Supporting Information

Scalable Asymmetric Synthesis of MK-8998, a T-type Calcium Channel Antagonist

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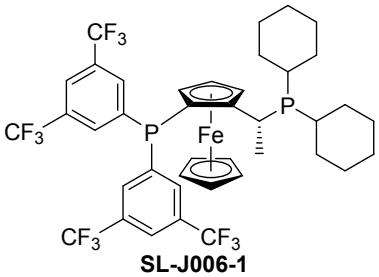
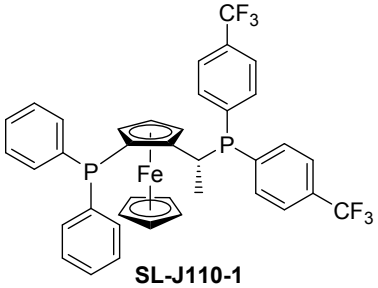
1. Structures of the ligands in Table 1:



SL-J006-1



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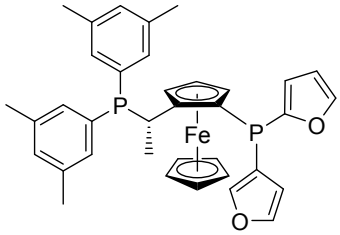

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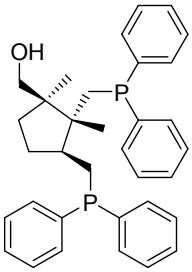
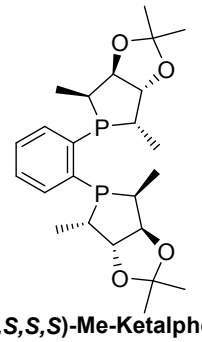
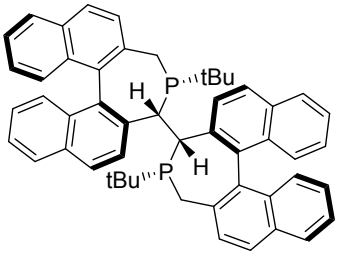


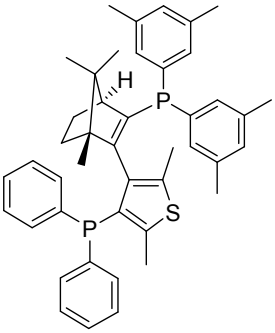
(+)-catASium I



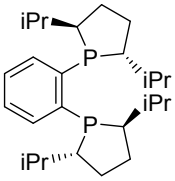
(*S,S,S,S*)-Me-Ketalphos



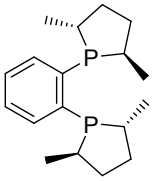
(*S*)-Binapine



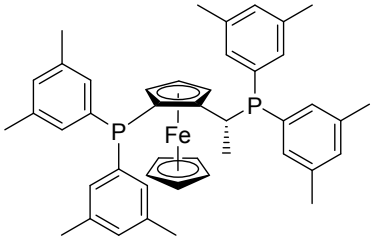
catASium T2(*R*)



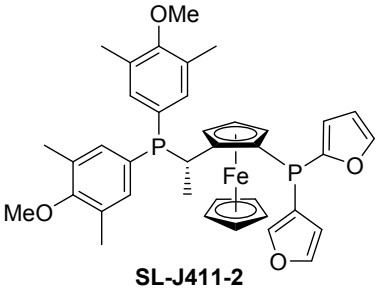
(*R,R*)-iPr-DuPhos



(*R,R*)-Me-DuPhos



SL-J408-1



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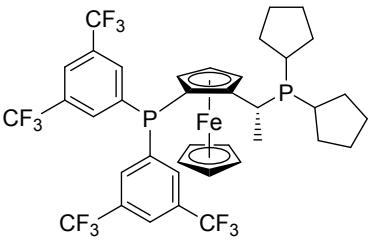

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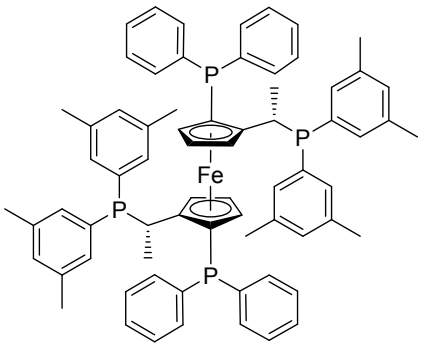
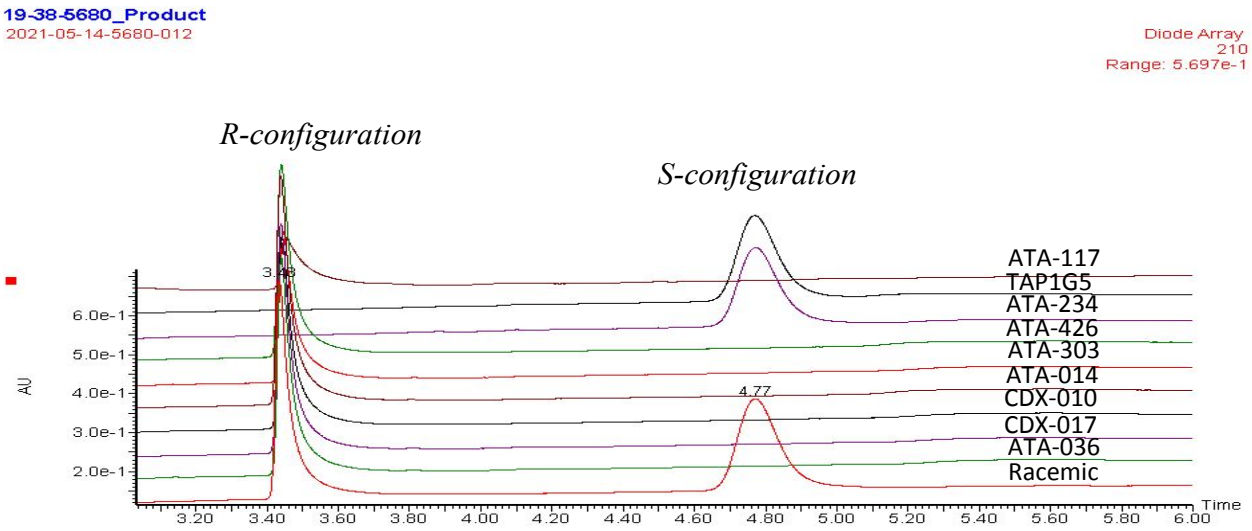


