Sustainable *ppm* Level Palladium-Catalyzed Aminations in Nanoreactors Under Mild, Aqueous Conditions

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Electronic Supplementary Information

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1. General Experimental Details

All manipulations were carried out under air unless otherwise noted. Diethyl ether, THF, ethyl acetate, methylene chloride, and hexanes were purchased from Fisher Scientific. THF and toluene were taken from Innovative Technologies Solvent Purification System (SPS) and used immediately. NaO-*t*-Bu, KO-*t*-Bu, 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD), and Proton Sponge were purchased from Sigma-Aldrich. $K_3PO_4 \bullet H_2O$, KOAc, Cs_2CO_3, and K_2CO_3 were purchased from Acros and used without any further purification. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from CombiBlocks. All liquid amines were purified by distillation. Ligated palladium complexes were either purchased from Strem Chemicals, Sigma-Aldrich or gifted by Johnson Matthey. [*t*-BuXPhos(Pd-π-cinnamyl)]OTf and [*t*-BuXPhos(Pd-π-crotyl)]OTf were synthesized according to the published procedure.[1] The scintillation reaction vials were purchased from VWR international. Pure NMR solvents were purchased from Cambridge Isotopes Laboratories. Dioxane was purchased from Sigma-Aldrich and used as such without further purification. The C-N cross coupling reactions were performed in 4 or 8 mL scintillation vials capped with rubber septum under argon atmosphere. TPGS-750-M was gifted by PHT International, Inc. (also commercially available from Sigma-Aldrich with catalog number 733857). Degassed HPLC grade water was used to prepare the aqueous solution of TPGS-750-M, which was stored under Ar.

Thin layer chromatography (TLC) was done using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was done in either glass columns or the automated Biotage system using Silica Gel 60 (EMD, 40-63 μm). ^{1}H, ^{13}C, and ^{19}F NMR were recorded at 25 °C on a Varian Unity Inova 400 MHz, a Varian Unity Inova 500 MHz or on a Varian Unity Inova 600 MHz spectrometers in $CDCl_3$ or DMSO-d_6 with residual $CHCl_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm), or in $(CD_3)_2SO$ with residual $(CH_3)_2SO$ (^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm) as internal standards. Chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, sept = septet, m = multiplet), coupling constant (if applicable) and integration. Carbonyl iron powder (CIP) used for reductions was 99.9% purity, R10 grade, with average particle size of 2.5-3.5 μm. This material was stored in air with no special precautions. Ammonium chloride was Fisher brand, ACS grade. High-resolution mass analyses were obtained using a 5975C Mass Selective

Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column, a HP-5MS cross-linked 5% phenylmethylpolysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min.

2. Reaction Optimization

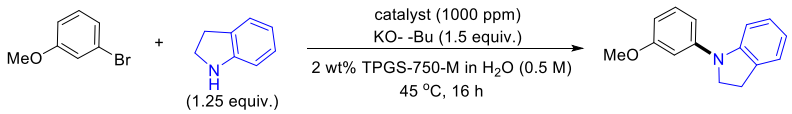
Preparation of a stock solution of pre-catalyst and reaction set-up:

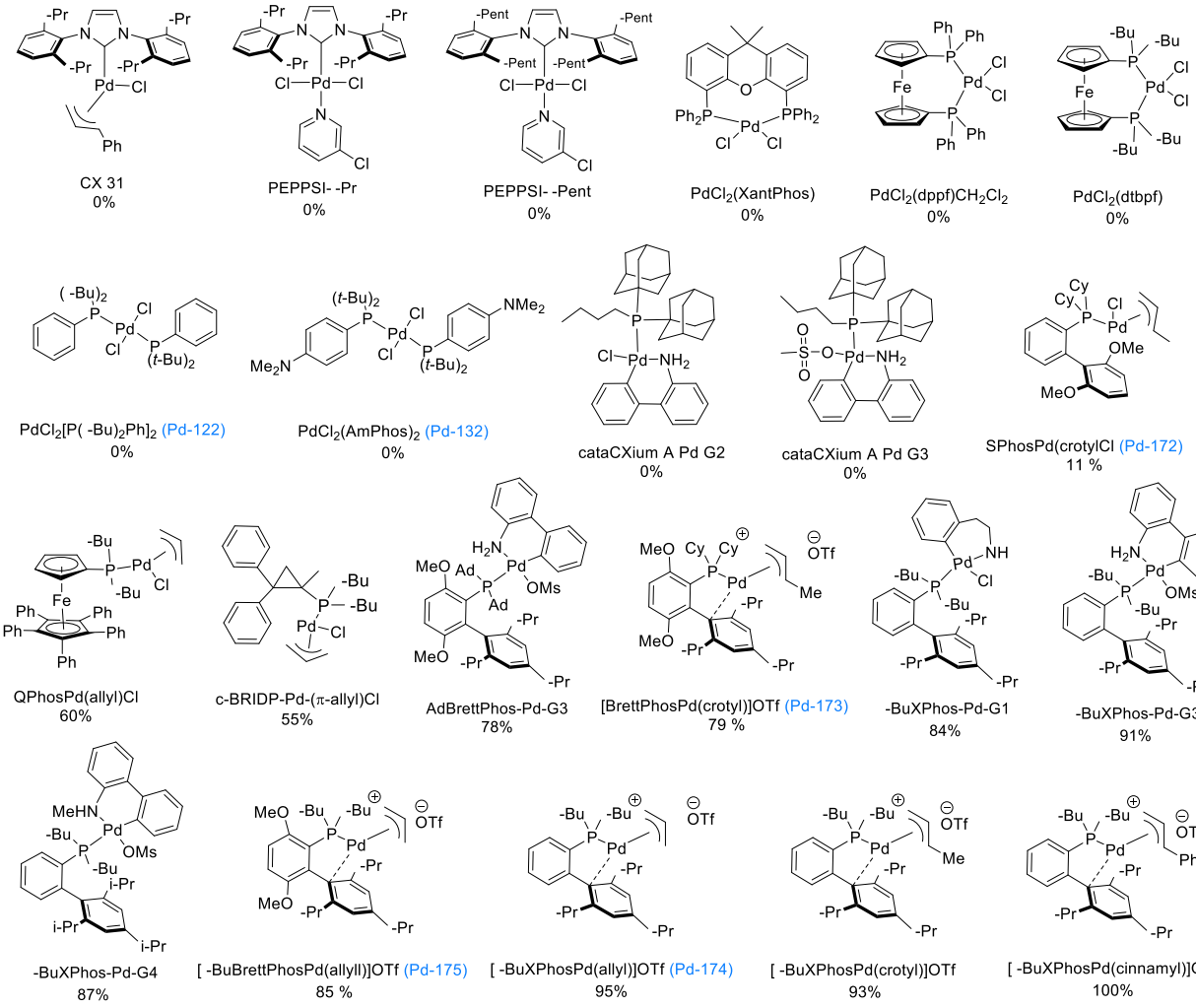
In a 4 mL reaction vial, about 5-10 mg of the defined LPd pre-catalysts (shown in Section **2a**) were accurately weighed on a balance. THF was added to make a stock solution at a concentration of 12.5 μmol/mL (i.e., 1.25 μmol /100 μL). A microliter syringe was then used to aliquot out the stock pre-catalyst solution into a 4 mL scintillation reaction vial. For a 0.25 mmol scale reaction, 20 μL of the aforementioned stock solution would contain 2.5 x 10^{-4} mmol (i.e., 0.25 μmol) catalyst, thus corresponding to 1000 ppm Pd level of the ligated Pd pre-catalyst. THF was then removed under reduced pressure and the atmosphere was replaced by argon using standard manifold techniques.

To the 4 mL reaction vial containing 1000 ppm pre-catalyst, a PTFE coated magnetic stir bar and *t*-BuOK (0.375 mmol, or alternative base as determined by base screening; *vide infra*) were added. A rubber septum was used to cap the reaction vial. The atmosphere of the reaction vial was switched to argon via standard manifold operation. A solution of 2 wt % TPGS-750-M (0.5 mL) was added to the reaction mixture, which was then briefly stirred for 1 min at 45 ºC. Then, 3-bromoanisole (32 μL, 0.25 mmol, 1.0 equiv) and indoline (35 μL, 0.312 mmol, 1.25 equiv) were added via syringe under Ar. The vial was closed and parafilm was used to seal the vial. The reaction mixture was then stirred vigorously (~600-800 rpm) at 45 ºC in an isotherm aluminum reaction block on an IKA plate for 16 h.

After 16 h, 1 mL EtOAc was added to the reaction mixture, which was then briefly stirred *gently* for 8 sec. The organic layer was pipetted out. A similar extraction procedure was repeated for two or three additional times. The combined extracts were dried over anhydrous sodium sulfate and the volatiles were evaporated under reduced pressure to obtain crude product. For yield determination, accurately weighed 2-bromomesitylene (ca. 5~10 mg) was added to the crude product as integration standard for crude ^{1}H NMR analysis. The yield values in Section **2a** of this S.I. were the average value from two experiments.

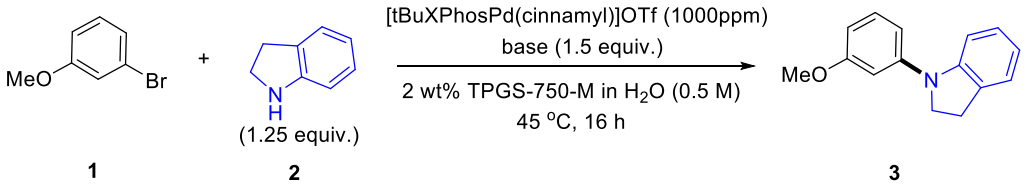
2a. Catalyst Screening





Conditions: 0.25 mmol 3-bromoanisole, 0.312 mmol indoline, 1000 ppm Pd complex, 0.375 mmol (1.5 equiv.) KO-*t*-Bu, 0.5 mL 2 wt % TPGS-750-M (0.5 M), 45 ºC, 16 h. *Yields based on NMR with 2-bromomesitylene used as internal standard. The "Pd - #" designation in parenthesis (shown in blue) were the Johnson Matthey catalog numbers for the catalysts.

2b. Base Screening

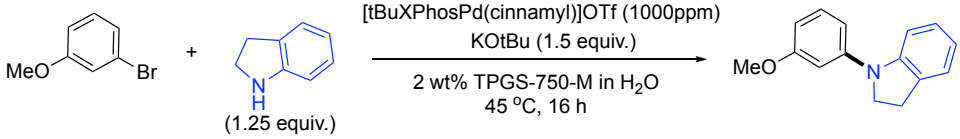


1 2 3

Base	Yiled (NMR)
KOtBu	100
NaOtBu	95
KOH	70
KOTMS	89
KOAc	11
K_3PO_4-H_2O	46
K_2CO_3	13
$CsCO_3$	38
NEt_3	34
DBU	41
TBD	60
H-Sponge	14

Conditions: 0.25 mmol 3-bromoanisole, 0.312 mmol indoline, 1,000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf, 0.375 mmol (1.5 equiv) base, 0.5 mL 2 wt % TPGS-750-M (0.5 M), 45 ºC, 16 h. *Yields based on NMR with 2-bromomesitylene used as internal standard.

2c. Global concentration of TPGS-750-M screening

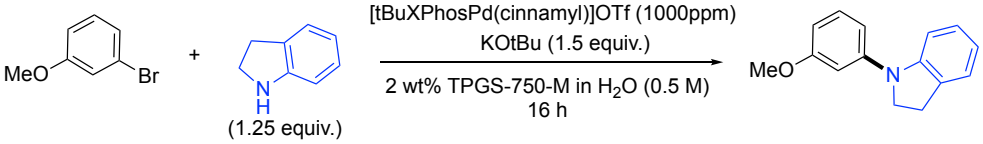


1 **2** **3**

entry	conc.	**3** (%)*
1	0.2	87
2	0.5	100
3	0.7	96
4	1.0	95

Conditions: 0.25 mmol 3-bromoanisole, 0.312 mmol indoline, 1,000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf, 0.375 mmol (1.5 equiv) KO-*t*-Bu, 2 wt % TPGS-750-M, 45 ºC, 16 h. *Yields based on NMR with 2-bromomesitylene used as internal standard

2d. Reaction temperature screening

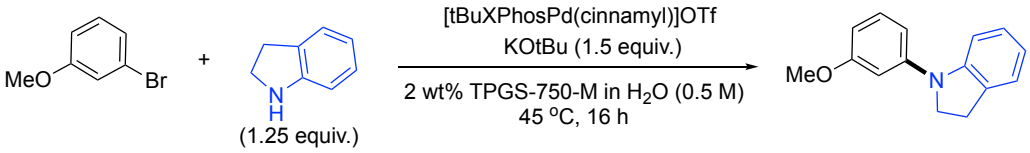


1 **2** **3**

entry	Temperature / ºC	**3** (%)*
1	25	70
2	35	72
3	45	100
4	55	88

Conditions: 0.25 mmol 3-bromoanisole, 0.312 mmol indoline, 1,000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf, 0.375 mmol (1.5 equiv.) KO-*t*-Bu, 0.5 mL 2 wt % TPGS-750-M, 16 h. *Yields based on NMR with 2-bromomesitylene used as internal standard.

2e. Catalyst loading screening



1 **2** **3**

entry	[tBuXPhosPd(cinnamyl)]OTf (ppm)	**3** (%)*
1	2000	99
2	1000	100
3	800	92
4	600	88
5	400	85

Conditions: 0.25 mmol 3-bromoanisole, 0.312 mmol indoline, 400–2000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf, 0.375 mmol (1.5 equiv) KO-*t*-Bu, 0.5 mL 2 wt % TPGS-750-M, 45 ºC, 16 h. *Yields based on NMR with 2-bromomesitylene used as internal standard.

3. Recommended General Procedure for ppm Pd-Catalyzed Aminations

Preparation of a stock solution of pre-catalyst.

In a 4 mL reaction vial, about 5-10 mg of [*t*-BuXPhos(Pd-π-cinnamyl)]OTf were accurately weighed on a balance. THF was added to make a stock at a concentration of 12.5 μmol/mL (i.e., 1.25 μmol /100 μL). A micro-syringe was then used to aliquot out the stock pre-catalyst solution into multiple 4 mL or 8 mL scintillation reaction vials. For a 0.25 mmol scale reaction, 20 μL of the aforementioned stock solution would contain 2.5 x 10^{-4} mmol catalyst, thus corresponding to 1000 ppm of the pre-catalyst. THF was then removed under reduced pressure and the atmosphere was switched to argon by standard manifold operation. Parafilm was used to seal the scintillation vials containing the solid pre-catalyst, and these vials were stored at 4 ºC in a fridge. No appreciable decrease of catalyst reactivity was observed within one month under such storage conditions.

Reaction set-up:

To the 4 mL reaction vial containing [*t*-BuXPhos(Pd-π-cinnamyl)]OTf (1000 ppm unless otherwise noted), a PTFE coated magnetic stir bar and *t*-BuOK (0.375 mmol) were added. Solid-state aryl halide (0.25 mmol) and/or amine (0.312 mmol) were then added into the vial. A rubber septum was used to cap the reaction vial. The atmosphere of the reaction vials was switched to argon via standard manifold operation. A solution of 2 wt % TPGS-750-M (0.5 mL) was added to the reaction mixture, which was then briefly stirred for 1 min at 45 ºC. The rest of the reagents that are liquid were added via syringe under Ar. In cases where organic co-solvent is needed, ~10-20 v/v % of 1,4-dioxane or THF was added via syringe. In cases where a viscous oil halide or amine was involved, the co-solvent, 1,4-dioxane, was firstly added to the oily reagent in a vial to dilute it, and the solution was then transferred into the reaction system via syringe. The vial was closed and parafilm was used to seal the vial. The reaction mixture was then stirred vigorously (~600-800 rpm) at 45 ºC (or lower in certain cases) in an isotherm aluminum reaction block on an IKA plate.

Reaction work-up (for 0.25 mmol scale):

Work-up procedure (A): After complete consumption of starting material, as monitored by GCMS or TLC, 1 mL EtOAc was added to the reaction mixture, which was then briefly stirred gently for 5 sec. The organic layer was pipetted out. A similar extraction procedure was repeated for 2-3 additional times. The combined extracts were dried over anhydrous sodium sulfate and volatiles were evaporated under reduced pressure to obtain crude product, which was further purified by flash chromatography over silica gel. After concentration, the product was further dried *in vacuo* at rt.

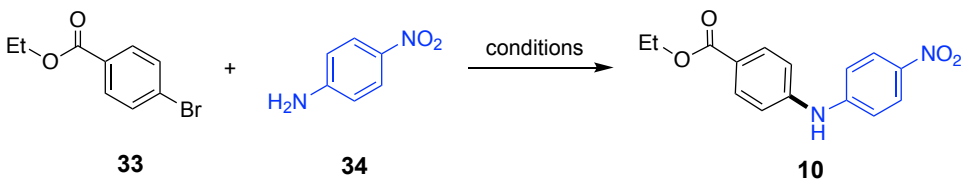
Work-up procedure (B):

After complete consumption of starting material, as monitored by GCMS or TLC, the solid organic product was collected via filtration on a glass-fritted funnel. H_2O (2 mL) were used to wash the solid product and the product was air-dried for ca. 2 h. Product was further purified via trituration/recrystallization in hexanes (or solvent of choice) and dried *in vacuo*.

Work-up procedure (C):

After complete consumption of starting material, as monitored by GCMS or TLC, 0.5 mL MeOH was added to the reaction mixture, which was then stirred at rt for 5 min. The solid organic product was collected via filtration on a glass-fritted funnel. Another 1 mL of 1:1 MeOH/H_2O was used to wash the solid product and the product was air-dried for ca. 2 h. Product was further dried *in vacuo* at rt overnight.

4. Recycle Study

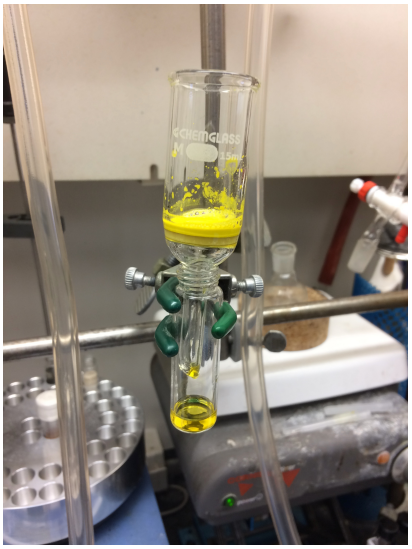


33 **34** **10**

Conditions: **34** (69 mg, 0.5 mmol), **33** (100 μL, 0.625 mmol), KOH (14 mg, 0.25 mmol), K_3PO_4-H_2O (81 mg, 0.35 mmol) 1000/500 ppm [tBuXPhosPd(cinnamyl)]OTf, 23 °C, 20 h.

500 ppm catalyst supply each additional cycle

recycling studies	cycle	0	1	2	3	4
	yield (%)	90	86	90	88	85



i) Initial reaction: In a 8 mL reaction vial containing 0.400 mg [*t*-BuXPhos(Pd-π-cinnamyl)]OTf (1000 ppm for 0.5 mmol scale reaction), a PTFE coated magnetic stir bar, 14 mg KOH (0.5 equiv), 81 mg K_3PO_4-H_2O (0.7 equiv), and 4-nitroaniline (69 mg, 0.5 mmol, 1.0 equiv) were added. The reaction vial was sealed with a rubber septum and the mixture was evacuated and back-filled with argon. An aqueous solution of TPGS-750-M (1 mL; 2 wt %) was added to the reaction vial via syringe and the mixture was stirred at rt for 1 min. Ethyl 4-bromobenzoate (100 μL, 0.625 mmol, 1.25 equiv) was added to the mixture. The reaction mixture was then stirred vigorously (~800-1000 rpm) at rt for 20 h under an atmosphere of

argon.

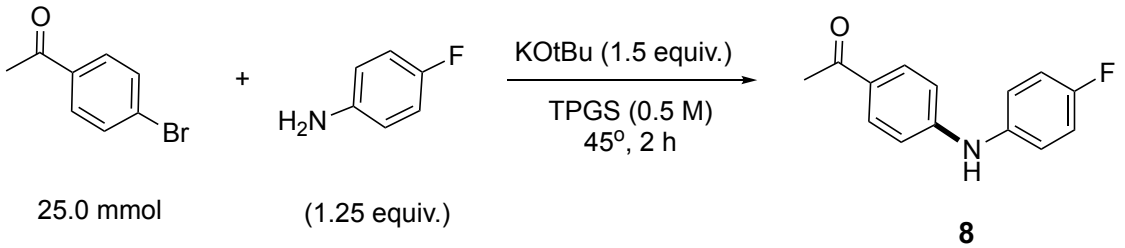
After complete consumption of the starting material as monitored by TLC, the mixture was gravity-filtered through a glass fritted funnel (medium pore size). Another 0.3 mL of 2 wt % TPGS-750-M was used to wash the filter cake, making the total volume of the filtrate to be ca. 1 mL. This filtrate was transferred and saved, as it would be the medium for the next coupling reaction. To obtain pure desired product, 1 mL of 50%/50% MeOH/H_2O was added to the filter cake and the mixture was stirred manually with a spatula while draining, and this process is repeated once more. Vacuum drying was applied at rt for 4 h. Trituration of the solid in 1 mL hexanes afforded the desired product as yellow power. R_f = 0.27 (3:7, EtOAc/hexanes); yield 129 mg, 90%.

ii) 1st recycle: *The aforementioned saved filtrate was transferred into a new 8 mL reaction vial. The system was degassed by argon sparging via a long needle at rt for ca. 10 min (some foaming is expected, and low argon flow is recommended).*

In an 8 mL reaction vial containing 0.200 mg [*t*-BuXPhos(Pd-π-cinnamyl)]OTf (500 ppm for 0.5 mmol scale reaction), a PTFE coated magnetic stir bar, 14 mg KOH, 81 mg K_3PO_4•H_2O, and 4-nitroaniline (69 mg, 0.5 mmol, 1.0 equiv) were added. The reaction vial was sealed with a rubber septum and the mixture was evacuated and back-filled with argon. The degassed aqueous medium from the original reaction was added into the vial via syringe under Ar and the mixture was stirred at rt for 1 min. Ethyl 4-bromobenzoate (100 µL, 0.625 mmol, 1.25 equiv) was added, and the reaction mixture was then stirred vigorously (~800-1000 rpm) at rt for 20 h under an atmosphere of argon. After completion, the same filtration protocol was followed as in the original coupling reaction, and 123 mg (86%) of the desired product was obtained.

iii) 2nd, 3rd, and 4th recycle: For the 2nd, 3rd, and 4th recycles, similar procedures were used as described above. Yields of 129 mg (90%), 126 mg (88%) and 121 mg (85%) for the 2nd, 3rd, and 4th recycles, respectively, were obtained.

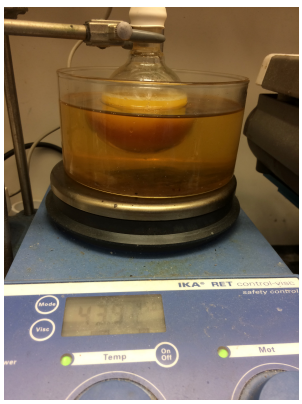
5. Gram-Scale Reaction and E Factor Determination

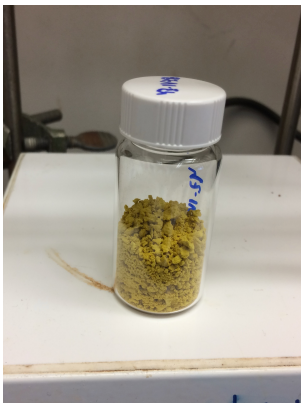


25.0 mmol (1.25 equiv.)

8

5.67 g, 99%



Experimental Procedure:

To a 100-mL round bottom flask containing a PTFE coated magnetic stir bar, 18.0 mg [*t*-BuXPhos(Pd-π-allyl)]OTf (1000 ppm for 25.0 mmol scale reaction), 4.58 g KO-*t*-Bu (1.5 equiv.), and 5.00 g 4-bromoacetophenone (25.0 mmol, 1.0 equiv) were added. The reaction flask was sealed with a rubber septum and the mixture was evacuated and back-filled with argon. An aqueous solution of TPGS-750-M (50 mL, 2 wt %) was added to the flask via syringe and the mixture was stirred at rt for 1 min. Under Ar, 4-fluoroaniline (3.00 mL, 31.25 mmol, 1.25 equiv) was added via a syringe. The reaction mixture was then stirred at 45 ºC in an oil bath for 45 min, upon which yellow solids precipitated out as chunks.

After complete consumption of the starting material as monitored by TLC, the mixture was filtered through a glass fritted funnel (medium pore size). Water (10 mL) was added to the filter

cake and the mixture was stirred manually with a spatula while draining, and this process is repeated 4 times. Vacuum-drying was applied at rt overnight and the desired product was obtained as a yellow powder. R_f = 0.15 (2:8, EtOAc/hexanes), yield 5.67 g, 99%. ^{1}H NMR analysis show ≥95% purity for the product. If needed, the product could be further purified by recrystallization from EtOAc/hexanes.

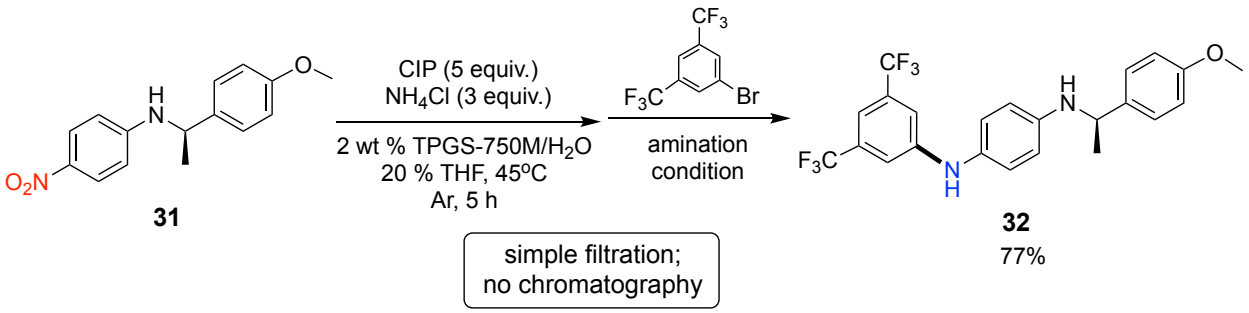
$$\text{E Factor} = \frac{\text{total of organic wastes (kg)}}{\text{product (kg)}}$$

$$= \frac{\begin{array}{c}(0.25 \text{ equiv. amine} + \\ 1.0 \text{ equiv. butanol by-product})\end{array}}{\text{isolated pure product}}$$

$$= \frac{0.70 \text{ g} + 1.87 \text{ g}}{5.67 \text{ g}}$$

$$= 0.5$$

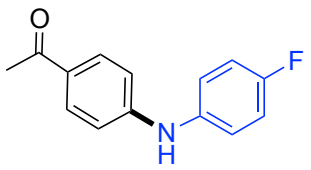
6. Tandem Process: Nitro Group Reduction Followed by ppm Pd-Catalyzed Amination



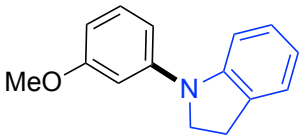
Into a 4 mL vial with a stir bar was added (*R*)-*N*-(1-(4-methoxyphenyl)ethyl)-4-nitroaniline (**31**) (85 mg, 0.312 mmol), carbonyl iron powder (88 mg, 5.0 equiv), and NH_4Cl (50 mg, 3.0 equiv). The vial was purged with argon, and 0.125 mM THF was added. The vial was capped and stirred in a block reactor at 45 ºC for ~2 min. Next, 2 wt % TPGS-750-M/H_2O was added and the vial was placed back in the 45 ºC block reactor and stirred at ~500 rpm. The reaction reached completion after 6 h. EtOAc (~1 mL) was added to the vial and the mixture was gently stirred briefly, then the contents of the vial were filtered through ~1 cm of Celite (in a pipette) into another clean scintillation vial. Additional EtOAc was used to rinse the material into the vial. The solvent was removed by rotary evaporation and the product was further dried under vacuum. To this vial was added 100 µL of THF and this solution will be used for the following C-N cross coupling reaction.

To the 4 mL reaction vial containing 0.50 mg [*t*-BuXPhos(Pd-cinnamyl)]OTf (2,500 ppm for 0.25 mmol scale reaction), a PTFE coated magnetic stir bar, KO-*t*-Bu (46 mg, 0.375 mmol, 1.25 equiv) were added. A rubber septum was used to cap the reaction vial. The atmosphere of the reaction vial was switched to argon via standard manifold operation. A solution of 2 wt % TPGS-750-M (0.5 mL) was added to the reaction mixture, which was then briefly stirred for 1 min at 45 ºC. Then, 1,3-bis(trifluoromethyl)5-bromobenzene (43 µL, 0.25 mmol, 1.0 equiv) and the aforementioned THF solution from the nitro group reduction product were added via syringe under Ar. The reaction mixture was then stirred vigorously (~600-800 rpm) at 45 ºC in an isotherm aluminum reaction block on an IKA plate for 24 h. The general work-up procedure (**A**) was then followed to obtain the desired product.

7. Comparison Study: Performing the Amination in Organic Solvent vs. TPGS-750-M/H_2O for Compounds 8 and 3.



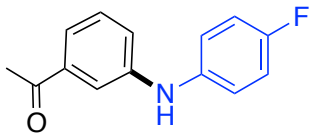
8



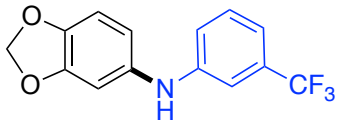
3

The reaction set-up for compounds **8** and **3** was the same as in the general reaction set-up for the micellar protocol used in this study, with the exception that degassed toluene or 1,4-dioxane was added instead of 2 wt % TPGS-750-M/H_2O. Both reactions were quenched after 16 h of stirring at 45 ºC and analyzed by crude ^1H NMR.

8. Residual Palladium Content in Products 5, 12, and 23.



5



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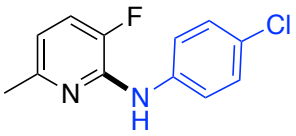

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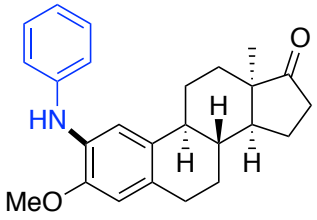

42

Compound **42** was prepared in two separate batches: the procedure in this work and via literature precedent. The general protocol was followed to make it as the product from this study; the exact thermal heating procedure as in the Supporting Information of the original publication (see ref. 25) was followed to obtain **42** for the "literature batch."

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CIB001

Min-Kyu Cho

Novartis Institute for Biomedical Research

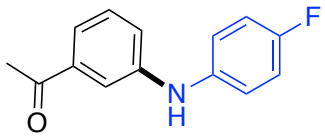
250 Mass. Ave.

Cambridge, Massachusetts 02139

Sample #: REILLJO3-002-EXP017 Test #: 1 Received: 08/10/2018 Completed: 08/13/2018

ICP-MS Palladium : 3 ppm

Services
ICP-MS



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www.robertson-microlit.com results@robertson-microlit.com

CIB001

Min-Kyu Cho

Novartis Institute for Biomedical Research

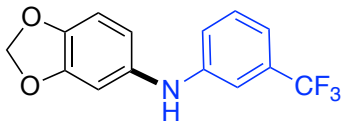
250 Mass. Ave.

Cambridge, Massachusetts 02139

Sample #: REILLJO3-002-EXP018 Test #: 1 Received: 08/10/2018 Completed: 08/13/2018

ICP-MS Palladium : 4 ppm

Services
ICP-MS



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CIB001

Min-Kyu Cho

Novartis Institute for Biomedical Research

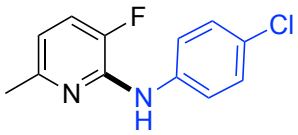
250 Mass. Ave.

Cambridge, Massachusetts 02139

Sample #: REILLJO3-002-EXP021 Test #: 1 Received: 08/10/2018 Completed: 08/13/2018

ICP-MS Palladium : 4 ppm

Services
ICP-MS



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CIB001

Min-Kyu Cho

Novartis Institute for Biomedical Research

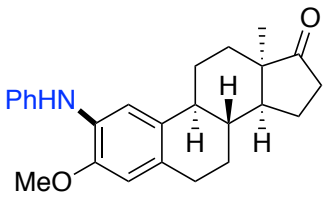
250 Mass. Ave.

Cambridge, Massachusetts 02139

Sample #: REILLJO3-002-EXP019 Test #: 1 Received: 08/10/2018 Completed: 08/13/2018

ICP-MS Palladium : 165 ppm

Services
ICP-MS



(literature method)

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www.robertson-microlit.com results@robertson-microlit.com

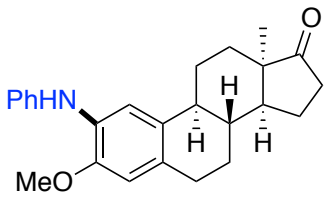
CIB001

Min-Kyu Cho
Novartis Institute for Biomedical Research
250 Mass. Ave.
Cambridge, Massachusetts 02139

Sample #: REILLJO3-002-EXP035 Test #: 1 Received: 10/23/2018 Completed: 10/23/2018

ICP-MS Palladium : 3 ppm

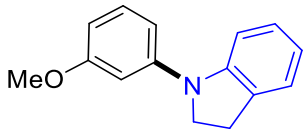
Services
ICP-MS



(method of this study)

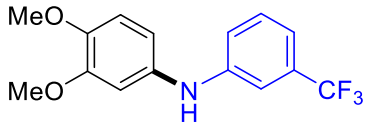
9. Analytical Data

1-(3-Methoxyphenyl)indoline (3)



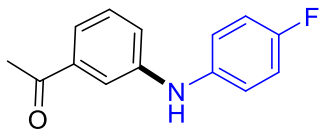
Compound **3** was obtained following general reaction set-up protocol and work-up procedure (**A**). Viscous oil, yield 54 mg (95% on 0.25 mmol scale). R_f 0.40 (1:9, Et_2O/hexanes). Spectral data were in agreement with the literature.[2]

3,4-Dimethoxy-*N*-(3-(trifluoromethyl)phenyl)aniline (4)



Compound **4** was obtained following general reaction set-up protocol and work-up procedure (**A**). Viscous oil, yield 70 mg (95% on 0.25 mmol scale). R_f 0.17 (1:4, EtOAc/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (t, J = 7.9 Hz, 1H), 7.13 (m, 1H), 7.08 – 7.01 (m, 2H), 6.87 – 6.81 (m, 1H), 6.73-6.68 (m, 2H), 5.73 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.84, 145.84, 145.66, 134.94, 131.77 (q, J = 31.9 Hz), 129.88, 124.27 (q, J = 272.3 Hz), 118.31, 115.82 (q, J = 3.9 Hz), 113.62, 112.27, 111.68 (q, J = 4.0 Hz), 106.41, 56.31, 55.97. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.90. **HRMS** (EI), $[C_{15}H_{14}F_3NO_2]^+$ calcd. 297.0977, found (*m*/*z*) 297.0989.

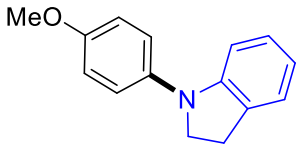
1-(3-((4-Fluorophenyl)amino)phenyl)ethan-1-one (5)



Compound **5** was obtained following general reaction set-up protocol and work-up procedure (**B**). Yellow solid, yield 54 mg (94% on 0.25 mmol scale). R_f 0.07 (1:4, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 1H), 7.44 (dt, J = 7.7, 1.4 Hz, 1H), 7.31 (t, J = 7.8

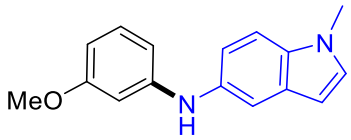
Hz, 1H), 7.19 – 7.12 (m, 1H), 7.11 – 7.04 (m, 2H), 7.04 – 6.97 (m, 2H), 5.78 (bs, 1H), 2.56 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.33, 159.58, 157.67, 144.80, 138.51, δ 138.22 (d, J = 2.7 Hz), 129.68, 121.56 (d, J = 7.9 Hz), 120.63 (d, J = 21.1 Hz), 116.27 (d, J = 22.5 Hz), 115.50, 26.86. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -120.75. **HRMS** (EI), $[C_{14}H_{12}FNO]^+$ calcd. 229.0903, found (*m*/*z*) 229.0900.

1-(4-Methoxyphenyl)indoline (6)



Compound **6** was obtained following general reaction set-up protocol and work-up procedure (**A**). Off-white solid, yield 51 mg (91% on 0.25 mmol scale). R_f 0.44 (1:9, Et_2O/hexanes). Spectral data were in agreement with the literature.[2]

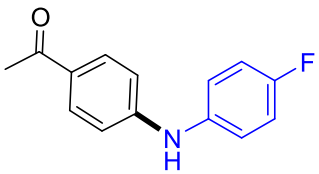
***N*-(3-Methoxyphenyl)-1-methyl-1H-indol-5-amine (7)**



Compound **7** was obtained following general reaction set-up protocol and work-up procedure (**A**). Off-white solid, yield 54 mg (86% on 0.25 mmol scale). R_f 0.18 (1:4, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, J = 2.1 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.6, 2.1 Hz, 1H), 7.07 (d, J = 3.1 Hz, 1H), 6.58 – 6.51 (m, 2H), 6.45 (dd, J = 3.1, 0.8 Hz, 1H), 6.41 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 5.66 (bs, 1H), 3.80 (s, 3H), 3.78 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.86, 148.00, 134.46, 133.97, 130.05, 129.58, 129.15, 118.32, 114.06, 109.89, 108.02, 104.27, 100.86, 100.65, 55.21, 33.03.

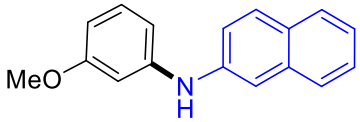
HRMS (EI), $[C_{16}H_{16}N_2O]^+$ calcd. 252.1263, found (*m*/*z*) 252.1270.

1-(4-((4-Fluorophenyl)amino)phenyl)ethan-1-one (8)



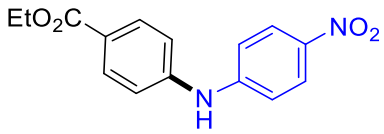
Compound **8** was obtained following general reaction set-up protocol and work-up procedure (**B**). Yellow solid, yield 53 mg (93% on 0.25 mmol scale). R_f 0.14 (1:4, EtOAc/hexanes). Spectral data were in agreement with the literature.[3]

***N*-(3-Methoxyphenyl)naphthalen-2-amine (9)**



Compound **9** was obtained following general reaction set-up protocol and work-up procedure (**A**). Off-white solid, yield 59 mg (95% on 0.25 mmol scale). R_f 0.24 (1:4, EtOAc/hexanes). Spectral data were in agreement with the literature.[4]

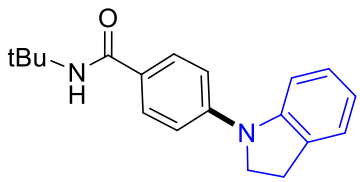
Ethyl 4-((4-nitrophenyl)amino)benzoate (10)



The synthesis of compound **10** follows general reaction set-up protocol with the exception that the amino compound was used as the limiting reagent, while the bromide was used in excess (1.25 equiv). Work-up procedure (**C**) was followed.

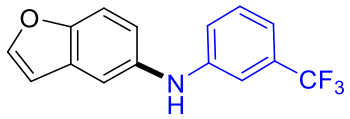
Yellow solid, yield 250 mg (87% on 1.00 mmol scale), R_f 0.30 (3:7, EtOAc/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 – 8.14 (m, 2H), 8.13 – 8.02 (m, 2H), 7.25 – 7.17 (m, 2H), 7.17 – 7.09 (m, 2H), 6.47 (bs, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.17, 148.24, 144.39, 141.09, 131.59, 126.24, 125.17, 118.69, 115.76, 61.07, 14.51. **HRMS** (ESI), $[C_{15}H_{14}N_2O_4 + Na]^+$ calcd. 309.0851, found (*m*/*z*) 309.0850.

***N*-(*t*-Butyl)-4-(indolin-1-yl)benzamide (11)**



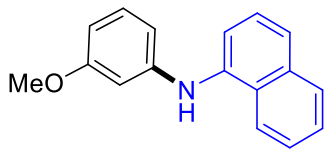
Compound **11** was obtained following general reaction set-up protocol with 20 v/v% 1,4-dioxane co-solvent and work-up procedure (**C**). Off-white solid, yield 65 mg (88% on 0.25 mmol scale), R_f 0.21 (1:4, EtOAc/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.67 (m, 2H), 7.27 – 7.17 (m, 4H), 7.11 (t, J = 7.6 Hz, 1H), 6.82 (t, J = 7.3 Hz, 1H), 5.95 (s, 1H), 3.97 (t, J = 8.4 Hz, 2H), 3.14 (t, J = 8.4 Hz, 2H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.52, 146.38, 145.79, 131.81, 128.09, 127.17, 126.99, 125.32, 119.93, 115.89, 109.04, 51.85, 51.48, 29.08, 28.10. **HRMS** (ESI), $[C_{19}H_{22}N_2O + Na]^+$ calcd. 317.1630, found (*m*/*z*) 317.1622.

***N*-(3-(Trifluoromethyl)phenyl)benzofuran-5-amine (12)**



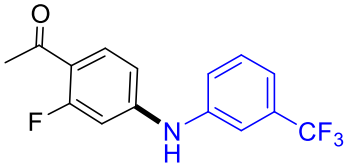
Compound **12** was obtained following general reaction set-up protocol and work-up procedure (**A**). Viscous oil, yield 49 mg (71% on 0.25 mmol scale). R_f 0.45 (1:4, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 – 7.63 (m, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.39 – 7.37 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.16 – 7.13 (m, 1H), 7.12 – 7.05 (m, 3H), 6.74 – 6.72 (m, 1H), 5.78 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.99, 146.10, 136.79, 131.86 (q, J = 32 Hz), 129.91, 128.58, 124.32 (q, J = 273 Hz), 123.64, 119.62, 118.33, δ 116.02 (q, J = 3.9 Hz), 113.88, 112.32, 111.81 (q, J = 3.9 Hz), 106.70. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.86. **HRMS** (EI), $[C_{15}H_{10}F_3NO]^+$ calcd. 281.0664, found (*m*/*z*) 281.0663.

