Graphical Abstract

Development of a cascade reaction to access complex tetrahydro-3,4'-biisoquinoline

Momar Toure*, Saul Jaime-Figueroa, George M. Burslem, Philipp M. Cromm, Gaspard Hedouin, and Craig M. Crews

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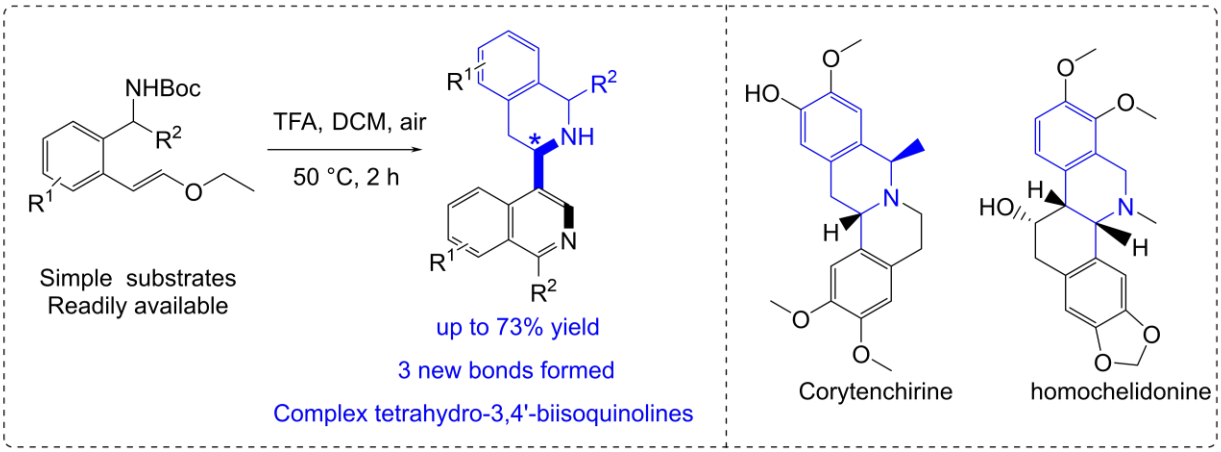

Development of a cascade reaction to access complex tetrahydro-3,4'-biisoquinoline.

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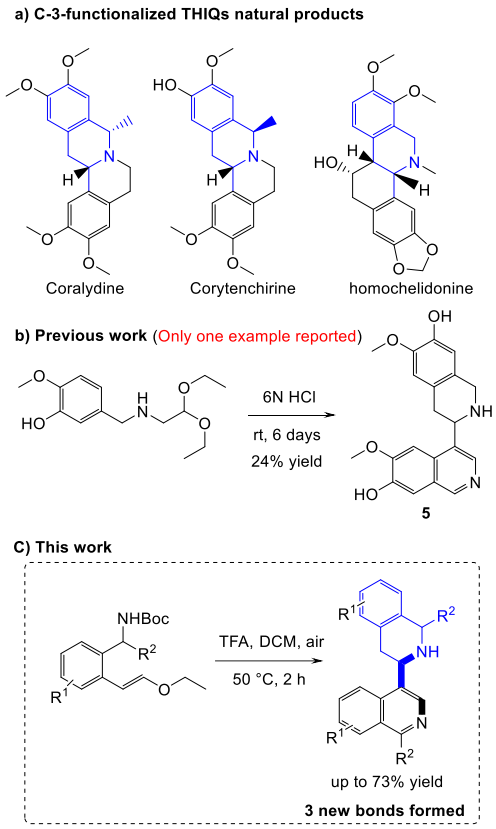
ABSTRACT

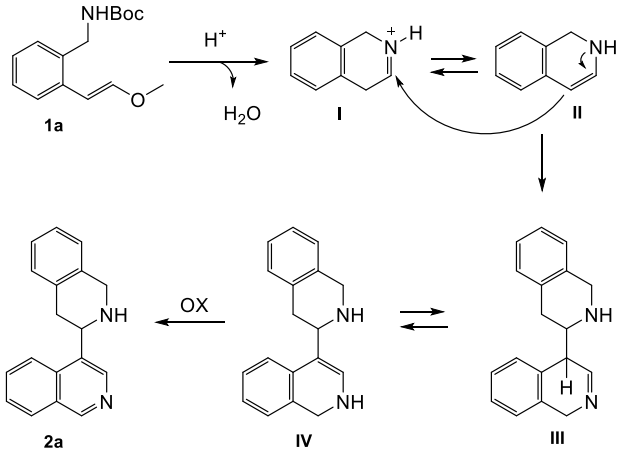
In an effort to develop a new synthetic route to access complex tetrahydro-3,4'-biisoquinolines (THBIQs) as novel lead structures of pharmaceutical interests, an unprecedented cascade reaction was developed. Starting from simple and readily accessible substrates, C-3-functionalized tetrahydrobiisoquinolines were obtained with high level of complexity and molecular diversity by the formation of 3 new bonds.

C-3-functionalized tetrahydroisoquinolines (THIQs) structural motifs are found in numerous natural products such as the tetrahydroprotoberberine alkaloids (coralydine and corytenchirine) and the benzophenanthridine alkaloids (homochelidonine, norchelidonine and chelamine, Scheme 1a).[1] These scaffolds are also highly valuable compounds in drug discovery. [2] Therefore, in the past few years, there has been a growing interest in developing new methods for the synthesis of these building blocks.[3] However, unlike C-1-functionalized tetrahydroisoquinolines which are easily accessible, the synthesis of C-3-arylated tetrahydroisoquinolines without prefunctionalization is highly challenging. Methodologies such as the Bischler-Napieralski cyclization/reduction sequence,[4] radical cyclization approach,[5] and palladium-catalysed aryl–aryl coupling/reduction reactions[6] were mostly used. However, all of these methods require multi step synthesis. Moreover, none of these strategies are of sufficiently general applicability, especially for the synthesis of the very rare tetrahydro-3,4'-biisoquinolines (THBIQs). THBIQs structural motifs are very scarce in the literature. Only one known example (**5**) was reported thus far by Bobbitt *et al*. in 1965 (Scheme 1b).[8] Using very long reaction time (6 days), **5** was isolated as a byproduct in 24% yield from a Friedel–Crafts approach to tetrahydroisoquinolines. Furthermore, NMR data were not reported for **5**. Intrigued by this complex tetrahydro-3,4'-biisoquinoline (**5**) and its potential utility in one of our medicinal chemistry project, we thought that a cascade reaction sequence could be more suitable to access this structurally interesting THBIQs scaffold (Scheme 1c).[9] Herein, we introduce an unprecedented cascade approach under mild conditions and using simple achiral/chiral and readily accessible substrates for the synthesis of various substituted tetrahydro-3,4'-biisoquinolines.



Scheme 1. C-3-functionalized tetrahydroisoquinolines.

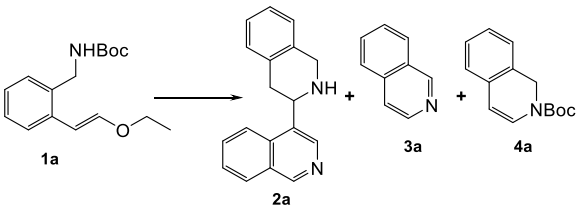
In an effort to develop a novel cascade approach to access tetrahydro-3,4'-biisoquinoline, we hypothesized that intermediate **1a**, which could be easy made through a Suzuki coupling from the corresponding bromobenzylcarbamate and 2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane,[10] could give iminium **I** under acidic condition (Scheme 2). **I** could be in equilibrium with the corresponding enamine **II** through an imine to enamine tautomerization step in order to start the cascade process.[8] In fact, we rationalized that as soon as **II** is generated, it will immediately react with **I** leading to intermediate **III**. The later can undergo another iminium/enamine equilibrium to give **IV**. Finally, in the presence of air, **IV** can be oxidized to the desired tetrahydro-3,4'-biisoquinoline **2a**.



Scheme 2. Our approach to C-3-functionalized tetrahydroisoquinolines.

Initial investigations focused on the reaction of **1a** in the presence of con. HCl to generate **2a**. We were pleased to find that with con. HCl as the solvent, this reaction provided isoquinoline **3a** in 35% yield and 8% yield of desired product **2a** after 16 h at room temperature (Table 1, entry 1). This initial experiment established the feasibility of the proposed sequence albeit in very low yield. We next examined the reaction in a variety of alternative solvents using organic acid as an additive. As shown in entries 2−8 of Table 1, these studies revealed that in the presence of acetic acid at reflux temperature, only enamine **4a** was isolated in 61% yield suggesting that acetic acid was insufficiently acidic to deprotect the BOC group under this condition. Gratifyingly, the reaction proceeded efficiently with trifluoroacetic acid (TFA) as the solvent, yielding 67% of the desired product after 2 h at room temperature. Heating **1a** at 50 ºC under TFA did not improve the yield (53% isolated). With further optimization, we found out that dichloromethane was the optimal cosolvent. In a dichloromethane/TFA mixture (1:1) at room temperature, the reaction proceeded efficiently giving the desired product in 58% yield. Finally, the best yields were obtained with a dichloromethane/TFA mixture (1v:1v) at 50 ºC. In this condition, the desired tetrahydro-3,4'-biisoquinoline is isolated in 73% yield.

Table 1. Optimization of the reaction conditions.

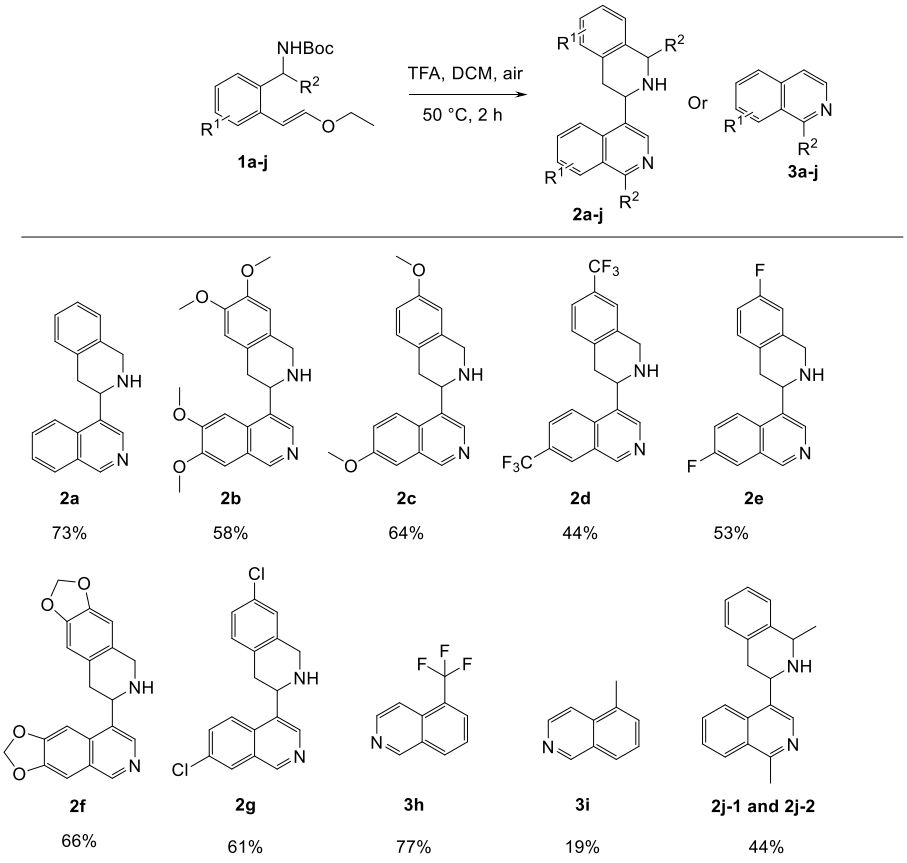


Entry[a]	solvent	additive	yield[f] (**2a**) %	yield[f] (**3a**) %	yield[f] (**4a**) %
1	con. HCl	none	8	35	-
2	Acetic acid	none	-	-	49[b]
3	TFA	non	67	trace	-
4	DCM	TFA[c]	58	trace	-
5	DCM	TFA[c]	73[d]	trace	-
6	DCM	TFA[e]	trace	trace	-
7	chloroform	TFA[c]	52[d]	trace	-
8	DCE	TFA[c]	63[d]	trace	-

[a]Conditions: **1a** (0.2 mmol), in 1 mL solvent for 2 h at rt. [b]at 100°C. [c] solvent/TFA 1mL, (1v/1v). [d] at 50°C. [e] 20 equiv. [f]Isolated yields after chromatography

The scope of this transformation was assessed next using a series of different vinylbenzylcarbamate (1b-1g). **1b**, **1c**, **1d, 1e**, **1f** and **1g** were synthesized and carried to the next step. The corresponding products **2b**, **2c**, **2d, 2e, 2f** and **2g** were isolated in moderate to acceptable yield from 40 to 66%. We discovered that this cascade reaction tolerated various electron-donating and electron-withdrawing groups, and that the outcome of this process is minimally perturbed by substitution on the aryl ring in position 4 and 5. However, the reaction does not tolerate substitution in the

position 1 on the aryl ring as highlighted by the isolation of product **3h** in 77% yield. In this case, 5-(trifluoromethyl)isoquinoline (**3h**) was observed along with unidentified by products. To evaluate whether this is due to steric or electron-withdrawing effects of the trifluoromethyl group, **1i** was synthesized and carried to the next step. In this case also, 5-methylisoquinoline (**3i**) was obtained in 19% yield confirming that steric hindrance has a major impact on the reaction outcome and yield. Finally, intrigued by the high sensitivity of reaction to steric effects, we synthesized reactant **1j** which has a methyl group in α-position to the NHBoc group. Interestingly, steric hindrance in this position is well tolerated since two separable diasteroisomers **2j-1** and **2j-2** were isolated in 44% overall yield (22% each). This finding highlights the robustness of this cascade reaction for the construction of C-3-substituted tetrahydroisoquinolines. The keystone of the present cascade process are the successive formation of two iminium intermediates as shown in Scheme 2.



Scheme 3. Substrate scope of the tetrahydro-3,4'-biisoquinoline synthesis.

In conclusion, we have successfully developed an unprecedented cascade approach using mild conditions to access complex tetrahydro-3,4'-biisoquinolines. The keystone of the present cascade process is the successive formation of two iminium intermediates resulting in the formation of 3 new bonds, therefore allowing creation of molecular complexity and diversity starting from simple substrates. The series of tetrahydro-3,4'-biisoquinoline reported in this work represent potential useful substrates for different fields of chemistry and promising molecules of biological interest.

Acknowledgements

We acknowledge the financial support of the Leukemia & Lymphoma Society and the NIH (R35CA197589).

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Supplementary Material

Supplementary data (experimental procedures and compound characterization) associated with this article can be found, in the online version.

SUPPORTING INFORMATION

Development of a cascade reaction to access complex tetrahydro-3,4'-biisoquinoline

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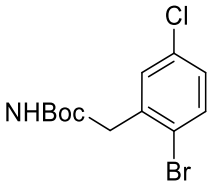
EXPERIMENTAL SECTION

General comments. Unless otherwise indicated, common reagents or materials were obtained from commercial source and used without further purification. Tetrahydrofuran (THF) and Dichloromethane (CH_2Cl_2) was dried by a PureSolv^{TM} solvent drying system. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV or KMnO4. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent DD$_2$ 500 (500 MHz ^{1}H; 125 MHz ^{13}C) or Agilent DD$_2$ 600 (600 MHz ^{1}H; 150 MHz ^{13}C) or Agilent DD$_2$ 400 (400 MHz ^{1}H; 100 MHz ^{13}C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual $CDCl_3$ (δ 7.26 ppm ^{1}H; δ 77.00 ppm ^{13}C), CD_3OD (δ 3.31 ppm ^{1}H; δ 49.00 ppm ^{13}C), or d^6-DMSO (δ 2.50 ppm ^{1}H; δ 39.52 ppm ^{13}C). NMR chemical shifts were expressed in ppm relative to internal solvent peaks, and coupling constants were measured in Hz. (bs = broad signal). ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as an internal standard (δ 0.0 ppm). Mass spectra were obtained using electrospray ionization (ESI) on a time of flight (TOF) mass spectrometer. All microwave reactions were conducted in sealed reaction vessels (2-5 mL) using a Biotage Initiator+ microwave reactor operating at the normal absorption level. The reaction temperatures were measured using IR. Reaction times refer to the hold time at the desired set temperature.

Synthesis of the bromo aryl precursor 0a-j.
Substrates **0a**, **0c**, **0f**, were purchased from commercial vendors. Substrates **0b**[1], **0d**[2], **0f**[1] were prepared according to references 1 and 2.

tert-butyl (2-bromo-5-chlorobenzyl)carbamate (**0g**).



To a solution of (2-bromo-5-chloro-phenyl)methanamine (500 mg, 2.27 mmol) in dry DCM (10 mL), under argon, was added TEA (0.35 ml, 2.49 mmol) and BOC anhydride (593.89 mg, 2.72 mmol) and the solution was stirred at room temperature overnight. The reaction mixture was washed with water (2x10 mL). The

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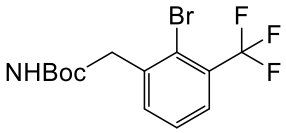
organic layer was dried over Na_2SO_4 and evaporated under vacuum to obtain the product 704 mg (96.8%) of tert-butyl N-[(2-bromo-5-chloro-phenyl)methyl]carbamate as a white solid.

^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 (d, *J* = 8.3 Hz, 1H), 7.35 (s, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 5.02 (bs, 1H), 4.34 (d, *J* = 5.4 Hz, 2H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, 500 MHz, Chloroform-d) δ: 155.64, 147.15, 139.72, 133.71, 129.25. 128.86, 120.98, 79.88, 44.58, 28.35.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{12}H_{16}BrClNO_2$, 320.0053. Found 320.0643.

tert-butyl (2-bromo-3-(trifluoromethyl)benzyl)carbamate (**0h**).



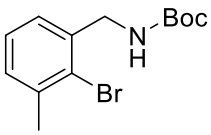
To a solution of [2-bromo-3-(trifluoromethyl)phenyl]methanamine;hydrochloride (1.00 g, 3.45 mmol, 1 eq) in dry DCM (10 mL), under argon, was added Triethylamine(0.72 mL, 5.16 mmol, 1.5 eq) and BOC anhydride (0.9017 g, 4.13 mmol, 1.2 eq) and the solution was stirred at room temperature overnight. The reaction mixture was washed with water (2x10 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to obtain the product as a white solid (1.17 g, 96 %).

^{1}H NMR (500 MHz, Chloroform-d) δ: 7.62 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 5.09 (br.s, 1H), 4.46 (d, J = 6.2 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-d) δ: 155.85, 140.83, 132.99, 130.98 (q, J = 30.8 Hz), 127.58, 127.07 (q, J = 5.5 Hz), 123.17 (q, J = 273.5 Hz), 121.34, 80.14, 45.43, 28.52.

LC/MS (ESI); m/z $[M+Na]^+$: Calcd. for $C_{13}H_{15}{}^{79}BrF_3NNaO_2$, 376.1570. Found 376.2290.

tert-butyl (2-bromo-3-methylbenzyl)carbamate (**0i**)**.**



To a mixture of (2-bromo-3-methyl-phenyl)methanamine (510,2 mg, 2,55 mmol), TEA (0,71 ml, 5,1 mmol) and DMAP (3,12 mg, 0,03 mmol) in Tetrahydrofuran (20 ml), BOC anhydride (0,73 ml, 3,19 mmol) was added and the reaction mixture stirred at rt for 16 h. The solvent was removed under reduced pressure and the crude purified via flash chromatography to yield 518 mg (68%) of tert-butyl N-[(2-bromo-3-methyl-phenyl)methyl]carbamate.

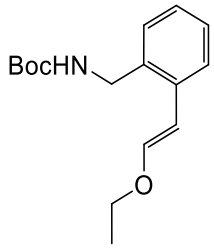
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 – 7.13 (m, 3H), 5.04 (s, 1H), 4.40 (d, J = 6.3 Hz, 2H), 2.42 (s, 3H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.86, 138.79, 138.42, 130.01, 127.26, 126.29, 79.70, 45.72, 28.55, 23.73.

LC/MS: calc. $[M\text{-}Boc+H]^+$ for $C_8H_{11}BrN$ = 200.0069; found = 200.0489.

Synthesis of 1.

tert-butyl (E)-(2-(2-ethoxyvinyl)benzyl)carbamate (**1a**).



To a solution of *tert*-butyl N-[(2-bromophenyl)methyl]carbamate (499 mg, 1.74 mmol, 1 eq) in Dioxane (21 mL) was added K_2CO_3 (746.7 mg, 5.40 mmol, 3.1 eq) and Water (5.00 mL). The reaction mixture was degassed under vacuum and purged with argon (5x). Then, Tricyclohexylphosphine (50.7 mg, 0.181 mmol, 0.1 eq), $Pd(dba)_2$ (49.7 mg, 0.09 mmol, 0.05 eq) and 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.35 mL, 1.66 mmol, 0.95 eq) were added into. The reaction mixture was heated with vigorous stirring at 80 °C and stirred for 2 h. The reaction was followed by TLC (DCM:Hexane, 1:1). After completion, it was poured onto an aqueous saturated solution of NaCl (100 mL) and the product was extracted with EtOAc (2x100 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The

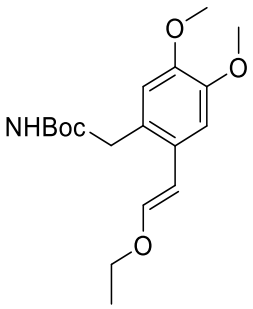
crude material was diluted in CH_2Cl_2 (2 mL) and purified by flash chromatography (SiO_2, 40 g, DCM: hexane, 1:1) to obtain a white solid (484 mg, 93%).

