

## Supporting Information

# Photochemical Uncaging of Aldehydes and Ketones via Photocyclization/Fragmentation Cascades of Enyne Alcohols: An Unusual Application for a Cycloaromatization Process

Adam T. Campbell,<sup>[a]</sup> Nikolas R. Dos Santos<sup>[a]</sup> and Igor Alabugin<sup>\*[a]</sup>

[a] Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306, USA, e-mail: [alabugin@chem.fsu.edu](mailto:alabugin@chem.fsu.edu)

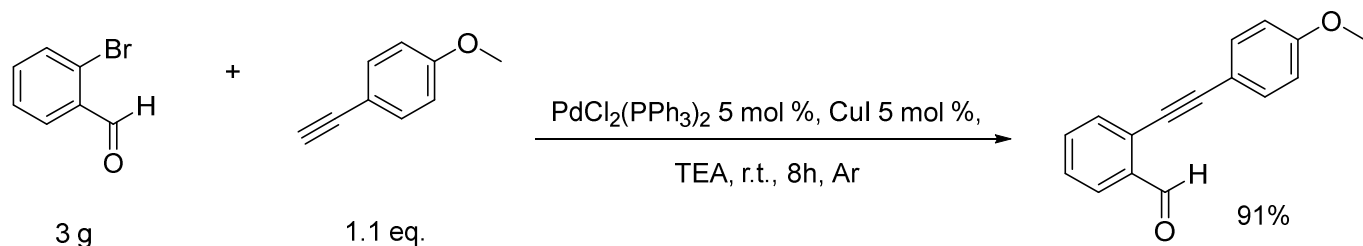
<b>I. Materials and Methods .....</b>	<b>S1</b>
<b>II. General Procedures .....</b>	<b>S1</b>
<b>III. Spectral Data for The New Compounds.....</b>	<b>S4</b>
<b>IV. References.....</b>	<b>S51</b>

### I. Materials and Methods

Tetrahydrofuran (THF) was purchased from Sigma Aldrich and collected through a Glass contour solvent purification system by SG Water USA, LLC. All other chemicals were purchased through Sigma Aldrich and used as received. The NMR spectra were measured on a Bruker spectrometer at 400/600 MHz for <sup>1</sup>H and 101/151 MHz for <sup>13</sup>C and referenced to the resonances of CDCl<sub>3</sub>. All irradiation was performed in a Luzchem LZC-4X photoreactor equipped with 14 Hitachi FL8BL-B UVA bulbs centered at 350 nm. The MS full scan spectra with accurate mass determination were obtained by Agilent 6230 time-of-flight TOF mass spectrometer. Ionization condition conditions: drying gas (N<sub>2</sub>) flow rate, 10.0 L/min; dry temperature, 350 °C; Nebulizer, 40 psi; Fragmentor, 175 V; Capillary voltage, 2000 V; Skimmer potential, 75 V; Hexapole RF, 250 V. All the operations, acquisition and analysis were controlled by Mass Hunter Workstation. UV-VIS spectroscopy was recorded on an Agilent Cary 60 UV-VIS at concentrations of 50 µM.

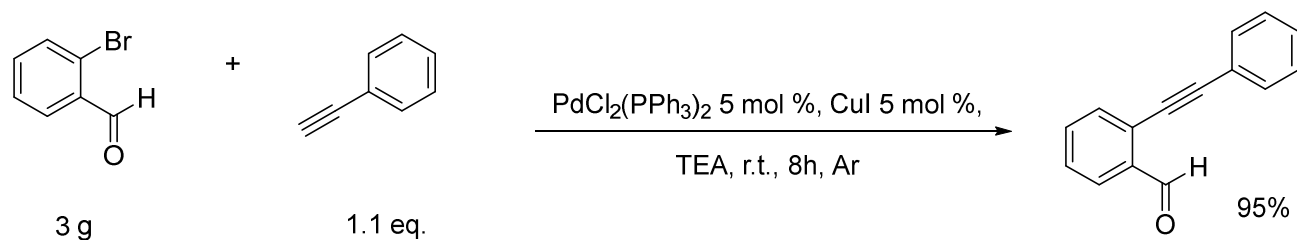
### II. General Procedures:

Sonogashira cross coupling to prepare benzaldehydes using p-OMephenylacetylene.



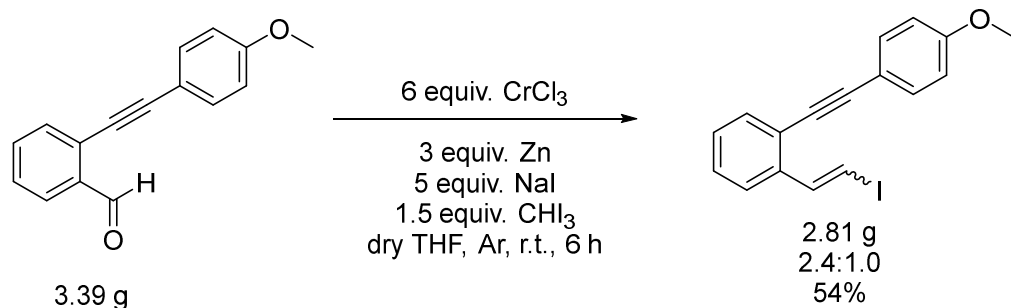
A suspension of 2-bromobenzaldehyde (16.2 mmol, 3.00 g),  $\text{PdCl}_2(\text{PPh}_3)_2$  (5 mol %, 0.811 mmol, 569 mg),  $\text{CuI}$  (5 mol %, 0.811 mmol, 154 mg), was dissolved in 100 mL of triethylamine and sparged with argon for 30 minutes in a 250 mL round bottom flask. The 1-ethynyl-4-methoxybenzene (1.1 equiv., 17.8 mmol, 2.36 g) was dissolved in a minimum amount of argon-sparged triethylamine, added slowly dropwise to the suspension, which quickly resulted in the formation of a dark brown precipitant. The solution was allowed to stir for 8 hours at room temperature. The reaction mixture was filtered through celite, concentrated on a rotary evaporator under reduced pressure, and purified via flash chromatography on silica gel using ethyl acetate and hexanes as an eluent to afford the aldehyde product in a 91% yield.

Sonogashira cross coupling to prepare benzaldehydes using phenylacetylene.



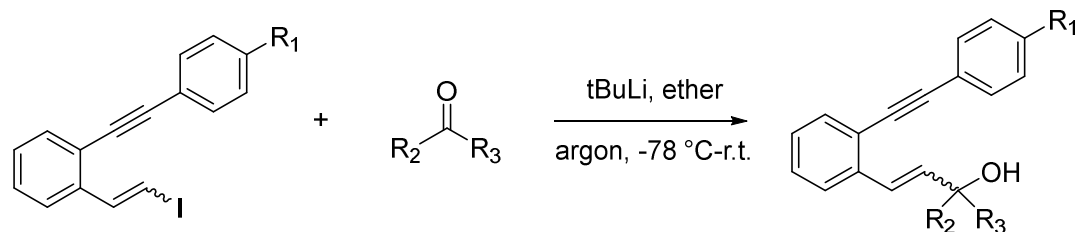
A suspension of 2-bromobenzaldehyde (16.2 mmol, 3.00 g),  $\text{PdCl}_2(\text{PPh}_3)_2$  (5 mol %, 0.811 mmol, 569 mg),  $\text{CuI}$  (5 mol %, 0.811 mmol, 154 mg), was dissolved in 100 mL of triethylamine and sparged with argon for 30 minutes in a 250 mL round bottom flask. The ethynylbenzene (1.1 equiv., 17.8 mmol, 1.82 g) was added slowly dropwise to the suspension which quickly resulted in the formation of a dark brown precipitant. The solution was allowed to stir for 8 hours at room temperature. The reaction mixture was filtered through celite, concentrated on a rotary evaporator under reduced pressure, and purified via flash chromatography on silica gel using ethyl acetate and hexanes as an eluent to afford the aldehyde product in a 95% yield.

Takai reaction to prepare vinyl iodides.



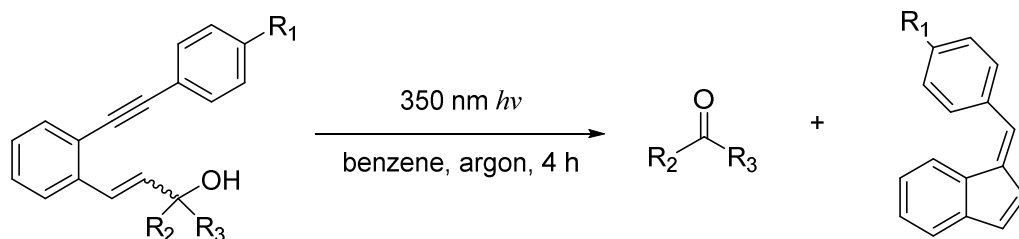
Based on Augé's<sup>1</sup> modified Takai protocol, a suspension of  $\text{CrCl}_3$  (6 equiv, 86.2 mmol, 13.7 g), Zn powder (3 equiv., 43.1 mmol, 2.82 g), and sodium iodide (5 equiv., 71.8 mmol, 10.8 g) was made by adding them to a dry 500 mL round bottom flask followed by 144 mL of dry tetrahydrofuran. In a separate dry round bottom flask, the aldehyde (14.4 mmol, 3.39 g) and iodoform (1.5 equiv., 21.6 mmol, 8.48 g) were dissolved in 72 mL of dry tetrahydrofuran. This solution was transferred to the suspension slowly via cannula which resulted in a steady darkening of the solution to a dark brown. The reaction mixture was stirred for 6 hours at room temperature. The reaction mixture was concentrated onto silica gel, and filtered through a silica gel plug to remove the inorganics. The crude reaction mixture was then purified via flash chromatography using ethyl acetate and hexanes as an eluent and the vinyl iodide was isolated in 50-54% yield as an E/Z mixture.

Lithium-halogen exchange addition reactions for synthesis of caged compounds.



A 200 mg portion of vinyl iodide was dissolved in 10 mL of dry ether over 4 Å molecular sieves under argon. 1.1 equivalents of ketone or aldehyde was dissolved in 10 mL of dry ether over 4 Å molecular sieves under argon. A 25 mL round bottom flask with stir bar was flame-dried and backfilled with argon. The dried vinyl iodide solution was then transferred to the round bottom flask, and cooled to -78 °C. 2.1 Equivalents of tertiary butyllithium in pentane solution was added dropwise, resulting in brief bursts of dark teal coloration with each drop, until the solution became fully dark teal at the end of the addition. The aldehyde or ketone solution is then immediately added via fast dropwise addition. After the addition of ketone or aldehyde, the solution steadily changes to a light brown or orange color. The solution was stirred at -78 °C for 1 hour and then allowed to warm to room temperature over 1 hour. The solution is then cooled again to -78 °C and quenched by dropwise addition of isopropanol, which lightens the solution to a transparent yellow. The crude reaction mixture is extracted with saturated ammonium chloride solution, then washed with deionized water before purification via silica gel flash chromatography using 15-20% ethyl acetate in hexanes as an eluent.

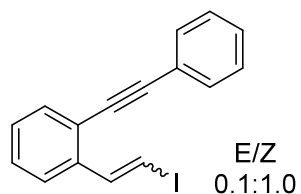
Photouncaging of enynols.



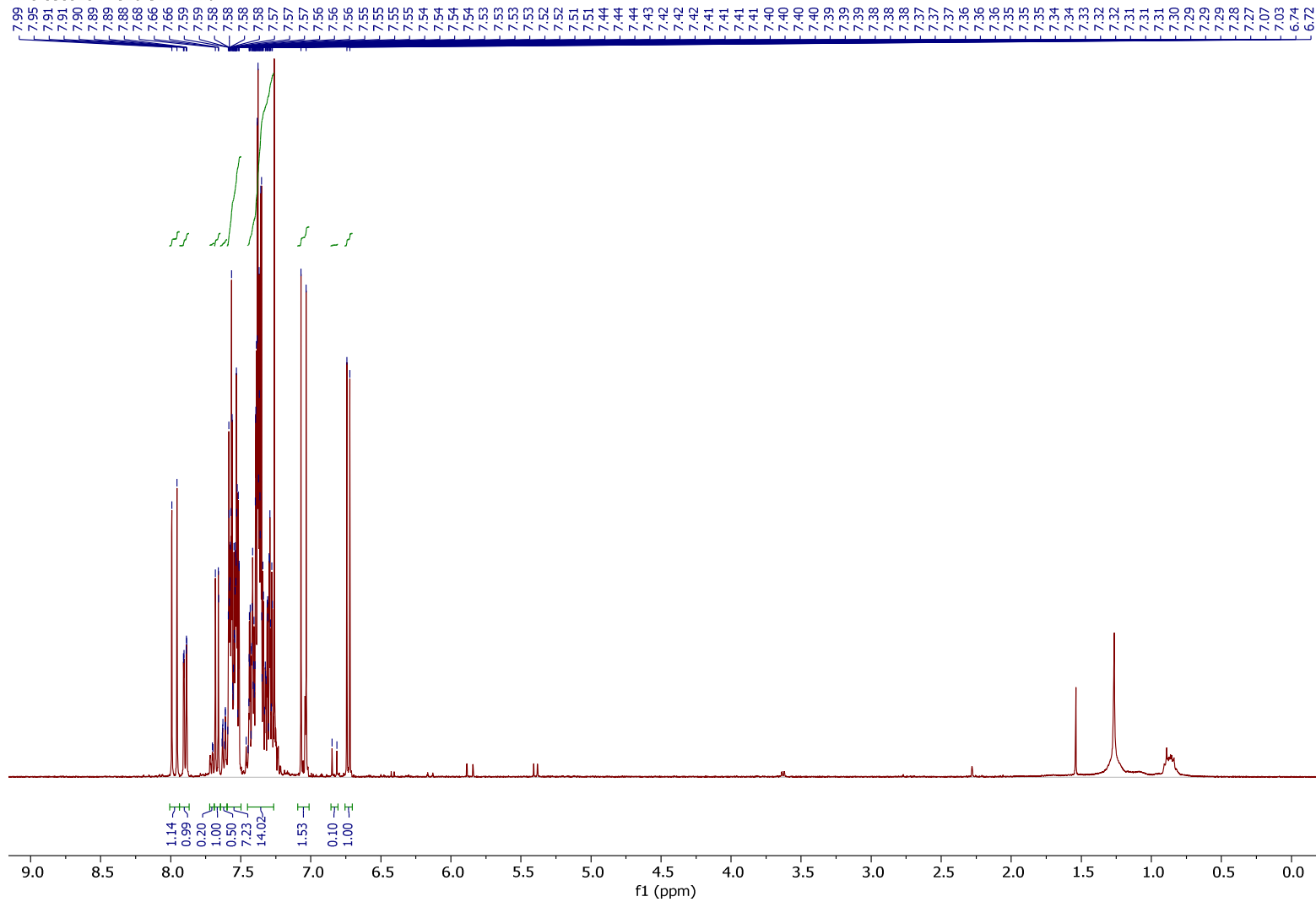
A 16  $\mu\text{mol}$  portion of the enynol is dissolved in 160 mL of benzene and sparged with argon for 1 h in a 250 mL round bottom flask with stir bar. The flask is then placed in a Luzchem LZC-4X photoreactor equipped with 14 Hitachi FL8BL-B UVA bulbs centered at 350 nm and stirred under irradiation for 4 hours. The solution starts with a very faint yellow color, which changes to a much brighter yellow indicative of benzofulvene formation. 1,3,5-trimethoxybenzene was added to the reaction mixture as an NMR standard to determine yields and the solvent was evaporated under reduced pressure.

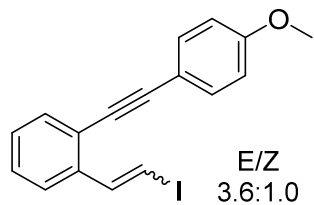
### III. Spectral Data for the new compounds:

Combination of singlet at 2.05 ppm, quartet at 4.12 ppm, and triplet at 1.26 ppm in various  $^1\text{H}$  NMR comes from EtOAc in sample.

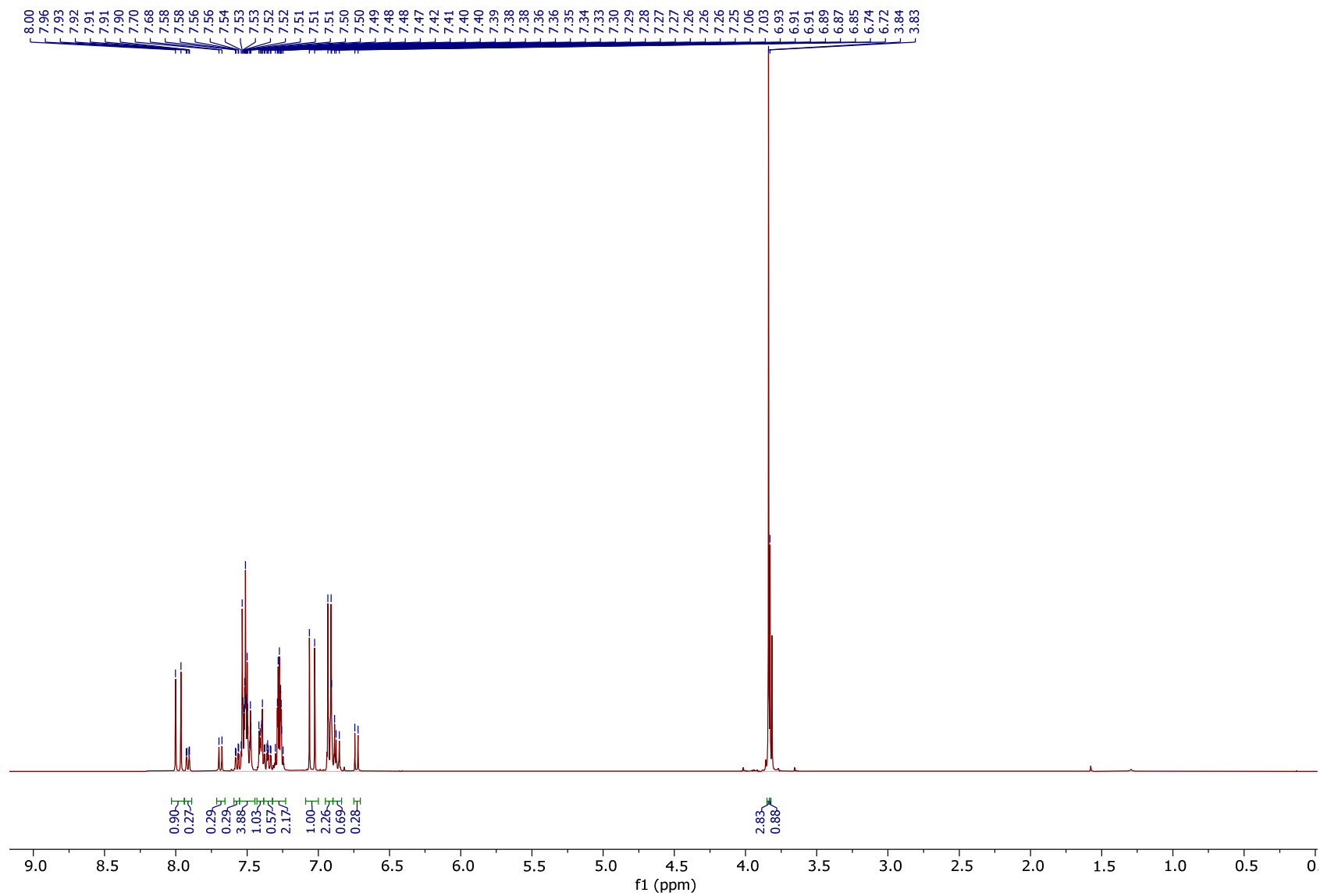


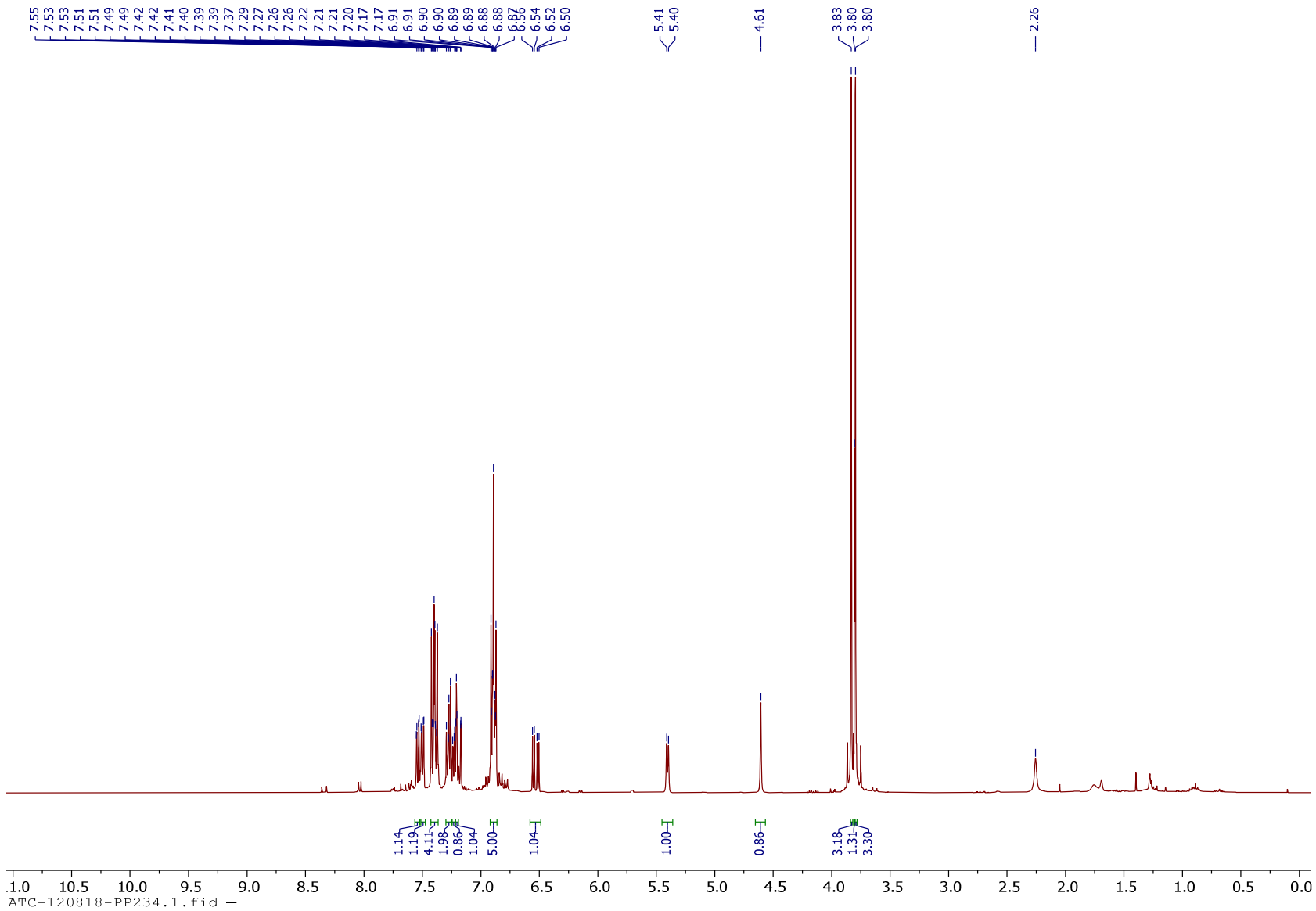
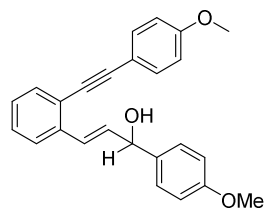
ATC-030520-PP326-S1F2.1.fid

