Electronic Supplementary Information

An environmentally responsible route to tezacaftor, a drug for treatment of cystic fibrosis prepared in water via ppm Au catalysis as entry to 2-substituted indoles

Nico Fleck,[a] Rohan M. Thomas,[a] Marcel Müller,[b] Stefan Grimme,[b] and Bruce H. Lipshutz[a,*]

[a] Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA-93106, USA

[b] Mulliken Center for Theoretical Chemistry, University of Bonn, Beringstraße 4, 53115 Bonn, Germany

*e-mail: lipshutz@chem.ucsb.edu

Table of Contents

General

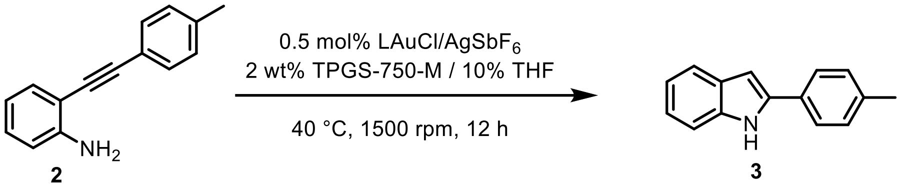
A solution of 2 wt % surfactant/H_2O was prepared by dissolving the surfactant in degassed HPLC grade water and was stored under argon. TPGS-750-M was obtained from a contract manufacturer, but is also available from Sigma-Aldrich (catalog #733857). All commercially available reagents were used without further purification. Thin layer chromatography (TLC) was done using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was done in glass columns using Silica Gel 60 (EMD, 40-63 µm). NMR spectra were recorded at 25 °C either on a Bruker Avance NEO 500 MHz or a Bruker Avance III HD 400 MHz spectrometer. Chemical shifts are reported relative to the residual solvent peak as an internal standard.[1] HRMS data were recorded on a Waters Micromass LCT TOF ES+ Premier mass spectrometer using ESI ionization HRMS.

Phosphine-based gold complexes cBRIDP-AuCl,[2] JohnPhosAuCl,[2] $Me_4{}^tBuXPhosAuCl$,[3] were obtained according to literature methods based on the phosphine ligand and $Me_2S\cdot AuCl$. IPrAuCl was obtained from Sigma Aldrich and used as received. SIPrAuCl was prepared following a procedure by Nolan et al. using the 4,5-dihydroimidazolium hydrochloride, $(Me_2S)AuCl$, and K_2CO_3 in acetone.[4] The cationic complex $SIPrAu(CH_3CN)SbF_6$ was prepared from SIPrAuCl by abstraction of the chloride ligand with $AgSbF_6$.[5]

Acid chloride **38** was prepared according to a patented procedure[6] with the corresponding acid being purchased from Combi-Blocks.

The aniline precursors for were prepared following a standard protocol for the respective Sonogashira coupling[7]. Indoles **29** – **31** were prepared from **S2** without chromatographic purification of the intermediate alkyne, the respective Sonogashira couplings were carried out following the patented procedure for tezacaftor.[6]

Catalyst screening



The reactions were performed in 1-dram vials at a scale of 0.5 mmol at a global concentration of 0.5 M. After 12 h, the reactions were extracted with 1 mL EtOAc, filtered through a pipette with a 10 mm silica-plug. The solvents were removed under reduced pressure and ^1H NMR spectra were acquired in $CDCl_3$. No side products were detected neither by TLC or NMR, thus, the yields are calculated from the aniline/indole ratio.

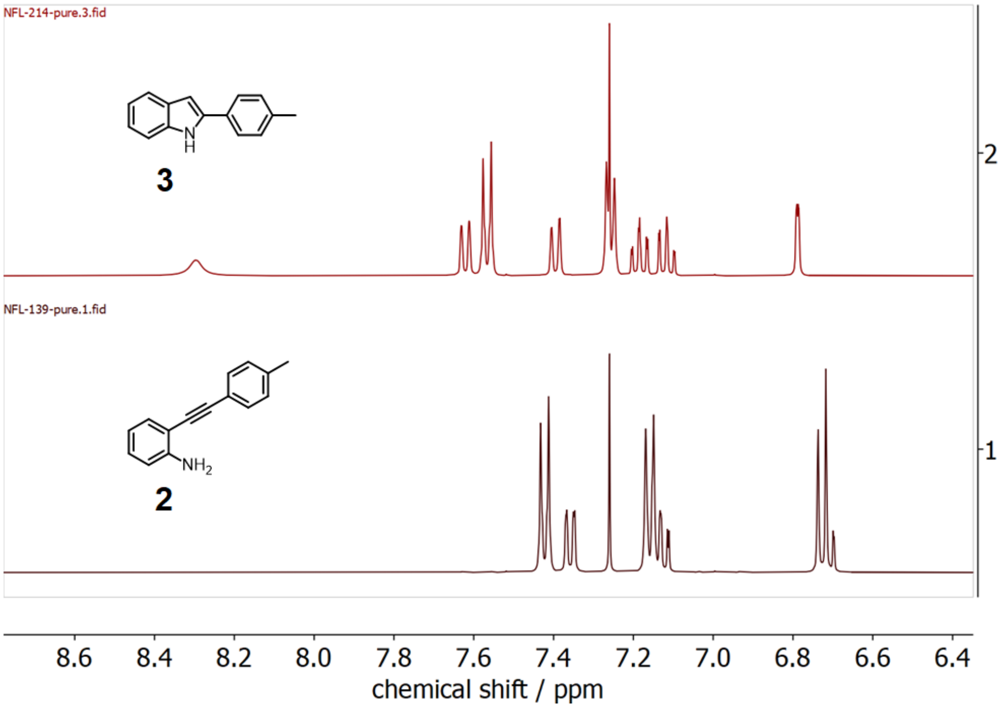


Figure S1: Overlaid NMR spectra of indole **3** (top) and aniline **2** (bottom).

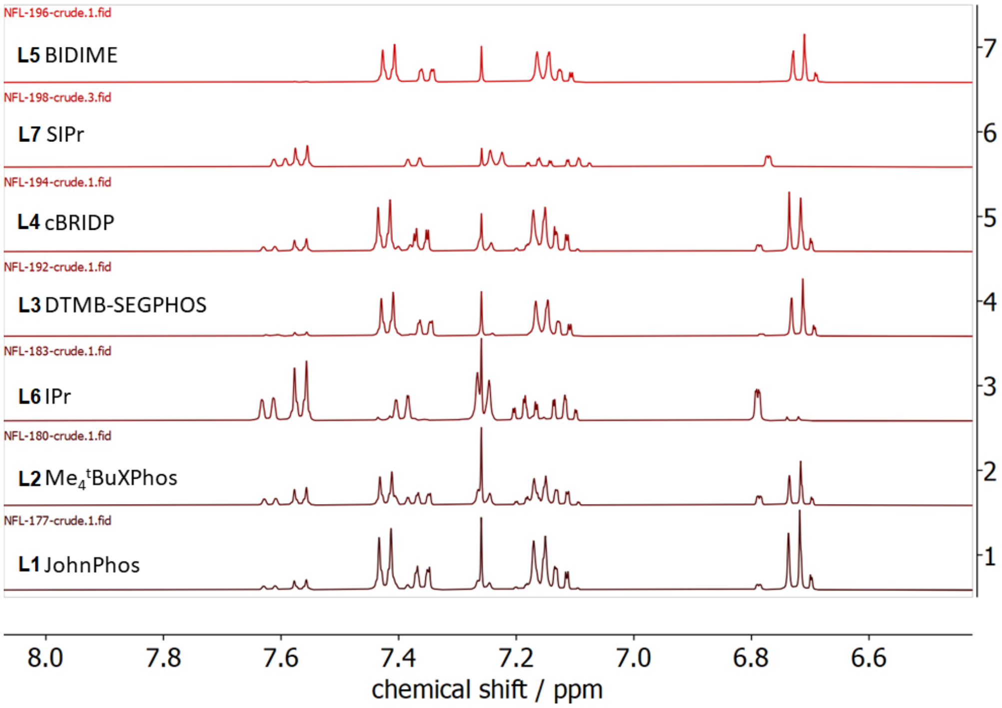
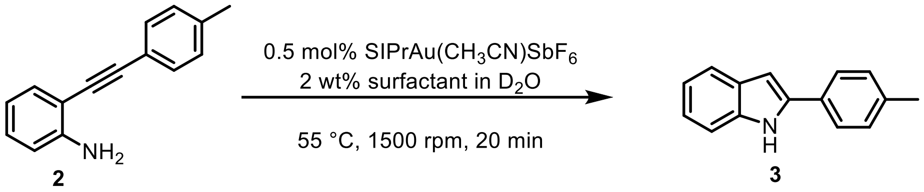


Figure S2: Overlaid NMR spectra of the catalyst screening; ligands are indicated to the left of the spectra.

Surfactant screening



The surfactant screen was performed using the model substrate **2** using standard conditions and SIPrAu(CH_3CN)SbF_6 to exclude any side-effects by the presence of silver in the reaction mixture. Carrying out the reactions in D_2O, deuteration of both the 1- and 3-position of the indole could be evaluated. Though minor differences occur among the set of examined surfactants, a rationalization of those is lacking at this point. As no side products were formed during this reaction, the yield was calculated as the conversion of the aniline to the indole as measured by ^{1}H NMR after extraction of the reaction mixtures with EtOAc.

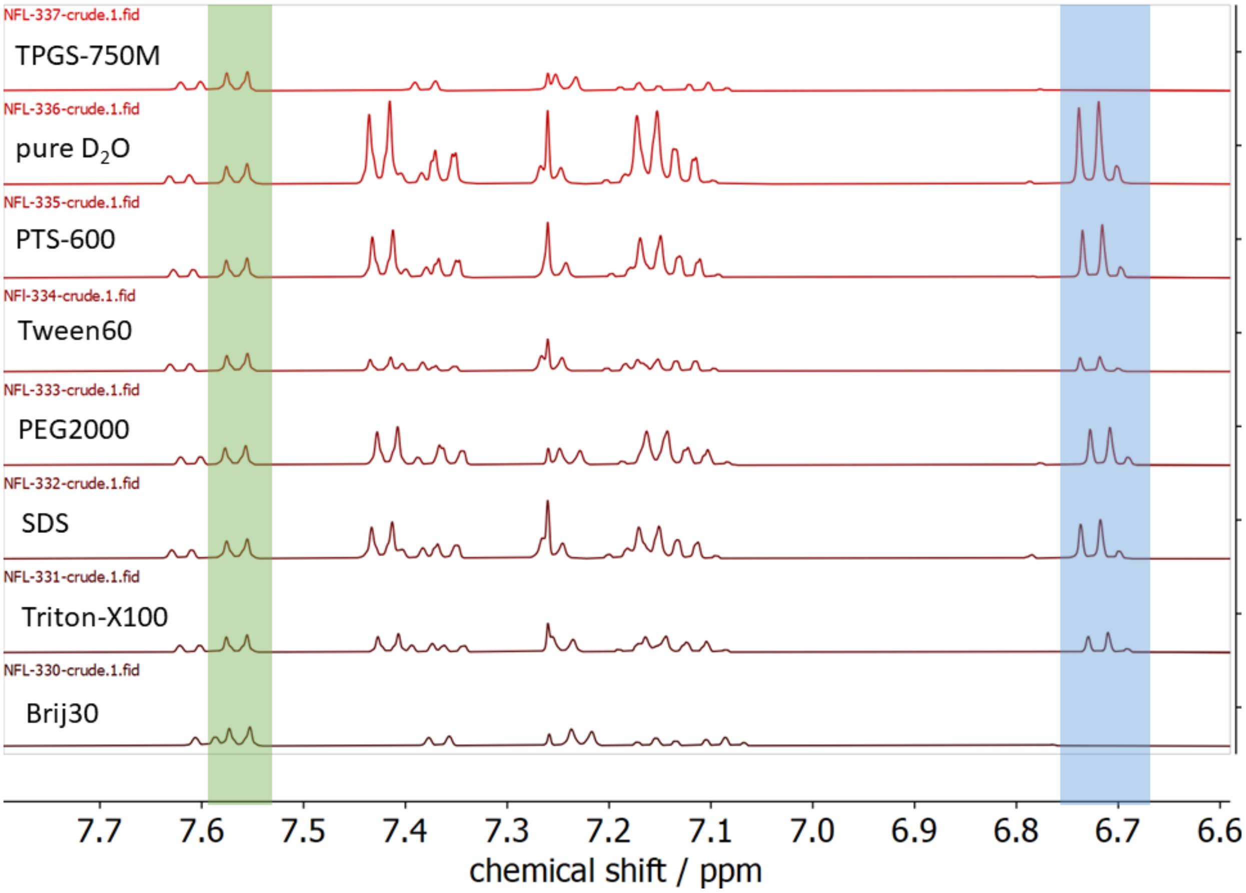


Figure S3: Crude ^{1}H NMR analysis of the reactions with the surfactant indicated at the left side of each spectrum. The signals taken into account are highlighted with the indole signal (2H, 7.56 ppm) in green and the aniline signal (2H, 6.72 ppm) in blue.

Table S1: Results from the surfactant screen.

Entry	Surfactant	Yield	%D at C-3
1	pure water	21%	93
2	PTS-600	31%	86
3	PEG2000	35%	82
4	SDS	37%	72
5	Triton-X100	49%	90
6	Tween60	57%	91
7	Brij30	96%	90
8	**TPGS-750-M**	**100%**	**92**

Recycling study

To quantify the active gold catalyst remaining within the surfactant solution, the catalyst amount was lowered systematically until the yield after 120 min reaction time dropped below 0.2 mol %. As full conversion was observed during the recycling experiment, >0.2 mol % of the catalyst is being recycled, amounting 40% of the initially used loading.

Table S2: Conversions with lowered catalyst loadings at 55 °C (reaction of **2** to **3**)

SIPrAu(CH_3CN)SbF_6 loading	**Yield [^1H NMR] after 120 min**
0.4 mol %	99%
0.3 mol %	99%
0.2 mol %	89%
0.1 mol %	57%

General procedure for indole synthesis

The reactions were conducted in 1-dram glass vials equipped with a PTFE-lined septum cap, in which the respective 2-alkynylarylamine (0.5 mmol) was placed together with a stir bar. Then, the gold catalyst was added as a solid (SIPrAuCl, 1.6 mg, 0.5 mol %), followed by 0.45 mL of a 2 wt % aqueous TPGS-750-M solution. Finally, $AgSbF_6$ (0.86 mg, 0.5 mol %, stock solution in 50 µL THF) was added through the septum and the reaction mixture was stirred vigorously at the indicated temperature. After the indicated reaction time, the reaction mixture was extracted with 2 x 1 mL EtOAc and the combined organic phases were dried onto silica. The products were then isolated via column chromatography on silica.

Synthesis of tezacaftor

Optimization studies

Sonogashira coupling from **33** to **S1**

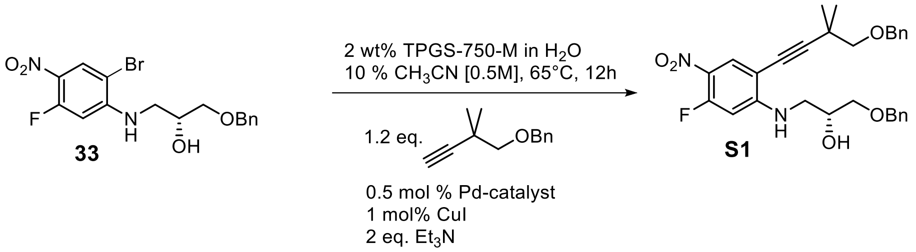


Table S3: Screening of conditions for cyclization of **33** to **S1**.

Pd catalyst	**NMR yield [^{1}H NMR]**	**NMR yield [^{19}F NMR]**
Pd(dppf)Cl_2	54%	57%
Pd(dtbfp)Cl_2	67%	73%
[Pd-μ-Br-(^{t}Bu$_3$P)]$_2$*	99%	99%
Pd(Ph_3P)$_4$	99%	99%
Pd(Ph_3P)$_4$**	15%	14%

0.25 mmol scale; *0.5 mol % Pd = 0.25 mol % catalyst **0.25 mol % Pd.

Cyclization of **35** to **36**

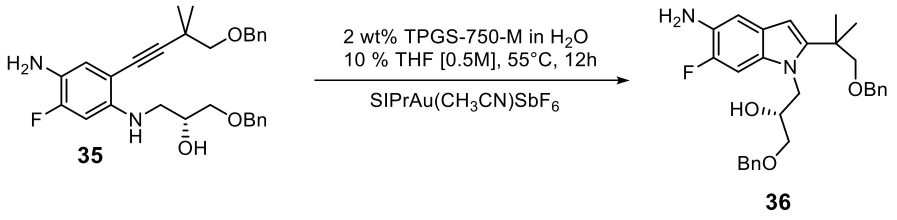


Table S4: Screening conditions for cyclization of **35** to **36**.

Au loading [mol %]	**NMR yield [^{1}H NMR]**	**NMR yield [^{19}F NMR]**
2	99%	99%
1	99%	99%
0.5	**99%**	**99%**
0.3	67%	68%

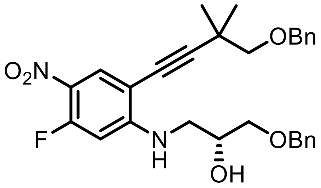
0.25 mmol scale

Procedure for step-wise synthesis of tezacaftor

1) Aniline **31** (1.00 g, 4.25 mmol), $Zn(ClO_4)_2\cdot 6H_2O$ (395 mg, 1.06 mmol, 25 mol %), and 2-(*R*)-benzyloxymethyloxirane (1.40 g, 8.50 mmol, 2.0 equiv) were placed in a 6-dram vial and heated to 70 °C while stirring at 150 rpm for 3 h. Afterwards, EtOAc (10 mL) was added and after stirring for 5 min, the reaction mixture was filtered through 2.0 g of silica. After evaporation of the solvents, the crude product was purified

by column chromatography on silica eluting with EtOAc/hexanes (40:60, v/v; R_f = 0.20) to obtain pure **33** as a slowly crystallizing yellow oil. Yield: 1.05 g (62%).

2) Compound **33** (657 mg, 1.64 mmol) and $Pd(Ph_3P)_4$ (9.5 mg, 0.5 mol %) were placed in a 6-dram vial sealed with a PTFE-lined septum cap. Then, 2 wt % TPGS-750 in H_2O (2.95 mL) was added, followed by a solution of CuI (3.1 mg, 1 mol %) in acetonitrile (310 µL), triethylamine (331 mg, 456 µL, 3.28 mmol, 2.00 equiv), and alkyne **34** (370 mg, 390 µL, 1.96 mmol, 1.2 equiv). The reaction mixture was stirred vigorously (1500 rpm) for 12 h at 65 °C after which TLC showed full conversion of **33** to **S1**. After the reaction mixture was cooled to rt, it was extracted with EtOAc (3 x 4 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and solvents were removed under reduced pressure. The crude product obtained in this way was then purified via column chromatography on silica eluting with EtOAc /hexanes (50:50, v/v, R_f = 0.25) to give **S1** as a slightly brown oil. Yield: 711 mg (91%).



^{1}H NMR (500 MHz, 298 °K, CD_3CN) δ: 7.95 (d, *J* = 8.5 Hz, 1H), 7.48 – 7.21 (m, 10H), 6.48 (d, *J* = 14.8 Hz, 1H), 6.05 (m, *J* = 6.2 Hz, 1H), 4.59 (s, 2H), 4.52 (s, 2H), 3.92 (m, 1H), 3.48 – 3.40 (m, 4H), 3.40 – 3.30 (m, 2H), 3.21 (m, 1H), 1.31 (s, 6H).

^{13}C-NMR (125 MHz, 298 °K, CD_3CN) δ: 159.02 (d, *J* = 261.1 Hz), 155.90 (d, *J* = 13.0 Hz), 139.71, 139.47, 130.70 – 130.37 (m), 129.33, 129.31, 128.64, 128.54, 128.51, 126.44 (d, *J* = 7.4 Hz), 105.06 (d, *J* = 1.8 Hz), 104.52, 97.92 (d, *J* = 26.7 Hz), 79.18, 74.65, 74.00, 73.86, 72.91, 69.33, 46.67, 34.26, 26.24.

*Not all carbons of the Bn groups are resolved in the ^{13}C spectra.

^{19}F NMR (470 MHz, 298 °K, CD_3CN) δ: -108.65.

HRMS (ESI+, *m/z*, $[M+Na]^+$): calcd. for $C_{29}H_{31}FN_2O_5Na$, 529.2115; found 529.2128

3) **S1** (620 mg, 1.30 mmol), carbonyl iron powder (215 mg, 3.9 mmol, 3.0 equiv), and ammonium chloride (278 mg, 5.2 mmol, 5.0 equiv) were placed in a 2-dram vial sealed with the PTFE-lined septum cap. Then, EtOAc (520 µL) was added and after stirring for 2 min at 400 rpm, 2 wt % TPGS-750-M in H_2O was added (2.08 mL), whereupon the reaction mixture was stirred vigorously (1500 rpm) for 12 h at 45 °C. Afterwards, EtOAc (2 mL) and 5% $NaHCO_3$ (2 mL) was added to the reaction mixture, which was subsequently filtered through 1.0 g of Celite. Then, the organic layer was separated, the aqueous one extracted with EtOAc (2 mL). The unified organic phases were washed with brine and dried over anhydrous Na_2SO_4, whereupon the solvents were removed under reduced pressure. The crude product was purified via column chromatography on silica eluting with EtOAc/hexanes (50:50, v/v, R_f = 0.45) to give **35** as a slightly brownish oil. Yield: 551 mg (89%).

4) Compound **35** (450 mg, 0.95 mmol) and $SIPrAu(CH_3CN)SbF_6$ (4.1 mg, 0.5 mol %) were placed in a 2-dram vial sealed with a PTFE-lined septum cap. Then, THF (190 µL) and 2 wt % TPGS-750-M in H_2O (1.71 mL) were added and the reaction mixture was stirred vigorously (1500 rpm) at 55 °C for 12 h. Afterwards, the mixture was extracted with EtOAc (2 x 2.0 mL), the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The crude product obtained after removal of solvents under reduced pressure was then purified via column chromatography on silica eluting with EtOAc/hexanes (40:60, v/v, R_f = 0.27) to obtain indole **36** as an oil that crystallized overnight. Yield: 418 mg (93%).

5) Indole **36** (418 mg, 0.88 mmol) was placed in a 2-dram vial sealed with a PTFE-lined septum cap, whereupon DIPEA (340 mg, 460 µL, 2.64 mmol, 3.0 equiv) and 2 wt % TPGS-750-M in H_2O (1.5 mL) were added. The reaction mixture was cooled to ca. 0 °C in an ice/water bath and stirred vigorously. Then, acid chloride **37** (274 mg, 1.06 mmol, 1.20 equiv) dissolved in 150 µL toluene was added dropwise to the mixture, which was stirred further for 1 h. Then, the reaction mixture was extracted with EtOAc (2 x 2 mL), the combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. The crude product obtained after evaporation of all solvents under reduced pressure was purified via column chromatography on silica eluting with EtOAc/hexanes (40:60, v/v, R_f = 0.38) and **38** is obtained as a slightly yellow oil. Yield: 534 mg (87%).

6) Compound **38** (376 mg, 0.54 mmol) and palladium-on-carbon (Evonik Noblyst® P1090, 5% Pd/C, 50% wet, 112 mg, 5 mol % Pd) were placed in a 6-dram vial sealed with the PTFE-lined septum cap, which is flushed with argon. Then, 3 M HCl in MeOH (1.5 mL) was added and the vial was purged with H_2. The reaction mixture was stirred under a hydrogen atmosphere (1 atm, balloon) for 5 h. After TLC indicated completion of the debenzylation, the vial was purged with argon and the mixture was filtered through 300 mg Celite to remove the catalyst. The solvents were removed under reduced pressure and the crude product was crystallized from *i*-PrOH/heptane as described in the patent literature[8] to obtain tezacaftor **1** as a white powder in a yield of 179 mg (65%). The comparably low yield was attributed to losses during crystallization, as the TLC showed full conversion of **38** to a single product.

Procedures for chromatography-free synthesis of tezacaftor

Since all intermediates were not isolated in pure form, yields were calculated by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

1) Aniline **31** (4.00 g, 17.02 mmol), $Zn(ClO_4)_2{\cdot}6H_2O$ (1.58 g, 4.25 mmol, 25 mol %), and 2-(*R*)-benzyloxymethyloxirane (5.6 g, 34.00 mmol, 2.0 equiv) were placed in a 6-dram vial and heated to 70 °C while stirring at 100 rpm. The reaction was monitored via TLC, showing a full consumption of the starting material after 5 h. Notably, only traces of the unreacted epoxide remained, while a side product with an R_f value <0.15 (EtOAc/hexanes, 40:60, v/v) appeared that was presumably condensation products of oligomerized epoxide.

For purification, 10 mL EtOAc was added to generate a fluid mixture after stirring at 40 °C for 15 min. Then, the liquid was diluted further with 10 mL EtOAc and 50 mL hexanes and stirred at rt for another 15 min. Filtration through 10 g silica yielded a light brown filtrate, giving the crude product after removal of the solvents under reduced pressure. If desired, **33** can be recrystallized from acetonitrile (1 mL/g).

Yield: 5.20 g, light brown oil, 82% purity (qNMR), 4.28 g corrected yield, 63%.

The crude product was used without further purification for the next steps.

2) An aliquot of the oil obtained in step 1 (3.26 g, equivalent to 2.67 g of **33**, 6.7 mmol) was placed in a 6-dram vial sealed with a PTFE-lined septum cap. The vial was transferred into a glove box where $(Ph_3P)_4Pd$ (38 mg, 0.5 mol %) was added and the vial was sealed under an argon atmosphere. Then, alkyne **34** (1.51 g, 8.04 mmol, 1.20 equiv), 2 wt % TPGS-750-M in H_2O (12.4 mL), triethylamine (1.86 g, 2.56 mL, 13.4 mmol, 2.0 equiv) and CuI (13 mg, 1 mol % in 1 mL acetonitrile) were added. The punctuated septum was then sealed with vinyl-made electrical tape to prevent access of oxygen, and the reaction mixture was heated to 65 °C for 12 h.

After the reaction mixture was cooled to rt, carbonyl iron powder (1.10 g, 20.0 mmol, 3.0 equiv) and ammonium chloride (1.79 g, 33.5 mmol, 5.0 equiv) were added. The reaction mixture was then acidified to pH ≈ 4 by addition of 12 M HCl (950 µL). Finally, 1.5 mL EtOAc was added and after closing the vial, the mixture was vigorously stirred (1500 rpm) at 45 °C for 4 h, after which TLC indicated completion of the reduction. Fast stirring is important insofar as: 1) a good emulsion is formed, and 2) the ferromagnetic CIP sticks to the stir bar and has less contact with the reaction medium if the stirring does not exceed the magnetic attraction.

After completion of the reaction, 5 mL EtOAc are added and the mixture is filtered through 3.0 g of Celite, which was then rinsed with further 10 mL EtOAc. The resulting biphasic mixture was treated with 20 mL of 5 % aqueous $NaHCO_3$, resulting in a pH of 8 for the aqueous phase. The organic phase was separated and filtered through 6 g of silica, which was further rinsed with 5 mL EtOAc. The crude product was obtained after removal of the solvents under reduced pressure.

Filtering through silica does not only dry the organic phase but also allows for removal of the remaining inorganic halides from solution, which reduce the reactivity of the cationic gold catalyst in the next step.

Yield: 3.765 g, light brown oil (72% purity (qNMR), equivalent to 2.71 g **35**, 85% yield over 2 steps.

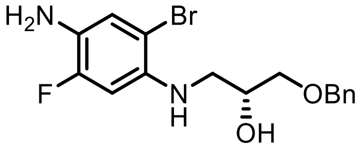
3) Crude **35** obtained from the previous step (1.97 g, equivalent to 1.42 g **35**, 2.98 mmol) was placed in a 6-dram vial sealed with a PTFE-lined septum cap and 2 wt % TPGS-750-M in H_2O (5.4 mL) were added, followed by a solution of $SIPrAu(CH_3CN)SbF_6$ in 0.6 mL THF. The punctuated septum was sealed with vinyl-made electric tape to prevent evaporation of the co-solvent, and the mixture was stirred at 55 °C for 12 h. Then, the aqueous phase was extracted with EtOAc (2 x 2.5 mL) and the solvent was removed from the combined organic phases, ultimately under high vacuum. Then, the resulting wax-like crude product was dissolved in 1.5 mL EtOAc, heated to 65 °C and 4.5 mL heptane was added. After slowly cooling down the mixture to rt, the pure indole **36** crystallized as an off-white solid and was isolated in a yield of 1.23 g (87%). The residual metal content listed in the main text was determined using a sample of this indole.

4) Indole **36** (1.1 g, 2.31 mmol) and DIPEA (1.2 g, 895 mg, 1.20 mL, 6.9 mmol, 3.0 equiv) were placed in a 2-dram vial equipped with a PTFE-lined septum cap. Then, acid chloride **37** (721 mg, 2.77 mmol, 1.2 equiv) dissolved in 900 µL toluene was added dropwise at 0 °C and the reaction mixture was stirred for 1 h. Then, EtOAc (3 mL) was added, the organic phase was separated and washed with 5 mL 10% NaOH and filtered through 1 g of silica, which was then rinsed with 1 mL of EtOAc.

After evaporation of the solvents under high vacuum at 40 °C, **38** was obtained as an almost colorless oil, containing 9 wt % EtOAc. Corrected yield 1.30 g (91%).

Characterization data for starting materials and products

Compound **S2**



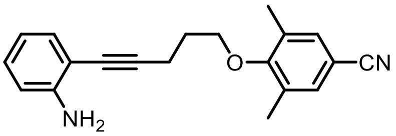
^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 7.34 (m, 5H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.43 (d, *J* = 12.9 Hz, 1H), 4.57 (s, 2H), 4.04 (ddd, *J* = 6.4, 4.1, 2.1 Hz, 1H), 3.66 – 3.48 (m, 2H), 3.23 (dd, *J* = 12.7, 4.5 Hz, 1H), 3.12 (dd, *J* = 12.7, 6.8 Hz, 1H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 152.32 (d, *J* = 238.0 Hz), 138.80 (d, *J* = 9.3 Hz), 137.79, 128.65, 128.07, 128.00, 125.76 (d, *J* = 14.8 Hz), 121.46 (d, *J* = 4.6 Hz), 104.50 (d, *J* = 3.3 Hz), 100.55 (d, *J* = 24.9 Hz), 73.73, 72.40, 69.03, 47.58.

^{19}F NMR (376 MHz, 298 °K, $CDCl_3$) δ: -132.83.

HRMS (ESI$^+$, *m/z*, $[M+Na]^+$): calcd. for $C_{16}H_{18}BrFN_2O_2Na$, 391.0443; found 391.0422.

Compound **S3**



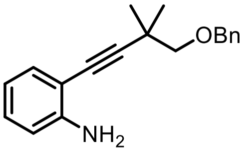
Yellow oil, yield 68%. column: SiO_2, 20% EtOAc/hexanes, R_f = 0.21.

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 7.32 (s, 2H), 7.22 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.09 (ddd, *J* = 8.5, 7.6, 1.6 Hz, 1H), 6.72 – 6.62 (m, 2H), 4.16 (bs, 2H), 3.97 (t, *J* = 6.0 Hz, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.31 (s, 6H), 2.12 (p, *J* = 6.5 Hz, 2H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 159.78, 147.81, 132.94, 132.74, 132.17, 129.23, 119.19, 118.01, 114.35, 108.57, 107.47, 94.22, 78.08, 70.74, 29.64, 16.55, 16.34.

HRMS (ESI$^+$, *m/z*, $[M+H]^+$): calcd. for $C_{20}H_{20}N_2OH$, 305.1654; found 305.1656

Compound **S4**



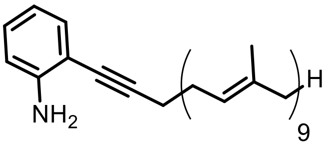
Colorless oil, yield: 87%. column: SiO_2, 10 % EtOAc/hexanes, R_f = 0.35.

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 7.43 – 7.27 (m, 6H), 7.07 (td, *J* = 7.7, 1.5 Hz, 1H), 6.68 – 6.60 (m, 2H), 4.64 (s, 2H), 4.17 (s, 2H), 3.45 (s, 2H), 1.36 (s, 6H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 147.98, 138.53, 131.61, 128.95, 128.37, 127.55, 127.51, 117.58, 113.95, 108.46, 101.34, 78.87, 73.41, 69.56, 33.40, 26.36.

HRMS (ESI$^+$, *m/z*, [M+H]$^+$): calcd. for $C_{19}H_{21}NOH$, 280.1701; found 280.1692.

Compound **S5**



Colorless oil, yield: 89%. column: SiO_2, 5% EtOAc/hexanes, R_f = 0.41.

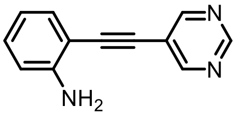
^{1}H NMR (400 MHz, 298 K, $CDCl_3$) δ: 7.24 – 7.21 (m, 1H), 7.15 – 7.00 (m, 1H), 6.70 – 6.61 (m, 2H), 5.34 – 5.21 (m, 1H), 5.16 – 5.05 (m, 8H), 4.16 (s, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.33 (q, *J* = 7.2 Hz, 2H), 2.16 – 1.94 (m, 32H), 1.67 (dd, *J* = 9.3, 1.4 Hz, 6H), 1.60 (d, *J* = 1.5 Hz, 24H).

^{13}C NMR (100 MHz, 298 K, $CDCl_3$) δ: 147.83, 137.04, 135.31, 135.12, 135.11, 135.09, 135.06, 135.04, 132.08, 131.40, 128.95, 124.56, 124.43, 124.42, 124.37, 124.19, 122.87, 117.93, 114.20, 109.03, 95.71, 39.90, 39.88, 27.79, 26.92, 26.87, 26.86, 26.83, 26.78, 25.85, 20.30, 17.83, 16.40, 16.20, 16.18, 16.15.

Note: not all ^{13}C signals are resolved for the isoprenyl chain.

HRMS (ESI$^+$, *m/z*, [M+H]$^+$): calcd. for $C_{54}H_{81}NH$, 744.6447; found 744.6447.

Compound **S6**



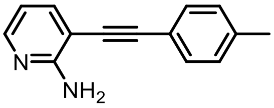
Yield: 79%, column: SiO_2 50% EtOAc/hexanes, R_f = 0.23.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$) δ: 9.14 (s, 1H), 8.85 (s, 2H), 7.38 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.20 (td, *J* = 7.7, 1.6 Hz, 1H), 6.78 – 6.70 (m, 2H), 4.29 (s, 2H).

^{13}C NMR (100 MHz, 298 K, $CDCl_3$) δ: 158.50, 156.75, 148.21, 132.60, 131.05, 120.17, 118.30, 114.76, 106.38, 93.37, 87.63.

HRMS (ESI$^+$, *m/z*, [M+H]$^+$): calcd. for $C_{12}H_9N_3H$, 196.0875; found 196.0885

Compound **S7**



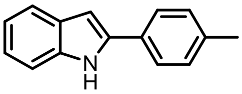
^{1}H NMR (400 MHz, 298 °K, DMSO-d_6) δ: 7.96 (d, *J* = 5.0 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.56 (dd, *J* = 7.4, 4.8 Hz, 1H), 6.26 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, 298 °K, DMSO-d$_6$) δ: 159.41, 148.11, 139.66, 138.30, 131.33, 129.17, 119.54, 112.03, 101.28, 94.68, 84.77, 21.05.

HRMS (ESI+, *m/z*, [M+H]$^+$): calcd. for $C_{14}H_{12}N_2H$, 209.1079; found 209.1077

Analytical data for indoles and tezacaftor intermediates

Indole **3**



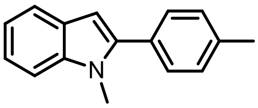
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 30 min
R$_f$ (SiO$_2$, hexanes/EtOAc 80:20) = 0.45
yield: 100 mg, 98%, off-white solid

^{1}H NMR (500 MHz, 298 °K, CDCl$_3$) δ: 8.30 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.56 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.24 (m, 2H), 7.18 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.11 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.78 (dd, *J* = 2.1, 0.9 Hz, 1H), 2.39 (s, 3H).

^{13}C NMR (125 MHz, 298 °K, CDCl$_3$) δ: 138.06, 137.67, 136.70, 129.73, 129.60, 129.35, 125.08, 122.14, 120.53, 120.21, 110.80, 99.42, 21.25.

The spectral data match that in the literature.[7]

Indole **4**



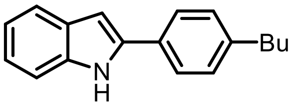
conditions: 0.05 mol % SIPrAu(CH$_3$CN)SbF$_6$, 70 °C, 12 h
R$_f$ (SiO$_2$, hexanes/CH$_2$Cl$_2$ 90:10) = 0.45
yield: 102 mg, 93%, off-white solid

^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 7.66 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.34 – 7.22 (m, 3H), 7.16 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.56 (s, 1H), 3.76 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 141.79, 138.40, 137.90, 130.07, 129.42, 129.34, 128.14, 121.63, 120.50, 119.92, 109.68, 101.44, 31.25, 21.42.

The spectral data match that in the literature.[9]

Indole **5**



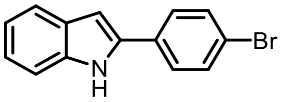
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 30 min
R$_f$ (SiO$_2$, hexanes/EtOAc 90:10) = 0.45
yield: 118 mg, 94%, slightly yellow solid

^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 8.30 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.18 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.12 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.82 – 6.76 (m, 1H), 2.65 (m, *J* = 7.6 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.39 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 142.74, 138.12, 136.72, 129.80, 129.38, 129.10, 125.10, 122.12, 120.54, 120.20, 110.81, 99.44, 35.41, 33.57, 22.38, 13.98.

The spectral data are in accordance with that in the literature.[10]

Indole **6**



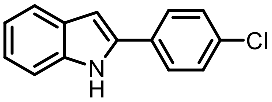
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 30 min
R$_f$ (SiO$_2$, hexanes/EtOAc 80:20) = 0.40
yield: 125 mg, 93%, off-white solid (contains ca. 1.7 wt % EtOAc, yield corrected for this).

^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 8.28 (s, 1H), 7.65 – 7.61 (m, 1H), 7.59 – 7.49 (m, 4H), 7.41 – 7.38 (m, 1H), 7.24 – 7.19 (m, 1H), 7.16 – 7.11 (m, 1H), 6.82 (dd, *J* = 2.2, 0.9 Hz, 1H).

^{13}C-NMR (100 MHz, 298 °K, CDCl$_3$) δ: 137.05, 136.81, 132.29, 131.46, 129.29, 126.72, 122.87, 121.66, 120.92, 120.63, 111.09, 100.68.

The spectral data are in accordance that in the literature.[11]

Indole **7**



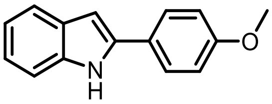
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 90 min
R$_f$ (SiO$_2$, hexanes/EtOAc 85:15) = 0.40
yield: 104 mg, 92%, off-white solid

^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 8.28 (s, 1H), 7.66 – 7.54 (m, 3H), 7.45 – 7.37 (m, 3H), 7.21 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.81 (dd, *J* = 2.2, 0.9 Hz, 1H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 136.92, 136.69, 133.47, 130.92, 129.25, 129.18, 126.33, 122.70, 120.77, 120.49, 110.94, 100.50.

The spectral data match that in the literature.[7]

Indole **8**



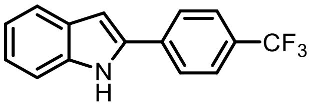
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 90 min
R$_f$ (SiO$_2$, hexanes/EtOAc 70:30) = 0.36
yield: 105 mg, 94%, off-white solid

^{1}H NMR (500 MHz, 298 °K, CDCl$_3$) δ: 8.25 (s, 1H), 7.66 – 7.59 (m, 3H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.74 (dd, *J* = 2.2, 0.9 Hz, 1H), 3.89 (s, 3H).

^{13}C NMR (125 MHz, 298 °K, CDCl$_3$) δ: 159.40, 137.97, 136.66, 129.45, 126.51, 125.22, 121.93, 120.38, 120.19, 114.50, 110.72, 98.86, 55.41.

The spectral data match that in the literature.[12]

Indole **9**



conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 30 min
R$_f$ (SiO$_2$, hexanes/EtOAc 70:30) = 0.43
yield: 118 mg, 91%, off-white solid

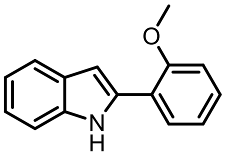
^{1}H NMR (500 MHz, 298 °K, DMSO-d$_6$) δ: 11.74 (s, 1H), 8.03 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.06 – 6.99 (m, 2H).

^{13}C NMR (125 MHz, 298 °K, DMSO-d$_6$) δ: 137.75, 136.31, 136.08, 128.65, 127.54 (q, *J* = 31.8 Hz), 126.08 (q, *J* = 3.8 Hz), 125.58, 124.78 (q, *J* = 272 Hz), 122.73, 120.79, 120.00, 111.83, 100.99.

^{19}F NMR (470 MHz, 298 °K, DMSO-d$_6$) δ: - 60.94.

The spectral data match that in the literature.[7]

Indole **10**



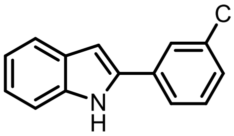
conditions: 1.0 mol % SIPrAuCl/AgSbF$_6$, 65 °C, 4 h
R$_f$ (SiO$_2$, hexanes/EtOAc 80:20) = 0.30
yield: 97 mg, 87%, white solid

^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 9.70 (s, 1H), 7.89 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.70 (d, *J* = 7.7, 1H), 7.47 (d, *J* = 8.1,), 7.32 (m, 1H), 7.24 (m, 1H), 7.18 (m, 1H), 7.10 (m, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 4.02 (s, 3H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 155.86, 136.22, 136.10, 128.66, 128.39, 128.21, 121.92, 121.63, 120.72, 120.37, 119.90, 112.03, 111.05, 99.94, 55.92.

The spectral data are in accordance with that in the literature.[12]

Indole **11**



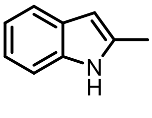
conditions: 2.0 mol % SIPrAuCl/AgSbF$_6$, 80 °C, 12 h
R$_f$ (SiO$_2$, hexanes/EtOAc 50:40) = 0.40
yield: 87 mg, 80%, light brownish solid

^{1}H NMR (400 MHz, 298 °K, DMSO-d$_6$) δ: 11.70 – 11.65 (m, 1H), 8.33 (t, *J* = 1.8 Hz, 1H), 8.18 (ddd, *J* = 7.8, 2.0, 1.0 Hz, 1H), 7.74 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.43 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.03 (tt, *J* = 7.8, 0.9 Hz, 1H).

^{13}C NMR (100 MHz, 298 °K, DMSO-d$_6$) δ: 137.40, 135.35, 133.48, 130.58, 130.19, 129.41, 128.40, 128.17, 122.41, 120.51, 119.75, 118.79, 112.15, 111.54, 100.46.

The spectral data are in accordance with that the literature.[12]

Indole **12**

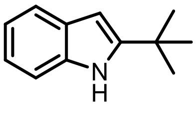


^{1}H NMR (400 MHz, 298 K, CDCl$_3$) δ: 7.79 (s, 1H), 7.54 (m, 1H), 7.32 – 7.25 (m, 1H), 7.18 – 7.05 (m, 2H), 6.24 (dq, *J* = 2.2, 1.0 Hz, 1H), 2.45 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 136.15, 135.16, 129.18, 121.03, 119.74, 110.32, 100.50, 13.81.

The spectral data are in accordance with that the literature.[13]

Indole **13**



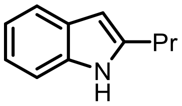
conditions: 0.5 mol % SIPrAuCl/$AgSbF_6$, 55 °C, 30 min
R_f (SiO_2, hexanes/EtOAc 90:10) = 0.43
yield: 82 mg, 95%, thick oil

^1H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 7.94 (s, 1H), 7.57 (d, *J* = 7.6, 1H), 7.34 (d, *J* = 7.6, 1H), 7.20 – 7.06 (m, 2H), 6.29 (dd, *J* = 2.3, 0.9 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 148.90, 135.88, 128.64, 121.20, 120.10, 119.73, 110.48, 97.08, 31.95, 30.44.

The spectral data are in accordance with that in the literature.[10]

Indole **14**



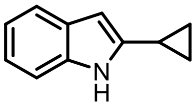
conditions: 0.5 mol % SIPrAuCl/$AgSbF_6$, 55 °C, 90 min
R_f (SiO_2, hexanes/EtOAc 90:10) = 0.40
yield: 69 mg, 87%, thick oil

^1H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 7.78 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.22 – 7.08 (m, 2H), 6.29 (d, *J* = 1.1 Hz, 1H), 2.73 (t, *J* = 7.4, 3H), 1.78 (h, *J* = 7.4 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 139.95, 135.93, 128.97, 121.01, 119.85, 119.67, 110.42, 99.62, 30.40, 22.58, 14.01.

The spectral data are in accordance with that in the literature.[14]

Indole **15**



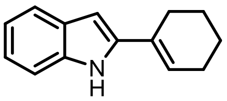
conditions: 0.5 mol % SIPrAuCl/$AgSbF_6$, 55 °C, 30 min
R_f (SiO_2, Et_2O/hexanes 80:20) = 0.47
yield: 70 mg, 90%, colorless oil that slowly turned into a solid

^1H-NMR (500 MHz, 298 °K, $CDCl_3$) δ: 7.87 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.25 – 7.15 (m, 2H), 6.24 (s, 1H), 1.98 (tdd, *J* = 7.3, 5.2, 3.4 Hz, 1H), 1.04 (ddt, *J* = 8.2, 4.2, 1.7 Hz, 2H), 0.90 – 0.80 (m, 2H).

^{13}C-NMR (125 MHz, 298 °K, $CDCl_3$) δ: 141.90, 135.85, 128.80, 121.06, 119.82, 119.77, 110.38, 97.67, 8.93, 7.46.

The spectral data are in accordance with that in the literature.[15]

Indole **16**



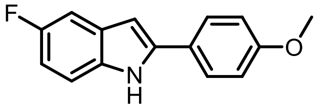
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 90 min
R_f (SiO$_2$, hexanes/EtOAc 90:10) = 0.40
yield: 88 mg, 90%, yellow oil

^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 8.09 (s, 1H), 7.59 – 7.52 (m, 1H), 7.31 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.14 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.06 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.45 (d, *J* = 2.1 Hz, 1H), 6.14 (m, 1H), 2.47 (m, 2H), 2.26 (m, 2H), 1.85 – 1.65 (m, 4H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 139.49, 136.19, 129.18, 128.95, 122.62, 121.97, 120.36, 119.74, 110.37, 98.74, 26.10, 25.54, 22.58, 22.23.

The spectral data are in accordance with that in the literature.[16]

Indole **17**



conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 30 min
R_f (SiO$_2$, hexanes/EtOAc 60:40) = 0.35
yield: 111 mg, 93%, white solid

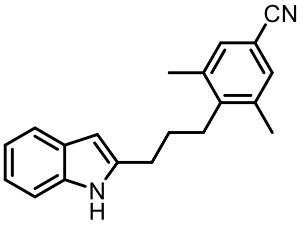
^{1}H NMR (400 MHz, 298 °K, DMSO-d$_6$) δ: 7.82 – 7.74 (m, 2H), 7.34 (dd, *J* = 8.7, 4.6 Hz, 1H), 7.23 (dd, *J* = 10.0, 2.5 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.89 (ddd, *J* = 9.6, 8.8, 2.6 Hz, 1H), 6.78 – 6.72 (m, 1H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, 298 °K, DMSO-d$_6$) δ: 159.01, 157.13 (d, *J* = 231.1 Hz), 139.74, 133.58, 129.08 (d, *J* = 10.6 Hz), 126.50, 124.52, 114.39, 111.87 (d, *J* = 9.9 Hz), 108.96 (d, *J* = 26.1 Hz), 104.16 (d, *J* = 23.2 Hz), 97.54 (d, *J* = 4.6 Hz), 55.22.

^{19}F NMR (376 MHz, 298 °K, DMSO-d$_6$) δ: -120.15.

The spectral data are in accordance with that in the literature.[17]

Indole **18**



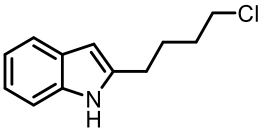
conditions: 2.0 mol % SIPrAuCl/$AgSbF_6$, 85 °C, 12 h
R_f (SiO_2, Et_2O/hexanes 60:40) = 0.36
yield: 122 mg, 85%, yellow solid

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 8.06 (s, 1H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.31 (d, *J* = 5.9 Hz, 3H), 7.19 – 7.04 (m, 2H), 6.30 (d, *J* = 2.2, 1H), 3.89 (t, *J* = 6.2 Hz, 2H), 3.04 (t, *J* = 7.5 Hz, 2H), 2.40 – 2.18 (m, 8H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 159.89, 138.52, 136.08, 132.95, 132.64, 128.85, 121.36, 119.97, 119.85, 119.17, 110.51, 107.45, 99.95, 71.63, 29.85, 24.94, 16.41.

HRMS (ESI+, *m/z*, $[M+H]^+$): calcd. for $C_{20}H_{20}N_2OH$, 305.1654; found 305.1662

Indole **19**



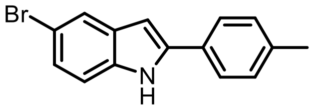
conditions: 0.5 mol % SIPrAuCl/$AgSbF_6$, 55 °C, 90 min
R_f (SiO_2, hexanes/EtOAc 85:15) = 0.35
yield: 92 mg, 88%, yellow oil

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 7.83 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.05 (m, 2H), 6.27 (d, *J* = 2.1 Hz, 1H), 3.62 – 3.54 (m, 2H), 2.86 – 2.75 (m, 2H), 1.88 (m, 4H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 138.86, 135.92, 128.79, 121.19, 119.86, 119.74, 110.39, 99.88, 44.81, 31.94, 27.49, 26.34.

The spectral data are in accordance with that in the literature.[16]

Indole **20**



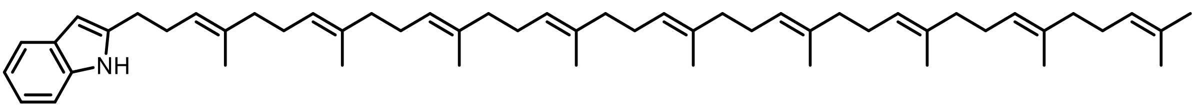
conditions: 0.5 mol % SIPrAuCl/$AgSbF_6$, 55 °C, 90 min.
R_f (SiO_2, hexanes/EtOAc 70:30) = 0.38
yield: 127 mg, 89%, yellowish solid

^{1}H NMR (500 MHz, 298 °K, $CDCl_3$) δ: 8.32 (s, 1H), 7.73 (q, *J* = 1.1 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.29 – 7.22 (m, 4H), 6.71 (d, *J* = 2.1 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, 298 °K, $CDCl_3$) δ: 139.46, 138.33, 135.41, 131.24, 129.95, 129.15, 125.30, 125.02, 123.08, 113.49, 112.32, 99.01, 21.42.

The spectral data are in accordance with that in the literature.[18]

Indole **21**



conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 90 min
R$_f$ (SiO$_2$, hexanes/Et$_2$O 90:10) = 0.40
yield: 176 mg, 94 %, light yellow waxy solid

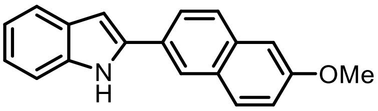
^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 7.95 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.21 – 7.00 (m, 2H), 6.27 (d, *J* = 2.1 Hz, 1H), 5.29 (t, *J* = 7.1 Hz, 1H), 5.15 (t, *J* = 6.9 Hz, 8H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.45 (q, *J* = 7.4 Hz, 2H), 2.21 – 2.06 (m, 16H), 2.01 (m, 16H), 1.71 (s, 3H), 1.63 (s, 24H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 139.89, 136.80, 136.01, 135.42, 135.15, 135.11, 135.09, 135.07, 135.04, 131.40, 128.90, 124.56, 124.43, 124.40, 124.34, 124.18, 123.52, 121.08, 119.92, 119.69, 110.38, 99.72, 39.90, 39.88, 39.85, 28.55, 27.90, 26.92, 26.86, 26.83, 26.71, 25.85, 17.83, 16.24, 16.22, 16.18, 16.15.

*Carbon atoms along the terpenoid-sidechain appear almost isochronous such that not every single signal is resolved at the given spectrometer frequency.

HRMS (ESI+, *m/z*, [M+H]$^+$): calcd. for C$_{54}$H$_{81}$NH, 744.6447; found 744.6451

Indole **22**



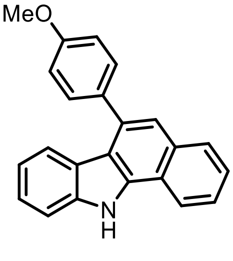
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 90 min
R$_f$ (SiO$_2$, hexanes/EtOAc 70:30) = 0.30
yield: 118 mg, 87 %, light brown solid

^{1}H NMR (500 MHz, 298 °K, CDCl$_3$) δ: 8.47 (s, 1H), 7.99 (s, 1H), 7.83 – 7.75 (m, 3H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.09 (m, 4H), 6.91 (d, *J* = 2.2 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (125 MHz, 298 °K, CDCl$_3$) δ: 158.09, 138.23, 137.04, 134.20, 129.62, 129.54, 129.15, 127.73, 127.70, 124.44, 123.16, 122.42, 120.70, 120.39, 119.63, 110.94, 106.01, 100.11, 55.50.

HRMS (ESI+, *m/z*, [M+H]$^+$): calcd. for C$_{15}$H$_{15}$NOH, 274.1232; found 274.1203

Carbazole **23**



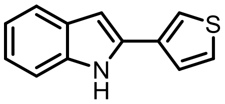
conditions: 1.0 mol % SIPrAuCl/$AgSbF_6$, 65 °C, 4 h.
R_f (SiO_2, hexanes/Et_2O 60:40) = 0.33
yield: 116 mg, 72%, orange solid (contains ca. 2.6 wt % EtOAc, yield corrected for this).

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 8.90 (s, 1H), 8.18 – 8.08 (m, 1H), 8.05 – 7.96 (m, 1H), 7.69 – 7.60 (m, 2H), 7.60 – 7.53 (m, 4H), 7.51 (s, 1H), 7.42 – 7.36 (m, 1H), 7.16 – 7.04 (m, 3H), 3.96 (s, 3H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 159.36, 138.82, 136.40, 135.41, 133.78, 132.31, 130.58, 128.93, 125.77, 125.42, 124.71, 124.08, 122.27, 120.97, 120.46, 120.21, 119.70, 117.09, 113.92, 111.01, 55.53.

The spectral data are in accordance with that in the literature.[19]

Indole **24**



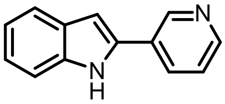
conditions: 0.5 mol % SIPrAuCl/$AgSbF_6$, 55 °C, 30 min
R_f (SiO_2, hexanes/EtOAc 90:10) = 0.40
yield: 98 mg, 98%, yellow oil

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 8.22 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.41 (m, 3H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.18 (m, 1H), 7.13 (m, 1H), 6.71 (d, *J* = 2.2, 1H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 136.42, 134.15, 133.95, 129.10, 126.68, 125.73, 122.29, 120.59, 120.29, 119.08, 110.75, 99.99.

