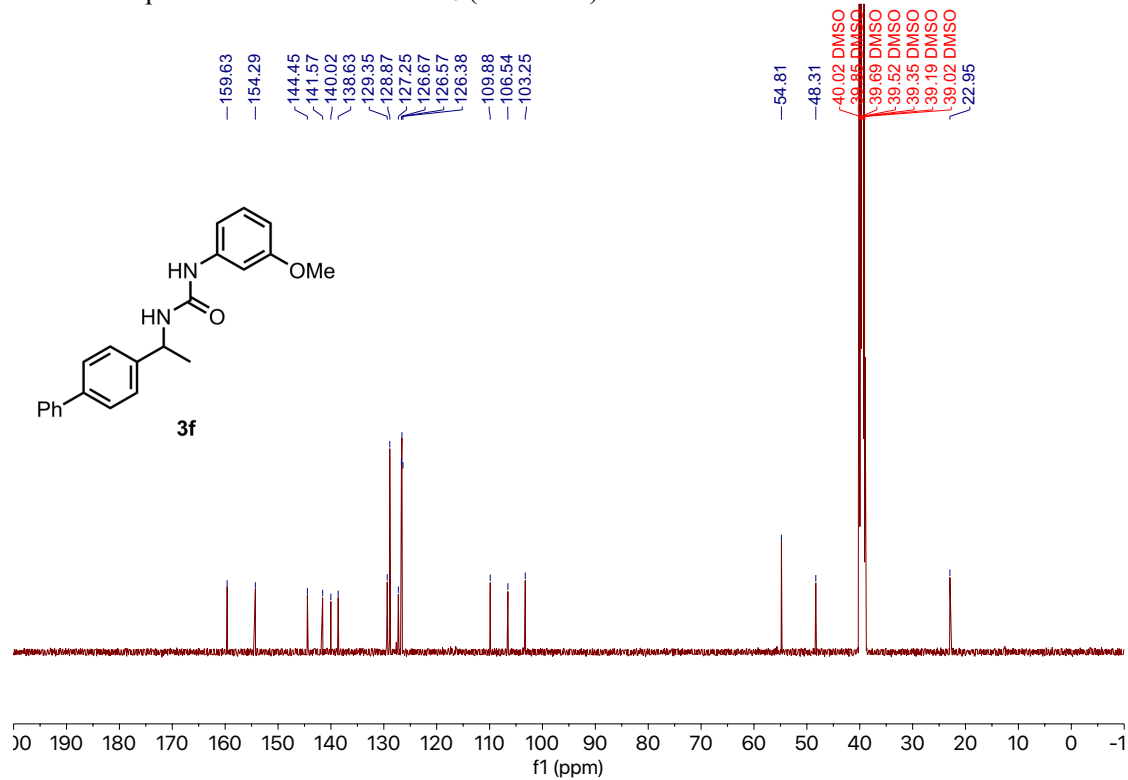
^{13}C NMR spectrum of **3e** in $\text{DMSO-}d_6$ (126 MHz)



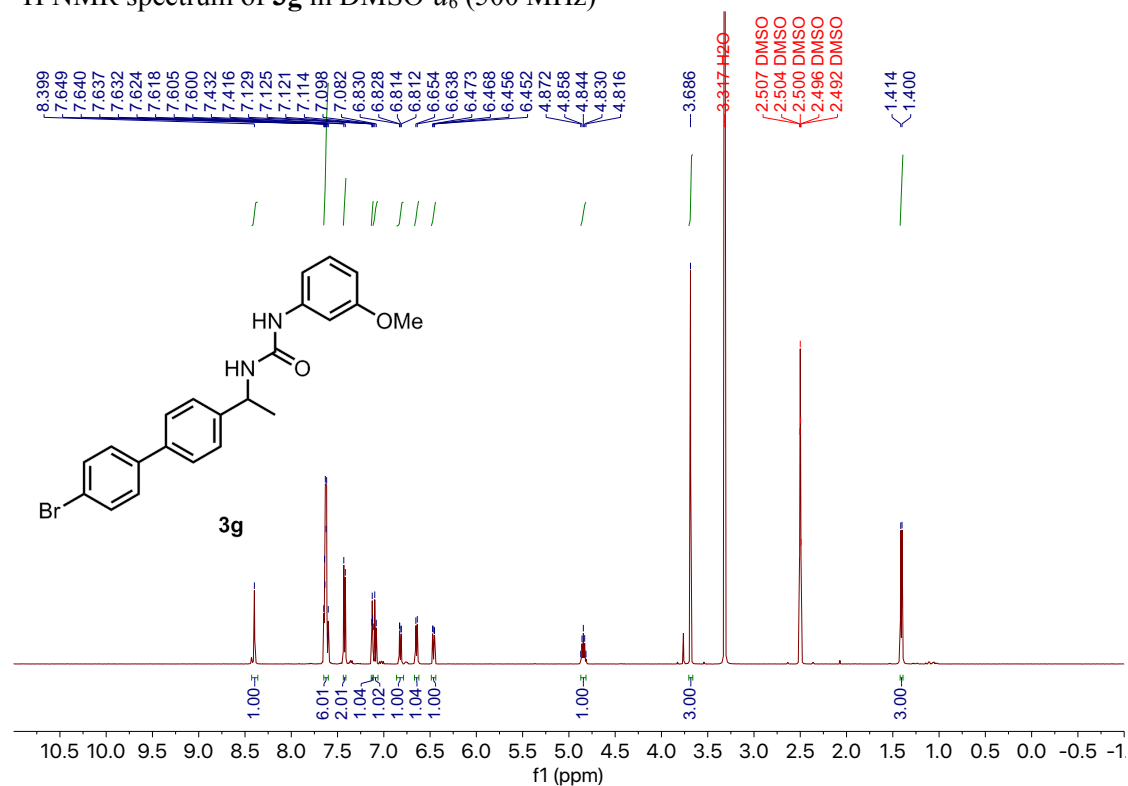
^1H NMR spectrum of **3f** in $\text{DMSO-}d_6$ (500 MHz)



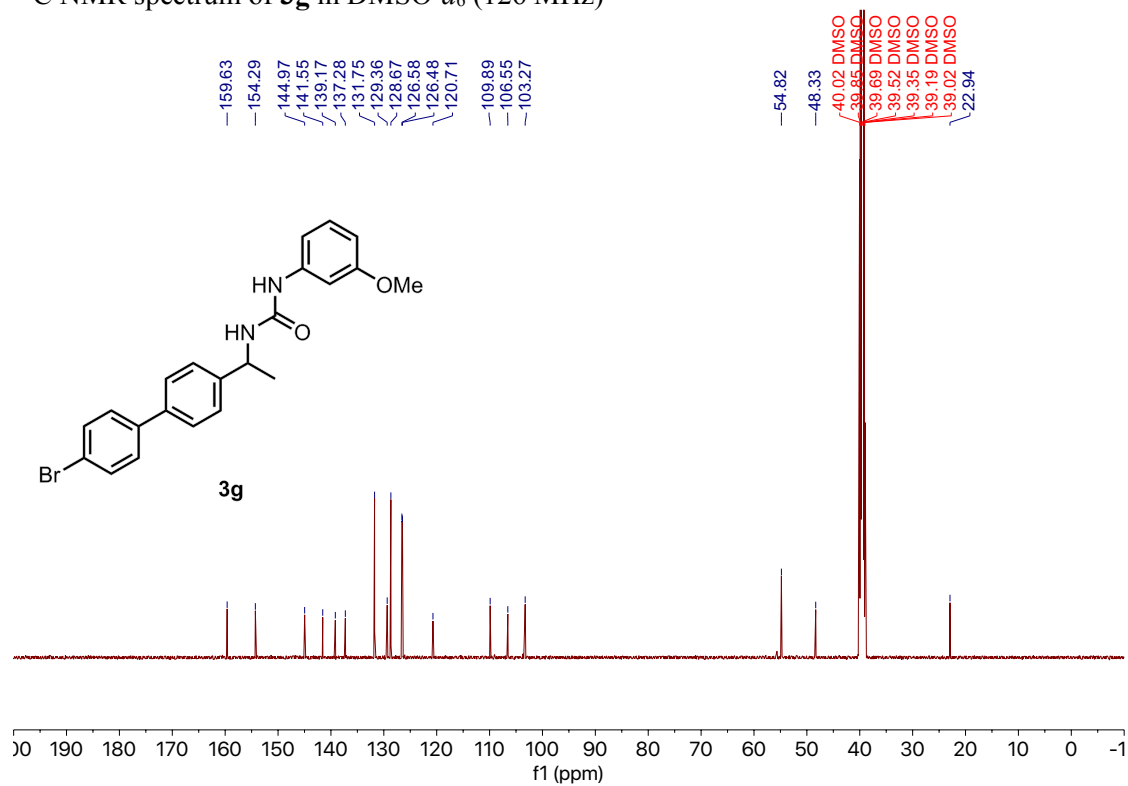
^{13}C NMR spectrum of **3f** in $\text{DMSO-}d_6$ (126 MHz)



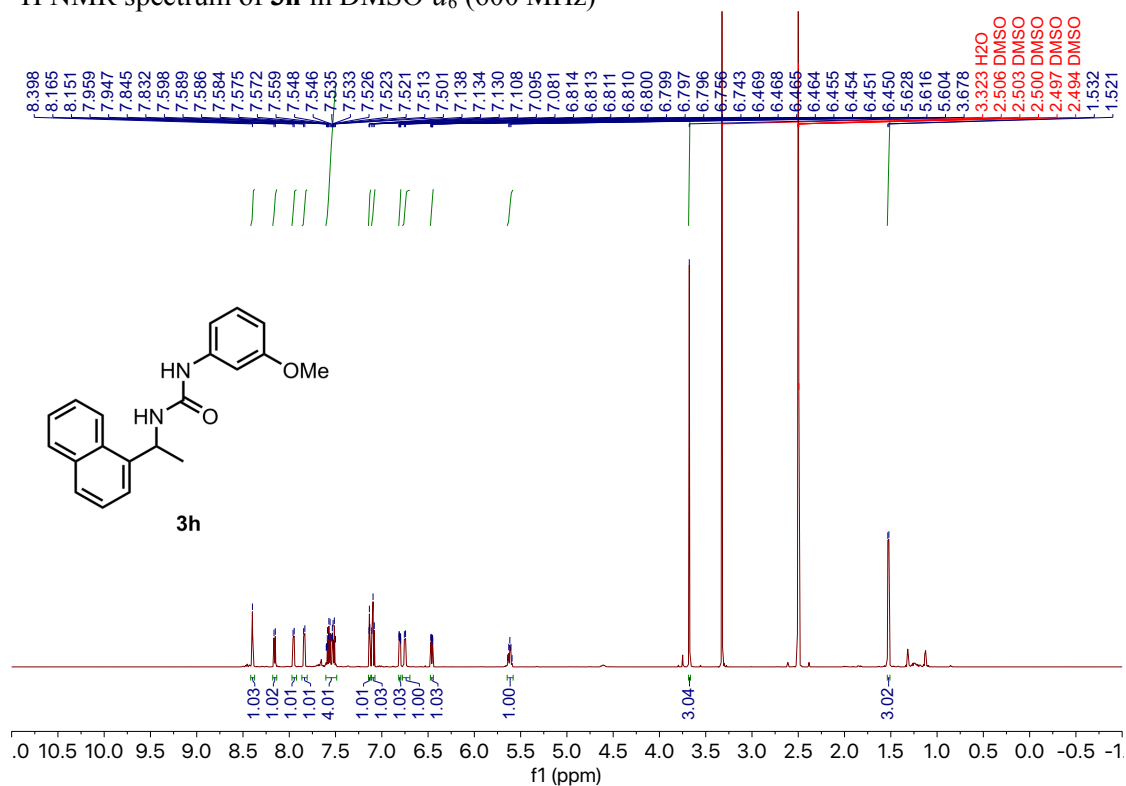
^1H NMR spectrum of **3g** in $\text{DMSO-}d_6$ (500 MHz)



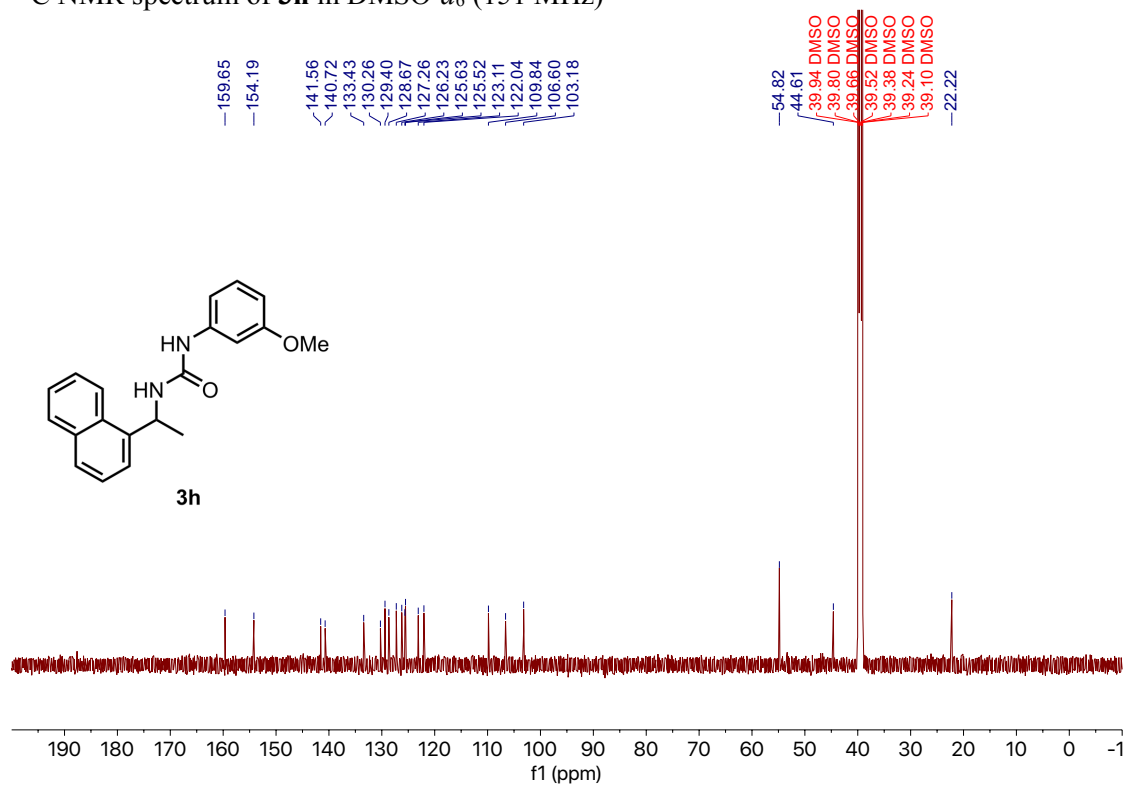
^{13}C NMR spectrum of **3g** in $\text{DMSO-}d_6$ (126 MHz)



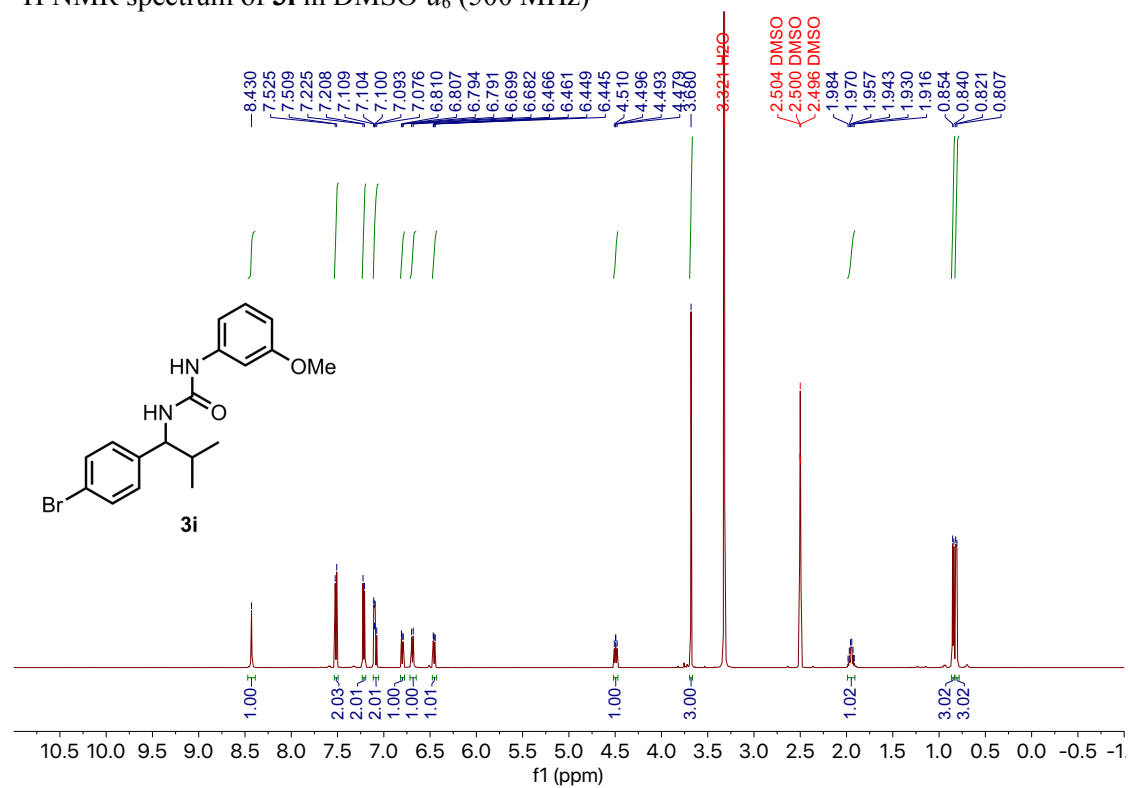
¹H NMR spectrum of **3h** in DMSO-*d*₆ (600 MHz)



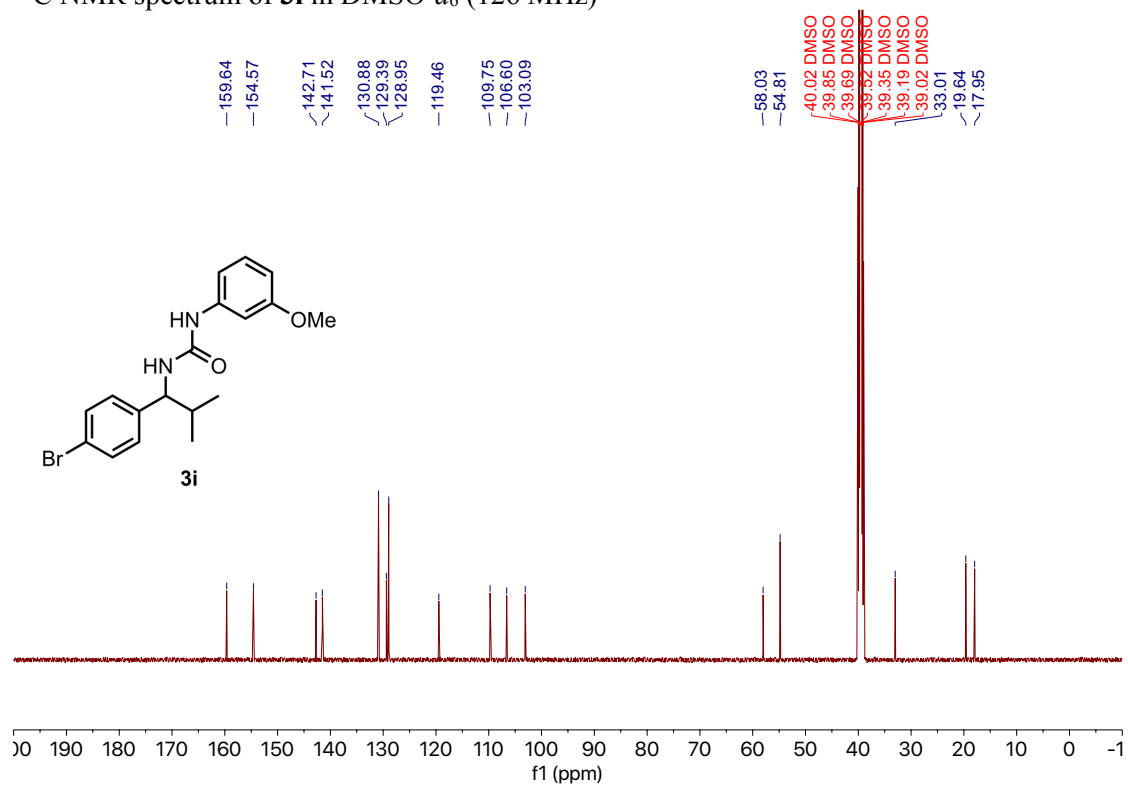
¹³C NMR spectrum of **3h** in DMSO-*d*₆ (151 MHz)



