Supporting Information

Enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkene catalyzed by chiral squaramides – a key step in the synthesis of pregabalin

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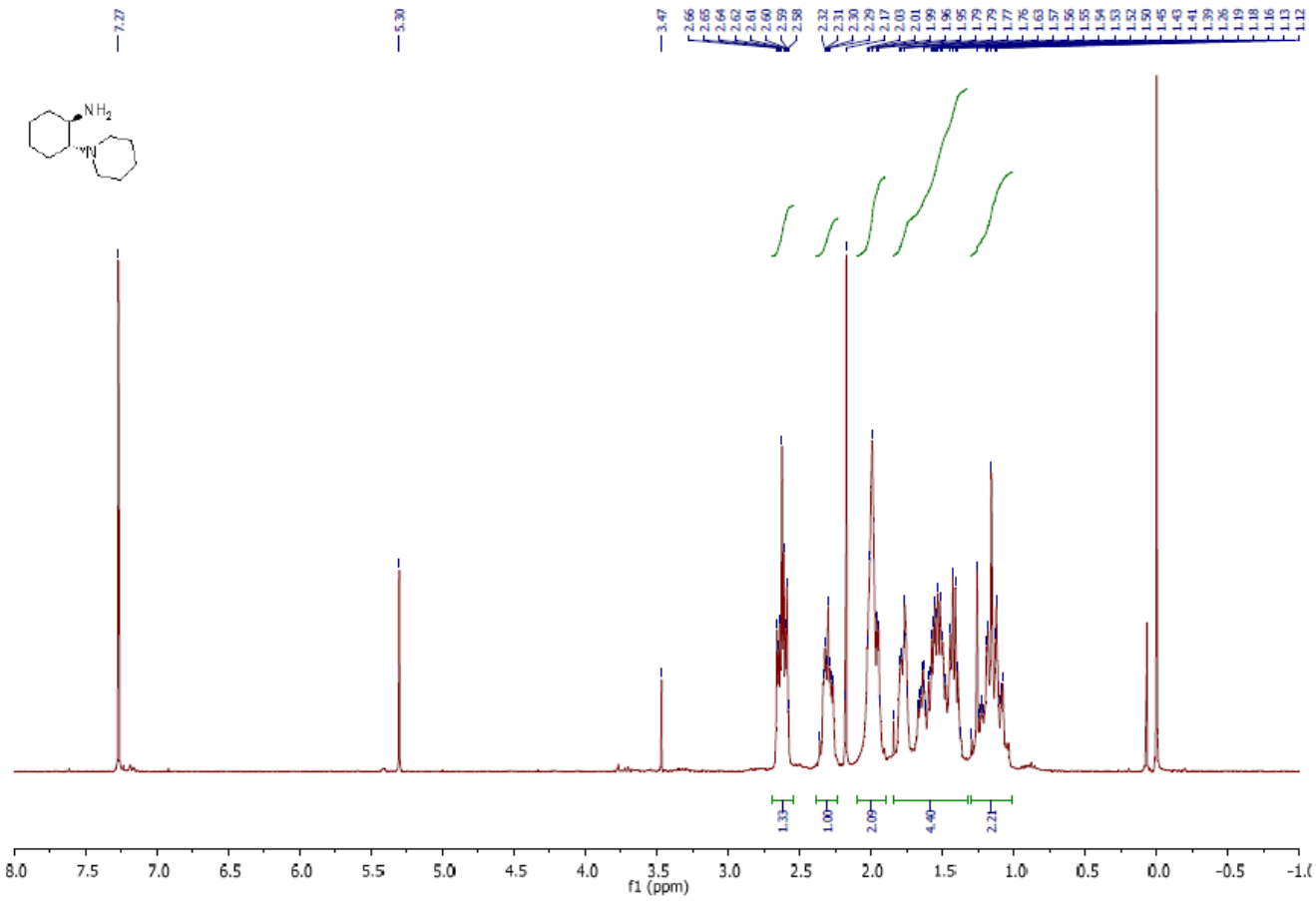
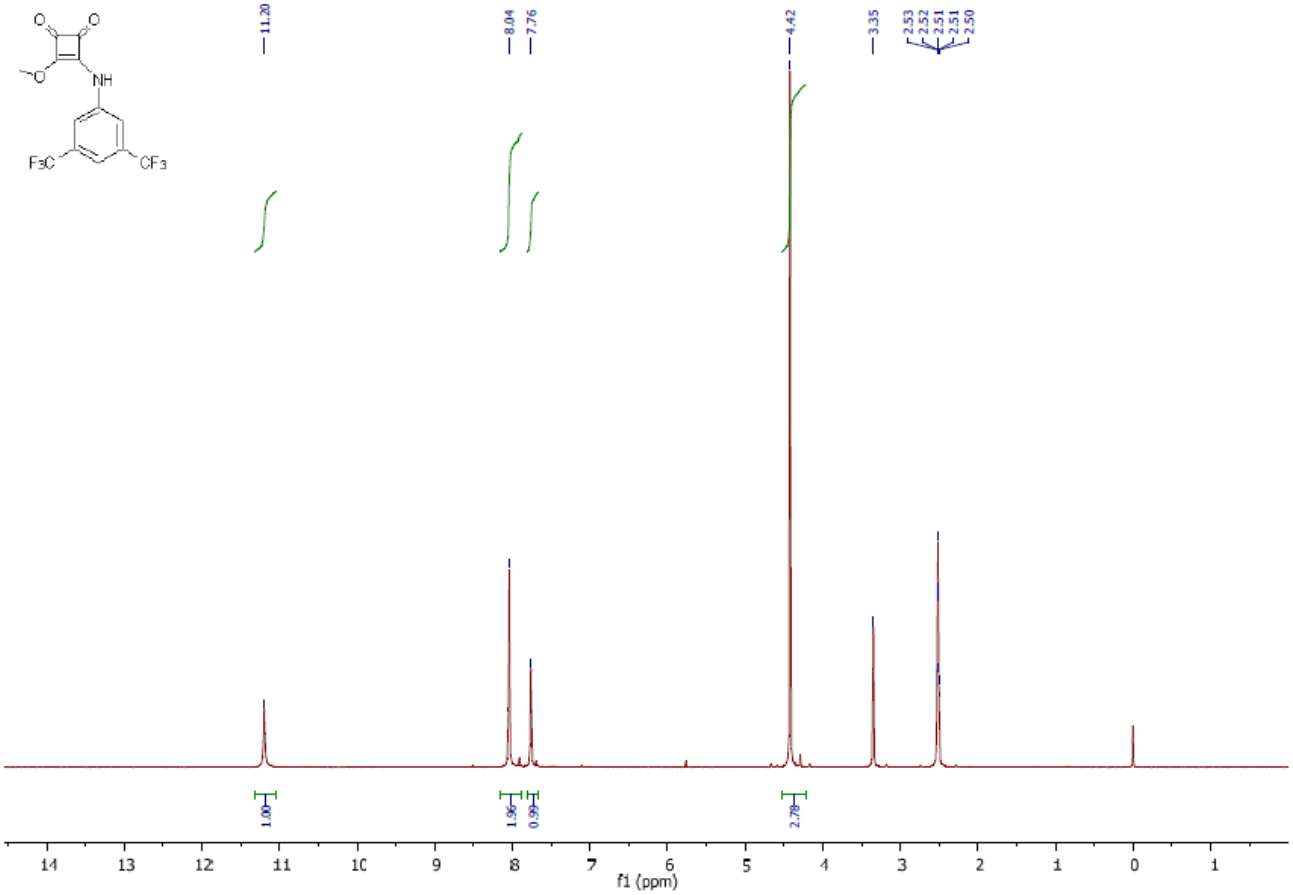
Contents

