Supporting Information

Acid-Catalyzed Functionalization of α-Hydroxycyclobutanone with Benzylic Alcohols

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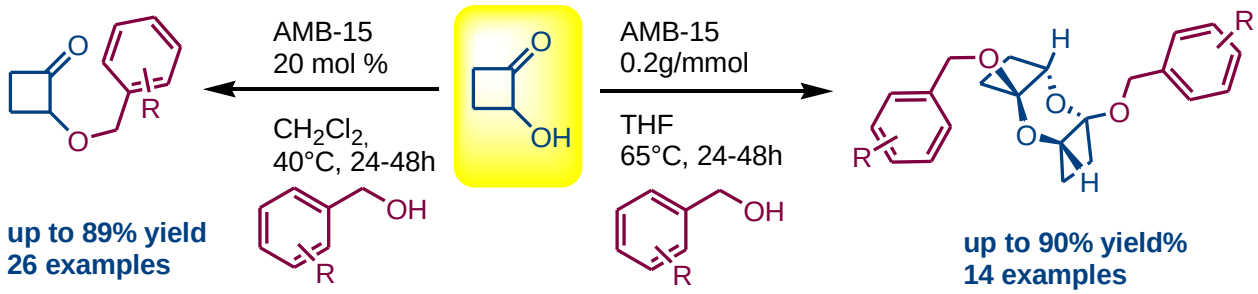

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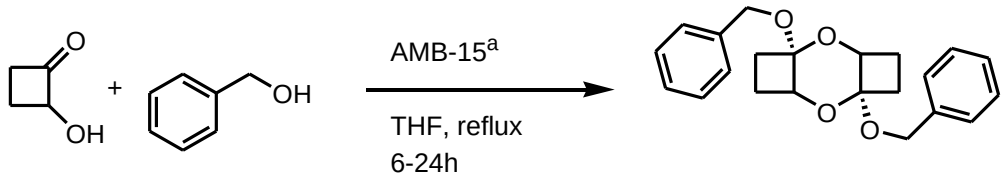
1. Materials and Methods

Unless stated otherwise, respectively the synthesis of compounds **3a-v** were performed at 40 °C and synthesis of compounds 5a-v were performed at 65 °C.
Commercially available reagents were used as received unless otherwise noted. Alcohols **2a-d, 2g, h, j, o, p, u, v, y, z** were purchased from Aldrich. The acids used in this work were purchased from Sigma Aldrich or Alfa-Aesar and used as received.
Alcohols **2f,i,l-n,q-t** were prepared from the corresponding aldehydes and ketones by reduction using $NaBH_4$ in THF/MeOH at 0°C.
^{1}H NMR spectra were recorded on 400 and 500 MHz Varian spectrometers at 27°C using $CDCl_3$, as solvent. ^{13}C NMR were recorded at 100 and 125 MHz at 27°C using $CDCl_3$, as solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and are reported in wavenumbers.
Low Mass spectra analysis were recorded on an Agilent-HP GC-MS (E.I. 70eV). High resolution mass spectra (HRMS) were obtained using a Bruker High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode or acquired using an Bruker micrOTOF-Q II 10027.
Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merk 70-200 mesh silica gel. Yields refer to chromatography and spectroscopically pure materials.

2. Amberlyst-15 recycling[1]

Amberlyst-15 was used as received and recovered from the crude reaction mixtures by simple filtration on DURAN sintered glass filters. The catalyst was washed twice with Et_2O and dried at 50°C under reduced pressure for 4h in order to be reused for further reaction cycles.



1a **2a** **4a**

Table S1. AMB-15 recycling and catalytic properties[1,2]

Entry	**1a** loading	Catalyst recovery %	AMB-15 mg recovery	**4a** yield[b]	**notes**
1	50 mg	>98 (spheres)	114mg	87	
2	49 mg	>98(spheres)	112mg	88	
3	48 mg	>98(spheres)	109 mg	85	
4	47 mg	94(spheres)	103 mg	86	
5	39 mg	87(spheres)	90 mg	73	
6	33 mg	85 (dark-brown powder)	76 mg	68	
7	22 mg	65(dark-brown powder)	50 mg	60	Unidentified products detected
8	13 mg	60(dark-brown powder)	29 mg	32	Unidentified products detected

Synthesis of substituted 2,7-dioxa-tricyclodecane **4a** and catalyst recovery. [a] Reaction conditions: in a vial, cyclobutanone **1a** (0.58 mmol) BnOH **2a** (1.0 equiv.), AMB-15 (0.2g/mmol, 0.116 g) in THF (2 mL) were stirred at 65° C for 48h. [b] Yields of **4a** were determined by weighting after flash chromatography purification.

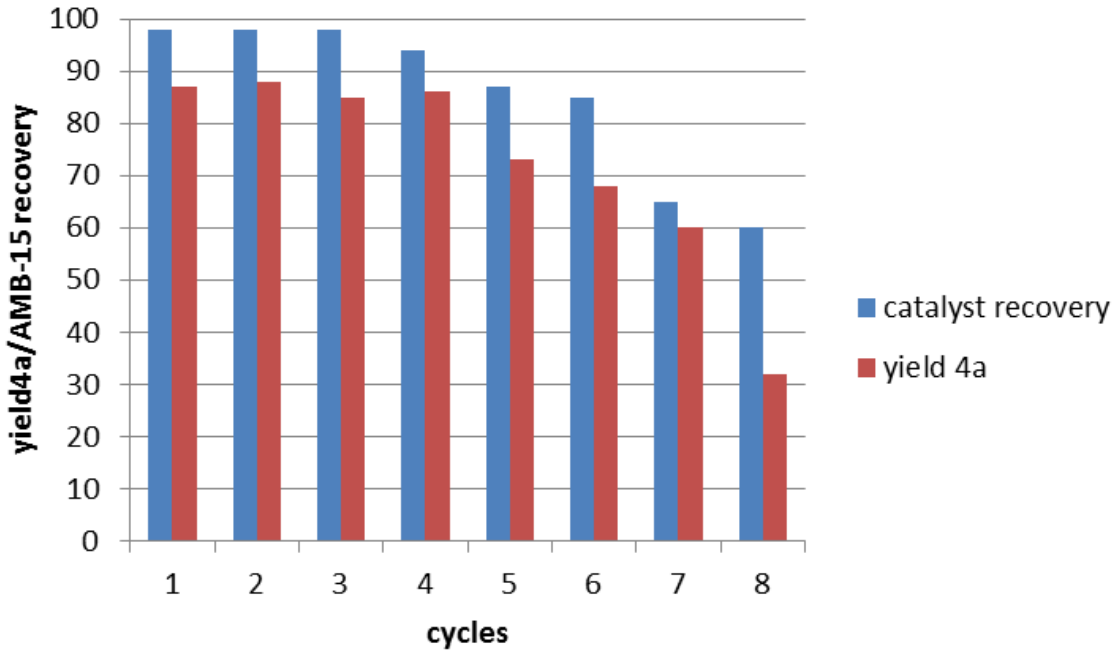


Figure S1. Catalyst recycling and compound 4a yields

1) a) Yadav, J. S., Reddy, B. V. S., Eshwaraiah, B., Anuradha, K., *Green Chem*., **2002**, *4*, 592–594;
2) Pal, R., Sarkar, T., Khasnobis, S., *Arkivoc*, **2012**, *1*, 570-609.

3. Theoretical calculations

Density Functional Theory (DFT) calculations were performed with the commercial suite of software Gaussian09.[3] All calculations were carried out with the hybrid Generalized Gradient Approximation (GGA) mPW1PW functional[4] and the full-electron split valence plus polarization basis sets in the Def2SVPP formulation[5,6] for all atomic species. NBO populations[7] were calculated at the optimized geometries, whose nature was verified by harmonic frequency calculations (no negative frequencies with module larger than 15 cm^{-1} were found). The results of the calculations were examined with GaussView 5.0.9[8] and Molden 5.3[9] programs.

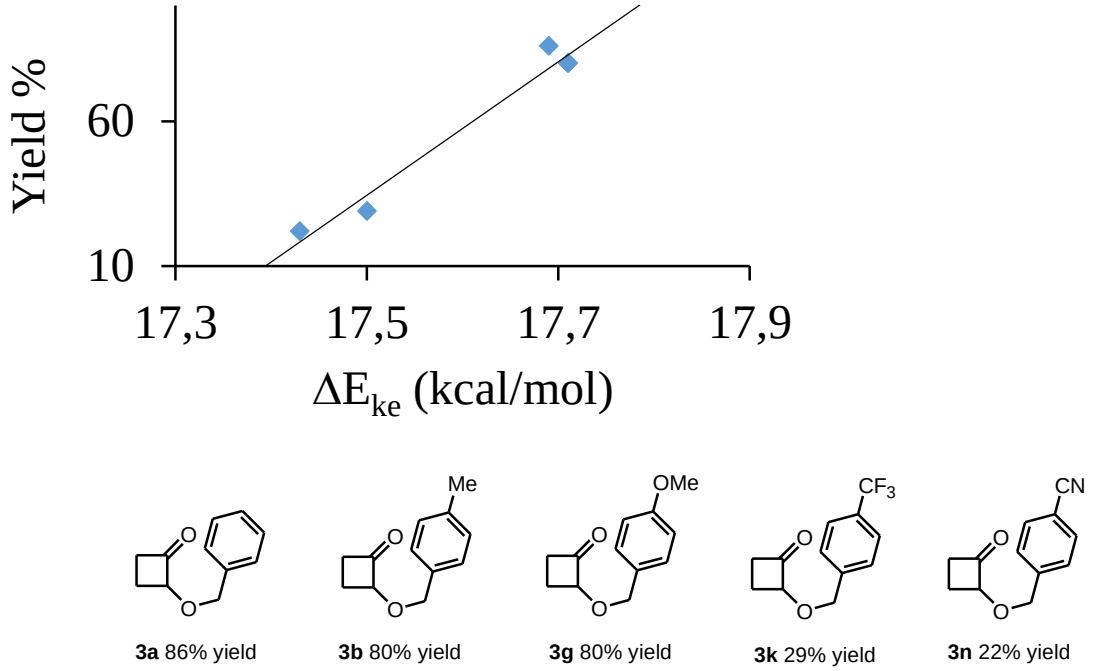
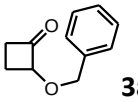


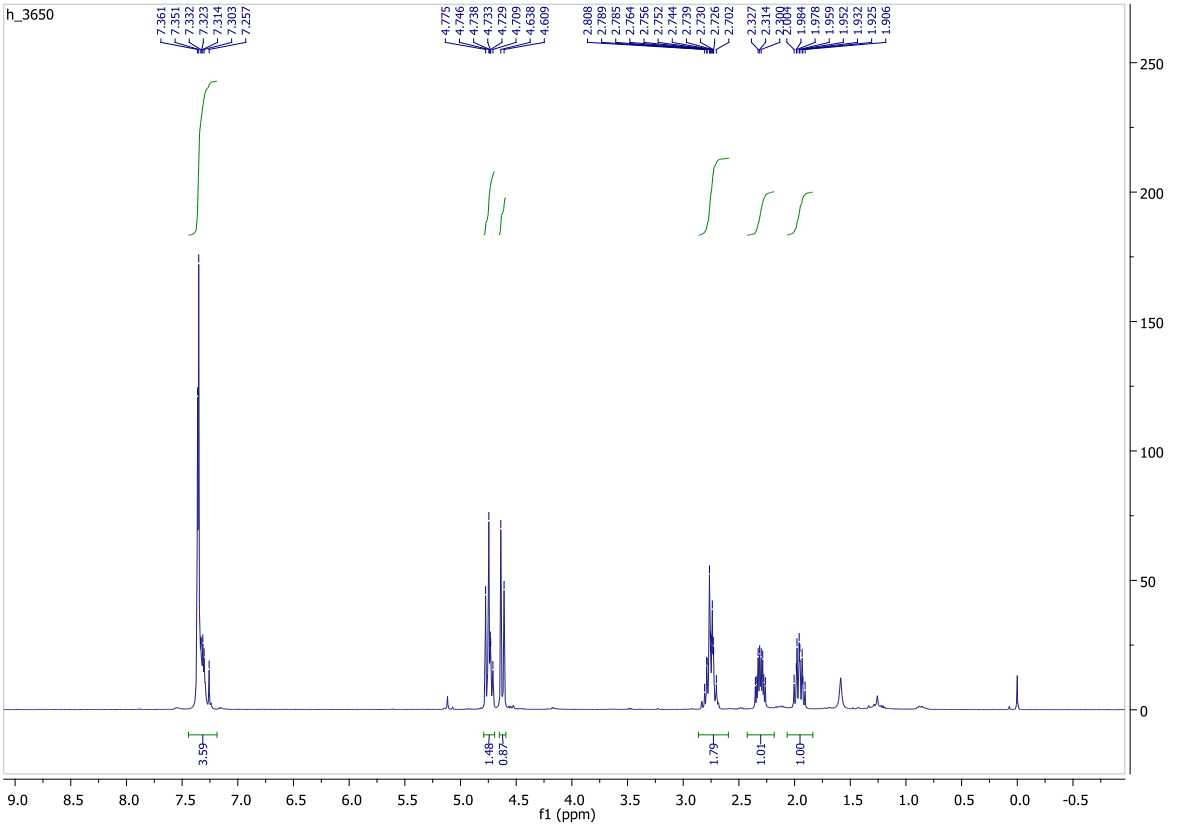
Figure S2. DFT-calculated total electronic energy difference calculated for the keto-enol equilibrium *iii* in Scheme 3 and reaction yield in the synthesis of **3a**, **b**, **g**, **k**, **n**.

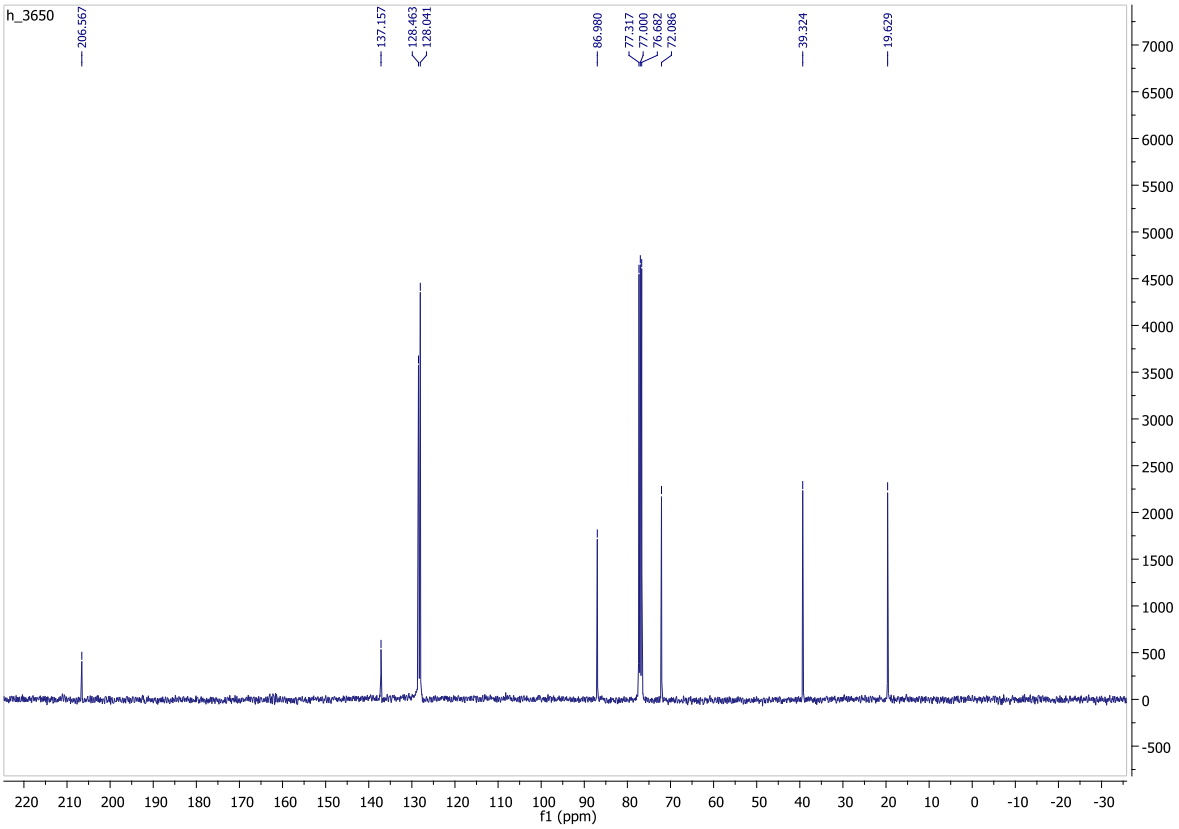
3) Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.
4) Adamo, C; Barone, V. *J. Chem. Phys*. **1998**, *108*, 664-675.
5) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys*., 2005, 7, 3297-3305.
6) F. Weigend, *Phys. Chem. Chem. Phys*., **2006**, *8*, 1057-1065.
7) (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys*. **1983**, *78*, 4066-4073; (b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735-746; c) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev*. **1988**, *88*, 899-926.
8) GaussView, Version 5, Dennington, R.; Keith, T.; Millam, J. Semichem Inc., Shawnee Mission KS, **2009**.
9) Schaftenaar, G.; Noordik, J. H. *J. Comput.–Aided Mol. Design* **2000**, *14*, 123-134.

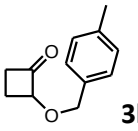
4. ^{1}H and ^{13}C NMR spectra of compounds 3a-3y



3a **2-Benzyloxy-cyclobutanone**







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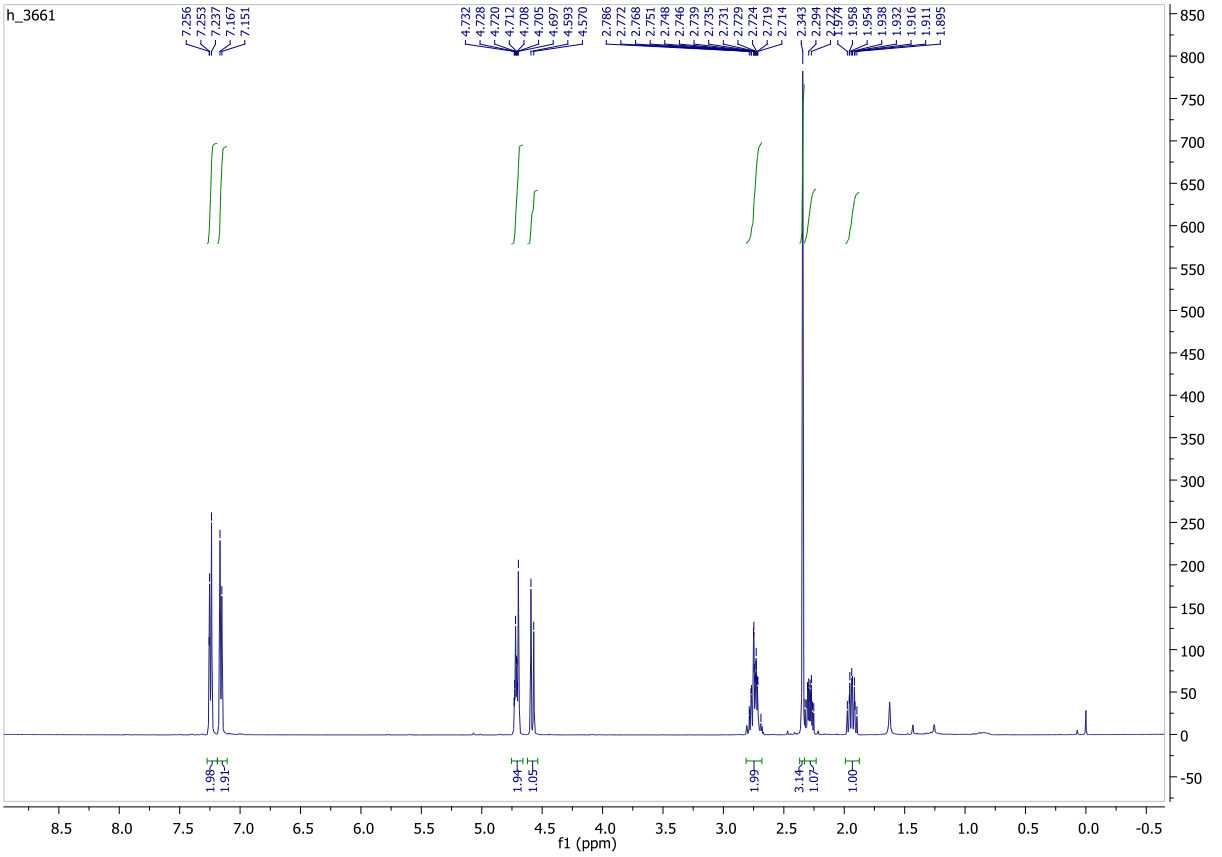

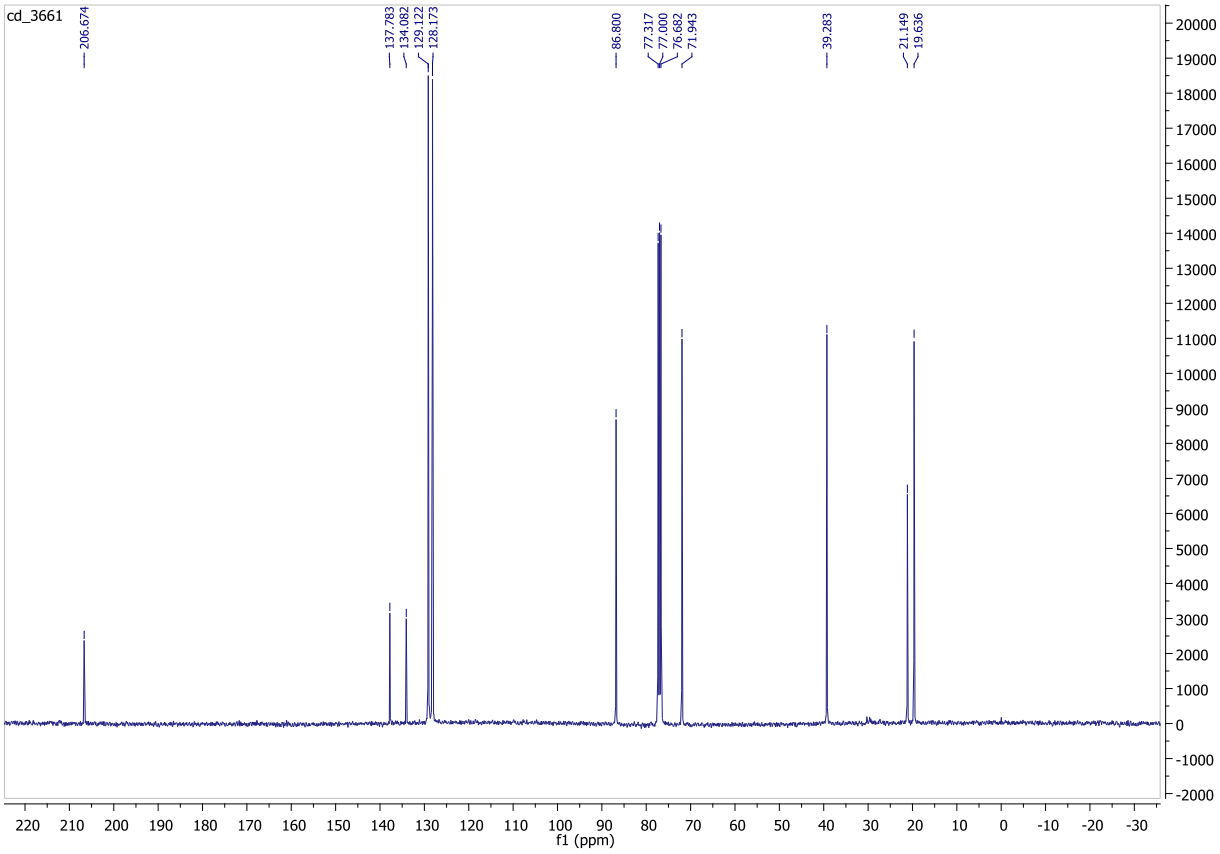

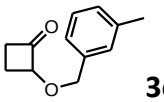

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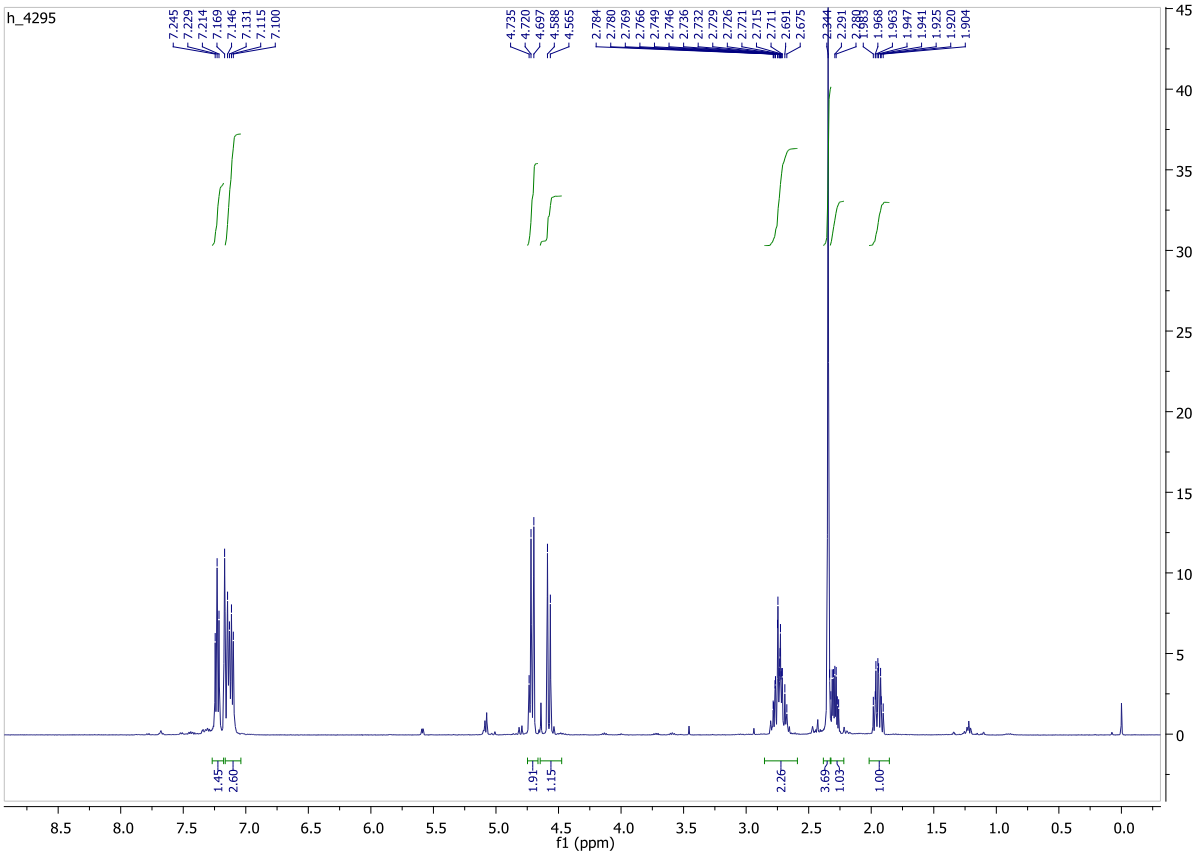

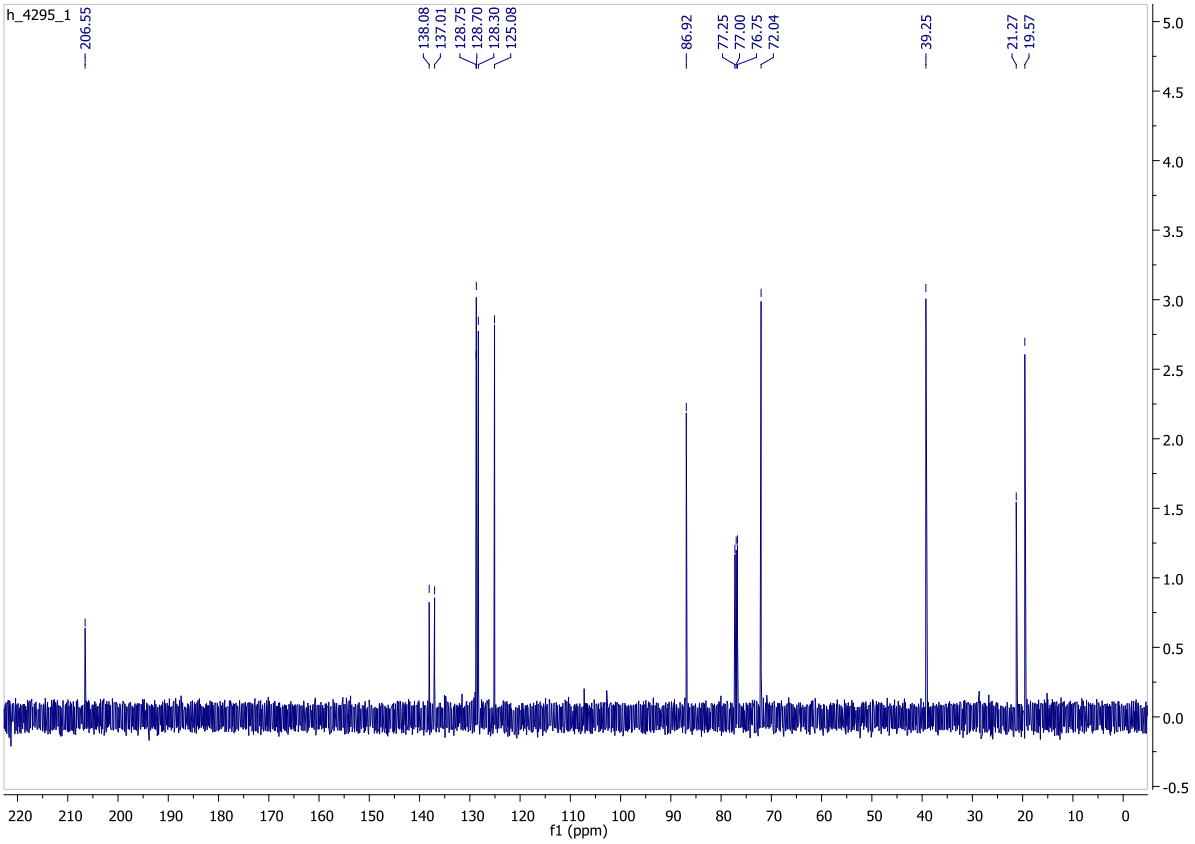

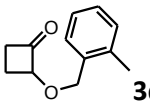

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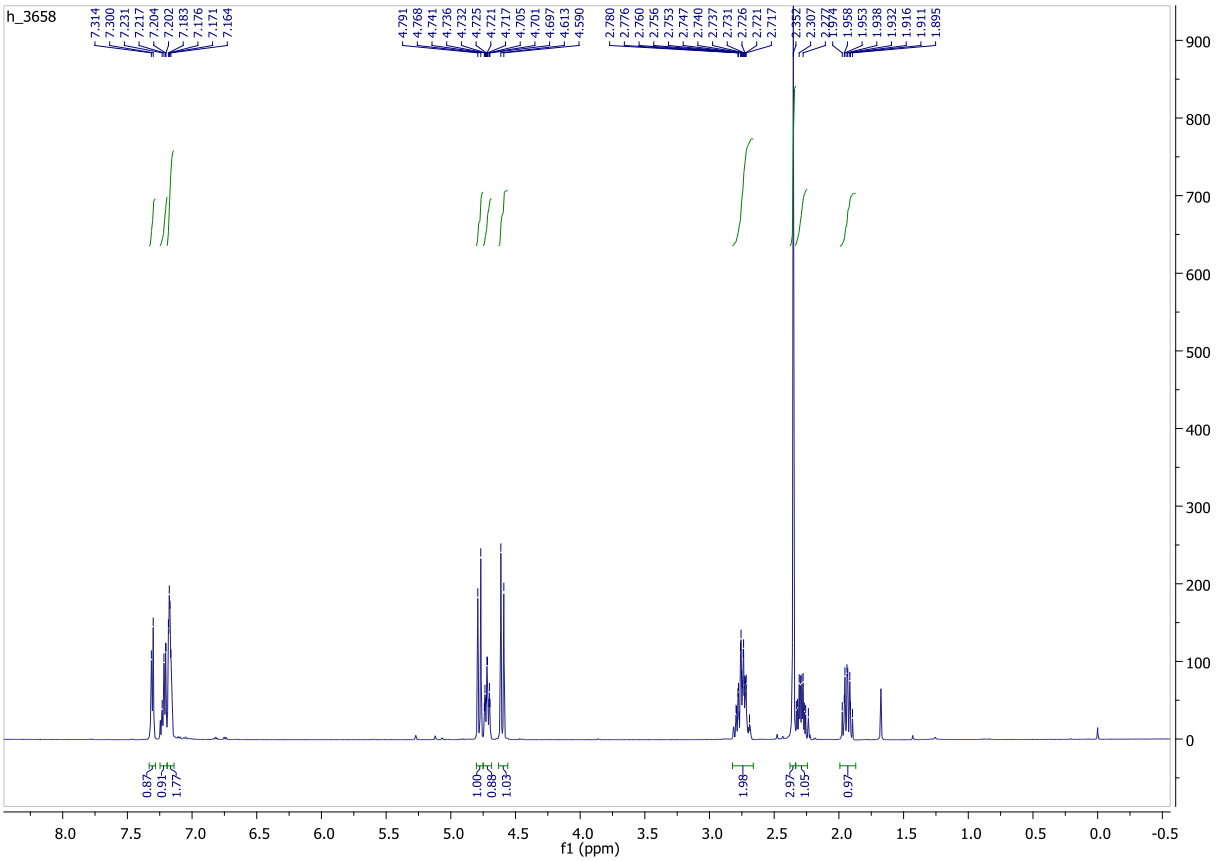