***N*-(3-Methoxyphenyl)naphthalen-1-amine (13)**



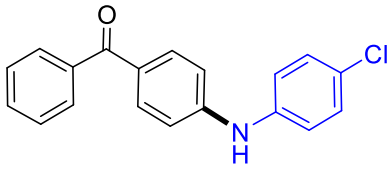
Compound **13** was obtained following general reaction set-up protocol without co-solvent and work-up procedure (**A**). Viscous oil, yield 53 mg (85% on 0.25 mmol scale) R_f 0.30 (1:9, EtOAc/hexanes). Spectral data were in agreement with the literature.[5]

1-(2-Fluoro-4-((3-(trifluoromethyl)phenyl)amino)phenyl)ethan-1-one (14)



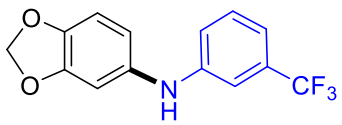
Compound **14** was obtained following general reaction set-up protocol and work-up procedure (**C**). Off-white solid, yield 65 mg (88% on 0.25 mmol scale), R_f 0.30 (1:4, EtOAc/hexanes). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.34 (bs, 1H), 7.76 (t, J = 8.8 Hz, 1H), 7.65 – 7.49 (m, 2H), 7.44 – 7.40 (m, 1H), 7.34 (d, J = 7.3 Hz, 1H), 6.92 (dd, J = 8.7, 2.2 Hz, 1H), 6.83 (dd, J = 14.2, 2.2 Hz, 1H), 2.48 (d, J = 4.7 Hz, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 192.81 (d, J = 3.7 Hz), 163.43 (d, J = 253.5 Hz), 149.45 (d, J = 12.0 Hz), 141.65, 132.13 (d, J = 4.3 Hz), 130.72, 130.24 (q, J = 32 Hz), 124.06 (q, J = 274 Hz), 122.68, 118.52 (q, J = 4 Hz), 116.34 (d, J = 12.6 Hz), 115.49 (q, J = 3.9 Hz), 111.42 (d, J = 1.9 Hz), 101.35 (d, J = 27.9 Hz), 30.70 (d, J = 6.8 Hz). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.45, -107.11. **HRMS** (ESI), $[C_{15}H_{11}F_4NO + H]^+$ calcd. 298.0855, found (*m*/*z*) 298.0848.

(4-((4-Chlorophenyl)amino)phenyl)(phenyl)methanone (15)



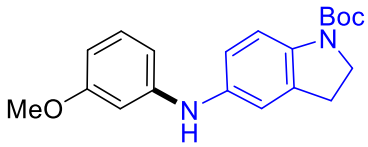
Compound **15** was obtained following general reaction set-up protocol with 15 v/v% THF co-solvent and work-up procedure (**C**). Off-white solid, yield 76 mg (99% on 0.25 mmol scale), R_f 0.18 (1:4, EtOAc/hexanes). Spectral data were in agreement with the literature.[6]

***N*-(3-(Trifluoromethyl)phenyl)benzo[d][1,3]dioxol-5-amine (16)**



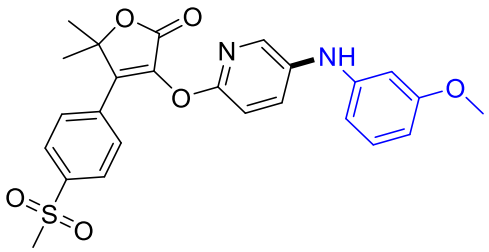
Compound **16** was obtained following general reaction set-up protocol and work-up procedure (**A**). Viscous oil, yield 70 mg (99% on 0.25 mmol scale) R_f 0.30 (1:4, Et_2O/hexanes). Analytical data were in agreement with the literature.[7]

***t*-Butyl 5-((3-methoxyphenyl)amino)indoline-1-carboxylate (17)**



Compound **17** was obtained following general reaction set-up protocol and work-up procedure (**A**). Viscous oil, yield 72 mg (85% on 0.25 mmol scale) R_f 0.20 (1:4, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.85 – 7.70 (m, 1H), 7.45 – 7.30 (m, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.00 – 6.87 (m, 2H), 6.58 – 6.47 (m, 2H), 6.41 (dd, J = 8.1, 2.4 Hz, 1H), 5.61 (s, 1H), 4.07 – 3.86 (m, 2H), 3.76 (s, 3H), 3.05 (t, J = 8.6 Hz, 2H), 1.57 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.82, 152.61, 146.30, 138.22, 137.22, 132.13, 130.13, 119.78, 117.51, 115.28, 108.91, 105.06, 101.88, 77.36, 55.25, 47.79, 28.60, 27.63. **HRMS** (ESI), $[C_{20}H_{24}N_2O_3 + Na]^+$ calcd. 363.1685, found (*m*/*z*) 363.1684.

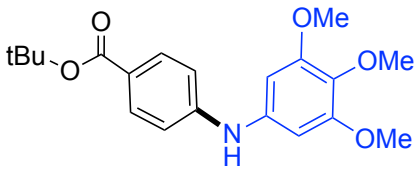
3-((5-((3-Methoxyphenyl)amino)pyridin-2-yl)oxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)furan-2(5H)-one (18)



The synthesis of compound **18** follows general reaction set-up protocol from a bromide from Merck Informer Library Compound X3 (Aldrich 901724). The reaction was let run at 55 ºC for

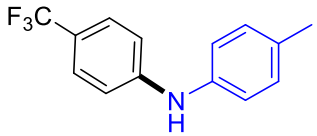
24 h. Work-up procedure (**A**) was then followed. Off white solid, yield 72 mg (60% on 0.25 mmol scale) R_f 0.42 (1:1, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 2.8 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.46 (dd, J = 8.8, 2.8 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.47 (d, J = 9.0 Hz, 1H), 6.42 (d, J = 8.1 Hz, 2H), 3.70 (s, 3H), 3.00 (s, 3H), 1.69 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.84, 159.25, 147.76, 144.53, 141.26, 138.37, 138.11, 136.21, 132.79, 131.39, 130.34, 128.99, 127.88, 111.38, 109.51, 106.33, 102.93, 84.28, 77.27, 77.01, 76.76, 55.27, 44.38, 26.45. **HRMS** (ESI), $[C_{25}H_{24}N_2O_6S + Na]^+$ calcd. 503.1253, found (*m*/*z*) 503.1251.

t-Butyl 4-((3,4,5-trimethoxyphenyl)amino)benzoate (19)



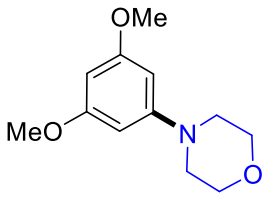
Compound **19** was obtained following general reaction set-up protocol with 15 v/v% 1,4-dioxane co-solvent and the reaction was let run for 26 h. Work-up procedure (**A**) was then followed. Viscous oil, yield 82 mg (90%), R_f 0.21 (1:4, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.39 (s, 2H), 6.17 – 6.12 (m, 1H), 3.82 (s, 3H), 3.80 – 3.77 (m, 6H), 1.57 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.86, 153.88, 148.14, 137.35, 134.08, 131.35, 122.91, 114.64, 98.48, 80.34, 61.08, 56.14, 28.37.
HRMS (ESI), $[C_{20}H_{25}NO_5 + Na]^+$ calcd. 382.1631, found (*m*/*z*) 382.1642.

4-Methyl-*N*-(4-(trifluoromethyl)phenyl)aniline (20)



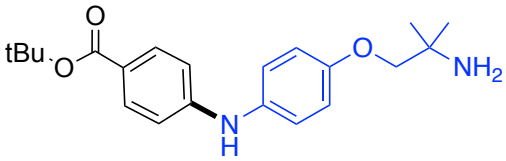
Compound **20** was obtained following general reaction set-up protocol and work-up procedure (**C**). Off-white solid, yield 47 mg (75% on 0.25 mmol scale) R_f 0.30 (1:9, EtOAc/hexanes). Analytical data were in agreement with the literature.[9]

4-(3,5-Dimethoxyphenyl)morpholine (21)



To the 4 mL reaction vial containing 0.50 mg [*t*-BuXPhos(Pd-π-cinnamyl)]OTf (2500 ppm for 0.25 mmol scale reaction), a PTFE coated magnetic stir bar, KOH (0.625 mmol, 2.5 equiv) and 1-bromo-3,5-dimethoxybenzene (54 mg, 0.25 mmol, 1.0 equiv) were added. A rubber septum was used to cap the reaction vial. The atmosphere of the reaction vial was switched to argon via standard manifold operation. A solution of 2 wt % TPGS-750-M (0.25 mL) was added to the reaction mixture, which was then briefly stirred for 1 min at 45 ºC. Morpholine (43 µL, 0.5 mmol, 2.0 equiv) was then added via syringe under Ar. The reaction mixture was then stirred vigorously (~600-800 rpm) at 45 ºC in an isotherm aluminum reaction block on an IKA plate for 44 h. Compound **21** was obtained following the work-up procedure (**A**). Viscous oil, yield 41 mg (74% on 0.25 mmol scale) R_f 0.35 (1:4, EtOAc/hexanes). Spectral data were in agreement with the literature.[10]

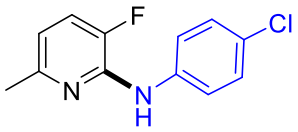
***t*-Butyl 4-((4-(2-amino-2-methylpropoxy)phenyl)amino)benzoate (22)**



The amine partner used for the reaction to make compound **22** was 4-(2-amino-2-methyl-propoxy)-phenylamine hydrochloride (1.25 equiv.), synthesis of which was previously describe in the patent literature.[11] The general reaction set-up protocol was followed with 2500 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf and excess KO-*t*-Bu (0..625 mmol, 2.5 equiv). Work-up procedure (**C**) was then followed. The product was isolated as a beige solid, yield 84 mg (94% on 0.25 mmol scale), R_f 0.45 (90:10:2, DCM/MeOH/Et_3N). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88

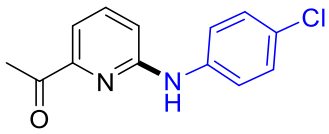
– 7.78 (m, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.96 – 6.87 (m, 2H), 6.84 – 6.73 (m, 2H), 5.80 (s, 1H), 3.69 (s, 2H), 1.57 (s, 9H), 1.24 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.99, 156.00, 149.43, 133.95, 131.38, 124.14, 122.12, 115.53, 113.36, 80.15, 78.26, 50.00, 28.42, 27.49. HRMS (ESI), $[C_{21}H_{28}N_2O_3 + H]^+$ calcd. 357.2178, found (*m*/*z*) 357.2183.

N-(4-Chlorophenyl)-3-fluoro-6-methylpyridin-2-amine (23)



The general reaction set-up protocol was followed with 2500 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf and work-up procedure (**A**) was then followed. Reaction was let run at 45 ºC for 28 h. Viscous oil, yield 52 mg (88% on 0.25 mmol scale) R_f 0.39 (1:4, Et_2O/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 2H), 7.31 – 7.28 (m, 1H), 7.28 – 7.26 (m, 2H), 7.17 (dd, J = 11.0, 8.0 Hz, 1H), 6.60 – 6.53 (m, 2H), 2.46 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.63 (d, J = 5.8 Hz), 145.36 (d, J = 251.1 Hz), 143.79 (d, J = 9.4 Hz), 138.86, 128.92, 126.61, 121.47 (d, J = 16.0 Hz), 119.79, 113.90 (d, J = 2.0 Hz), 23.84 (d, J = 1.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -144.72 (d, J = 11.0 Hz). **HRMS** (ESI), $[C_{12}H_{10}ClFN_2 + H]^+$ calcd. 237.0595, found (*m*/*z*) 237.0592.

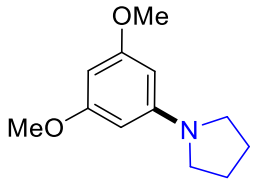
1-(6-((4-Chlorophenyl)amino)pyridin-2-yl)ethan-1-one (24)



The general reaction set-up protocol was followed with 2500 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf and 15 v/v% THF as the co-solvent. Reaction was let run at 45 ºC for 25 h. Work-up procedure (**C**) was then followed. Yellow solid, yield 56 mg (91% on 0.25 mmol scale), R_f 0.57 (4:6, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.3 Hz, 1H), 6.69 – 6.56 (m, 1H), 2.68 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.39, 154.79, 151.97,

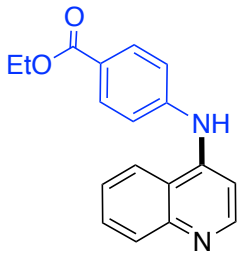
138.94, 138.43, 129.21, 127.51, 120.95, 113.55, 113.33, 77.41, 77.16, 76.91, 26.22. **HRMS** (ESI), $[C_{13}H_{11}ClN_2O + H]^+$ calcd. 247.0638, found (*m*/*z*) 247.0632.

1-(3,5-Dimethoxyphenyl)pyrrolidine (25)



To the 4 mL reaction vial containing 0.50 mg [*t*-BuXPhos(Pd-π-cinnamyl)]OTf (2,500 ppm for 0.25 mmol scale reaction), a PTFE coated magnetic stir bar, KOH (0.625 mmol, 2.5 equiv) and 1-bromo-3,5-dimethoxybenzene (54 mg, 0.25 mmol, 1.0 equiv) were added. A rubber septum was used to cap the reaction vial. The atmosphere of the reaction vial was switched to argon via standard manifold operation. A solution of 2 wt % TPGS-750-M (0.25 mL) was added to the reaction mixture, which was then briefly stirred for 1 min at 45 ºC. Pyrrolidine (41 µL, 0.5 mmol, 2.0 equiv.) was then added via syringe under Ar. The reaction mixture was then stirred vigorously (~600-800 rpm) at 45 ºC in an isotherm aluminum reaction block on an IKA plate for 44 h. Compound **25** was obtained following the work-up procedure (**A**). Viscous oil, yield 40 mg (78% on 0.25 mmol scale) R_f 0.50 (1:4, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.76 (d, *J* = 2.2 Hz, 2H), 3.79 (s, 6H), 3.32 – 3.24 (m, 4H), 2.03 – 1.94 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.74, 149.82, 90.98, 88.05, 77.42, 77.16, 76.91, 55.29, 47.86, 25.57. **HRMS** (ESI), $[C_{12}H_{17}NO_2 + H]^+$ calcd. 208.1338, found (*m*/*z*) 208.1339.

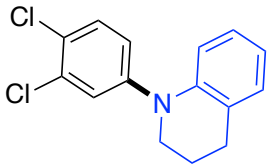
Ethyl 4-(quinolin-4-ylamino)benzoate (26)



The general reaction set-up protocol was followed with 2500 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf and K_3PO_4•H_2O (0.312 mmol, 1.25 equiv) used as base. Reaction was run at 35

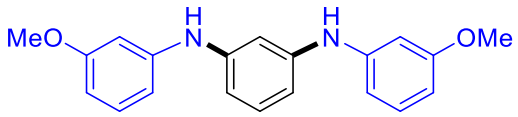
ºC for 20 h. Work-up procedure (**C**) was then followed. White solid, yield 47 mg (64% on 0.25 mmol scale), R_f 0.57 (4:6, EtOAc/hexanes). Spectral data were in agreement with the literature.[12]

1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydroquinoline (27)



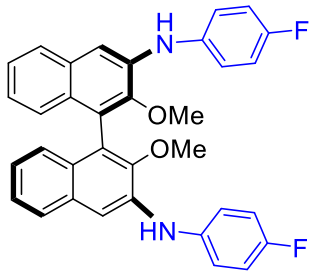
The general reaction set-up protocol was followed with 2500 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf and the reaction was let run at 45 ºC for 42 h. Work-up procedure (**A**) was then followed. Viscous oil, yield 36 mg (50% on 0.25 mmol scale), R_f 0.43 (1:9, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.11 – 7.04 (m, 2H), 7.03 – 6.96 (m, 1H), 6.87 (dd, J = 8.3, 1.1 Hz, 1H), 6.80 (td, J = 7.3, 1.2 Hz, 1H), 3.68 – 3.51 (m, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.13 – 1.89 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.10, 143.05, 132.96, 130.78, 129.60, 126.64, 126.61, 125.66, 124.67, 122.53, 120.13, 117.26, 50.50, 27.62, 23.05. **HRMS** (EI), $[C_{15}H_{13}Cl_2N]^+$ calcd. 277.0425, found (*m*/*z*) 277.0427.

***N*1,*N*3-bis(3-Methoxyphenyl)benzene-1,3-diamine (28)**



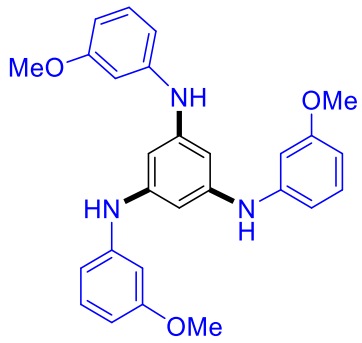
The general reaction set-up protocol was followed with 2500 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf. For the double amination of 1,3-dibromobenzene (limiting reagent), 2.5 equiv *m*-anisidine and 3.0 equiv KO-*t*-Bu were used. The reaction was let run at 45 ºC for 36 h. Work-up procedure (**A**) was then followed. Viscous oil, yield 73 mg (91% on 0.25 mmol scale) R_f 0.22 (1:4, EtOAc/hexanes). Spectral data were in agreement with the literature.[13]

***N*3,*N*3'-bis(4-Fluorophenyl)-2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diamine (29)**



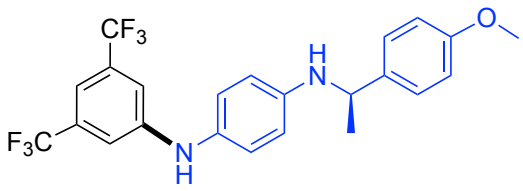
The general reaction set-up protocol was followed with 5000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf with 20 v/v% 1,4-dioxane as the organic co-solvent. For the double amination of the dibromide, 3.0 equiv 4-fluoroaniline and 3.0 equiv KO-*t*-Bu were used. The reaction was run at 45 ºC for 44 h. Work-up procedure (**C**) was then followed and the filtered solid material was subjected to column chromatography to obtain analytically pure product. Off-white solid, yield 123 mg (93% on 0.25 mmol scale) R_f 0.37 (1:4, EtOAc/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.29 (s, 1H), 8.10 (d, J = 8.4, 1H), 7.78 (d, J = 8.4, 1H), 7.71 (t, J = 8.0, 1H), 7.58 (d, J = 4.8, 2H), 7.56 (t, J = 7.2, 1H), 7.41–7.35 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.74 (d, J = 241.5 Hz), 147.03, 137.73 (d, J = 2.7 Hz), 137.36, 131.74, 128.40, 126.38, 125.83, 125.54, 124.67, 123.51, 122.72 (d, J = 7.9 Hz), 116.31 (d, J = 22.5 Hz), 107.75, 60.70. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -120.22 (dt, J = 8.3, 3.9 Hz). **HRMS** (ESI), $[C_{34}H_{26}F_2N_2O_2 + Na]^+$ calcd. 555.1860, found (*m*/*z*) 555.1857.

***N*1,*N*3,*N*5-tris(3-Methoxyphenyl)benzene-1,3,5-triamine (30)**



The general reaction set-up protocol was followed with 5000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf with 20 v/v% 1,4-dioxane as organic co-solvent. For the triple amination of the starting 1,3,5-tribromobenzene, 4.3 equiv *m*-anisidine and 3.75 equiv KO-*t*-Bu were used. The reaction was let run at 45 ºC for 44 h. Work-up procedure (A) was then followed. Viscous oil, yield 96 mg (87%) R_f 0.35 (3:7, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.0 Hz, 3H), 6.71 – 6.63 (m, 6H), 6.51 – 6.47 (m, 3H), 6.36 (s, 3H), 5.64 (s, 3H), 3.77 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.74, 145.16, 144.25, 130.14, 111.20, 106.62, 104.39, 100.03, 55.34. **HRMS** (ESI), $[C_{27}H_{27}N_3O_3 + H]^+$ calcd. 442.2131, found (*m*/*z*) 442.2141.

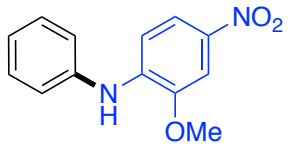
(*R*)-*N*1-(3,5-bis(trifluoromethyl)phenyl)-*N*4-(1-(4-methoxyphenyl)ethyl)benzene-1,4-diamine (32)



Viscous oil, yield 87 mg (77% on 0.25 mmol scale). R_f 0.25 (1:4, EtOAc/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.29 (s, 1H), 8.10 (d, *J* = 8.4, 1H), 7.78 (d, *J* = 8.4, 1H), 7.71 (t, *J* = 8.0, 1H), 7.58 (d, *J* = 4.8, 2H), 7.56 (t, *J* = 7.2, 1H), 7.41–7.35 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.73, 148.02, 145.47, 137.13, 132.52 (q, *J* = 32.8 Hz), 129.45, 127.02, 125.62, 123.65 (q, *J* = 273 Hz), 114.38, 114.23, 113.17 (d, *J* = 3.6 Hz), 111.09 (m), 55.37, 53.29, 25.15. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.16. **HRMS** (ESI), $[C_{23}H_{20}F_6N_2O + H]$+ calcd. 445.1558, found (*m*/*z*) 445.1542.

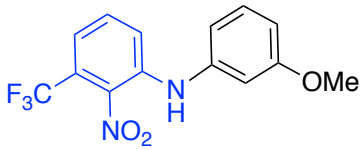
The following compounds were targets in the direct literature comparison study.

2-Methoxy-4-nitro-N-phenylaniline (35)[14]



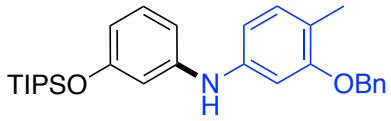
Both coupling partners were obtained via commercial venders. Compound **35** was obtained following general reaction set-up protocol without co-solvent and work-up procedure (**A**). Orange solid, yield 54 mg (89% on 0.25 mmol scale) R_f 0.34 (1:4, EtOAc/hexanes). Analytical data were in agreement with the literature.[14]

***N*-(3-Methoxyphenyl)-2-nitro-3-(trifluoromethyl)aniline (36)[15]**



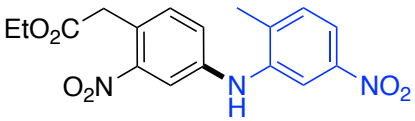
Both coupling partners were obtained via commercial venders. Compound **36** was obtained following general reaction set-up protocol without co-solvent and work-up procedure (**A**). Orange solid, yield 56 mg (72% on 0.25 mmol scale) R_f 0.33 (1:9, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 8.6, 1.1 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.22 (d, J = 7.7 Hz, 1H), 6.78 – 6.68 (m, 3H), 3.82 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.02, 140.65, 139.46, 136.32, 132.00, 130.70, 125.57 (q, J = 33 Hz), 122.42 (q, J = 274 Hz), 121.83, 118.16 (q, J = 5.5 Hz), 114.38, 110.39, 108.07, 55.48; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -59.75. **HRMS** (EI), $[C_{14}H_{11}F_3N_2O_3]^+$ calcd. 312.0722, found (*m*/*z*) 312.0726.

3-(Benzyloxy)-4-methyl-N-(3-((triisopropylsilyl)oxy)phenyl)aniline (37)[16]



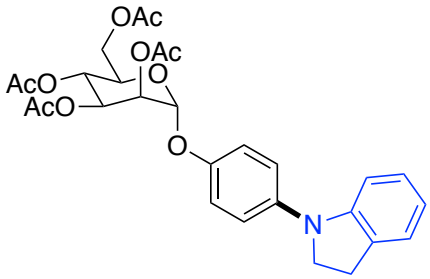
The bromide used for this coupling, (3-bromophenoxy)triisopropylsilane, was prepared following a literature procedure.[17] The amino component, 3-(benzyloxy)-4-methylaniline, was prepared following literature protocol.[18] The general reaction set-up protocol was followed with 3000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf with 20 v/v% 1,4-dioxane as organic co-solvent. K_3PO_4•H_2O (0.50 mmol, 2.0 equiv.) was used as base for this coupling. The reaction was run at 45 ºC for 20 h. Work-up procedure (**A**) was then followed. Viscous oil, yield 92 mg (80% on 0.25 mmol scale) R_f 0.44 (1:9, EtOAc/hexanes). Spectral data were in agreement with the literature.[16]

Ethyl 2-(4-((2-methyl-5-nitrophenyl)amino)-2-nitrophenyl)acetate (38)[19]



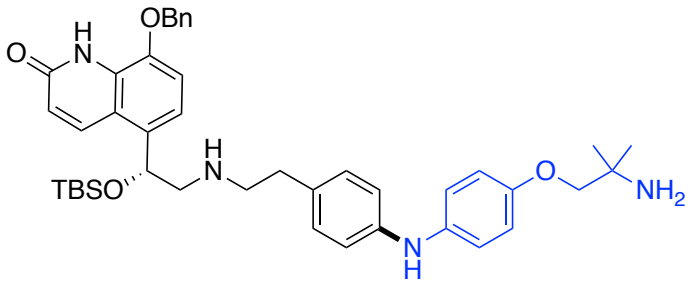
Both coupling partners were obtained via commercial venders. The general reaction set-up protocol was followed with 3000 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf (0.30 mol %) with 20 v/v% 1,4-dioxane as organic co-solvent. The reaction was run at 35 ºC for 24 h. Work-up procedure (C) was then followed. Off-white solid, yield 58 mg (80% on 0.25 mmol scale). R_f 0.16 (1:4, EtOAc/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, J = 2.3 Hz, 1H), 7.83 (dd, J = 8.4, 2.3 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.36 (dd, J = 8.3, 0.9 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.19 (dd, J = 8.3, 2.5 Hz, 1H), 5.95 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.94 (s, 2H), 2.34 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.65, 149.59, 147.34, 143.25, 140.87, 136.57, 134.51, 131.91, 122.32, 121.81, 117.87, 113.98, 113.47, 61.42, 39.31, 18.30, 14.28. **HRMS** (ESI), $[C_{17}H_{17}N_3O_6 + Na]^+$ calcd. 382.1015 , found (*m*/*z*) 382.1021.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-(4-(indolin-1-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (39)[20]



The bromide coupling partner, (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(acetoxymethyl)-6-(4-bromophenoxy)-tetrahydro-2H-pyran-3,4,5-triyl triacetate, was prepared according to the general procedure on mannosylation of phenols via a literature procedure.[20] The general reaction set-up was followed with 0.75 mol % (7500 ppm) [*t*-BuXPhos(Pd-π-cinnamyl)]OTf with 20 v/v% 1,4-dioxane as organic co-solvent. Reaction was run at 45 ºC for 40 h. Work-up procedure (A) was then followed. Off-white solid, yield 76 mg (70% on 0.20 mmol scale). R_f 0.27 (3:7, EtOAc/hexanes). Spectral data were in agreement with the literature.[20]

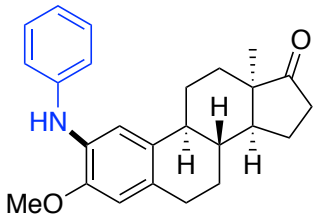
(*R*)-5-(2-((4-((4-(2-Amino-2-methylpropoxy)phenyl)amino)phenethyl)amino)-1-((*t*-butyldimethylsilyl)oxy)ethyl)-8-(benzyloxy)quinolin-2(1H)-one (40)[21-24]



The bromide component for the reaction to make compound **40** used was (*R*)-8-(benzyloxy)-5-(2-((4-bromophenethyl)amino)-1-((*t*-butyldimethylsilyl)oxy)ethyl)quinolin-2(1*H*)-one, hydrochloride salt of which was previously described in a patent.[22] The free-base form of this compound was used in the coupling. The amino component for the reaction to make compound **40** was 4-(2-amino-2-methyl-propoxy)-phenylamine hydrochloride (1.25 equiv), synthesis of

which was previously described in a patent.[11] The general reaction set-up protocol was followed with 0.60 mol % (6000 ppm) [*t*-BuXPhos(Pd-cinnamyl)]OTf. Excess K_3PO_4•H_2O (0.50 mmol, 2.5 equiv) was employed together with 20 v/v% 1,4-dioxane as organic co-solvent. Reaction was run at 45 ºC for 28 h. Work-up procedure (**A**) was then followed. Viscous oil, yield 90 mg (64% on 0.20 mmol scale). R_f 0.18 (5:1:94, MeOH/Et_3N/EtOAc). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.16 (bs, 1H), 8.28 (d, *J* = 9.9 Hz, 1H), 7.45 – 7.36 (m, 5H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.06 – 7.00 (m, 4H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.89 – 6.80 (m, 4H), 6.65 (d, *J* = 9.9 Hz, 1H), 5.45 (s, 1H), 5.15 (s, 3H), 3.67 (s, 2H), 3.00 – 2.64 (m, 6H), 1.23 (s, 6H), 0.82 (s, 9H), 0.02 (s, 3H), -0.21 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.50, 154.65, 144.02, 143.41, 137.52, 136.42, 135.61, 132.44, 130.98, 129.60, 129.34, 128.94, 128.77, 128.06, 122.08, 121.58, 120.93, 117.40, 116.33, 115.56, 110.77, 78.21, 73.46, 71.15, 58.18, 51.18, 50.21, 35.60, 27.30, 25.89, 18.21, -4.54, -4.92.; **HRMS** (ESI), $[C_{42}H_{54}N_4O_4Si + H]^+$ calcd 707.3992 , found (*m/z*) 707.3998.

(8*R*,9*S*,13*R*,14*S*)-3-Methoxy-13-methyl-2-(phenylamino)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (42)[25]



The bromide coupling partner, (8*R*,9*S*,13*R*,14*S*)-2-bromo-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (**41**), was prepared following a literature protocol.[26] The general reaction set-up protocol was followed with 2500 ppm [*t*-BuXPhos(Pd-π-cinnamyl)]OTf with 20 v/v% 1,4-dioxane as organic co-solvent. Work-up procedure (**C**) was then followed and the filtered solid material was subjected to column chromatography to obtain analytically pure product. Off-white solid, yield 84 mg (89% on 0.25 mmol scale). R_f 0.25 (1:4, EtOAc/hexanes). Spectral data were in agreement with the literature.[25]

