

Synthesis of Functionalised 2,3-Dihydroquinolin-4(1H)-ones vs. Quinoline or N-Alkenylindole Derivatives through Sequential Reactions of 2-Alkynylanilines with Ketones

Vincenzo Marsicano,^a Antonio Arcadi,^{*a} Marco Chiarini,^b Giancarlo Fabrizi,^c Antonella Goggiamani,^c and Antonia Iazzetti.^c

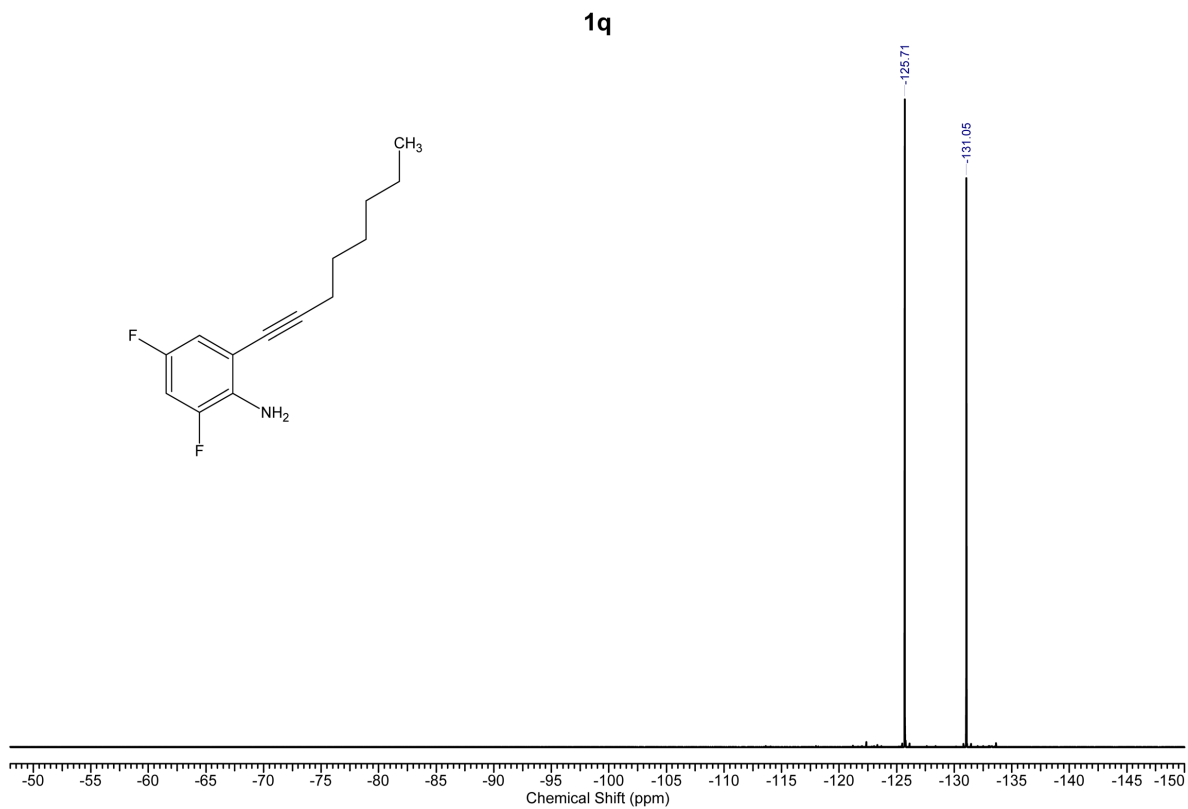
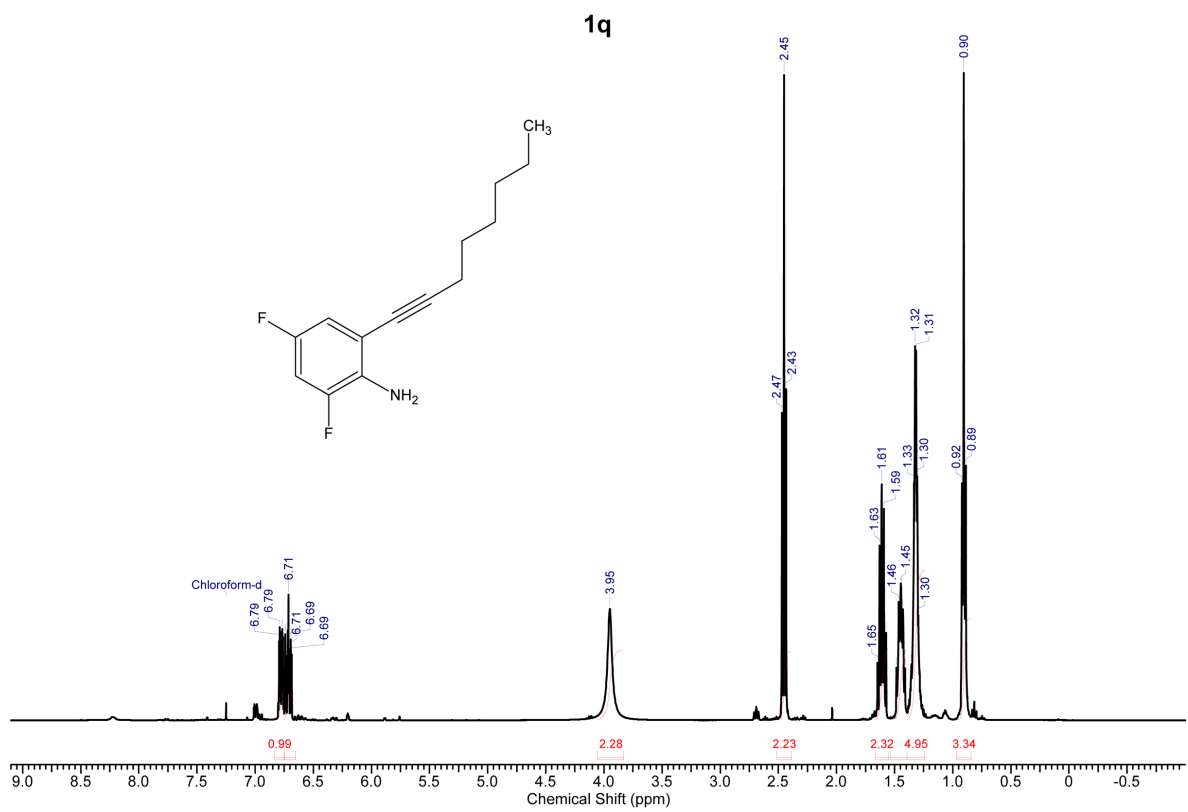
^a *Dipartimento di Scienze Fisiche e Chimiche Università degli Studi di L'Aquila; Via Vetoio, 67100 Coppito (AQ), Italy*

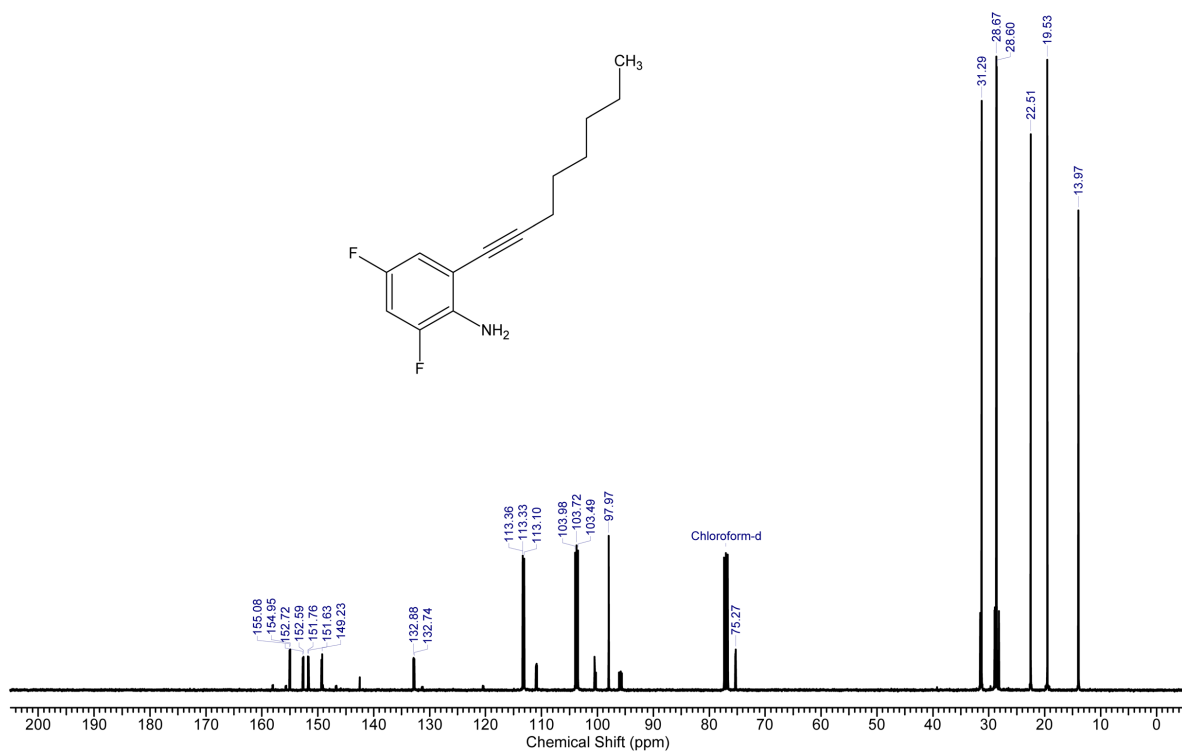
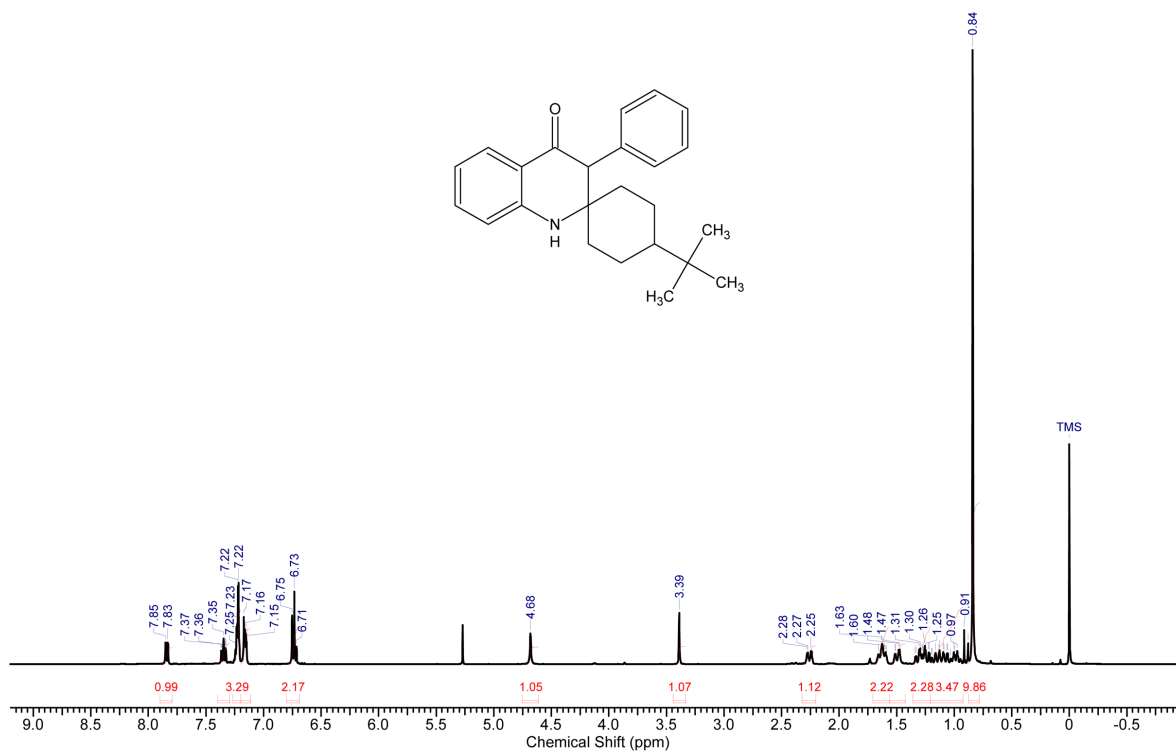
^b *Facoltà di Bioscienze e Tecnologie Agro-alimentari e Ambientali, Università di Teramo, Via Balzarini 1, 64100 Teramo (TE), Italy*

