

Stereocontrolled New efficient asymmetric synthesis of taranabant, a CB1R inverse agonist for the treatment of obesity

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General

All reagents were used directly from a commercial source without any further purification. Solvents were found to contain 50 ppm water or less via Kf titration. All reactions were performed under a nitrogen atmosphere using glassware stored at ambient temperature and humidity. Flash column chromatography was performed with Silica gel 60 (0.04-0.063 mm particle size). Thin layer chromatography was performed with Silica Gel 60 F₂₅₄ precoated plates (2.5x7.5 cm, 250 um thickness). ¹H and ¹³C NMR spectra were recorded using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) and referenced to the solvent signal (CHCl₃ and CDCl₃ for ¹H and ¹³C, respectively. ¹³C NMR spectra were recorded with composite pulse (Waltz16) proton decoupling. Chemical ionization and high resolution mass spectra were acquired using electrospray ionization in the positive ion mode. Optical rotations were recorded at 20 °C using a cell length of 1.0 dm. [α]_D was calculated according to the following equation:

$$[\alpha]_D = \alpha_{(\text{observed})} / (d * c)$$

where *d* refers to the cell length in decimeters and *c* refers to the concentration in g/mL. Chiral stationary phase HPLC signals were recorded at both 210 nm and 250 nm.

Direct synthesis of **1** via asymmetric hydrogenation of cyanoenamide **6**

In a N₂-filled glove box, ligand **16** (364 mg, 0.61 mmol) and COD₂Rh BF₄ (23.8 mg, 0.59 mmol) were added to a 50 mL vial containing a stir bar, followed by 1,2-dichloroethane (10 mL). The resulting solution was aged at RT with stirring for 1 hour, and transferred to rinse chamber stainless steel bomb. An extra 15 mL of 1,2-

dichloroethane was used to rinse the vial and this was also charged to the rinse chamber of the bomb.

In a N₂-filled glove box, a solution of enamide **6** (12.0 g, 23.4 mmol) in 100 mL of 1,2-dichloroethane was charged to the main chamber of the stainless steel bomb followed by a rinse of 25 mL of 1,2-dichloroethane. The stainless steel bomb was removed from the glove box and connected to a stainless steel autoclave. The autoclave was degassed with N₂ five times and then placed under partial vacuum. The substrate solution was drawn into the autoclave followed by the catalyst solution. The autoclave was sealed and degassed with N₂ purges three times. The autoclave was then degassed with H₂ purges three times, and pressurized up to 500 psi. The stirrer was initiated, and the temperature was raised to 80 °C. The reaction was aged at 500 psi, 80 °C for 7 hours. The reaction was cooled to room temperature, and the resulting solution was assayed for ee and purity (11.5 g assay of **1**, 95% yield, 95.0 LCAP, 84.0% ee). Separation of enantiomers by HPLC (Chiralcel OD-H, 93% hexane, 7% EtOH, 0.7 mL/min, Tr=10.5, 12.8 min). Treatment of an MTBE solution (10 mL/g) of this crude hydrogenation product with Ecosorb C-941, followed by crystallization via addition of heptane, afforded **1** as an MTBE hemisolvate (12.2 g isolated, 88% yield from **6**). Subsequent ee upgrade and isolation of the anhydrous form of **1** was performed as described in reference 4.