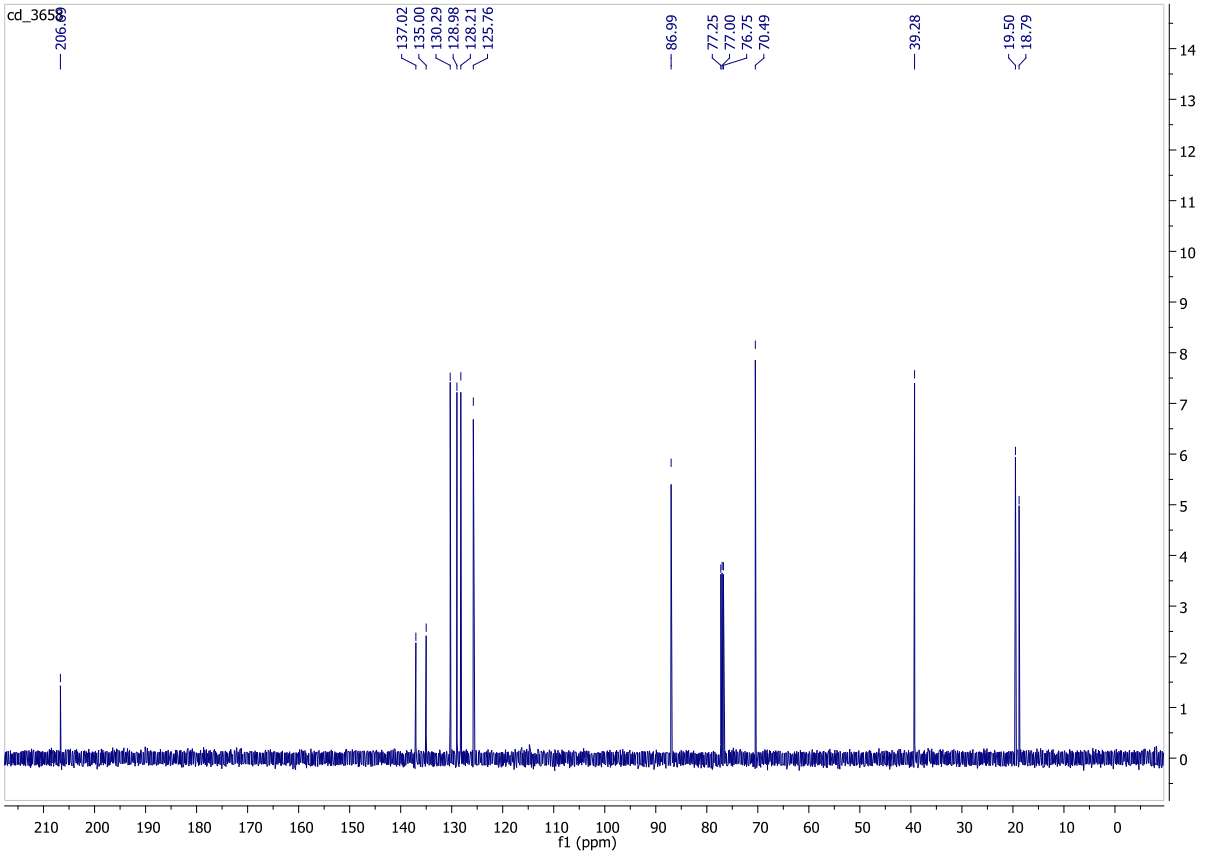

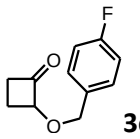

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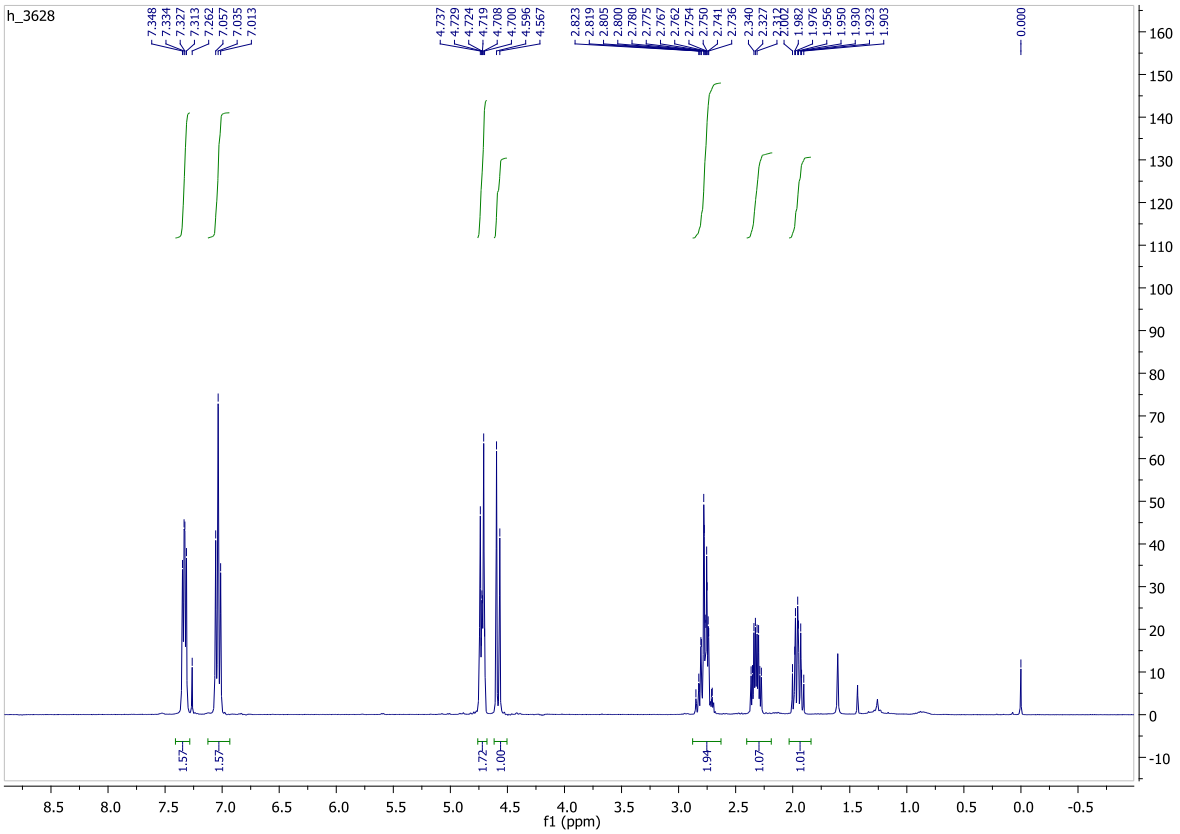

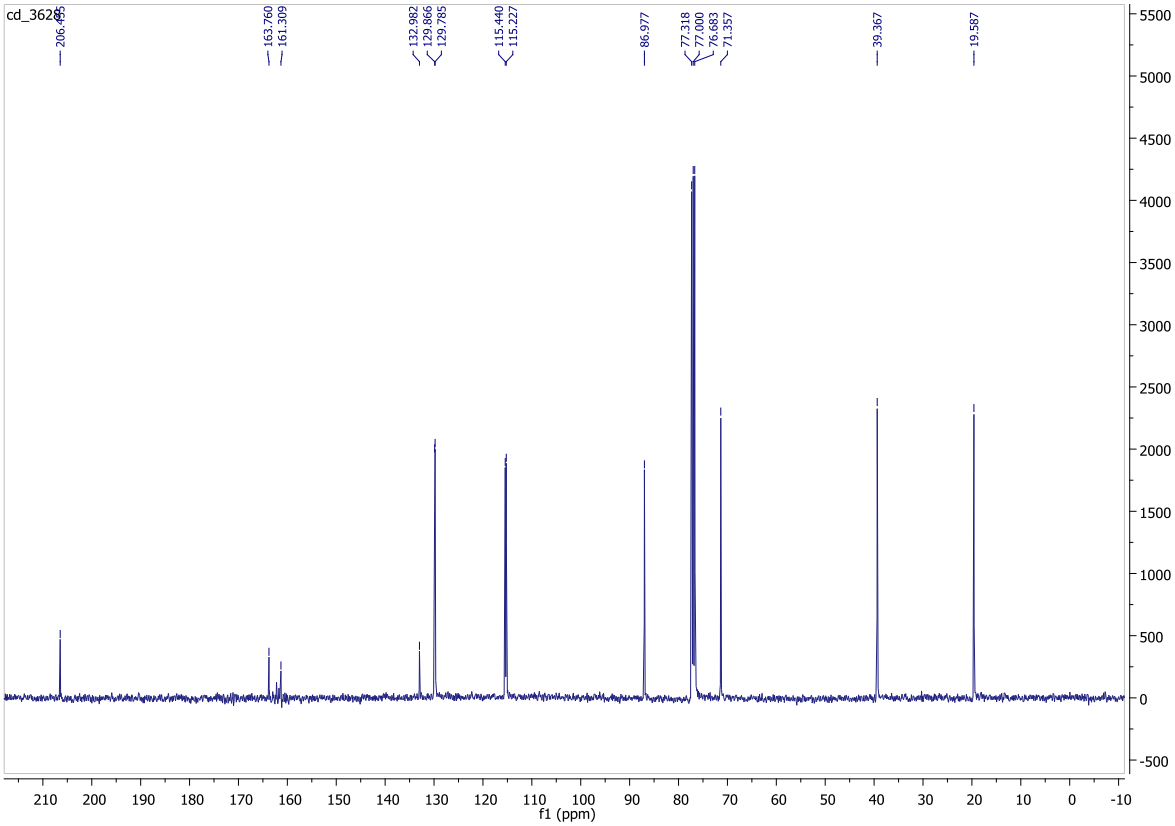

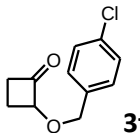

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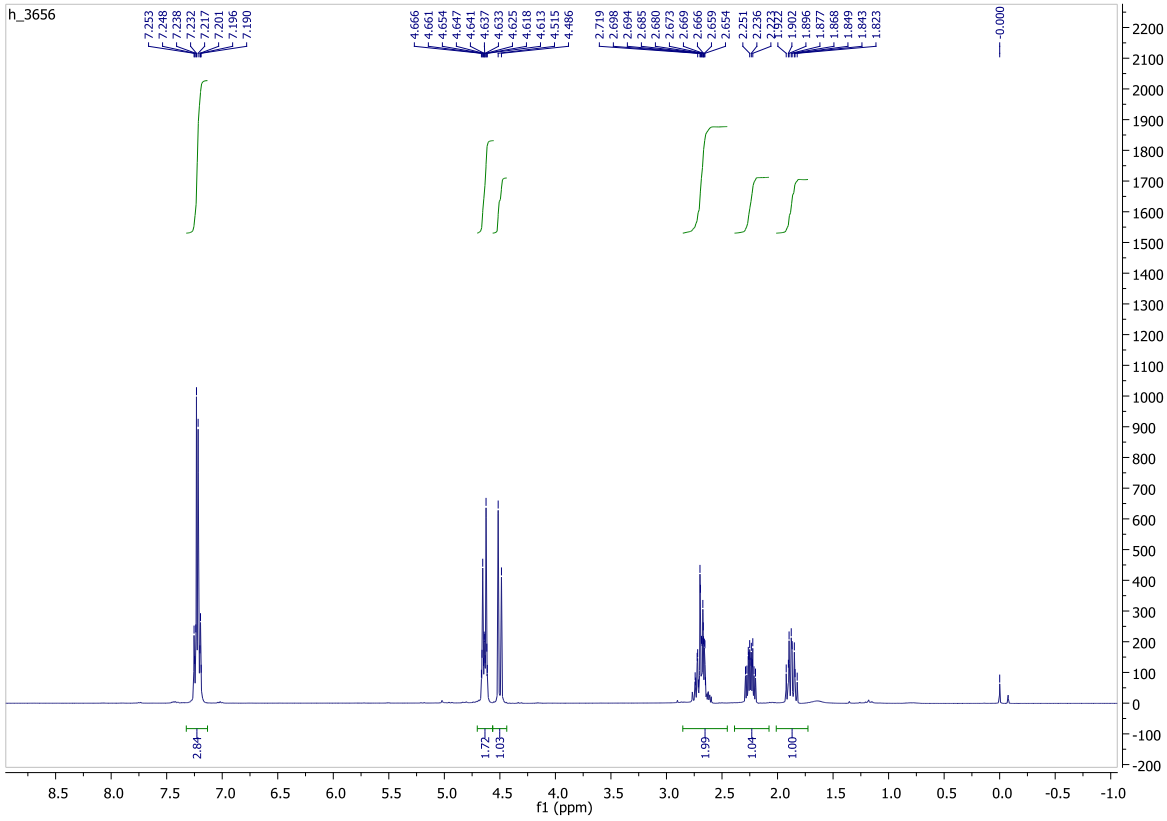

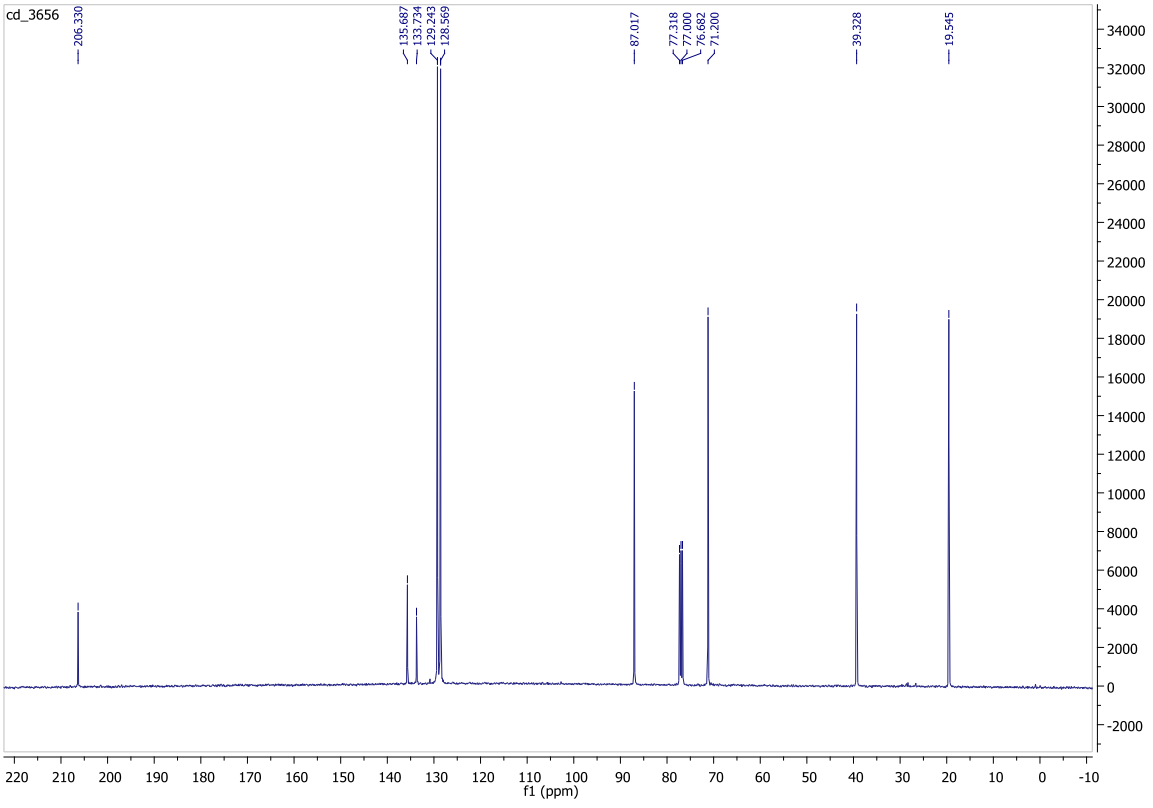

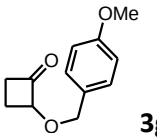

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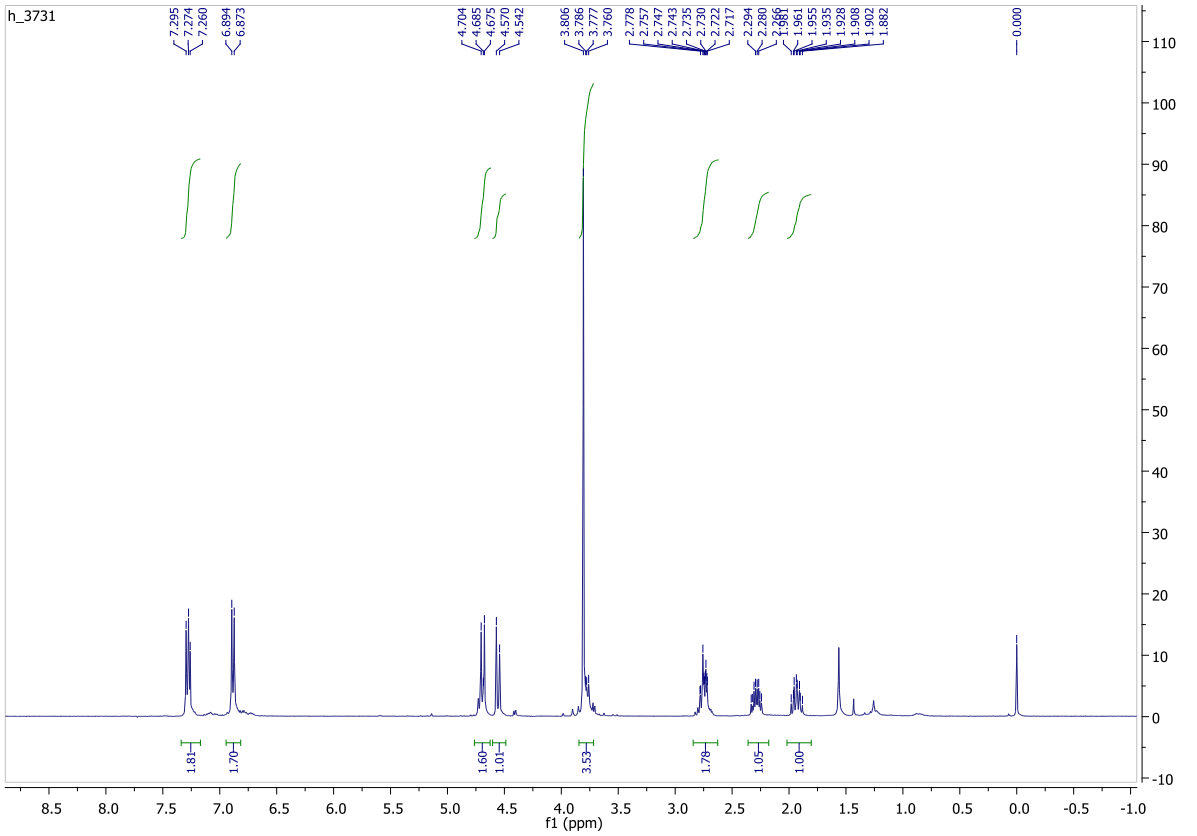

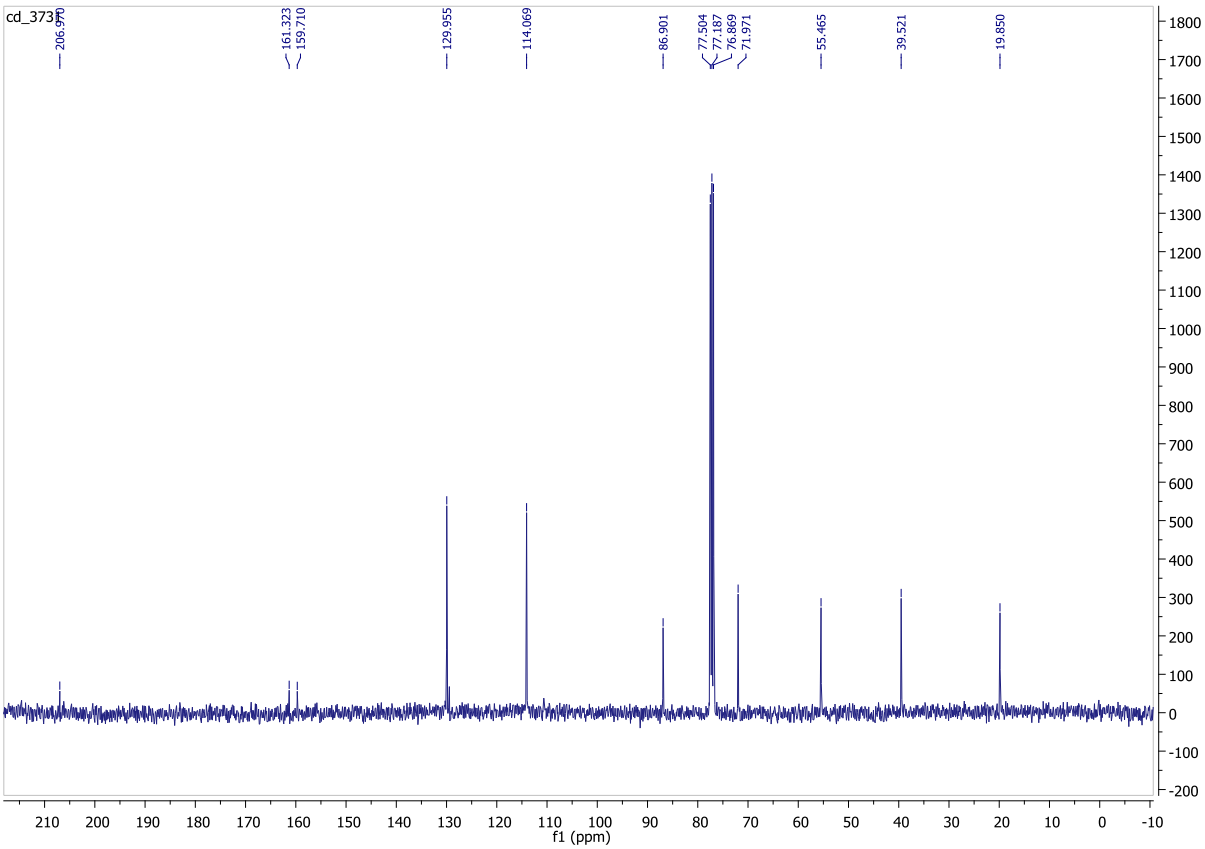

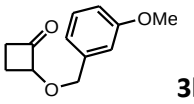

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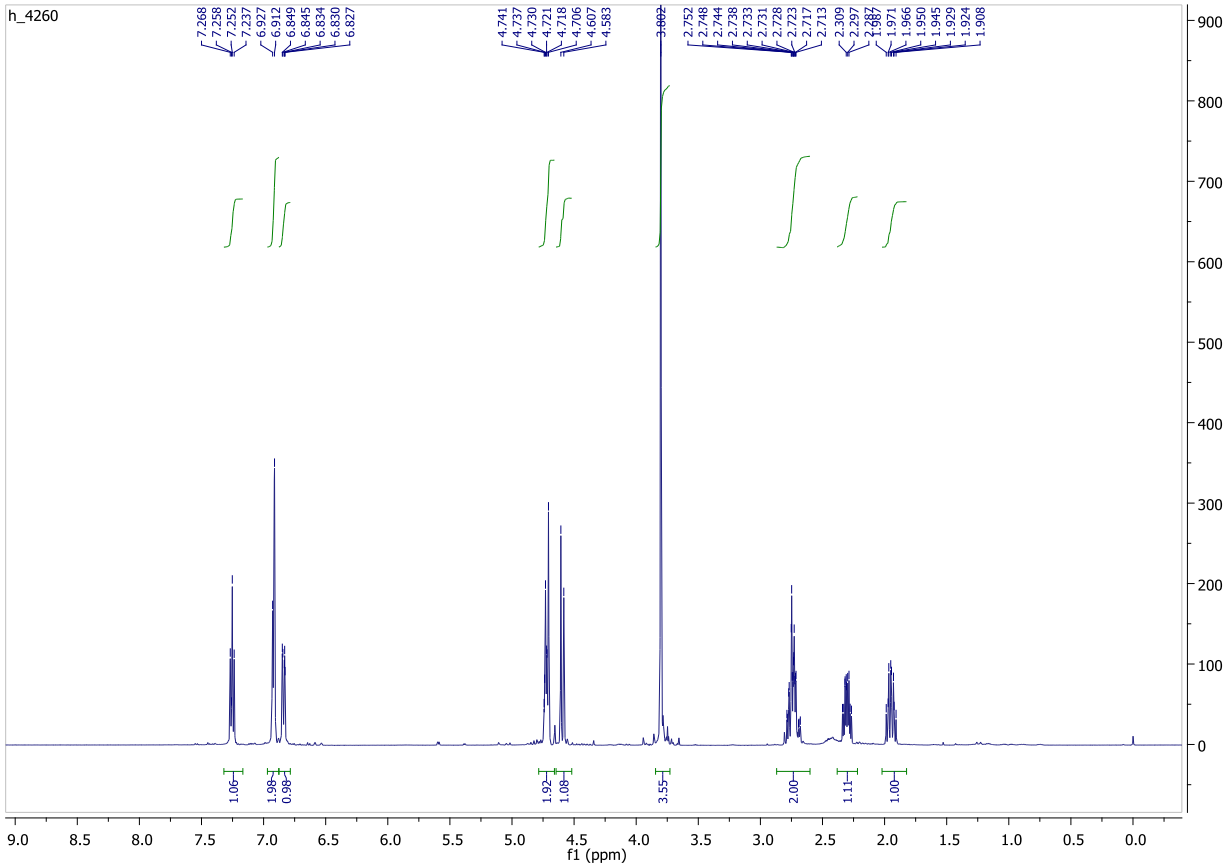
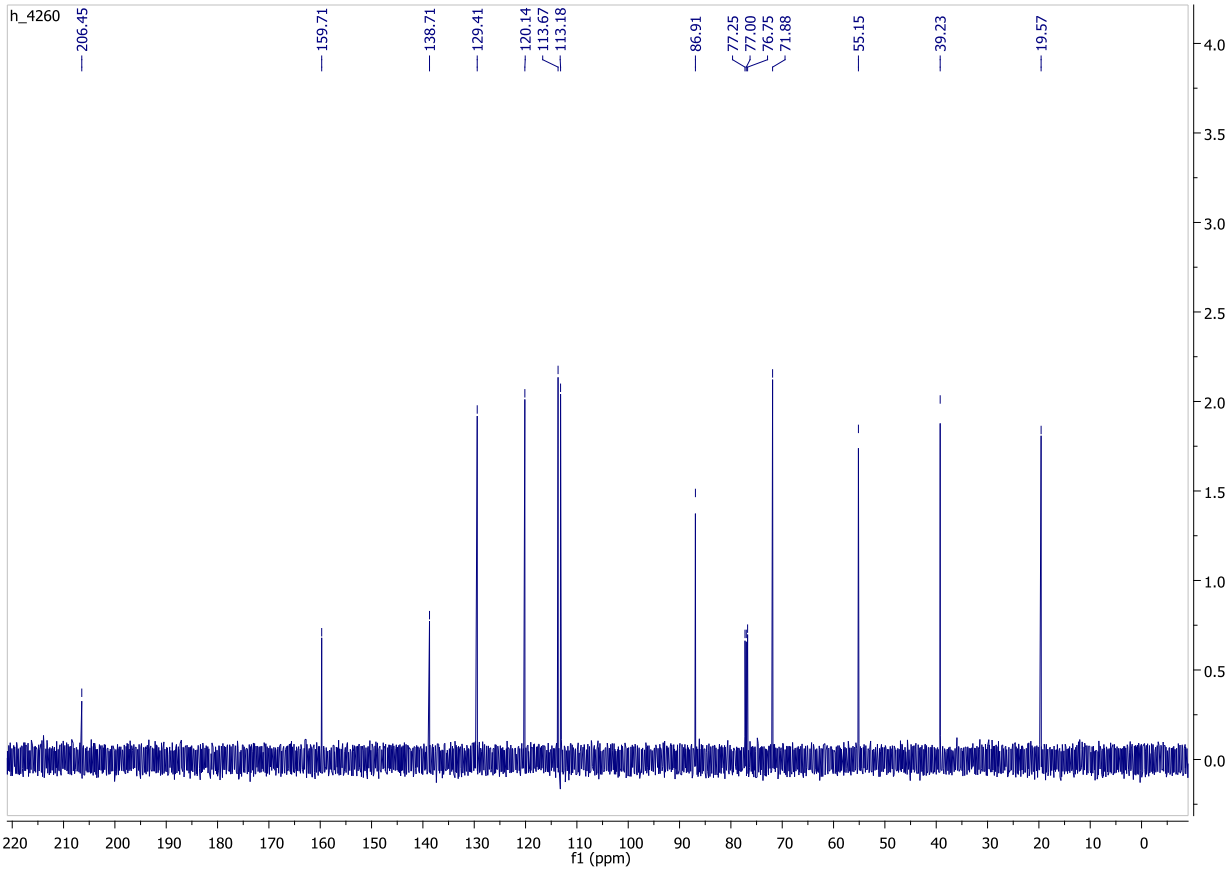
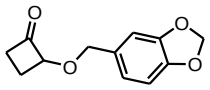
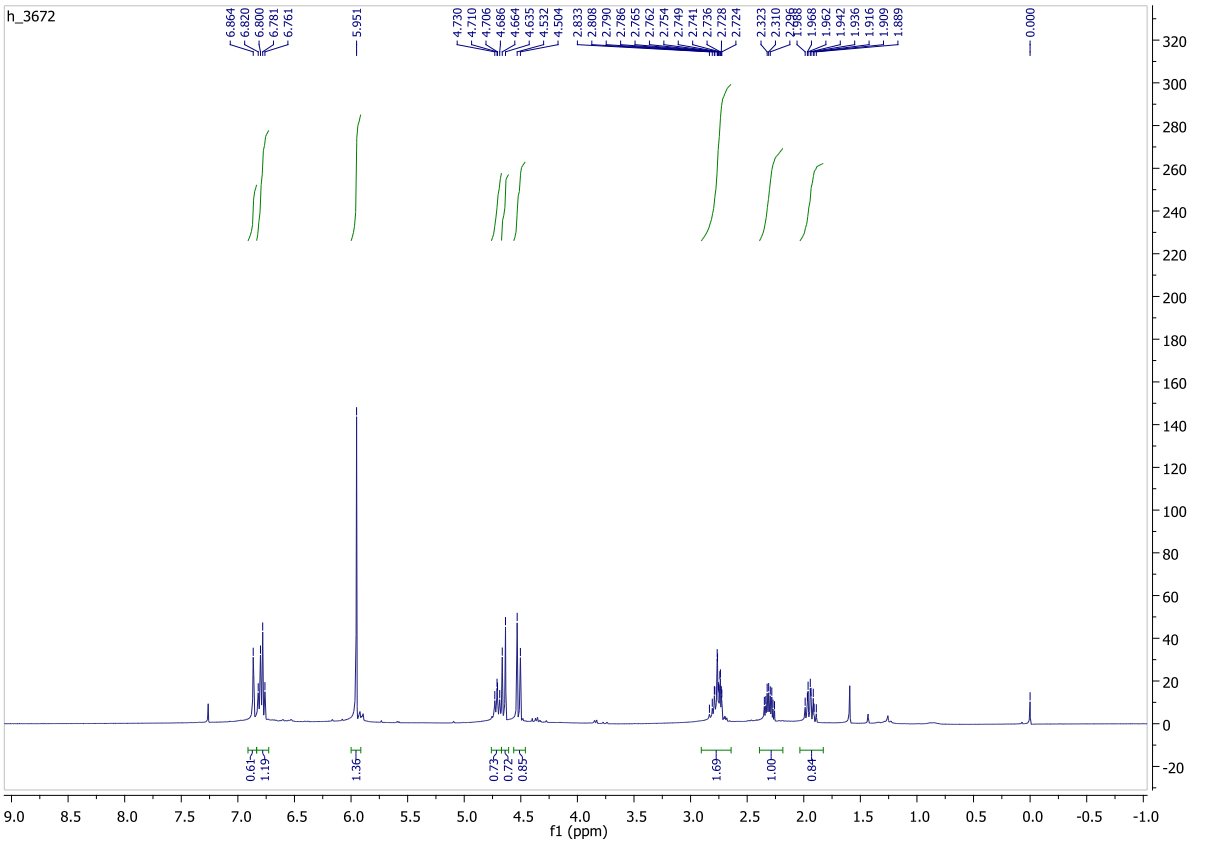
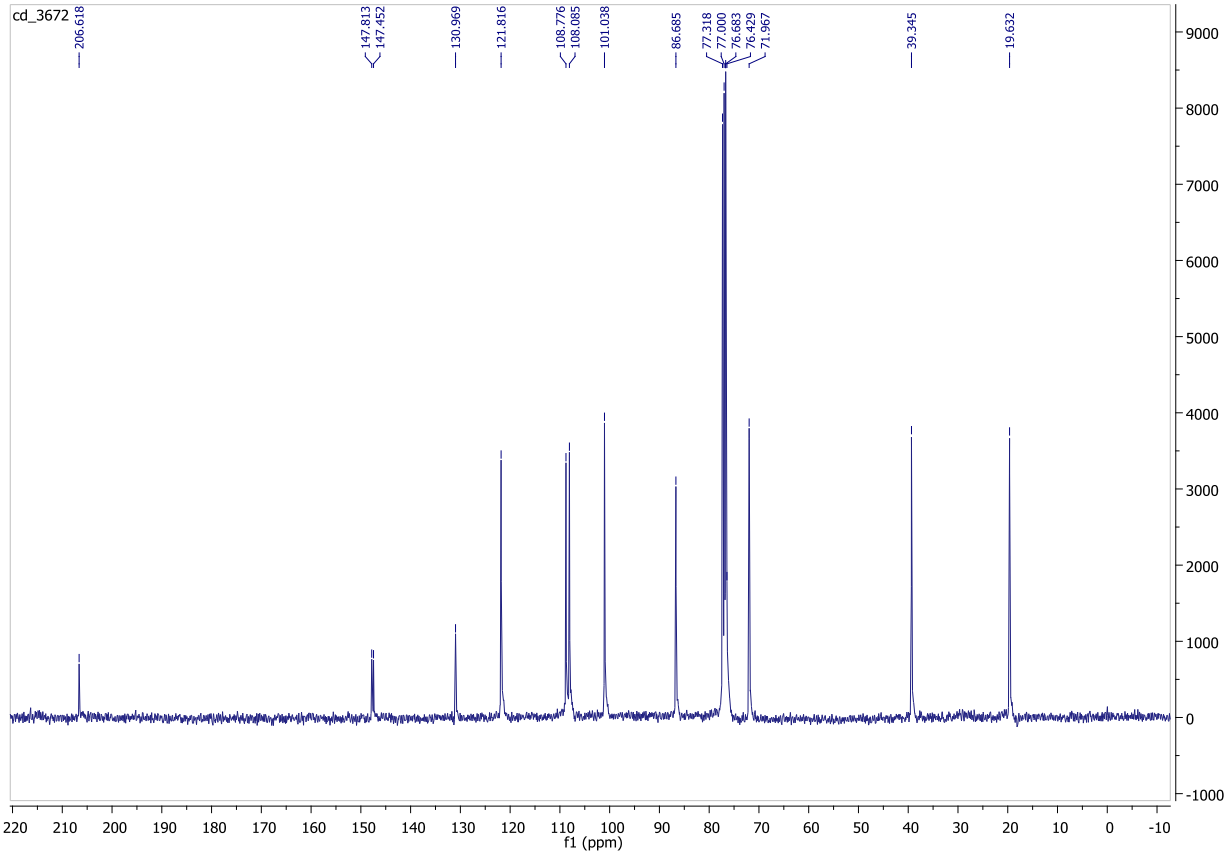