^{1}H NMR (500 MHz, DMSO-d6) δ 7.32 (d, J = 7.6 Hz, 1H), 7.21 (bs, 1H), 7.15 – 7.06 (m, 3H), 6.89 (d, J = 12.7 Hz, 1H), 5.99 (d, J = 12.7 Hz, 1H), 4.08 (d, J = 5.0 Hz, 2H), 3.99 (q, J = 7.0 Hz, 2H), 1.37 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, DMSO-d6) δ 149.48, 136.01, 134.91, 128.49, 127.36, 125.85, 124.99, 102.85, 78.16, 65.41, 42.12, 28.70, 15.09.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{16}H_{24}NO_3$, 278.3720. Found 278.1963.

tert-butyl (E)-(2-(2-ethoxyvinyl)-4,5-dimethoxybenzyl)carbamate (**1b**).



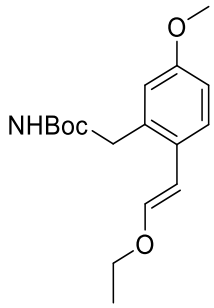
To a solution of tert-butyl N-[(2-bromo-4,5-dimethoxy-phenyl)methyl]carbamate (400 mg, 1.16 mmol) in Dioxane (12 ml) and water (3 mL) in a microwave vial was added K_2CO_3 (479.02 mg, 3.47 mmol), Tricyclohexylphosphine (32.4 mg, 0.12 mmol), 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.24 ml, 1.16 mmol) and $Pd(dba)_2$ (33.22 mg, 0.06 mmol). The cap was sealed ander a stream of argon then the reaction mixture was heated at 100 °C in a microwave reactor for 2 h. The reaction poured onto an aqueous saturated solution of NaCl (100 mL) and the product was extracted with EtOAc (2x100 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in CH_2Cl_2 (5 mL) and purified by flash chromatography (SiO_2, 11g, Hexane:AcOEt, 100% to 90:10 in 25 min) to give 2362 mg (92.9%) of tert-butyl N-[[2-[(E)-2-ethoxyvinyl]-4,5-dimethoxy-phenyl]methyl]carbamate as a yellow oil

^{1}H NMR (500 MHz, Chloroform-d) δ 6.79-6.74 (m, 3H), 5.95 (d, *J* = 12.7 Hz, 1H), 4.64 (bs, 1H), 4.25 (d, *J* = 5.1 Hz, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 1.45 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, 500 MHz, Chloroform-d) δ: 155.60, 148.42, 148.25, 147.42, 127.79, 127.19, 112.68, 108.79, 102.55, 79.35, 65.35, 56.00, 55.96, 42.66, 28.39, 14.77.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{18}H_{28}NO_5$, 338.1967. Found 339.0214.

tert-butyl (E)-(2-(2-ethoxyvinyl)-5-methoxybenzyl)carbamate (**1c**).



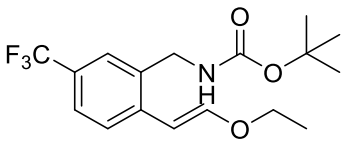
To a solution of tert-butyl N-[(2-bromo-5-methoxy-phenyl)methyl]carbamate (515.9 mg, 1.63 mmol, 1 eq) in Dioxane (20mL) was added K_2CO_3 (688.1 mg, 4.98 mmol, 3 eq) and water (5.00 mL). The reaction mixture was degassed under vacuum and purged with argon (5x). Then, Tricyclohexylphosphine (48.4 mg, 0.173 mmol, 0.1 eq), $Pd(dba)_2$ (50.9 mg, 0.09 mmol, 0.05 eq) and 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.35 mL, 1.66 mmol, 1 eq) were added into. The reaction mixture was heated with vigorous stirring at 80 °C and stirred overnight. The reaction was followed by TLC (DCM:Hexane, 1:1). After completion, it was poured onto an aqueous saturated solution of NaCl (100 mL) and the product was extracted with EtOAc (2x100 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated under vacuum. The crude material was diluted in DCM (2 mL) and purified by flash chromatography (SiO_2, 40 g, Hexane:AcOEt, 9:1) to obtain a pale-yellow solid(229.8mg, 45.8 %).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.26-7.21 (m, 2H), 6.84 (d, *J* = 13.0 Hz, 1H), 6.72-6.70 (m, 2H), 5.89 (d, *J* = 13.0 Hz, 1H), 4.06 (d, *J* = 5.9 Hz, 2H), 3.85 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 1.38 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, DMSO-*d6*) δ: 158.12, 155.59, 148.07, 136.16, 127.68, 126.74, 114.25, 113.13, 102.16, 79.40, 65.22, 55.30, 43.03, 28.37, 14.75.

LC/MS (ESI); m/z $[M+Na]^+$: Calcd. for $C_{17}H_{25}NNaO_4$, 330.3798. Found 330.1286.

tert-butyl (E)-(2-(2-ethoxyvinyl)-5 (trifluoromethyl)benzyl)carbamate (**1d**).



To a solution of tert-butyl N-[[2-bromo-5-(trifluoromethyl)phenyl]methyl]carbamate (90 mg, 0.25 mmol) in Dioxane (4 ml) and water (1 mL) in a microwave vial was added K_2CO_3 (105 mg, 0.76 mmol), Tricyclohexylphosphine (7.1 mg, 0.025 mmol), 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70.5 mg, 0.35 mmol) and $Pd(dba)_2$ (7.3 mg, 0.013 mmol). Then the reaction mixture was de-gassed under vacuum and purged with argon (5x). The vial was caped and sealed under a stream of argon, then the reaction mixture was heated at 100 °C in a microwave reactor for 2 h. By TLC no SM (Hex:AcOEt, 9:1), the reaction mixture was filtered in vacuo over a celite pad, filtrate was poured onto an aqueous saturated solution of NaCl (20 mL) and the product was extracted with EtOAc (2x20 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in CH_2Cl_2 and purified by flash chromatography (SiO_2, 12g, Hexane:AcOEt, 100% to 90:10 in 25 min) to give 69 mg (78.6%) of tert-butyl N-[[2-[(E)-2-ethoxyvinyl]-5-(trifluoromethyl)phenyl]methyl]- carbamate.

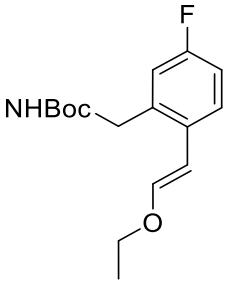
^{1}H NMR (500 MHz, Chloroform-d) δ 7.51 – 7.41 (m, 2H), 7.38 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 12.6 Hz, 1H), 5.97 (d, J = 12.7 Hz, 1H), 4.75 (bs, 1H), 4.36 (s, 2H), 3.94 (q, J = 7.0 Hz, 2H), 1.46 (s, 9H), 1.35 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 155.50 , 150.72 , 139.13 , 135.10 , 127.71 (q, J = 32.5 Hz), 125.20 (q, J = 3.8 Hz), 125.07 , 124.18 (q, J = 272 Hz), 124.45 (d, J = 4.7 Hz), 101.38 , 79.68 , 65.56 , 42.64 , 28.27 , 14.61.

^{19}F NMR (470 MHz, cdcl3) δ -62.34.

LC/MS (ESI); m/z $[M+H\text{-}BOC]^+$: Calcd. for $C_{12}H_{15}F_3NO$, 246.1105. Found 246.1530.

tert-butyl (E)-(2-(2-ethoxyvinyl)-5-fluorobenzyl)carbamate (**1e**).



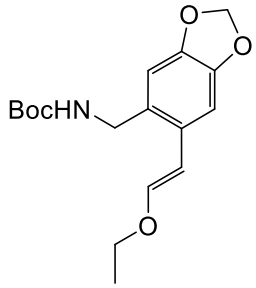
To a solution of *tert*-butyl (2-bromo-3-fluorobenzyl)carbamate (503.9 mg, 1.66 mmol, 1 eq) in Dioxane (21 mL) was added K_2CO_3 (591.7 mg, 4.97 mmol, 3 eq) and Water (5.00 mL). The reaction mixture was degassed under vacuum and purged with argon (5x). Then, Tricyclohexylphosphine (49.5 mg, 0.177 mmol, 0.1 eq), $Pd(dba)_2$ (50.7 mg, 0.09 mmol, 0.05 eq) and 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.35 mL, 1.66 mmol, 1 eq) were added into. The reaction mixture was heated with vigorous stirring at 80 °C and stirred for 5h. The reaction was followed by TLC (DCM:Hexane, 1:1). After completion, it was poured onto an aqueous saturated solution of NaCl (100 mL) and the product was extracted with EtOAc (2x100 mL)**.** The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in DCM (2 mL) and purified by flash chromatography (SiO_2, 40 g, Hexane:AcOEt, 95:5) to obtain a yellow oil (277.0 mg, 56.6 %).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.22 (dd, *J* = 8.5, 5.7 Hz, 1H), 6.96 (dd, *J* = 9.5, 2.7 Hz, 1H), 6.89 (td, *J* = 8.4, 2.7 Hz, 1H), 6.76 (d, *J* = 12.7 Hz, 1H), 5.89 (d, *J* = 12.7 Hz, 1H), 4.72 (br.s, 1H), 4.30 (d, *J* = 5.5 Hz, 2H), 3.90 (q, *J* = 7.0 Hz, 2H), 1.46 (s, 9H), 1.34 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ: 161.54 (d, J = 245.1 Hz), 155.59, 149.06, 137.05 (d, J = 5.8 Hz), 131.03, 127.51 (d, J = 6.9 Hz), 114.95 (d, J = 23.2 Hz, 114.38 (d, J = 20.1 Hz), 101.67, 79.64, 65.37, 42.57, 28.35, 14.73.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{16}H_{23}FNO_3$, 296.3624. Found 396.3117.

tert-butyl (E)-((6-(2-ethoxyvinyl)benzo[d][1,3]dioxol-5-yl)methyl)carbamate (**1f**).



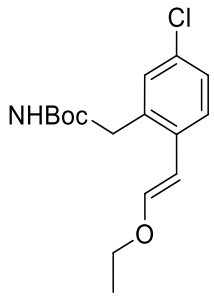
To a solution of tert-butyl N-[(6-bromo-1,3-benzodioxol-5-yl)methyl]carbamate (500 mg, 1.51 mmol) in Dioxane (12 ml) and water (3 mL) in a microwave vial was added K_2CO_3 (627.86 mg, 4.54 mmol), Tricyclohexylphosphine (42.47 mg, 0.15 mmol), 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.32 ml, 1.51 mmol) and $Pd(dba)_2$ (43.54 mg, 0.08 mmol). The cap was sealed ander a stream of argon then the reaction mixture was heated at 100 °C in a microwave reactor for 2 h. The reaction poured onto an aqueous saturated solution of NaCl (100 mL) and the product was extracted with EtOAc (2x100 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in CH_2Cl_2 (5 mL) and purified by flash chromatography (SiO_2, 11g, Hexane:AcOEt, 100% to 90:10 in 25 min) to give 212 mg (72.6%) of tert-butyl N-[[6-[(E)-2-ethoxyvinyl]-1,3-benzodioxol-5-yl]methyl]carbamate as a white solid.

^{1}H NMR (500 MHz, Chloroform-d) δ 6.78-6.72 (m, 3H), 5.98-5.91 (m, 3H), 4.63 (bs, 1H), 4.22 (d, *J* = 5.1 Hz, 2H), 3.88 (q, *J* = 7.1 Hz, 2H), 1.45 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, 500 MHz, Chloroform-d) δ: 155.53, 148.41, 147.19, 145.91, 128.25, 109.32, 105.55, 102.57, 101.73, 100.92, 79.38, 65.35, 42.73, 28.37, 14.73.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{17}H_{24}NO_5$, 322.1654. Found 322.1146.

tert-butyl (E)-(5-chloro-2-(2-ethoxyvinyl)benzyl)carbamate (**1g**).



To a solution of tert-butyl N-[(2-bromo-4,5-dimethoxy-phenyl)methyl]carbamate (500 mg, 1.56 mmol) in Dioxane (15 ml) and water (3 mL) in a microwave vial was added K_2CO_3 (646.60 mg, 4.68 mmol), 2-[(E)-

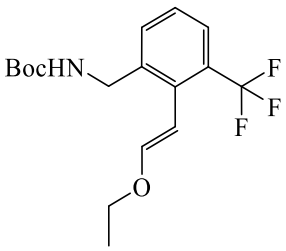
2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.33 ml, 1.56 mmol), Tricyclohexylphosphine (43.7mg, 0.16 mmol) and $Pd(dba)_2$ (44.84 mg, 0.08 mmol). The cap was sealed under a stream of argon then the reaction mixture was heated at 100 °C in a microwave reactor for 2 h. The reaction poured onto an aqueous saturated solution of NaCl (100 mL) and the product was extracted with EtOAc (2x100 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in CH_2Cl_2 (5 mL) and purified by flash chromatography (SiO_2, 11g, Hexane:AcOEt, 100% to 90:10 in 25 min) to give 362 mg (74.4%) of tert-butyl N-[[2-[(E)-2-ethoxyvinyl]-4,5-dimethoxy-phenyl]methyl]carbamate as a white solid oil

^{1}H NMR (500 MHz, Chloroform-d) δ 7.22-7.19 (m, 2H), 7.16-7.12 (m, 1H), 6.84 (d, *J* = 13.0 Hz, 1H), 5.89 (d, *J* = 13.0 Hz, 1H), 4.70 (bs, 1H), 4.29 (d, *J* = 5.9 Hz, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 1.45 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, 500 MHz, Chloroform-d) δ: 155.53, 149.52, 136.45, 131.44, 128.94, 128.35, 127.71, 126.53, 101.51, 79.65, 65.44, 42.56, 28.35, 14.69.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{16}H_{23}ClNO_3$, 312.1366. Found 312.2113.

tert-butyl (E)-(2-(2-ethoxyvinyl)-3-(trifluoromethyl)benzyl)carbamate (**1h**).



To a solution of *tert*-butyl N-[[2-bromo-3-(trifluoromethyl)phenyl]methyl]carbamate (500 mg, 1.41 mmol, 1 eq) in Dioxane (21 mL) was added K_2CO_3 (591.7 mg, 4.28 mmol, 3 eq) and Water (5.00 mL). The reaction mixture was degassed under vacuum and purged with argon (5x). Then, Tricyclohexylphosphine (41.4 mg, 0.148 mmol, 0.1 eq), $Pd(dba)_2$ (41.4 mg, 0.07 mmol, 0.05 eq) and 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.30 mL, 1.42 mmol, 1 eq) were added into. The reaction mixture was heated with vigorous stirring at 80 °C and stirred overnight. The reaction was followed by TLC (DCM:Hexane, 1:1). After completion, it was poured onto an aqueous saturated solution of NaCl (100 mL)

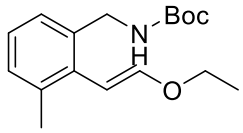
and the product was extracted with EtOAc (2x100 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in CH_2Cl_2 (2 mL) and purified by flash chromatography (SiO_2, 40 g, DCM:hexane, 1:1) to obtain a yellow oil (311.3 mg, 63.8%).

^{1}H NMR (500 MHz, Chloroform-d) δ: 7.57 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 6.40 (d, J = 13.2 Hz, 1H), 5.78 (d, J = 13.2 Hz, 1H), 4.80 (br.s, 1H), 4.40 (d, J = 5.3 Hz, 2H), 3.92 (q, J = 7.0 Hz, 2H), 1.45 (s, 9H), 1.35 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ: 155.88, 150.96, 139.62, 134.19, 131.46, 130.25 (q, J = 28.4 Hz), 126.75, 125.12 (q, J = 5.4 Hz, 124.38 (q, J = 273.9 Hz), 98.31, 79.82, 65.22, 42.85, 28.53, 14.81.

LC/MS (ESI); m/z $[M+Na]^+$: Calcd. for $C_{17}H_{22}F_3NNaO_3$, 368.3520. Found 368.1667.

tert-butyl (E)-(2-(2-ethoxyvinyl)-3-methylbenzyl)carbamate (**1i**).



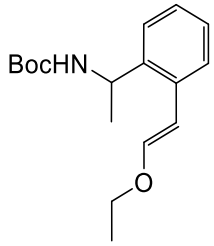
To a solution of tert-butyl N-[(2-bromo-3-methyl-phenyl)methyl]carbamate (300 mg, 1 mmol) in Dioxane (2 ml) and water (0.5 mL) in a microwave vial K_2CO_3 (414,34 mg, 3 mmol), tricyclohexylphosphane (28,03 mg, 0,1 mmol), 2-[(E)-2-methoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (183,92 mg, 1 mmol) and Pd(dba)2 (28,73 mg, 0,05 mmol) were added. The cap was sealed under argon and the reaction mixture was heated to 100 °C for 2 h using microwave irradiation. The reaction mixture was poured onto sat. NaCl (100 mL) and the product was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography to yield 285 mg (98%) of tert-butyl N-[[2-[(E)-2-ethoxyvinyl]-3-methyl-phenyl]methyl]carbamate as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 – 7.06 (m, 3H), 6.40 (d, J = 13.2 Hz, 1H), 5.69 (d, J = 13.2 Hz, 1H), 4.70 (s, 1H), 4.35 (d, J = 5.6 Hz, 2H), 3.91 (q, J = 7.0 Hz, 2H), 2.31 (s, 3H), 1.45 (s, 9H), 1.35 (t, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.81, 150.32, 143.47, 137.46, 137.13, 129.37, 126.49, 125.99, 100.93, 77.36, 65.20, 43.51, 28.57, 21.33, 14.94.

LC/MS: calc. $[M\text{-}Boc+H]^+$ for $C_{12}H_{18}NO$ = 192.1383; found = 192.1426 $[M\text{-}Boc+H]^+$.

tert-butyl (E)-(1-(2-(2-ethoxyvinyl)phenyl)ethyl)carbamate (**1j**).



To a solution of tert-butyl (1-(2-bromophenyl)ethyl)carbamate (500 mg, 1.67 mmol) in Dioxane (12 ml) and water (3 mL) in a microwave vial was added K_2CO_3 (627.86 mg, 4.54 mmol), Tricyclohexylphosphine (42.47 mg, 0.15 mmol), 2-[(E)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.32 ml, 1.51 mmol) and $Pd(dba)_2$ (43.54 mg, 0.08 mmol). The cap was sealed ander a stream of argon then the reaction mixture was heated at 100 °C in a microwave reactor for 2 h. The reaction poured onto an aqueous saturated solution of NaCl (100 mL) and the product was extracted with EtOAc (2x100 mL). The EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in CH_2Cl_2 (5 mL) and purified by flash chromatography (SiO2, 11g, Hexane:AcOEt, 100% to 90:10 in 25 min) to give 331 mg (68.2%) of tert-butyl (E)-(1-(2-(2-ethoxyvinyl)phenyl)ethyl)carbamate as a colorless oil

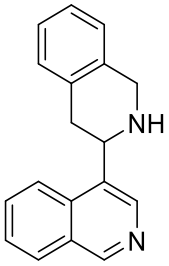
^{1}H NMR (500 MHz, Chloroform-d) δ 7.53 (d, J = 7.7 Hz, 0.6H), 7.34-7.28 (m, 1.4H), 7.19-7.16 (m, 1.4H), 7.11-7.06 (m, 0.6H), 8.81 (d, J = 12.7 Hz, 1H), 6.09 (d, J = 12.7 Hz, 1H), 5.03 (bs, 1H), 4.75 (bs, 1H), 3.91 (q, J = 7.0 Hz, 2H), 1.42 (bs, 12H), 1.34 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 149.11, 128.42, 127.69, 127.27, 126.39, 126.26, 126.12, 124.57, 102.72, 79.23, 65.08, 46.76, 28.36, 21.71, 14.72.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{17}H_{26}NO_3$, 292.1913. Found 292.0872.

Synthesis of 2.

1,2,3,4-tetrahydro-3,4'-biisoquinoline (**2a**)



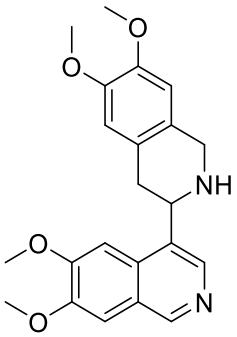
A solution of N-[[2-[(E)-2-ethoxyvinyl]phenyl]methyl]-2-methyl-propan-2-amine (70 mg, 0.3 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) was stirred for 2h at 50 ^{o}C under air. The solvent was evaporated under vacuum and the residue purified by flash chromatography (1/10/60 : NH_4OH/methanol/DCM) 50% and 50% DCM to give to give 24 mg (73%) as a foamy solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 9.23 (s, 1H), 8.62 (s, 1H), 8.36 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.79 (t, J = 7.7, 1H), 7.68 (t, J = 7.3 Hz, 1H), 7.18-7.06 (m, 5H), 4.68 (dd, J = 10.5, 4.2 Hz, 1H), 4.19 (d, J = 15.9 Hz, 1H), 4.07 (d, J = 15.9 Hz, 1H), 3.09-2.97 (m, 2H).

^{13}C NMR (151 MHz, DMSO-d6) δ 152.44, 140.88, 136.01, 135.23, 133.54, 130. 85, 129.26, 128.67, 128.34, 127.47, 126.50, 126.27, 126.22, 126.20, 123.64, 53.22, 48.97, 36.53.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{18}H_{17}N_2$, 261.3480. Found 261.1544.

6,6',7,7'-tetramethoxy-1,2,3,4-tetrahydro-3,4'-biisoquinoline (**2b**).



A solution of tert-butyl N-[[2-[(E)-2-ethoxyvinyl]-4,5-dimethoxy-phenyl]methyl]carbamate (120 mg, 0.35 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) was stirred for 2h at 50 °C under air. The solvent was evaporated and the product was extracted with AcOEt(2x20 mL) and aqueous $NaHCO_3$.

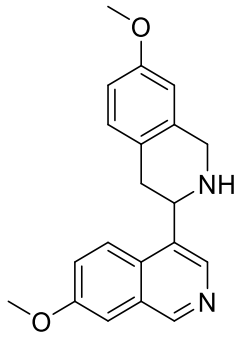
The organic extract were combined, dried (NA_2SO_4) and evaporated under vacuum. The crude product was purified by flash chromatography 5% MeOH in DCM to give 38.9 mg (58%) of 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-3-yl)-6,7-dimethoxy-isoquinoline as foamy yellow solid

^{1}H NMR (500 MHz, Chloroform-d) δ 8.99 (s, 1H), 8.53 (s, 1H), 7.55 (s, 1H), 7.23 (s, 1H), 6.64 (s, 2H), 4.59 (dd, J = 10.8, 3.9 Hz, 1H), 4.31 (d, J = 15.2 Hz, 1H), 4.17 (d, J = 15.2 Hz, 1H), 4.04(s, 3H), 4.01 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.17 (dd, J = 15.8 Hz, 11.0 Hz, 1H), 3.03 (dd, J = 15.8 Hz, 3.5 Hz, 1H), 2.08 (bs, 1H).