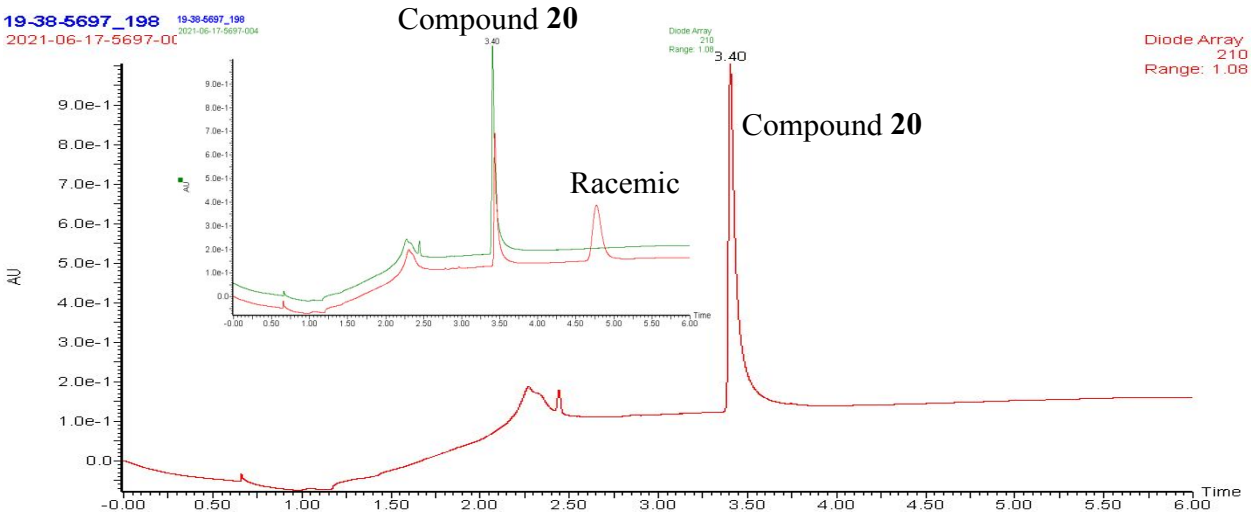
SL-J852-2

2. Copies of chiral SFC spectra for the Table 2.



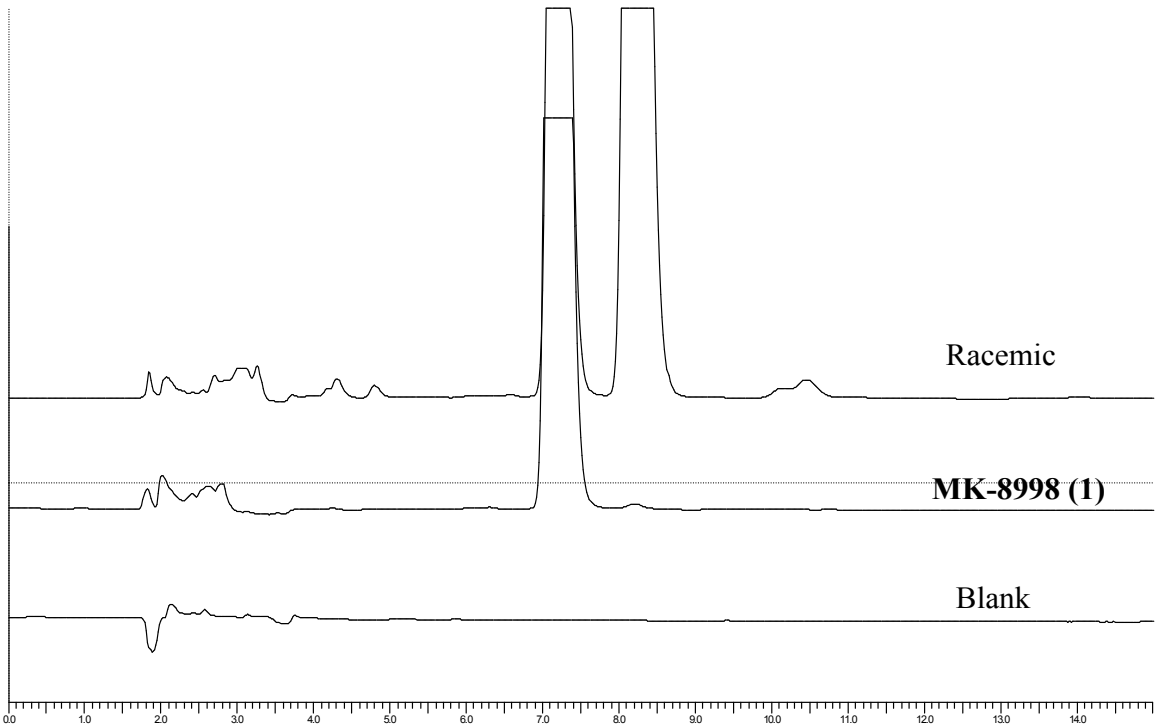
Column: CHIRALPAK IG-3, 150 x 4,6 mm, 3 µm (87524). Mobile Phase A: CO2; Mobile Phase B: 25 mM isobutylamine in ethanol; Gradient conditions: t = 0: 99% A, 1% B; t = 5.00 min, 60% A, 40% B; t = 6.00 min: 60% A, 40% B. Flow rate: 3 mL/min. Wavelength: 210 nm. Column temperature: 40 °C.