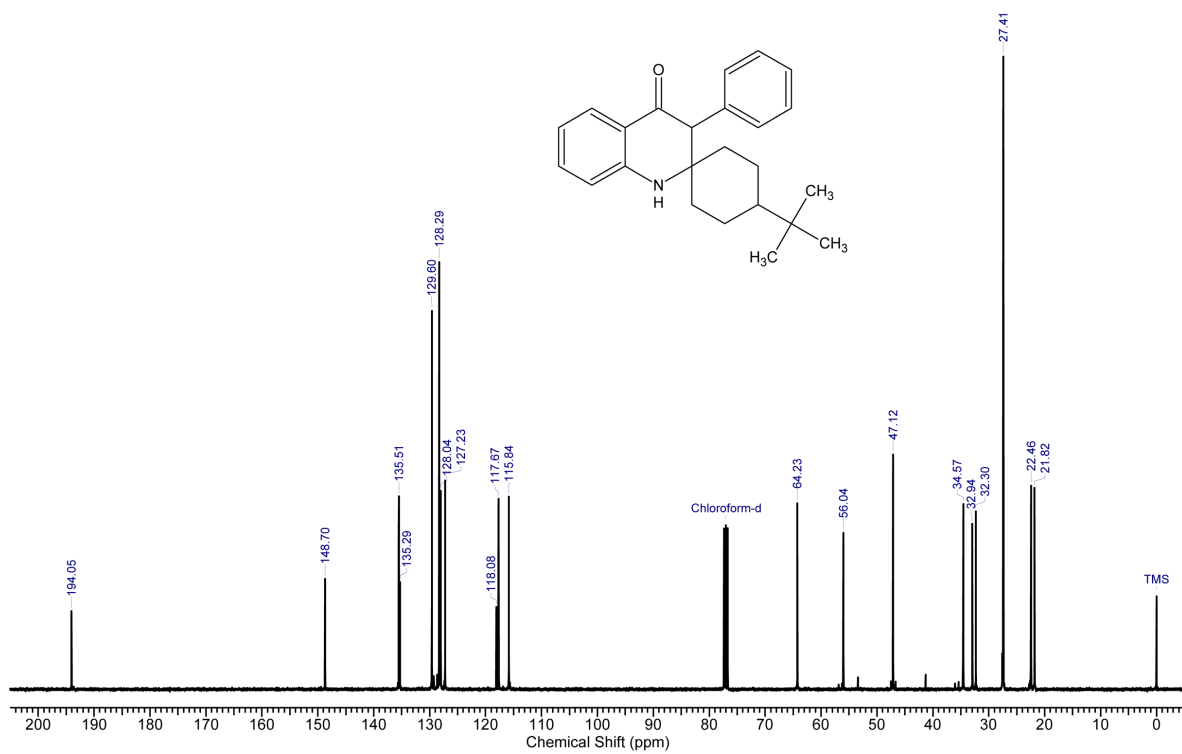
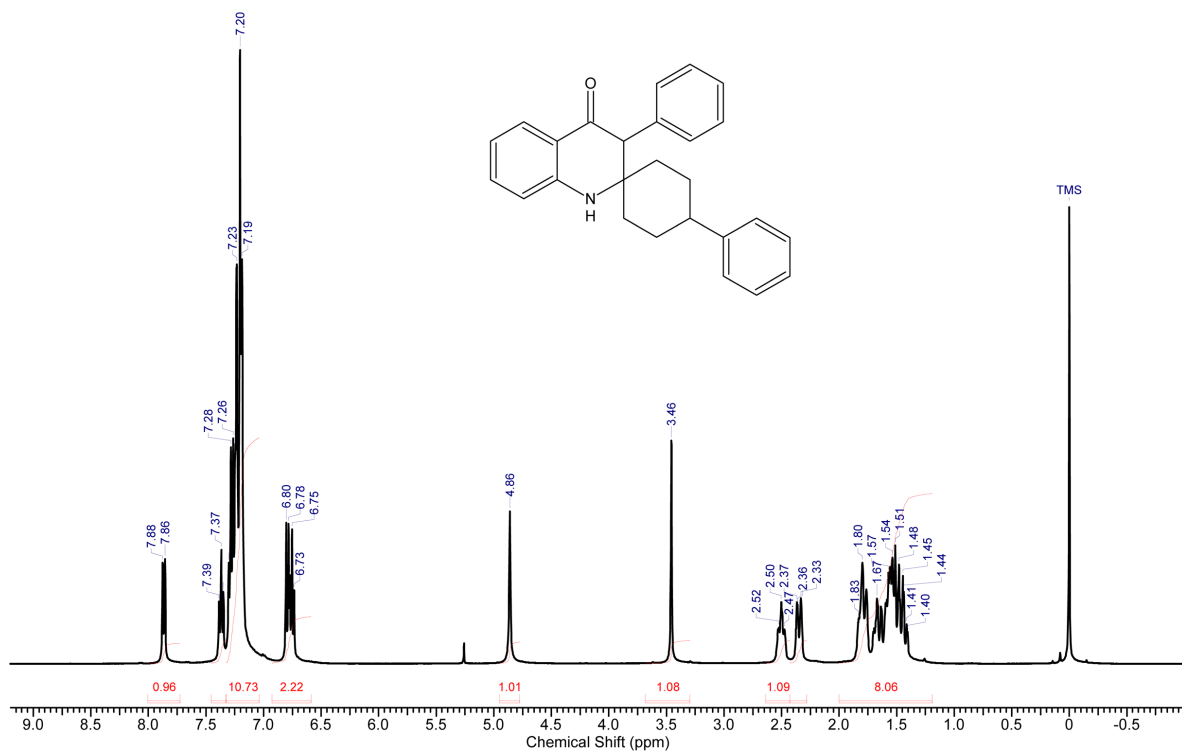
^c *Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza, Università di Roma, P.le A. Moro 5, 00185 Roma, Italy.*

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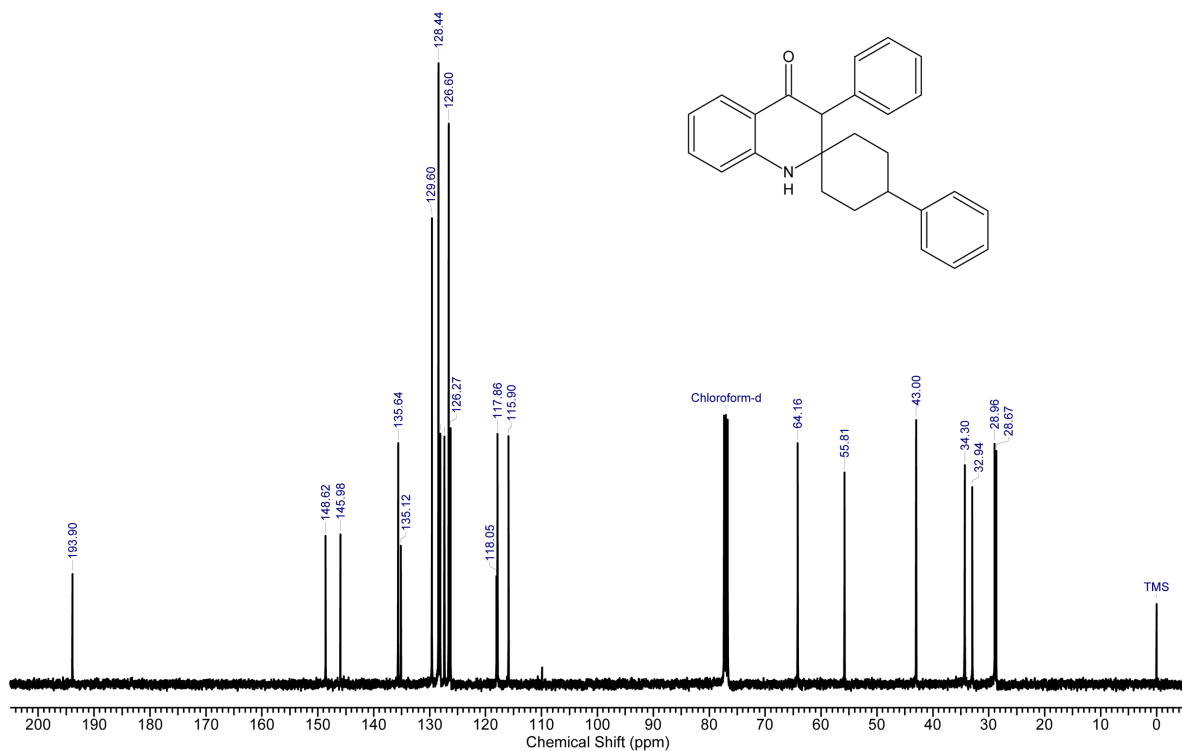
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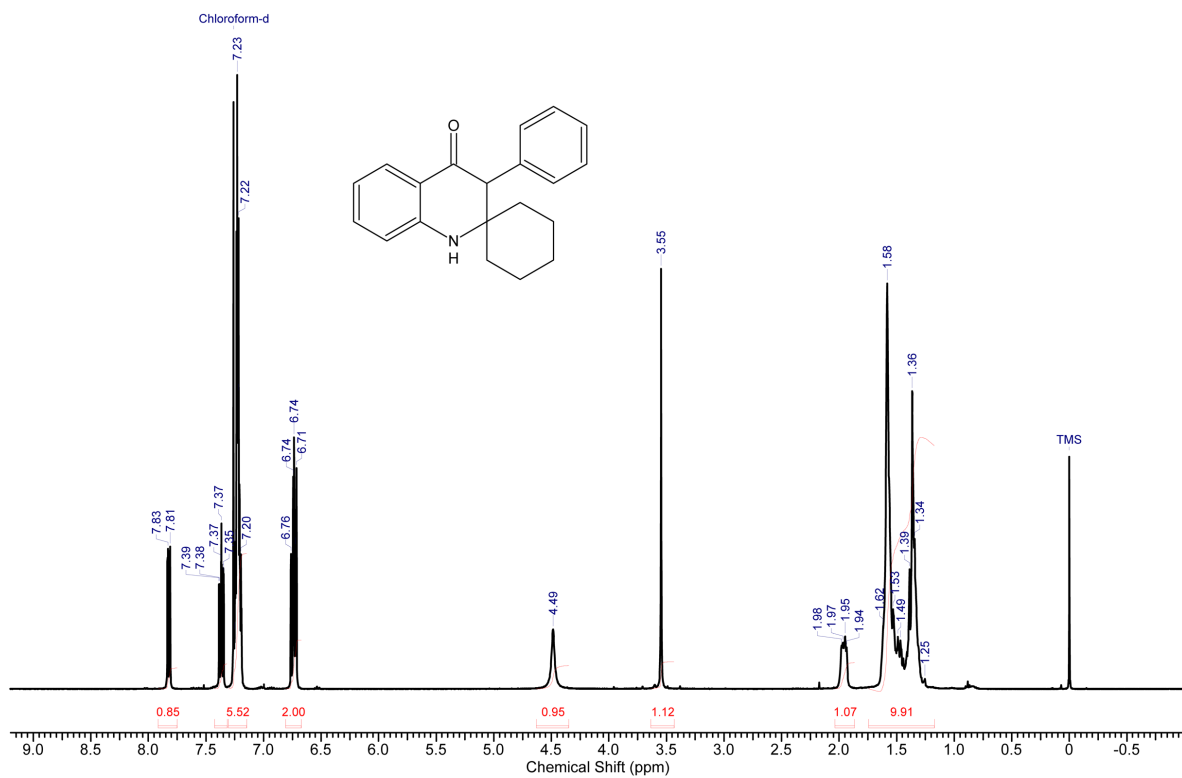
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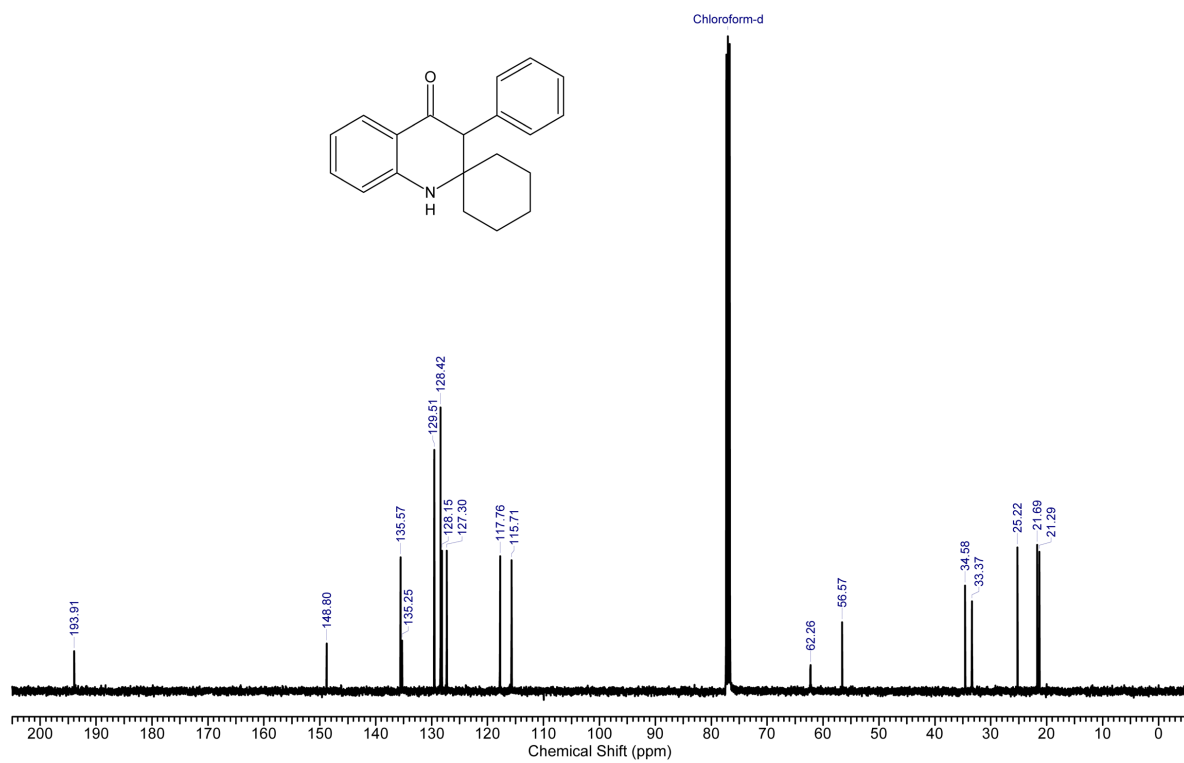
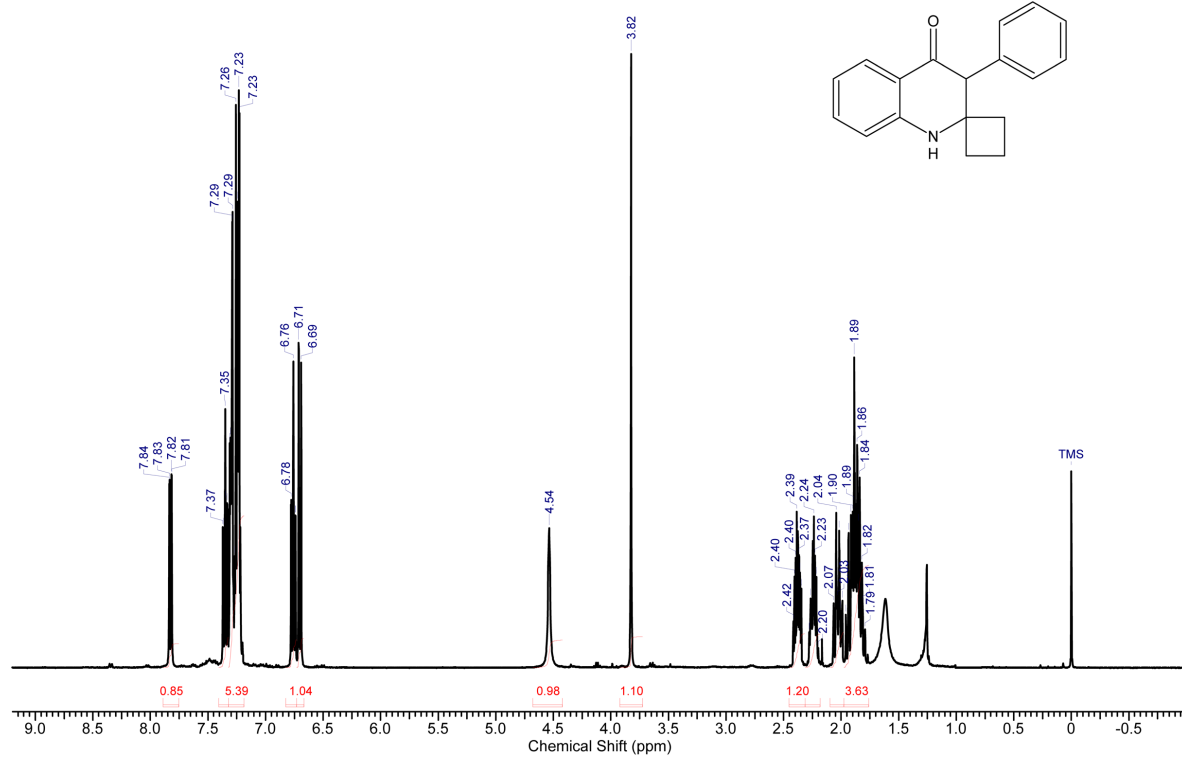
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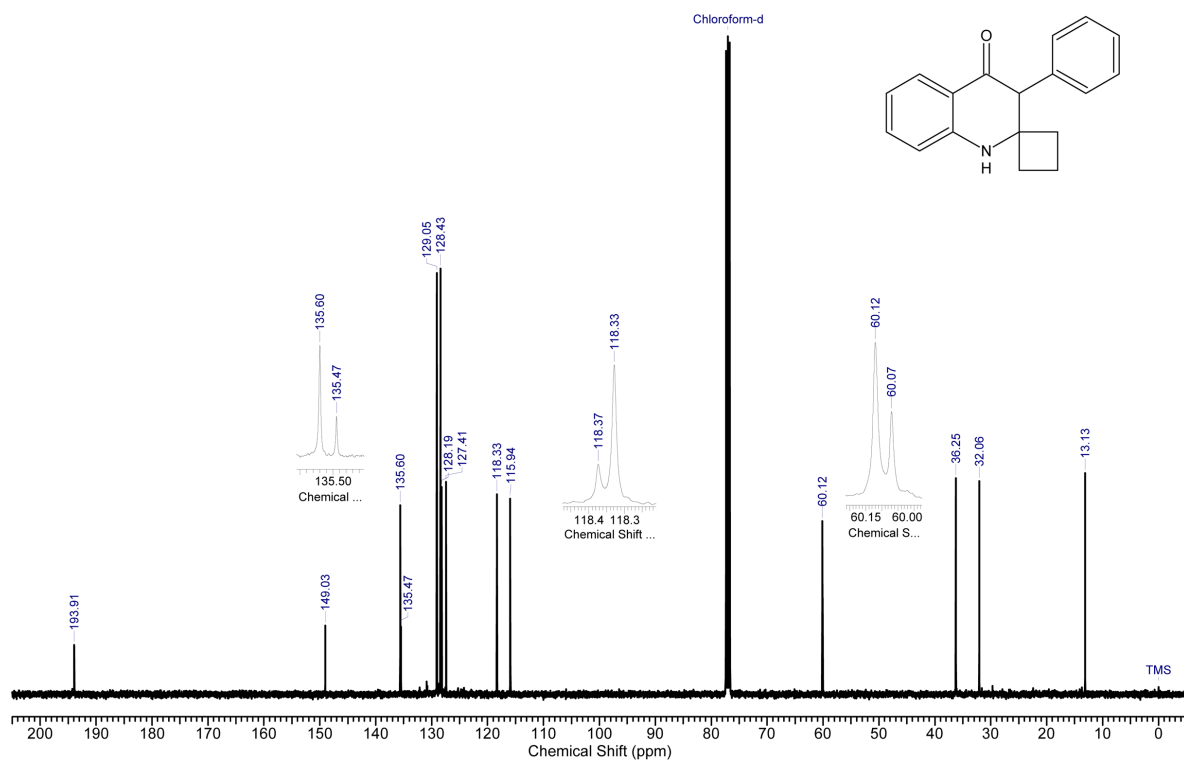