10. References

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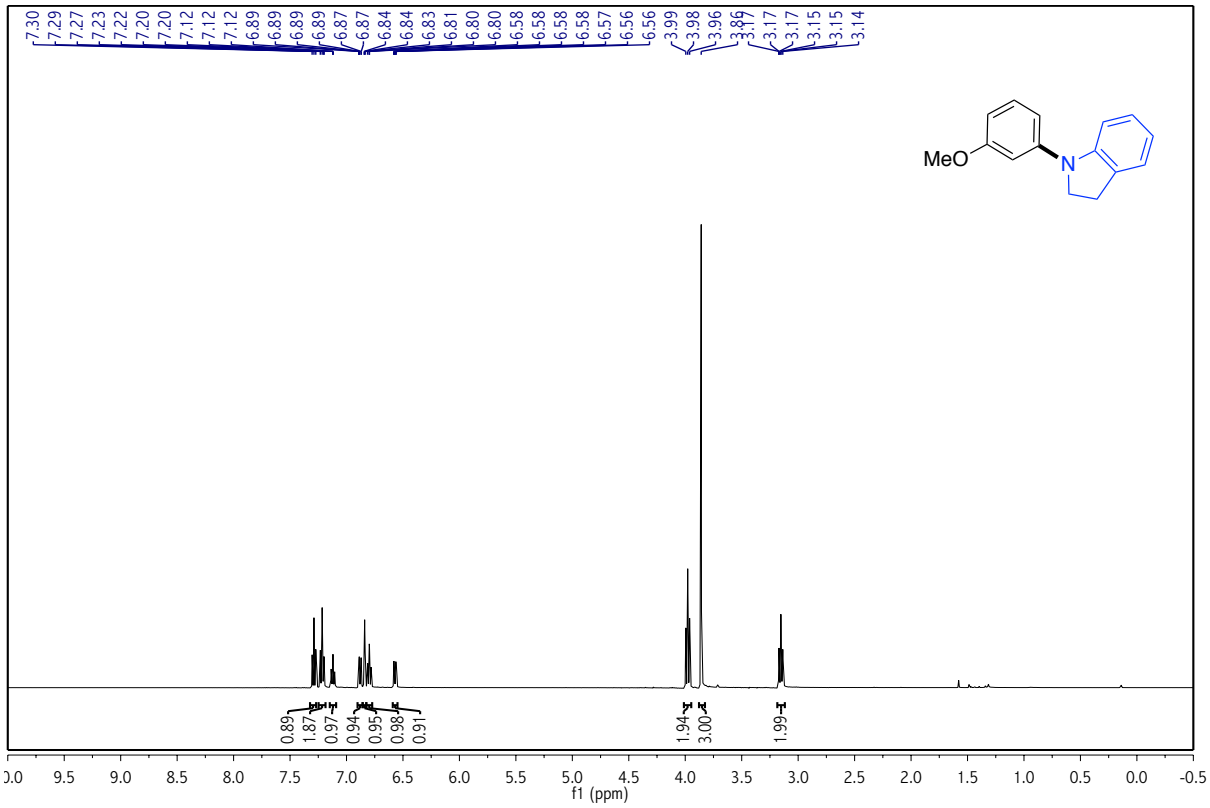
11. NMR Spectra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3.86
3.17
3.17
3.17
3.15
3.15
3.14
MeO
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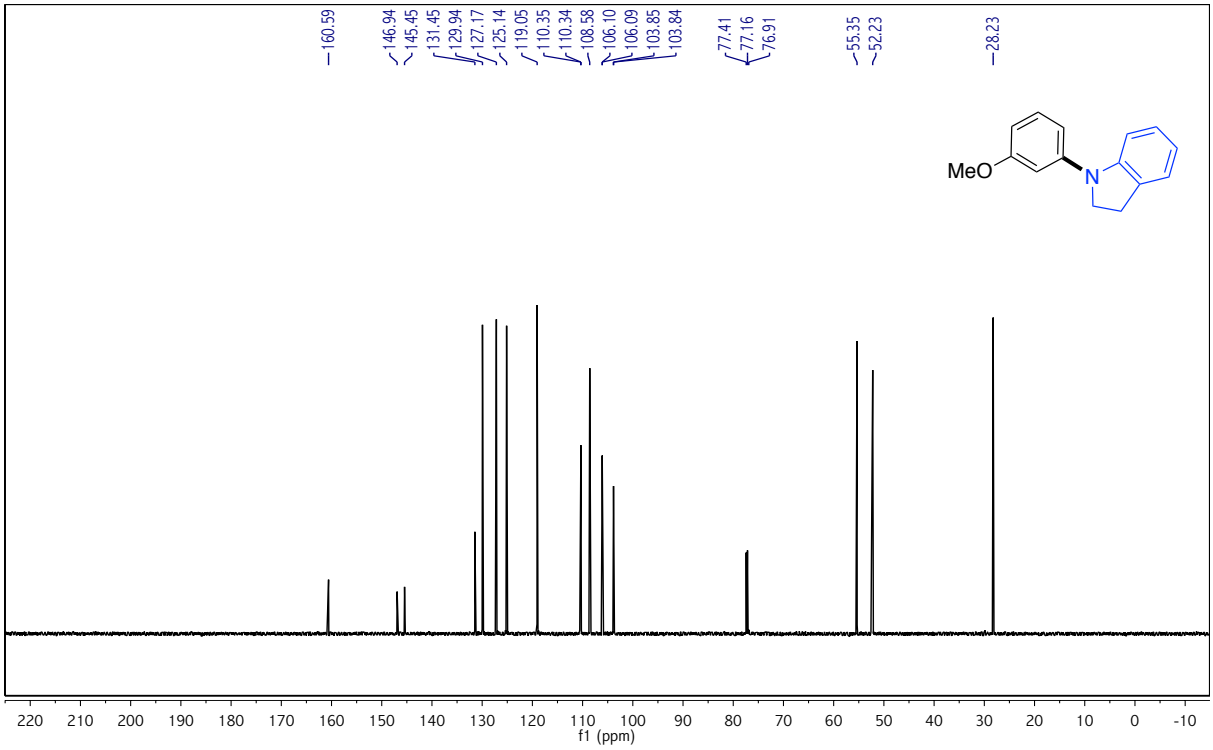
f1 (ppm)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52.23
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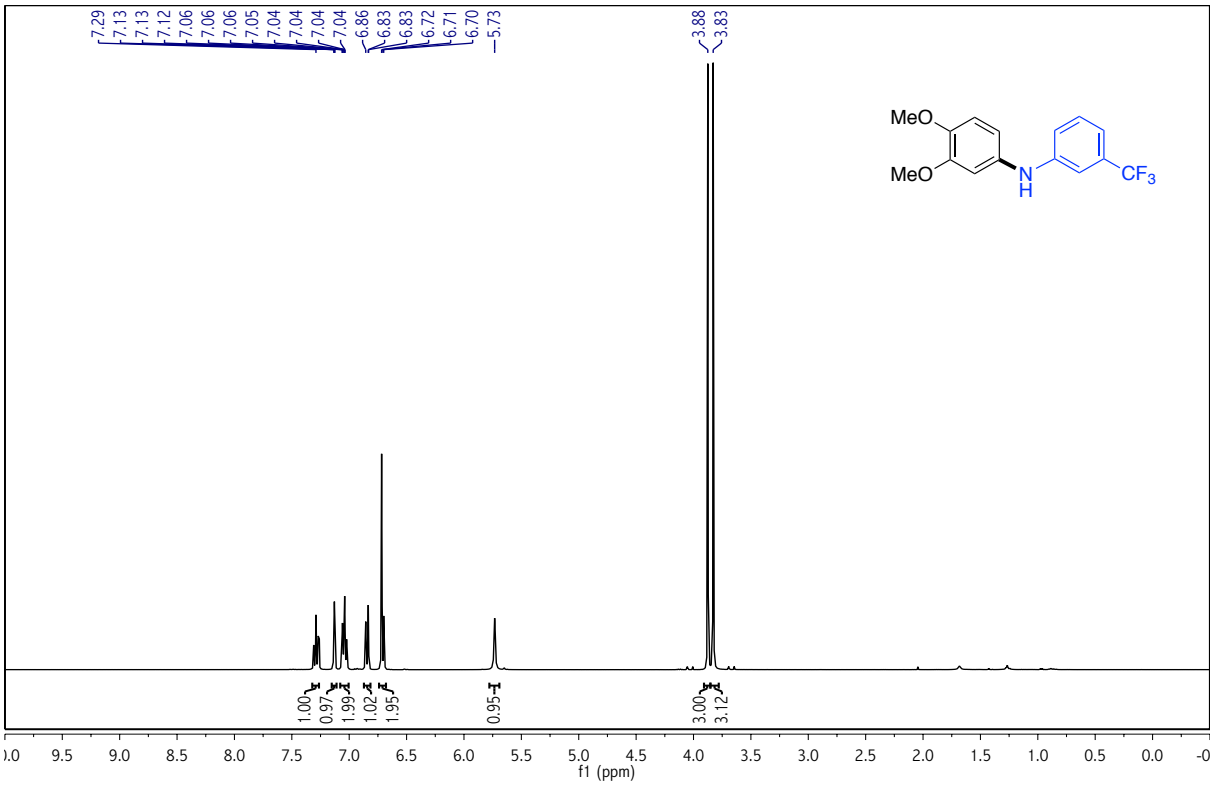
N
f1 (ppm)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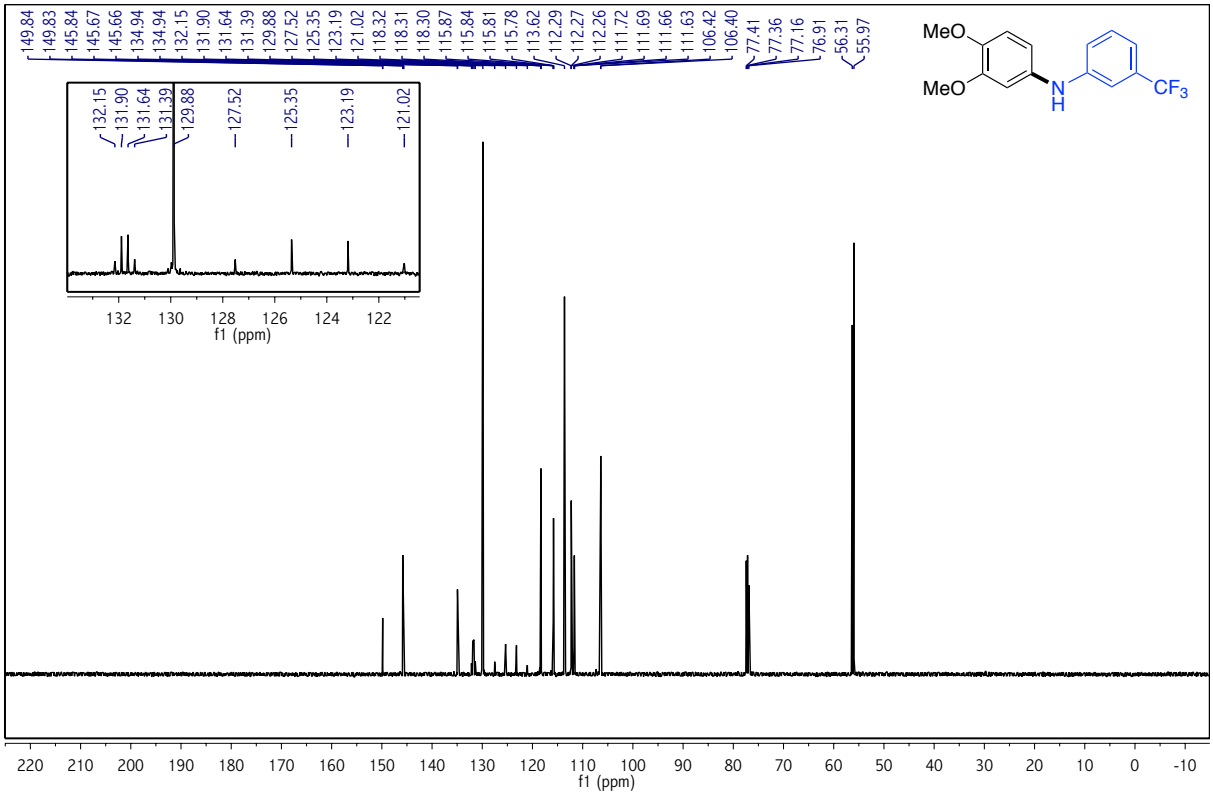
f1 (ppm)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N
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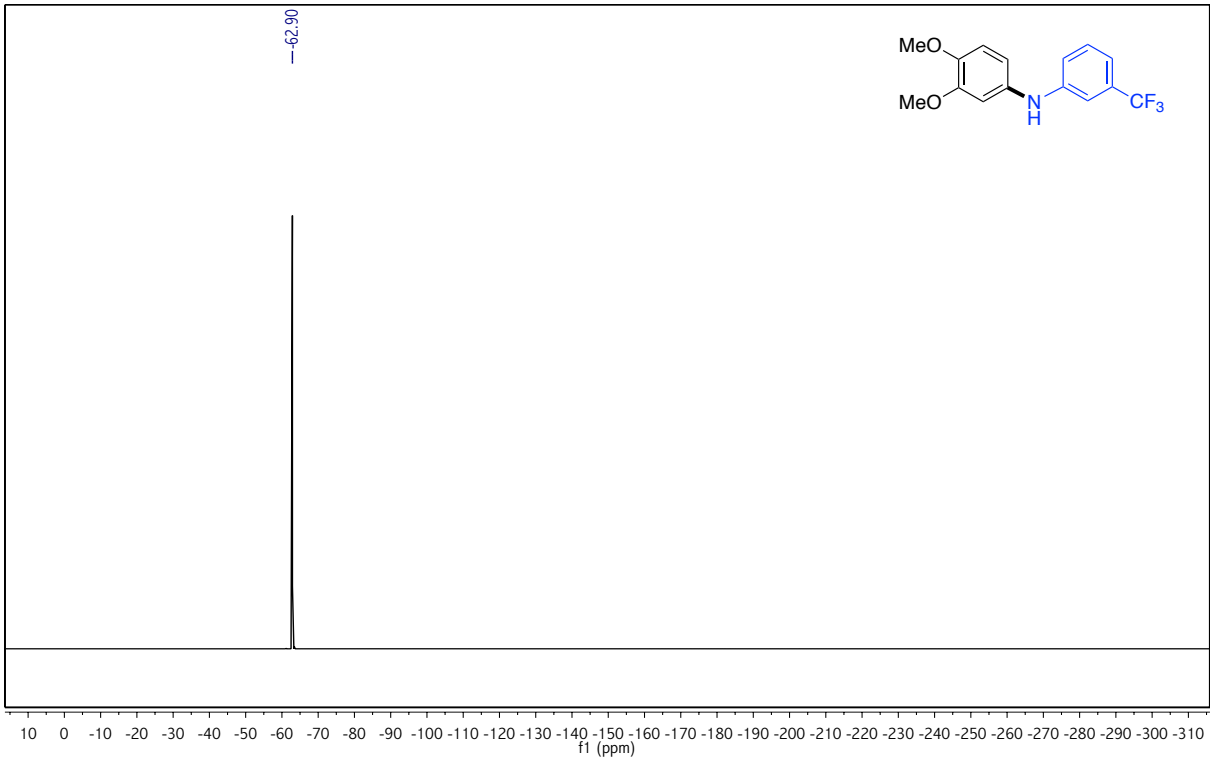
CF3
f1 (ppm)
f1 (ppm)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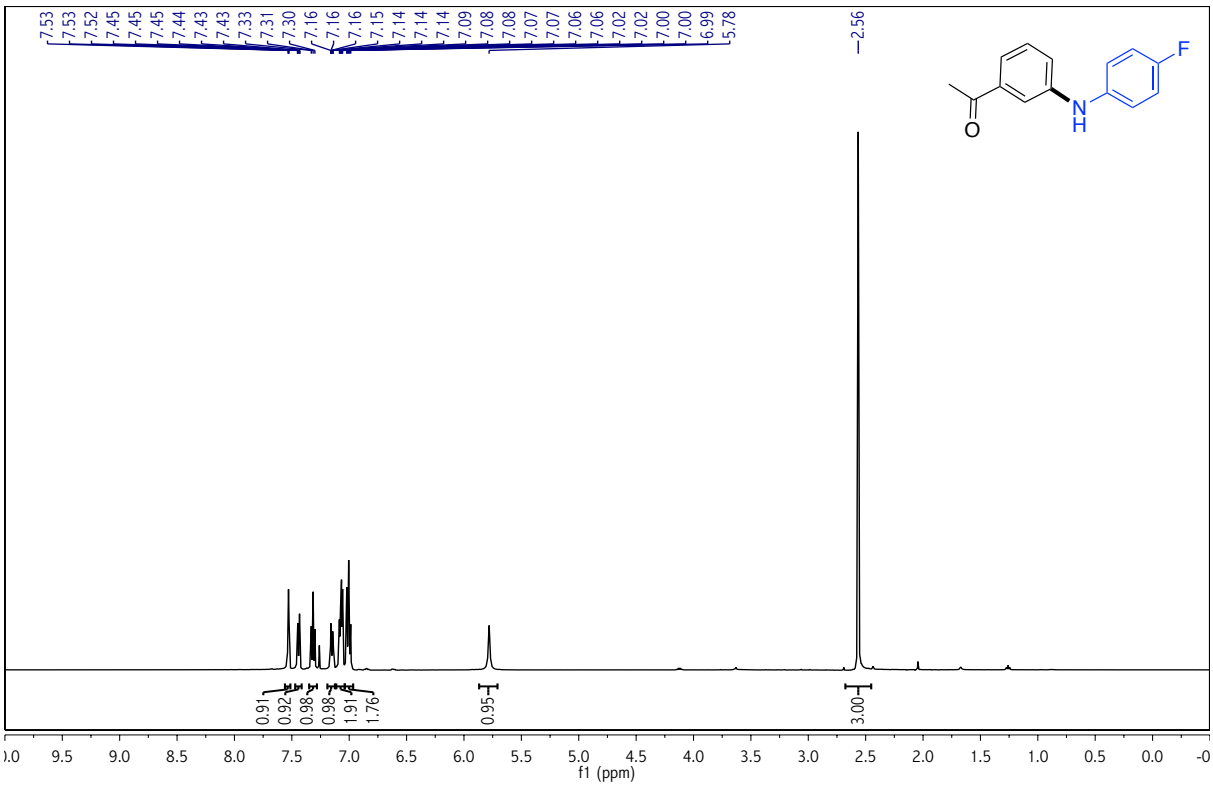
f1 (ppm)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2.56
F
N
H
O
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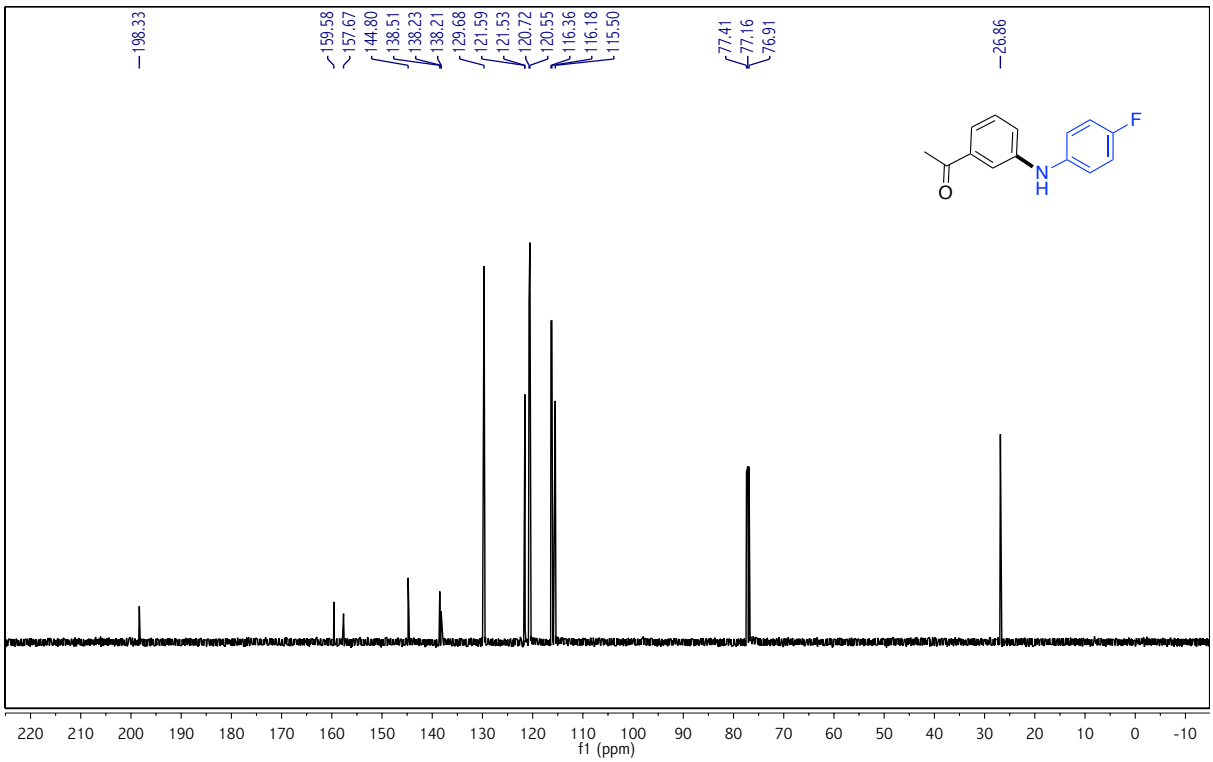
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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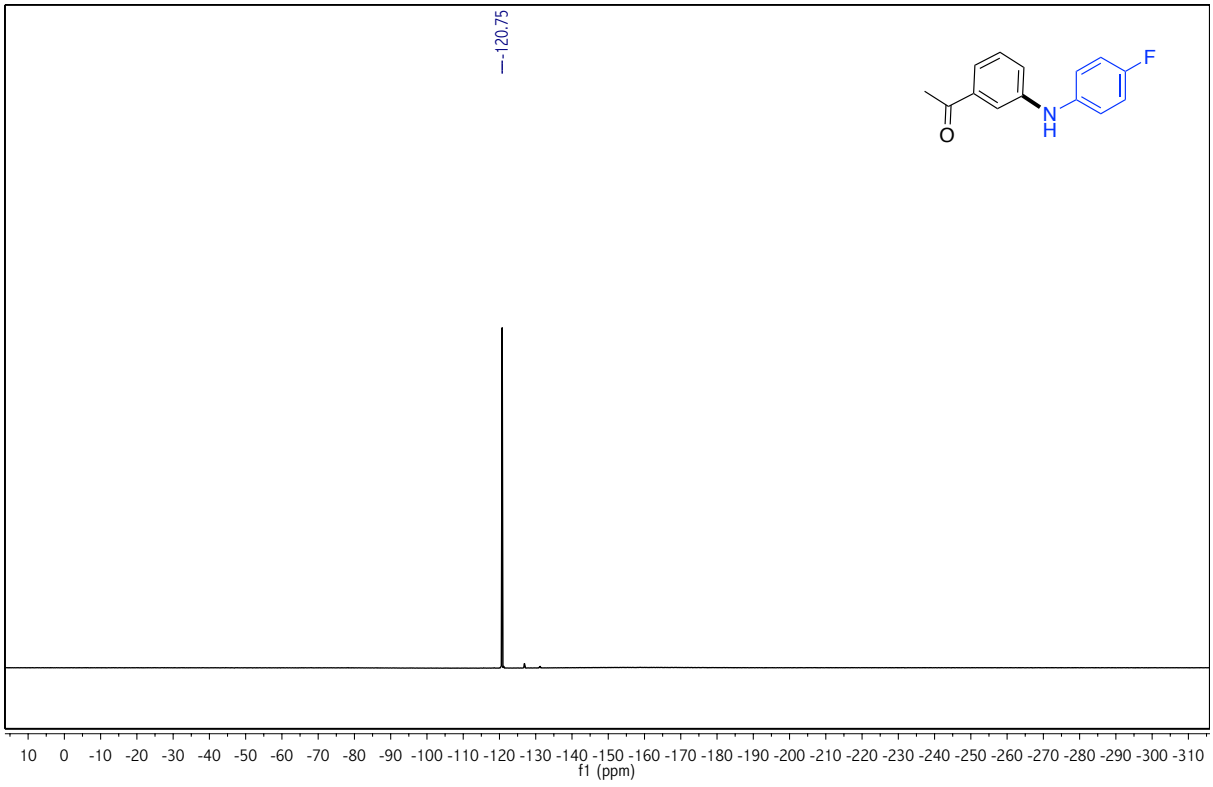
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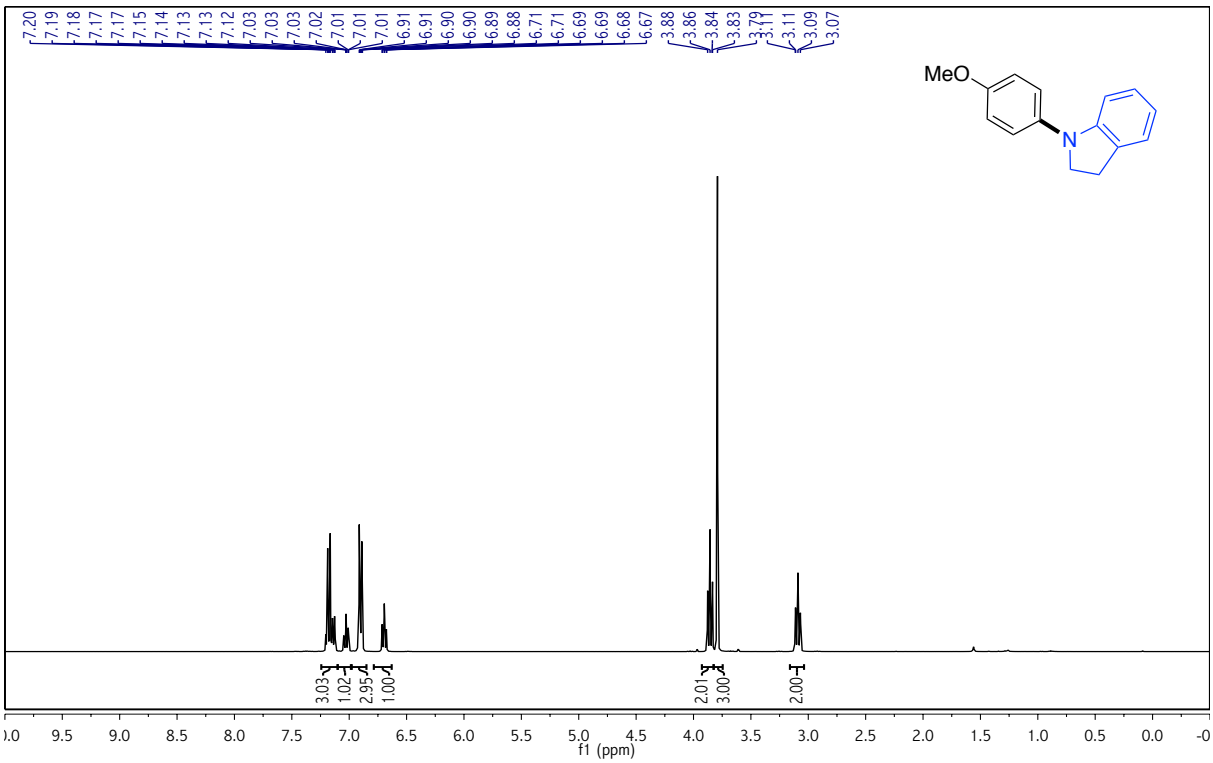
f1 (ppm)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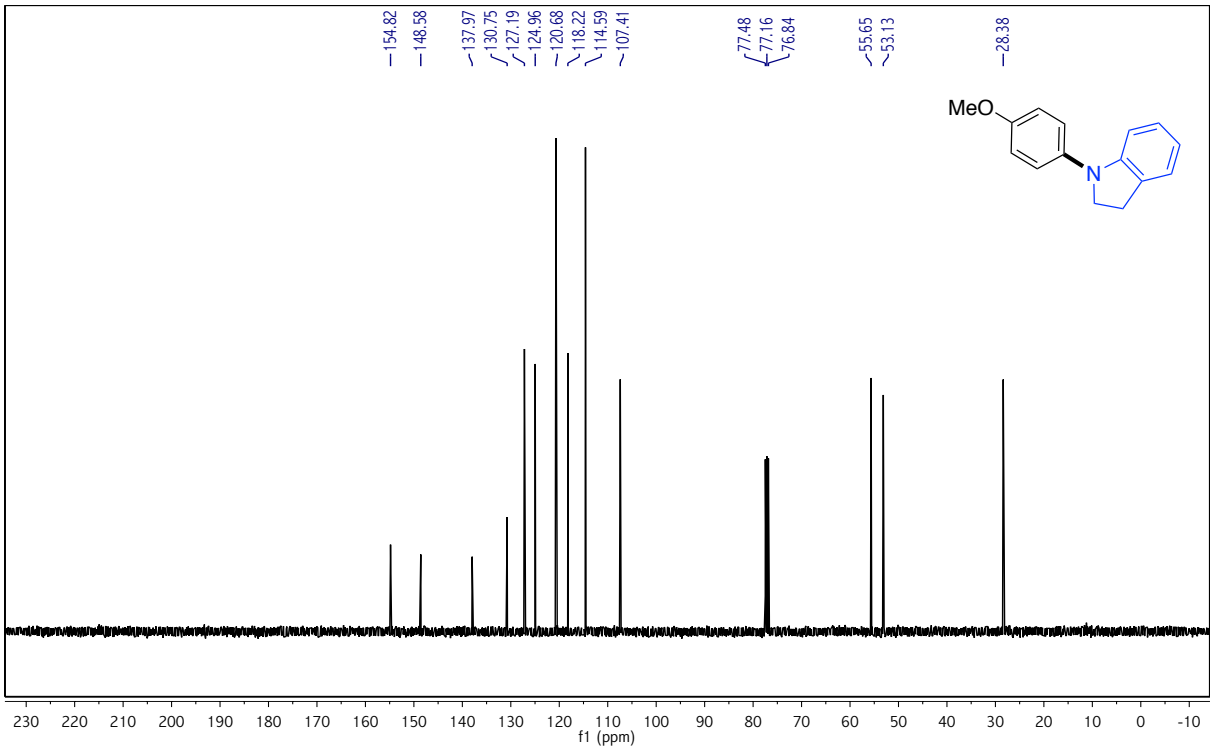
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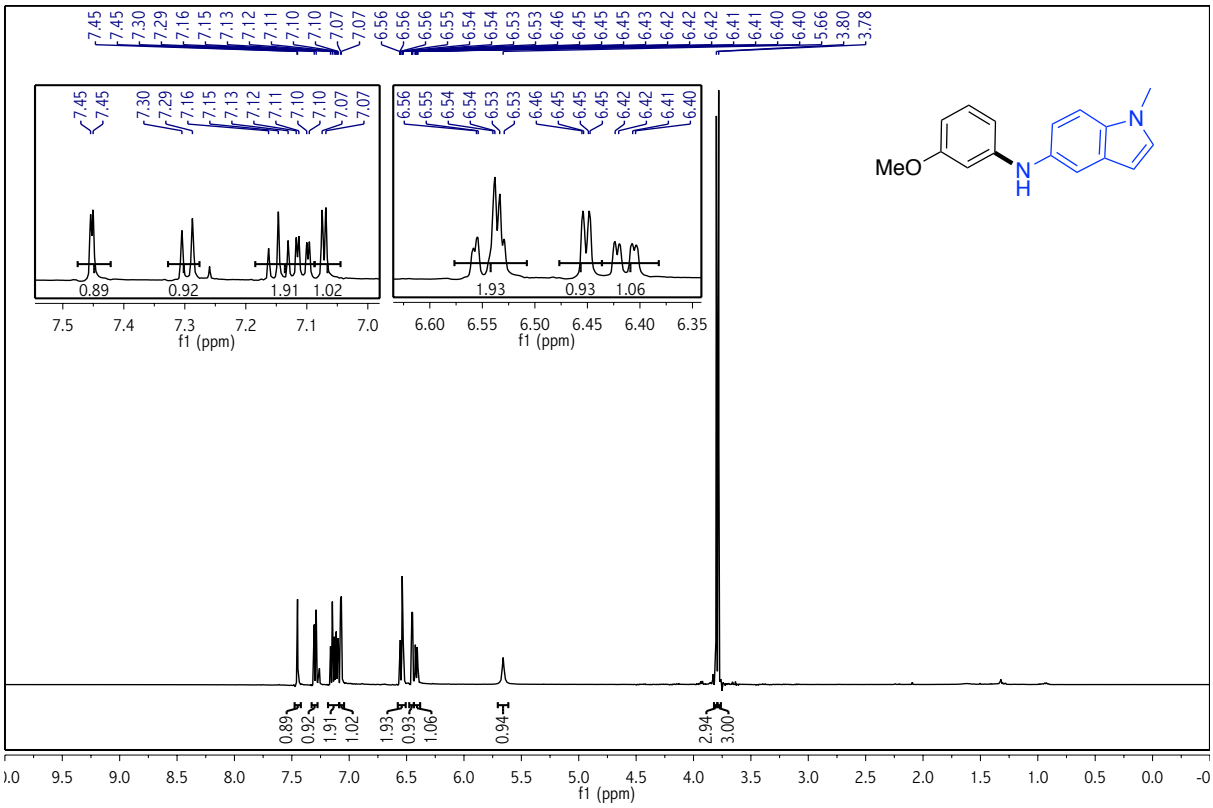
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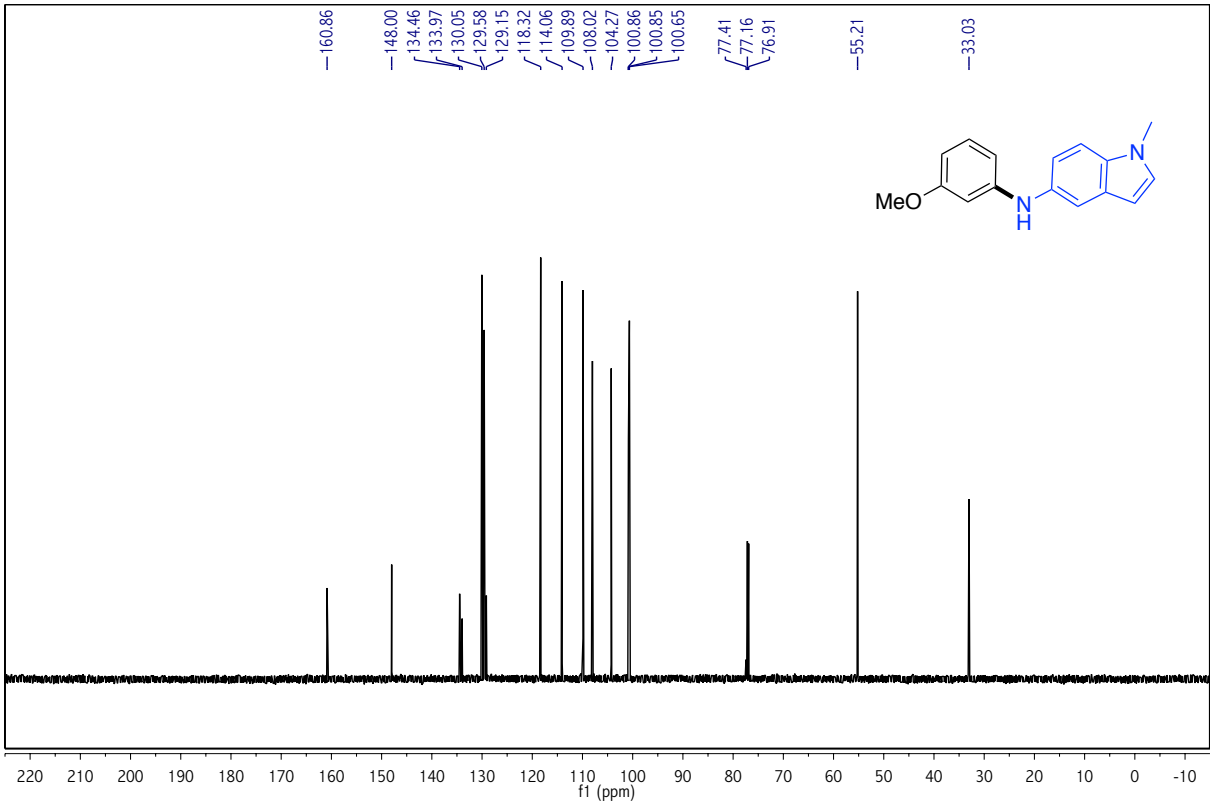
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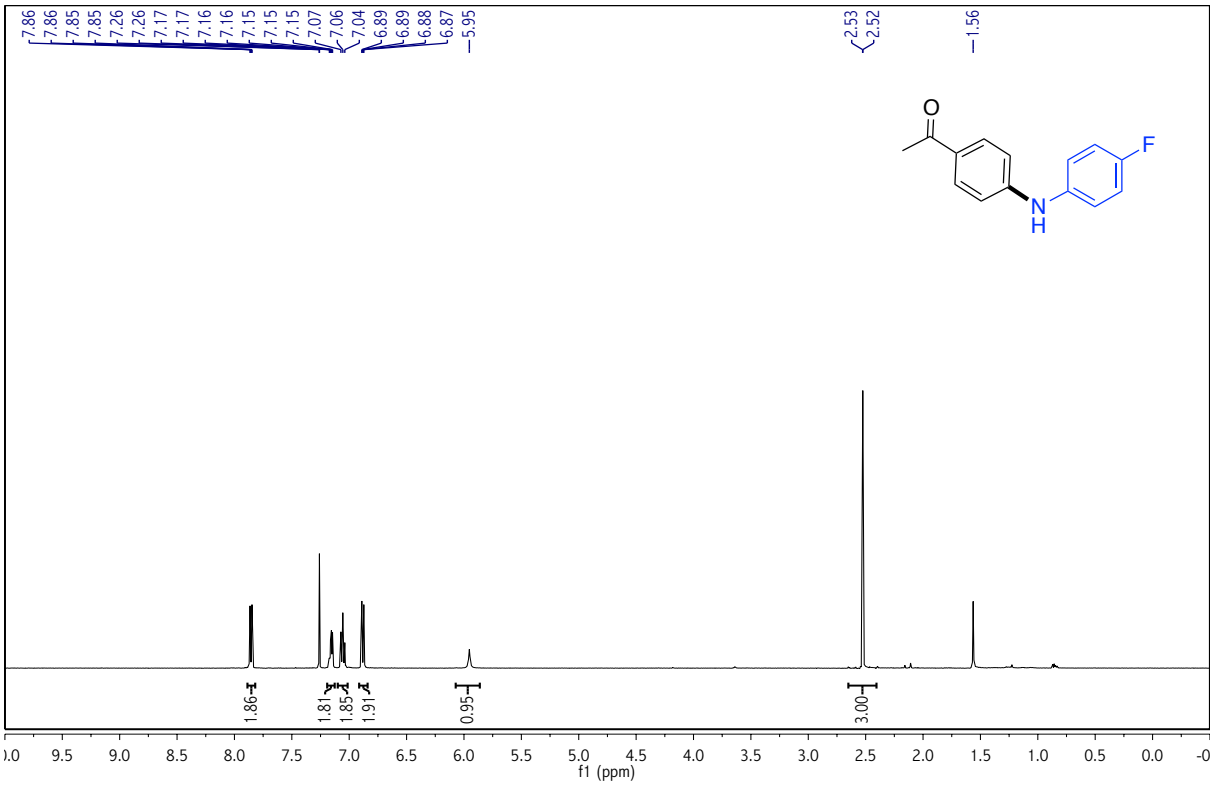
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7.06
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6.89
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N
H
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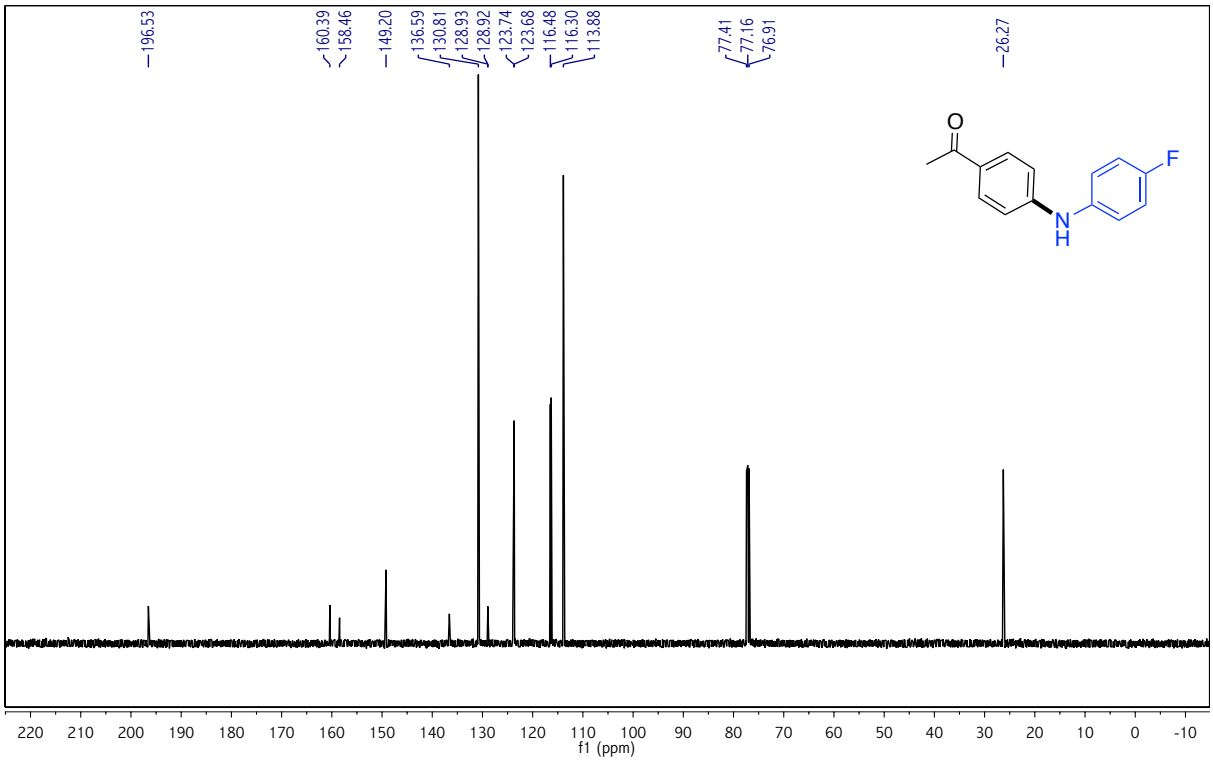
f1 (ppm)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N
H
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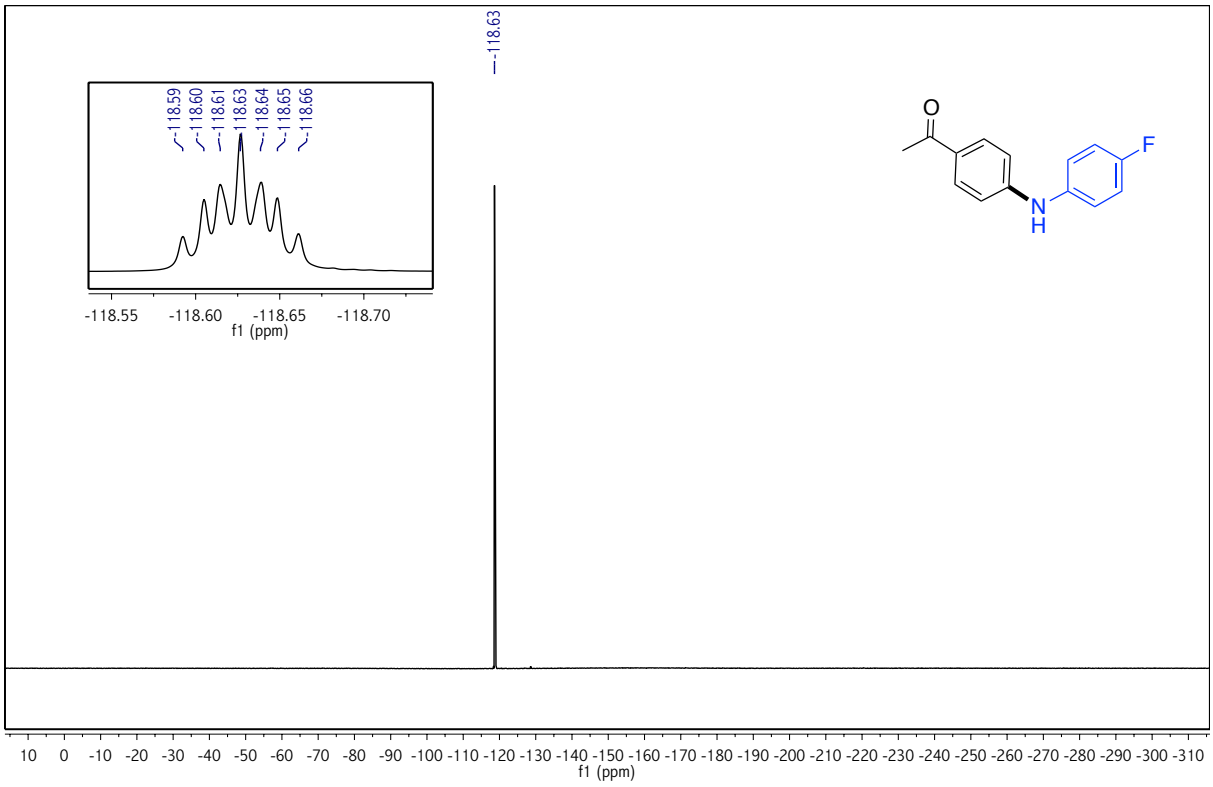
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F
N
H
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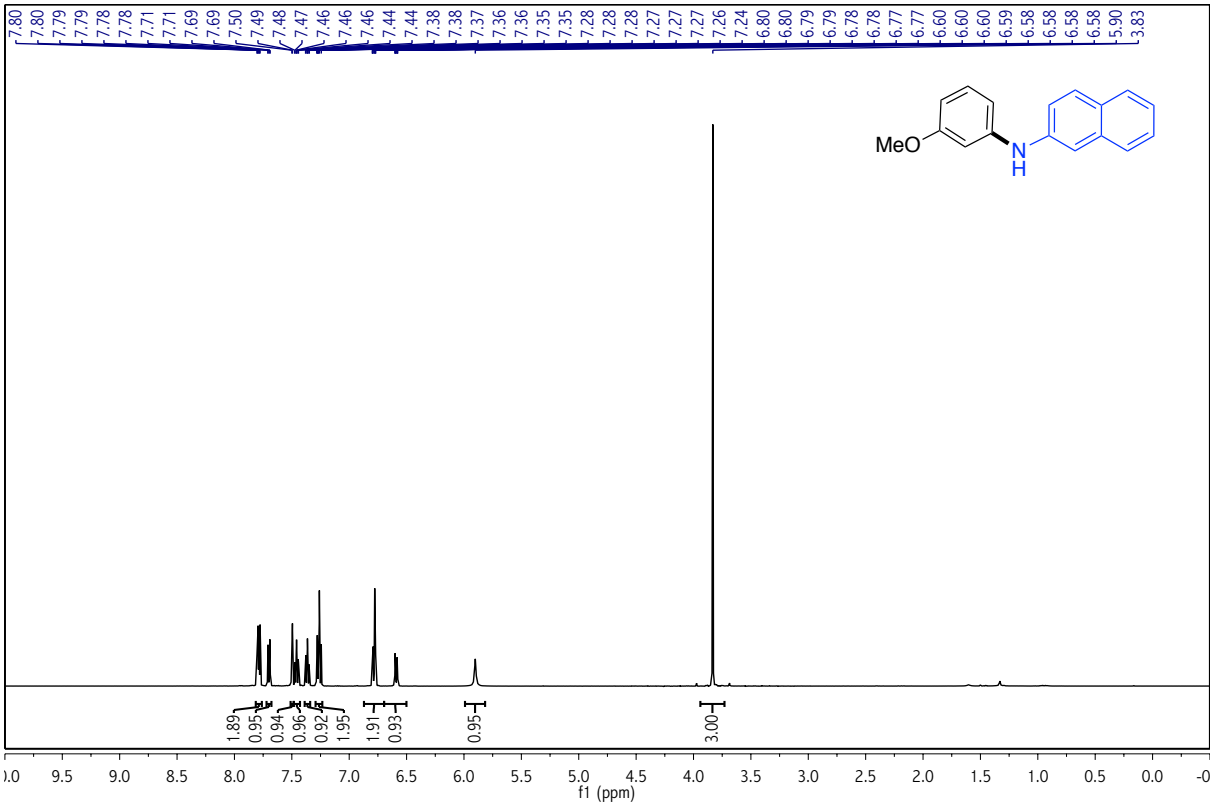
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H
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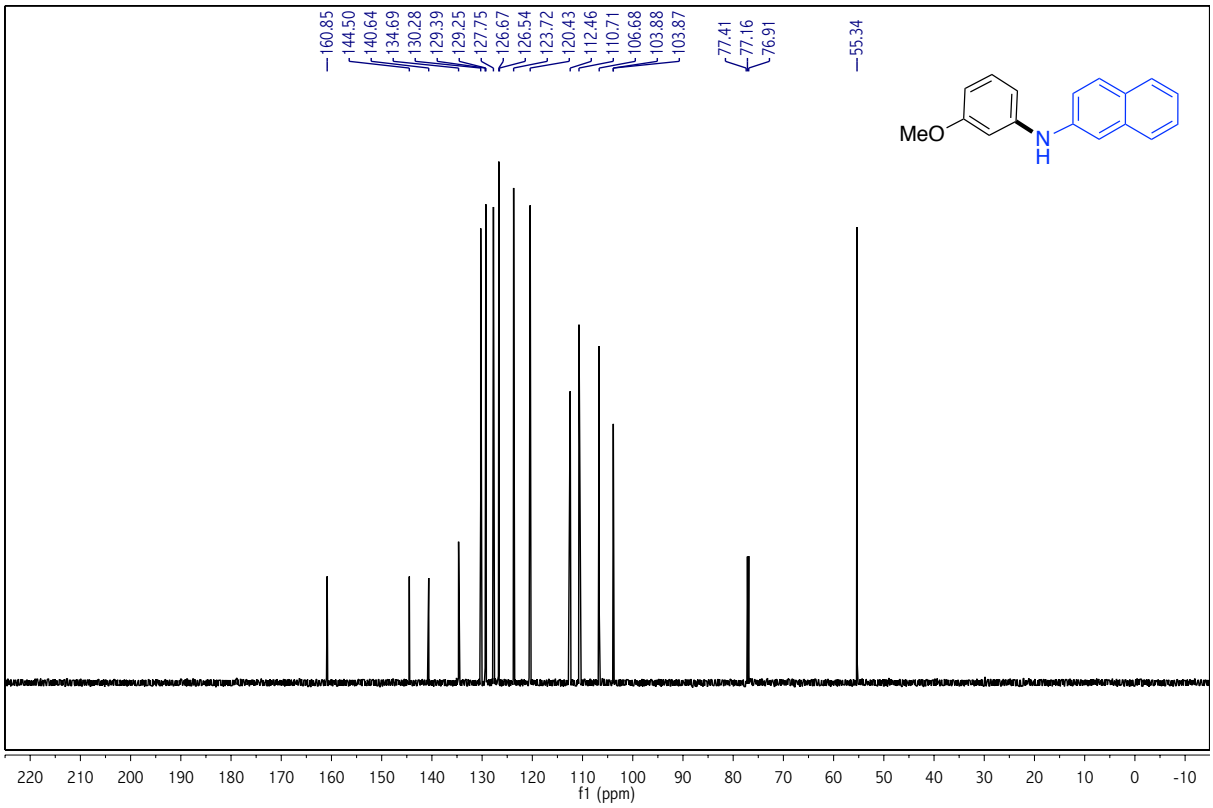
f1 (ppm)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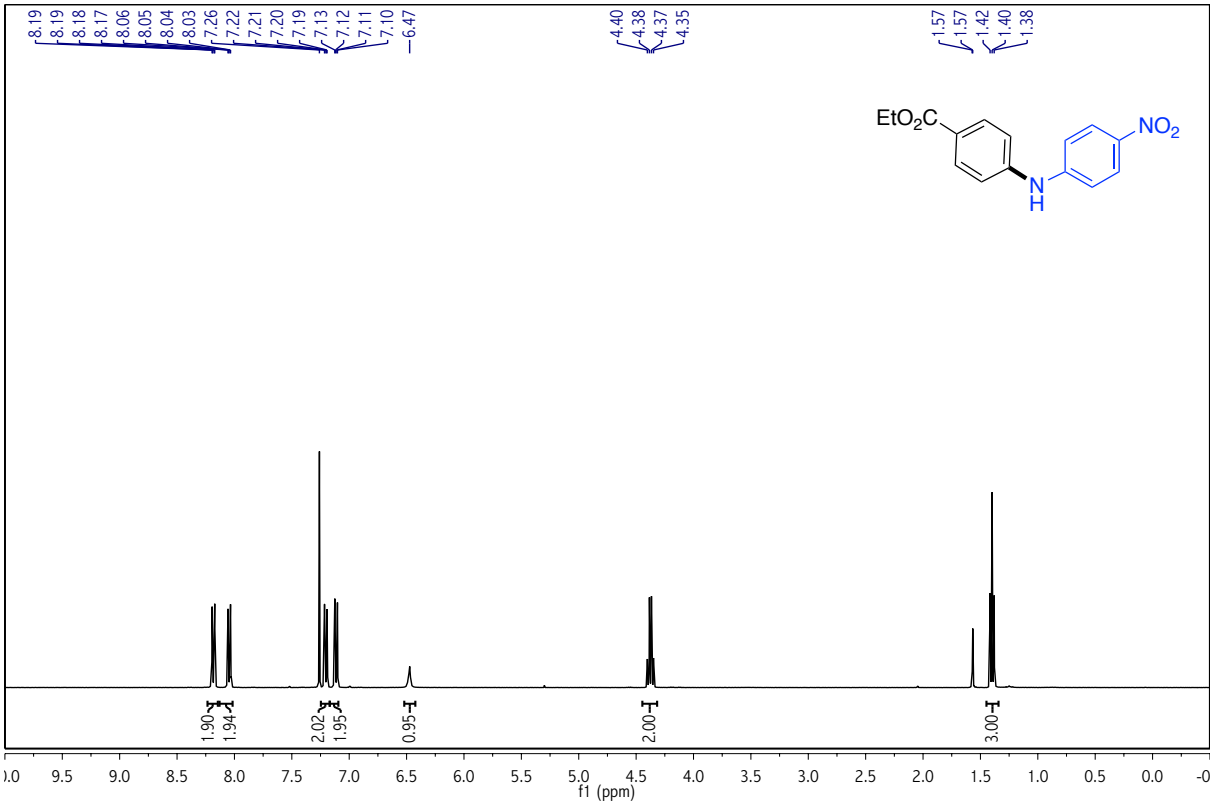
55.34
MeO
N
H
f1 (ppm)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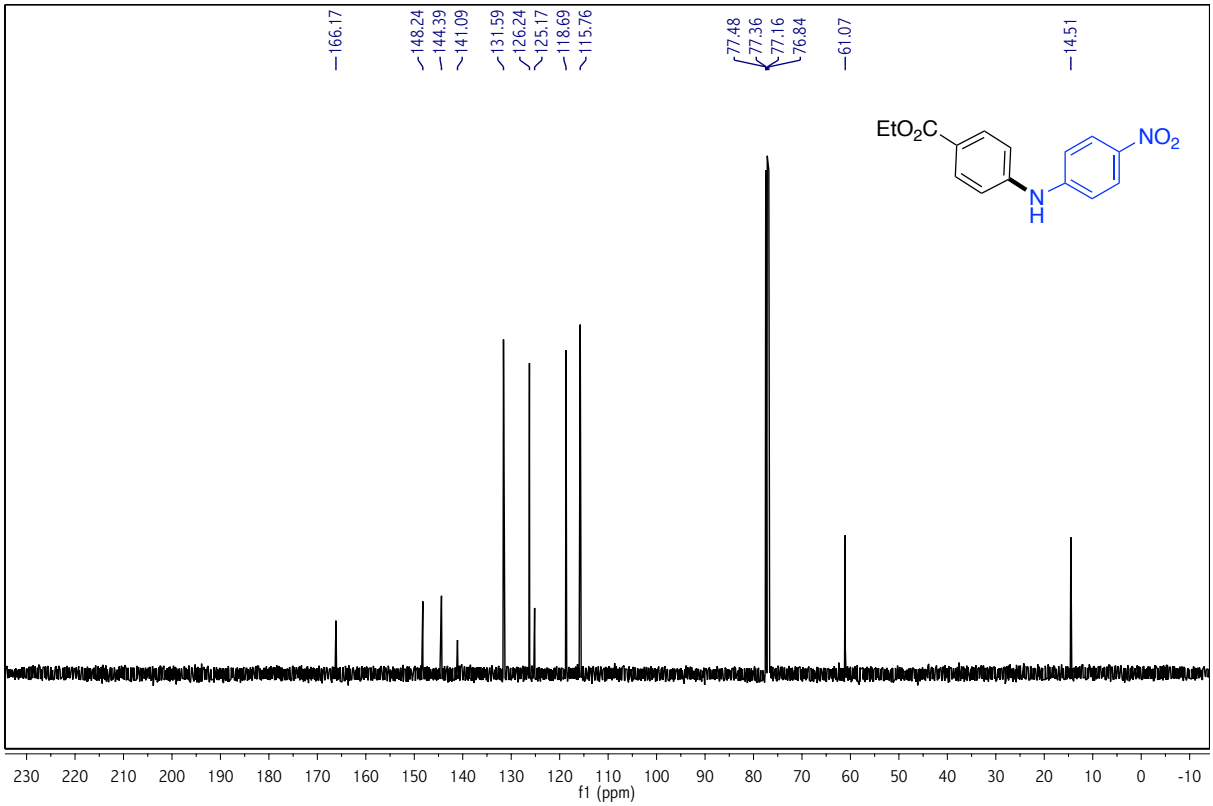
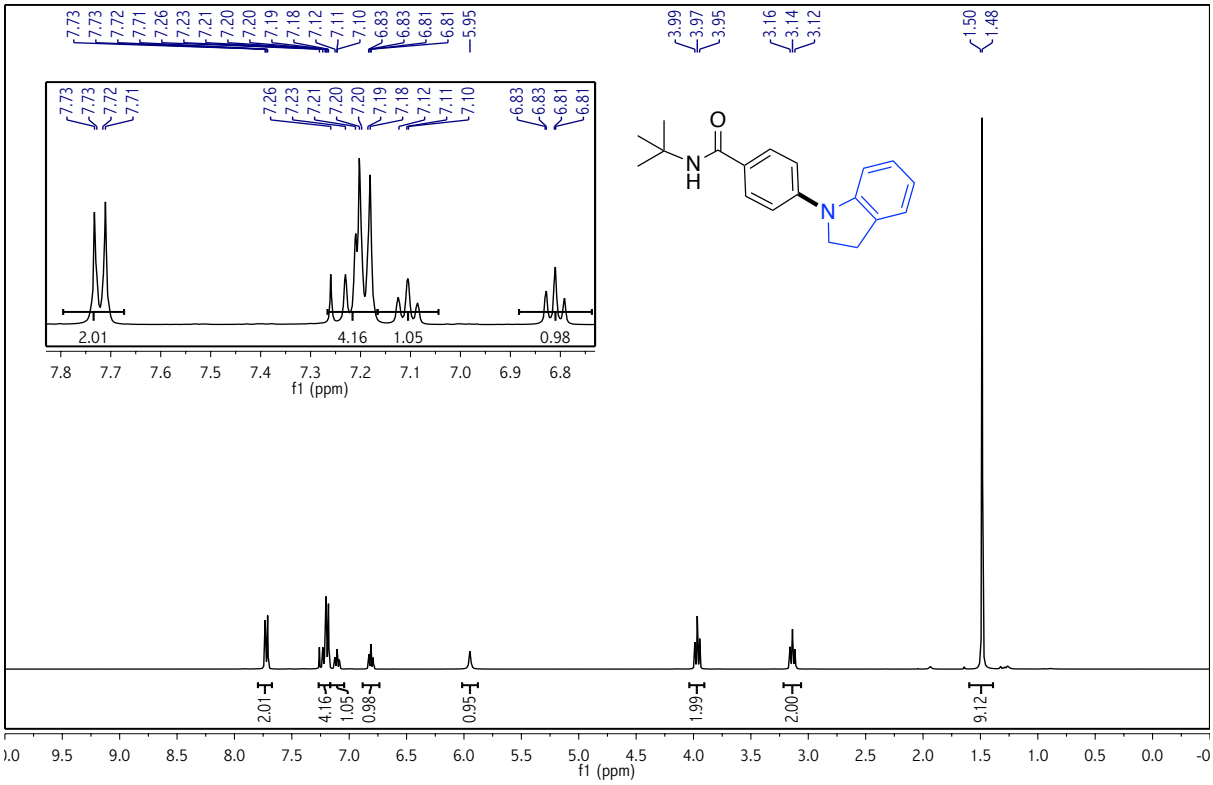
7.13
7.12
7.11
7.10
6.47
4.40
4.38
4.37
4.35
1.57
1.57
1.42
1.40
1.38
EtO2C
NO2
N
H
1.90
1.94
2.02
1.95
0.95
2.00
3.00
f1 (ppm)


