

Supporting Information for

Synthesis of diverse dihydropyrimidine-related scaffolds by fluororous benzaldehyde-based Biginelli reaction and post-condensation modifications

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*Corresponding author

LC-MS, ^1H NMR and ^{13}C NMR data and spectra for compounds
4c, 5a, 6b, 7b, 8b, 9

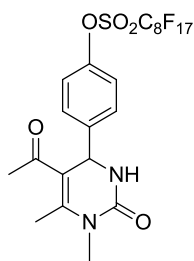
General methods:

The ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Varian NMR spectrometer, in CDCl_3 solvent with tetramethylsilane as the internal standard. The temperature was 25 °C (accuracy ± 1 °C). Splitting patterns of ^1H NMR spectra are designated as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. LC-MS spectra were recorded on an Agilent 2100 system. A C18 column (5.0 μm , 6.0 \times 50 mm) was used for the separation. The mobile phases were methanol and water, both containing 0.05% formic acid. A linear gradient was used to increase the ratio from 25:75 v/v methanol/water to 100% methanol over 5.0 min at a flow rate of 0.7 mL/min. The UV measurements were made at 210 nm and 254.4 nm. Mass spectra were recorded by atmospheric-pressure chemical ionization. All reactions were carried out in a self-tuning single mode Biotage Initiator Microwave Synthesizer. Purification of intermediates took place in a Thermo Scientific 16 SPE Vacuum Manifold.

General procedure for the preparation of dihydropyrimidinones and dihydropyrimidinthiones derivatives and spectral data for selected compounds.

A general procedure for the synthesis of dihydropyrimidinone compound 4c. A solution of *p*-perfluorooctanesulfonyl benzaldehyde **1** (1.2 g, 2.0 mmol), methylurea **2** (0.18 g, 2.4 mmol), methyl acetoacetate **3** (0.35 g, 3.0 mmol) and Yb(OTf)₃ (124 mg, 0.2 mmol) in acetonitrile (2 mL) in a microwave reaction tube was heated in Biotage microwave reactor at 120 °C for 20 min. The resulting mixture was purified by F-SPE eluted with 40 mL of 80:20 MeOH/H₂O and then 40 mL of acetone. The acetone (fluorous) fraction was concentrated to give **4c** (1.3 g, 90% yield).

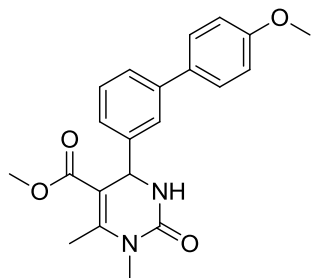
5-Acetyl-4-(4-(perfluorooctylsulfonyloxy)phenyl)-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (4c):



LC-MS (APCI⁺) m/z 743 [M + 1]⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.34 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 7.7 Hz, 2H), 6.27 (d, J = 3.0 Hz, 1H), 5.45 (d, J = 3.0 Hz, 1H), 3.23 (s, 3H), 2.47 (s, 3H), 2.24 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 195.8, 153.8, 149.3, 148.8, 142.8, 133.6, 128.2, 121.9, 121.0, 120.3, 119.9, 118.6, 117.4, 116.6, 114.8, 113.5, 53.2, 30.6, 29.7, 17.2; HRMS (ES⁺): m/z [M + H]⁺ calcd for C₂₂H₁₅F₁₇N₂O₅S: 743.0508; found: 743.0514.

A general procedure for Suzuki reactions. Synthesis of compounds 5a. A solution of **4a** (75 mg, 0.1 mmol), 4-methoxyphenylboronic acid **10** (23 mg, 0.15 mmol), Cs₂CO₃ (81 mg, 0.25 mmol) and Pd(dppf)Cl₂ (16 mg, 0.02 mmol) in 4:1:4 acetone:H₂O:toluene (3 mL) was heated under microwave irradiation at 140 °C for 30 min. The resulting mixture was purified by flash chromatography with 0–50% gradient of EtOAc/hexanes to give **5a** (24 mg, 67% yield).

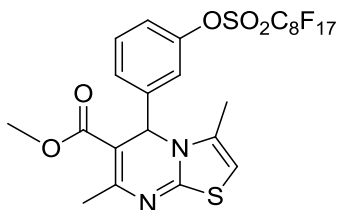
Methyl 4-(4'-methoxy-[1,1'-biphenyl]-3-yl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5a)



LC-MS (APCI⁺) m/z 367 [M + 1]⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.57 (d, J = 11.7 Hz, 1H), 7.49–7.42 (m, 3H), 7.34 (t, J = 15.3 Hz, 1H), 7.19–6.95 (m, 2H), 6.76 (s, 1H), 6.03 (d, J = 3.0 Hz, 1H), 5.45 (d, J = 3.0 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.24 (s, 3H), 2.53 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 166.5, 154.2, 149.7, 142.1, 140.6, 140.5, 128.8, 128.7, 127.4, 127.3, 126.9, 126.5, 103.9, 54.9, 54.3, 53.2, 30.4, 16.6; HRMS (ES⁺): m/z [M + H]⁺ calcd for C₂₁H₂₂N₂O₄: 367.1658; found: 367.1659.

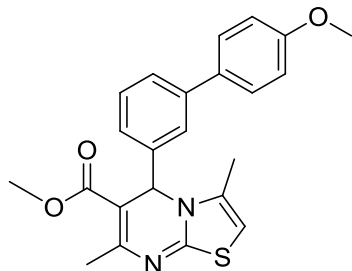
A general procedure for the synthesis of compounds 8b. A solution of 3,4-dihydropyrimidine-thione **4f** (0.76 g, 1 mmol), chloroacetone (185 mg, 1.5 mmol) in water (2 mL) was heated under microwave at 120 °C for 30 min. The resulting mixture was purified by F-SPE eluted with 30 mL of 80:20 MeOH/H₂O and then 30 mL of acetone. The Acetone (fluorous) fraction was concentrated to give **8b** (0.67 g, 85% yield).

Methyl 3,7-dimethyl-5-(3-(perfluorooctylsulfonyloxy)phenyl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (8b)



LC-MS (APCI⁺) m/z 799 [M + 1]⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.85 (d, J = 7.5 Hz, 2H) 7.74 (d, J = 2.7 Hz, 2H), 7.43–7.32 (m, 3H), 7.27–7.18 (m, 2H), 6.22 (s, 1H), 6.06 (s, 1H), 3.85 (s, 3H), 2.40 (s, 3H), 2.07 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 169.7, 165.5, 153.8, 152.7, 149.6, 143.2, 135.0, 131.2, 128.5, 126.3, 121.6, 120.5, 119.5, 118.9, 118.3, 117.7, 117.0, 116.2, 114.4, 113.7, 57.2, 51.1, 23.1, 13.8.

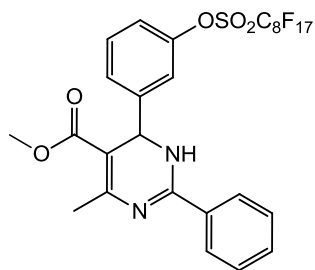
Methyl-5-(4'-methoxy-[1,1'-biphenyl]-3-yl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (6b).



LC-MS (APCI⁺) m/z 407 [M + 1]⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.49–7.41 (m, 3H), 7.32–6.09 (m, 3H), 6.96 (d, J = 10.0 Hz, 2H), 6.68 (s, 1H), 6.16 (s, 1H), 3.84 (s, 3H), 2.40 (s, 6H), 2.12 (s, 3H); ¹³C NMR (75.474 MHz, CDCl₃) δ 169.8, 166.5, 153.8, 152.7, 147.8, 141.1, 136.4, 132.9, 129.2, 128.1, 126.4, 124.6, 114.2, 57.2, 55.3, 51.3, 24.5, 13.9; HRMS (ES⁺): m/z [M + H]⁺ calcd for C₂₃H₂₂N₂O₃S: 407.1426; found: 407.1429.