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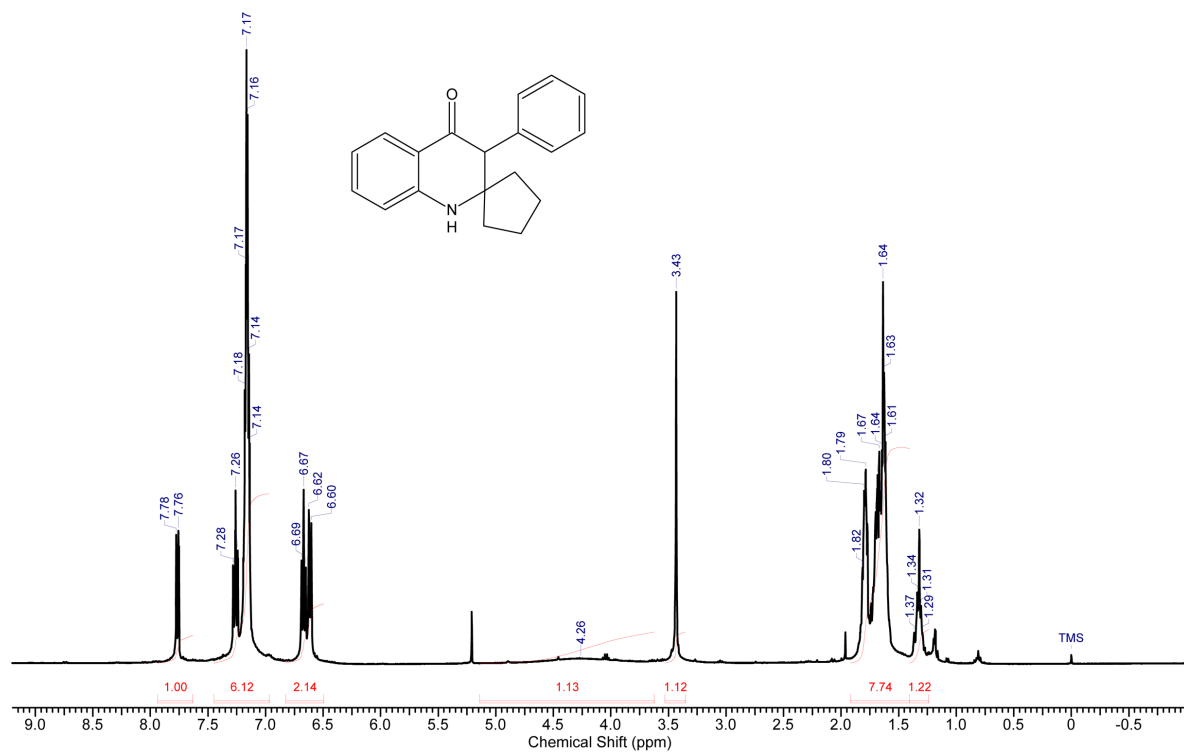


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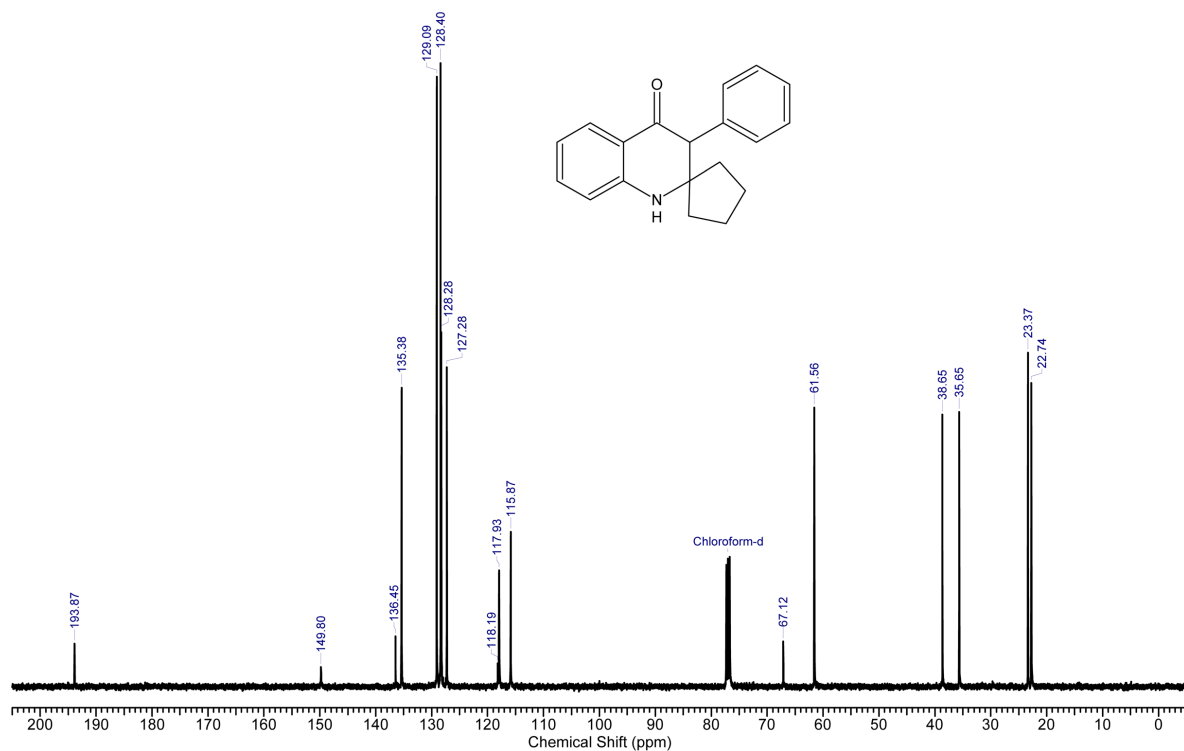
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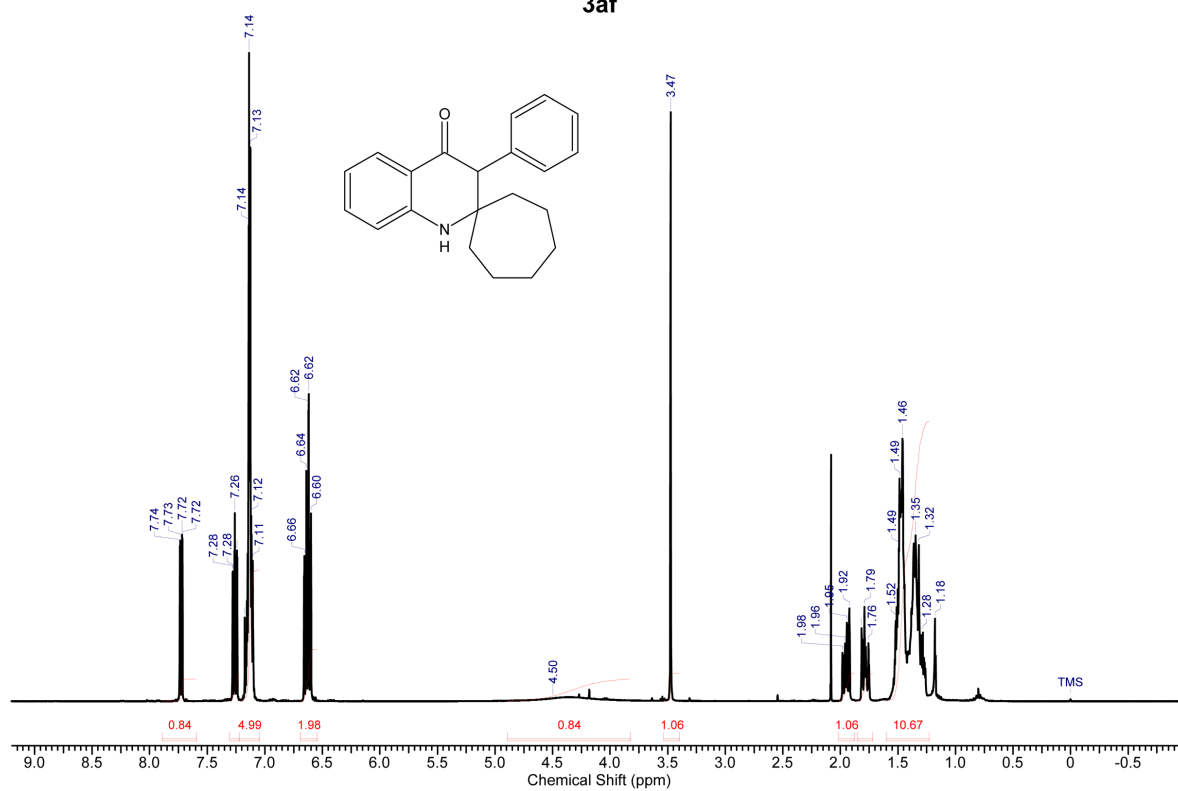
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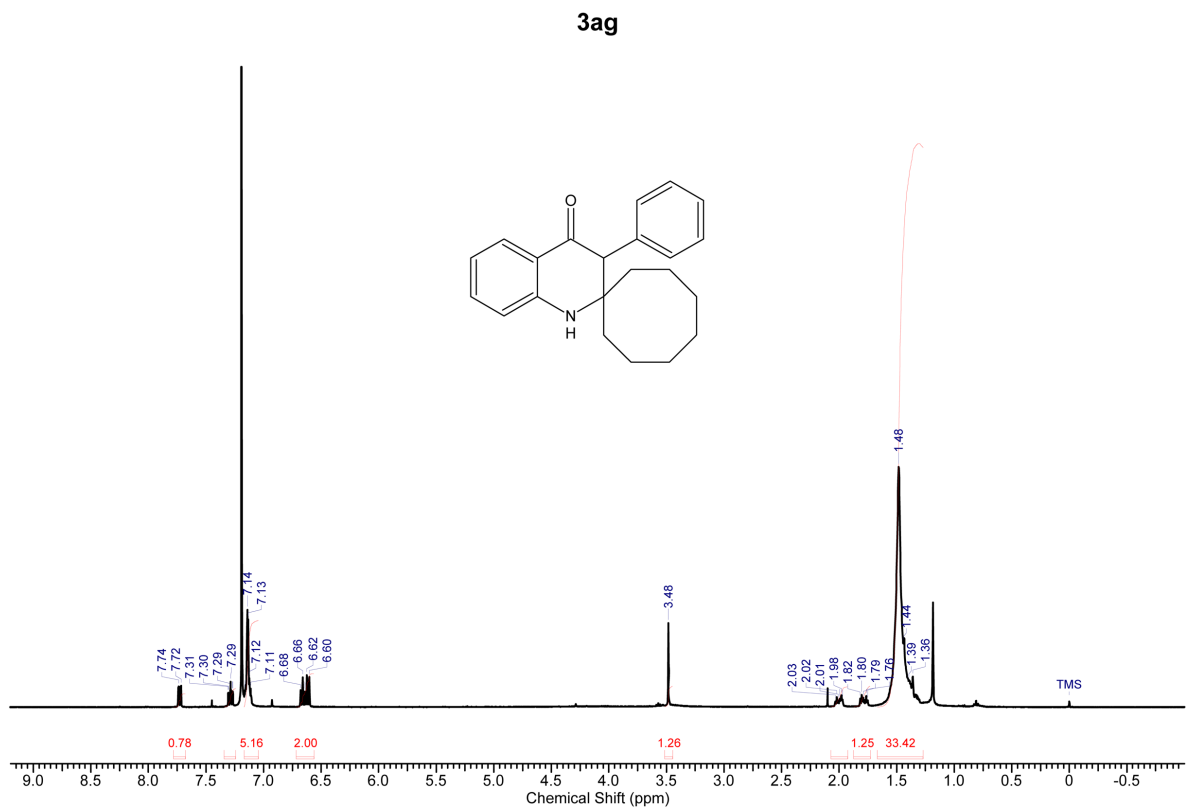
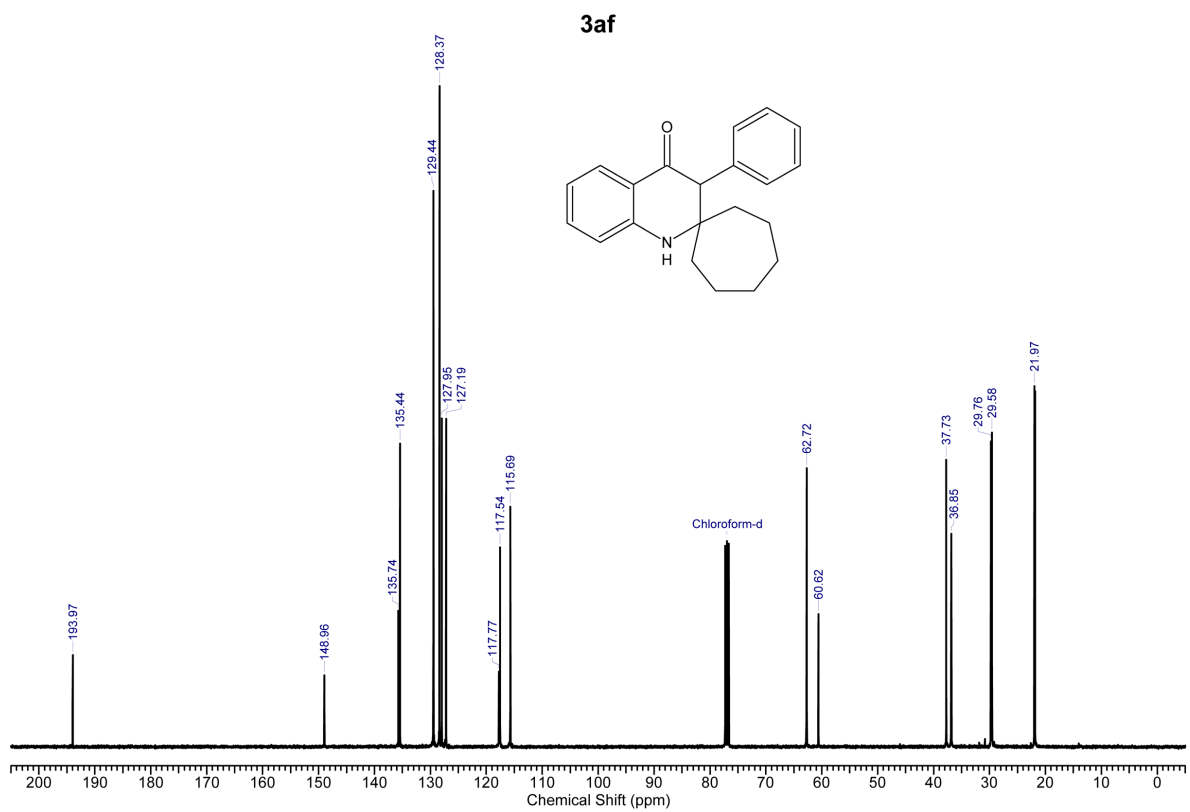