166.17
148.24
144.39
141.09
131.59
126.24
125.17
118.69
115.76
77.48
77.36
77.16
76.84
61.07
14.51
EtO2C
NO2
N
H
f1 (ppm)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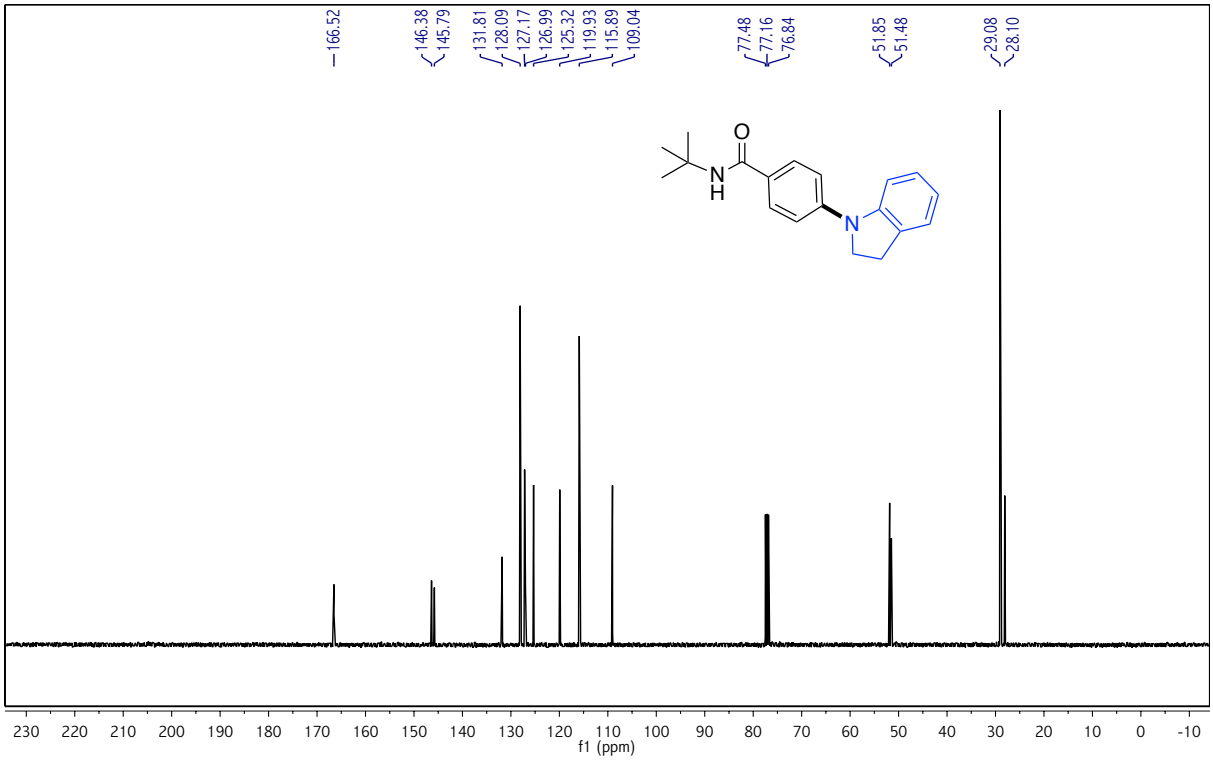
7.73
7.72
7.71
7.26
7.23
7.21
7.20
7.20
7.19
7.18
7.12
7.11
7.10
6.83
6.83
6.81
6.81
5.95
3.99
3.97
3.95
3.16
3.14
3.12
1.50
1.48
2.01
4.16
1.05
0.98
0.95
1.99
2.00
9.12
O
N
H
N
f1 (ppm)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125.32
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115.89
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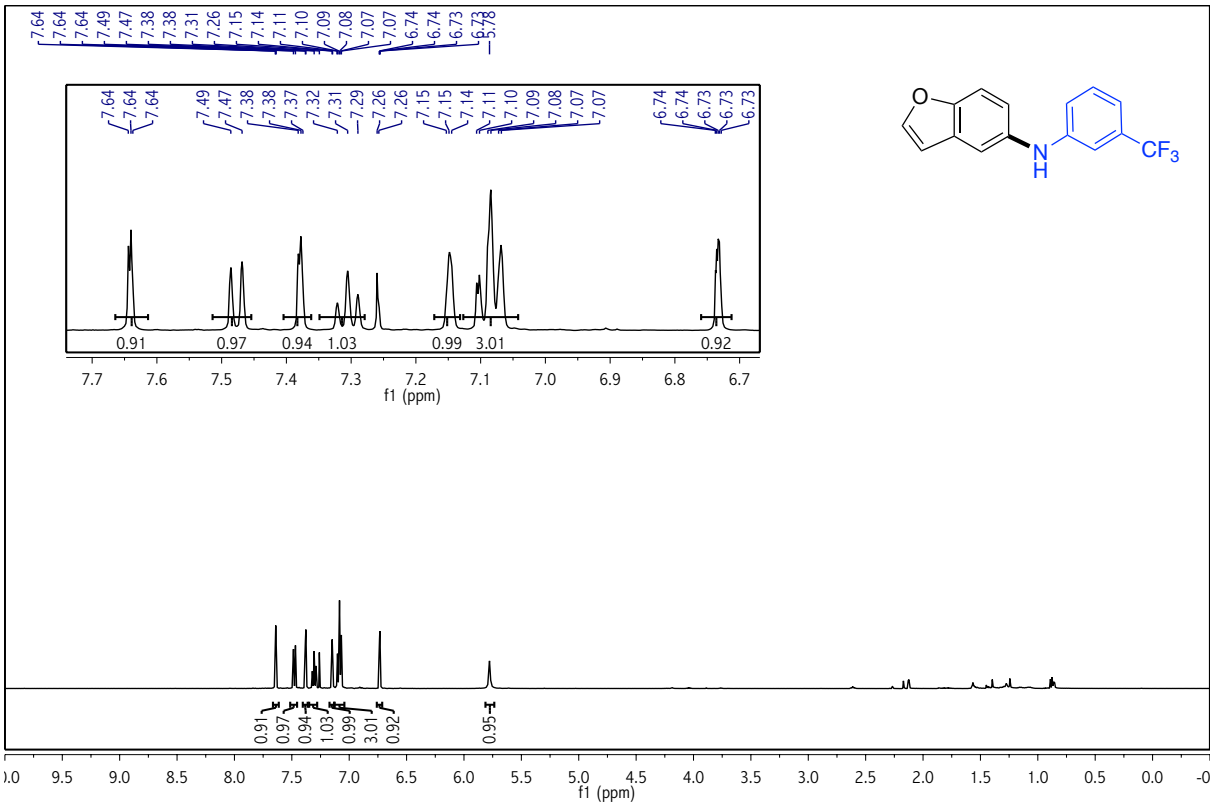
77.16
76.84
51.85
51.48
29.08
28.10
O
N
H
N
f1 (ppm)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7.64
7.64
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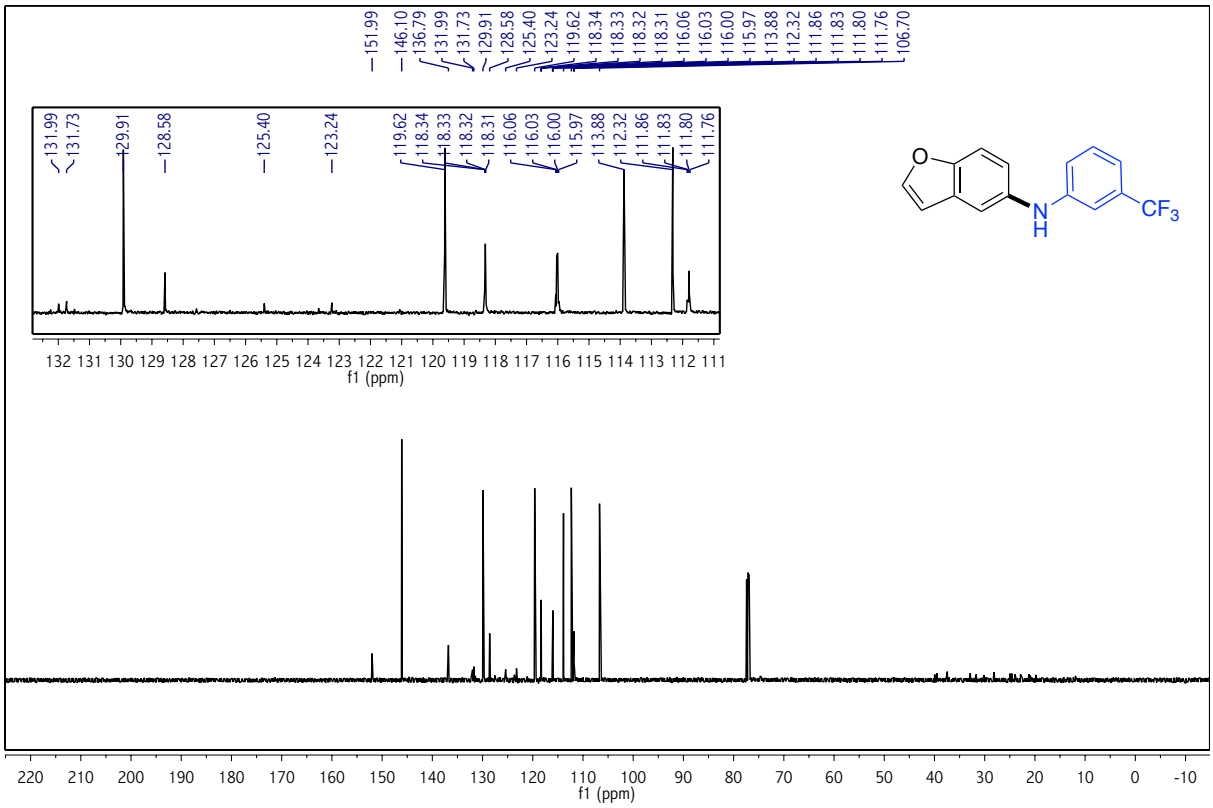
7.31
7.26
7.15
7.14
7.11
7.10
7.09
7.08
7.07
7.07
6.74
6.74
6.73
6.73
3.78
O
N
H
CF3
0.91
0.97
0.94
1.03
0.99
3.01
0.92
0.95
f1 (ppm)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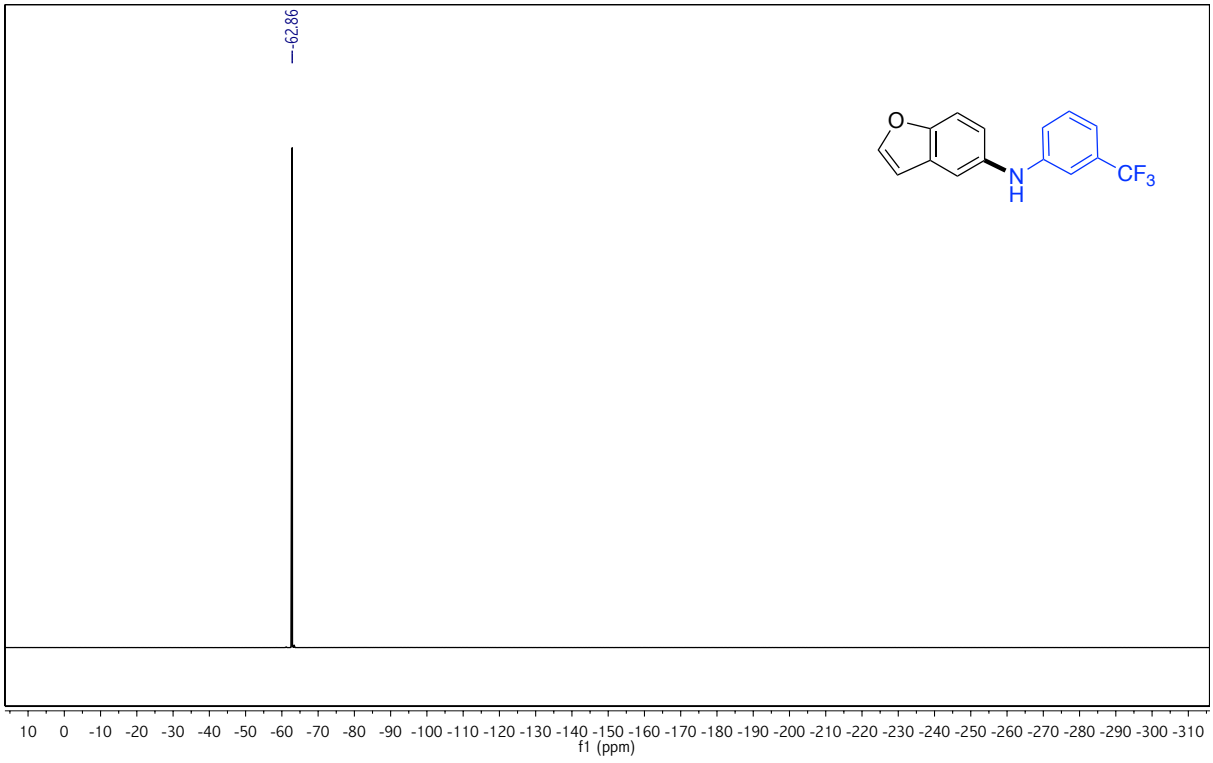
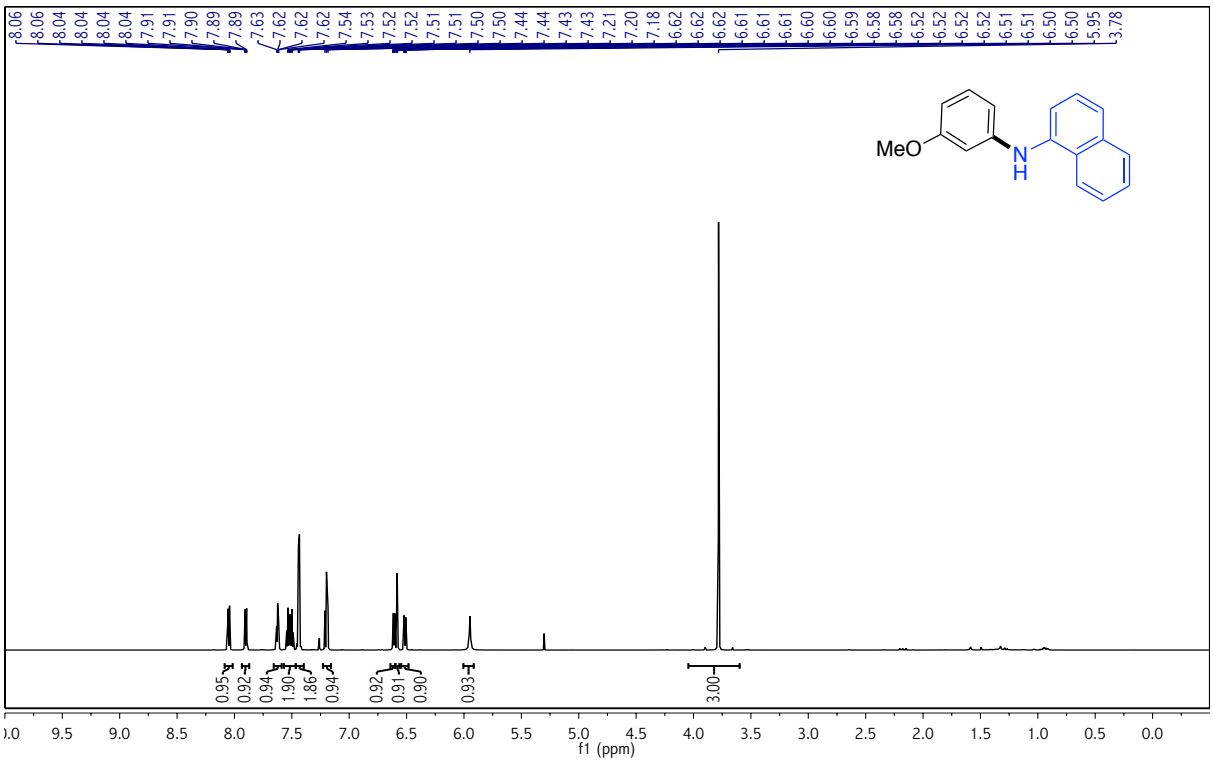
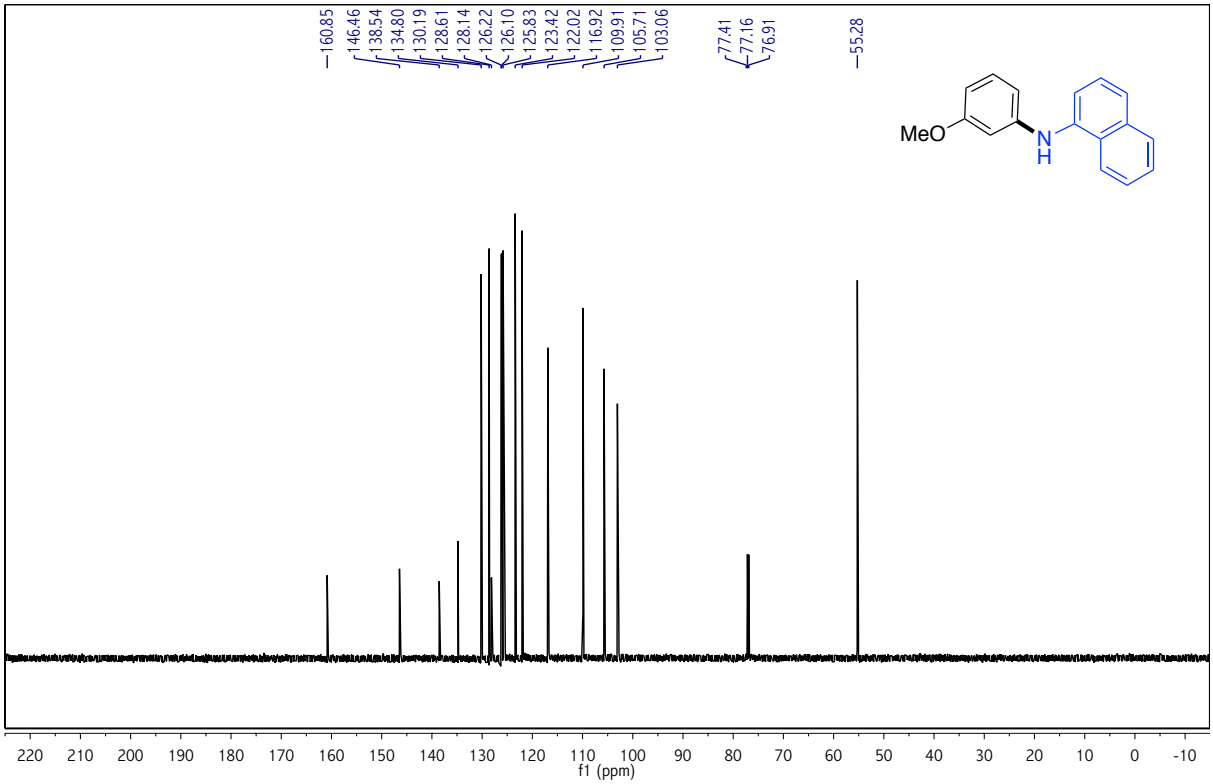
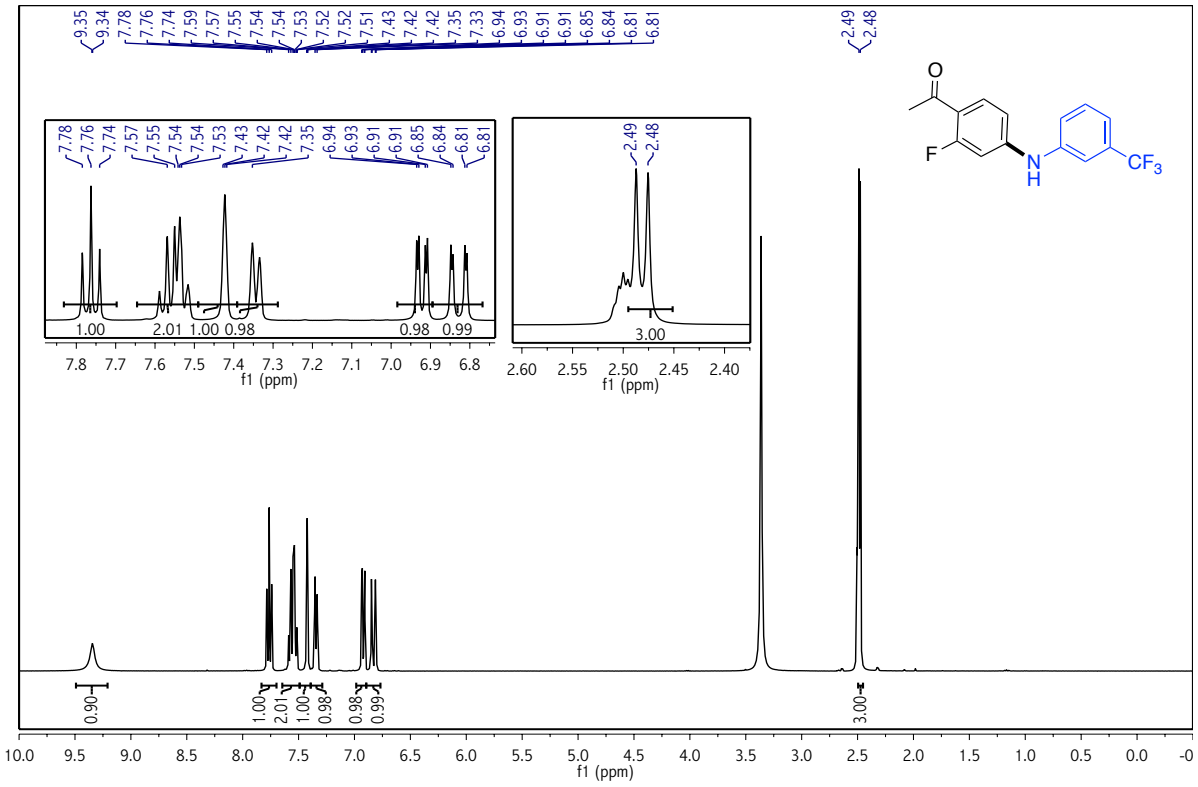
118.33
118.32
118.31
116.06
116.03
116.00
115.97
113.88
112.32
111.86
111.83
111.80
111.76
106.70
O
N
H
CF3
132 131 130 129 128 127 126 125 124 123 122 121 120 119 118 117 116 115 114 113 112 111
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-62.86
O
N
H
CF3
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300 -310
f1 (ppm)


8.06 8.06 8.04 8.04 8.04 8.04 8.04 7.91 7.91 7.90 7.89 7.89 7.63 7.62 7.62 7.62 7.54 7.53 7.52 7.52 7.51 7.51 7.50 7.50 7.44 7.44 7.43 7.43 7.21 7.20 7.18 6.62 6.62 6.62 6.61 6.61 6.61 6.61 6.60 6.60 6.59 6.58 6.58 6.52 6.52 6.52 6.52 6.51 6.51 6.50 6.50 5.95 3.78
MeO
N
H
0.95 0.92 0.94 1.90 1.86 0.94 0.92 0.91 0.90 0.93 3.00
f1 (ppm)


160.85 146.46 138.54 134.80 130.19 128.61 128.14 126.22 126.10 125.83 123.42 122.02 116.92 109.91 105.71 103.06
77.41 77.16 76.91
55.28
MeO
N
H
f1 (ppm)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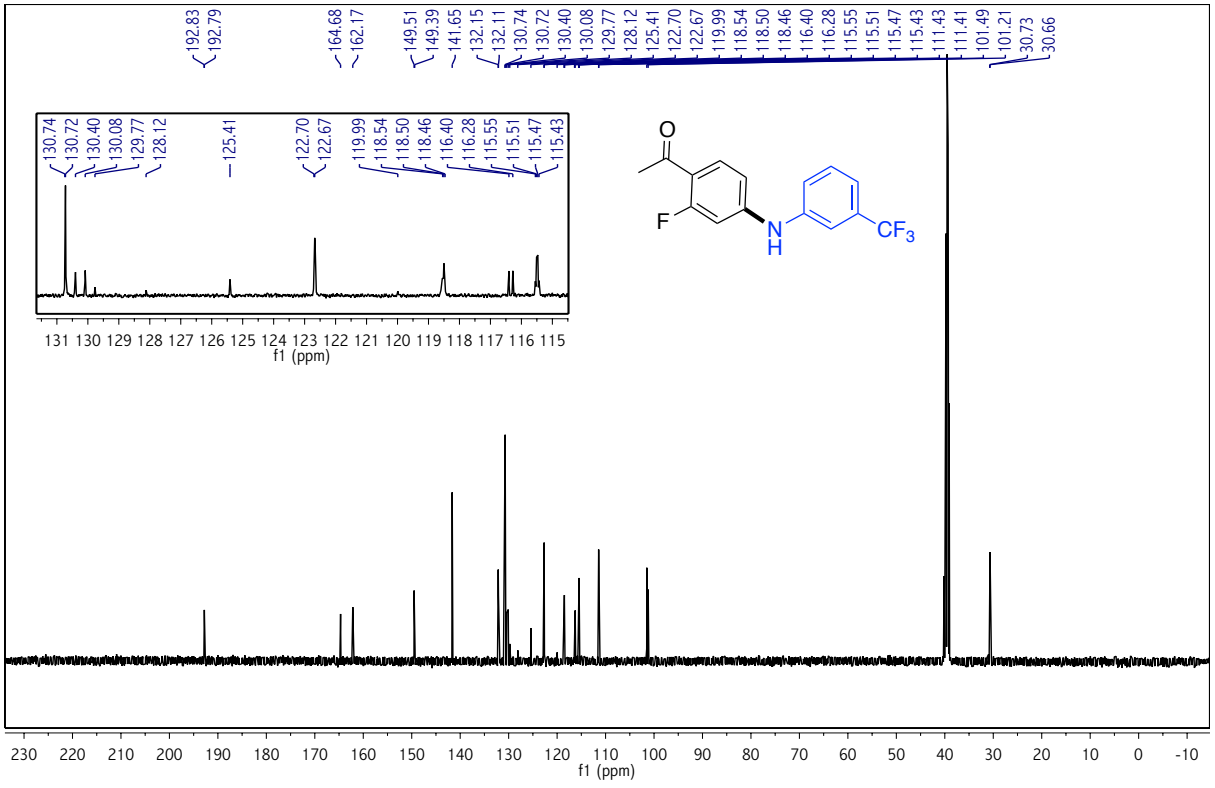
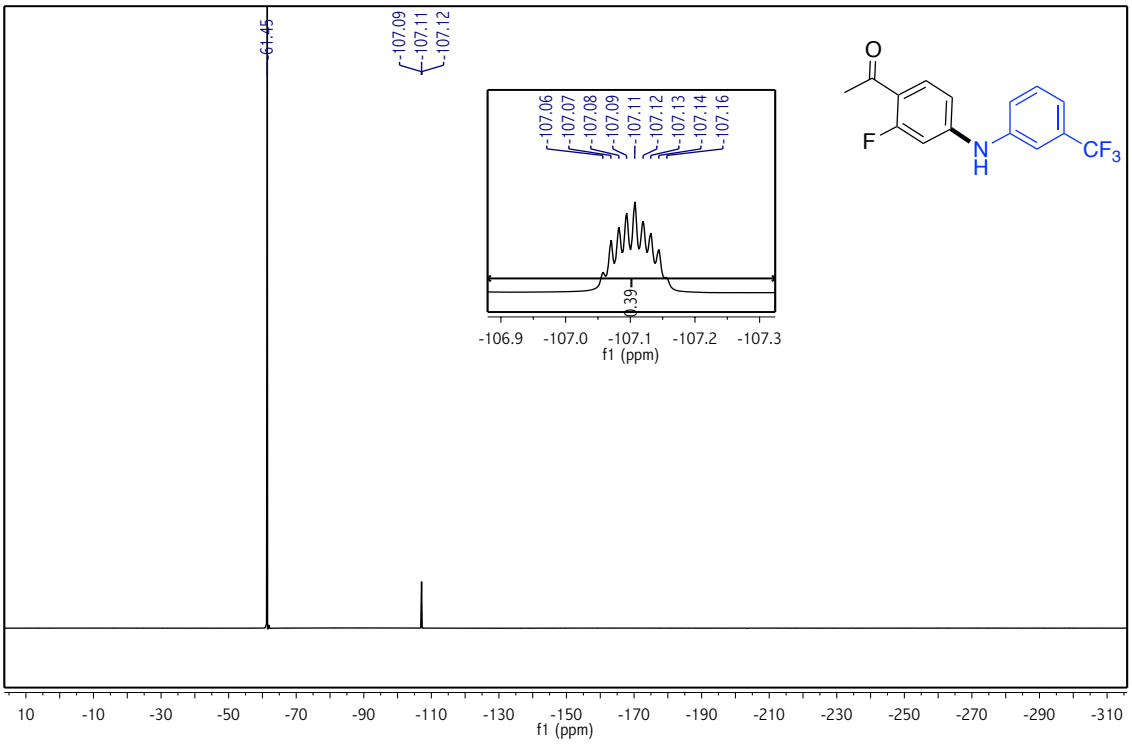

f1 (ppm)


-61.45
-107.09
-107.11
-107.12
-107.06
-107.07
-107.08
-107.09
-107.11
-107.12
-107.13
-107.14
-107.16
0.39
-106.9
-107.0
-107.1
-107.2
-107.3
f1 (ppm)
O
F
N
H
CF3
10
-10
-30
-50
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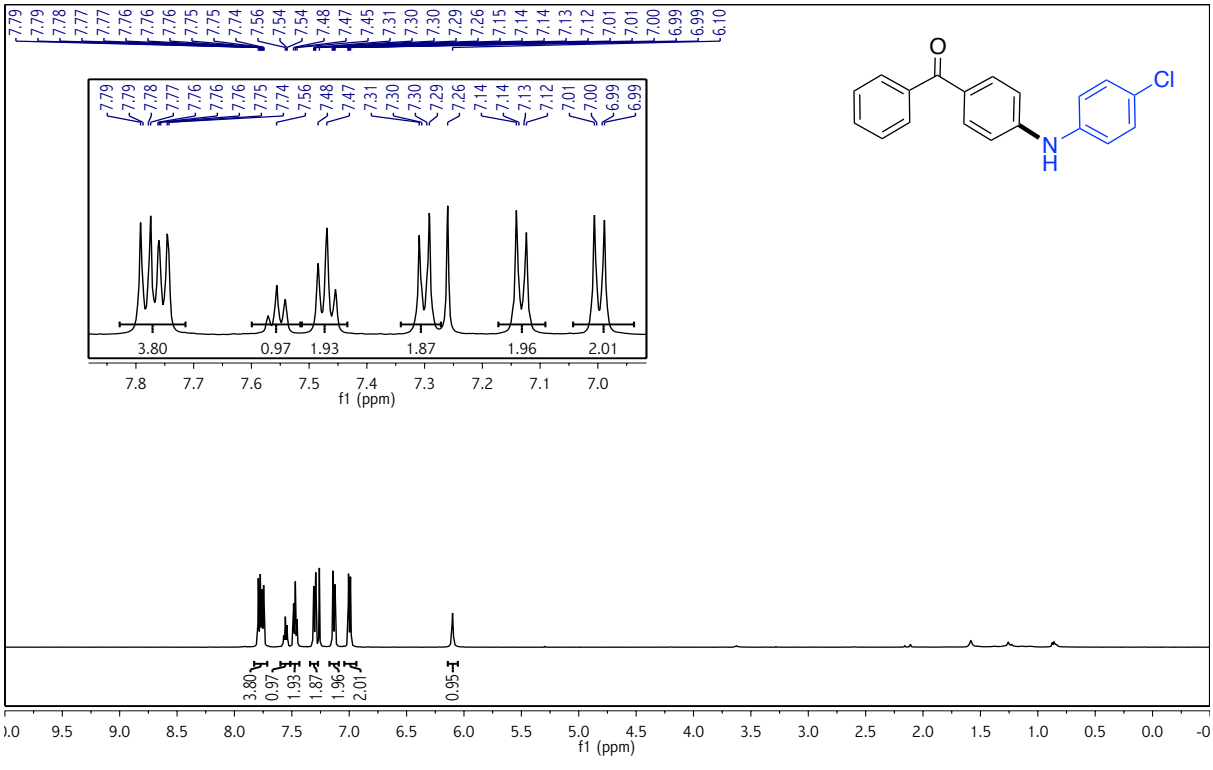
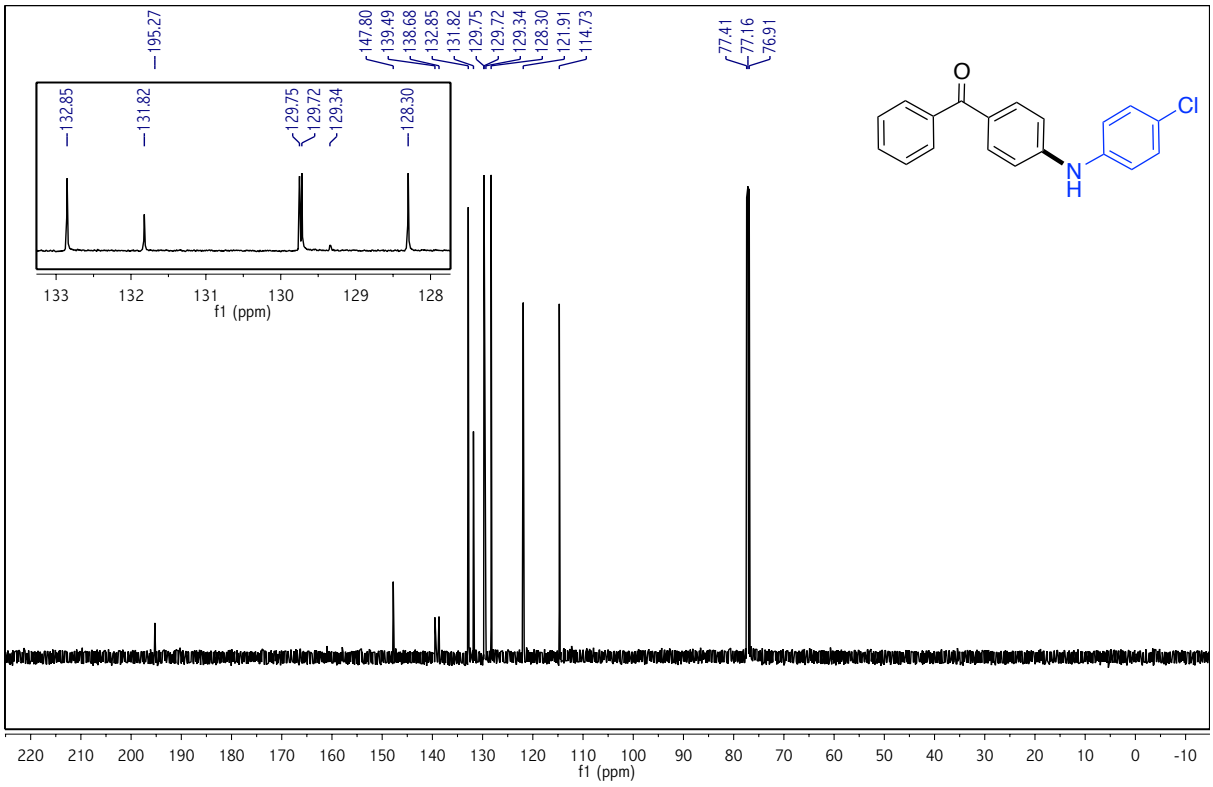
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290
-310
f1 (ppm)


7.79
7.79
7.78
7.77
7.77
7.76
7.76
7.76
7.75
7.75
7.74
7.56
7.54
7.54
7.48
7.47
7.45
7.31
7.30
7.30
7.29
7.26
7.15
7.14
7.14
7.13
7.12
7.01
7.01
7.00
6.99
6.99
6.10
3.80
0.97
1.93
1.87
1.96
2.01
0.95
f1 (ppm)
O
Cl
N
H
f1 (ppm)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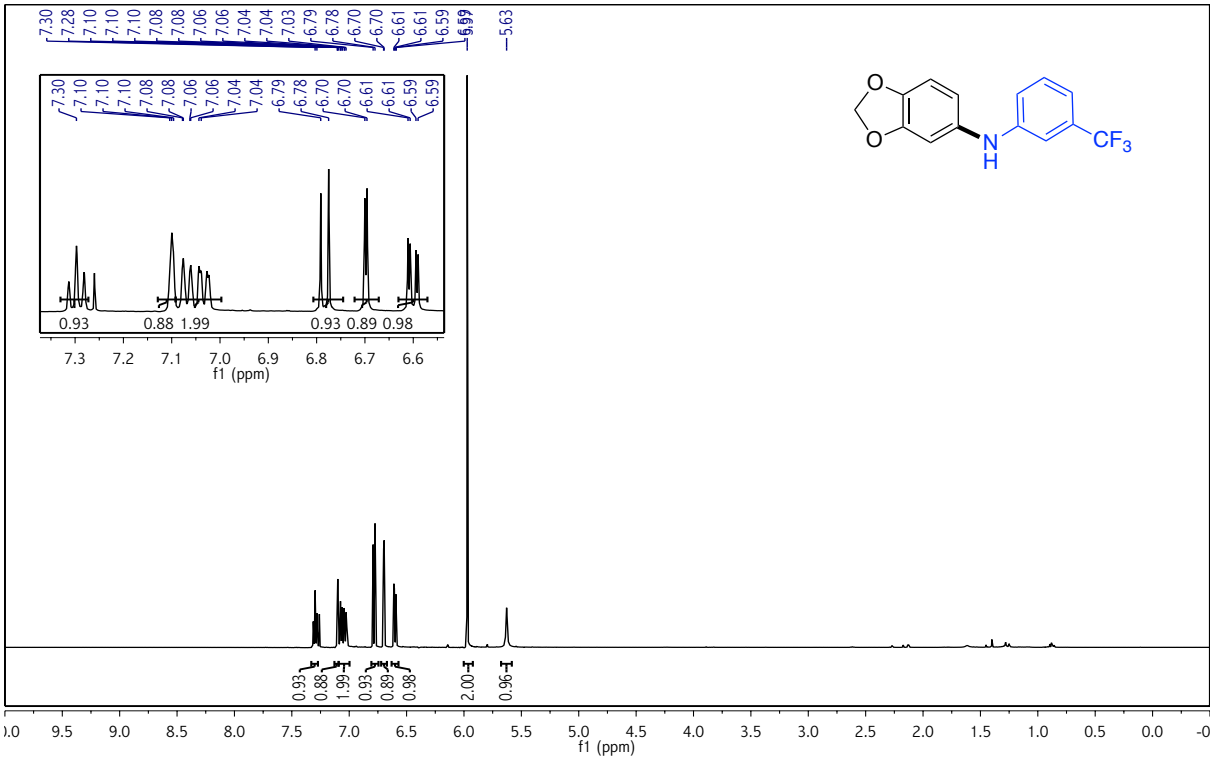
139.49
138.68
132.85
131.82
129.75
129.72
129.34
128.30
121.91
114.73
77.41
77.16
76.91
132.85
131.82
129.75
129.72
129.34
128.30
f1 (ppm)
O
N
H
Cl
f1 (ppm)