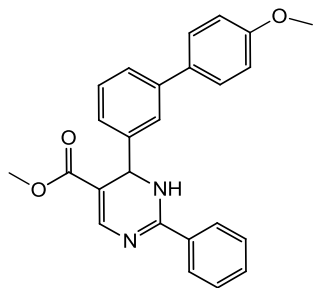
A general procedure for the synthesis of compound 9. A solution of 3,4-dihydropyrimidine-thione **4f** (152 mg, 0.20 mmol), phenylboronic acid **10** (82 mg, 0.3 mmol), CuTC (95 mg, 0.6 mmol), and Pd(PPh₃)₄ (3mol %) in THF (2 mL) was heated under microwave at 100 °C for 25 min. The mixture was purified by F-SPE eluted with 30 mL of 80:20 MeOH/H₂O and then 30 mL of acetone. The acetone (fluorous) fraction was concentrated to give **9** (0.85 g, 76 % yield).

Methyl 4-methyl-6-(3-(perfluorooctylsulfonyloxy)phenyl)-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (9).



LC-MS (APCI⁺) m/z 805 [M + 1]⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.73–7.23 (m, 3H), 7.19–7.04 (m, 2H), 5.62 (s, 1H), 3.58 (s, 3H), 3.72 (s, 3H), 2.41 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 170.1, 166.9, 160.2, 153.0, 149.9, 146.0, 133.6, 132.3, 130.4, 128.9, 127.8, 127.3, 127.0, 120.5, 120.2, 119.7, 118.6, 117.6, 116.4, 114.9, 55.9, 51.4, 29.7, 23.8; HRMS (ES⁺): m/z [M + H]⁺ calcd for C₂₇H₁₇F₁₇N₂O₅S: 805.0665; found: 805.0670.

Methyl-6-(4'-methoxy-[1,1'-biphenyl]-3-yl)-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (7b).

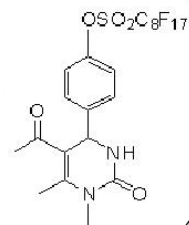


LC-MS (APCI⁺) m/z 413 [M + 1]⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, J = 8.1 Hz, 2H), 7.68 (s, 1H), 7.56–7.48 (m, 3H), 7.40–7.26 (m, 3H), 6.74 (d, J = 8.1 Hz, 2H), 5.79 (s, 1H), 3.64 (s, 6H), 2.65 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 170.2, 166.7, 153.8, 152.7, 149.6, 141.1, 136.4, 133.0, 132.3, 130.2, 129.4, 129.2, 128.4, 126.7, 124.6, 114.2, 57.2, 55.9, 51.7, 23.5; HRMS (ES⁺): m/z [M + H]⁺ calcd for C₂₁H₂₄N₄O₅: 413.1865; found: 413.1864.

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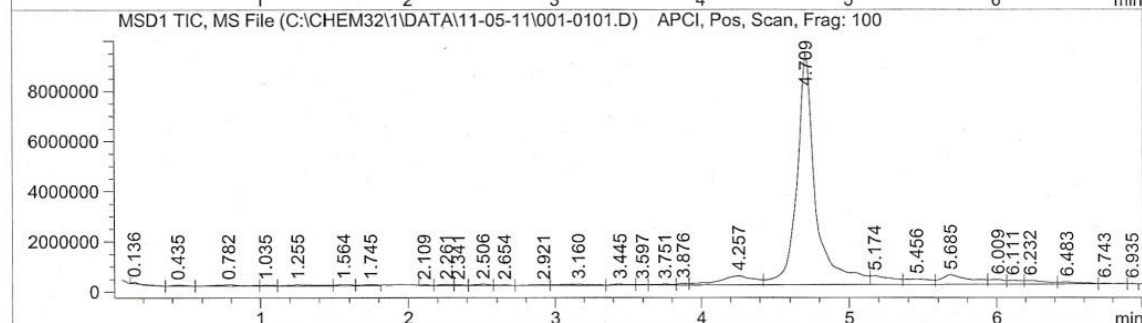
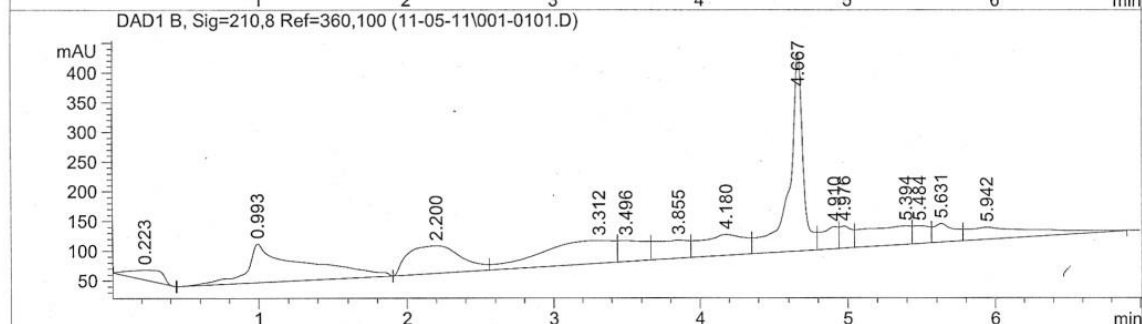
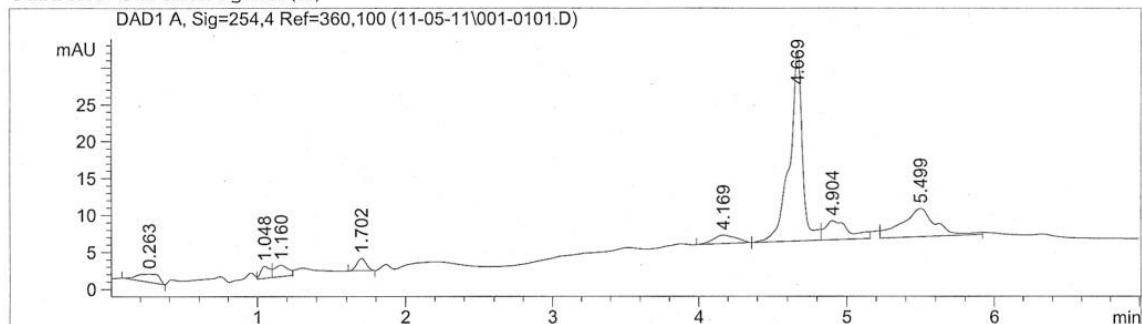
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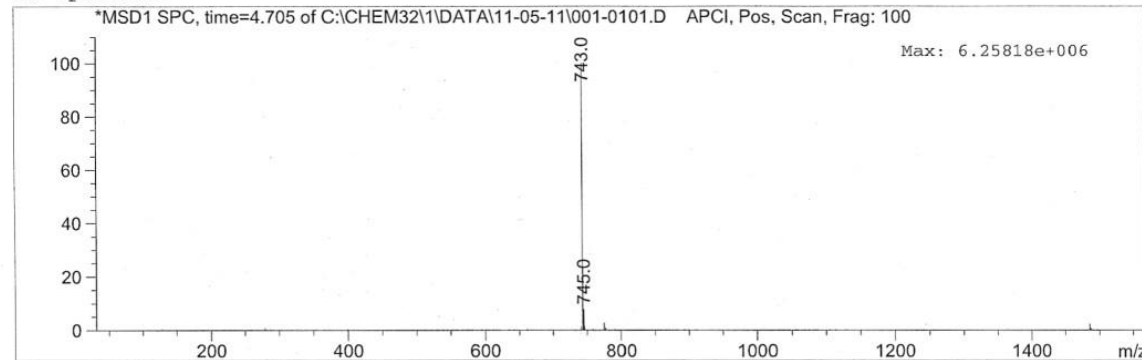


4c

Current Chromatogram(s)