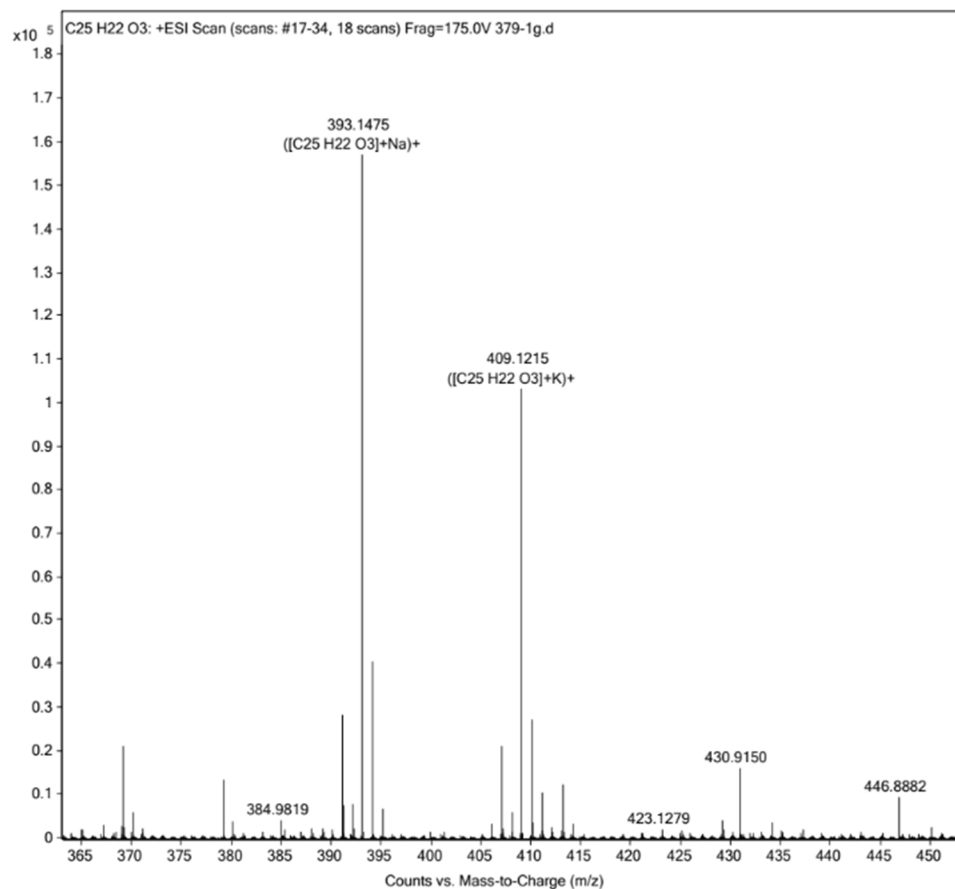


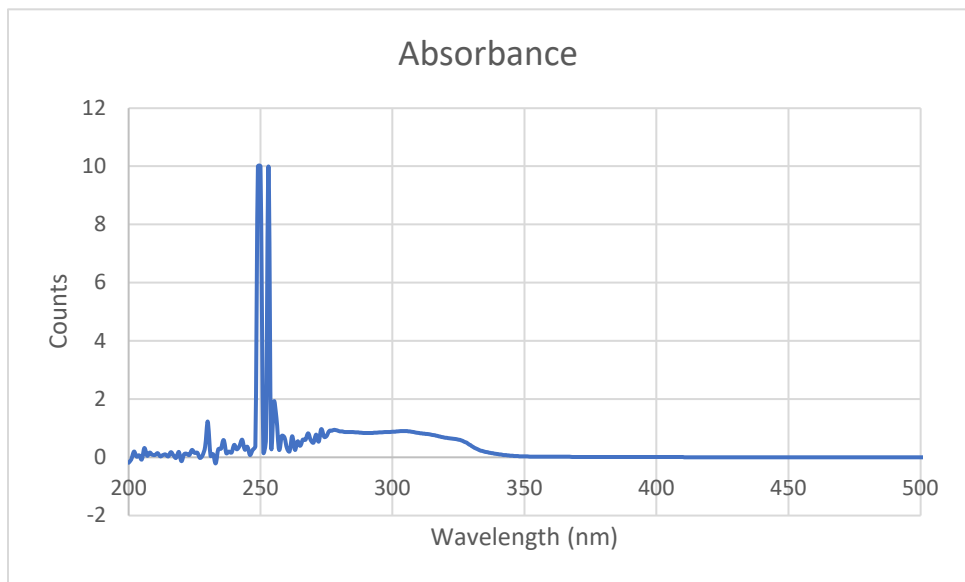
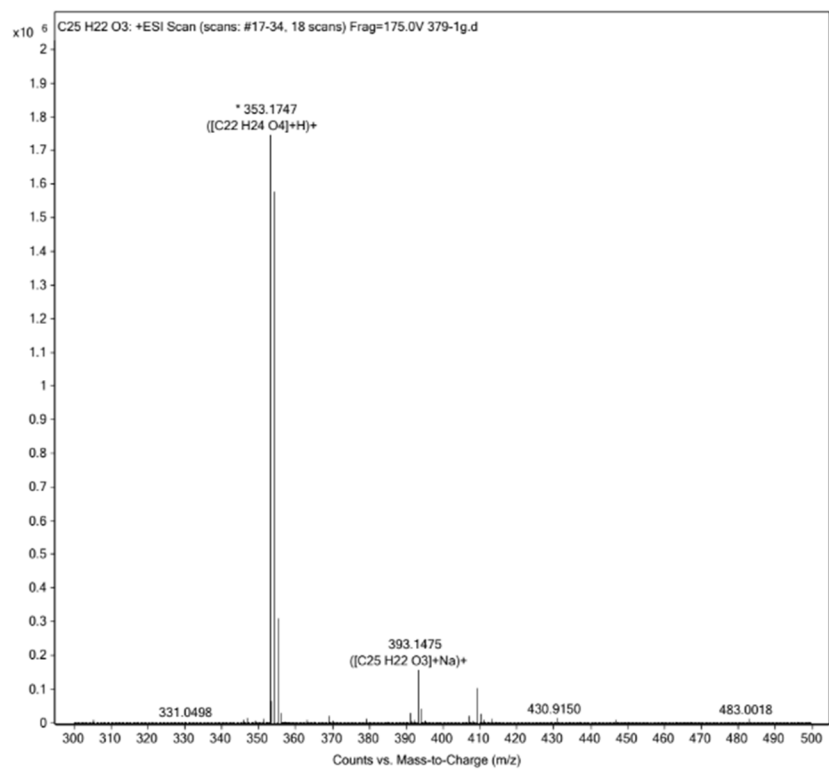


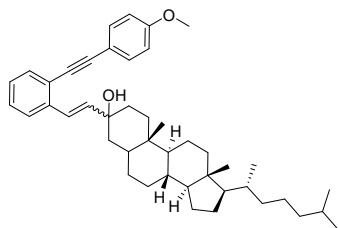
ATC-011719-238-Yellow.1.fid



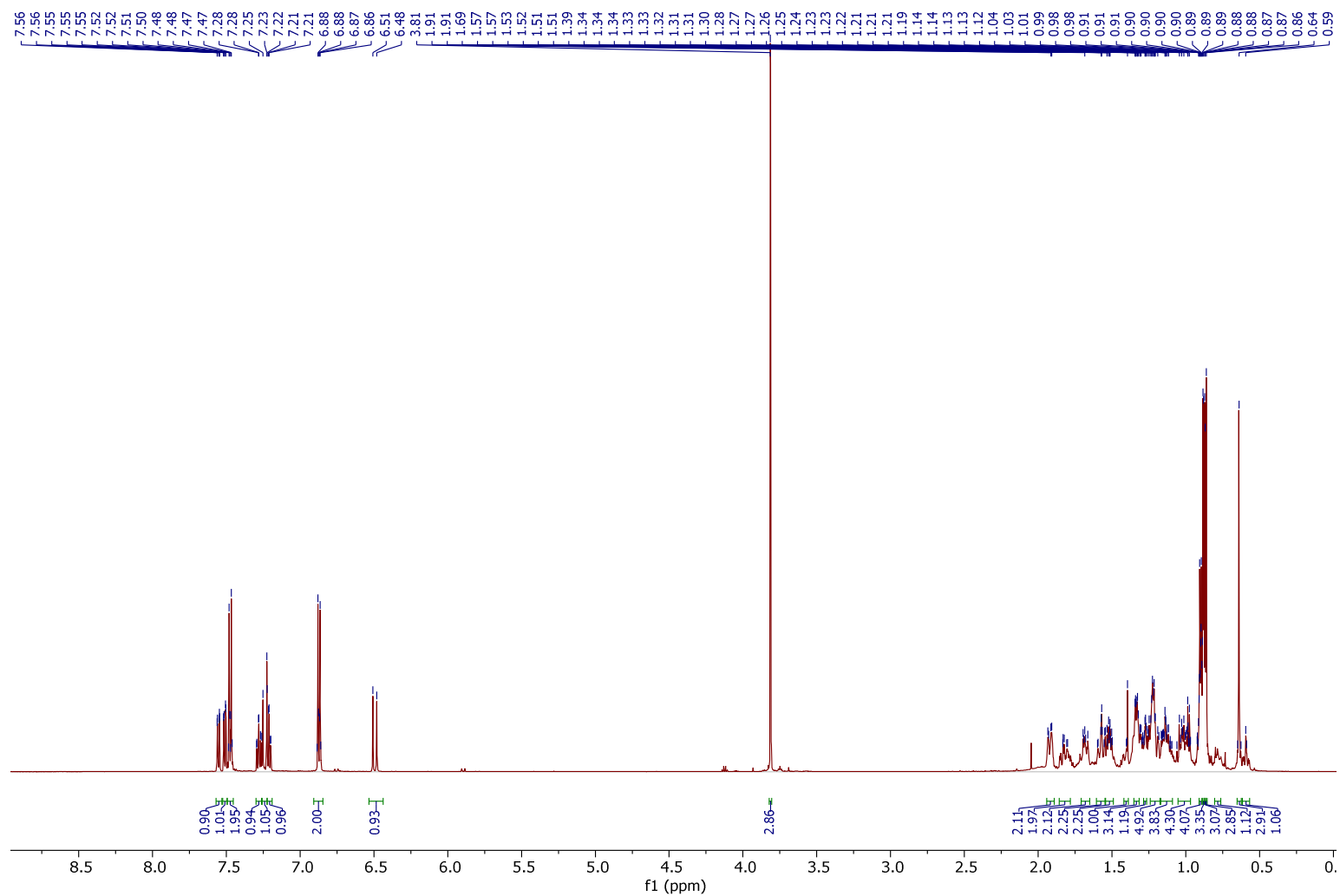




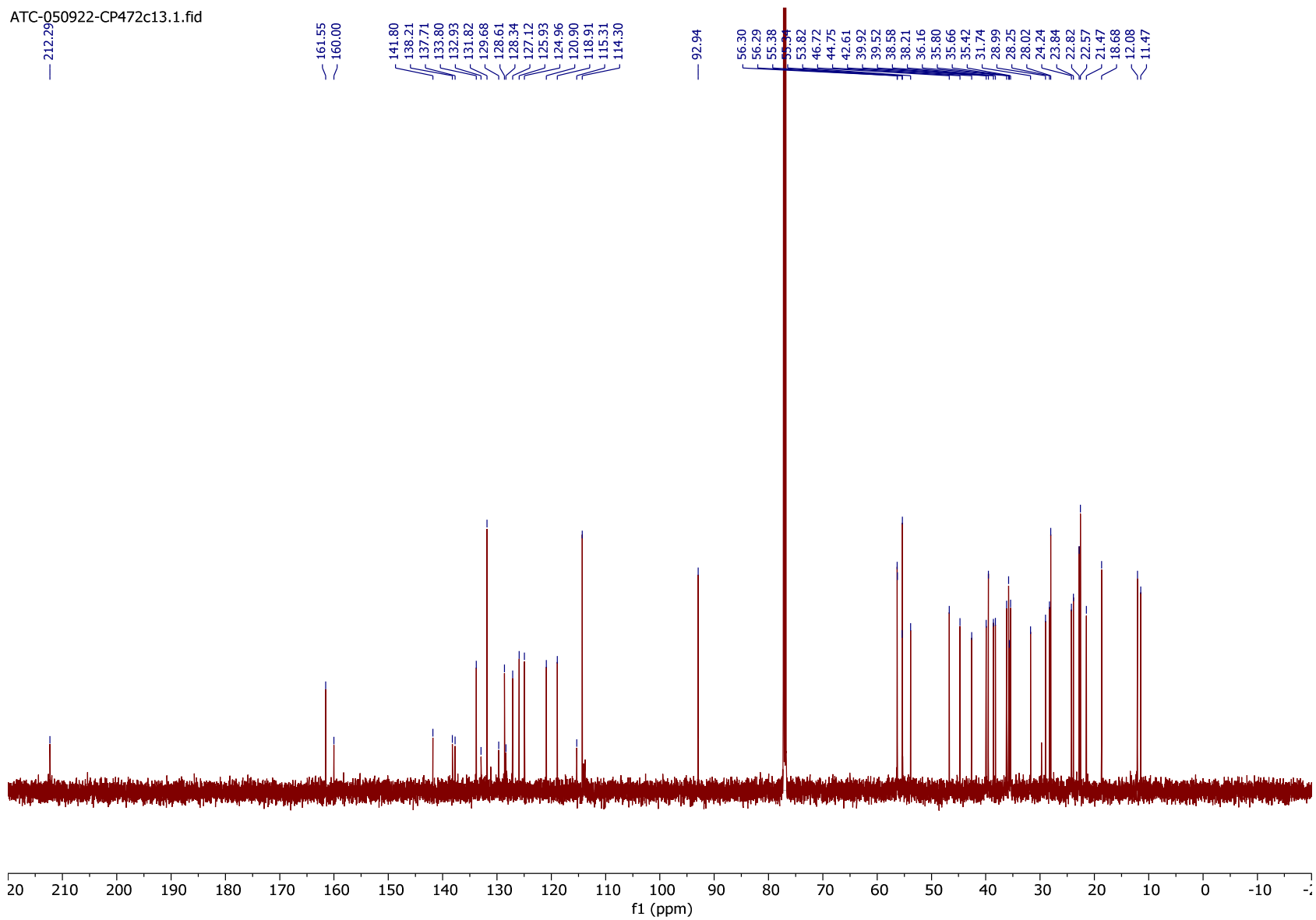


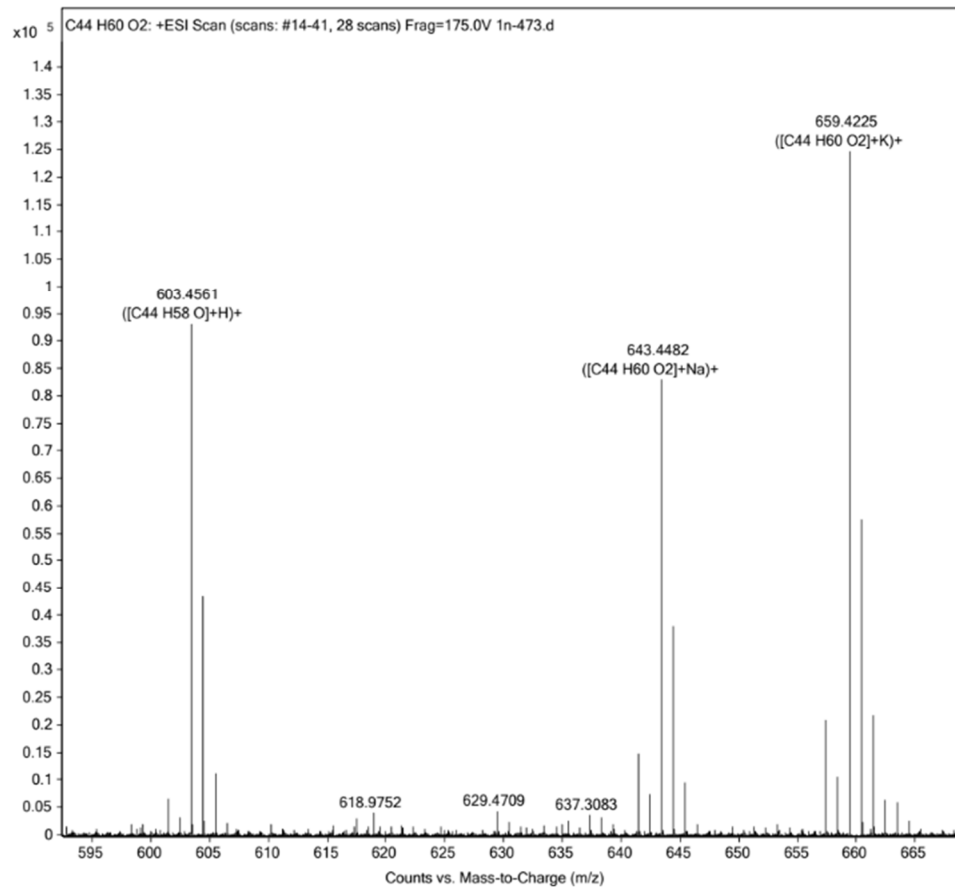


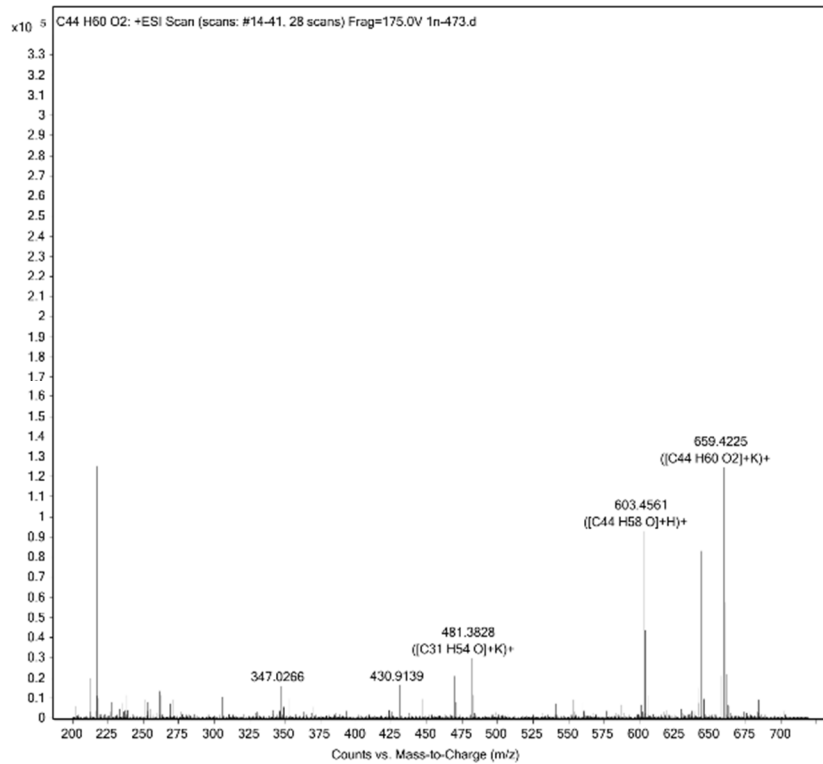
ATC-050522-472-S3steroid.1.fid

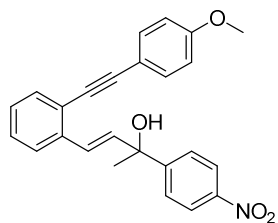


ATC-050922-CP472c13.1.fid

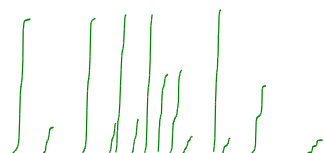








8.17  
8.15  
8.00  
7.98  
7.73  
7.70  
7.32  
7.30  
7.15  
7.11  
6.87  
6.85  
6.81  
6.78  
6.60  
6.56  
6.22  
6.19