The spectral data are in accordance with that the literature.[20]

Indole **25**



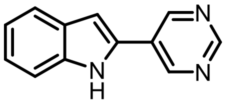
conditions: 2.0 mol % SIPrAuCl/$AgSbF_6$, 80 °C, 12 h.
R_f (SiO_2, hexanes/EtOAc 50:40) = 0.40
yield: 72 mg, 74%, pale-yellow solid

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 8.98 (d, *J* = 2.4 Hz, 1H), 8.81 (s, 1H), 8.56 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.95 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.42 (d, *J* = 8.2, 1H), 7.37 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.17 – 7.12 (m, 1H), 6.90 (dd, *J* = 2.2, 0.9 Hz, 1H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 148.62, 146.53, 137.39, 134.62, 132.53, 129.12, 128.70, 123.99, 123.16, 121.04, 120.71, 111.27, 101.42.

The spectral data are in accordance with that in the literature.[21]

Indole **26**



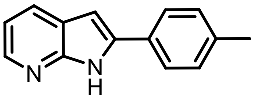
conditions: 1.0 mol % SIPrAuCl/AgSbF$_6$, 65 °C, 12 h
R$_f$ (SiO$_2$, hexanes/EtOAc 60:30) = 0.37
yield: 82 mg, 84%, off-white solid

^{1}H NMR (400 MHz, 298 °K, DMSO-d$_6$) δ: 11.79 (s, 1H), 9.25 (s, 2H), 9.08 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.2, 1H), 7.20 – 7.10 (m, 2H), 7.03 (m, 1H).

^{13}C NMR (100 MHz, 298 °K, DMSO-d$_6$) δ: 156.78, 153.01, 137.69, 131.26, 128.37, 126.55, 122.86, 120.71, 120.04, 111.71, 101.23.

HRMS (ESI+, *m/z*, [M+H]$^+$): calcd. for $C_{12}H_9N_3H$, 196.0875; found 196.0873.

Indole **27**



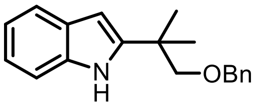
0.25 mmol scale, 85 °C, 12 h
R$_f$ (CH$_2$Cl$_2$/MeOH 90:10) = 0.40
with 70 mg, 90%, colorless oil that slowly turned into a solid
with 2.0 mol % SIPrAuCl/AgSbF$_6$: 29 mg yield (56%)
with 2.0 mol % SIPrAu(CH$_3$CN)SbF$_6$: 27 mg yield (52%)
with 2.0 mol % SIPrAu(CH$_3$CN)SbF$_6$ / 1 equiv Cu(BF$_4$)$_2$: 37 mg yield (71%)

^{1}H NMR (500 MHz, 298 °K, DMSO-d$_6$) δ: 12.05 (s, 1H), 8.18 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.90 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.04 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (125 MHz, 298 °K, DMSO-d$_6$) δ: 149.61, 142.55, 138.43, 137.51, 129.51, 128.86, 127.60, 125.30, 121.02, 115.97, 96.47, 20.86.

HRMS (ESI+, *m/z*, [M+H]$^+$): calcd. for $C_{14}H_{12}N_2H$, 209.1079; found 209.1077.

Indole **28**



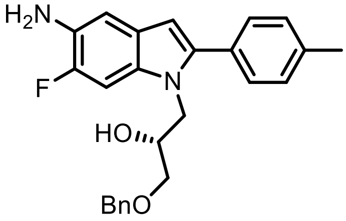
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 4 h
R$_f$ (SiO$_2$, hexanes/Et$_2$O:40) = 0.35
yield: 111 mg, 90%, thick oil

^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 8.94 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.28 (m, 7H), 7.19 – 7.03 (m, 2H), 4.60 (s, 2H), 3.54 (s, 2H), 1.42 (s, 6H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 146.82, 138.14, 135.83, 128.59, 128.40, 127.87, 127.72, 121.05, 119.99, 119.32, 110.58, 97.10, 80.06, 73.69, 36.04, 25.61.

HRMS (ESI+, *m/z*, $[M+Na]^+$): calcd. for $C_{19}H_{21}NONa$, 302.1521; found 302.1535.

Indole **29**



conditions: 0.5 mol % SIPrAuCl/$AgSbF_6$, 55 °C, 12 h.
R_f (SiO_2, hexanes/EtOAc 60:40) = 0.40
yield: 187 mg, 89%, light brown solid (based on the respective bromoaniline)

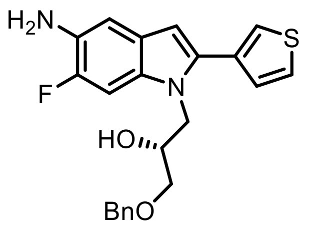
^{1}H NMR (500 MHz, 298 °K, CD_2Cl_2) δ: 7.41 – 7.19 (m, 8H), 7.14 (d, *J* = 11.8 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.32 (d, *J* = 0.8 Hz, 1H), 4.36 (s, 2H), 4.26 – 4.11 (m, 2H), 3.94 (p, *J* = 5.9 Hz, 1H), 3.59 (s, 2H), 3.29 (dd, *J* = 9.7, 3.9 Hz, 1H), 3.14 (dd, *J* = 9.7, 5.5 Hz, 1H), 2.39 (s, 3H), 2.23 (s, 1H).

^{13}C NMR (125 MHz, 298 °K, CD_2Cl_2) δ: 150.92 (d, *J* = 233.7 Hz), 142.50 (d, *J* = 4.1 Hz), 138.47 (d, *J* = 2.7 Hz), 132.14 (d, *J* = 11.2 Hz), 130.56, 129.81 (d, *J* = 2.0 Hz), 129.67, 128.88, 128.32, 128.26, 125.22 (d, *J* = 1.4 Hz), 106.72 (d, *J* = 4.0 Hz), 101.89 (d, *J* = 1.5 Hz), 97.85 (d, *J* = 24.7 Hz), 73.79, 71.93, 70.08, 47.21, 21.53.

^{19}F NMR (470 MHz, 298 °K, CD_2Cl_2) δ: -137.17.

HRMS (ESI+, *m/z*, $[M+H]^+$): calcd. for $C_{25}H_{25}FN_2O_2H$, 405.1978; found 405.2012.

Indole **30**



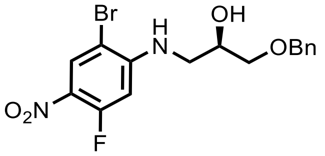
conditions: 0.5 mol % SIPrAuCl/AgSbF$_6$, 55 °C, 12 h
R$_f$ (SiO$_2$, hexanes/CH$_2$Cl$_2$ 80:20) = 0.20
yield: 154 mg, 78%, light brown oil

^{1}H NMR (500 MHz, 298 °K, CD$_2$Cl$_2$) δ: 7.51 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.42 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.39 – 7.26 (m, 7H), 7.12 (d, *J* = 11.9 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.40 (s, 1H), 4.46 (s, 2H), 4.26 – 4.20 (m, 2H), 4.09 (dd, *J* = 6.6, 3.6 Hz, 1H), 3.65 – 3.55 (m, 2H), 3.43 (dd, *J* = 9.7, 4.1 Hz, 1H), 3.30 (dd, *J* = 9.7, 5.6 Hz, 1H), 2.33 (s, 1H).

^{13}C NMR (125 MHz, 298 °K, CD$_2$Cl$_2$) δ: 151.05 (d, J = 234.1 Hz), 138.45, 137.20 (d, J = 4.1 Hz), 133.79, 132.05 (d, J = 11.1 Hz), 129.87 (d, J = 15.2 Hz), 129.21, 128.95, 128.37, 128.33, 126.44, 124.99, 123.99, 106.67 (d, J = 3.8 Hz), 101.84, 97.66 (d, J = 24.5 Hz), 73.94, 72.09, 70.25, 47.46.^{19}F-NMR (470 MHz, 298 K, CD$_2$Cl$_2$) δ: -136.87.

HRMS (ESI+, *m/z*, [M+H]$^+$): calcd. for $C_{22}H_{21}O_2N_2FH$, 397.1386; found 397.1437

Compound **33**



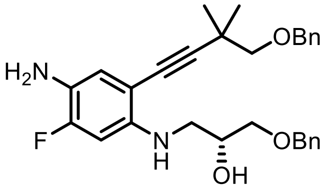
^{1}H NMR (400 MHz, 298 °K, CDCl$_3$) δ: 8.27 (d, *J* = 7.8 Hz, 1H), 7.35 (m, *J* = 6.5 Hz, 5H), 6.37 (d, *J* = 13.7 Hz, 1H), 5.69 (bs, 1H), 4.59 (s, 2H), 4.13 – 4.04 (m, 1H), 3.64 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.56 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.39 (dd, *J* = 13.0, 4.4 Hz, 1H), 3.30 (dd, *J* = 13.0, 4.4 Hz, 1H), 2.49 (bs, 1H).

^{13}C NMR (100 MHz, 298 °K, CDCl$_3$) δ: 157.77 (d, *J* = 263.1 Hz), 151.20 (d, 12.1 Hz), 137.30, 130.47 (d, *J* = 1.5 Hz), 128.76, 128.35, 128.15, 126.67 (d, *J* = 7.3 Hz), 102.96 (d, *J* = 2.0 Hz), 98.15 (d, *J* = 27.1 Hz), 73.95, 71.87, 68.51, 46.65.

^{19}F NMR (376 MHz, 298 °K, CDCl$_3$) δ: -113.26.

The spectral data are in accordance with that in the literature.[8]

Compound **35**



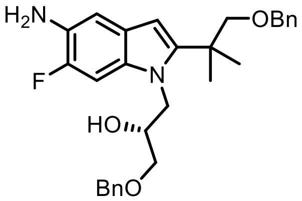
^{1}H NMR (400 MHz, 298 °K, $CDCl_3$) δ: 7.39 – 7.29 (m, 10H), 6.75 (d, *J* = 9.6 Hz, 1H), 6.35 (d, *J* = 13.1 Hz, 1H), 4.63 (s, 2H), 4.55 (s, 2H), 3.98 – 3.91 (m, 1H), 3.57 – 3.44 (m, 3H), 3.41 (s, 2H), 3.21 – 3.14 (m, 2H), 3.08 – 3.02 (m, 2H), 1.34 (s, 6H).

^{13}C NMR (100 MHz, 298 °K, $CDCl_3$) δ: 153.12 (d, *J* = 240.3 Hz), 143.62 (d, *J* = 9.8 Hz), 138.56, 137.85, 128.52, 128.40, 127.89, 127.80 (d, *J* = 3.4 Hz), 127.52 (d, *J* = 6.6 Hz), 124.18 (d, *J* = 14.4 Hz), 120.89 (d, *J* = 5.0 Hz), 104.79 (d, *J* = 3.2 Hz), 101.17 (d, *J* = 1.8 Hz), 98.79 (d, *J* = 24.4 Hz), 78.67, 76.52 (d, *J* = 1.6 Hz), 73.53, 73.40, 72.28, 69.18, 47.07, 33.36, 26.33.

HRMS (ESI+, *m/z*, $[M+Na]^+$): calcd. for $C_{29}H_{33}FN_2O_3Na$, 499.2373; found 499.2373.

^{19}F NMR (376 MHz, 298 °K, $CDCl_3$) δ: -129.90.

Compound **36**



^{1}H NMR (500 MHz, 298 °K, CD_3CN) δ: 7.46 – 7.21 (m, 11H), 7.11 (d, *J* = 12.6 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 6.14 (s, 1H), 4.56 (s, 2H), 4.44 (s, 2H), 4.31 (dd, *J* = 15.1, 3.5 Hz, 1H), 4.22 – 4.07 (m, 2H), 3.77 (s, 2H), 3.63 (s, 2H), 3.49 (d, *J* = 5.0 Hz, 2H), 3.16 (d, *J* = 5.0 Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H).

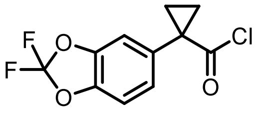
^{13}C NMR (500 MHz, 298 °K, CD_3CN) δ: 150.76 (d, *J* = 230.5 Hz), 147.13 (d, *J* = 4.1 Hz), 139.64, 139.59, 132.81 (d, *J* = 11.2 Hz), 130.21 (d, *J* = 15.2 Hz), 129.33, 129.24, 128.70, 128.68, 128.55, 128.45, 124.95, 106.24 (d, *J* = 4.1 Hz), 100.71, 98.44 (d, *J* = 24.9 Hz), 79.32, 73.95, 73.75, 73.37, 70.94, 49.41, 38.24, 27.18, 26.98.

^{19}F NMR (470 MHz, 298 °K, CD_3CN) δ: -141.50.

The spectral data are in accordance with that in the literature (only ^{1}H NMR data provided therein).[22]

HRMS (ESI+, *m/z*, $[M+Na]^+$): calcd. for $C_{29}H_{33}FN_2O_3Na$, 499.2373; found 499.2376.

Compound **37**



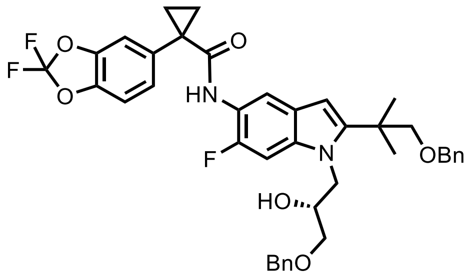
^{1}H NMR (500 MHz, 298 °K, CD_3CN) δ: 7.11 – 7.06 (m, 2H), 7.03 (d, *J* = 8.9 Hz, 1H), 1.98 (q, *J* = 4.5 Hz, 2H), 1.50 – 1.44 (m, 2H).

^{13}C NMR (125 MHz, 298 °K, CD_3CN) δ: 176.37, 143.81, 143.70, 131.83 (t, *J* = 256.0 Hz), 126.34, 112.30, 109.50.

^{19}F NMR (470 MHz, 298 °K, CD_3CN) δ: -49.79.

HRMS not submitted due to the especially irritating nature of this compound.

Compound **38**

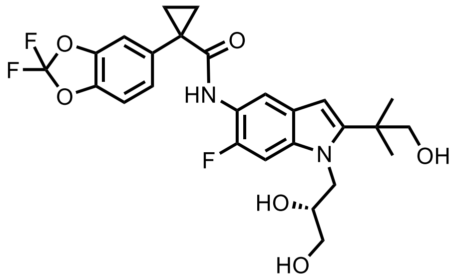


^{1}H NMR (400 MHz, 298 °K, DMSO-d$_6$) δ: 8.30 (s, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.38 – 7.03 (m, 10H), 6.25 (s, 1H), 5.13 (d, *J* = 5.5 Hz, 1H), 4.53 (s, 2H), 4.43 (s, 2H), 4.38 (dd, *J* = 15.2, 3.0 Hz, 1H), 4.10 (dd, *J* = 15.2, 8.6 Hz, 1H), 4.03 – 3.96 (m, 1H), 3.63 (d, *J* = 9.2 Hz, 1H), 3.55 (d, *J* = 9.3 Hz, 1H), 3.51 – 3.39 (m, 2H), 1.47 (q, *J* = 3.9 Hz, 2H), 1.40 (d, *J* = 3.5 Hz, 6H), 1.13 (q, *J* = 3.9 Hz, 2H).

^{19}F NMR (376 MHz, 298 °K, DMSO-d$_6$) δ: -44.03, -126.70 (dd, *J* = 11.9, 7.8 Hz).

HRMS (ESI+, *m/z*, [M+Na]$^+$): calcd. for $C_{40}H_{39}F_3N_2O_6Na$, 723.2658; found 723.2667.

Compound **1:** tezacaftor



^{1}H NMR (500 MHz, 298 °K, CD$_3$CN) δ: 7.66 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.36 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.30 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 12.0 Hz, 1H), 6.31 (s, 1H), 4.31 – 4.25 (m, 2H), 4.08 (dt, *J* = 7.1, 5.2 Hz, 1H), 3.86 (d, *J* = 11.4 Hz, 1H), 3.59 – 3.47 (m, 3H), 3.23 (bs, 1H), 1.58 – 1.52 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 1.16 – 1.12 (m, 2H).

^{13}C NMR (125 MHz, 298 °K, CD$_3$CN) δ: 171.87, 151.79 (d, *J* = 235.9 Hz), 147.51 (d, *J* = 3.6 Hz), 143.77, 143.16, 135.40 (d, *J* = 11.6 Hz), 131.72 (t, *J* = 252.6 Hz), 127.11, 123.46, 118.67 (d, *J* = 14.2 Hz), 115.37 (d, *J* = 2.2 Hz), 112.78, 110.08, 101.40, 97.28, 97.08, 70.38, 69.85, 63.93, 47.87, 38.67, 30.57, 26.47, 24.91, 15.84.

^{19}F NMR (470 MHz, 298 °K, CD$_3$CN) δ: - 50.96, - 135.10.

HRMS (ESI+, *m/z*, [M+Na]$^+$):   calcd. for $C_{26}H_{27}F_3N_2O_6Na$, 543.1719; found 543.1718.

Spectra data matches that in the literature (only ^{1}H NMR provided).[8]

ICP MS

The residual metal content was determined by ICP-MS and the respective analysis was carried out in the Nano and Pico Characterization Laboratory in CNSI at UCLA. Inductively coupled plasma mass spectrometry (ICP-MS, NexION 2000, PerkinElmer) analysis was performed to detect Palladium and Gold in the powder samples. All samples were used as received without further purification or modification. Each sample transferred to clean Teflon vessel for acid digestion. Digestion was carried out with a mixture of concentrated HNO_3 (65-70%, Trace Metal Grade, Fisher Scientific) and HCl (35-38%, Trace Metal Grade, Fisher Scientific) in a ratio of 1:3 with a supplement of H_2O_2 (30%, Certified ACS, Fisher Scientific) at 200 °C for 50 min in a microwave digestion system (Titan MPS, PerkinElmer). Once the sample was cooled to rt, it subsequently diluted to make a final volume of 50 mL by adding filtered DI water for analysis. The calibration curve was established using a standard solution while the dwell time was 50 ms with thirty sweeps and three replicates with background correction.

Table S5: results for ICP-MS analyses

sample name	compound	Au [ppm]	Pd [ppm]	comment
NFL-410	**1** (tezacaftor)	not detected	0.335 ± 0.006	tezacaftor from surfactant process
NFL-361-B	Indole **36**	not applicable	16810 ± 131	from patent process, one crystallization after filtration of the reaction mixture through short silica plug.
NFL-361	Indole **36**	18.678 ± 0.057	0.444 ± 0.000	from surfactant process

Silver-free variant

When the AuCl-type complex is activated with $AgSbF_6$ *in situ*, thermally labile AgCl forms which decomposes to black Ag^0 over the course of the reaction, as evident from Figure S4 taken during the reaction towards **25**, carried out at 80 °C.

Figure S4: Reaction towards **25** with $SIPrAuCl/AgSbF_6$ (left) and $SIPrAu(CH_3CN)SbF_6$ (right).

Calculation of the cEF

Classical process

To compare the surfactant process with the conventional one, the complete E Factor (cEF) was used according to its definition by *Roschangar* et al.:[23]

$$cEF = \frac{\sum solvents + \sum water + \sum reactants/reagents + \sum others - m(product)}{m(product)}$$

As for the classical process, the procedures as disclosed in the patent[22] were used. As yields are not provided for every stage therein, another patent[6] including a step-wise approach was used as the source of the respective information. Solvent amounts given in “volumes” were considered as respective to the reactant/product. If absolute masses were not given, the calculations were exemplarily made for 1 mol. Moreover, the patented procedure involves the synthesis of the tosylate salt of **S2**, presumably to enable a better handling of the compound. As this was not deemed necessary for our case, this extra step was omitted for the calculation of the cEF value.

STEP 1
Epoxide opening and nitro group reduction

Yield of 60% assumed for epoxide opening,[6] 90% for the nitro group reduction.

Compound	**Mass [g]**
starting material **31**	233
molecular sieves (4A)	117
$Zn(ClO_4)_2 \cdot 6H_2O$	59.4
toluene (10 vol)	2020
epoxide **32**	328
ethyl acetate (10 vol)	2101
ammonium chloride	186
water for NH_4Cl solution	745
sodium bicarbonate	23.3
water for $NaHCO_3$ solution	909
isopropyl acetate (10 vol)	2020
platinum-on-carbon (5%, 1.5 mol %)	58.4
Celite	117
dichloromethane (12 vol)	3660
total	11013.7
product	198
step 1 cEF	54.62 kg/kg

STEP 2
Sonogashira coupling and cyclization to the indole

Yield of 27 – 38%, average of 32.5% assumed for both steps.

Compound	**Mass [g]**
starting material **S2**	368
$Pd(OAc)_2$	2.24
1,4-bis(diphenylphosphino)butane	6.4
CuI	2.85
alkyne **34**	206.8
acetonitrile (5.5 vol)*	1590
Celite (0.5 wt. equiv assumed)	184
potassium carbonate	414
$Pd(CH_3CN)_2Cl_2$	25.9
CuI	19
Celite (0.5 wt. equiv assumed)	184
ethyl acetate (7.5 vol)	2489
ammonium chloride	368
water for NH_4Cl solution	1472
sodium chloride	92
water for NaCl solution	828
silica	662
TMT-modified silica	36.8
dichloromethane	978
heptane (wash)	503
heptane (cryst)	755
ethyl acetate	332
total	12675
product	154.7
step 2 cEF	80.93 kg/kg

STEP 3
Amide formation

Yield not provided, assumed as 95%.
Masses used from patented procedure.[6]

Compound	**Mass [g]**
starting material **36**	0.8
acyl chloride **37**	0.524
triethylamine	0.508
dichloromethane	4.3
sodium hydroxide	0.28
water for NaOH solution	2.52
total	8.93
product	0.99

step 3 cEF	8.02 kg/kg

Surfactant process

When crude products were used without further purification, the yield of the individual products was determined via quantitative ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

STEP 1
Epoxide Opening

Compound	**Mass [g]**
starting material **31**	5
epoxide **32**	7.04
$Zn(ClO_4)_2·6\ H_2O$	2.39
ethyl acetate	22.5
hexanes	32.6
silica	10
total	79.53
product	5.3
step 1 cEF	14.01 kg/kg

STEP 2
Sonogashira coupling and nitro group reduction

Compound	**Mass [g]**
starting material **33**	2.67
alkyne **34**	1.51
$Pd(Ph_3P)_4$	0.038
copper iodide	0.013
acetonitrile	0.79
triethylamine	1.86
2 wt % TPGS-750-M in H_2O	12.4
carbonyl iron powder (CIP)	1.84
ammonium chloride	1.08
12M dydrochloric acid	0.8
ethyl acetate (cosolvent)	1.35
ethyl acetate (extraction)	4.5
Celite	3
ethyl acetate (rinse)	9
sodium bicarbonate	1
water for $NaHCO_3$ solution	19
silica	6

ethyl acetate (rinse)	4.5
total	71.35
product (85 % yield)	2.71
step 2 cEF	25.32 kg/kg

STEP 3

Cyclization to the indole

Compound	**Mass [g]**
starting material **35**	1.42
2 wt % TPGS-750-M in H_2O	5.4
$\mathrm{SIPrAu(CH_3CN)SbF_6}$	0.013
tetrahydrofurane	0.53
ethyl acetate (extraction)	4.5
ethyl acetate (crystallization)	1.35
heptane	3.08
total	16.29
step 3 cEF	12.24 kg/kg

STEP 4

Amide formation

Compound	**Mass [g]**
starting material **36**	1.1
acyl chloride **37**	0.778
N,N-diisopropylethylamine	0.895
2 wt % TPGS-750-M in H_2O	3.3
toluene	0.783
ethyl acetate	2.7
silica	1
ethyl acetate (rinse)	0.9
sodium hydroxide	0.5
water for NaOH solution	4.5
total	16.84
product (91 % yield)	1.30
cEF Step 4	11.96

Theoretical calculations

Computational details: The TURBOMOLE V7.5.1[24] suite of programs was used for geometry optimizations and frequency calculations.

Initial conformational searching for stable minimum structures was carried out by use of CREST[25] at the GFN2-xTB[26] (ALPB[27][solvent]) level of theory. The CENSO[28] workflow was applied for re-ranking of the obtained conformer ensemble. For the transition state structures, no conformer dependence could be observed by CREST. Subsequent geometry optimization of the lowest-energy conformer was conducted at the DFT composite method r^{2}SCAN-3c[29](D-COSMORS[30][solvent]) level based on the r^{2}SCAN meta-GGA density functional[31] with a modified def2-TZVP[32] basis set and corrections for dispersion[33] and basis set superposition error[34]. The density-fitting RI-J approach[35–37] was applied throughout to accelerate the single-point calculations. The convergence thresholds for all single-point SCF calculations with TURBOMOLE 7.5.1 were set to 10^{-7} E_H. For calculations at the r^{2}SCAN-3c level, the m4 numerical grid was applied and the setting for the number of radial grid points was set to 10.

Vibrational frequency analysis was used to identify the nature of located stationary points and to provide thermal and free-energy corrections G_{mRRHO} according to the modified ideal gas-rigid rotor-harmonic oscillator model.[38] Structures were characterized as true minima (with no relevant imaginary frequency).

Electronic energies for the lowest-energy conformers were calculated at the ωB97M-V[39]/def2-QZVP[32] hybrid DFT level. Effective core potentials belonging to the def2 family[32] of basis sets were used throughout for the gold center. The final free energies in solvent solution used in the discussion (in kcal mol^{-1}) were obtained from the composite scheme of the hybrid DFT electronic single-point energies and COSMO-RS (BP86/def-TZVP) solvation free energies (default G_{solv} using the BP_TZVP_C30_1601.ctd parameter file)[40,41] together with the thermal and free-energy G_{mRRHO} contributions at the r^{2}SCAN-3c level of theory (*vide supra*).

By multiplication with the conversion factor 627.50947428 kcal mol$^{-1}E_H^{-1}$, the relative Gibbs free energies given in the manuscript can be obtained from Table S6.

Table S6: the ωB97M-V/def2-QZVP // r^{2}SCAN-3c (DCOSMO-RS [Solvent]) single-point electronic energies, the COSMO-RS(Solvent) solvation free energy corrections (G_{solv}), the G_{mRRHO} contributions calculated at the r^{2}SCAN-3c level of theory and total free energies at 328 K.

Species	**$E_{electronic}$**	**G_{solv}**	**G_{mRRHO}**	**G_{total} (328 K)**
	E_H	E_H	E_H	E_H
$[LAuS]^+$ in hexane	-1891.547224	-0.073185	0.714378	-1890.906030
TS$[LAuS]^+$ in hexane	-1891.522857	-0.073964	0.713602	-1890.883220
$[LAuS]^+$ in water	-1891.544626	-0.048791	0.713173	-1890.880244
TS$[LAuS]^+$ in water	-1891.523247	-0.048250	0.714317	-1890.857180
$[LAu]^+$ in hexane	-1296.644771	-0.069387	0.521932	-1296.192225
S in hexane	-594.810075	-0.013557	0.163361	-594.660271
H_2O in hexane	-76.433555	0.002222	0.001529	-76.429804
$[LAuH_2O]^+$ in hexane	-1373.134050	-0.074963	0.544115	-1372.664898
$[LAu]^+$ in water	-1296.644662	-0.049406	0.521960	-1296.172108
S in water	-594.809731	-0.006523	0.163485	-594.652768
H_2O in water	-76.433448	-0.005628	0.001256	-76.437820
$[LAuH_2O]^+$ in water	-1373.132915	-0.063635	0.544593	-1372.651956

$[LAuS]^+$ (H_2O) TS of $[LAuS]^+$ (H_2O)

$[LAuS]^+$ (Hexane) TS of $[LAuS]^+$ (Hexane)

Figure S5: Optimized calculated structures at the r^{2}SCAN-3c (D-COSMORS[Solvent]) level of theory from Table S6.

Catalytic cycle

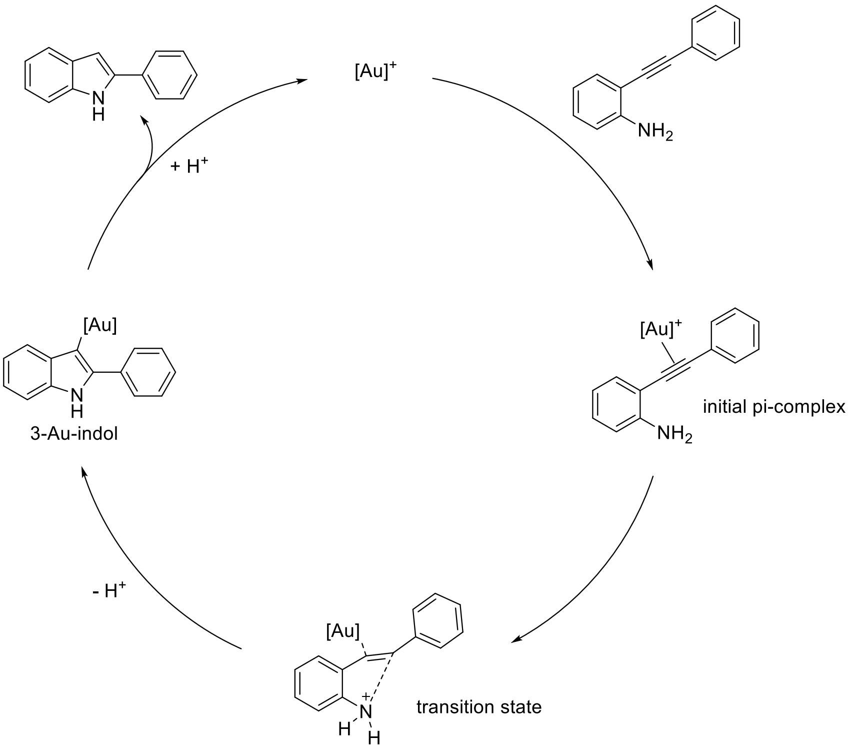


Figure S6: The catalytic cycle is assumed to be as discussed in previous literature.[42]

References

1 G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, R. Gan and H. Apiezon, *Organometallics*, 2010, **29**, 2176–2179.

2 P. Mauleón, R. M. Zeldin, A. Z. González and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 6348–6349.

3 Y. Wang, K. Ji, S. Lan and L. Zhang, *Angew. Chem. Int. Ed.*, 2012, **51**, 1915–1918.

4 A. Collado, A. Gómez-Suárez, A. R. Martin, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.*, 2013, **49**, 5541–5543.

5 V. M. Lau, C. F. Gorin and M. W. Kanan, *Chem. Sci.*, 2014, **5**, 4975–4979.

6 C. Zhang, J. Chakma, *WO 2016/109362*, **2016**.

7 M. Shen, B. E. Leslie and T. G. Driver, *Angew. Chem. Int. Ed.*, 2008, **47**, 5056–5059.

8 D. Belmont, C. Harrison, Y. Jung, E. Lee, B. Littler, P. Rose, D. Siesel, G. Tanoury, *US 9035072*, **2011**.

9 B. Liégault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047–1060.

10 N. Sakai, K. Annaka, A. Fujita, A. Sato and T. Konakahara, *J. Org. Chem.*, 2008, **73**, 4160–4165.

11 H. Sakai, K. Tsutsumi, T. Morimoto and K. Kakiuchia, *Adv. Synth. Catal.*, 2008, **350**, 2498–2502.

12 L. Ackermann, S. Barfüßer and H. K. Potukuchi, *Adv. Synth. Catal.*, 2009, **351**, 1064–1072.

13 P. Rubio-Marqués, M. A. Rivero-Crespo, A. Leyva-Pérez and A. Corma, *J. Am. Chem. Soc.*, 2015, **137**, 11832–11837.

14 K. Okuro, J. Gurnham and H. Alper, *J. Org. Chem.*, 2011, **76**, 4715–4720.

15 H. Jiang, H. Fu, R. Qiao, Y. Jiang and Y. Zhao, *Synthesis*, 2008, **2008**, 2417–2426.

16 Y. Miyazaki and S. Kobayashi, *J. Comb. Chem.*, 2008, **10**, 355–357.

17 D. Kaufmann, M. Pojarová, S. Vogel, R. Liebl, R. Gastpar, D. Gross, T. Nishino, T. Pfaller and E. von Angerer, *Bioorg. Med. Chem.*, 2007, **15**, 5122–5136.

18 S. Pradhan, C. K. Shahi, A. Bhattacharyya and M. K. Ghorai, *Chem. Commun.*, 2018, **54**, 8583–8586.

19 K. Hirano, Y. Inaba, N. Takahashi, M. Shimano, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2011, **76**, 1212–1227.

20 Y. Q. Fang and M. Lautens, *J. Org. Chem.*, 2008, **73**, 538–549.

21 Y. Fang, C. Wang, S. Su, H. Yu and Y. Huang, *Org. Biomol. Chem.*, 2014, **12**, 1061–1071.

22 F. Van Goor, H. Binch, M. Botfield, L. Fannin, P. Grootenhuis, D. Hurley, M. Numa, O. Sheth, A. Silina, X. Yang, G. Zlokarnik, *US 2011/0257223*, **2011**.

23 F. Roschangar, R. A. Sheldon and C. H. Senanayake, *Green Chem.*, 2015, **17**, 752–768.

24 TURBOMOLE V7.5.1, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989-2020, TURBOMOLE GmbH, since 2007; available from http://www.turbomole.com, 2019.

25 P. Pracht, F. Bohle and S. Grimme, *Phys. Chem. Chem. Phys.*, 2020, **22**, 7169–7192.

26 C. Bannwarth, S. Ehlert and S. Grimme, *J. Chem. Theory Comput.*, 2019, **15**, 1652–1671.

27 S. Ehlert, M. Stahn, S. Spicher and S. Grimme, *J. Chem. Theory Comput.*, 2021, **17**, 4250–4261.

28 S. Grimme, F. Bohle, A. Hansen, P. Pracht, S. Spicher and M. Stahn, *J. Phys. Chem. A*, 2021, **125**, 4039–4054.

29 S. Grimme, A. Hansen, S. Ehlert and J. M. Mewes, *J. Chem. Phys.*, 2021, **154**, 64103.

30 A. Klamt and M. Diedenhofen, *J. Phys. Chem. A*, 2015, **119**, 5439–5445.

31 J. W. Furness, A. D. Kaplan, J. Ning, J. P. Perdew and J. Sun, *J. Phys. Chem. Lett.*, 2020, **11**, 8208–8215.

32 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297–3305.

33 E. Caldeweyher, S. Ehlert, A. Hansen, H. Neugebauer, S. Spicher, C. Bannwarth and S. Grimme, *J. Chem. Phys.*, 2019, **150**, 154122.

34 H. Kruse and S. Grimme, *J. Chem. Phys.*, 2012, **136**, 154101.

35 K. Eichkorn, O. Treutler, H. Öhm, M. Häser and R. Ahlrichs, *Chem. Phys. Lett.*, 1995, **240**, 283–290.

36 K. Eichkorn, F. Weigend, O. Treutler and R. Ahlrichs, *Theor. Chem. Accounts 1997 971*, 1997, **97**, 119–124.

37 F. Weigend, *Phys. Chem. Chem. Phys.*, 2006, **8**, 1057–1065.

38 S. Grimme, *Chem. Eur. J.*, 2012, **18**, 9955–9964.

39 N. Mardirossian and M. Head-Gordon, *J. Chem. Phys.*, 2016, **144**, 214110.

40 F. Eckert and A. Klamt, *AIChE J.*, 2002, **48**, 369–385.

41 F. Eckert, A. Klamt, pp. COSMOtherm, Version C3.0, Release 16.01; COSMOlogic GmbH & Co. KG, Leverkusen, Germany, 2015.

42 O. S. Morozov, A. V. Lunchev, A. A. Bush, A. A. Tukov, A. F. Asachenko, V. N. Khrustalev, S. S. Zalesskiy, V. P. Ananikov and M. S. Nechaev, *Chem. Eur. J.*, 2014, **20**, 6162–6170.

DFT Structures

Table S2: The r^{2}SCAN-3c (D-COSMORS[CH_2Cl_2])-optimized cartesian coordinates (in Ångström). For each structure, the structure labelling and number of atoms are followed by atom name and atomic coordinates

.

[LAuS]$^+$_hexane.xyz

94

C	0.9723486	3.7523652	-0.1624137
C	-0.5554817	3.8044093	0.0066152
N	1.2154324	2.2990203	-0.3262989
C	0.1369643	1.5778473	-0.0233949
N	-0.8906577	2.3800992	0.2570467
C	2.5220547	1.7481946	-0.5445126
C	-2.2300285	1.9454099	0.5270678
H	1.5089703	4.1186021	0.7224936
H	1.3266481	4.3032511	-1.0387147
H	-0.8762928	4.4312513	0.8437242
H	-1.0686140	4.1450021	-0.9021681
Au	0.1096674	-0.4411745	-0.0278165
C	-3.5994062	-3.5465147	-2.2701196
C	-4.6543917	-3.0923486	-1.4656453
C	-4.4186020	-2.4936090	-0.2428868
C	-3.1073931	-2.3250769	0.2347117
C	-2.0352641	-2.7845004	-0.5801900
C	-2.3030317	-3.3853024	-1.8306371
C	-0.6969550	-2.6253970	-0.1693240
N	-2.8796219	-1.7764509	1.4671305
H	-3.6029027	-1.1759522	1.8360532
C	0.5300889	-2.5807563	0.0633910
C	1.8191461	-3.0911280	0.4406612
C	2.9895117	-2.3723479	0.1609470
C	4.2242316	-2.8938194	0.5214344
C	4.3032767	-4.1289085	1.1605652
C	3.1410475	-4.8467538	1.4410882
C	1.9005598	-4.3359794	1.0868863
H	-3.7994474	-4.0185071	-3.2262654
H	-5.6795759	-3.2130090	-1.8051072
H	-5.2495610	-2.1547614	0.3700387
H	-1.4632101	-3.7168246	-2.4336492
H	2.9241770	-1.4091636	-0.3389036
H	5.1280476	-2.3339378	0.3002616
H	5.2710347	-4.5348375	1.4406070
H	3.2025417	-5.8098898	1.9393043
H	0.9910751	-4.8873913	1.3055763
C	2.9408471	1.5300687	-1.8679025
C	3.3327668	1.4604457	0.5658598
C	4.6016945	0.9327777	0.3173251
C	2.8770473	1.6837242	1.9965234
H	5.2563369	0.6970071	1.1517413
C	5.0364949	0.6992614	-0.9804339
H	6.0274188	0.2880338	-1.1531816
C	4.2128072	0.9892836	-2.0615520
H	4.5668450	0.7938686	-3.0694592
C	2.0362270	1.8147159	-3.0524051
H	1.2077644	2.4439575	-2.7047376
C	2.7553340	2.5769989	-4.1727902
C	1.4267657	0.5061137	-3.5804100
H	0.7468500	0.7085025	-4.4153000
H	2.2122904	-0.1712338	-3.9342929
H	0.8635180	-0.0124529	-2.7941024
H	3.5242432	1.9624415	-4.6520397
H	2.0367179	2.8638526	-4.9476428
H	3.2346245	3.4856299	-3.7936023
C	3.7957867	2.6734765	2.7286048
H	1.8690855	2.1158939	1.9789461
C	2.7837877	0.3528883	2.7570244
H	4.8056959	2.2658040	2.8428784
H	3.8768578	3.6207416	2.1849544
H	3.4051109	2.8815856	3.7304988
H	3.7615204	-0.1364151	2.8221114
H	2.4210409	0.5222752	3.7764666
H	2.0975634	-0.3400991	2.2558982
C	-3.0688192	1.6010573	-0.5446280
C	-2.6587596	1.9217151	1.8659833
C	-4.3724250	1.2014351	-0.2397590
C	-2.6219780	1.6656630	-1.9934507
H	-5.0480004	0.9216749	-1.0430625
C	-4.8217178	1.1708437	1.0728628
H	-5.8458312	0.8758465	1.2868847
C	-3.9734933	1.5268606	2.1167926
H	-4.3442520	1.5015826	3.1372629
C	-1.7138561	2.2514237	3.0073635
H	-1.5802848	2.0079255	-2.0223318
C	-2.6616424	0.2798823	-2.6513837
C	-3.4669303	2.6756850	-2.7856588
H	-3.6765294	-0.1318953	-2.6557645
H	-2.3166375	0.3425288	-3.6890521
H	-2.0198065	-0.4281121	-2.1165128
H	-4.5099627	2.3490871	-2.8552881
H	-3.4564567	3.6642072	-2.3142638
H	-3.0789633	2.7740453	-3.8051580
H	-0.9022577	2.8727227	2.6095734
C	-2.3839600	3.0392316	4.1385878
C	-1.0743207	0.9608866	3.5458713
H	-2.9030542	3.9247420	3.7575122
H	-3.1087219	2.4280788	4.6862941
H	-1.6274532	3.3670433	4.8588810
H	-0.5287750	0.4290118	2.7561992
H	-0.3687900	1.1878090	4.3526040
H	-1.8432575	0.2894328	3.9465603
H	-1.9435849	-1.4520890	1.6658332

[LAuS]$^+$_h2o.xyz
94

C	0.5981094	3.8425473	0.0421866
C	-0.9268899	3.8181239	0.2407604
N	0.9459575	2.4045053	0.1653323
C	-0.1352926	1.6308863	0.0836486
N	-1.2372227	2.3786617	0.0504235
C	2.2813638	1.8889687	0.0996358
C	-2.5665578	1.8468561	0.0913566
H	1.1185001	4.4378778	0.7969506
H	0.8840268	4.2031684	-0.9545386
H	-1.2230161	4.1265245	1.2519970
H	-1.4634041	4.4309940	-0.4887357
Au	-0.1157594	-0.3821512	-0.0255520
C	3.8962047	-3.0035052	-2.1815509
C	4.8316057	-2.8950421	-1.1359990
C	4.4363777	-2.6885310	0.1666229
C	3.0676148	-2.5782374	0.5003818
C	2.1136036	-2.6953787	-0.5612880
C	2.5563607	-2.8988228	-1.8917219
C	0.7440907	-2.5944121	-0.3001007
N	2.6885474	-2.3709324	1.7743177
H	3.3826919	-2.2828708	2.5013810
C	-0.4943007	-2.4974077	-0.1251805
C	-1.7972256	-3.0878610	0.0564464
C	-1.9146877	-4.4840284	0.1596010
C	-3.1662947	-5.0619532	0.3212989
C	-4.3082534	-4.2629649	0.3830911
C	-4.1951589	-2.8783947	0.2835236
C	-2.9478410	-2.2900321	0.1195760
H	4.2271037	-3.1647465	-3.2020179
H	5.8929029	-2.9713975	-1.3577303
H	5.1724439	-2.5967488	0.9601480
H	1.8075224	-2.9725637	-2.6744301

H	-1.0225231	-5.1017915	0.1127058
H	-3.2522158	-6.1418689	0.4002894
H	-5.2858306	-4.7198390	0.5075642
H	-5.0809689	-2.2520704	0.3323697
H	-2.8582134	-1.2095125	0.0388438
C	2.8103572	1.5133583	-1.1449768
C	2.9915138	1.7432412	1.3018154
C	4.2632089	1.1741565	1.2366566
C	2.3713061	2.1231101	2.6334812
H	4.8356815	1.0270863	2.1475786
C	4.8009862	0.7740719	0.0190832
H	5.7869093	0.3190888	-0.0113541
C	4.0859570	0.9460983	-1.1580829
H	4.5215481	0.6261242	-2.1006466
C	2.0589454	1.7157771	-2.4478858
H	1.0713039	2.1345235	-2.2217894
C	2.7940580	2.7205388	-3.3472736
C	1.8308505	0.3897883	-3.1837127
H	2.7796802	-0.0824824	-3.4588923
H	1.2780061	-0.3153535	-2.5523661
H	1.2538332	0.5601447	-4.0989143
H	3.7714734	2.3301403	-3.6511305
H	2.2098064	2.9141799	-4.2532304
H	2.9554480	3.6720250	-2.8297525
C	3.3627926	2.8084022	3.5792198
H	1.5585125	2.8331741	2.4416434
C	1.7492647	0.8861877	3.2992571
H	3.8470846	3.6633610	3.0962524
H	2.8358574	3.1686228	4.4688278
H	4.1429134	2.1184488	3.9169850
H	1.0210676	0.4041249	2.6361664
H	2.5256828	0.1503490	3.5356565
H	1.2408728	1.1667050	4.2285537
C	-3.2747740	1.7371446	-1.1169365
C	-3.1090219	1.4503370	1.3242296
C	-4.5642207	1.2059934	-1.0672962
C	-2.6409126	2.1076574	-2.4438902
H	-5.1356384	1.0913966	-1.9836193
C	-5.1263856	0.8137939	0.1419821
H	-6.1334792	0.4062303	0.1617024
C	-4.4066358	0.9324999	1.3232505
H	-4.8561606	0.6102371	2.2585048
C	-2.3377268	1.5432464	2.6271306
H	-1.7732031	2.7465379	-2.2426817
C	-2.1265396	0.8410284	-3.1464586
C	-3.5888147	2.8926937	-3.3567500
H	-2.9583930	0.1648281	-3.3749108
H	-1.6232130	1.1006613	-4.0842498
H	-1.4150543	0.2992377	-2.5107385
H	-4.4282408	2.2764180	-3.6947988
H	-3.9932586	3.7726263	-2.8460669
H	-3.0485671	3.2296193	-4.2473896
H	-1.3479924	1.9666608	2.4199445
C	-3.0410597	2.4725652	3.6261848
C	-2.1198595	0.1495523	3.2332852
H	-3.1979619	3.4682785	3.1984106
H	-4.0173731	2.0705255	3.9175916
H	-2.4353662	2.5774532	4.5325047
H	-1.5173499	0.2229042	4.1448771
H	-3.0739753	-0.3223031	3.4918492
H	-1.5977169	-0.5069888	2.5265069
H	1.7160956	-2.3065880	2.0327920

TS[LAuS]$^+$_hexane.xyz

94

C	-3.9618408	0.2845528	-0.4026897
C	-3.8328262	0.3999410	1.1319969
N	-2.5542917	0.1033363	-0.8321626
C	-1.7094491	0.0910163	0.1972612
N	-2.3744301	0.2487498	1.3407448
C	-2.1857333	-0.1136039	-2.1998395
C	-1.7482785	0.3019929	2.6293082
H	-4.3808368	1.1862704	-0.8630789
H	-4.5648229	-0.5753276	-0.7155320
H	-4.1687931	1.3708881	1.5134565
H	-4.3757608	-0.3880073	1.6661520
Au	0.3010004	-0.0715998	0.1062041
C	3.5149536	-0.8342591	3.7704340
C	4.8932911	-0.8436391	3.5628705
C	5.4207031	-0.7253018	2.2783308
C	4.5645161	-0.5868285	1.1904389
C	3.1666033	-0.5420575	1.4037167
C	2.6509555	-0.6811880	2.6931073
C	2.3767987	-0.2337495	0.2316073
N	4.9982703	-0.4303545	-0.1433772
C	2.7973414	0.0751454	-0.9336660
C	2.8620505	0.3494259	-2.3156199
C	3.6277394	1.4329127	-2.7889987
C	3.6732979	1.7023411	-4.1468306
C	2.9435016	0.9181010	-5.0407477
C	2.1701440	-0.1458751	-4.5777676
C	2.1338387	-0.4444603	-3.2257397
H	3.1155209	-0.9297510	4.7754242
H	5.5680654	-0.9554064	4.4065272
H	6.4959460	-0.7597134	2.1227845
H	1.5752477	-0.6354629	2.8457473
H	4.8574785	-1.2649602	-0.7051780
H	4.1809967	2.0392176	-2.0793122
H	4.2716420	2.5311976	-4.5131585
H	2.9778998	1.1382206	-6.1038465
H	1.5986834	-0.7496045	-5.2755076
H	1.5320333	-1.2680270	-2.8526621
C	-2.2117936	-1.4256307	-2.7009577
C	-1.8281323	0.9898099	-2.9912522
C	-1.5021667	0.7493276	-4.3270697
C	-1.7430267	2.3974599	-2.4329179
H	-1.2160866	1.5794403	-4.9667331
C	-1.5365098	-0.5361573	-4.8504072
H	-1.2923445	-0.7008181	-5.8965989
C	-1.8790943	-1.6134877	-4.0437203
H	-1.8891901	-2.6151396	-4.4644970
C	-2.5345117	-2.6219510	-1.8252878
H	-2.8822238	-2.2555094	-0.8522950
C	-3.6495982	-3.4934402	-2.4188147
C	-1.2639562	-3.4472818	-1.5681943
H	-1.4817348	-4.2888621	-0.9017480
H	-0.8649855	-3.8506773	-2.5058080
H	-0.4860530	-2.8303253	-1.1022079
H	-3.9177455	-4.2901476	-1.7168966
H	-4.5474008	-2.9030479	-2.6299752
H	-3.3332418	-3.9698571	-3.3526913
C	-2.5643596	3.3983997	-3.2571616
H	-2.1525960	2.3890309	-1.4155884
C	-0.2739506	2.8385240	-2.3328363
H	-2.5586232	4.3794922	-2.7703678
H	-2.1497220	3.5270099	-4.2624985
H	-3.6041891	3.0709514	-3.3609039
H	-0.2030412	3.8447569	-1.9052231
H	0.2979177	2.1507863	-1.6976517
H	0.1979083	2.8519603	-3.3221967
C	-1.5829446	-0.8938883	3.3472636
C	-1.3068247	1.5434191	3.1157806
C	-0.9518812	-0.8202533	4.5904646
C	-2.0153731	-2.2387473	2.7941377
H	-0.8012767	-1.7264828	5.1704854
C	-0.5065982	0.3954770	5.0937396
H	-0.0185855	0.4327591	6.0638531
C	-0.6795300	1.5634676	4.3626575
H	-0.3184752	2.5050966	4.7666395
C	-1.4595860	2.8283854	2.3238026
H	-2.5893608	-2.0651048	1.8762372
C	-0.7854870	-3.0764950	2.4111106
C	-2.9207429	-3.0013555	3.7708580
H	-1.0931256	-4.0342199	1.9774738
H	-0.1648744	-2.5483359	1.6765690
H	-0.1654331	-3.2842505	3.2902848
H	-3.2895372	-3.9197661	3.3018431
H	-2.3799103	-3.2890268	4.6784095
H	-3.7829187	-2.3960533	4.0700245
H	-2.0287340	2.6065436	1.4132422
C	-2.2379153	3.8917747	3.1118425

C	-0.0874322	3.3607883	1.8834399
H	-2.4041748	4.7766133	2.4880712
H	-3.2114630	3.5121041	3.4397387
H	-1.6856795	4.2121841	4.0016336
H	-0.2068260	4.2592001	1.2679900
H	0.5296657	3.6222181	2.7500887
H	0.4539314	2.6081364	1.2970896
H	5.9657740	-0.1381452	-0.2249577

TS[LAuS]$^+$_h2o.xyz
94

C	-3.9723674	0.3712682	-0.4070735
C	-3.8729794	0.3527023	1.1332573
N	-2.5721398	0.1032908	-0.8181649
C	-1.7347135	0.1121720	0.2160279
N	-2.4078211	0.2891365	1.3517534
C	-2.1547846	-0.0388398	-2.1802286
C	-1.7824964	0.3041858	2.6397239
H	-4.2909254	1.3460691	-0.7961639
H	-4.6432072	-0.3997203	-0.7983261
H	-4.2926336	1.2516832	1.5951737
H	-4.3540629	-0.5281182	1.5758572
Au	0.2718818	-0.0678651	0.1289677
C	3.5449357	-0.4657158	3.7908209
C	4.9199982	-0.5073336	3.5599973
C	5.4265888	-0.5333306	2.2615283
C	4.5529949	-0.5087480	1.1760040
C	3.1604453	-0.4252422	1.4115557
C	2.6643351	-0.4218893	2.7161771
C	2.3483772	-0.2384824	0.2290365
N	4.9593291	-0.5043024	-0.1755007
C	2.7464809	-0.0639191	-0.9714531
C	2.7838794	0.0564634	-2.3762033
C	3.3203349	1.2108656	-2.9782998
C	3.3068859	1.3337544	-4.3579367
C	2.7518697	0.3235630	-5.1452654
C	2.2142076	-0.8200801	-4.5555883
C	2.2339374	-0.9644805	-3.1782053
H	3.1619811	-0.4498276	4.8069201
H	5.6089427	-0.5316585	4.3997389
H	6.4977144	-0.5909389	2.0892865
H	1.5911024	-0.3538163	2.8788379
H	4.7860313	-1.3921981	-0.6410990
H	3.7391351	1.9911703	-2.3506768
H	3.7220019	2.2214122	-4.8255469
H	2.7362825	0.4300383	-6.2262266
H	1.7769641	-1.5983146	-5.1734864
H	1.8142506	-1.8459754	-2.7029273
C	-2.1871345	-1.3190251	-2.7557293
C	-1.7024715	1.0908385	-2.8802017
C	-1.2842074	0.9105265	-4.2001139
C	-1.6217021	2.4662184	-2.2458619
H	-0.9172457	1.7615862	-4.7673281
C	-1.3158039	-0.3440022	-4.7935033
H	-0.9787080	-0.4647105	-5.8193460
C	-1.7578826	-1.4492062	-4.0771307
H	-1.7558582	-2.4282200	-4.5481197
C	-2.5916364	-2.5432346	-1.9574164
H	-3.0602955	-2.2090090	-1.0248982
C	-3.6112491	-3.4171316	-2.6965314
C	-1.3418031	-3.3517074	-1.5758437
H	-1.6167534	-4.2140787	-0.9585701
H	-0.8308332	-3.7183277	-2.4735497
H	-0.6344241	-2.7321269	-1.0110653
H	-3.9410573	-4.2345739	-2.0467947
H	-4.4908312	-2.8352035	-2.9909369
H	-3.1802468	-3.8641550	-3.5984020
C	-2.4777375	3.4879333	-3.0066350
H	-2.0122064	2.4014190	-1.2235956
C	-0.1619045	2.9341852	-2.1504439
H	-2.4626863	4.4522441	-2.4875846
H	-2.0959797	3.6461294	-4.0210212
H	-3.5176766	3.1536844	-3.0833314
H	-0.1061499	3.9057248	-1.6474460
H	0.4412147	2.2144963	-1.5835428
H	0.2847307	3.0362880	-3.1456764
C	-1.5372295	-0.9145300	3.2924213
C	-1.3997315	1.5410710	3.1831845
C	-0.8905172	-0.8689975	4.5295560
C	-1.9051352	-2.2531169	2.6815834
H	-0.6771182	-1.7943041	5.0578539
C	-0.5010746	0.3424190	5.0866722
H	0.0079142	0.3566843	6.0465883
C	-0.7501459	1.5350925	4.4186181
H	-0.4257129	2.4733978	4.8597375
C	-1.6133121	2.8447598	2.4386323
H	-2.4350445	-2.0715918	1.7395153
C	-0.6410011	-3.0591687	2.3480330
C	-2.8425162	-3.0533234	3.5958074
H	-0.9090269	-4.0032165	1.8615800
H	0.0133957	-2.4951832	1.6716409
H	-0.0728156	-3.2906324	3.2557635
H	-3.1548026	-3.9768434	3.0969186
H	-2.3438825	-3.3294023	4.5311116
H	-3.7388215	-2.4760667	3.8456832
H	-2.2591263	2.6468475	1.5757200
C	-2.3123702	3.8987556	3.3057192
C	-0.2751016	3.3715040	1.8980531
H	-2.5261259	4.7909456	2.7078983
H	-3.2575497	3.5173776	3.7058592
H	-1.6843392	4.2062091	4.1484742
H	-0.4317210	4.2874283	1.3177757
H	0.4132537	3.5976572	2.7202718
H	0.2034187	2.6270737	1.2492830
H	5.9277072	-0.2295951	-0.3139176

