

Synthesis of Novel Heterocycles by Amide Activation and Umpolung Cyclization

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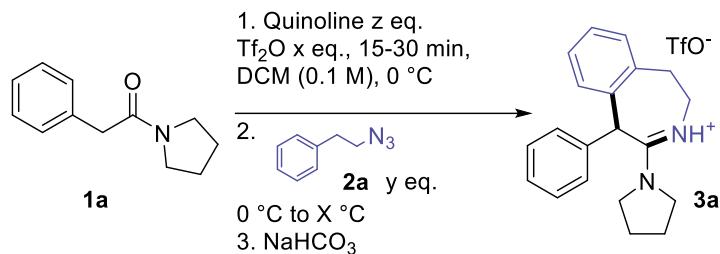
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1. General Information

Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon with anhydrous solvents. Triflic anhydride was distilled over P₂O₅ prior to use. All other reagents were used as received from commercial suppliers unless otherwise stated. Reaction requiring higher temperature were heated in an oil bath. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). DMA mixture for column chromatography was made of DCM, MeOH, concentrated ammonia (90:10:1). Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (vmax) are reported in cm-1. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All ¹H NMR and ¹³C NMR spectra were recorded using a Bruker AV-400, AV-600 and AV-700 spectrometer at 300K. Chemical shifts were given in parts per million (ppm, δ) and coupling constants (J) are quoted in Hz, referenced to the solvent peak of CDCl₃, defined at δ = 7.26 ppm (¹H NMR) and δ = 77.16 (¹³C NMR). Coupling constants are quoted in Hz (J). ¹H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Selected ¹³C NMR spectra were recorded using the attached proton test (APT) to facilitate the confirmation and assignment of the structure.

2. Optimization

2.1. Amidine



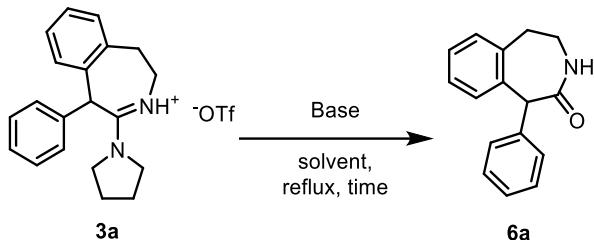
Entry	x (eq)	t (min)	y (eq)	Quinoline	z (eq)	T	Yield
1	2	15	2		5	rt	48%
2	2	15	2		5	rt	-
3	2	15	2		5	rt	-
4	2	15	2		2	rt	63%
5	2	15	2		2	rt	75%
6	2	15	2		2	40 °C	63%
7	2	15	2		2	rt	66%
8	2	15	1.1		2	rt	78%
9	1.1	15	1.1		2	rt	53%
10	1.1	30	1.1		2	rt	59%
11	1.4	15	1.1		2	rt	67%

Table S1 Reaction optimization. Yields refer to isolated product. Reactions were carried out on 0.2 mmol scale.

2.2. Hydrolysis of Amidine

To a solution of **3a** in [solvent] was added aqueous [base]. The mixture was stirred for [time] under reflux. After cooling down and quenching with NH_4Cl (sat.), the layers were separated and the aqueous phase was washed with DCM (3x). The combined organic layers were dried over Na_2SO_4 and

concentrated under reduced pressure. The product was purified via column chromatography (silica, DMA-DCM gradient, 0 to 20%).



Entry	Base	Solvent	Time	Yield ^a
1	1.0 mL NaOH (1 M, 5 eq)	1.0 mL THF	15 h	56 %
2	2.0 mL NaOH (1 M, 10 eq)	2.0 mL THF	24 h	43 %
3	1.0 mL NaOH (5 M, 25 eq)	1.0 mL THF	24 h	5 %
4	1.0 mL NaOH (1 M, 5 eq)	1.0 mL EtOH	15 h	7 %
5	1.0 mL KOH (1 M, 5 eq)	1.0 mL THF	15 h	10 %
6	1.0 mL NaOH (1 M, 5 eq)	1.0 mL Dioxane	15 h	22 %
7	1.0 mL NaOH (1 M, 5 eq)	5.0 mL THF	15 h	0 %
8	1.0 mL NaOH (1 M, 5 eq) TPA-OH (0.1 eq)	1.0 mL THF	15 h	63 %

Table S2 Hydrolysis optimization. Yields refer to isolated product. Reactions were carried out on 0.2 mmol scale.

Reaction conditions: A mixture of **3a** (0.2 mmol, 1 eq.), solvent and base were stirred under reflux for 15 h. ^aIsolated yields.

3. Substrates

3.1. Amide Synthesis

General Procedure A

To a solution of the amine (1.0 eq.) and triethylamine (2.0 eq.) in DCM (0.1 M) at 0 °C, the corresponding acyl chloride (1.2 eq.) was added dropwise and the resulting reaction mixture was allowed to warm up to room temperature while stirring for 14 h. Afterwards, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the biphasic system was separated. After extraction of the aqueous phase with DCM (2x), the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate, 40:60) to afford the desired compound.

General Procedure B

The acyl chloride was first prepared *via* addition of oxalyl chloride (3 eq.) to a mixture of carboxylic acid (1 eq.) and catalytic amount of *N,N*-dimethylformamide (0.1 eq.) in DCM (0.2 M) at room temperature. After stirring for 14 h, the solvent and excess of oxalyl chloride were removed under reduced pressure. The crude acyl chloride was directly dissolved in DCM (0.2 M) and pyrrolidine (5 eq.) was added. The mixture was stirred for 5 h at room temperature. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate. After separation, the organic layer was washed with HCl (1 M), NaHCO₃ (sat.) and brine. The product was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The pure product was used without further purification.

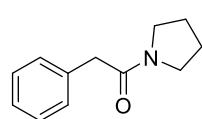
General Procedure C

To a solution of carboxylic acid (1.0 eq.), HOEt (1.0 eq.) and EDCI (1.0 eq.) in DCM (0.5 M) were added the secondary amine (1.0 eq.) and triethylamine (1.0 eq.). The mixture was stirred for 16 h under argon atmosphere at room temperature. The mixture was diluted with EtOAc (5 DCM volumes). The organic layer was washed with HCl 1M. then a saturated solution of NaHCO₃ then brine. The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure.

General Procedure D

HATU (1.2 eq.) was added to a solution of secondary amine (1.2 eq.), carboxylic acid (1 eq.) and triethylamine (2.4 eq.) in 0.4 M DMF. The reaction was stirred overnight at room temperature before quenching with 1M NaOH. The mixture was then extracted with ether, washed with sat. NH₄Cl solution, dried over Na₂SO₄, and then evaporated.

2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one **1a**

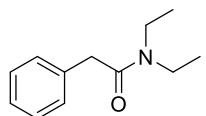


The desired amide was prepared using procedure **A** with 10.0 mmol pyrrolidine (821 µL), 12.0 mmol phenylacetyl chloride (1.62 mL) and 20.0 mmol of Et₃N (2.79 mL).

Yield (yellow-white solid): 91 % (1.72 g).

Spectroscopic data are in agreement with the literature.¹

N,N-Diethyl-2-phenylacetamide **1b**

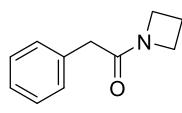


The desired amide was prepared using procedure **C** with 7.34 mmol diethylamine (760 µL), 7.34 mmol phenylacetic acid (1.00 g), 7.34 mmol HOBr (992 mg), 7.34 mmol EDCI.HCl (1.41 g) and 7.34 mmol of Et₃N (1.02 mL). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

Yield (colourless oil): 82 % (1.15 g).

Spectroscopic data are in agreement with the literature.²

1-(azetidin-1-yl)-2-phenylethan-1-one **1c**



The desired amide was prepared using procedure **C** with 10 mmol azetidine hydrochloride (936 µL), 10 mmol phenylacetic acid (1.36 g), 10 mmol HOBr (1.35 g), 10 mmol EDCI.HCl (1.92 g) and 20 mmol of Et₃N (2.79 mL). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

Yield (colourless oil): 29 % (505 mg).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.35 – 7.21 (m, 5H), 4.14 – 4.08 (m, 2H), 4.06 – 4.00 (m, 2H), 3.45 (s, 2H), 2.28 – 2.17 (m, 2H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 170.8, 134.7, 129.0 (2C), 128.6 (2C), 126.8, 50.6, 48.1, 39.1, 15.1.

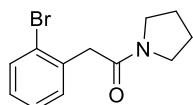
HRMS (ESI) m/z calculated for [M+H]⁺ C₁₁H₁₄NO⁺: 176.1070, found 176.1073.

ATR-FTIR (cm⁻¹): 2951, 1638, 1424, 1298, 1118, 720, 695.

¹ Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 5713–5715.

² Bannwart, L.; Abele, S.; Tortoioli, S. *Synthesis* **2016**, *48*, 2069–2078.

2-(2-bromophenyl)-1-(pyrrolidin-1-yl)ethan-1-one **1d**



The desired amide was prepared using procedure **C** with 3.06 mmol pyrrolidine (251 µL), 3.06 mmol 2-bromophenylacetic acid (658 mg), 3.06 mmol HOBr (468 mg), 3.06 mmol EDCI.HCl (586 mg) and 3.06 mmol of Et₃N (426 µL). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

Yield (colourless oil): 97 % (780 mg).

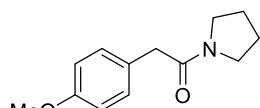
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.55 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 10.8, 3.4 Hz, 1H), 7.13 – 7.09 (m, 1H), 3.77 (s, 2H), 3.52 (t, *J* = 6.9 Hz, 2H), 3.48 (t, *J* = 6.8 Hz, 2H), 1.96 (m, 2H), 1.87 (m, 2H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 168.6, 135.4, 132.7, 131.1, 128.6, 127.7, 125.0, 47.0, 46.1, 42.2, 26.3, 24.6.

HRMS (ESI) m/z calculated for [M+Na]⁺ C₁₂H₁₄BrNNaO⁺: 290.0151, found 290.0149.

ATR-FTIR (cm⁻¹): 2951, 2880, 1638, 1424, 1118, 720, 695.

2-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)ethan-1-one **1e**

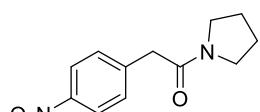


The desired amide was prepared using procedure **B** with 1.0 mmol 4-Methoxyphenylacetic Acid (166 mg), 0.10 mmol DMF (7.7 µL), 3.0 mmol oxalyl chloride (254 µL) and 5.0 mmol pyrrolidine (411 µL).

Yield (yellow oil): 95 % (209 mg).

Spectroscopic data are in agreement with the literature.³

2-(4-nitrophenyl)-1-(pyrrolidin-1-yl)ethan-1-one **1f**



The product was obtained using general procedure **D** from 5.0 mmol 4-nitrophenylacetic acid (906 mg), 6.0 mmol pyrrolidine (493 µL), 6.0 mmol HATU (2.28 g) and 12 mmol triethylamine (1.67 mL). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

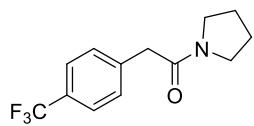
Yield (yellow oil): 81 % (945 mg)

Spectroscopic data are in agreement with the literature.⁴

³ Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058–1067.

⁴ Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925–9932.

1-(pyrrolidin-1-yl)-2-(4-(trifluoromethyl)phenyl)ethan-1-one **1g**

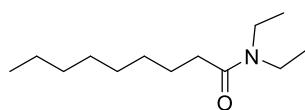


The desired amide was prepared using modified procedure **C** with THF as solvent and 3.76 mmol pyrrolidine (309 µL), 2.89 mmol 4-trifluorophenylacetic acid (590 mg), 3.76 mmol HOt (508 mg), 3.76 mmol EDCI.HCl (720 mg) and 7.51 mmol of Et₃N (1.05 mL). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

Yield (white solid): 88 % (653 mg).

Spectroscopic data are in agreement with the literature.⁴

N,N-diethylnonanamide **S1**

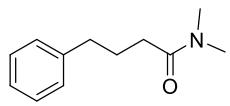


The desired amide was prepared using procedure **A** with 6.0 mmol diethylamine (621 µL), 5.0 mmol nonanoyl chloride (901 µL) and 10.0 mmol of Et₃N (1.39 mL).

Yield (yellow oil): quant. (1.01 g).

Spectroscopic data are in agreement with the literature.⁵

N,N-dimethyl-4-phenylbutanamide **S2**



The product was prepared according to general procedure **C** from 2.46 g 4-phenylbutyric acid and 4-nitrobenzenesulfonyl chloride (15.0 mmol) and 7.5 mL dimethylamine (2.0 M in THF), (15.0 mmol). The crude product was purified by column chromatography (Heptane /EtOAc, from 80%/20% to 0%/100%).

Yield (yellow oil): 71% (2.04 g). in 71% (2.04 g) yield.

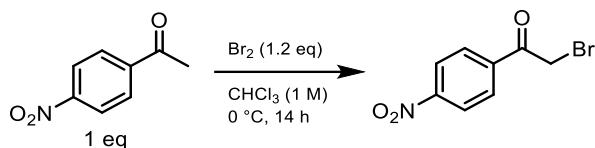
Spectroscopic data are in agreement with the literature.⁶

⁵ Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. *Org. Lett.* **2006**, *8*, 1383–1386.

⁶ Zhou, X.; Zhang, G.; Gao, B.; Huang, *Org. Lett.* **2018**, *20*, 2208–2212.

3.2. Bromide Synthesis

2-bromo-1-(4-nitrophenyl)ethan-1-one S3



A solution of 6 mmol bromine (307 µL) in chloroform (2 mL) was slowly added to a solution of 5 mmol 4-nitroacetophenone (826 mg) in chloroform (5 mL) at 0° C under continuous stirring. The temperature of the reaction mixture was maintained at 0–5 °C during the addition. After stirring for 14 h at r.t., the solvent was removed under reduced pressure. The product was purified by recrystallization in EtOH (ca. 10 mL) to yield pure compound.

Yield (yellow-white solid): 32 % (386 mg).

Spectroscopic data are in agreement with the literature.⁷

3.3. Azide Synthesis

General Procedure E

A solution of bromide (1 eq.) and NaN₃ (1.5 eq.) in DMF (0.2 M) was stirred at 80 °C overnight. After 14 h, the reaction mixture was cooled to r.t., diluted with Et₂O or EtOAc. The biphasic system was separated and the organic layer was washed with ice-cooled H₂O (4x) and brine (1x). The pure product was obtained after drying over anhydrous Na₂SO₄ and evaporation of the solvent under reduced pressure to obtain the pure product which was used without further purifications.

General Procedure F

The corresponding halide was added to a solution of NaN₃ (1.5 eq. or 3 eq.) in DMSO (0.5 M) at 0 °C and the reaction mixture was stirred at 23 °C for 10 min or 14 h. Ice-cooled H₂O was added to the mixture and the mixture was extracted with diethyl ether (3x). The combined organic layers were washed with ice-cooled H₂O (4x) and brine (1x), dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure to obtain the pure product which was used without further purifications.

General Procedure G

The corresponding chloride was added to a suspension of NaN₃ (1.5 eq.) in acetone (0.2 M) and stirred for 36 h. Afterwards, the mixture was filtered. The filtrate was evaporated under reduced pressure to obtain the pure product which was used without further purification.

⁷ Tada, N.; Ban, K.; Hirashima, S.; Miura, T.; Itoh, A. Direct Synthesis of α-Bromoketones from Alkylarenes by Aerobic Visible Light Photooxidation. *Org. Biomol. Chem.* **2010**, *8*, 4701–4704.

(2-azidoethyl)benzene **2a**

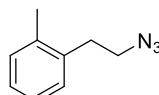


The product was prepared using procedure **E** with 10 mmol (2-Bromoethyl)benzene (1.37 mL) and 15 mmol sodium azide (975 mg) in DMF.

Yield (yellow oil): 87 % (1.29 g).

Spectroscopic data are in agreement with the literature.⁸

1-(2-azidoethyl)-2-methylbenzene **2b**

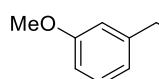


The product was prepared using procedure **E** with 1 mmol 2-Methylphenethyl bromide (169 µL) and 1.5 mmol sodium azide (97.5 mg) in DMF.

Yield (yellow oil): 93 % (150 mg).

Spectroscopic data are in agreement with the literature.⁹

1-(2-azidoethyl)-3-methoxybenzene **2c**



The product was prepared using procedure **E** with 1 mmol 3-methoxyphenethyl bromide (215 mg) and 1.5 mmol sodium azide (97.5 mg) in DMF.

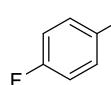
Yield (clear oil): 90 % (160 mg).

Spectroscopic data are in agreement with the literature.⁹

⁸ Kalkeren, H. A. van; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, F. L. *Advanced Synthesis & Catalysis* **2012**, *354*, 1417–1421.

⁹ Suzuki, T.; Ota, Y.; Ri, M.; Bando, M.; Gotoh, A.; Itoh, Y.; Tsumoto, H.; Tatum, P. R.; Mizukami, T.; Nakagawa, H.; et al. *J. Med. Chem.* **2012**, *55*, 9562–9575.

1-(2-azidoethyl)-4-fluorobenzene 2d

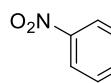


To a 0.5 M solution of NaN_3 (1.1 eq., 2.2 mmol, 143 mg) in 4 mL DMSO was added *p*-Fluorophenethyl bromide (1.0 eq., 2 mmol, 0.28 mL), and the mixture was stirred at 80 °C and periodically monitored by TLC. When the reaction was completed, the mixture was quenched with water and stirred until it cooled down to room temperature and then extracted with Et_2O . The organic layer was separated, washed with water and brine, and dried over Na_2SO_4 . Filtration, concentration in *vacuo*, and purification of the residue by silica gel flash column chromatography gave the corresponding alkyl azide.

Yield (clear oil): quantitative (330 mg).

Spectroscopic data are in agreement with the literature.⁹

1-(2-azidoethyl)-3-nitrobenzene 2e

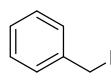


The product was prepared using procedure E with 1 mmol bromide (230 mg) and 1.5 mmol sodium azide (97.5 mg) in DMF.

Yield (yellow oil): 99 % (191 mg).

Spectroscopic data are in agreement with the literature.⁹

Benzyl azide 2f

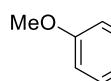


The product was obtained using general procedure E from 10 mmol benzyl bromide (1.19 mL) and 15 mmol sodium azide (975 mg).

Yield (yellow oil): quantitative (1.35 g).

Spectroscopic data are in agreement with the literature.¹⁰

1-(azidomethyl)-3-methoxybenzene 2g



The product was prepared using procedure E with 1 mmol 3-Methoxybenzyl bromide (143 μL) and 1.5 mmol sodium azide (97.5 mg) in DMF.

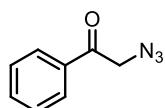
Yield (clear oil): 93% (151 mg).

Spectroscopic data are in agreement with the literature.¹¹

¹⁰ Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Eur. J. Org. Chem.* **2010**, 2010 (10), 1875–1884

¹¹ Montanari, S.; Scalvini, L.; Bartolini, M.; Belluti, F.; Gobbi, S.; Andrisano, V.; Ligresti, A.; Di Marzo, V.; Rivara, S.; Mor, M.; et al. *J. Med. Chem.* **2016**, 59, 6387–6406.

2-azido-1-phenylethan-1-one **7a**

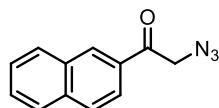


The product was prepared using procedure **F** with 5 mmol phenacyl bromide (995 mg) and 15 mmol sodium azide (975 mg) in DMSO.

Yield (orange oil): 92% (743 mg).

Spectroscopic data are in agreement with the literature.⁹

2-azido-1-(naphthalen-2-yl)ethan-1-one **7b**

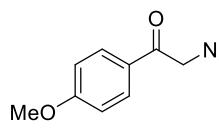


The product was prepared using procedure **F** with 1 mmol 2-Bromo-2'-acetonaphthone (249 mg) and 3 mmol sodium azide (195 mg) in DMSO.

Yield (orange solid): 94 % (198 mg).

Spectroscopic data are in agreement with the literature.¹²

2-azido-1-(4-methoxyphenyl)ethan-1-one **7c**

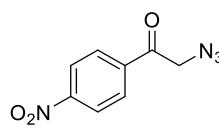


The product was prepared using procedure **F** with 1 mmol 2-Bromo-4'-methoxyacetophenone (229 mg) and 3 mmol sodium azide (195 mg) in DMSO.

Yield (yellow solid): 95 % (181 mg).

Spectroscopic data are in agreement with the literature.¹³

2-azido-1-(4-nitrophenyl)ethan-1-one **7d**



The product was prepared using procedure **F** with 1 mmol **S3** (244 mg) and 3 mmol sodium azide (195 mg) in DMSO.

Yield (red oil): 74 % (153 mg).

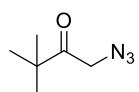
Spectroscopic data are in agreement with the literature.¹⁴

¹² Neyyappadath, R. M.; Chisholm, R.; Greenhalgh, M. D.; Rodríguez-Escrich, C.; Pericàs, M. A.; Hähner, G.; Smith, A. D. *ACS Catal.* **2018**, *8*, 1067–1075.

¹³ Yokoi, T.; Tanimoto, H.; Ueda, T.; Morimoto, T.; Kakiuchi, K. *J. Org. Chem.* **2018**, *83*, 12103–12121.

¹⁴ Gong, P. K.; Blough, B. E.; Brieaddy, L. E.; Huang, X.; Kuhar, M. J.; Navarro, H. A.; Carroll, F. I. *J. Med. Chem.* **2007**, *50* (15), 3686–3695.

1-azido-3,3-dimethylbutan-2-one **7e**

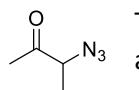


The product was prepared using procedure **G** with 1 mmol 1-Chloropinacoline (131 µL) and 1.5 mmol sodium azide (97.5 mg) in acetone.

Yield (yellow oil): 79 % (153 mg)

Spectroscopic data are in agreement with the literature.¹⁵

3-azidobutan-2-one **7f**

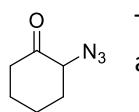


The product was prepared using procedure **G** with 2 mmol 3-Chloro-2-butanone (202 µL) and 3 mmol sodium azide (195 mg) in acetone.

Yield (yellow oil): 90 % (203 mg).

Spectroscopic data are in agreement with the literature.¹⁶

2-azidocyclohexan-1-one **7g**



The product was prepared using procedure **F** with 5 mmol 2-Chlorocyclohexanone (572 µL) and 7.5 mmol sodium azide (488 mg) in DMSO and stirring for 14 h.

Yield (brown oil): 78 % (545 mg).

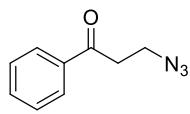
Spectroscopic data are in agreement with the literature.¹⁷

¹⁵ Streefkerk, D. E.; Schmidt, M.; Ippel, J. H.; Hackeng, T. M.; Nuijens, T.; Timmerman, P.; van Maarseveen, J. H. *Org. Lett.* **2019**, *21*, 2095–2100.

¹⁶ Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62* (8), 1864–1876.

¹⁷ Myers, E. L.; Raines, R. T. A. *Angew. Chem. Int. Ed.* **2009**, *48* (13), 2359–2363.

3-azido-1-phenylpropan-1-one 7h

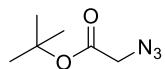


The product was prepared using procedure **F** with 5 mmol 3-Chloropropiophenone (843 mg) and 7.5 mmol sodium azide (488 mg) in DMSO and stirring for 14 h. Additional purification via column chromatography on silica gel (heptane/EtOAc 9:1) was performed.

Yield (yellow oil): 68 % (598 mg).

Spectroscopic data are in agreement with the literature.¹⁸

tert-butyl 2-azidoacetate 7i



The product was prepared using procedure **F** with 5 mmol *tert*-butyl bromoacetate (729 µL) and 7.5 mmol sodium azide (488 mg) in DMSO and stirring for 14 h.

Yield (yellow oil): 56 % (442 mg).

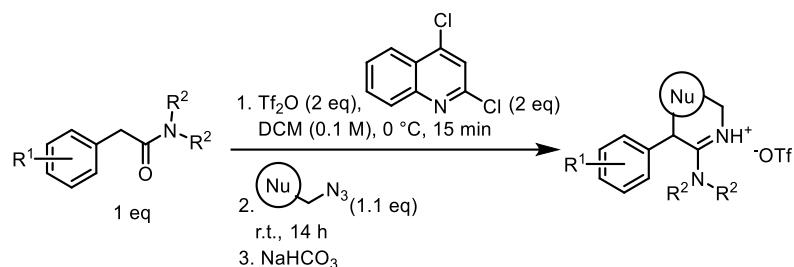
Spectroscopic data are in agreement with the literature.¹⁹

¹⁸ Singh, P. N. D.; Muthukrishnan, S.; Murthy, R. S.; Klima, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdóttir, A. D. *Tetrahedron Lett.* **2003**, 44, 9169–9171.

¹⁹ Asano, K.; Matsubara, S. *Org. Lett.* **2010**, 12, 4988–4991.

4. Amidines, Oxazines and Oxazinones

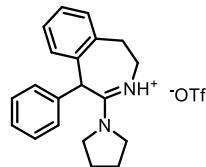
General Procedure H



To a mixture of amide (1.0 eq.), 2,4-dichloroquinoline (2.0 eq.) in anhydrous DCM (0.1 M), triflic anhydride (2.0 eq.) was added dropwise under vigorous stirring at 0 °C. After 15 min, the azide (1.1 eq.) was added and the mixture was stirred at r.t. for 14 h. The reaction was then quenched with a saturated aqueous solution of sodium bicarbonate for 1 h. After separation of the biphasic system and extraction of the aqueous phase with DCM (3×), the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure.

4.1. Amidines

5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium- trifluoromethanesulfonate 3a



The amidine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange solid): 78 % (69 mg).

Gram Scale Reaction

To a mixture of amide **1a** (757 mg, 4.0 mmol, 1.0 eq.), 2,4-dichloroquinoline (1.58 g, 8.0 mmol, 2.0 eq.) in anhydrous DCM (40 mL), triflic anhydride (1.35 mL, 8.0 mmol, 2.0 eq.) was added dropwise under vigorous stirring at 0 °C. After 15 min, azide **2a** (648 mg, 4.4 mmol, 1.1 eq.) was added and the mixture was stirred at r.t. for 14 h. The reaction was then quenched with a saturated aqueous solution of sodium bicarbonate for 1 h. After separation of the biphasic system and extraction of the aqueous phase with DCM (3×), the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70). The product was obtained as an orange solid (1.45 g, 83%).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 8.94 (br.s, 1H), 7.38 (m, 1H), 7.34 (m, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.27 – 7.23 (m, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 5.44 (s, 1H), 4.01 – 3.86 (m, 2H), 3.80 (dt, J = 12.6, 6.5 Hz, 1H), 3.75 – 3.65 (m, 1H), 3.53 – 3.41 (m, 2H), 3.17 (m, 1H), 2.96 (dt, J = 17.8, 3.5 Hz, 1H), 2.30 – 2.03 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 164.8, 137.7, 137.0, 133.0, 132.4, 129.8 (2C), 129.7, 129.6, 128.4, 127.6, 125.8 (2C), 52.6, 51.1, 49.6, 40.5, 32.1, 25.5, 25.1.

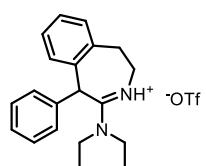
¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₀H₂₃N₂⁺: 291.1856, found 291.1858.

ATR-FTIR (cm⁻¹): 3295, 3233, 3066, 2962, 2929, 1642, 1496, 1451, 1279, 1157, 1030, 672.

Mp.: 178–180 °C

4-(diethylamino)-5-phenyl-2,5-dihydro-1H-benzo[d]azepin-3-ium- trifluoromethanesulfonate 3b



The amidine was prepared using procedure **H** with 0.20 mmol amide **1b** (38.3 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 51 % (45 mg)

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.13 (br.s, 1H), 7.43 – 7.38 (m, 1H), 7.38 – 7.29 (m, 4H), 7.28 (m, 1H), 7.18 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 7.7 Hz, 2H), 5.42 (s, 1H), 3.95 – 3.76 (m, 2H), 3.68 (m, 1H), 3.61 (m, 2H), 3.49 – 3.34 (m, 1H), 3.32 – 3.16 (m, 1H), 2.99 – 2.91 (m, 1H), 1.43 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

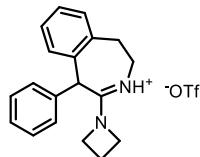
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 166.4, 137.7 (2C), 133.2, 132.8, 129.9 (2C), 129.7, 129.3, 128.4, 127.7, 125.5 (2C), 50.3, 47.7, 46.2, 40.0, 32.1, 14.9, 11.7.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₀H₂₅N₂⁺: 293.2012, found 293.2013.

ATR-FTIR (cm⁻¹): 3280, 3229, 2982, 2928, 1631, 1584, 1495, 1449, 1243, 1224, 1198, 1154, 1029, 748, 636.

4-(azetidin-1-yl)-5-phenyl-2,5-dihydro-1H-benzo[d]azepin-3-i um-trifluoromethanesulfonate 3c



The amidine was prepared using procedure **H** with 0.20 mmol amide **1c** (35.0 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange solid): 69 % (59 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 8.90 (s, 1H), 7.34 – 7.27 (m, 3H), 7.25 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 2H), 4.86 (s, 1H), 4.52 (m, 3H), 4.43 (m, 1H), 3.37 (m, 2H), 3.00 (ddd, J = 15.5, 10.5, 4.6 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.53 (m, 1H), 2.48 – 2.37 (m, 1H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 164.6, 137.6, 136.5, 132.5, 132.1, 130.1, 129.7 (2C), 129.6, 128.4, 127.7, 126.2 (2C), 53.2, 52.3, 49.3, 40.8, 32.0, 14.8.

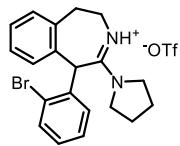
¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.3.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₁₉H₂₁N₂⁺: 277.1699, found 277.1697.

ATR-FTIR (cm⁻¹): 3219, 3092, 2950, 1656, 1495, 1448, 1244, 1157, 1029, 725, 636, 517.

Mp.: 163–165 °C.

5-(2-bromophenyl)-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-i um-trifluoromethane-sulfonate 3d



The amidine was prepared using procedure **H** with 0.20 mmol amide **1d** (53.6 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (yellow solid): 70 % (73 mg).

¹H NMR (600 MHz, CDCl₃) δ (ppm) 8.81 (br.s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.34 (m, 2H), 7.28 – 7.22 (m, 2H), 7.19 (d, J = 7.4 Hz, 1H), 6.76 – 6.61 (m, 1H), 5.21 (s, 1H), 4.29 (m, 1H), 3.75 (m, 2H), 3.63 – 3.52 (m, 2H), 3.44 – 3.30 (m, 2H), 3.01 (m, 1H), 2.23 – 2.01 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 163.8, 138.0, 137.1, 134.6, 133.0, 132.0, 131.1, 130.4, 130.1, 128.3, 128.1, 128.1, 121.6, 53.2, 50.7, 49.7, 38.9, 32.3, 25.4, 24.9.

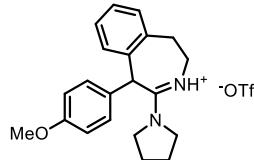
¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₀H₂₂BrN₂⁺: 371.0940, found 371.0954.

ATR-FTIR (cm⁻¹): 3287, 3220, 3071, 2980, 2960, 2929, 1637, 1466, 1244, 1157, 1029, 757, 729, 636.

Mp.: 212–215 °C.

5-(4-methoxyphenyl)-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium- trifluoromethane-sulfonate **3e**



The amidine was prepared using procedure **H** with 0.20 mmol amide **1e** (43.9 mg), 0.40 mmol Tf₂O (67 μ L), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 45 % (42 mg)

¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.03 (br.s, 1H), 7.39 (m, 1H), 7.33 – 7.22 (m, 3H), 7.16 (d, J = 7.6 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.2 Hz, 2H), 5.36 (s, 1H), 3.95 – 3.85 (m, 2H), 3.85 – 3.80 (m, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.54 (m, 2H), 3.24 – 3.10 (m, 1H), 2.98 (m, 1H), 2.26 – 2.06 (m, 4H).

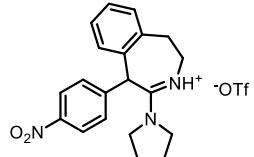
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 164.9, 159.5, 137.8, 132.8, 132.4, 130.0, 129.6, 128.7, 127.5, 127.0 (2C), 115.1 (2C), 55.5, 52.0, 51.0, 49.6, 40.5, 32.1, 25.50, 25.1.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₁H₂₅N₂O⁺: 321.1961, found 321.1962.

ATR-FTIR (cm⁻¹): 3293, 3226, 3064, 2959, 2935, 1639, 1510, 1455, 1242, 1153, 1027, 732, 635, 516.

5-(4-nitrophenyl)-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium- trifluoromethane-sulfonate **3f**



The amidine was prepared using procedure **H** with 0.20 mmol amide **1f** (46.9 mg), 0.40 mmol Tf₂O (67 μ L), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 0:100 to 30:70).

Yield (orange-brown oil): 13 % (13 mg)

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.18 (br.s, 1H), 8.20 (d, J = 12.5 Hz, 2H), 7.49 – 7.41 (m, 1H), 7.36 (dd, J = 7.5, J = 7.5 Hz, 1H), 7.31 (d, J = 6.6 Hz, 1H), 7.21 (d, J = 10.1 Hz, 1H), 7.16 (d, J = 8.5 Hz, 2H), 5.46 (s, 1H), 3.97 (m, 1H), 3.95 – 3.88 (m, 2H), 3.81 – 3.72 (m, 1H), 3.57 (m, 1H), 3.34 (m, 1H), 3.29 – 3.17 (m, 1H), 2.98 (m, 1H), 2.36 – 2.06 (m, 4H).

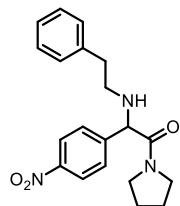
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 163.7, 147.8, 144.1, 137.6, 132.9 (2C), 130.4, 128.4, 128.0, 127.2 (2C), 124.9 (2C), 52.5, 51.3, 50.0, 40.7, 32.1, 25.5, 25.1.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₀H₂₂N₃O₂⁺: 336.1707, found 336.1711.

ATR-FTIR (cm⁻¹): 3230, 3080, 2960, 2931, 1645, 1521, 1347, 1159, 1030, 637.

2-(4-nitrophenyl)-2-(phenethylamino)-1-(pyrrolidin-1-yl)ethan-1-one **S4**



The α -aminated product was formed as the major product during the synthesis of **3f**. Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 0:100 to 30:70).

Yield (orange oil): 37 % (26 mg).

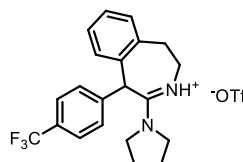
¹H NMR (600 MHz, CDCl₃): δ (ppm) 8.16 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.27 (m, 2H), 7.23 – 7.12 (m, 3H), 4.43 (s, 1H), 3.59 – 3.51 (m, 1H), 3.47 (m, 1H), 3.43 – 3.35 (m, 1H), 3.09 (m, 1H), 2.88 – 2.74 (m, 3H), 2.65 (m, 1H), 2.37 – 2.17 (br.s, 1H), 1.98 – 1.71 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 169.4, 147.7, 146.1, 139.8, 128.9 (2C), 128.8 (2C), 128.6 (2C), 126.4, 124.1 (2C), 64.1, 49.3, 46.3, 46.2, 36.9, 26.1, 24.1.

HRMS (ESI) m/z calculated for [M-H]⁺ C₂₀H₂₄N₃O₃⁺: 354,1812, found 354.1813.

ATR-FTIR (cm⁻¹): 3330, 3026, 2949, 2877, 1640, 1604, 1519, 1429, 1345, 1109, 842, 752, 731, 700.

4-(pyrrolidin-1-yl)-5-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-benzo[d]azepin-3-ium-trifluoromethanesulfonate **3g**



The amidine was prepared using procedure **H** with 0.20 mmol amide **1g** (51.5 mg), 0.40 mmol Tf₂O (67 μ L), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 45 % (46 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.01 (br.s, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.36 (m, 1H), 7.27 (m, 1H), 7.21 (d, *J* = 6.4 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.38 (s, 1H), 3.96 – 3.73 (m, 3H), 3.73 – 3.61 (m, 1H), 3.51 – 3.39 (m, 1H), 3.32 (m, 1H), 3.18 – 3.04 (m, 1H), 2.90 (m, 1H), 2.28 – 1.97 (m, 4H).

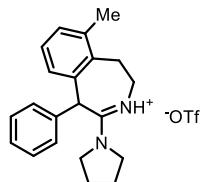
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 164.0, 141.1, 137.6, 132.9, 132.6, 130.8 (q, *J* = 33.2 Hz, 1C), 130.1, 128.9, 126.7 (q, *J* = 3.0 Hz, 2C), 126.5 (2C), 122.2 (dd, *J* = 320.1 Hz, *J* = 487.7 Hz, 1C), 52.5, 51.2, 49.9, 40.7, 32.0, 25.4, 25.1.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) -62.76, -78.3.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₁H₂₂F₃N₂⁺: 359,1730, found 359.1729.

ATR-FTIR (cm⁻¹): 3295, 3229, 3080, 2961, 2930, 1644, 1327, 1246, 1161, 1121, 1069, 1030, 638.

9-methyl-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium-trifluoromethane-sulfonate 3h



The amidine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2b** (35.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown solid): 61 % (55 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.14 (br.s, 1H), 7.38 – 7.27 (m, 4H), 7.22 (dd, *J* = 17.4, 9.8 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 2H), 5.43 (1H), 3.95 (m, 1H), 3.89 – 3.79 (m, 2H), 3.79 – 3.68 (m, 1H), 3.59 (m, 1H), 3.52 – 3.43 (m, 1H), 3.02 (ddd, *J* = 17.9, 12.8, 5.0 Hz, 1H), 2.74 (m, 1H), 2.32 – 2.23 (m, 3H), 2.24 – 2.07 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 165.0, 140.1, 137.3, 136.1, 131.7, 131.2, 129.8 (2C), 129.0, 128.4, 127.3, 125.7 (2C), 53.0, 50.9, 49.6, 39.9, 30.0, 25.5, 25.2, 20.7.

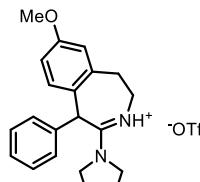
¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₁H₂₅N₂O⁺: 305.2012, found 305.2017.

ATR-FTIR (cm⁻¹): 3220, 3060, 1632, 1443, 1243, 1158, 1029, 731, 700, 636, 517.

Mp.: 243–245 °C.

8-methoxy-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium-trifluoromethane-sulfonate 3i



The amidine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2c** (39.0 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown solid): 93 % (88 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 8.97 (br.s, 1H), 7.39 – 7.28 (m, 3H), 7.10 (d, *J* = 8.5, 1H), 6.88 (d, *J* = 9.4 Hz, 2H), 6.84 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.76 (d, *J* = 2.6 Hz, 1H), 5.38 (s, 1H), 3.96 – 3.86 (m, 2H), 3.82 (s, 3H), 3.80 (m, 1H), 3.72 (m, 1H), 3.55 – 3.35 (m, 2H), 3.24 – 3.05 (m, 1H), 2.94 (m, 1H), 2.28 – 2.03 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 165.0, 160.3, 139.1, 137.4, 134.2, 129.7 (2C), 128.3, 125.8 (2C), 121.4, 116.9, 113.6, 55.5, 51.8, 51.0, 49.6, 40.3, 32.4, 25.5, 25.2.

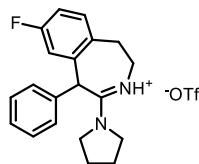
¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₁H₂₅N₂O⁺: 321.1961, found 321.1961.

ATR-FTIR (cm⁻¹): 3291, 3229, 3062, 2960, 2937, 1639, 1499, 1451, 1242, 1156, 1028, 731, 700, 635, 517.

Mp.: 160–162 °C.

7-fluoro-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-i um-trifluoromethane-sulfonate 3j



The amidine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2d** (36.3 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 39 % (36 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.13 (br.s, 1H), 7.43 – 7.29 (m, 3H), 7.26 – 7.22 (m, 1H), 7.12 (m, 1H), 6.97 – 6.92 (m, 1H), 6.88 (m, 2H), 5.37 (s, 1H), 3.97 – 3.86 (m, 2H), 3.81 (m, 2H), 3.55 (m, 1H), 3.46 (m, 1H), 3.17 (m, 1H), 2.95 (m, 1H), 2.33 – 2.02 (m, 4H).

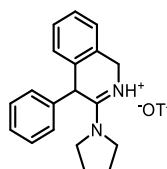
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 164.2, 161.5 (d, *J* = 24.7 Hz, 1C), 136.3, 134.2 (d, *J* = 7.5 Hz, 1C), 133.5 (d, *J* = 4.5 Hz, 1C), 131.25 (d, *J* = 6.0 Hz, 1C), 130.0 (2C), 128.7, 125.7 (2C), 119.3 (d, *J* = 22.6 Hz, 1C), 116.9 (d, *J* = 21.1 Hz, 1C), 52.3, 51.1, 49.8, 40.6, 31.5, 25.5, 25.2.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.3, –115.1.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₀H₂₂FN₂⁺: 309.1762, found 359.1773.

ATR-FTIR (cm⁻¹): 3295, 3229, 3064, 2961, 2928, 1640, 1498, 1450, 1241, 1152, 1060, 733, 699, 635, 516.

4-phenyl-3-(pyrrolidin-1-yl)-1,4-dihydroisoquinolin-2-i um-trifluoro-methanesulfonate 3l



The amidine was prepared using procedure **H** with 0.40 mmol amide **1a** (75.7 mg), 0.80 mmol Tf₂O (135 µL), 0.80 mmol 2,4-dichloroquinoline (158 mg) and 0.44 mmol azide **2f** (64.8 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (orange-brown oil): 49 % (87 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.74 (br.s, 1H), 7.40 – 7.29 (m, 6H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 5.15 (s, 1H), 4.86 (d, *J* = 15.9 Hz, 1H), 4.65 (d, *J* = 17.2 Hz, 1H), 3.87 – 3.78 (m, 3H), 3.53 – 3.46 (m, 1H), 2.18 – 2.05 (m, 3H), 2.00 – 1.93 (m, 1H).