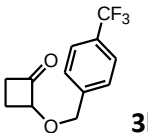




3j **2-(Benzo[1,3]dioxol-5-ylmethoxy)-cyclobutanone**







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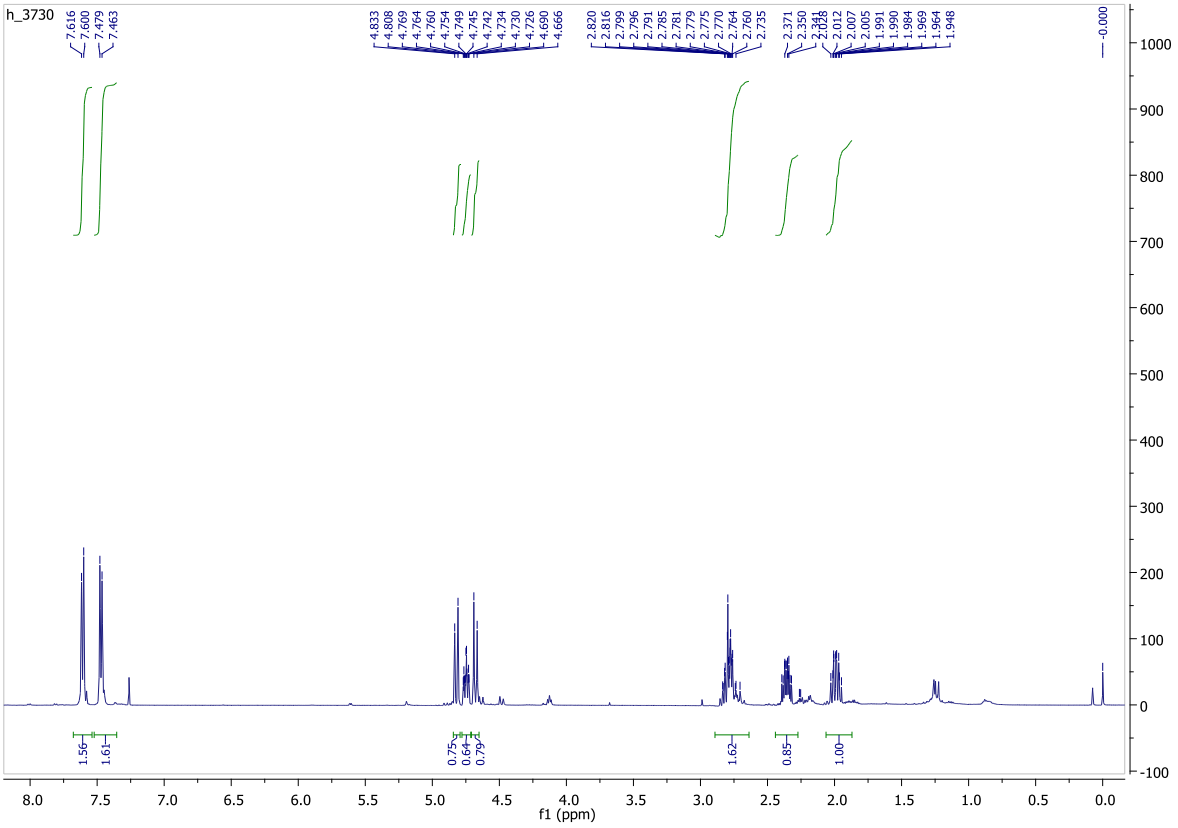
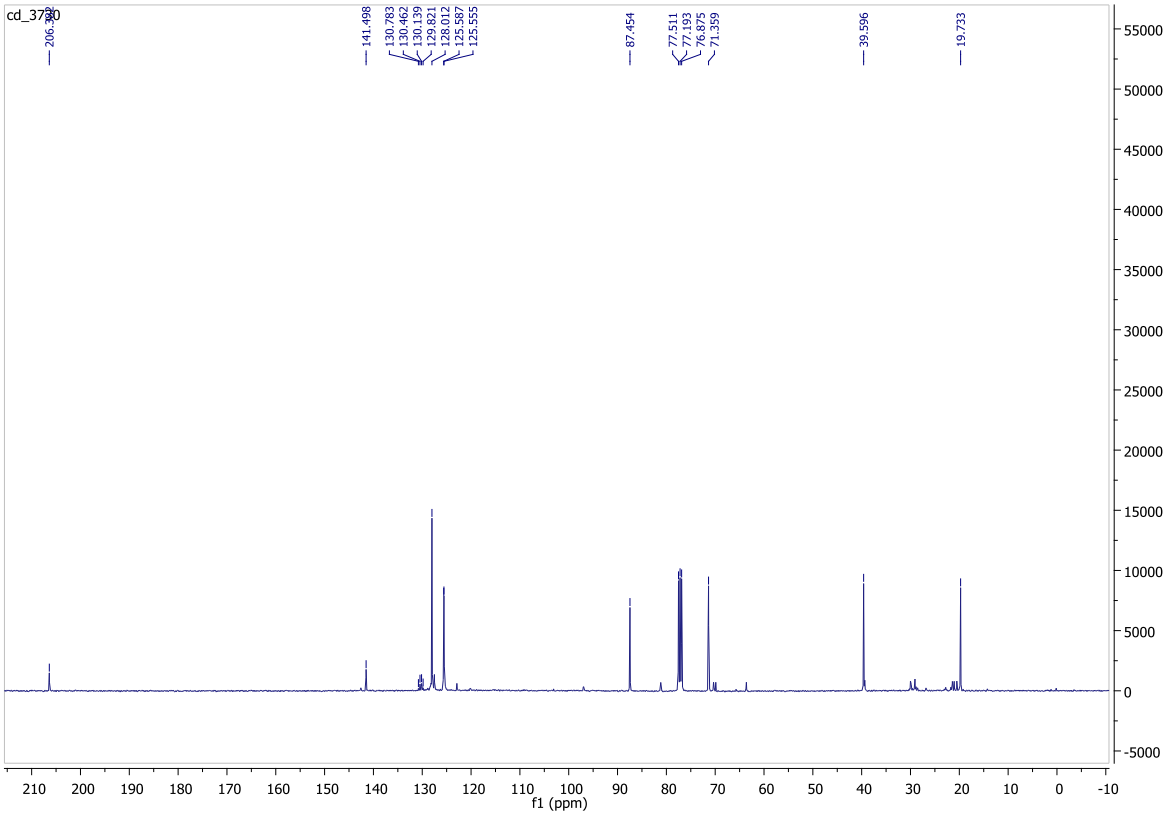
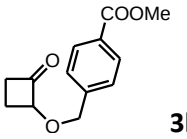
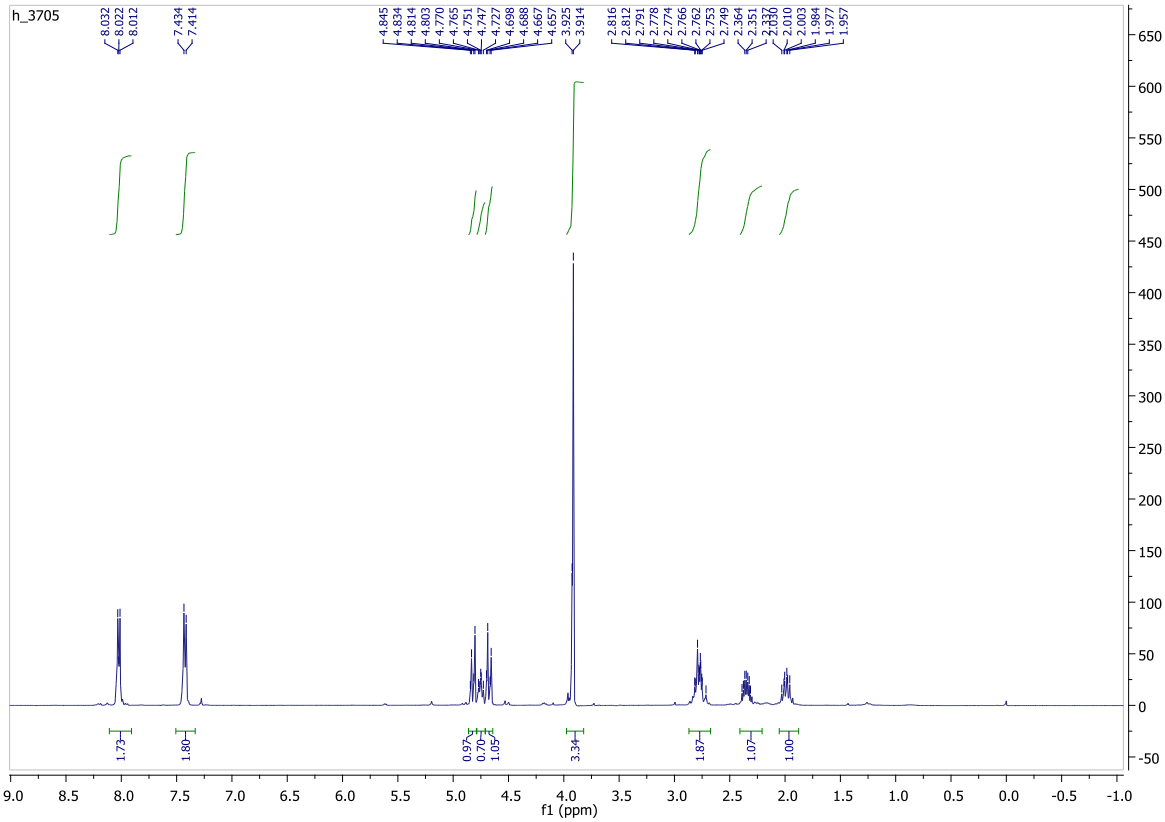
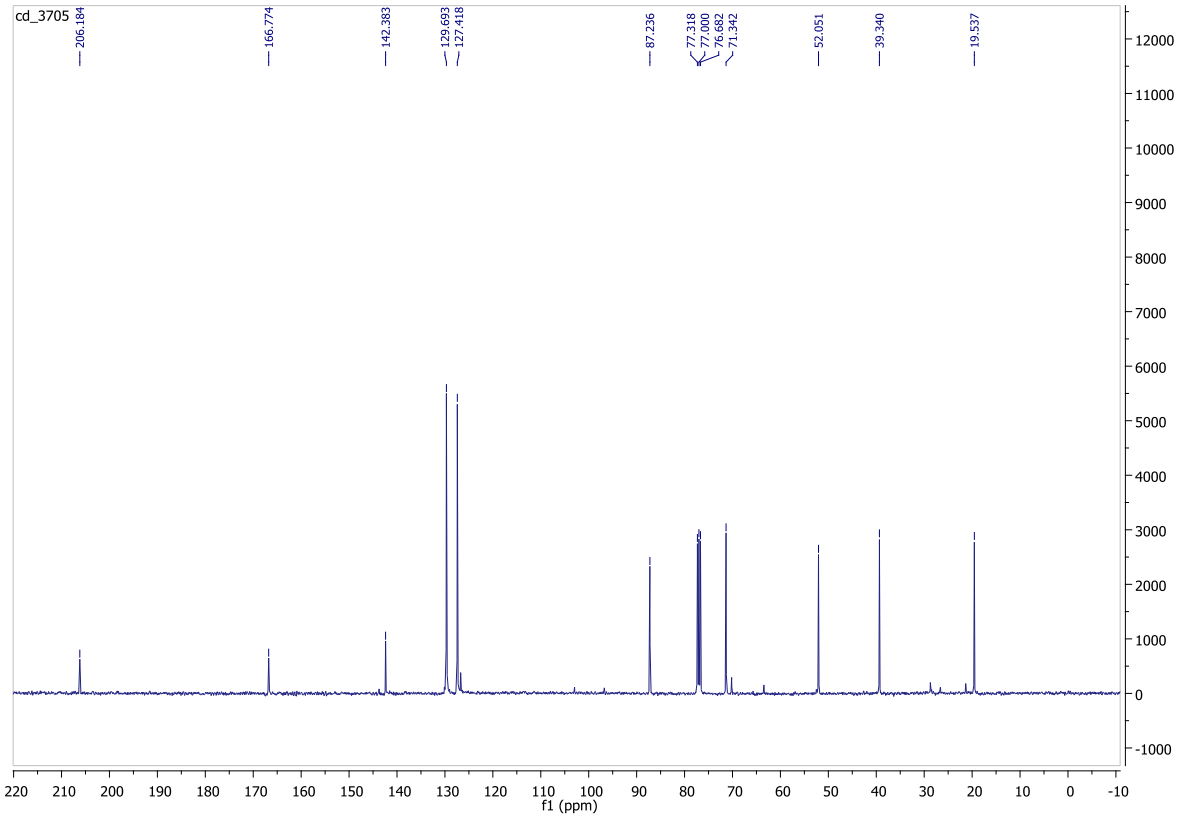


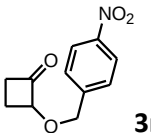




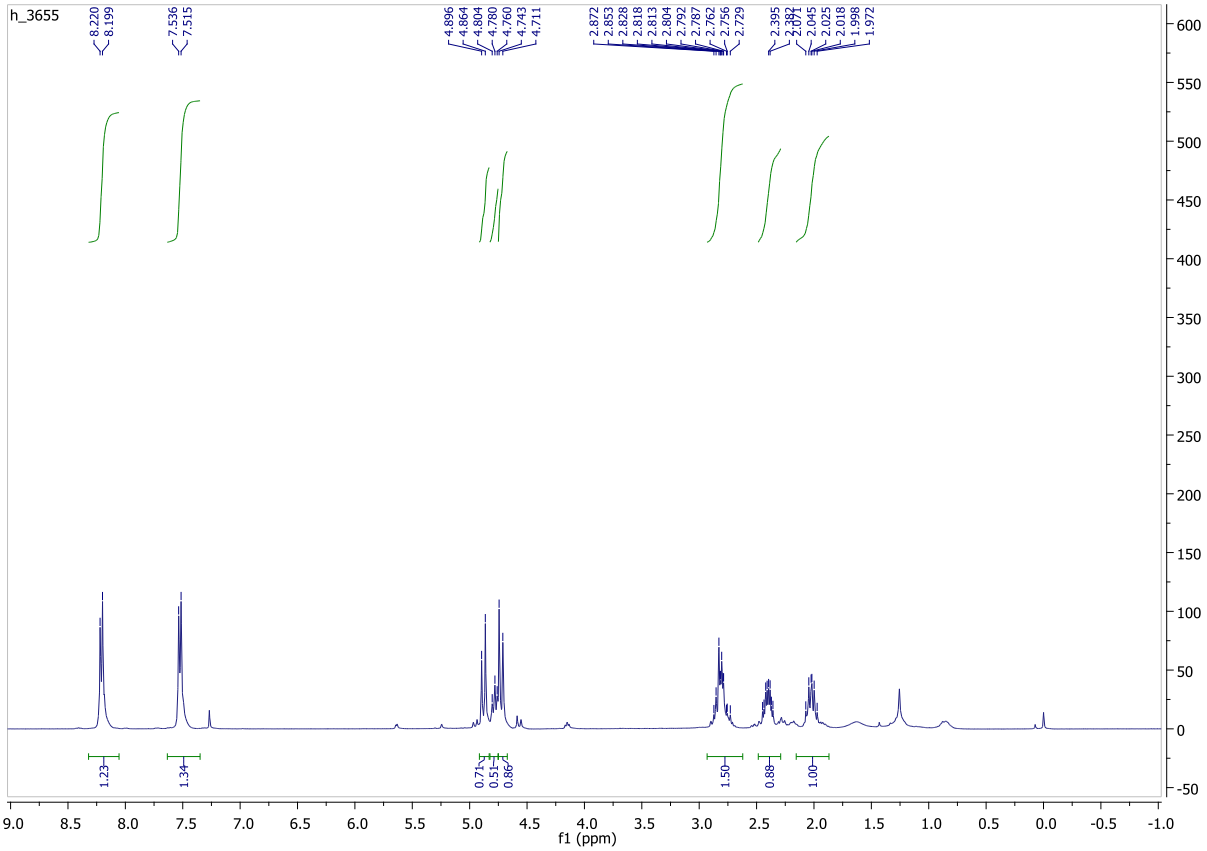
3l **4-(2-Oxo-cyclobutoxymethyl)-benzoic acid methyl ester**

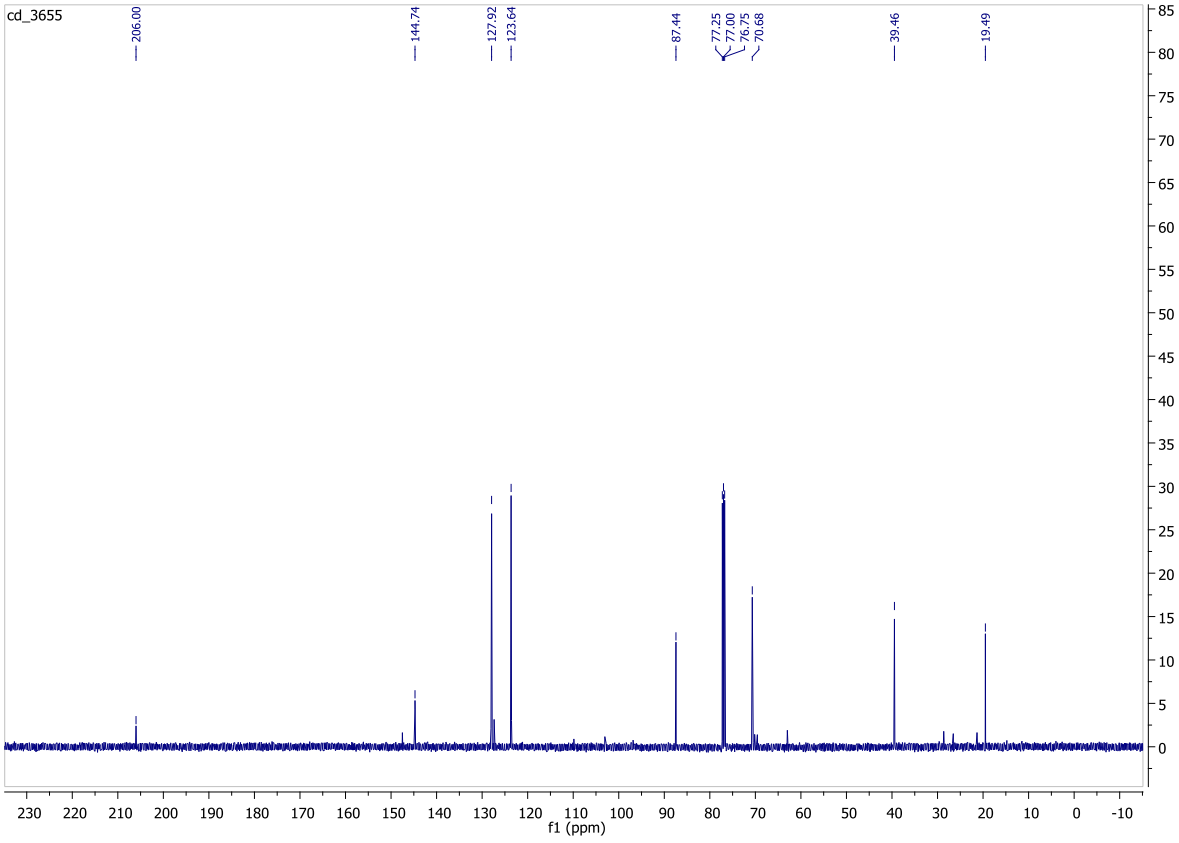


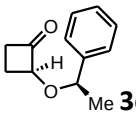




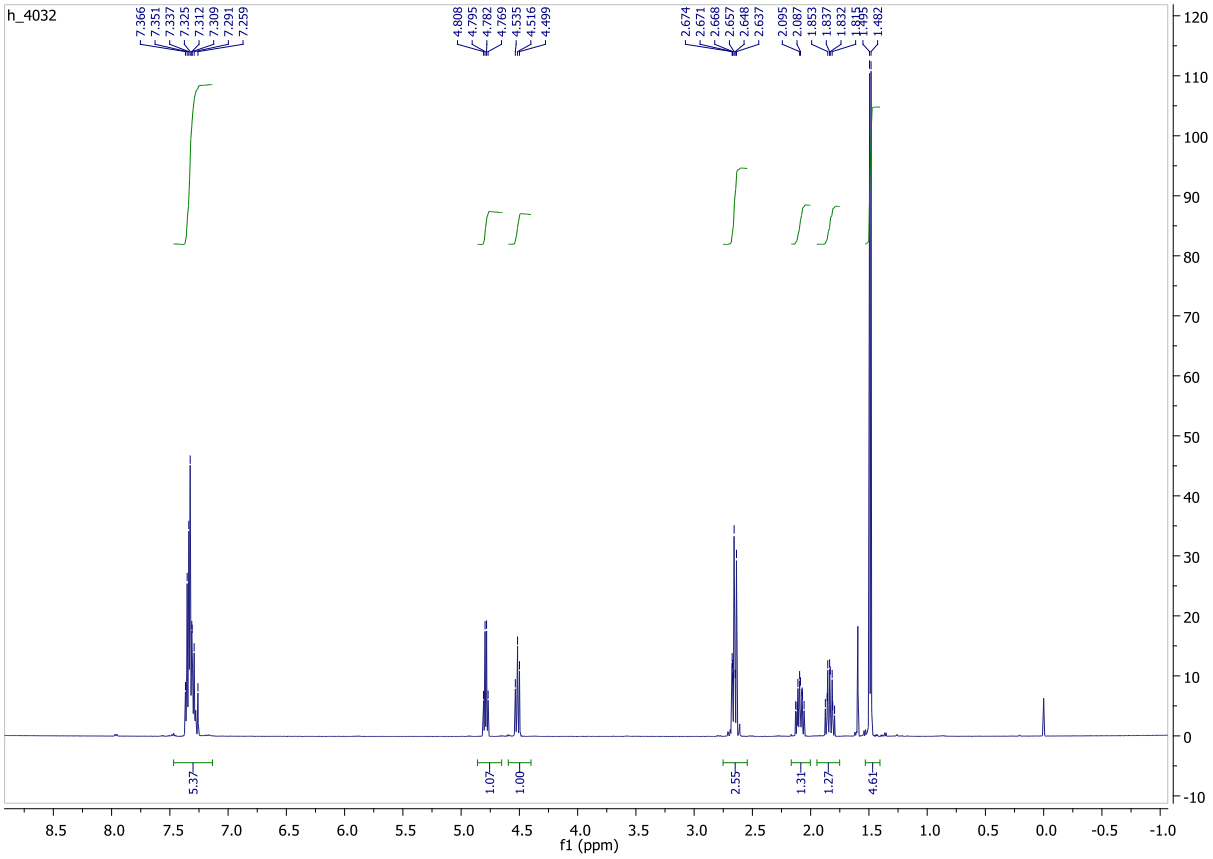
3m **2-(4-Nitro-benzyloxy)-cyclobutanone**