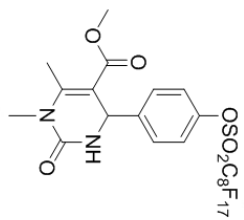


MS Spectrum

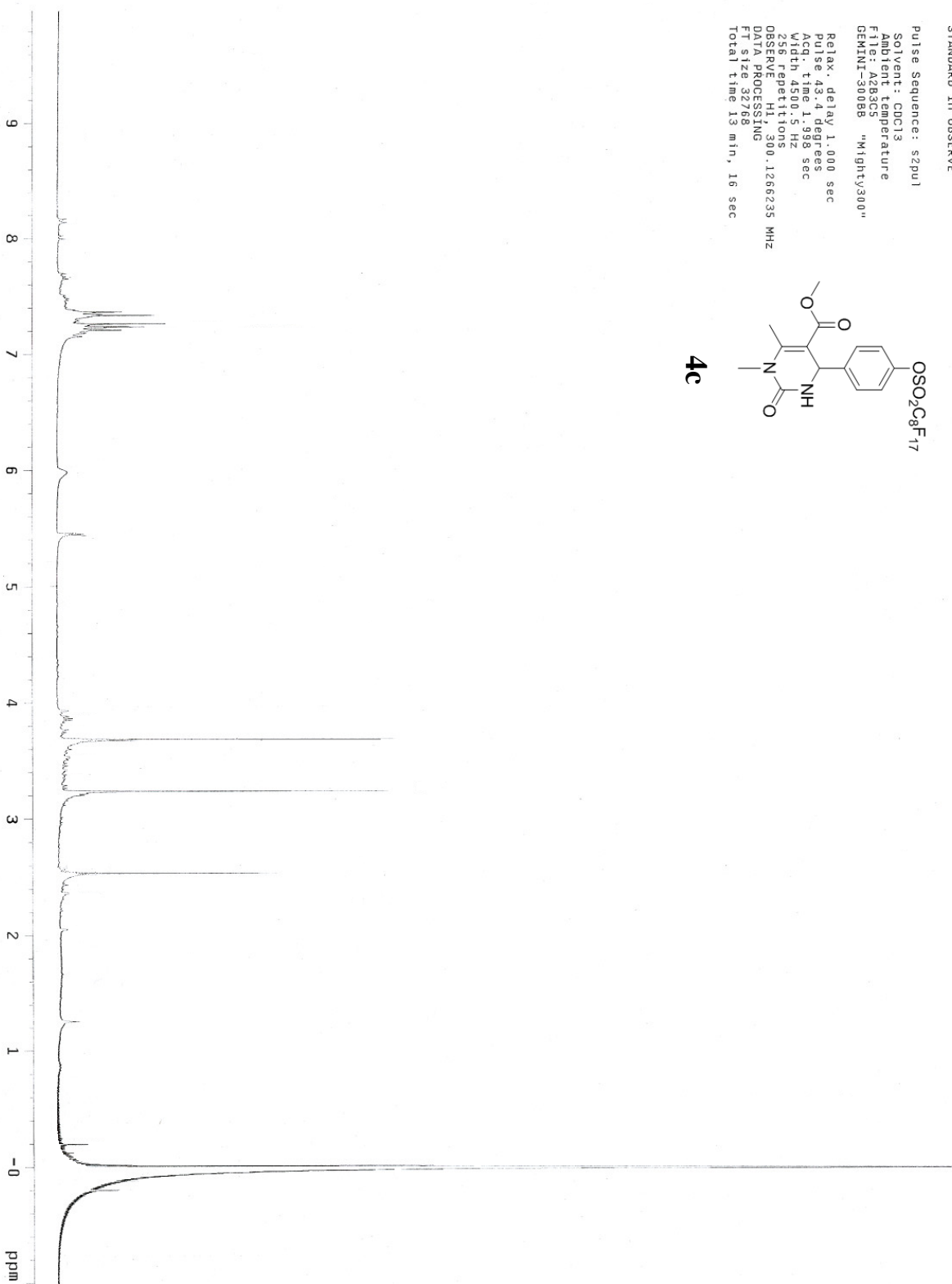


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4c

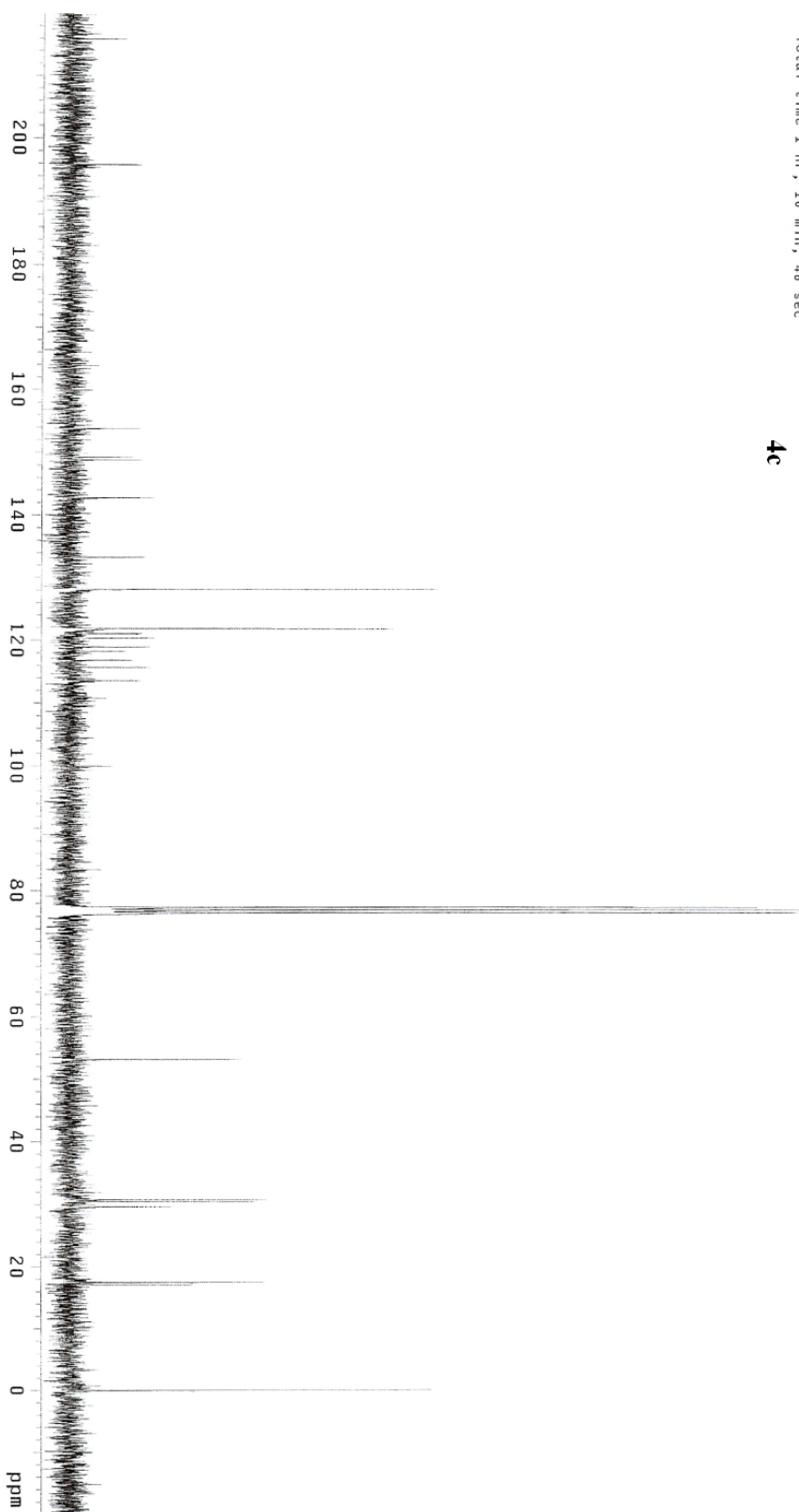
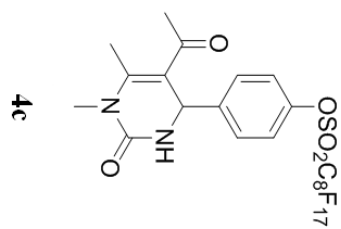


