

Supporting Information for

One Step Access to Oxindole-based β -Lactams through Ugi Four-Center Three-Component Reaction

Giulia Rainoldi,^a Giordano Lesma,^a Claudia Picozzi,^b Leonardo Lo Presti^a and Alessandra Silvani^{a,*}

^aDipartimento di Chimica, Università degli Studi di Milano, via Golgi 19, Milano, 20133, Italy.

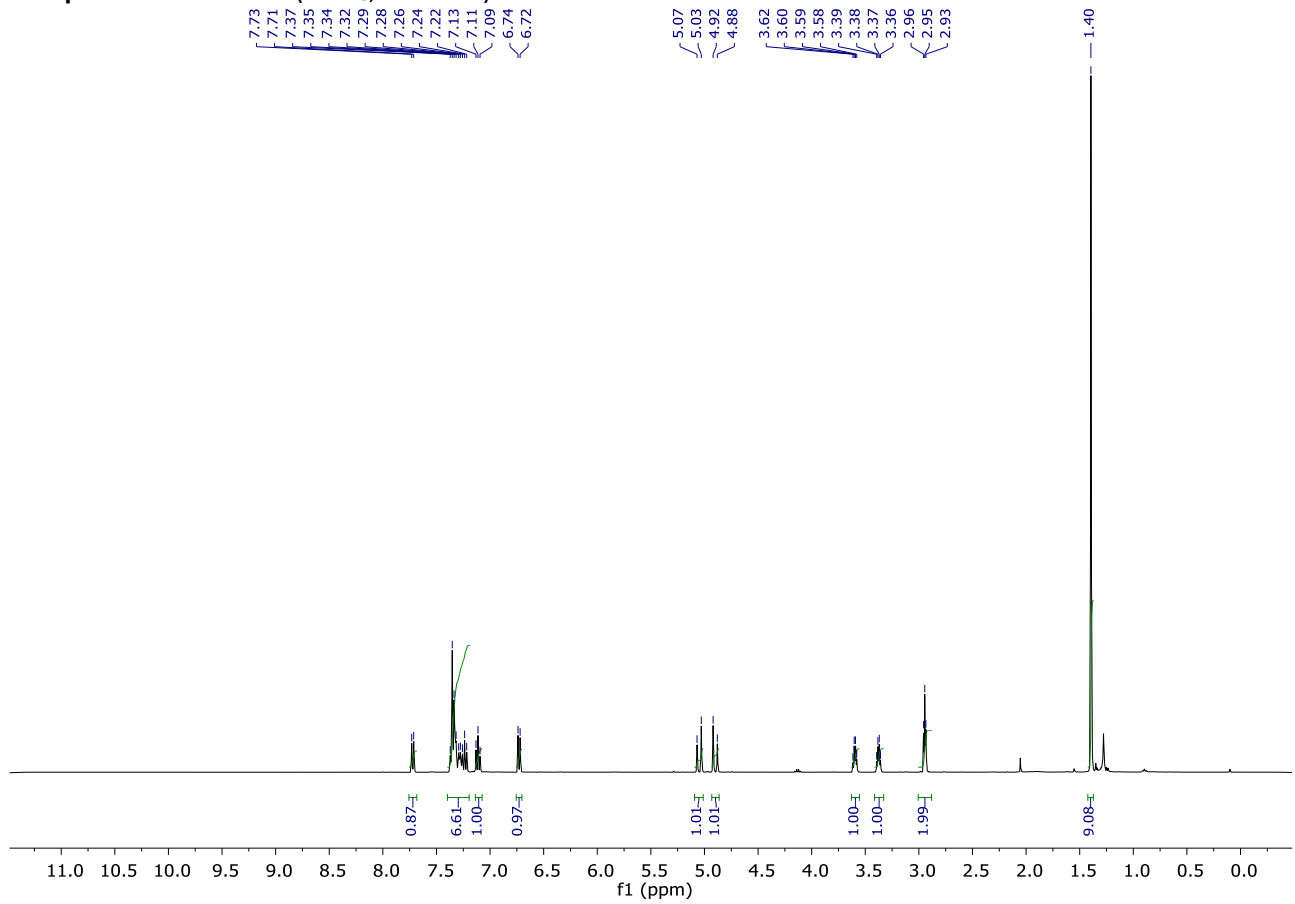
^bDepartment of Food, Environmental and Nutritional Sciences (DeFENS), Division of Food Microbiology and Bioprocessing, via Celoria 2, 20133 Milan, Italy.

alessandra.silvani@unimi.it

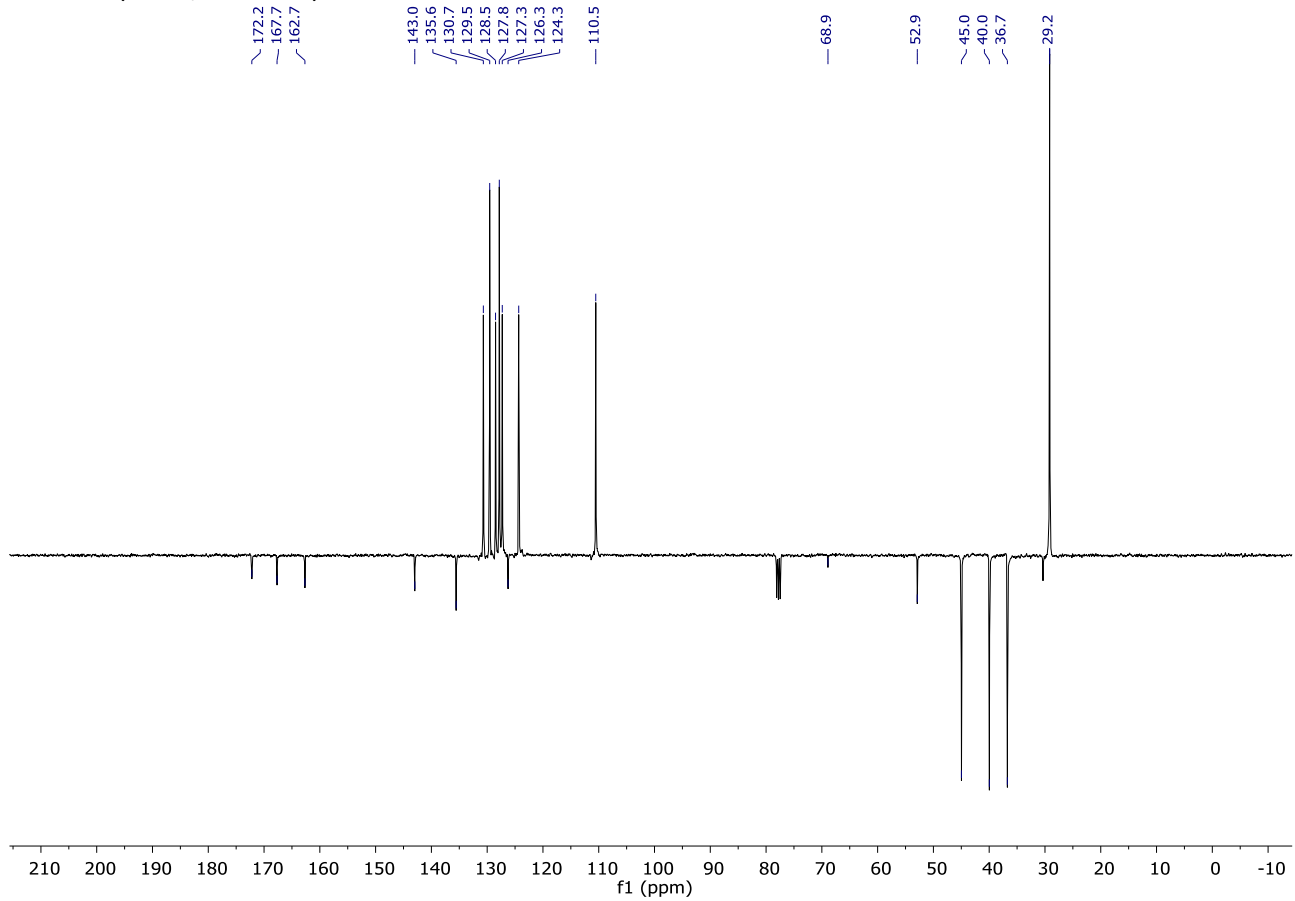
Table of Contents

¹ H NMR and ¹³ C NMR spectra for all new compounds	S2-S22
Experimental for X-ray analysis (compound 4oa)	S22-S24
Table of calculated physicochemical properties	S25
References	S26

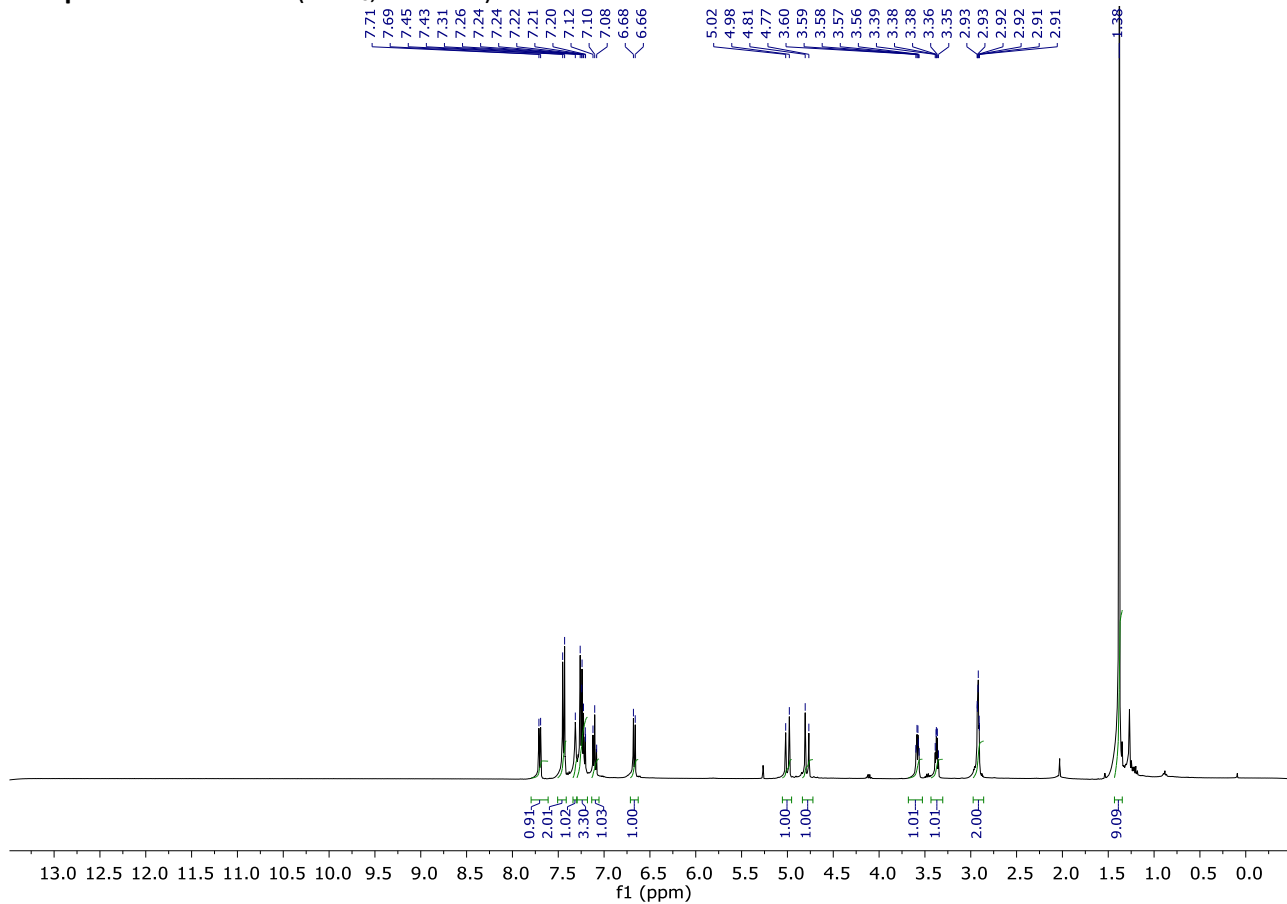
Compound 4a: ¹H NMR (CDCl₃, 400MHz)



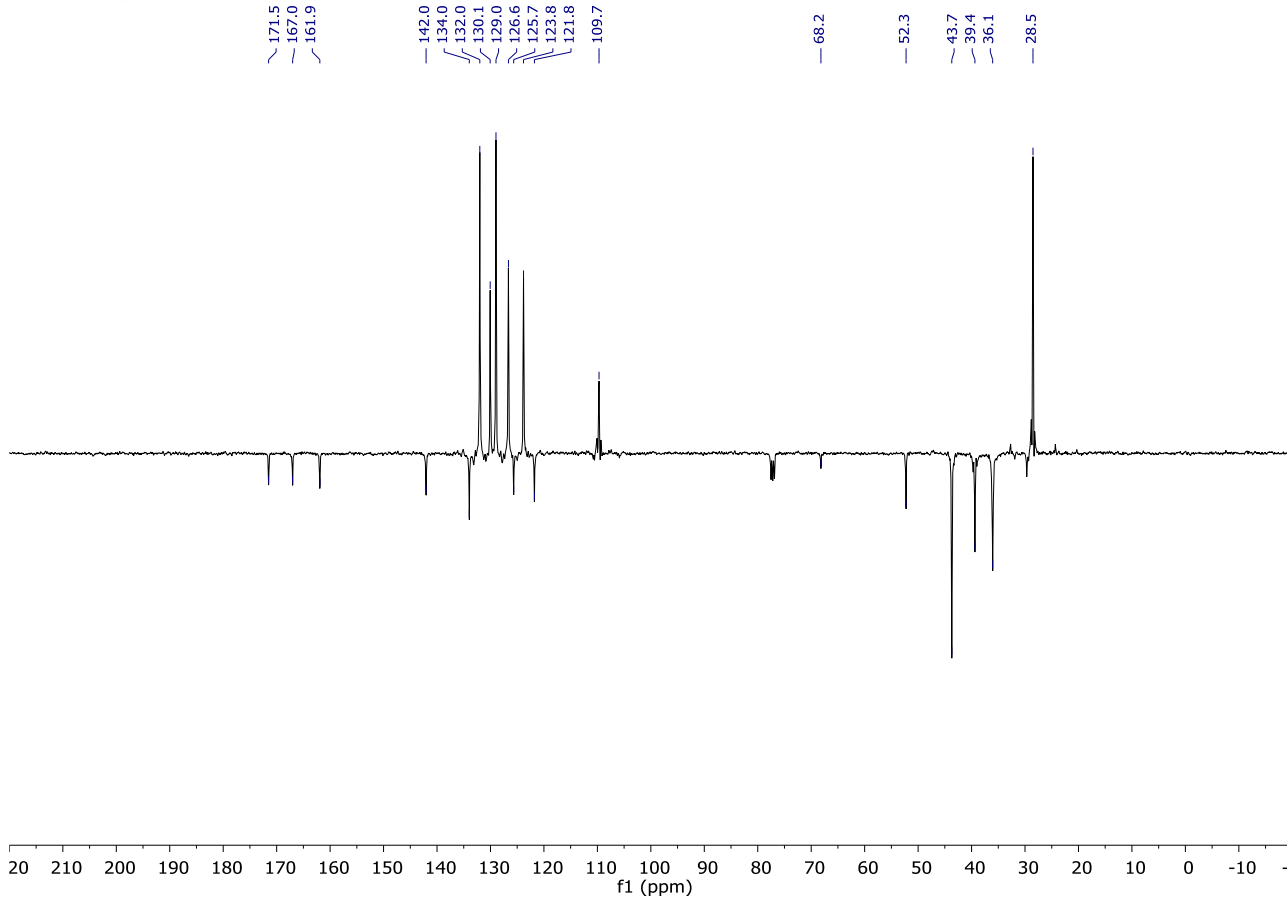
¹³C NMR (CDCl₃, 101 MHz)



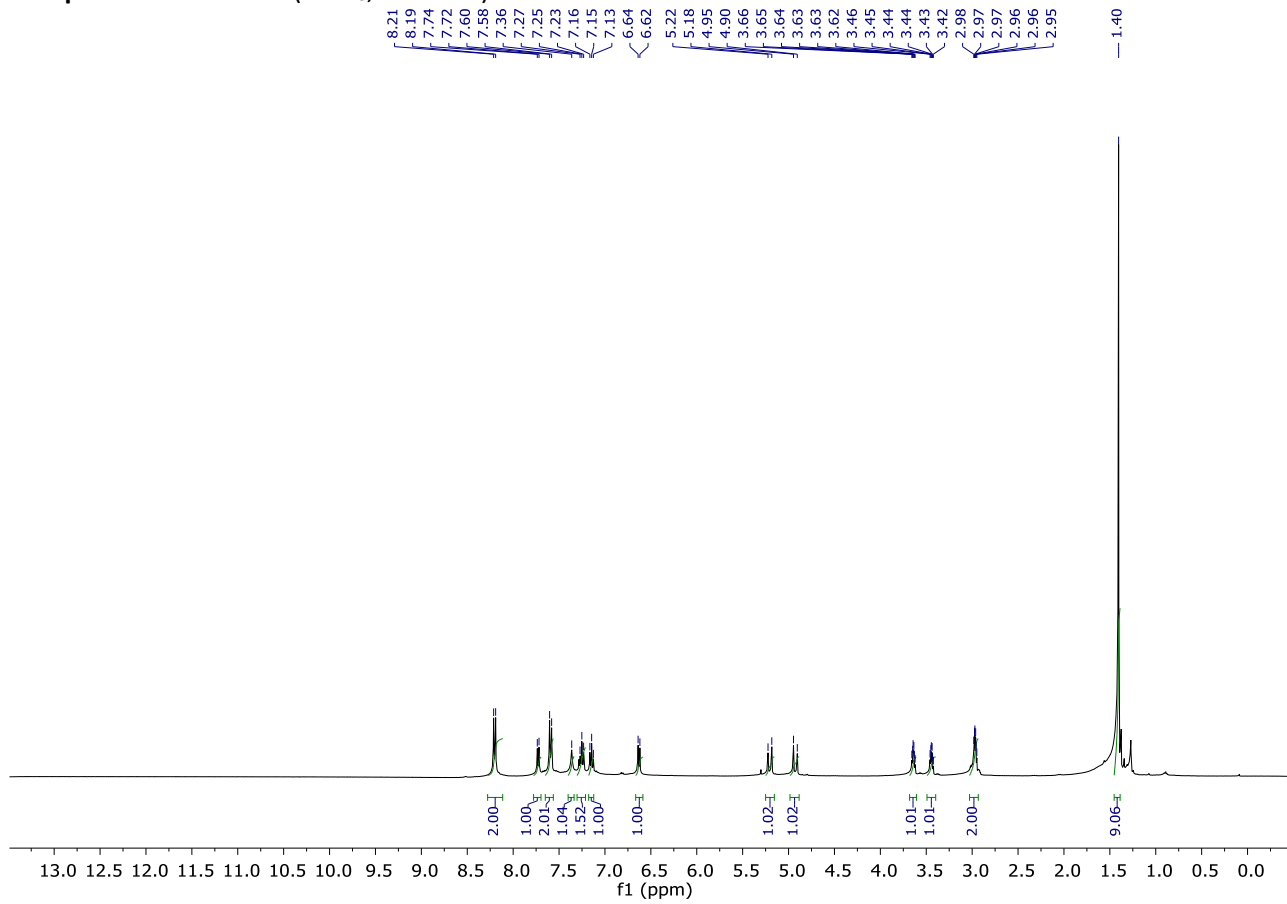
Compound 4b: ¹H NMR (CDCl₃, 400MHz)



