Optimization of the Microwave-Assisted Mannich Reaction: Developing a Laboratory Module for Use in Undergraduate Chemistry Courses

Erika De Graef

Senior Comprehensive Project

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Allegheny College

Department of Chemistry

Meadville, PA 16335

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Erika Floetta De Graef
Allegheny College - Senior Comprehensive Project
Department of Chemistry
Meadville, PA 16335

Advisor:
Dr. Matthew Betush

Committee:
Dr. Mark Ams
Dr. Moira Flanagan

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I hereby recognize and pledge to fulfill my responsibilities, as defined in the Honor Code of Allegheny College, and to maintain the integrity of both myself and the College community.



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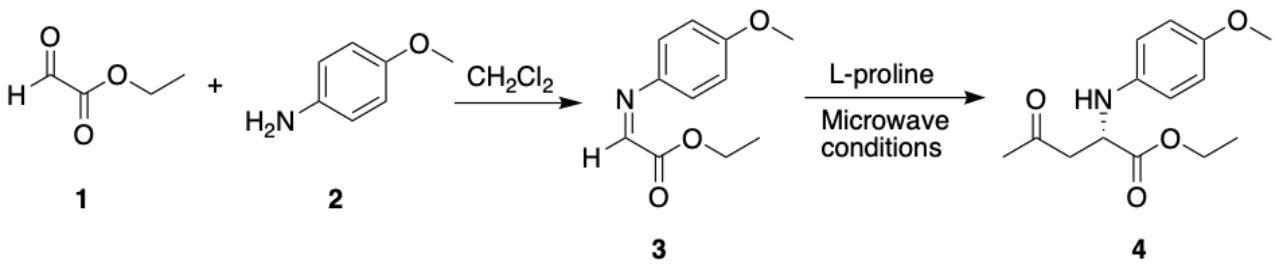
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Abstract



With the ultimate goal of determining whether a stereoselective Mannich reaction is suitable for an undergraduate laboratory module, the proline-catalyzed Mannich reaction was adapted to microwave conditions in order to efficiently synthesize *N*-(4-methoxyphenyl)-4-oxonorvaline ethyl ester (**4**). Synthesis of the intermediate imine (**3**) was achieved in high yield (95%+) and can be used without purification, however the Mannich reaction itself resulted in variable yields, low purity, and poor reproducibility.

Introduction and Background

The Mannich Reaction

Microwave optimization of a proline-catalyzed Mannich reaction seeks to develop an efficient synthesis of *p*-methoxyphenyl-protected *β*-amino carbonyls. These are useful precursors for the structural motif of *α*-amino-*γ*-butyrolactones, commonly found in both natural and pharmaceutical products.[1,2] One such butyrolactone, *γ*-hydroxynorvaline (Figure 1, **A**), shows antidiabetic properties, while others are used as pesticides (**B**), bacteria inhibitors (**C**), and ACE inhibitors (**D**).[2] The Mannich reaction is an efficient way to synthesize intermediates in the quest for *α*-amino-*γ*-butyrolactones; the stereochemistry of the *β*-amino carbonyls formed can be very specifically controlled via application of organocatalysts.[1]

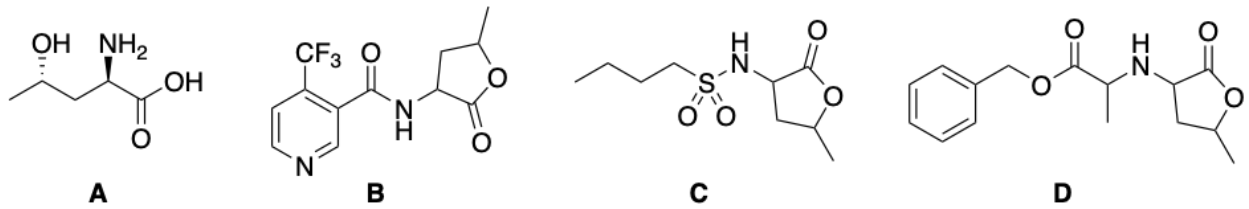
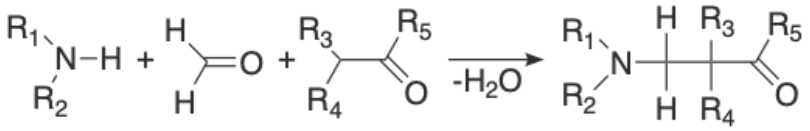


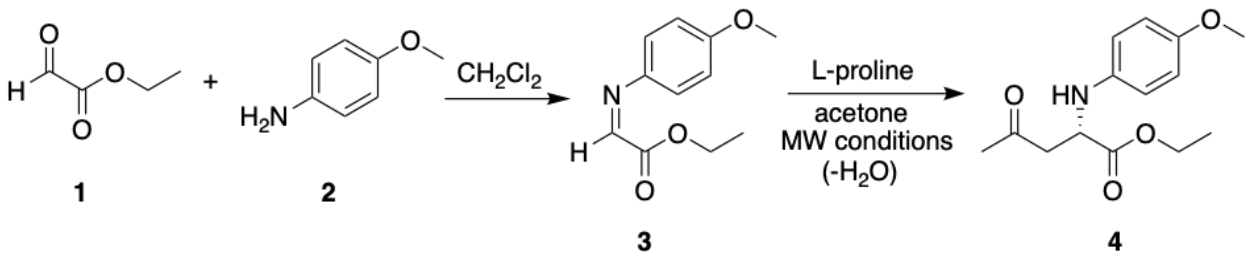
Figure 1. Butyrolactones with diverse functionalities.[2]

The Mannich reaction itself consists of the nucleophilic addition of an amine to a carbonyl, which is dehydrated to form the enamine, followed by addition of an imine serving as an electrophile in order to form the β-amino carbonyl, or Mannich base (Scheme 1).[3] Generally, the Mannich reaction is used in order to form new carbon-carbon bonds in nitrogen-containing molecules, which are motifs found in myriad natural products.[4]



Scheme 1. Generic Mannich reaction.

The specific Mannich reaction studied here, which aims to synthesize *N*-(4-methoxyphenyl)-4-oxonorvaline ethyl ester (**4**) through an imine intermediate (**3**) (Scheme 2), has been performed by a number of research groups over the years. Wang et. al. and Hosseini et. al. provide very similar conditions for the Mannich reaction, both using approximately 2:1 dimethyl sulfoxide (DMSO) and acetone as the solvent, but where Hosseini began to employ the microwave to speed up the reaction, Wang performed the reaction at room temperature for two and a half hours.[5, 6] These two procedures were central to the development of the conditions used in this study, and adjustments were made in accordance with information presented by Notz & Watanabe. Where most literature accepts DMSO and acetone as the ideal solvent system, Notz & Watanabe tested eight different solvents and found that using acetone as both the electron donor and the lone solvent increased the yield and the enantiomeric excess.[7] Although this study did not involve the microwave, the results helped inform the decision to use only acetone as the solvent in the initial microwave reaction trials. The literature review confirmed that, regardless of the electron donor used, the most substituted enamine intermediate always attacked the N-PMP-protected α-imino ethyl glyoxylate.[7] Additionally, electron-deficient acceptor imines, namely gyloxylates, preferentially formed the syn-diastereomer when reacted with the more substituted enamine.[7]



Scheme 2. Two-step synthesis of *N*-(4-methoxyphenyl)-4-oxonorvaline ethyl ester (**4**).[5, 6, 8]

Personal study of this reaction began during Multistep Synthesis with Professor Betush in the Spring of 2021. The laboratory module provided in that course was open-ended: adapt the

given Mannich reaction to microwave conditions. The goal was, of course, to maintain high yields while minimizing the reaction time, but due to the nature of the module, there was no "right answer". While there is literature available on the appropriate microwave conditions for similar reactions, the goal of the work was to hypothesize on and test what students thought to be the ideal conditions. Students were able to develop an understanding of how each independent variable might affect the reaction, resulting in varying degrees of success. The reaction required the synthesis of an intermediate, N-PMP-protected α-imino ethyl glyoxylate (Methyl 2-[(4-methoxyphenyl)imino]acetate) (**3**), referred to here simply as the imine (Scheme 2), which was generally successful throughout the class. As per literature suggestion, the imine was not purified prior to use in the Mannich reaction, and the final product was not purified before NMR analysis. Ultimately, there was no consensus about the optimal conditions for the microwave-assisted Mannich reaction; some groups were able to produce high crude yields that were difficult to reproduce, while others were never able to produce a satisfactory product in any yield. Ultimately, the research question is this: how can the module be adjusted such that, after developing their own hypotheses, the students would be able to adapt the literature conditions and see higher, more consistent yields?

The most notable example of microwave acceleration of the proline-catalyzed Mannich reaction was published by Westermann & Neuhaus in 2005. This study brought proline back to the forefront of carbonyl reaction catalysis as a means to stereoselectively synthesize carbohydrates.[9] Westermann first varied the solvent while running the Mannich reaction at room temperature, testing numerous solvents and seeing best results using trifluoroethanol (TFE) and a reaction time of 20 hours. The highest yield achieved at room temperature was 75% (10 mol% L-proline; 95% ee), but a higher concentration of L-proline (30 mol%) afforded comparable

yield (72%) with a higher enantiomeric excess (99%).[9] The latter conditions were carried forward for application of microwave irradiation with selected solvents (Table 1, Entries 1-4). Using 300 W of maximal irradiated power and decreasing the reaction time to only 10 minutes, the yield was maintained with a minor reduction of enantiomeric excess (94%). Given the novelty of using proline as a catalyst in the Mannich reaction at the time, a yield of 73% was celebrated, but since then a few other studies endeavored to improve upon the work of Westermann & Neuhaus.

Table 1. Selected Microwave Mannich reactions from Westermann (1-4) and Hosseini (5-6).[6, 9]

Entry	Solvent	Mol % catalyst	Time (min)	Power (W)	Temp (°C)	Yield (%)	ee (%)
1	TFE	30	5	300	n/a	18	94
2	TFE	30	10	300	n/a	73	94
3	TFE	30	10	100	n/a	64	95
4	DMSO	30	10	300	n/a	18	n/a
5	DMSO	20	5	n/a	60	81	98
6	DMSO	20	10	n/a	60	91	>99

In 2007, Hosseini et. al. published an article in which oil baths and microwaves were used to optimize the reaction.[6] In this study, DMSO was used as the primary solvent and the reaction showed its highest yields at 60ºC with a ten minute reaction time (Table 1, entry 6). These results indicate that the Mannich reaction (Scheme 2) can be hastened while maintaining high yields, however previous personal involvement with that particular procedure has shown that it is not reliable. Rodriguez & Bolm present another example of a successful asymmetric Mannich reaction catalyzed by L-proline, however even under microwave conditions, the reaction takes at least an hour.[4] The best results (96% yield) were seen with a reaction time of 2.5 hours and a microwave temperature of 46ºC.[4] The purpose of my research is to drastically

shorten the reaction time by using the microwave, and as such the work of Rodriguez & Bolm falls outside of my chosen parameters despite their use of L-proline as the catalyst.

L-proline

For the purposes of this research, L-proline (Figure 2) has been chosen as the catalyst in order to access an asymmetric Mannich reaction that will yield a particular diastereomer of the *β*-amino carbonyl. L-proline is often referred to as (S)-proline in the literature, however for clarity, it will be referred to as L-proline. This particular reaction uses an *α*-imino ethyl glyoxylate as the electron acceptor and a ketone as the donor. Such conditions are generally ideal for the formation of functionalized *α*-amino acids with good diastereo-, regio-, and enantioselectivities; in the case of the N-PMP-protected *α*-imino ethyl glyoxylate (Scheme 2, **3**) used here, an (S)-*β*-amino ketone is the target.[6]

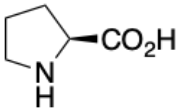


Figure 2. L-proline.