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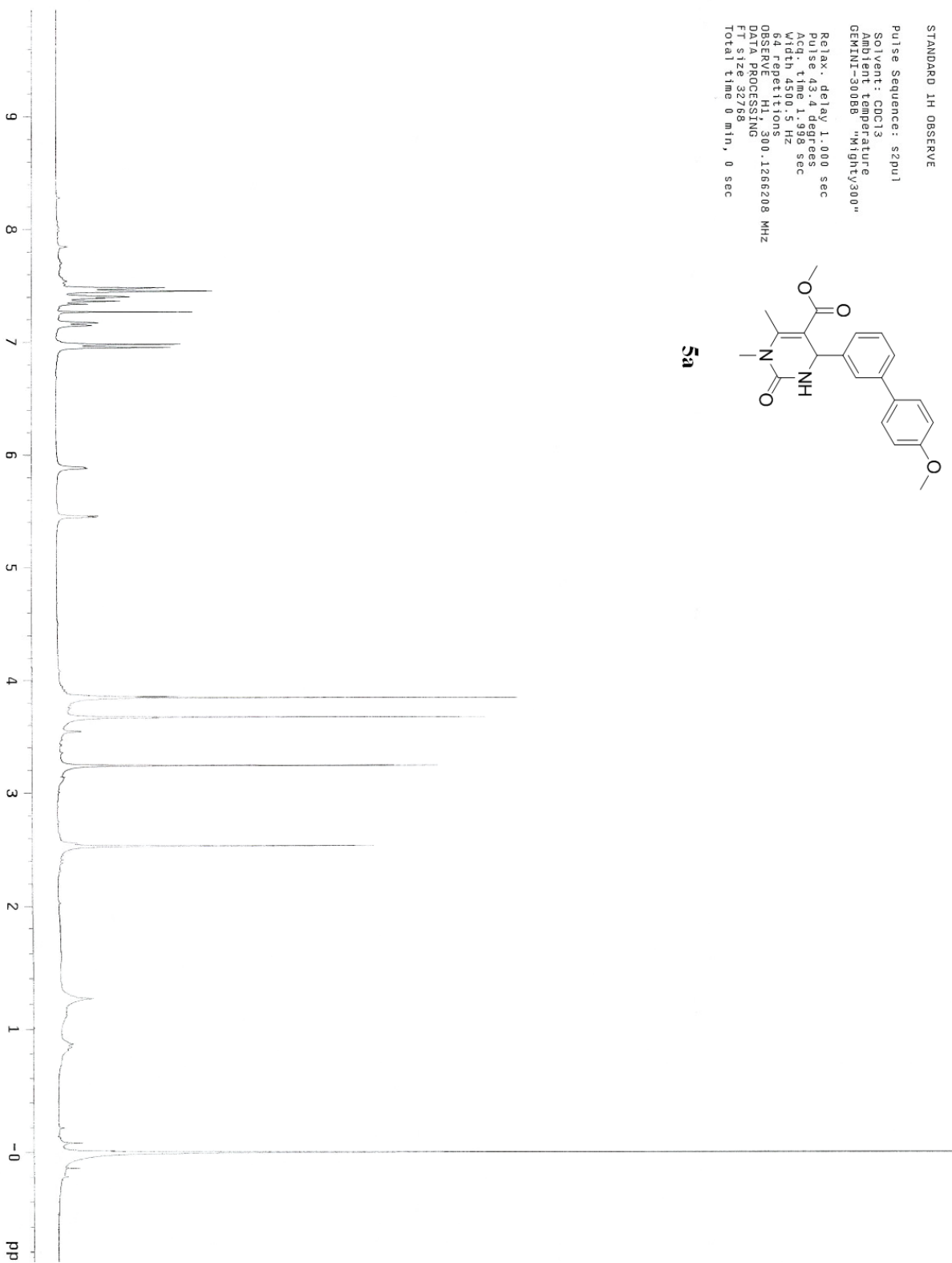
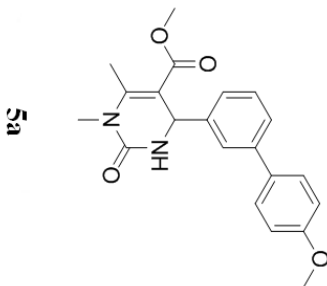
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DATA PROCESSING
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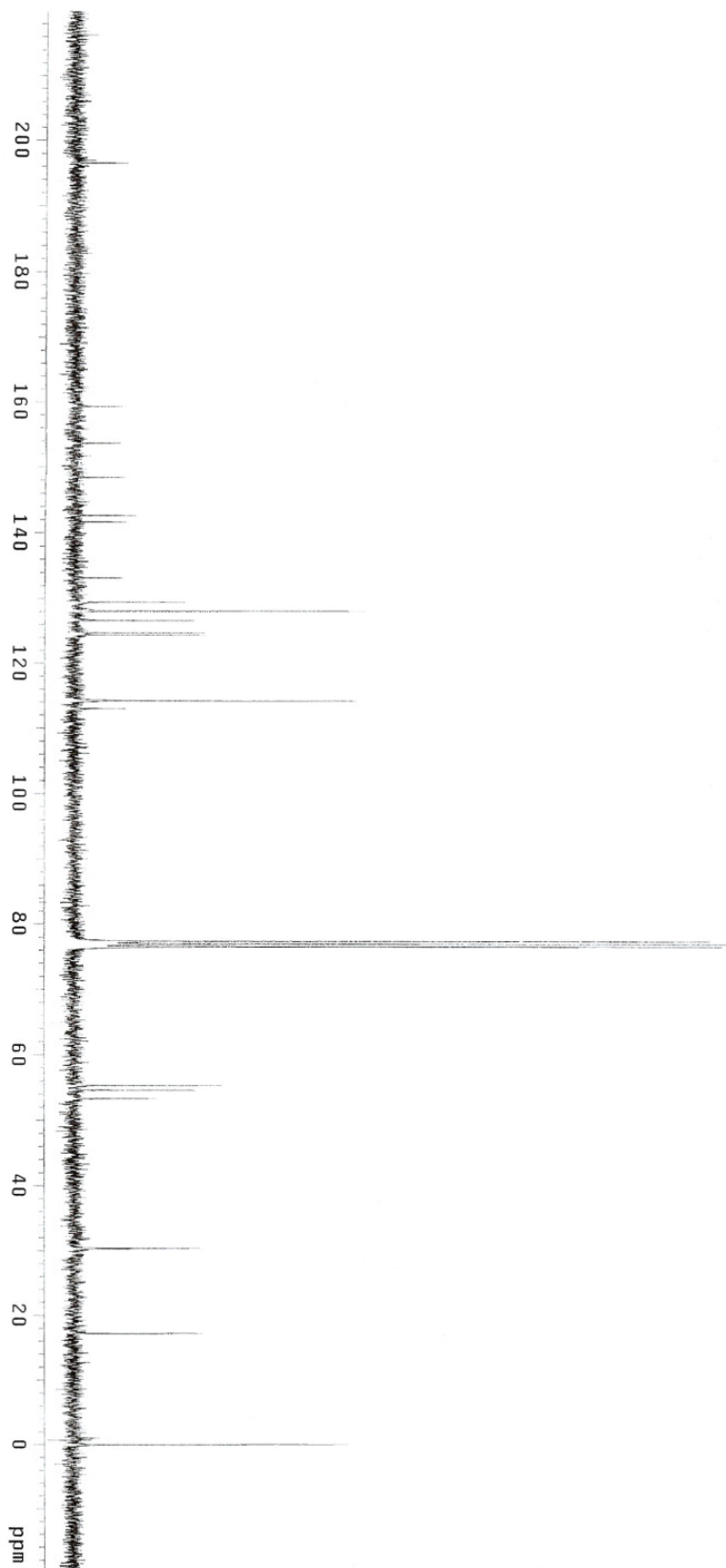
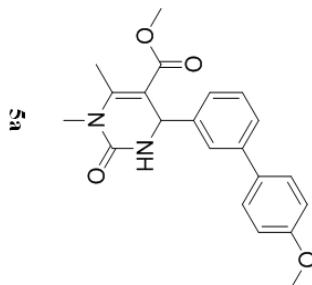
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Total time 0 min, 0 sec