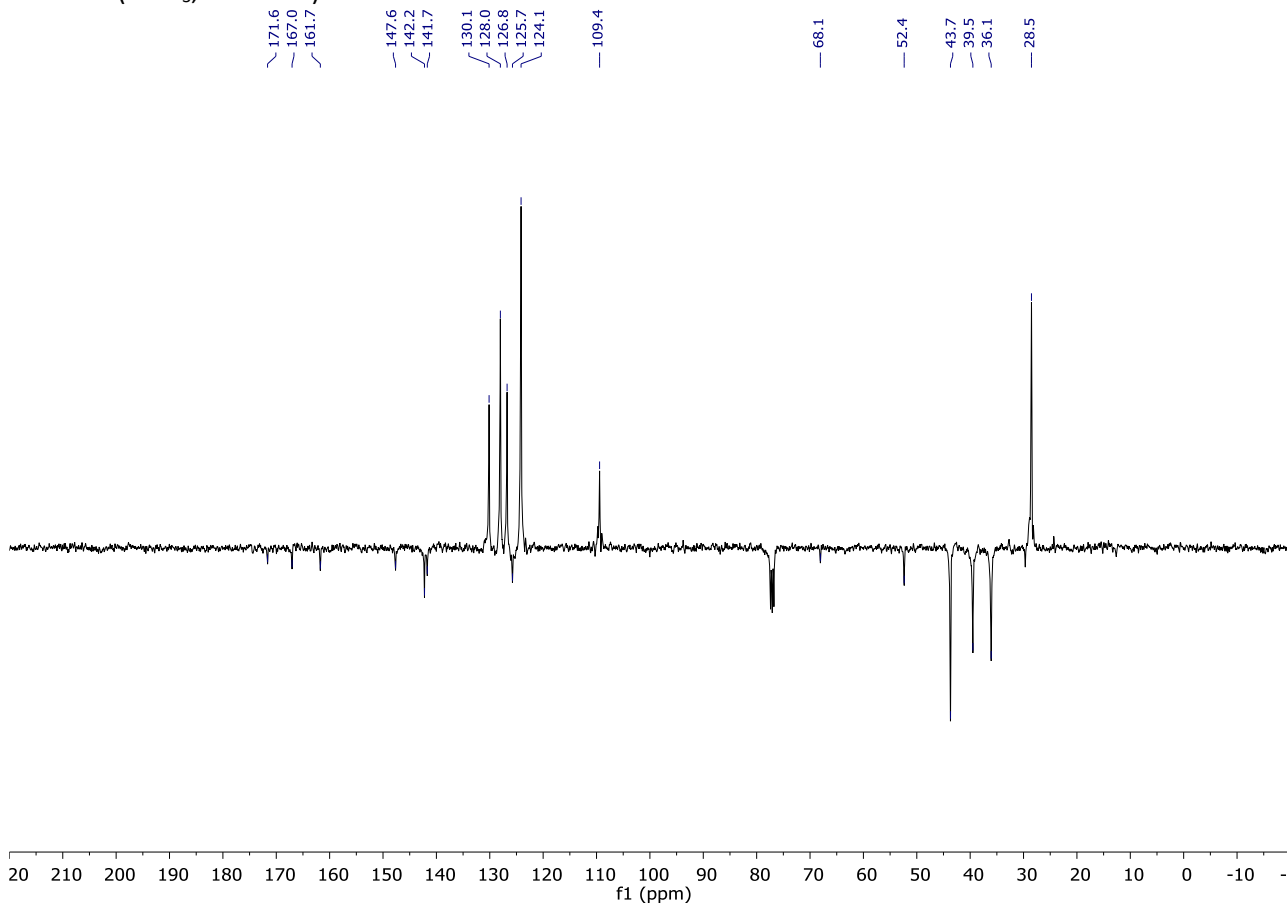
¹³C NMR (CDCl₃, 101 MHz)



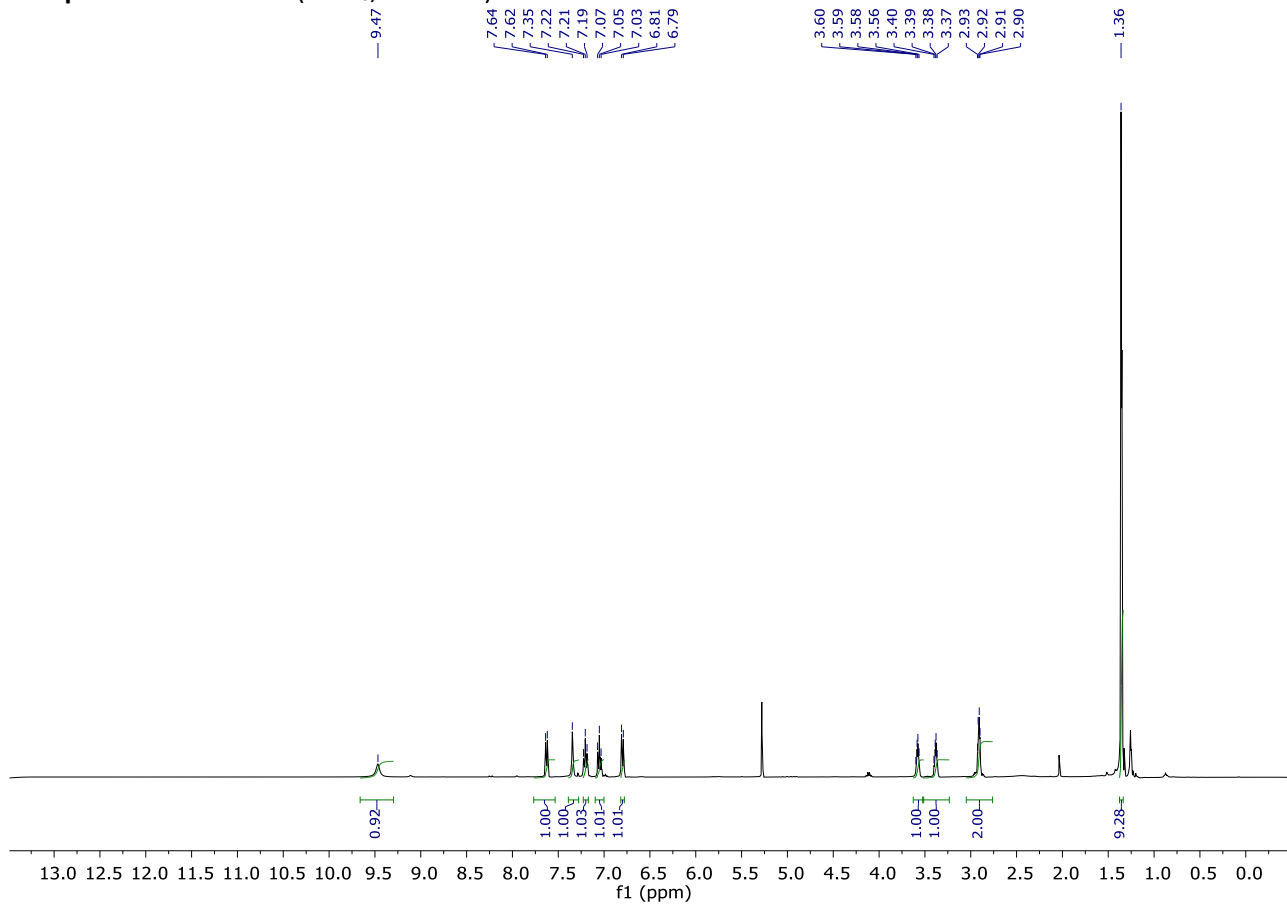
Compound 4c: ^1H NMR (CDCl_3 , 400MHz)



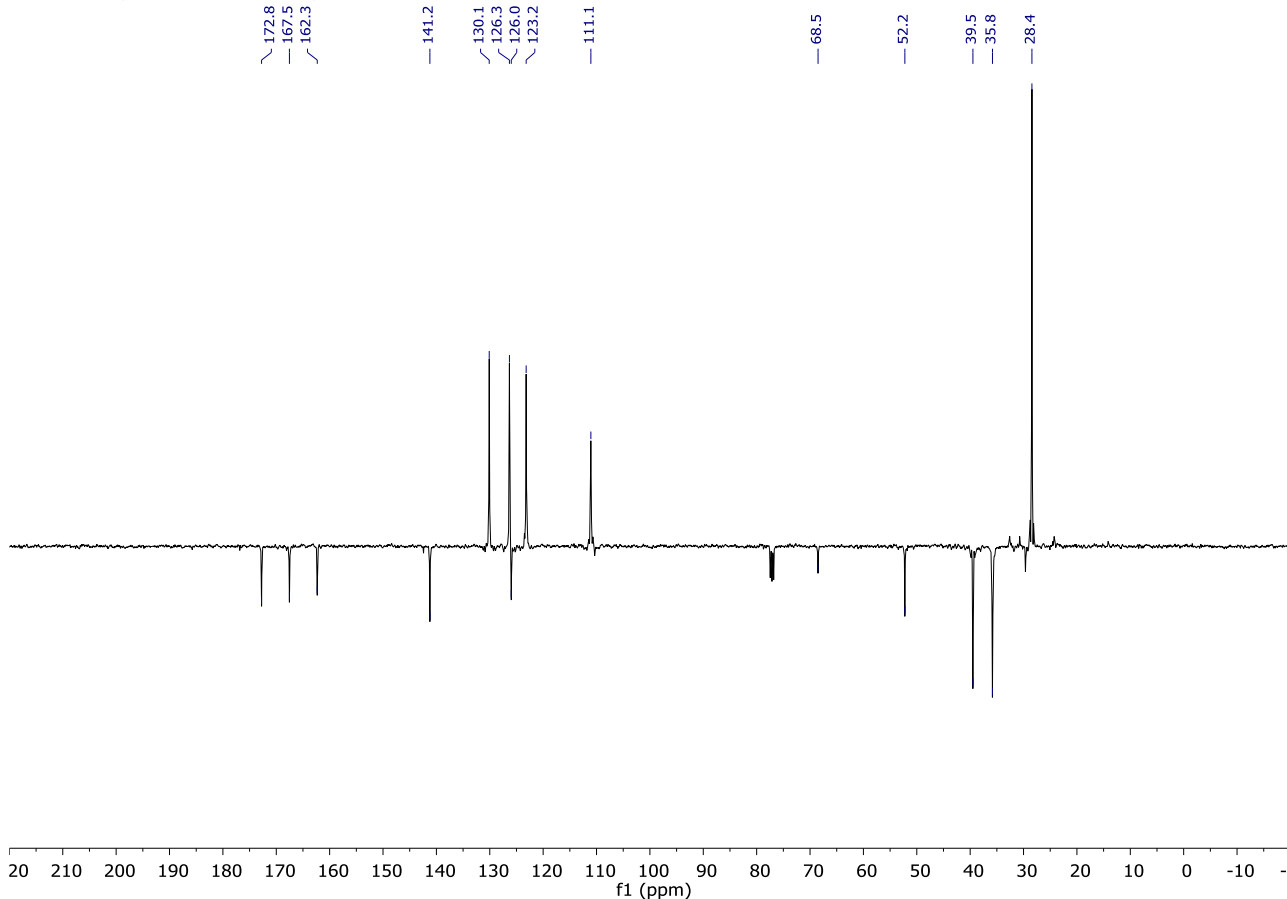
^{13}C NMR (CDCl_3 , 101 MHz)



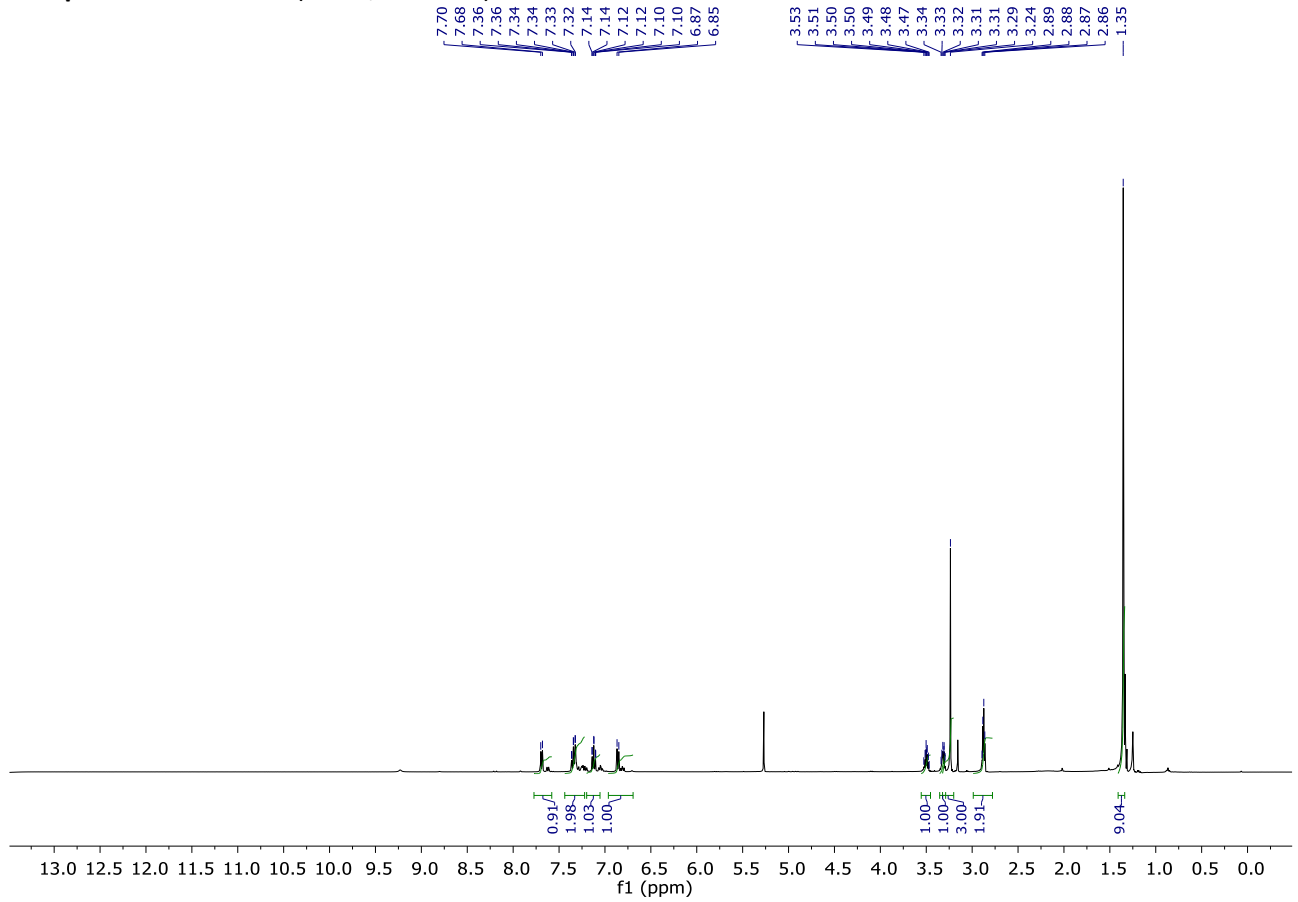
Compound 4d: ¹H NMR (CDCl₃, 400MHz)



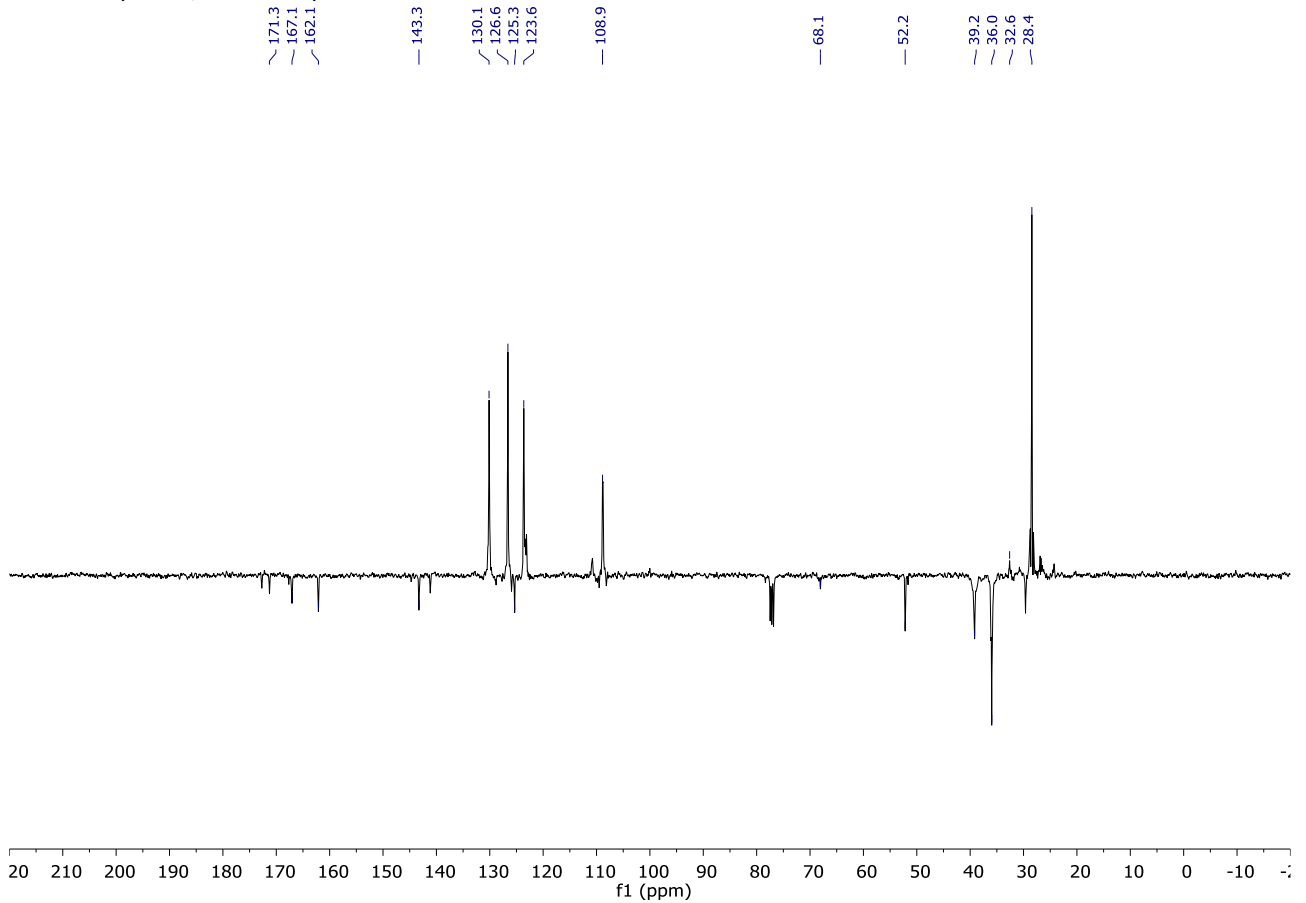
¹³C NMR (CDCl₃, 101 MHz)



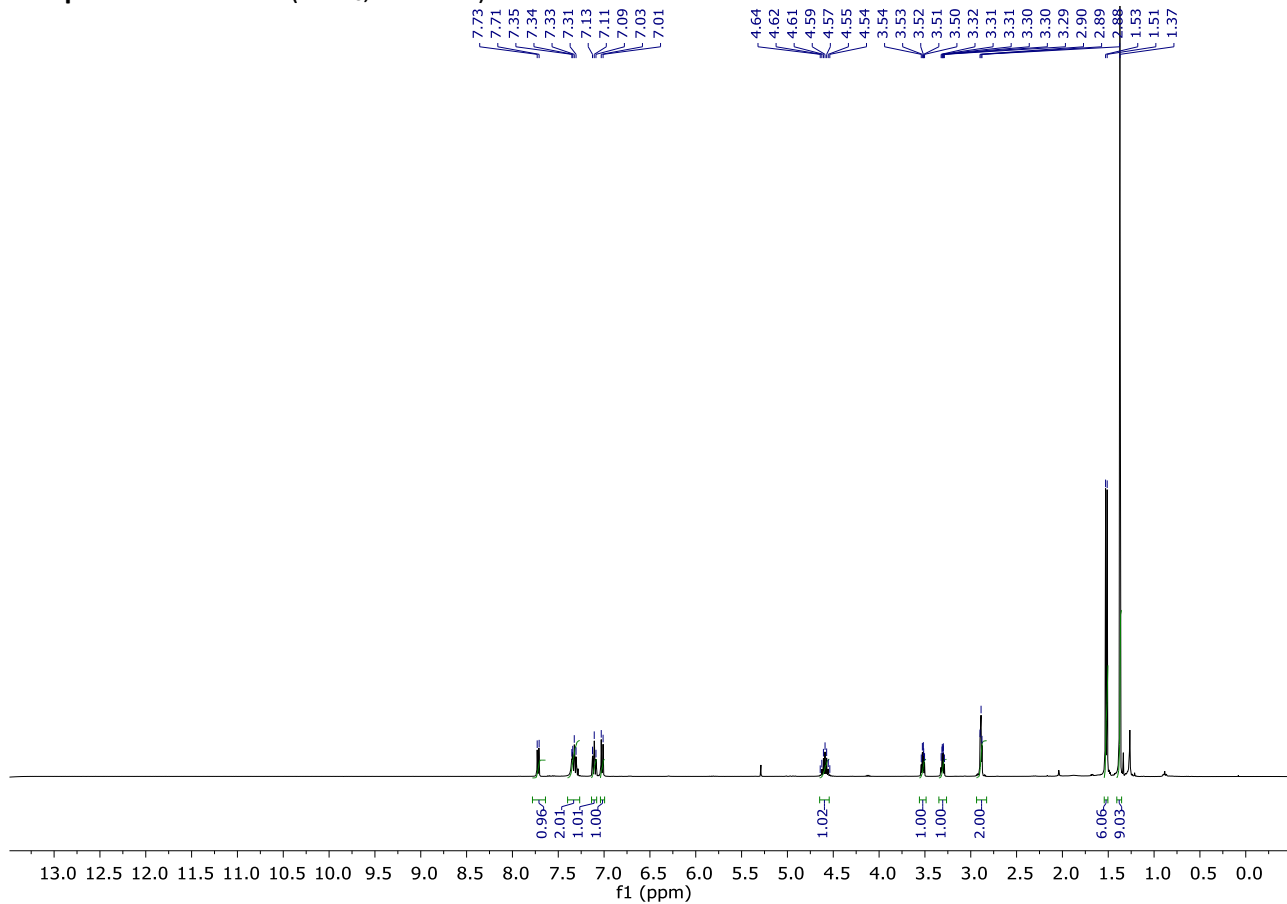
Compound 4e: ^1H NMR (CDCl_3 , 400MHz)