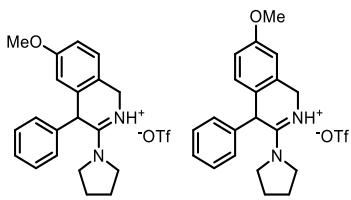
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 161.7, 135.5, 132.0, 130.2 (2C), 129.8, 128.9, 128.8, 128.5, 127.8, 126.7 (2C), 126.5, 49.9, 49.5, 47.9, 45.4, 25.5, 24.9.

¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₁₉H₂₁N₂⁺: 277.1699, found 277.1712.

ATR-FTIR (cm⁻¹): 3213, 2859, 1653, 1457, 1223, 1154, 1027, 910, 727, 601.

methoxy-4-phenyl-3-(pyrrolidin-1-yl)-1,4-dihydroisoquinolin-2-i um trifluoromethanesulfonate
(regioisomer mixture) **3m**



The amidine was prepared using procedure **H** with 0.40 mmol amide **1a** (75.7 mg), 0.80 mmol Tf₂O (135 µL), 0.80 mmol 2,4-dichloroquinoline (158 mg) and 0.44 mmol azide **2f** (64.8 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70) to obtain a mixture of regioisomer.

Yield (orange-brown oil): 84 % (77 mg).

¹H NMR (600 MHz, CDCl₃) δ (ppm) 9.57 (s, 0.4H), 9.54 (s, 0.6H), 7.39 – 7.20 (m, 5H), 7.17 (d, J = 7.4 Hz, 1H), 6.89 – 6.82 (m, 1.4H), 6.72 (m, 0.6H), 5.55 (s, 0.4H), 5.15 (s, 0.6H), 4.81 (m, 0.4H), 4.79 (m, 0.6H), 4.65 (d, J = 5.6 Hz, 0.6H), 4.62 (d, J = 5.5 Hz, 0.4H), 3.91 (s, 1H), 3.89 – 3.82 (m, 1H), 3.76 (s, 4H), 3.55 (m, 0.4H), 3.47 (m, 0.6H), 2.14 – 2.00 (m, 3H), 2.00 – 1.88 (m, 1H).

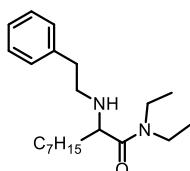
¹³C NMR (151 MHz, CDCl₃) δ (ppm) {162.1}, 162.0, 159.5, (155.8), 136.2, (135.1), (131.7), 130.9, 130.1 (2C), (129.7), (129.5), 129.1, 128.7, (128.6), (127.3), 126.6 (2C), 124.0, (120.9), (118.5), 115.4, 110.7, (110.1), (55.8), 55.6, 50.0, (49.9), 49.3, 47.1, 45.5, (45.4), (41.4), 25.4, (25.4), (24.9), 24.8. When distinguishable, the signals of the second minor are reported in brackets.

¹⁹F NMR (565 MHz, CDCl₃) δ (ppm) -78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₀H₂₃N₂O⁺: 307.1805, found 307.1806.

4.2. α -Amination

N,N-diethyl-2-(phenethylamino)nonanamide S5



The α -minated amide was prepared using procedure **H** with 0.20 mmol amide **S1** (42.7 mg), 0.40 mmol Tf₂O (67 μ L), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (orange-brown oil): 39% (36 mg).

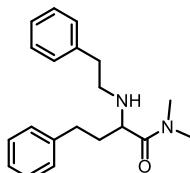
¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.26 (m, 2H), 7.18 (m, 3H), 3.54 (m, 1H), 3.36 (m, 2H), 3.26 – 3.13 (m, 2H), 2.86 – 2.75 (m, 2H), 2.72 (m, 1H), 2.65 – 2.56 (m, 1H), 2.27 – 1.89 (br.s, 1H), 1.57 – 1.45 (m, 2H), 1.41 (m, 1H), 1.31 – 1.22 (m, 9H), 1.20 – 1.13 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 174.4, 140.3, 128.8 (2C), 128.4 (2C), 126.1, 58.1, 50.1, 41.4, 40.5, 37.2, 34.5, 31.9, 29.8, 29.3, 26.1, 22.7, 15.0, 14.2, 13.2.

HRMS (ESI) m/z calculated for [M+H]⁺ C₂₁H₃₇N₂O⁺: 333.2900, found 333.2901.

ATR-FTIR (cm⁻¹): 2954, 2926, 2854, 1636, 1454, 1427, 1378, 1362, 1259, 1128, 845, 749, 699.

N,N-dimethyl-2-(phenethylamino)-4-phenylbutanamide S6



The α -minated amide was prepared using procedure **H** with 0.20 mmol amide **S2** (35.5 mg), 0.40 mmol Tf₂O (67 μ L), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **2a** (32.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (orange-brown oil): 63% (39 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.32 – 7.24 (m, 4H), 7.24 – 7.13 (m, 6H), 3.40 (dd, J = 7.6, 5.4 Hz, 1H), 2.94 (s, 3H), 2.87 – 2.79 (m, 2H), 2.79 – 2.76 (m, 1H), 2.75 (s, 3H), 2.75 – 2.69 (m, 2H), 2.58 (m, 1H), 1.99 (br.s, 1H), 1.85 – 1.73 (m, 2H).

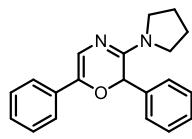
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 175.0, 141.8, 140.4, 128.9 (2C), 128.7 (2C), 128.5 (2C), 128.4 (2C), 126.1, 126.0, 57.1, 50.2, 37.2, 36.6, 35.8, 35.2, 32.0.

HRMS (ESI) m/z calculated for [M+H]⁺ C₂₀H₂₇N₂O⁺: 311.2118, found 311.2117.

ATR-FTIR (cm⁻¹): 3025, 2927, 2855, 1640, 1495, 1454, 1397, 1258, 1121, 1030, 750, 699

4.3. Oxazines and Oxazinone

2,6-diphenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine 8a



The oxazine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7a** (35.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow solid): 90% (55 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.47 – 7.43 (m, 2H), 7.41 (m, 2H), 7.36 – 7.30 (m, 3H), 7.25 – 7.20 (m, 2H), 7.12 (m, 1H), 6.78 (s, 1H), 5.87 (s, 1H), 3.80 – 3.05 (m, 4H), 2.05 – 1.79 (m, 4H).

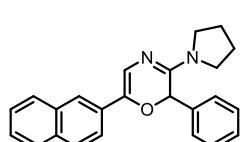
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 151.7, 135.5, 135.3, 134.4, 129.1, 128.8 (2C), 128.3 (2C), 128.0 (2C), 126.7, 123.5 (2C), 116.0, 71.6, 46.5 (2C), 25.1 (2C).

HRMS (ESI) m/z calculated for [M+H]⁺ C₂₀H₂₁N₂O⁺: 305,1648, found 305,1651.

ATR-FTIR (cm⁻¹): 3071, 3025, 2962, 2872, 1599, 1567, 1488, 1447, 1342, 1055, 1026, 951, 761, 750, 690, 479.

Mp.: 218–221 °C.

6-(naphthalen-2-yl)-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine 8b



The oxazine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7b** (46.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow solid): 81% (57 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.88 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.53 (dd, J = 8.7, 1.4 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.42 (m, 1H), 7.38 – 7.28 (m, 4H), 6.94 (s, 1H), 5.93 (s, 1H), 3.82 – 3.07 (m, 4H), 2.07 – 1.81 (m, 4H).

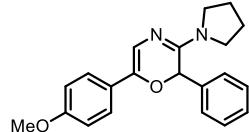
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 152.0, 135.5, 135.3, 133.7, 132.5, 131.7, 129.1, 128.8 (2C), 128.1, 127.8 (2C), 127.7, 127.6, 126.1, 125.4, 121.8, 121.4, 116.9, 71.7, 46.4 (2C), 24.9 (2C).

HRMS (ESI) m/z calculated for [M+H]⁺ C₂₄H₂₃N₂O⁺: 355,1805, found 355,1798.

ATR-FTIR (cm⁻¹): 3058, 2968, 2869, 1561, 1448, 1338, 1212, 1060, 857, 817, 747, 699, 476.

Mp.: 179–181 °C.

6-(4-methoxyphenyl)-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine 8c



The oxazine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 μ L), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7c** (42.1 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow solid): 56% (37 mg).

¹H NMR (600 MHz, CDCl₃): δ 7.45 (d, *J* = 6.7 Hz, 2H), 7.35 – 7.29 (m, 5H), 6.82 – 6.74 (m, 2H), 6.63 (s, 1H), 5.85 (s, 1H), 3.75 (s, 3H), 3.37 (m, 4H), 2.03 – 1.80 (m, 4H).

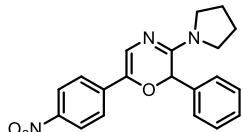
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 158.8, 151.3, 135.6, 135.4, 129.1, 128.8 (2C), 127.9 (2C), 127.2, 125.0 (2C), 114.4, 113.8 (2C), 71.6, 55.4, 46.4 (2C), 24.9 (2C).

HRMS (ESI) m/z calculated for [M+H]⁺ C₂₁H₂₃N₂O₂⁺: 335,1754, found 335,1758.

ATR-FTIR (cm⁻¹): 3061, 2966, 2870, 1606, 1576, 1509, 1458, 1446, 1339, 1248, 1175, 1059, 1031, 829, 699.

Mp.: 159–162 °C.

6-(4-nitrophenyl)-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine 8d



The oxazine was prepared using procedure **H** with 0.2 mmol amide **1a** (37.9 mg), 0.4 mmol Tf₂O (67.3 μ L), 0.4 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7d** (45.4 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (red solid): 81% (57 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 8.09 – 7.99 (m, 2H), 7.51 – 7.46 (m, 2H), 7.41 – 7.38 (m, 2H), 7.36 – 7.32 (m, 3H), 7.01 (s, 1H), 5.88 (s, 1H), 3.70 (m, 2H), 3.53 (m, 1H), 3.19 (m, 1H), 2.04 – 1.84 (m, 4H).

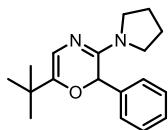
¹³C NMR (151 MHz, CDCl₃): δ (ppm) 152.9, 145.6, 140.8, 134.5, 133.6, 129.5, 129.0 (2C), 127.8 (2C), 123.9 (2C), 122.7 (2C), 120.8, 71.6, 47.1, 46.5, 25.9, 24.5.

HRMS (ESI) m/z calculated for [M+H]⁺ C₂₀H₂₀N₃O₃⁺: 350,1499, found 350,1500.

ATR-FTIR (cm⁻¹): 3061, 2960, 2878, 1559, 1503, 1460, 1333, 1257, 1182, 1112, 1058, 947, 838, 750, 694.

Mp.: 187–190 °C.

6-(tert-butyl)-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine **8e**



The oxazine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7e** (31.1 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow oil): 88 % (50 mg).

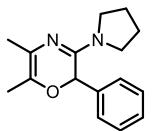
¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.39 – 7.31 (m, 5H), 5.99 (s, 1H), 5.69 (s, 1H), 3.50 (m, 4H), 2.01 – 1.69 (m, 4H), 0.83 (s, 9H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 150.5, 145.3, 134.2, 129.3, 128.7 (2C), 128.6 (2C), 109.8, 71.6, 46.6 (2C), 33.0, 27.3 (3C), 25.0 (2C).

HRMS (ESI) m/z calculated for [M+H]⁺ C₁₈H₂₅N₂O⁺: 285.1861, found 285.1866.

ATR-FTIR (cm⁻¹): 2963, 2869, 1659, 1623, 1582, 1447, 1341, 1358, 1341, 1158, 1030, 762, 699, 638, 518.

5,6-dimethyl-2-phenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine **8f**



The oxazine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7f** (24.9 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow oil): 59 % (30 mg).

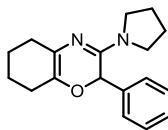
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.42 – 7.28 (m, 5H), 5.64 (s, 1H), 3.51 (m, 4H), 2.04 – 1.86 (m, 4H), 1.85 (app.d, J = 0.8 Hz, 3H), 1.66 (app.d, J = 0.8 Hz, 3H).

¹³C NMR (151 MHz, DMSO): δ (ppm) 150.2, 136.3, 128.7, 128.6 (2C), 128.1, 127.2 (2C), 118.7, 69.9, 46.6 (2C), 24.7 (2C), 17.1, 15.4.

HRMS (ESI) m/z calculated for [M+H]⁺ C₁₆H₂₁N₂O⁺: 257.1648, found 257.1650.

ATR-FTIR (cm⁻¹): 2950, 2920, 2869, 1725, 1659, 1585, 1444, 1340, 1279, 1156, 1140, 1031, 752, 737, 638.

2-phenyl-3-(pyrrolidin-1-yl)-5,6,7,8-tetrahydro-2H-benzo[b][1,4]oxazine **8g**



The oxazine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7g** (30.6 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 20:80).

Yield (yellow oil): 70 % (40 mg).

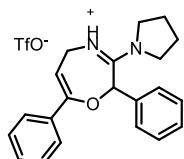
¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.41 – 7.28 (m, 5H), 5.59 (s, 1H), 3.37 (m, 4H), 2.35 – 2.25 (m, 1H), 2.15 (m, 1H), 2.06 (m, 1H), 1.97 – 1.88 (m, 2H), 1.87 – 1.77 (m, 3H), 1.70 – 1.64 (m, 1H), 1.61 – 1.47 (m, 2H), 1.42 – 1.31 (m, 1H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 150.9, 136.0, 131.4, 128.9, 128.7 (2C), 127.7 (2C), 121.6, 71.5, 46.7 (2C), 28.2, 26.5, 25.1 (2C), 23.2, 23.0.

HRMS (ESI) m/z calculated for [M+H]⁺ C₁₈H₂₃N₂O⁺: 283.1805, found 283.1808.

ATR-FTIR (cm⁻¹): 2928, 2857, 1656, 1578, 1491, 1442, 1341, 1246, 1145, 1029, 913, 735, 699, 637, 517.

2,7-diphenyl-3-(pyrrolidin-1-yl)-2,5-dihydro-1,4-oxazepin-4-i um-trifluoromethanesulfonate 8h



The oxazine was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7h** (38.5 mg). Purification was performed with column chromatography on silica gel (DMA/DCM gradient, 5:95 to 30:70).

Yield (yellow solid): 72 % (67 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.48 (br.s, 1H), 7.54 (m, 2H), 7.47 (m, 3H), 7.42 – 7.34 (m, 5H), 6.15 (s, 1H), 5.78 (dd, J = 6.9, 4.4 Hz, 1H), 4.22 (dd, J = 16.9, 6.9 Hz, 1H), 4.11 (dd, J = 16.9, 4.4 Hz, 1H), 3.83 (m, 2H), 3.66 (m, 1H), 3.28 (m, 1H), 2.15 – 1.95 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 161.5, 154.7, 133.9, 132.5, 130.5, 130.0 (2C), 129.7, 128.8 (2C), 126.1 (2C), 125.1 (2C), 105.0, 77.5, 50.6, 50.1, 40.6, 25.7, 24.6.

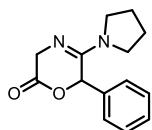
¹⁹F NMR (565 MHz, CDCl₃): δ (ppm) –78.2.

HRMS (ESI) m/z calculated for [M-TfO]⁺ C₂₁H₂₃N₂O⁺: 319.1805, found 319.1804.

ATR-FTIR (cm⁻¹): 3218, 3080, 2956, 1653, 1452, 1246, 1159, 1030, 757, 697, 574, 518

Mp.: 217–219 °C.

6-phenyl-5-(pyrrolidin-1-yl)-3,6-dihydro-2H-1,4-oxazin-2-one 8i



The oxazinone was prepared using procedure **H** with 0.20 mmol amide **1a** (37.9 mg), 0.40 mmol Tf₂O (67 µL), 0.40 mmol 2,4-dichloroquinoline (79.2 mg) and 0.22 mmol azide **7i** (37.6 mg). Due to its high sensitivity, the purification was performed by dissolving the crude product in ACN and washing with heptane (5x).

Yield (yellow oil): 70 % (34 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.41 (m, 3H), 7.37 – 7.32 (m, 2H), 6.07 (s, 1H), 4.30 (d, J = 19.9 Hz, 1H), 3.81 (d, J = 19.9 Hz, 1H), 3.41 (m, 4H), 2.01 – 1.84 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 170.1, 156.1, 133.4, 129.9, 129.6 (2C), 127.4 (2C), 77.3, 49.0, 46.9 (2C), 25.4 (2C).

HRMS (ESI) m/z calculated for [M+H]⁺ C₁₄H₁₇N₂O₂⁺: 245.1285, found 245.1286.

ATR-FTIR (cm⁻¹): 2968, 2870, 2106, 1744, 1620, 1446, 1312, 1236, 1186, 1028, 911, 739, 699, 637, 517.

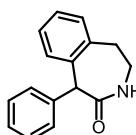
5. Derivatisation of Amidines

5.1. Hydrolysis

General Procedure I

A mixture of amidine (0.20 mmol, 1 eq.), THF (1 mL), NaOH (1 mL, 5 M, 5 eq.) and TPA-OH (4 μ L, 0.02 mmol, 0.1 eq) were stirred under reflux for 15 h. Purification was performed *via* addition of NH₄Cl and extraction with (3x) DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure.

1-phenyl-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one 4a



The benzoazepinone was obtained using procedure I with amidine **3a** (88.1 mg). The crude product was further purified by flash chromatography on silica gel (DMA/DCM gradient, 0:100 to 10:90).

Yield (yellow oil): 63 % (30 mg).

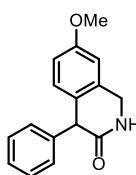
¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.28 (m, 3H), 7.27 – 7.24 (m, 1H), 7.23 (m, 1H), 7.20 (m, 1H), 7.18 – 7.16 (m, 1H), 7.12 – 7.08 (m, 2H), 6.71 (br.s, 1H), 5.15 (s, 1H), 3.37 (ddd, J = 19.2, 9.6, 4.7 Hz, 1H), 3.12 – 3.05 (m, 1H), 3.04 – 2.95 (m, 2H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 175.1, 139.8, 137.8, 133.5, 132.9, 131.2, 128.8 (2C), 127.9, 127.1, 126.9, 126.9 (2C), 60.5, 39.7, 33.8.

HRMS (ESI) m/z calculated for [M+H]⁺ C₁₆H₁₆NO⁺: 238.1226, found 238.1228.

ATR-FTIR (cm⁻¹): 3199, 3081, 2935, 1666, 1493, 1406, 1342, 806, 759, 749, 706.

7-methoxy-4-phenyl-1,4-dihydroisoquinolin-3(2H)-one 4ba



The isolated, hydrolysed regioisomer was obtained using procedure I with isomeric-mixture **3m**. The crude product was further purified by flash chromatography on silica gel (DMA/DCM gradient, 0:100 to 10:90).

Yield (brown amorphous solid): 17 % (8.6 mg).

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.28 (m, 2H), 7.23 (m, 1H), 7.19 – 7.13 (m, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.5 Hz, 1H), 6.75 (d, J = 2.5 Hz, 1H), 6.71 (br.s, 1H), 4.76 (s, 1H), 4.54 (d, J = 15.8 Hz, 1H), 4.35 (dd, J = 15.8, 4.1 Hz, 1H), 3.82 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 173.0, 158.8, 139.0, 132.9, 130.1, 128.8 (2C), 128.1 (2C), 127.4, 127.3, 113.9, 110.7, 55.5, 51.8, 45.4.

HRMS (ESI) m/z calculated for [M+H]⁺ C₁₆H₁₆NO₂⁺: 254.1176, found 254.1177.

ATR-FTIR (cm⁻¹): 3219, 3061, 2930, 2838, 1668, 1613, 1493, 1324, 1272, 1240, 1035, 738, 700.

6-methoxy-4-phenyl-1,4-dihydroisoquinolin-3(2H)-one **4bb**



The isolated, hydrolysed regioisomere was obtained using procedure I with isomeric mixture **3m**. The crude product was further purified by flash chromatography on silica gel (DMA/DCM gradient, 0:100 to 10:90).

Yield (white amorphous solid): 7 % (3.5 mg).

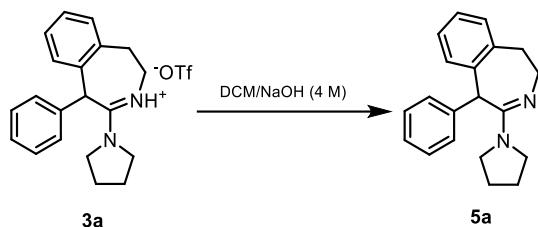
¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.28 (m, 1H), 7.24 (m, 2H), 7.21 (m, 3H), 6.84 (m, 2H), 6.27 (br.s, 1H), 5.17 (s, 1H), 4.61 (d, J = 15.7 Hz, 1H), 4.32 (dd, J = 15.7, 4.8 Hz, 1H), 3.75 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 172.8, 156.9, 138.3, 133.3, 128.7 (2C), 128.4, 127.7 (2C), 127.2, 124.1, 117.7, 109.6, 55.7, 46.6, 45.3.

HRMS (ESI) m/z calculated for [M+H]⁺ C₁₆H₁₆NO₂⁺: 254.1176, found 254.1177.

ATR-FTIR (cm⁻¹): 3210, 3059, 2931, 2839, 1671, 1595, 1471, 1256, 1072, 782, 745, 700.

5.2. Deprotonation



5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepine **5a**

The free base of **3a** was obtained by extraction DCM/NaOH 4 M. The organic layer was dried over K₂CO₃, filtered and evaporated.

Yield (brown oil): 99% (58 mg).

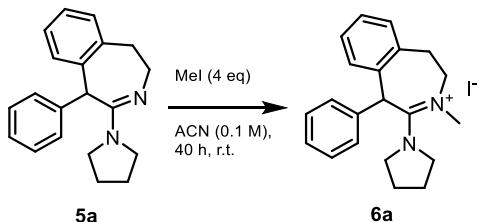
¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.26 (m, 3H), 7.23 – 7.16 (m, 3H), 7.12 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 8.1 Hz, 2H), 5.24 (s, 1H), 3.63 – 3.52 (m, 5H), 3.32 (ddd, J = 13.8, 4.4, 4.4 Hz, 1H), 2.99 – 2.92 (m, 2H), 1.99 – 1.91 (m, 4H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 162.1, 142.2, 140.6, 134.5, 132.6, 131.7, 128.6 (2C), 127.6, 126.4 (2C), 126.3, 125.9, 53.2, 47.5 (2C), 45.1, 33.9, 25.7.

HRMS (ESI) m/z calculated for [M+H]⁺ C₂₀H₂₃N₂⁺: 291.1856, found 291.1858.

ATR-FTIR (cm⁻¹): 3058, 3022, 2921, 2867, 1611, 1493, 1421, 1362, 1336, 1263, 950, 909, 748, 721, 696, 636, 569.

5.3. Methylation



3-methyl-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1H-benzo[d]azepin-3-ium 6a

The methylated product **6a** was obtained by dropwise addition of MeI (50 µL, 0.80 mmol, 3.0 eq) to a mixture of **5a** (47.5 mg, 0.20 mmol, 1.0 eq) in ACN (0.1 M). The reaction progress was followed by LCMS. After 40h, the mixture was diluted with MeOH and concentrated under reduced pressure. Purification was performed by flash column chromatography on silica gel (DMA/DCM gradient, 0:100 to 20:80).

Yield (brown-yellow oil): 56 % (48 mg); 61% brsm

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.35 (m, 3H), 7.32 – 7.26 (m, 2H), 7.25 – 7.20 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 5.67 (s, 1H), 4.30 (m, 1H), 4.18 – 3.88 (m, 4H), 3.58 (s, 3H), 3.39 – 3.29 (m, 1H), 3.20 (m, 1H), 3.01 (m, 1H), 2.33 (m, 1H), 2.12 (m, 3H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 170.0, 137.6, 136.8, 133.1, 131.8, 129.8 (2C), 129.7, 129.5, 128.2, 127.7, 126.2 (2C), 55.8, 53.3, 51.4, 51.3, 45.2, 31.0, 25.4, 25.3.

HRMS (ESI) m/z calculated for [M]⁺ C₂₁H₂₅N₂⁺: 305.2012, found 305.2014.

ATR-FTIR (cm⁻¹): 3144, 3042, 2954, 2924, 2874, 1726, 1634, 1494, 1447, 1338, 1268, 1159, 759, 731, 701

6. X-ray Analysis

The X-ray intensity data were measured on Bruker D8 Venture diffractometer equipped with multilayer monochromators, Mo K α INCOATEC micro focus sealed tubes and Oxford system. The structure was solved by *direct methods* and refined by *full-matrix least-squares techniques*. Non-hydrogen atoms were refined with *anisotropic displacement parameters*. Hydrogen atoms were inserted at calculated positions and refined with riding model. The following software was used: *Bruker SAINT software package*²⁰ using a narrow-frame algorithm for frame integration, *SADABS*²¹ for absorption correction, *OLEX2*²² for structure solution, refinement, molecular diagrams and graphical user-interface, *Shelxle*²³ for refinement and graphical user-interface *SHELXS-2015*²⁴ for structure solution, *SHELXL-2015*²⁵ for refinement, *Platon*²⁶ for symmetry check and π - π Interactions. Experimental data and CCDC-Codes (Available online: <http://www.ccdc.cam.ac.uk/conts/retrieving.html>) can be found in Table 1. Crystal data, data collection parameters and structure refinement details are given in Tables 2 to 5. Crystal structures and Packing views are visualized in Figures 1 to 4.

Table S3 Experimental parameter and CCDC-Codes.

Sample	Machine	Source	Temp.	Detector Distance	Time/Frame	#Frames	Frame width	CCDC
	Bruker		[K]	[mm]	[s]		[°]	
8a	D8	Mo	120	40	15	1176	0.500	1983046
3a	D8	Mo	100	40	10	360	0.500	1983045

²⁰ Bruker SAINT v8.38A/B & SAINT v7.56/7.68A Copyright © 2005–2019 Bruker AXS.

²¹ Krause, L.; Herbst-Irmer, R.; Sheldrick G. M.; Stalke D. *J. Appl. Cryst.* **2015**, *48*, 3–10.

²² Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *OLEX2*, *J. Appl. Cryst.* **2009**, *42*, 339–341.

²³ Huebschle, C. B.; Sheldrick G. M.; Dittrich B.; ShelXle: a Qt graphical user interface for SHELXL, *J. Appl. Cryst.* **2011**, *44*, 1281–1284.

²⁴ Sheldrick, G. M. *Acta Cryst.* **2008**, A64, 112–122.

²⁵ Sheldrick, G. M. *Acta Cryst.* **2015**, C71, 3–8.

²⁶ A. L. Spek, *Acta Cryst.* **2009**, D65, 148–155.

-2,6-diphenyl-3-(pyrrolidin-1-yl)-2H-1,4-oxazine

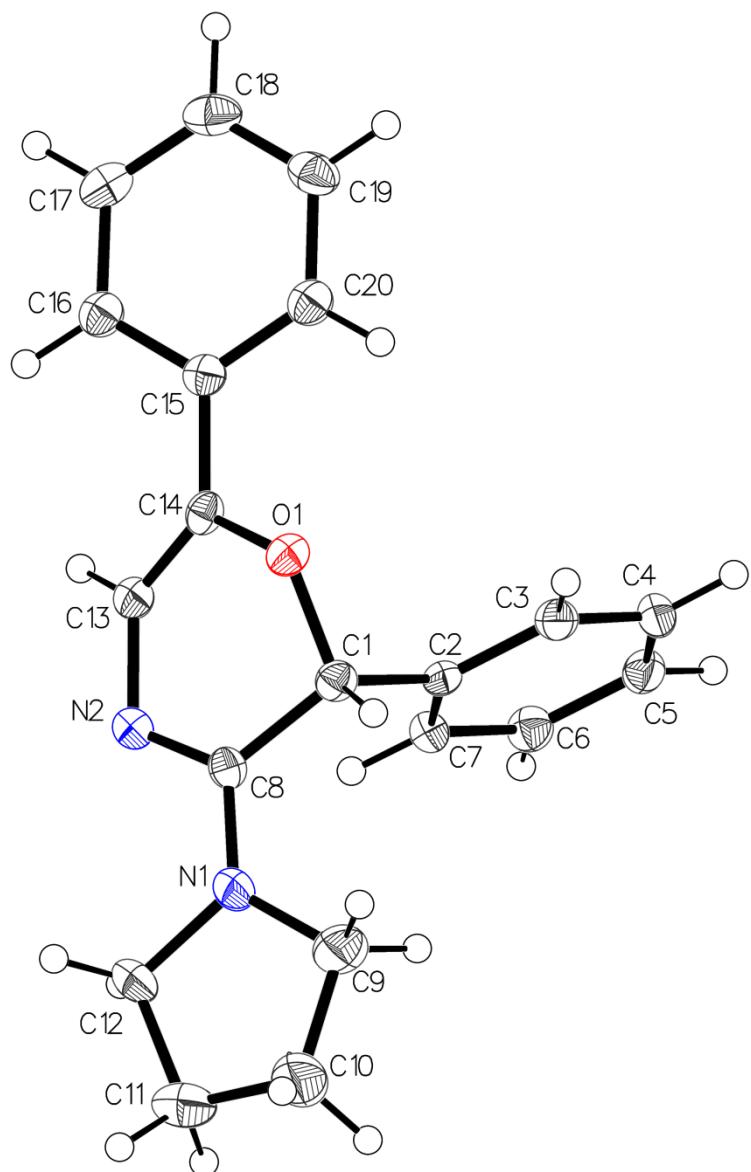


Figure S1 Crystal structure, drawn with 50% displacement ellipsoid. The bond precision for C-C single bonds is 0.0032Å.

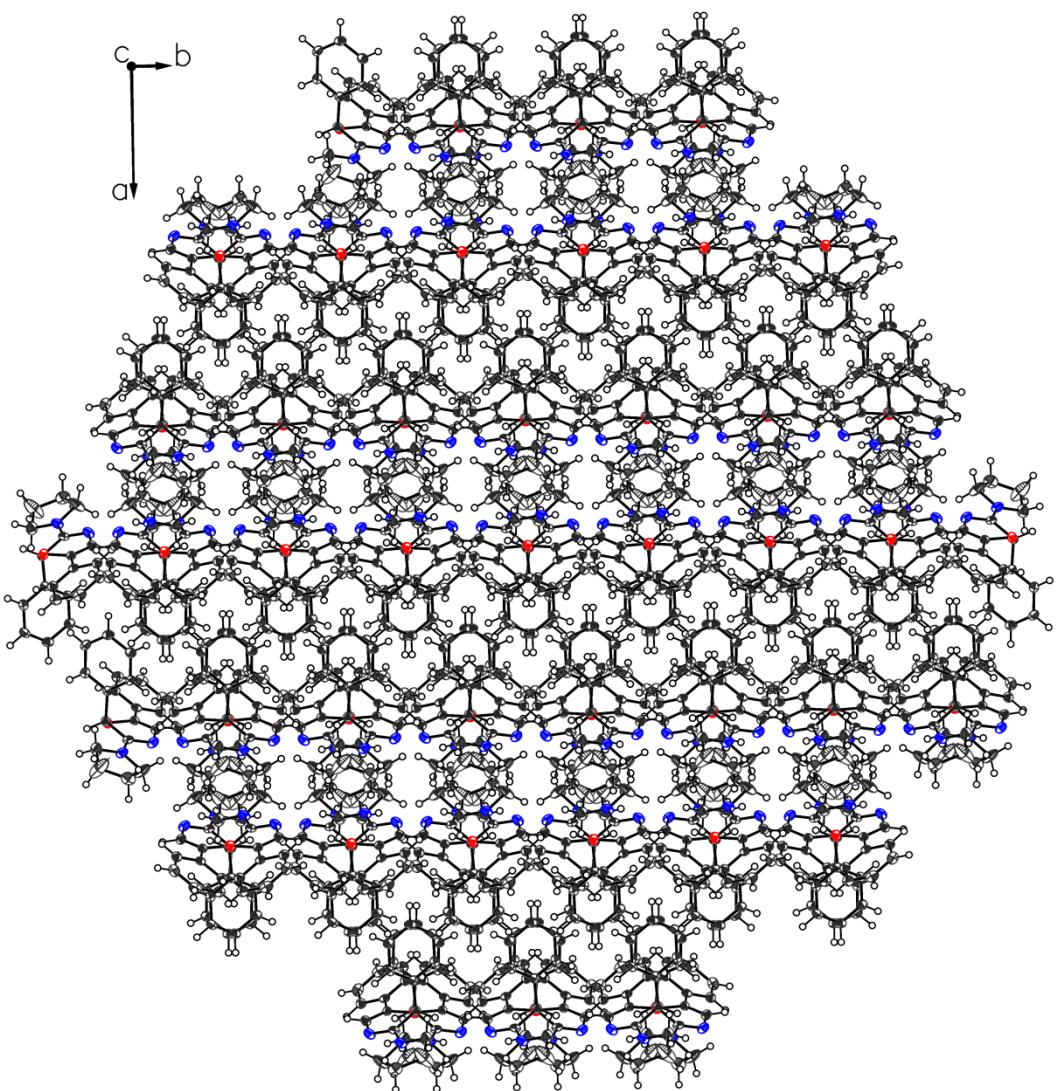


Figure S2 Packing view.

Table S4 Sample and crystal data.

Chemical formula	C20H20N2O	Crystal system	monoclinic	
Formula weight [g/mol]	304.38	Space group	C2/c	
Temperature [K]	120	Z	8	
Measurement method	\f and \w scans	Volume [Å³]	3128.3(3)	
Radiation (Wavelength [Å])	MoKα ($\lambda = 0.71073$)	Unit cell dimensions [Å] and [°]	31.2597(15)	90
Crystal size / [mm³]	0.581 × 0.148 × 0.046		5.7581(3)	116.0874(16)
Crystal habit	clear yellow plate		19.3514(9)	90
Density (calculated) / [g/cm³]	1.293	Absorption coefficient / [mm⁻¹]	0.08	
Abs. correction Tmin	0.3486	Abs. correction Tmax	0.746	
Abs. correction type	multiscan	F(000) [e⁻]	1296	

Table S5 Data collection and structure refinement.

Index ranges	-37 ≤ h ≤ 37, -6 ≤ k ≤ 6, -23 ≤ l ≤ 21	Theta range for data collection [°]	4.688 to 50.678	
Reflections number	26343	Data / restraints / parameters	2846/6/212	
Refinement method	Least squares	Final R indices	all data	R1 = 0.0682, wR2 = 0.1648
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$		I>2σ(I)	R1 = 0.0625, wR2 = 0.1588
Goodness-of-fit on F²	1.054	Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0747P)^2+7.3558P]$	
Largest diff. peak and hole [e Å⁻³]	0.65/-0.57		where P=(F _o ² +2F _c ²)/3	

-5-phenyl-4-(pyrrolidin-1-yl)-2,5-dihydro-1*H*-benzo[*d*]azepin-3-i^{um}- trifluoromethanesulfonate

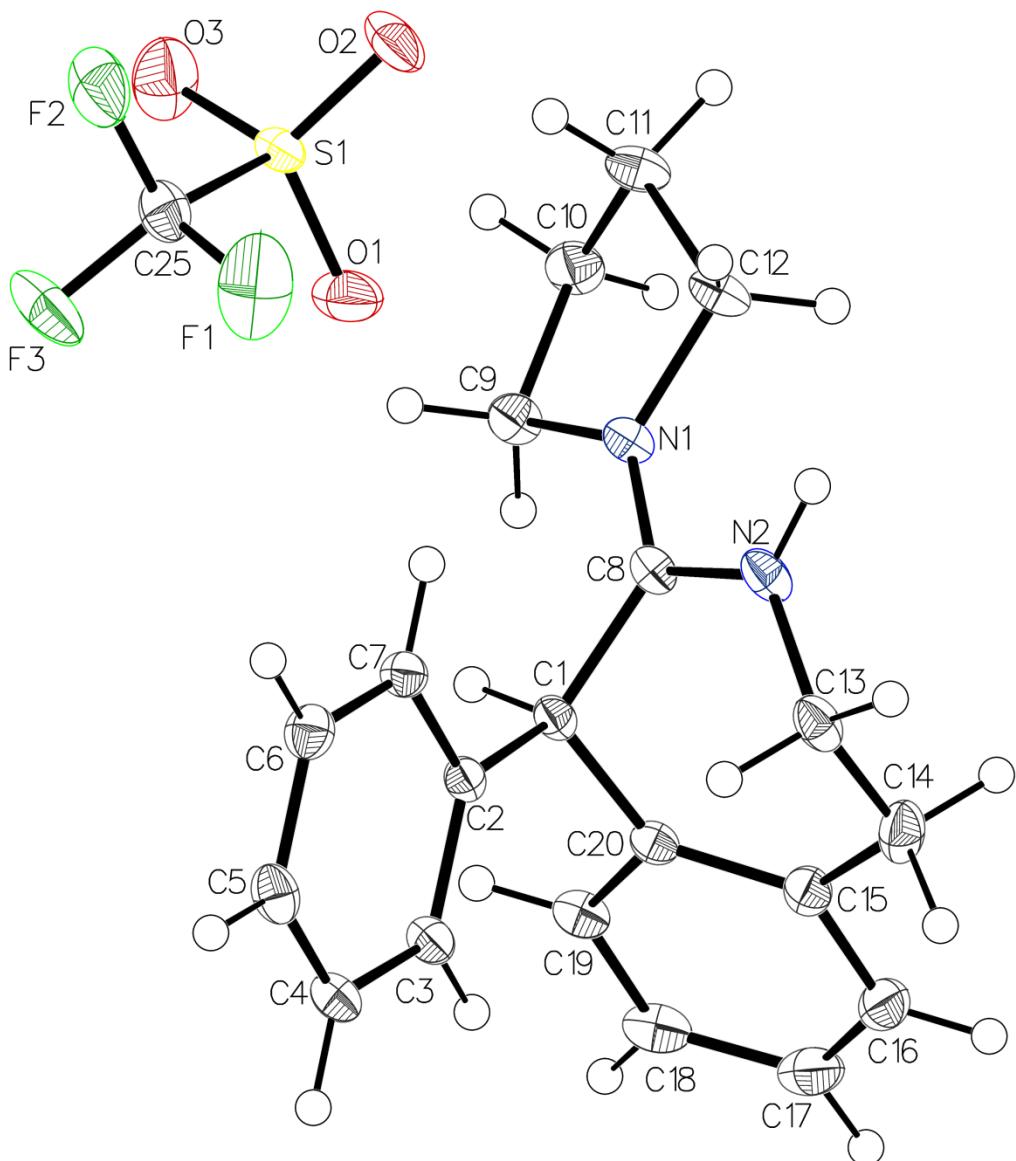


Figure S3 Crystal structure, drawn with 50% displacement ellipsoid. The bond precision for C-C single bonds is 0.0043 Å.

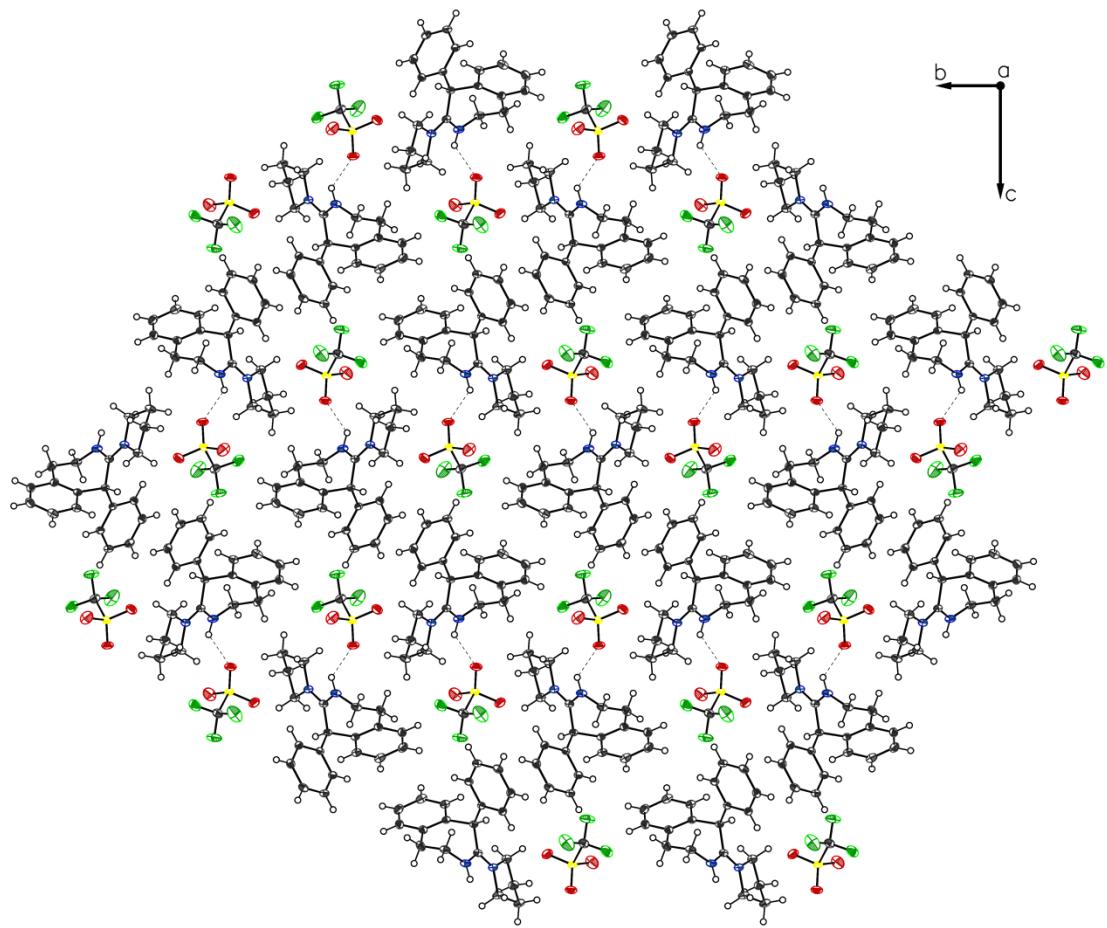


Figure S4 In the packing view one hydrogen bond on trifluoromethanesulfonate was detected with a bond length 2.083 Å.

Table S6 Sample and crystal data.