^{13}C NMR (151 MHz, 500 MHz, Chloroform-d) δ: 152.85, 149.96, 149.78, 147.59, 139.48, 131.49, 130.50, 126.90, 126.47, 124.75, 111.74, 109.10, 105.99, 101.49, 56.15, 56.02, 55.99, 55.97, 54.19, 53.43, 48.98, 35.55.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{22}H_{25}N_2O_4$, 381.1814. Found 381.2709.

7,7'-dimethoxy-1,2,3,4-tetrahydro-3,4'-biisoquinoline (**2c**).



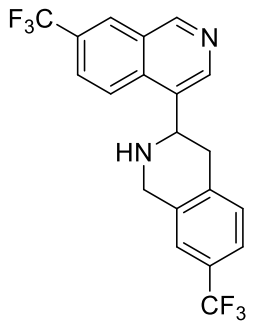
A solution of tert-butyl (E)-(2-(2-ethoxyvinyl)-5-methoxybenzyl)carbamate (70 mg, 0.22 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) was stirred for 2h at 50 °C under air. The solvent was evaporated and the product purified by flash chromatography (1/10/60 : NH4OH/methanol/DCM) 50% and 50% DCM to give 23.2 mg (63.6%) of 7,7'-dimethoxy-1,2,3,4-tetrahydro-3,4'-biisoquinoline as brown foamy solid

^{1}H NMR (500 MHz, DMSO-d6) δ 9.13 (s, 1H), 8.47 (s, 1H), 8.29 (d, J = 9.2 Hz, 1H), 7.53 (s, 1H), 7.41 (dd, J = 9.2 Hz, 1.7 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.74-6.72 (m, 2H), 4.55 (dd, J = 10.3, 4.2 Hz, 1H), 4.14 (d, J = 16.1 Hz, 1H), 4.03 (d, J = 16.1 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 2.98-2.88 (m, 2H).

^{13}C NMR (151 MHz, DMSO-*d6*) δ: 157.99, 157.80, 150.80, 139.08, 137.22, 133.66, 130.10, 129.91, 129.05, 127.21, 125.59, 123.22, 112.68, 111.06, 106.17, 55.87, 55.44, 53.67, 49.22, 35.81.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{20}H_{21}N_2O_2$, 321.4000. Found 321.1798.

7,7'-bis(trifluoromethyl)-1,2,3,4-tetrahydro-3,4'-biisoquinoline (**2d**).



A solution of tert-butyl N-[[2-[(E)-2-ethoxyvinyl]-5-(trifluoromethyl)phenyl]methyl]carbamate (56 mg, 0.162 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) was stirred for 2h at 50 ^{o}C under air. The solvent was evaporated under vacuum, and crude product was purified by PTLC (DCM:MeOH:NH_4OH, 10:1:0.1) to give 13 mg (40.5%) of pure 7-(trifluoromethyl)-4-[7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]isoquinoline.

^{1}H NMR (400 MHz, Chloroform-d) δ 9.31 (s, 1H), 8.79 (s, 1H), 8.50 (d, J = 8.9 Hz, 1H), 8.32 (d, J = 1.2 Hz, 1H), 7.90 (dd, J = 9.0, 1.9 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.24 (s, 1H), 4.73 (dd, J = 10.5, 4.2 Hz, 1H), 4.39 (d, J = 16.0 Hz, 1H), 4.29 (d, J = 16.0 Hz, 1H), 3.35 – 3.13 (m, 2H), 2.18 (bs, 1H).

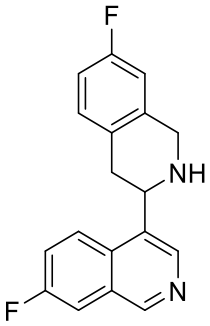
^{13}C NMR (151 MHz, Chloroform-d) δ 153.51, 142.85, 138.38, 135.68, 135.32, 132.38, 129.65, 129.17 (q, J = 33.0 Hz), 128.77 (q, J = 32.3 Hz), 127.48, 126.38 (q, J = 4.4 Hz), 126.14 (q, J = 2.9 Hz), 124.73, 124.32

(q, J = 271.9 Hz), 123.85 (q, J = 272.3 Hz), 123.43 (q, J = 3.7 Hz), 123.24 (q, J = 3.7 Hz), 53.94, 49.06, 36.24 .

^{19}F NMR (376 MHz, Chloroform-d) δ -62.43, -62.78.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{20}H_{15}F_6N_2$, 397.1139. Found 397.2723.

7,7'-difluoro-1,2,3,4-tetrahydro-3,4'-biisoquinoline (**2e**).



A solution of tert-butyl (E)-(2-(2-ethoxyvinyl)-5-fluorobenzyl)carbamate (88.6 mg, 0.3 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) under air was stirred for 2h at 50 °C. The solvent was evaporated and the product purified by flash chromatography (1/10/60 : NH_4OH/methanol/DCM) 50% and 50% DCM to give 23.5 mg (52.9%) of 7,7'-difluoro-1,2,3,4-tetrahydro-3,4'-biisoquinoline as a foamy brown solid.

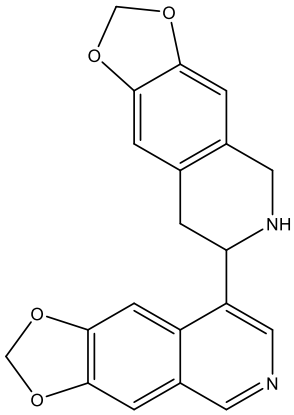
^{1}H NMR (500 MHz, Chloroform-d) δ 9.16 (s, 1H), 8.63 (s, 1H), 8.38 (dd, J = 9.2 Hz, 5.3 Hz, 1H), 7.61 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 7.53-7.49 (m, 1H), 7.10-7.06 (m, 1H), 6.69 (t, J = 8.6 Hz, 1H), 6.84 (d, J = 9.3 Hz, 1H), 4.65 (dd, J = 10.6, 4.2 Hz, 1H), 4.33 (d, J = 16.1 Hz, 1H), 4.22 (d, J = 16.1 Hz, 1H), 3.38-3.16 (m, 1H), 3.11-3.08 (m, 1H), 1.19 (bs, 1H).

^{13}C NMR (151 MHz, Chloroform-d) δ 161.35 (d, J = 243.9 Hz), 161.11 (d, J = 249.7 Hz), 151.80 (d, J = 4.6 Hz) 140.12 (d, J = 2.3 Hz), 136.69 (d, J = 6.9 Hz), 132.53, 130.90, 130.45 (d, J = 8.1 Hz), 129.80 (d, J = 3.5 Hz), 129.2 (d, J = 8.1 Hz), 129.16 (d, J = 8.1 Hz), 120.88 (d, J = 25.4 Hz), 113. 52 (d, J = 22.0 Hz), 112.71 (d, J = 21.1 Hz), 111.31 (d, J = 19.6 Hz), 54.11, 49.11, 35.57.

^{19}F NMR (376 MHz, Chloroform-d) δ -111.90, -116.63.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{18}H_{15}F_2N_2$, 297.3288. Found 297.1363.

5,6,7,8-tetrahydro-7,8'-bi[1,3]dioxolo[4,5-g]isoquinoline (**2f**).



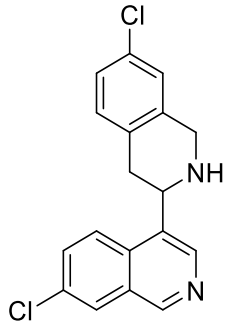
A solution of tert-butyl N-[[6-[(E)-2-ethoxyvinyl]-1,3-benzodioxol-5-yl]methyl]carbamate (100 mg, 0.32 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) was stirred for 2h at 50 °C under air. The solvent was evaporated and the product was extracted with AcOEt(2x20 mL) and aqueous $NaHCO_3$. The organic extract were combined, dried (NA_2SO_4) and evaporated under vacuum. The crude product was purified by flash chromatography 5% MeOH in DCM to give 35.7 mg (65.9%) of 8-(5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-7-yl)-[1,3]dioxolo[4,5-g]isoquinoline as foamy yellow solid.

^{1}H NMR (500 MHz, Chloroform-d) δ 8.92 (s, 1H), 8.48 (s, 1H), 7.59 (s, 1H), 7.21 (s, 1H), 6.58 (s, 2H), 6.10 (s, 2H), 5.92 (s, 2H), 4.48 (dd, J = 10.8, 3.9 Hz, 1H), 4.24 (d, J = 15.7 Hz, 1H), 4.01 (d, J = 17.2 Hz, 1H), 3.13 (dd, J = 15.9 Hz, 11.0 Hz, 1H), 3.03 (dd, J = 15.9 Hz, 3.9 Hz, 1H), 1.92 (bs, 1H).

^{13}C NMR (151 MHz, 500 MHz, Chloroform-d) δ: 151.09, 150.24, 147.94, 146.09, 146.07, 139.82, 132.26, 132.01, 127.90, 127.36, 125.94, 108.73, 106.18, 103.78, 101.66, 100.70, 99.72, 54.32, 49.23, 35.84.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{20}H_{17}N_2O_4$, 349.1188. Found 349.1677.

7,7'-dichloro-1,2,3,4-tetrahydro-3,4'-biisoquinoline (**2g**).



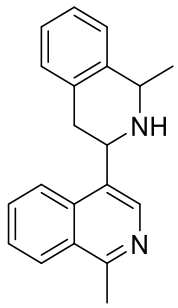
A solution of tert-butyl N-[[5-chloro-2-[(E)-2-ethoxyvinyl]phenyl]methyl]carbamate (100 mg, 0.32 mmol) (100 mg, 0.32 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) was stirred for 2h at 50 °C under air. The solvent was evaporated and the product was extracted with AcOEt(2x20 mL) and aqueous NaHCO3. The organic extract were combined, dried (NA2SO4) and evaporated under vacuum. The crude product was purified by Prep TLC 10% MeOH in DCM to give 32.1 mg (60.8%) of 7-chloro-4-(7-chloro-1,2,3,4-tetrahydroisoquinolin-3-yl)isoquinoline as foamy yellow solid.

^{1}H NMR (500 MHz, DMSO-d6) δ 9.13 (s, 1H), 8.65 (s, 1H), 8.29 (d, J = 9.2 Hz, 1H), 7.99 (s, J = 2.2 Hz, 1H), 7.66 (dd, J = 9.2 Hz, 2.2 Hz, 1H), 7.17-7.11 (m, 2H), 7.05 (d, J = 8.3 Hz, 1H), 4.63 (dd, J = 10.3, 4.2 Hz, 1H), 4.31 (d, J = 16.0 Hz, 1H), 4.20 (d, J = 16.0 Hz, 1H), 3.17 (dd, J = 16.0 Hz, 10.8 Hz, 1H), 3.08 (dd, J = 16.0 Hz, 4.2 Hz, 1H), 2.00 (bs, 1H).

^{13}C NMR (151 MHz, 500 MHz, DMSO-*d6*) δ: 151.62, 140.90, 136.59, 132.8, 132.68, 132.39, 132.14, 131.77, 131.35, 130.34, 129.15, 127.05, 126.54, 126.23, 125.10, 53.94, 48.85, 35.65

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{18}H_{15}Cl_2N_2$, 329.0612. Found 329.1154.

1,1'-dimethyl-1,2,3,4-tetrahydro-3,4'-biisoquinoline (**2j**).



A solution of tert-butyl N-[1-[2-[(E)-2-ethoxyvinyl]phenyl]ethyl]carbamate (100 mg, 0.34 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) was stirred for 2h at 50 °C under air. The solvent was evaporated and the product extracted with AcOEt(2x20 mL) and aqueous $NaHCO_3$. The organic extract were combined, dried (NA_2SO_4) and evaporated under vacuum. The crude product was purified by flash chromatography 5% MeOH in DCM to give 11 mg (22%) of **2j-1** and 11 mg (22%) of **2j-2**.

2j-1

^{1}H NMR (400 MHz, Chloroform-d) δ 8.59 (s, 1H), 8.1 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.71 (t, J = 7.7, 1H), 7.62 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.6, 1H), 7.12(d, J = 7.6 Hz, 1H), 4.74 (dd, J = 11.2, 3.4 Hz, 1H), 4.45 (q, J = 6.2 Hz, 1H), 3.29 (dd, J = 15.8, 11.2 Hz, 1H), 3.31 (dd, J = 15.8, 3.4 Hz, 1H), 2.98 (s, 3H), 1.86 (bs, 1H), 1.58 (d, J = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 158.24, 139.76, 139.17, 134.87, 133.86, 131.24, 129.91, 129.00, 127.16, 126.63, 126.36, 126.27, 126.17, 125.38, 123.39, 53.76, 53.73, 37.48, 22.59, 22.36.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{20}H_{21}N_2$, 289.4020. Found 289.2601.

2j-2

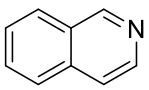
^{1}H NMR (400 MHz, Chloroform-d) δ 8.53 (s, 1H), 8.2 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.74 (t, J = 7.7, 1H), 7.62 (t, J = 7.7 Hz, 1H), 7.22-7.11 (m, 4H), 4.98 (dd, J = 9.8, 4.4 Hz, 1H), 4.42 (q, J = 6.8 Hz, 1H), 3.24-3.14 (m, 2H), 2.97 (s, 3H), 1.85 (bs, 1H), 1.64 (d, J = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 158.22, 139.70, 139.34, 134.33, 134.08, 130.91, 129.93, 128.99, 127.22, 126.90, 126.60, 126.40, 126.21, 126.10, 123.23, 53.53, 46.84, 36.38, 23.98, 22.60.

LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{20}H_{21}N_2$, 289.4020. Found 289.2601

Synthesis of 3.

isoquinoline (**3a**).



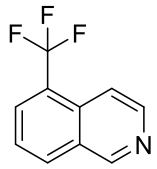
A solution of N-[[2-[(E)-2-ethoxyvinyl]phenyl]methyl]-2-methyl-propan-2-amine (40 mg, 0.17 mmol) in conc. HCl (1 mL) was stirred at rt for 12h under microwave assisted conditions. The reaction mixture was poured (carefully) into an aqueous solution of Na_2CO_3 (100 mL, 2M) and the product was extracted with AcOEt(2x10 mL). The organic extract were combined, dried (NA_2SO_4) and evaporated under vacuum. The crude product was purified by prep TLC DCM/MeOH 95:5 to give 7.3 mg (33%) of isoquinoline

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.77 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 8.07 – 7.96 (m, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H).

^{13}C NMR (151 MHz, dmso) δ 148.75, 143.32, 129.55, 129.47, 127.94, 127.34, 127.29, 121.36.

These data are in accord with those reported in the literature.[3]

5-(trifluoromethyl)isoquinoline (**3h**).



A solution of tert-butyl (E)-(2-(2-ethoxyvinyl)-3-(trifluoromethyl)benzyl)carbamate (100 mg, 0.3 mmol) in TRIFLUOROACETIC ACID (0.5 ml) and DCM (0.5 mL) under air was stirred for 2h at 50 °C The solvent was evaporated and the product was extracted with AcOEt(2x20 mL) and aqueous $NaHCO_3$. The organic extract combined, dried (NA_2SO_4) and evaporated under vacuum. The crude was purified by flash chromatography (1/10/60 : NH_4OH/methanol/DCM) 50% and 50% DCM to give 43.7 mg (76.5%) of pure product as a colorless oil.

^{1}H NMR (500 MHz, DMSO-d6) δ: 9.50 (s, 1H), 8.69 (d, J = 6.1 Hz, 1H), 8.46 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.89 (d, J = 4.6 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H).

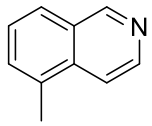
LC/MS (ESI); m/z $[M+H]^+$: Calcd. for $C_{10}H_7F_3N$, 198.1682. Found 198.0600.

These data are in accord with those reported in the literature.[4]

[3] Varyani, Manish et al Tetrahedron Letters, 57(7), 723-727; 2016

[4] A. Lishchynskyi, G. Berthon, V. V. Grushin, *Chem. Commun*. **2014**, *50*, 10237-10240.

5-methylisoquinoline (**3i**).



A solution of tert-butyl tert-butyl N-[[2-[(E)-2-ethoxyvinyl]-3-methyl-phenyl]methyl]carbamate (50 mg, 0,17 mmol) in TFA (0.5 ml) and DCM (0.5 mL) was stirred for 2 h at 50 °C under air. The solvent was evaporated and the crude material was purified by PTLC (DCM/MeOH/Ammonia 86.7/13/0.3) to yield 4,7 mg (19%) of 5-methylisoquinoline.

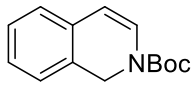
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.24 (s, 1H), 8.56 (d, J = 5.9 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 6.0 Hz, 1H), 7.56 – 7.47 (m, 2H), 2.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.09, 143.09, 135.40, 133.69, 130.79, 128.88, 127.09, 125.93, 117.25, 18.65.

LC/MS: calc. $[M+H]^+$ for $C_{10}H_9N$ = 144.0808; found = 144.0816 $[M+H]^+$.

Synthesis of 4.

tert-butyl isoquinoline-2(1H)-carboxylate (**4a**).



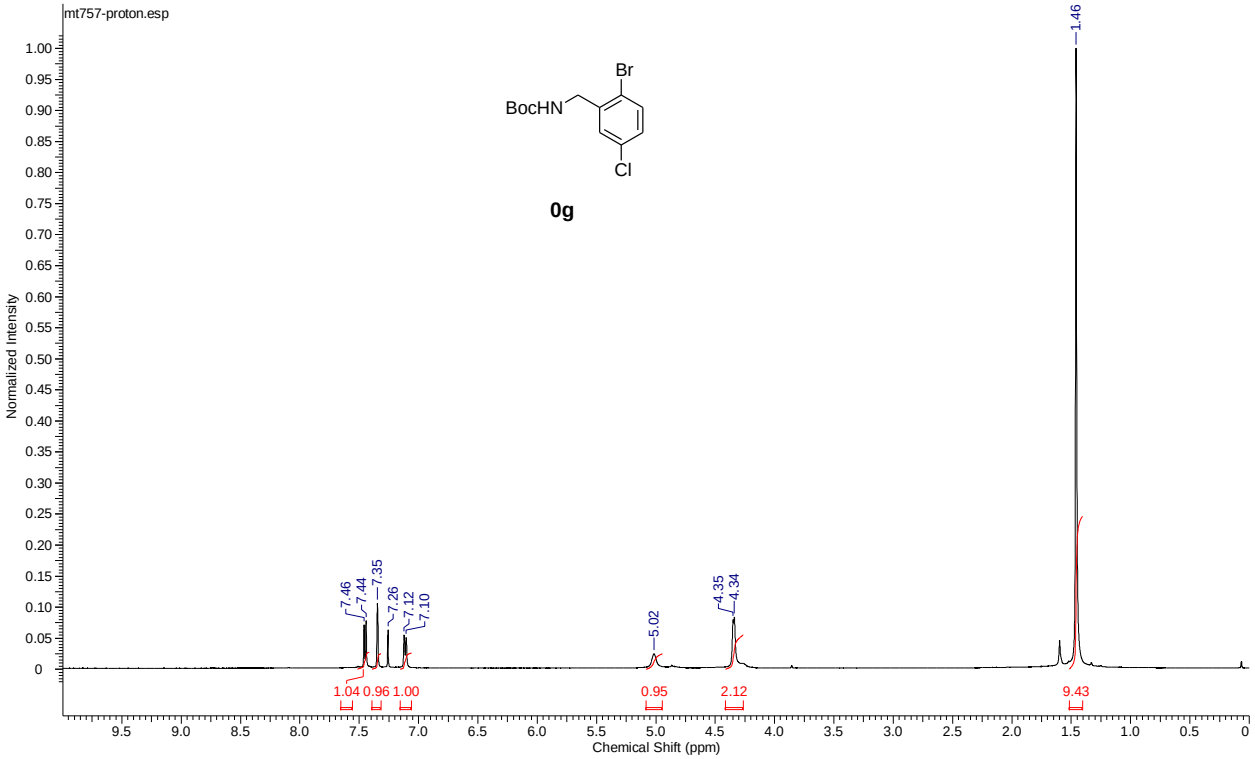
A solution of (tert-butyl N-[[2-[(E)-2-ethoxyvinyl]phenyl]methyl]carbamate (50 mg, 0.18 mmol) in Acetic Acid (1 ml) under air was stirred for 12h at 110 ºC. The solvent was evaporated and the product was extracted with AcOEt(2x20 mL) and aqueous $NaHCO_3$. The organic extract combined, dried (NA_2SO_4) and evaporated under vacuum. Crude was purified by flash chromatography ethyl acetate/hexane: 30%/70% to give 20.5 mg (49.5%) of tert-butyl isoquinoline-2(1H)-carboxylate.