Notz & Watanabe employed catalytic L-proline throughout their study and found that, as expected, they were able to specifically synthesize (S)-stereochemistry about the *α*-stereocenter of the product.[7] Their study employed unmodified aldehydes as the nucleophilic donors, and it is advantageous in synthetic and pharmaceutical chemistry as the stereospecific products serve unique functions. This is advantageous in this study because it allows students to predict and experimentally prove the effects of a chiral catalyst on product formation.[7] Beyond the scope of the *β*-amino carbonyl synthesis performed in this research, catalytic L-proline has also proven itself useful in the stereospecific synthesis of *β*-aryl-*β*-trifluoromethyl-*β*-aminoketones,[10] 2,3-disubstituted tetrahydropyridines,[11] 2,3-piperidines,[12] and *α*-amino-*γ*-ketophosphonates.[13]

The stereoselectivity that L-proline provides is incredibly useful to the organic chemist, and given that the studies mentioned above show high yield, purity, and reproducibility, L-proline was seen as a logical choice of catalyst in this research.

Motivation: Applications in Education

This project is motivated by a desire to better understand the stereospecific availability of the Mannich reaction, as well as a desire to develop coursework that will benefit chemistry students in the future. Students will be able to use this guided laboratory module to practice independent optimization of an assigned reaction through adjustments to microwave conditions, purification steps, solvent systems, and equivalencies in each step of the synthesis in order to develop a better understanding of the functions of each component of the reaction.

Developing a more reliable outline for this synthesis affords advanced chemistry students the opportunity to practice their practical skills while enhancing their understanding of the effect of each component of a synthesis on the final product. Although experiencing an attempted synthesis that yields little to no product is an important learning experience in an undergraduate chemistry lab, it is also important to present students with materials that *will* yield the predicted results. By finding the optimum conditions for the microwave-assisted synthesis, we will provide a guided laboratory module that allows students to develop their own theories about how to optimize the reaction and test those theories, after which they will be able to run the reaction under the predetermined optimum conditions in order to produce the desired product. A search in the Journal of Chemical Education indicates that current undergraduate laboratory modules do not tend to link the Mannich reaction to microwave conditions. Coupling reactions,[14] esterifications,[15, 16] and cycloadditions [17, 18] are the most common reactions employed to teach

students standard microwave procedures, with particular focus on catalysis studies[15] and biochemistry.

The lack of laboratory modules that connect the Mannich reaction to microwave conditions does not mean that the Mannich reaction is not taught; it is often used in organic laboratories in order to form key intermediates for further study. The Petasis Borono-Mannich reaction has been used to introduce undergraduate chemists to multicomponent reactions and the use of boronic acids as environmentally friendly reagents.[19] This particular experimental plan, produced by Candeias et. al., requires thirty minutes of preparation time the day before a 4 hour lab period, which is not feasible in many undergraduate lab courses. Similarly, Kasting et. al. have produced a joint organic/inorganic laboratory procedure that employs the Mannich reaction as a means to synthesize amine-bis(phenols) as ligands.[20] The Mannich component is estimated to take 24 hours, and the complete study takes several laboratory sessions. The synthesized amine-bis(phenols), which are the Mannich product of this study, are then analyzed through several of the standard methods: melting point; FTIR; and ^{1}H, ^{13}C, DEPT-135, and HSQC NMR.[20] Such analyses are very useful for the undergraduate chemist, however the duration of the experiments is cause for concern. It could be beneficial to run this Mannich reaction under microwave conditions so as to decrease the time spent on the first step of the module. The Kasting module also requires that the students be adept in both organic and inorganic procedures, which may present problems for students who take organic chemistry without completing the other coursework of a chemistry major.[20]

Overall, current modules presented in the Journal of Chemical Education do not provide much focus on the Mannich reaction, and they particularly do not focus on the advantages of using the microwave to accelerate the Mannich reaction. The modules highlighted above do

provide students with opportunities to perform the Mannich reaction, but they do not treat the Mannich reaction as the primary target of the study. By performing the Mannich reaction using microwave conditions, students will gain an understanding of the reaction itself as well as the advantages of the microwave in time-restricted laboratories, the effect of an organic catalyst, and the effect of a stereospecific catalyst on the stereochemistry of the product. This module requires students to: perform a standard imine synthesis; analyze the imine via ^{1}H NMR; scale the Mannich reaction down from the given literature to the appropriate quantities for the microwave vial; perform the microwave reaction; and analyze the Mannich product via ^{1}H and ^{13}C NMR.

Results and Discussion

Imine Synthesis

Table 2. Imine syntheses. All performed using DCM as solvent, all % yields are by mass.

ID Number	Time (hr)	Drying Agent	Crude Yield (%)
EFD0201-01	1.5	Na_2SO_4	90.91
EFD0208-02	1.5	Na_2SO_4	104.4
EFD0220-01	19	$MgSO_4$	n/a
EFD0222-01	1.5	$MgSO_4$	131

In order to improve the likelihood of producing a Mannich product in high yield and purity, the first component of this project was to determine whether the intermediate imine needed to be purified before further use. Literature review indicated that the imine could be used in its crude form with little to no effect on the Mannich reaction, however personal experience showed that impurities within the imine may cause the Mannich reaction to be less effective and less reliable. Flash column chromatography was employed to purify the imine in the hopes that a more pure imine could improve Mannich results. Although the imine was technically stable on the column, after several attempts it was determined that purification was overly difficult and time consuming and did not greatly improve the quality of the imine.

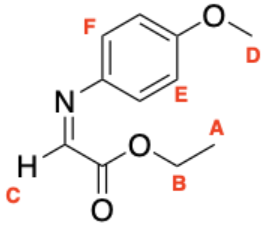


Figure 3. Imine intermediate with labeled hydrogens.

The best of the crude imines (Table 2, **EFD0208-02, EFD0222-01**) aligned well with literature ^{1}H NMR data (Figure 3): methyl group **A** is found at δ 1.34, while methyl group **D** is around 3.77. **B** is found at 4.3, **C** at 7.9, and the phenyl hydrogens, all labeled **E** and **F**, are seen

as two sets of doublets at 6.87 and 7.30, although there is little certainty as to which set of doublets corresponds to which section of the ring. There is some evidence of remaining starting material (δ 1.2, 4.2, 7.1), but as the literature does not require purification, all further Mannich reactions were performed with crude imine. The yields are high (>100%), but given the presence of starting material in the ^{1}H NMR, that is to be expected. It is also relevant to note that the peak seen at or around δ 2.3 in all of the imine **3** ^{1}H NMRs is attributed to toluene, as the ethyl glyoxylate used in this research was 50% in toluene, rather than the solid used in the literature.

Mannich Reaction

Table 3. Mannich Reactions.

ID Number	Solvent	Time (min)	Temperature (°C)	Crude Yield (%)
EFD0212-01	Acetone	10	60	77.13
EFD0214-01	DMSO	150	r.t	63.74
EFD0217-01	Acetone	15	60	67.89
EFD0223-01	Acetone	10	60	95.24
EFD0225-01	Aceone	10	60	40.24

The Mannich reaction was performed under both microwave and standard conditions, of which the microwave yielded a better crude product (Table 3). At room temperature, with a reaction time of 2.5 hours, the crude NMR showed minor evidence of product formation (63.73% by mass, **EFD0214-01**). The peaks were not very strong, however some key indicators of the product (δ 1.23, 2.15, 2.94, 3.76) were present. Purification was attempted, but the product did not come off the column as literature and TLC evidence predicted, resulting in a final yield of only 2.36% (**EFD0215-01**). Although this procedure followed that of Simon et. al., the purified yield was far from the literature yield of 86%.[2]

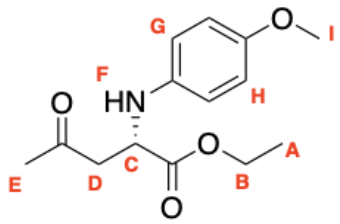
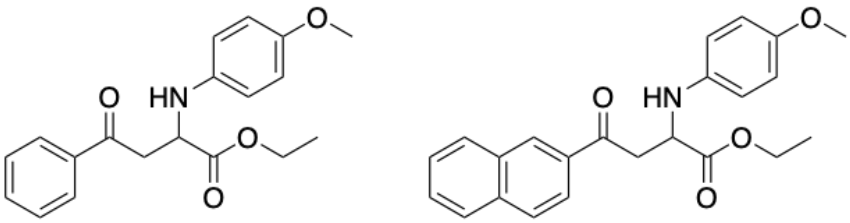


Figure 4. Mannich product with labeled hydrogens.

^{1}H NMR of the first microwave product (**EFD0212-01**) showed evidence of product formation at δ 1.33-1.41, 2.14, 3.70, 4.10, 4.34, and 6.68-6.88. The literature[21] indicates distinct peaks for **B, F,** and **C** (Figure 4) appeared as a quartet further downfield (δ 4.17) than that which appears in personal data (δ 4.10), and as such the noise between 4.12 and 4.30 has been attributed to the -NH group that is not distinctly identified elsewhere. There is a notable lack of a peak at δ 2.96; literature attributes the peak to the hydrogens of carbon **D**, however its presence in personal data was not reliable. There is a small peak around 2.7 that could be attributed to that, however it is not reliably present either.



5 **6**

Figure 5. Mannich products using larger donors.

Efforts were made to synthesize a slightly different Mannich product using a larger electron donor than acetone. Following a non-microwave Mannich procedure,[22] acetophenone and 2'-acetonaphthone were used in the hopes that the bulky side of the donors would encourage interaction between the imine and the free carbon of the donor. These were one-pot, 24+ hour syntheses that, in the long run, were not successful. The first step, the imine synthesis, worked well (^{1}H NMR **EFD0220-01**), however the reaction between that imine and the electron donor

did not occur in any significant yield. NMR analysis of the crude Mannich products showed some evidence of product formation, but purification of the acetophenone product yielded no clear NMR data. Purification was not attempted on product **6**; this method was abandoned and focus returned to the original target product.

Using imine **EFD0222-01**, several Mannich reactions were performed. **EFD0223-01** (Table 3) was formed using the standard microwave conditions with ~10 minutes of pre-stirring at room temperature of the L-proline in acetone before addition of the imine. This product was relatively clean by ^{1}H NMR, with the exception of some areas (δ 7.0-7.5) where the non-product peaks can be attributed to unreacted starting material. The key peaks (δ 1.2, 2.2, 2.9, 3.7, 4.1-4.3, 6.6-6.8) are present and prominent, especially the peak at 2.9 that denotes the hydrogens of **D** (Figure 4). Of the Mannich products formed via microwave, this crude product has the clearest peak at 2.9. This sample shows the most clarity for almost all of the critical peaks. While there is some noise around the upfield peaks (particularly at δ 2.15), the overall spectrum is cleaner than the other crude products analyzed.

Another trial of the microwave Mannich reaction (**EFD0225-01**) showed evidence of product formation, however the original crude spectrum was illegible due to an overwhelming ethyl acetate peak. The product was then rotovapped again at a higher temperature, which brought out not only the desired product peaks but also a large amount of unknown, unwanted peaks (δ 0.8-1.2, 2.0, 3.8-4.05, 5.25-6.0). As such, further efforts were made to purify the product using a more elaborate solvent system. The literature identifies two mobile phases (CH_2Cl_2 in EtOAc;[2] EtOAc in petroleum ether[6]) that personal investigation proved were not ideal. TLC analysis indicated that a more polar solvent is needed for the product than for the

impurities, so a solvent system of 45% EtOAc in hexanes was used to hopefully push off the impurities before flushing the column with pure methanol.

The collected fractions from the initial 45% EtOAc system showed some evidence of product, despite the fact that the product was not expected to come off the column until methanol was added. The ^{1}H NMR of those fractions (**EFD0226-01**) was much cleaner than that of the crude product, however there were some inconsistencies indicating that it may not have been the desired product. Namely, the aromatic region did not align with the literature, and there was still considerable evidence of undesirable products (δ 0.8-1.05, 7.0-8.5). The fractions collected during the methanol flush (**EFD0226-02**) also showed some evidence of the desired product, but had a considerable amount of noise and undesirable peaks. Mannich product was evident at δ 1.2, 3.75, 4.2, and 6.7-6.9, but none of the peaks were particularly clear. There was a great deal of noise throughout the spectra, so trituration was attempted. The two phases, solid (**EFD0227-01**) and filtrate (**EFD0227-02**), were analyzed, however neither had a substantial amount of material and it was difficult to collect a large enough sample of the solid to get a clear ^{1}H NMR. The NMR of the solid had a very prominent solvent peak, but after some digging into the spectrum, several of the key product peaks were visible. The same can be said for the ^{1}H NMR of the filtrate: a large ethyl acetate peak obscured the product peaks, but they are present. The filtrate spectrum aligned somewhat better with the literature, however it is missing two key peaks that account for the -NH hydrogen and the -O$\underline{CH_2}CH_3$ hydrogens. Neither of the phases collected from the trituration of what came off the column can be definitively identified as the desired product. Overall, purification of the Mannich product has proven to be more difficult than expected, and efforts should be made to find a better purification method.