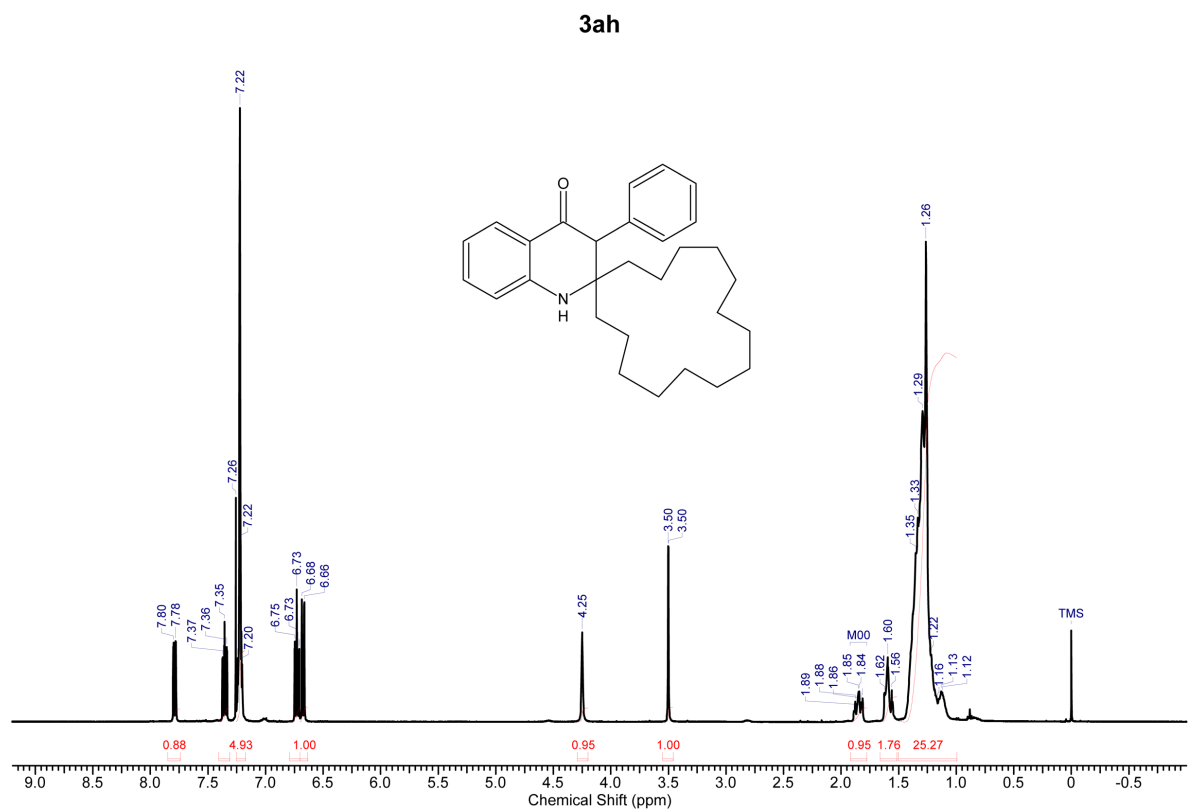
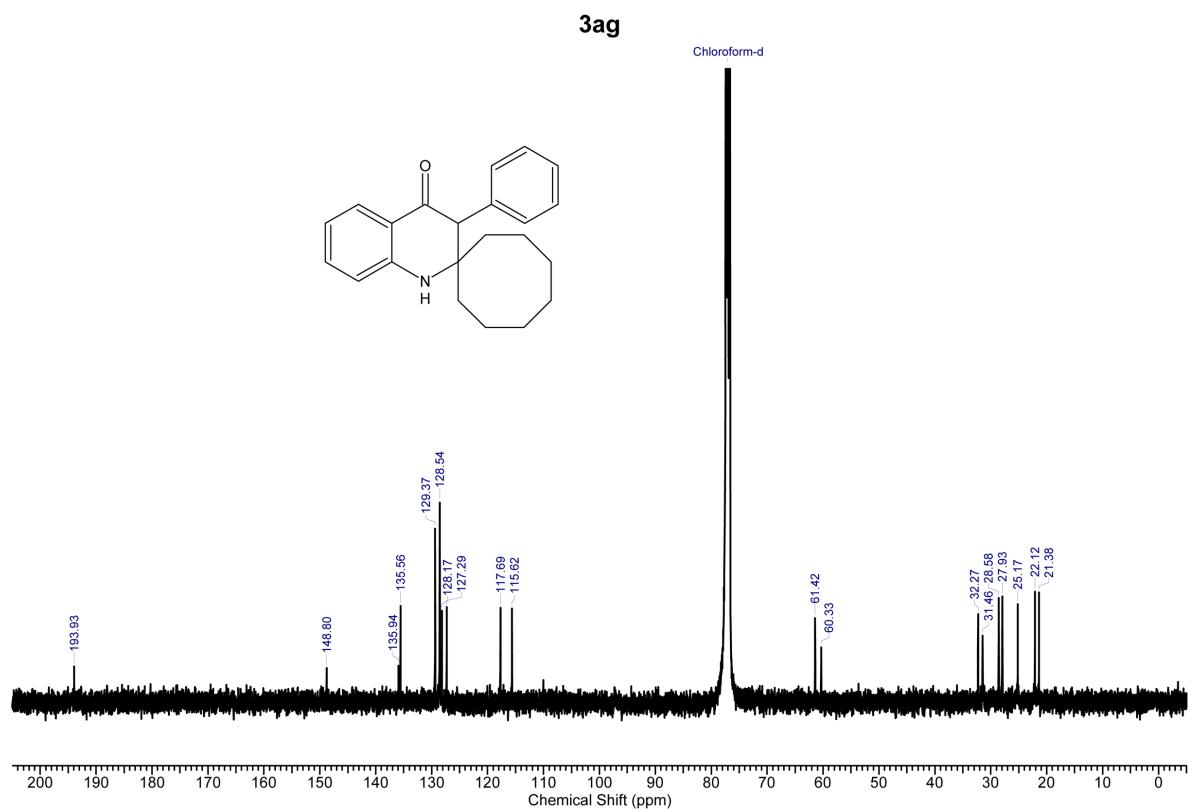
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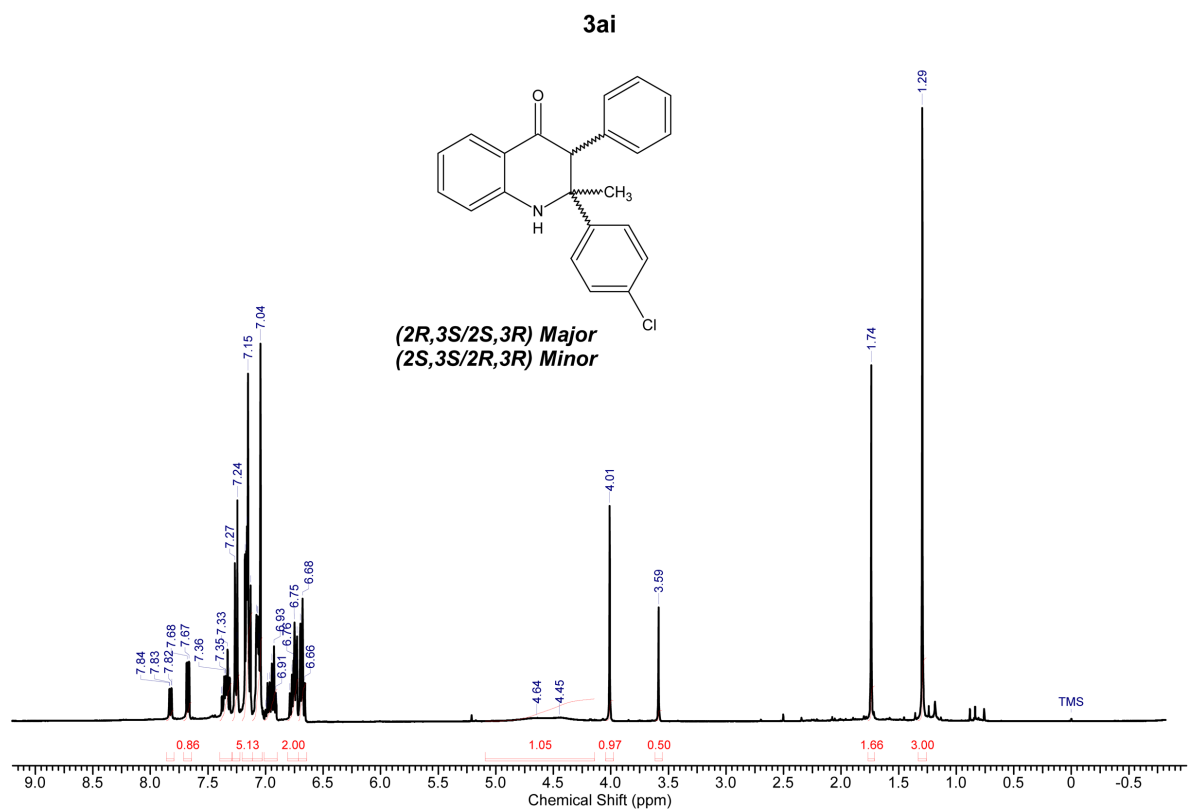
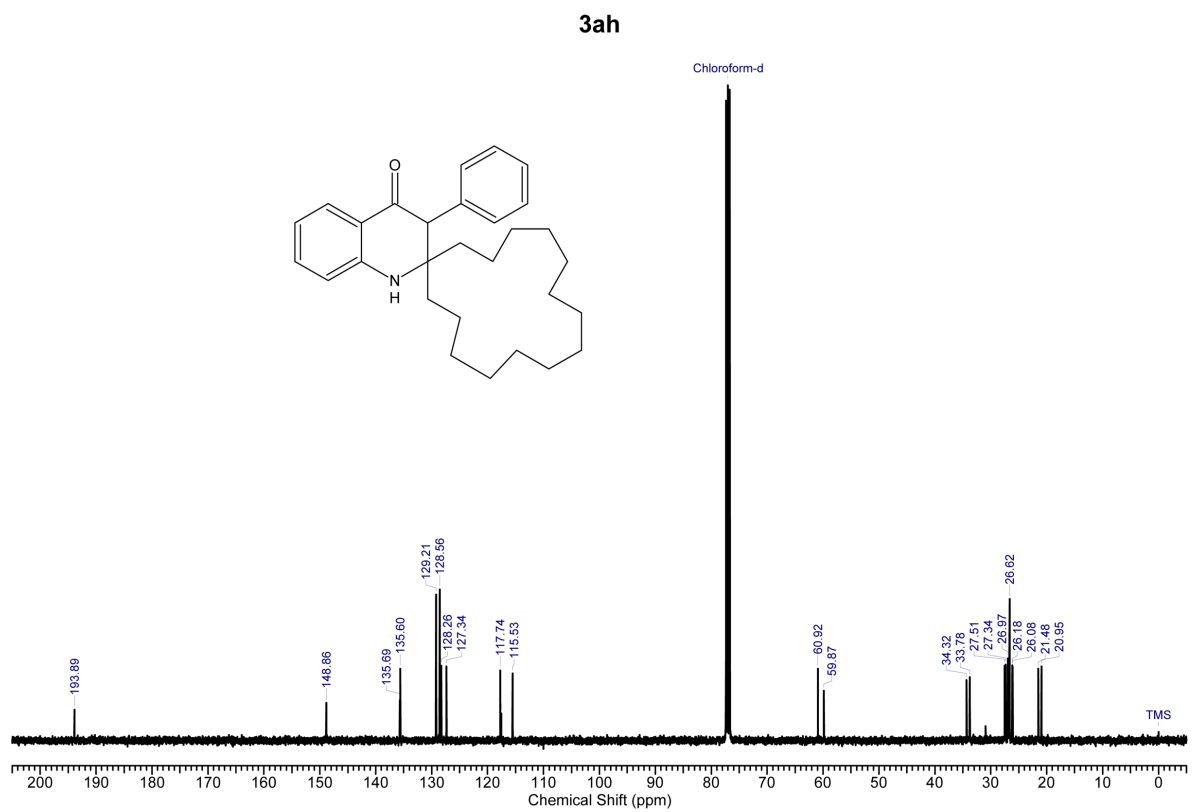


