Synthesis of Oxindoles and Benzofuranones *via* Oxidation of 2-Heterocyclic BMIDAs

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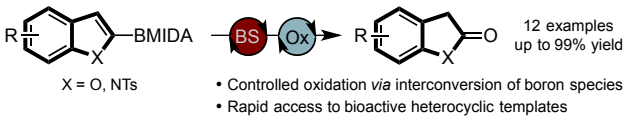


Received:
Accepted:
Published online:
DOI:

Abstract: The synthesis of functionalized oxindoles and benzofuranones *via* oxidation of 2-BMIDA indoles and benzofurans, respectively, is described. Interconversion of boron species (BMIDA→BF_3K) was necessary to enable oxidation and overcome boronic acid stability issues associated with a difficult BMIDA hydrolysis. Overall, a robust process was developed that allowed access to a small library of oxindole and benzofuranone products and facilitated the step-efficient synthesis of biologically-active compounds containing the oxindole pharmacophore.

Key words: Boron, oxidation, heterocycles, lactams, lactones

The oxindole motif is present in the core of numerous biologically active natural products as well as pharmaceuticals such as tenidap, coreulescine, and semaxanib (Figure 1).[1] Consequently, numerous methods have been and continue to be developed to allow access to this privileged chemotype.

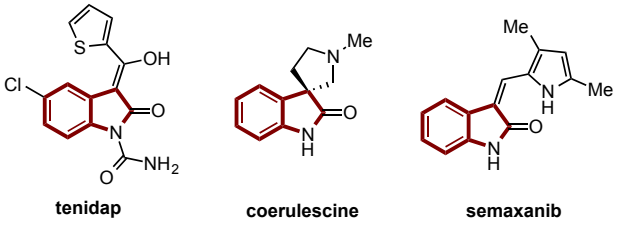
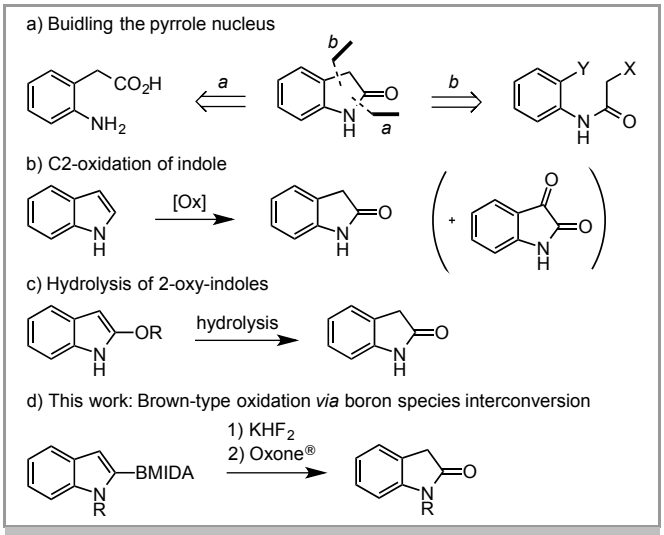


Figure 1 Pharmaceutically relevant oxindoles.

The most common synthetic approaches towards the oxindole framework forge the pyrrole nucleus either *via* disconnection at the amide C-N bond to provide a phenylacetic acid precursor,[2] or at the C-3 position to afford an anilide precursor (Scheme 1a).[3] Despite significant research, preparation of oxindoles beginning from the corresponding indole starting materials are comparatively limited,[4] with oxidative methods often suffering from the problem of over-oxidation to deliver isatins (Scheme 1b).[5] Hydrolysis of 2-oxy-indoles gives the corresponding oxindoles; however, this requires a pre-oxygenated indole as a starting material (Scheme 1c).[6] We recently disclosed a one-pot synthesis of 2-heterocyclic BMIDA's,[7] which are bench stable, free flowing solids that can be stored indefinitely without degradation.[8] Here we present the utility of 2-BMIDA indoles and benzofurans as readily accessible precursors to oxindoles and benzofuranones, respectively, and the scope and limitations of this process (Scheme 1d).

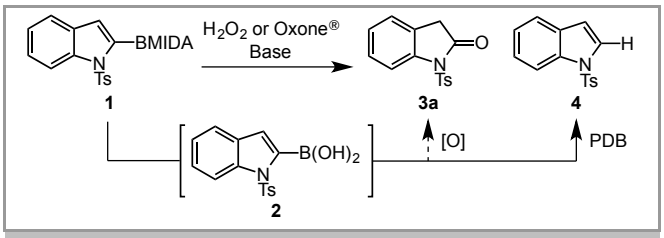


Scheme 1 Methods for the synthesis of oxindoles.

Oxidation of 2-borylated indoles is limited to two single examples using two specific 2-BPin indole substrates.[9] This class of compounds is generally difficult to access/handle due to issues with protodeboronation.[10] Consequently, a BMIDA-based process would offer significant synthetic advantages due to the accessibility and stability of these organoboron derivatives.[8]

Our initial studies commenced with *N*-Ts-indole-2-BMIDA **1**, using well-established Brown-type reaction conditions: H_2O_2 in

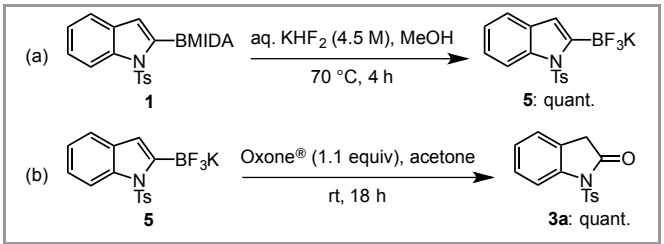
a range of solvent/water mixtures and in the presence of base (Scheme 2 – see Supporting Information for full details).[11]



Scheme 2 Attempted direct hydrolysis/oxidation of 2-BMIDA indole **1**. PDB = protodeboronation.

Based on the base lability of BMIDA and the well studied slow or fast release of the parent boronic acid,[10] we planned an *in situ* hydrolysis of **1** to deliver **2** that would then be oxidized to deliver **3a**. To our surprise, when using a base/oxidant system of NaOH/H_2O_2 at room temperature (fast hydrolysis conditions), the BMIDA group remained intact, *i.e.* no hydrolysis was observed, even in the presence of excess aq. NaOH. In an attempt to drive the hydrolysis step, the reaction was heated to 50 °C with increasing quantities of NaOH. However, while hydrolysis could be induced, these reactions returned the protodeboronated product **4** in quantitative yields in all cases, presumably due to the sensitivity of **2** under these reaction conditions. Attempting to temper the reaction conditions using a slow hydrolysis protocol with either K_3PO_4 or K_2CO_3 in the presence of H_2O_2 returned starting material (**1**) only. Changing the oxidant to Oxone® had a small positive effect – hydrolysis remained sluggish, requiring extended reaction times or elevated temperatures and although trace quantities of **3a** were observed under these conditions, protodeboronation product **4** dominated along with degradation of **3a**.

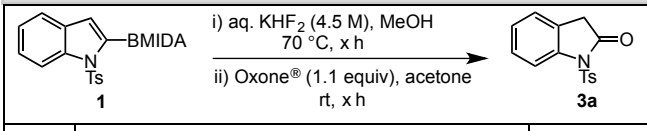
These initial investigations highlighted a compatibility issue between the conditions required to hydrolyze the BMIDA unit and the stability of the intermediate boronic acid (as well as the oxindole product). To overcome these issues, we postulated that a simple boron species interconversion process might be achieved under mild reaction conditions to deliver an organoboron derivative that could then be oxidized under conditions sufficiently mild to inhibit degradation of the organoboron intermediate or product. In particular, BMIDA species can be converted to the potassium organotrifluoroborate (BF_3K) derivative under relatively mild reaction conditions[12] and BF_3K species can also be oxidized under mild conditions.[13] However, BMIDA-BF_3K interconversion on this template was unknown. Accordingly, we evaluated conversion of BMIDA **1** to the BF_3K derivative **5**.



Scheme 3 Conversion of BMIDA **1** to BF_3K **5**.

A short survey of reaction conditions found that **1** could be quantitatively converted to **5** upon treatment with aq. KHF_2 in MeOH at 70 °C (Scheme 3a). In addition, **5** could be quantitatively converted to the desired oxindole product **3a** using Oxone®. Combining these two events proved to be straightforward (Table 1). Oxidation of intermediate **5** was found to be sluggish in MeOH; however, a solvent switch to acetone before addition of the oxidant was more effective (entry 1 *vs.* entry 2). A short optimization of reaction time and KHF_2 stoichiometry (entries 2-5) revealed that the overall two-step process could be completed in 6 hours using 5 equiv. of KHF_2 to facilitate conversion to **5**, ultimately delivering 99% conversion to **3a**. Interestingly, while oxidation of the intermediate BF_3K **5** was facile with Oxone®, $NaBO_3$ and H_2O_2 were ineffective for oxidation of this intermediate (entries 6 and 7, respectively).

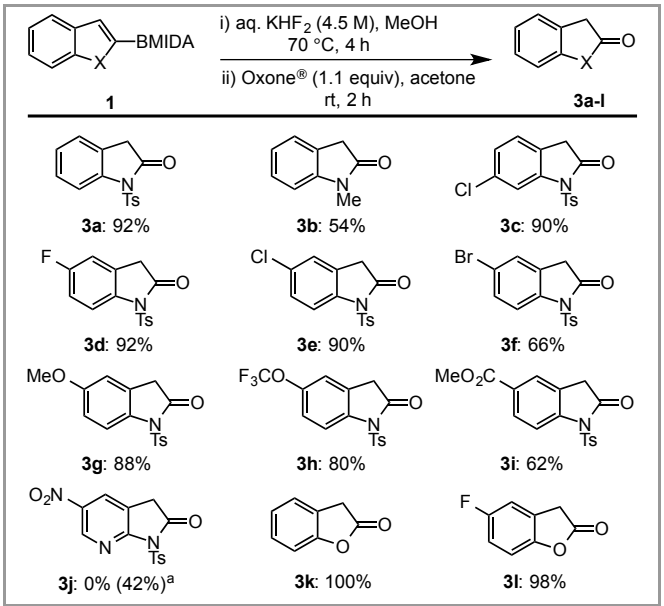
Table 1 Oxidation of Indole BMIDA *via* speciation



Entry	Conditions	**3a** (%)[a]
1	aq. KHF_2 (3 eq), 2 h/ Oxone®, 18 h[b]	27
2	aq. KHF_2 (3 eq), 2 h/ Oxone®, 18 h[c]	44
3	aq. KHF_2 (5 eq), 2 h/ Oxone®, 18 h[c]	92
4	aq. KHF_2 (5 eq), 4 h/ Oxone®, 18 h[c]	99
5	aq. KHF_2 (5 eq), 4 h/ Oxone®, 2 h[c]	99
6	aq. KHF_2 (5 eq), 4 h/ $NaBO_3$, 4 h[c]	0
7	aq. KHF_2 (5 eq), 4 h/ H_2O_2, 4 h[c]	0

[a]Determined by HPLC analysis against an internal standard. [b]Oxidant added directly. [c]Solvent switch to acetone before addition of Oxidant.

With optimum conditions in hand, the scope of the reaction was investigated by application to a range of substituted 2-BMIDA indole architectures (Scheme 4).



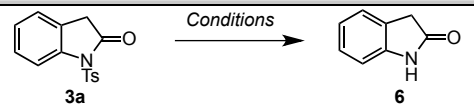
Scheme 4 Substrate scope of the oxidation process. Isolated yields. [a]Determined by ^{1}H NMR analysis.

The reaction was found to be tolerant of both electron-donating and electron-withdrawing groups (**3g**, **3h**, **3i**). Halogenated substrates were also effective, providing a synthetic handle for

further functionalization (**3c**, **3d**, **3e**, **3f**). In addition, azaindoline **3j** was delivered in moderate yield by NMR (42%) with the mass balance consisting of the product of protodeboronation. However, this product was found to be labile to hydrolysis on silica. The *N*-tosyl group could be replaced with a methyl unit but resulted in a decrease in yield of the corresponding oxindole (**3b**). Other *N*-protecting groups were not assessed. Lastly, in addition to oxindoles, the oxidation process was applicable to 2-BMIDA benzofurans to allow access to benzofuranones in excellent yields (**3k**, **3l**).

In keeping with our interests in medicinal chemistry,[14] we sought to utilize the oxindole products as building blocks in the synthesis of biologically active molecules. In particular, the ubiquity of the oxindole motif in kinase drug discovery[15] led us to target compounds of this class. First steps into derivatization of our oxindole products quickly identified an issue with deprotection of the *N*-tosyl. Specifically, the lactam was found to be readily hydrolyzed under both acidic and basic conditions.[16] To the best of our knowledge, no methods exist for the deprotection of *N*-Ts-oxindole, although sulfonamides have been removed from C3-substituted oxindoles using several approaches.[17] Accordingly, we surveyed reaction conditions commonly used for sulfonamide cleavage; however, neither NaOH or TBAF afforded any of the desired product **6** (Table 2 entries 1-3);[17d] these conditions all resulted in hydrolysis of the lactam at room temperature.

Table 2 Deprotection of *N*-Ts oxindole **3a**.



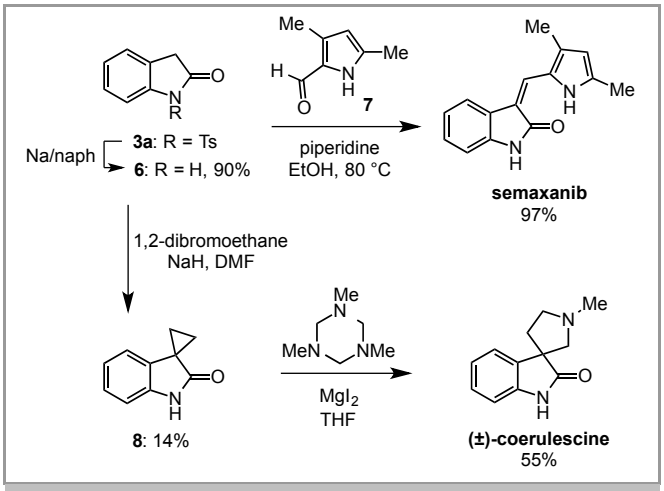
3a **6**

Entry	Conditions	**6** (%)[a]
1	6 M NaOH, 1,4-dioxane, rt	0
2	1 M NaOH, 1,4-dioxane, rt	0
3	1 M TBAF, THF, rt	0
4	Mg, MeOH, rt	0
5	SmI_2, pyrrolidine, H_2O, rt	0
6	Na, naphthalene, –78 °C	90

[a]Isolated yields.

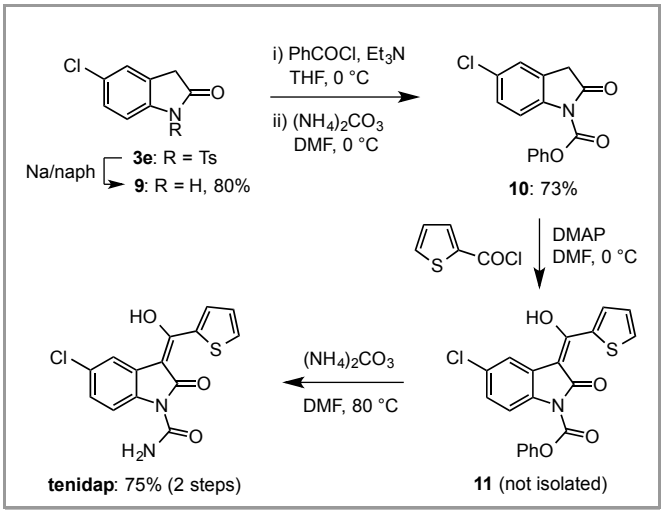
To limit exposure to basic reaction conditions, we evaluated several single-electron methods. Mg powder in MeOH resulted in solvolysis of **3a**.[17b] SmI_2 conditions led to full consumption of the starting material within five minutes of addition; however, none of the desired oxindole was observed, delivering only an unidentifiable mixture of products.[18] Fortunately, application of sodium naphthalenide at –78 °C provided clean conversion to the desired oxindole product in 90% isolated yield.[19]

With effective conditions for the deprotection now available, we were able to prepare several biologically active products (Scheme 5 and 6). Both the natural product (±)-coerulescine[20] and kinase inhibitor semaxanib[21] could be quickly accessed through common oxindole **3a** following tosyl deprotection (Scheme 5). From this common intermediate, condensation with commercially available pyrrole **7** afforded semaxanib in excellent yield, while C3 alkylation followed by ring expansion[22] enabled access to (±)-coerulescine in moderate overall yield. Although the dialkylation to form the cyclopropane proceeded with good conversion by NMR (*ca.* 60%), the desired spirocycle **8** was found to be highly unstable on silica, thereby limiting the yield of this process.



Scheme 5 Synthesis of semaxanib and (±)-coerulescine. Isolated yields.

Tenidap, a potent COX inhibitor,[23] was efficiently synthesized in five steps from oxindole **3e** (Scheme 6). Tosyl deprotection gave the free oxindole **9**, which, upon treatment with phenyl chloroformate followed by ammonium carbonate, gave oxindole **10** in 73% yield. Condensation with 2-thiophenecarbonyl chloride and susbsequent exposure to ammonium carbonate afforded tenidap in excellent yield.



Scheme 6 Synthesis of tenidap. Isolated yields.

In conclusion, we have reported a novel method for the preparation of oxindoles from 2-BMIDA indoles. A boron species (BMIDA to BF_3K) interconversion was used to overcome the instability of the intermediate indole 2-boronic acid towards the conditions required for hydrolysis of an unusually robust BMIDA species. The BF_3K species was readily oxidized to the corresponding oxindole under mild conditions allowing one-pot access to oxindole products. The scope of the reaction was evaluated by application towards a series of substrates and further exemplified in the context of the synthesis of kinase inhibitors semaxanib and tenidap, and the natural product coerulescine.

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All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Where necessary, purification was carried out according to standard laboratory methods.[24] Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5 mL microwave vials. Room temperature was generally *ca.* 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer. Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel. Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer at 376 MHz. ^{11}B NMR spectra were obtained on a Bruker AV 400 spectrometer at 128 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 125 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.0 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C). ^{11}B NMR spectra are referenced to BF_3•Et2O. High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

General Procedure – Oxidation products (Scheme 4).

An oven dried 10 mL microwave vial was charged with R-BMIDA (0.1 mmol, 1 equiv) before the addition of 4 mL MeOH. The vial was capped before the addition of KHF_2 (100 µL, 4.5 M aq. solution, 0.5 mmol, 5 equiv). The reaction was then heated to 70 °C for 4 h. At this point the reaction was cooled, vented, decapped, and the MeOH solution was transferred to a clean flask and concentrated under reduced pressure to provide a white solid. The residue was diluted with hot acetone and the BF_3K solution was transferred to a 5 mL flask (2×2 mL) and concentrated under reduced pressure. The resulting residue was diluted with 0.5 mL acetone before the addition of Oxone® (35 mg, 0.11 mmol, 1.1 equiv) in 0.5 mL H_2O. The reaction was left to stir for 2 h before the addition of 1 M HCl (2 mL). The reaction mixture was then diluted with water (2 mL) and extracted with CH_2Cl_2 (2×5 mL). The organics were filtered through 2 cm of silica gel and washed through with a further 20 mL CH_2Cl_2. The resulting solution was concentrated under vacuum to afford the desired product.

1-Tosylindolin-2-one (3a)

Prepared according to the general procedure from (1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester (43 mg). Yield: 27 mg, 92%. Off-white amorphous solid.

IR (solid): 3092, 3058, 2962, 2947, 1768, 1595, 1478, 1465, 1377 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.29–7.20 (m, 3H), 7.13 (d, *J* = 7.4, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 3.47 (s, 2H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.3, 145.2, 139.9, 134.8, 129.3, 128.1, 127.5, 124.2, 124.1, 122.7, 113.2, 35.6, 21.2.

HRMS (NSI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{14}NO_3S$: 288.0689; found: 288.0690.

1-Methylindolin-2-one (3b)

Prepared according to the general procedure from (1-methyl-1*H*-indol-2-yl)boronic acid, MIDA ester (29 mg). Yield: 8 mg, 54%. Dark green liquid.

IR (solid): 3060, 2924, 2855, 1698, 1614, 1496, 1470, 1370, 1349 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.26 (m, 1H), 7.26–7.22 (m, 1H), 7.05 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.52 (s, 2H), 3.21 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.6, 144.7, 127.4, 123.8, 121.9, 107.6, 35.3, 25.7.

HRMS (NSI): *m/z* [M+H]$^+$ calcd for $C_9H_{10}NO$: 148.0757; found: 148.0753.

6-Chloro-1-tosylindolin-2-one (3c)

Prepared according to the general procedure from (6-chloro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester (46 mg). Yield: 29 mg, 90%. White amorphous solid.

IR (solid): 2924, 2857, 1768, 1610, 1595, 1424, 1372, 1333, 1236 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07–7.88 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 1.1 Hz, 2H), 3.52 (s, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.3, 146.0, 141.2, 135.0, 134.4, 129.9, 128.1, 125.5, 125.4, 124.7, 121.5, 114.4, 35.7, 21.7.

HRMS (TOF): *m/z* [M+H]$^+$ calcd for $C_{15}H_{13}ClNO_3S$: 322.0305; found: 322.0304.

5-Fluoro-1-tosylindolin-2-one (3d)

Prepared according to the general procedure from (5-fluoro-1*H*-indol-2-yl)boronic acid, MIDA ester (44 mg). Yield: 28 mg, 92%. Off-white amorphous solid.

IR (solid): 3073, 2973, 2924, 1761, 1610, 1599, 1476, 1368 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06–7.93 (m, 2H), 7.88 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.04 (td, *J* = 9.0, 2.8 Hz, 1H), 6.98–6.94 (m, 1H), 3.55 (s, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.3, 159.9 (d, $^{1}J_{C\text{-}F}$ = 244.0 Hz), 145.8, 135.1, 129.8, 128.0, 124.9 (d, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 115.1 (d, $^{2}J_{C\text{-}F}$ = 23.3 Hz), 114.9 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 112.4 (d, $^{2}J_{C\text{-}F}$ = 24.9 Hz), 36.2, 21.7.

^{19}F NMR ($CDCl_3$, 471 MHz): δ –117.57

HRMS (TOF): *m/z* [M+H]$^+$ calcd for $C_{15}H_{12}FNO_3S$: 306.0600; found: 306.0602.

5-Chloro-1-tosylindolin-2-one (3e)

Prepared according to the general procedure from (5-chloro-1*H*-indol-2-yl)boronic acid, MIDA ester (46 mg). Yield: 29 mg, 90%. White amorphous solid.

IR (solid): 2956, 2922, 1755, 1599, 1470, 1370, 1232 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99–7.94 (m, 2H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.36–7.29 (m, 3H), 7.22–7.19 (m, 1H), 3.55 (s, 2H), 2.43 (s, 3H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 172.0, 145.9, 138.9, 135.0, 130.2, 129.8, 128.6, 128.0, 125.0, 124.9, 114.8, 35.9, 21.7.

HRMS (NSI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{13}ClNO_3S$: 322.0299; found: 322.0302.

5-Bromo-1-tosylindolin-2-one (3f)

Prepared according to the general procedure from (5-bromo-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester (51 mg). Yield: 24 mg, 66%. Light brown amorphous solid.

IR (solid): 3088, 2958, 2924, 2854, 1757, 1599, 1469, 1455, 1375 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01–7.96 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.51–7.46 (m, 1H), 7.39–7.33 (m, 3H), 3.58 (s, 2H), 2.45 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.4, 145.5, 138.9, 134.4, 131.0, 129.4, 127.5, 127.4, 124.7, 117.2, 114.7, 35.3, 21.3.

HRMS (NSI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{13}Br_1N_1O_3S_1$: 365.9794; found: 365.9798.

