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Synthesis of Aromatic Fluorinated Ketones for Evaluation at the GABA Receptor

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SYNTHESIS OF AROMATIC FLUORINATED KETONES FOR EVALUATION AT THE GABA RECEPTOR

By

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ABSTRACT

MADELINE GRIFFIN: Synthesis of Aromatic Fluorinated Ketones for Evaluation at the GABA Receptor

(Under the direction of David A. Colby)

GABA is a neurotransmitter that inhibits the excitation of neurons. Targeting this specific receptor has the potential to inhibit the central nervous system and possibly treat addiction, anxiety, or mood disorders. Previous research has shown that fluorinated ketones can have valuable applications in the medicinal chemistry of addiction. Some fluorinated ketones have shown activity at the GABA receptor. The main goal of this project was to synthesize aromatic fluorinated ketones for biological evaluation at the $GABA_B$ receptor. Another goal was to compare both the monofluorinated and difluorinated analogues synthesized in order to quantify differences in activity from fluorination state. New fluorinated agonists for the $GABA_B$ receptor present potential for pharmacological development because of the distinct structure in comparison to other GABA analogues. These compounds may assist in overcoming some of the current limitations in drug discovery at the $GABA_B$ receptor and are to be submitted for biological evaluation.

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LIST OF ABBREVIATIONS

GABA	γ-aminobutyric acid
GPCR	G-protein coupled receptor
CNS	central nervous system
Ser	serine
Tyr	tyrosine
Asp	aspartic acid
TLC	thin layer chromatography
NMR	nuclear magnetic resonance
LiBr	lithium bromide
THF	tetrahydrofuran
Et_3N	triethylamine
NH_4Cl	ammonium chloride
EtOAc	ethyl acetate
Na_2SO_4	sodium sulfate

1. Introduction

1.1 *Neurotransmitter Signaling within the Central Nervous System*

The central nervous system in the human body is composed of the brain and the spinal cord. Within the brain, there are chemical compounds known as neurotransmitters. The brain uses neurotransmitters as chemical messengers to communicate throughout the nervous system and between individual brain cells, or neurons. The small distance between two individual neurons is known as the synapse or synaptic cleft. The first neuron that releases a neurotransmitter into the synaptic cleft is referred to as the presynaptic neuron. After it is released, a neurotransmitter can either be received by another neuron, taken back up into the presynaptic neuron, or broken down within the cleft. The neuron that receives the chemical messenger is referred to as the postsynaptic neuron.

The postsynaptic neuron contains receptors for various messengers. When a neurotransmitter binds to a receptor, the receptor is activated leading to increased or reduced transmission of a particular signal. Excitatory neurotransmitters activate receptors to continue or increase signals, while inhibitory neurotransmitters activate receptors to decrease or cease signals from firing. The balance of inhibitory and excitatory signals within the brain is a major intrinsic regulatory mechanism for numerous physiological processes.

1.2 *The Role of GABA in the Body*

GABA stands for γ-aminobutyric acid (Figure 1). GABA is the primary inhibitory neurotransmitter. Inhibitory neurotransmitters can stop an action potential from depolarizing a postsynaptic neuron and can also inhibit the release of other excitatory neurotransmitters such as dopamine, serotonin, noradrenaline, and acetylcholine. The main function of GABA is to regulate the excitation of neurons and release of other neurotransmitters.[1]

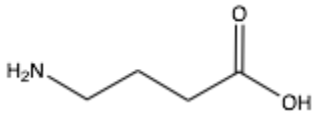


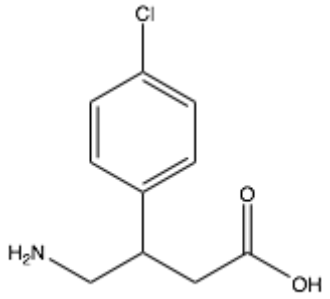
Figure 1 Structure of GABA

GABA has two main receptors, $GABA_A$ and $GABA_B$. These two receptors are structurally and functionally unique. The $GABA_A$ receptor is an ionotropic receptor, or an ion channel-linked receptor. When the receptor is activated, the ion channel opens and there is an influx of chloride ions into the cell, causing the cell to become hyperpolarized and leading to reduced transmission of the signal. The $GABA_B$ receptor is a metabotropic receptor, or G-protein coupled receptor. G-protein coupled receptors, or GPCRs, can inhibit the release of many neurotransmitters. These receptors inhibit the activation of calcium (Ca^{2+}) voltage-gated ion channels via a G-protein dependent process, inhibit adenylyl cyclase activity, and act on potassium (K+) channels.[2] Most GABA-related pharmaceuticals target specifically the $GABA_A$ receptor, while there are few that are selective to the $GABA_B$ receptor except for baclofen (Figure 2), a commonly used muscle relaxant.[2]

1.3 *Addiction Epidemic and Potential Treatment Strategies*

Addiction is a complex disease state that affects millions of lives across the world. With that fact and the recent opioid crisis in the United States, there is a push to find new treatment options for those that are suffering. One reason that the research conducted in this project focuses on the GABA receptor is to exploit the major inhibitory effects that accompany GABA in the CNS. By developing agonists, or substances that activate a receptor and increase the activity of that receptor, there is potential to reduce anxiety in patients that are suffering from addiction as well as cravings and symptoms of withdrawal.

Some GABA agonists have been investigated for use in the treatment of addiction, alcoholism, and addiction-related processes such as anxiety, pain, and depression.[3] The FDA approved drug, baclofen, which is also a $GABA_B$ agonist, has been used "off-label" for the treatment of opioid addiction.[4,5] Baclofen, however, is not considered an ideal drug due to poor therapeutic qualities, including a narrow therapeutic window, low brain accumulation, quick metabolism, and rapid development of drug tolerance.[8] This project focuses on developing novel agonists selective to the $GABA_B$ receptor that will overcome some of the existing deficiencies of baclofen. One way that has been proven to improve drug characteristics is the addition of a fluorine atom.[6]



baclofen

Figure 2 Structure of baclofen

1.4 *Benefits of Fluorine Addition in Pharmaceuticals*

The addition of a fluorine atom in pharmaceuticals is growing due to its beneficial effects. Around 25% of drugs on the market are fluorinated. Fluorine is a unique atom because it has a high ionization energy, or the kinetic energy it takes to remove an electron from the outermost orbital of a fluorine atom, proving its tendency to remain stable. It also is the most electronegative atom on the periodic table.

Drugs must proceed through all phases of pharmacokinetics, including absorption, distribution, metabolism, and excretion. Compounds that contain fluorine have been shown to have higher efficacy to receptors and improved lipophilicity, making it easier to diffuse through the nonpolar lipid membranes of cells to exhibit the desired response. This leads to an increase in molecular absorption. A drug with improved characteristics and lipophilicity can increase the bioavailability of the drug.

2. Results and Discussion

2.1 *Synthesis of Aromatic Difluorinated Ketones*

Agonists bind to receptors through physical and chemical interactions. Developing new agonists to a receptor involves some knowledge of how that receptor binds to endogenous and/or synthetic compounds. An "active-site" is the part of a receptor that interacts with a molecule or ligand. The $GABA_B$ receptor has three known active-sites that are amino acid residues. These residues, Ser246, Tyr366, and Asp471, have shown binding activity with baclofen.[7]

Specifically, the interaction of the carboxylate in baclofen and the Ser246 residue presented promise for the conformation of α-fluorinated ketones to successfully interact with the $GABA_B$ receptor. The discovery of a novel method to synthesize α,α-difluorinated ketones was a driving force for evaluation of these specific ketones as agonists to $GABA_B$. A desirable property of α,α-difluorinated, or difluoromethyl, ketones includes the ability to convert to a hydrate, or gem diol, in water due the presence of the two electron-withdrawing fluorine atoms, which in turn changes the three-dimensional conformation and increases the aqueous solubility of the compound.[7] Previous investigations into difluoromethyl ketones as $GABA_B$ agonists have shown implications of the ketones in serving as potent agonists of $GABA_B$ with selectivity over $GABA_A$.[7] A selection of three difluoromethyl ketones paired from three unique aldehydes (Figure 3) were synthesized in this project using a novel method for trifluoroacetate release and subsequent aldol addition.

