Electronic Supplementary Material (ESI)

Site-Selective C-H Functionalization of (Hetero)arenes via Transient, Non-symmetric Iodanes

Stacy C. Fosu,[1†] Chido M. Hambira,[2†] Andrew D. Chen,[1]
James R. Fuchs,[2*] David A. Nagib[1*]

[1]Department of Chemistry & Biochemistry
The Ohio State University
151 W Woodruff Ave., Columbus, OH 43210

[2]Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy
The Ohio State University
500 West 12th Ave., Columbus, OH 43210

Corresponding Authors
* E-mail: nagib.1@osu.edu
*E-mail: fuchs.42@osu.edu

Table of Contents

(with links)

I. General Information

All chemicals and reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, TCI, or ChemImplex. Silicycle F60 (230-400 mesh) silica gel was used for column chromatography unless otherwise stated. Thin layer chromatography (TLC) analyses were performed using Merck silica gel 60 F_{254} plates and visualized under UV, $KMNO_4$ or iodine stain. Melting points were determined using a Thermo Scientific Mel-Temp or a Thomas Hoover Uni-melt capillary melting point apparatus. ^1H, ^{19}F, ^{13}C NMR spectra were recorded using a Bruker AVIII 400 MHz, AVIII 600 MHz, or AVIII 700 MHz NMR spectrometer. ^1H NMR and ^{13}C NMR chemical shifts are reported in parts per million and referenced with respect to $CDCl_3$ (^1H: residual $CHCl_3$ at δ 7.26, ^{13}C: $CDCl_3$ triplet at δ 77.16). ^1H NMR data are reported as chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), relative integral. ^{13}C and ^{19}F NMR data are reported as chemical shifts (δ ppm). High resolution mass spectra were obtained using Bruker MicrOTOF (ESI) or Thermo LTQ Orbitrap. IR spectra were recorded using a Thermo Fisher Nicolet iS10 FT-IR or Thermo Scientific Nicolet 6700 FT-IR and are reported in terms of frequency of absorption (cm^{-1}). Unless otherwise indicated, all hydrochloric acid solutions are in water.

Experimental

General Procedure for Amine Protection (GP1)

Trimethylacetyl chloride (1 equiv) was added to a solution of arene (1 equiv.) and triethylamine (1.1 eq) in dichloromethane (1 M) at 0 °C. The solution was warmed to room temperature and stirred for 16 hours. The solution was washed with water and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by recrystallization from dichloromethane and hexanes.

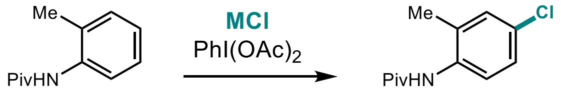
General Procedure for Chlorination of Arenes (GP2)

To an 8 mL dram vial was added iodobenzene diacetate (0.6 mmol, 1.5 equiv), arene (0.4 mmol, 1 eq.), dichloroethane (2 mL), then 1 M hydrochloric acid (2 mL, 5 equiv). The solution was allowed to stir (1000 rpm) at 50 °C for the indicated amount of time. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. The crude mixture was then purified by column chromatography.

General Procedure for Chlorination of Heteroarenes (GP3)

To an 8 mL dram vial was added iodobenzene diacetate (0.6 mmol, 1.5 equiv), and heteroarene (0.4 mmol, 1 eq.), anhydrous dichloroethane (1 mL), then chloride source (5 equiv). The solution was allowed to stir (1000 rpm) at 50 °C for the indicated amount of time. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. The crude mixture was then purified by column chromatography.

II. Anion Source Investigation

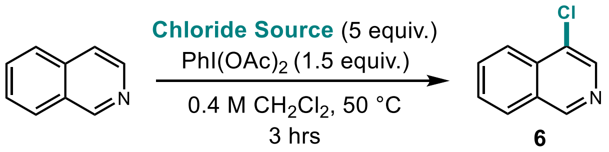


5

Chloride Source	% Yield	% Recovered Starting Material
HCl	88%	0%
$ZnCl_2$	85%	0%
$MgCl_2$	73%	0%
LiCl	68%	0%
$CuCl_2$	60%	0%
AcCl	56%	0%
KCl	0%	<52%
Me_3SiCl	0%	<55%
NaCl	0%	63%
NH_4Cl	0%	73%
Bu_4NCl	0%	84%
$FeCl_2$	Trace	89%

Table S1: Effect of chloride sources on functionalization of model arene

All reactions were carried out according to GP2 using N-(o-tolyl)pivalamide **S1** as the test substrate (50 mg, 0.26 mmol), and the respective chloride sources (1.3 mmol) indicated in the table for 3 hours. The crude mixtures were then purified by column chromatography eluting with 10% ethyl acetate/hexanes to provide **5**.



6

Chloride Source	% Yield	% Recovered Starting Material
$MgCl_2$	0%	91%
Bu_4NCl	0%	65%
NaCl	0%	64%
$ZnCl_2$	0%	45%
Me_3SiCl	28%	35%
C_6F_5COCl	4%	0%
AcCl	86%	0%
EtOCOCl	92%	0%

Table S2: Effect of chloride sources on functionalization of model heteroarene

All reactions were carried out according to GP3 using the respective chloride sources (2 mmol, 5 equiv.) indicated in the table for 3 hours. The crude mixtures were then purified by column chromatography eluting with 0.5% methanol in dichloromethane to provide **6**.

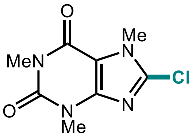
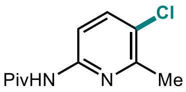
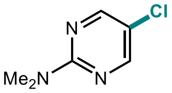
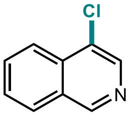
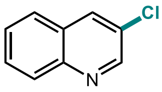
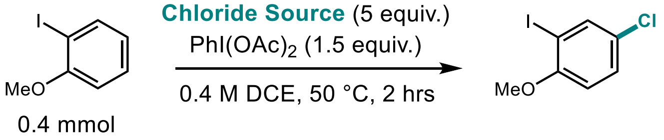
Chloride Source					
C_6F_5COCl	65%	55%	52%	4%	63%
AcCl	63%	54%	57%	86%	0%
EtOCOCl	5%	0%	36%	92%	24%

Table S3: Effect of various acyl chlorides on heteroarene chlorination

All reactions were carried out according to GP3 using the respective chloride sources (2 mmol, 5 equiv.) indicated in the table. Reaction progress was monitored by TLC and mass spectrometry. The crude mixtures were then purified by column chromatography. Isolated yields. *Reaction times and purification conditions can be found in the characterization data section for each substrate.*

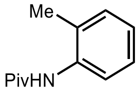


Chloride Source	% Yield	% Recovered Starting Material
C_6F_5COCl	41%	0%
AcCl	56%	0%
EtOCOCl	0%	75%

Table S4: Effect of various acyl chlorides on model arene chlorination

To an 8 mL dram vial was added iodobenzene diacetate (96.6 mg, 0.3 mmol), 2-iodoanisole (46.8 mg, 0.2 mmol), dichloroethane (1 mL), and respective chloride sources (1 mmol). The solution was allowed to stir (1000 rpm) at 50 °C for 30 minutes. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. Yields are based on ^{1}H NMR using isopropyl acetate as a standard.

III. Substrate Synthesis and Characterization



S1

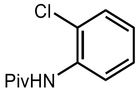
N-(o-tolyl)pivalamide (S1). Prepared according to GP1. 2-methyl anilide (3.20 mL, 30 mmol) and triethylamine (4.60 mL, 33 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. Trimethylacetyl chloride (4.30 mL, 36 mmol) was added and the reaction was allowed to stir at room temperature for 16 hours. The reaction was washed with 5% HCl, then saturated sodium bicarbonate. The organic layers were combined, dried over sodium sulfate and concentrated. The product was recrystallized from dichloromethane and hexanes to yield **S1** (3.57 g, 62%) as a white solid.

R_f: 0.26 (15% ethyl acetate/hexanes)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.87 (d, J = 8.0 Hz, 1H), 7.26 – 7.15 (m, 3H), 7.06 (td, J = 7.5 Hz, 1.2 Hz, 1H), 2.26 (s, 3H), 1.34 (s, 9H)

^{13}C NMR (101 MHz, CDCl$_3$): δ =176.5, 136.0, 130.5, 128.7, 127.0, 125.0, 122.9 39.9, 27.9, 17.8

Spectral data consistent with literature[1]



S2

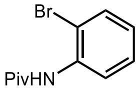
N-(2-chlorophenyl)pivalamide (S2). Prepared according to GP1. 2-chloroaniline (2.50 mL, 24 mmol) was reacted with trimethylacetyl chloride (3.60 mL, 29 mmol) and triethylamine (3.7 mL, 26 mmol) in tetrahydrofuran (80 mL) for 3 hours. The reaction was quenched with brine and extracted with ether. The crude product was recrystallized from ethanol to yield **S2** (4.77 g, 94%) as a white powder.

R_f: 0.30 (5% ethyl acetate/hexanes)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.42 (dd, J = 8.2, 1.5 Hz, 1H), 8.01 (s, 1H), 7.36 (dd, J = 8.0, 1.5 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.03 (td, J = 7.8, 1.5 Hz, 1H), 1.35 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.6, 134.8, 128.7, 127.8, 124.3, 122.9, 121.4, 40.2, 27.6

Spectral data consistent with literature[2]



S3

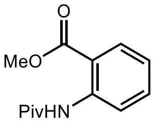
bromo 2-pivalamidobenzoate (S3). Prepared according to GP1. 2-bromoaniline (1.10 mL, 10 mmol) was reacted with triethylamine (1.70 mL, 12 mmol) and trimethylacetyl chloride (1.40 mL,

---

[1] Brasche, G., García-Fortanet, J., and Buchwald, S.L. (2008). Twofold C−H functionalization: palladium-catalyzed ortho arylation of anilides. Org. Lett. *10*, 2207–2210.

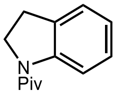
[2] Sadig, J.E.R., Foster, R., Wakenhut, F., and Willis, M.C. (2012). Palladium-catalyzed synthesis of benzimidazoles and quinazolinones from common precursors. J. Org. Chem. *77*, 9473–9486.

11 mmol) in dichloromethane (30 mL). Crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **S3** in quantitative yield as an off white solid.
R$_f$: 0.22 (5% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.40 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.00 (s, 1H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.00 – 6.92 (m, 1H), 1.36 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.8, 136.0, 128.5, 125.0, 121.8, 132.2, 113.8, 40.4, 27.7
Spectral data consistent with literature[3]



S4

methyl 2-pivalamidobenzoate (S4). Prepared according to GP1. Methyl 2-aminobenzoateaniline (1.30 mL, 10 mmol) was reacted with triethylamine (1.70 mL, 12 mmol) and trimethylacetyl chloride (1.40 mL, 11 mmol) in dichloromethane (30 mL). Crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **S4** in quantitative yield as low melting solid.
R$_f$: 0.24 (5% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 11.31 (s, 1H), 8.78 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.58 – 7.49(m, 1H), 7.11 – 7.02 (m, 1H), 3.93 (s, 3H), 1.35 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 178.1, 169.0, 142.2, 134.8, 131.0, 122.3, 120.5, 115.1, 52.5, 40.5, 27.8



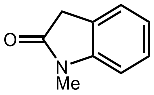
S5

1-(indolin-1-yl)-2,2-dimethylpropan-1-one (S5). Prepared according to GP1. Indoline (1.10 mL, 10 mmol) was reacted with triethylamine (1.70 mL, 12 mmol) and trimethylacetyl chloride (1.40 mL, 11 mmol) in dichloromethane (15 mL). Crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to to yield **S5** (1.88 g, 92%) as a colorless oil.
R$_f$: 0.14 (5% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.26 – 8.21 (m, 1H) 7.21 – 7.17 (m, 2H), 7.01 (td, *J* = 7.4, 1.0 Hz, 1H), 4.23 (t, *J* = 8.2 Hz, 2H), 3.14 (t, *J* = 8.2 Hz, 2H), 1.38 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.7, 144.9, 130.9, 127.5, 124.4, 123.7, 118.6, 49.6, 40.3, 29.5, 27.9
Spectral data consistent with literature[4]

---

[3] Zheng, N., Andersen, K.W., Huang, X., Nguyen, H.N., and Buchwald, S.L. (2007). A palladium-catalyzed regiospecific synthesis of N-aryl benzimidazoles. Angew. Chem. Int. Ed. *46*, 7509–7512.

[4] Park, J., Mishra, K.M., Sharma, S., Han, S., Shin, Y., Jeong, T., Oh, J.S., Kwak, J.H, Jung, Y.H, and Kim, I.S. (2015). Mild Rh(III)-catalyzed C7-allylation of indolines with allylic carbonates. J. Org. Chem. *80*, 1818−1827.



S6

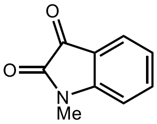
1-methylindolin-2-one (S6). 60% sodium hydride (800 mg, 20 mmol) was added to a solution of oxindole (2.66 g, 20 mmol) in toluene (60 mL) and stirred at 100 °C for 1 hour. Dimethyl sulfate (1.90 mL, 20 mmol) was added and allowed to stir for an additional 2 hours. The reaction was quenched with water, extracted with ethyl acetate, and concentrated. The crude product was purified by column chromatography eluting with 20% ethyl acetate/hexanes to yield **S6** (1.17 g, 40%) as an off white solid.

R$_f$: 0.13 (20% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.32 – 7.26 (m, 1H), 7.26 – 7.23 (m, 1H), 7.04 (td, *J* = 7.6, 0.9 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.52 (s, 2H), 3.21 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 175.3, 145.4, 128.0, 124.7, 124.5, 122.5, 108.2, 35.9, 26.3

Spectral data consistent with literature[5]



S7

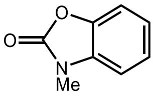
1-methylindoline-2,3-dione (S7). 60% sodium hydride (652 mg, 16.3 mmol) was added to a solution of isatin (2.00 g, 13.6 mmol) in DMF (5.0 mL) at 0 °C. Iodomethane (1.0 mL, 16.3 mmol) was added dropwise and stirred at 0 °C for 1 hour. The mixture was poured over cold water and the solid was filtered. The solid was dissolved in dichloromethane, washed with water, dried over sodium sulfate and filtered. The filtrate was collected and the solvent was removed under reduced pressure to yield **S7** (1.27 g, 7.87 mmol, 58%) as a bright red-orange solid.

R$_f$: 0.08 (20% ethyl acetate/hexanes)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.64 – 7.58 (m, 2H), 7.13 (td, *J* = 7.6, 0.8 Hz, 1H), 6.93 – 6.87(m, 1H), 3.26 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 183.5, 158.4, 151.6, 138.5, 125.4, 124.0, 117.6, 110.0, 26.4

Spectral data consistent with literature[6]



S8

6-chloro-3-methylbenzo[d]oxazol-2(3H)-one (S8). 60% sodium hydride (1.44 g, 36 mmol) was added to a solution of benzoxindolidinone (3.38 g, 25 mmol) in THF (20 mL) at 0 °C, and stirred at 0 °C for 30 minutes. Iodomethane (2.30 mL, 37.5 mmol) was added dropwise and stirred at

---

[5] Liégault, B., Petrov, I., Gorelsky, S.I., and Fagnou, K. (2010). Modulating reactivity and diverting selectivity in palladium-catalyzed heteroaromatic direct arylation through the use of a chloride activating/blocking group. J. Org. Chem. *75*, 1047–1060.

[6] Liégault, B., Petrov, I., Gorelsky, S.I., and Fagnou, K. (2010). Modulating reactivity and diverting selectivity in palladium-catalyzed heteroaromatic direct arylation through the use of a chloride activating/blocking group. J. Org. Chem. *75*, 1047–1060.; Katritzky, A.R., Fan, W.-Q., Liang, D.-S., and Li, Q.-L. (1989). Novel dyestuffs containing dicyanomethylidene groups. J. Heterocyclic Chemistry *26*, 1541–1545.

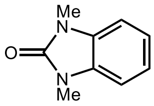
room temperature for 9 hours. The reaction mixture was diluted with ethanol and concentrated. The residue was diluted with water and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The product was purified by column chromatography eluting with 25% ethyl acetate/hexanes to yield **S8** (1.62 g, 43%) as an off white solid.

R$_f$: 0.25 (25% ethyl acetate/hexanes)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.22 – 7.17 (m, 2H), 7.15 – 7.09 (m, 1H), 6.98 – 6.95 (m, 1H), 3.41 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 154.9, 142.8, 131.9, 124.0, 122.6, 110.1, 108.2, 28.2

Spectral data consistent with literature[7]



S9

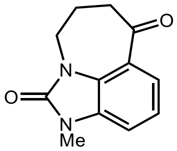
1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (S9). Prepared according literature.[8] 2-hydroxybenzimidazole (2.68 g, 20 mmol) was dissolved in DMF (15 mL) and potassium tert-butoxide (4.49 g, 40 mmol) was added and stirred for 30 minutes. Iodomethane (2.5 mL, 40 mmol) was added slowly and stirred further for 30 minutes. Potassium tert-butoxide (1.12 g, 20 mmol) was added along with iodomethane (600 µL, 10 mmol) and heated to 60 °C for 1.5 hours. The mixture was cooled to room temperature and extracted with ethyl acetate. The organic layers were combined and washed with brine and dried over sodium sulfate, filtered, and concentrated. The product was purified by column chromatography eluting with 35% ethyl acetate/hexanes to yield **S9** (2.17, 67%) as a light yellow solid.

R$_f$: 0.15 (35% ethyl acetate/hexanes)

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.10 (dd, *J* = 5.7, 3.2 Hz, 2H), 6.97 (dd, *J* = 5.7, 3.2 Hz, 2H), 3.42 (s, 6H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 154.8, 130.2, 121.3, 107.4, 27.3

Spectral data consistent with literature[9]



S10

2-methyl-8,9-dihydro-2,9a-diazabenzo[cd]azulene-1,6(2H,7H)-dione (S10). 8,9-dihydro-2,9a-diazabenzo[cd]azulene-1,6(2H,7H)-dione (1.50 g, 7.4 mmol) was dissolved in DMF (10 mL). Potassium tert-butoxide (1.25 g, 11.1 mmol) was added and allowed to stir for 30 minutes. After which iodomethane (691 µL, 11.1 mmol) was added and allowed to stir at room temperature for 2

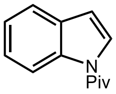
---

[7] Chiarotto, I., Feroci, M., Orsini, M., Sotgiu, G., and Inesi, A. (2009). Electrogenerated N-heterocyclic carbenes: N-functionalization of benzoxazolones. Tetrahedron *65*, 3704–3710.

[8] Lin, S.-Y., Yeh, T.-K., Kuo, C.-C., Song, J.-S., Cheng, M.-F., Liao, F.-Y., Chao, M.-W., Huang, H.-L., Chen, Y.-L., Yang, C.-Y., et al. (2016). Phenyl benzenesulfonylhydrazides exhibit selective indoleamine 2,3-dioxygenase inhibition with potent in vivo pharmacodynamic activity and antitumor efficacy. J. Med. Chem. *59*, 419–430.

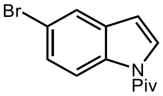
[9] Jin, Y., Ou, L., Yang, H., and Fu, H. (2017). Visible-light-mediated aerobic oxidation of N-alkylpyridinium salts under organic photocatalysis. J. Am. Chem. Soc. *139*, 14237–14243.

hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The product was purified by column chromatography eluting with 2% methanol/dichloromethane to yield **S10** (628 mg, 39%) as a light yellow solid.
R$_f$: 0.19 (2% methanol/dichloromethane)
mp: 150.8 – 152.9 ºC
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.84 – 7.78 (m, 1H), 7.18 – 7.13 (m, 2H), 4.15 – 4.11 (m, 2H), 3.47 (s, 3H), 3.10 – 3.04 (m, 2H), 2.27 – 2.21 (m, 2H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 197.3, 154.0, 131.3, 129.1, 122.8, 120.8, 118.8, 111.8, 45.6, 44.7, 27.5, 20.5
HRMS (ESI-TOF) *m/z*: calc'd for $C_{12}H_{12}N_2NaO_2$ $[M+Na]^+$ 239.0796, found 239.0802
IR (film) cm^{-1}: 2949, 2929, 1709, 1664, 1616, 1489, 1458, 1433, 1157, 1014, 796, 742, 592



S11

1-(1H-indol-1-yl)-2,2-dimethylpropan-1-one (S11). Prepared according to GP1. Indole (1.17 g, 10 mmol) was reacted with triethylamine (2.10 mL, 15 mmol) and trimethylacetyl chloride (1.50 mL, 12 mL) and DMAP (122 mg, 1 mmol) in dichloromethane (15 mL). The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **S11** (1.91 g, 95%) as a light yellow solid.
R$_f$: 0.38 (5% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.52 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 3.8 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.38 – 7.31 (m, 1H), 7.30 – 7.24 (m, 1H), 6.62 (dd, *J* = 3.9, 0.6 Hz, 1H), 1.53 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 177.2, 136.9, 129.5, 125.8, 125.2, 123.7, 120.6, 117.5, 108.4, 41.4, 28.9
Spectral data consistent with literature[10]



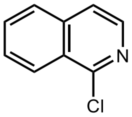
S12

1-(5-bromo-1H-indol-1-yl)-2,2-dimethylpropan-1-one (S12). Prepared according to GP1. 5-bromo-indole (980 mg, 5 mmol) was reacted with triethylamine (1.00 mL, 7.5 mmol) and trimethylacetyl chloride (739 µL, 6 mmol) and DMAP (61.0 mg, 0.5 mmol) in dichloromethane (10 mL). The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **S12** (1.33 g, 84%) as a white solid.
R$_f$: 0.30 (5% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.39 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 3.9 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.56 (dd, *J* = 3.9, 0.6 Hz, 1H), 1.52 (s, 9H)

---

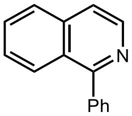
[10] Cornella, J., Lu, P., and Larrosa, I. (2009). Intermolecular decarboxylative direct C-3 arylation of indoles with benzoic acids. Org. Lett. *11*, 5506–5509.

^{13}C NMR (151 MHz, CDCl$_3$): δ = 177.1, 135.7, 131.3, 128.0, 126.9, 123.3, 118.9, 117.0, 107.5, 41.5, 28.8
Spectral data consistent with literature[11]



S13

1-chloroisoquinoline (S13). 3-Chloroperbenzoic acid (11.0 g, 45 mmol) was added to a solution of isoquinoline (3.50 mL, 30 mmol) in dichloromethane (150 mL) at 0 °C. The solution was stirred at room temperature for six hours. Sodium thiosulfate was added and the reaction mixture was washed with saturated K_2CO_3, dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in chloroform (30 mL), then $POCl_3$ (8.80 mL, 93 mmol) was added and the mixture was allowed to reflux for 2 hours. The reaction mixture was poured over ice and ammonium hydroxide was added until the solution was basic. The reaction was extracted with ethyl acetate, dried over sodium sulfate and concentrated. The product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **S13** (1.82 g, 11 mmol, 37%) as a yellow oil.
R$_f$: 0.24 (5% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.37 – 8.33 (m, 1H), 8.28 (d, *J* = 5.6 Hz, 2H), 7.88 – 7.83 (m, 1H), 7.79 – 7.73 (m, 1H), 7.73 – 7.67 (m, 1H), 7.61 (d, *J* = 5.7 Hz, 1H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 151.8, 141.7, 138.0, 131.3, 128.7, 127.2, 127.1, 126.6, 120.9
Spectral data consistent with literature[12]



S14

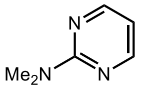
1-phenylisoquinoline (S14). Synthesized according to literature.[9] **S13** (491 mg, 3 mmol) and $FeBr_3$ (26.6 mg, 0.09 mmol) were dissolved in tertbutyl methyl ether (15 mL). Phenylmagnesium bromide (1M in THF, 6.90 mL, 6.9 mmol) was added dropwise and the reaction was allowed to stir at room temperature for 10 minutes. After which it was quenched with brine and extracted with ethyl acetate. The organic layers were dried over sodium sulfate, filtered, and concentrated. The product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **S14** (474 mg, 77%) as a white solid.
R$_f$: 0.14 (10% ethyl acetate/hexanes)
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.62 (d, *J* = 5.7 Hz, 1H), 8.11 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.72 – 7.68 (m, 3H), 7.65 (d, *J* = 5.7 Hz, 1H), 7.56 – 7.48 (m, 4H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 161.0, 142.4, 139.8, 137.1, 130.1, 130.1, 128.7, 128.5, 127.8, 127.3, 127.1, 126.9, 120.0

---

[11] Islam, S., and Larrosa, I. (2013). "On Water", phosphine-free palladium-catalyzed room temperature C-H arylation of indoles. Chem. Eur. J. *19*, 15093–15096.

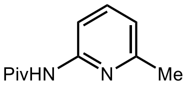
[12] Cortright, S.B., and Johnston, J.N. (2002). IAN-amines: direct entry to a chiral C2-symmetric zirconium(IV) β-diketimine complex. Angew. Chem. Int. Ed. *41*, 345–348.

Spectral data consistent with literature[13]



S15

N,N-dimethylpyrimidin-2-amine (S15). Prepared according to literature.[14] 60% sodium hydride (2.60 g, 65 mmol) was added to a stirred solution of 2-aminopyrimidine (2.50 g, 26 mmol) in dimethylformamide (10 mL). The solution was cooled to 0 °C, then iodomethane was added dropwise and allowed to stir at 0 °C for 16 hours. The reaction was quenched with water, extracted with ethyl acetate, dried over sodium sulfate, and concentrated. The crude product was purified by column chromatography eluting with 15% ethyl acetate/hexanes to yield **S15** (1.18 g, 37%) as a yellow oil.
R_f: 0.26 (15% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 4.8 Hz, 2H), 6.41 (t, *J* = 4.7 Hz, 1H), 3.16 (s, 6H)
^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3, 157.5, 109.0, 37.1
Spectral data consistent with literature[15]



S16

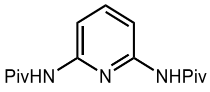
N-(6-methylpyridin-2-yl)pivalamide (S16). 6-methylpyridin-2-amine (2.00 g, 19 mmol), 4-dimethylaminopyridine (232 mg, 1.9 mmol) and triethylamine (3.20 mL, 22.8 mmol) was dissolved in dichloromethane (40 mL) and cooled to 0 °C. Trimethylacetyl chloride (2.60 mL, 20.9 mmol) was added dropwise and the solution was allowed to stir at room temperature for 18 hours. The solution was washed with water and dissolved in dichloromethane and hexanes. The solid was filtered and the filtrate was concentrated to yield **S16** (2.50 g, 69%) as a white solid.
R_f: 0.11 (10% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.3 Hz, 1H), 7.94 (s,1H), 7.58 (t, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 2.45 (s, 3H), 1.32 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2, 156.8, 151.1, 138.8, 119.3, 110.8, 39.9, 27.7, 27.3, 24.1
Spectral data consistent with literature[12]

---

[13] Kuzmina, O.M., Steib, A. K., Flubacher, D., and Knochel, P. (2012). Iron-catalyzed cross-coupling of N-heterocyclic chlorides and bromides with arylmagnesium reagents. Org. Lett. *14*, 4818–4821.

[14] Mita, T., Michigami, K., and Sato, Y. (2013). Iridium- and rhodium-catalyzed dehydrogenative silylations of C(sp3)-H bonds adjacent to a nitrogen atom using hydrosilanes. Chem. Asian J. *8*, 2970–2973.

[15] Corr, M.J., Gibson, K.F., Kennedy, A.R., and Murphy, J.A. (2009). Amidine dications: isolation and [Fe]-hydrogenase-related hydrogenation. J. Am. Chem. Soc. *131*, 9174–9175.



S17

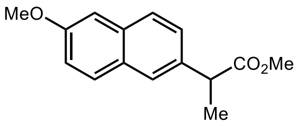
N,N'-(pyridine-2,6-diyl)bis(2,2-dimethylpropanamide) (S17). Trimethylacetyl chloride (4.40 mL, 36 mmol) was added to a stirred solution of 2,6 diaminopyridine (1.64 g, 15 mmol) and triethylamine (6.30 mL, 45 mmol) in dichloromethane at 0 °C. The solution was allowed to stir at room temperature for 21 hours. The reaction mixture was washed with water and back extracted with dichloromethane. The product was purified by column chromatography eluting with 20% ethyl acetate/hexanes to yield **S17** (3.67, 13.2 mmol, 88%) as a light yellow solid.

R$_f$: 0.28 (20% ethyl acetate/hexanes).

^{1}H NMR (600 MHz, CDCl$_3$): δ =7.92 (d, *J* = 8.1 Hz, 2H), 7.73 (s, 2H), 7.69 (t, *J* = 8.1 Hz, 1H), 1.32 (s, 18H)

^{13}C NMR (150 MHz, CDCl$_3$): δ = 176.9, 149.8, 140.9, 109.5, 39.9, 27.6

Spectral data consistent with literature[16]



S18

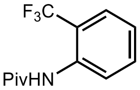
methyl 2-(6-methoxynaphthalen-2-yl)propanoate (S18). Naproxen (800 mg, 3.47 mmol) was dissolved in methanol (150 mL) and concentrated sulfuric acid (4 mL) was added and refluxed for 18 hours. The solution was allowed to cool to room temperature, then washed with water and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to yield **S18** (830 mg, 98%) as a white solid.

R$_f$: 0.14 (5% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.70 (d, *J* = 8.5 Hz, 2H, 7.66 (d, *J* =1.8 Hz, 1H), 7.40 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.16 – 7.10 (m, 2H), 3.91 (s, 3H), 3.86 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 175.3, 157.8, 135.8, 133.9, 129.4, 129.1, 127.3, 126.3, 126.1, 119.1, 105.8, 55.5, 52.2, 45.5, 18.7

Spectral data consistent with literature[17]



S19

N-(2-(trifluoromethyl)phenyl)pivalamide (S19). Prepared according to GP1. 2-(trifluoromethyl)aniline (3.80 mL, 30 mmol) was reacted with triethylamine (4.60 mL, 33 mmol) and trimethylacetyl chloride (4.30 mL, 36 mmol) in dichloromethane (30 mL). Crude product was

---

[16] Zhou, J., Li, B., Hu, F., and Shi, B.-F. (2013). Rhodium(III)-catalyzed oxidative olefination of pyridines and quinolines: multigram-scale synthesis of naphthyridinones. Org. Lett. *15*, 3460–3463.

[17] Munoz-Muniz, O., and Juaristi, E. (2003). Enantioselective protonation of prochiral enolates in the asymmetric synthesis of (S)-naproxen. Tetrahedron. Lett. *44*, 2023–2026.

purified by recrystallization from dichloromethane and hexanes to yield **S19** in quantitative yield as white crystals.

R$_f$: 0.22 (5% ethyl acetate/hexanes)

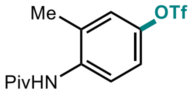
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.25 (d, *J* = 8.1 Hz, 1H), 7.79 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.24 – 7.18 (m, 1H), 1.33 (s, 9H)

^{13}C NMR (101 MHz, CDCl$_3$): δ =176.8, 135.9, 133.0, 126.1 (q, *J* = 5.3 Hz), 125.8, 124.3, 124.2, 123.1, 120.1, 119.8

^{19}F NMR (377 MHz, CDCl$_3$): δ = -60.79

Spectral data consistent with literature[18]

IV. (Hetero)arene Halogenation and Oxygenation Synthesis and Characterization



1

3-methyl-4-pivalamidophenyl trifluoromethanesulfonate (1). To an 8 mL dram vial was added triflic acid (71 µL, 0.8 mmol) to iodobenzene diacetate (258 mg, 0.8 mmol) in dichloromethane (1 mL) at room temperature. **S1** (76.5 mg, 0.4 mmol) in dichloromethane (1 mL) added dropwise to the solution and allowed to stir at 1000 rpm at room temperature for 45 minutes. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate, and concentrated. The crude mixture was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield the **1** (54.9 mg, 40%, isolated; 53% by crude ^{19}F NMR using trifluorotoluene as in internal standard) as a light yellow solid.

R$_f$: 0.14 (10% ethyl acetate/hexanes).

mp: 105.9 – 107.1 °C

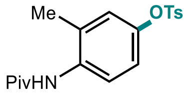
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.03 (d, *J* = 8.5 Hz, 1H), 7.27 (s, 1H), 7.15 – 7.10 (m, 2H), 2.29 (s, 3H), 1.34 (s, 1H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.7, 145.7, 136.2, 130.8, 124.0, 123.1, 120.5, 119.6, 40.0, 27.8, 17.9

^{19}F NMR (377 MHz, CDCl$_3$): -72.83

HRMS (ESI-TOF) *m/z*: calc'd for $C_{13}H_{17}F_3NO_4S$ $[M+H]^+$ 340.0830, found 340.0819

IR (film) cm^{-1}: 3296, 2972, 2929, 1651, 1491, 1419, 1207, 1130, 941, 876, 814, 602



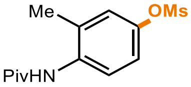
2

3-methyl-4-pivalamidophenyl 4-methylbenzenesulfonate (2). To an 8 mL dram vial was added iodobenzene diacetate (193 mg, 0.6 mmol, 1.5 equiv), **S1** (76.5 mg, 0.4 mmol) dichloroethane (2 mL), and p-toluenesulfonic acid monohydrate (114 mg, 0.6 mmol). The solution was allowed to stir at 1000 rpm at 50 °C for 1 hour. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate, and concentrated. The crude mixture was

---

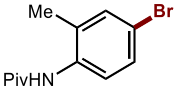
[18] Zhang, L.-S., Chen, K., Chen, G., Li, B.-J., Luo, S., Guo, Q.-Y., Wei, J.-B., and Shi, Z.-J. (2013). Palladium-catalyzed trifluoromethylation of aromatic C–H bond directed by an acetamino group. Org. Lett. *15*, 10–13.

then purified by column chromatography eluting with 20% ethyl acetate/hexanes to yield **2** (94.7 mg, 65%) as a light brown solid.
Rf: 0.08 (20% ethyl acetate/hexanes)
mp: 135.1 – 137.2 °C
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 1H), 6.93 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 8.8, 2.7 Hz, 1H), 2.44 (s, 3H), 2.19 (s, 3H), 1.31 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.6, 146.1, 145.4, 135.0, 132.7, 130.3, 129.9, 128.7, 124.4, 123.5, 120.4, 40.0, 27.8, 21.8, 17.8
HRMS (ESI-TOF) *m/z*: calc'd for $C_{19}H_{24}NO_4S$ [M+H]$^+$ 362.1426, found 362.1403
IR (film) cm^{-1}: 3282, 2970, 2929, 1645, 1523, 1371, 1346, 1173, 941, 806, 548



3

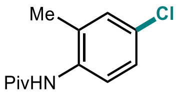
3-methyl-4-pivalamidophenyl methanesulfonate (3). To an 8 mL dram vial was added methanesulfonic acid (78 µL, 1.2 mmol) to iodobenzene diacetate (193 mg, 0.6 mmol) in dichloromethane (1 mL) at room temperature. S1 (76.5 mg, 0.4 mmol) in dichloromethane (1 mL) added dropwise to solution and allowed to stir at 1000 rpm at room temperature for 45 minutes. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate, and concentrated. The crude mixture was purified by column chromatography eluting with 30% ethyl acetate/hexanes to yield **3** (75.5 mg, 66%) as a light yellow solid.
Rf: 0.09 (30% ethyl acetate/hexanes)
mp: 93.9 – 96.2 °C
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.91 (d, *J* = 8.7 Hz, 1H) 7.25 (s, 1H), 7.14 – 7.08 (m, 2H), 3.10 (s, 3H), 2.26 (s, 3H), 1.33 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.7, 145.7, 135.3, 131.1, 124.2, 123.9, 120.1, 39.9, 37.3, 27.8, 17.8
HRMS (ESI-TOF) *m/z*: calc'd for $C_{13}H_{19}NO_4SNa$ [M+Na]$^+$ 308.0932, found 308.0930
IR (film) cm^{-1}: 3286, 2973, 2929, 1649, 1512, 1358, 1178, 1132, 945, 827, 514



4

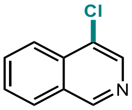
N-(4-bromo-2-methylphenyl)pivalamide (4). To an 8 mL dram vial was added iodobenzene diacetate (142 mg, 0.44 mmol, 1.1 equiv), N-(o-tolyl)pivalamide S1 (76.5 mg, 0.4 mmol) dichloroethane (2 mL), and 48% hydrobromic acid (226 µL, 2 mmol). The solution was allowed to stir at 1000 rpm at 50 °C for 2 hours. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. The crude mixture was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **4** (105 mg, 97%) as white crystals.
Rf: 0.22 (10% ethyl acetate/hexanes)
mp: 120.0 – 121.6 °C
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.72 (d, *J* = 9.2 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.21 (s, 1H), 2.20 (s, 3H), 1.32 (s, 9H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.6, 135.1, 133.1, 131.0, 129.8, 124.5, 117.7, 39.9, 27.6, 17.5
HRMS (ESI-TOF) *m/z*: calc'd for $C_{12}H_{16}BrNONa$ [M+Na]$^+$ 292.0313, found 292.0303
IR (film) cm^{-1}: 3334, 2976, 2927, 2918, 2870, 1647, 1504, 1477, 1250, 1182, 874, 802, 607
Spectral data consistent with literature[19]



5

N-(4-chloro-2-methylphenyl)pivalamide (5). Prepared according to GP2. Anilide **S1** (50 mg, 0.26 mmol) was reacted with iodobenzene diacetate (126.1 mg, 0.39 mmol) and 1 M HCl (1.31 mL, 1.31 mmol) in dichloroethane (1 mL) for 4 hours. The crude product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **5** (51.8 mg, 88%) as a white solid.
R$_f$: 0.65 (10% ethyl acetate/hexanes).
mp: 112 °C
^{1}H NMR (600 MHz, CDCl$_3$): δ 7.77 – 7.72 (m, 1H), 7.21 (s, 1H), 7.17 – 7.12 (m, J = 7.0, 2.4 Hz, 2H), 2.20 (s, 3H), 1.32 (s, 9H)
^{13}C NMR (151 MHz, CDCl$_3$): δ 176.6, 134.6, 131.0, 130.2, 130.0, 126.8, 124.4, 39.8, 27.8, 17.6
HRMS (ESI-TOF) *m/z*: calc'd for $C_{12}H_{16}ClNO$ [M+H]$^+$ 226.0993, found 226.0991
IR (film) cm^{-1}: 3314, 1646, 1505, 811



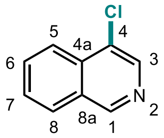
6

4-chloroisoquinoline (6). Prepared according to GP3. Isoquinoline (51.7 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and ethylchloroformate (191 µL, 2 mmol) for 3 hours. The reaction mixture was purified by column chromatography eluting with 0.5% methanol/dichloromethane to yield **6** (60.5 mg, 92% yield) as a clear oil.
R$_f$: 0.05 (0.5% methanol/dichloromethane)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.13 (s, 1H), 8.56 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 151.2, 142.0, 133.6, 131.5, 129.5, 128.6, 128.3, 127.8, 123.4
HRMS (ESI-TOF) *m/z*: calc'd for C_9H_6ClN [M+H]$^+$ 164.0262, found 164.0260
IR (film) cm^{-1}: 1572, 1379, 1254, 979, 888, 794
Spectral data consistent with literature[20]

---

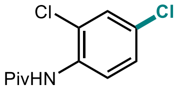
[19] Bedford, R.B., Engelhart, J.U., Haddow, M.F., Mitchell, C.J., and Webster, R.L. (2010). Solvent-free aromatic C–H functionalisation/halogenation reactions. Dalton Trans. *39*, 10464–10472.

[20] van Veldhuizen, A., van Dijk, M., and Sanders, G.M. (1980). ^{13}C NMR spectra of some 1-,3- and 4-monosubstituted and disubstituted isoquinolines. Org. Mag. Res. *13*, 105–109.



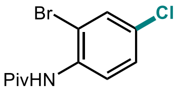
position	^{1}H	^{13}C	HMBC correlations
1	9.12	151.22	3, 4, 4a, 5, 8, 8a
3	8.56	141.96	1, 4, 4a, 5, 6, 8a,
4		128.56	
4a		133.65	
5	8.17	123.42	4, 4a, 7, 8a
6	7.80	131.54	4, 4a, 5, 7, 8, 8a
7	7.66	128.29	4a, 5, 6, 8, 8a
8	7.97	127.85	1, 4, 4a, 6, 7, 8a
8a		129.52	

Table S5: Determination of chlorination regioselectivity of **6**.
(400 MHz ^{1}H NMR and 101 MHz ^{13}C correlation data of **6** in $CDCl_3$)



7

N-(2,4-dichlorophenyl)pivalamide (7). Prepared according to GP2. Anilide **S2** (84.7 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 22 hours. The crude product was purified by column chromatography eluting with 3% ethyl acetate/hexanes to yield **7** (75.6 mg, 77%) as white crystals.
R$_f$: 0.20 (3% ethyl acetate/hexanes).
mp: 57.2 – 58.2 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.9 Hz, 1H), 7.94 (s, 1H), 7.37 (d, *J* =2.4 Hz, 1H), 7.24 (dd, *J* =8.9, 2.4 Hz, 1H), 1.33 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.6, 133.7, 128.9, 128.7, 128.0, 123.5, 122.2, 40.3, 27.7
HRMS (ESI-TOF) *m/z*: calc'd for $C_{11}H_{13}Cl_2NONa$ $[M+Na]^+$ 268.0272, found 268.0278
IR (film) cm^{-1}: 2977, 2952, 1655, 1576, 1504, 1474, 1383, 1171, 1099, 1056, 865, 806, 744, 585, 554
Spectral data consistent with literature[21]

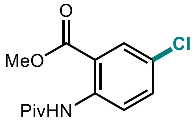


8

---

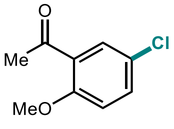
[21] Gowda, S., and Gowda, B.T. (2007). ^{1}H and ^{13}C NMR spectral studies on N-(j,k-dichlorophenyl)- and N-(j,k-dimethylphenyl)-acetamides and substituted acetamides. Zeitschrift fuer Naturforschung, A: Physical Sciences *62*, 84–90.

N-(2-bromo-4-chlorophenyl)pivalamide (8). Prepared according to GP2. Anilide **S3** (102 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 4.5 hours. The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **8** (90.4 mg, 78%) as colorless crystals.
R$_f$: 0.31 (5% ethyl acetate/hexanes)
mp: 66.2 – 68.1 °C
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.36 (d, *J* = 8.9 Hz, 1H), 7.95 (bs, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 8.9, 2.4 Hz, 1H), 1.34 (s, 9H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 176.8, 134.8, 131.7, 129.3, 128.6, 122.4, 113.8, 40.4, 27.7
HRMS (ESI-TOF) *m/z*: calc'd for $C_{11}H_{14}BrClNO$ $[M+H]^+$ 289.9947, found 289.9927
IR (film) cm^{-1}: 3292, 2974, 1653, 1502, 1471, 1369, 1167, 804
Spectral data consistent with literature[22]



9

methyl 5-chloro-2-pivalamidobenzoate (9). Prepared according to GP2. Anilide **S4** (94.1 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 13 hours. The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **9** (66.1 mg, 61%) as an off white solid.
R$_f$: 0.28 (5% ethyl acetate/hexanes).
mp: 84.4 – 86.8 °C
^{1}H NMR (400 MHz, CDCl$_3$): δ = 11.23 (bs, 1H), 8.76 (d, *J* = 9.2 Hz, 1H), 7.98 (d, *J* = 2.6 Hz, 1H) 7.47 (dd, *J* = 9.1, 2.6 Hz, 1H) 3.93 (s, 3H), 1.33 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 178.0, 167.9, 140.7, 134.6, 130.5, 127.3, 121.9, 116.3, 52.7, 40.5, 27.7
HRMS (ESI-TOF) *m/z*: calc'd for $C_{13}H_{16}ClNO_3Na$ $[M+Na]^+$ 292.0716, found 292.0700
IR (film) cm^{-1}: 1303, 3129, 2956, 2912, 1689, 1583, 1510, 1428, 1394, 1284, 1240, 1146, 960, 920, 832, 785, 694, 534



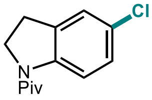
10

1-(5-chloro-2-methoxyphenyl)ethan-1-one (10). Prepared according to GP2. 1-(2-methoxyphenyl)ethan-1-one (57 µL, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 4.5 hours. The crude product

---

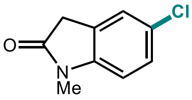
[22] Yan, J.-X., Li, H., Liu, X.-W., Shi, J.-L., Wang, X., and Shi, Z.-J. (2014). Palladium-catalyzed C(sp^3)-H activation: a facile method for the synthesis of 3,4-dihydroquinolinone derivatives. Angew. Chem. Int. Ed. *53*, 4945–4949.

was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **10** (53.5 mg, 72%) as a yellow oil.
R$_f$: 0.17 (5% ethyl acetate/hexanes).
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.68 (d, *J* = 2.7 Hz, 1H), 7.38 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 3.89 (s, 3H), 2.59 (s, 3H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 198.4, 157.6, 133.3, 130.1, 129.4, 126.1, 113.2, 56.0, 31.8
HRMS (ESI-TOF) *m/z*: calc'd for $C_{11}H_{13}Cl_2NONa$ $[M+Na]^+$ 207.0189, found 207.0185
IR (film) cm^{-1}: 3001, 2939, 2835, 1664, 1591, 1398, 1217, 1180, 1142, 1022, 814, 580
Spectral data consistent with literature[23]



11

1-(5-chloroindolin-1-yl)-2,2-dimethylpropan-1-one (11). Prepared according to GP2. Indoline **S5** (81.3 mg, 0.4 mmol) was reacted with iodobenzene diacetate (155 mg, 0.48 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 2 hours. The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **11** (80.6 mg, 85%) as a colorless oil.
R$_f$: 0.11 (5% ethyl acetate/hexanes).
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.18 – 8.12 (m, 1H), 7.16 – 7.11 (m, 2H), 4.23 (d, *J* = 8.2 Hz, 2H), 3.11 (t, *J* = 8.2 Hz, 2H), 1.36 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.7, 143.5, 132.8, 128.5, 127.3, 124.5, 119.3, 49.7, 40.3, 29.2, 27.8
HRMS (ESI-TOF) *m/z*: calc'd for $C_{13}H_{16}ClNONa$ $[M+Na]^+$ 260.0818, found 260.0802
IR (film) cm^{-1}: 2964, 1641, 1589, 1465, 1354, 1327, 818



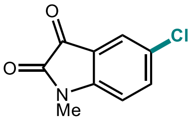
12

5-chloro-1-methylindolin-2-one (12). Prepared according to GP2. Oxindole **S6** (58.9 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (1 mL) for 45 minutes. The crude product was purified by column chromatography eluting with 15% ethyl acetate/hexanes to yield **12** (51.2 mg, 70%) as pink crystals.
R$_f$: 0.09 (15% ethyl acetate/hexanes).
mp: 99.7 – 101.1 °C
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28 – 7.24 (m, 1H), 7.23 – 7.22 (m, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 3.51 (s, 2H), 3.20 (s, 3H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 174.5, 143.9, 127.9, 127.8, 126.2, 124.9, 109.0, 35.7, 26.4

---

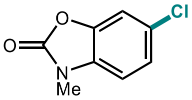
[23] Zhong, Z., Snowden, T.S., Best, M.D., and Anslyn, E.V. (2004). Rate of enolate formation is not very sensitive to the hydrogen bonding ability of donors to carboxyl oxygen lone pair acceptors; a ramification of the principle of non-perfect synchronization for general-base-catalyzed enolate formation. J. Am. Chem. Soc. *126*, 3488–3495.

HRMS (ESI-TOF) *m/z*: calc'd for $C_9H_8ClNONa$ $[M+ Na]^+$ 204.0192, found 204.0192
IR (film) cm^{-1}: 2939, 2920, 2853, 1697, 1607, 1490, 1337, 1272, 1098, 1062, 869, 815, 664, 545, 523
Spectral data consistent with literature[24]



13

5-chloro-1-methylindoline-2,3-dione (13). Prepared according to GP2. Isatin **S7** (58.7 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 4 hours. The crude product was purified by column chromatography eluting with 20% ethyl acetate/hexanes to yield **13** (48.8 mg, 63%) as orange needles.
R$_f$: 0.09 (20% ethyl acetate/hexanes)
mp: 175.1 – 176.9 °C
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.59 – 7.55 (m, 2H), 6.88 – 6.84 (m, 1H), 3.25 (s, 3H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 182.4, 157.8, 149.8, 137.9, 129.8, 125.4, 118.4, 111.3, 26.5
HRMS (ESI-TOF) *m/z*: calc'd for $C_9H_6ClNO_2Na$ $[M+ Na]^+$ 217.9985, found 217.9995
IR (film) cm^{-1}: 3048, 1723, 1604, 1444, 1326, 1174, 1107, 1068, 906, 825, 726, 598, 527
Spectral data consistent with literature[25]



14

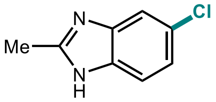
6-chloro-3-methylbenzo[d]oxazol-2(3H)-one (14). Prepared according to GP2. Benzoxindolidinone **S8** (59.7 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 4 hours. The crude product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **14** (54.5 mg, 74%) as a white powder.
R$_f$: 0.11 (10% ethyl acetate/hexanes).
mp: 105.7 – 106.7 °C
^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.22 (d, J = 1.9 Hz, 1H), 7.18 (dd, J = 8.3 Hz, 1.9 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 3.39 (s, 3H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 154.5, 143.0, 130.6, 128.1, 124.1, 111.0, 108.7, 28.4
HRMS (ESI-TOF) *m/z*: calc'd for $C_8H_6ClNO_2Na$ $[M+Na]^+$ 205.9985, found 205.9981
IR (film) cm^{-1}: 1743, 1616, 1748, 1380, 1356, 1281, 1244, 1078, 1051, 910, 823, 742, 585

---

[24] Zhang, Q.-B., Jia, W.-L., Ban, Y.-L., Zheng, Y., Liu, Q., and Wu, L.-Z. (2016). Autoxidation/aldol tandem reaction of 2-oxindoles with ketones: a green approach for the synthesis of 3-hydroxy-2-oxindoles. Chem. Eur. J. *22*, 2595–2598.

[25] Tang, B.-X., Song, R.-J., Wu, C.-Y., Liu, Y., Zhou, M.-B., Wei, W.-T., Deng, G.-B., Yin, D.-L., and Li, J.-H. (2010). Copper-catalyzed intramolecular C−H oxidation/acylation of formyl-N-arylformamides leading to indoline-2,3-diones. J. Am. Chem. Soc. *132*, 8900–8902.

Spectral data consistent with literature[26]



15

5-chloro-2-methyl-1H-benzo[d]imidazole (15): Prepared according to GP2. 2-methylbenzimidazole (50.0 mg, 0.38 mmol), and tetrabutylammonium chloride (526 mg, 1.89 mmol). After 1.5 hours, the reaction mixture was purified by chromatography eluting with 5% methanol/dichloromethane to provide the **15** (45.6 mg, 72% yield) as a white amorphous solid.

R$_f$: 0.3 (5% methanol/dichloromethane)

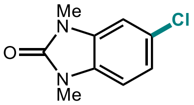
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.61 (s, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.20 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.63 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ 152.2, 128.2, 123.1, 115.4, 114.7, 15.1

HRMS (ESI-TOF) *m/z*: calc'd for $C_8H_7ClN_2$ $[M+H]^+$ m/z 167.0371, found 167.0369

IR (film) cm^{-1}: 3315, 1647, 1506, 811

Spectral data consistent with literature[27]



16

5-chloro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (16). Prepared according to GP2. Benzoxindolidinone **S9** (64.9 mg, 0.4 mmol) was reacted with iodobenzene diacetate (142 mg, 0.44 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 1 hour to give 81% of **16** (by crude ^{1}H NMR). An analytical sample was purified by preparatory thin layer chromatography eluting with 2% methanol/dichloromethane to yield **16** as a white solid.

R$_f$: 0.16 (2% methanol/dichloromethane)

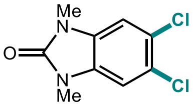
mp: 160.8 – 162.5°C

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.07 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 3.41 (s, 3H), 3.40 (s, 3H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 154.8, 131.1, 128.8, 127.0, 121.2, 108.1, 108.0, 27.4

HRMS (ESI-TOF) *m/z*: calc'd for $C_9H_9ClN_2NaO$ $[M+Na]^+$ 219.0301, found 219.0305

IR (film) cm^{-1}: 1703, 1655, 1446, 1394, 1342, 1228, 912, 744



17

5,6-dichloro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (17). Prepared according to GP2. Benzoxindolidinone **S9** (64.9 mg, 0.4 mmol) was reacted with iodobenzene diacetate (322

---

[26] Gershon, H., Clarke, D.D., and Gershon, M. (1993). Reexamination of the thermolytic rearrangement of 4-halophenyl azides to 2-aminophenols and other products. Monatshefte fur Chemie *124*, 367–379. (DMSO-d_6)

[27] Cai, H., Liu, Q., Gao, D., Wang, T., Chen, T., Yan, G., Chen, K., Xu, Y., Wang, H., Li, Y., and Zhu, W. (2015). Novel fatty acid binding protein 4 (FABP4) inhibitors: virtual screening, synthesis and crystal structure determination. Eur. J. Med. Chem. *90*, 241–250.

mg, 1 mmol) and 1 M HCl (4 mL, 4 mmol) in dichloroethane (2 mL) for 2 hours. The crude product was purified by column chromatography eluting with 1% methanol/dichloromethane to yield **17** (70.0 mg, 70%) as white needles.

R$_f$: 0.24 (1% methanol/dichloromethane)

mp: 233.1 – 236.0 °C

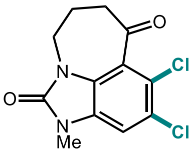
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.00 (s, 2H), 3.37 (s, 6H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 154.8, 129.7, 125.0, 109.0, 27.5

HRMS (ESI-TOF) *m/z*: calc'd for $C_9H_8Cl_2N_2ONa$ $[M+Na]^+$ 252.9911, found 252.9904

IR (film) cm^{-1}: 1716, 1679, 1621, 1484, 1463, 1431, 1378, 1258, 1023, 927, 747, 579

Spectral data consistent with literature[28]



18

4,5-dichloro-2-methyl-8,9-dihydro-2,9a-diazabenzo[cd]azulene-1,6(2H,7H)-dione (18). Prepared according to GP2, Benzoxindolidinone **S10** (43.2 mg, 0.2 mmol) was reacted with iodobenzene diacetate (161 mg, 0.5 mmol) and 1 M HCl (4 mL, 4 mmol) in dichloroethane (2 mL) for 2 hours. The crude product was purified by column chromatography eluting with 1% methanol/dichloromethane to yield **18** (48.0 mg, 84%) as a white powder.

R$_f$: 0.5 (5% methanol/dichloromethane)

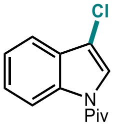
mp: 202.7 – 205.1°C

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.13 (s, 1H), 4.06 – 4.00 (m, 2H), 3.41 (s, 3H), 3.07 (t, *J* = 6.8 Hz, 2H), 2.24 – 2.34 (m, 2H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 154.2, 129.9, 128.2, 127.5, 123.2, 121.7, 110.9, 45.5, 27.6, 23.8

HRMS (ESI-TOF) *m/z*: calc'd for $C_{24}H_{20}Cl_4N_4NaO_4$ $[2M+Na]^+$ 593.0107, found 593.0119

IR (film) cm^{-1}: 2918, 1712, 1672, 1620, 1485, 1431, 1379, 1155, 1022, 924, 847, 739, 673



19

1-(3-chloro-1H-indol-1-yl)-2,2-dimethylpropan-1-one (19). Prepared according to GP2. Indole **S11** (80.5 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1M HCl (2 mL, 2.0 mmol) for 55 minutes. The reaction mixture was purified by column chromatography with 5% ethyl acetate/hexanes to yield **19** (66.7 mg, 71%) as a clear oil.

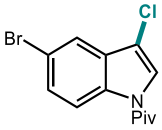
R$_f$: 0.65 (5% ethyl acetate/hexanes)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.52 (s, 9H), 7.38 – 7.33 (m, 1H), 7.44 – 7.39 (m, 1H), 7.59 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.73 (s, 1H), 8.52 (d, *J* = 8.4 Hz, 1H).

---

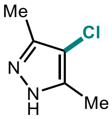
[28] Kamplain, J.W., Lynch, V.M., and Bielawski, C.W. (2007). Synthesis and study of differentially substituted dibenzotetraazafulvalenes. Org. Lett. *9*, 5401–5404. (DMSO-d$_6$)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 28.8, 41.4, 113.3, 117.6, 118.3, 122.1, 124.2, 126.6, 127.2, 136.1, 176.6
HRMS (ESI-TOF) *m/z*: calc'd for $C_{13}H_{15}ClNO$ $[M+H]^+$ 236.0842, found 236.0841
IR (film) cm^{-1}: 3167, 2985, 2935, 1689, 1446, 1306, 1178, 1151, 985, 895, 746
Spectral data consistent with literature[29]



20

1-(5-bromo-3-chloro-1H-indol-1-yl)-2,2-dimethylpropan-1-one (20). Prepared according to GP2. Indole **S12** (62.9 mg, 0.2 mmol) was reacted with iodobenzene diacetate (77.0 mg, 0.24 mmol) for 1 hour. The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **20** (55.8 mg, 87%) as white needles.
R$_f$: 0.42 (5% ethyl acetate/hexanes).
mp: 170.1 – 171.0 °C
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.38 (d, *J* = 8.9 Hz, 1H), 7.73 (s, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.9, 2.0 Hz, 1H), 1.51 (s, 9H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.4, 134.7, 129.4, 128.9, 123.1, 121.0, 119.1, 117.6, 112.2, 41.4, 28.7
HRMS (ESI-TOF) *m/z*: calc'd for $C_{13}H_{13}BrClNONa$ $[M+Na]^+$ 335.9767, found 335.9758
IR (film) cm^{-1}: 3178, 2993, 2976, 2931, 1697, 1441, 1300, 1174, 987, 901, 781, 600

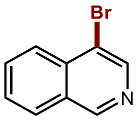


21

4-chloro-3,5-dimethyl-1H-pyrazole (21). Prepared according to GP3. 3,5-Dimethylpyrazole (50.0 mg, 0.52 mmol) was reacted with tetrabutylammonium chloride (723 mg, 2.6 mmol), and iodobenzene diacetate (503 mg, 1.56 mmol) for 2 hours. The crude product was purified by column chromatography eluting with 50% ethyl acetate/hexanes to yield **21** (46.5 mg, 69%) as a white solid.
R$_f$: 0.9 (2% methanol/dichloromethane)
mp: 88.2 – 90.0 °C
^{1}H NMR (600 MHz, CDCl$_3$): δ = 9.45 (s, 1H), 2.22 – 2.67 (m, 6H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 141.2, 108.1, 10.5
HRMS (ESI-TOF) *m/z*: calc'd for $C_5H_8ClN_2$ $[M+H]^+$131.0376, found 131.0376
IR (film) cm^{-1}: 3201, 3122, 3059, 1654, 1597, 1479, 1122, 1041, 912, 829, 742
Spectral data consistent with literature[30]

---

[29] Wang, M., Zhang, Y., Wang, T., Wang, C., Xue, D., and Xiao, J. (2016). Story of an age-old reagent: an electrophilic chlorination of arenes and heterocycles by 1-chloro-1,2-benziodoxol-3-one. Org. Lett. *18*, 1976–1979.
[30] Stefani, H.A., Pereira, C.M.P., Almeida, R.B., Braga, R.C., Guzen, K.P., and Cella, R. (2005). A mild and efficient method for halogenation of 3,5-dimethyl pyrazoles by ultrasound irradiation using N-halosuccinimides. Tetrahedron Lett. *46*, 6833–6837.



22

4-bromoisoquinoline (22): Prepared according to GP3. Isoquinoline (51.7 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and dried fine KBr powder (238 mg, 2 mmol). After 14 hours, the reaction mixture was purified by column chromatography eluting with 0.5% methanol/dichloromethane to yield **22** (58.3 mg, 70% yield) as a brown oil.

R$_f$: 0.2 (0.25% methanol/dichloromethane)

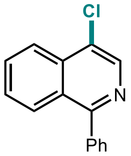
^{1}H NMR (600 MHz, CDCl$_3$): δ 9.18 (s, 1H), 8.72 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.84 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.65 – 7.74 (m, 1H)

^{13}C NMR (151 MHz, CDCl$_3$): δ 151.7, 144.4, 135.1, 132.0, 129.9, 128.1, 128.5, 126.1, 119.9

HRMS (ESI-TOF) *m/z*: calc'd for C_9H_6BrN $[M+H]^+$ 207.9756, found 207.9747

IR (film) cm^{-1}: 1375, 1215, 958, 772

Spectral data consistent with literature[20]



23

4-chloro-1-phenylisoquinoline (23). Prepared according to GP3 with modifications, **S14** (82.1 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and pentafluorobenzoyl chloride (288 µL, 2 mmol) in dichloroethane (1 mL) at 70 °C for 12 hours. The solution was stirred with saturated sodium bicarbonate for 1 hour and extracted with dichloromethane and concentrated. The product was purified by column chromatography eluting with 3% ethyl acetate/hexanes to yield **23** (56.4 mg, 59%) as a white solid.

R$_f$: 0.15 (3% ethyl acetate/hexanes)

mp: 124.3 – 126.2 °C

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.67 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.84 – 7.79 (m, 1H), 7.69 – 7.65 (m, 2H), 7.63 – 7.58 (m, 1H), 7.57 – 7.50 (m, 3H)

^{13}C NMR (151 MHz, CDCl$_3$): δ =159.8, 141.2, 139.1, 134.4, 131.1, 130.1, 130.0, 128.6, 128.2, 128.0, 127.7, 127.5, 123.8

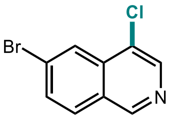
HRMS (ESI-TOF) *m/z*: calc'd for $C_{15}H_{10}ClNNa$ $[M+Na]^+$ 240.0589 found, 240.0587

IR (film) cm^{-1}: 3356, 3300, 2974, 2935, 1651, 1491, 1419, 1207, 1130, 943, 876, 814, 602

Spectral data consistent with literature[31]

---

[31] Kalyani, D., Dick, A.R., Anani, W.Q., and Sanford, M.S. (2006). Scope and selectivity in palladium-catalyzed directed C–H bond halogenation reactions. Tetrahedron *62*, 11483–11498.



24

6-bromo-4-chloroisoquinoline (24). Prepared according to GP3. 6-bromo-4-chloroisoquinoline (21.0 mg, 0.1 mmol) was reacted with iodobenzene diacetate (97.0 mg, 0.3 mmol) and acetyl chloride (71 µL, 1 mmol) in dichloroethane (1 mL) at 50 °C for 13 hours. The product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **24** (16.2 mg, 67%) as a white solid.

R$_f$: 0.12 (10% ethyl acetate/hexanes)

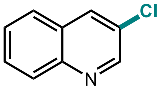
mp: 117.8 – 120.6 °C

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.13 (s, 1H), 8.62 (s, 1H), 8.42 – 8.37(m, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.78 (dd, *J* = 8.7, 1.8 Hz, 1H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 151.0, 142.9, 134.7, 126.0, 132.1, 129.5, 127.9, 127.4, 12.9

HRMS (ESI-TOF) *m/z*: calc'd for C_9H_6BrClN $[M+H]^+$ 241.9372, found 241.9365

IR (film) cm^{-1}: 1608, 1342, 1227, 1065, 983, 912, 746



25

3-chloroquinoline (25): Prepared according to GP3. Quinoline (47 µL, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and pentafluorobenzoyl chloride (288 µL, 2.0 mmol) in anhydrous dichloroethane (0.5 ml, 0.8 M) for 17 hours. The reaction mixture was quenched with saturated sodium bicarbonate and extracted using dichloromethane. The organic layer was further washed with 1M sodium hydroxide followed by saturated sodium thiosulfate, then concentrated. The crude mixture was purified by column chromatography eluting with 100% dichloromethane to yield **25** (41.2 mg, 63% yield) as a clear oil.

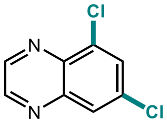
R$_f$: 0.3 (100% dichloromethane)

^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.83 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 8.10 (dd, *J* = 8.5, 0.4 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 149.8, 146.9, 146.4, 134.1, 129.8, 129.6, 128.6, 127.9, 127.2

HRMS (ESI-TOF) *m/z*: calc'd for C_9H_7ClN $[M+H]^+$ 164.0267, found 164.0265

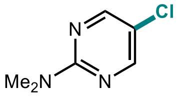
IR (film) cm^{-1}: 2919, 2850, 2359, 953, 751



26

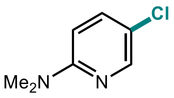
5,7-dichloroquinoxaline (26). Prepared according to GP3. Quinoxaline (52.1 mg, 0.4 mmol) was reacted with iodobenzene diacetate (322 mg, 1 mmol) and pentafluorobenzoyl chloride (288 µL, 2.0 mmol) for 4 hours. The crude product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **26** (38.8 mg, 49%) as a white solid

R$_f$: 0.18 (10% ethyl acetate/hexanes)
mp: 148.2 – 150.1°C
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.95 (d, *J* = 1.8 Hz, 1H), 8.92 (d, *J* = 1.8 Hz, 1H), 8.07 (d, *J* = 2.2 Hz, 1H), 7.89 (d, *J* = 2.2 Hz, 1H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 146.6, 145.3, 144.1, 138.7, 135.7, 134.5, 131.1, 127.8
HRMS (ESI-TOF) *m/z*: calc'd for $C_8H_5Cl_2N_2$ [M+H]$^+$ 198.9830, found 198.9835
IR (film) cm^{-1}: 1655, 1030, 984, 912, 885, 746



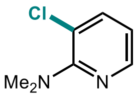
27

5-chloro-N,N-dimethylpyrimidin-2-amine (27). Prepared according to GP3. N,N-dimethylpyrimidin-2-amine **S15** (49.3 uL, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and acetyl chloride (2 mmol) for 1.5 hours. The crude product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield to yield **27** (35.8 mg, 57%) as a yellow oil.
R$_f$: 0.25 (5% ethyl acetate/hexanes)
H NMR (400 MHz, CDCl$_3$): δ = 8.21 (s, 2H), 3.15 (s, 6H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 160.7, 155.8, 117.7, 37.5
HRMS (ESI-TOF) *m/z*: calc'd for $C_6H_9ClN_3$ [M+H]$^+$ 158.0485 found 158.0500
IR (film) cm^{-1}: 2252, 1587, 1531, 1412, 1377
Spectral data consistent with literature[32]



_p_-28

+



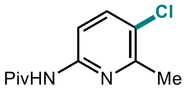
_o_-28

Prepared according to GP3. N,N-dimethylpyridin-2-amine (50 µL, 0.4 mmol) was reacted with iodobenzene diacetate (116 mg, 0.9 mmol) and pentafluorobenzoyl chloride (144 µL, 2 mmol) for 1 hour. The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **28** (59%, 3.2:1 *para:ortho* by ^{1}H NMR using mesitylene as an internal standard) as a colorless oil.
5-chloro-N,N-dimethylpyridin-2-amine (_p_-28).
R$_f$: 0.19 (5% ethyl acetate/hexanes)
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.08 (d, *J* = 2.7 Hz, 1H), 7.37 (dd, *J* = 9.1, 2.7 Hz, 1H), 6.43 (d, *J* = 9.1 Hz, 1H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 157.8, 146.3, 136.9, 118.7, 106.6, 38.4
HRMS (ESI-TOF) *m/z*: calc'd for $C_7H_{10}ClN_2$ [M+H]$^+$ 157.0533, found 157.0552
IR (film) cm^{-1}: 1706, 1657, 1595, 1496, 1442, 1390, 912, 742
3-chloro-N,N-dimethylpyridin-2-amine (_o_-28).

---

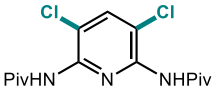
[32] Gupton, J.T., Wysong, E., Norman, B., Hertel, G., and Idoux, J.P. (1985). The reaction of activated aryl and heteroaryl dihalides with HMPA. A regioselectivity study. Synthetic Communications *15*, 43–52.

R$_f$: 0.19 (5% ethyl acetate/hexanes)
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.14 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.75 (dd, *J* = 7.7, 4.8 Hz, 1H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 159.23, 145.56, 138.95, 121.26, 116.82, 41.55
HRMS (ESI-TOF) *m/z*: calc'd for $C_7H_{10}ClN_2$ $[M+H]^+$ 157.0533, found 157.0552



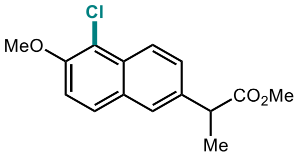
29

N-(5-chloro-6-methylpyridin-2-yl)pivalamide (29). Prepared according to GP3. N-(6-methylpyridin-2-yl)pivalamide **S16** (38.0 mg, 0.2 mmol) was reacted with iodobenzene diacetate (96.6 mg, 0.3 mmol) and pentafluorobenzoyl chloride (144 µL, 1 mmol) for 12 hours. The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **29** (33.2 mg, 74%) as a yellow oil.
R$_f$: 0.08 (5% ethyl acetate/hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.05 (dd, *J* = 8.7, 0.4 Hz, 1H), 7.94 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 2.51 (s, 3H), 1.32 (s, 9H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 177.1, 154.1, 149.3, 138.7, 125.8, 112.4, 40.0, 27.6, 22.2
HRMS (ESI-TOF) *m/z*: calc'd for $C_{11}H_{16}ClN_2O$ $[M+H]^+$ 227.0951, found 227.0948
IR (film) cm^{-1}: 2962, 2871, 1685, 1504, 1429, 1358, 1300, 1132, 1047, 833



30

N,N'-(3,5-dichloropyridine-2,6-diyl)bis(2,2-dimethylpropanamide) (30). Prepared according to GP3, N,N'-(pyridine-2,6-diyl)bis(2,2-dimethylpropanamide) **S17** (111 mg, 0.4 mmol) was reacted with iodobenzene diacetate (322 mg, 1 mmol) and acetyl chloride (285 µL, 4 mmol) in dichloroethane (2 mL) for 12 hours. The crude product was purified by column chromatography eluting with 2% methanol/dichloromethane to yield **30** (84.5 mg, 62%) as a white solid.
R$_f$: 0.21 (2% methanol/dichloromethane).
mp: >250 °C
^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.96 (s, 2H), 7.77 (s, 1H), 1.32 (s, 18H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 176.1, 145.1, 139.7, 120.6, 40.1, 27.6
HRMS (ESI-TOF) *m/z*: calc'd for $C_{15}H_{21}Cl_2N_3O_2Na$ $[M+Na]^+$ 368.0909, found 368.0892
IR (film) cm^{-1}: 3222, 2968, 1674, 1510, 1421, 1369, 1174, 943



31

methyl 2-(5-chloro-6-methoxynaphthalen-2-yl)propanoate (31). Naproxen methyl ester **S18** (36.6 mg, 0.15 mmol) was reacted with iodobenzene diacetate (74 mg, 0.23 mmol) and 1M hydrochloric acid (750 µL, 0.75 mmol) in dichloroethane (1 mL) for 1.5 hours. The crude product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **31** (30.7 mg, 73%) as a white solid

R$_f$: 0.14 (5% ethyl acetate/hexanes)

mp: 106.3 – 108.0 °C

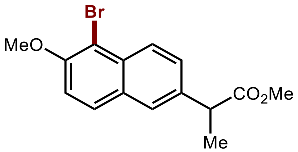
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.18 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.53 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 4.03 (s, 3H), 3.88 (q, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 175.0, 152.8, 136.7, 131.3, 129.7, 128.0, 127.6, 126.3, 124.2, 117.1, 114.3, 57.2, 52.2, 45.4, 18.6

HRMS (ESI-TOF) *m/z*: calc'd for $C_{15}H_{15}ClO_3Na$ $[M+Na]^+$ 301.0607, found 301.0592

IR (film) cm^{-1}: 2976, 2954,1736, 1599, 1331, 1273, 1151, 1066, 881, 798, 526

^{1}H NMR Spectral data consistent with literature[33]



32

methyl 2-(5-chloro-6-methoxynaphthalen-2-yl)propanoate (32). Naproxen methyl ester **S18** (36.6 mg, 0.15 mmol) was reacted with iodobenzene diacetate (74.1 mg, 0.23 mmol) and 48% hydrobromic acid (102 µL, 0.75 mmol) in dichloroethane (1 mL) for 1.5 hours. The crude product was purified by column chromatography eluting with 10% ethyl acetate/hexanes to yield **32** (32.8 mg, 68%) as a white solid.

R$_f$: 0.06 (5% ethyl acetate/hexanes)

mp: 92.7 – 94.3°C

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.18 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 4.03 (s, 3H), 3.87 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 1H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 175.0, 153.9, 136.7, 132.5, 130.0, 129.0, 127.8, 126.9, 126.3, 114.1, 108.7, 57.2, 52.3, 45.3, 18.6

HRMS (ESI-TOF) *m/z*: calc'd for $C_{15}H_{15}BrNaO_3$ $[M+Na]^+$ 345.0102, found 345.0072

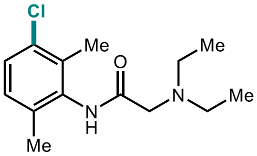
IR (film) cm^{-1}: 904, 727, 650

Spectral data consistent with literature[34]

---

[33] Belmadoui, N., Climent, M.J., and Miranda, M.A. (2006). Photochemistry of a naphthalene–thymine dyad in the presence of acetone. Tetrahedron *62*, 1372–1377.

[34] Koul, S., Koul, J.L., Singh, B., Kapoor, M., Parshad, R., Manhas, K.S., Taneja, S.C., and Qazi, G.N. (2005). Trichosporon beigelli esterase (TBE): a versatile esterase for the resolution of economically important racemates. Tetrahedron: Asymmetry *16*, 2575–2591.



33

N-(3-chloro-2,6-dimethylphenyl)-2-(diethylamino)acetamide (33). Prepared according to GP2. Lidocaine (27.1 mg, 0.1 mmol) was reacted with iodobenzene diacetate (48.3 mg, 0.15 mmol) and 1M hydrochloric acid (500 µL, 0.5 mmol) in dichloroethane (1 mL) for 2 hours. The reaction was allowed to cool to room temperature then diluted with 1M hydrochloric acid (10 mL). The aqueous layer was basified with 10% NaOH and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered, and concentrated. Crude product was purified by column chromatography on grade I basic alumina eluting with 10% ethyl acetate/hexanes to yield **33** (16.0 mg, 60%) as a white solid.

R$_f$: 0.34 (2% methanol/dichloromethane)

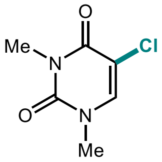
mp: 51.1 – 53.6 °C

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.98 (s, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 3.23 (s, 2H), 2.70 (q, J = 7.1 Hz, 4H), 2.27 (s, 3H), 2.20 (s, 3H), 1.14 (t, J = 7.1 Hz, 6H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 170.5, 135.3, 134.0, 133.6, 132.6, 128.6, 128.0, 57.6, 49.1, 18.6, 15.9, 12.8

HRMS (ESI-TOF) *m/z*: calc'd for $C_{14}H_{21}ClN_2O$ $[M+H]^+$ 269.1421, found 269.1402

IR (film) cm^{-1}: 3240, 2964, 2927, 2804, 160, 1493, 1448, 1207, 1011, 818



34

5-chloro-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (34). Prepared according to GP2. 1,3-dimethyluracil (56.1 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 2M HCl in diethyl ether (1.0 ml, 2.0 mmol) for 40 minutes. The reaction mixture was purified by chromatography eluting with 1% methanol/dichloromethane to yield **34** (59.8 mg, 86%) as a white amorphous solid.

R$_f$: 0.3 (2% methanol/dichloromethane)

mp: 142 ºC

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.42 (s, 1H), 3.41 (s, 3H), 3.38 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 159.6, 151.0, 140.0, 108.1, 37.4, 29.1

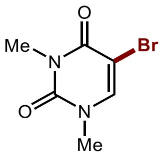
HRMS (ESI-TOF) *m/z*: calc'd for $C_6H_7ClN_2O_2Na$ $[M+Na]^+$ 197.0088, found 197.0077

IR (film) cm^{-1}: 1717, 1661, 1445, 1340, 757

Spectral data consistent with literature[35]

---

[35] Asakura, J., and Robins, M.J. (1990). Cerium(IV)-mediated halogenation at C-5 of uracil derivatives. J. Org. Chem. *55*, 4928–4933.



35

5-chloro-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (35). Prepared according to GP2. 1,3-dimethyluracil (29.2 mg, 0.21 mmol) was reacted with iodobenzene diacetate (74.1 mg, 0.23 mmol) and 48% hydrobromic acid (2.2 mL) for 1.5 hours. The reaction mixture was purified by column chromatography eluting with 100% ethyl acetate to yield **35** (32.6 mg 71%) as a white solid.

R$_f$: 0.62 (100% ethyl acetate)

mp: 183.4 – 184.8 °C

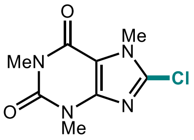
^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.53 (s, 1H), 3.42 (s, 3H), 3.40 (s, 3H)

^{13}C NMR (151 MHz, CDCl$_3$): δ = 159.6, 151.2, 142.5, 95.9, 37.4, 29.3

HRMS (ESI-TOF) *m/z*: calc'd for $C_6H_7BrN_2O_2Na$ $[M+Na]^+$ 240.9589, found 240.9585

IR (film) cm^{-1}: 2252, 1712, 1655, 1448, 1333, 1331, 1227, 912, 742, 650

^{13}C NMR Spectral data consistent with literature[36]



36

8-chloro-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (36). Prepared according to GP3. Caffeine (77.7 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and pentafluorobenzoyl chloride (288 µL, 2.0 mmol) for 4 hours. The reaction mixture was quenched with saturated sodium bicarbonate and extracted using dichloromethane. The organic layer was further washed with 1M sodium hydroxide followed by saturated sodium thiosulfate, then concentrated. The reaction mixture was purified by column chromatography eluting with 1% methanol/dichloromethane to yield **36** (60.1 g, 65%) as a white solid.

R$_f$: 0.5 (3% methanol/dichloromethane)

mp: 188 ºC

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.95 (s, 3H), 3.55 (s, 3H), 3.40 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 154.7, 151.4, 147.3, 139.1, 108.4, 32.8, 29.9, 28.1

HRMS (ESI-TOF) *m/z*: calc'd for $C_8H_9ClN_4O_2$ $[M+H]^+$ m/z 229.0487, found 229.0474.

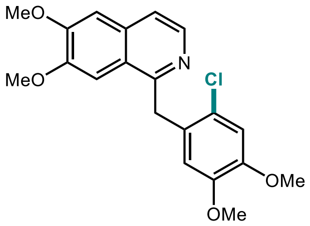
IR (film) cm^{-1}: 1707, 1664, 1369, 755

Spectral data consistent with literature[37]

---

[36] Celewicz, L., and Koroniak, H. (1985). The synthesis of 5-bromo-1,3-dimethyluracil and its 6-alkyl derivatives. Synthetic Communications *15*, 1001–1005.

[37] Maddox, S.M., Nalbandian, C.J., Smith, D.E., and Gustafson, J.L. (2015). A practical lewis base catalyzed electrophilic chlorination of arenes and heterocycles. Org. Lett. *17*, 1042–1045.



37

1-(2-chloro-4,5-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (37): Prepared according to GP2 using HCl (67.9 mg, 2 mmol). After 4 hours, the reaction mixture was purified by column chromatography eluting with 1% methanol/dichloromethane to yield **37** (70.4 g, 94% yield) as an off-white foamy solid.

R$_f$: 0.5 (1% methanol/dichloromethane)

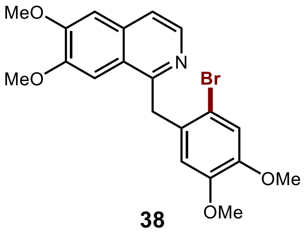
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.36 (d, J = 5.7 Hz, 1H), 7.43 (d, J = 5.7 Hz, 1H), 7.36 (s, 1H), 7.03 (s, 1H), 6.87 (s, 1H), 6.69 (s, 1H), 4.63 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.82 (s, 3H), 3.61 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.5, 152.8, 150.2, 148.3, 148.2, 140.7, 133.5, 129.0, 123.9, 123.0, 119.0, 113.0, 112.2, 105.3, 104.2, 56.3, 56.2, 56.1, 56.0, 38.5, 29.8

HRMS (ESI-TOF) *m/z*: calc'd for $C_{20}H_{20}ClNO_4$ $[M+H]^+$ 374.1154, found 374.1129

IR (film) cm^{-1}: 2360, 1508, 1272, 1235, 1160, 858

Spectral data consistent with literature[38]



38

1-(2-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (38): Prepared according to GP2 using 48.8% aqueous HBr (111 µL, 2 mmol). After 2.5 hours, the reaction mixture was purified by column chromatography eluting with 1.5% methanol/dichloromethane to yield **38** (82.8 g, 99%) as a foamy brown solid.

R$_f$: 0.5 (100% dichloromethane)

^{1}H NMR (600 MHz, CDCl$_3$): δ 8.37 (d, J = 5.6 Hz, 1H), 7.43 (d, J = 5.6 Hz, 1H), 7.33 (s, 1H), 7.04 (d, J = 1.1 Hz, 2H), 6.66 (s, 1H), 4.64 (s, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 3.83 (s, 3H), 3.59 (s, 3H)

^{13}C NMR (151 MHz, CDCl$_3$): δ 157.6, 152.8, 150.3, 148.8, 148.5, 141.0, 133.5, 131.2, 123.2, 119.0, 115.3, 113.8, 113.2, 105.4, 104.5, 56.5, 56.3, 56.1, 56.0, 41.6

HRMS (ESI-TOF) *m/z*: calc'd for $C_{20}H_{20}BrNO_4$ $[M+H]^+$ 418.0648, found 418.0627

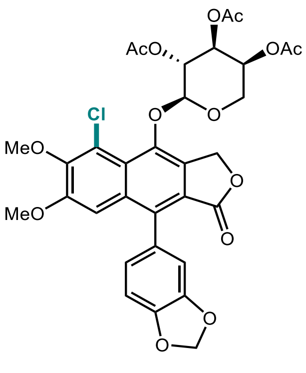
IR (film) cm^{-1}: 1508, 1235, 1159, 1030, 857, 731

Spectral data consistent with literature[39]

---

[38] Rodriguez, R.A., Pan, C.-M., Yabe, Y., Kawamata, Y., Eastgate, M.D., and Baran, P.S. (2014). Palau'chlor: a practical and reactive chlorinating reagent. J. Am. Chem. Soc. *136*, 6908–6911. (TFA salt)

[39] Martinez, E., Martinez, L., Treus, M., Estevez, J.C., Estevez, R.J., and Castedo, L. (2000). From phenylacetylphenylacetic acids and 1-benzylisoquinolines to 6,11-dihydrobenzo[b]naphtho[2,3-d]furan-6,11-diones,



39

6-Chloro-2”-acetyl phyllanthusmin D (39). Synthesis of **39** began from a known natural product derivative 2”-acetyl phyllanthusmin D[40] prepared according to literature procedures.[41-42] To an 8 mL dram vial was added iodobenzene diacetate (96.6 mg, 0.3 mmol), 2”-acetyl phyllanthusmin D (65.6 mg, 0.1 mmol), dichloroethane (1 mL), and tetrabutylammonium chloride (139.0 mg, 0.5 mmol). The solution was allowed to stir at 1000 rpm at room temperature for 48 hours. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. The crude mixture was purified by column chromatography eluting with 10% acetonitrile in toluene, followed by 20% acetone in hexanes to yield **39** (30.1 mg, 45%) as a white solid.