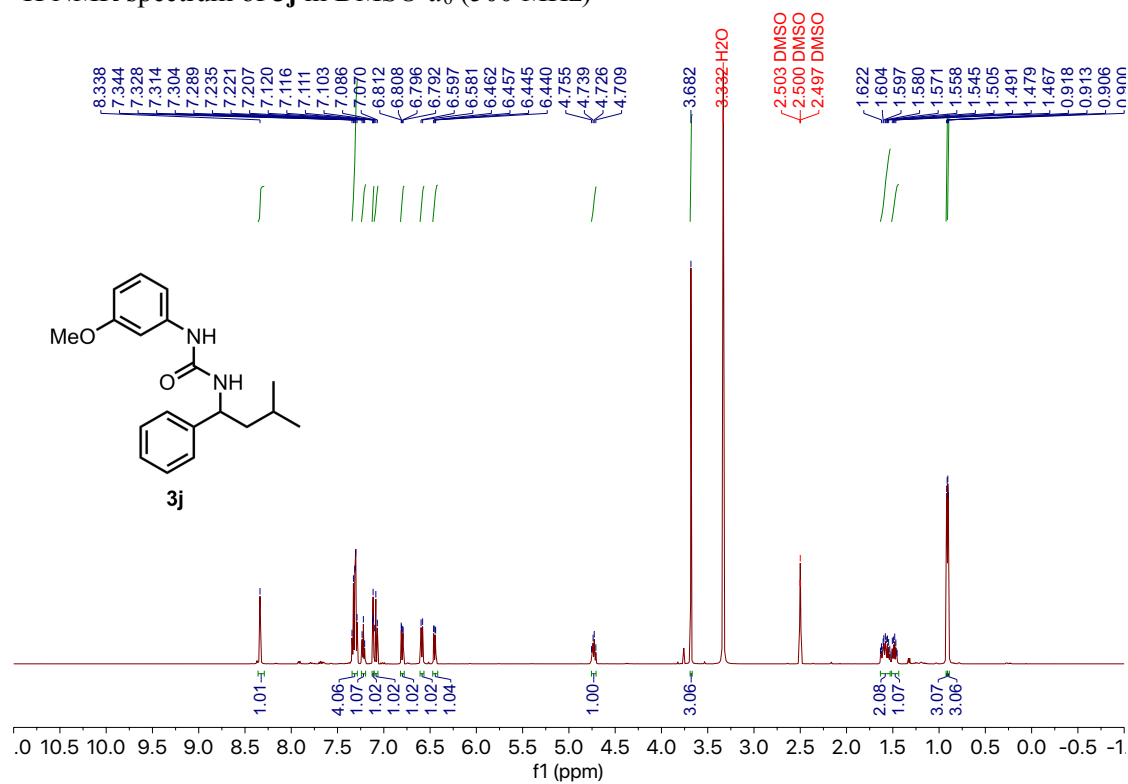
¹H NMR spectrum of **3i** in DMSO-*d*₆ (500 MHz)



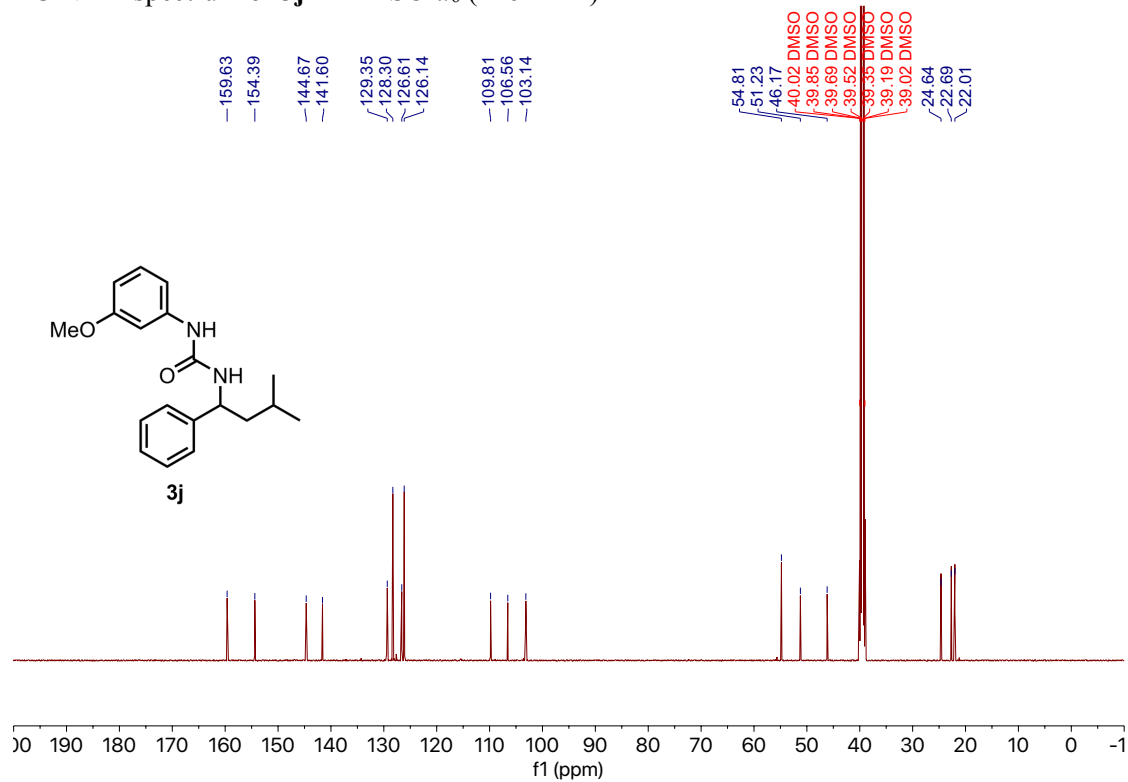
¹³C NMR spectrum of **3i** in DMSO-*d*₆ (126 MHz)



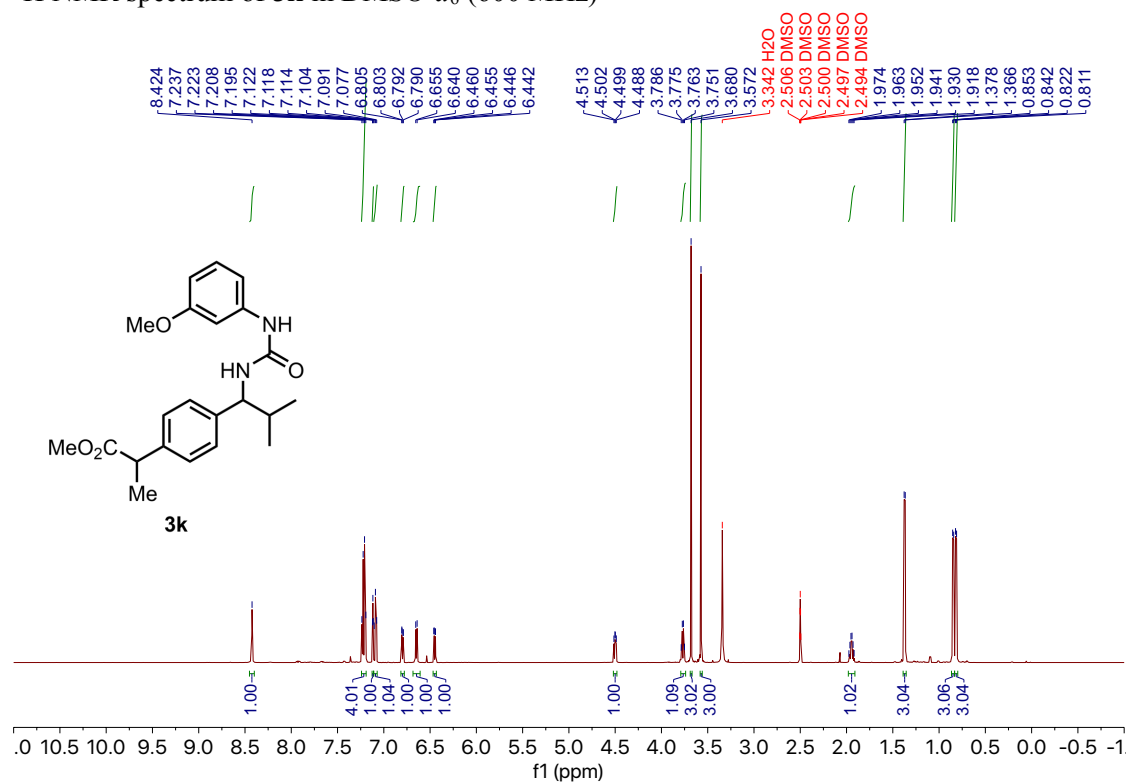
¹H NMR spectrum of **3j** in DMSO-*d*₆ (500 MHz)



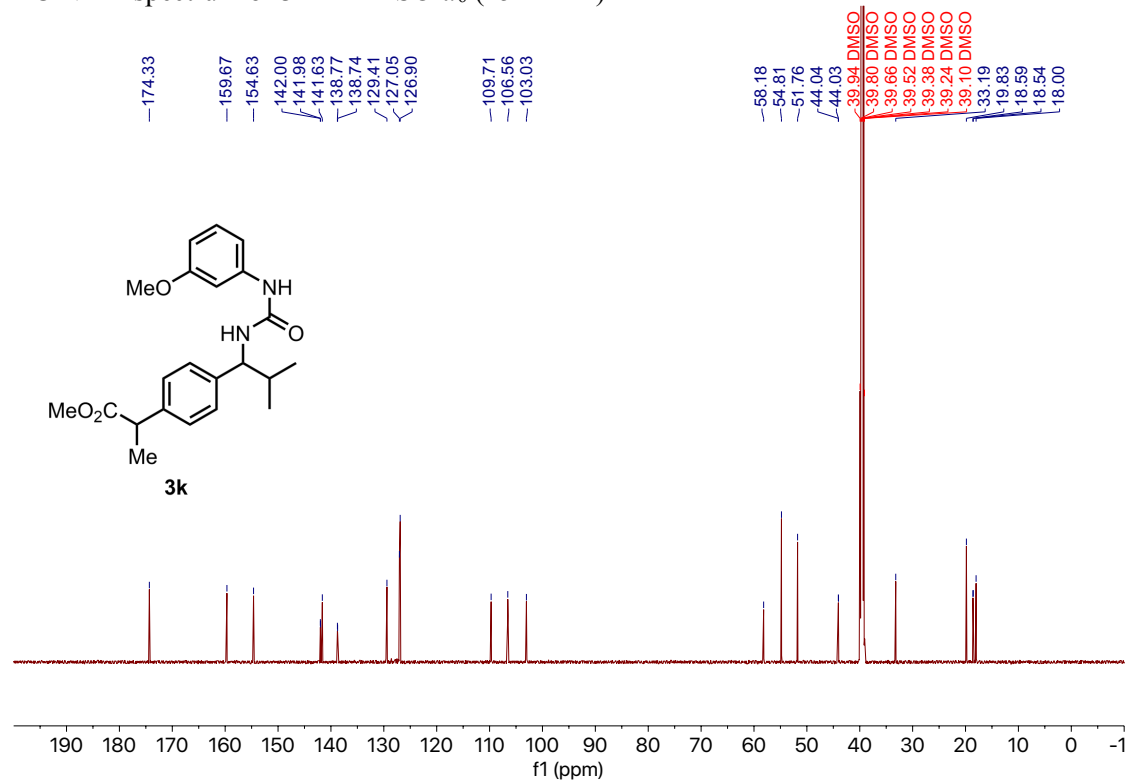
¹³C NMR spectrum of **3j** in DMSO-*d*₆ (126 MHz)



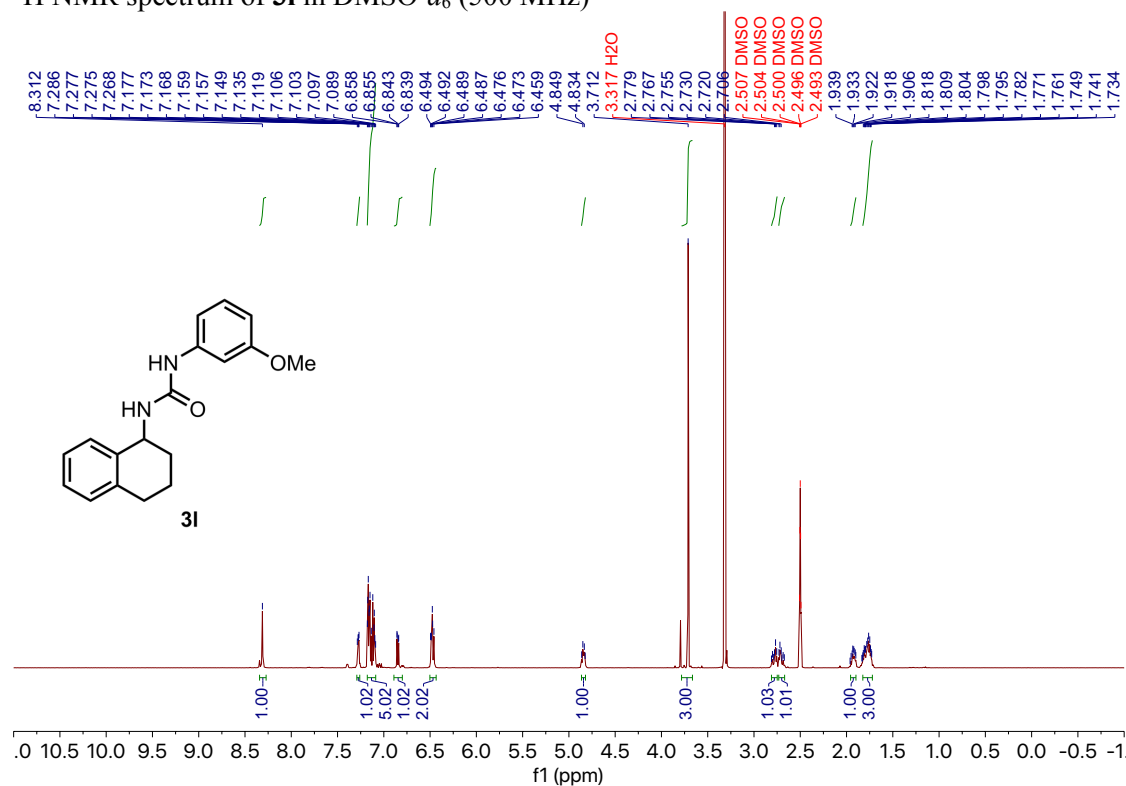
¹H NMR spectrum of **3k** in DMSO-*d*₆ (600 MHz)



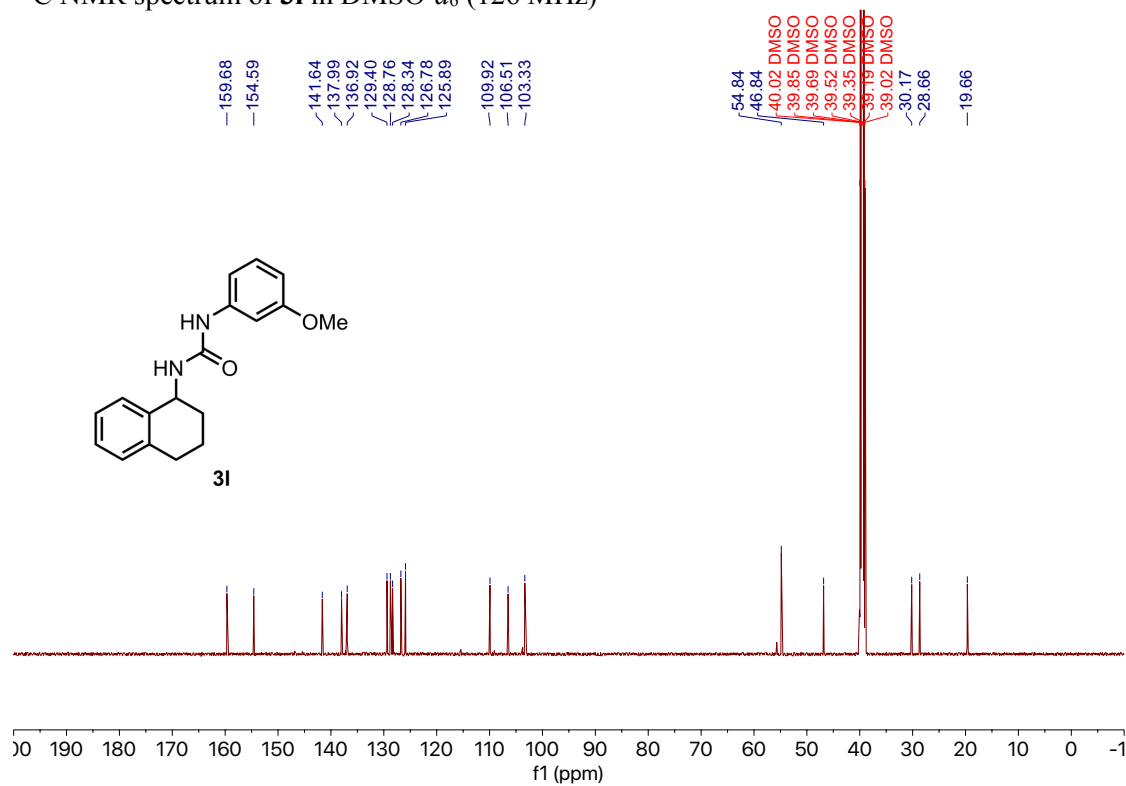
¹³C NMR spectrum of **3k** in DMSO-*d*₆ (151 MHz)



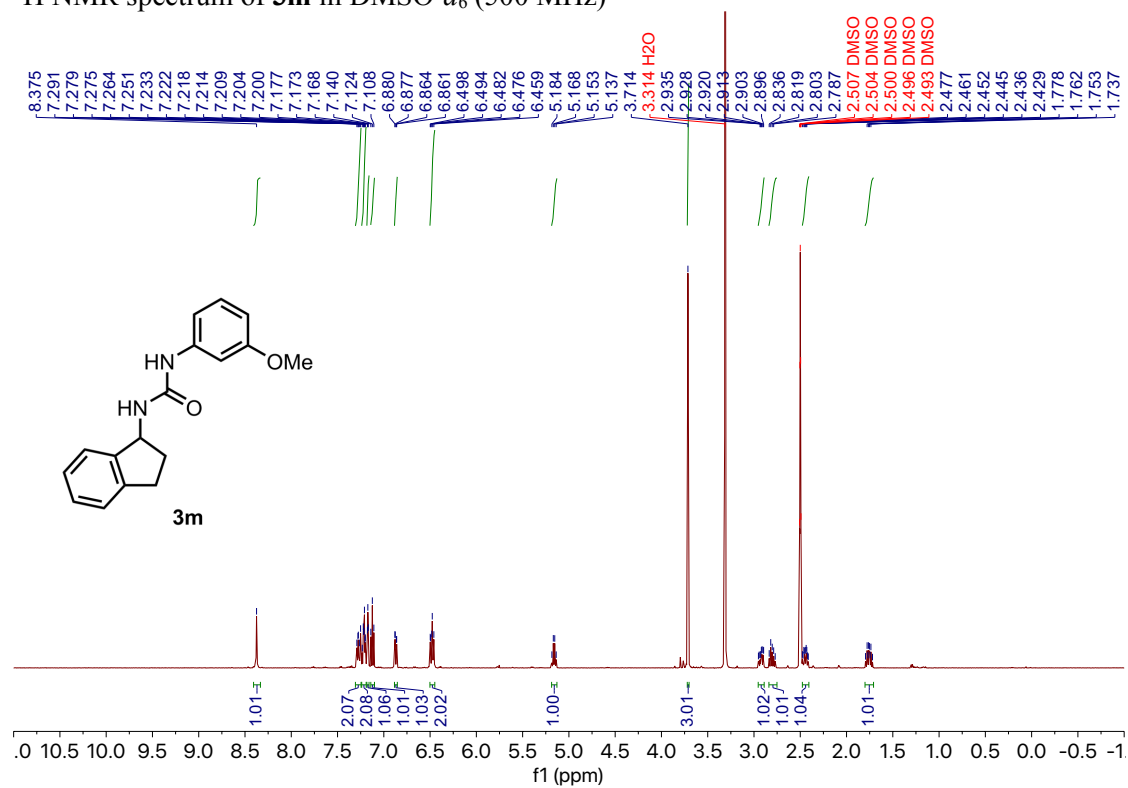
¹H NMR spectrum of **3I** in DMSO-*d*₆ (500 MHz)