7.30
7.28
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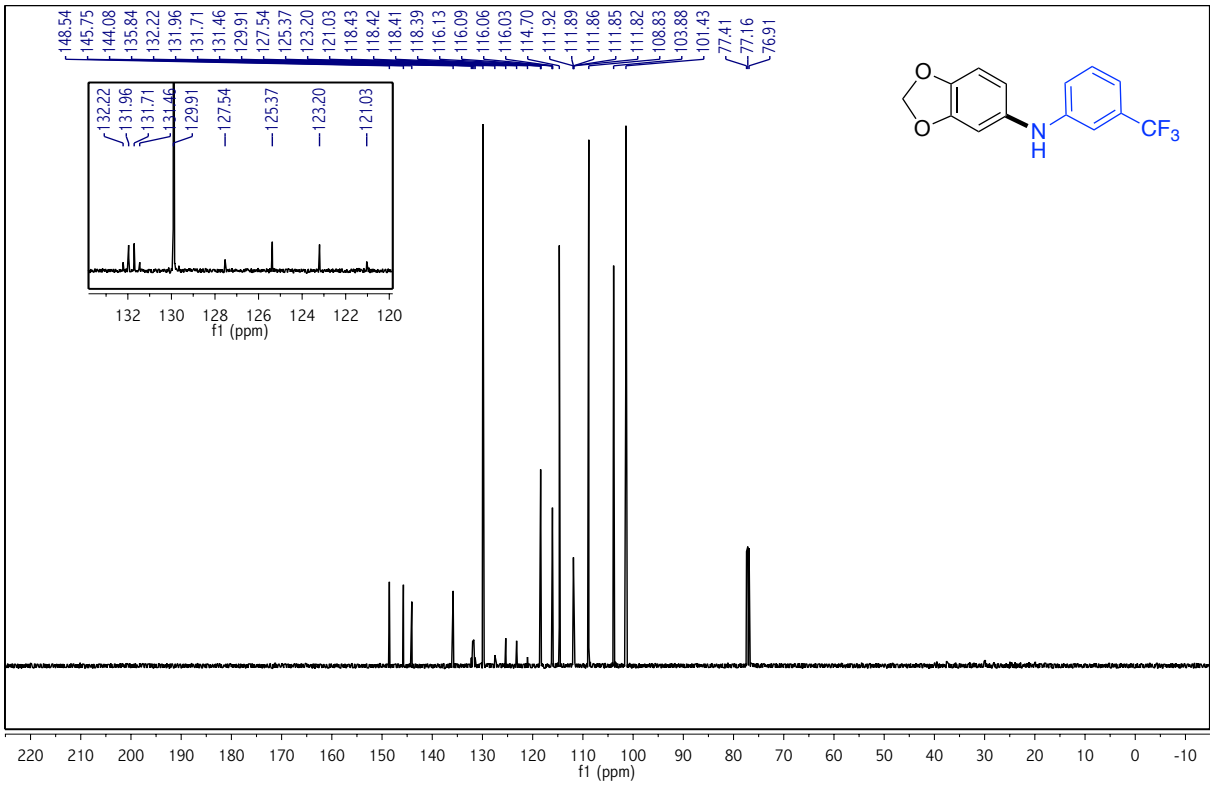
7.10
7.10
7.08
7.08
7.06
7.06
7.04
7.04
7.03
6.79
6.78
6.70
6.70
6.61
6.61
6.59
5.63
0.93
0.88
1.99
0.93
0.89
0.98
2.00
0.96
f1 (ppm)
O
O
N
H
CF3
f1 (ppm)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145.75
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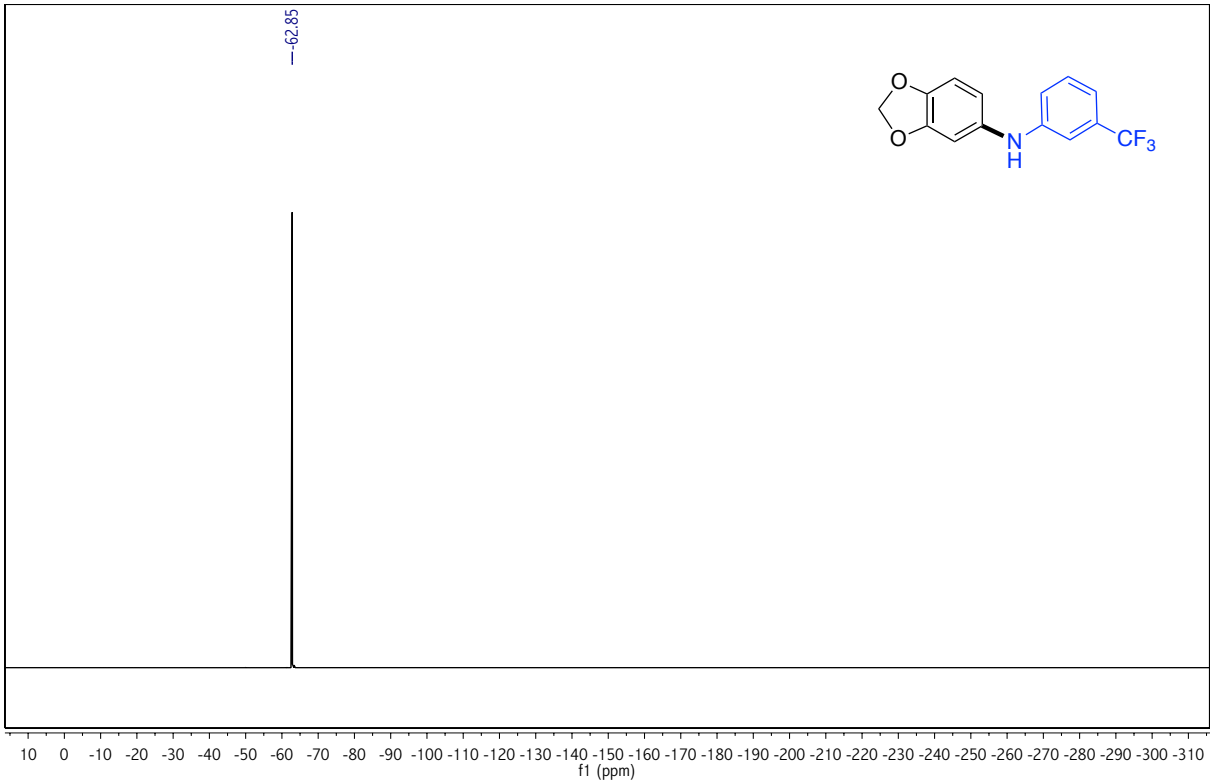
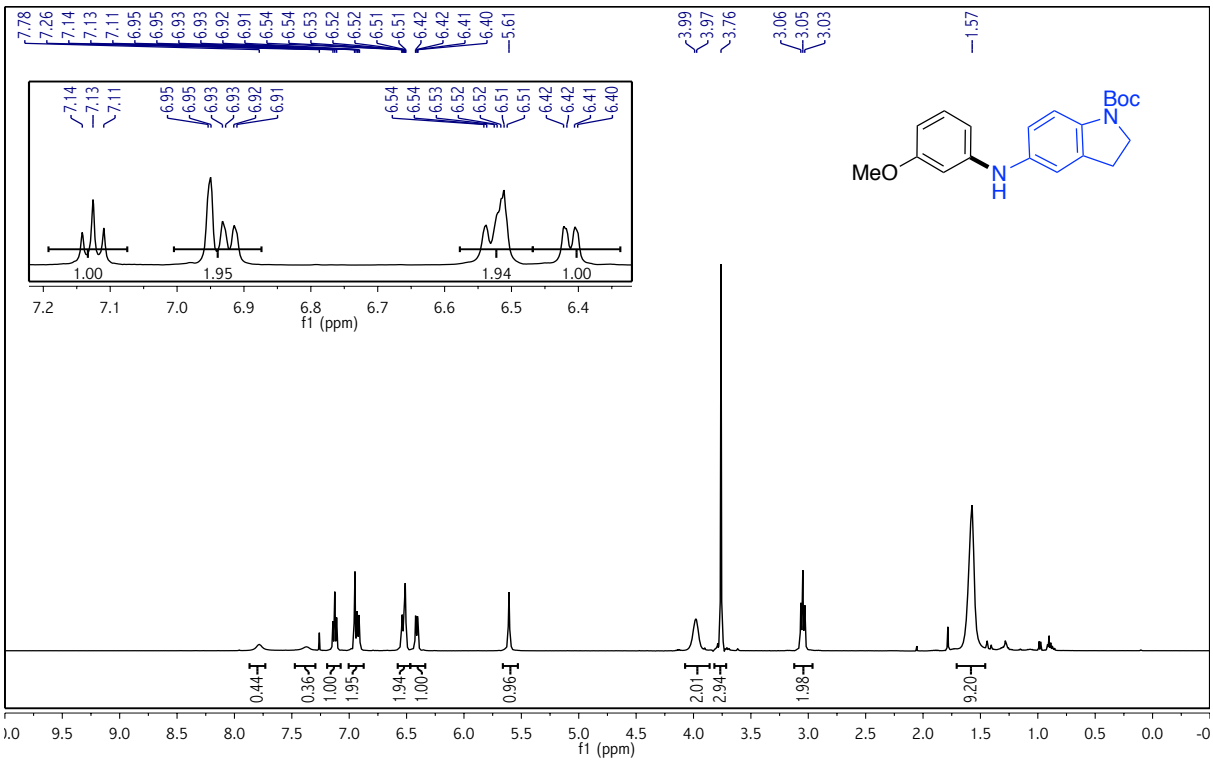
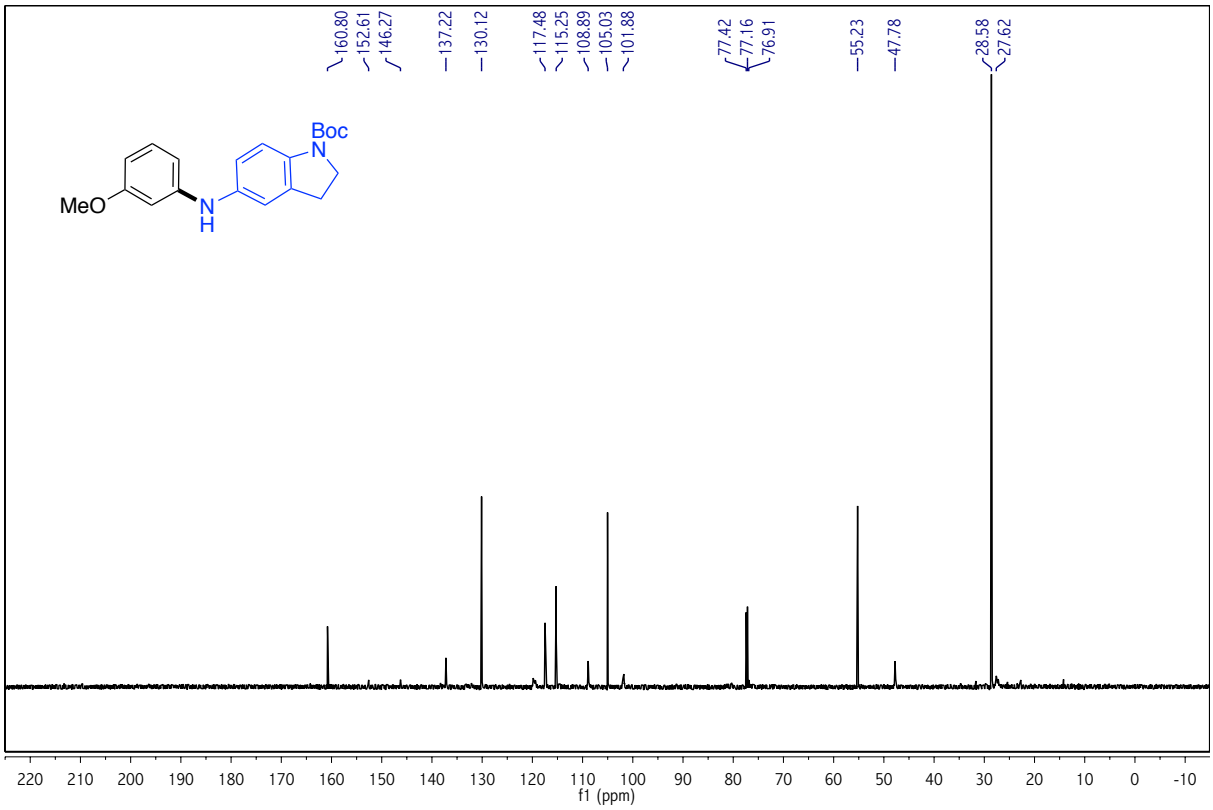
135.84
132.22
131.96
131.71
131.46
129.91
127.54
125.37
123.20
121.03
118.43
118.42
118.41
118.39
116.13
116.09
116.06
116.03
114.70
111.92
111.89
111.86
111.85
111.82
108.83
103.88
101.43
77.41
77.16
76.91
132.22
131.96
131.71
131.46
129.91
127.54
125.37
123.20
121.03
132 130 128 126 124 122 120
f1 (ppm)
O
O
N
H
CF3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-62.85
O
O
N
H
CF3
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300 -310
f1 (ppm)


7.78
7.26
7.14
7.13
7.11
6.95
6.93
6.93
6.92
6.91
6.54
6.54
6.53
6.52
6.52
6.51
6.51
6.42
6.41
6.40
5.61
3.99
3.97
3.76
3.06
3.05
3.03
1.57
Boc
N
MeO
N
H
1.00
1.95
1.94
1.00
f1 (ppm)
0.44
0.36
1.00
1.95
1.94
1.00
0.96
2.01
2.94
1.98
9.20
f1 (ppm)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117.48
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108.89
105.03
101.88
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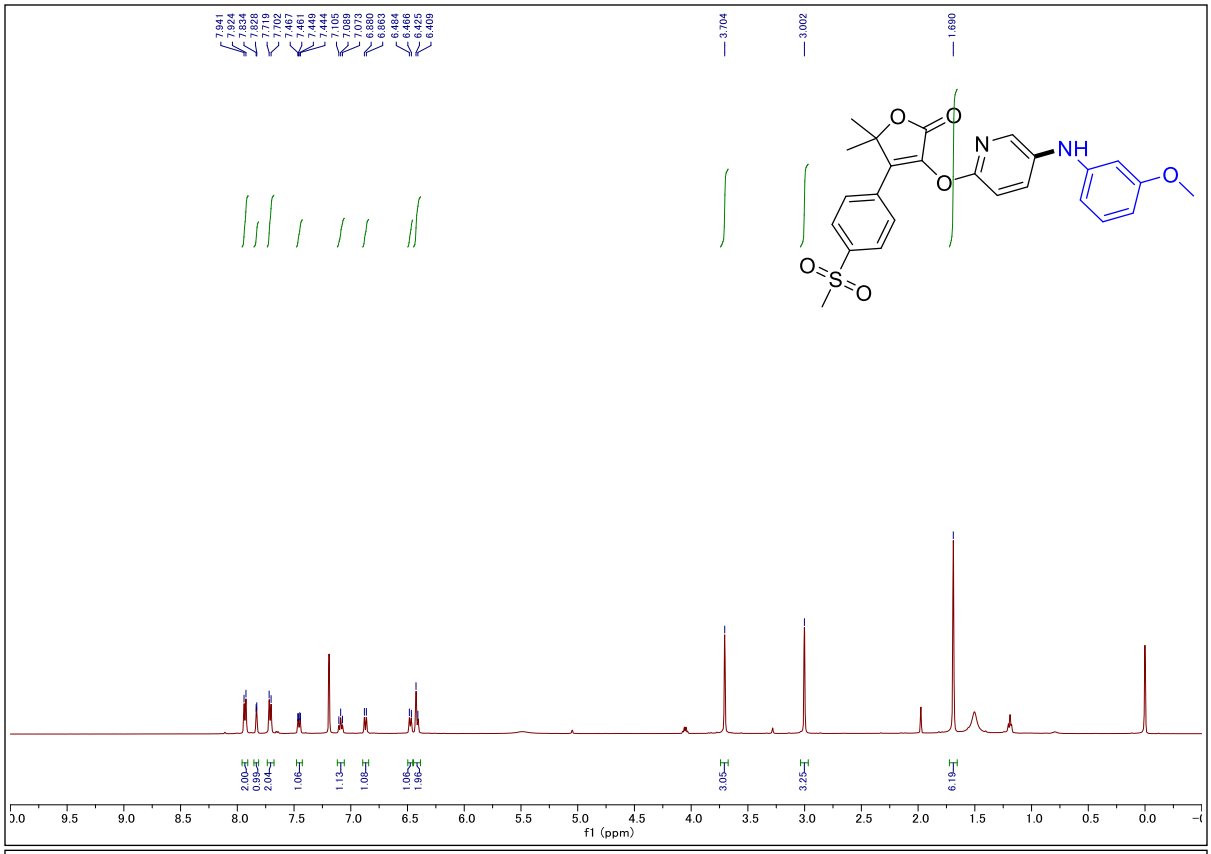
76.91
55.23
47.78
28.58
27.62
Boc
N
MeO
N
H
f1 (ppm)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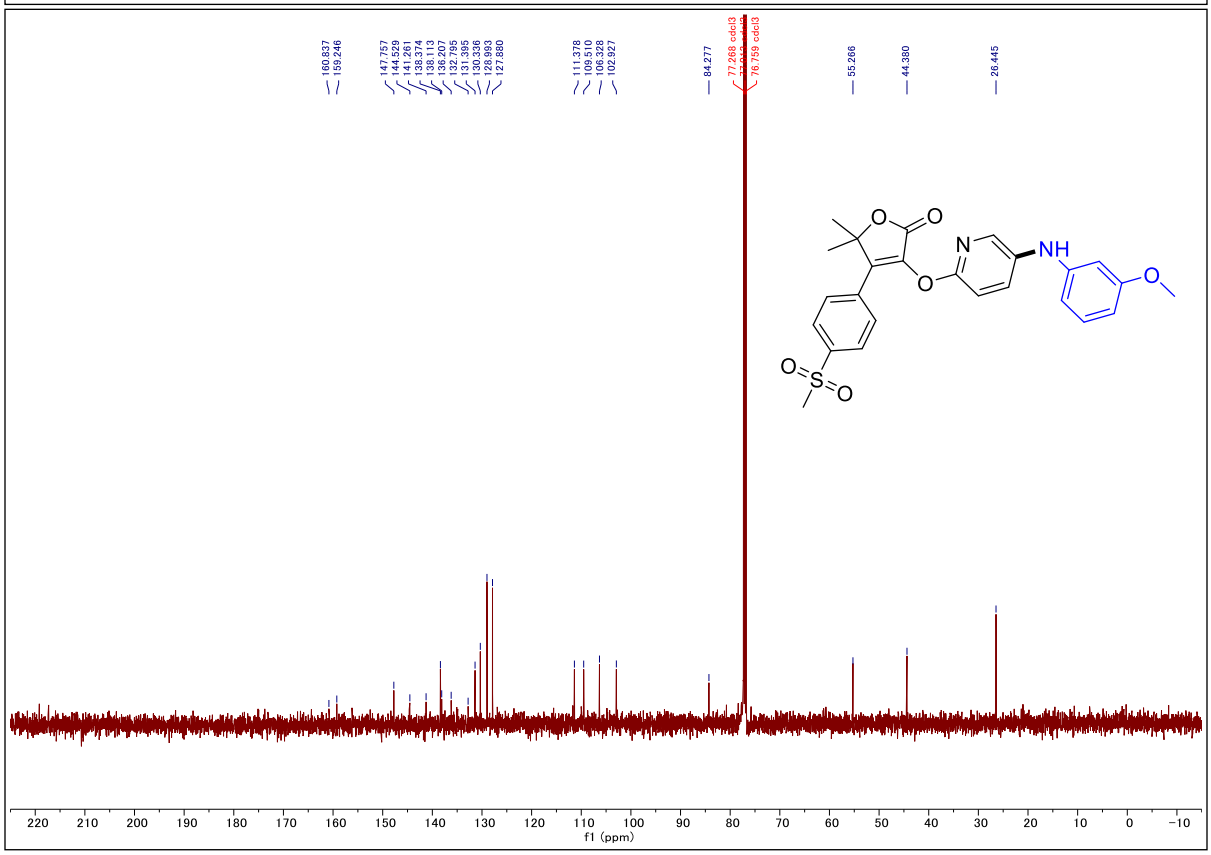
7.934
7.834
7.828
7.719
7.702
7.467
7.461
7.449
7.444
7.105
7.089
7.073
6.880
6.863
6.484
6.466
6.425
6.409
3.704
3.002
1.690
2.00
0.98
2.04
1.06
1.13
1.08
1.06
1.96
3.05
3.25
6.19
f1 (ppm)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135.297
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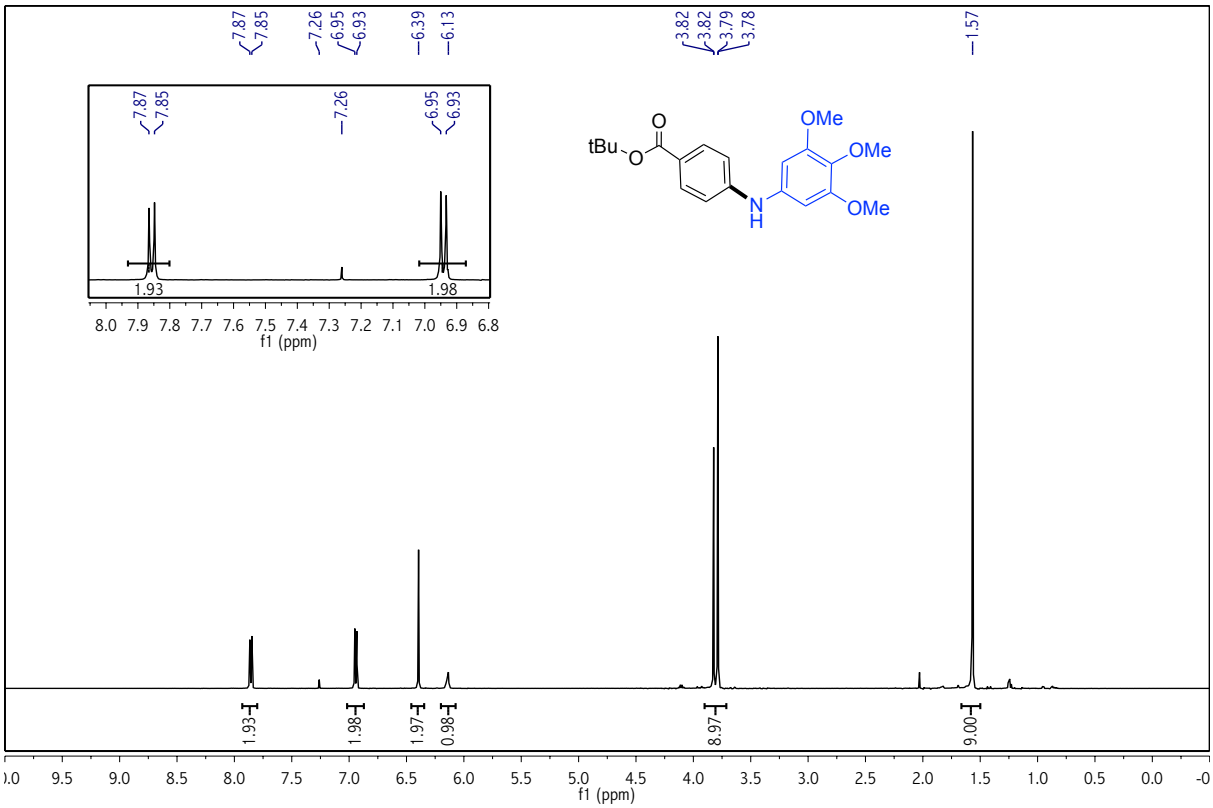
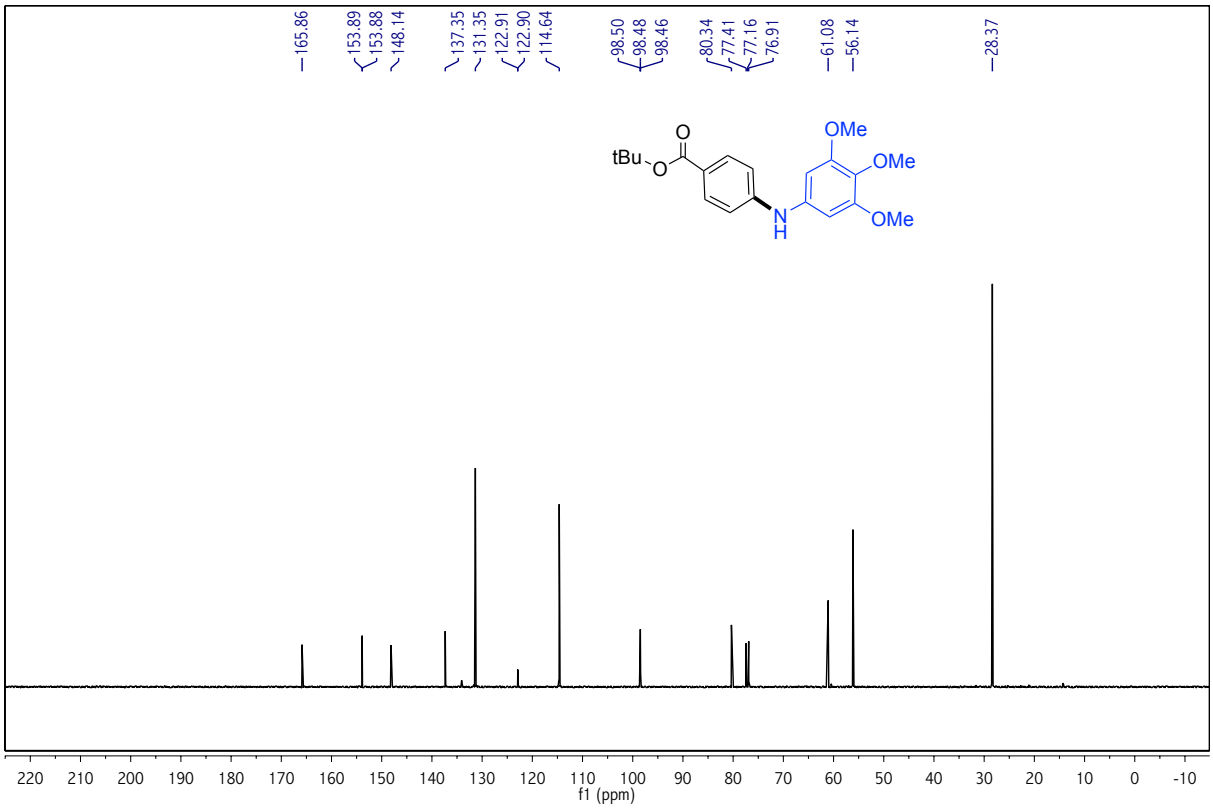
128.993
127.880
111.378
109.510
106.328
102.927
84.277
77.288 cdcl3
76.759 cdcl3
55.266
44.380
26.445
f1 (ppm)


7.87
7.85
7.26
6.95
6.93
6.39
6.13
3.82
3.82
3.79
3.78
1.57
1.93
1.98
f1 (ppm)
tBu
O
OMe
OMe
OMe
N
H
1.93
1.98
1.97
0.98
8.97
9.00
f1 (ppm)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153.89
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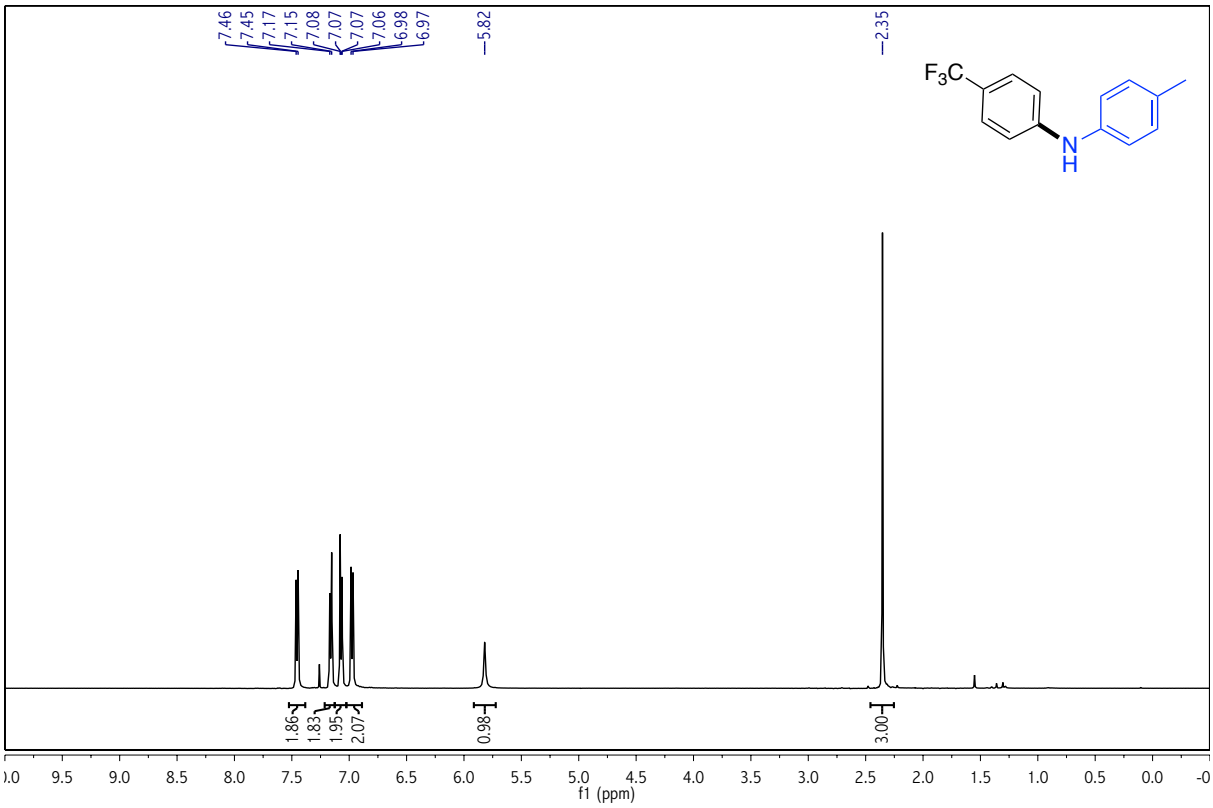
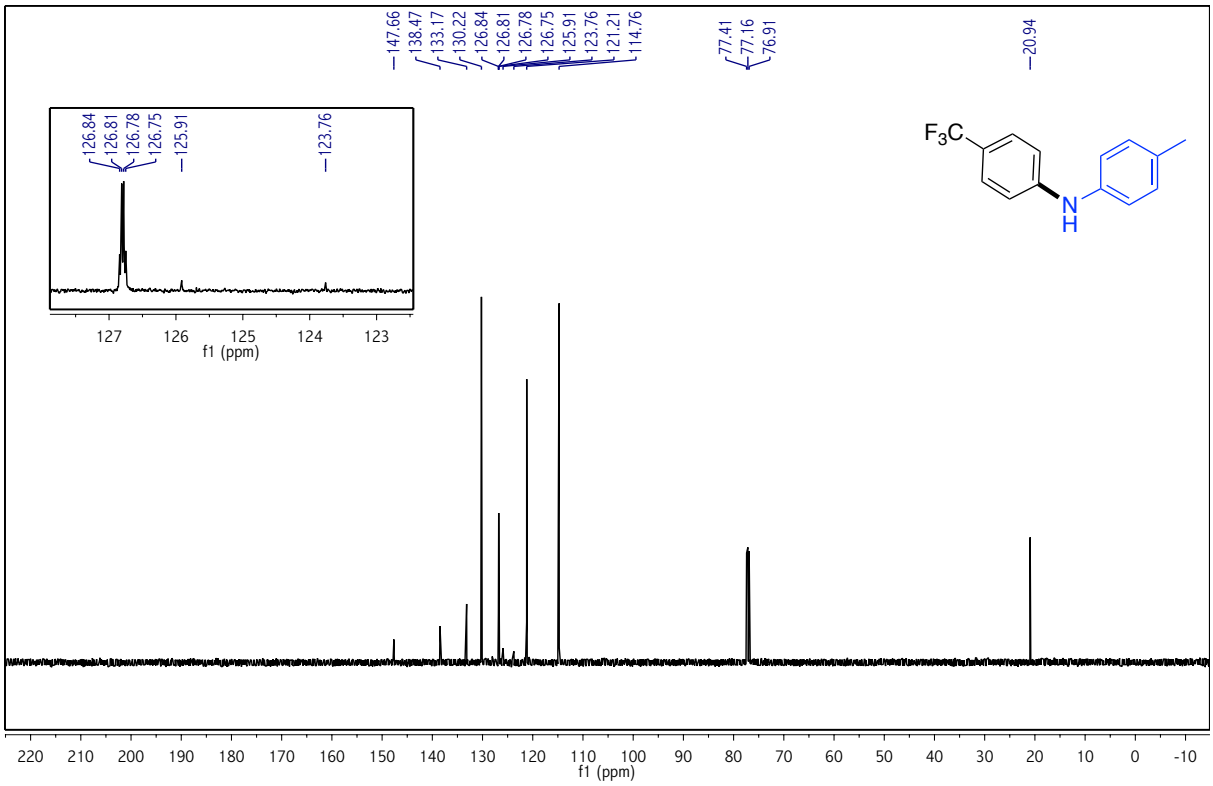
148.14
137.35
131.35
122.91
122.90
114.64
98.50
98.48
98.46
80.34
77.41
77.16
76.91
61.08
56.14
28.37
tBu
O
OMe
OMe
OMe
N
H
f1 (ppm)