R$_f$: 0.3 **(**10% acetonitrile/90% toluene)

^{1}H NMR (700 MHz, CDCl$_3$): δ = 7.13 (d, *J* = 0.9 Hz, 1H), 6.96 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.81 – 6.74 (m, 2H), 6.11 – 6.05 (m, 2H), 5.62 (dd, *J* = 9.9, 7.3 Hz, 1H), 5.53 (dd, *J* = 14.9, 4.2 Hz, 1H), 5.45 (dd, *J* = 14.9, 2.6 Hz, 1H), 5.30 (d, *J* = 0.9 Hz, 1H), 5.21 (dd, *J* = 7.3, 2.3 Hz, 1H), 5.16 (dd, *J* = 9.8, 3.4 Hz, 1H), 4.00 – 3.98 (m, 1H), 3.98 (s, 3H), 3.77 (d, *J* = 0.6 Hz, 3H), 3.54 (d, *J* = 13.4 Hz, 1H), 2.22 (s, 3H), 2.14 (d, *J* = 0.5 Hz, 3H), 2.07 (s, 3H)

Doubling and splitting of specific peaks has been previously and independently reported in structurally similar compounds by the Charlton[42] and Kinghorn[41] groups. This effect is attributed to the hindered rotation about the C1’-C7’ bond. In the characterization data below major peaks are listed (with all signals observed in parentheses).

^{13}C NMR (176 MHz, CDCl$_3$): δ =170.4, 170.3, 169.7 (169.64, 169.65), 169.3, 152.5, 149.3, 147.9, 147.8, 143.6 (143.56, 143.57), 137.1, 134.7 (134.61, 134.68), 134.1, 128.1, 124.1, 123.8, 123.6, 122.00, 121.95, 121.4, 110.8 (110.75, 110.76), 110.6 (110.56, 110.58), 108.5, 107.3 (107.24, 107.25, 107.26), 102.2 (102.14, 102.15), 101.5, 70.4, 69.7, 68.1 (68.12, 68.14), 67.8, 64.5, 60.9, 55.9 (55.93, 55.95), 31.7, 29.9, 21.1 (21.08, 21.09, 21.11, 21.13), 20.8 (20.81, 20.82)

HRMS (ESI-TOF) *m/z*: calc’d for C$_{32}$H$_{29}$ClNaO$_{14}$ [M+Na]$^+$ 695.11380 found 695.11267

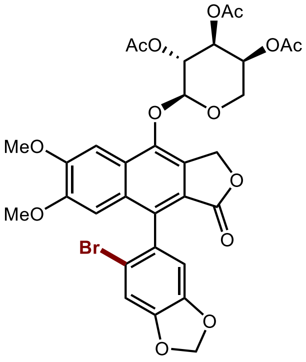
6H-dibenzo[c,h]chroman-6-ones and 7,12-dihydro-5H-dibenzo[c,g]chroman-5,7,12-triones via 2-phenyl-3-hydroxy-1,4-dihydro-1,4-naphthalenediones or 2-phenyl-1-naphthols. Tetrahedron *56*, 6023–6030.

[40] Ren, Y., Lantvit, D.D., Deng, Y., Kanagasabai, R., Gallucci, J.C., Ninh, T.N., Chai, H.-B., Soejarto, D.D., Fuchs, J.R., Yalowich, J.C., Yu, J., Swanson, S.M., and Kinghorn, A.D. (2014). Potent cytotoxic arylnaphthalene lignan lactones from Phyllanthus poilanei. J. Nat. Prod. 77, 1494–1504.

[41] Charlton, J.L., Oleschuk, C.J., and Chee, G-L. (1996). Hindered rotation in arylnaphthalene lignans. J. Org. Chem. *61*, 3452–3457.

[42] Woodard, J.L., Huntsman, A.C., Patel, P.A., Chai, H.B., Kanagasabai, R., Karmahapatra, S., Young, A.N., Ren, Y., Cole, M.S., Herrera, D., Yalowich, J.C., Kinghorn, A.D., Burdette, J.E., and Fuchs, J.R. (2018). Synthesis and antiproliferative activity of derivatives of the phyllanthusmin class of arylnaphthalene lignan lactones. Bioorganic Med. Chem. *26*, 2354–2364.

IR (film) cm^{-1}: 2921, 2850, 1749, 1488, 1457, 1417, 1224, 1068, 1037



40

6’-Bromo-2”-acetyl phyllanthusmin D (40). Synthesis of **40** began from a known natural product derivative 2”-acetyl phyllanthusmin D[41] prepared according to literature procedures.[42-43] To an 8 mL dram vial was added iodobenzene diacetate (24.2 mg, 0.075 mmol), 2”-acetyl phyllanthusmin D (34.5 mg, 0.05 mmol), dichloroethane (1 mL), and lithium bromide (23.5 mg, 0.27 mmol). The solution was allowed to stir at 1000 rpm at room temperature for 1 hour. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. The crude mixture was purified by column chromatography eluting with 50% acetone in hexanes to yield **40** (35.6 mg, 99%) as an orange solid.

R$_f$: 0.5 **(**50% acetone/50% hexanes)

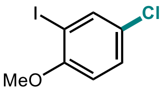
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.56 (d, *J* = 4.8 Hz, 1H), 7.20 (d, *J* = 1.7 Hz, 1H), 6.83 (s, 1H), 6.71 (d, *J* = 9.8 Hz, 1H), 6.10 (dd, *J* = 10.4, 9.2 Hz, 2H), 5.70 (dd, *J* = 9.5, 6.9 Hz, 1H), 5.47 (qd, *J* = 14.6, 7.9 Hz, 3H), 5.39 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.19 (dd, *J* = 9.5, 3.5 Hz, 1H), 5.13 (dd, *J* = 13.7, 6.9 Hz, 1H), 4.21 (dt, *J* = 13.0, 2.9 Hz, 1H), 3.82 (s, 3H), 4.09 (s, 3H), 3.75 (ddd, *J* = 13.1, 7.7, 1.7 Hz, 1H), 2.11 (s, 3H), 2.22 (d, *J* = 0.7 Hz, 3H), 2.09 (d, *J* = 1.5 Hz, 3H)

Doubling and splitting of specific peaks has been previously and independently reported in structurally similar compounds by the Charlton[42] and Kinghorn[41] groups. This effect is attributed to the hindered rotation about the C1’-C7’ bond. In the characterization data below major peaks are listed (with all signals observed in parentheses).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 170.3 (170.33, 170.34), 170.2 (170.19, 170.23), 169.7, 169.6, 169.2 (169.17, 169.20), 152.3 (152.23, 152.27), 151.0 (150.95, 150.96), 148.8 (148.75, 148.76), 147.6 (147.58, 147.62), 144.8 (144.78, 144.80), 134.5 (134.47, 134.57), 134.5 (134.47, 134.57), 130.3 (130.24, 130.32), 128.9 (128.90, 128.91), 127.1, 126.3, 126.2 (126.23, 126.25), 120.2 (120.17, 120.18), 114.8 (114.78, 114.80), 113.0 (112.94, 113.01), 111.1 (111.05, 111.16), 105.6 (105.63, 105.69), 102.2, 101.0 (100.83, 100.99, 101.21, 101.40), 77.4, 70.2 (70.17, 70.21), 69.5 (69.49, 69.54), 67.3 (67.31, 67.33, 67.36, 67.37), 64.0 (63.98, 64.10), 56.4 (56.40, 56.42), 56.1, 34.8, 34.7, 31.7, 29.2, 27.1, 25.4, 22.8, 21.1 (21.08, 21.10, 21.13), 20.8 (20.82, 20.83, 20.84)

HRMS (ESI-TOF) *m/z*: calc’d for $C_{32}H_{29}ClNaO_{14}$ $[M+Na]^+$ 717.08134 found 717.08371

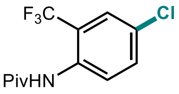
IR (film) cm^{-1}: 2922, 1749, 1506, 1488, 1475, 1433, 1217, 1031, 669



41

4-chloro-2-iodo-1-methoxybenzene. Prepared according to GP2. 2-iodoanisole (52 µL, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 1.5 eq) and 1 M HCl (2 mL, 5 equiv) in dichloroethane (2 mL) for 5 hours. Crude product was purified by column chromatography eluting with hexanes to yield **41** (79.1 mg, 74%) as colorless oil.
R$_f$: 0.32 (100% hexanes)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.75 (d, *J* = 2.5 Hz, 1H), 7.28 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H)
^{13}C NMR (101 MHz, CDCl$_3$): δ = 138.8, 129.4, 126.5, 111.5, 56.8
Spectral data consistent with literature[43]

Extra Substrates

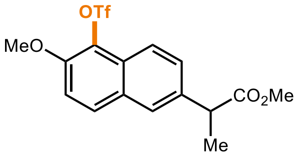


S20

N-(4-chloro-2-(trifluoromethyl)phenyl)pivalamide (S20). Prepared according to GP2. Anilide **S19** (98.1 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and 1 M HCl (2 mL, 2 mmol) in dichloroethane (2 mL) for 18 hours. Another 1.5 equivalents of iodobenzene diacetate (193 mg, 0.6 mmol) was added and allowed to stir further for 46 hours. The crude product was purified by column chromatography eluting with 5% ethyl acetate/hexanes to yield **S20** (55.5 mg, 50%) as a white solid.
R$_f$: 0.28 (5% ethyl acetate/hexanes)
mp: 92.4 – 93.0 °C
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.23 (d, *J* = 8.9 Hz, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 1.32 – 1.30 (m, 9H)
^{13}C NMR (151 MHz, CDCl$_3$): δ = 176.8, 134.5, 132.9, 129.6, 126.2 (q, $^3J_{CF}$ = 5.7 Hz), 125.6, 123.5 (q, $^1J_{CF}$ = 273.5 Hz), 121.2 (q, $^2J_{CF}$ = 30.3 Hz), 40.0, 27.4
^{19}F NMR (376 MHz, CDCl$_3$): δ = -61.33
HRMS (ESI-TOF) *m/z*: calc'd for $C_{12}H_{13}ClF_3NNaO$ $[M+Na]^+$ 302.0535, found 302.0514.
IR (film) cm^{-1}: 2974, 2931, 2875, 1658, 1491, 1456, 1317, 1273, 1157, 1113, 1055, 933, 773

---

[43] Conway, B., Crosbie, E., Kennedy, A.R., Mulvey, R.E., and Robertson, S.D. (2012). Regioselective heterohalogenation of 4-halo-anisoles via a series of sequential ortho-aluminations and electrophilic halogenations. Chem. Commun. *48*, 4674–4676.



S21

methyl 2-(5-chloro-6-methoxynaphthalen-2-yl)propanoate (S21). Under an atmosphere of nitrogen, Si(Me)$_3$OTf (42 µL, 0.23 mmol) was added dropwise to a solution of iodobenzene diacetate (74.1 mg, 0.23 mmol) in dichloromethane (1 mL). A solution of naproxen methyl ester S18 (36.6 mg, 0.15 mmol) in dichloromethane (1 mL) was added to the solution of Si(Me)$_3$OTf and iodobenzene diacetate dropwise over 5 minutes. The solution stirred at room temperature for 30 minutes. The crude product was purified by column chromatography eluting with 20% ethyl acetate/hexanes yield **S21** (17% by ^{19}F NMR using trifluorotoluene as an internal standard) as a yellow oil.

R$_f$: 0.21 (20% ethyl acetate/hexanes)

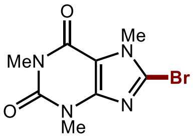
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.92 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.56 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 4.03 (s, 3H), 3.88 (q, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ = 174.8, 148.5, 137.3, 132.5, 129.4, 129.3, 128.5, 126.8, 126.3, 120.5, 120.5, 114.2, 52.3, 45.4, 29.8, 18.6

^{19}F NMR (377 MHz, CDCl$_3$): δ = -73.06

HRMS (ESI-TOF) *m/z*: calc'd for $C_{16}H_{15}F_3NaO_6S$ [M+Na]$^+$ 415.0439, found 415.0416

IR (film) cm^{-1}: 1707, 1655, 1448, 1342, 1223, 1074, 912, 742



S22

8-bromo-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (S22). Prepared according to GP3. Caffeine (77.7 mg, 0.4 mmol) was reacted with iodobenzene diacetate (193 mg, 0.6 mmol) and lithium bromide (173.7 mg, 2.0 mmol) for 3 hours. The reaction mixture was quenched with saturated sodium bicarbonate and extracted using dichloromethane. The organic layer was further washed with saturated sodium thiosulfate, then concentrated. The reaction mixture was purified by column chromatography eluting with 1% methanol/dichloromethane to yield **S22** (31.1 mg, 29%) as a white powder.

R$_f$: 0.2 (1% methanol/dichloromethane)

mp: 205.1 – 207.0 ºC

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.95 (s, 1H), 3.54 (s, 1H), 3.39 (s, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 154.6, 151.4, 148.2, 128.3, 109.5, 34.1, 30.0, 28.2

HRMS (ESI-TOF) *m/z*: calc'd for $C_8H_{10}BrN_4O_2$ [M+H]$^+$ m/z 272.9987, found 272.9984

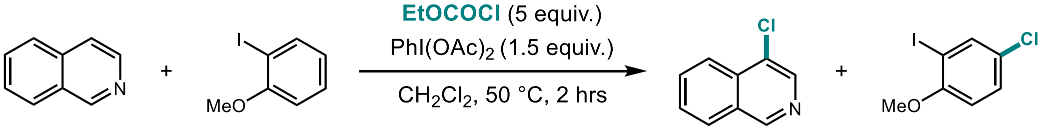
IR (film) cm^{-1}: 1707, 1664, 1454, 1457, 1353, 743

Spectral data consistent with literature[44]

---

[44] Maddox, S.M., Nalbandian, C.J., Smith, D.E., and Gustafson, J.L. (2015). A practical lewis base catalyzed electrophilic chlorination of arenes and heterocycles. Org. Lett. *17*, 1042–1045.

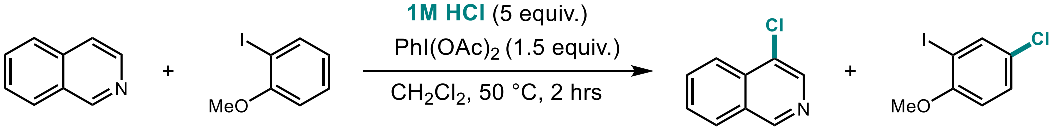
V. Competition Experiments



	% Yield	% Recovered Starting Material
4-chloroisoquinoline, **6**	63%	0%
4-chloroiodoanisole, **42**	0%	93%

Table S6: Chlorination competition experiment of isoquinoline and 2-iodoanisole using ethyl chloroformate

To an 8 mL dram vial was added iodobenzene diacetate (96.6 mg, 0.3 mmol), isoquinoline (25.8 mg, 0.2 mmol), 2-iodoanisole (46.8 mg, 0.2 mmol), dichloroethane (1 mL), and ethyl chloroformate (109 mg, 1 mmol). The solution was allowed to stir (1000 rpm) at 50 °C for 2 hours. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. Yields are based on ^{1}H NMR using isopropyl acetate as an internal standard.

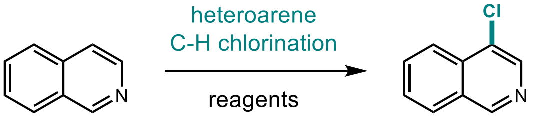


	% Yield	% Recovered Starting Material
4-chloroisoquinoline, **6**	0%	97%
4-chloroiodoanisole, **42**	65%	10%

Table S7: Chlorination competition experiment of isoquinoline and 2-iodoanisole using 1M HCl

To an 8 mL dram vial was added iodobenzene diacetate (96.6 mg, 0.3 mmol), isoquinoline (25.8 mg, 0.2 mmol), 2-iodoanisole (46.8 mg, 0.2 mmol), dichloroethane (1 mL), and 1 M hydrochloric acid (1 mL, 1 mmol). The solution was allowed to stir at 1000 rpm at 50 °C for 2 hours. After which the solution was washed with saturated sodium bicarbonate, followed by saturated sodium thiosulfate and concentrated. Yields are based on ^{1}H NMR using isopropyl acetate as an internal standard.

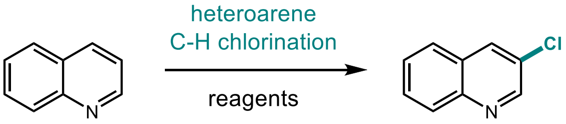
VI. Comparison of Chlorinating Reagents



6

Chlorinating Reagent	Conditions	% Yield of **6**	% Recovered Starting Material
NCS	A	0%	100%
Palau'chlor	B	0%	97%
Palau'chlor	C	0%	91%
IBA-Cl	D	0%	60%
IBA-Cl	E	0%	41%
RCl, PhI(OAc)$_2$	GP3	92%	0%

Table S8: Effect of various chlorinating reagents on functionalization of isoquinoline



25

Chlorinating Reagent	Conditions	% Yield of **25**	% Recovered Starting Material
tBuOCl	F	0%	74%
NCS	G	0%	81%
Palau'chlor	B	0%	78%
Palau'chlor	C	0%	86%
IBA-Cl	D	0%	92%
IBA-Cl	E	0%	89%
RCl, PhI(OAc)$_2$	GP3	63%	0%

Table S9: Effect of various chlorinating reagents on functionalization of quinoline

Conditions A (NCS). To a solution of isoquinoline (0.1 mmol), in acetonitrile (1 ml) was added N-chlorosuccinimide (NCS) (18.6 mg, 0.14 mmol). The solution was left to stir at room temperature for 4 hours. ^{1}H NMR analysis of reaction showed complete retention of starting material using isopropyl acetate as an internal standard.

Conditions B (Palau'chlor). To a solution of quinoline or isoquinoline (0.1 mmol), in chloroform (1 ml) was added chlorobis(methoxycarbonyl)guanidine (CBMG or Palau'chlor) (31.4 mg, 0.15 mmol). The solution was left to stir at room temperature for 12 hours. After which the reactions were concentrated and analyzed by ^{1}H NMR spectroscopy using isopropyl acetate as an internal standard.

Conditions C[45] (Palau'chlor). To a solution of quinoline or isoquinoline (0.1 mmol), in acetonitrile (1 ml) was added chlorobis(methoxycarbonyl)guanidine (CBMG or Palau'chlor) (31.4 mg, 0.15 mmol). The solution was left to stir at room temperature for 12 hours. After which the reactions were concentrated and analyzed by ^{1}H NMR spectroscopy using isopropyl acetate as an internal standard.

Conditions D (IBA-Cl). To a solution of quinoline or isoquinoline (0.3 mmol) in dichloroethane (1 mL) was added 1- chloro-1,2-benziodoxol-3-one (102 mg, 0.36 mmol) and stirred at 50 °C for 12 hours (quinoline) or 24 hours (isoquinoline). Yield determined by crude ^{1}H NMR spectroscopy using mesitylene as an internal standard.

Conditions E[46] (IBA-Cl). To a solution of quinoline or isoquinoline (0.3 mmol) in DMF (1 mL) was added 1-chloro-1,2-benziodoxol-3-one (102 mg, 0.36 mmol) and stirred at 23 °C 12 hours (quinoline) or 24 hours (isoquinoline). Yield determined by crude ^{1}H NMR spectroscopy using mesitylene as an internal standard.

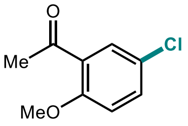
Conditions F (tBuOCl). To a solution of quinoline (47 µL, 0.4 mmol) in dichloroethane (1 mL) was added tBuOCl (68 µL, 0.4 mmol) and stirred at 50 °C for 4 hours. Yield determined by crude ^{1}H NMR spectroscopy using mesitylene as an internal standard.

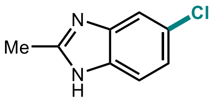
Conditions G (NCS). To a solution of quinoline (47 µL, 0.4 mmol) in dichloroethane (1 mL) was added N-chlorosuccinimide (80 mg, 0.6 mmol) and stirred at 50 °C for 4 hours. Yield determined by crude ^{1}H NMR spectroscopy using mesitylene as an internal standard.

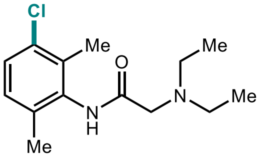
---

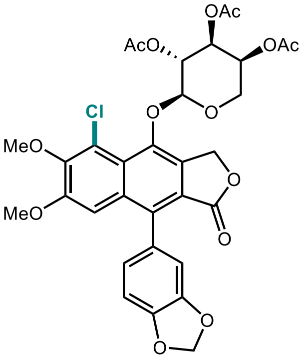
[45] Acetonitrile used for challenging substrates in chlorination using Palau'chlor: Rodriguez, R.A., Pan, C.-M., Yabe, Y., Kawamata, Y., Eastgate, M.D., and Baran, P.S. (2014). Palau'chlor: a practical and reactive chlorinating reagent. J. Am. Chem. Soc. *136*, 6908–6911.

[46] Wang, M., Zhang, Y., Wang, T., Wang, C., Xue, D., and Xiao, J. (2016). Story of an Age-Old Reagent: An electrophilic chlorination of arenes and heterocycles by 1-chloro-1,2-benziodoxol-3-one. Org. Lett. *18*, 1976–1979.









Conditions	**anisole, 10**	**benzimidazole, 15**	**lidocaine, 33**	**acetyl phyllanthusmin D, 39**
$PhICl_2$	**5%**	**<10%**	**20%**	**0%**
this strategy	**72%**	**72%**	**60%**	**63%**

Table S10: Comparison of chlorination to $PhICl_2$

Although $PhICl_2$ is a known chlorinating reagent, when compared to our conditions $PhICl_2$ gave inferior results as seen with the examples above. For instance, in the case of 2-methyl benzimidazole less than 10% aryl chlorination was observed. Major products from the reaction using $PhICl_2$ were N-Cl and benzyl-Cl. However, under our conditions only aryl chlorination was observed in 72% isolated yield.

VII. Mechanistic Studies

^{1}H NMR Analysis of Active Oxidant

Iodobenzene diacetate was stirred with X equivalents of 1M hydrochloric acid at room temperature for 15 minutes. 600 MHz ^{1}H NMR spectra were taken in $CDCl_3$. With 0.5 equivalents of 1M hydrochloric acid and iodobenzene diacetate, conversion of the diacetate to the monoacetate could be observed by the chemical shift at 8.13 ppm. With two equivalents of hydrochloric acid, almost full conversion of iodobenzene diacetate to iodobenzene dichloride was observed with the appearance of the dichloride peak at 8.19 ppm. Slower ligand exchange was observed between iodobenzene diacetate and acetyl chloride as compared to hydrochloric acid. To confirm the identity of the monoacetate species at 8.13 ppm, iodobenzene dichloride was stirred with one equivalent of acetic anhydride for 15 minutes. The ^{1}H NMR spectrum also showed a peak at 8.13 ppm, as evidence of a ligand exchange forming a monoacetate species. Also concluding that the ligand exchange is reversible.

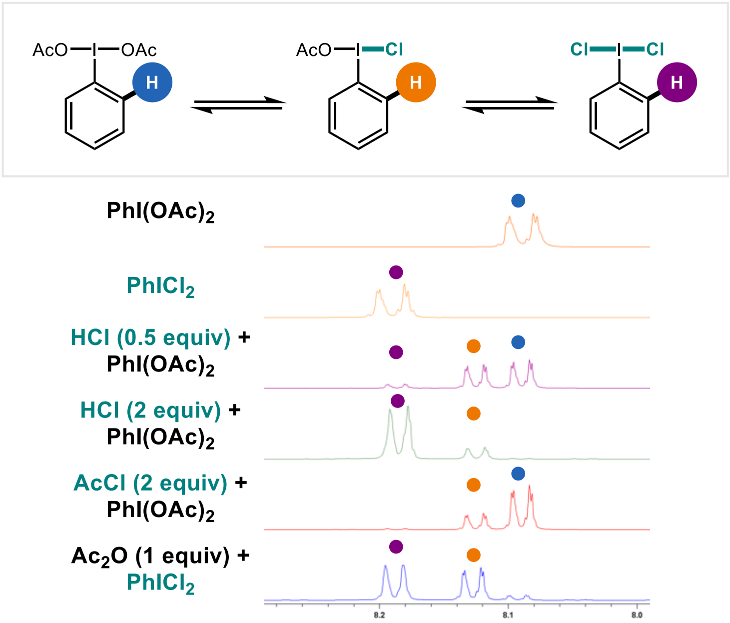
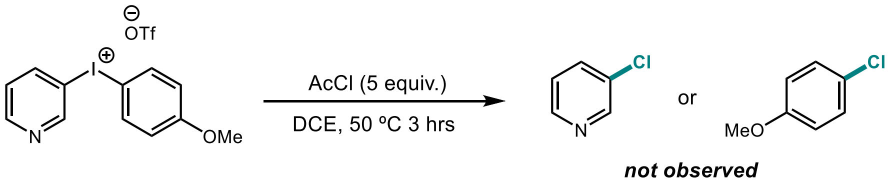


Figure S1: ^{1}H NMR observation of non-symmetric iodane.

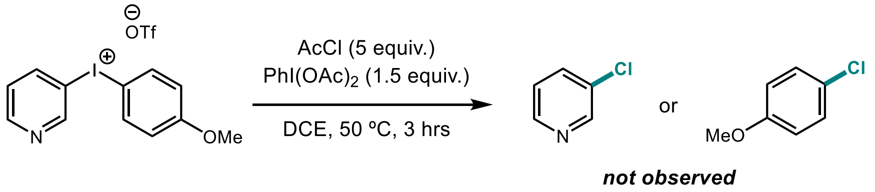
Diaryliodonium Intermediate

To investigate the plausibility of heteroarene functionalization via an iodonium intermediate the following investigations were carried out.



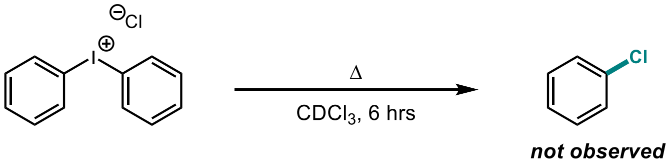
Scheme S1: Diaryliodonium with acetyl chloride does not provide aryl chloride upon heating.

To a solution of 4-methoxyphenyl(3-pyridyl)iodonium triflate[47] (17.4 mg, 0.038 mmol) in dichloroethane (0.075 M) was added acetyl chloride (14.9 mg, 0.19 mmol). The solution was stirred at 50 °C for 3 hours and then concentrated. Mass spectrometric analysis of crude mixture did not indicate formation of chlorinated pyridine or anisole, but rather oxysulfonylated anisole.



Scheme S2: Diaryliodonium with acetyl chloride and iodobenzene diacetate does not provide aryl chloride upon heating.

To a solution of 4-methoxyphenyl(3-pyridyl)iodonium triflate[47] (26.3 mg, 0.057 mmol) in dichloroethane (0.075 M) was added iodobenzene diacetate (27.5 mg, 0.09 mmol) then acetyl chloride (22.4 mg, 0.29 mmol). The solution was stirred at 50 °C for 3 hours and then concentrated. Mass spectrometric analysis of crude mixture did not indicate formation of chlorinated pyridine or anisole, but rather oxysulfonylated anisole, iodobenzene and unreacted 4-methoxyphenyl(3-pyridyl)iodonium triflate.

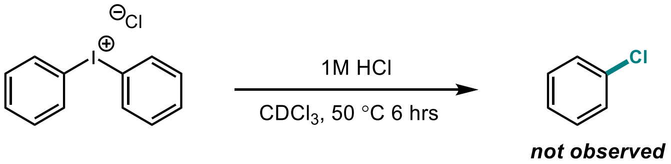


Scheme S3: Diaryliodonium chloride does not provide aryl chloride upon heating.

---

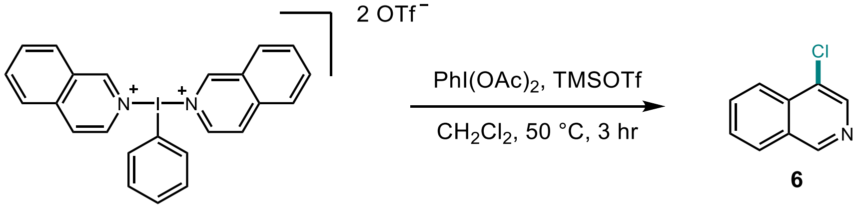
[47] Bielawski, M., Malmgren, J., Pardo, L.M., Wikmark, Y., and Olofsson, B. (2014). One-pot synthesis and applications of N-heteroaryl iodonium salts. *ChemistryOpen 3*, 19–22.

Diphenyliodonium chloride (20 mg, 0.06 mmol) in $CDCl_3$ (1 mL) was stirred at 50 °C for 6 hours. ^1H NMR analysis of the crude mixture did not indicate formation of chlorobenzene, only decomposition to iodobenzene.



Scheme S4: Diaryliodonium chloride does not provide aryl chloride in the presence of 1M HCl and upon heating.

Diphenyliodonium chloride (20 mg, 0.06 mmol) and 1M HCl (300 µL, 0.3 mmol) in $CDCl_3$ (1 mL) was stirred at 50 °C for 6 hours. ^1H NMR analysis of the crude mixture did not indicate formation of chlorobenzene, only decomposition to iodobenzene.



Chlorinating Reagent	Conditions	% Yield of **6**	% Recovered Iodonium	Comment
AcCl	A	0%	0%	4% isoquinoline recovered
EtO_2CCl	B	0%	0%	decomposition
$PhICl_2$	C	3%	0%	78% isoquinoline recovered
AcCl, $PhI(OAc)_2$	D	1%	0%	100% isoquinoline recovered

Table S11: N-donor hypervalent iodine reagent investigation.

1,1'-(phenyl-l3-iodanediyl)bis(isoquinolin-2-ium) trifluoromethanesulfonate was prepared according to literature procedure[48] and immediately subjected to chlorination conditions (below). Results in table above.

---

[48] Kelley, B.T., Walters, J.C., and Wengryniuk. S.E. (2016). Access to diverse oxygen heterocycles via oxidative rearrangement of benzylic tertiary alcohols. Org. Lett. *18*, 1896–1899.

Conditions A (AcCl). To a solution of isoquinolinium hypervalent iodine reagent (0.041 mmol), in anhydrous dichloromethane (0.5 ml) was added acetyl chloride (32.2 mg, 0.41 mmol). The solution was left to stir at 50 °C for 3 hours. After cooling to room temperature, dichloromethane (1 mL) was added and the reaction was extracted with saturated sodium bicarbonate (1 ml x 3), followed by a 10% sodium thiosulfate solution (2 mL). The organic layer was concentrated and analyzed by ^{1}H NMR analysis using isopropyl acetate as an internal standard.

Conditions B (EtO_2Cl). To a solution of isoquinolinium hypervalent iodine reagent (0.041 mmol), in anhydrous dichloromethane (0.5 ml) was added ethyl chloroformate (44.5 mg, 0.41 mmol). The solution was left to stir at 50 °C for 3 hours. After cooling to room temperature, dichloromethane (1 mL) was added and the reaction was extracted with saturated sodium bicarbonate (1 ml x 3), followed by a 10% sodium thiosulfate solution (2 mL). The organic layer was concentrated and analyzed by ^{1}H NMR analysis using isopropyl acetate as an internal standard.

Conditions C ($PhICl_2$). To a solution of isoquinolinium hypervalent iodine reagent (0.041 mmol), in anhydrous dichloromethane (0.5 ml) was added iodobenzene dichloride (56.4 mg, 0.41 mmol). The solution was left to stir at 50 °C for 3 hours. After cooling to room temperature, dichloromethane (1 mL) was added and the reaction was extracted with saturated sodium bicarbonate (1 ml x 3), followed by a 10% sodium thiosulfate solution (2 mL). The organic layer was concentrated and analyzed by ^{1}H NMR analysis using isopropyl acetate as an internal standard.

Conditions D (AcCl, $PhI(OAc)_2$). To a solution of isoquinolinium hypervalent iodine reagent (0.041 mmol), in anhydrous dichloromethane (0.5 ml) was added acetyl chloride (32.2 mg, 0.41 mmol) followed by iodobenzene diacetate (13.2 mg, 0.08 mmol). The solution was left to stir at 50 °C for 3 hours. After cooling to room temperature, dichloromethane (1 mL) was added and the reaction was extracted with saturated sodium bicarbonate (1 ml x 3), followed by a 10% sodium thiosulfate solution (2 mL). The organic layer was concentrated and analyzed by ^{1}H NMR analysis using isopropyl acetate as an internal standard.

VIII. Miscellaneous

Chlorination of the following substrates were attempted, however were not amenable to our conditions.

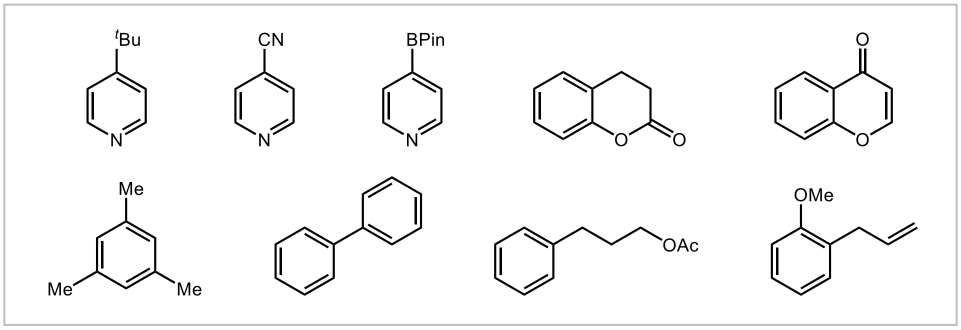


Figure S2: Substrates that did not afford isolable aryl chlorides.

IX. DFT Calculations

Computational Details

All geometry optimizations and single-point energy calculations for the *N* and *N*-1 systems were performed using the Gaussian 16 (revision A.03) suite of programs using Becke's three-parameter hybrid exchange functional and the Lee-Yang-Parr correlation functional (B3LYP) density functional theory (DFT) method. Population analysis on both the *N* and *N*-1 systems were carried out with Weinhold's Natural Bond Order (NBO) program (version 3.1), also included in Gaussian 16 suite of programs.

Molecular geometries for the *N* electron systems were performed with the 6-311+g(d,p) basis set with "very tight" convergence criteria, and confirmed as stationary points with no imaginary frequencies. Fukui index values for electrophilic attack were derived by comparison of the population analyses, and the corresponding maps were gradient colored via conditional formatting within Microsoft Excel 2016.

General Method[49, 50]

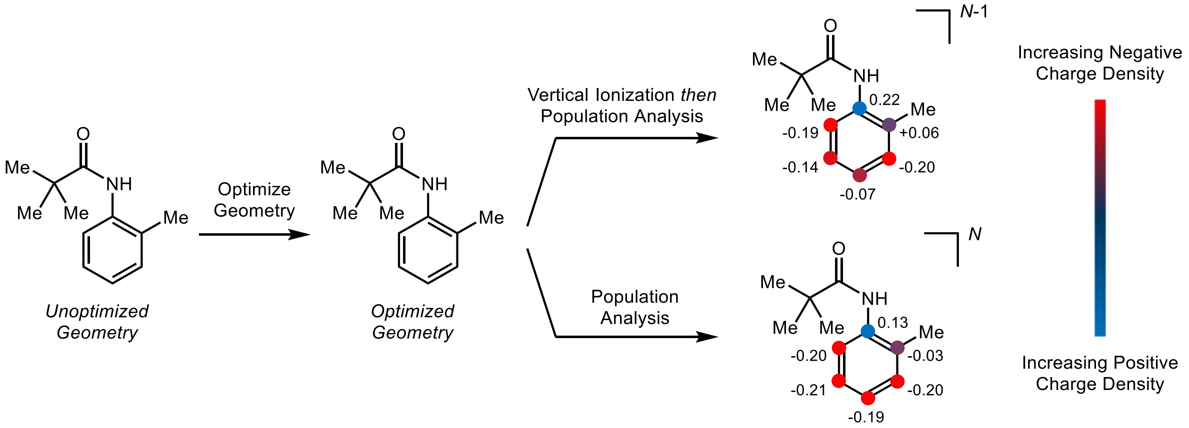


Figure S3: Explanation of DFT calculations performed.

The geometries of all structures were first optimized. From there, population analysis was performed on both the *N* electron system as well as the vertically ionized *N*-1 system (*i.e.* no additional geometry optimization was performed after removal of the electron). The population values are per atom charge density, equivalent to their atomic partial charges. For example, a value of -0.20 indicates a partial negative charge of 20% of an electron's charge. Conversely, a value of +0.30 indicates a partial positive charge of 30% of a proton's charge.

For our heterocycle examples, the nuclei of the *N* electron system calculated to be the most negative are consistent with experimentally observed sites of chlorination. This correlation is suggestive of a more EAS-like mechanism to explain bond formation.

---

[49] Boursalian, G.B., Ham, W.S., Mazzotti, A.R., and Ritter, T. (2016). Charge-transfer-directed radical substitution enables para-selective C-H functionalization. Nat. Chem. *8*, 810–815.

[50] Ohio Supercomputer Center. 1987. Ohio Supercomputer Center. Columbus OH: Ohio Supercomputer Center. http://osc.edu/ark:/19495/f5s1ph73.

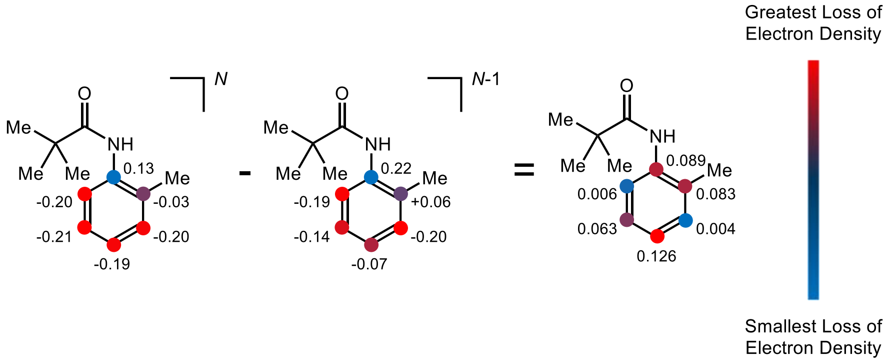


Figure S4: Electron density color map.

Those same population values were then used to determine the Fukui index values for electrophilic attack, which are defined as subtracting the charge densities of the *N*-1 system from the *N* system. These Fukui values represent the loss in electron density per atom that is accompanied by a one electron global oxidation of the molecule.

For our arene examples, the nuclei with the highest Fukui values are consistent with experimentally observed sites of chlorination. This correlation is suggestive of a one electron oxidation to a radical cation intermediate preceding bond formation.

Summary of DFT Predictions

Below is a summary of the predicted sites of chlorination based on either analysis of partial charges or from the Fukui function relative to the observed experimental outcome.

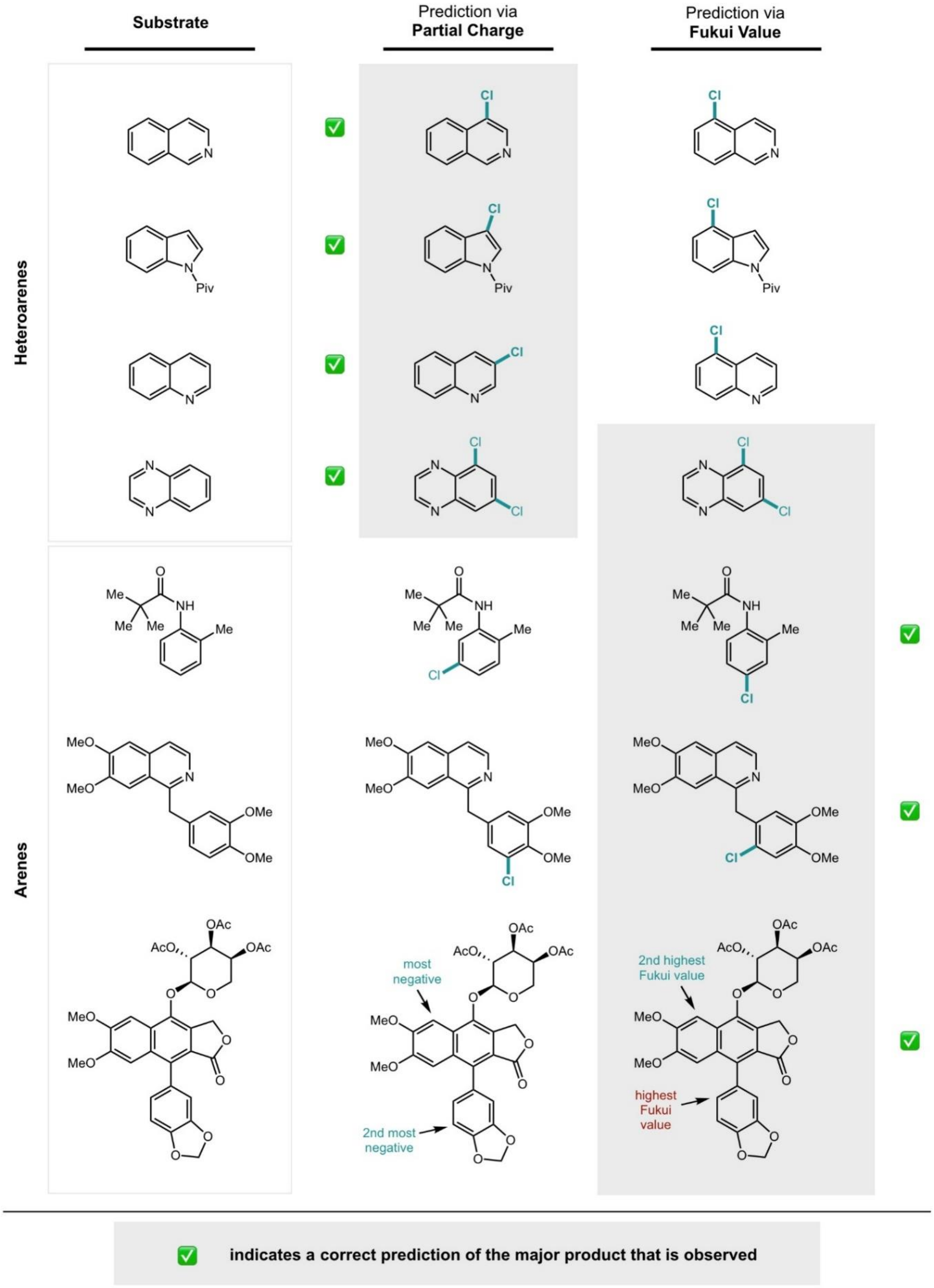


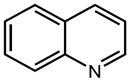
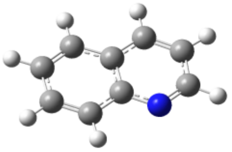
Figure S5: Summary of predictions of chlorination selectivity.

Optimized Geometries

Optimized geometries and electronic energies were calculated for the following compounds:

Quinoline
Quinolinium
Isoquinoline
Isoquinolinium
Quinoxaline
5-Chloroquinoxaline
6-Chloroquinoxaline
1-(1H-indol-1-yl)-2,2-dimethylpropan-1-one
N-(o-tolyl)pivalamide
2”-Acetyl phyllanthusmin D
Papaverine

Quinoline

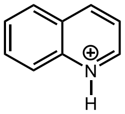
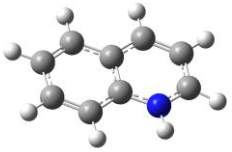
	
Electronic Energy + Zero-point Energy (hartree)	-401.895993
Electronic Energy + Thermal Energy Correction (hartree)	-401.889298
Electronic Energy + Thermal Enthalpy Correction (hartree)	-401.888354
Electronic Energy + Thermal Free Energy Correction (hartree)	-401.927155

Cartesian Coordinates

C	1.26183000	1.35268700	0.00000000
C	0.00000000	0.70459100	0.00000000
C	-0.04404300	-0.72485300	0.00000000
C	1.17223200	-1.45536400	0.00000000
C	2.37910900	-0.79833800	0.00000000
C	2.42256000	0.61700100	0.00000000
H	1.27235800	2.43603200	0.00000000
H	1.13398100	-2.53994600	0.00000000
H	3.30502700	-1.36217400	0.00000000
H	3.38286100	1.12039100	0.00000000
C	-2.44489800	-0.55228000	0.00000000
H	-3.43826400	-0.98508600	0.00000000
C	-1.32072500	-1.33878700	0.00000000
H	-1.39353600	-2.42173500	0.00000000
C	-2.29066400	0.85593600	0.00000000
H	-3.17312700	1.49160800	0.00000000
N	-1.12881500	1.47105100	0.00000000

Table S12: Optimized geometries of electronic energies of quinoline

Quinolinium

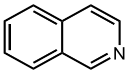
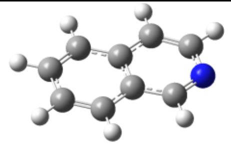
	
Electronic Energy + Zero-point Energy (hartree)	-402.259403
Electronic Energy + Thermal Energy Correction (hartree)	-402.252560
Electronic Energy + Thermal Enthalpy Correction (hartree)	-402.251616
Electronic Energy + Thermal Free Energy Correction (hartree)	-402.290669

Cartesian Coordinates

C	1.17925800	1.44243200	0.00000000
C	0.00000000	0.67901500	0.00000000
C	0.04211500	-0.74682100	0.00000000
C	1.31159500	-1.38075500	0.00000000
C	2.45925300	-0.62667400	0.00000000
C	2.39087700	0.78688800	0.00000000
H	1.13213300	2.52571600	0.00000000
H	1.35732000	-2.46327200	0.00000000
H	3.42770200	-1.11112100	0.00000000
H	3.30800100	1.36347500	0.00000000
C	-2.39120600	-0.78673800	0.00000000
H	-3.33283800	-1.31806800	0.00000000
C	-1.17916000	-1.45447900	0.00000000
H	-1.15877900	-2.53883800	0.00000000
C	-2.39390200	0.60435800	0.00000000
H	-3.30116700	1.19424400	0.00000000
H	-1.27189400	2.29359700	0.00000000
N	-1.23906500	1.27870100	0.00000000

Table S13: Optimized geometries of electronic energies of quinolinium

Isoquinoline

	
Electronic Energy + Zero-point Energy (hartree)	-401.894018
Electronic Energy + Thermal Energy Correction (hartree)	-401.887298
Electronic Energy + Thermal Enthalpy Correction (hartree)	-401.886354
Electronic Energy + Thermal Free Energy Correction (hartree)	-401.925219

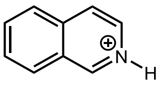
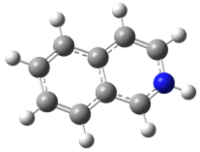
Cartesian Coordinates

C	-1.22451500	-1.39775100	0.00000000
C	0.00843700	-0.69843400	0.00000000
C	0.00995800	0.72728500	0.00000000
C	-1.23197200	1.41347400	0.00000000
C	-2.41305100	0.70981000	0.00000000
C	-2.41235900	-0.70649300	0.00000000

H	-1.21573100	-2.48276500	0.00000000
H	-1.23637600	2.49822400	0.00000000
H	-3.35849800	1.24069700	0.00000000
H	-3.35521000	-1.24125400	0.00000000
C	2.41774300	0.61788500	0.00000000
H	3.39397200	1.09198500	0.00000000
C	1.26737800	-1.35866800	0.00000000
H	1.29021100	-2.44725700	0.00000000
C	1.27146100	1.37378500	0.00000000
H	1.32810600	2.45688300	0.00000000
N	2.42786500	-0.74312400	0.00000000

Table S14: Optimized geometries of electronic energies of isoquinoline

Isoquinolinium

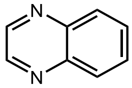
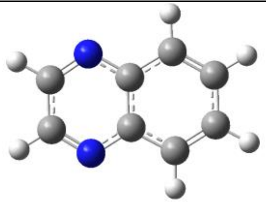
	
Electronic Energy + Zero-point Energy (hartree)	-402.258460
Electronic Energy + Thermal Energy Correction (hartree)	-402.251612
Electronic Energy + Thermal Enthalpy Correction (hartree)	-402.250668
Electronic Energy + Thermal Free Energy Correction (hartree)	-402.289756

Cartesian Coordinates

C	1.26216100	-1.41298800	0.00000000
C	0.03353800	-0.69997100	0.00000000
C	0.03320300	0.73782700	0.00000000
C	1.27119900	1.41570900	0.00000000
C	2.44714300	0.69833300	0.00000000
C	2.44537600	-0.71859200	0.00000000
H	1.25303200	-2.49671900	0.00000000
H	1.28585600	2.49902100	0.00000000
H	3.39482100	1.22390800	0.00000000
H	3.38802100	-1.25179100	0.00000000
C	-2.38322900	0.70584200	0.00000000
H	-3.36667700	1.15302700	0.00000000
C	-1.19853900	-1.36123000	0.00000000
H	-1.28178300	-2.44083800	0.00000000
C	-1.21731500	1.41155700	0.00000000
H	-1.25417100	2.49356400	0.00000000
H	-3.21568600	-1.17500600	0.00000000
N	-2.33780400	-0.66629800	0.00000000

Table S15: Optimized geometries of electronic energies of isoquinolinium

Quinoxaline

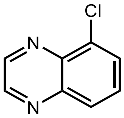
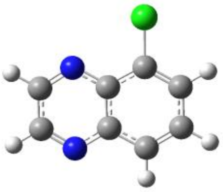
	
Electronic Energy + Zero-point Energy (hartree)	-417.946322
Electronic Energy + Thermal Energy Correction (hartree)	-417.939756
Electronic Energy + Thermal Enthalpy Correction (hartree)	-417.938812
Electronic Energy + Thermal Free Energy Correction (hartree)	-417.977417

Cartesian Coordinates

C	0.00000000	1.19267300	1.40974200
C	0.00000000	-0.04210100	0.71460400
C	0.00000000	-0.04210100	-0.71460400
C	0.00000000	1.19267300	-1.40974200
C	0.00000000	2.37440700	-0.70866900
C	0.00000000	2.37440700	0.70866900
H	0.00000000	1.16735000	2.49293300
H	0.00000000	1.16735000	-2.49293300
H	0.00000000	3.31920000	-1.24024100
H	0.00000000	3.31920000	1.24024100
C	0.00000000	-2.31724500	-0.71014200
H	0.00000000	-3.25881500	-1.25339800
C	0.00000000	-2.31724500	0.71014200
H	0.00000000	-3.25881500	1.25339800
N	0.00000000	-1.21059200	1.41579500
N	0.00000000	-1.21059200	-1.41579500

Table S16: Optimized geometries of electronic energies of quinoxaline

5-Chloroquinoxaline

	
Electronic Energy + Zero-point Energy (hartree)	-877.574312
Electronic Energy + Thermal Energy Correction (hartree)	-877.566530
Electronic Energy + Thermal Enthalpy Correction (hartree)	-877.565586
Electronic Energy + Thermal Free Energy Correction (hartree)	-877.607566

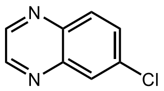
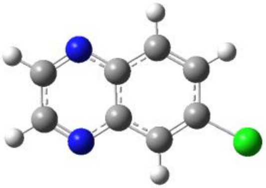
Cartesian Coordinates

C	1.25256000	0.02325600	0.00000000
C	-0.14085300	-0.27364800	0.00000000
C	-1.06372500	0.82109600	0.00000000
C	-0.58813000	2.15435300	0.00000000
C	0.76372100	2.39281100	0.00000000

C	1.69138600	1.32524700	0.00000000
H	-1.31598400	2.95613800	0.00000000
H	1.13864600	3.40960900	0.00000000
H	2.75433600	1.53007600	0.00000000
C	-2.79782000	-0.65794800	0.00000000
H	-3.86753900	-0.85021900	0.00000000
C	-1.87866000	-1.73921600	0.00000000
H	-2.24034100	-2.76409000	0.00000000
N	-0.57944100	-1.55750000	0.00000000
N	-2.40708100	0.59423000	0.00000000
Cl	2.41209800	-1.28319600	0.00000000

Table S17: Optimized geometries of electronic energies of 5-chloroquinoxaline

6-Chloroquinoxaline

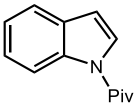
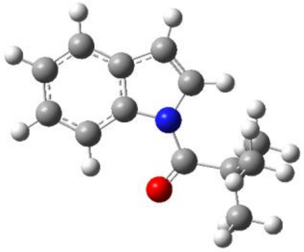
	
Electronic Energy + Zero-point Energy (hartree)	-877.577749
Electronic Energy + Thermal Energy Correction (hartree)	-877.569963
Electronic Energy + Thermal Enthalpy Correction (hartree)	-877.569018
Electronic Energy + Thermal Free Energy Correction (hartree)	-877.611039

Cartesian Coordinates

C	-0.70032000	-0.97415300	0.00000000
C	0.66468000	-0.59547200	0.00000000
C	1.01646400	0.78847200	0.00000000
C	-0.01219000	1.76313500	0.00000000
C	-1.33014000	1.38068500	0.00000000
C	-1.66155600	0.00396900	0.00000000
H	0.27226100	2.80837800	0.00000000
H	-2.12358100	2.11690000	0.00000000
C	3.21957900	0.22641300	0.00000000
H	4.26535100	0.52196400	0.00000000
C	2.86969600	-1.15004600	0.00000000
H	3.64822600	-1.90848700	0.00000000
N	1.62369400	-1.56305800	0.00000000
N	2.31915600	1.18204400	0.00000000
H	-0.95053200	-2.02677700	0.00000000
Cl	-3.35935000	-0.44134700	0.00000000

Table S18: Optimized geometries of electronic energies of 6-chloroquinoxaline

1-(1H-indol-1-yl)-2,2-dimethylpropan-1-one

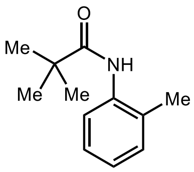
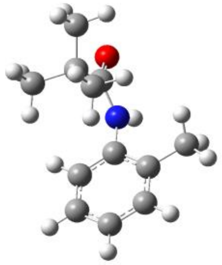
Electronic Energy + Zero-point Energy (hartree)	-634.322939
Electronic Energy + Thermal Energy Correction (hartree)	-634.309266
Electronic Energy + Thermal Enthalpy Correction (hartree)	-634.308322
Electronic Energy + Thermal Free Energy Correction (hartree)	-634.363015

Cartesian Coordinates

C	3.48920900	0.84167600	0.00000000
C	2.09621100	0.97217600	0.00000000
C	1.27550900	-0.18082400	-0.00000100
C	1.82759000	-1.46364400	0.00000000
C	3.21658700	-1.56648100	0.00000100
C	4.04145100	-0.43219600	0.00000100
H	4.12202700	1.72223900	0.00000100
H	1.20070100	-2.34026400	0.00000000
H	3.66718300	-2.55251800	0.00000100
H	5.11870900	-0.55375400	0.00000200
C	-0.05054000	1.66570800	-0.00000100
H	-0.95888500	2.23466600	-0.00000200
C	1.22501900	2.11935600	-0.00000100
H	1.52087600	3.15730500	-0.00000100
N	-0.07372900	0.25704100	-0.00000100
C	-1.18706000	-0.60921200	-0.00000100
O	-0.99673100	-1.80774700	-0.00000300
C	-2.63105100	-0.03875600	0.00000100
C	-2.91105000	0.78100700	1.28189600
H	-3.96571200	1.06969200	1.29768300
H	-2.71926700	0.17762000	2.17323700
H	-2.31880400	1.69146700	1.36581500
C	-2.91105300	0.78100700	-1.28189400
H	-2.71927200	0.17762000	-2.17323600
H	-3.96571500	1.06969300	-1.29767900
H	-2.31880700	1.69146700	-1.36581500
C	-3.59128700	-1.24565800	0.00000200
H	-4.62220200	-0.88128600	0.00000300
H	-3.44404900	-1.87310800	-0.87994700
H	-3.44404700	-1.87310900	0.87995000

Table S19: Optimized geometries of electronic energies of 1-(1H-indol-1-yl)-2,2-dimethylpropan-1-one

N-(o-tolyl)pivalamide

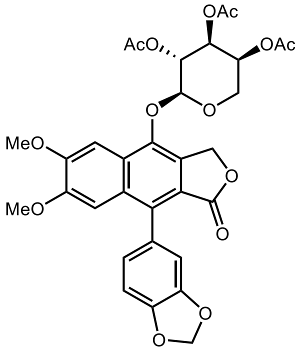
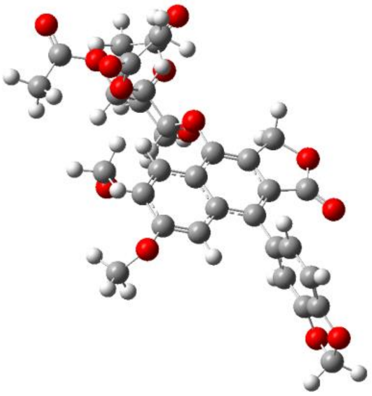
Electronic Energy + Zero-point Energy (hartree)	-597.410008
Electronic Energy + Thermal Energy Correction (hartree)	-597.395185
Electronic Energy + Thermal Enthalpy Correction (hartree)	-597.394240
Electronic Energy + Thermal Free Energy Correction (hartree)	-597.452595

Cartesian Coordinates

C	0.97431500	0.11683100	-0.56469600
C	1.32334500	-1.20146800	-0.86427100
C	2.52773400	-1.73711800	-0.41573300
C	3.40333100	-0.93885500	0.31522500
C	3.07233900	0.38795100	0.58178300
C	1.86335000	0.94199000	0.14977400
H	0.64767200	-1.79818500	-1.46436100
H	2.78397000	-2.76417700	-0.64884800
H	4.34579700	-1.34217700	0.66790200
H	3.76411900	1.00988800	1.14029300
C	1.53004800	2.38380800	0.43746200
H	2.27739400	2.82990300	1.09575200
H	1.49828800	2.97942900	-0.48104300
H	0.54989900	2.48249400	0.90987400
N	-0.24769300	0.66893300	-1.06605100
H	-0.15465700	1.30715400	-1.84803900
C	-1.58597000	0.49491600	-0.75607700
O	-2.40799700	1.05061000	-1.46999900
C	-2.04664500	-0.36210600	0.45341700
C	-1.16965300	-0.18334600	1.70850200
H	-0.15967500	-0.57138100	1.58319600
H	-1.10224600	0.86895700	1.99883700
H	-1.62869200	-0.72285500	2.54215900
C	-2.07630800	-1.84957300	0.03128900
H	-1.07588900	-2.25276700	-0.12917800
H	-2.54875900	-2.44092300	0.82130700
H	-2.65884100	-1.98464000	-0.88374800
C	-3.48476600	0.07455300	0.79792400
H	-4.15199900	-0.04807300	-0.05458600
H	-3.85584400	-0.53085700	1.62986900
H	-3.51942400	1.12531000	1.09537100

Table S20: Optimized geometries of electronic energies of N-(o-tolyl)pivalamide

2”-Acetyl phyllanthusmin D

Electronic Energy + Zero-point Energy (hartree)	-2290.621614
Electronic Energy + Thermal Energy Correction (hartree)	-2290.578439
Electronic Energy + Thermal Enthalpy Correction (hartree)	-2290.577495
Electronic Energy + Thermal Free Energy Correction (hartree)	-2290.703975

Cartesian Coordinates

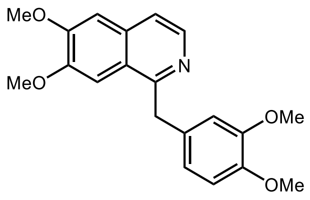
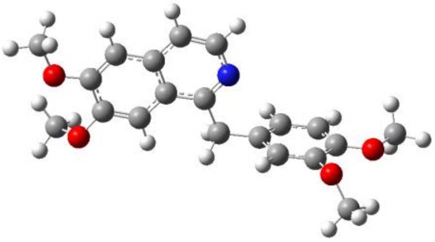
C	2.32813300	3.11170500	0.30678800
C	2.99413200	1.92373000	0.13960500
C	2.31667500	0.72950500	-0.22838500
C	0.88770700	0.78975700	-0.39336300
C	0.22658000	2.03554700	-0.24484400
C	0.91915100	3.17361100	0.08875600
H	4.06407800	1.90801800	0.29802100
C	3.02033000	-0.50534100	-0.41381900
C	0.17963500	-0.40231200	-0.71341800
H	-0.83964600	2.11747200	-0.40934100
C	0.86417000	-1.57179800	-0.88428900
C	2.26296800	-1.61883300	-0.73511700
C	0.37817100	-2.93943200	-1.26525700
H	-0.29938600	-3.36995900	-0.52676100
H	-0.10743600	-2.96091700	-2.24422600
O	1.57163600	-3.74358500	-1.33021000
C	2.69737000	-3.01334700	-1.03161600
O	3.79015900	-3.50577200	-1.03962300
C	4.50377900	-0.57628500	-0.26814500
C	5.06509600	-1.25014000	0.83535900
C	5.33196300	0.01929900	-1.22327700
C	6.43760500	-1.28458900	0.92165400
H	4.44466000	-1.73537100	1.57716800
C	6.73149700	-0.03670600	-1.12767600
H	4.88434800	0.52707600	-2.06924000
C	7.25460200	-0.69449100	-0.03663200
H	7.37007900	0.40916200	-1.87915000
C	8.55406000	-1.46663800	1.60405100
H	8.82927700	-0.68149500	2.31959800

H	9.23180500	-2.31781300	1.65740400
O	7.21617500	-1.90404400	1.87011100
O	8.57206300	-0.92424100	0.27717900
O	0.24643000	4.35423200	0.26348800
O	3.03106200	4.24685200	0.62389100
C	0.37499200	5.29715600	-0.81577900
H	-0.07256800	4.88984400	-1.72709500
H	-0.17572500	6.18455600	-0.50741300
H	1.42386000	5.55065700	-0.98914200
C	2.84107300	4.73628000	1.96084600
H	3.44086600	5.64222900	2.03836800
H	1.79048500	4.96892600	2.14932100
H	3.19803100	3.99936000	2.68799100
O	-1.19645300	-0.36340900	-0.93652600
C	-2.01991600	-0.44835300	0.19081100
C	-3.43746900	-0.03929900	-0.23915600
H	-1.65341000	0.21946000	0.98638600
C	-4.39331900	-0.20669800	0.94627400
H	-3.75865900	-0.68713100	-1.05312500
C	-2.85430800	-1.98515000	1.78872400
C	-4.31439800	-1.64741900	1.47720000
H	-4.09010600	0.47118000	1.74857000
H	-2.76258700	-3.03763300	2.05349800
H	-2.50909000	-1.37565000	2.63739300
H	-4.90849400	-1.73467800	2.38994500
O	-3.43951000	1.33992400	-0.60879100
O	-5.73821400	0.05320100	0.54576900
O	-4.75896200	-2.56241600	0.47349600
O	-2.01673700	-1.78586200	0.65673400
C	-6.03300900	-3.07904800	0.39269500
C	-6.41258500	1.23183000	0.79303700
C	-3.46584400	1.78212900	-1.91603200
C	-3.67605700	0.77029300	-3.01353200
H	-2.86245600	0.04246700	-3.03039300
H	-4.61690800	0.23035100	-2.87916400
H	-3.70396200	1.30787900	-3.95848400
C	-5.70485800	2.32823300	1.55219200
H	-5.45280200	2.00520100	2.56660600
H	-4.78579600	2.62845900	1.04663000
H	-6.38392700	3.17538200	1.61504800
C	-6.99096300	-2.82649300	1.53265500
H	-6.57727600	-3.15857200	2.48871900
H	-7.22982300	-1.76412100	1.60312800
H	-7.90163900	-3.38453300	1.32770900
O	-7.54114900	1.30394200	0.39718000
O	-6.29906900	-3.73113500	-0.57620500

O	-3.33587500	2.96106300	-2.09147000

Table S21: Optimized geometries of electronic energies of 2”-Acetyl phyllanthusmin D

Papaverine

	
Electronic Energy + Zero-point Energy (hartree)	-1130.300727
Electronic Energy + Thermal Energy Correction (hartree)	-1130.276887
Electronic Energy + Thermal Enthalpy Correction (hartree)	-1130.275943
Electronic Energy + Thermal Free Energy Correction (hartree)	-1130.356649

Cartesian Coordinates

C	-2.47920900	0.98430900	0.03273000
C	-1.81181400	-0.26849500	0.05382300
C	-2.59710100	-1.45207400	-0.04190700
C	-4.00645100	-1.35167800	-0.17089000
C	-4.62748800	-0.12243200	-0.20063700
C	-3.84305000	1.07158100	-0.08343500
H	-1.92759800	1.91294800	0.09869800
H	-4.58073200	-2.26472300	-0.25788800
C	-0.38969400	-0.40979200	0.17406500
C	-0.55611900	-2.70688700	0.11367400
H	-0.00775100	-3.64358700	0.14217600
N	0.20210500	-1.58502400	0.20444200
O	-4.42927300	2.30630100	-0.17554300
O	-5.96392200	0.07204700	-0.34905900
C	-1.92124200	-2.69673300	-0.00876000
H	-2.47784200	-3.62479100	-0.08009600
C	0.48583000	0.83534600	0.27890700
H	0.26035200	1.48866600	-0.57159100
H	0.18052000	1.39609400	1.17024600
C	1.97380000	0.58332800	0.33430100
C	2.72225200	0.46542100	-0.84141900
C	2.64349800	0.46937200	1.54821500
C	4.08995200	0.22835500	-0.81761200
H	2.24586000	0.54105800	-1.81299900
C	4.01762000	0.22545500	1.59651300
H	2.09379400	0.55843900	2.47930600
C	4.75310500	0.09268300	0.41955100
H	4.50313800	0.13112100	2.55877200
O	4.74987300	0.05597200	-2.01095000
O	6.09438400	-0.16949200	0.36635400

C	5.70798900	1.06197000	-2.35352700
H	6.52456800	1.09678500	-1.62936200
H	6.09806100	0.78570600	-3.33303800
H	5.22606900	2.04437800	-2.41870900
C	6.78530000	-0.39931400	1.58560800
H	6.36170700	-1.25070700	2.12914500
H	7.81359200	-0.62492700	1.30671800
H	6.77118500	0.48701300	2.22985300
C	-5.25444100	2.70460800	0.92699500
H	-4.66755400	2.73117700	1.85174200
H	-5.60482700	3.70869900	0.69100000
H	-6.10874300	2.03552300	1.04566700
C	-6.79935300	-1.06579700	-0.53399600
H	-6.76728900	-1.72847800	0.33710600
H	-7.80789100	-0.67526900	-0.65671500
H	-6.51213800	-1.62392900	-1.43074400

Table S22: Optimized geometries of electronic energies of papaverine

Population Analysis and Visualization

Population Analysis and Visualization was performed on the following compounds:
Quinoline
Quinolinium
Isoquinoline
Isoquinolinium
Quinoxaline
5-Chloroquinoxaline
6-Chloroquinoxaline
1-(1H-indol-1-yl)-2,2-dimethylpropan-1-one
N-(o-tolyl)pivalamide
2”-Acetyl phyllanthusmin D
Papaverine

Key for Table Entries:
Atom: the atom numbering corresponding to the structure under “Legend”;
ρ(*N*): the natural population of the corresponding atom for the *N*-electron system, obtained from NBO
δ(*N*): the partial charge of the corresponding atom for the *N*-electron system, obtained by subtracting **ρ(*N*)** from that atom’s normal electron count (*i.e* carbon has 6, nitrogen has 7, etc.).
RGB Code: the color code assigned from the conditional formatting generated in Excel on a range from red (255 0 0) to blue (0 112 192).
ρ(*N*-1): the natural population of the corresponding atom for the *N*-1 electron system, obtained from NBO
f^-: the Fukui function value corresponding to the substrate behaving as a nucleophile, obtained by subtracting **ρ(*N*-1)** from **ρ(*N*)**.

Quinoline

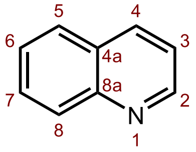
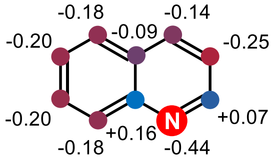
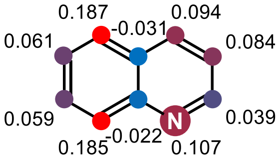
<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3">
</td><td colspan="2">
</td><td colspan="2">
</td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N\text{-}1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>1</td><td>7.44492</td><td>-0.44</td><td>255 0 0</td><td>7.33784</td><td>0.107</td><td>161 42 71</td></tr>
<tr><td>2</td><td>5.92948</td><td>0.07</td><td>40 94 162</td><td>5.89042</td><td>0.039</td><td>81 77 131</td></tr>
<tr><td>3</td><td>6.24881</td><td>-0.25</td><td>173 36 61</td><td>6.16443</td><td>0.084</td><td>134 53 91</td></tr>
<tr><td>4</td><td>6.14024</td><td>-0.14</td><td>128 56 96</td><td>6.04597</td><td>0.094</td><td>146 48 82</td></tr>
<tr><td>4a</td><td>6.09436</td><td>-0.09</td><td>109 64 110</td><td>6.12496</td><td>-0.031</td><td>0 112 192</td></tr>
<tr><td>5</td><td>6.17991</td><td>-0.18</td><td>145 48 83</td><td>5.99329</td><td>0.187</td><td>255 0 0</td></tr>
<tr><td>6</td><td>6.19933</td><td>-0.20</td><td>153 45 77</td><td>6.13837</td><td>0.061</td><td>107 65 112</td></tr>
<tr><td>7</td><td>6.19635</td><td>-0.20</td><td>153 45 77</td><td>6.13731</td><td>0.059</td><td>105 66 113</td></tr>
<tr><td>8</td><td>6.18235</td><td>-0.18</td><td>146 48 82</td><td>5.99712</td><td>0.185</td><td>253 1 2</td></tr>
<tr><td>8a</td><td>5.83558</td><td>0.16</td><td>0 112 192</td><td>5.85791</td><td>-0.022</td><td>9 108 185</td></tr>
</table>

Table S23: Population analysis and visualization of quinoline

Quinolinium

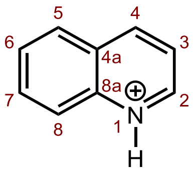
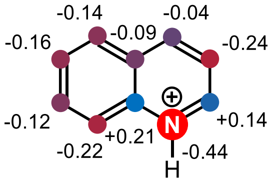
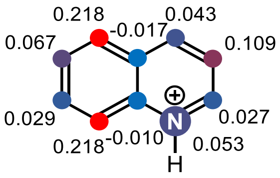
<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3">
</td><td colspan="2">
</td><td colspan="2">
</td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N\text{-}1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>1</td><td>7.43933</td><td>-0.44</td><td>255 0 0</td><td>7.38662</td><td>0.053</td><td>75 79 136</td></tr>
<tr><td>2</td><td>5.86130</td><td>0.14</td><td>28 100 171</td><td>5.83409</td><td>0.027</td><td>47 92 157</td></tr>
<tr><td>3</td><td>6.24278</td><td>-0.24</td><td>178 34 58</td><td>6.13383</td><td>0.109</td><td>136 53 90</td></tr>
<tr><td>4</td><td>6.04271</td><td>-0.04</td><td>99 68 117</td><td>5.99961</td><td>0.043</td><td>65 84 144</td></tr>
<tr><td>4a</td><td>6.08835</td><td>-0.09</td><td>116 60 104</td><td>6.10523</td><td>-0.017</td><td>0 112 192</td></tr>
<tr><td>5</td><td>6.14053</td><td>-0.14</td><td>138 51 88</td><td>5.92223</td><td>0.218</td><td>255 0 0</td></tr>
<tr><td>6</td><td>6.16458</td><td>-0.16</td><td>147 47 81</td><td>6.09775</td><td>0.067</td><td>90 73 124</td></tr>
<tr><td>7</td><td>6.11832</td><td>-0.12</td><td>129 55 95</td><td>6.08976</td><td>0.029</td><td>49 91 155</td></tr>
<tr><td>8</td><td>6.21898</td><td>-0.22</td><td>169 38 65</td><td>6.00146</td><td>0.218</td><td>255 0 0</td></tr>
<tr><td>8a</td><td>5.79211</td><td>0.21</td><td>0 112 192</td><td>5.80204</td><td>-0.010</td><td>7 109 187</td></tr>
</table>

Table S24: Population analysis and visualization of quinolinium

Isoquinoline

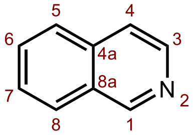
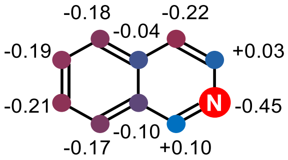
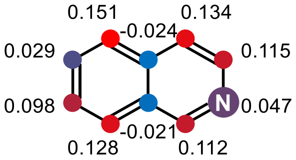
<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3">
</td><td colspan="2">
</td><td colspan="2">
</td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N\text{-}1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>1</td><td>5.90030</td><td>0.10</td><td>0 112 192</td><td>5.78864</td><td>0.112</td><td>197 26 44</td></tr>
<tr><td>2</td><td>7.45351</td><td>-0.45</td><td>255 0 0</td><td>7.40701</td><td>0.047</td><td>102 67 115</td></tr>
<tr><td>3</td><td>5.96847</td><td>0.03</td><td>32 98 168</td><td>5.85383</td><td>0.115</td><td>201 24 41</td></tr>
<tr><td>4</td><td>6.21894</td><td>-0.22</td><td>147 47 81</td><td>6.08515</td><td>0.134</td><td>229 12 20</td></tr>
<tr><td>4a</td><td>6.04109</td><td>-0.04</td><td>65 83 143</td><td>6.06510</td><td>-0.024</td><td>0 112 192</td></tr>
<tr><td>5</td><td>6.18410</td><td>-0.18</td><td>131 54 93</td><td>6.03290</td><td>0.151</td><td>255 0 0</td></tr>
<tr><td>6</td><td>6.18522</td><td>-0.19</td><td>132 54 93</td><td>6.15593</td><td>0.029</td><td>77 78 134</td></tr>
<tr><td>7</td><td>6.20534</td><td>-0.21</td><td>141 50 86</td><td>6.10697</td><td>0.098</td><td>178 34 58</td></tr>
<tr><td>8</td><td>6.16572</td><td>-0.17</td><td>123 58 99</td><td>6.03776</td><td>0.128</td><td>221 15 26</td></tr>
<tr><td>8a</td><td>6.10248</td><td>-0.10</td><td>94 71 121</td><td>6.12316</td><td>-0.021</td><td>4 110 189</td></tr>
</table>

Table S25: Population analysis and visualization of isoquinoline

Isoquinolinium

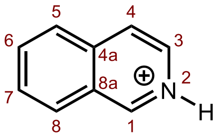
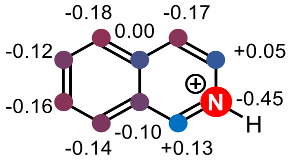
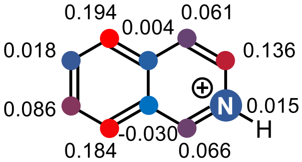
<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3">
</td><td colspan="2">
</td><td colspan="2">
</td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N\text{-}1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>1</td><td>5.83763</td><td>0.16</td><td>0 112 192</td><td>5.77135</td><td>0.066</td><td>109 65 110</td></tr>
<tr><td>2</td><td>7.44747</td><td>-0.45</td><td>255 0 0</td><td>7.43277</td><td>0.015</td><td>50 90 154</td></tr>
<tr><td>3</td><td>5.95496</td><td>0.05</td><td>50 90 155</td><td>5.81900</td><td>0.136</td><td>188 30 51</td></tr>
<tr><td>4</td><td>6.16686</td><td>-0.17</td><td>138 51 88</td><td>6.10556</td><td>0.061</td><td>103 67 115</td></tr>
<tr><td>4a</td><td>6.00329</td><td>0.00</td><td>70 81 139</td><td>5.99970</td><td>0.004</td><td>37 96 164</td></tr>
<tr><td>5</td><td>6.17603</td><td>-0.18</td><td>142 49 85</td><td>5.98164</td><td>0.194</td><td>255 0 0</td></tr>
<tr><td>6</td><td>6.11589</td><td>-0.12</td><td>117 60 104</td><td>6.09793</td><td>0.018</td><td>54 89 152</td></tr>
<tr><td>7</td><td>6.16211</td><td>-0.16</td><td>136 52 89</td><td>6.07562</td><td>0.086</td><td>132 54 93</td></tr>
<tr><td>8</td><td>6.14308</td><td>-0.14</td><td>128 55 95</td><td>5.95866</td><td>0.184</td><td>243 5 9</td></tr>
<tr><td>8a</td><td>6.09655</td><td>-0.10</td><td>109 64 110</td><td>6.12620</td><td>-0.030</td><td>0 112 192</td></tr>
</table>

Table S26: Population analysis and visualization of isoquinolinium

Quinoxaline

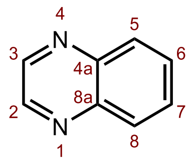
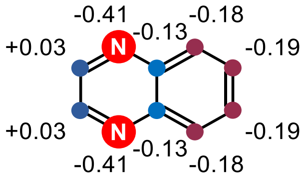
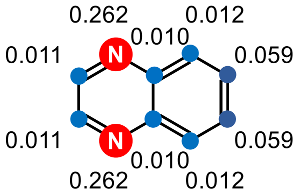
<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3">
</td><td colspan="2">
</td><td colspan="2">
</td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N\text{-}1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>1</td><td>7.40503</td><td>-0.41</td><td>255 0 0</td><td>7.14274</td><td>0.262</td><td>255 0 0</td></tr>
<tr><td>2</td><td>5.97207</td><td>0.03</td><td>48 91 156</td><td>5.96118</td><td>0.011</td><td>1 112 191</td></tr>
<tr><td>3</td><td>5.97207</td><td>0.03</td><td>48 91 156</td><td>5.96118</td><td>0.011</td><td>1 112 191</td></tr>
<tr><td>4</td><td>7.40503</td><td>-0.41</td><td>255 0 0</td><td>7.14274</td><td>0.262</td><td>255 0 0</td></tr>
<tr><td>4a</td><td>5.87297</td><td>0.13</td><td>0 112 192</td><td>5.86341</td><td>0.010</td><td>0 112 192</td></tr>
<tr><td>5</td><td>6.18437</td><td>-0.18</td><td>150 46 79</td><td>6.17279</td><td>0.012</td><td>2 112 191</td></tr>
<tr><td>6</td><td>6.19106</td><td>-0.19</td><td>153 45 77</td><td>6.13234</td><td>0.059</td><td>49 91 155</td></tr>
<tr><td>7</td><td>6.19106</td><td>-0.19</td><td>153 45 77</td><td>6.13234</td><td>0.059</td><td>49 91 155</td></tr>
<tr><td>8</td><td>6.18437</td><td>-0.18</td><td>150 46 79</td><td>6.17279</td><td>0.012</td><td>2 112 191</td></tr>
<tr><td>8a</td><td>5.87297</td><td>0.13</td><td>0 112 192</td><td>5.86341</td><td>0.010</td><td>0 112 192</td></tr>
</table>

Table S27: Population analysis and visualization of quinoxaline

5-Chloroquinoxaline

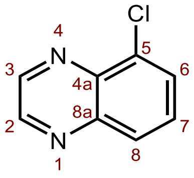
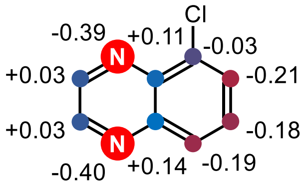
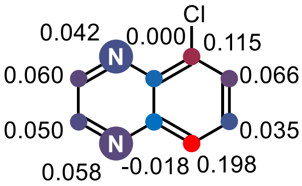
<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3">
</td><td colspan="2">
</td><td colspan="2">
</td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N\text{-}1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>1</td><td>7.40365</td><td>-0.40</td><td>255 0 0</td><td>7.34559</td><td>0.058</td><td>90 73 125</td></tr>
<tr><td>2</td><td>5.96831</td><td>0.03</td><td>53 88 152</td><td>5.91853</td><td>0.050</td><td>80 77 132</td></tr>
<tr><td>3</td><td>5.96645</td><td>0.03</td><td>52 89 153</td><td>5.90686</td><td>0.060</td><td>91 72 123</td></tr>
<tr><td>4</td><td>7.39385</td><td>-0.39</td><td>251 2 3</td><td>7.35227</td><td>0.042</td><td>70 81 139</td></tr>
<tr><td>4a</td><td>5.89212</td><td>0.11</td><td>18 104 179</td><td>5.89235</td><td>0.000</td><td>21 103 176</td></tr>
<tr><td>5</td><td>6.03046</td><td>-0.03</td><td>82 76 130</td><td>5.91501</td><td>0.115</td><td>157 43 74</td></tr>
<tr><td>6</td><td>6.21338</td><td>-0.21</td><td>167 38 66</td><td>6.14747</td><td>0.066</td><td>99 69 118</td></tr>
<tr><td>7</td><td>6.17913</td><td>-0.18</td><td>151 45 78</td><td>6.14453</td><td>0.035</td><td>62 85 145</td></tr>
<tr><td>8</td><td>6.18858</td><td>-0.19</td><td>155 43 75</td><td>5.99090</td><td>0.198</td><td>255 0 0</td></tr>
<tr><td>8a</td><td>5.85539</td><td>0.14</td><td>0 112 192</td><td>5.87371</td><td>-0.018</td><td>0 112 192</td></tr>
</table>

Table S28: Population analysis and visualization of 5-chloroquinoxaline

6-Chloroquinoxaline

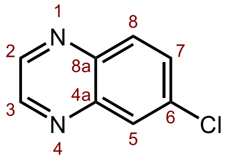
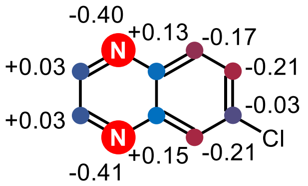
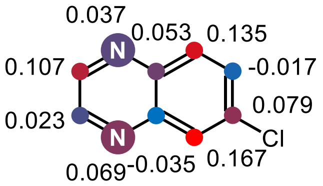
Legend			**Partial Charges of *N* System**		**Gradient Map for Fukui Function**	
						
Atom	***ρ*(*N*)**	***δ*(*N*)**	**RGB Code**	***ρ*(*N*-1)**	f^-	**RGB Code**
1	7.40225	-0.40	254 0 1	7.36526	0.037	91 72 124
2	5.97311	0.03	56 87 150	5.86599	0.107	179 34 57
3	5.96672	0.03	56 87 150	5.94355	0.023	73 80 137
4	7.40590	-0.41	255 0 0	7.33718	0.069	131 55 94
4a	5.85398	0.15	0 112 192	5.88933	-0.035	0 112 192
5	6.21316	-0.21	166 39 67	6.04604	0.167	255 0 0
6	6.02866	-0.03	81 76 131	5.95004	0.079	143 49 84
7	6.21079	-0.21	165 39 67	6.22761	-0.017	23 102 175
8	6.16744	-0.17	145 48 82	6.03252	0.135	214 18 31
8a	5.87070	0.13	8 108 186	5.81797	0.053	110 64 109