13C OBSERVE

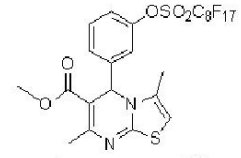
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continuously on
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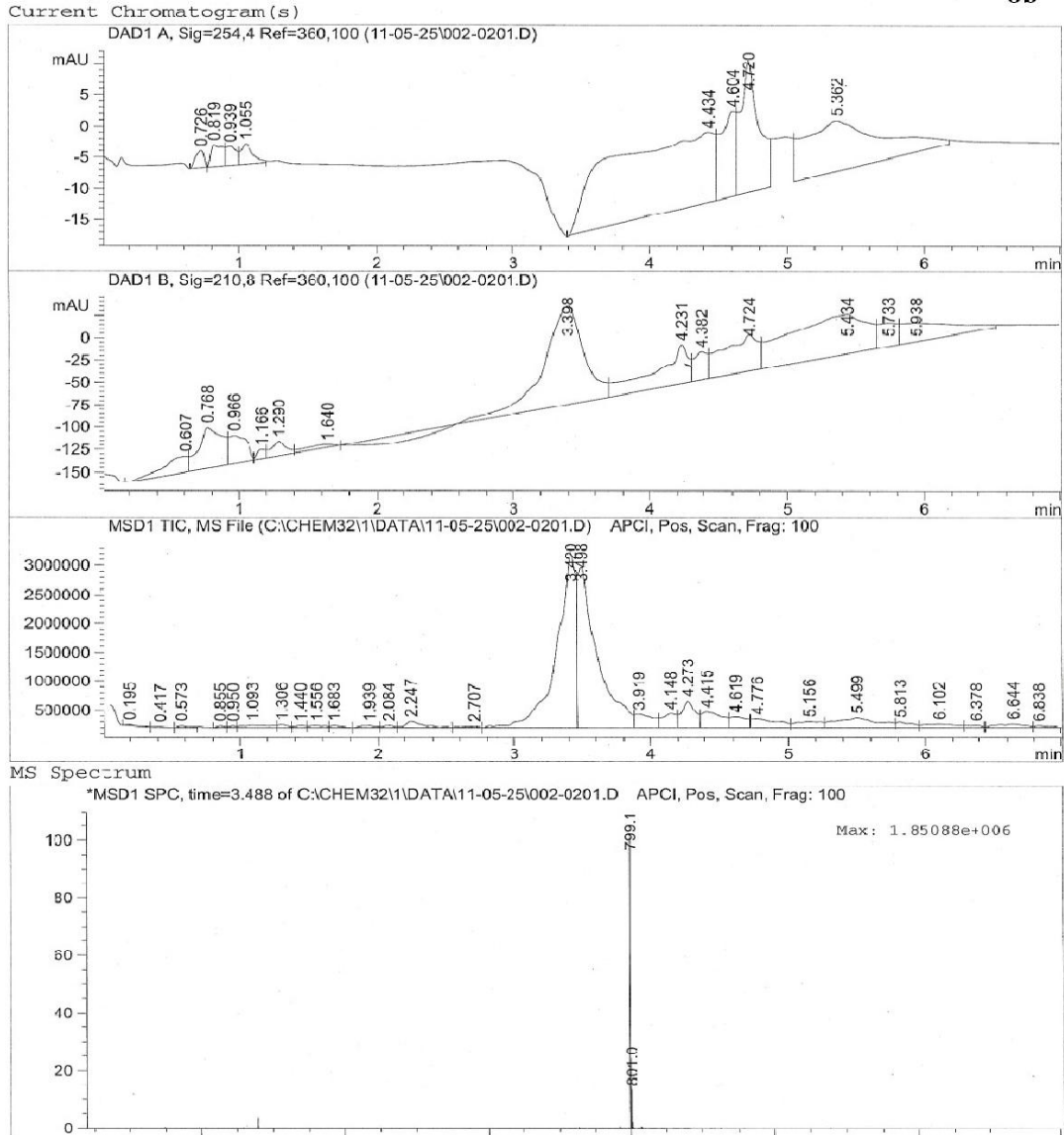


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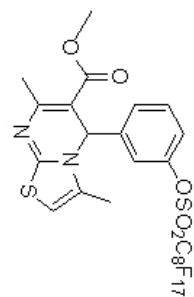
8b



STANLAKU JII UDSJLKV.

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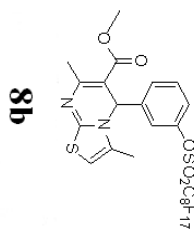
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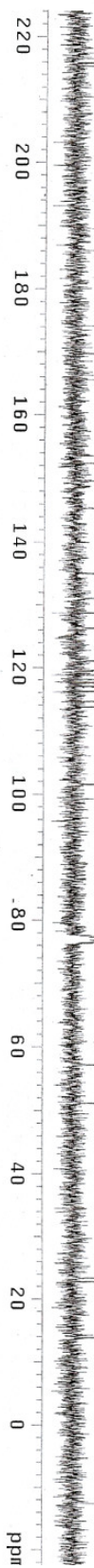
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continuously on
VALTZ-16 modulated
DATA PROCESSING
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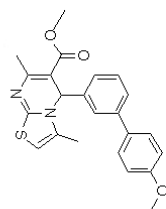
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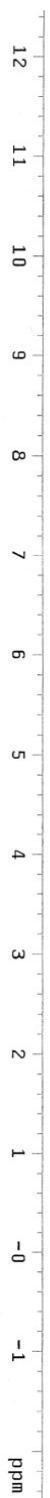
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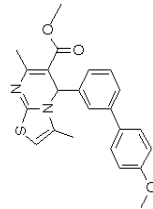
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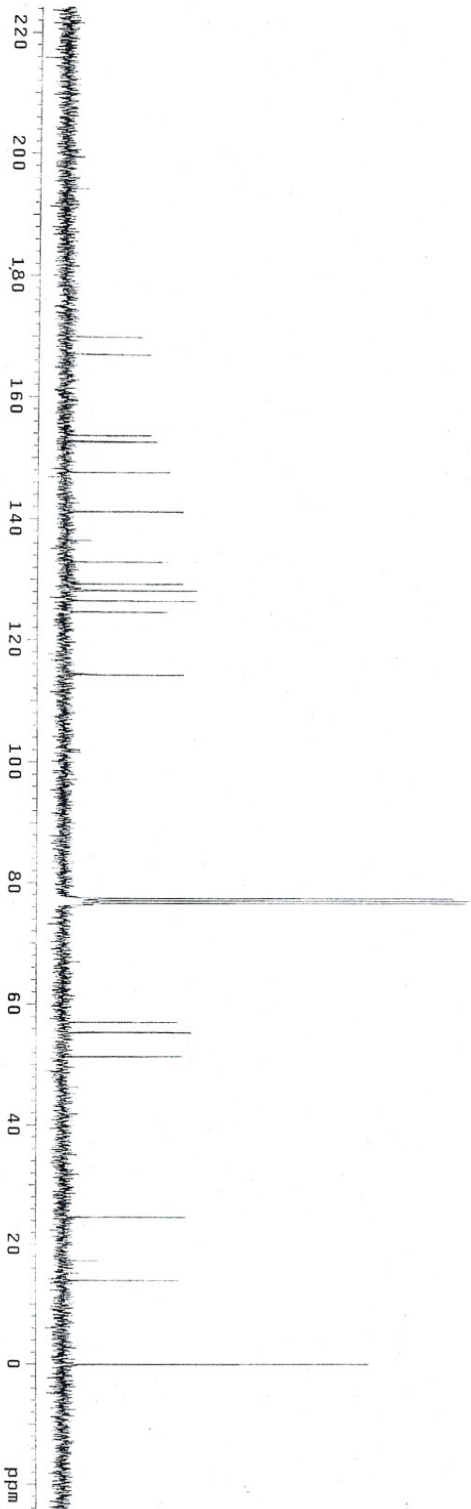
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DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
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Total time 1 hr, 12 min, 7 sec