3. Copies of chiral SFC spectra for compounds 20



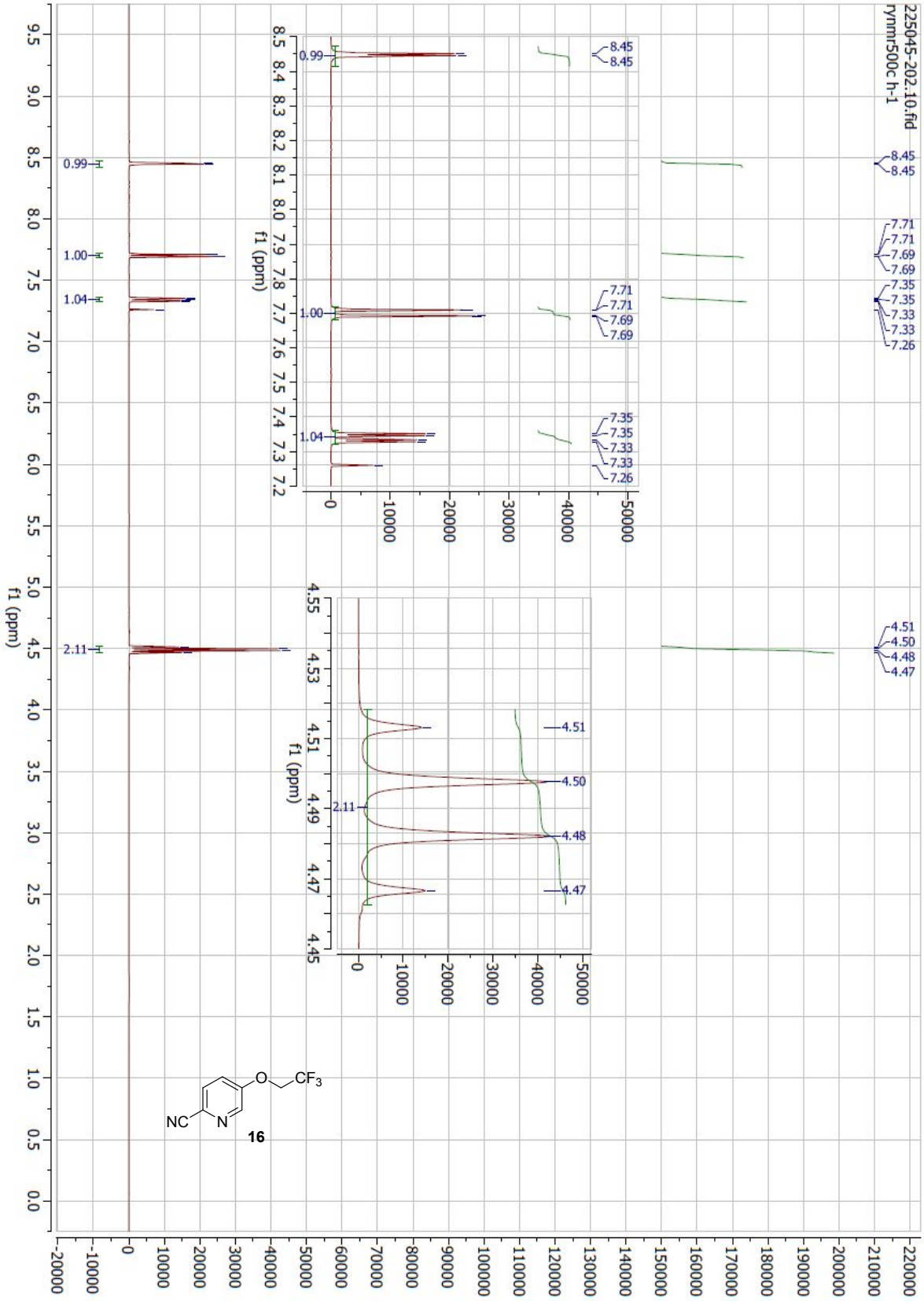
4. Copies of chiral HPLC spectra for compound 1

Instrument: HP1100: Column: Chiralcel OJ-RH, 5u, 4.6 mmID, 150 mm; Detection: UV 220 nm; Injection volume: 10 µL; Column temperature: ambient; Flow Rate 1.0 mL/min; Run Time 15 min; Mobile Phase Composition: isocratic 55/45 A/B (A: water, B: acetonitrile); Sample concentration: ~ 0.2 mg/ml in 80/20 H_2O/MeCN; Retention Time: API major enantiomer (**MK-8998**): ~7.2 min; minor undesired enantiomer: ~8.2 min.