Conclusion

Based on the results discussed above, we can conclude that the Mannich reaction, and the synthesis of its imine intermediate, are useful tools for the undergraduate organic laboratory. The imine synthesis is simple and results in high yields, and it has the added benefit of not requiring purification before being used in the Mannich reaction. While purification techniques are very important to learn, it is advantageous for a multistep synthesis in an undergraduate level course to not require purification of the intermediate. Students will be able to follow the "General Synthesis of Methyl 2-[(4-methoxyphenyl)imino]acetate (**3**)" procedure (and, more specifically, **EFD0222-01**) with confidence that the imine will function in the Mannich reaction without having to take the time to purify it first. The procedure for the Mannich reaction ("General Microwave Mannich Reaction Procedure"), particularly the conditions used in the synthesis of **EFD0223-01**, can then be used to provide a high (unpurified) yield of *N*-(4-methoxy-phenyl)-4-oxonorvaline ethyl ester (**4**). The Mannich product then requires purification, so far via flash column chromatography, providing students the opportunity to practice that skill.

Based on the available literature in the Journal of Chemical Education,[14-18] the procedure developed in this research will serve as a useful tool in the undergraduate organic chemistry laboratory. By following this module, students will develop an understanding of the imine synthesis as well as the factors affecting the ability to use that intermediate without purification. They will also develop a functional knowledge of the microwave, enabling them to hasten reactions by understanding how to scale for microwave conditions. While this project has improved the conditions of the microwave reaction, students following this module will still have the opportunity to adjust variables and try to optimize the reaction further.

Although the work performed in this project has led us closer to a functional laboratory module for undergraduate chemistry courses, there is still room for improvement. The results presented above indicate that the imine synthesis works well and forms a product that does not need to be purified before being used in the Mannich reaction. As for the Mannich reaction itself, these results show that the microwave adaptations employed do provide a significant yield most of the time, however the product is not particularly pure, there are times when the microwave decreases yield substantially, and the crude product is difficult to purify by flash column. Future work should aim to continue honing the synthesis and purification of the Mannich product. Varying the solvent system of the column has proven to be a good way to improve product recovery, however further analysis of the ideal solvent system would be prudent. It would also be beneficial to attempt other purification techniques for the Mannich product, as the flash column has not been a reliable method. A new technique could then be a good addition to the laboratory module, introducing undergraduate chemists to a new method of purification. Overall, the procedures developed will work as an open-ended laboratory module, allowing students some independence in determining conditions but still providing guidance to promote confidence.

Narrative Experimental

General Synthesis of Methyl 2-[(4-methoxyphenyl)imino]acetate (3):[8] In a round bottom flask, p-anisidine (1 eq.) was dissolved in 25 mL dichloromethane. Ethyl glyoxylate (1 eq, 50% in toluene) was added, and the reaction was stirred for 30 min. Drying agent was added, and stirring continued for 1 hr. The reaction mixture was then vacuum filtrated and rotary evaporated.

EFD0201-01 1.33 mmol scale (0.1636 g p-anisidine; 0.29 mL ethyl glyoxylate). Drying agent: sodium sulfate (Na_2SO_4). Crude yield of 0.2509 g (90.91% by mass), column purification attempted but unsuccessful. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.34 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 4.43 – 4.35 (m, 2H), 3.82 – 3.81 (m, 3H), 1.41 – 1.36 (m, 3H).

EFD0208-02 13.5 mmol scale (1.6847 g p-anisidine; 3.0 mL ethyl glyoxylate). Drying agent: Na_2SO_4. Crude yield of 2.922 g (104.4% by mass), used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.30 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 4.35 (q, J = 7.2, 3.8 Hz, 2H), 3.77 (s, 3H), 1.36 – 1.32 (t, 3H).

EFD0220-01 2.41 mmol scale (0.2968 g p-anisidine; 0.5 mL ethyl glyoxylate). Drying agent: magnesium sulfate ($MgSO_4$). Reaction stirred for 3 hrs before vacuum filtration, after which fresh $MgSO_4$ was added and the reaction was stirred for an additional 16 hrs. Crude mass was not recorded, as Mannich reaction was performed immediately in the same flask. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.33 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

EFD0222-01 15.1 mmol scale (1.8792 g p-anisidine; 3.33 mL ethyl glyoxylate). Drying agent: $MgSO_4$. Crude yield of 4.0854 g (131% by mass), used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.31 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.36 (dd, *J* = 7.1, 5.2 Hz, 2H), 3.75 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

Mannich Reaction under standard conditions (4):[2] In a 50 mL round bottom flask, L-proline (0.1152 g, 1.00 mmol) was dissolved in 10.0 mL DMSO and 5.0 mL acetone under constant agitation. crude imine (0.7412 g, 3.57 mmol) was dissolved in a small amount of acetone, then added to the round bottom flask and stirred at room temperature for 2.5 hours. The reaction mixture was transferred to a separatory funnel with 50 mL NaCl solution, to which was added 25 mL ethyl acetate. The organic phase was washed consecutively with NH_4Cl solution and water (50 mL each), then dried over Na_2SO_4. After rotary evaporation, the crude yield was 0.6047 g (63.73% by mass; **EFD0214-01**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 – 6.69 (m, 4H), 4.40 – 4.32 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.76 (dd, *J* = 7.7, 6.1 Hz, 3H), 2.94 (d, *J* = 5.6 Hz, 2H), 2.15 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). Flash column chromatography was attempted (95:5 DCM:EtOAc) with a final yield of 0.0224 g (2.36% yield by mass; **EFD0215-02**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 – 6.71 (m, 4H), 4.28 (dd, *J* = 7.1, 2.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.80 – 3.71 (m, 3H), 2.95 (d, *J* = 5.6 Hz, 2H), 2.16 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

General Microwave Mannich Reaction Procedure (4):[6] In a 10 mL microwave vial, catalytic L-proline was dissolved in 5 mL acetone. Crude imine **3** (1 eq) was added, and the reaction was put in the microwave oven for 10 minutes at 60°C. The reaction mixture was quenched with saturated NH_4Cl solution, then extracted with diethyl ether (3x20 mL). The combined organic phase was dried over solid drying agent, then concentrated via rotary evaporation.

EFD0212-01 0.81 mmol scale (0.1674 g imine); 10 mol % catalyst (0.0172 g L-proline). Drying agent: Na_2SO_4. Crude yield of 0.1653 g (77.13% by mass). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.68 (m, 4H), 4.34 (dd, *J* = 14.3, 7.1 Hz, 2H), 4.10 – 4.05 (m, 1H), 3.70 (s, 3H), 2.14 (s, 3H), 1.41 – 1.33 (m, 3H).

EFD0217-01 1.4 mmol scale (1.436 g imine); 10 mol % catalyst (0.0275 g L-proline). Drying agent: Na_2SO_4. Reaction time of 10 minutes, with 5 minutes of pre-stirring. Crude yield of 0.2586 g (67.89% by mass). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 – 6.74 (m, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 4.31 (dd, *J* = 10.1, 7.2 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 2H), 2.11 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

EFD0223-01 1.03 mmol scale (0.2132 g imine); 30 mol % catalyst (0.0678 g L-proline). 10 min. pre-stirring of L-proline in acetone. Drying agent: $MgSO_4$. Crude yield of 0.2599 g (95.24% by mass). Crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 – 6.72 (m, 2H), 6.64 – 6.60 (m, 2H), 4.30 (t, *J* = 5.6 Hz, 1H), 4.18 – 4.11 (m, 2H), 3.71 (d, *J* = 1.2 Hz, 3H), 2.94 (d, *J* = 5.6 Hz, 2H), 2.15 (s, 3H), 1.23 – 1.18 (m, 3H).

EFD0225-01 1.07 mmol scale (0.2217 g imine); 50 mol % catalyst (0.1106 g L-proline). 10 min. pre-stirring of L-proline in acetone. Drying agent: $MgSO_4$. Rotovapped at high heat (~50ºC). Crude yield of 0.1142 g (40.24% by mass). Crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.60 (m, 4H), 4.32 – 4.29 (m, 1H), 4.24 – 4.20 (m, 2H), 3.76 (s, 3H), 2.94 (d, *J* = 5.6 Hz, 2H), 2.16 (s, 3H), 1.23 (t, *J* = 1.9 Hz, 3H). Purified by flash column (mobile phase: ~200 mL 45% EtOAc in hexanes, followed by ~100 mL pure methanol, followed by ~50 mL DCM). Recovered products were assessed by ^{1}H NMR (**EFD0226-01, EFD0226-02**), then the latter was triturated in an

attempt to purify it further. Both the filtrate (**EFD0227-02**) and the solid (**EFD0227-01**) showed some evidence of product, but neither was substantial in quantity or purity.

EFD0226-01 ^{1}H NMR (400 MHz, CHLOROFORM-*D*) δ 6.97 – 6.81 (m, 4H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.07 – 4.00 (m, 2H), 3.78 (d, *J* = 4.3 Hz, 3H), 2.96 – 2.89 (m, 2H), 2.19 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H).

EFD0226-02 ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.81 (m, 4H), 4.43 – 4.38 (m, 3H), 4.20 (d, *J* = 8.2 Hz, 2H), 3.77 (s, 3H), 2.93 (d, *J* = 8.5 Hz, 2H), 2.16 (s, 3H), 1.28 – 1.22 (m, 3H).

EFD0227-01 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.79 (m, 4H), 4.26 (d, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 2.03 (d, *J* = 4.1 Hz, 3H), 1.23 (s, 3H).

EFD0227-02 ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 – 6.77 (m, 4H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.99 (d, *J* = 4.6 Hz, 2H), 2.24 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H).

Mannich Reaction with acetophenone (5).[22] In a 50 mL round bottom flask, ethyl glyoxylate (0.5 mL, 2.4 mmol, 50% in toluene) was added to 20 mL DCM. p-Anisidine (0.2900 g, 2.4 mmol) and around magnesium sulfate (~2 g) were added, and the reaction was stirred at room temperature for 4 hours. TLC (50% ethyl acetate in hexanes) showed product formation with some remaining reactant. The reaction mixture was vacuum filtrated, and the filtrate was returned to a 50 mL round bottom flask. Acetophenone (0.30 mL, 2.6 mmol) was added, and the reaction was stirred for 20 hours. Crude yield of 0.6894 g (87.74 %, **EFD0219-01**). Crude: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 2H), 7.56 – 7.51 (m, 1H), 7.36 – 7.32 (m, 2H), 6.93 – 6.63 (m, 4H), 4.38 (t, *J* = 6.9 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). Purification was attempted, but no product was recovered from column.

Mannich Reaction with 2'-acetonaphthone (6).[22] **EFD0220-01** was vacuum filtrated, and 2'-acetonaphthone (0.4461 g, 2.6 mmol) was added to the filtrate and stirred for 26 hours. The product was concentrated in vacuo (thin yellow oil). Crude yield of 0.3660 g (37.30 % yield, **EFD0220-02)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.01 – 7.87 (m, 4H), 7.57 – 7.48 (m, 3H), 6.91 – 6.84 (m, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 1H), 1.35 (t, *J* = 7.2 Hz, 2H).