Current Data Parameters
NAME 055
EXPNO 1
PROCNO 1

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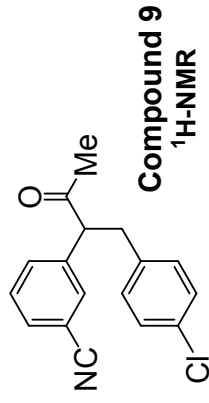
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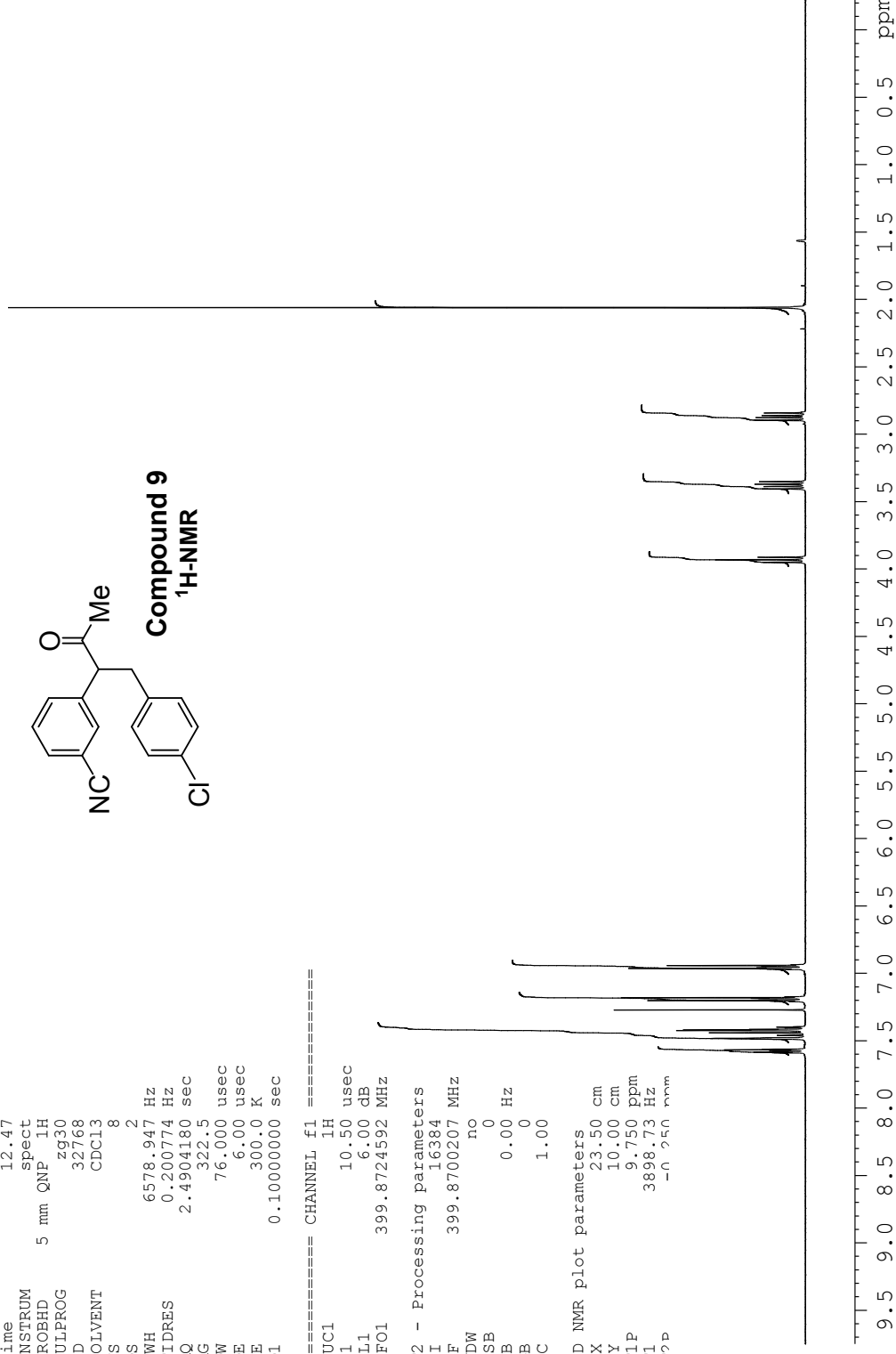
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1D NMR plot parameters

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CY 10.00 cm
F1P 9.750 ppm
F1 3898.73 Hz
F2P -0.250 ppm



Compound 9
¹H-NMR



Current Data Parameters

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PROCNO 1

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PL1 5.00 dB
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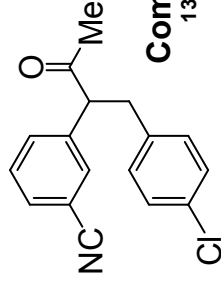
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131.36
130.29
129.86
128.71
118.35
113.30

60.72
76.75
77.07
77.39

37.95

29.92



Compound 9
¹³C-NMR

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Current Data Parameters
NAME 055
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters

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TD 32768
SOLVENT CDCl3
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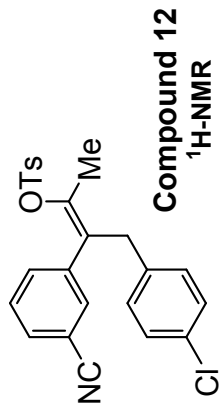
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1D NMR plot parameters

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CY 10.00 cm
F1P 9.750 ppm
F1 3898.73 Hz
F2P -0.250 mm