[LAu]$^+$_h2o.xyz
68

C	-0.7726025	0.0096059	-2.0602483
C	0.7724058	-0.0092538	-2.0606354
N	-1.0978364	-0.0044458	-0.6106825
C	0.0003669	-0.0001067	0.1339362
N	1.0981857	0.0051552	-0.6112176
C	-2.4372067	-0.0043034	-0.1028812
C	2.4377567	0.0045652	-0.1040545
H	-1.2070865	-0.8692297	-2.5477164
H	-1.1849493	0.9126440	-2.5227937
H	1.1844391	-0.9125415	-2.5230695
H	1.2065219	0.8694102	-2.5486071
Au	0.0017528	-0.0021851	2.0876336
C	-3.0608033	1.2274765	0.1482055
C	-3.0680544	-1.2376312	0.1211298
C	-4.3700127	-1.2130634	0.6237132
C	-2.3656016	-2.5604177	-0.1179696
H	-4.8870993	-2.1478439	0.8216301
C	-5.0106480	-0.0077590	0.8831102
H	-6.0237218	-0.0092025	1.2755763
C	-4.3634737	1.1991221	0.6491673
H	-4.8757441	2.1324376	0.8661597
C	-2.3531920	2.5523061	-0.0626970
H	-1.3917929	2.3596489	-0.5526599
C	-3.1551369	3.4891891	-0.9751249
C	-2.0536455	3.2223741	1.2866172
H	-1.4543612	2.5640384	1.9275594
H	-1.4971677	4.1532476	1.1336386
H	-2.9814946	3.4605198	1.8182625
H	-4.1014328	3.7847733	-0.5101029
H	-2.5806689	4.4003484	-1.1718340
H	-3.3811246	3.0100123	-1.9332631
C	-3.1821730	-3.4868024	-1.0277888
H	-1.4126075	-2.3622519	-0.6218546
C	-2.0430793	-3.2450860	1.2187271
H	-3.4239282	-2.9961864	-1.9763089
H	-2.6101905	-4.3948790	-1.2448550
H	-4.1204090	-3.7894978	-0.5512383
H	-2.9621084	-3.4870376	1.7638659
H	-1.4909158	-4.1751734	1.0463385
H	-1.4316904	-2.5943495	1.8559893
C	3.0697478	1.2376488	0.1180818
C	3.0605300	-1.2274449	0.1480129

C	4.3726327	1.2125622	0.6181625
C	2.3667713	2.5606186	-0.1184836
H	4.8908255	2.1470949	0.8142615
C	5.0127884	0.0070552	0.8777380
H	6.0267927	0.0081361	1.2678693
C	4.3640218	-1.1995611	0.6468835
H	4.8757282	-2.1330003	0.8645022
C	2.3515269	-2.5520309	-0.0598723
H	1.4146366	2.3631385	-0.6242395
C	2.0420801	3.2405867	1.2201728
C	3.1834299	3.4912583	-1.0237423
H	1.4300217	2.5875126	1.8543884
H	2.9604063	3.4808646	1.7672630
H	1.4899294	4.1711420	1.0502837
H	4.1199237	3.7946584	-0.5442412
H	3.4282887	3.0042201	-1.9732797
H	2.6099352	4.3988262	-1.2389925
H	1.3892319	-2.3593676	-0.5481428
C	3.1509780	-3.4905247	-0.9728613
C	2.0543746	-3.2203429	1.2909157
H	2.5757968	-4.4018318	-1.1667768
H	3.3746358	-3.0127736	-1.9323008
H	4.0983450	-3.7855714	-0.5096491
H	2.9832425	-3.4592010	1.8204482
H	1.4576351	-2.5606686	1.9329723
H	1.4962738	-4.1506316	1.1402599

S_h2o.xyz
26

C	3.9018120	1.5645598	-0.0049996
C	4.6446309	0.3799495	-0.0143812
C	4.0131011	-0.8542309	-0.0093149
C	2.6126760	-0.9482999	0.0035058
C	1.8530606	0.2540900	0.0138749
C	2.5188222	1.4943789	0.0095185
C	0.4425221	0.1987572	0.0201941
N	1.9880665	-2.1780986	-0.0492218
C	-0.7732510	0.1393775	0.0172045
C	-2.1883651	0.0997607	0.0094362
C	-2.9329219	1.2949563	0.0187621
C	-4.3202901	1.2533274	0.0064009
C	-4.9896835	0.0304277	-0.0149185
C	-4.2600753	-1.1576804	-0.0230720
C	-2.8722092	-1.1305425	-0.0111954
H	4.3999505	2.5287593	-0.0077246
H	1.9200078	2.4004846	0.0185291
H	-2.4102948	2.2465314	0.0349434
H	-4.8839086	2.1820300	0.0132324
H	-6.0753561	0.0038616	-0.0255697
H	-4.7766854	-2.1131703	-0.0393210
H	-2.3031522	-2.0553188	-0.0183705
H	1.0434518	-2.2099883	0.3134551
H	2.5517381	-2.9630029	0.2532848
H	5.7304292	0.4203667	-0.0217477
H	4.5989911	-1.7698018	-0.0159563

H_2O_h2o.xyz
3

O	-0.0000056	0.0000000	-0.3965819
H	-0.7631792	0.0000000	0.1982894
H	0.7631848	0.0000000	0.1982925

[LAuH_2O]$^+$_h2o.xyz
71

C	-0.7593740	0.1490547	2.1977676
C	0.7803636	0.2127341	2.1848511
N	-1.0877047	0.0546242	0.7552837
C	0.0003485	0.0251516	-0.0139084
N	1.0960586	0.1053546	0.7396073
C	-2.4352965	-0.0040688	0.2787875
C	2.4445667	0.0208984	0.2702223
H	-1.2166397	1.0460450	2.6289986
H	-1.1443954	-0.7297085	2.7273783
H	1.1698070	1.1575761	2.5800931
H	1.2438903	-0.6142460	2.7334635
Au	-0.0315079	-0.0398672	-1.9845001
C	-3.0433308	-1.2604523	0.1301453
C	-3.1026735	1.1995673	0.0049501
C	-4.4166378	1.1189143	-0.4593293
C	-2.4265704	2.5481980	0.1627607
H	-4.9604407	2.0294429	-0.6953778
C	-5.0374964	-0.1127321	-0.6276439
H	-6.0607080	-0.1560342	-0.9905113
C	-4.3593614	-1.2895904	-0.3345151
H	-4.8589636	-2.2441949	-0.4742629
C	-2.3032678	-2.5539580	0.4142156
H	-1.3546484	-2.3086344	0.9053431
C	-3.0873923	-3.4717161	1.3604401
C	-1.9655632	-3.2779159	-0.8977137
H	-1.3715440	-2.6348998	-1.5583422
H	-1.3908000	-4.1877783	-0.6936893
H	-2.8802926	-3.5616675	-1.4301791
H	-4.0136709	-3.8277039	0.8977459
H	-2.4831600	-4.3493539	1.6129660
H	-3.3472489	-2.9535959	2.2894011
C	-3.2388222	3.4926181	1.0578385
H	-1.4542379	2.3937430	0.6441575
C	-2.1569473	3.1825001	-1.2095225
H	-3.4161989	3.0479333	2.0426749
H	-2.6965737	4.4336599	1.1973776
H	-4.2102598	3.7299899	0.6117217
H	-3.0953790	3.3846568	-1.7377370
H	-1.6185889	4.1291095	-1.0912682
H	-1.5501352	2.5161070	-1.8346542
C	3.0548290	-1.2427718	0.2215635
C	3.1170007	1.2017198	-0.0815039
C	4.3864878	-1.3030973	-0.1914804
C	2.3042634	-2.5169850	0.5603948
H	4.8891566	-2.2647682	-0.2464768
C	5.0775803	-0.1481484	-0.5359340
H	6.1174528	-0.2148385	-0.8434183
C	4.4476362	1.0894351	-0.4898435
H	4.9983192	1.9808614	-0.7769890
C	2.4288513	2.5537909	-0.0824635
H	1.3237027	-2.2456630	0.9675506
C	2.0553602	-3.3439530	-0.7097149
C	3.0309042	-3.3472477	1.6260642
H	1.5029121	-2.7593494	-1.4548005
H	3.0026749	-3.6619704	-1.1591018
H	1.4714936	-4.2396424	-0.4716289
H	2.4206825	-4.2125708	1.9054262
H	3.9906630	-3.7217912	1.2550472
H	3.2220638	-2.7553107	2.5271808
H	1.4473292	2.4417344	0.3931321
C	3.2106464	3.6083257	0.7098908
C	2.1918821	3.0289237	-1.5235714
H	4.1810114	3.8174705	0.2474224
H	2.6455541	4.5464289	0.7288090
H	3.3861131	3.2842792	1.7408265
H	1.6541007	3.9832054	-1.5260982
H	3.1436289	3.1683640	-2.0482680
H	1.5973090	2.2968332	-2.0836450
O	-0.0859115	-0.0973271	-4.0985647
H	-0.9493098	0.1893487	-4.4447896
H	0.5764092	0.4849534	-4.5100515

[LAu]$^+$_hexane.xyz
68

C	0.7729210	-0.0038717	-2.0125208
C	-0.7729090	0.0038808	-2.0125166
N	1.1016907	-0.0009358	-0.5638024
C	0.0000035	-0.0000058	0.1708716
N	-1.1016925	0.0009401	-0.5637983
C	2.4464623	-0.0040570	-0.0623321
C	-2.4464682	0.0040610	-0.0623325
H	1.2042352	0.8822104	-2.4900160
H	1.1952184	-0.8976764	-2.4838673
H	-1.1952042	0.8976752	-2.4838843
H	-1.2042430	-0.8821908	-2.4899942

Au	0.0000718	-0.0000329	2.1341084
C	3.0718540	-1.2396549	0.1669930
C	3.0802275	1.2287901	0.1585326
C	4.3905588	1.1976957	0.6382023
C	2.3856940	2.5571644	-0.0761054
H	4.9143620	2.1299449	0.8295512
C	5.0343312	-0.0095740	0.8779797
H	6.0549137	-0.0117432	1.2502233
C	4.3823895	-1.2140770	0.6464384
H	4.8998905	-2.1485404	0.8439476
C	2.3685228	-2.5650205	-0.0584821
H	1.3818565	-2.3653298	-0.4943734
C	3.1376732	-3.4551273	-1.0453395
C	2.1364926	-3.2910696	1.2752469
H	3.0871730	-3.5355981	1.7610945
H	1.5554303	-2.6681219	1.9667926
H	1.5891091	-4.2252793	1.1112600
H	2.5649151	-4.3639018	-1.2578459
H	3.3230834	-2.9341918	-1.9905640
H	4.1056700	-3.7606116	-0.6349580
C	3.1596747	3.4344107	-1.0706548
H	1.3971673	2.3608184	-0.5092631
C	2.1600771	3.2947595	1.2523733
H	4.1305674	3.7358604	-0.6641322
H	3.3397929	2.9052936	-2.0123576
H	2.5931005	4.3456859	-1.2889148
H	3.1129087	3.5359699	1.7356442
H	1.6196233	4.2317954	1.0816929
H	1.5749608	2.6813975	1.9489560
C	-3.0802329	-1.2287885	0.1585257
C	-3.0718624	1.2396593	0.1669956
C	-4.3905667	-1.1976901	0.6381854
C	-2.3856991	-2.5571641	-0.0761045
H	-4.9143523	-2.1299267	0.8295643
C	-5.0343378	0.0095765	0.8779728
H	-6.0549171	0.0117208	1.2502063
C	-4.3824011	1.2140838	0.6464441
H	-4.8999116	2.1485495	0.8439493
C	-2.3685244	2.5650228	-0.0584886
H	-1.3971743	-2.3608142	-0.5092590
C	-2.1600616	-3.2947678	1.2523670
C	-3.1596793	-3.4344146	-1.0706495
H	-1.5749594	-2.6813966	1.9489616
H	-3.1128940	-3.5359680	1.7356311
H	-1.6196236	-4.2318218	1.0816881
H	-3.3397998	-2.9052971	-2.0123572
H	-2.5930893	-4.3456898	-1.2888888
H	-4.1305824	-3.7358546	-0.6641269
H	-1.3818593	2.3653381	-0.4943838
C	-3.1376798	3.4551320	-1.0453513
C	-2.1364860	3.2910601	1.2752465
H	-2.5649216	4.3639090	-1.2578466
H	-3.3230967	2.9342072	-1.9905759
H	-4.1056799	3.7606102	-0.6349698
H	-1.5891202	4.2252747	1.1112703
H	-3.0871638	3.5355864	1.7610840
H	-1.5554296	2.6681209	1.9668030

S_hexane.xyz

26

C	3.9393340	1.5928147	-0.0663299
C	4.6720147	0.4037046	-0.0246700
C	4.0294869	-0.8246524	0.0123464
C	2.6296702	-0.9031672	0.0092361
C	1.8788412	0.3029920	-0.0305660
C	2.5554080	1.5353694	-0.0684175
C	0.4682825	0.2505081	-0.0254957
N	1.9860248	-2.1238826	-0.0101211
C	-0.7464574	0.1773045	-0.0215187
C	-2.1609832	0.1307973	-0.0209741
C	-2.9111175	1.3197598	0.0546649
C	-4.2981358	1.2728639	0.0541355
C	-4.9635709	0.0500244	-0.0199899
C	-4.2291266	-1.1324708	-0.0952295
C	-2.8415889	-1.0988563	-0.0969499
H	4.4462220	2.5521288	-0.0954970
H	1.9638614	2.4456011	-0.0972964
H	-2.3906160	2.2707402	0.1130158
H	-4.8651098	2.1979297	0.1124526
H	-6.0493256	0.0189364	-0.0199849
H	-4.7419404	-2.0885397	-0.1549178
H	-2.2693220	-2.0195633	-0.1599216
H	1.0196230	-2.1138990	0.2839975
H	2.5099522	-2.9074318	0.3484552
H	5.7582296	0.4346756	-0.0201185
H	4.6103435	-1.7436875	0.0396947

H$_2$O_hexane.xyz

3

O	-0.0000047	0.0000000	-0.3948028
H	-0.7593045	0.0000000	0.1973977
H	0.7593091	0.0000000	0.1974051

[LauH$_2$O]$^+$_hexane.xyz

71

C	-0.7723990	-0.1434314	-2.8772863
C	0.7718364	-0.1420471	-2.8781590
N	-1.0954624	-0.0773662	-1.4323708
C	0.0008529	-0.0436544	-0.6790530
N	1.0961476	-0.0794541	-1.4334575
C	-2.4395934	-0.0533334	-0.9327295
C	2.4407342	-0.0515478	-0.9352898
H	-1.1978179	-1.0535949	-3.3145055
H	-1.1993175	0.7225117	-3.3953137
H	1.1985909	-1.0500200	-3.3185171
H	1.1966203	0.7263613	-3.3939094
Au	0.0031677	0.0548477	1.2858027
C	-3.0748858	-1.2741474	-0.6538359
C	-3.0682822	1.1893843	-0.7532790
C	-4.3744797	1.1851754	-0.2605859
C	-2.3690257	2.5048084	-1.0421033
H	-4.8912977	2.1273871	-0.1010524
C	-5.0237130	-0.0076468	0.0308601
H	-6.0408043	0.0104829	0.4124477
C	-4.3807716	-1.2236255	-0.1632579
H	-4.9029871	-2.1471478	0.0707075
C	-2.3814850	-2.6118940	-0.8345844
H	-1.4108545	-2.4363626	-1.3137736
C	-2.1023297	-3.2658362	0.5273279
C	-3.1842110	-3.5535171	-1.7434043
H	-4.1386559	-3.8336446	-1.2856982
H	-3.3996037	-3.0859845	-2.7098936
H	-2.6200250	-4.4748297	-1.9231852
H	-1.4929539	-2.6068746	1.1583020
H	-3.0362272	-3.4785486	1.0592279
H	-1.5636245	-4.2104492	0.3952149
C	-2.0926480	3.2695751	0.2613708
H	-1.3977696	2.2863236	-1.5021425
C	-3.1655846	3.3694791	-2.0295571
H	-1.5494452	4.1974633	0.0522647
H	-3.0277153	3.5305028	0.7690566
H	-1.4896980	2.6654422	0.9504866
H	-2.5973215	4.2705435	-2.2837663
H	-3.3799056	2.8236250	-2.9543752
H	-4.1201716	3.6903759	-1.5997818
C	3.0664359	1.1931241	-0.7585691
C	3.0796310	-1.2703478	-0.6559083
C	4.3732747	1.1930513	-0.2675784
C	2.3629218	2.5063999	-1.0470594
H	4.8878829	2.1368395	-0.1101989
C	5.0260587	0.0023210	0.0243861
H	6.0436675	0.0236988	0.4044473
C	4.3860412	-1.2156124	-0.1671802
H	4.9110825	-2.1373716	0.0673340
C	2.3872937	-2.6097855	-0.8283260
H	1.3907534	2.2849687	-1.5037376
C	2.0884930	3.2720938	0.2562839
C	3.1543379	3.3717536	-2.0380836
H	3.0243721	3.5363653	0.7607176

H	1.5420138	4.1981594	0.0476548
H	1.4895218	2.6671206	0.9481105
H	4.1091535	3.6960050	-1.6113484
H	3.3678269	2.8250103	-2.9625825
H	2.5828181	4.2707855	-2.2922508
H	1.4166605	-2.4380482	-1.3089715
C	3.1901323	-3.5582879	-1.7296644
C	2.1084472	-3.2538601	0.5383991
H	4.1452510	-3.8336136	-1.2704897
H	2.6265966	-4.4818083	-1.9001624
H	3.4040104	-3.0992058	-2.7005283
H	1.5702859	-4.1997471	0.4132701
H	3.0425522	-3.4619834	1.0717397
H	1.4987603	-2.5905853	1.1645771
O	0.0065450	0.2097886	3.4243613
H	-0.7767685	-0.1801295	3.8393203
H	0.7730382	-0.2114454	3.8401888

NMR spectra

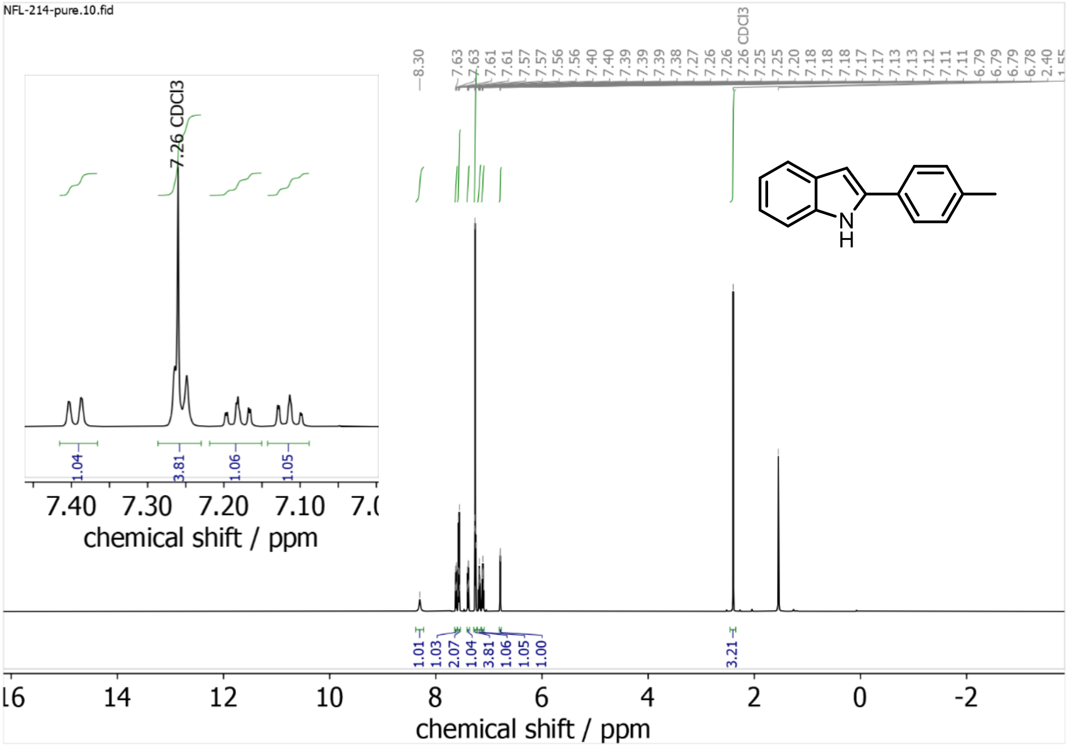


Figure S7: ^{1}H NMR spectrum of **3**. *The $CDCl_3$ peak overlaps with one aromatic dublet of the p-tolyl-substituent, leading to a false integration of 3.81 for this peak.*

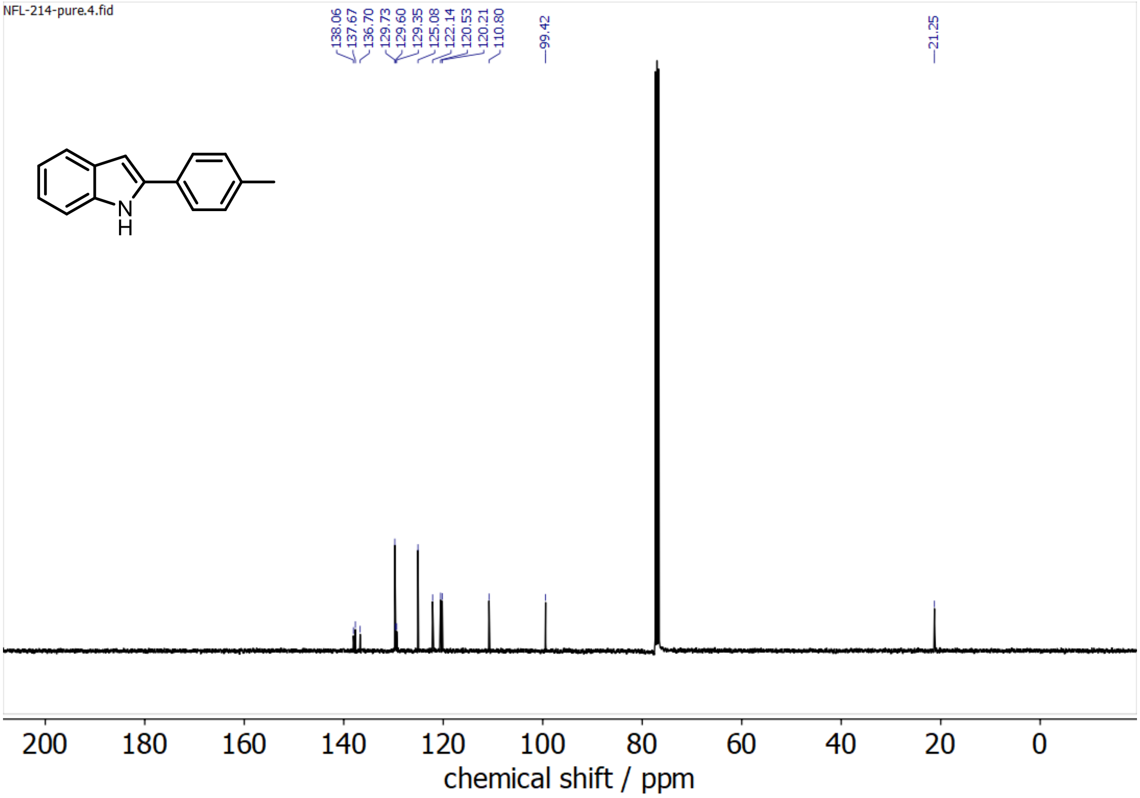


Figure S8: ^{13}C NMR spectrum of **3**.

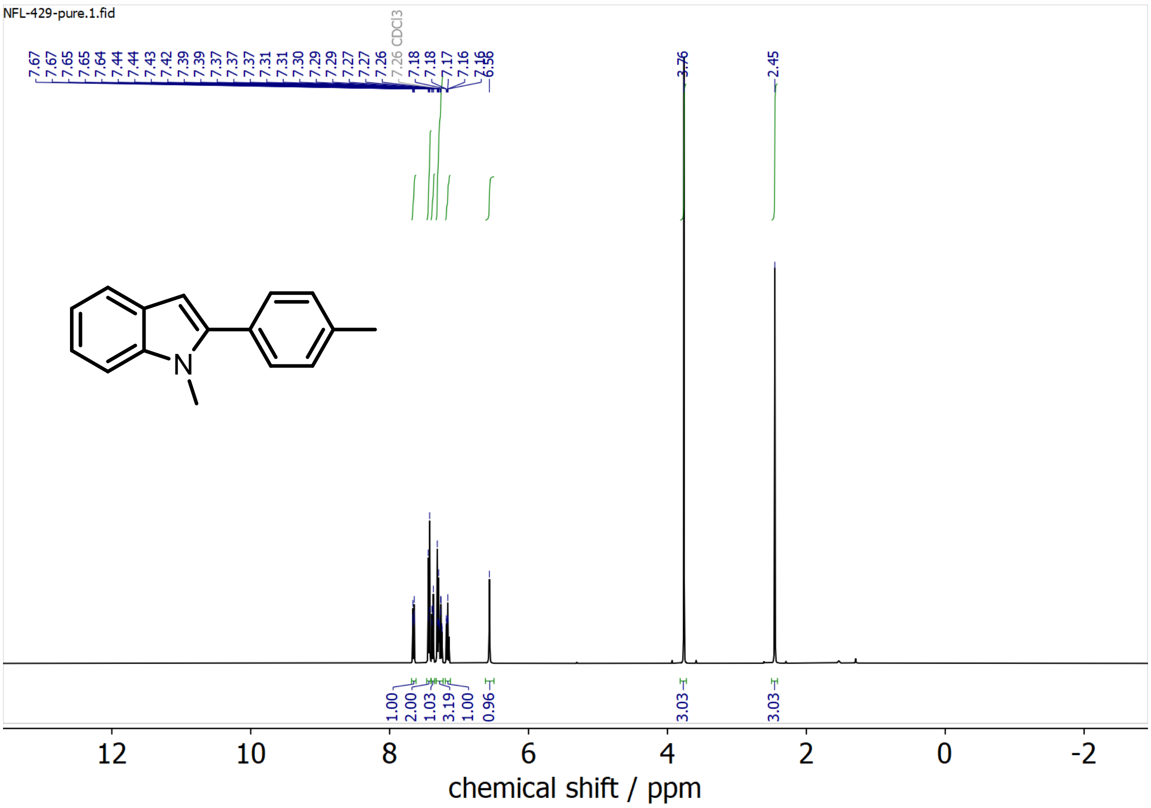


Figure S9: ^{1}H NMR spectrum of **4**.

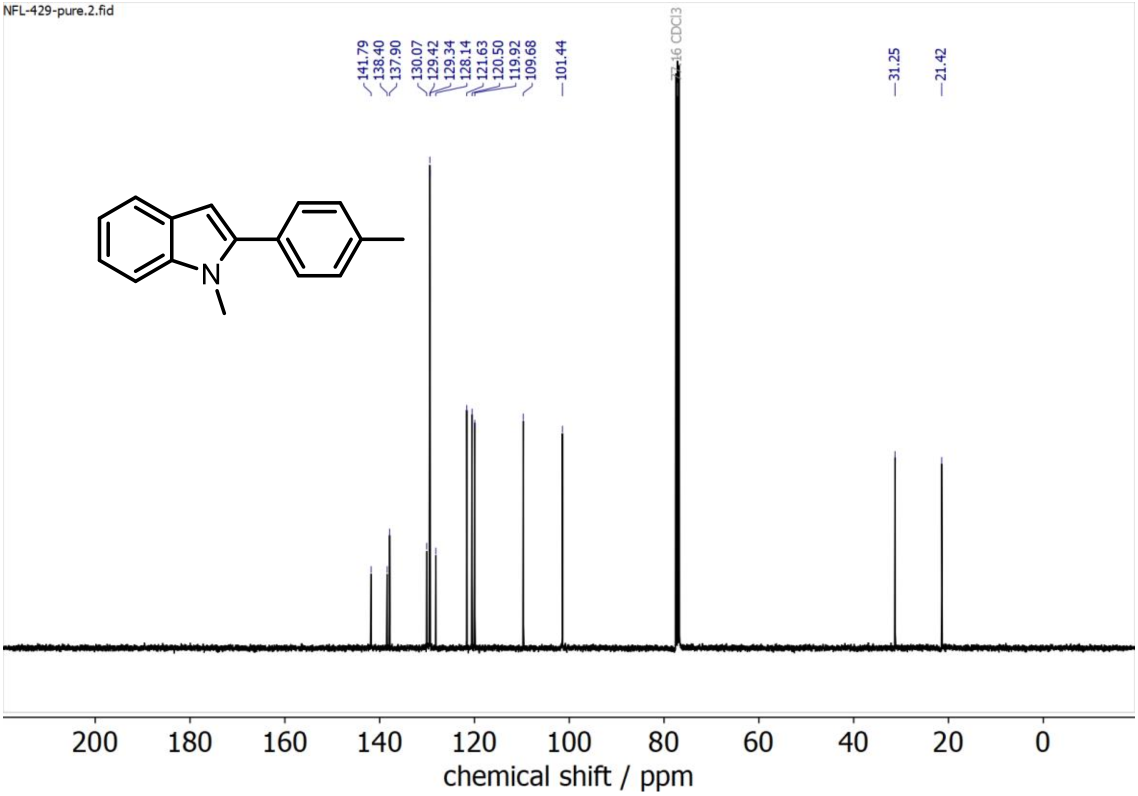


Figure S10: ^{13}C NMR spectrum of **4**.

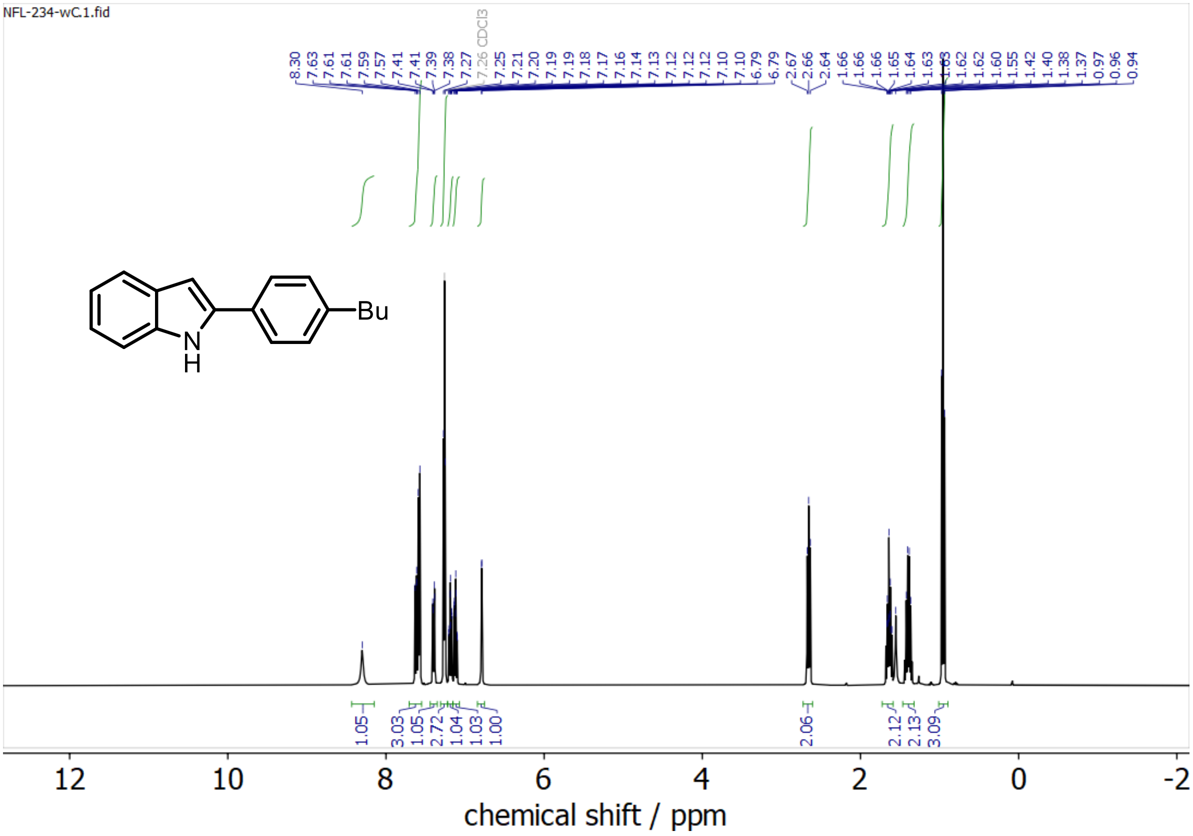


Figure S11: ^{1}H NMR spectrum of **5**.

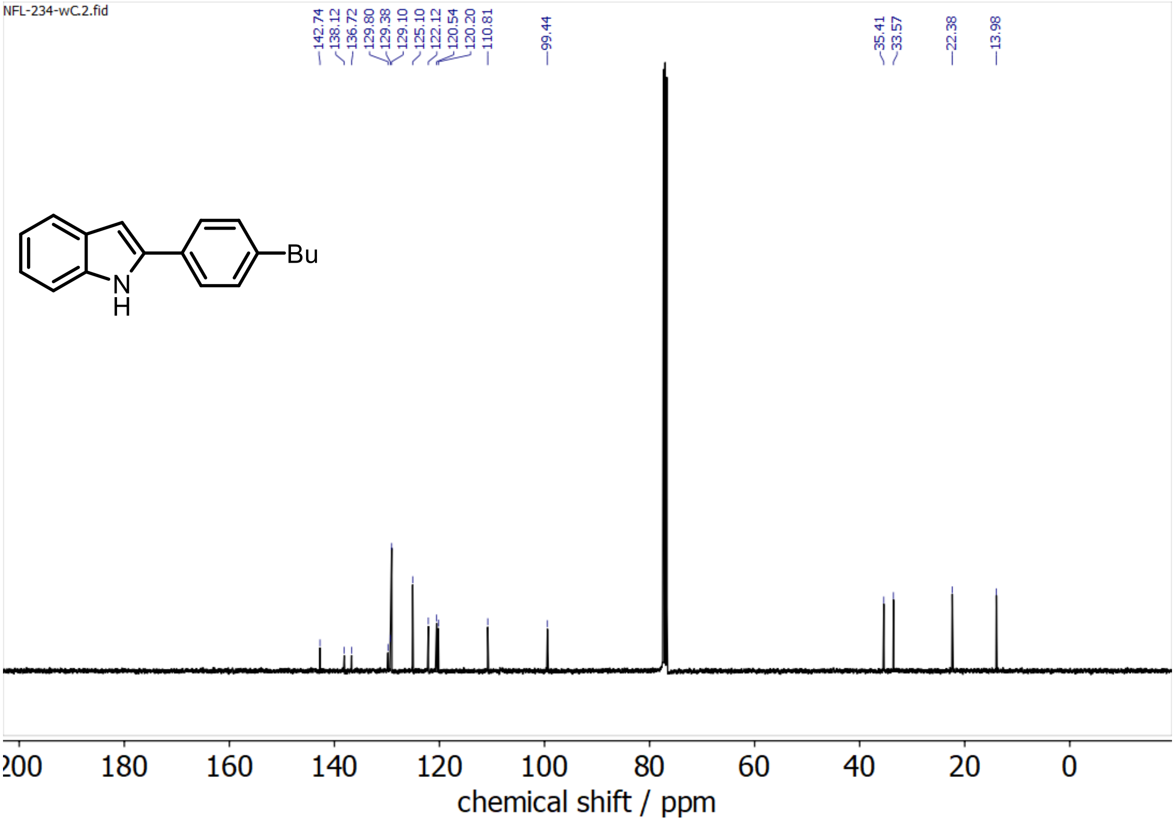


Figure S12: ^{13}C NMR spectrum of **5**.

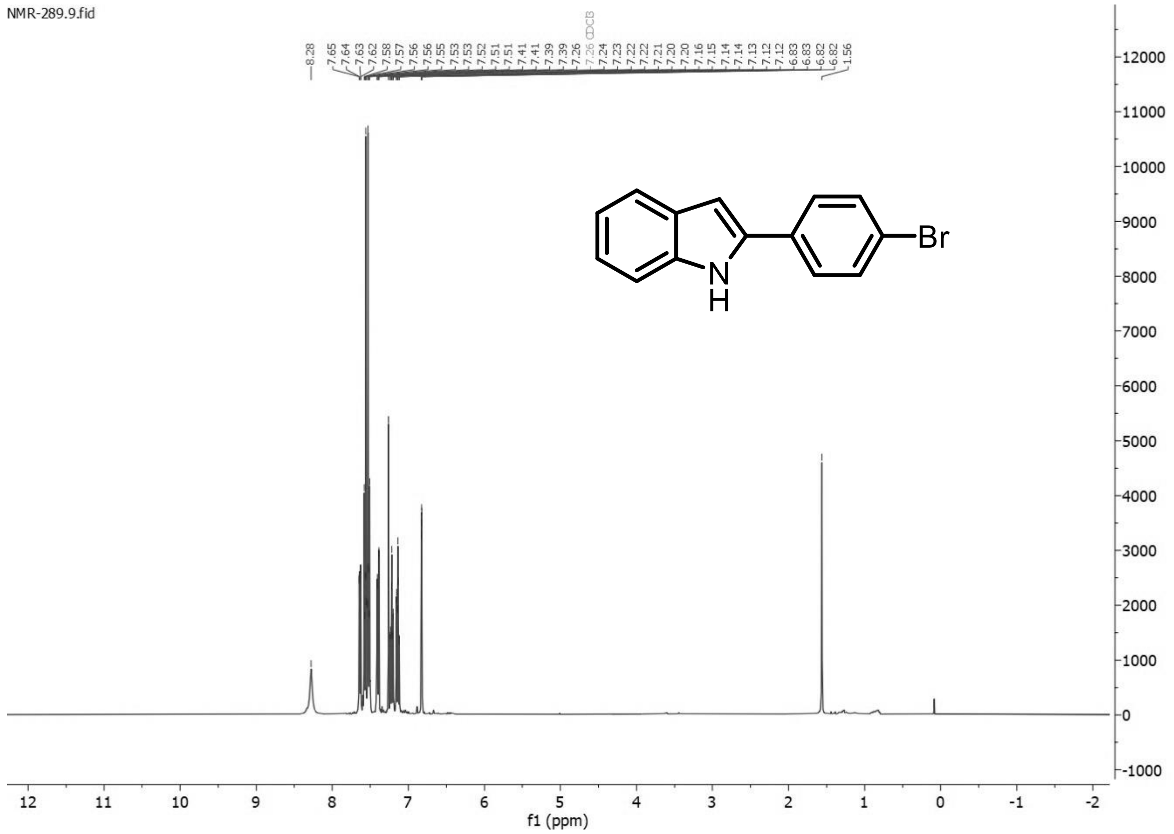


Figure S13: ^{1}H NMR spectrum of **6**.

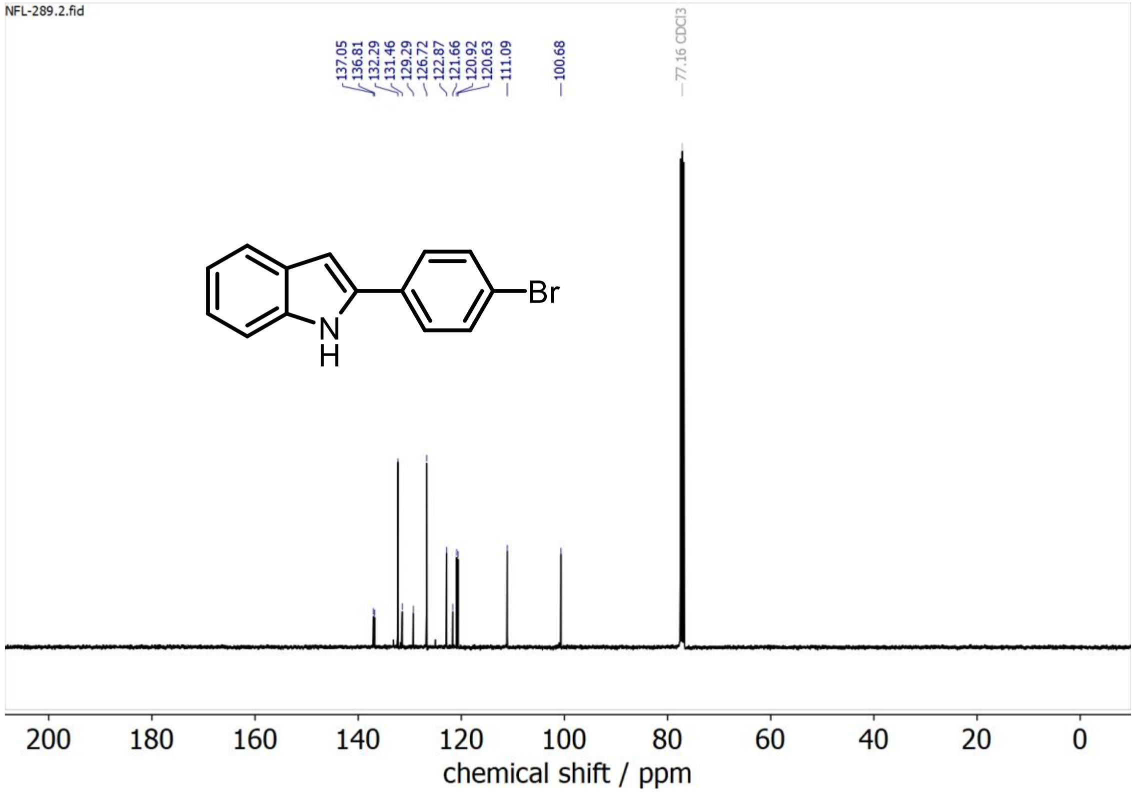


Figure S14: ^{13}C NMR spectrum of **6**.

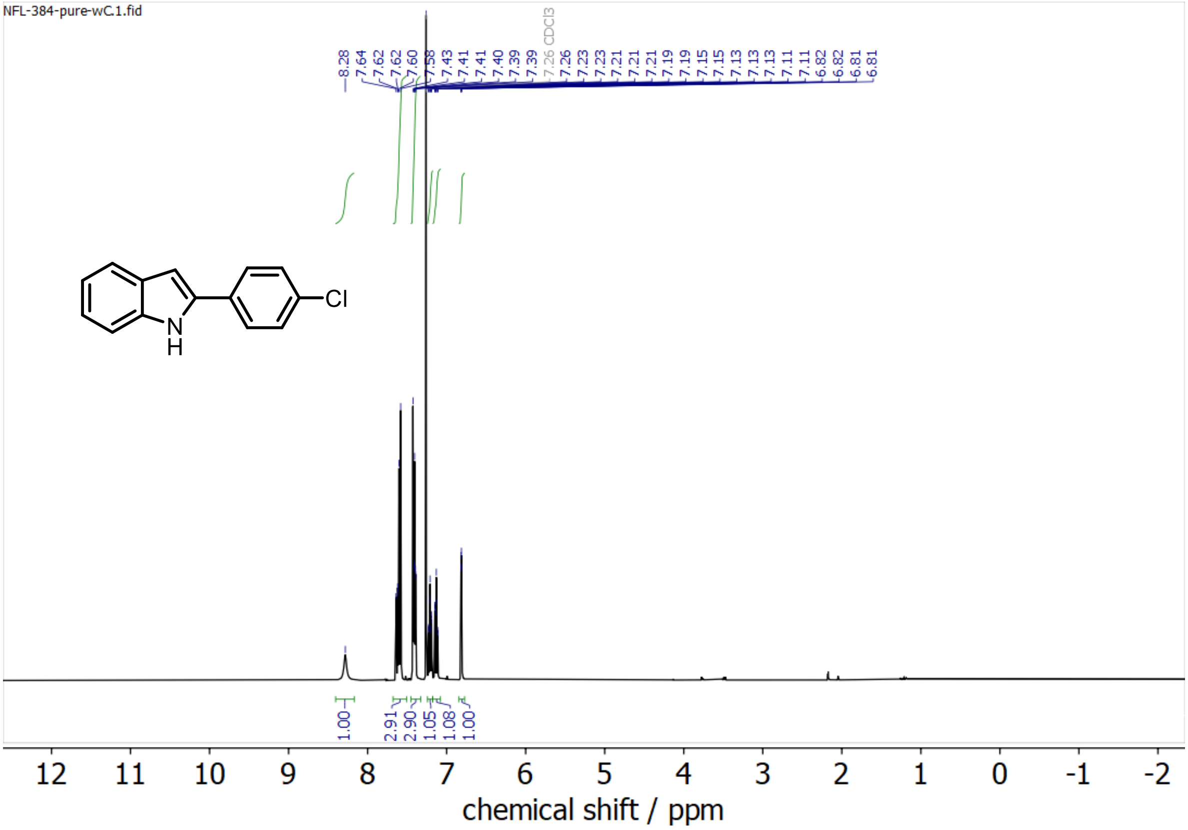


Figure S15: ^{1}H NMR spectrum of **7**.

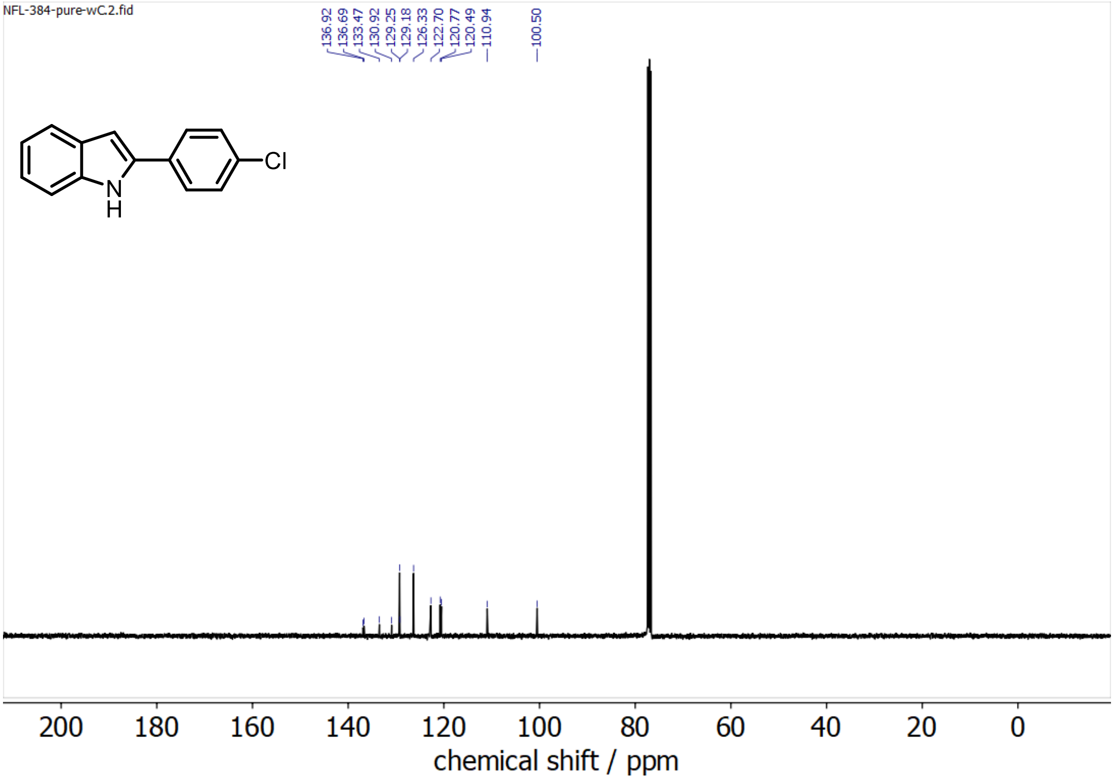


Figure S16: ^{13}C NMR spectrum of **7**.

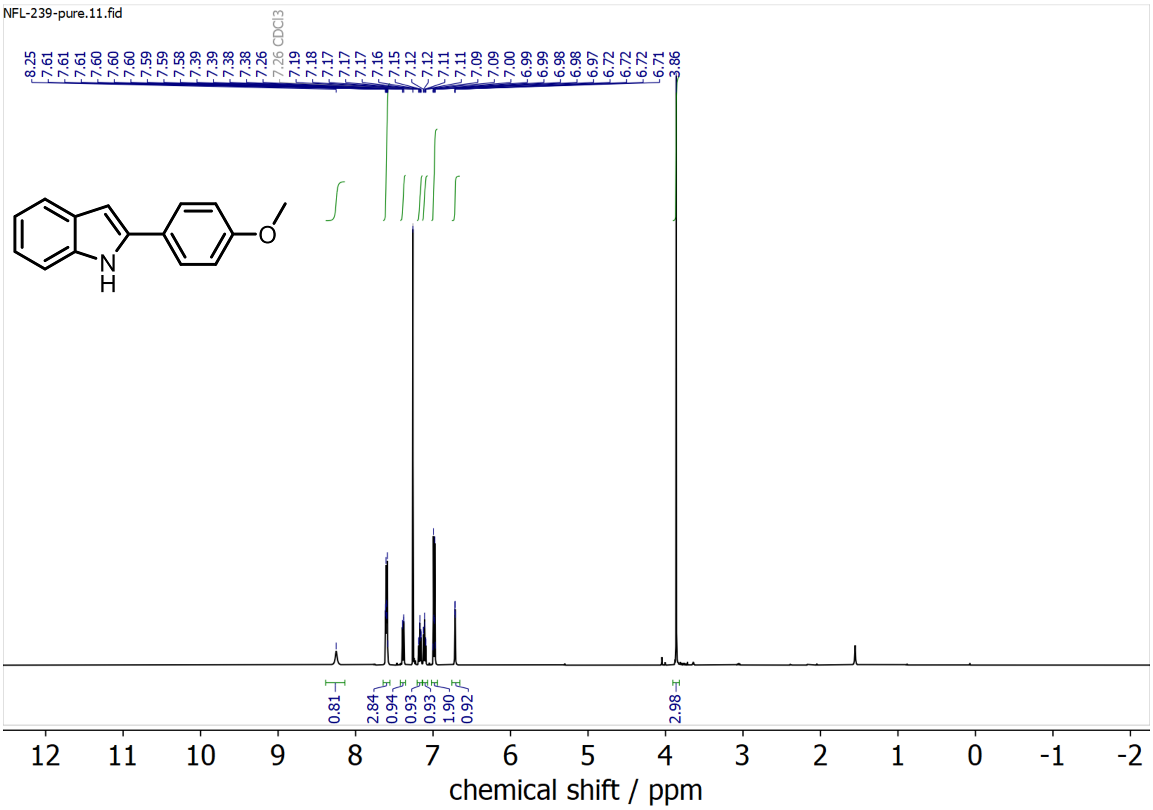


Figure S17: ^{1}H NMR spectrum of **8**.

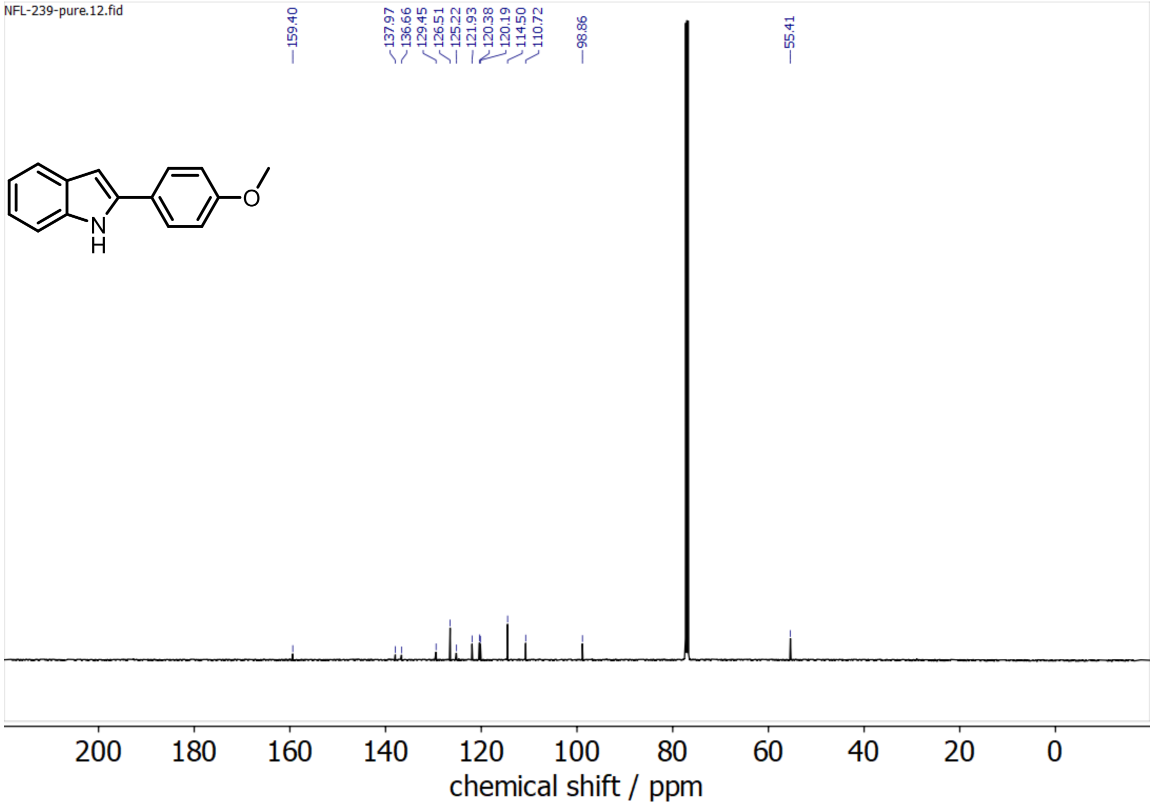


Figure S18: ^{13}C NMR spectrum of **8**.

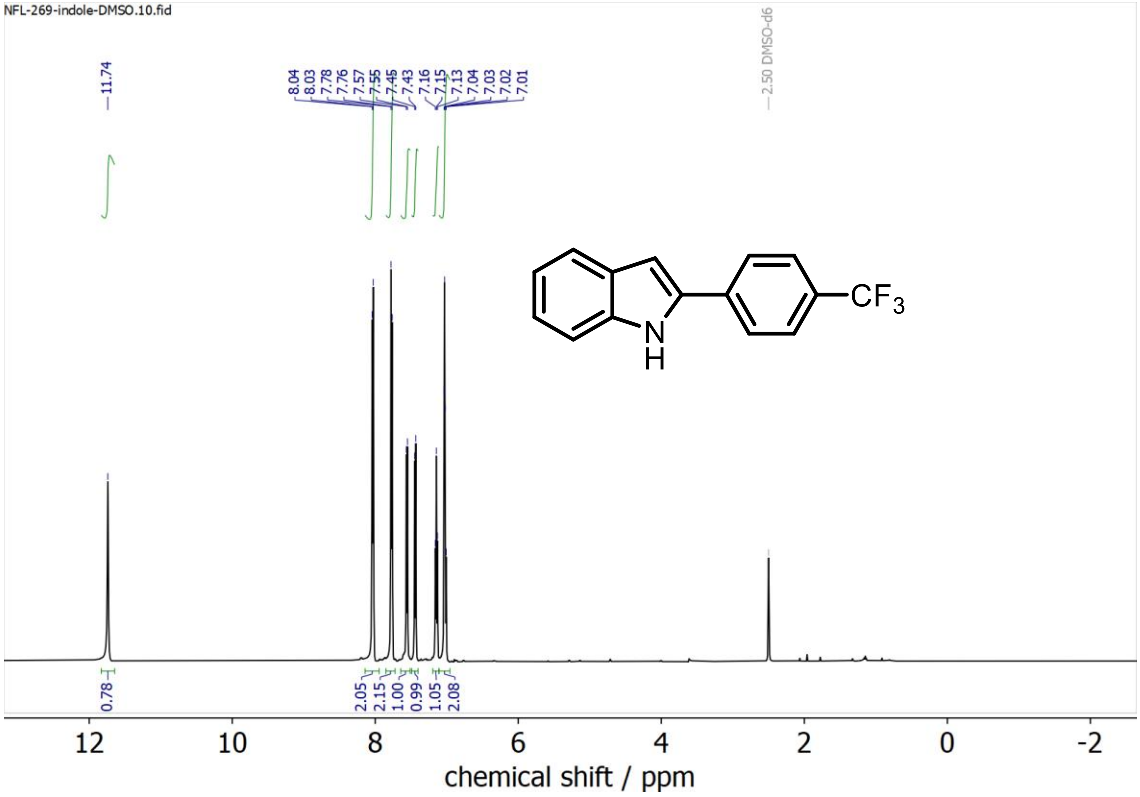


Figure S19: ^{1}H NMR spectrum of **9**.