^{1}H NMR and ^{13}C NMR of squaramideorganocatalysts and their precursors

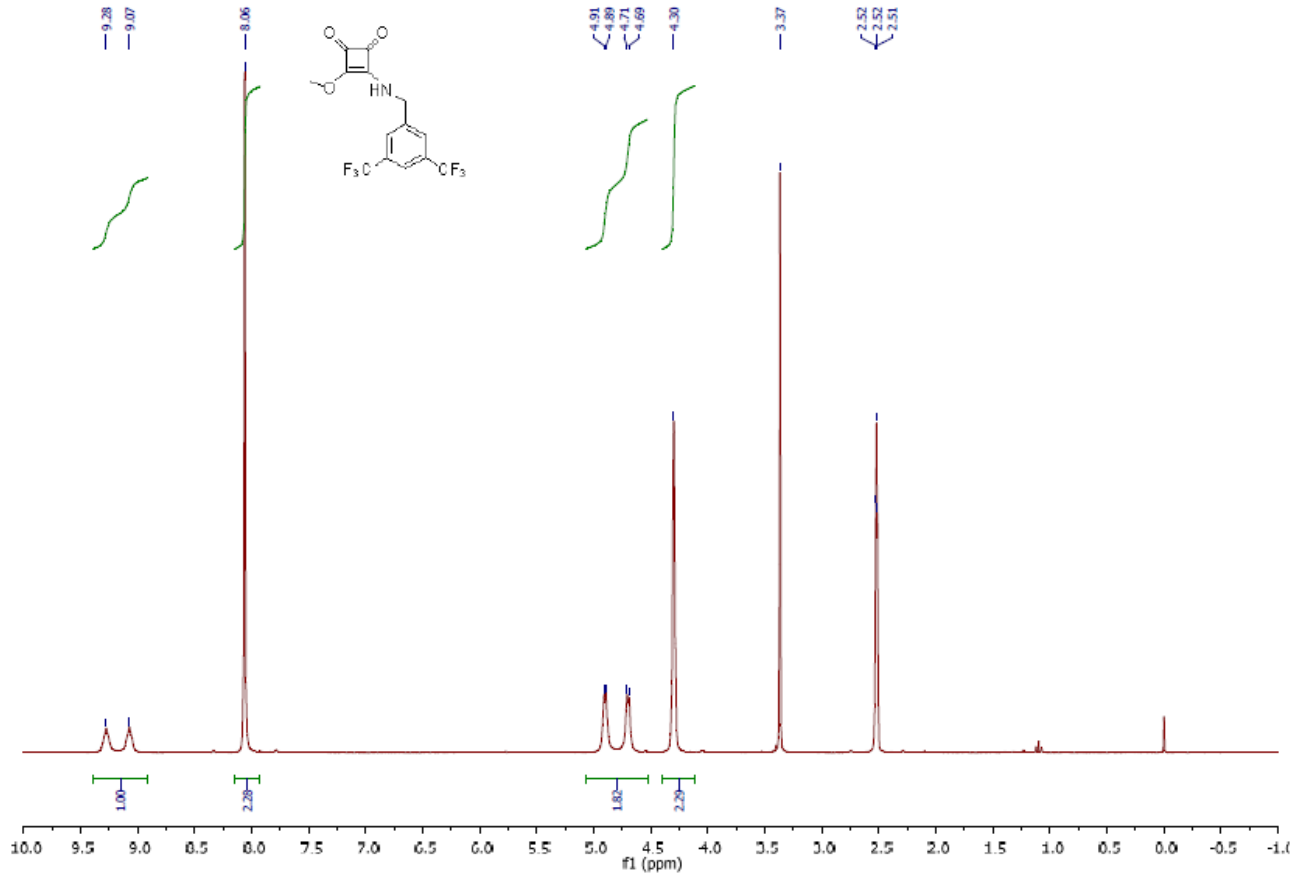
^{1}H NMR of **3**



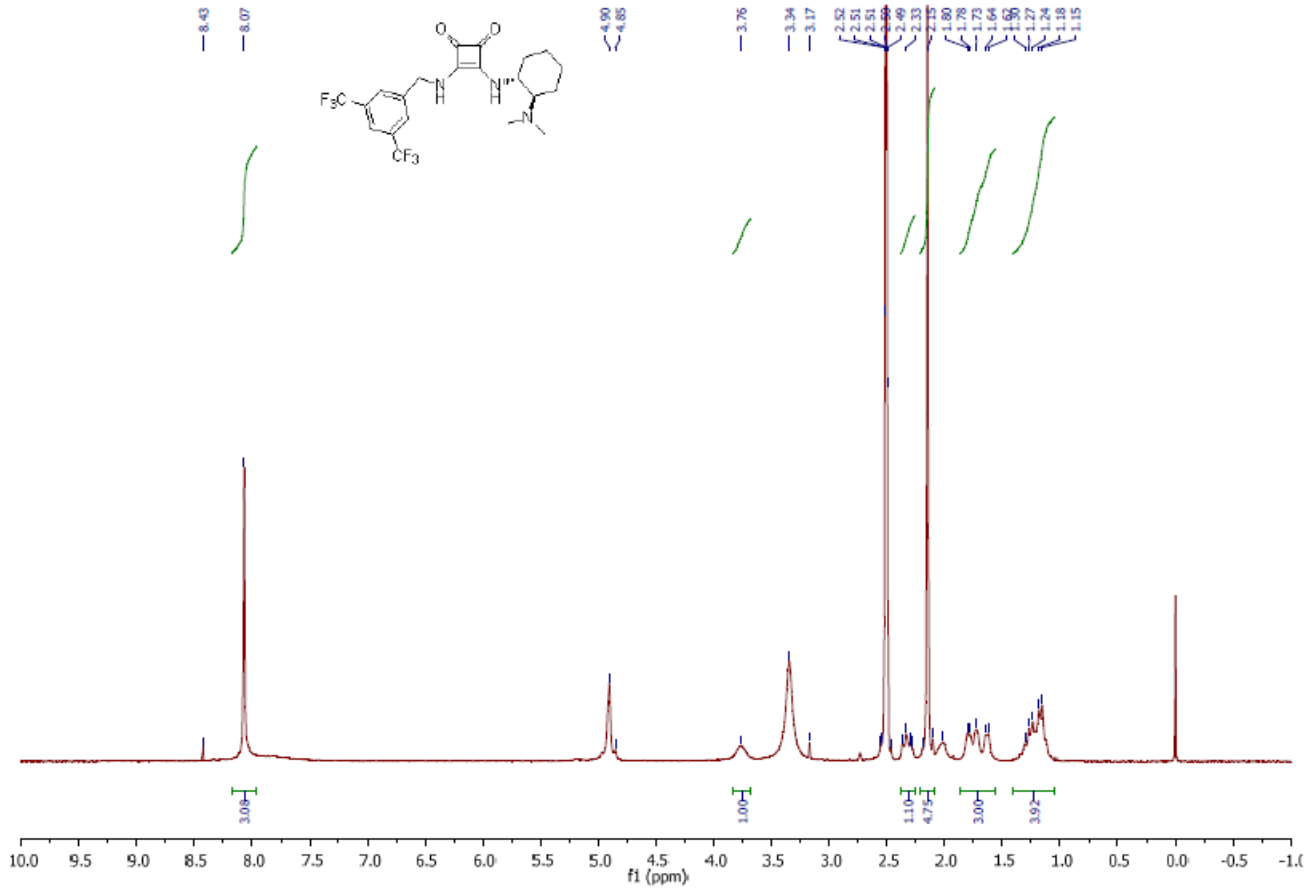
^{1}H NMR of 3-[3,5-bis(trifluoromethyl)phenyl]amino-4-methoxycyklobut-3-ene-1,2-dione



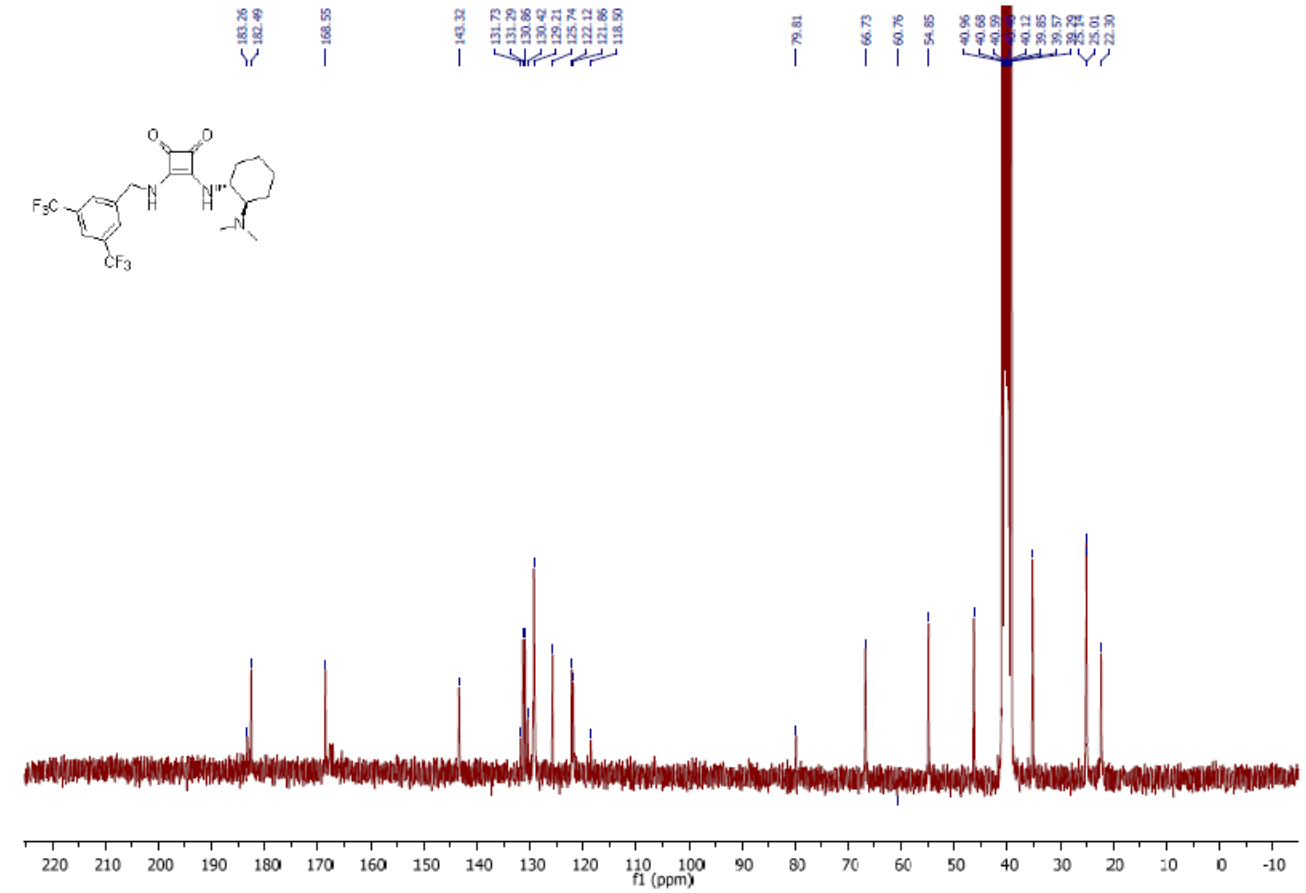
^{1}H NMR of 3-[3,5-bis(trifluoromethyl)benzyl]amino-4-methoxycyclobut-3-ene-1,2-dione