Table S29: Population analysis and visualization of 6-chloroquinoxaline

1-(1H-indol-1-yl)-2,2-dimethylpropan-1-one

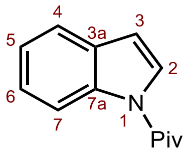
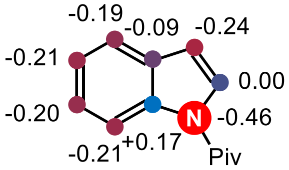
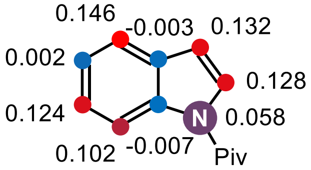
Legend			**Partial Charges of *N* System**		**Gradient Map for Fukui Function**	
						
Atom	***ρ*(*N*)**	***δ*(*N*)**	**RGB Code**	***ρ*(*N*-1)**	f^-	**RGB Code**
1	7.46122	-0.46	255 0 0	7.40282	0.058	108 65 111
2	6.00220	0.00	70 81 139	5.87374	0.128	225 13 23
3	6.24414	-0.24	168 38 66	6.11258	0.132	230 11 19
3a	6.08967	-0.09	105 65 113	6.09226	-0.003	6 110 188
4	6.18929	-0.19	146 48 82	6.04333	0.146	255 0 0
5	6.21185	-0.21	156 43 75	6.21002	0.002	13 106 182
6	6.20169	-0.20	151 46 78	6.07745	0.124	218 16 28
7	6.21413	-0.21	156 43 75	6.11187	0.102	181 33 56
7a	5.83016	0.17	0 112 192	5.83669	-0.007	0 112 192

Table S30: Population analysis and visualization of 1-(1H-indol-1-yl)-2,2-dimethylpropan-1-one

N-(o-tolyl)pivalamide

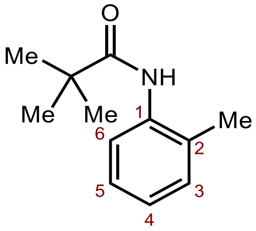
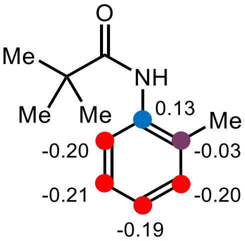
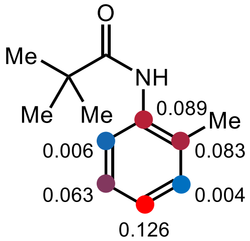
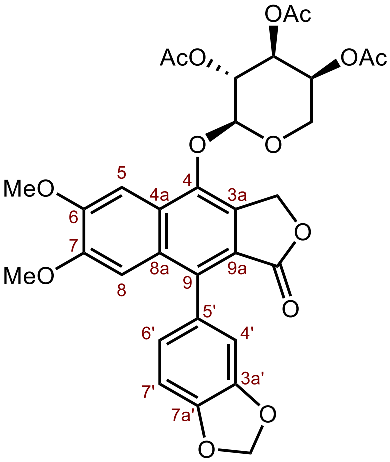
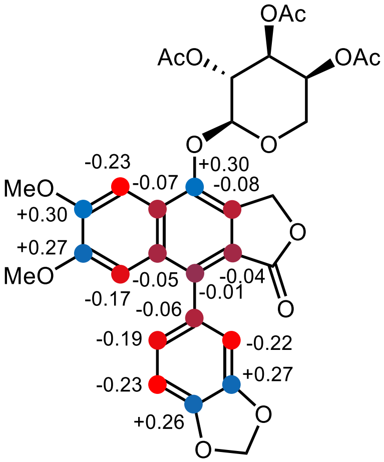
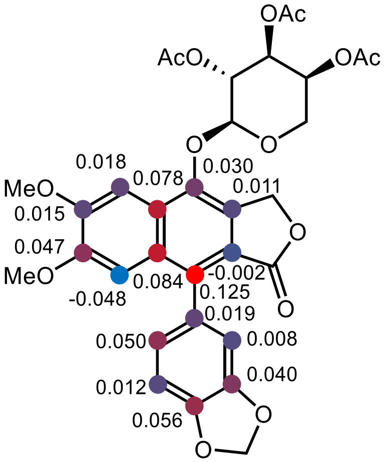
<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3"> </td><td colspan="2"> </td><td colspan="2"> </td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N-1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>1</td><td>5.86901</td><td>0.13</td><td>0 112 192</td><td>5.77968</td><td>0.089</td><td>183 32 55</td></tr>
<tr><td>2</td><td>6.02700</td><td>-0.03</td><td>120 59 101</td><td>5.94390</td><td>0.083</td><td>170 37 64</td></tr>
<tr><td>3</td><td>6.19862</td><td>-0.20</td><td>252 1 2</td><td>6.20265</td><td>-0.004</td><td>0 112 192</td></tr>
<tr><td>4</td><td>6.19318</td><td>-0.19</td><td>246 4 7</td><td>6.06720</td><td>0.126</td><td>255 0 0</td></tr>
<tr><td>5</td><td>6.20566</td><td>-0.21</td><td>255 0 0</td><td>6.14293</td><td>0.063</td><td>130 55 94</td></tr>
<tr><td>6</td><td>6.20085</td><td>-0.20</td><td>252 1 2</td><td>6.19438</td><td>0.006</td><td>20 103 177</td></tr>
</table>

Table S31: Population analysis and visualization of N-(o-tolyl)pivalamide

2”-Acetyl phyllanthusmin D

<table>
<tr><th colspan="3">Legend</th><th colspan="2">Partial Charges of <i>N</i> System</th><th colspan="2">Gradient Map for Fukui Function</th></tr>
<tr><td colspan="3"> </td><td colspan="2"> </td><td colspan="2"> </td></tr>
<tr><th>Atom</th><th>$\rho(N)$</th><th>$\delta(N)$</th><th>RGB Code</th><th>$\rho(N-1)$</th><th>f^-</th><th>RGB Code</th></tr>
<tr><td>3a</td><td>6.08422</td><td>-0.08</td><td>185 31 53</td><td>6.07318</td><td>0.011</td><td>86 74 127</td></tr>
<tr><td>4</td><td>5.70024</td><td>0.30</td><td>0 112 192</td><td>5.67023</td><td>0.030</td><td>114 62 106</td></tr>
<tr><td>4a</td><td>6.06873</td><td>-0.07</td><td>177 34 58</td><td>5.99108</td><td>0.078</td><td>184 31 53</td></tr>
<tr><td>5</td><td>6.23178</td><td>-0.23</td><td>255 0 0</td><td>6.21335</td><td>0.018</td><td>97 70 119</td></tr>
<tr><td>6</td><td>5.69983</td><td>0.30</td><td>0 112 192</td><td>5.68456</td><td>0.015</td><td>93 72 122</td></tr>
<tr><td>7</td><td>5.73011</td><td>0.27</td><td>15 105 181</td><td>5.68345</td><td>0.047</td><td>139 51 88</td></tr>
<tr><td>8</td><td>6.17099</td><td>-0.17</td><td>226 12 21</td><td>6.21907</td><td>-0.048</td><td>0 112 192</td></tr>
<tr><td>8a</td><td>6.04692</td><td>-0.05</td><td>167 38 66</td><td>5.96312</td><td>0.084</td><td>194 27 46</td></tr>
<tr><td>9</td><td>6.00588</td><td>-0.01</td><td>147 47 81</td><td>5.88063</td><td>0.125</td><td>255 0 0</td></tr>
<tr><td>9a</td><td>6.03726</td><td>-0.04</td><td>162 40 70</td><td>6.03971</td><td>-0.002</td><td>67 83 142</td></tr>
</table>

3a’	5.72949	0.27	15 105 181	5.68953	0.040	129 56 95
4’	6.21933	-0.22	250 2 4	6.21136	0.008	82 76 130
5’	6.06371	-0.06	175 35 60	6.04517	0.019	98 69 119
6’	6.19049	-0.19	236 8 14	6.14016	0.050	144 49 83
7’	6.22947	-0.23	255 0 0	6.21786	0.012	87 74 126
7a’	5.73751	0.26	19 104 178	5.68199	0.056	152 46 78

Table S32: Population analysis and visualization of 2”-Acetyl phyllanthusmin D

Papaverine

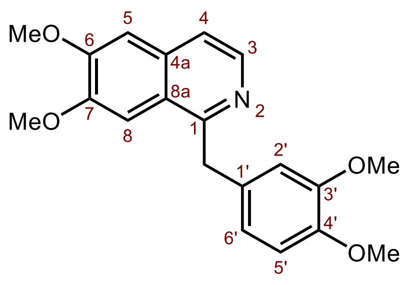
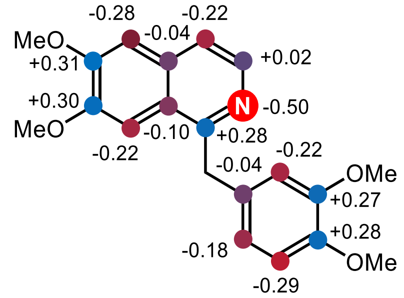
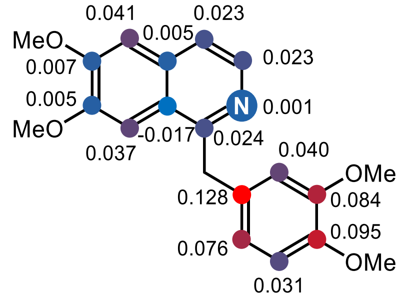
Legend			**Partial Charges of *N* System**		**Gradient Map for Fukui Function**	
						
Atom	**$\rho(N)$**	**$\delta(N)$**	**RGB Code**	**$\rho(N\text{-}1)$**	**f^-**	**RGB Code**
1	5.72383	0.28	12 107 183	5.69957	0.024	72 81 138
2	7.50149	-0.50	255 0 0	7.50034	0.001	32 98 168
3	5.97871	0.02	92 71 123	5.95532	0.023	71 81 139
4	6.21825	-0.22	167 38 66	6.19560	0.023	70 82 140
4a	6.03597	-0.04	110 64 109	6.03134	0.005	38 96 164
5	6.27894	-0.28	128 30 52	6.23812	0.041	101 68 116
6	5.68793	0.31	0 112 192	5.68070	0.007	42 94 160
7	5.70401	0.30	6 109 188	5.69907	0.005	38 95 163
8	6.21811	-0.22	167 39 66	6.18087	0.037	95 70 120
8a	6.10014	-0.10	130 55 94	6.11732	-0.017	0 112 192
1’	6.04142	-0.04	111 63 108	5.91352	0.128	255 0 0
2’	6.22169	-0.22	168 38 66	6.18213	0.040	99 69 117
3’	5.73052	0.27	14 106 181	5.64699	0.084	177 35 59
4’	5.71939	0.28	10 107 184	5.62484	0.095	196 26 45
5’	6.28766	-0.29	188 29 50	6.25631	0.031	85 75 128
6’	6.18389	-0.18	156 43 74	6.10770	0.076	164 40 69

Table S33: Population analysis and visualization of papaverine

Order of Chlorination for Quinoxaline

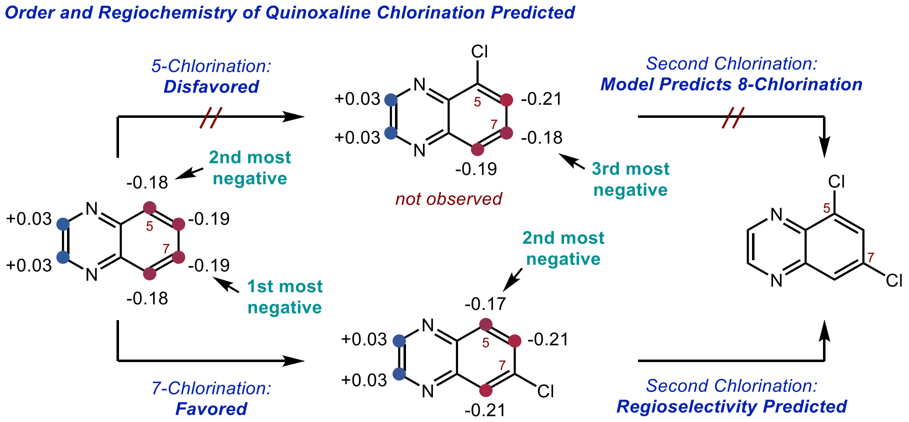


Figure S6: Predicted chlorination regioselectivity of quinoxaline

The dichlorination observed for quinoxaline to 5,7-dichloroquinoxaline can be rationalized using the above partial charge analysis which indicate C-5 and C-7 as the second most and most negative sites, respectively. It follows that C-7 should chlorinate before C-5, leading to 7-chloroquinoxazline[51] (bottom route) as a monochloride intermediate, which was observed. The partial charges of 7-chloroquinoxazline reveal that the 5-position is the second most negative site, which is consistent the observed 5,7-dichloroquinoxazline. While C-6 and C-8 are both more negative than C-5, chlorination at either would be sterically disfavored.

Alternatively, an initial C-5 chlorination (top route) would result in an intermediate more reactive at the C-8 position, which inconsistent with the isolated product.

---

[51] The numbering convention here follows the figure for clarity; this is technically 6-chloroquinoxaline

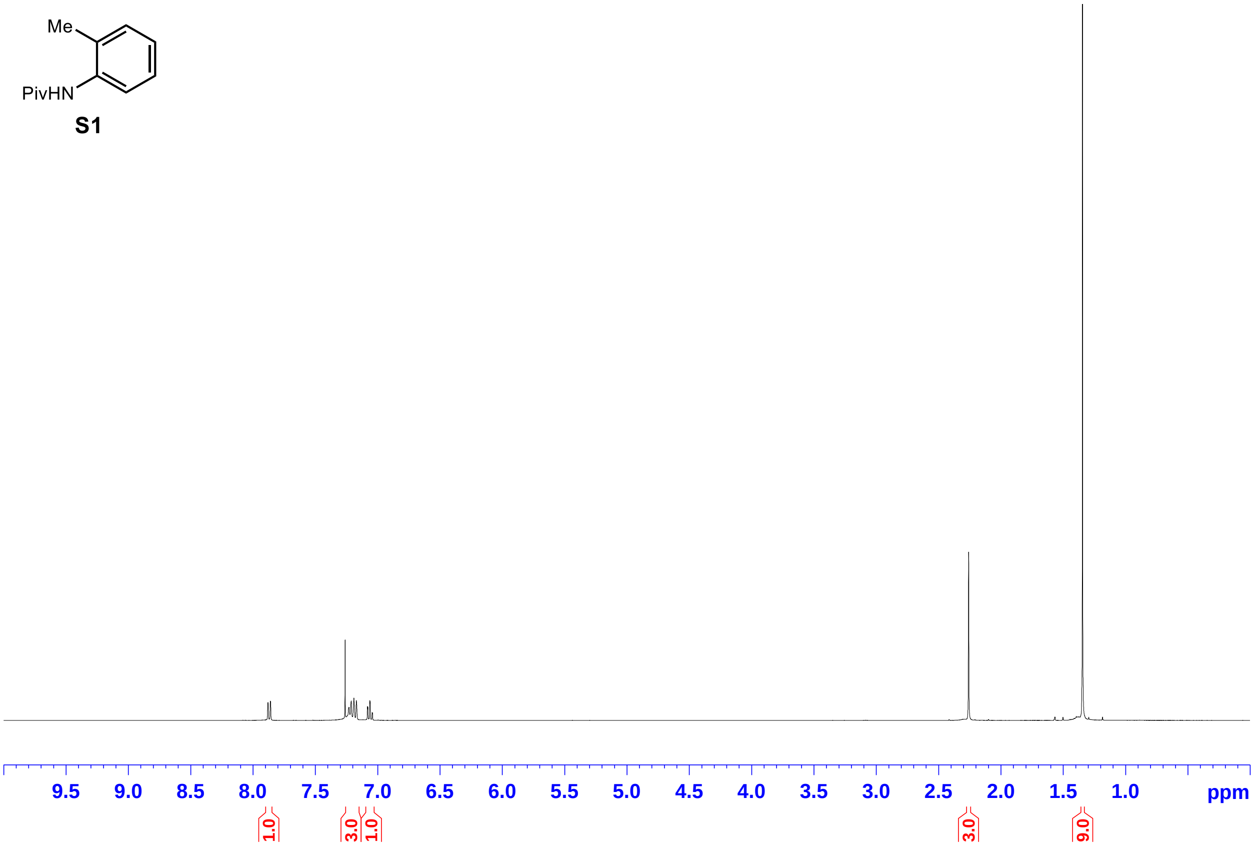


Figure S7: 400 MHz ^{1}H NMR spectrum of **S1** in $CDCl_3$

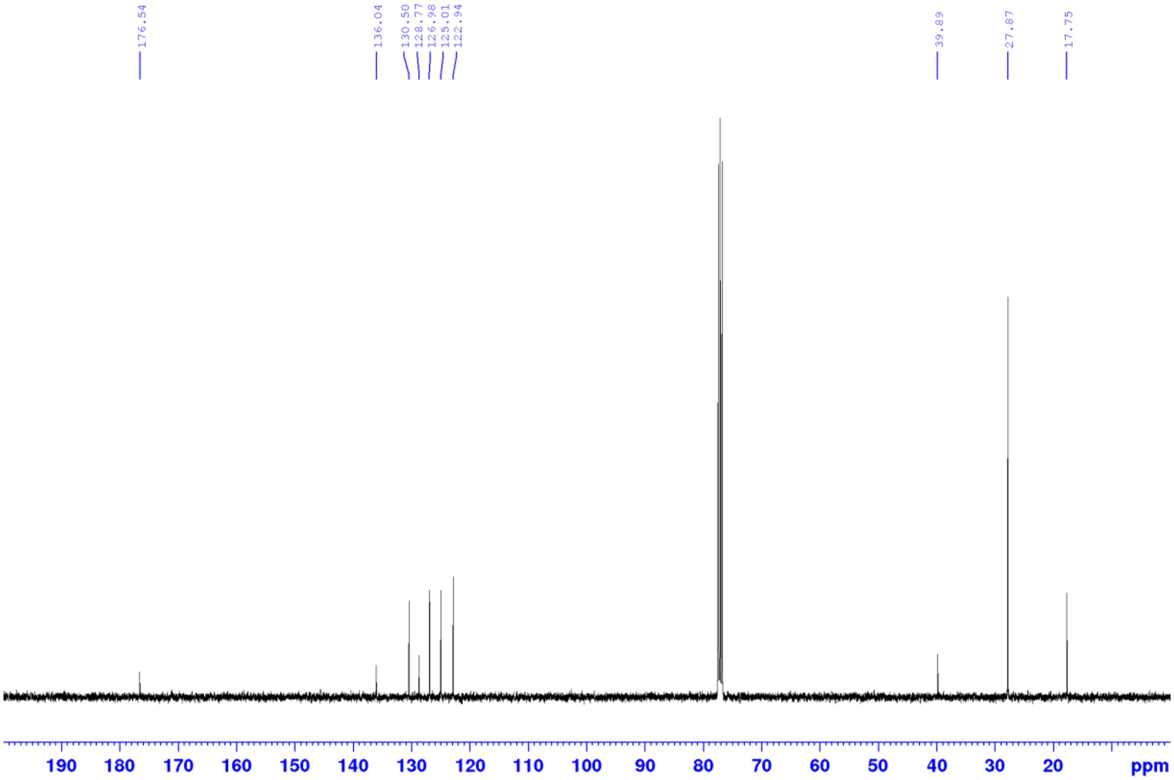


Figure S8: 101 MHz ^{13}C NMR spectrum of **S1** in $CDCl_3$

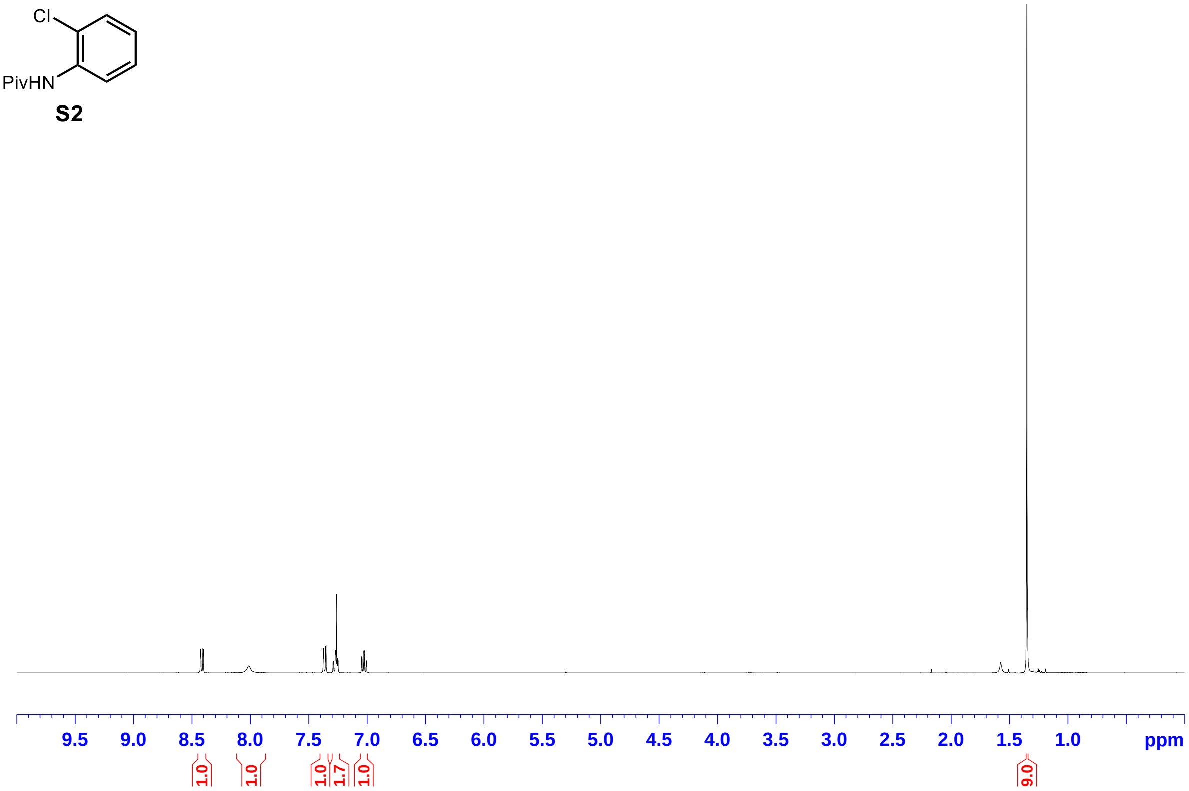


Figure S9: 400 MHz ^{1}H NMR spectrum of **S2** in $CDCl_3$

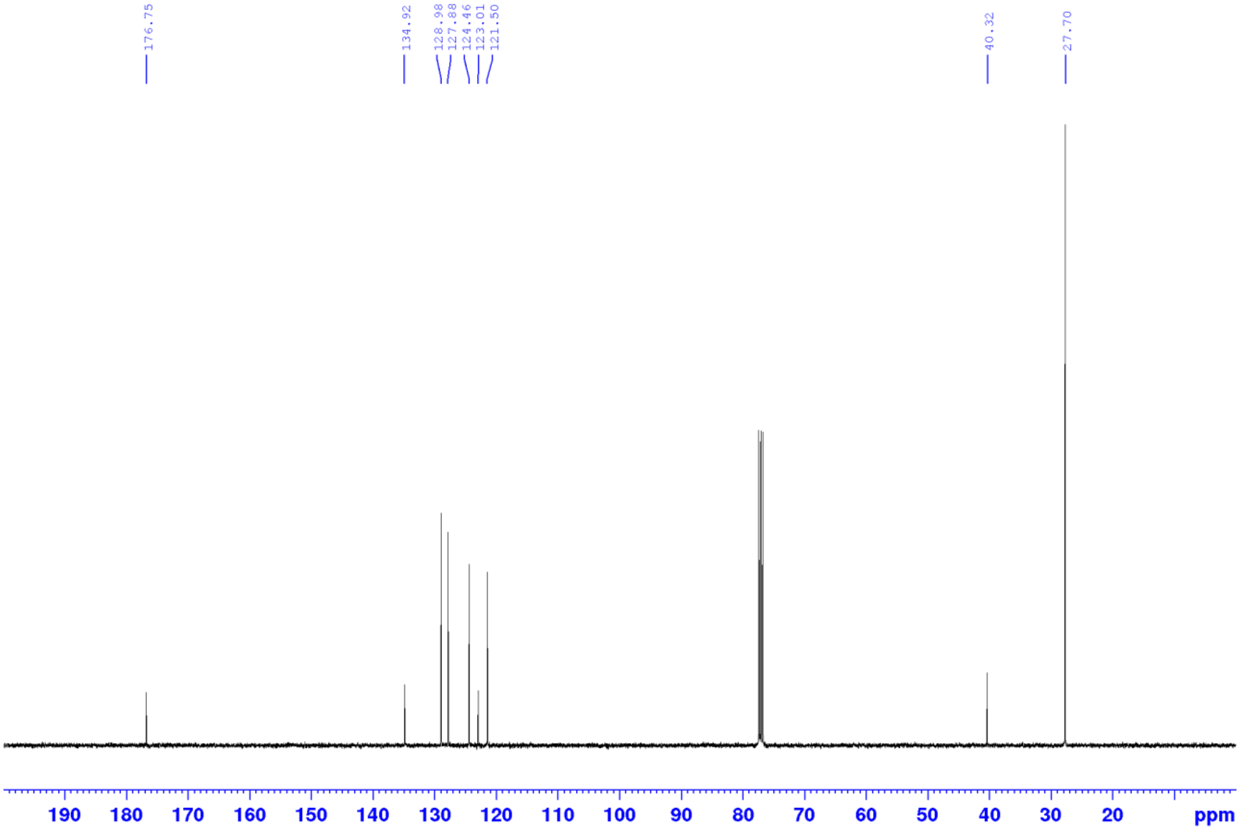


Figure S10: 101 MHz ^{13}C NMR spectrum of **S2** in $CDCl_3$

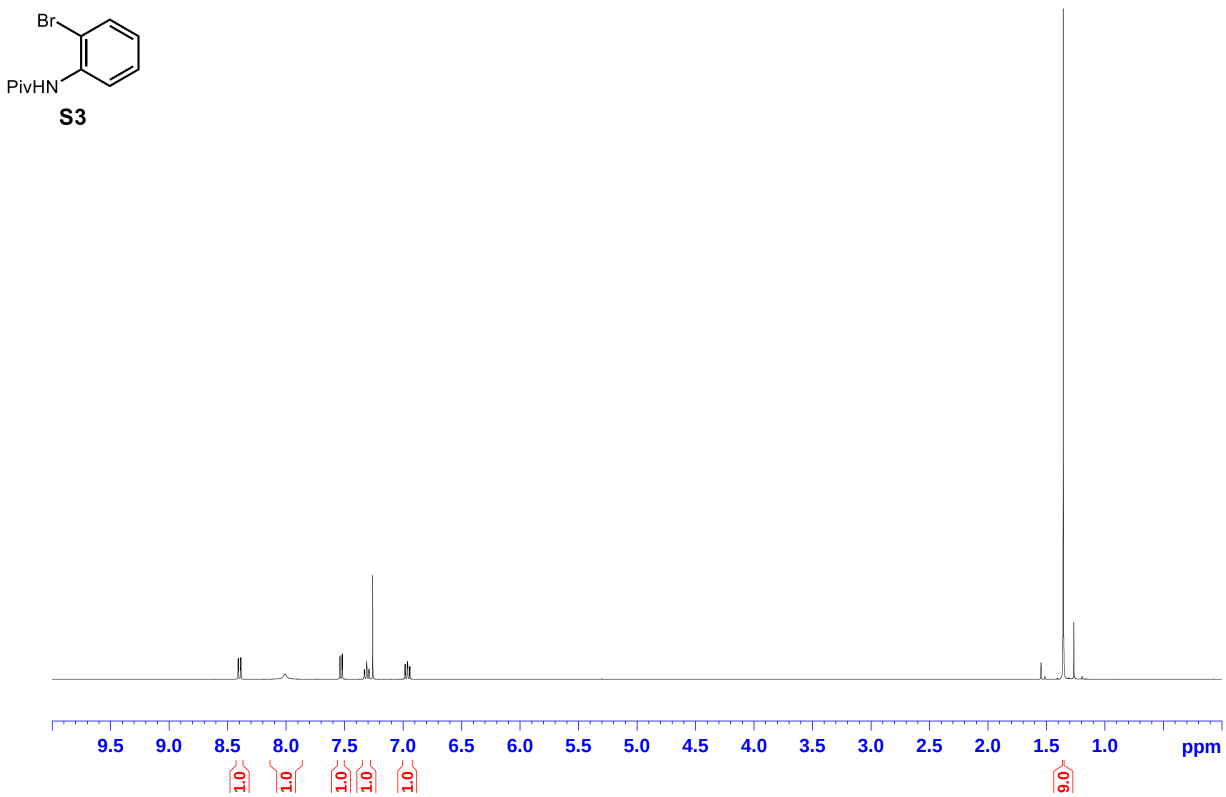


Figure S11: 400 MHz ^{1}H NMR spectrum of **S3** in $CDCl_3$

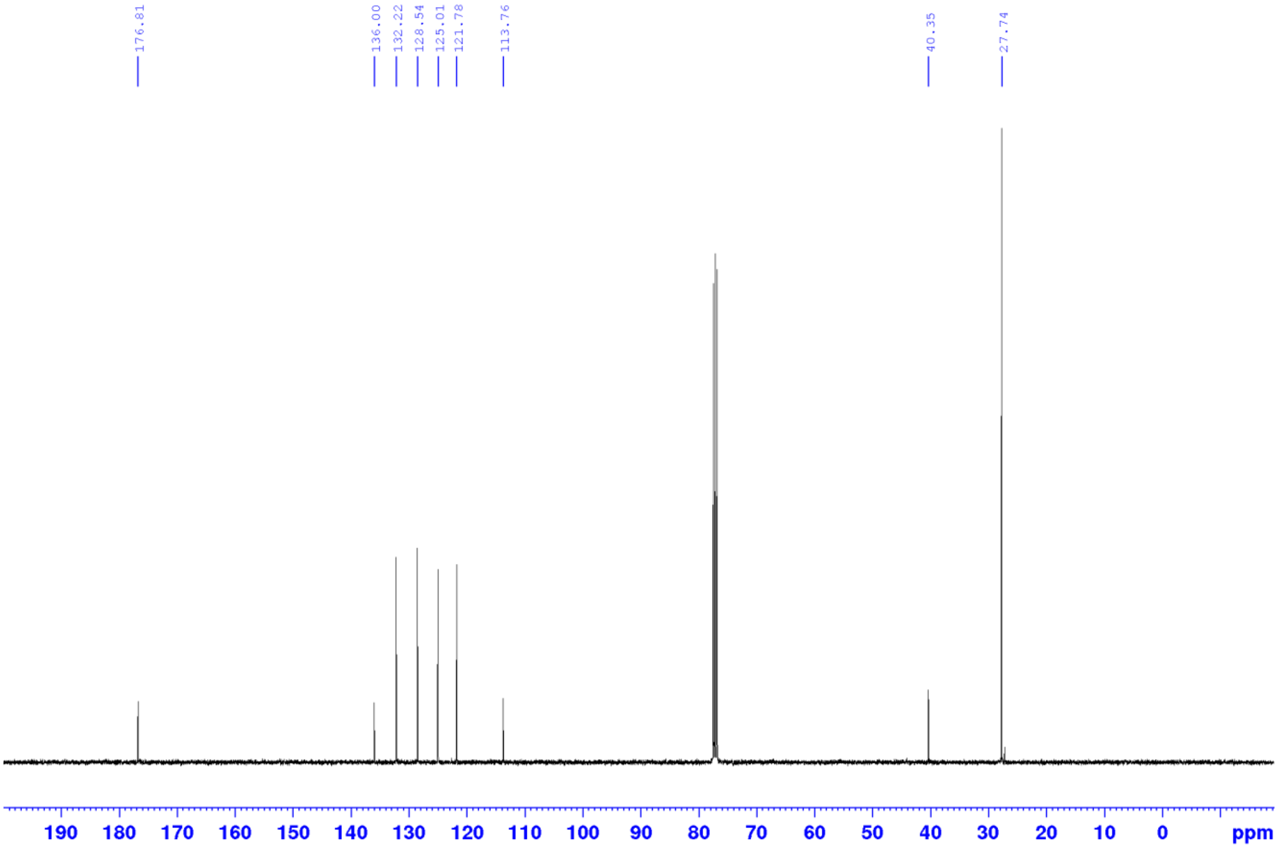


Figure S12: 101 MHz ^{13}C NMR spectrum of **S3** in $CDCl_3$

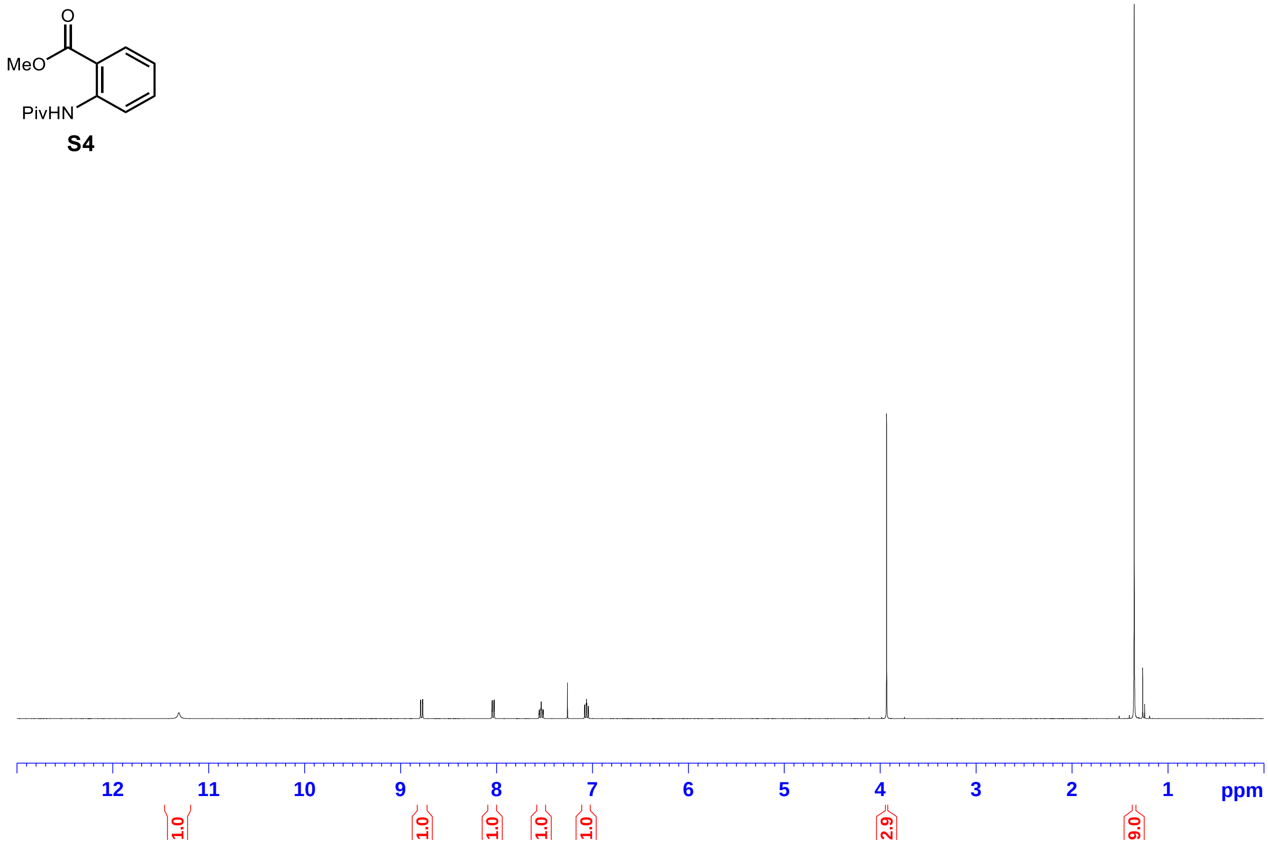


Figure S13: 400 MHz ^{1}H NMR spectrum of **S4** in $CDCl_3$

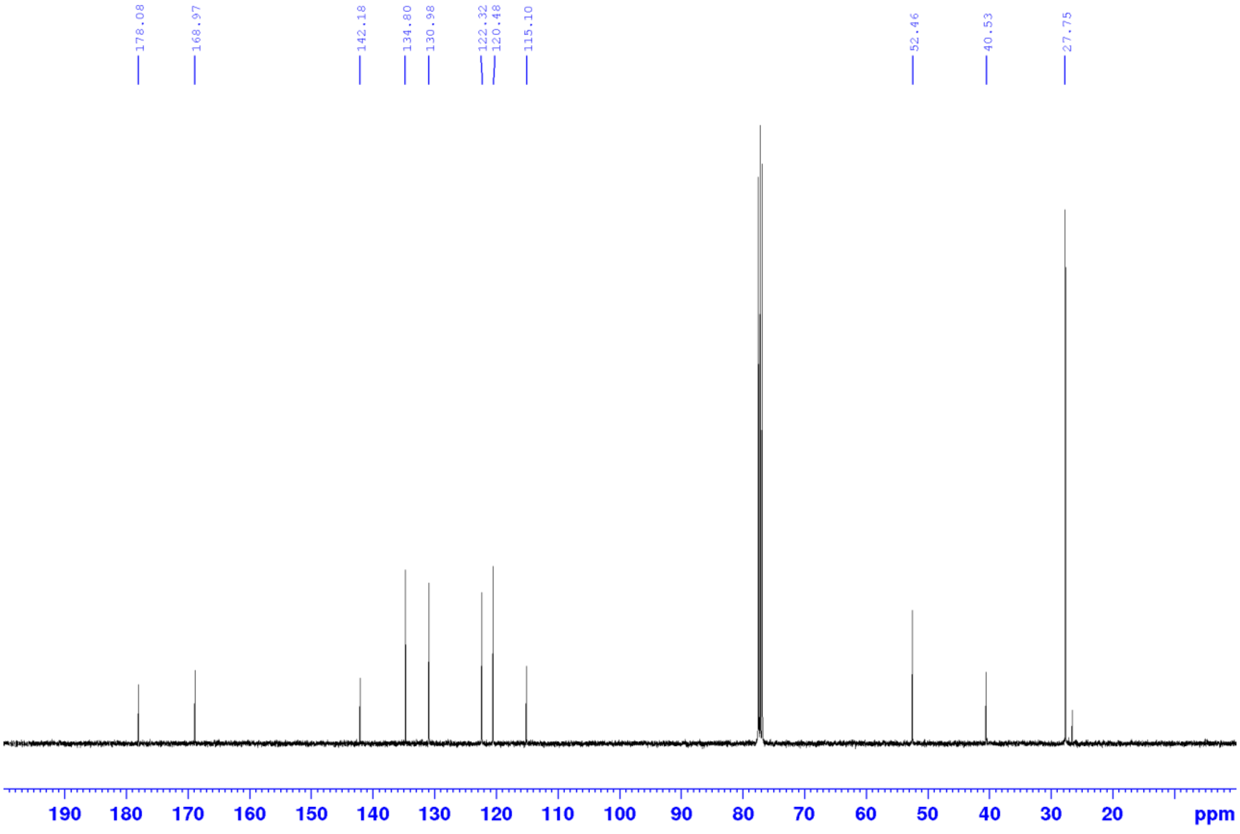


Figure S14: 101 MHz ^{13}C NMR spectrum of **S4** in $CDCl_3$

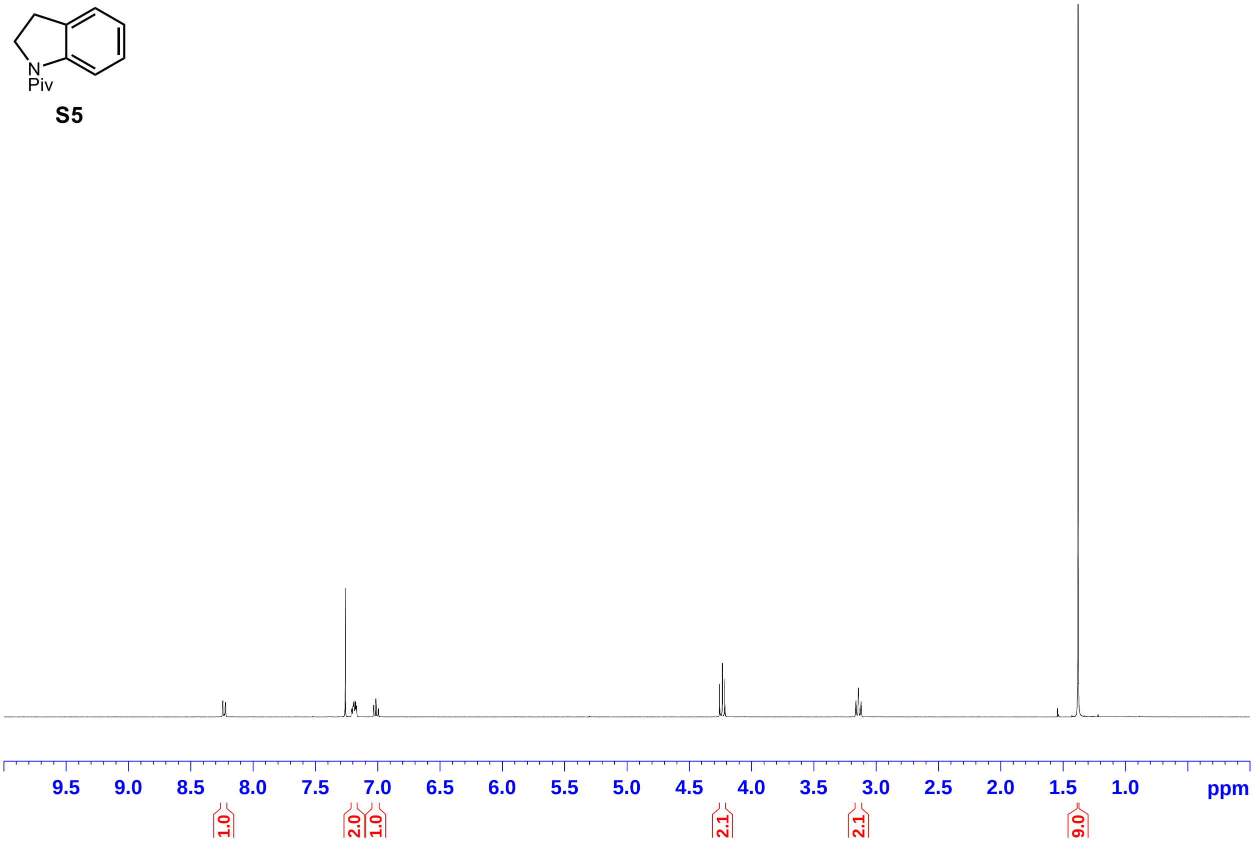


Figure S15: 400 MHz ^{1}H NMR spectrum of **S5** in CDCl$_3$

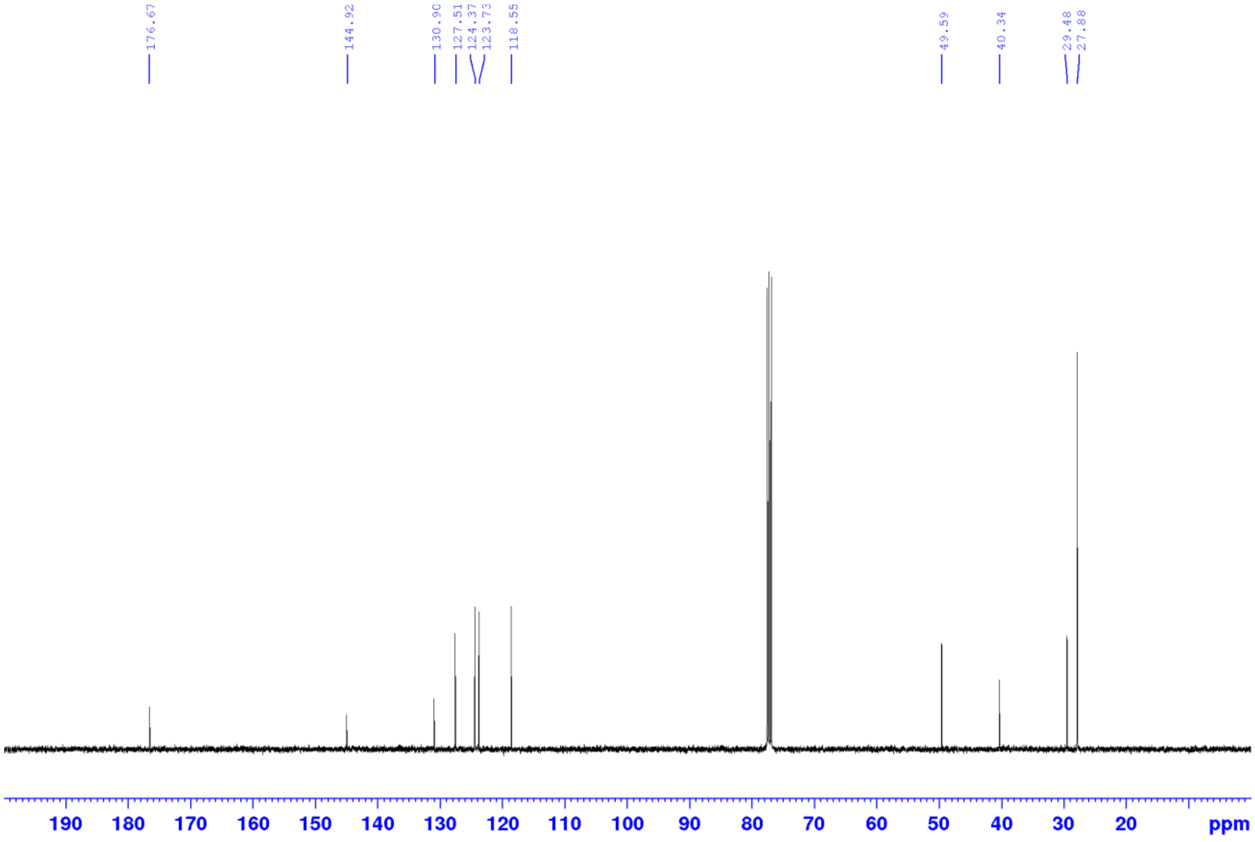


Figure S16: 101 MHz ^{13}C NMR spectrum of **S5** in CDCl$_3$

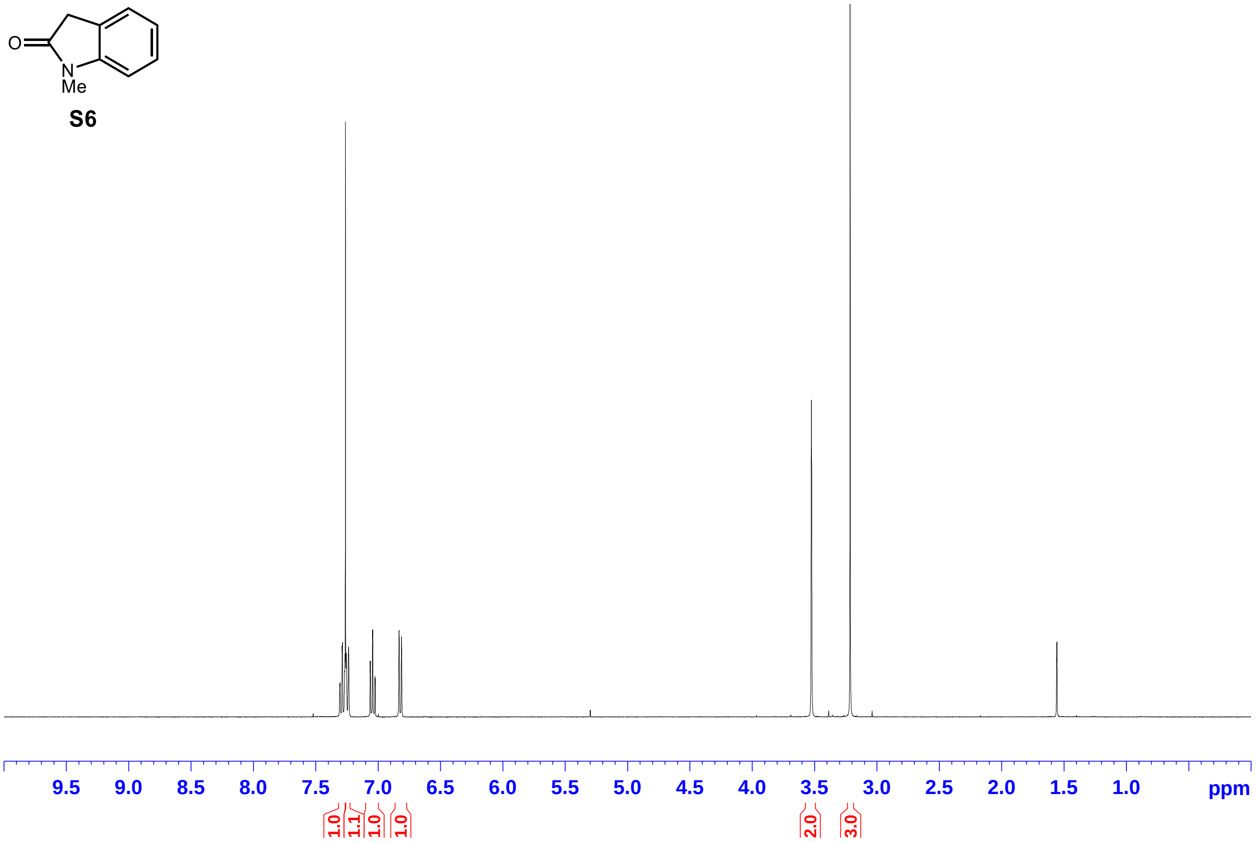


Figure S17: 400 MHz ^{1}H NMR spectrum of **S6** in $CDCl_3$

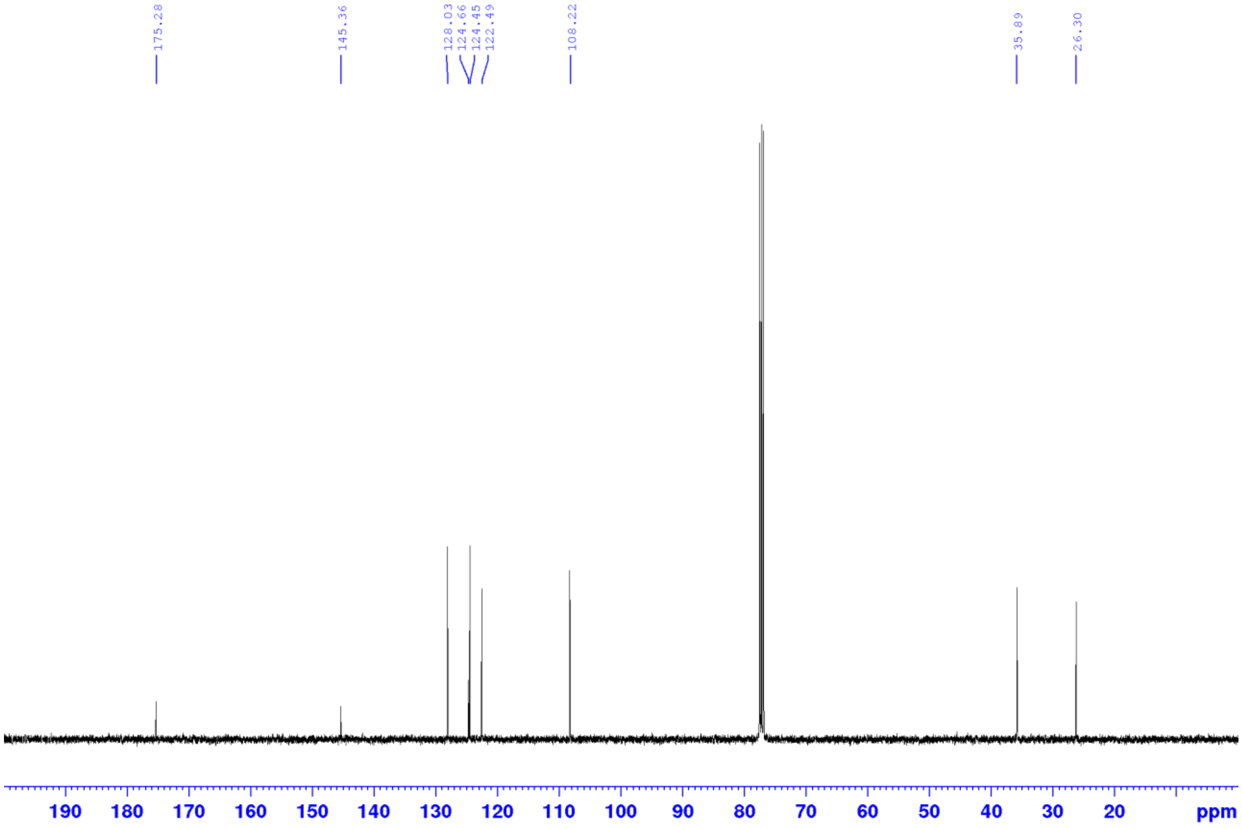
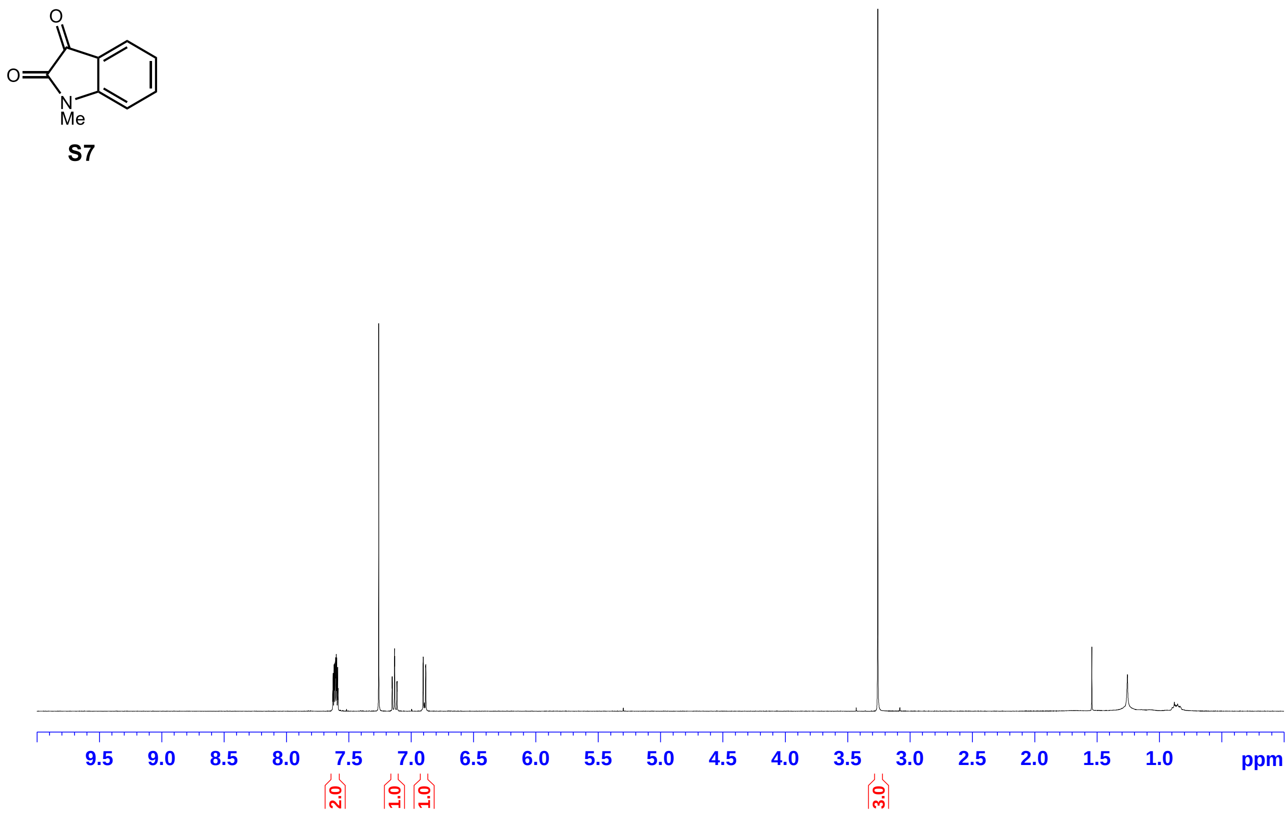


Figure S18: 101 MHz ^{13}C NMR spectrum of **S6** in $CDCl_3$



S7

Figure S19: 400 MHz ^{1}H NMR spectrum of **S7** in $CDCl_3$

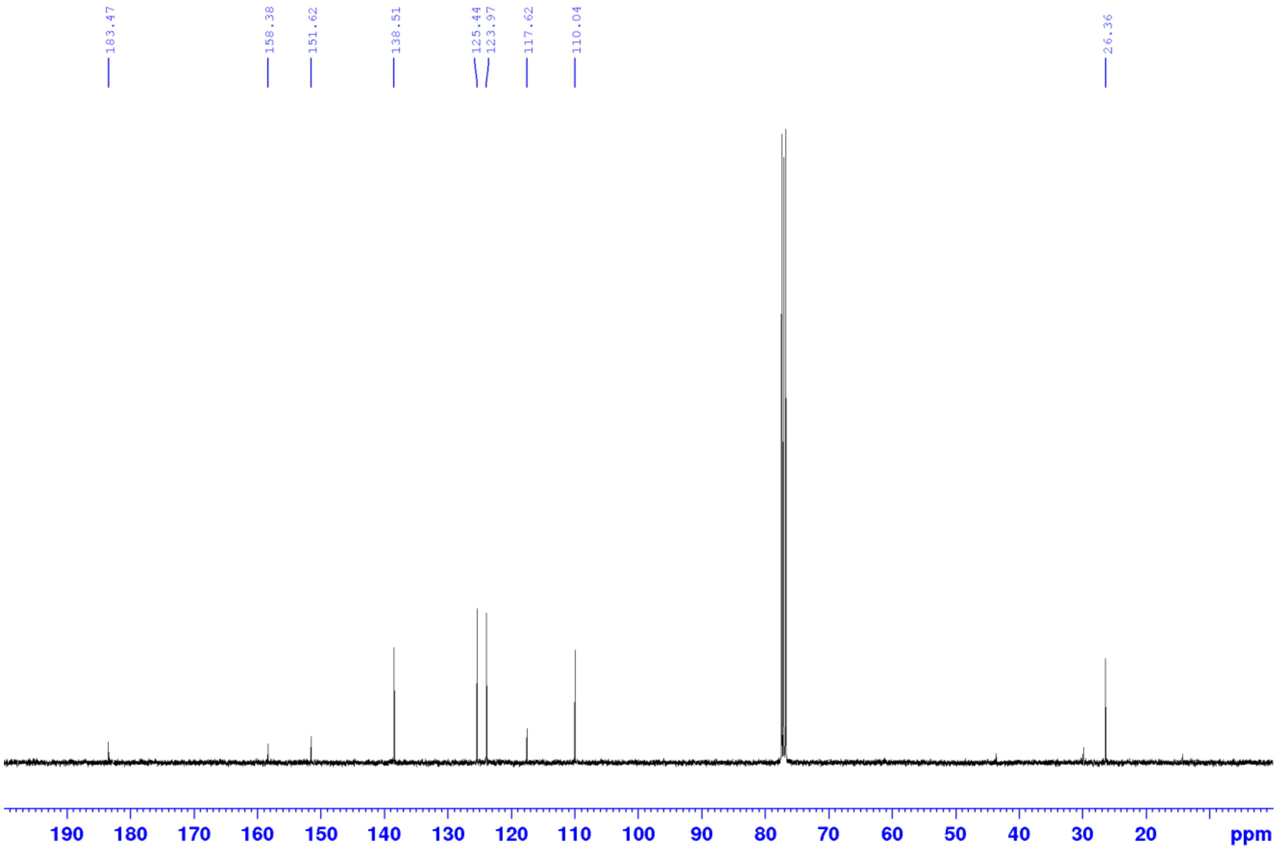


Figure S20: 101 MHz ^{13}C NMR spectrum of **S7** in $CDCl_3$

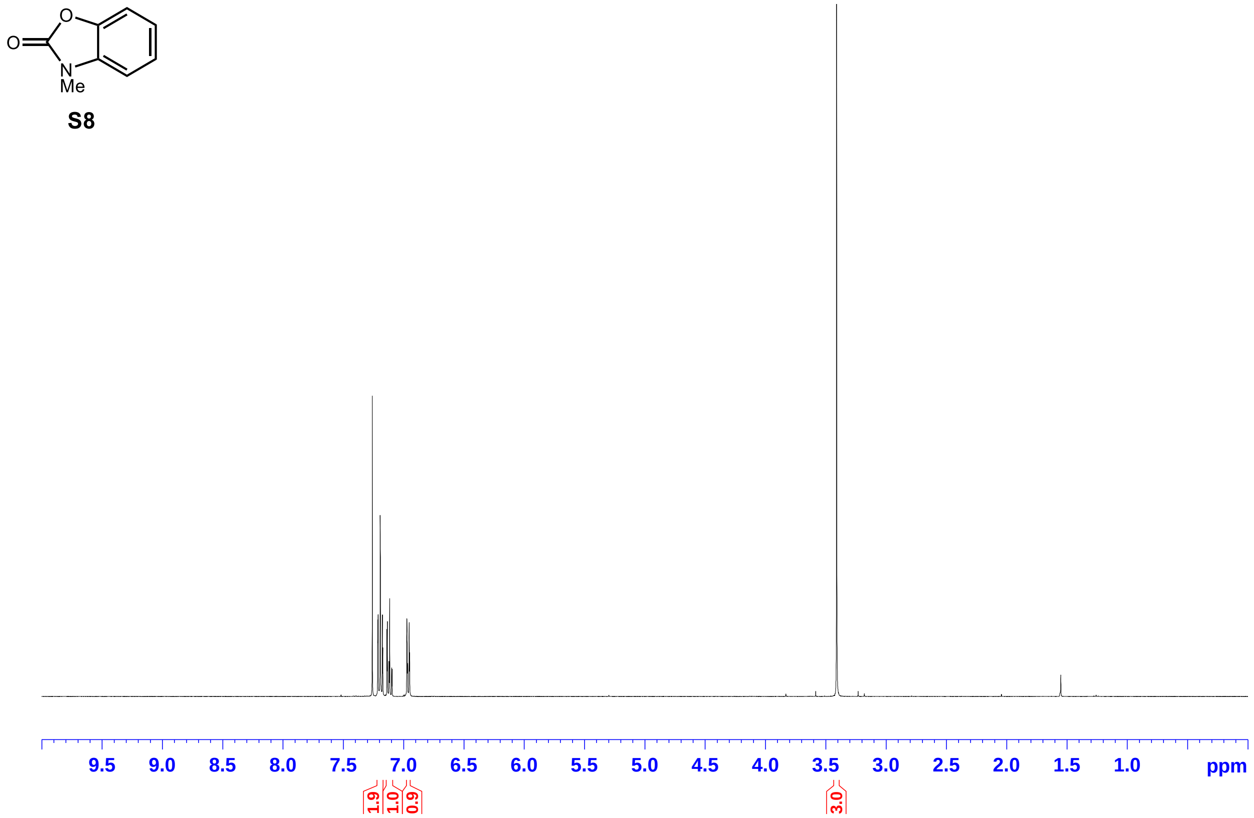


Figure S21: 400 MHz ^{1}H NMR spectrum of **S8** in $CDCl_3$

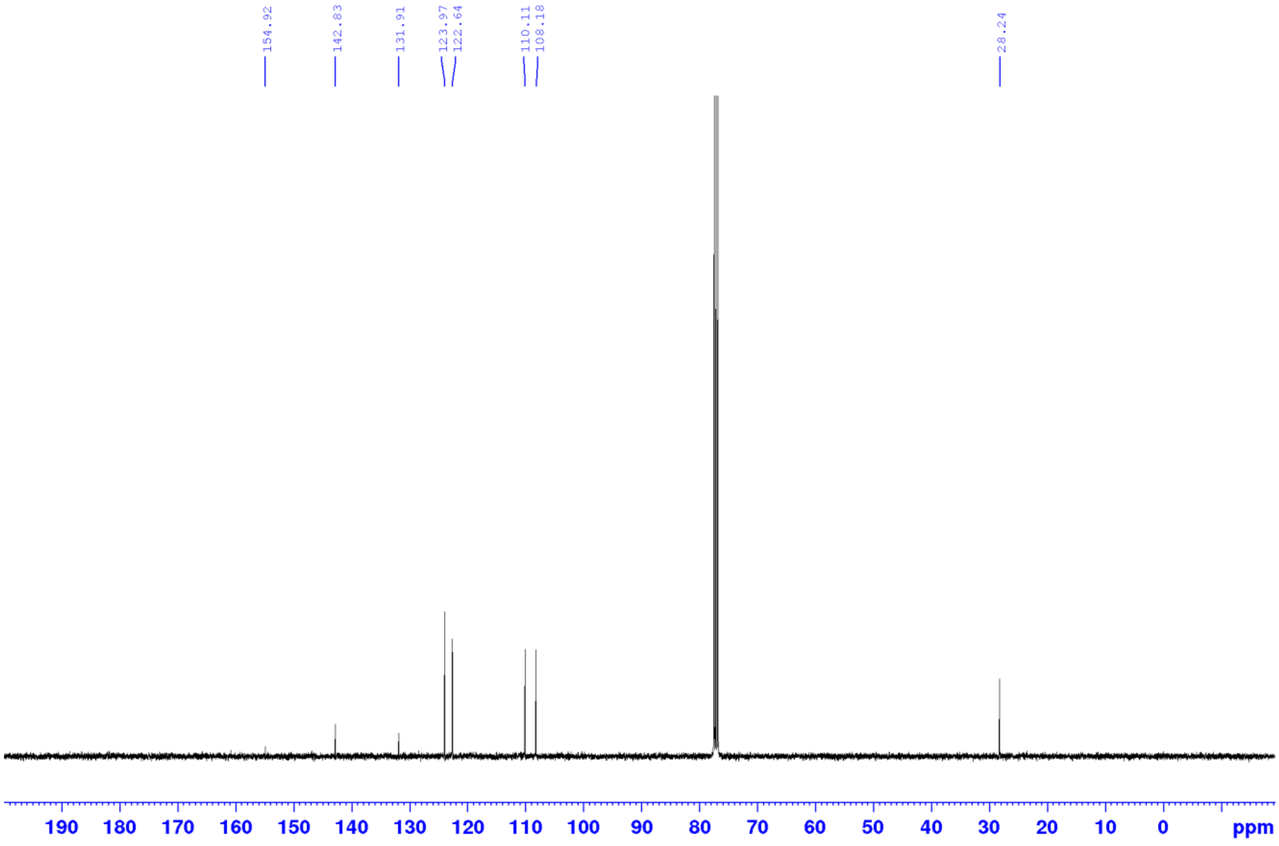


Figure S22: 101 MHz ^{13}C NMR spectrum of **S8** in $CDCl_3$

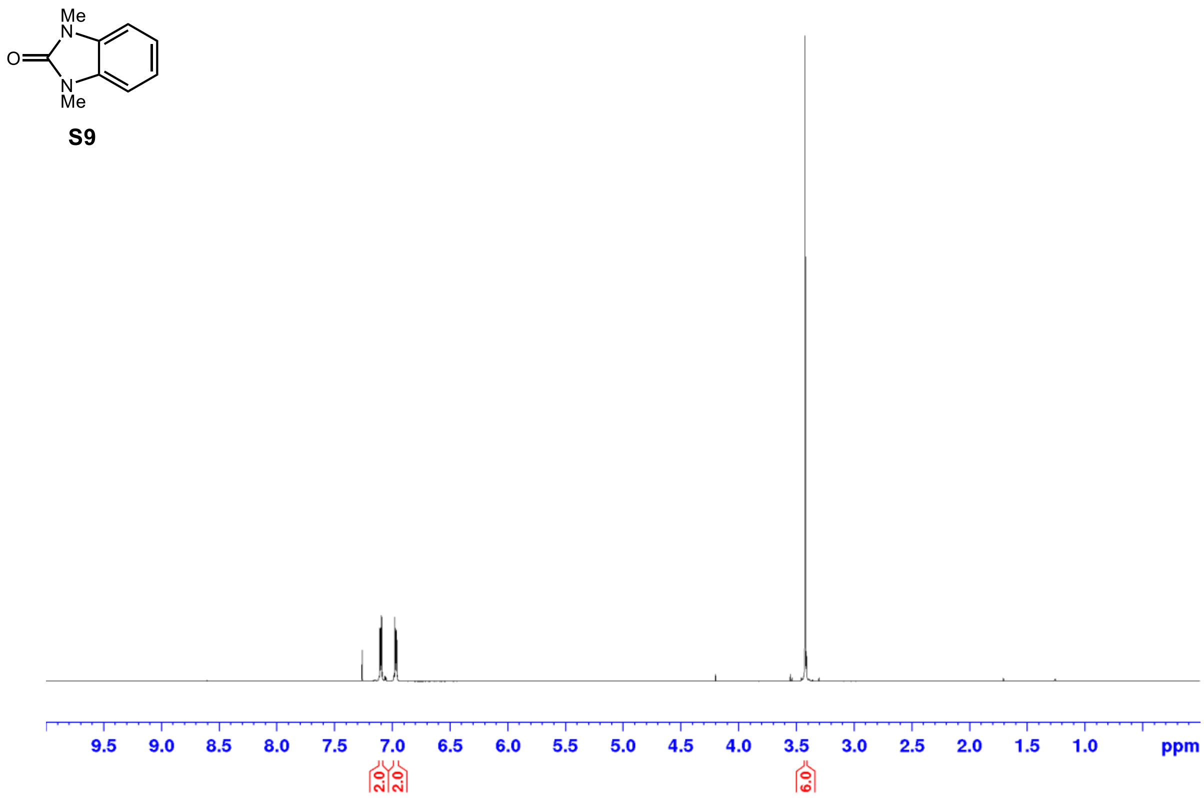


Figure S23: 400 MHz ^{1}H NMR spectrum of **S9** in $CDCl_3$

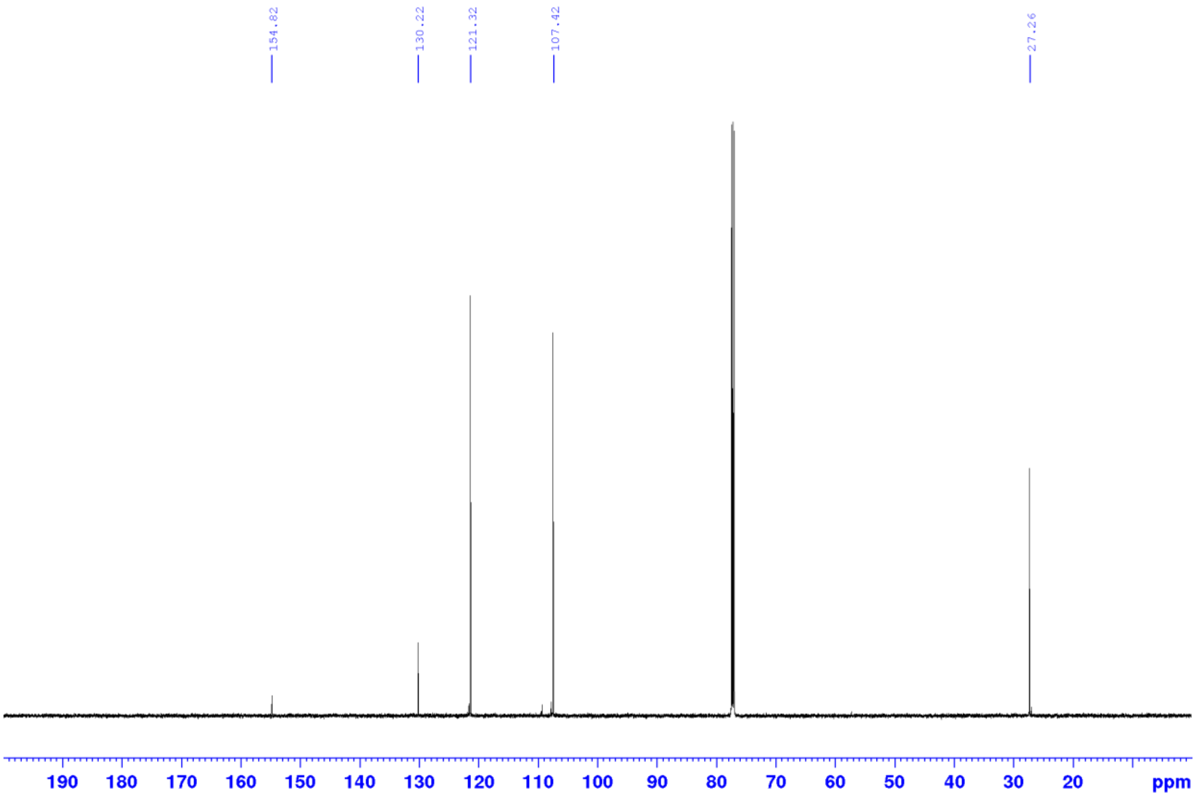


Figure S24: 101 MHz ^{13}C NMR spectrum of **S9** in $CDCl_3$

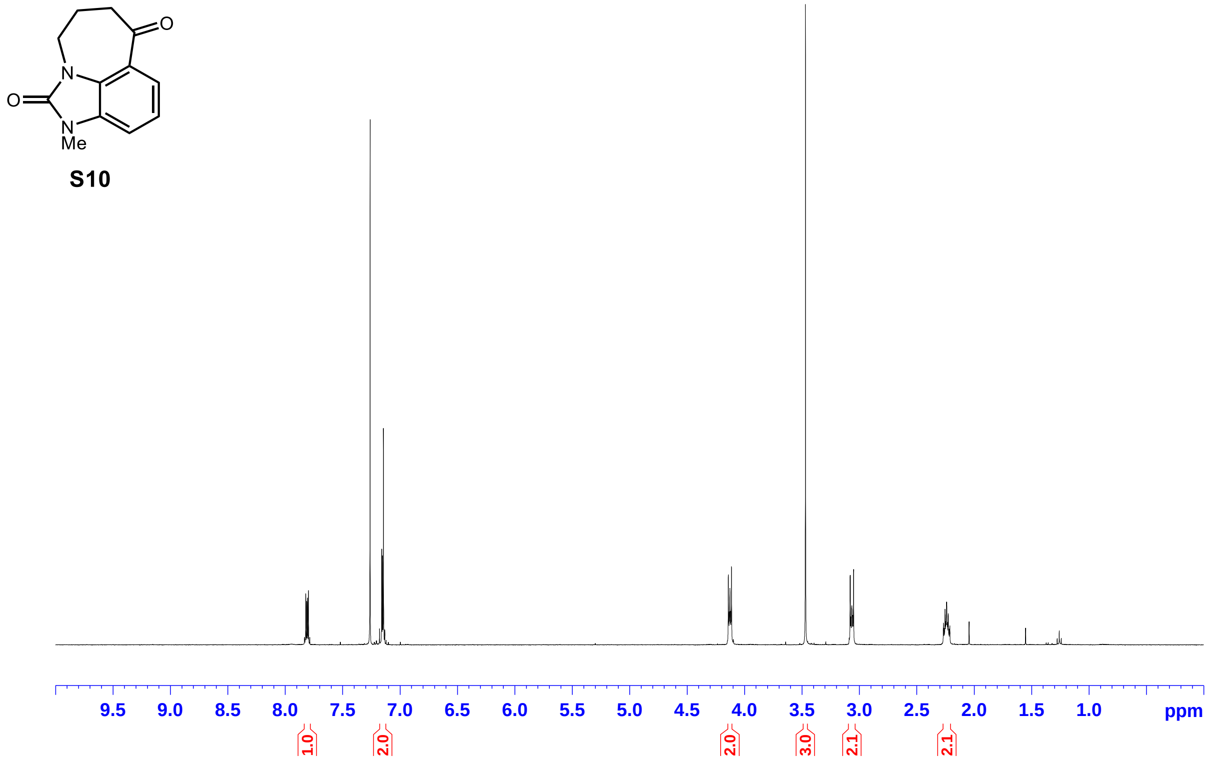


Figure S25: 400 MHz ^{1}H NMR spectrum of **S10** in $CDCl_3$

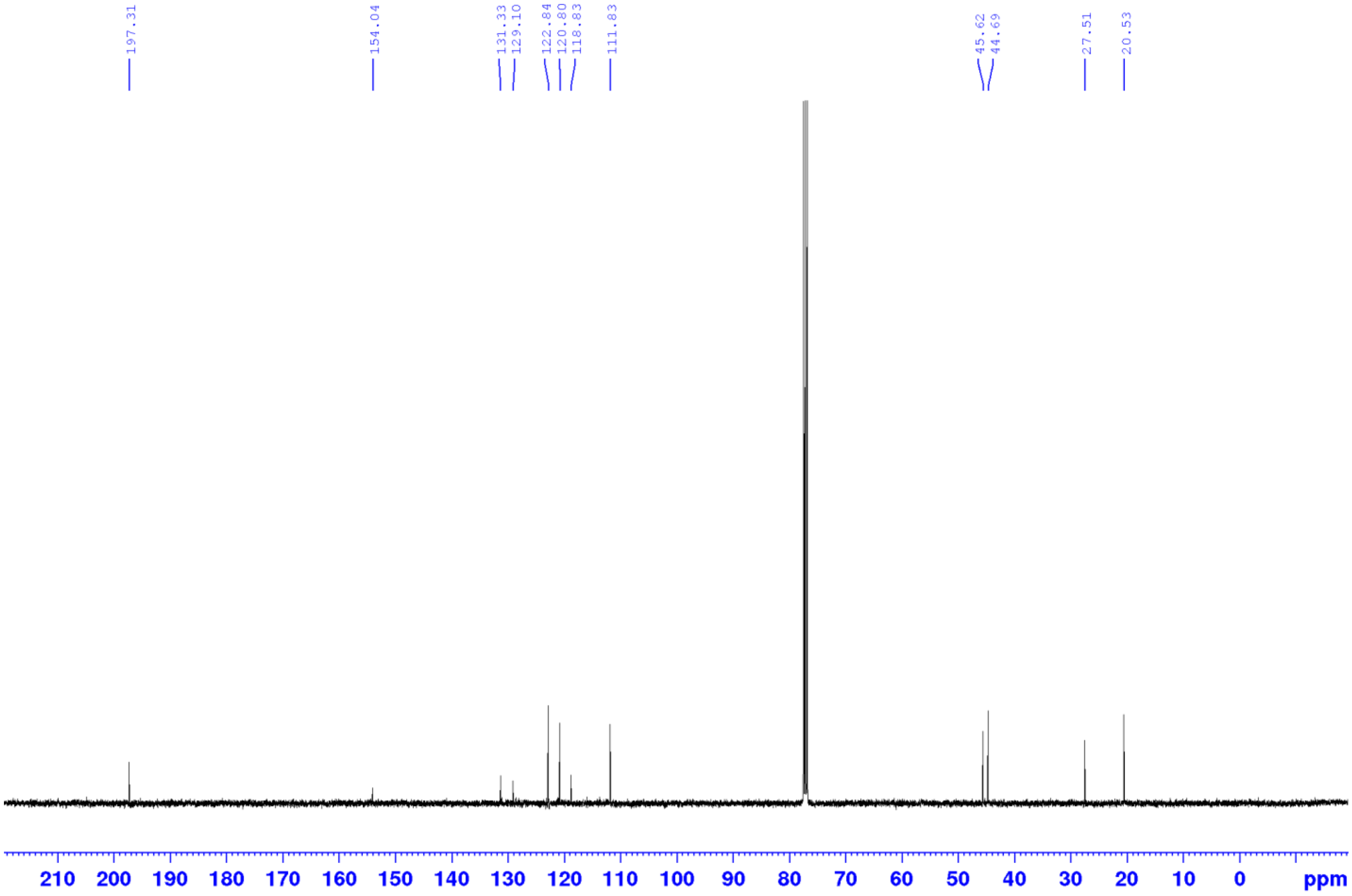


Figure S26: 101 MHz ^{13}C NMR spectrum of **S10** in $CDCl_3$

Figure S27: 400 MHz ^{1}H NMR spectrum of **S11** in $CDCl_3$

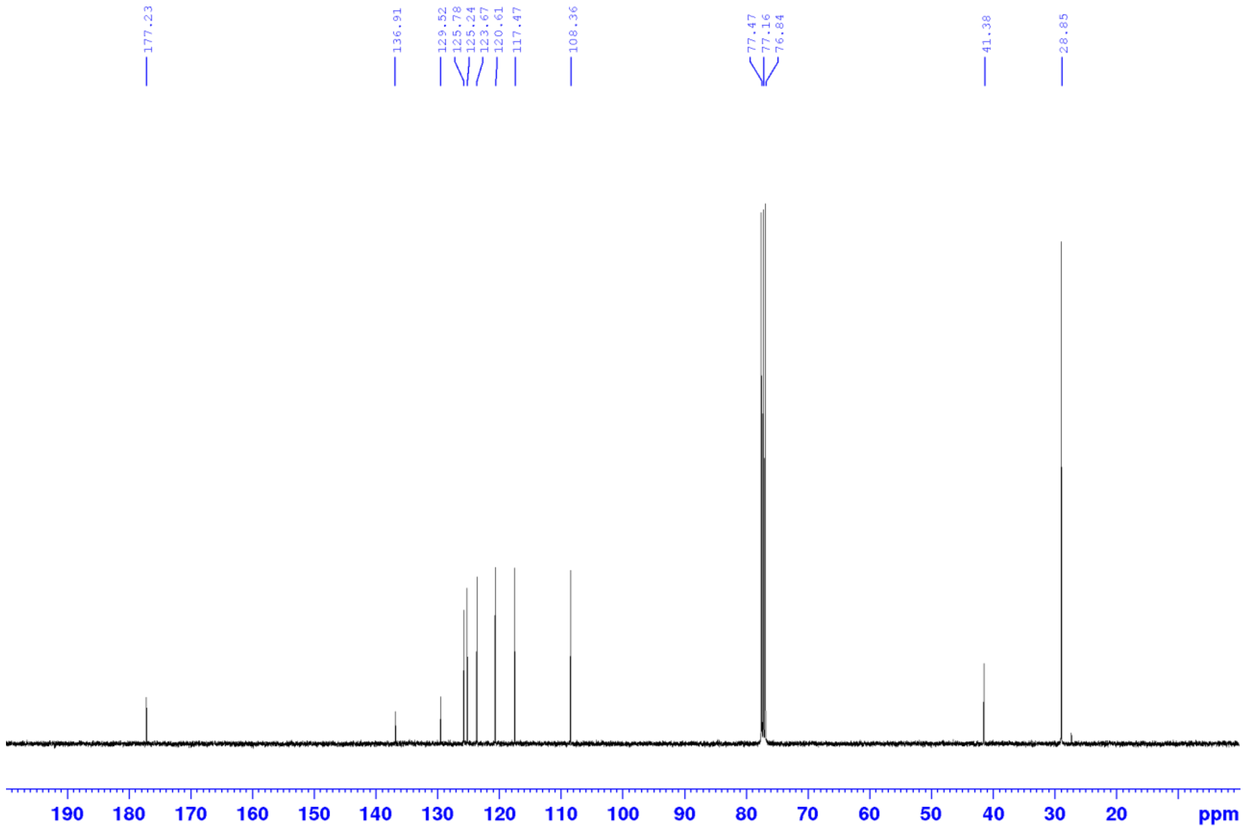
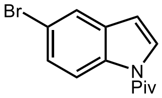