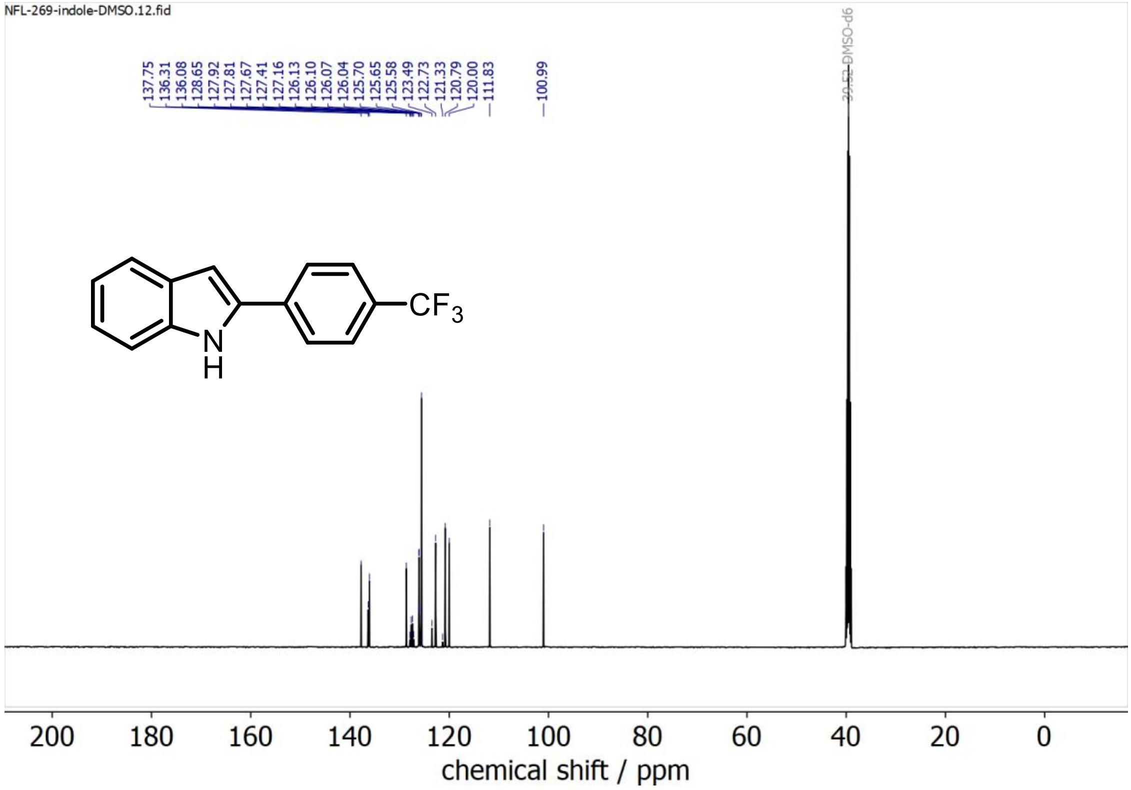


Figure S20: ^{13}C NMR spectrum of **9**.

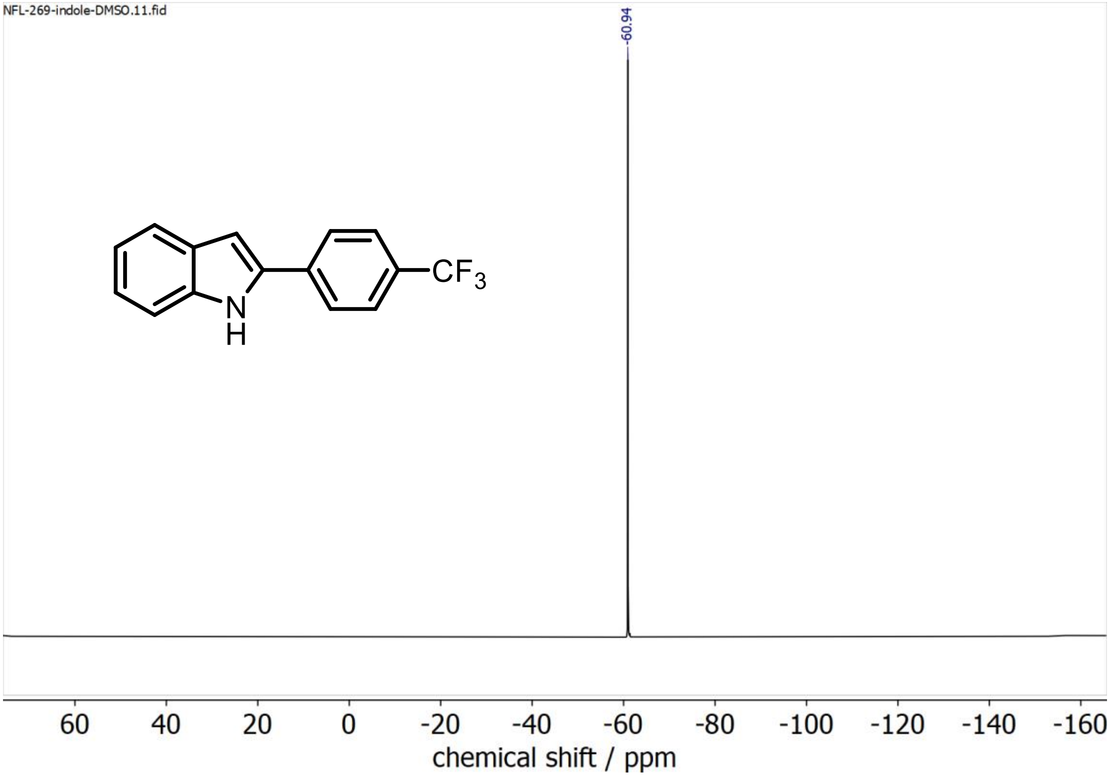


Figure S21: ^{19}F NMR spectrum of **9**.

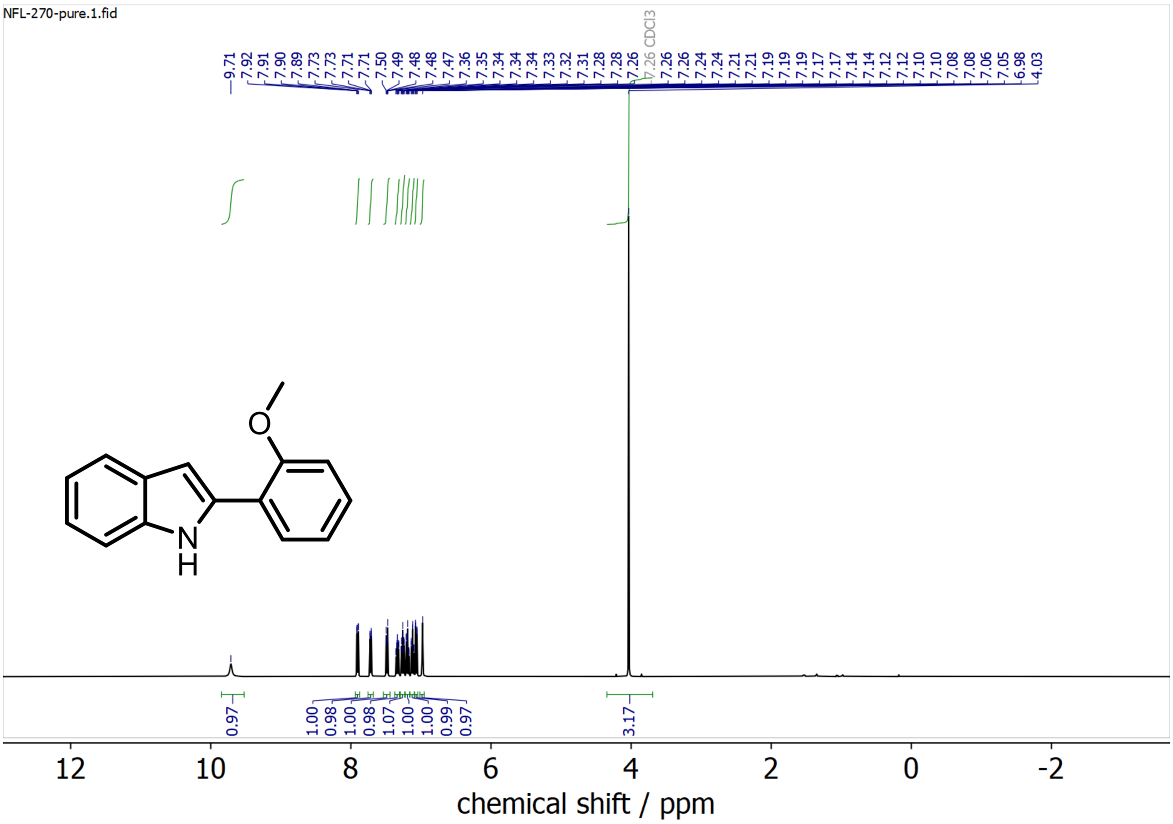


Figure S22: ^{1}H NMR spectrum of **10**.

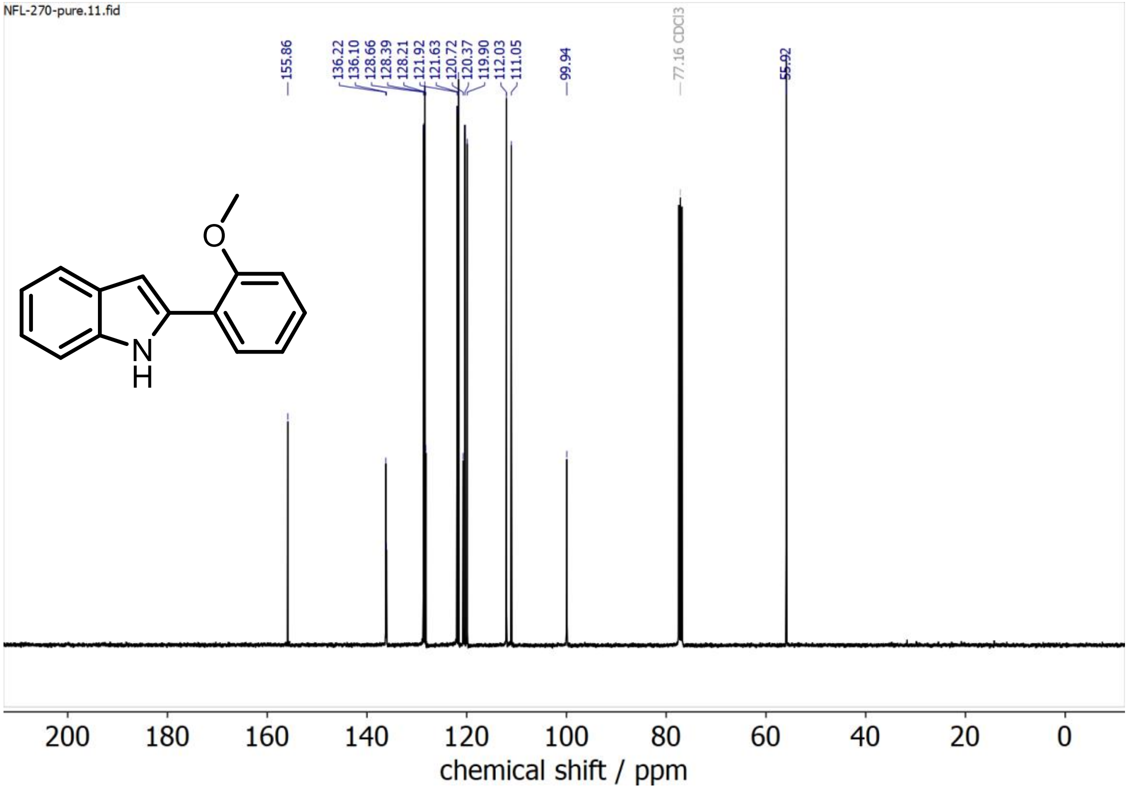


Figure S23: ^{13}C NMR spectrum of **10**.

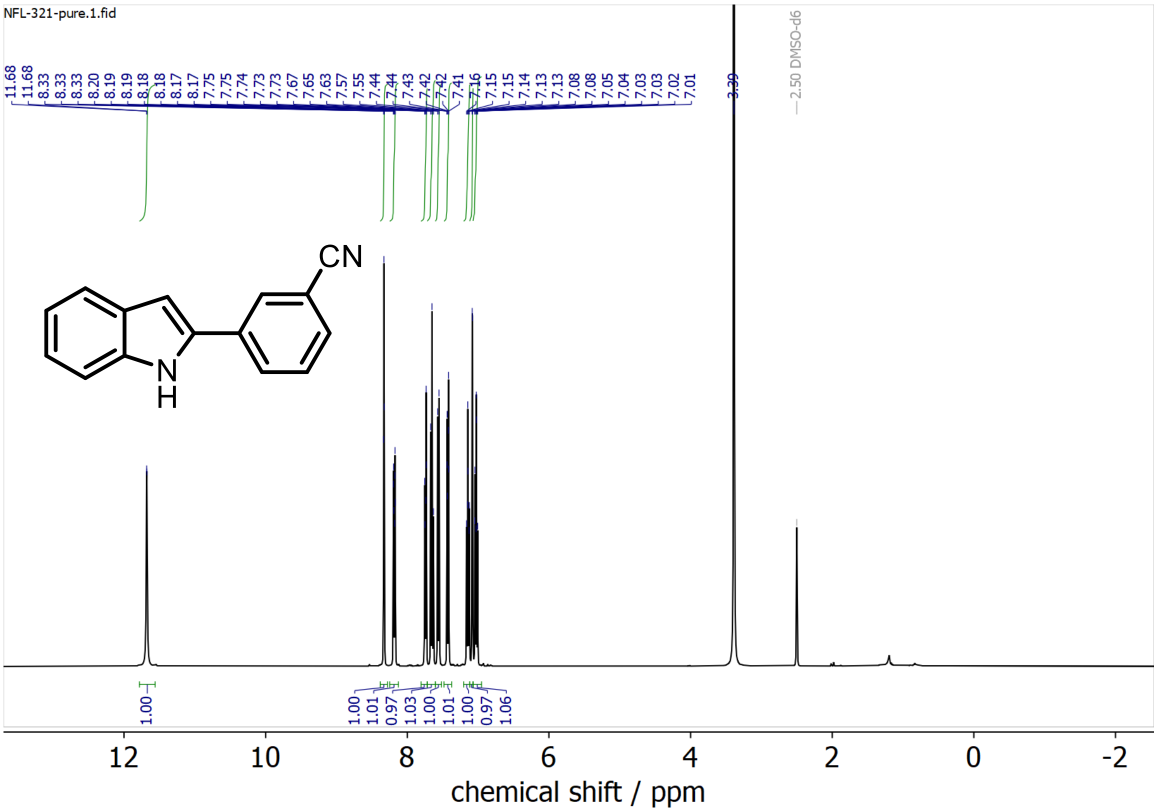


Figure S24: ^{1}H NMR spectrum of **11**.

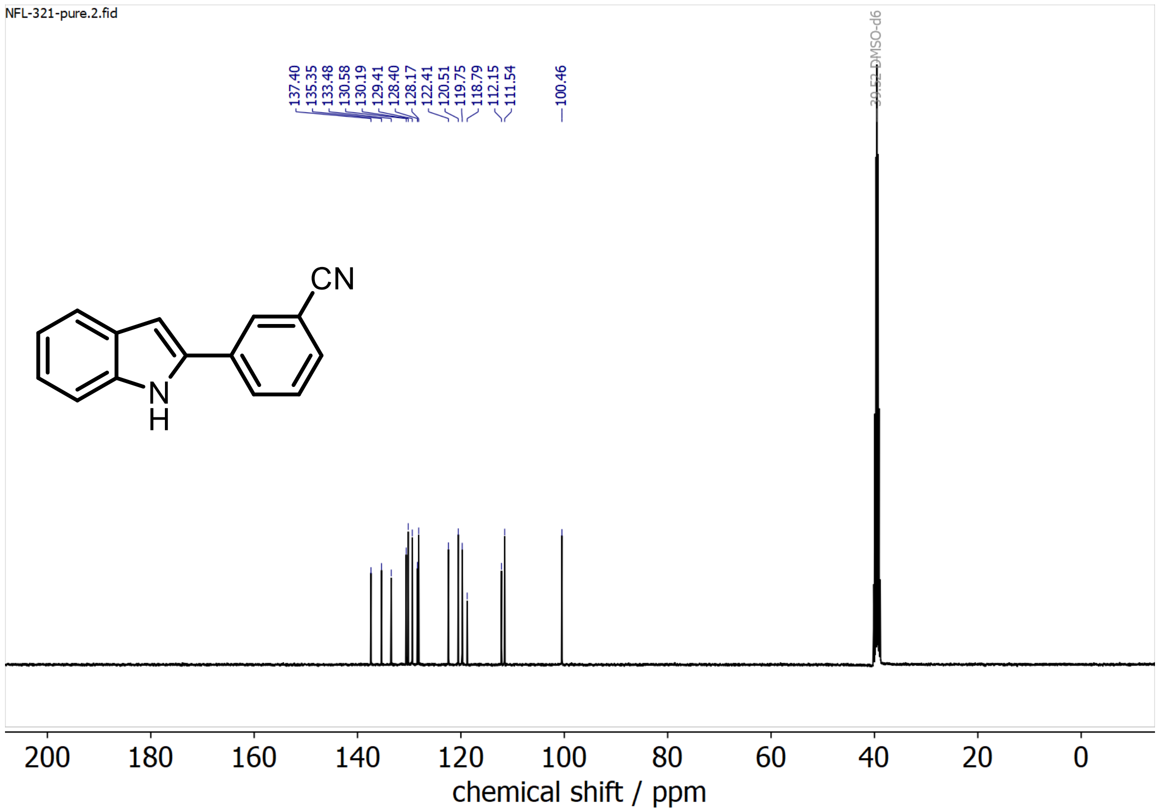


Figure S25: ^{13}C NMR spectrum of **11**.

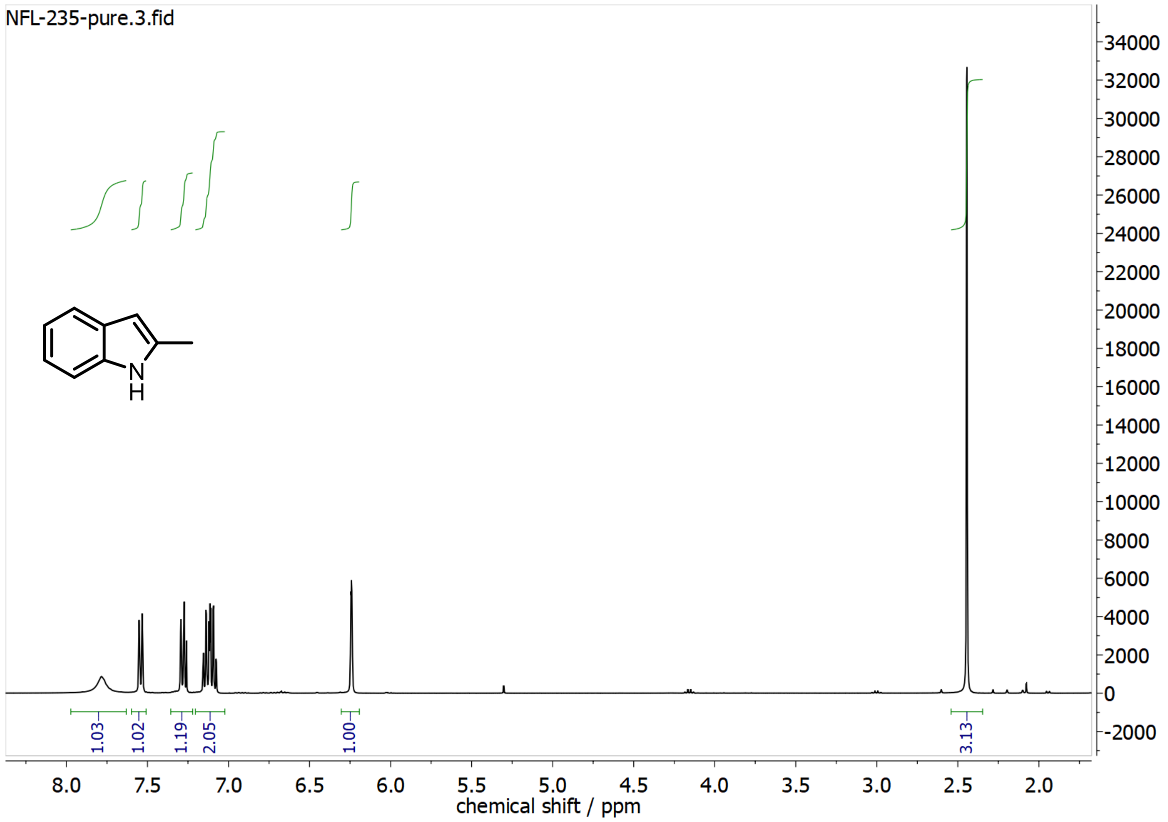


Figure S26: ^{1}H NMR spectrum of **12**.

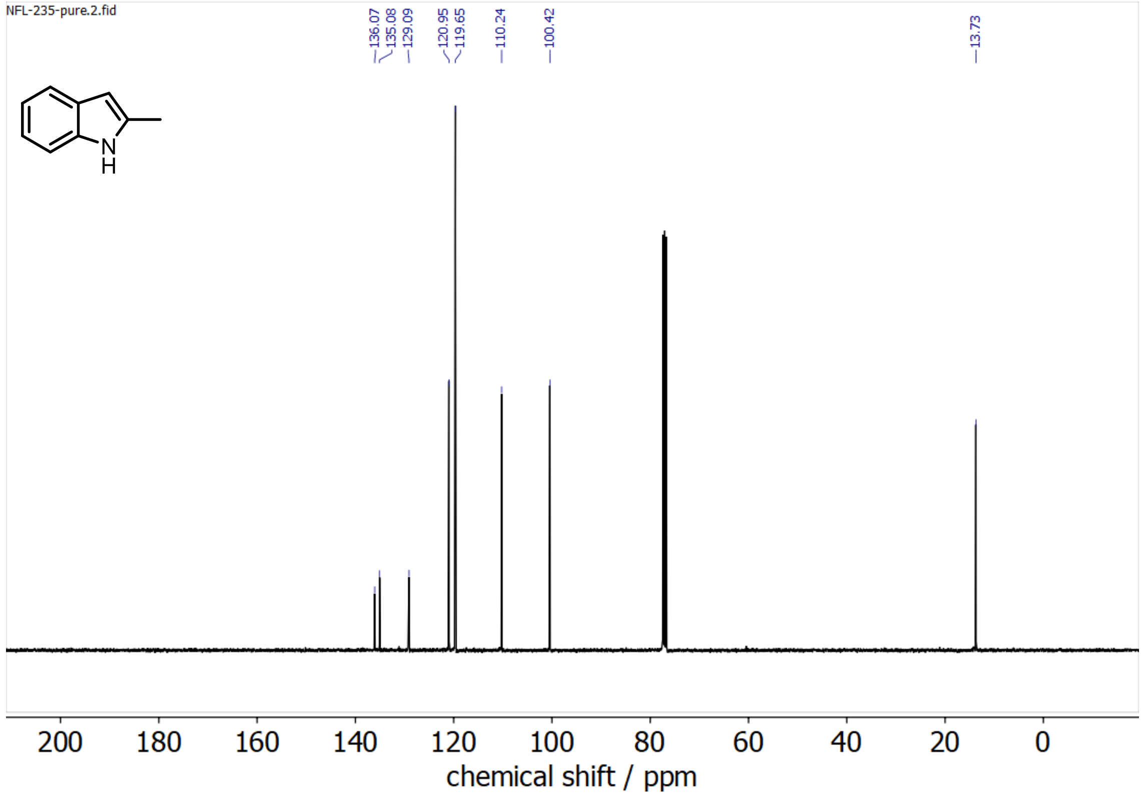


Figure S27: ^{13}C NMR spectrum of **12**.

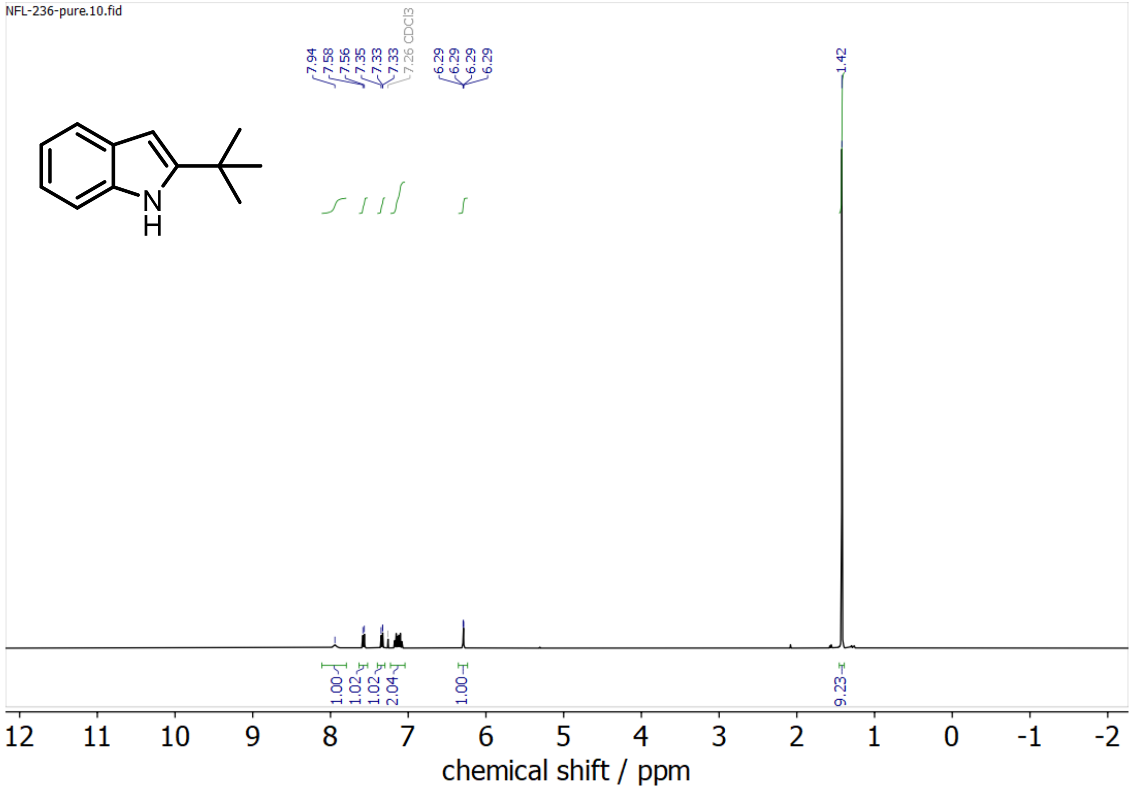


Figure S28: ^{1}H NMR spectrum of **13**.

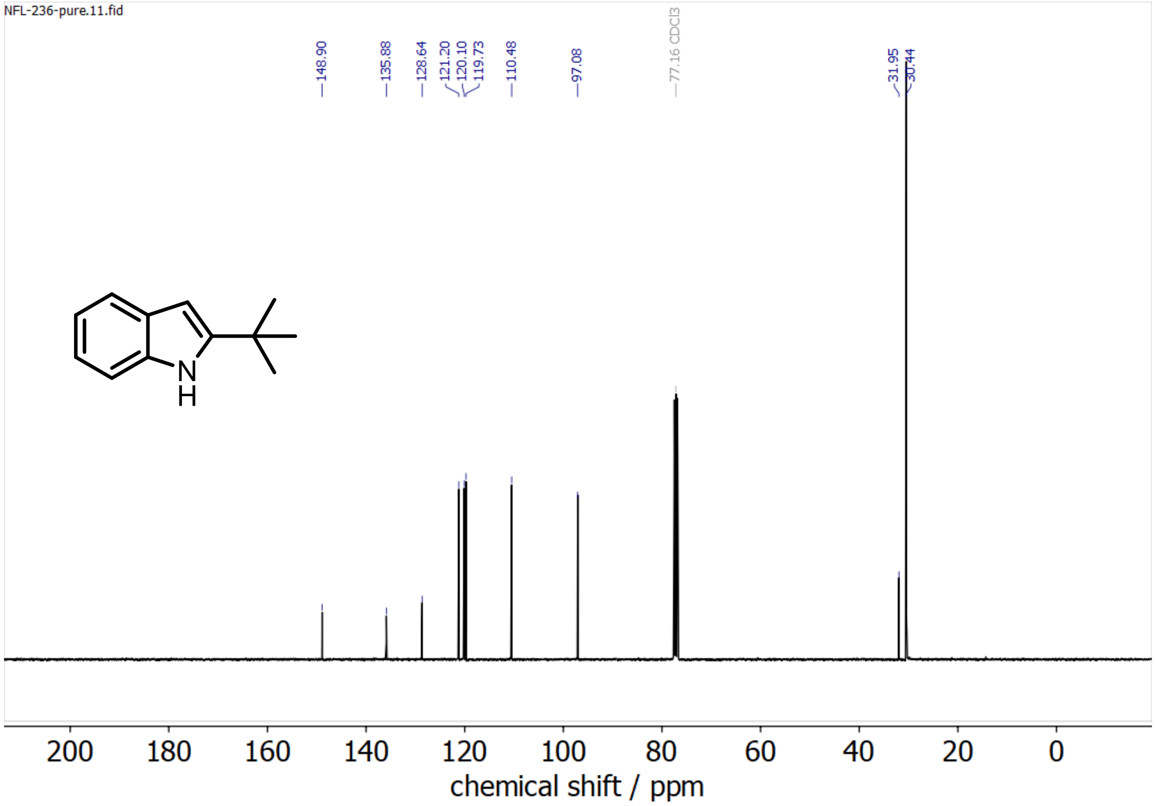


Figure S29: ^{13}C NMR spectrum of **13**.

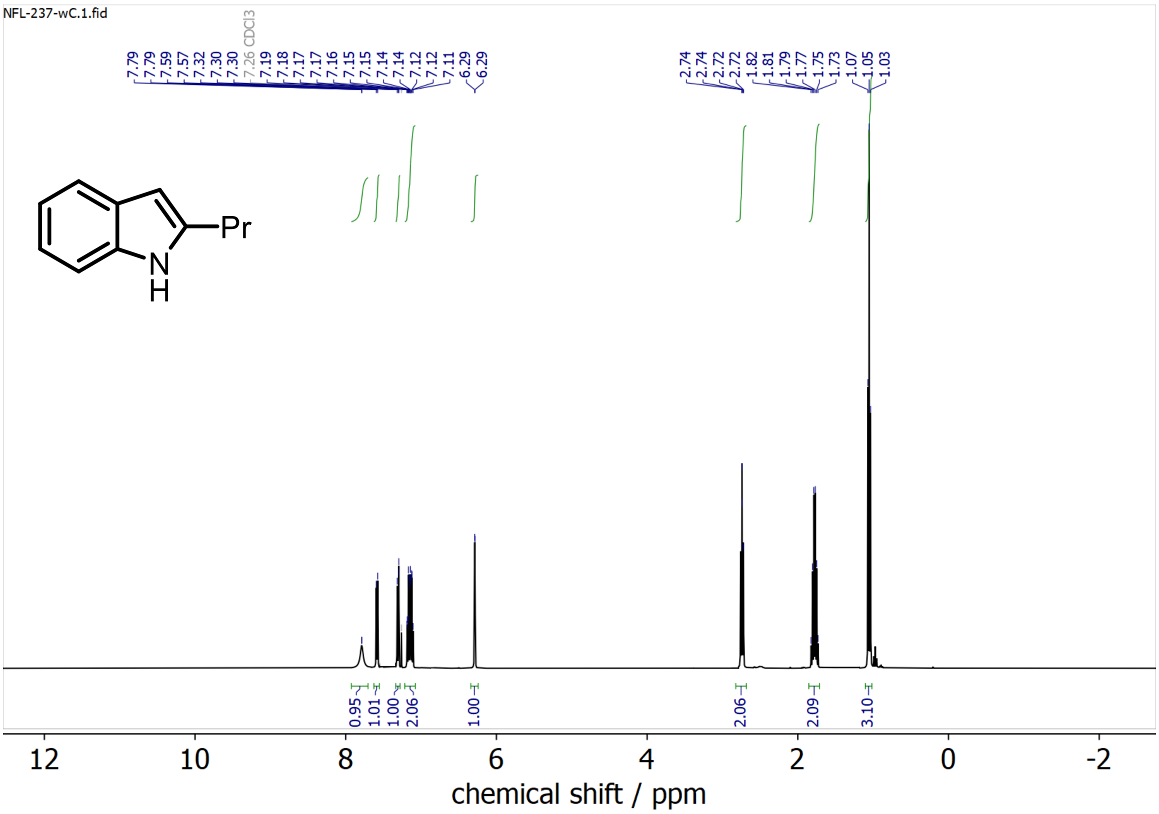


Figure S30: ^{1}H NMR spectrum of **14**.

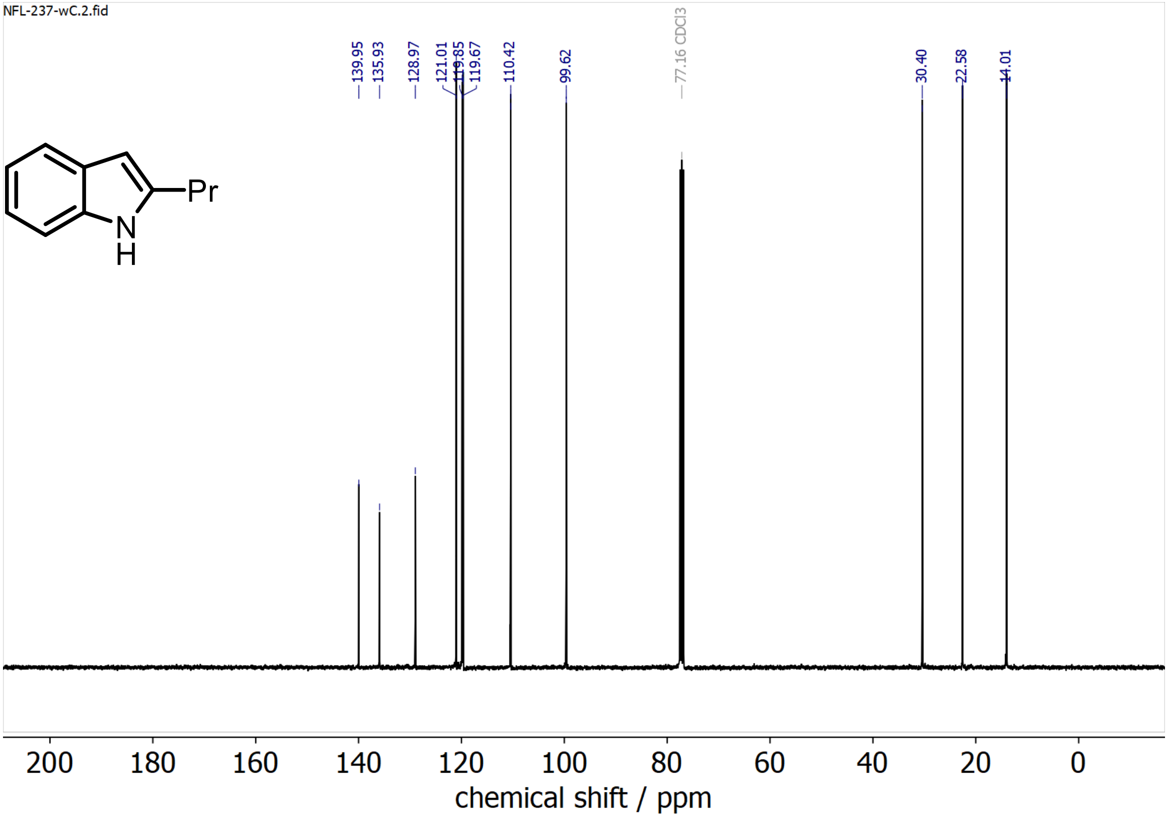


Figure S31: ^{13}C NMR spectrum of **14**.

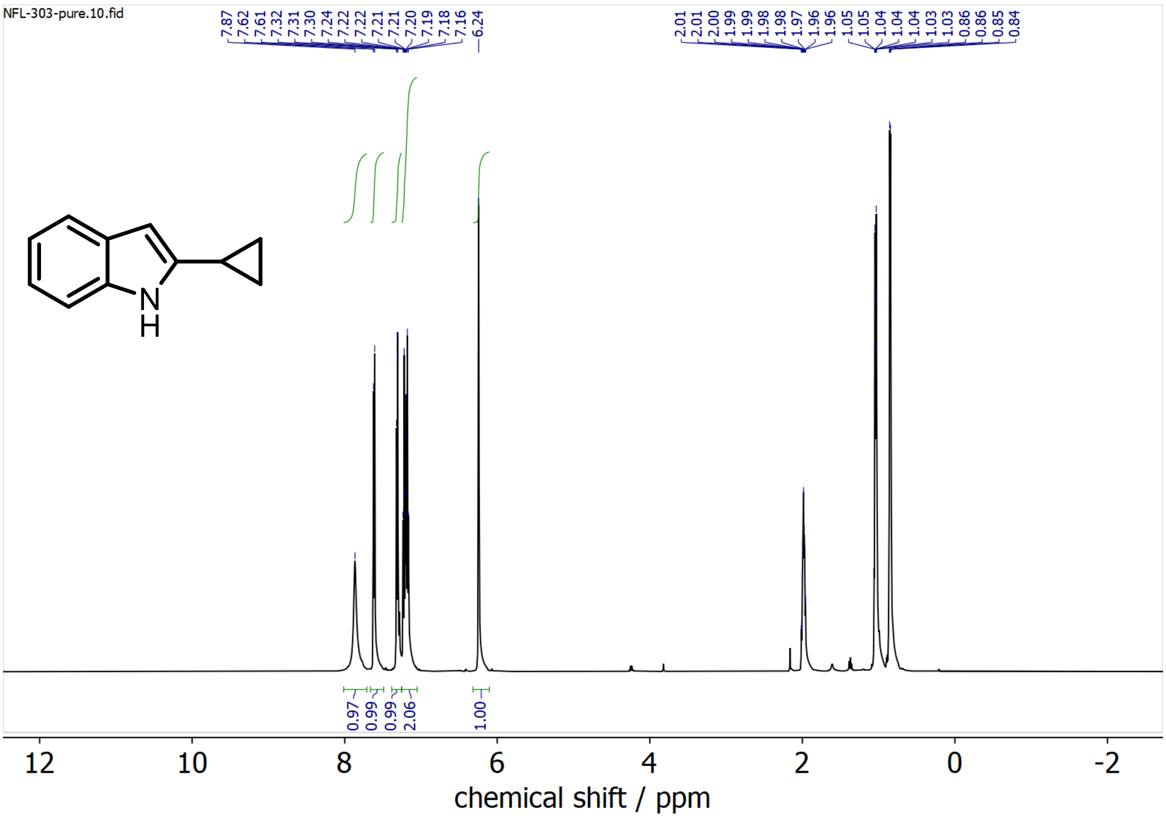


Figure S32: ^{1}H NMR spectrum of **15**.

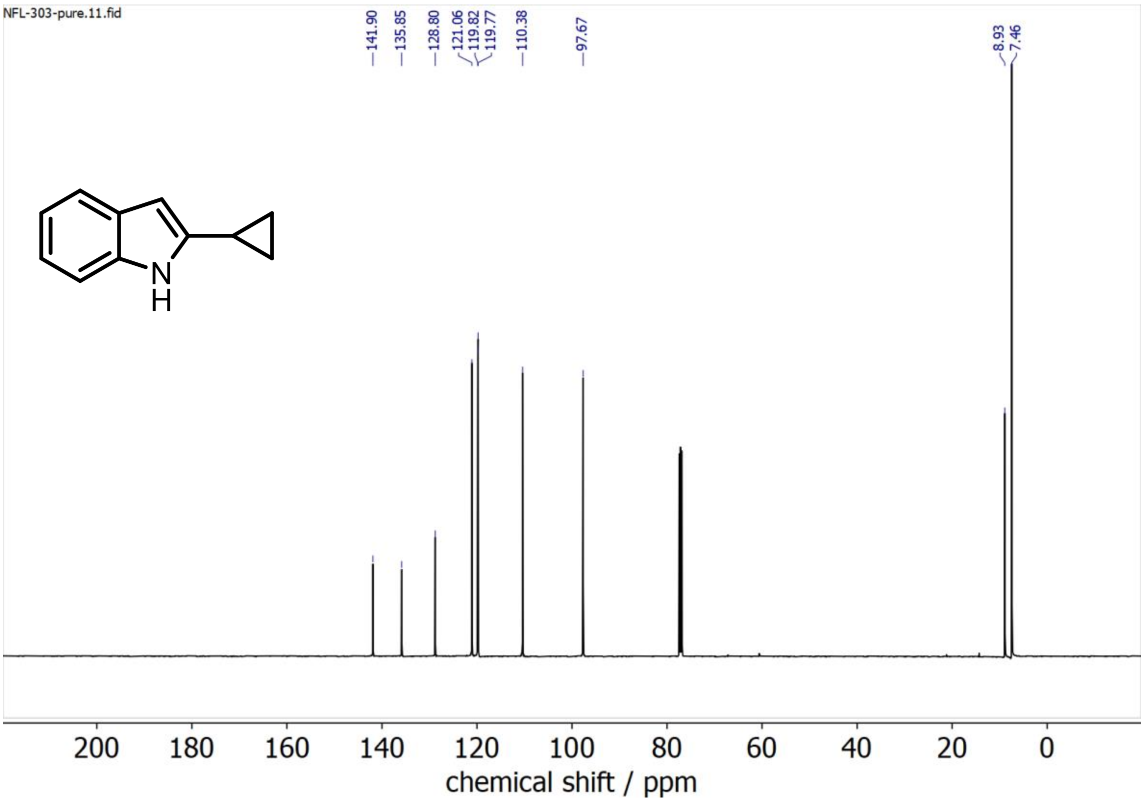


Figure S33: ^{13}C NMR spectrum of **15**.

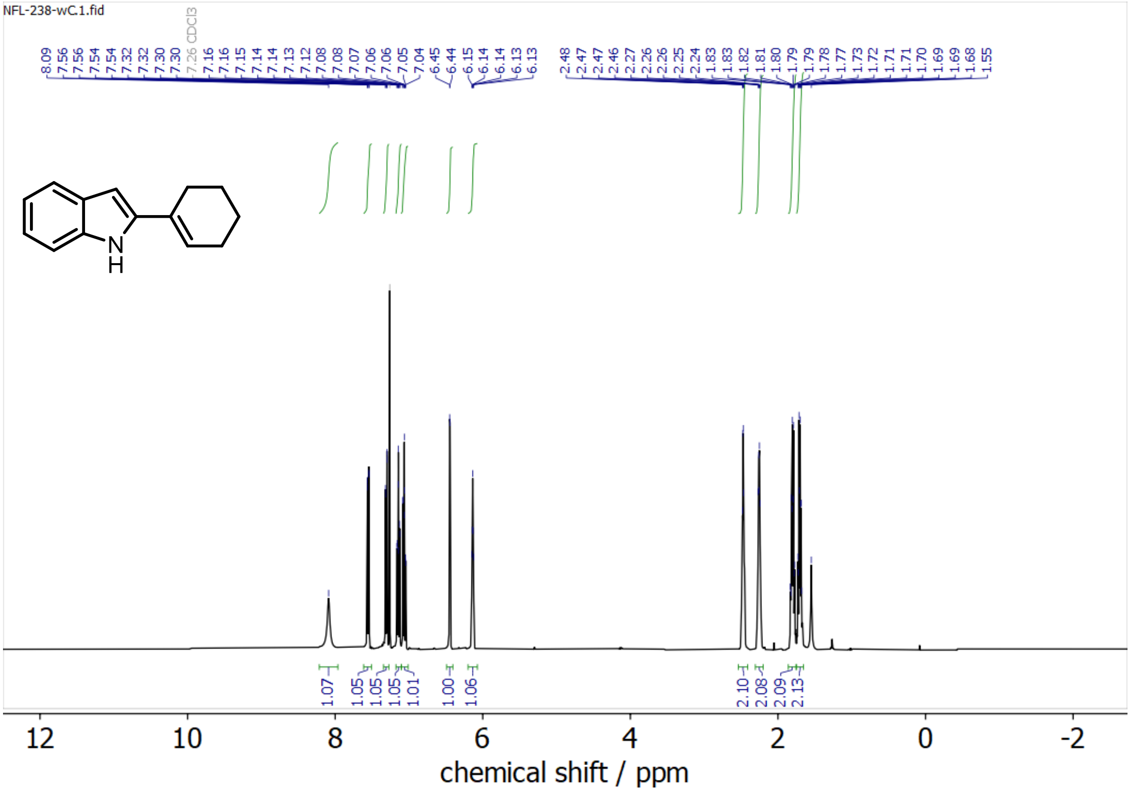


Figure S34: ^{1}H NMR spectrum of **16**.

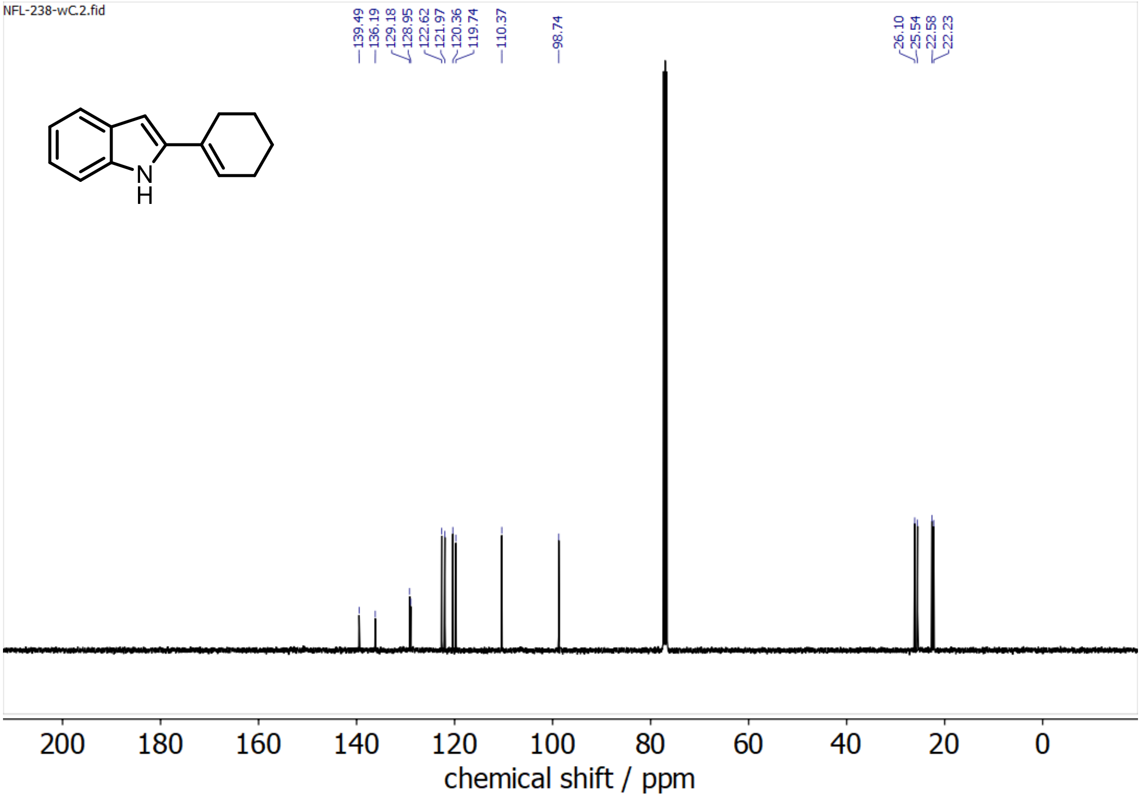


Figure S35: ^{13}C NMR spectrum of **16**.

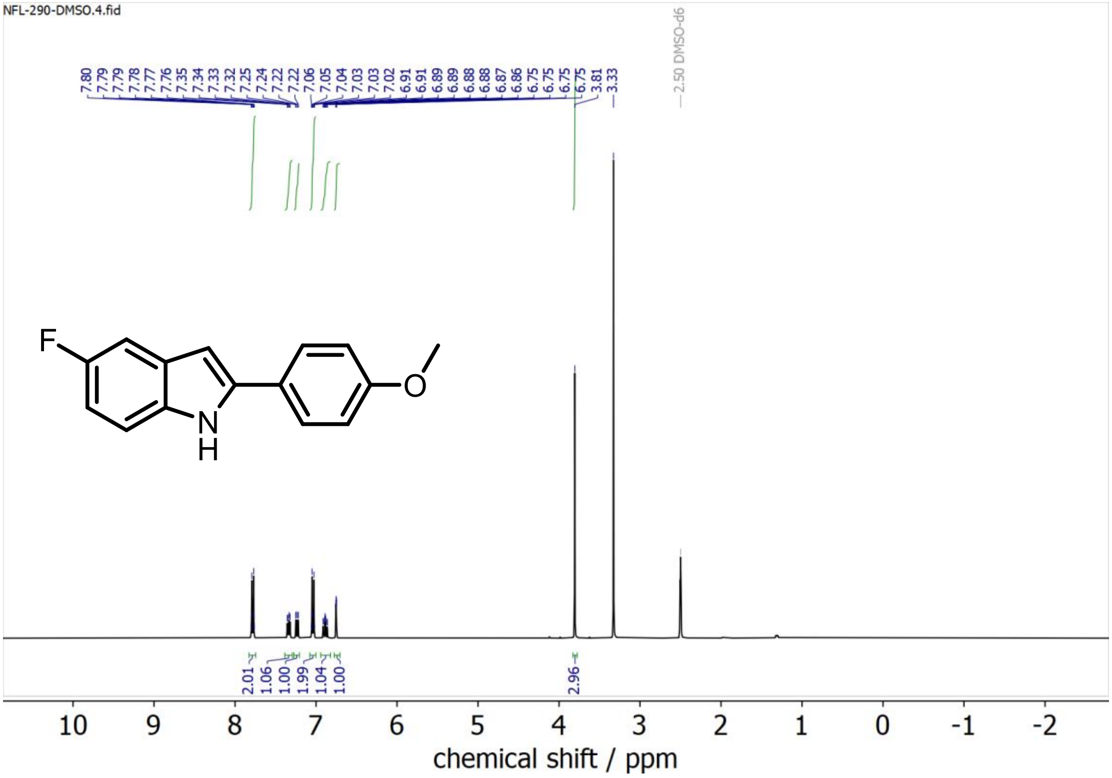


Figure S36: ^{1}H NMR spectrum of **17**.

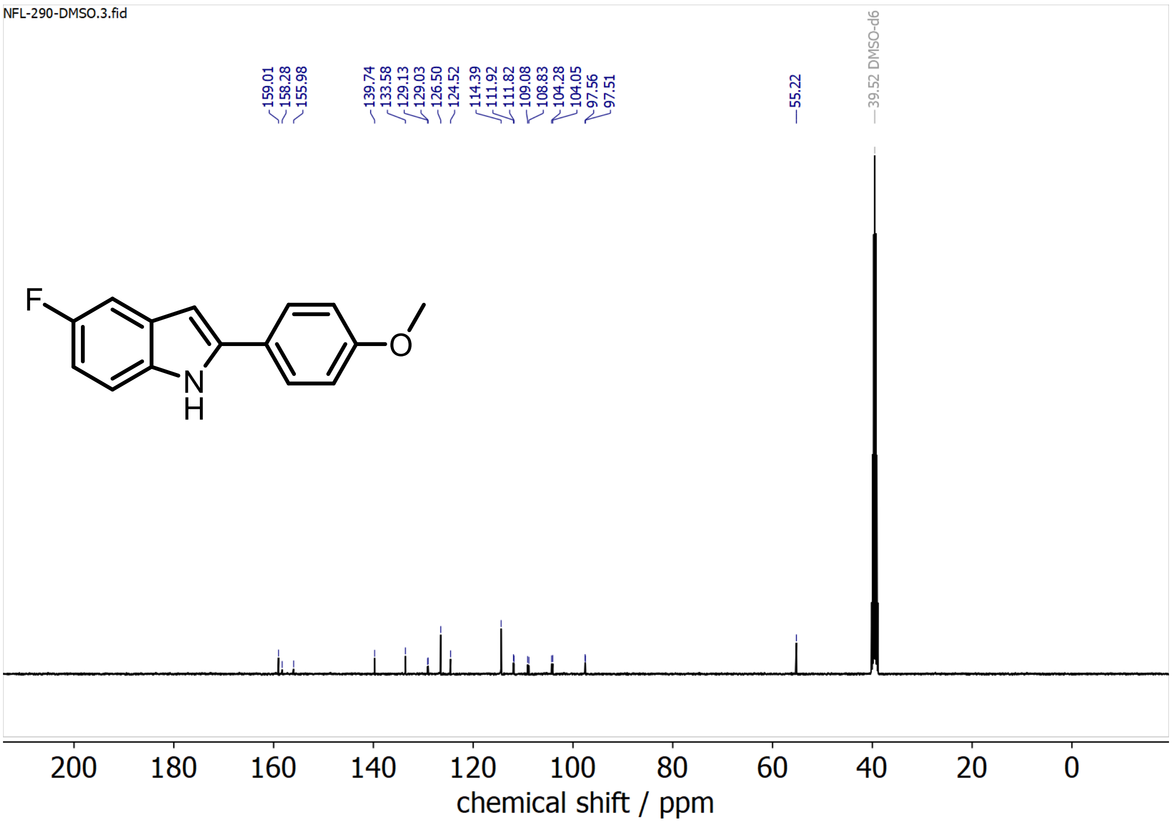


Figure S37: ^{13}C NMR spectrum of **17**.

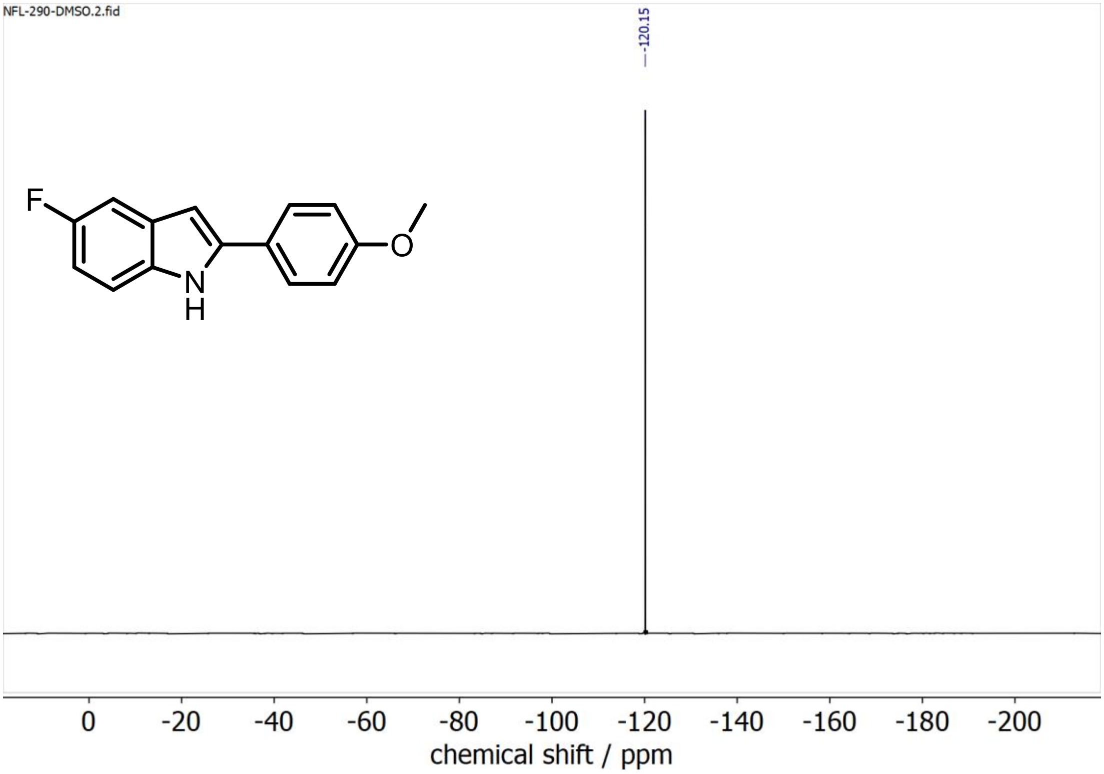


Figure S38: ^{19}F NMR spectrum of **17**.