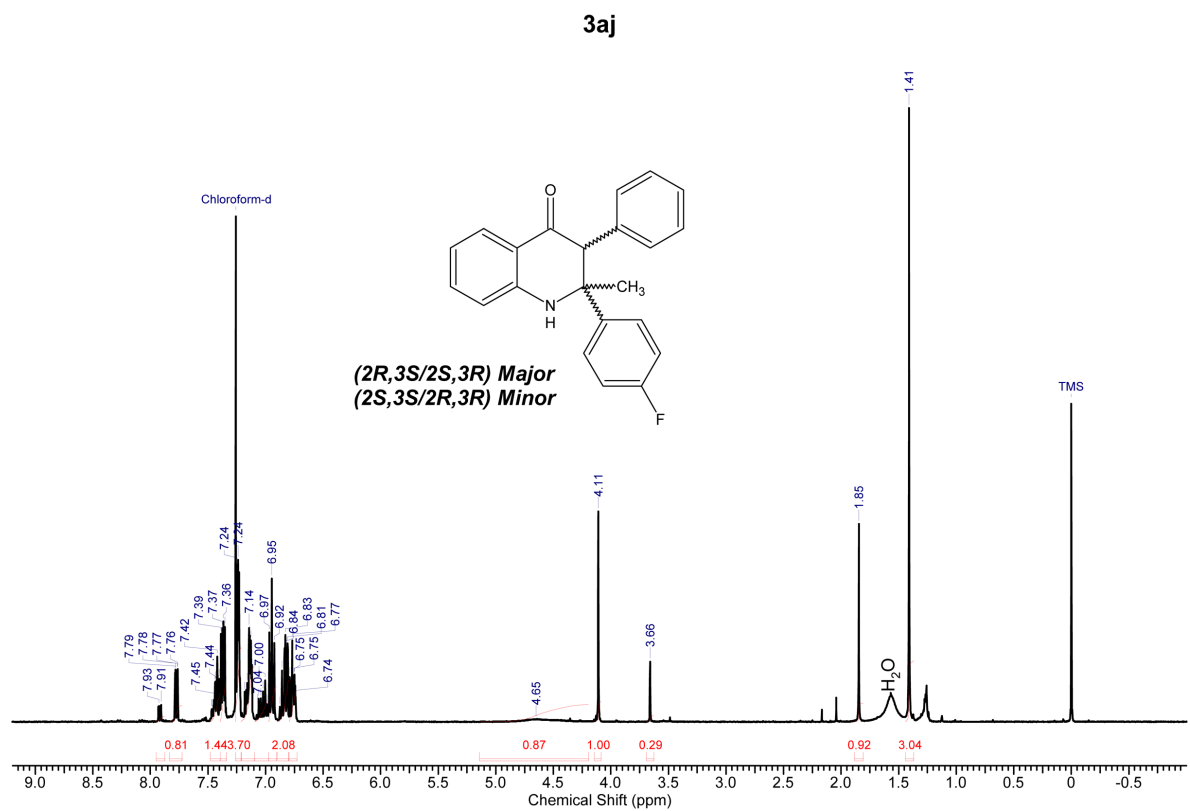
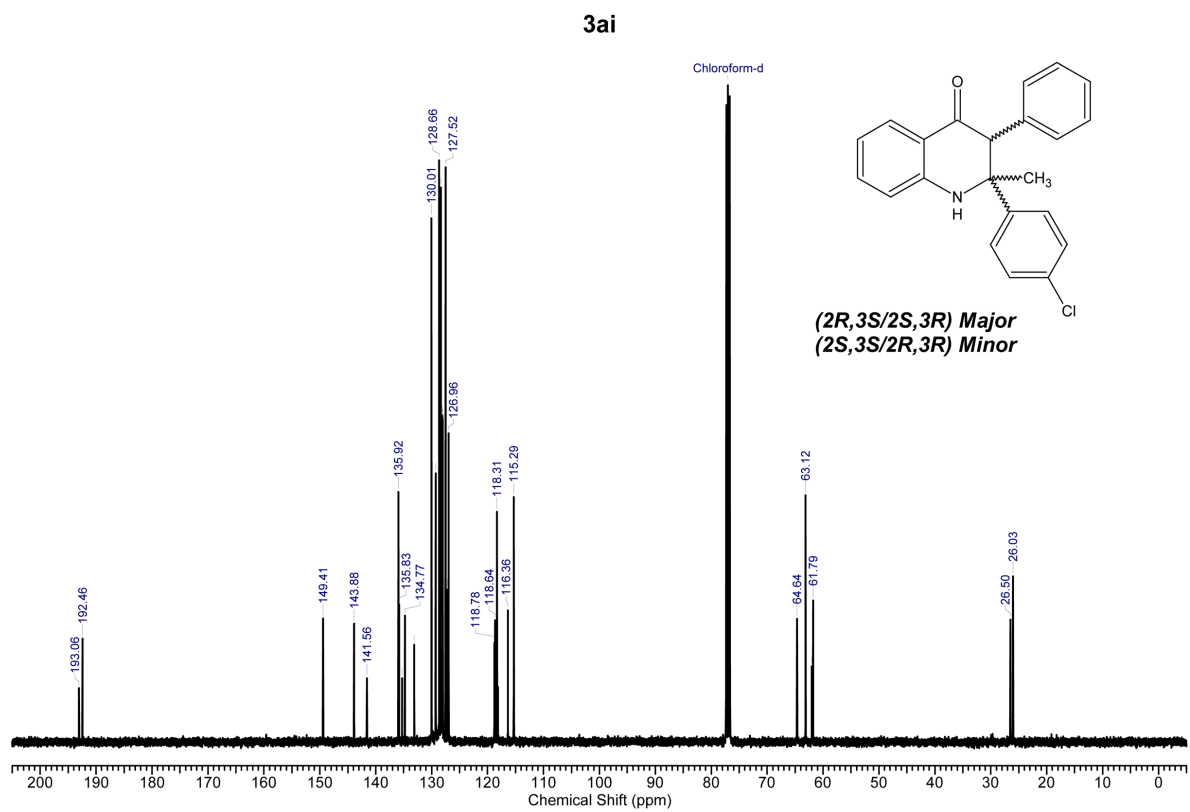
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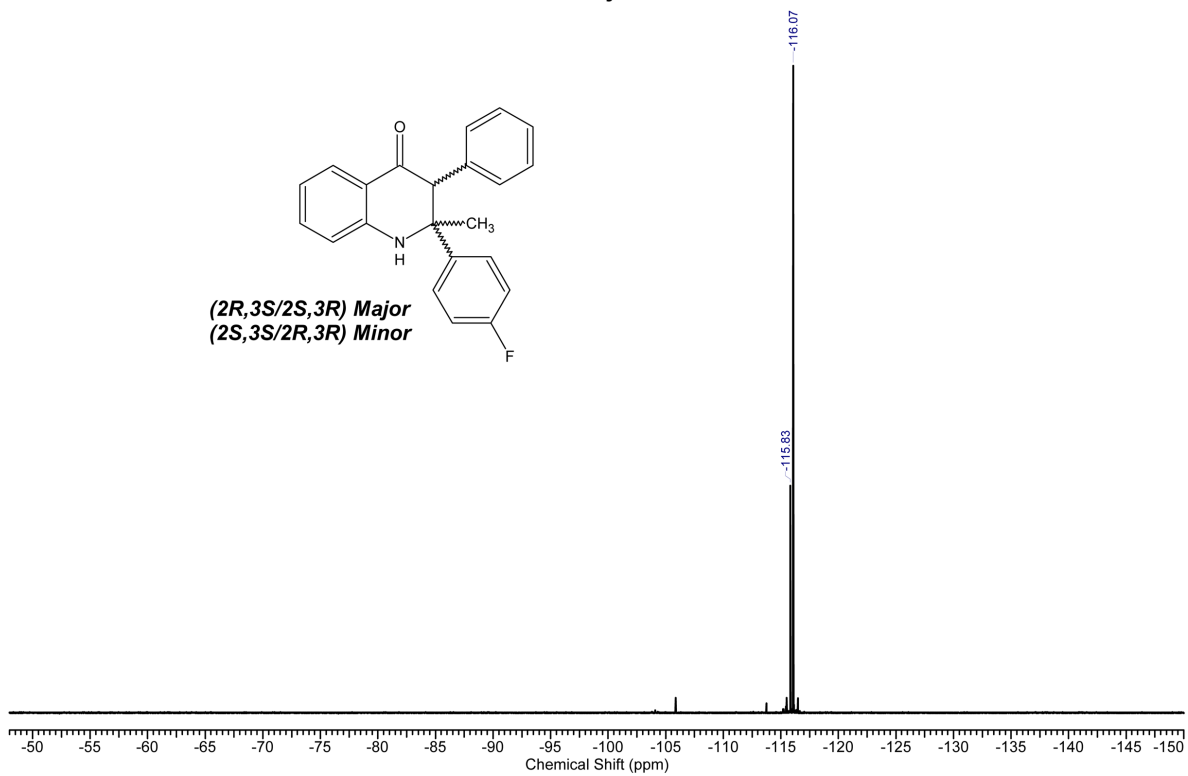
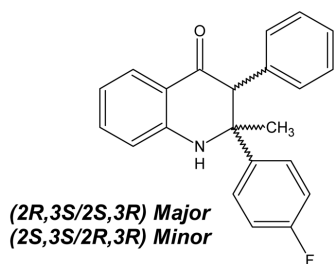




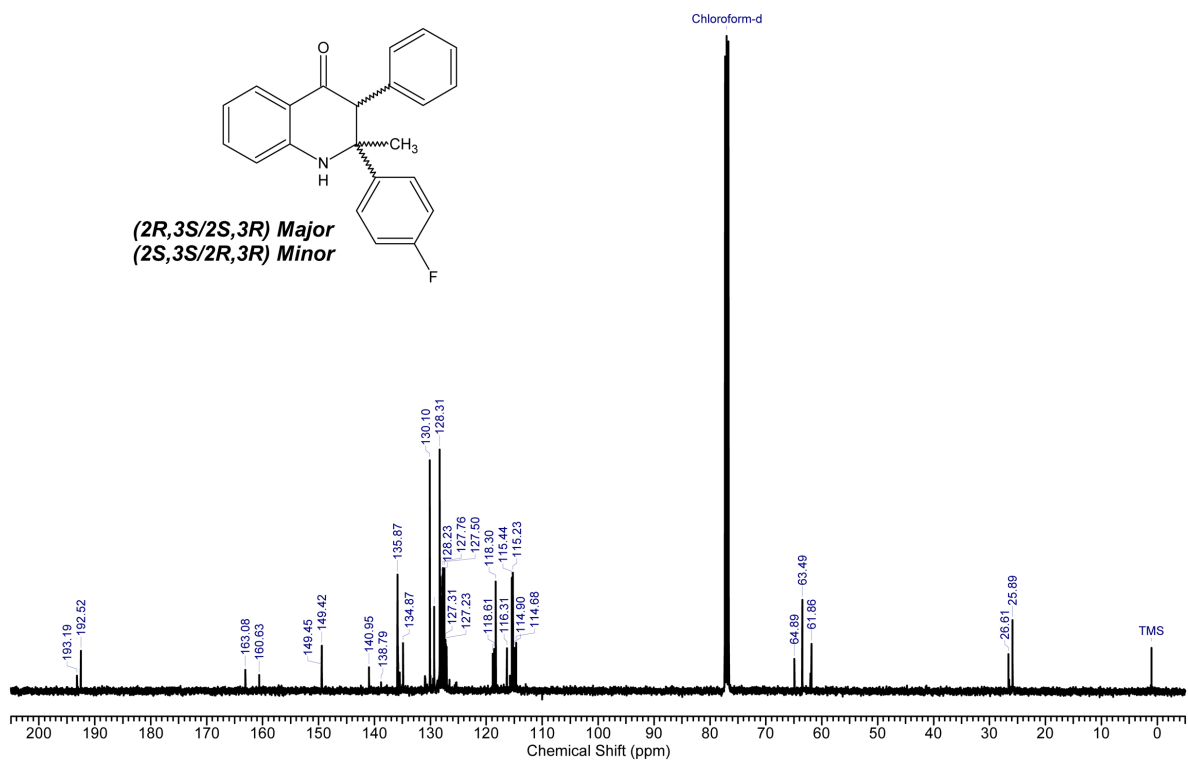
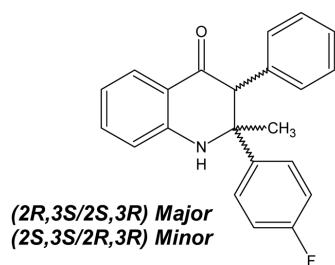




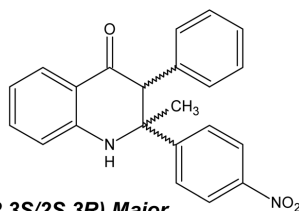
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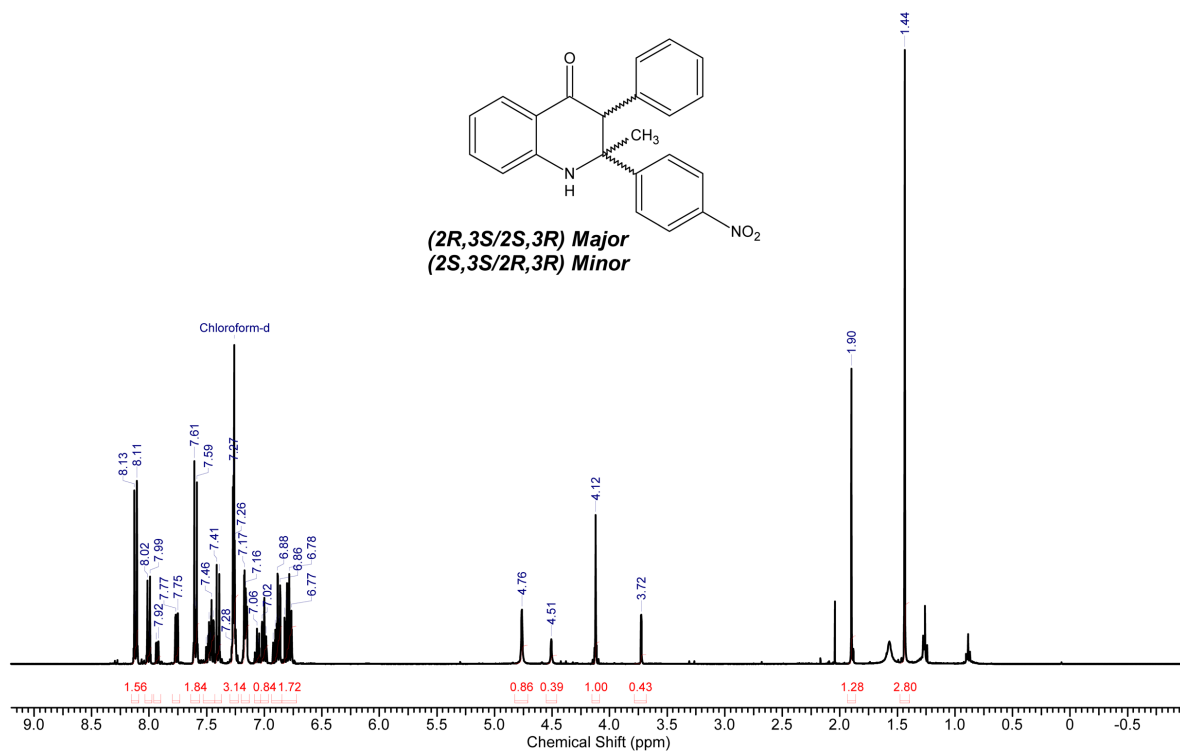
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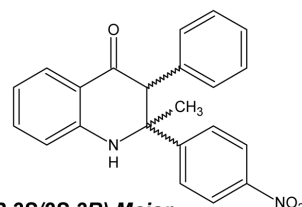
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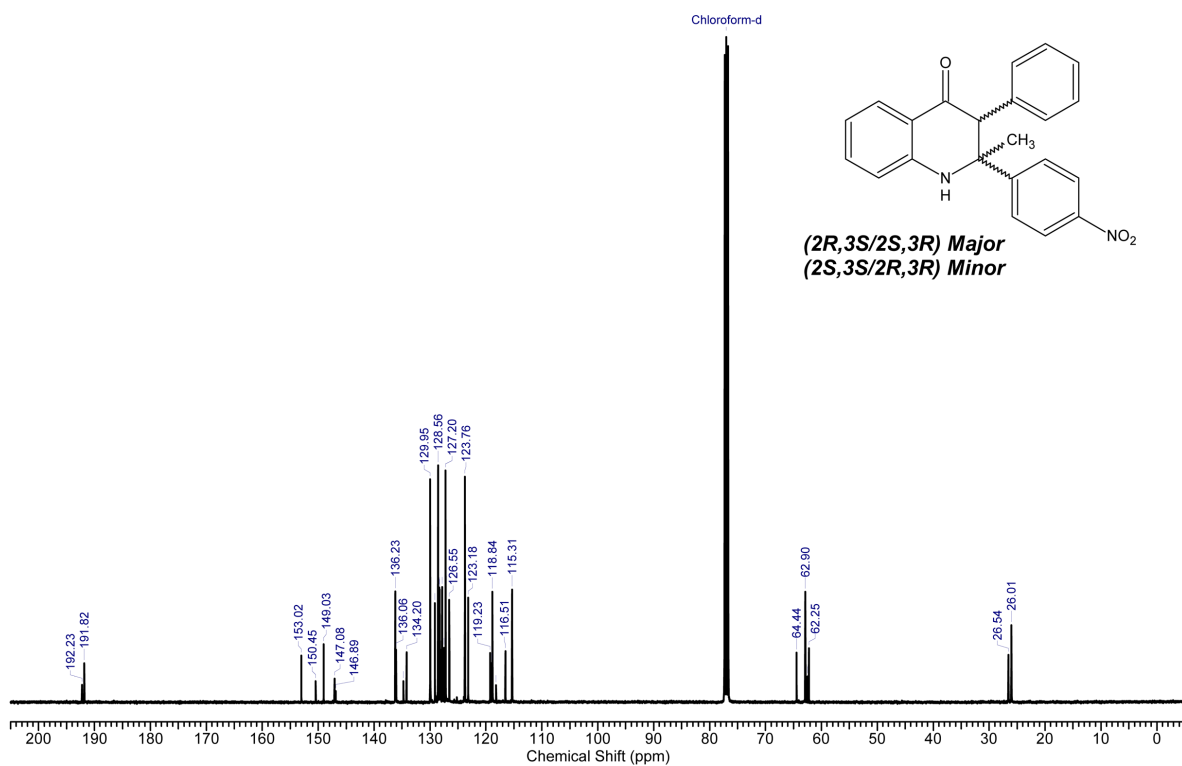
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(2*S*,3*S*)/2*R*,3*R*) Minor