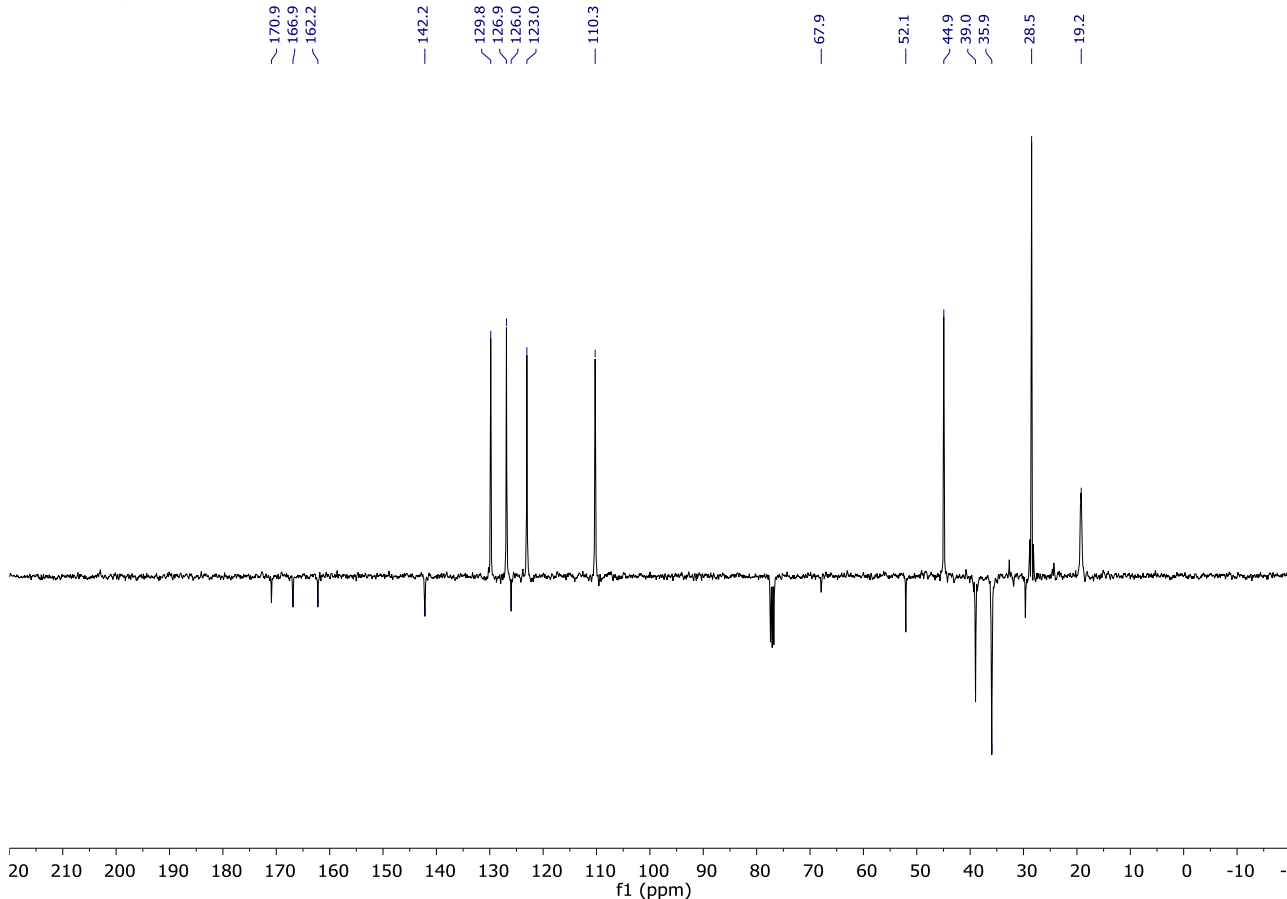
^{13}C NMR (CDCl_3 , 101 MHz)



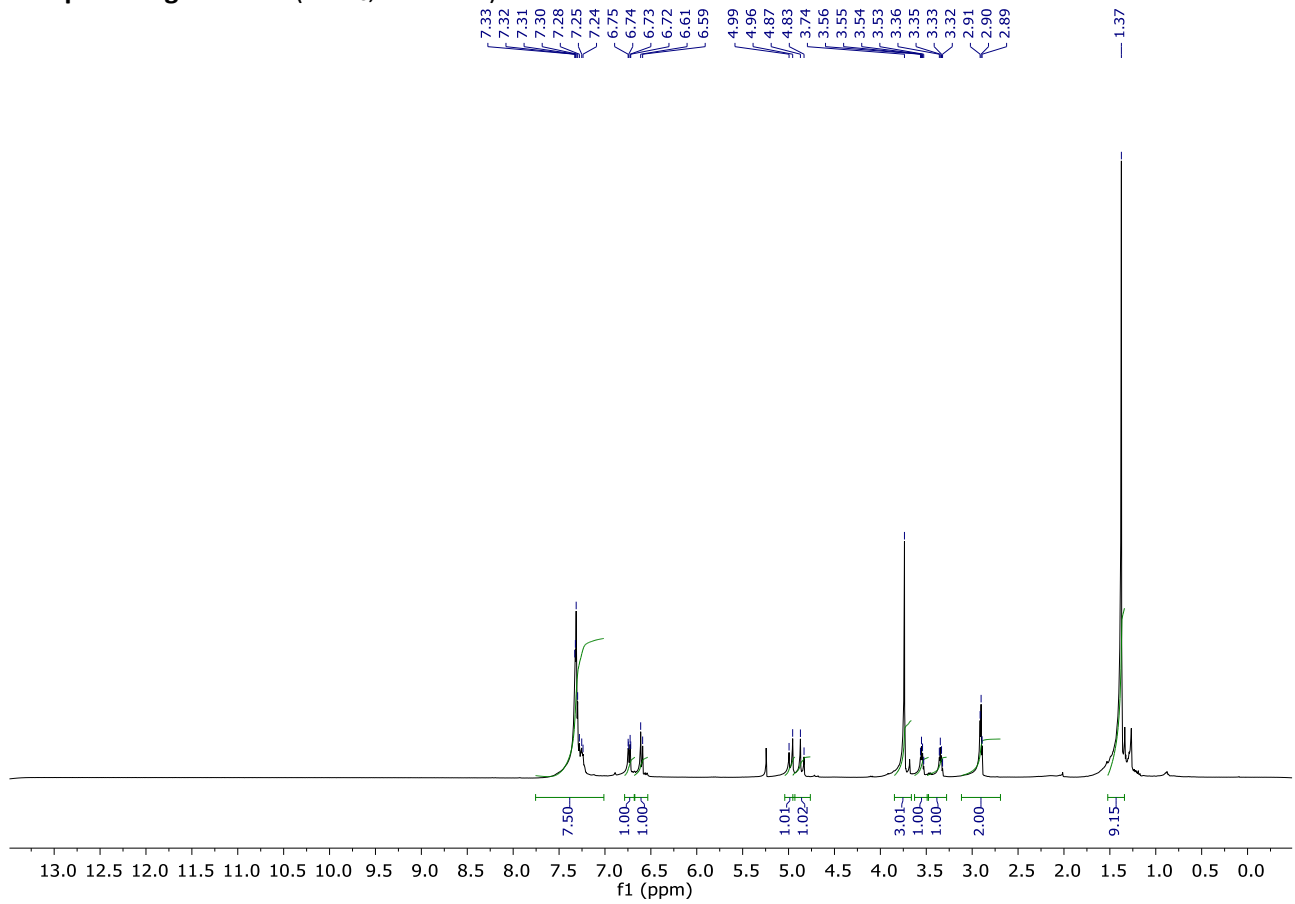
Compound 4f: ^1H NMR (CDCl_3 , 400MHz)



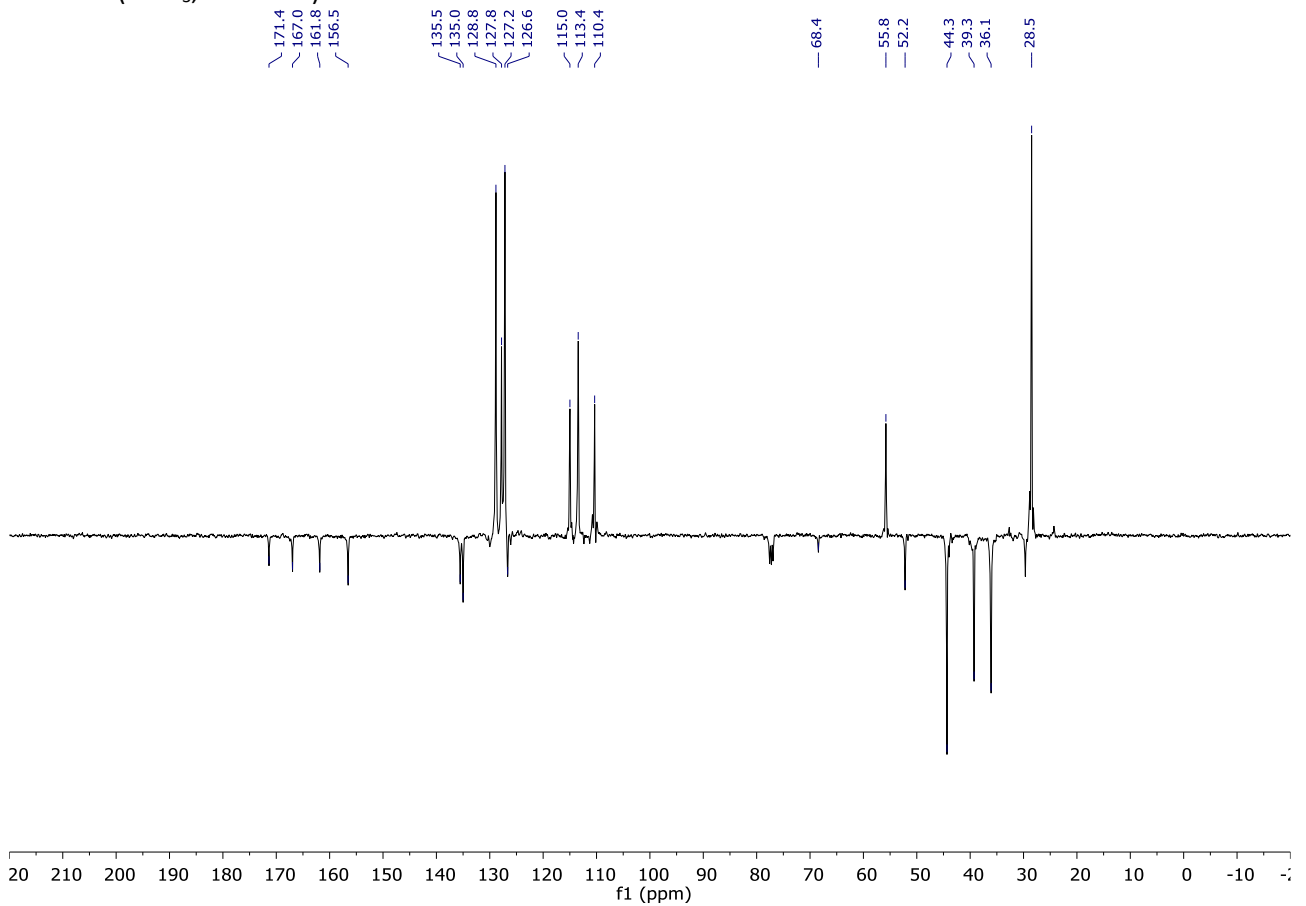
^{13}C NMR (CDCl_3 , 101 MHz)



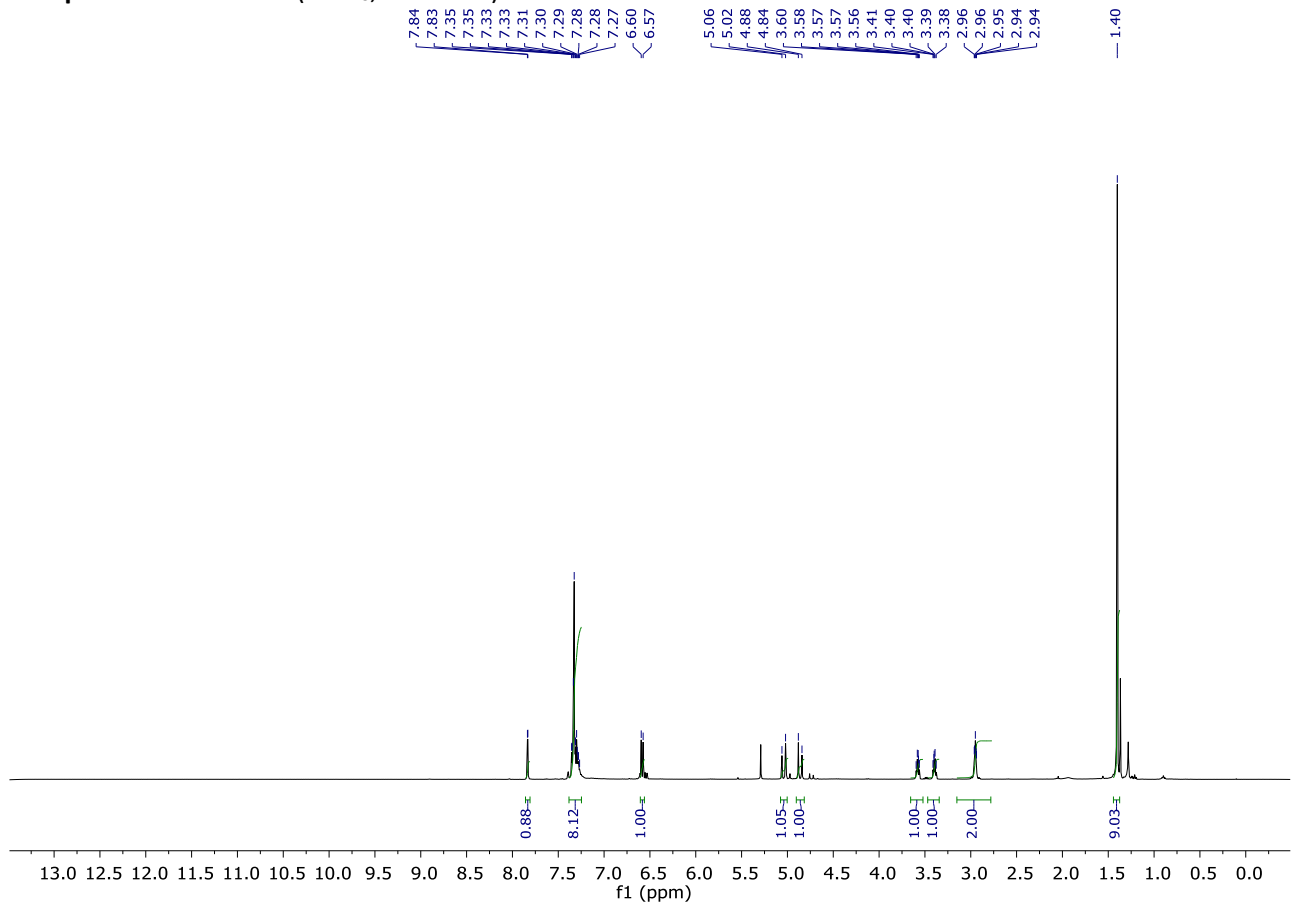
Compound 4g: ^1H NMR (CDCl_3 , 400 MHz)



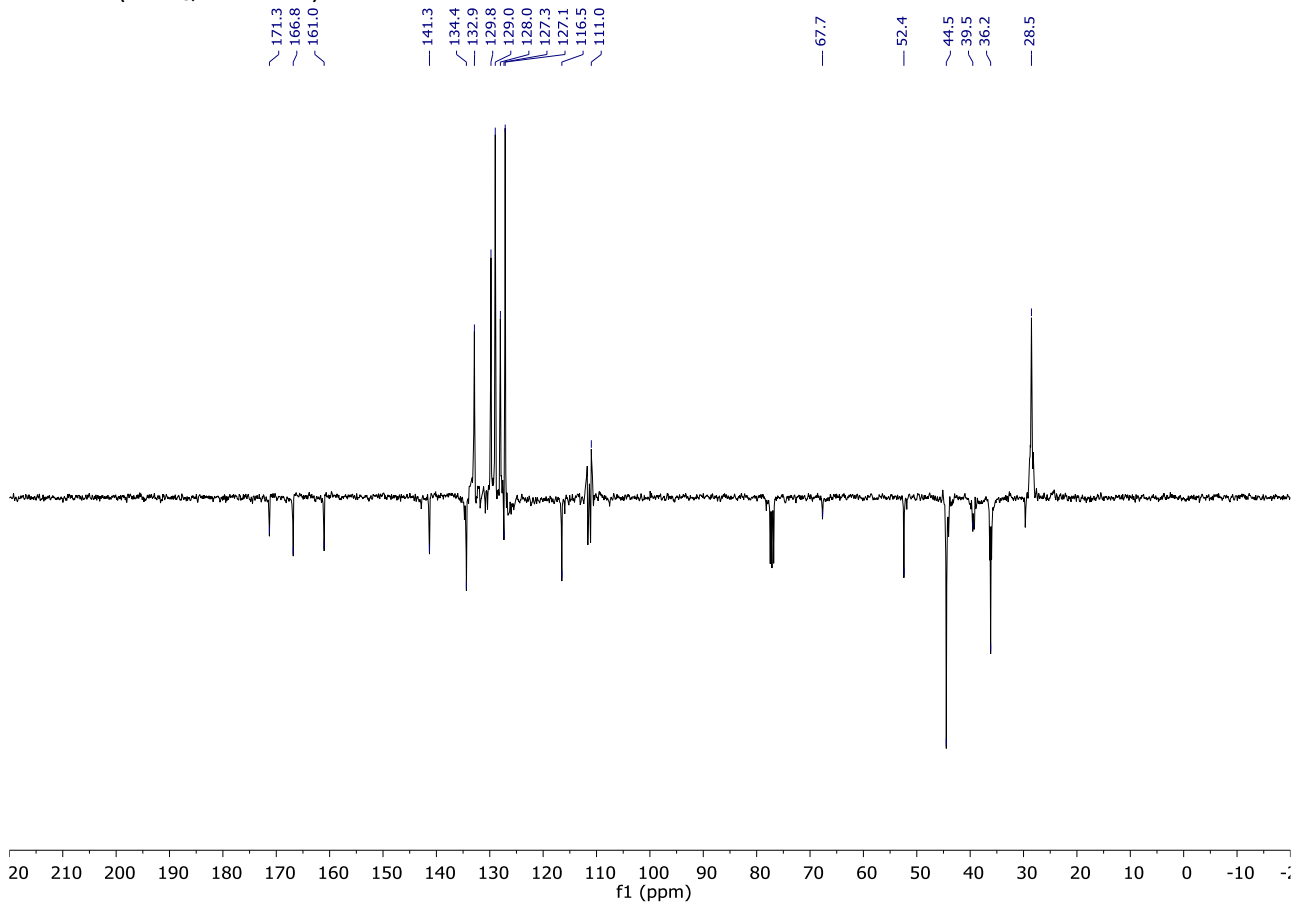
^{13}C NMR (CDCl_3 , 101 MHz)