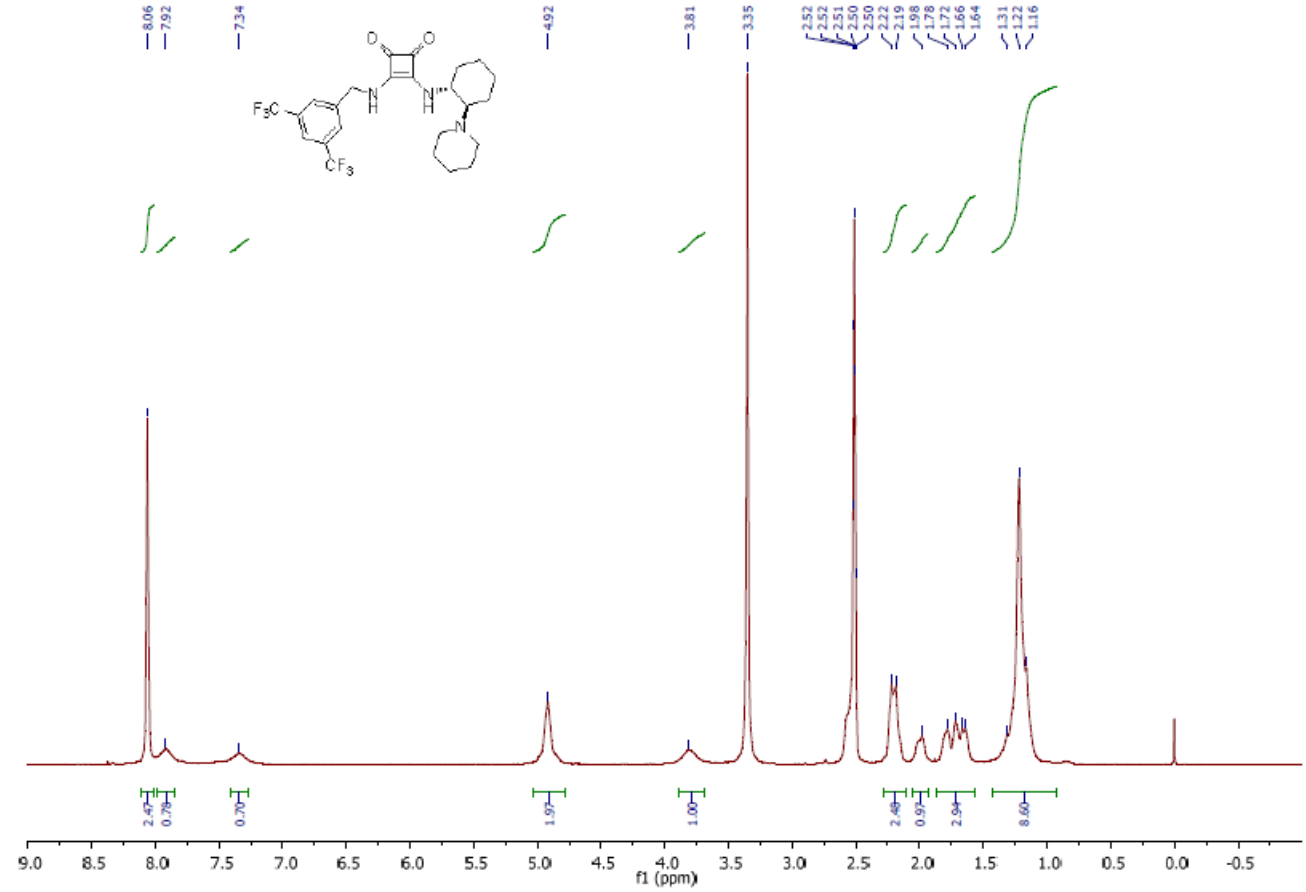
^{1}H NMR of **C1**



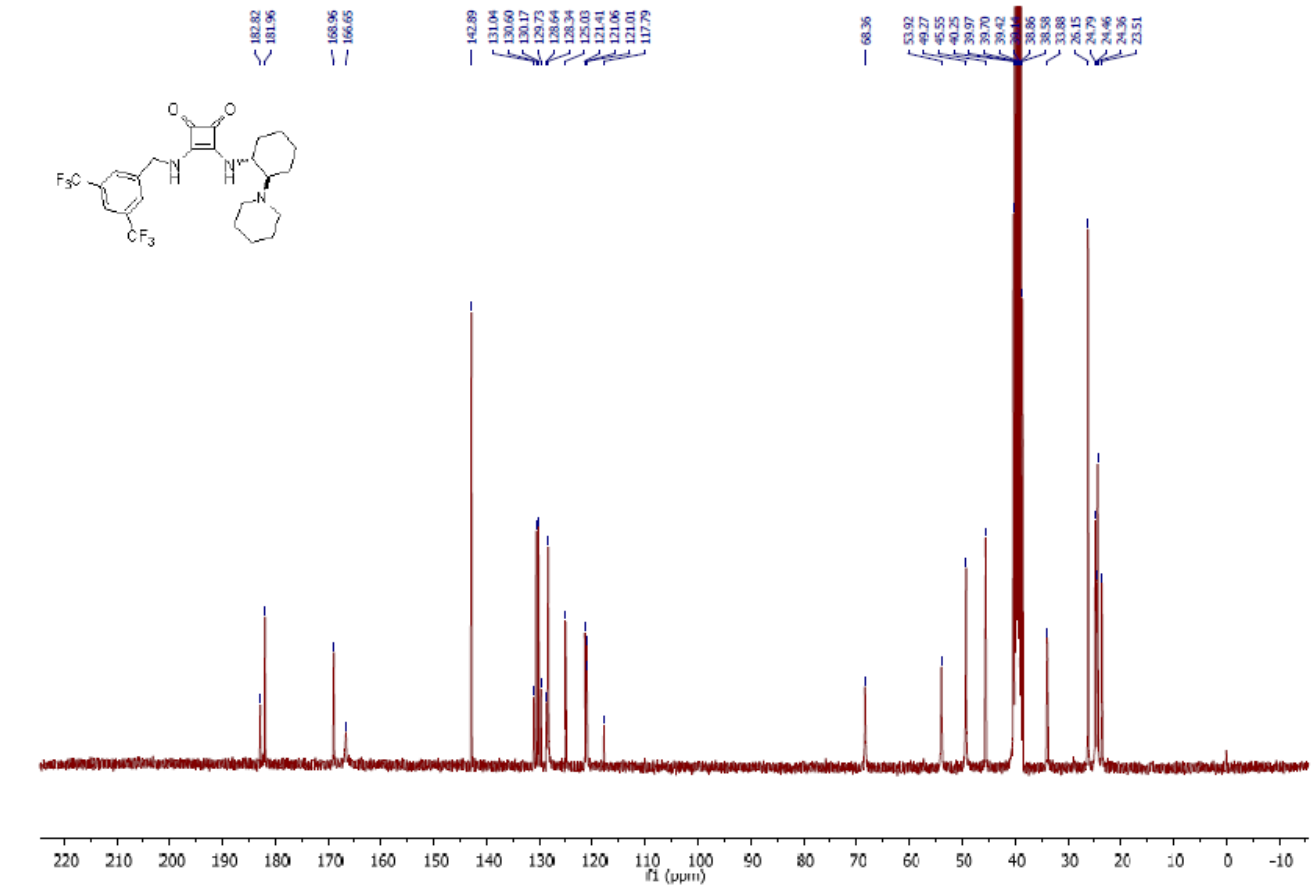
^{13}C NMR of **C1**



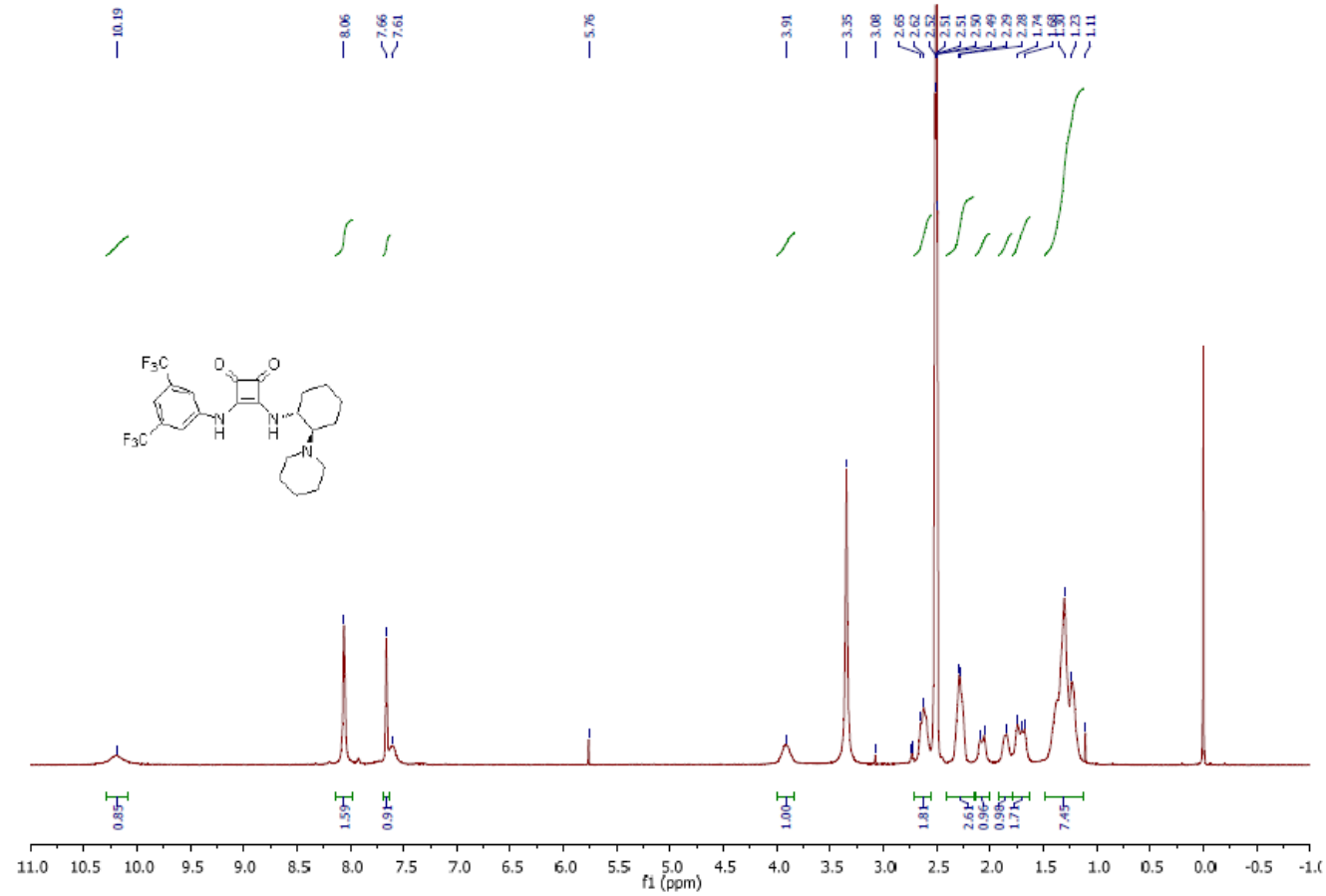
^{1}H NMR of**C2**



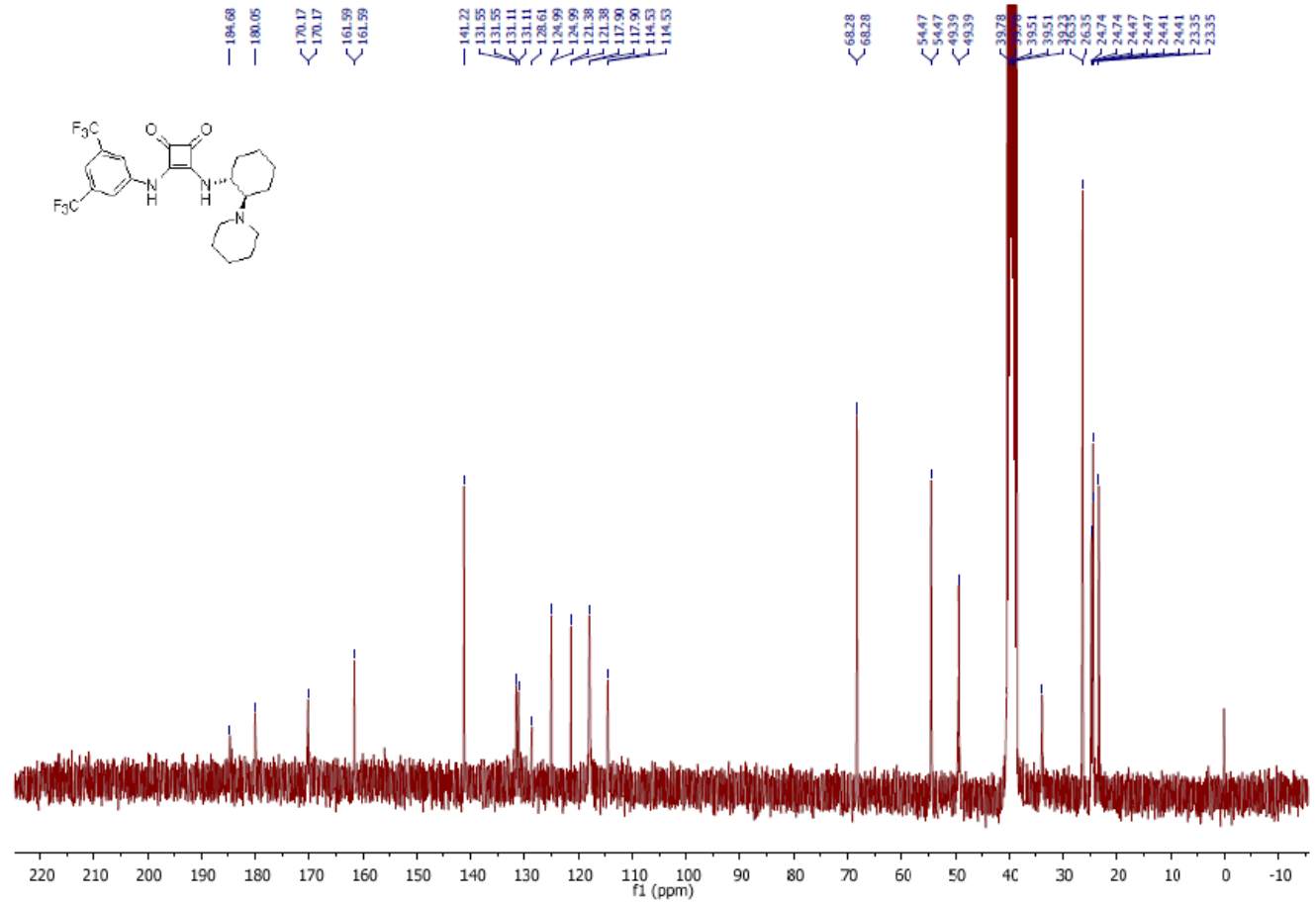
^{13}C NMR of**C2**