7.46
7.45
7.17
7.15
7.08
7.07
7.07
7.06
6.98
6.97
5.82
2.35
F3C
N
H
1.86
1.83
1.95
2.07
0.98
3.00
f1 (ppm)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126.84
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126.75
125.91
123.76
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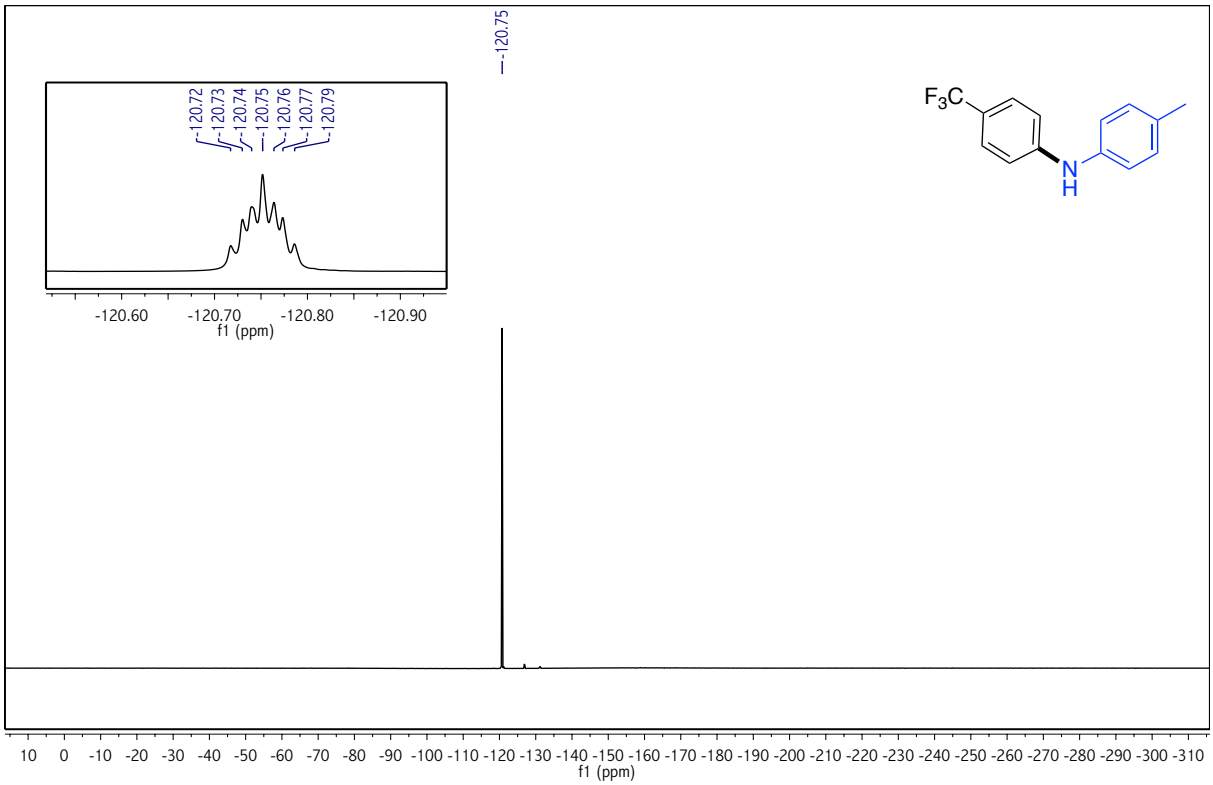
77.41
77.16
76.91
20.94
F3C
N
H
f1 (ppm)
f1 (ppm)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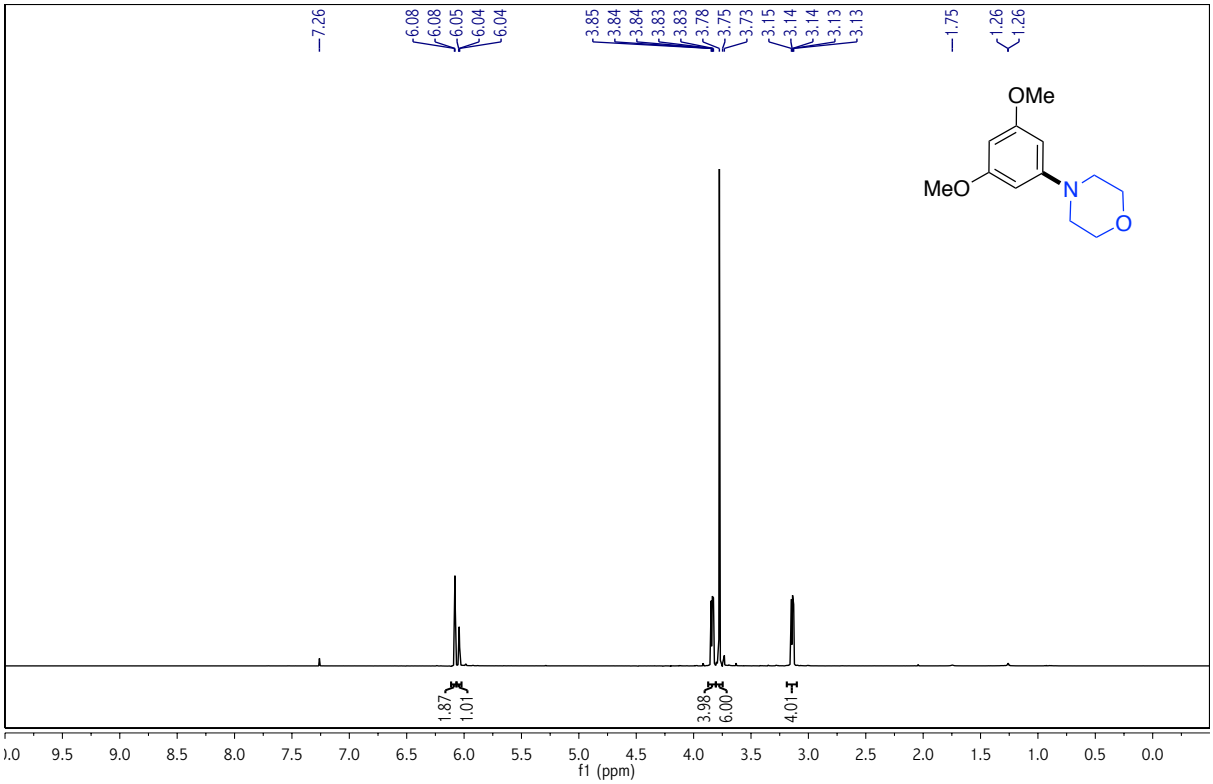
-120.73
-120.74
-120.75
-120.76
-120.77
-120.79
-120.60
-120.70
-120.80
-120.90
f1 (ppm)
F3C
N
H
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300 -310
f1 (ppm)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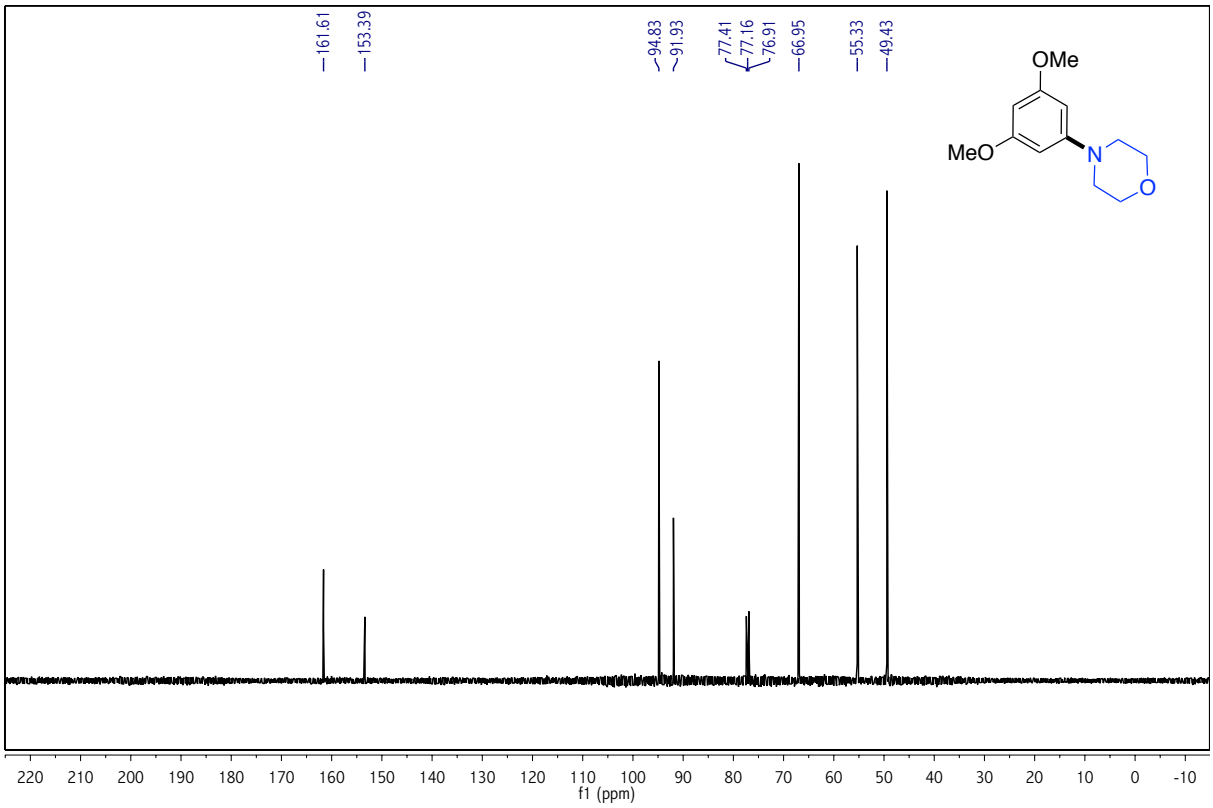
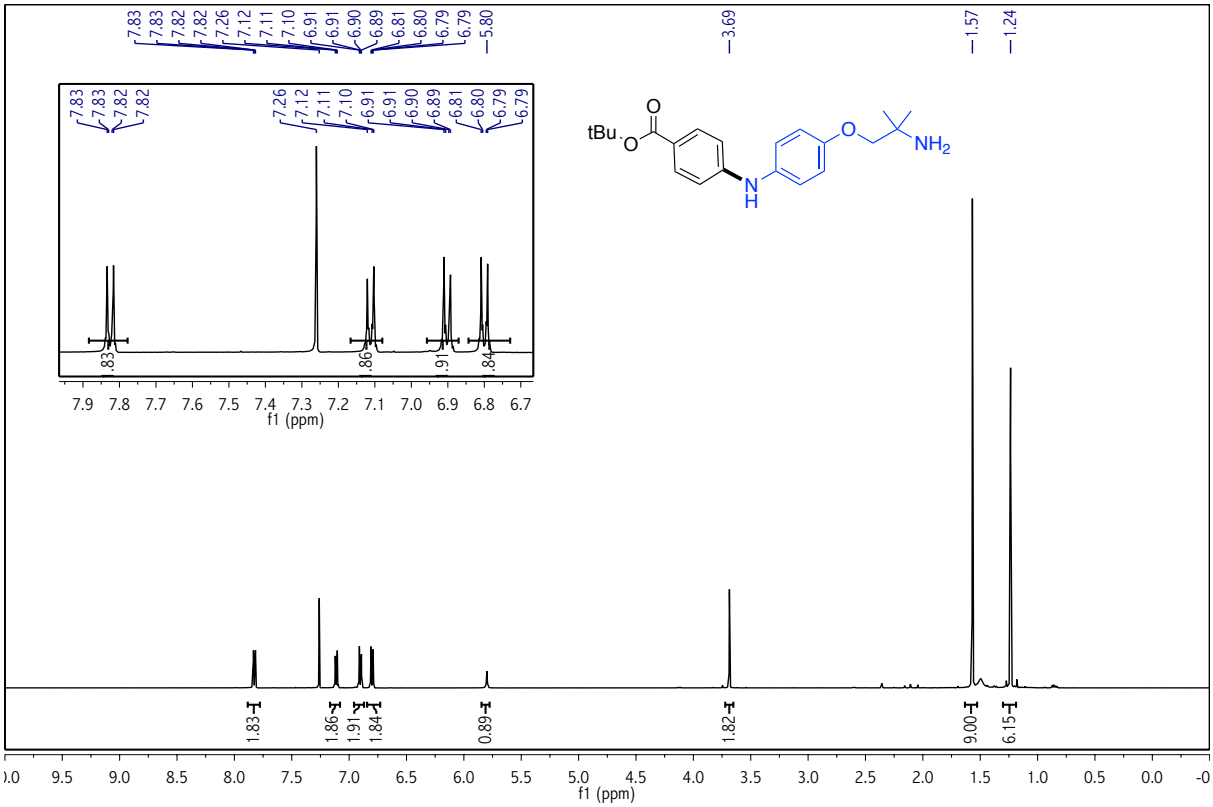
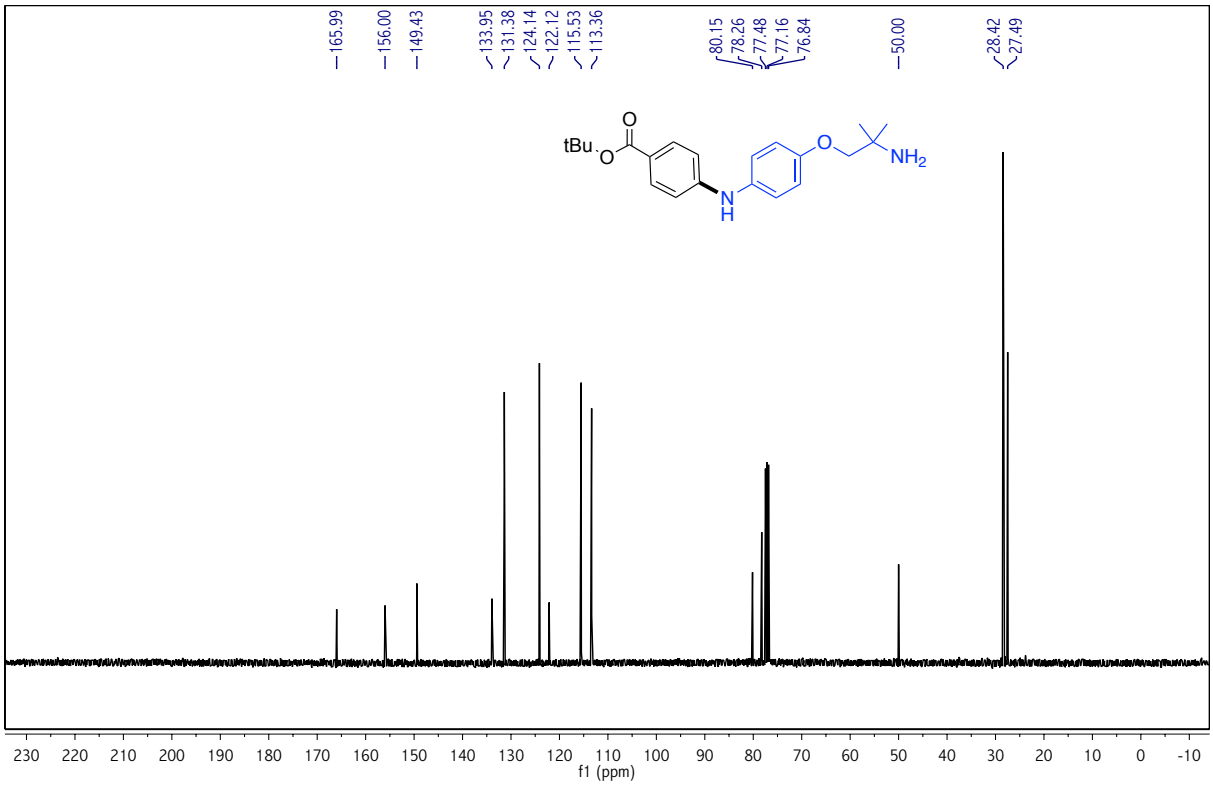
6.08
6.08
6.05
6.04
6.04
3.85
3.84
3.84
3.83
3.83
3.78
3.75
3.73
3.15
3.14
3.14
3.13
3.13
1.75
1.26
1.26
OMe
MeO
N
O
1.87
1.01
3.98
6.00
4.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


161.61
153.39
94.83
91.93
77.41
77.16
76.91
66.95
55.33
49.43
OMe
MeO
N
O
f1 (ppm)


7.83
7.83
7.82
7.82
7.26
7.12
7.11
7.10
6.91
6.91
6.90
6.89
6.81
6.80
6.79
6.79
5.80
3.69
1.57
1.24
tBu
O
NH2
N
H
1.83
1.86
1.91
1.84
0.89
1.82
9.00
6.15
f1 (ppm)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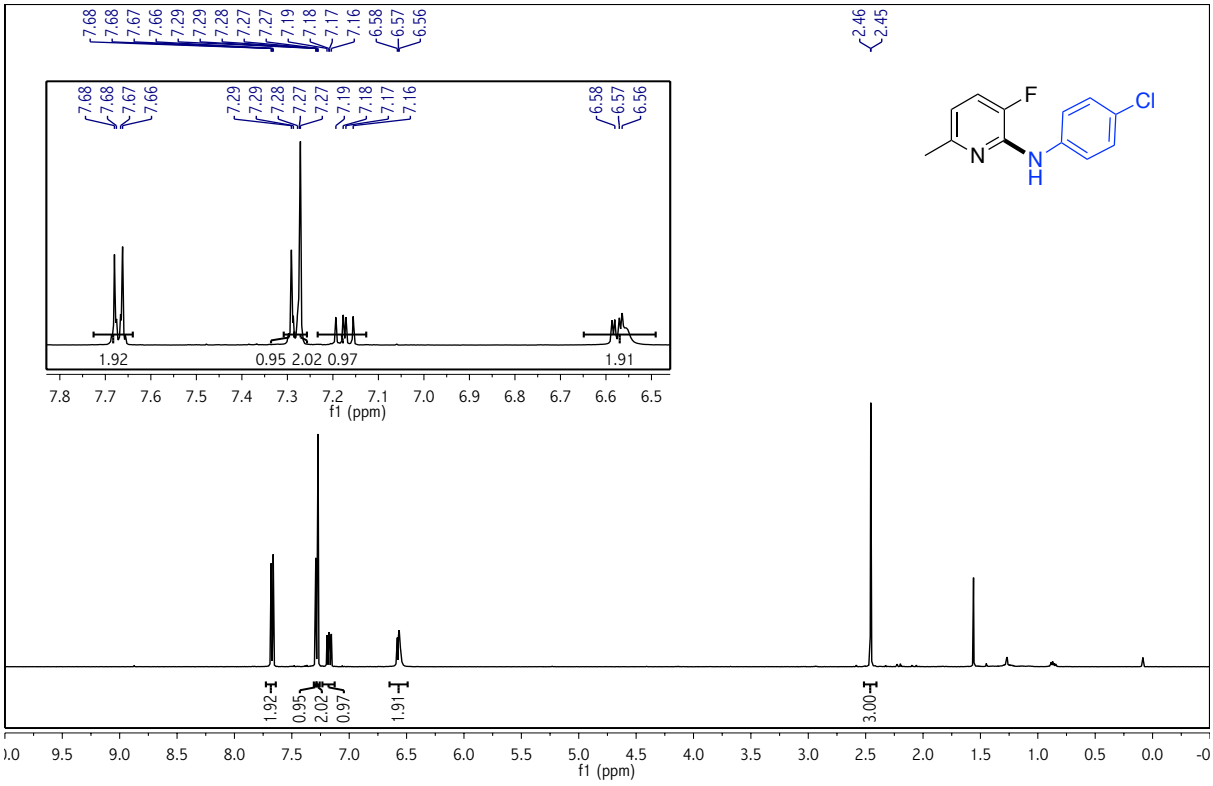
124.14
122.12
115.53
113.36
80.15
78.26
77.48
77.16
76.84
50.00
28.42
27.49
tBu
O
O
O
NH2
N
H
f1 (ppm)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7.68
7.67
7.67
7.66
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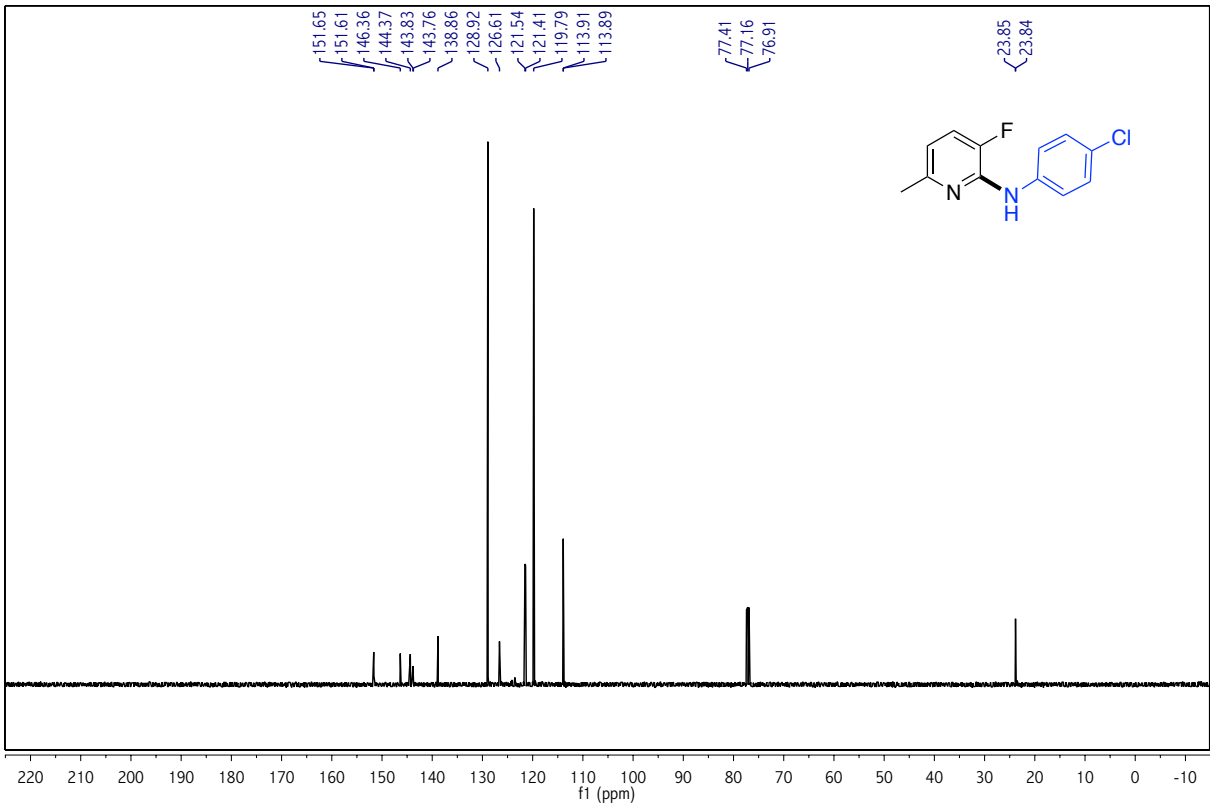
7.29
7.28
7.27
7.27
7.19
7.18
7.17
7.16
6.58
6.57
6.56
2.46
2.45
F
Cl
N
N
H
1.92
0.95
2.02
0.97
1.91
3.00
f1 (ppm)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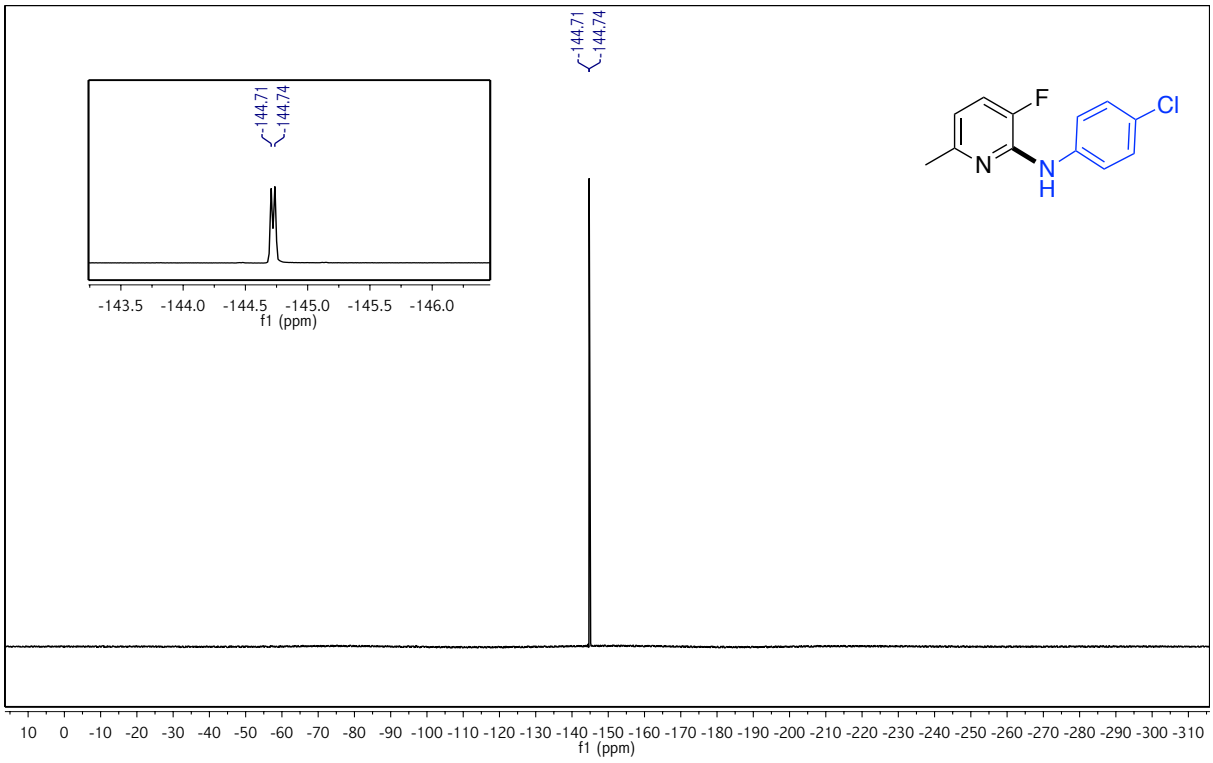
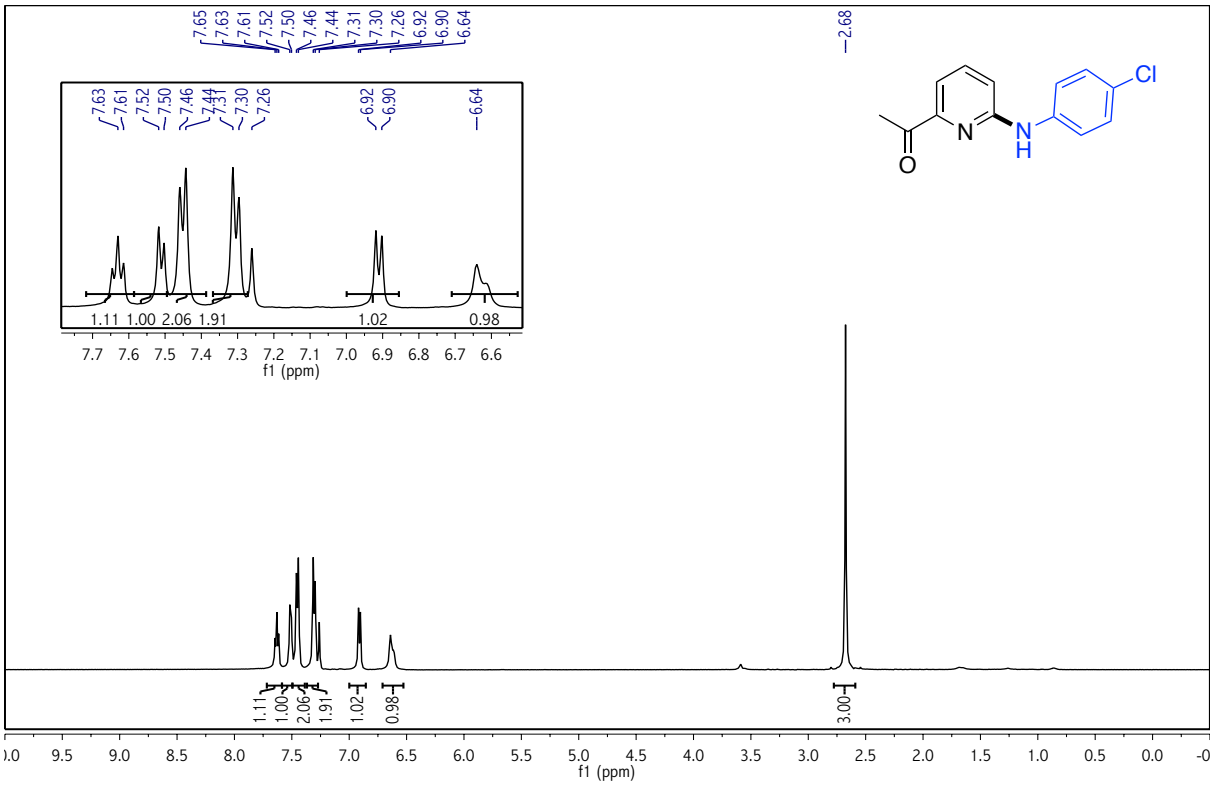
151.61
146.36
144.37
143.83
143.76
138.86
128.92
126.61
121.54
121.41
119.79
113.91
113.89
77.41
77.16
76.91
23.85
23.84
F
Cl
N
H
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-144.71
-144.74
-144.71
-144.74
F
Cl
N
H
-143.5 -144.0 -144.5 -145.0 -145.5 -146.0
f1 (ppm)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300 -310
f1 (ppm)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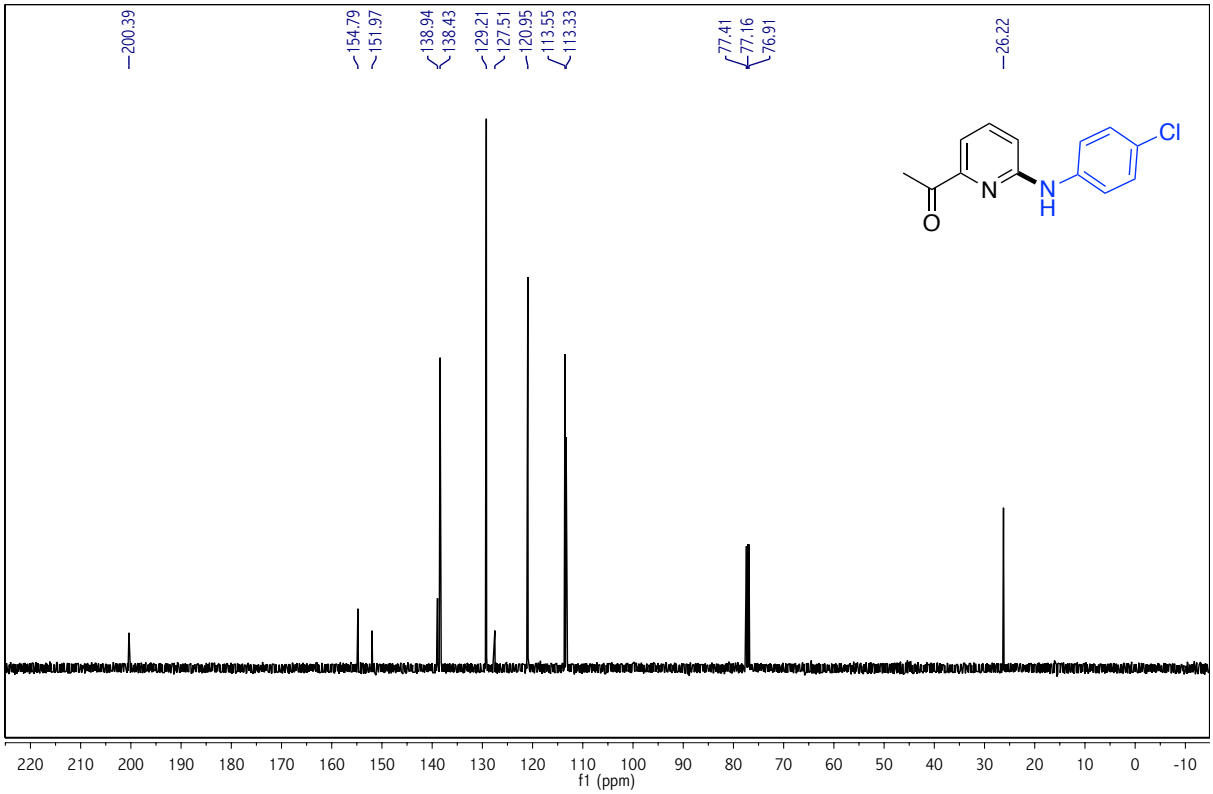
7.63
7.61
7.52
7.50
7.46
7.44
7.31
7.30
7.26
6.92
6.90
6.64
2.68
1.11 1.00 2.06 1.91 1.02 0.98
3.00
f1 (ppm)
Cl
N
H
O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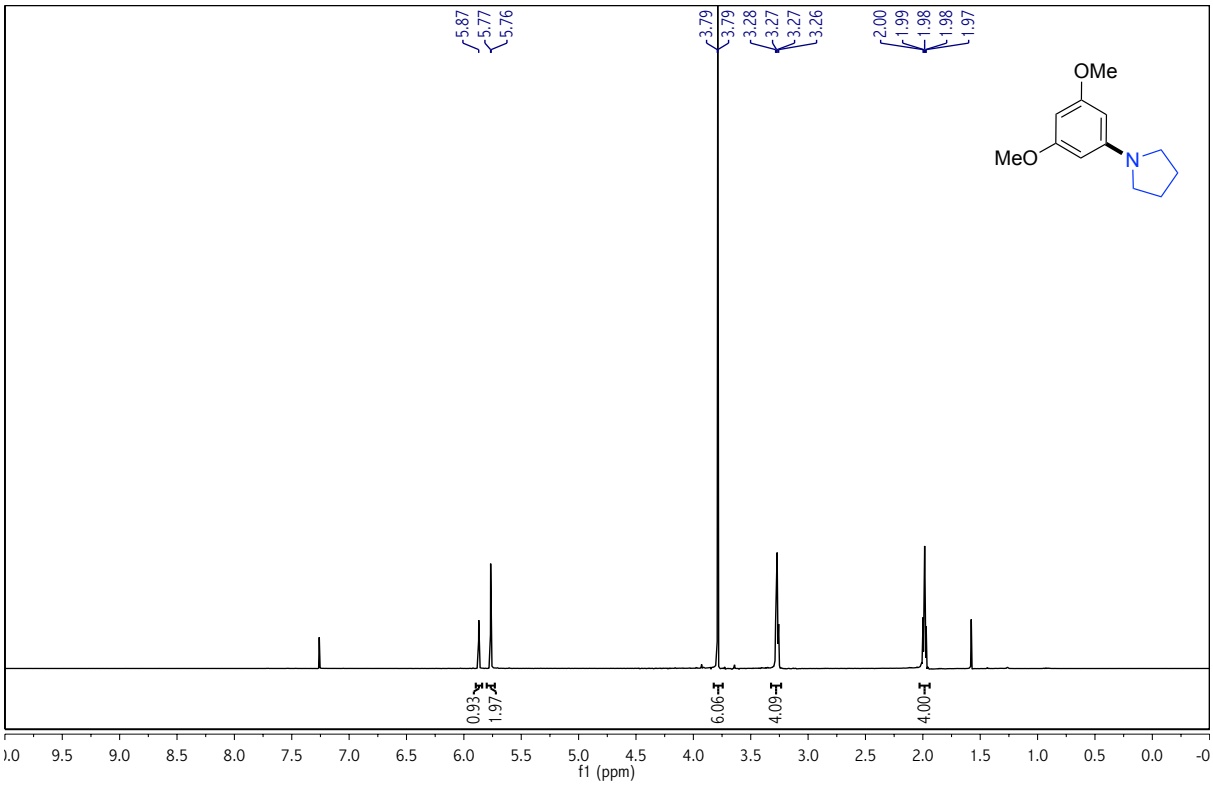
154.79
151.97
138.94
138.43
129.21
127.51
120.95
113.55
113.33
77.41
77.16
76.91
26.22
f1 (ppm)
Cl
N
H
O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5.77
5.76
3.79
3.79
3.28
3.27
3.27
3.26
2.00
1.99
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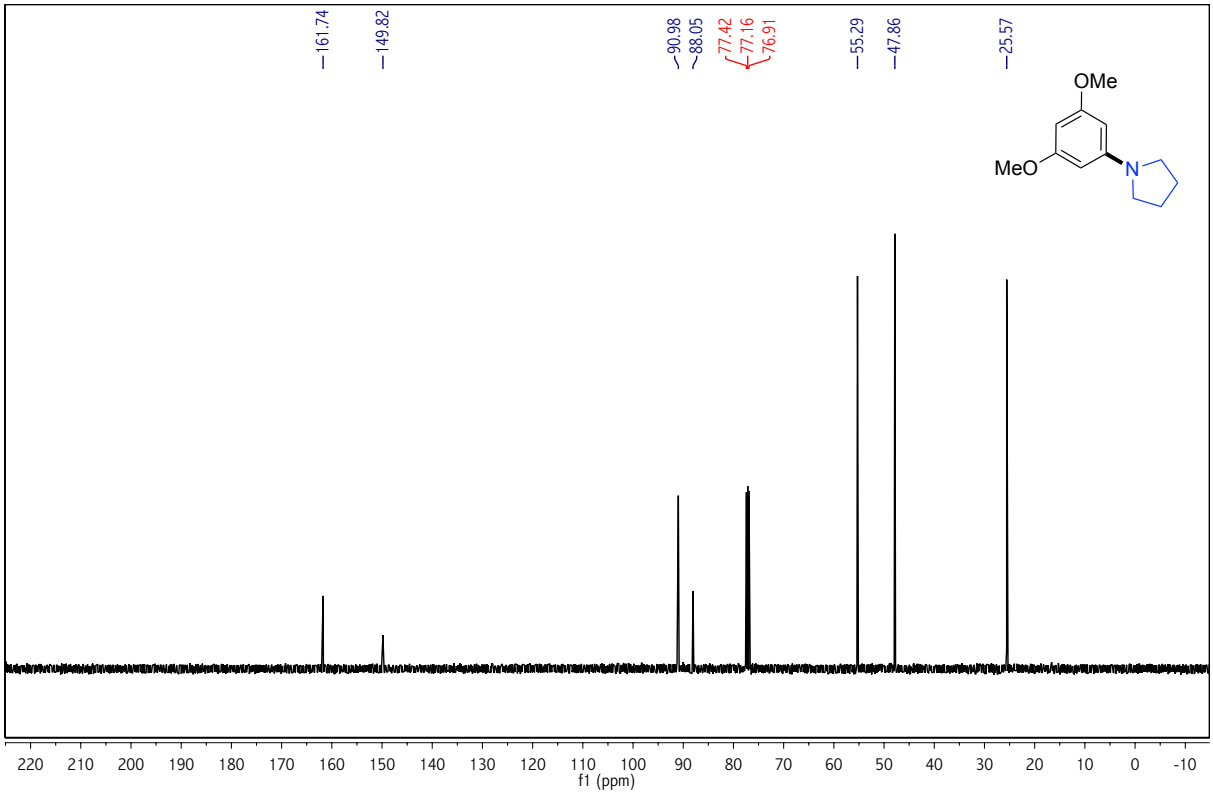
1.98
1.97
OMe
MeO
N
0.93
1.97
6.06
4.09
4.00
f1 (ppm)


161.74
149.82
90.98
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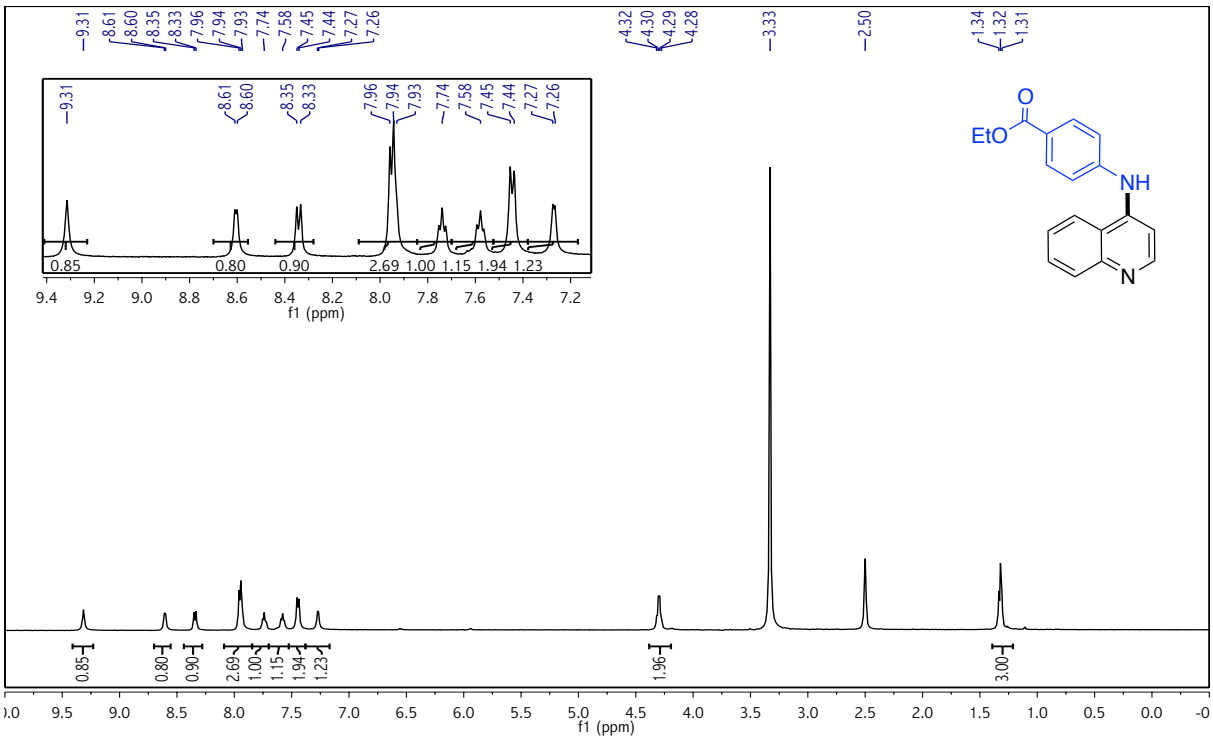
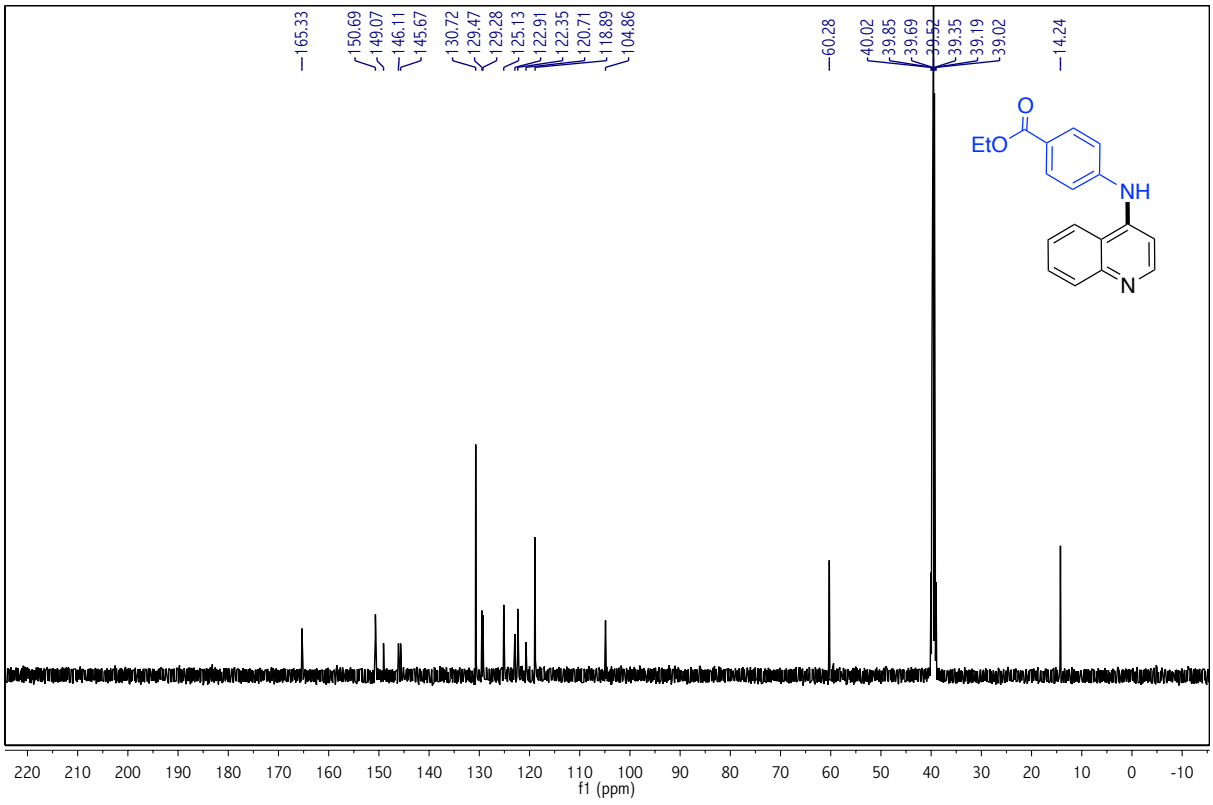
77.42
77.16
76.91
55.29
47.86
25.57
OMe
MeO
N
f1 (ppm)


9.31
8.61
8.60
8.35
8.33
7.96
7.94
7.93
7.74
7.58
7.45
7.44
7.27
7.26
4.32
4.30
4.29
4.28
3.33
2.50
1.34
1.32
1.31
0.85
0.80
0.90
2.69
1.00
1.15
1.94
1.23
1.96
3.00
EtO
O
NH
N
f1 (ppm)