5-Methoxy-1-tosylindolin-2-one (3g)

Prepared according to the general procedure from (5-methoxy-1*H*-indol-2-yl)boronic acid, MIDA ester (46 mg). Yield: 28 mg, 88%. Light brown amorphous solid.

IR (solid): 2950, 2924, 2855, 1757, 1601, 1483, 1470, 1372 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.85 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.79 (s, 1H), 3.79 (s, 3H), 3.53 (s, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.7, 157.0, 145.6, 135.2, 133.8, 129.8, 127.9, 124.5, 114.5, 113.2, 111.2, 55.7, 36.5, 21.7.

HRMS (NSI): *m/z* [M+H]$^+$ calcd for $C_{16}H_{16}NO_4S$: 318.0795; found: 318.0796.

1-Tosyl-5-(trifluoromethoxy)indolin-2-one (3h)

Prepared according to the general procedure from (1-tosyl-5-(trifluoromethoxy)-1*H*-indol-2-yl)boronic acid, MIDA ester (51 mg). Yield: 30 mg, 80%. Off-white amorphous solid.

IR (solid): 2958, 2928, 2857, 1761, 1601, 1480, 1374 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.9 Hz, 1H), 7.04 (s, 1H), 3.51 (s, 2H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.0, 146.0, 138.9, 135.0, 129.9, 128.1, 124.8, 121.6, 119.4, 118.2, 114.7, 36.1, 21.7. Trifluoromethyl carbon not observed.

^{19}F NMR ($CDCl_3$, 471 MHz): δ –58.21.

HRMS (TOF): *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}F_3NO_4S$: 372.0517; found: 372.0527.

Methyl 2-oxo-1-tosylindoline-5-carboxylate (3i)

Prepared according to the general procedure from (5-(methoxycarbonyl)-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester (48 mg). Yield: 22 mg, 62%. White amorphous solid.

IR (solid): 2956, 2924, 2855, 1766, 1711, 1623, 1601, 1483, 1450, 1374 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.98 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 7.0 Hz, 3H), 7.83 (s, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.84 (s, 3H), 3.53 (s, 2H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.9, 165.8, 145.6, 143.6, 134.4, 130.2, 129.4, 127.6, 126.1, 125.5, 122.8, 112.8, 51.8, 35.3, 21.3.

HRMS (NSI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}NO_5S$: 346.0744; found: 346.0746.

Benzofuran-2(3*H*)-one (3k)[25a]

Prepared according to the general procedure from benzofuran-2-ylboronic acid, MIDA ester (27 mg). Yield: 14 mg, 100%. White amorphous solid.

IR (solid): 2956, 2926, 1798, 1779, 1616, 1601, 1480, 1465, 1299 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.19 (m, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 3.66 (s, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.6, 154.2, 128.4, 124.1, 123.6, 122.6, 110.3, 32.5.

5-Fluorobenzofuran-2(3*H*)-one (3l)

Prepared according to the general procedure from (5-fluorobenzofuran-2-yl)boronic acid, MIDA ester (29 mg). Yield: 15 mg, 98%. White amorphous solid.

IR (solid): 3081, 2958, 2926, 2855, 1796, 1634, 1610, 1483, 1400, 1388 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.07–6.82 (m, 3H), 3.69 (s, 2H).

^{13}C NMR ($CDCl_3$, 500 MHz): δ 173.6, 159.4 (d, $^1J_{C\text{-}F}$ = 242.5 Hz), 150.6, 124.4 (d, $^3J_{C\text{-}F}$ = 9.5 Hz), 115.5 (d, $^2J_{C\text{-}F}$ = 24.3 Hz), 112.2 (d, $^2J_{C\text{-}F}$ = 25.6 Hz), 111.7 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 33.5.

^{19}F NMR ($CDCl_3$, 471 MHz): δ –118.2.

HRMS (TOF): *m/z* $[M+H]^+$ calcd for $C_8H_5FO_2$: 153.0352; found: 153.0354.

Oxindole (6)[25b]

A 10 mL flask was charged with sodium metal (138 mg, 6 mmol, 60 equiv) and naphthalene (385 mg, 3 mmol, 30 equiv) before the addition of DME (5 mL) and the reaction mixture was stirred at room temperature for 30 min to form a blue/green solution. A solution of 1-tosylindolin-2-one (28 mg, 0.1 mmol, 1 equiv) in DME (0.5 mL, 0.2 M) was cooled to –78 °C and the Na-naphthalenide solution was then added dropwise until an orange/red colour persisted (1.5 mL). The solution was then warmed to room temperature and a further 0.5 mL na-naphthalenide solution was added. The reaction was then quenched with H_2O (2 mL), extracted with EtOAc (5 mL), and washed with brine (5 mL). The organics were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel, 10-40% EtOAc/petroleum ether) to afford the desired product. Yield: 12 mg, 90%. Beige amorphous solid.

IR (solid): 3161, 1692, 1618, 1469, 1332 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 9.20 (s, 1H), 7.24 (t, *J* = 7.4 Hz, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 3.57 (s, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.7, 142.1, 127.4, 124.8, 124.1, 121.8, 109.3, 35.8.

Semaxanib

A 25 mL flask was charged with oxindole (133 mg, 1 mmol, 1 equiv) and 3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (148 mg, 1.2 mmol, 1.2 equiv) before the addition of EtOH (10 mL, 0.5 M). Piperidine (12 µL, 0.01 mmol, 0.01 equiv) was then added and the flask was equipped with a condenser before heating to reflux for 4 h. The reaction mixture was then cooled to room temperature and concentrated under vacuum to afford a red/orange solid. The precipitate was collected by filtration and washed with chloroform to afford the desired product. Yield: 230 mg, 97%. Red/orange amorphous solid.

IR (solid): 3166, 3122, 2917, 2842, 1668, 1617, 1565, 1554, 1539, 1463, 1455, 1340, 1316, 1204 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 13.12 (s, 1H), 8.00 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.13 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05 (td, *J* = 7.6, 1.1 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 5.98 (d, *J* = 2.5 Hz, 1H), 2.39 (s, 3H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.8, 137.0, 136.9, 132.6, 127.1, 126.6, 125.6, 123.6, 121.5, 117.4, 112.7, 111.8, 109.2, 13.9, 11.6.

HRMS (NSI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}N_2O$: 239.1179; found: 239.1177.

Spiro[cyclopropane-1,3'-indolin]-2'-one (8)

An oven dried flask was charged with oxindole (133 mg, 1 mmol, 1 equiv) before the addition of dry DMF (1.25 mL, 0.8 M) and dibromoethane (94 µL, 1.1 mmol, 1.1 equiv). The solution was then cooled to 0 °C before the addition of NaH (60% dispersion in mineral oil, 180 mg, 4.5 mmol, 4.5 equiv) portionwise over 20 min. The reaction mixture was then warmed to room temperature and stirred overnight before being quenched with H_2O (3 mL) and extracted with EtOAc (5 mL). The organics were then washed with H_2O (2 × 5 mL) and brine (2 × 5 mL). The organics were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel, 20-40% EtOAc/petroleum ether) to afford the desired product. Yield: 23 mg, 14%. Red/brown amorphous solid.

IR (solid): 3200, 1701, 1684, 1671, 1627, 1474, 1357 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.34 (s, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 1.76 (d, *J* = 3.0 Hz, 2H), 1.54 (d, *J* = 2.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.1, 140.6, 131.3, 126.7, 122.0, 118.6, 109.7, 27.4, 19.5.

HRMS (NSI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{10}NO$: 160.0757; found: 160.0753.

Coerulescine

A 5 mL microwave vial equipped with a stirrer bar was charged with spiro[cyclopropane-1,3'-indolin]-2'-one (20 mg, 0.125 mmol, 1 equiv) and MgI_2 (1.74 mg, 6.25 µmol, 5 mol%) before being capped and purged with N_2. THF (0.2 mL, 0.6 M) and trimethyl triazinane (18 µL, 0.125 mmol, 1 equiv) were then added and the reaction mixture was heated to 125 °C in a sandbath for 60 h. The reaction mixture was then cooled to room temperature before being diluted with EtOAc (5 mL) and washed with H_2O (5 mL) and brine (5 mL). The organics were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel, 50% EtOAc/petroleum ether followed by 20% MeOH/DCM) to afford the desired product. Yield: 14 mg, 55%. Pale yellow oil.

IR (solid): 3192, 3060, 2943, 2787, 1707, 1619, 1472, 1336, 1195 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (s, 1H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.19 (td, *J* = 7.7, 1.2 Hz, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 3.11–3.00 (m, 1H), 2.91 (s, 2H), 2.88–2.74 (m, 1H), 2.49 (s, 3H), 2.41 (ddd, *J* = 12.5, 7.7, 4.7 Hz, 1H), 2.12 (dt, *J* = 12.9, 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 182.7, 140.1, 136.0, 127.8, 123.4, 122.9, 109.5, 66.2, 56.7, 53.6, 41.8, 38.0.

HRMS (NSI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{15}N_2O$: 203.1179; found: 203.1177.

5-Chloroindolin-2-one (9)

To a 10 mL flask charged with sodium metal (83 mg, 3.6 mmol, 60 equiv) and naphthalene (231 mg, 1.8 mmol, 30 equiv) was added DME (5 mL) and the reaction mixture was stirred at room temperature for 30 min to form a blue/green solution. A solution of 5-chloro-1-tosylindolin-2-one (20 mg, 0.06 mmol, 1 equiv) in DME (0.3 mL, 0.2 M) was cooled to -78 °C and the Na-naphthalenide solution was then added dropwise until an orange/red colour persisted (1.5 mL). The solution was then warmed to room temperature and a further 0.5 mL Na-naphthalenide solution was added. The reaction was then quenched with H_2O (2 mL), extracted with EtOAc (5 mL), and washed with brine (5 mL). The organics were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel, 10-40% EtOAc/petroleum ether) to afford the desired product. Yield: 8 mg, 80%. Off-white amorphous solid.

IR (solid): 3159, 3047, 2960, 2926, 2855, 1699, 1621, 1478, 1379, 1316 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.20 (d, *J* = 11.5 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 1H), 3.54 (s, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.5, 139.8, 127.0, 126.7, 125.9, 124.1, 109.4, 35.0.

HRMS (NSI): *m/z* $[M+H]^+$ calcd for C_8H_7ClNO: 168.0211; found: 168.0207.

Phenyl 5-chloro-2-oxoindoline-1-carboxylate (10)

Step 1: Phenyl 5-chloro-2-((phenoxycarbonyl)oxy)-1*H*-indole-1-carboxylate.

To a flask charged with 5-chloro-2-oxindole (1 g, 6 mmol, 1 equiv) was added 20 mL dry THF followed by triethylamine (1.75 mL, 12.6 mmol, 2.1 equiv). The reaction mixture was cooled to 0 °C before the dropwise addition of phenyl chloroformate (1.6 mL, 13.2 mmol, 2.2 equiv). The mixture was stirred at 0 °C for 1 h. The resulting precipitate was then removed by filtration and the filter cake was washed with THF (2×20 mL). The filtrate was then concentrated under vacuum to obtain a pink solid which was stirred in 20 mL H_2O to form an emulsion. This was then filtered, washed with H_2O (2×20 mL), and dried by drawing air through the filter cake to afford the desired product phenyl 5-chloro-2-((phenoxycarbonyl)oxy)-1*H*-indole-1-carboxylate. Yield: 2.4 g (crude weight). White solid. The product was used directly in the next step without further purification.

Step 2

A solution of phenyl 5-chloro-2-((phenoxycarbonyl)oxy)-1*H*-indole-1-carboxylate (1.11 g, 2.75 mmol, 1 equiv) in dry DMF (10 mL) was cooled to 0 °C, followed by the portionwise addition of ammonium carbonate powder (300 mg, 3.16 mmol, 1.15 equiv). The resulting solution was stirred for 1 h at 0 °C. Upon consumption of the starting material the pale yellow solution was then poured into 30 mL ice water to provide a white precipitate. The suspension was then stirred for 30 min before being filtered, washed with H_2O (2×10 mL) and dried by pulling air through the filter cake to afford the desired product **10**. Yield: 585 mg, 73% over two steps. White amorphous solid.

IR (solid): 3137, 3060, 2956, 2932, 1770, 1737, 1595, 1478 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 8.7 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.37–7.29 (m, 5H), 3.80 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.5, 150.0, 149.4, 138.9, 130.5, 129.7, 128.5, 126.6, 125.0, 124.6, 121.5, 116.7, 36.3.

HRMS (NSI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{11}ClNO_3$: 288.0422; found: 288.0423.

Tenidap

Step 1: Phenyl (*E*)-5-chloro-3-(hydroxy(thiophen-2-yl)methylene)-2-oxoindoline-1-carboxylate (**11**). To a 50 mL flask charged with phenyl 5-chloro-2-oxoindoline-1-carboxylate (100 mg, 0.35 mmol, 1 equiv) and 4-dimethylaminopyridine 10.7 g (74 mg, 0.735 mmol, 2.1 equiv) was added anhydrous DMF (1.4 mL, 0.25 M), and cooled to 0 °C. A solution of thiophene-2-carbonyl chloride (56 mg, 0.385 mmol, 1.1 equiv) in dry DMF (0.6 mL) was then added dropwise and the resulting suspension was stirred at 0 °C until consumption of the starting material (approx. 1 h). The solution was then poured into 3 mL ice water, acidified to pH 2–3 with concentrated hydrochloric acid and stirred for 3 h. The resulting precipitate was then filtrated, washed with H_2O (2×5 mL), and dried by drawing air through the filter cake to afford the desired product **11.** Yield: 111 mg (crude weight). Pale yellow solid. The product was used directly in the next step without further purification.

Step 2: To a solution of phenyl (*E*)-5-chloro-3-(hydroxy(thiophen-2-yl)methylene)-2-oxoindoline-1-carboxylate (12 mg, 0.03 mmol, 1 equiv) in dry DMF (0.2 mL, 0.15 M) was added ammonium carbonate powder (3 mg, 0.03 mmol, 1 equiv). The resulting solution was then stirred at 80 °C for 4 h. The reaction mixture was then cooled to room temperature before being diluted with EtOAc (5 mL) and washed with H_2O (5 mL). The organics were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel, 0-100% $MeOH/CH_2Cl_2$) to afford the desired product. Yield: 9 mg, 75% over two steps. Yellow amorphous solid.

IR (solid): 3330, 2254, 1694, 1627, 1595, 1571, 1457, 1424 cm^{-1}.

^{1}H NMR (DMSO, 500 MHz): δ 9.35 (s, 1H), 8.59 (d, *J* = 3.3 Hz, 1H), 8.16 (d, *J* = 1.8 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 4.9 Hz, 1H), 7.11 – 7.04 (m, 2H), 6.79 (dd, *J* = 8.5, 2.3 Hz, 1H).

^{13}C NMR (DMSO, 101 MHz): δ 176.8, 165.7, 154.7, 149.1, 132.0, 130.1, 129.5, 129.1, 126.9, 126.0, 118.3, 117.3, 113.9, 94.3.

HRMS (NSI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{10}ClN_2O_3S$: 321.0095; found: 321.0099.

Acknowledgment

We thank the Carnegie Trust for a PhD studentship (CPS) and the EPSRC UK National Mass Spectrometry Facility at Swansea University for analyses.

Supporting Information

Optimization data, and ^{1}H and ^{13}C NMR spectra for all new compounds.

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Synthesis of Oxindoles and Benozfuranones via Oxidation of 2-Heterocyclic BMIDAs

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Contents

1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[1]

1.1 Purification of Solvents

DMF was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves, Acetone, MeOH, CH_2Cl_2, Et_2O, EtOAc, MeCN, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification.

1.3 Experimental Details

Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5 mL microwave vials. The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally *ca.* 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

1.4 Purification of Products

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

1.5 Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer at 376 MHz. ^{11}B NMR spectra were obtained on a Bruker AV 400 spectrometer at 128 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 125 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.0 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C). ^{11}B NMR spectra are referenced to $BF_3 \bullet Et_2O$. High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Reversed phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column. Analysis was performed using a gradient method, eluting with 5–80% MeCN/H_2O over 16 minutes at a flow rate of 2 mL/min. Samples for HPLC analysis were prepared through the addition of 2 mL of caffeine standard in MeCN to the completed reaction mixture. The resulting solution was then stirred before the removal of a 200 μL aliquot. The aliquot was diluted to 1 mL with MeCN. A 200 μL aliquot of the diluted solution was then filtered through cotton wool and further diluted with 800 μL MeCN and 500 μL H_2O for HPLC analysis against established conversion factors.

2. Optimization of Hydrolysis/Oxidation procedure

2.1 General procedure for optimization reactions.

A 10 mL microwave vial was charged with *N*-tosylindole-2-BMIDA (43 mg, 0.1 mmol, 1 equiv) before the addition of **solvent** (0.4 mL, 0.25 M) and **base** (**x equiv**). To the resulting solution was added **oxidant** (**x equiv**). The reaction mixture was stirred at **X** °C for **X** h before being quenched with sodium metabisulfite (10 mg). The reaction mixtures were then analyzed by reverse phase HPLC against established conversion factors.

2.2 H_2O_2 optimization

Carried out according to the general procedure using 30% w/v H_2O_2 (0.2 mL, 2.5 mmol, 25 equiv) for 1 hr.

Entry	Base (vol/mass)	Base equiv	Solvent	Temp (°C)	Conversion %
1	aq. NaOH (0.3 M, 1 mL)	3	MeCN	rt	0
2	aq. NaOH (0.3 M, 1.67 mL)	5	MeCN	rt	0
3	aq. NaOH (0.3 M, 3.3 mL)	10	MeCN	rt	0
4	aq. NaOH (0.3 M, 1 mL)	3	MeCN	50	0
5	aq. NaOH (0.3 M, 1.67 mL)	5	MeCN	50	0
6	aq. NaOH (0.3 M, 3.3 mL)	10	MeCN	50	0
7	K_3PO_4 (64 mg)	3	THF	rt	0
8	K_3PO_4 (64 mg)	3	MeCN	rt	0
9	K_3PO_4 (64 mg)	3	THF	50	0
10	K_3PO_4 (64 mg)	3	MeCN	50	0
11	K_3PO_4 (64 mg)	3	THF	rt	0
12	K_3PO_4 (64 mg)	3	MeCN	rt	0
13	K_3PO_4 (64 mg)	3	THF	50	0
14	K_3PO_4 (64 mg)	3	MeCN	50	0
15	K_3PO_4 (64 mg)	3	THF	rt	0
16	K_3PO_4 (64 mg)	3	MeCN	rt	0
17	K_3PO_4 (64 mg)	3	THF	50	0
18	K_3PO_4 (64 mg)	3	MeCN	50	0

2.3 Oxone optimization

Carried out according to the general procedure for 24 hr.

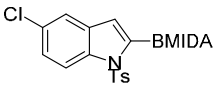
Entry	Oxone® equiv (mass)	K_3PO_4 equiv (mass)	Temperature (°C)	Solvent	Conversion %
1	10 (307 mg)*	3 (64 mg)	50	THF	0
2	10 (307 mg)*	3 (64 mg)	60	THF	0
3	10 (307 mg)*	3 (64 mg)	70	THF	0
4	2.5 (77 mg)	3 (64 mg)	60	MeCN	0
5	2.5 (77 mg)	3 (64 mg)	70	MeCN	0
6	2.5 (77 mg)	-	60	MeCN	15
7	2.5 (77 mg)	-	70	MeCN	16
8	10 (307 mg)*	-	50	THF	11
9	10 (307 mg)*	-	60	THF	11
10	10 (307 mg)*	-	70	THF	4

* Oxone was added to the reaction as a solution in 2 mL H_2O

4. Compound characterization data

Synthesis of starting materials.
Compounds **1a, b, c, f, g, h, i** and **l** were synthesized according to ref 7. Compounds **1d** and **j** were purchased from commercial suppliers and used as received.

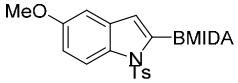
Synthesis of (5-chloro-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester 1e



To an oven dried 50 mL flask was added *N*-(2-iodo-4-chlorophenyl)-4-methylbenzenesulfonamide (1.02 g, 2.5 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (540 mg, 3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 2 mol%), CuI (48 mg, 0.25 mmol, 10 mol%), $Cu(OAc)_2$ (136 mg, 0.75 mmol, 30 mol%), and K_3PO_4 (530 mg, 2.5 mmol, 1 equiv). The flask was then sealed and purged with N_2 before addition of DMF (20 mL, 0.125 M). The reaction mixture was then heated to 30 °C for 4 h before being heated to 55 °C for a further 14 h. The reaction mixture was allowed to cool to room temperature before the solution was then dried and concentrated under reduced pressure before being diluted with EtOAc (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then dried and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as an off-white solid (790 mg, 69%).

υ_{max} (solid): 2972, 1763, 1599, 1526, 1448, 1340, 1295 cm^{-1}.
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.12 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 1.7 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.05 (s, 1H), 4.47 (d, *J* = 17.5 Hz, 2H), 4.23 (d, *J* = 17.5 Hz, 2H), 2.95 (s, 3H), 2.33 (s, 3H).
^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.1, 145.5, 136.9, 134.7, 131.1, 130.0, 128.0, 126.6, 125.0, 120.9, 120.8, 115.8, 64.3, 49.4, 21.0. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.38.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}ClN_2O_6SB$) requires *m/z* 461.0749, found *m/z* 461.0766.

Synthesis of (5-methoxy-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester 1g



To an oven dried 5 mL microwave vessel was added *N*-(2-iodo-4-methoxyphenyl)-4-methylbenzenesulfonamide (202 mg, 0.5 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (109 mg, 0.6 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 2 mol%), CuI (9.5 mg, 0.05 mmol, 10 mol%), $Cu(OAc)_2$ (27.2 mg, 0.15 mmol, 30 mol%), and K_3PO_4 (106 mg, 0.5 mmol, 1 equiv). The vessel was then capped and purged with N_2 before addition of DMF (4 mL, 0.125 M). The reaction mixture was then heated to 30 °C in a sand bath for 4 h before being heated to 55 °C for a further 14 h. The vessel was allowed to cool to room temperature, vented, and decapped. The solution was then dried and concentrated under reduced pressure before being diluted with EtOAc (20 mL) and washed with water (2 × 40 mL) and brine (2 × 40 mL). The organics were then dried and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as a white solid (150 mg, 66%).