3.84

2.34

1.82

2.00

0.38

2.01

0.44

2.06

0.51

2.07

1.18

1.23

0.24

2.14

0.22

1.00

0.19

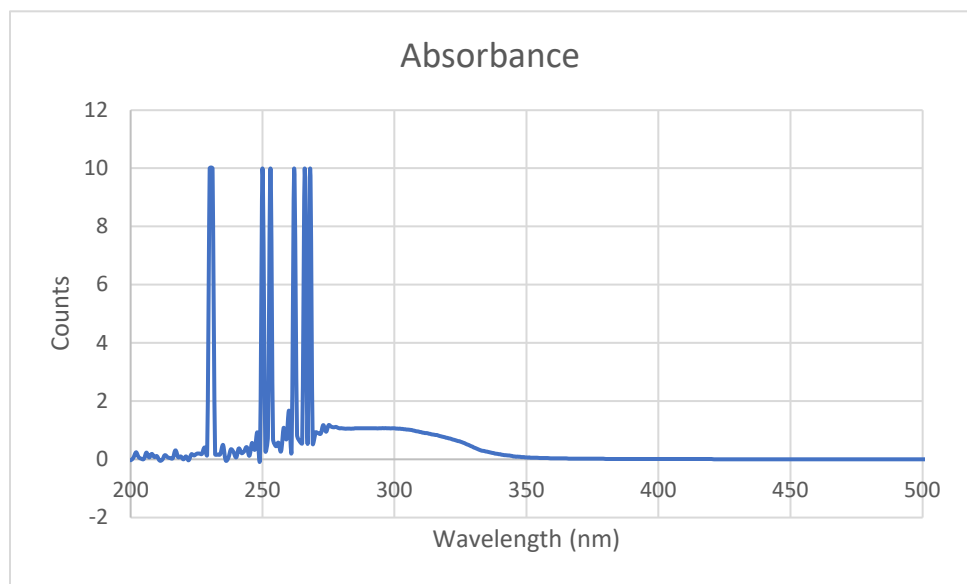
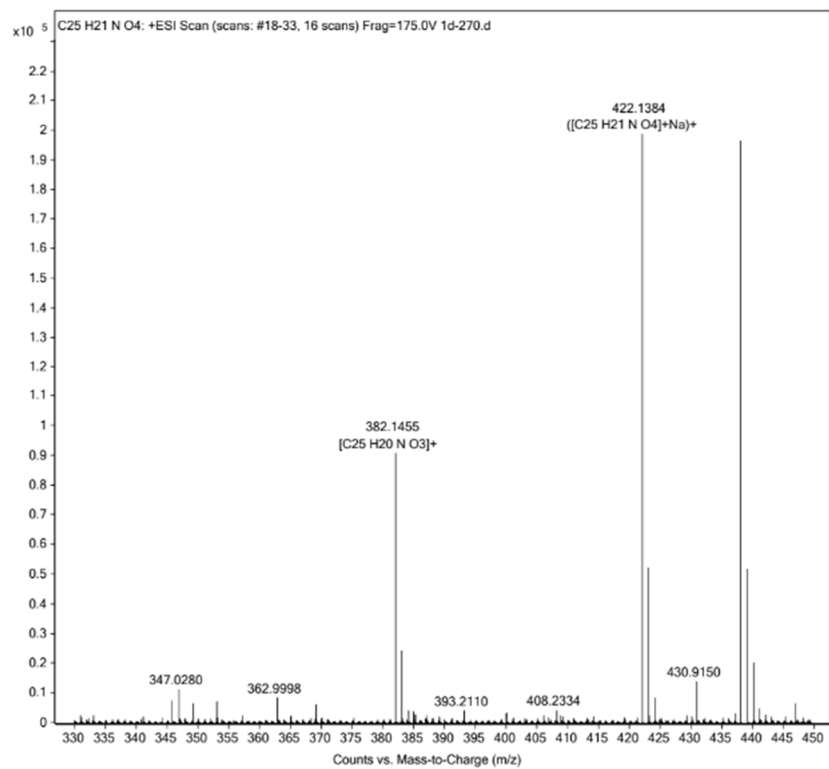
3.32

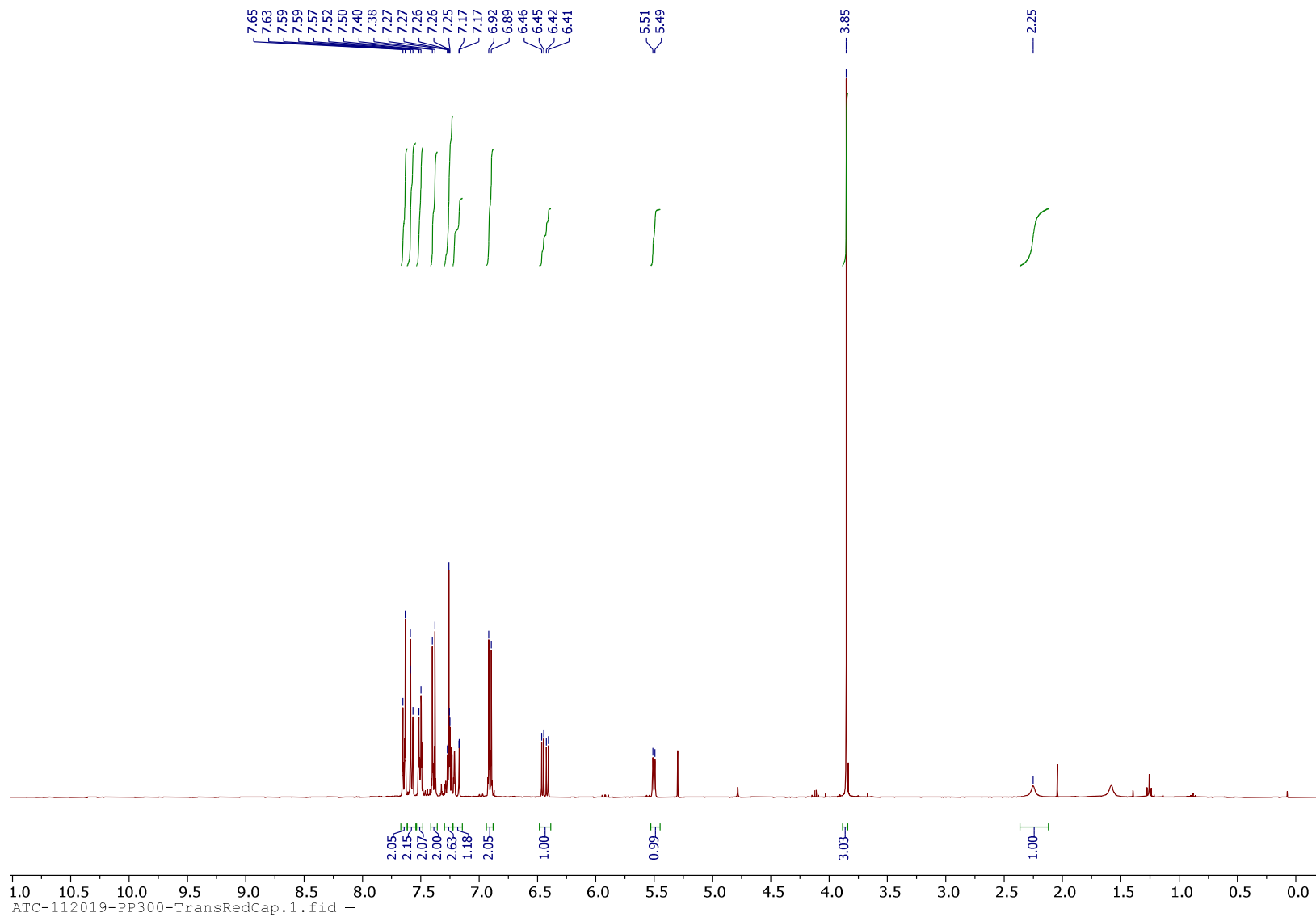
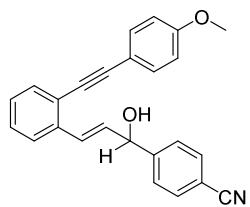
1.00

3.02

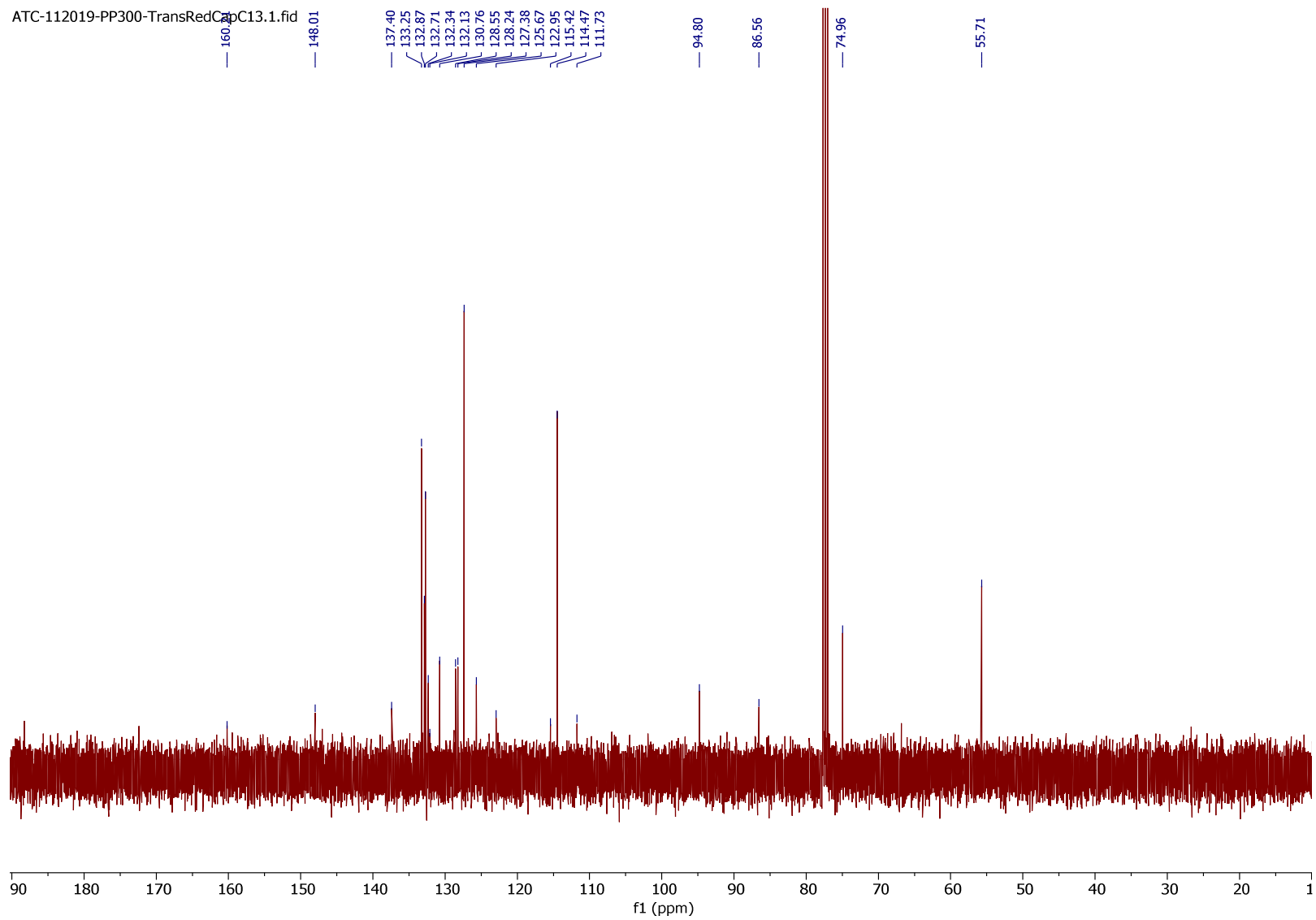
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