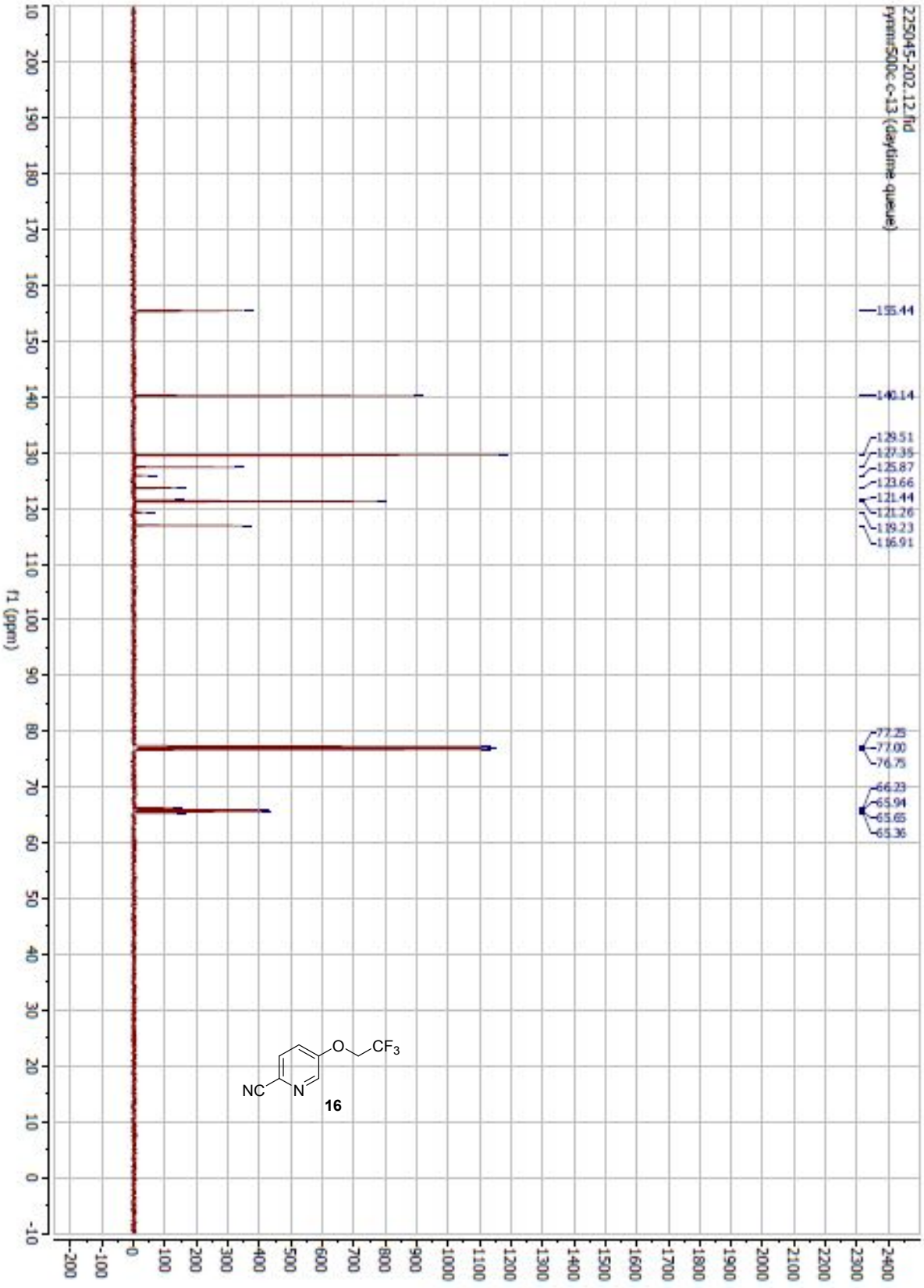

Racemic
MK-8998 (1)
Blank
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0

5. Copies of 1H and 13C NMR spectra for compounds 16, 13, 19, 20 and 1