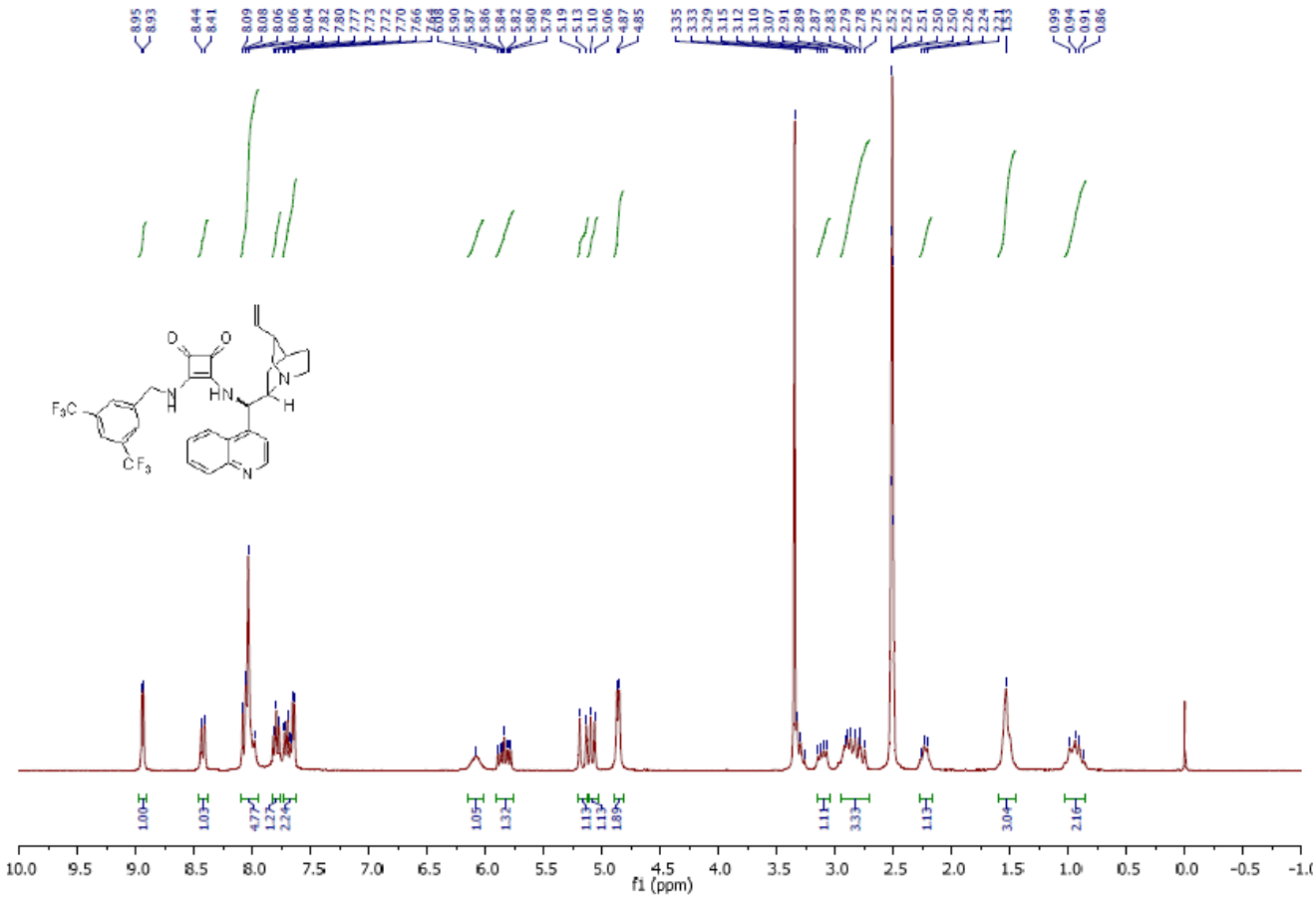
^{1}H NMR of**C3**



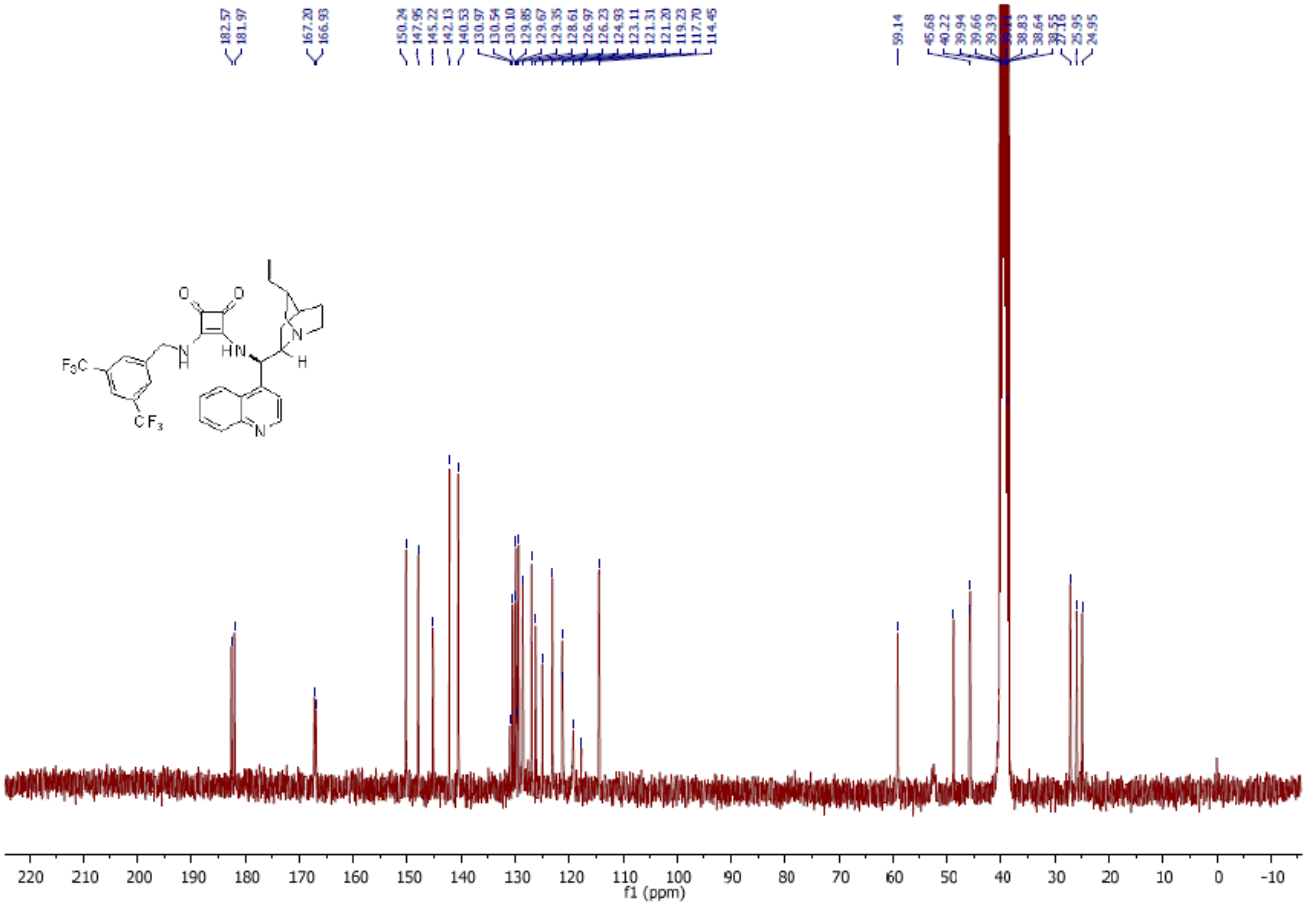
^{13}C NMR of**C3**



^{1}H NMR of**C4**

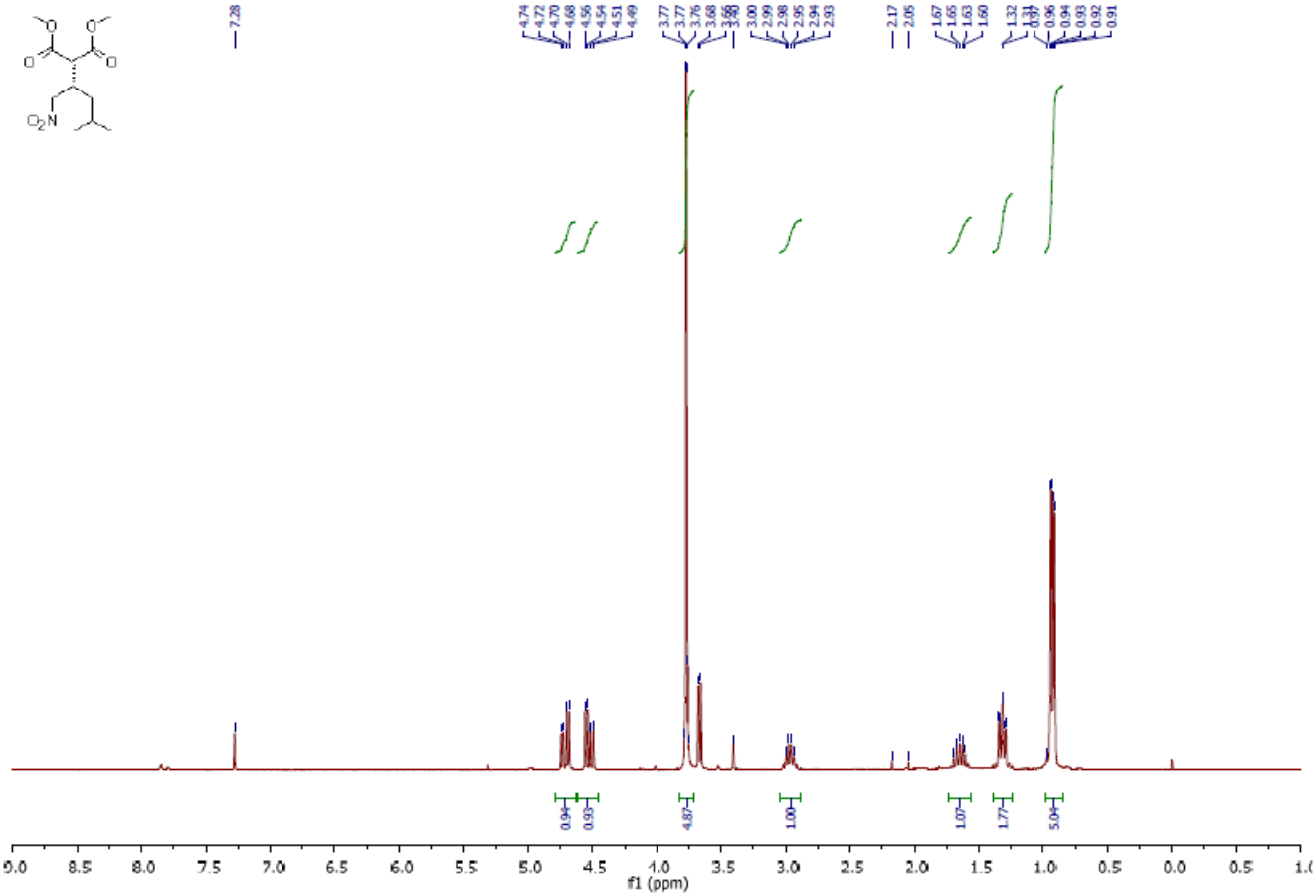


^{13}C NMR of**C4**

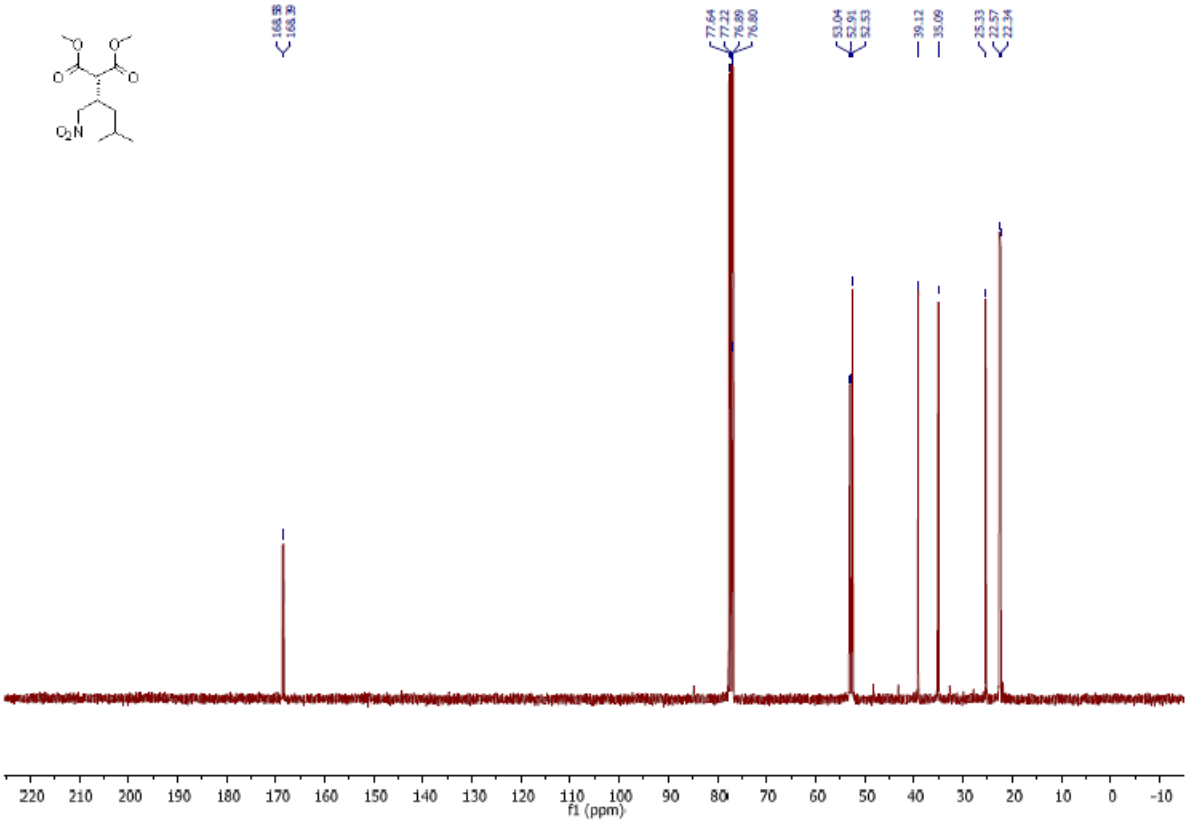