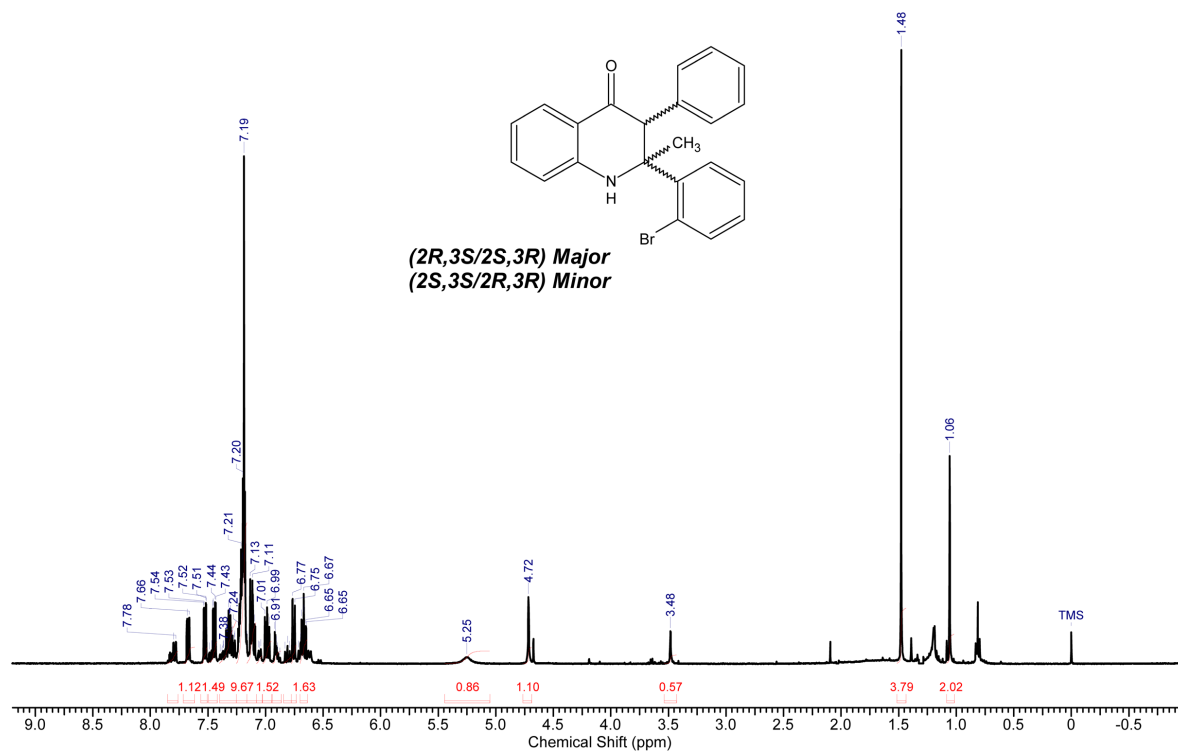
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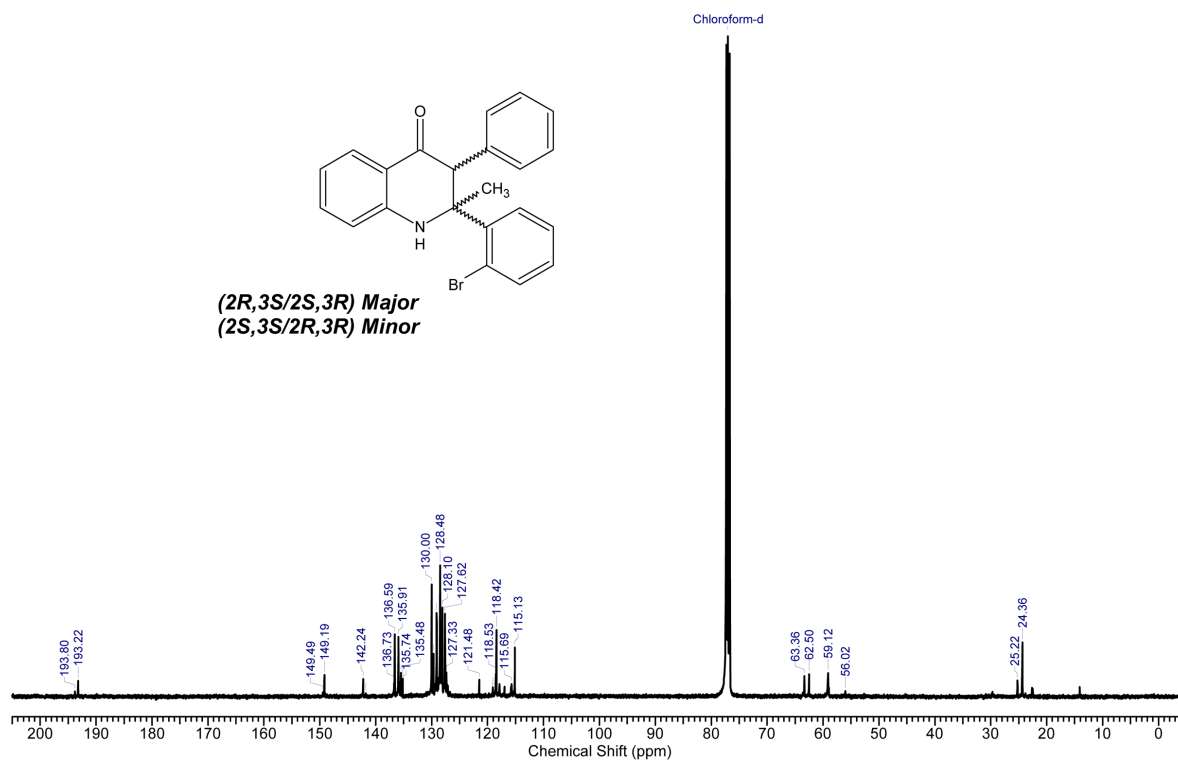
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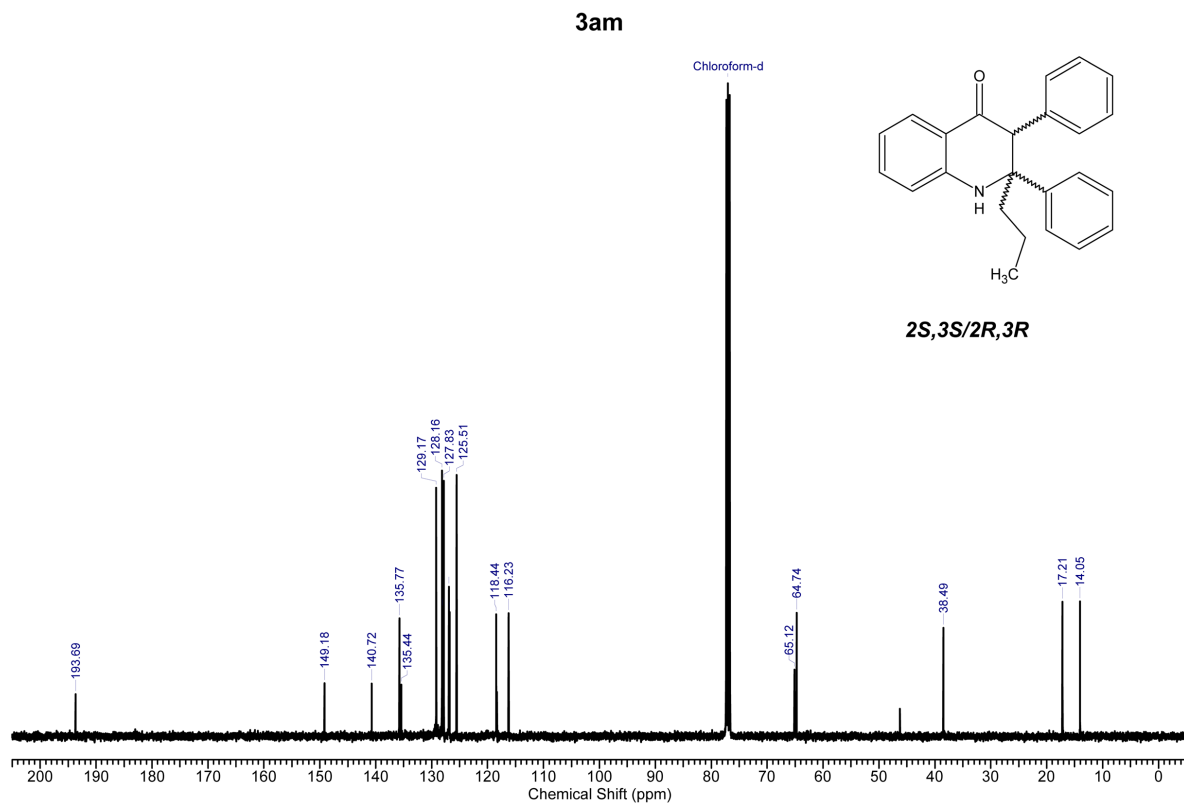
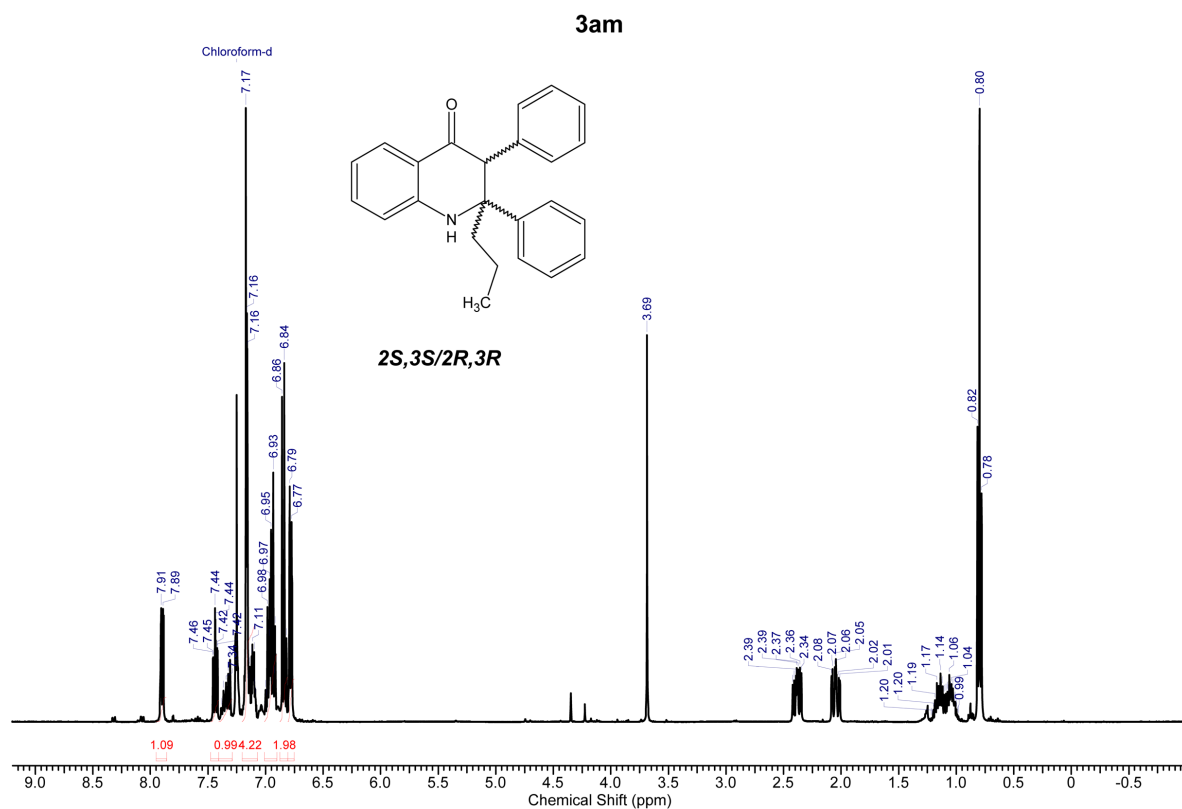