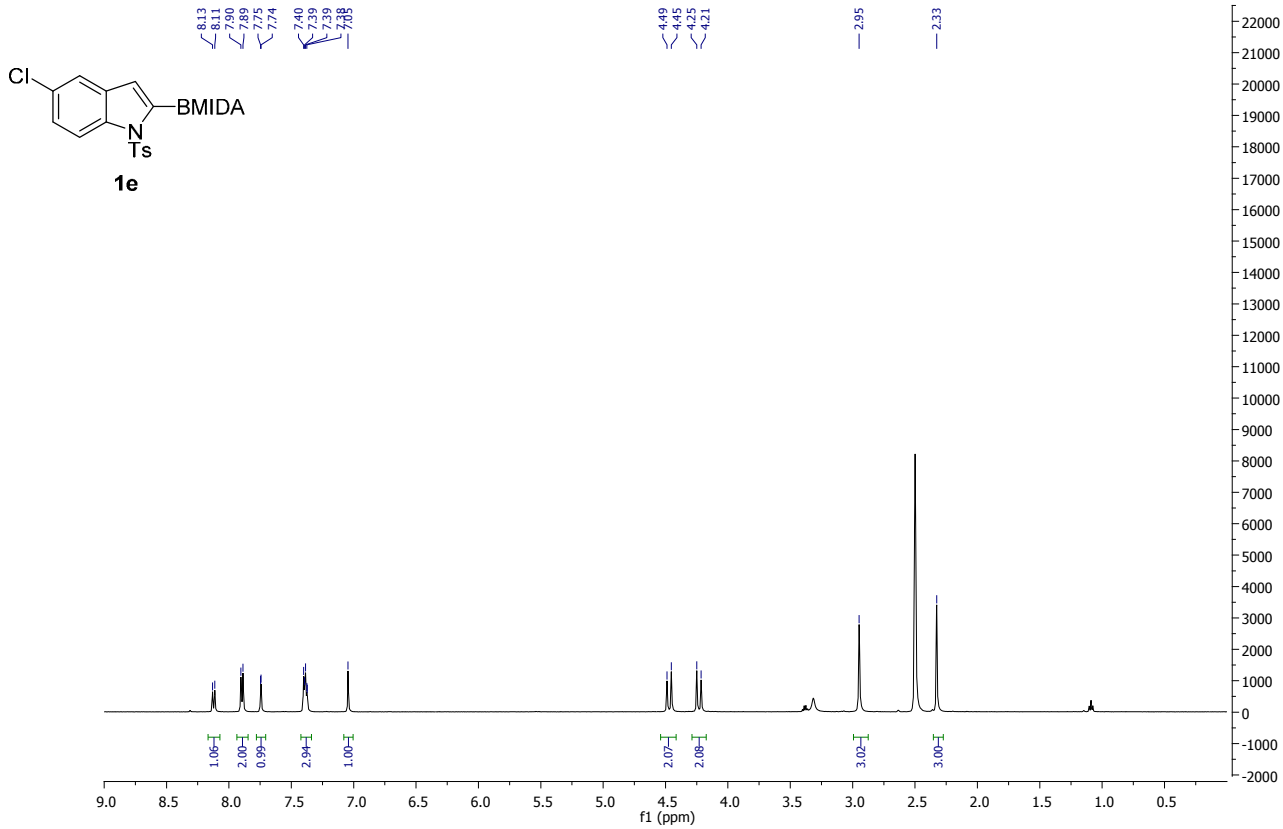
υ_{max} (solid): 2960, 2926, 2855, 1763, 1617, 1532, 1464, 1340, 1299 cm^{-1}.
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.01 (d, *J* = 9.1 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.00–6.94 (m, 2H), 4.46 (d, *J* = 17.5 Hz, 2H), 4.23 (d, *J* = 17.4 Hz, 2H), 3.76 (s, 3H), 2.96 (s, 3H), 2.33 (s, 3H).
^{13}C NMR (DMSO-d_6, 101 MHz): δ 168.9, 155.8, 144.9, 134.8, 132.9, 130.5, 129.6, 126.3, 121.6, 114.9, 114.0, 103.3, 64.0, 55.2, 49.2, 20.8. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.33.
HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{21}H_{25}BN_3O_7S$) requires *m/z* 474.1505, found *m/z* 474.1497.

5. References

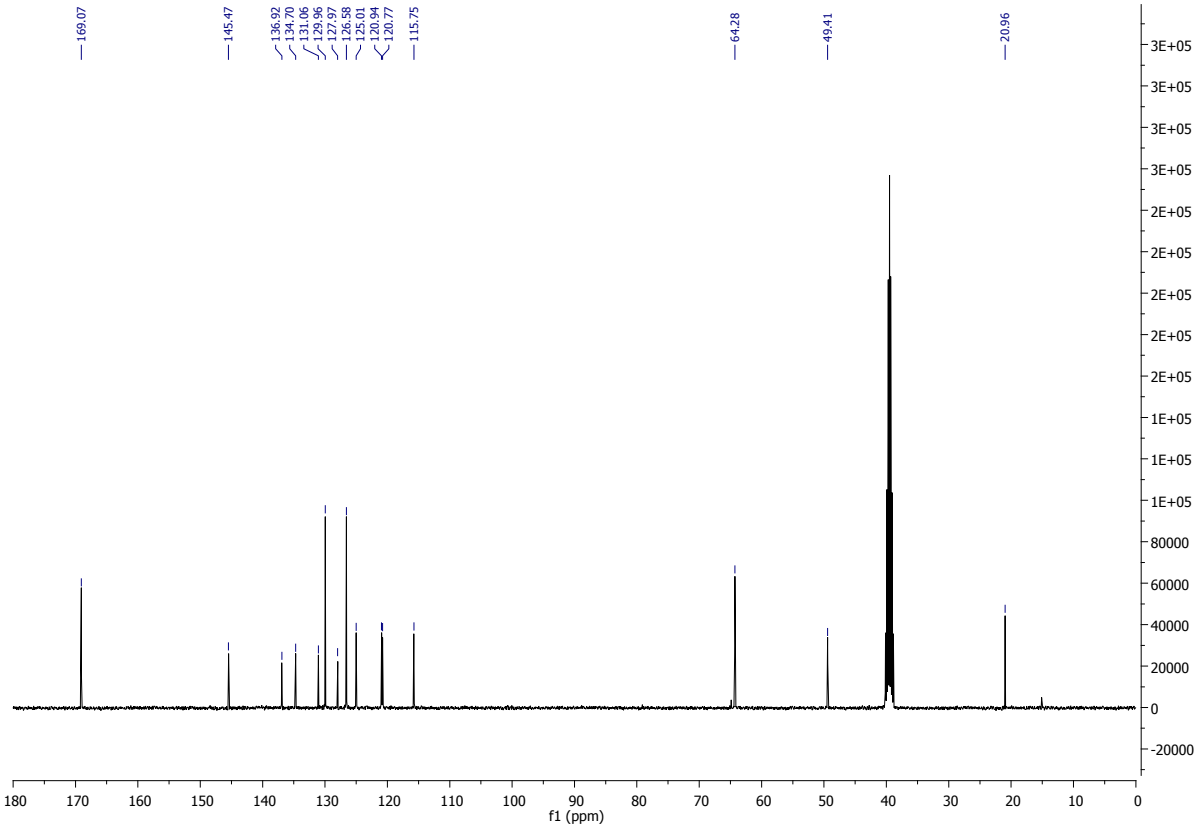
1. W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals, 7th ed.*, Elsevier, Oxford, 2013.