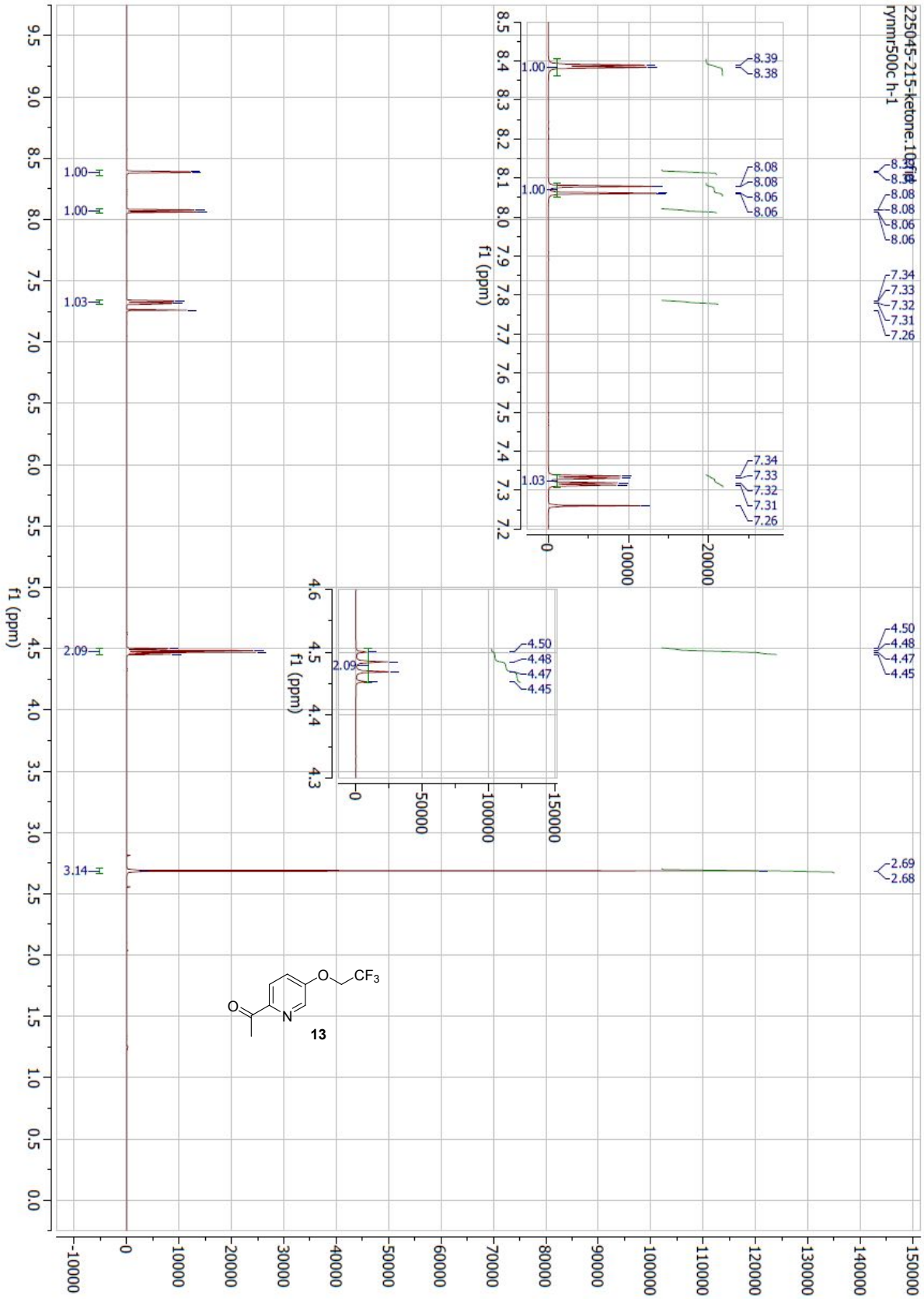
500 MHz NMR for ^{1}H, $CDCl_3$



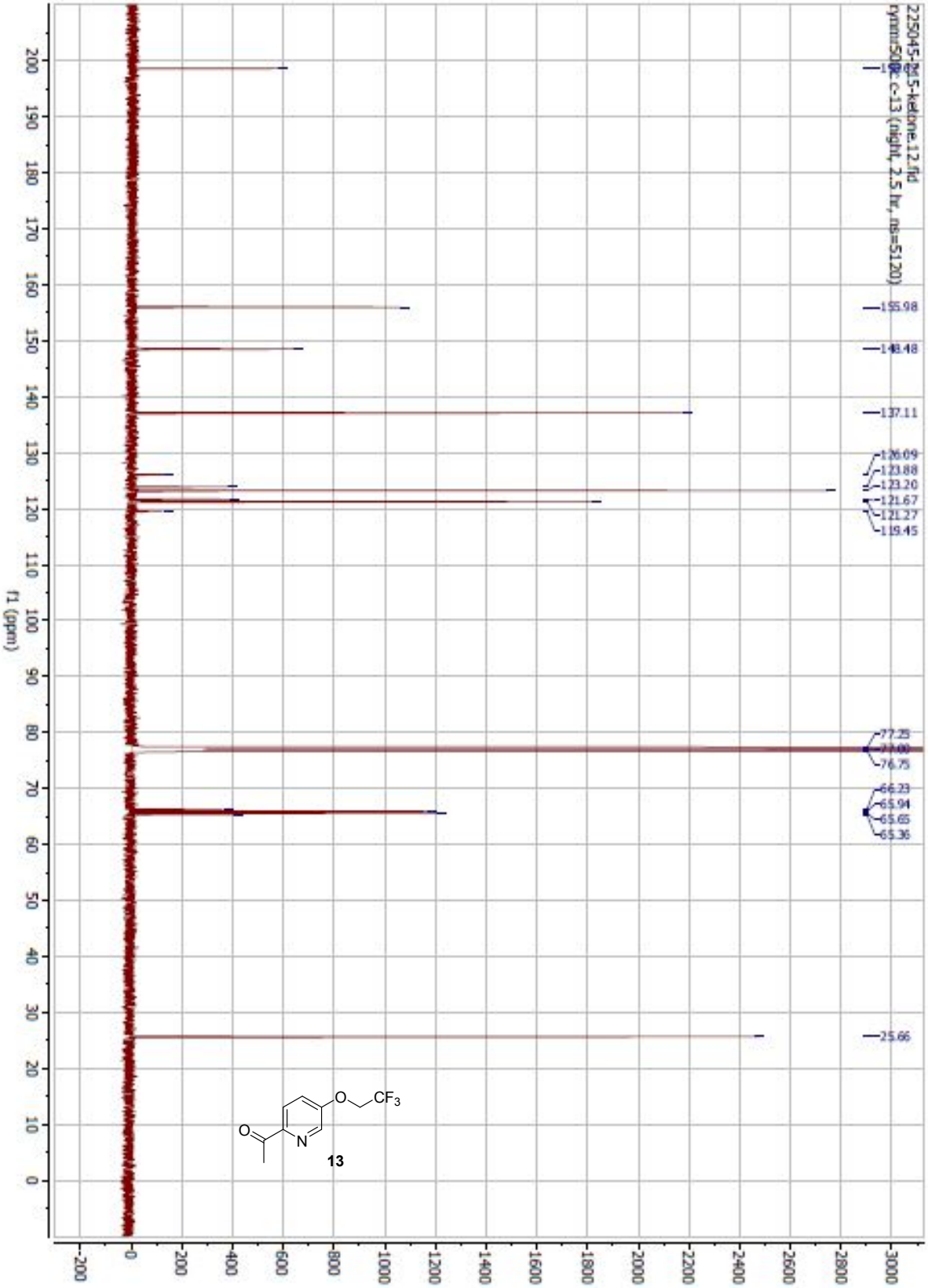
125 MHz NMR for $^{13}C\{^{1}H\}$, $CDCl_3$