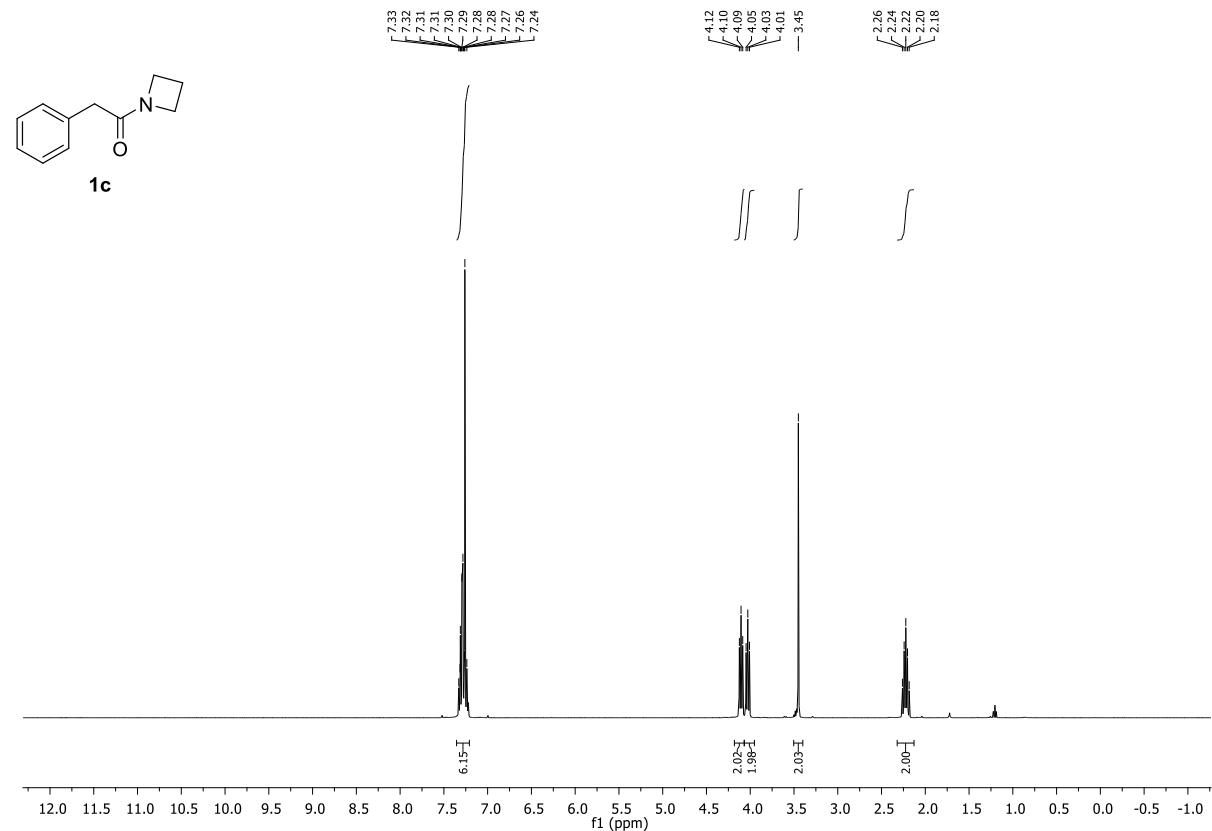
Chemical formula	C21H23F3N2O3S	Crystal system	orthorhombic	
Formula weight [g/mol]	440.47	Space group	<i>P</i> 21 <i>2</i> 1 <i>2</i> 1	
Temperature [K]	100	Z	4	
Measurement method	\f and \w scans	Volume [Å³]	2034.84(8)	
Radiation (Wavelength [Å])	MoKα ($\lambda = 0.71073$)	Unit cell dimensions [Å] and [°]	6.48180(10)	90
Crystal size / [mm³]	0.579 × 0.244 × 0.144		12.5595(3)	90
Crystal habit	clear colourless block		24.9955(6)	90
Density (calculated) / [g/cm³]	1.438	Absorption coefficient / [mm⁻¹]	0.212	
Abs. correction Tmin	0.6553	Abs. correction Tmax	0.7467	
Abs. correction type	multiscan	F(000) [e⁻]	920	

Table S7 Data collection and structure refinement.

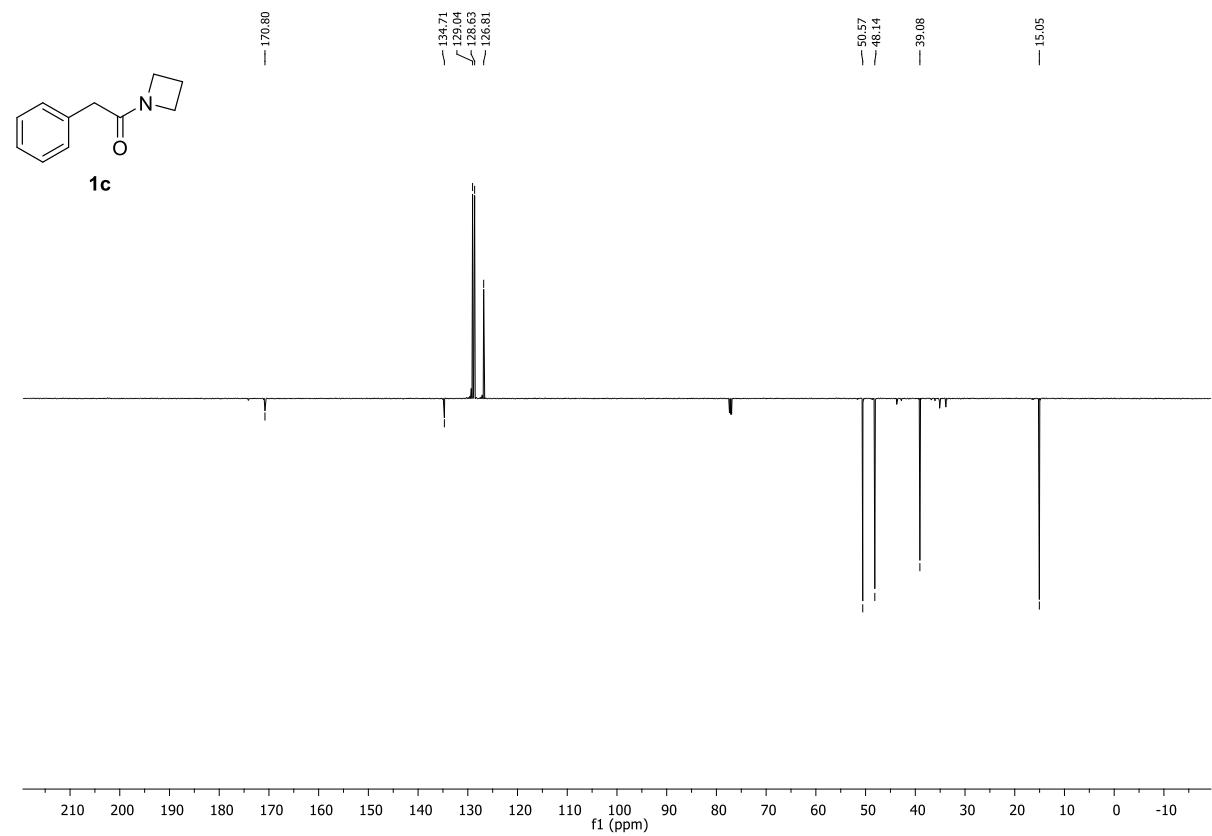
Index ranges	-9 ≤ h ≤ 8, -17 ≤ k ≤ 19, -38 ≤ l ≤ 39	Theta range for data collection [°]	4.598 to 68.018	
Reflections number	21905	Data / restraints / parameters	7198/0/271	
Refinement method	Least squares	Final R indices	all data	R1 = 0.0615, wR2 = 0.1365
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$		I>2σ(I)	R1 = 0.0433, wR2 = 0.0970
Goodness-of-fit on F^2	1.185	Weighting scheme	$w=1/[\sigma^2(Fo^2)+2.4717P]$	
Largest diff. peak and hole [$e \text{ \AA}^{-3}$]	0.59/-0.72		where P=($F_o^2+2F_c^2)/3$	

6. NMR

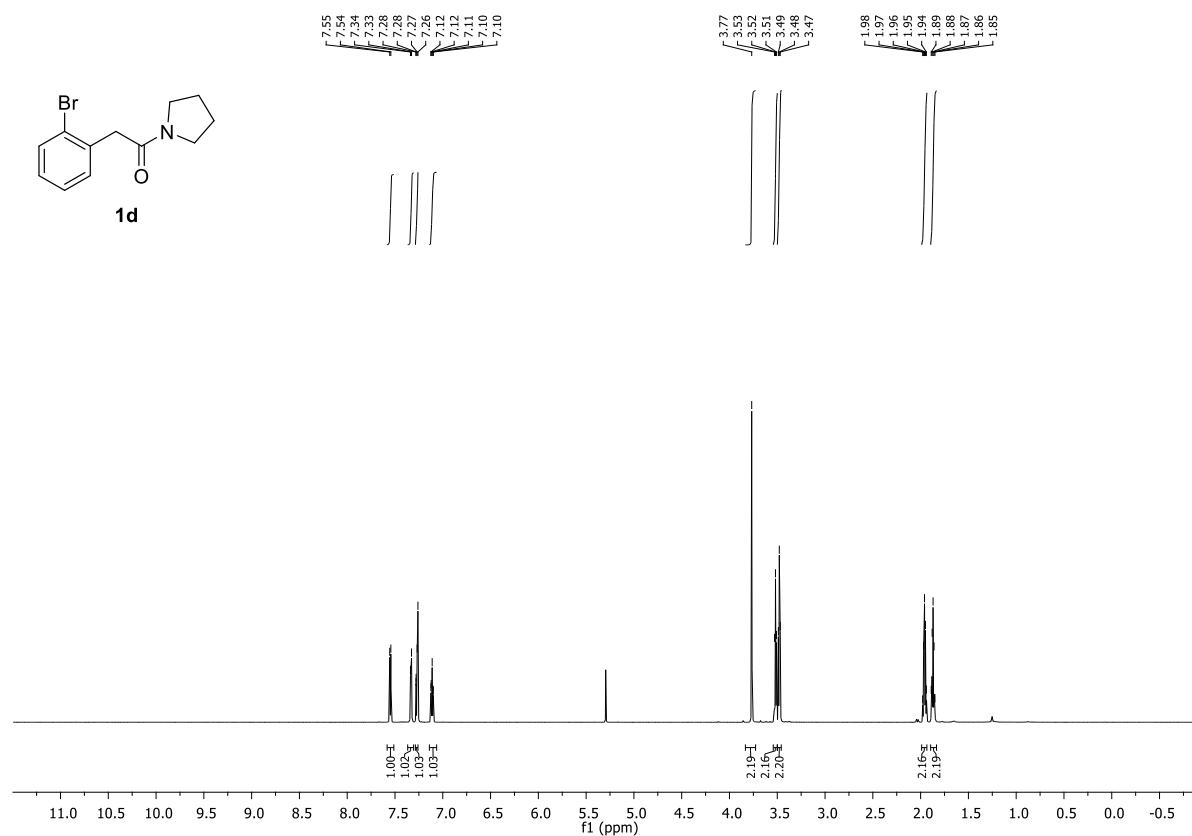
^1H NMR (400 MHz, CDCl_3)



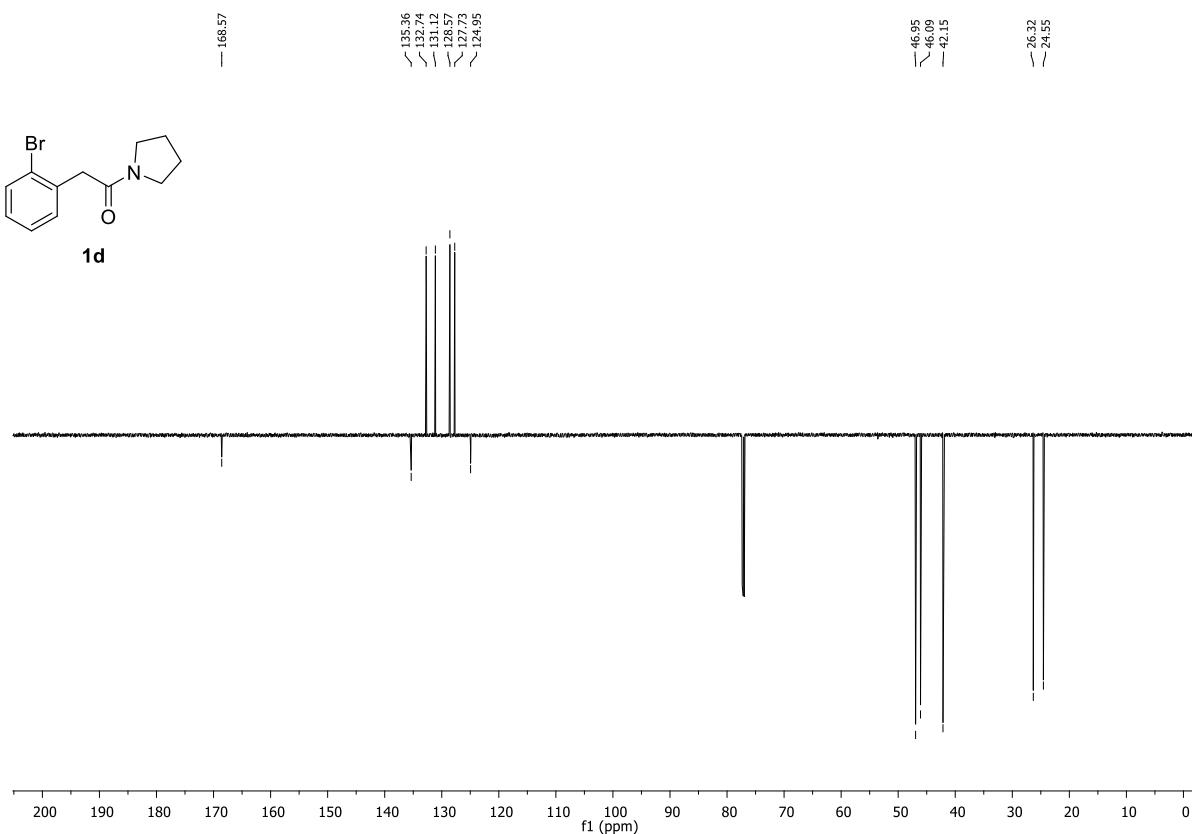
^{13}C NMR (151 MHz, CDCl_3)



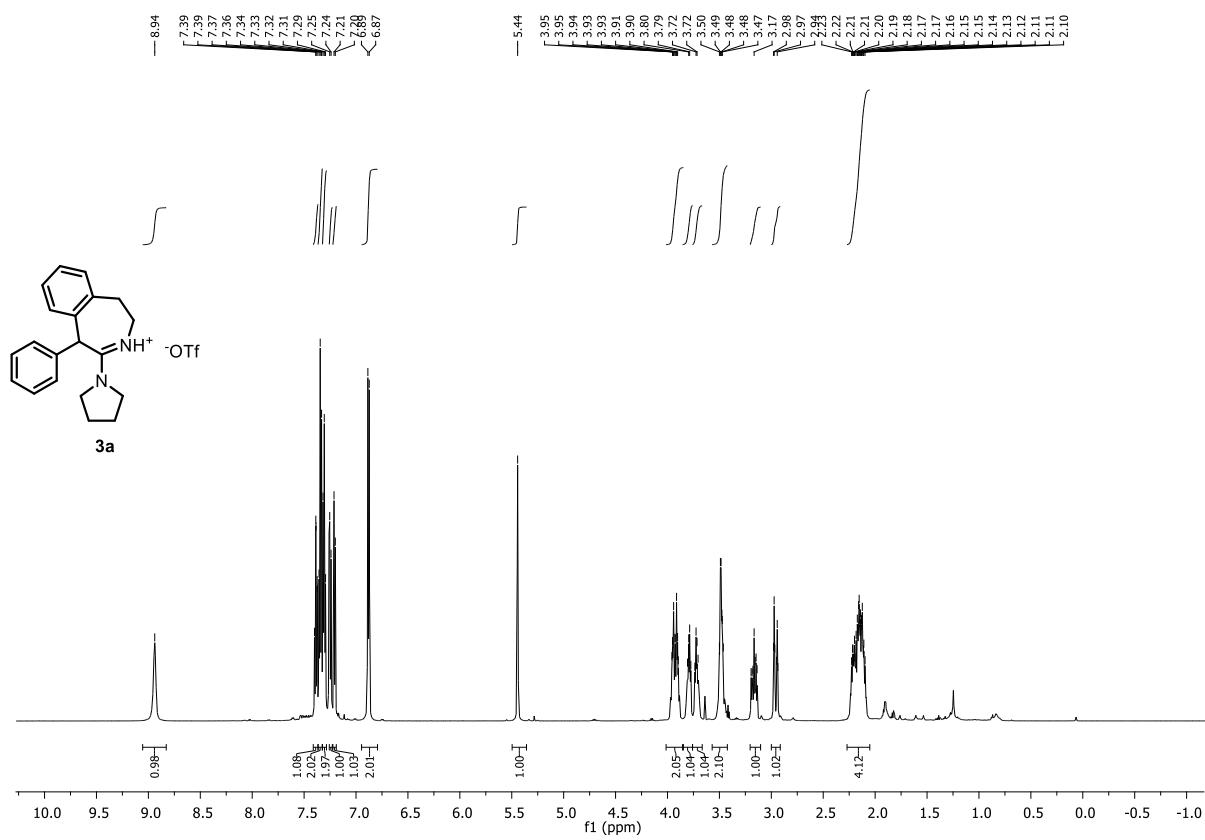
¹H NMR (400 MHz, CDCl₃)



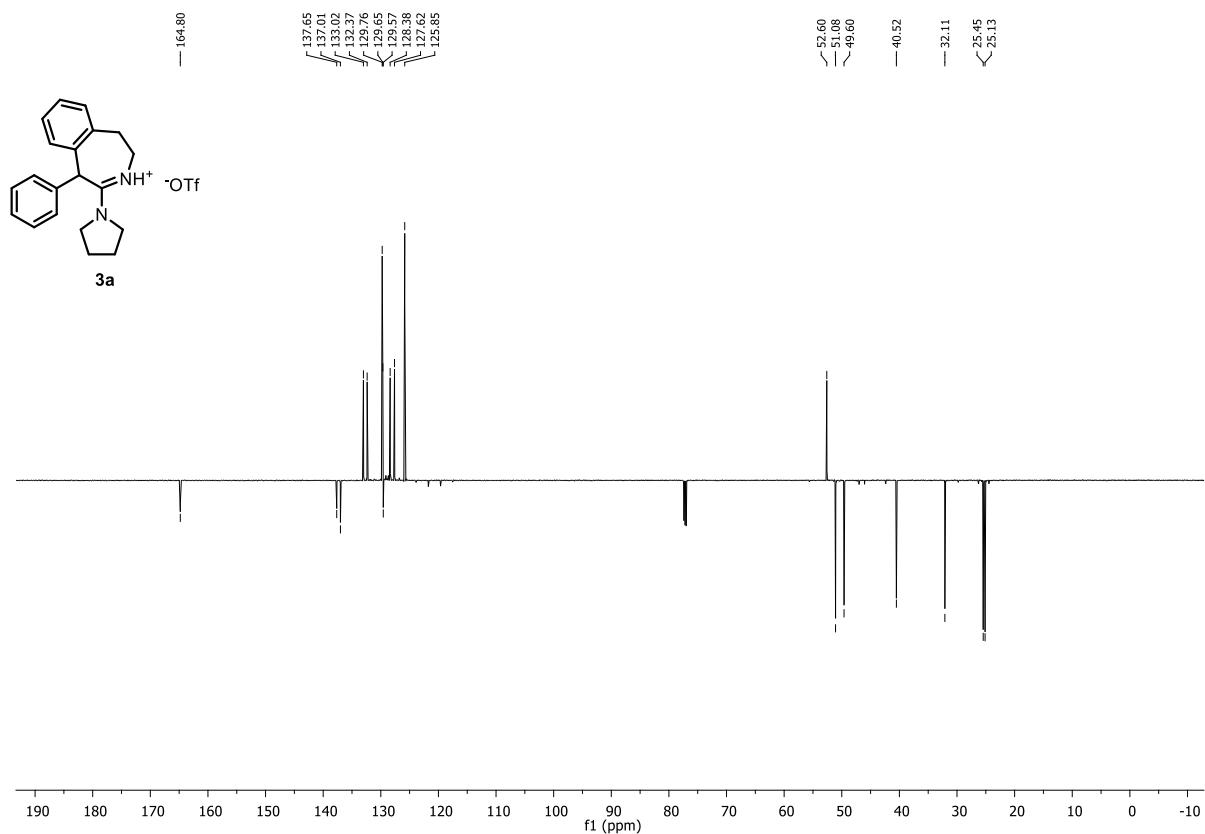
¹³C NMR (151 MHz, CDCl₃)



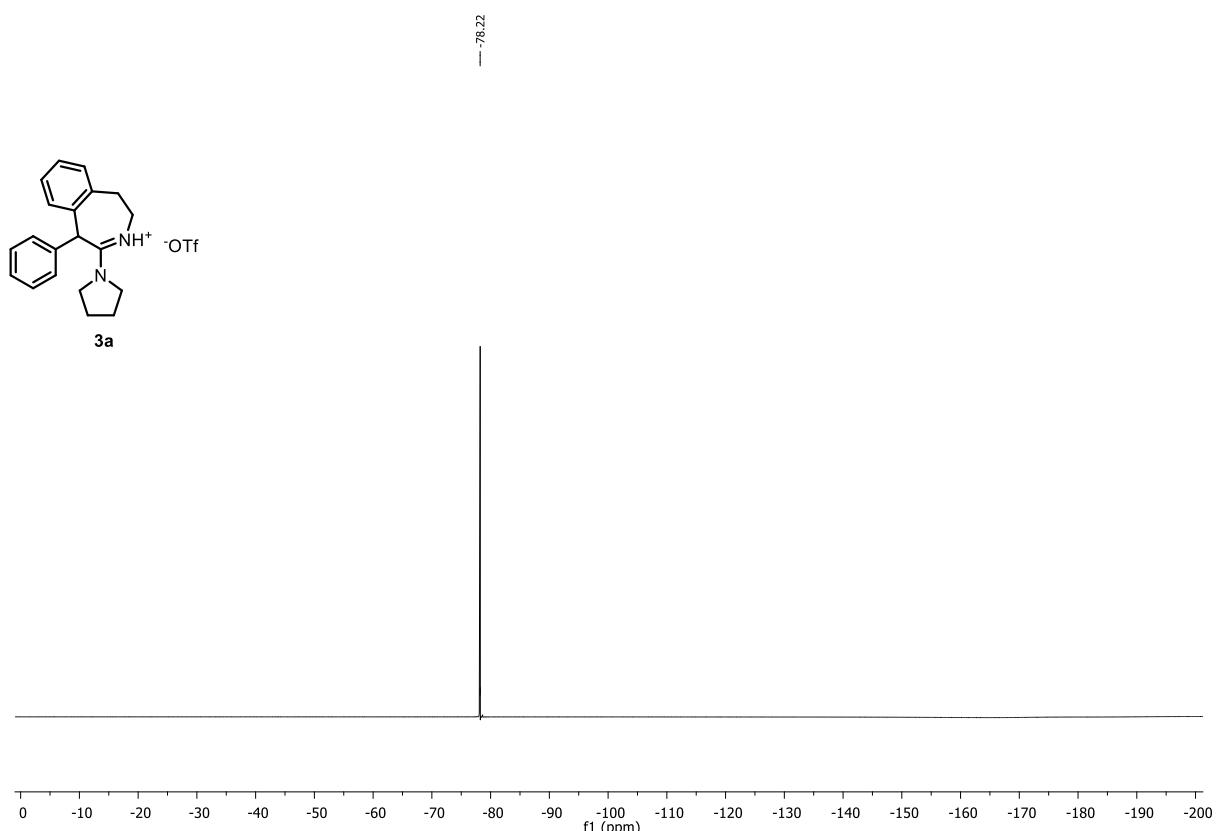
¹H NMR (600 MHz, CDCl₃)



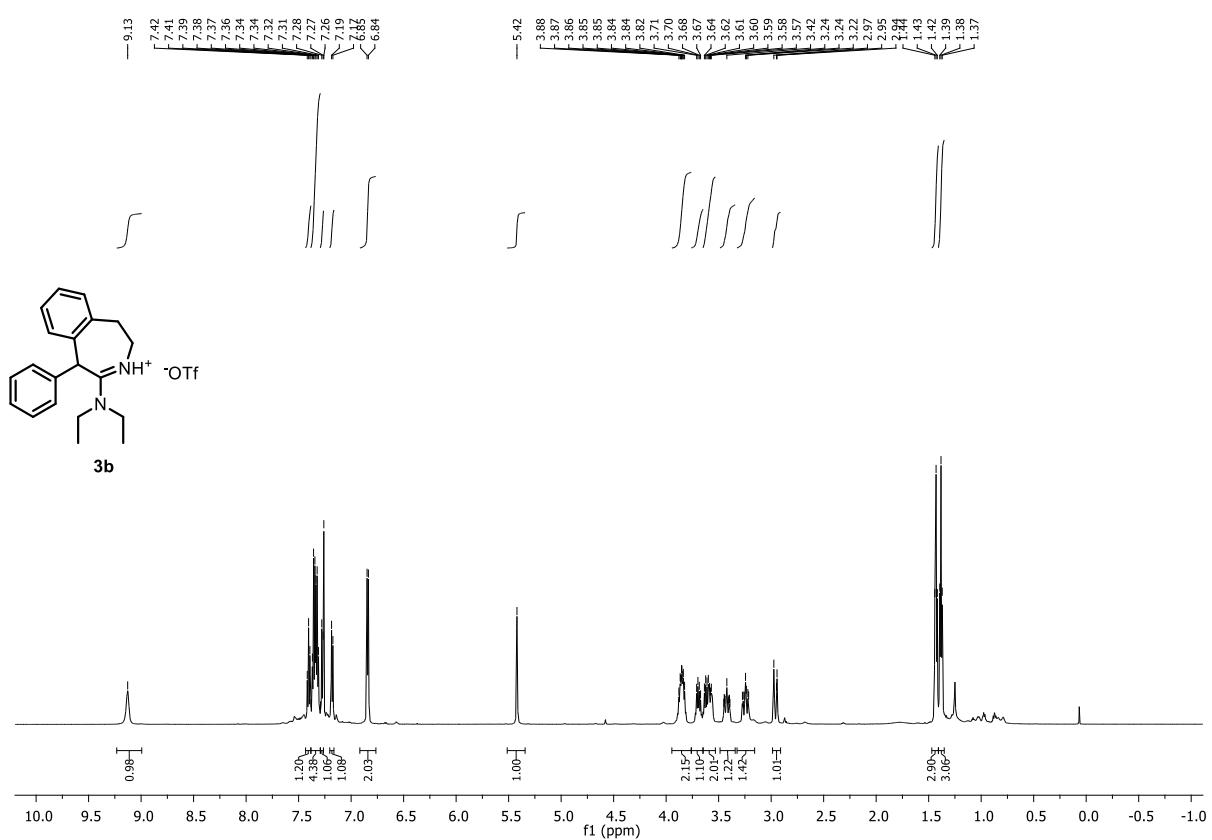
¹³C NMR (151 MHz, CDCl₃)



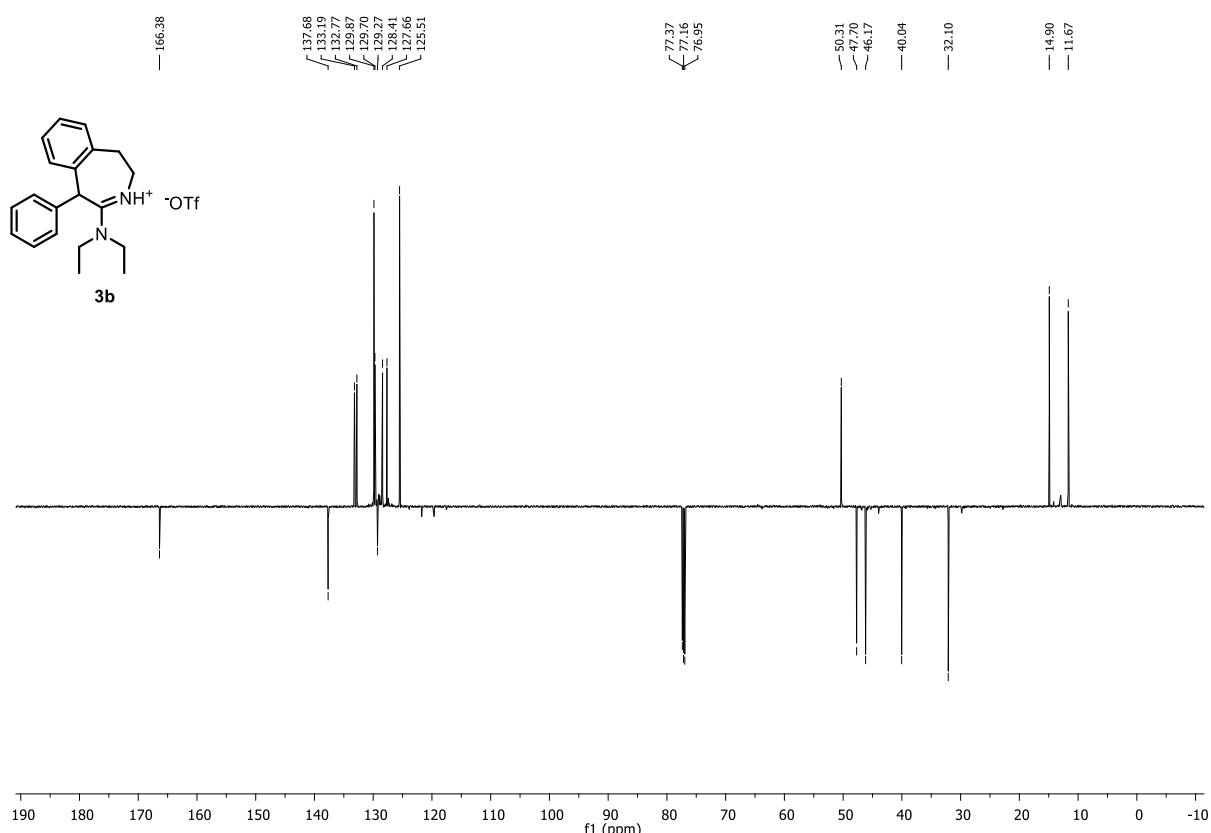
¹⁹F NMR (565 MHz, CDCl₃)



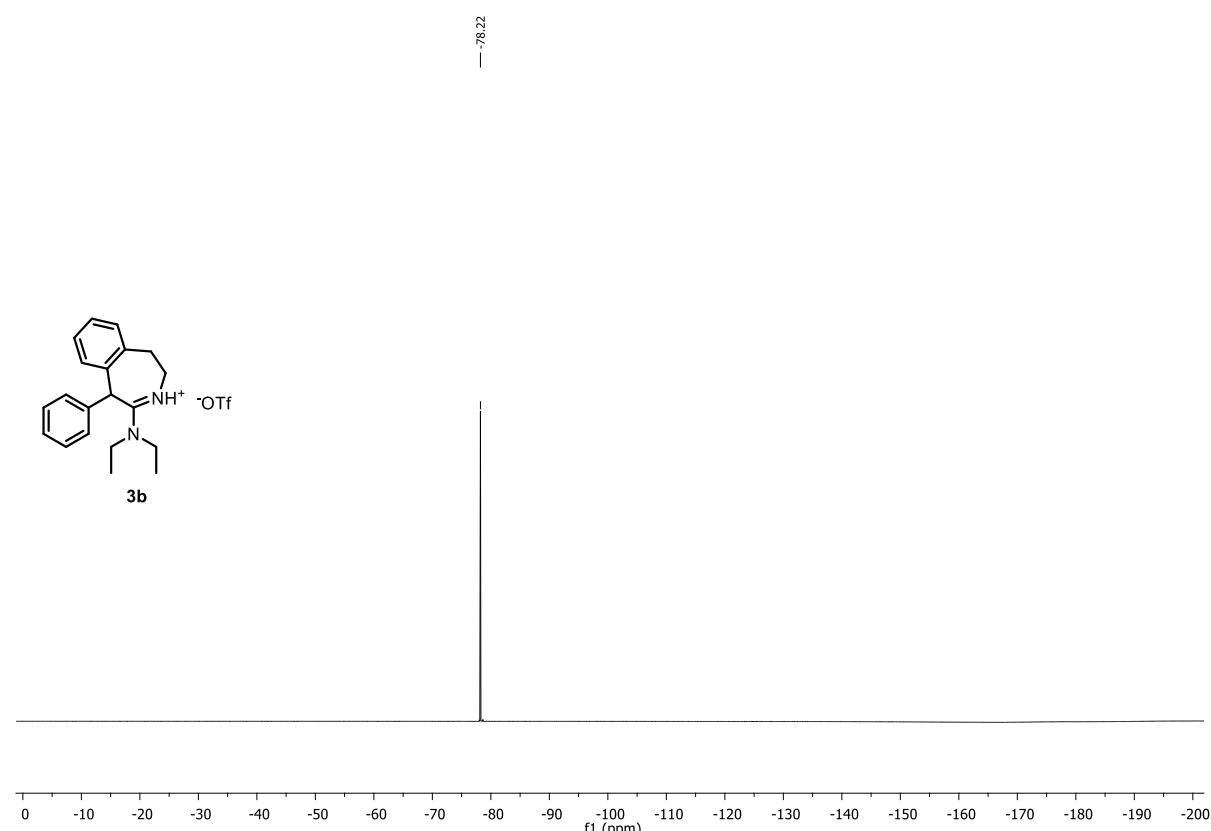
¹H NMR (600 MHz, CDCl₃)



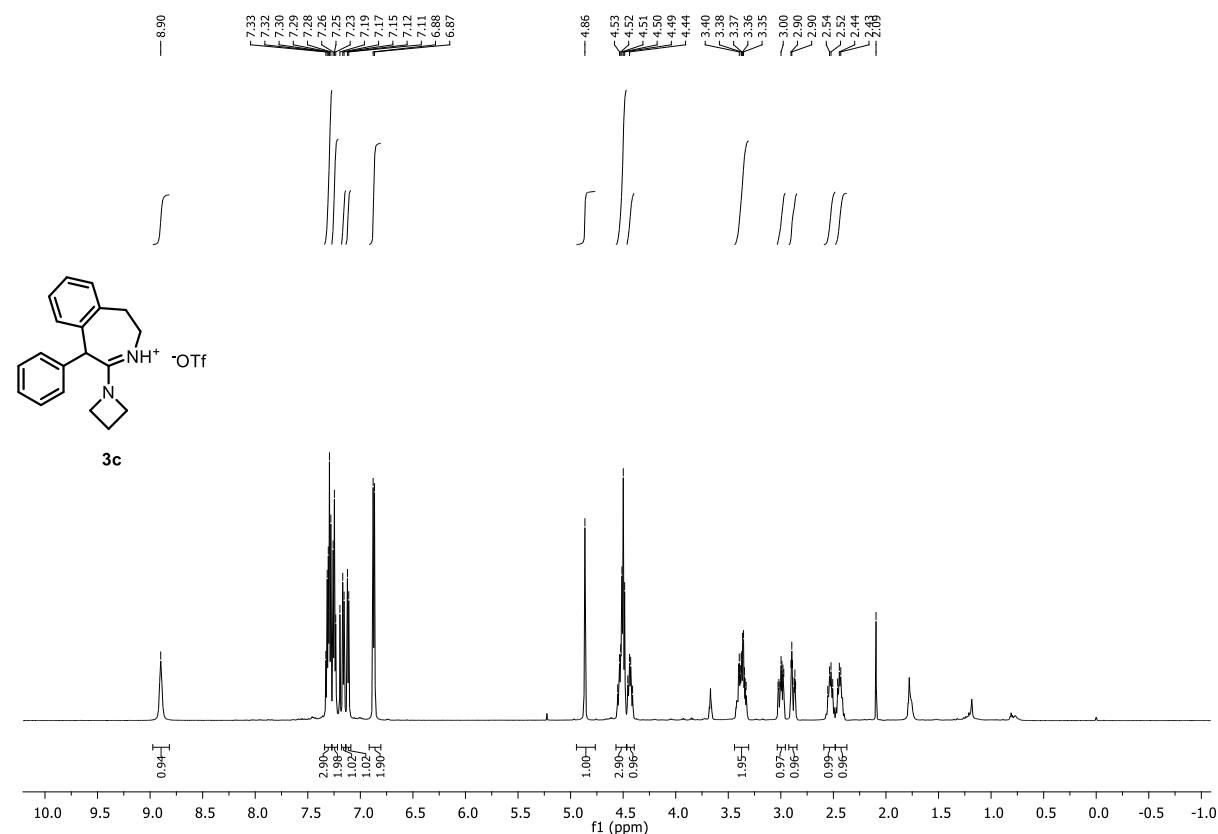
¹³C NMR (151 MHz, CDCl₃)



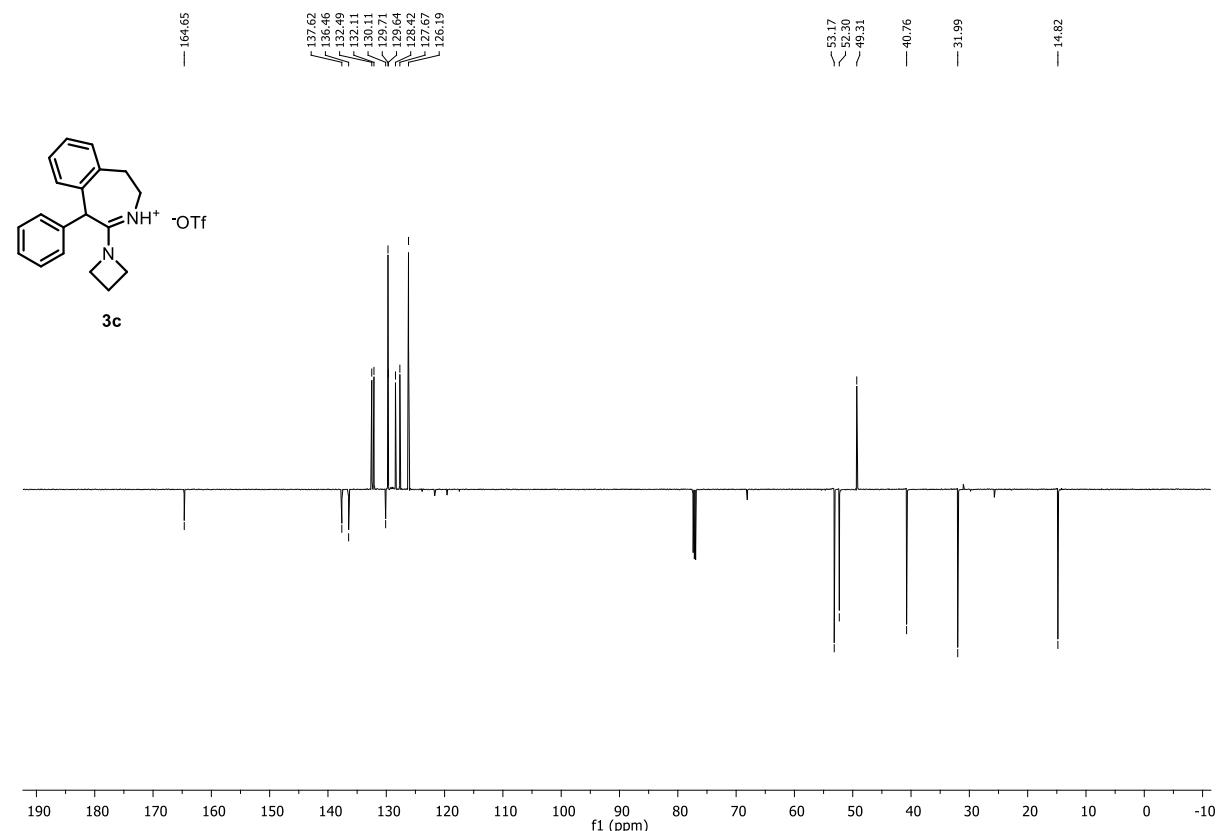
¹⁹F NMR (565 MHz, CDCl₃)



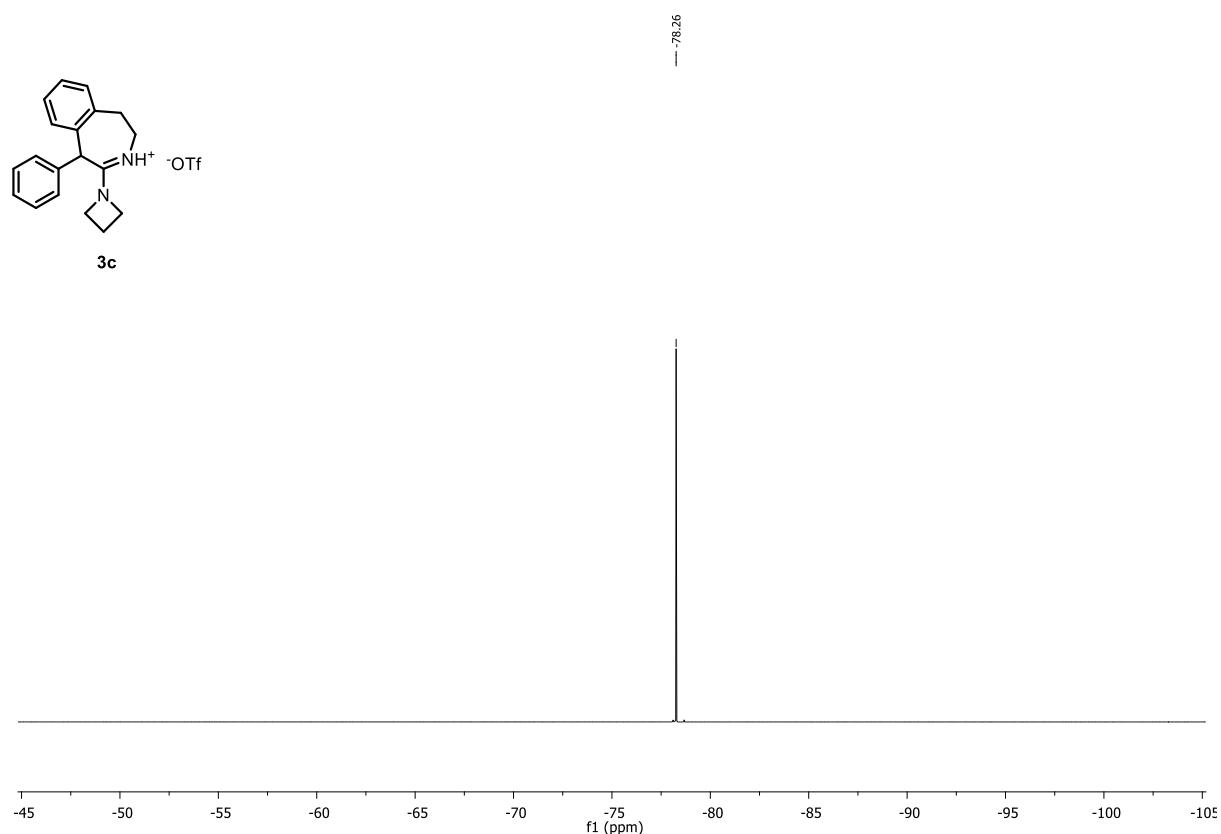
¹H NMR (600 MHz, CDCl₃)