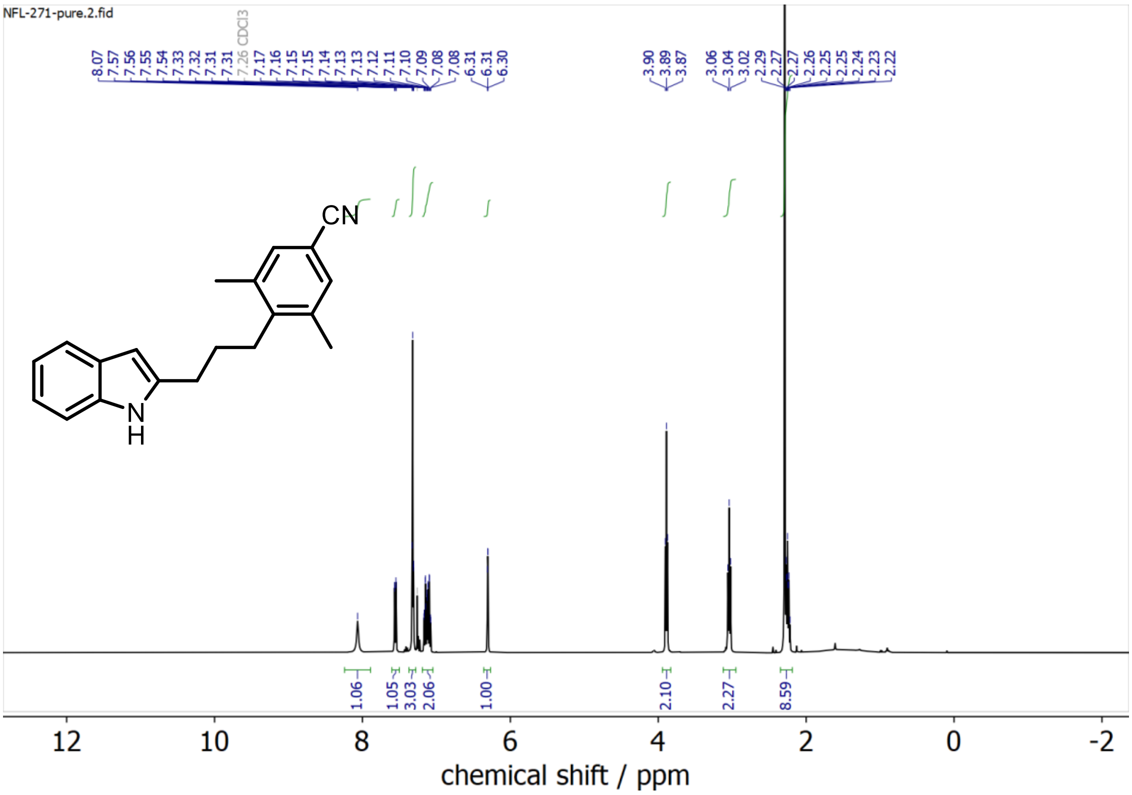


Figure S39: ^{1}H NMR spectrum of **18**.

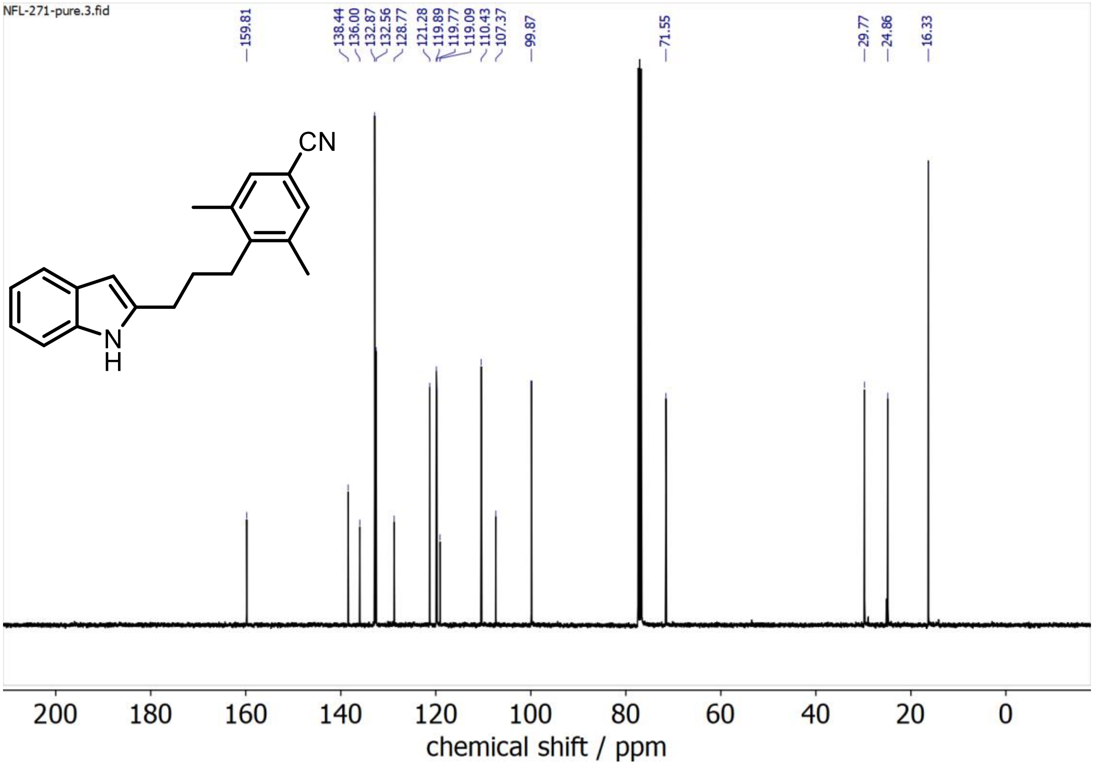


Figure S40: ^{13}C NMR spectrum of **18**.

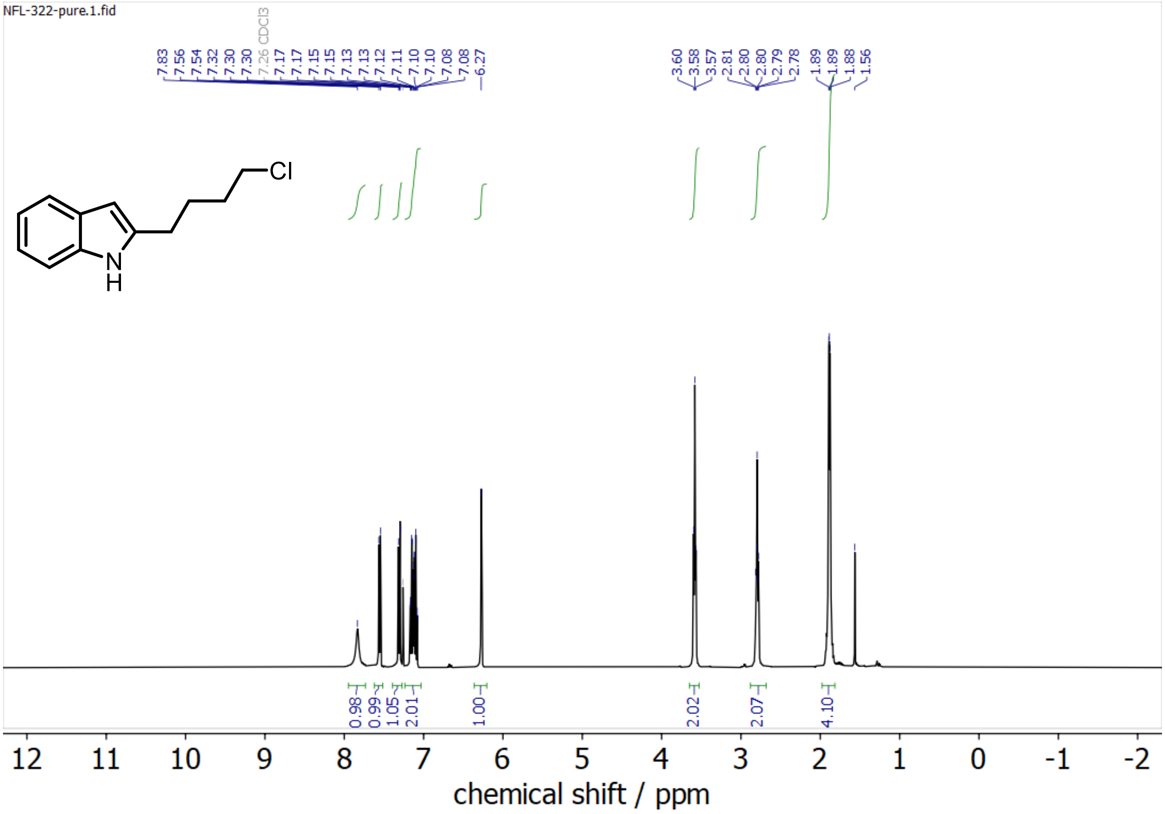


Figure S41: ^{1}H NMR spectrum of **19**.

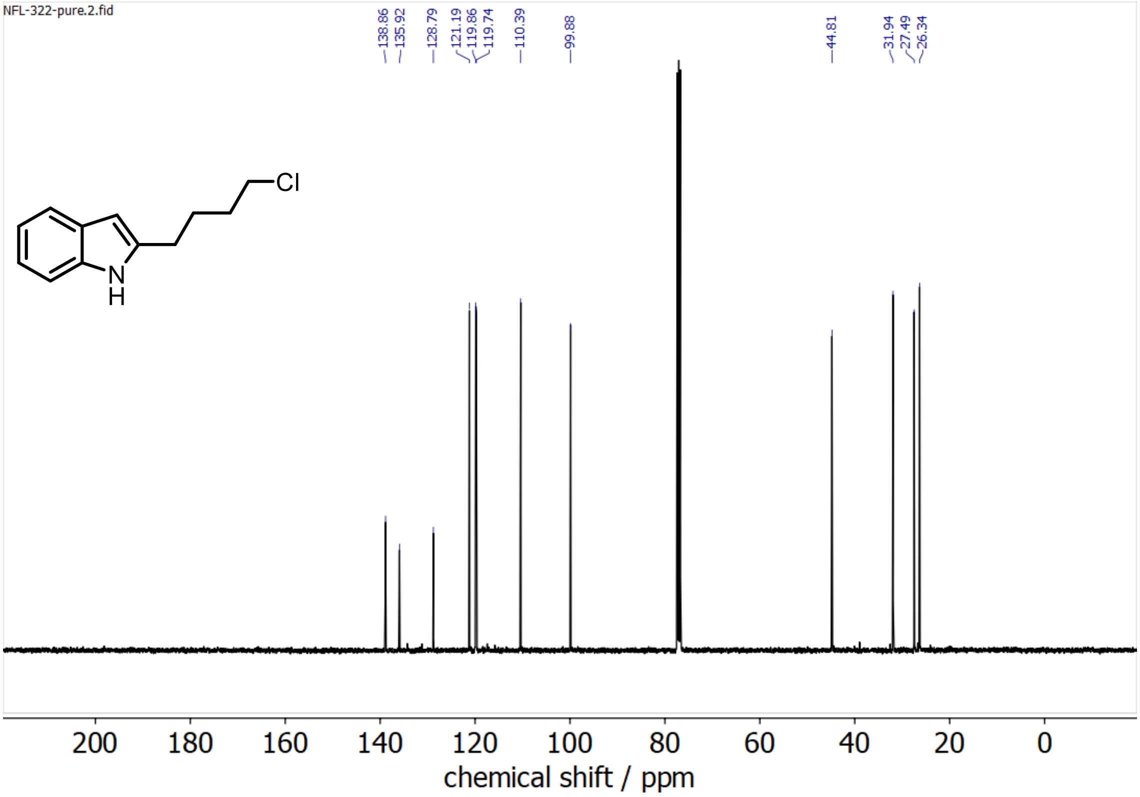


Figure S42: ^{13}C NMR spectrum of **19**

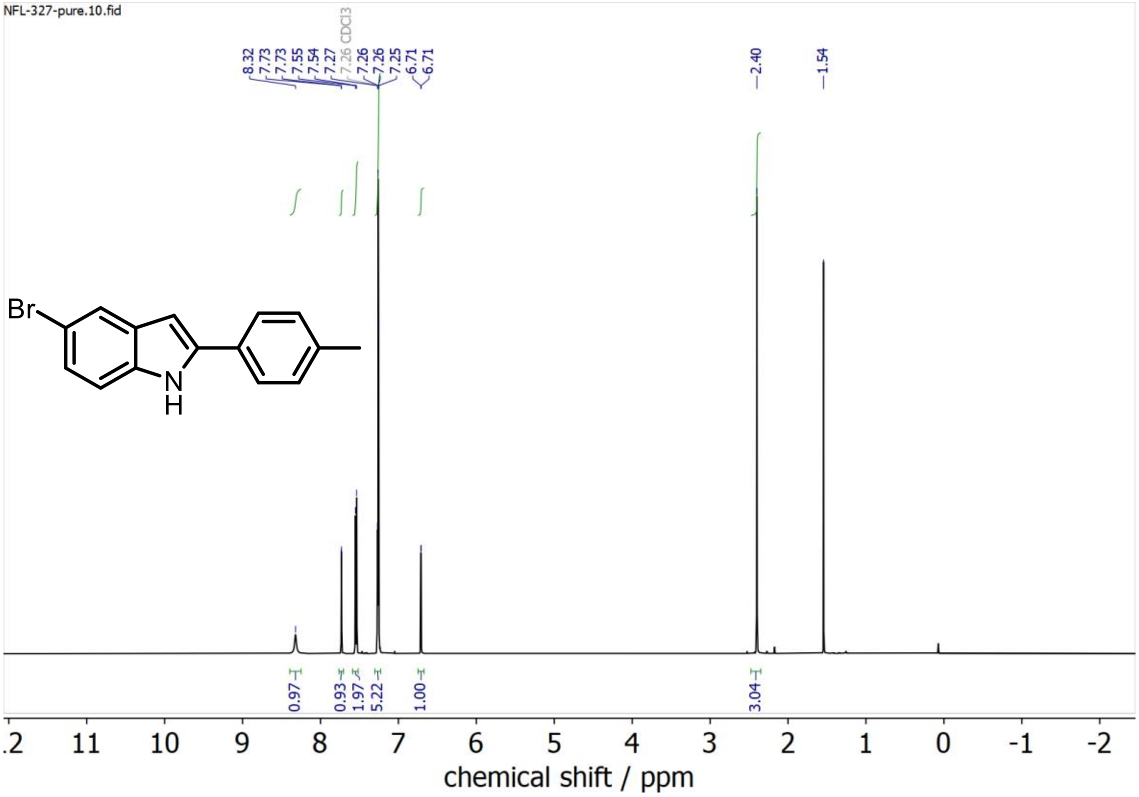


Figure S43: ^{1}H NMR spectrum of **20**.

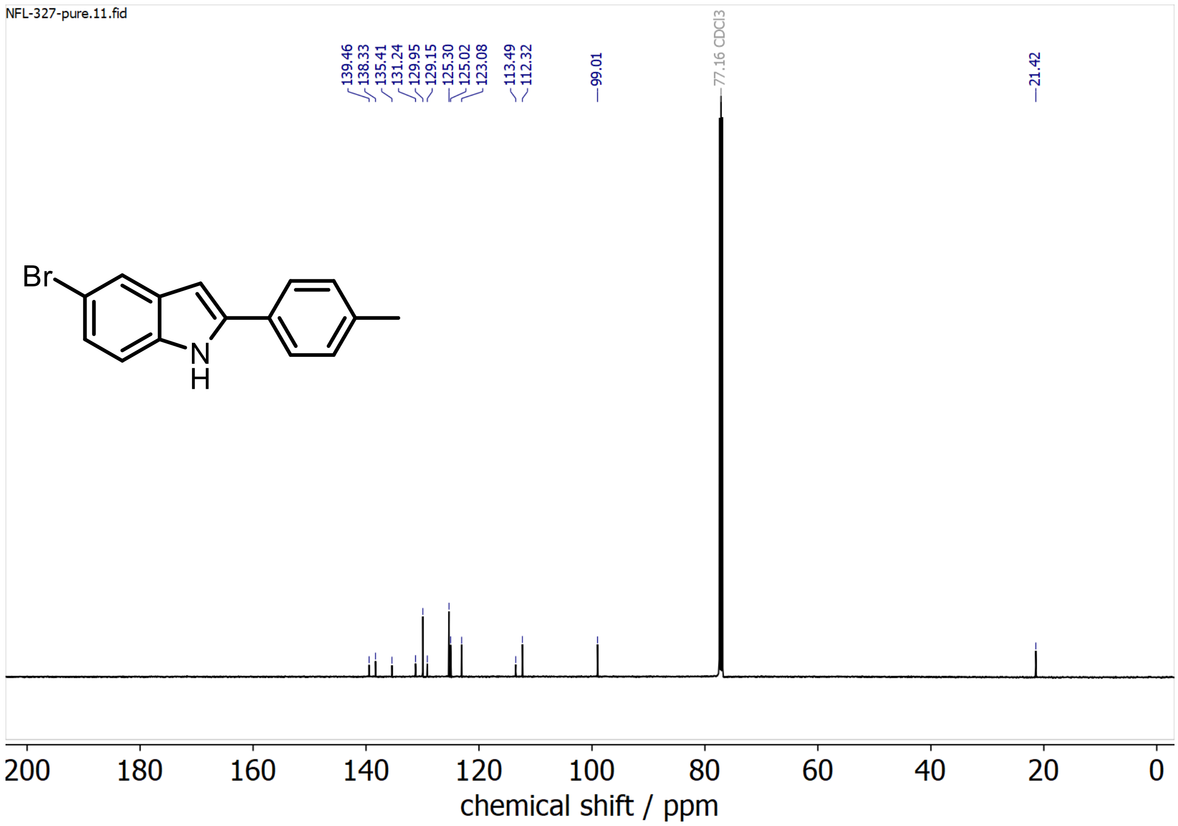


Figure S44: ^{13}C NMR spectrum of **20**.

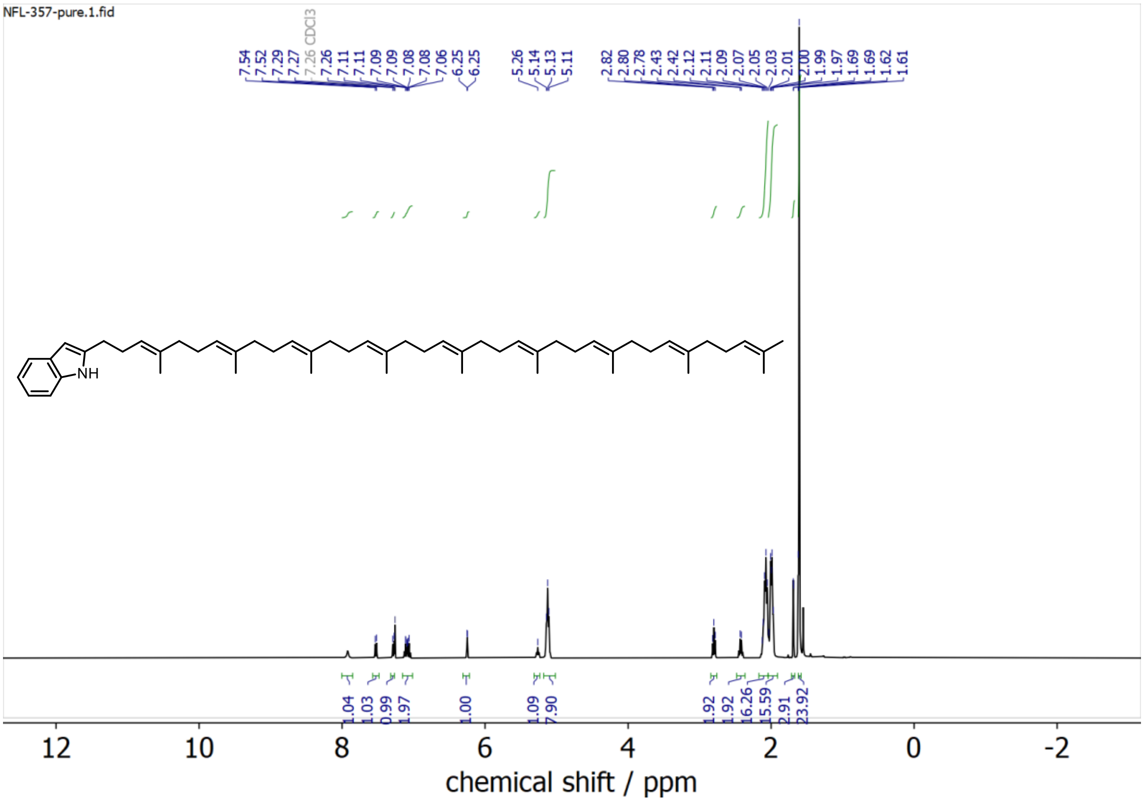


Figure S45: ^{1}H NMR spectrum of **21**.

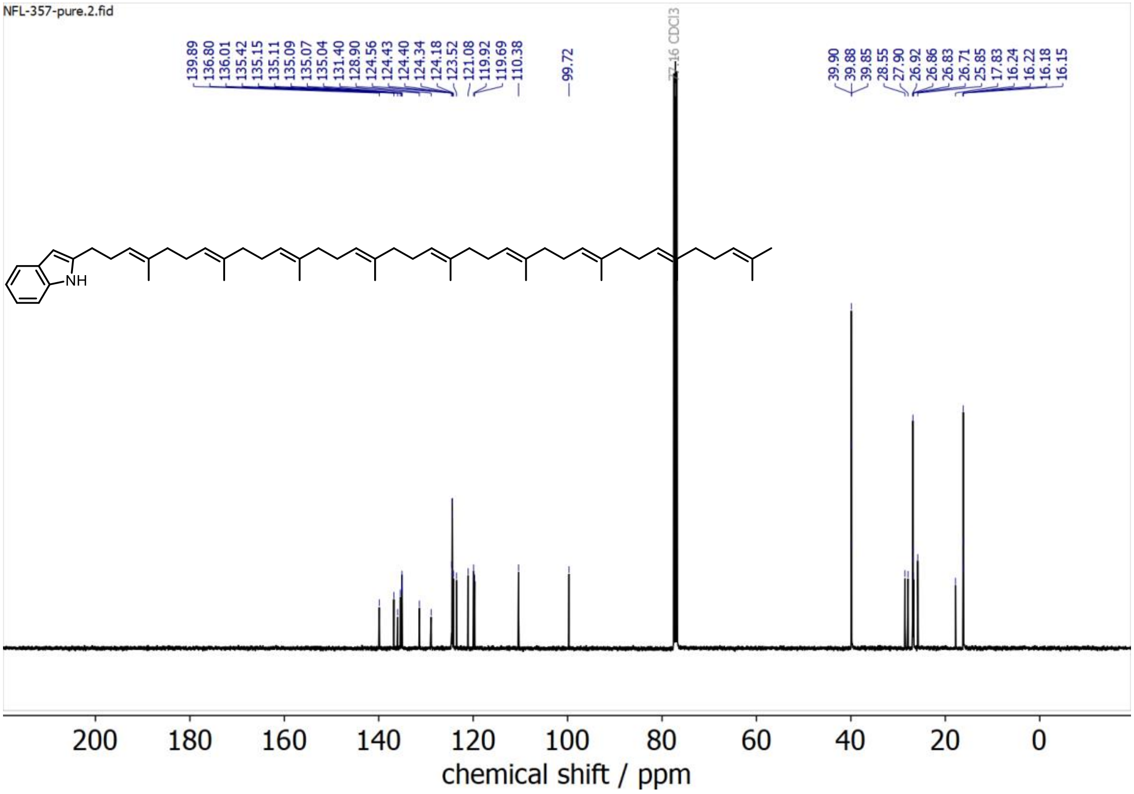


Figure S46: ^{13}C NMR spectrum of **21**.

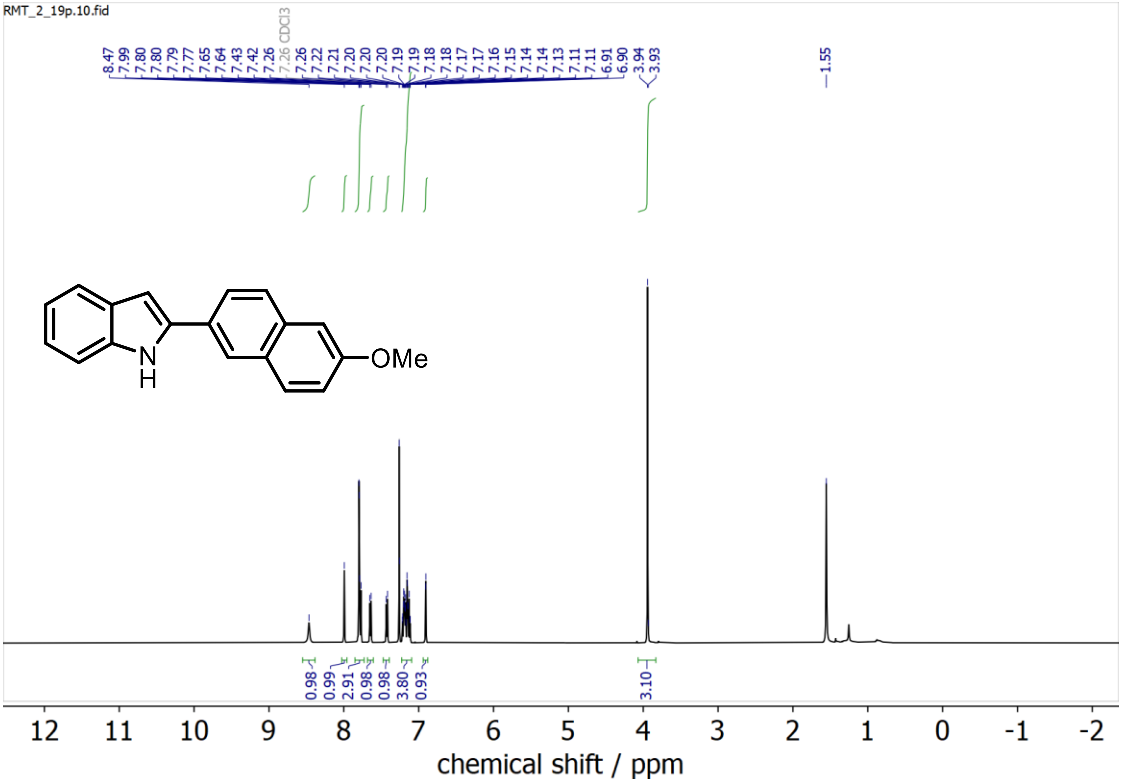


Figure S47: ^{1}H NMR spectrum of **22**.

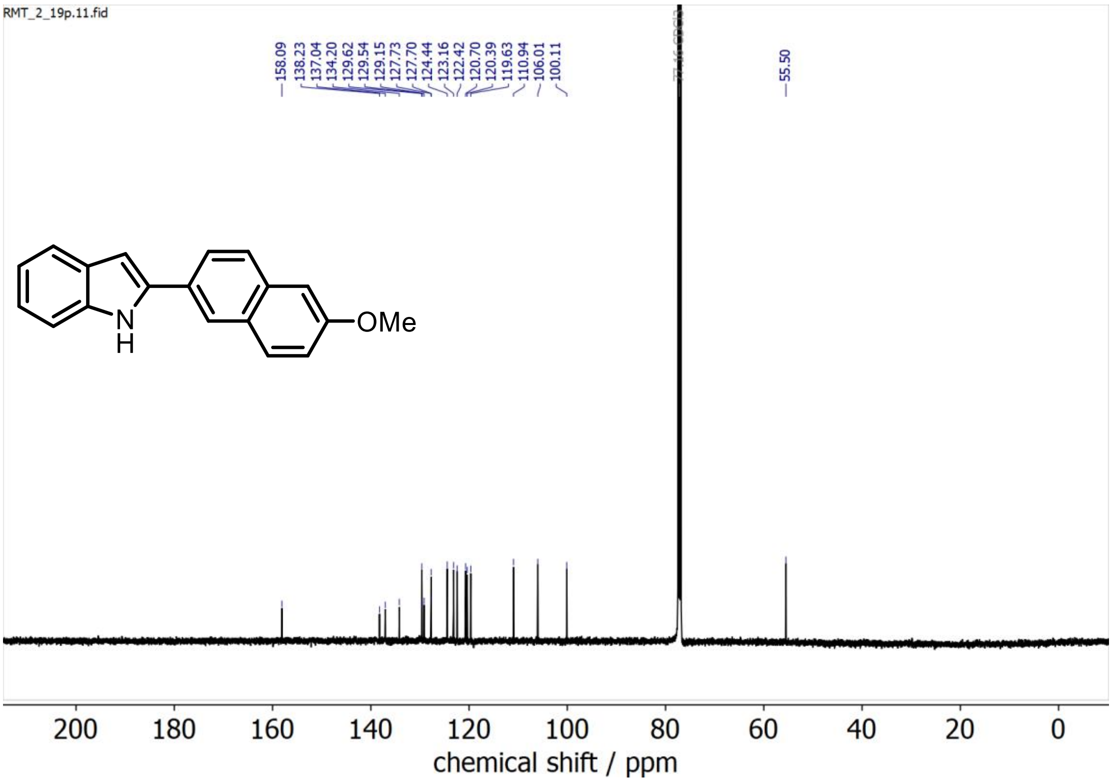


Figure S48: ^{13}C NMR spectrum of **22**.

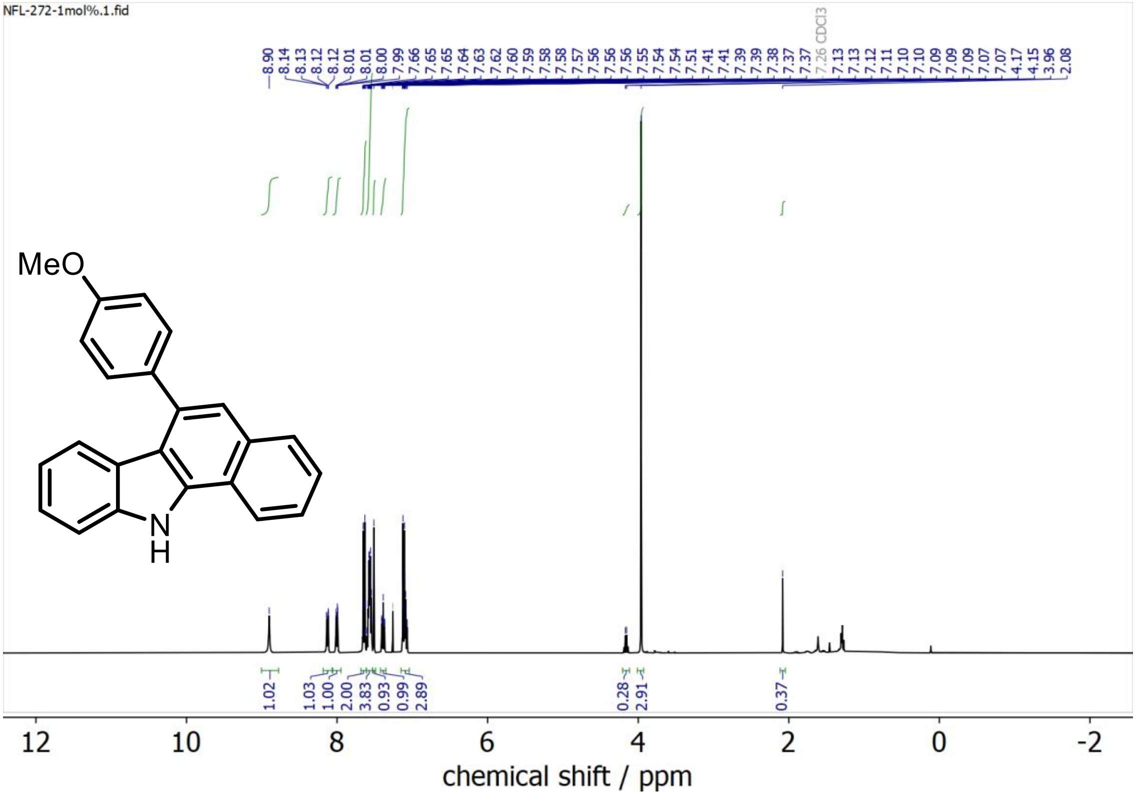


Figure S49: ^{1}H NMR spectrum of **23**.

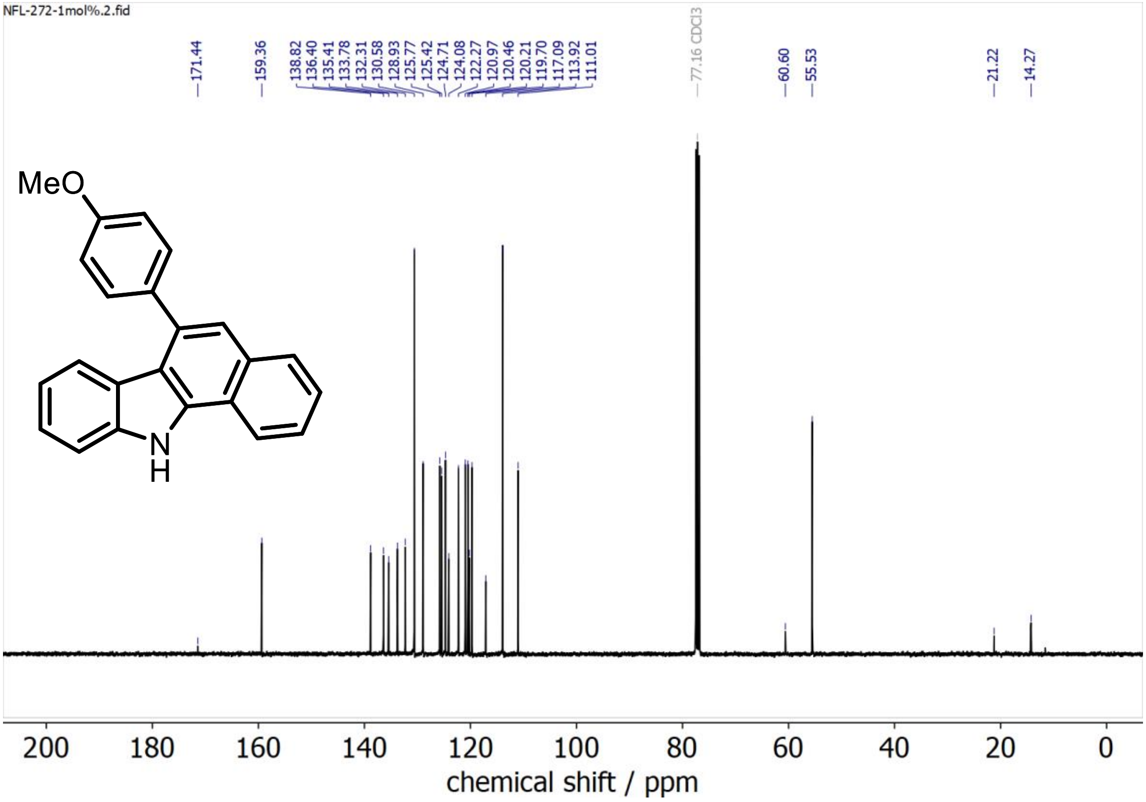


Figure S50: ^{13}C NMR spectrum of **23**.

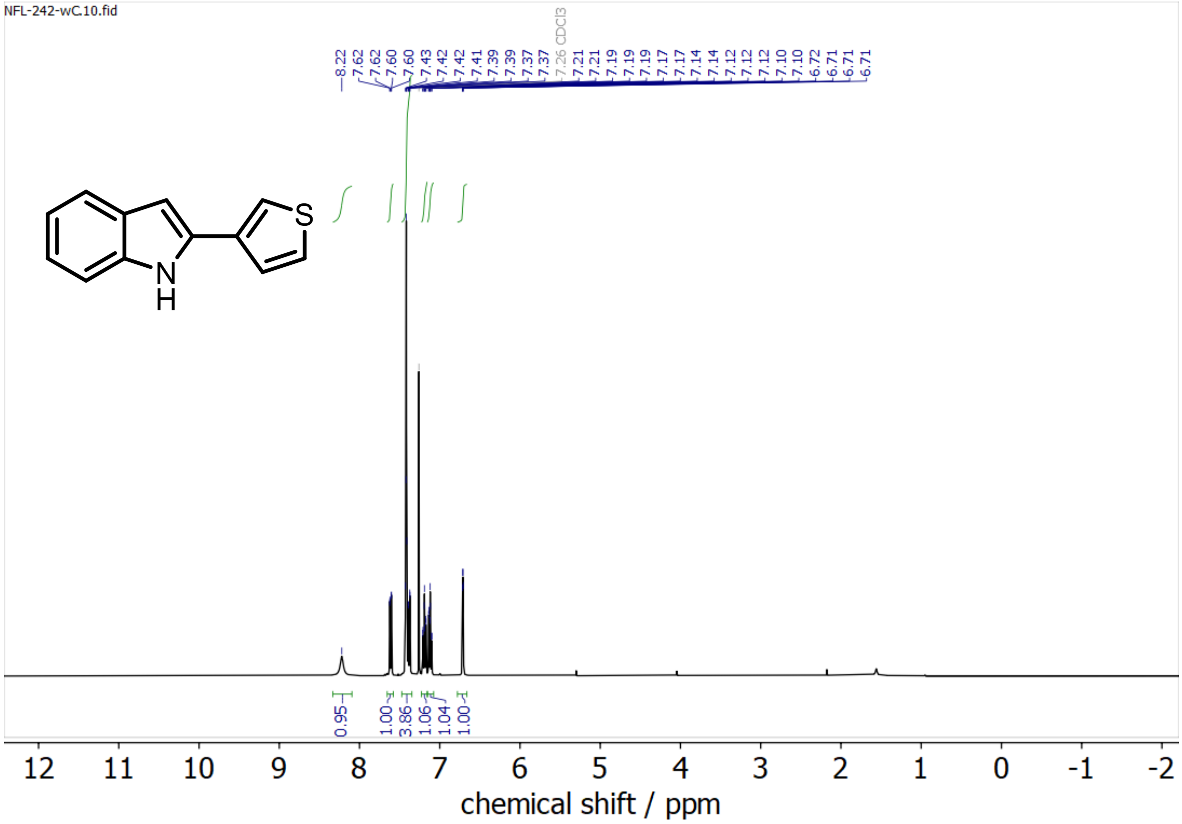


Figure S51: ^{1}H NMR spectrum of **24**.

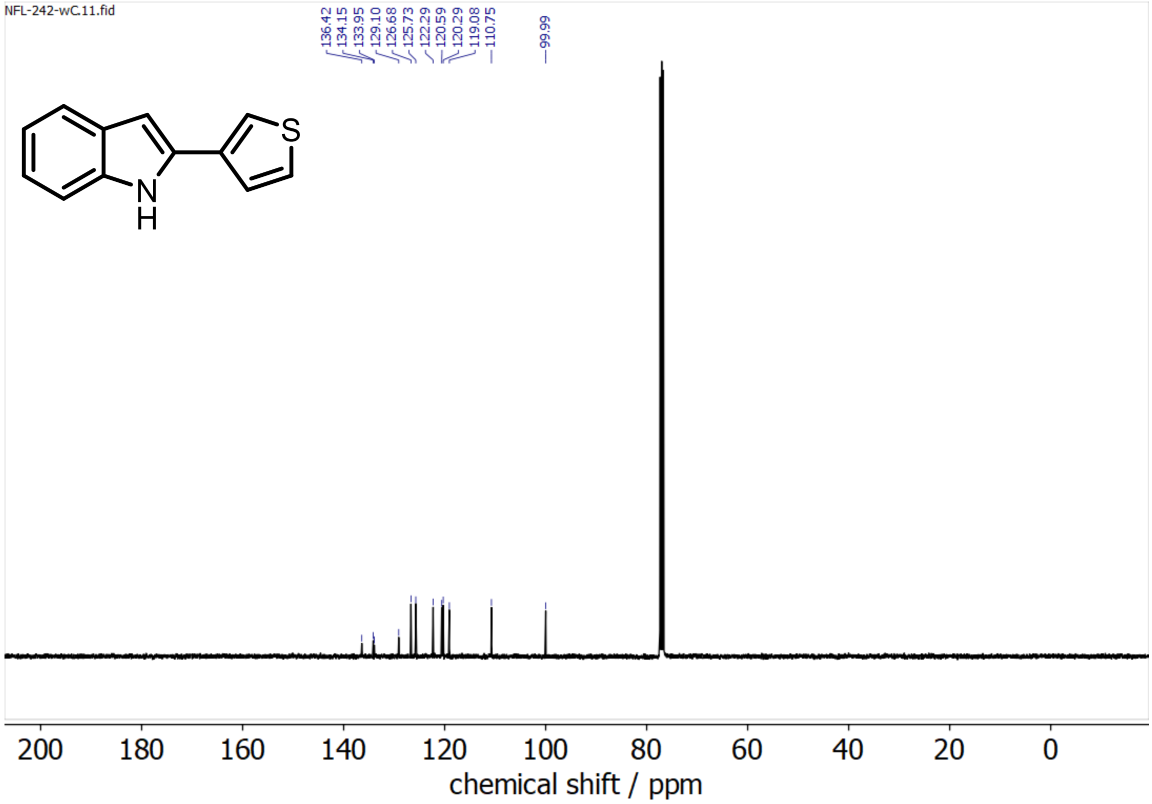


Figure S52: ^{13}C NMR spectrum of **24**.

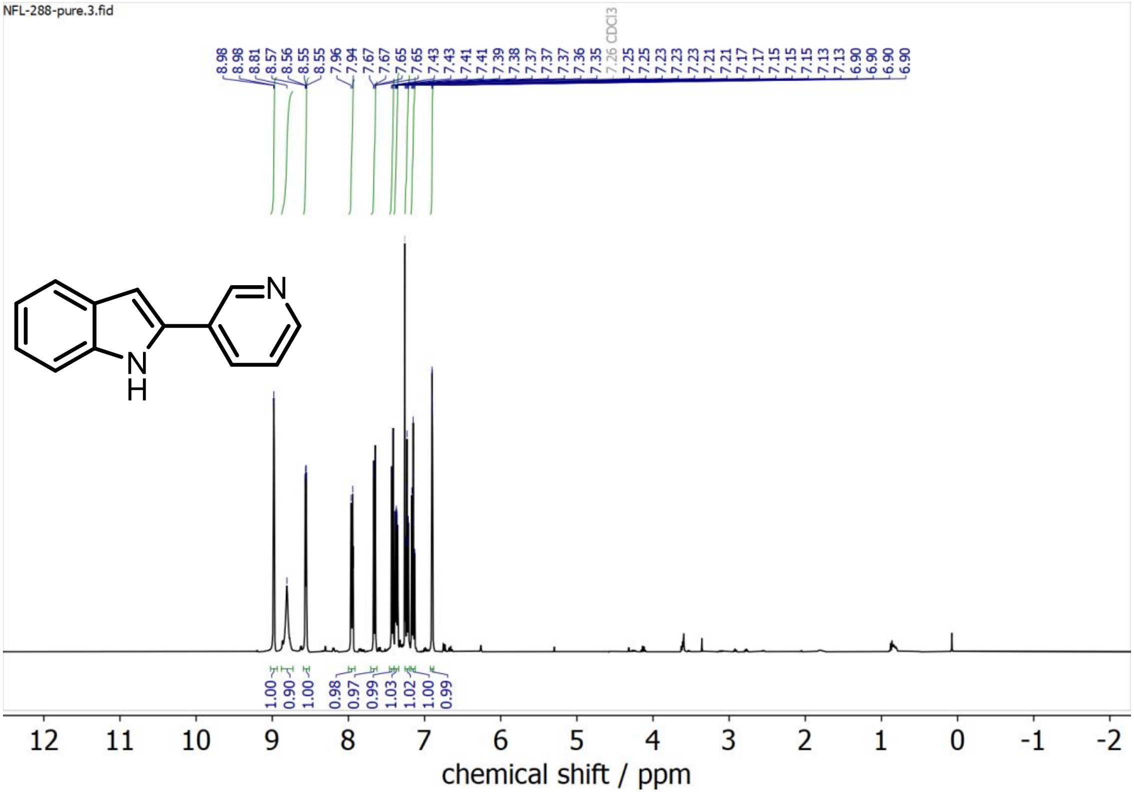


Figure S53: ^{1}H NMR spectrum of **25**.

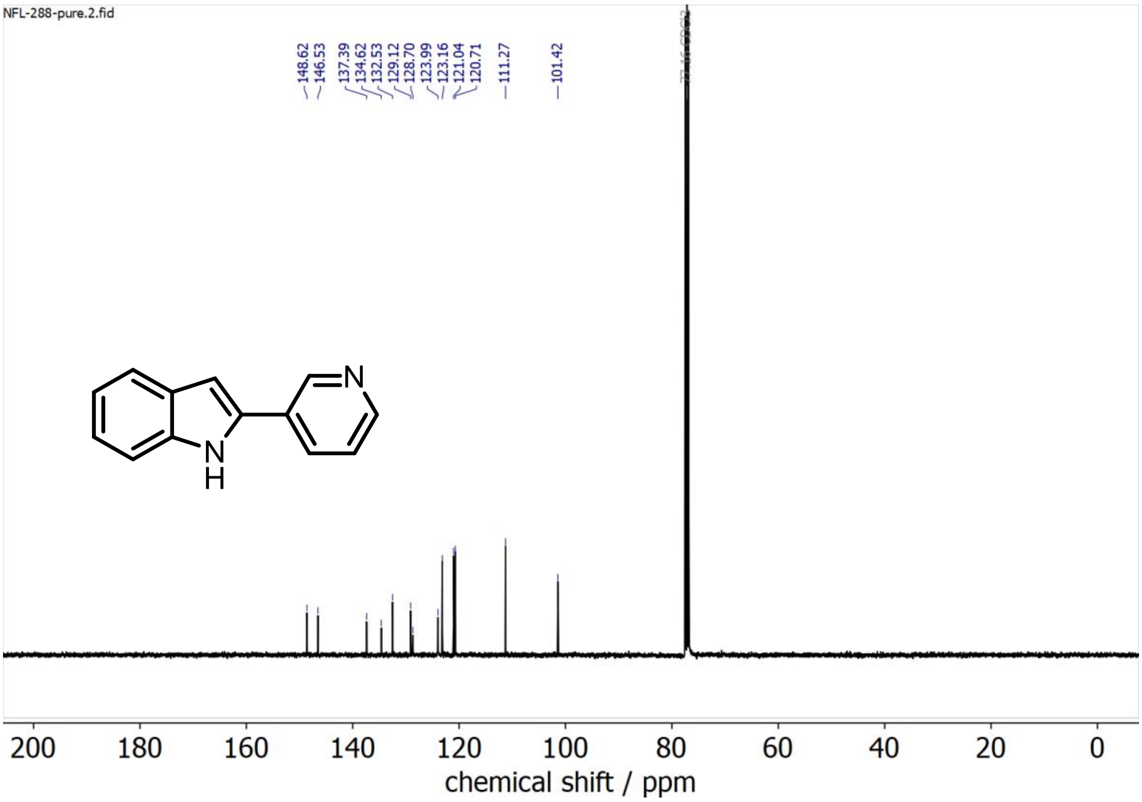


Figure S54: ^{13}C NMR spectrum of **25**.

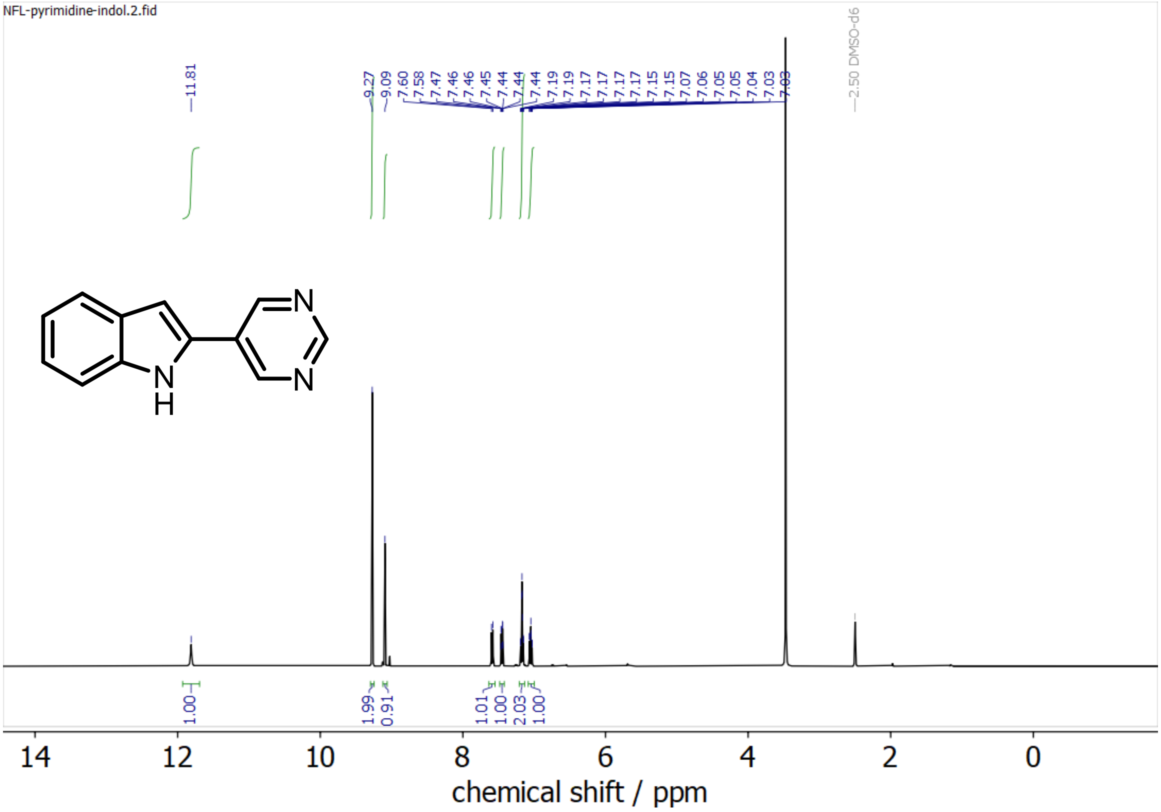


Figure S55: ^{1}H NMR spectrum of **26**.

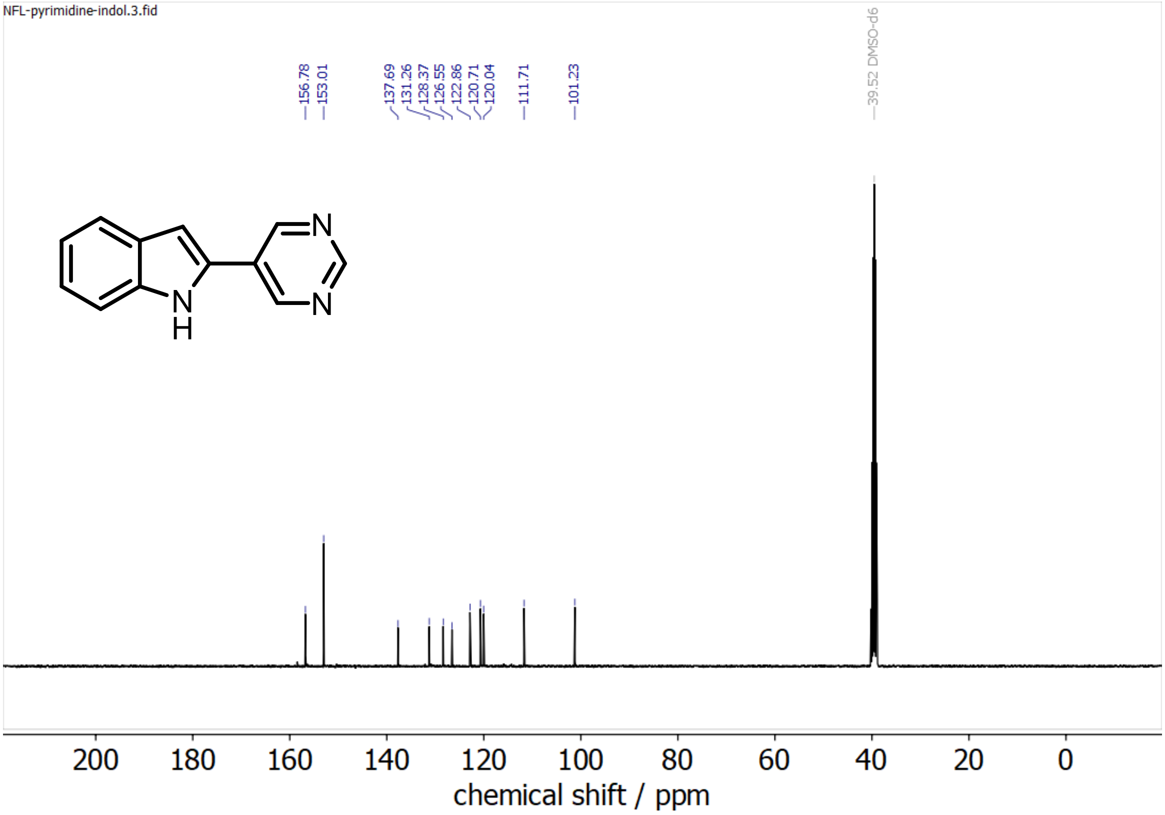


Figure S56: ^{13}C NMR spectrum of **26**.

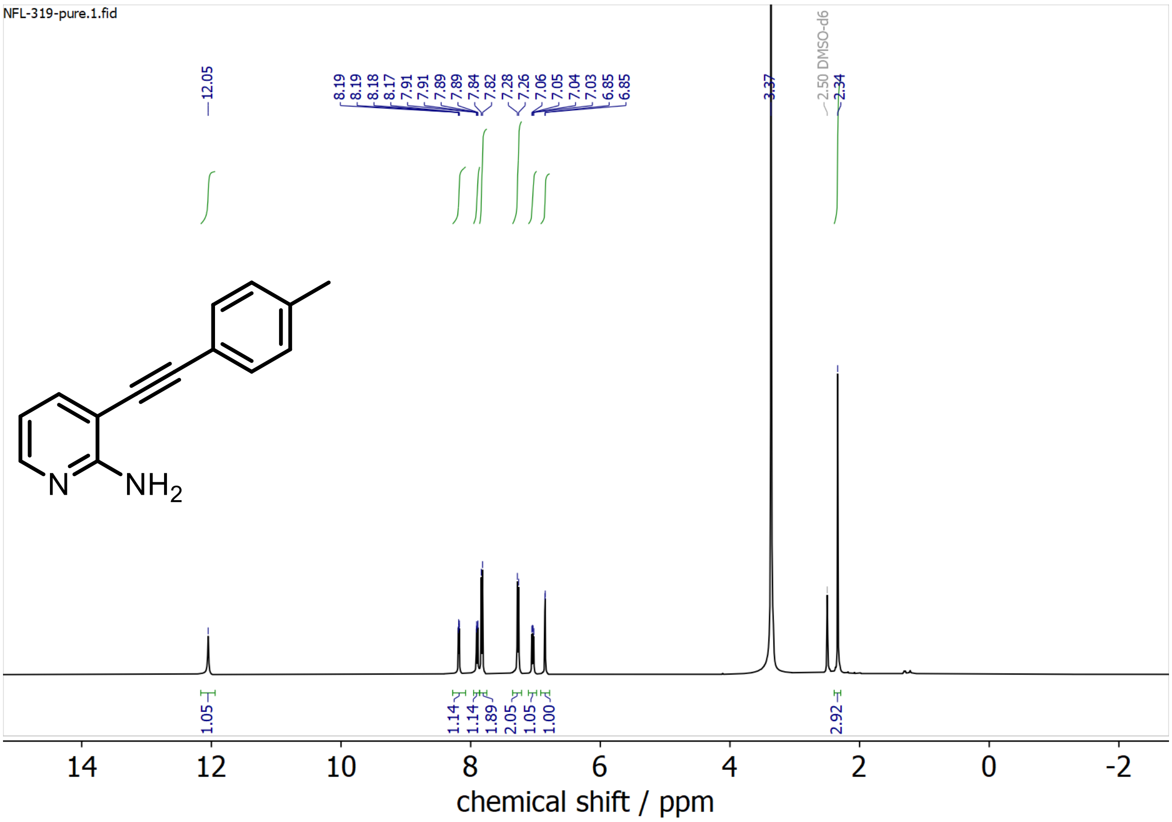


Figure S57: ^{1}H NMR spectrum of **27**.