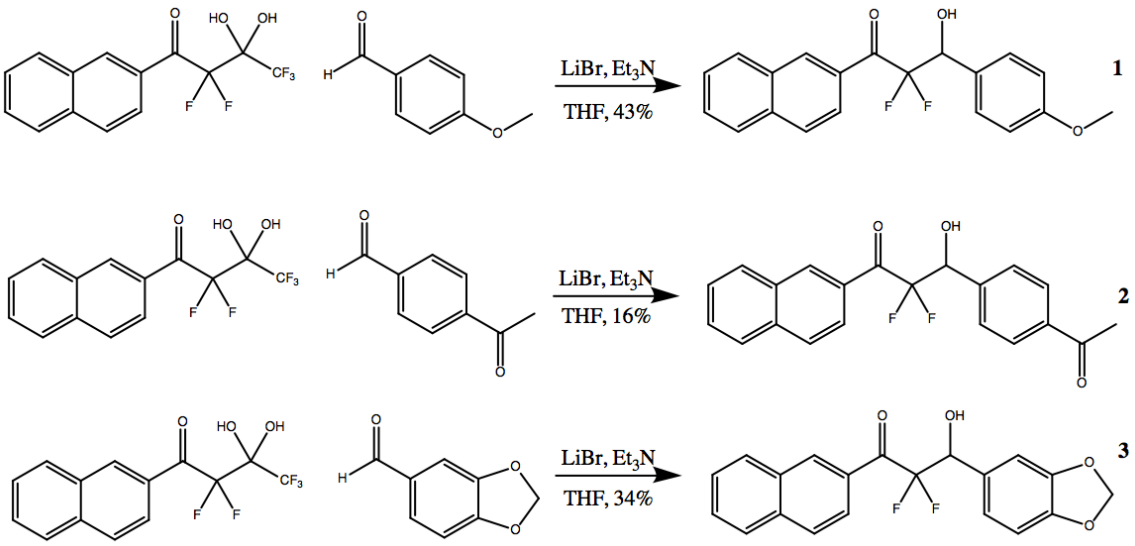
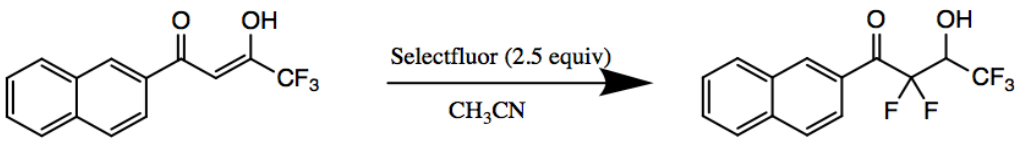


Figure 3 Synthesis of aromatic difluorinated ketones

The novel method of synthesis using trifluoroacetate release, discovered in the Colby laboratory, uses a commercially available starting material, a type of 1,1,1-trifluoro-2,4-dione, existing in the enol form.[8] The dione used for this project was (*Z*)-4,4,4-trifluoro-3-hydroxy-1-(naphthalen-2-yl)-but-2-en-1-one and was reacted with a fluorinating agent, Selectfluor, under anhydrous conditions to yield the desired α,α-di-fluorinated ketone (Figure 4). This reaction used mild conditions and is applicable with many substrates.[8] This project capitalized on this synthetic method to use the generated ketone (2,2,4,4,4,-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one) as a scaffold to produce unique ketones with varying aromatic functional groups by aldol reactions. The products were analyzed and yield values were obtained and reported (see experimental details).



(Z)-4,4,4-trifluoro-3-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one

2,2,4,4,4-pentafluoro-3-hydroxy-1-(naphthalen-2-yl)butan-1-one

Figure 4 Fluorination of starting material

2.2 *Synthesis of Aromatic Monofluorinated Ketones*

This project also produced the monofluorinated analogues for side-by-side comparison to each of the aromatic difluorinated ketones at the $GABA_B$ receptor. Synthesizing the monofluorinated ketones involved similar reaction methods and the same three aldehydes. In order to produce the scaffold (2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one) for monofluorinated ketones, the reaction was run with Selectfluor in the presence of water, rather than under anhydrous conditions stated previously (Figure 5). These reactions also needed a lower temperature in order to react successfully rather than room temperature for the difluorinated counterparts. Also, the monofluorinated reaction using 4-acetylbenzaldehyde, was purified with a preparative TLC plate after failing to purify using flash chromatography. The yield for compound 4 and its ^{1}H NMR spectra were not obtained for this report due to the restrictions on laboratory access after COVID-19 pandemic in the spring of 2020.

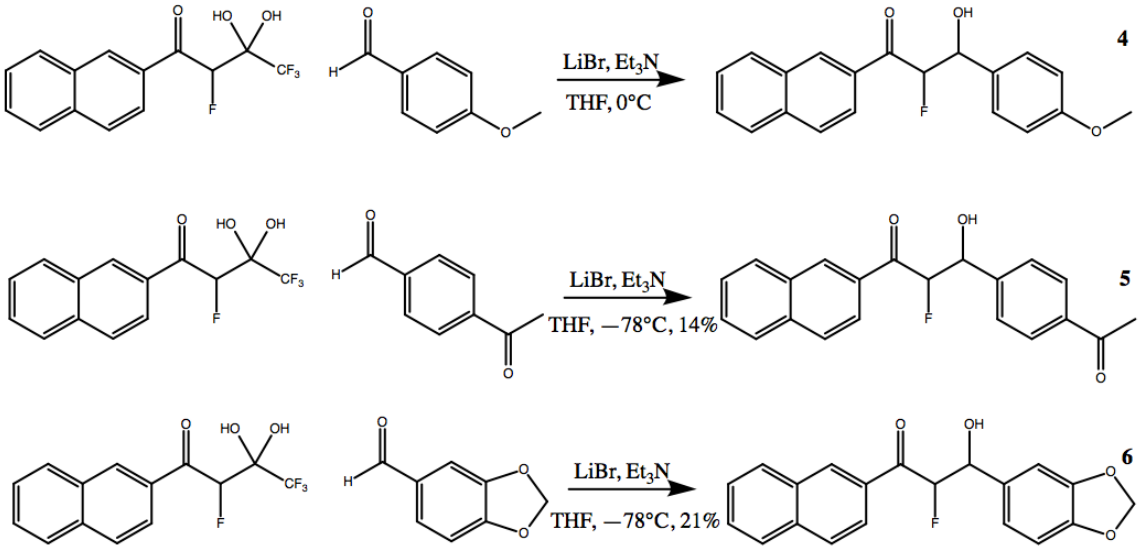


Figure 5 Synthesis of monofluorinated ketones

2.3 *Compound Analysis and Purification Methods*

To purify the compounds produced in this project, the main procedure used was silica flash chromatography, or column purification. For this method, a solvent system is chosen that will be able to load the product onto silica and separate the desired compound from impurities or side products. The idea of column purification is that the different compounds present in the crude mixture will separate in the solvent system, move through the silica, and flow out of the gel at different rates according to the polarity of each compound in the mixture. The solvent system used in previous literature helped set a baseline for solvent system testing. To help pick a solvent system that would work best for each specific product, thin layer chromatography or TLC plates were used. The crude compound was spotted onto a TLC plate and placed in a small amount of solvent system. The plate was later analyzed to see which solvent system had the best separation of product.

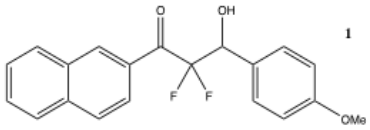
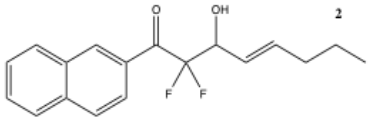
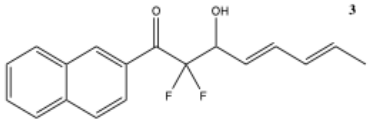
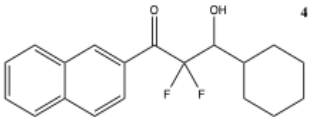
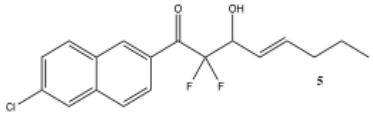
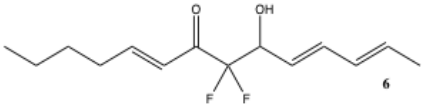
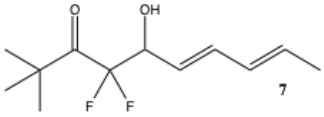
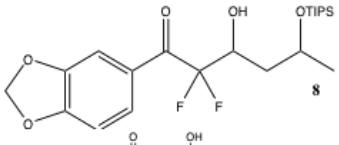
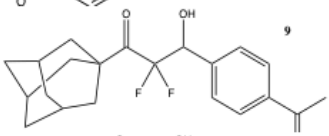
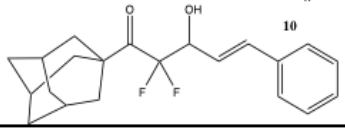
To analyze the structure of the product, nuclear magnetic resonance imaging was used. Both proton and fluorine NMR spectra were taken for each product. Spectra were analyzed in order to deduce the structure of the products of each reaction by using key expected peaks as well as to visualize if any side products or impurities were still present in the product mixture. Fluorine NMR was especially important in order to ensure monofluorination instead of difluorination of the products. Purity and confirmation of structure are both important to document prior to the acquisition of biological data for the compounds. Some NMR spectra collected may be inclusive on the complete purity of compounds found in the product, as well as the presence of both fluorinations in the same mixture. Also, racemic mixtures were not separated as a part of this project.