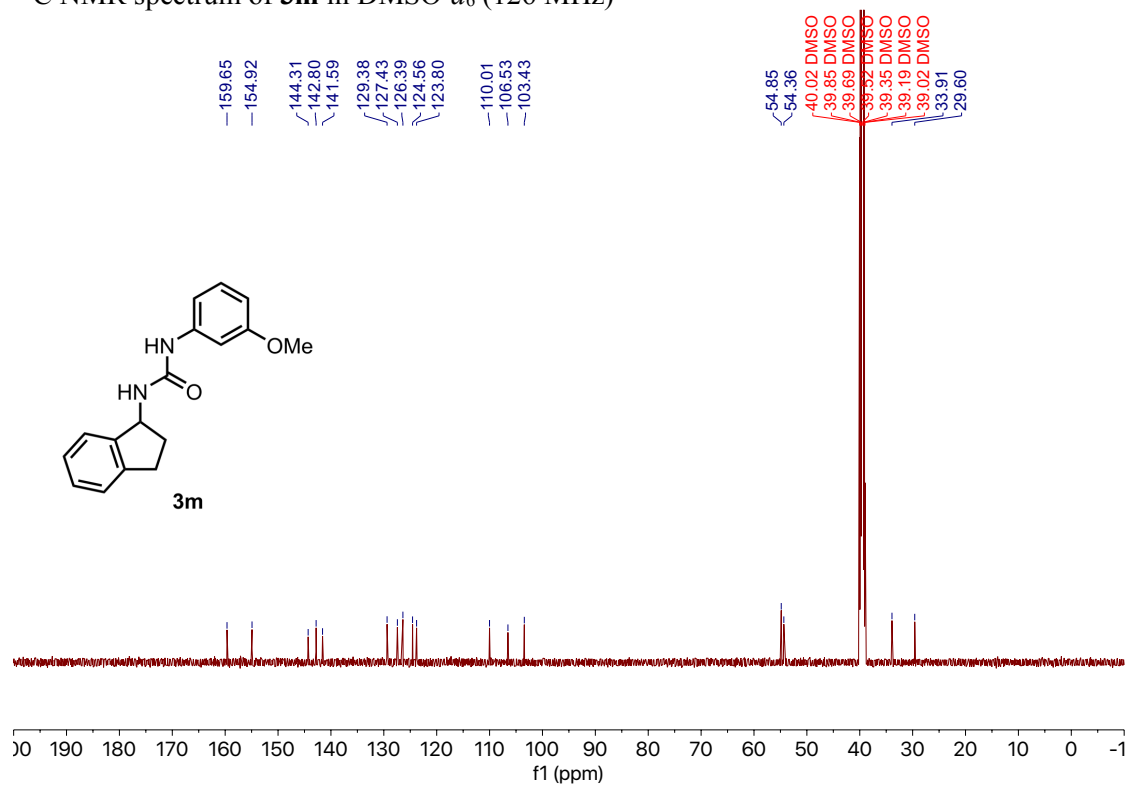
¹³C NMR spectrum of **3I** in DMSO-*d*₆ (126 MHz)



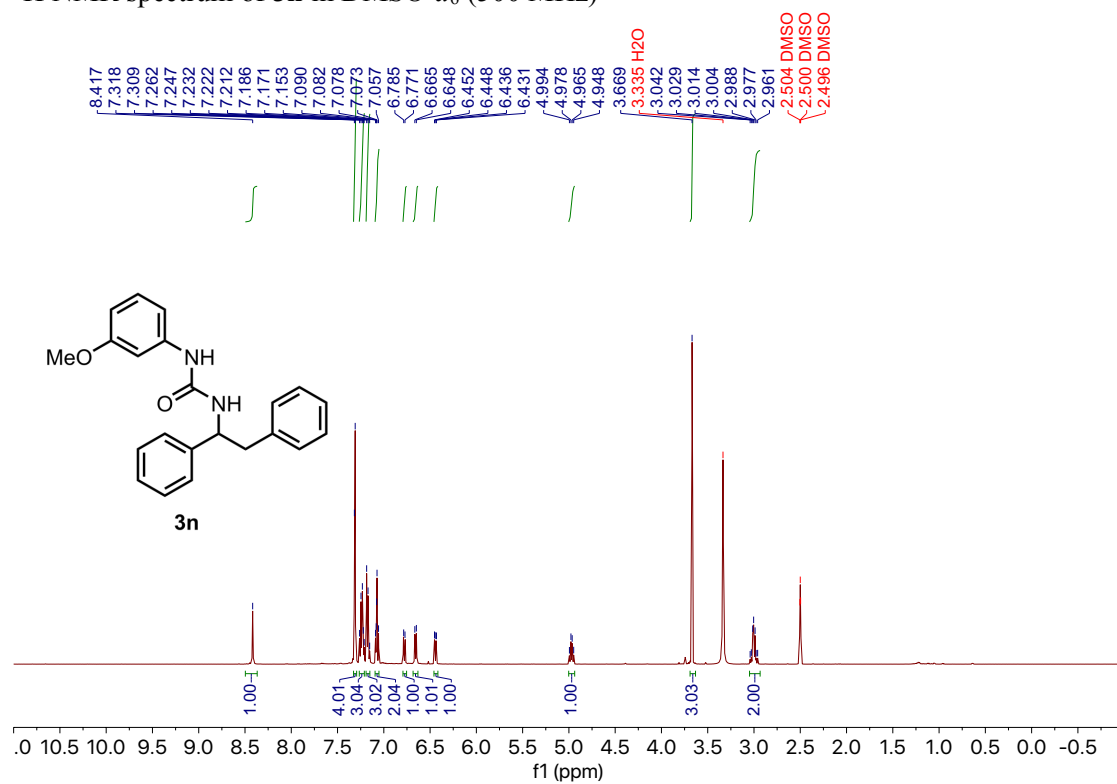
^1H NMR spectrum of **3m** in $\text{DMSO-}d_6$ (500 MHz)



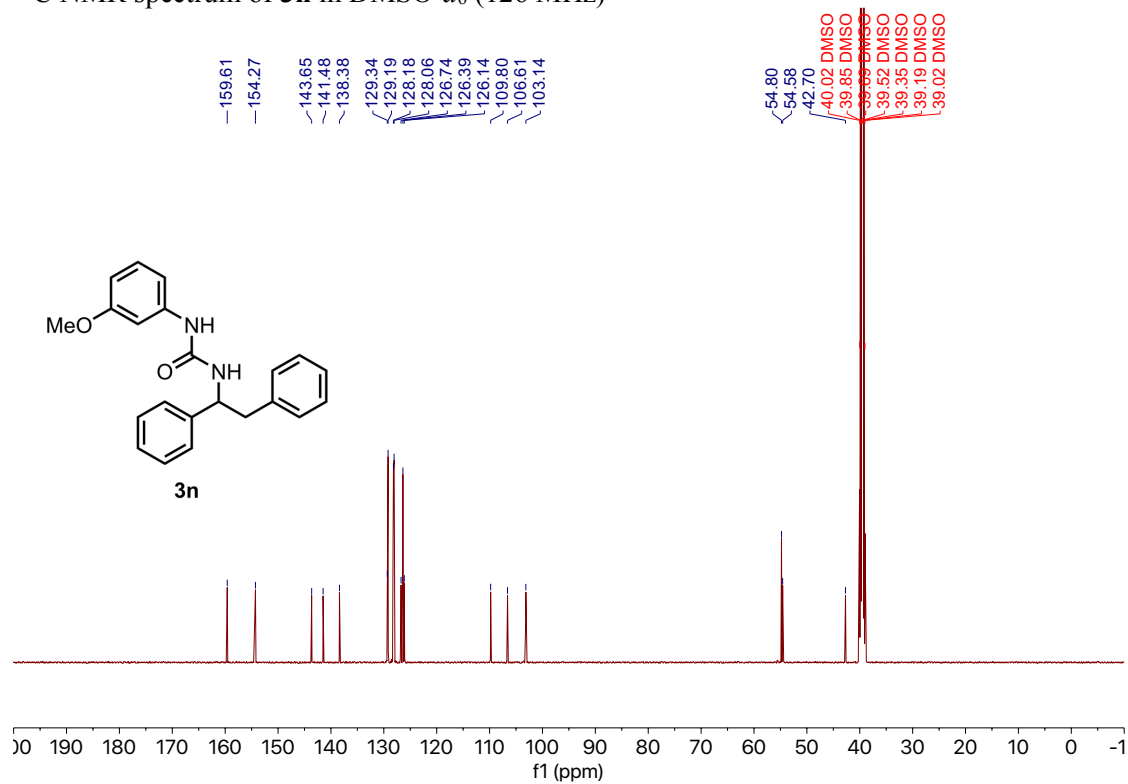
^{13}C NMR spectrum of **3m** in $\text{DMSO-}d_6$ (126 MHz)



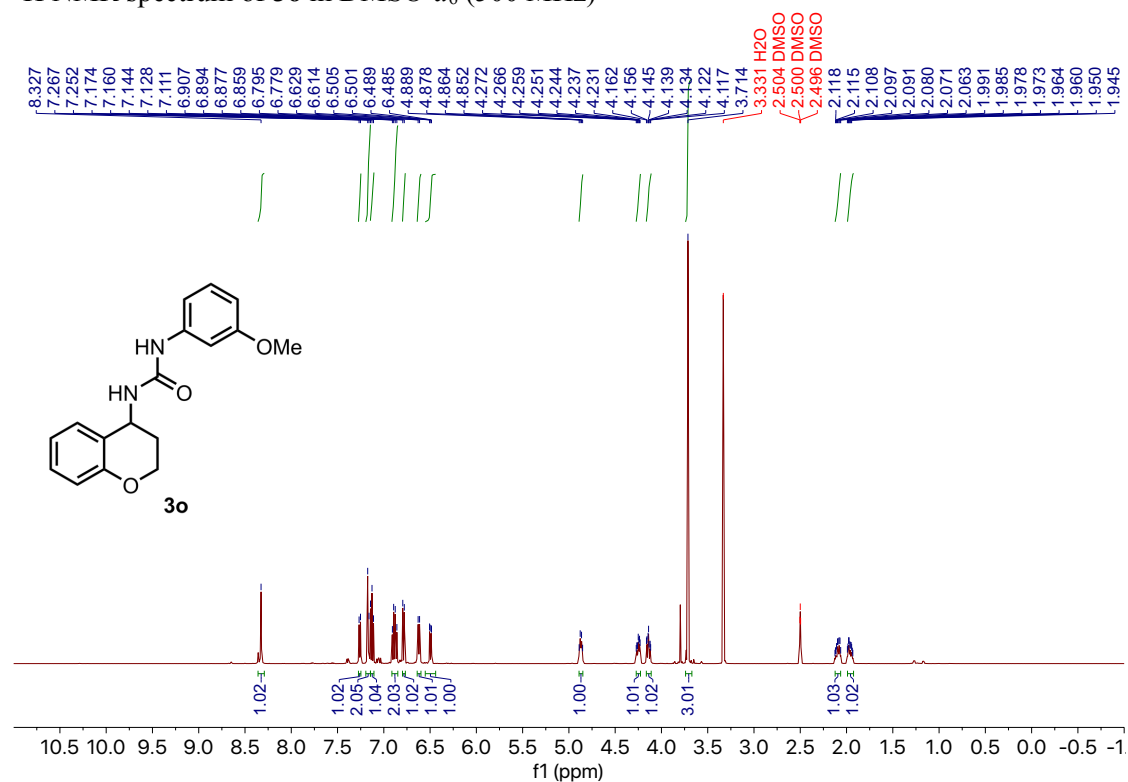
^1H NMR spectrum of **3n** in $\text{DMSO-}d_6$ (500 MHz)



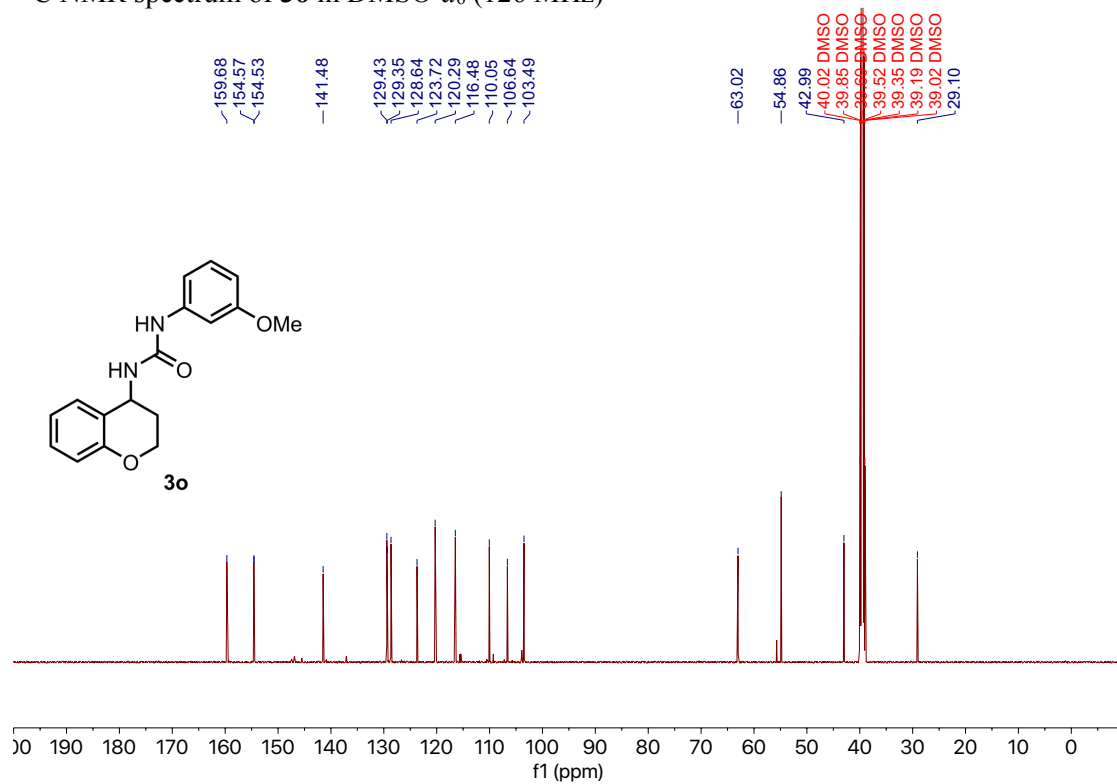
^{13}C NMR spectrum of **3n** in $\text{DMSO-}d_6$ (126 MHz)



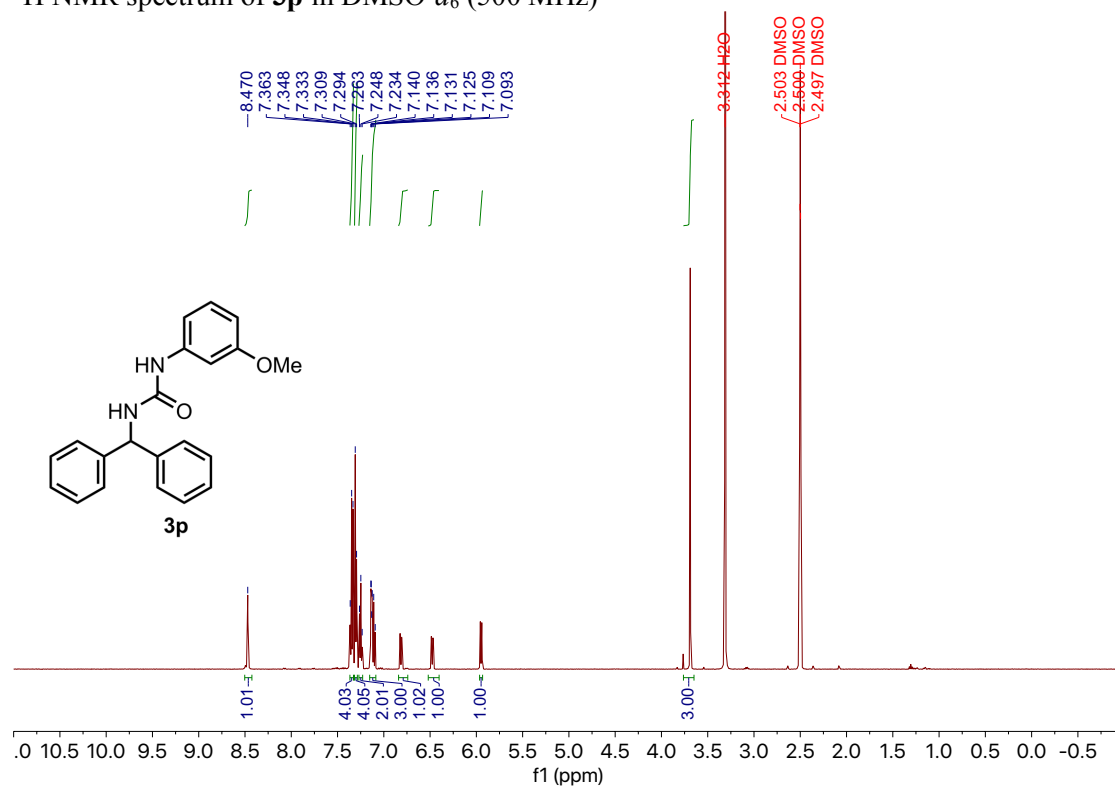
^1H NMR spectrum of **3o** in $\text{DMSO-}d_6$ (500 MHz)



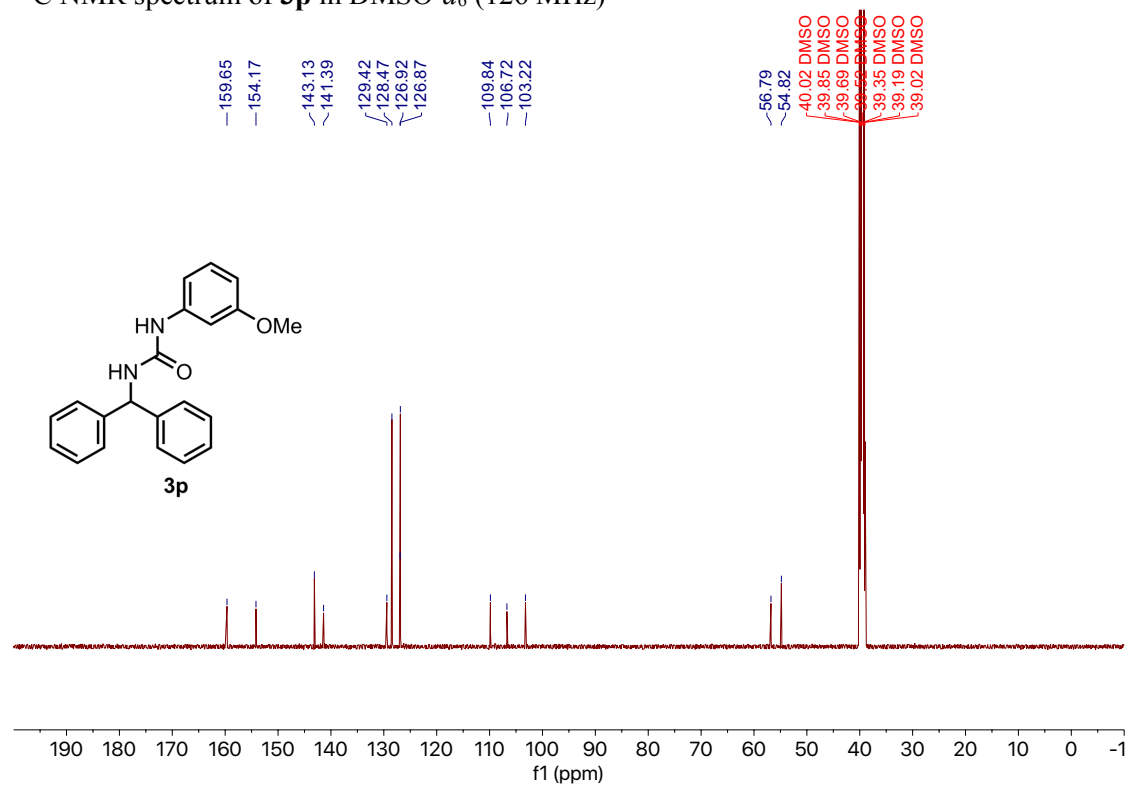
^{13}C NMR spectrum of **3o** in $\text{DMSO-}d_6$ (126 MHz)