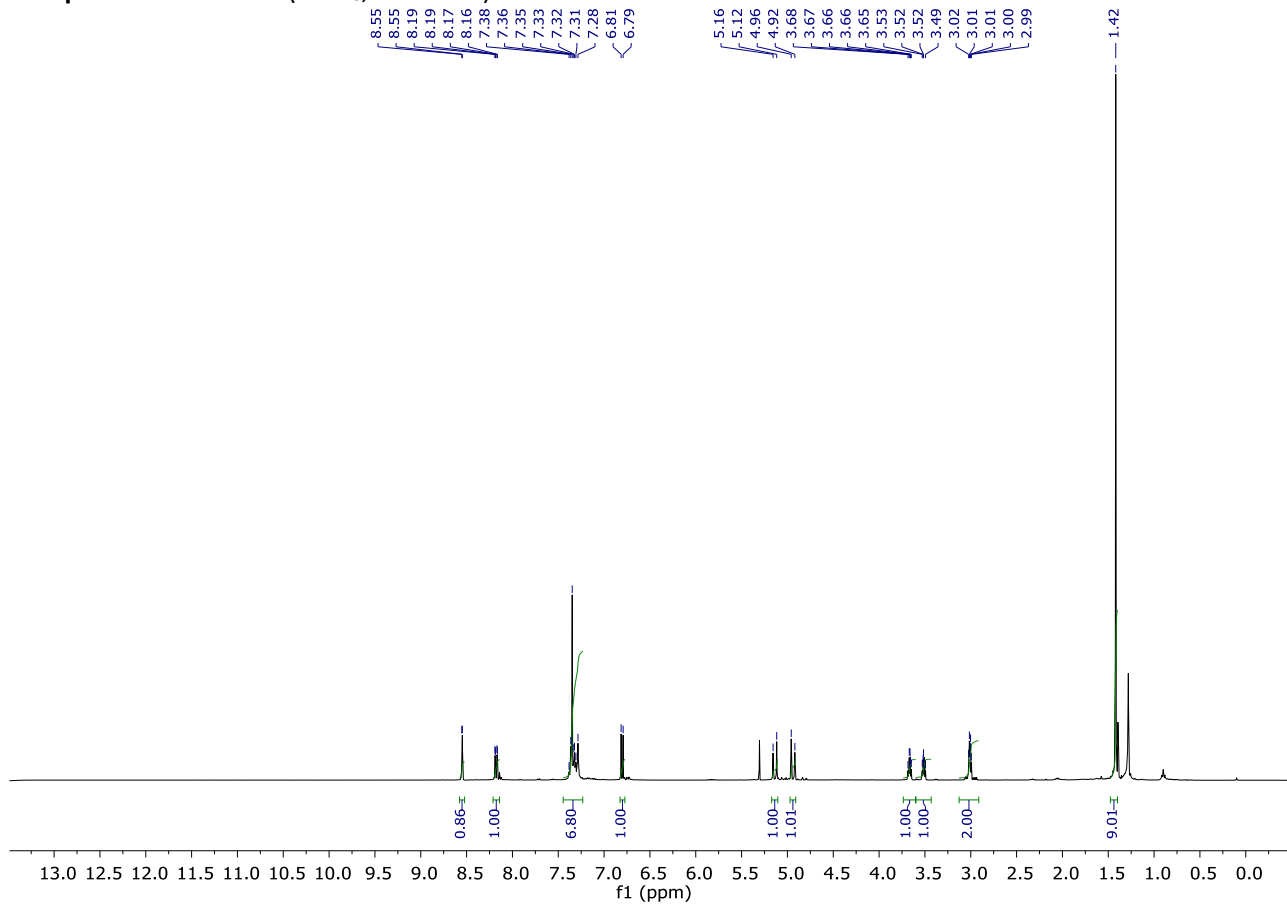
Compound 4h: ¹H NMR (CDCl₃, 400 MHz)



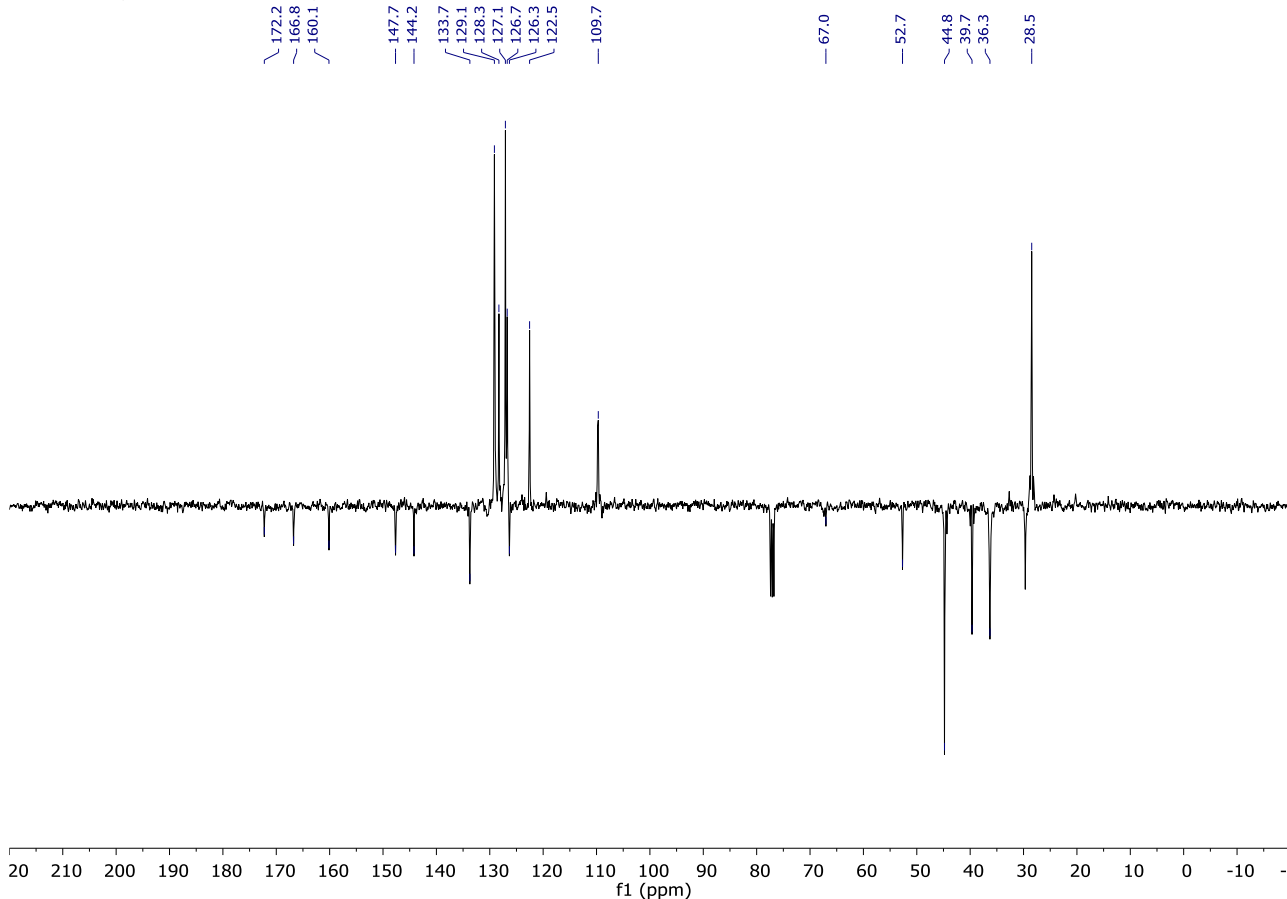
¹³C NMR (CDCl₃, 101 MHz)



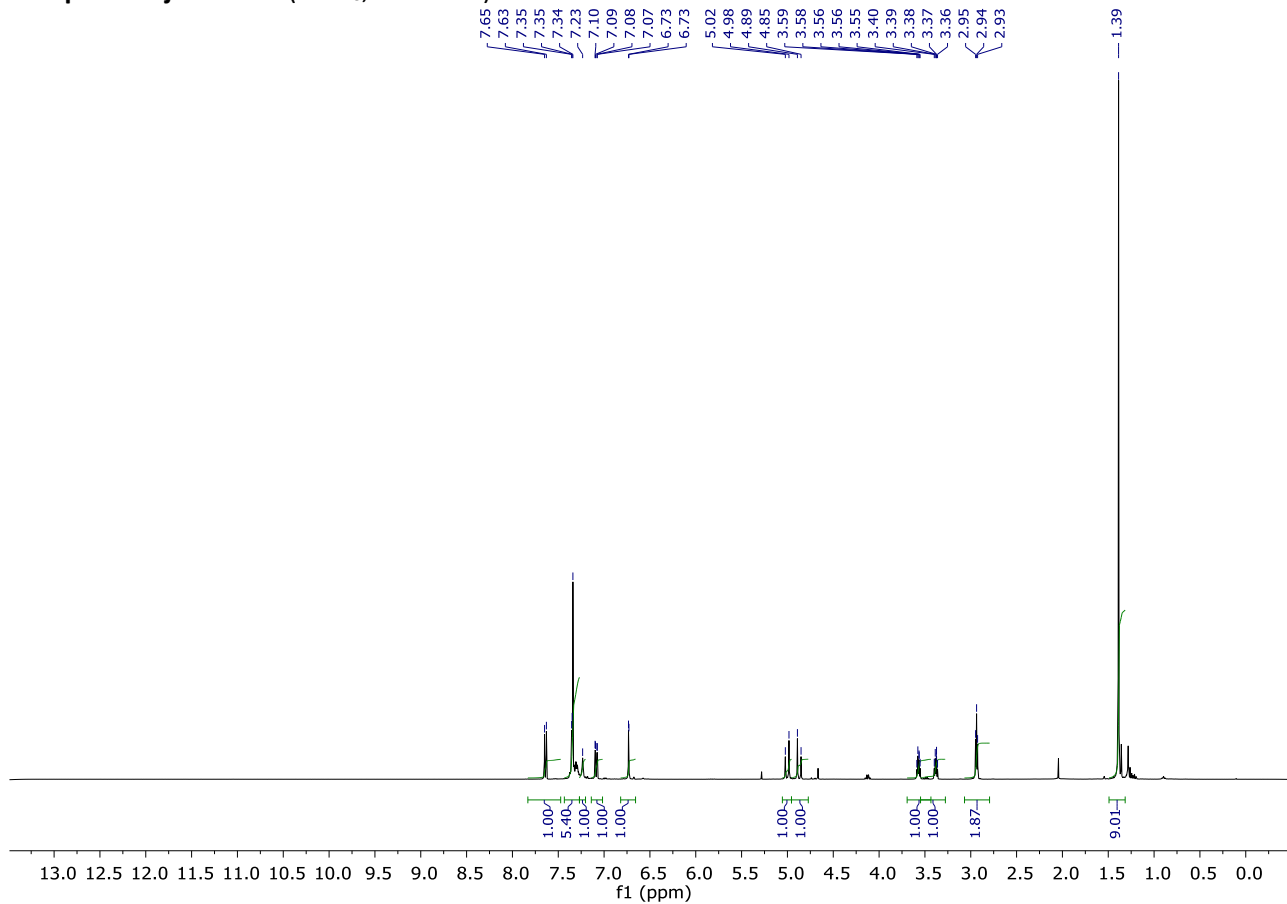
Compound 4i: ¹H NMR (CDCl₃, 400 MHz)



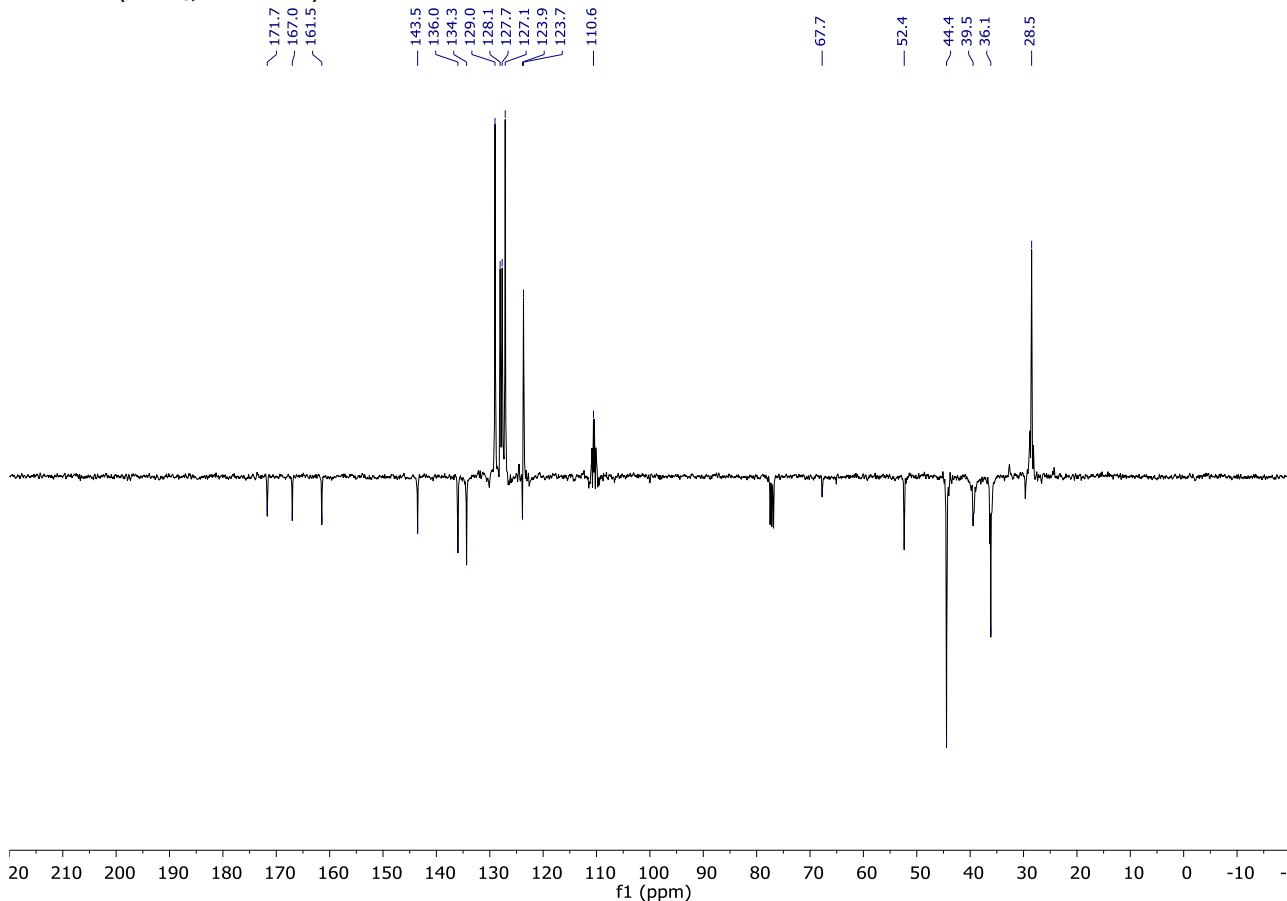
¹³C NMR (CDCl₃, 101 MHz)



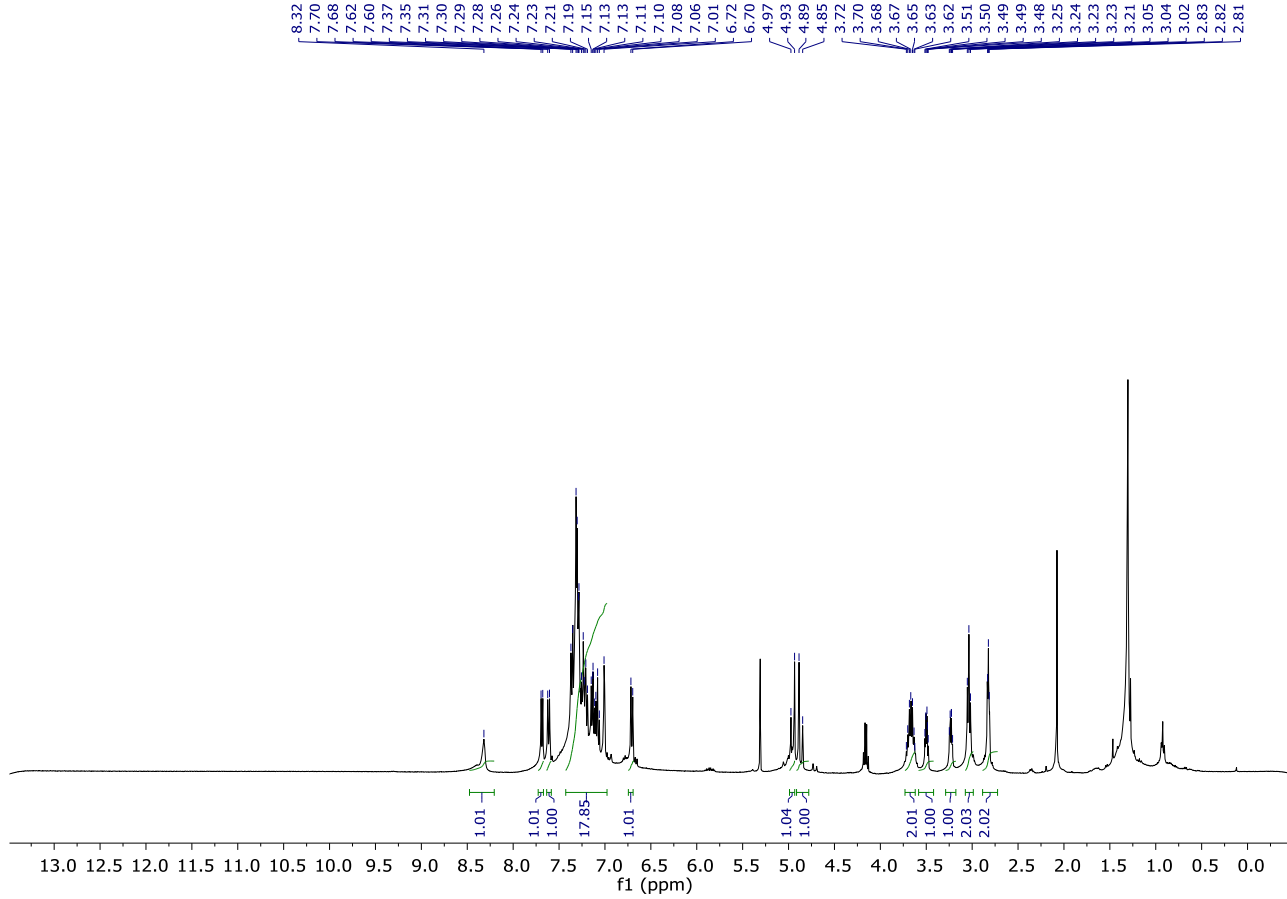
Compound 4j: ^1H NMR (CDCl_3 , 400 MHz)