2.4 *Future Biological Analysis*

The molecules synthesized in this project are to be submitted for biological evaluation at the $GABA_B$ receptor for activity and potency similar to previously investigated difluoromethyl ketones. Prior research into the evaluation of difluoromethyl ketones, baclofen, and GABA was performed to quantify activity as agonists at both the $GABA_B$ and $GABA_A$ receptors (Table 1).[7] Dose response curves and EC_{50} values, which measure compound potency, were obtained in previous studies. The ketones were found to be agonists at the GABA receptor, with less potency than GABA and baclofen, but were selective to $GABA_B$ over $GABA_A$.

Other data gathered included behavioral rodent assays. These assays tested plain acoustic startle and fear-potentiated startle and can be a measure of the potential for a compound to progress into a drug that can treat an anxiety disorder, including those effects associated with addiction.[7] Later, data will be quantified in order to compare activities and differentiate potency between monofluorination and difluorination. No data has been received of the compounds synthesized in this project at this time.

Table 1 $GABA_B$ and $GABA_A$ Assay Data

Compound	*$GABA_B$ EC_{50} (μM)*[a]	*$GABA_A$ EC_{50} (μM)*[a]
baclofen	1.7 ± 0.10	>100
Rac-BHFF	1.9 ± 0.90	>100
GABA	0.53 ± 0.33	2.30 ± 0.59
	61.8 ± 3.01	>100
	66.9 ± 1.19	>100
	99.3 ± 3.78	>100
	53.5 ± 1.76	>100
	>100	nd
	>100	nd
	>100	nd
	>100	nd
	24.9 ± 1.30	>100
	40.0 ± 3.59	>100

Source: Han, C.; Salyer, A.E.; Kim, E. H.; Jiang, H.; Jarrard, R.E.; Powers, M.S.; Kirchoff, A.M.; Salvador, T.K.; Chester, J.A.; Hockerman, G.H.; Colby, D.A. Evaluation of Difluoromethyl Ketones as Agonists of the γ-Aminobutryic Acid Type B ($GABA_B$) Receptor. *Med. Chem*. **2013**, 56, 2456–2465

3. Conclusion

In conclusion, this project involved the synthesis of six aromatic fluorinated ketones. Three of the ketones were difluorinated, and the other three ketones were the monofluorinated analogue of each. Each compound was synthesized using trifluoroacetate release, purified by either silica flash chromatography or preparative TLC, and analyzed with nuclear magnetic resonance. All products will be sent for biological evaluation at the $GABA_B$ receptor, where potency will be measured as well as potency differentials between fluorinations.

4. Experimental Details

2,2,Difluoro-3-hydroxy-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)-propan-1-one, 1. Both LiBr (40.4 mg, 0.4650 mmol), and *p*-anisaldehyde (38.0 µL, 0.3122 mmol), were added to a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (50 mg, 0.16 mmol) dissolved in THF (1 mL). Et_3N (22.0 µL, 0.16 mmol) was added dropwise to the mixture, and the reaction was stirred for 3 min at rt. After 3 min, the reaction was quenched with NH_4Cl (3 mL). The resulting mixture was extracted with EtOAc (3 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (8.5:1.5 hexanes/EtOAc) was performed and afforded the product with 43% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 5H), 8.25 (d, J = 9.5 Hz, 2H), 8.03–7.86 (m, 12H), 7.66 (t, J = 20 Hz, 4H), 7.58 (t, J = 20 Hz, 4H), 7.46 (d, J = 20 Hz, 8H), 3.81 (s, 15H); ^{19}F NMR (500 MHz, $CDCl_3$) δ –105 (dd, J = 390 Hz, 1F), –116 (dd, J = 405 Hz, 1F).

3-(4-Acetylphenyl)-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)-propan-1-one, 2. Both LiBr (71.2 mg, 0.82 mmol), and 4-acetylbenzaldehyde (83.7 mg, 0.5652 mmol), were added to a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (90.5 mg, 0.283 mmol) dissolved in THF (1.8 mL). Et_3N (39.0 µL, 0.283 mmol) was added dropwise to the mixture, and the reaction was stirred for 24 hr at rt. After 24 hr, the reaction was quenched with NH_4Cl (6 mL). The resulting mixture was extracted with EtOAc (6 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (8:2 hexanes/EtOAc) was performed and afforded the product with 16% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ

8.66 (s, 1H), 8.07 (d, J = 10 Hz, 1H), 8.00 (d, J = 5 Hz, 2H), 7.95–7.88 (m, 3H), 7.66 (d, J = 10 Hz, 3H), 7.57 (t, J = 15 Hz, 1H), 5.54 (d, J = 15 Hz, 1H), 2.62 (s, 3H); ^{19} NMR (500 MHz, $CDCl_3$) δ –103 (d, J = 5 Hz, 1F), –104 (d, J = 5 Hz, 1F).

3-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)-propan-1-one, 3. Both LiBr (160 mg, 1.8 mmol), and benzo[*d*][1,3]dioxole-5-carbaldehyde (65.6 mg, 0.437 mmol), were added to a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (70.0 mg, 0.22 mmol) dissolved in THF (1.4 mL). Et_3N (30.5 µL, 0.22 mmol) was added dropwise to the mixture, and the reaction was stirred for 24 hr at rt. Next, the reaction was quenched with NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (6 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (7:3 hexanes/EtOAc) was performed and afforded the product with 34% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.06 (d, J = 10 Hz, 1H), 7.95–7.87 (m, 4H), 7.61 (dt, J = 50 Hz, 3H), 7.06 (s, 1H), 6.98 (d, J = 10 Hz, 1H), 6.83 (d, J = 10 Hz, 3H), 5.97 (d, J = 5 Hz, 3H), 5.35 (dt, J = 30 Hz, 2H), 3.07 (d, J = 5 Hz, 1H); ^{19}F NMR (500 MHz, $CDCl_3$) δ –105 (dd, J = 315 Hz, 1F), –116 (dd, J = 325 Hz, 1F).

2-Fluoro-3-hydroxy-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)-propan-1-one), 4. Both LiBr (97.5 mg, 1.12 mmol), and *p*-anisaldehyde (57.0 µL, 0.468 mmol), were added to a solution of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (100.0 mg, 0.312 mmol) dissolved in THF (2.0 mL). Et_3N (0.2 mL, 1.2 mmol) was added dropwise to the mixture, and the reaction was stirred for 24 hr at 0°C. Next, the reaction was quenched with NH_4Cl (5 mL) and washed with H_2O (5 mL). The resulting mixture

was extracted with EtOAc (5 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (7:3 hexanes/EtOAc) was performed and afforded the product with an *undetermined* yield: ^{19}F NMR (400 MHz, $CDCl_3$) δ –202 (dd, J = 1165 Hz, 1F).

3-(4-Acetylphenyl)-2-fluoro-3-hydroxy-1-(naphthalen-2-yl)-propan-1-one, 5. Both LiBr (97.5 mg, 1.123 mmol), and 4-acetylbenzaldehyde (70.0 mg, 0.47 mmol), were added to a solution of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (100.0 mg, 0.312 mmol) dissolved in THF (2.0 mL). Et_3N (0.17 mL, 1.25 mmol) was added dropwise to the mixture, and the reaction was stirred for 24 hr at –78°C. Next, the reaction was quenched with NH_4Cl (5 mL) and washed with H_2O (5 mL). The resulting mixture was extracted with EtOAc (5 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (10:1 dichloromethane/ether) was performed and afforded the product with a 14% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 32 Hz, 1H), 7.94 (d, J = 8 Hz, 2H), 7.87 (t, J = 12 Hz, 2H), 7.59 (dt, J = 40 Hz, 3H), 5.30 (s, 1H), 4.12 (q, J = 16 Hz, 2H), 3.74 (s, 2H), 2.04 (s, 3H), 1.26 (s, 4H); ^{19}F NMR (400 MHz, $CDCl_3$) δ –188 (dd, J = 52 Hz, 1F), –197 (dd, J = 60 Hz, 1F).

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-fluoro-3-hydroxy-1-(naphthalen-2-yl)-propan-1-one, 6. Both LiBr (97.5 mg, 1.123 mmol), and benzo[*d*][1,3]dioxole-5-carbaldehyde (70.3 mg, 0.47 mmol), were added to a solution of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (100.0 mg, 0.312 mmol) dissolved in THF (2.0 mL). Et_3N (0.2 mL,

1.25 mmol) was added dropwise to the mixture, and the reaction was stirred for 24 hr at –78°C. Next, the reaction was quenched with NH_4Cl (5 mL) and washed with H_2O (5 mL). The resulting mixture was extracted with EtOAc (5 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (10:1 dichloromethane/methanol) was performed and afforded the product with a 21% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 80 Hz, 1H), 7.97–7.87 (m, 5H), 7.61 (dt, J = 48 Hz, 2H), 6.98 (d, J = 12 Hz, 1H), 6.89 (t, J = 12 Hz, 1H), 6.75 (dd, J = 28 Hz, 1H), 5.91 (d, J = 16 Hz, 2H), 5.66 (dd, J = 44 Hz, 1H), 5.30 (s, 1H), 3.73 (s, 1H), 1.60 (t, J = 236 Hz, 10H); ^{19}F NMR (500 MHz, $CDCl_3$) δ –189 (dd, J = 48 Hz, 4F), –195 (dd, J = 56 Hz, 1F).