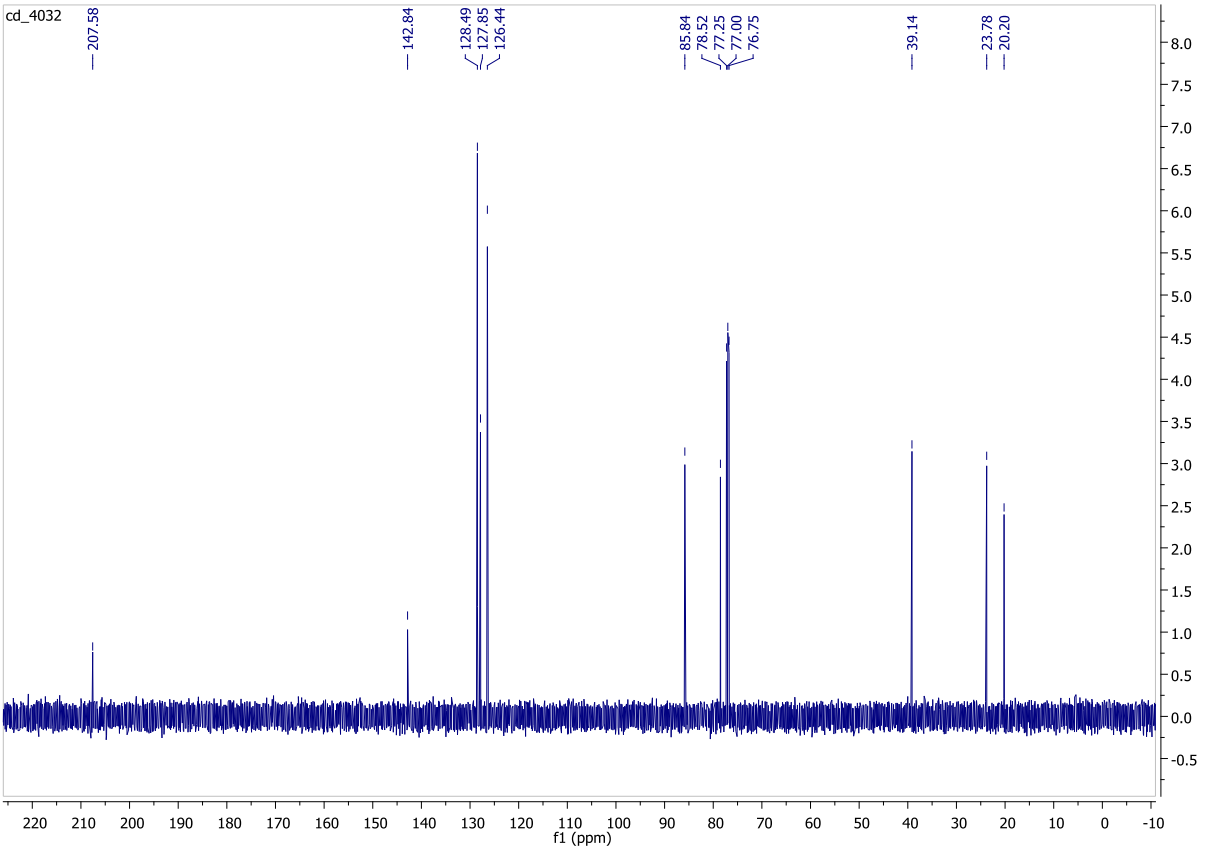


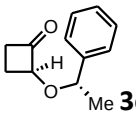




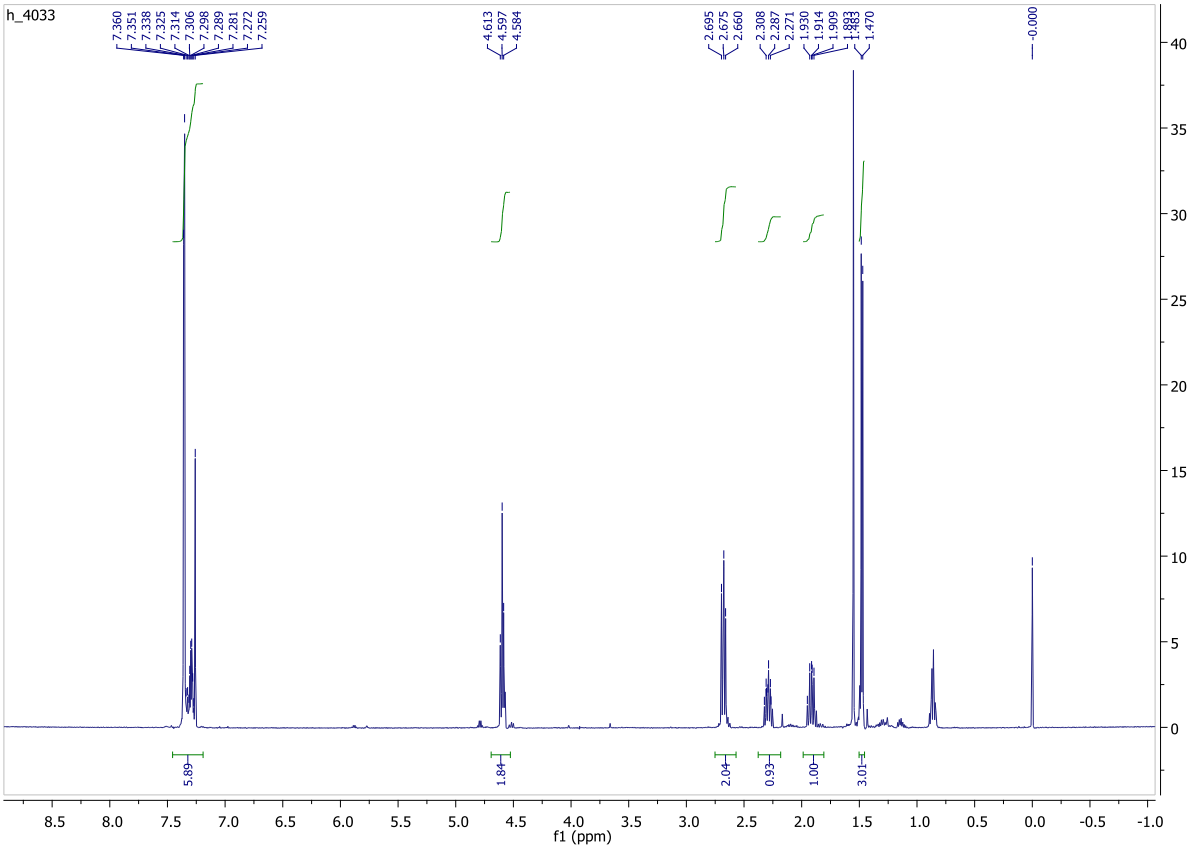
3o **2-(1-Phenyl-ethoxy)-cyclobutanone (Major)**

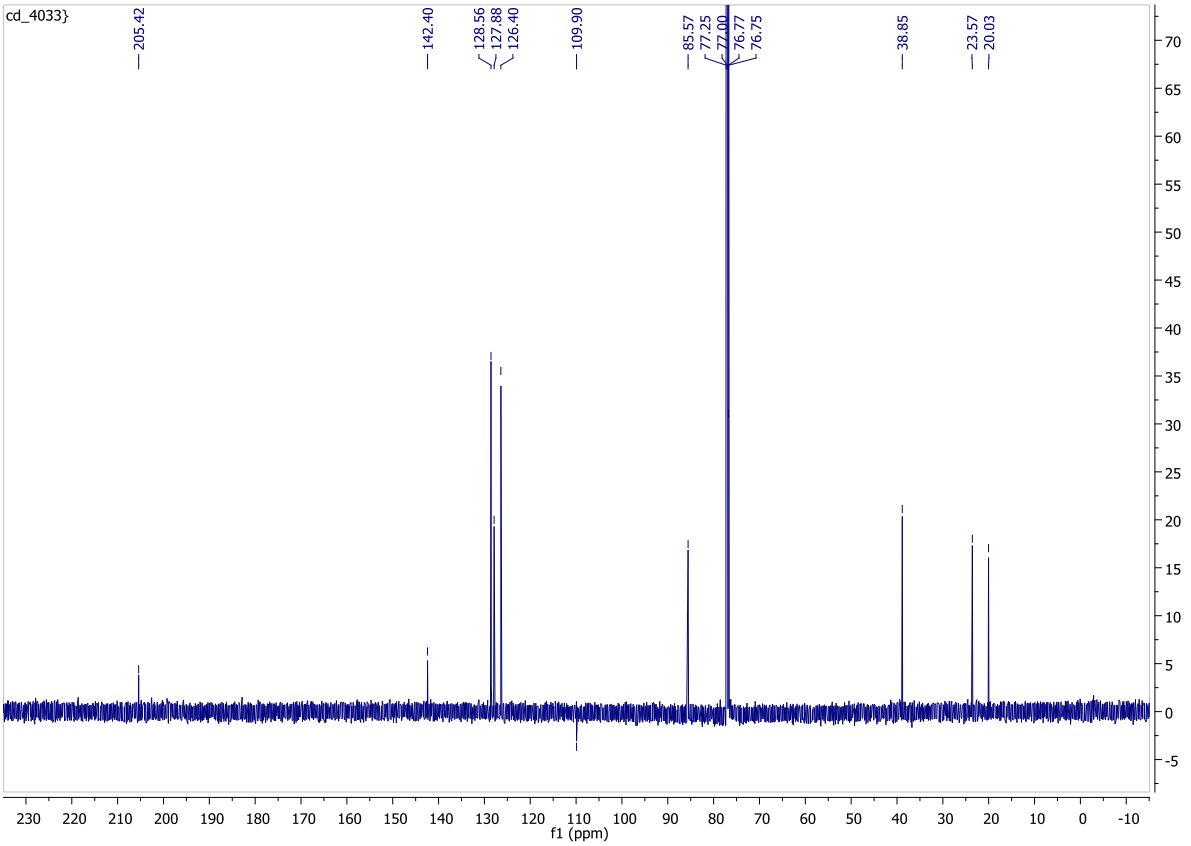


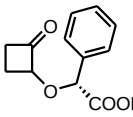




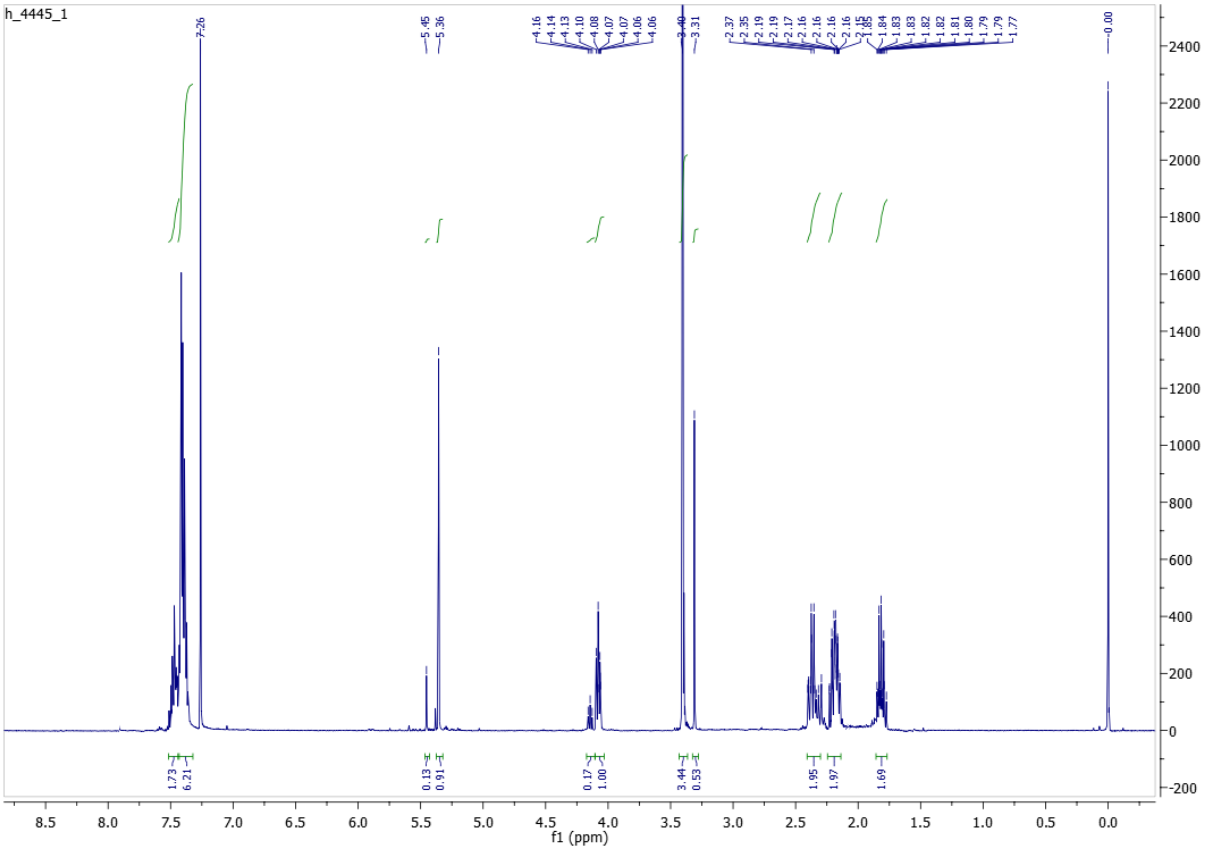
3o **2-(1-Phenyl-ethoxy)-cyclobutanone (Minor)**

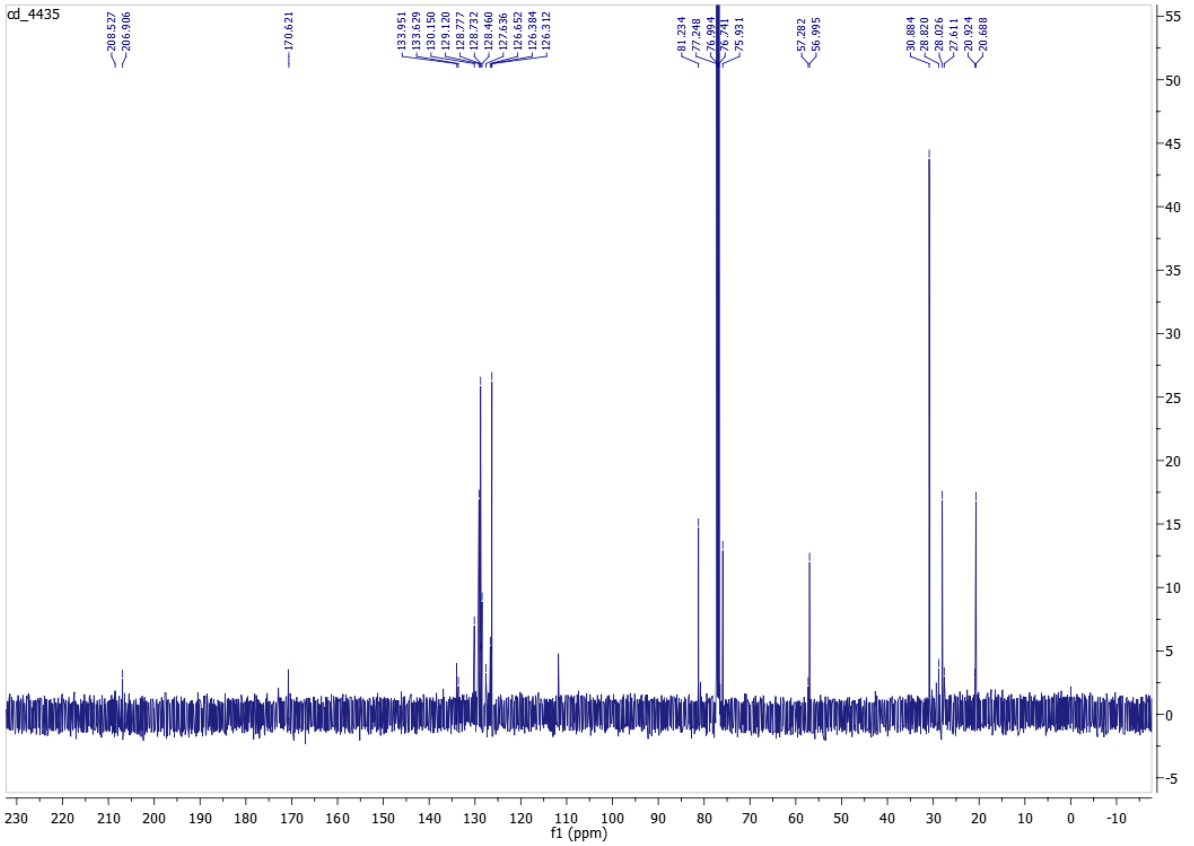


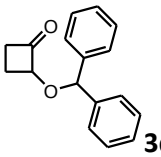




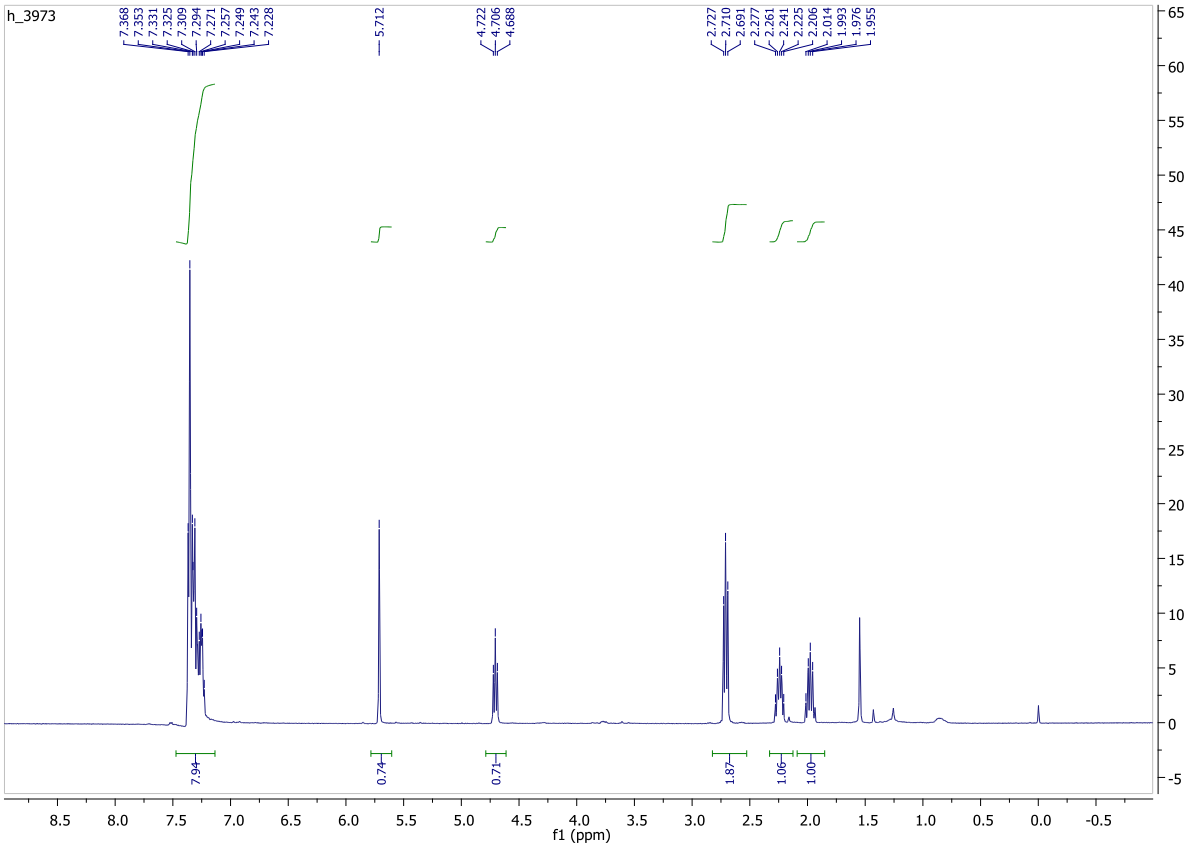
3p **(2-Oxo-cyclobutoxy)-phenyl-acetic acid ethyl ester**

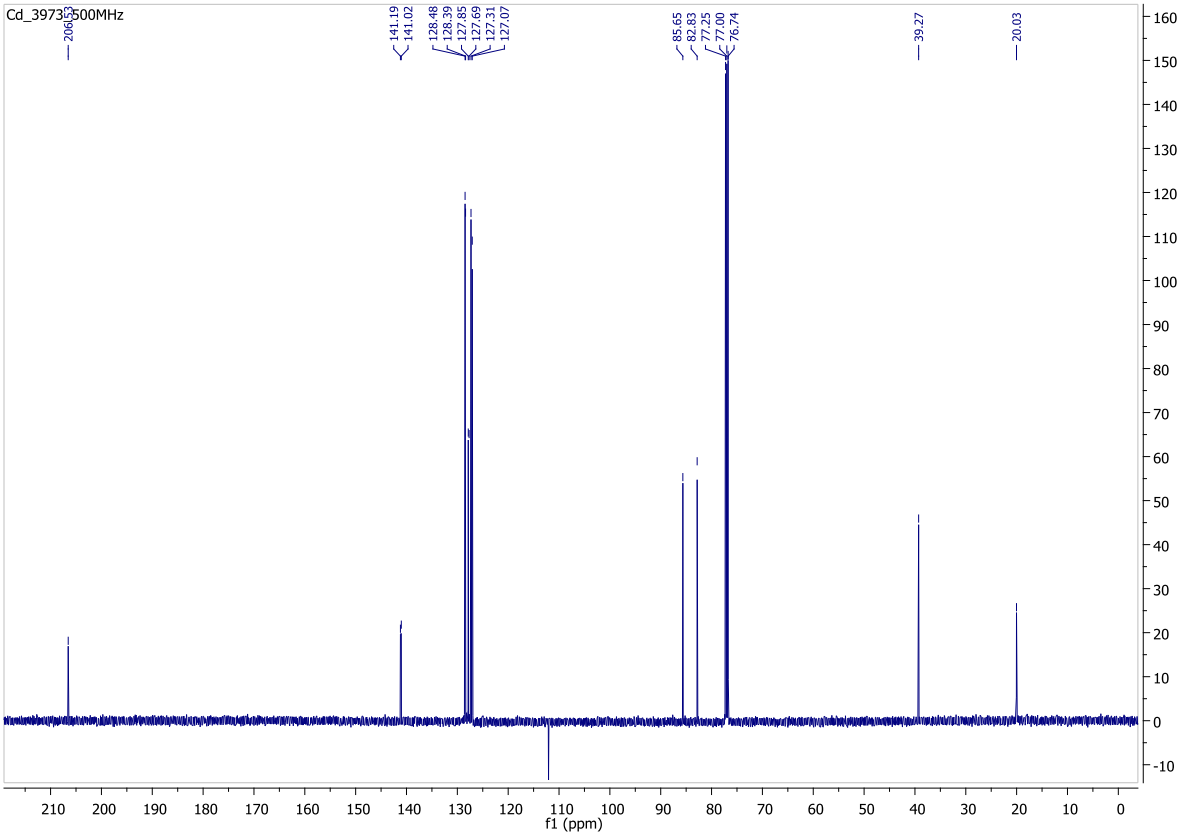


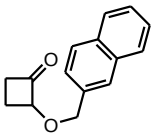




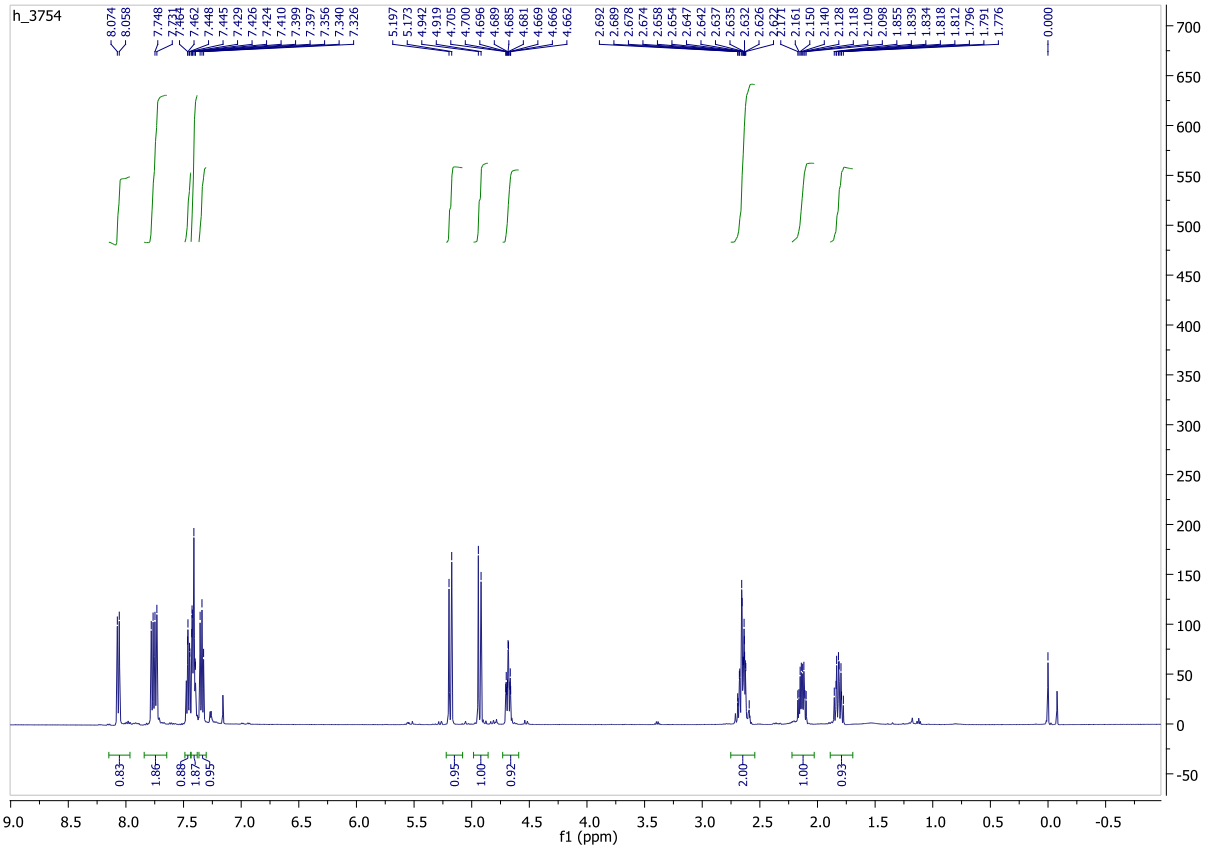
3q **2-Benzhydryloxy-cyclobutanone**

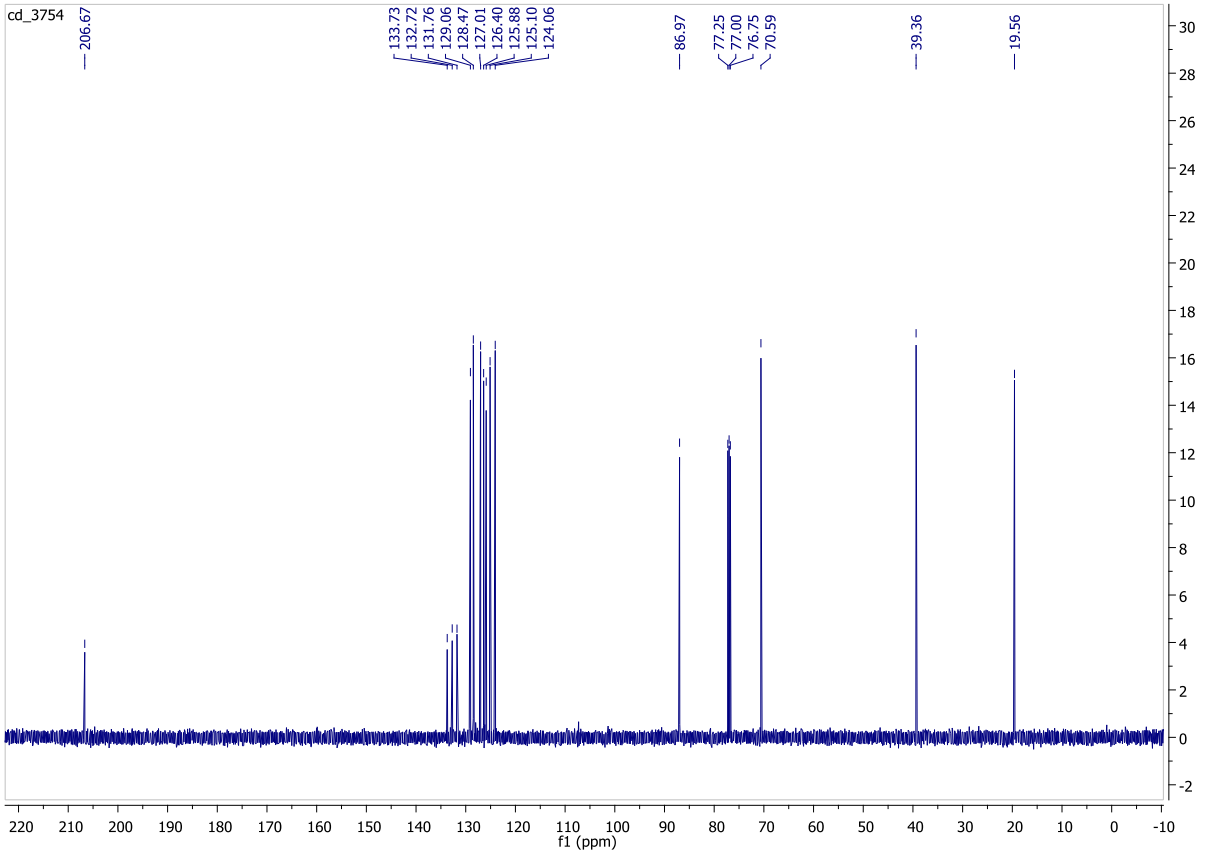


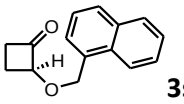




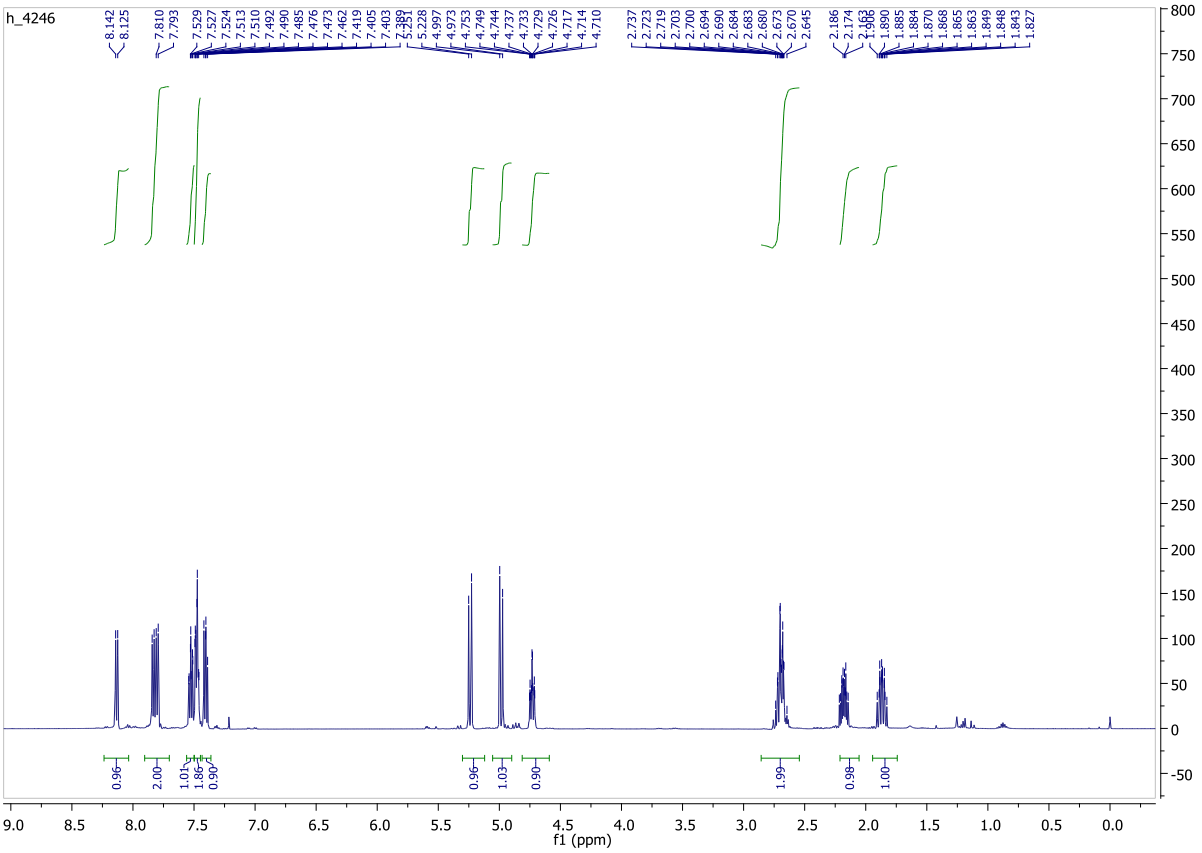
3r **2-(Naphthalen-2-ylmethoxy)-cyclobutanone**