Compound 12
¹H-NMR



```

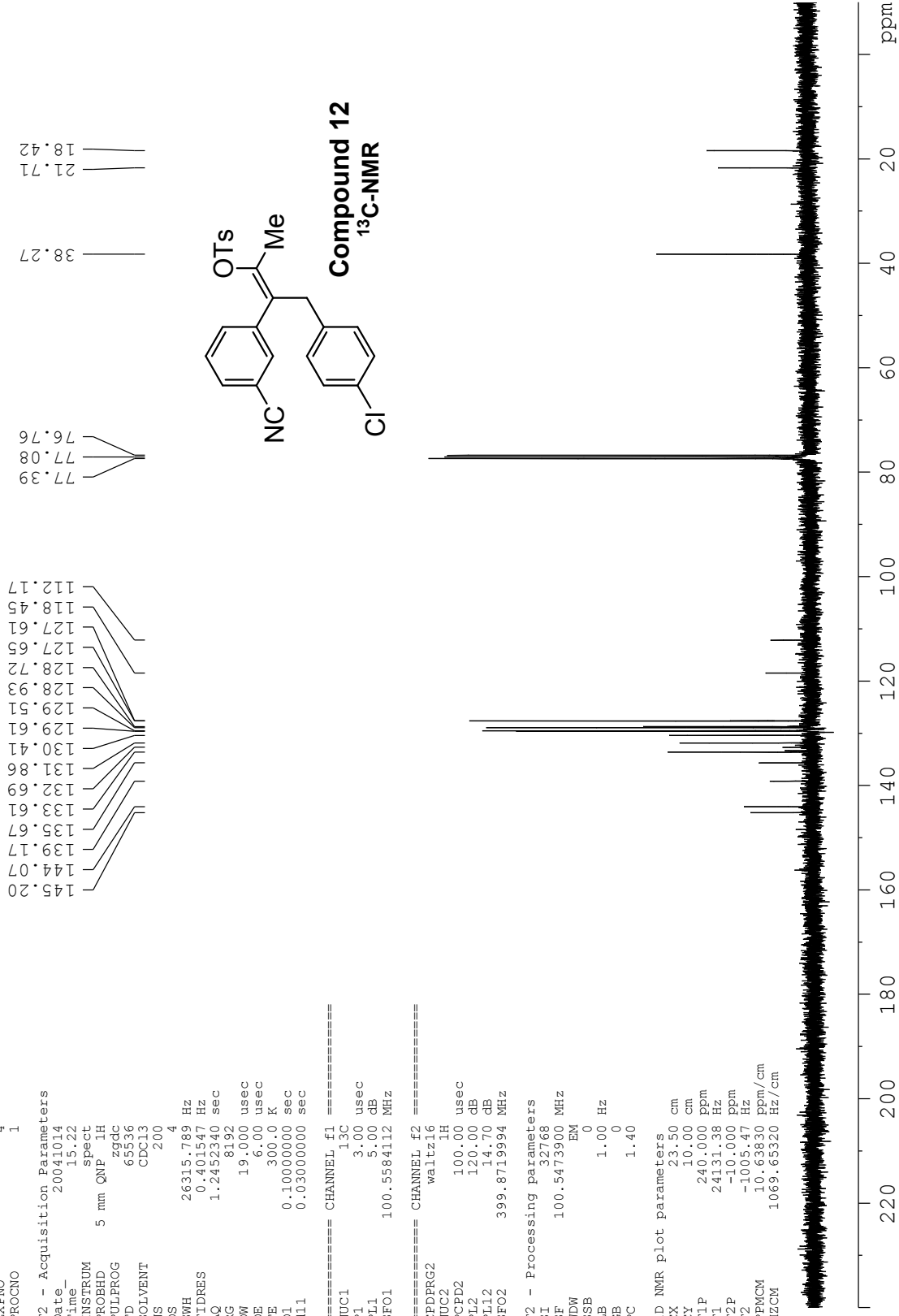
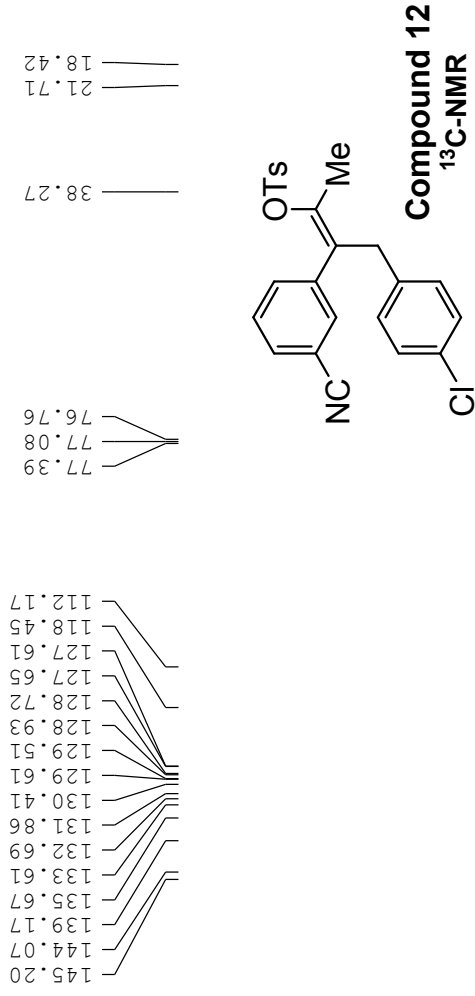
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SOLVENT            CDCl3
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FIDRES             0.401547 Hz
AQ                 1.2452340 sec
RG                 8192
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DE                 6.00 usec
TE                 300.0 K
D1                 0.10000000 sec
d11                0.03000000 sec

===== CHANNEL f1 =====
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P1                  3.00 usec
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===== CHANNEL f2 =====
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PL2                120.00 dB
PL12               14.70 dB
SFO2               399.8719994 MHz

F2 - Processing parameters
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WDW                EM
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LB                 1.00 Hz
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PC                 1.40
  
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Current Data Parameters
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PROCNO 1