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Evaluation of Difluoromethyl Ketones as Agonists of the γ-Aminobutyric Acid Type B ($GABA_B$) Receptor. *J. Med. Chem*. **2013**, 56, 2456–1465.

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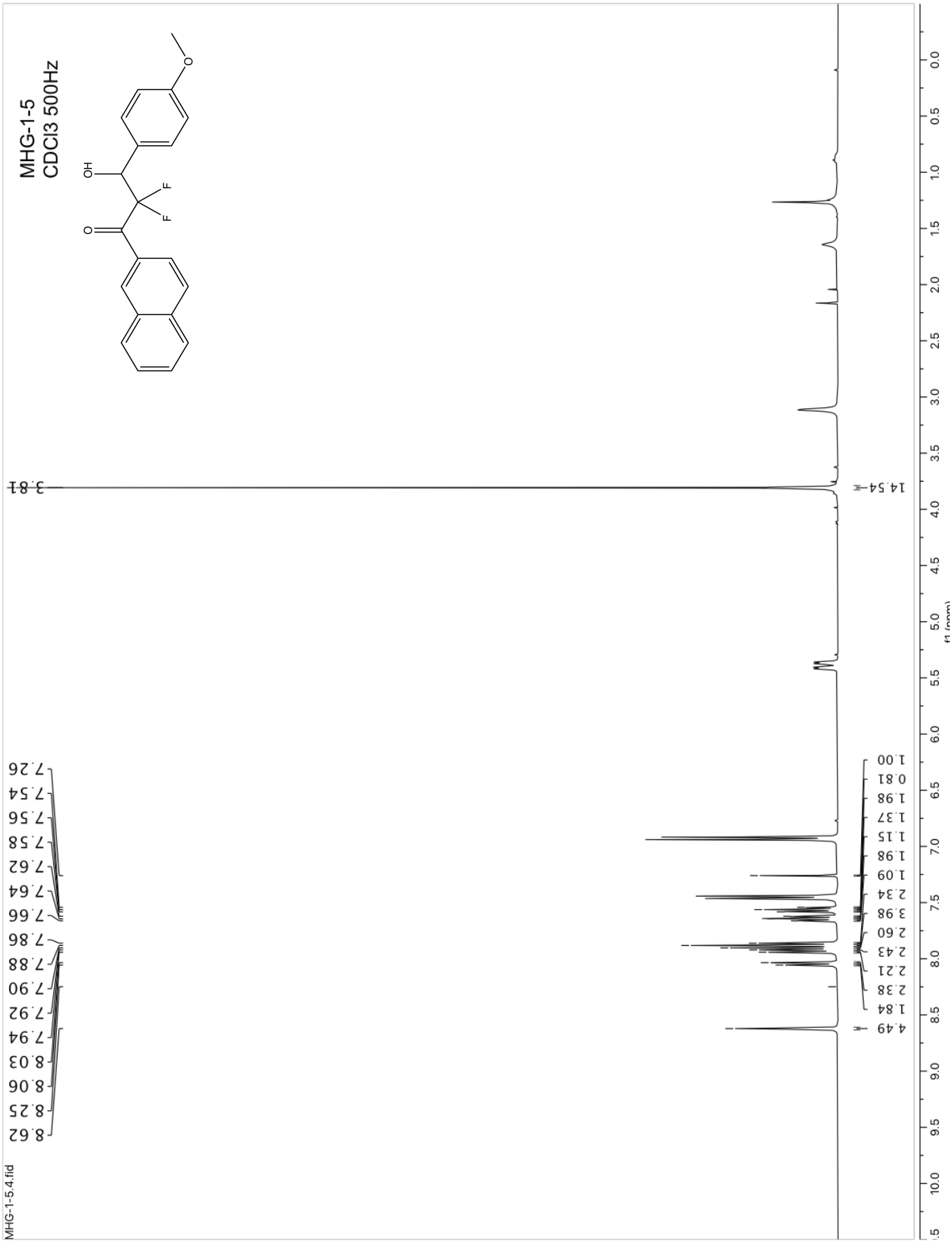
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F
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8.25
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7.92
7.90
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7.62