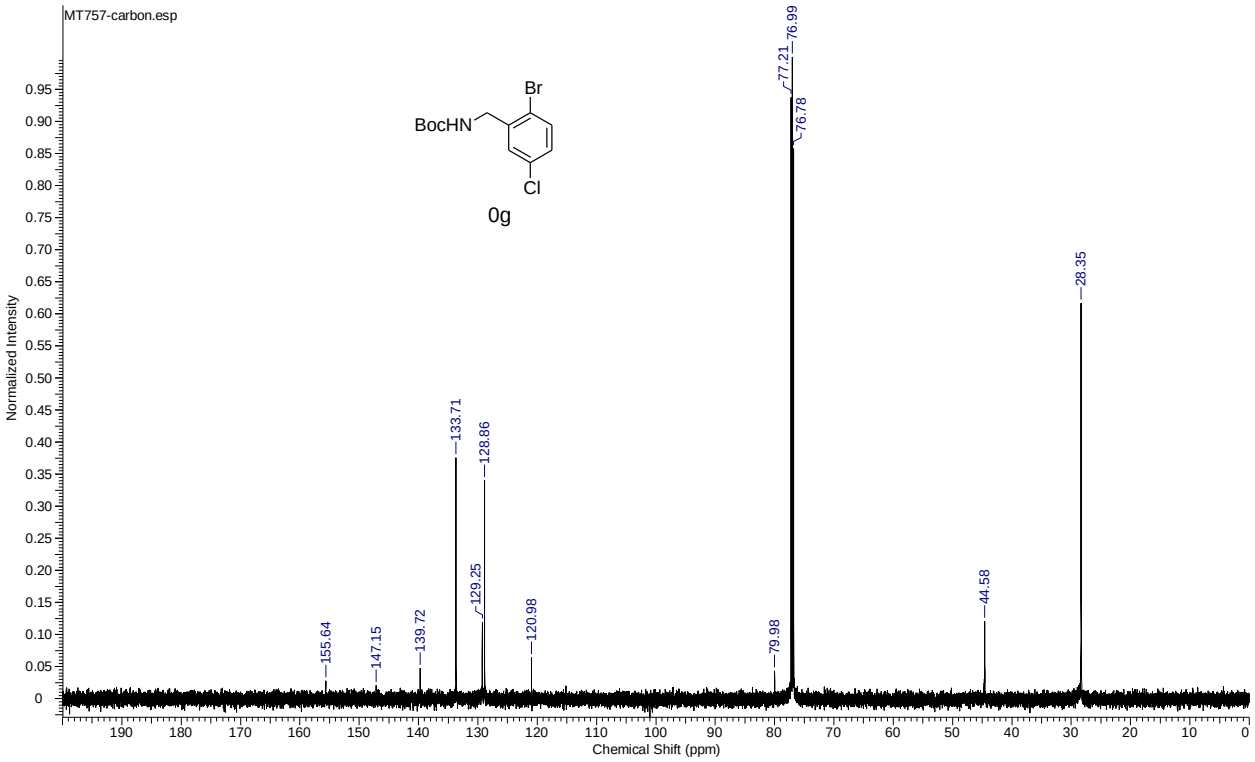
^{1}H NMR (500 MHz, DMSO-d6) δ: 7.18-7.10 (m, 3H), 7.03 (d, J = 7.1 Hz, 1H), 6.82 (bs, 1H), 5.80 (bs, 1H), 4.71 (s, 2H), 1.52 (s, 9H).

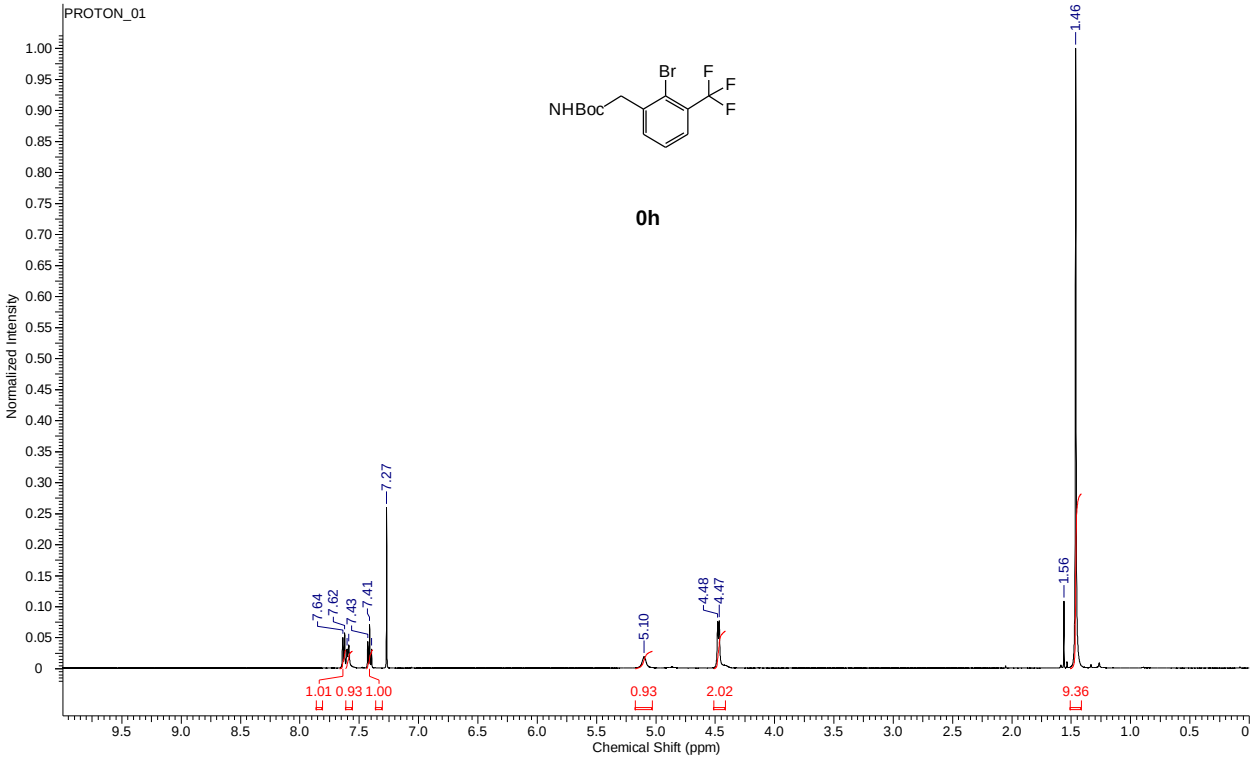
^{13}C NMR (151 MHz, DMSO-*d6*) 151.44, 131.32, 129.09, 128.11 (2C), 127.23, 126.29, 124.63, 107.74, 81.48, 45.24, 28.26.

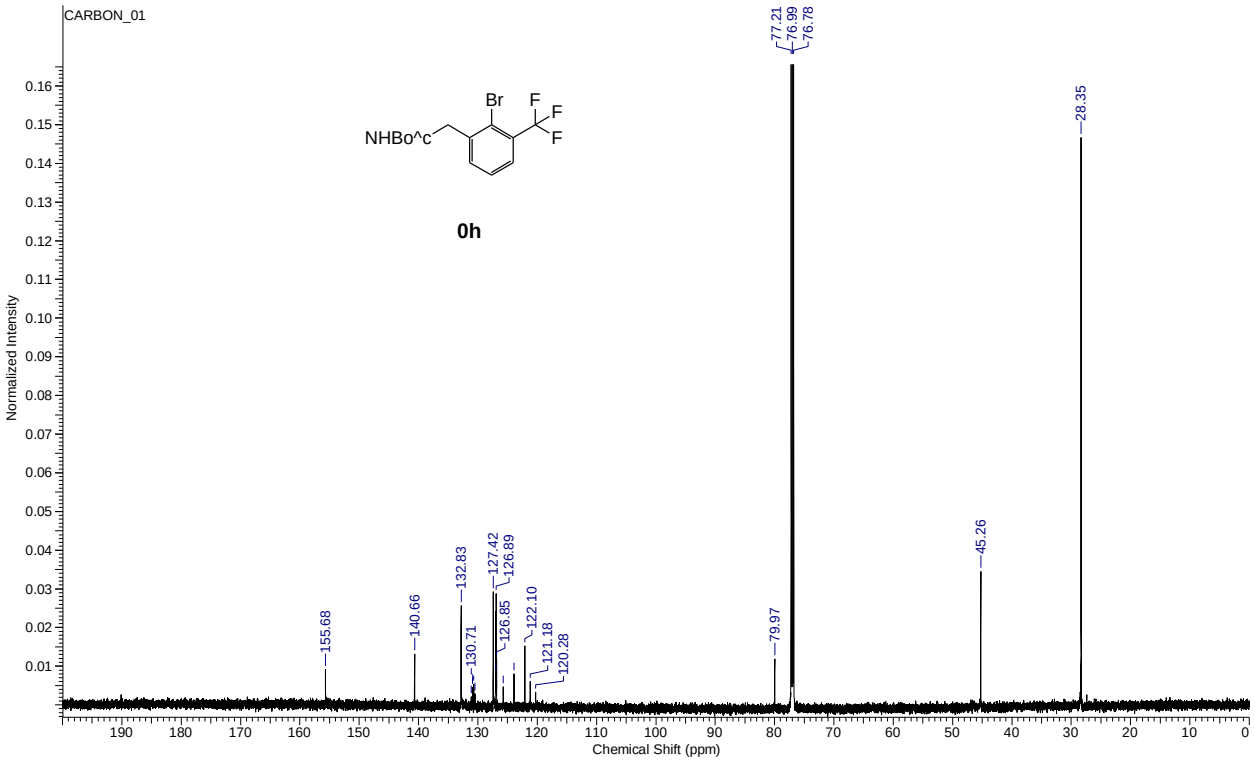
LC/MS (ESI); m/z $[M\text{-}Boc+H]^+$: Calcd. for $C_9H_{10}N$, 132.1860. Found 131.9623.

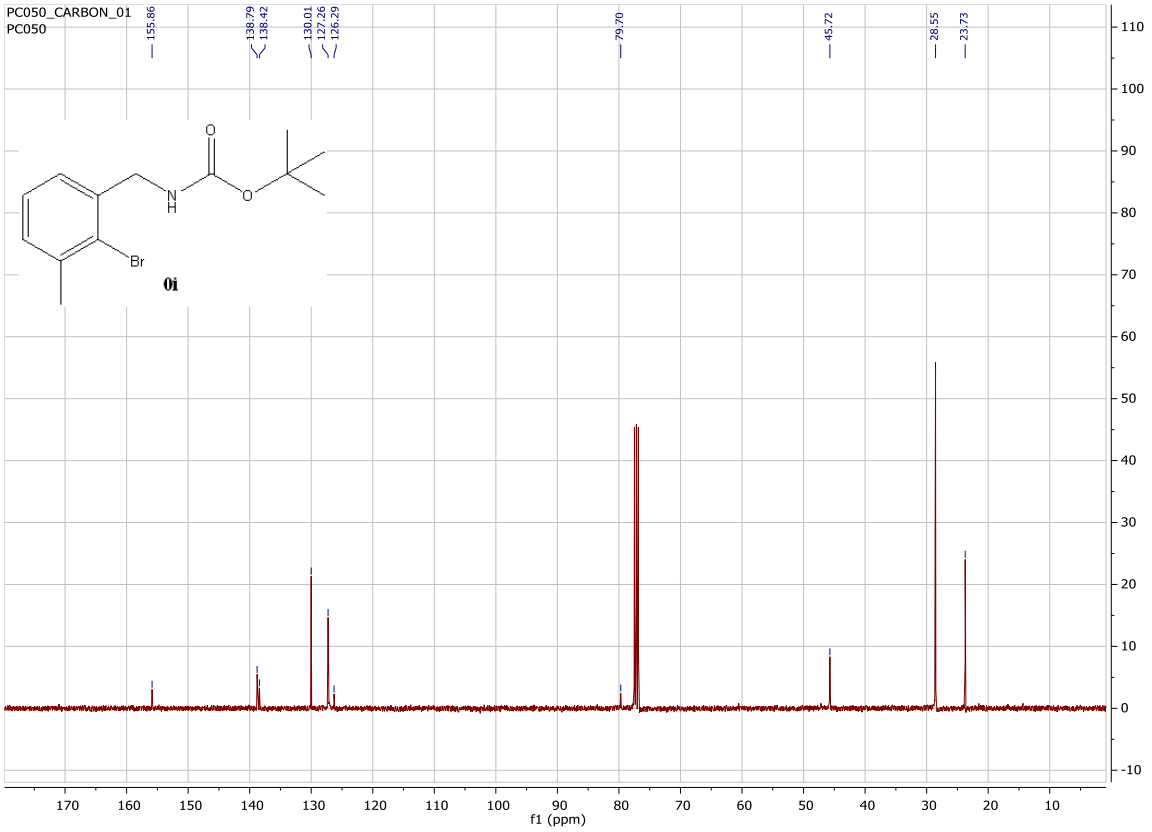
NMR Spectra.