^{1}H NMR and ^{13}C NMR of Michael addition products

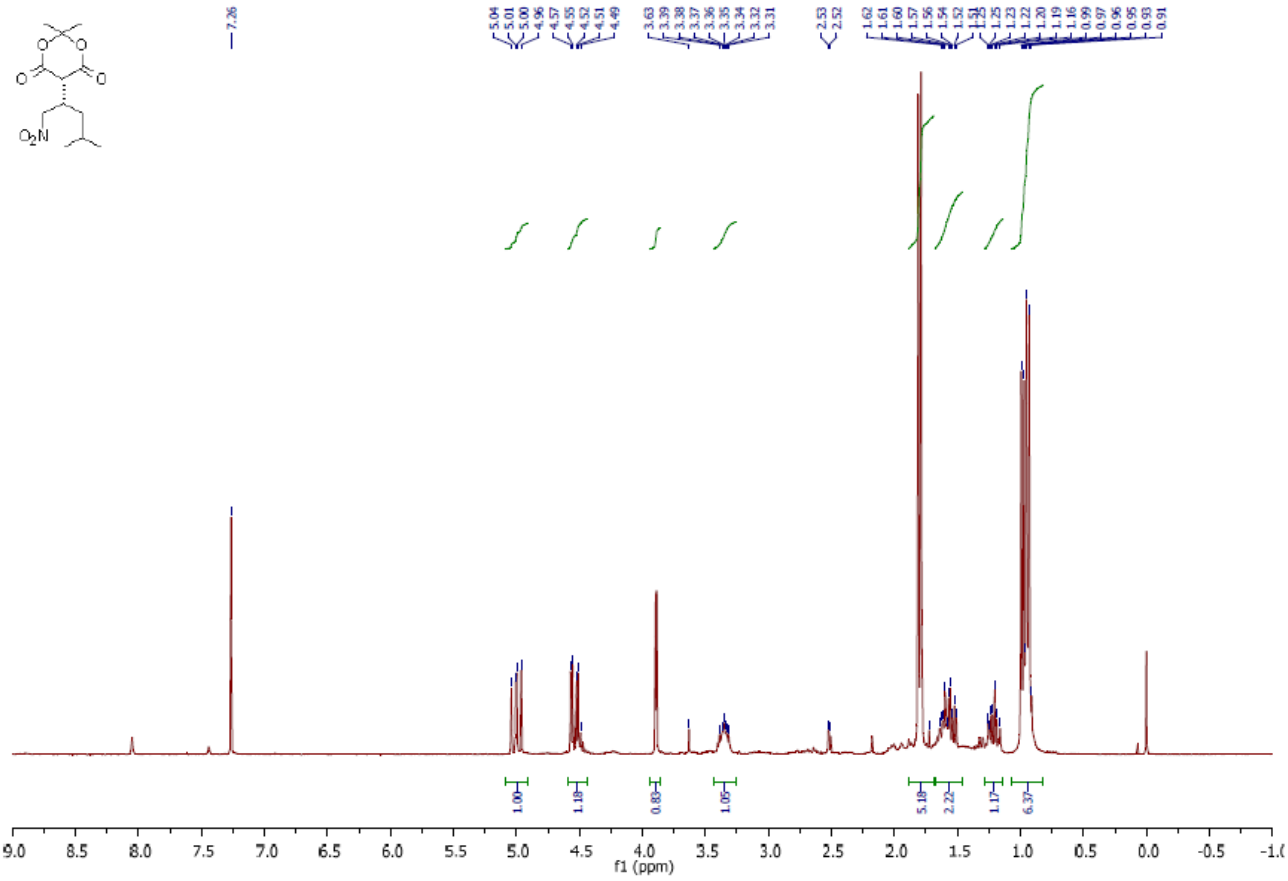
^{1}H NMR of**6a**



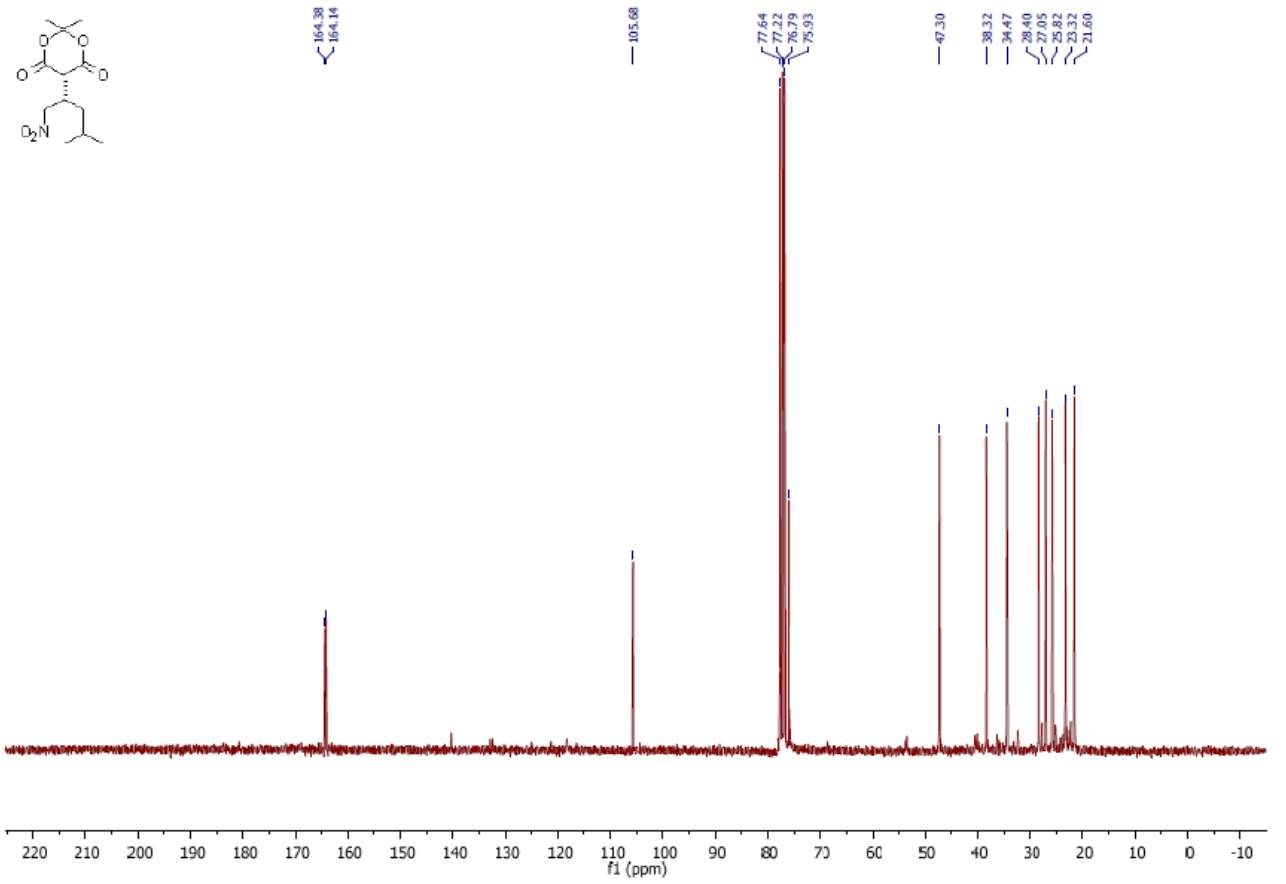
^{13}C NMR of**6a**



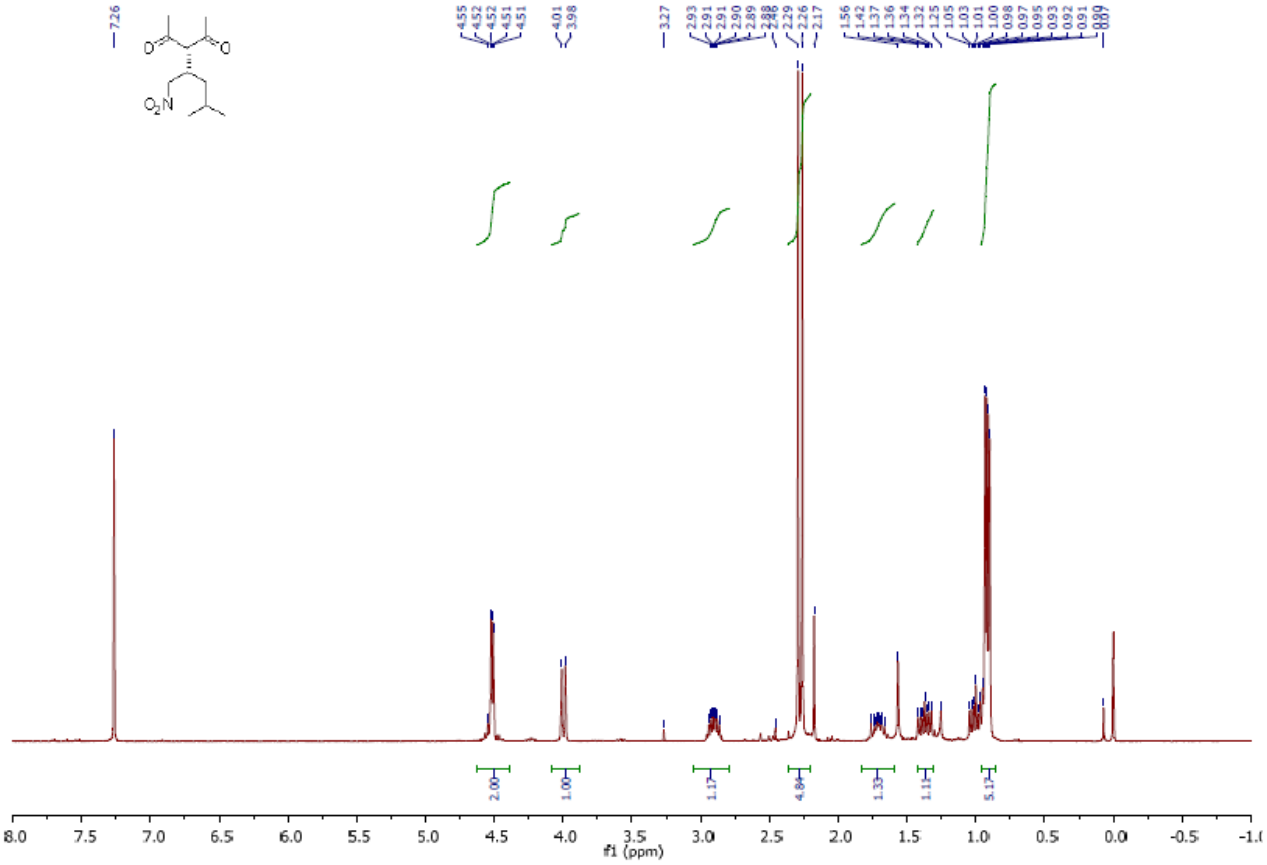
^{1}H NMR of **6b**



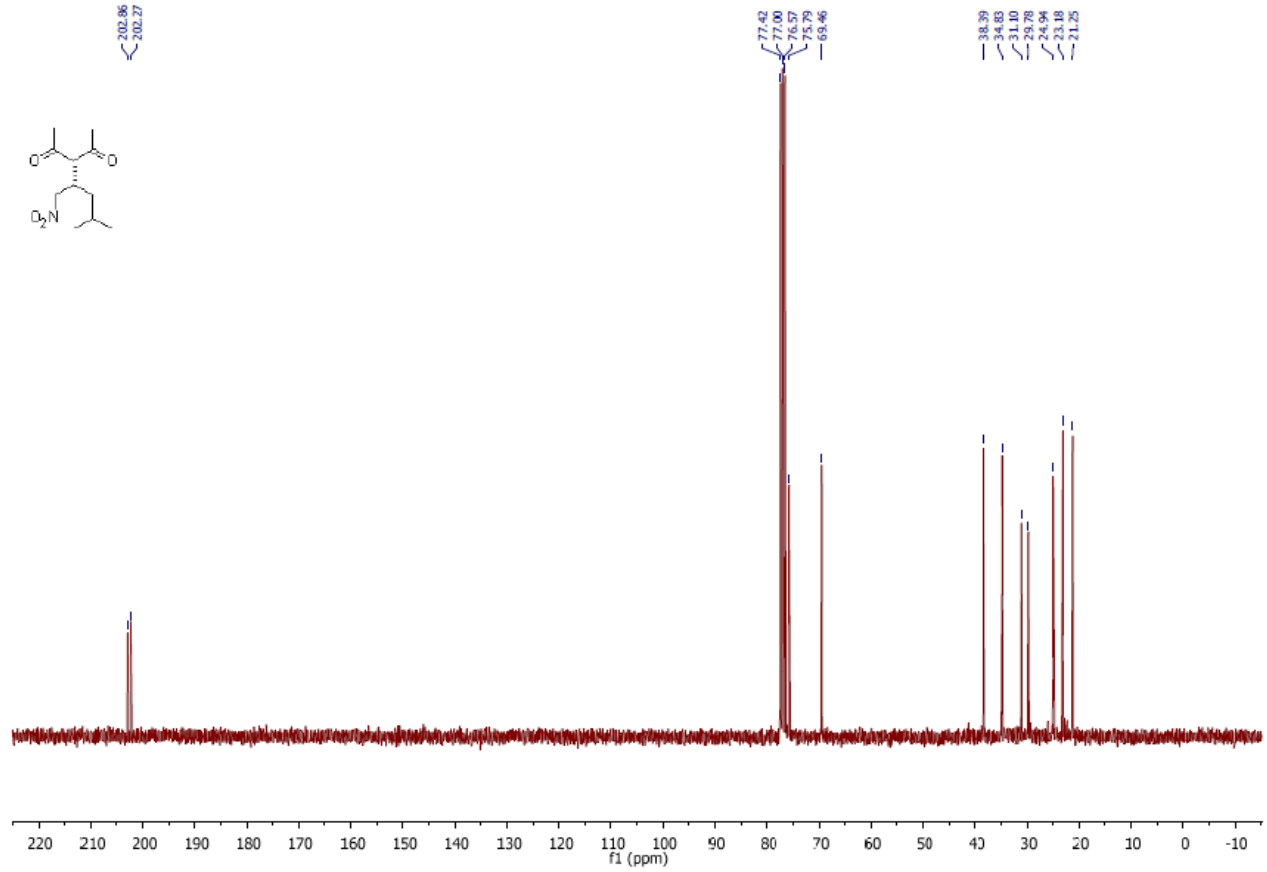