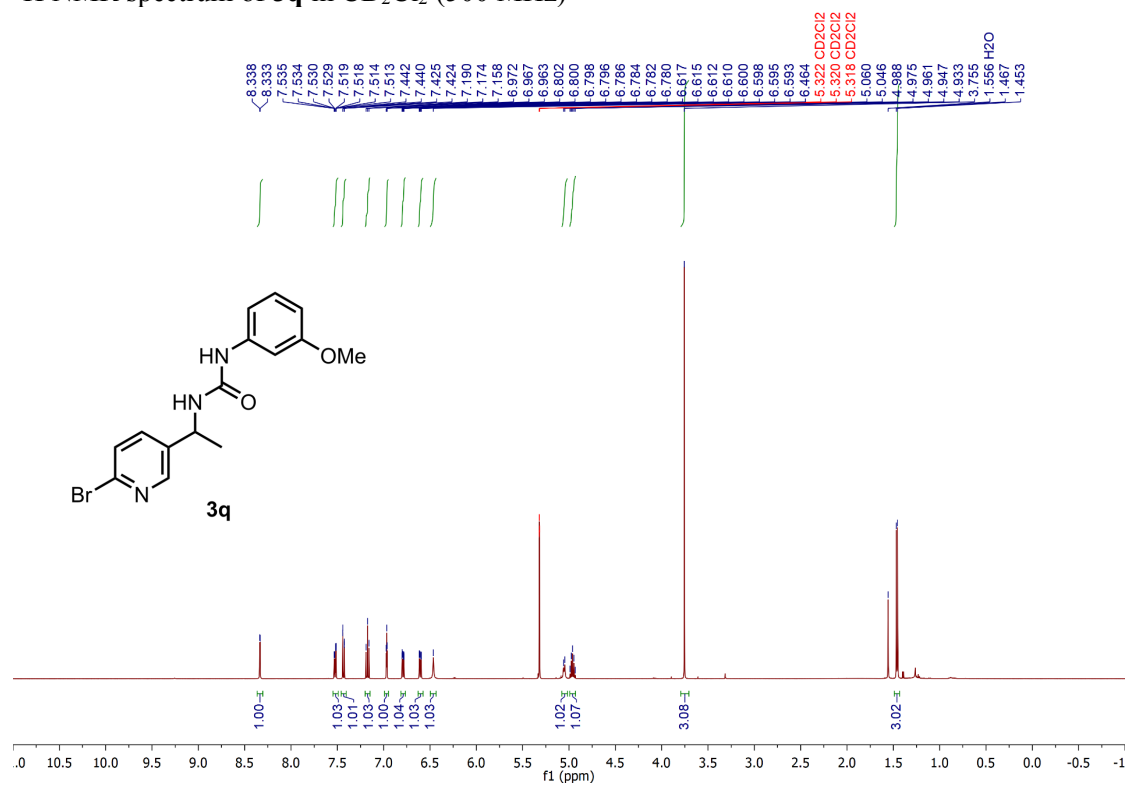
^1H NMR spectrum of **3p** in $\text{DMSO-}d_6$ (500 MHz)



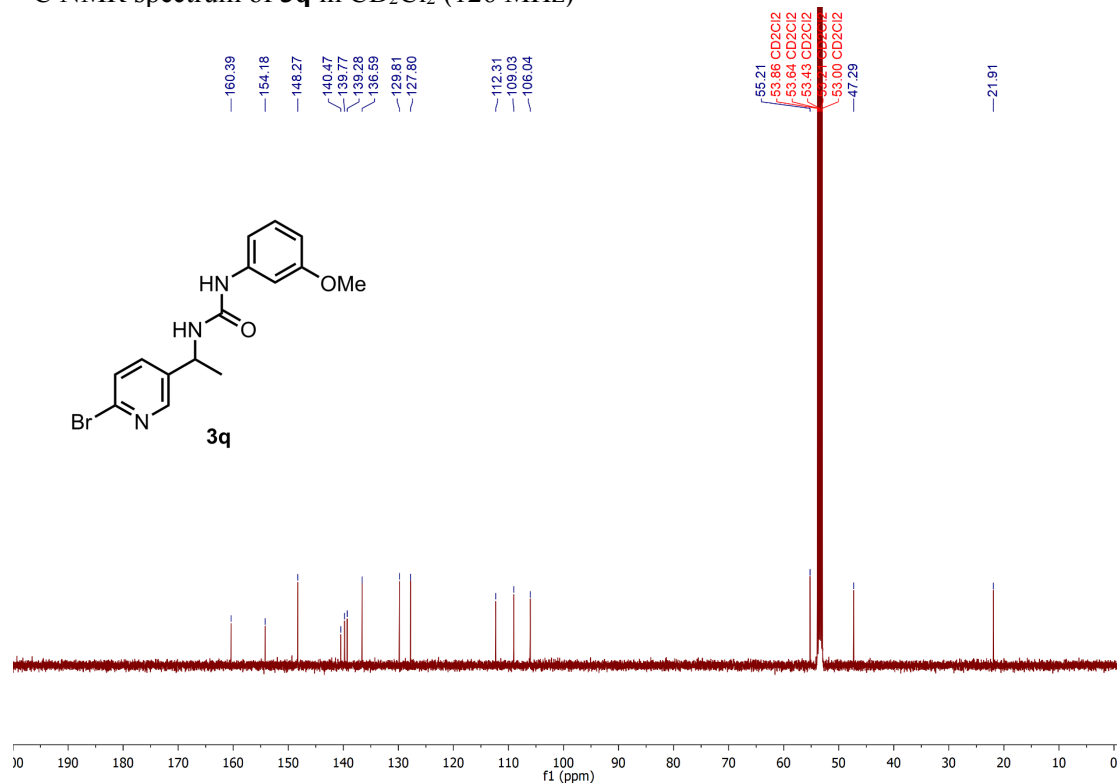
^{13}C NMR spectrum of **3p** in $\text{DMSO-}d_6$ (126 MHz)



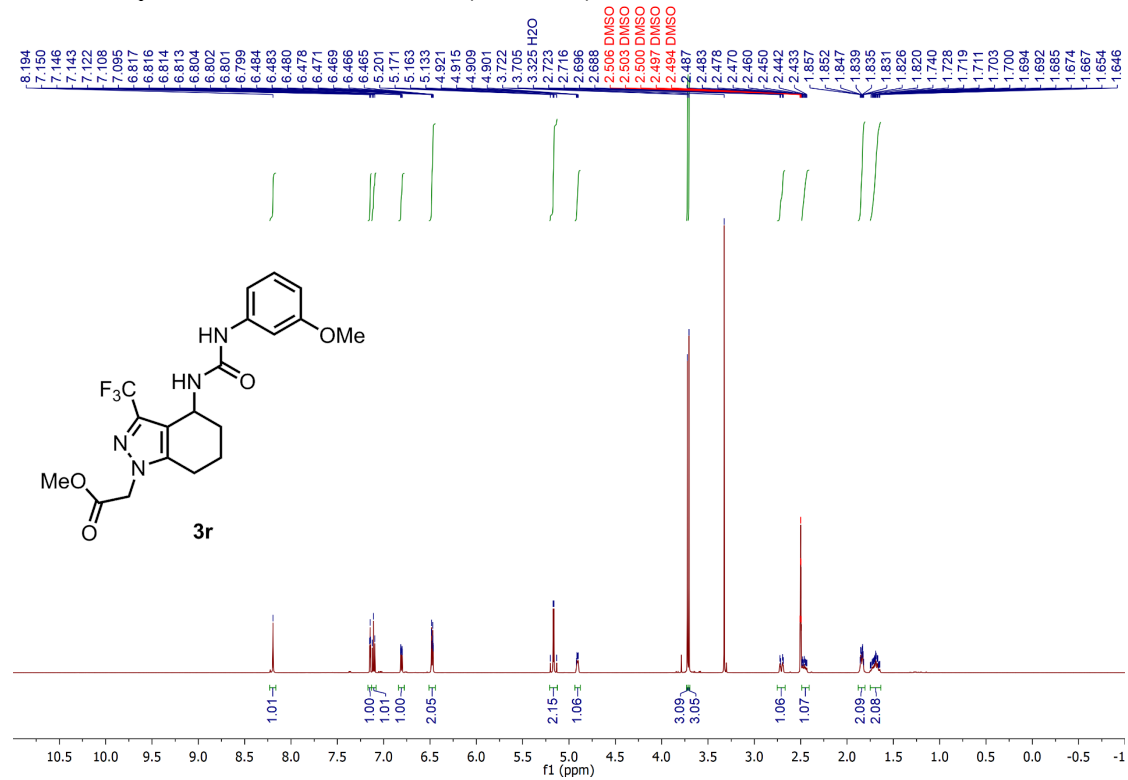
¹H NMR spectrum of **3q** in CD₂Cl₂ (500 MHz)



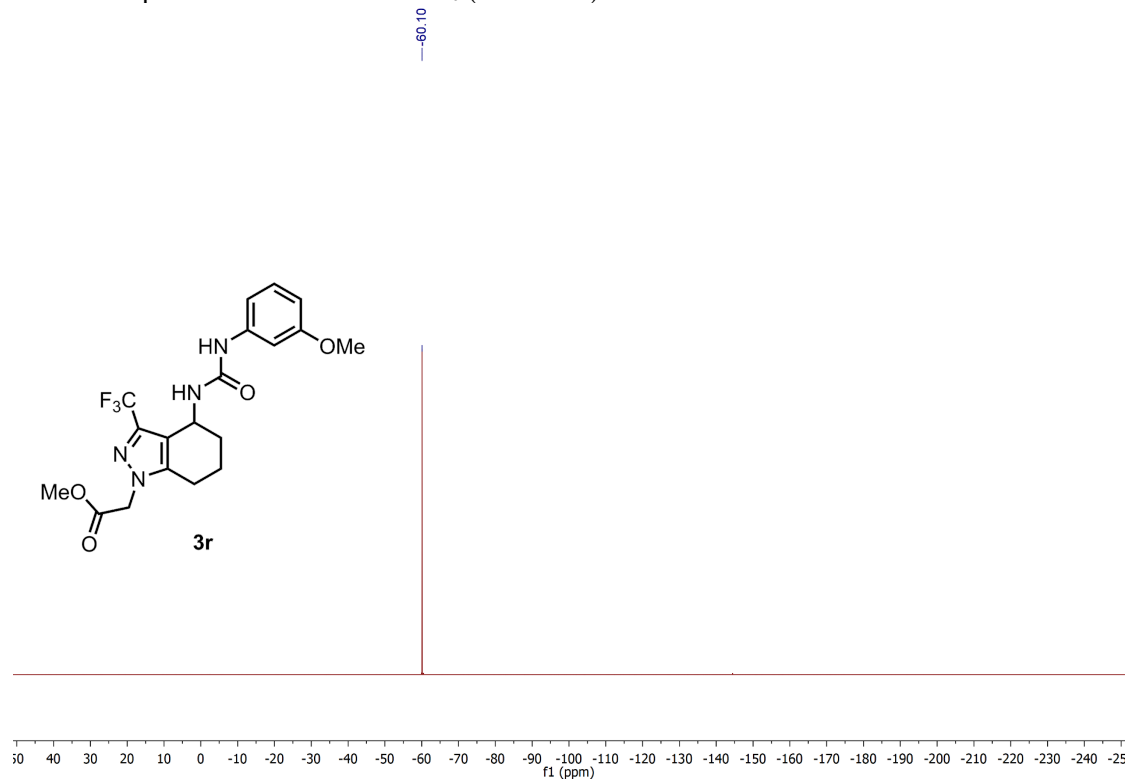
¹³C NMR spectrum of **3q** in CD₂Cl₂ (126 MHz)



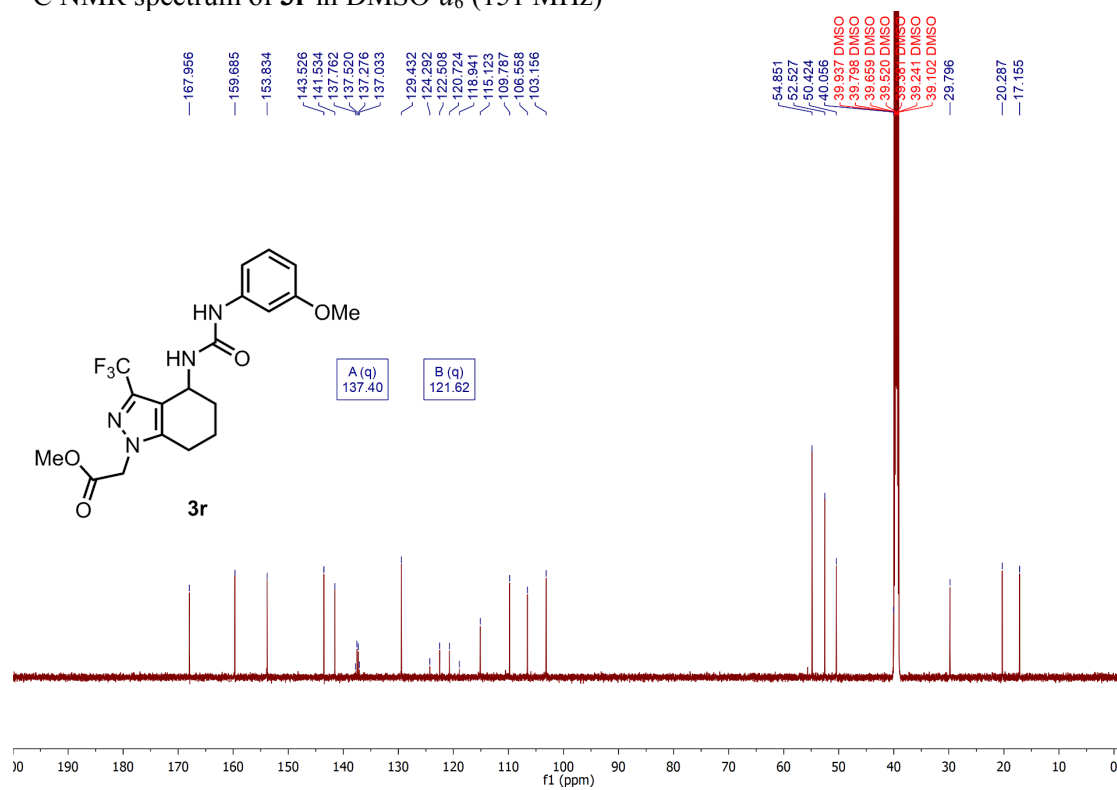
¹H NMR spectrum of **3r** in DMSO-*d*₆ (600 MHz)



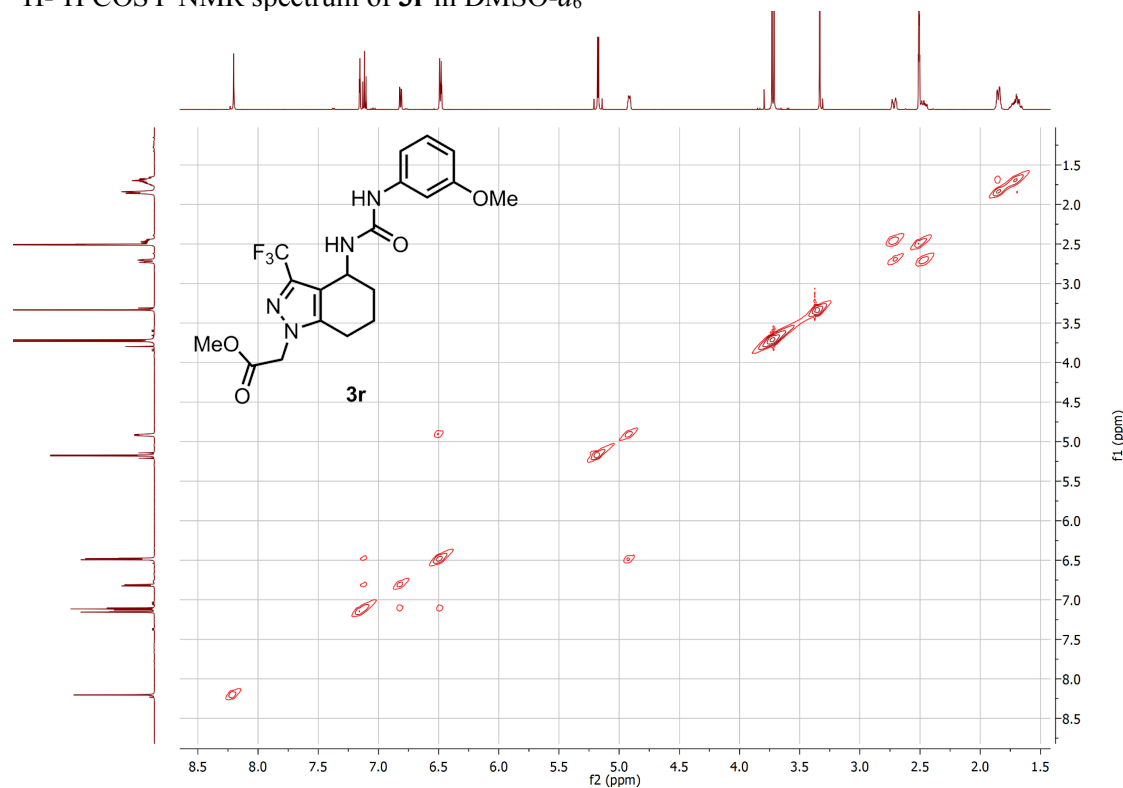
¹⁹F NMR spectrum of **3r** in DMSO-*d*₆ (564 MHz)



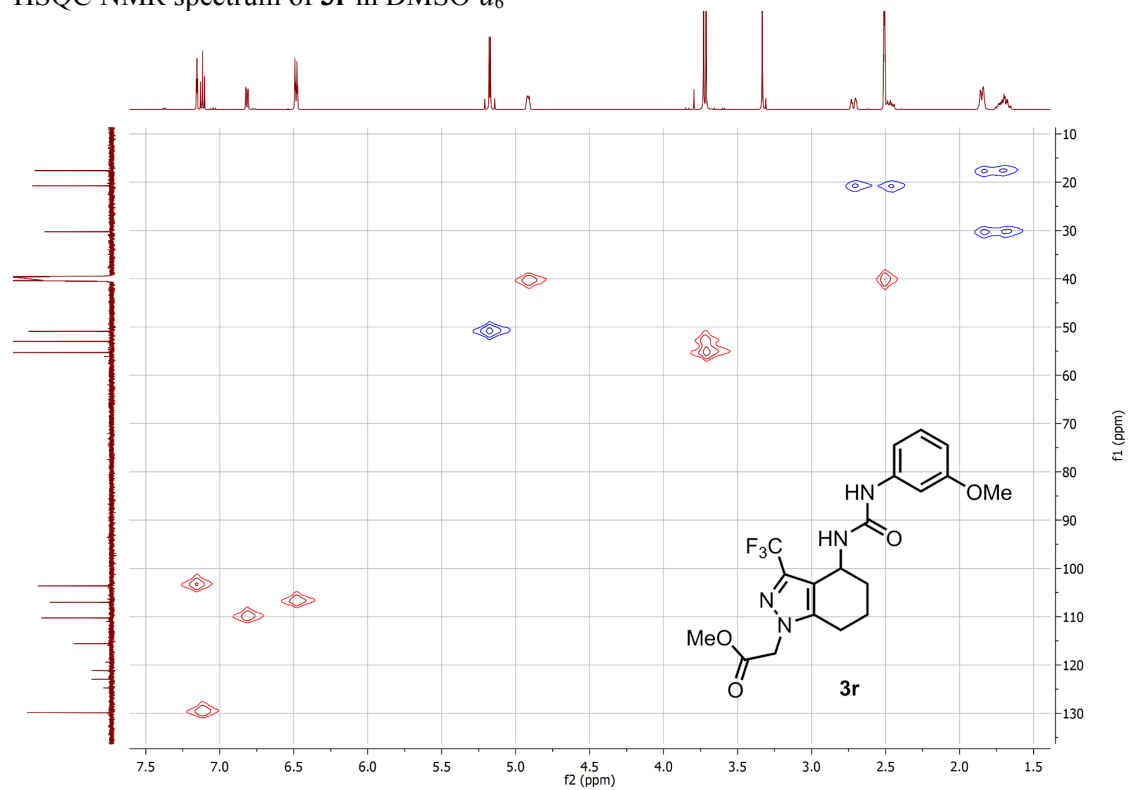
^{13}C NMR spectrum of **3r** in $\text{DMSO-}d_6$ (151 MHz)