Figure S28: 101 MHz ^{13}C NMR spectrum of **S11** in $CDCl_3$



S12

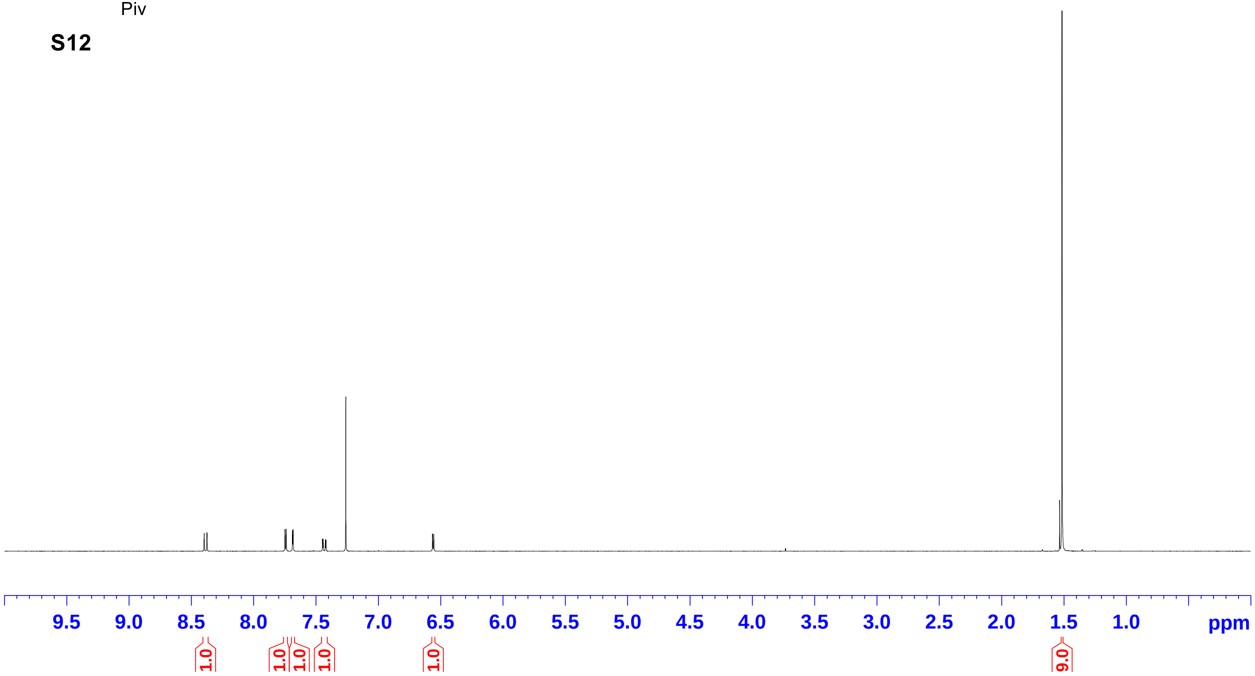


Figure S29: 400 MHz ^{1}H NMR spectrum of **S12** in CDCl$_3$

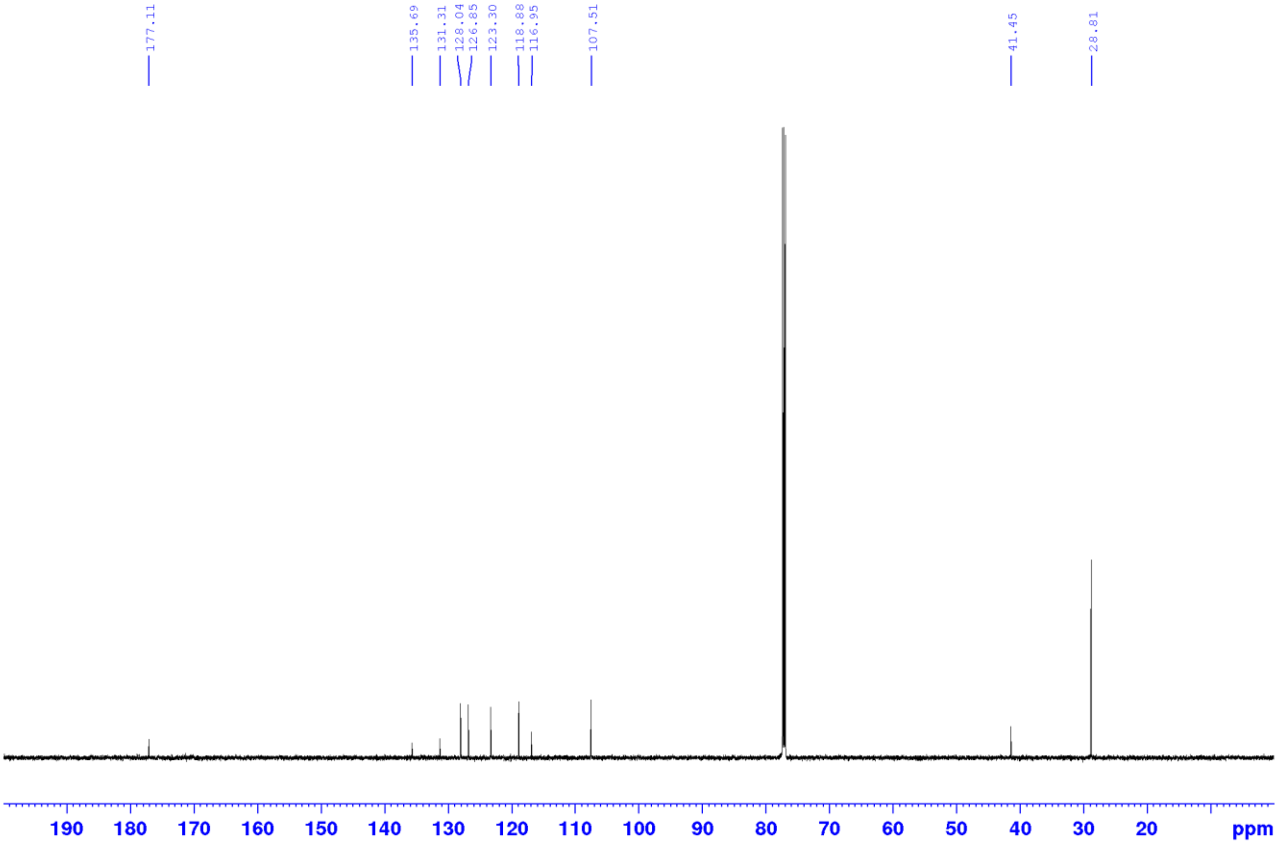


Figure S30: 101 MHz ^{13}C NMR spectrum of **S12** in CDCl$_3$

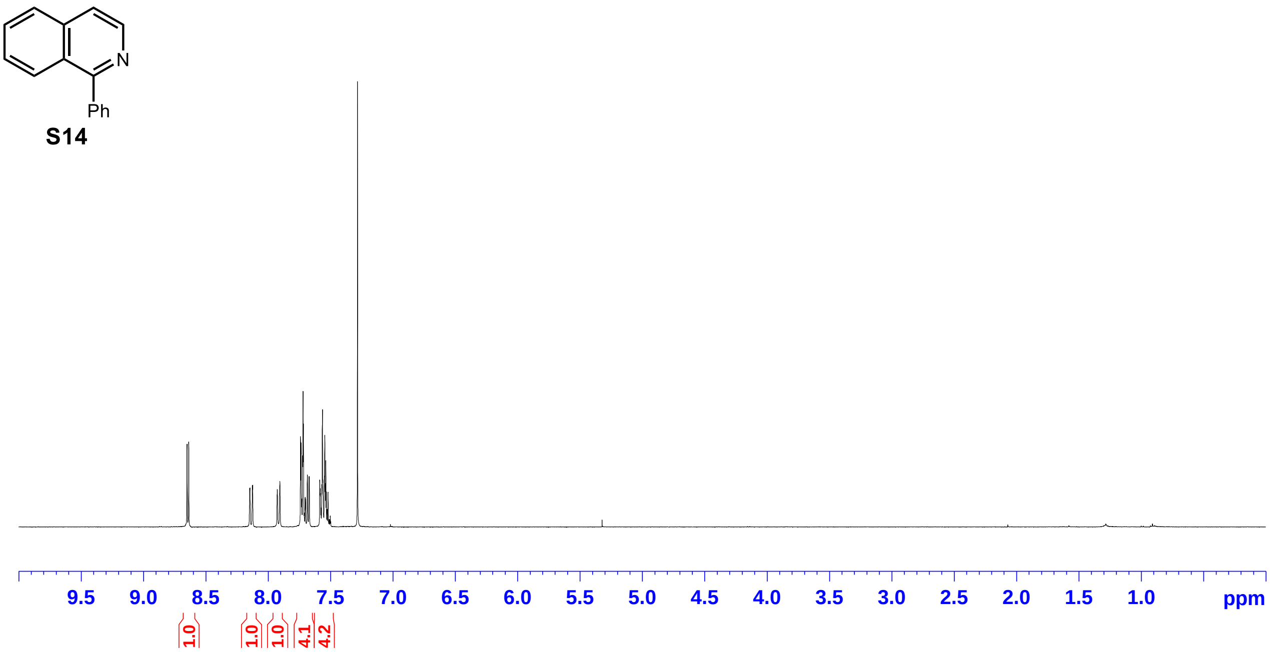


Figure S31: 400 MHz ^{1}H NMR spectrum of **S14** in CDCl$_3$

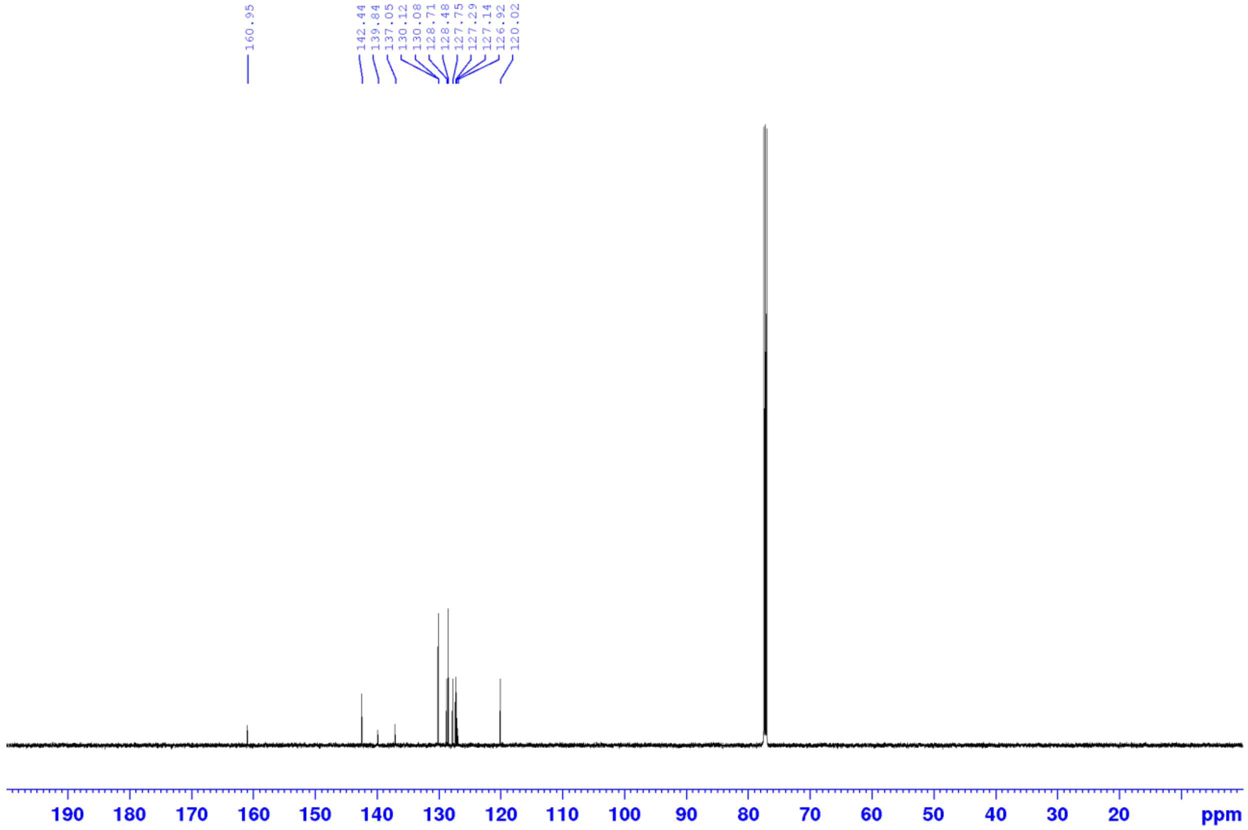
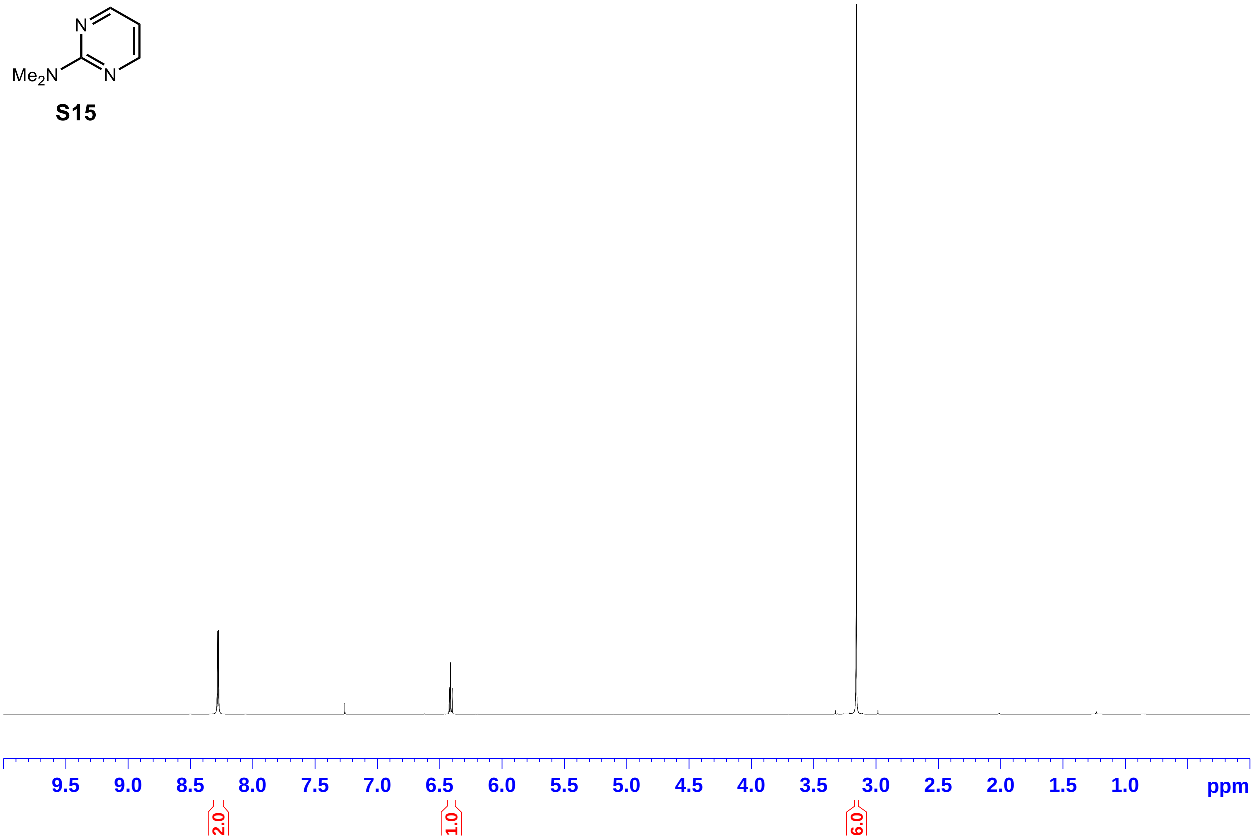


Figure S32: 101 MHz ^{13}C NMR spectrum of **S14** in CDCl$_3$



S15

Figure S33: 400 MHz ^{1}H NMR spectrum of **S15** in CDCl$_3$

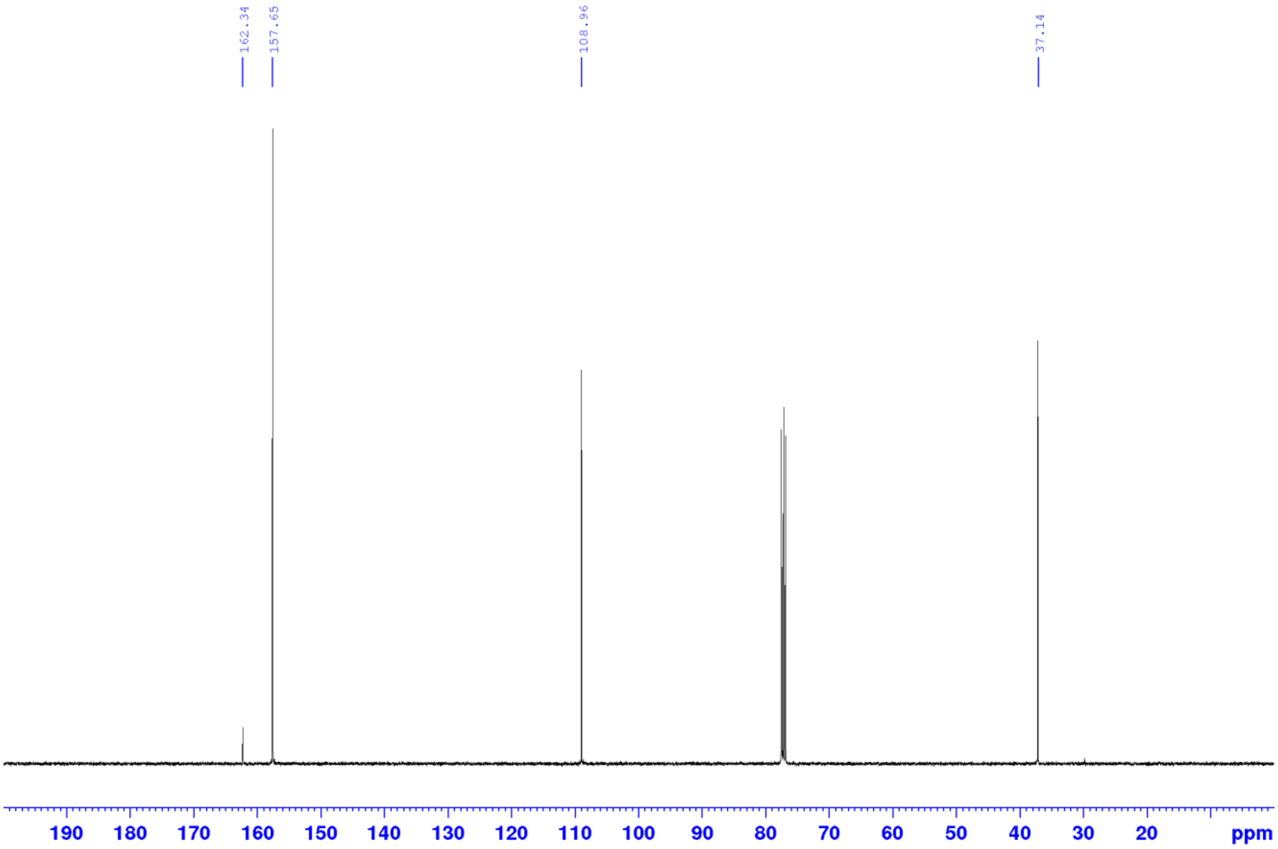


Figure S34: 101 MHz ^{13}C NMR spectrum of **S15** in CDCl$_3$

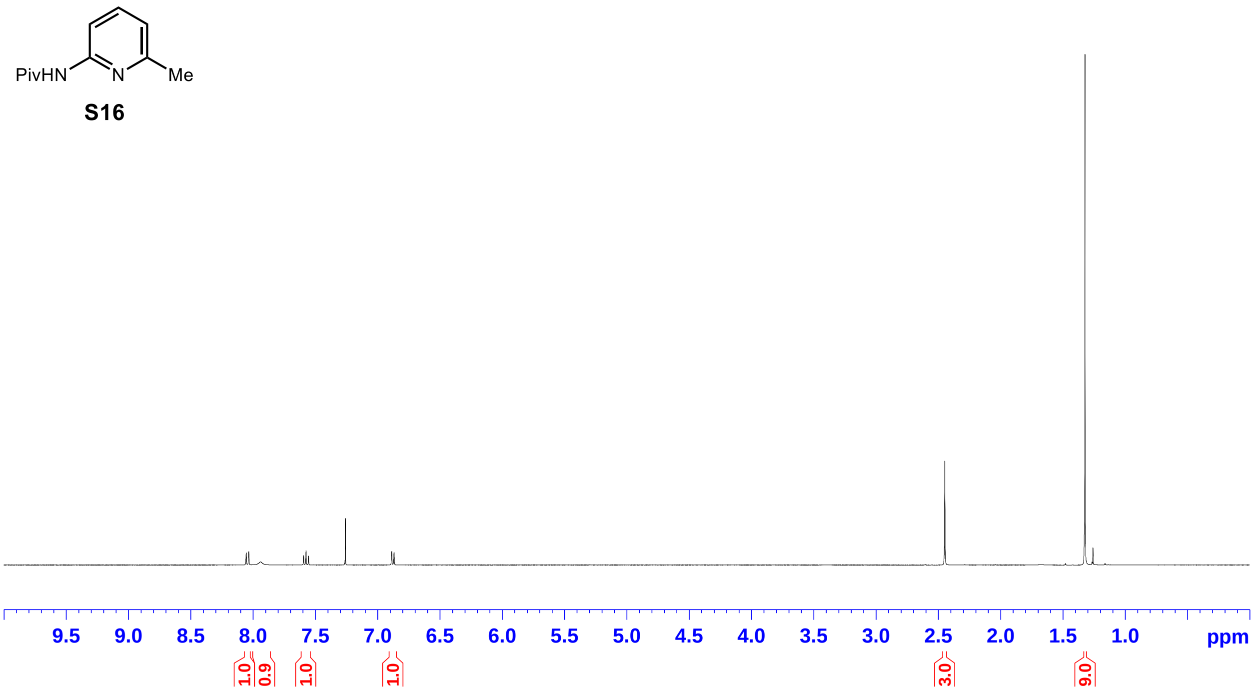


Figure S35: 400 MHz ^{1}H NMR spectrum of **S16** in CDCl$_3$

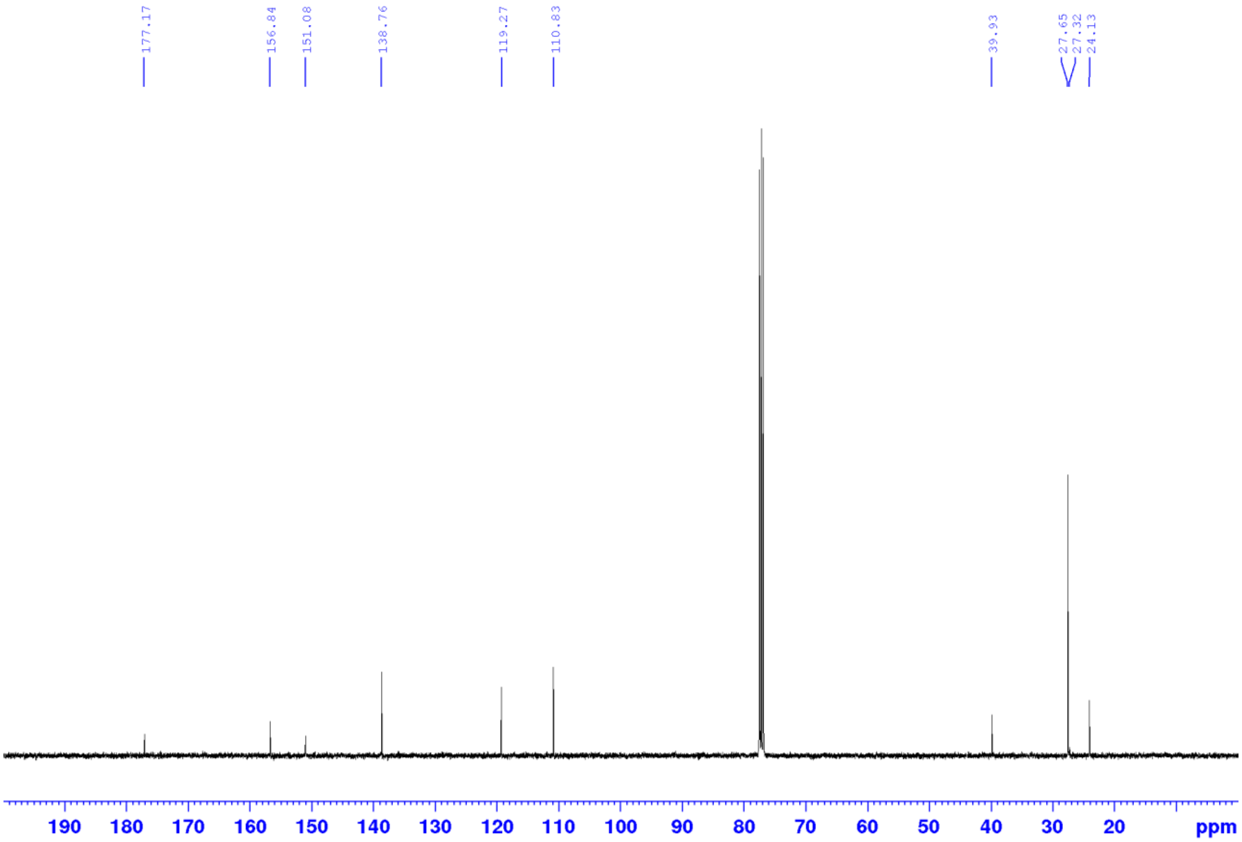


Figure S36: 101 MHz ^{13}C NMR spectrum of **S16** in CDCl$_3$

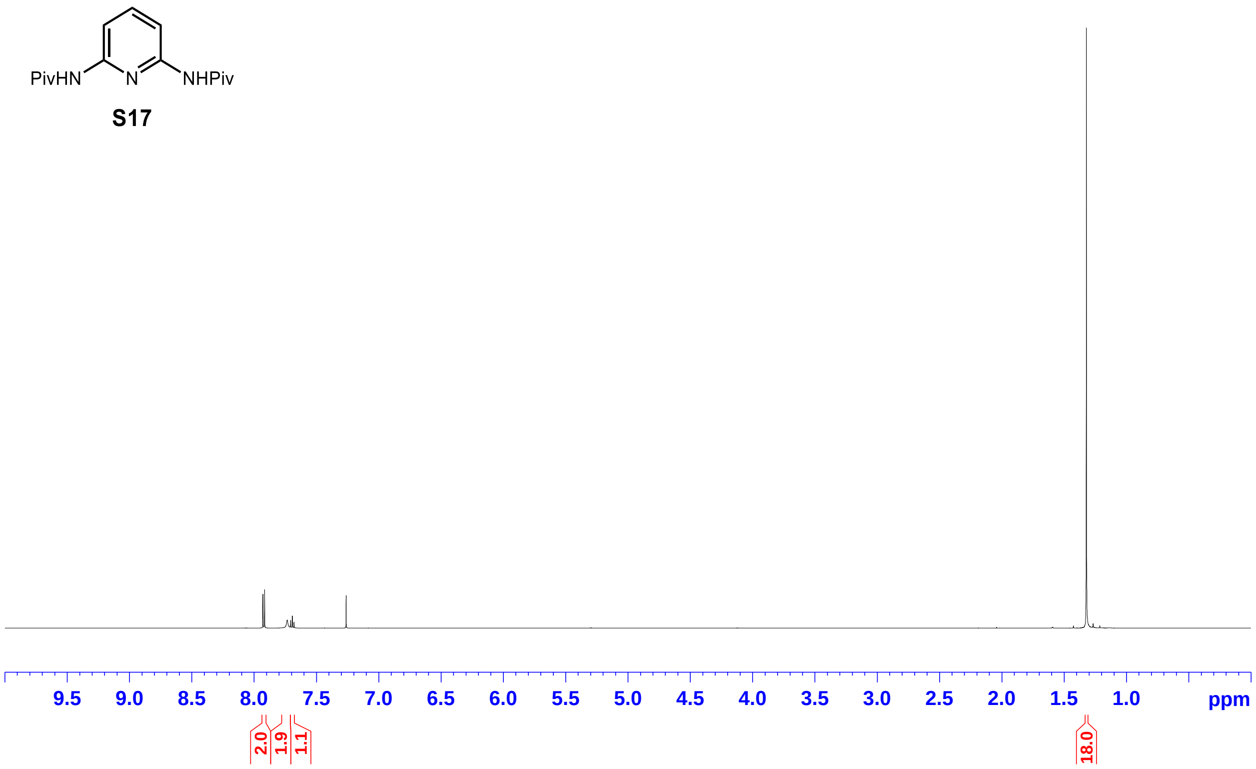


Figure S37: 600 MHz ^{1}H NMR spectrum of **S17** in $CDCl_3$

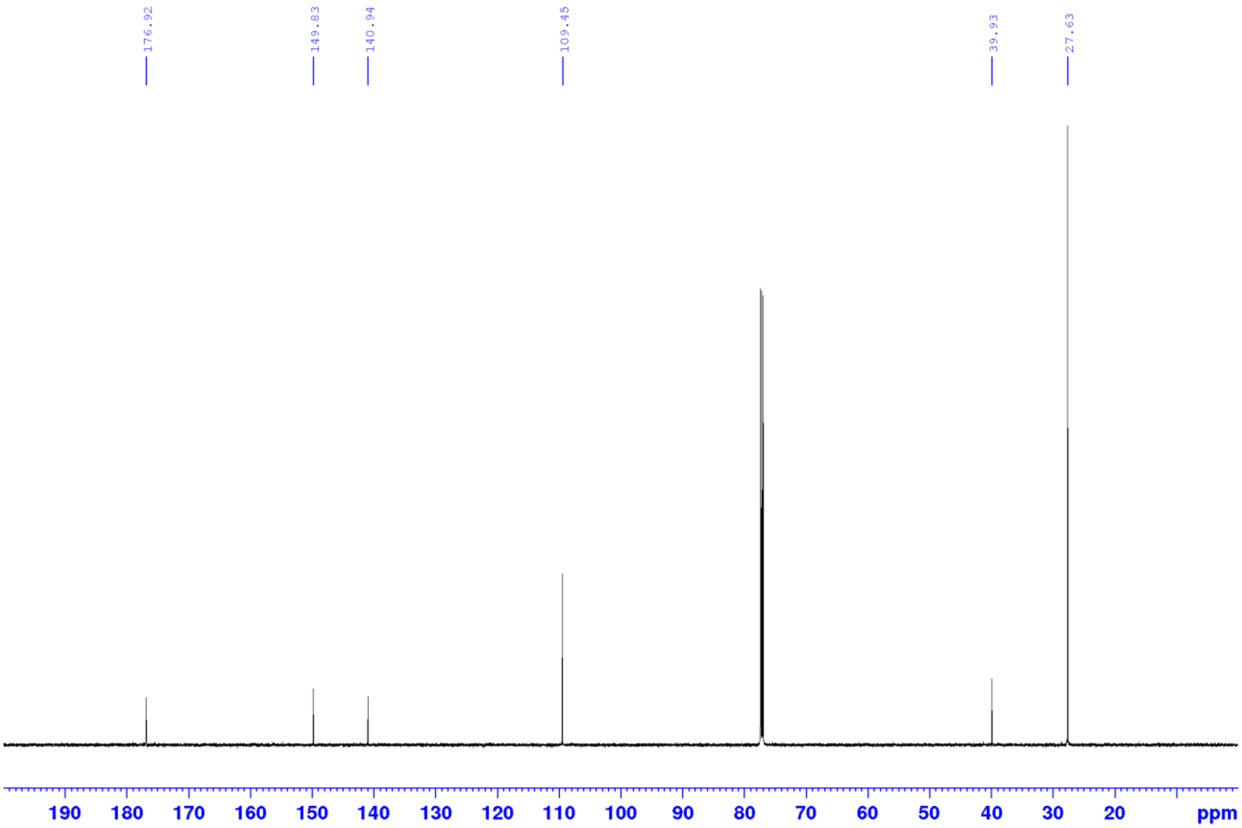


Figure S38: 150 MHz ^{13}C NMR spectrum of **S17** in $CDCl_3$

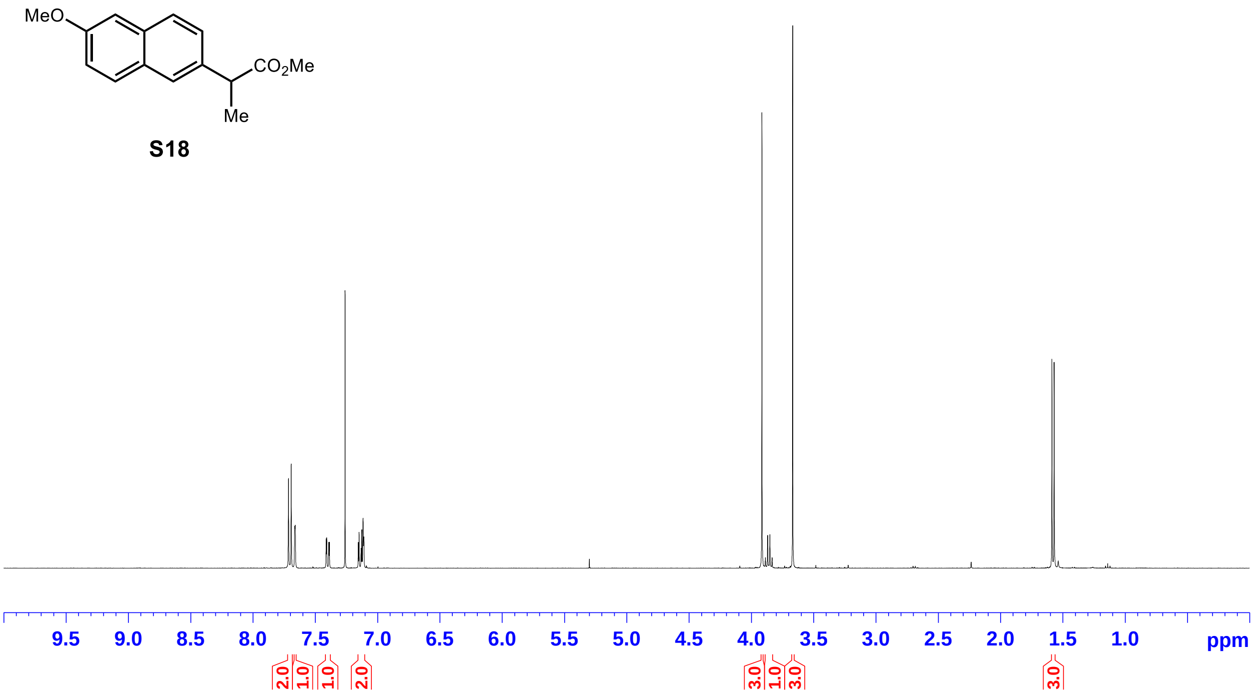


Figure S39: 400 MHz ^{1}H NMR spectrum of **S18** in $CDCl_3$

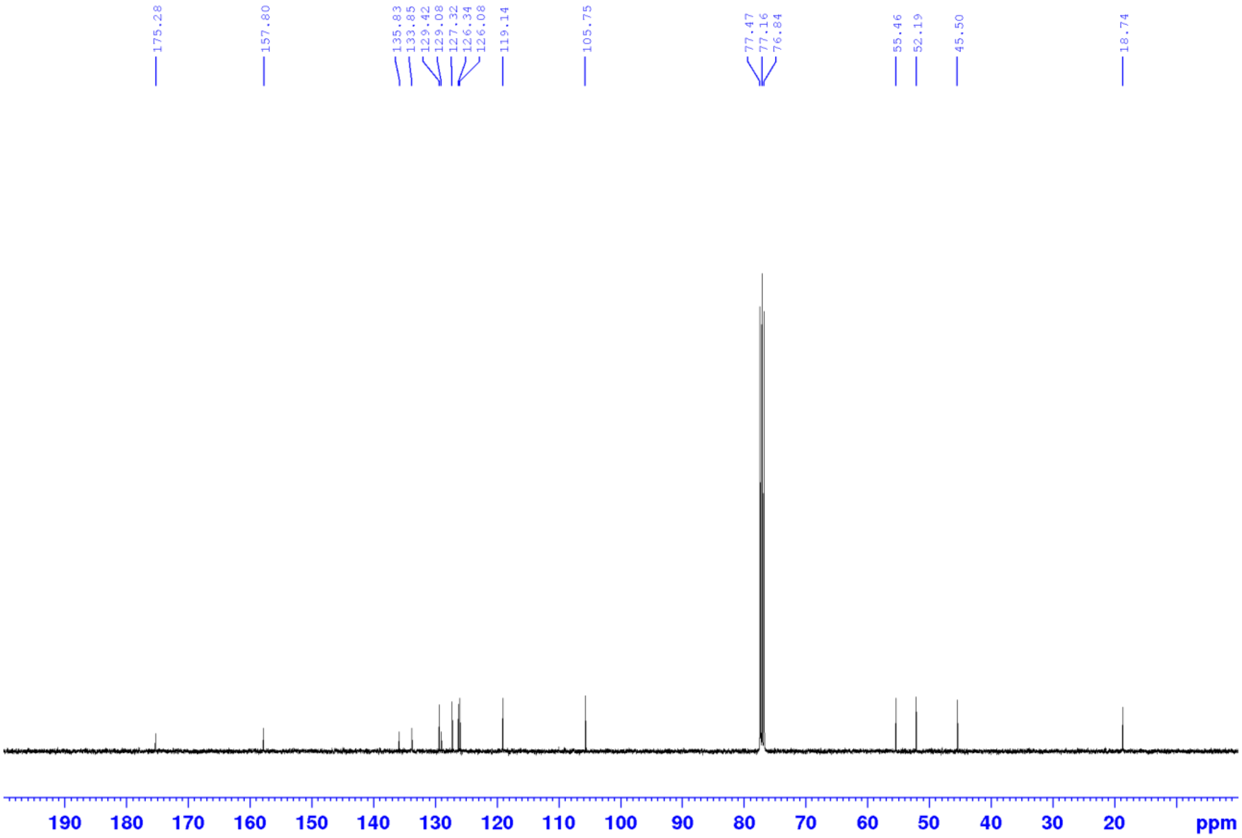


Figure S40: 101 MHz ^{13}C NMR spectrum of **S18** in $CDCl_3$

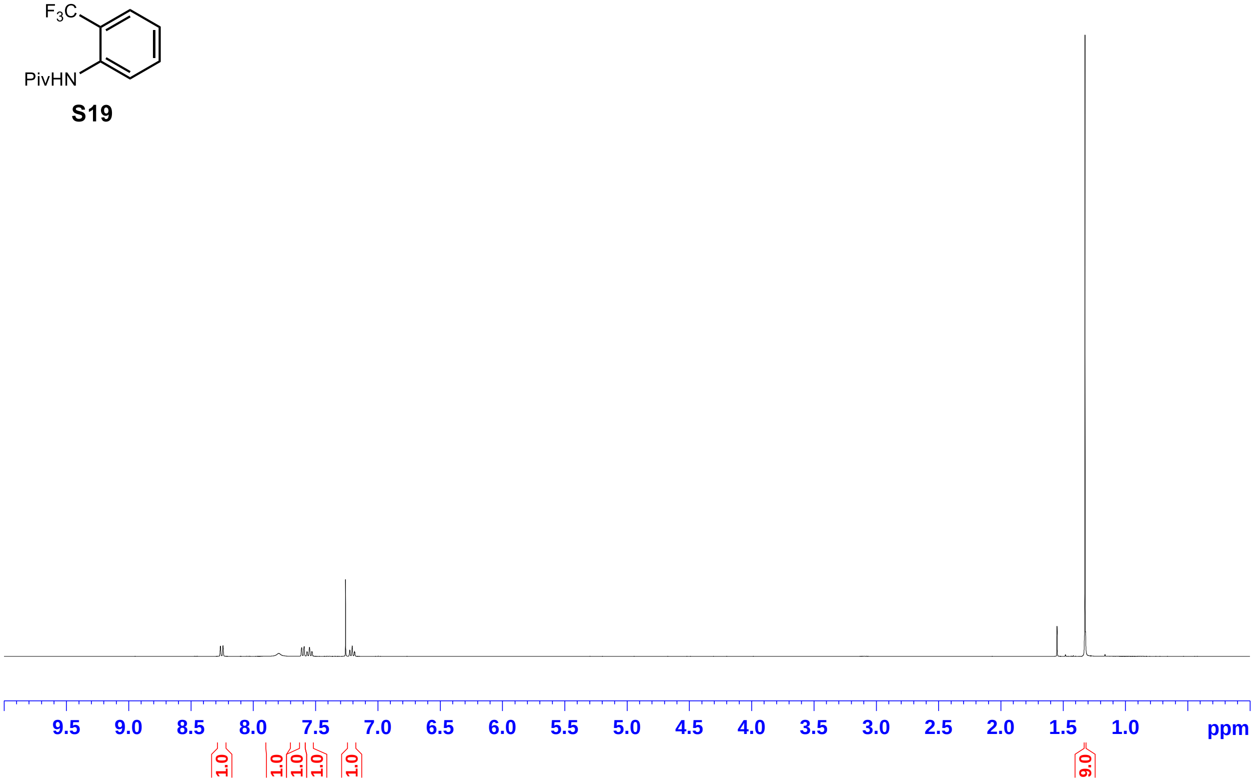


Figure S41: 400 MHz ^{1}H NMR spectrum of **S19** in $CDCl_3$

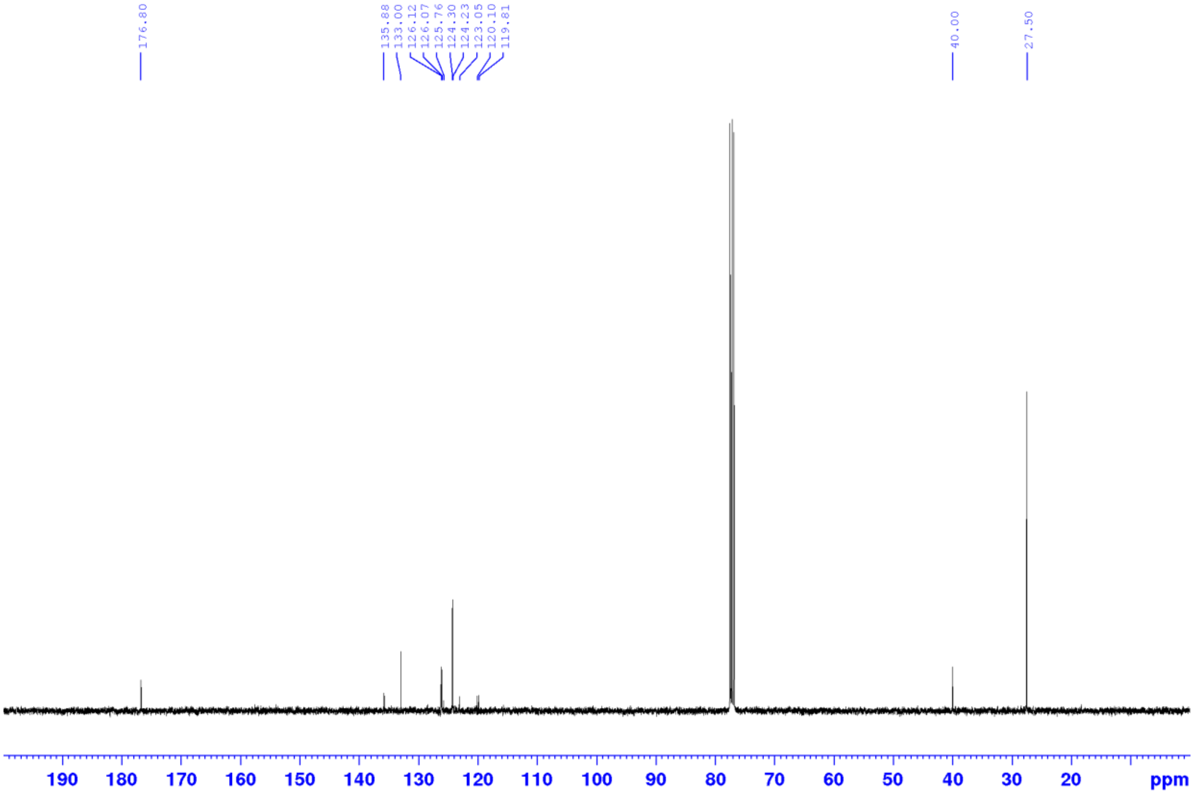
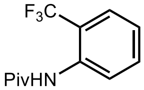


Figure S42: 101 MHz ^{13}C NMR spectrum of **S19** in $CDCl_3$



S19

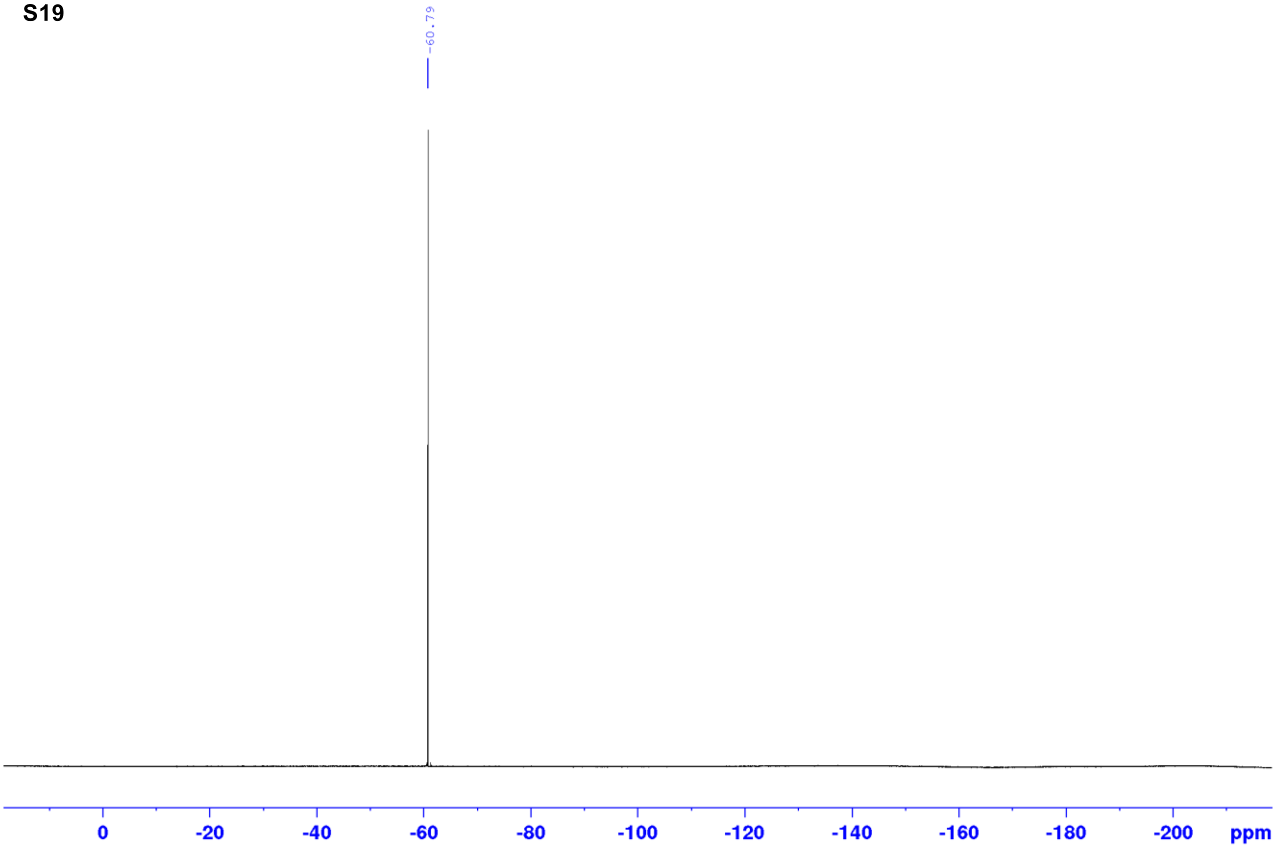


Figure S43: 377 MHz ^{19}F NMR spectrum of **S19** in $CDCl_3$

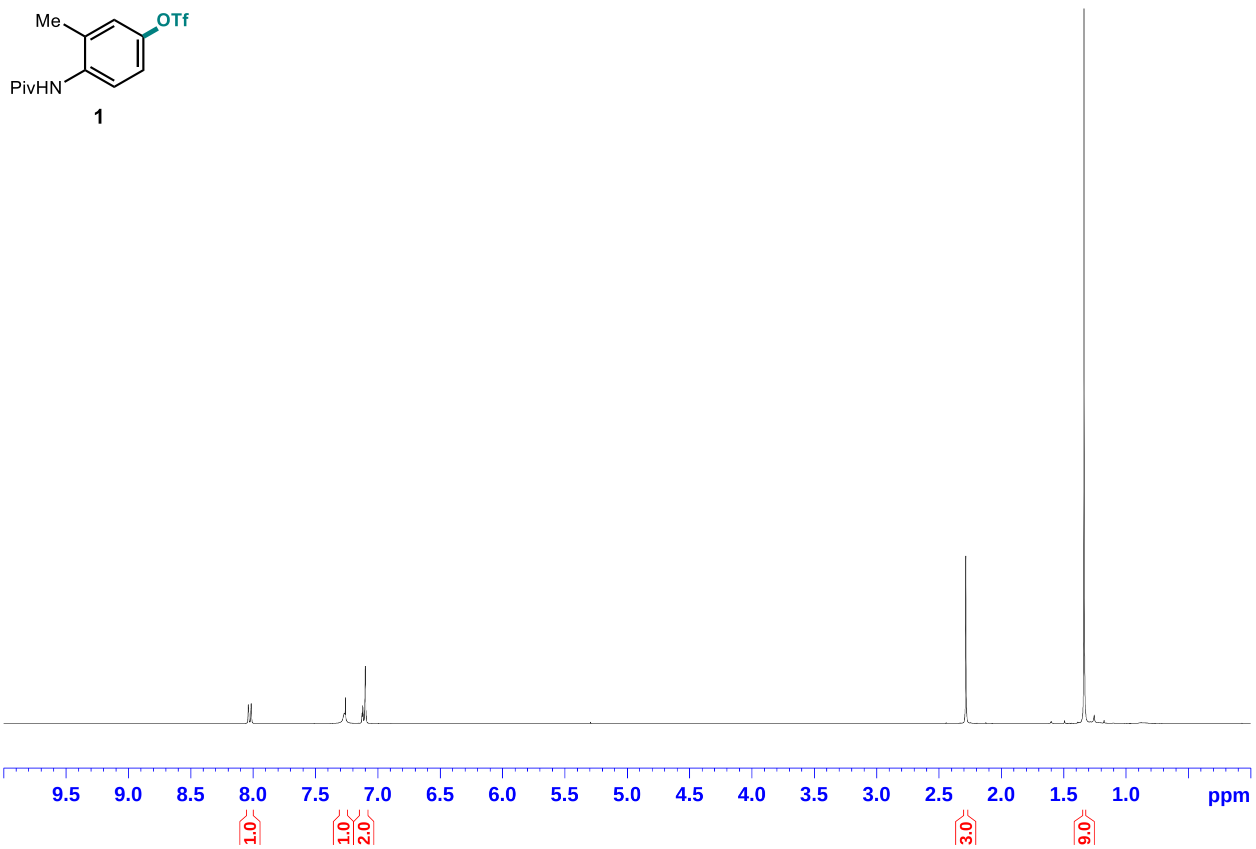


Figure S44: 400 MHz ^{1}H NMR spectrum of **1** in $CDCl_3$

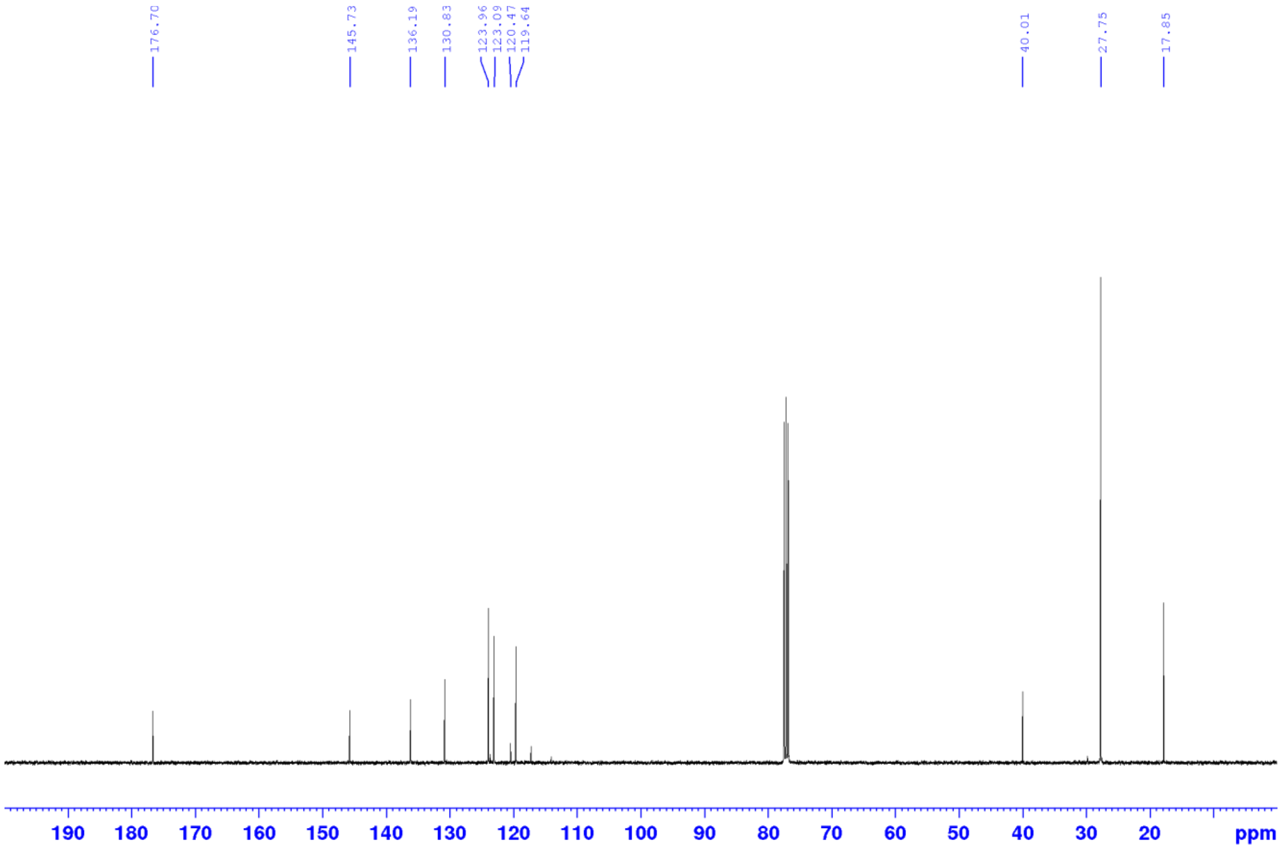


Figure S45: 101 MHz ^{13}C NMR spectrum of **1** in $CDCl_3$

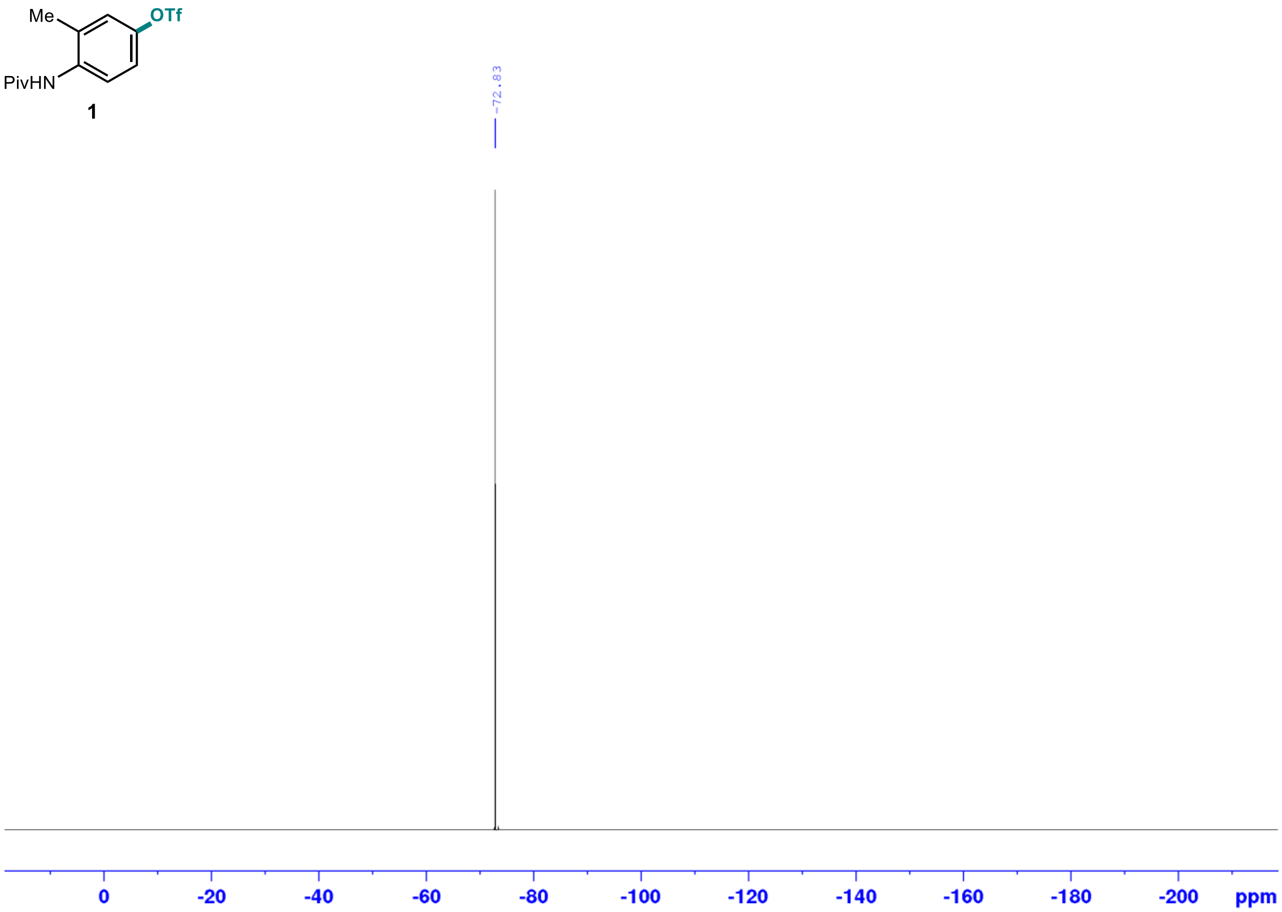


Figure S46: 377 MHz ^{19}F NMR spectrum of **1** in $CDCl_3$

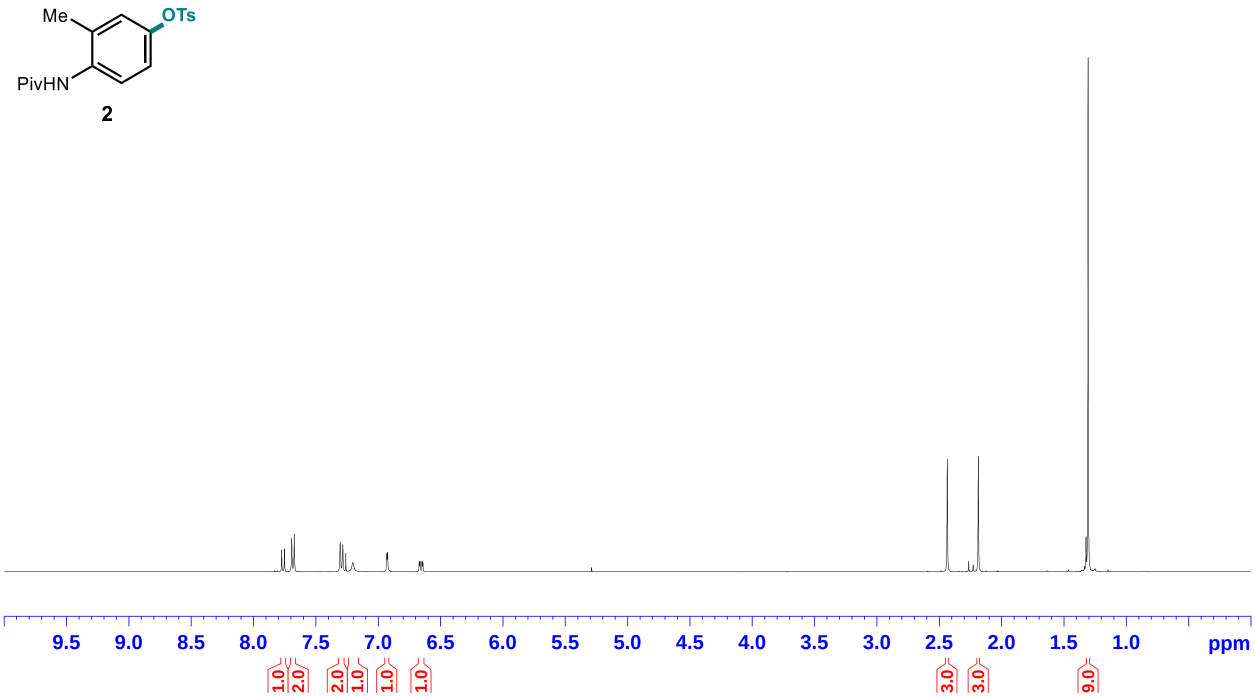


Figure S47: 400 MHz ^{1}H NMR spectrum of **2** in $CDCl_3$

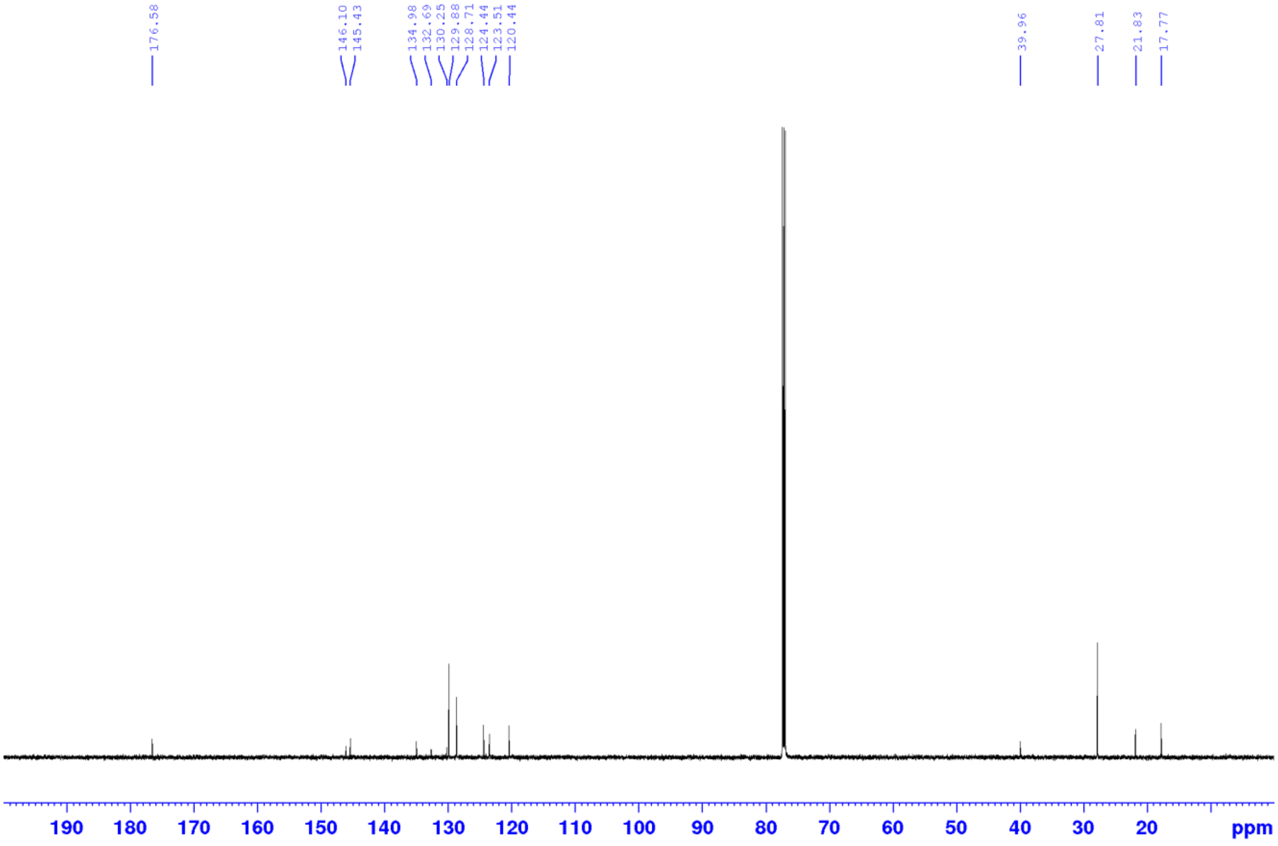


Figure S48: 101 MHz ^{13}C NMR spectrum of **2** in $CDCl_3$

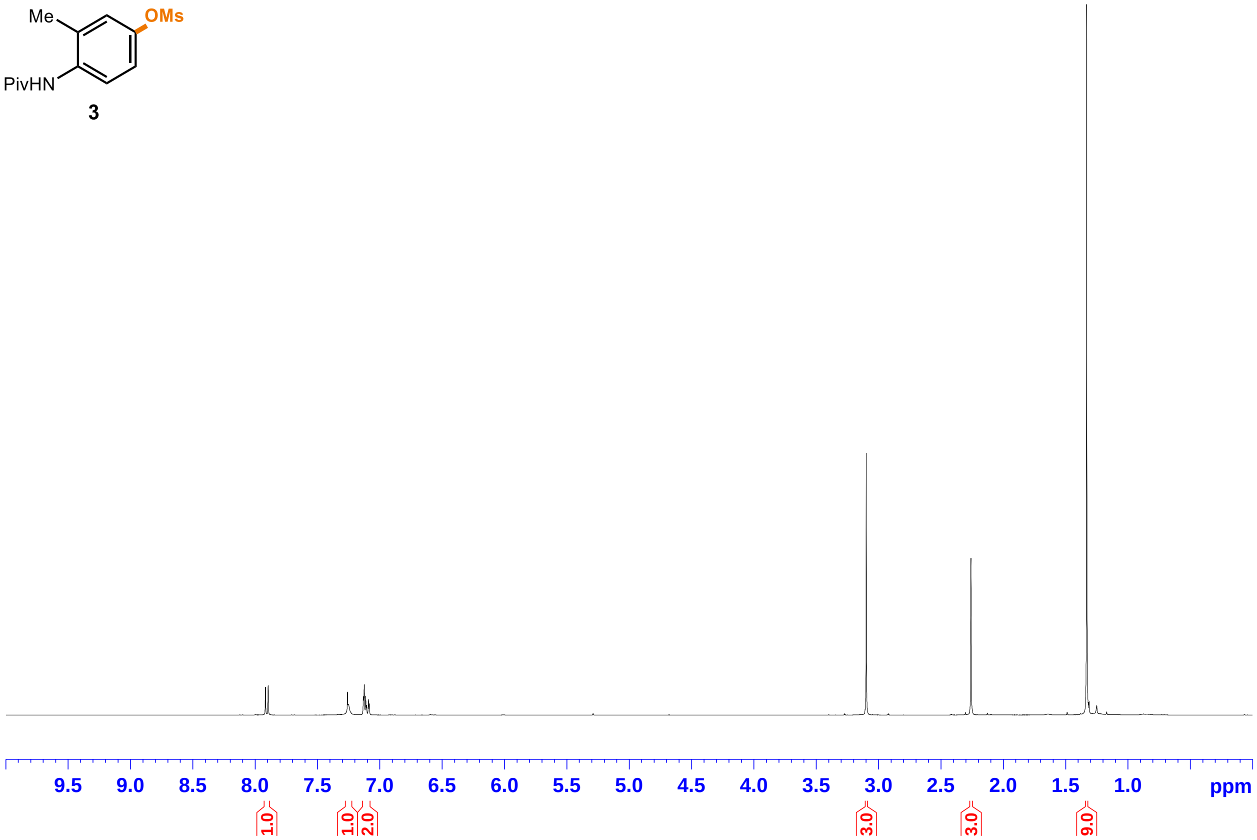


Figure S49: 400 MHz ^{1}H NMR spectrum of **3** in $CDCl_3$

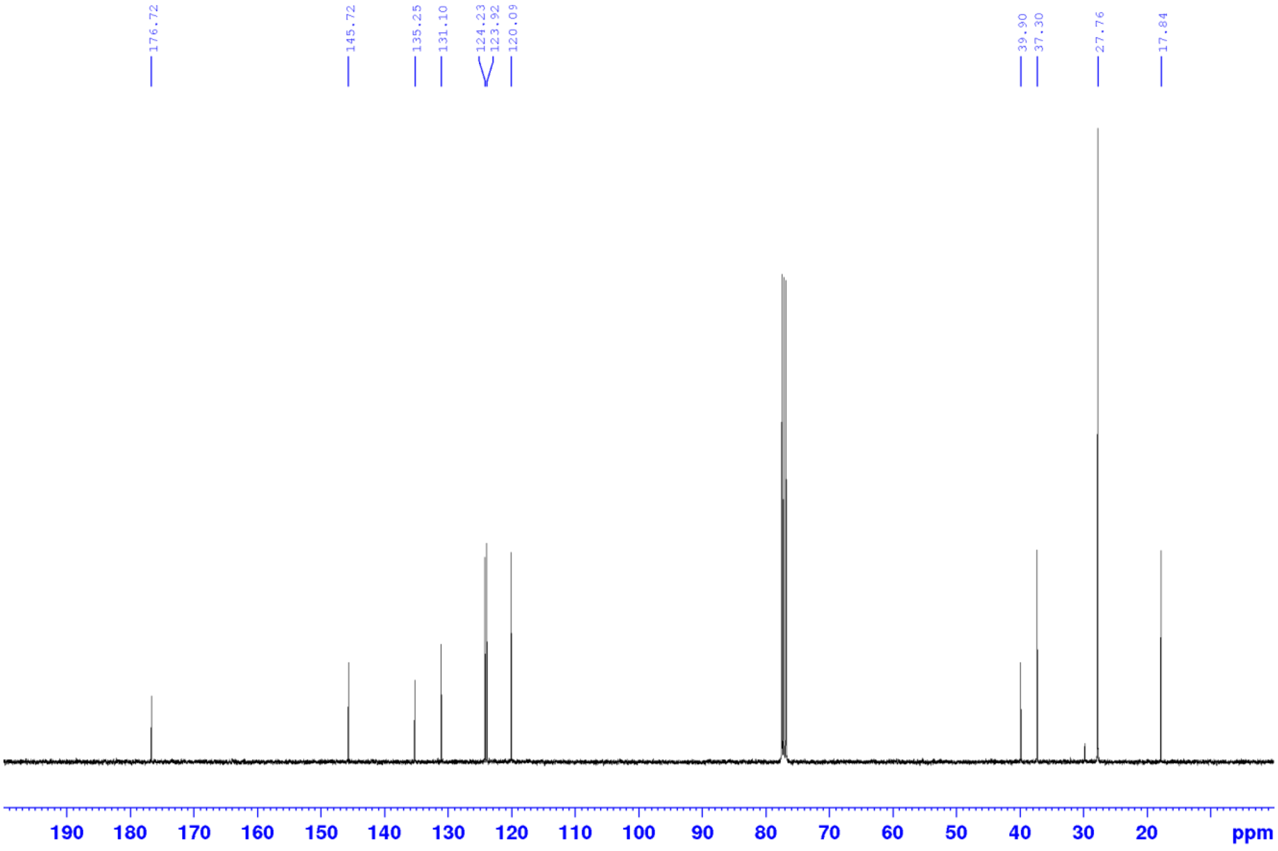


Figure S50: 101 MHz ^{13}C NMR spectrum of **3** in $CDCl_3$

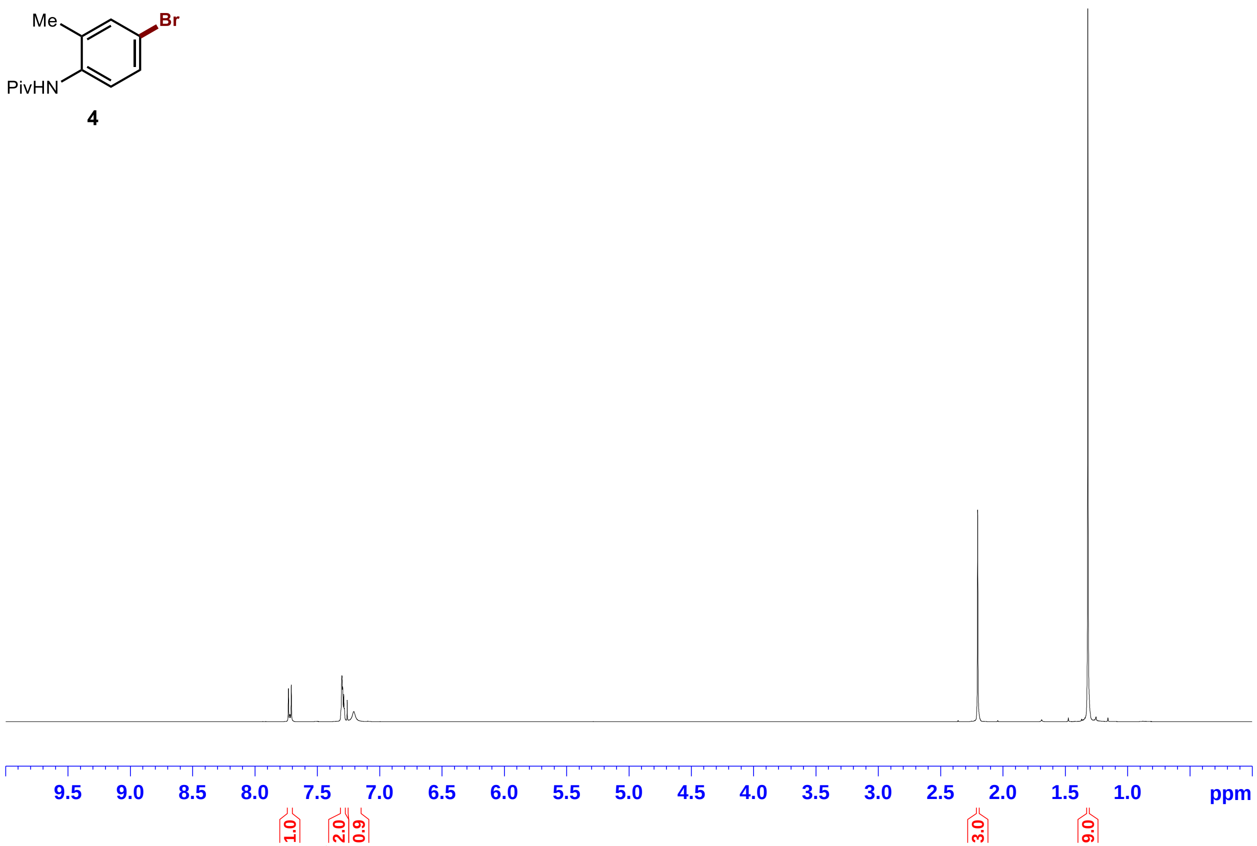


Figure S51: 400 MHz ^{1}H NMR spectrum of **4** in CDCl$_3$

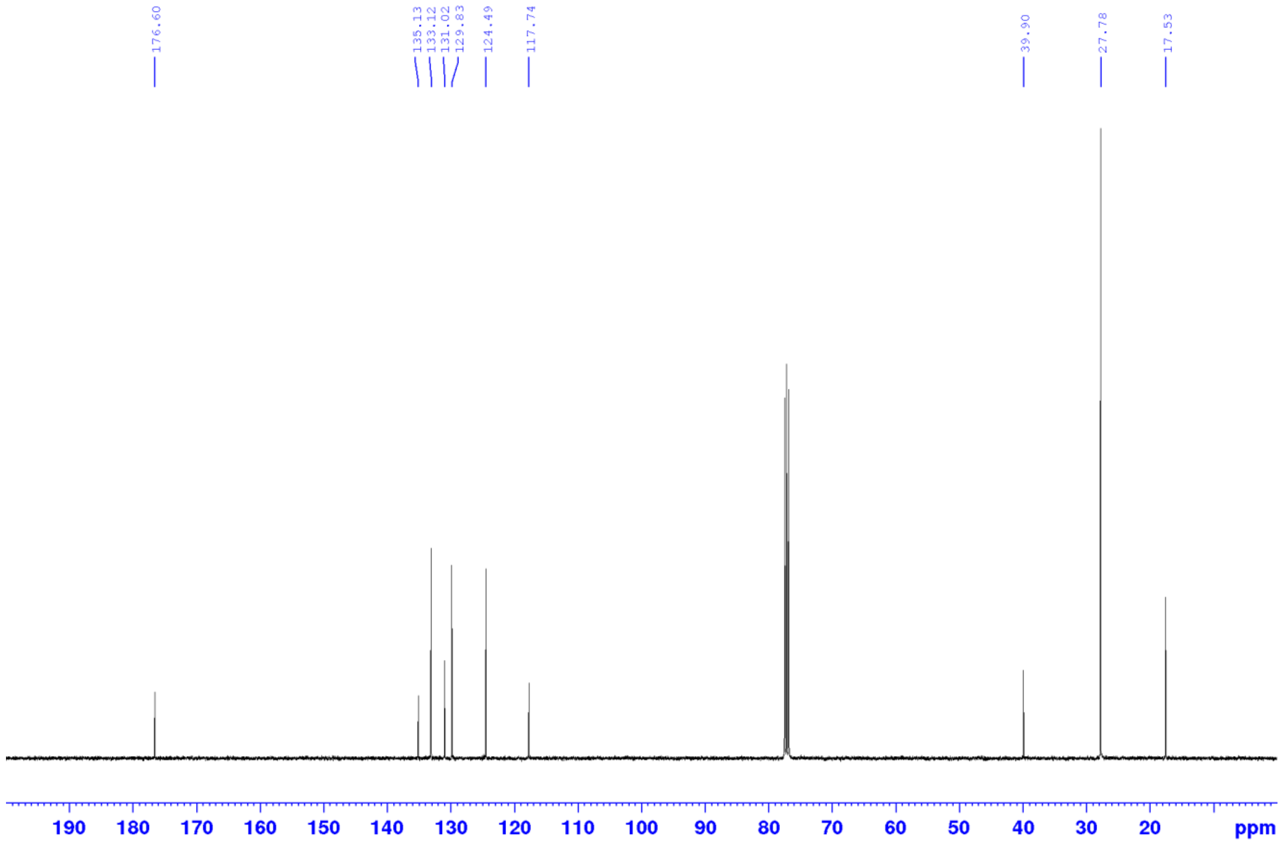
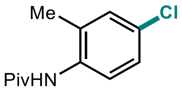


Figure S52: 101 MHz ^{13}C NMR spectrum of **4** in CDCl$_3$



5

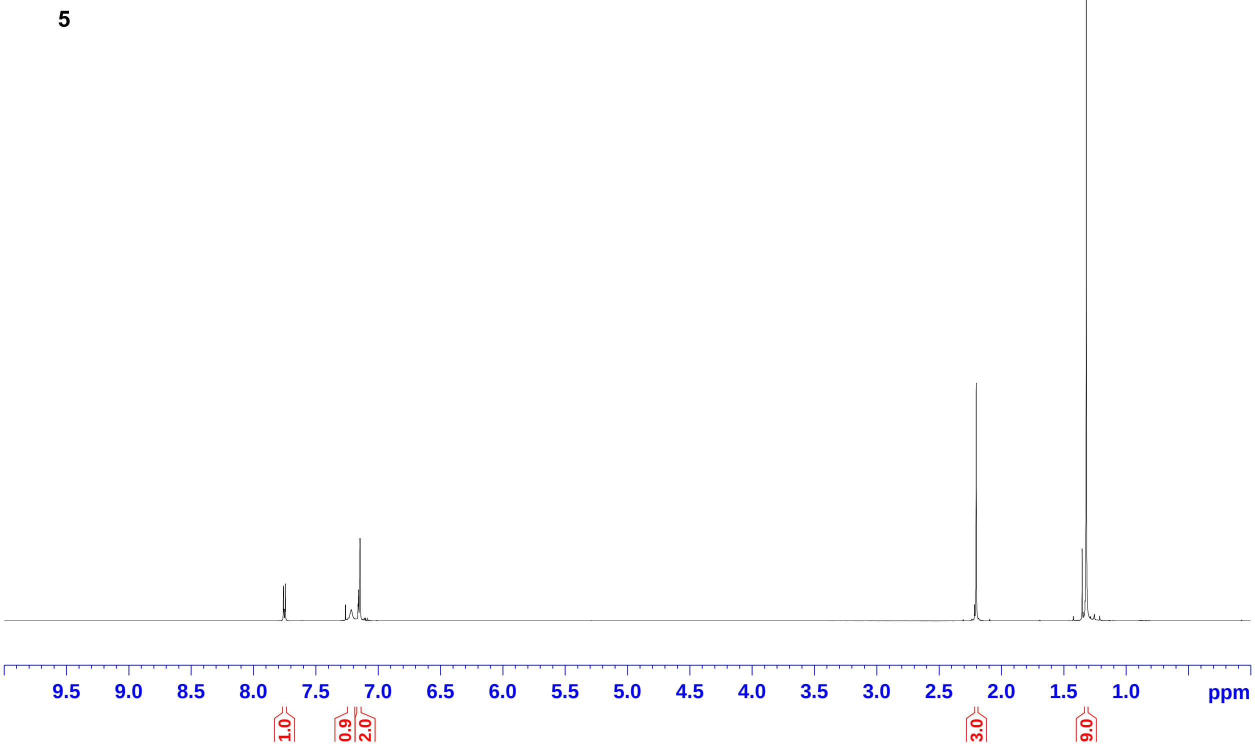


Figure S53: 400 MHz ^{1}H NMR spectrum of **5** in $CDCl_3$

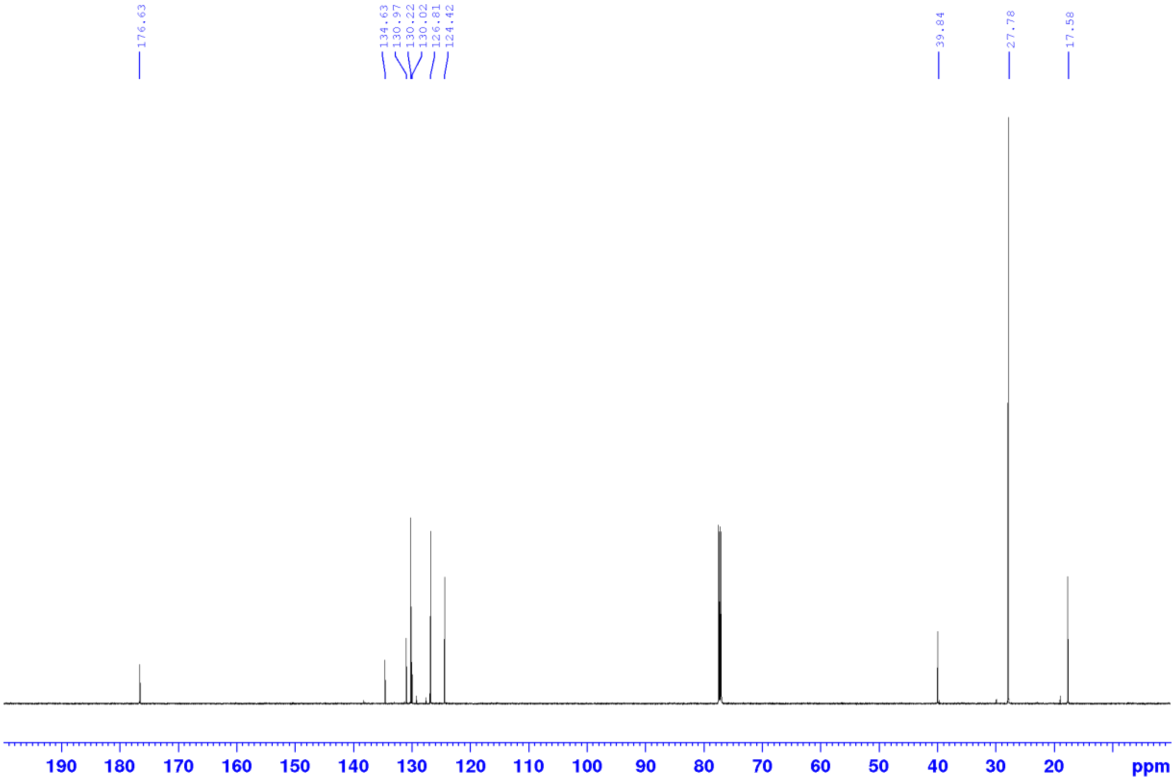
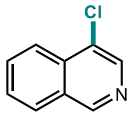