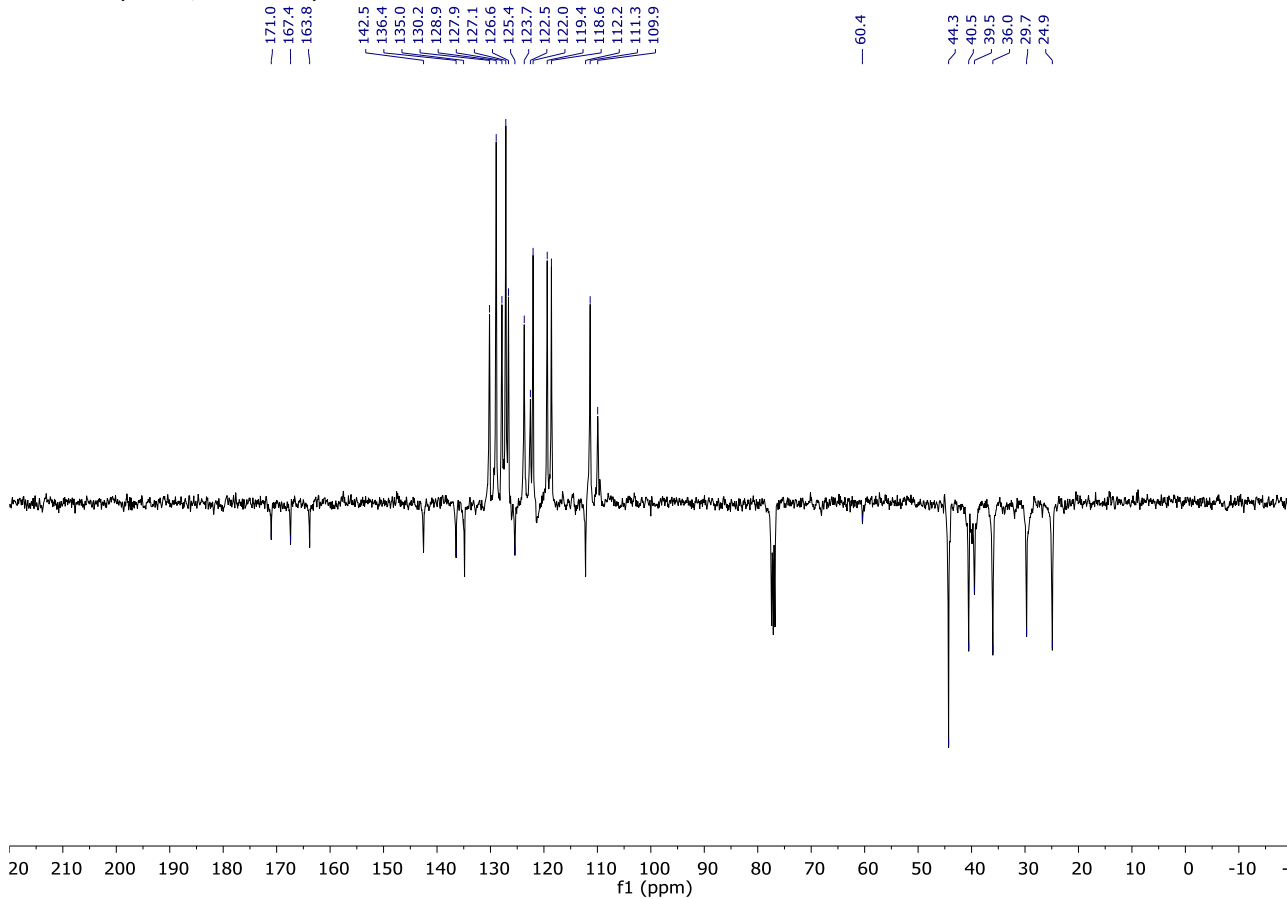
^{13}C NMR (CDCl_3 , 101 MHz)



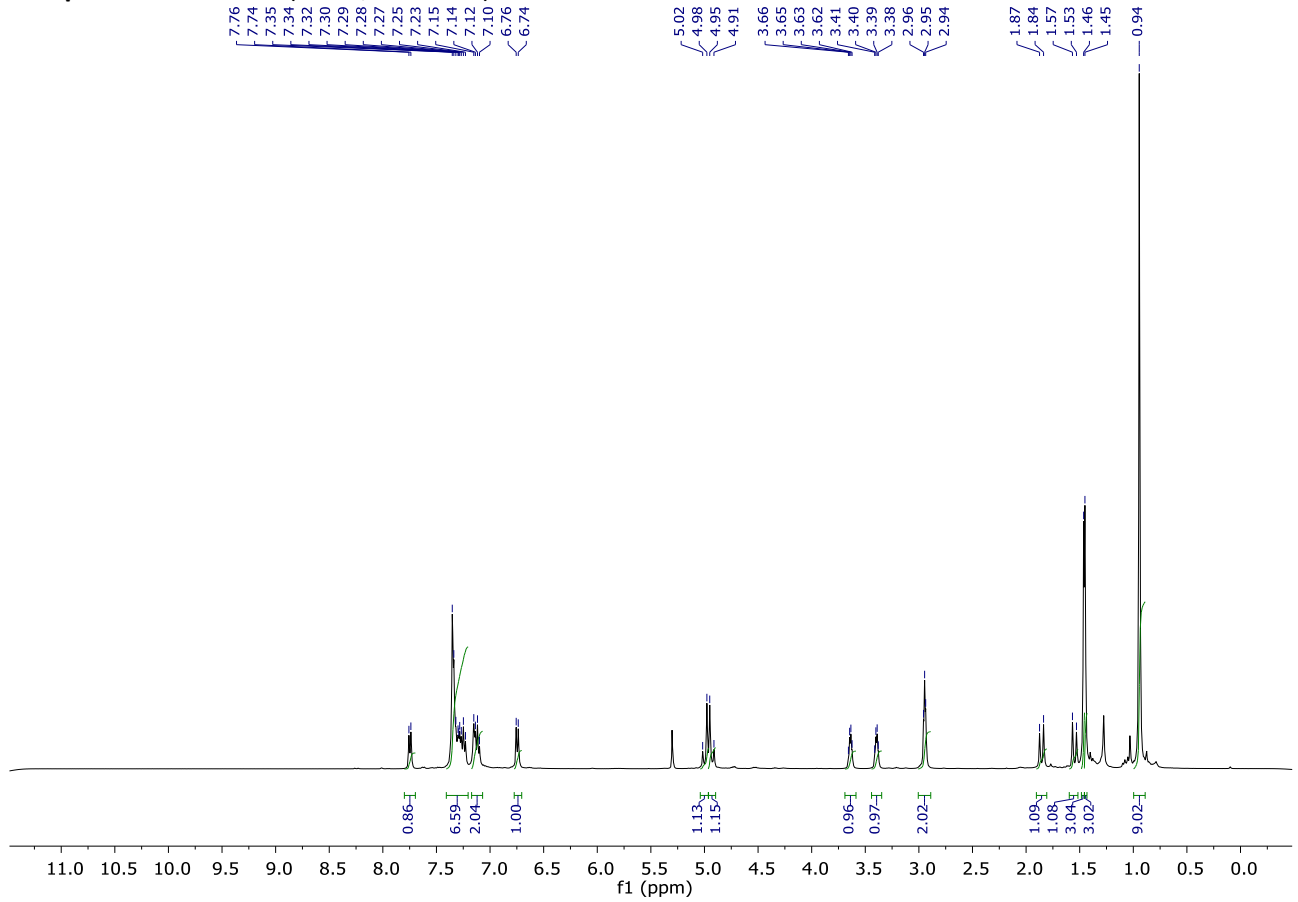
Compound 4k: ^1H NMR (CDCl_3 , 400 MHz)



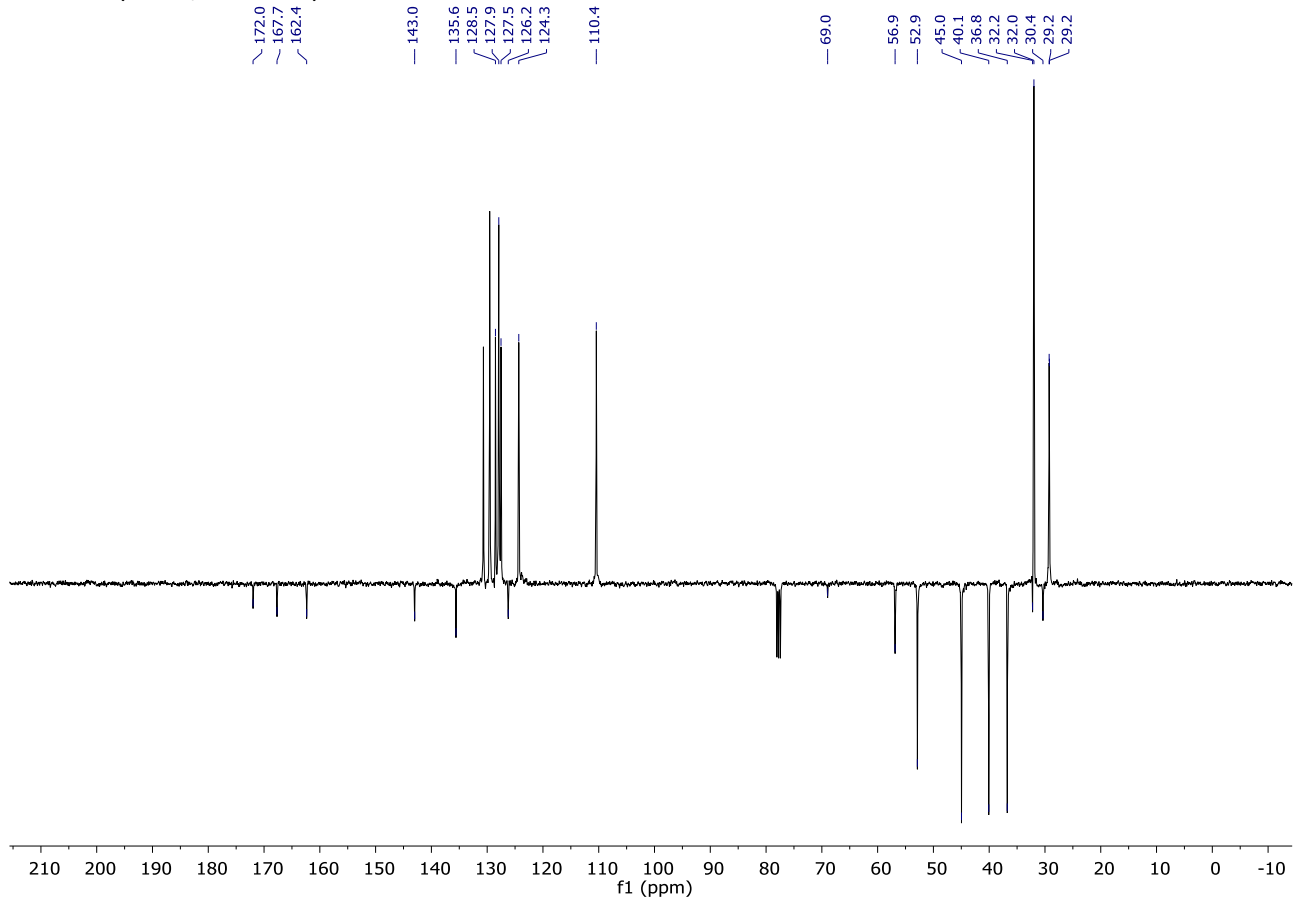
^{13}C NMR (CDCl_3 , 101 MHz)



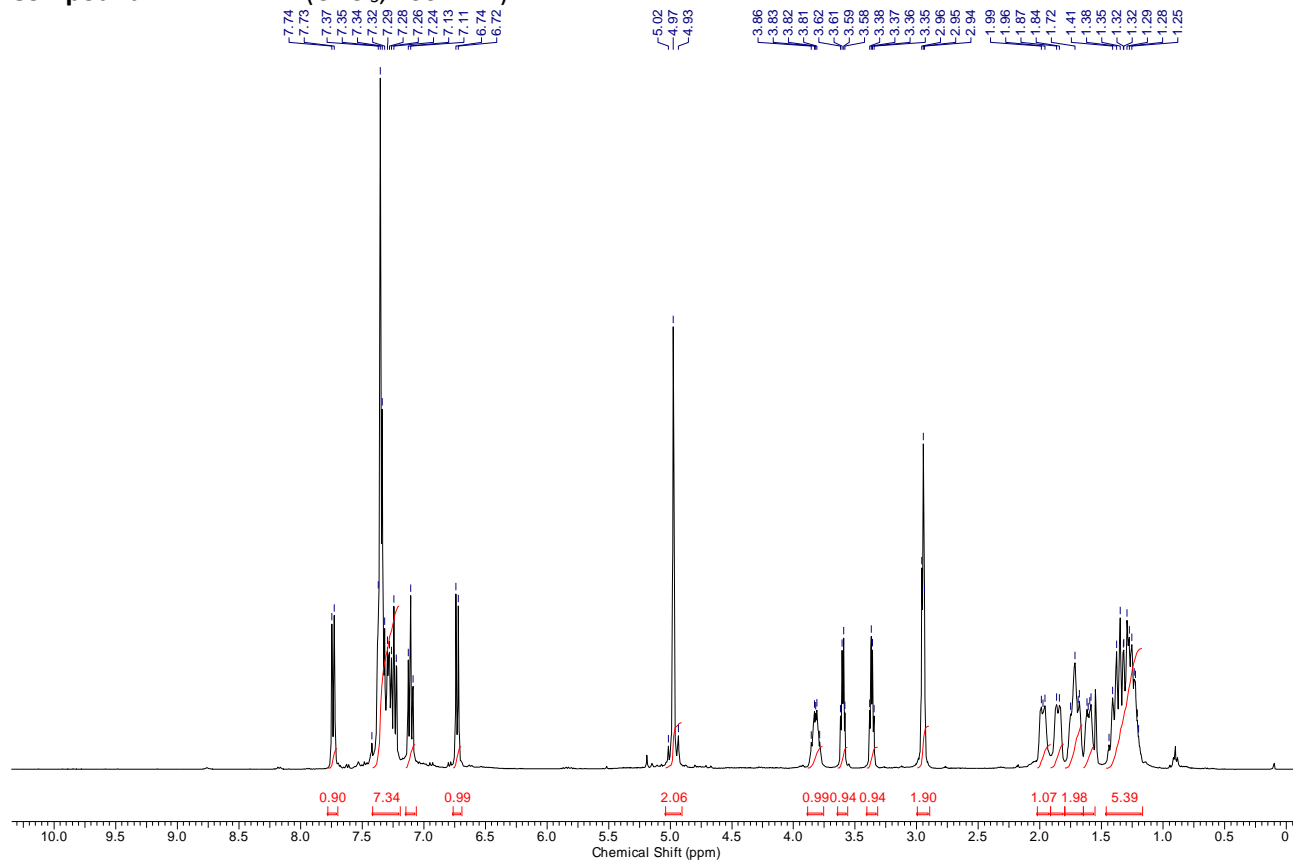
Compound 4I: ^1H NMR (CDCl_3 , 400 MHz)



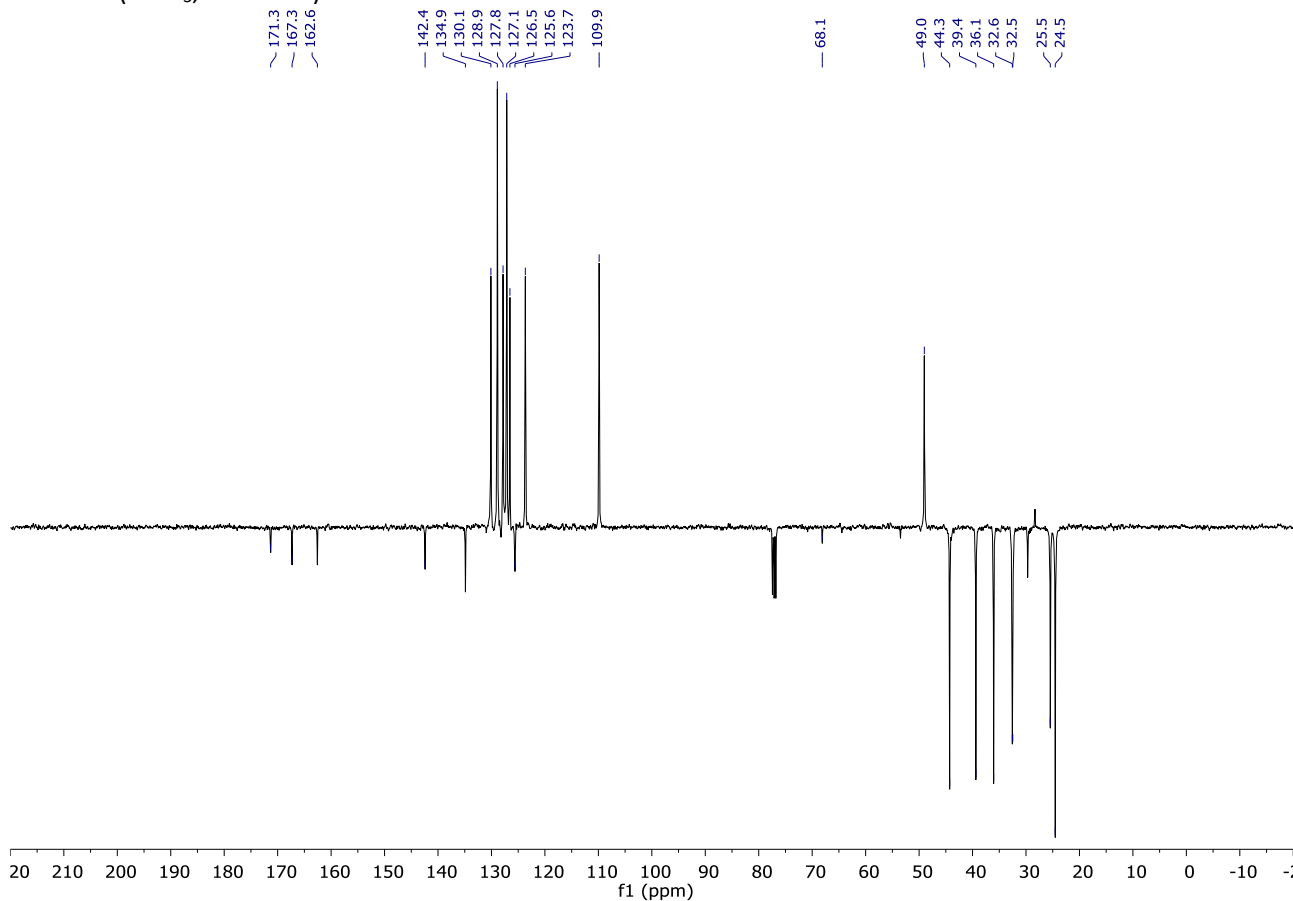
^{13}C NMR (CDCl_3 , 101 MHz)



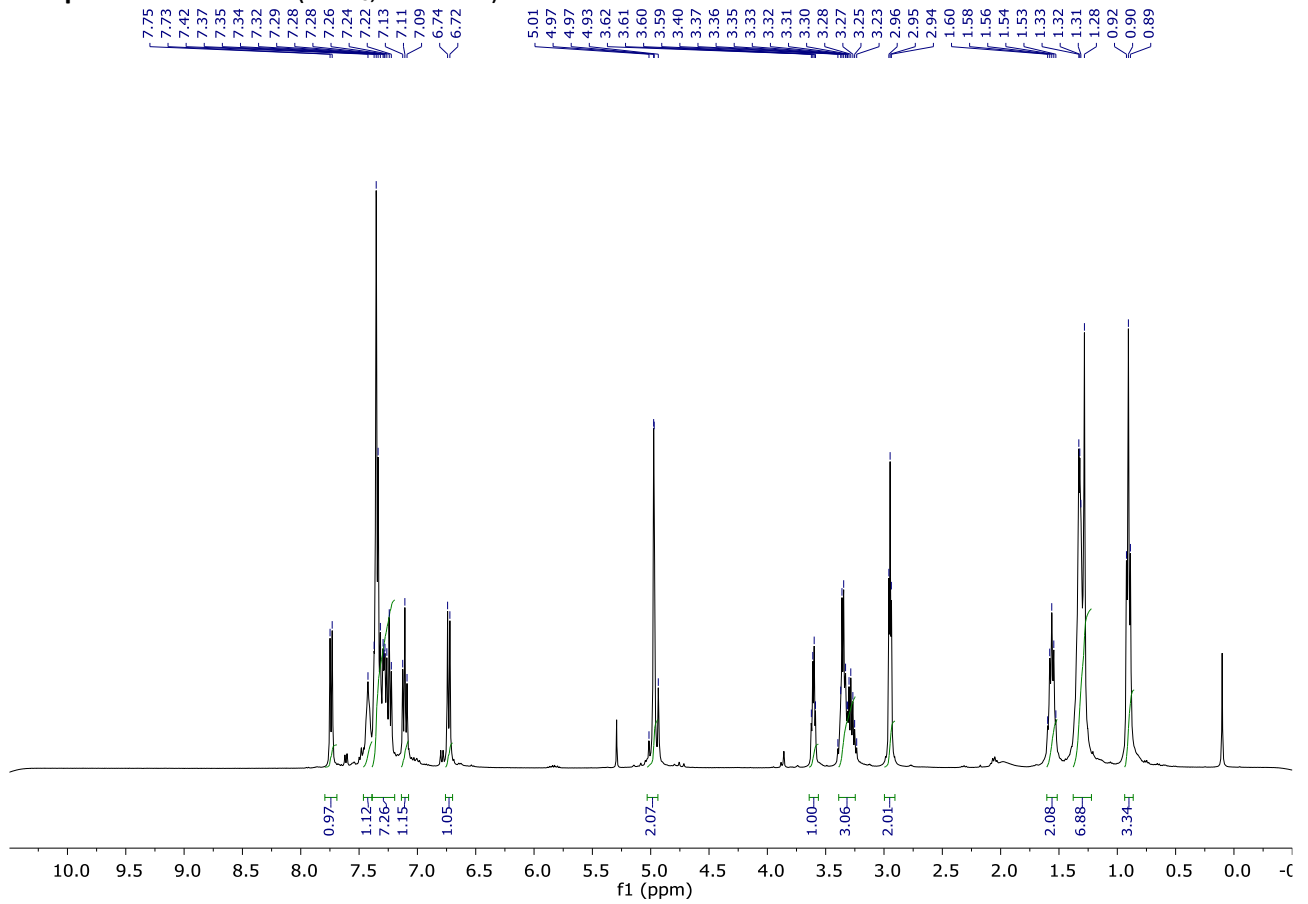
Compound 4m: ^1H NMR (CDCl_3 , 400 MHz)