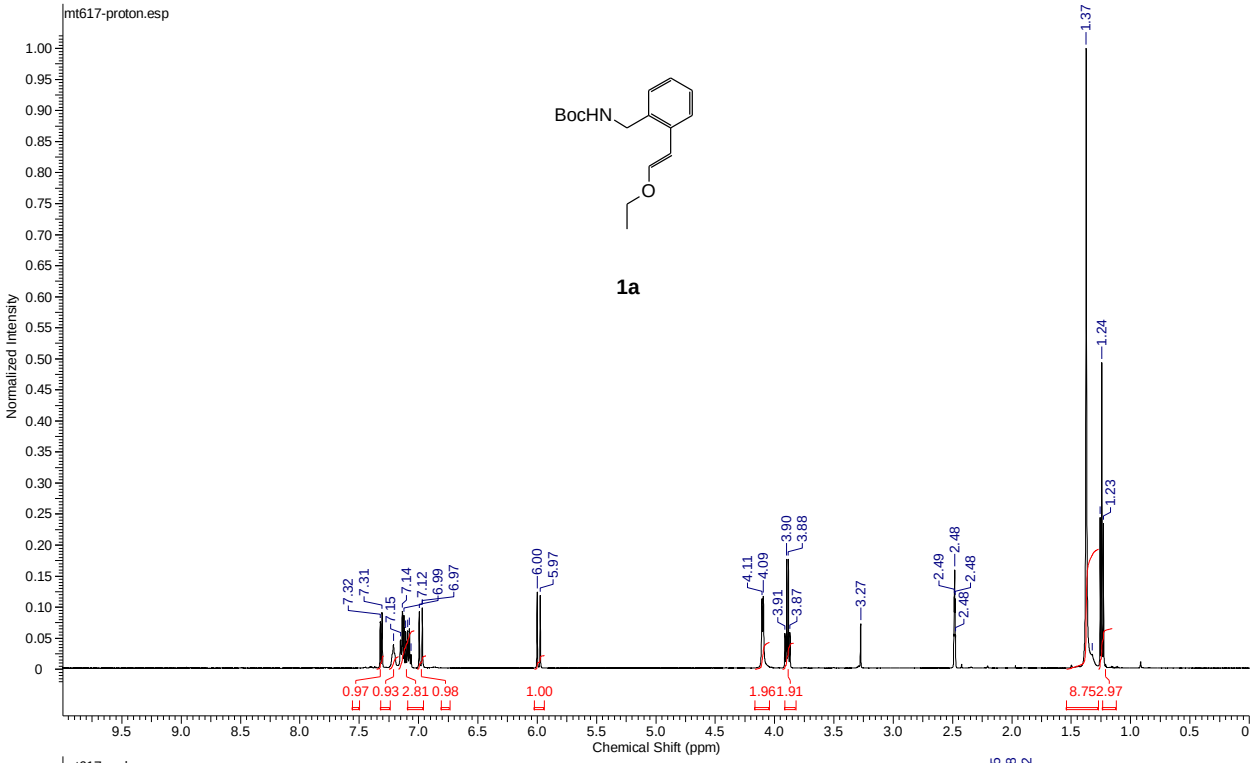


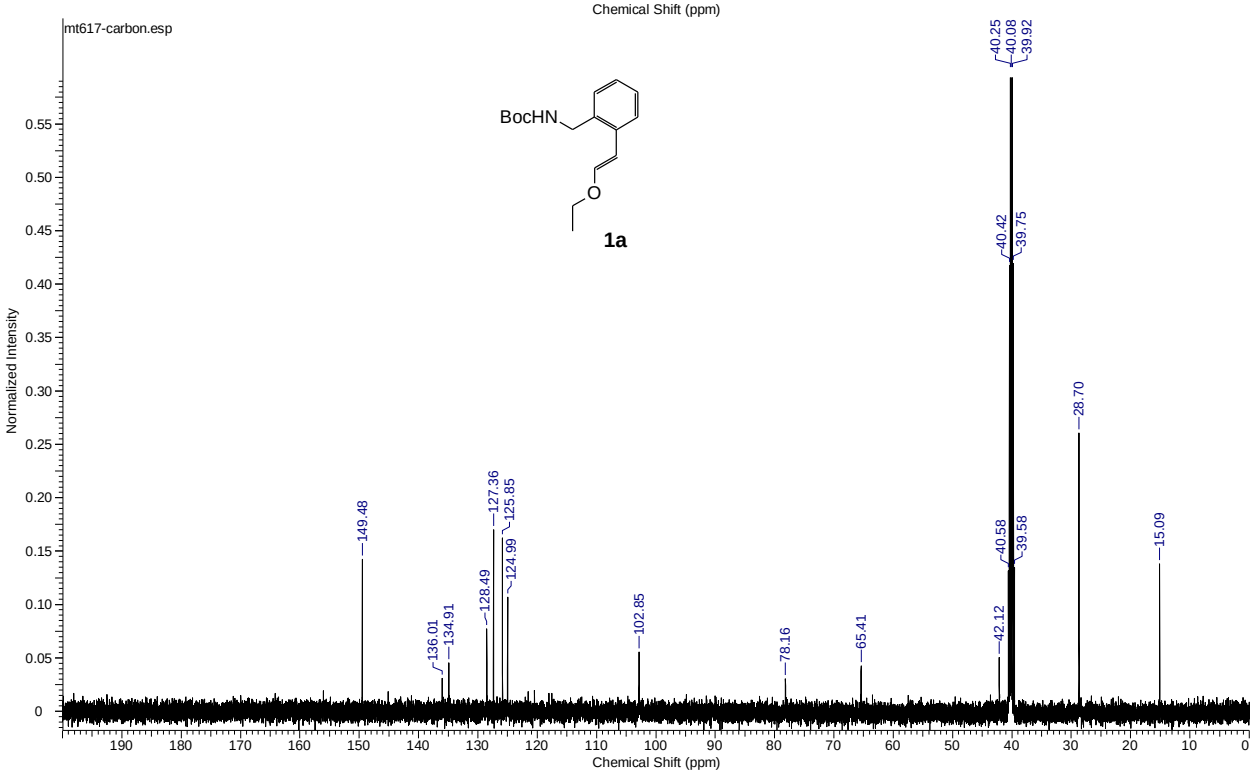


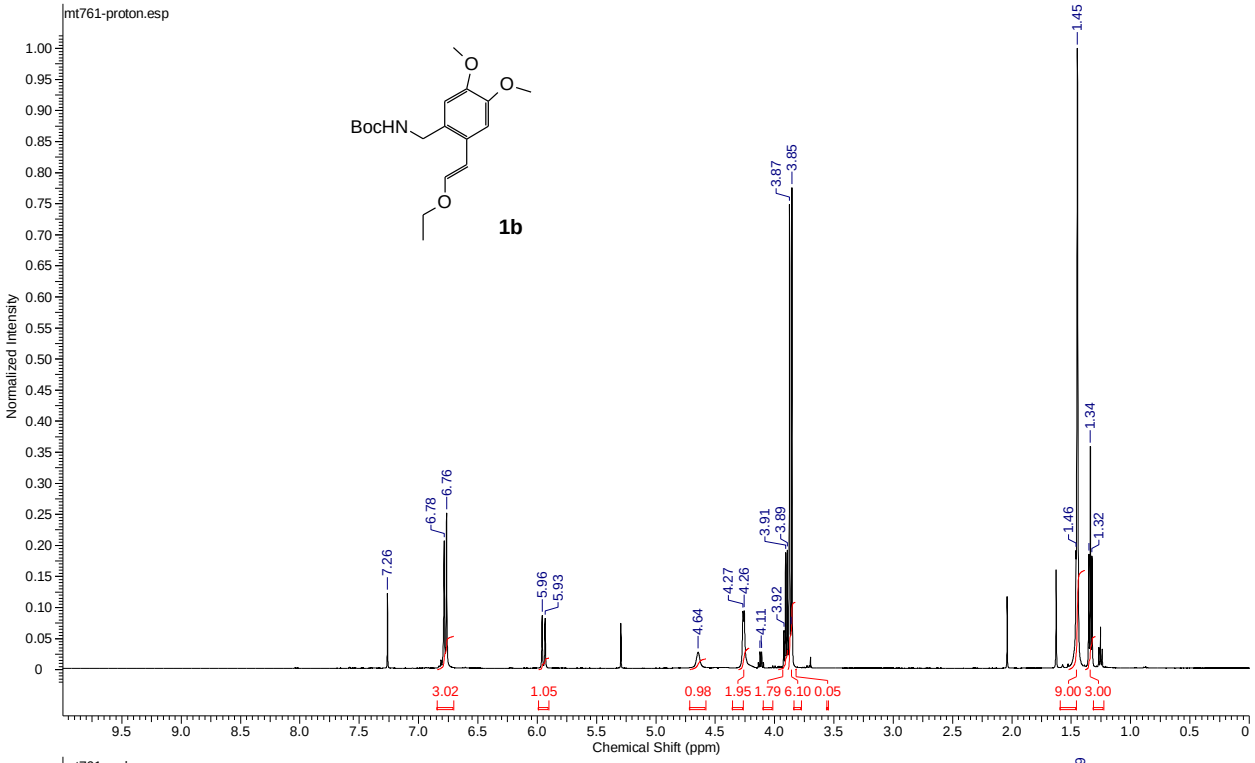


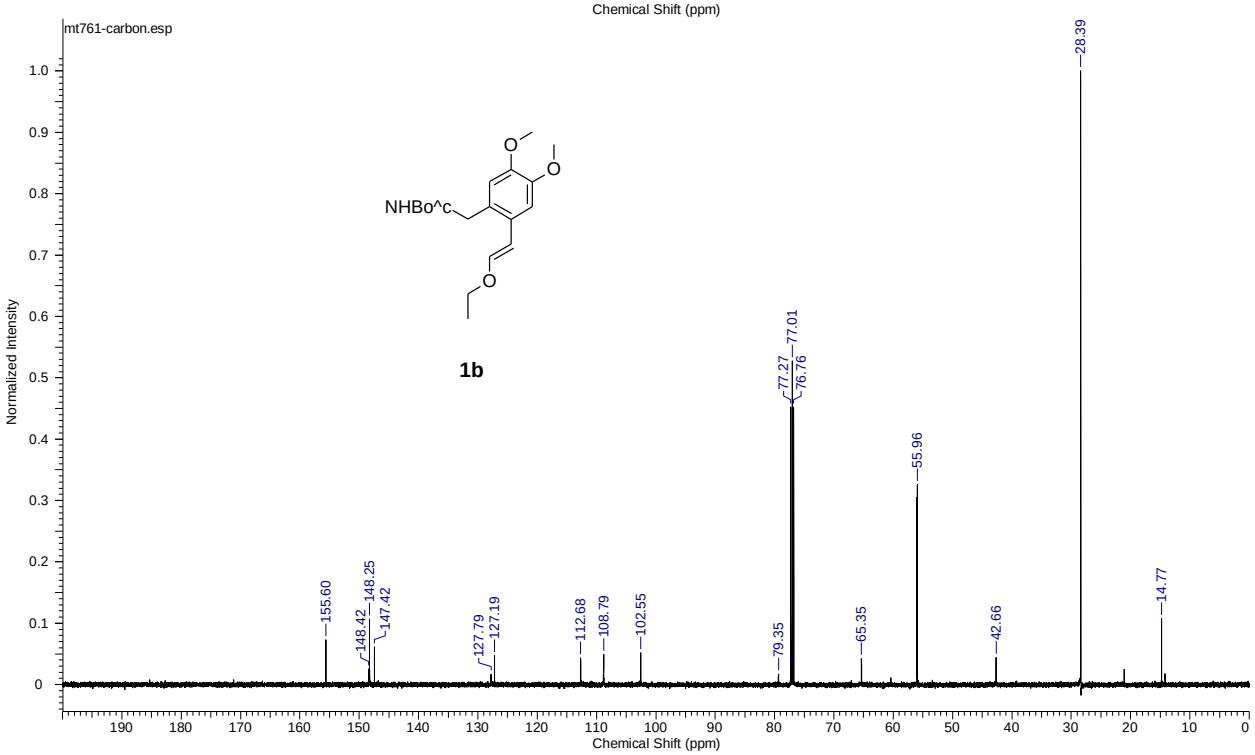


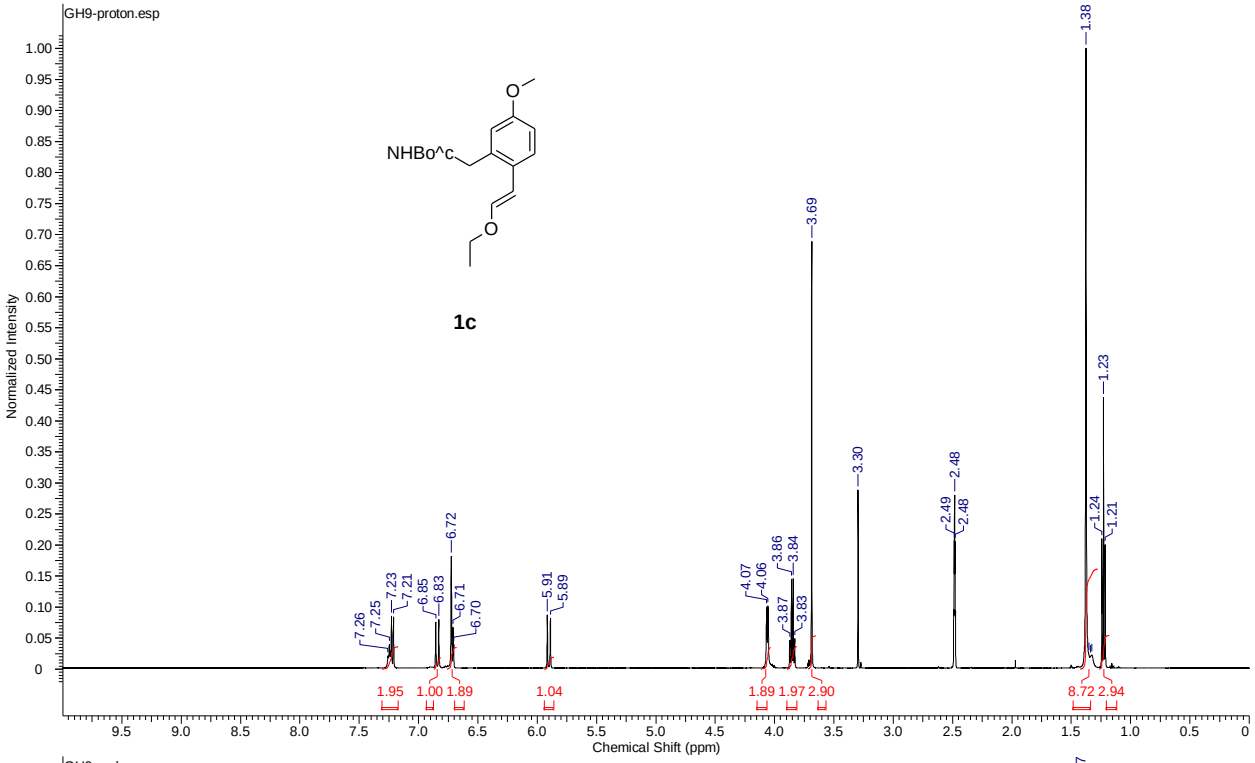


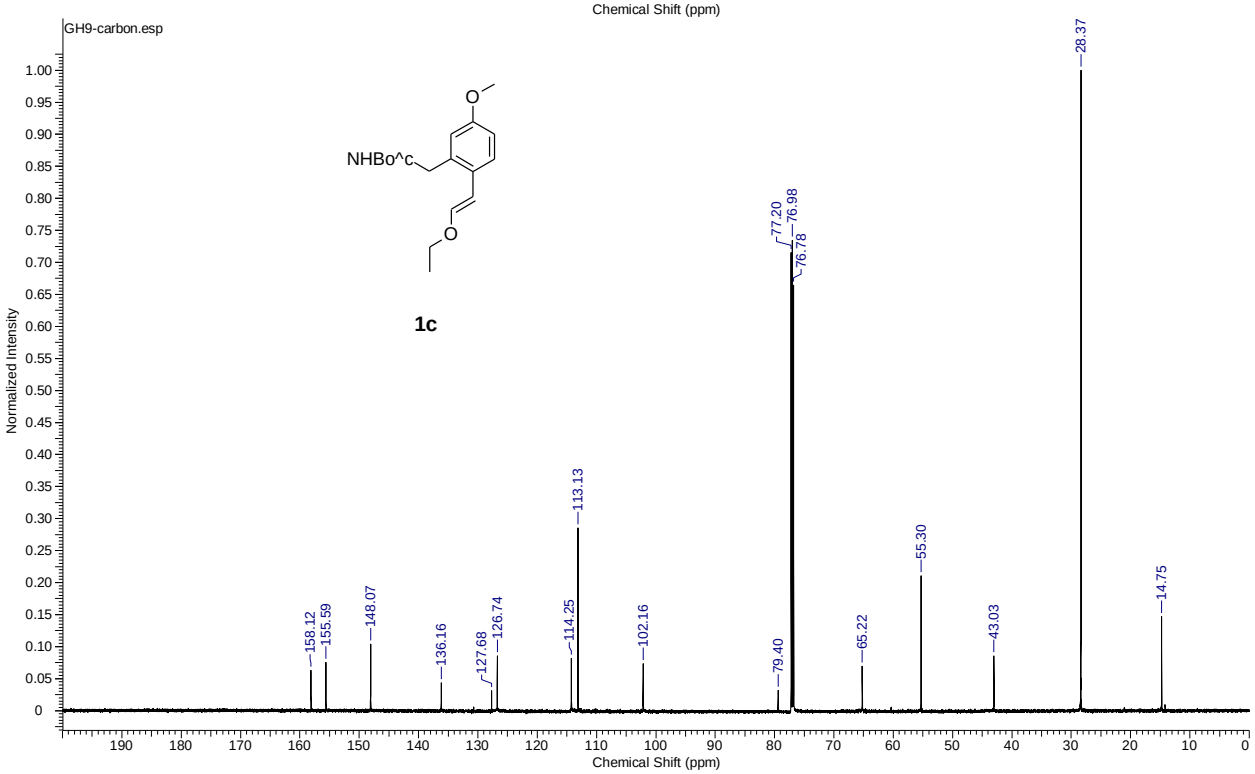


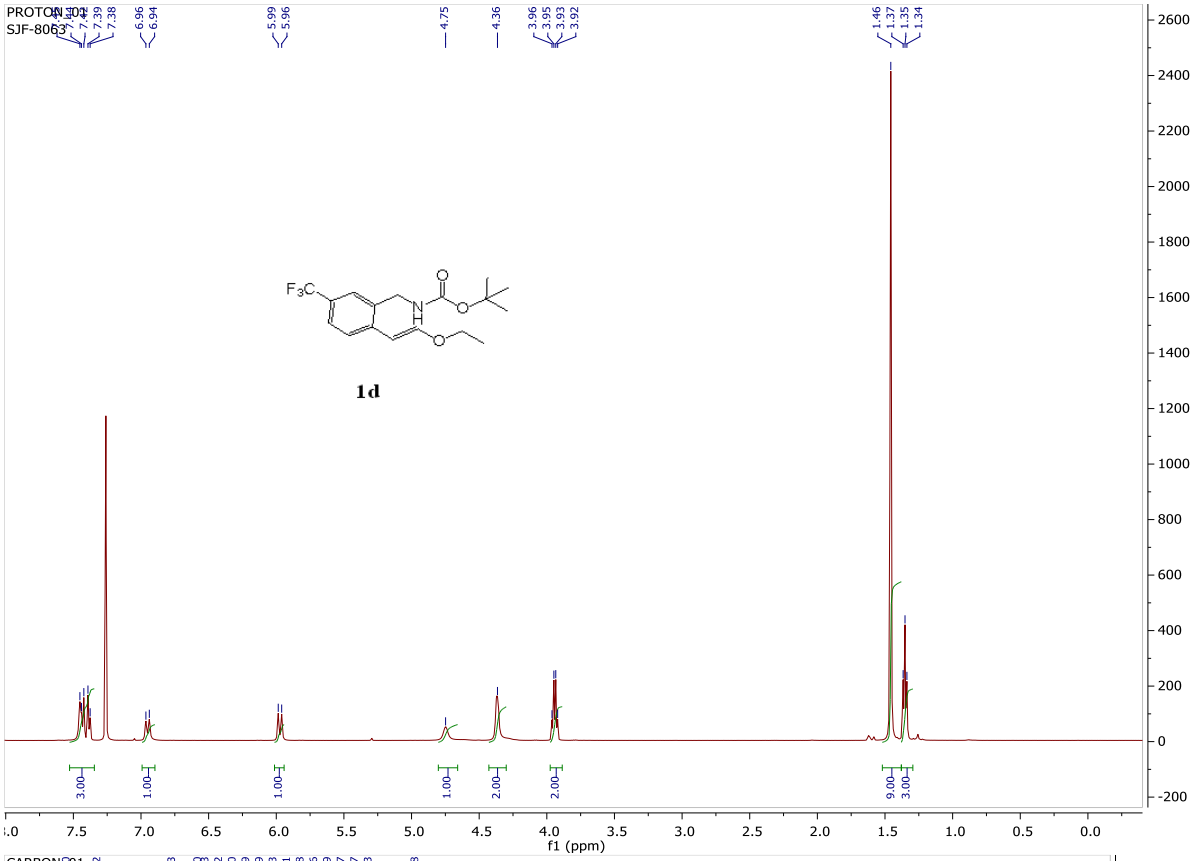


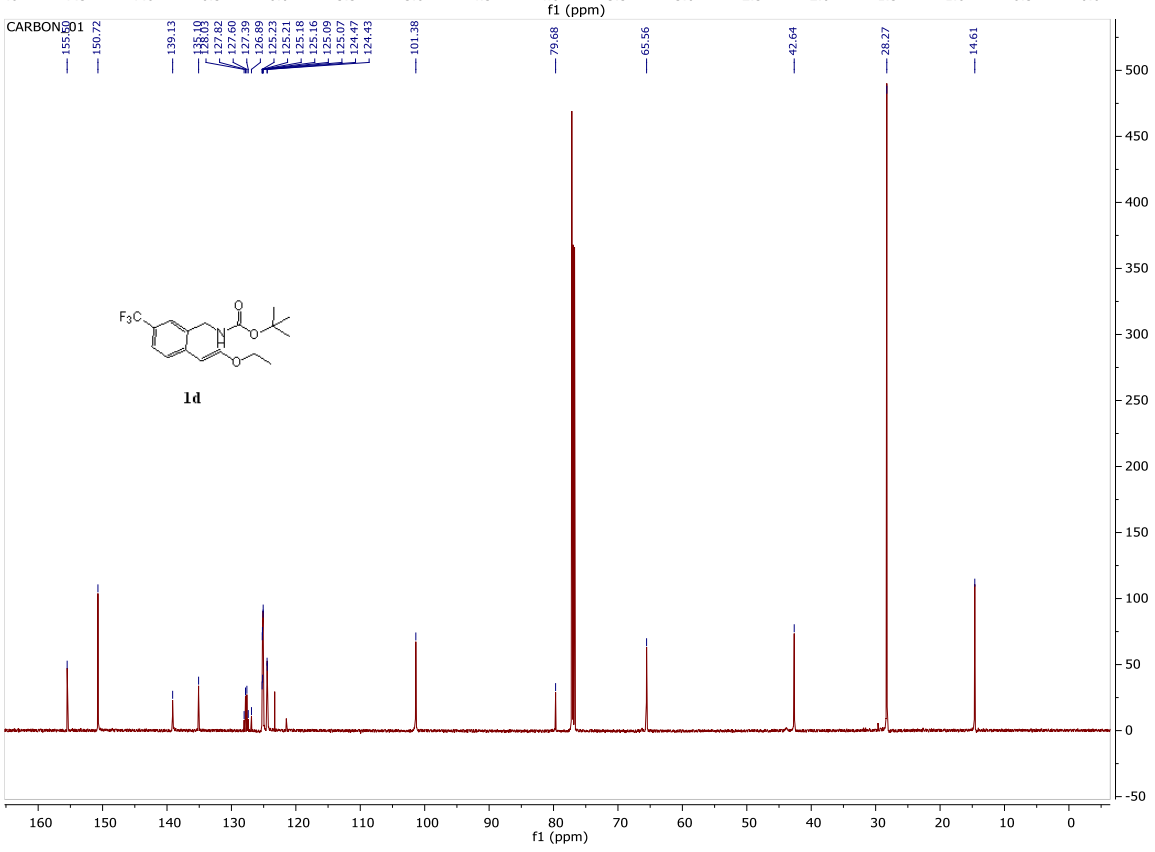


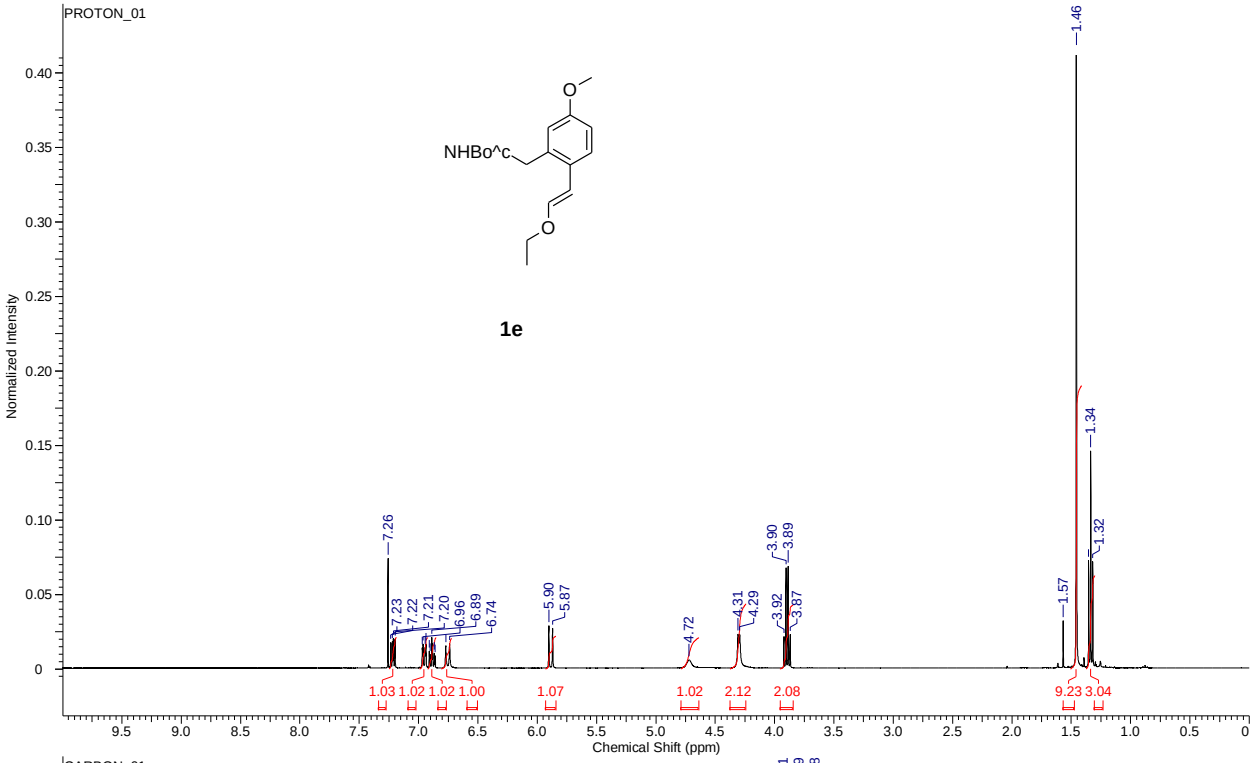