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7.54
7.26
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1.84
2.38
2.21
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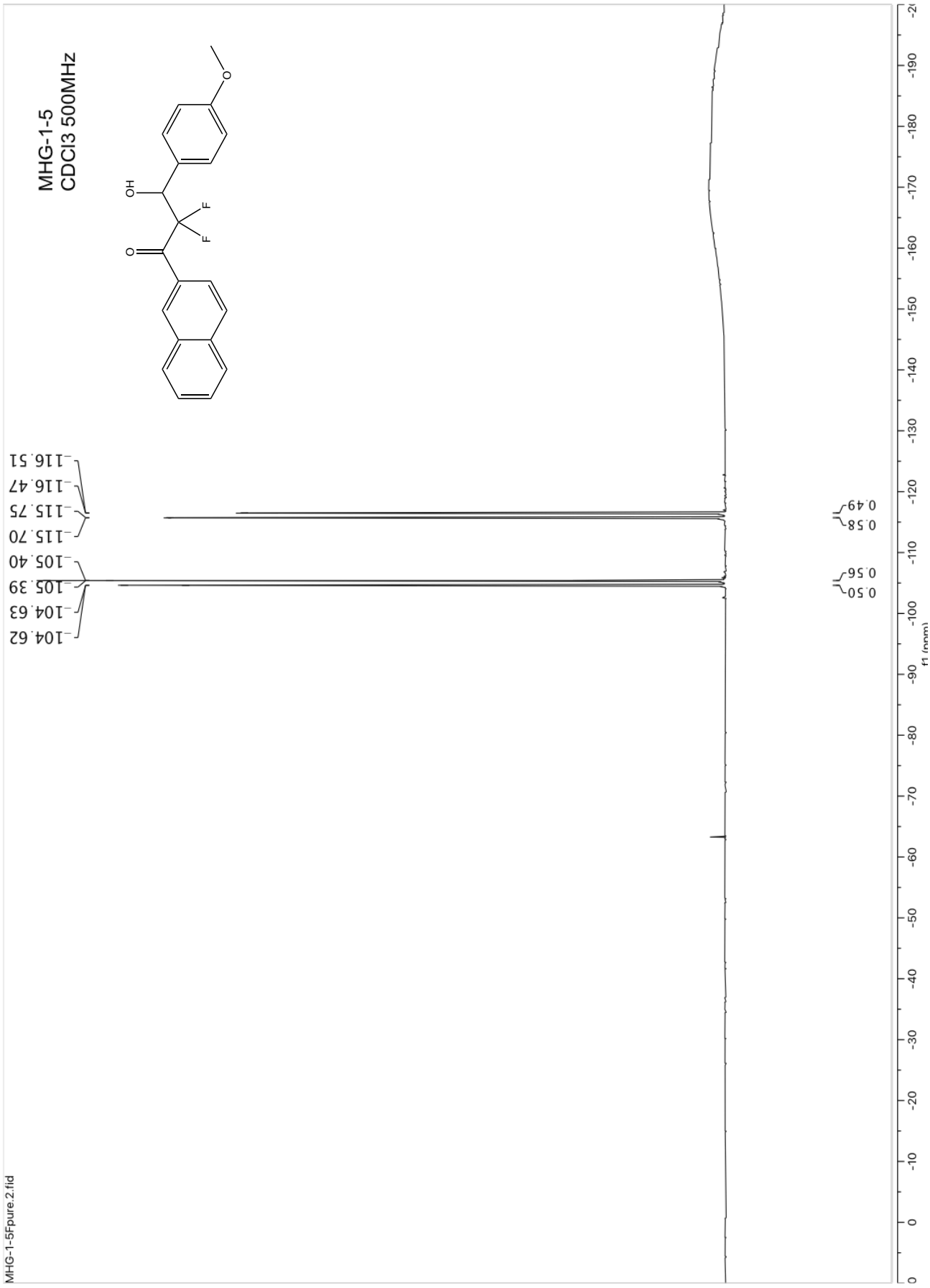
1.98
0.81
1.00
f1 (ppm)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O
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0.58
0.56
0.50
f1 (ppm)
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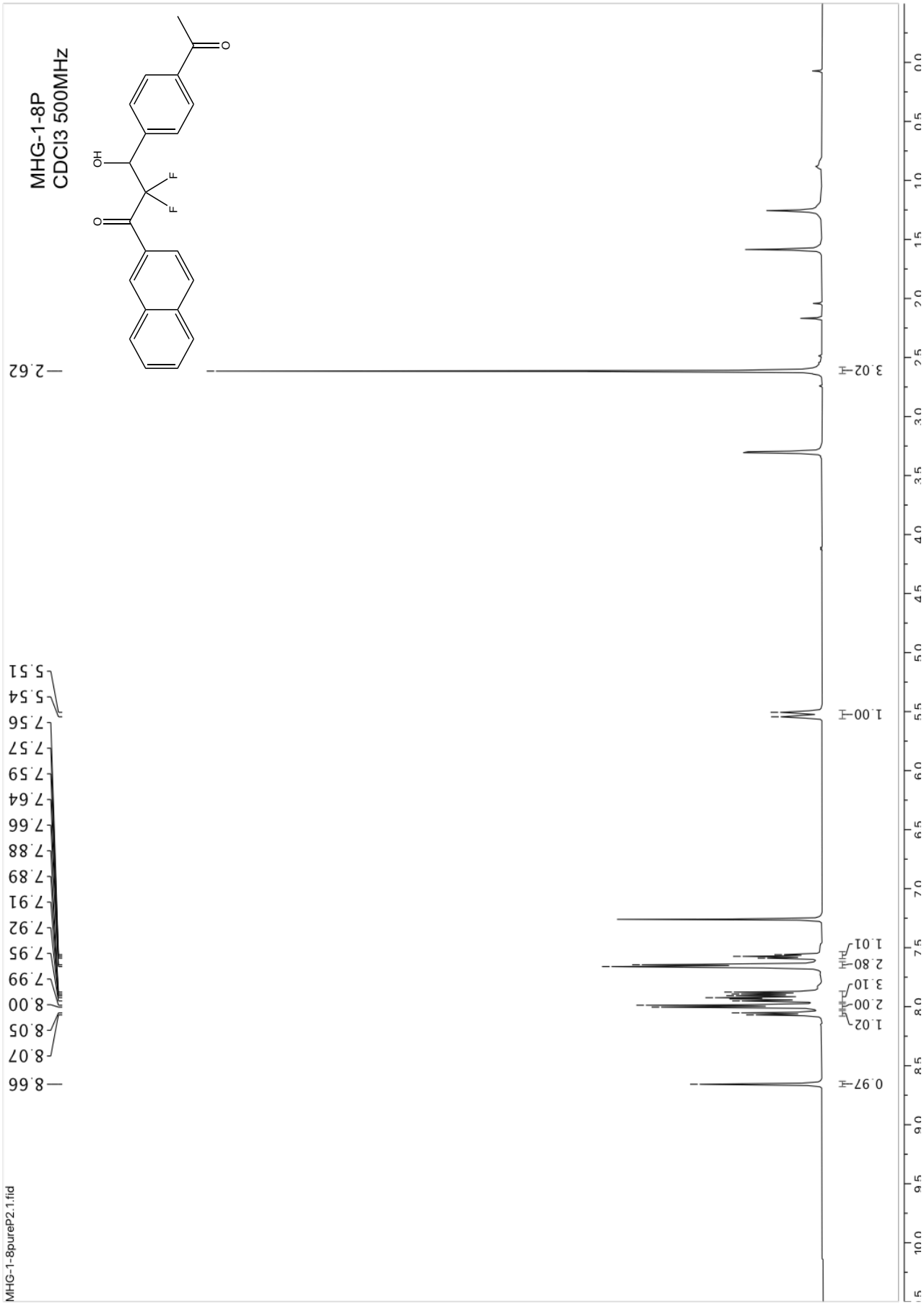
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7.91
7.89
7.88
7.66
7.64
7.59
7.57