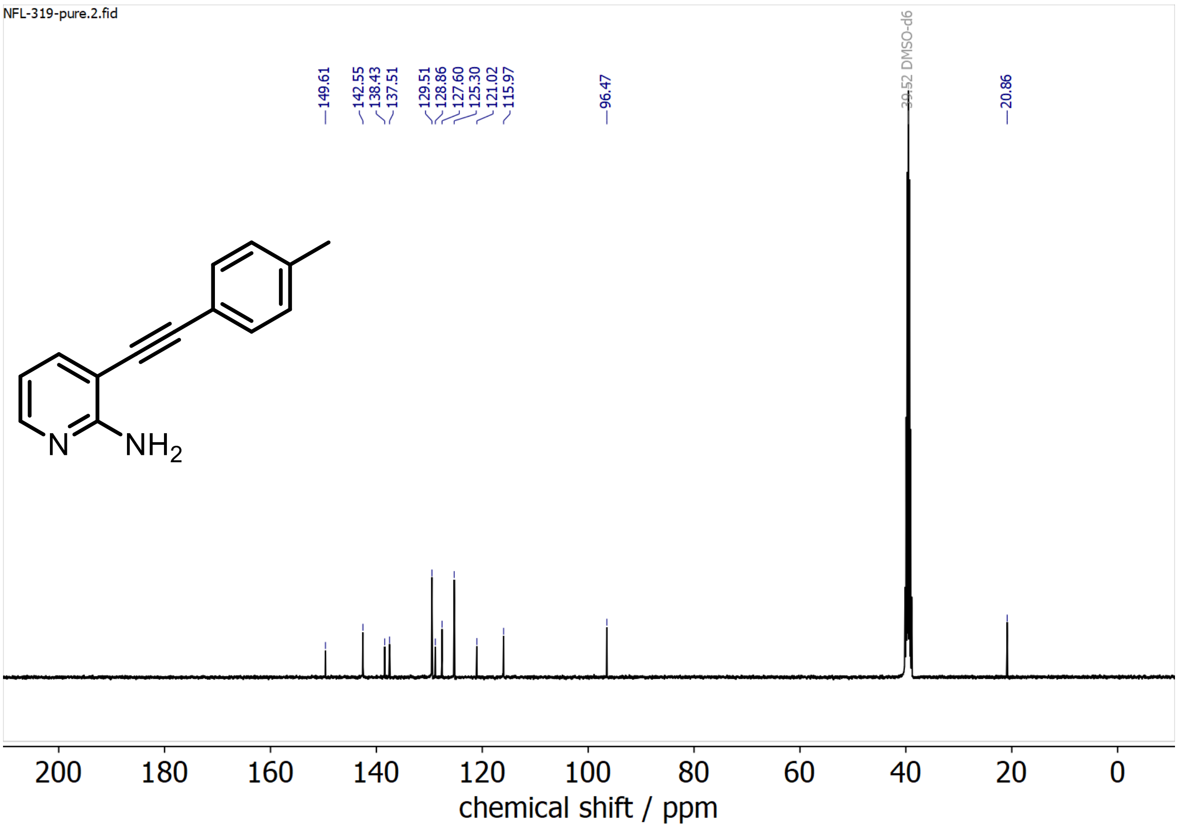


Figure S58: ^{13}C NMR spectrum of **27**.

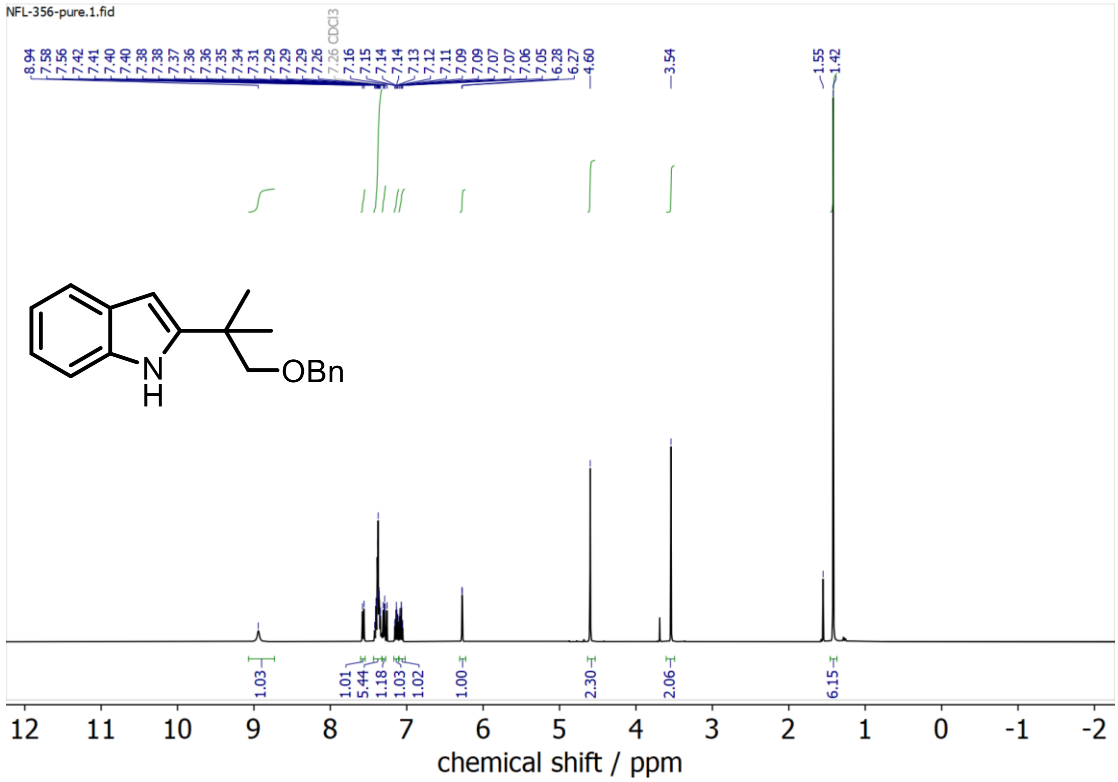


Figure S59: ^{1}H NMR spectrum of **28**.

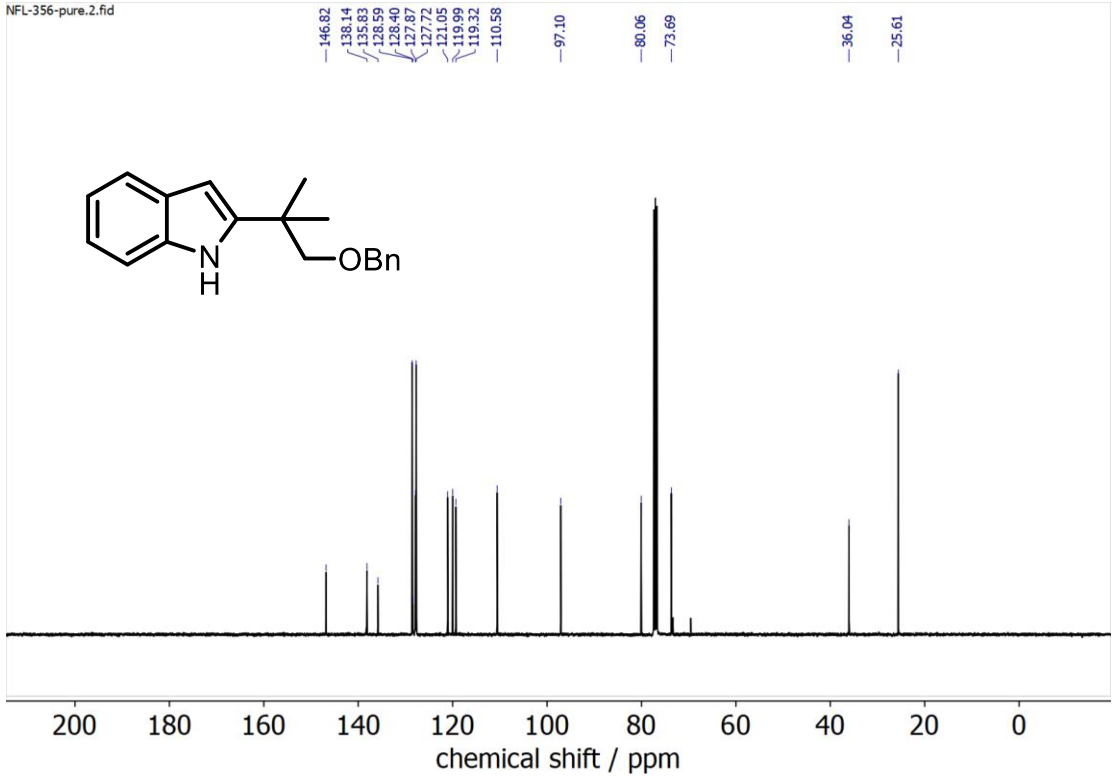


Figure S60: ^{13}C NMR spectrum of **28**.

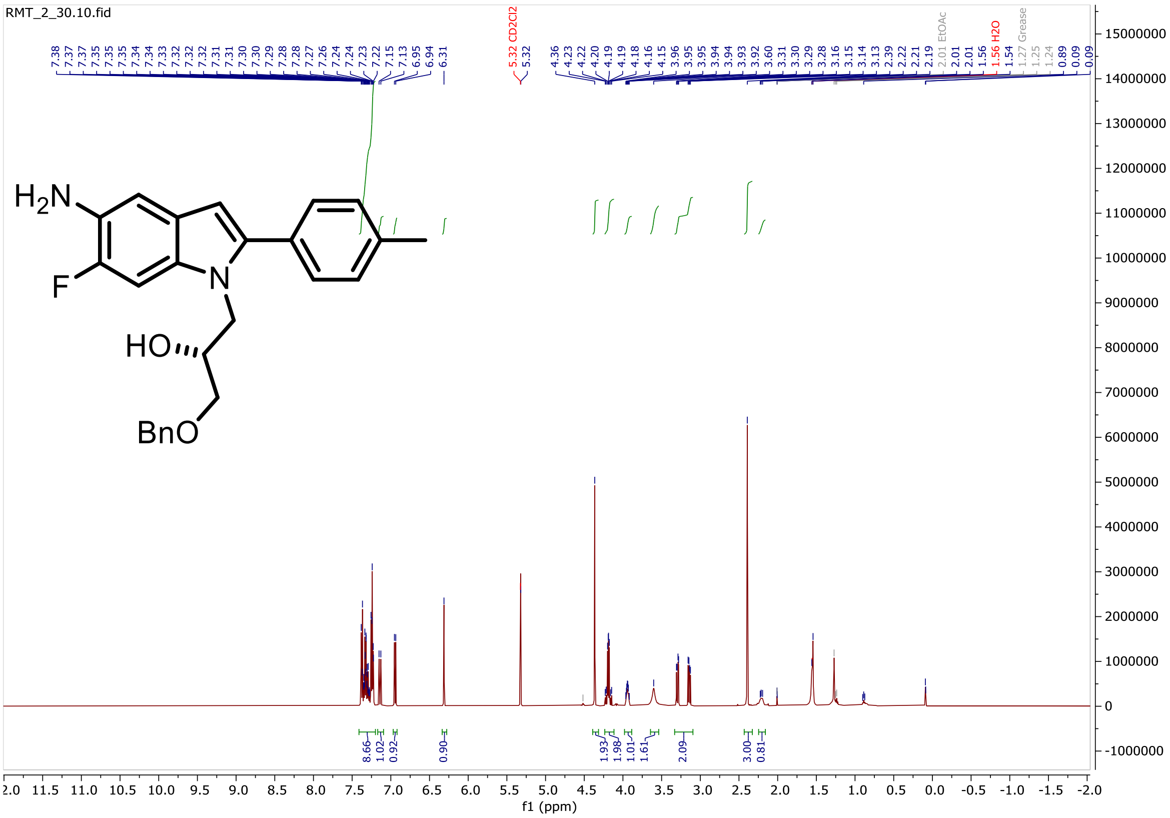


Figure S61: ^{1}H NMR spectrum of **29**.

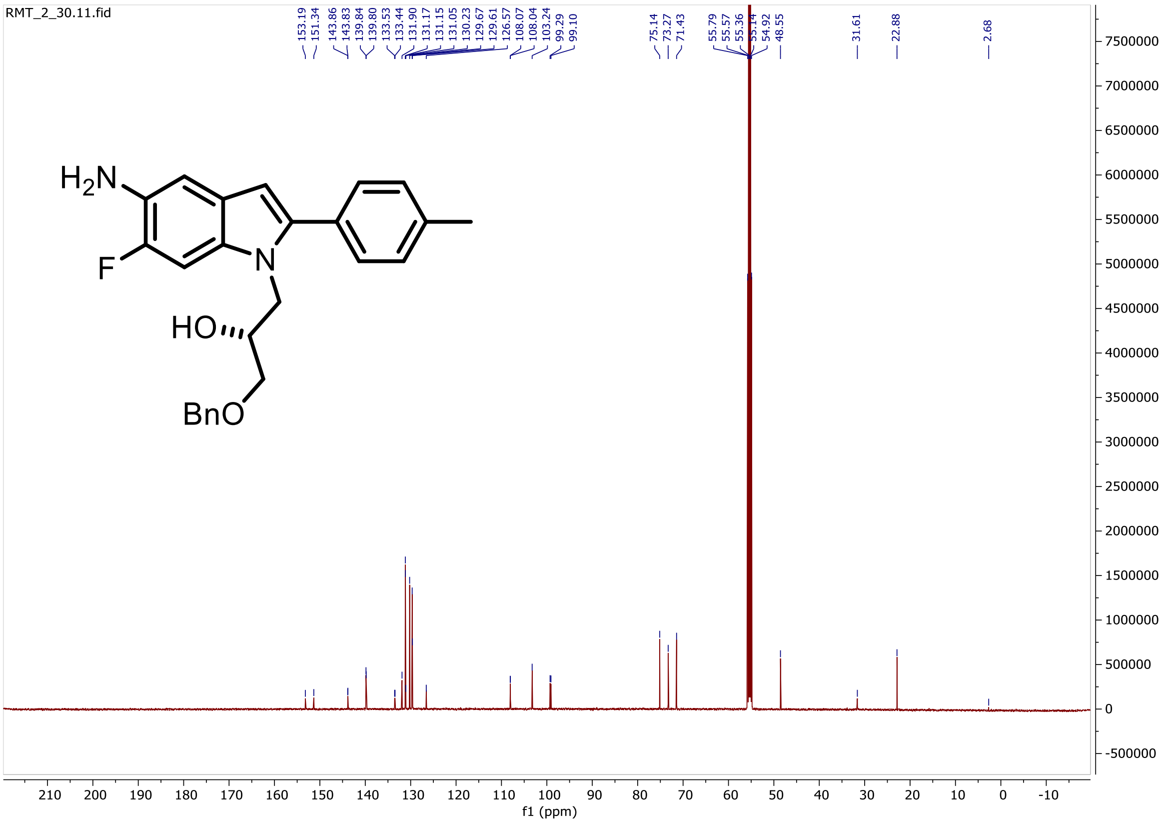


Figure S62: ^{13}C NMR spectrum of **29**.

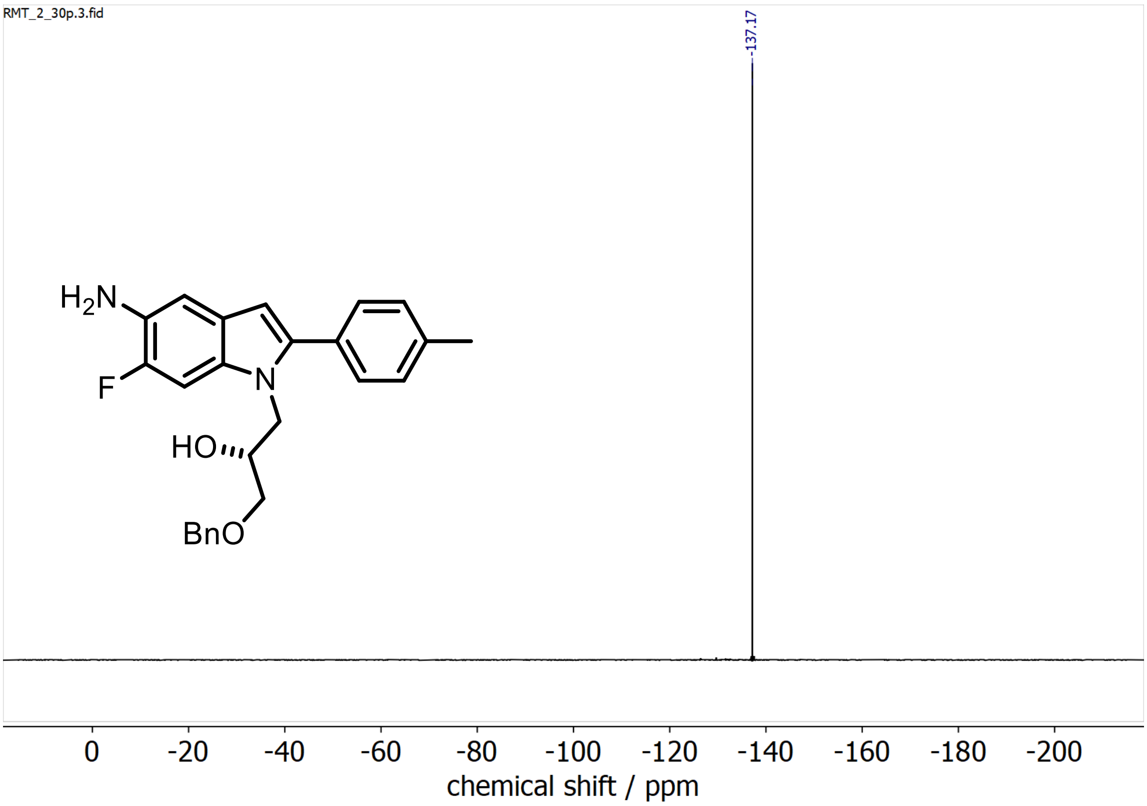


Figure S63: ^{19}F NMR spectrum of **29**.

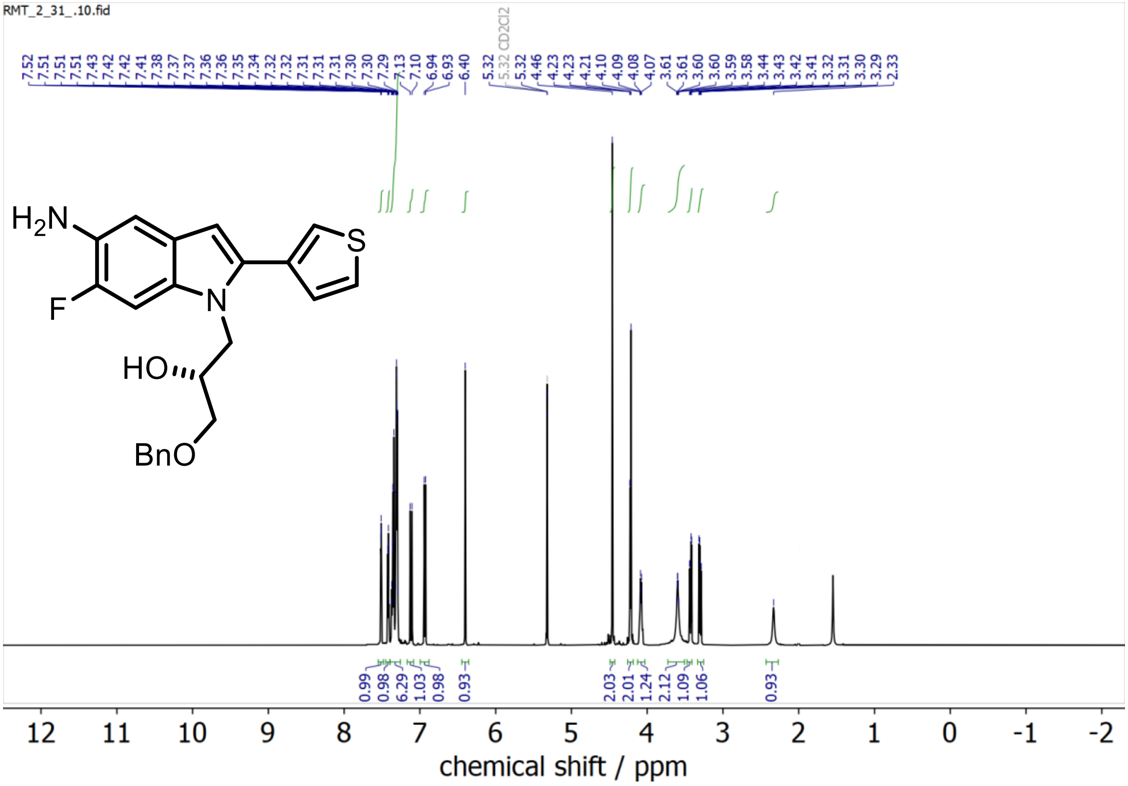


Figure S64: ^{1}H NMR spectrum of **30**.

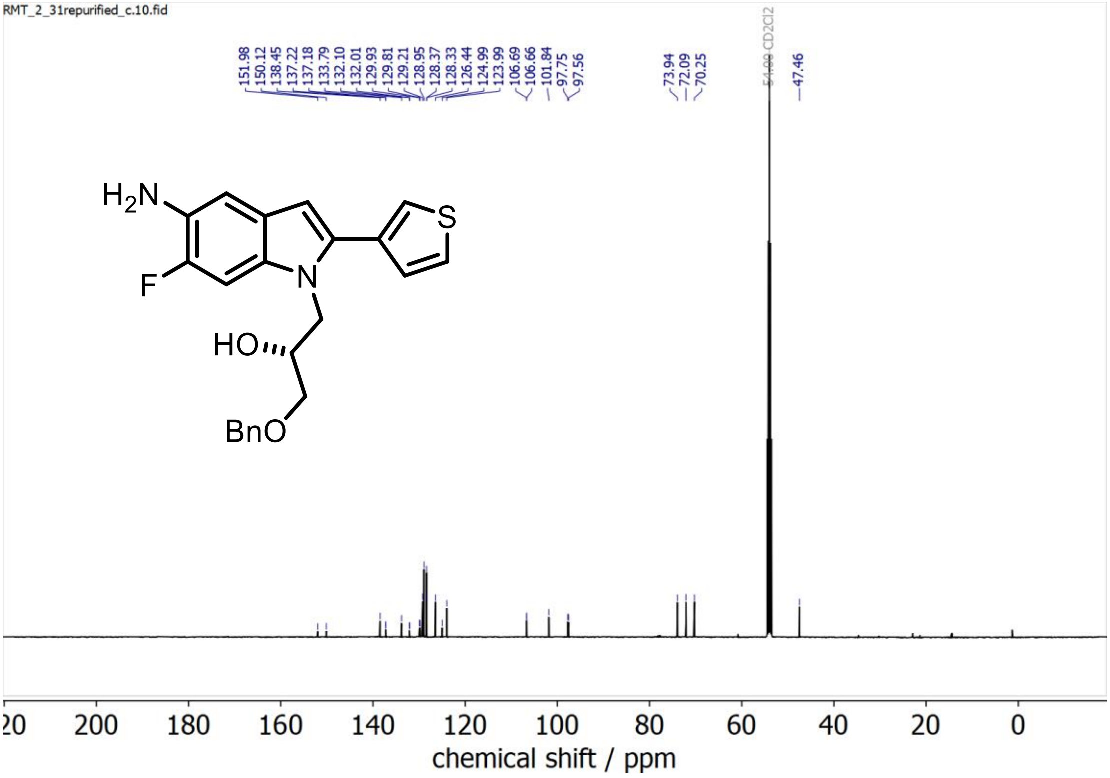


Figure S65: ^{13}C NMR spectrum of **30**.

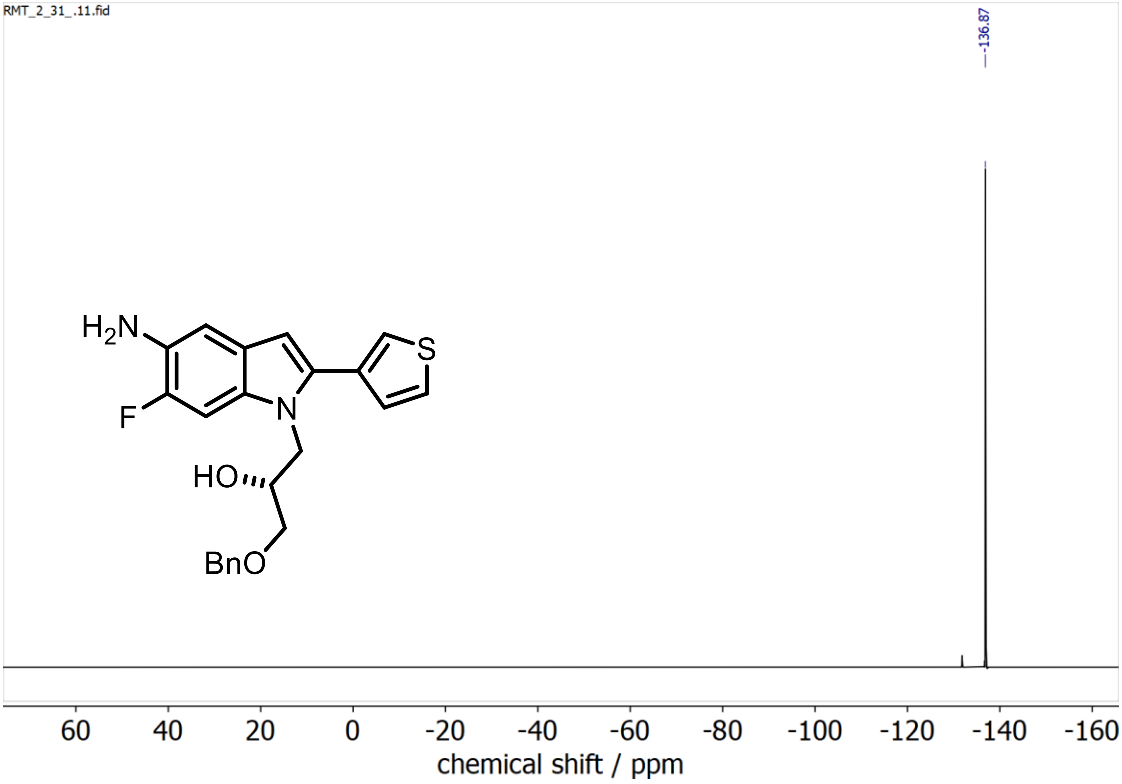


Figure S66: ^{19}F NMR spectrum of **30**.

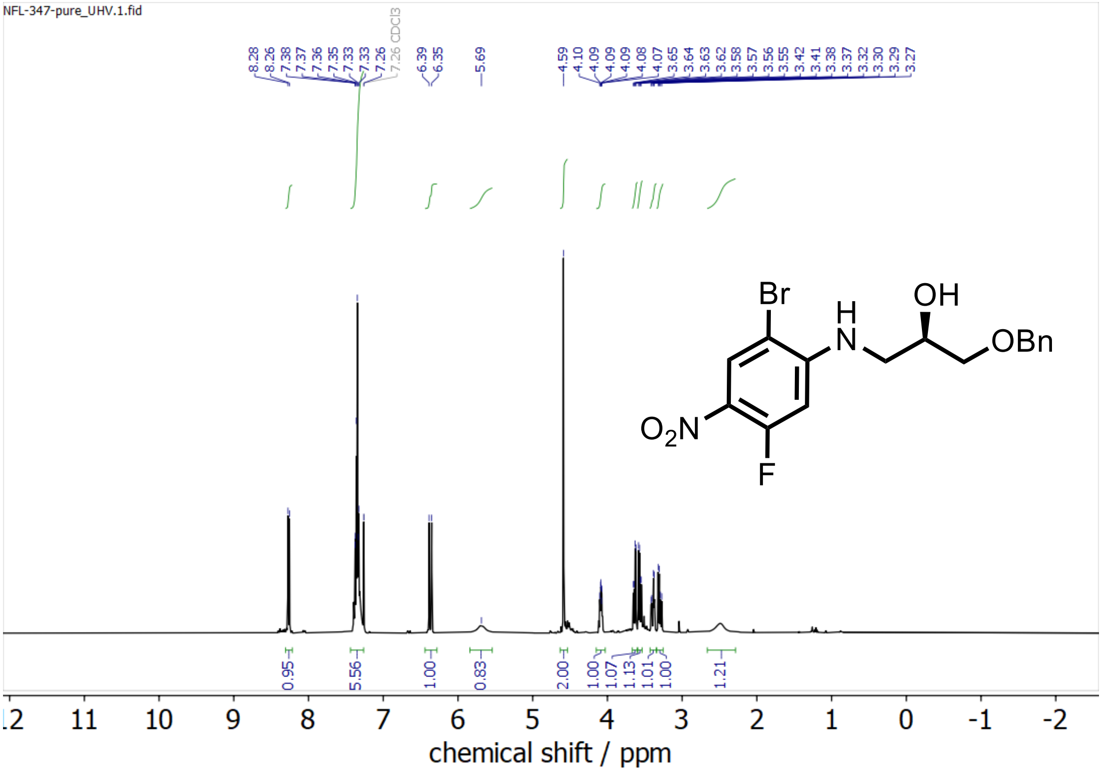


Figure S67: ^{1}H NMR spectrum of **33**.

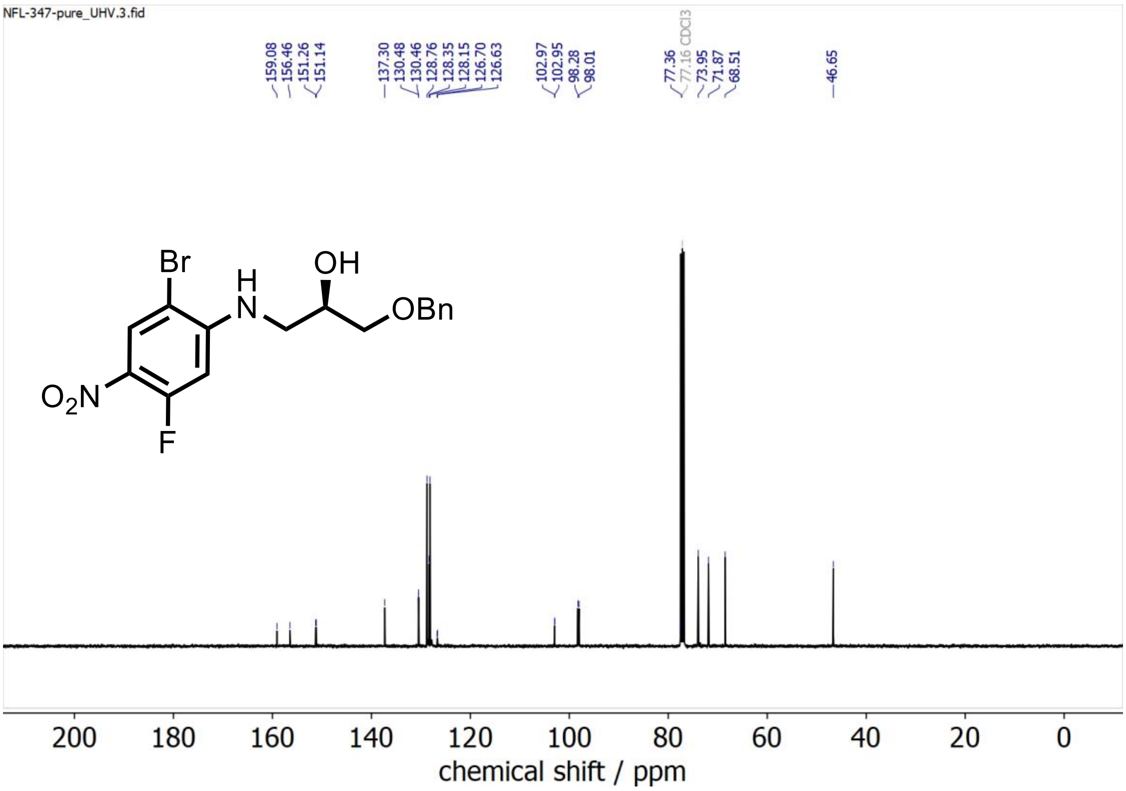


Figure S68: ^{13}C NMR spectrum of **33**.

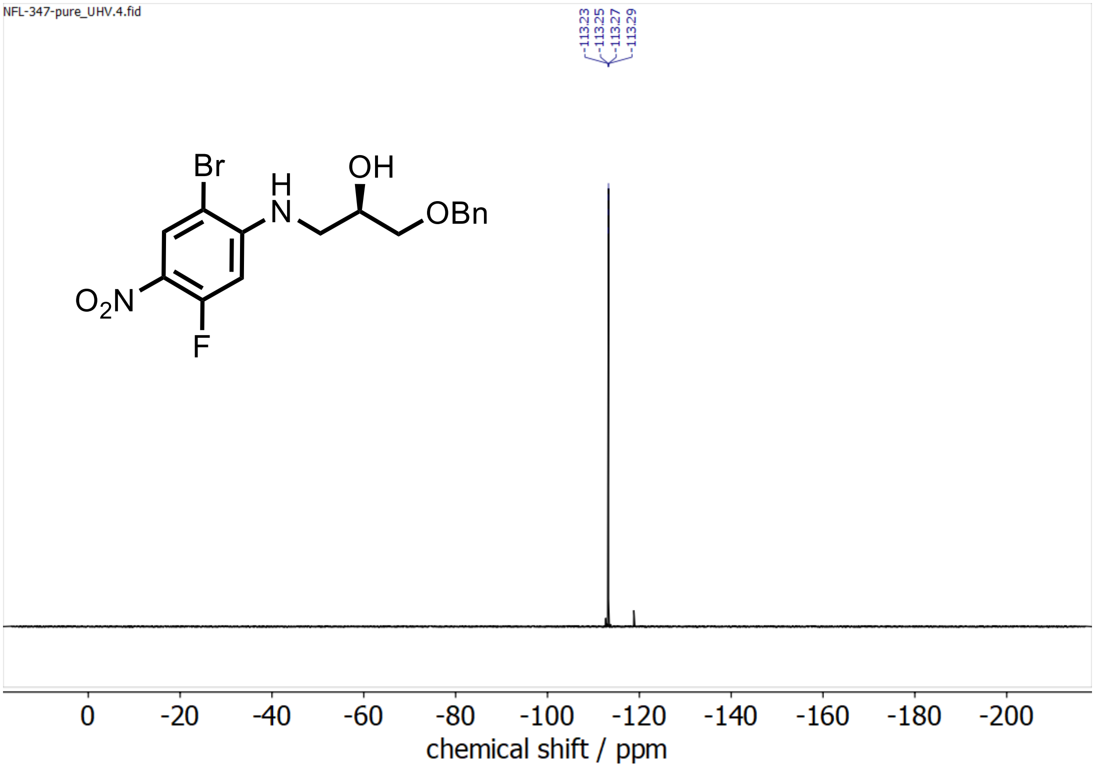


Figure S69: ^{19}F NMR spectrum of **33**.

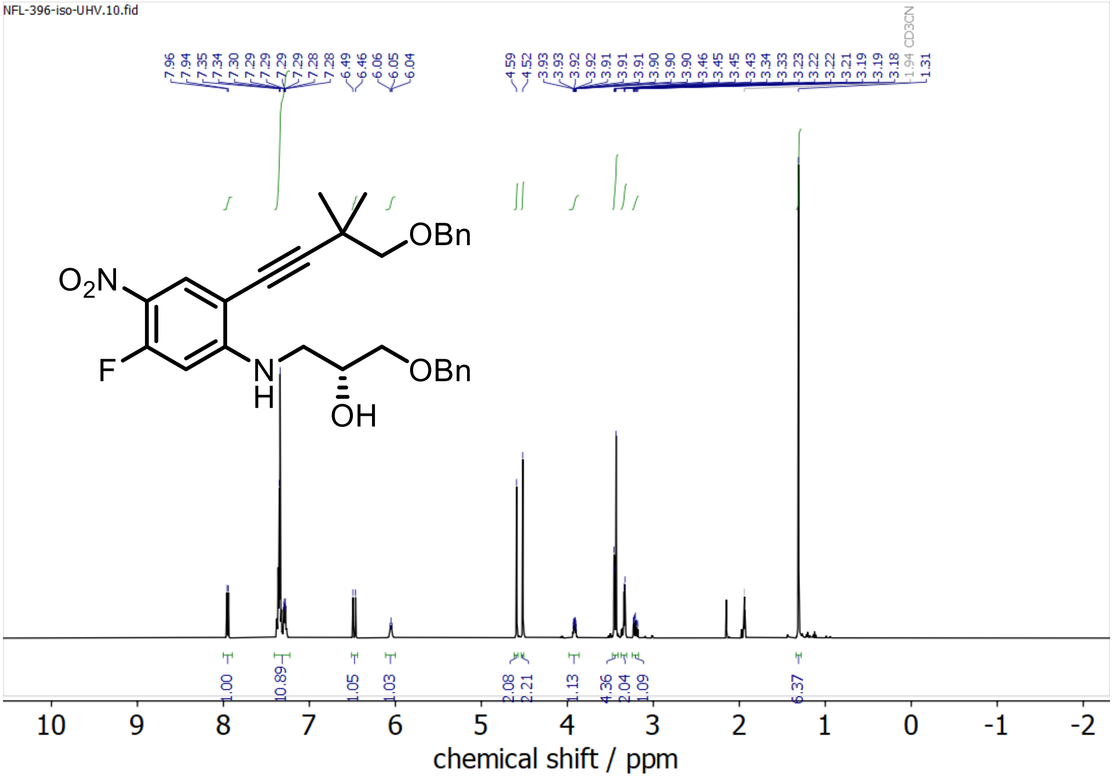


Figure S70: ${}^{1}H$ NMR spectrum of **S1**.

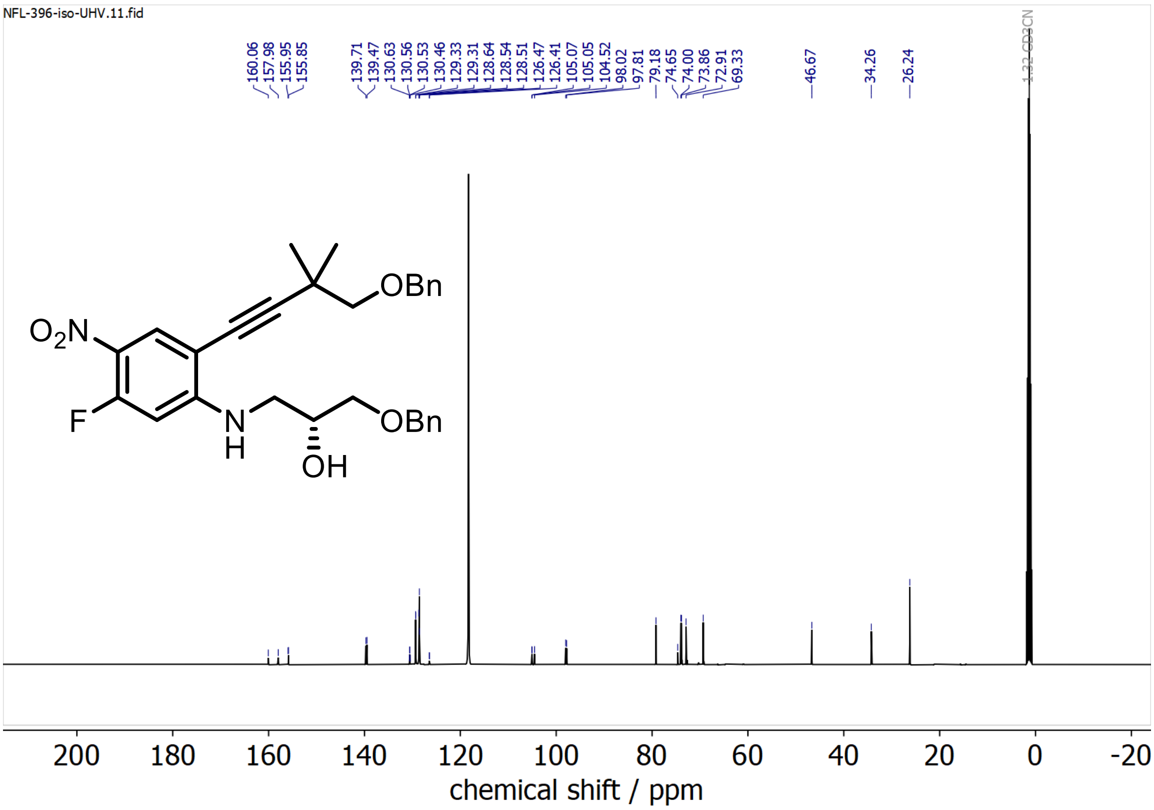


Figure S71: ${}^{13}C$ NMR spectrum of **S1**.

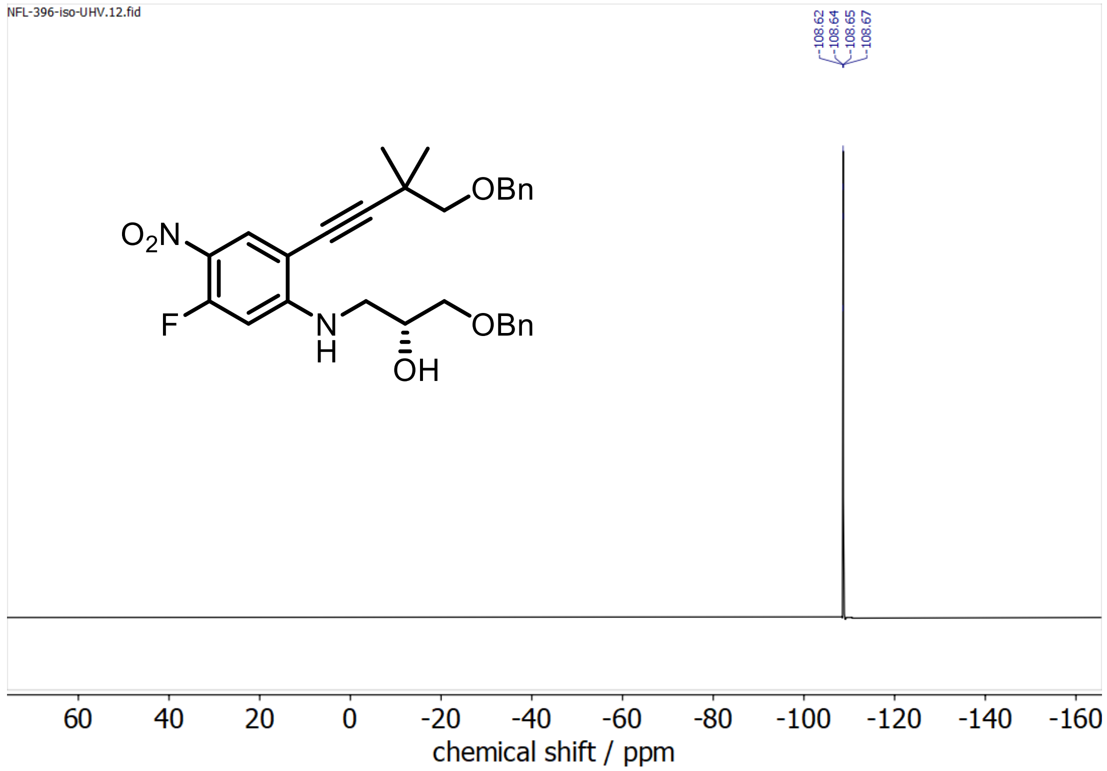


Figure S72: ^{19}F NMR spectrum of **S1**.

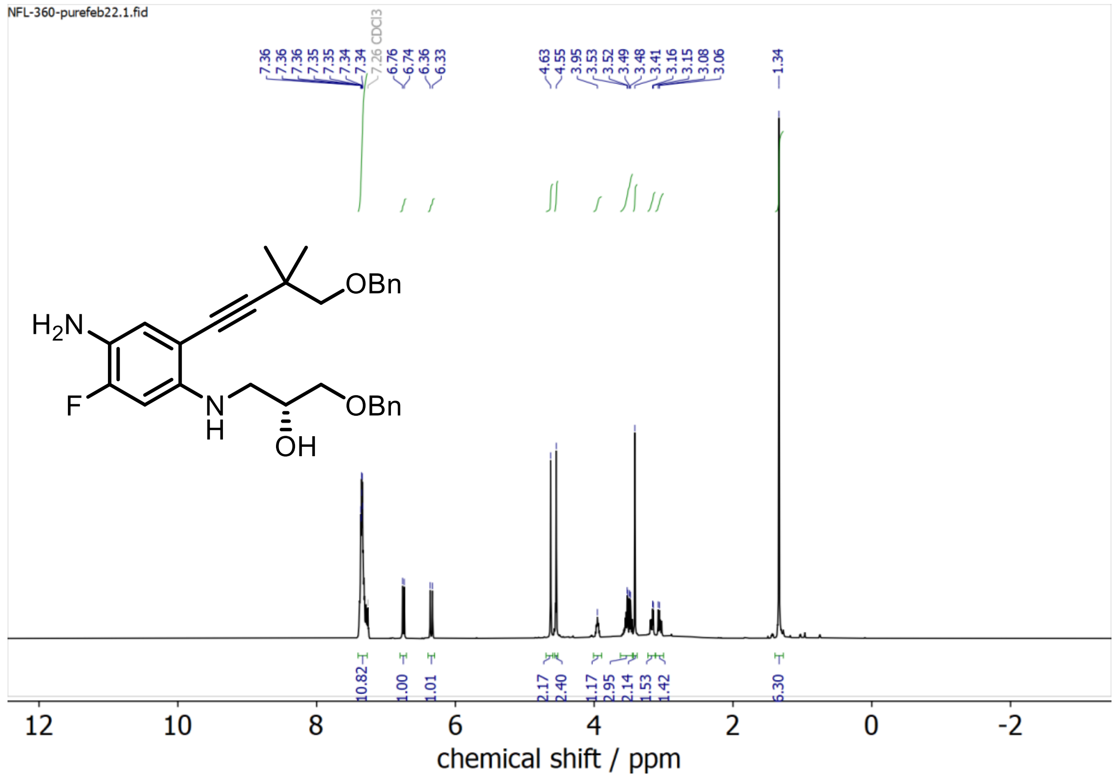


Figure S73: ^{1}H NMR spectrum of **35**.

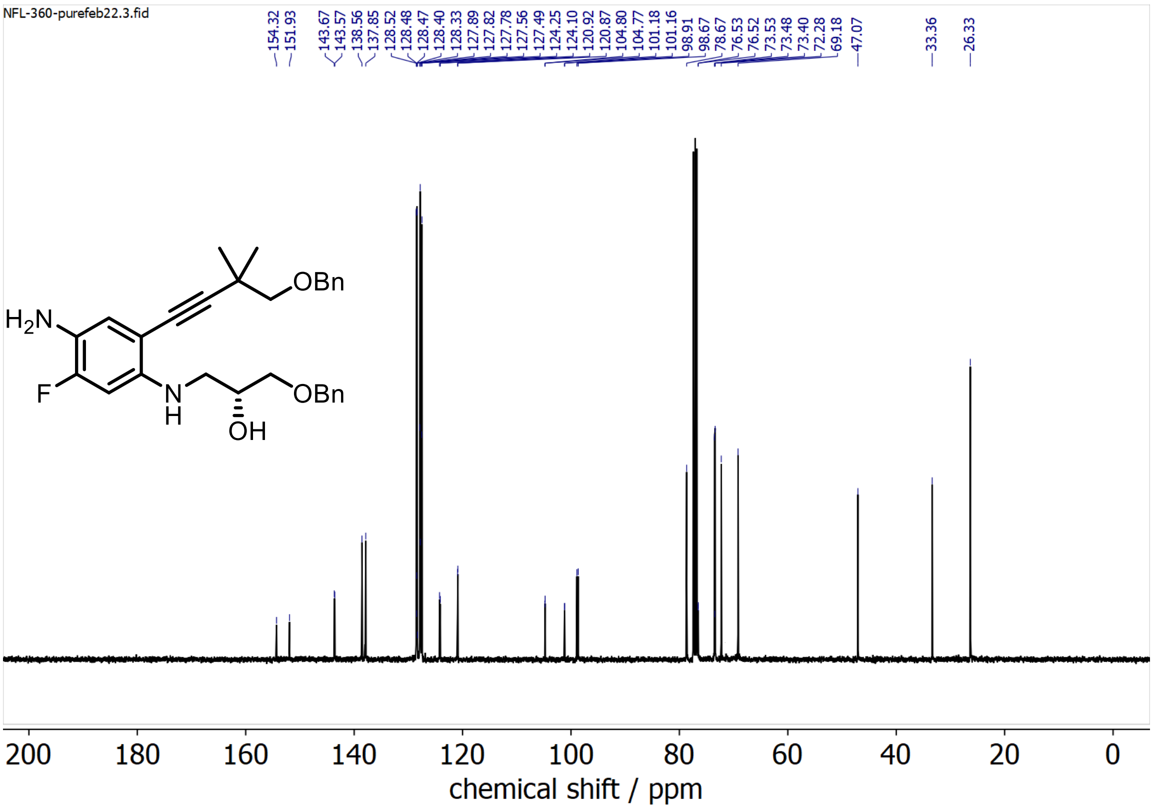


Figure S74: ^{13}C NMR spectrum of **35**.

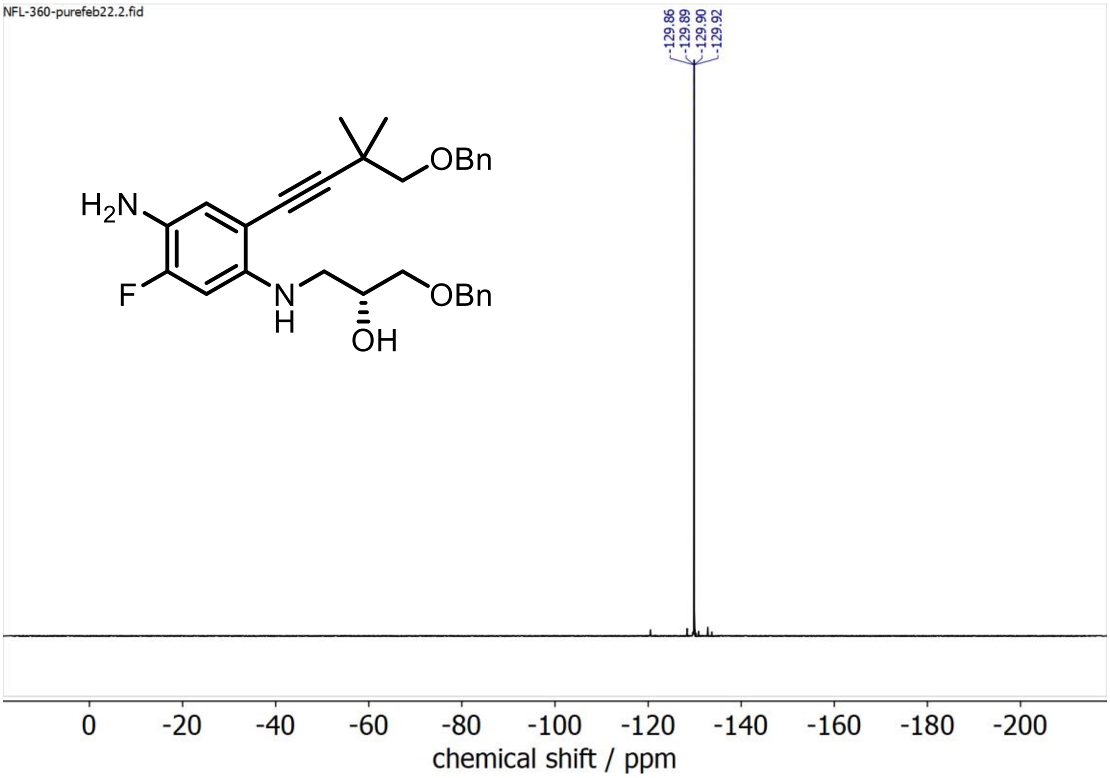


Figure S75: ^{19}F NMR spectrum of **35**.

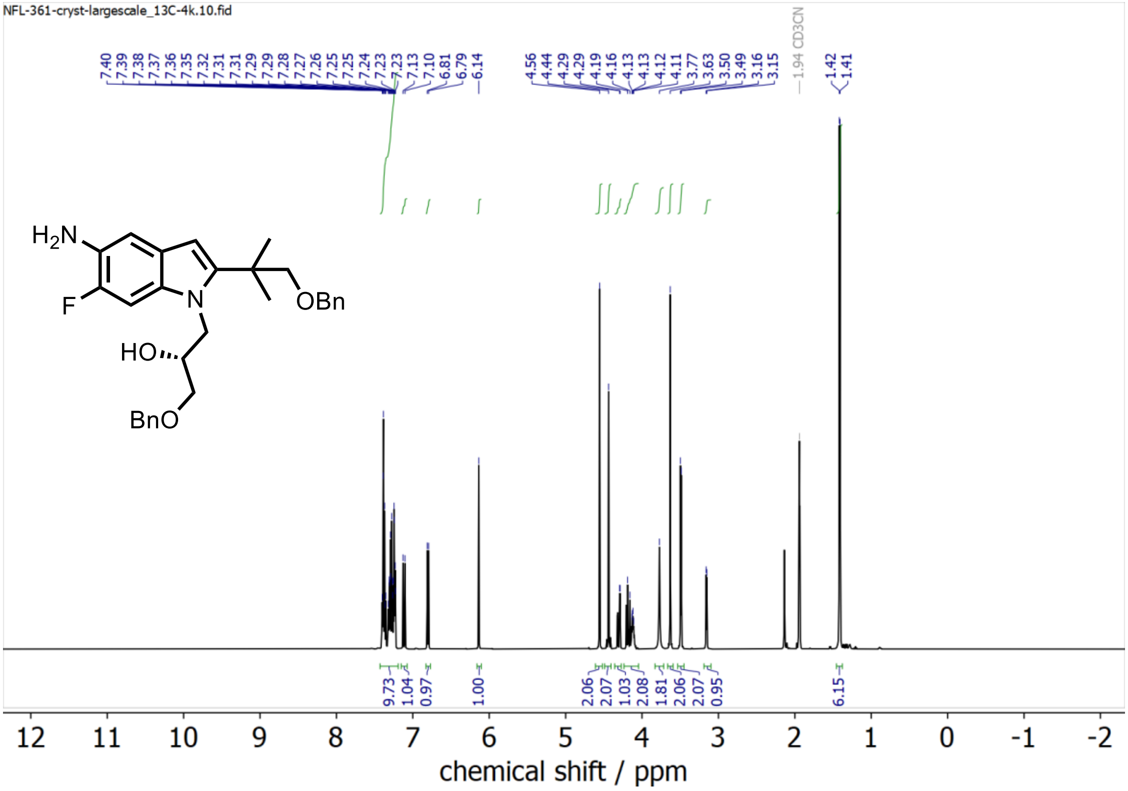


Figure S76: ^{1}H NMR spectrum of **36**.