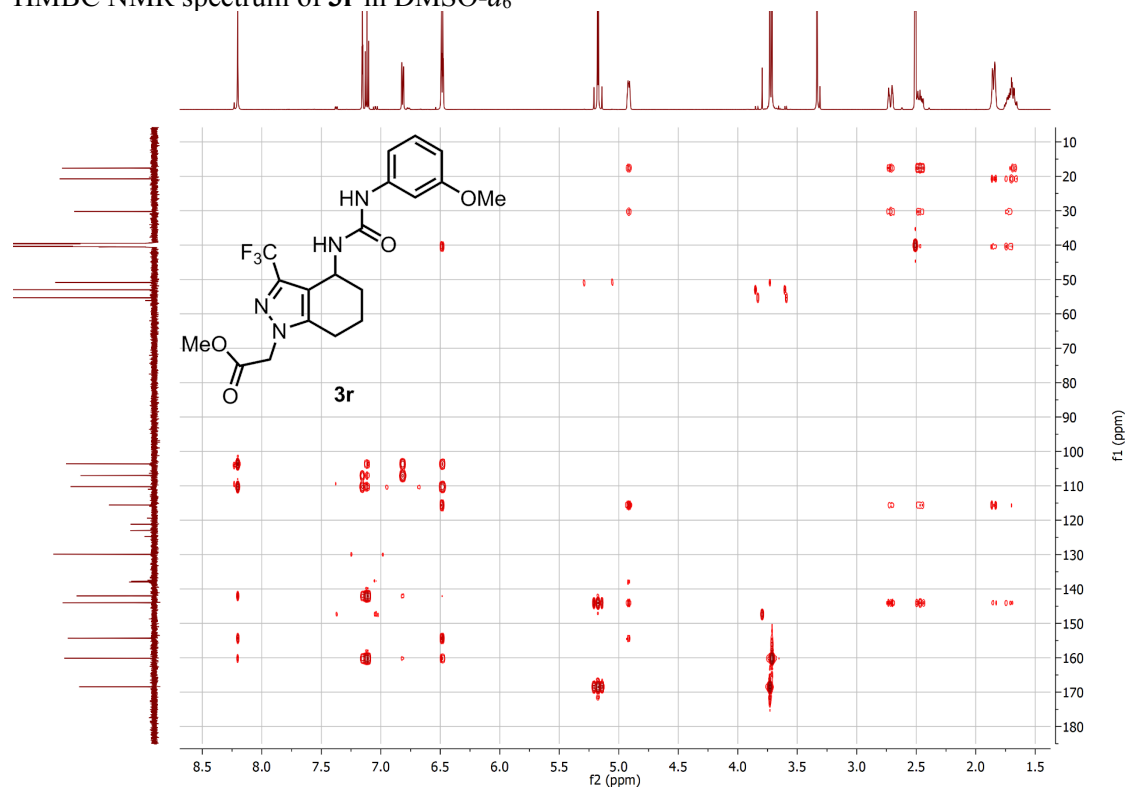
$^1\text{H-}^1\text{H}$ COSY NMR spectrum of **3r** in $\text{DMSO-}d_6$



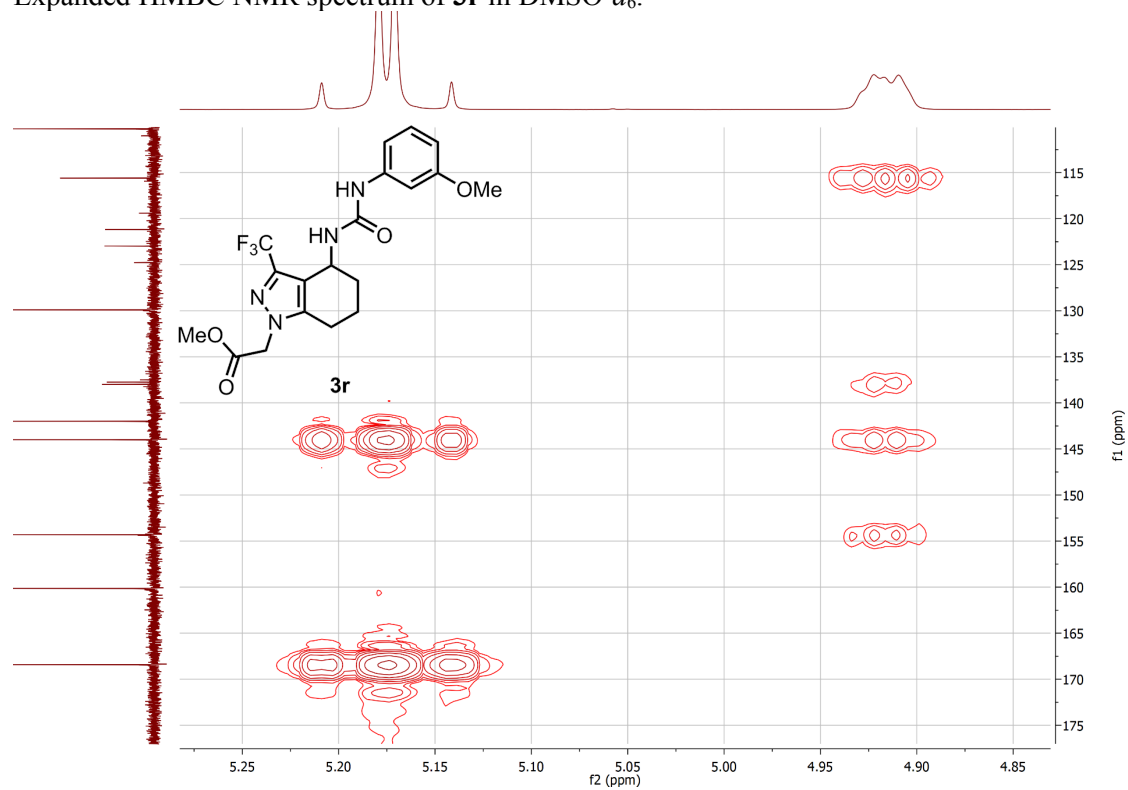
HSQC NMR spectrum of **3r** in DMSO-*d*₆



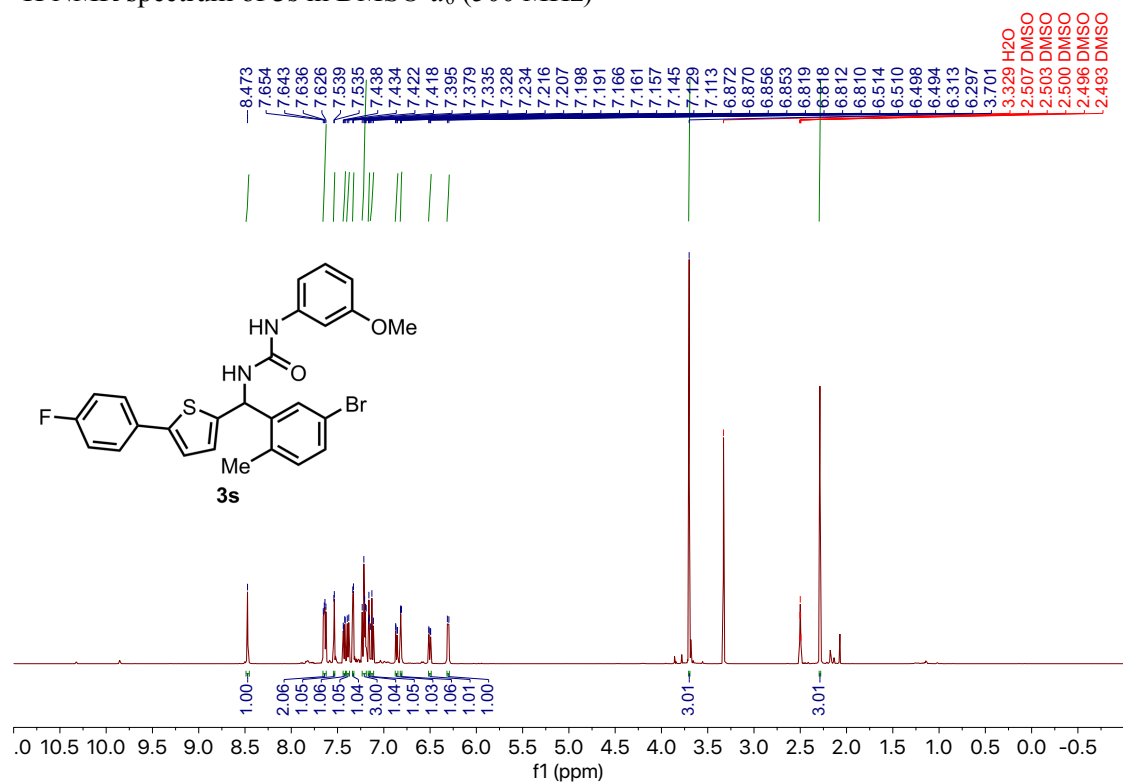
HMBC NMR spectrum of **3r** in DMSO-*d*₆



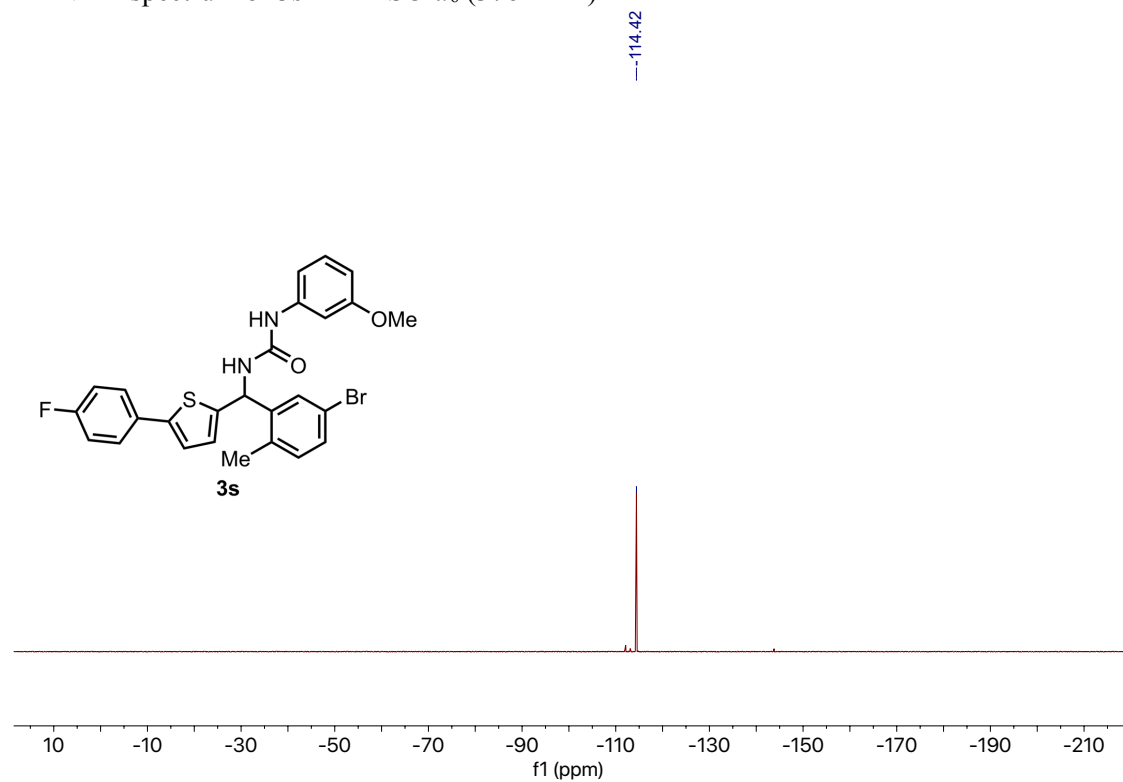
Expanded HMBC NMR spectrum of **3r** in DMSO-*d*₆.



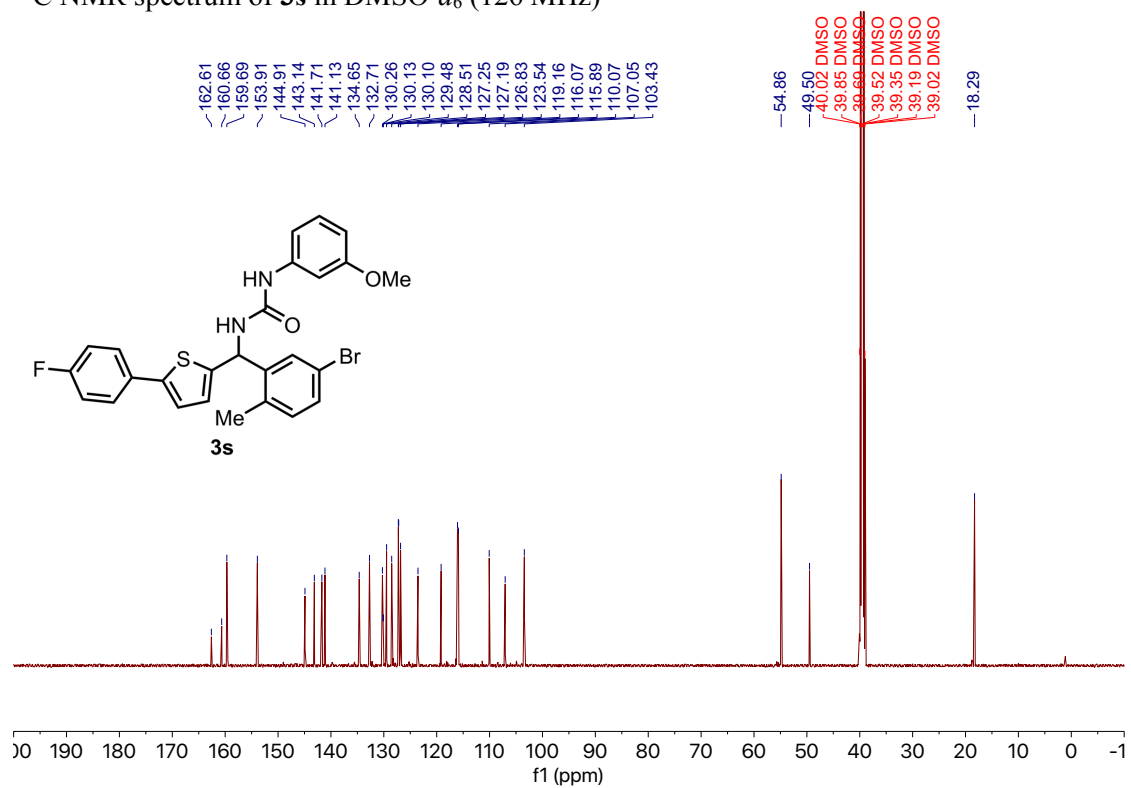
^1H NMR spectrum of **3s** in $\text{DMSO-}d_6$ (500 MHz)



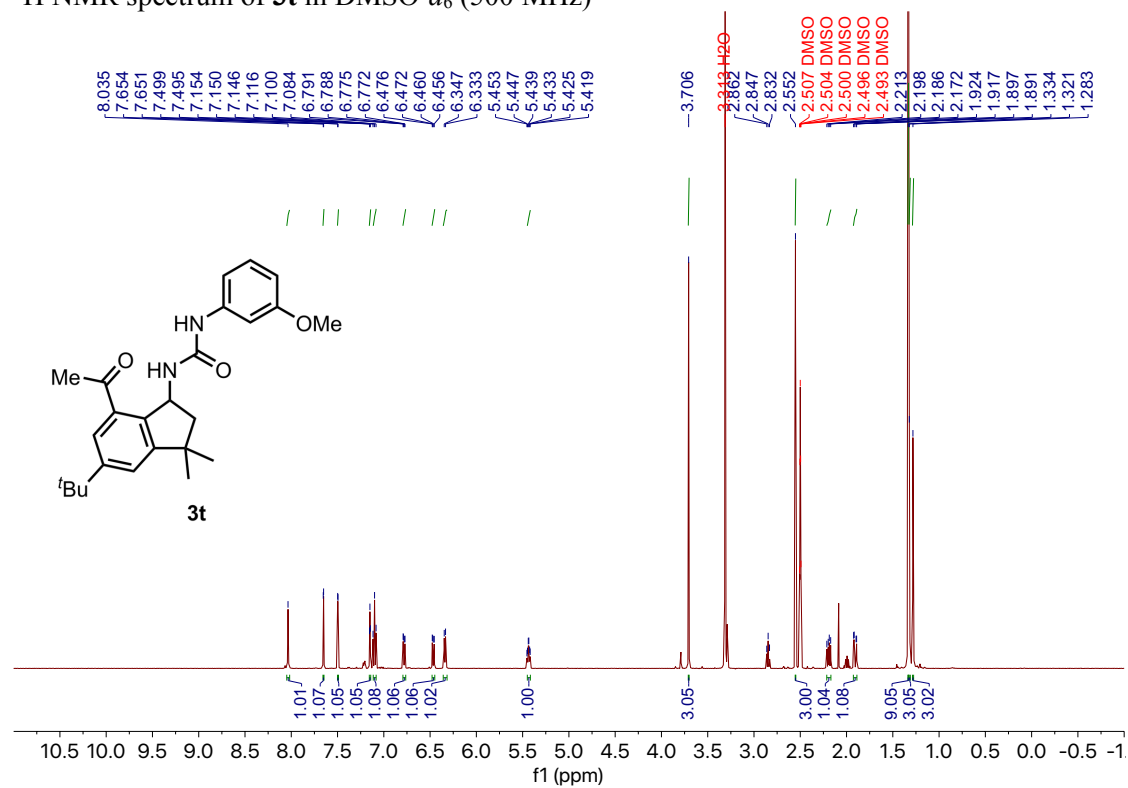
^{19}F NMR spectrum of **3s** in $\text{DMSO-}d_6$ (376 MHz)



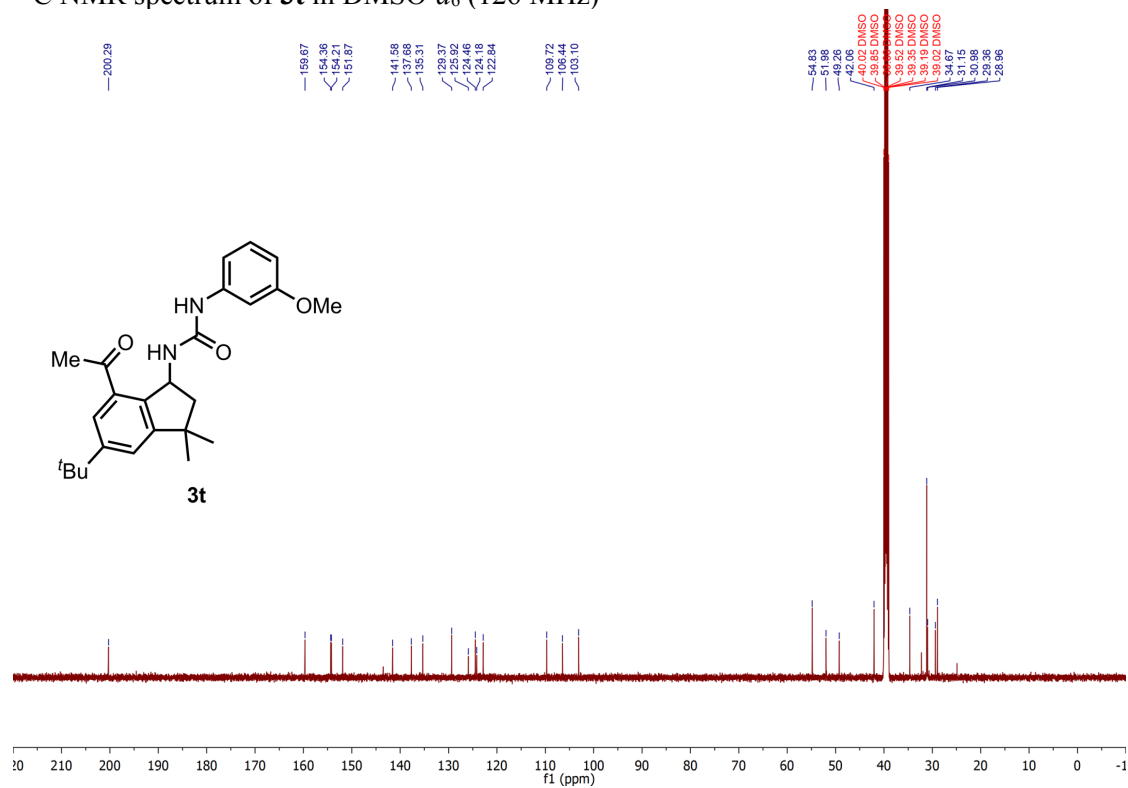
^{13}C NMR spectrum of **3s** in $\text{DMSO-}d_6$ (126 MHz)