F2 - Acquisition Parameters

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TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
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D1 0.1000000 sec

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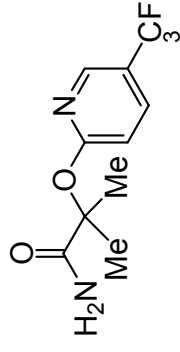
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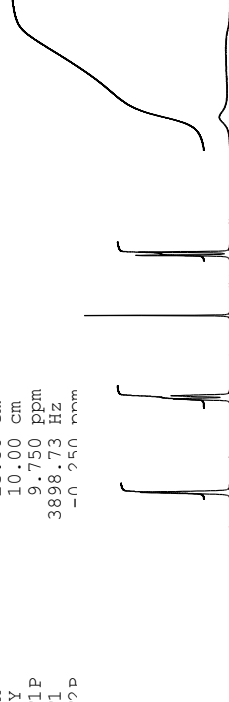
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LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters

CX 23.50 cm
CY 10.00 cm
F1P 9.750 ppm
F1 3898.73 Hz
F2P -0.250 mm



Compound 8
¹H-NMR



9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

Current Data Parameters
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PROCNO 1

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FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
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TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec

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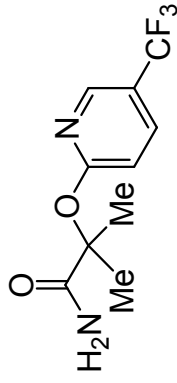
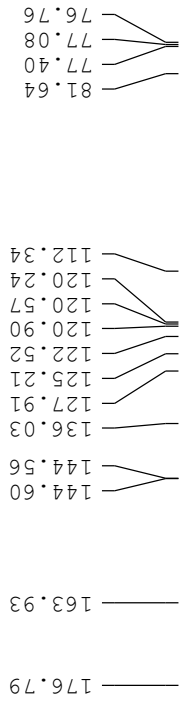
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PL12 14.70 dB
SFO2 399.8719994 MHz

F2 - Processing parameters