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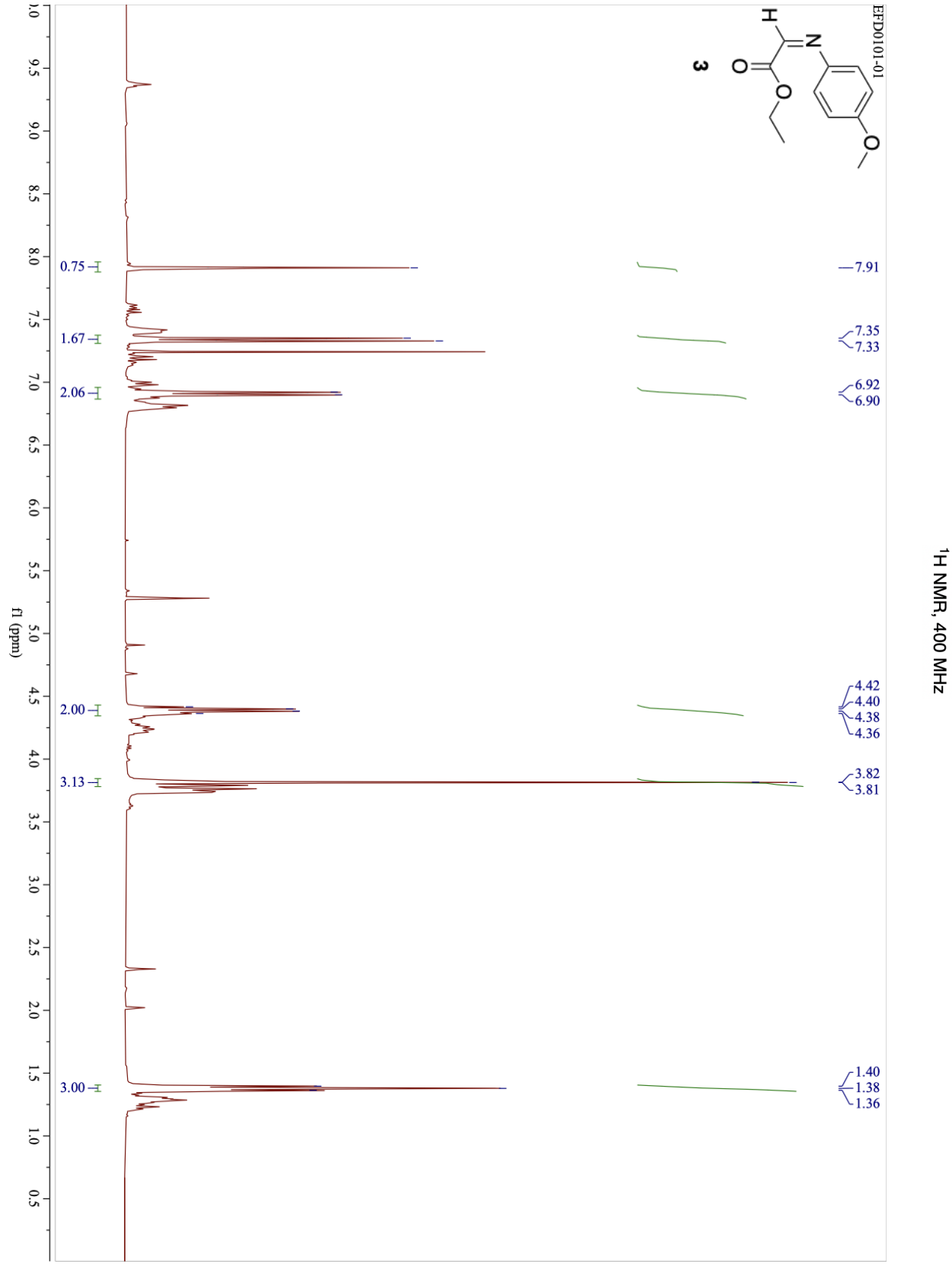
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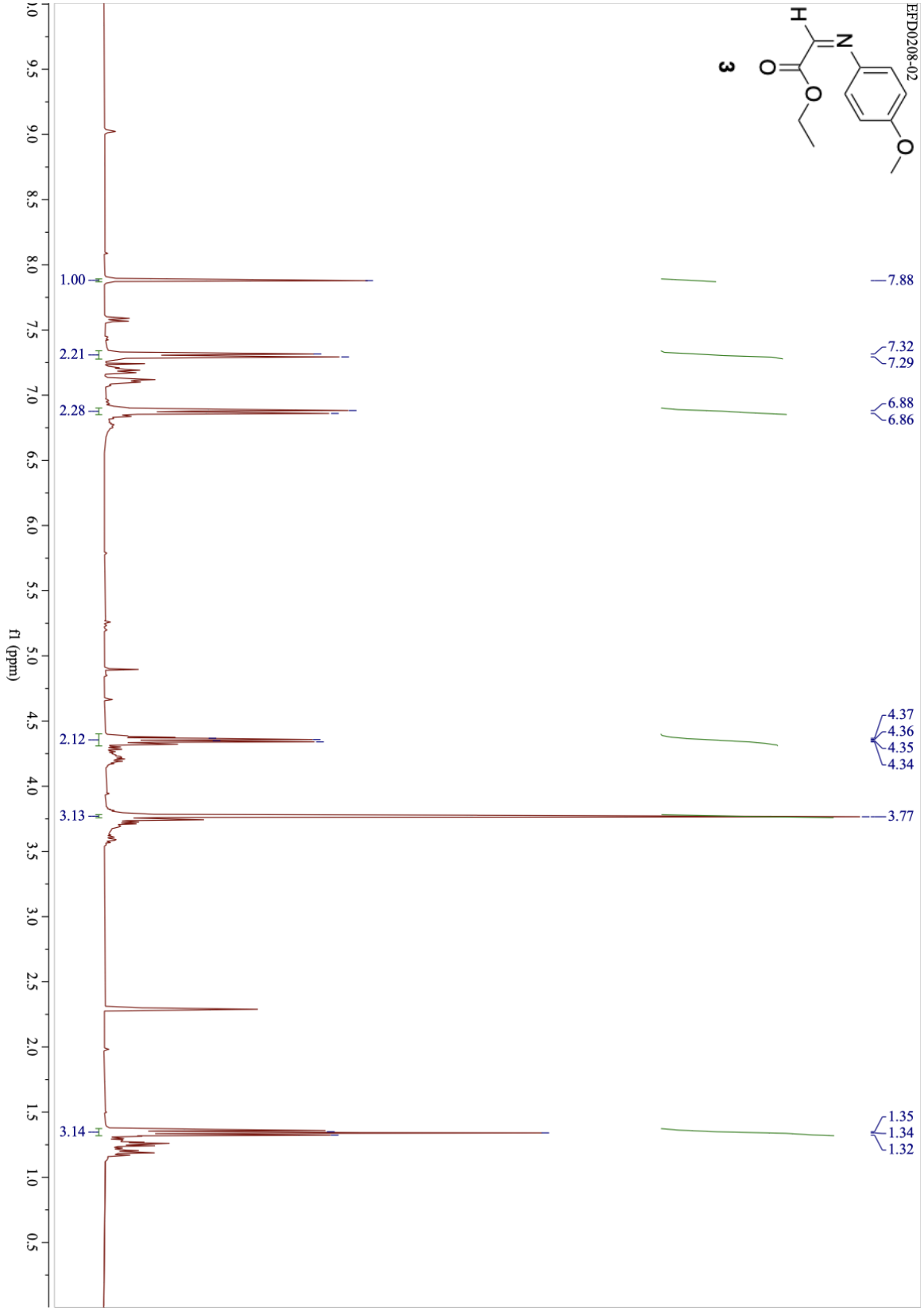
Supporting Materials

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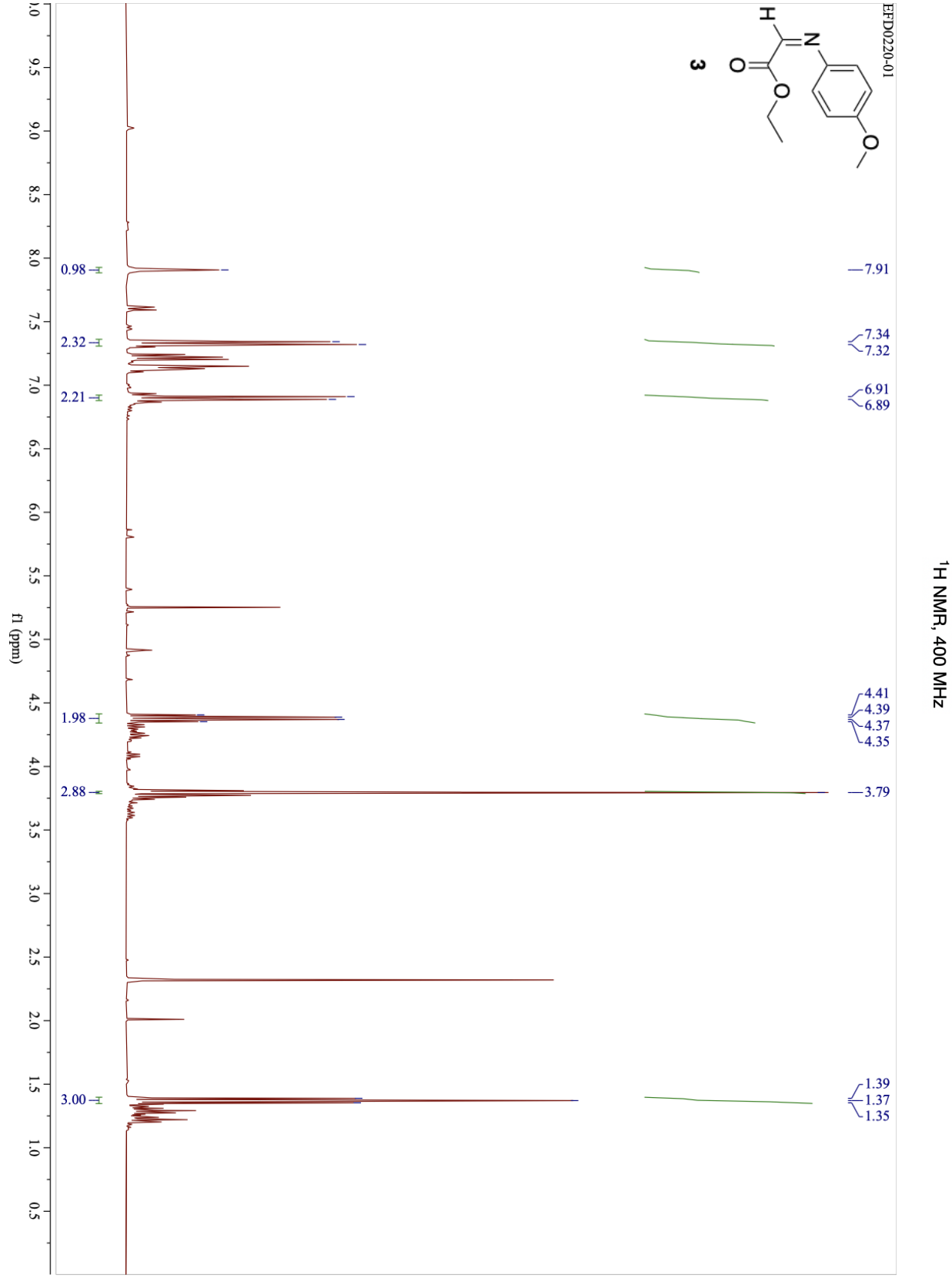
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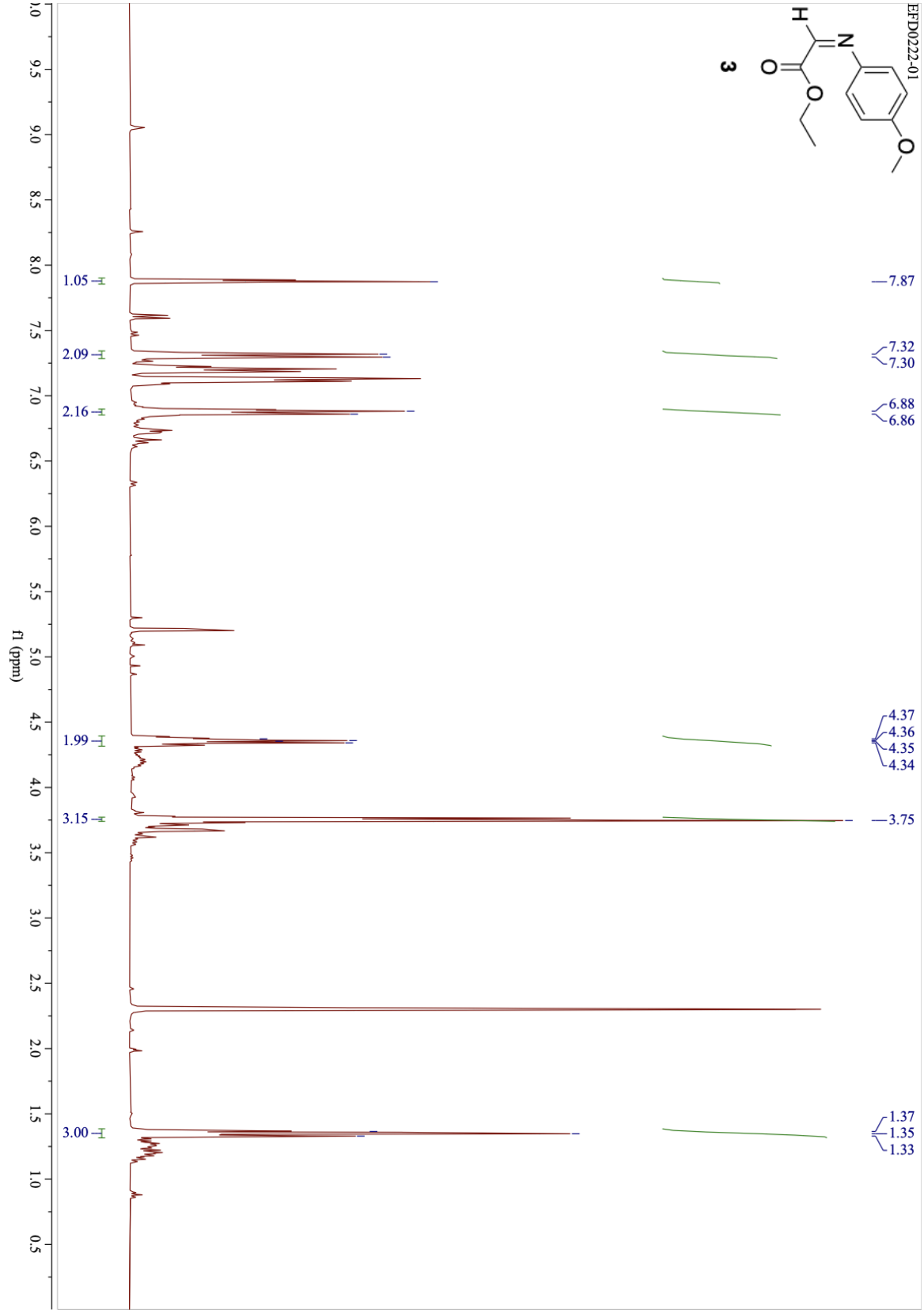