6. NMR and HRMS spectra for intermediates and products

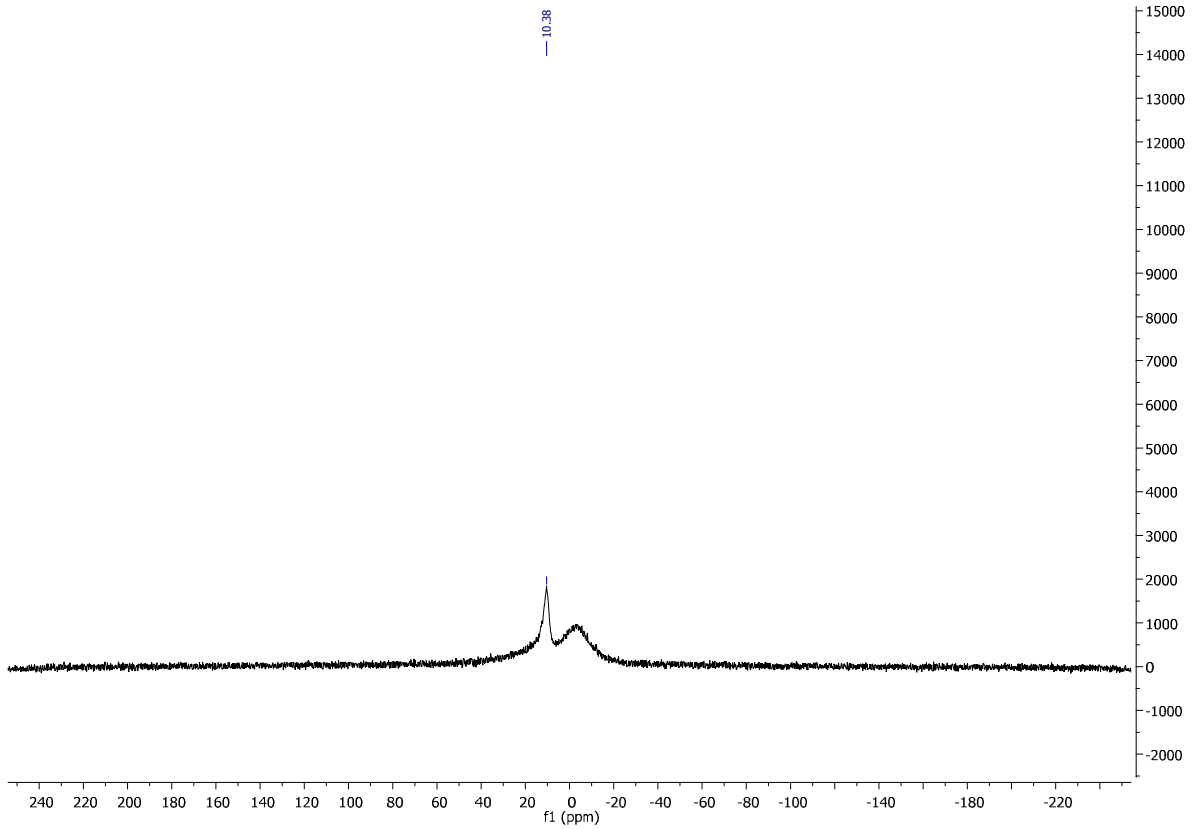
^{1}H NMR of 1e



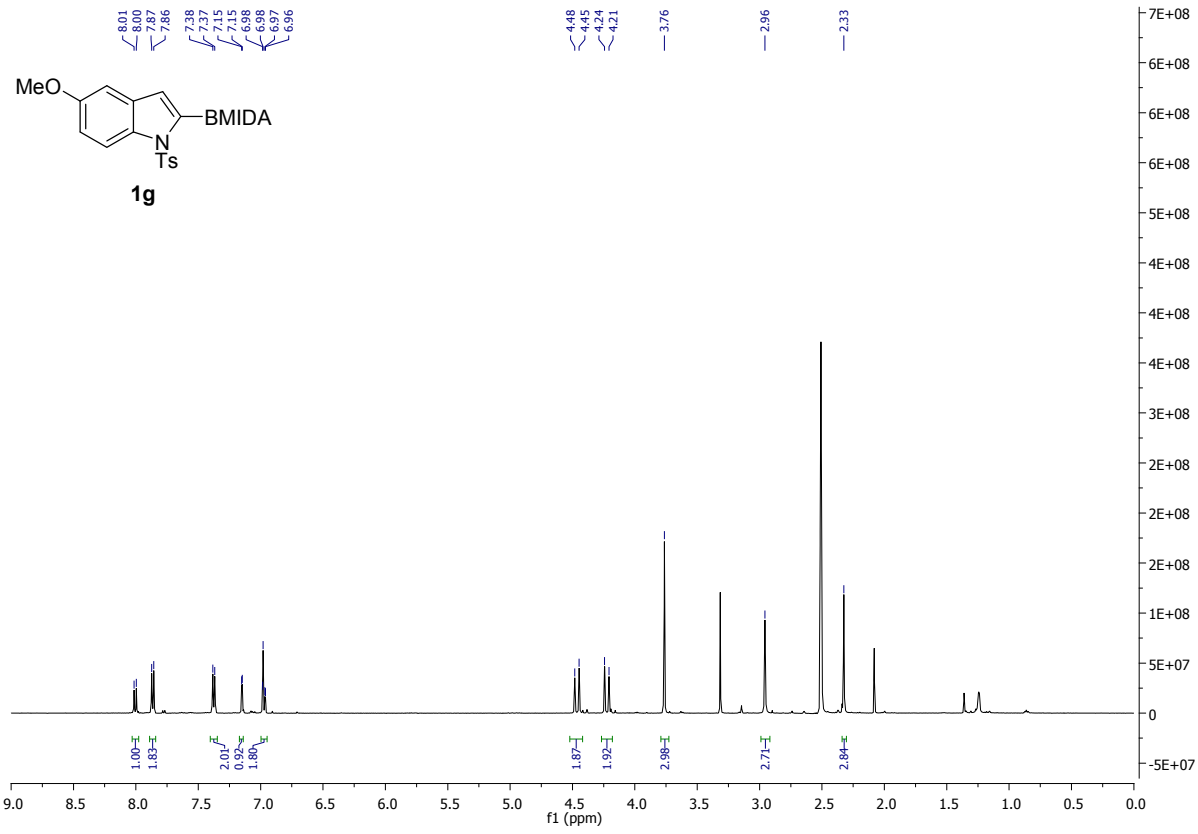
^{13}C NMR of 1e



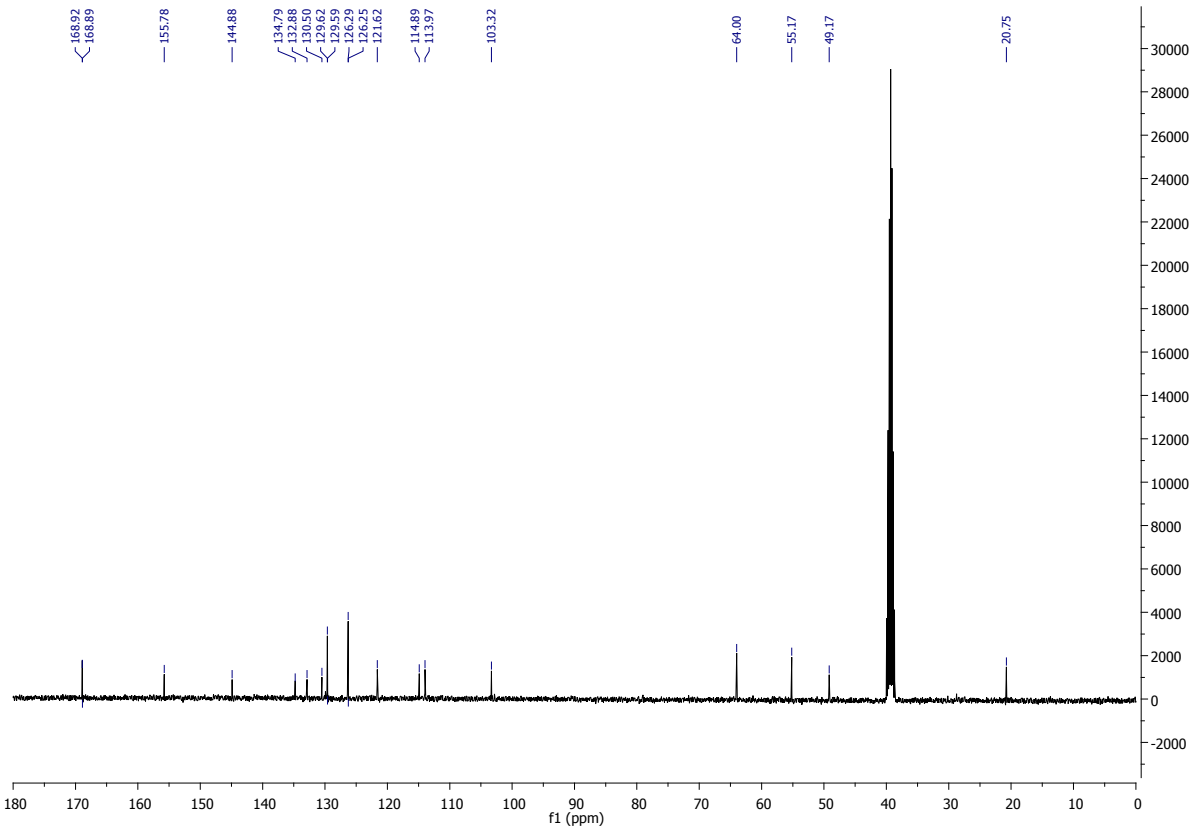
^{11}B NMR of 1e



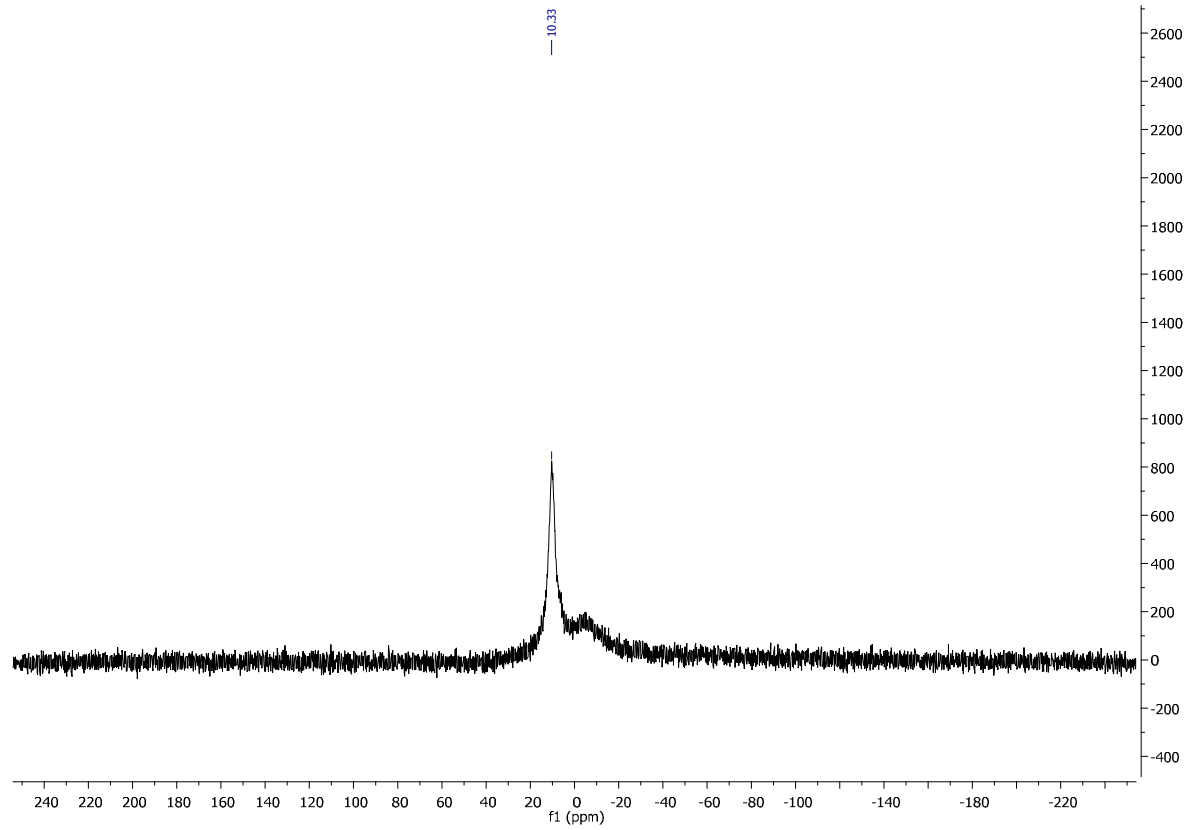
^{1}H NMR of 1g



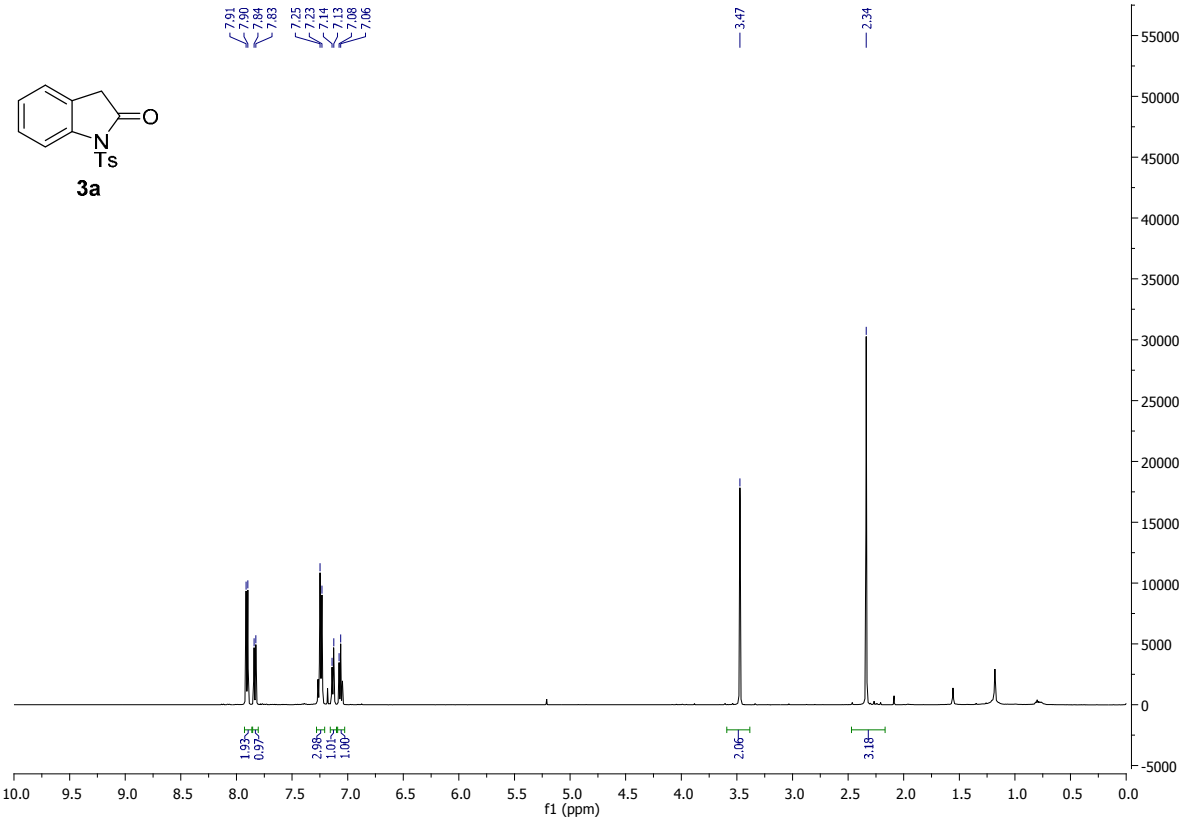
^{13}C NMR of 1g



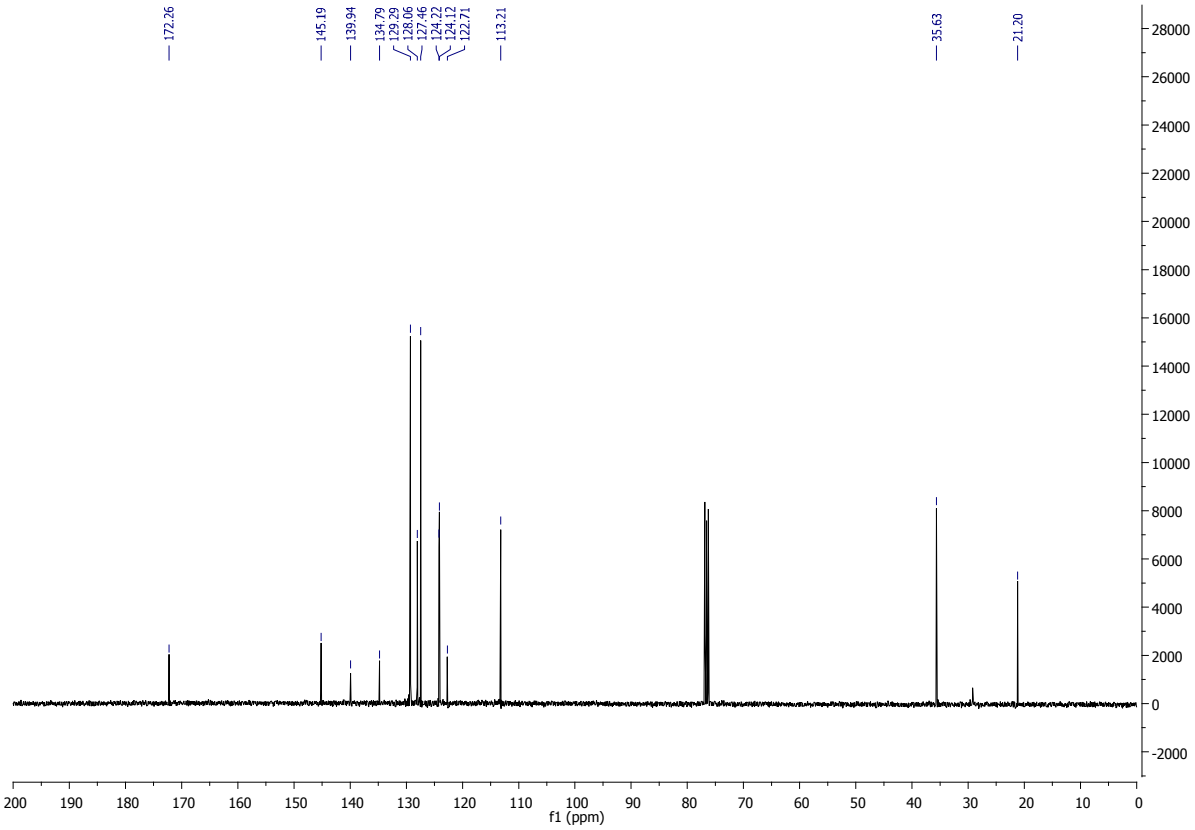
^{11}B NMR of 1g



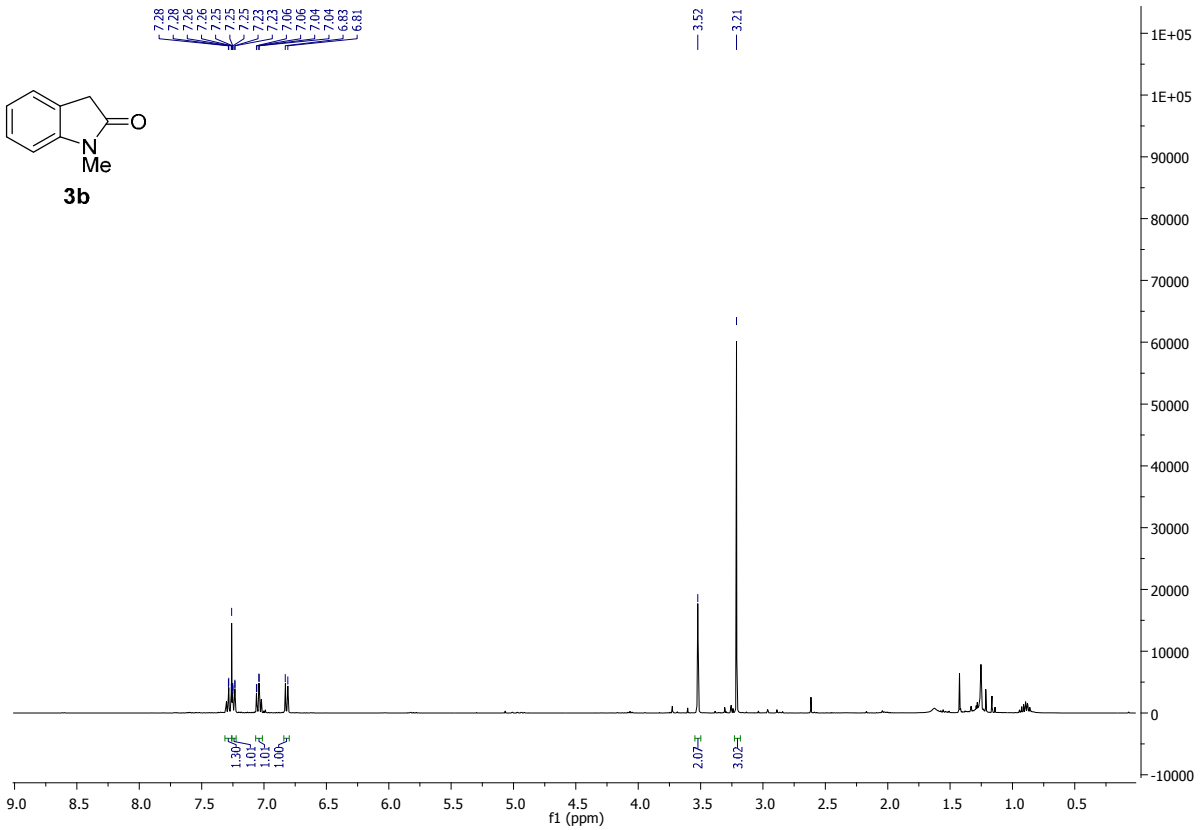
^{1}H NMR of 3a



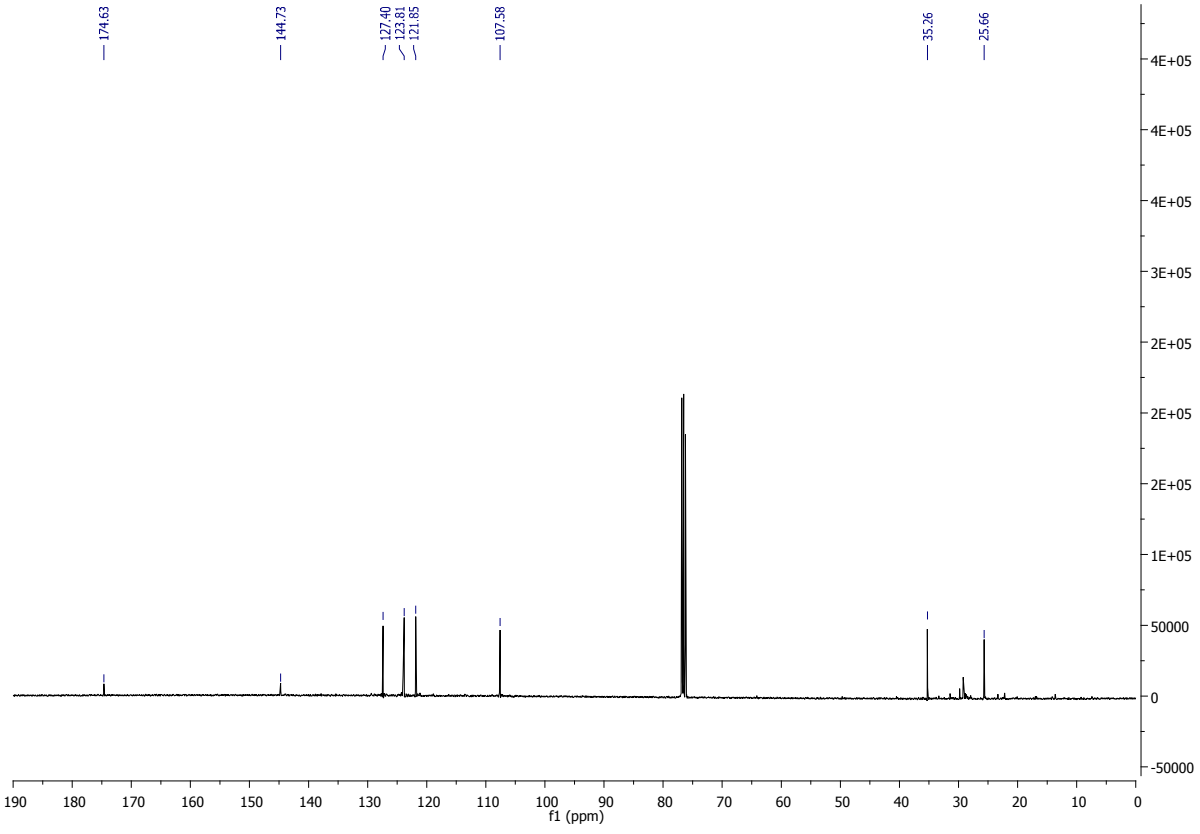
^{13}C NMR of 3a