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SF 100.5473900 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters

CX 23.50 cm
CY 10.00 cm
F1F 240.000 ppm
F1 24131.38 Hz
F2P -10.000 ppm
F2 -1005.47 Hz
PPMCM 10.63830 ppm/cm
HZCM 1069.65320 Hz/cm



Compound 8
¹³C-NMR

Current Data Parameters
NAME 055
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters

Date_ 20041015
Time_ 11.35
INSTRUM spect
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PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
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FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 64
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DE 6.00 usec
TE 300.0 K
D1 0.1000000 sec

===== CHANNEL f1 =====

NUC1 1H
P1 10.50 usec
PL1 6.00 dB
SFO1 399.8724592 MHz

F2 - Processing parameters

SI 16384
SF 399.8700207 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters

CX 23.50 cm
CY 10.00 cm
F1P 9.750 ppm
F1 3898.73 Hz
F2P -0.250 mm



Current Data Parameters
NAME 055
EXPNO 8
PROCNO 1

F2 - Acquisition Parameters

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FIDRES 0.401547 Hz
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RG 8192
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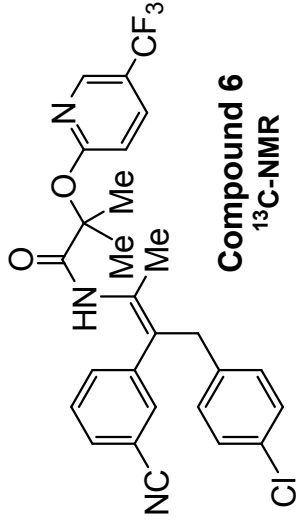