Figure S54: 101 MHz ^{13}C NMR spectrum of **5** in $CDCl_3$



6

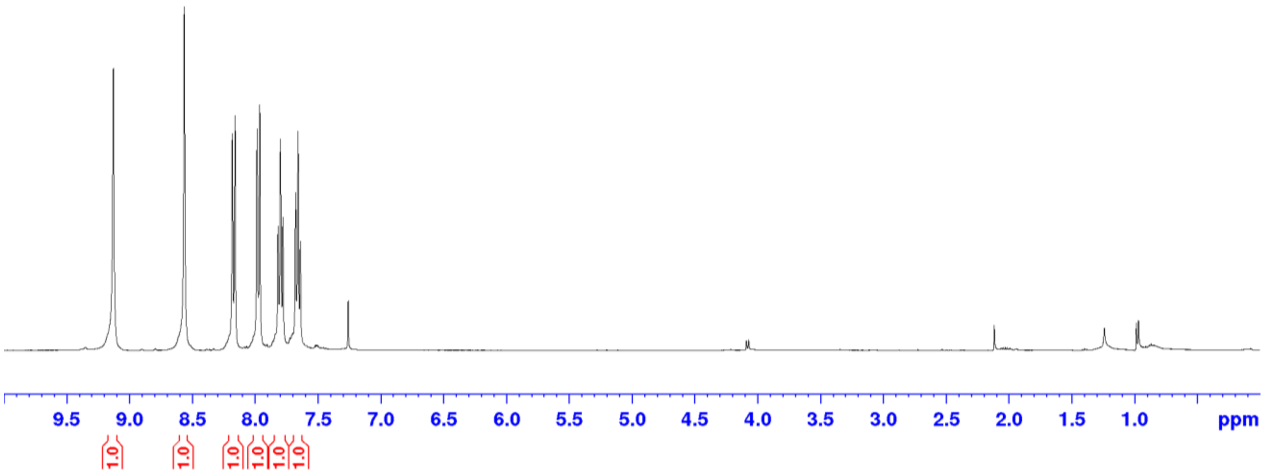


Figure S55: MHz ^{1}H NMR spectrum of **6** in CDCl$_3$

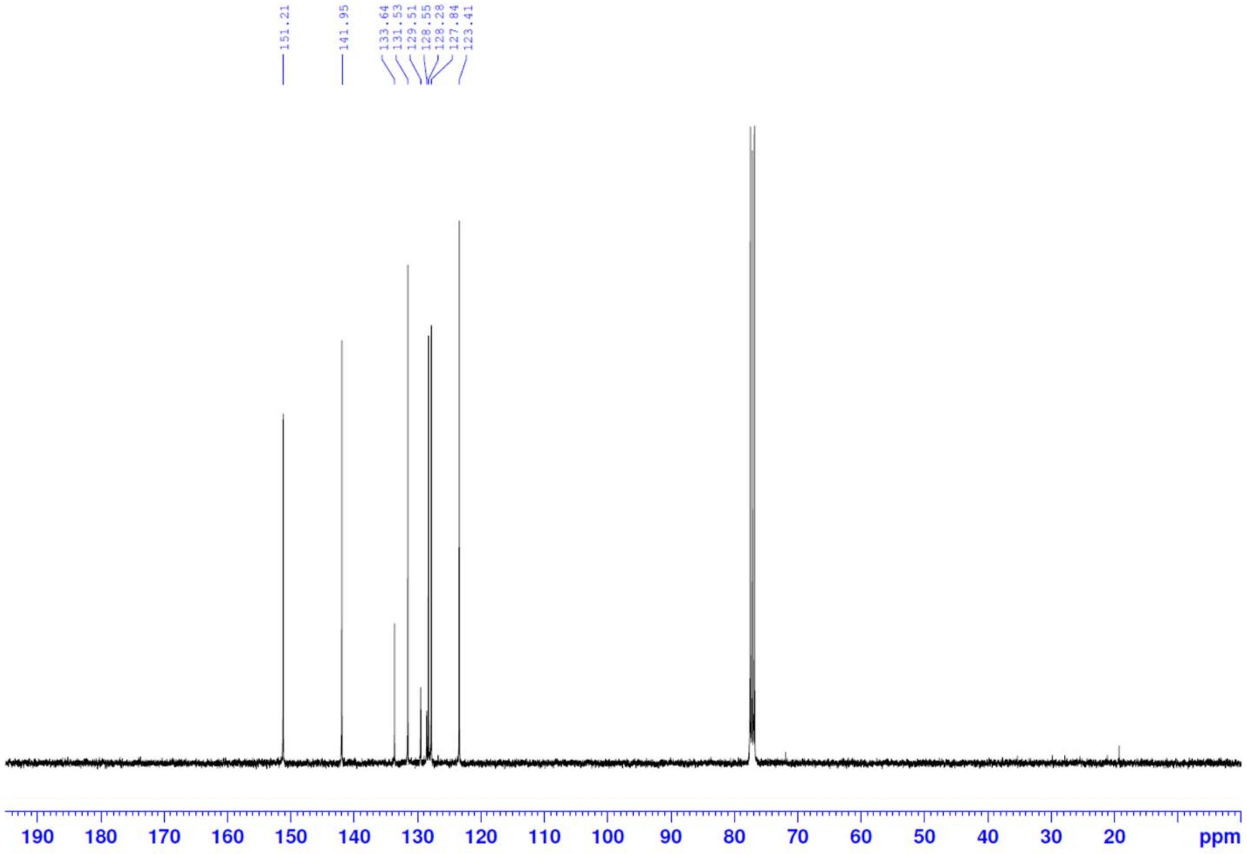
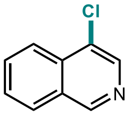


Figure S56: 101 MHz ^{13}C NMR spectrum of **6** in CDCl$_3$



6

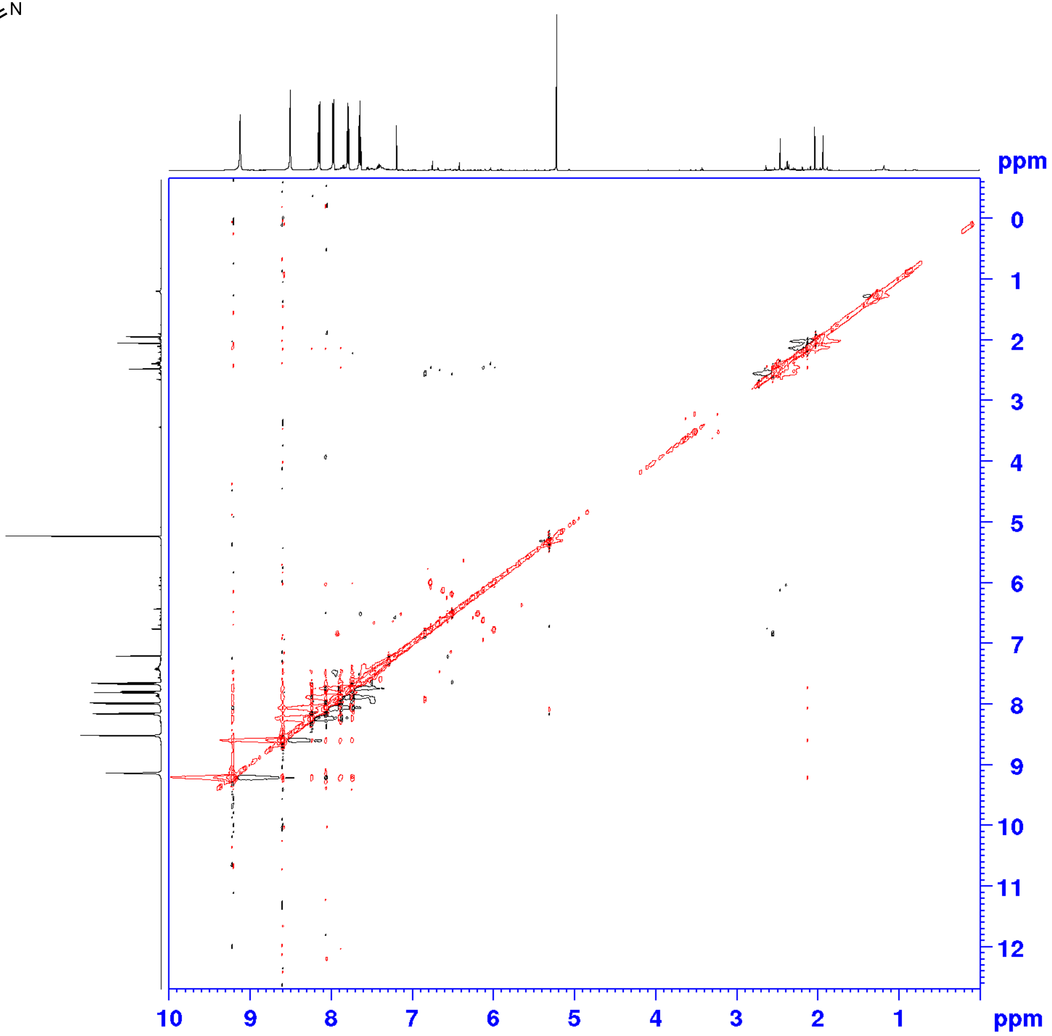
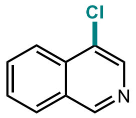


Figure S57: nOe NMR spectrum of **6** in $CDCl_3$



6

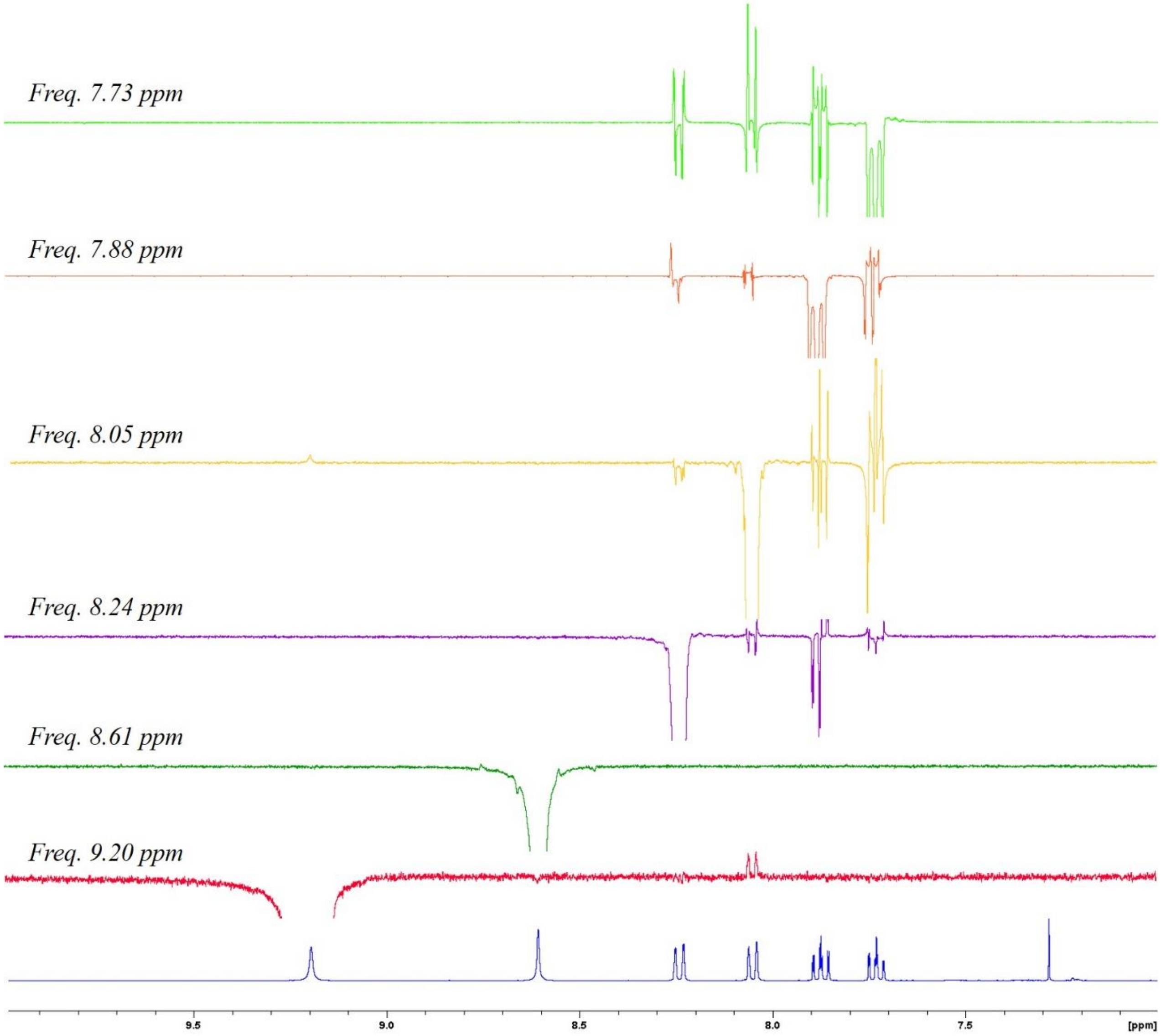
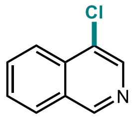


Figure S58: Selective Gradient 1D NOESY of **6** (400 MHz in $CDCl_3$)



6

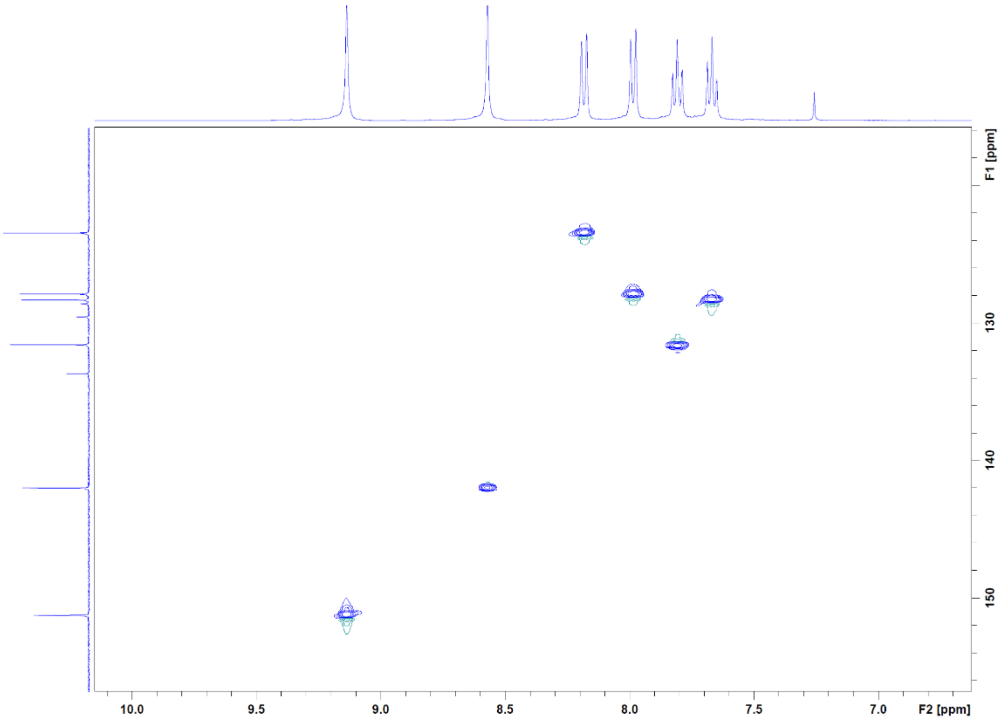


Figure S59: HSQC NMR spectrum of **6** in $CDCl_3$

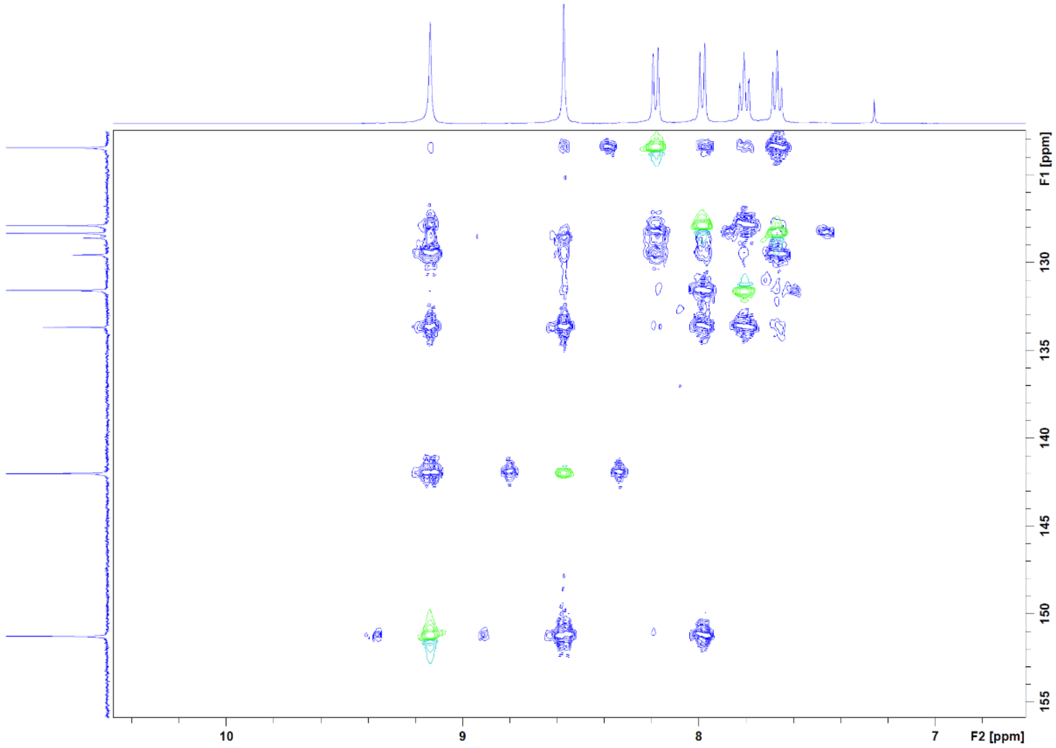


Figure S60: HMBC NMR spectrum of **6** in $CDCl_3$

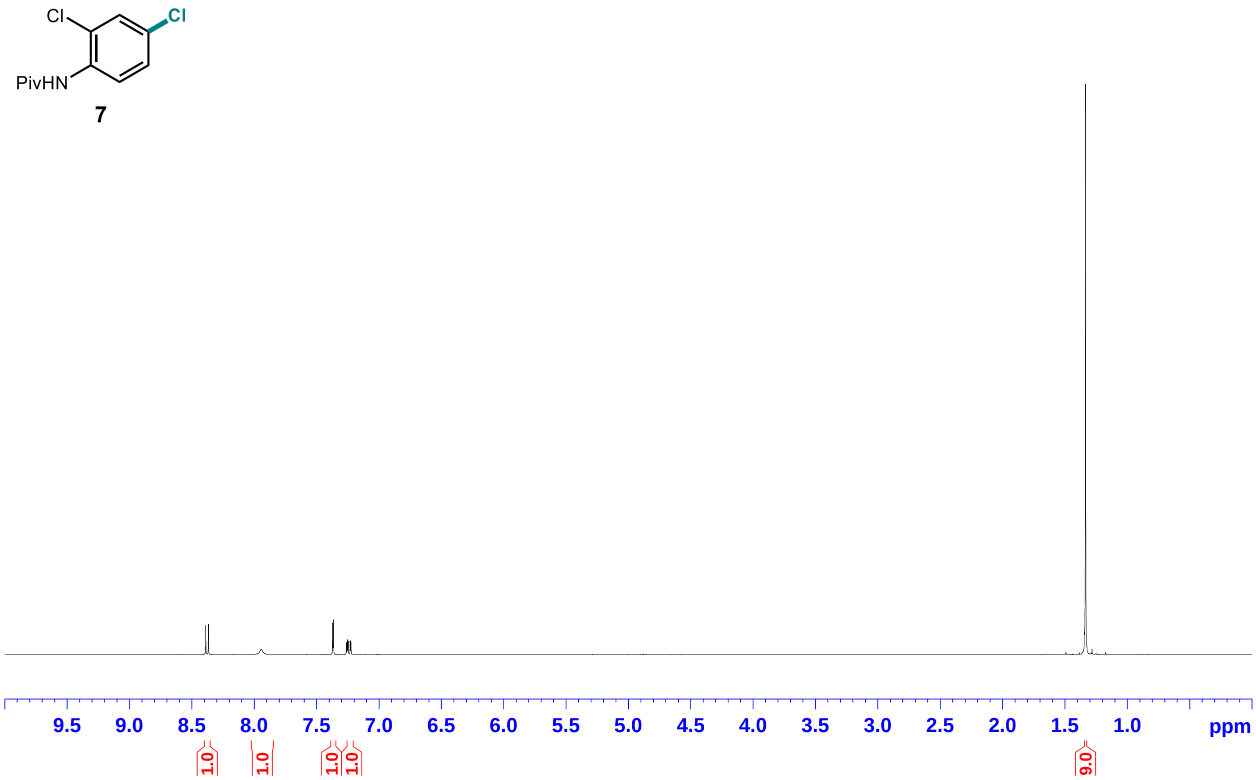


Figure S61: 400 MHz ^{1}H NMR spectrum of **7** in $CDCl_3$

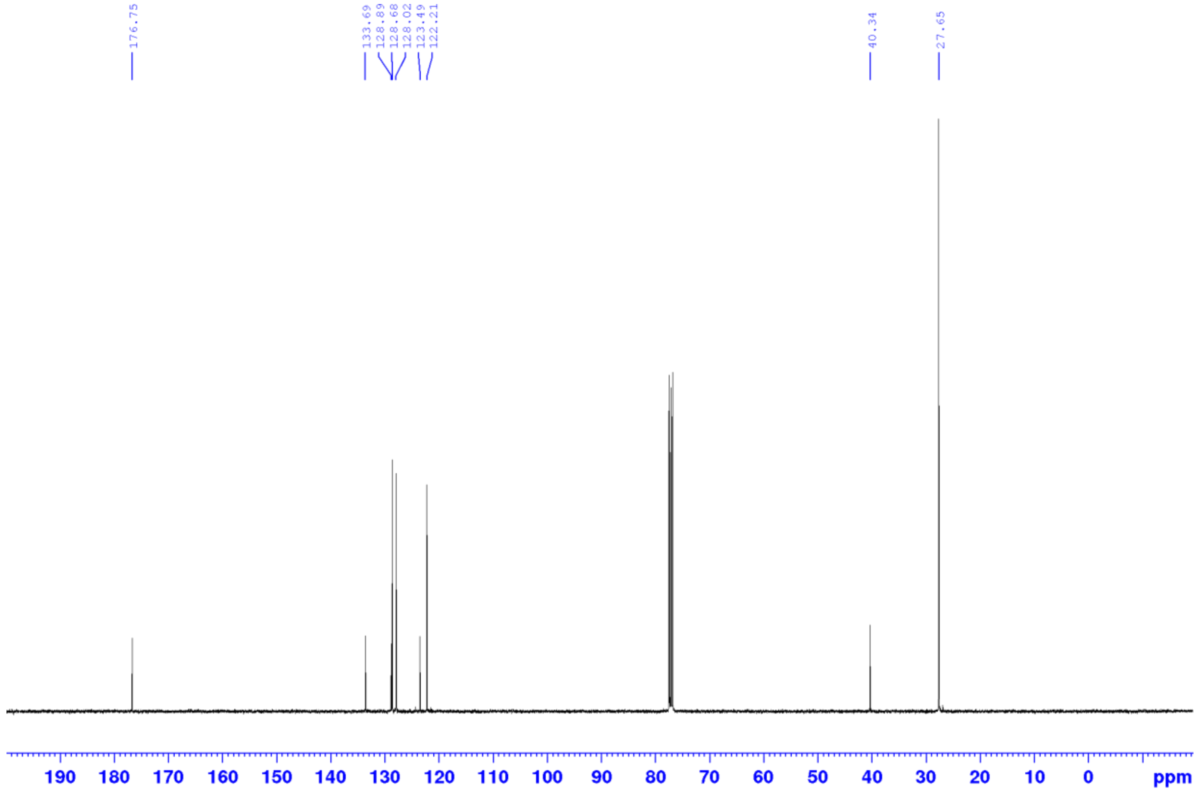
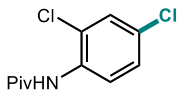


Figure S62: 101 MHz ^{13}C NMR spectrum of **7** in $CDCl_3$



7

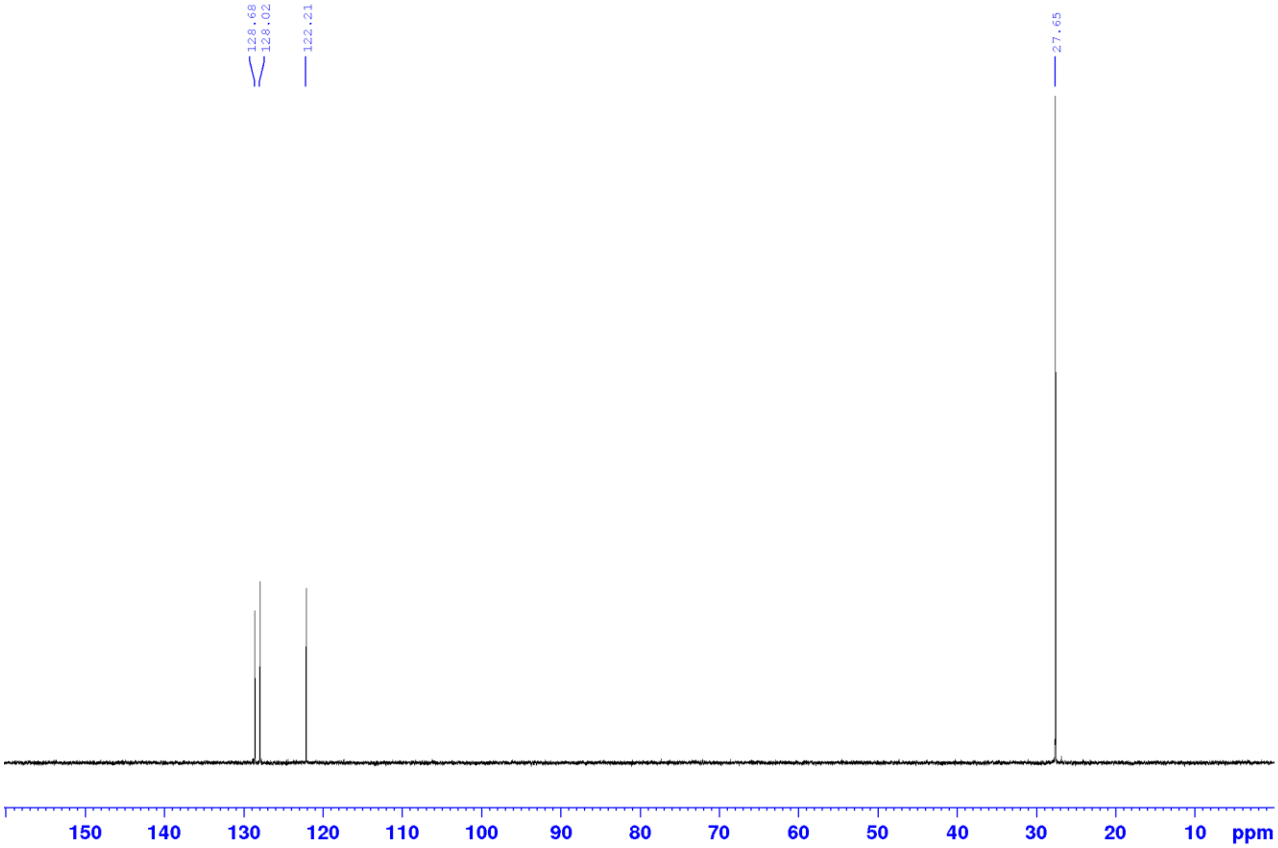


Figure S63: DEPT 135 spectrum of **7** in $CDCl_3$

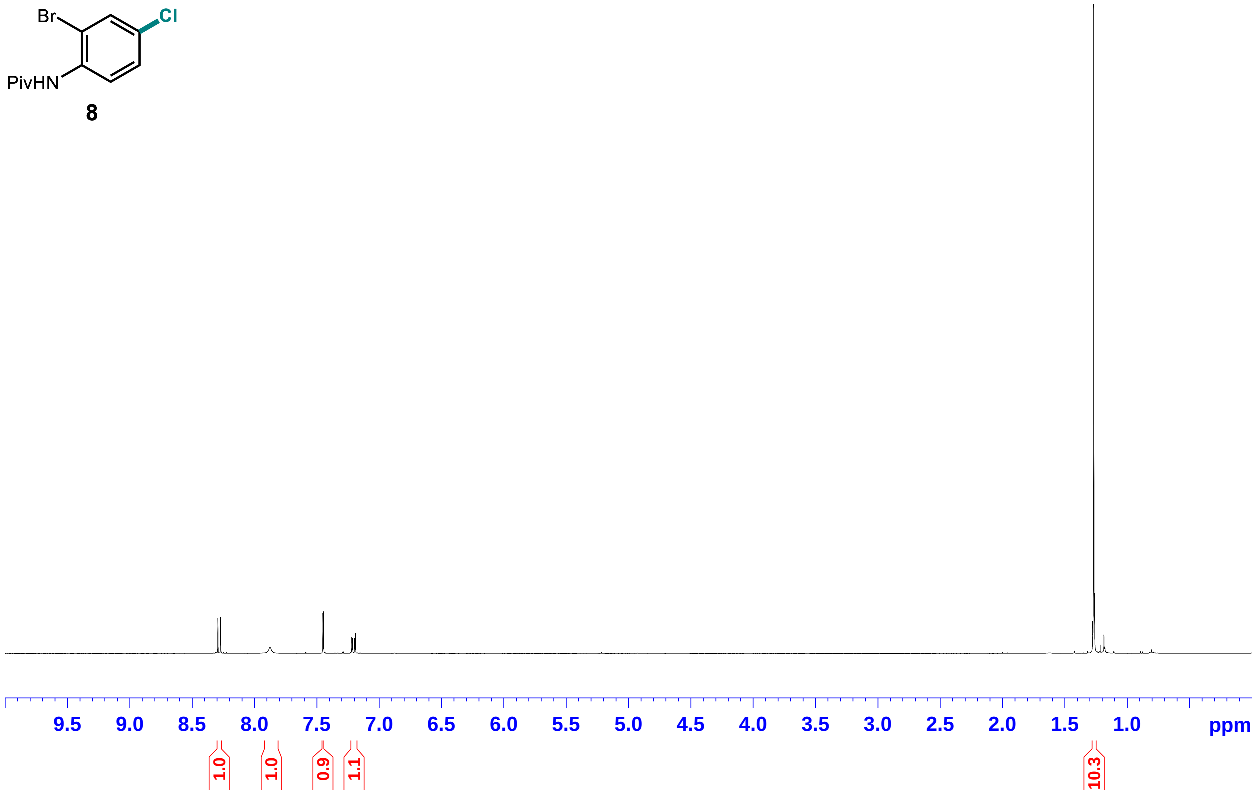


Figure S64: 400 MHz ^{1}H NMR spectrum of **8** in $CDCl_3$

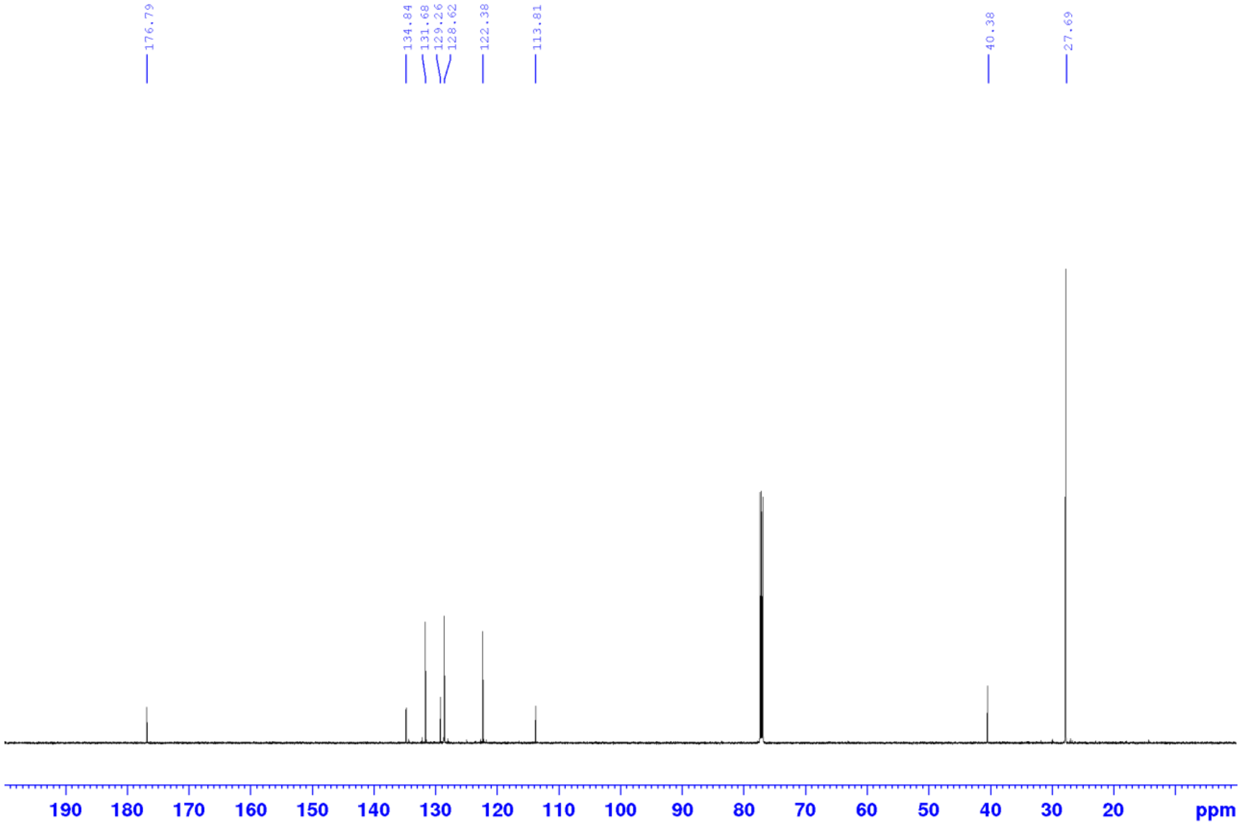


Figure S65: 101 MHz ^{13}C NMR spectrum of **8** in $CDCl_3$

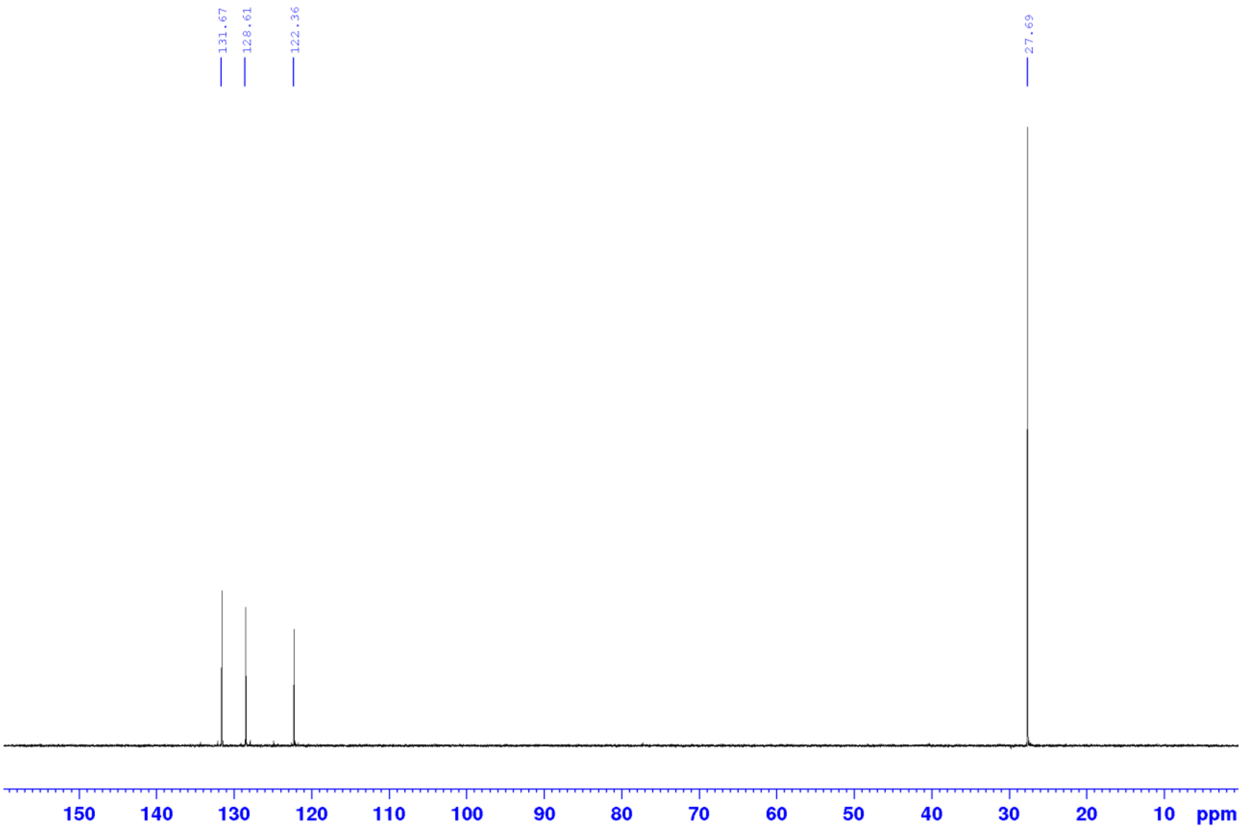


Figure S66: DEPT 135 spectrum of **8** in $CDCl_3$

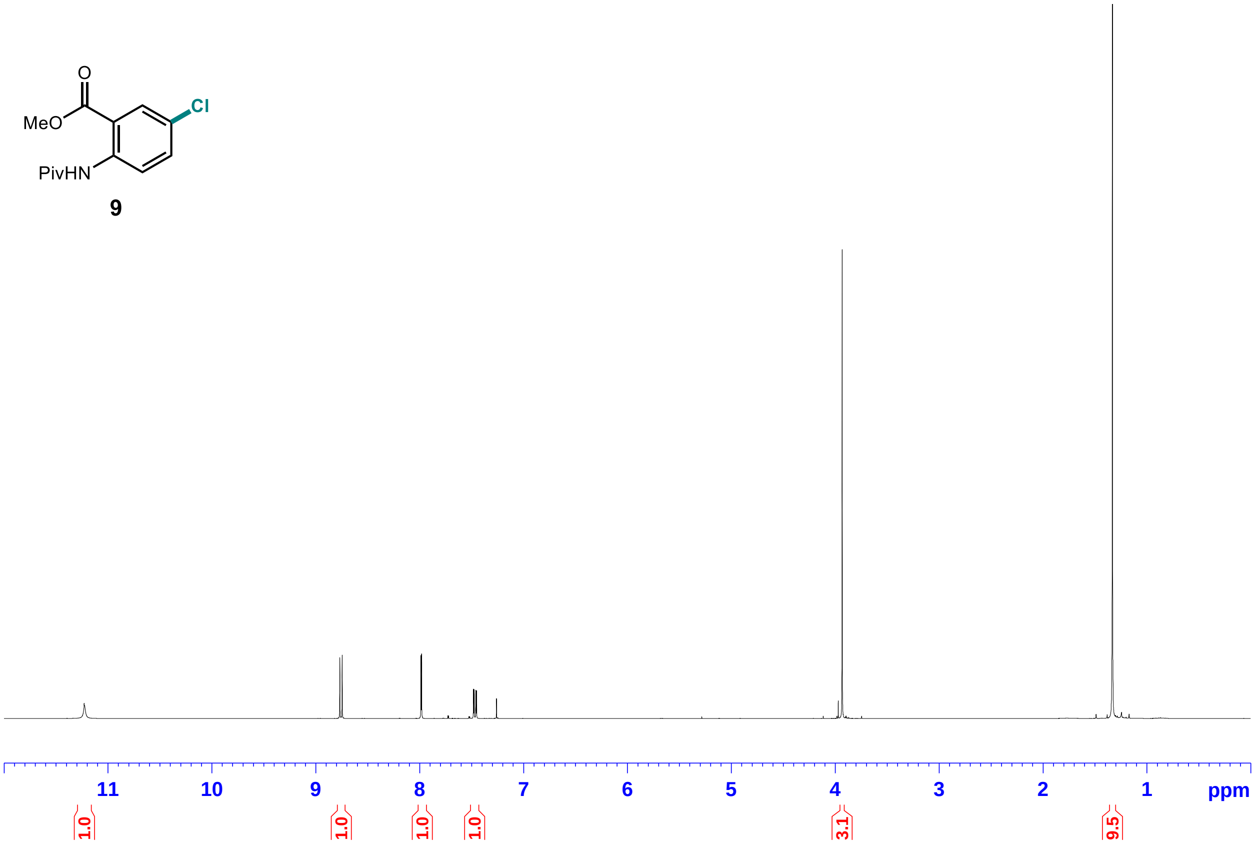


Figure S67: 400 MHz ^1H NMR spectrum of **9** in $CDCl_3$

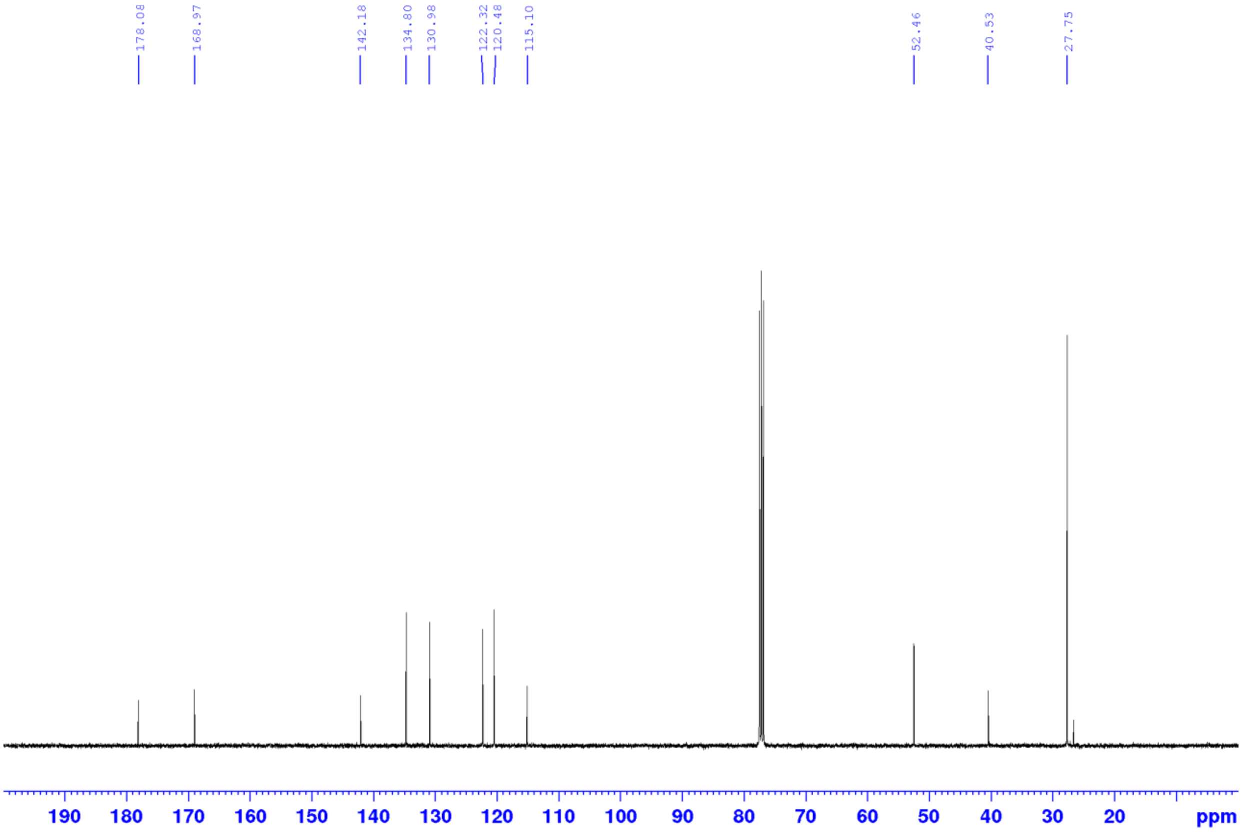
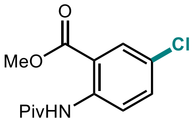


Figure S68: 101 MHz ^{13}C NMR spectrum of **9** in $CDCl_3$



9

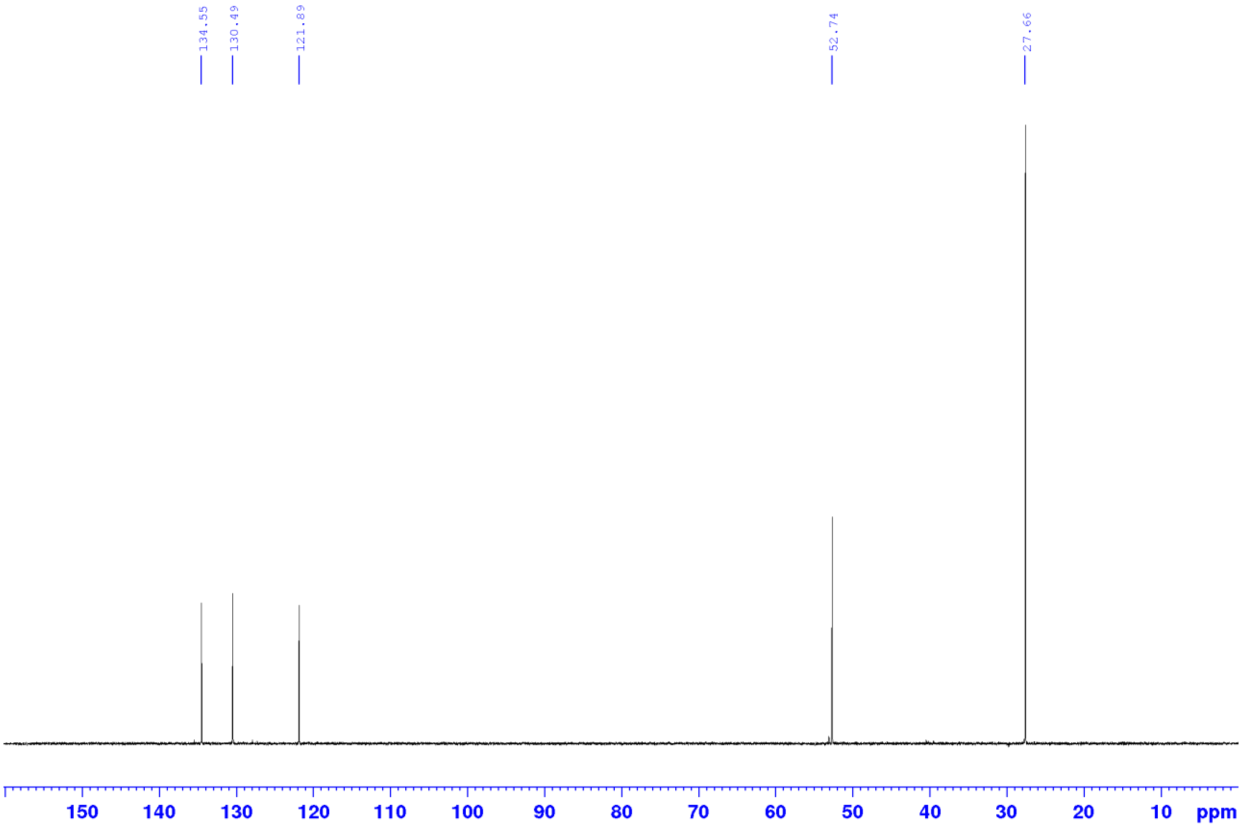


Figure S69: DEPT 135 NMR spectrum of **9** in $CDCl_3$

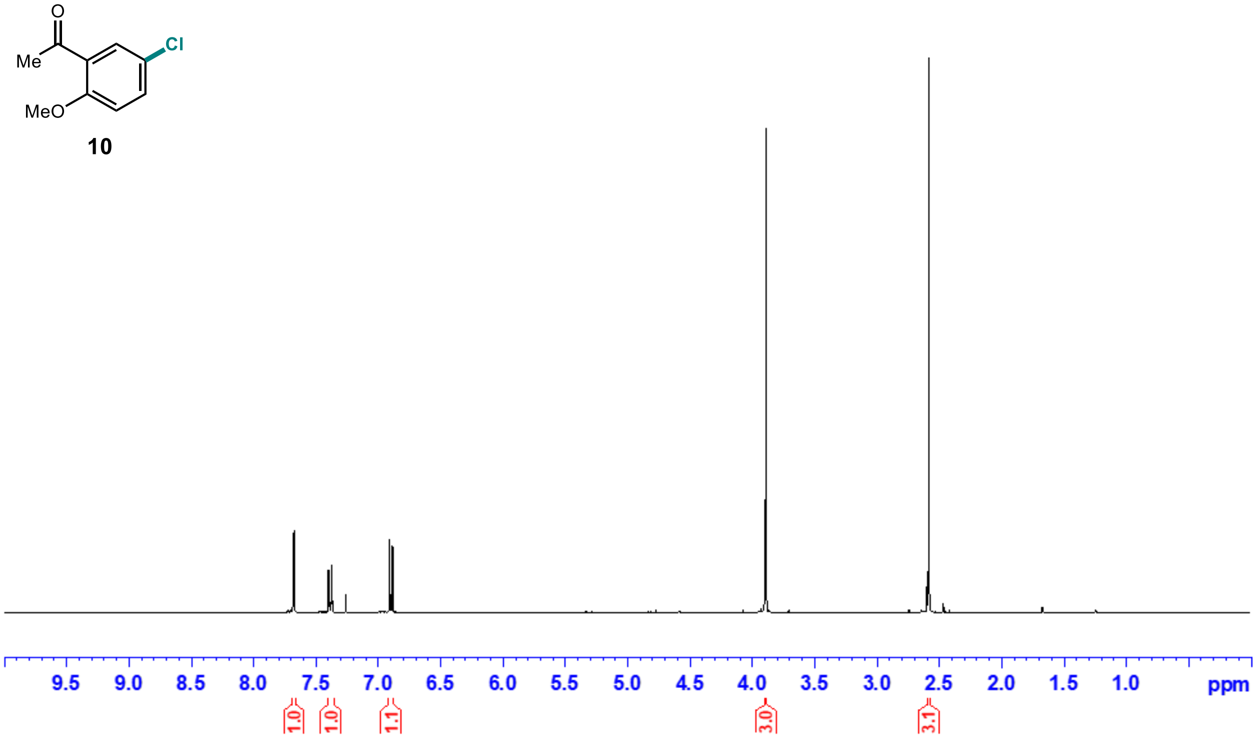


Figure S70: 400 MHz ^{1}H NMR spectrum of **10** in CDCl$_3$

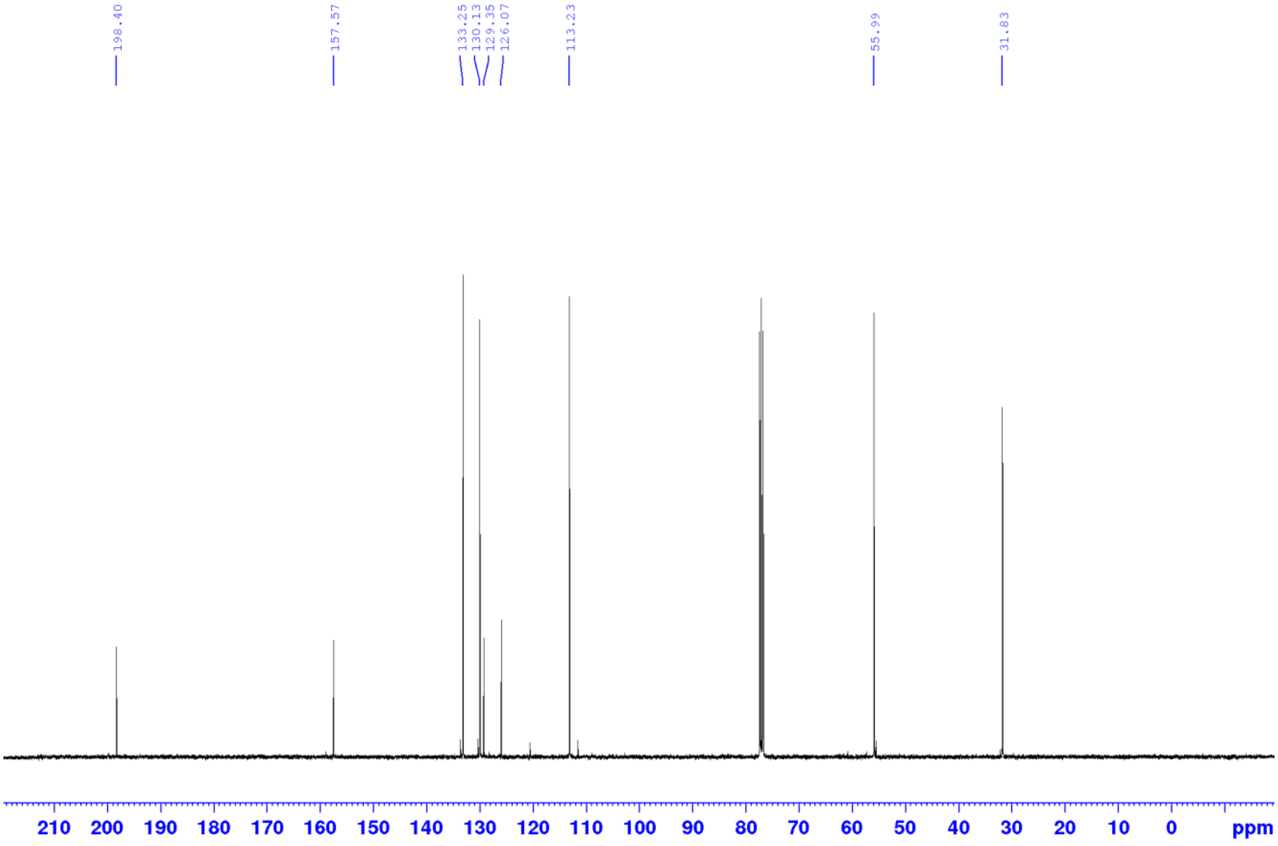
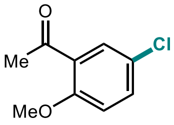


Figure S71: 101 MHz ^{13}C NMR spectrum of **10** in CDCl$_3$



10

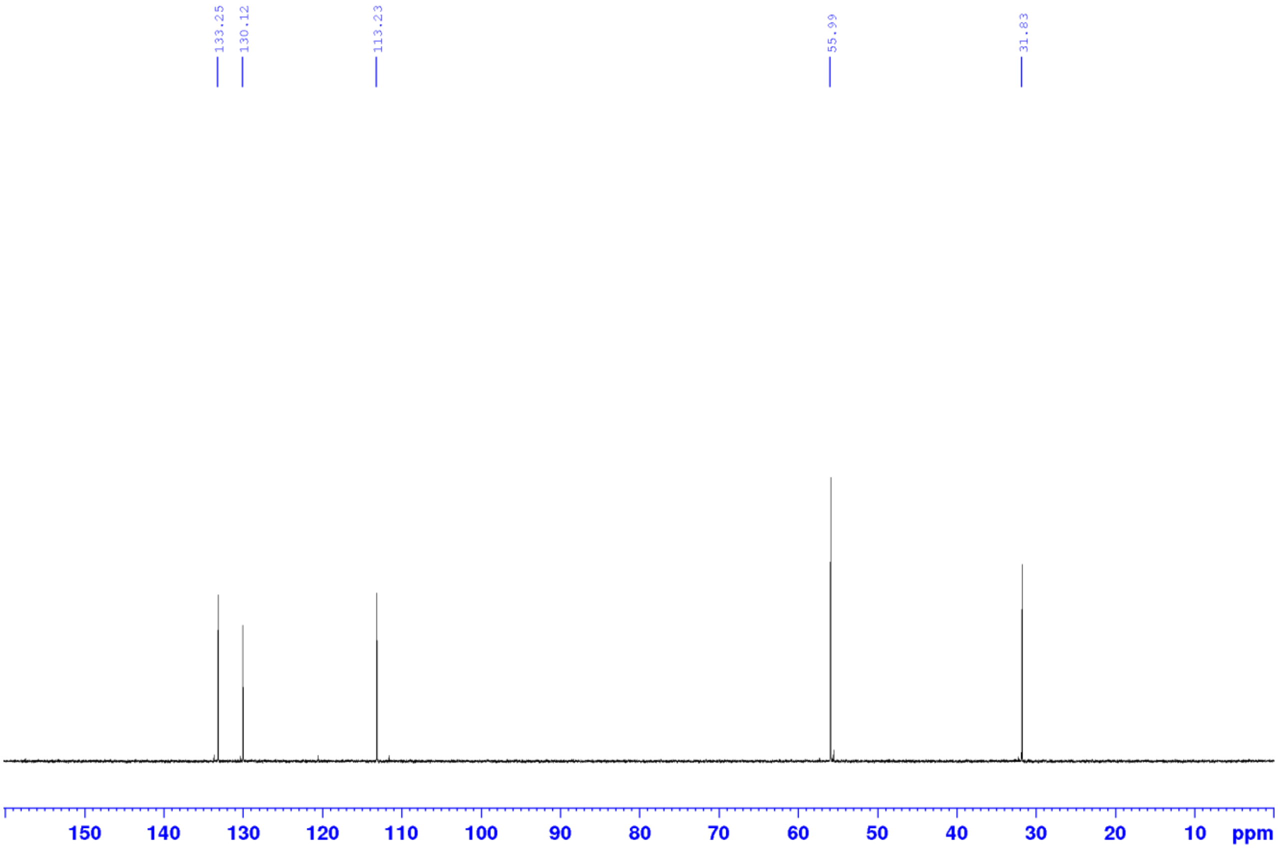


Figure S72: DEPT 135 NMR spectrum of **10** in $CDCl_3$

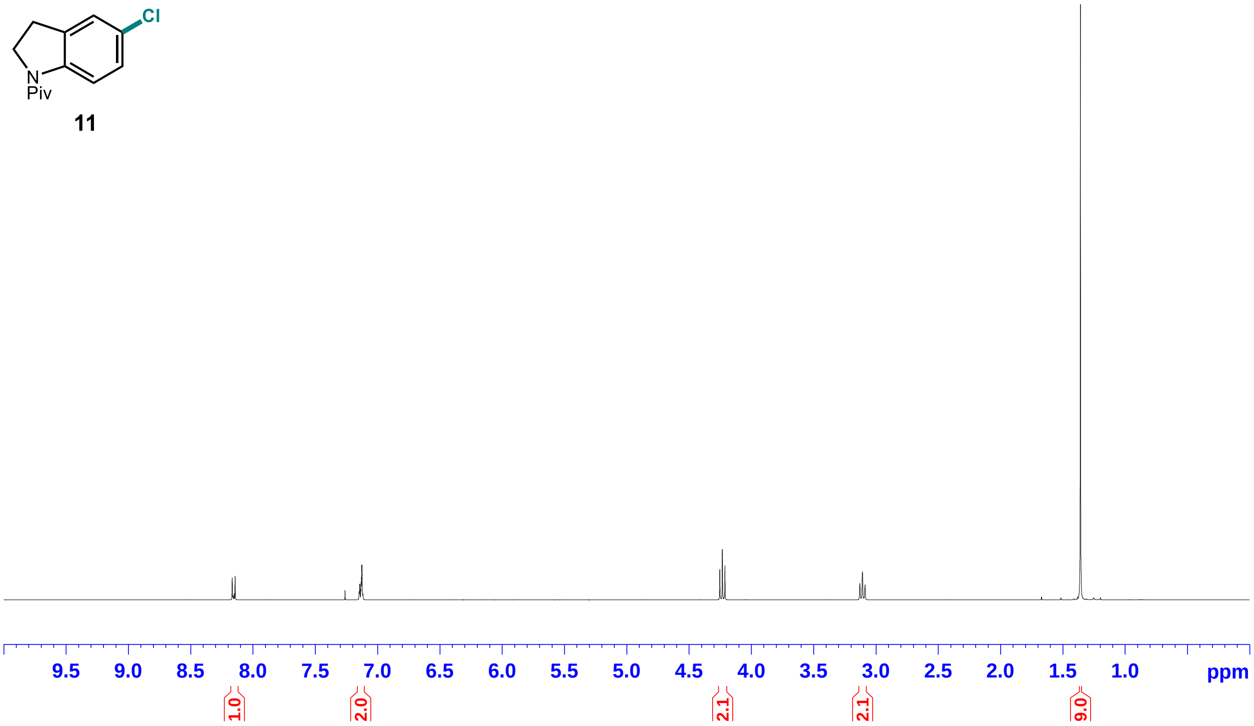


Figure S73: 400 MHz ^{1}H NMR spectrum of **11** in $CDCl_3$

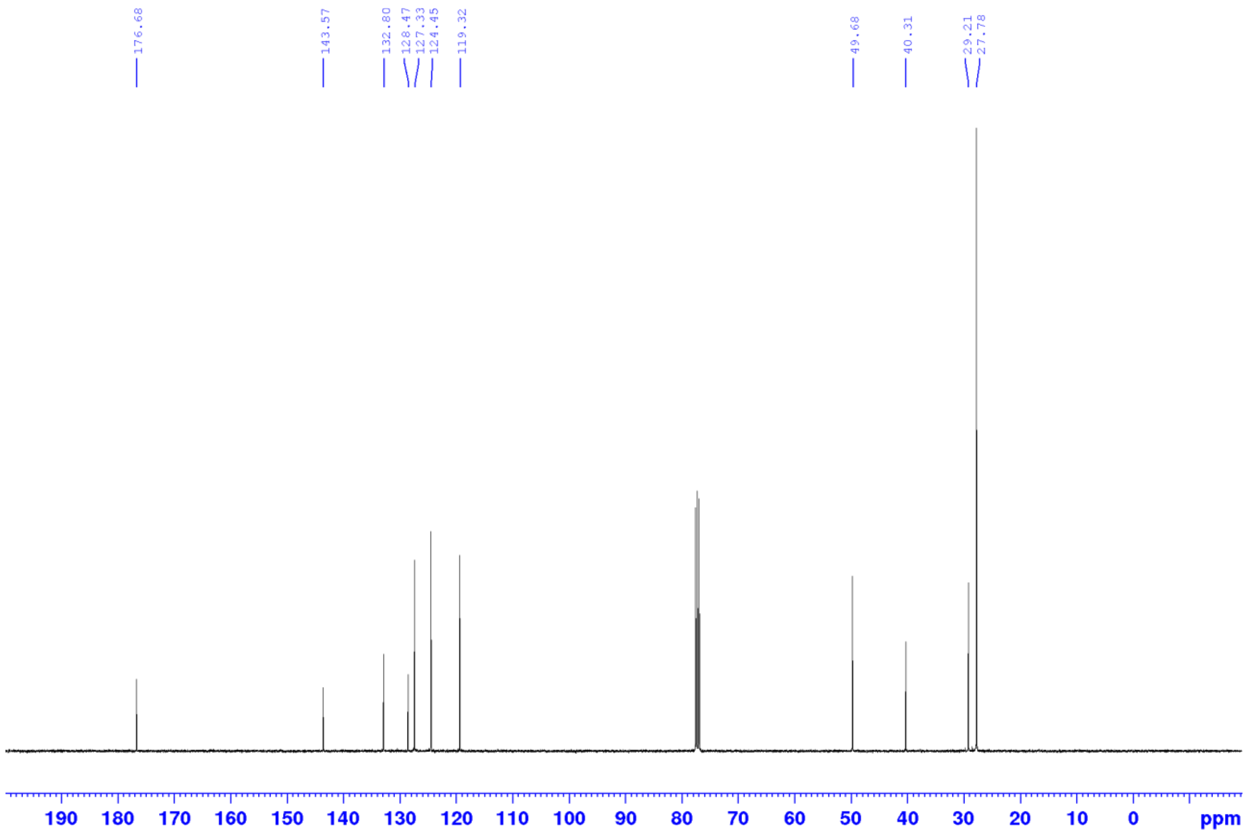
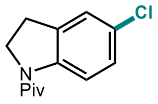


Figure S74: 101 MHz ^{13}C NMR spectrum of **11** in $CDCl_3$



11

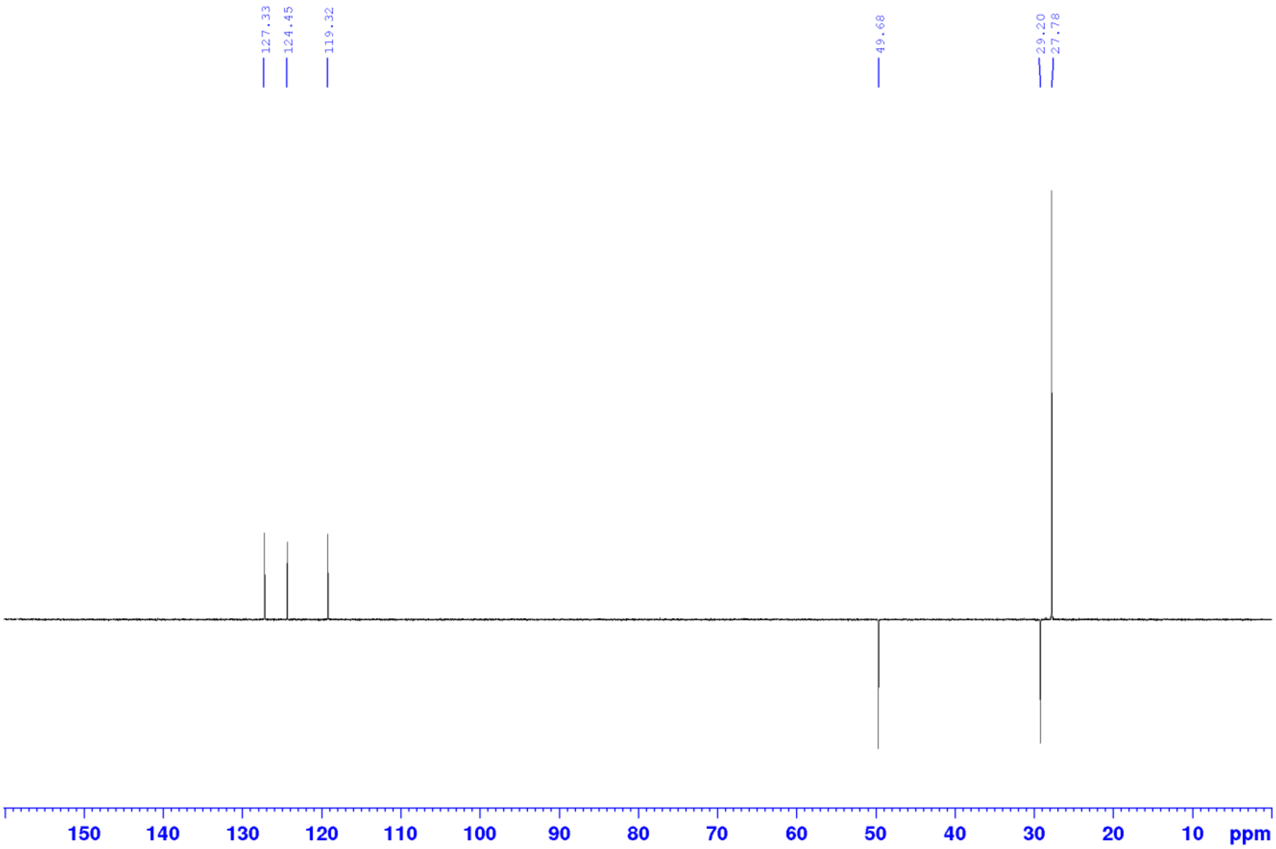


Figure S75: DEPT 135 NMR spectrum of **11** in $CDCl_3$

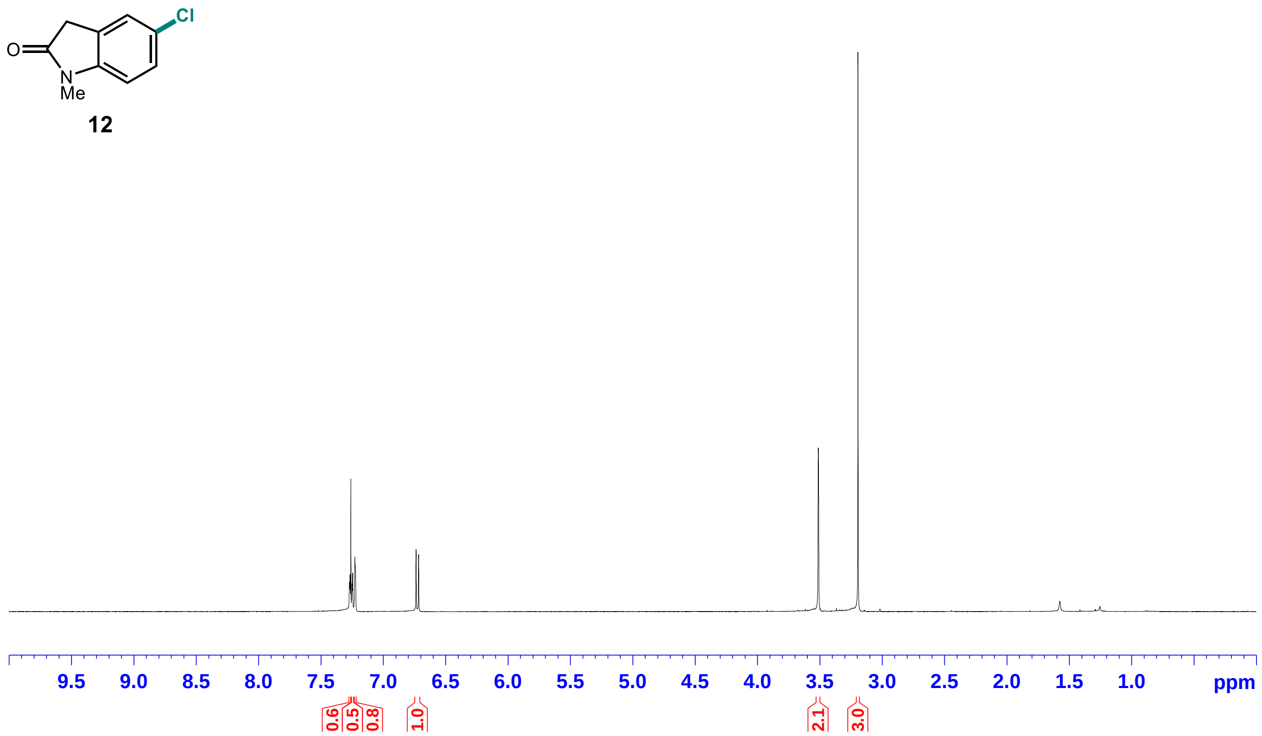


Figure S76: 400 MHz ^{1}H NMR spectrum of **12** in $CDCl_3$

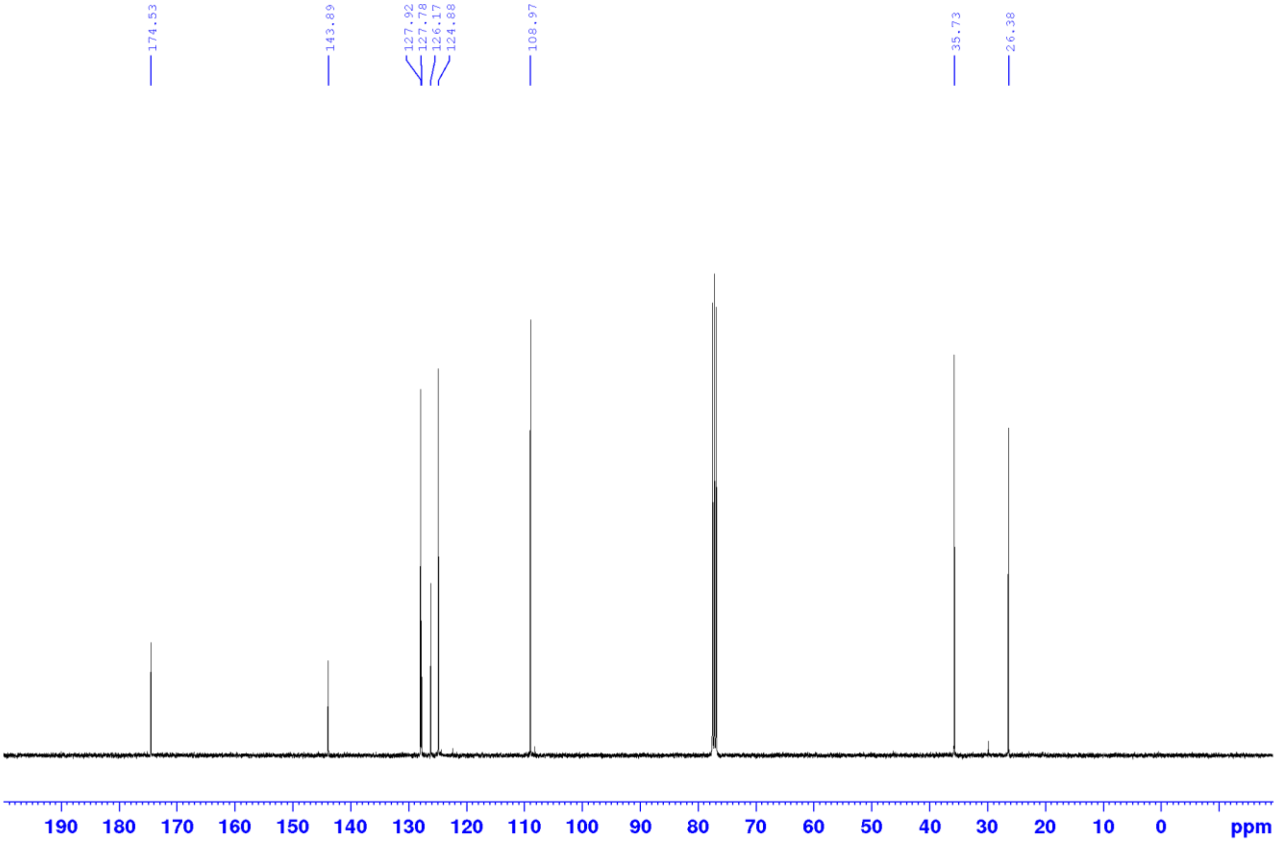
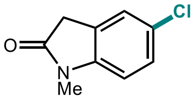


Figure S77: 101 MHz ^{13}C NMR spectrum of **12** in $CDCl_3$



12

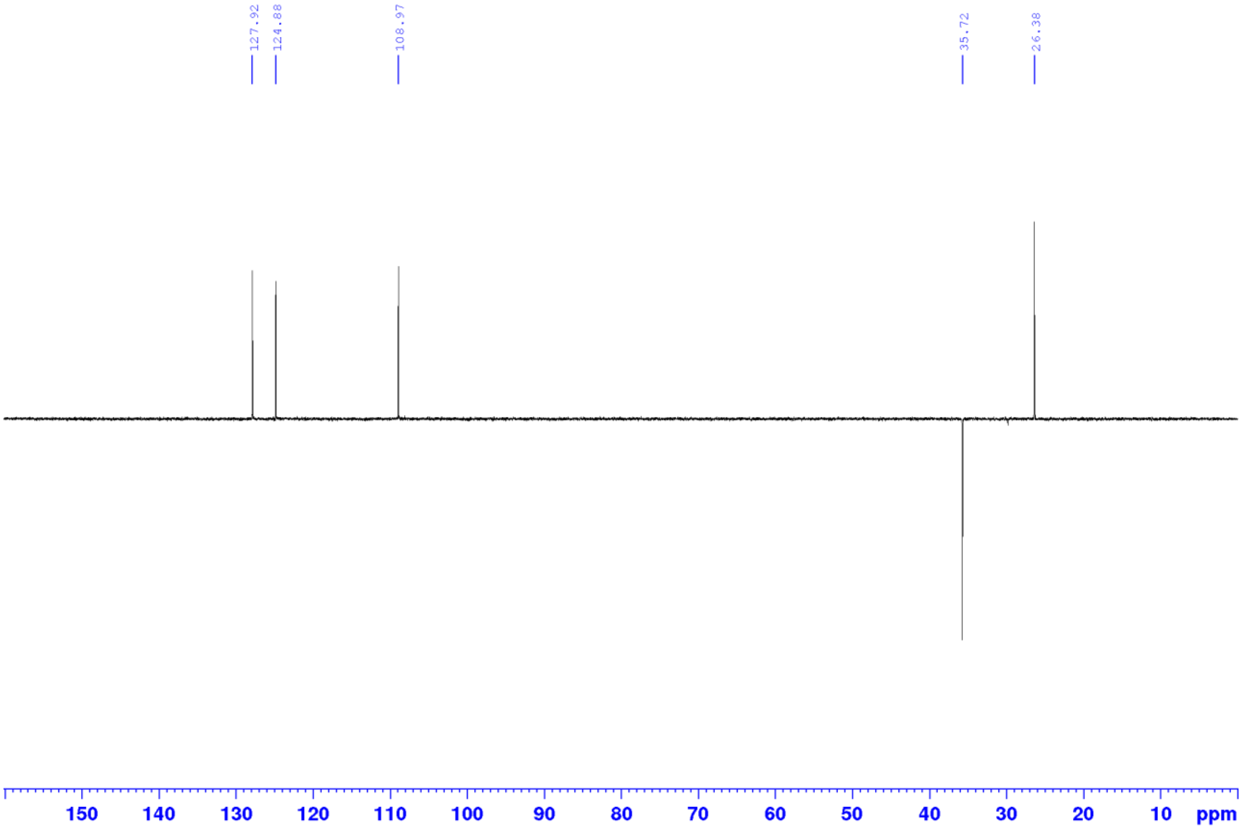


Figure S78: DEPT 135 NMR spectrum of **12** in $CDCl_3$

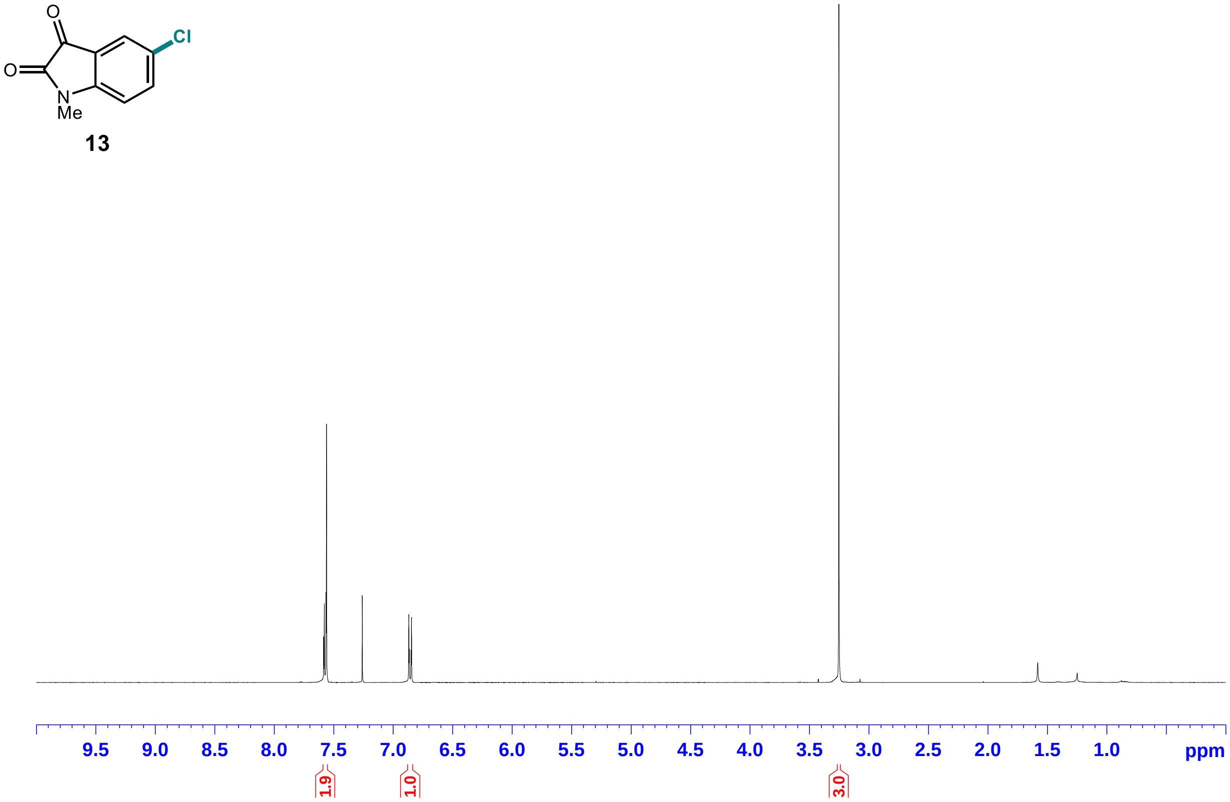


Figure S79: 400 MHz ^{1}H NMR spectrum of **13** in $CDCl_3$

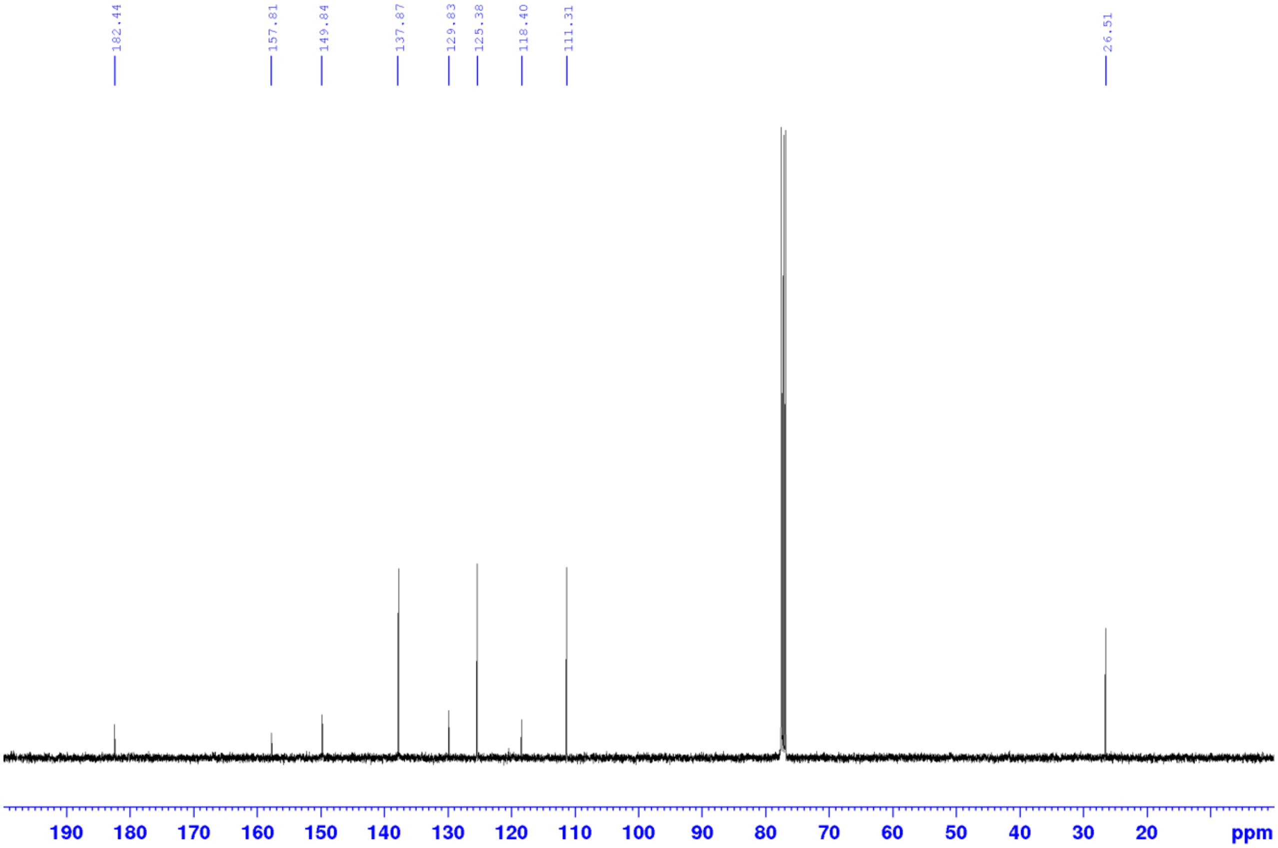
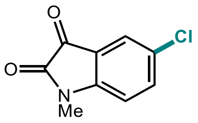