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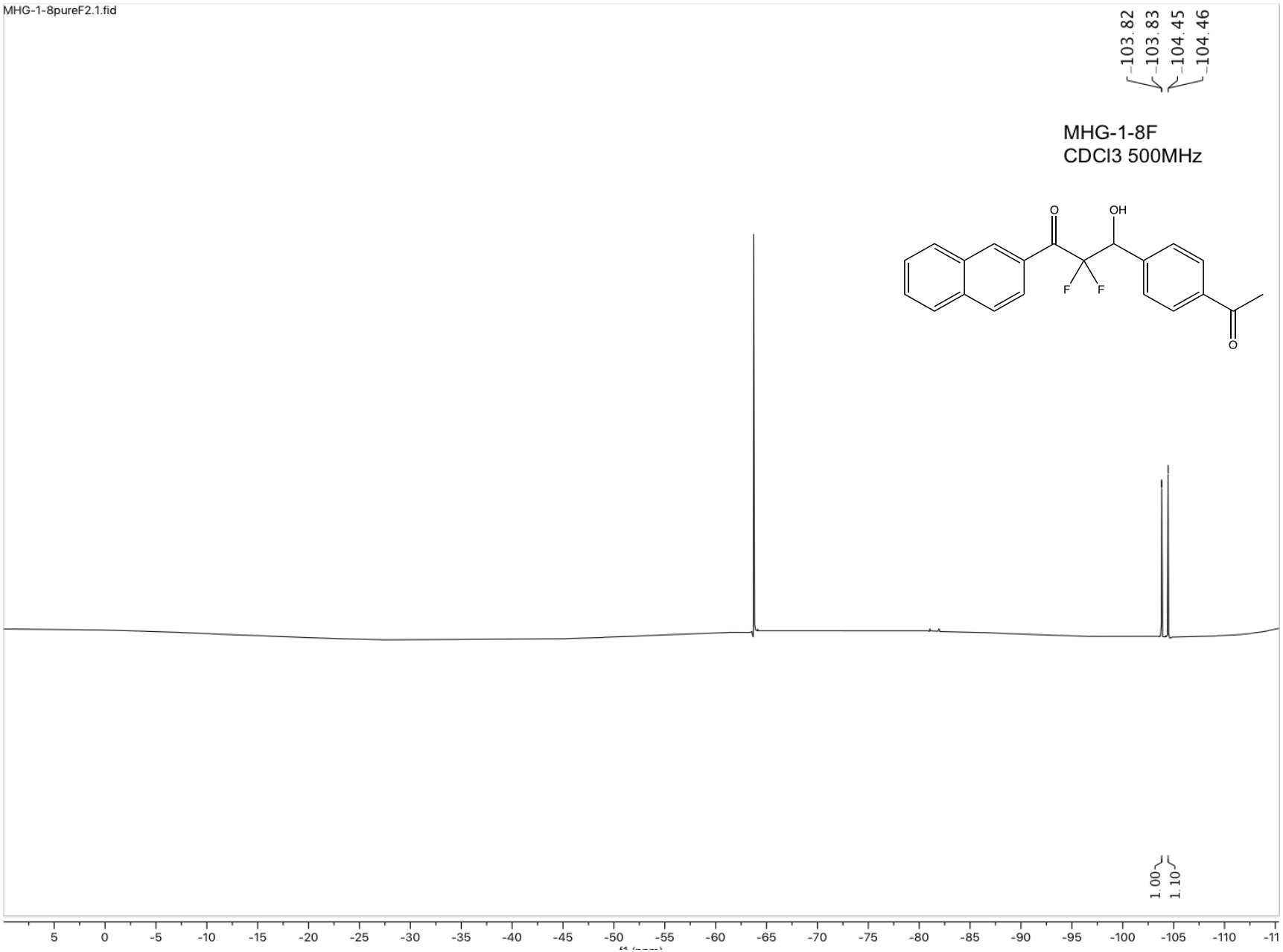
2.00
1.02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OH
F
F
O
1.00
1.10
5
0
-5
-10
-15
-20
-25
-30
-35
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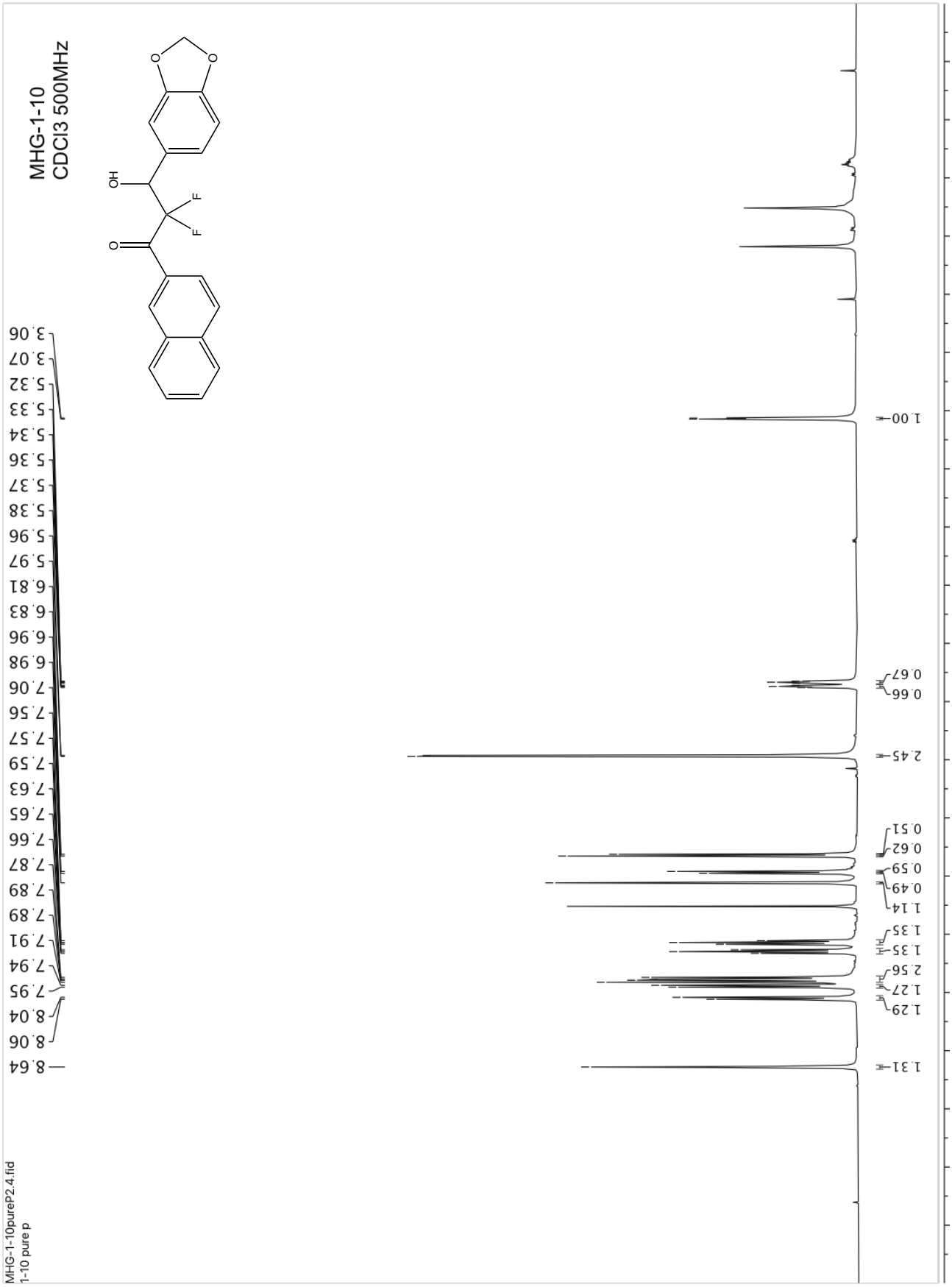
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F
F
O
O
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5.33
5.32
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3.06
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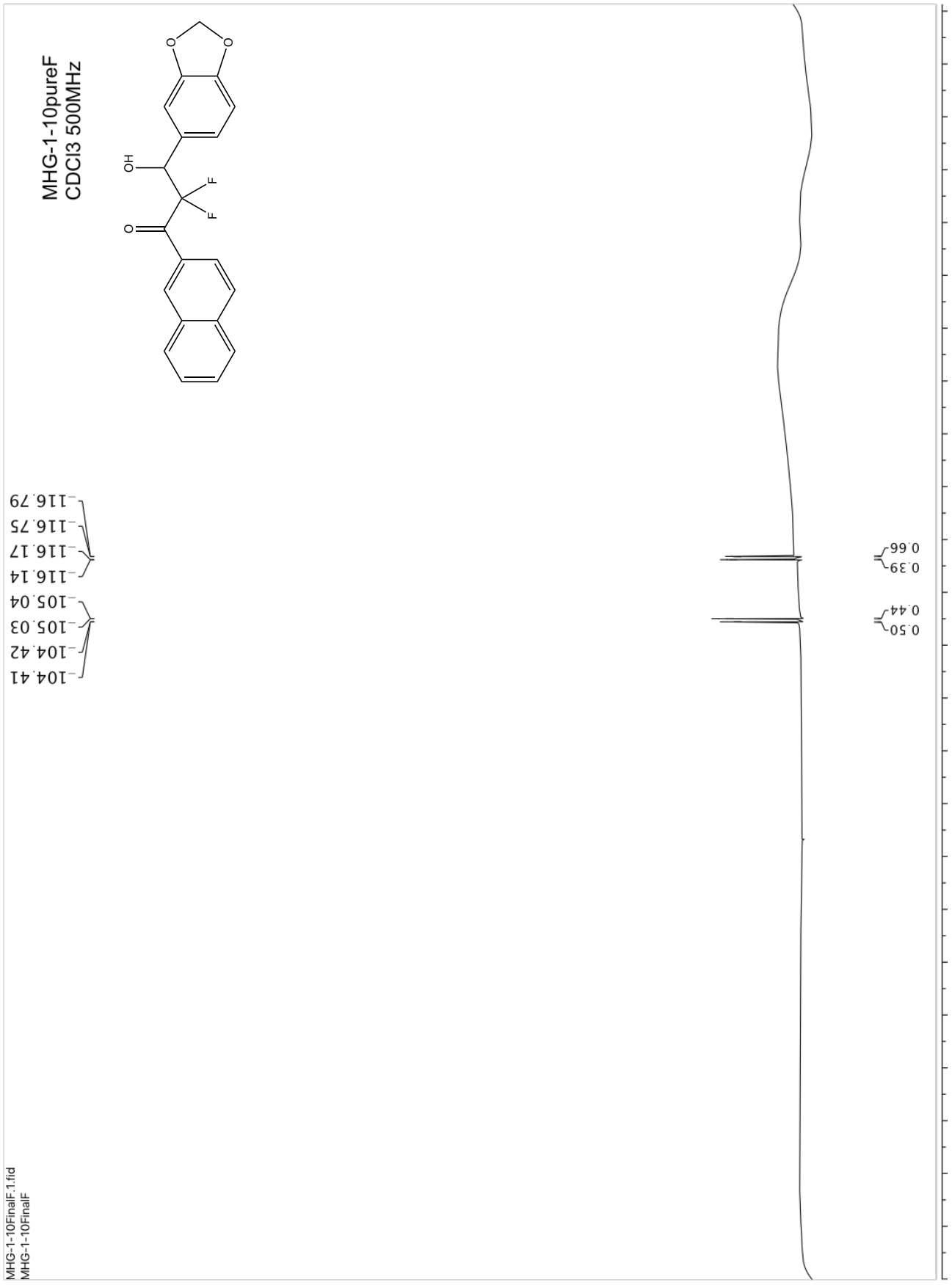