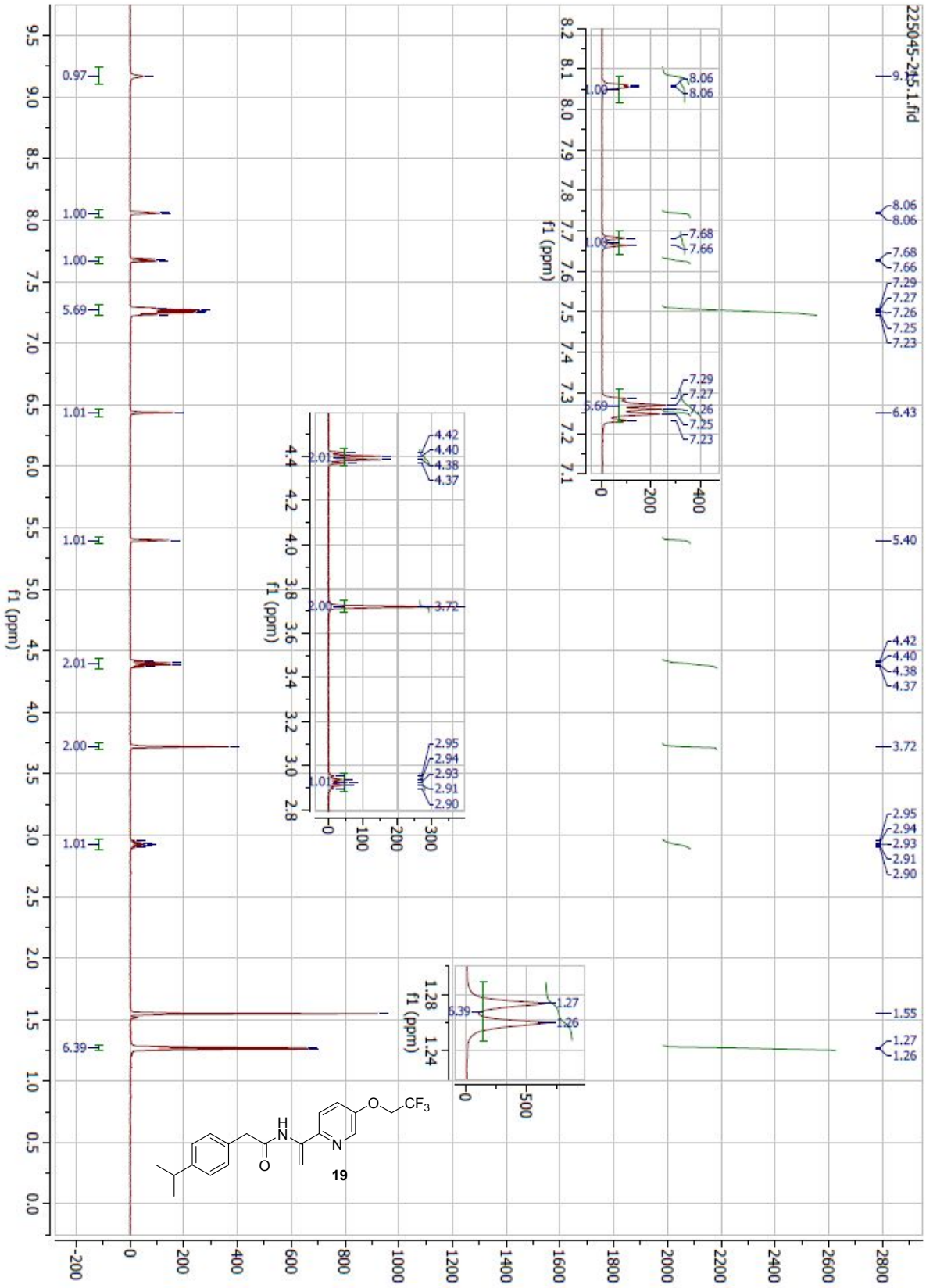
500 MHz NMR for ^{1}H, $CDCl_3$



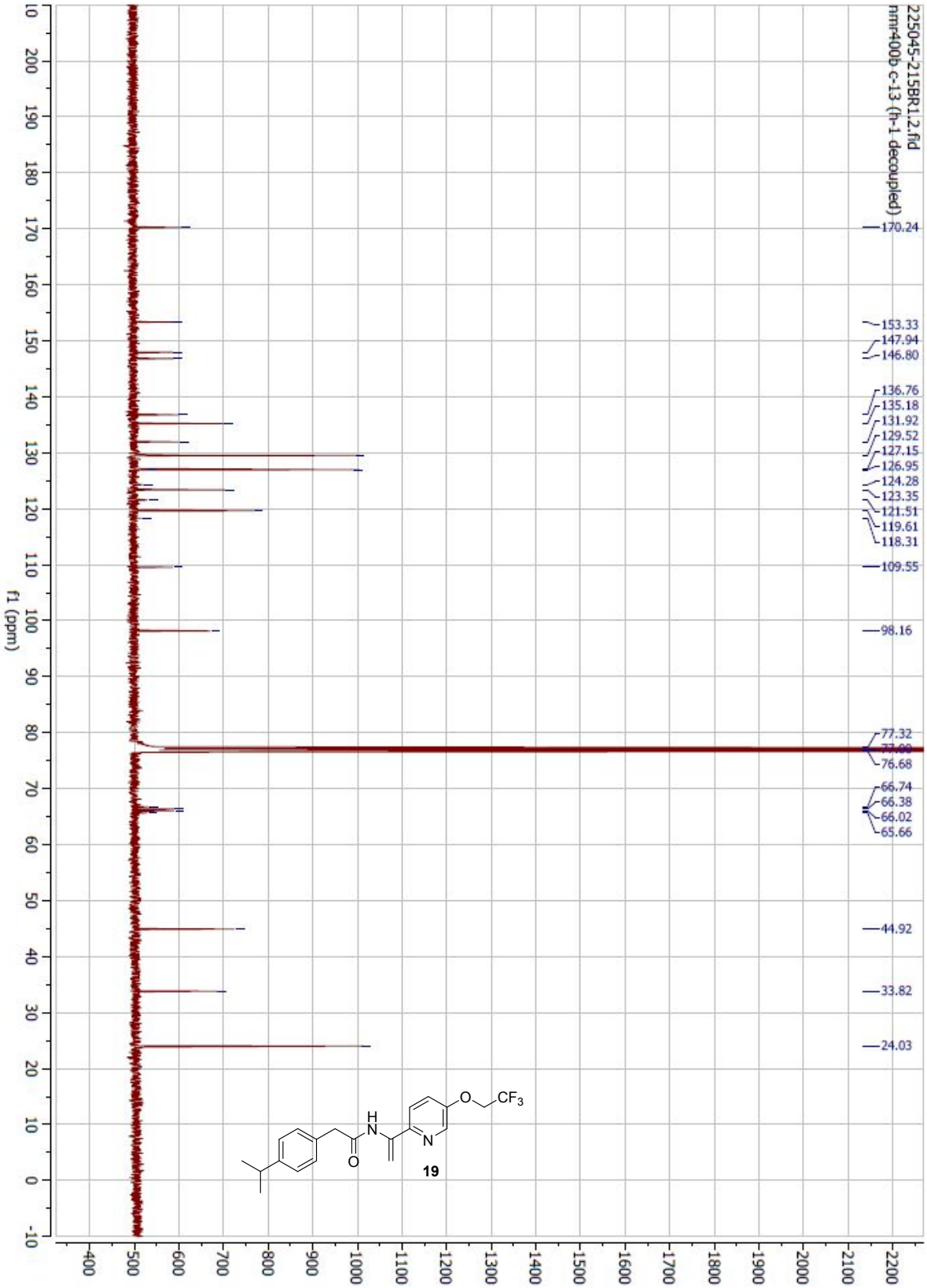
125 MHz NMR for $^{13}C\{^{1}H\}$, $CDCl_3$