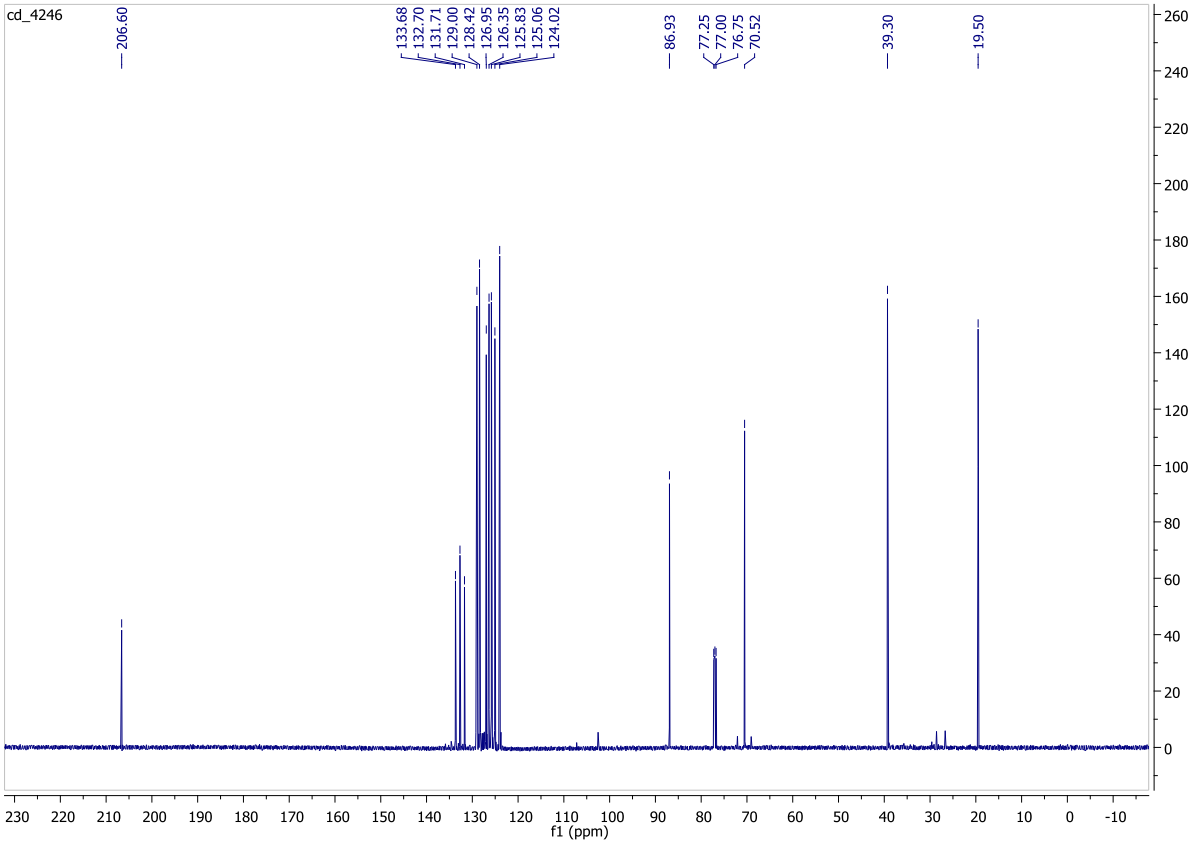


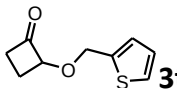




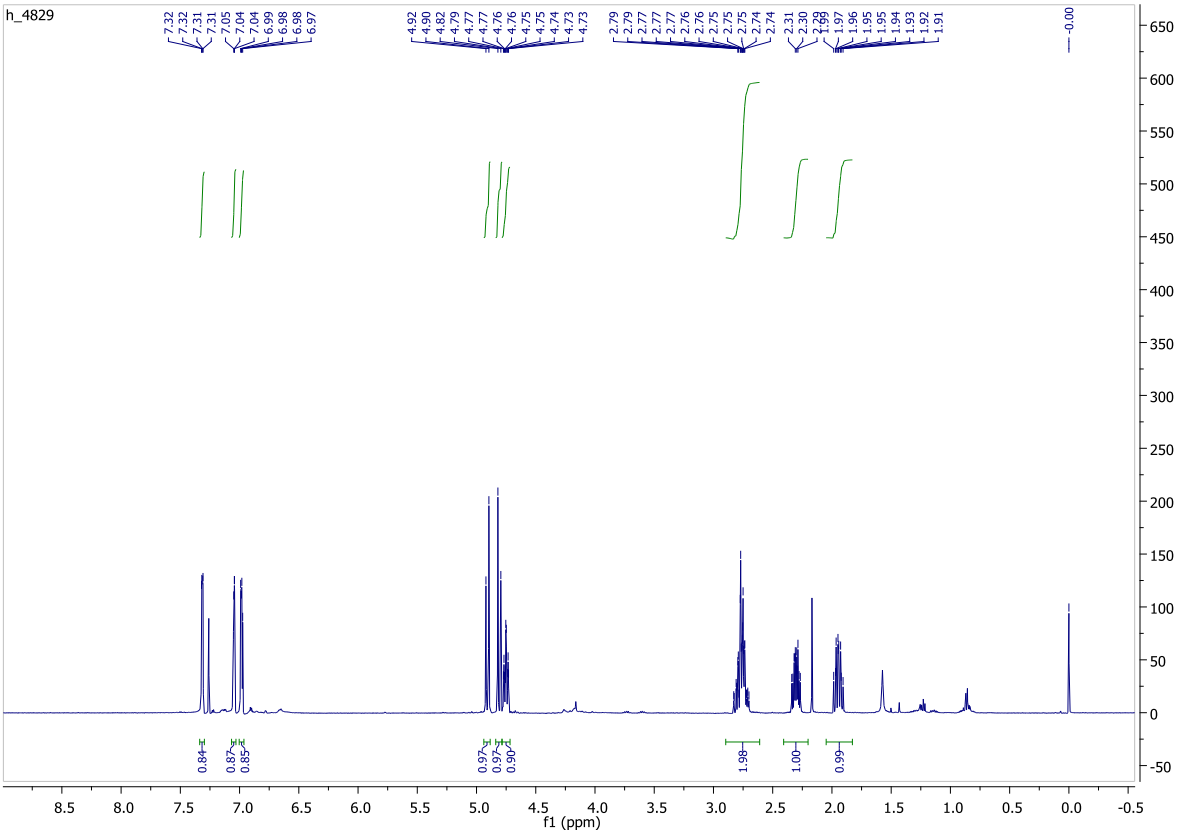
3s **2-(Naphthalen-1-ylmethoxy)-cyclobutanone**

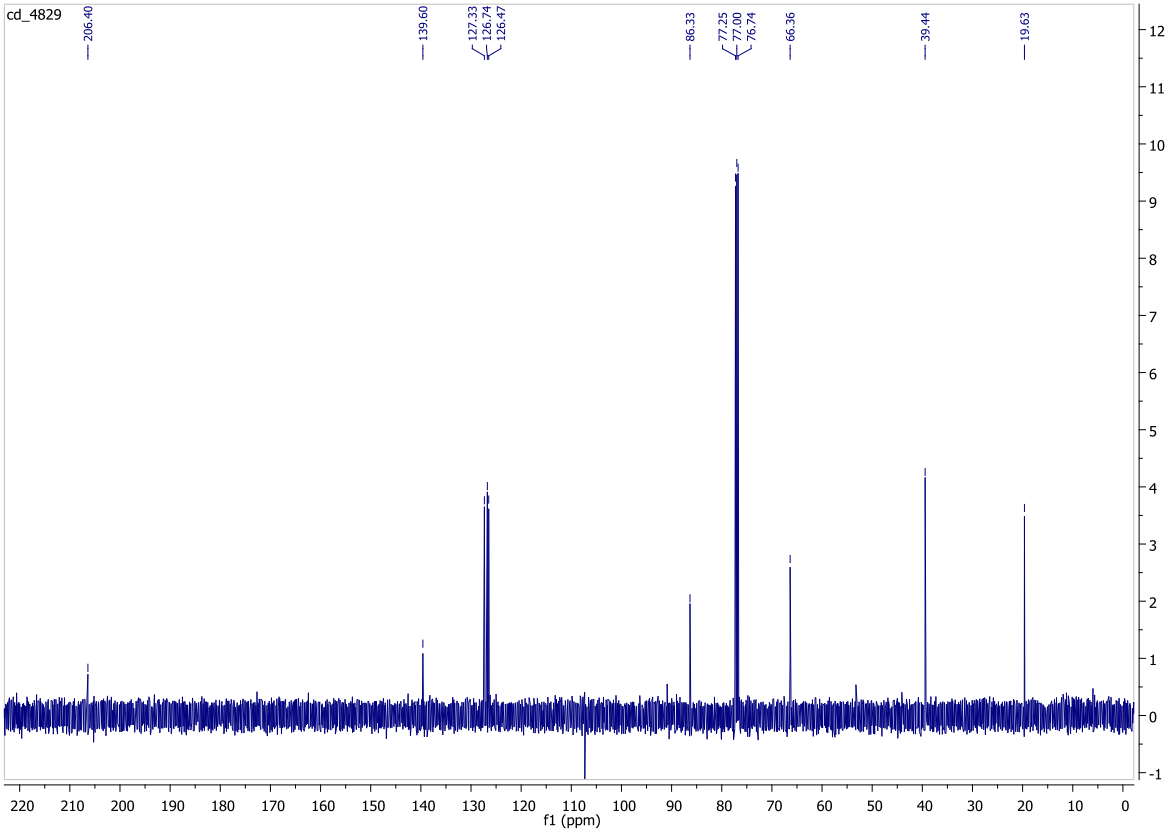


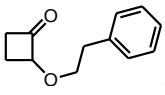




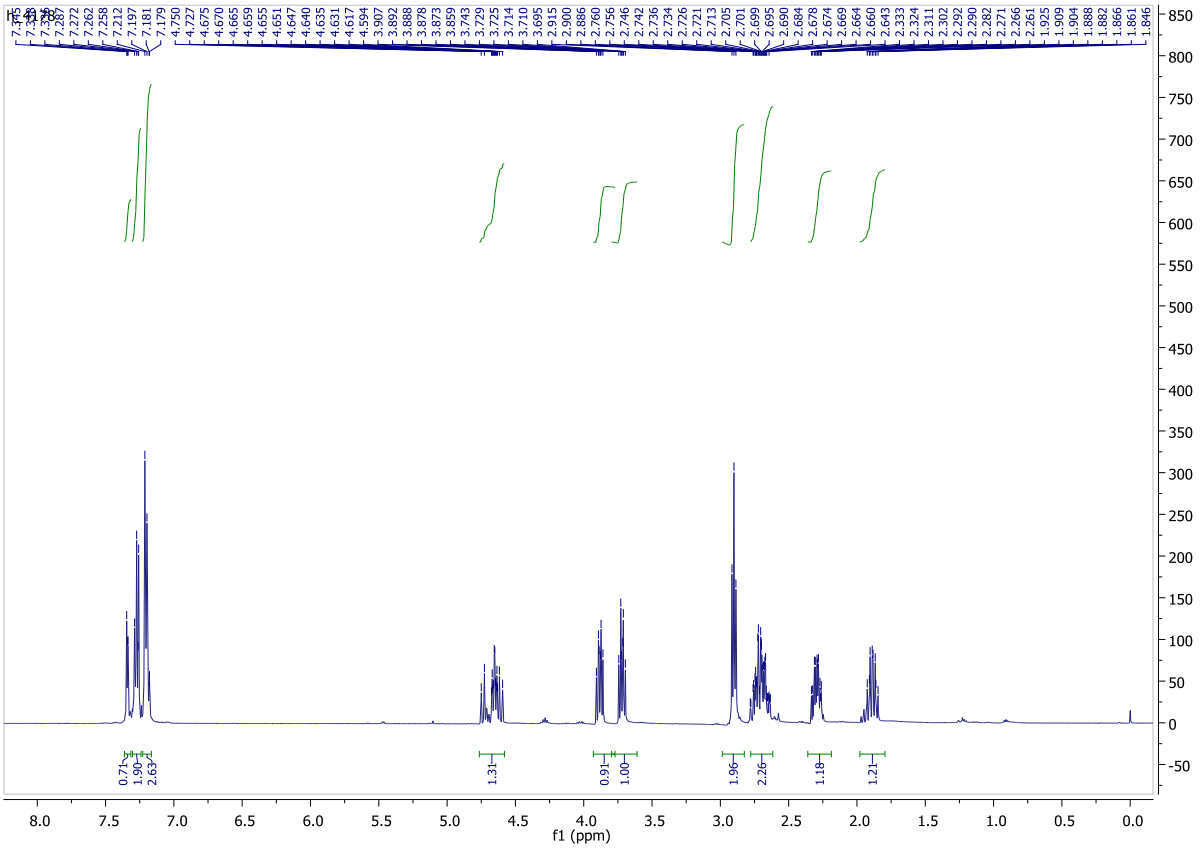
3t **2-(Thiophen-2-ylmethoxy)-cyclobutanone**

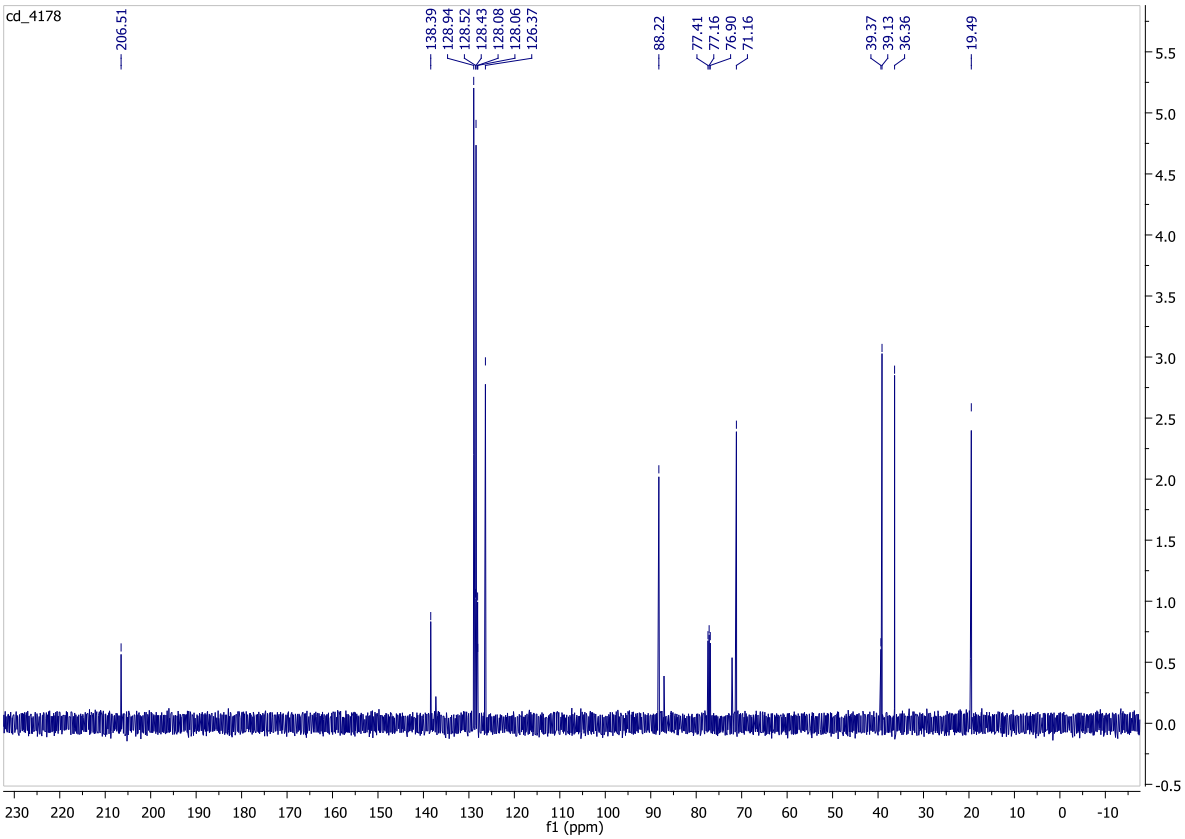


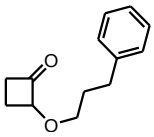




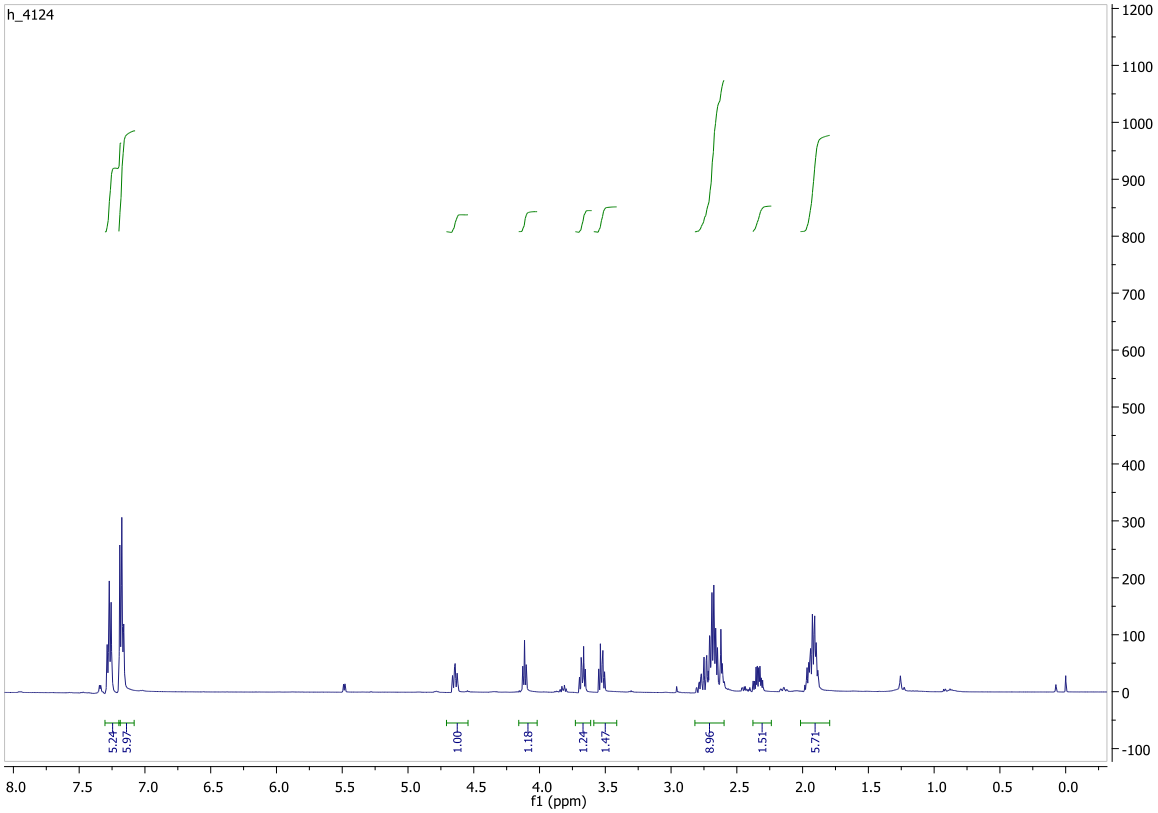
3w **2-Phenethyloxy-cyclobutanone**

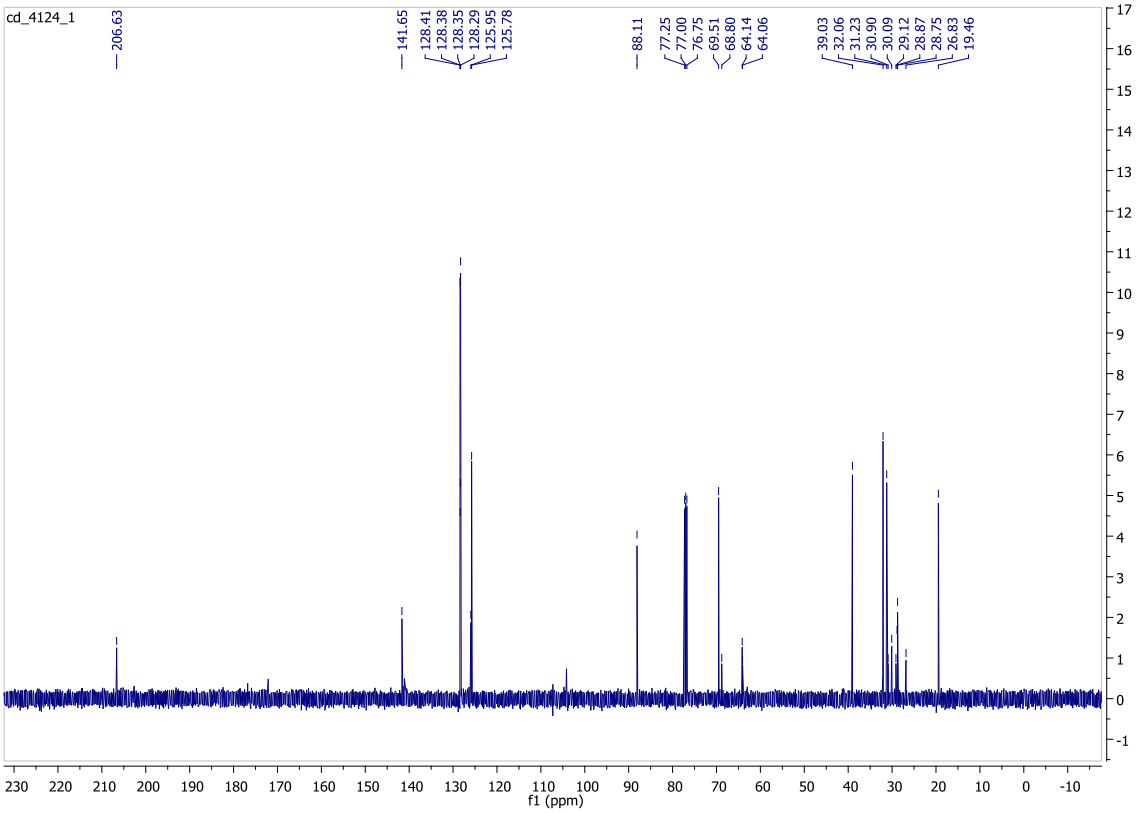


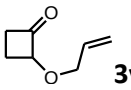




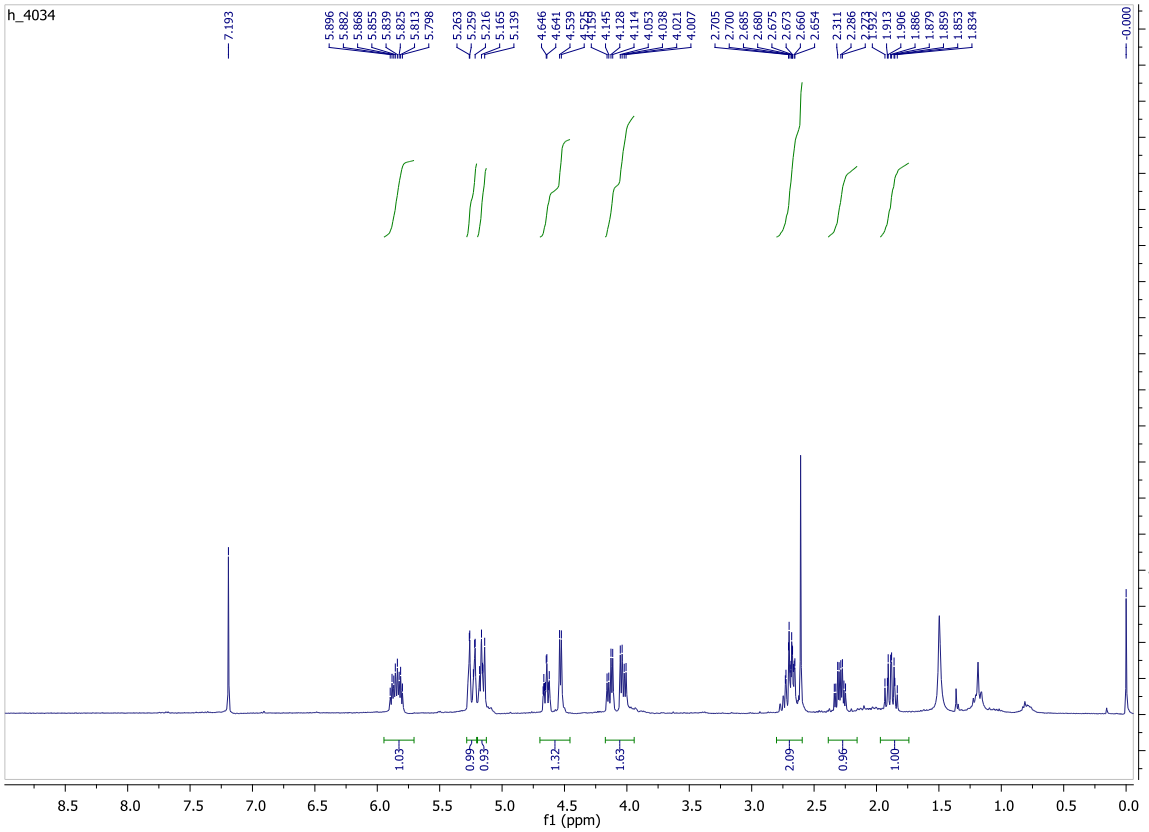
3x **2-(3-Phenyl-propoxy)-cyclobutanone**

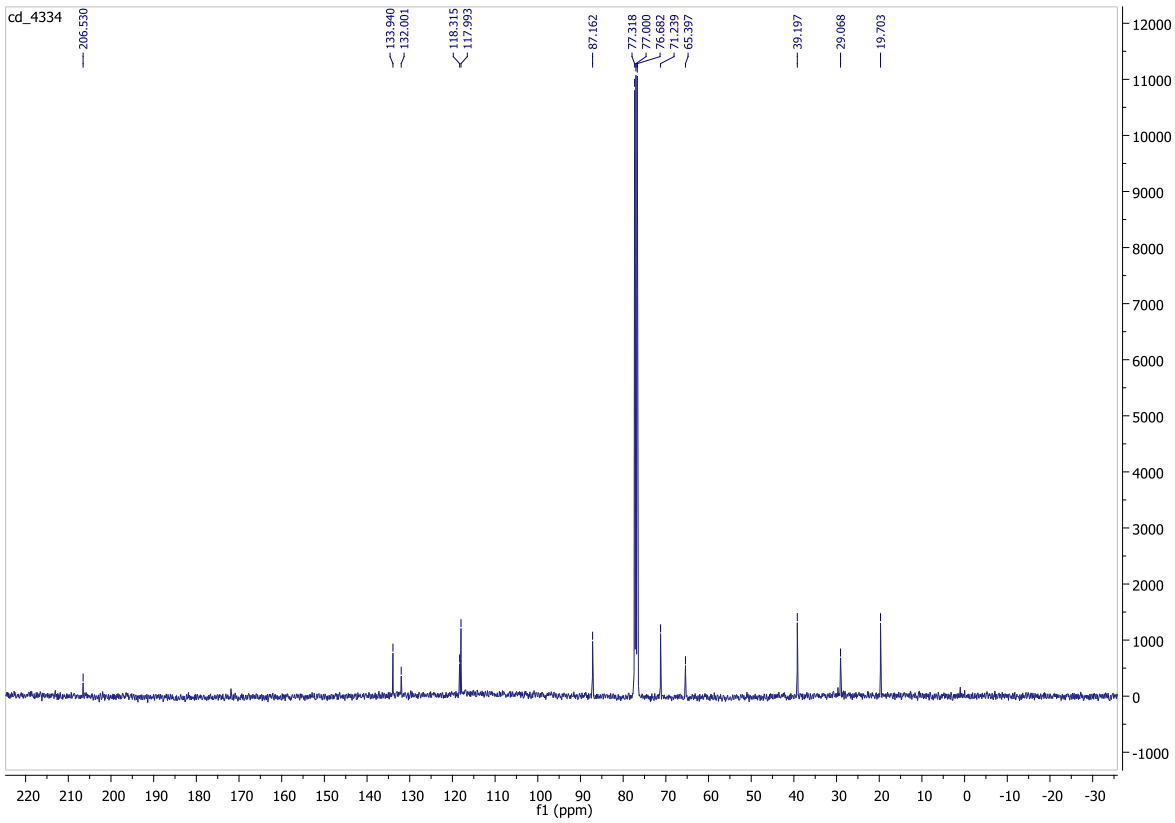




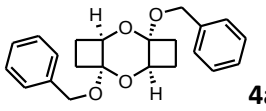


3y **2-Allyloxy-cyclobutanone**

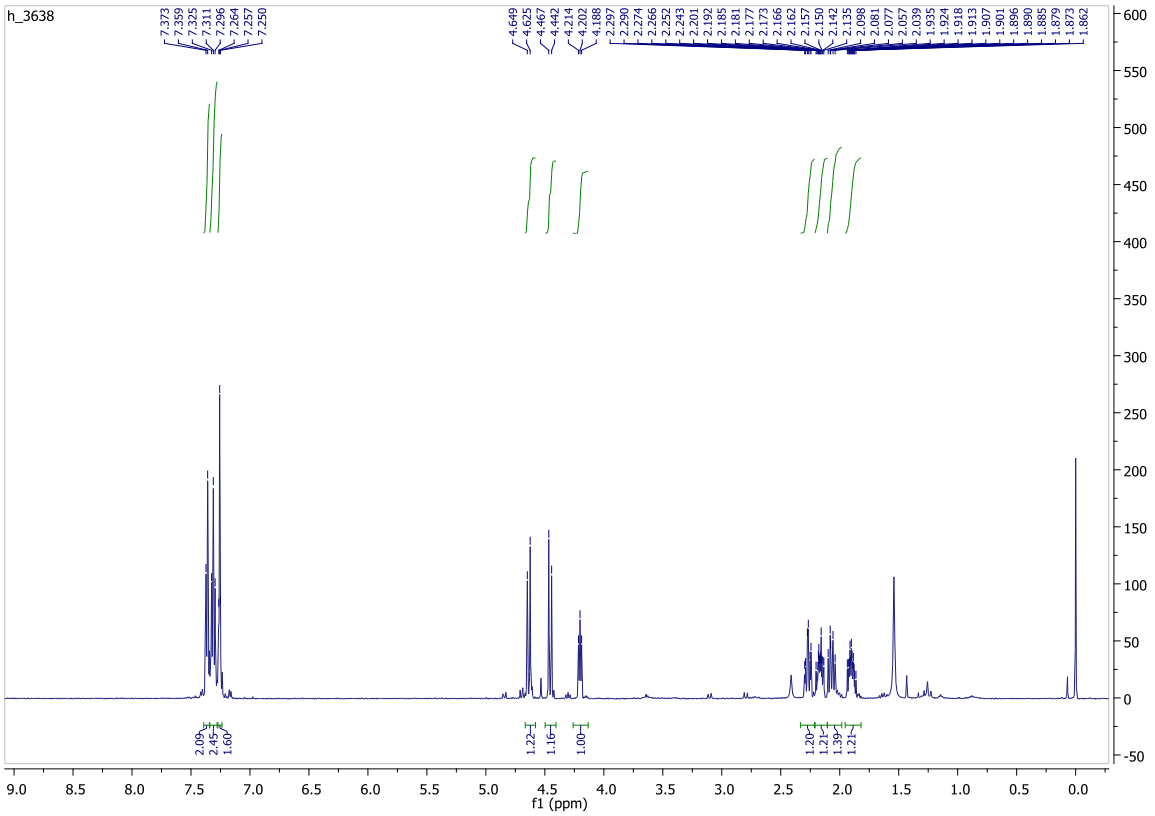


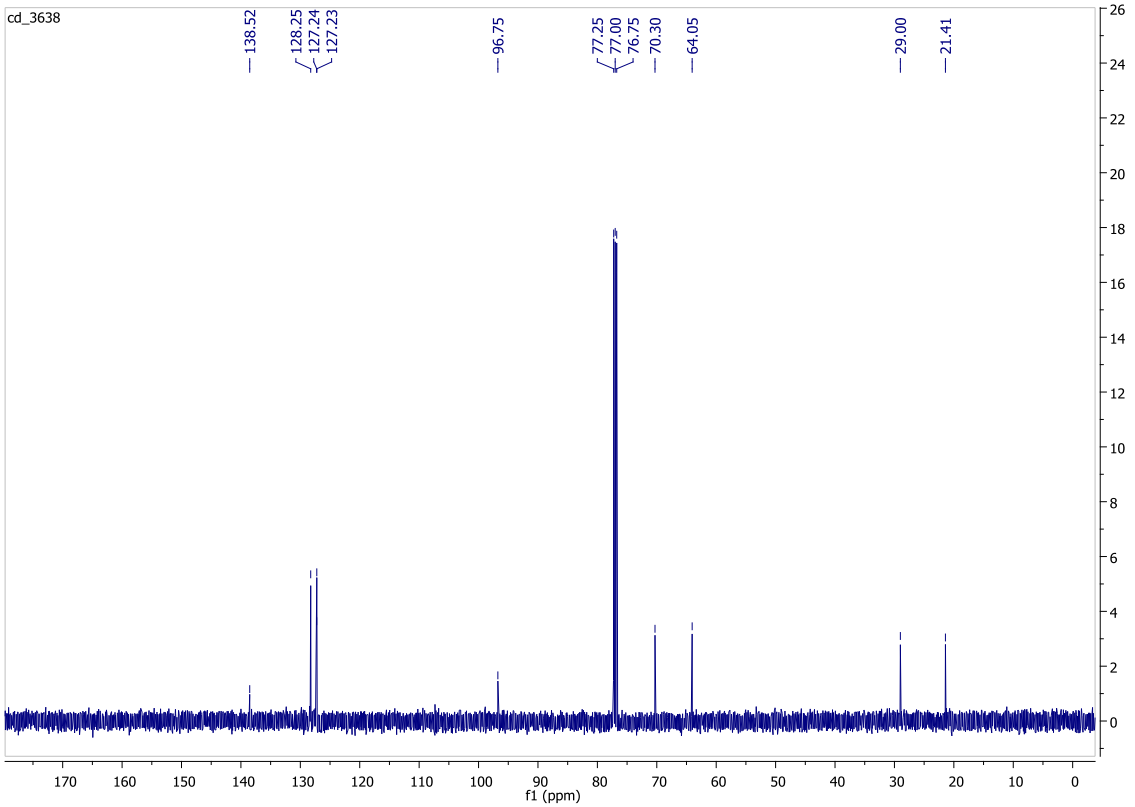


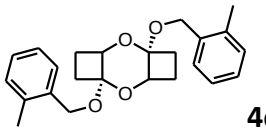
^{1}H and ^{13}C NMR spectra of compounds 4a,c,d,f,g,h,k,n,s,t,z and 9