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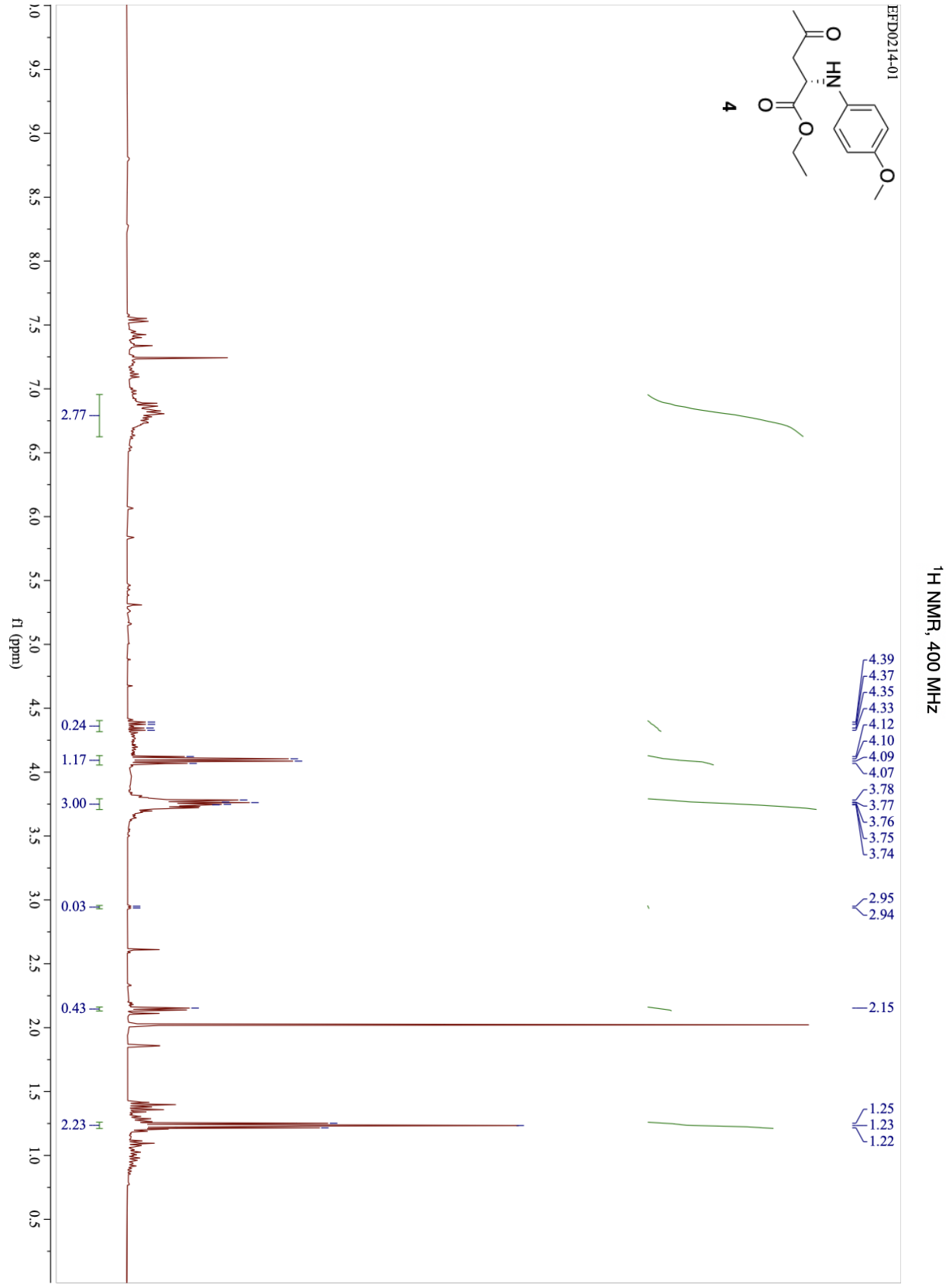

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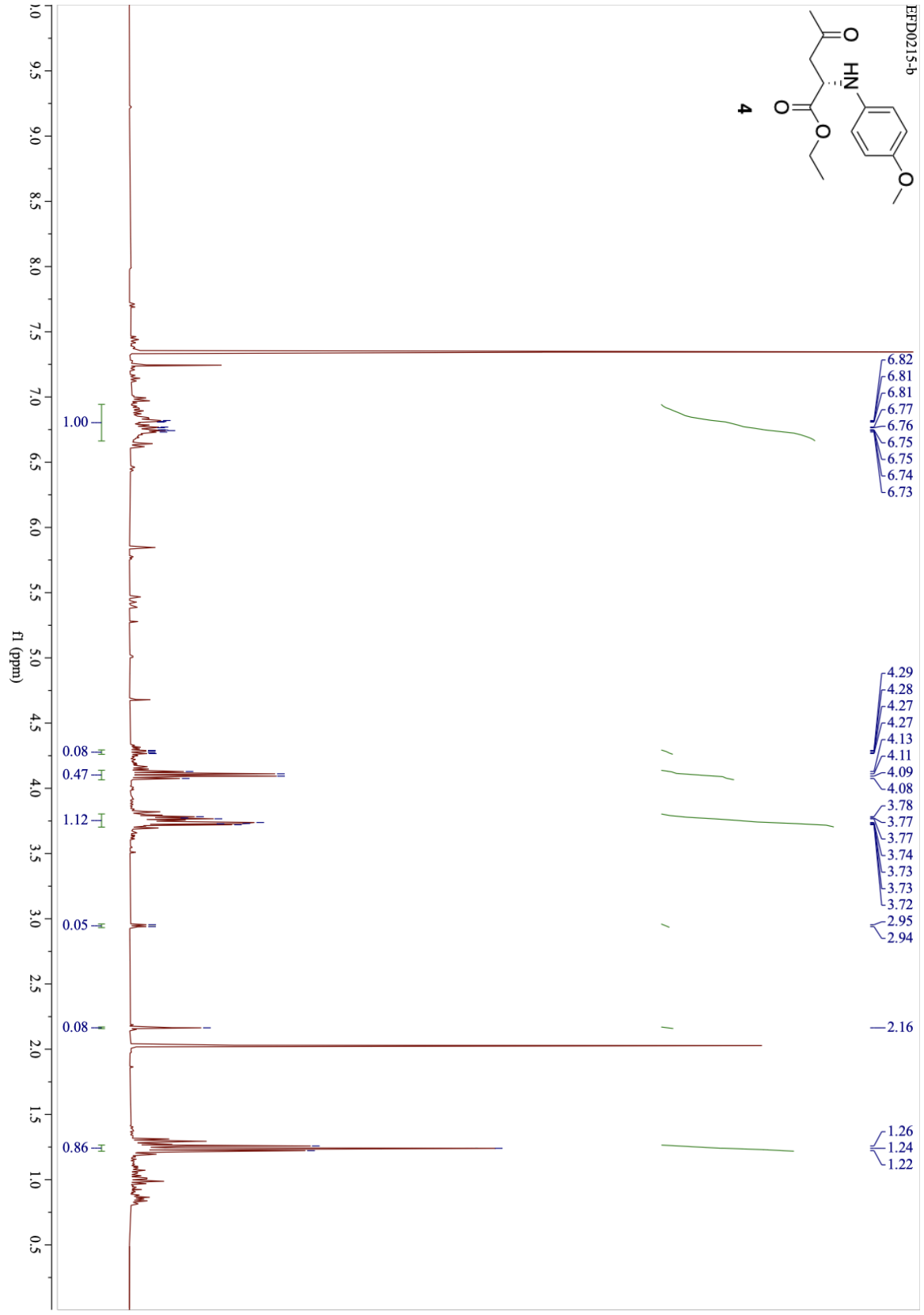


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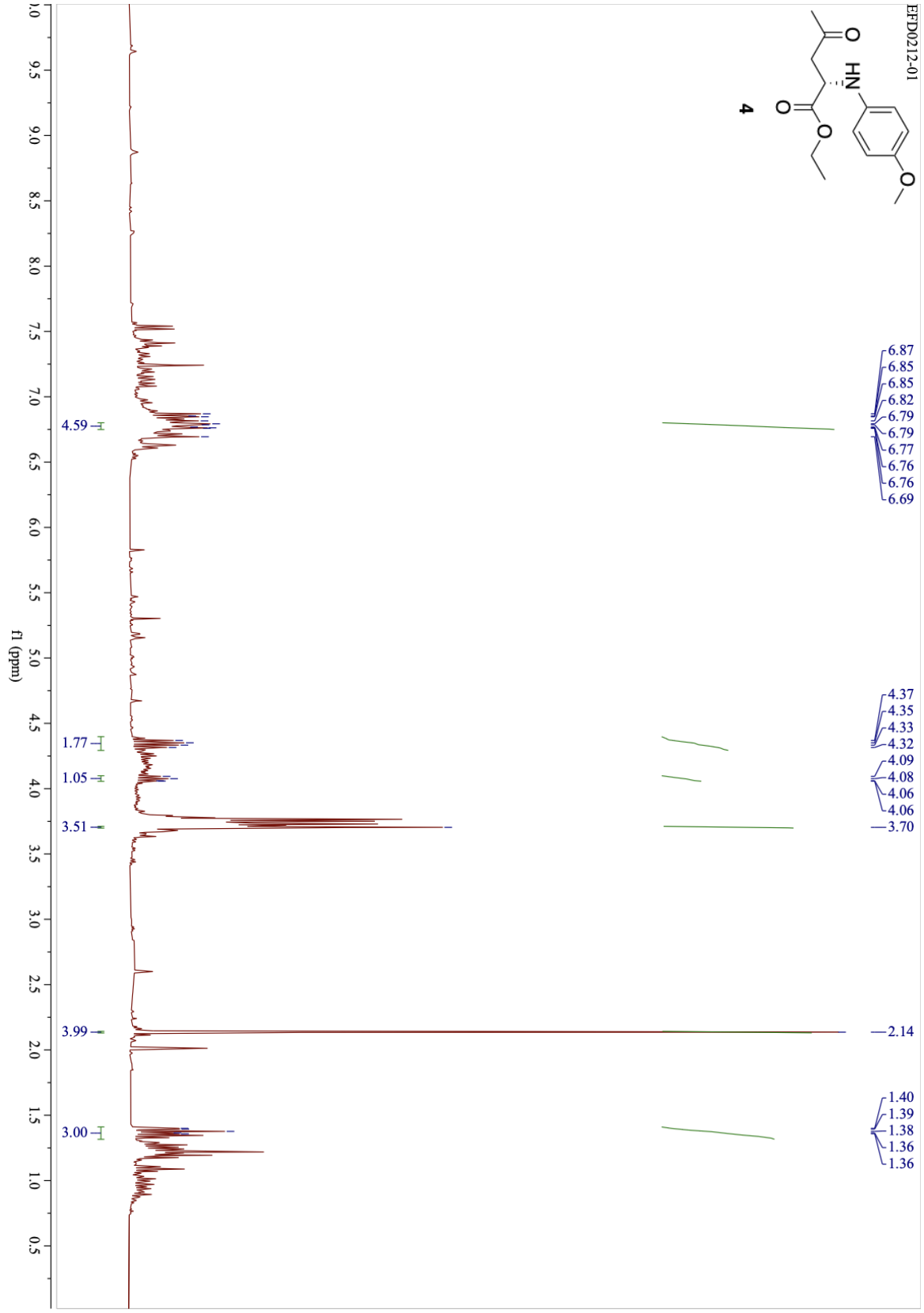