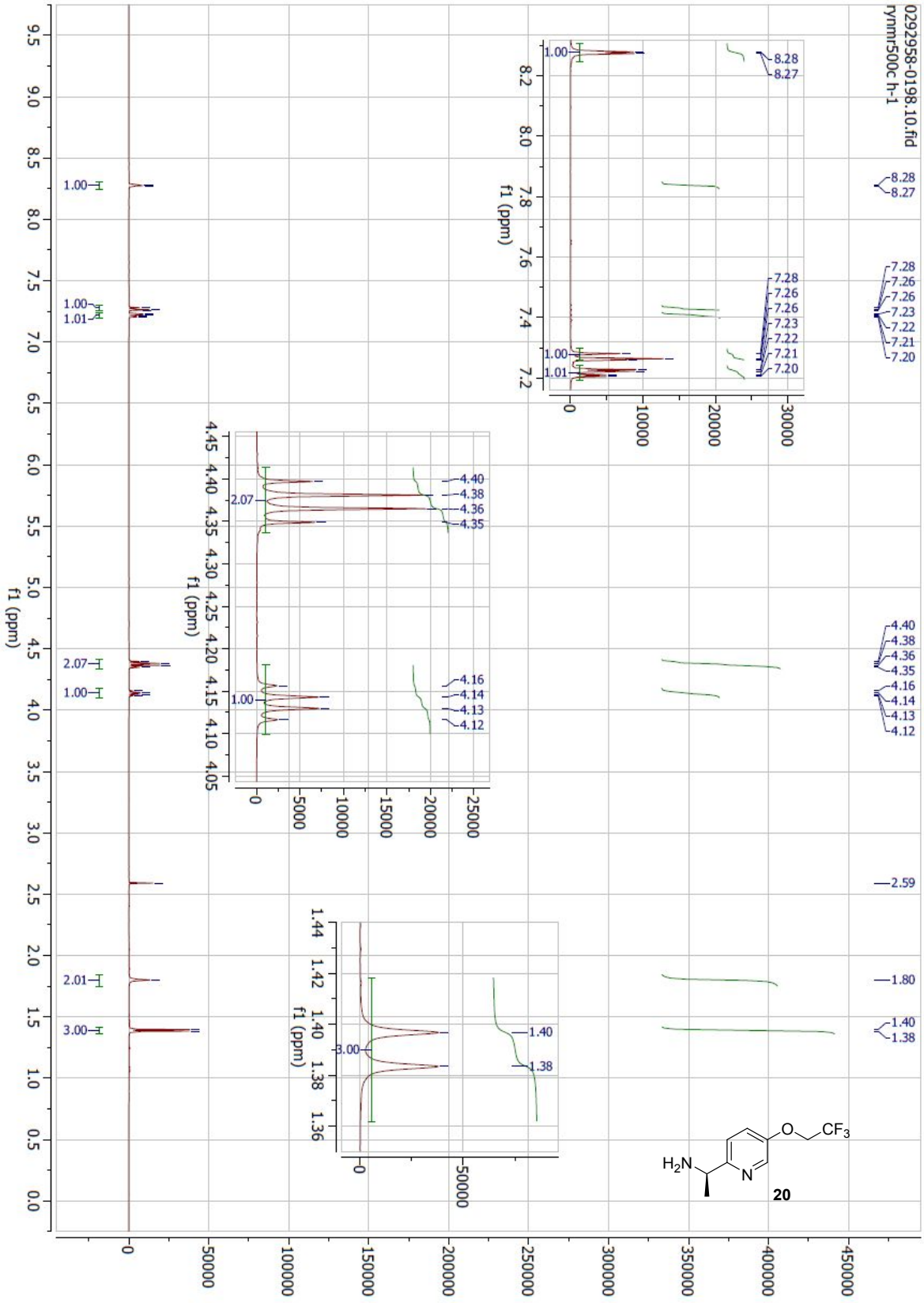
500 MHz NMR for ^{1}H, $CDCl_3$



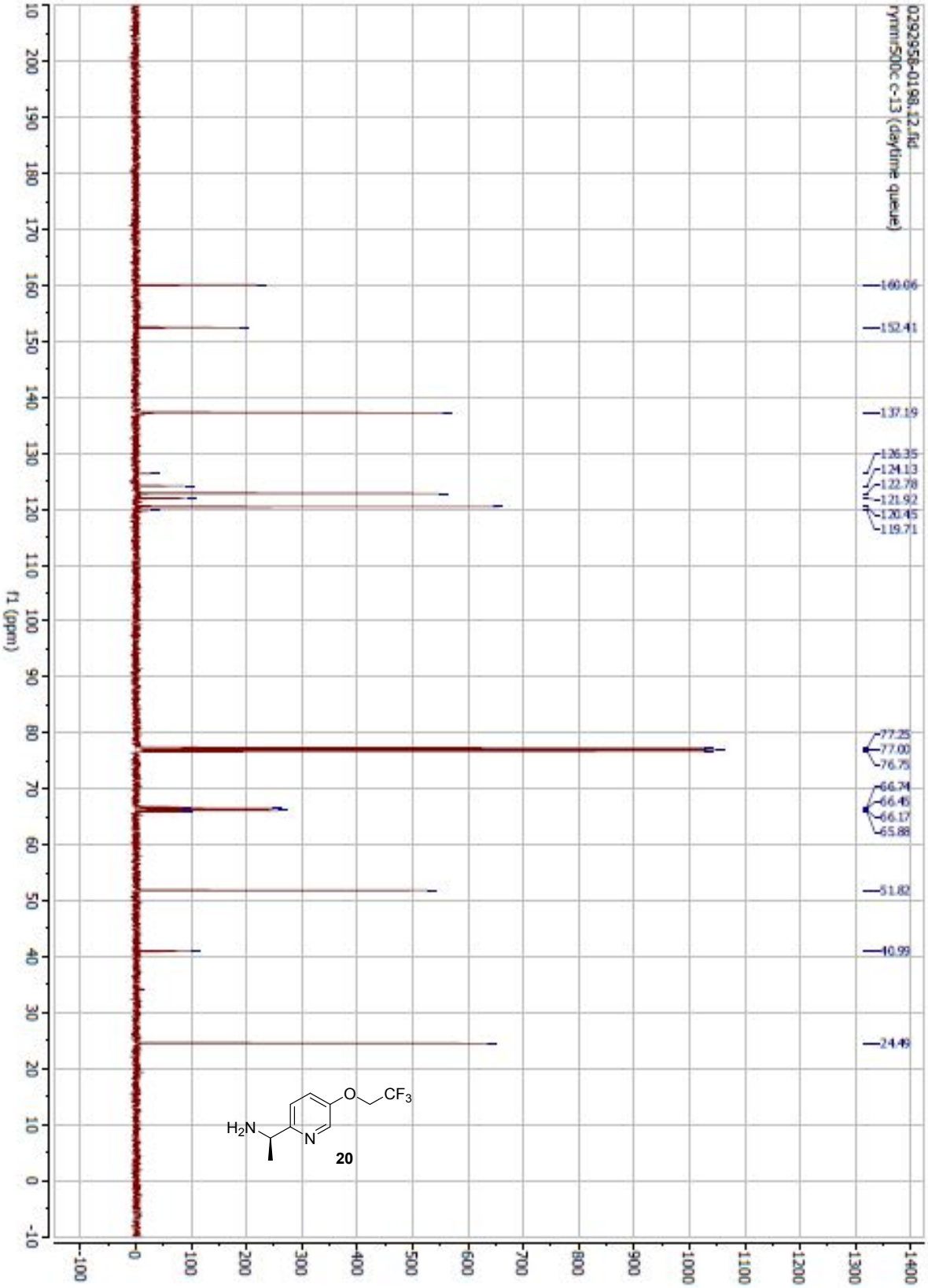
100 MHz NMR for $^{13}C\{^{1}H\}$, $CDCl_3$