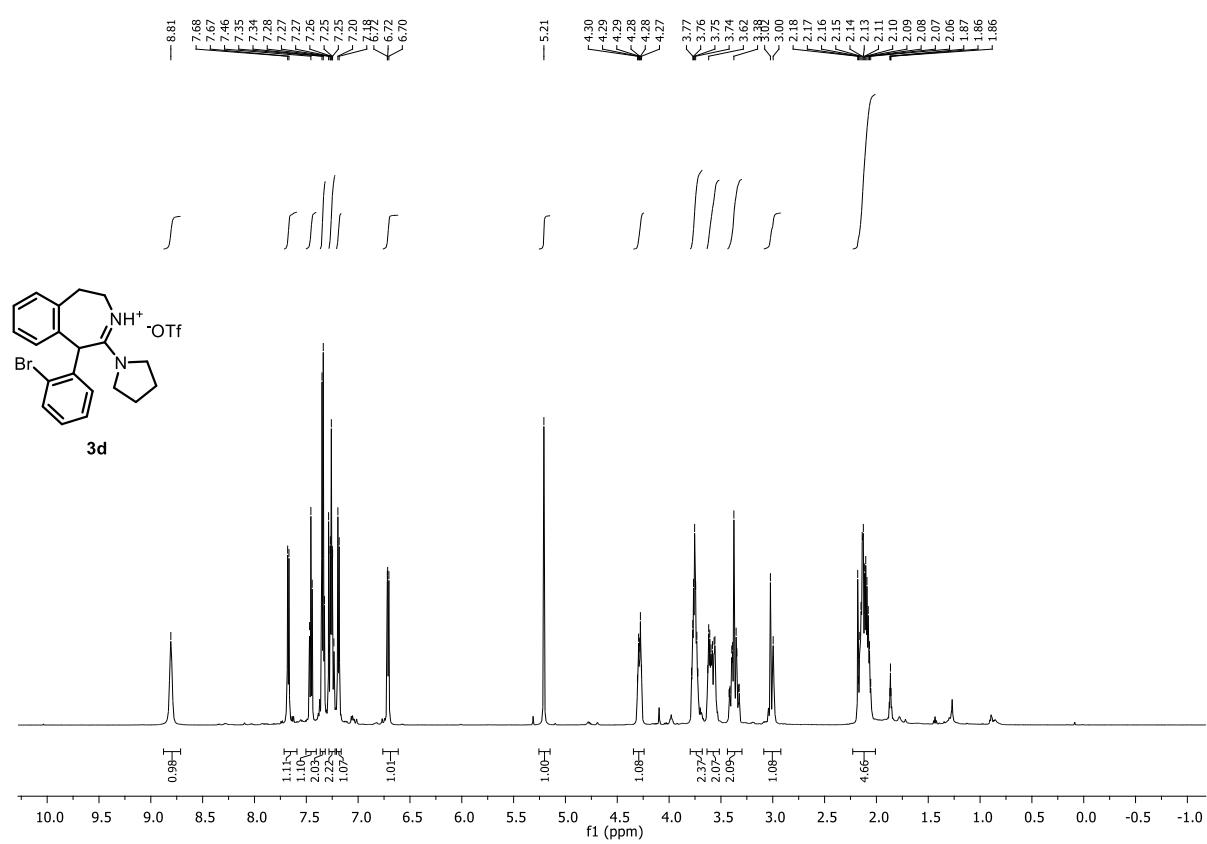
¹³C NMR (151 MHz, CDCl₃)



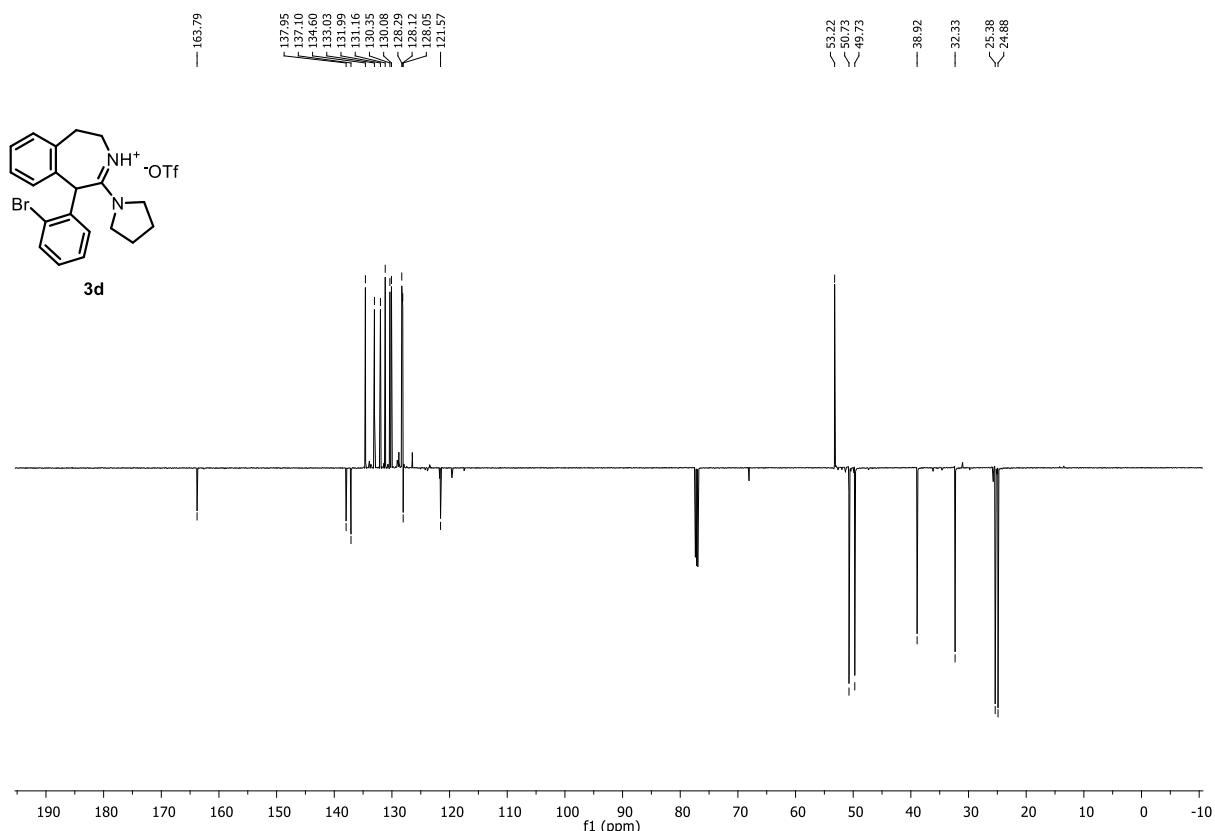
¹⁹F NMR (565 MHz, CDCl₃)



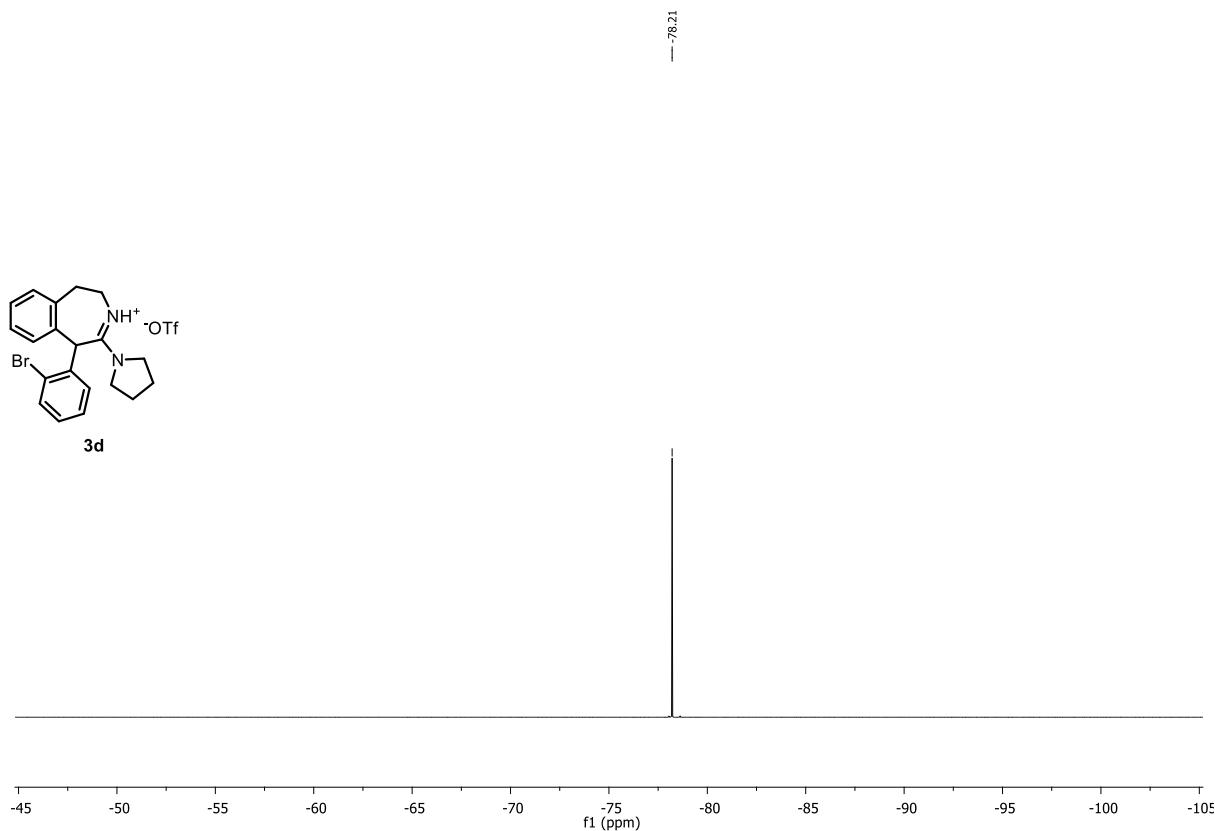
¹H NMR (600 MHz, CDCl₃)



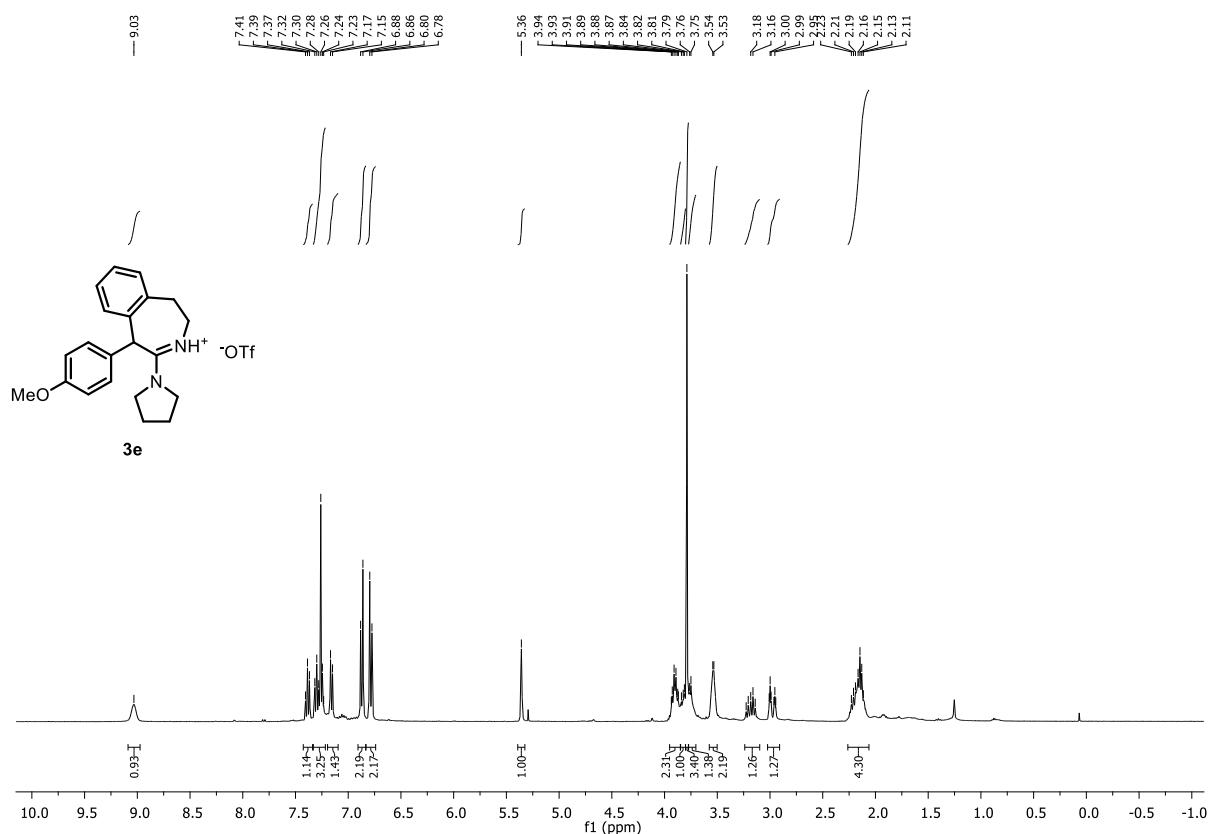
¹³C NMR (151 MHz, CDCl₃)



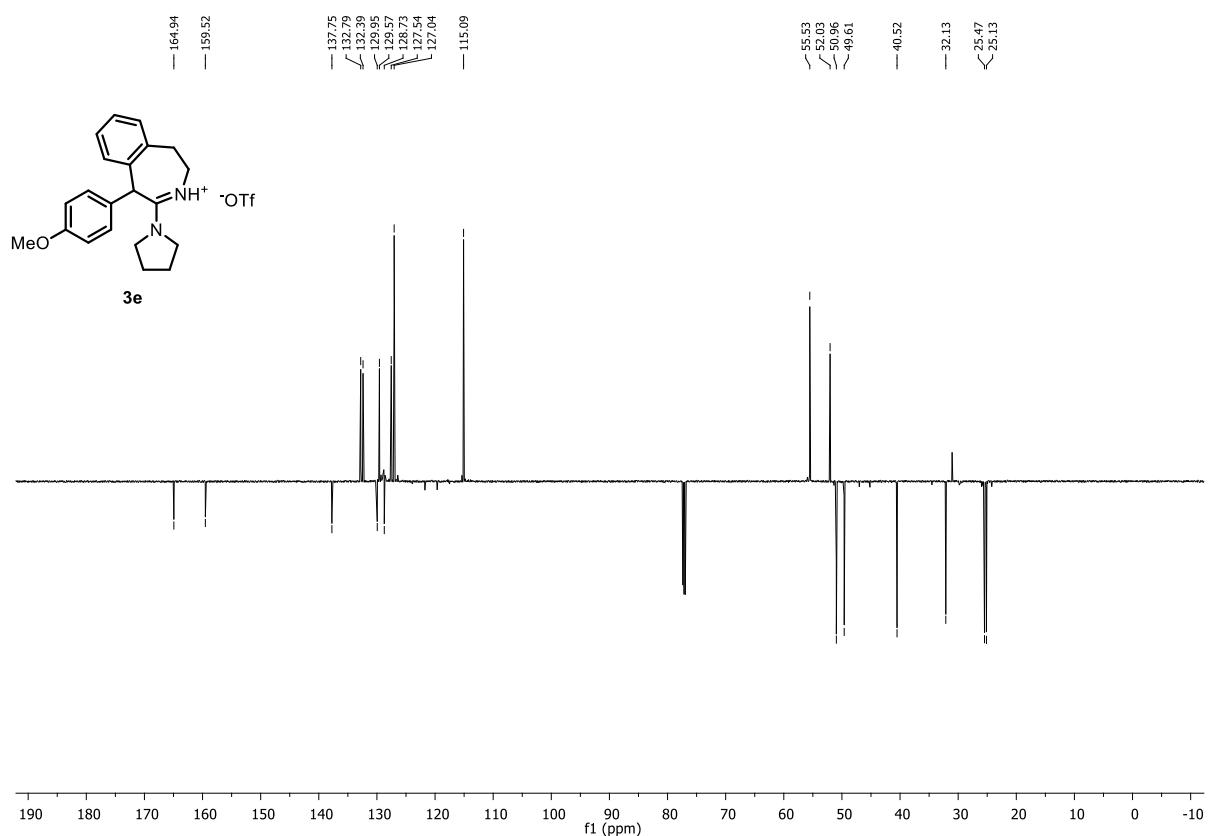
¹⁹F NMR (565 MHz, CDCl₃)



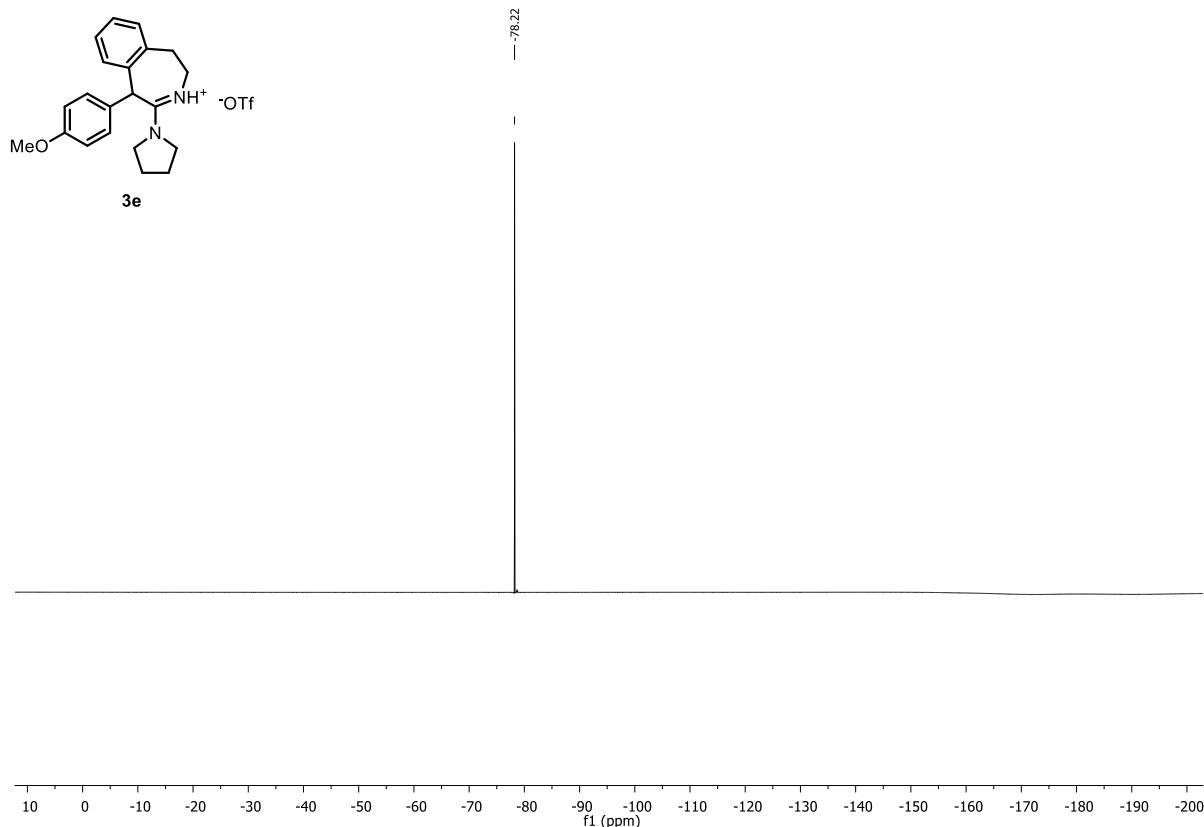
¹H NMR (400 MHz, CDCl₃)



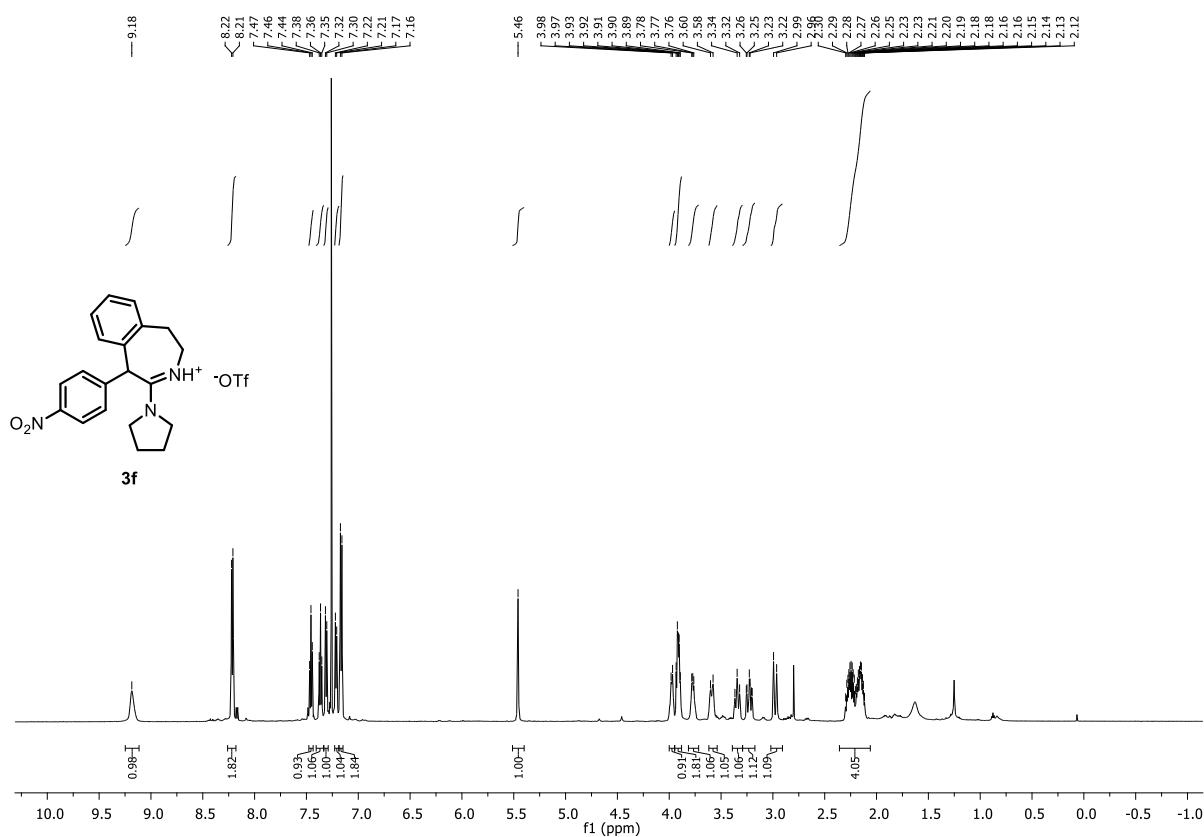
¹³C NMR (151 MHz, CDCl₃)



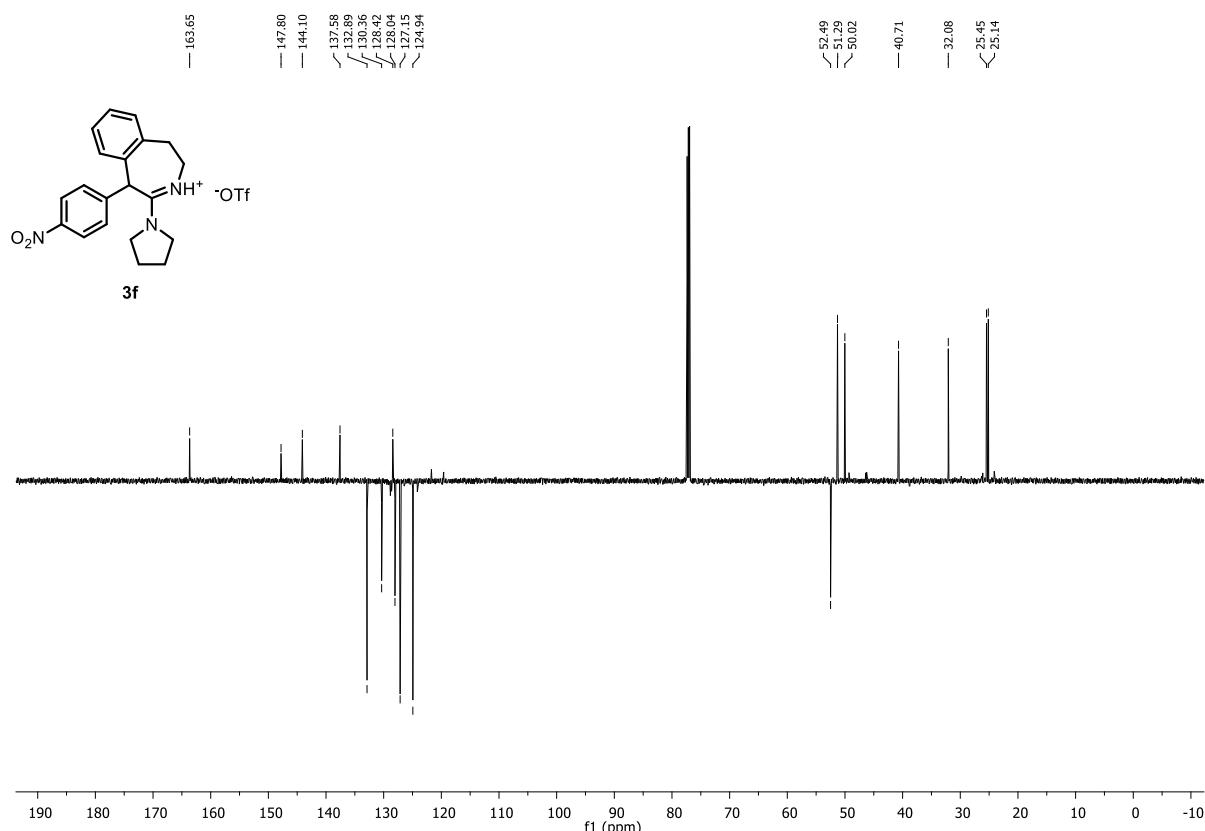
¹⁹F NMR (565 MHz, CDCl₃)



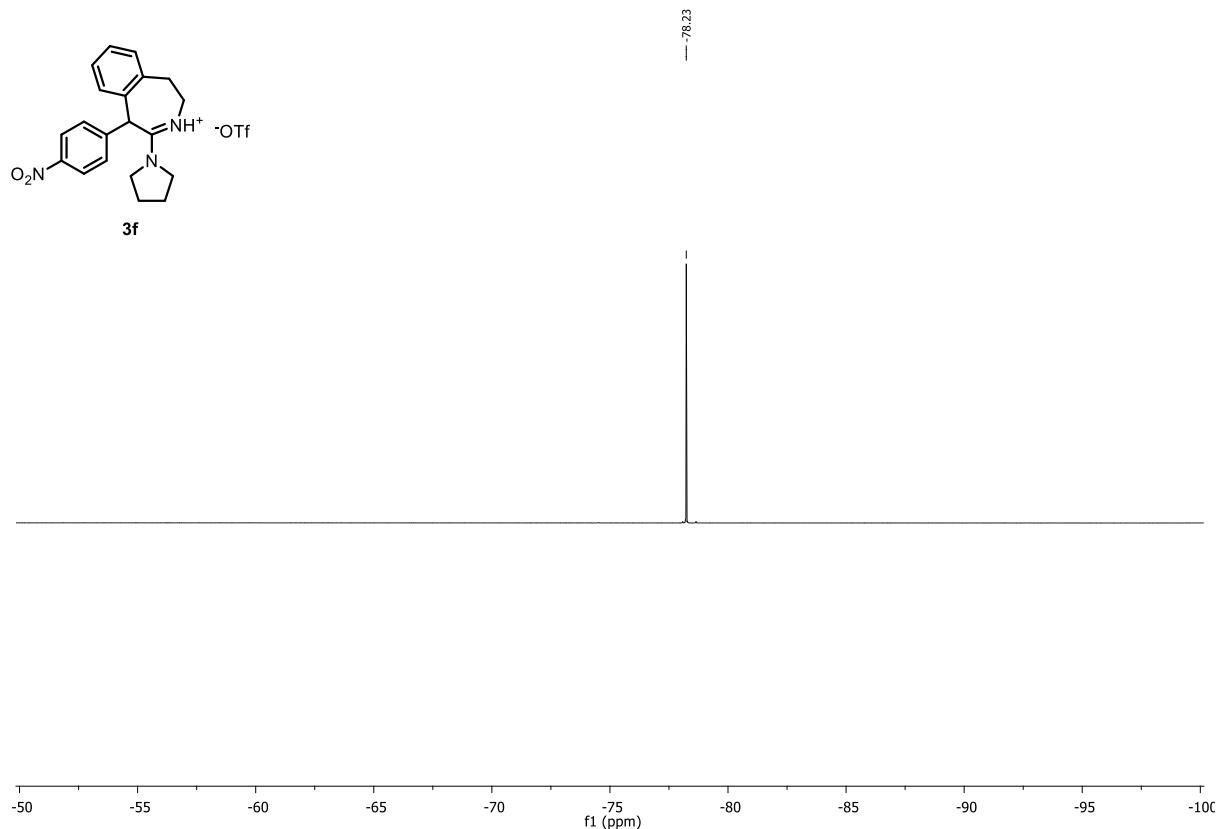
¹H NMR (600 MHz, CDCl₃)