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PL12 14.70 dB
SFO2 399.8719994 MHz

F2 - Processing parameters
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SF 100.5473900 MHz
WDW EM
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LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 23.50 cm
CY 10.00 cm
F1F 240.000 ppm
F1 24131.38 Hz
F2P -10.000 ppm
F2 -1005.47 Hz
PPMCM 10.63830 ppm/cm
HZCM 1069.65320 Hz/cm

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Compound 6
¹³C-NMR

ppm

Current Data Parameters
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EXPNO 10
PROCNO 1

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FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
DM 19.000 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
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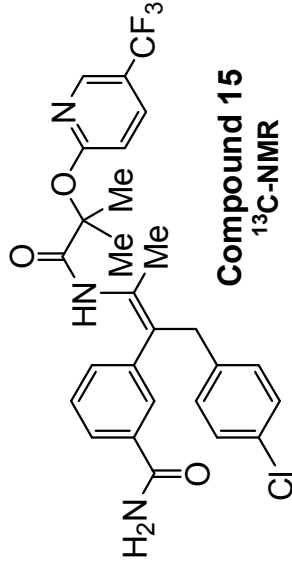
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F2 - Processing parameters

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1D NMR plot parameters
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F2P -10.000 ppm
F2 -1005.47 Hz
PPMCM 10.63830 ppm/cm
HZCM 1069.65320 Hz/cm

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Compound 15