6b

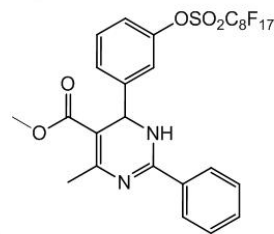


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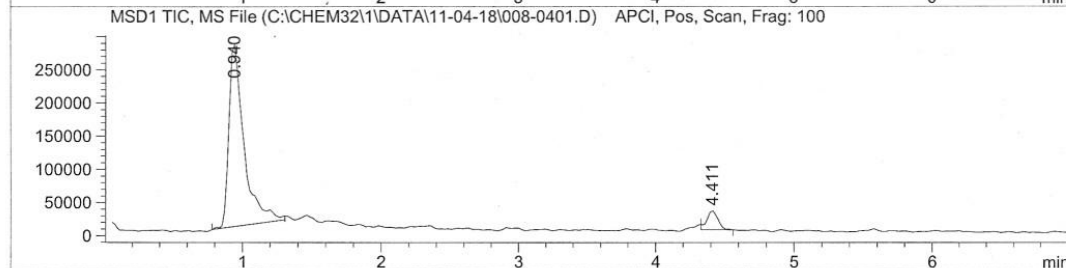
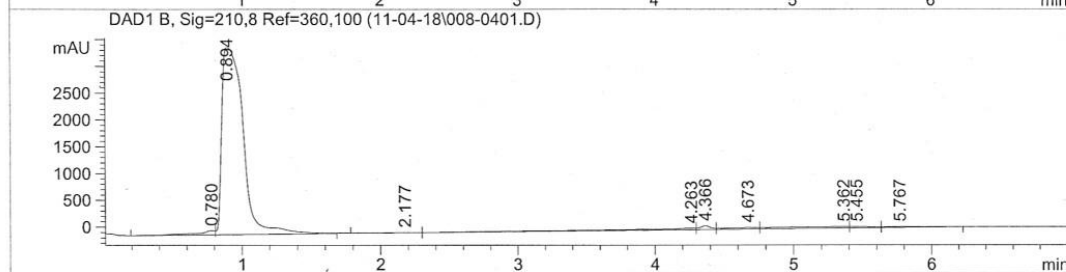
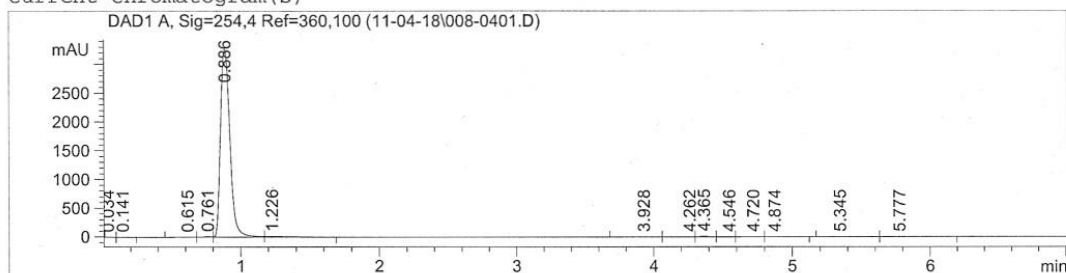
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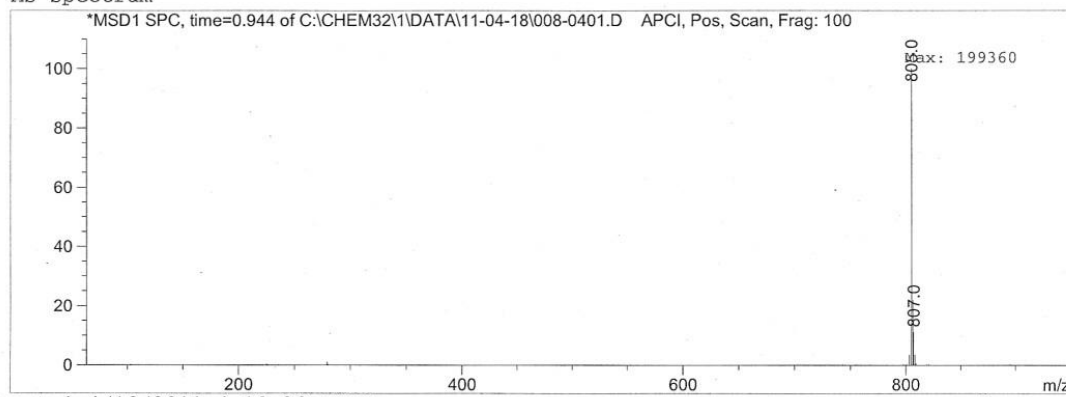
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Current Chromatogram(s)



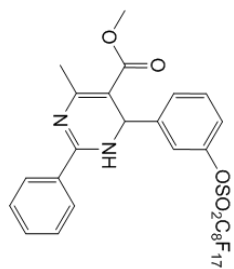
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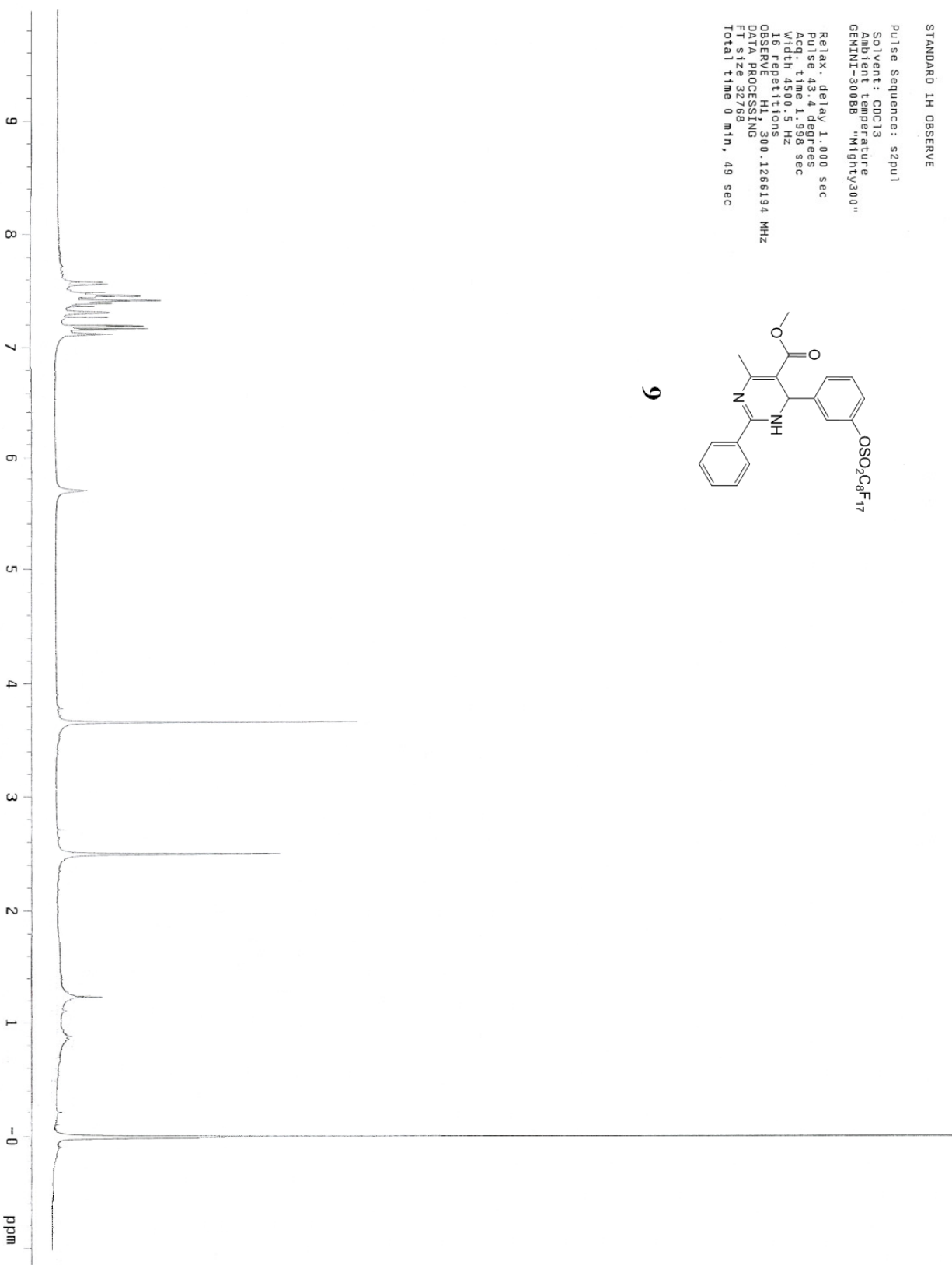
STANDARD 1H OBSERVE