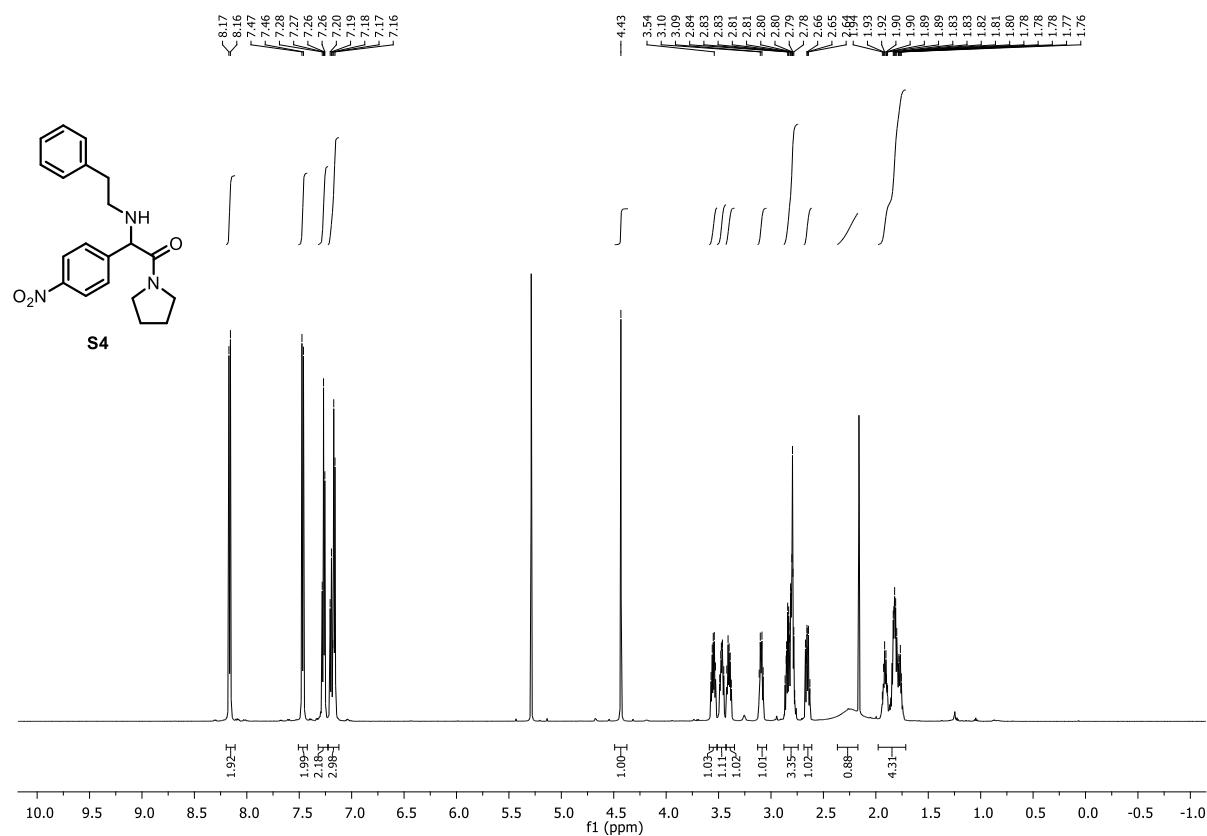
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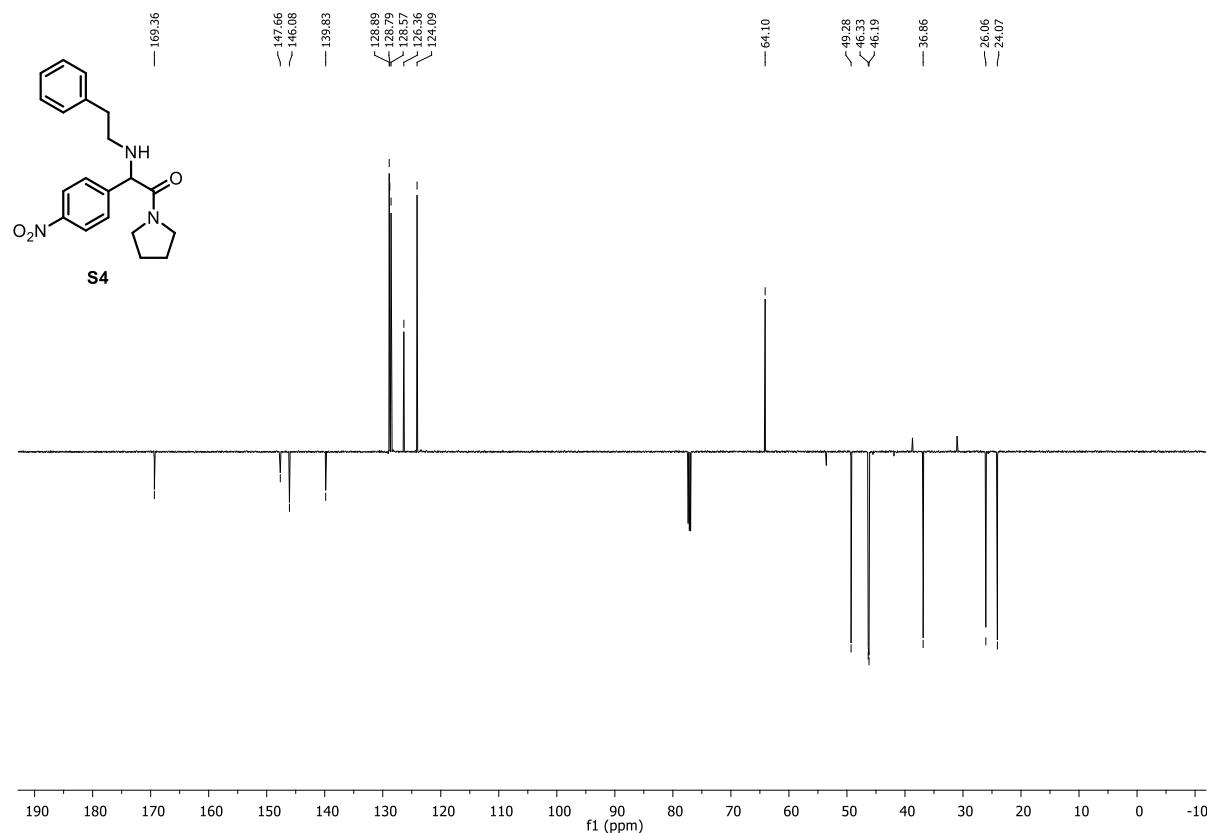
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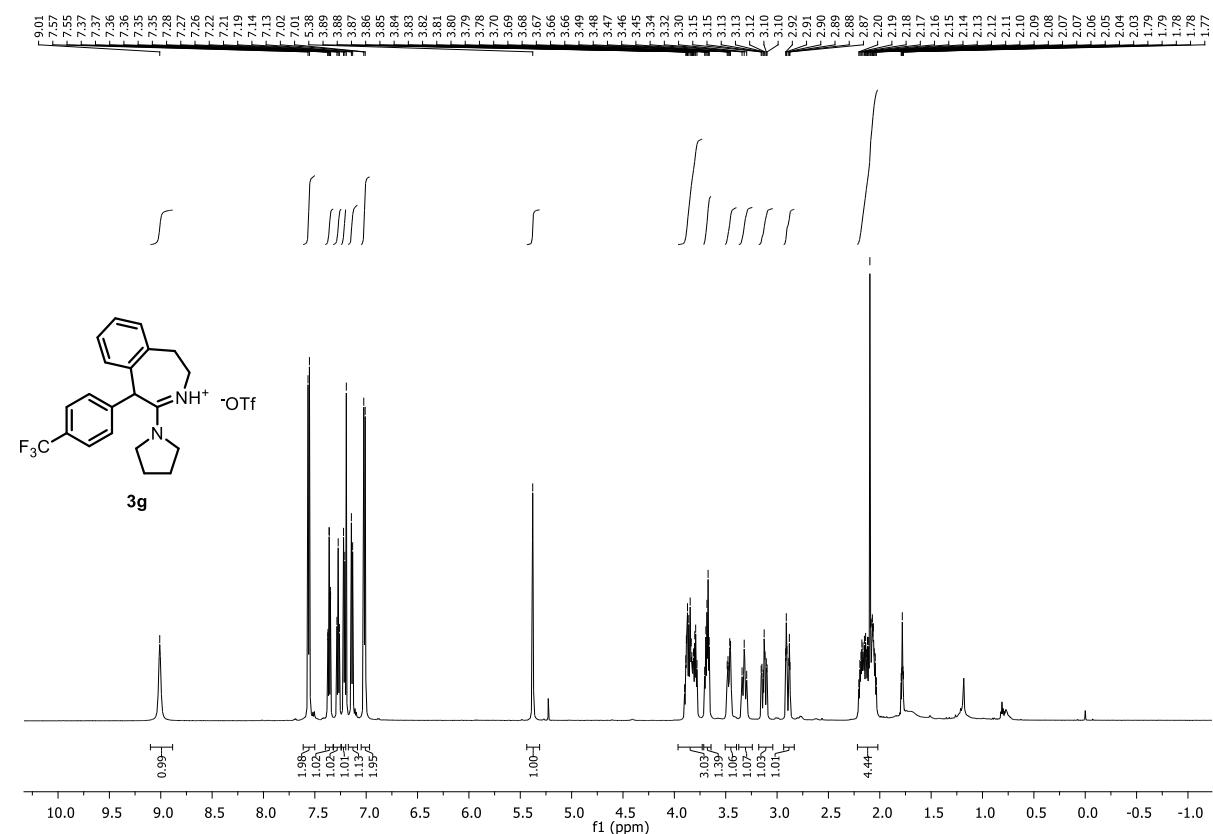
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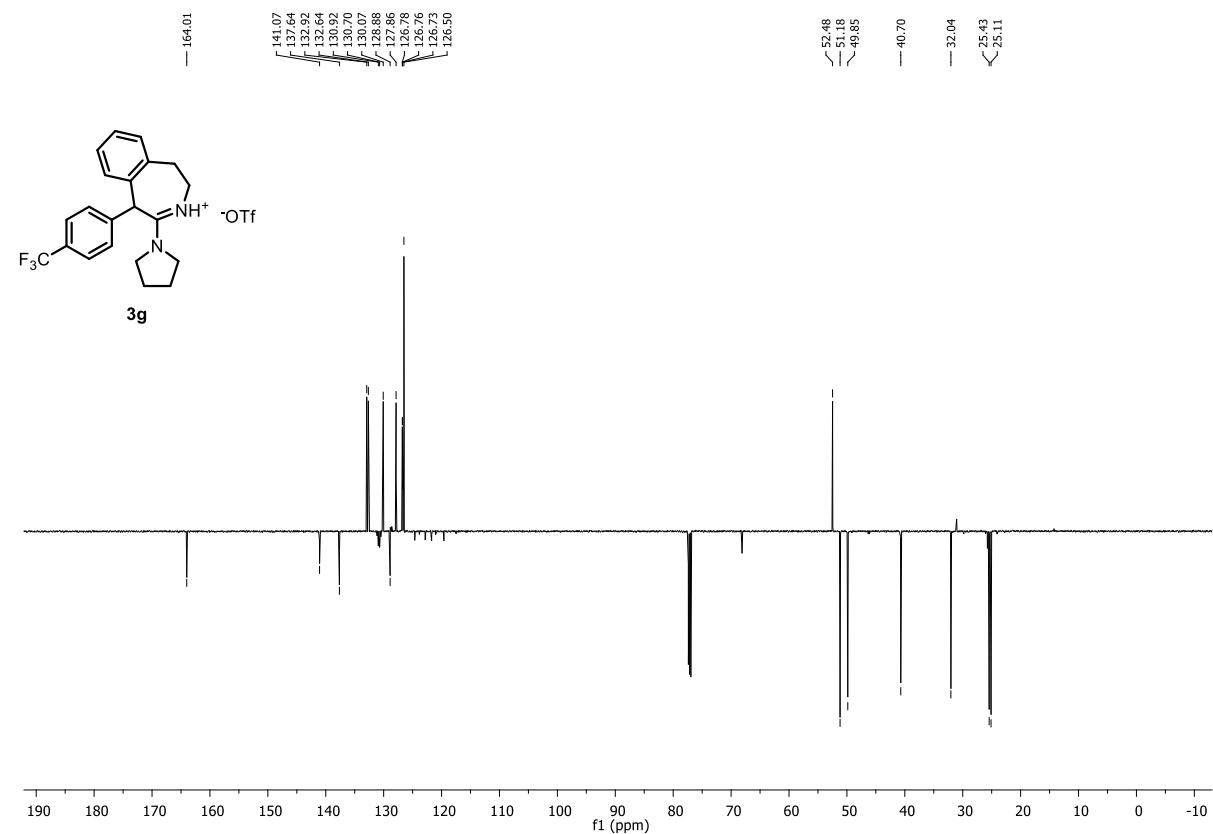
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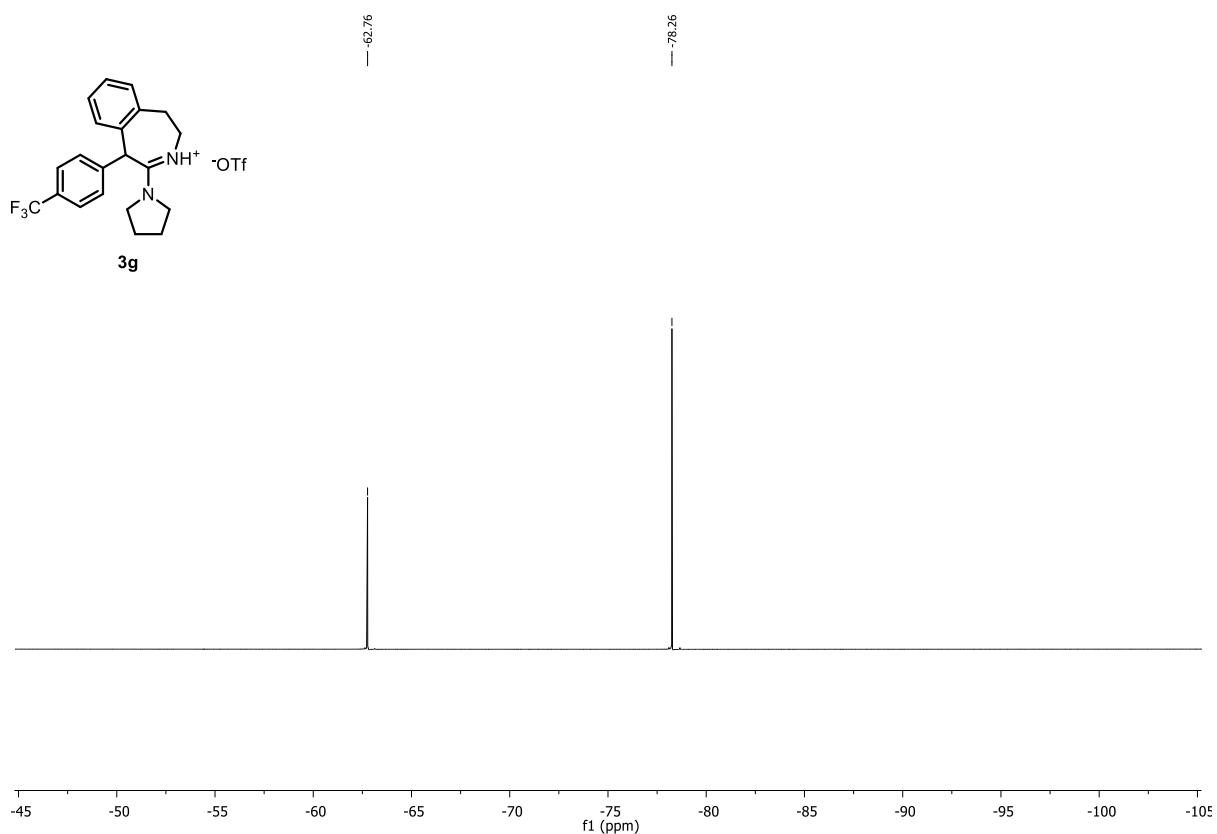
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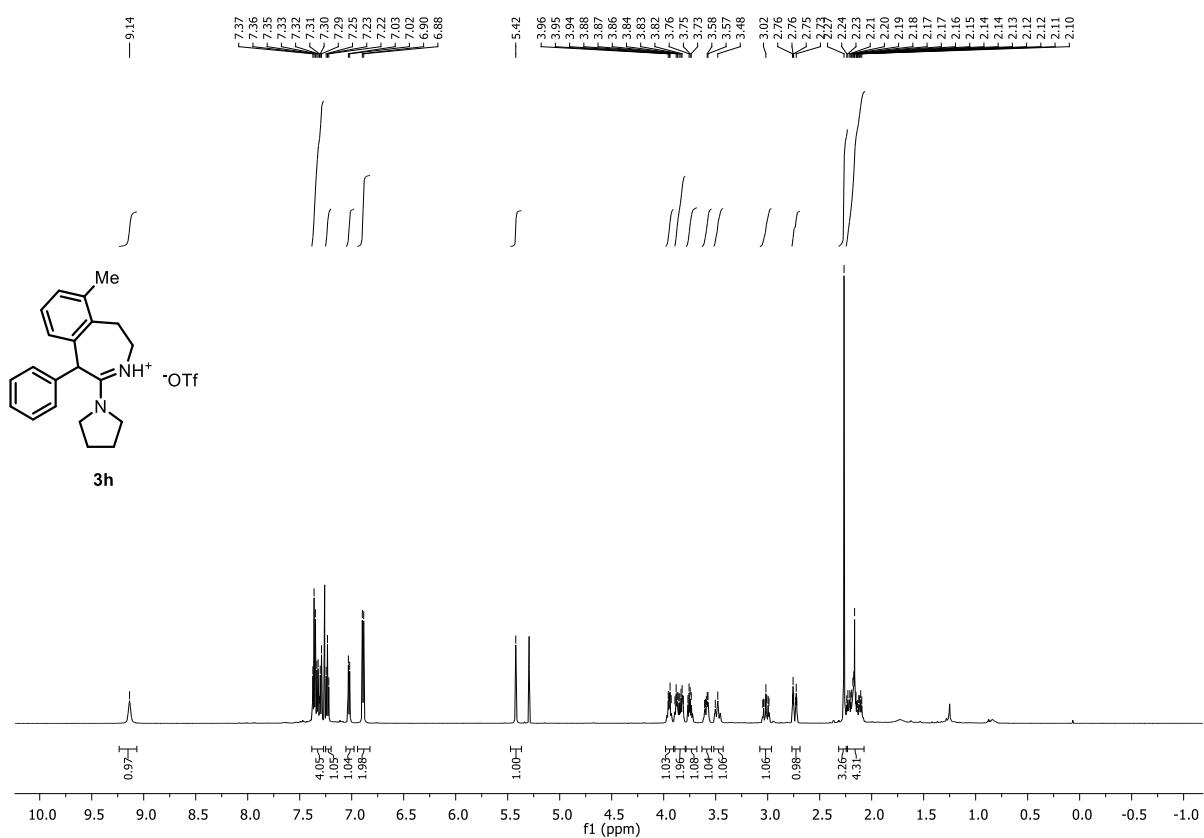
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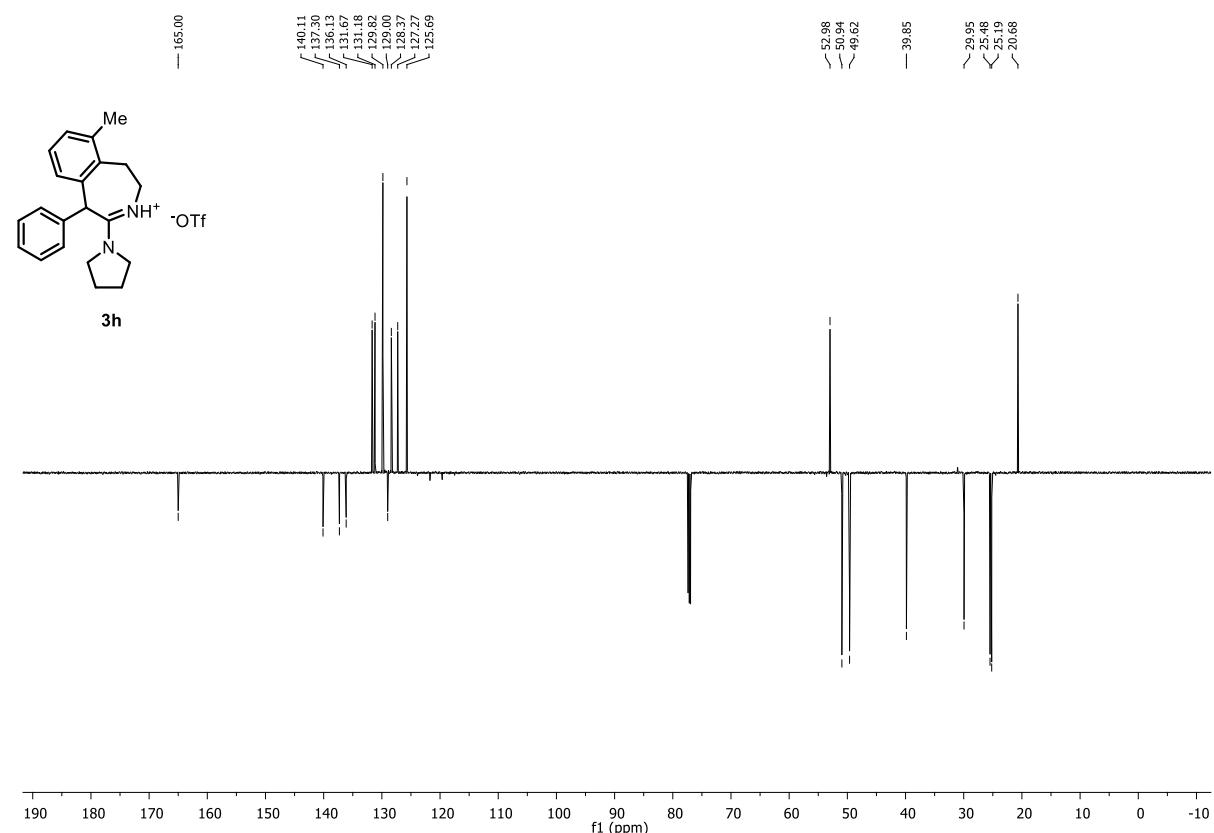
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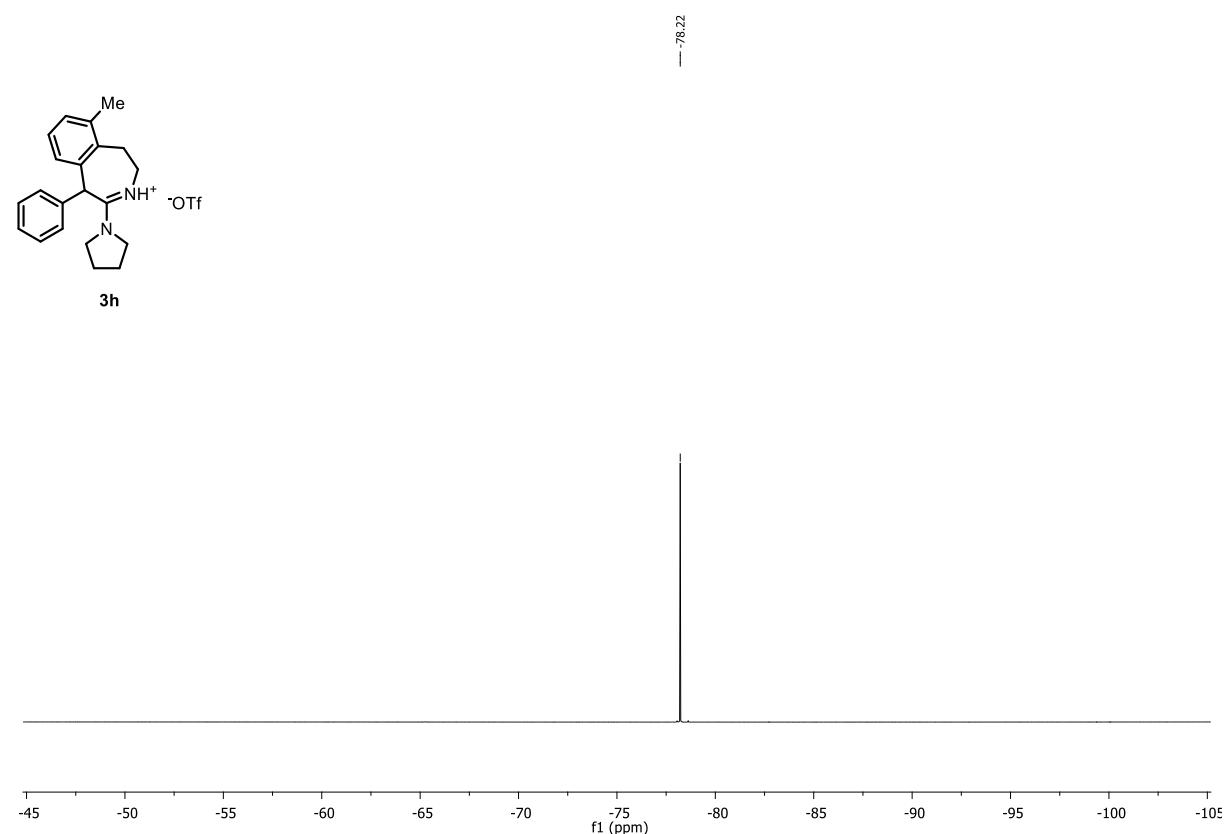
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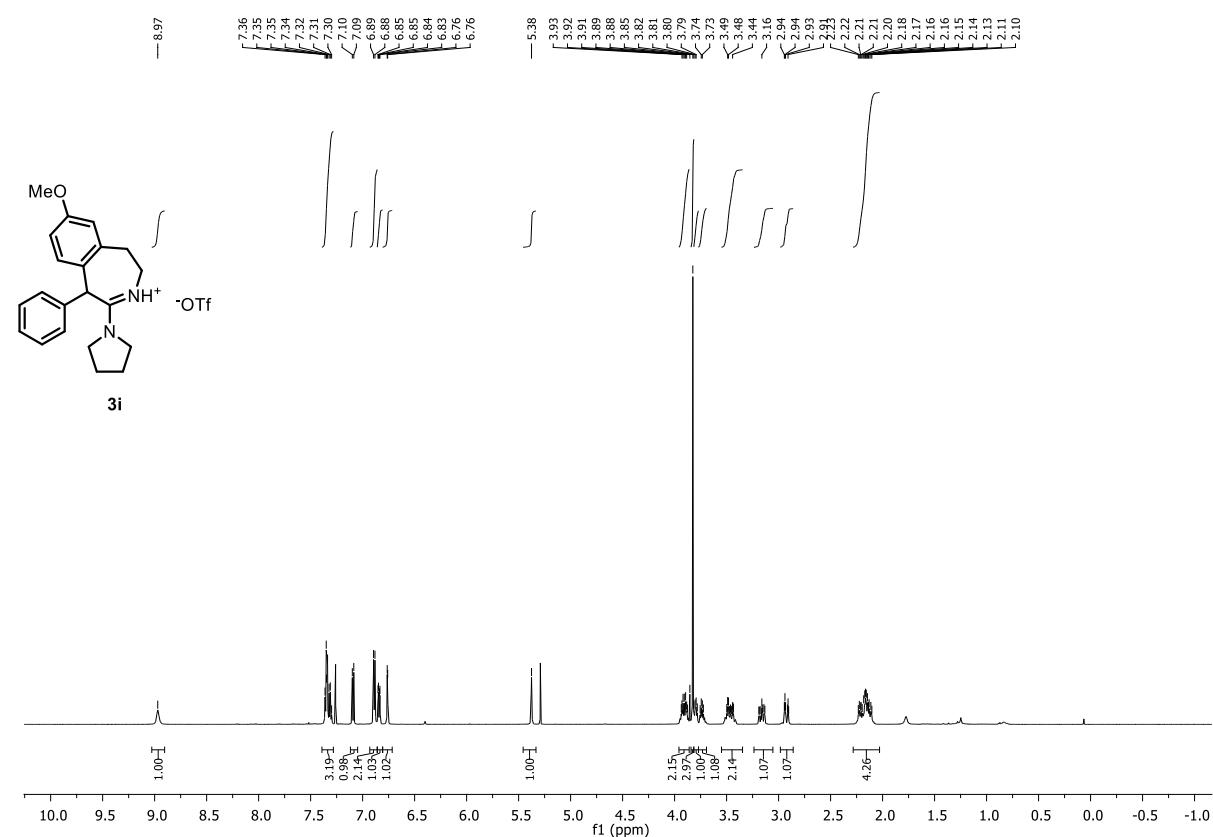
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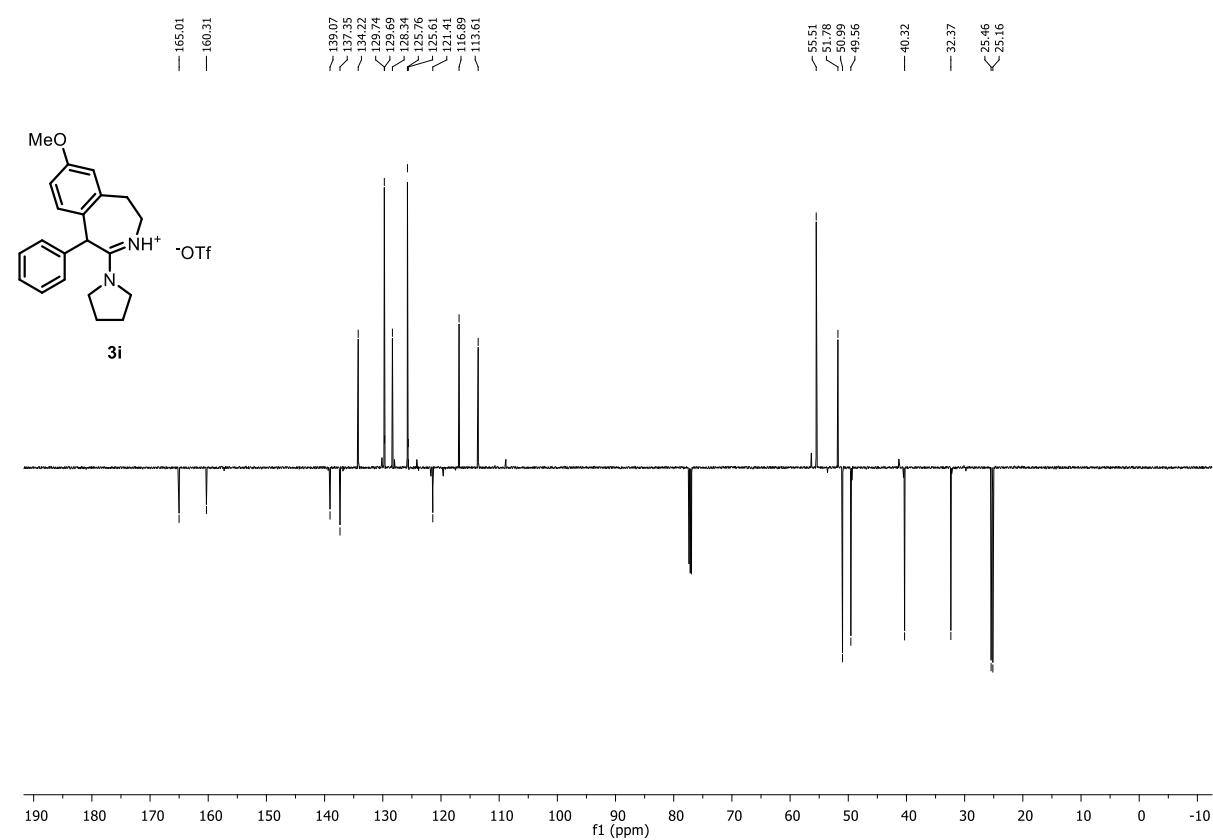
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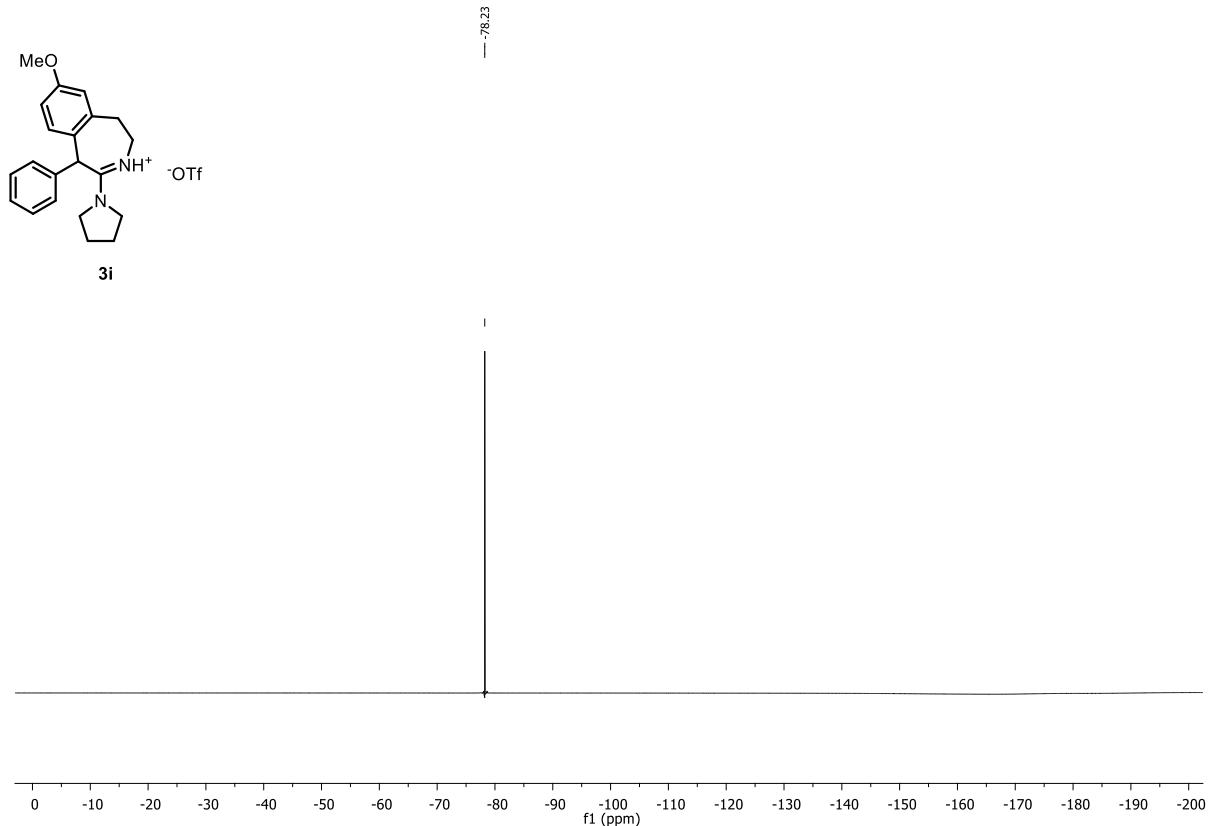
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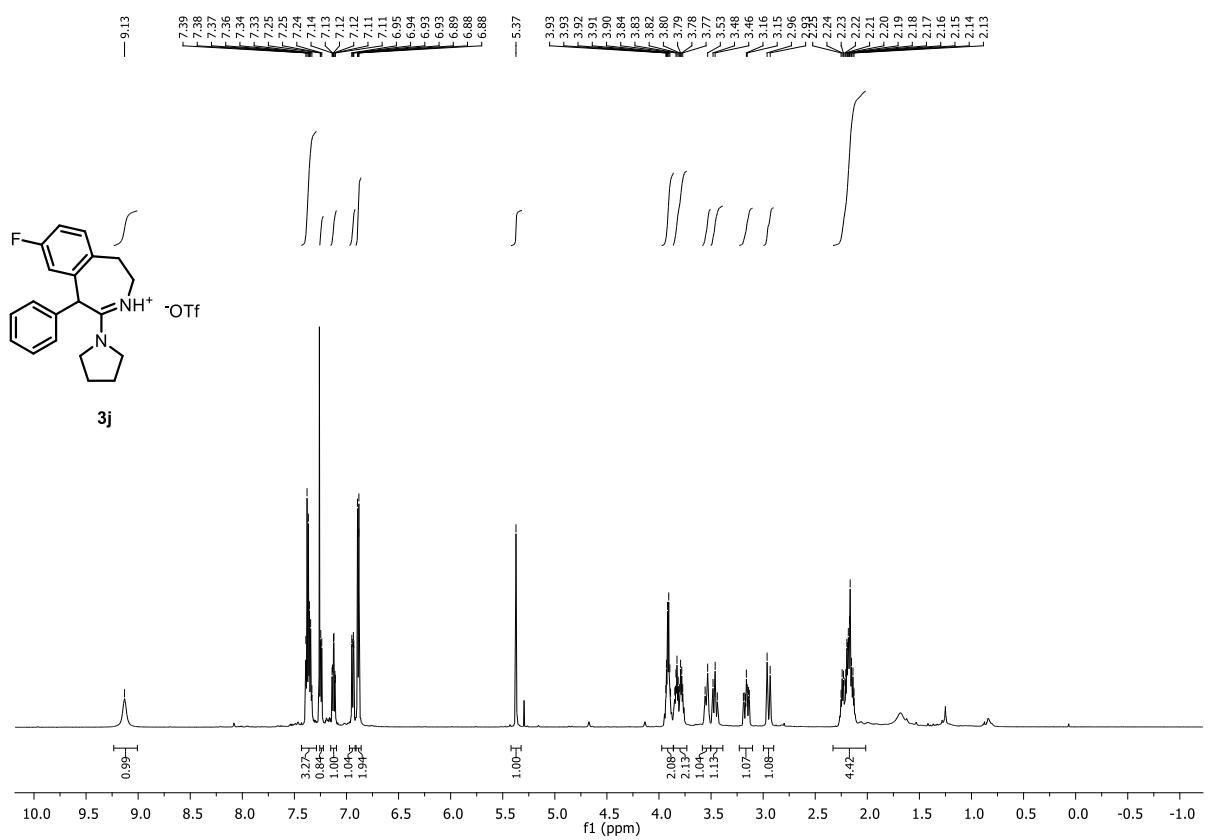
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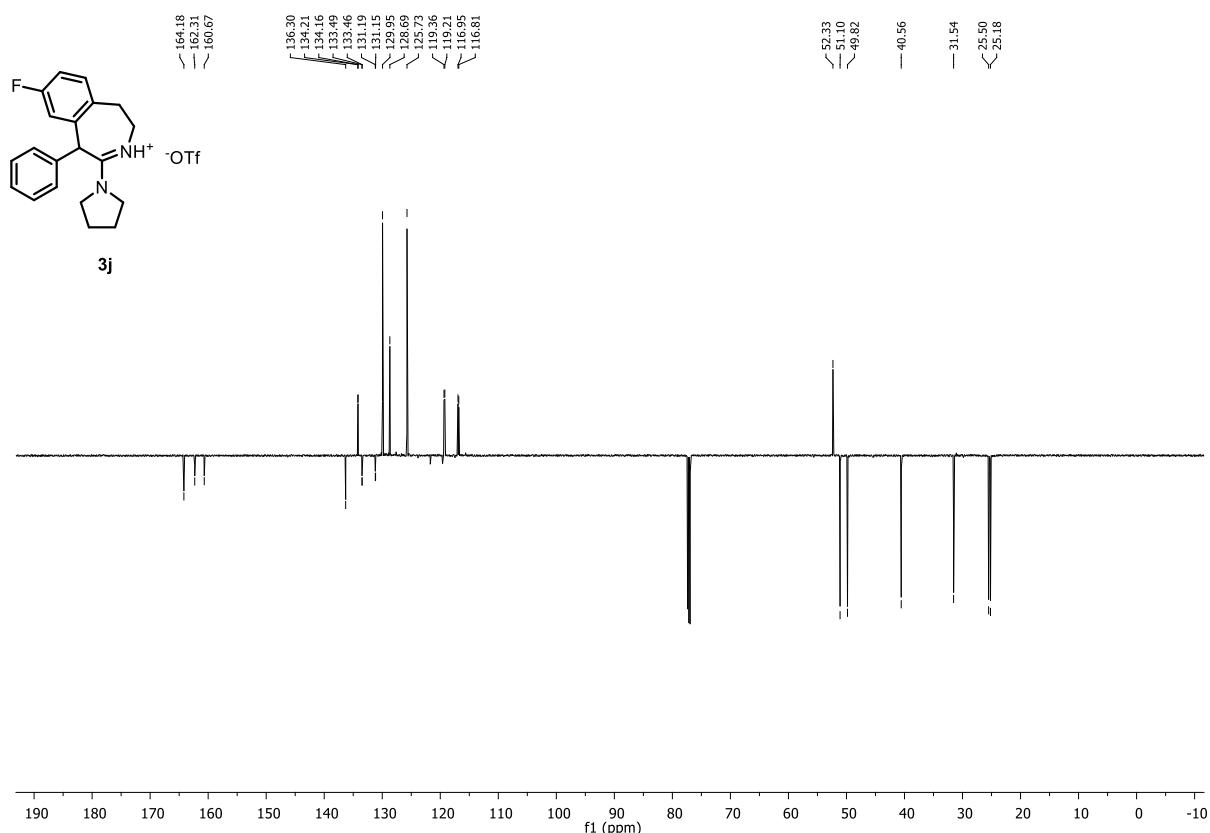
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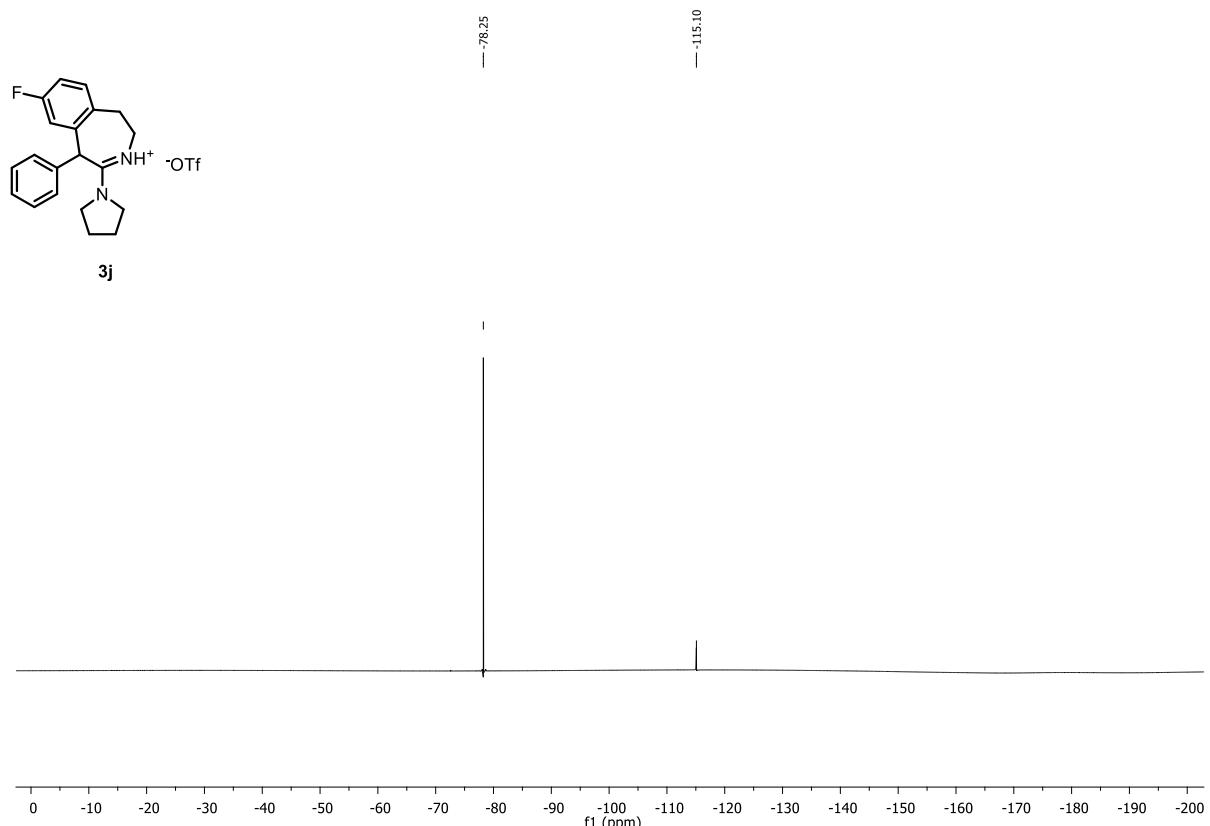
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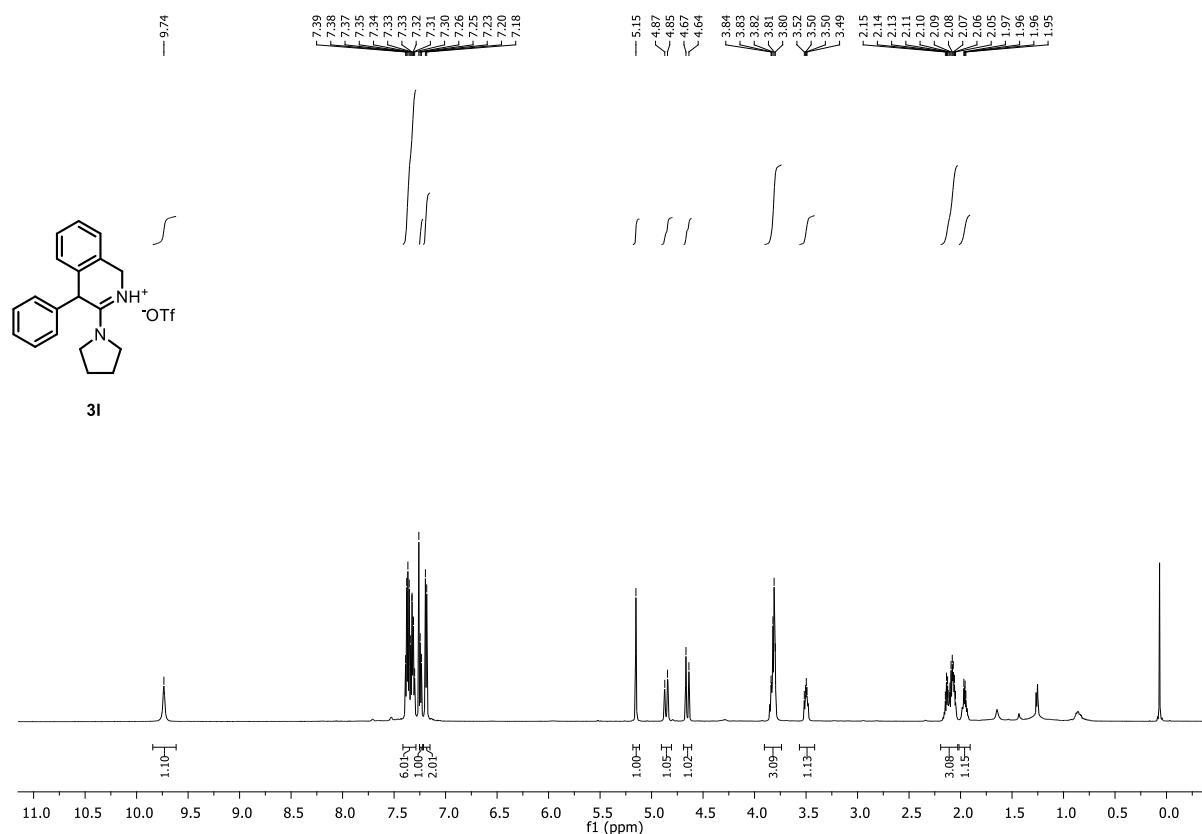
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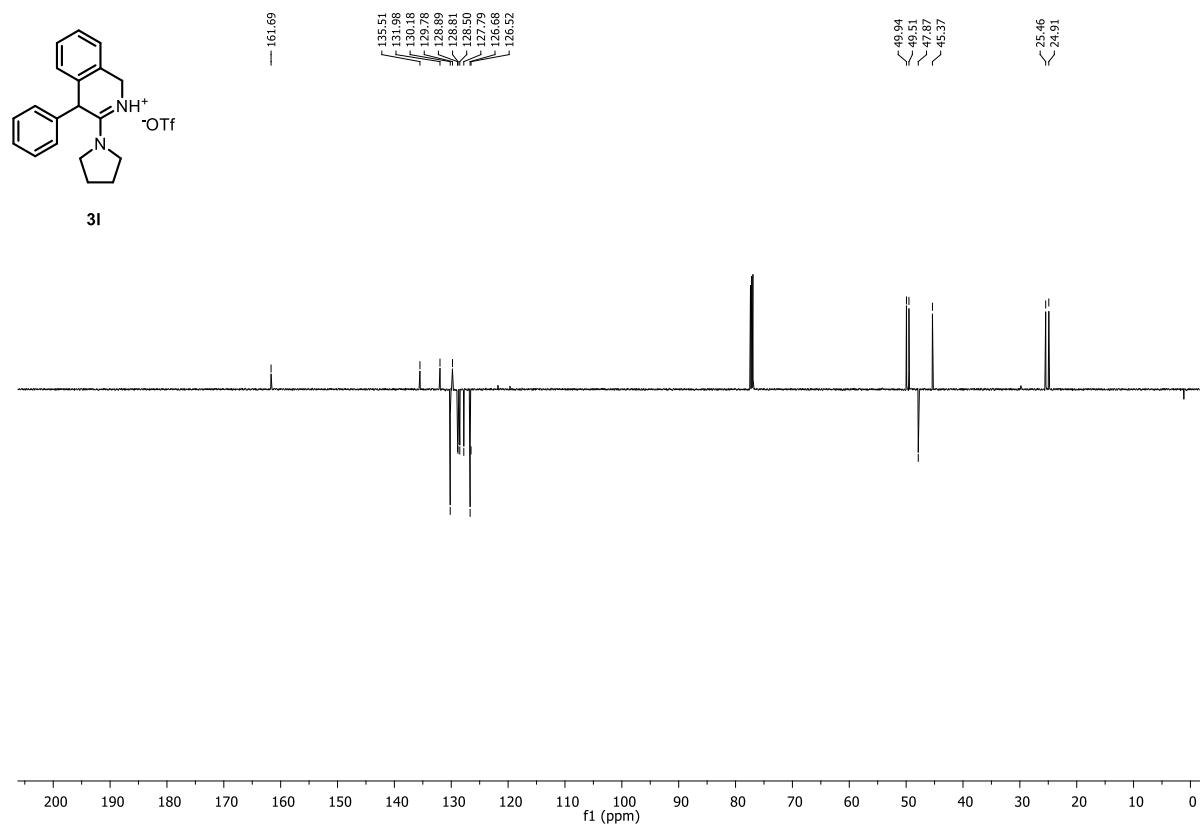
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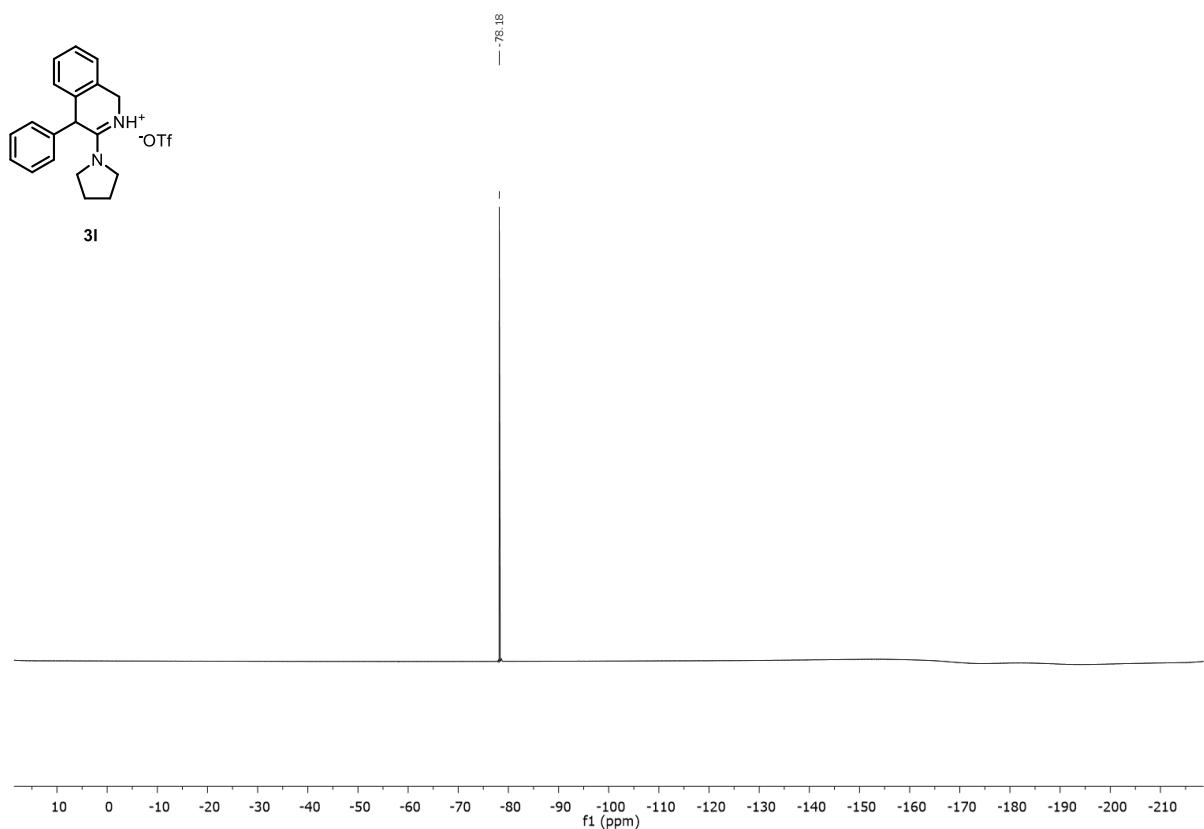
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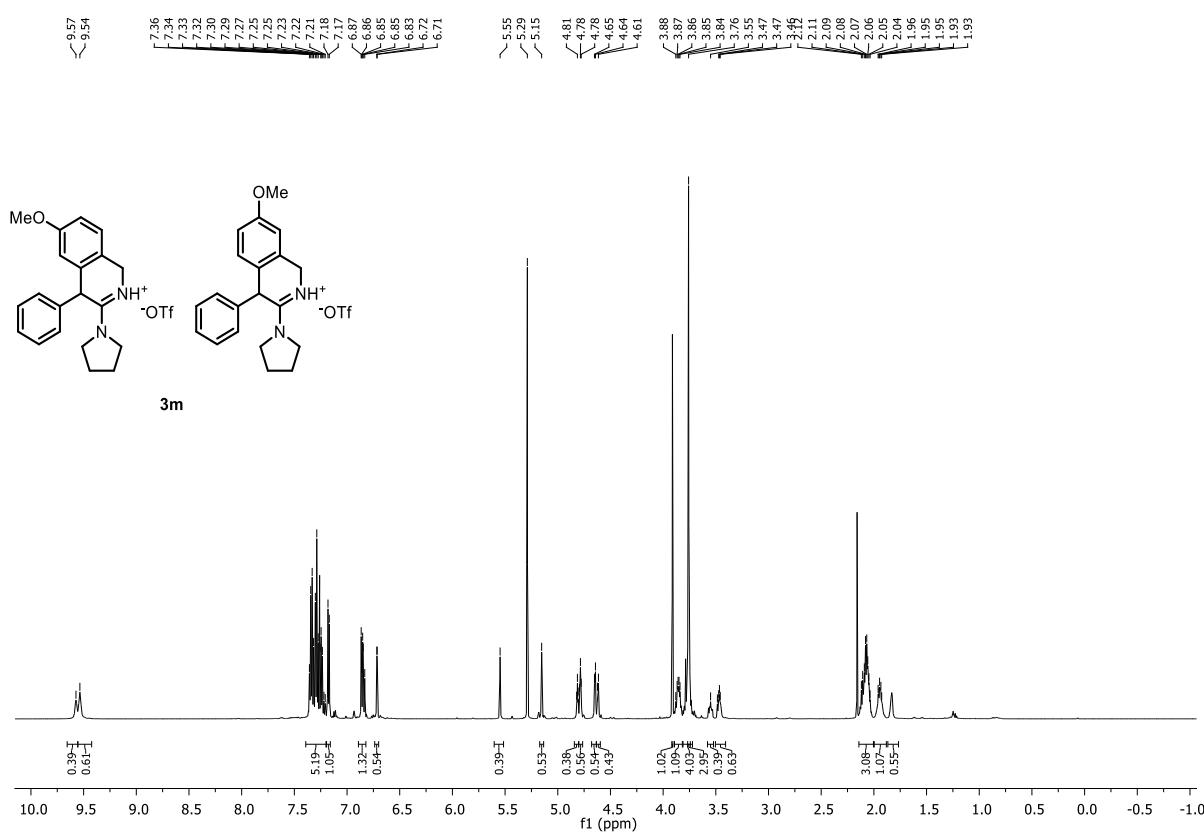
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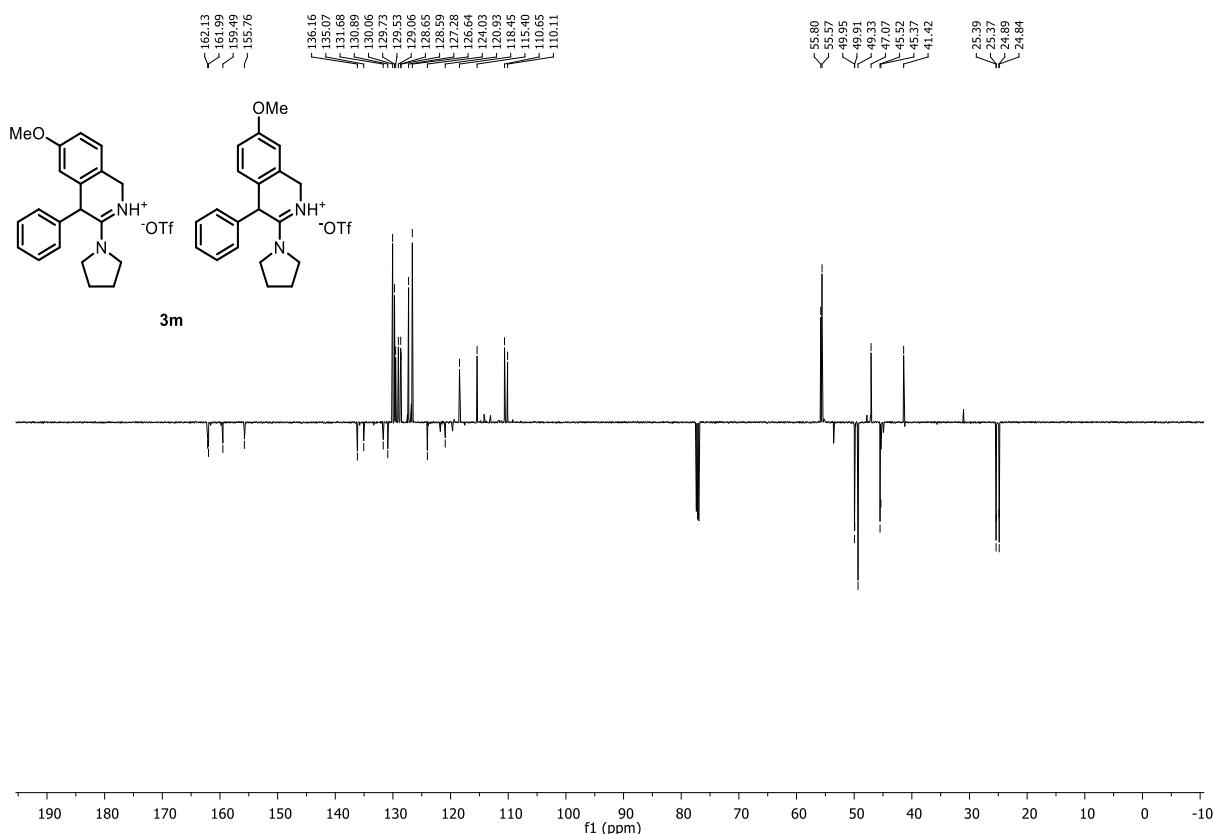
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¹H NMR (600 MHz, CDCl₃)