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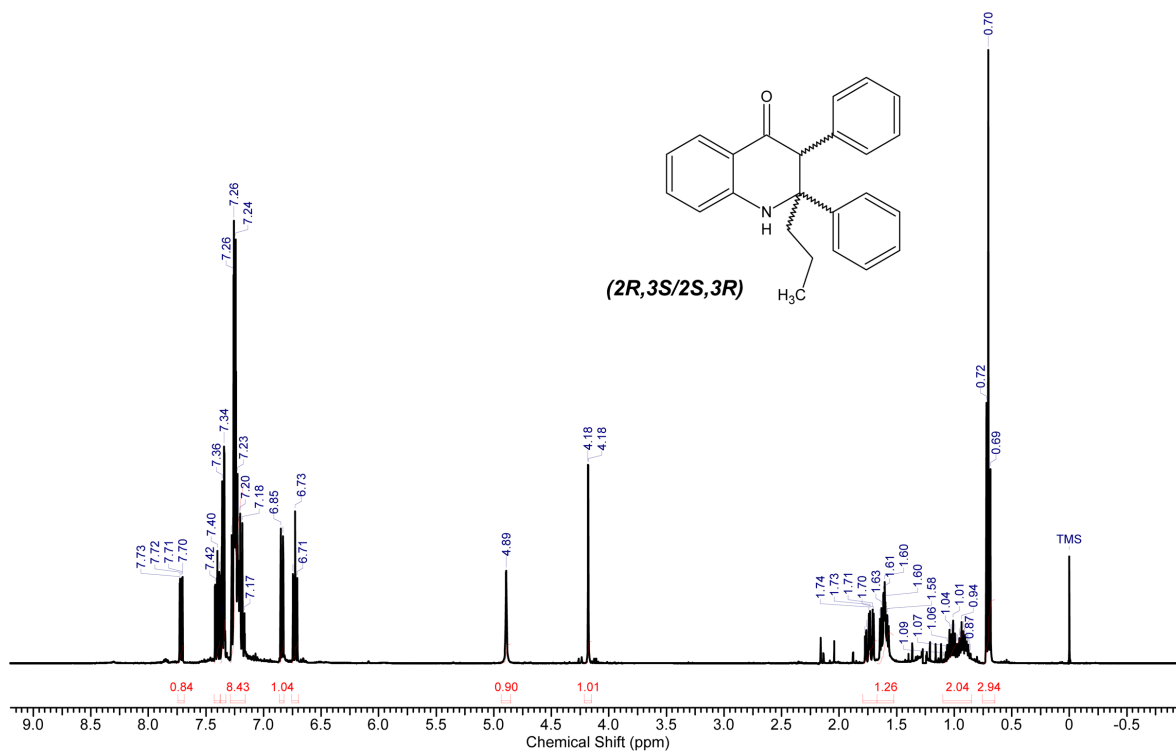


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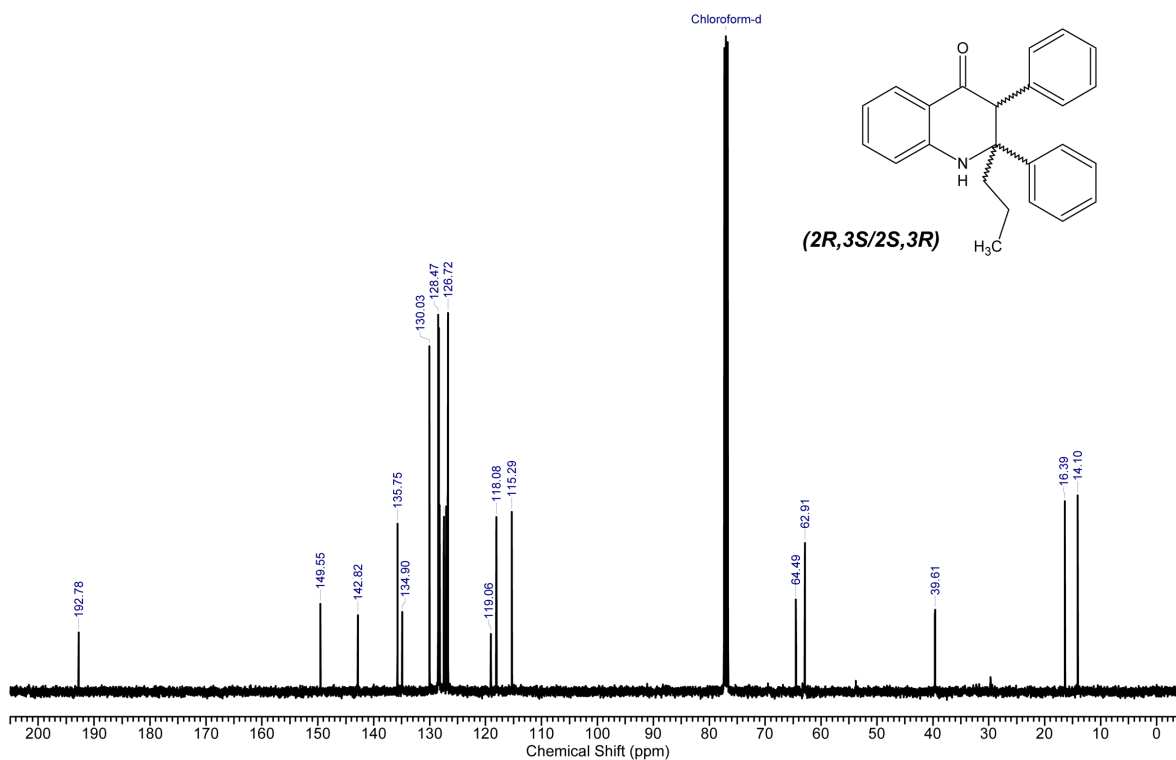




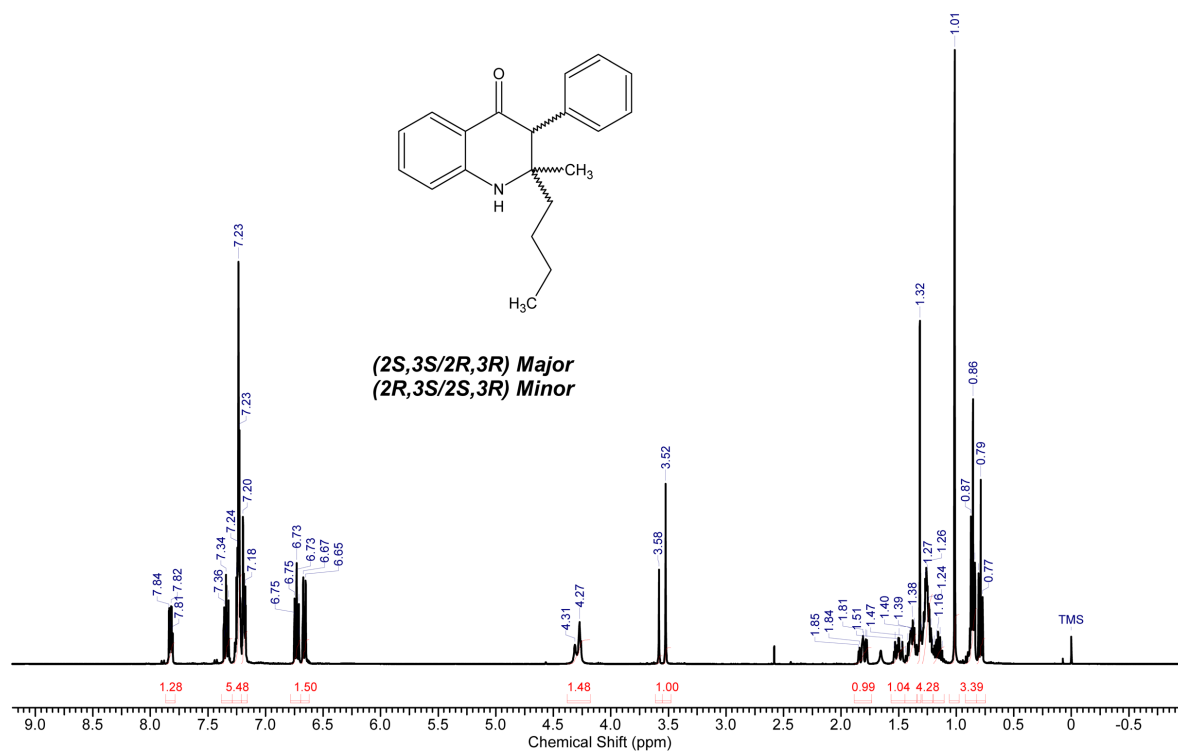
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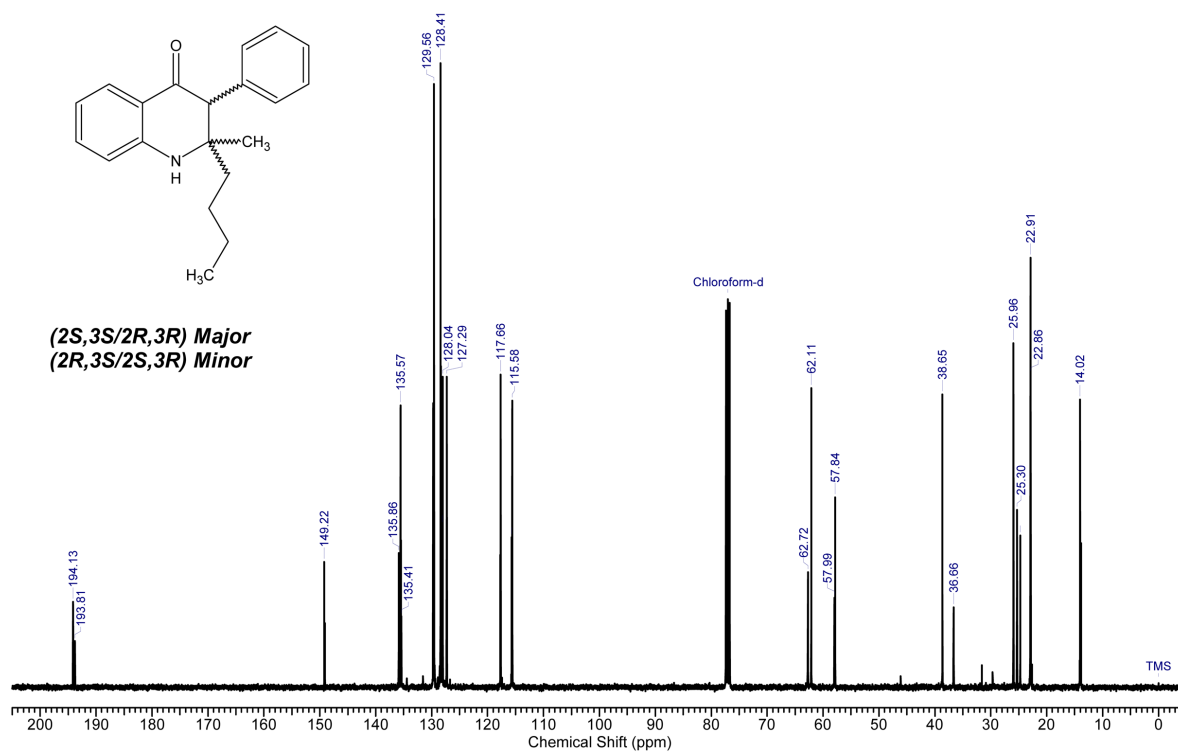
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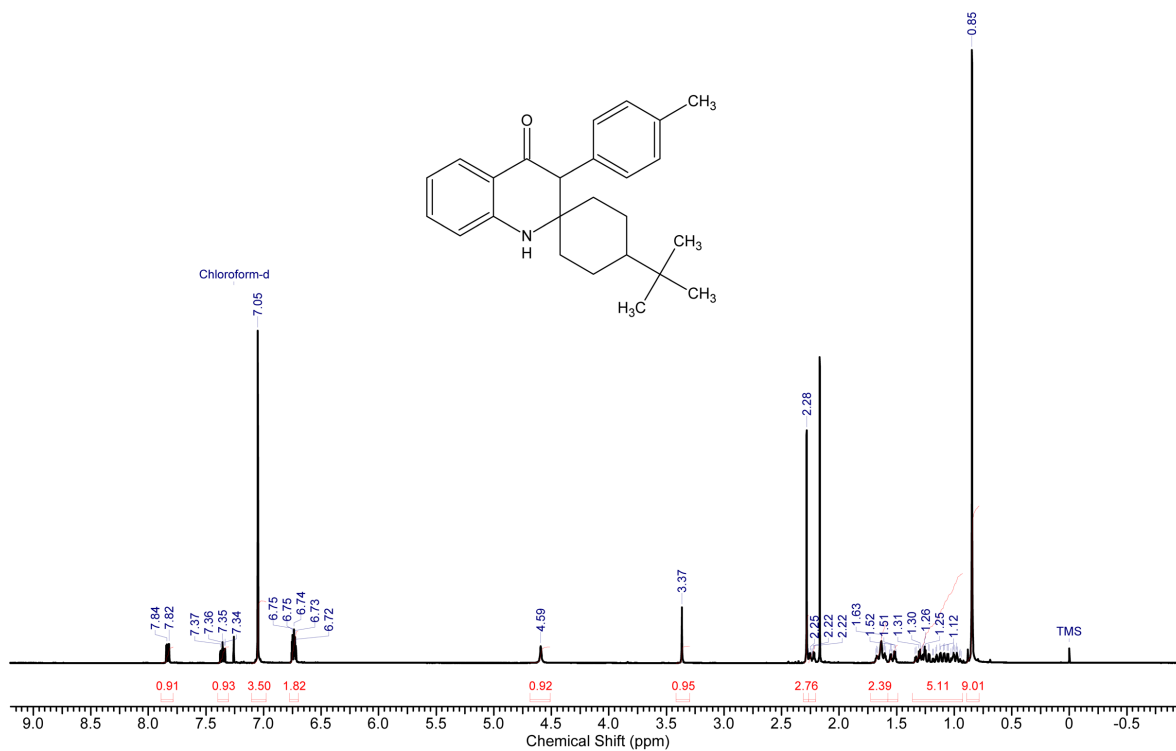
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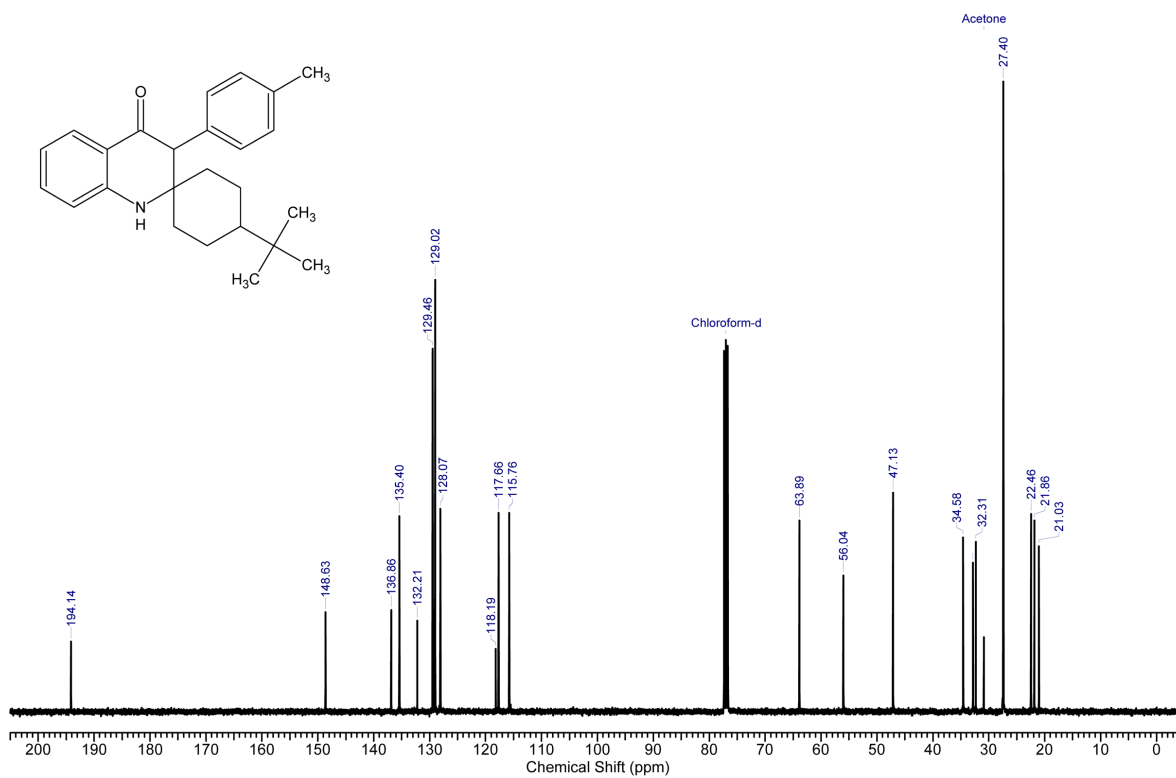
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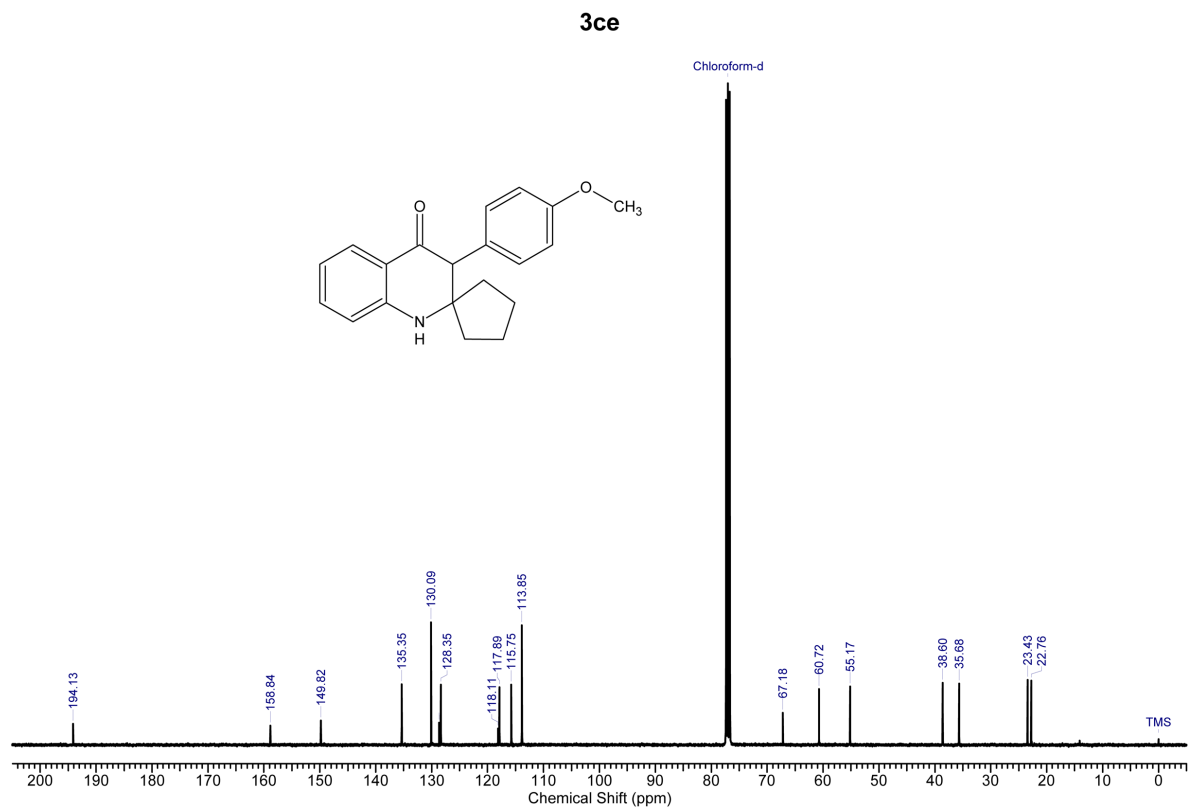
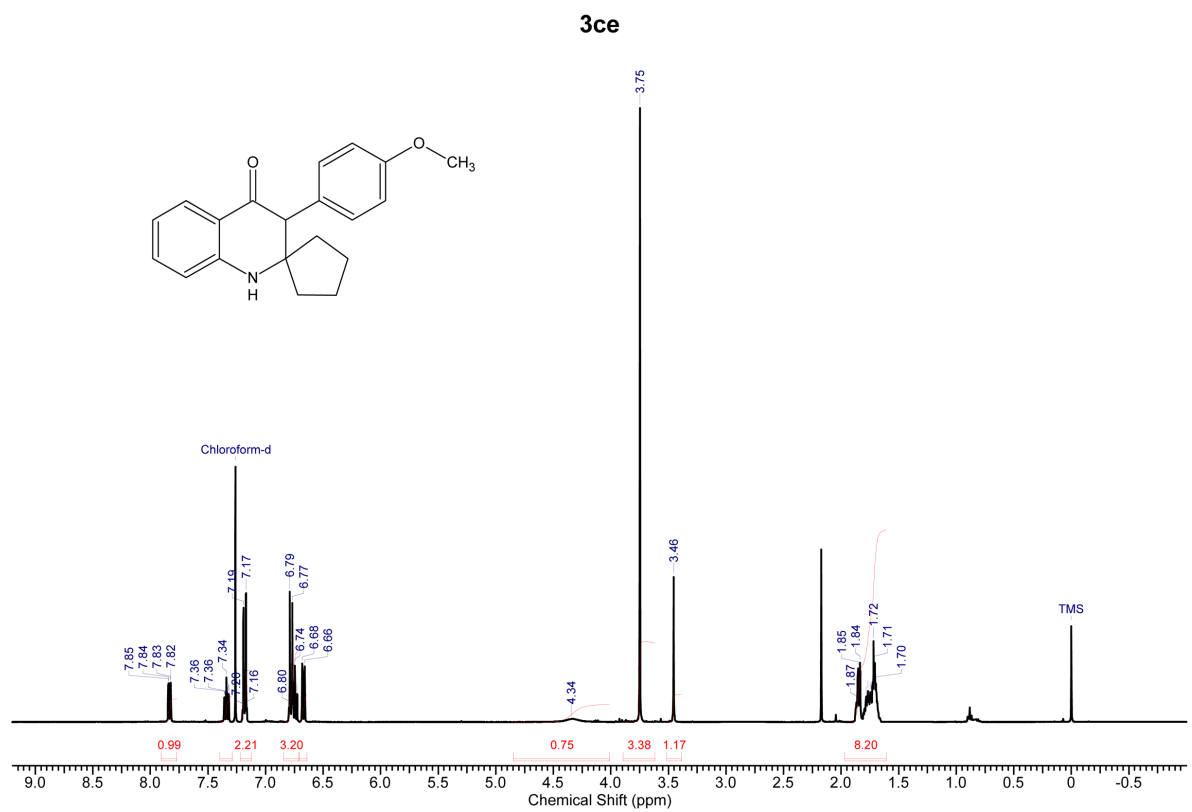