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9

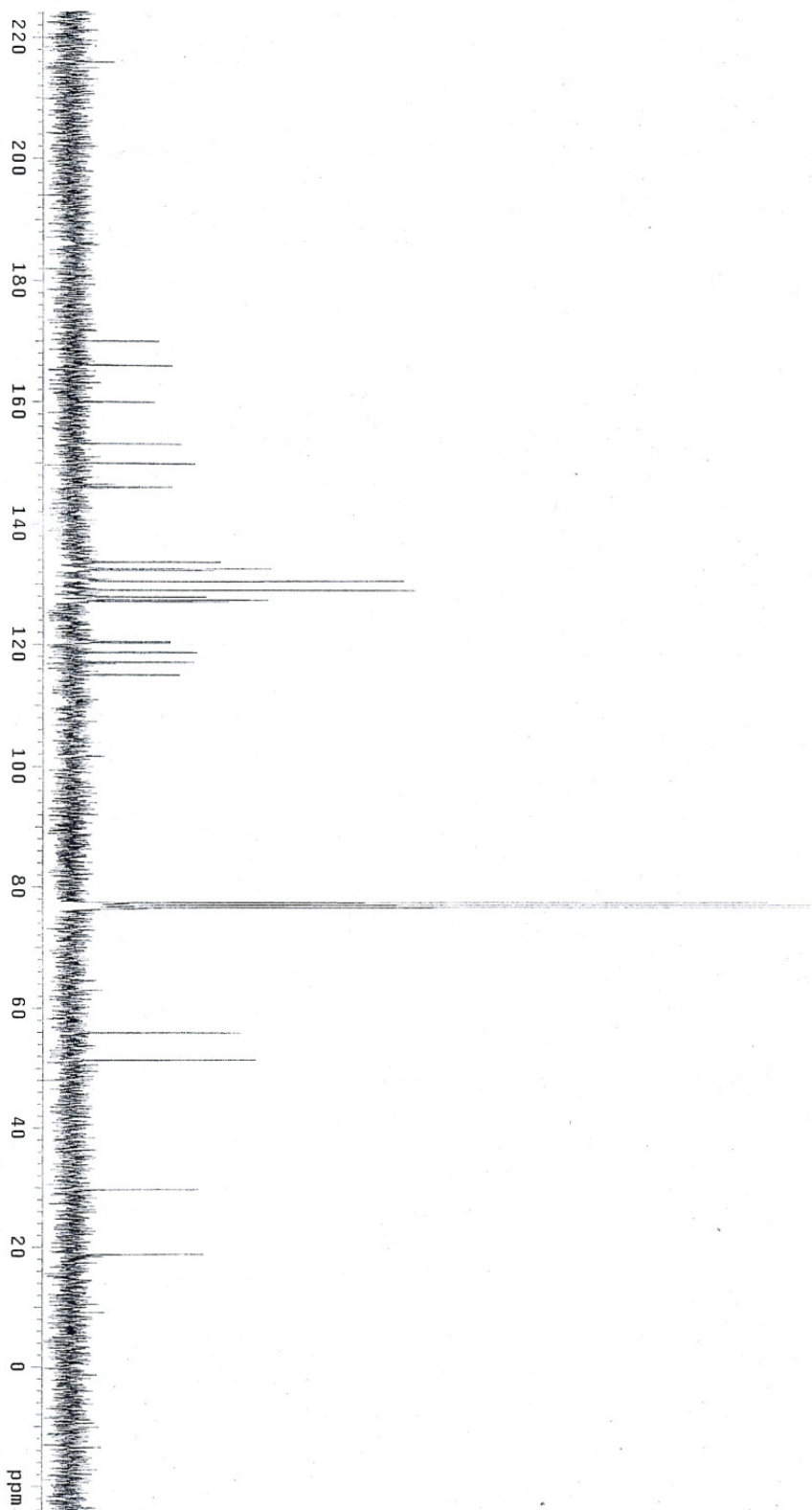
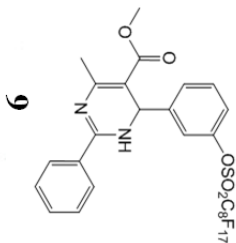


13C OBSERVE

Pulse Sequence: s2pu1

Solvent: CDCl3
Ambient temperature
GEMINI-300B "Mighty300"

Pulse 75.9 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
3072 repetitions
OBSERVE C13, 75.4669010 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 db
continuously on
VAlTz-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 48 min, 10 sec



Print of all graphic windows

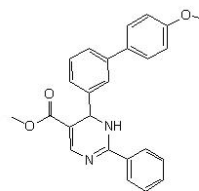
Data File : C:\CHEM32\1\DATA\11-01-04\SIG1000001.D

Sample Name : Suz Lib-S 412

=====
Acq. Operator : Bruno
Acq. Instrument : Instrument 1
Injection Date : 1/4/2011 2:22:04 PM