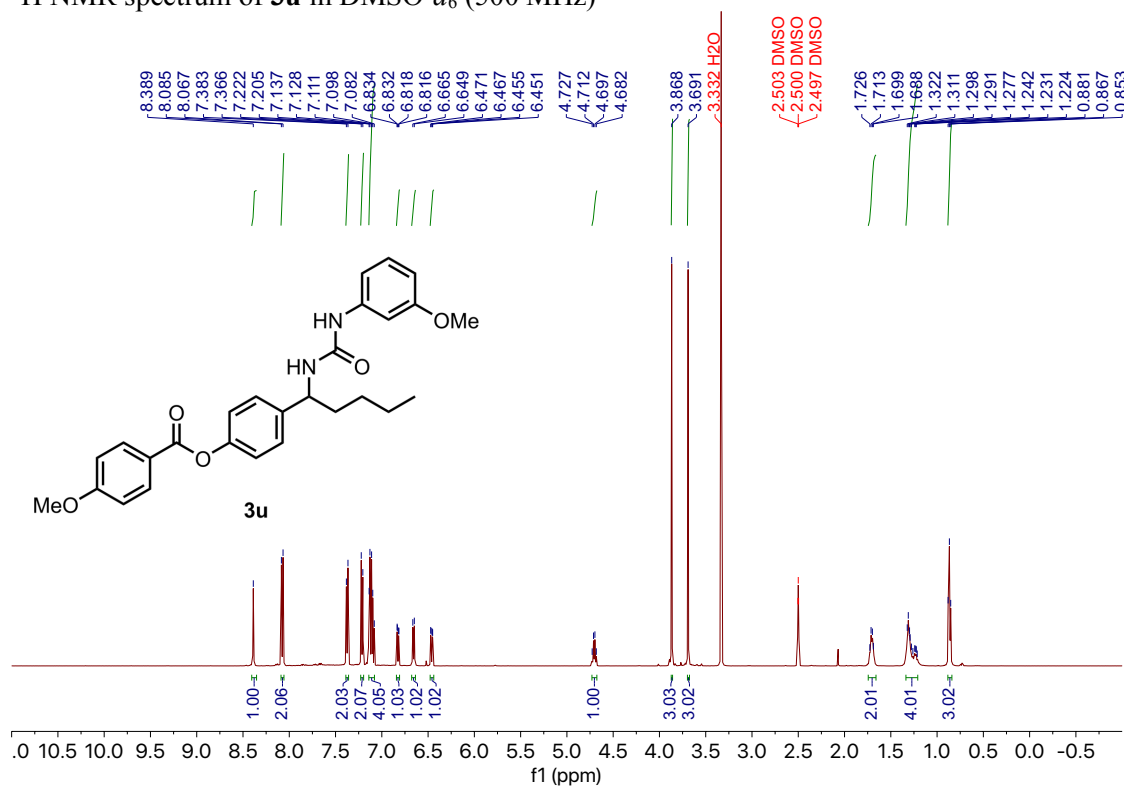
^1H NMR spectrum of **3t** in $\text{DMSO-}d_6$ (500 MHz)



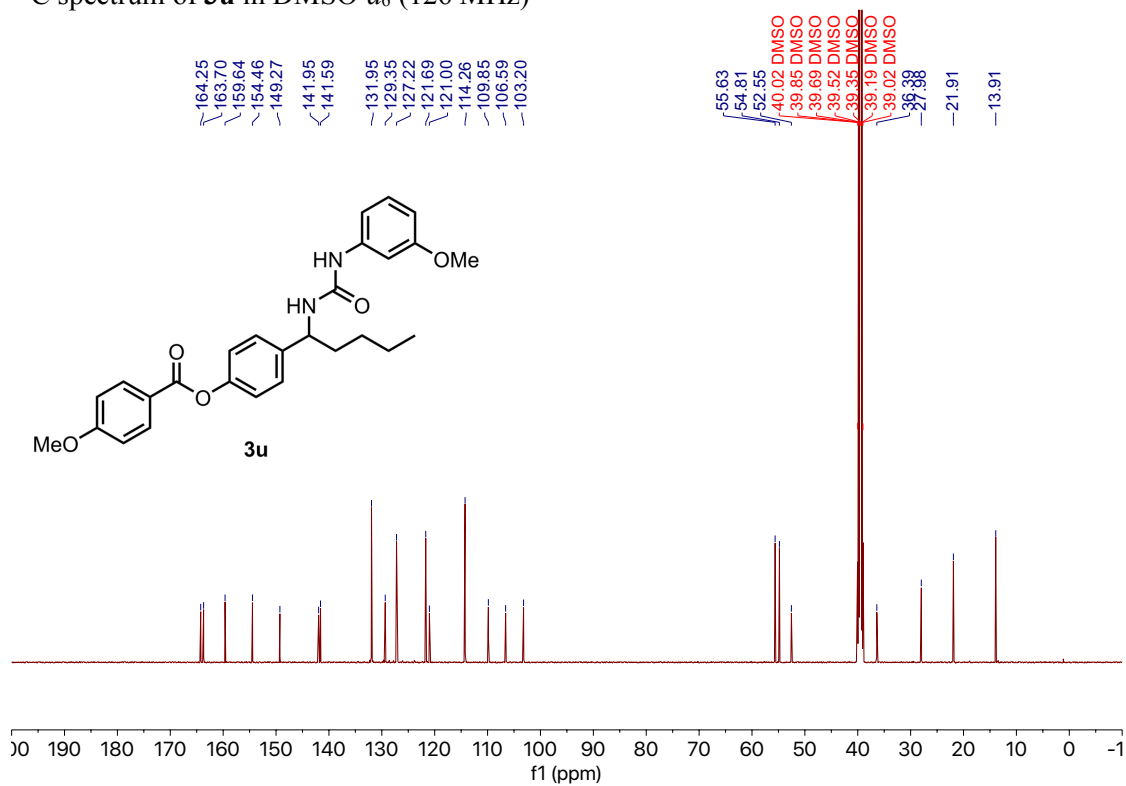
^{13}C NMR spectrum of **3t** in $\text{DMSO-}d_6$ (126 MHz)



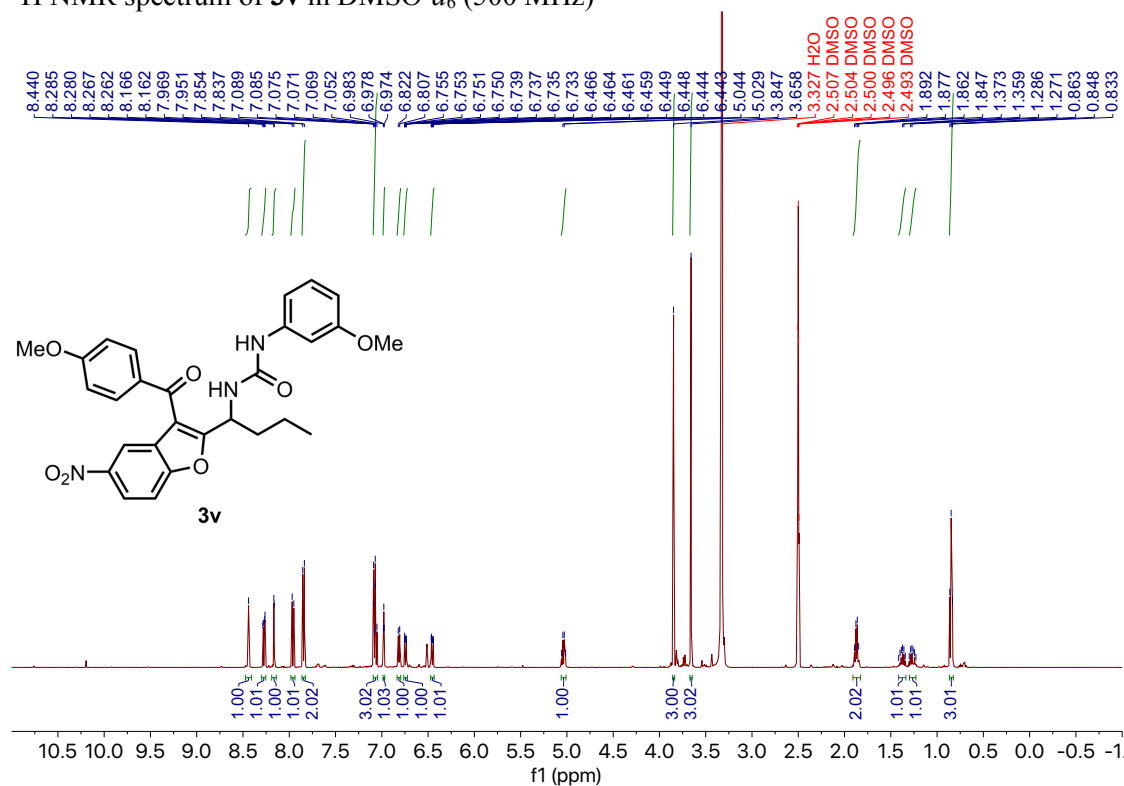
^1H NMR spectrum of **3u** in $\text{DMSO-}d_6$ (500 MHz)



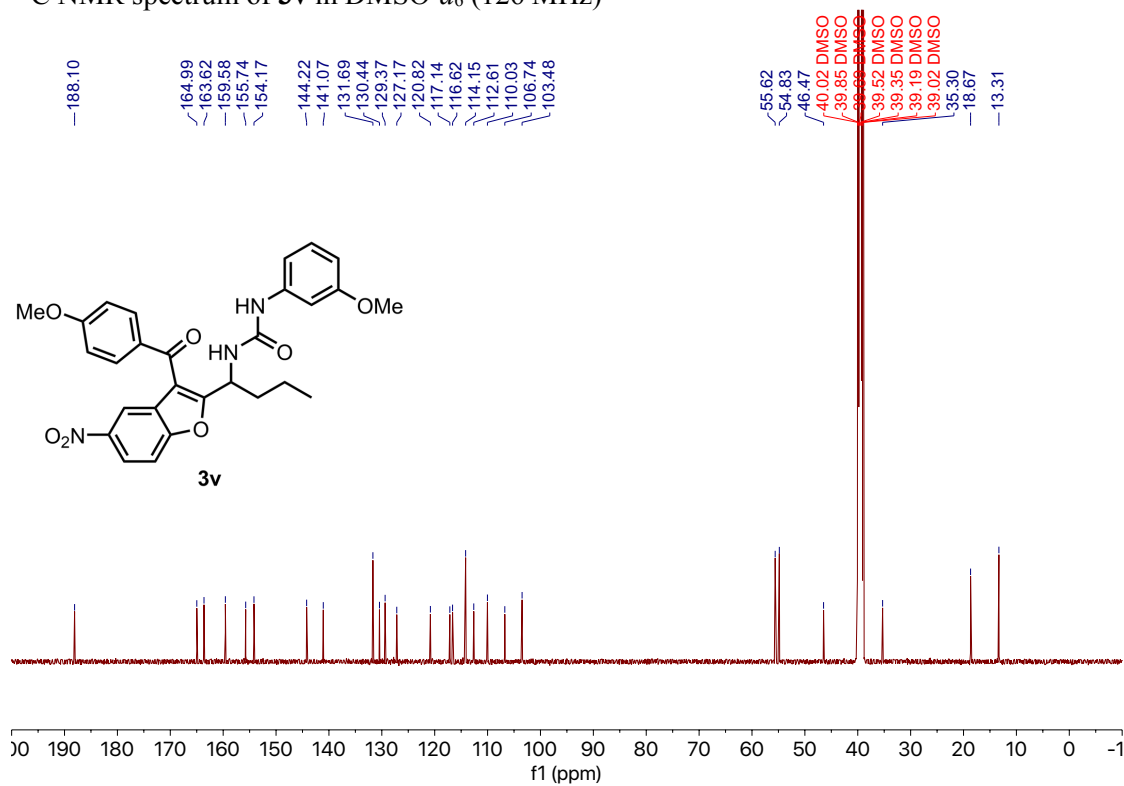
^{13}C spectrum of **3u** in $\text{DMSO-}d_6$ (126 MHz)



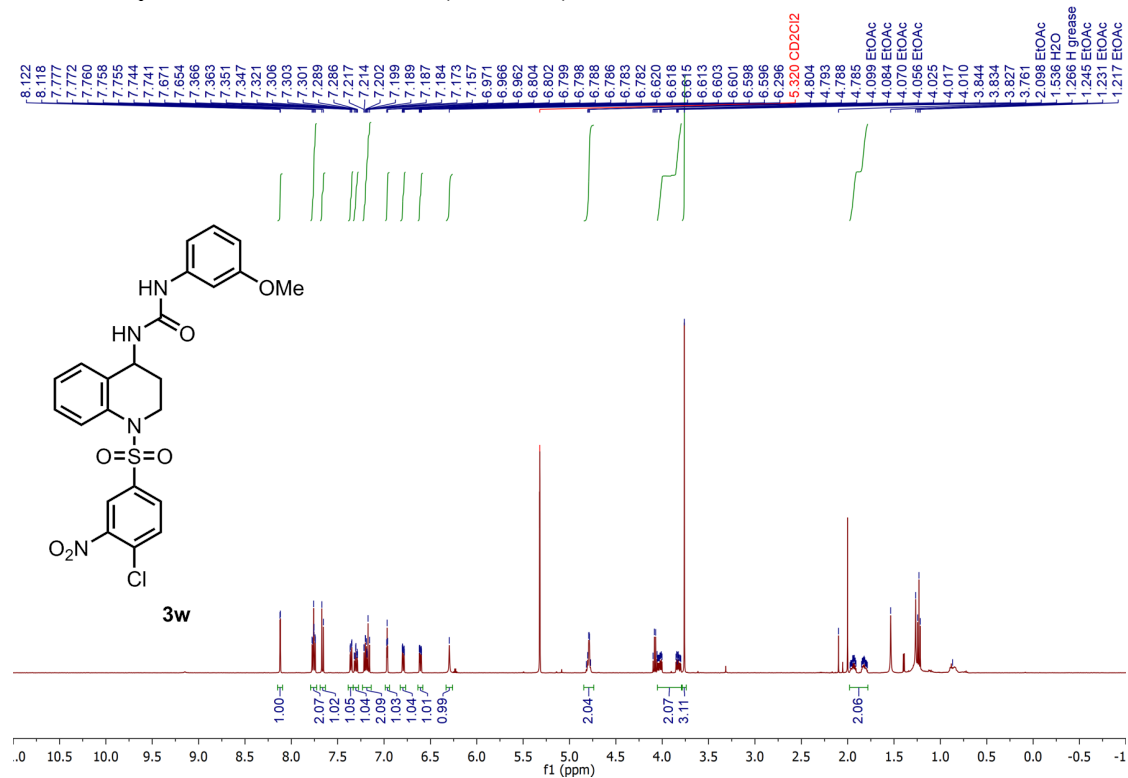
¹H NMR spectrum of **3v** in DMSO-*d*₆ (500 MHz)



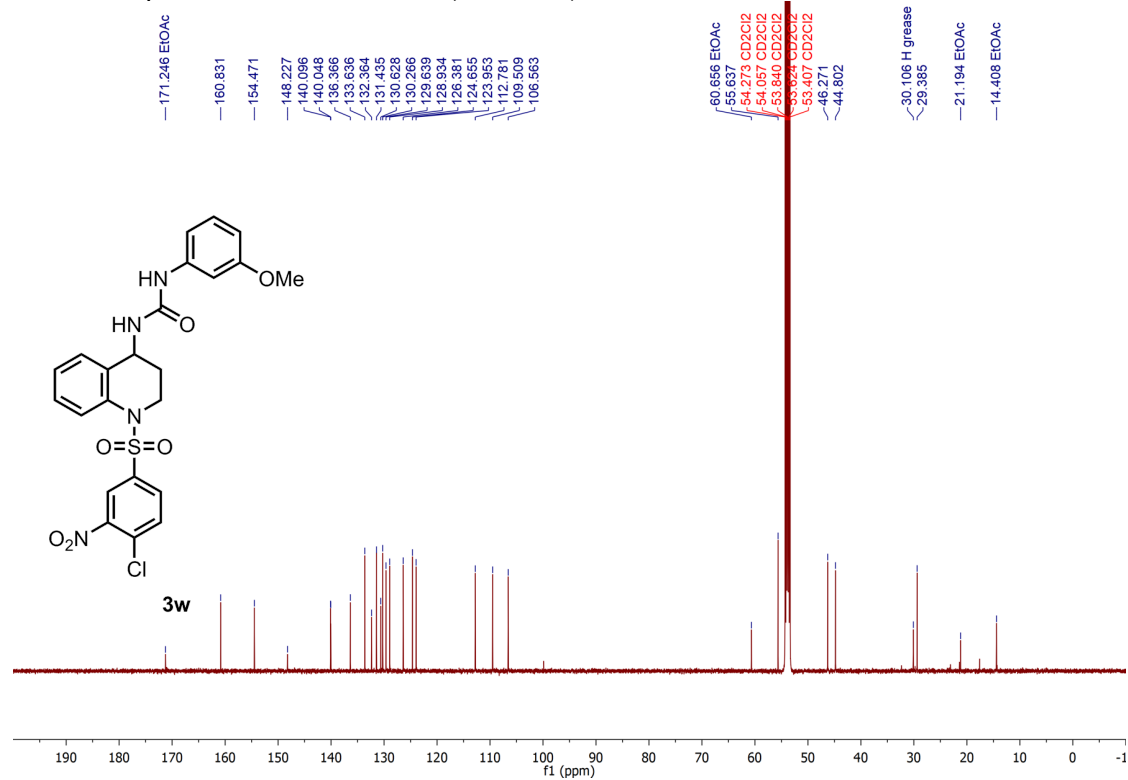
¹³C NMR spectrum of **3v** in DMSO-*d*₆ (126 MHz)



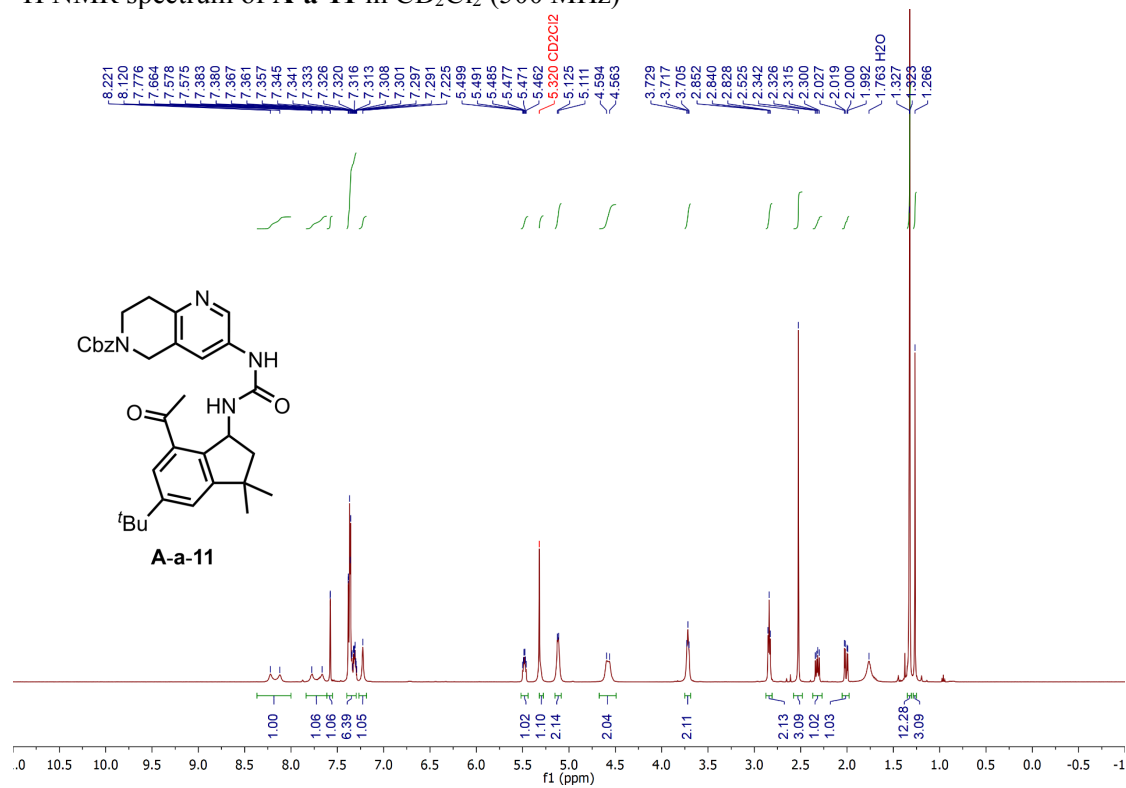
¹H NMR spectrum of **3w** in CD₂Cl₂ (500 MHz)