^{13}C NMR of **6b**



^{1}H NMR of **6c**



^{13}C NMR of **6c**



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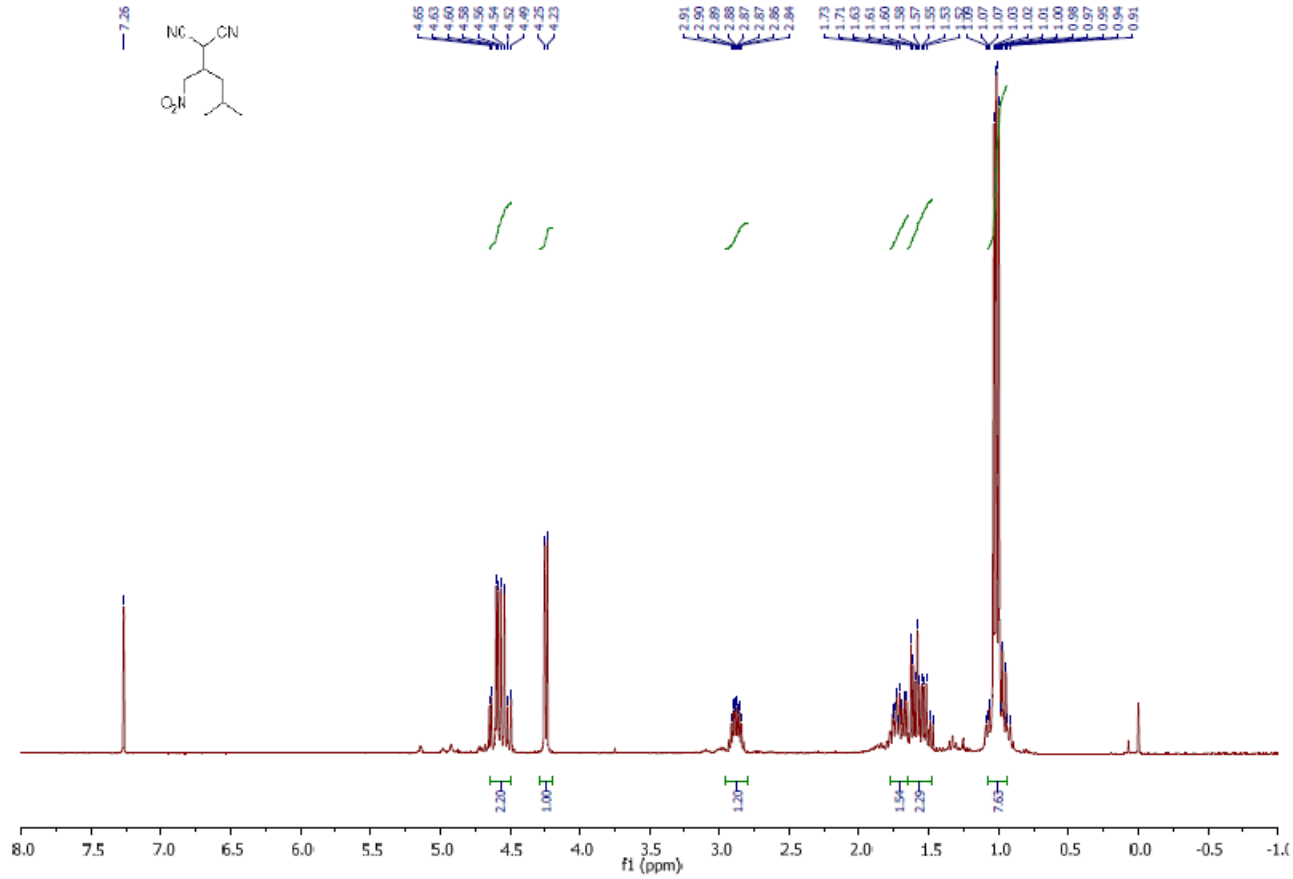
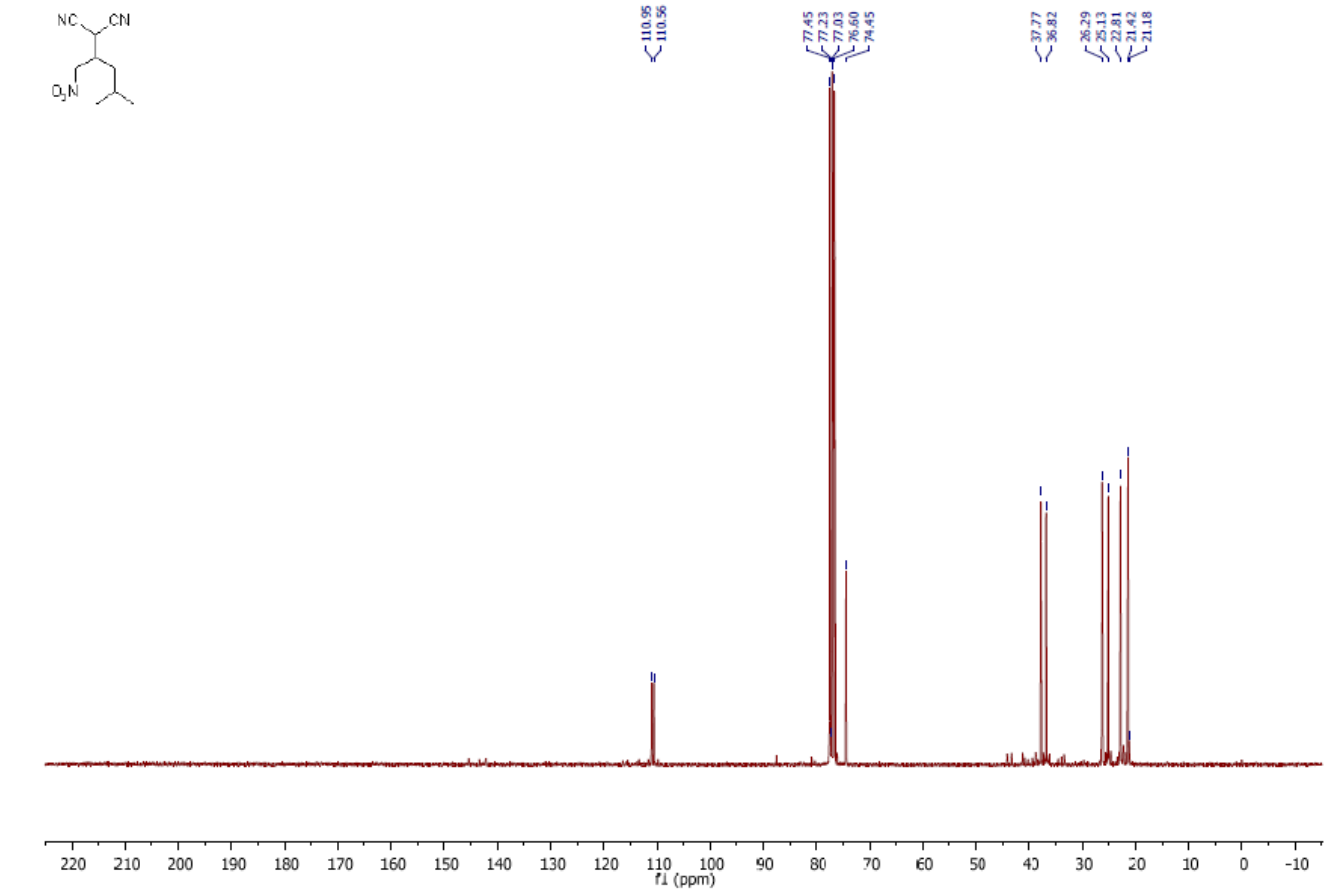
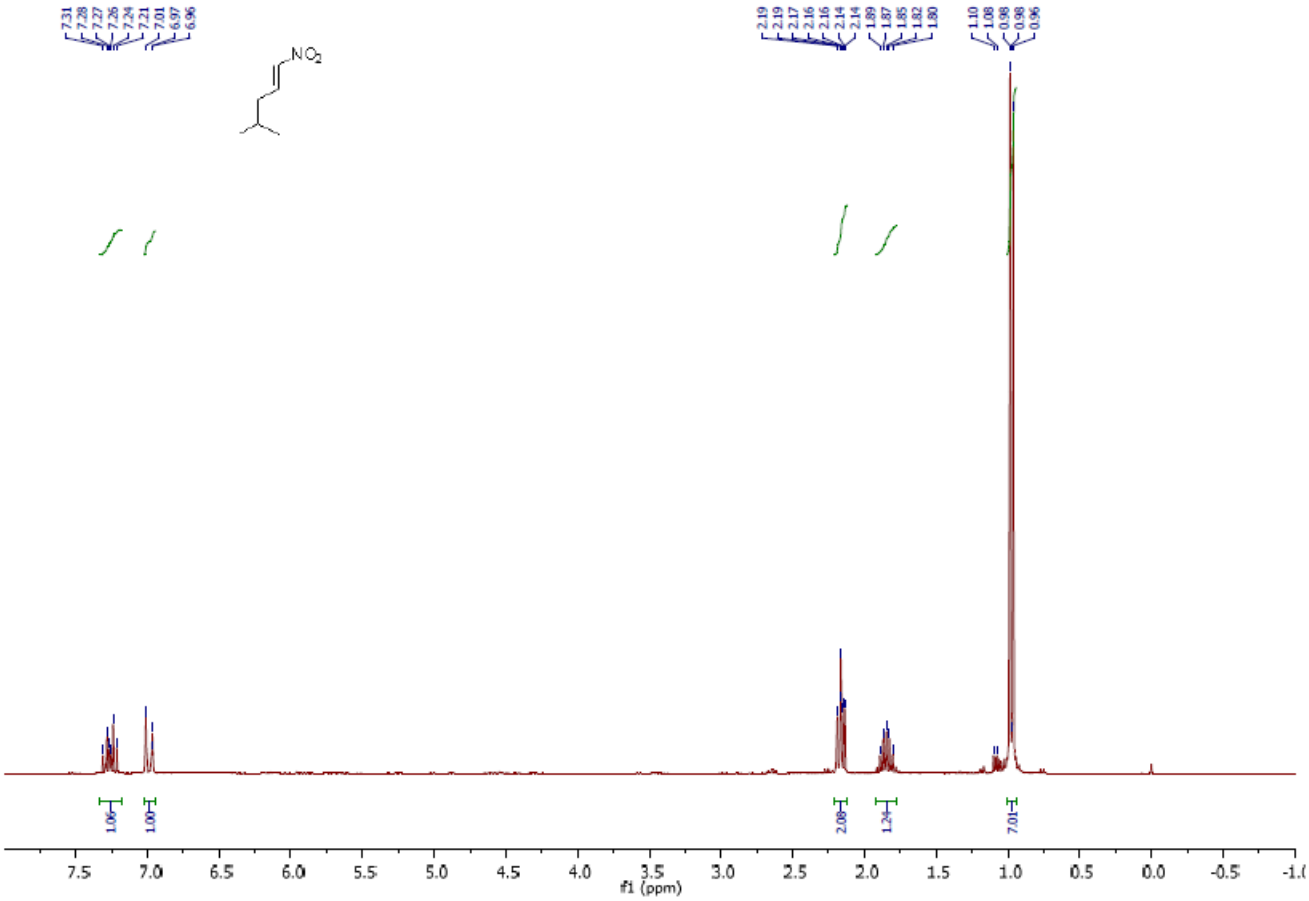