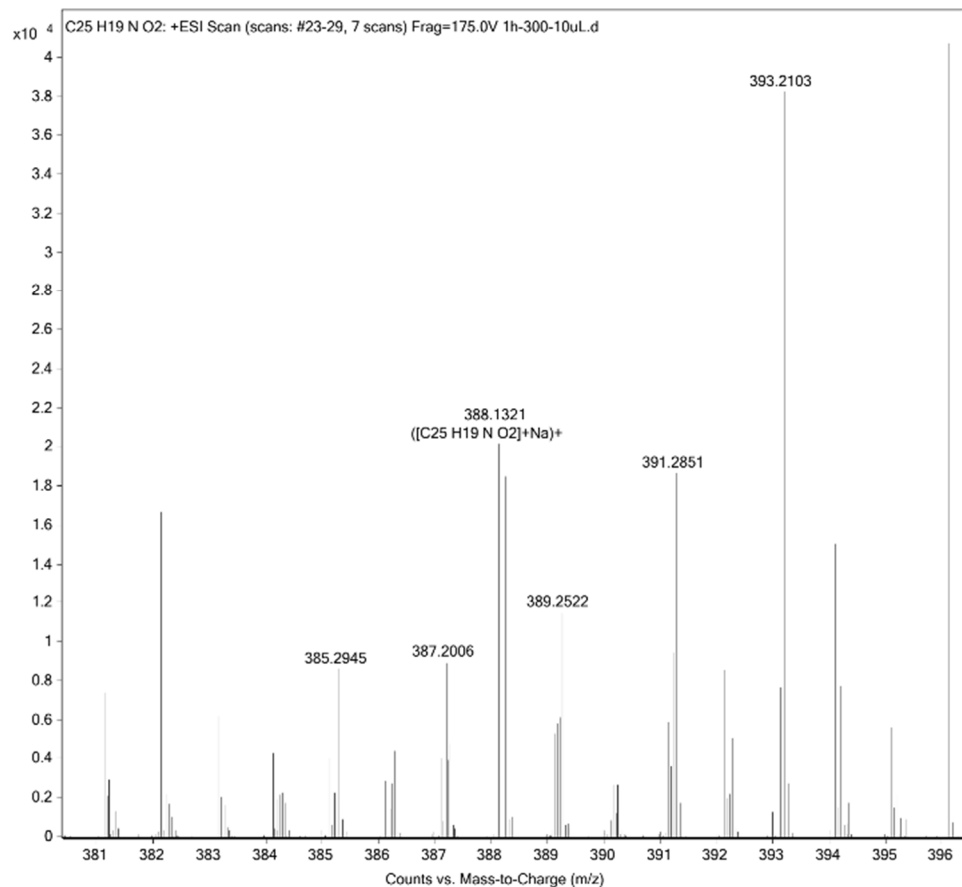
ATC-012719-PP242-S3.1.fid

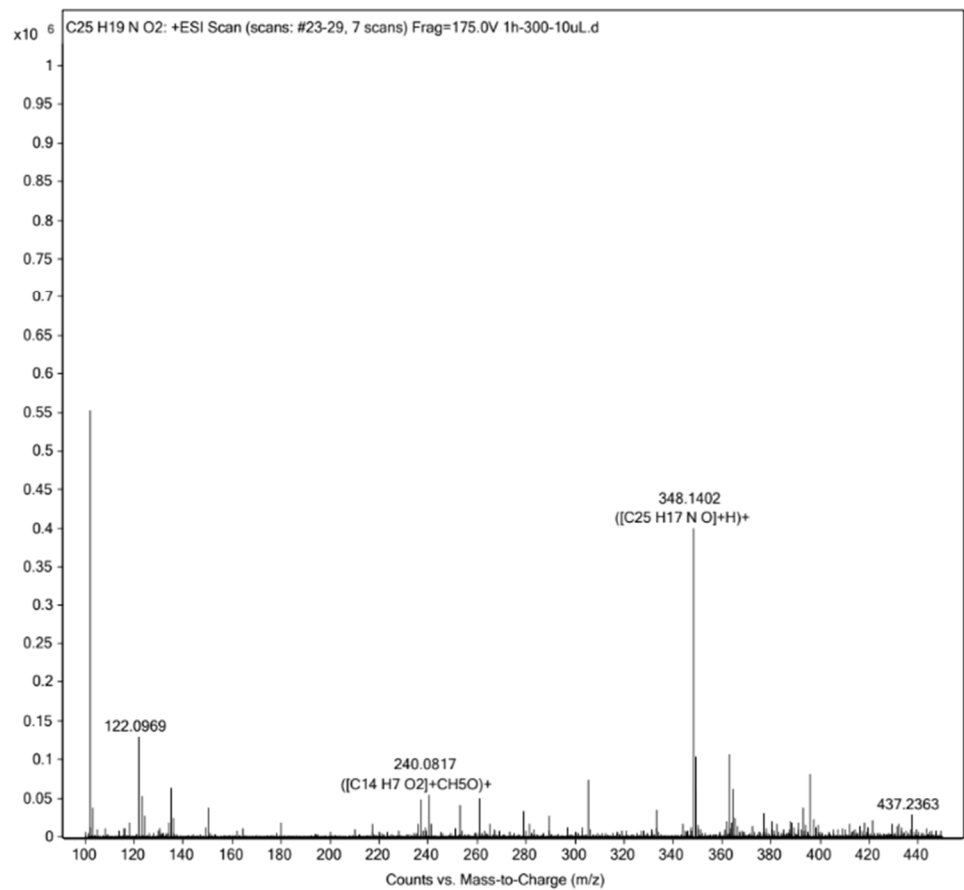


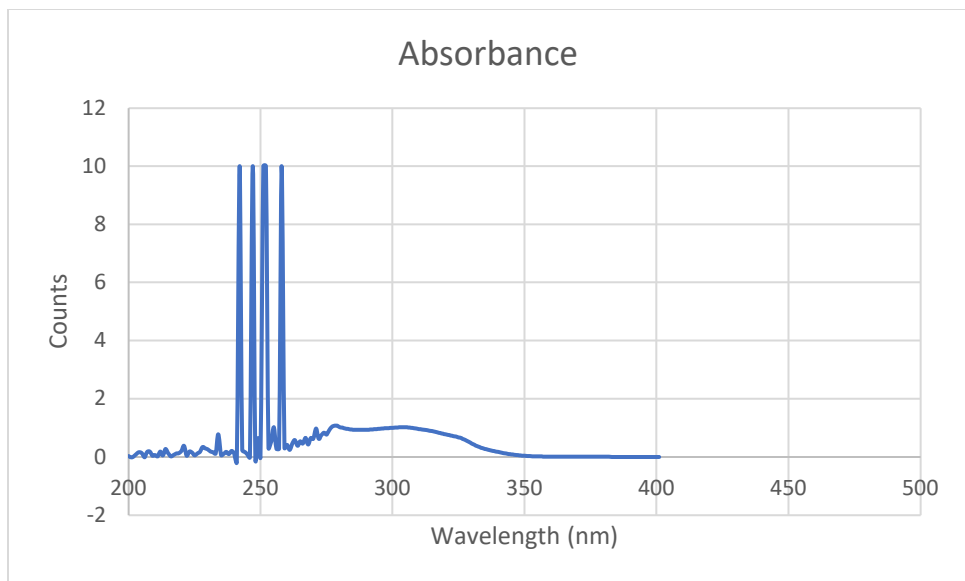


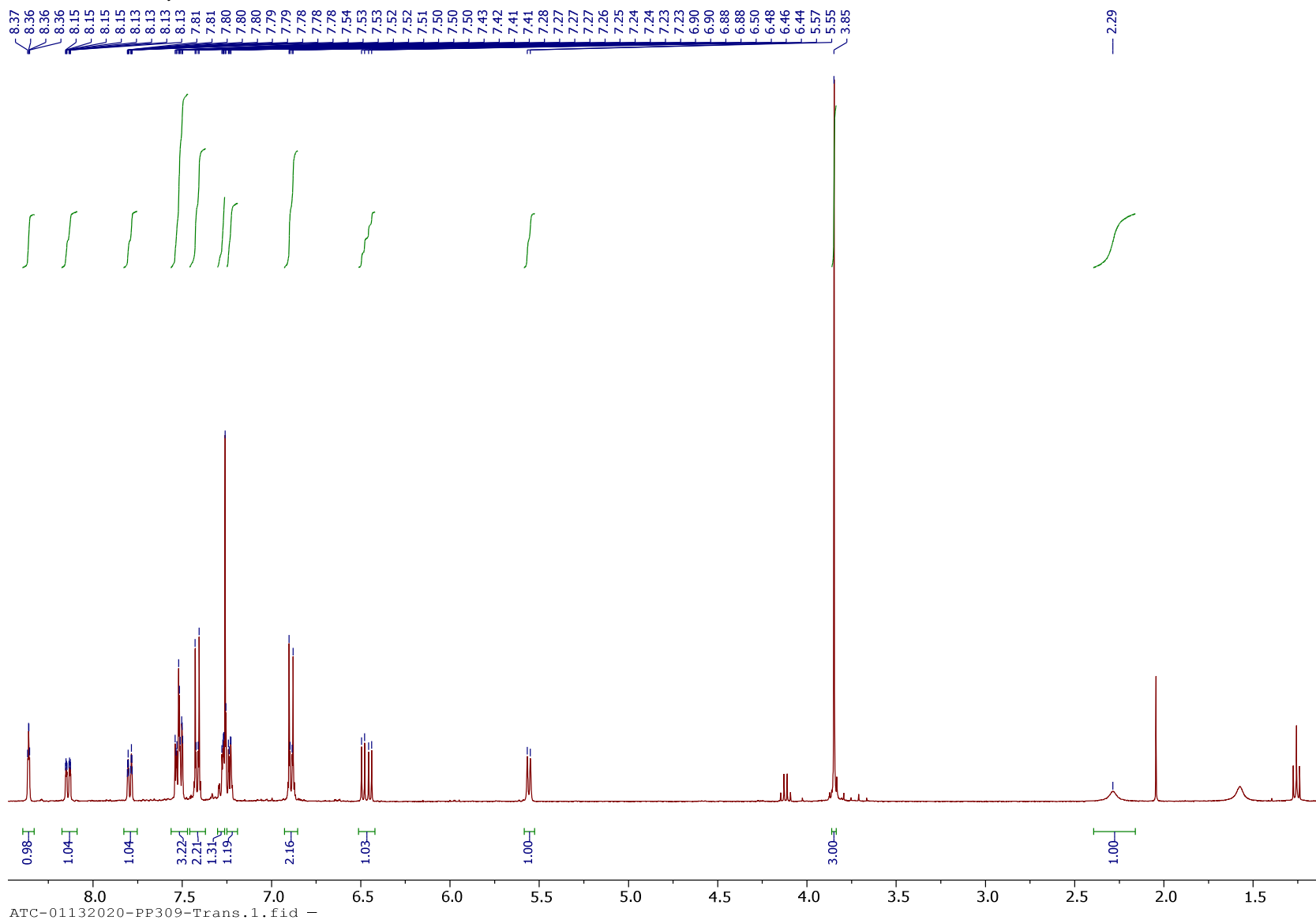
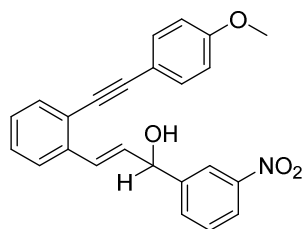
ATC-112019-PP300-TransRedCapC13.1.fid