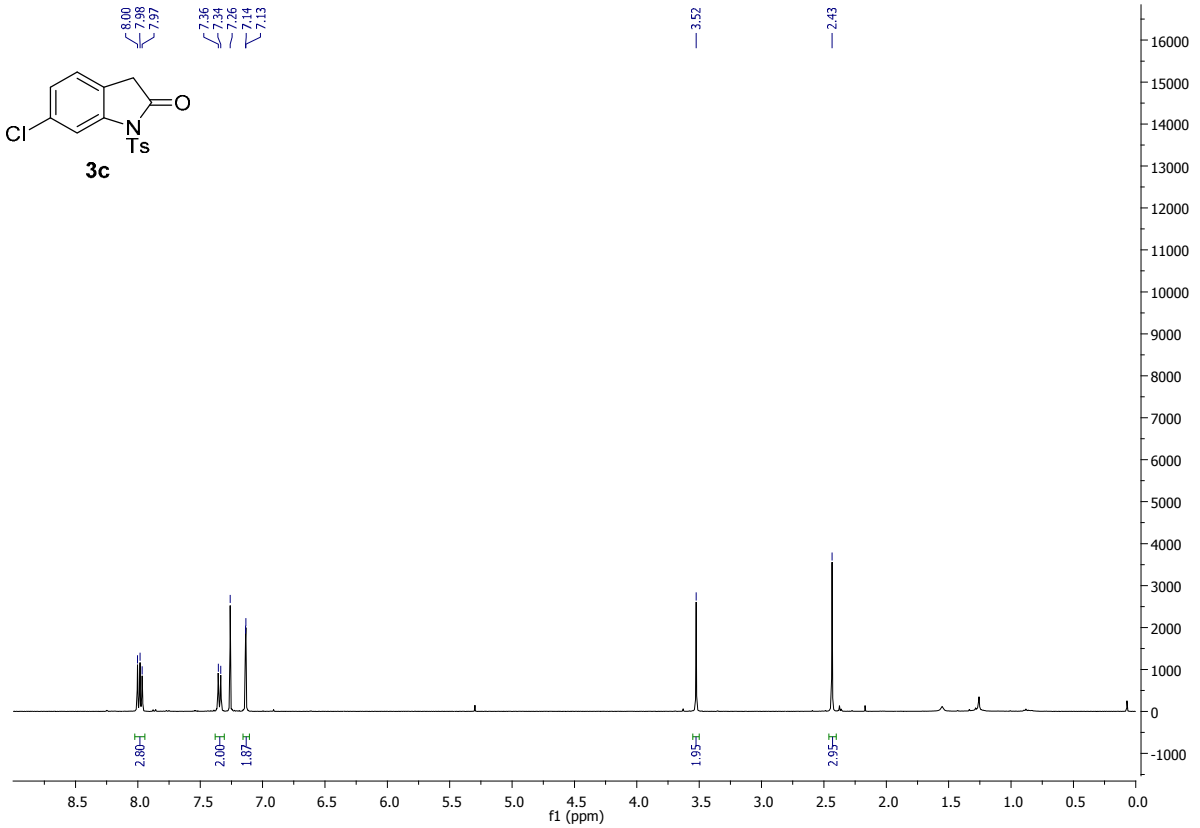
^{1}H NMR of 3b



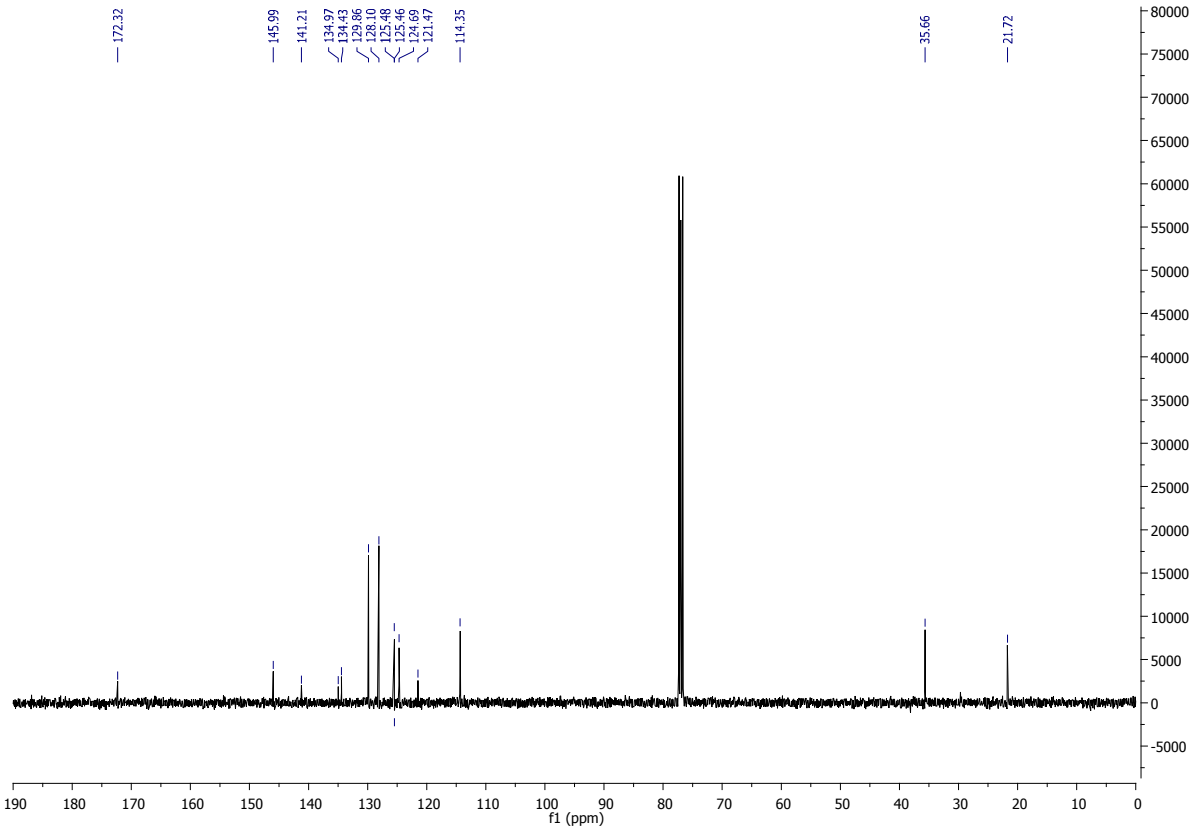
^{13}C NMR of 3b



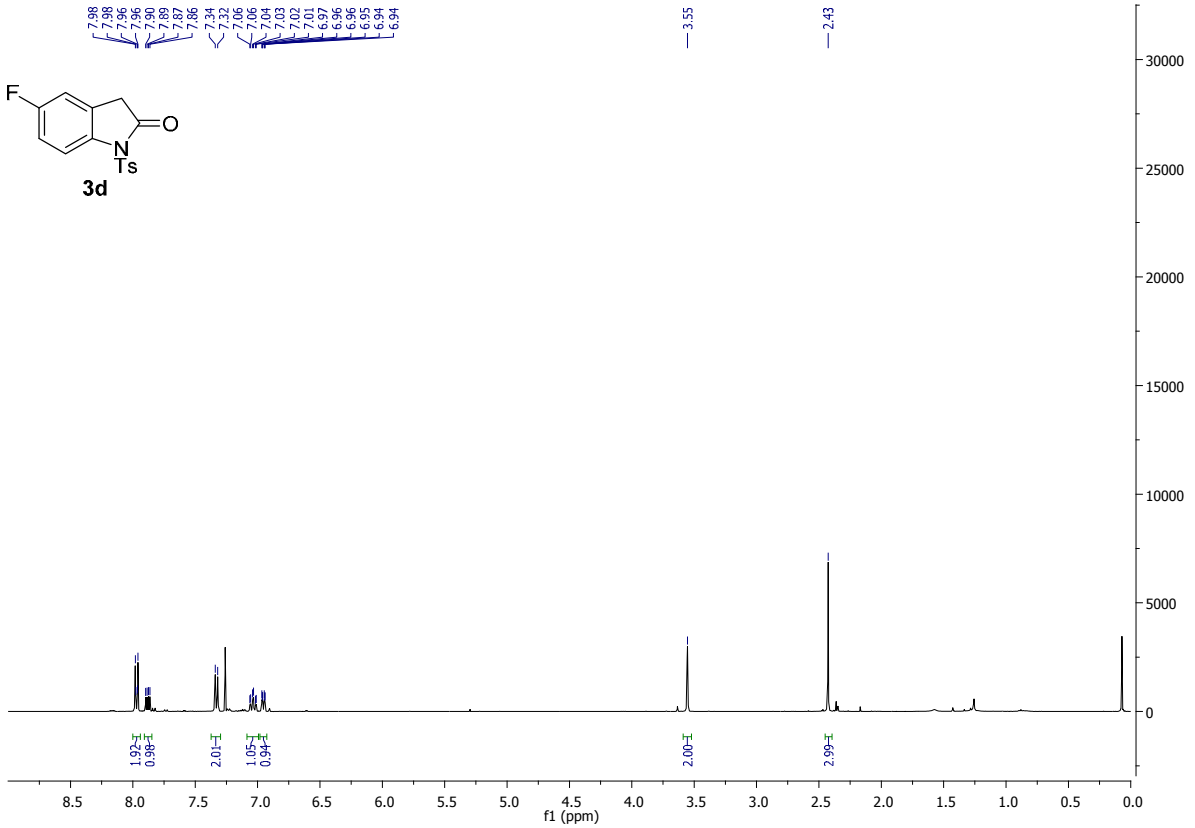
^{1}H NMR of 3c



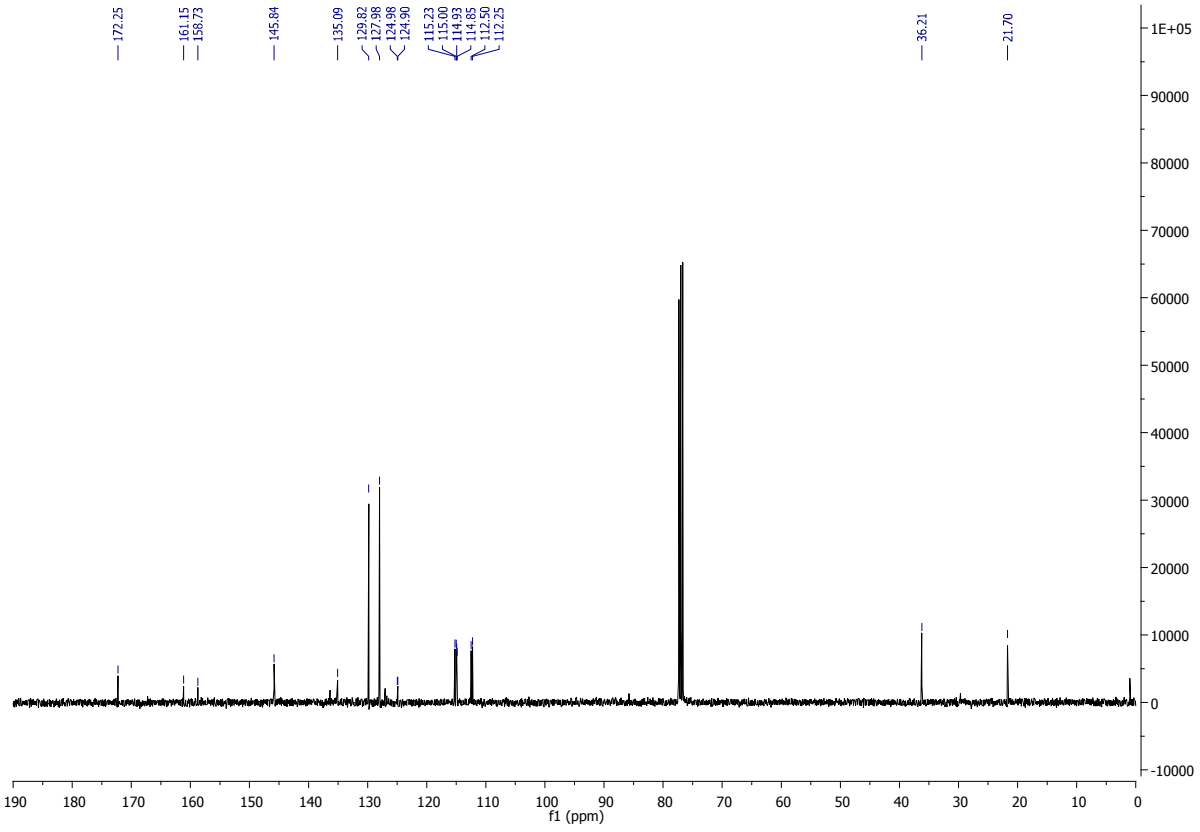
^{13}C NMR of 3c



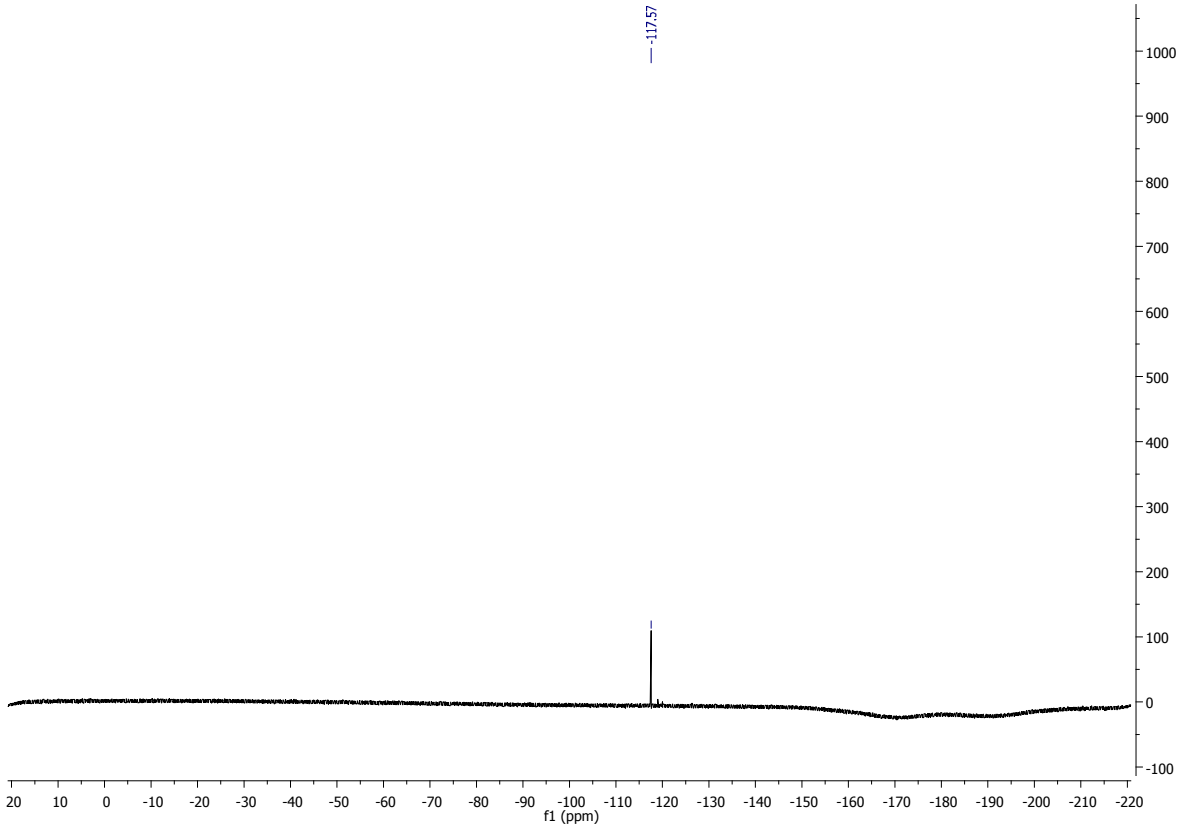
^{1}H NMR of 3d



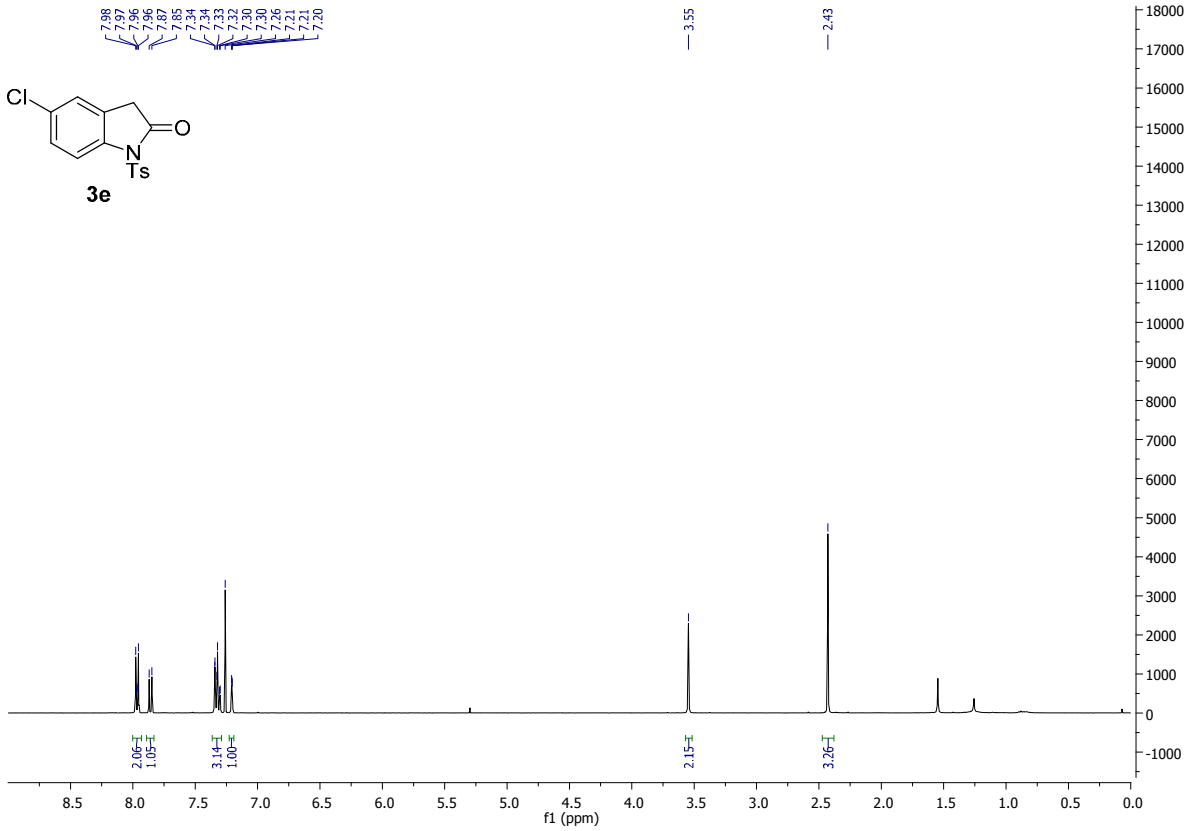
^{13}C NMR of 3d



^{19}F NMR of 3d

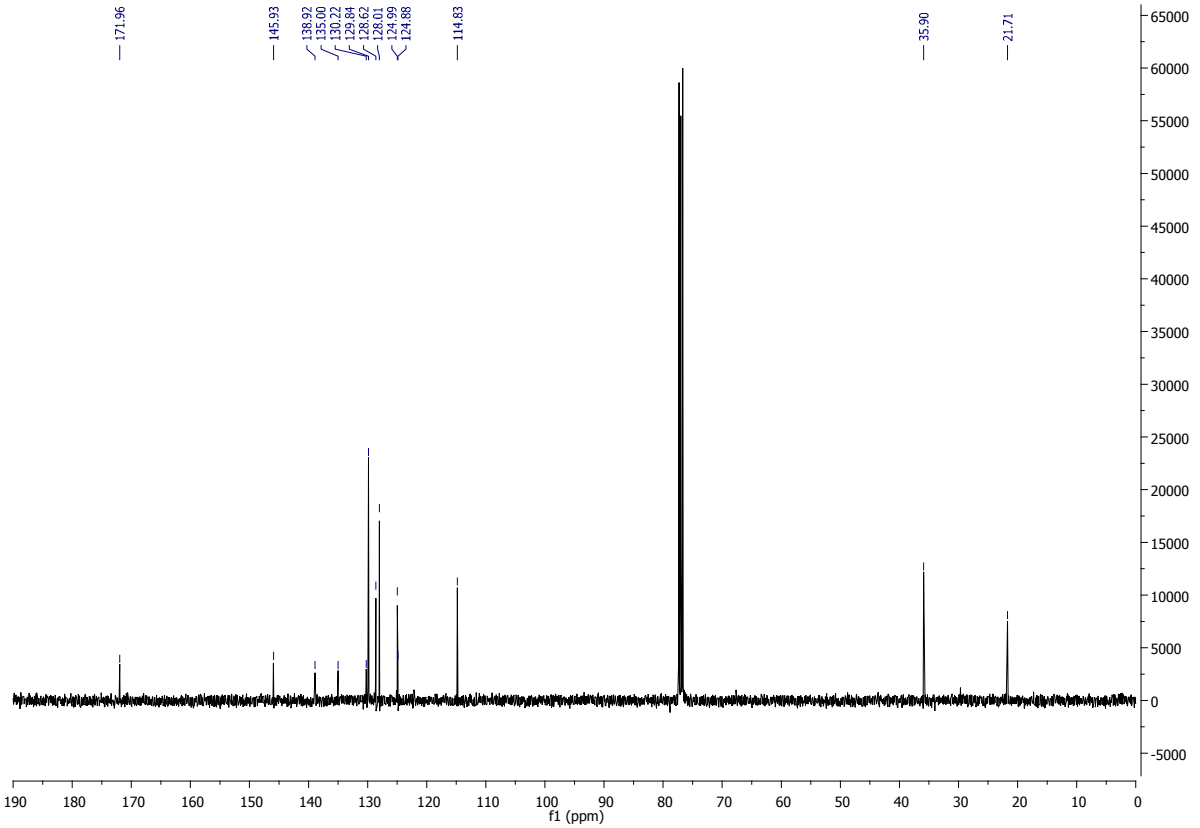


^{1}H NMR of 3e

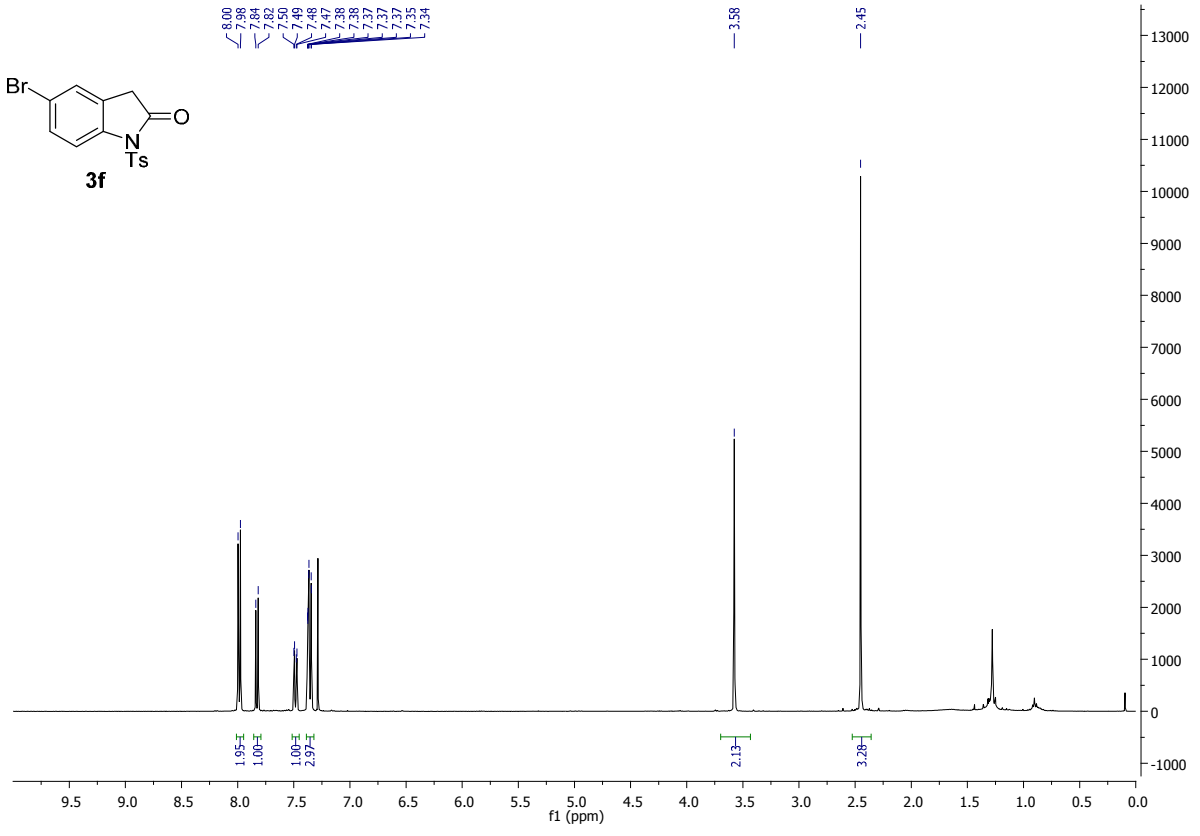


3e

^{13}C NMR of 3e

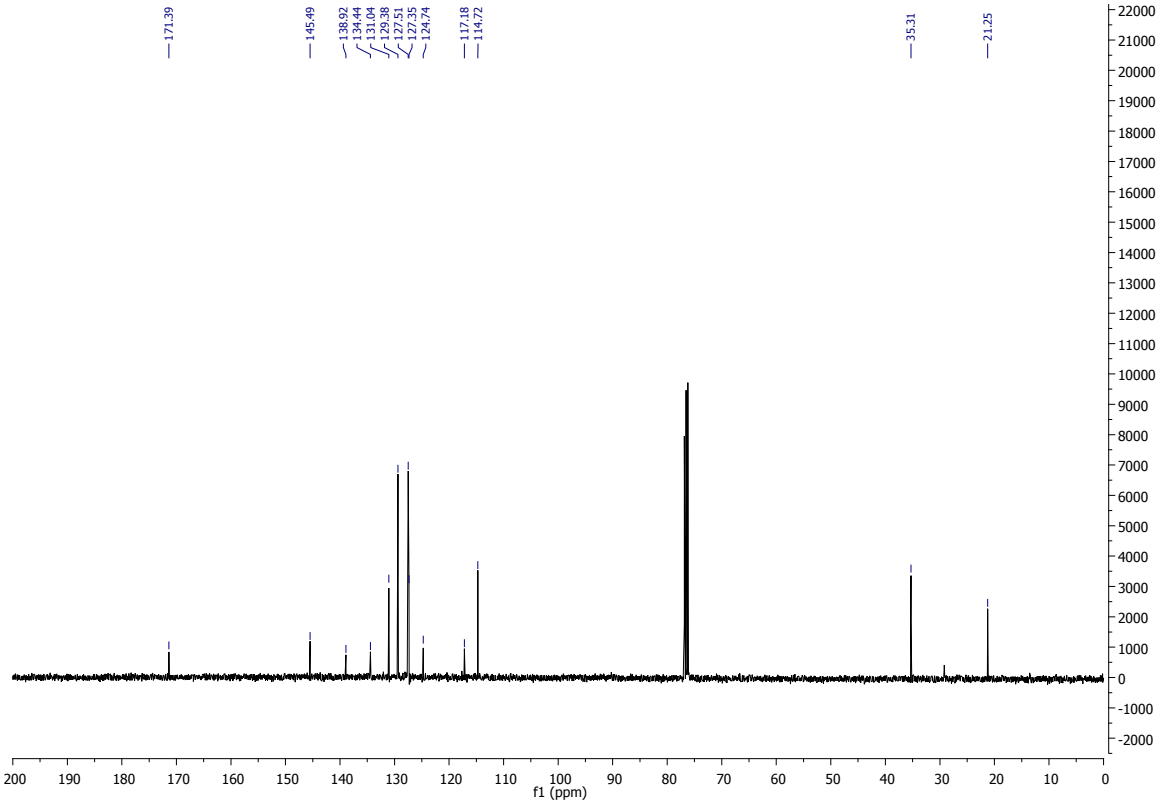


^{1}H NMR of 3f