^{13}C NMR of **6d**

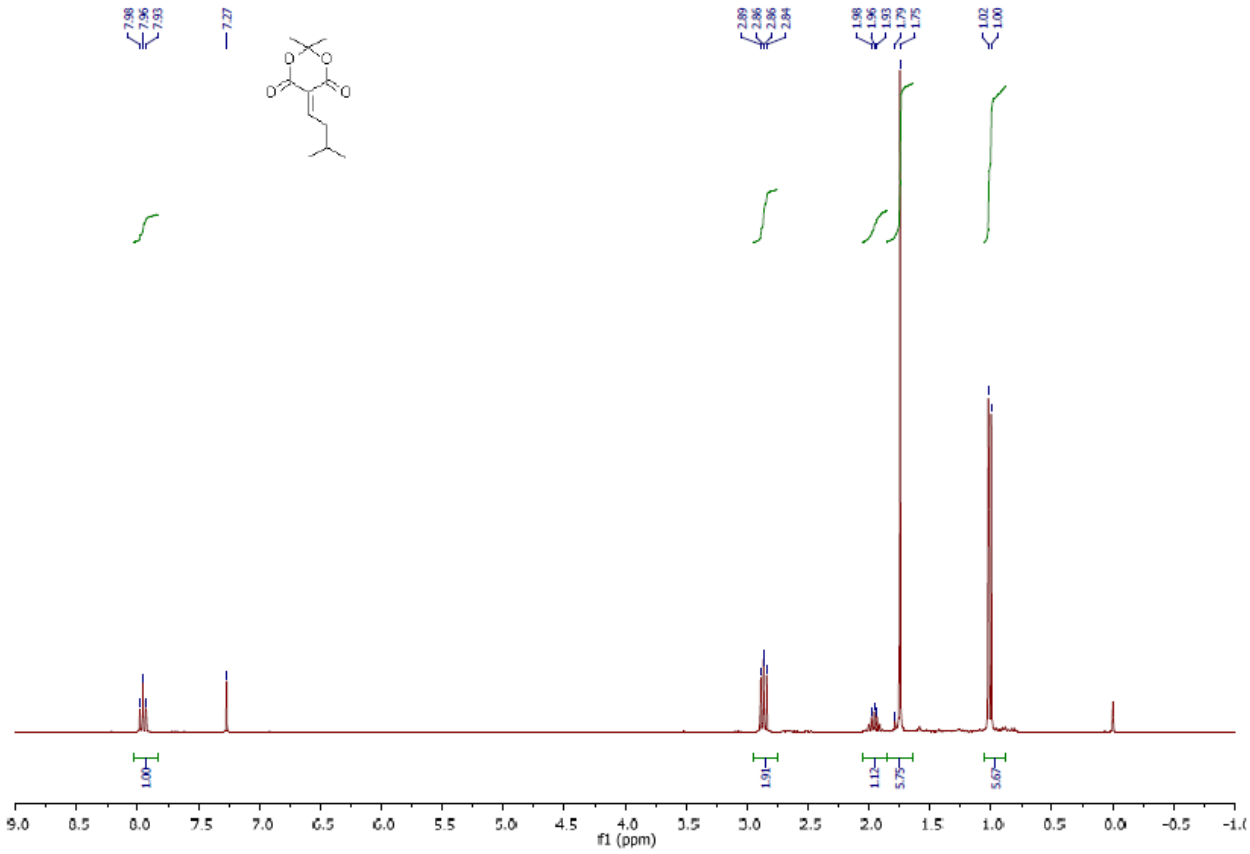


^{1}H NMR and ^{13}C NMR of pregabalin and ist intermediates

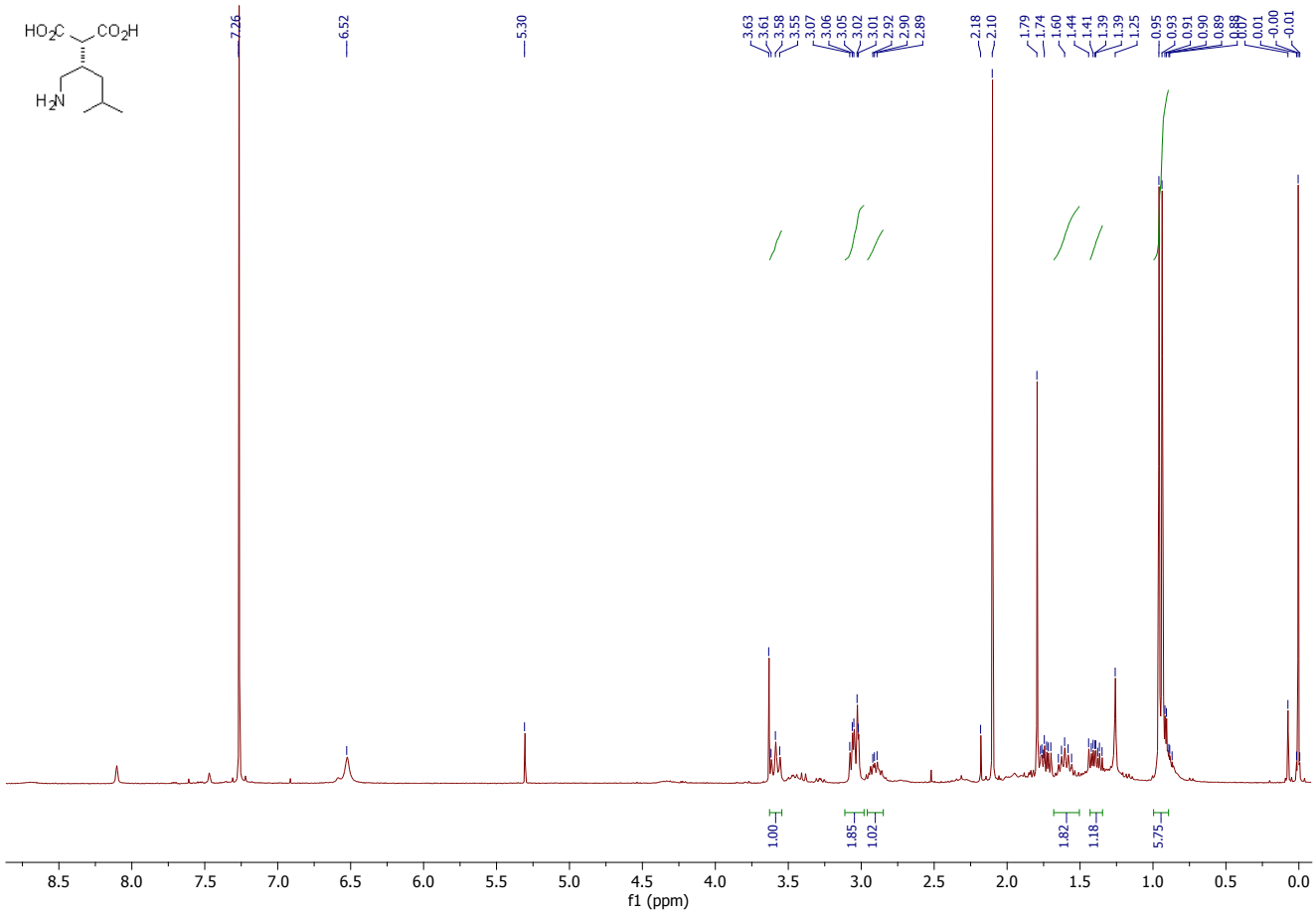
^{1}H NMR of**4**



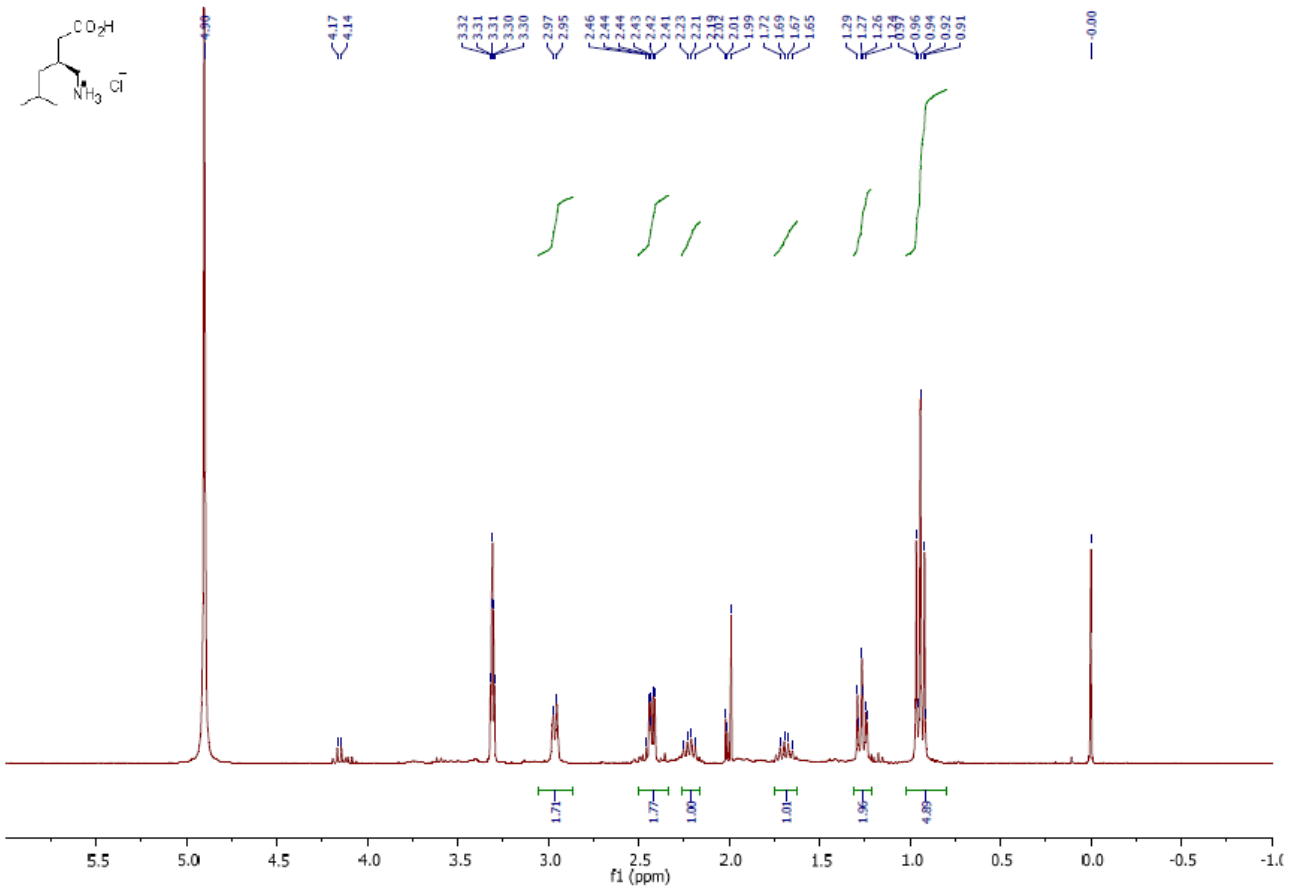
^{1}H NMR of**7**



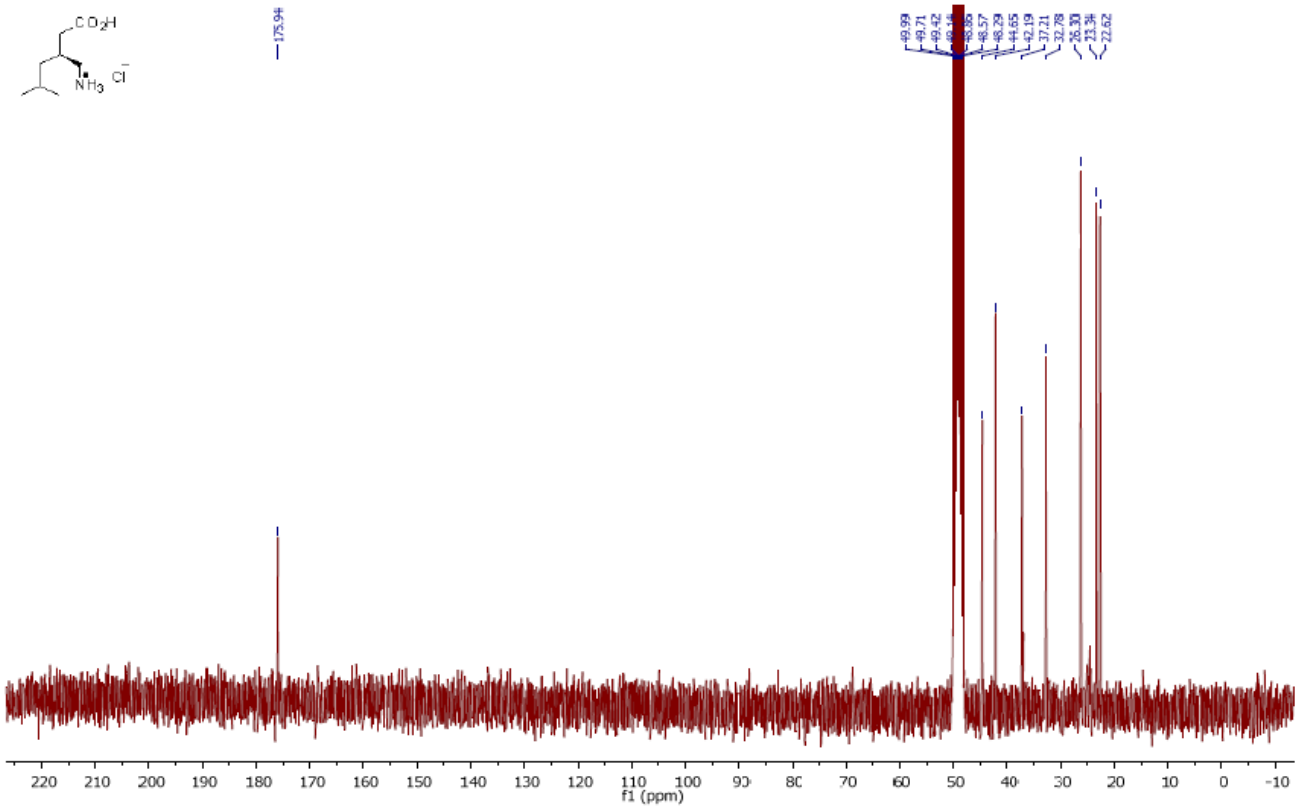
^{1}H NMR of **8**



^{1}H NMR of **9**

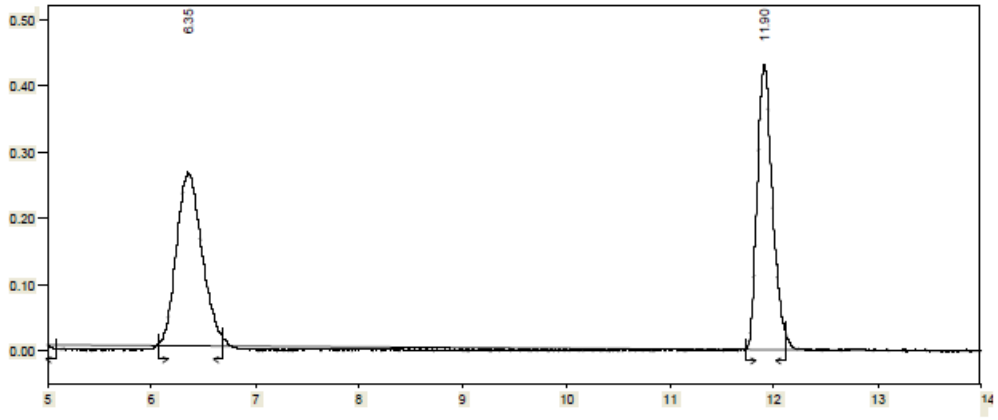


^{13}C NMR of **9**

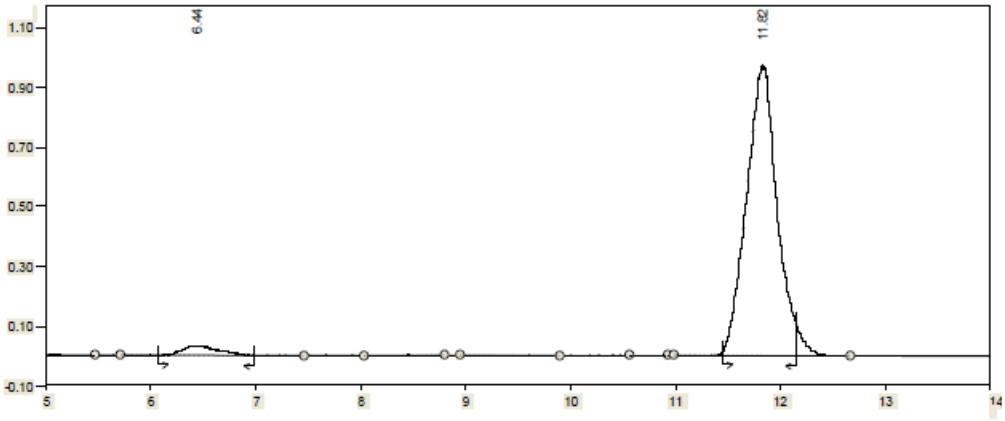

CO2H
NH3
Cl
175.94
49.99
49.71
49.42
48.57
48.29
44.65
42.19
37.21
32.78
26.30
13.34
22.62
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

HPLC chromatograms

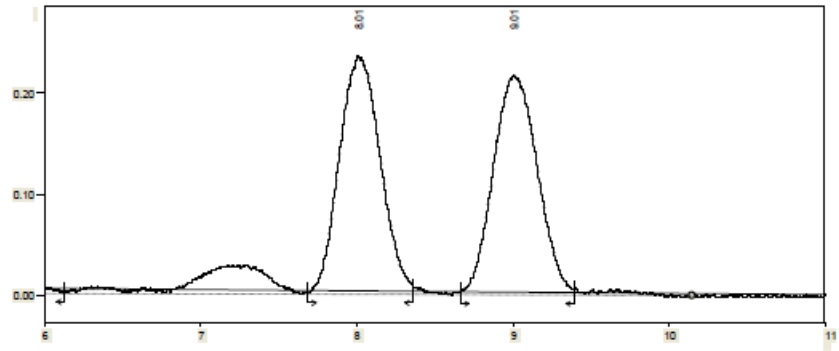
rac-**6a**



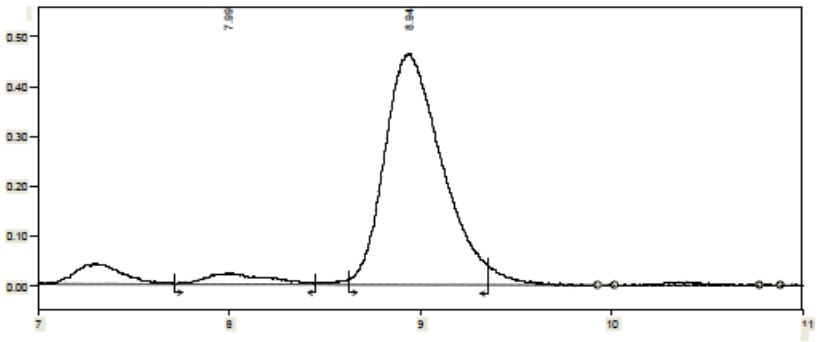
6a



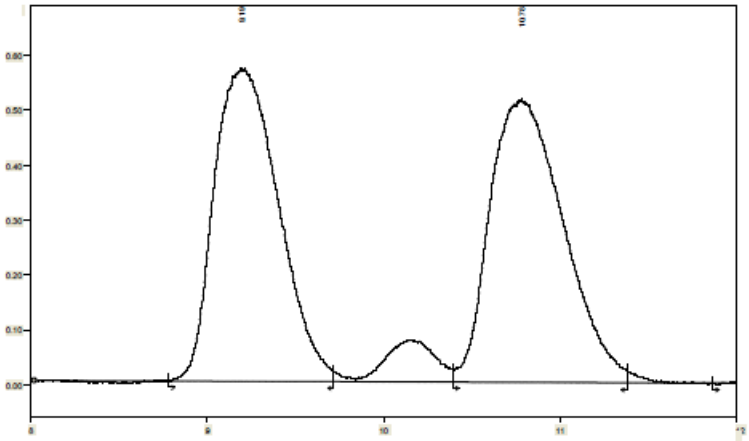
rac-**6c**



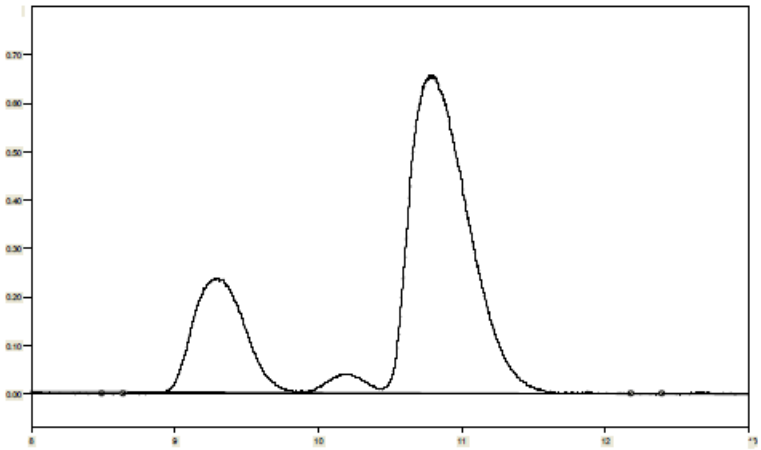
6c



rac-**6d**



6d



DFT calculation

Transition state was first pre-optimized at the semiempirical AM1 followed by optimization at HF level (3-21G base) using Spartan 8 program package.[1] Finally transition state was refined at RI-DFT level[2,3] with BP86 functional[4,5] using def2-SVP basis set[6] as implemented in Turbomole package.[7] The transition state was characterized by frequency calculation at RI-DFT level[8] with BP86 functional using def2-SVP base. The transition state has just one imaginary vibration corresponding to C-C bond breaking (verified by visualization).

The Cartesian coordinates and energy of TS

(DFT, BP86/def2-SVP)
E= -2778.153461792 au
Imaginary frequency: 1 (-204.6 cm^{-1})

C 4.58005090 -4.34137595 1.67845503
C 2.28986809 -5.68239259 1.59291390
N 0.00403457 -4.51656166 1.09970500
O -1.99806987 -5.74893170 1.14824160
O -0.02003816 -2.12557815 0.54842590
C 6.90100377 -5.63676465 2.73598138
C 7.16442153 -5.46440541 5.66008949
H 2.14666070 -7.74472713 1.70956891
H 4.43535017 -2.30268987 2.08387414
H 8.61787658 -4.77316301 1.90105919
H 6.99944814 -3.42842144 6.17874194
C 5.10368155 -6.92411372 7.09129805
C 9.81215644 -6.36414312 6.45354790
H 6.91617254 -7.65691839 2.15811950
H 11.32362807 -5.25257274 5.51731760
H 10.08127769 -6.19284430 8.52531749
H 10.10086279 -8.38097729 5.94712135
H3.17924721 -6.24845479 6.61862951
H5.35750740 -6.73322797 9.16369067
H5.18288528 -8.97206305 6.63429520
C-1.25263042 3.91283798 1.95371132
C-3.72808854 3.08197368 1.28529660
C-2.03936271 6.60395811 2.02736031
C-4.75594722 5.73999803 1.48605793
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N-4.55045582 0.73442676 0.71330278
O-6.79990021 6.77759256 1.24118789