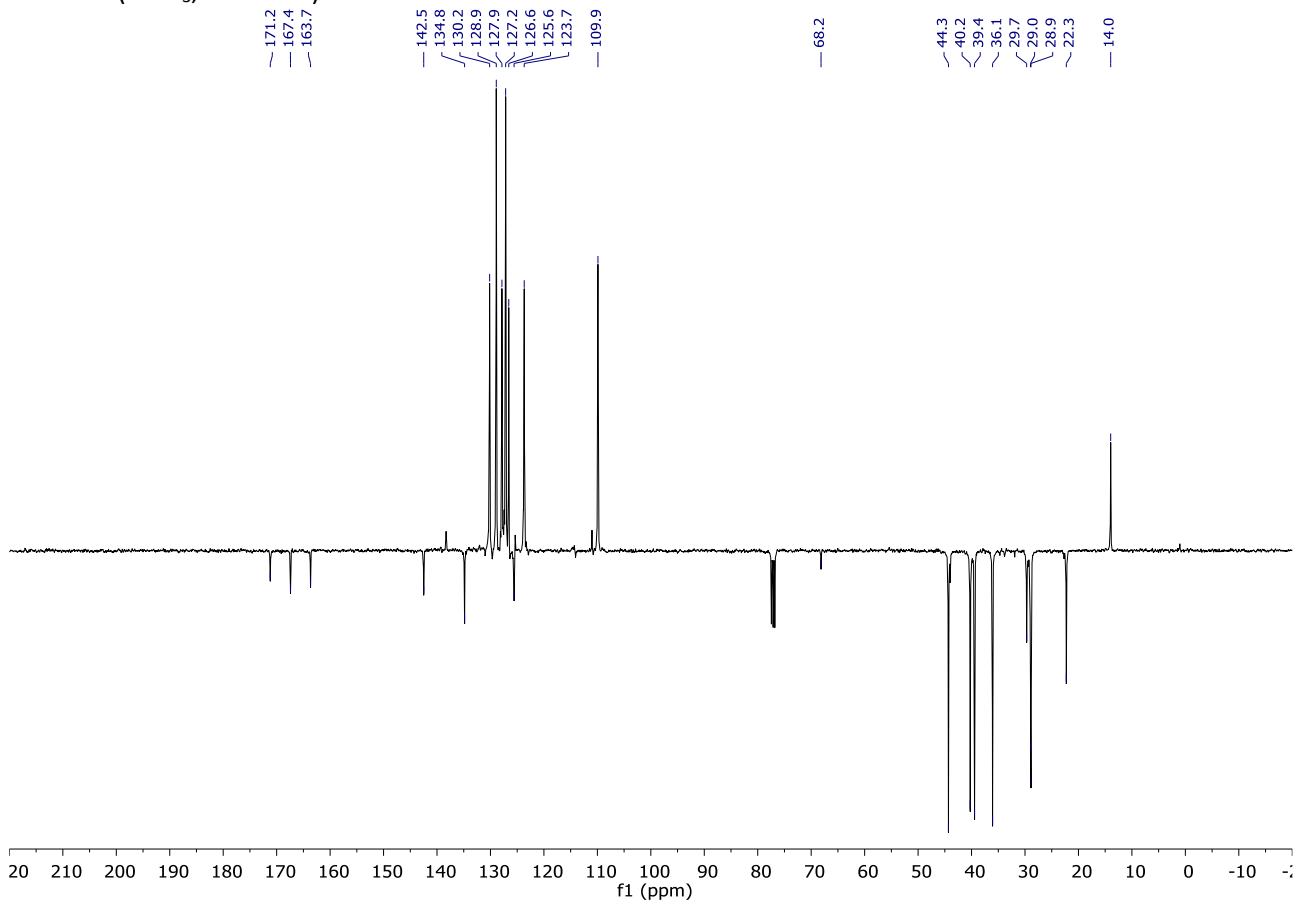
^{13}C NMR (CDCl_3 , 101 MHz)



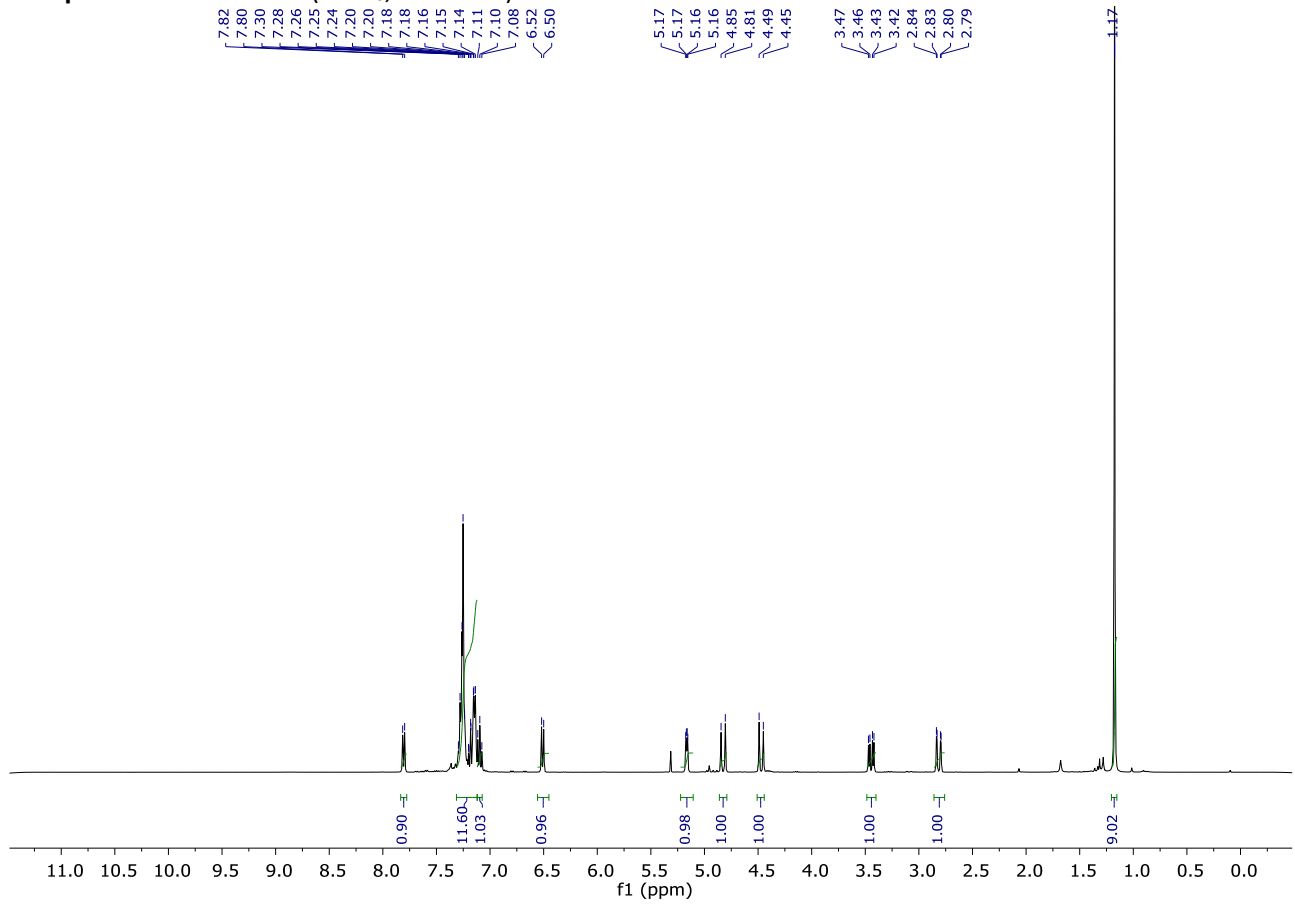
Compound 4n: ^1H NMR (CDCl_3 , 400 MHz)



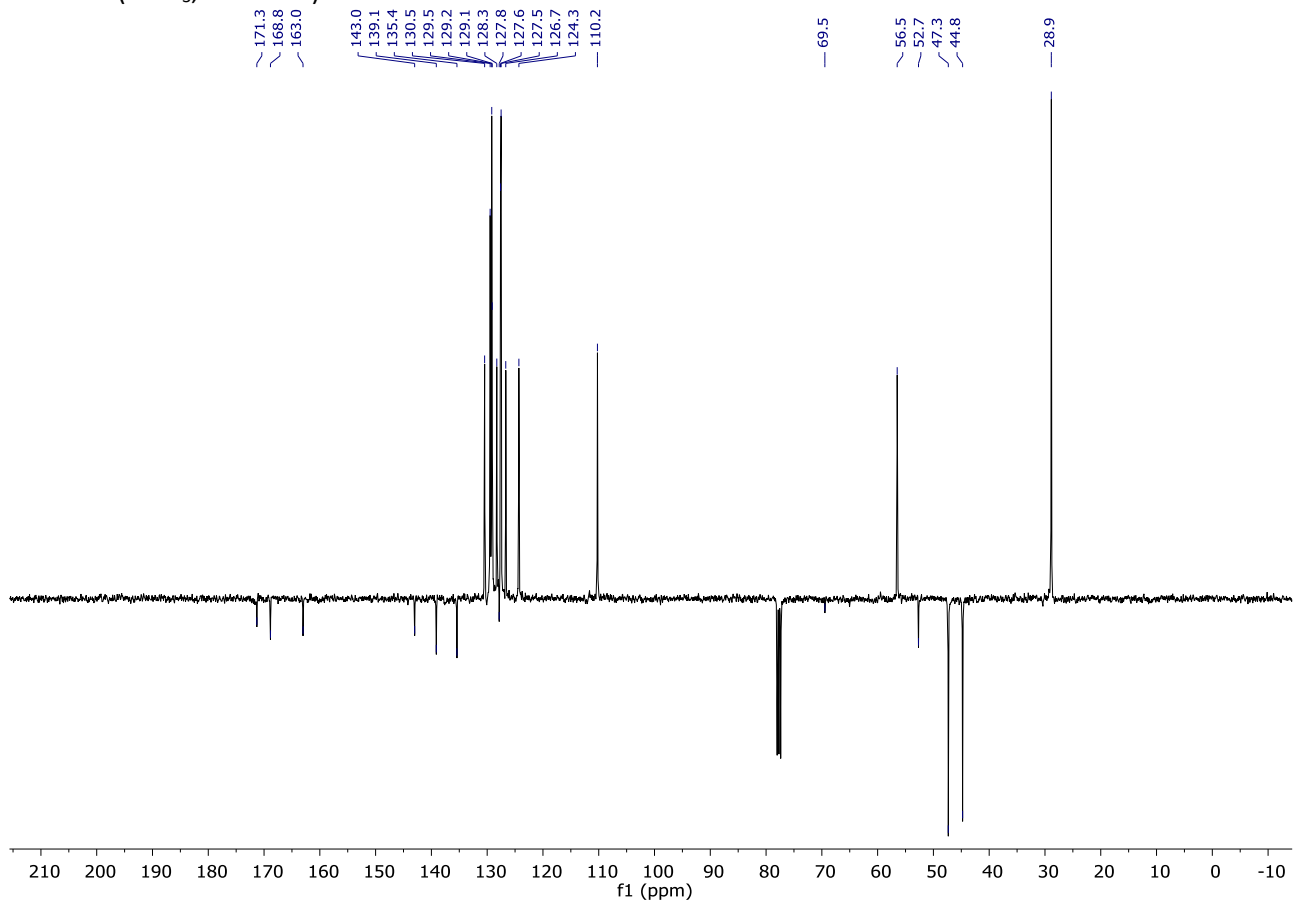
^{13}C NMR (CDCl_3 , 101 MHz)



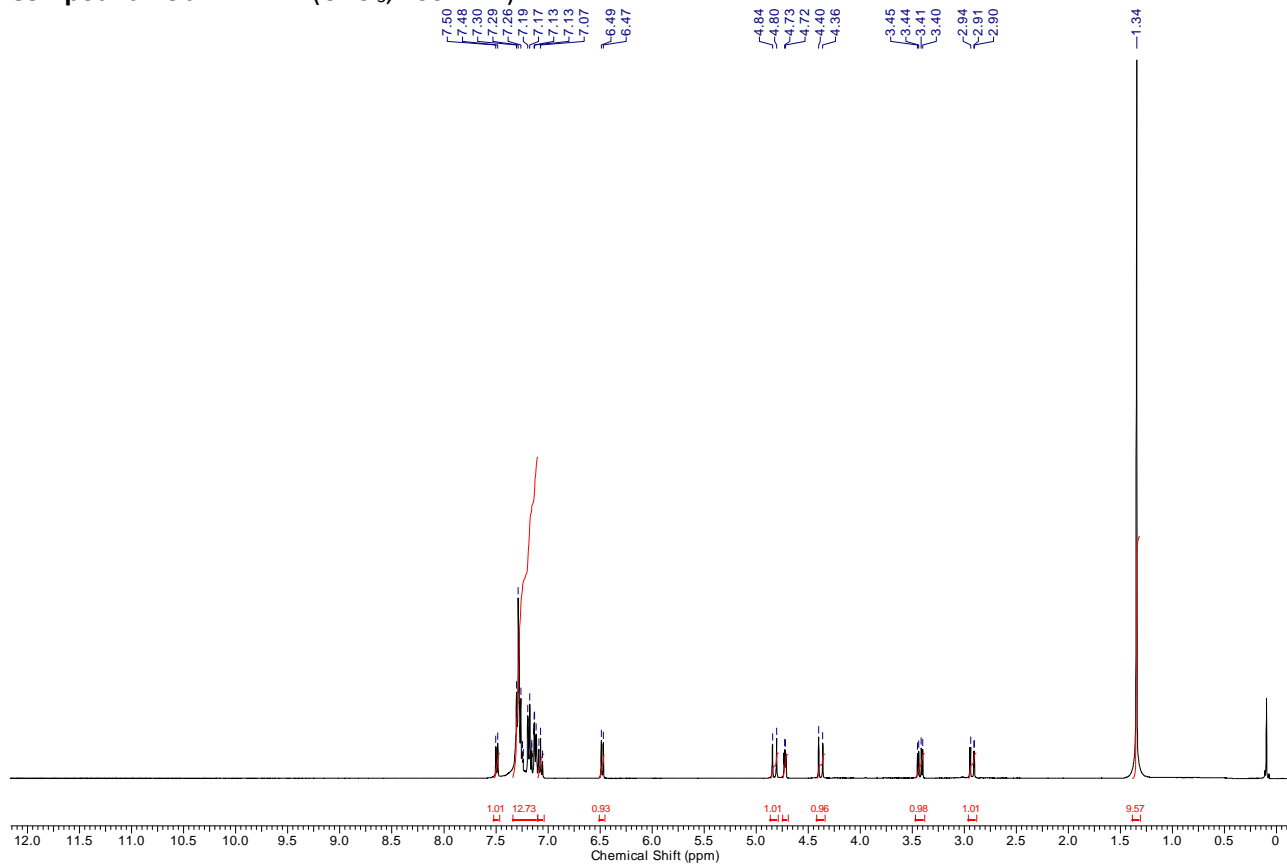
Compound 4oa: ^1H NMR (CDCl_3 , 400 MHz)



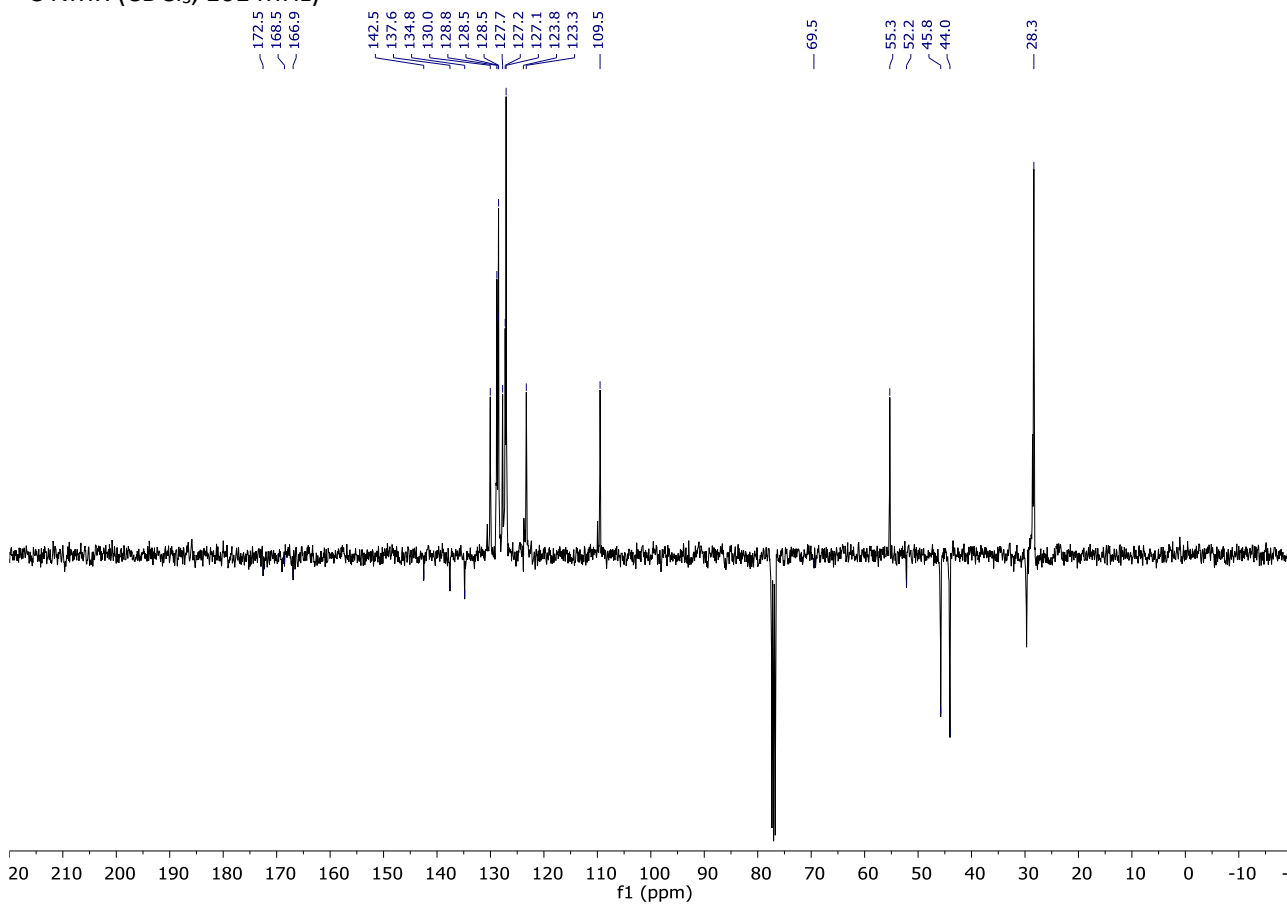
^{13}C NMR (CDCl_3 , 101 MHz)