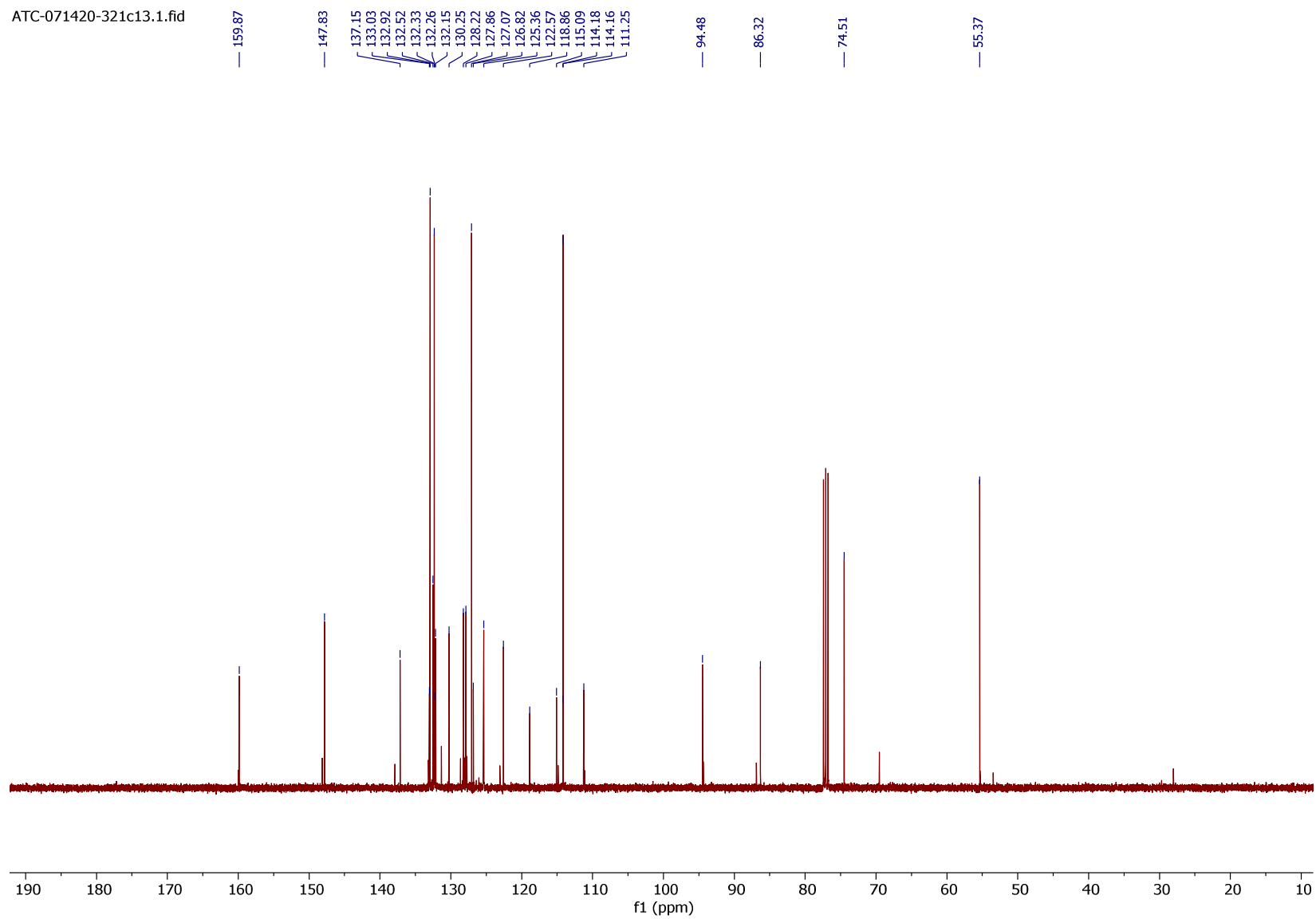


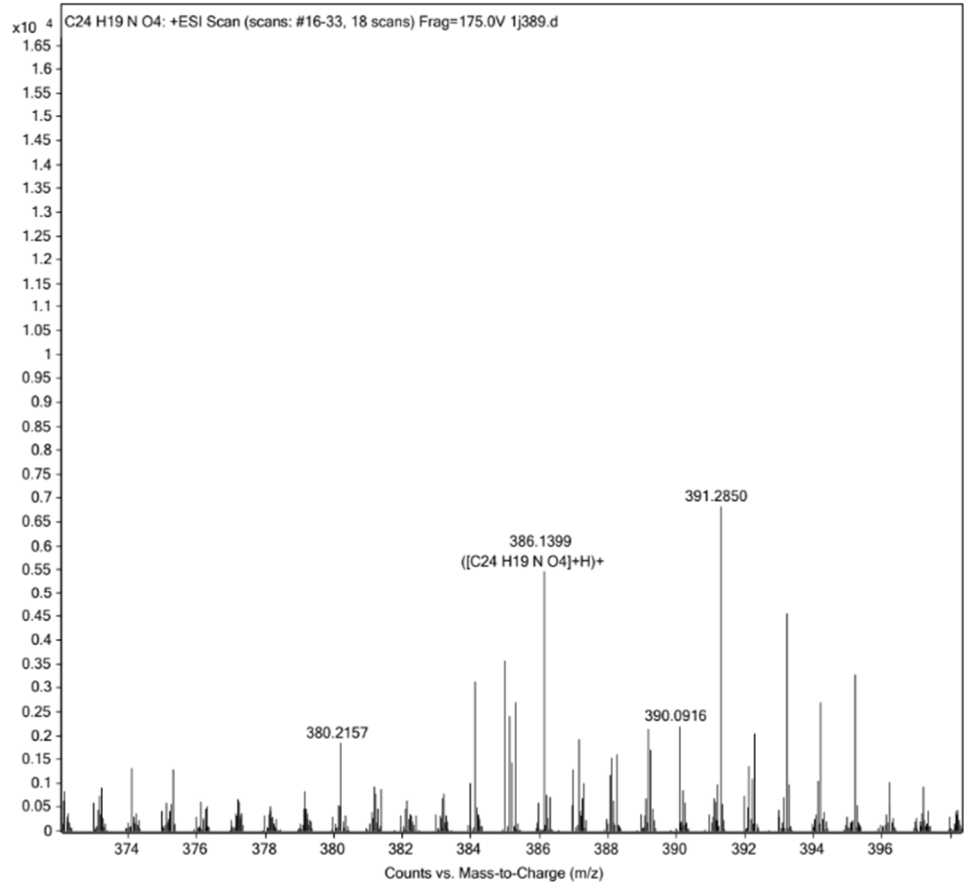


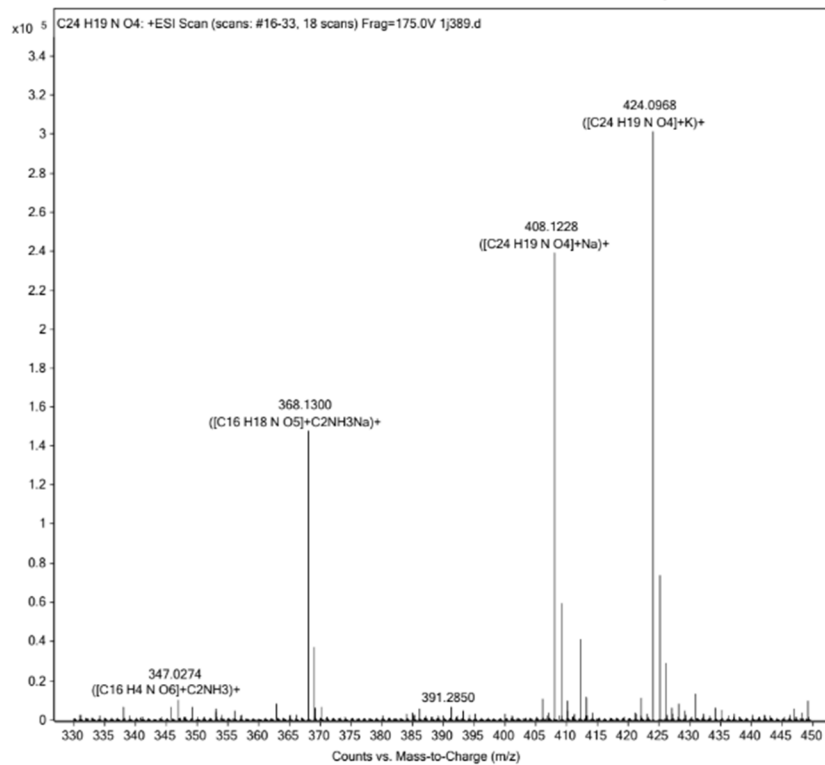




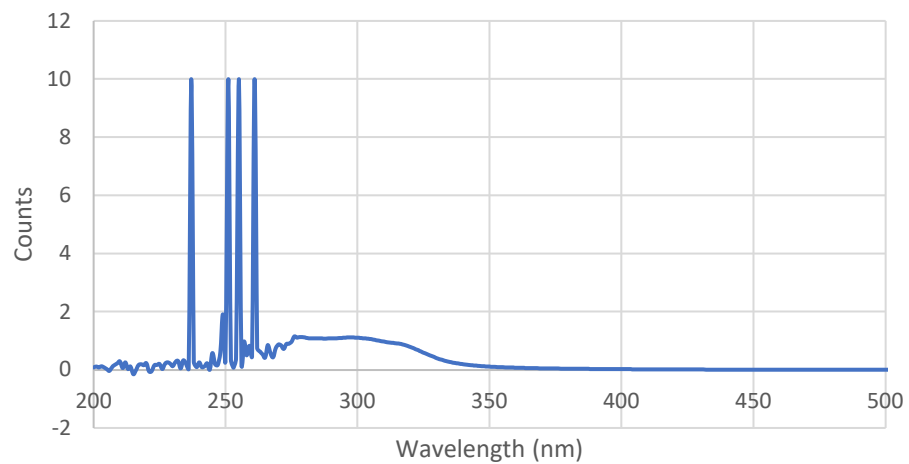
ATC-071420-321c13.1.fid

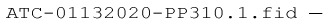


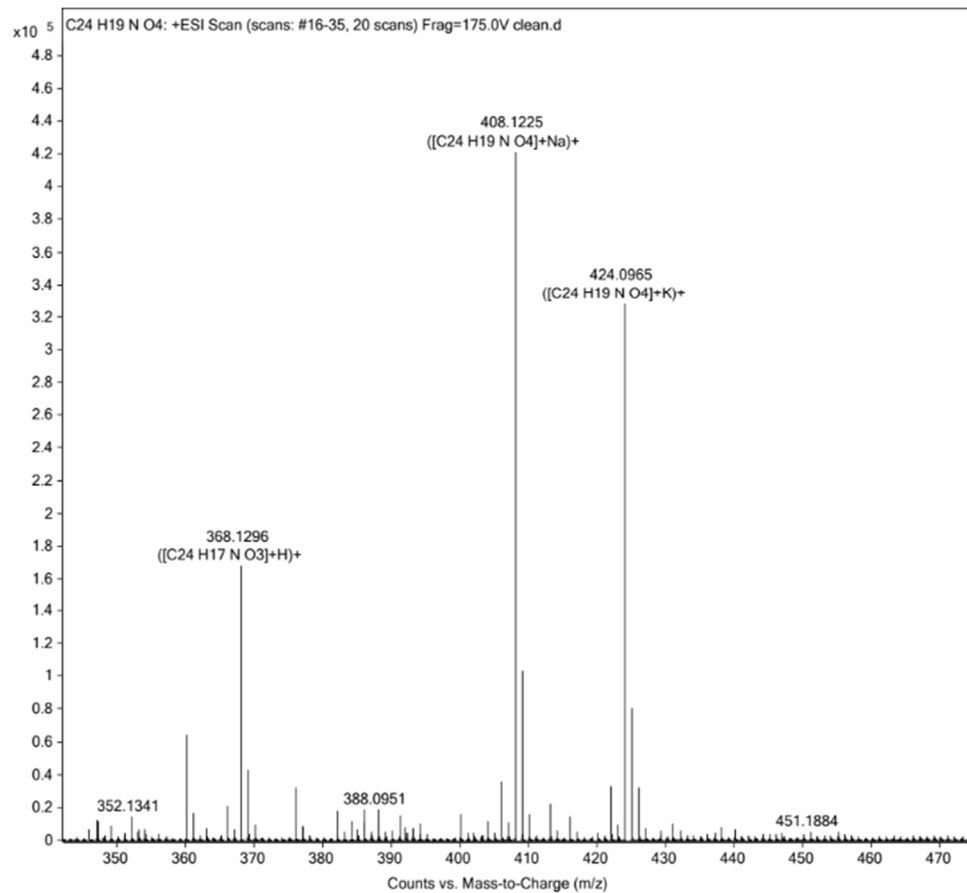


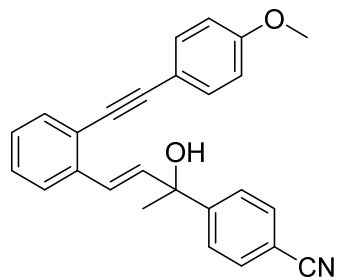


### Absorbance

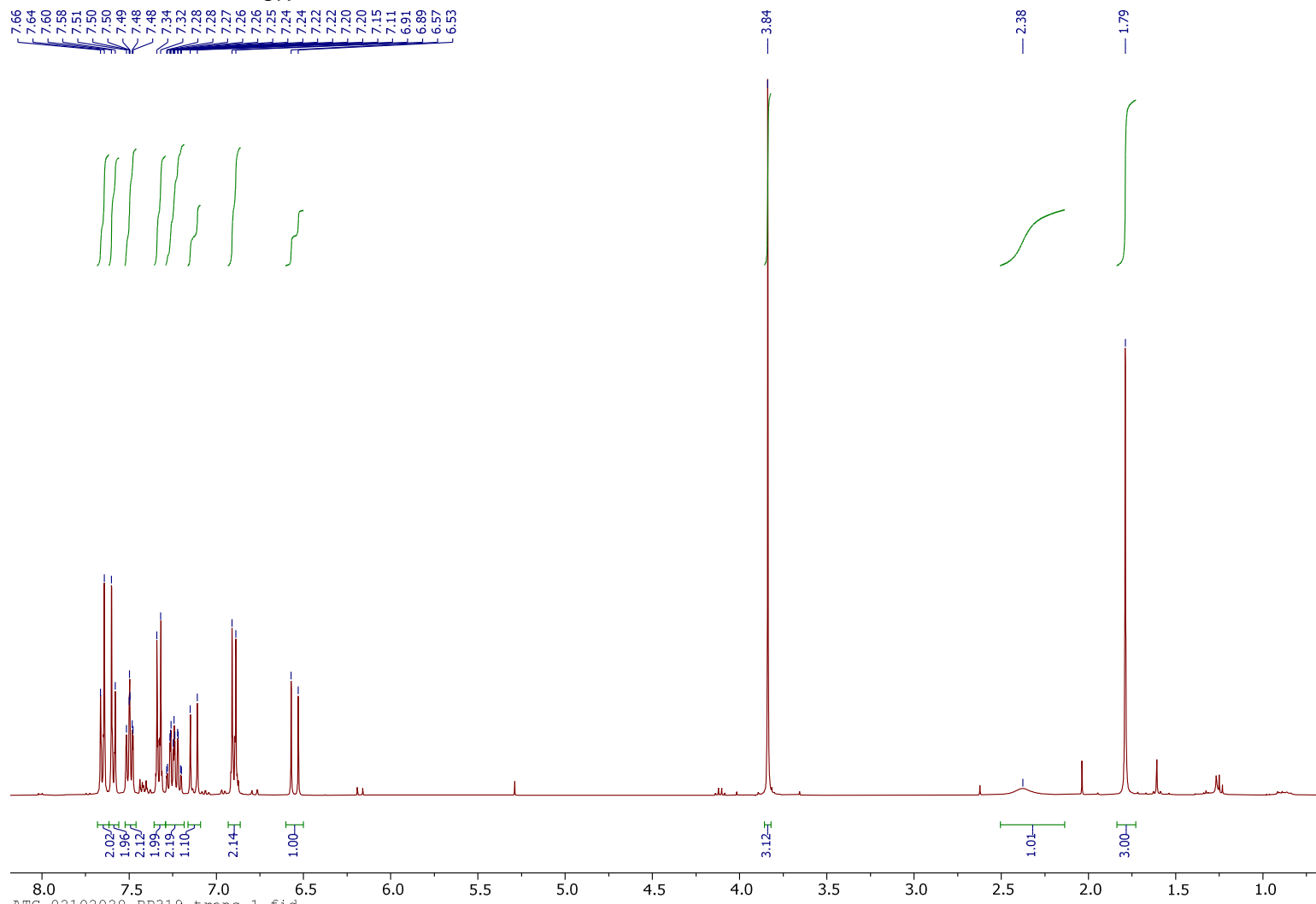






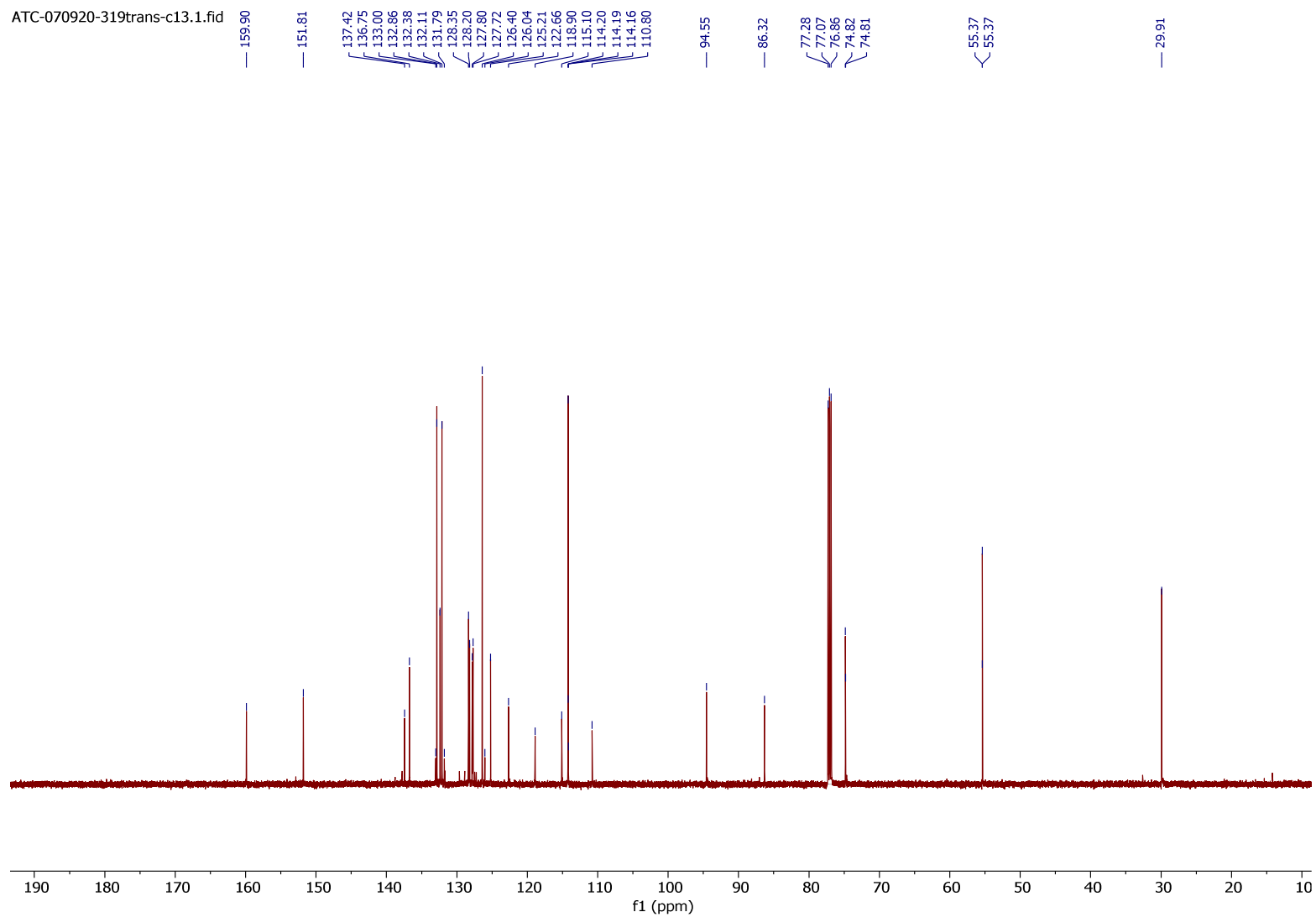


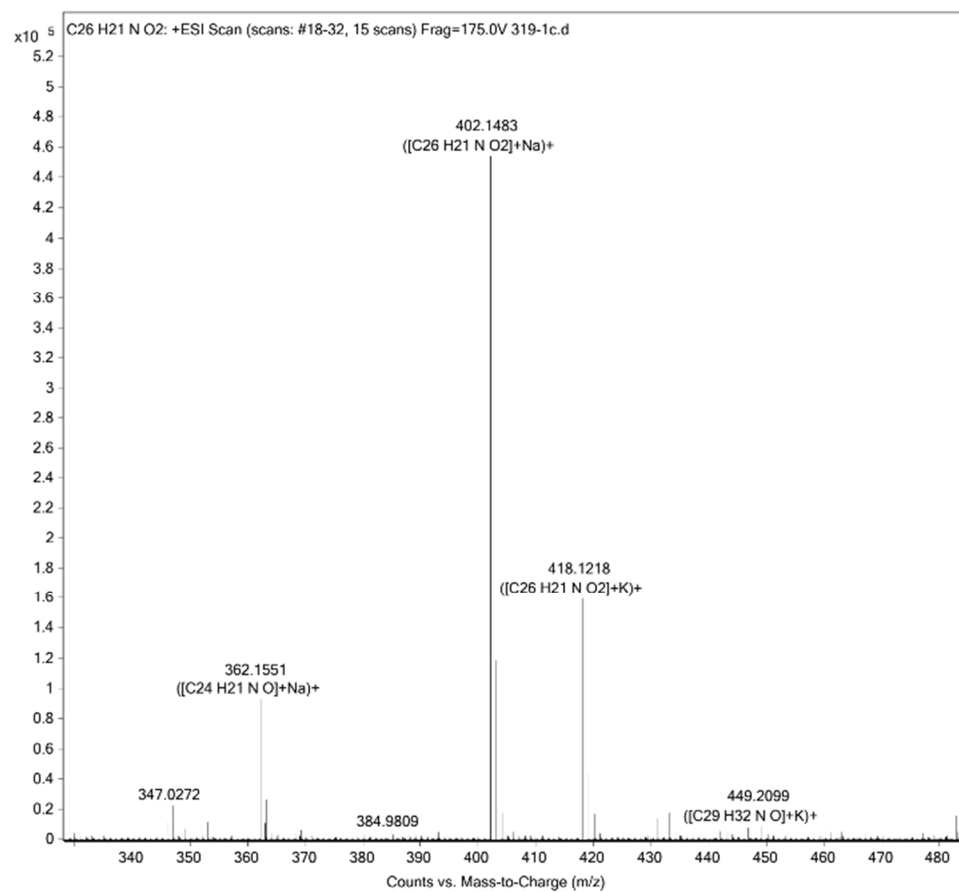
7.66  
7.64  
7.60  
7.58  
7.51  
7.50  
7.50  
7.49  
7.48  
7.48  
7.34  
7.32  
7.28  
7.28  
7.27  
7.26  
7.26  
7.25  
7.24  
7.24  
7.22  
7.22  
7.20  
7.20  
7.15  
7.11  
6.91  
6.89  
6.57  
6.53

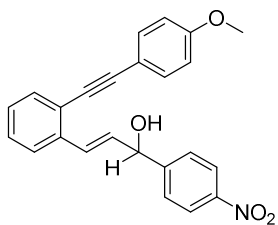


ATC-02102020-PP319-trans.1.fid -

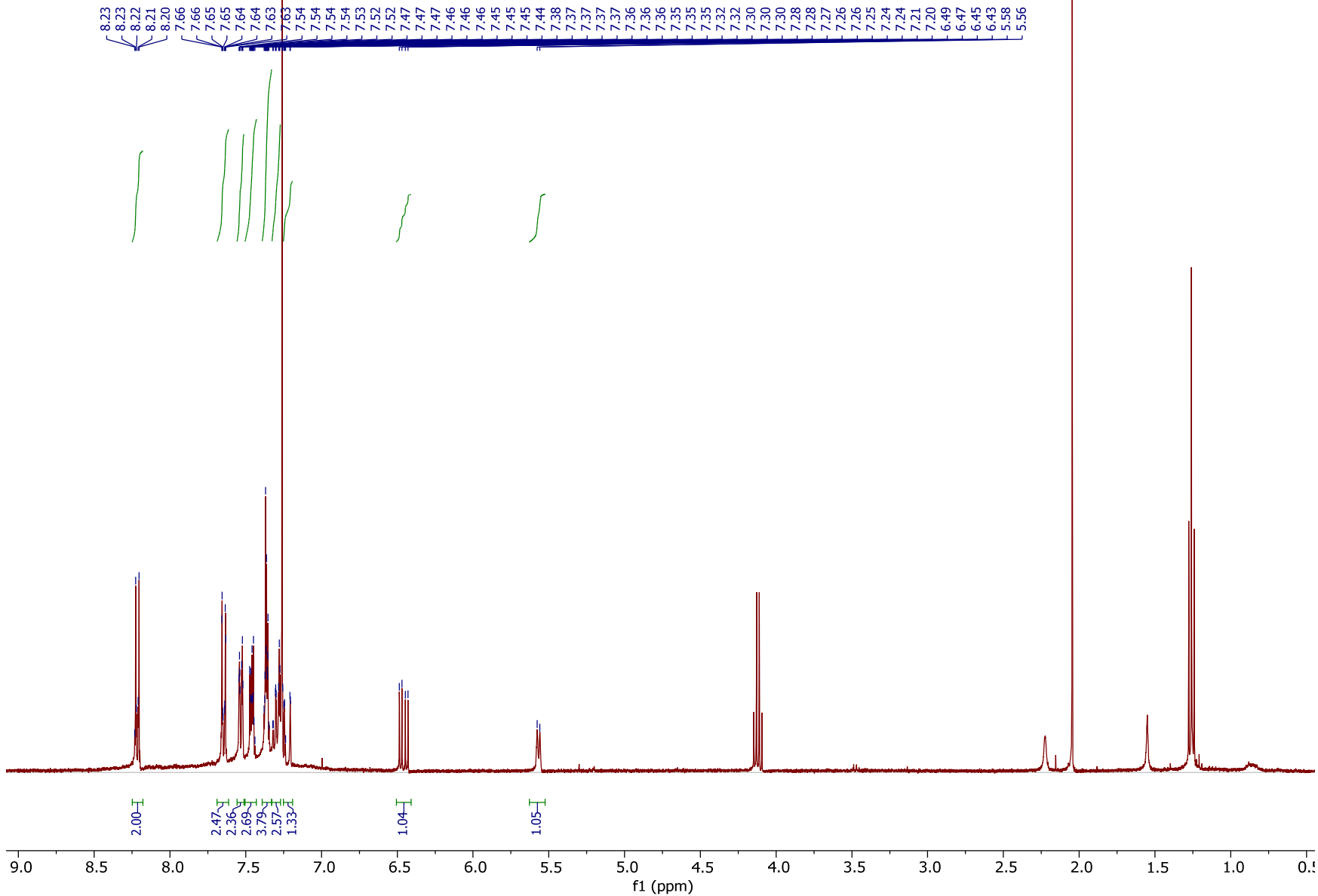
ATC-070920-319trans-c13.1.fid





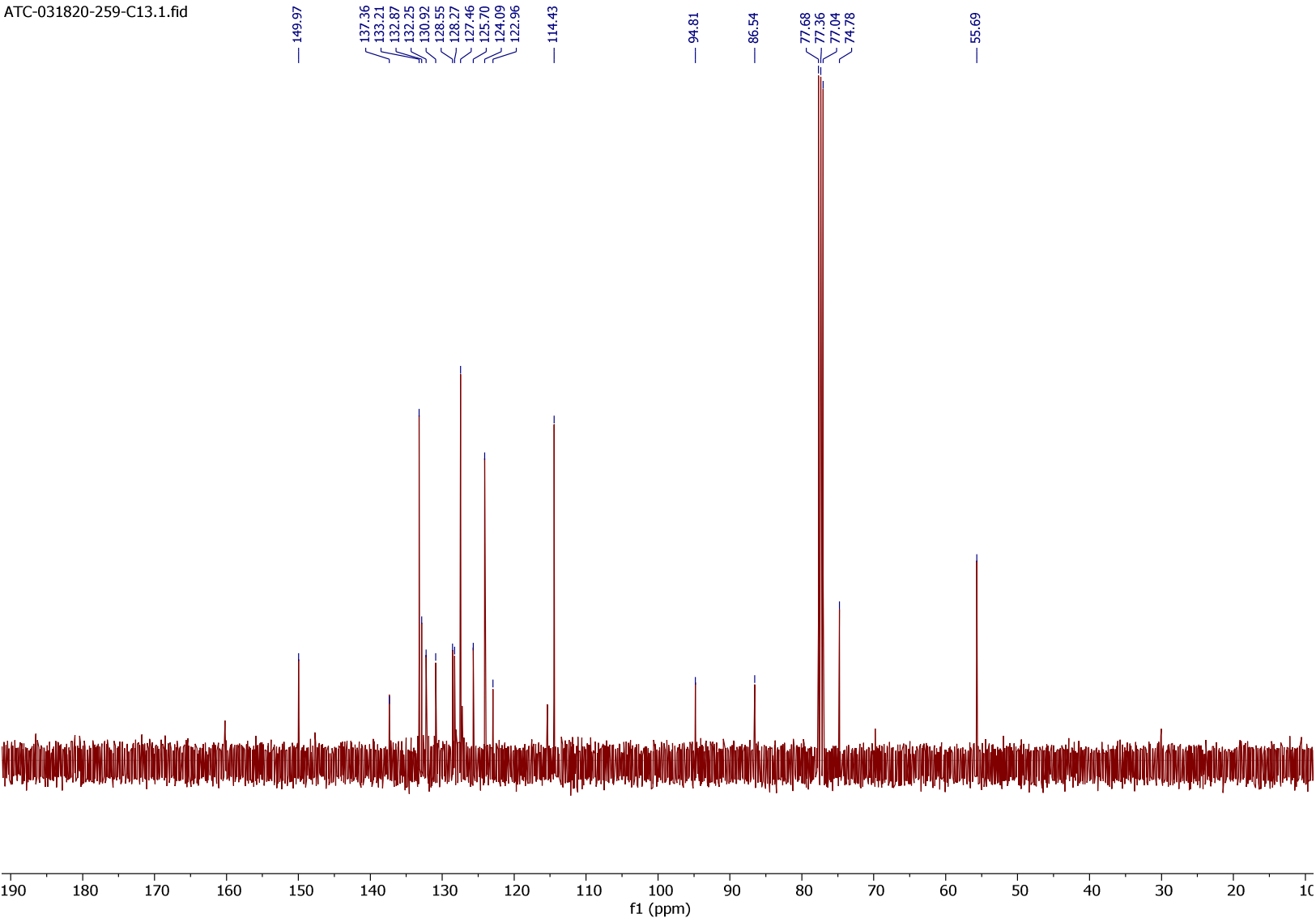


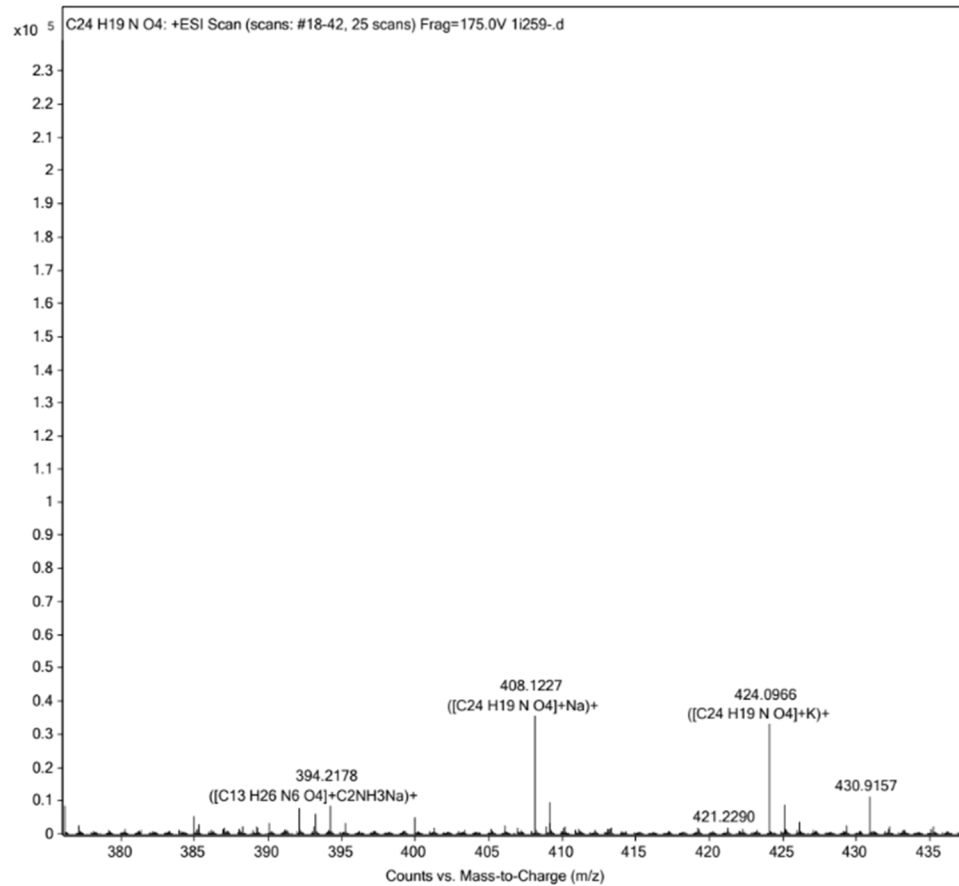
ATC-030720-PP328 p-NitroBenzaldehyde.1.fid



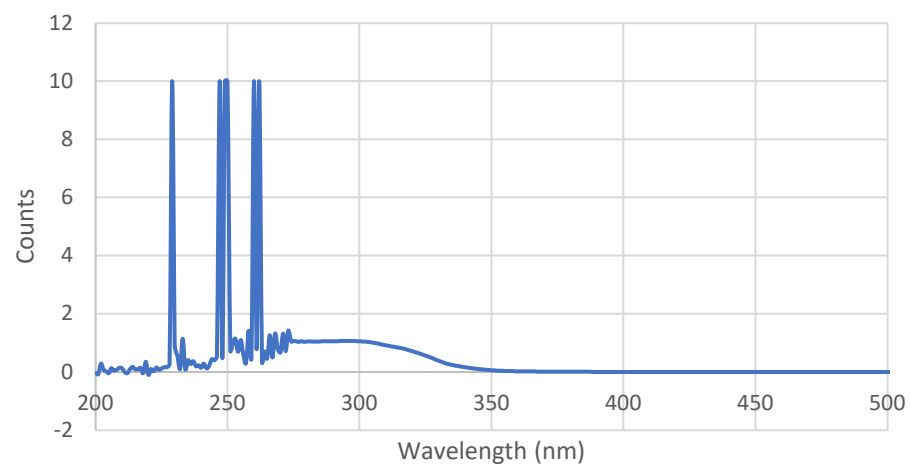
<sup>1</sup>H Peak at 2.25 = 1H from OH. 1.56= Water