¹³C-NMR

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Current Data Parameters
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 PROCNO 1

F2 - Acquisition Parameters

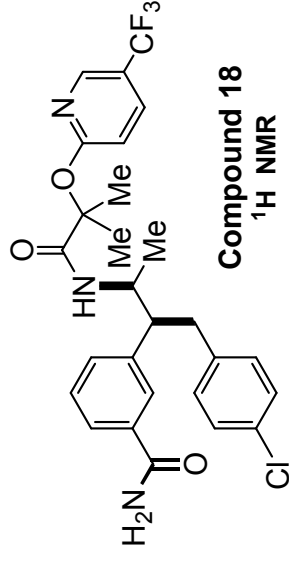
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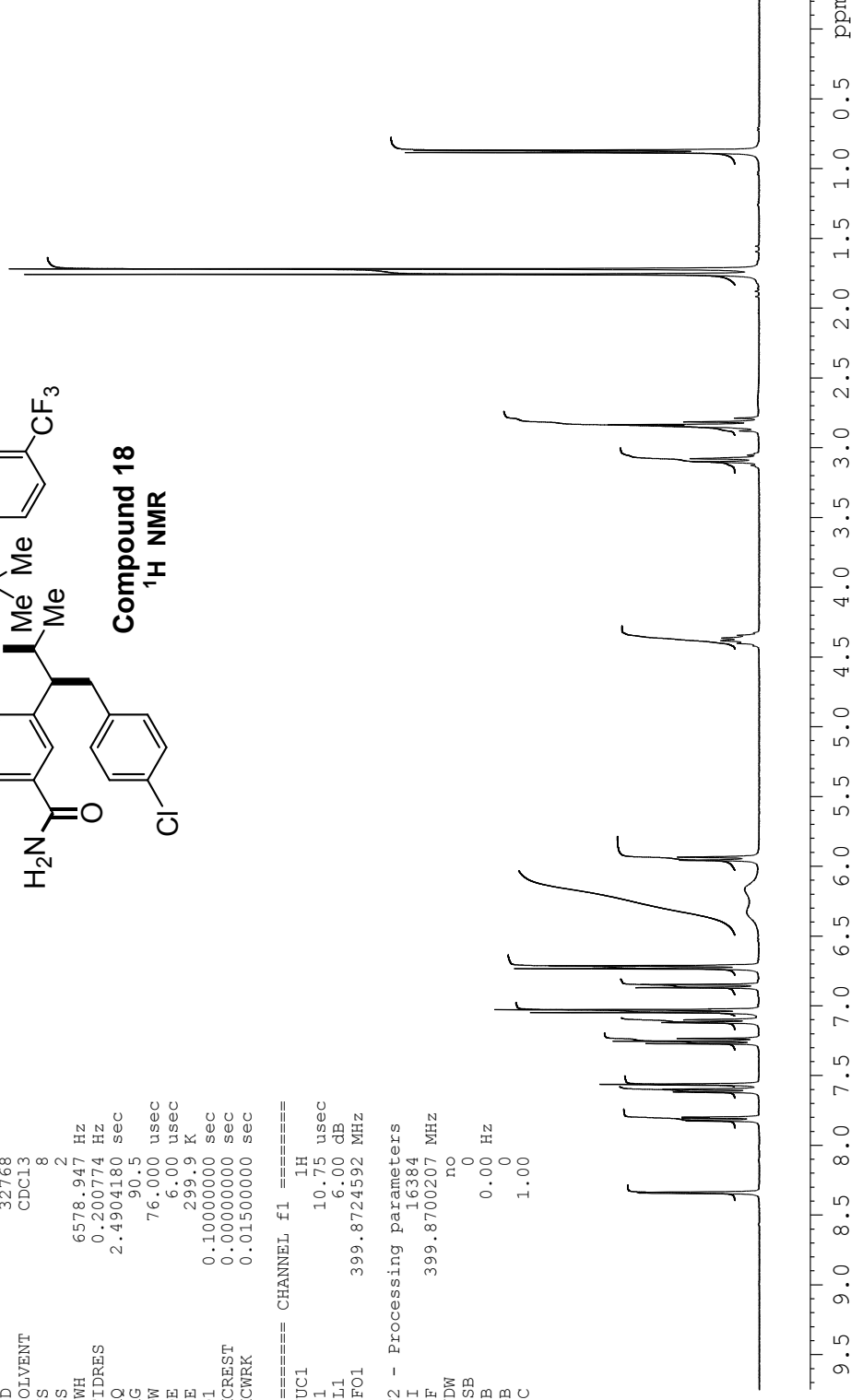
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F2 - Processing parameters

SI 16384
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Compound 18
¹H NMR



Current Data Parameters

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EXPNO 2
PROCNO 1

F2 - Acquisition Parameters

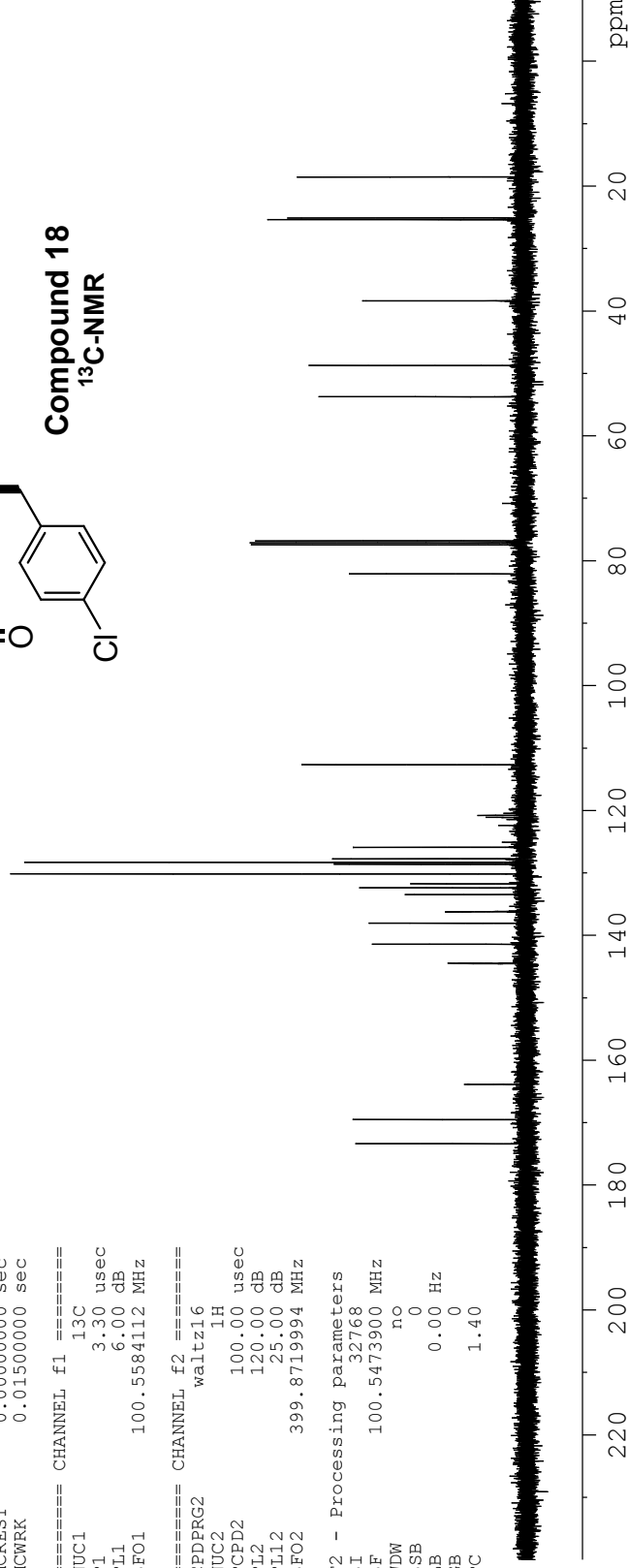
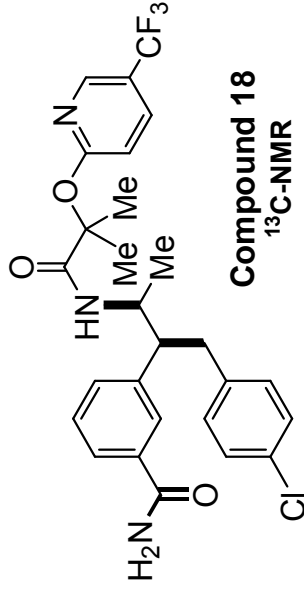
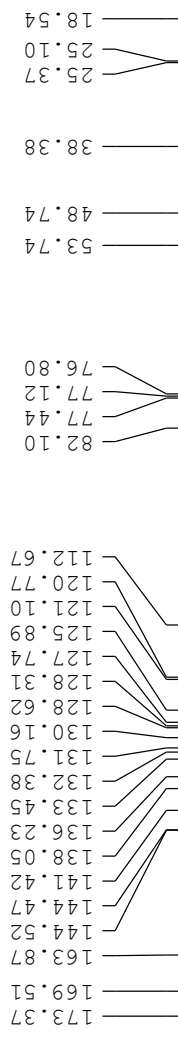
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DE 6.00 usec
TE 300.0 K
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d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
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SFO1 100.5584112 MHz

===== CHANNEL f2 =====
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PL12 25.00 dB
SFO2 399.8719994 MHz

F2 - Processing parameters

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GB 0
PC 1.40



Current Data Parameters
NAME 055
EXPNO 15