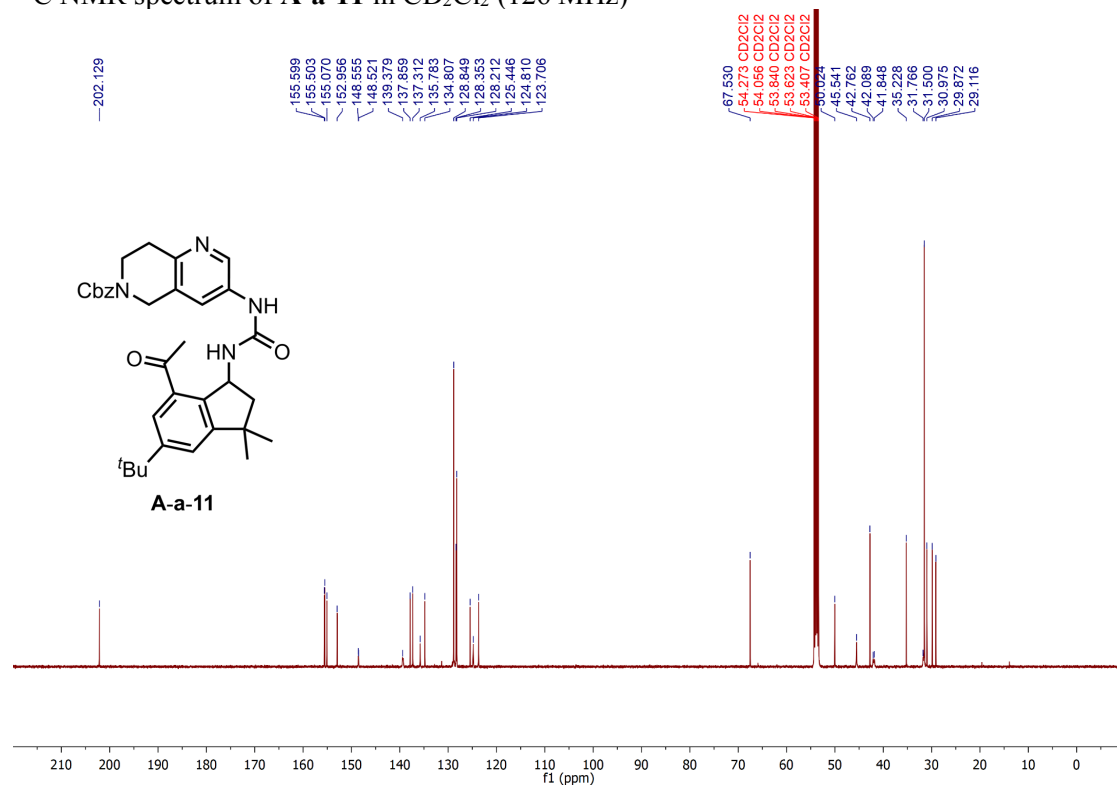
¹³C NMR spectrum of **3w** in CD₂Cl₂ (126 MHz)



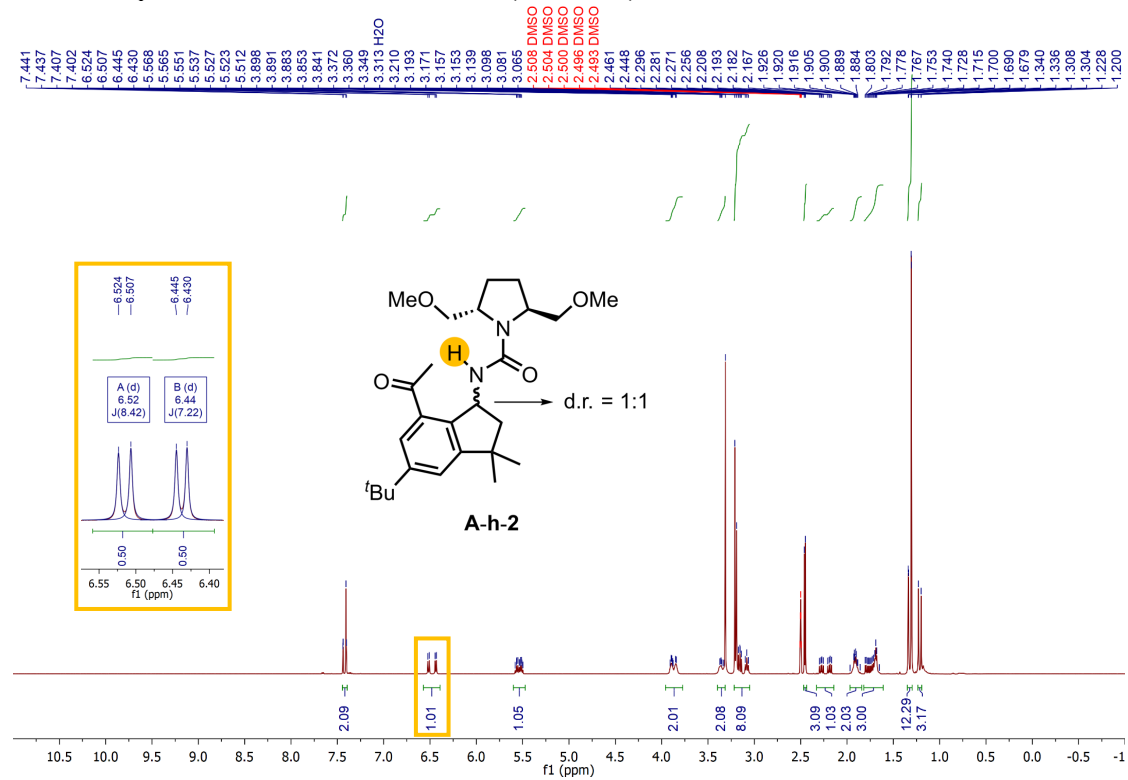
¹H NMR spectrum of **A-a-11** in CD₂Cl₂ (500 MHz)



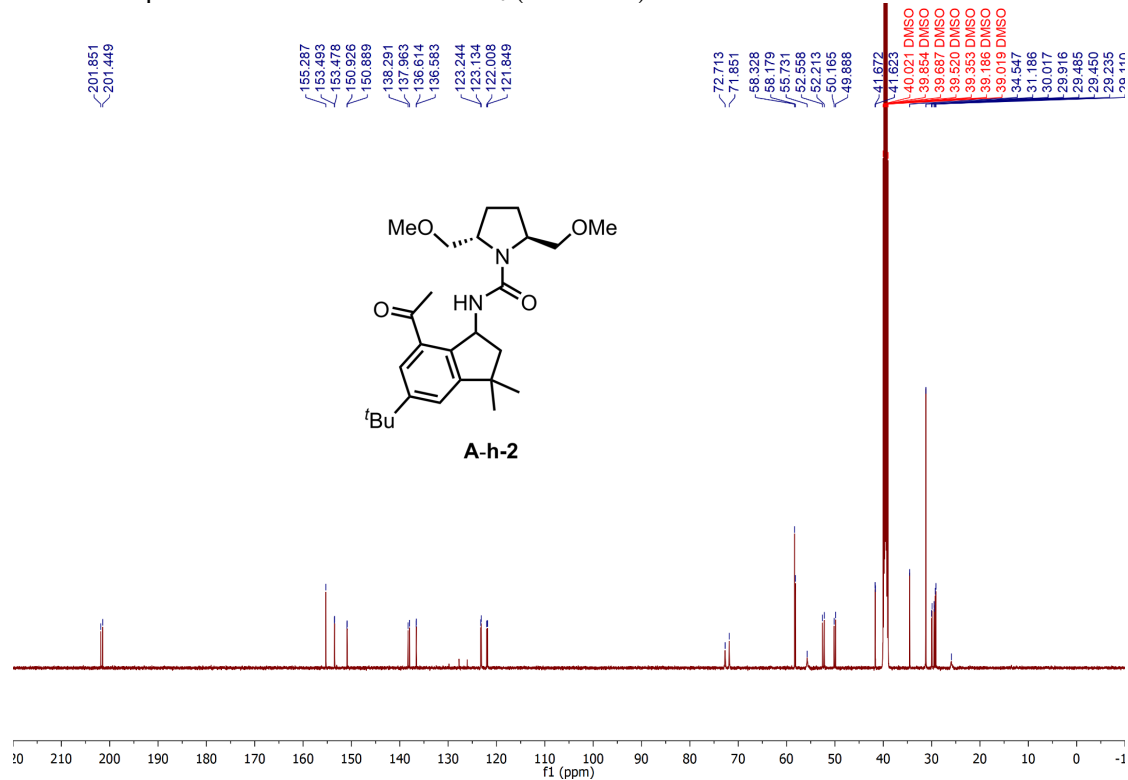
¹³C NMR spectrum of **A-a-11** in CD₂Cl₂ (126 MHz)



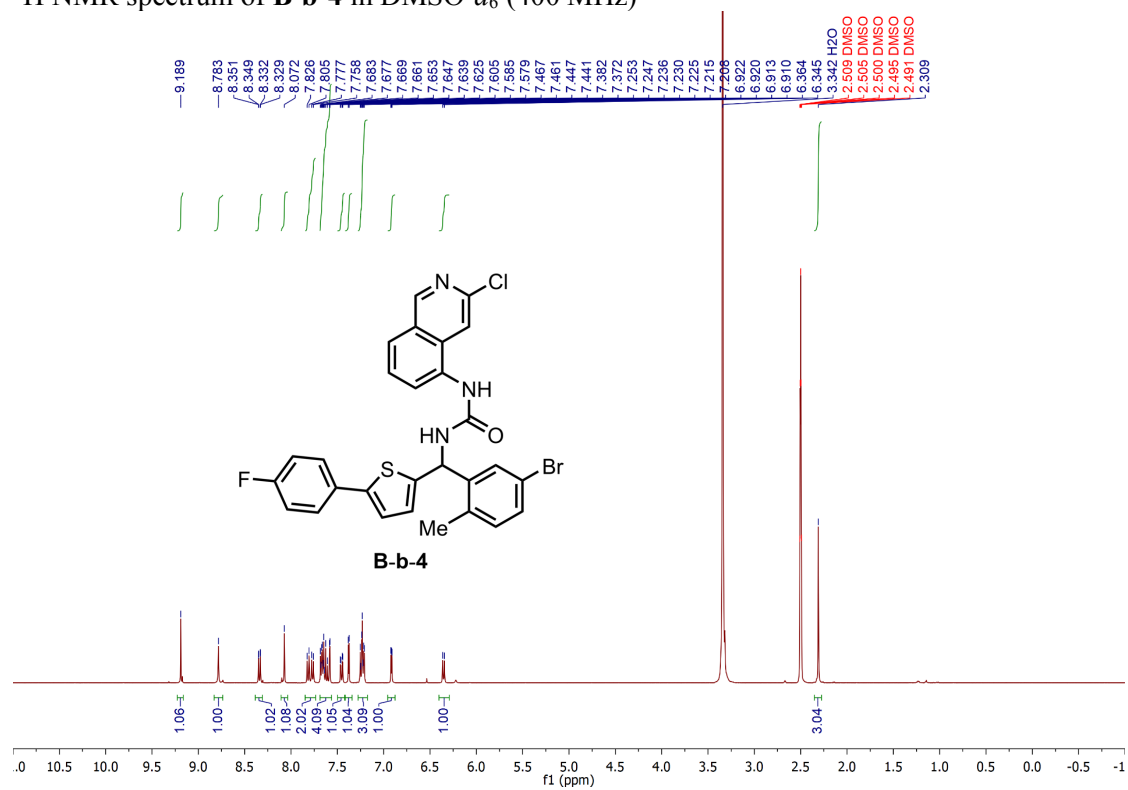
¹H NMR spectrum of **A-h-2** in DMSO-*d*₆ (500 MHz)



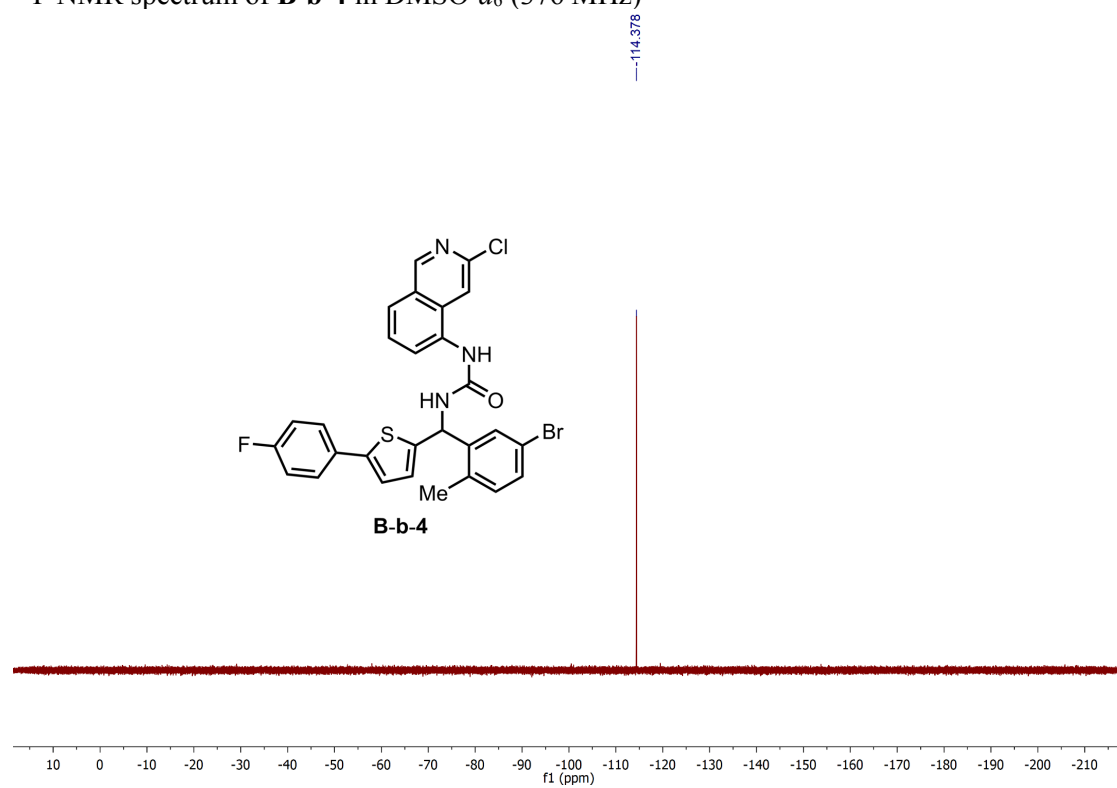
¹³C NMR spectrum of **A-h-2** in DMSO-*d*₆ (126 MHz)



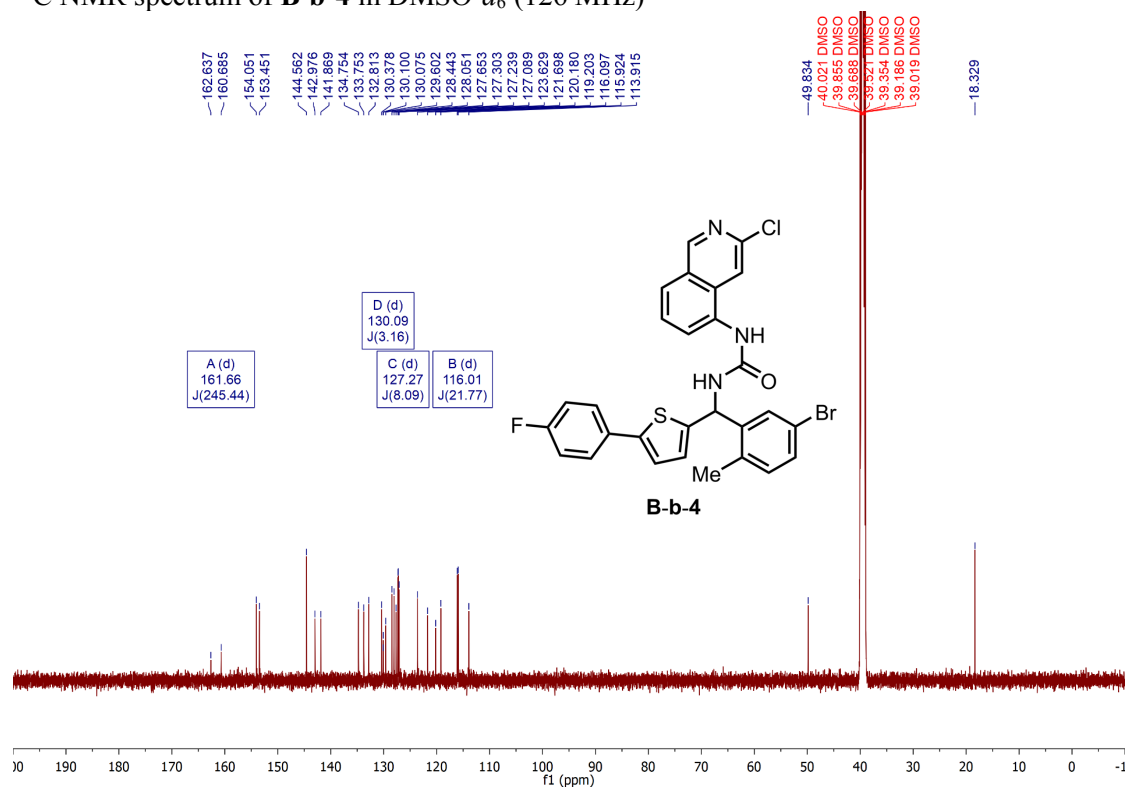
^1H NMR spectrum of **B-b-4** in $\text{DMSO-}d_6$ (400 MHz)



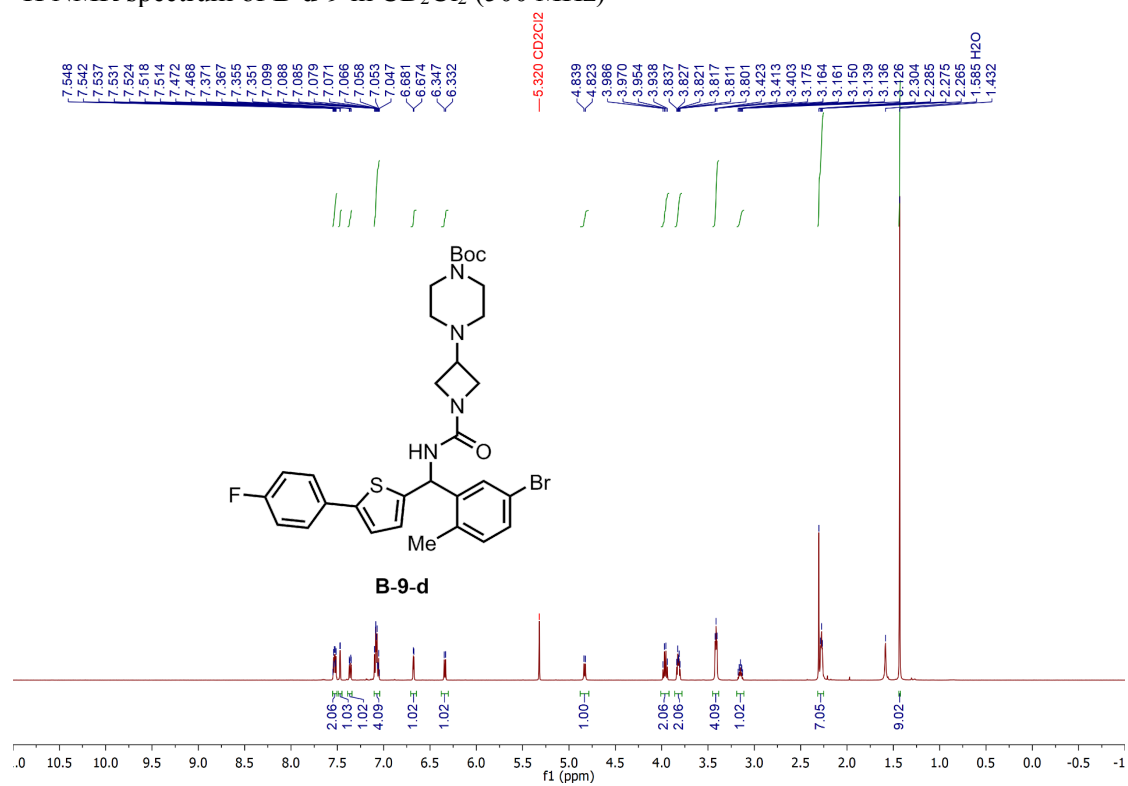
^{19}F NMR spectrum of **B-b-4** in $\text{DMSO-}d_6$ (376 MHz)