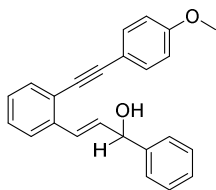
ATC-031820-259-C13.1.fid



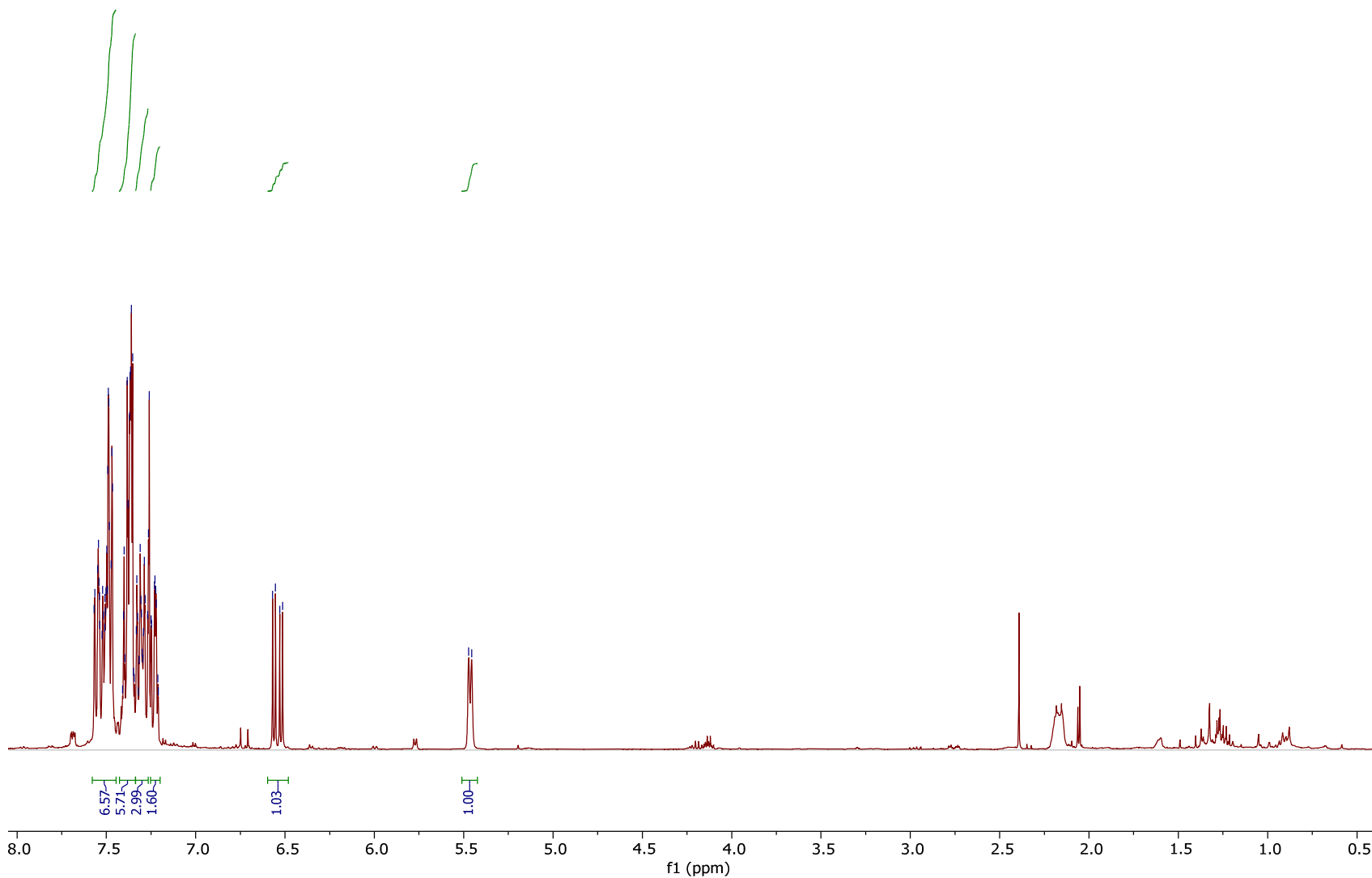


Absorbance



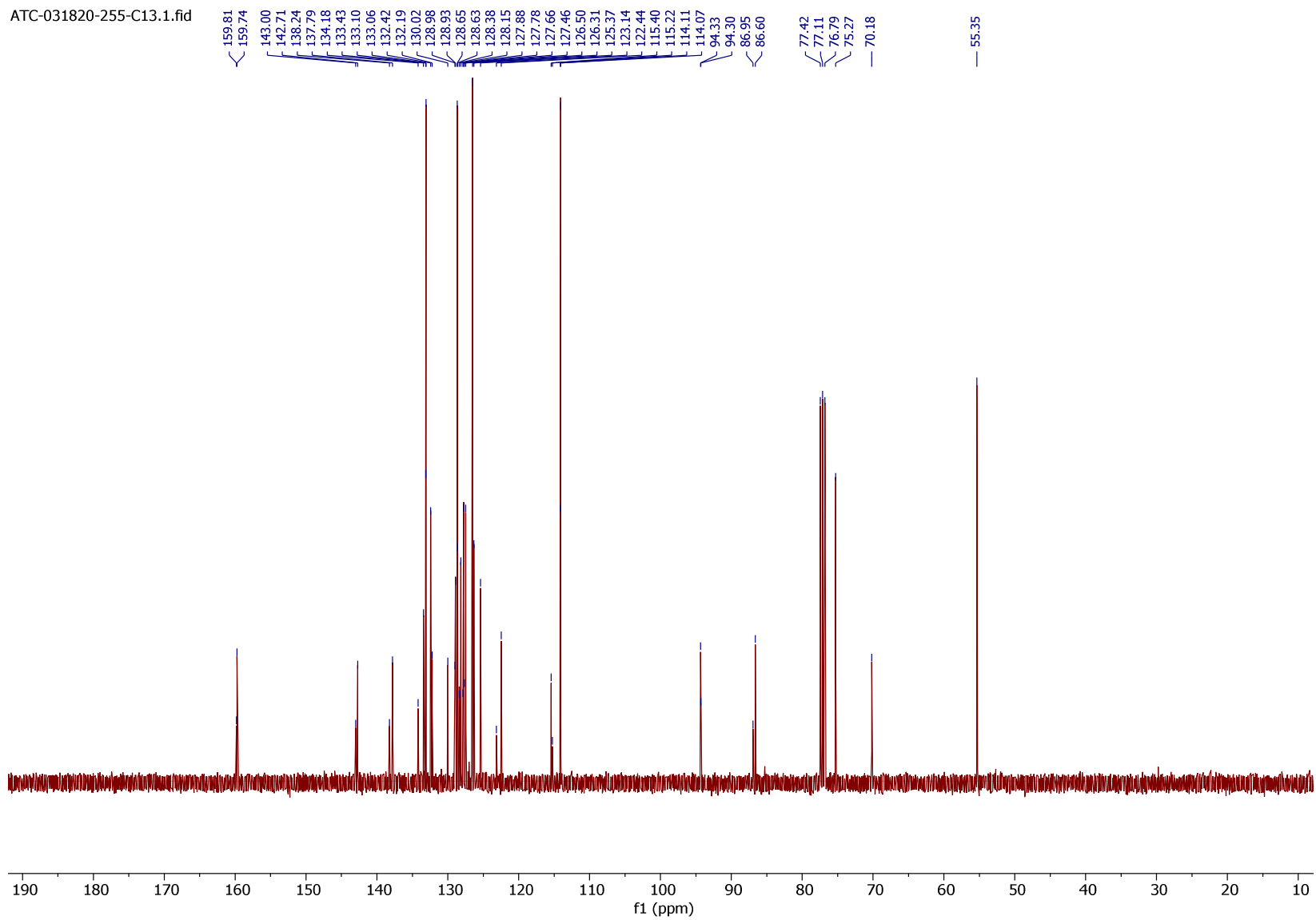


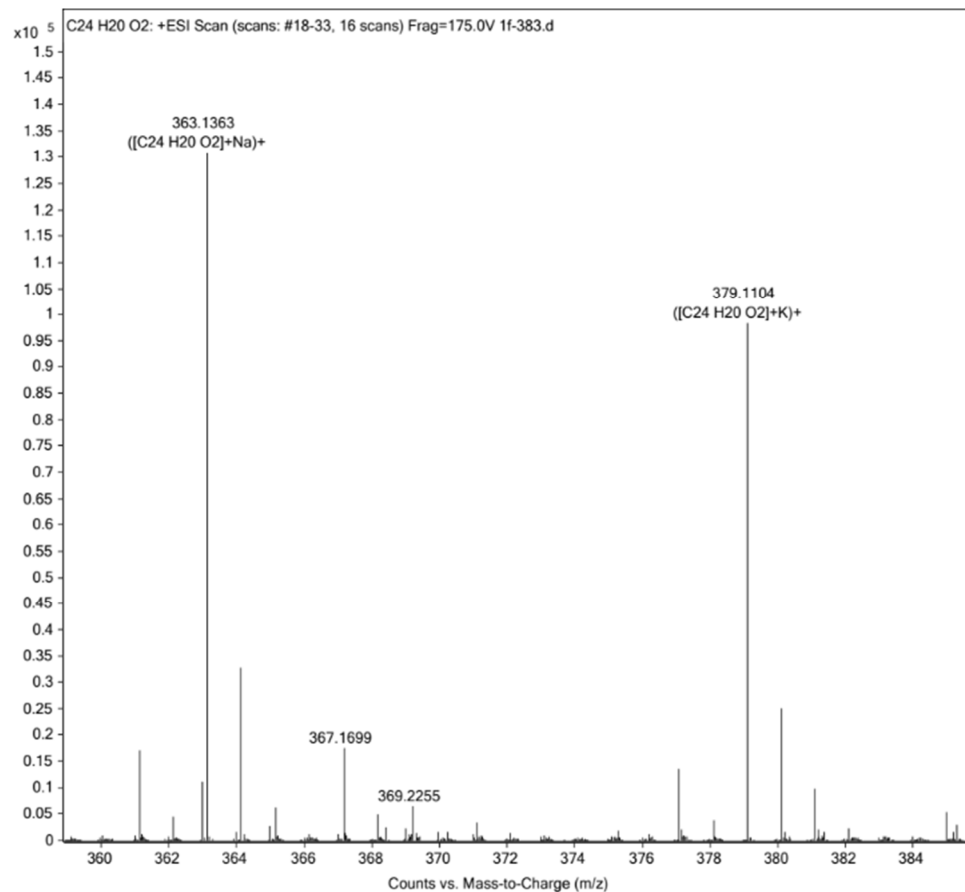
ATC-030920-PP334.1.fid

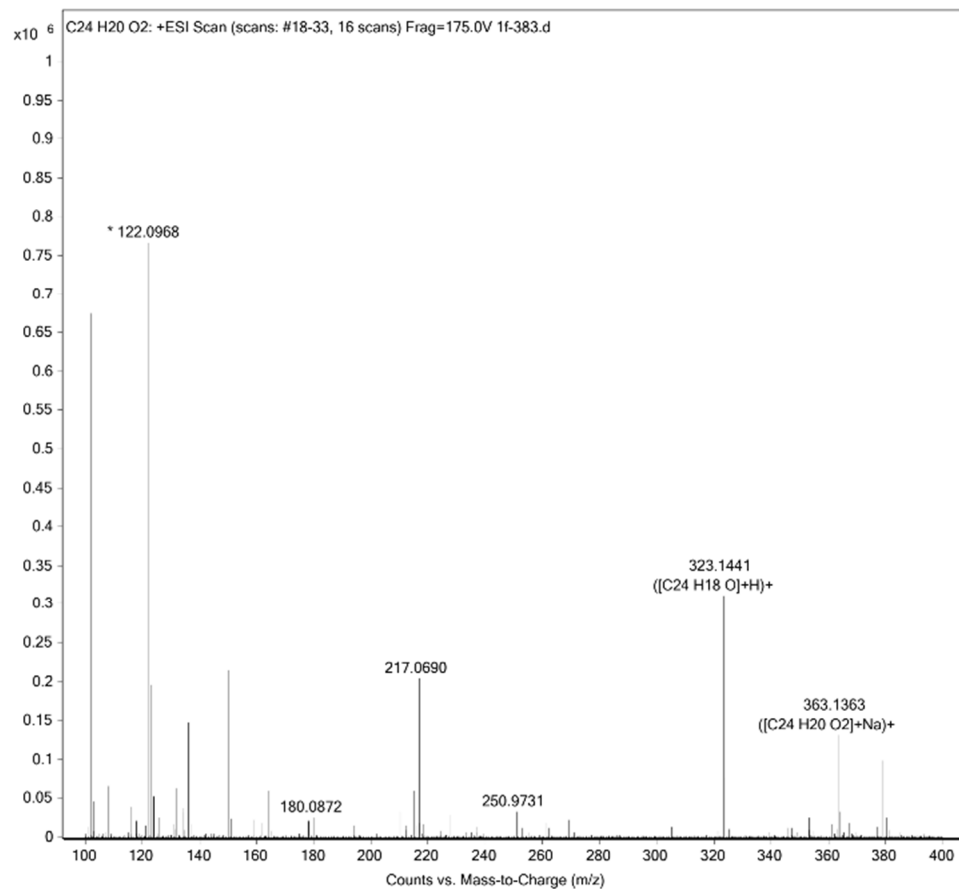


$^1\text{H}$  broad Peak at 2.2 = 1H from OH. Singlet at 2.36 from Toluene. 1.56= Water.