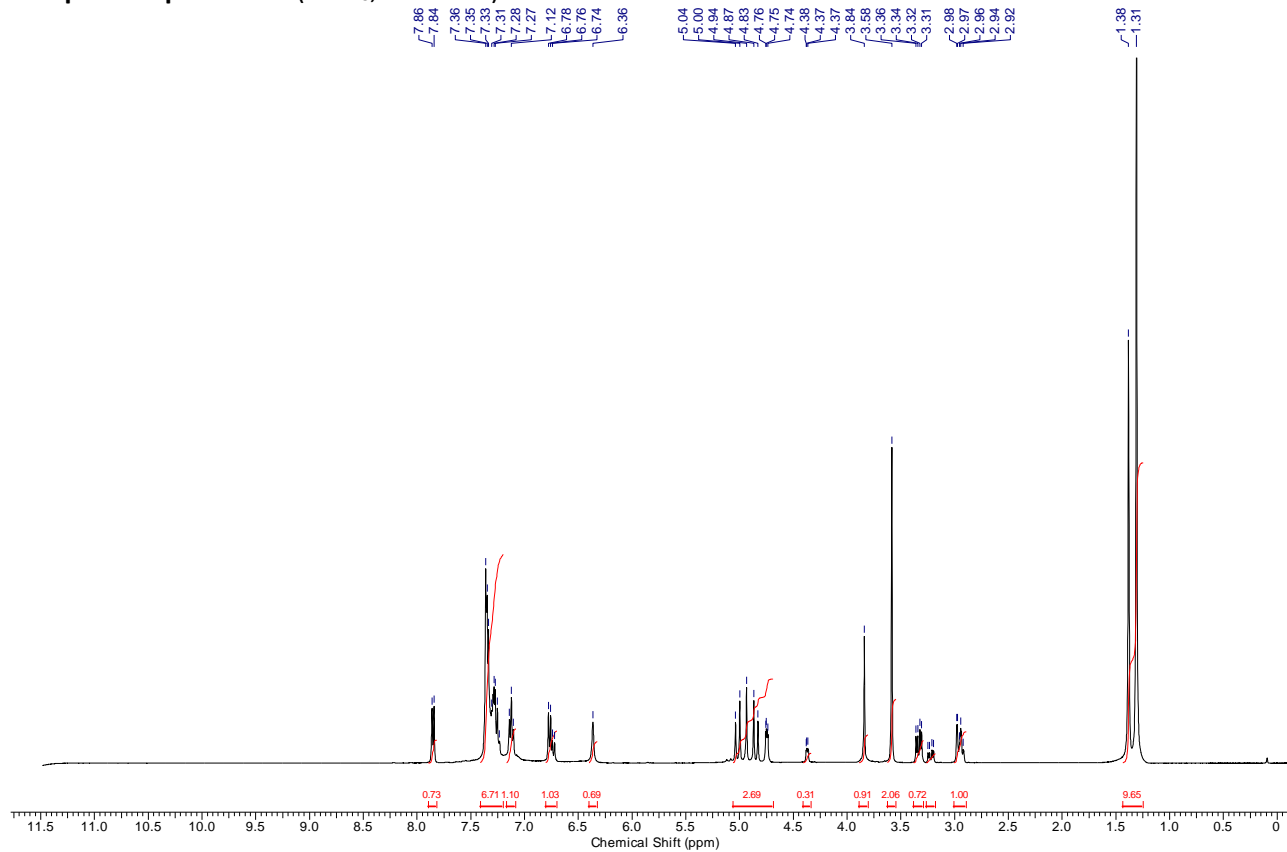
Compound 4ob: ¹H NMR (CDCl₃, 400 MHz)



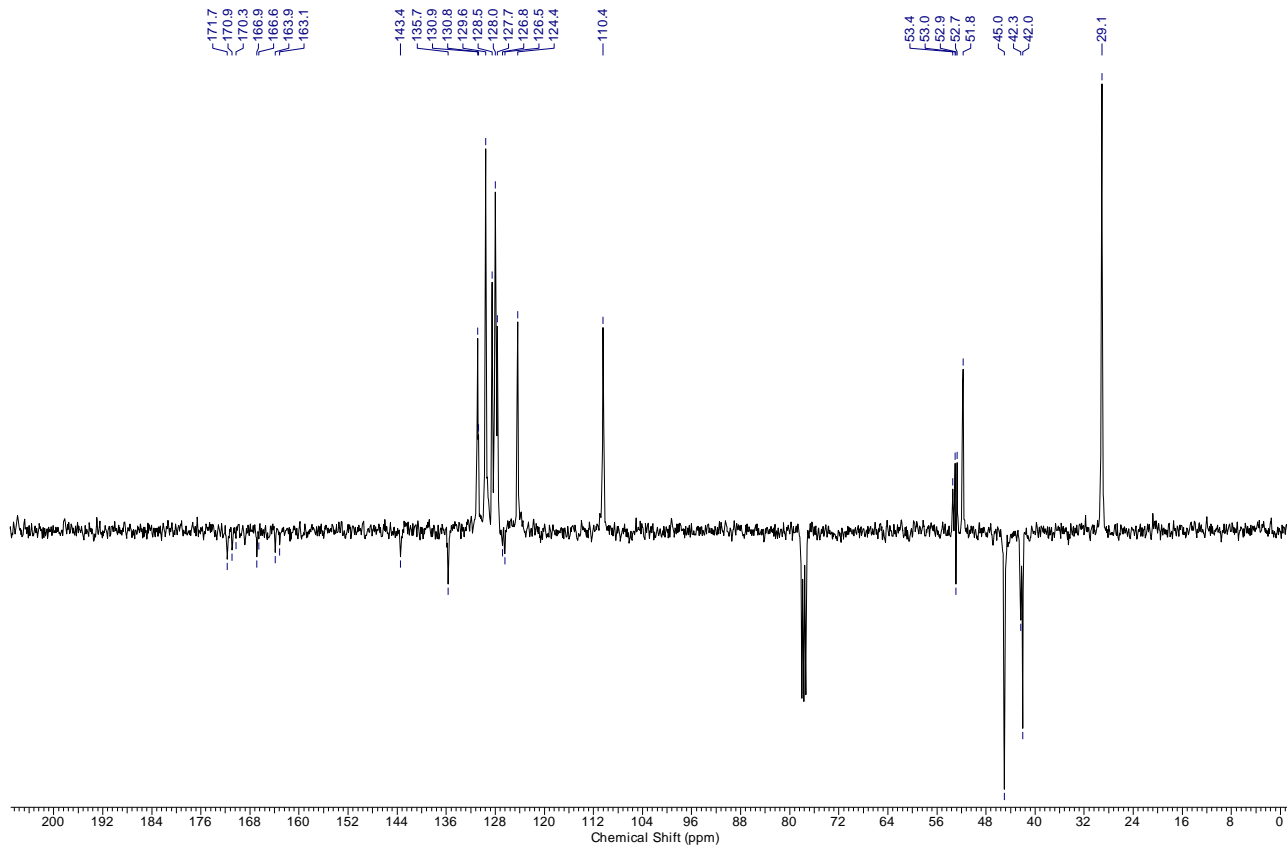
¹³C NMR (CDCl₃, 101 MHz)



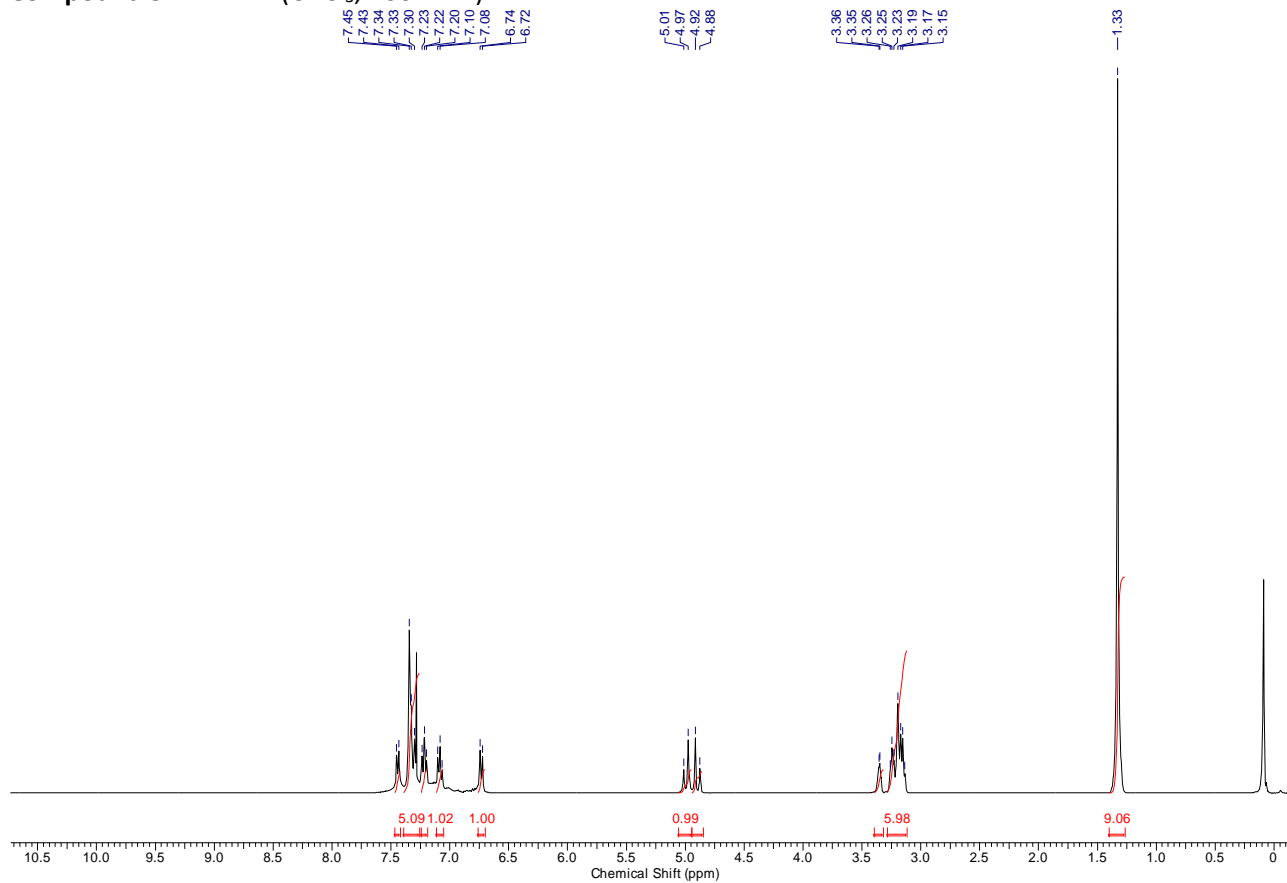
Compound 4p: ^1H NMR (CDCl_3 , 400 MHz)



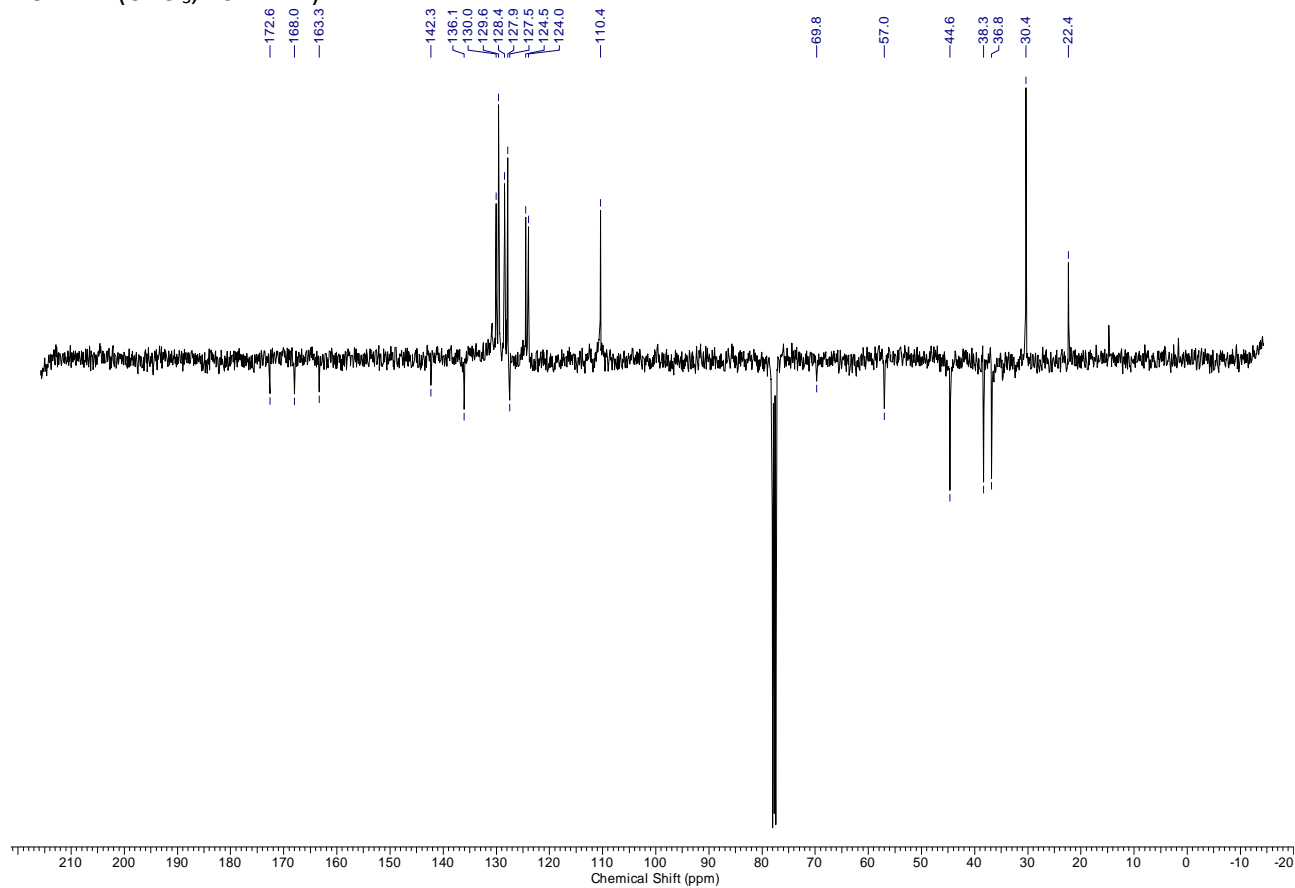
^{13}C NMR (CDCl_3 , 101 MHz)



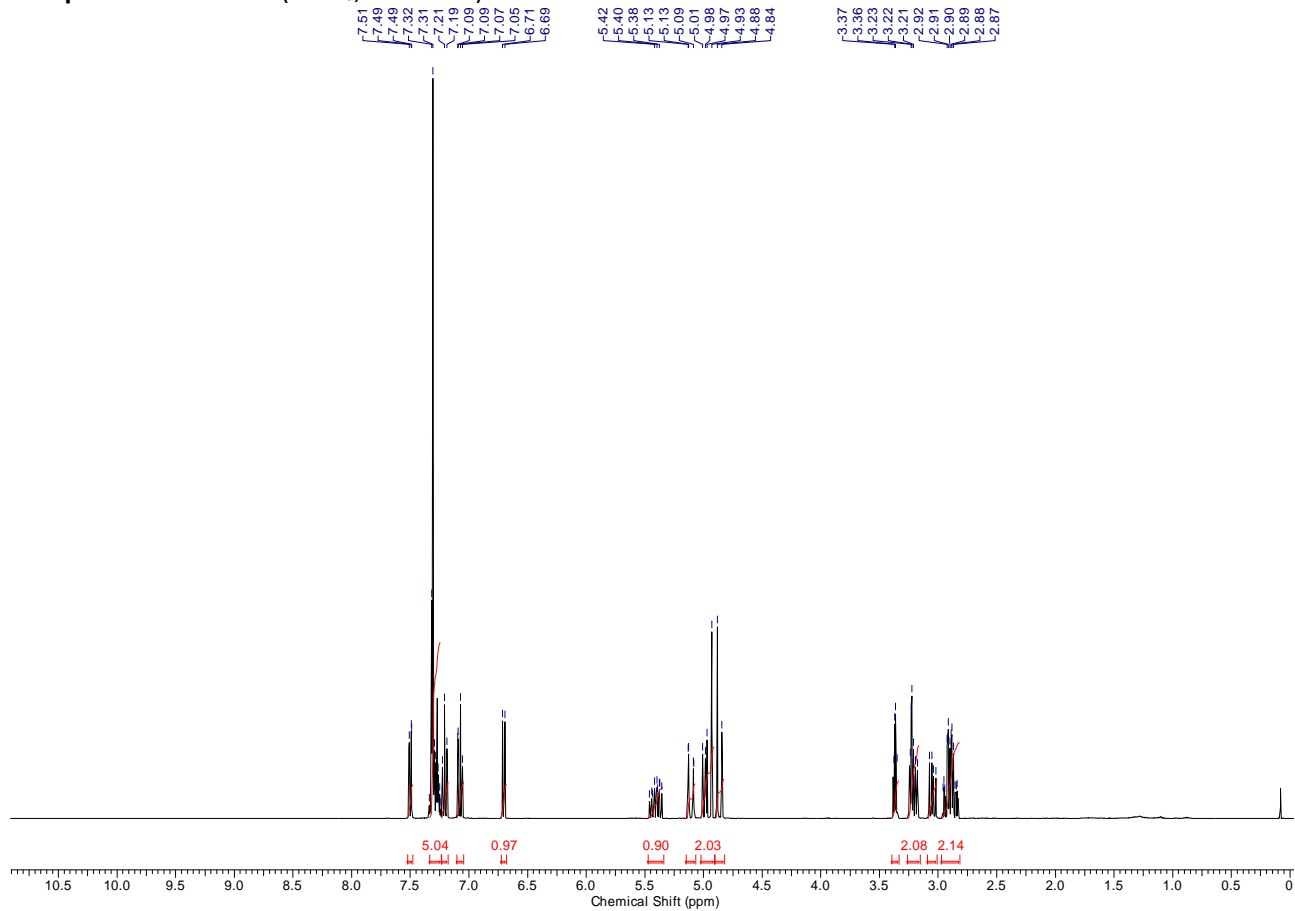
Compound 5: ^1H NMR (CDCl_3 , 400 MHz)



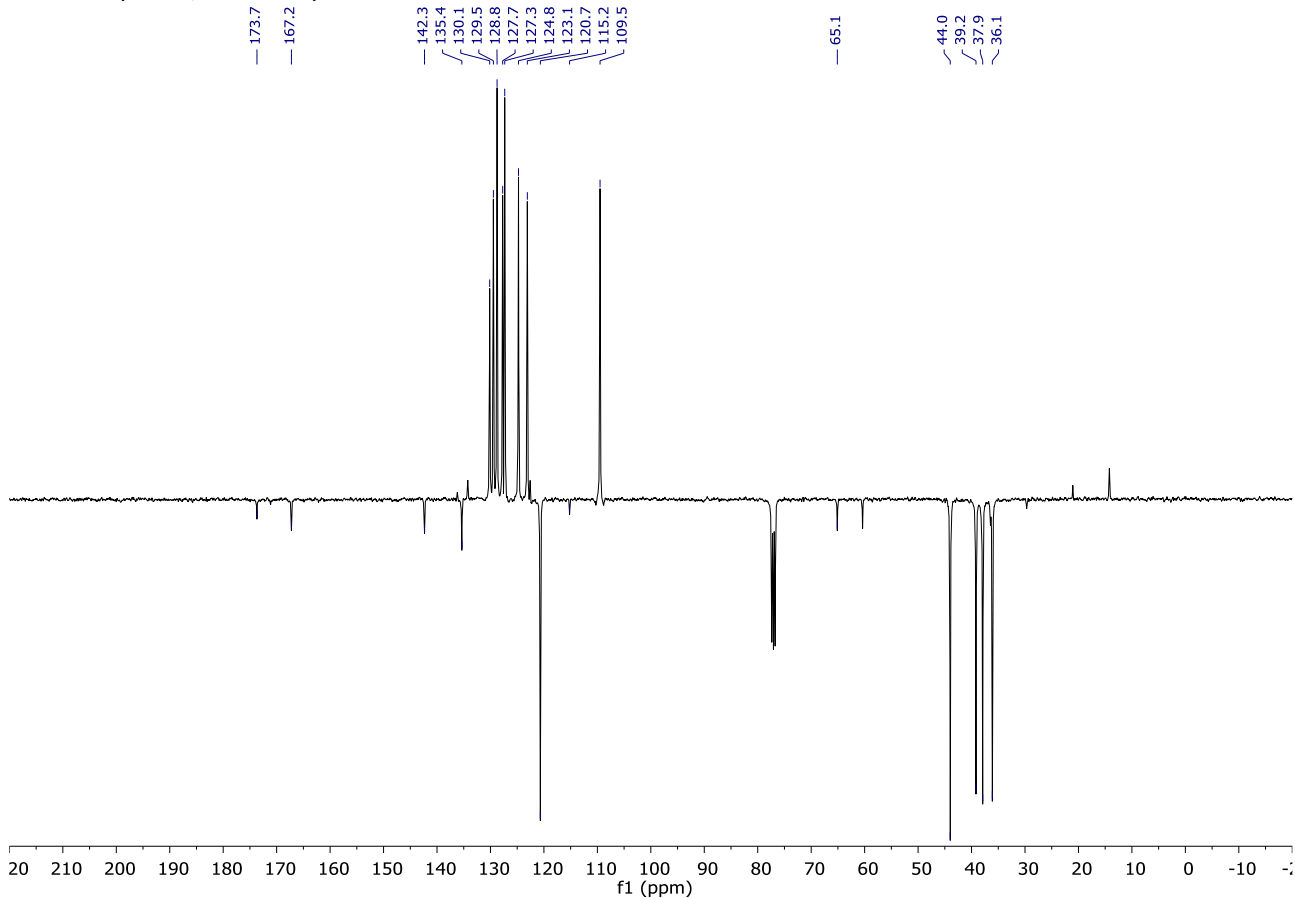
^{13}C NMR (CDCl_3 , 101 MHz)