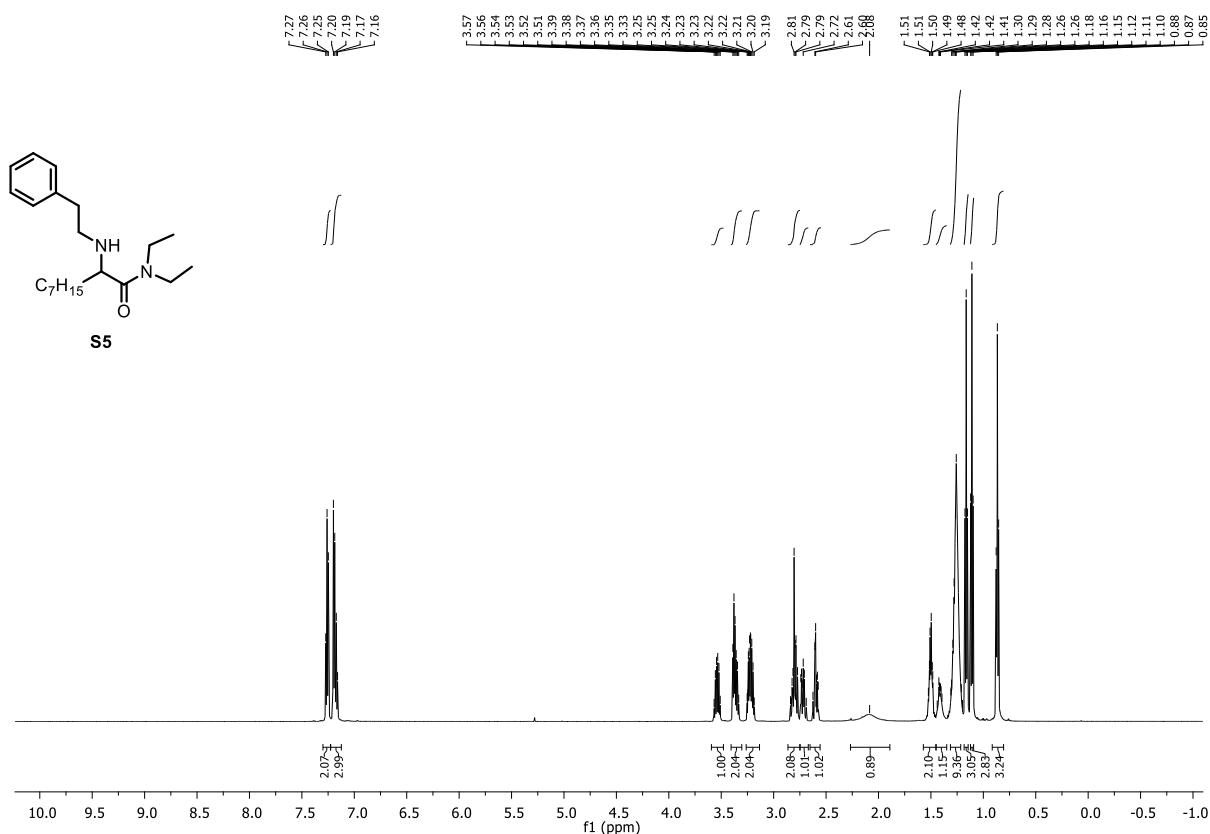
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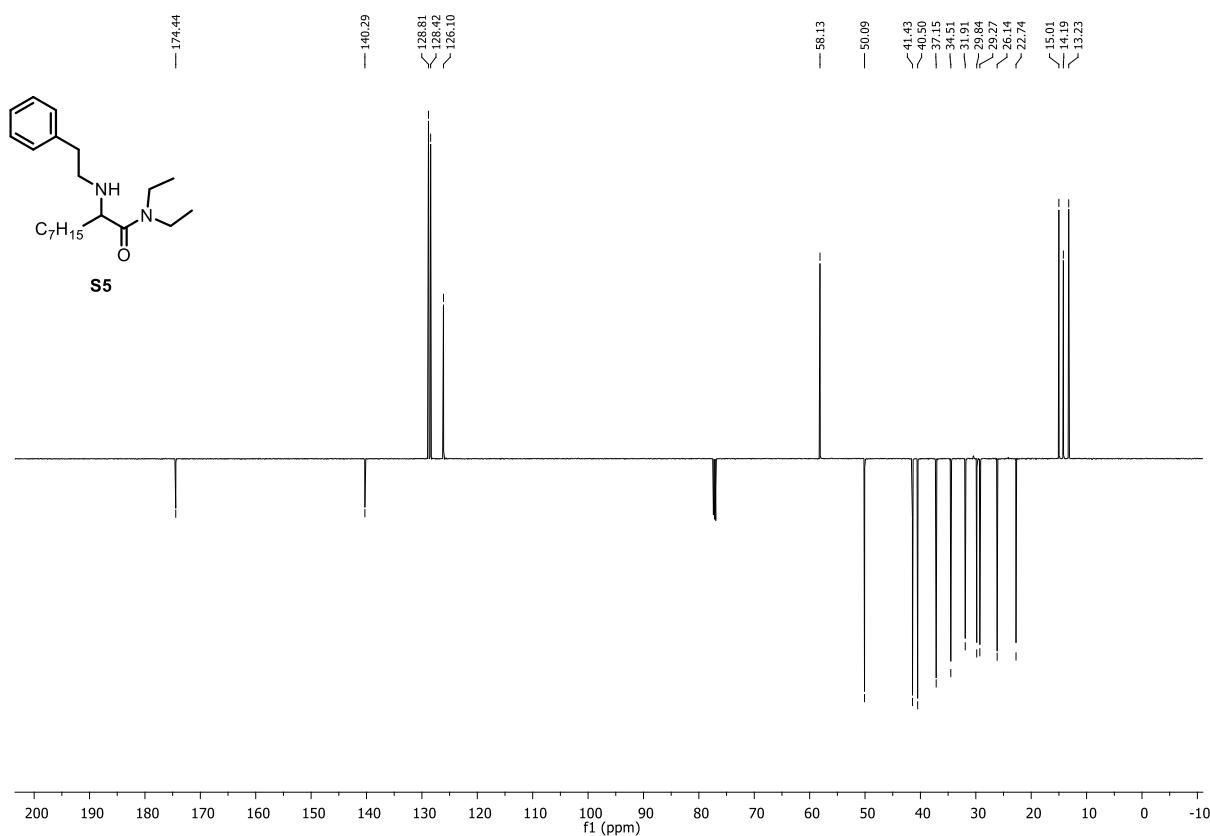
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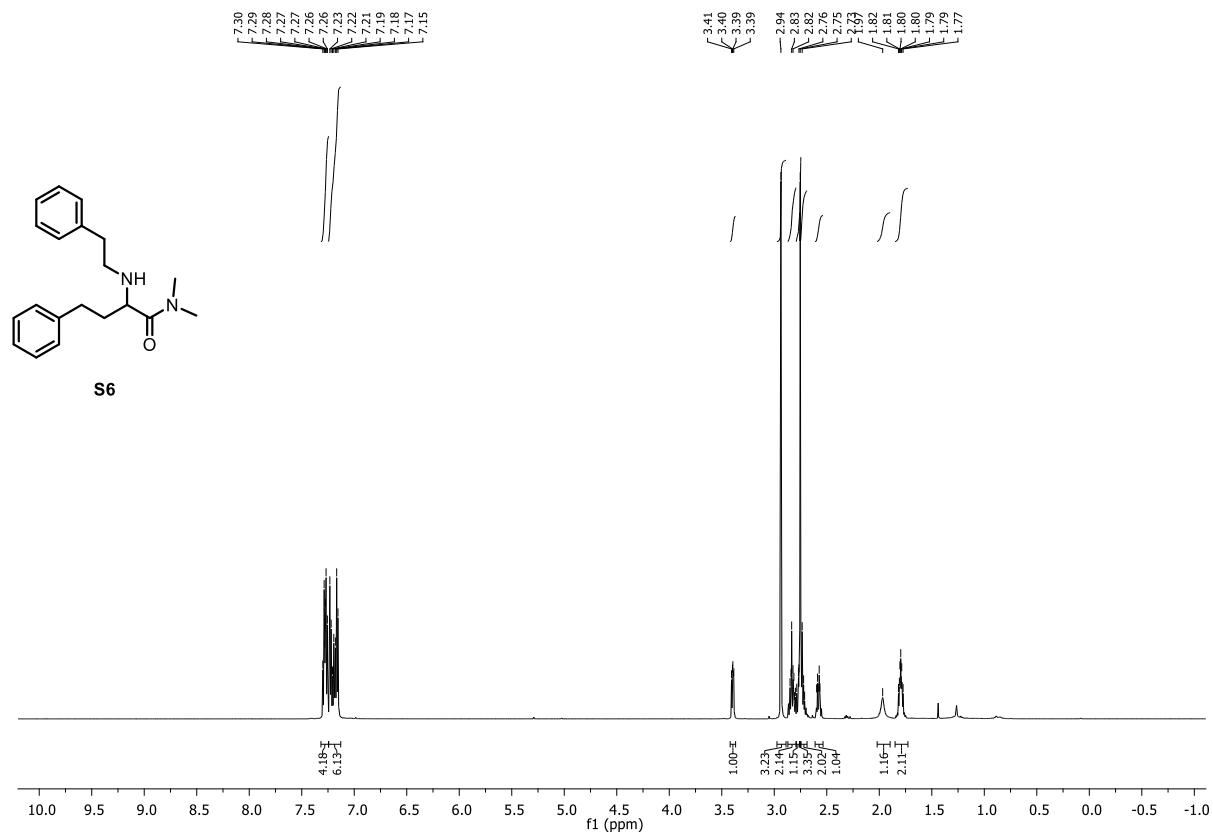
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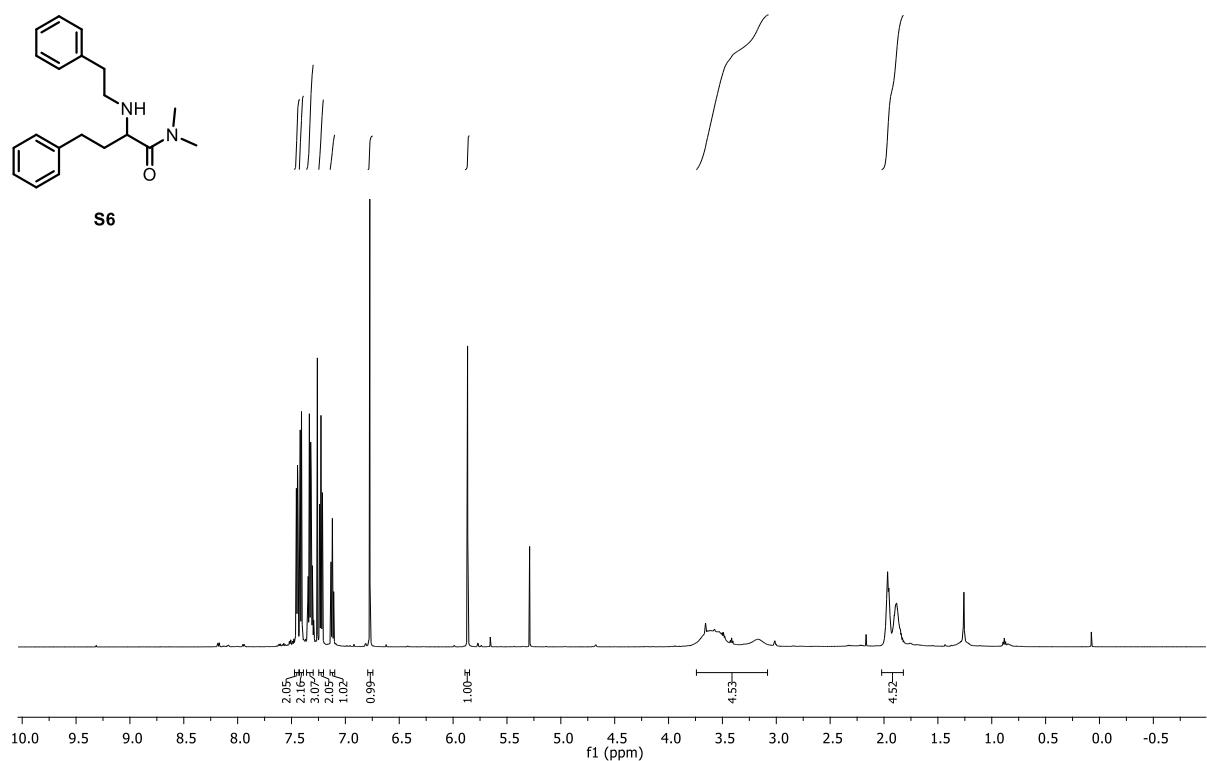
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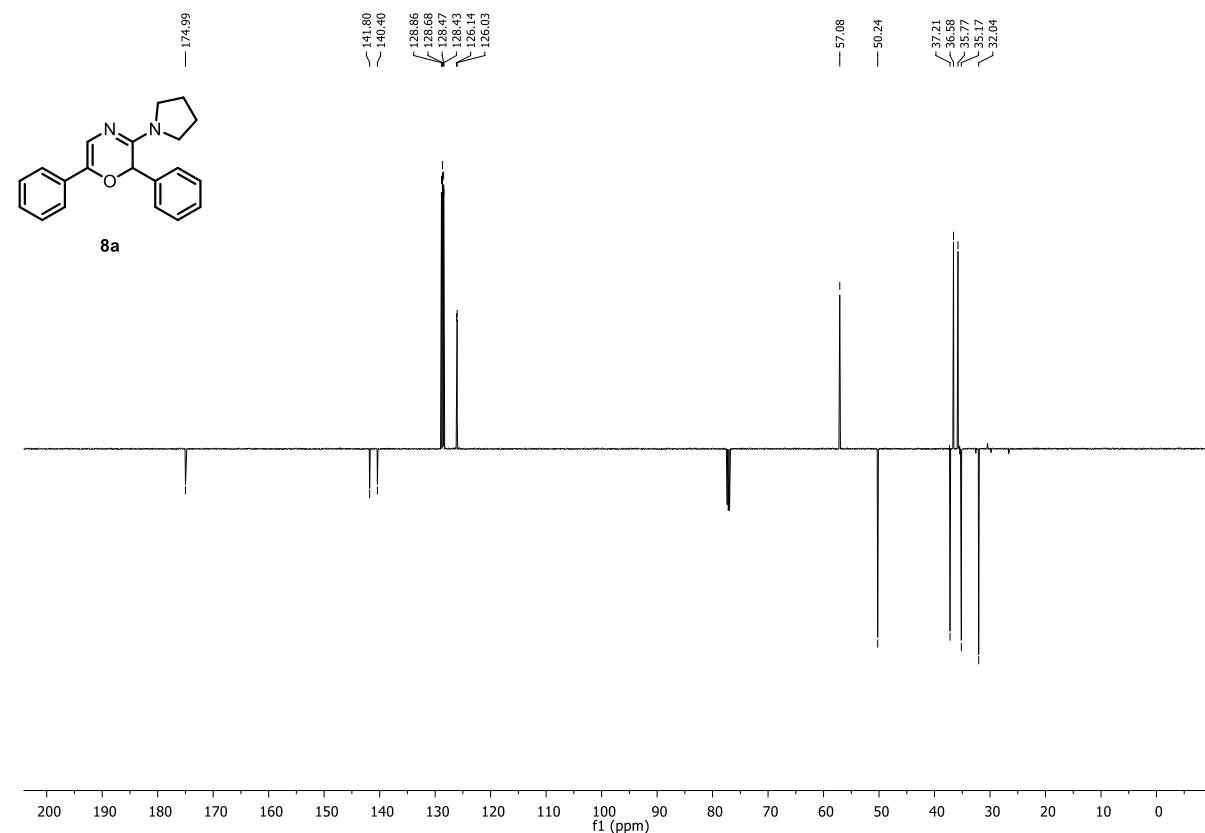
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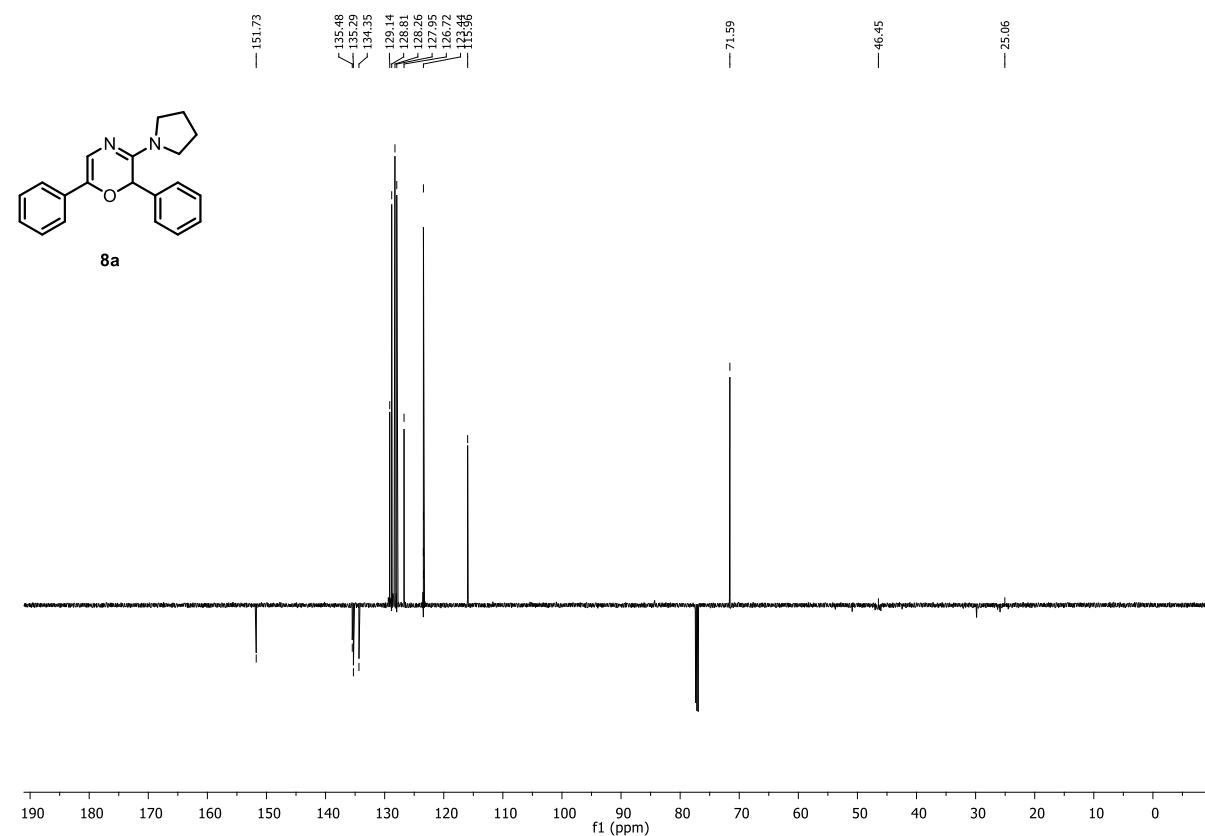
¹³C NMR (151 MHz, CDCl₃)



¹H NMR (600 MHz, CDCl₃)

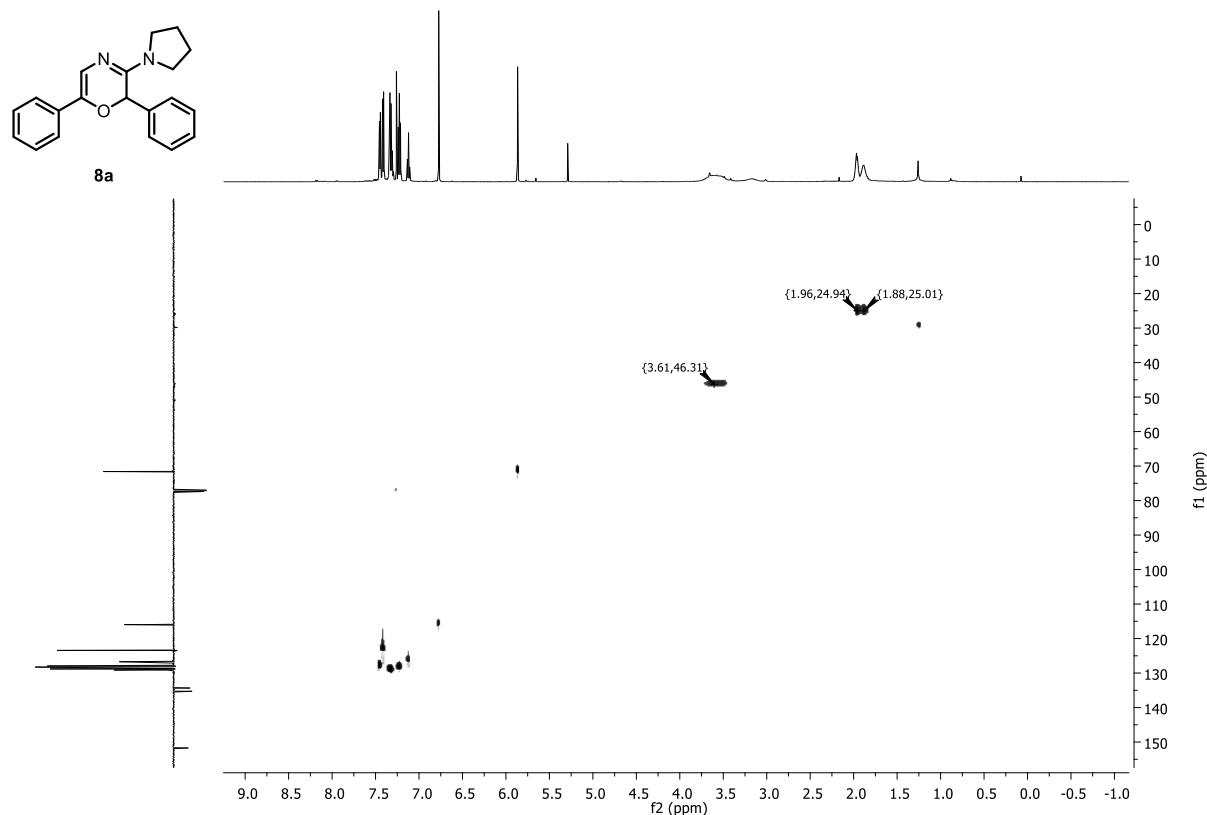


¹³C NMR (151 MHz, CDCl₃)

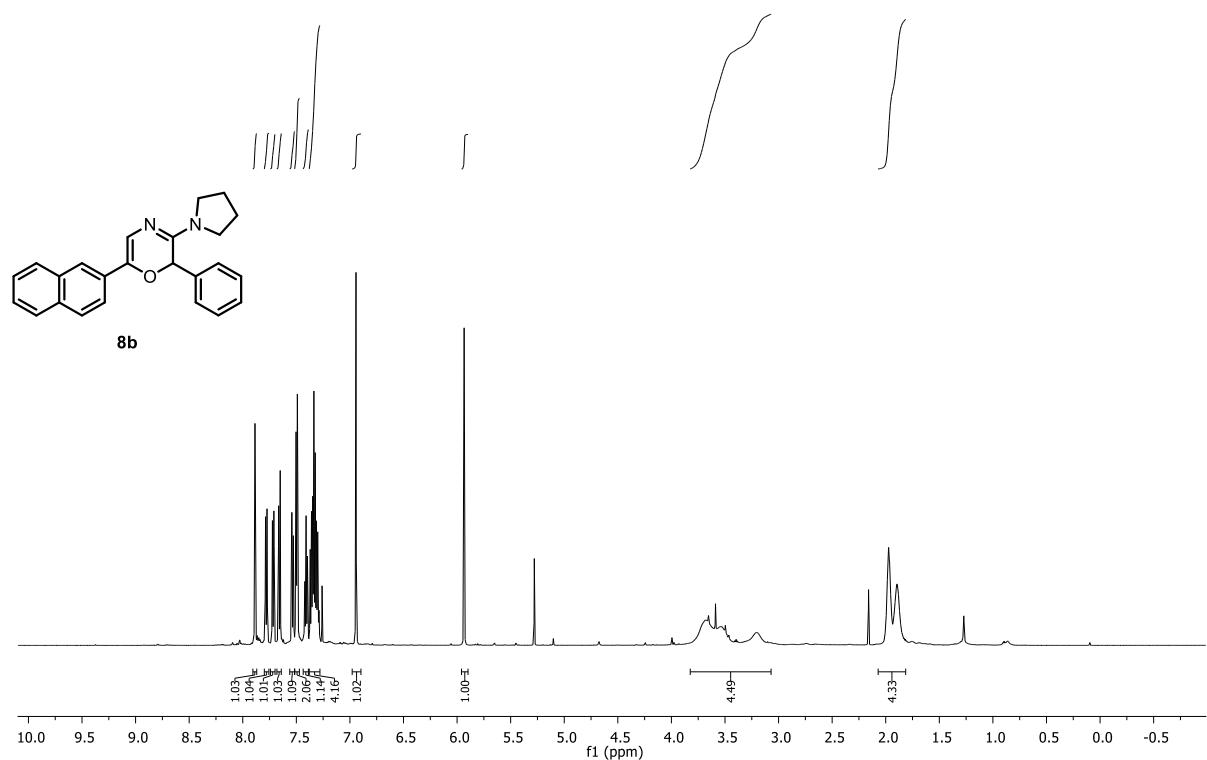


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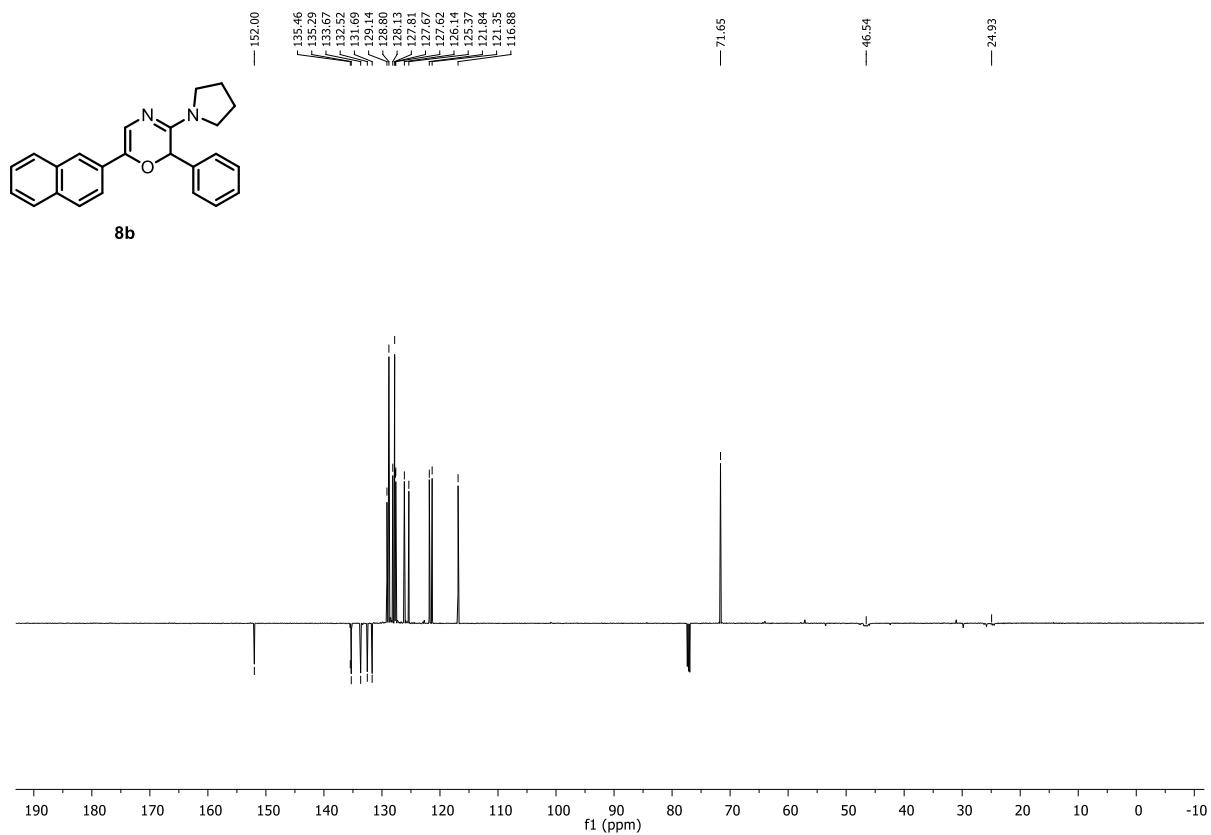
¹H NMR (600 MHz, CDCl₃), ¹³C NMR (151 MHz, CDCl₃)



¹H NMR (600 MHz, CDCl₃)

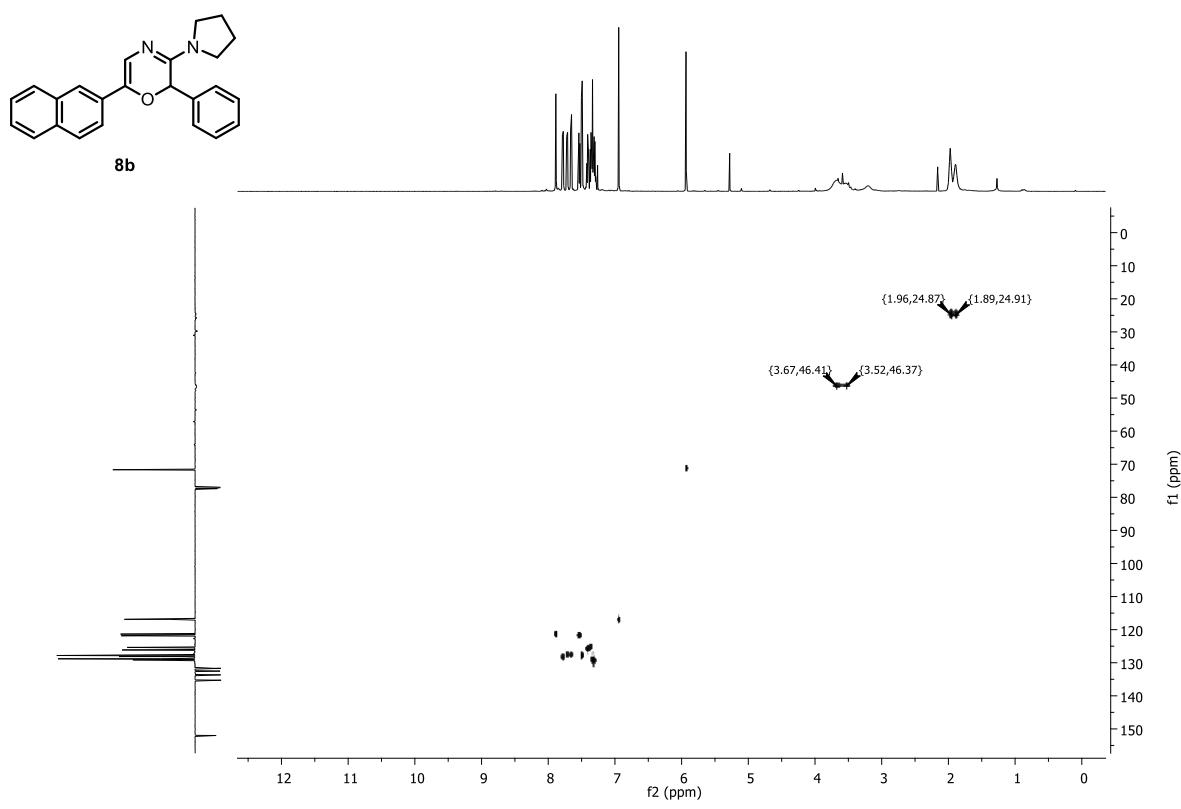


¹³C NMR (151 MHz, CDCl₃)

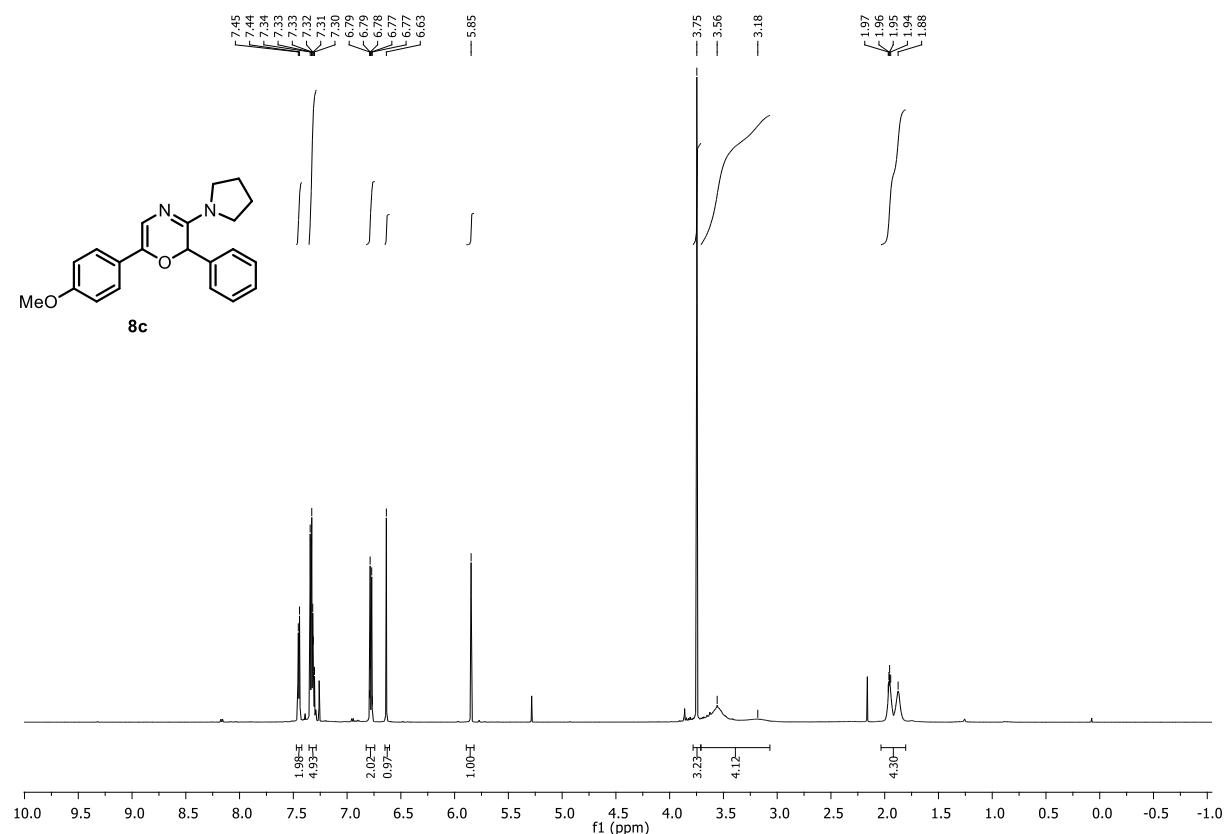


HSQC

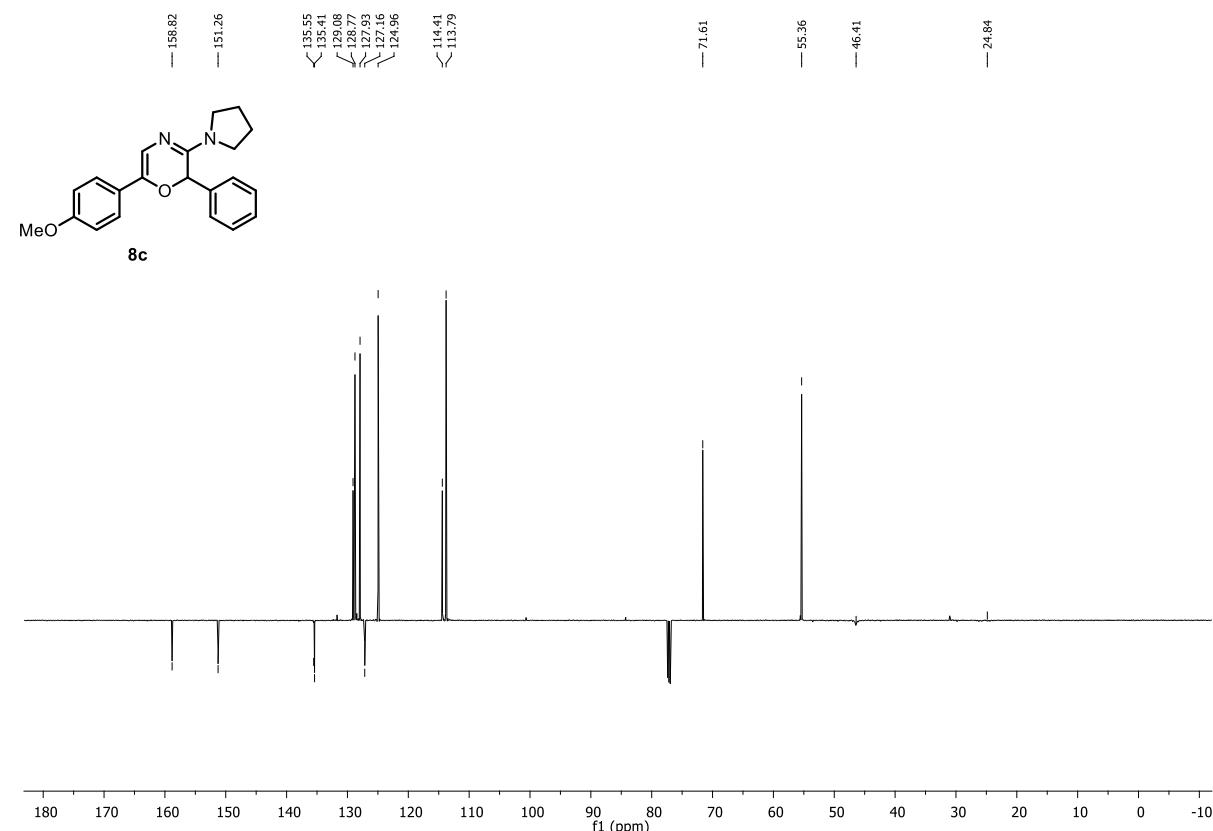
¹H NMR (600 MHz, CDCl₃), ¹³C NMR (151 MHz, CDCl₃)