PROCNO 1

F2 - Acquisition Parameters

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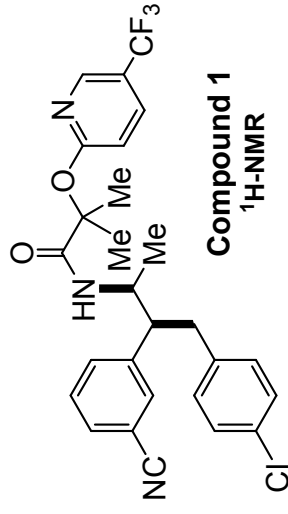
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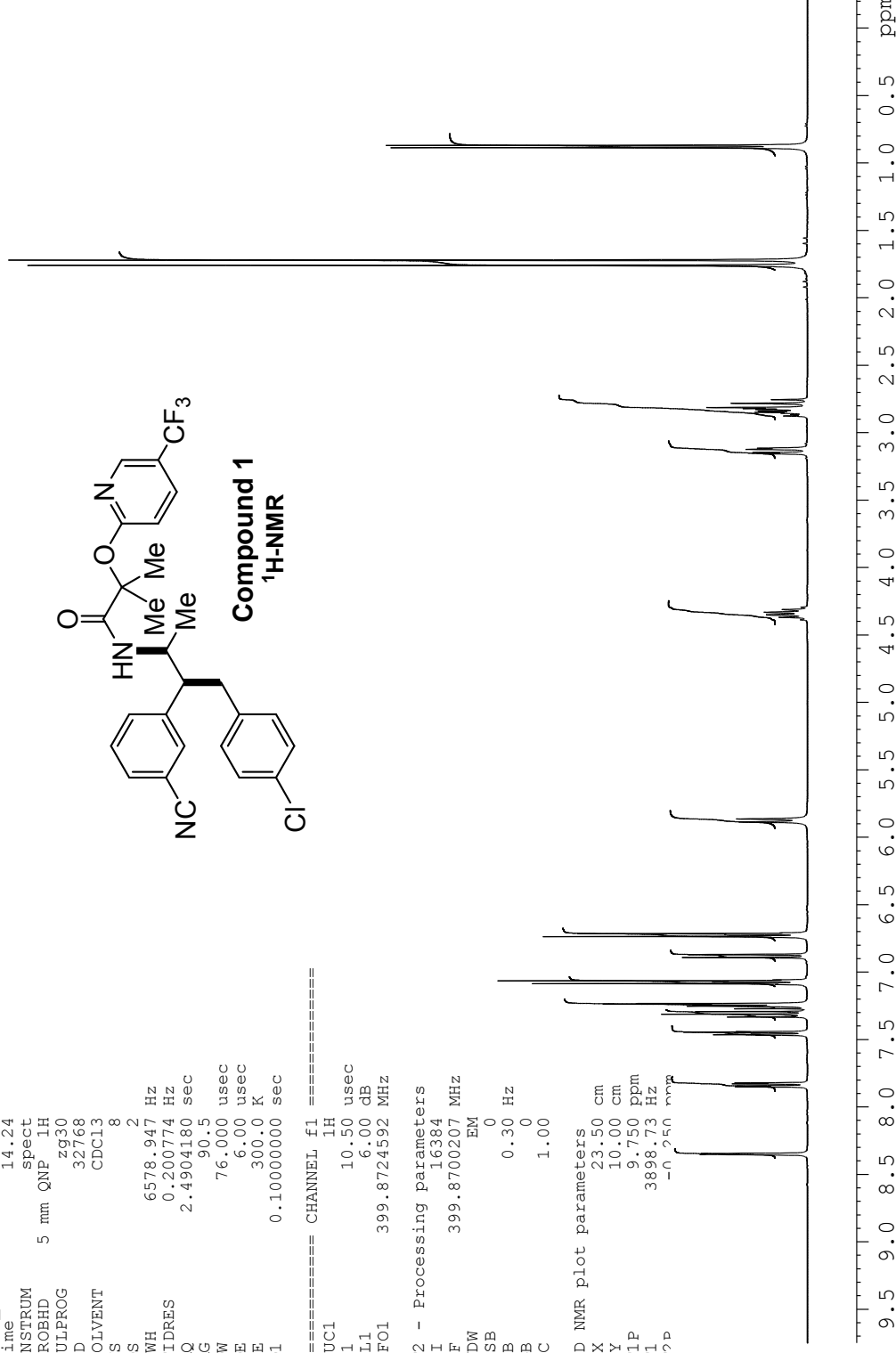
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GB 0
PC 1.00

1D NMR plot parameters

CX 23.50 cm
CY 10.00 cm
F1P 9.750 ppm
F1 3898.73 Hz
F2P -0.250 ppm



Compound 1
¹H-NMR



Current Data Parameters
NAME 055
EXPNO 16
PROCNO 1

F2 - Acquisition Parameters

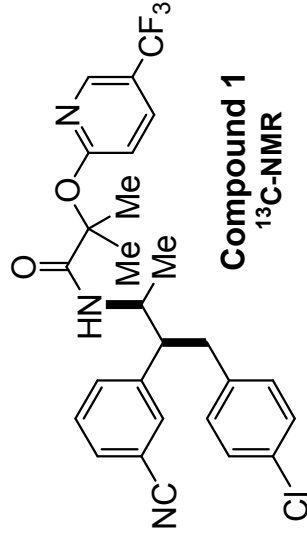
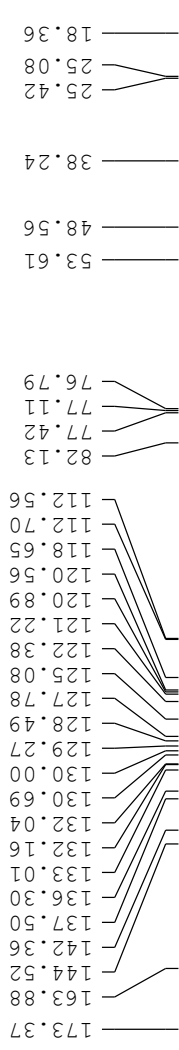
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SOLVENT CDCl3
NS 600
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FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 5792.6
DM 19.000 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec

===== CHANNEL f1 =====
NUC1 13C
P1 3.00 usec
PL1 5.00 dB
SFO1 100.5584112 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 14.70 dB
SFO2 399.8719994 MHz

F2 - Processing parameters
SI 32768
SF 100.5473900 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 23.50 cm
CY 10.00 cm
F1F 148.113 ppm
F1 14892.33 Hz
F2P 107.826 ppm
F2 10841.58 Hz
PPMCM 1.71434 ppm/cm
HZCM 172.37238 Hz/cm



Compound 1
13C-NMR