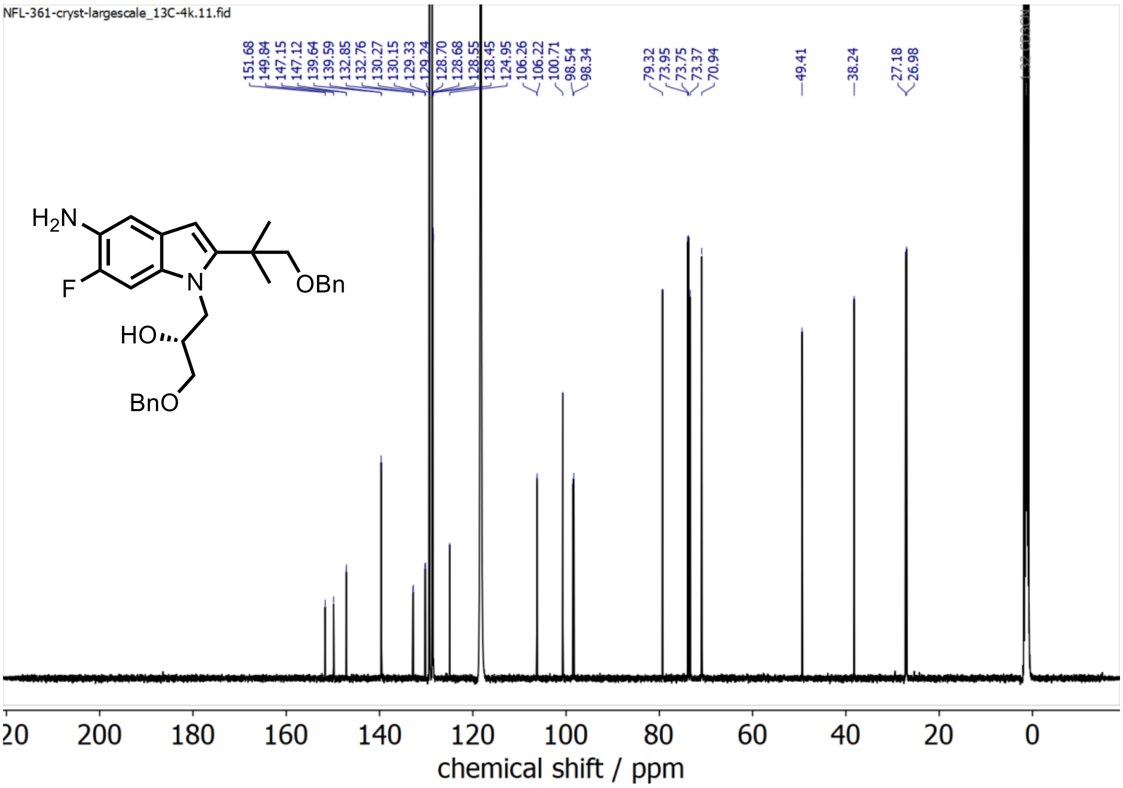


Figure S77: ^{13}C NMR spectrum of **36**.

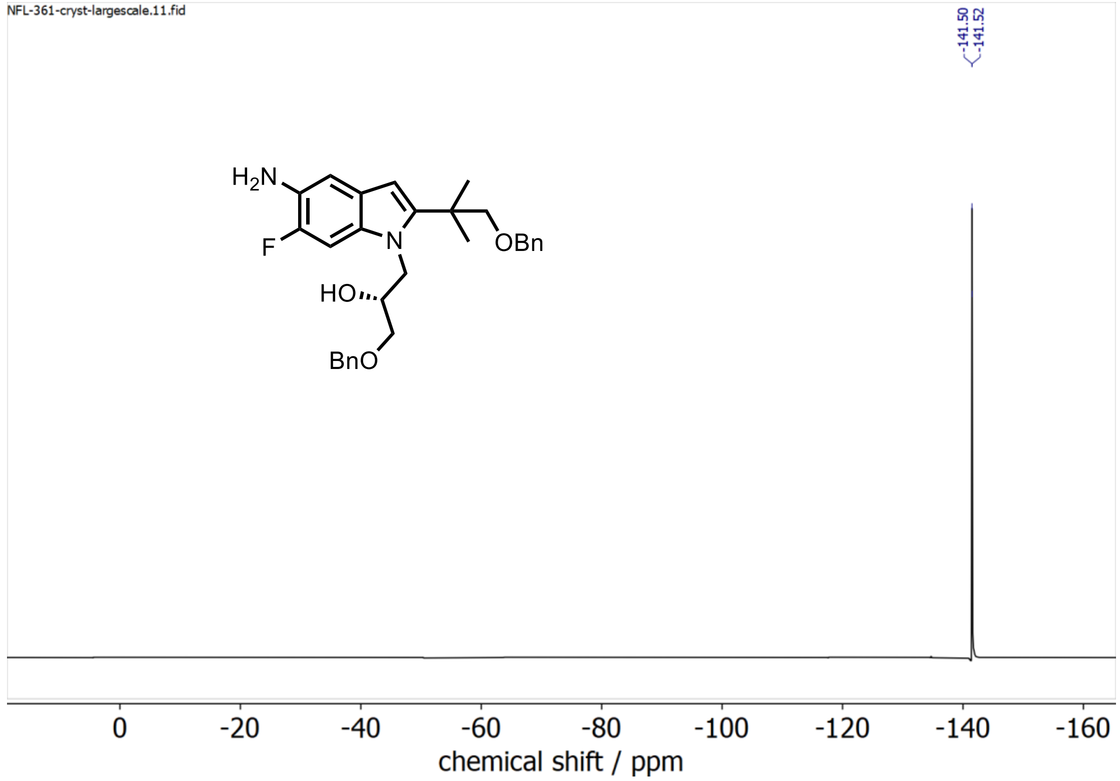


Figure S78: ^{19}F NMR spectrum of **36**.

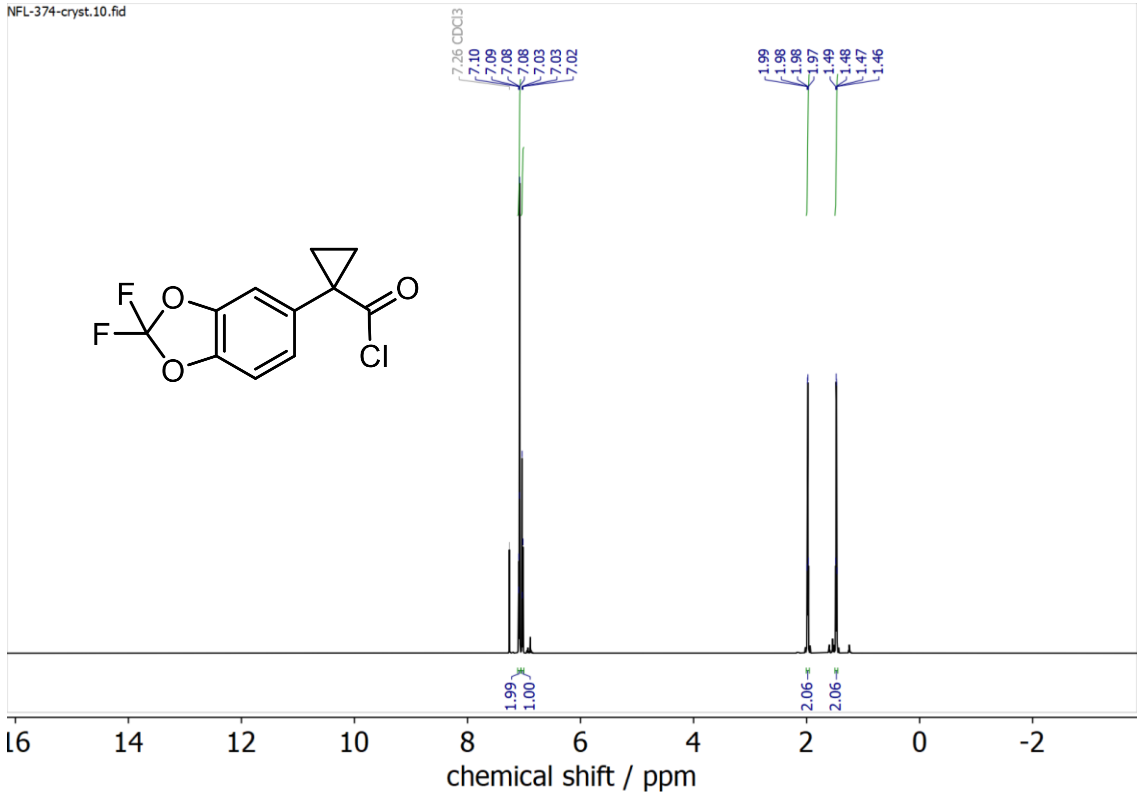


Figure S79: ^{1}H NMR spectrum of **37**.

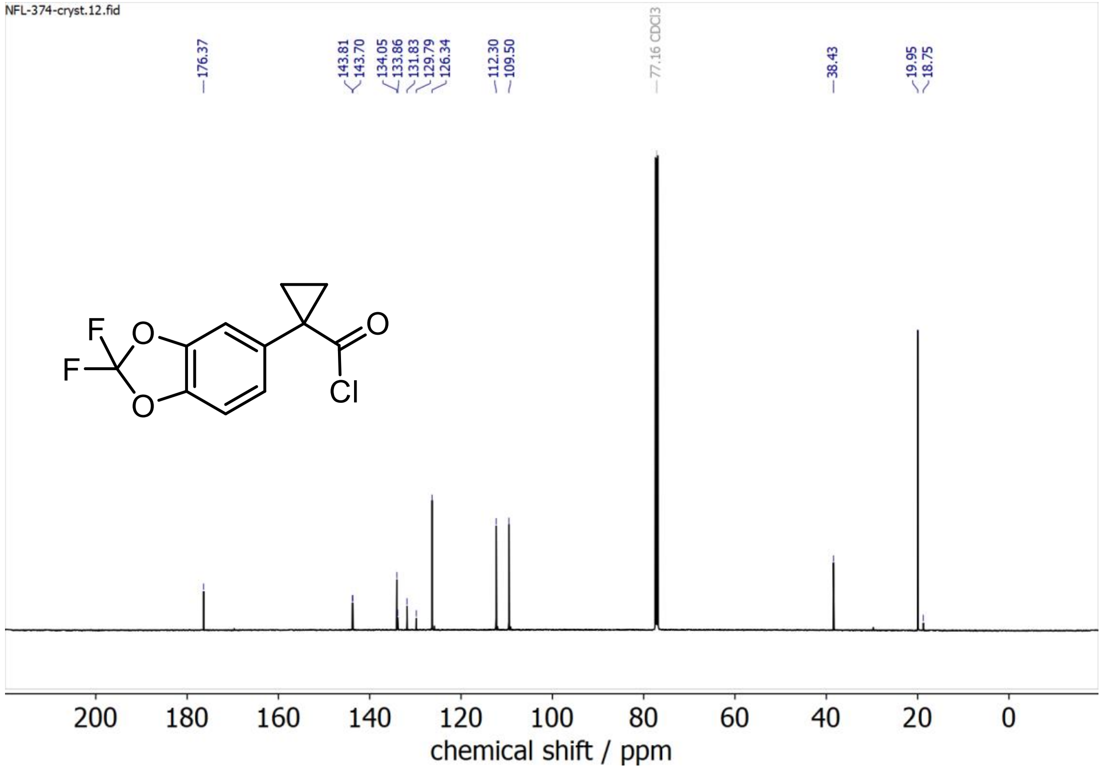


Figure S80: ^{13}C NMR spectrum of **37**.

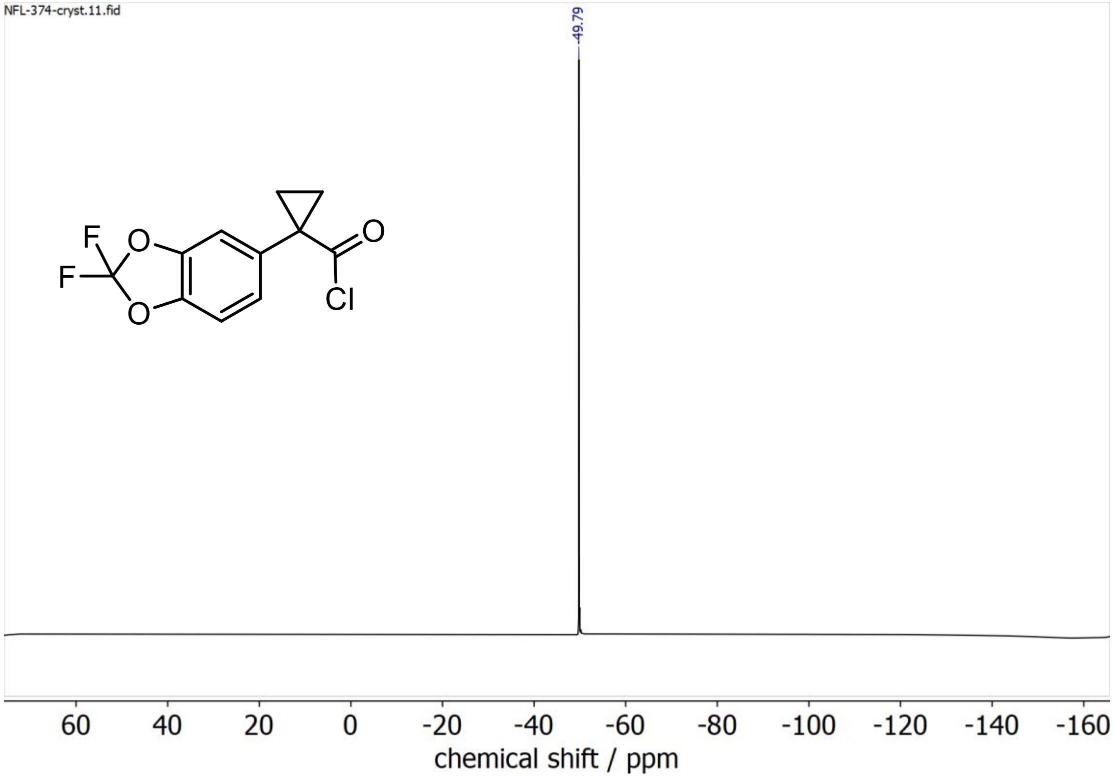


Figure S81: ^{19}F NMR spectrum of **37**.

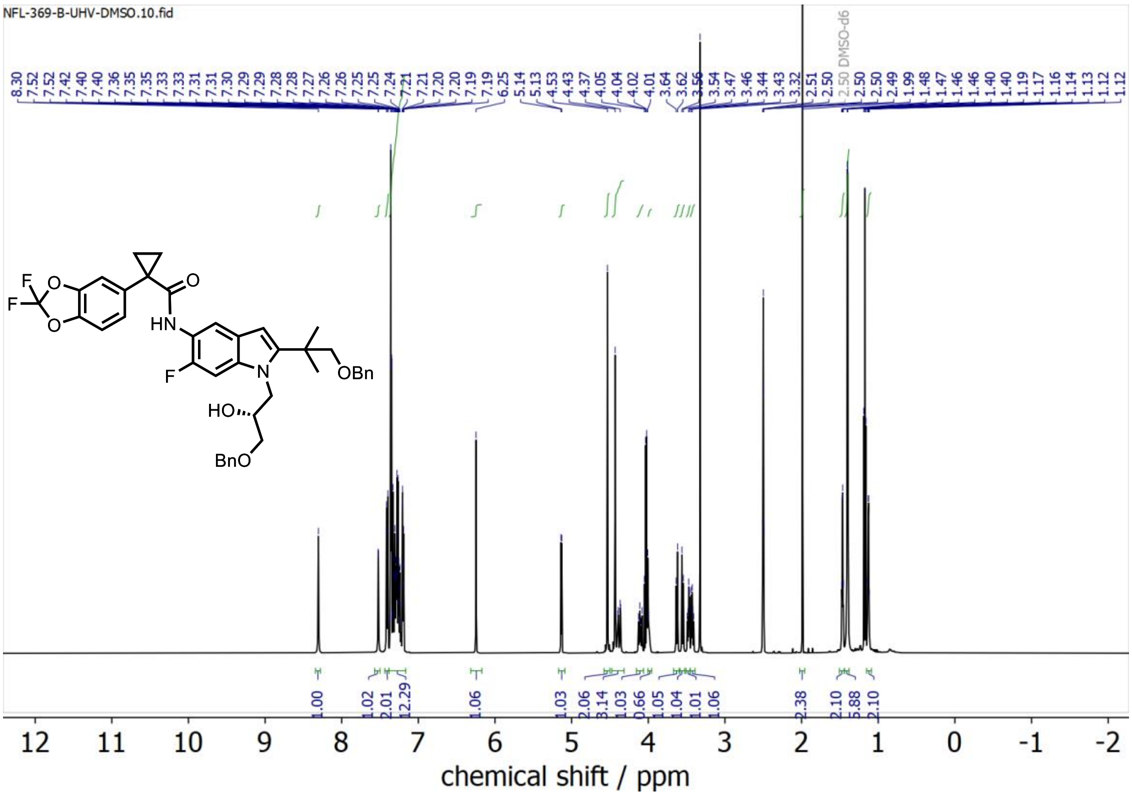


Figure S82: ^{1}H NMR spectrum of **38**.

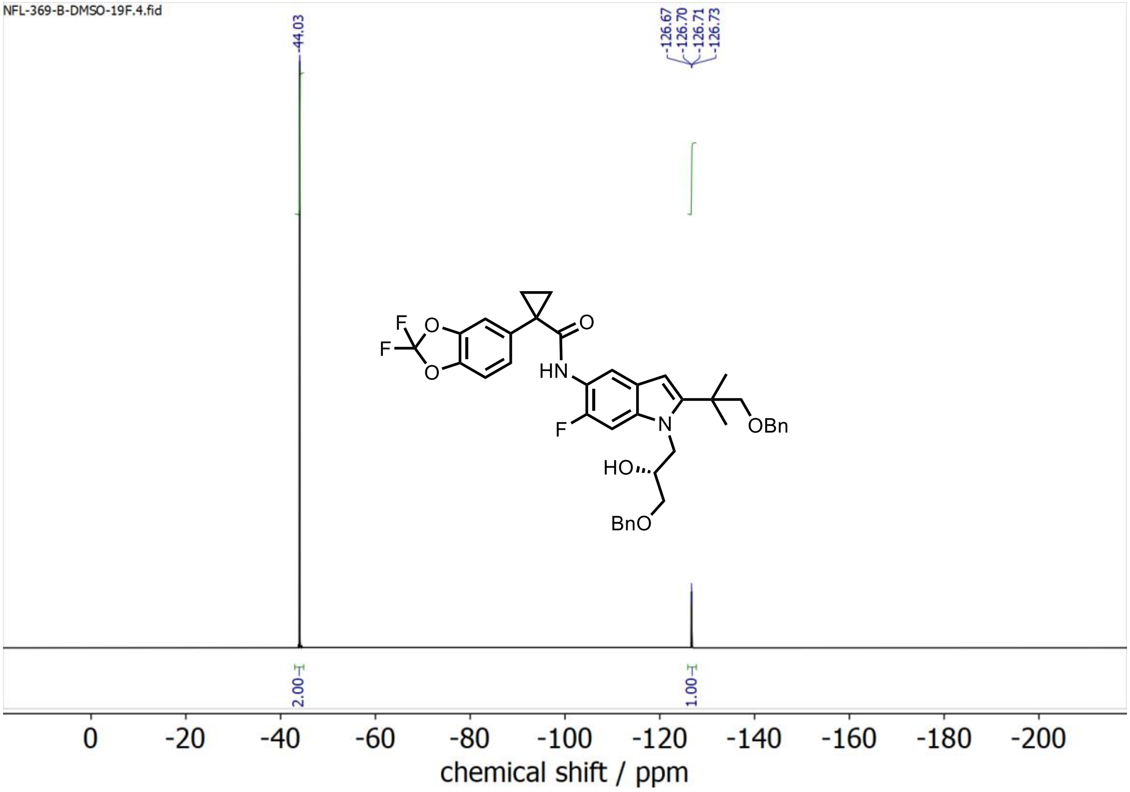


Figure S83: ^{19}F NMR spectrum of **38**.

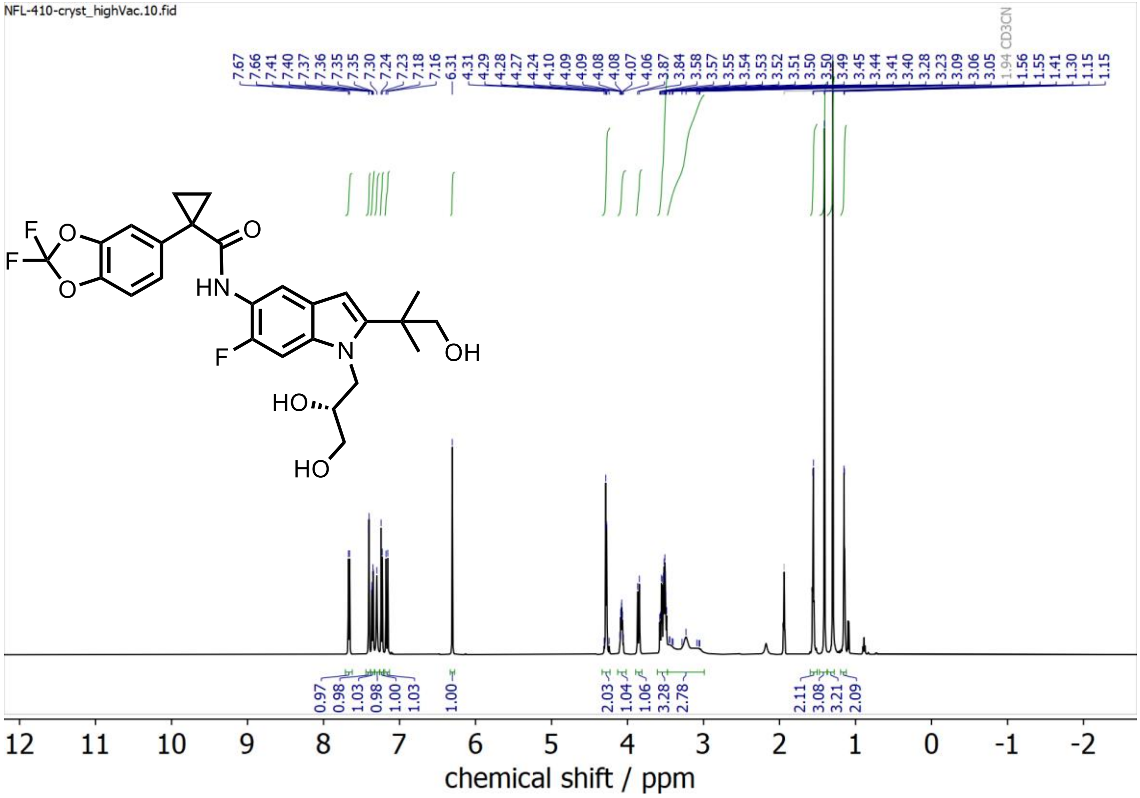


Figure S84: ^{1}H NMR spectrum of tezacaftor **1**.

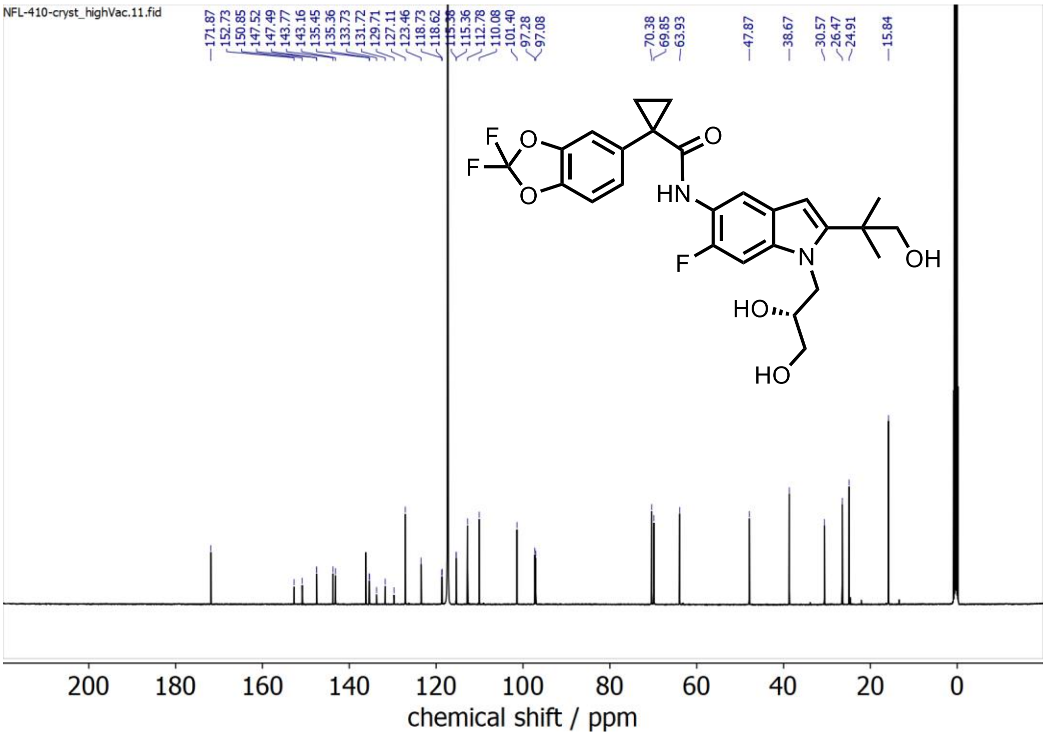


Figure S85: ^{13}C NMR spectrum of tezacaftor **1**.

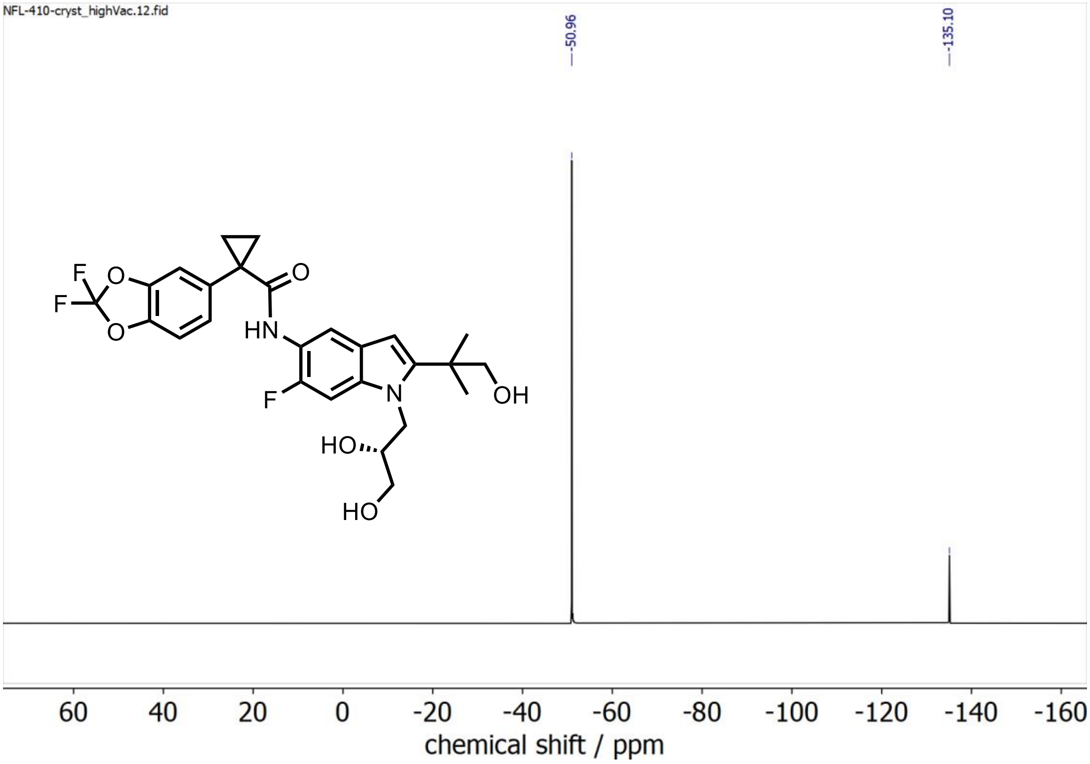


Figure S86: ^{19}F NMR spectrum of tezacaftor **1**.

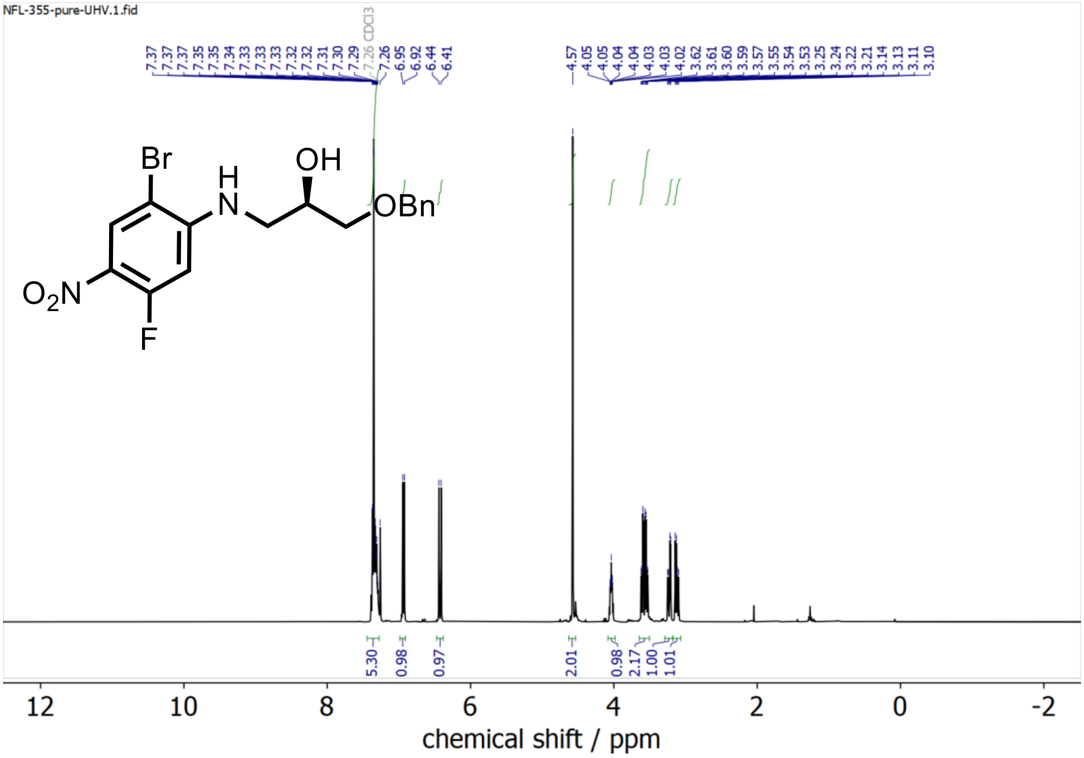


Figure S87: ^{1}H NMR spectrum of **S2**.

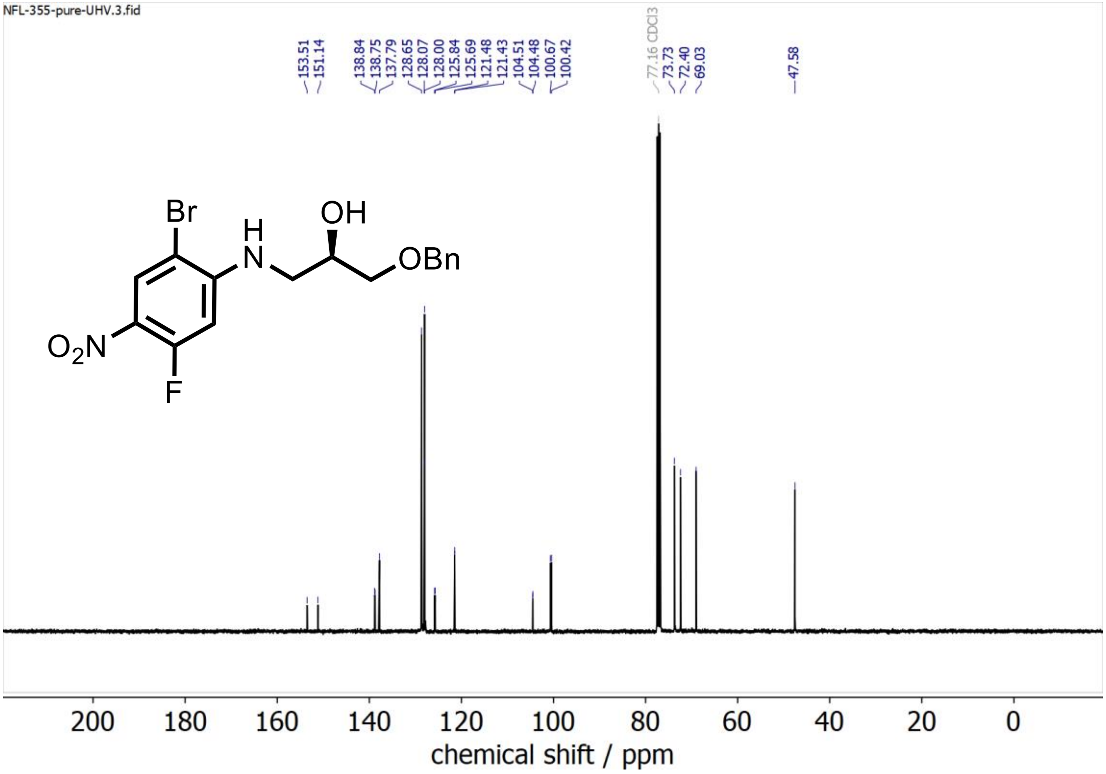


Figure S88: ^{13}C NMR spectrum of **S2**.

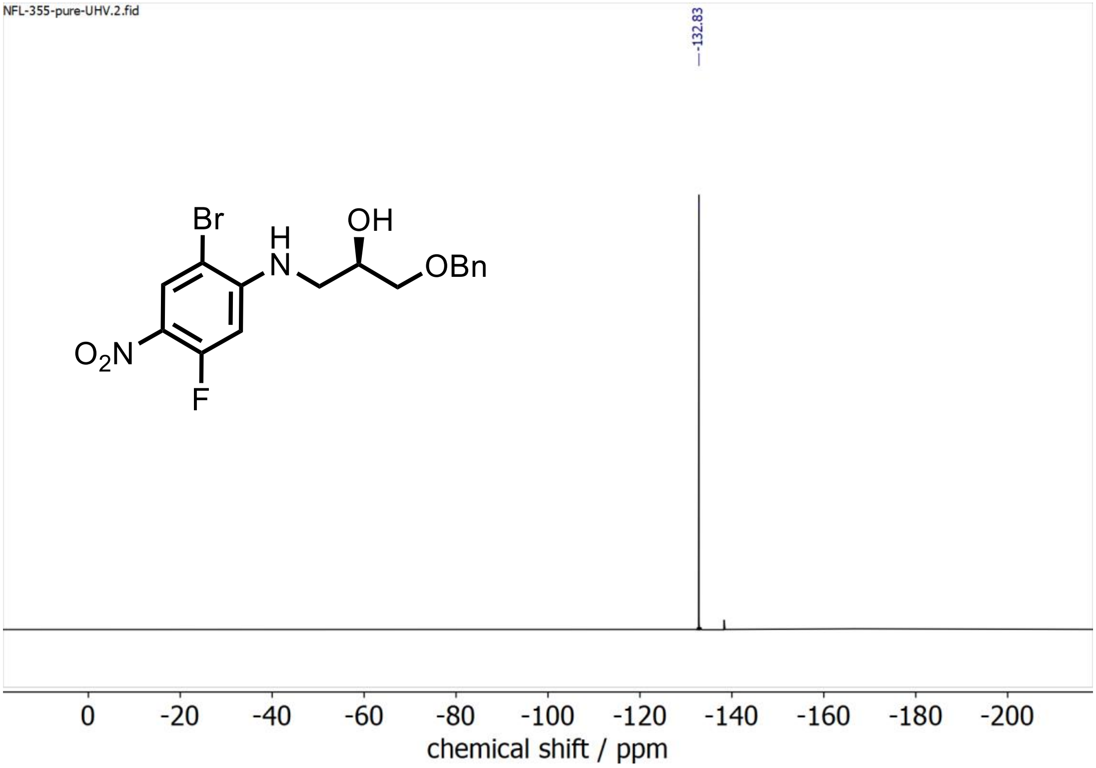


Figure S89: ^{19}F NMR spectrum of **S2**.

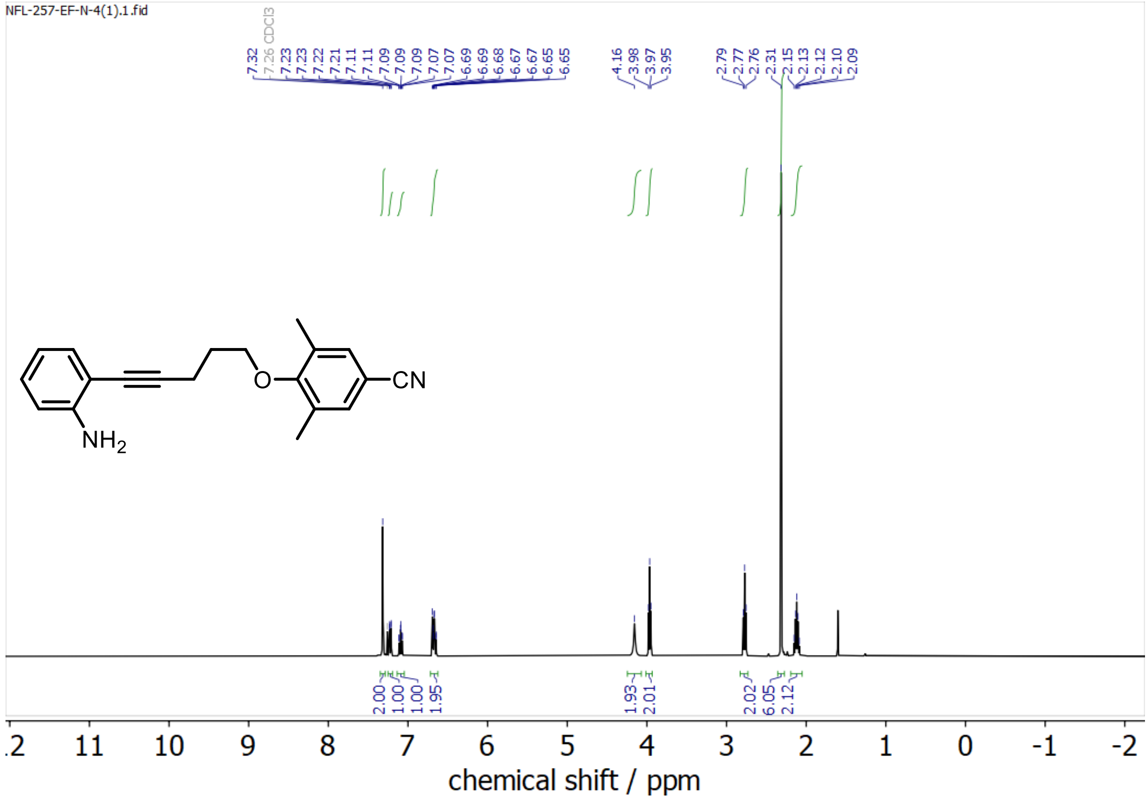


Figure S90: ^{1}H NMR spectrum of **S3**.

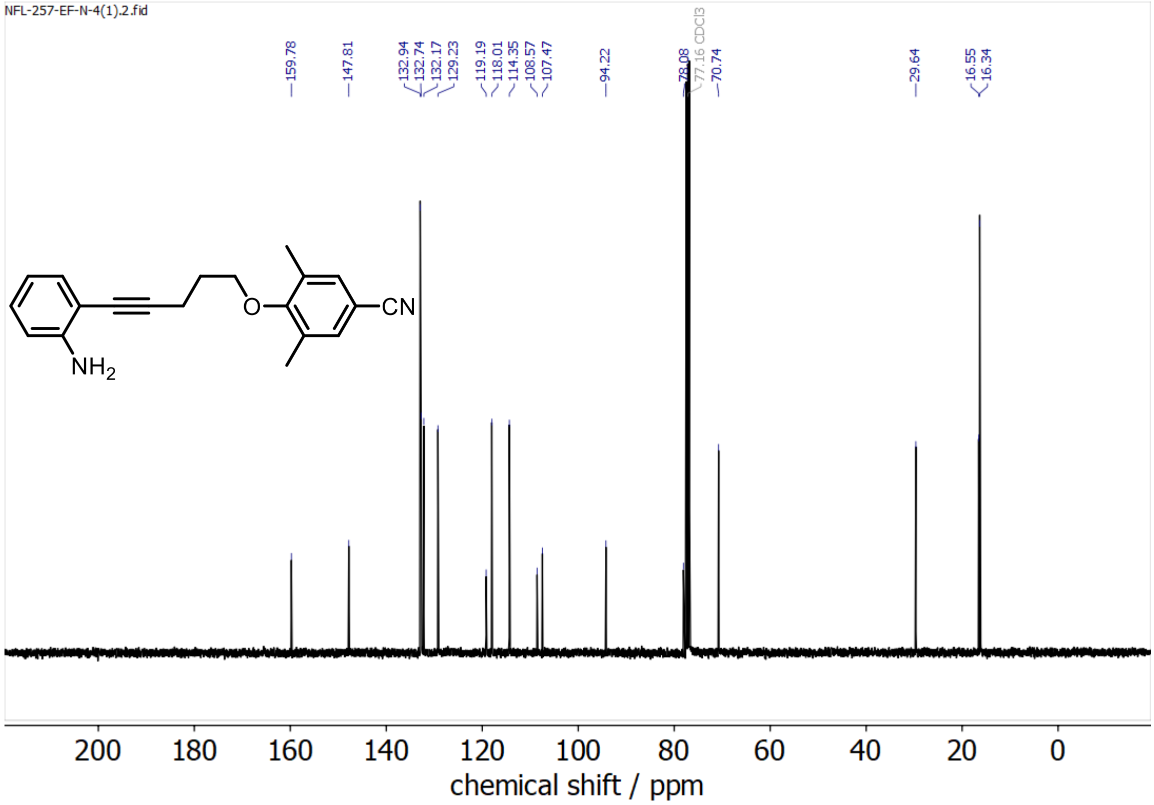


Figure S91: ^{13}C NMR spectrum of **S3**.

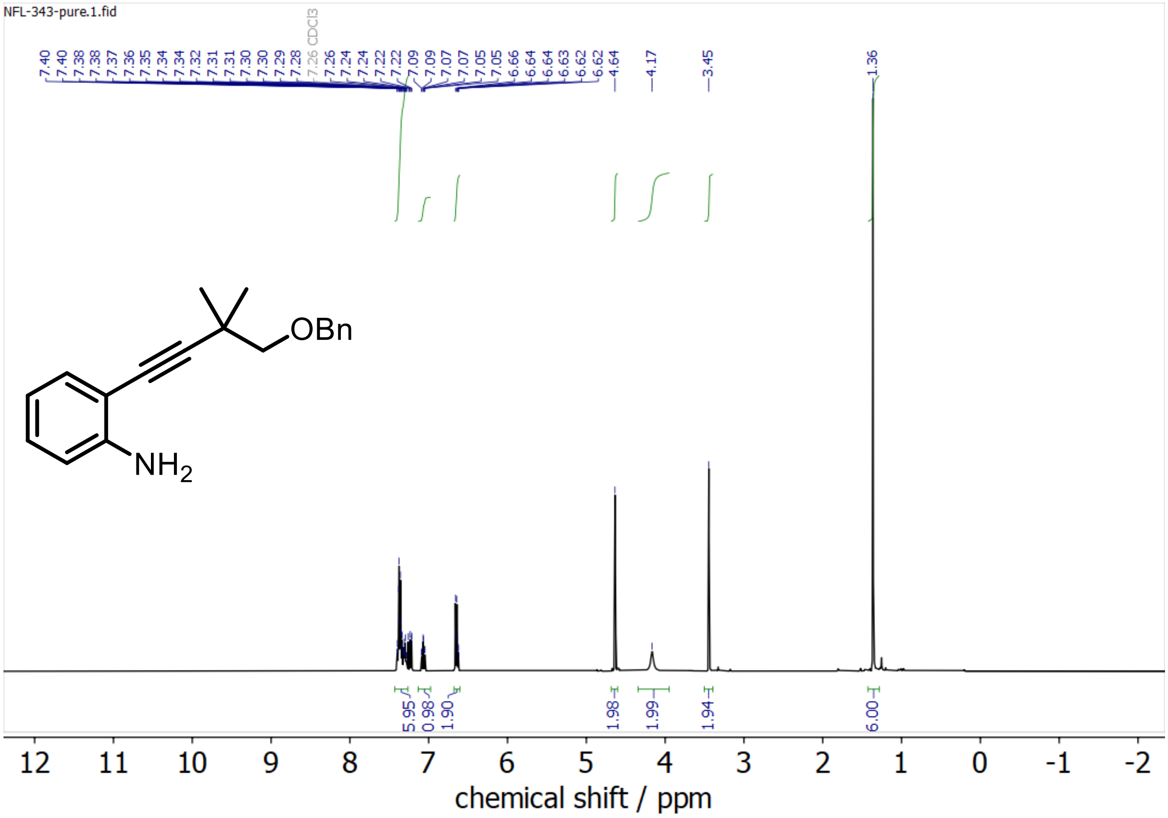


Figure S92: ^{1}H NMR spectrum of **S4**.

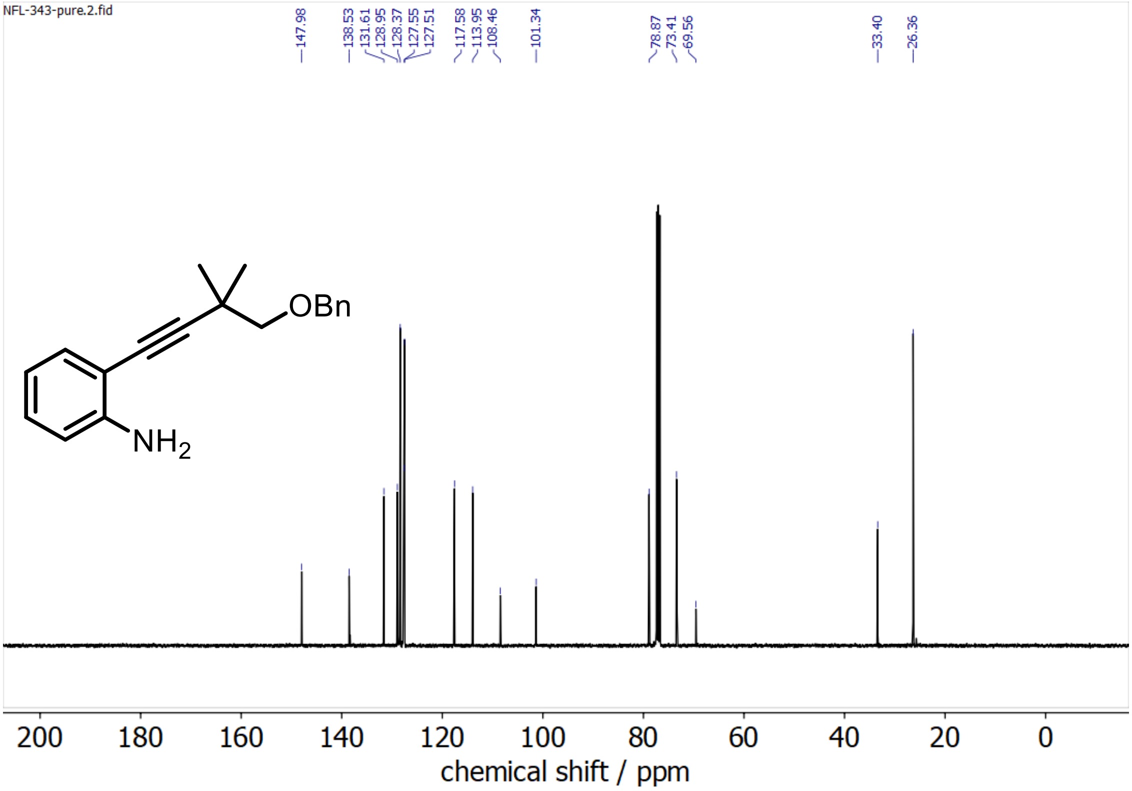


Figure S93: ^{13}C NMR spectrum of **S4**.

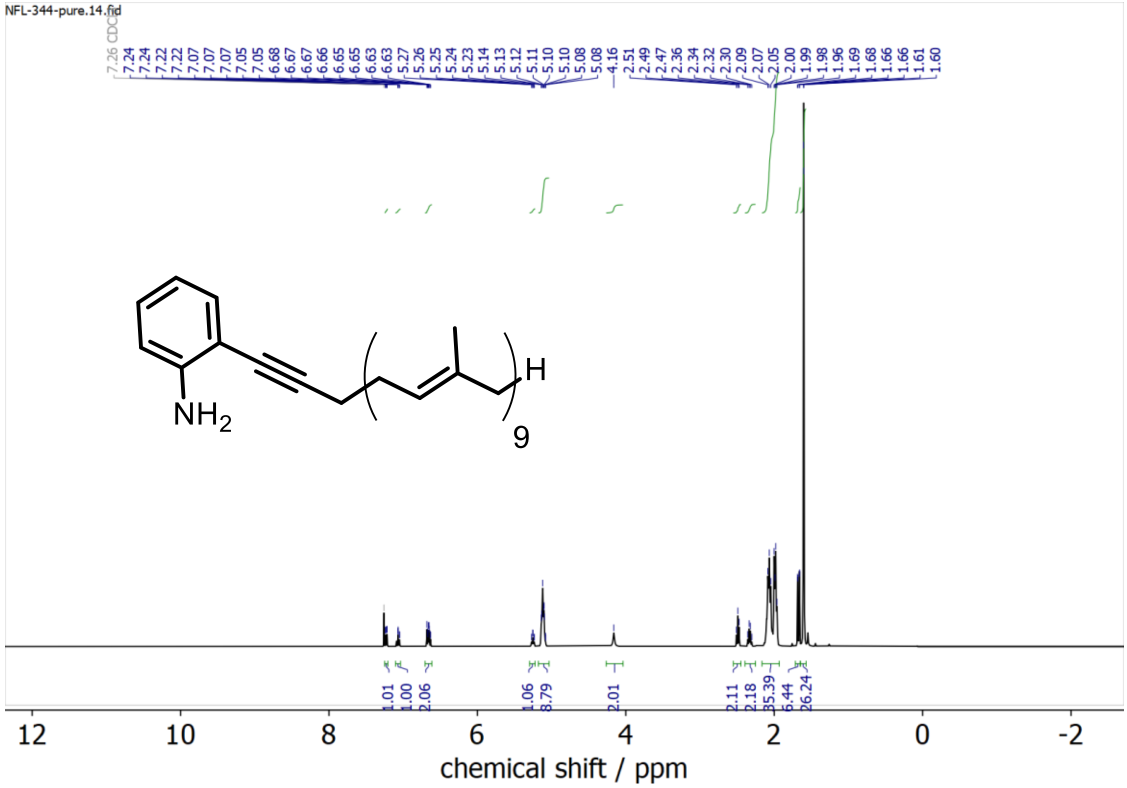


Figure S94: ^{1}H NMR spectrum of **S5**.

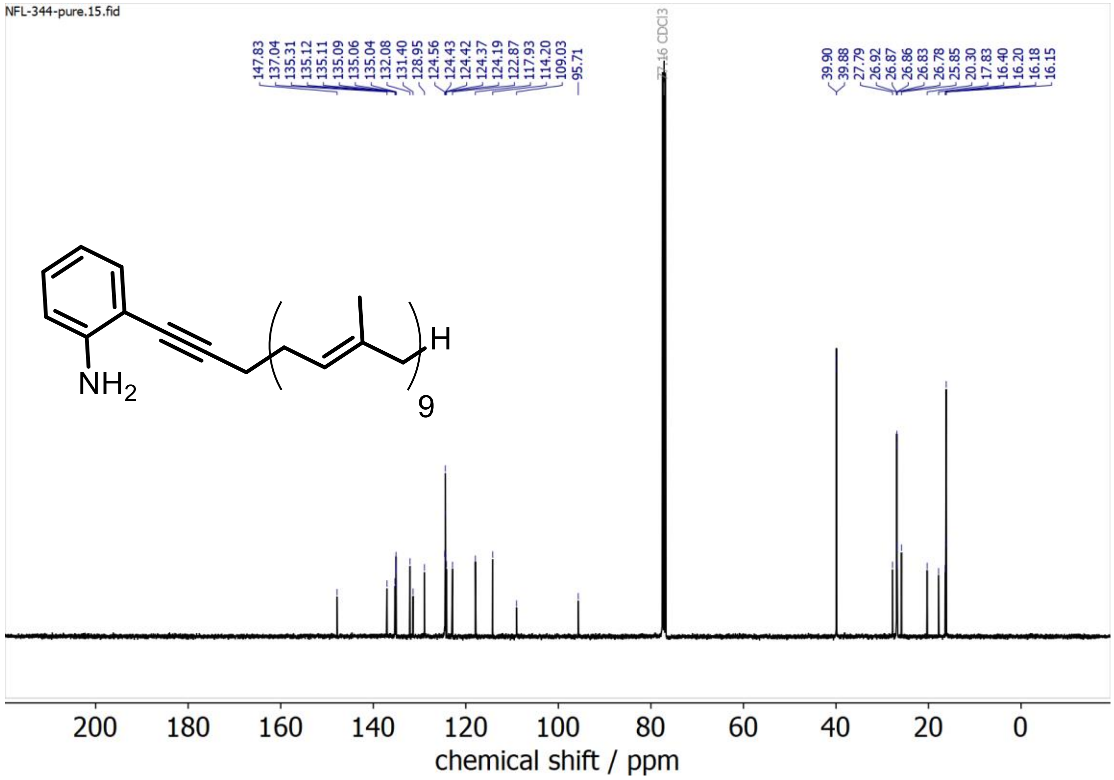


Figure S95: ^{13}C NMR spectrum of **S5**.

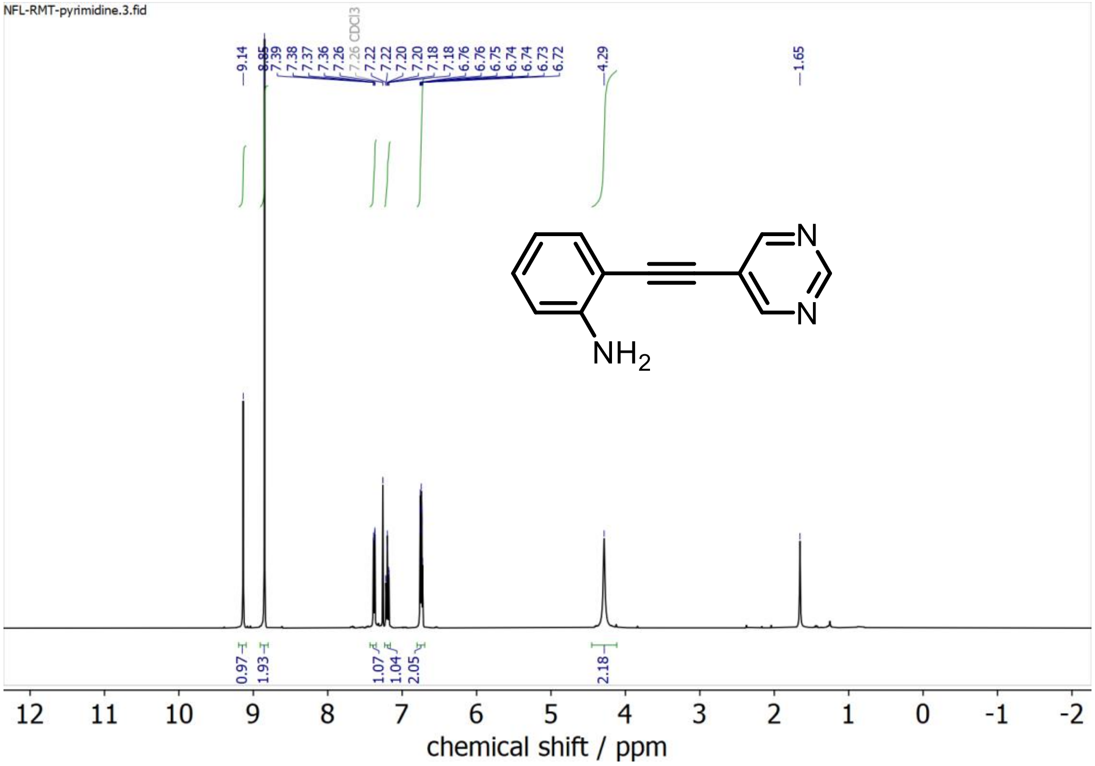


Figure S96: ^{1}H NMR spectrum of **S6**.