¹H NMR (600 MHz, CDCl₃)

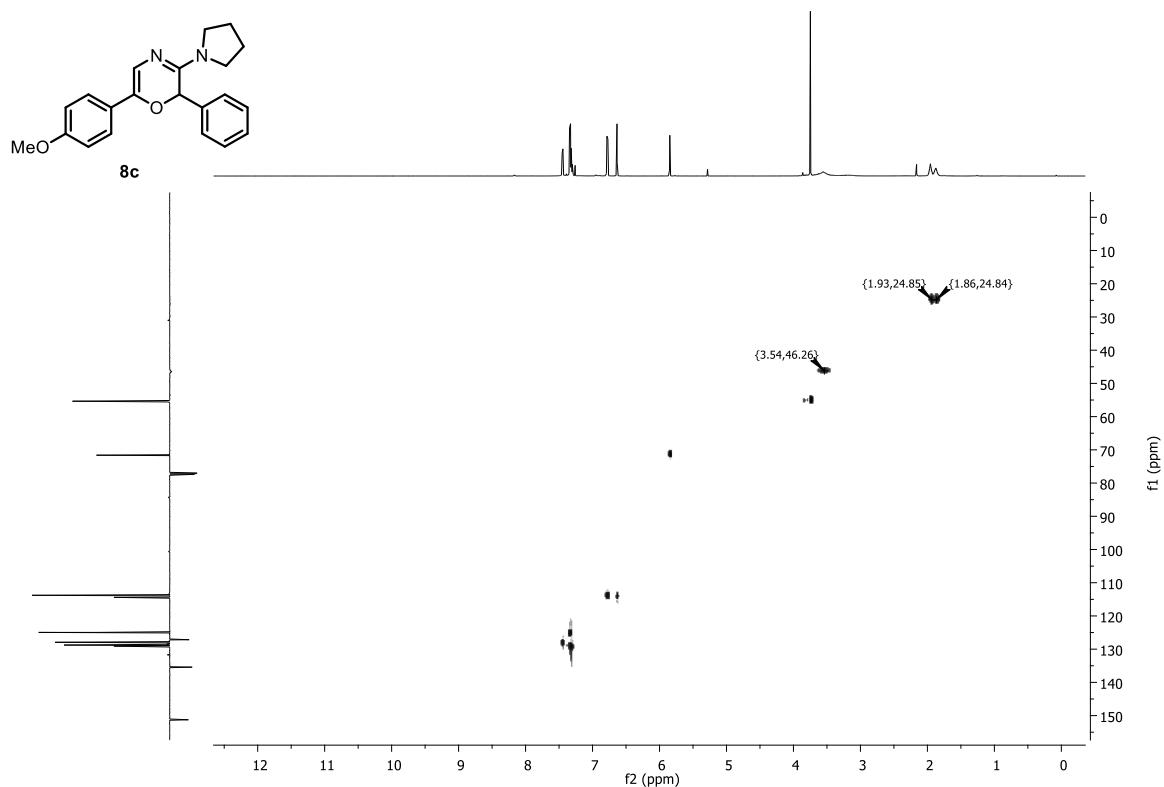


¹³C NMR (151 MHz, CDCl₃)

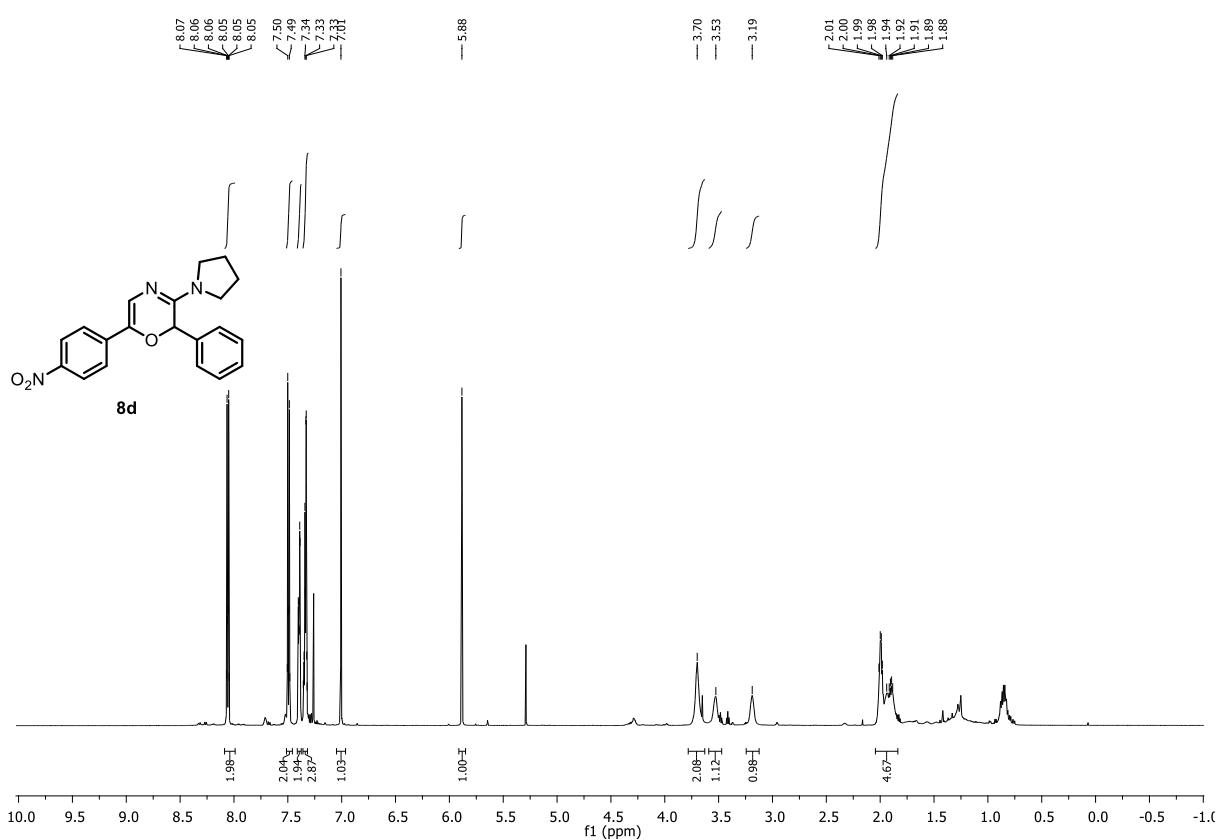


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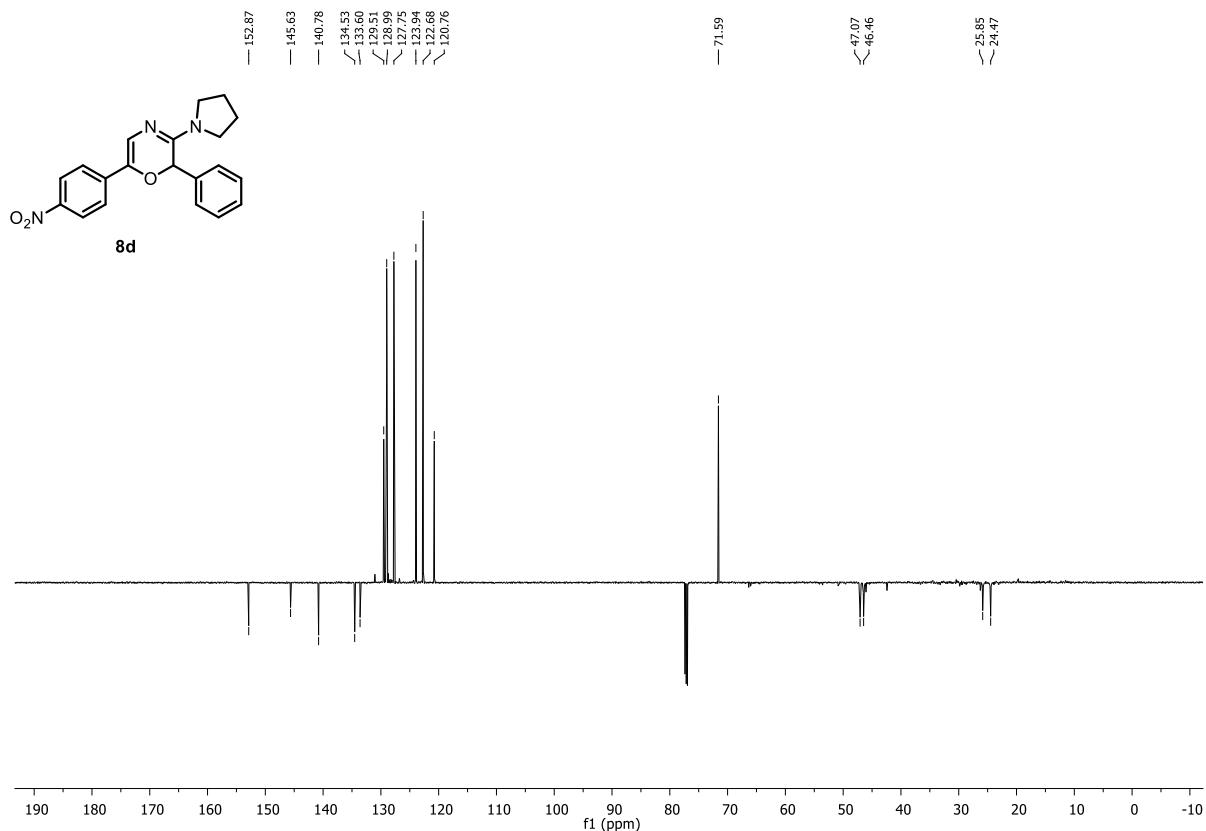
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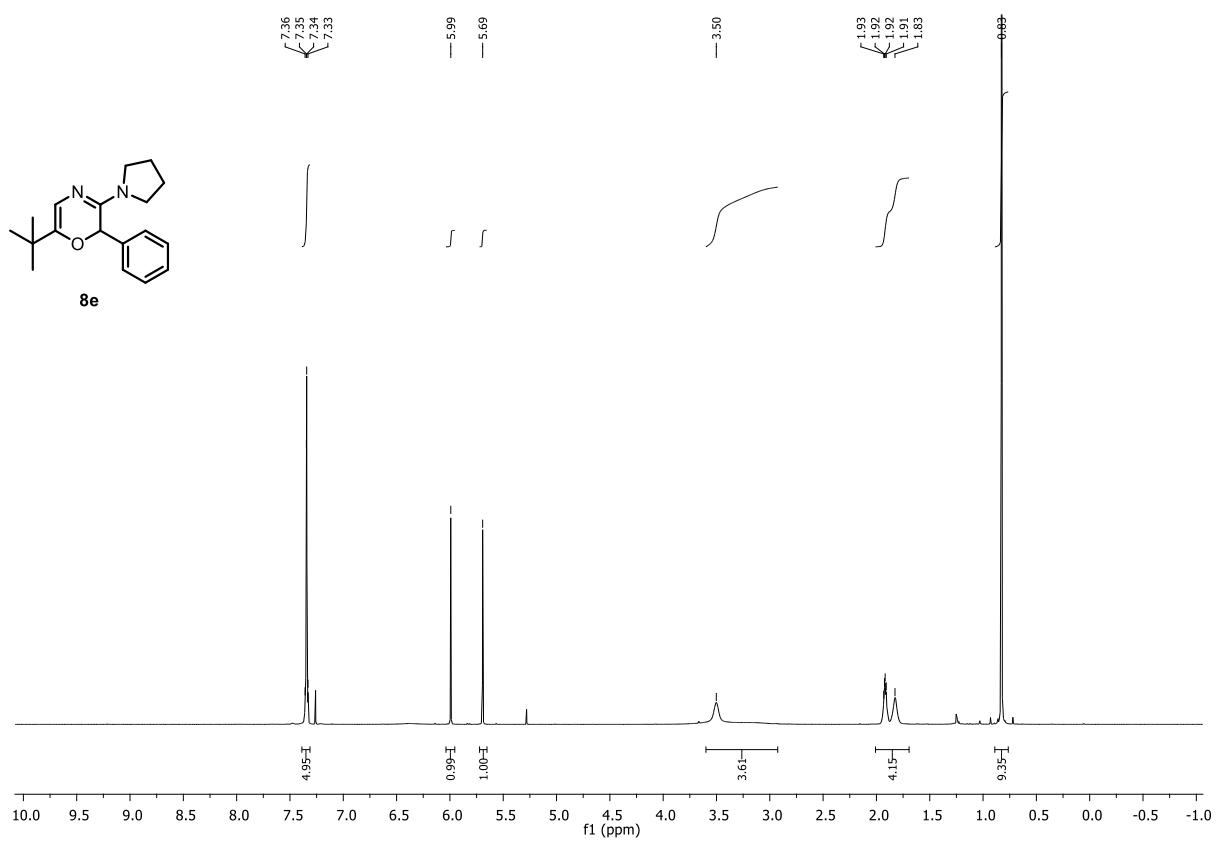
¹H NMR (600 MHz, CDCl₃)



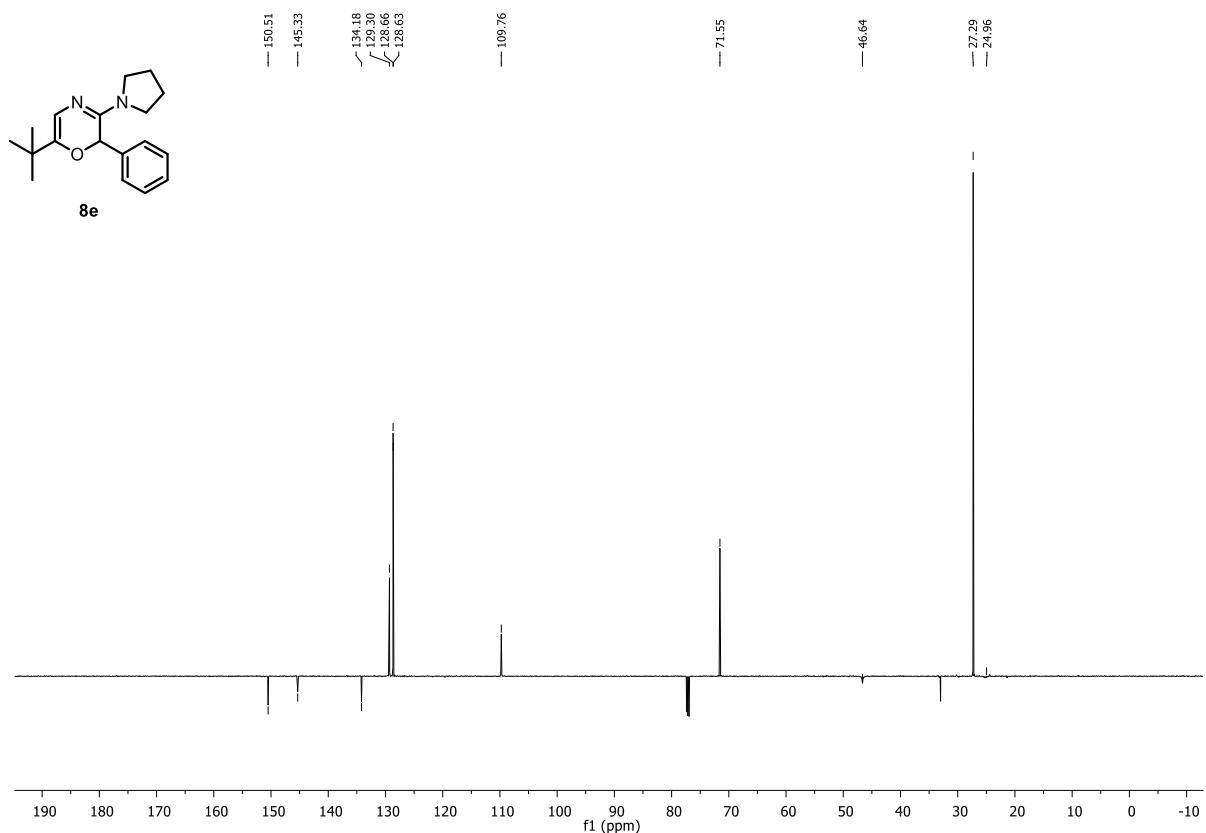
¹³C NMR (151 MHz, CDCl₃)



¹H NMR (600 MHz, CDCl₃)

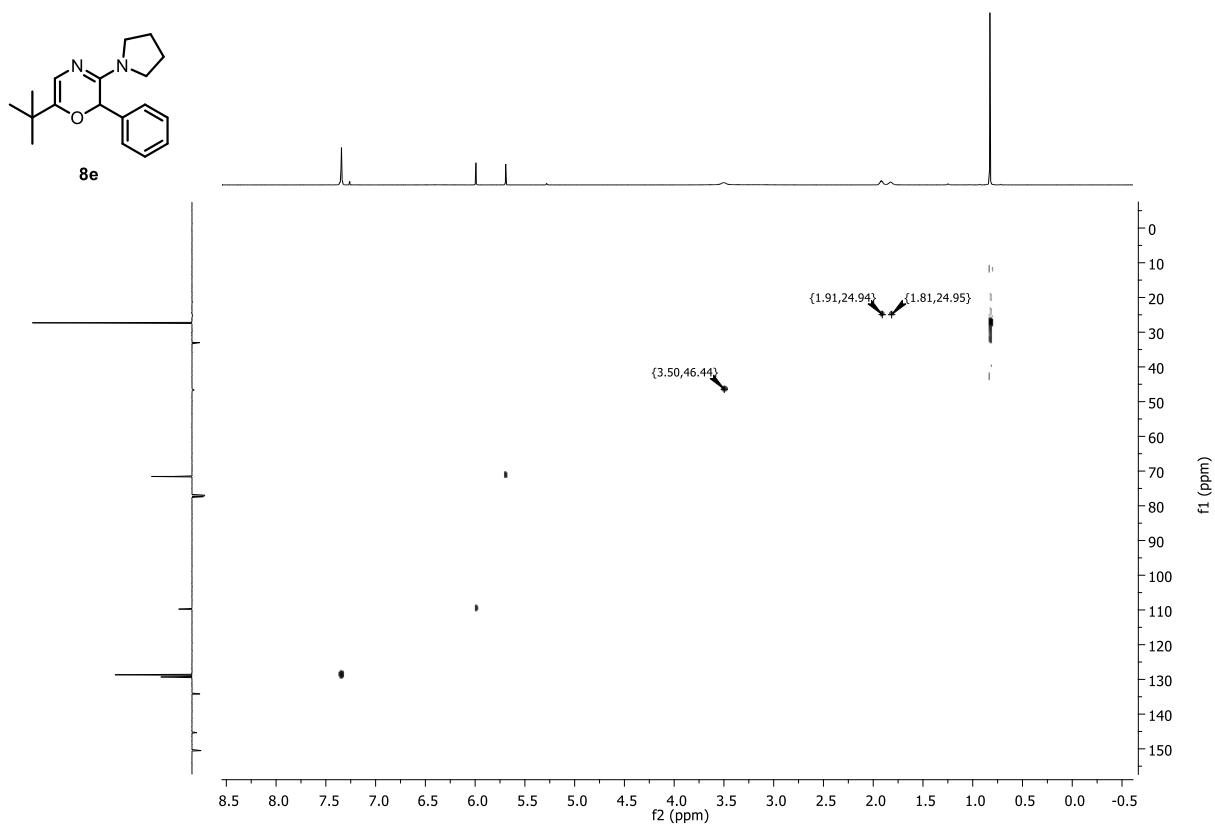


^{13}C NMR (151 MHz, CDCl_3)

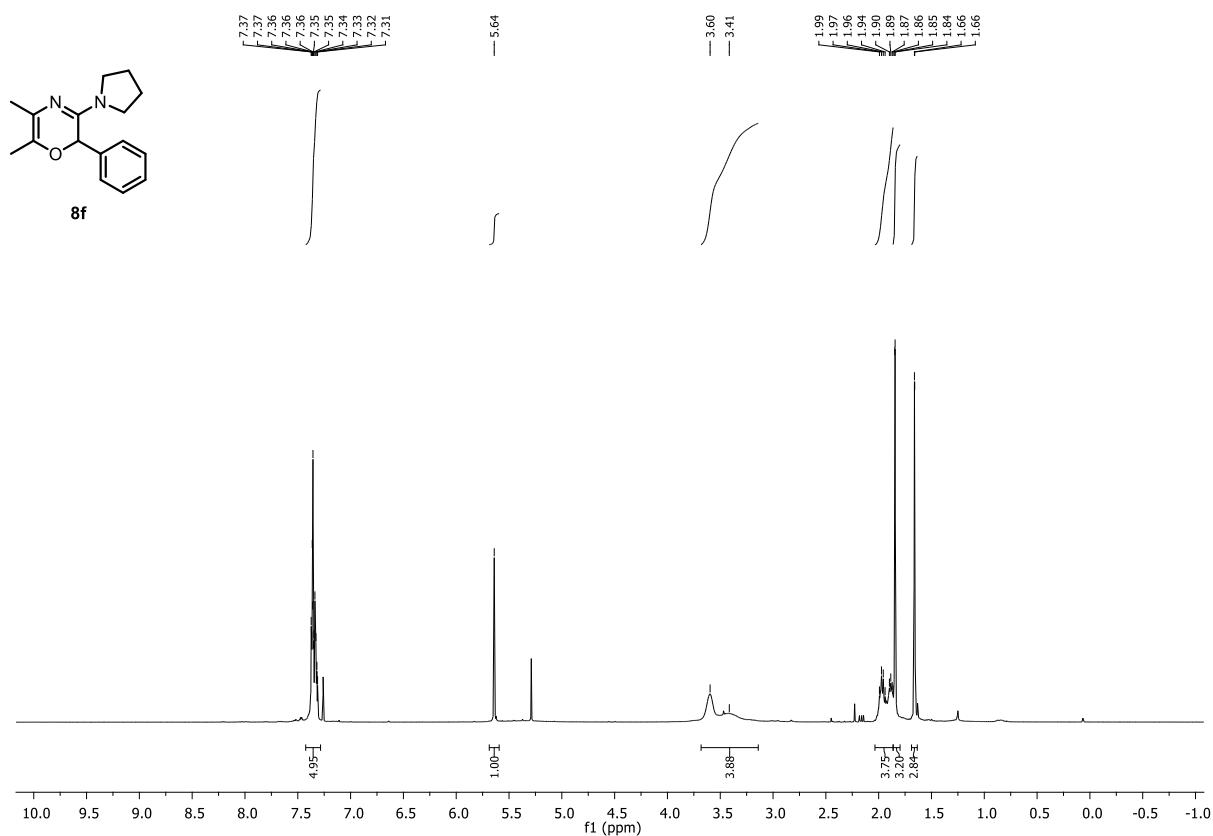


HSQC

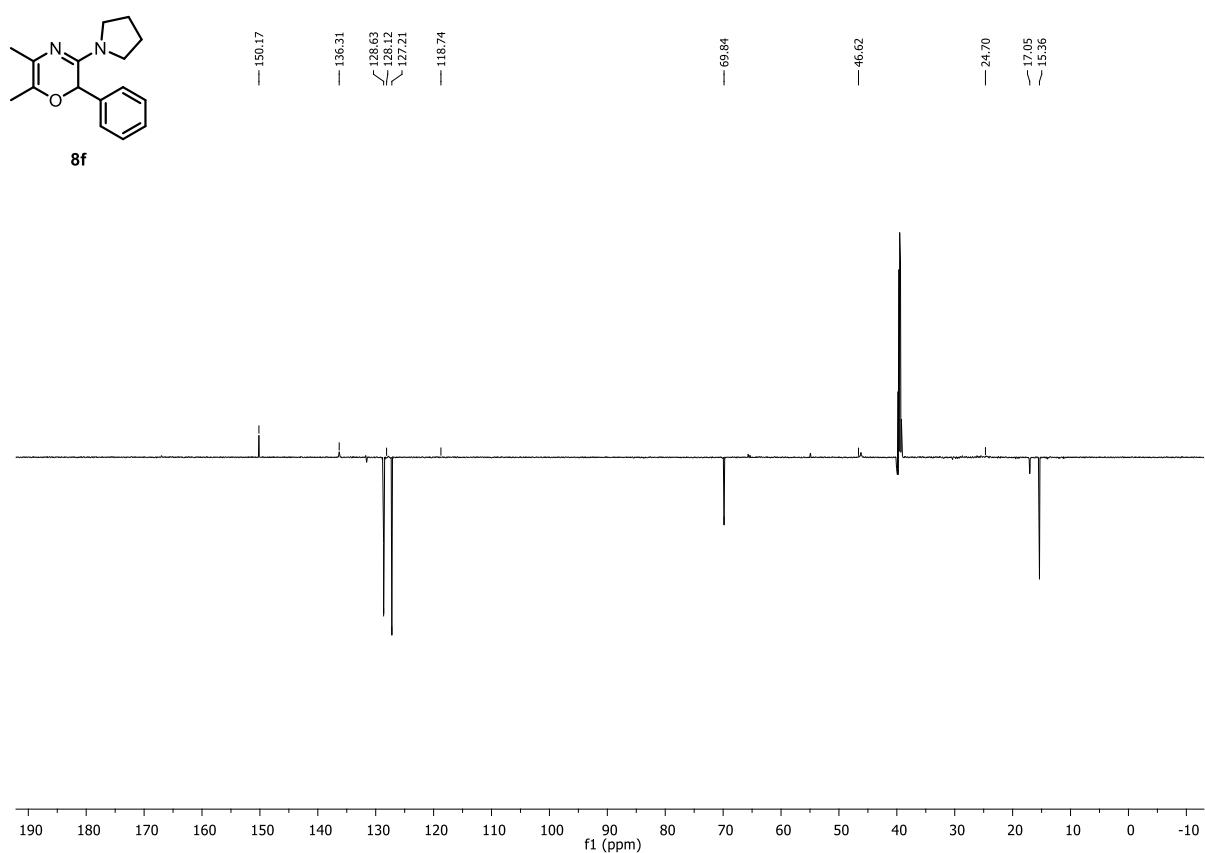
^1H NMR (600 MHz, CDCl_3), ^{13}C NMR (151 MHz, CDCl_3)



¹H NMR (400 MHz, CDCl₃)

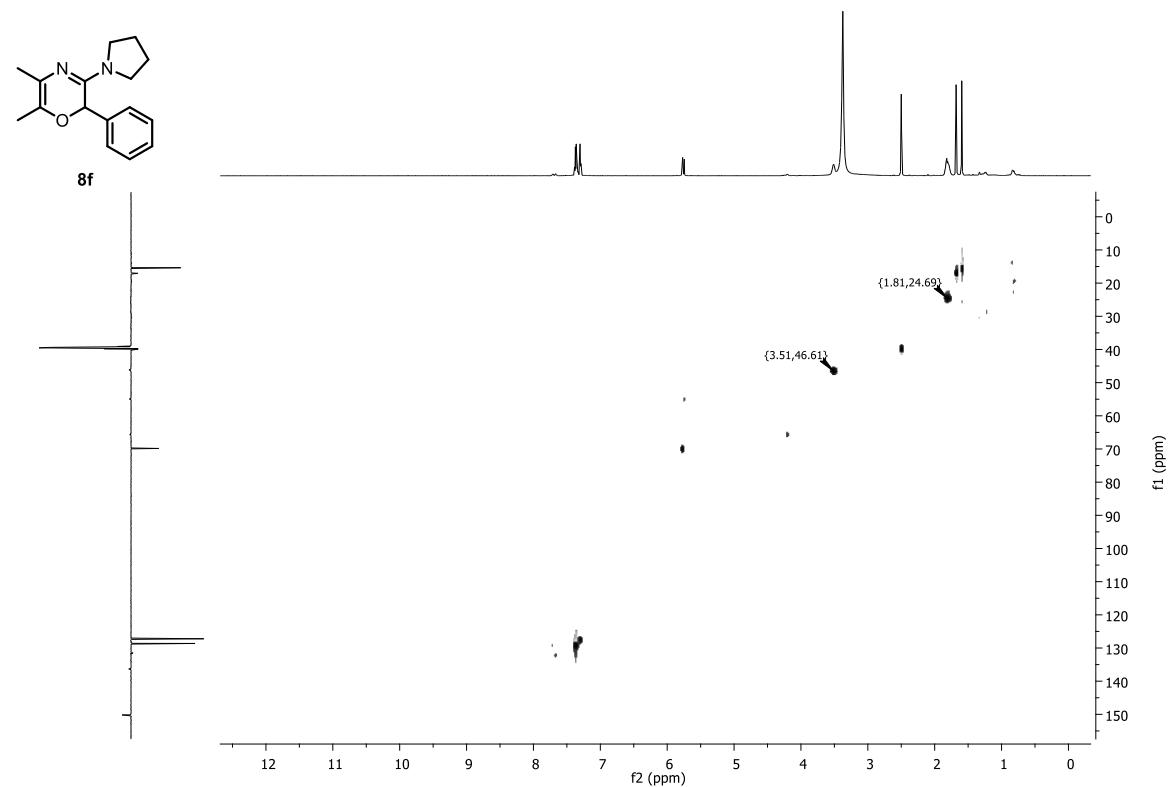


¹³C NMR (151 MHz, DMSO)



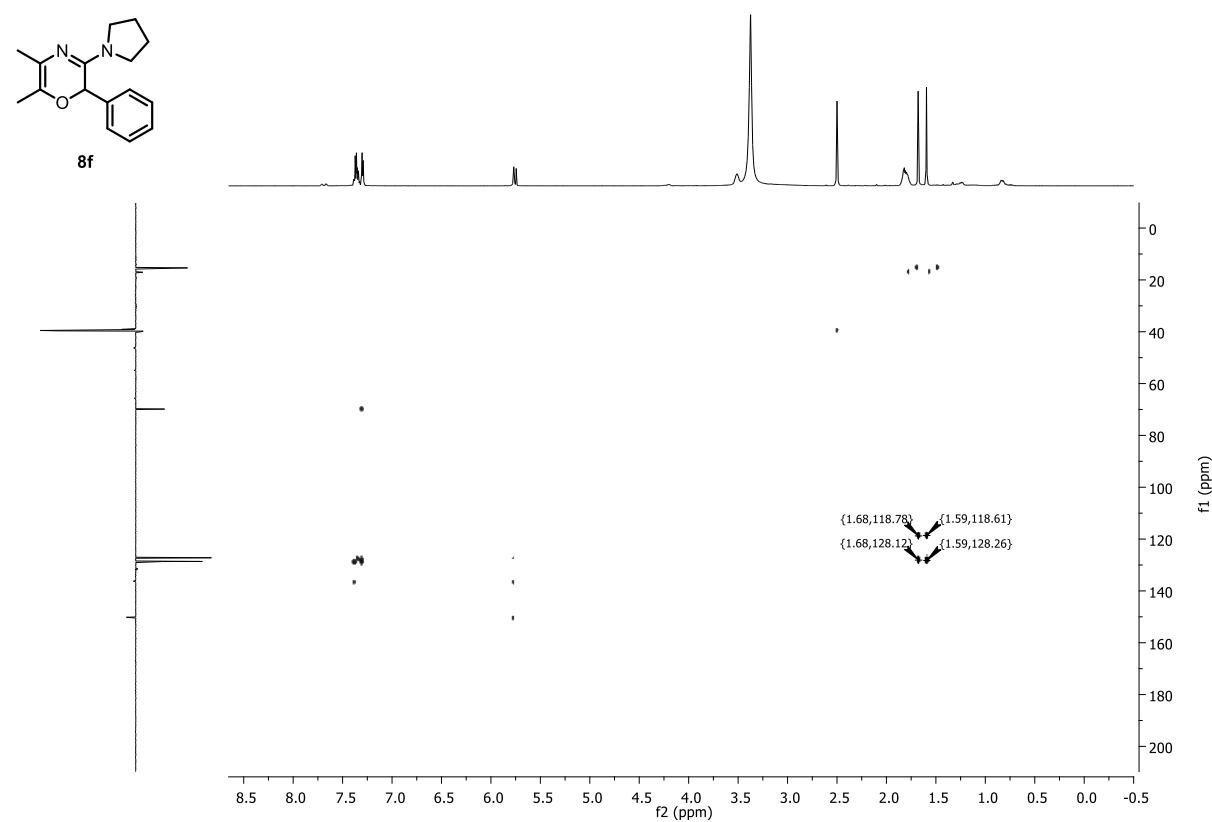
HSQC

¹H NMR (600 MHz, CDCl₃), ¹³C NMR (151 MHz, DMSO)