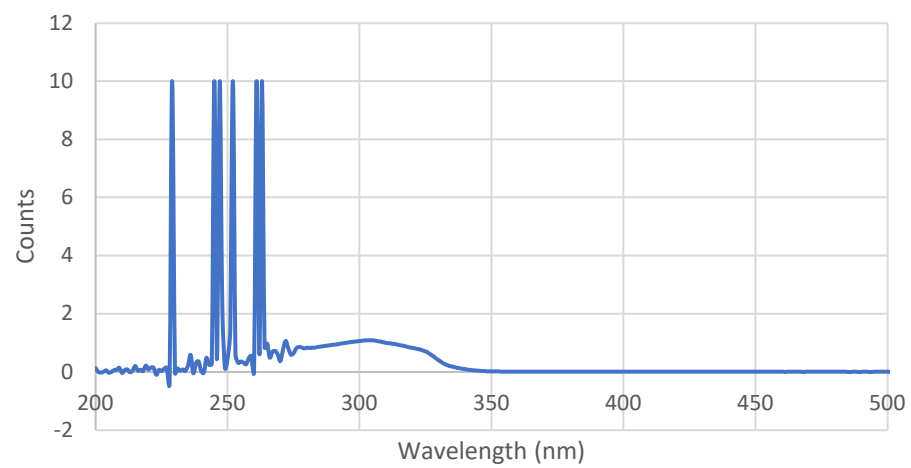
ATC-031820-255-C13.1.fid

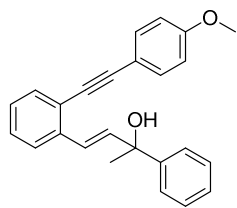




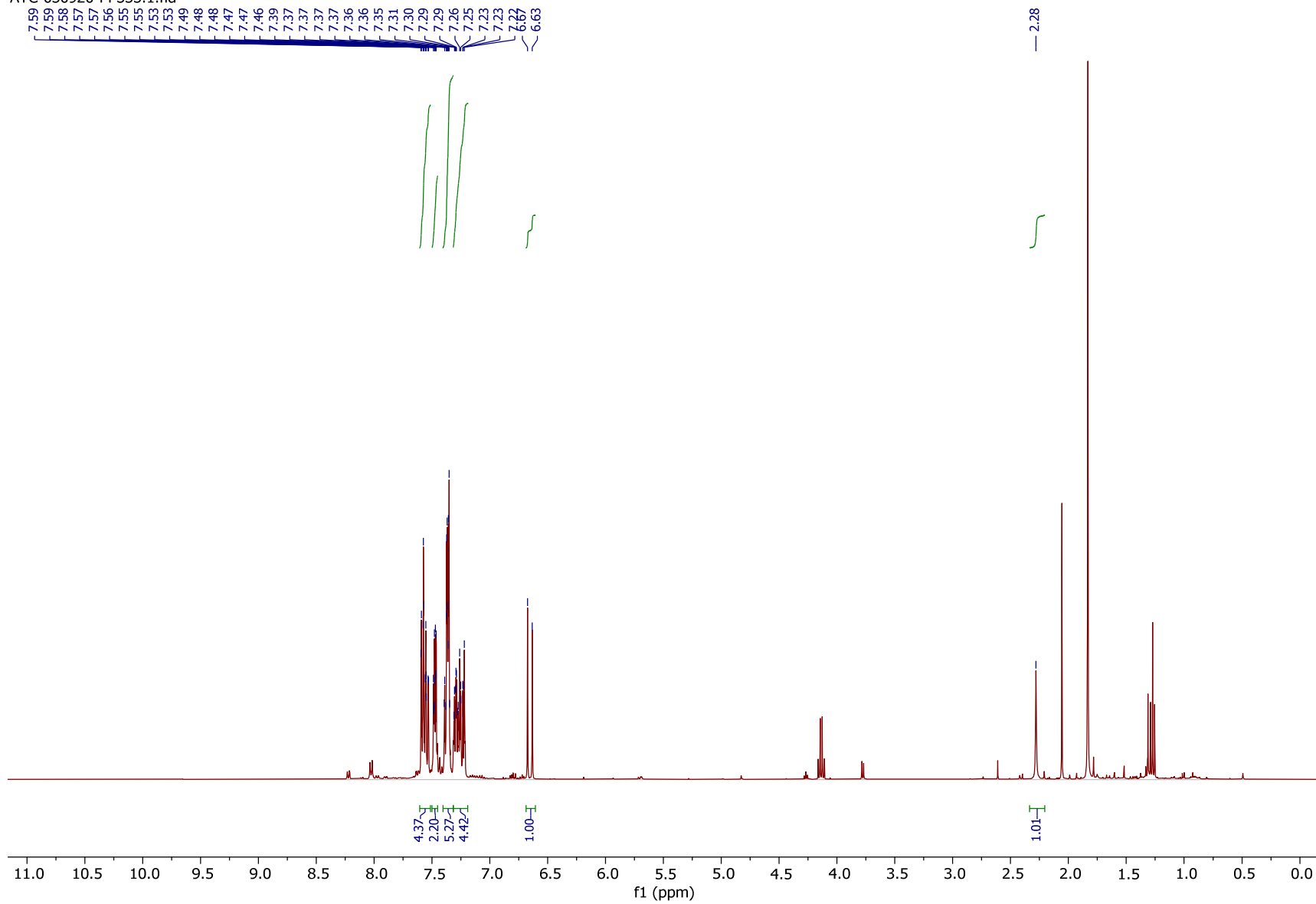


Absorbance

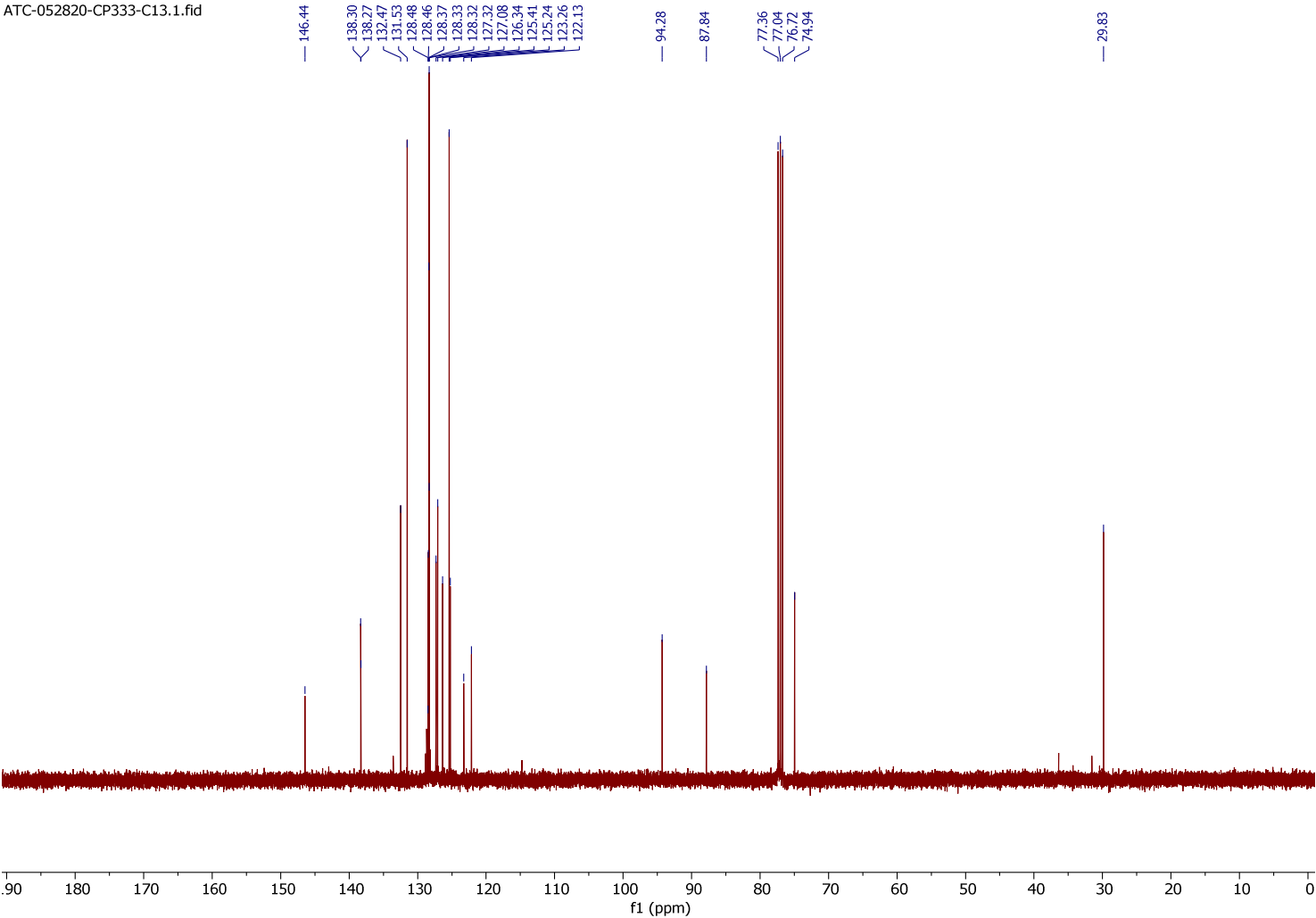


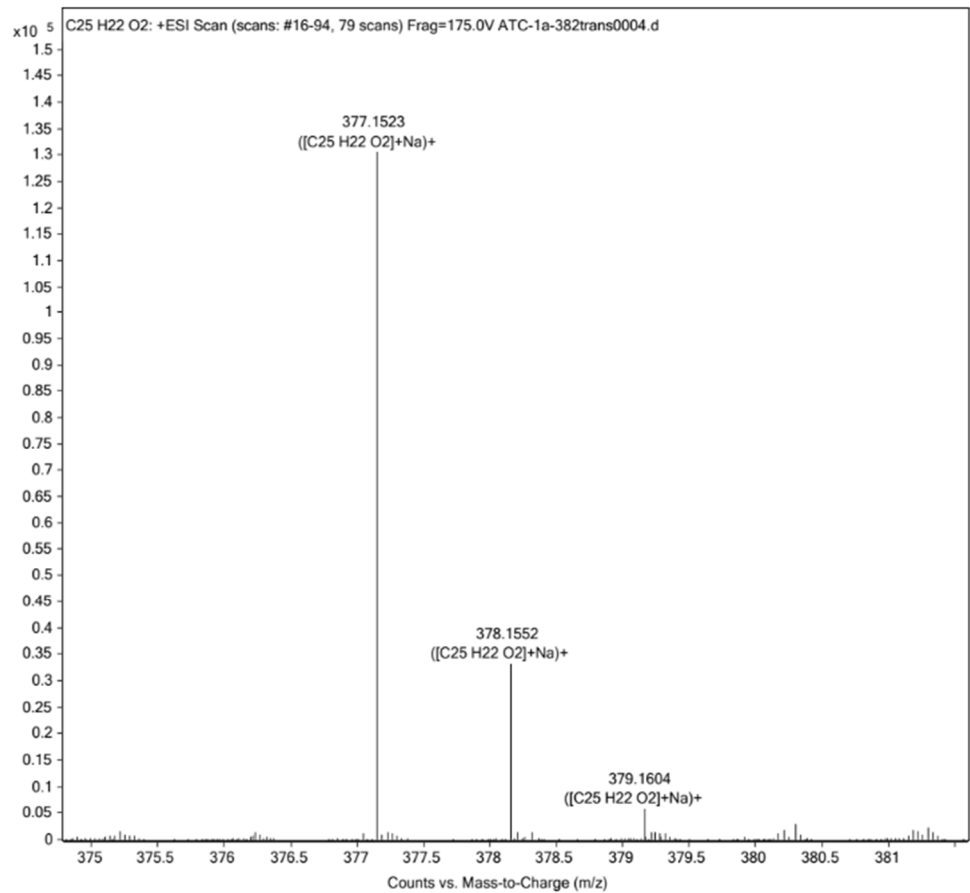


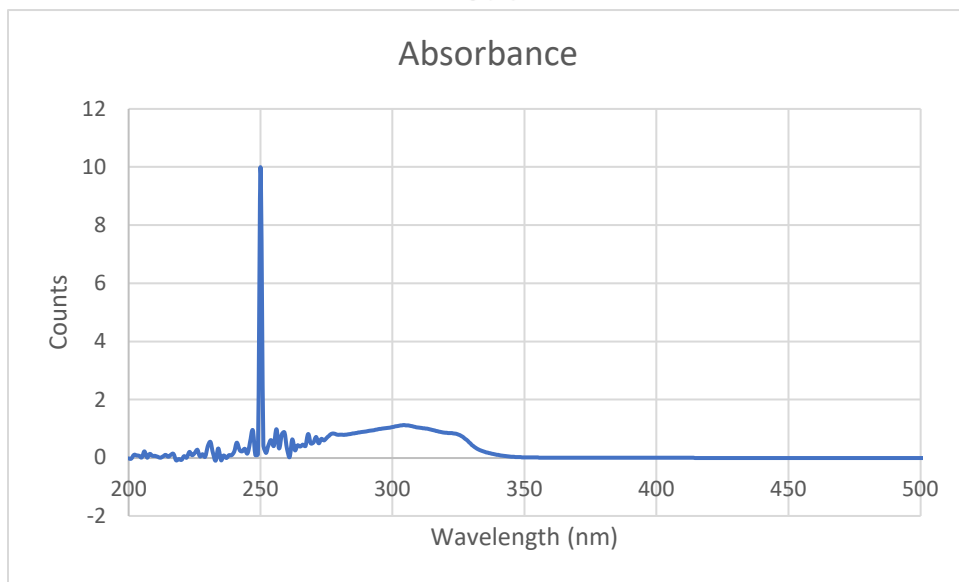
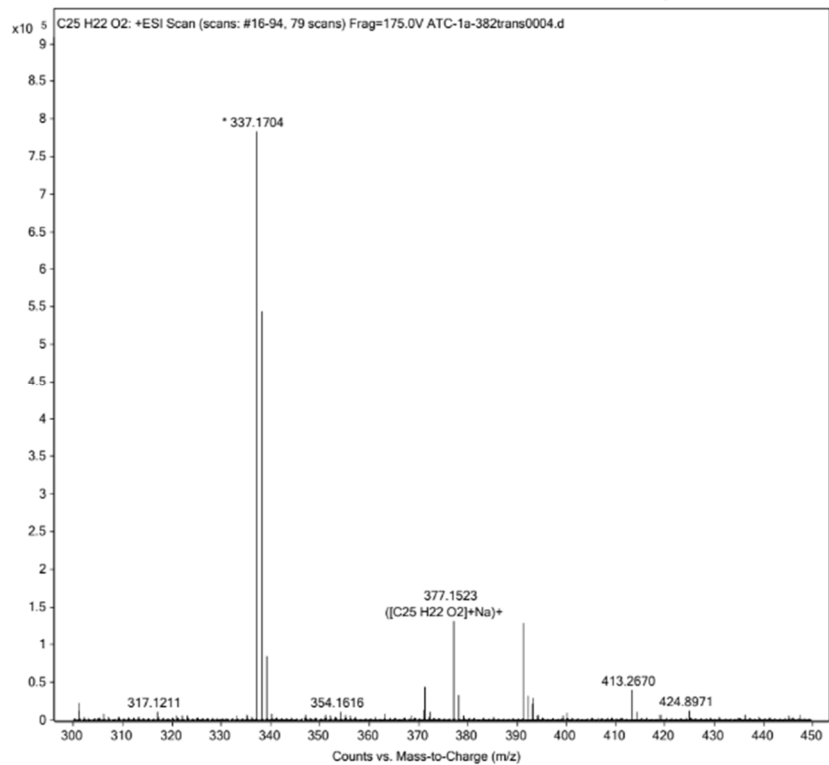
ATC-030920-PP333.1.fid

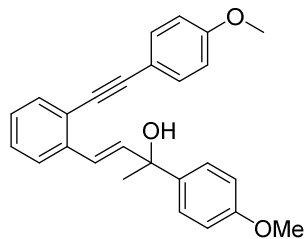


ATC-052820-CP333-C13.1.fid

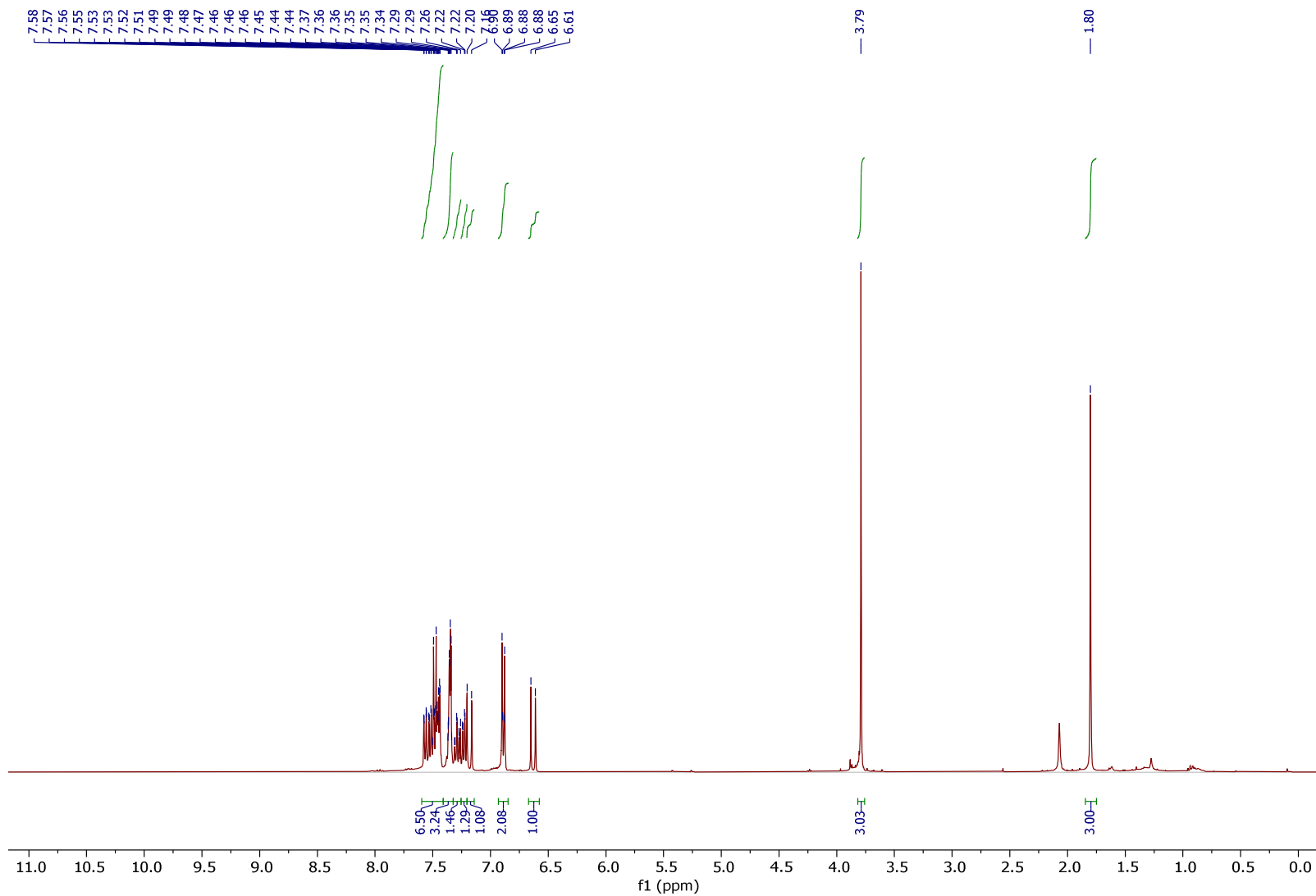






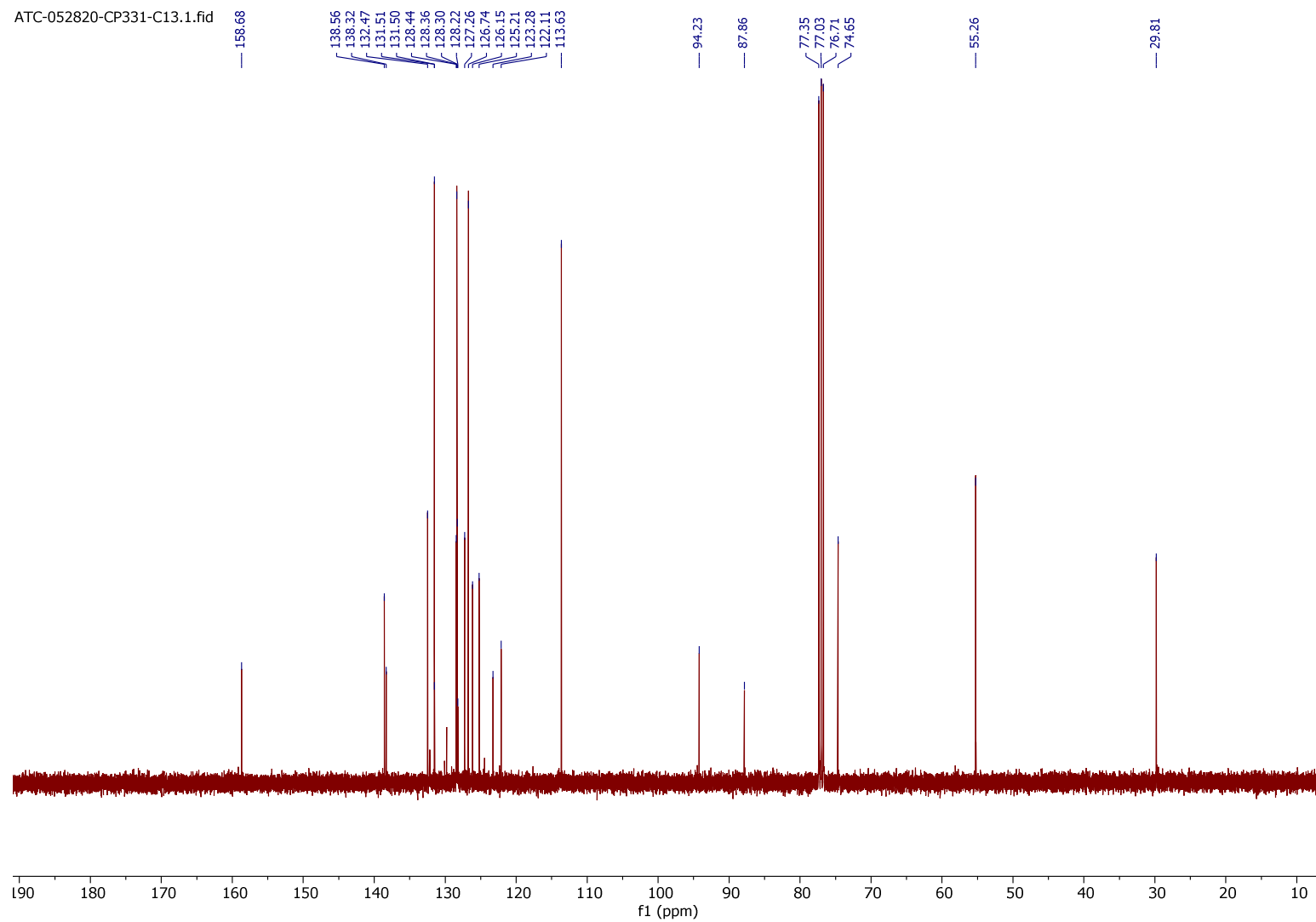


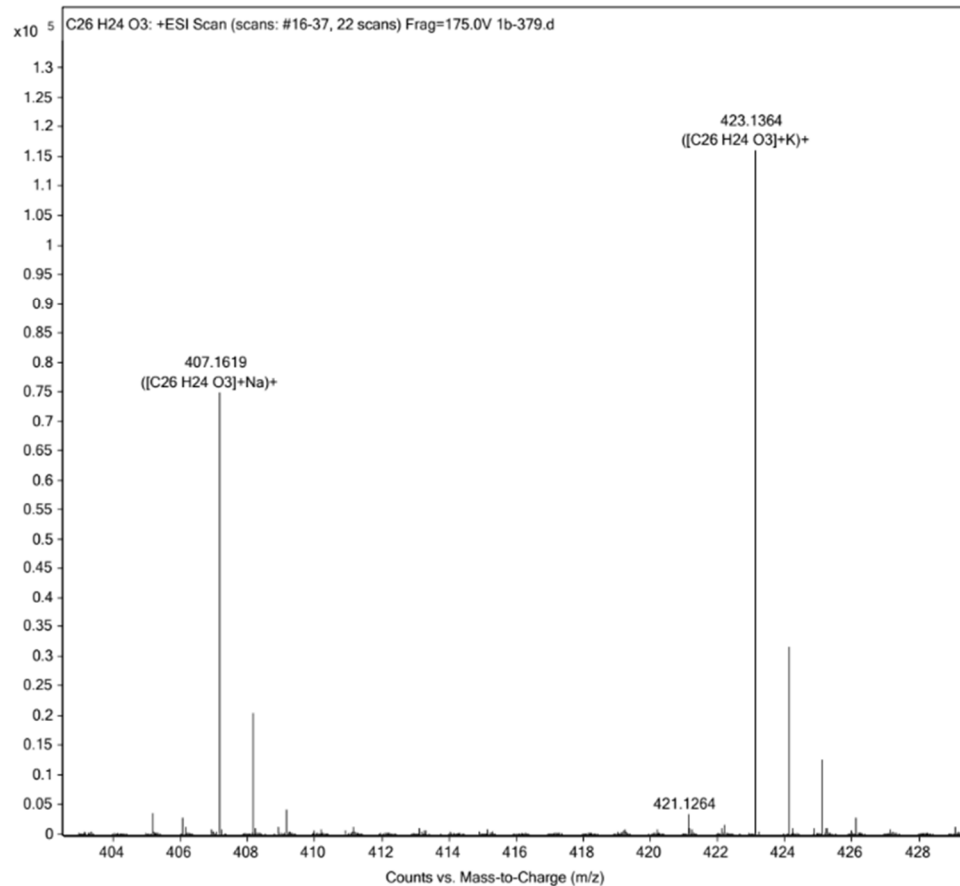
ATC-030920-PP331.1.fid

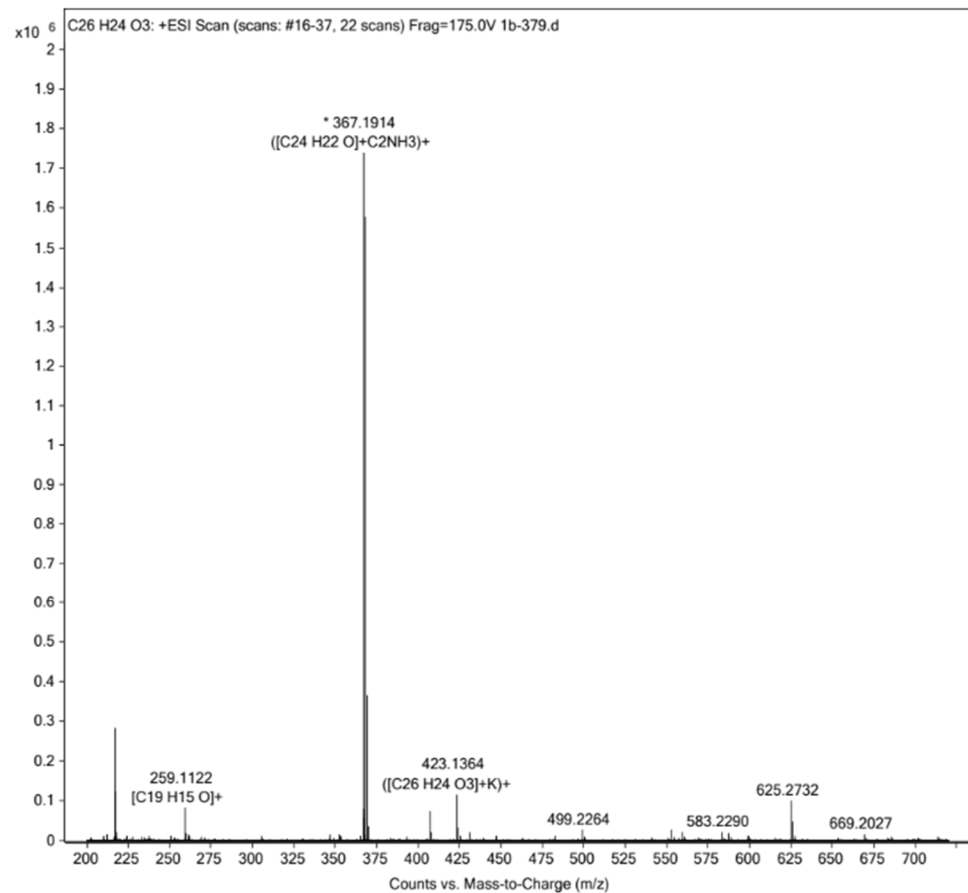


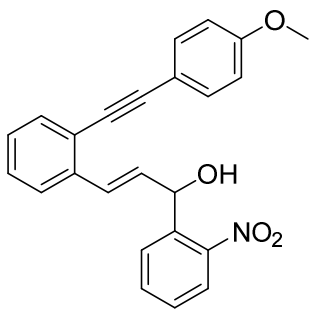
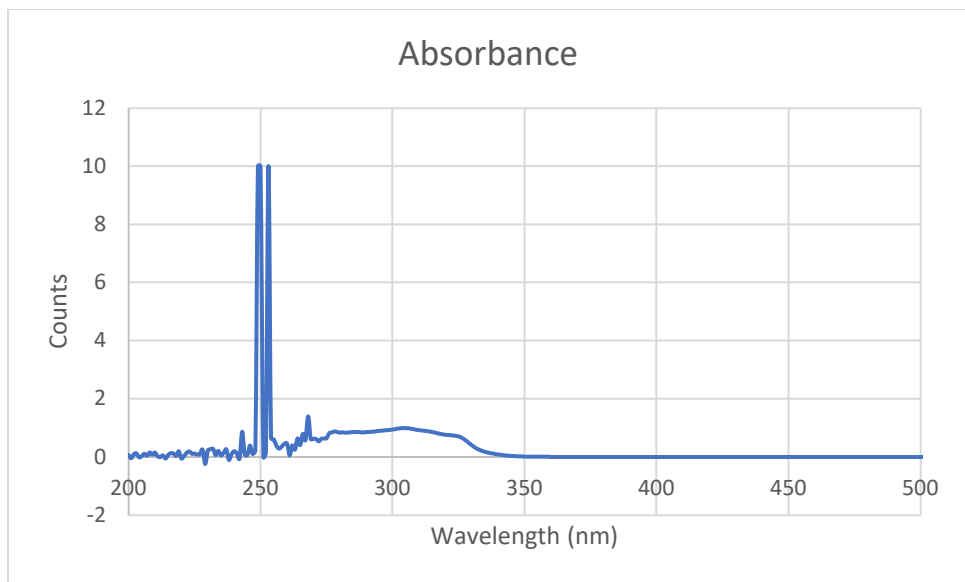
<sup>1</sup>H broad Peak at 2.1 = 1H from OH