165.33
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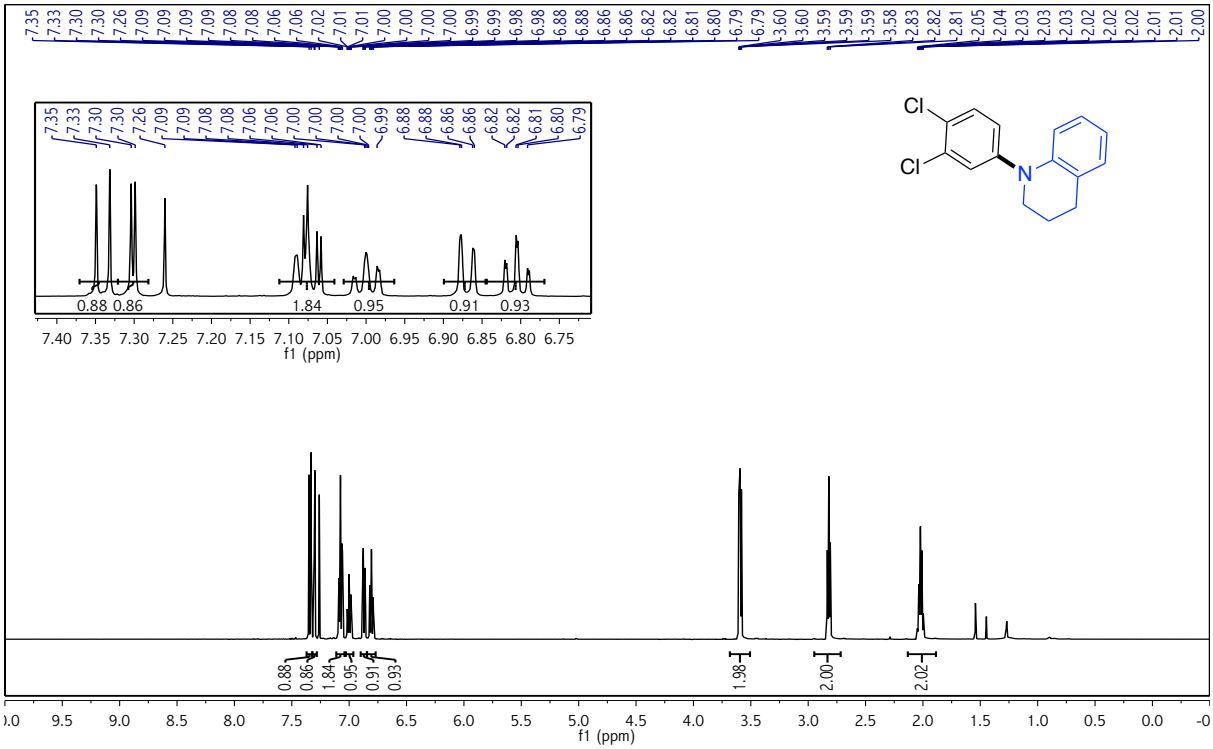
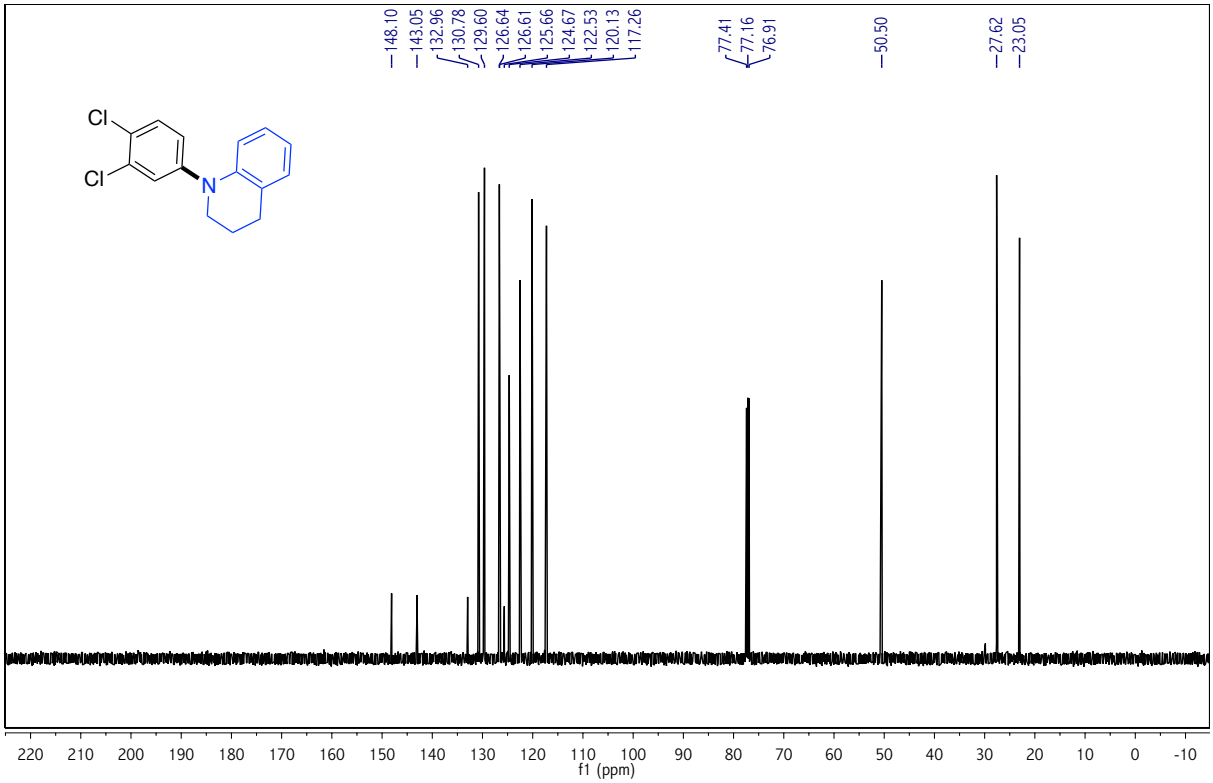
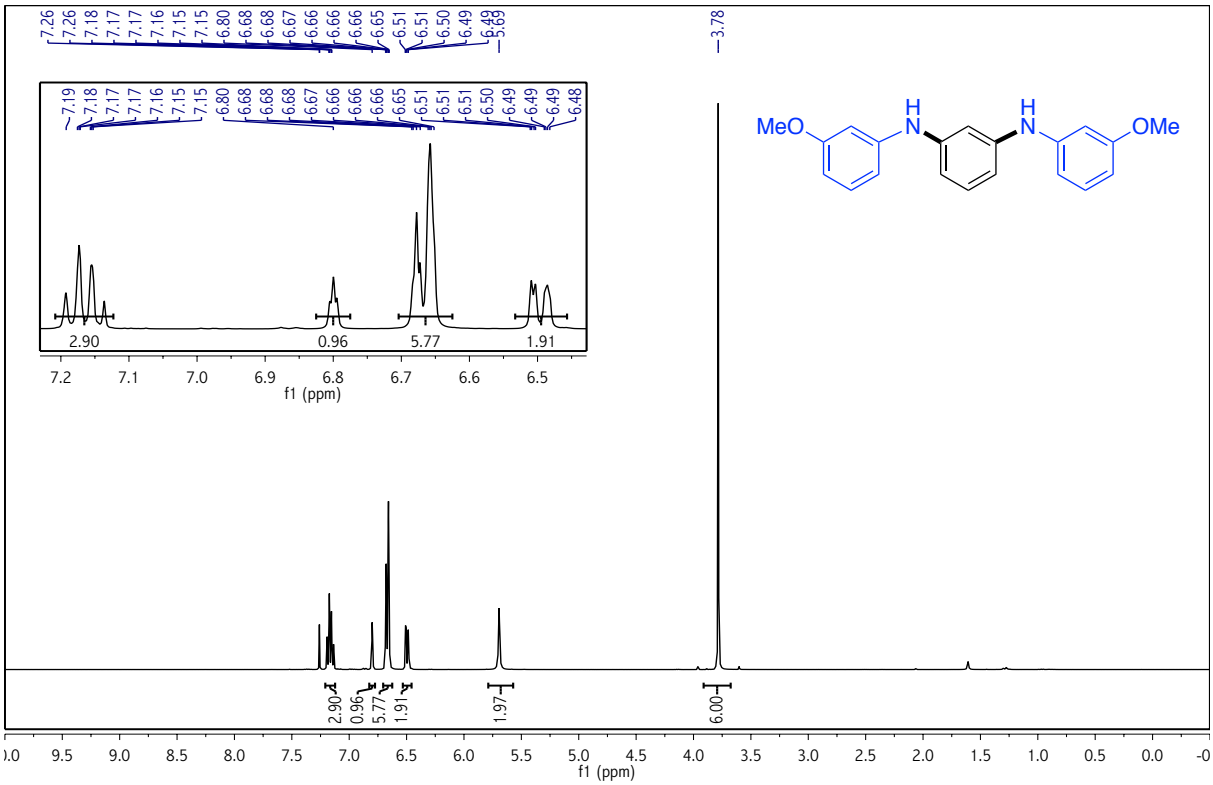
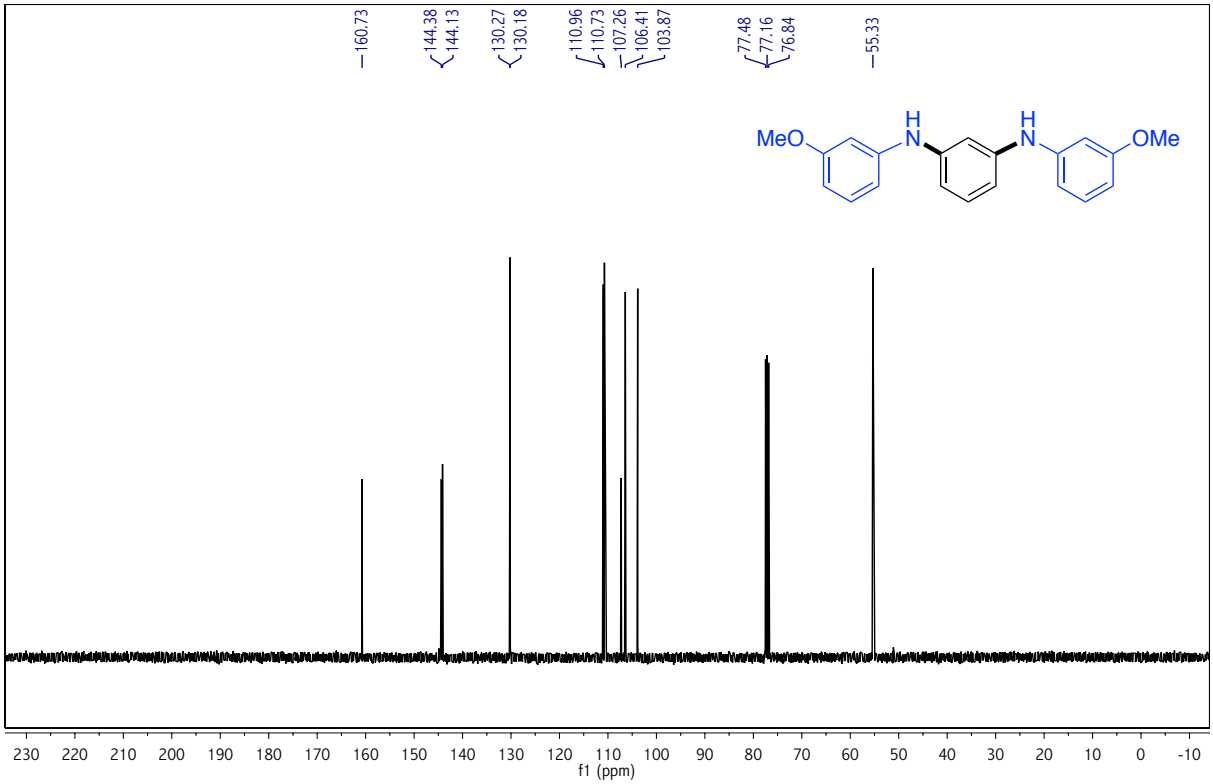
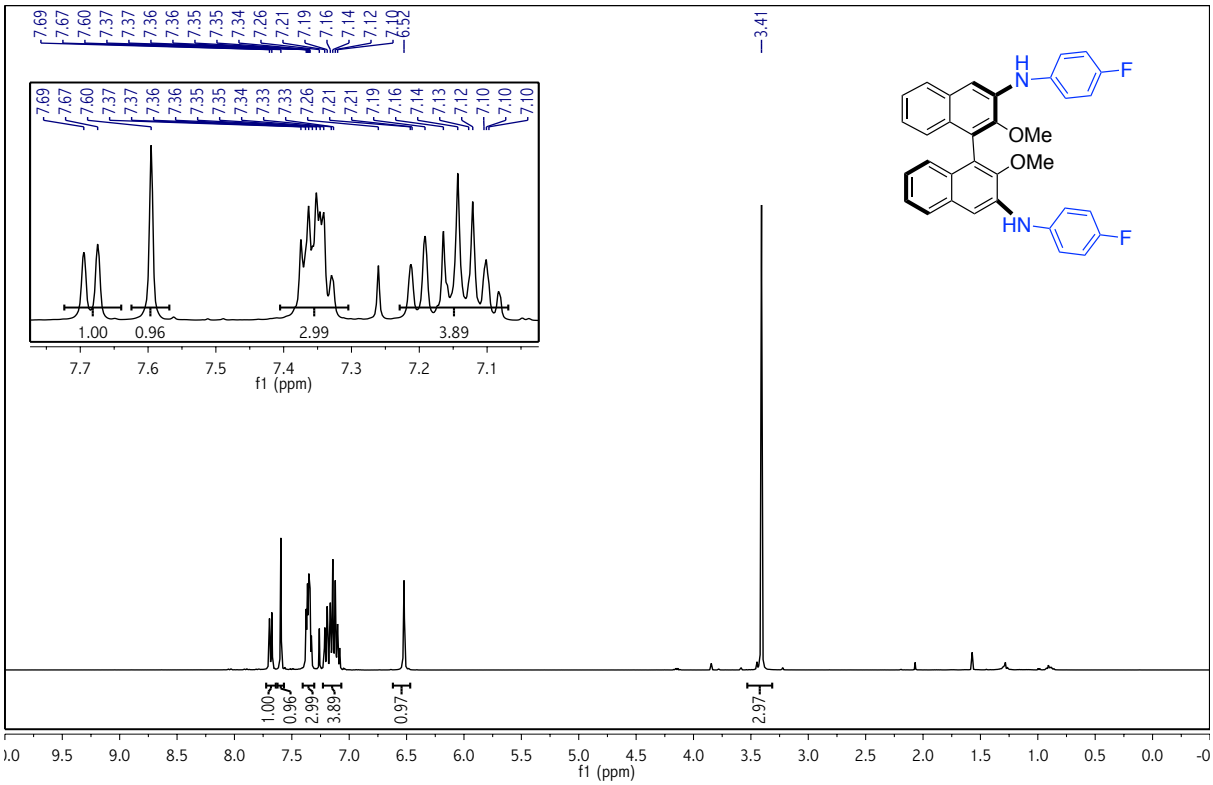
145.67
130.72
129.47
129.28
125.13
122.91
122.35
120.71
118.89
104.86
60.28
40.02
39.85
39.69
39.52
39.35
39.19
39.02
14.24
EtO
O
NH
N
f1 (ppm)

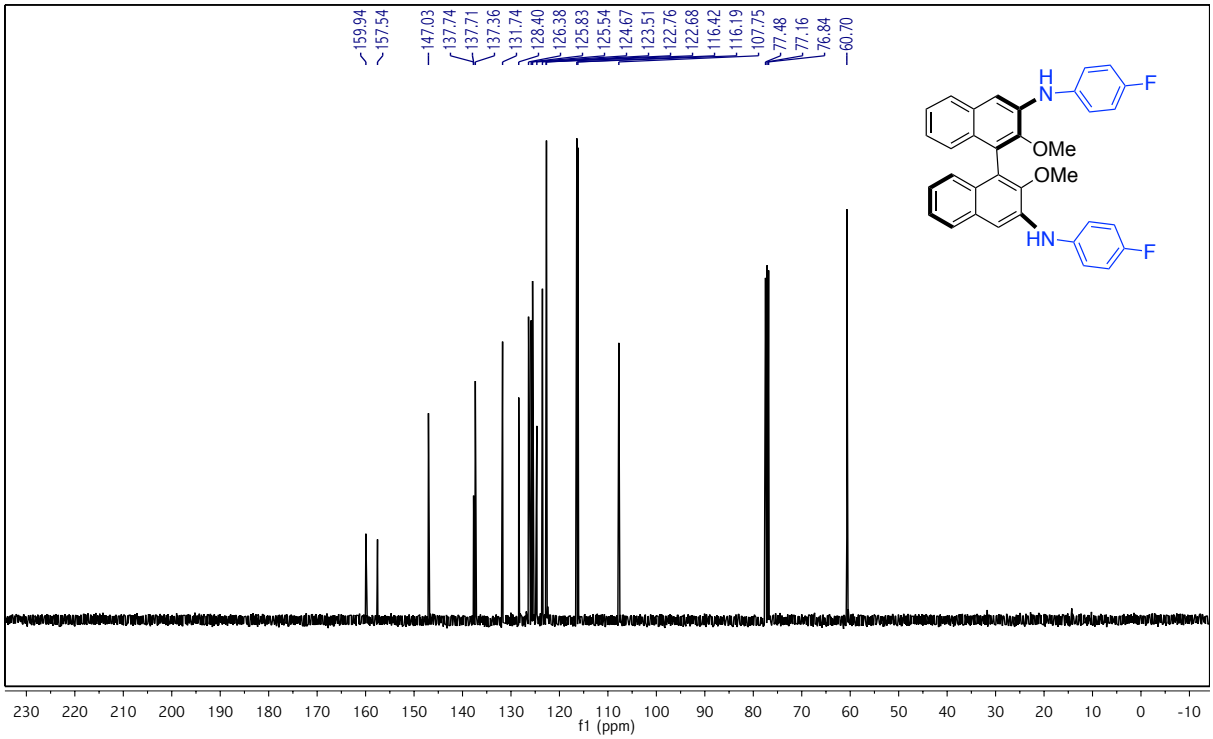

Cl
Cl
N
0.88 0.86
1.84
0.95
0.91
0.93
f1 (ppm)
1.98
2.00
2.02

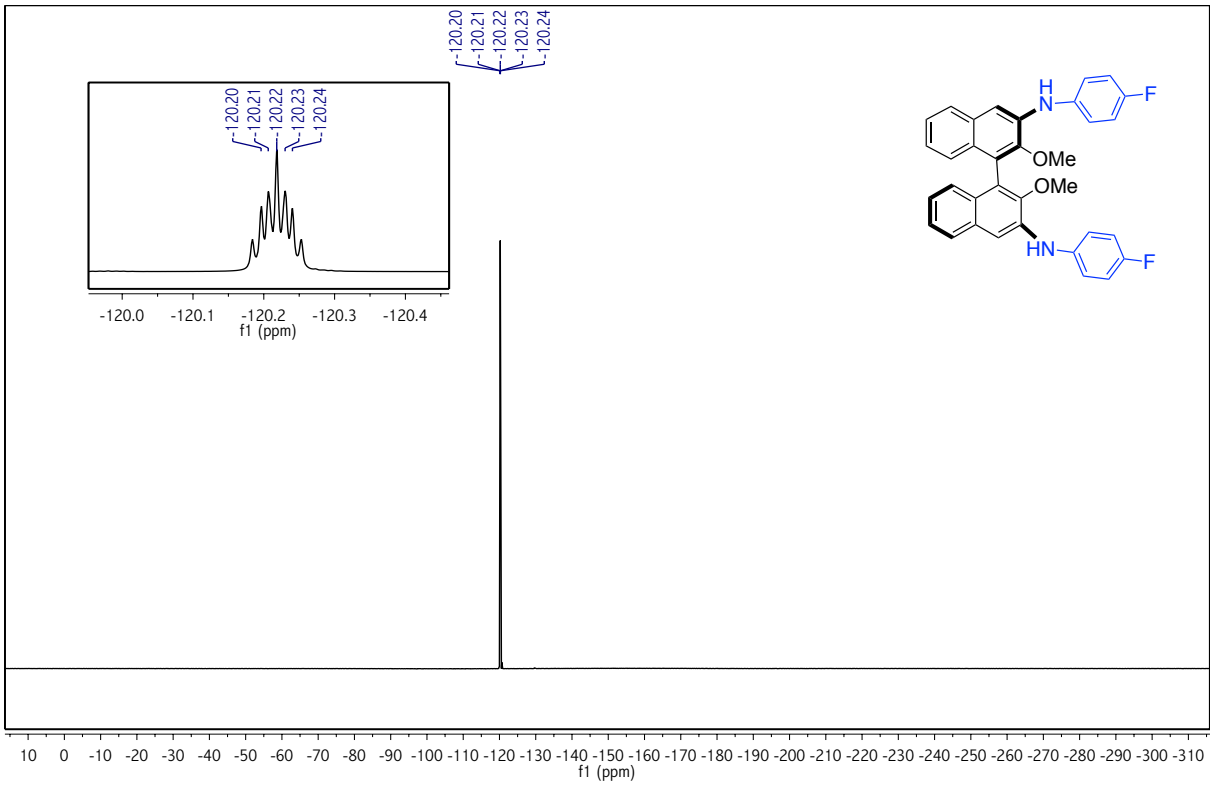

148.10
143.05
132.96
130.78
129.60
126.64
126.61
125.66
124.67
122.53
120.13
117.26
77.41
77.16
76.91
50.50
27.62
23.05
Cl
Cl
N
f1 (ppm)

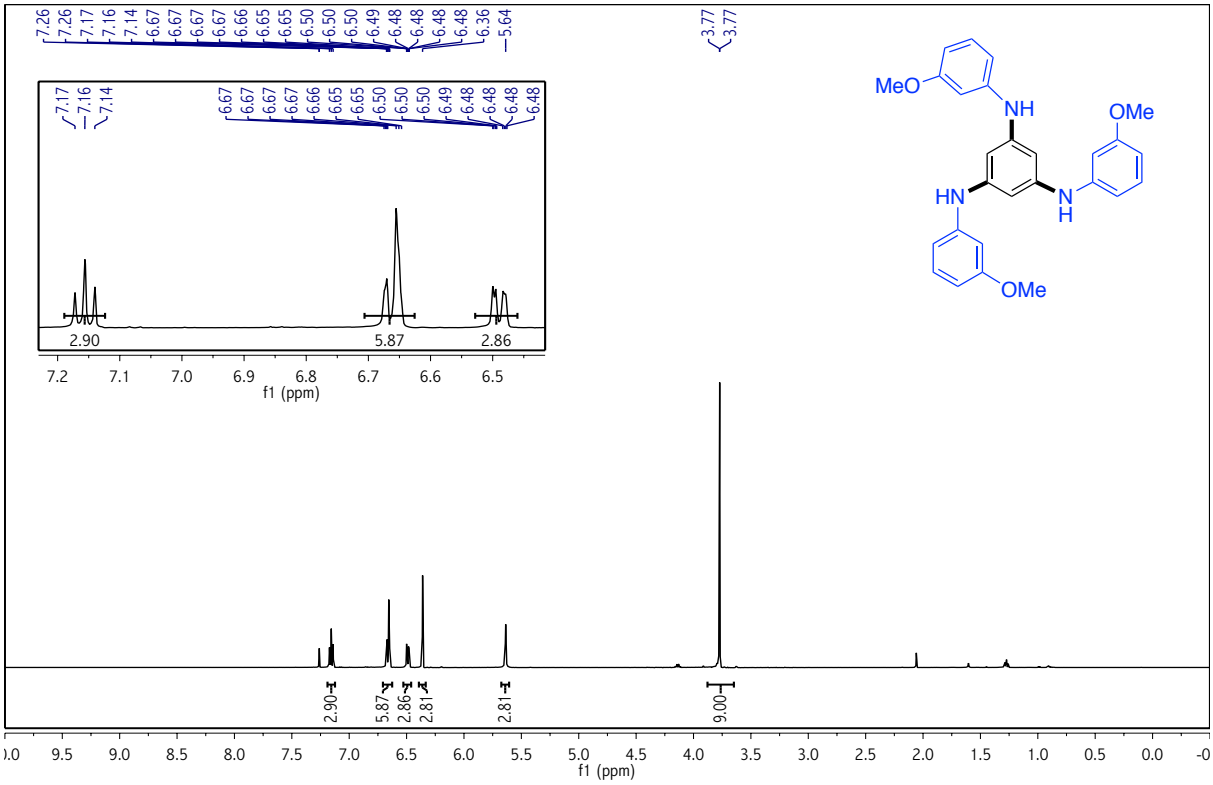

7.26
7.26
7.18
7.17
7.17
7.16
7.15
7.15
6.80
6.68
6.68
6.67
6.66
6.66
6.66
6.65
6.51
6.51
6.50
6.49
6.49
5.69
3.78
MeO
H
N
H
N
OMe
2.90
0.96
5.77
1.91
1.97
6.00
f1 (ppm)

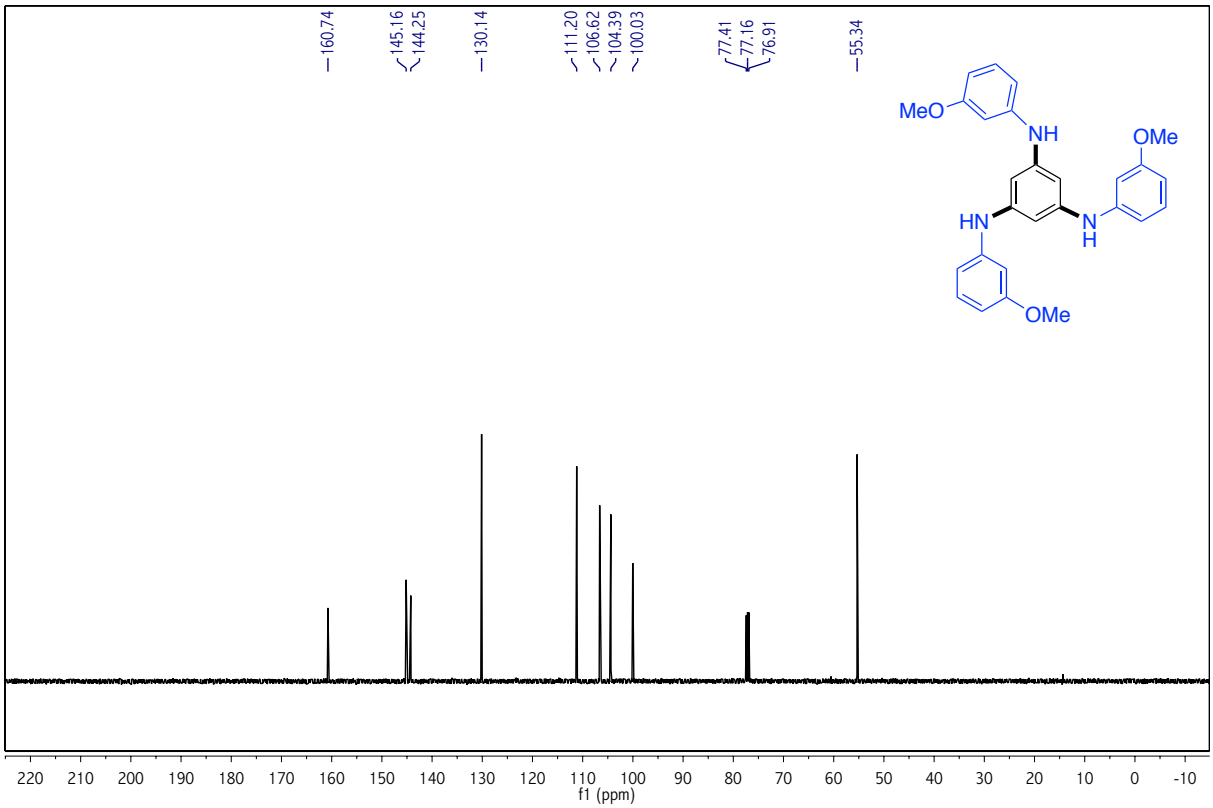

160.73
144.38
144.13
130.27
130.18
110.96
110.73
107.26
106.41
103.87
77.48
77.16
76.84
55.33
MeO
H
N
H
N
OMe
f1 (ppm)

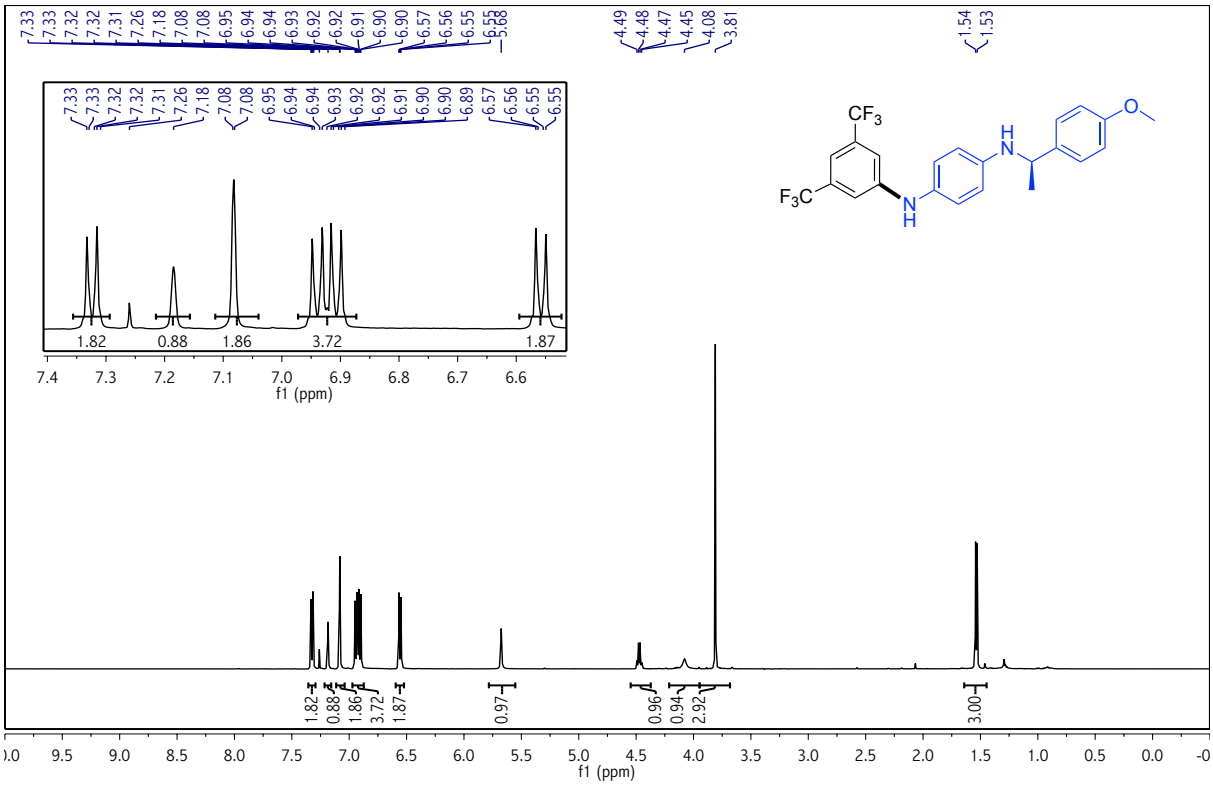

7.69
7.67
7.60
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.26
7.21
7.19
7.16
7.14
7.12
6.52
3.41
1.00
0.96
2.99
3.89
0.97
2.97
f1 (ppm)
H
N
F
OMe
OMe
HN
F


159.94
157.54
147.03
137.74
137.71
137.36
131.74
128.40
126.38
125.83
125.54
124.67
123.51
122.76
122.68
116.42
116.19
107.75
77.48
77.16
76.84
60.70
f1 (ppm)
H
N
F
OMe
OMe
HN
F


-120.20
-120.21
-120.22
-120.23
-120.24
-120.0
-120.1
-120.2
-120.3
-120.4
f1 (ppm)
H
N
F
OMe
OMe
HN
F
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300 -310
f1 (ppm)


7.26
7.17
7.16
7.14
6.67
6.66
6.65
6.50
6.49
6.48
6.36
5.64
3.77
2.90
5.87
2.86
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
f1 (ppm)
MeO
NH
OMe
HN
N
H
OMe
2.90
5.87
2.86
2.81
2.81
9.00
f1 (ppm)


160.74
145.16
144.25
130.14
111.20
106.62
104.39
100.03
77.41
77.16
76.91
55.34
MeO
NH
OMe
HN
N
H
OMe
f1 (ppm)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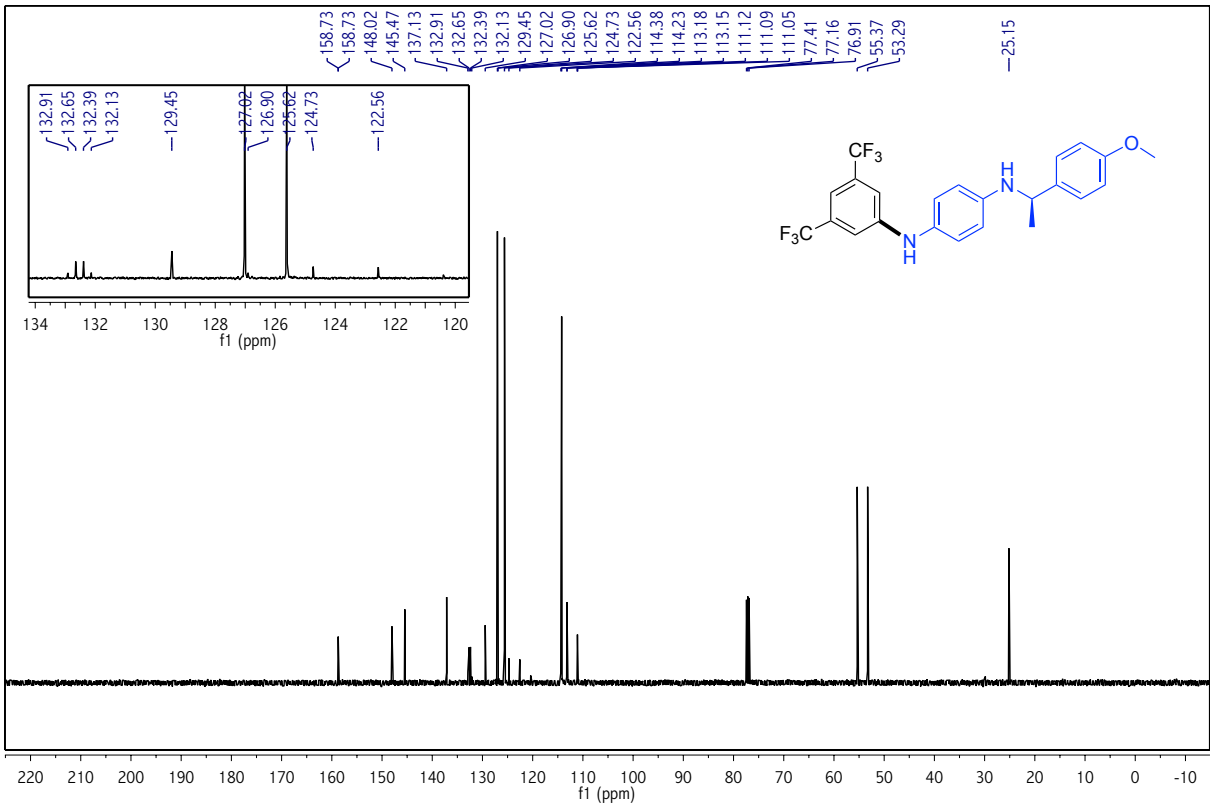
7.33
7.32
7.32
7.31
7.26
7.18
7.08
7.08
6.95
6.94
6.94
6.93
6.92
6.92
6.91
6.90
6.90
6.57
6.56
6.55
6.55
5.68
4.49
4.48
4.47
4.45
4.08
3.81
1.54
1.53
CF3
F3C
N
H
H
N
O
1.82
0.88
1.86
3.72
1.87
0.97
0.96
0.94
2.92
3.00
f1 (ppm)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158.73
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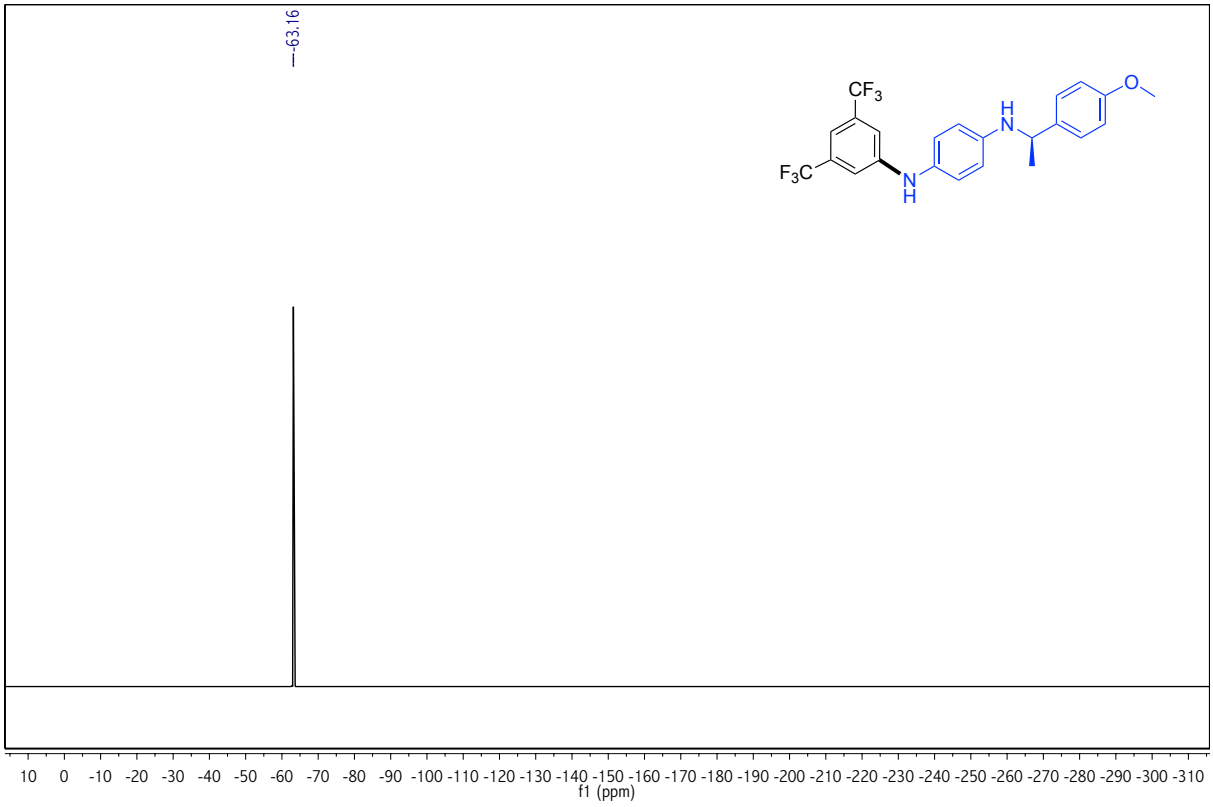
145.47
137.13
132.91
132.65
132.39
132.13
129.45
127.02
126.90
125.62
124.73
122.56
114.38
114.23
113.18
113.15
111.12
111.09
111.05
77.41
77.16
76.91
55.37
53.29
25.15
CF3
F3C
N
H
H
N
O
f1 (ppm)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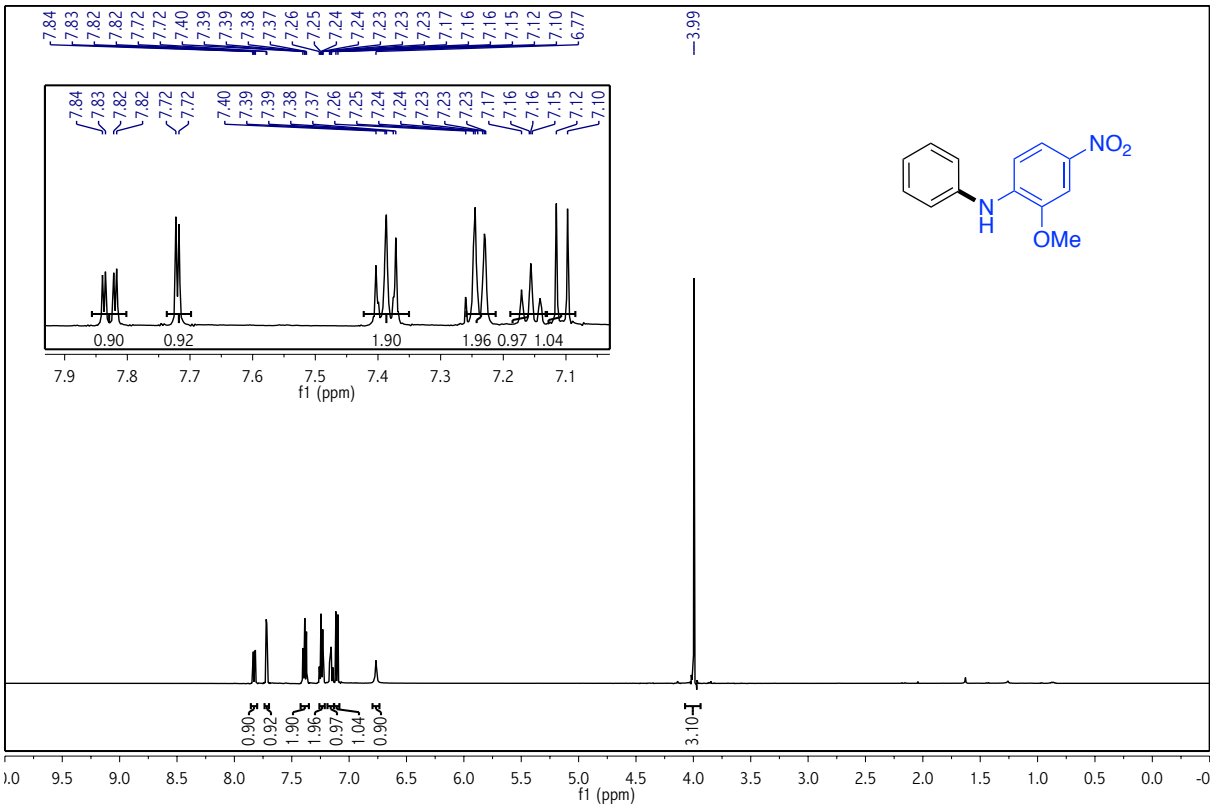
CF3
F3C
N
H
H
N
O
f1 (ppm)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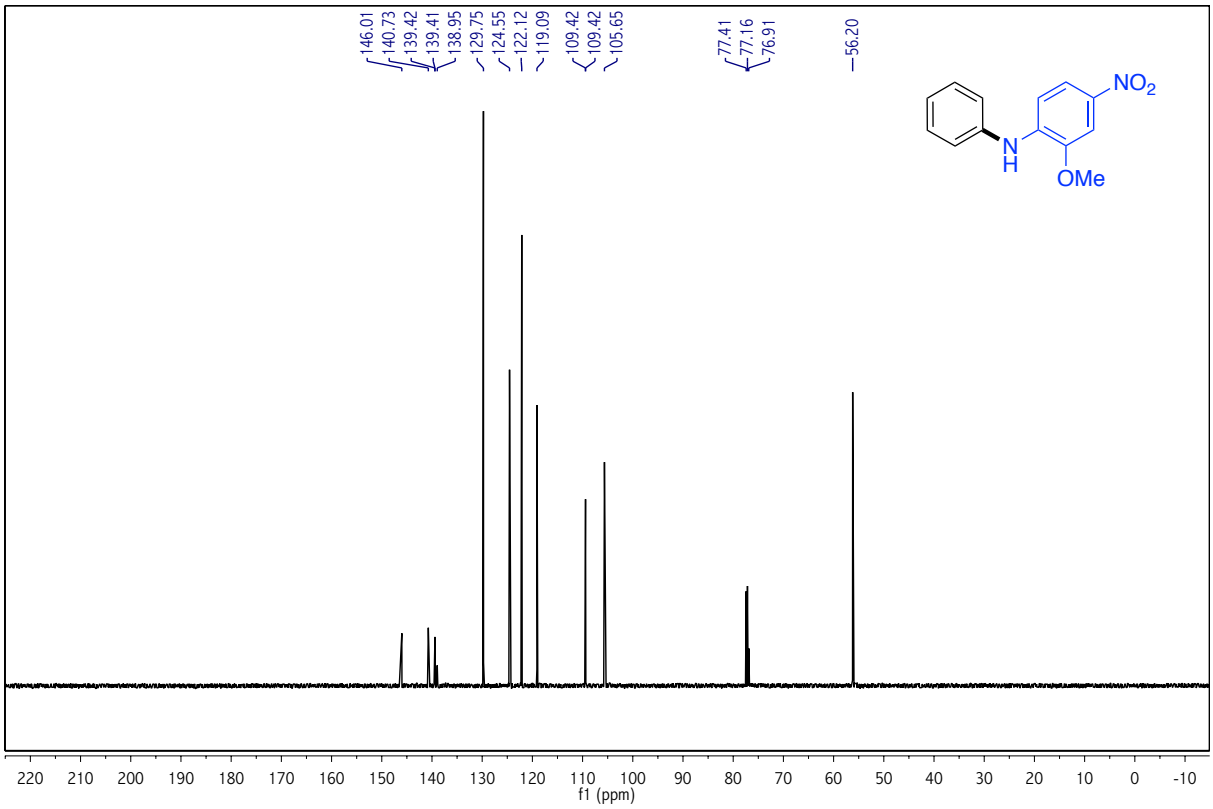
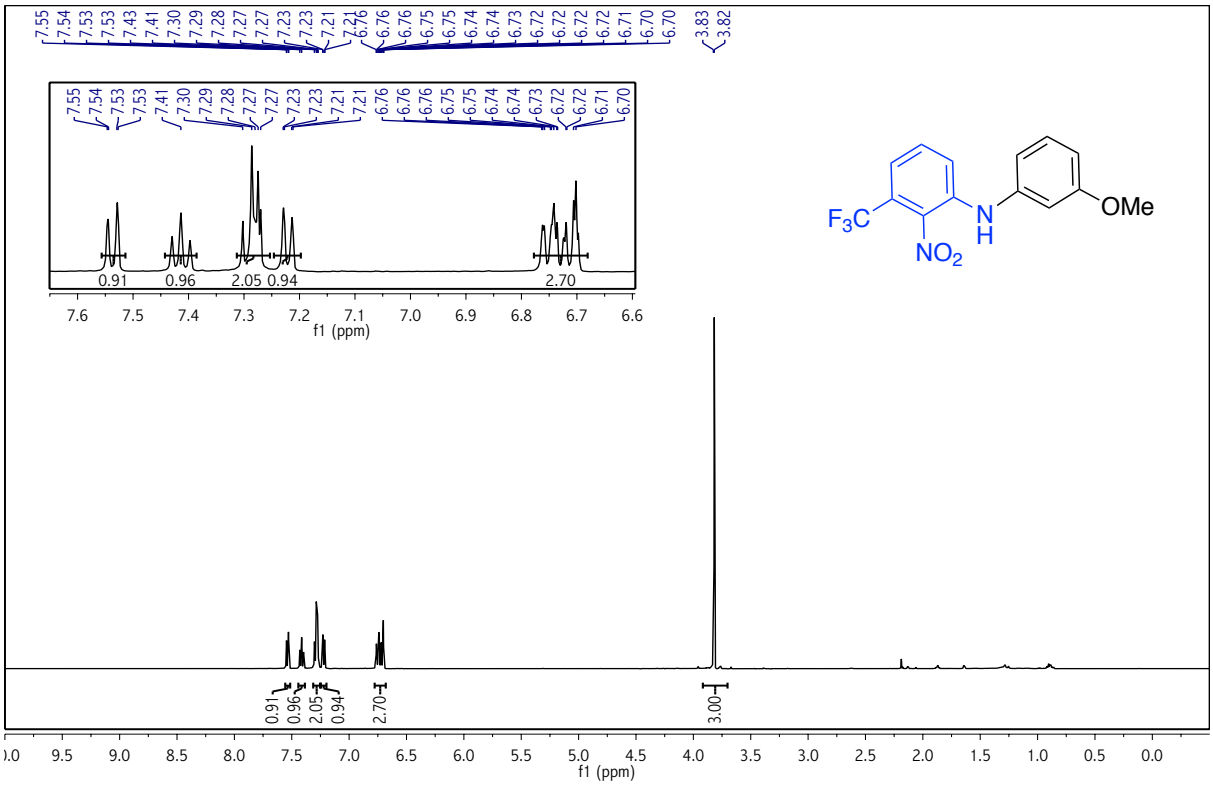
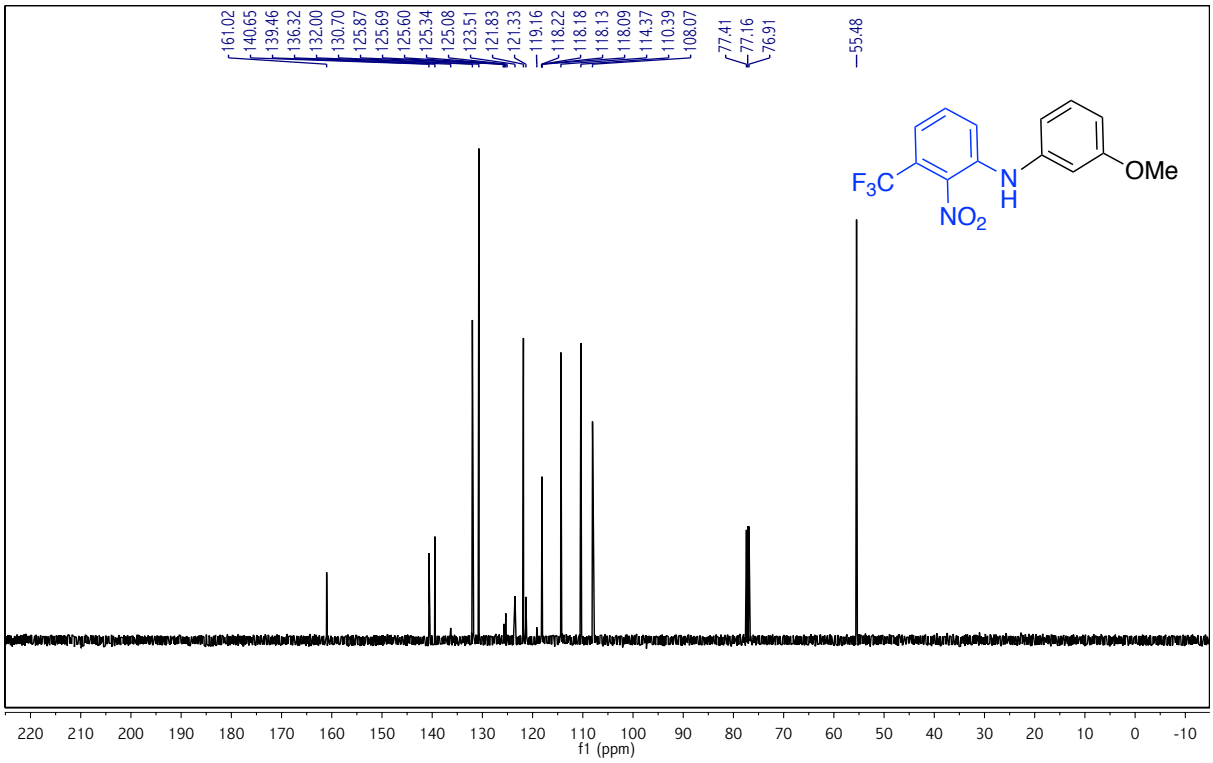
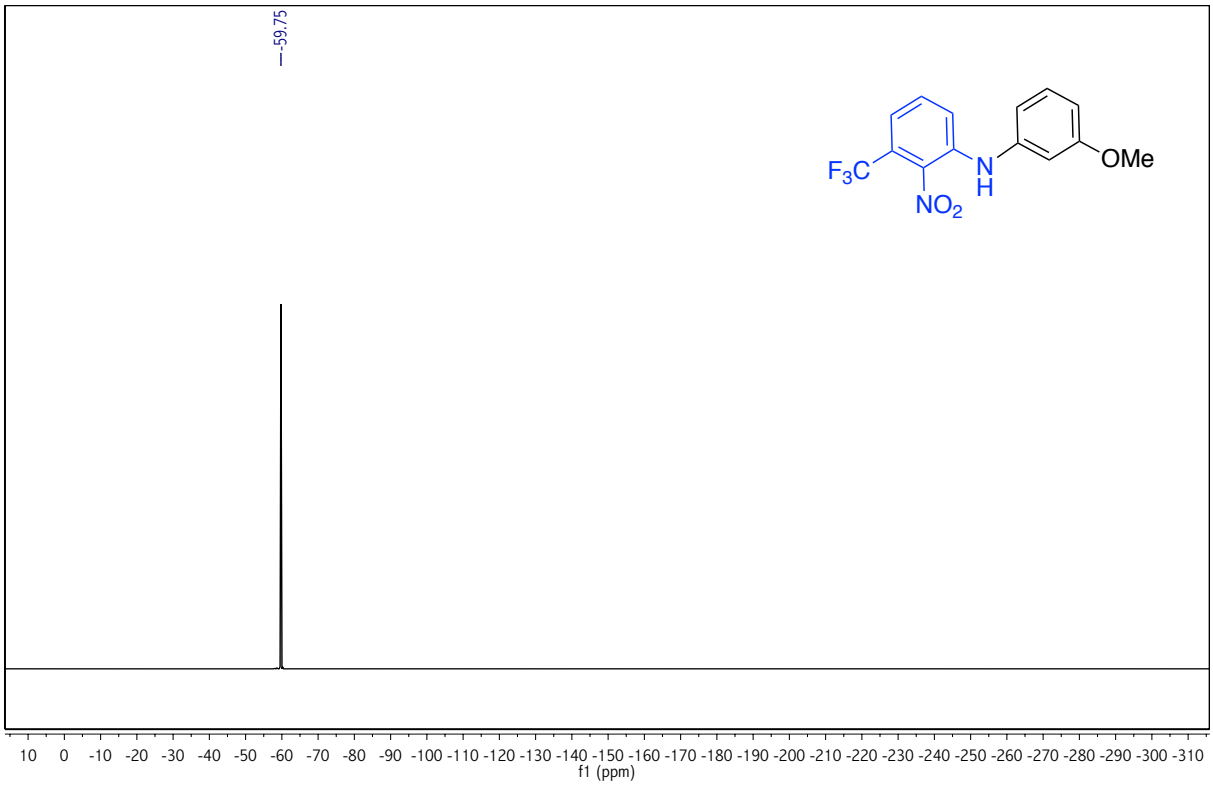
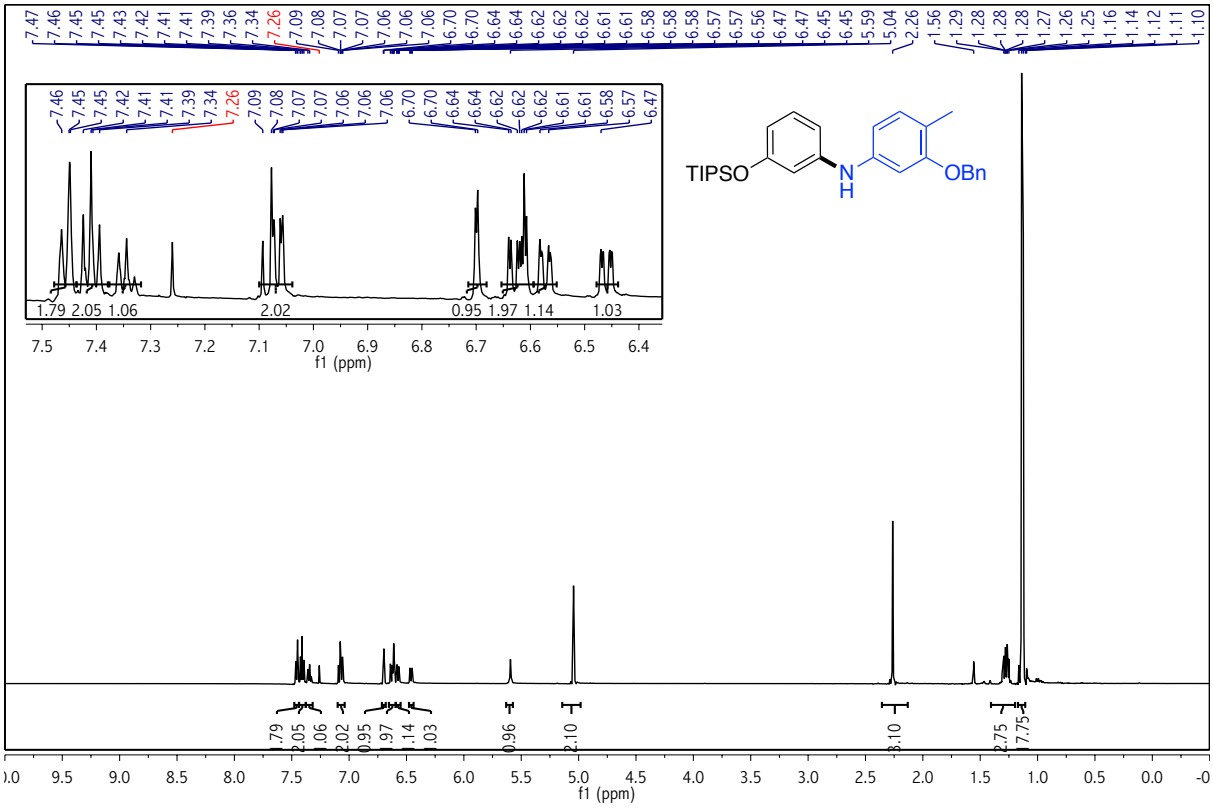
7.83
7.82
7.82
7.72
7.72
7.40
7.39
7.39
7.38
7.37
7.26
7.25
7.24
7.24
7.23
7.23
7.23
7.17
7.16
7.15
7.12
7.10
6.77
3.99
0.90
0.92
1.90
1.96
0.97
1.04
3.10
f1 (ppm)
NO2
N
H
OMe