Figure S80: 101 MHz ^{13}C NMR spectrum of **13** in $CDCl_3$



13

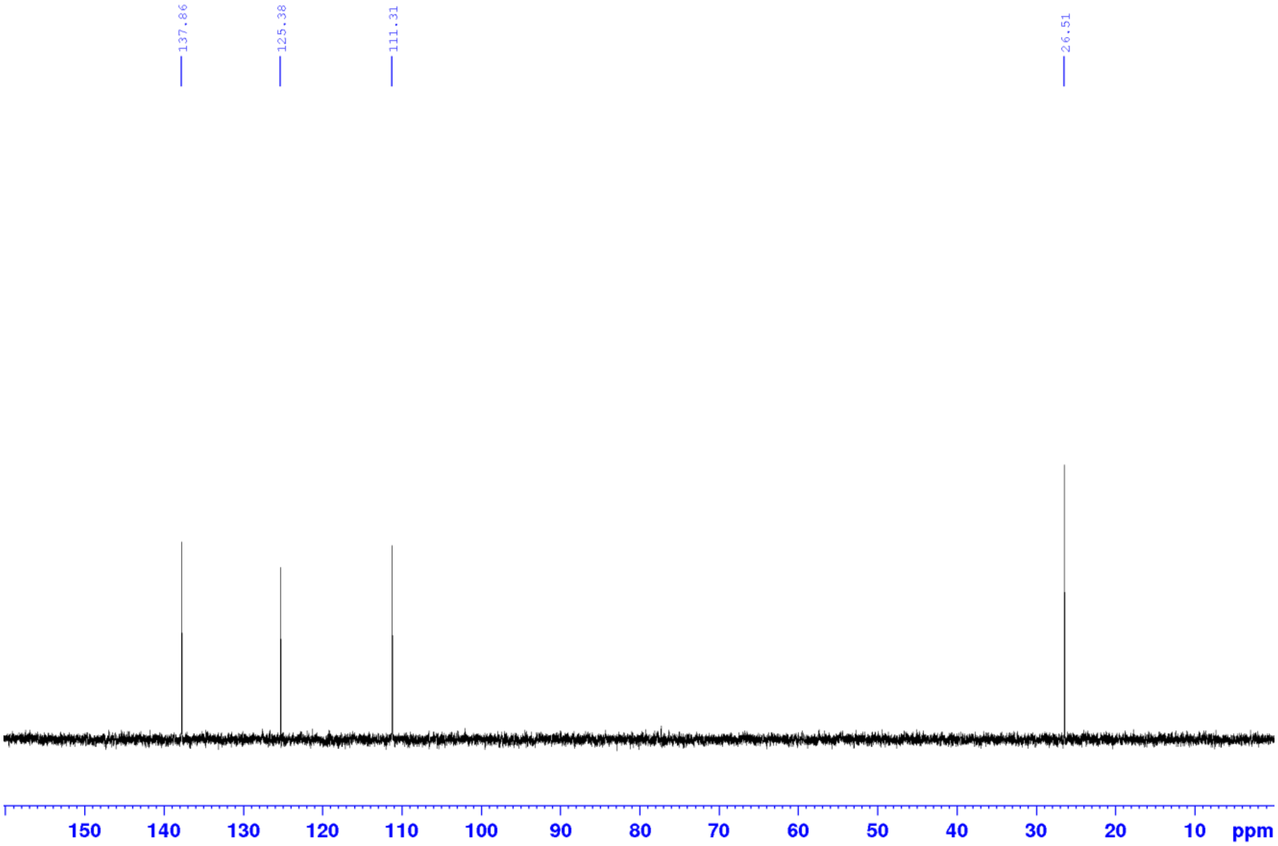


Figure S81: DEPT 135 NMR spectrum of **13** in $CDCl_3$

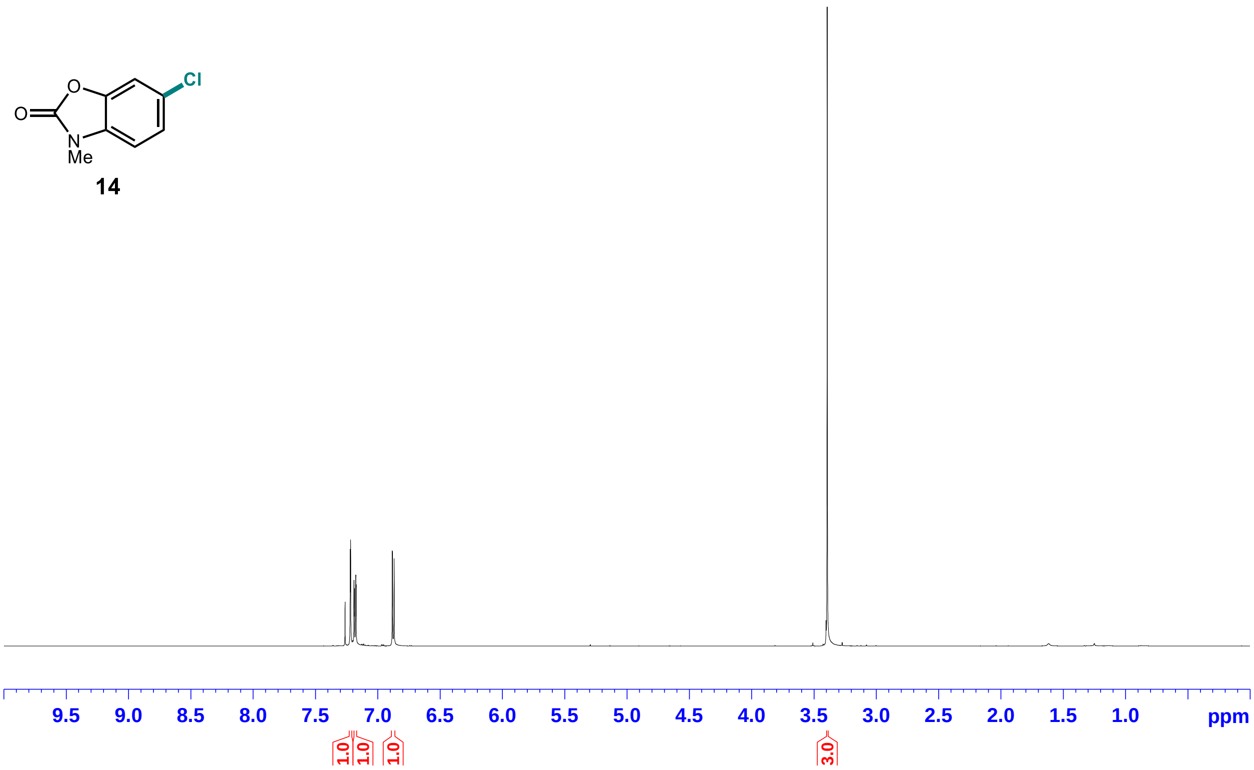


Figure S82: 400 MHz ^{1}H NMR spectrum of **14** in $CDCl_3$

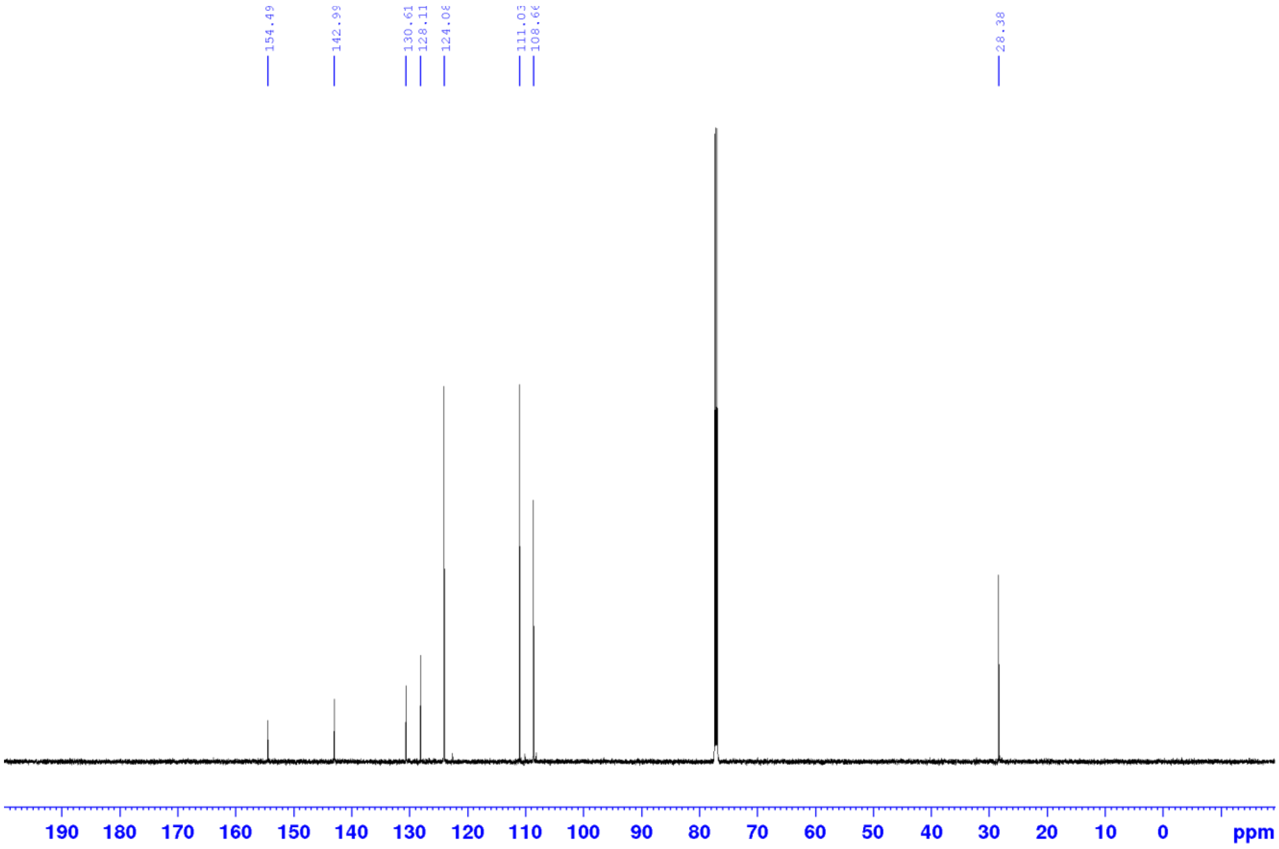


Figure S83: 101 MHz ^{13}C NMR spectrum of **14** in $CDCl_3$

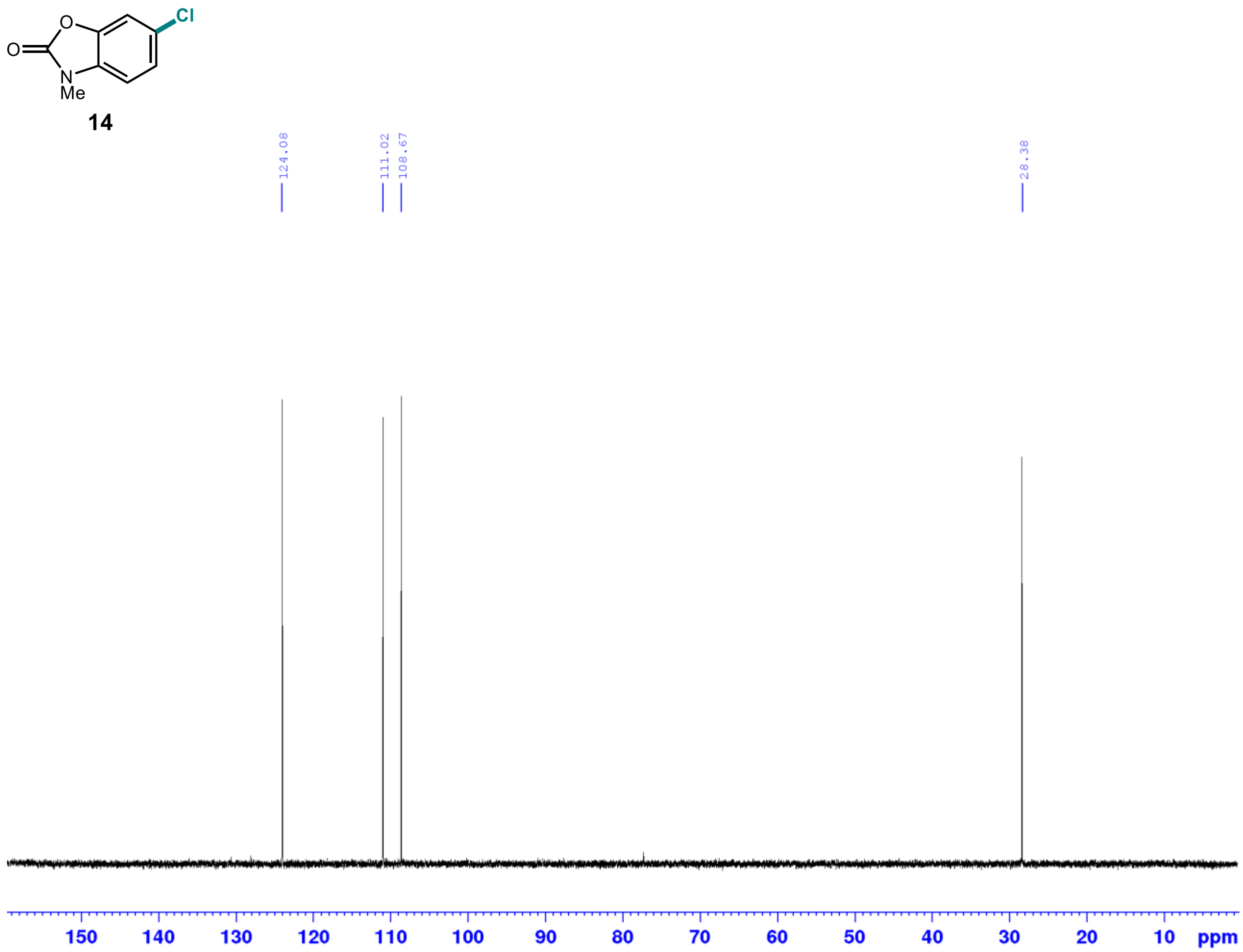


Figure S84: DEPT 135 NMR spectrum of **14** in $CDCl_3$

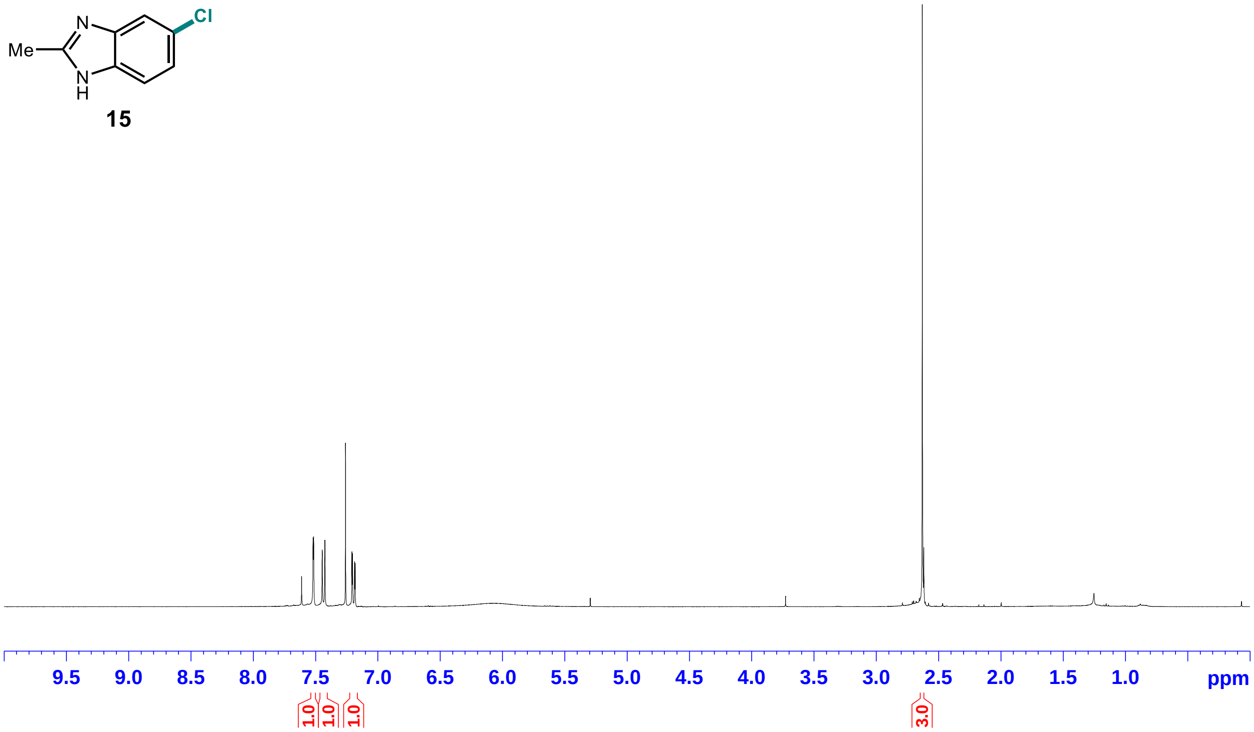


Figure S85: 400 MHz ^{1}H NMR spectrum of **15** in $CDCl_3$

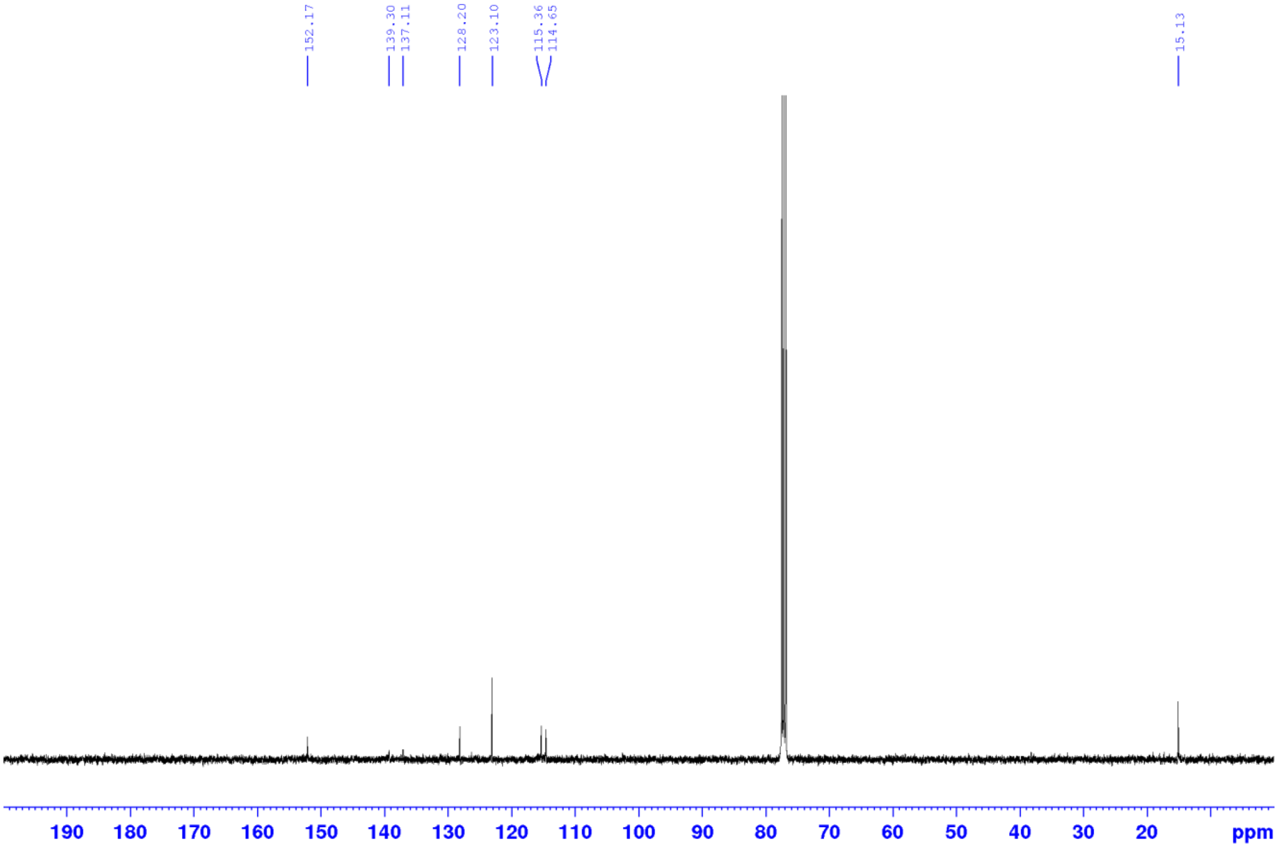
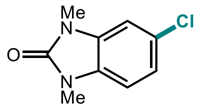


Figure S86: 101 MHz ^{13}C NMR spectrum of **15** in $CDCl_3$



16

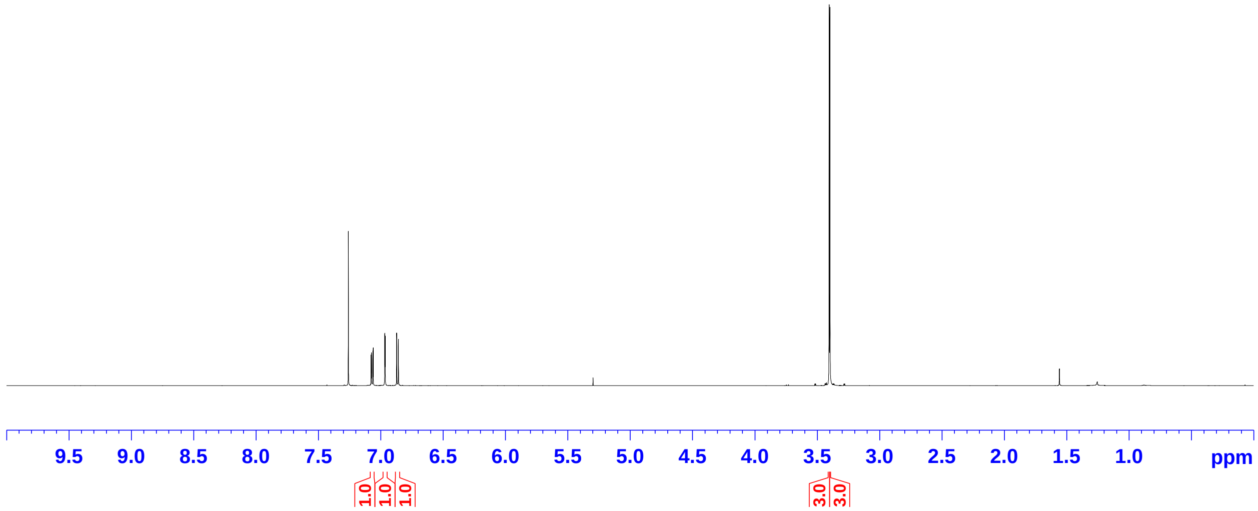


Figure S87: 600 MHz ^{1}H NMR spectrum of **16** in CDCl$_3$

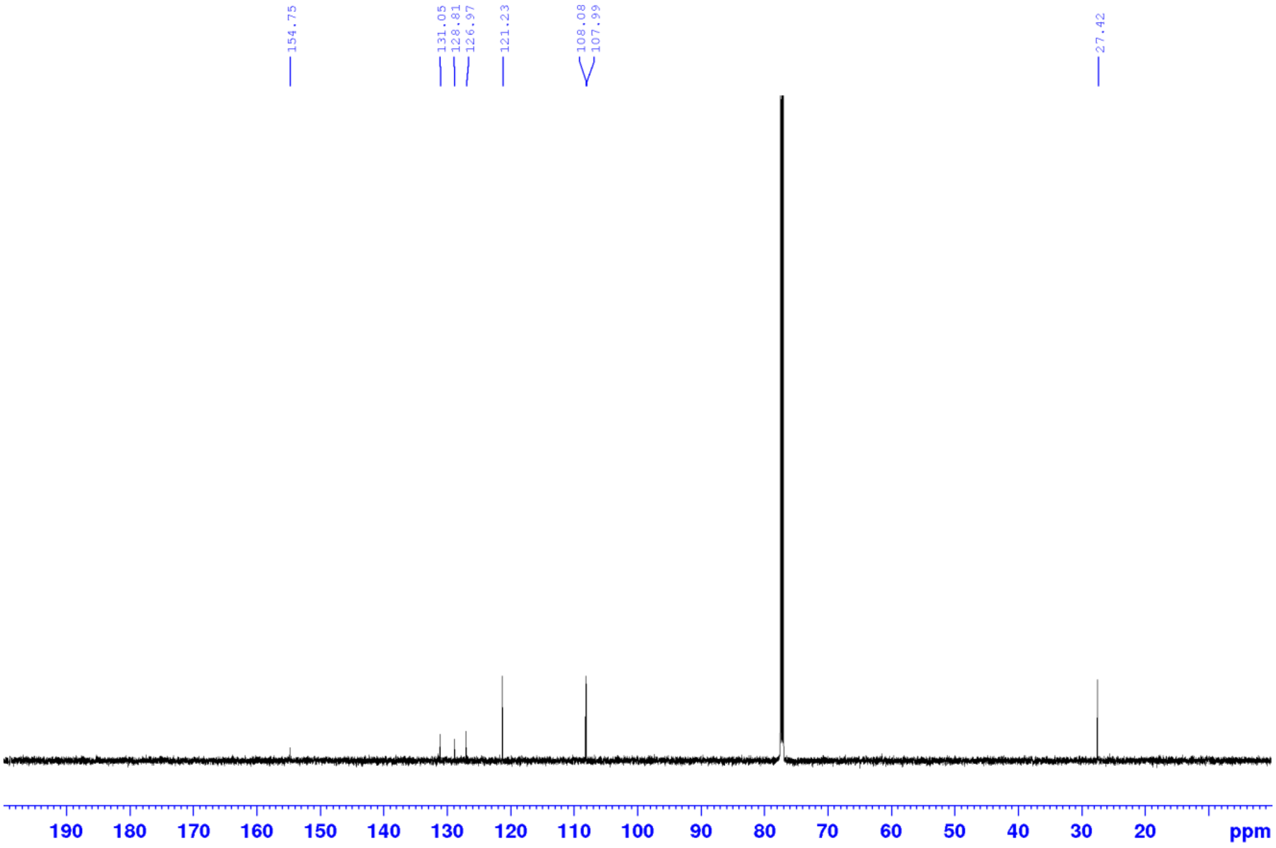
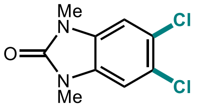


Figure S88: 151 MHz ^{13}C NMR spectrum of **16** in CDCl$_3$



17

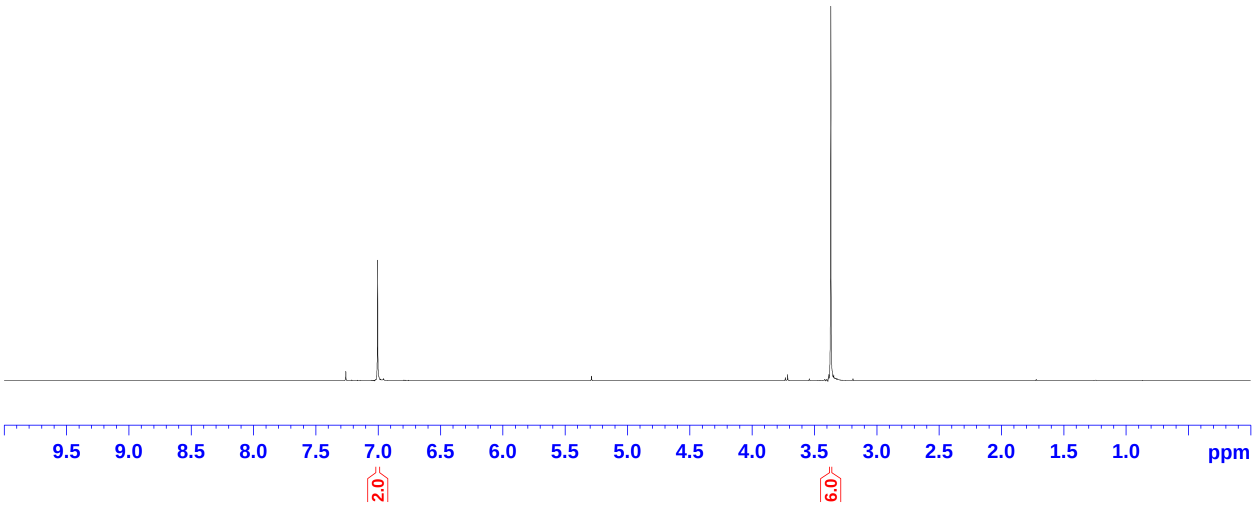


Figure S89: 400 MHz ^{1}H NMR spectrum of **17** in CDCl$_3$

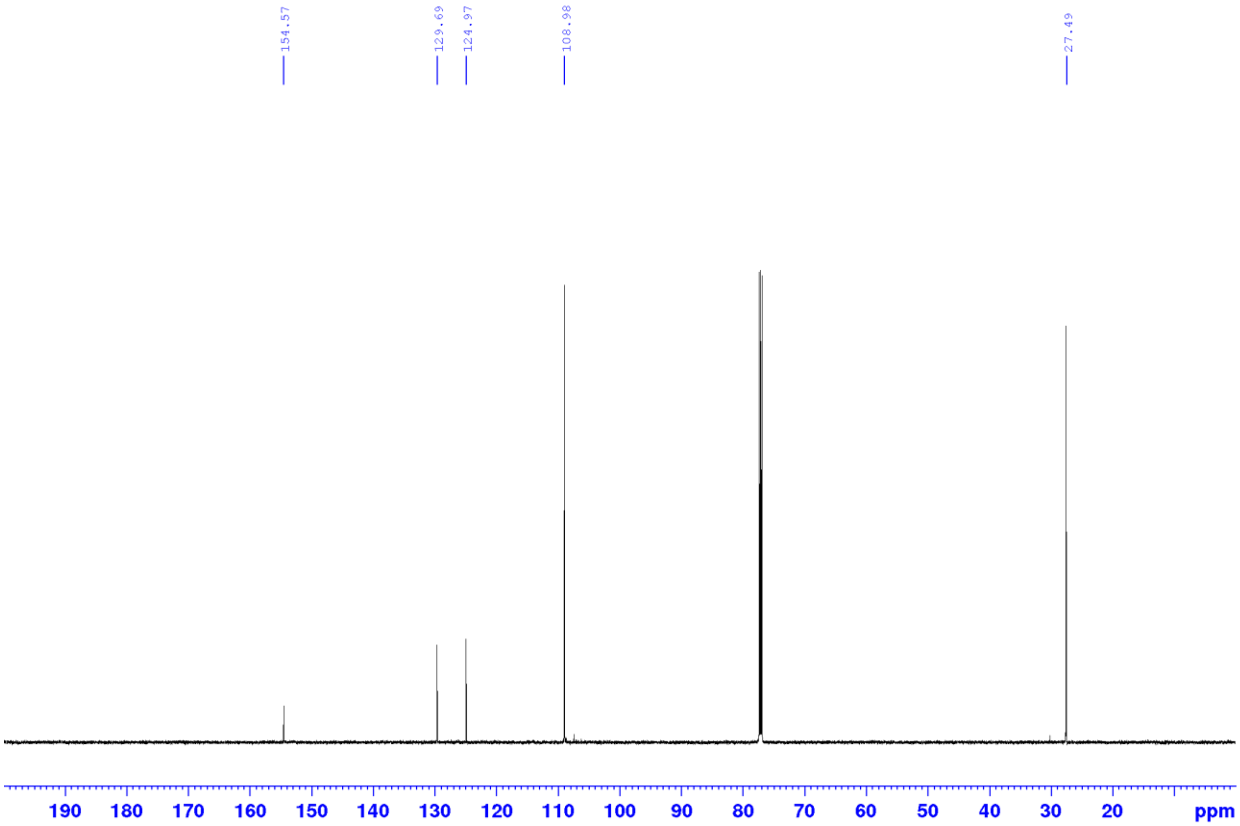
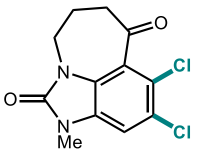


Figure S90: 151 MHz ^{13}C NMR spectrum of **17** in CDCl$_3$



18

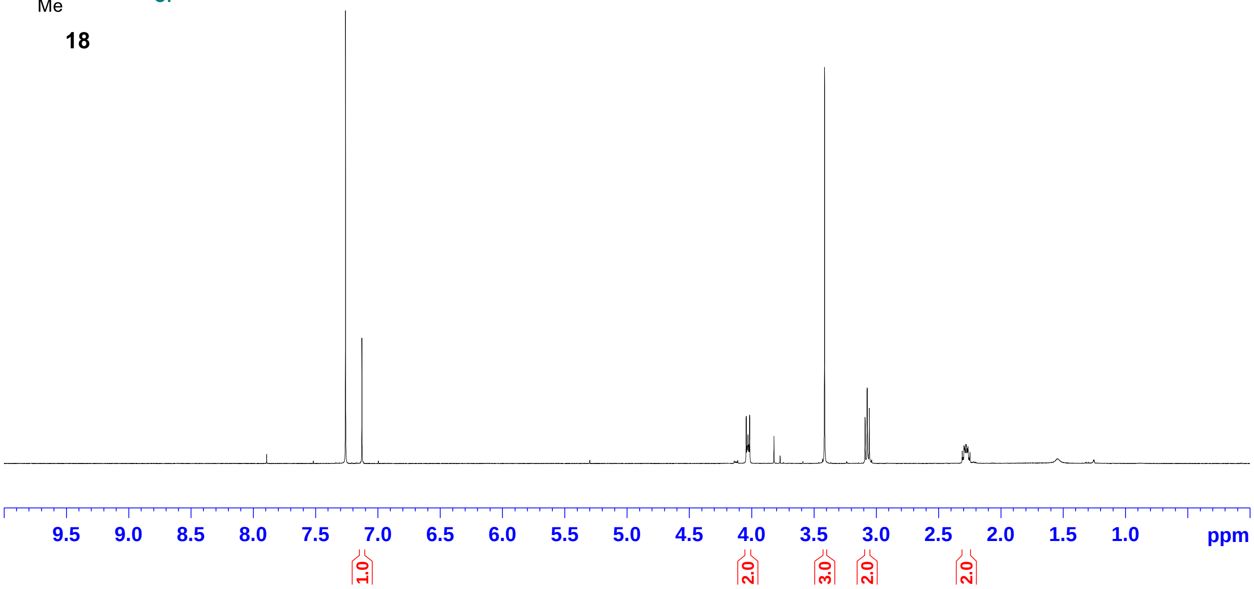


Figure S91: 400 MHz ^{1}H NMR spectrum of **18** in $CDCl_3$

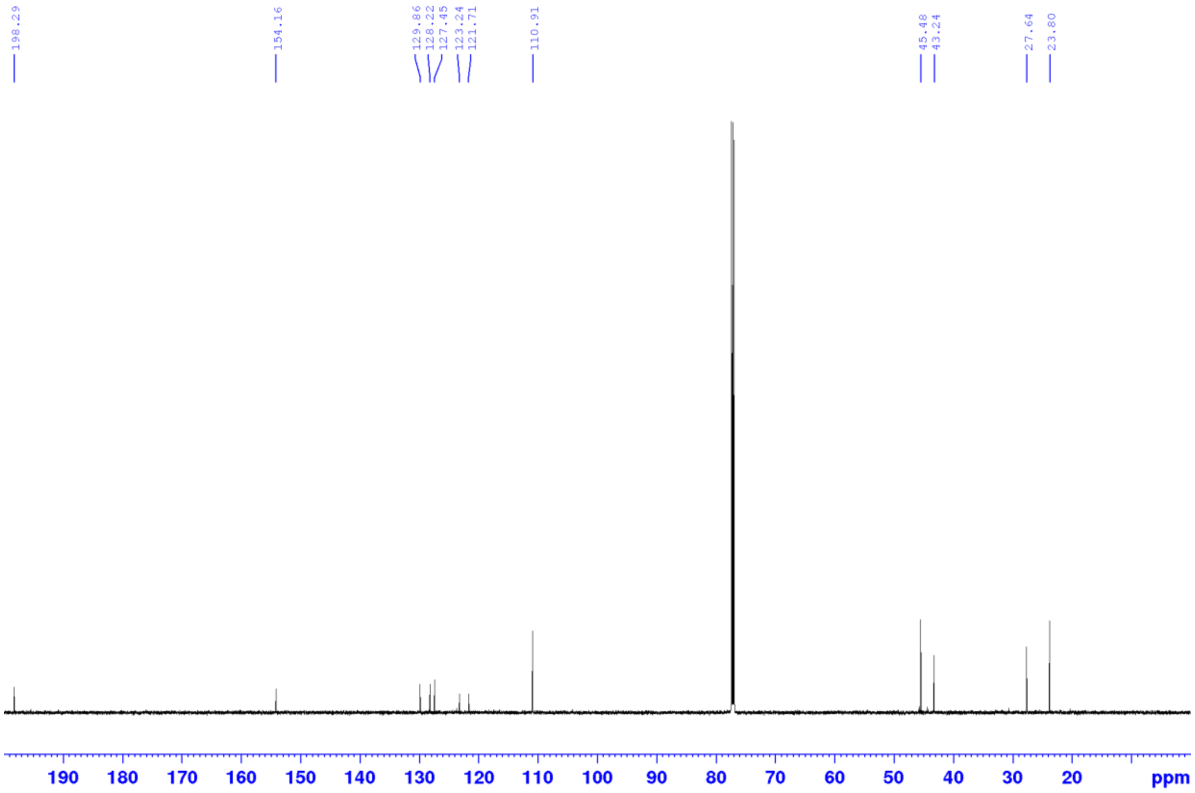
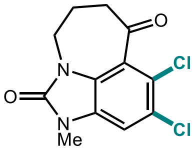


Figure S92: 151 MHz ^{13}C NMR spectrum of **18** in $CDCl_3$



18

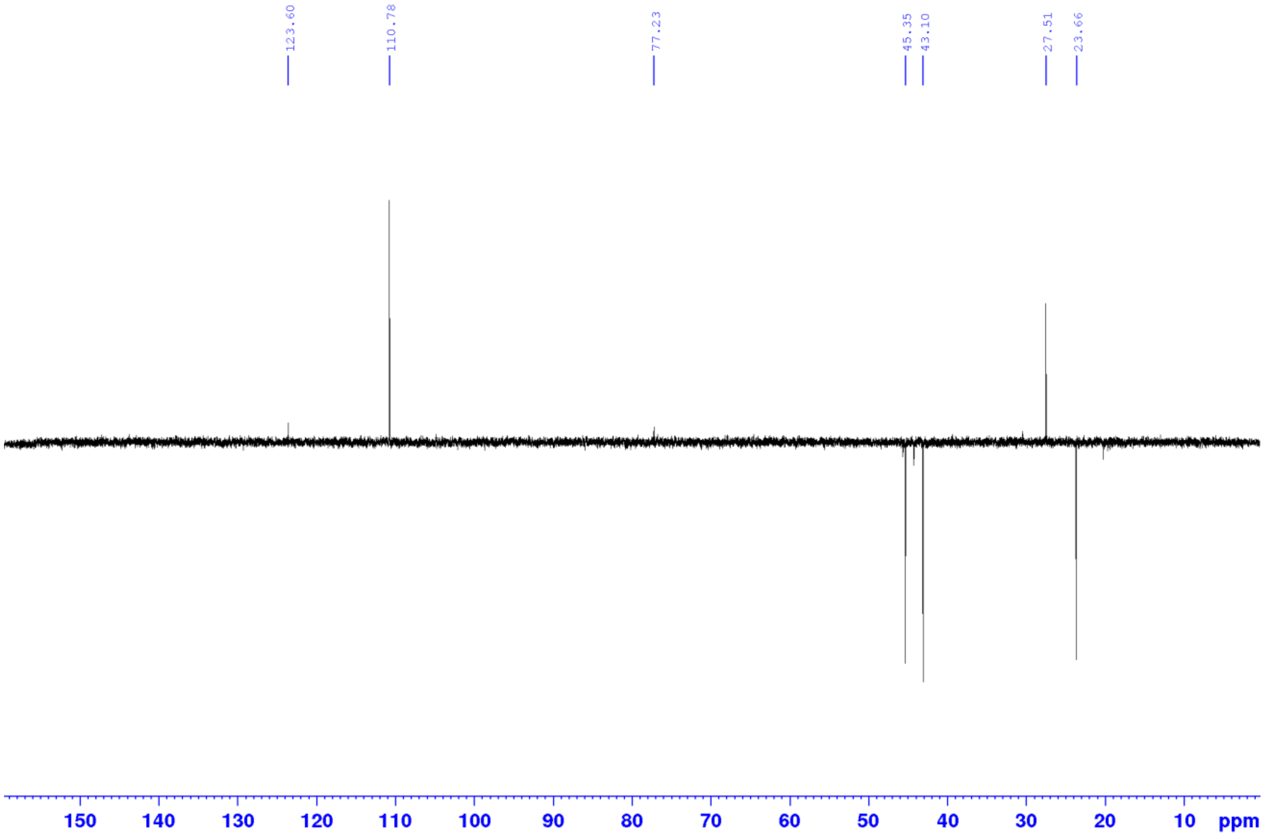


Figure S93: DEPT 135 NMR spectrum of **18** in $CDCl_3$

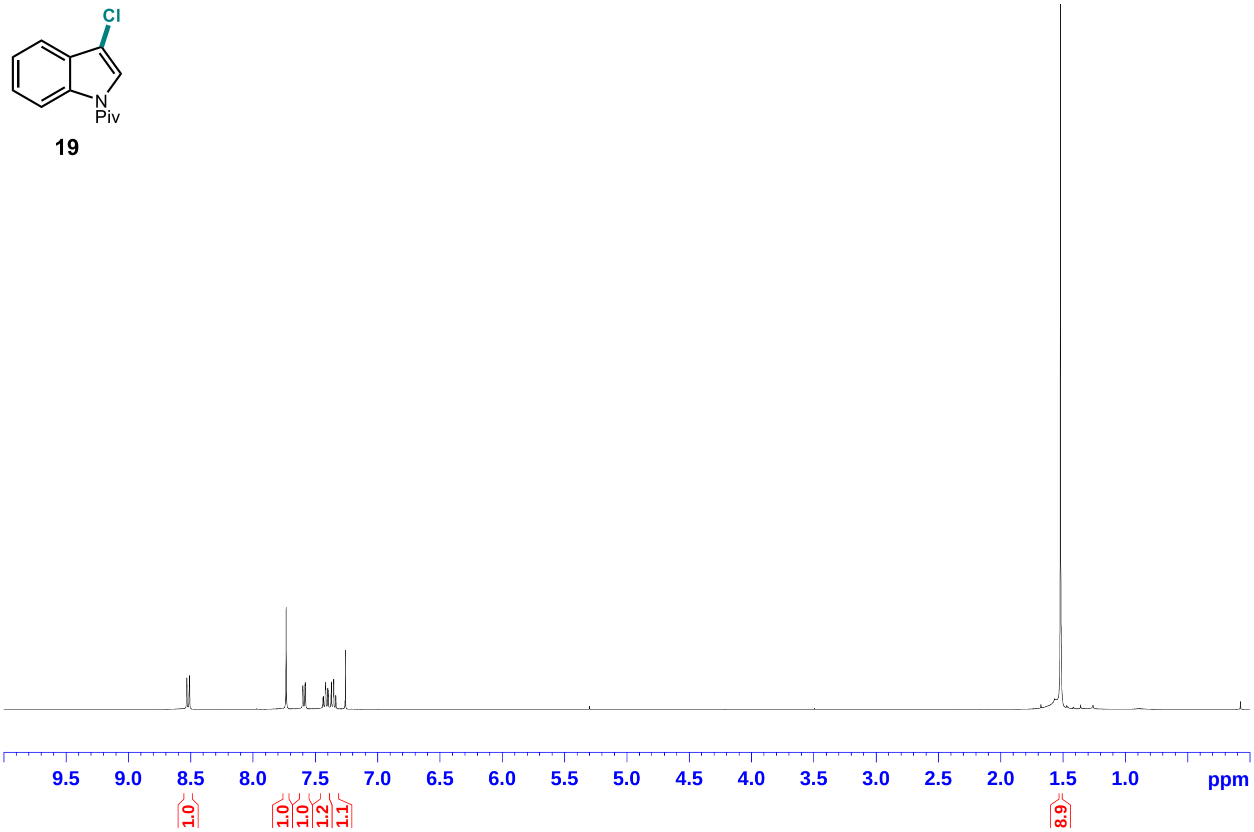


Figure S94: 400 MHz ^{1}H NMR spectrum of **19** in CDCl$_3$

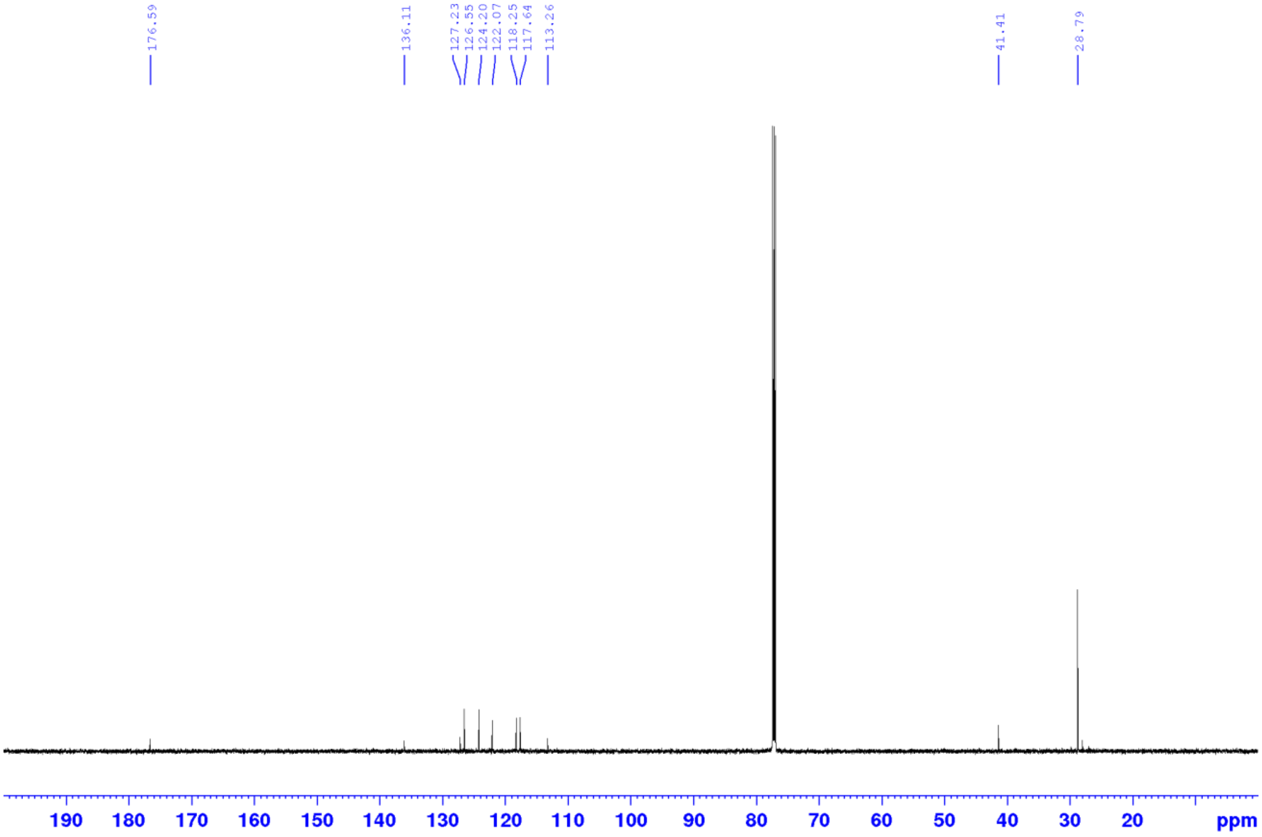


Figure S95: 101 MHz ^{13}C NMR spectrum of **19** in CDCl$_3$

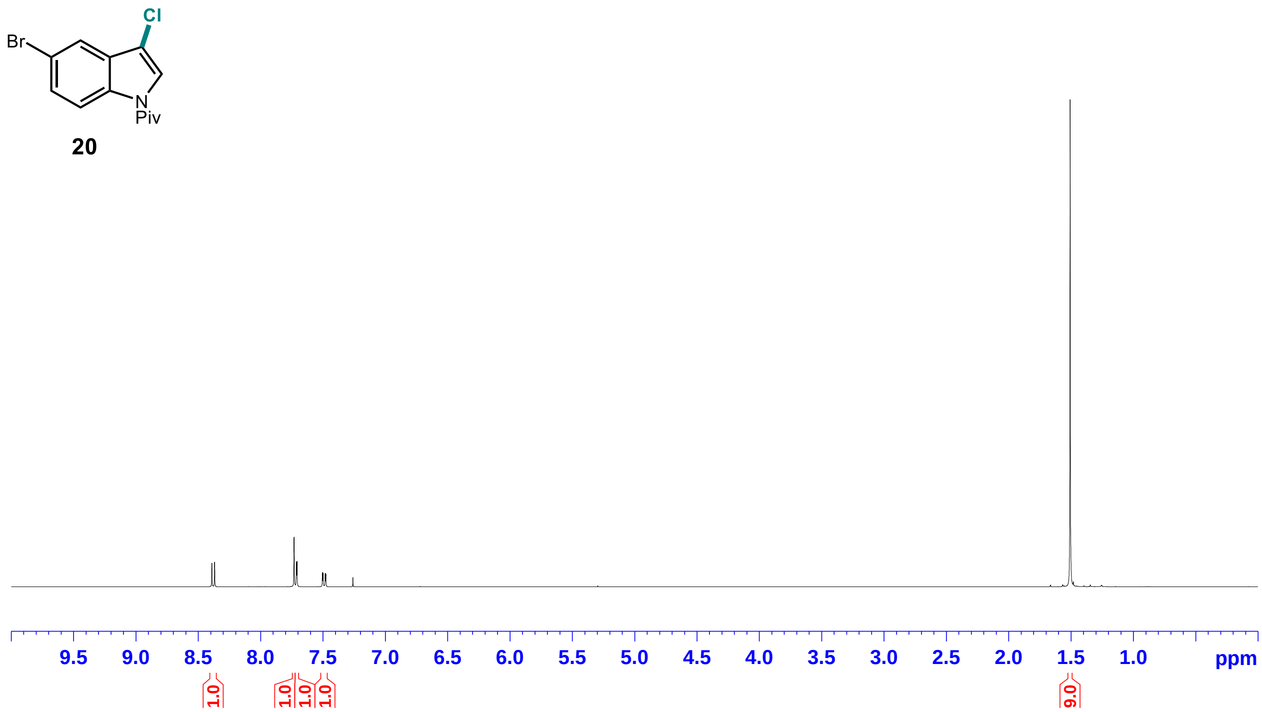


Figure S96: 400 MHz ^{1}H NMR spectrum of **20** in $CDCl_3$

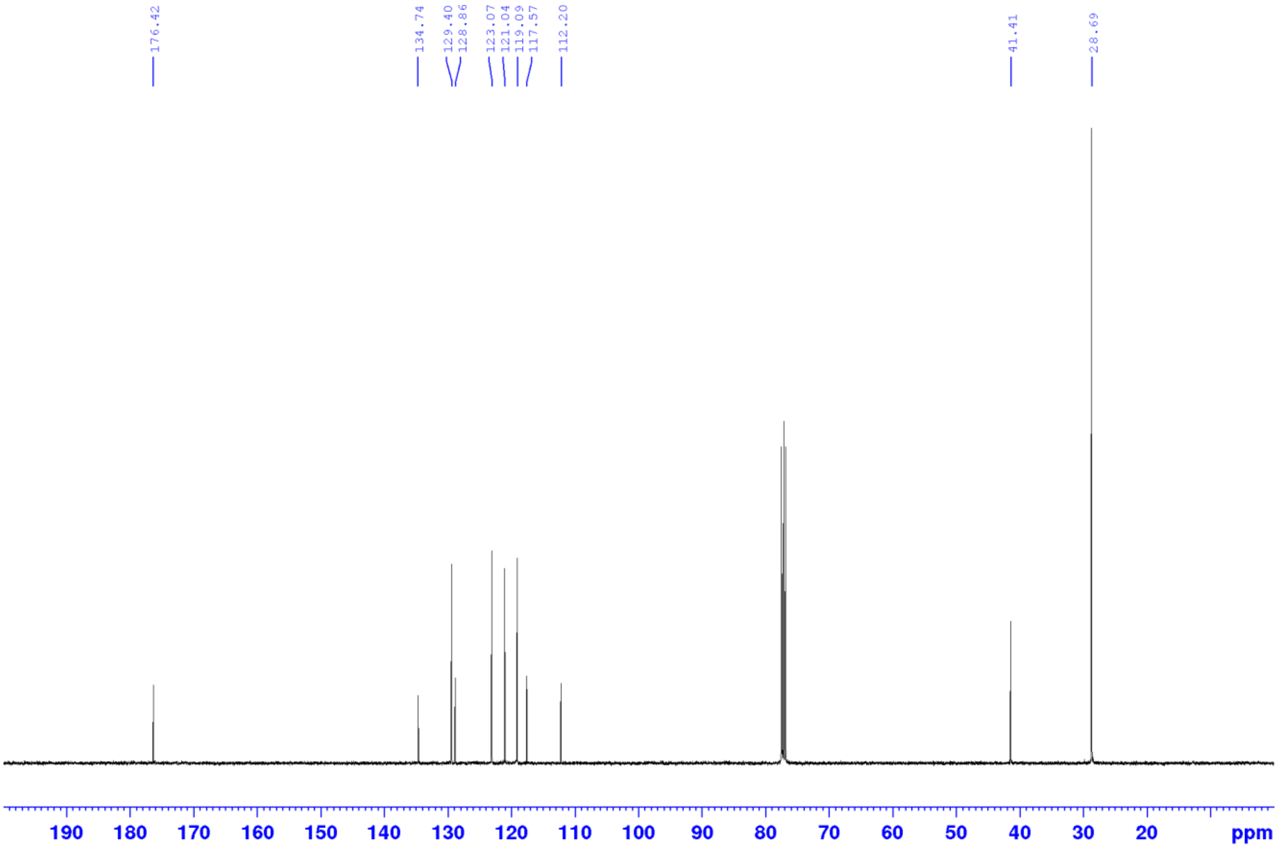
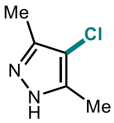


Figure S97: 101 MHz ^{13}C NMR spectrum of **20** in $CDCl_3$



21

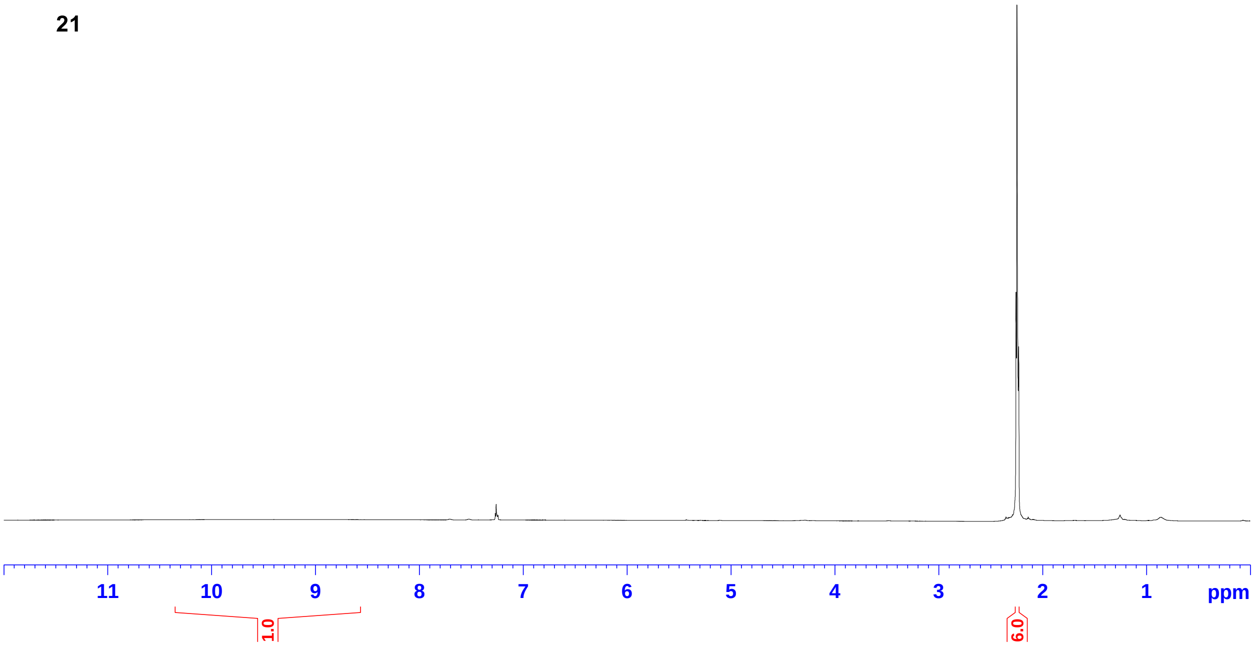


Figure S98: 600 MHz ^{1}H NMR spectrum of **21** in CDCl$_3$

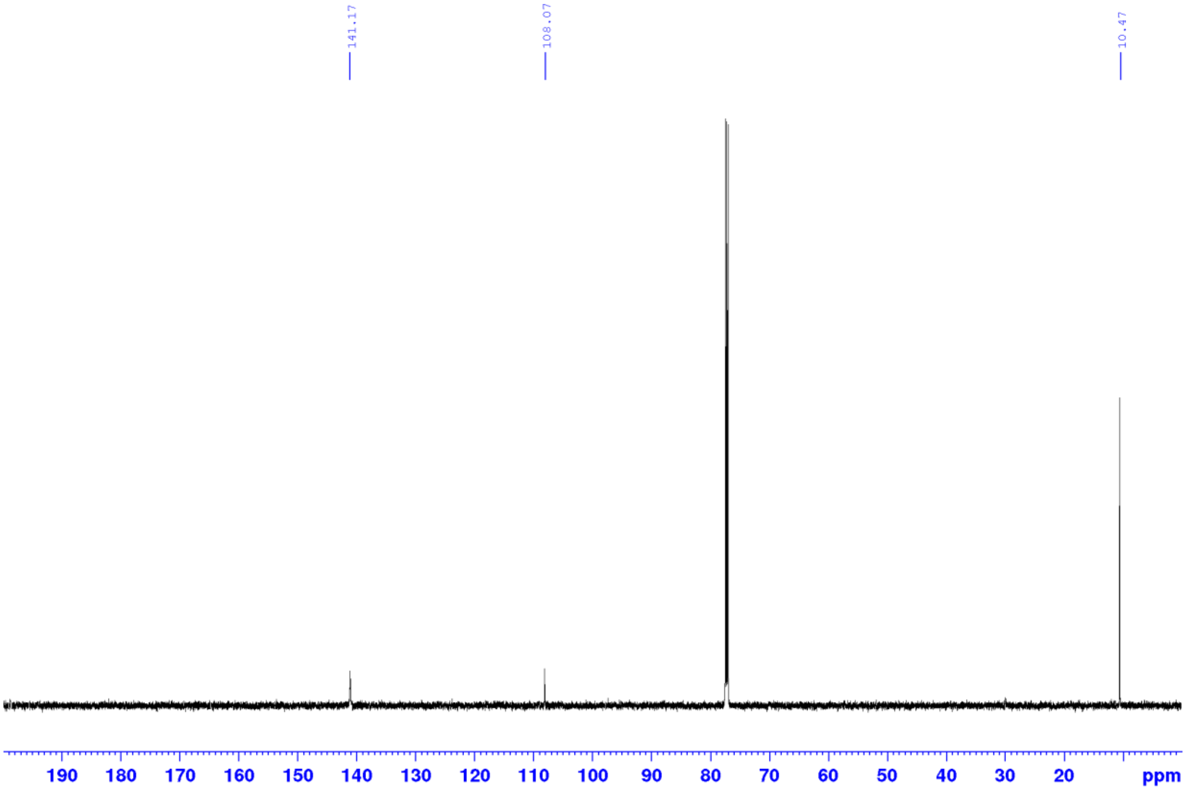


Figure S99: 151 MHz ^{13}C NMR spectrum of **21** in CDCl$_3$

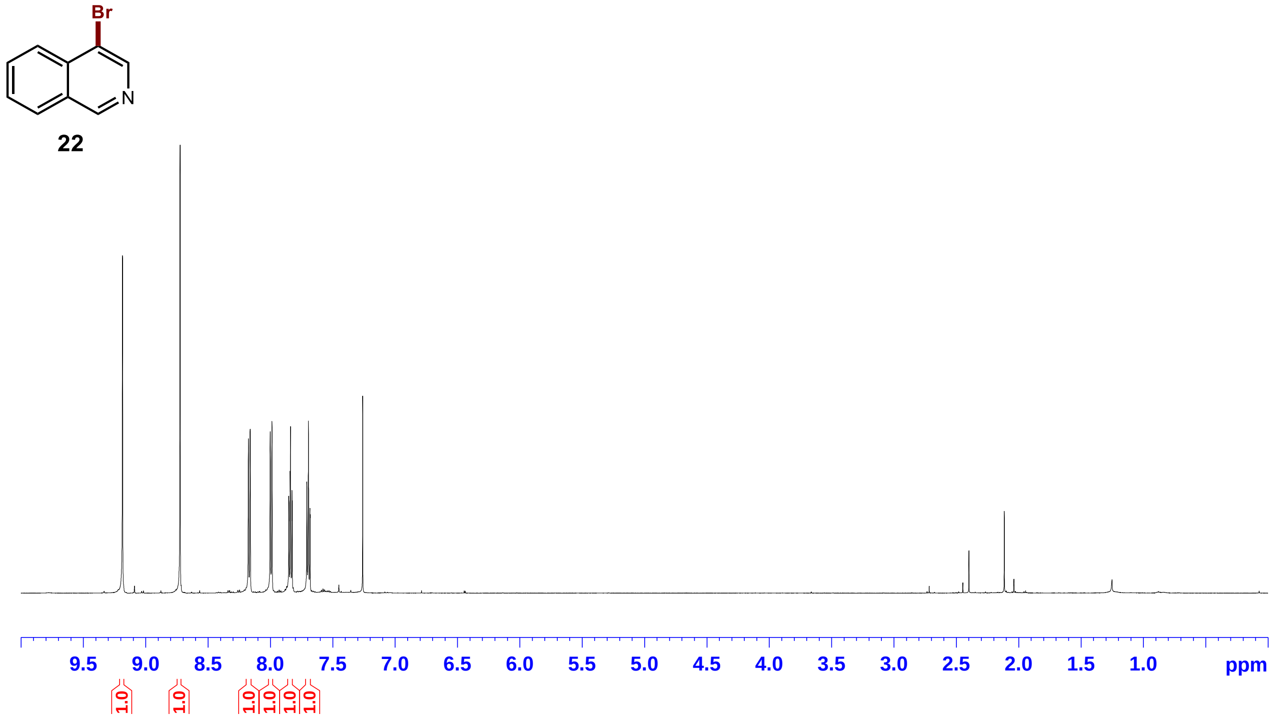


Figure S100: 600 MHz ^{1}H NMR spectrum of **22** in $CDCl_3$

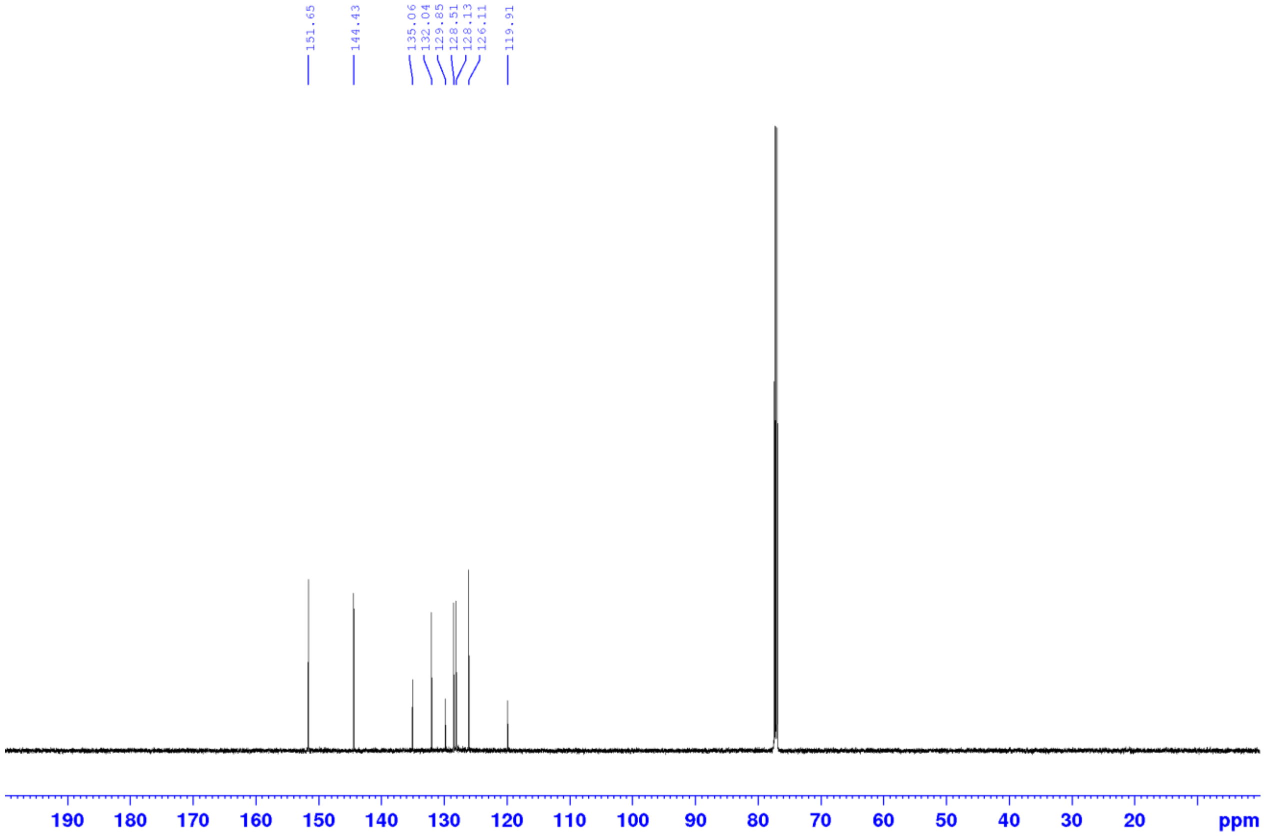
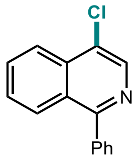


Figure S101: 151 MHz ^{13}C NMR spectrum of **22** in $CDCl_3$



23

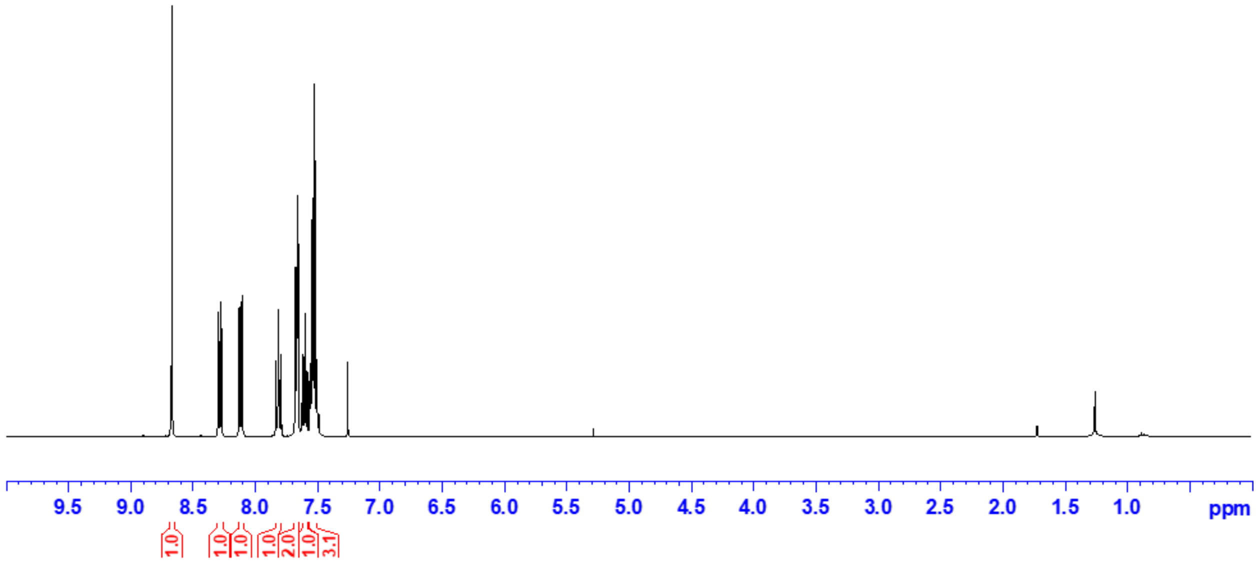


Figure S102: 400 MHz ^{1}H NMR spectrum of **23** in $CDCl_3$

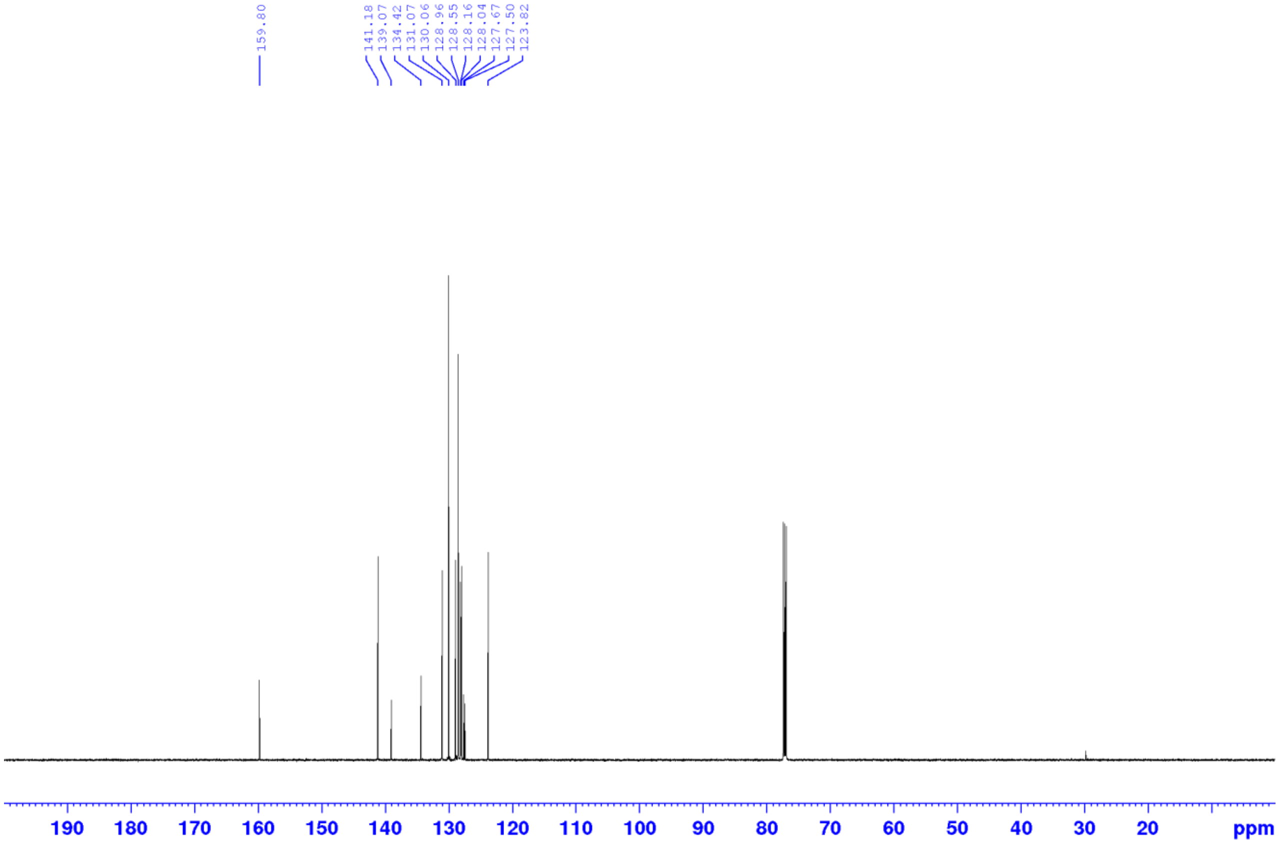


Figure S103: 101 MHz ^{13}C NMR spectrum of **23** in $CDCl_3$

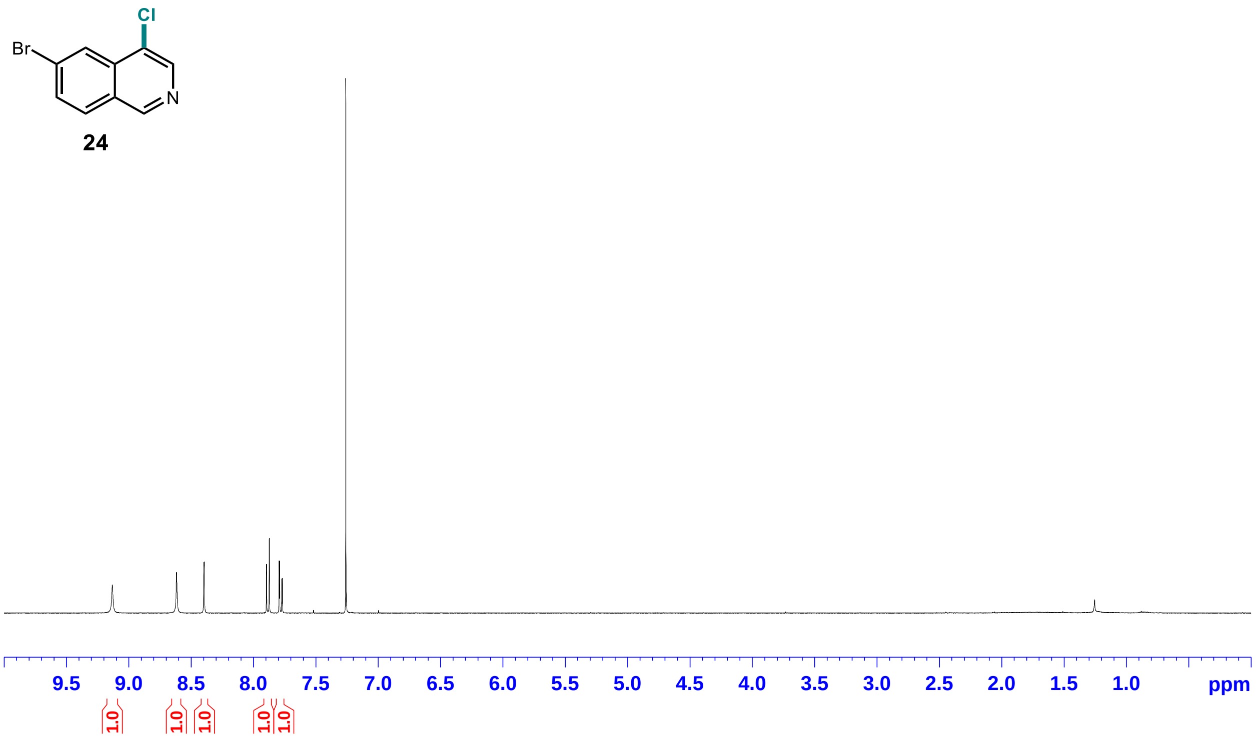


Figure S104: 400 MHz ^{1}H NMR spectrum of **24** in $CDCl_3$

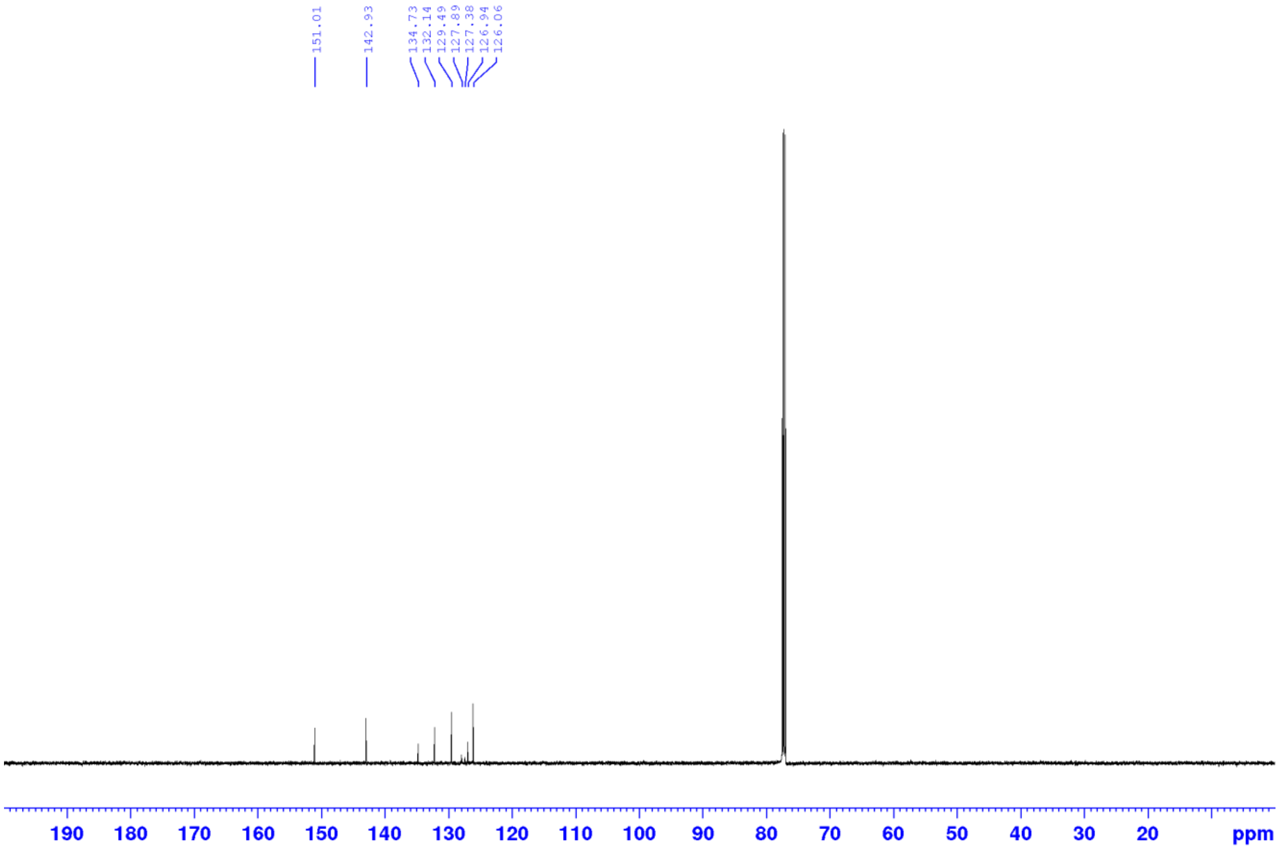


Figure S105: 151 MHz ^{13}C NMR spectrum of **24** in $CDCl_3$

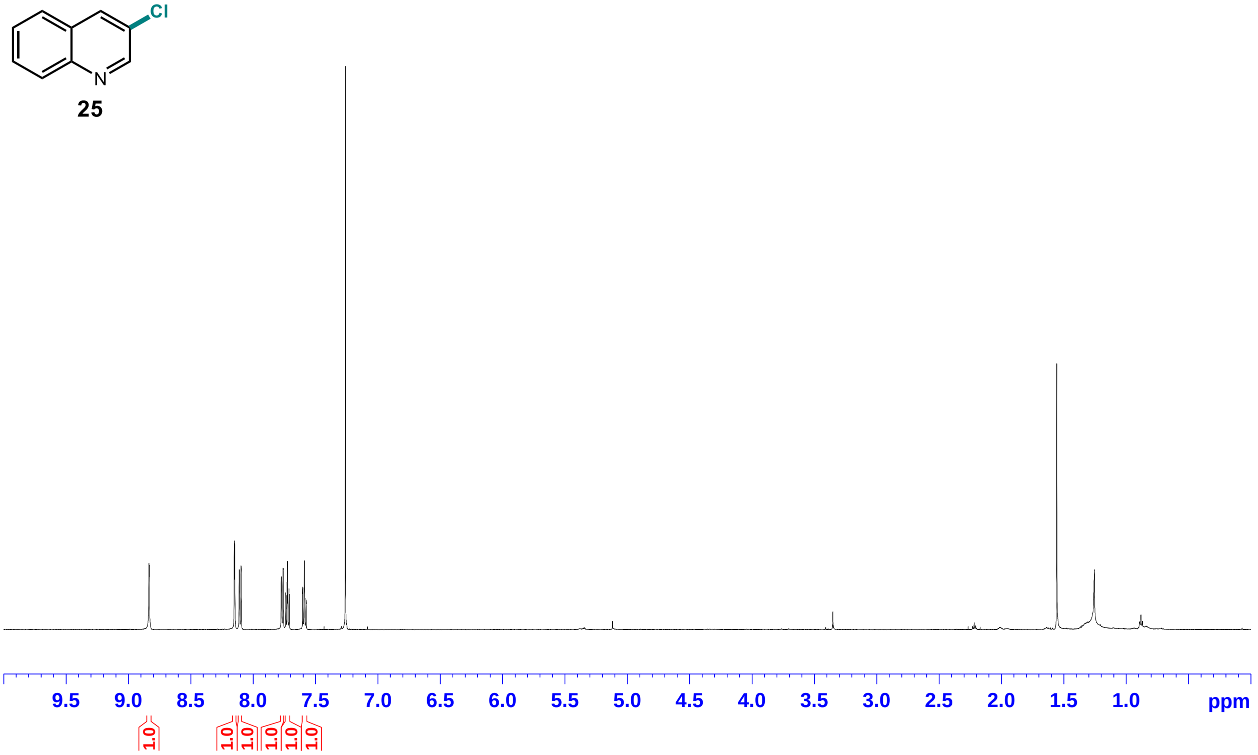


Figure S106: 400 MHz ^{1}H NMR spectrum of **25** in CDCl$_3$

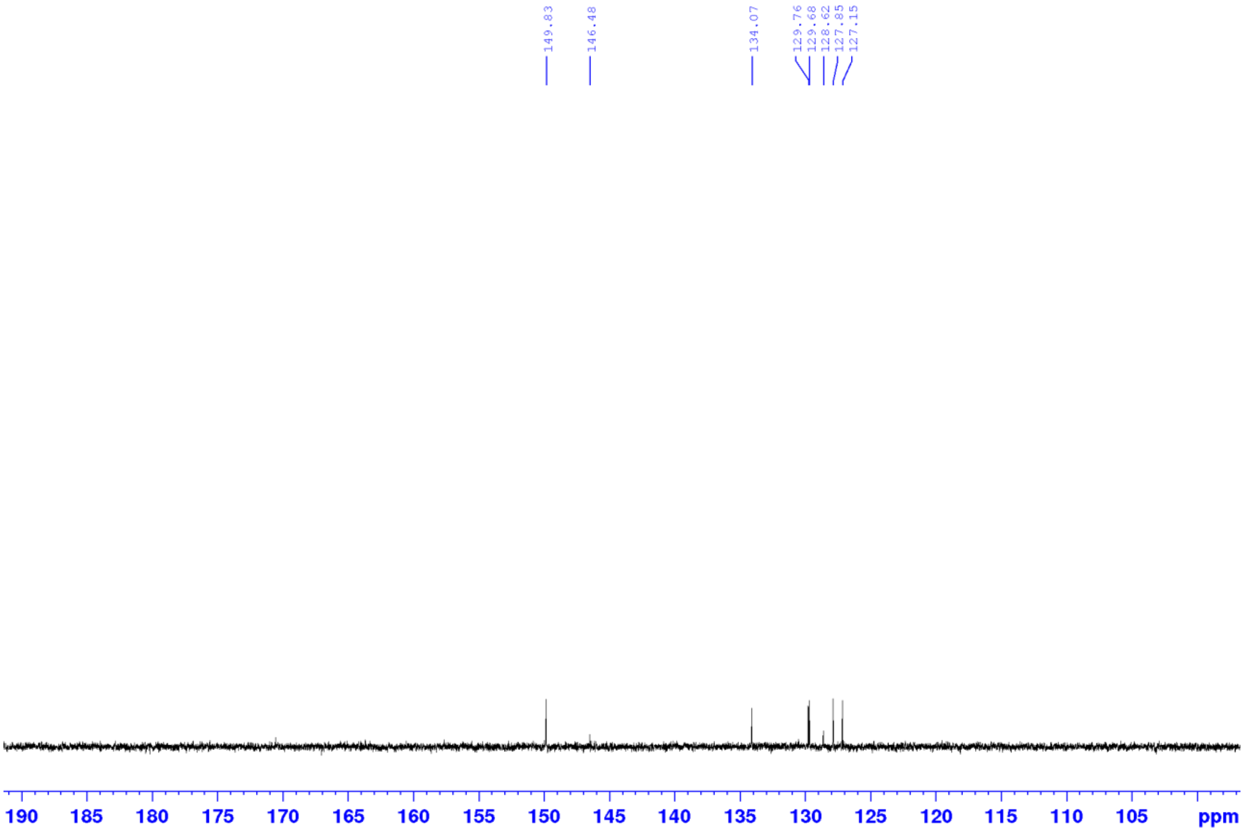
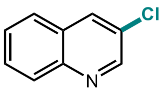