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F
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O
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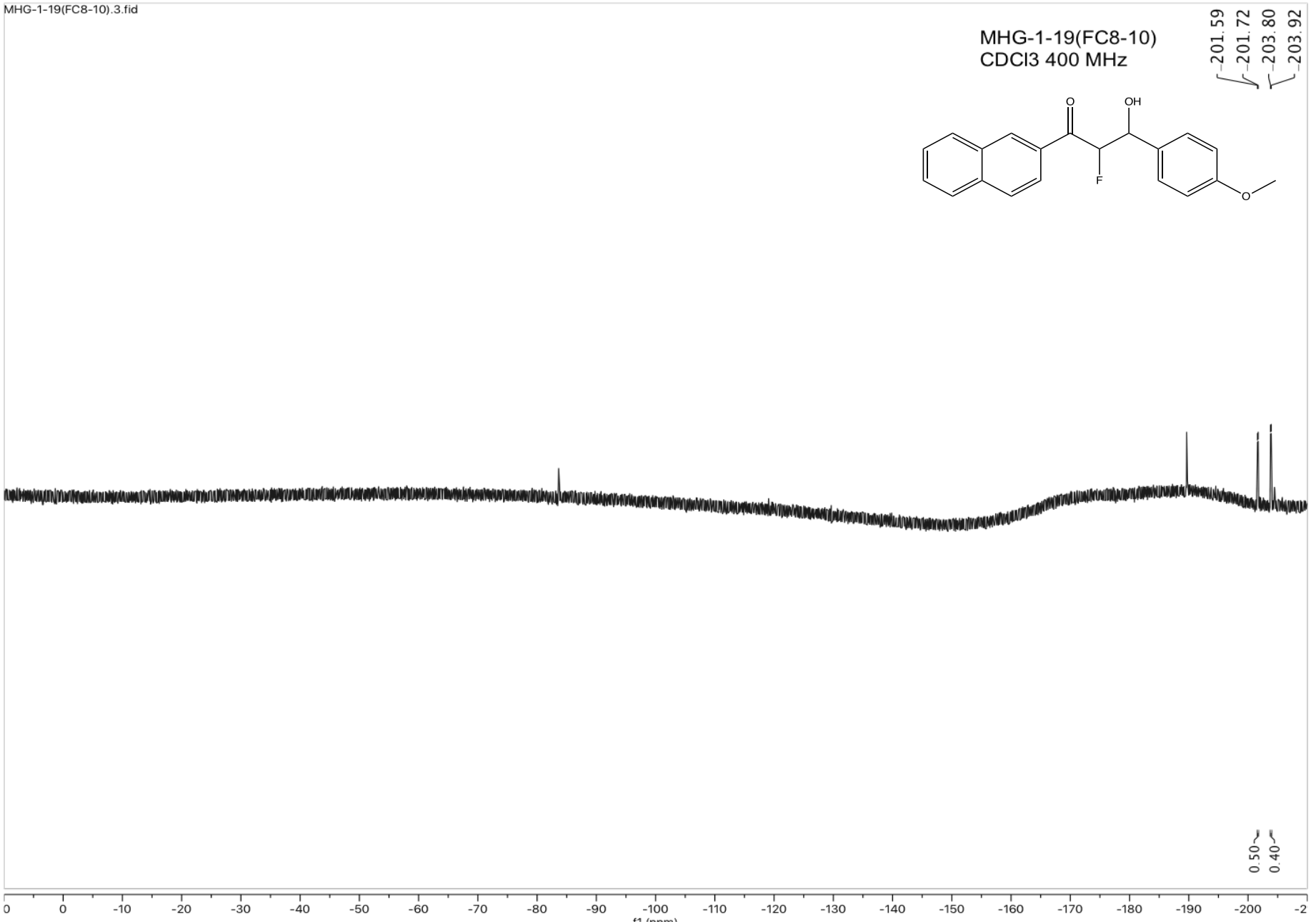
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F
O
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0.40
0
0
-10
-20
-30
-40
-50
-60
-70
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-180
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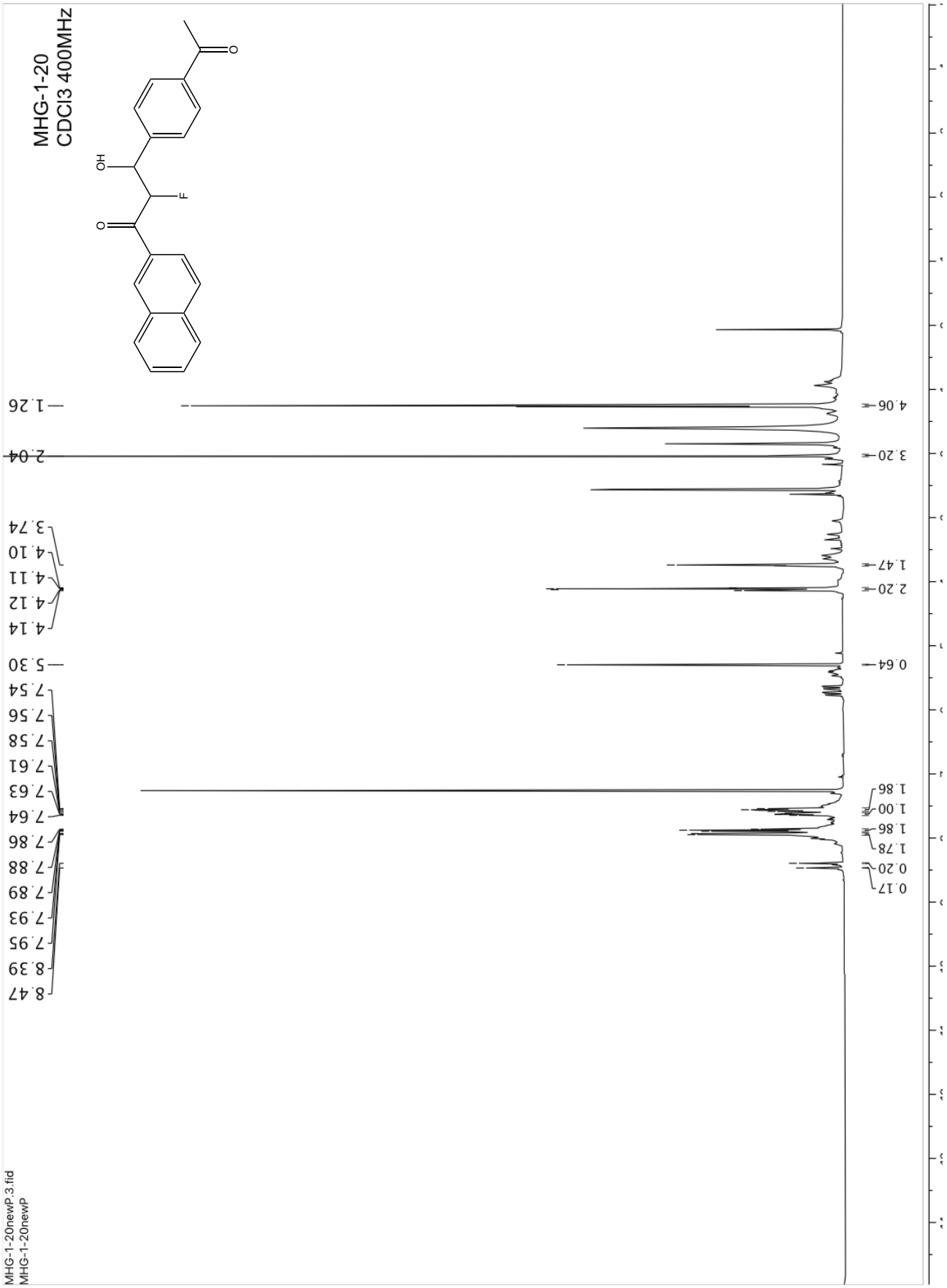
-200
-2