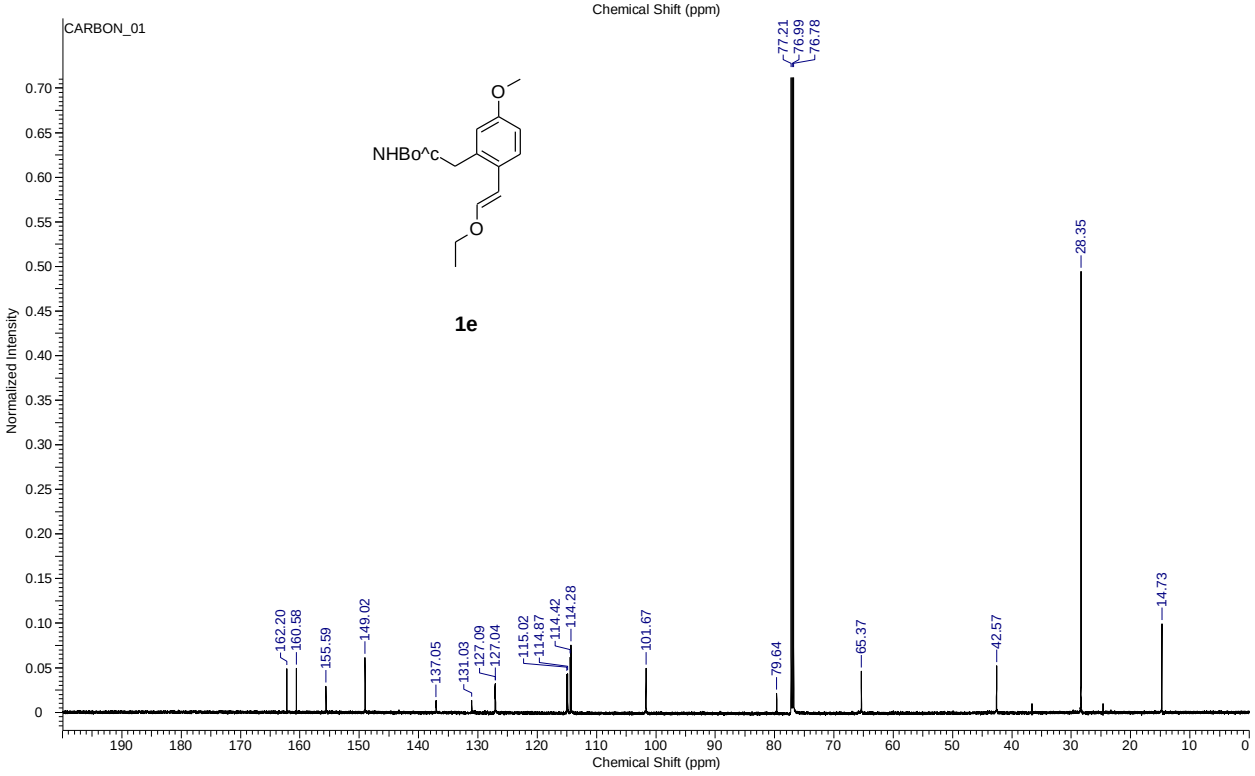


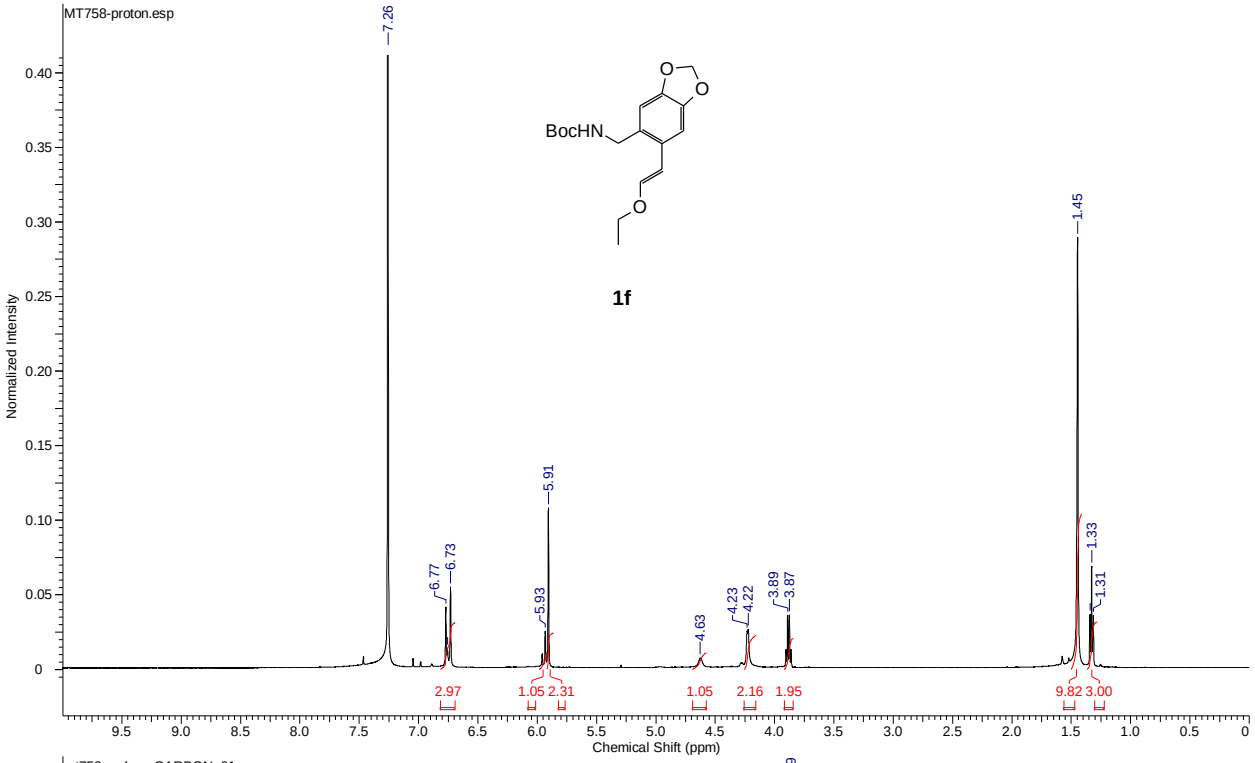


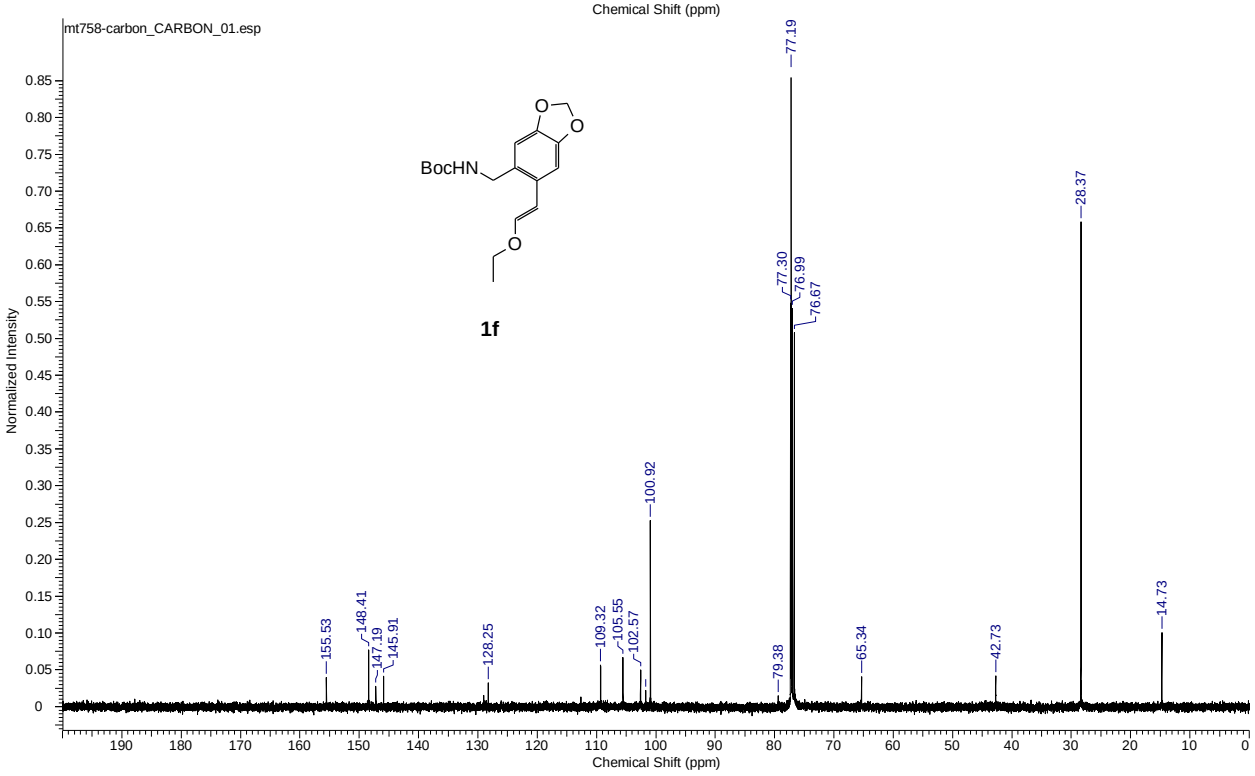


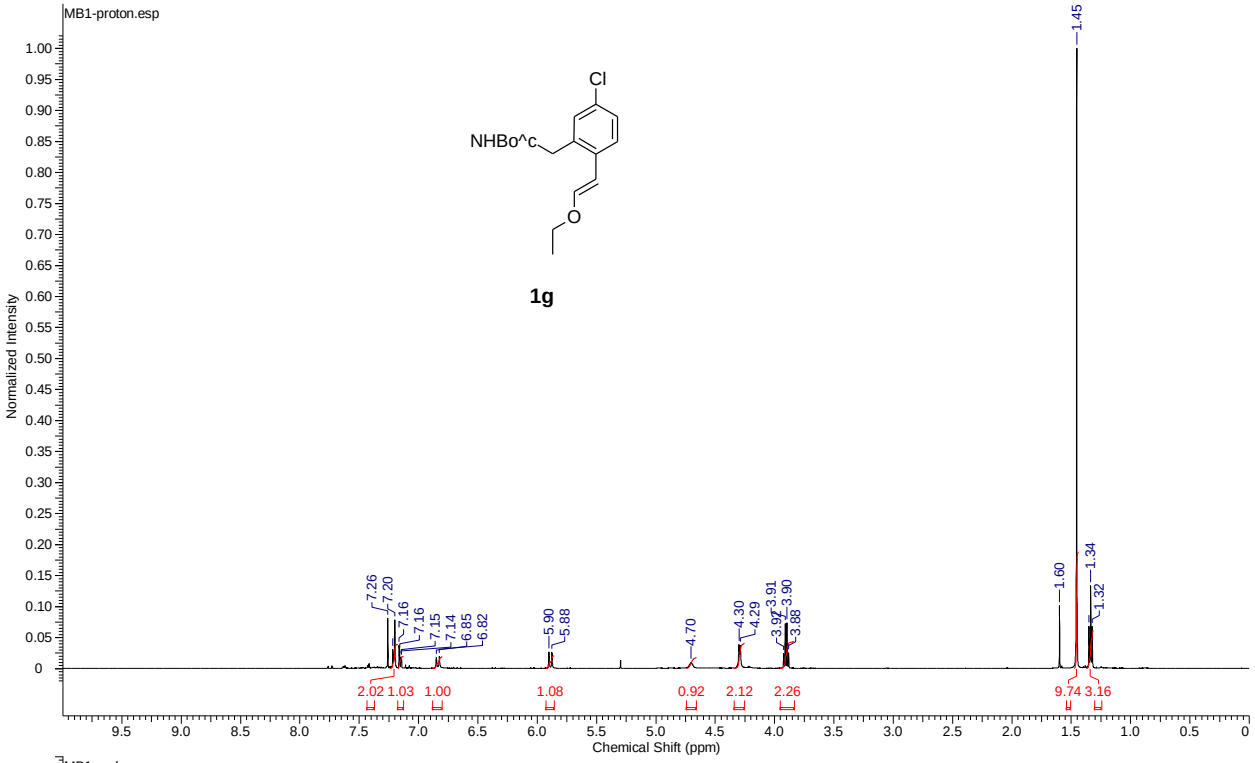


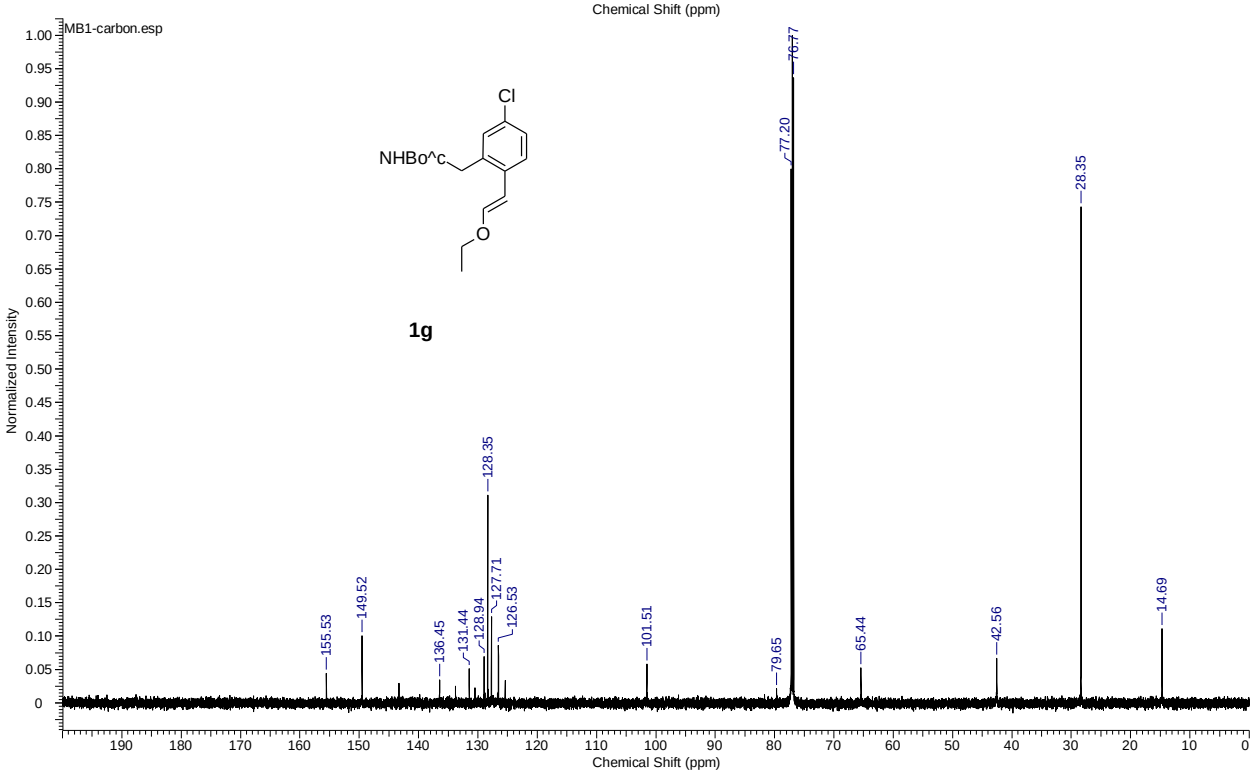


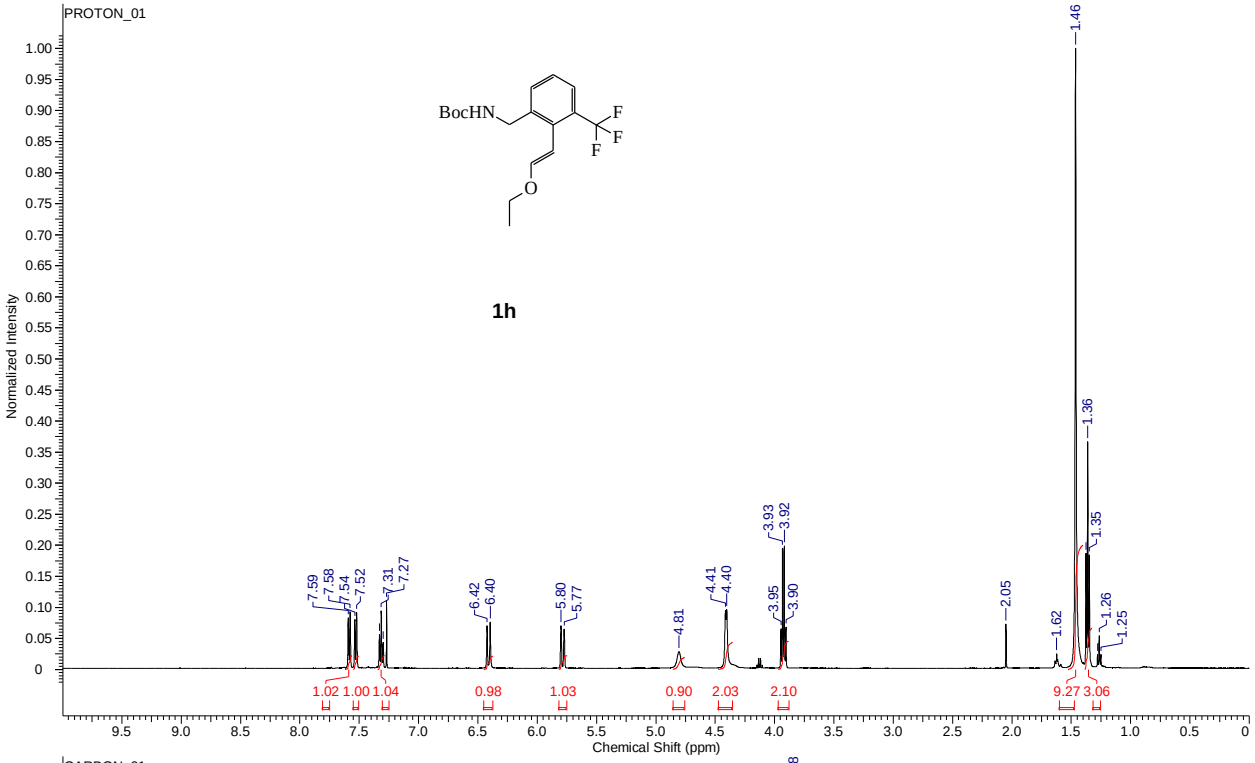


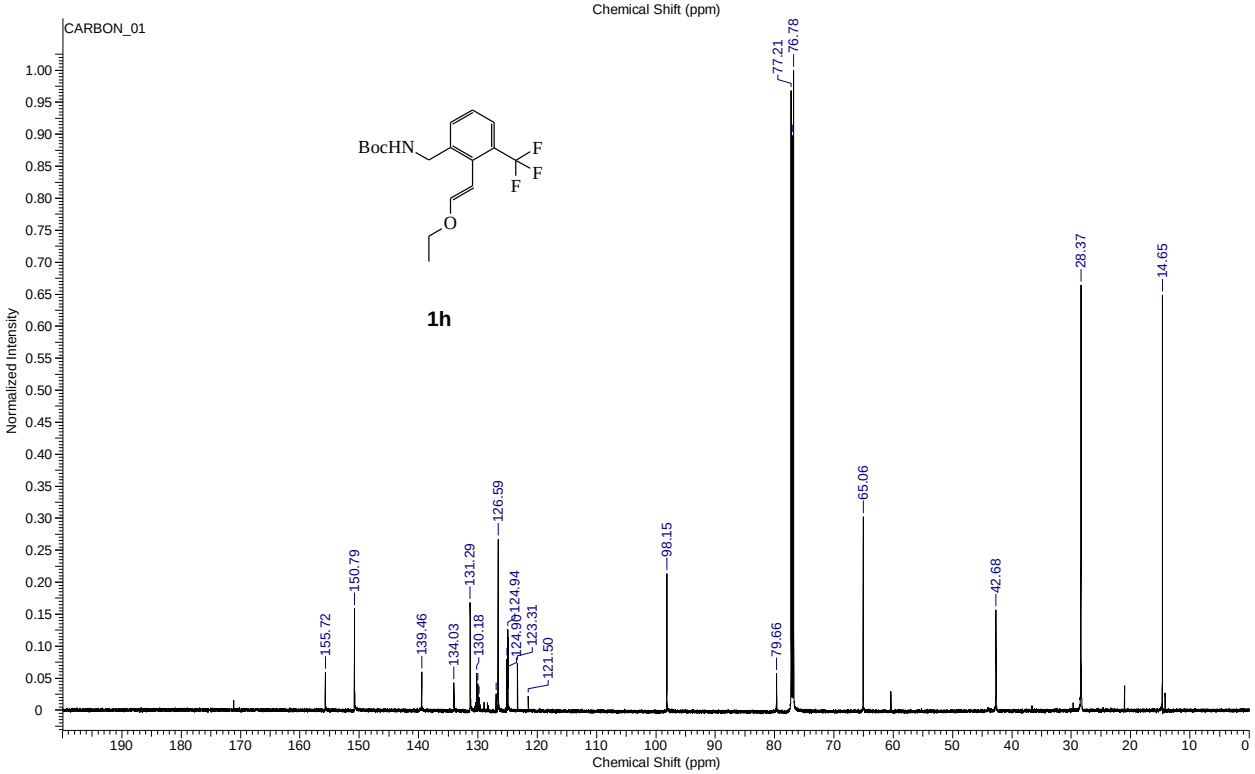


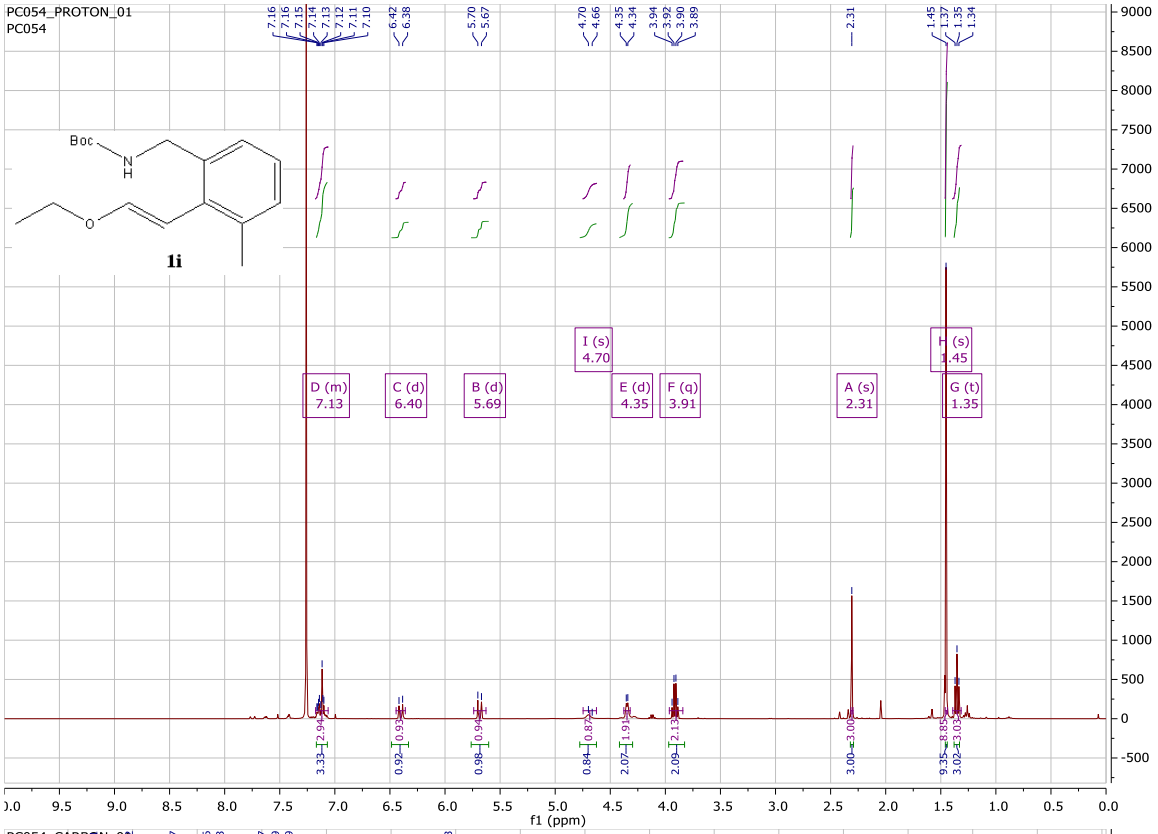