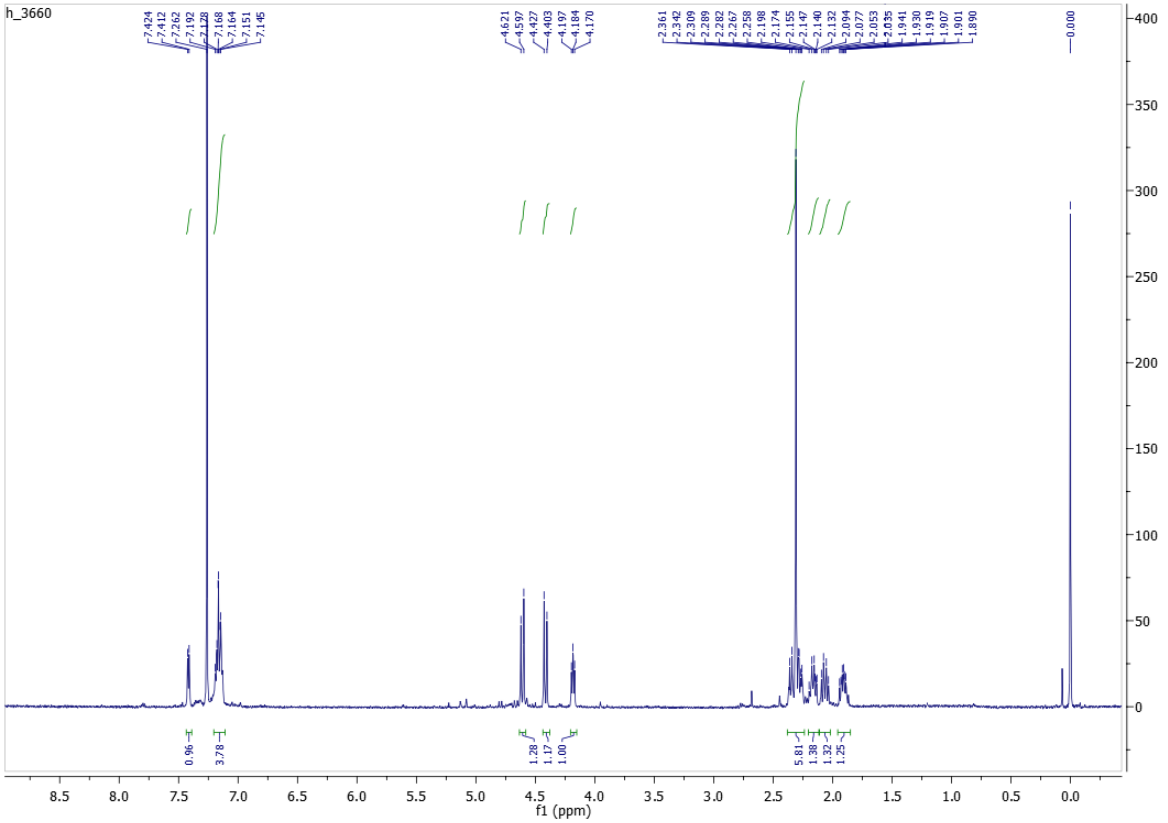
4a 1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane

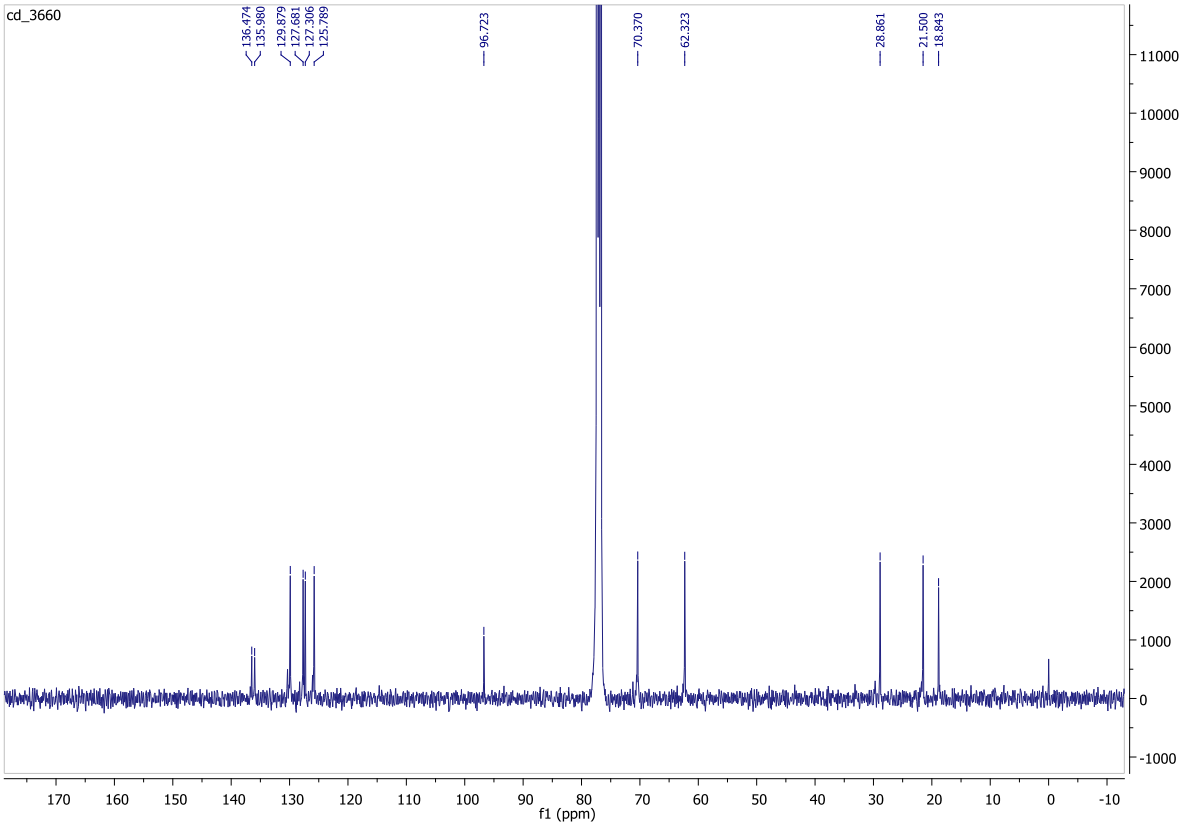


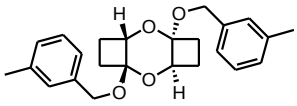




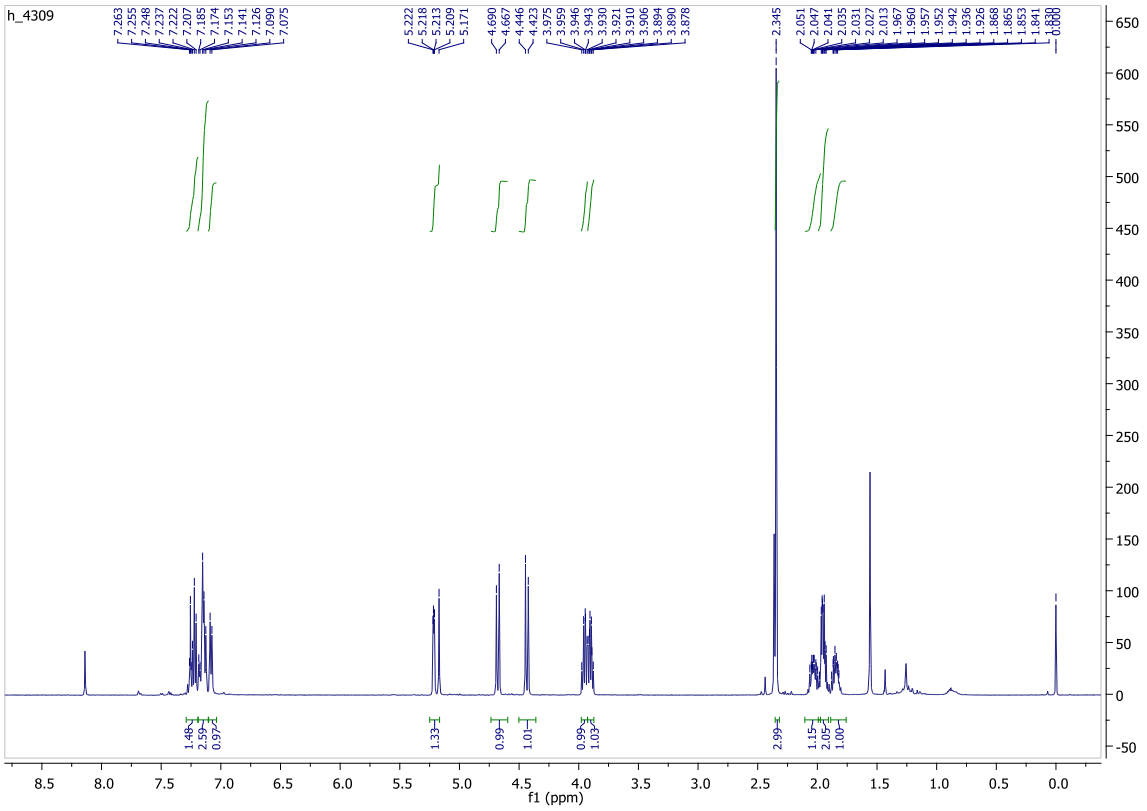
4c **1,6-Bis-(2-methylbenzyloxy)-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

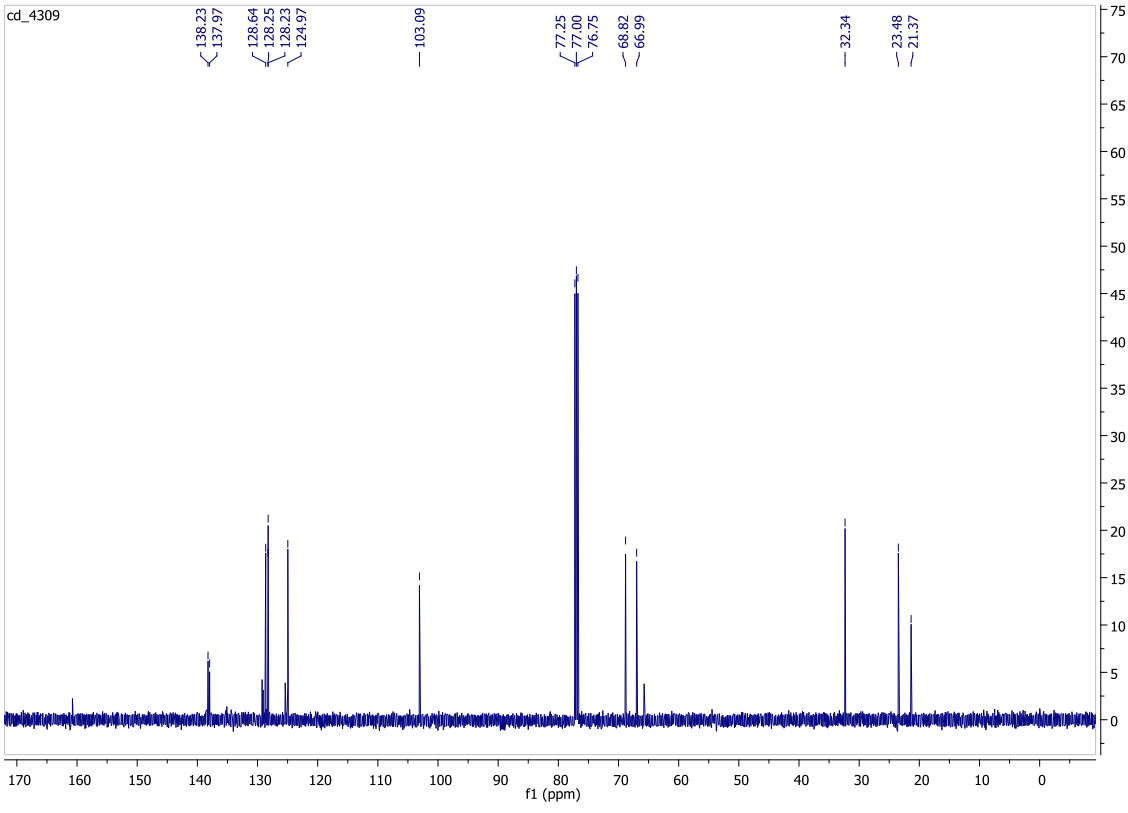


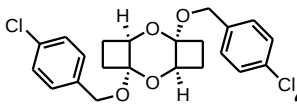




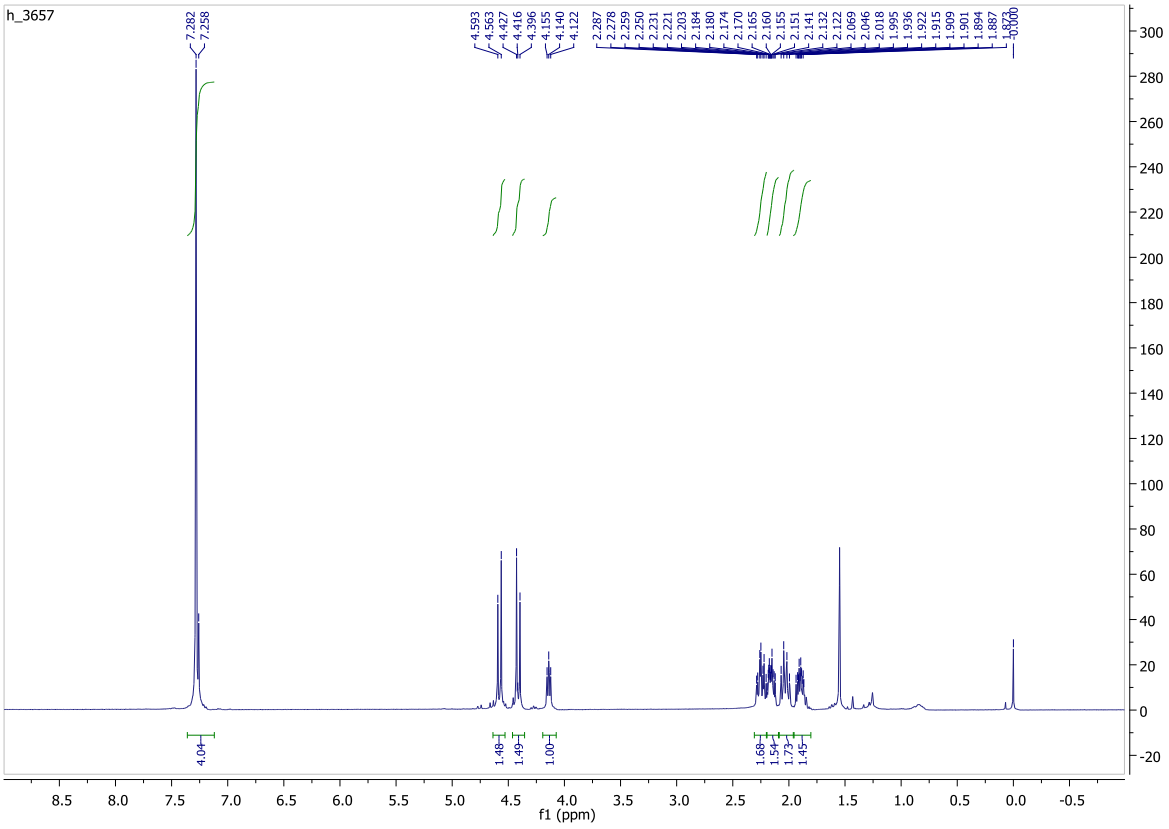
4d **1,6-Bis-(3-methylbenzyloxy)-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

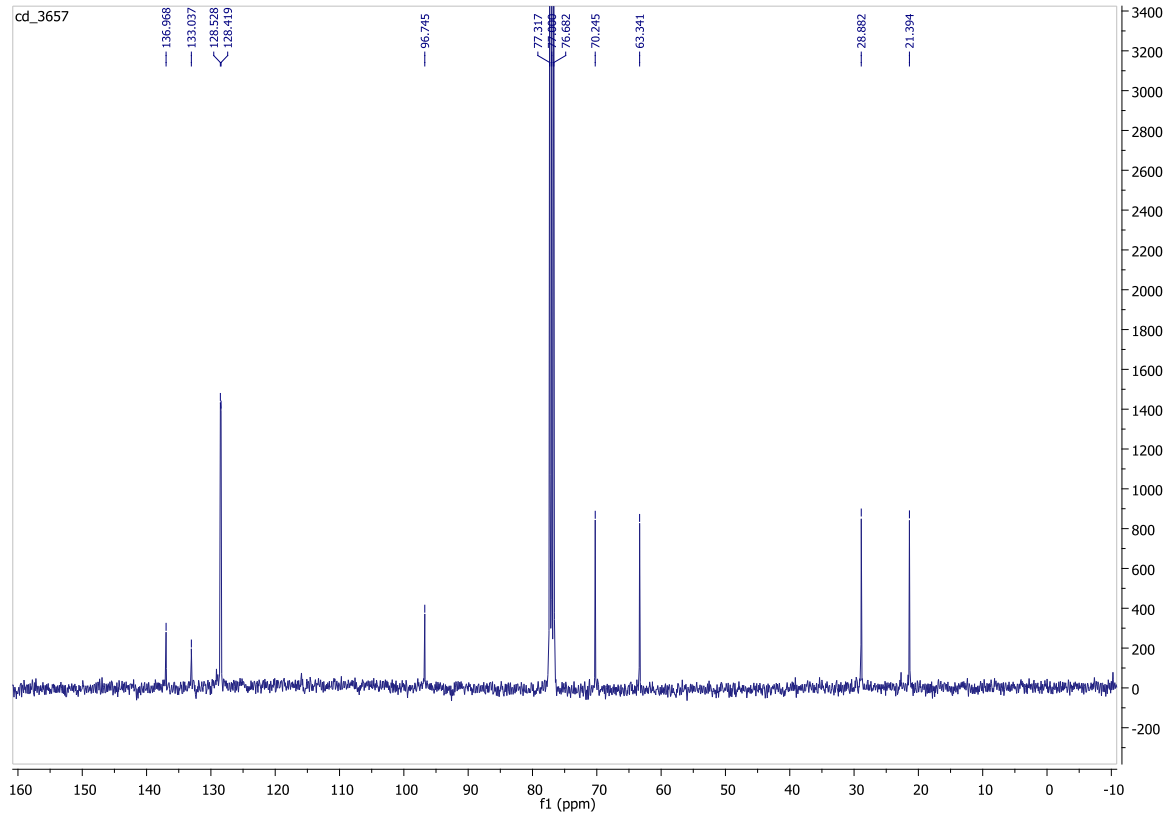


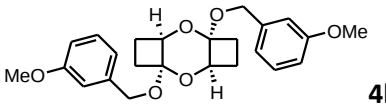




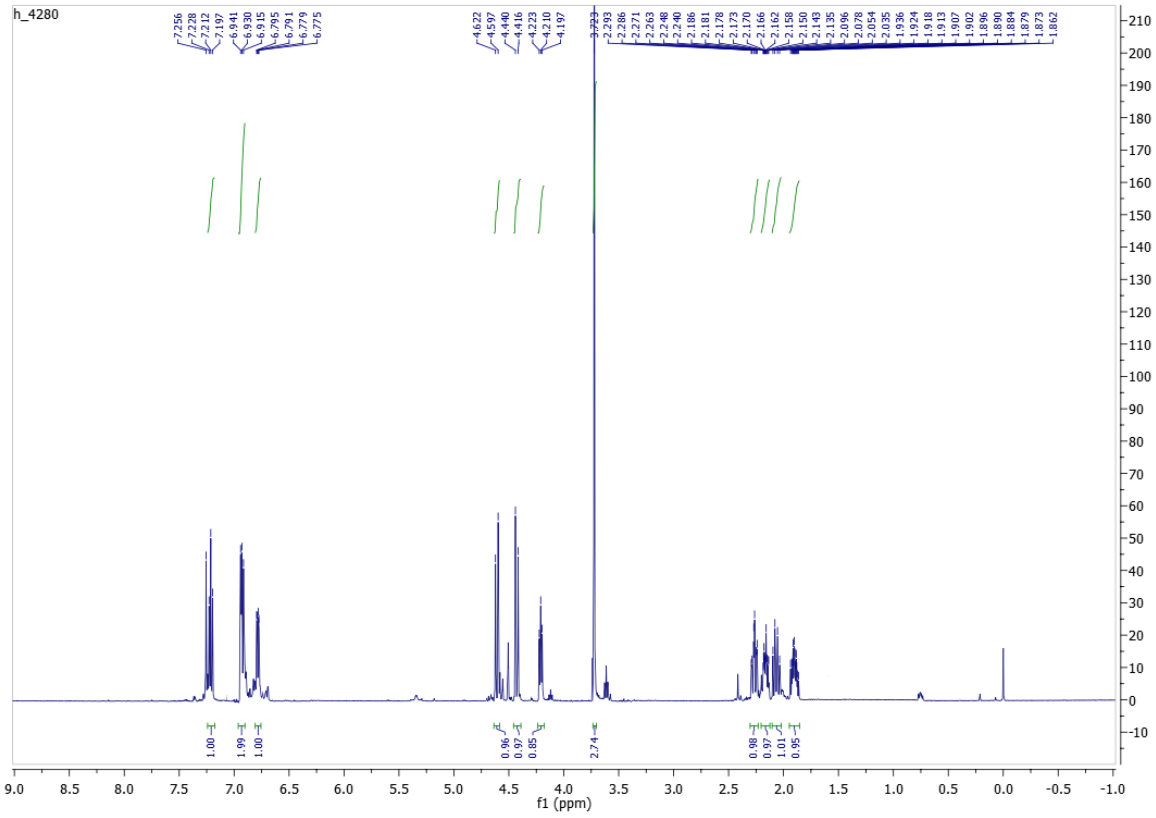
4f **1,6-Bis-(4-chlorobenzyloxy)-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

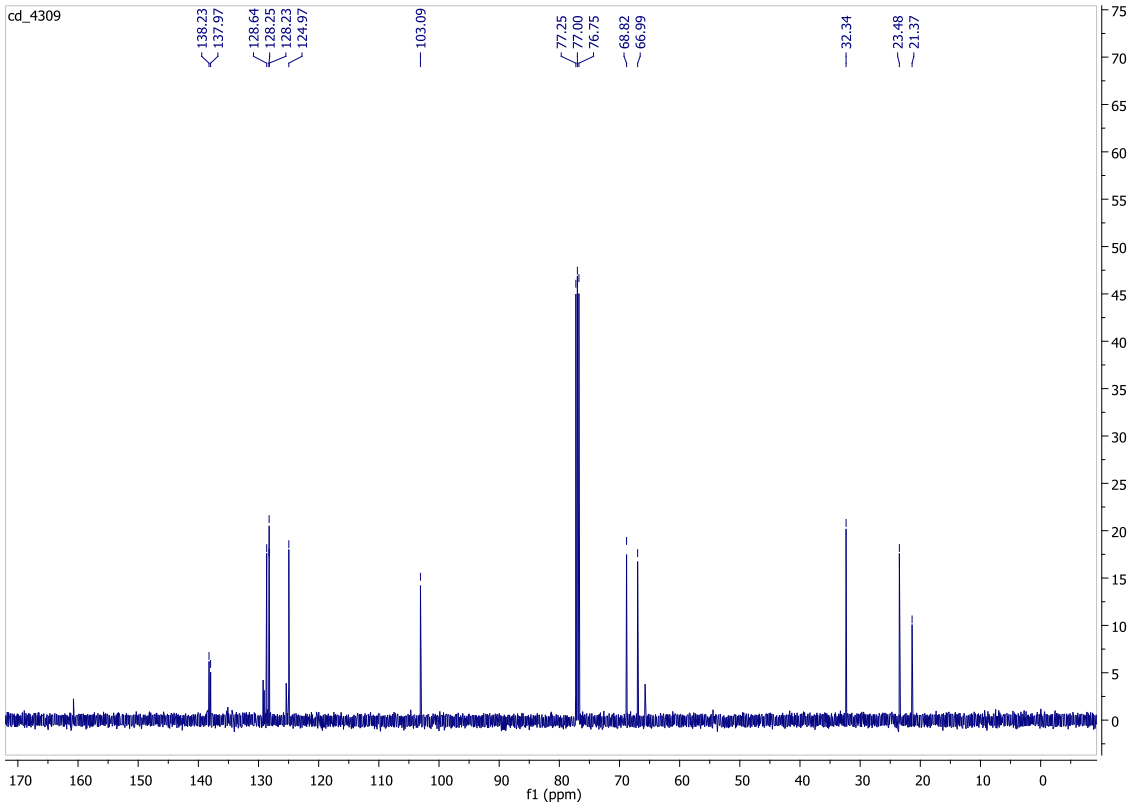


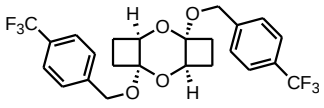




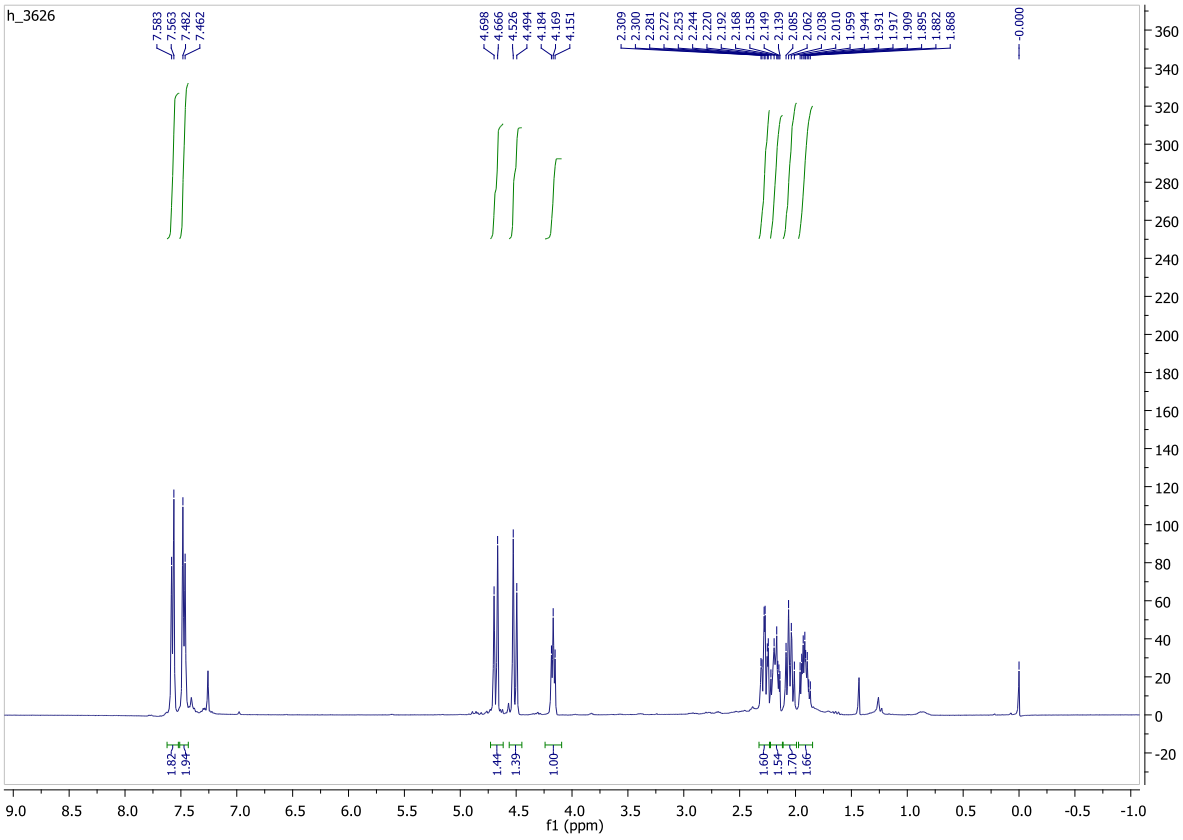
4h **1,6-Bis-(3-methoxybenzyloxy)-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