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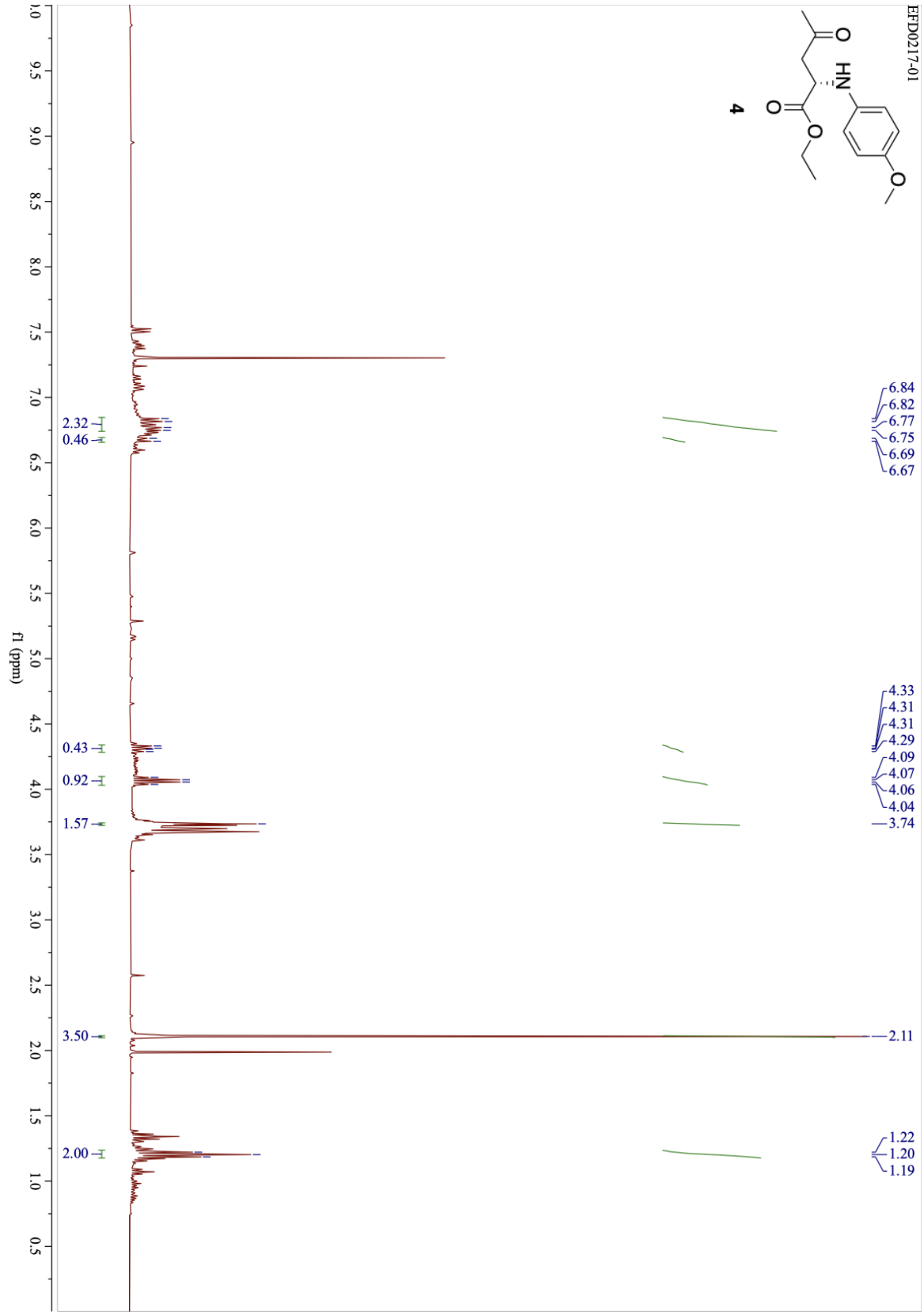
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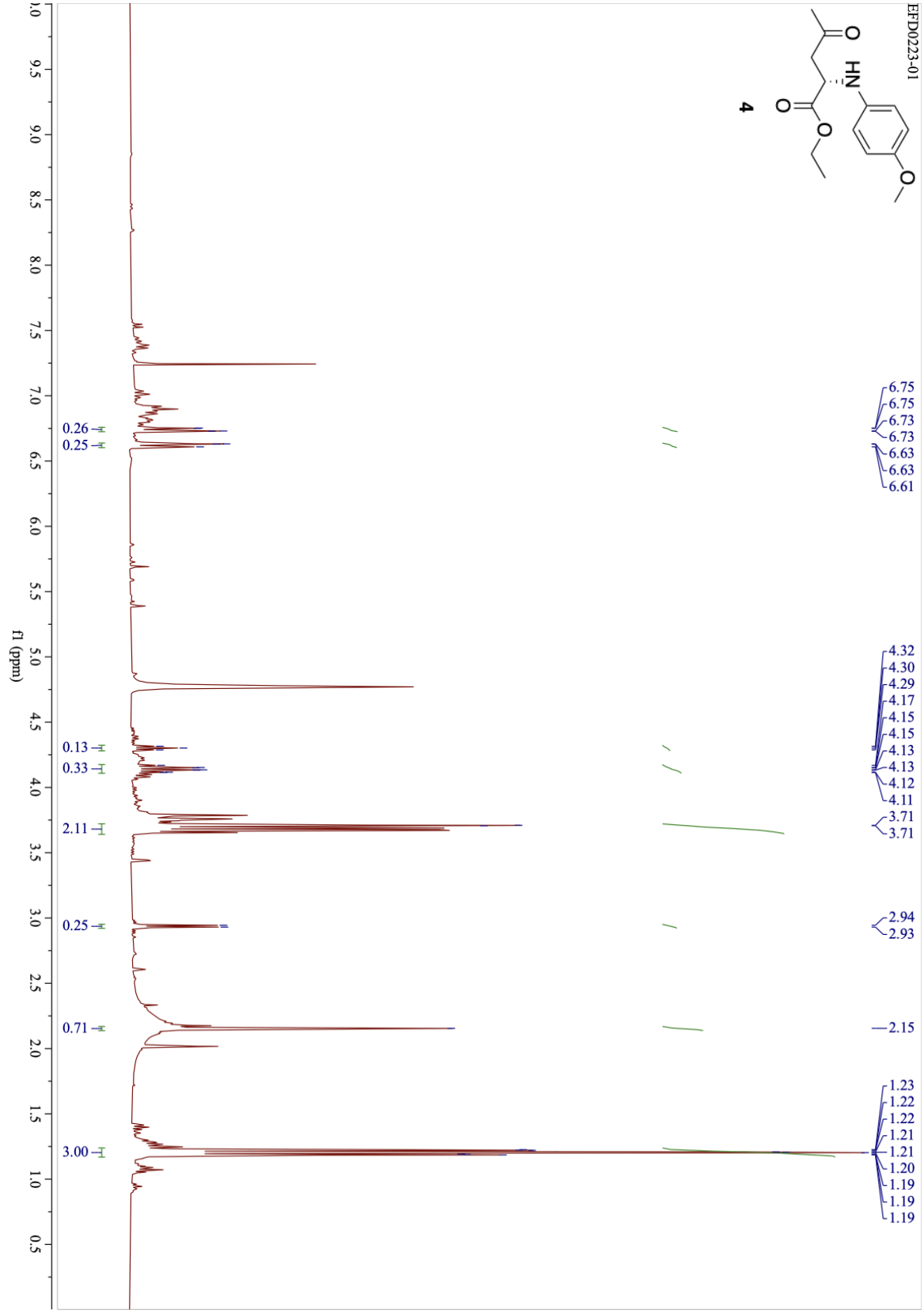
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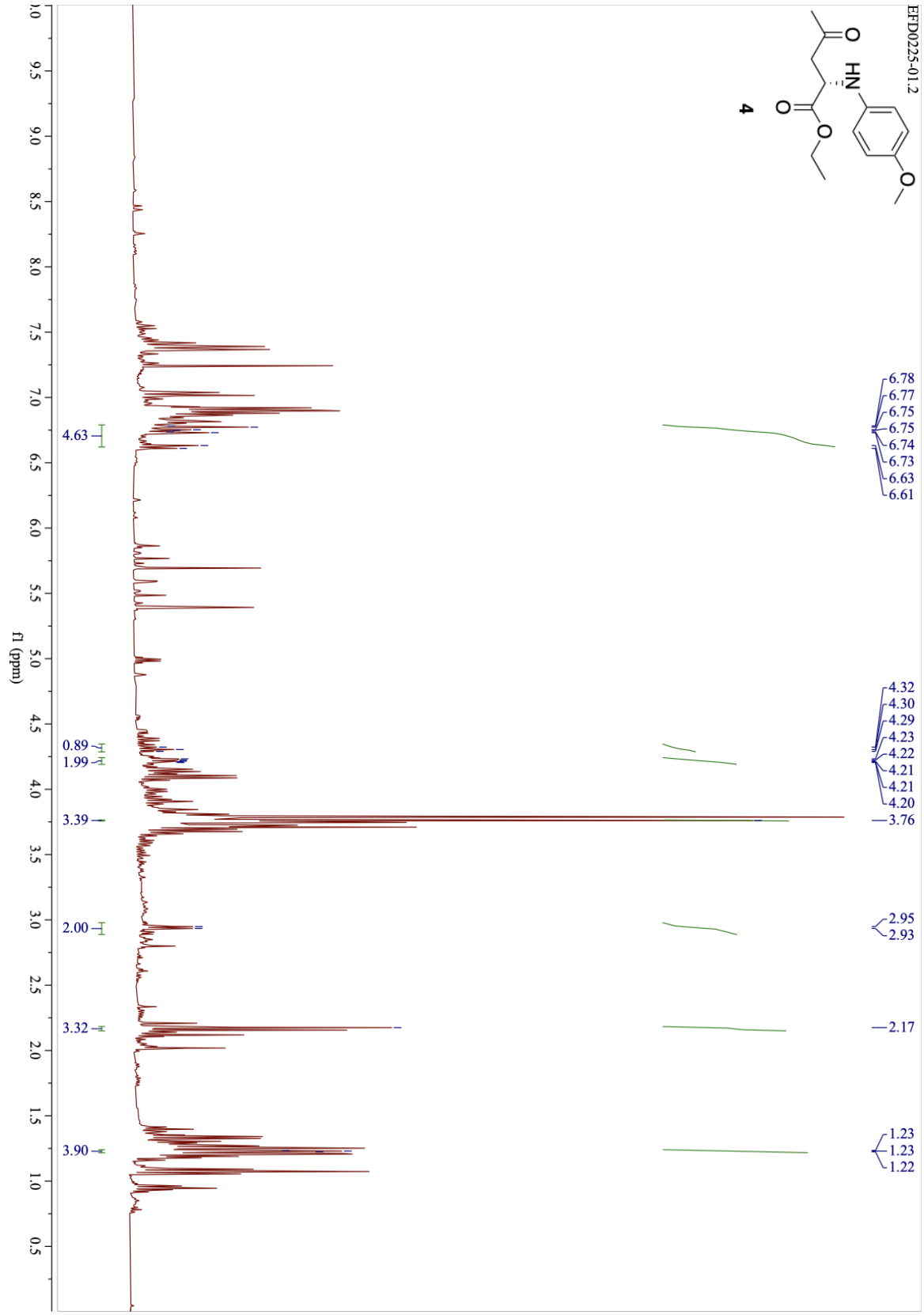
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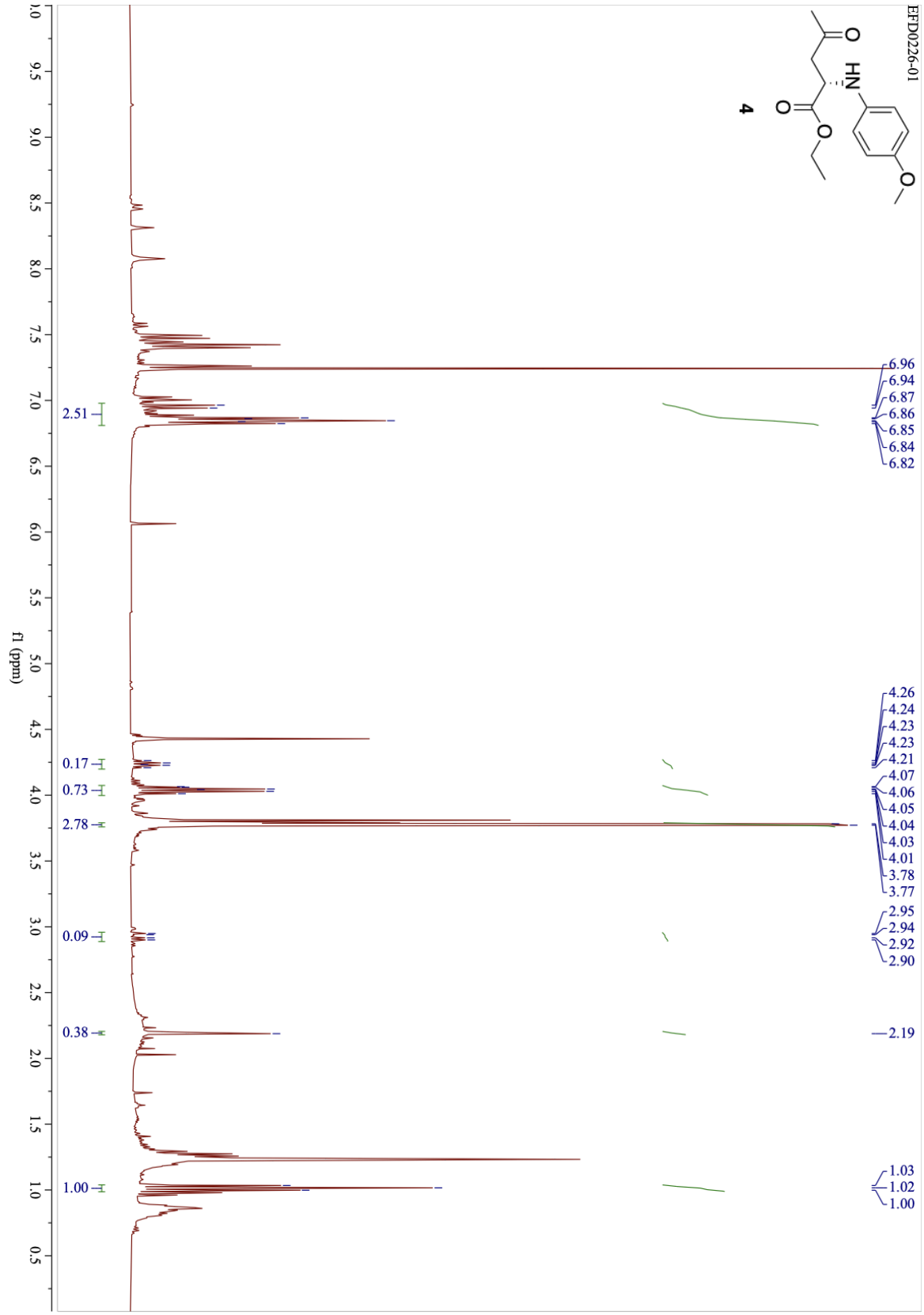