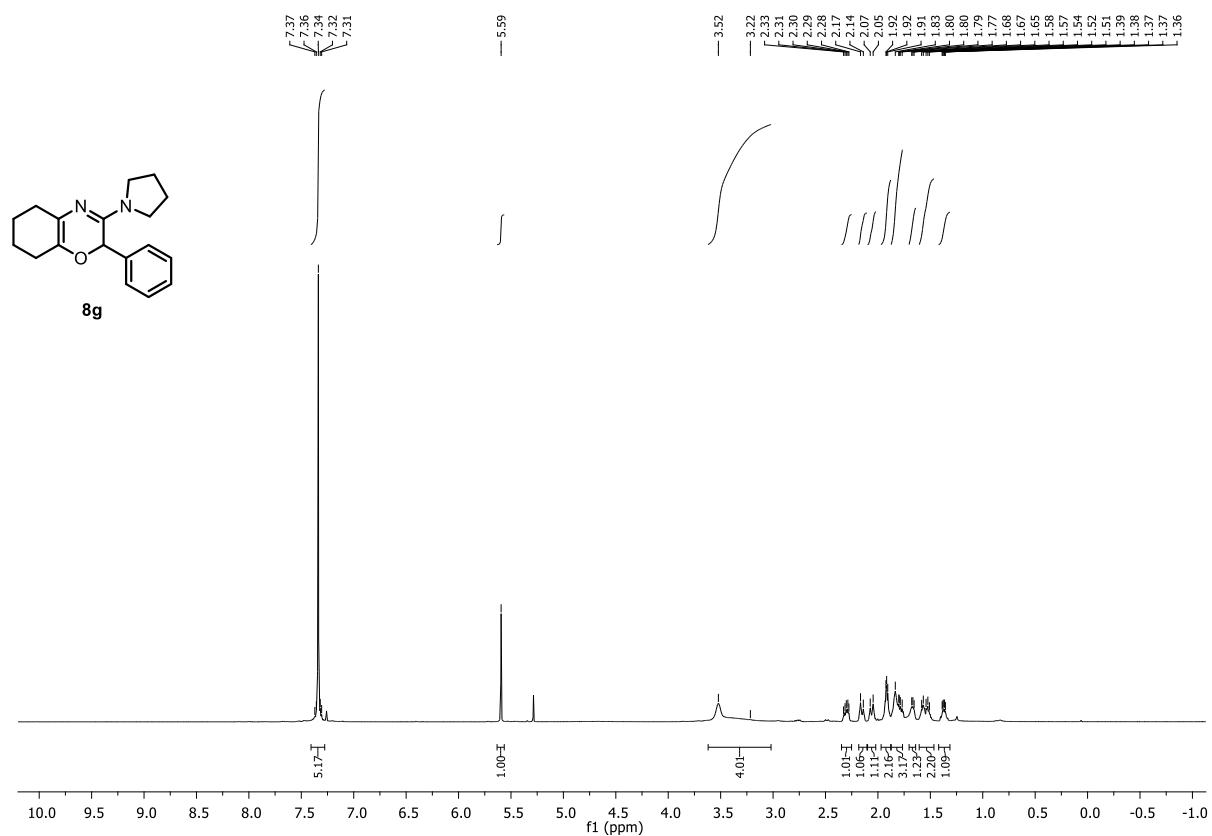


HMBC

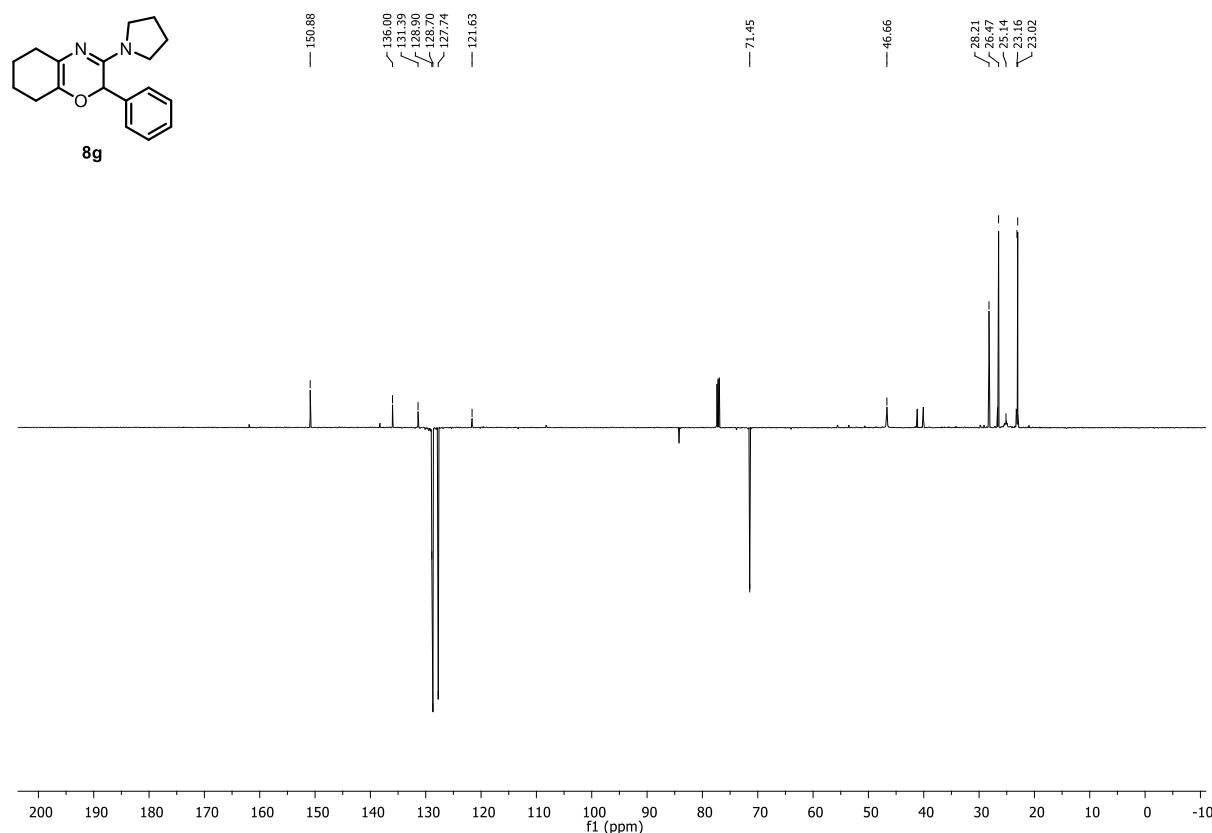
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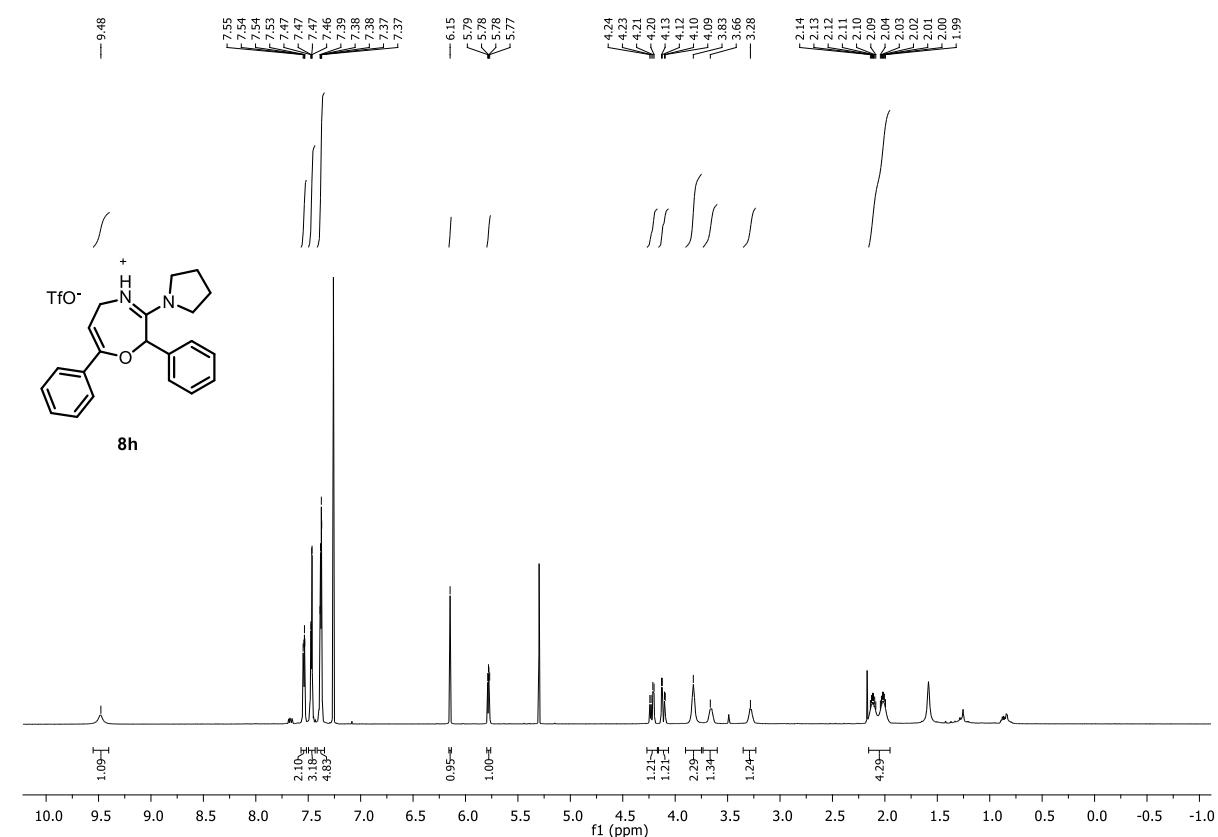
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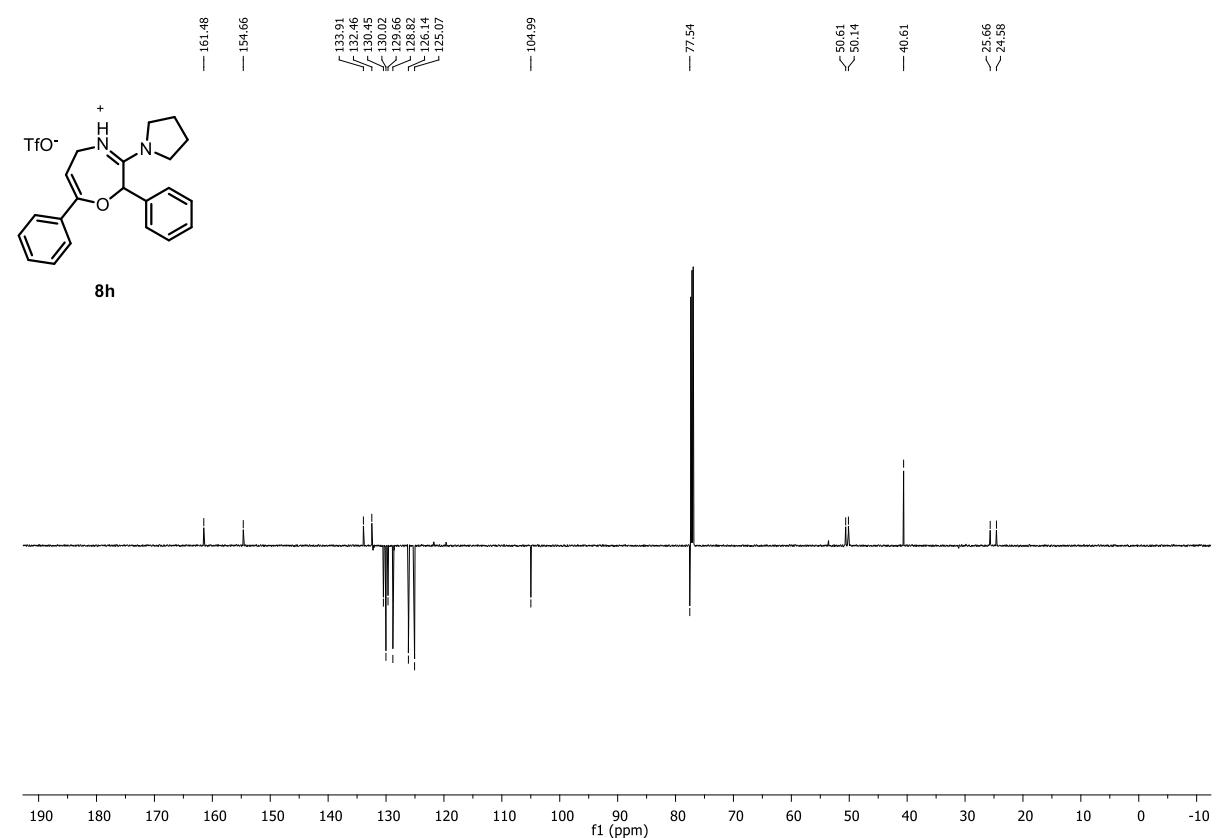
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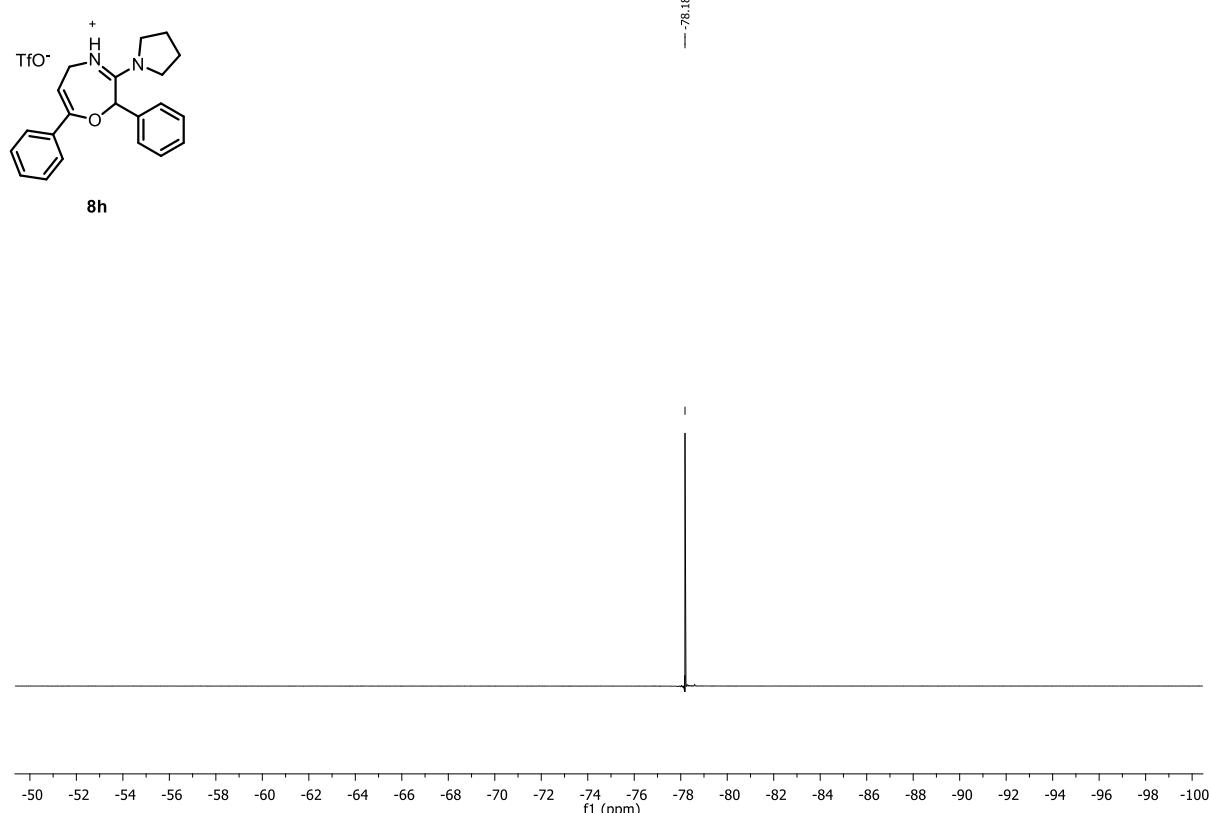
¹H NMR (600 MHz, CDCl₃)



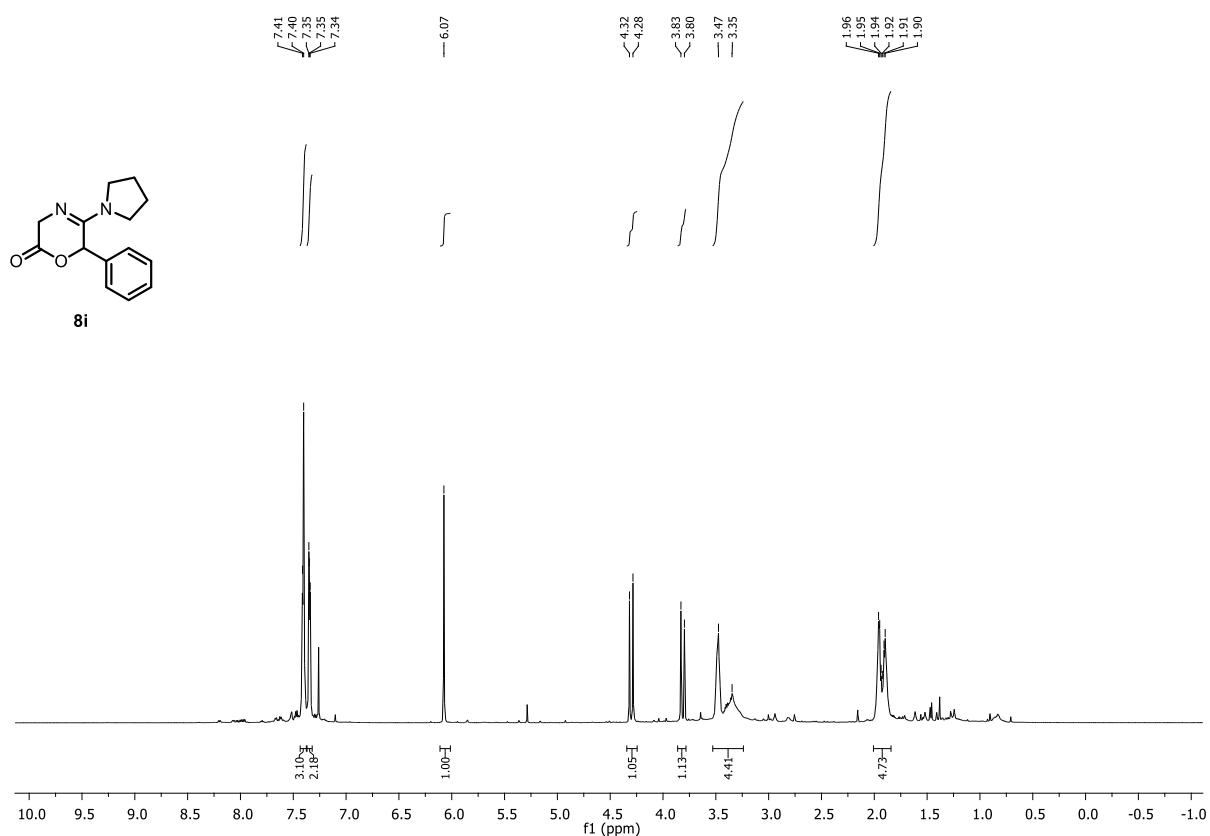
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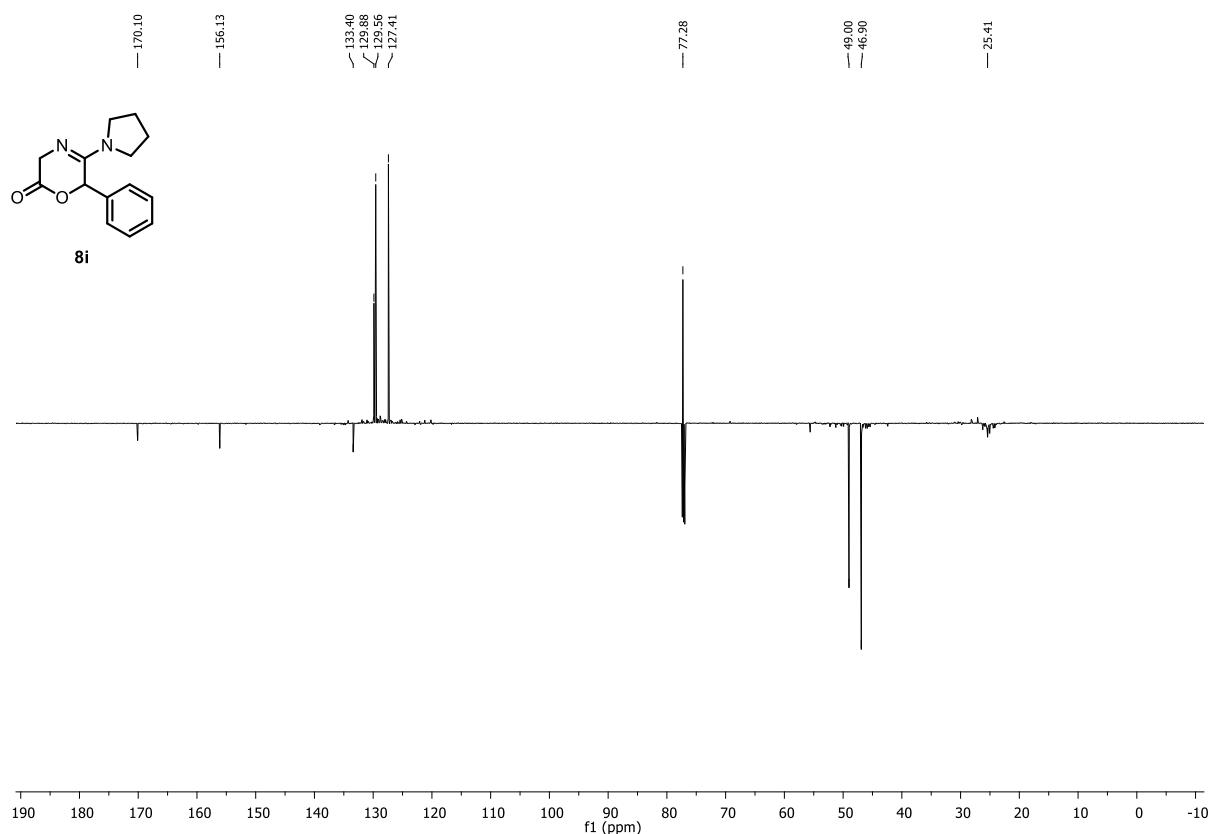
¹⁹F NMR (565 MHz, CDCl₃)



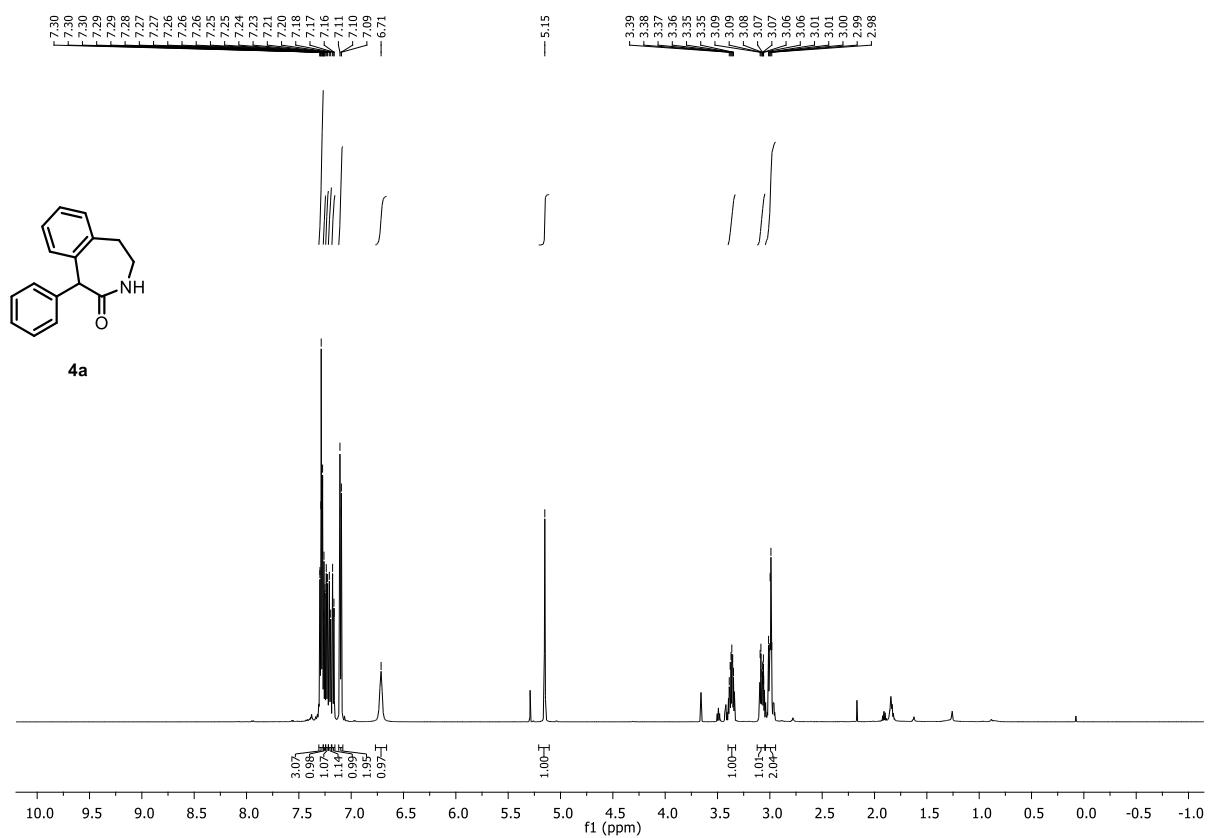
¹H NMR (600 MHz, CDCl₃)



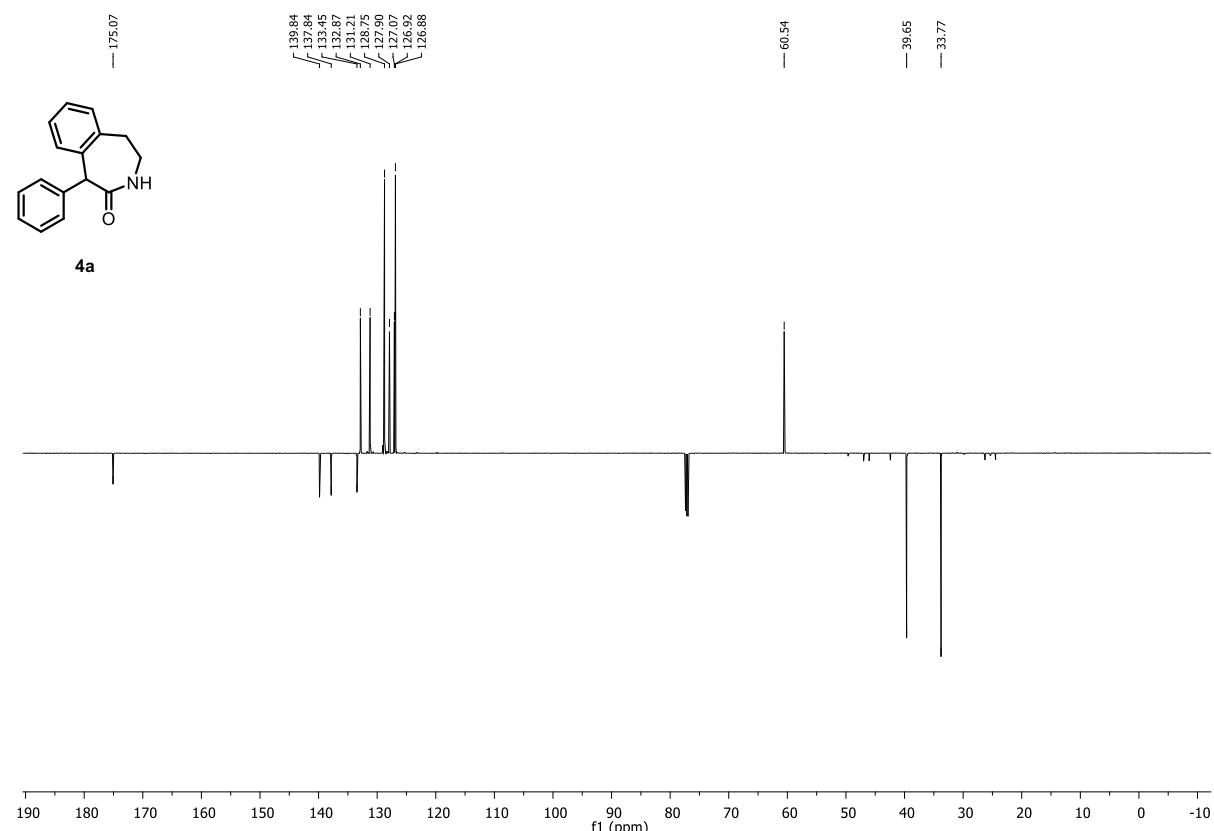
¹³C NMR (151 MHz, CDCl₃)



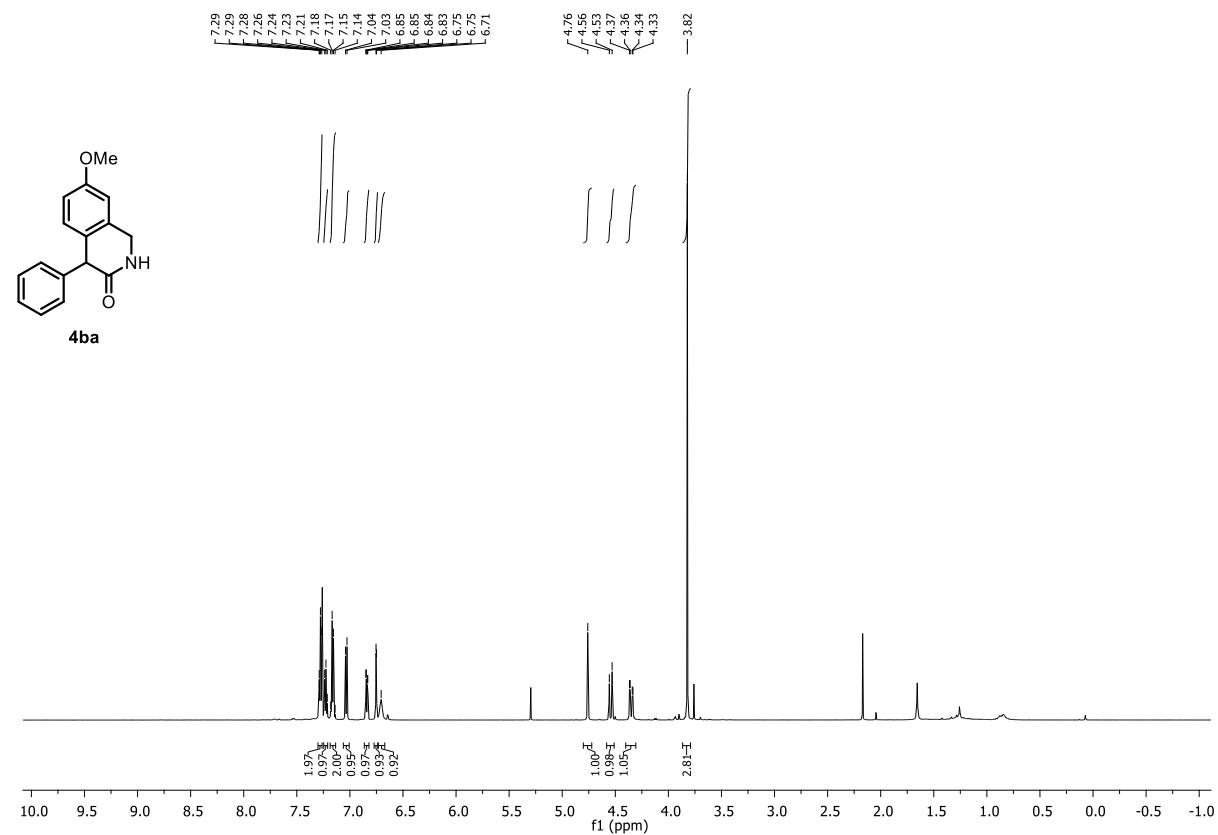
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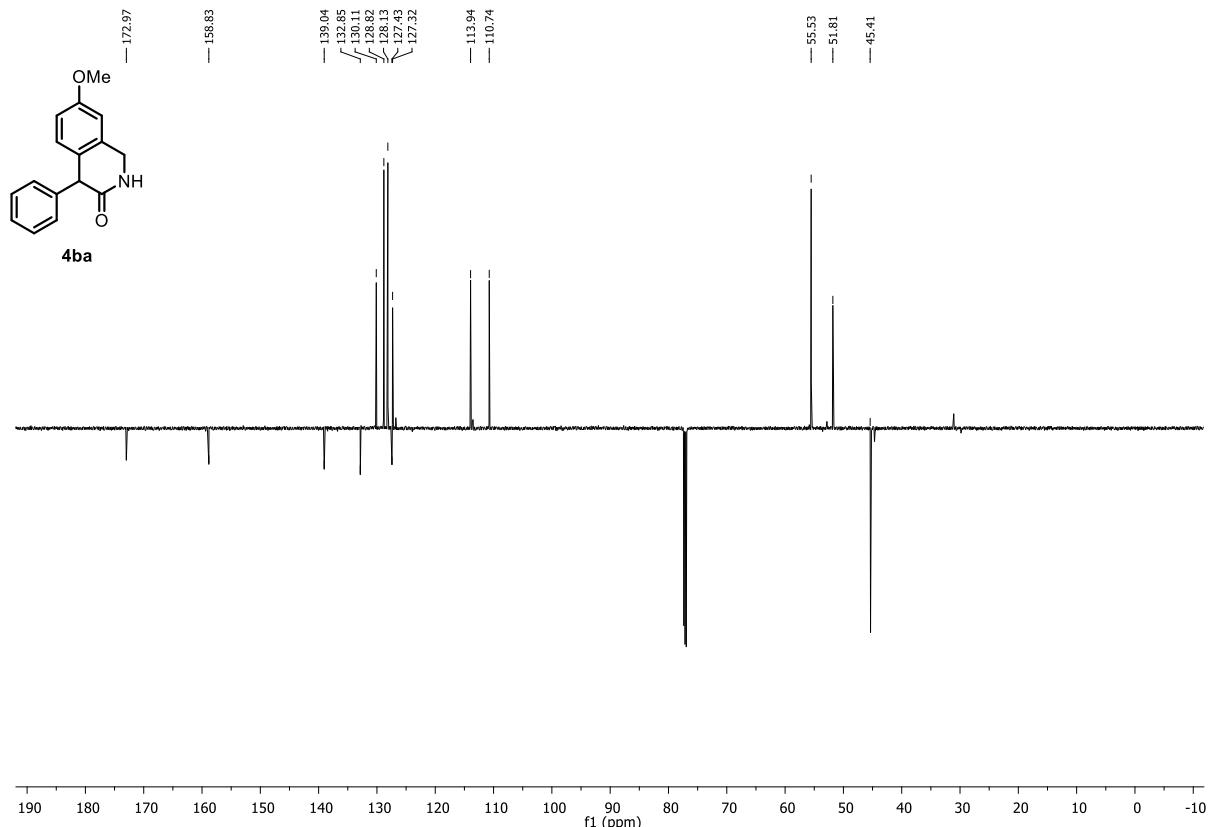
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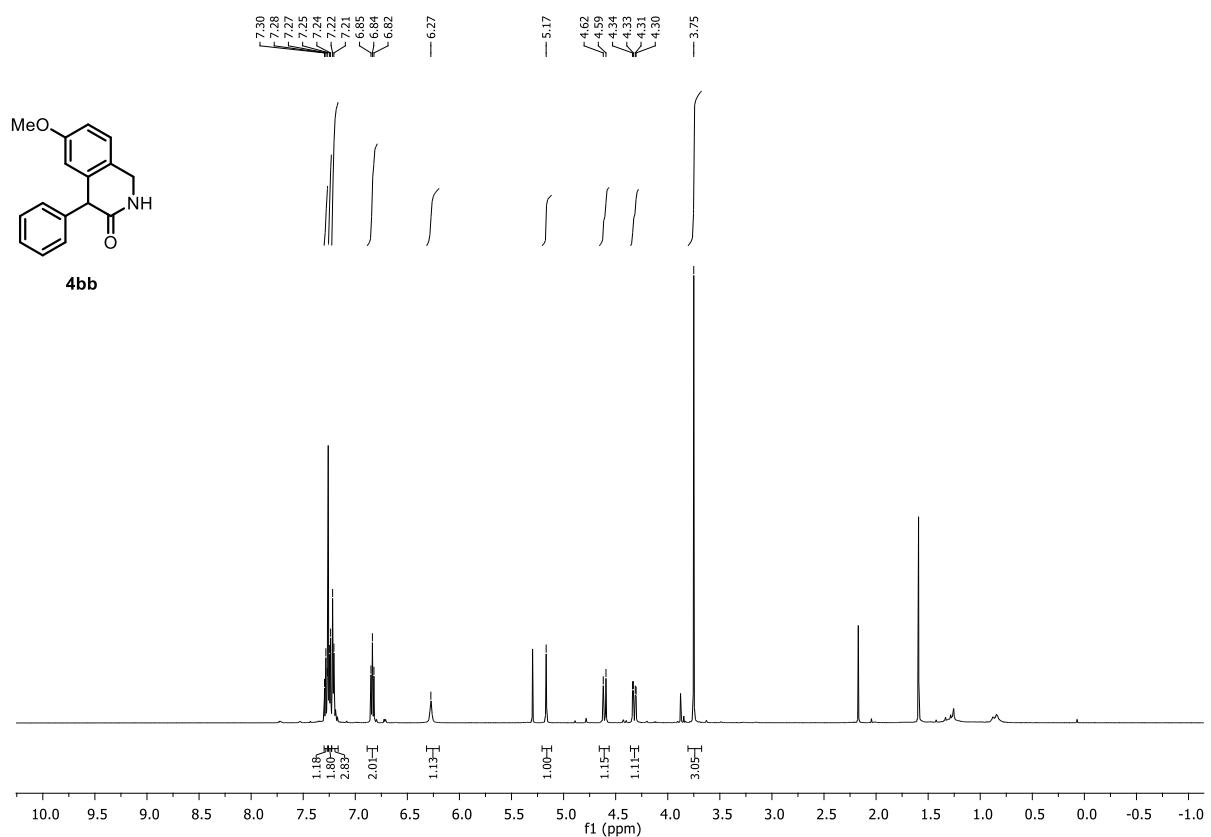
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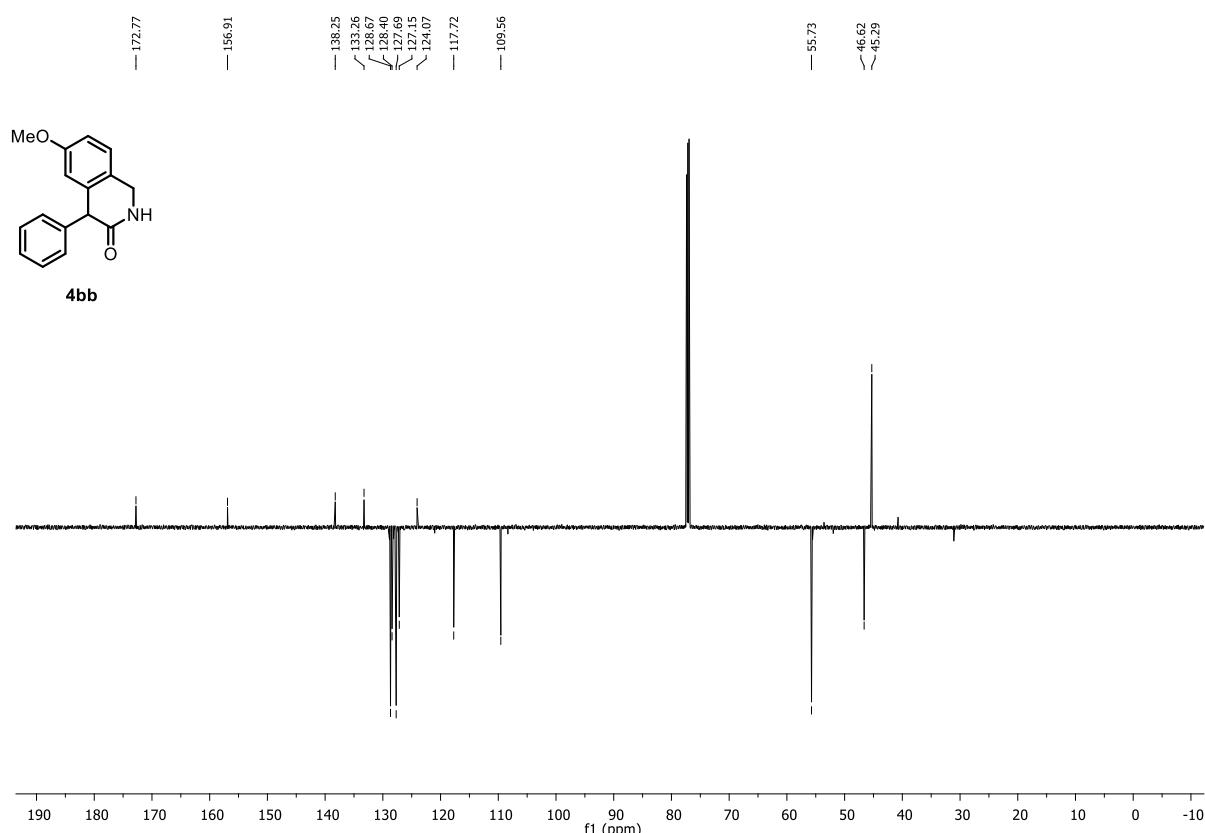
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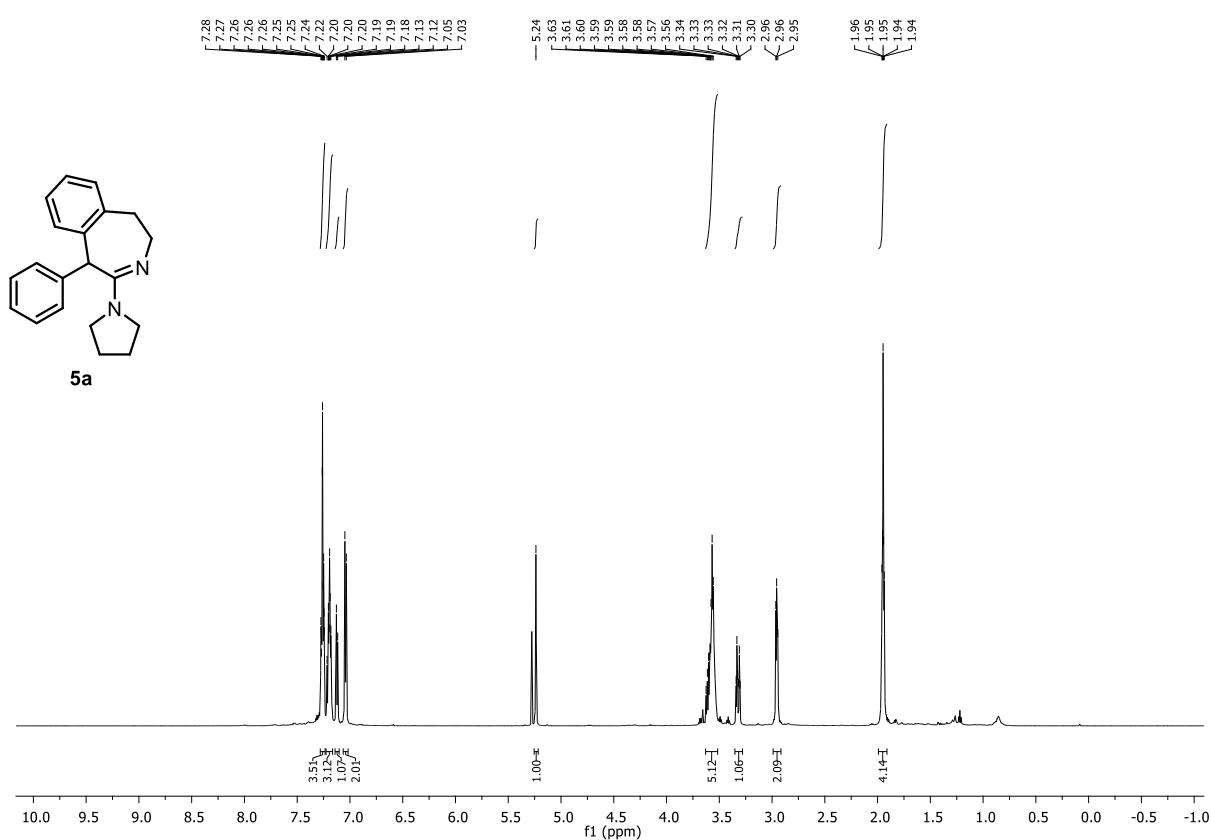
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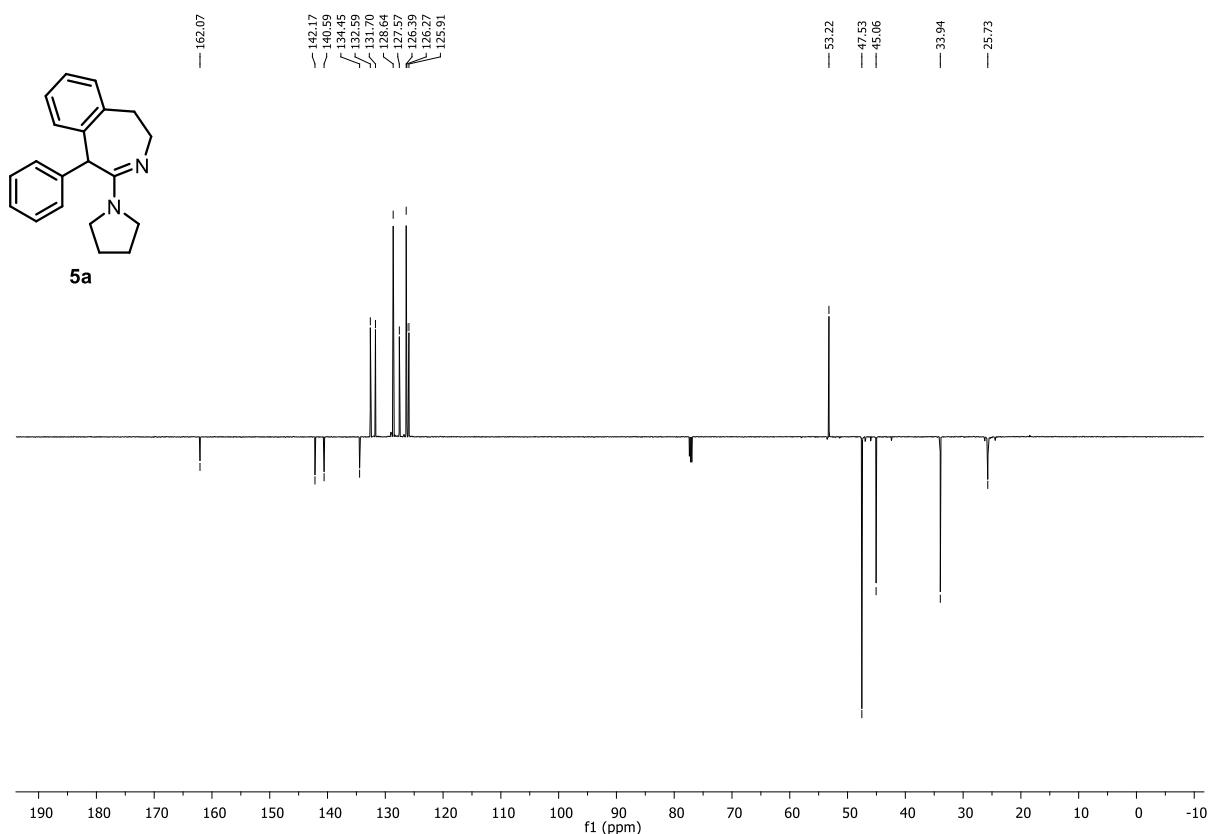
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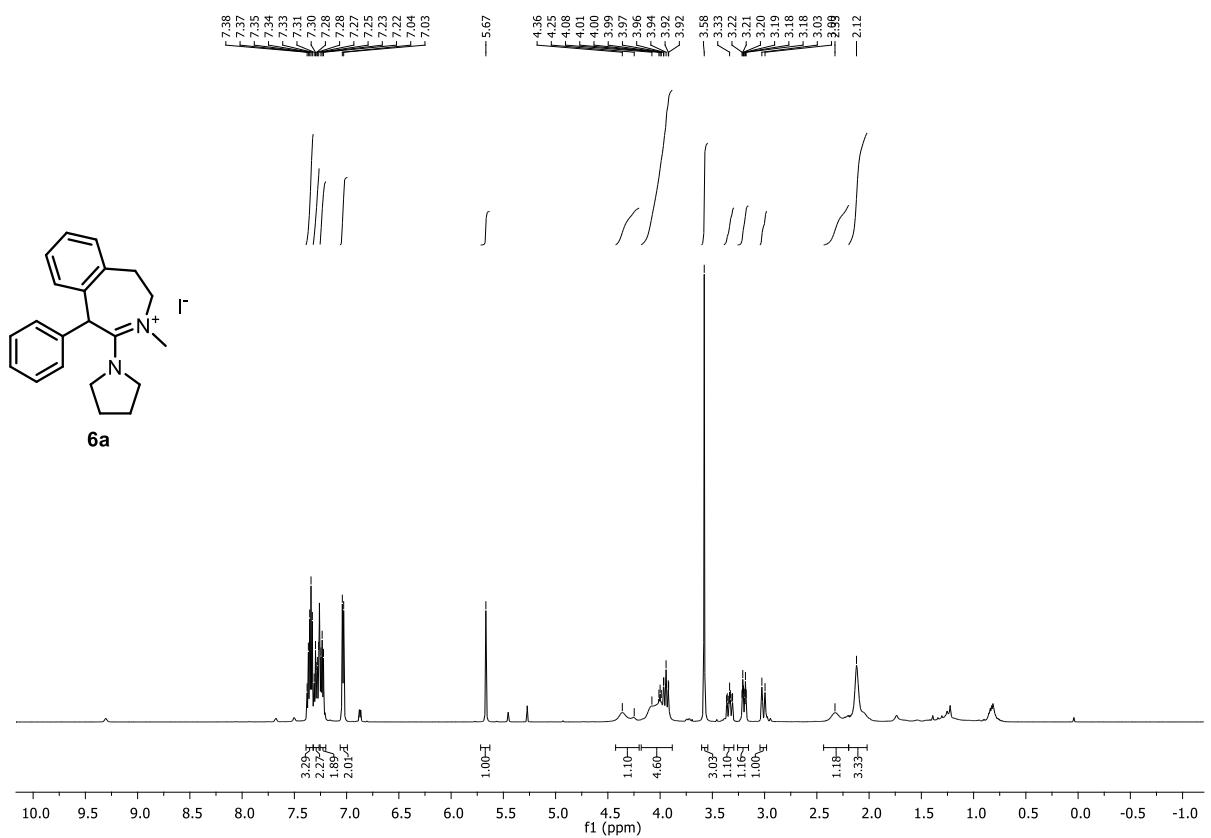
¹H NMR (600 MHz, CDCl₃)



¹³C NMR (151 MHz, CDCl₃)



¹H NMR (600 MHz, CDCl₃)



¹³C NMR (151 MHz, CDCl₃)