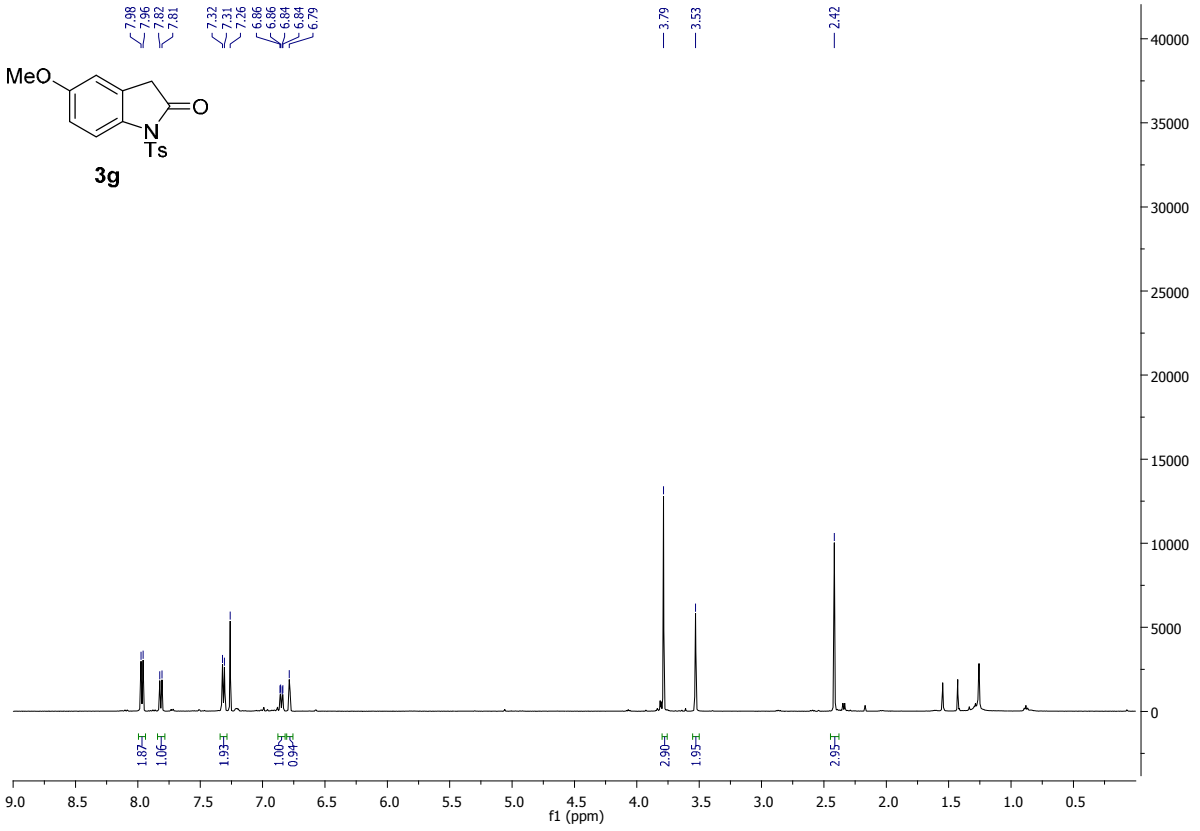


3f

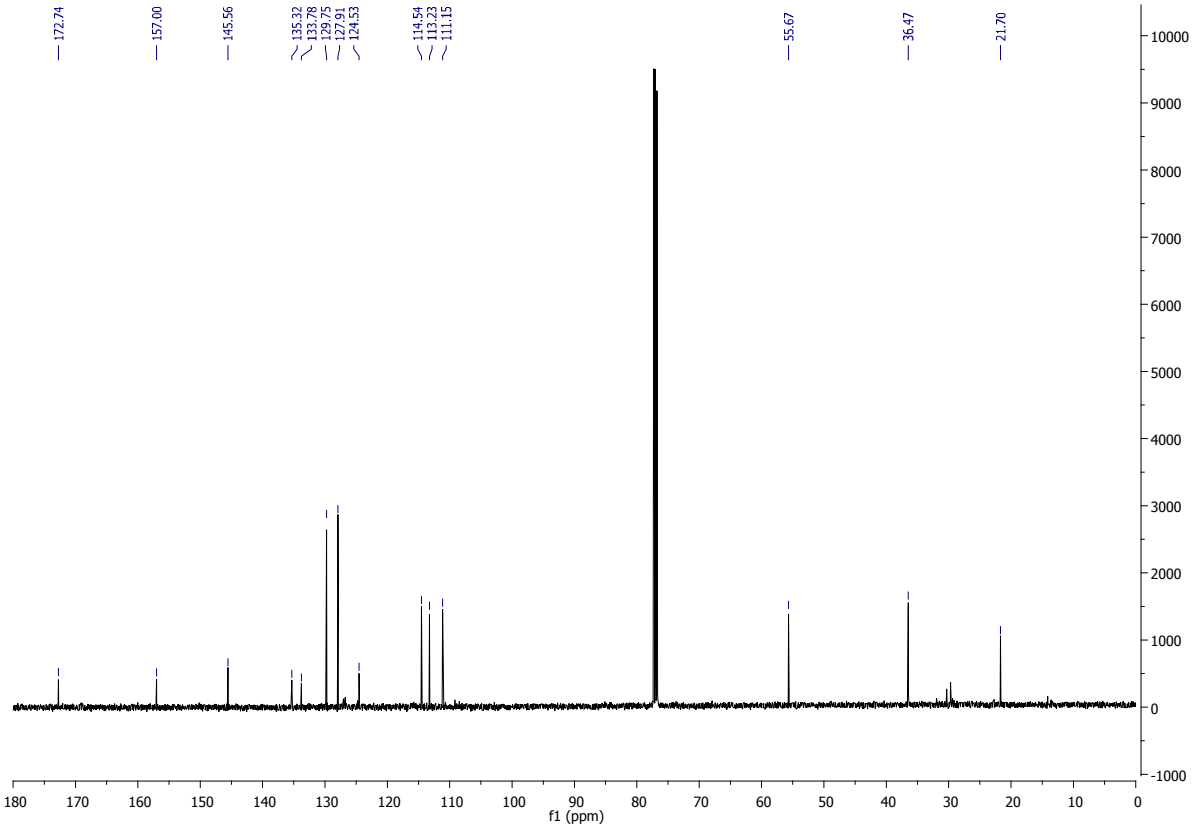
^{13}C NMR of 3f



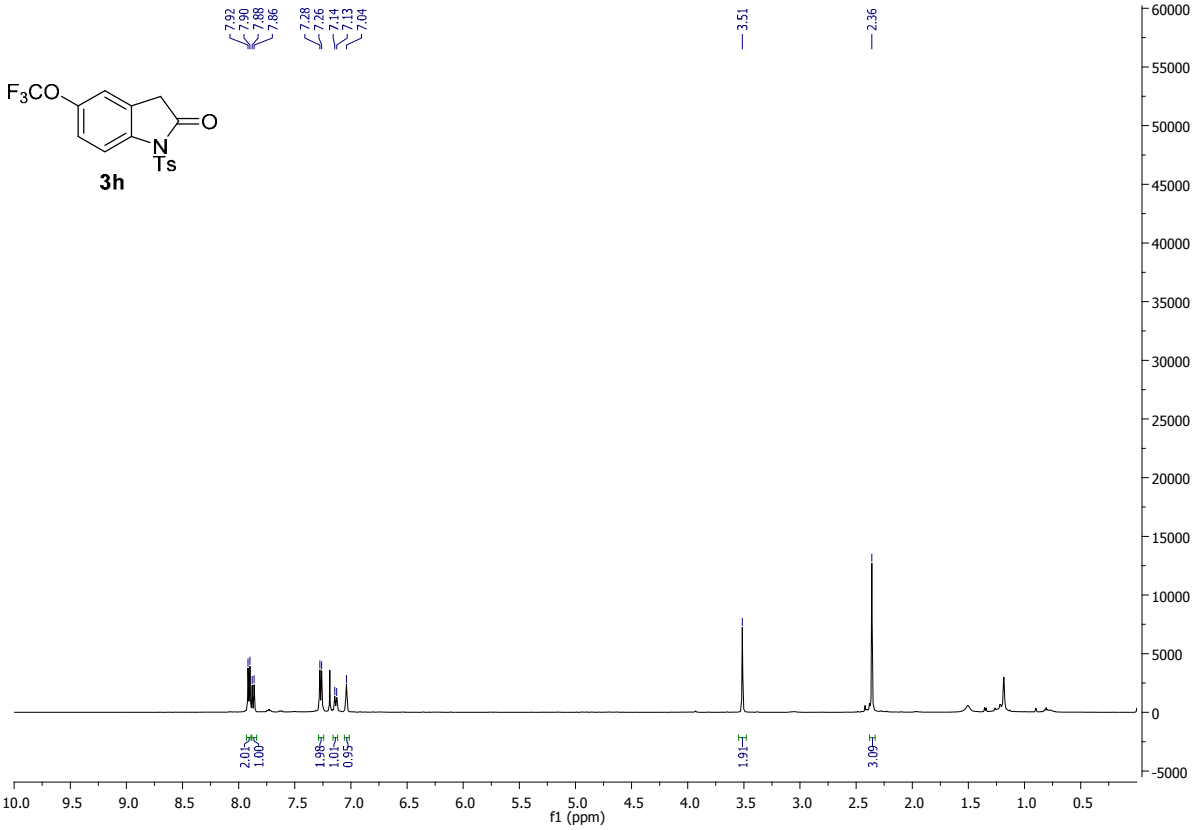
^{1}H NMR of 3g



^{13}C NMR of 3g

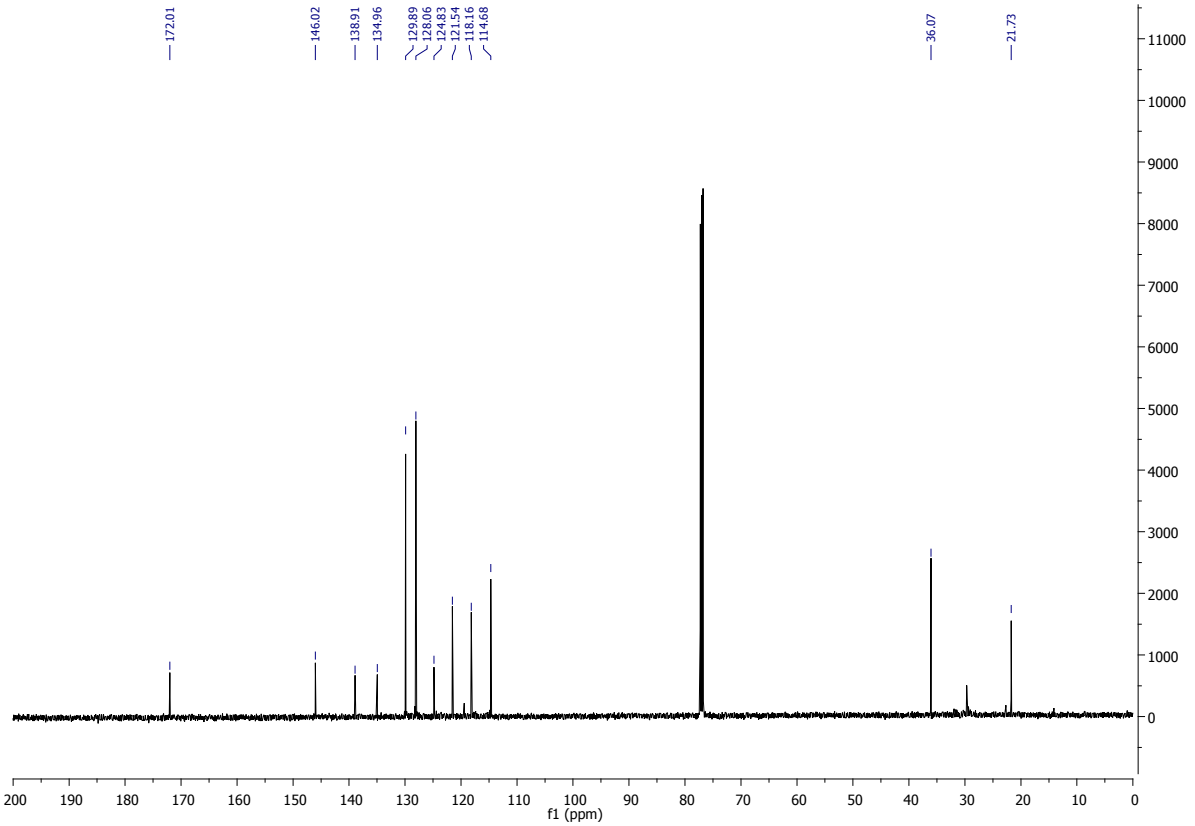


^{1}H NMR of 3h

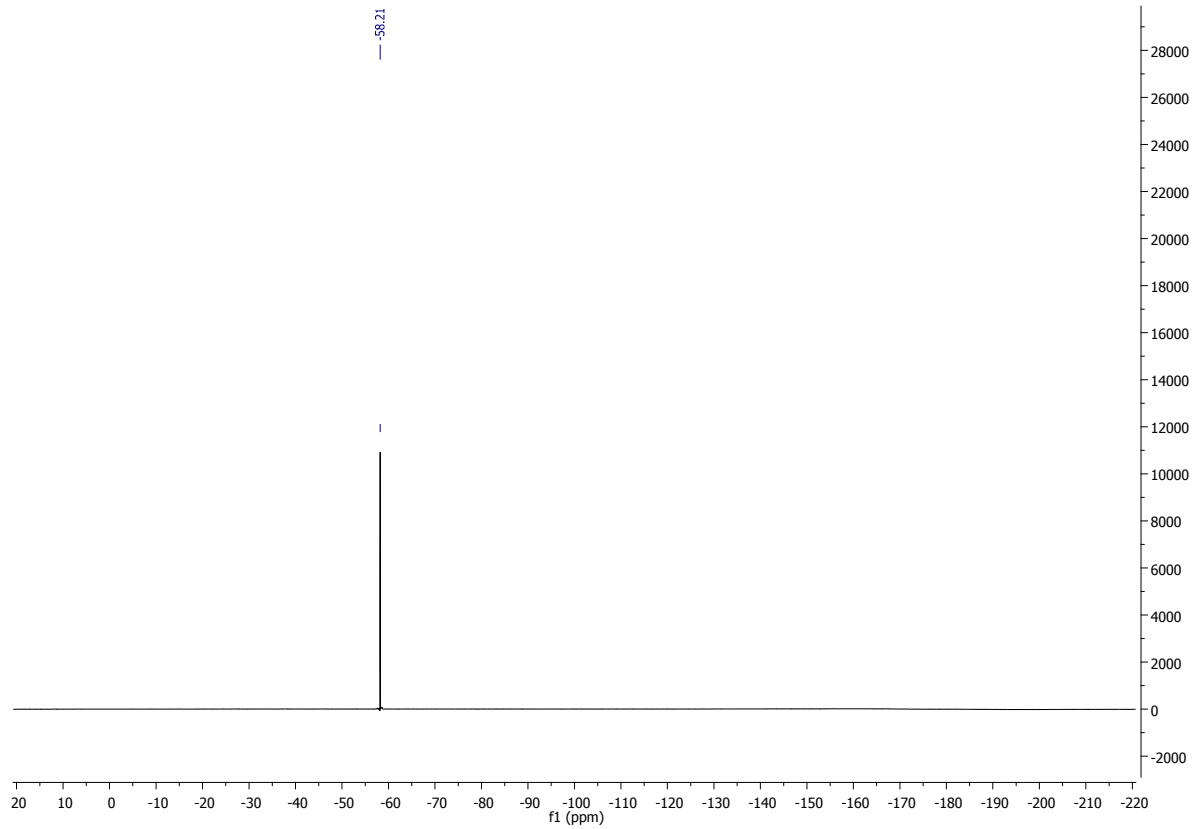


3h

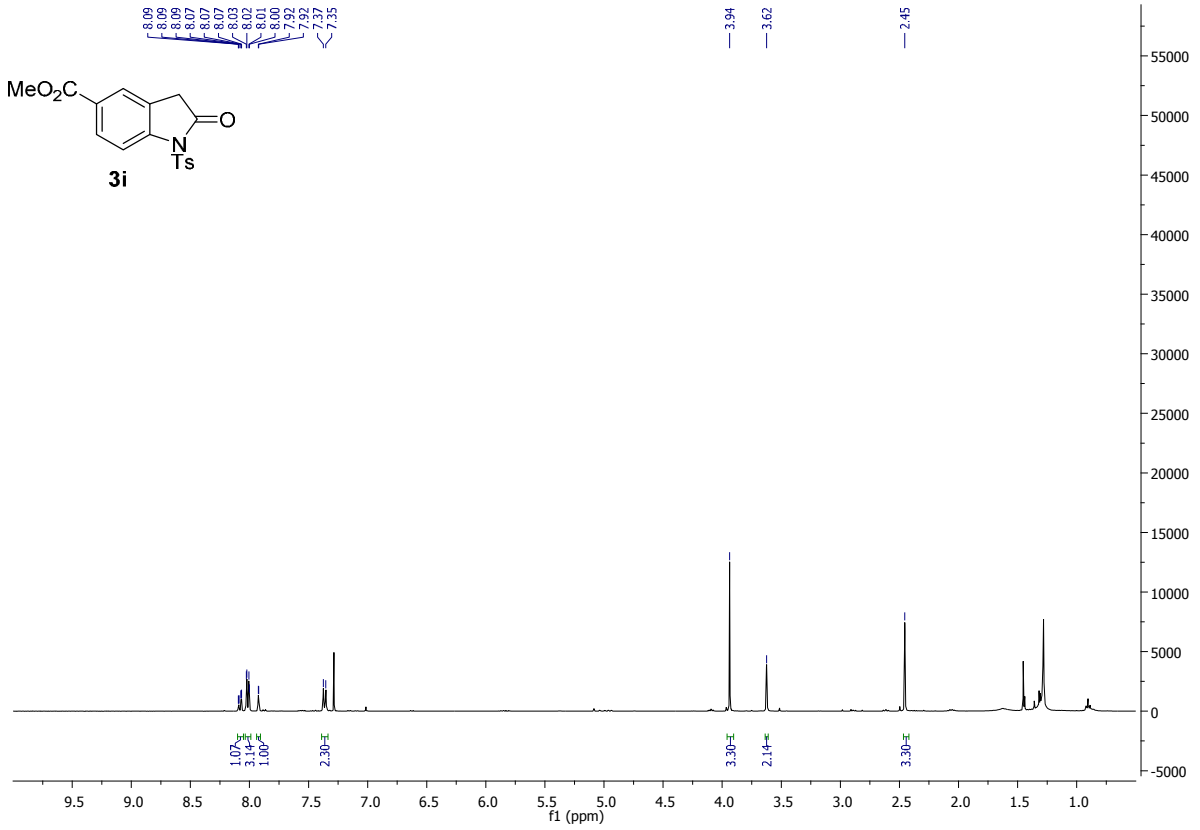
^{13}C NMR of 3h



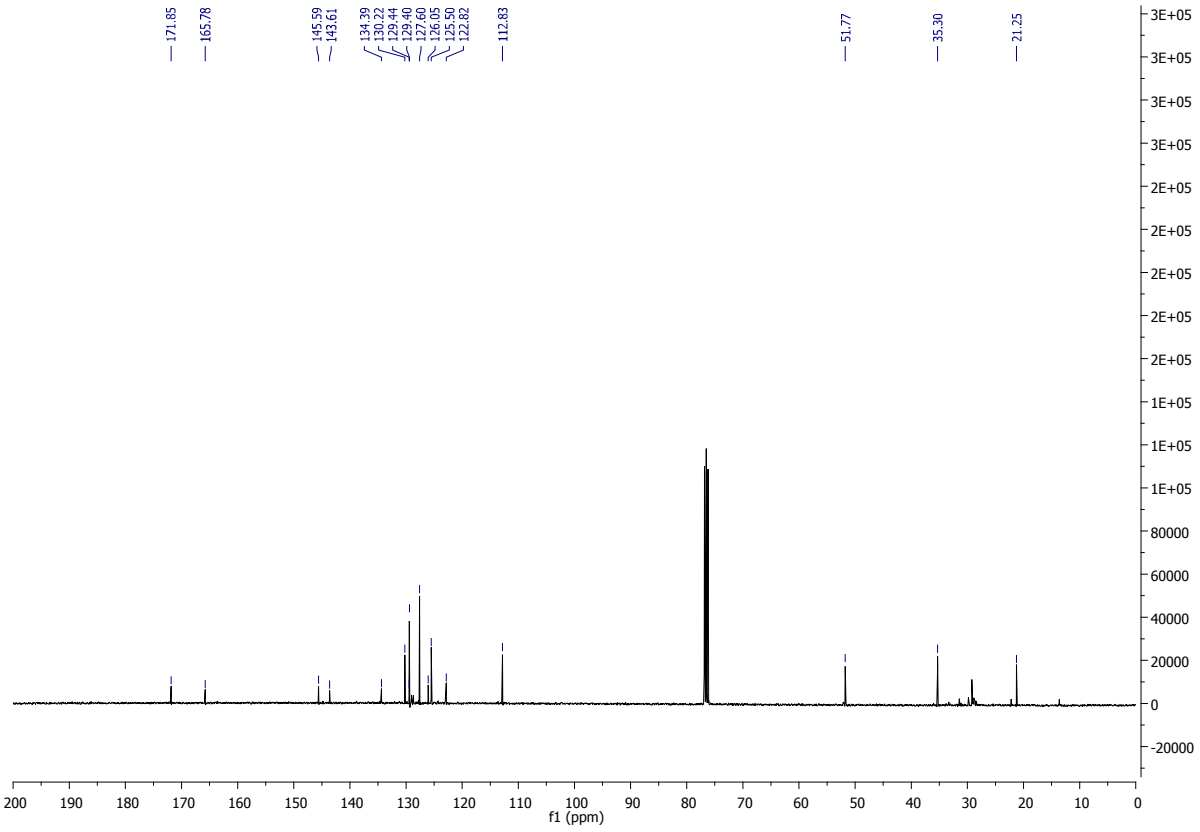
^{19}F NMR of 3h



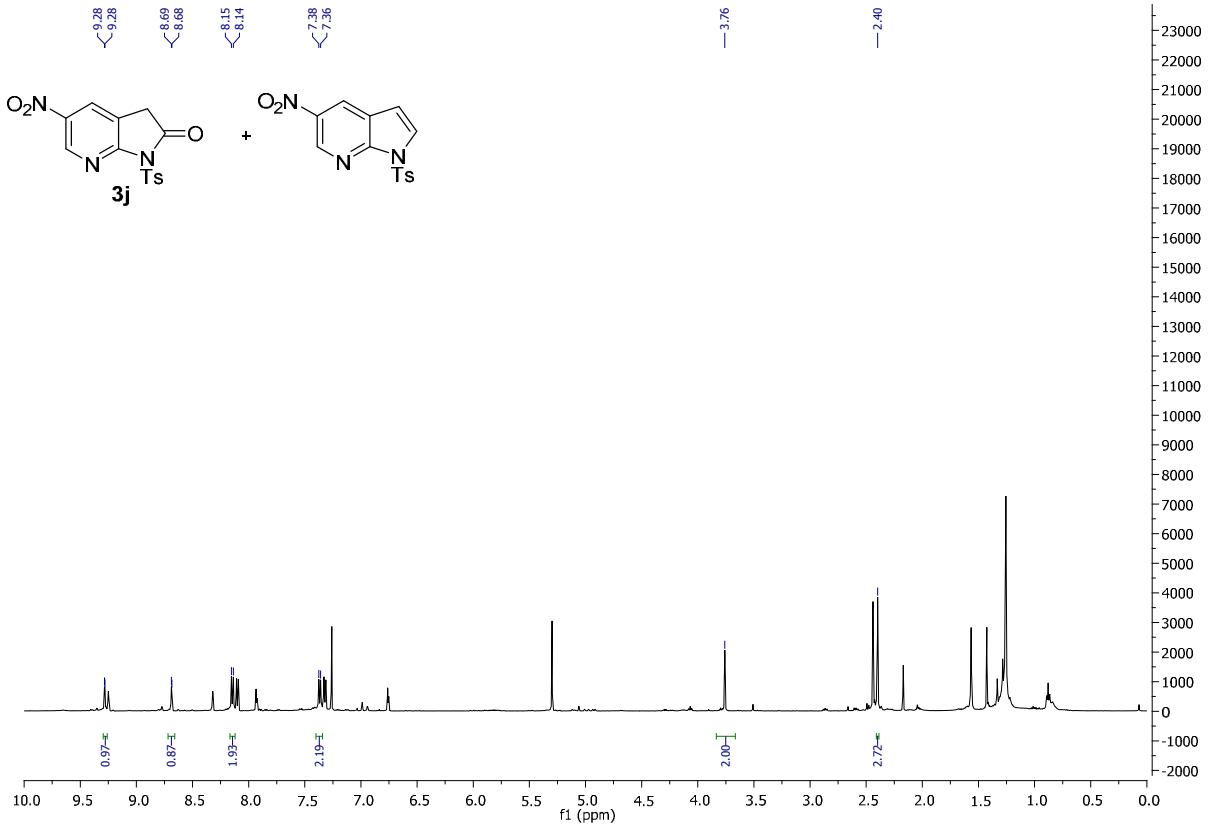
^{1}H NMR of 3i



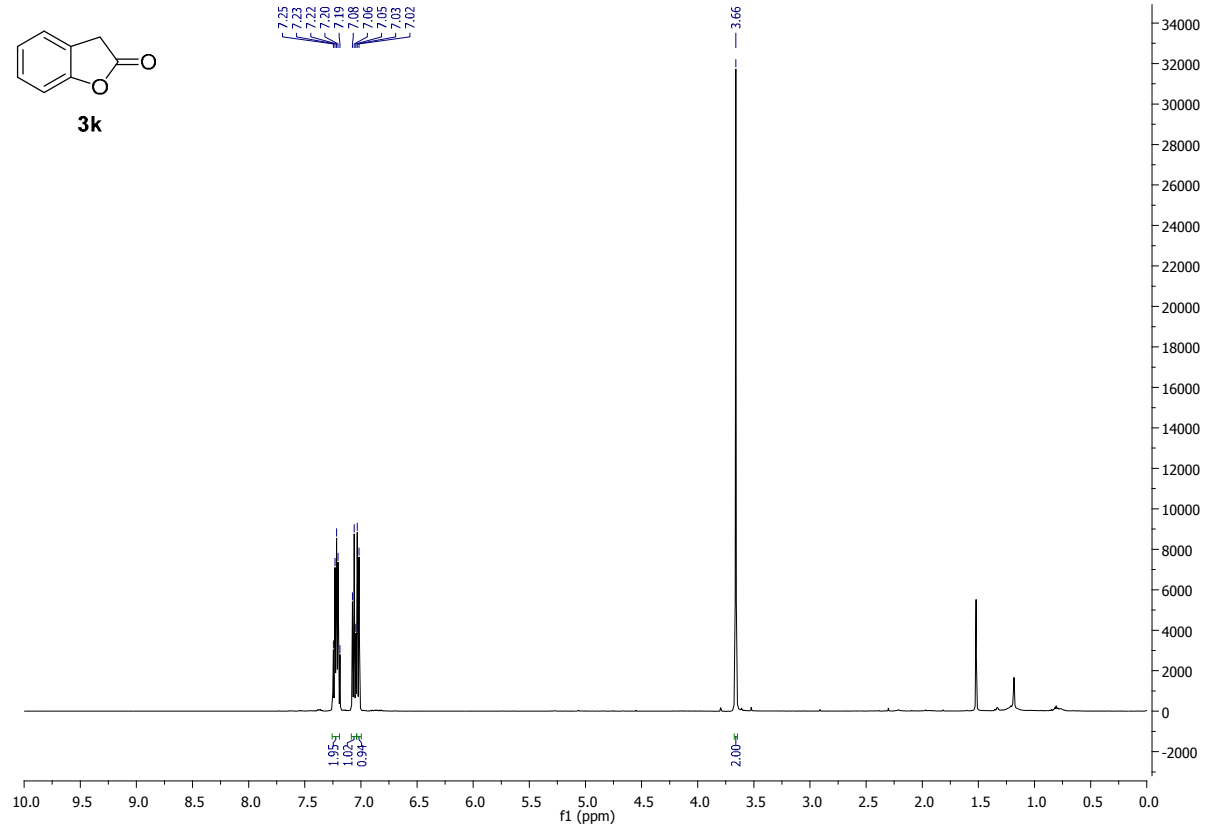
^{13}C NMR of 3i



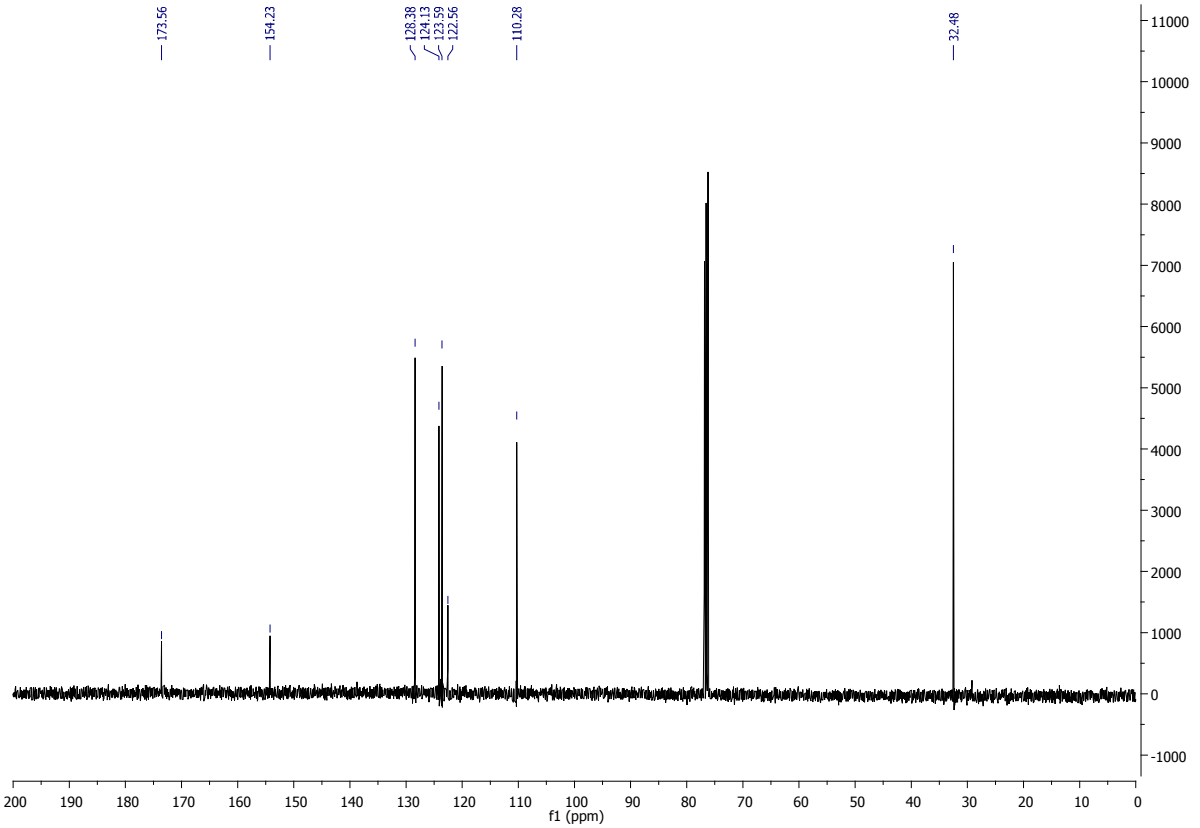