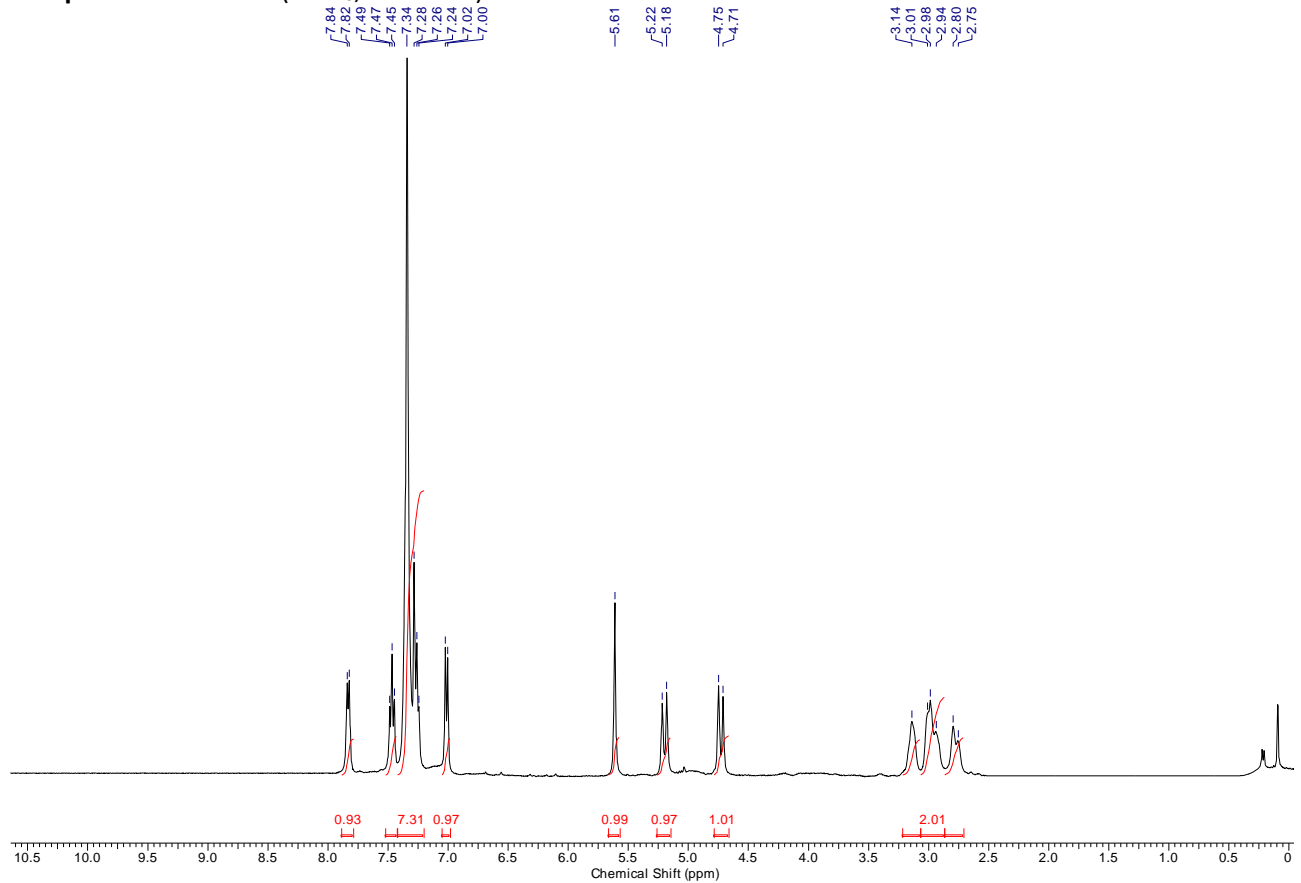
Compound 6: ^1H NMR (CDCl_3 , 400 MHz)



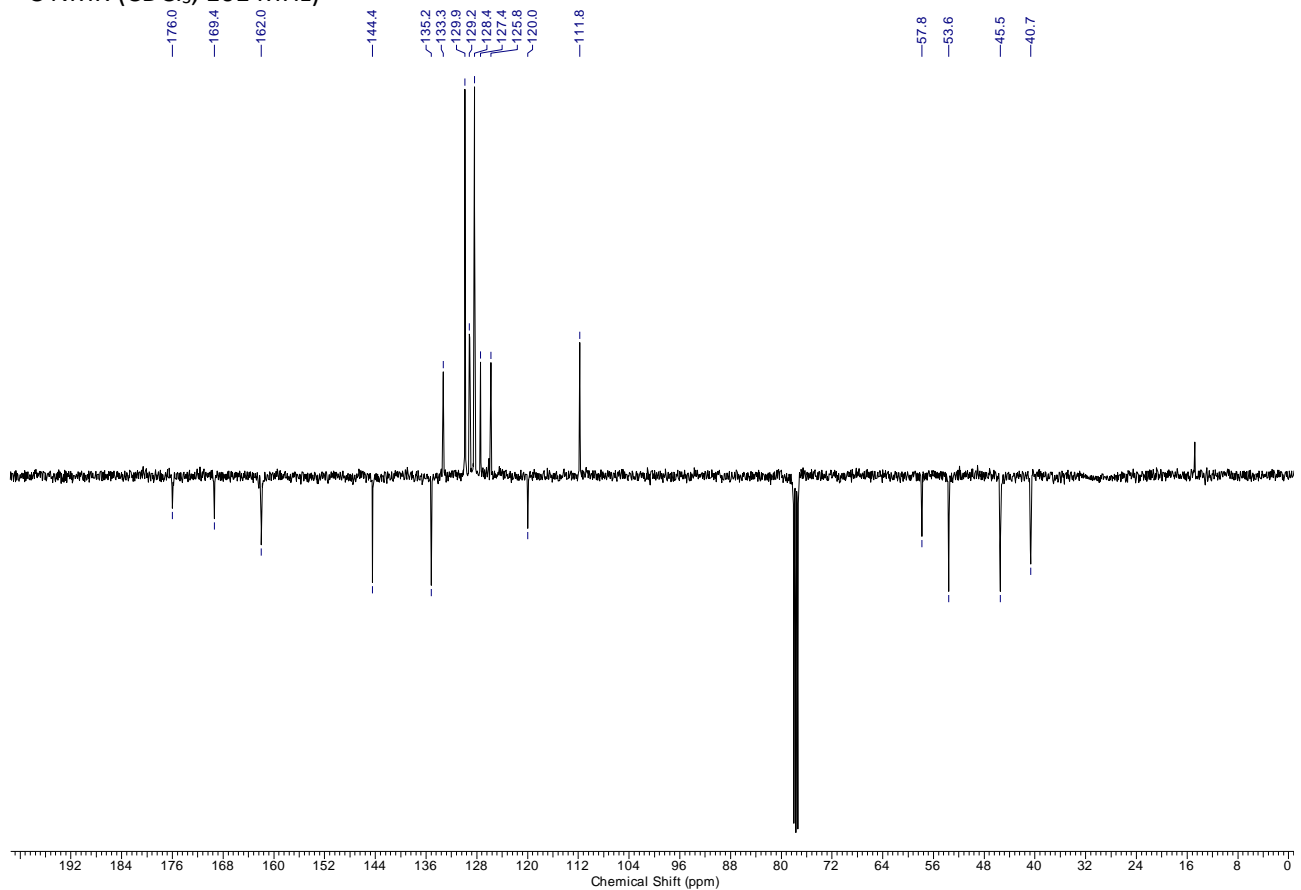
^{13}C NMR (CDCl_3 , 101 MHz)



Compound 7: ^1H NMR (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 101 MHz)



Single-crystal X-ray diffraction analysis report for sample 40a

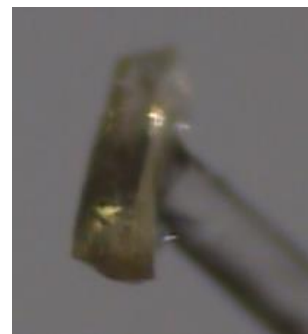
Material Appearance: yellowish prisms
Crystallization attempts: MeOH:*n*-hexane 1:1, in a glass tube
Time of the last crystallization: 3 days
Crystallization method: slow evaporation at RT

Sample specs:

Sample description: prism, yellow, transparent, with dimensions 0.375 x 0.175 x 0.125 mm.

Mounting: on a glass fiber, with a drop of perfluorinated oil.

Comments: The sample shows pleochroism from yellow to grey in polarized light. It was cut from a greater crystal using a thin needle and polished by mechanical ablation in a drop of perfluorinated oil.



Instrumental specs (see CCDC 1849730 for the full crystallographic information file):

Device: Bruker AXS Smart APEX 3-circle diffractometer

Source: normal focus sealed tube

Detector: APEX-II CCD

Experiment temperature: 298(2) K

Wavelength: graphite-monochromated Mo K α (0.71073 Å).

Data collection extent: full sphere within $\sin\theta/\lambda = 0.65 \text{ \AA}^{-1}$ (Cu-sphere)

Data collections specs: Detector-to-sample distance: 50 mm,

- ω -scan, $2\theta = \omega_i = 0 \text{ deg}$, ω -sweep 180 deg, $\Delta\omega = 0.25 \text{ deg}$, $t/\text{frame} = 30 \text{ s}$, 1 runs ($\phi = 0 \text{ deg}$)

- ω -scan, $2\theta = \omega_i = -30 \text{ deg}$, ω -sweep 180 deg, $\Delta\omega = 0.25 \text{ deg}$, $t/\text{frame} = 45 \text{ s}$, 4 runs ($\phi = 0, 90, 180, 270 \text{ deg}$).

Measured reflections: 39041 (not merged)

Symmetry-independent reflections: 5901, 3901 with $I > 2\sigma(I)$

Maximum resolution (2θ): 55 deg

Completeness: 100.0 %

Data reduction programs:

Integration: SAINT+

Reduction: SADABS, XPREP

Structure solution and refinement: shelxs (direct methods), shelxl

Unit cell, lattice and crystal system:

Bravais lattice: Orthorhombic, primitive

Space group: P2₁2₁2₁, n^o 19, acentric, chiral

Point group: 222 (D₂)

Laue group: mmm, number 3

Unit cell (Å, deg, Å³): a = 8.8838(18), b = 13.895(3), c = 20.744(4), V = 2560.7(9) as estimated from 3443 intense reflections among 4.9 e 35.2 deg of 2θ (final integration result).

Formula units in cell (Z): 4

Formula units in the asymmetric unit (Z'): 1

Number of electrons in cell (F₀₀₀): 992

Computed density: 1.213 g/cm³

Linear absorption coefficient (μ): 0.079 mm⁻¹

Main statistical results:

Final stats for the spherical atom model (shelxl):

Scale factor: 0.1821(8)

$\langle \Delta/\sigma \rangle = 0.000$

$R_1(F) = 0.0591$ for $3901 F_o > 4\sigma(F_o)$, 0.0885 for all the independent data

$wR(F^2) = 0.1952$ for all the measured data

Goodness-of-fit: 1.017

Flack's parameter: Not meaningful

$\Delta\rho_{\text{MAX}/\text{MIN}} = +0.30 / -0.24 \text{ e}/\text{\AA}^3$

Molecular schemes^{S1}

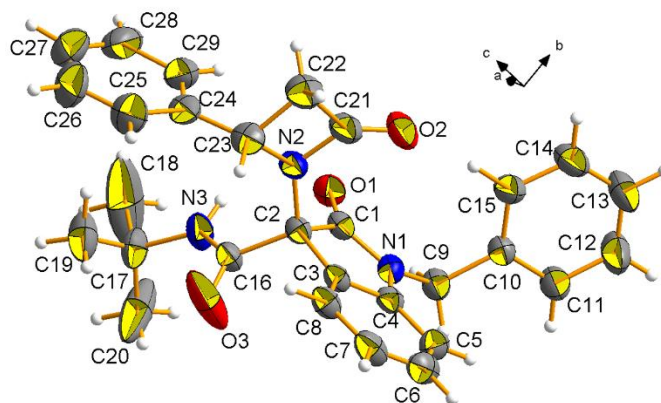


Figure S1. Asymmetric unit of **4oa**, with the atom-numbering scheme. Thermal ellipsoids of non-H atoms at RT were drawn at the 30 % probability level. The usual colour code was employed to draw atoms (grey: C; white: H; blue: N; red: O).

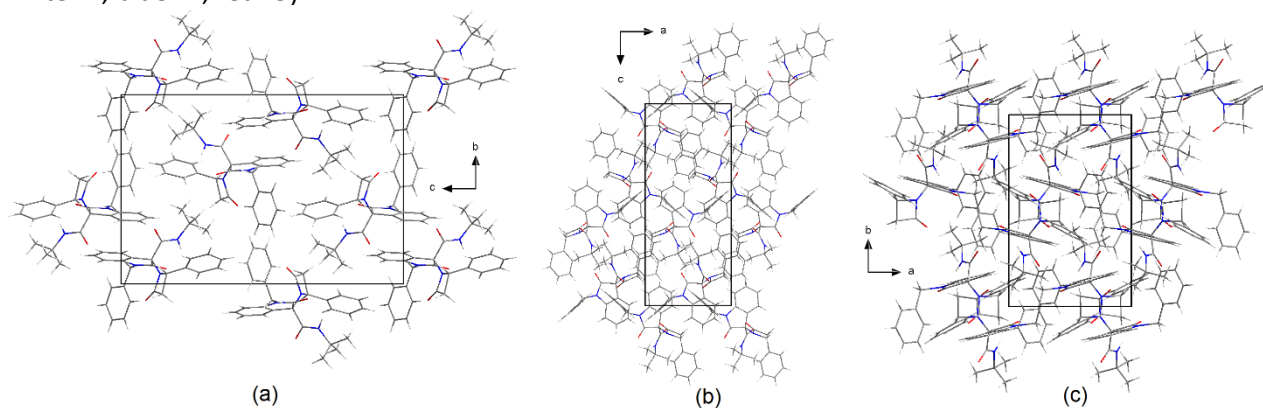


Figure S2. Wires-stick representation of the crystal packing of **4oa**, as seen (a) along the *a* cell axis; (b) the *b* cell axis; (c) the *c* cell axis. Colour code as in Figure S1.

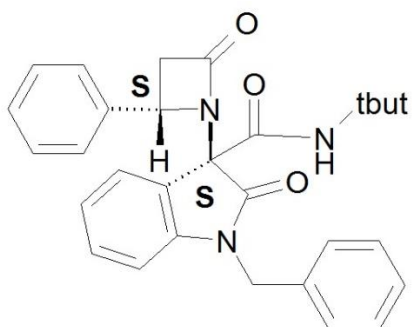


Figure S3. Molecular structure of one enantiomer of **4oa**, with the Cahn-Ingold-Prelog descriptors highlighted.

Compound **4oa** is enantiopure and crystallizes in the acentric chiral space group $P2_12_12_1$ with one molecule per asymmetric unit. Figures S1 and S3 show the absolute configuration of the chiral centres. The relative configuration was unequivocally determined by the X-ray diffraction experiment; the following configurational descriptors are assigned to the stereogenic centres C2 (S) and C23 (S). Due to the lack of anomalous scatterers, the present wavelength does not allow to unequivocally determine the absolute configuration. However, the enantiomer has been assigned by reference to an unchanging chiral centre (C23(S)) in the synthetic procedure.

4oa has several bulky terminal substituents that are involved in low-frequency internal librational motions. More in detail, C16 and C17 belong to a terminal t-butyl group, which likely bears some amount of librational disorder at room temperature. Also, the phenyl rings are probably involved in quite large librations around their C23–C24 and C9–C10 axes. Data collections at lower temperatures are required to improve the description of the thermal parameters of these groups.

Figure S2 shows the main packing motifs of **4oa**. The only possible hydrogen bond (HB) donor is the amide N3-H3 group, which is involved in an intramolecular HB contact with the O1 carbonyl (Table S1). No extended HB networks are thus formed in this structure, whose packing seems to be mainly dictated by steric requirements. More in details, neighbouring layers of roughly parallel indole rings are formed orthogonal to the (*a*,*b*) plane (Figure S2c), and bulky phenyl rings are allocated in the free space between them.

The β -lactam ring is very close to be completely planar. A very small puckering amplitude of $Q(2) = +0.070$ Å according to Cremer & Pople^{S2} was detected. This results in a slight displacement (0.0327(1) Å) of the C23 corner atom from the least squares plane of the 4-membered ring.

Table S1. Geometric parameters for the intramolecular hydrogen-bonded contacts N3-H3...O1 in **4oa** at room temperature. Values in Å e deg, with sensible standard deviations reported in parentheses.

D-H...A	D-H	H...A	D...A	D-H...A	Symmetry operation
N3-H3...O1	0.86	2.267	2.900(4)	130.5(2)	x, y, z

Table S2. Calculated physicochemical properties of all synthesized compounds using DruLito.^{S3}

Title	MW	logP	AlogP	HBA	HBD	TPSA	AMR	nRB	nAtom	nAcid Group	RC	nRigid Bond	SAlerts	nArom Ring	nHB
4a.mol	391	1.4	0.871	6	1	69.72	116.9	6	54	0	4	26	2	2	7
4b.mol	469	1.6	1.324	6	1	69.72	124.43	6	54	0	4	27	2	2	7
4c.mol	436	1.0	1.084	6	1	112.86	120.12	7	56	0	4	28	2	7	4
4d.mol	301	0.6	-0.348	6	2	78.51	82.45	4	41	0	3	20	2	1	8
4e.mol	315	0.3	-0.246	6	1	69.72	88.15	4	44	0	3	21	2	1	7
4f.mol	343	1.2	-0.296	6	1	69.72	97.65	5	50	0	3	22	2	1	7
4g.mol	421	1.5	0.372	7	1	78.95	123.54	7	58	0	4	27	2	2	8
4h.mol	469	2.0	1.324	6	1	69.72	124.43	6	54	0	4	27	2	2	7
4i.mol	436	1.4	1.084	6	1	112.86	120.12	7	56	0	4	28	4	2	7
4j.mol	425	1.8	1.24	6	1	69.72	121.62	6	54	0	4	27	2	2	7
4k.mol	478	1.4	0.196	7	2	81.75	147.27	8	62	0	6	33	2	4	9
4l.mol	433	2.5	1.988	6	1	69.72	130.29	7	63	0	4	28	2	2	7
4m.mol	417	1.5	-1.653	6	1	69.72	115.36	6	58	0	5	29	2	7	2
4n.mol	405	2.1	-0.964	6	1	69.72	116.75	9	57	0	4	24	2	7	3
4o.mol	467	2.6	2.017	6	1	69.72	145.32	7	64	0	5	32	3	7	2
4p.mol	463	1.3	0.855	8	1	96.02	132.12	9	63	0	4	28	2	9	4
5.mol	405	1	0.973	6	0	60.93	122.6	6	57	0	4	27	2	2	6
6.mol	332	1	1.242	4	0	40.62	104.97	5	45	0	4	23	2	2	4
7.mol	335	0	-0.163	6	1	83.71	97.4	4	42	0	4	24	2	2	7

MW: molecular weight; log P: compound's hydrophilicity; Alog P: Ghose-Crippen-Viswanadhan octanol-water partition coefficient; HBA: hydrogen bonding acceptor; HBD: hydrogen bonding donor; TPSA: the polar surface area prediction; AMR: molecular refractivity, nRB: number of rotational bonds; nAtom: number of atoms; nAcidicGroup: number of acidic groups; RC: rotational bond count; nRigidBond: number of rigid bonds; SAlerts: structure alerts; nAromRing: number of aromatic rings; nHB: number of hydrogen bonds.

References

(S1) All the crystallographic images in this work were drawn with Diamond 3.2k, (c) 1997–2014 Crystal Impact GbR, Bonn, Germany – Author: Klaus Branderburg

(S2) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.*, **1975**, *97*, 1354-1358.

(S3) DruLiTo, http://www.niper.gov.in/pi_dev_tools/DruLiToWeb/DruLiTo_index.html