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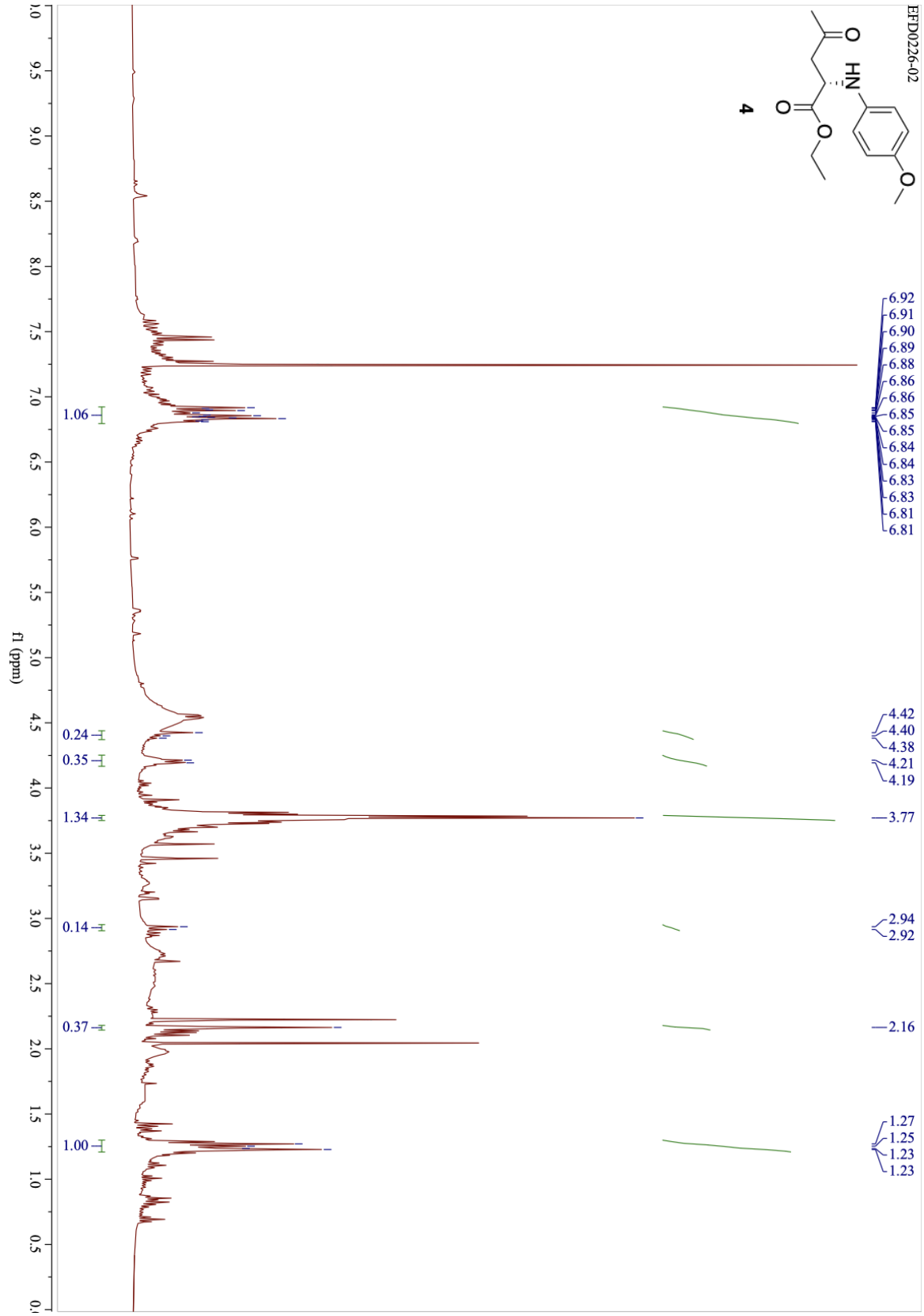

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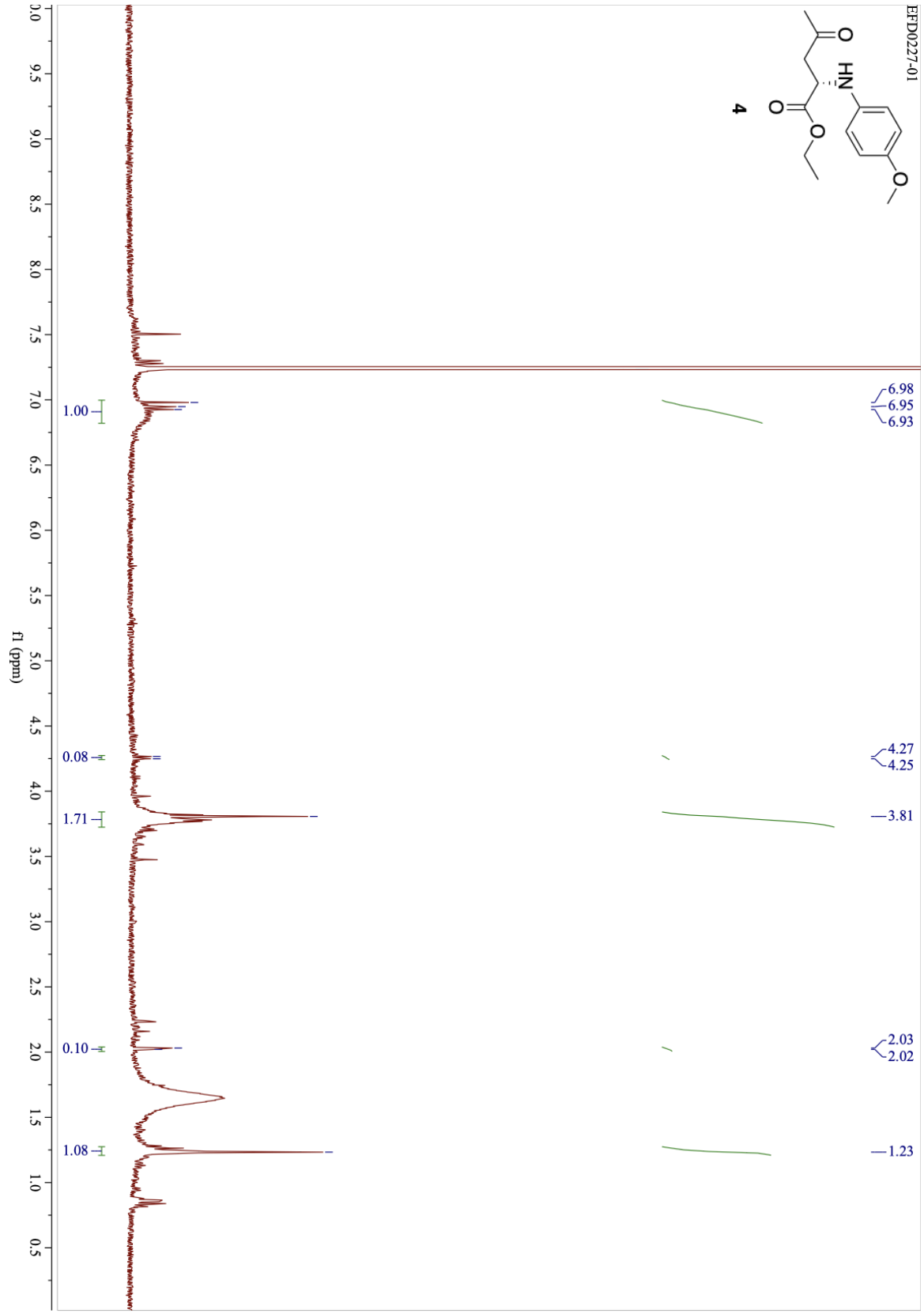