Crude ^{1}H NMR of 3j



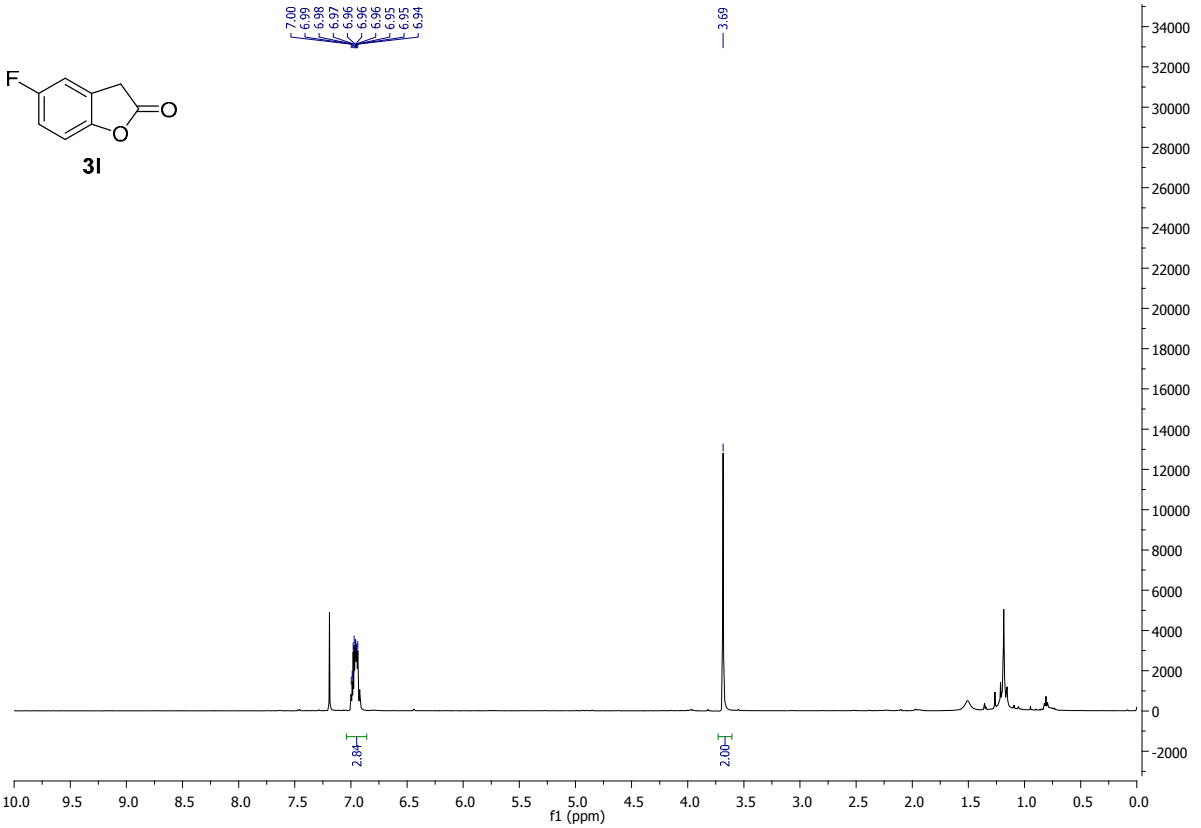
^{1}H NMR of 3k



^{13}C NMR of 3k

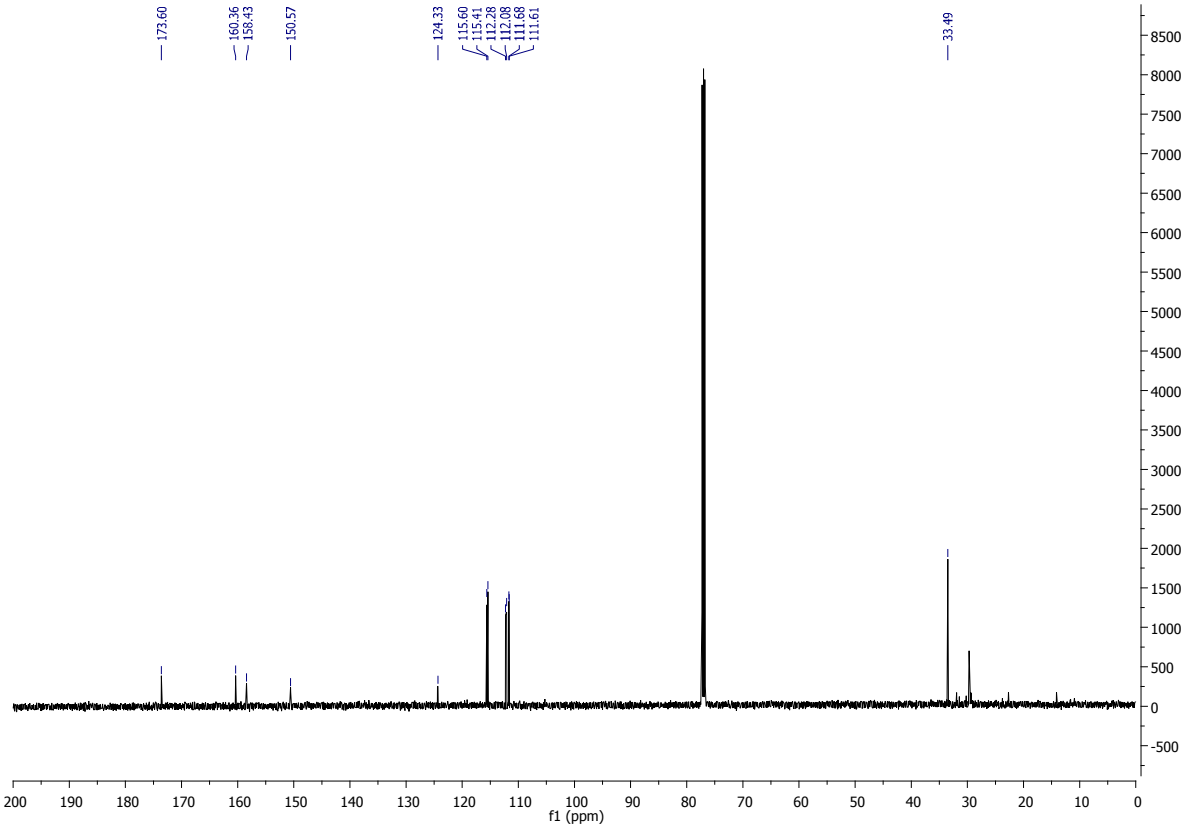


^{1}H NMR of 3l

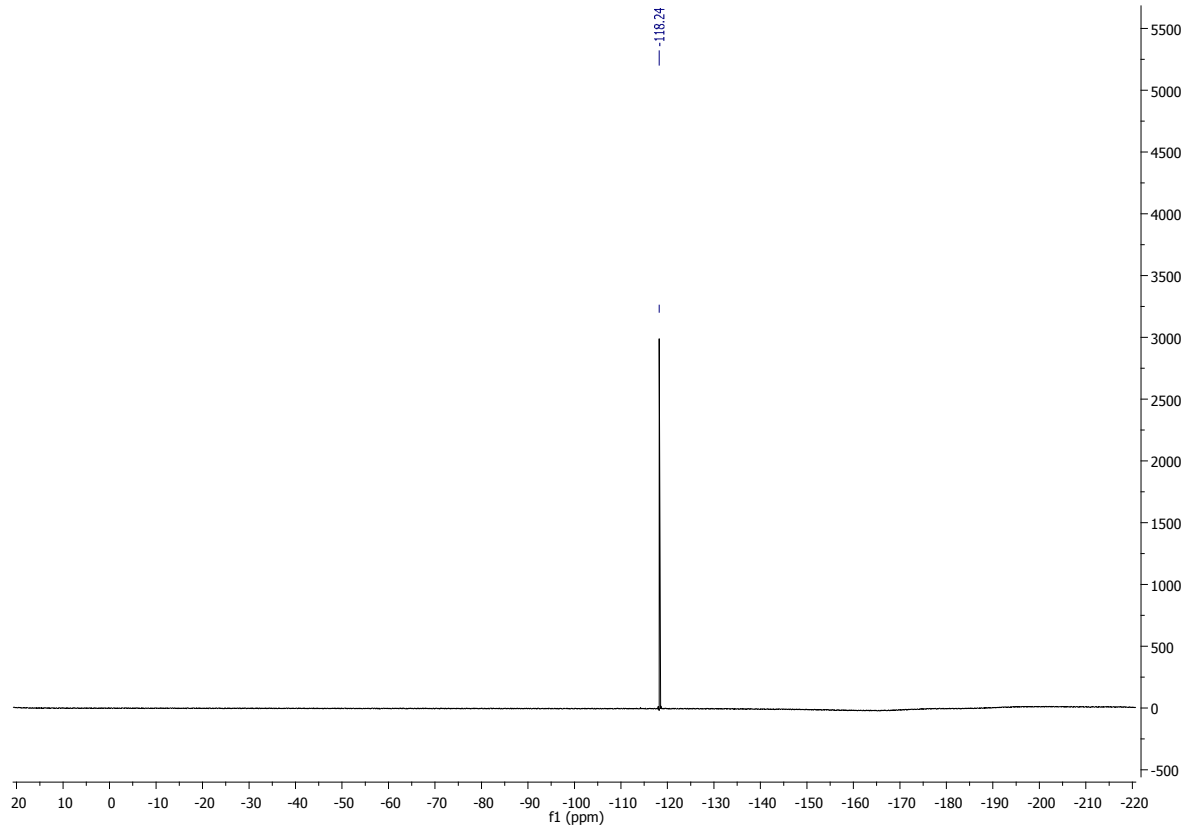


3l

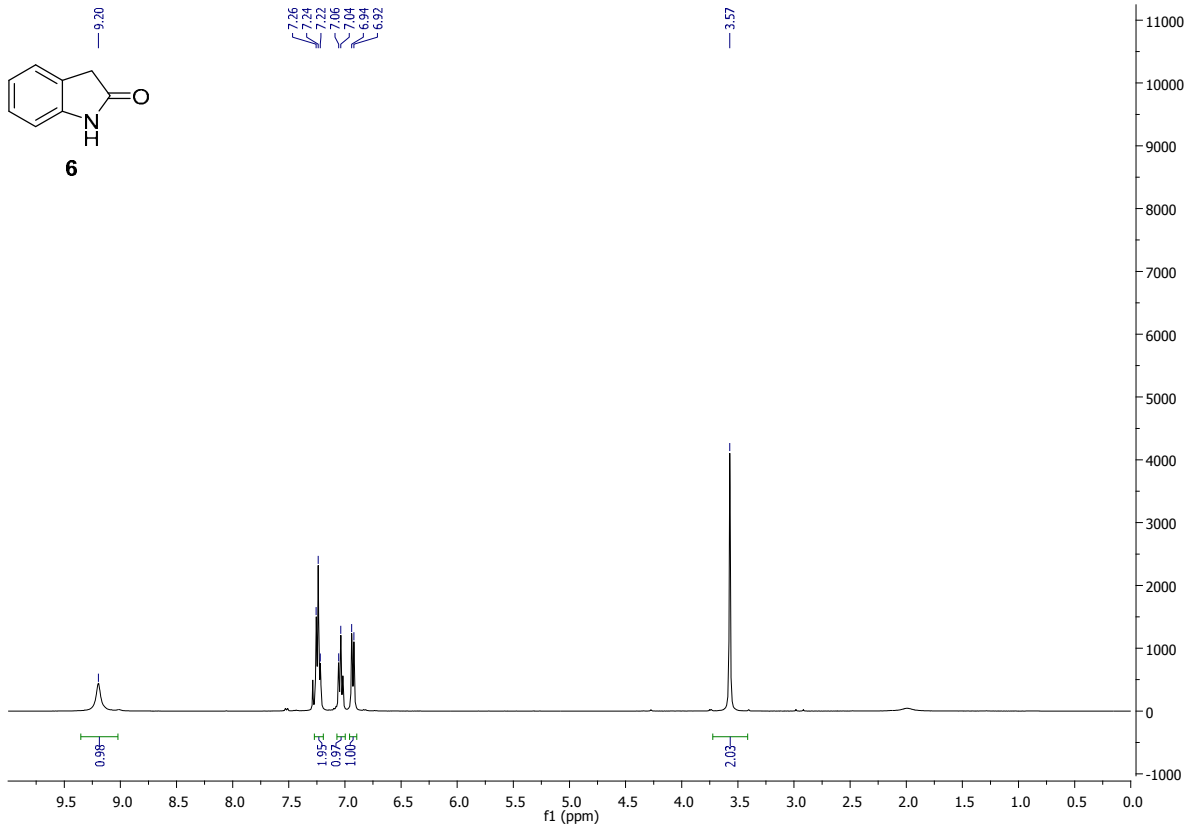
^{13}C NMR of 3l



^{19}F NMR of 3l

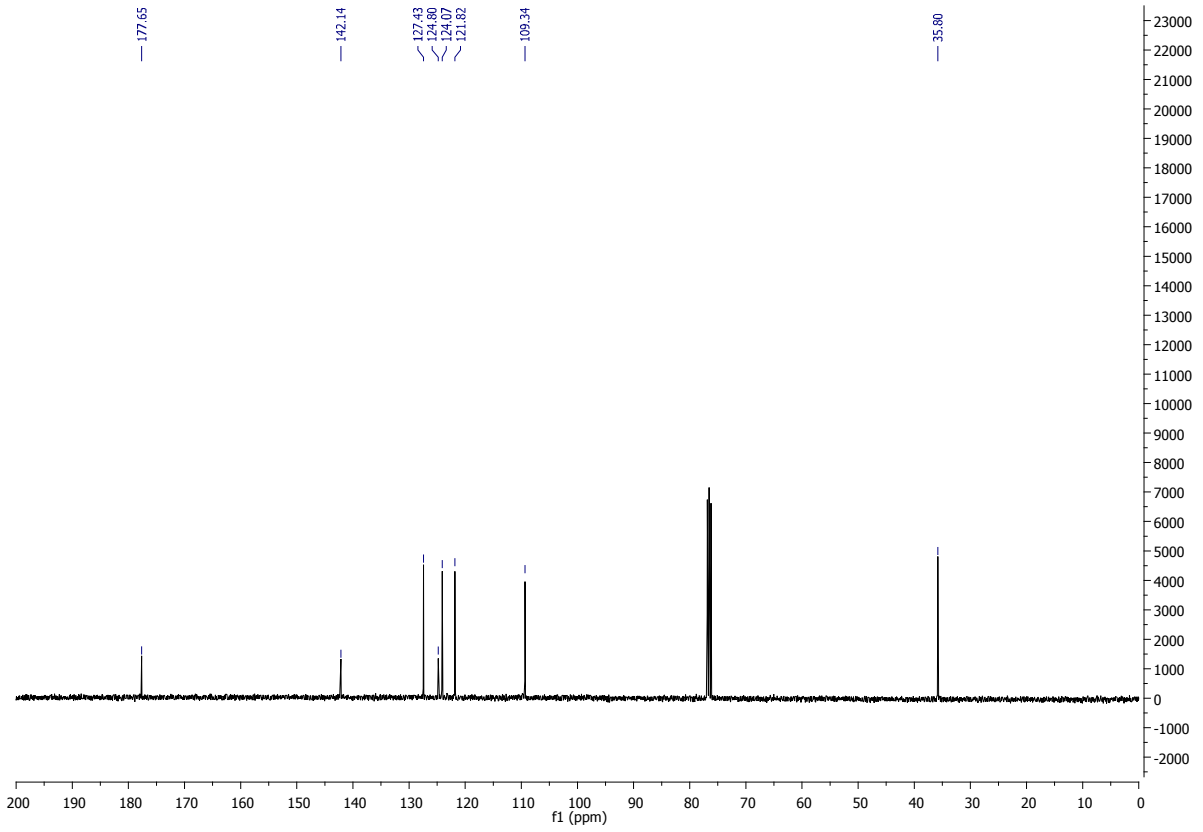


^{1}H NMR of 6

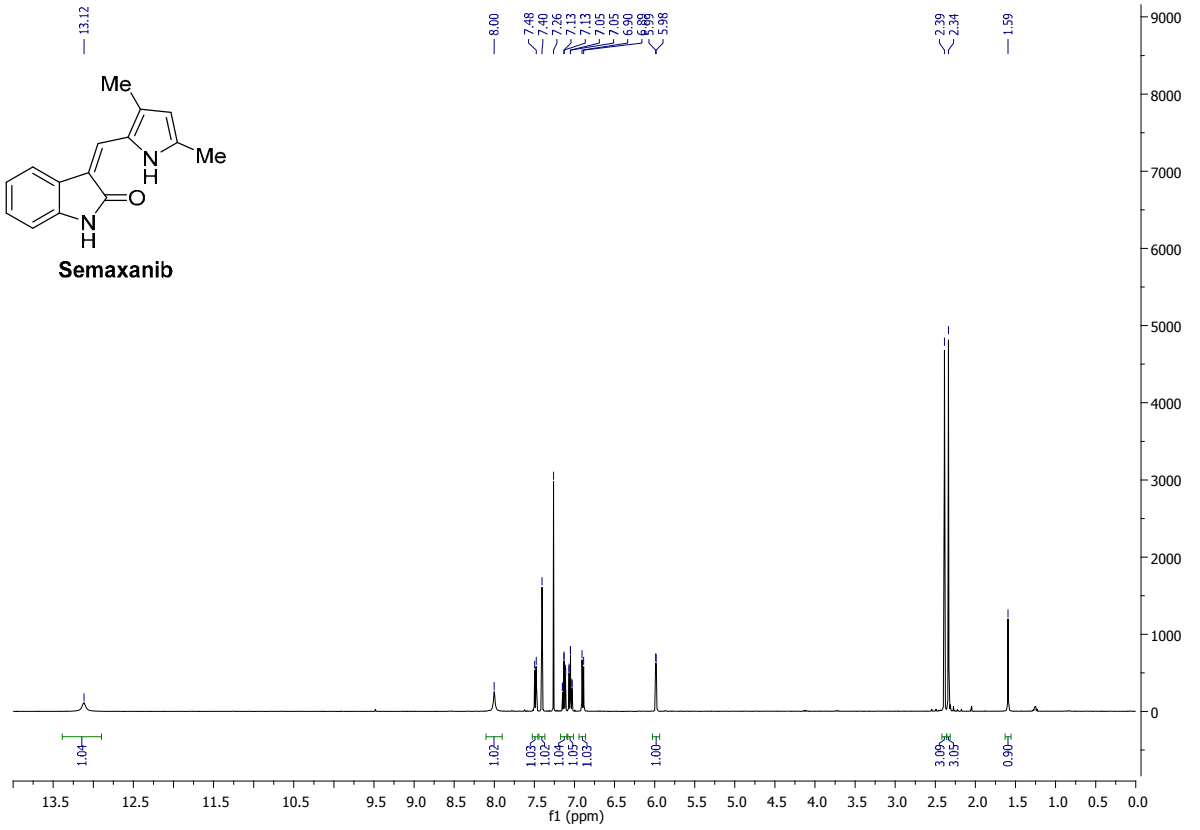


6

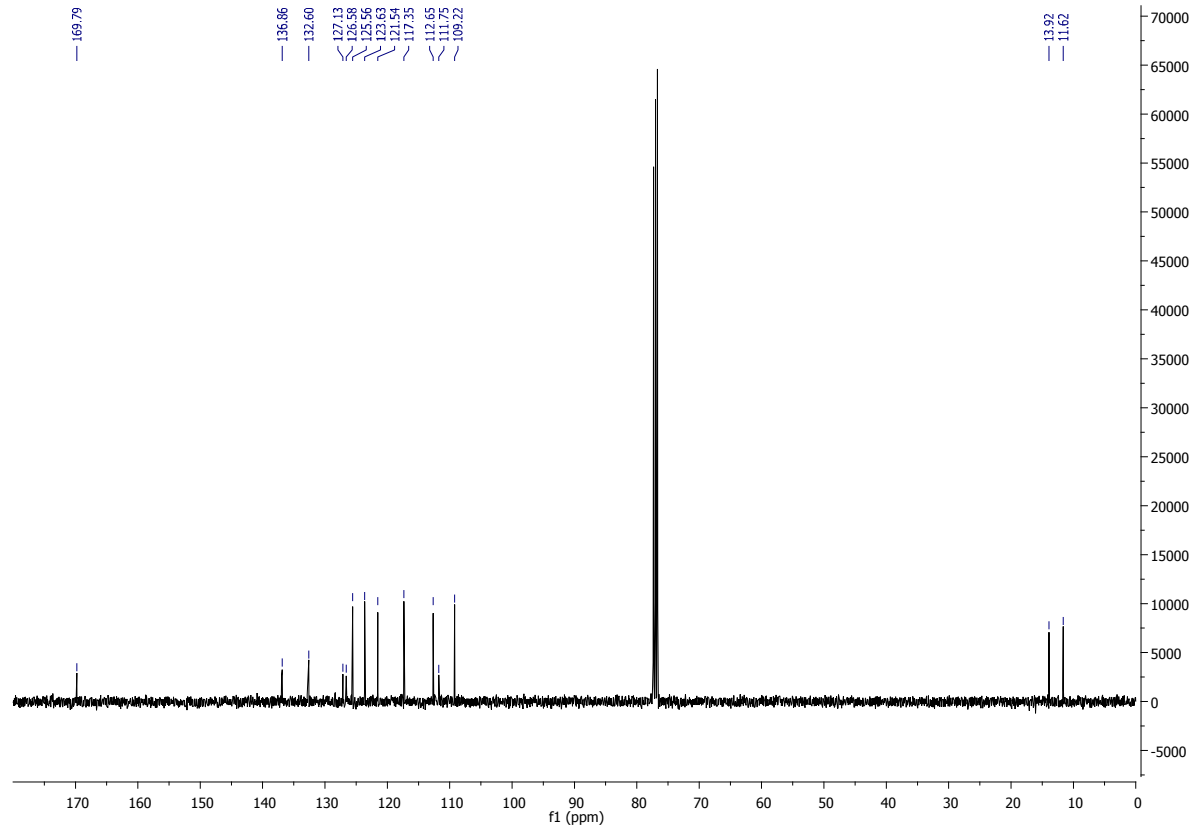
^{13}C NMR of 6



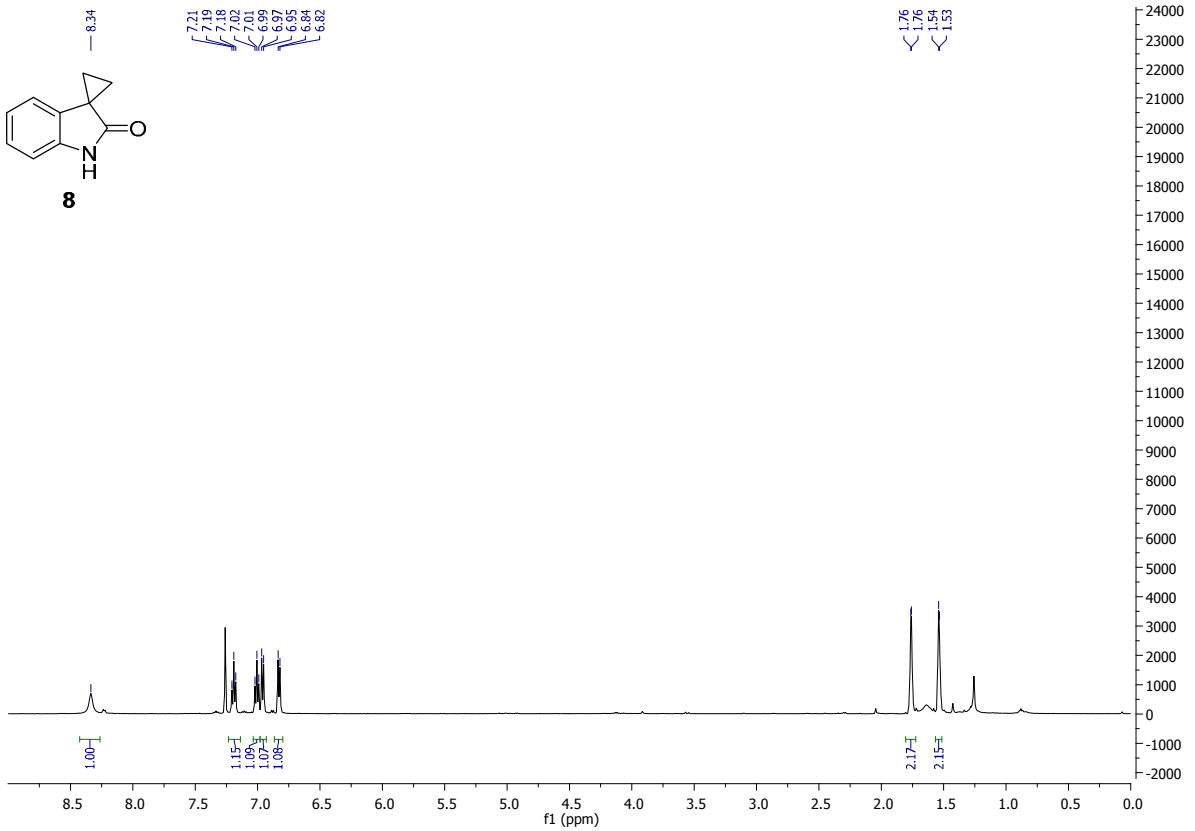
^{1}H NMR of semaxanib



^{13}C NMR of semaxanib