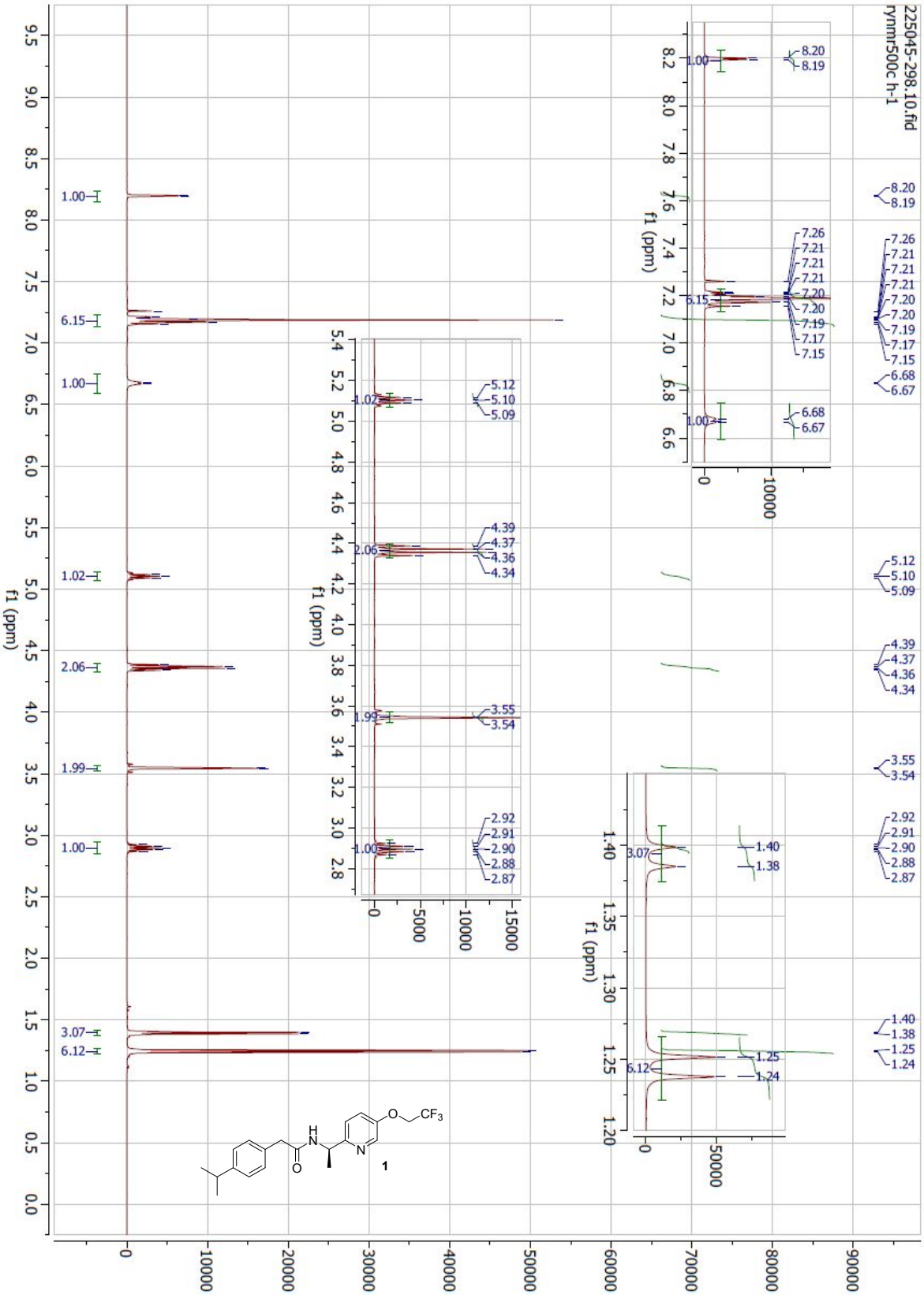
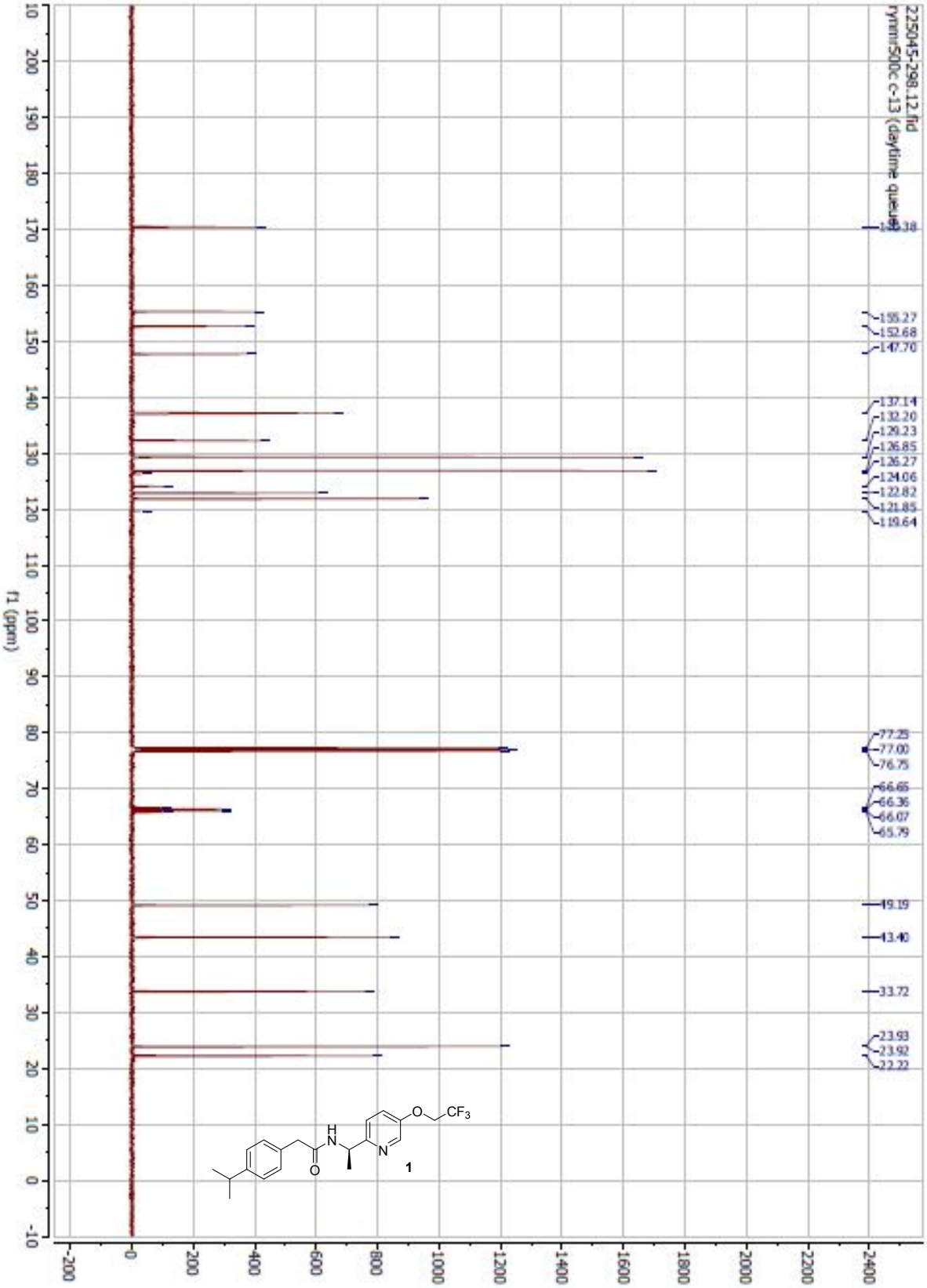
500 MHz NMR for ^{1}H, $CDCl_3$



125 MHz NMR for $^{13}C\{^{1}H\}$, $CDCl_3$



500 MHz NMR for ^1H, $CDCl_3$



125 MHz NMR for $^{13}C\{^{1}H\}$, $CDCl_3$