Figure S107: 101 MHz ^{13}C NMR spectrum of **25** in CDCl$_3$



25

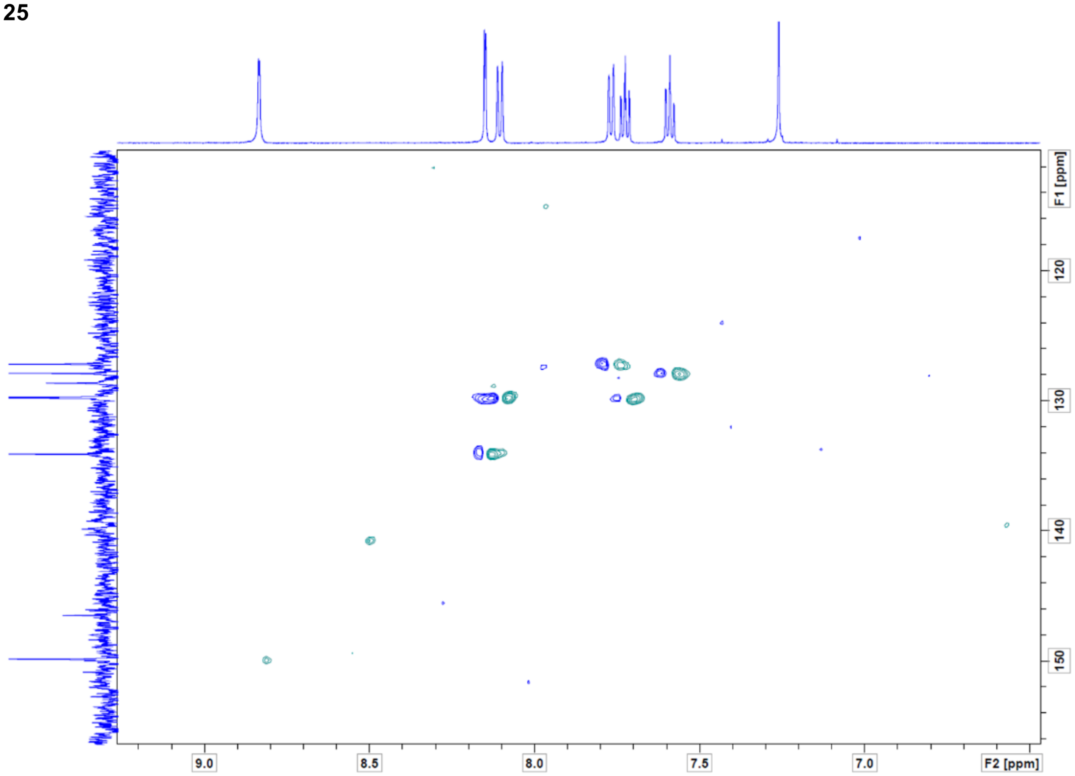


Figure S108: HSQC spectrum of **25** in $CDCl_3$ in $CDCl_3$

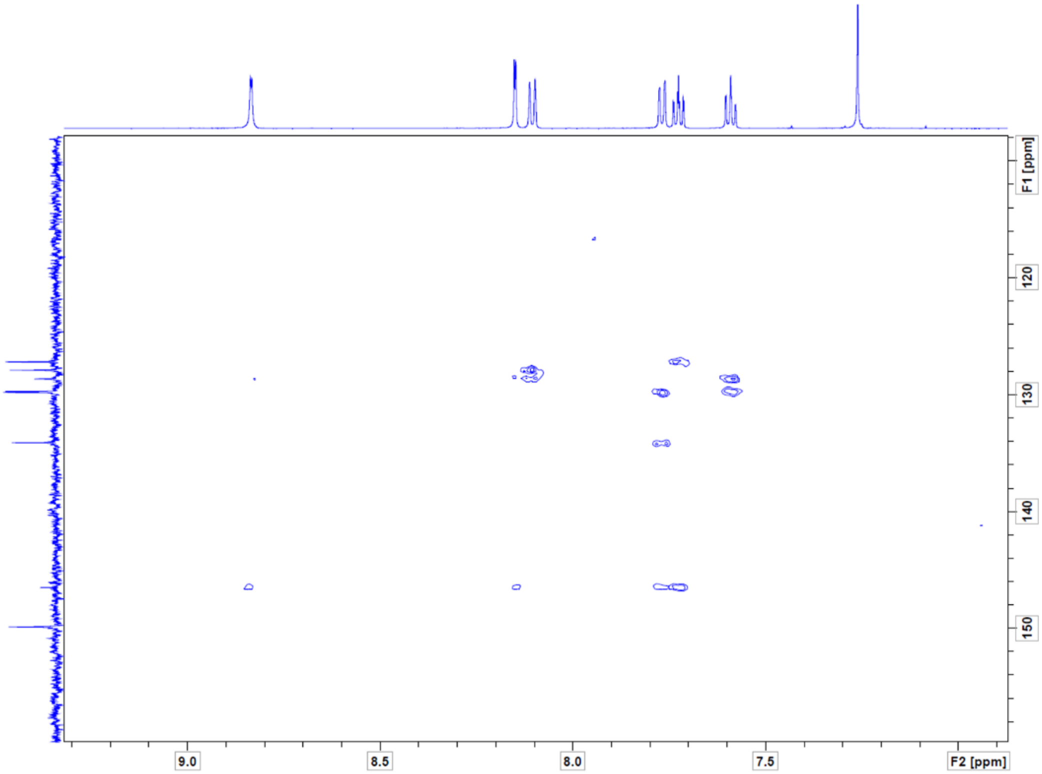


Figure S109: HMBC spectrum of **25** in $CDCl_3$

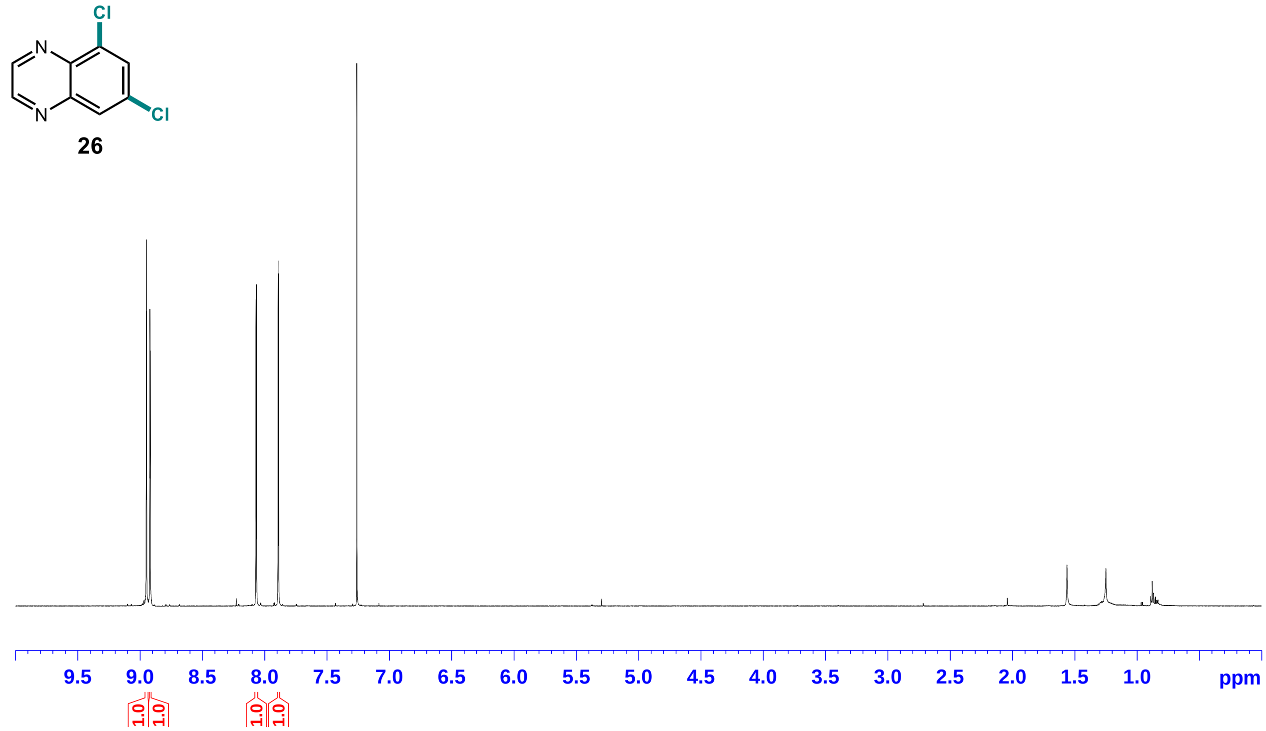


Figure S110: 600 MHz ^{1}H NMR spectrum of **26** in $CDCl_3$

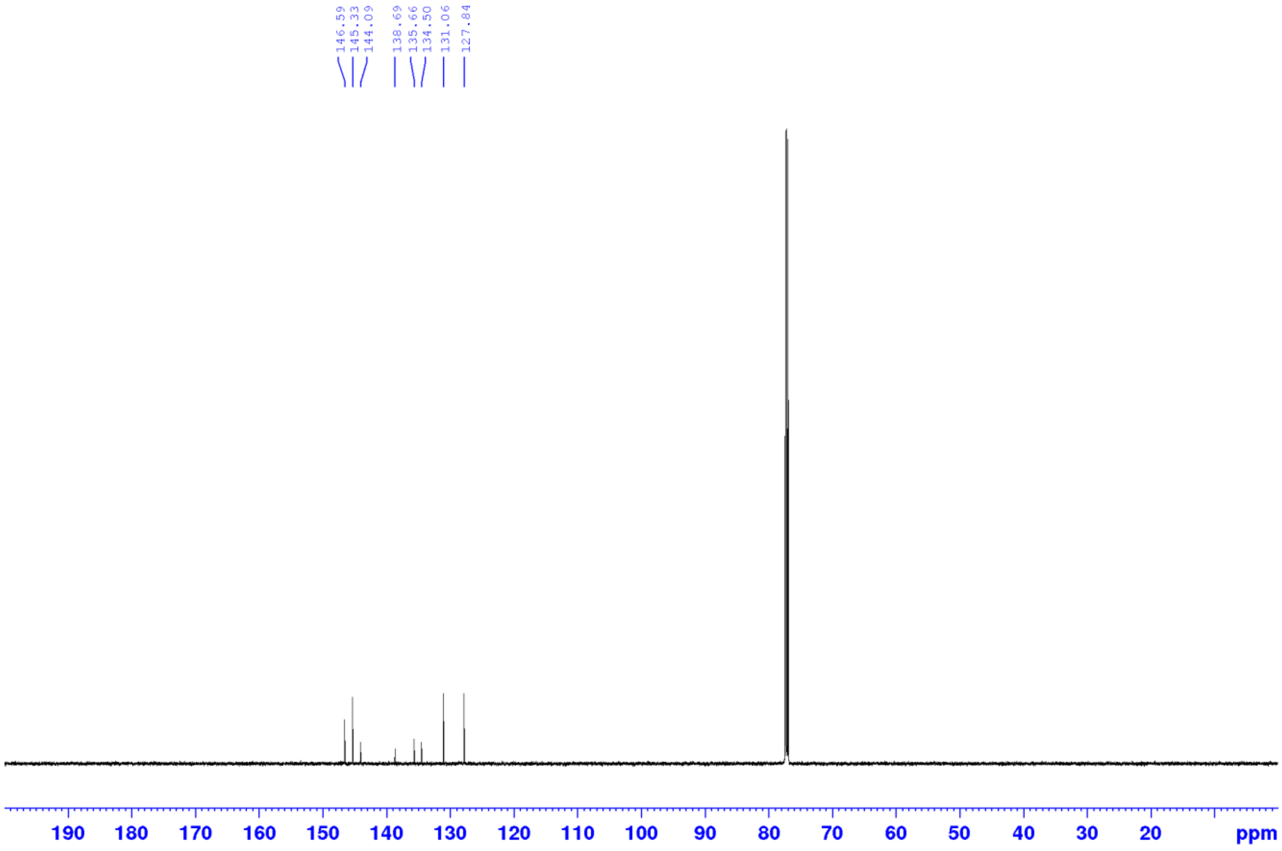


Figure S111: 151 MHz ^{13}C NMR spectrum of **26** in $CDCl_3$

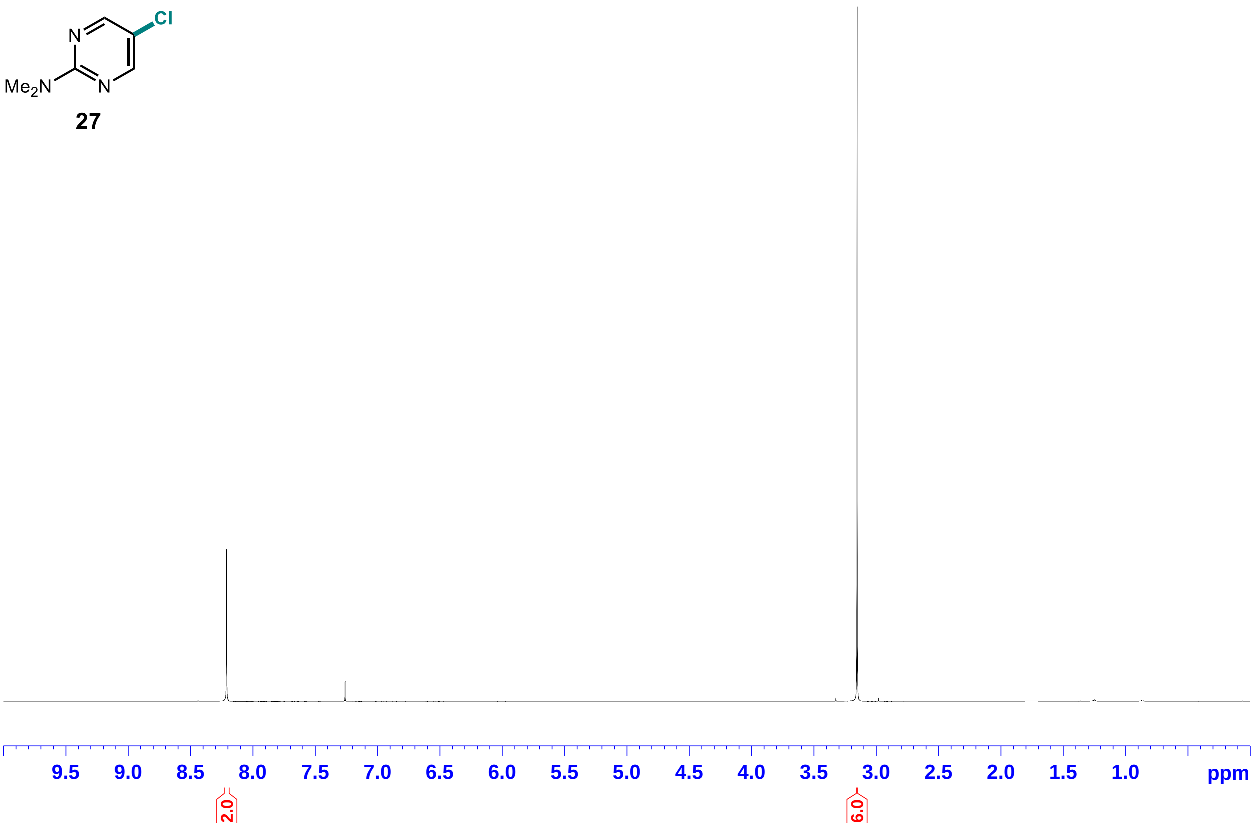


Figure S112: 400 MHz ^{1}H NMR spectrum of **27** in CDCl$_3$

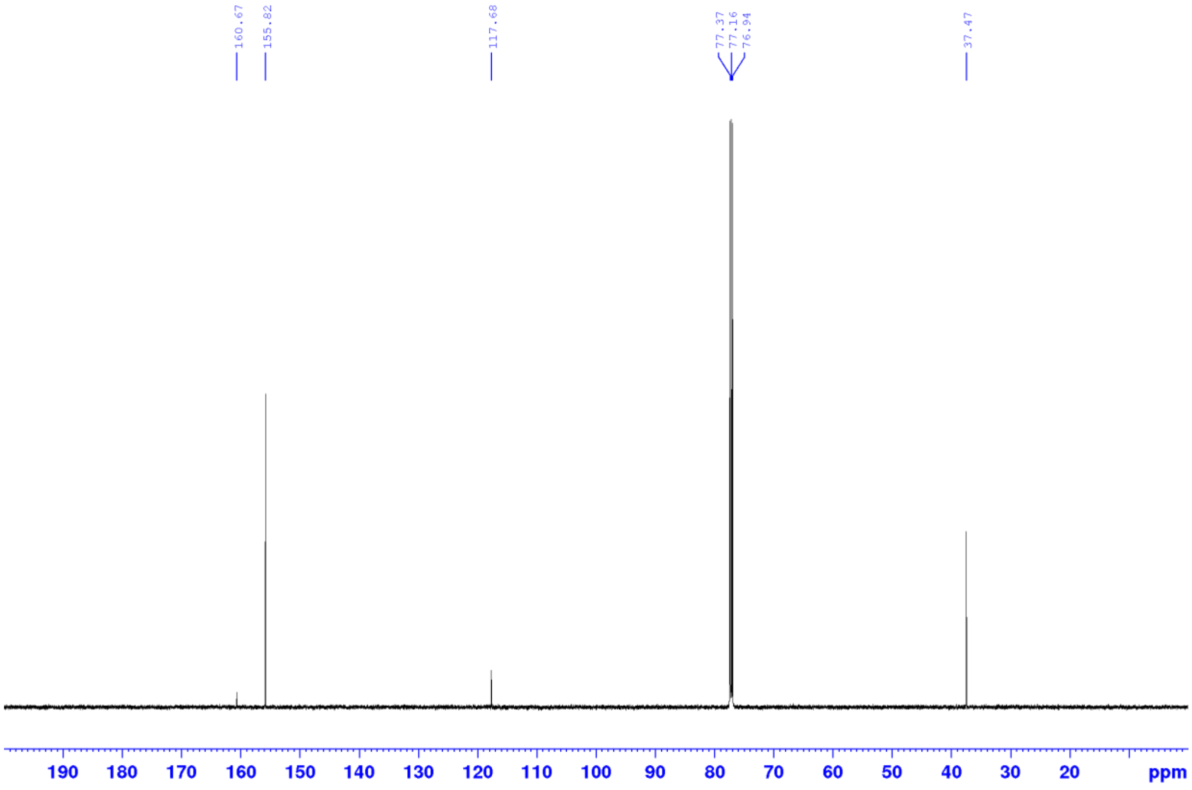
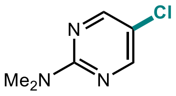


Figure S113: 101 MHz ^{13}C NMR spectrum of **27** in CDCl$_3$



27

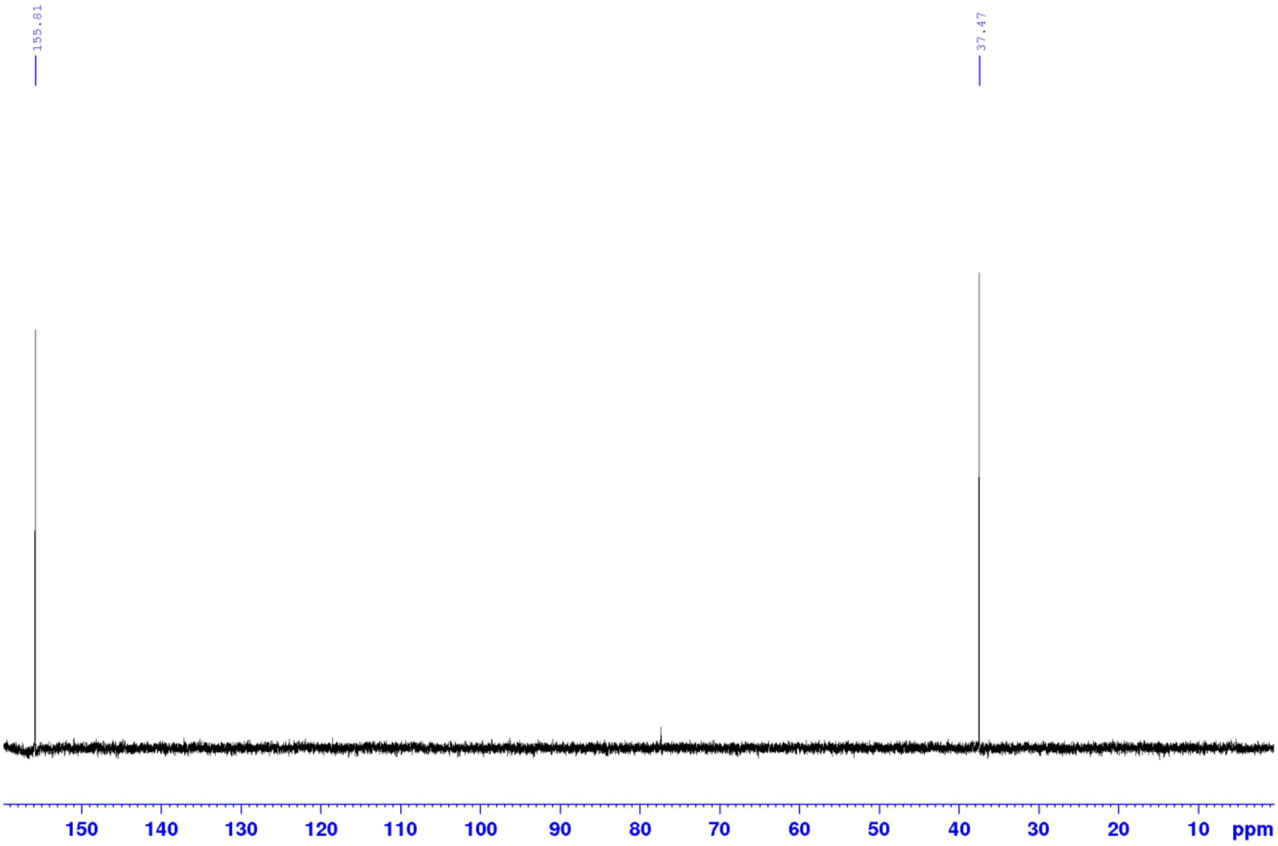


Figure S114: DEPT 135 NMR spectrum of **27** in

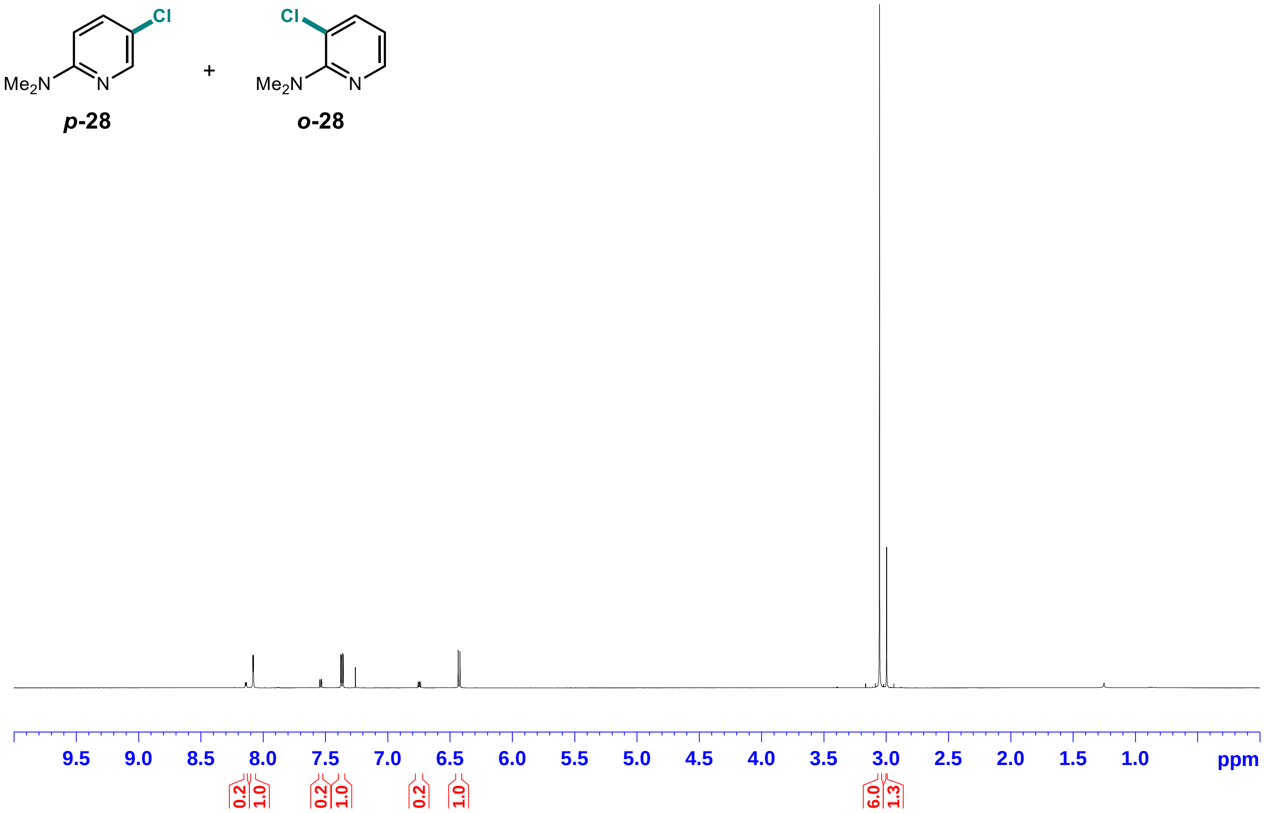


Figure S115: 400 MHz ^{1}H NMR spectrum of **28** in CDCl$_3$

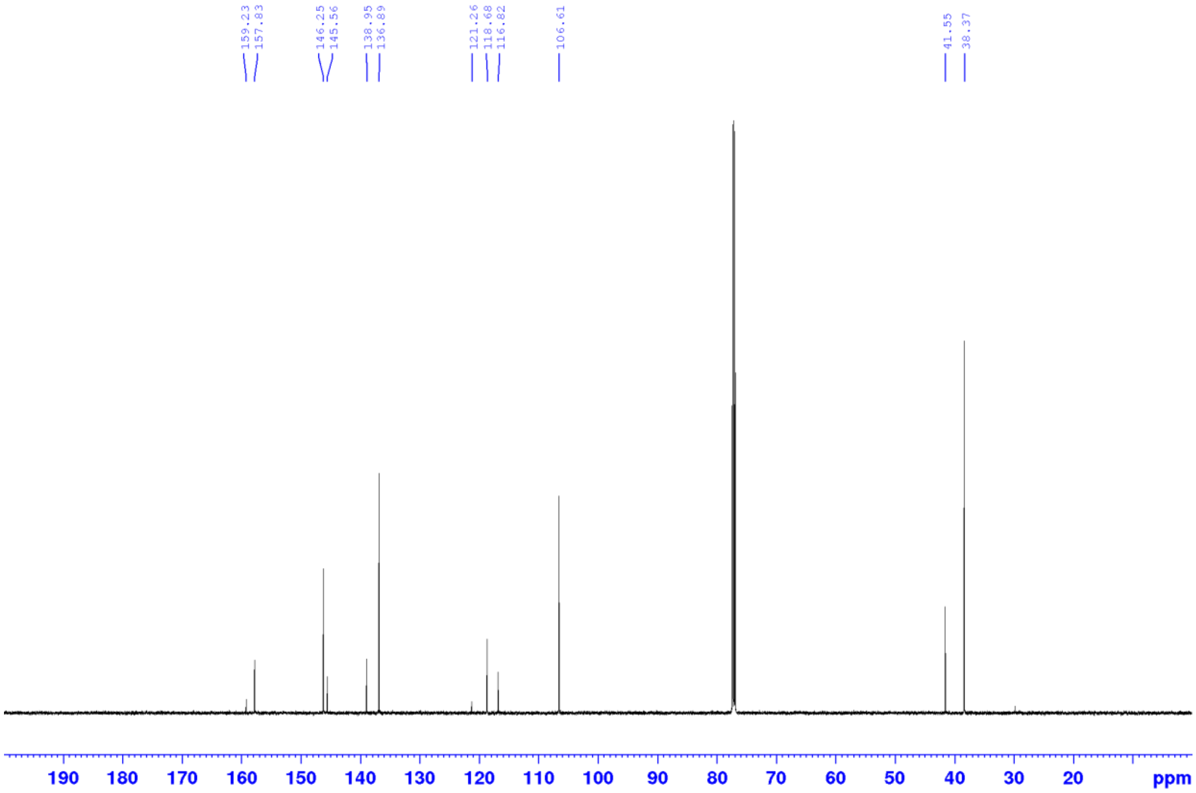


Figure S116: 101 MHz ^{13}C NMR spectrum of **28** in CDCl$_3$

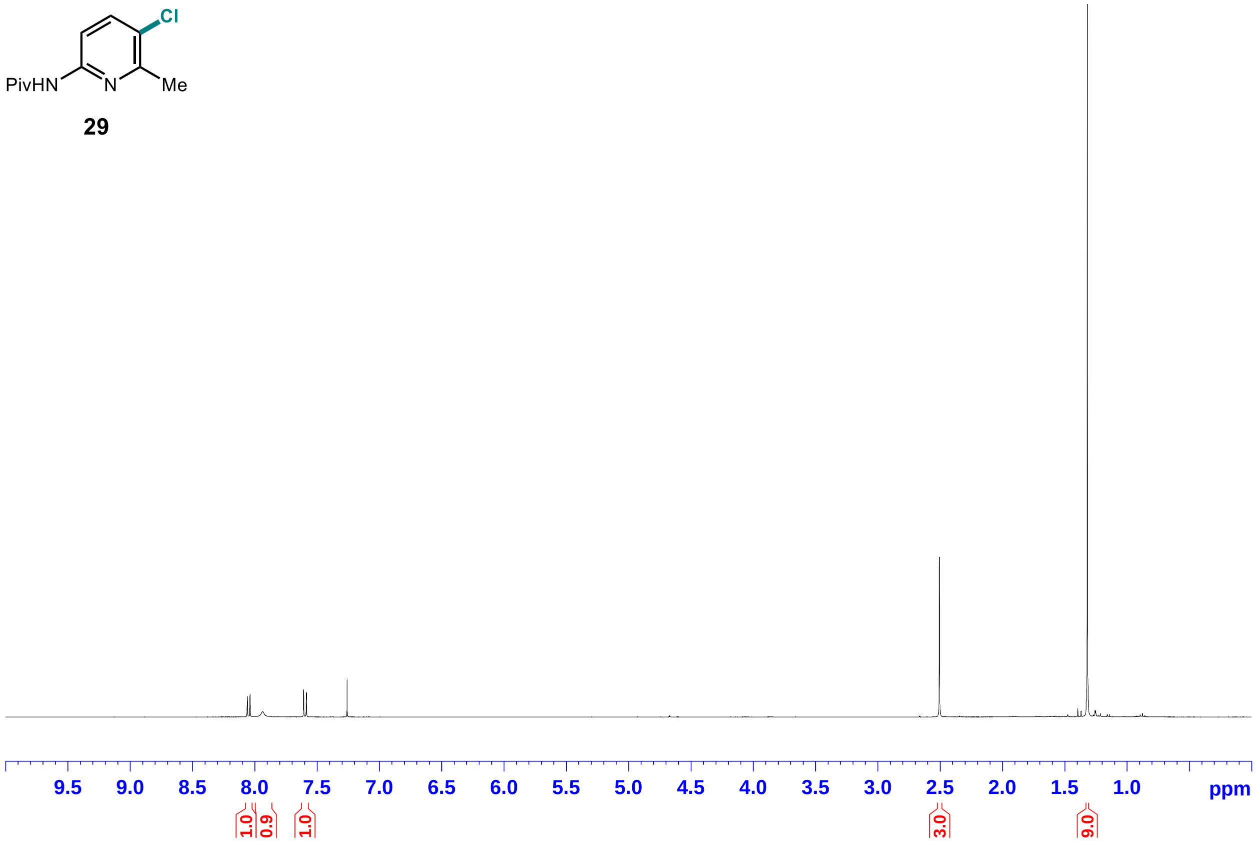


Figure S117: 400 MHz ^{1}H NMR spectrum of **29** in $CDCl_3$

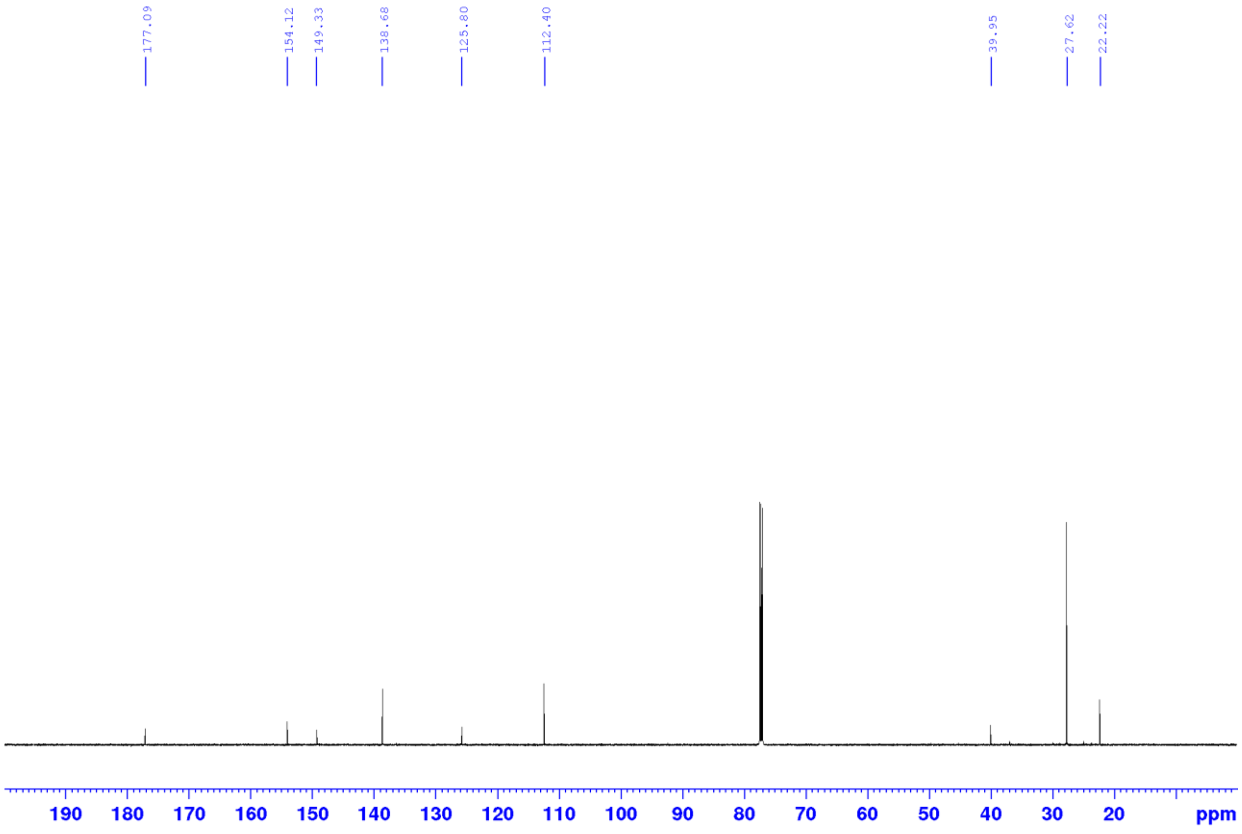
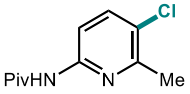


Figure S118: 101 MHz ^{13}C NMR spectrum of **29** in $CDCl_3$



29

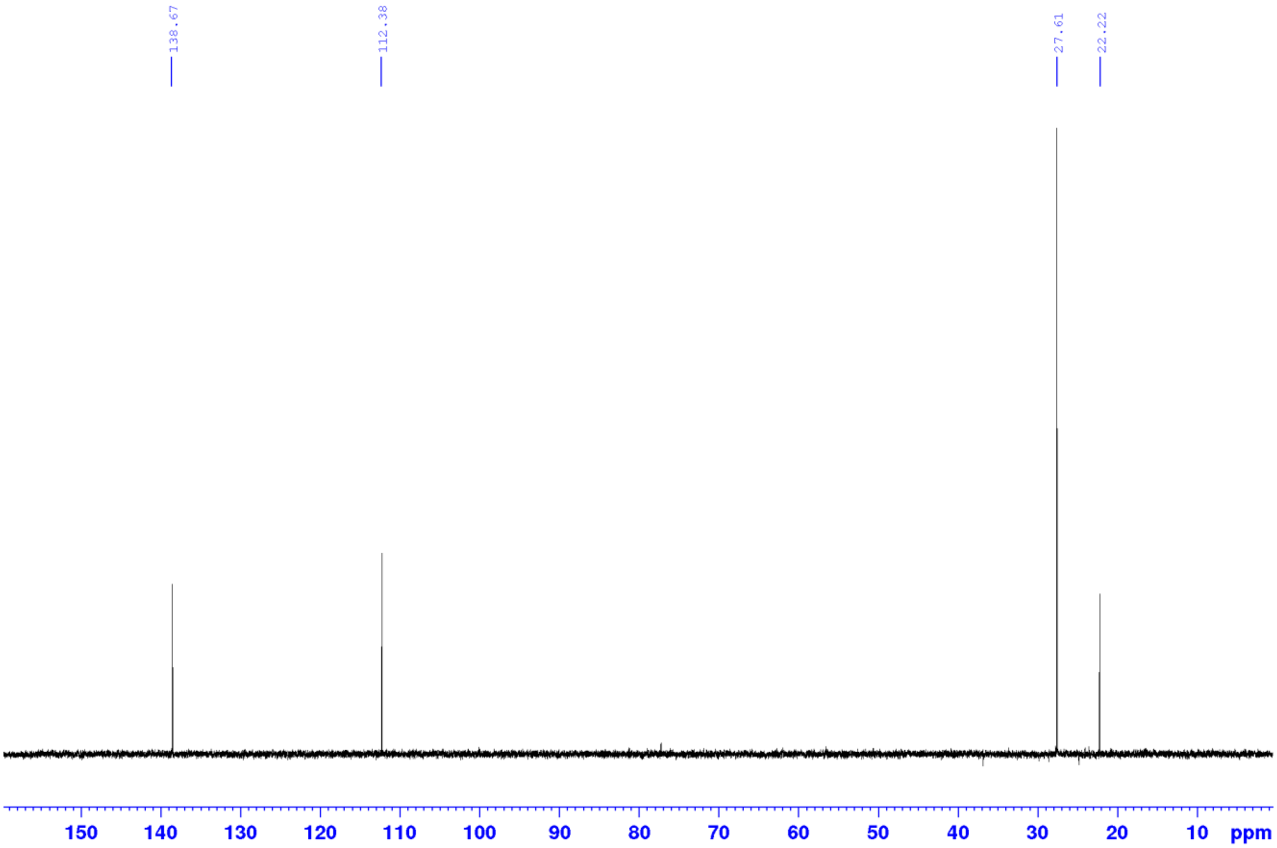


Figure S119: DEPT 135 NMR spectrum of **29** in $CDCl_3$

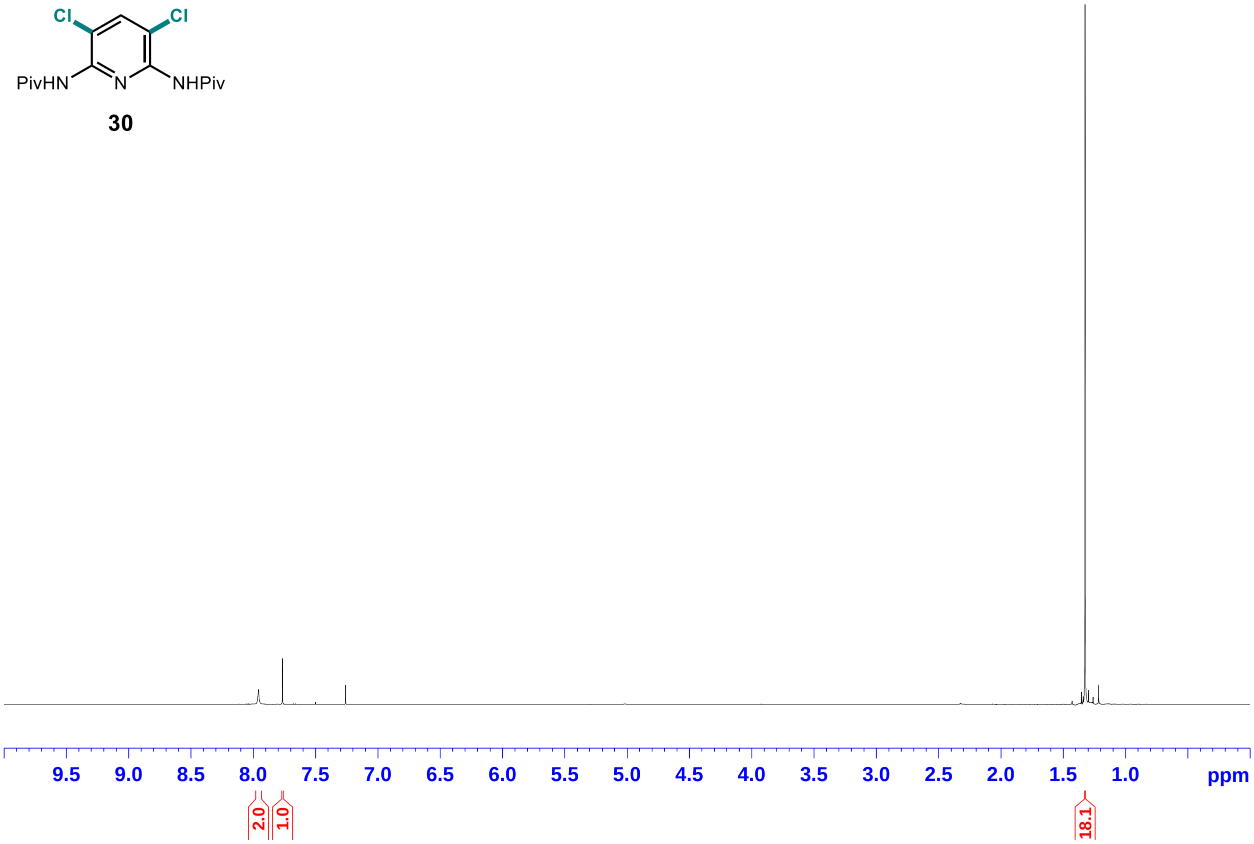


Figure S120: 600 MHz ^{1}H NMR spectrum of **30** in $CDCl_3$

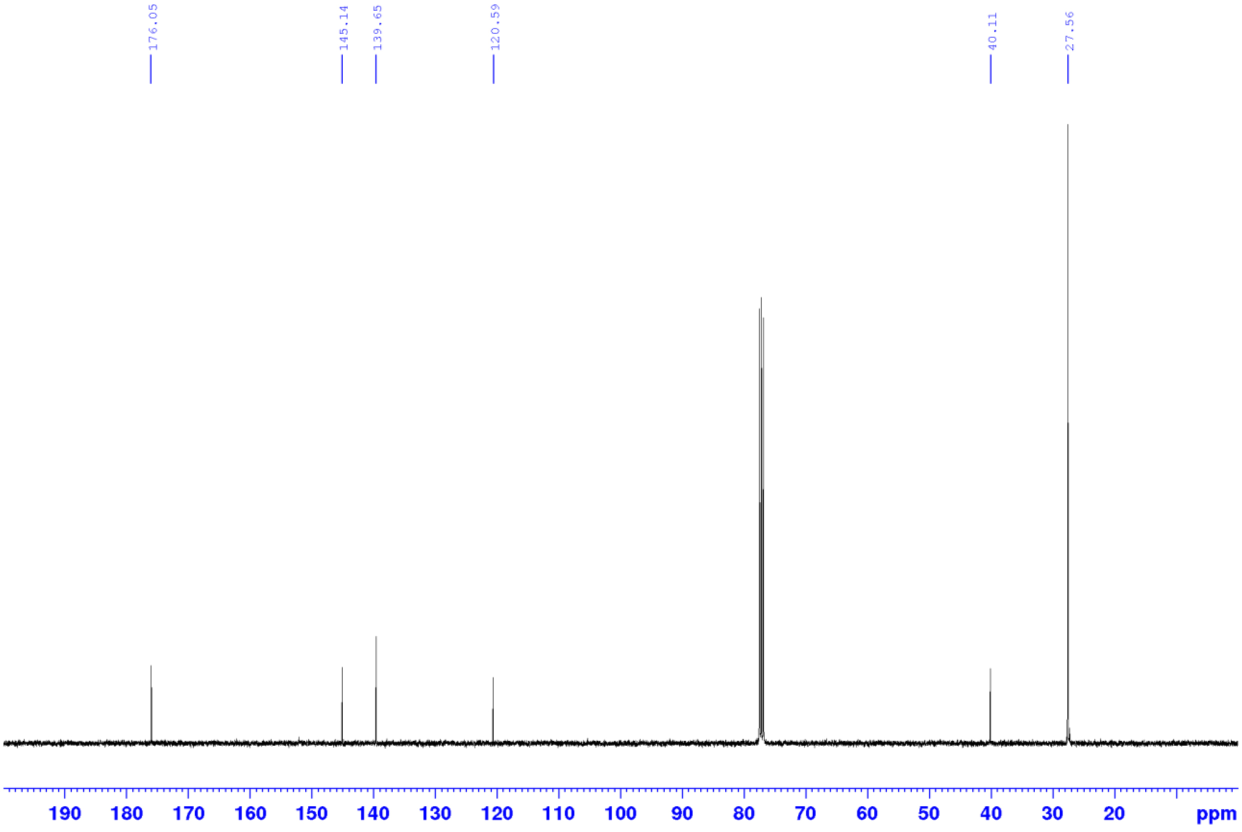
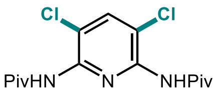


Figure S121: 101 MHz ^{13}C NMR spectrum of **30** in $CDCl_3$



30

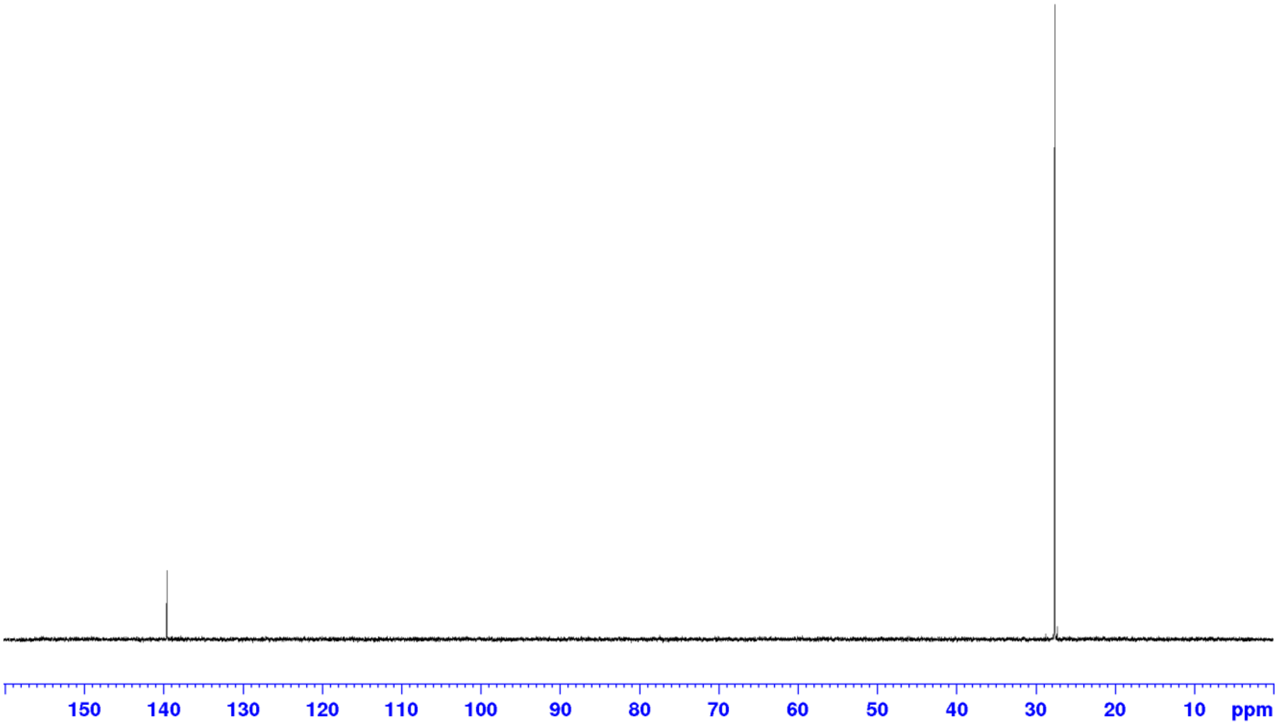
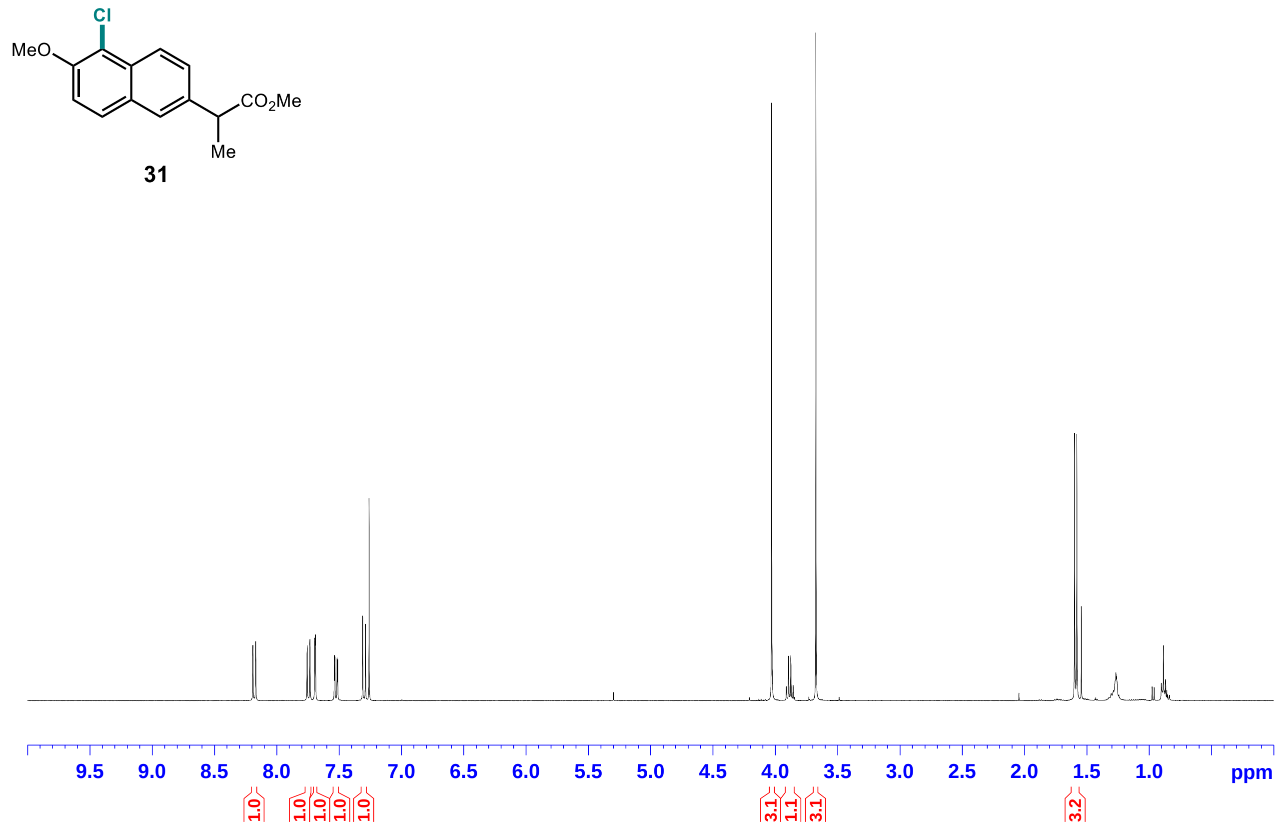


Figure S122: DEPT 135 NMR spectrum of **30** in $CDCl_3$



31

Figure S123: 400 MHz ^{1}H NMR spectrum of **31** in CDCl$_3$

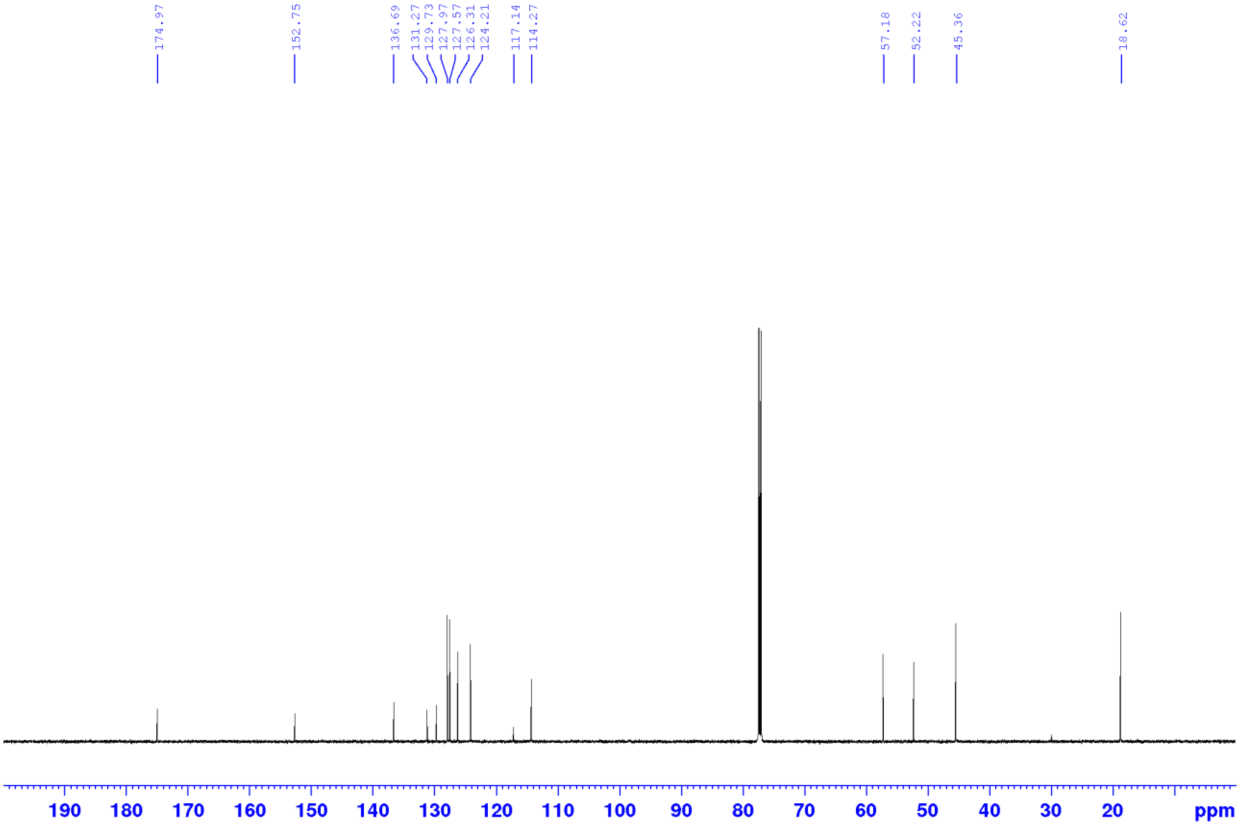
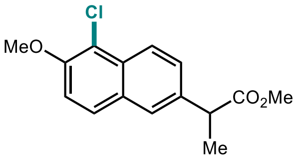


Figure S124: 101 MHz ^{13}C NMR spectrum of **31** in CDCl$_3$



31

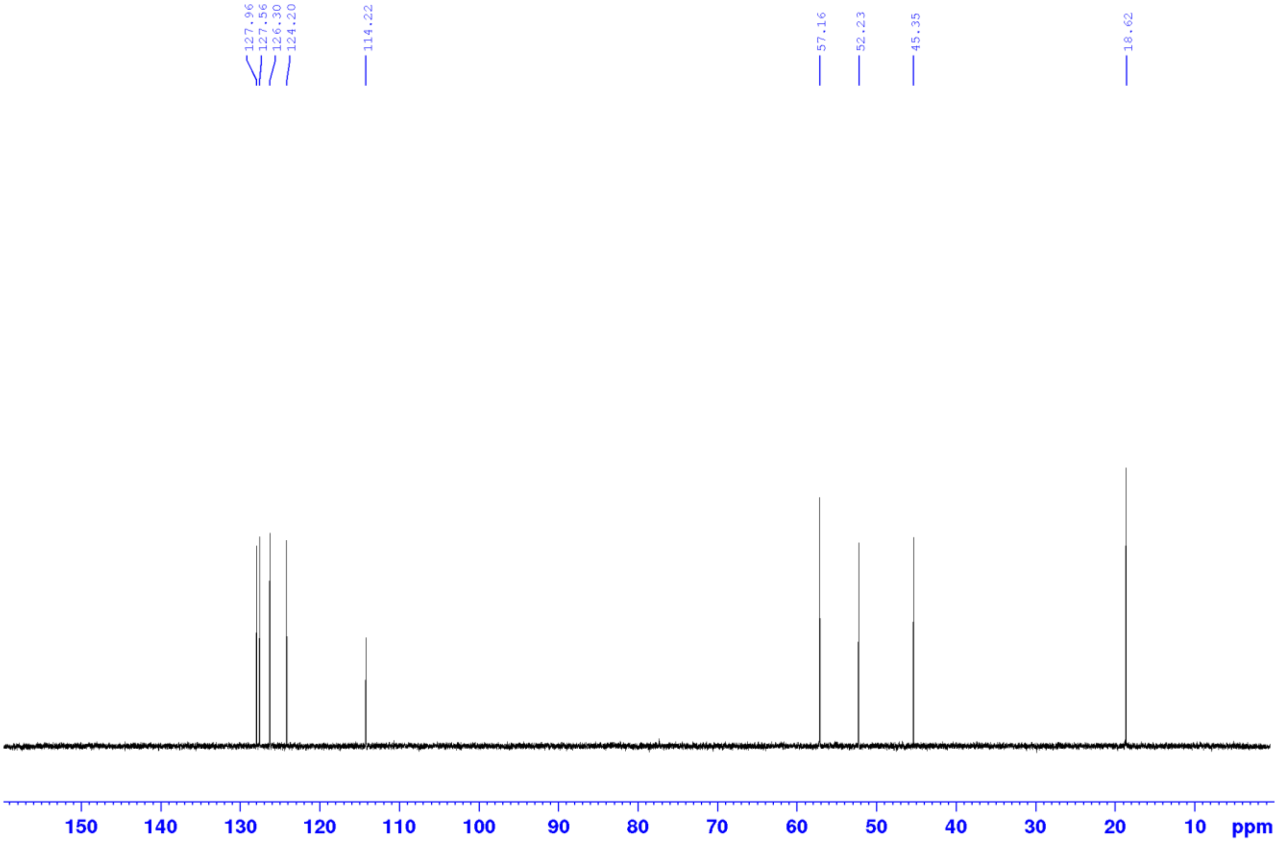


Figure S125: DEPT 135 NMR spectrum of **31** in $CDCl_3$

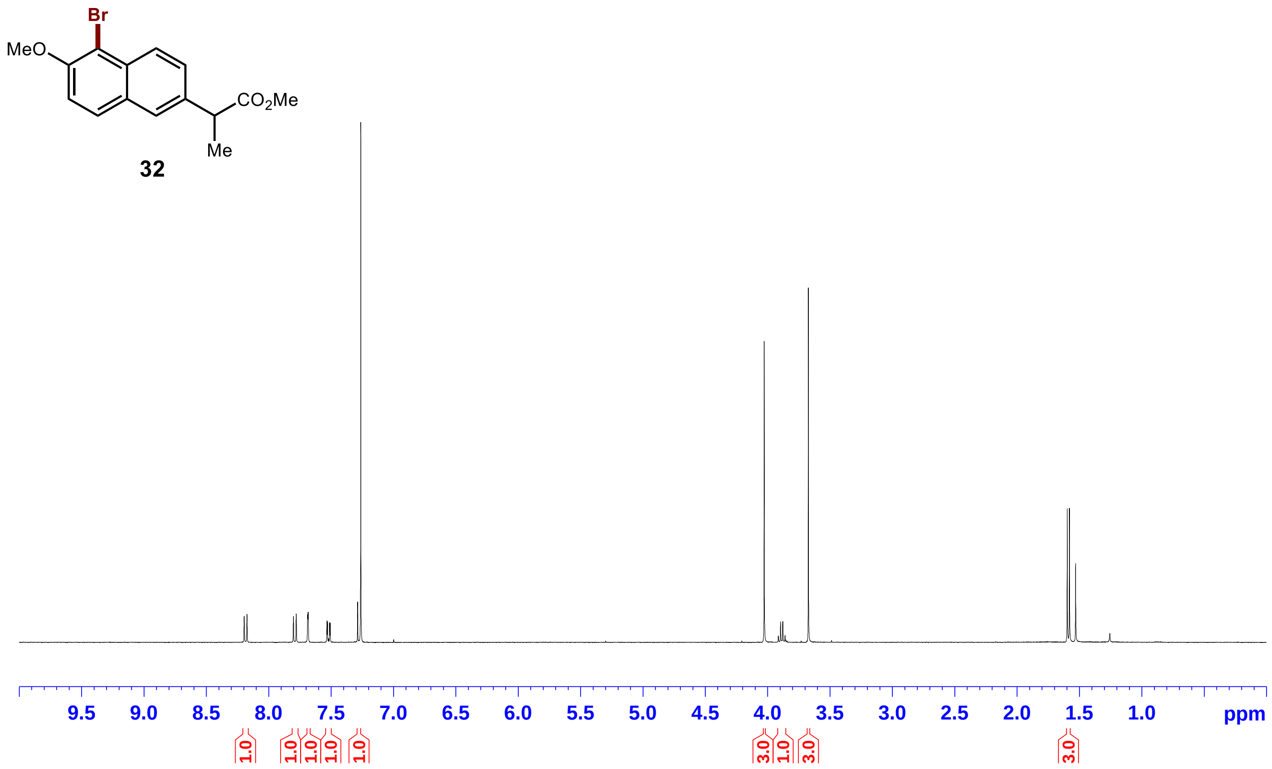


Figure S126: 400 MHz ^{1}H NMR spectrum of **32** in $CDCl_3$

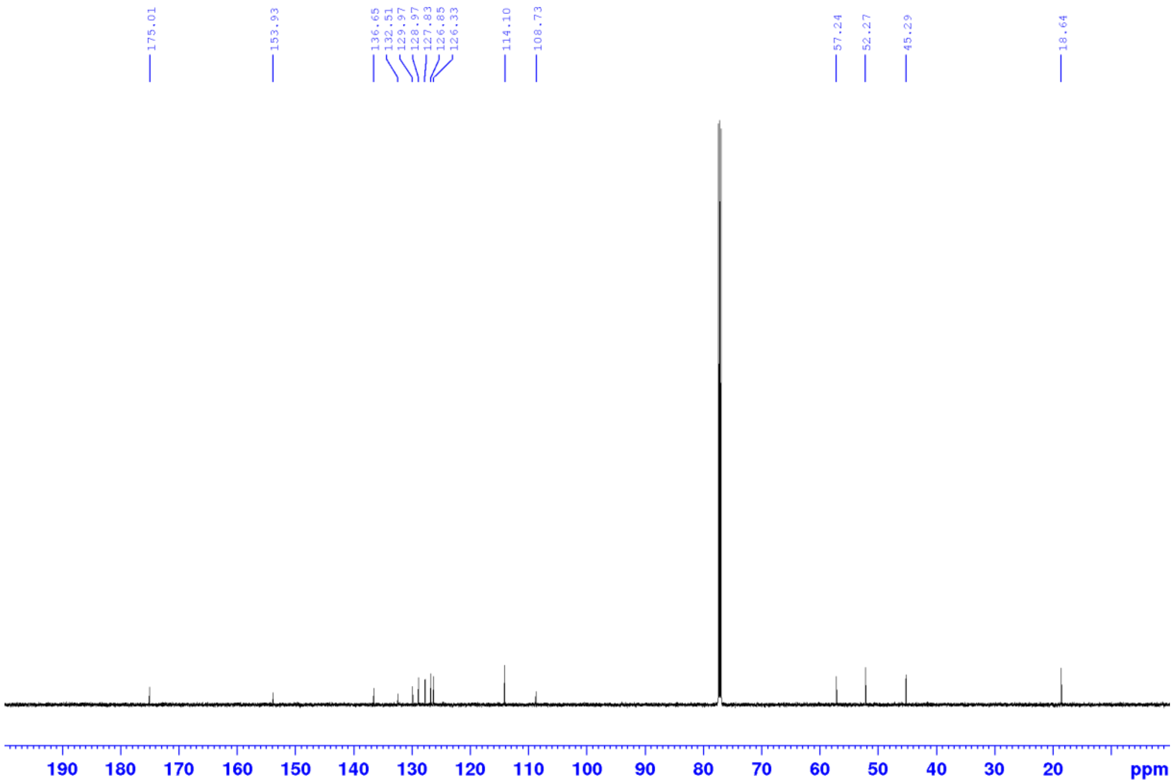
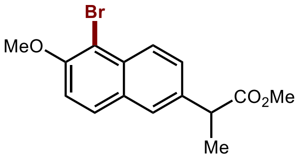


Figure S127: 151 MHz ^{13}C NMR spectrum of **32** in $CDCl_3$



32

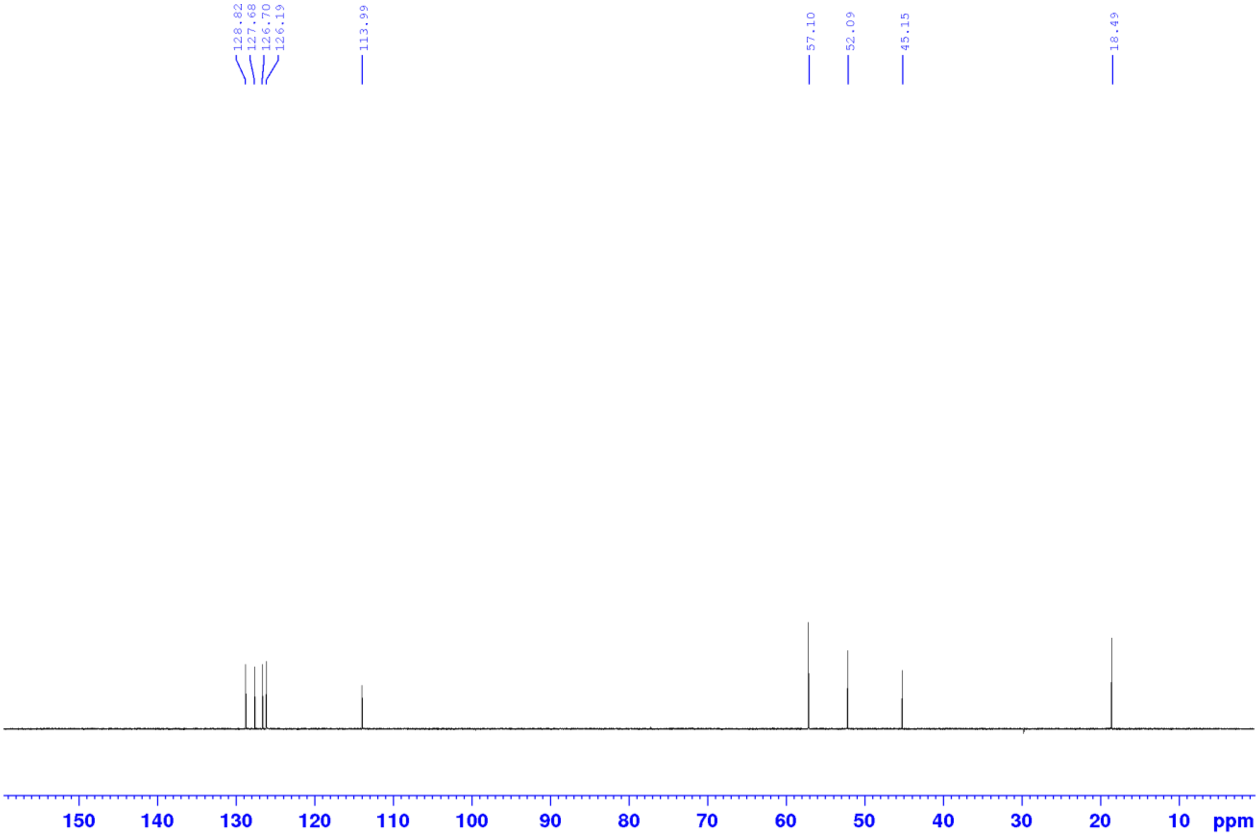


Figure S128: DEPT 135 NMR spectrum of **32** in $CDCl_3$

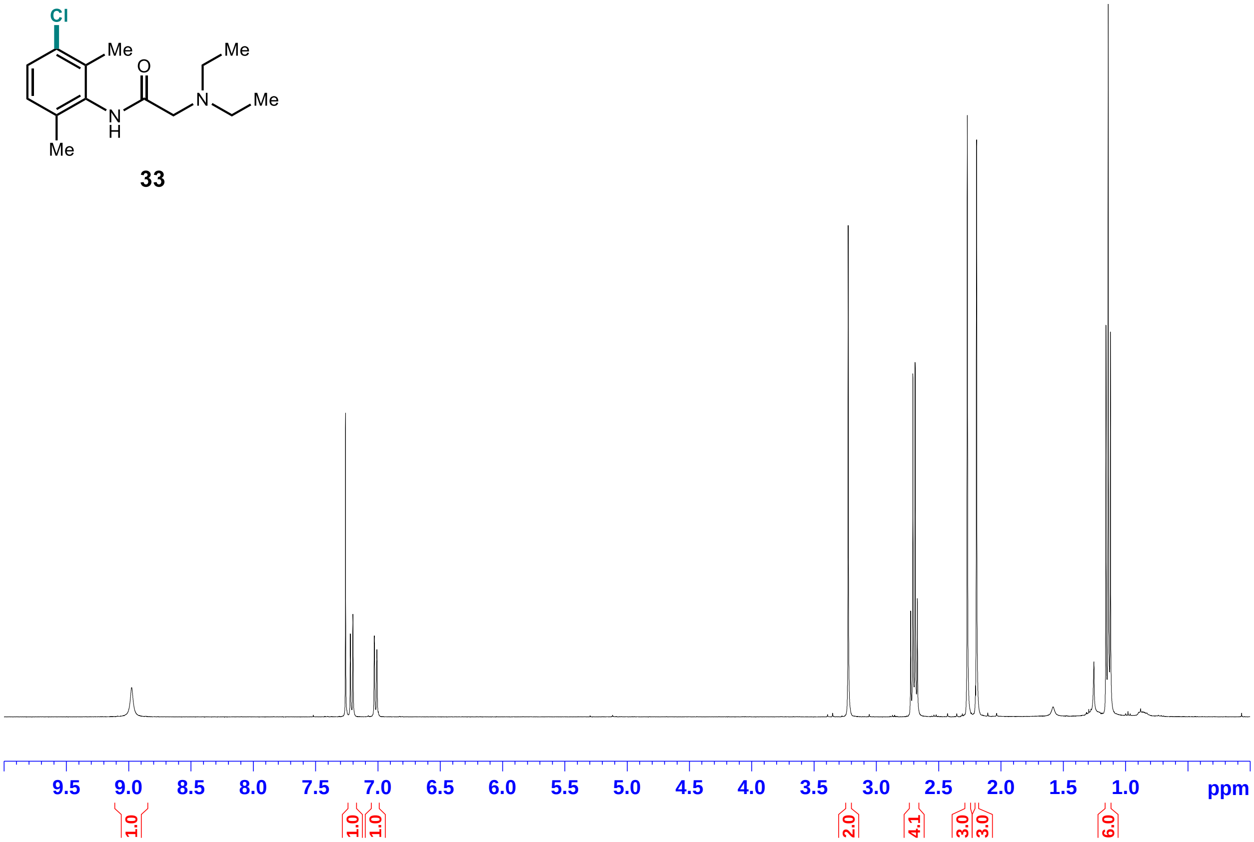


Figure S129: 400 MHz ^{1}H NMR spectrum of **33** in $CDCl_3$

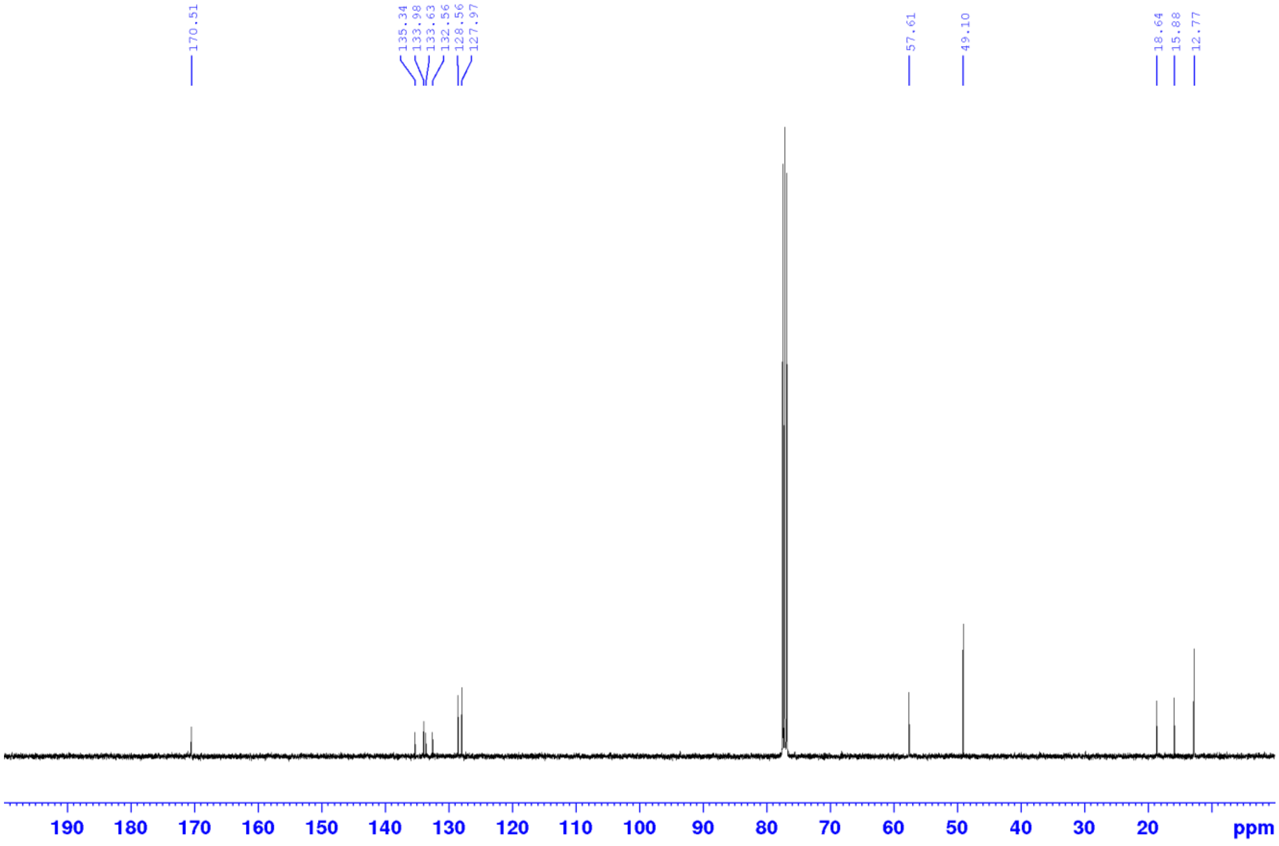
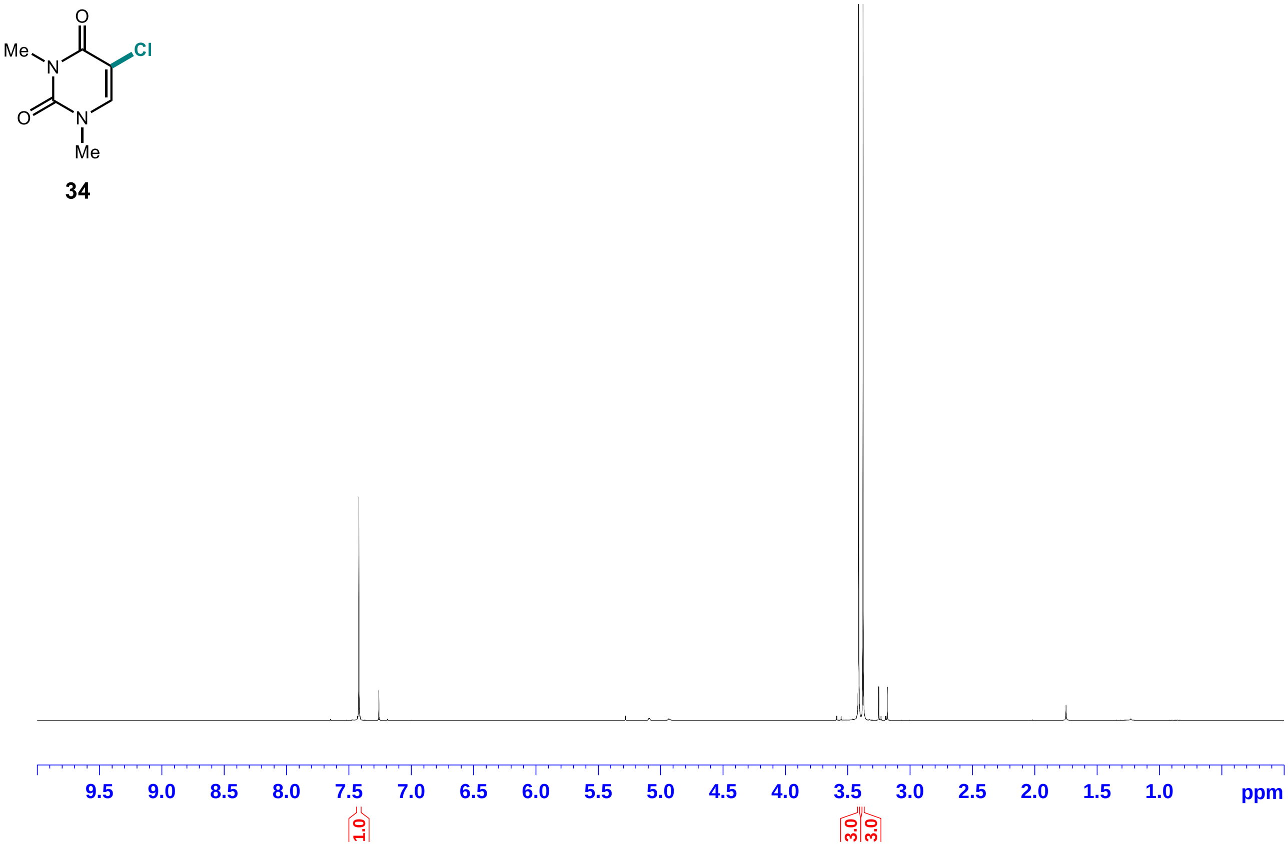