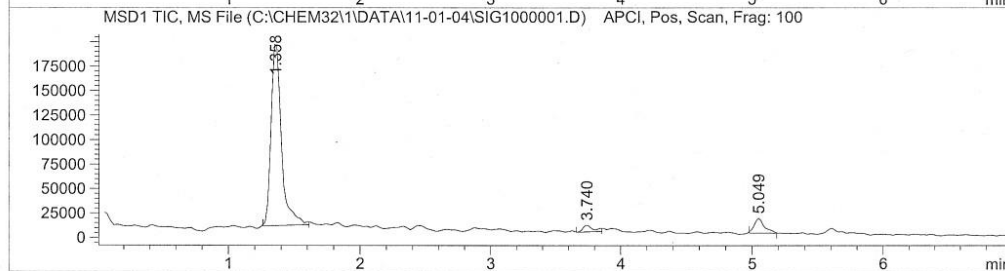
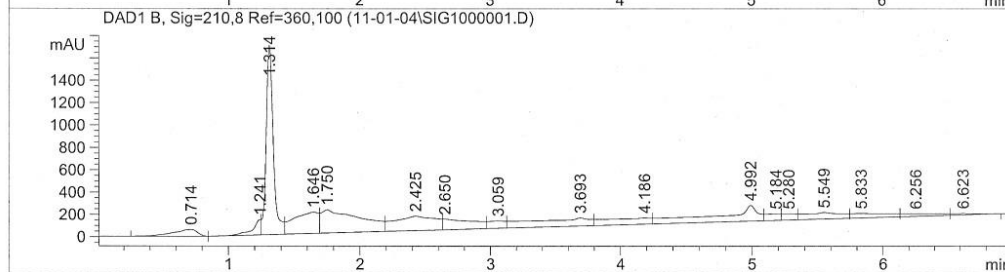
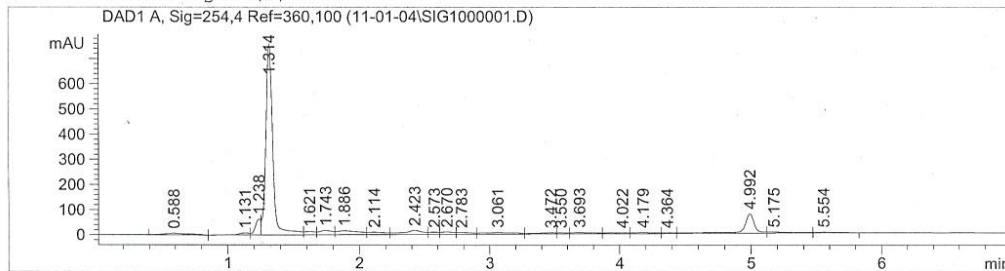
Seq. Line : 1
Location : Vial 5
Inj : 1
Inj Volume : 4 µl

Acq. Method : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed : 12/23/2010 11:36:52 AM by Zijuan
Analysis Method : C:\CHEM32\1\METHODS\CINCHONA.M
Last changed : 9/23/2010 6:12:44 PM by Stephanie

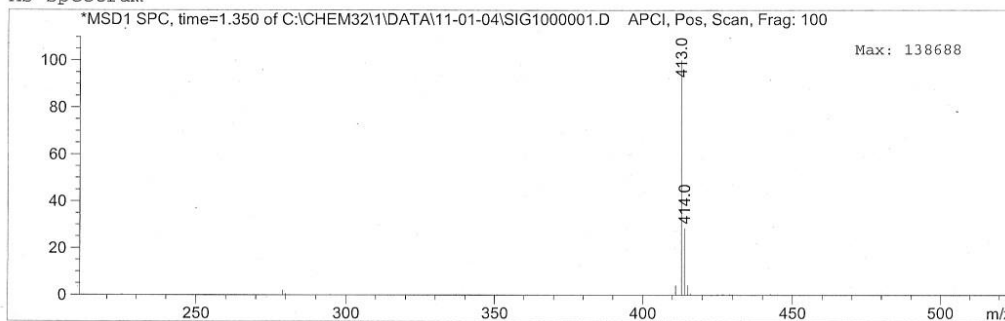


7b

Current Chromatogram(s)



MS Spectrum

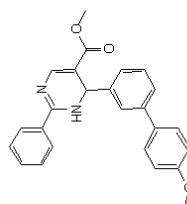


STANDARD 1H OBSERVE

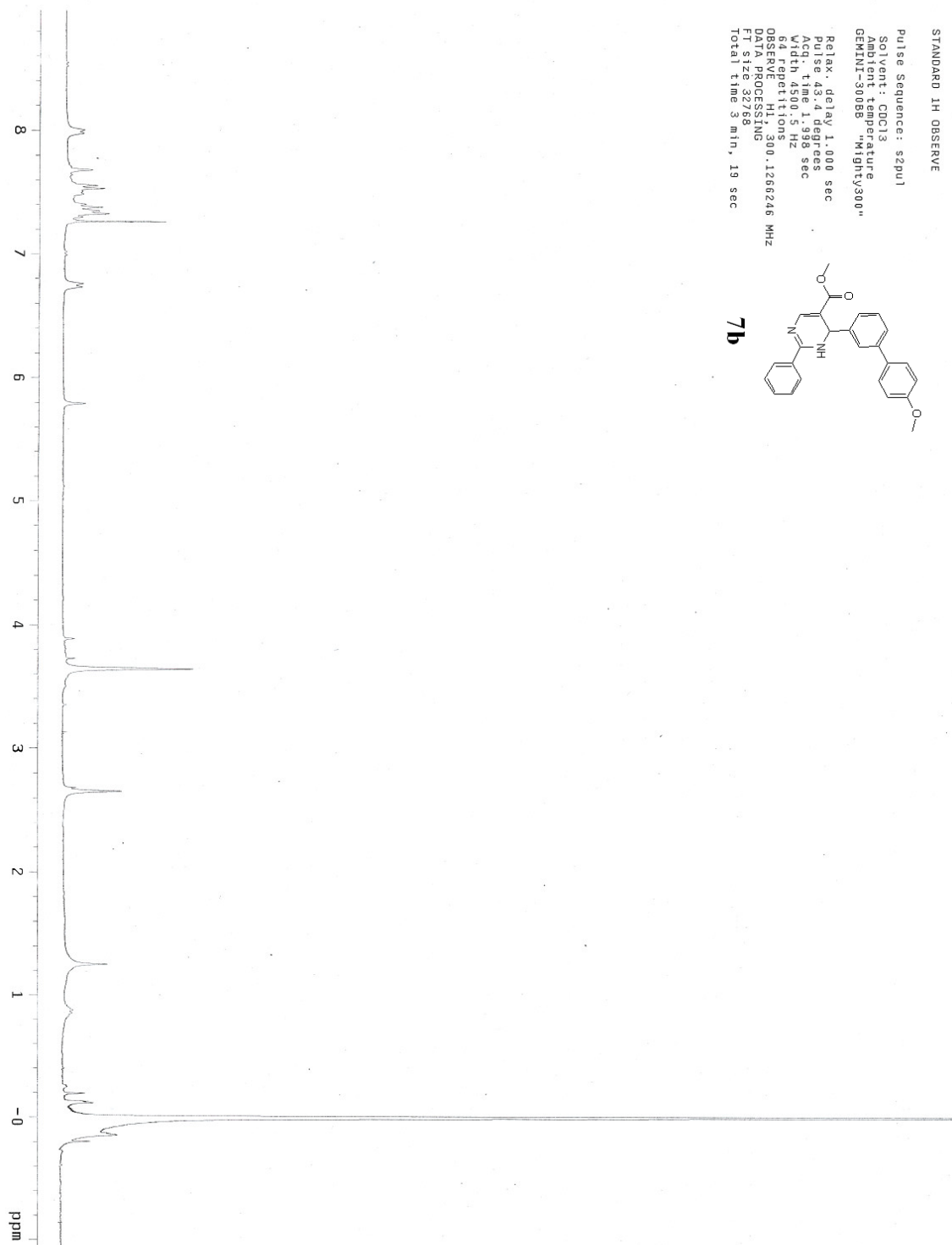
Pulse Sequence: s2pu1

Solvent: CDCl3
SOLVENT_TEMPERATURE
GEMINAL300BS Magnity300"

Relax: delay 1.000 sec
Pulse: 4.310 degrees
Acq: time 1.998 sec
Width: 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1265248 MHz
DATA PROCESSING
F1: size 32768
Total time 3 min, 19 sec

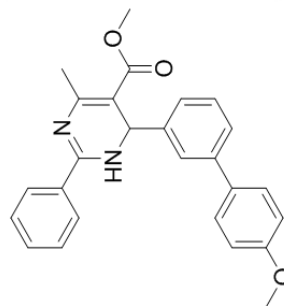


7b



13C OBSERVE

Pulse Sequence: s2pu1
Solvent: CDCl3
Acq. Temperature
GEMINI-300BB "Mighty300"
Relax. delay 2.000 sec
Pulse 67.8 degrees
Acq. time 1.815 sec
Width 20000.0 Hz
3300 repetitions
OBSERVE C13, 75.466900 MHz
DECODE C13, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
F1 size 131072
Total time 1 hr, 45 min, 17 sec



7b