ATC-052820-CP331-C13.1.fid

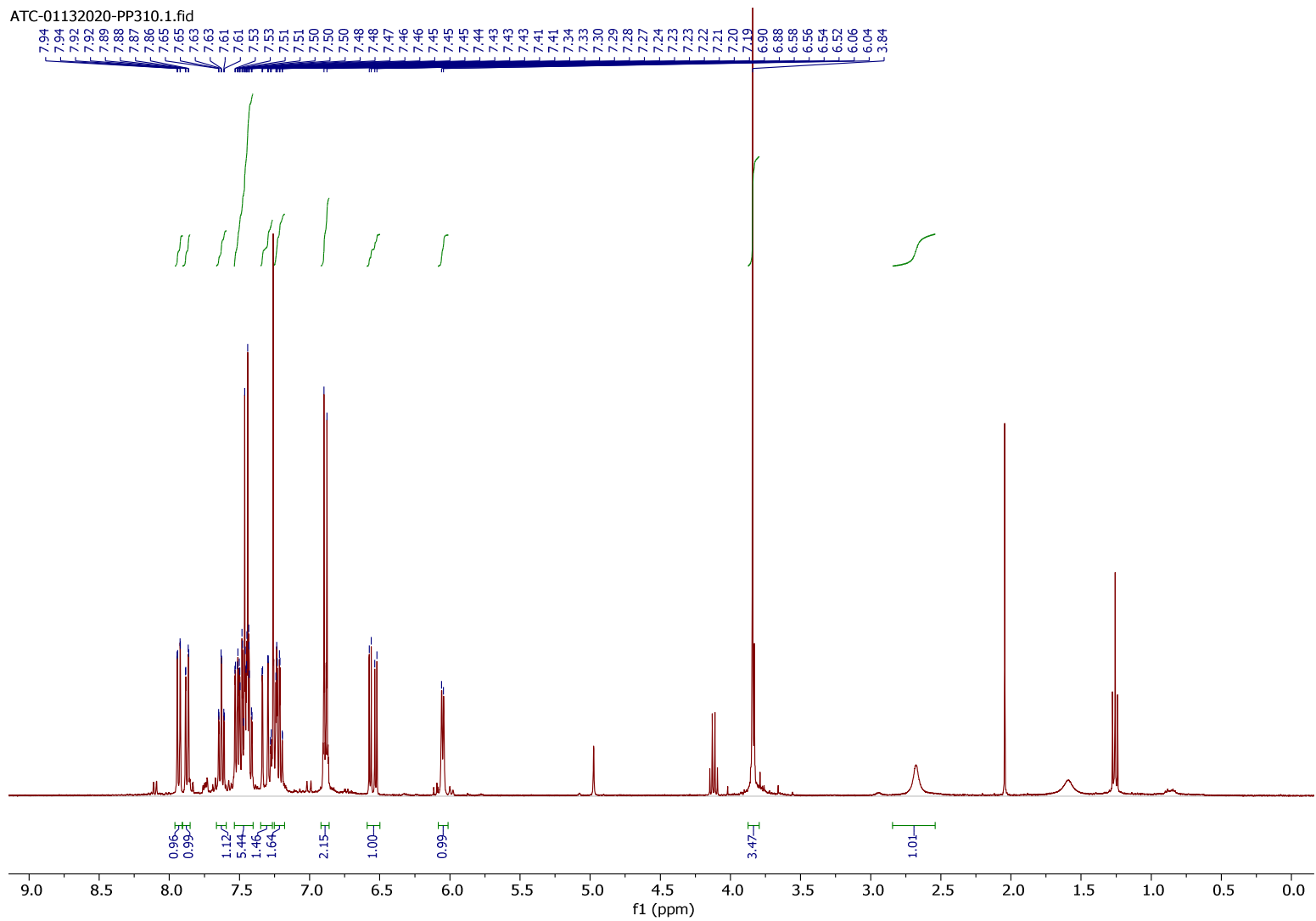


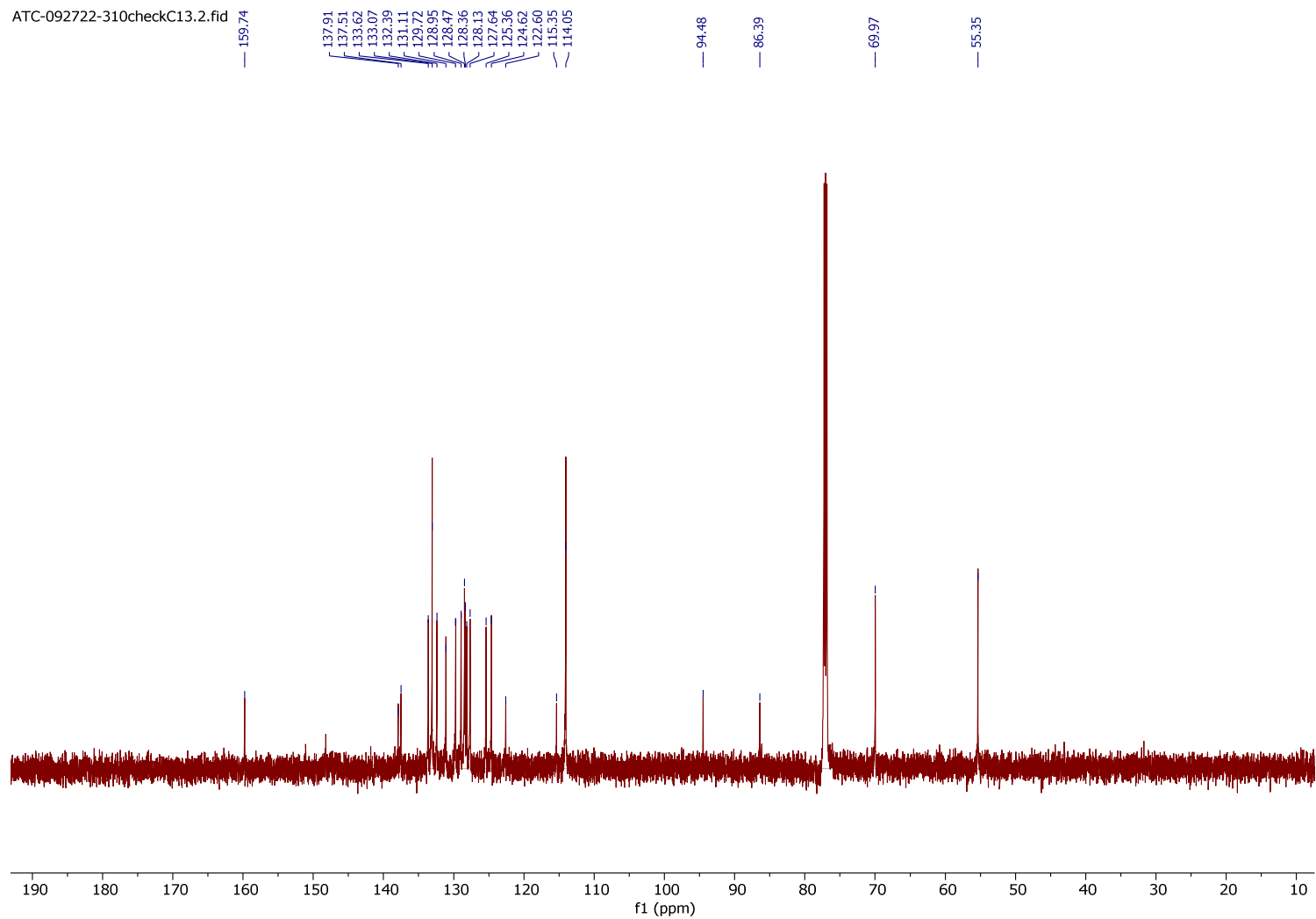


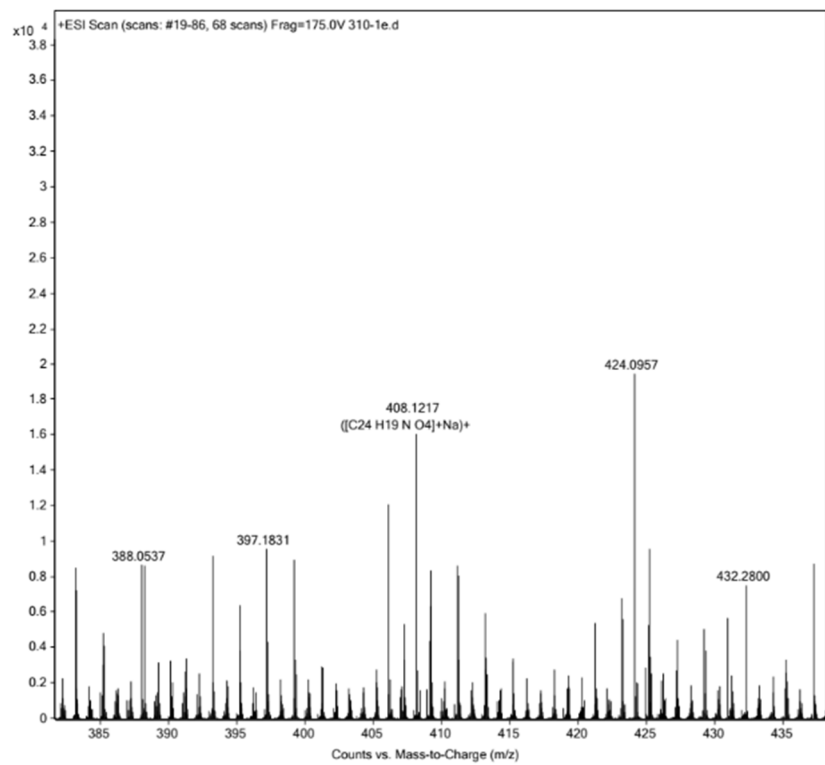


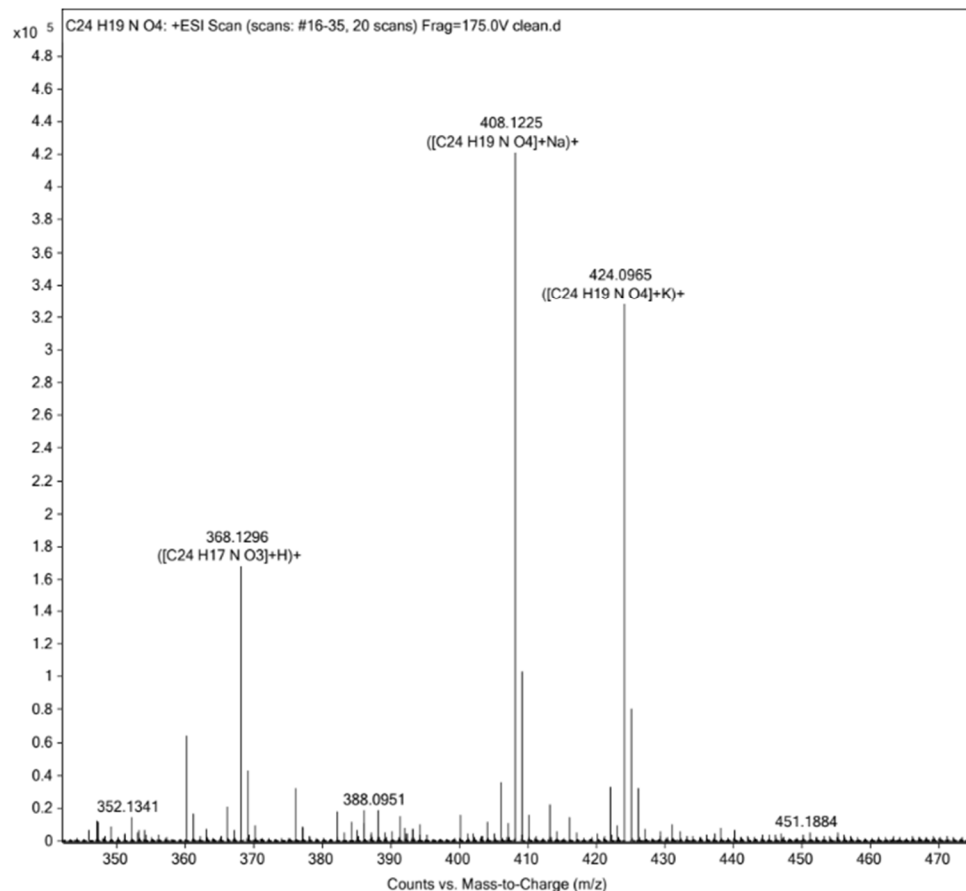


ATC-01132020-PP310.1.fid









#### IV. References

- (1) Mohamed, R. K.; Mondal, S.; Jorner, K.; Delgado, T. F.; Lobodin, V. V.; Ottosson, H.; Alabugin, I. V. The Missing C1–C5 Cycloaromatization Reaction: Triplet State Antiaromaticity Relief and Self-Terminating Photorelease of Formaldehyde for Synthesis of Fulvenes from Enynes. *J. Am. Chem. Soc.* **2015**, *137* (49), 15441–15450. <https://doi.org/10.1021/jacs.5b07448>.
- (2) Sheehan, J. C.; Umezawa, K. Phenacyl Photosensitive Blocking Groups. *J. Org. Chem.* **1973**, *38* (21), 3771–3774. <https://doi.org/10.1021/jo00961a027>.
- (3) Literák, J.; Dostálová, A.; Klán, P. Chain Mechanism in the Photocleavage of Phenacyl and Pyridacyl Esters in the Presence of Hydrogen Donors. *J. Org. Chem.* **2006**, *71* (2), 713–723. <https://doi.org/10.1021/jo0521551>.
- (4) Patchornik, A.; Amit, B.; Woodward, R. B. Photosensitive Protecting Groups. *J. Am. Chem. Soc.* **1970**, *92* (21), 6333–6335. <https://doi.org/10.1021/ja00724a041>.
- (5) Walker, J. W.; Reid, G. P.; McCray, J. A.; Trentham, D. R. Photolabile 1-(2-Nitrophenyl)Ethyl Phosphate Esters of Adenine Nucleotide Analogs. Synthesis and Mechanism of Photolysis. *J. Am. Chem. Soc.* **1988**, *110* (21), 7170–7177. <https://doi.org/10.1021/ja00229a036>.

- (6) Givens, R. S.; Matuszewski, B. Photochemistry of Phosphate Esters: An Efficient Method for the Generation of Electrophiles. *J. Am. Chem. Soc.* **1984**, *106* (22), 6860–6861. <https://doi.org/10.1021/ja00334a075>.
- (7) Lin, W.; Lawrence, D. S. A Strategy for the Construction of Caged Diols Using a Photolabile Protecting Group. *J. Org. Chem.* **2002**, *67* (8), 2723–2726. <https://doi.org/10.1021/jo0163851>.
- (8) Barltrop, J. A.; Schofield, P. Photosensitive Protecting Groups. *Tetrahedron Lett.* **1962**, *3* (16), 697–699. [https://doi.org/10.1016/S0040-4039\(00\)70935-X](https://doi.org/10.1016/S0040-4039(00)70935-X).
- (9) Wang, P.; Wang, Y.; Hu, H.; Spencer, C.; Liang, X.; Pan, L. Sequential Removal of Photolabile Protecting Groups for Carbonyls with Controlled Wavelength. *J. Org. Chem.* **2008**, *73* (16), 6152–6157. <https://doi.org/10.1021/jo8008275>.
- (10) Karas, L. J.; Campbell, A. T.; Alabugin, I. V.; Wu, J. I. Antiaromaticity Gain Activates Tropone and Nonbenzenoid Aromatics as Normal-Electron-Demand Diels–Alder Dienes. *Org. Lett.* **2020**, *22* (18), 7083–7087. <https://doi.org/10.1021/acs.orglett.0c02343>.
- (11) Wu, C.-H.; Karas, L. J.; Ottosson, H.; Wu, J. I.-C. Excited-State Proton Transfer Relieves Antiaromaticity in Molecules. *Proc. Natl. Acad. Sci.* **2019**, *116* (41), 20303–20308. <https://doi.org/10.1073/pnas.1908516116>.
- (12) Slanina, T.; Ayub, R.; Toldo, J.; Sundell, J.; Rabten, W.; Nicaso, M.; Alabugin, I.; Fdez. Galván, I.; Gupta, A. K.; Lindh, R.; Orthaber, A.; Lewis, R. J.; Grönberg, G.; Bergman, J.; Ottosson, H. Impact of Excited-State Antiaromaticity Relief in a Fundamental Benzene Photoreaction Leading to Substituted Bicyclo[3.1.0]Hexenes. *J. Am. Chem. Soc.* **2020**, *142* (25), 10942–10954. <https://doi.org/10.1021/jacs.9b13769>.
- (13) Fernández, I.; Alabugin, I. V.; Campbell, A. T. *Aromaticity - Modern Computational Methods and Applications*; Elsevier, 2021.
- (14) Lage Robles, J.; Bochet, C. G. Photochemical Release of Aldehydes from  $\alpha$ -Acetoxy Nitroveratryl Ethers. *Org. Lett.* **2005**, *7* (16), 3545–3547. <https://doi.org/10.1021/ol051280w>.
- (15) Gravel, D.; Murray, S.; Ladouceur, G. O-Nitrobenzyl Alcohol, a Simple and Efficient Reagent for the Photoreversible Protection of Aldehydes and Ketones. *J. Chem. Soc. Chem. Commun.* **1985**, No. 24, 1828–1829. <https://doi.org/10.1039/C39850001828>.
- (16) Wang, P.; Hu, H.; Wang, Y. Novel Photolabile Protecting Group for Carbonyl Compounds. *Org. Lett.* **2007**, *9* (8), 1533–1535. <https://doi.org/10.1021/ol070346f>.
- (17) McHale, W. A.; Kutateladze, A. G. An Efficient Photo-SET-Induced Cleavage of Dithiane–Carbonyl Adducts and Its Relevance to the Development of Photoremovable Protecting Groups for Ketones and Aldehydes. *J. Org. Chem.* **1998**, *63* (26), 9924–9931. <https://doi.org/10.1021/jo981697y>.
- (18) Alabugin, I. V.; Manoharan, M. Radical-Anionic Cyclizations of Eneidyne: Remarkable Effects of Benzannulation and Remote Substituents on Cycloaromatization Reactions. *J. Am. Chem. Soc.* **2003**, *125* (15), 4495–4509. <https://doi.org/10.1021/ja029664u>.
- (19) Baird, N. C. Quantum Organic Photochemistry. II. Resonance and Aromaticity in the Lowest  $3\pi\pi^*$  State of Cyclic Hydrocarbons. *J. Am. Chem. Soc.* **1972**, *94* (14), 4941–4948. <https://doi.org/10.1021/ja00769a025>.
- (20) Augé, J.; Boucard, V.; Gil, R.; Lubin-Germain, N.; Picard, J.; Uziel, J. An Alternative Procedure in the Takai Reaction Using Chromium(III) Chloride Hexahydrate as a Convenient Source of Chromium(II). *Synth. Commun.* **2003**, *33* (21), 3733–3739. <https://doi.org/10.1081/SCC-120025182>.
- (21) Neumann, H.; Seebach, D. Stereospecific Preparation of Terminal Vinylolithium Derivatives by Br/Li-Exchange with *t*-Butyllithium. *Tetrahedron Lett.* **1976**, *17* (52), 4839–4842. [https://doi.org/10.1016/S0040-4039\(00\)78926-X](https://doi.org/10.1016/S0040-4039(00)78926-X).
- (22) Palei, B. A.; Gavrilenko, V. V.; Zakharkin, L. I. Comparative Reactivity of Alkyl, Vinyl, and Acetylene Derivatives of Aluminum. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1969**, *18* (12), 2590–2595. <https://doi.org/10.1007/BF00912549>.