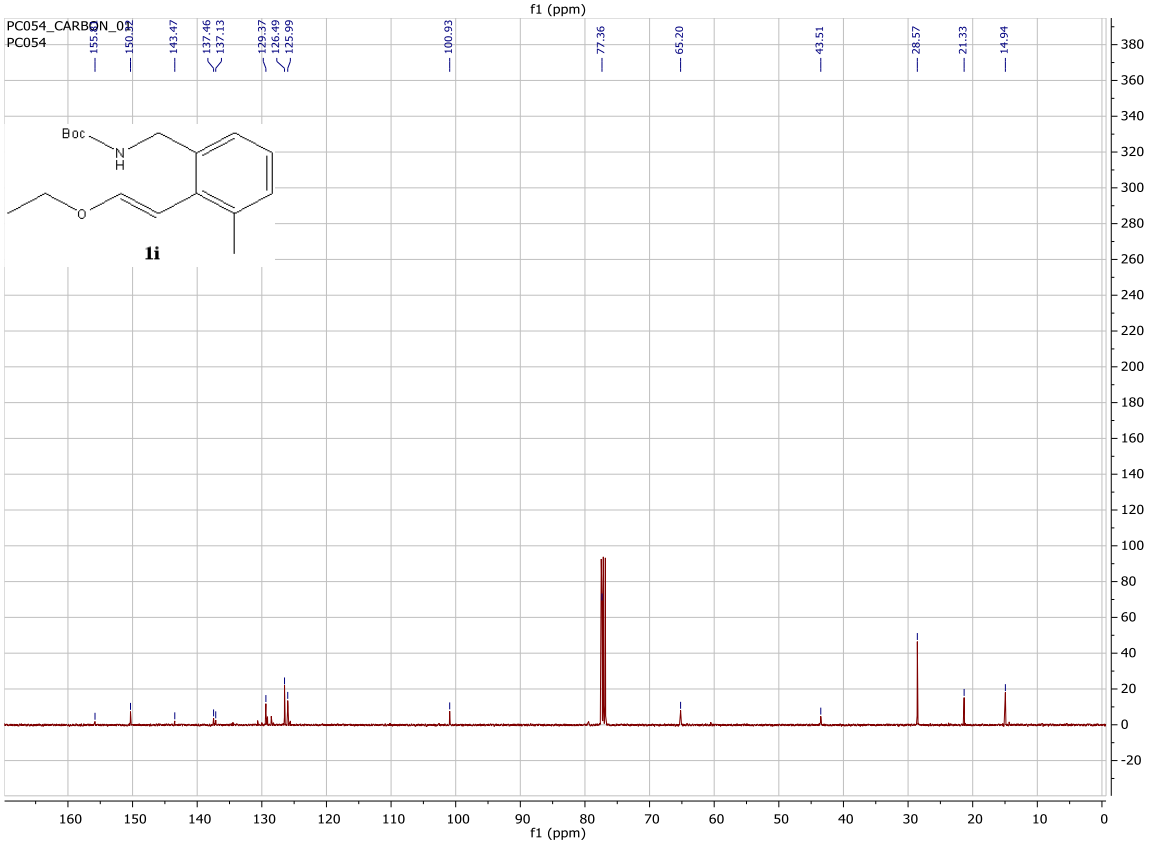


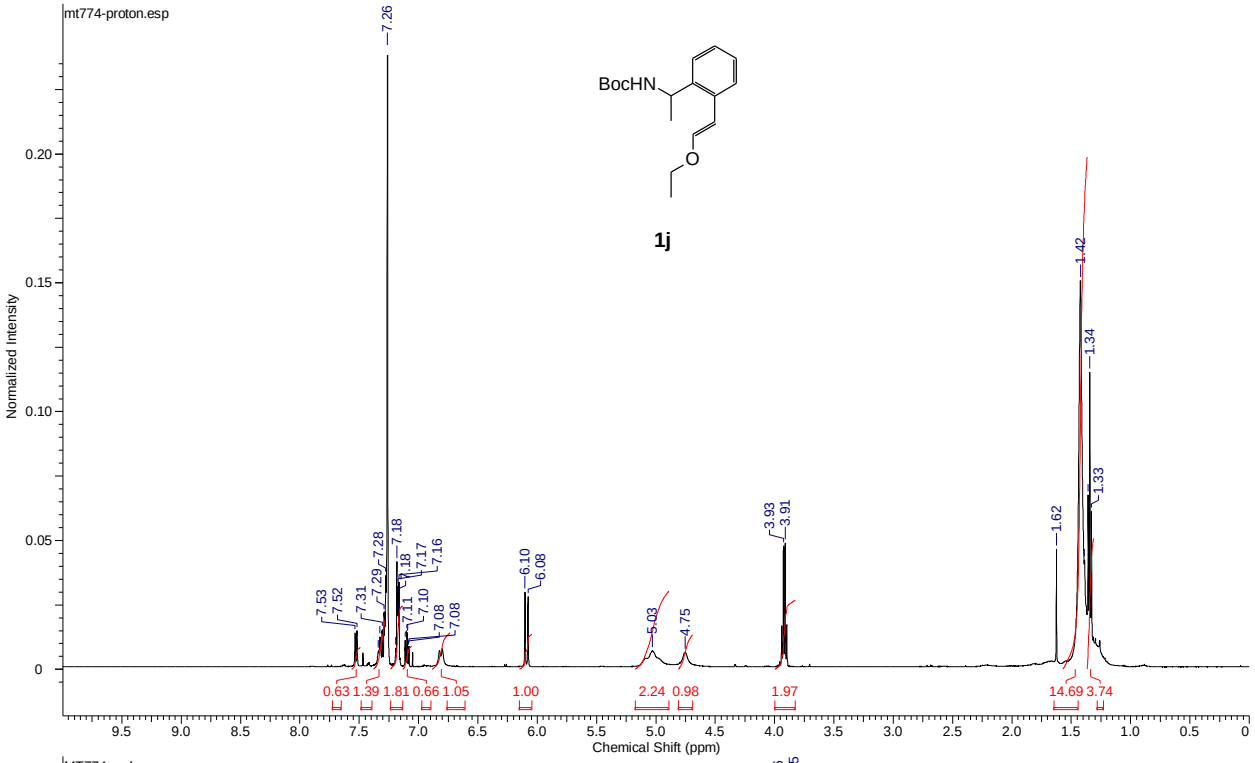


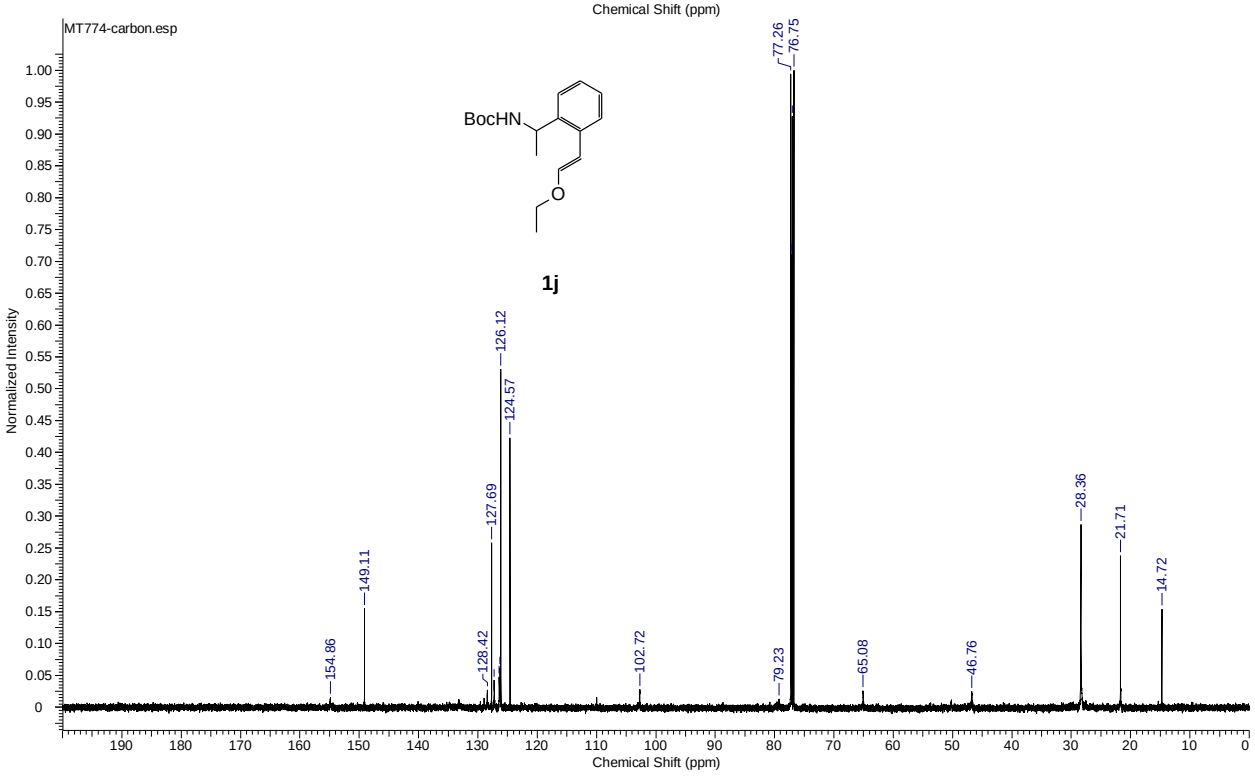


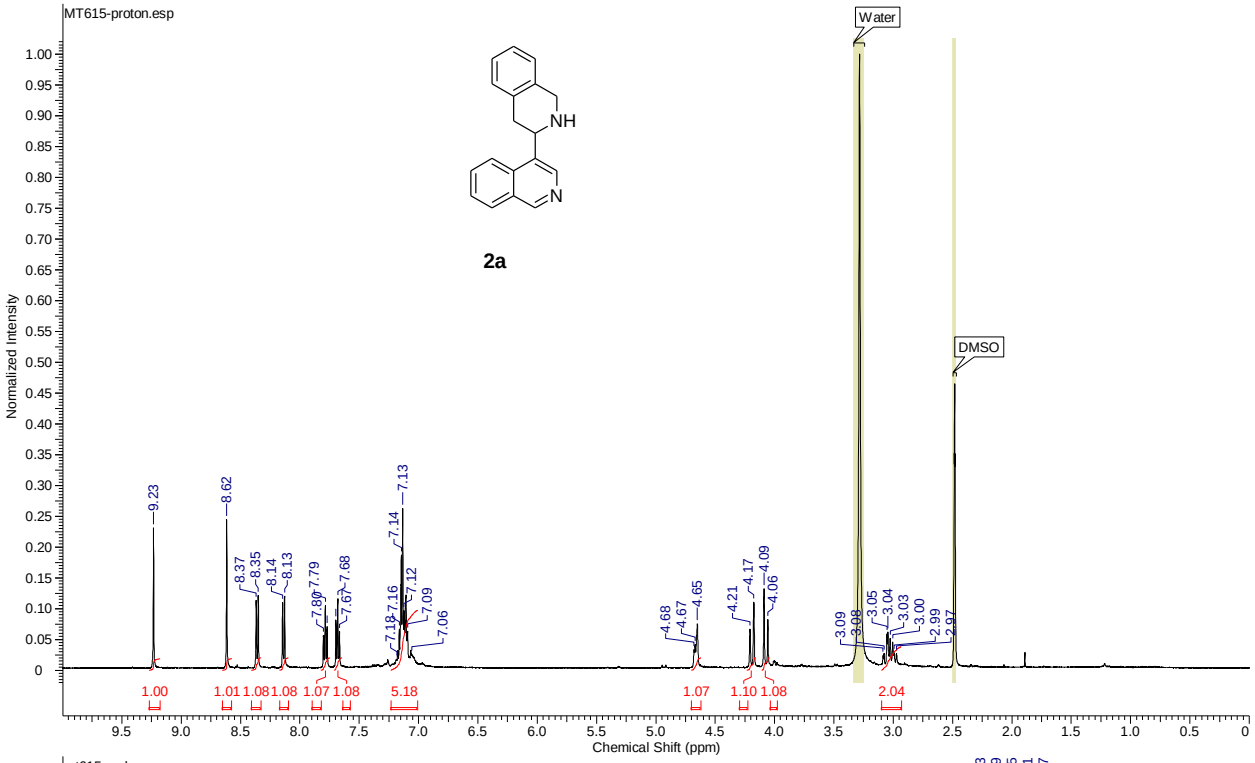


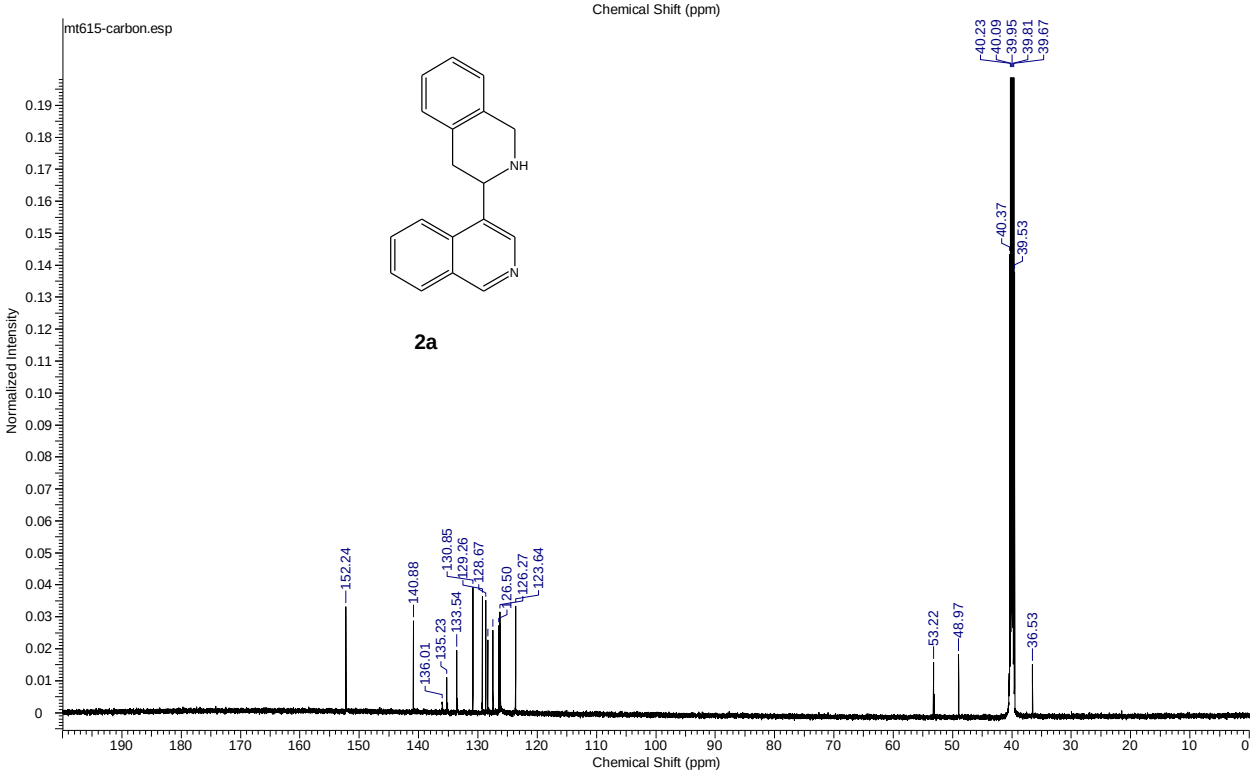


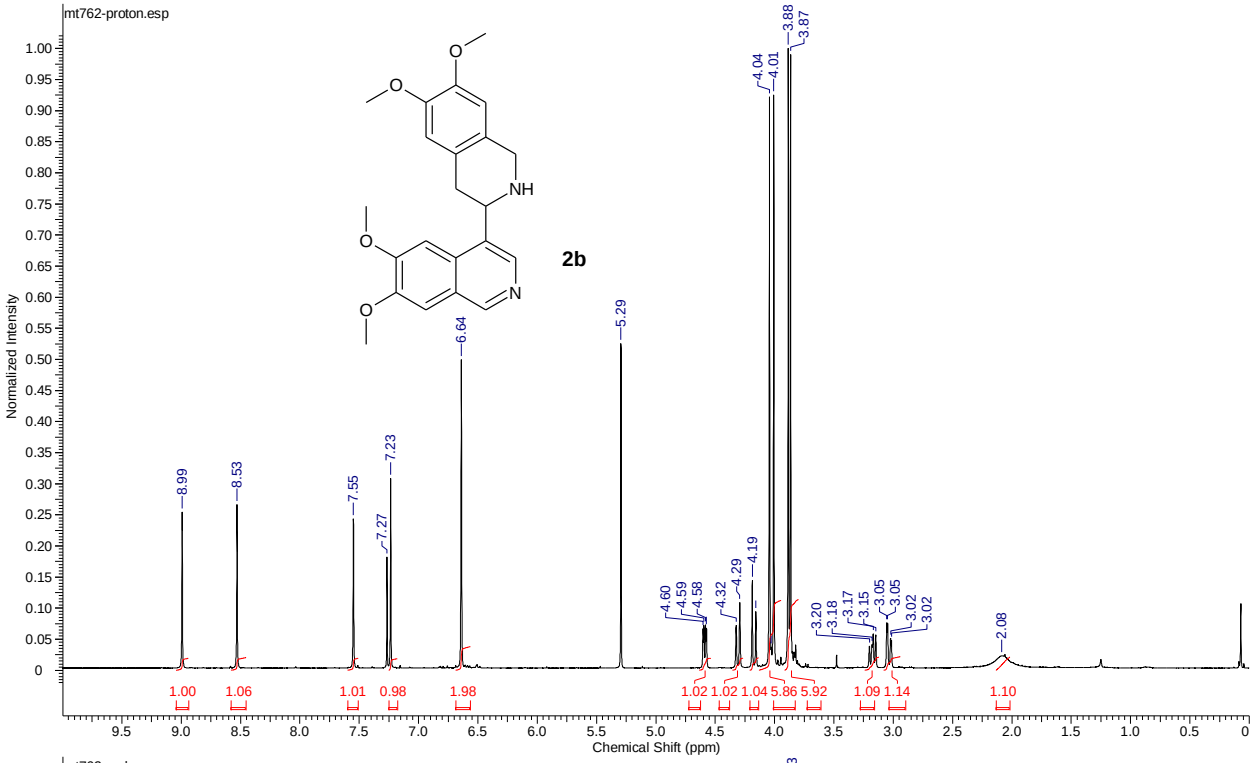


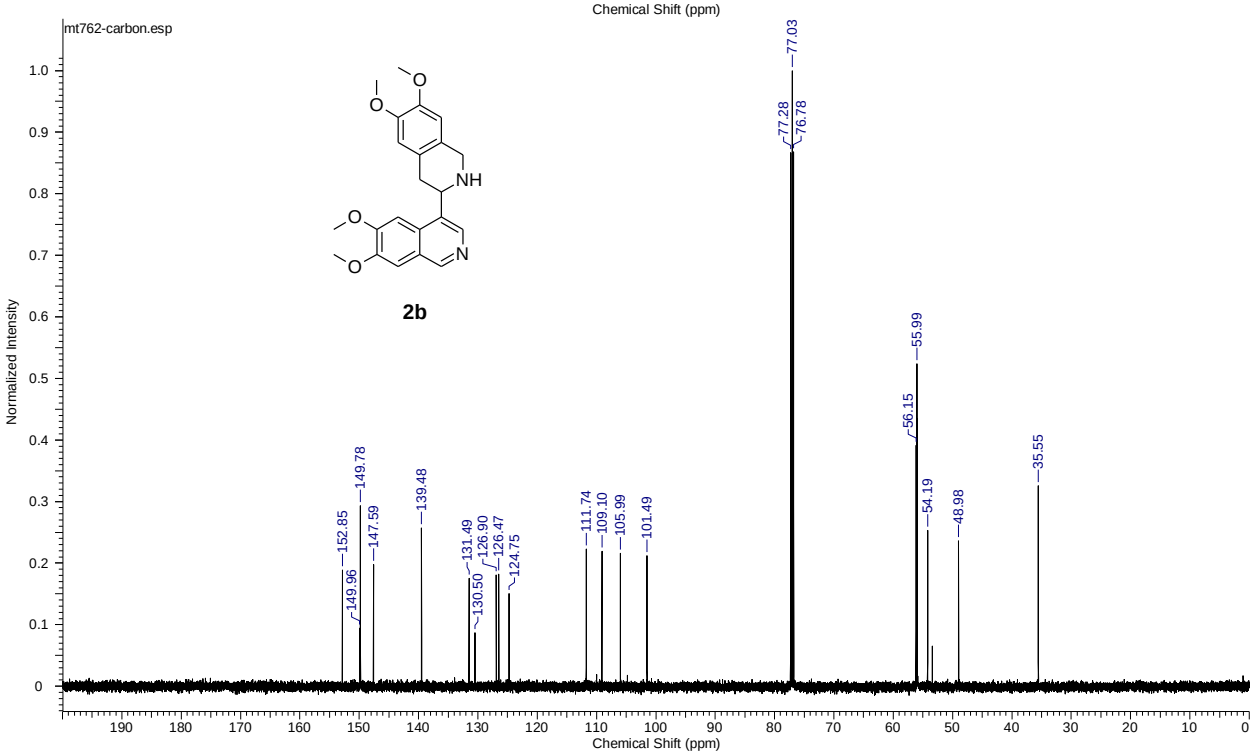


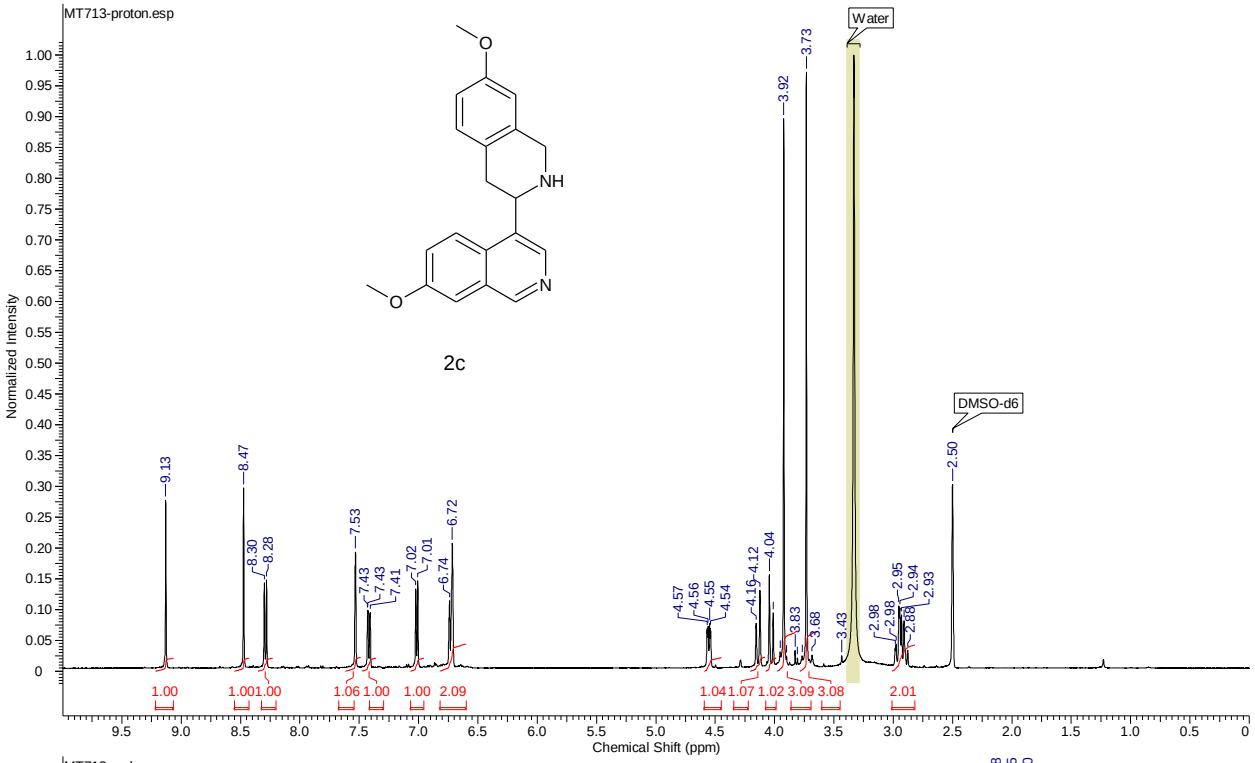


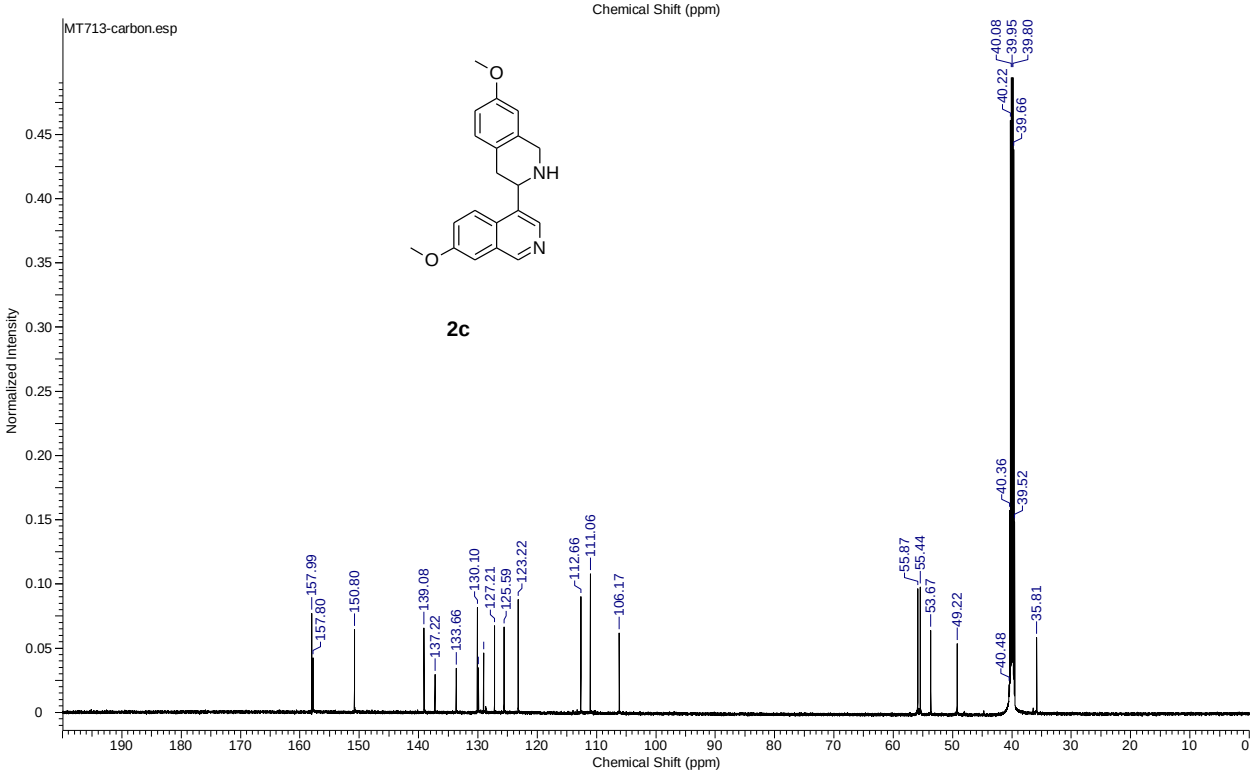