O-0.93513353 8.63613863 2.29957331
H 0.97045277 0.74673469 1.87571030
H-3.13963673 -0.65661988 0.66125856
C-6.99592787 -0.07674207 0.04822955
C -11.79683867 -1.96921420 -1.31903687
C -7.32206432 -2.68317446 -0.44620355
C-9.07984161 1.58205059 -0.12176208
C -11.45276468 0.61279741 -0.80694695
C -9.71180496 -3.60163738 -1.13201321
C 3.32742465 3.86039192 3.04154937
C 6.86821155 7.03610147 2.47403576
C5.43706874 5.91249784 6.89749163
C6.47640307 7.99955843 5.18615234
C2.99248517 4.85408716 5.77325254
C4.41764846 5.98190853 1.30009395

[1]Spartan ´08, Wavefunction, Inc., Irvine, CA.
[2]K. Eichkorn, O. Treutler, H. Oehm, M. Haeser, R. Ahlrichs*Chem. Phys. Lett.***1995**, *242*, 652- 660.
[3]K. Eichkorn, F. Weigend, O. Treutler, R. Ahlrichs*Theo. Chem. Acc*. **1997**, *97*, 119-124.
[4]O. Treutler, R. Ahlrichs*J. Chem. Phys*. **1995**, *102*, 346-354.
[5]M. v.Arnim, R. Ahlrichs*J. Comp. Chem.* **1998**, *19*, 1746-1757.
[6]F. Weigend*Phys. Chem. Chem. Phys*. **2006**, *8*, 1057-1065.
[7]TURBOMOLE V6.4, TURBOMOLE GmbH, Karlsruhe, 2012.
[8]Deglmann, P.; May, K.; Furche, F.; Ahlrichs, R. *Chem. Phys. Lett.***2004**, *384*, 103-107.

H4.74714224 2.31133461 3.05919937
H2.23743281 3.27778373 6.93058419
H5.08216194 6.64463269 8.82989777
H6.86440559 4.37949812 7.09422054
H8.29827236 8.73899608 5.91498895
H8.33241454 5.52504305 2.47491237
H7.60874286 8.61014734 1.31131730
H -5.70313638 -3.97920128 -0.24756346
H -13.66840515 -2.70356992 -1.82702199
H -8.85534157 3.61248278 0.29499294
H 2.97948625 7.50439454 1.15552798
H 5.13807318 9.61876475 5.16138684
C -10.01695827 -6.37748626 -1.76433133
C -13.65850273 2.41651657 -1.09555391
F -13.57896577 4.31088266 0.61858135
F -13.67164713 3.50524595 -3.42233847
F -15.90989101 1.21858505 -0.82098968
F -12.44653464 -7.15318175 -1.49509254
F -8.56287897 -7.86290325 -0.27681734
F-9.34435211 -6.85765418 -4.19607607
N4.90980869 4.95623661 -1.38774471
C2.57851444 4.75665988 -3.05154488
C6.94206803 6.29142218 -2.89616280
C1.63123327 7.33207463 -3.95172094
C3.69758135 8.78610798 -5.37986893
H8.69113174 6.31782779 -1.76365521
H7.30898412 5.03350339 -4.53161798
H3.03898073 10.71410209 -5.86836862
H4.10856019 7.81751447 -7.20105677
H3.16714298 3.56950667 -4.67740798
H1.14377096 3.69315340 -1.98720378
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C5.48371834 -3.34467604 -2.13150804
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O9.92614471 -2.41428866 -2.22985629
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