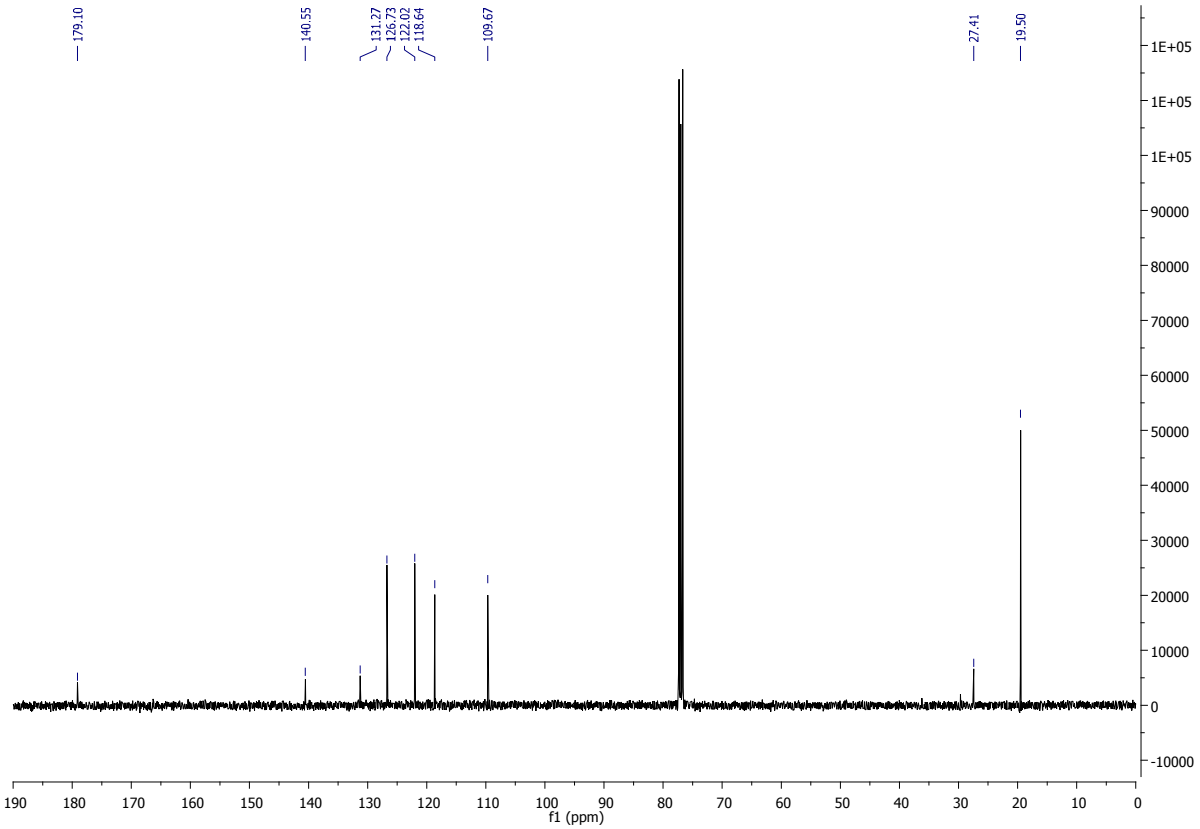


^{1}H NMR of 8

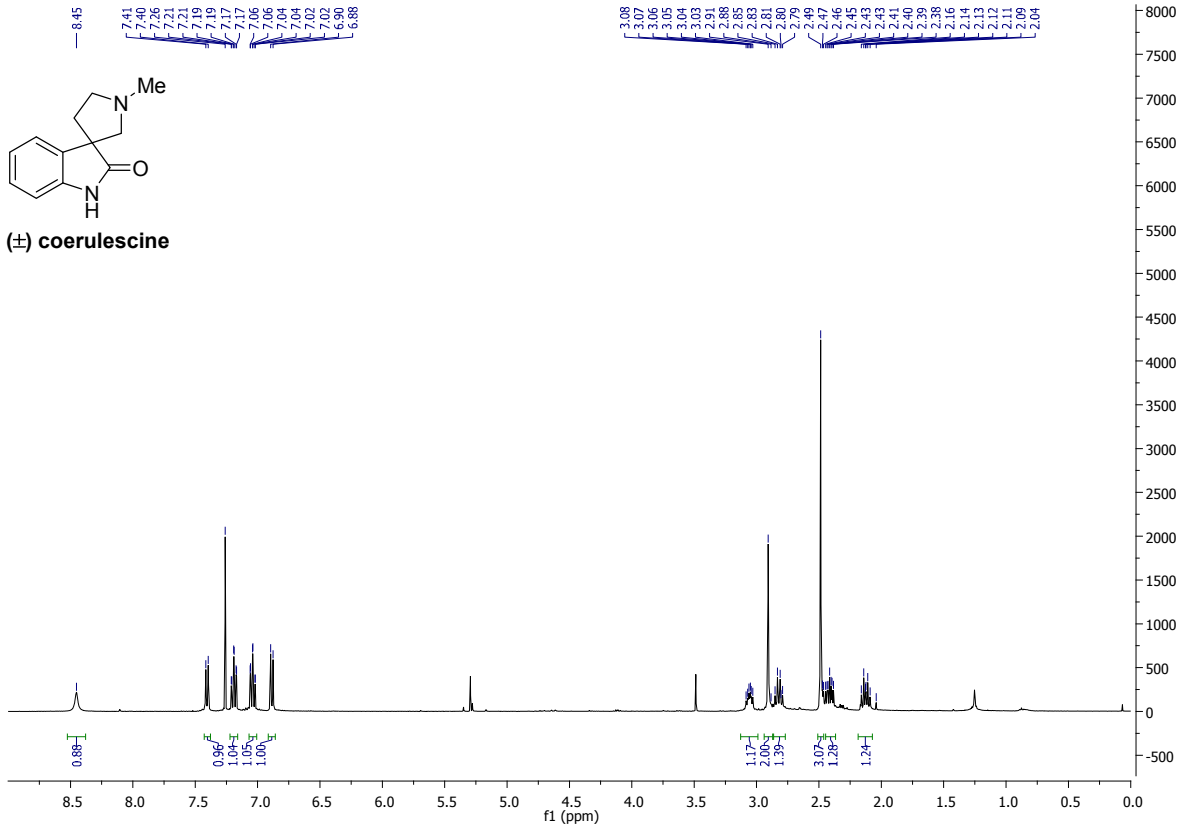


8

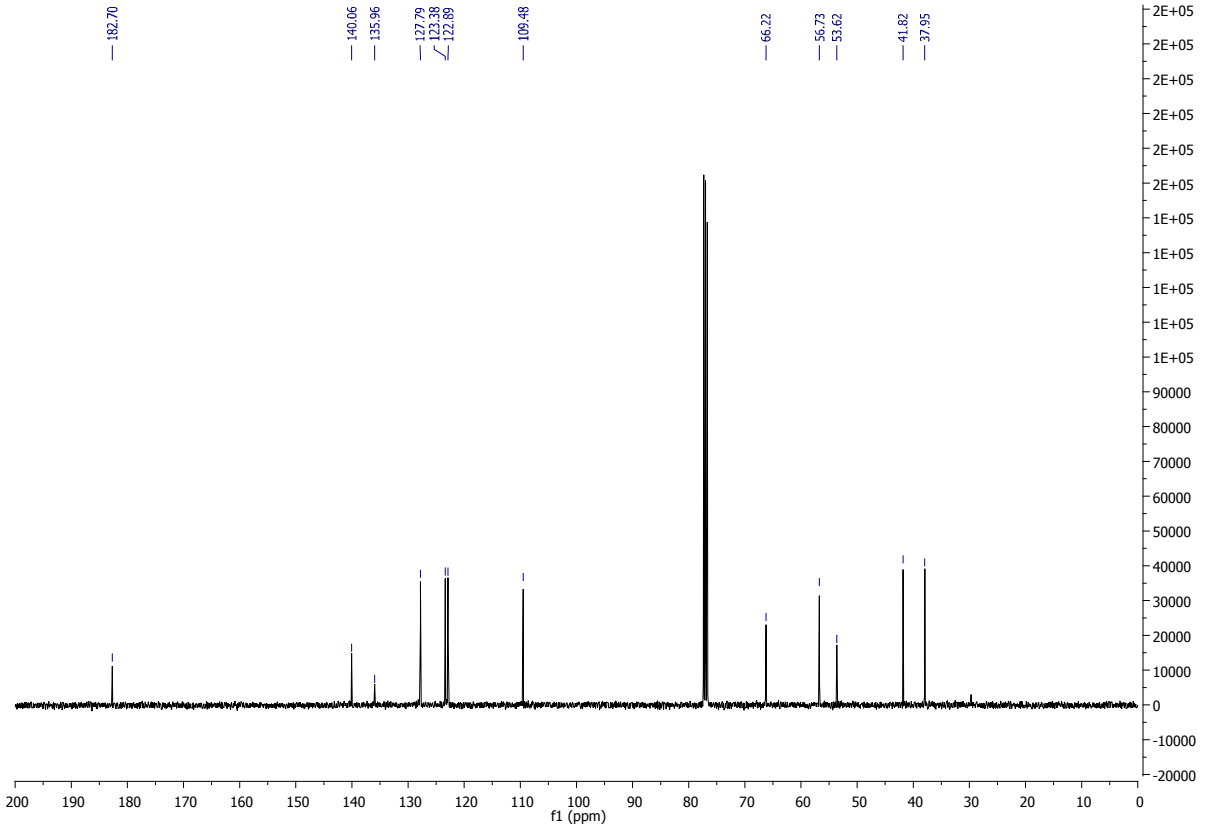
^{13}C NMR of 8



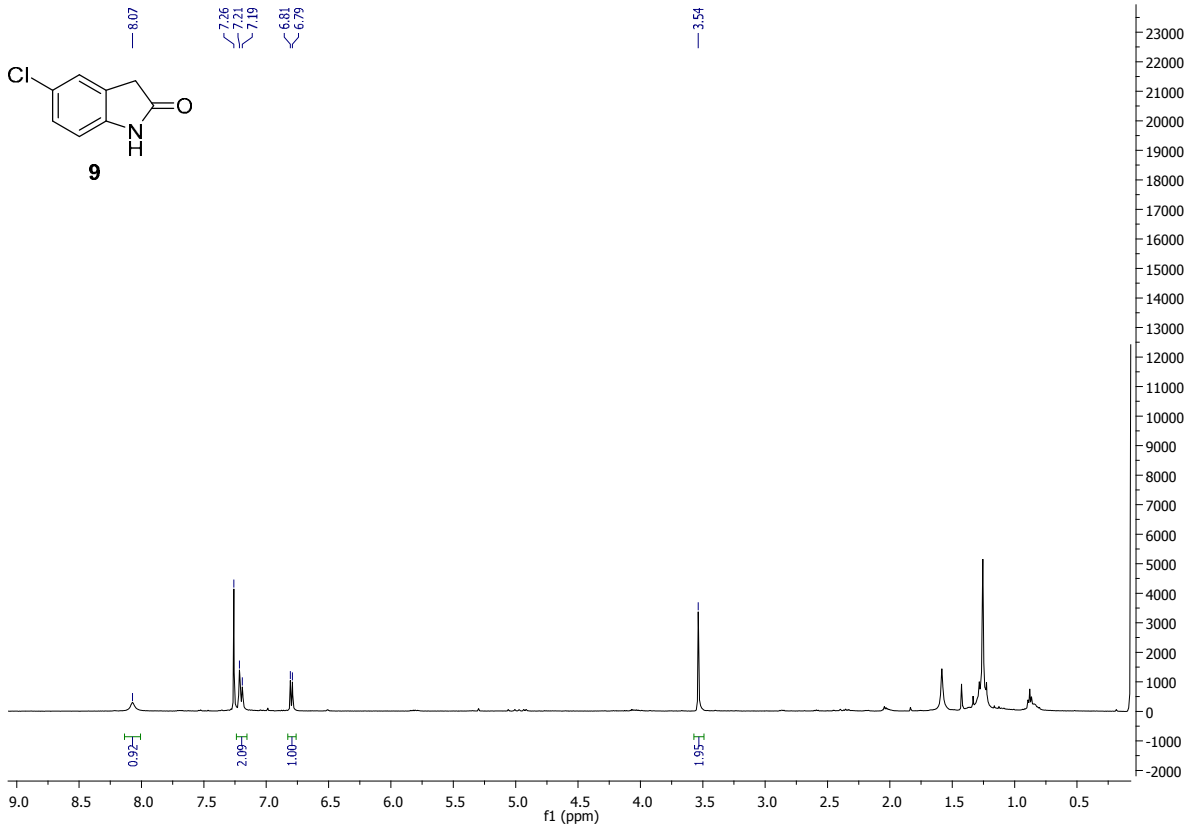
^{1}H NMR of (±) coerulescine



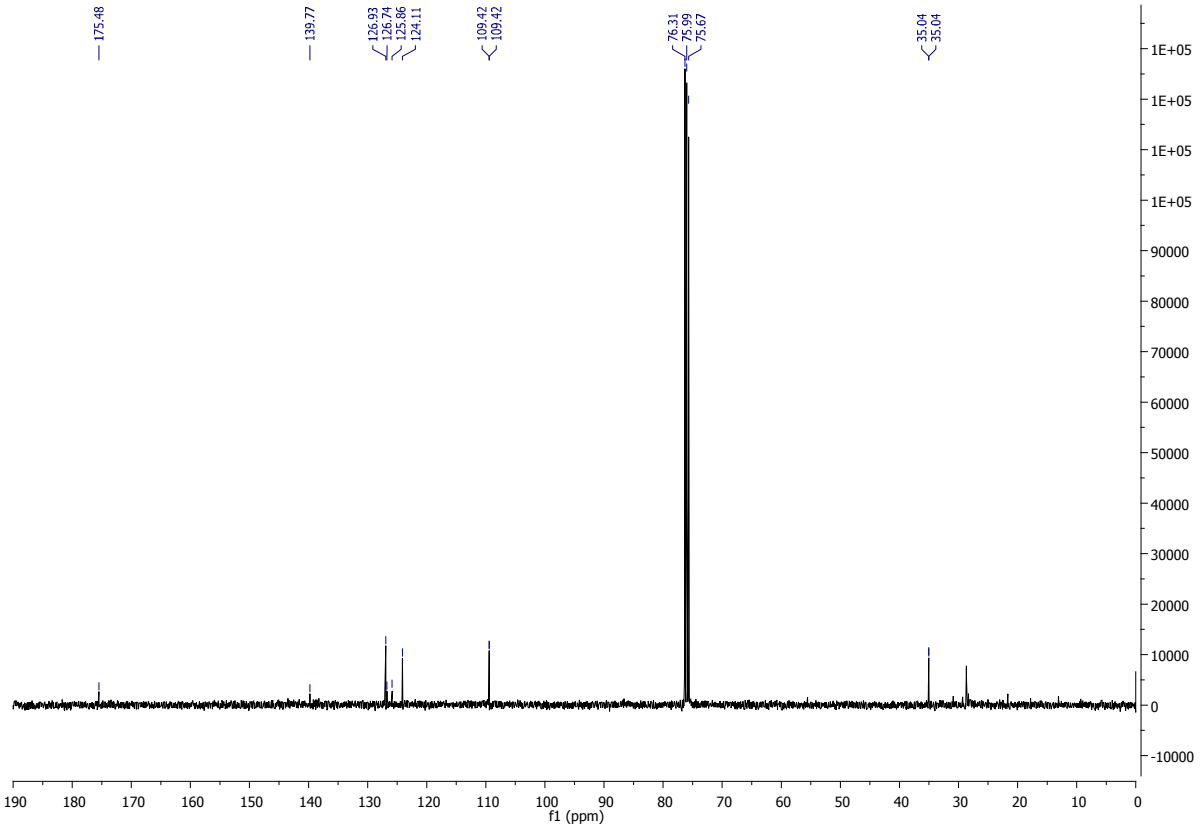
^{13}C NMR of (±) coerulescine



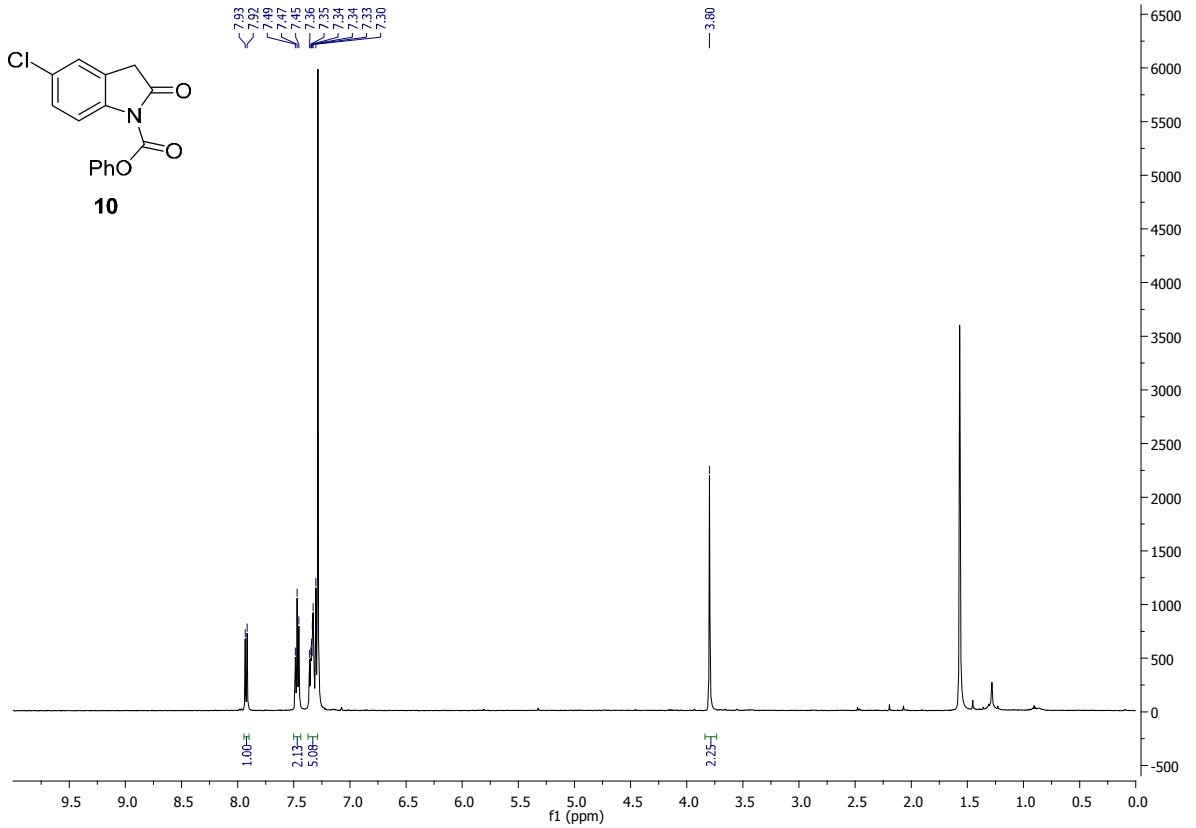
^{1}H NMR of 9



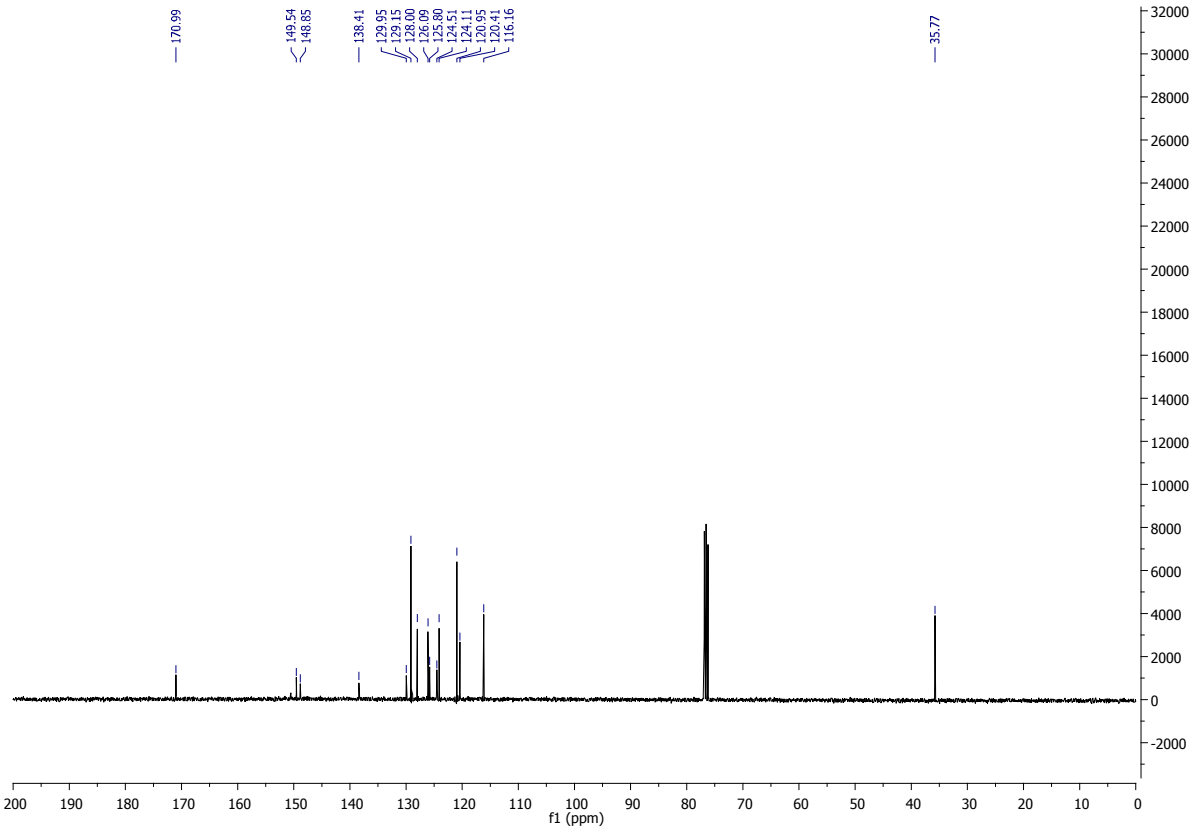
^{13}C NMR of 9



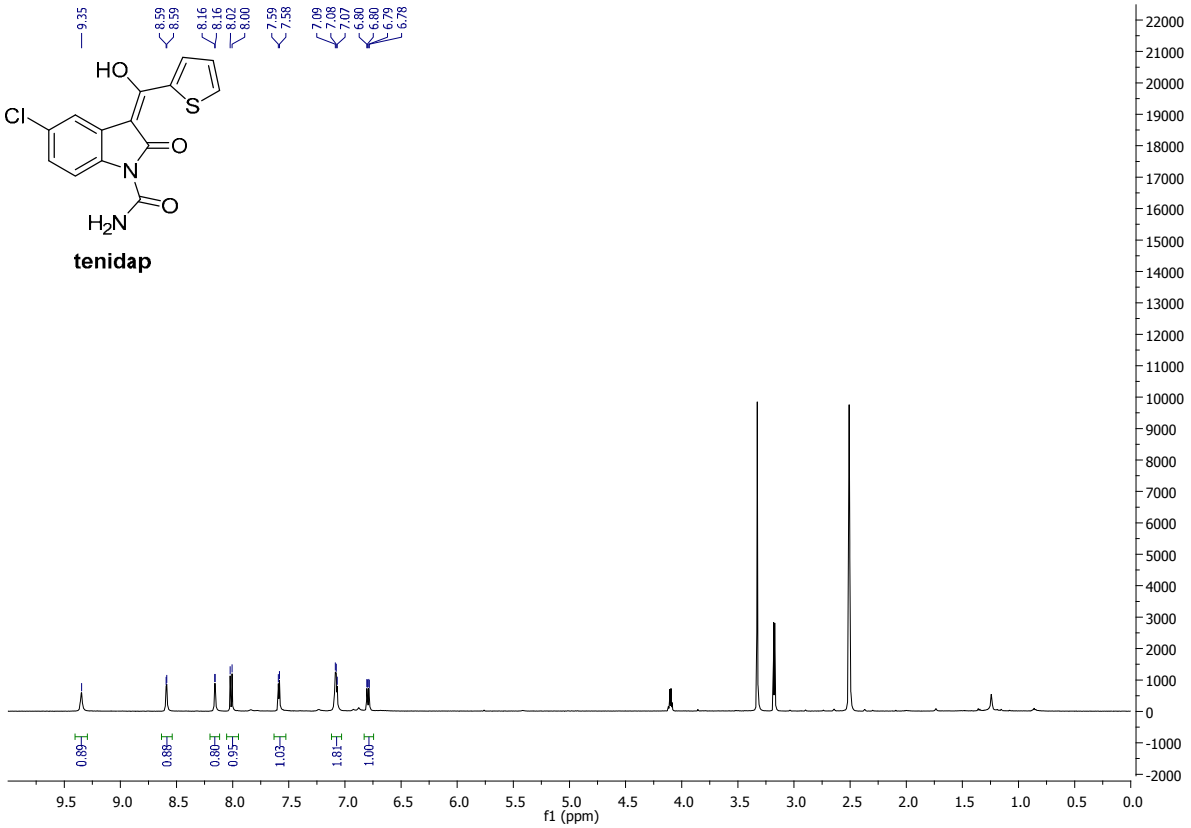
^{1}H NMR of 10



^{13}C NMR of 10



^{1}H NMR of tenidap



^{13}C NMR of tenidap