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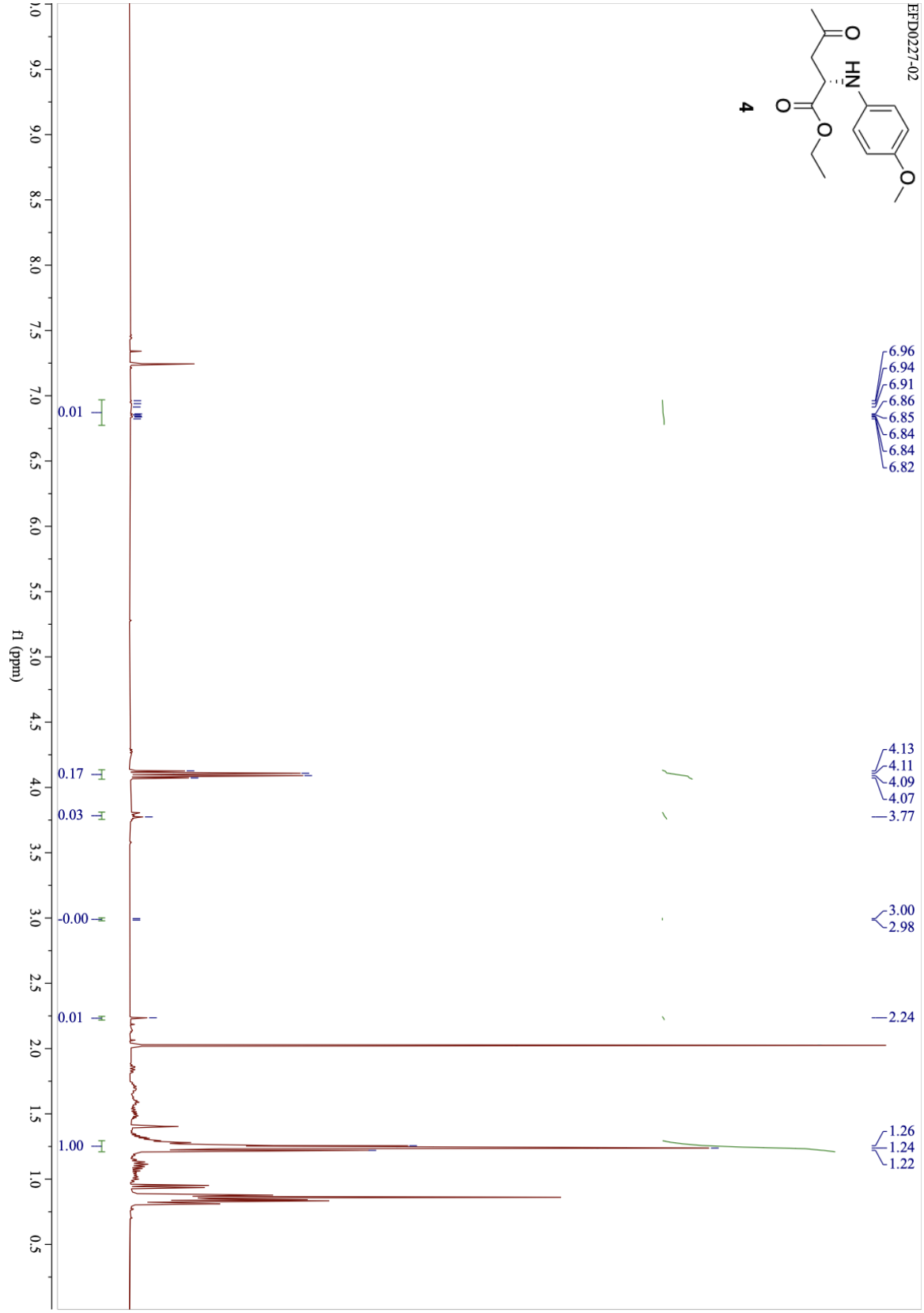
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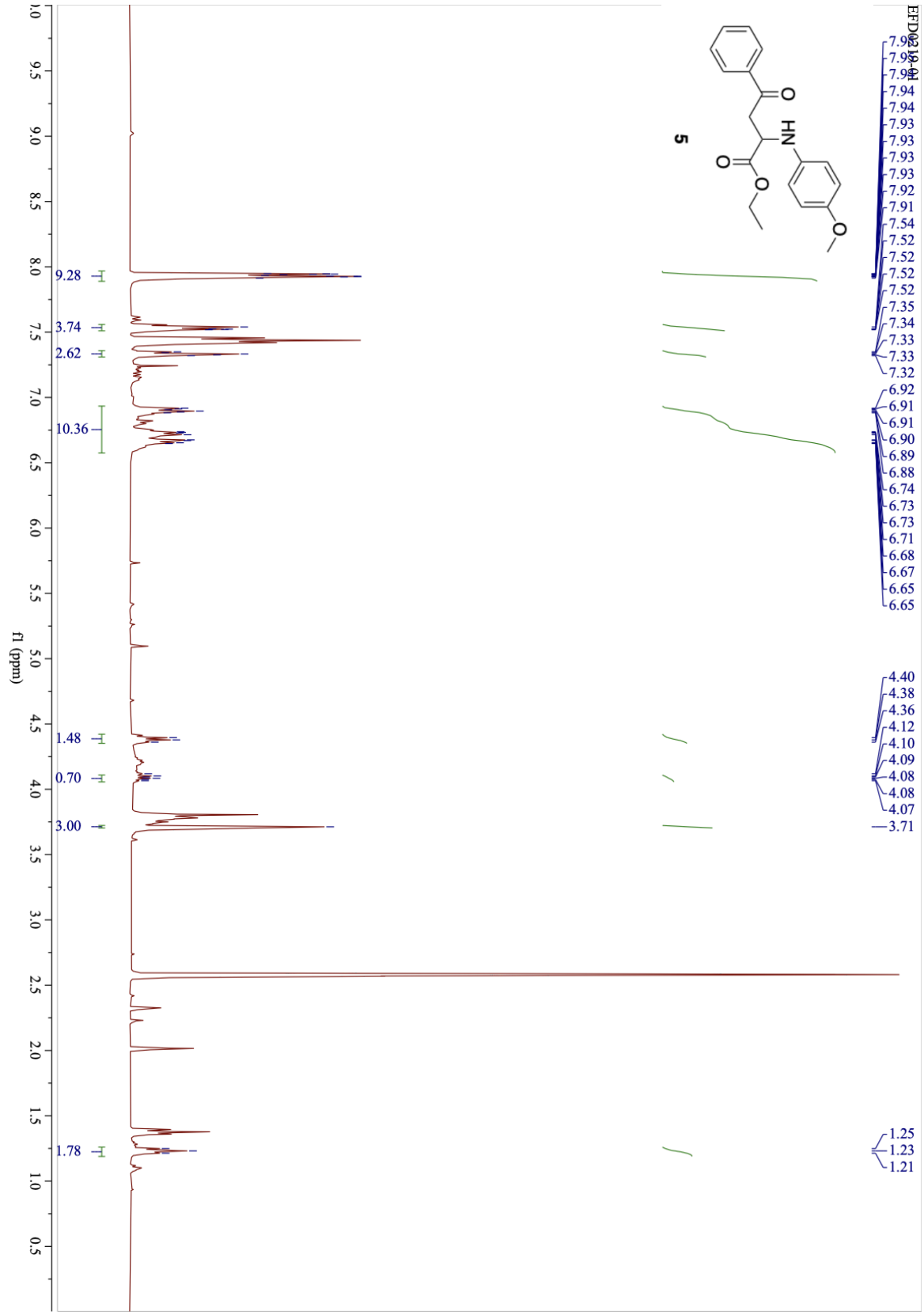
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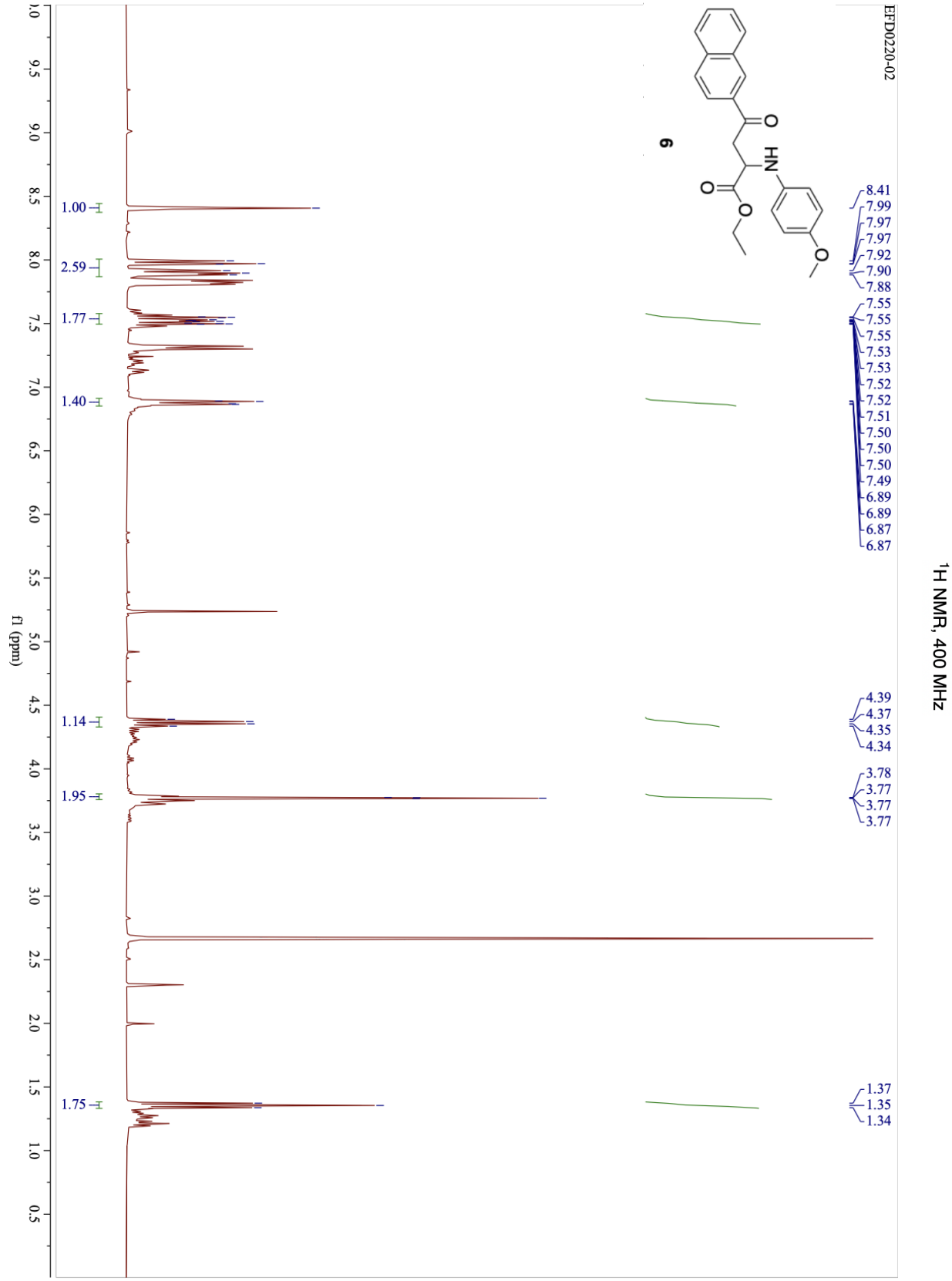

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3.77
3.00
2.98
2.24
1.26
1.24
1.22
^{1}H NMR, 400 MHz

EFD0219-01



^{1}H NMR, 400 MHz

EFD0220-02


EFD0220-02
6
8.41
7.99
7.97
7.97
7.92
7.90
7.88
7.55
7.55
7.55
7.53
7.53
7.52
7.52
7.51
7.50
7.50
7.50
7.49
6.89
6.89
6.87
6.87
4.39
4.37
4.35
4.34
3.78
3.77
3.77
3.77
1.37
1.35
1.34
1.00
2.59
1.77
1.40
1.14
1.95
1.75
f1 (ppm)
1H NMR, 400 MHz