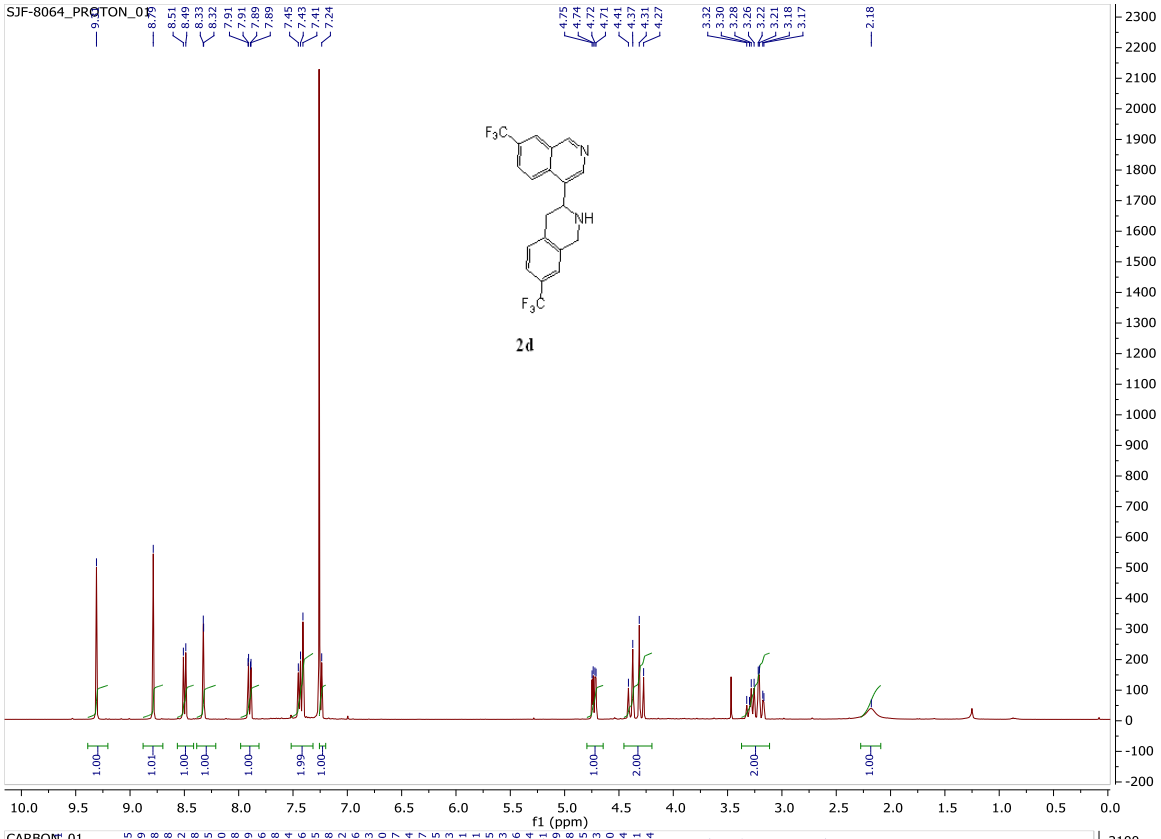


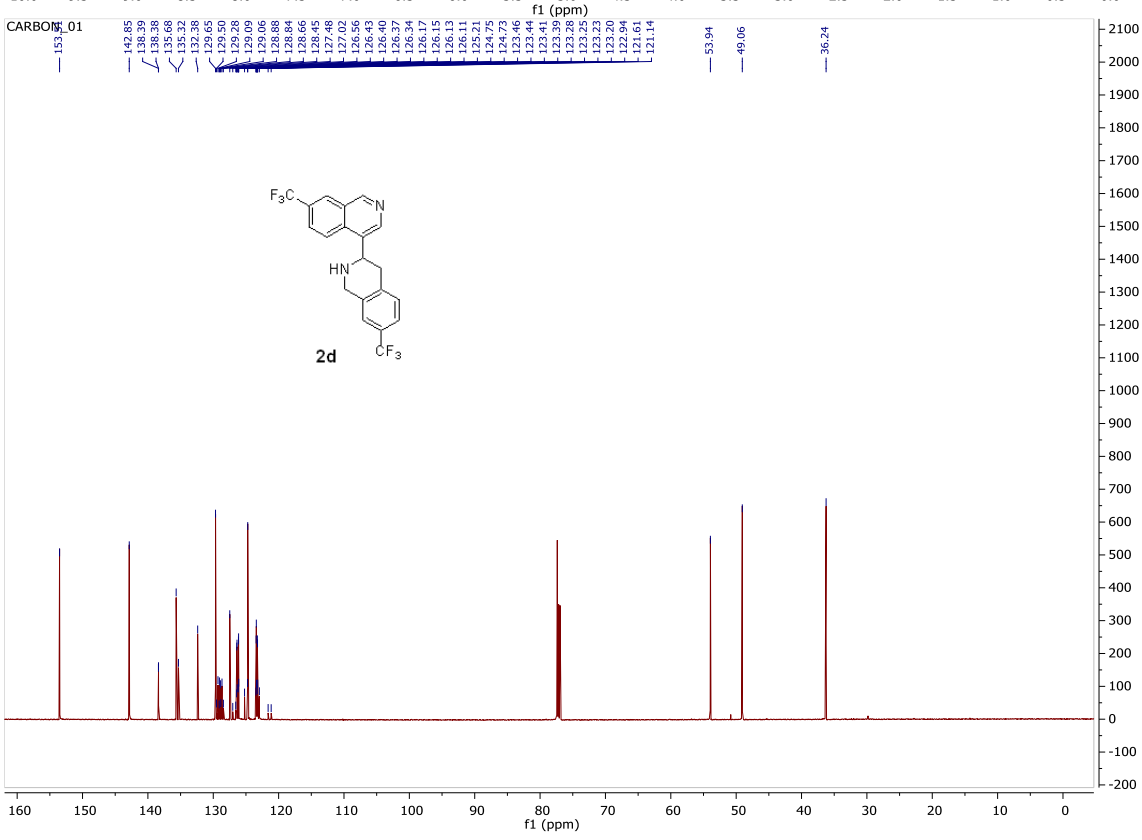


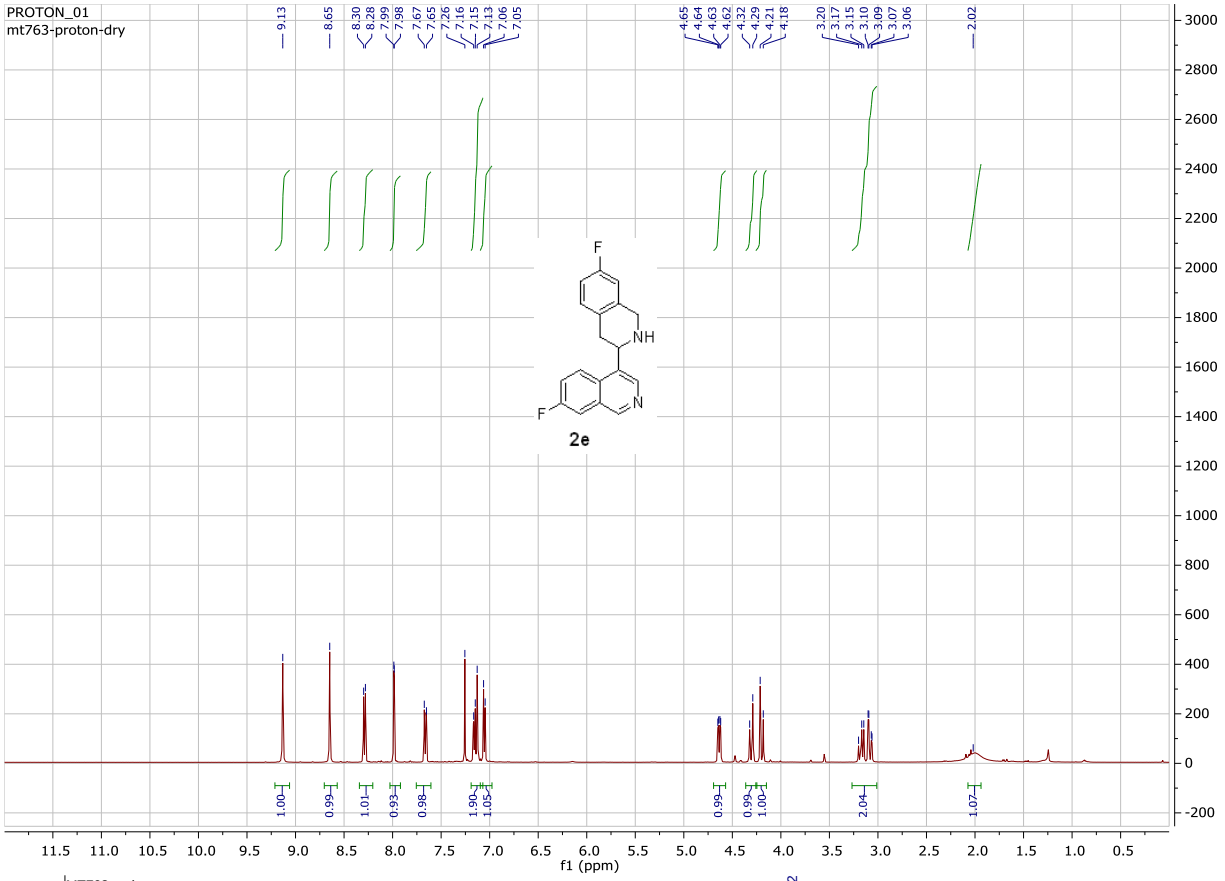


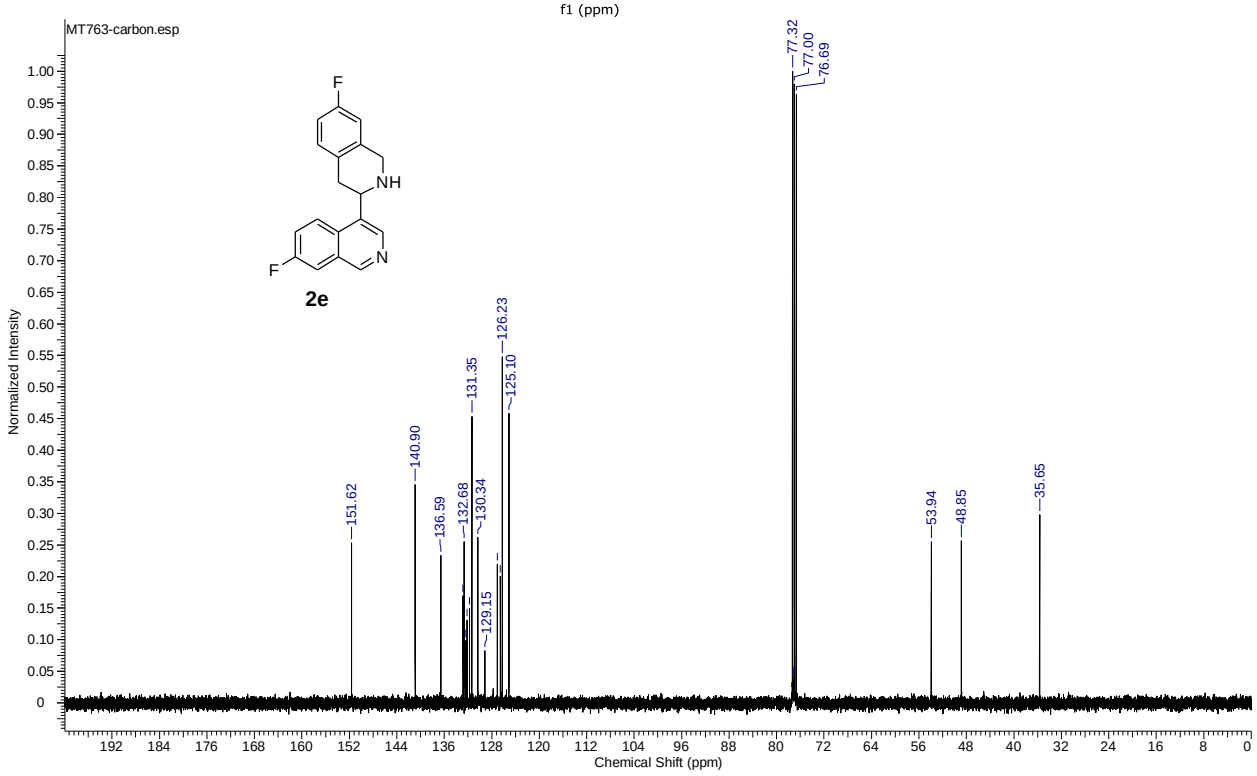


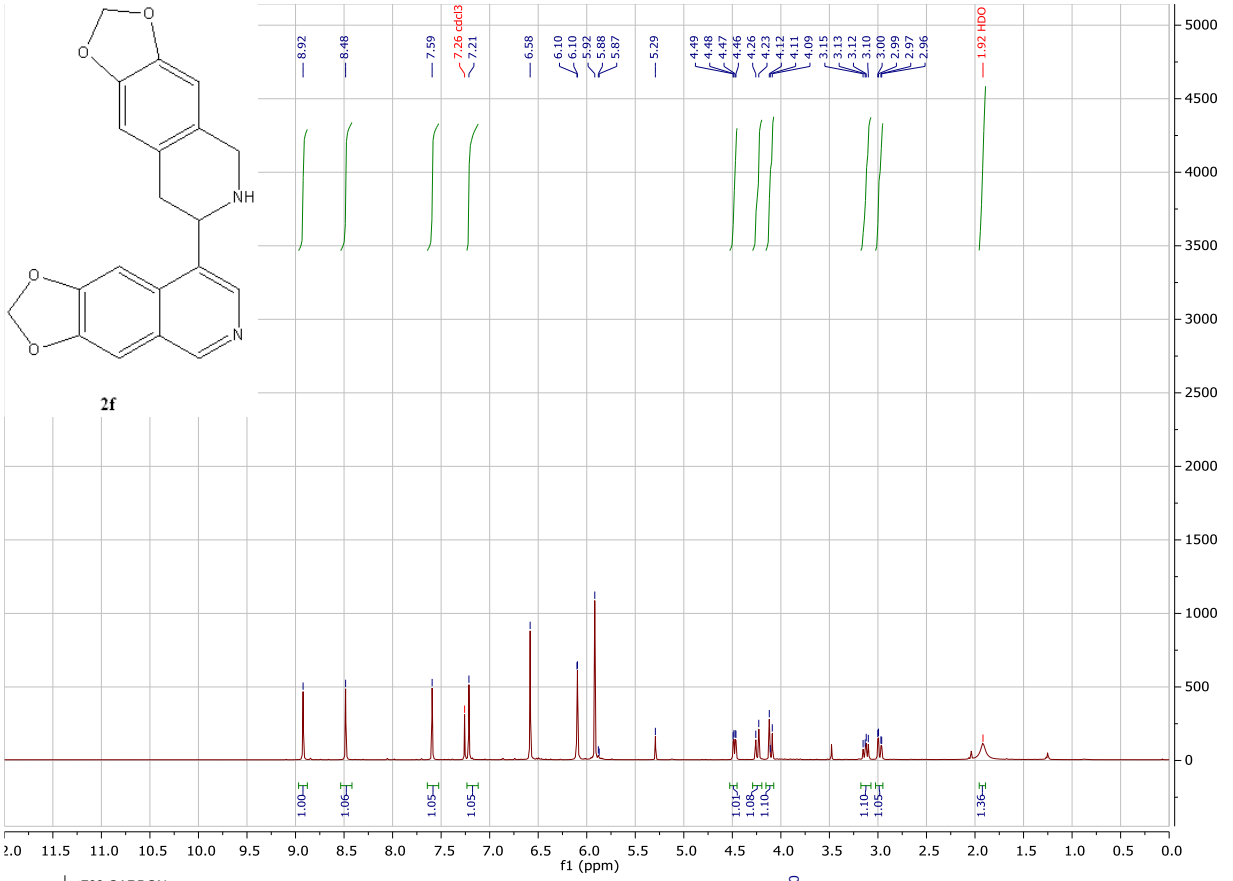












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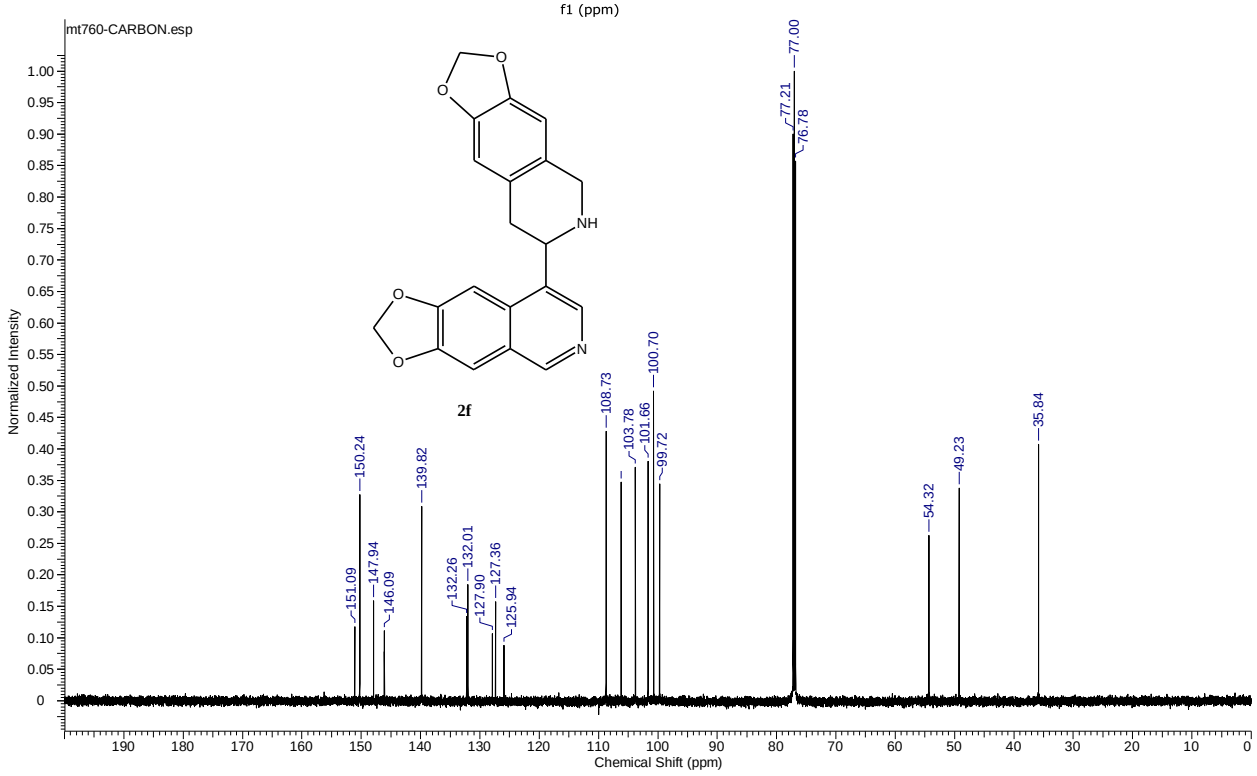

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