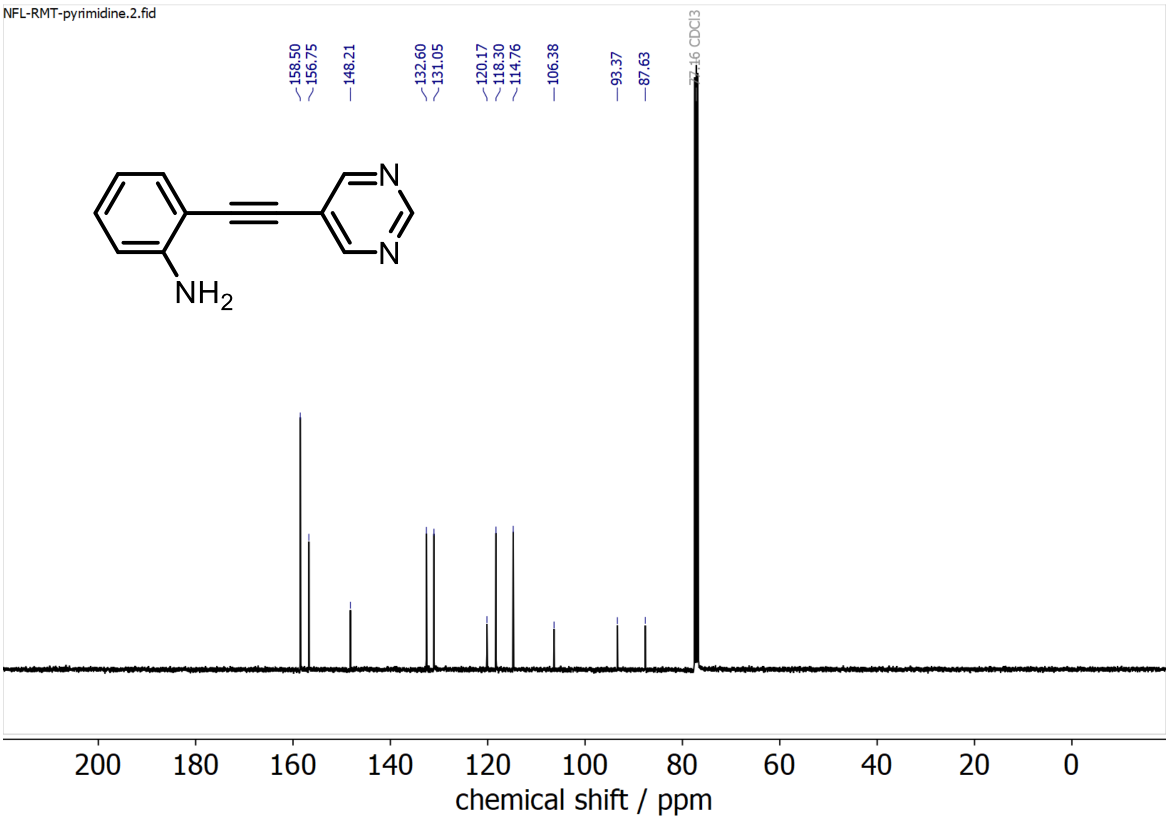


Figure S97: ^{13}C NMR spectrum of **S6**.

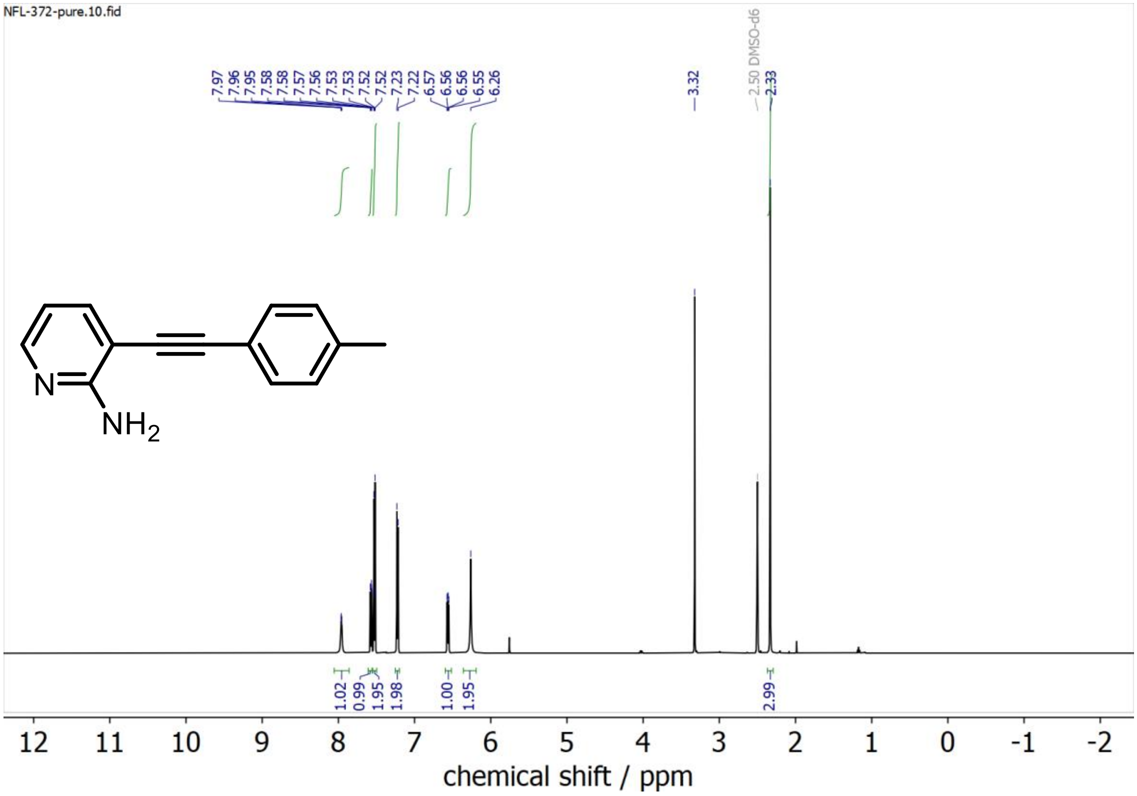


Figure S98: ^{1}H NMR spectrum of **S7**

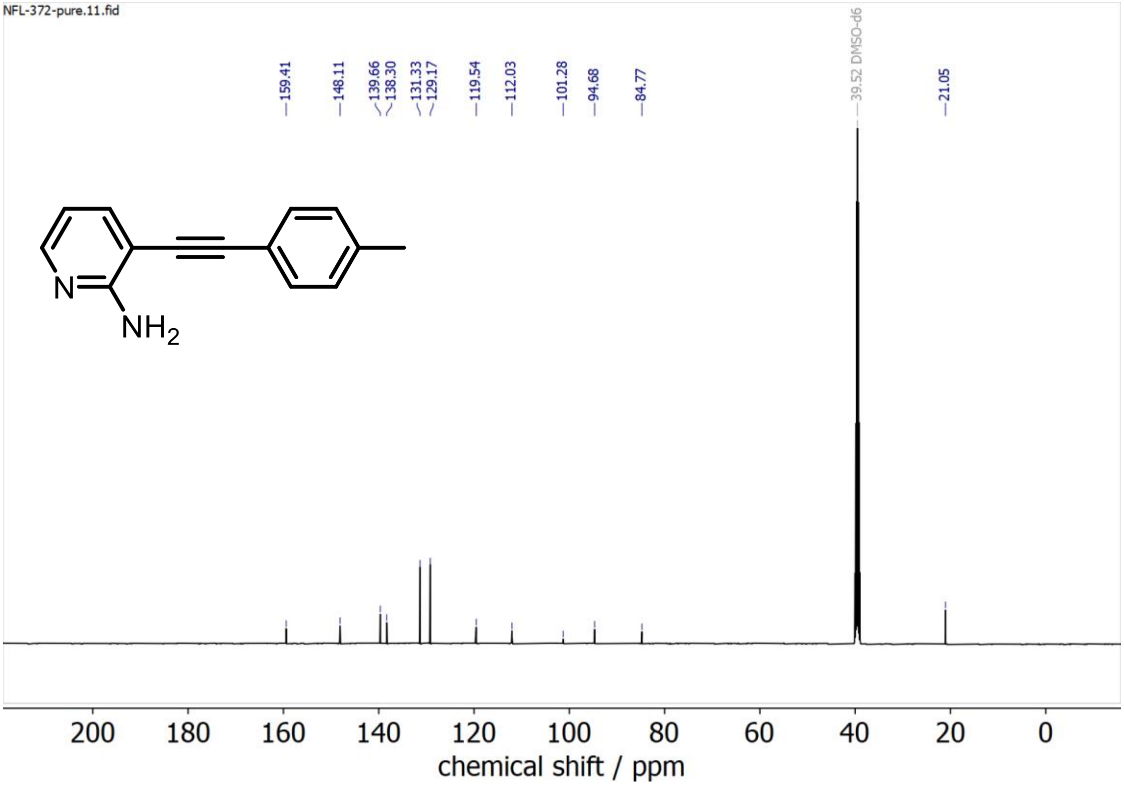


Figure S99: ^{13}C NMR spectrum of **S7**.

HRMS data

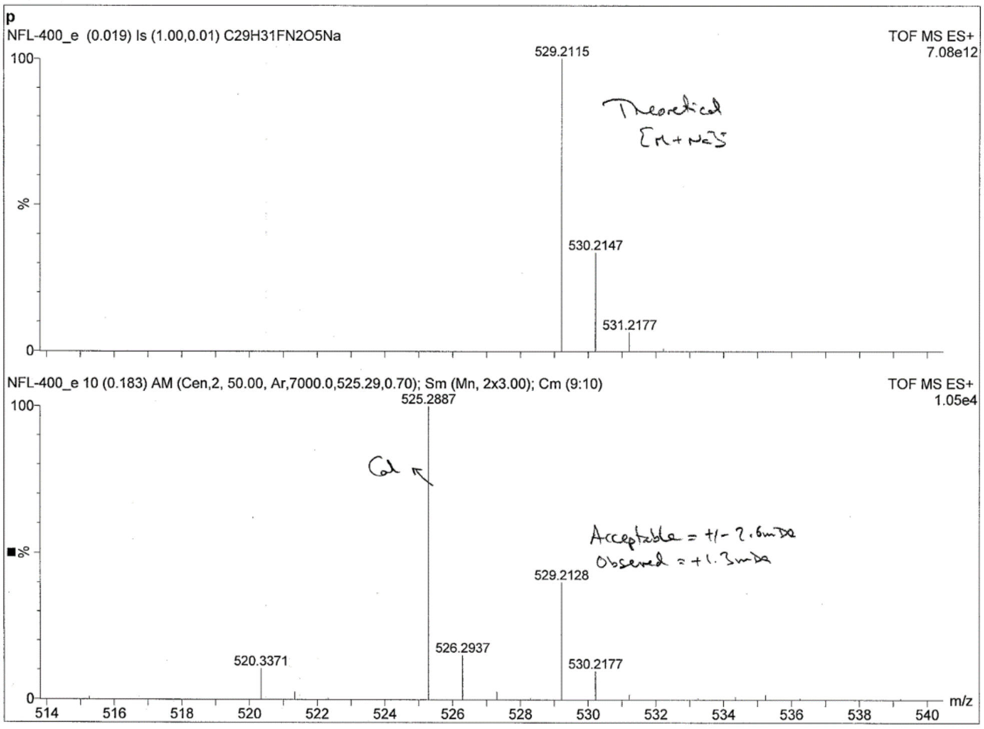


Figure S100: ESI(+)-HRMS spectrum of **S1** (bottom) together with the calculated pattern (top).

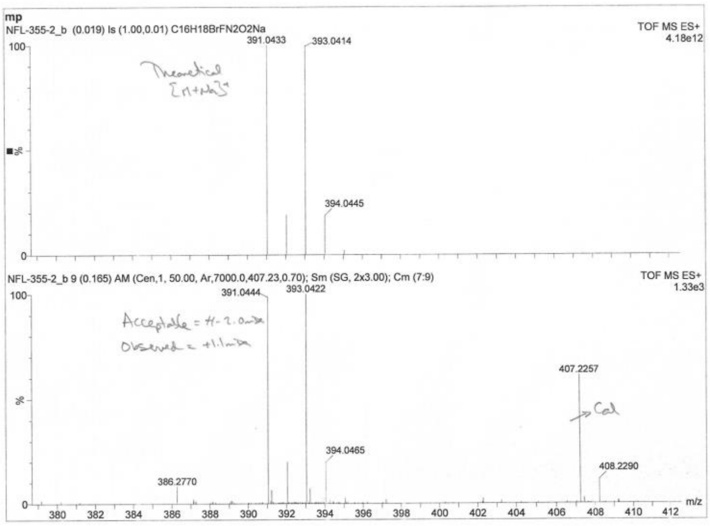
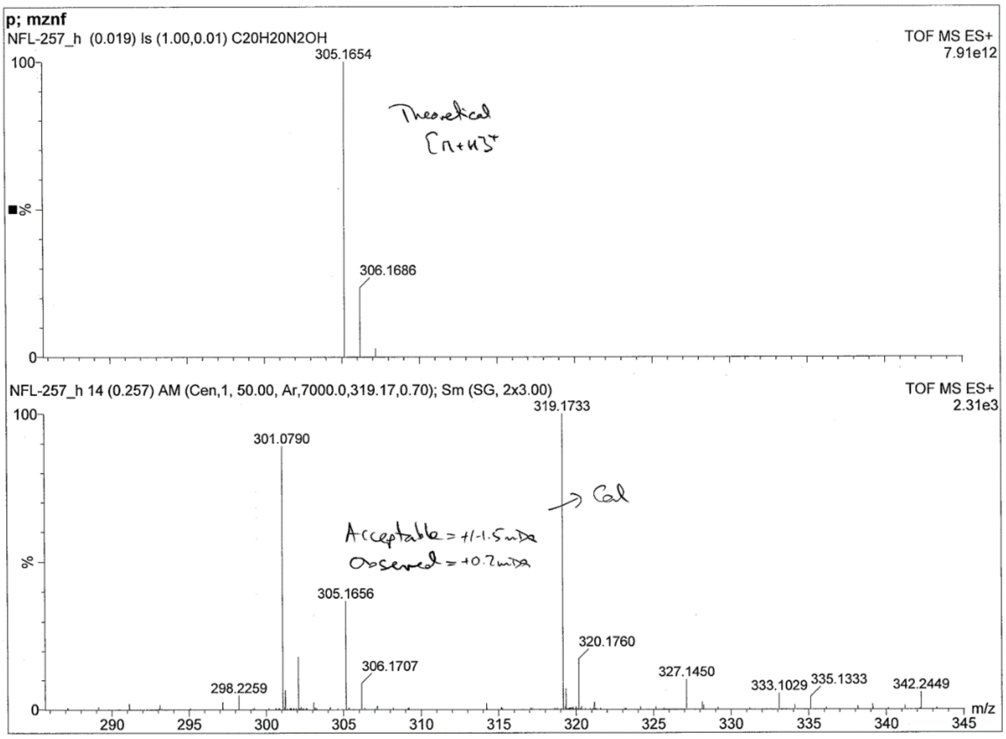


Figure S101: ESI(+)-HRMS spectrum of **S2** (bottom) together with the calculated pattern (top).

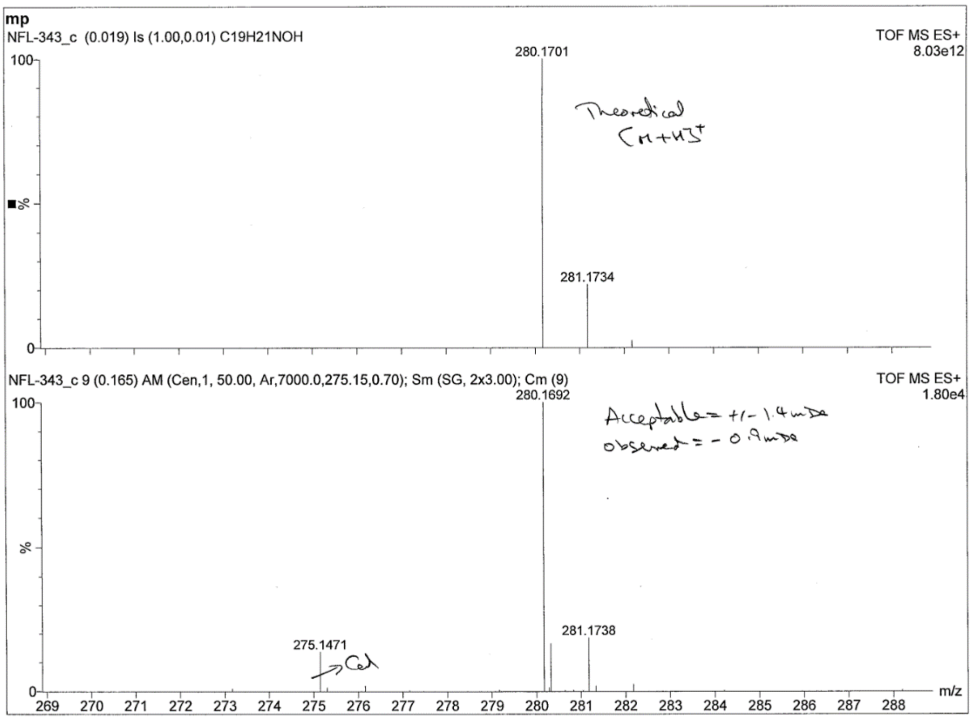


Theoretical [M+H]+

→ Cal

Acceptable = +/-1.5mDa
Observed = +0.7mDa

Figure S102: ESI(+)-HRMS spectrum of **S3** (bottom) together with the calculated pattern (top).



Theoretical [M+H]+

Acceptable = +/- 1.4mDa
observed = - 0.9mDa

→ Cal

Figure S103: ESI(+)-HRMS spectrum of **S4** (bottom) together with the calculated pattern (top).

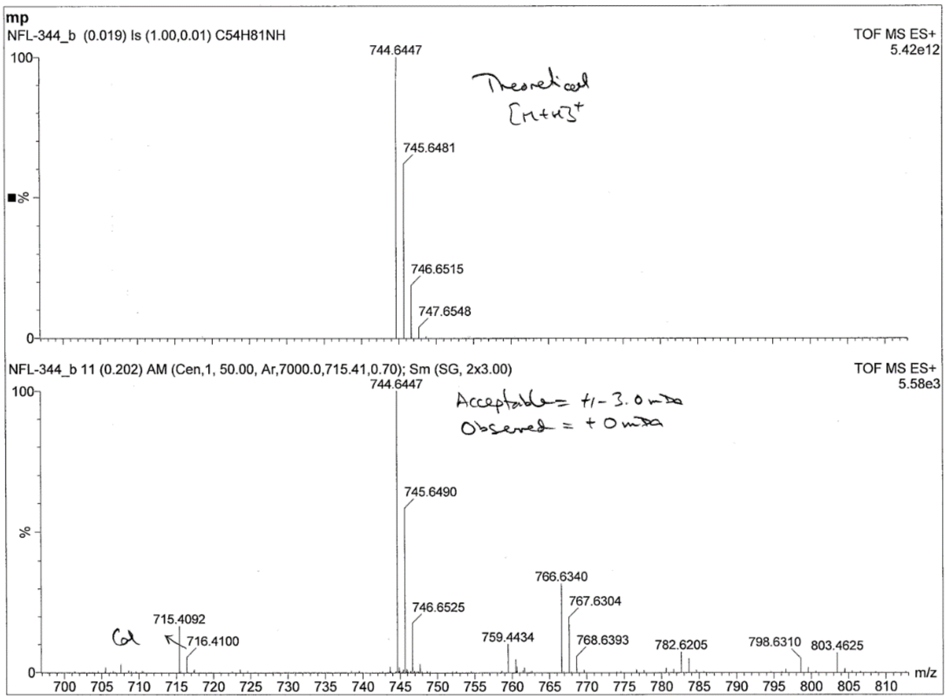


Figure S104: ESI(+)-HRMS spectrum of **S5** (bottom) together with the calculated pattern (top).

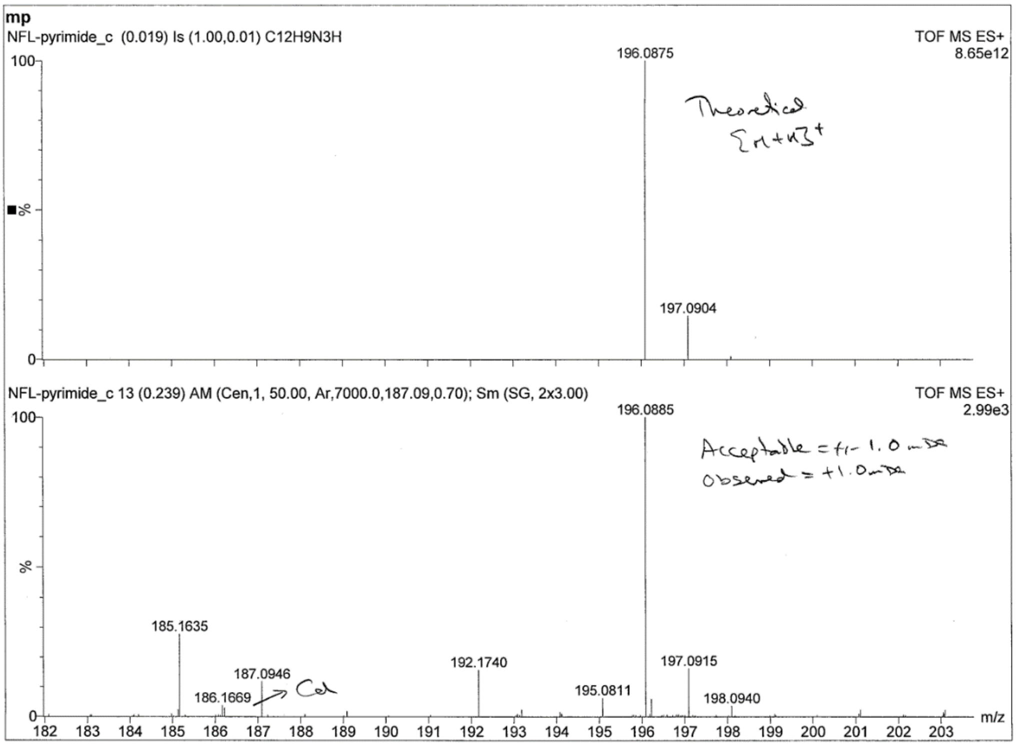


Figure S105: ESI(+)-HRMS spectrum of **S6** together with the calculated pattern (top).

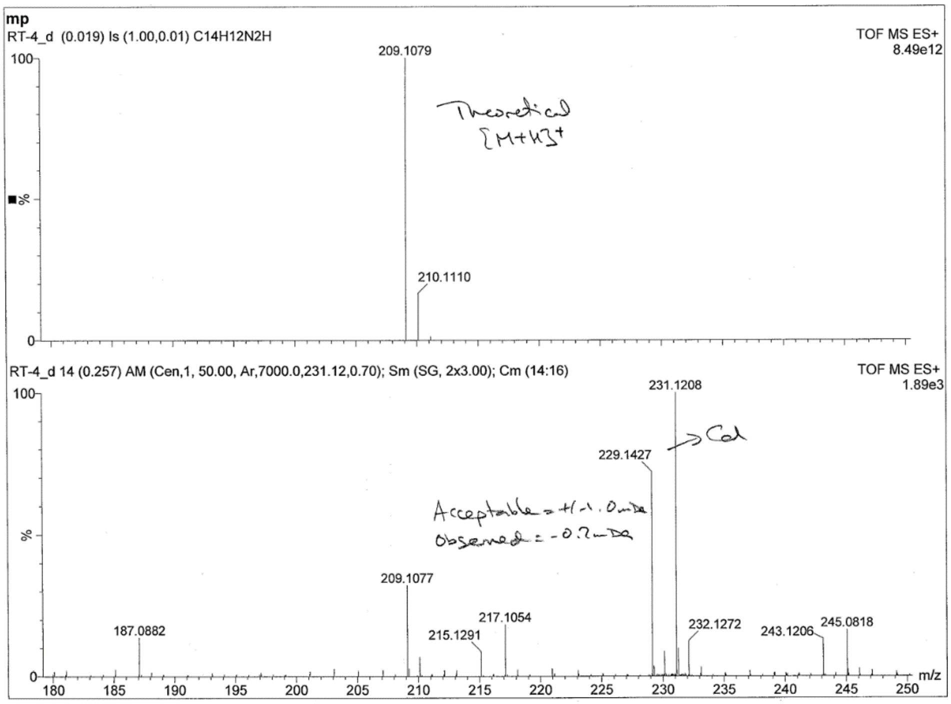


Figure S106: ESI(+)-HRMS spectrum of **S7** (bottom) together with the calculated pattern (top).

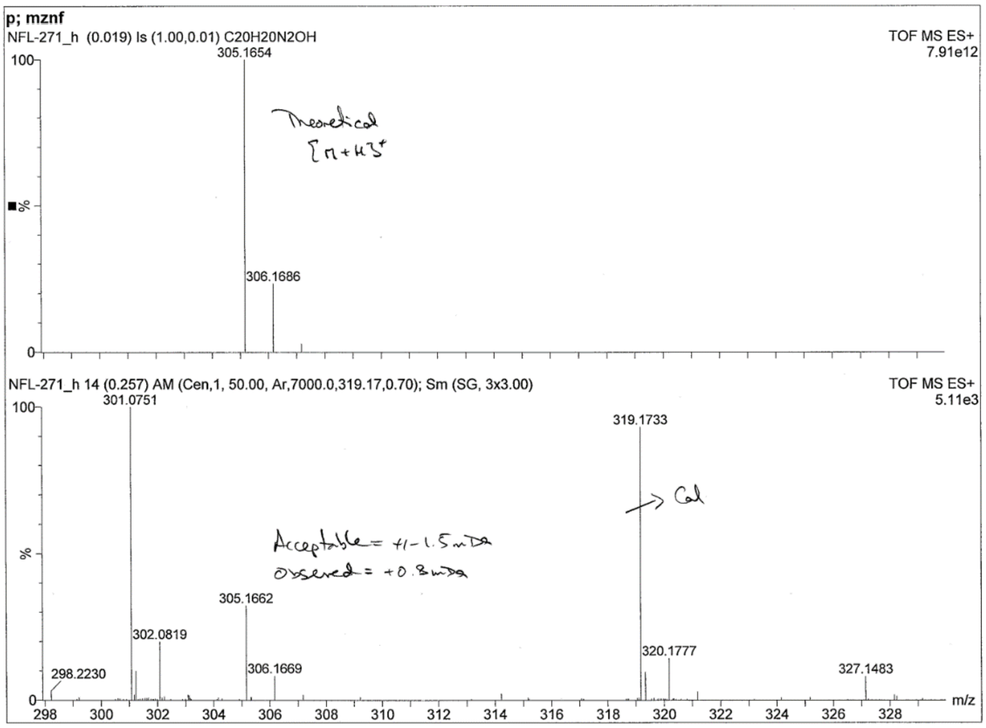


Figure S107: ESI(+)-HRMS spectrum of **18** (bottom) together with the calculated pattern (top).

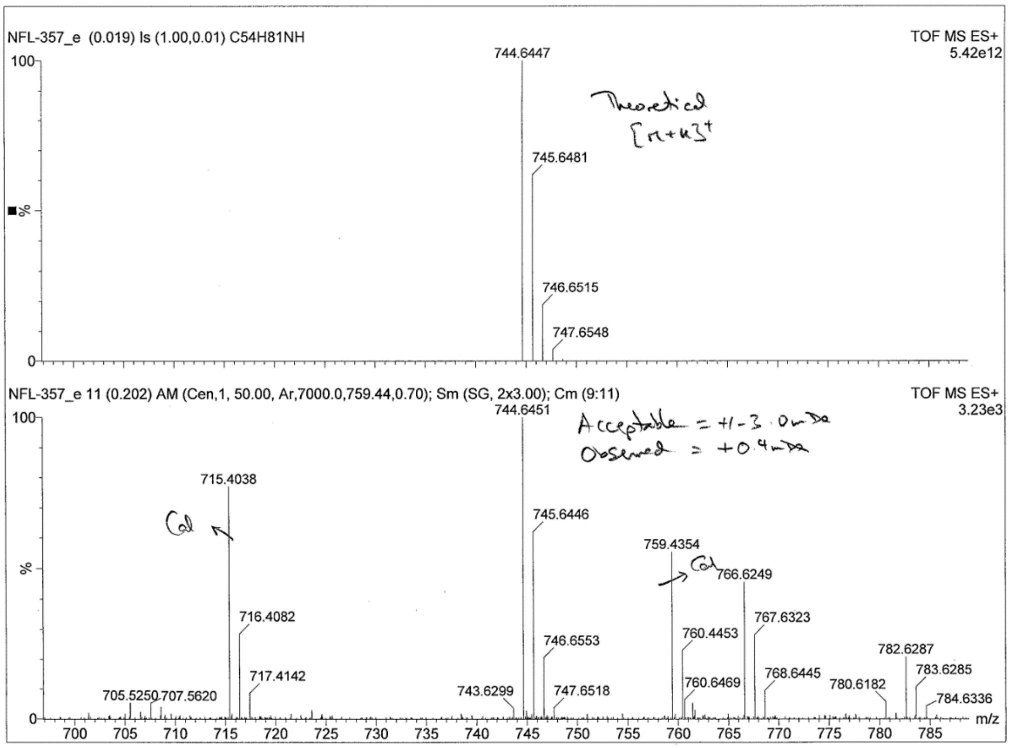


Figure S108: ESI(+)-HRMS spectrum of **21** (bottom) together with the calculated pattern (top).

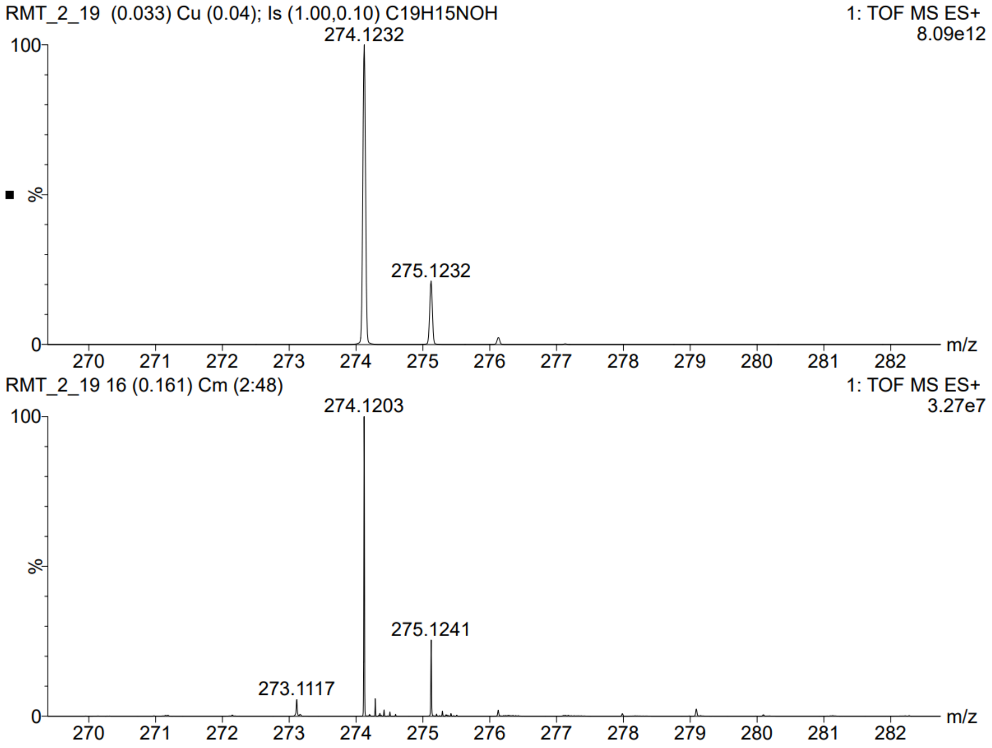


Figure S109: ESI(+)-HRMS spectrum of **22** (bottom) together with the calculated pattern (top).

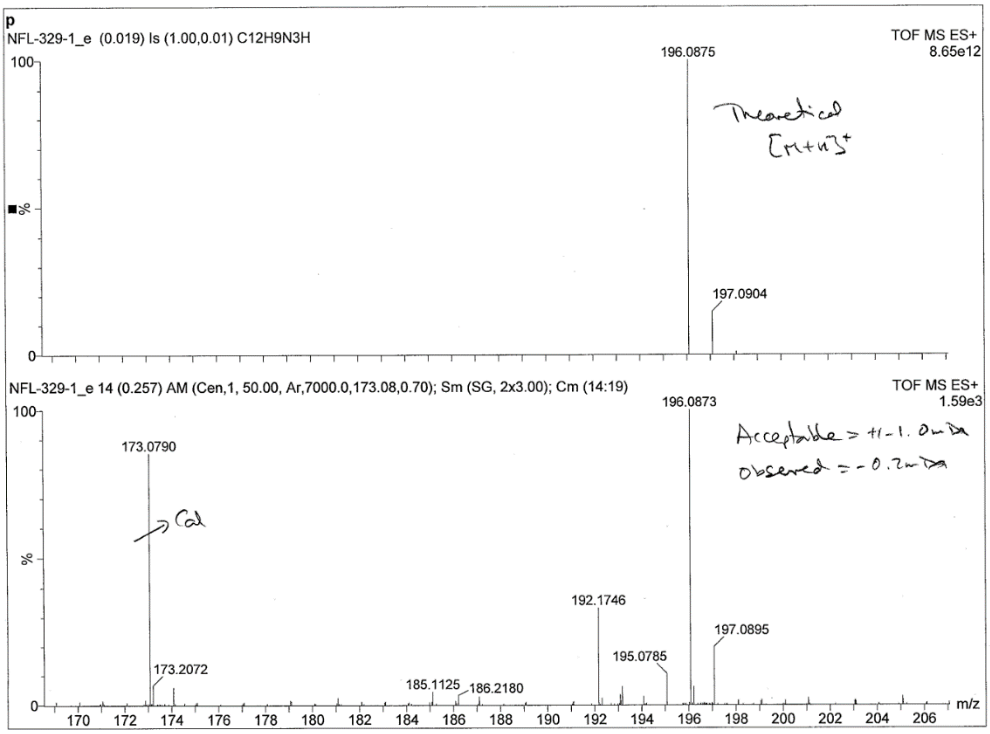


Figure S110: ESI(+)-HRMS spectrum of **26** (bottom) together with the calculated pattern (top).

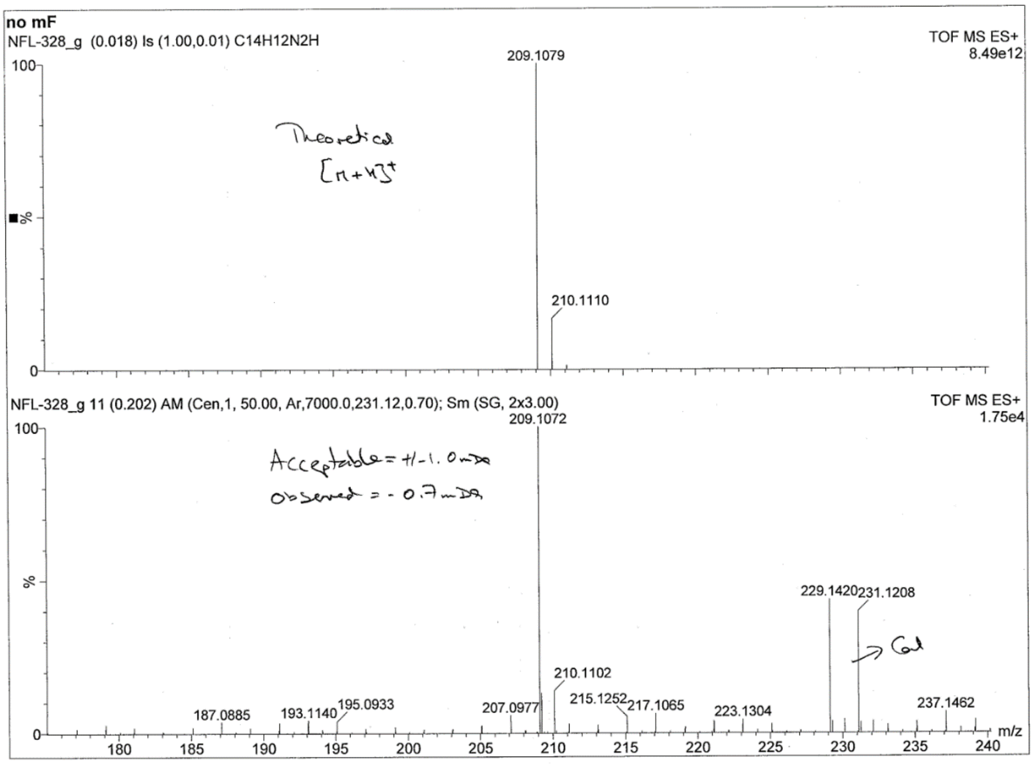


Figure S111: ESI(+)-HRMS spectrum of **27** (bottom) together with the calculated pattern (top).

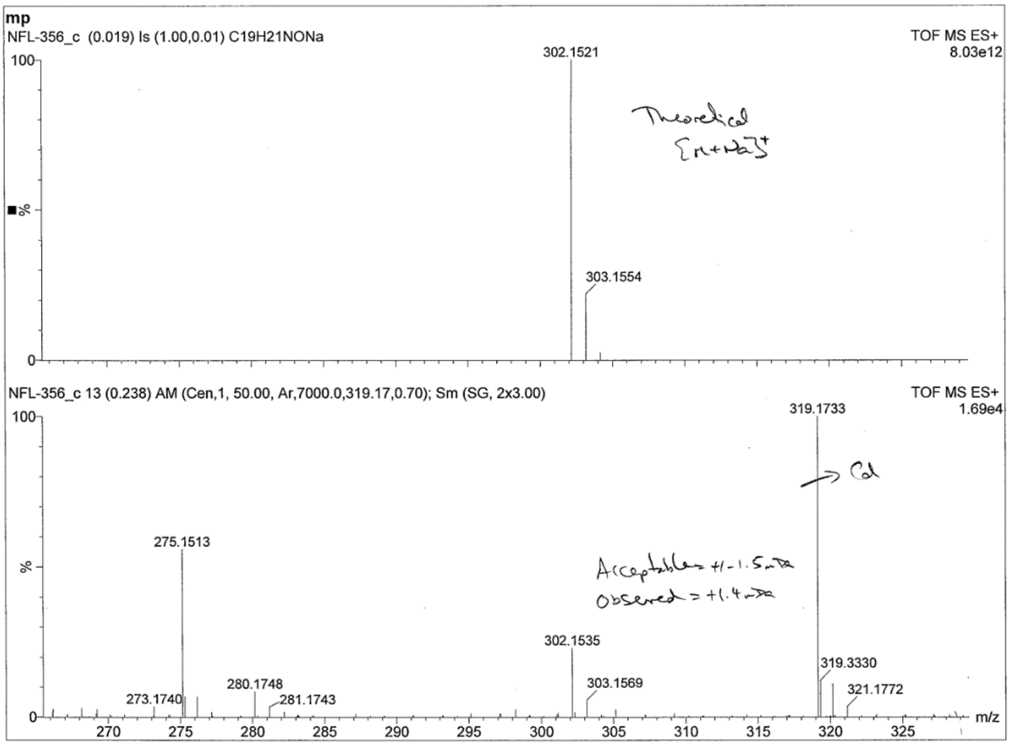


Figure S112: ESI(+)-HRMS spectrum of **28** (bottom) together with the calculated pattern (top).

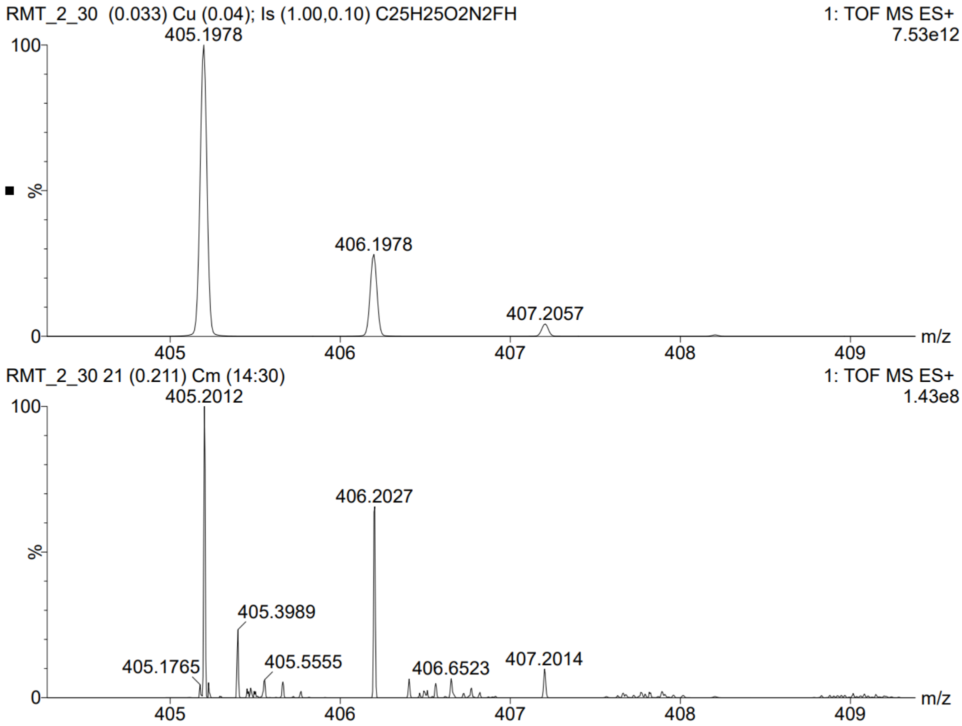


Figure S113: ESI(+)-HRMS spectrum of **29** (bottom) together with the calculated pattern (top).

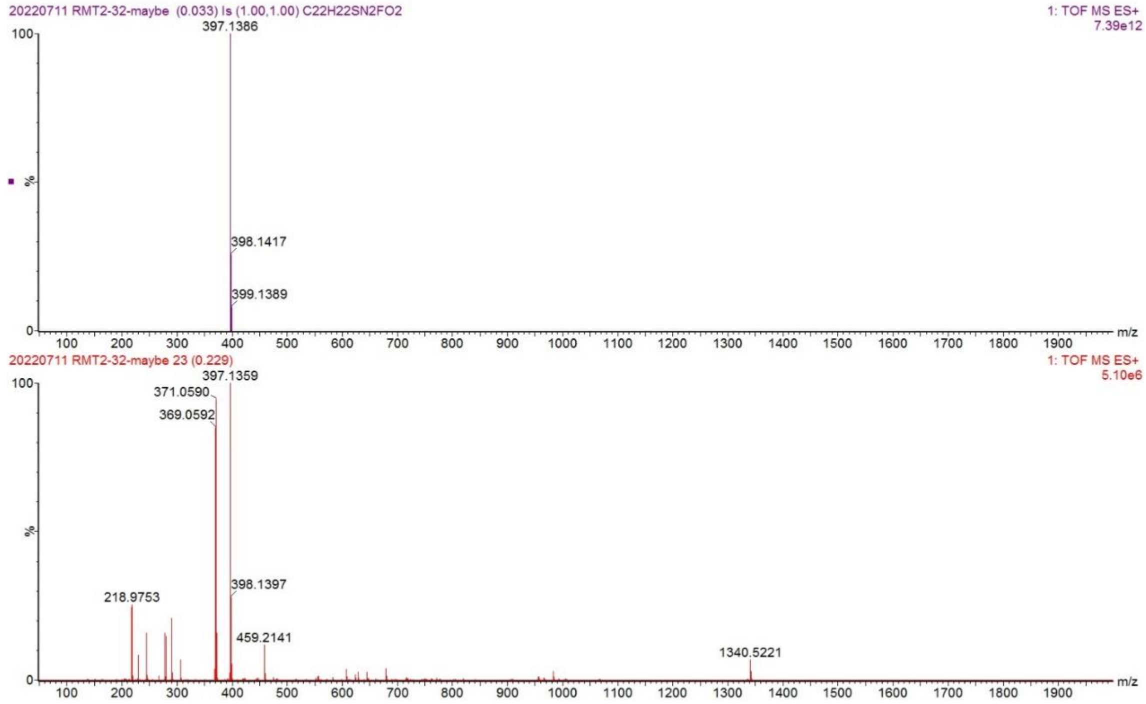


Figure S114: ESI(+)-HRMS spectrum of **30** (bottom) together with the calculated pattern (top).

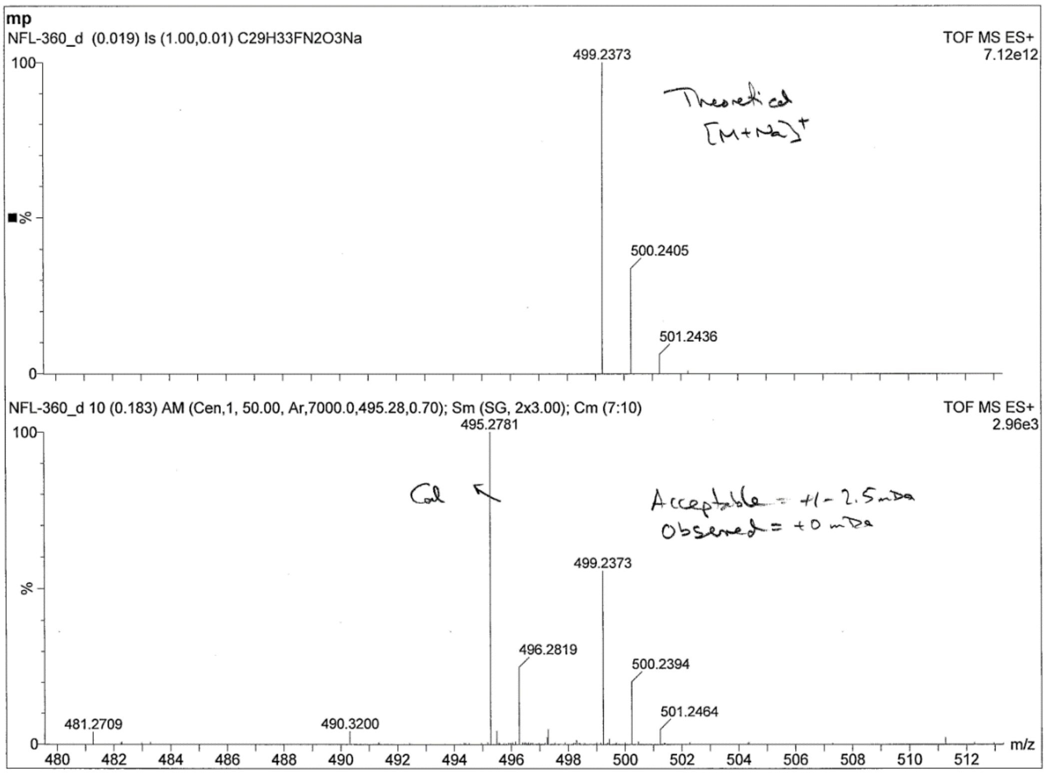


Figure S115: ESI(+)-HRMS spectrum of **35** (bottom) together with the calculated pattern (top).

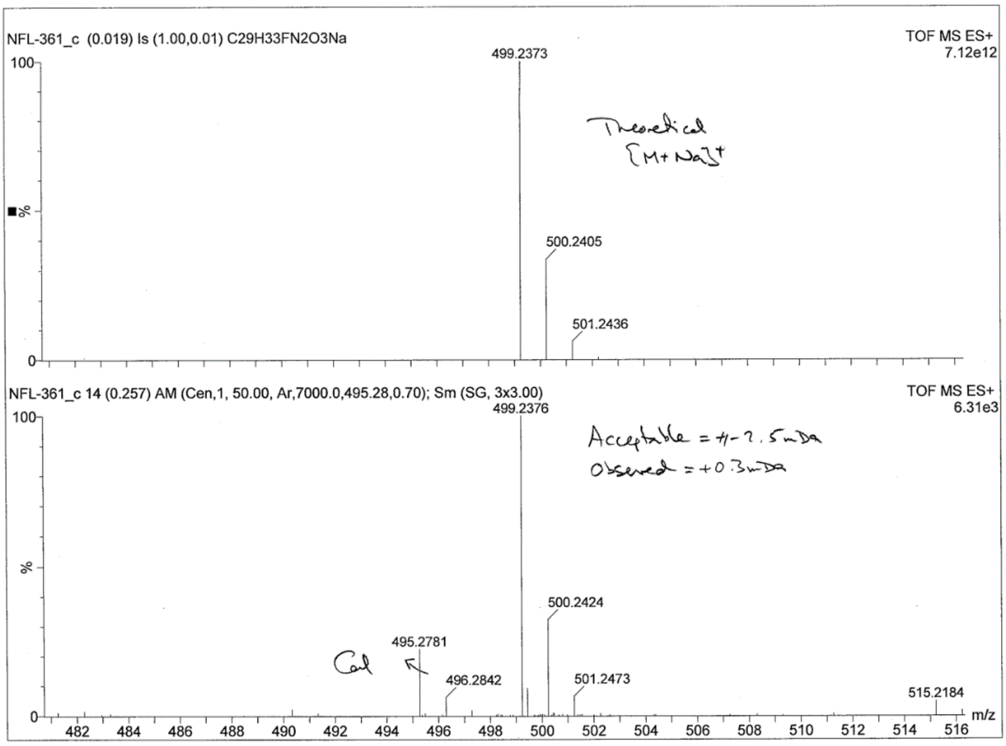


Figure S116: ESI(+)-HRMS spectrum of **36** (bottom) together with the calculated pattern (top).

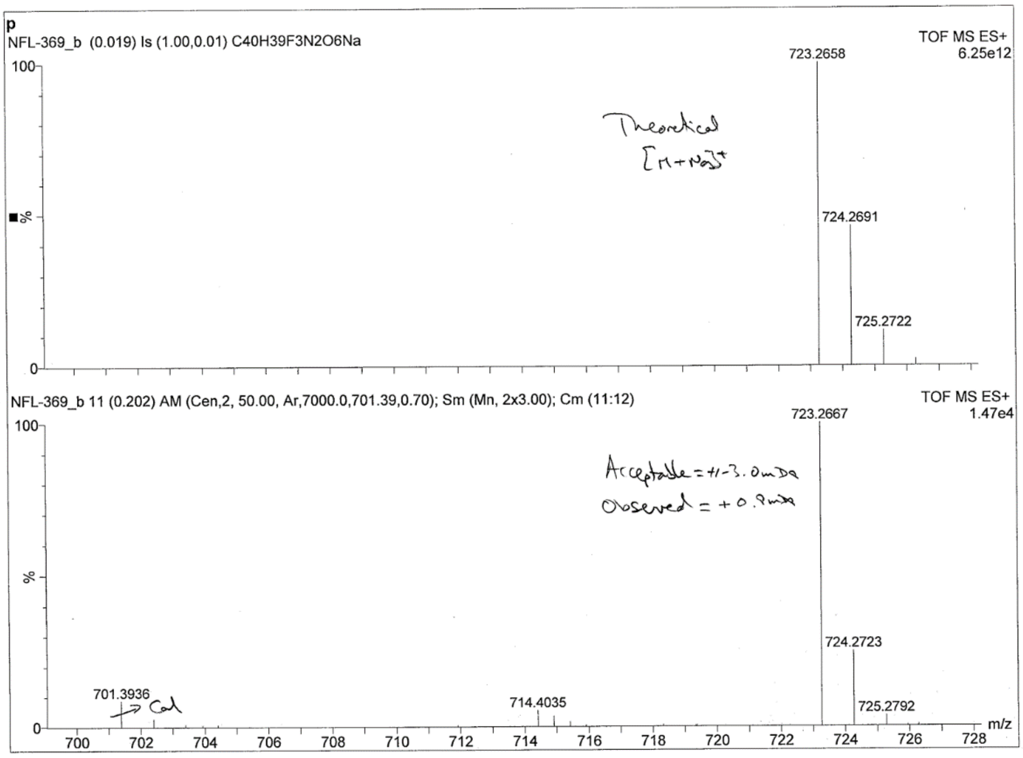


Figure S117: ESI(+)-HRMS spectrum of **38** (bottom) together with the calculated pattern (top).

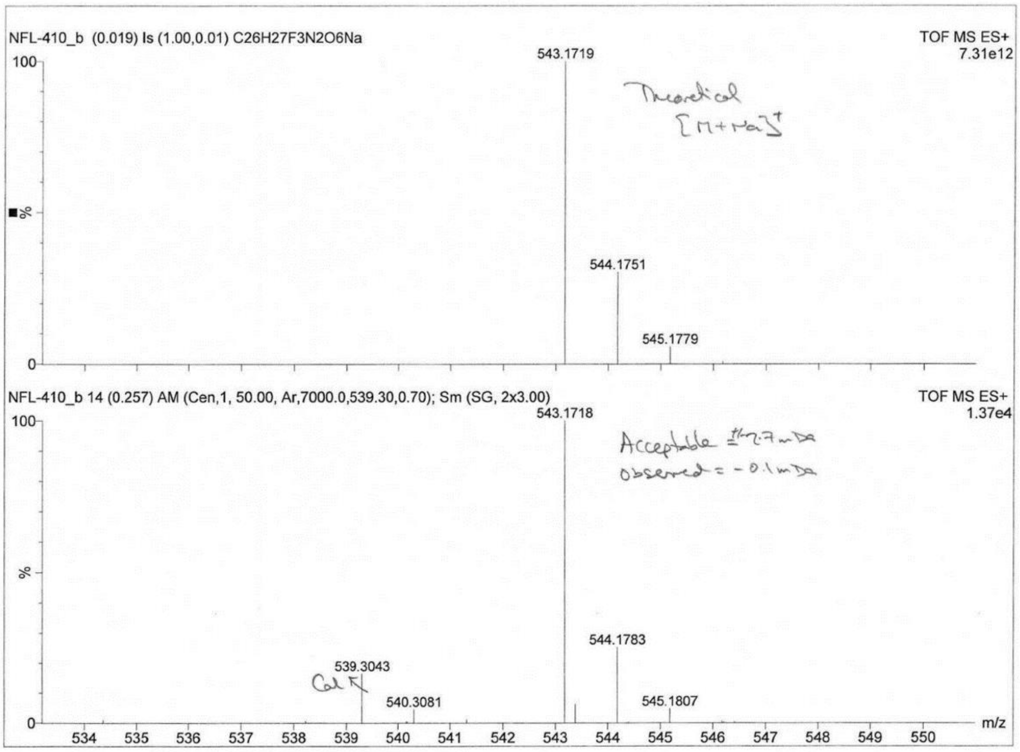


Figure S118: ESI(+)-HRMS spectrum of tezacaftor **1** (bottom) together with the calculated pattern (top).