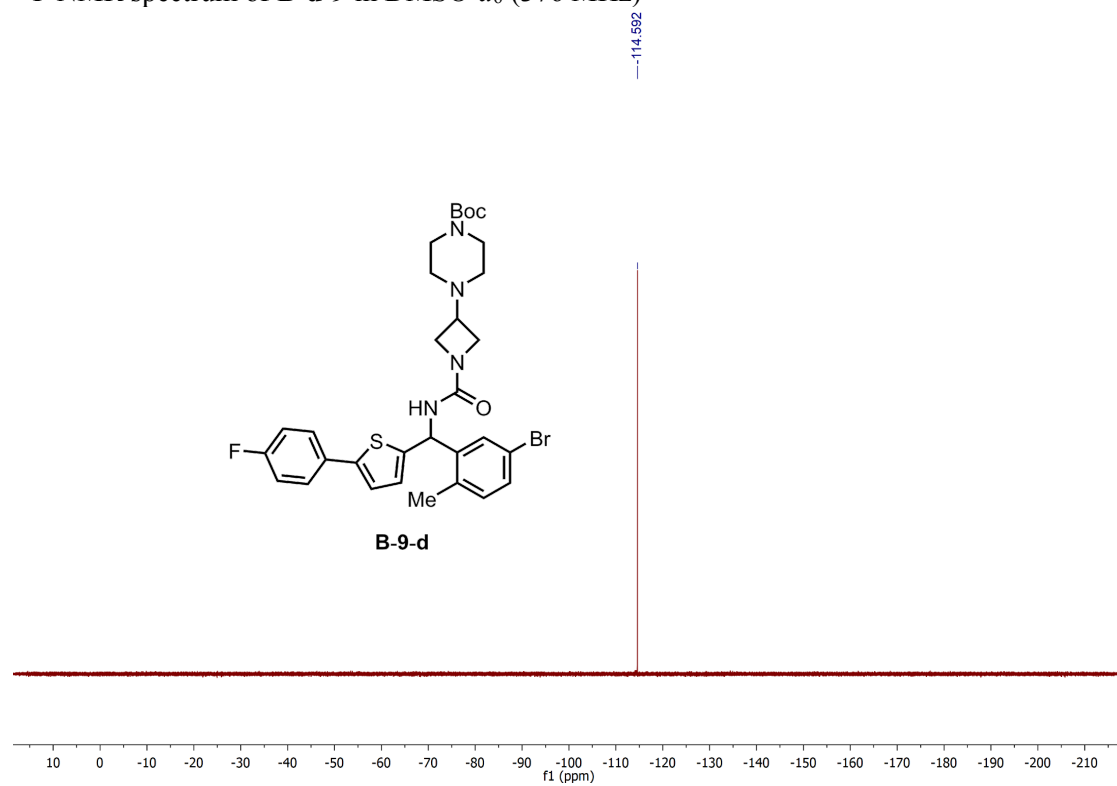
^{13}C NMR spectrum of **B-b-4** in $\text{DMSO-}d_6$ (126 MHz)



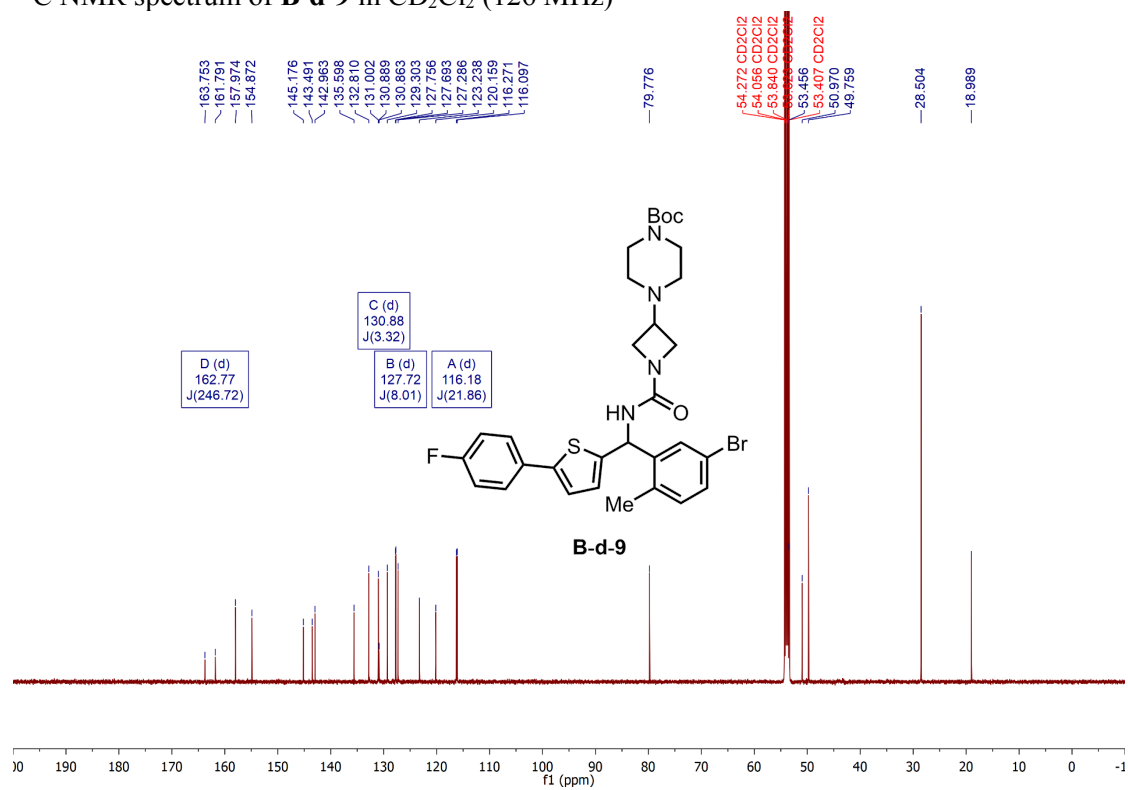
^1H NMR spectrum of **B-d-9** in CD_2Cl_2 (500 MHz)



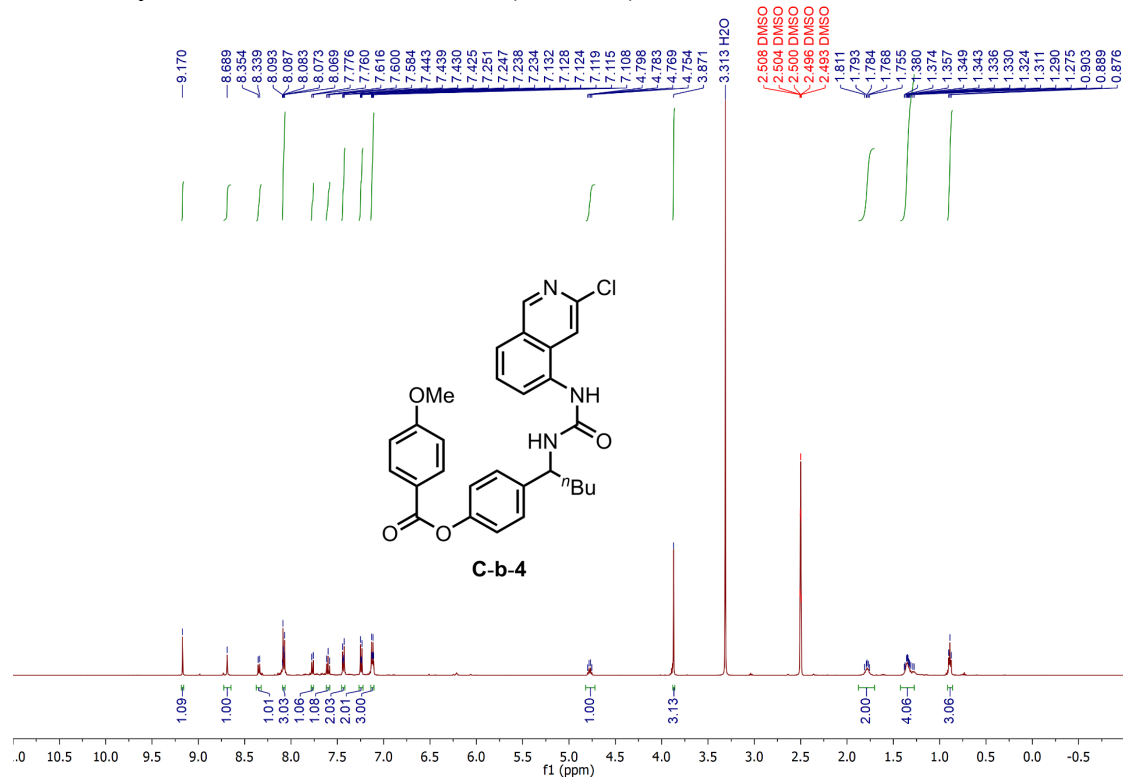
^{19}F NMR spectrum of **B-d-9** in $\text{DMSO}-d_6$ (376 MHz)



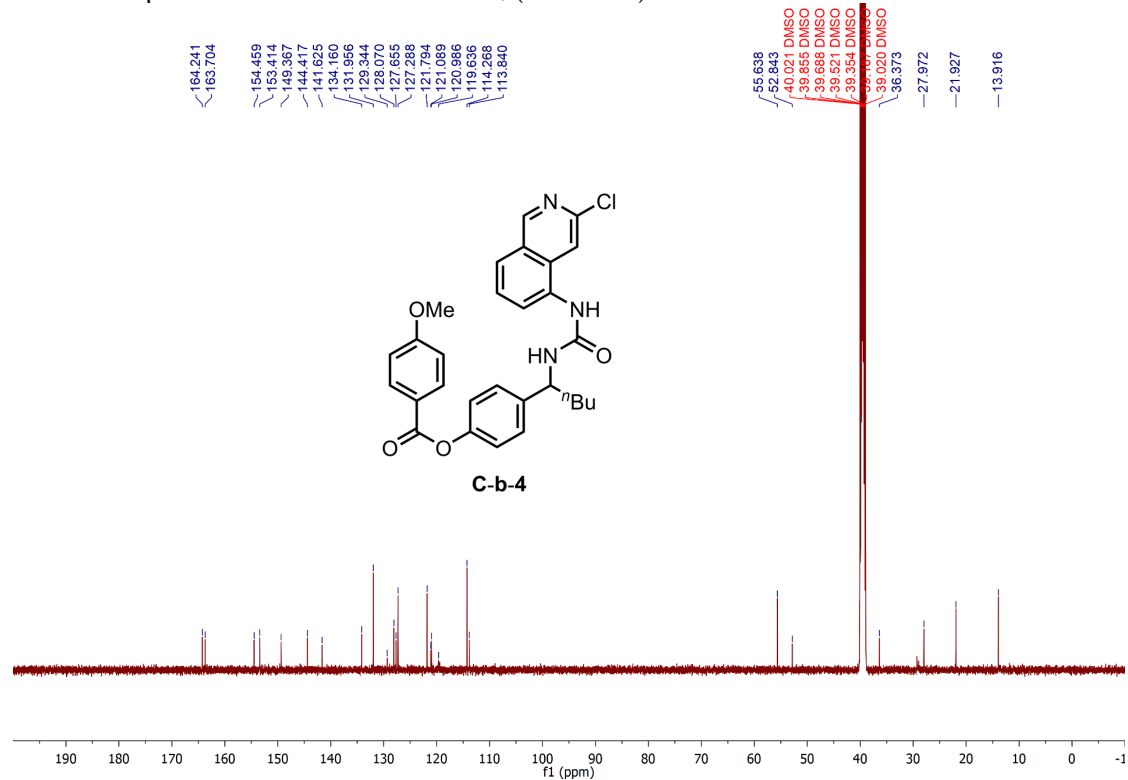
^{13}C NMR spectrum of **B-d-9** in CD_2Cl_2 (126 MHz)



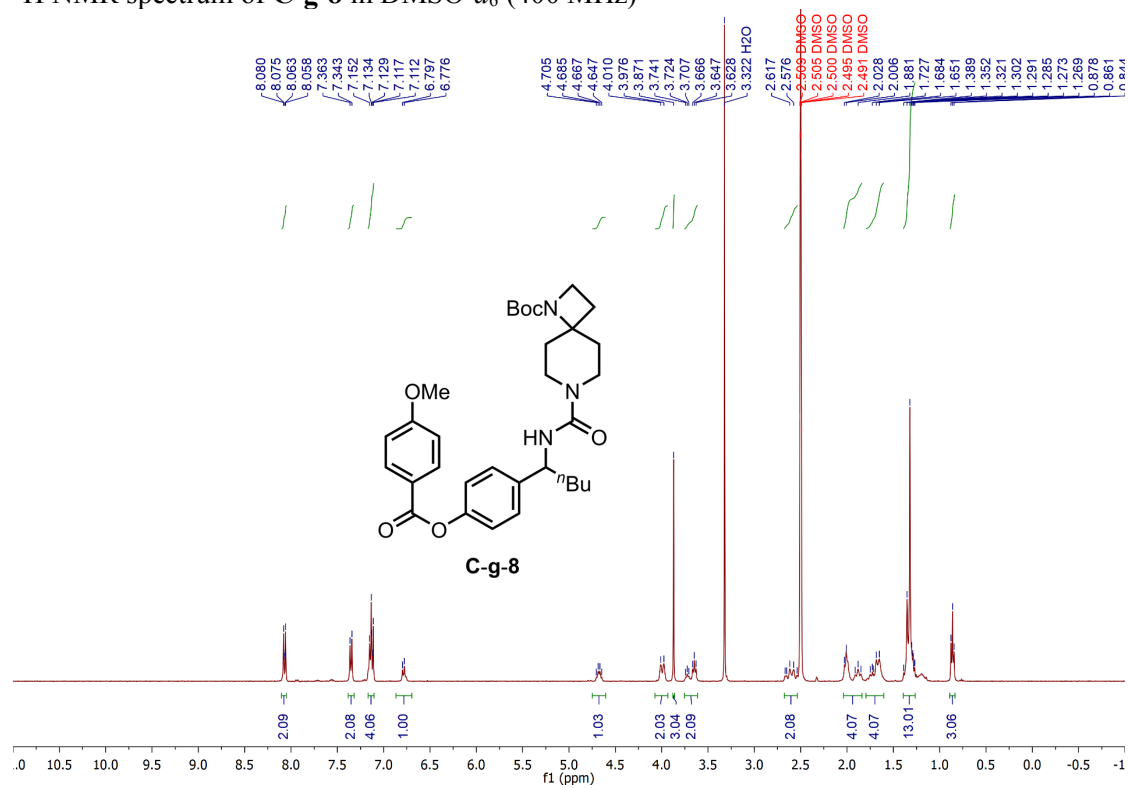
¹H NMR spectrum of C-b-4 in DMSO-d₆ (500 MHz)



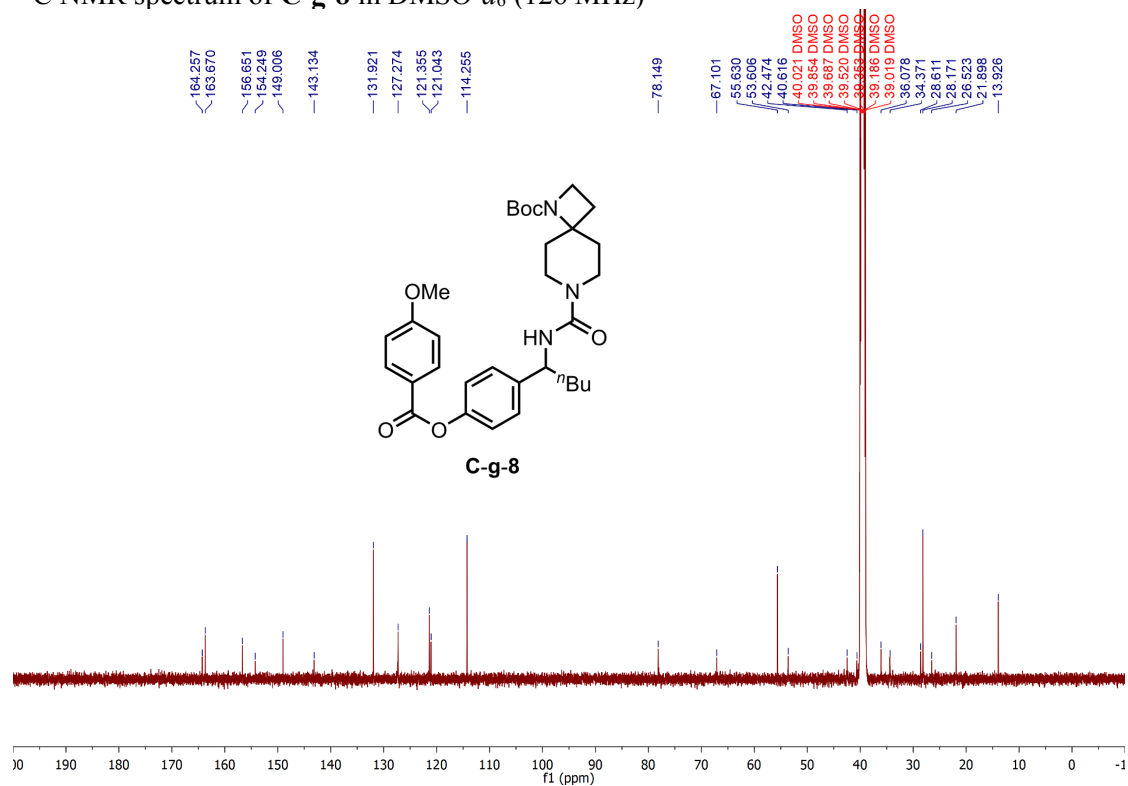
¹³C NMR spectrum of C-b-4 in DMSO-d₆ (126 MHz)



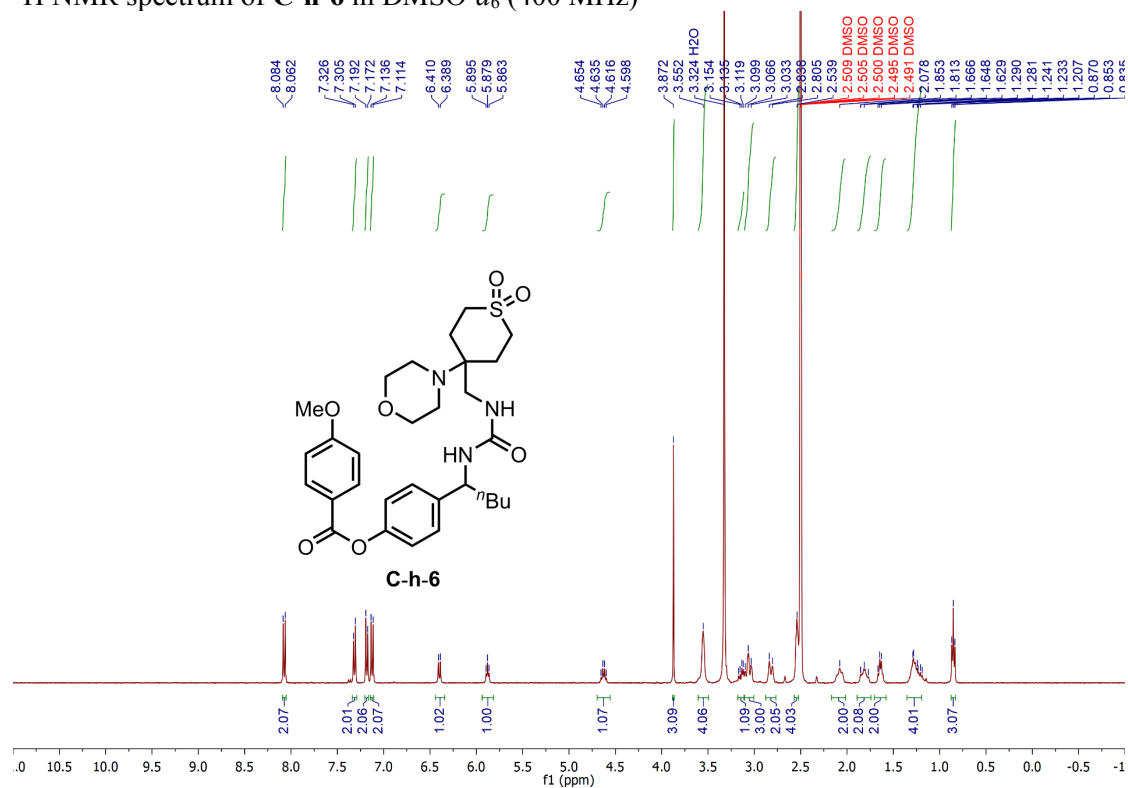
¹H NMR spectrum of C-g-8 in DMSO-d₆ (400 MHz)



¹³C NMR spectrum of C-g-8 in DMSO-d₆ (126 MHz)



¹H NMR spectrum of C-h-6 in DMSO-d₆ (400 MHz)



¹³C NMR spectrum of C-h-6 in DMSO-d₆ (126 MHz)