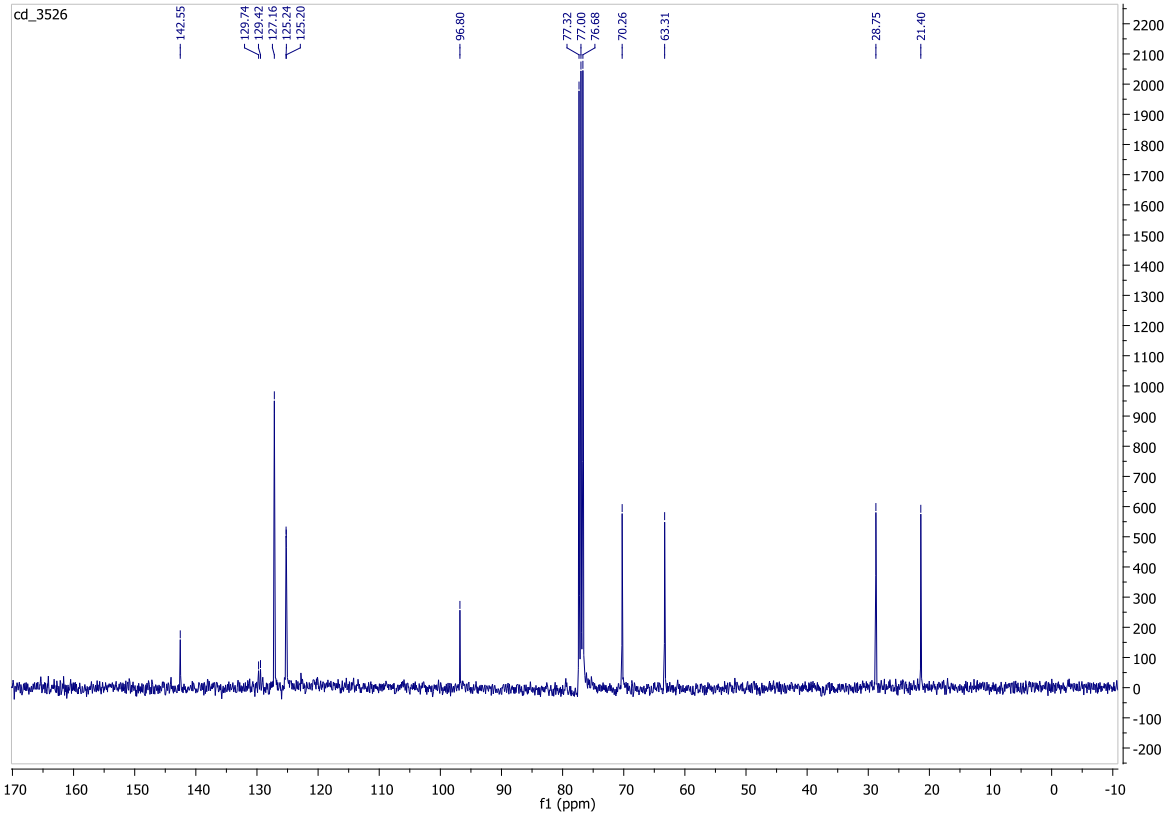


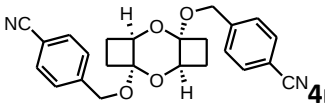




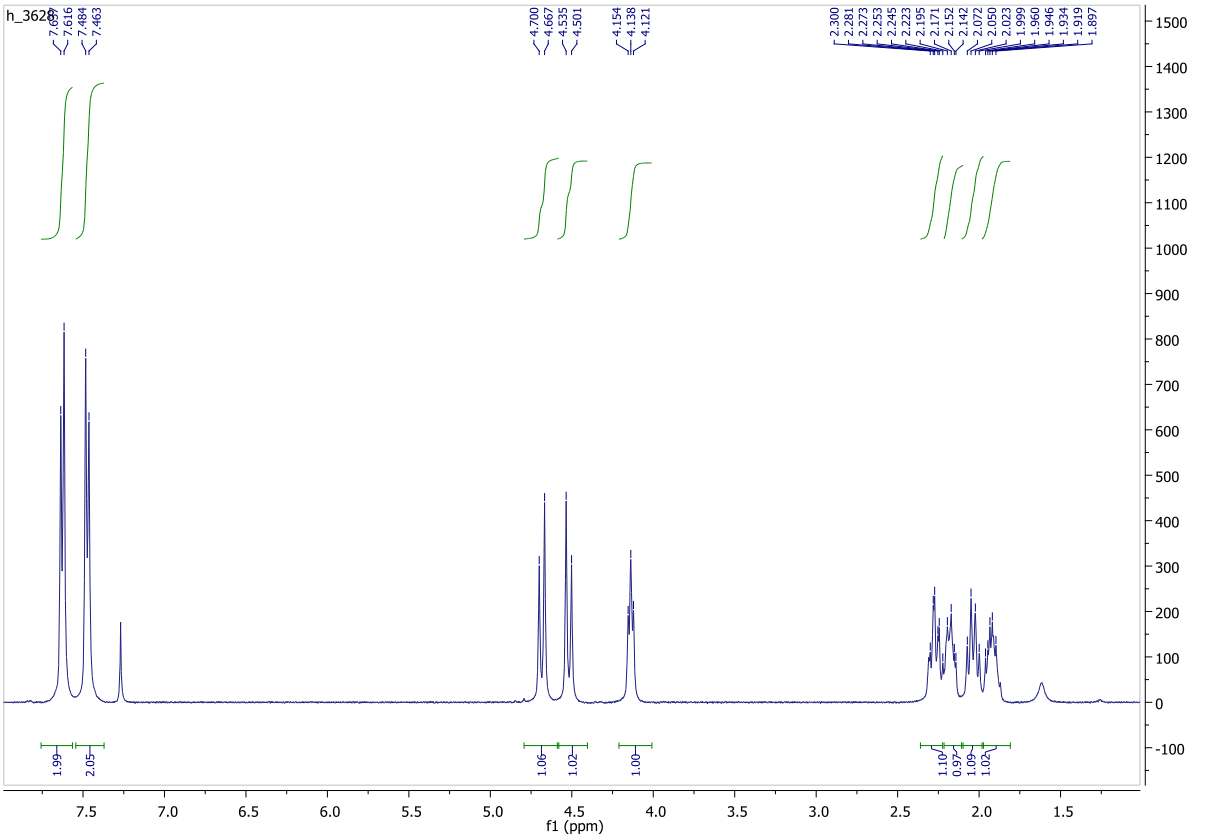
4k **1,6-Bis-(4-trifluoromethylbenzyloxy)-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

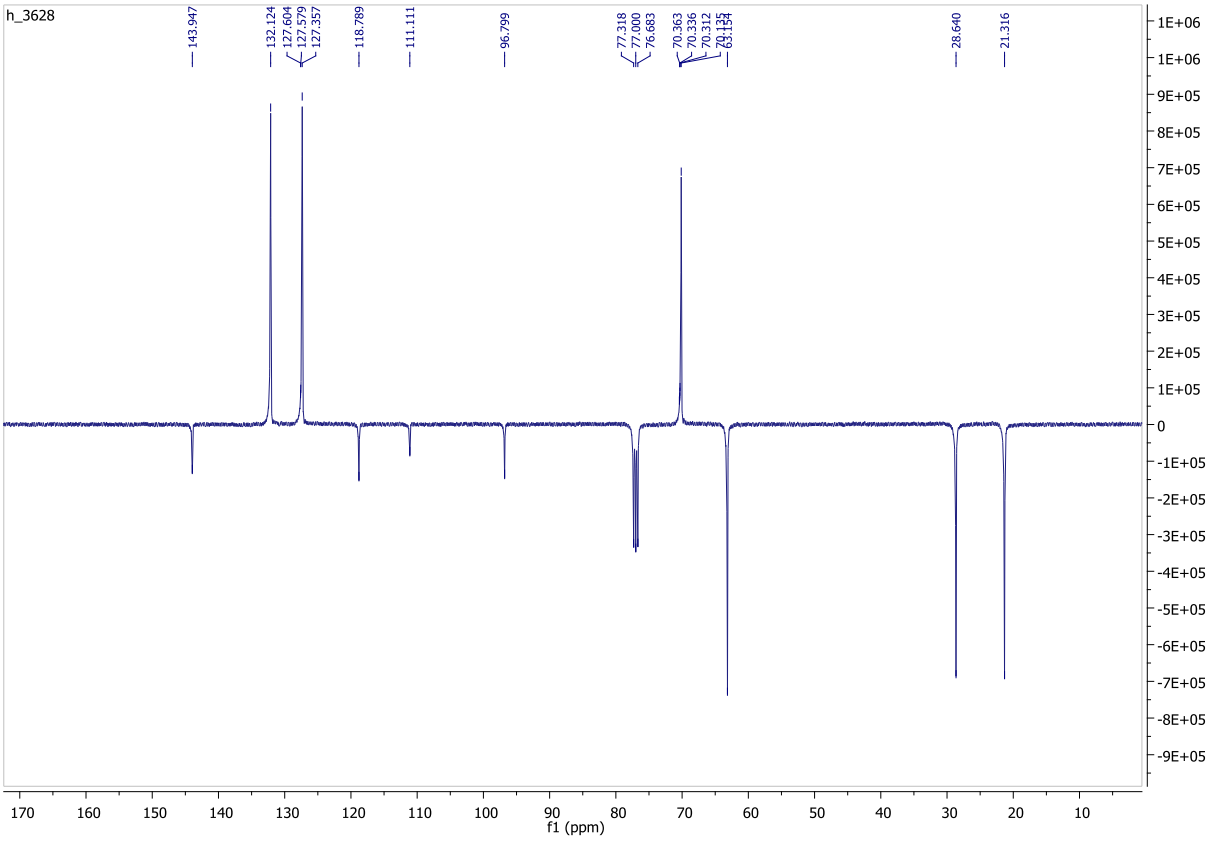


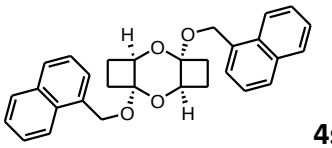




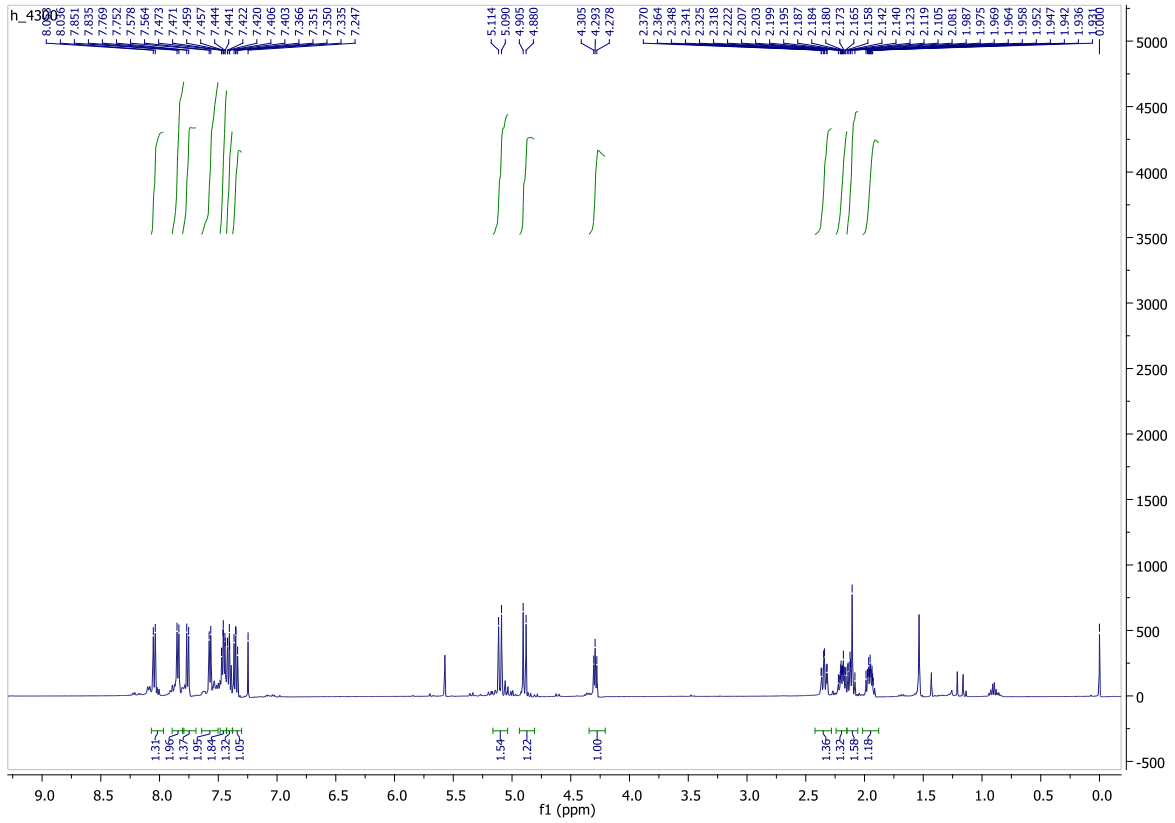
4n **1,6-Bis-(4-cyanobenzyloxy)-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

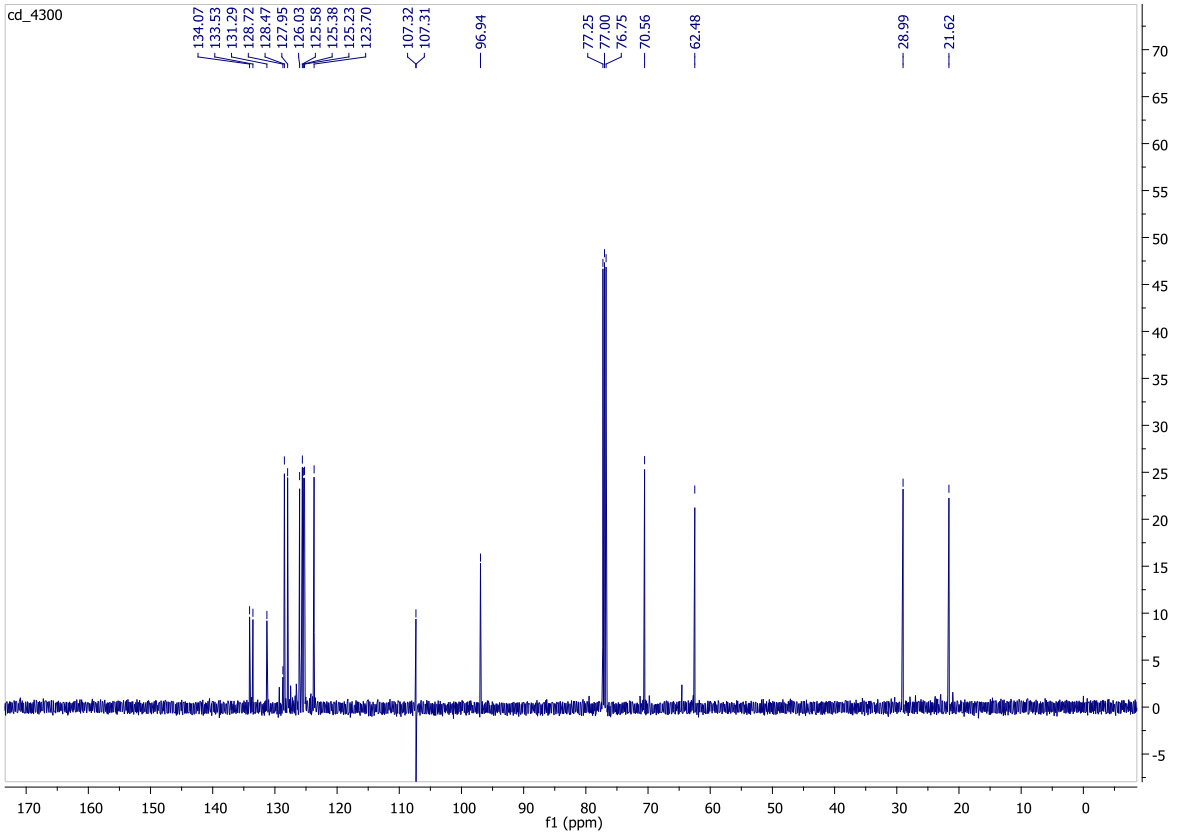


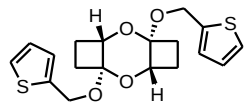




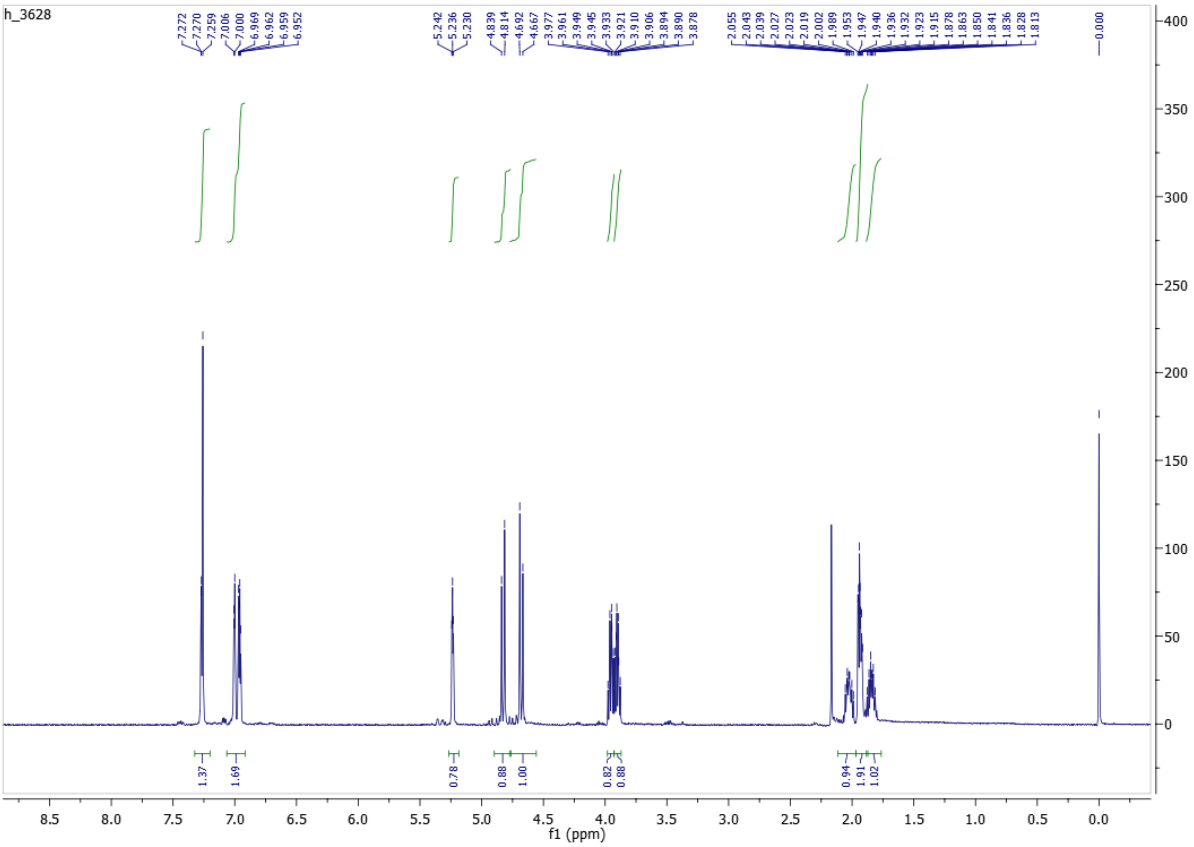
4s **1,6-Bis-(1-naphthylmethyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

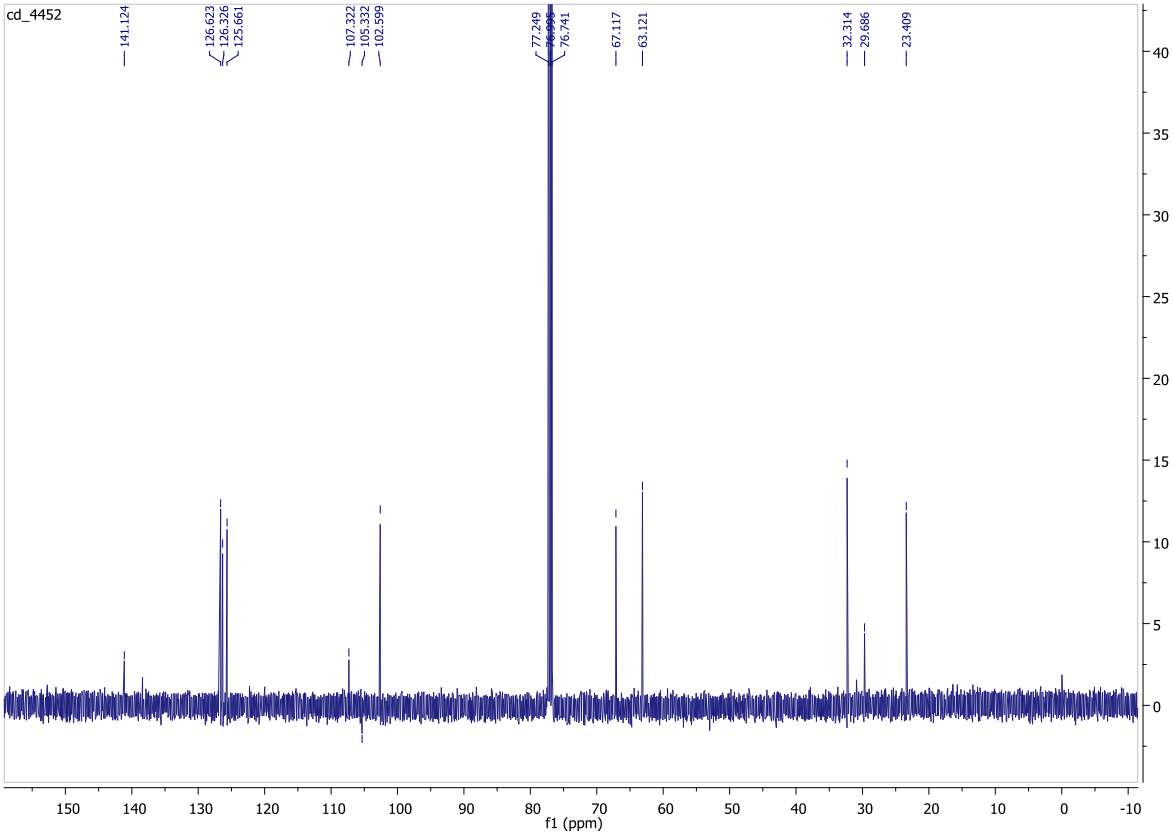


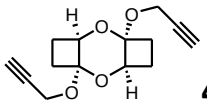




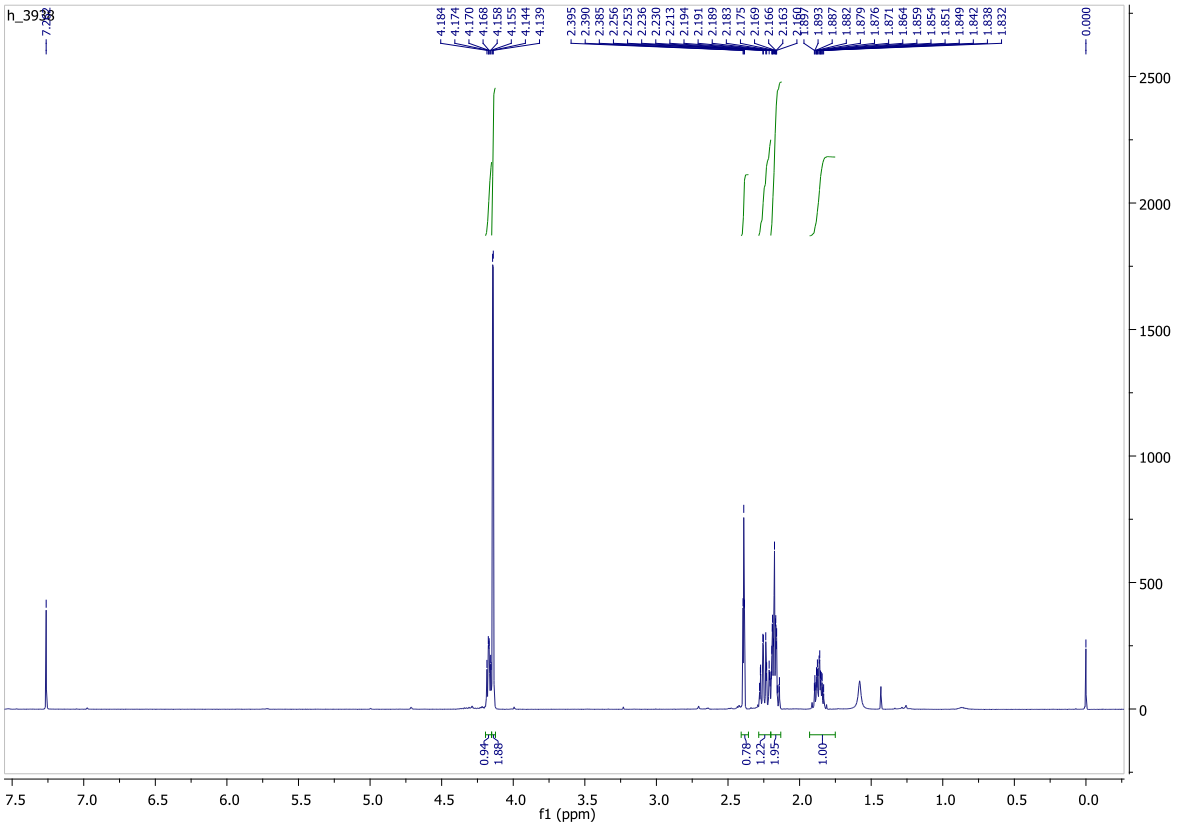
4t **1,6-Bis-(thiophen-2-ylmethoxy)-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

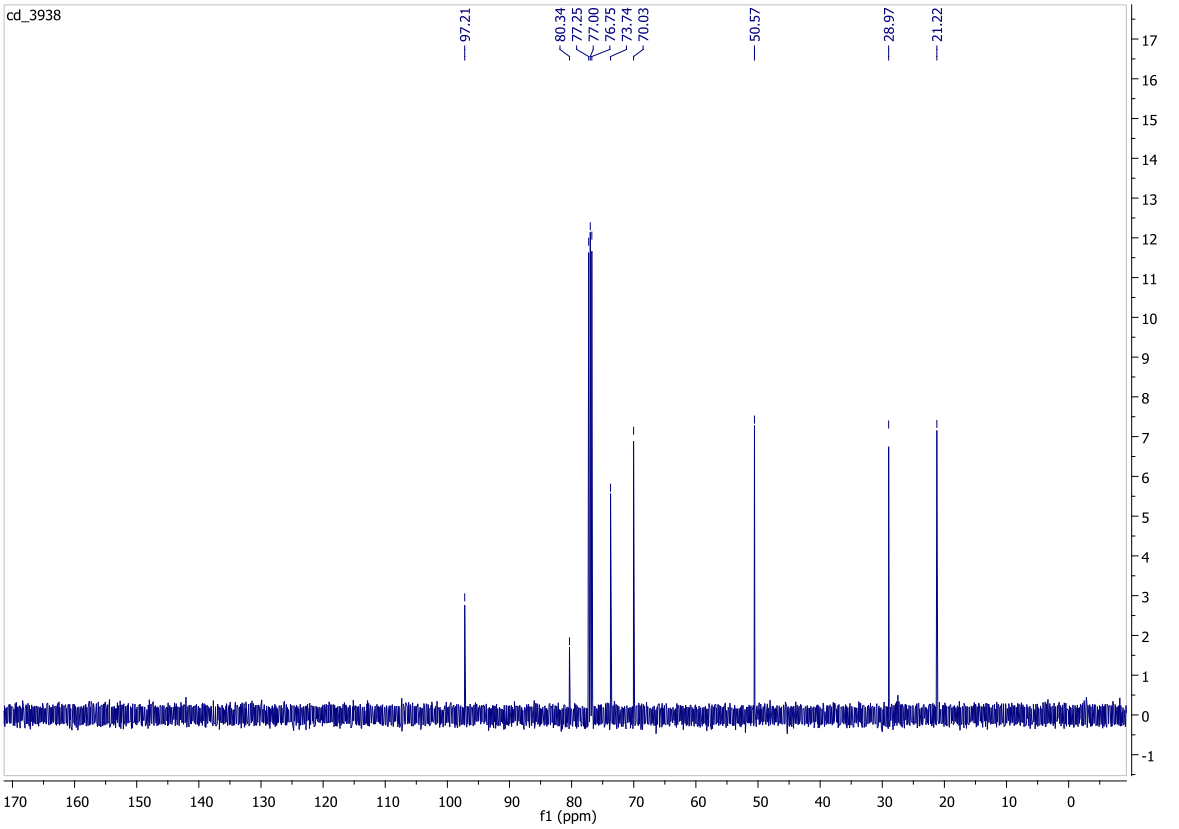


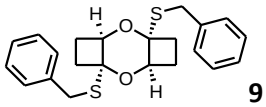




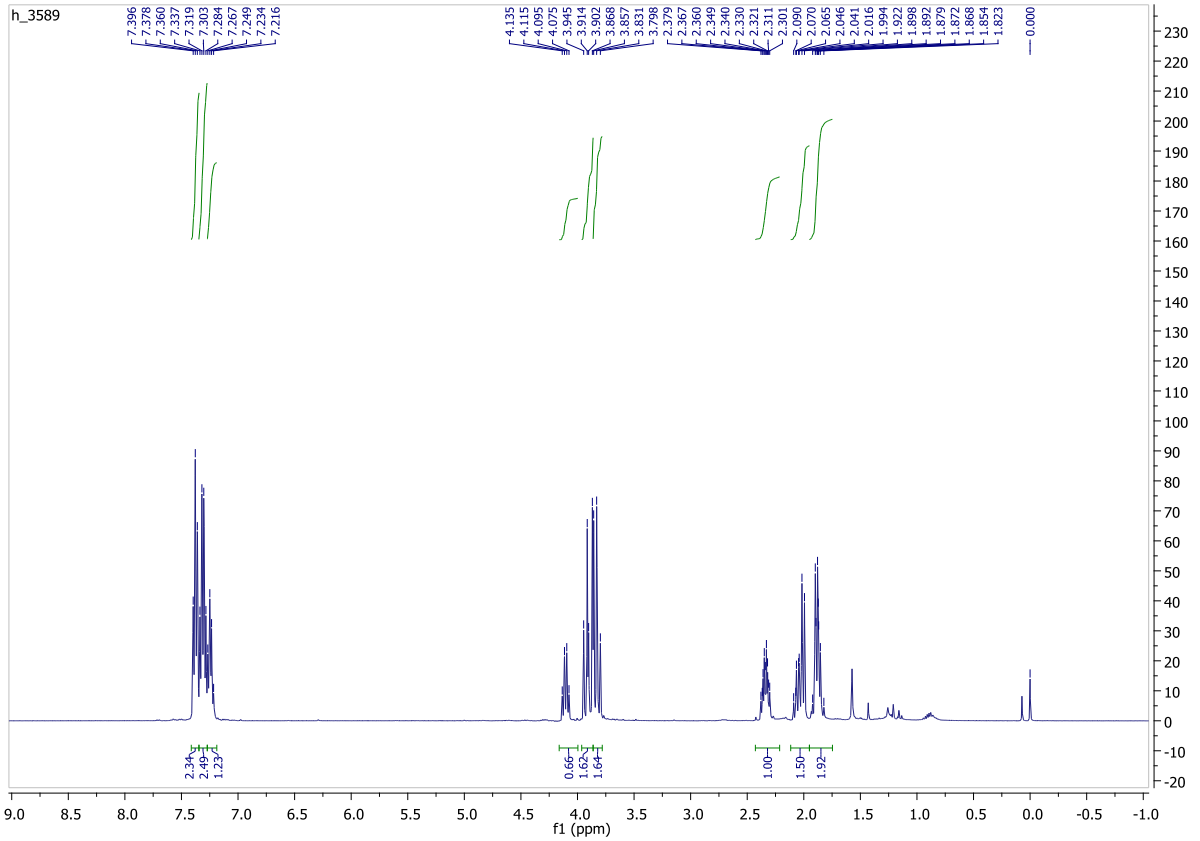
4z **1,6-Bis-propynoxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