Figure S130: 101 MHz ^{13}C NMR spectrum of **33** in $CDCl_3$



34

Figure S131: 400 MHz ^{1}H NMR spectrum of **34** in $CDCl_3$

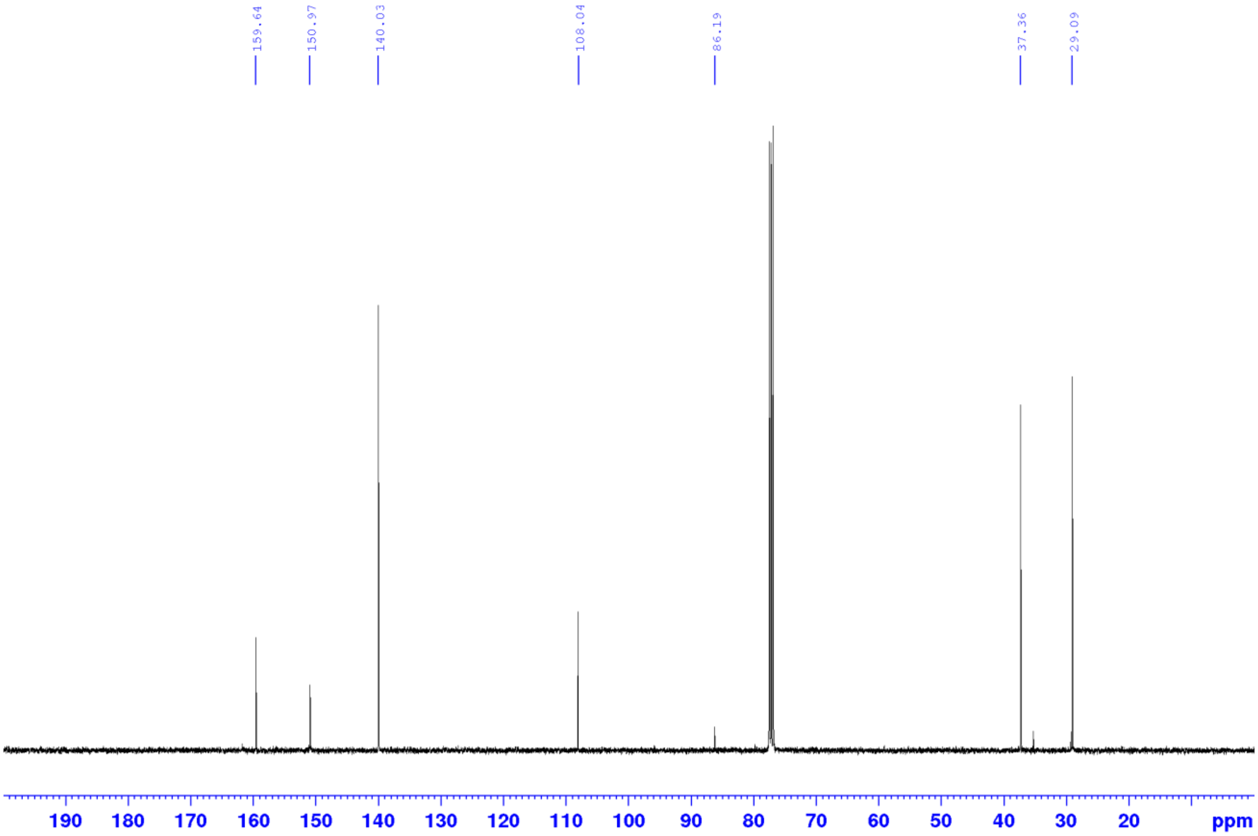


Figure S132: 101 MHz ^{13}C NMR spectrum of **34** in $CDCl_3$

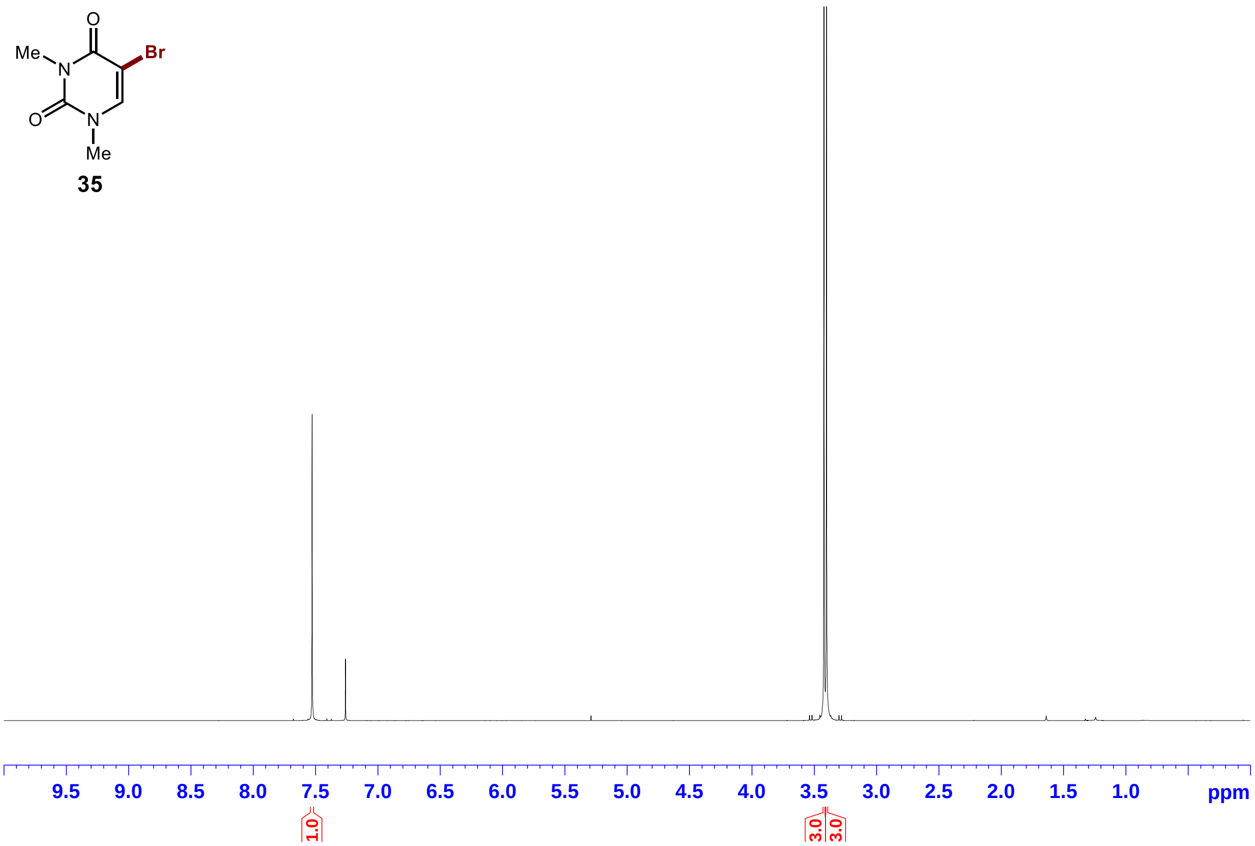


Figure S133: 600 MHz ^{1}H NMR spectrum of **35** in $CDCl_3$

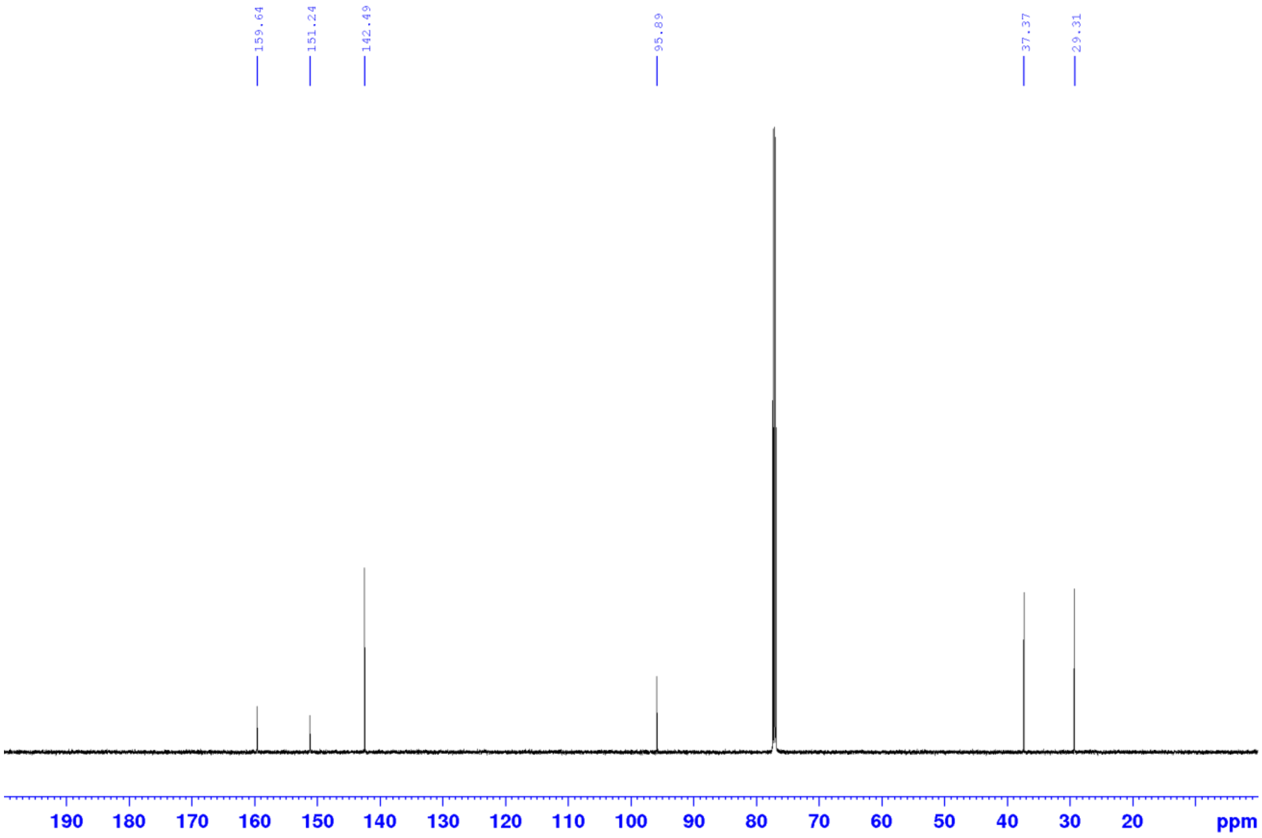


Figure S134: 151 MHz ^{13}C NMR spectrum of **35** in $CDCl_3$

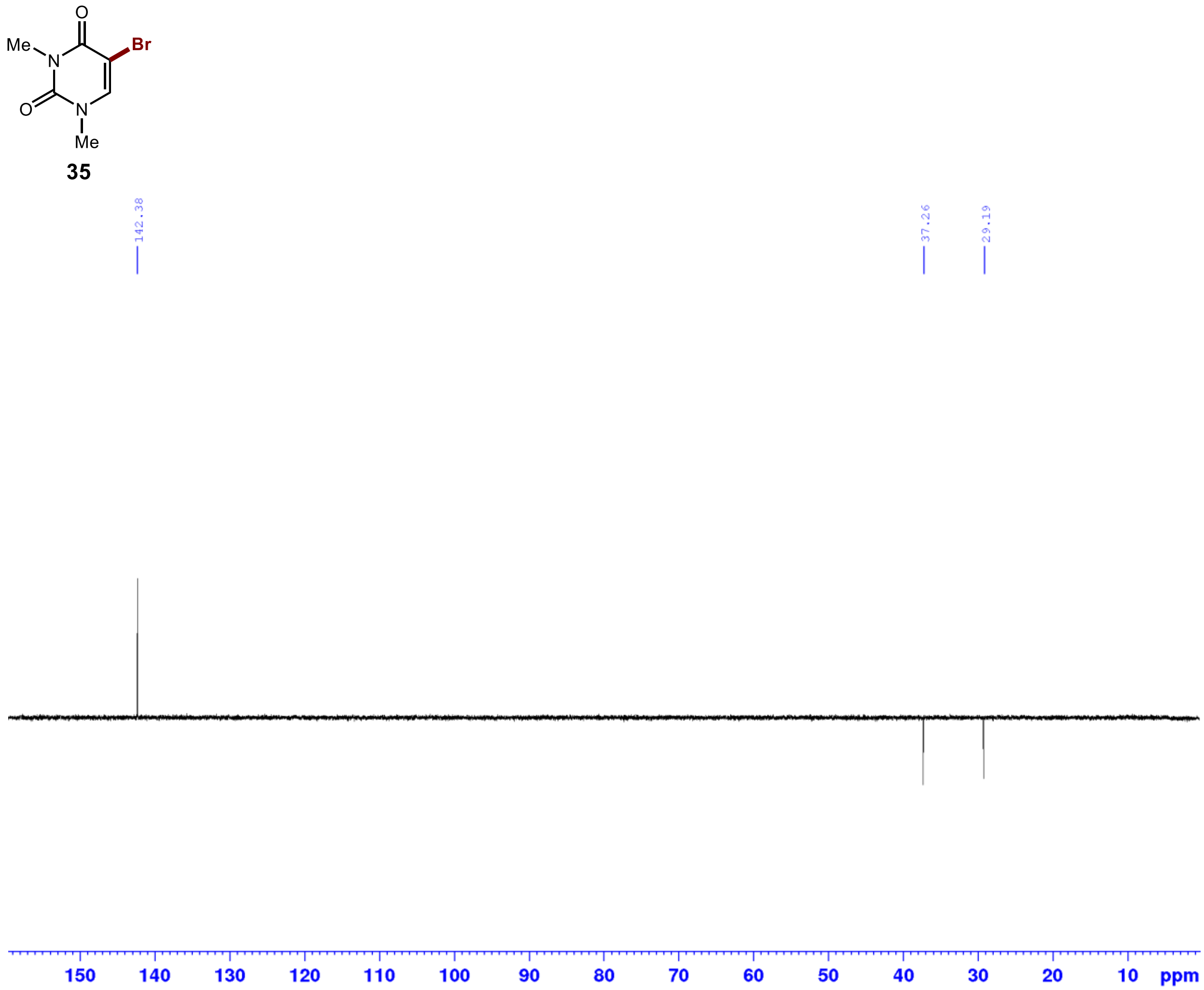


Figure S135: DEPT135 NMR spectrum of **35** in $CDCl_3$

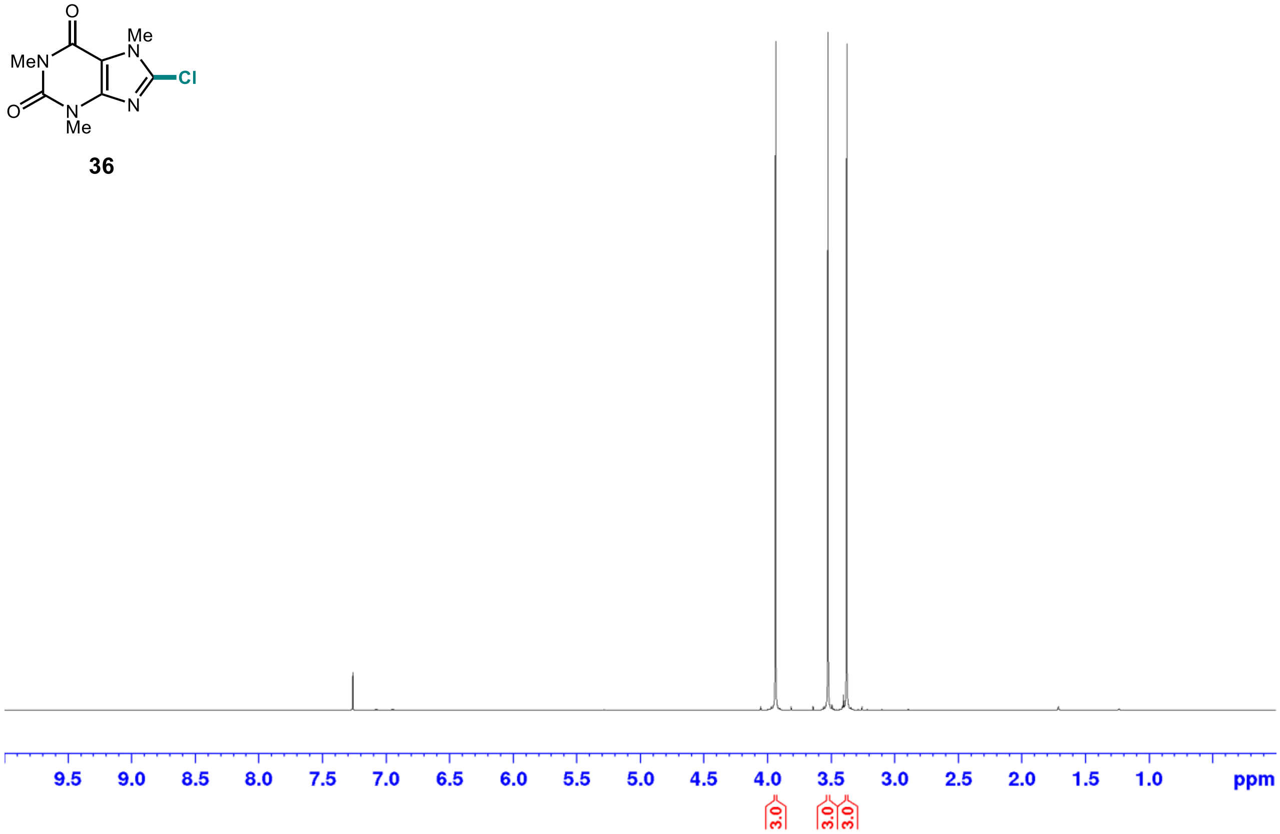


Figure S136: 400 MHz ^{1}H NMR spectrum of **36** in CDCl$_3$

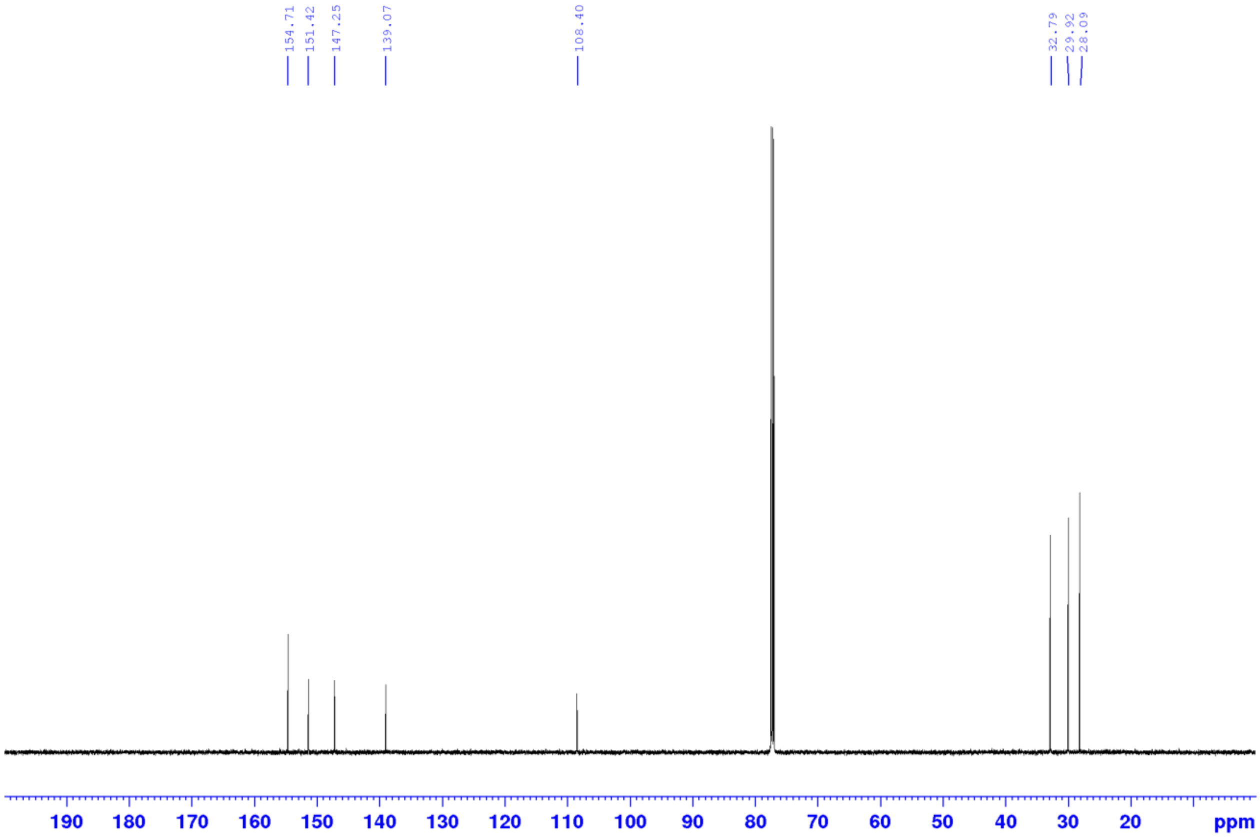


Figure S137: 101 MHz ^{1}H NMR spectrum of **36** in CDCl$_3$

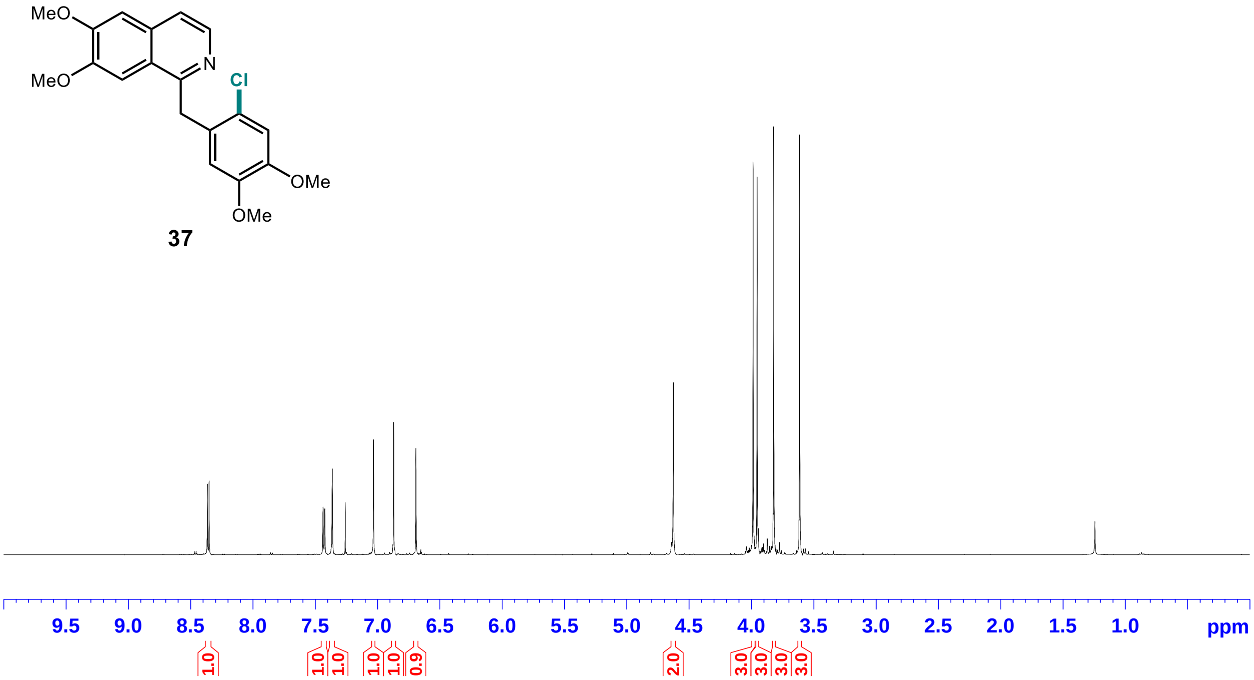


Figure S138: 400 MHz ^{1}H NMR spectrum of **37** in CDCl$_3$

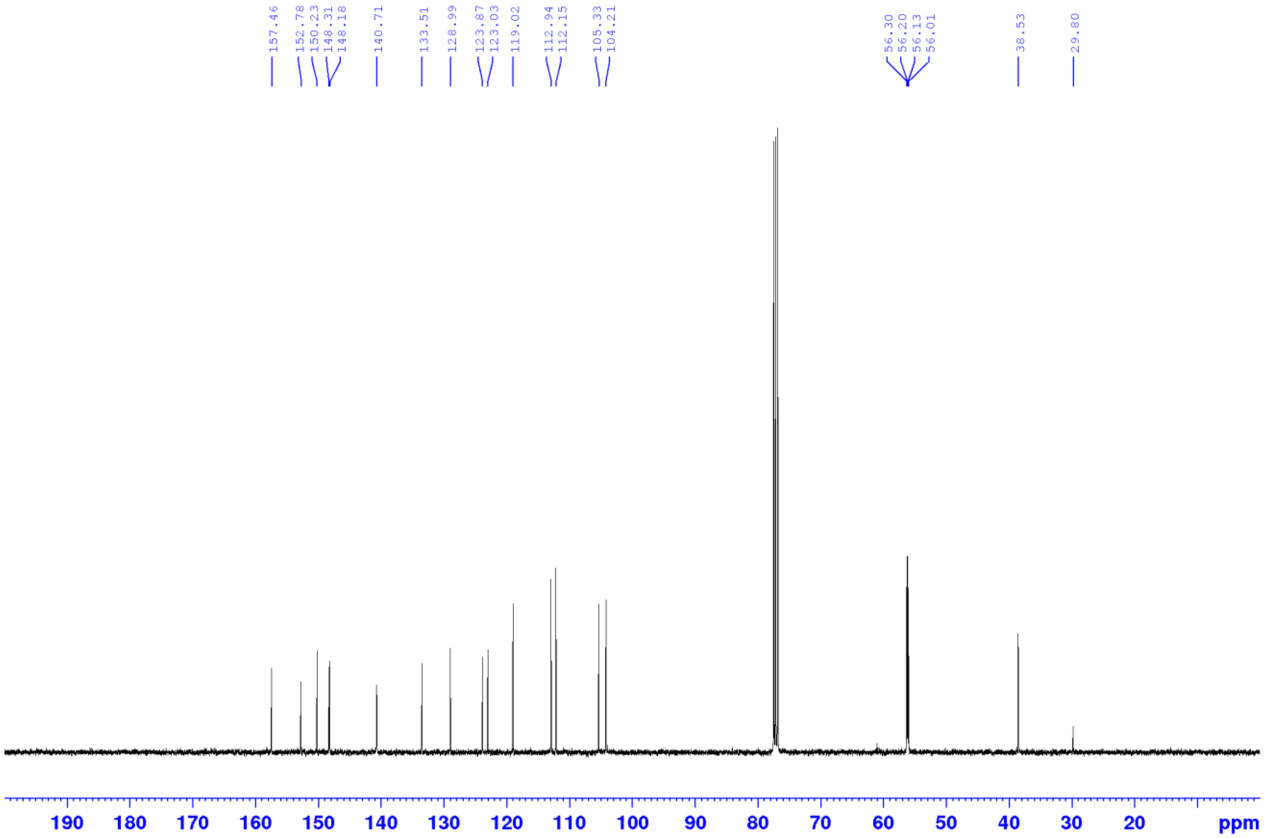


Figure S139: 101 MHz ^{13}C NMR spectrum of **37** in CDCl$_3$

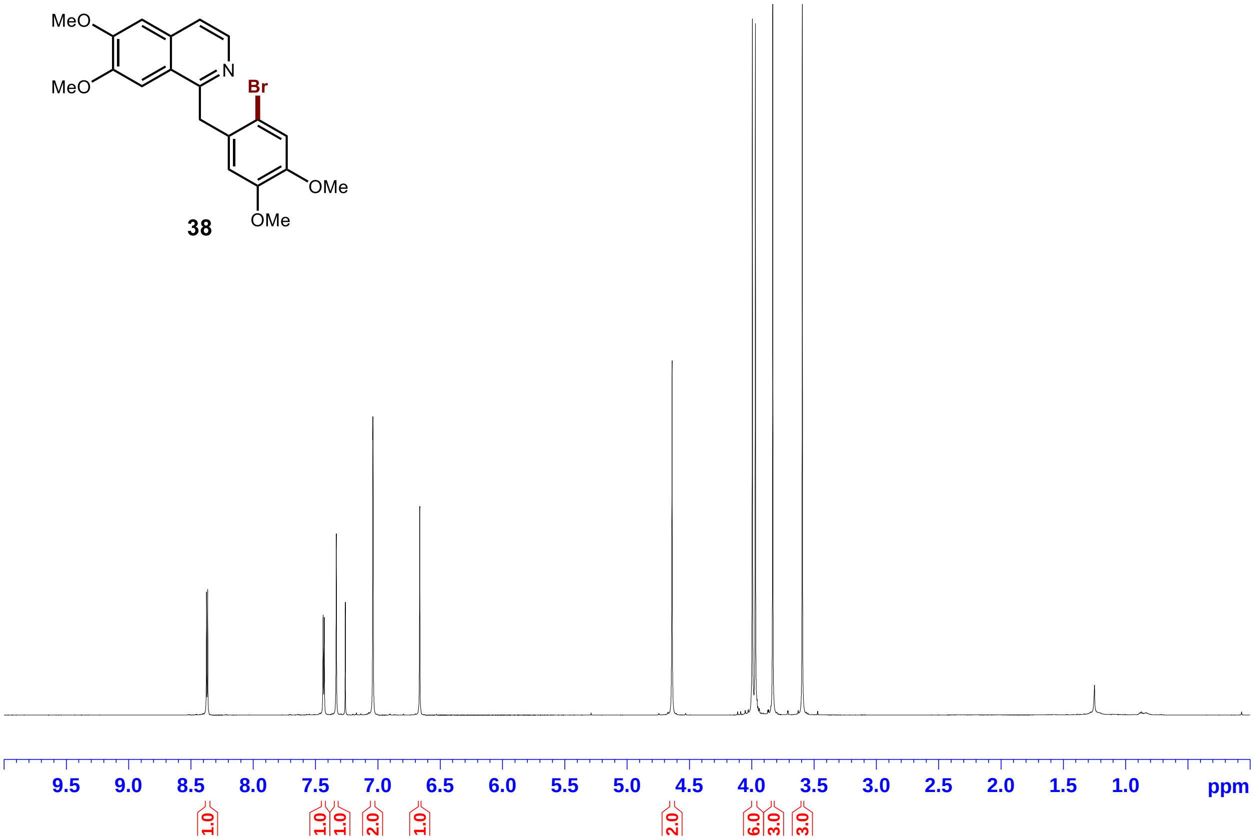


Figure S140: 400 MHz ^{1}H NMR spectrum of **38** in CDCl$_3$

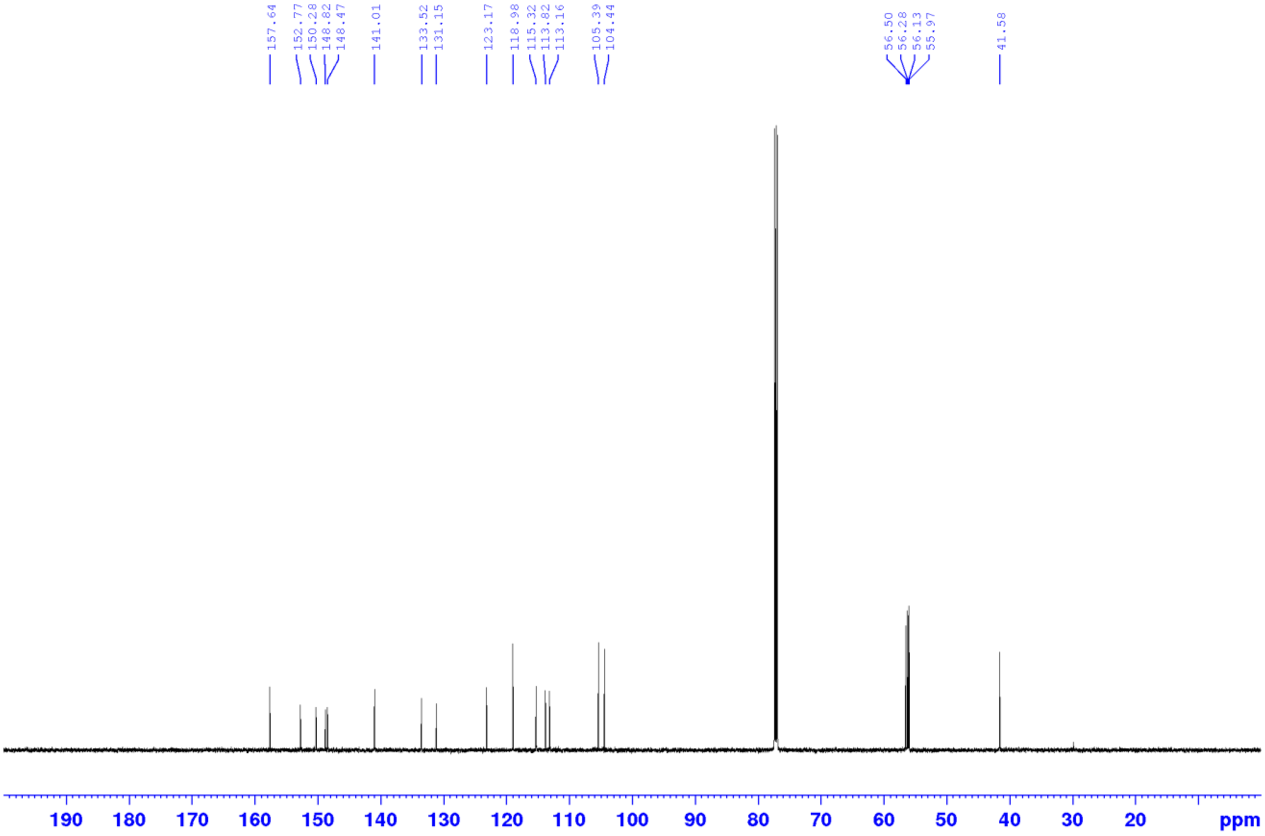
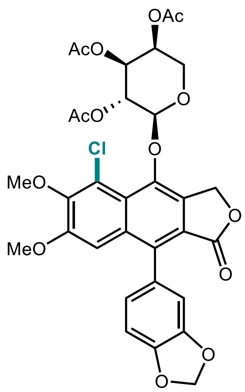


Figure S141: 101 MHz ^{13}C NMR spectrum of **38** in CDCl$_3$



39

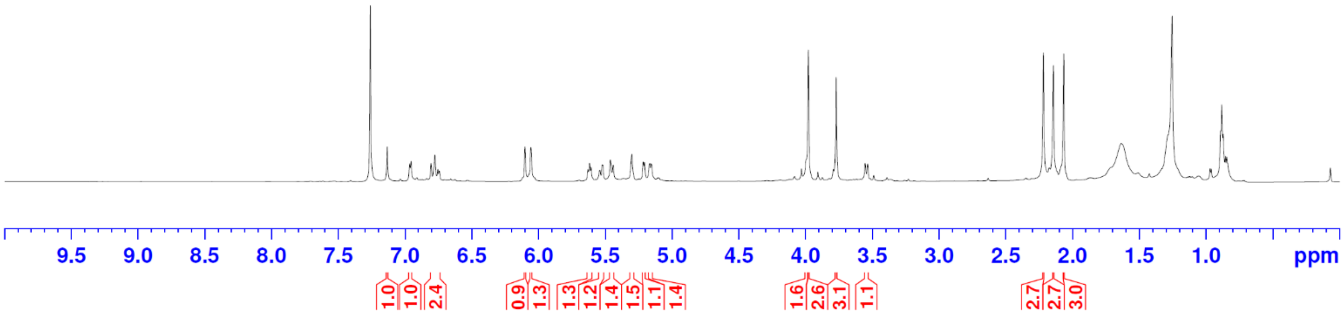


Figure S142: 700 MHz ^{1}H NMR spectrum of **39** in CDCl$_3$

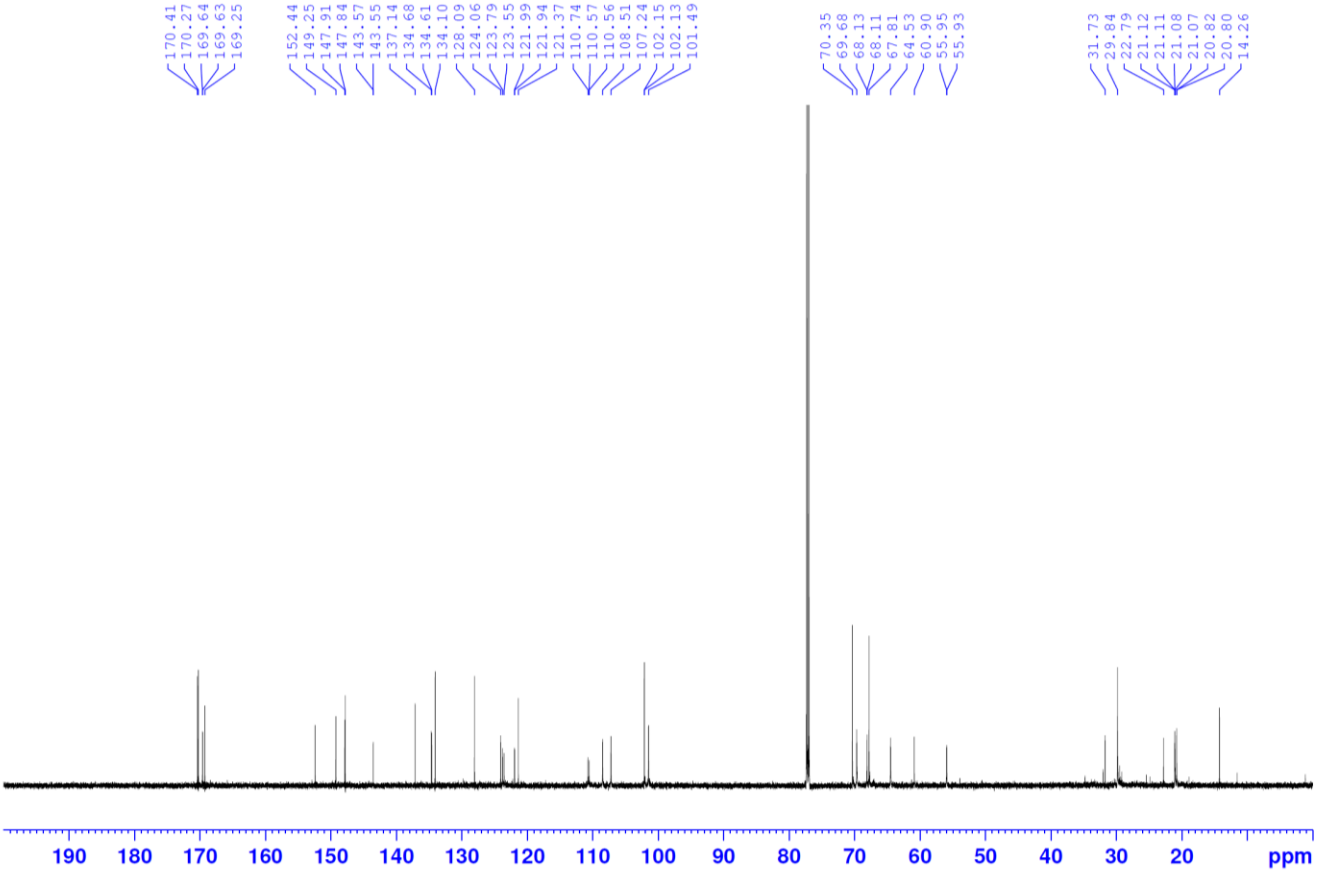


Figure S143: 176 MHz ^{13}C NMR spectrum of **39** in CDCl$_3$

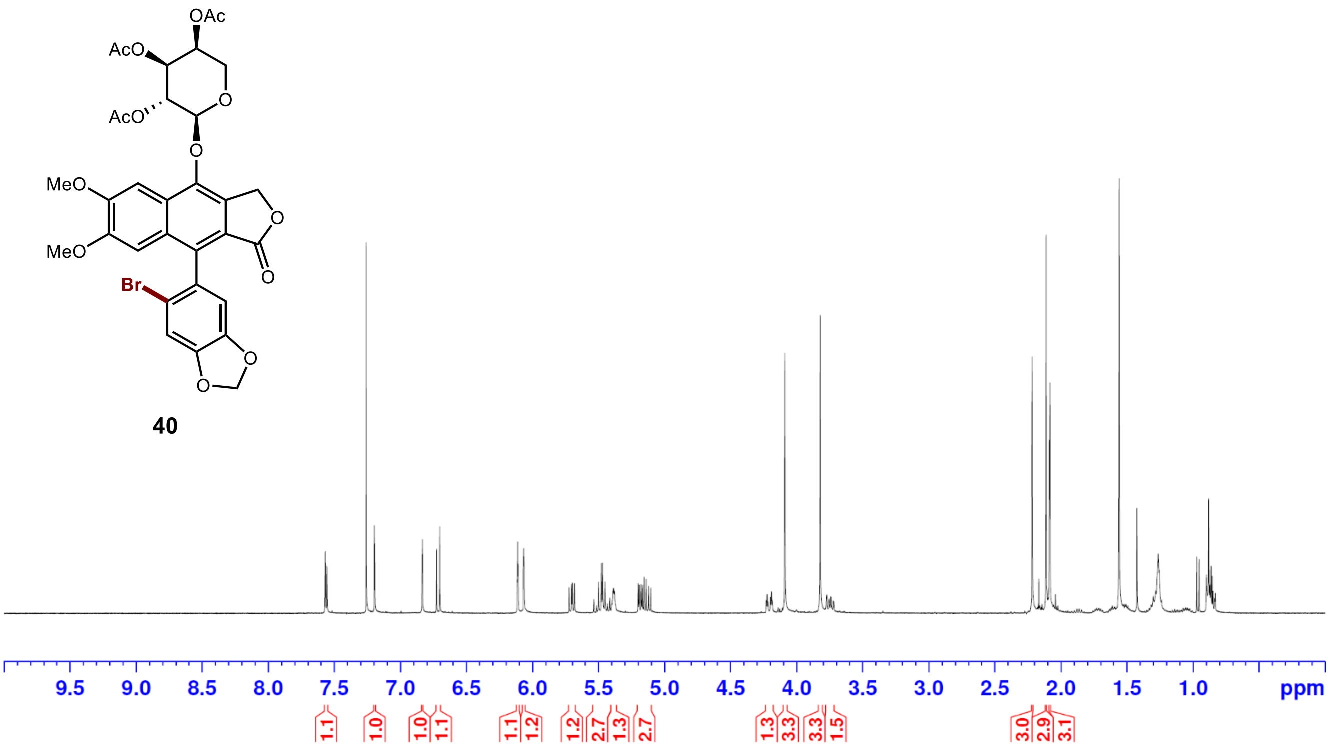


Figure S144: 400 MHz ^{1}H NMR spectrum of **40** in $CDCl_3$

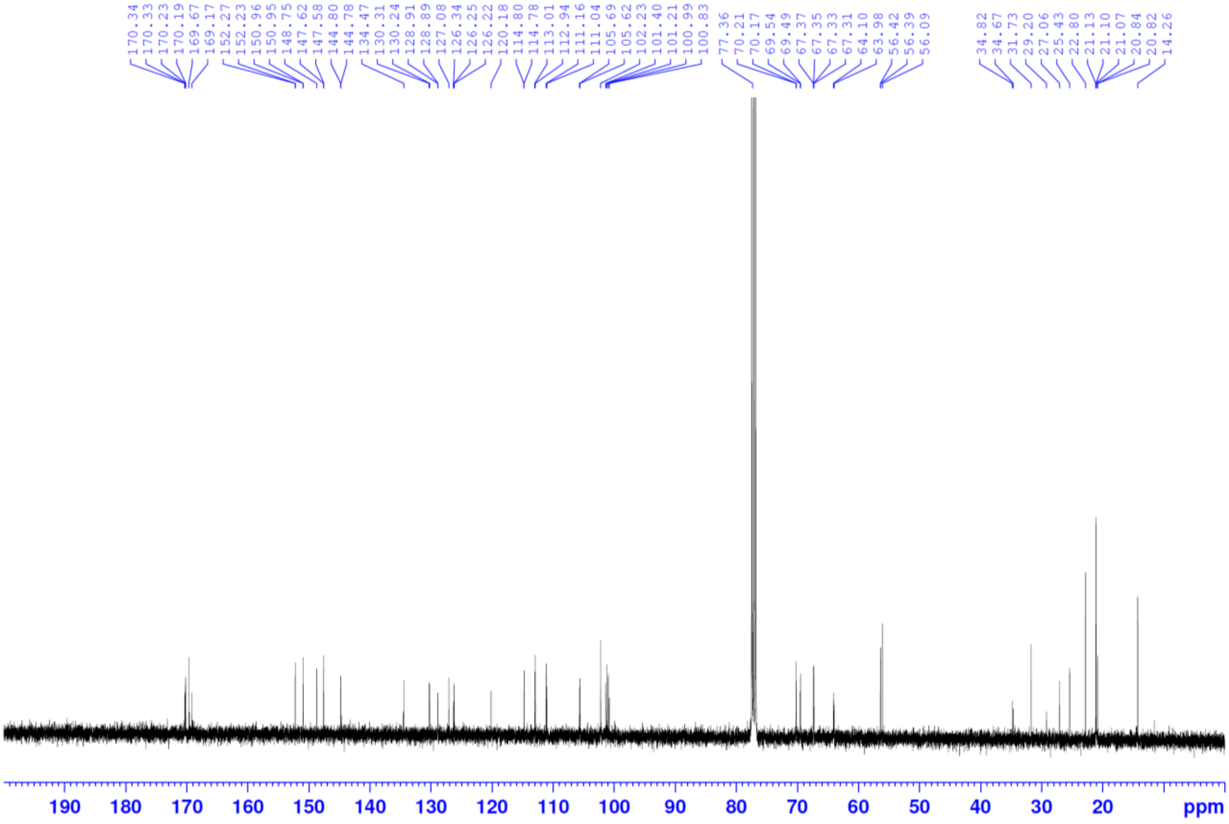
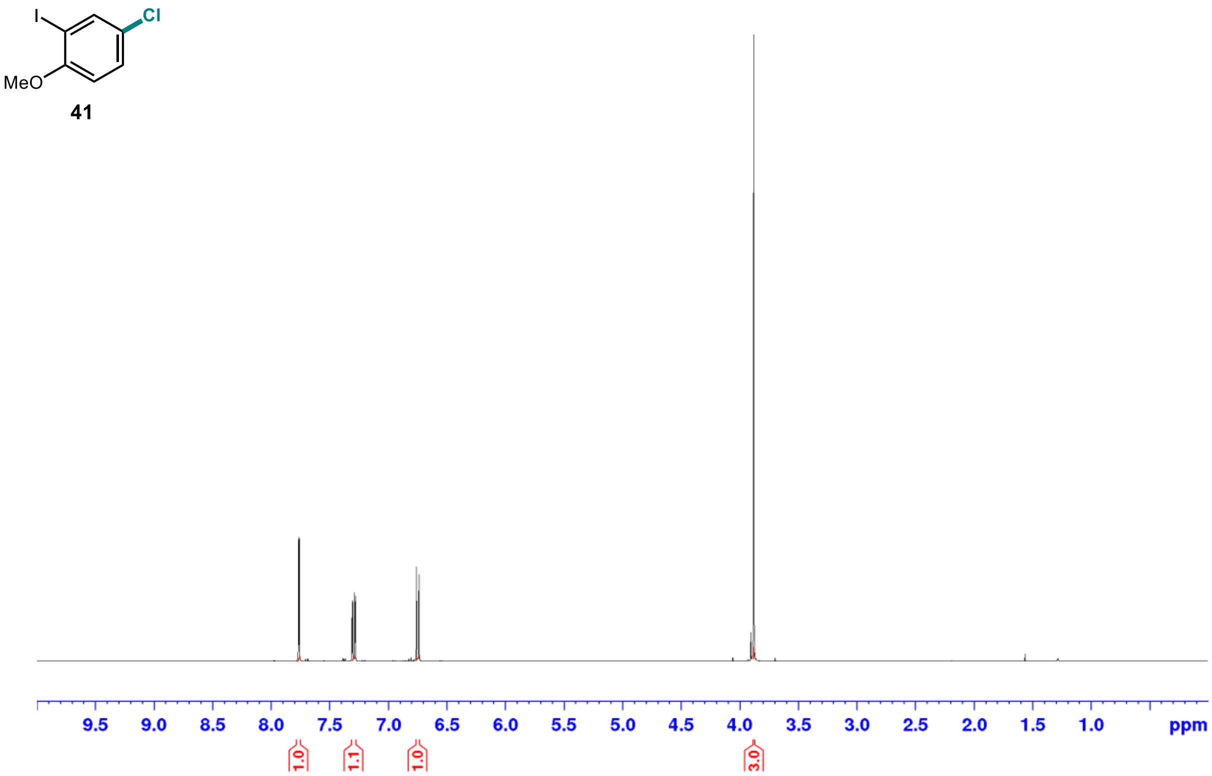


Figure S145: 101 MHz ^{13}C NMR spectrum of **40** in $CDCl_3$



41

Figure S146: 400 MHz ^{1}H NMR spectrum of **41** in $CDCl_3$

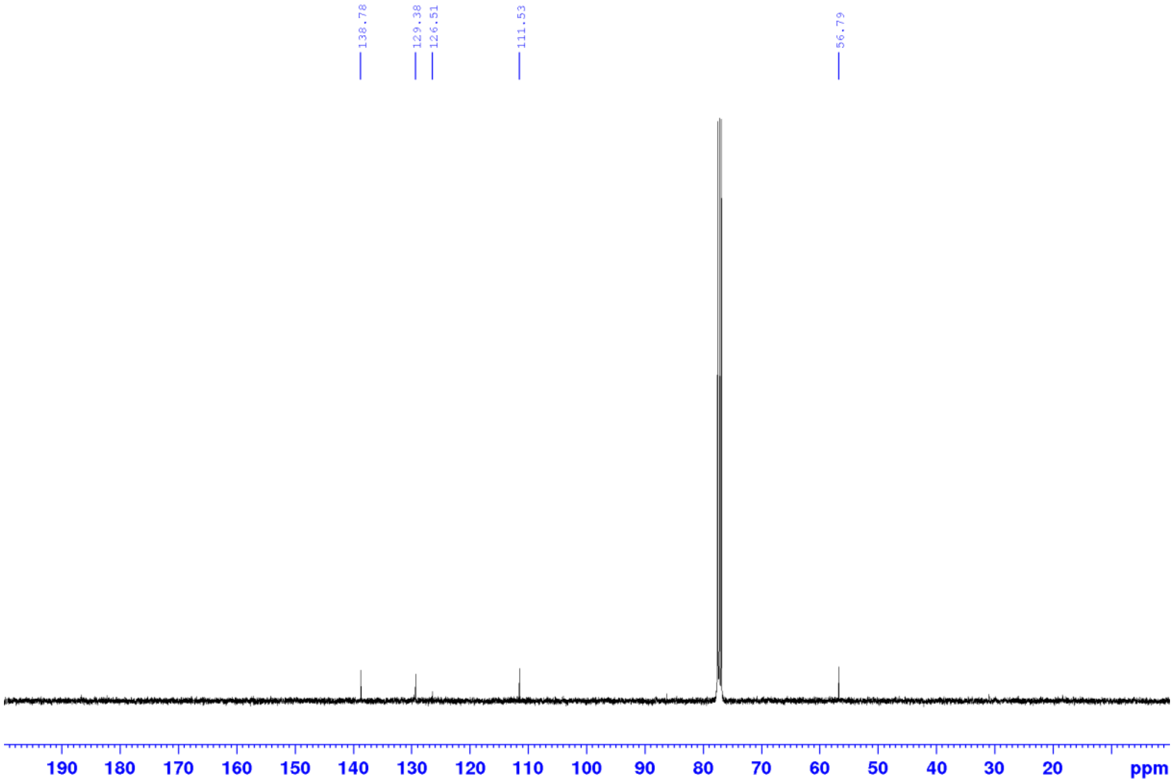
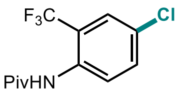


Figure S147: 101 MHz ^{13}C NMR spectrum of **41** in $CDCl_3$



S20

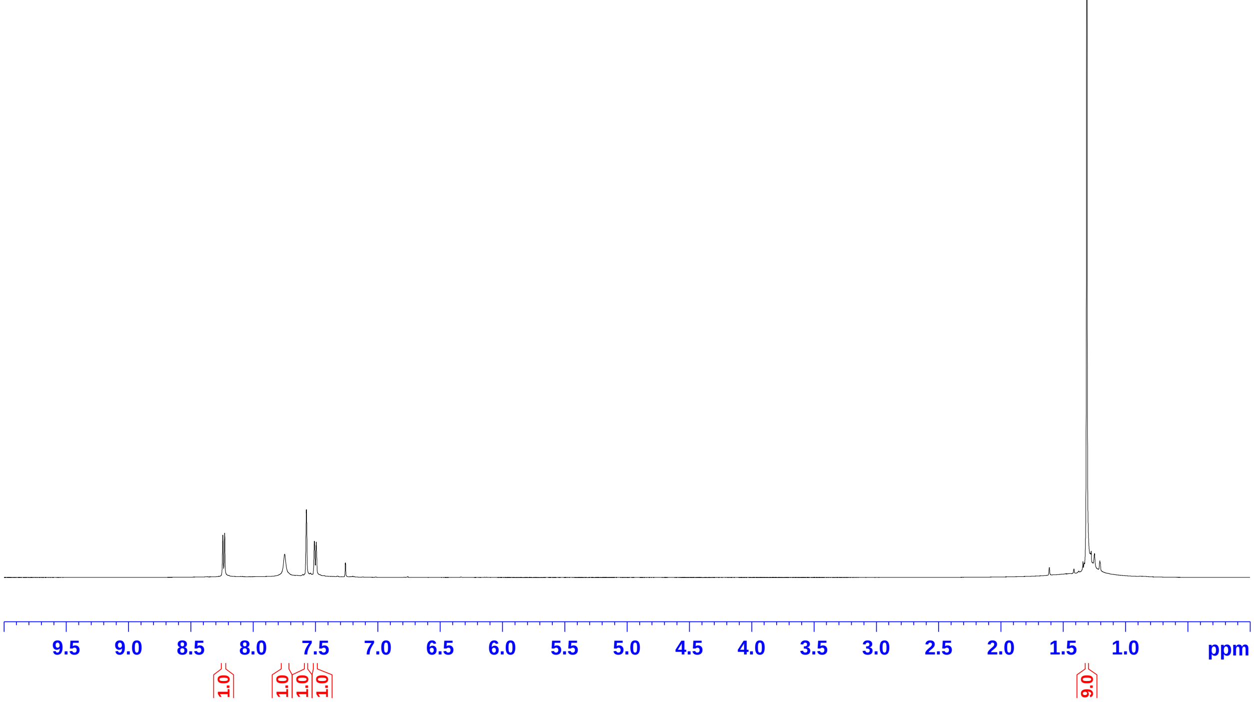


Figure S148: 600 MHz ^{1}H NMR spectrum of **S20** in CDCl$_3$

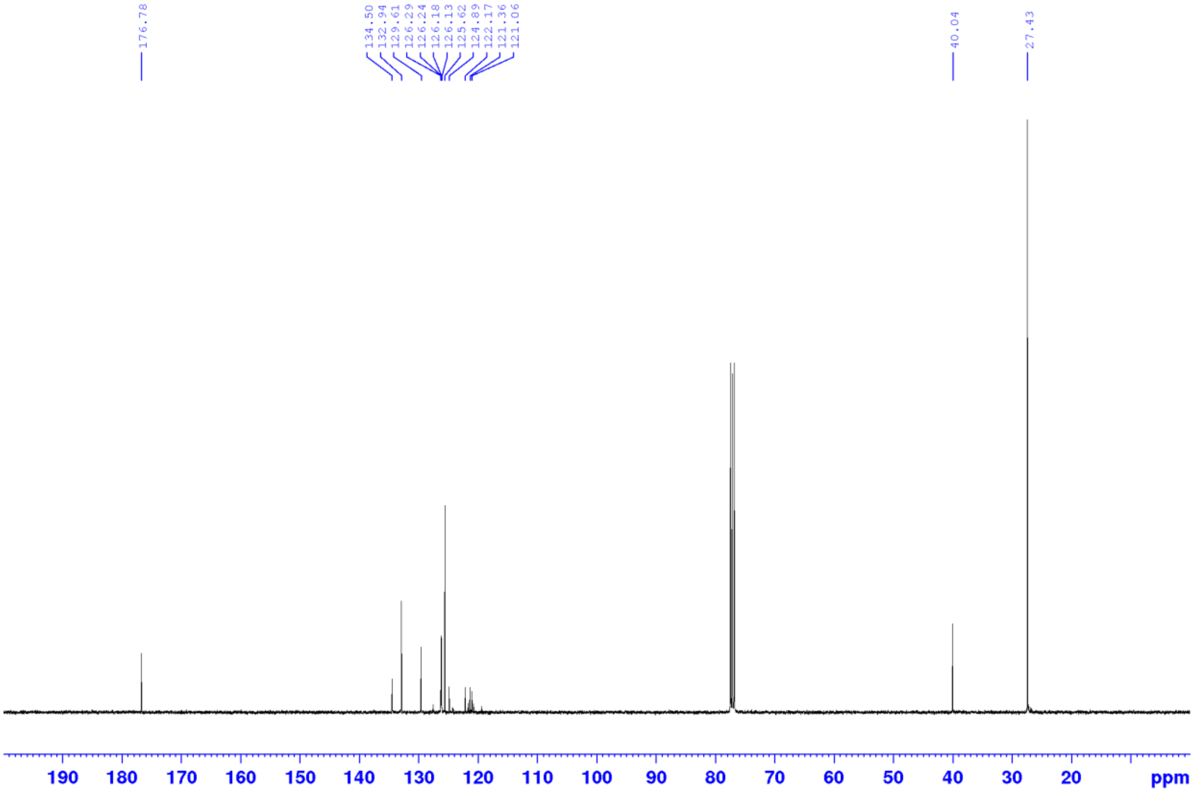


Figure S149: 151 MHz ^{13}C NMR spectrum of **S20** in CDCl$_3$

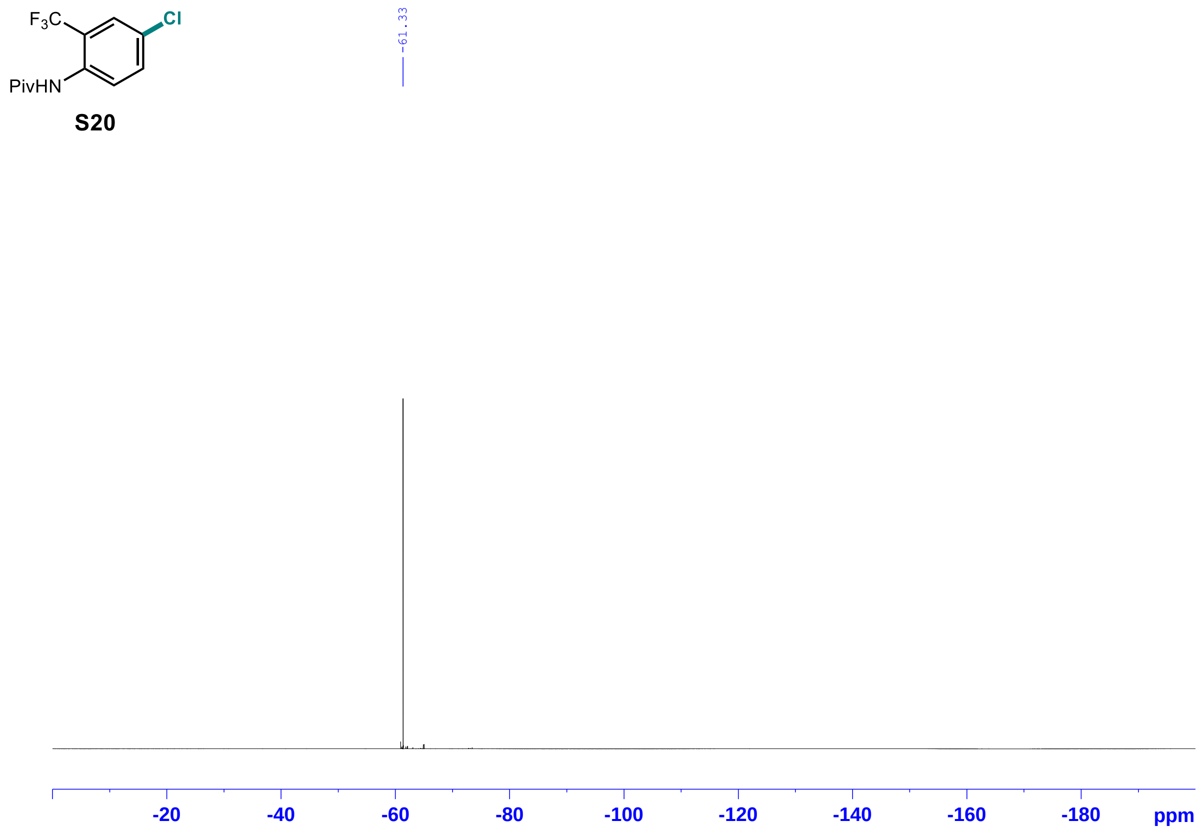


Figure S150: 377 MHz ^{19}F NMR spectrum of **S20** in $CDCl_3$

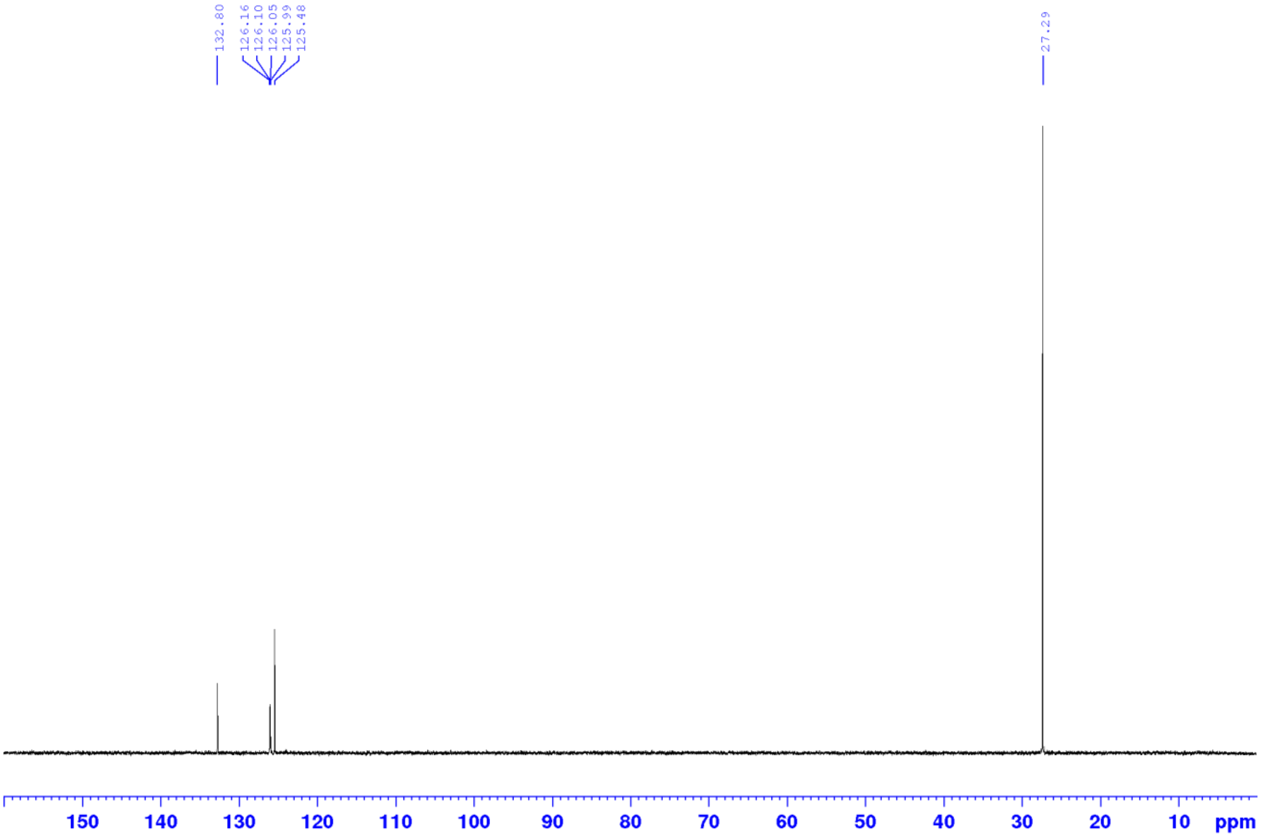
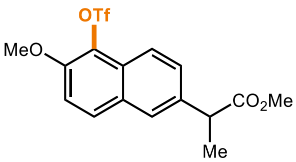


Figure S151: DEPT 135 NMR spectrum of **S20** in $CDCl_3$



S21

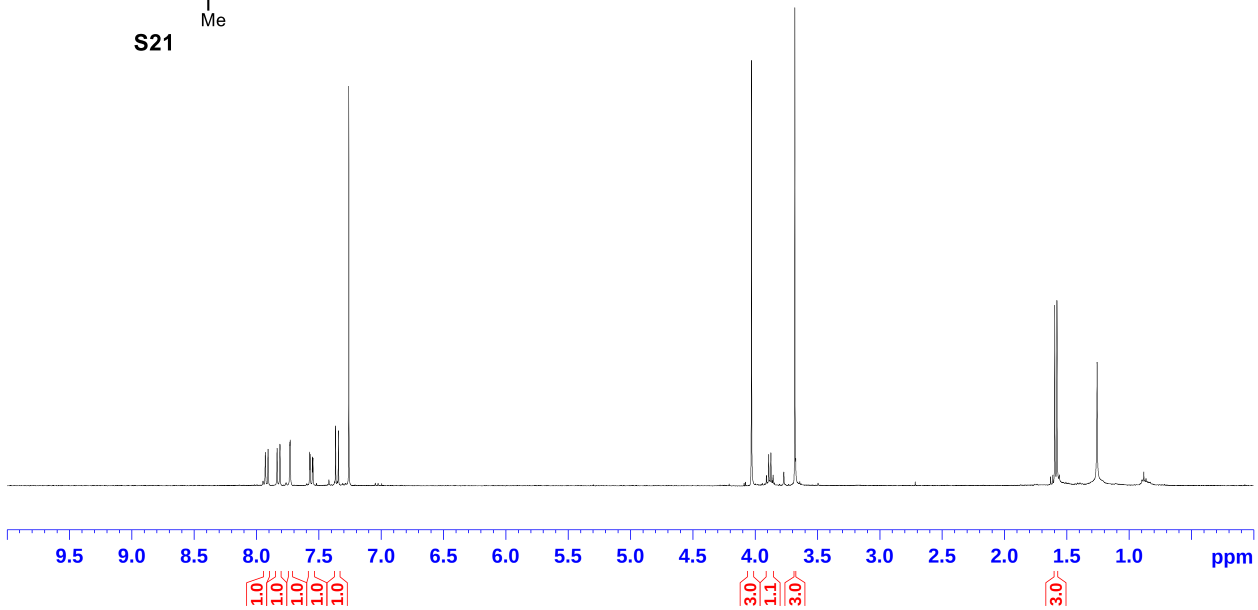


Figure S152: 400 MHz ^{1}H NMR spectrum of **S21** in CDCl$_3$

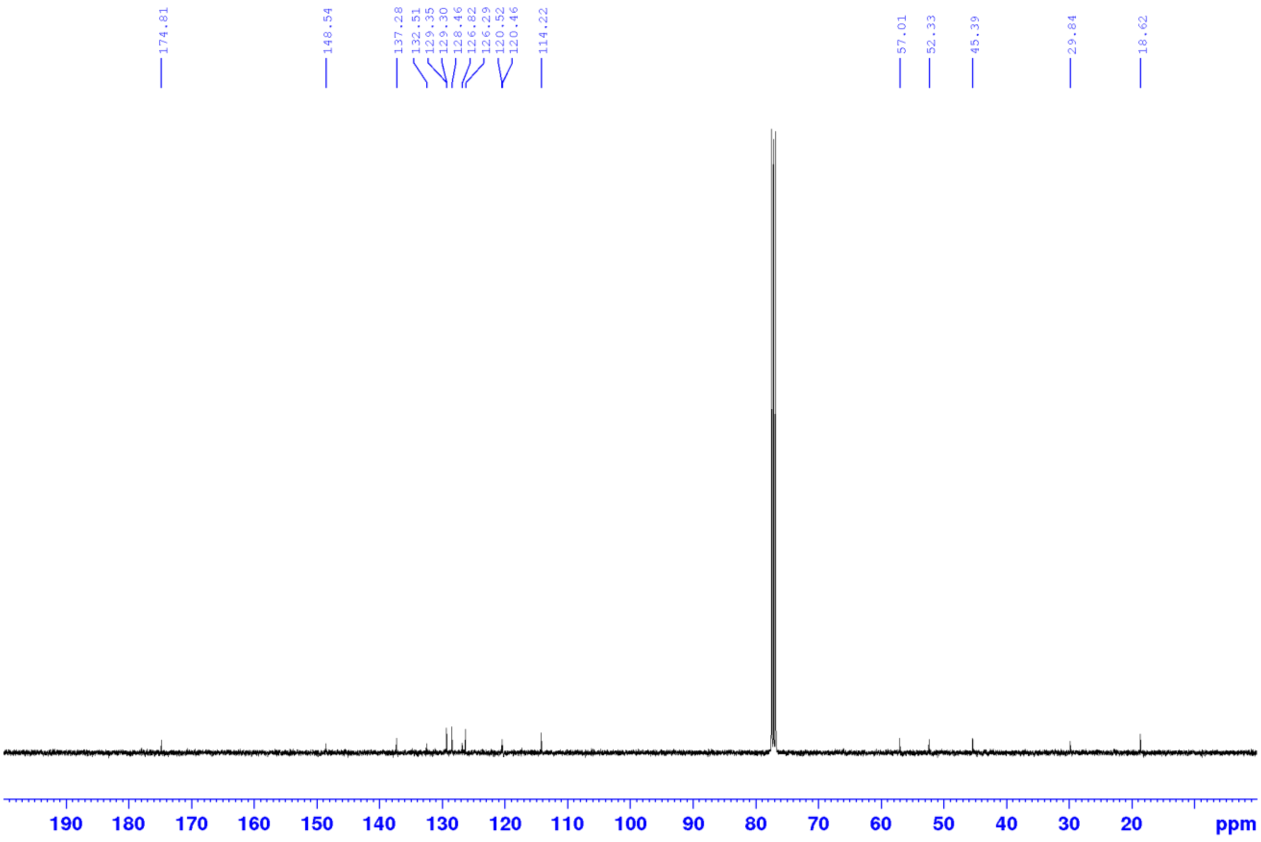


Figure S153: 101 MHz ^{13}C NMR spectrum of **S21** in CDCl$_3$

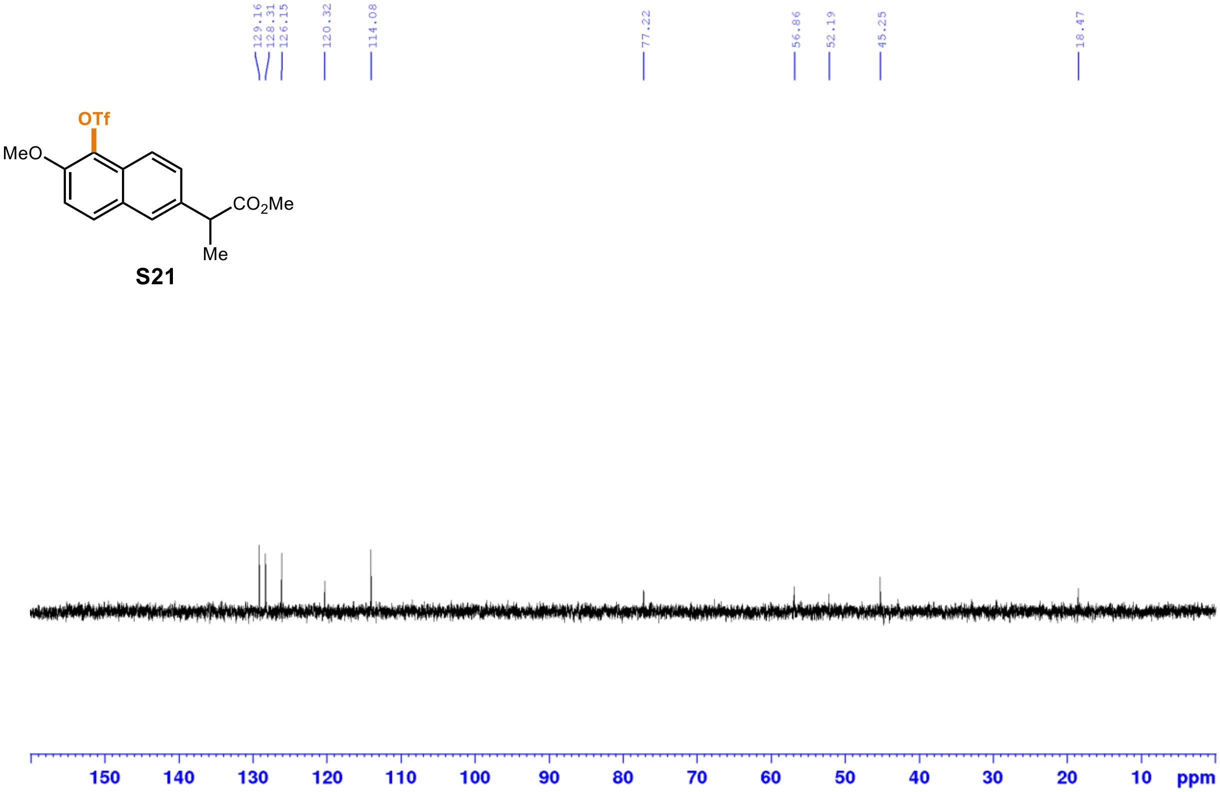


Figure S154: DEPT 135 NMR spectrum of **S21** in $CDCl_3$

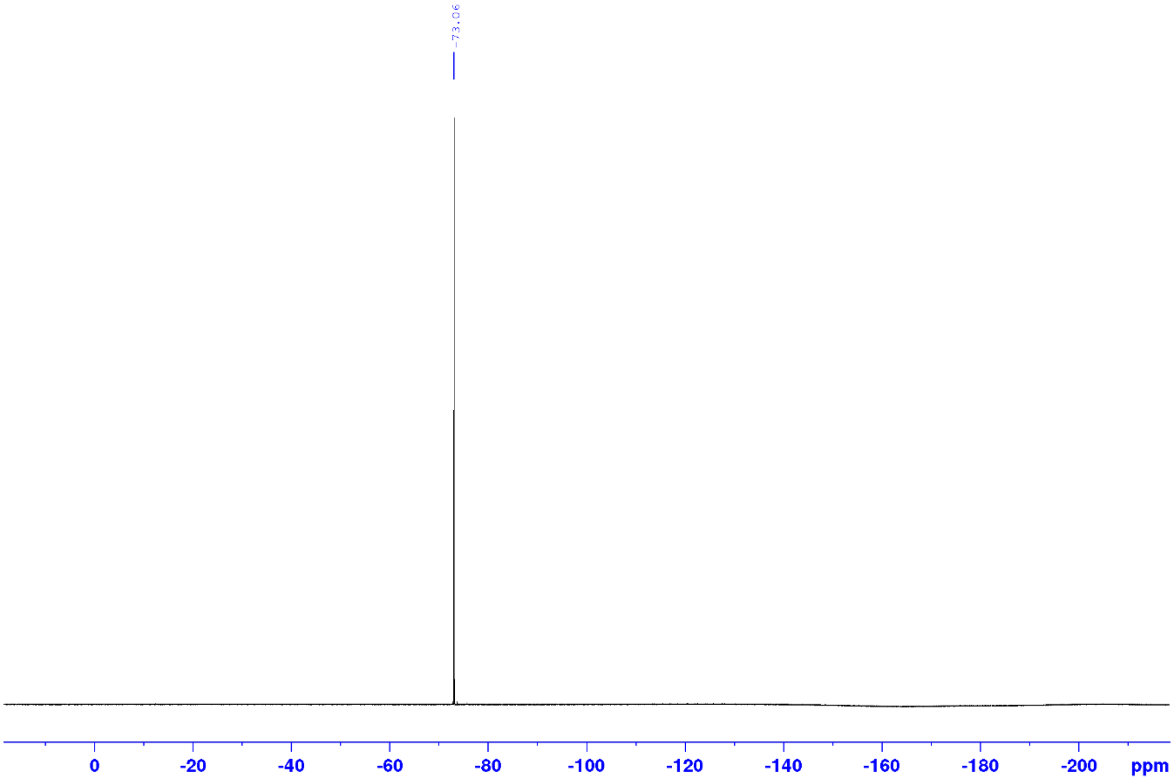
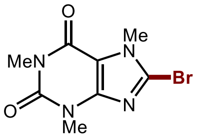


Figure S155: 377 MHz ^{19}F NMR spectrum of **S21** in $CDCl_3$



S22

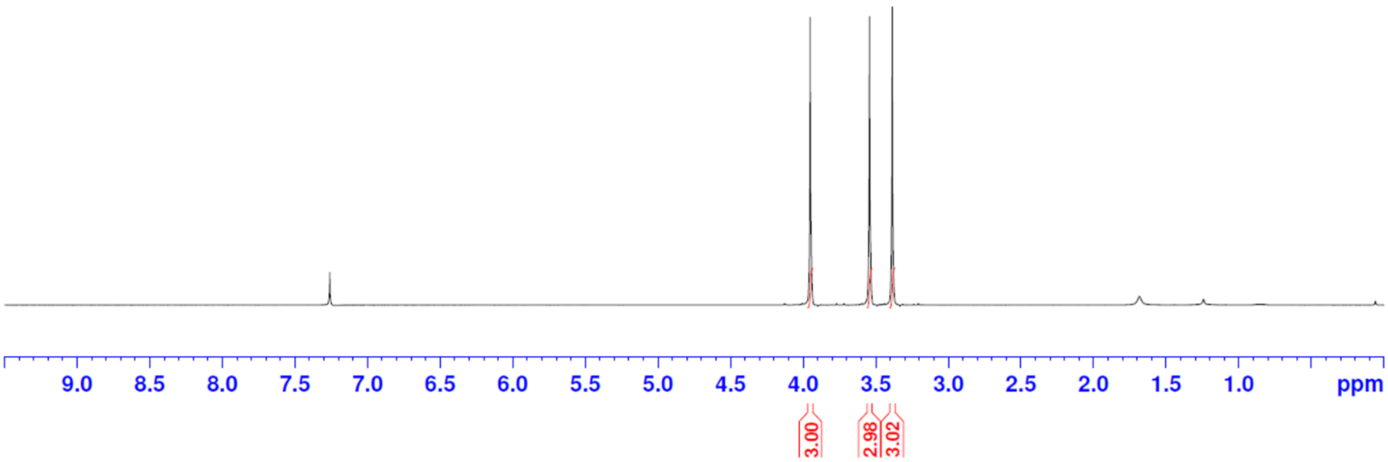


Figure S156: 400 MHz ^{1}H NMR spectrum of **S22** in CDCl$_3$

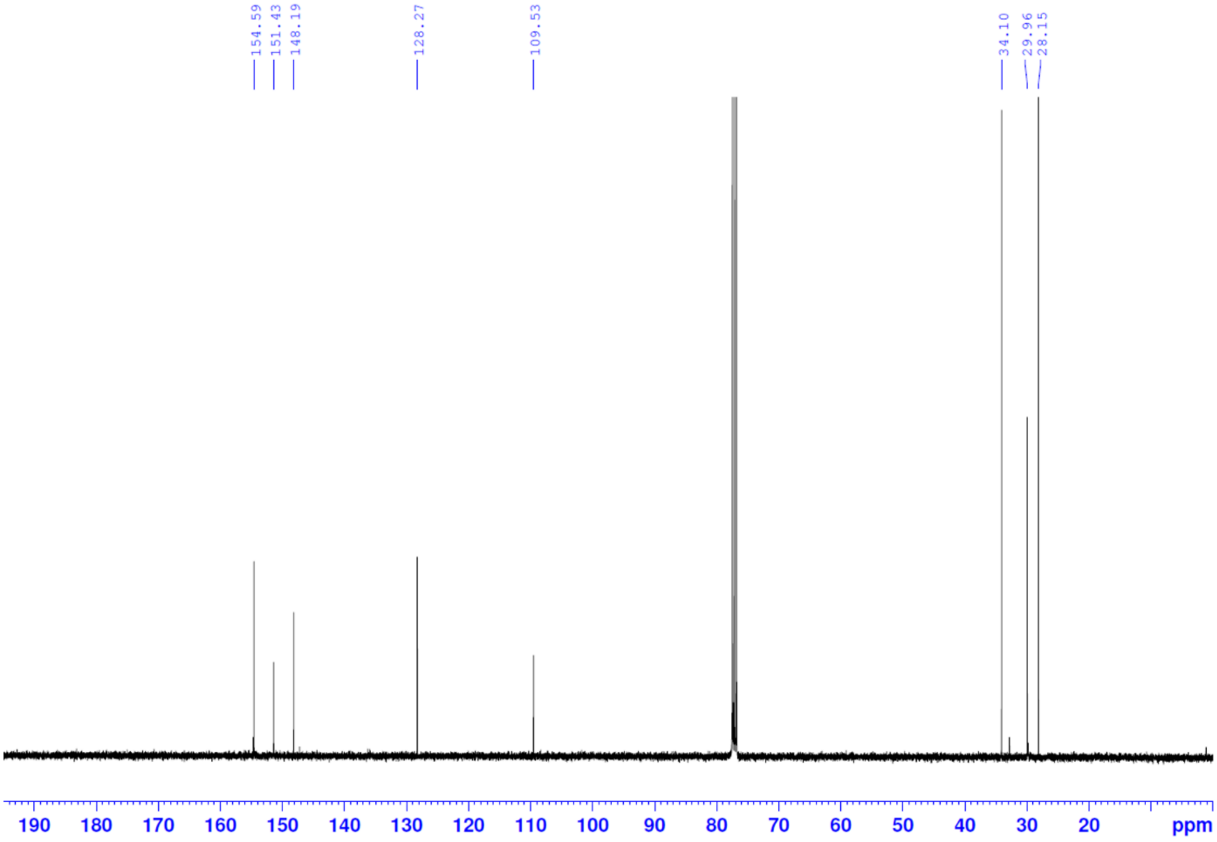


Figure S157: 101 MHz ^{13}C NMR spectrum of **S22** in CDCl$_3$