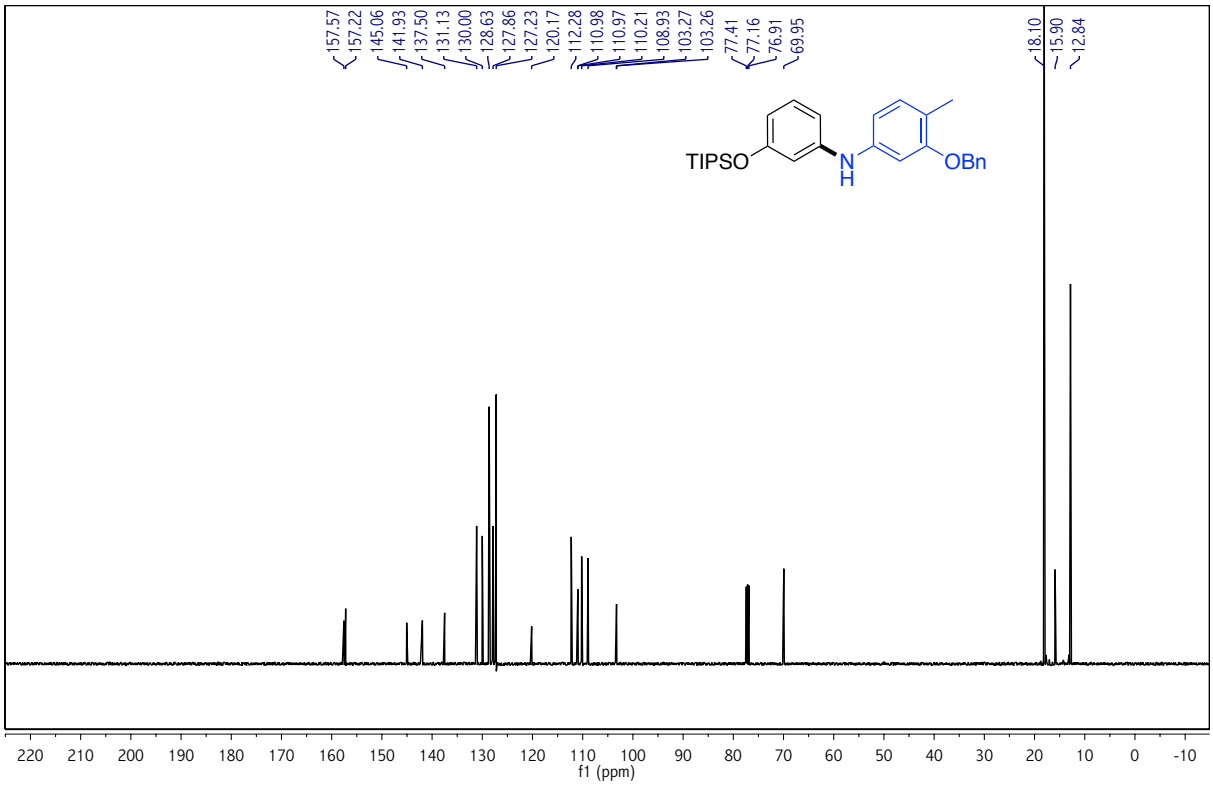

146.01
140.73
139.42
139.41
138.95
129.75
124.55
122.12
119.09
109.42
109.42
105.65
77.41
77.16
76.91
56.20
f1 (ppm)
NO2
N
H
OMe


7.55 7.54 7.53 7.53 7.43 7.41 7.30 7.29 7.28 7.27 7.27 7.23 7.23 7.21 7.21 6.76 6.76 6.76 6.75 6.75 6.74 6.74 6.73 6.72 6.72 6.72 6.72 6.71 6.70 6.70 3.83 3.82
0.91 0.96 2.05 0.94 2.70
f1 (ppm)
F3C
NO2
N
H
OMe
0.91 0.96 2.05 0.94 2.70 3.00
f1 (ppm)


161.02 140.65 139.46 136.32 132.00 130.70 125.87 125.69 125.60 125.34 125.08 123.51 121.83 121.33 119.16 118.22 118.18 118.13 118.09 114.37 110.39 108.07
77.41 77.16 76.91
55.48
F3C
NO2
N
H
OMe
f1 (ppm)


-59.75
F3C
NO2
N
H
OMe
f1 (ppm)


TIPSO
N
H
OBn
1.79 2.05 1.06
2.02
0.95 1.97 1.14
1.03
f1 (ppm)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127.23
120.17
112.28
110.98
110.97
110.21
108.93
103.27
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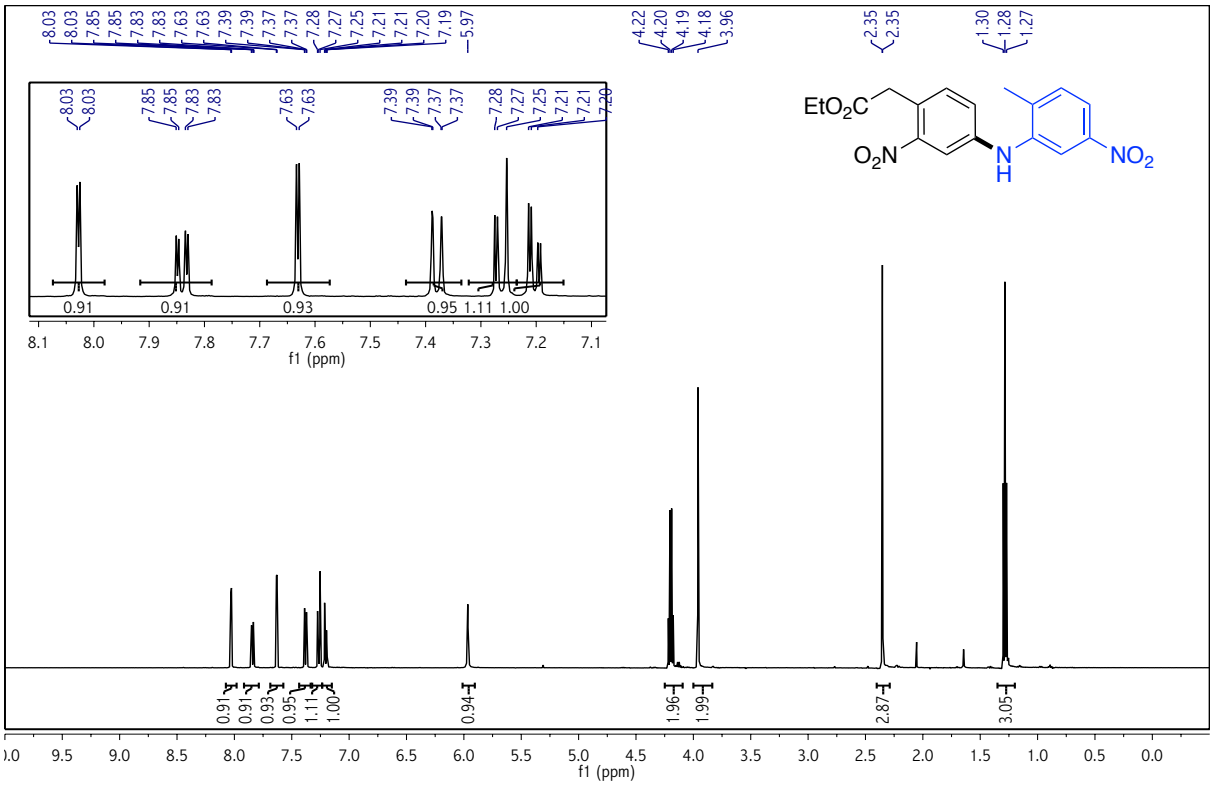
77.16
76.91
69.95
18.10
15.90
12.84
TIPSO
N
H
OBn
f1 (ppm)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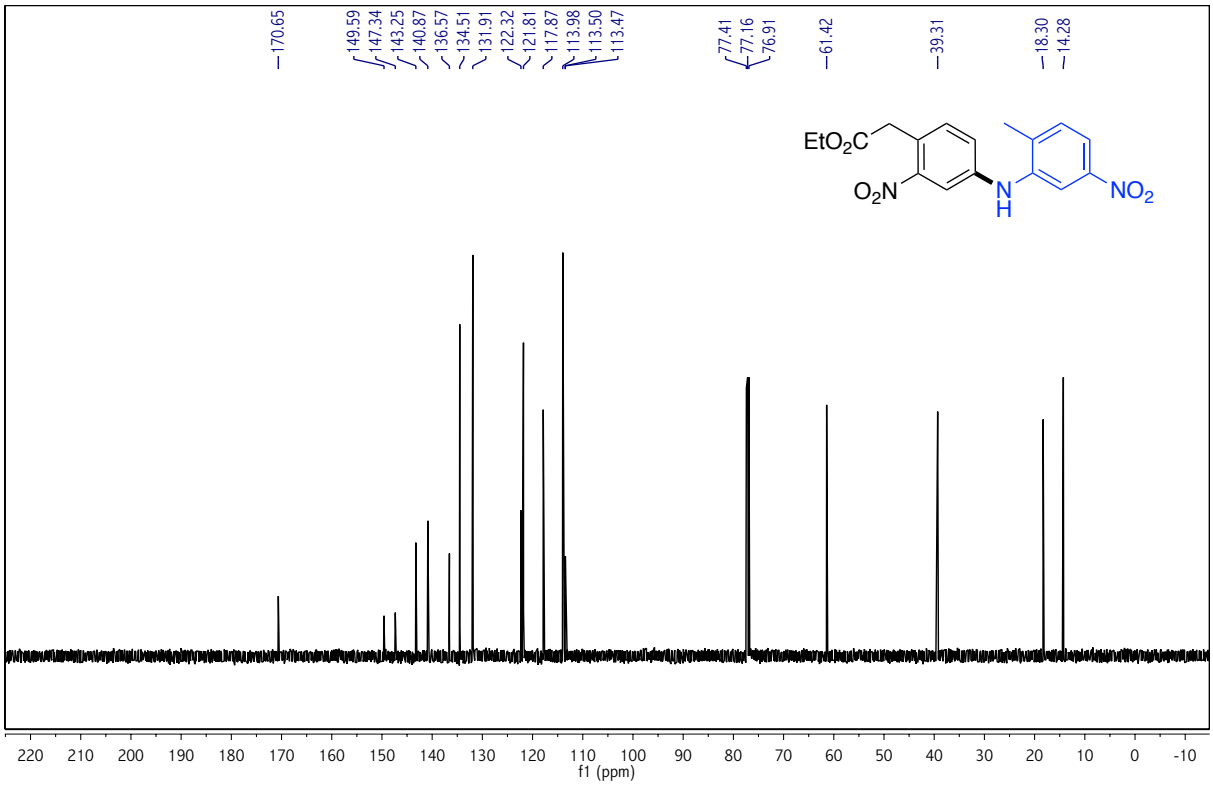
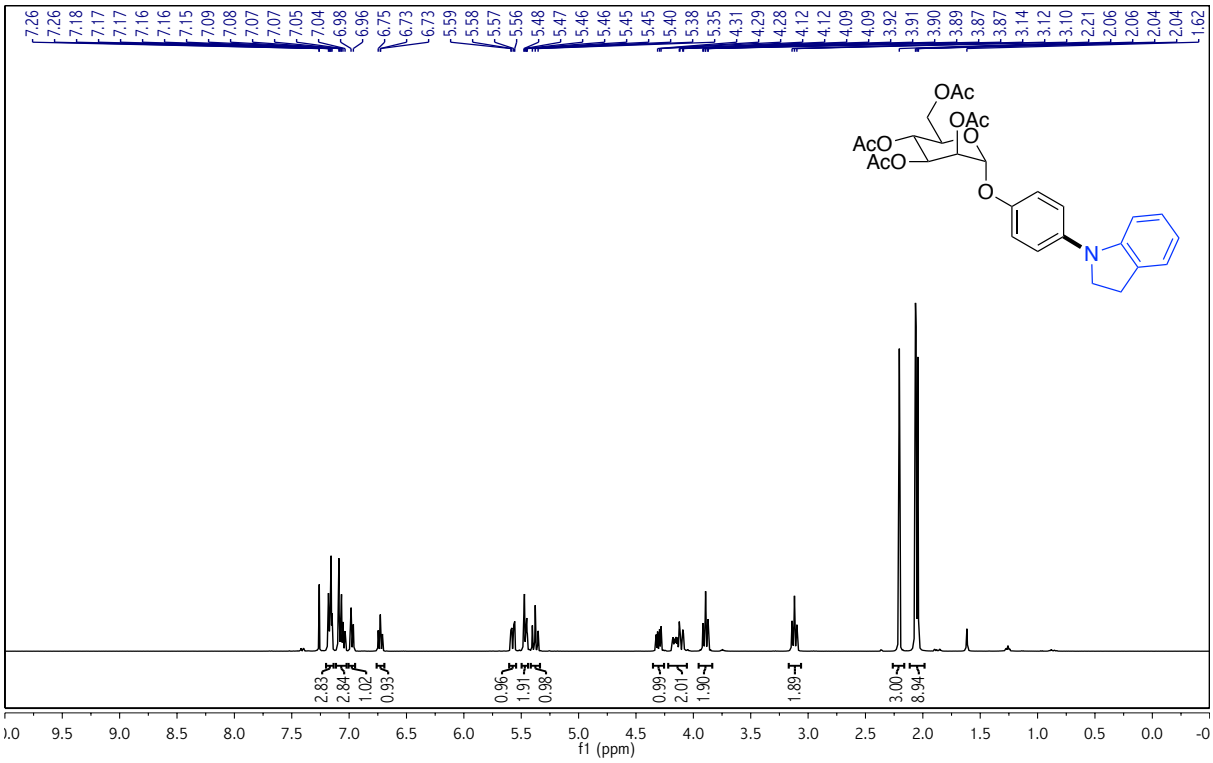
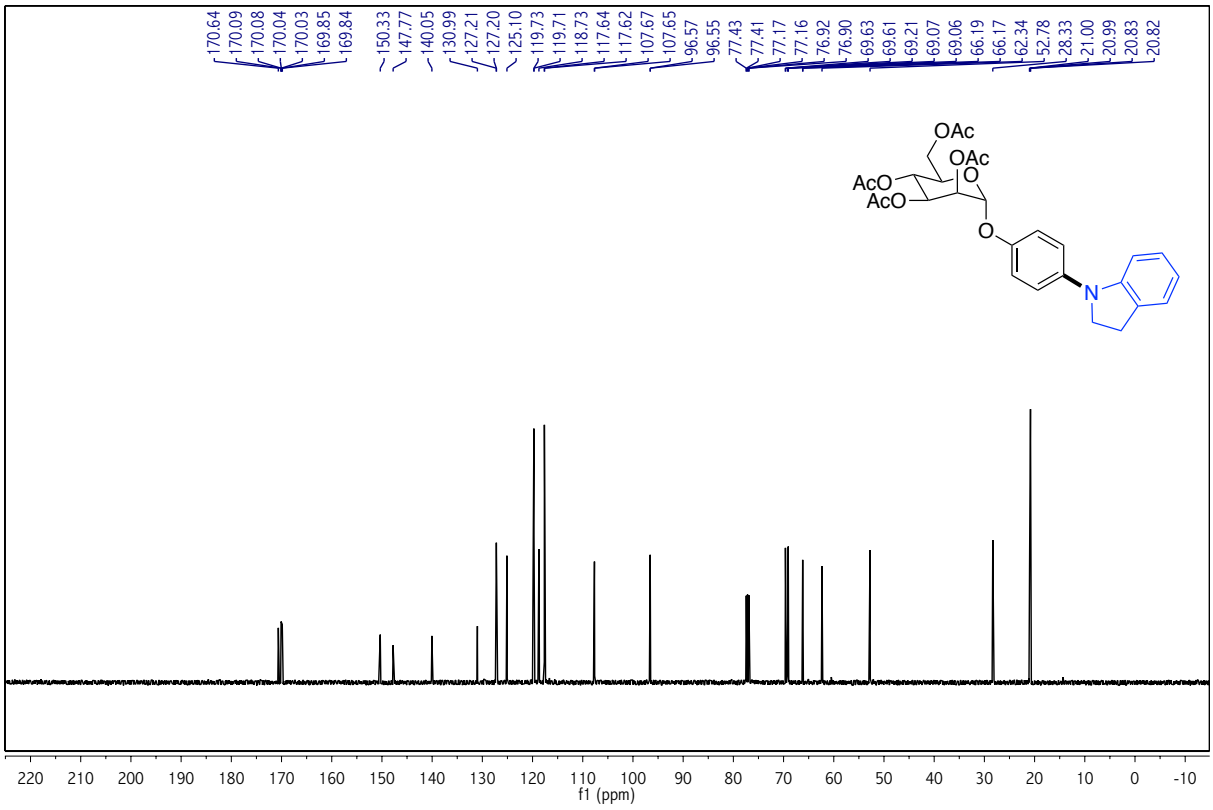
8.03
7.85
7.85
7.83
7.83
7.63
7.63
7.39
7.39
7.37
7.37
7.28
7.27
7.25
7.21
7.21
7.20
7.19
5.97
4.22
4.20
4.19
4.18
3.96
2.35
2.35
1.30
1.28
1.27
EtO2C
O2N
N
H
NO2
0.91
0.91
0.93
0.95
1.11
1.00
0.94
1.96
1.99
2.87
3.05
f1 (ppm)


170.65
149.59
147.34
143.25
140.87
136.57
134.51
131.91
122.32
121.81
117.87
113.98
113.50
113.47
77.41
77.16
76.91
61.42
39.31
18.30
14.28
EtO2C
O2N
N
H
NO2
f1 (ppm)


OAc
OAc
AcO
AcO
O
O
N
2.83
2.84
1.02
0.93
0.96
1.91
0.98
0.99
2.01
1.90
1.89
3.00
8.94
f1 (ppm)


170.64
170.09
170.08
170.04
170.03
169.85
169.84
150.33
147.77
140.05
130.99
127.21
127.20
125.10
119.73
119.71
118.73
117.64
117.62
107.67
107.65
96.57
96.55
77.43
77.41
77.17
77.16
76.92
76.90
69.63
69.61
69.21
69.07
69.06
66.19
66.17
62.34
52.78
28.33
21.00
20.99
20.83
20.82
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OAc
AcO
AcO
O
O
N
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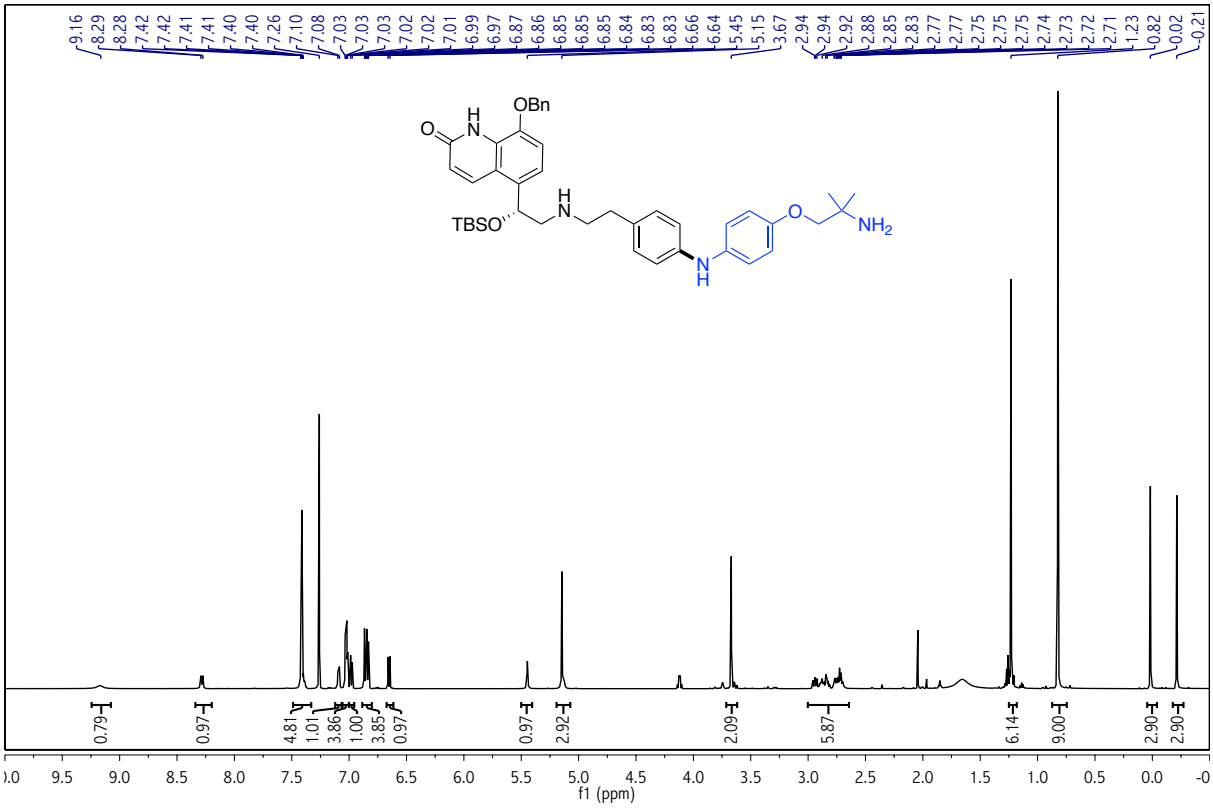
f1 (ppm)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7.03
7.03
7.02
7.02
7.01
6.99
6.97
6.87
6.86
6.85
6.85
6.85
6.84
6.83
6.83
6.66
6.64
5.45
5.15
3.67
2.94
2.94
2.92
2.88
2.85
2.83
2.77
2.77
2.75
2.75
2.75
2.74
2.73
2.72
2.71
1.23
0.82
0.02
-0.21
OBn
H
N
O
H
N
TBSO
O
NH2
N
H
0.79
0.97
4.81
1.01
3.86
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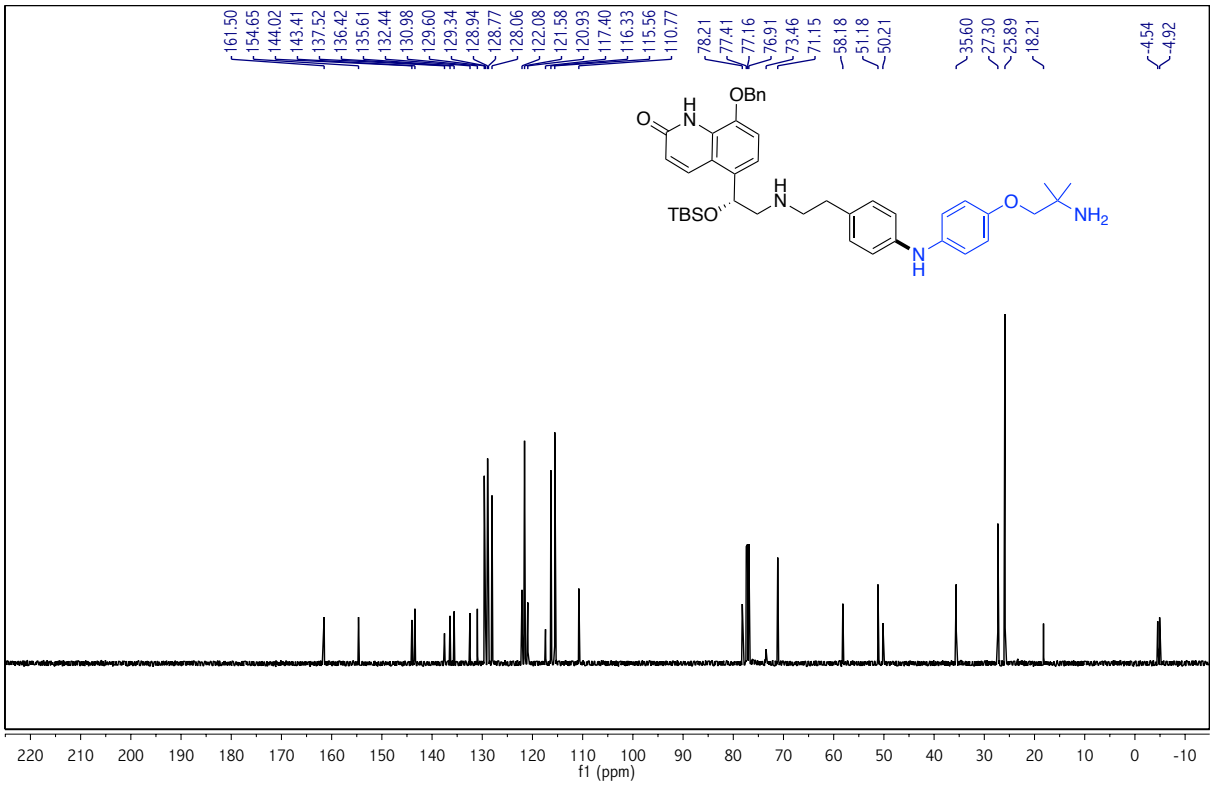
2.90
f1 (ppm)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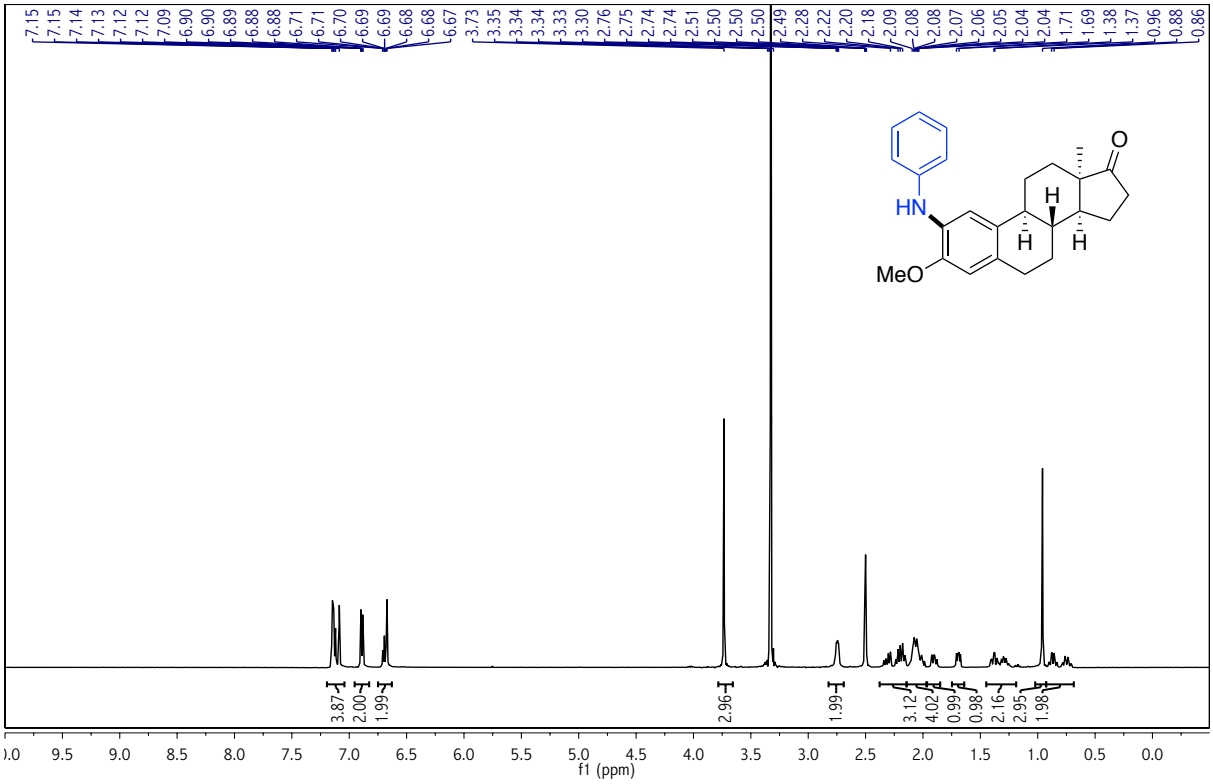
128.06
122.08
121.58
120.93
117.40
116.33
115.56
110.77
78.21
77.41
77.16
76.91
73.46
71.15
58.18
51.18
50.21
35.60
27.30
25.89
18.21
-4.54
-4.92
OBn
H
N
O
H
N
TBSO
O
NH2
N
H
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.13
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6.88
6.71
6.71
6.70
6.69
6.69
6.68
6.68
6.67
3.73
3.35
3.34
3.34
3.33
3.30
2.76
2.75
2.74
2.74
2.51
2.50
2.50
2.50
2.49
2.28
2.22
2.20
2.18
2.09
2.08
2.08
2.07
2.06
2.05
2.04
2.04
1.71
1.69
1.38
1.37
0.96
0.88
0.86
HN
O
H
H
H
MeO
3.87
2.00
1.99
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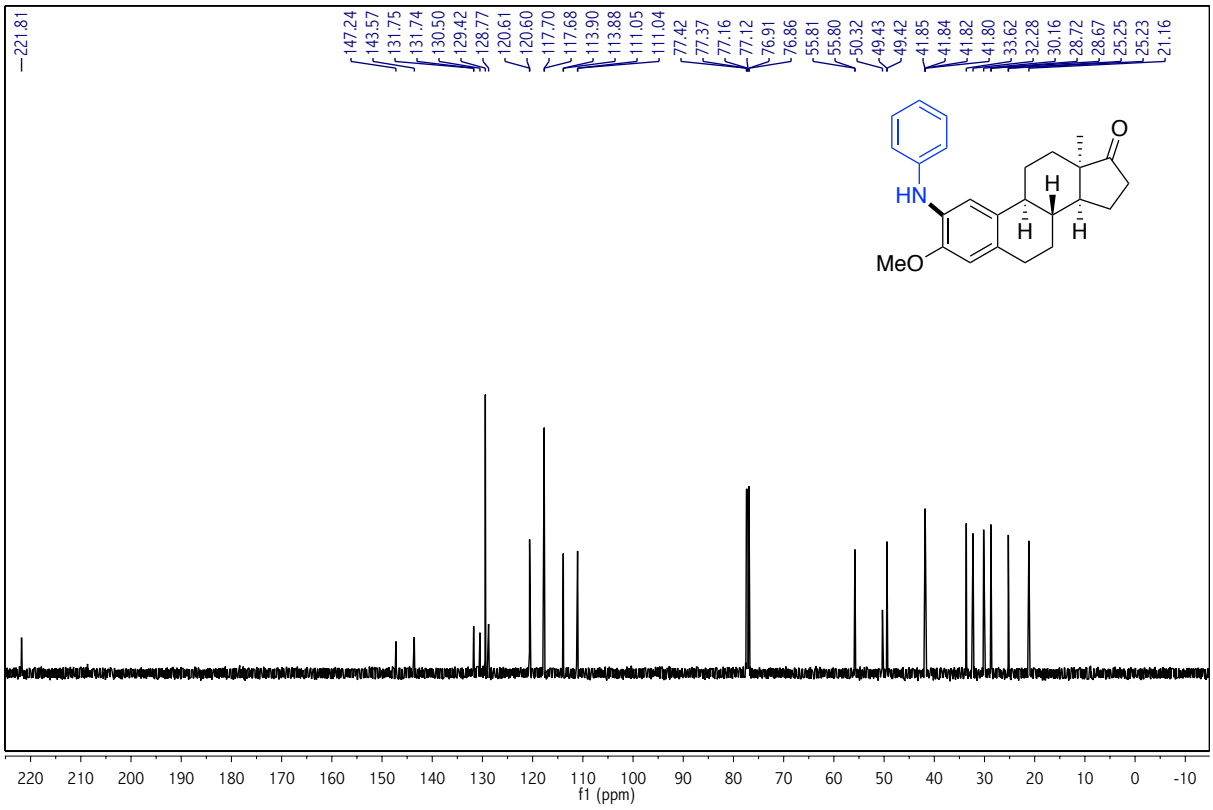
1.99
3.12
4.02
0.99
0.98
2.16
2.95
1.98
f1 (ppm)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120.60
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113.90
113.88
111.05
111.04
77.42
77.37
77.16
77.12
76.91
76.86
55.81
55.80
50.32
49.43
49.42
41.85
41.84
41.82
41.80
33.62
32.28
30.16
28.72
28.67
25.25
25.23
21.16
HN
MeO
H
H
H
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)