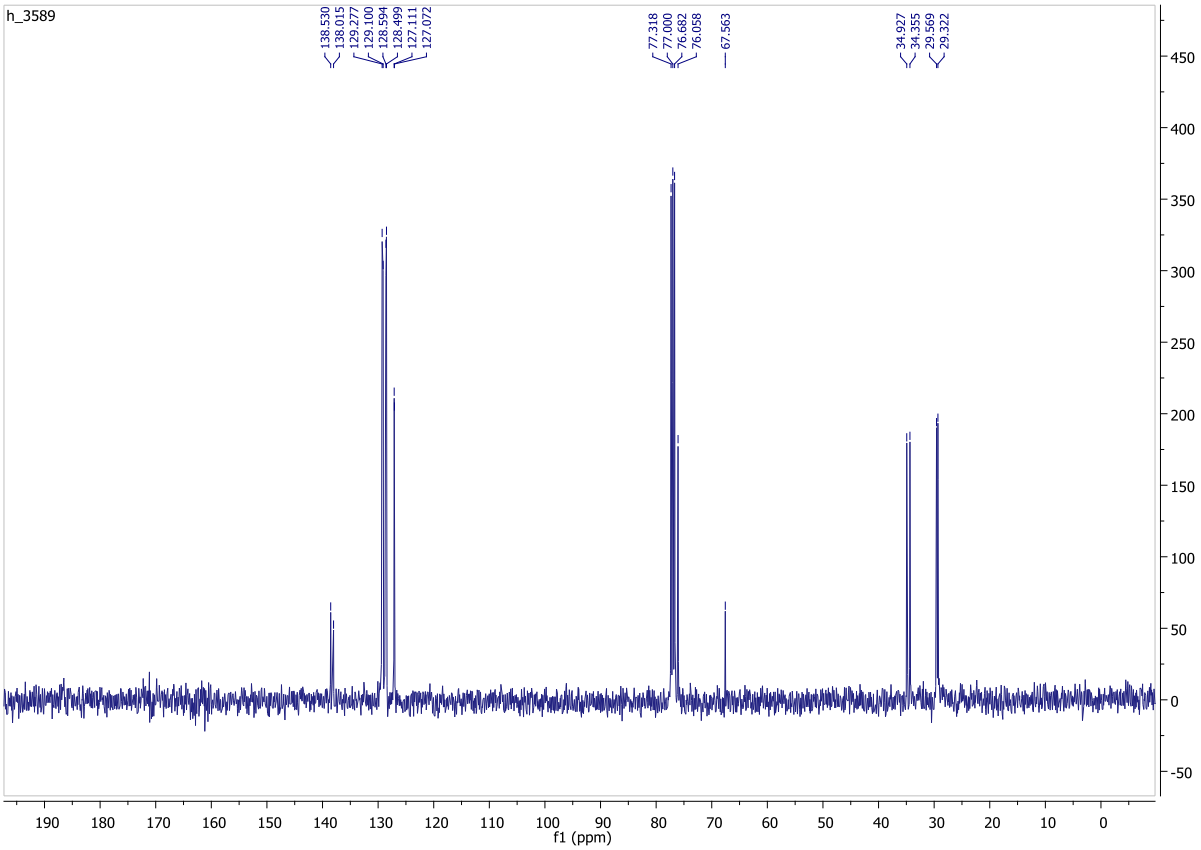


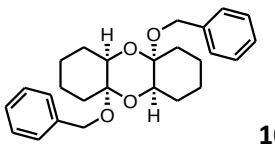




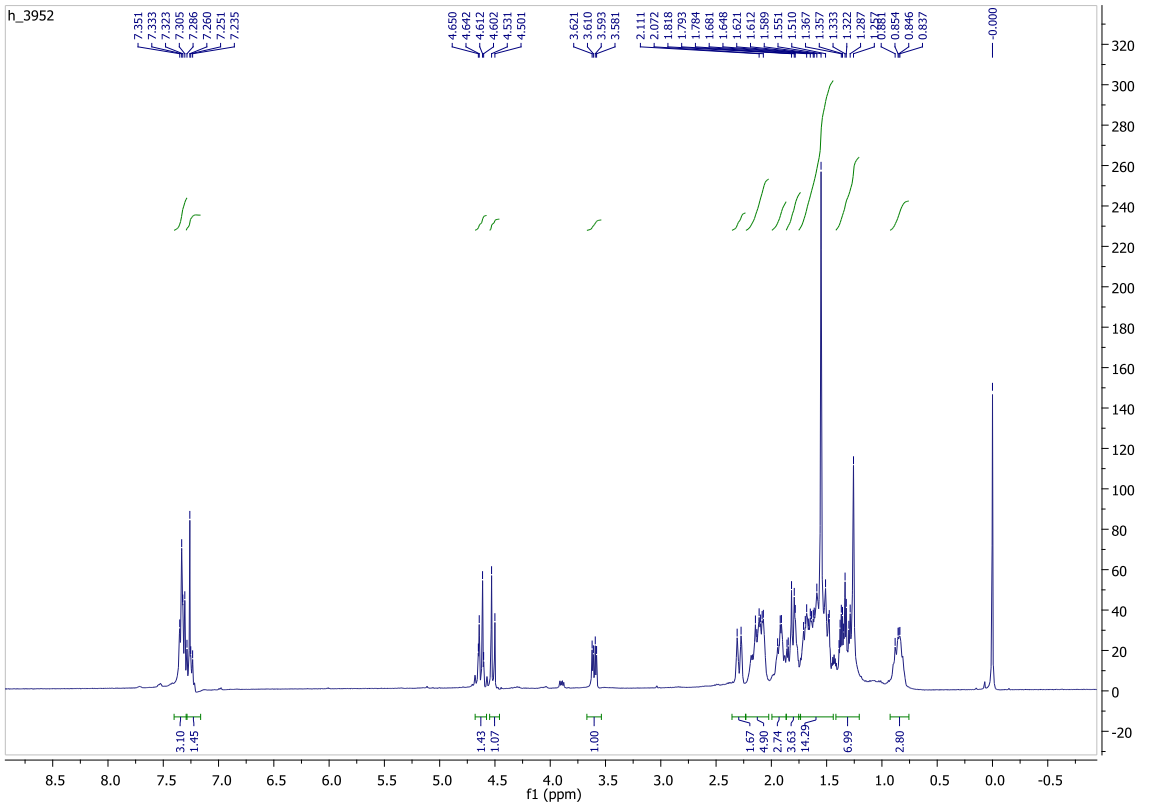
9 **1,6-Bis-benzylthio-2,7-dioxa-tricyclo[6.2.0.03,6]decane**

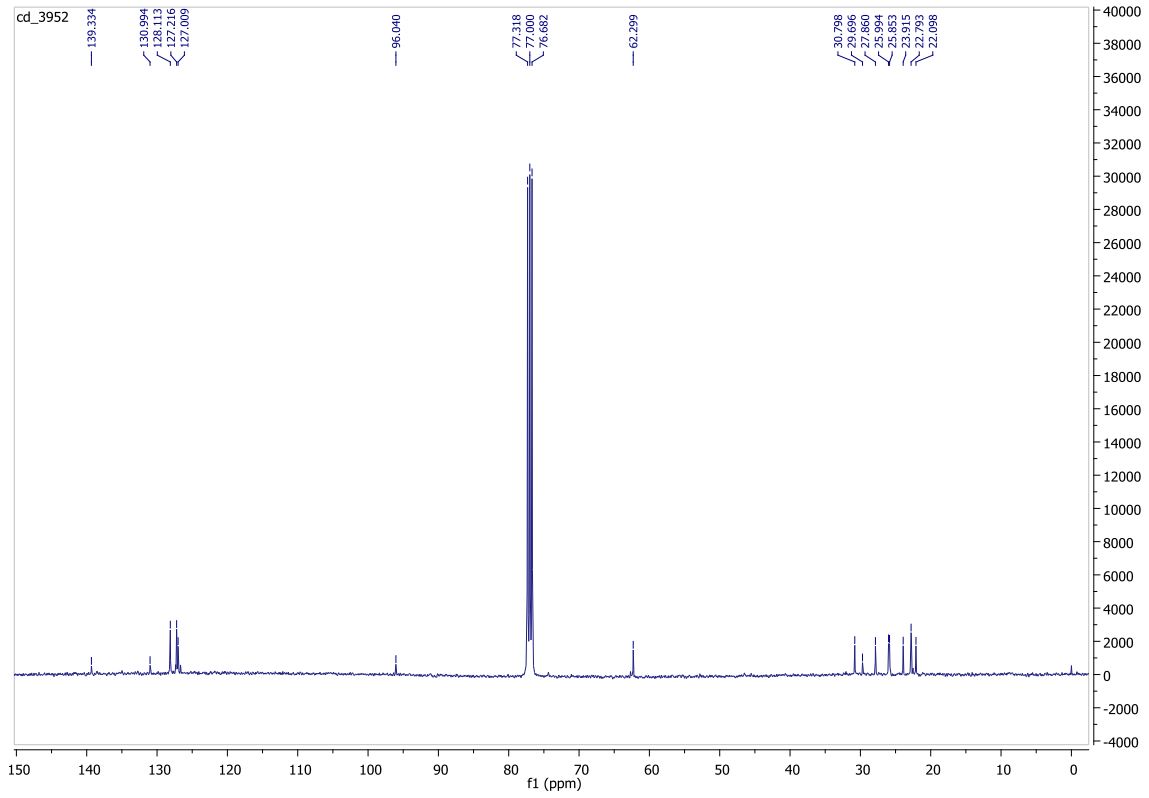




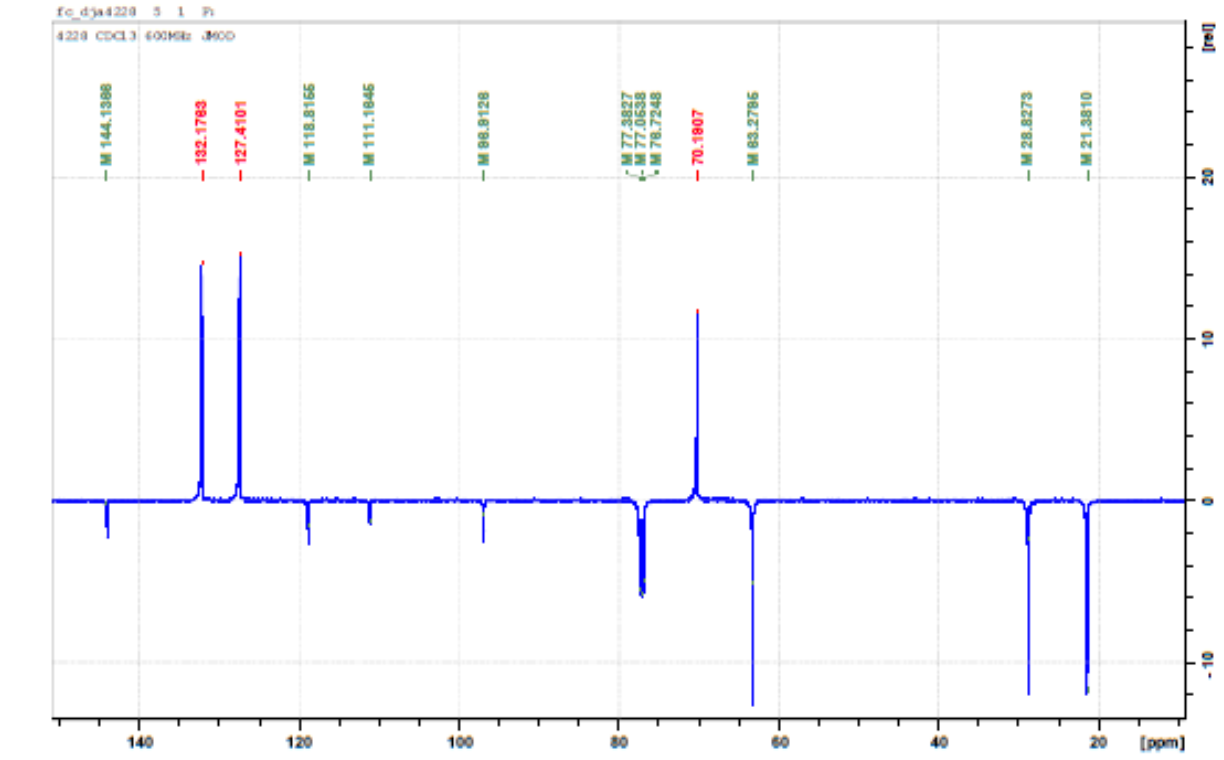


10 Bis-benzyloxy-dodecahydro-dibenzo[1,4]dioxine

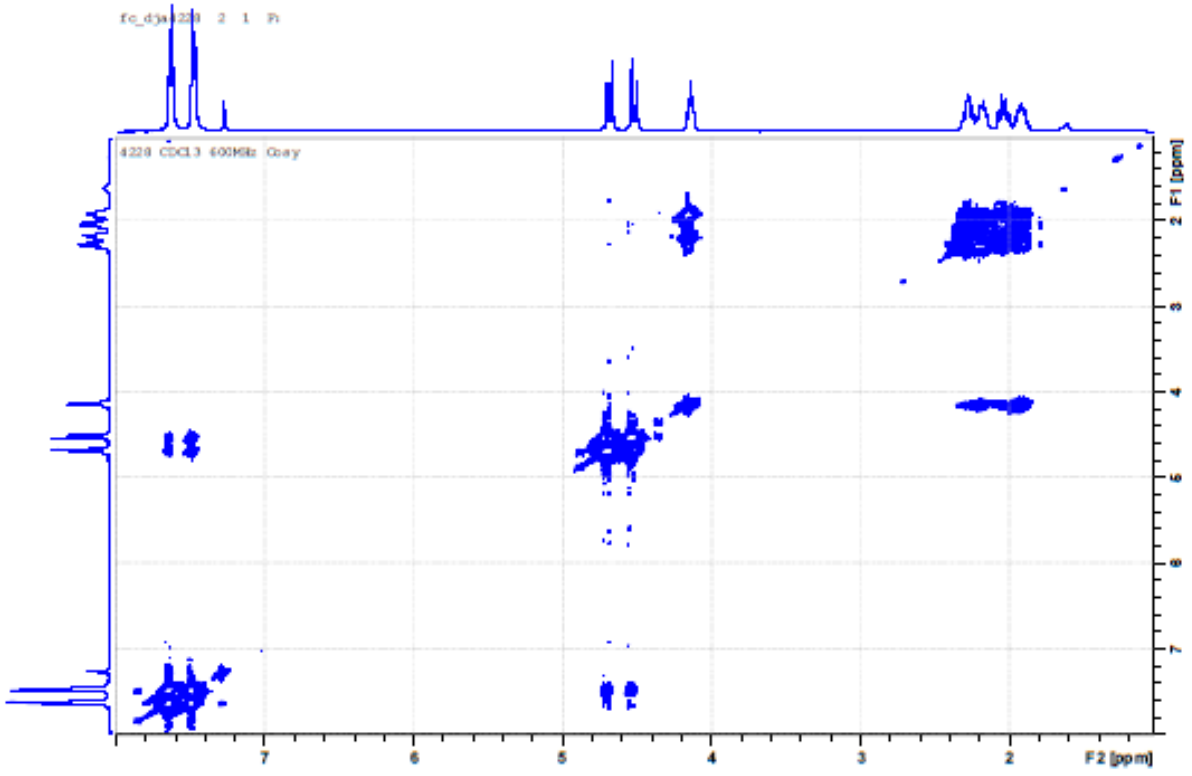




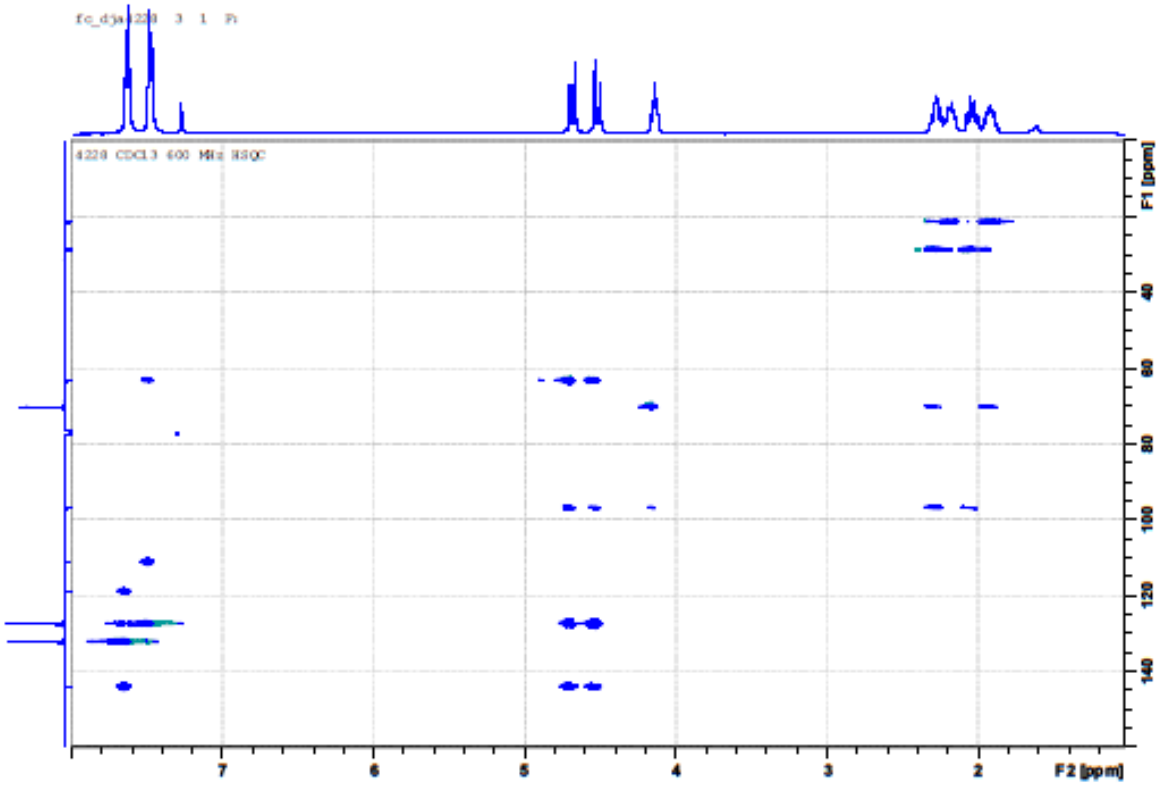
JMOD of compound 4n



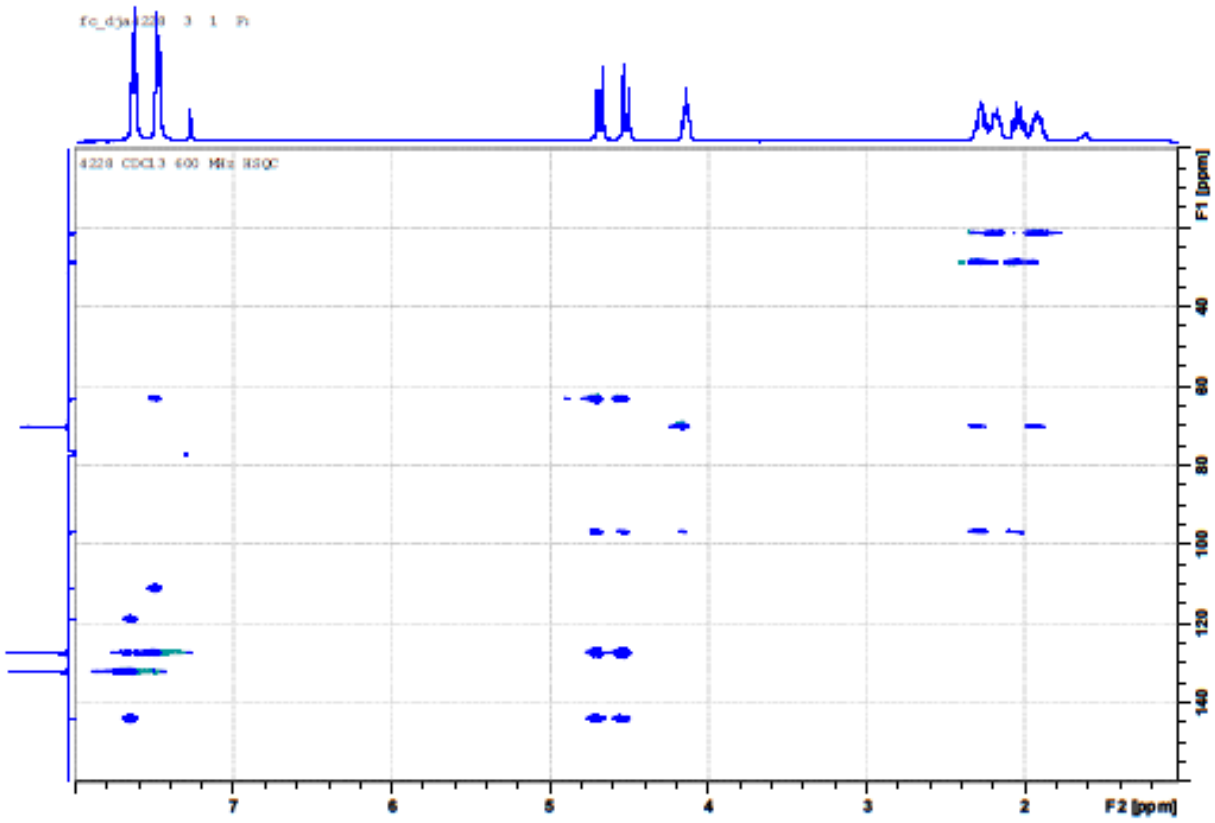
COSY of compound 4n



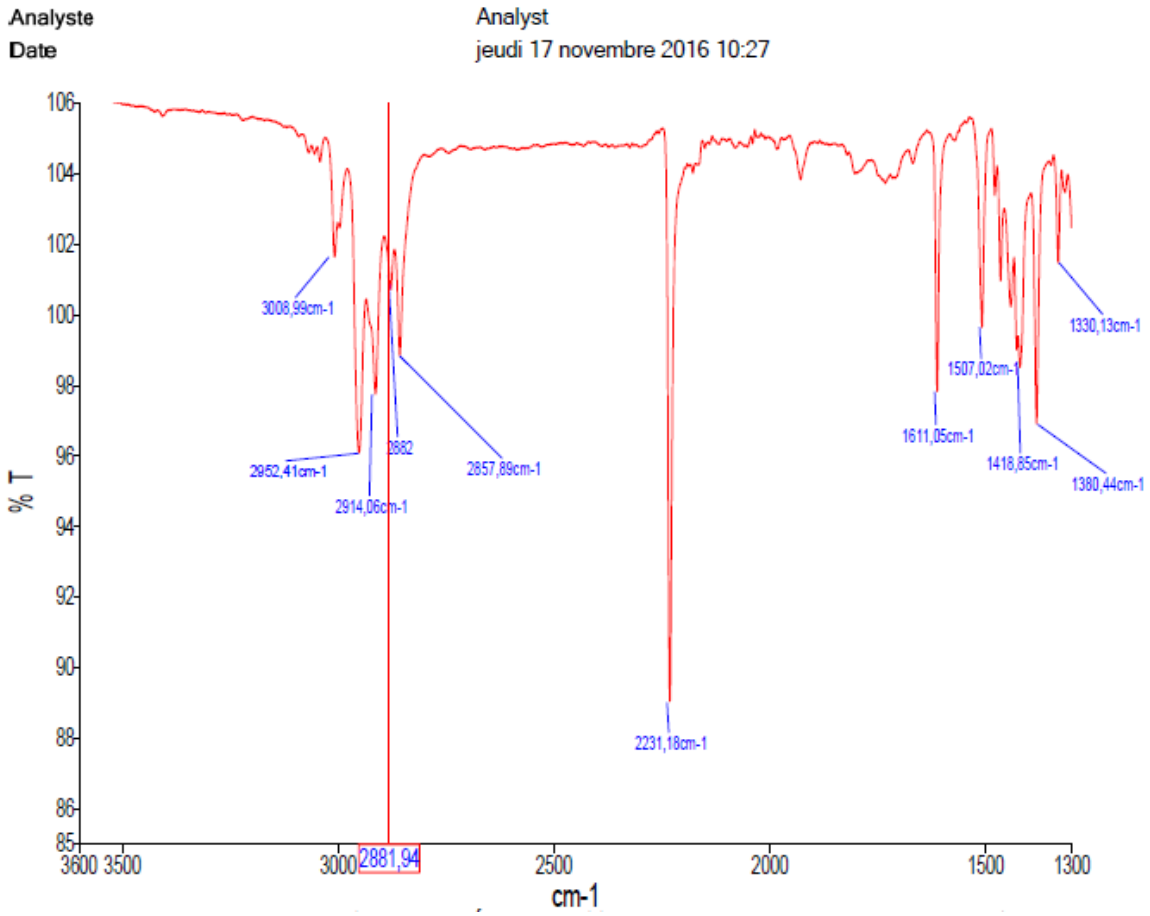
HMBC of compound 4n



HSQC of compound 4n



IR spectra of compound 4n



Mass spectra (HRMS) of compound 4n

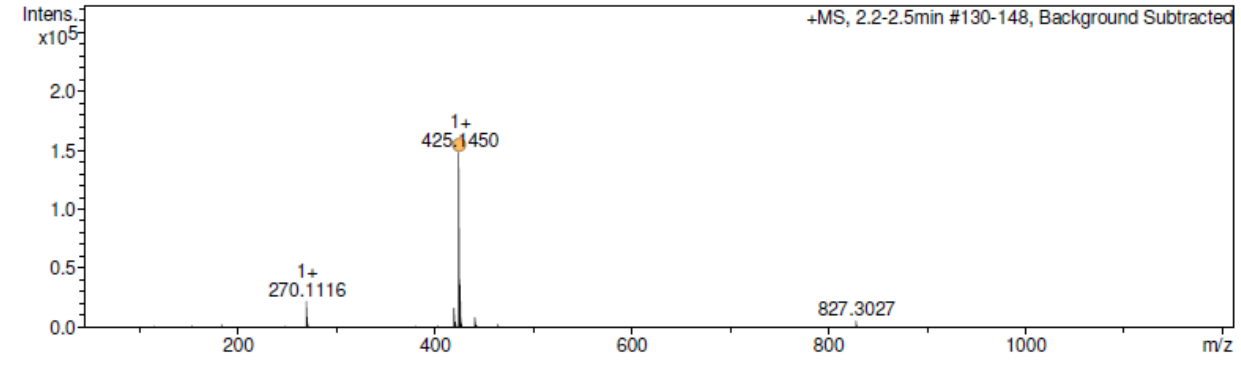
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\2016\cp3a\charnay\Fc_dja4228_RB6_01_4572.d	Acquisition Date	11/17/2016 3:41:22 PM
Method	ms_fia_tw_50_1200_pos.m		
Sample Name	Fc_dja4228	Operator	BDAL@DE
Comment		Instrument / Ser#	micrOTOF-Q II 8228888.10027

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1200 m/z	Set Collision Cell RF	50.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	mSigma
425.144957	1	C24H22N2NaO4	425.147178	-2.2	-5.2	3.5

X-Ray Structure of compound 4n

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 2456GuillotICMMO

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: 2456GuillotICMMO

```
Bond precision:  C-C = 0.0030 A          Wavelength=0.71073

Cell:            a=19.2545(11)     b=15.5146(10)     c=13.4314(9)
                 alpha=90          beta=90           gamma=90
Temperature:     100 K
```

	Calculated	Reported
Volume	4012.3(4)	4012.3(4)
Space group	P b c n	P b c n
Hall group	-P 2n 2ab	-P 2n 2ab
Moiety formula	C24 H22 N2 O4	C24 H22 N2 O4
Sum formula	C24 H22 N2 O4	C24 H22 N2 O4
Mr	402.44	402.43
Dx,g cm-3	1.332	1.332
Z	8	8
Mu (mm-1)	0.092	0.092
F000	1696.0	1696.0
F000'	1696.80	
h,k,lmax	27,22,19	27,22,18
Nref	6168	6103
Tmin,Tmax	0.974,0.990	0.959,0.995
Tmin'	0.971	

```
Correction method= # Reported T Limits: Tmin=0.959 Tmax=0.995
AbsCorr = MULTI-SCAN

Data completeness= 0.989          Theta(max)= 30.560

R(reflections)= 0.0580( 3368)     wR2(reflections)= 0.1918( 6103)

S = 1.019                  Npar= 271
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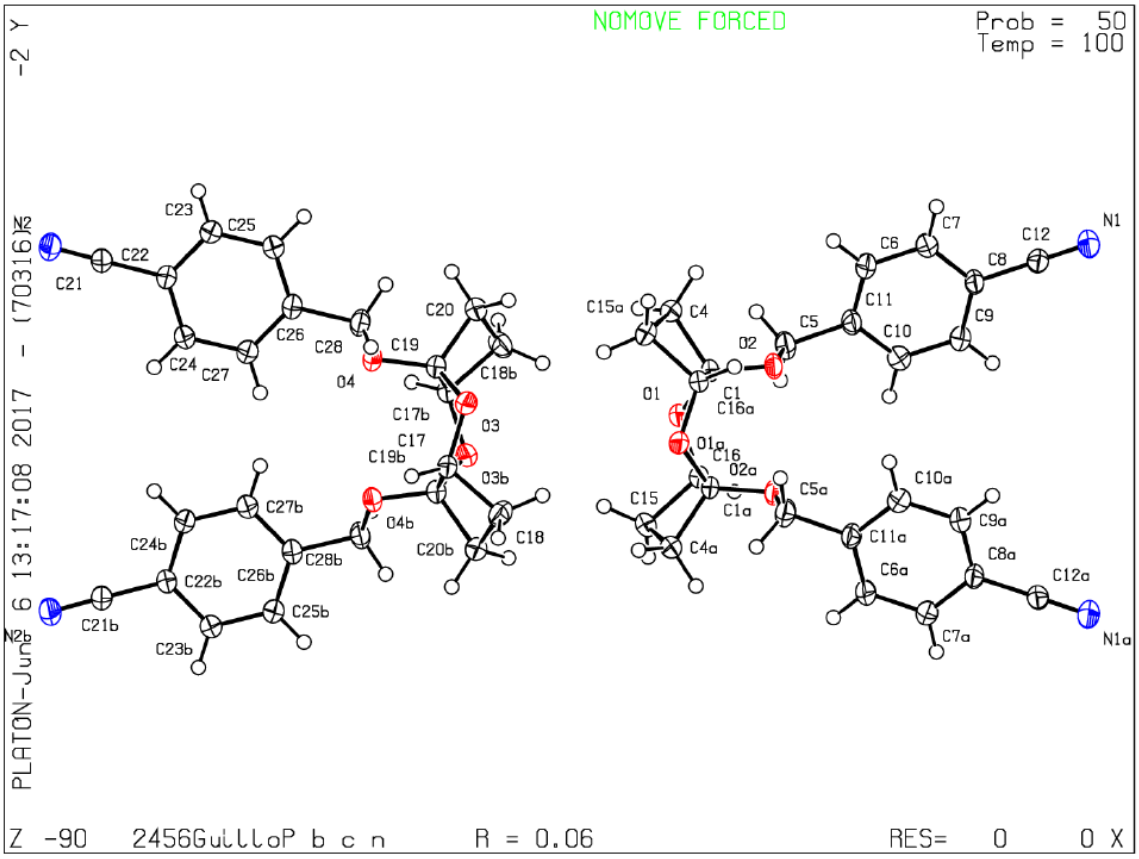
The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

PLATON version of 27/03/2017; check.def file version of 24/03/2017

Datablock 2456GuillotICMMO - ellipsoid plot



2456GuilloP b c n R = 0.06 : Jun 06 14:13:36 2017

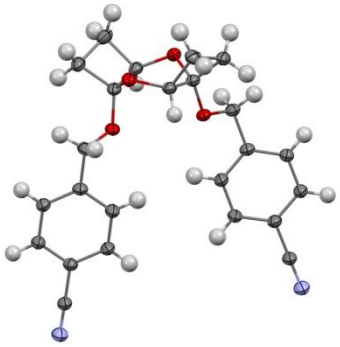


Fig. 2. ORTEP diagram of compound **cis-4n**, showing 30% probability ellipsoids. Only one molecule of the asymmetric unit is shown. X-ray diffraction data for the two compound **cis-4n** were collected by using a X8 APEXII CCD Bruker diffractometer with graphite-monochromated MoKα radiation. X-ray diffraction Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. For compounds, the temperature of the crystal was maintained at the selected value (100K)

by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97[10] and refined against F^2 by full-matrix least-squares techniques using SHELXL-2014[1] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.[11] The crystal data collection and refinement parameters are given in Table S2 CCDC 1557855 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure.

10) G. M. Sheldrick, Acta Crystallogr., Sect. A: Found. Crystallogr., **2008**, 64, 112-122

11) Farrugia, L. J. *J. Appl. Cryst*., **1999**, *32*, 837.

Table S2 Crystallographic data and structure refinement details for **cis-4n**.

Compounds	**cis-4n**
Empirical Formula	$C_{24}\ H_{22}\ N_2\ O_4$
M_r	402.43
Crystal size, mm^3	0.32 x 0.24 x 0.11
Crystal system	orthorhombic
Space group	*P b c n*
a, Å	19.2545(11)
b, Å	15.5146(10)
c, Å	13.4314(9)
α, °	90
β, °	90
γ, °	90
Cell volume, $Å^3$	4012.3(4)
Z ; Z’	8 ; 1
T, K	100(1)
Radiation type ; wavelength Å	MoKα ; 0.71073
F_{000}	1696
μ, mm^{-1}	0.092
θ range, °	1.686 - 30.560
Reflection collected	41 326
Reflections unique	6 103
R_{int}	0.0742
GOF	1.019
Refl. obs. (I>2σ(I))	3 368
Parameters	391
wR_2 (all data)	0.1918
R value (I>2σ(I))	0.0580
Largest diff. peak and hole (e-.$Å^{-3}$)	0.529 ; -0.275