f1 (ppm)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7.95
8.39
8.47
4.06
3.20
1.47
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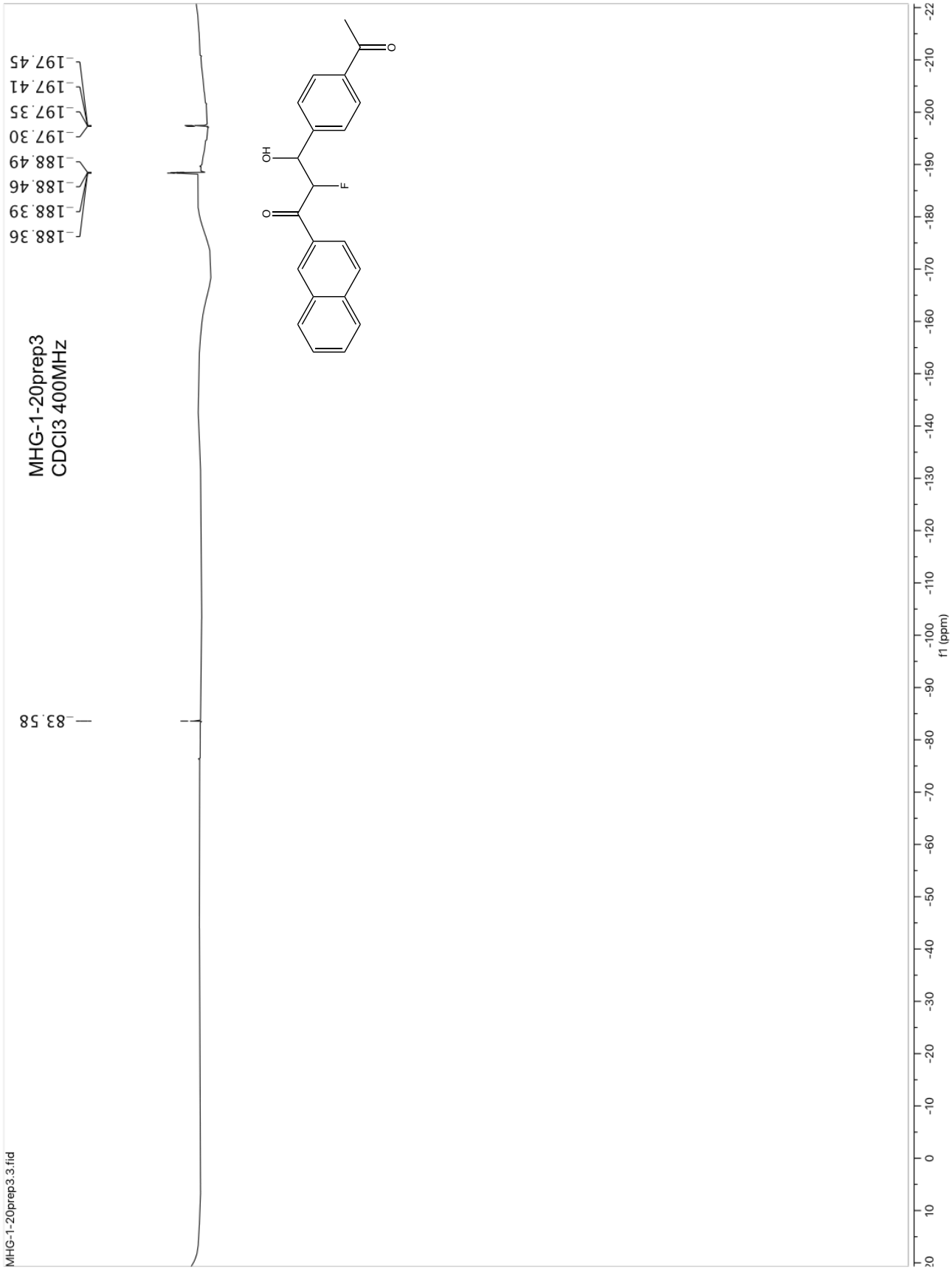
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O
O
f1 (ppm)
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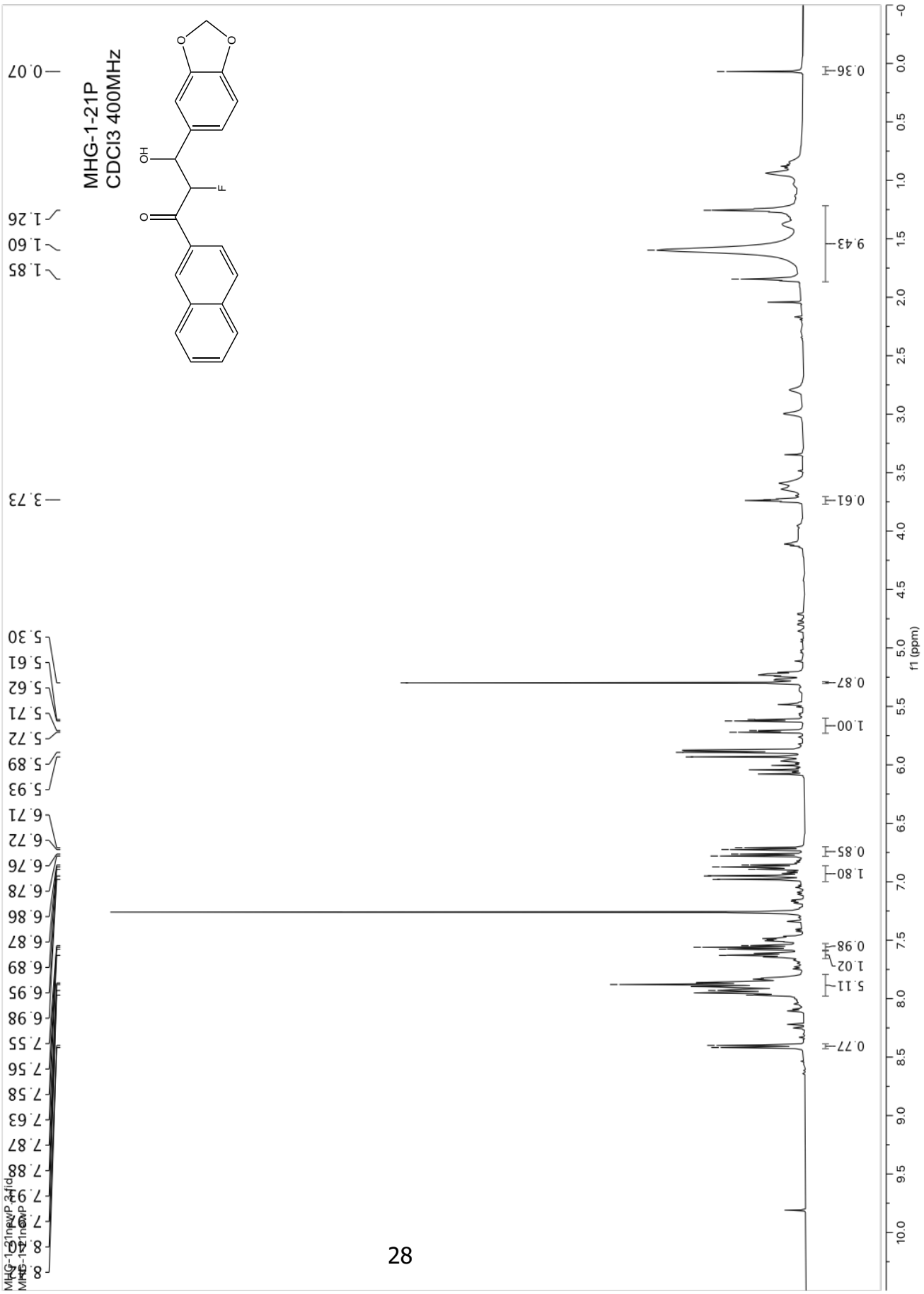
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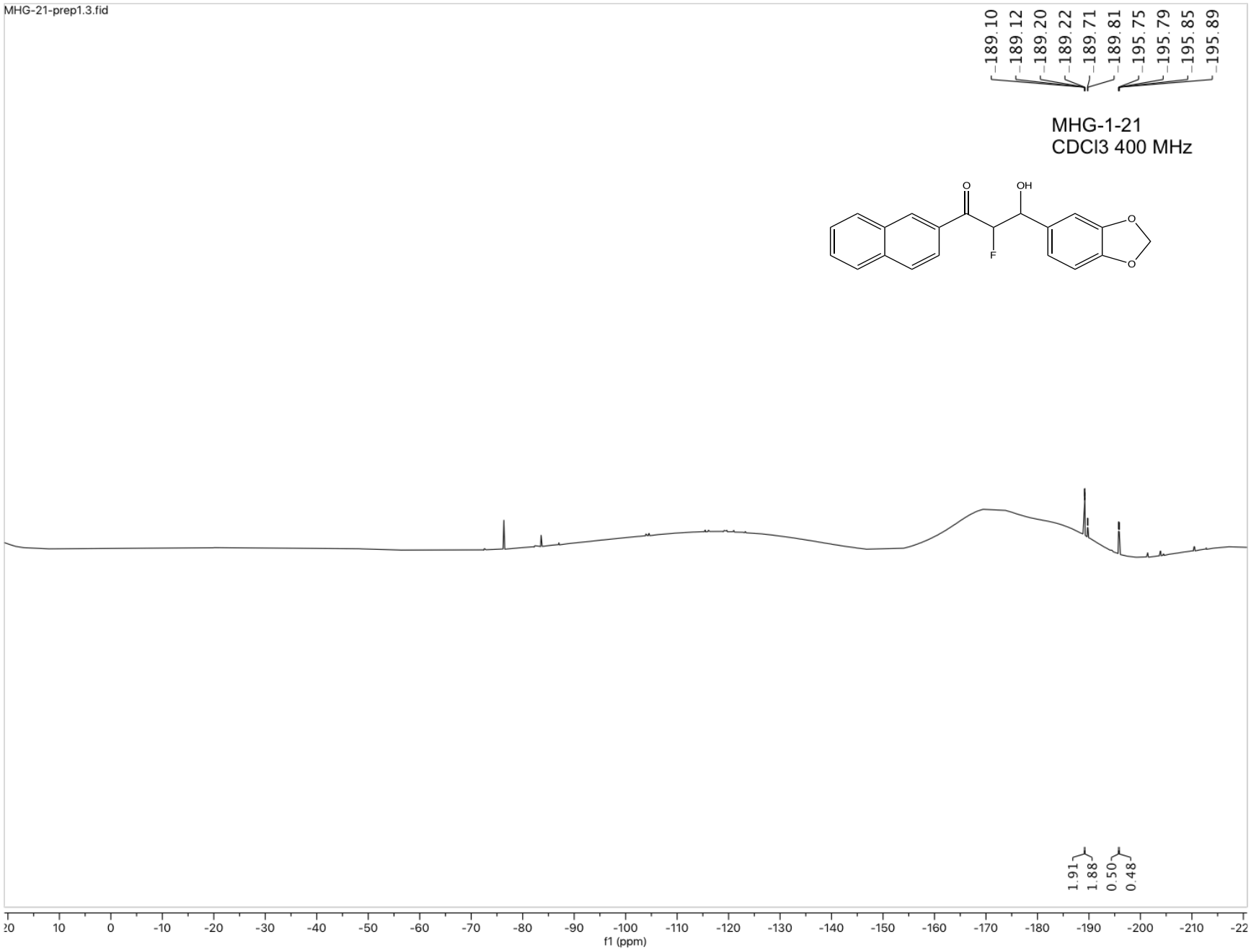
O
O
f1 (ppm)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195.89
MHG-1-21
CDCl3 400 MHz
O
OH
F
O
O
1.91
1.88
0.50
0.48
f1 (ppm)