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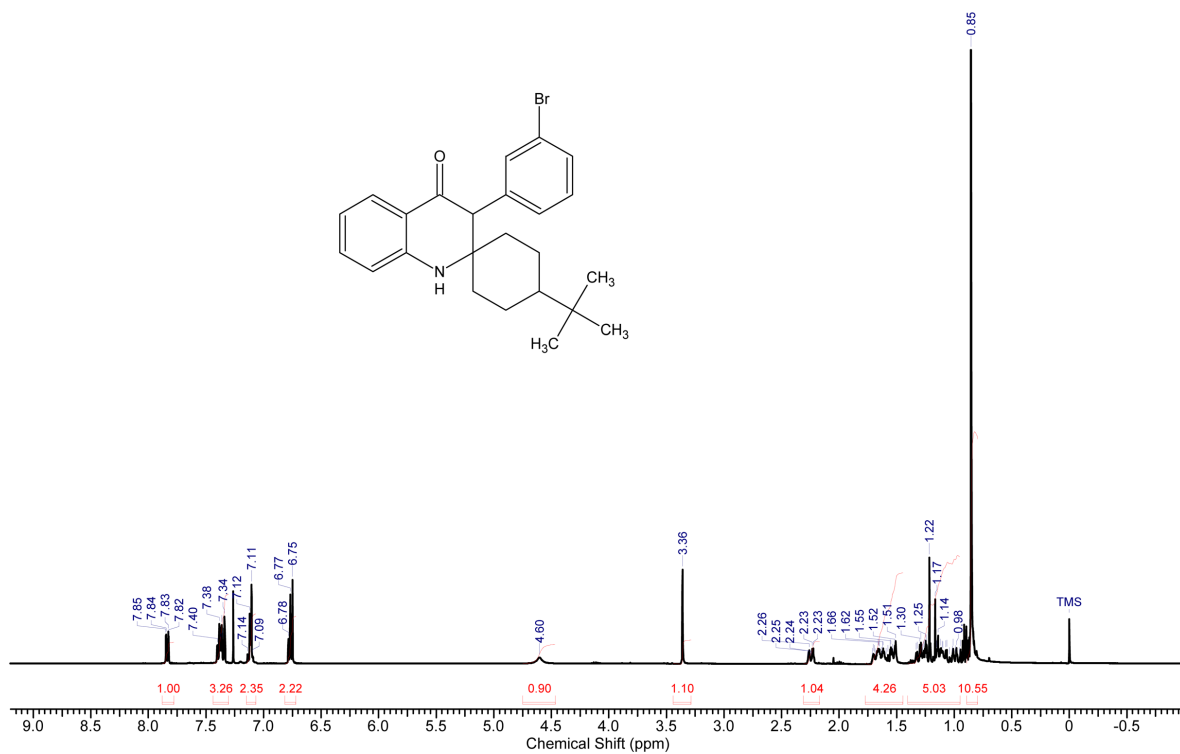


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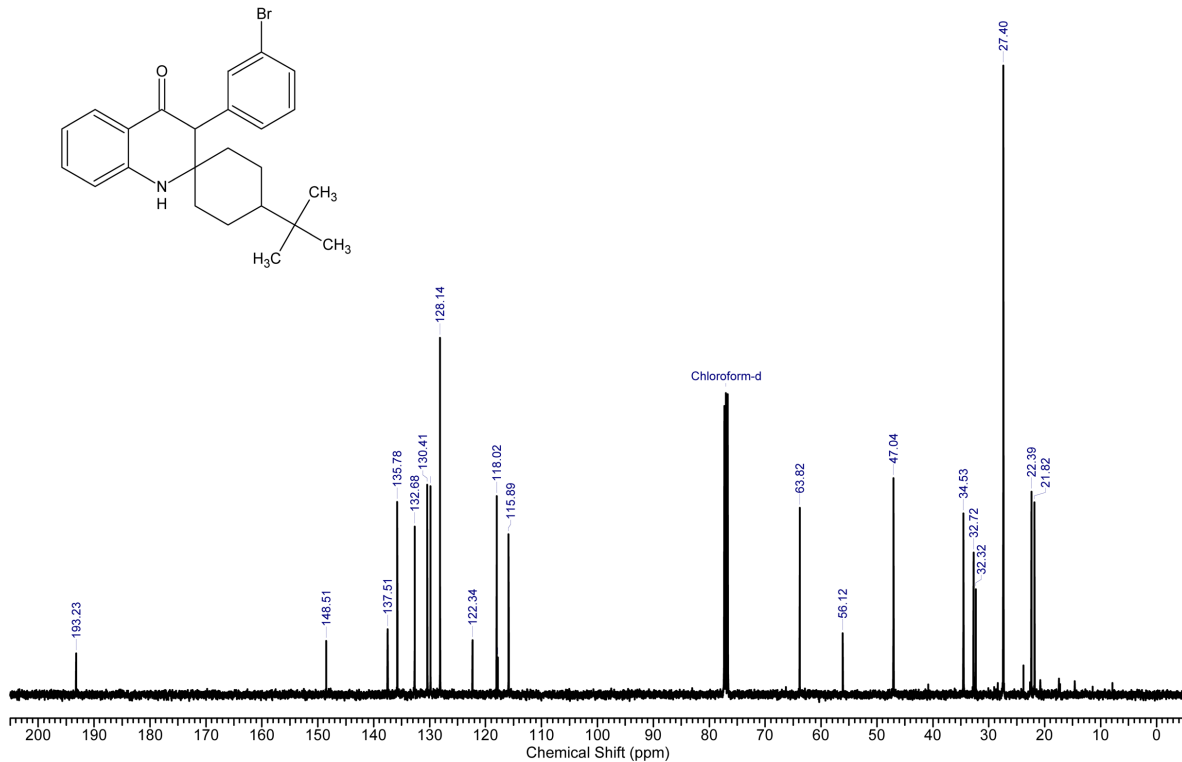




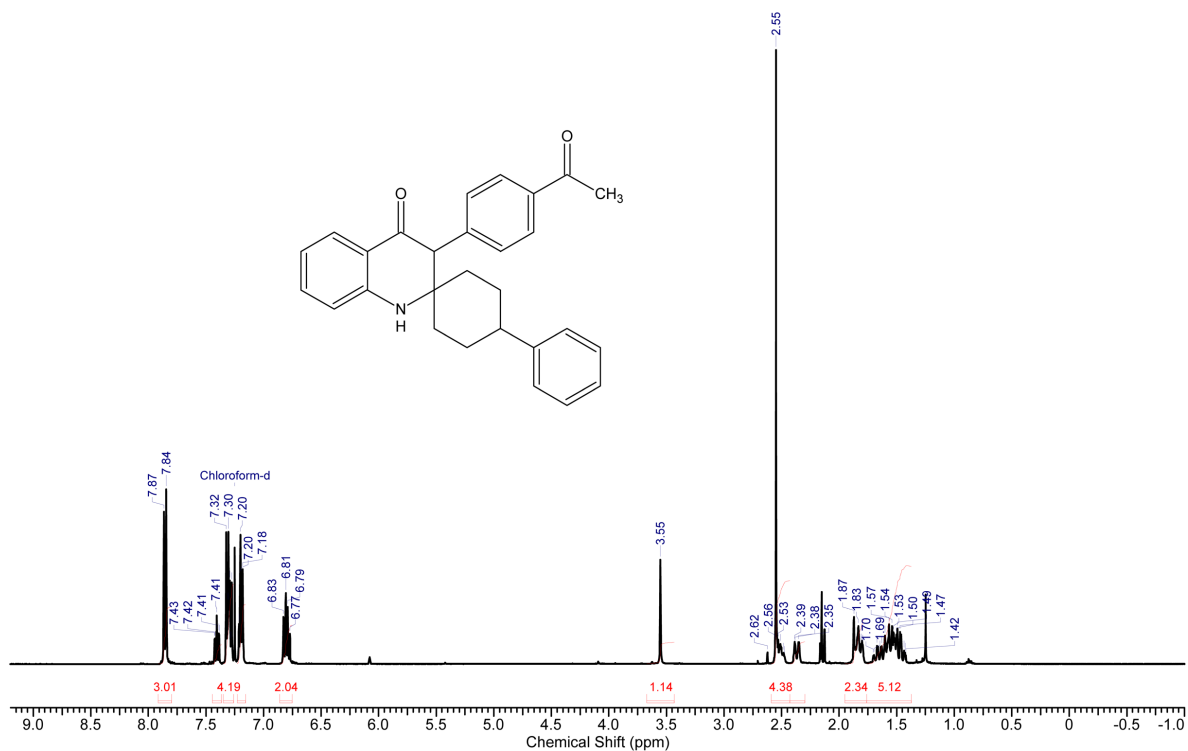
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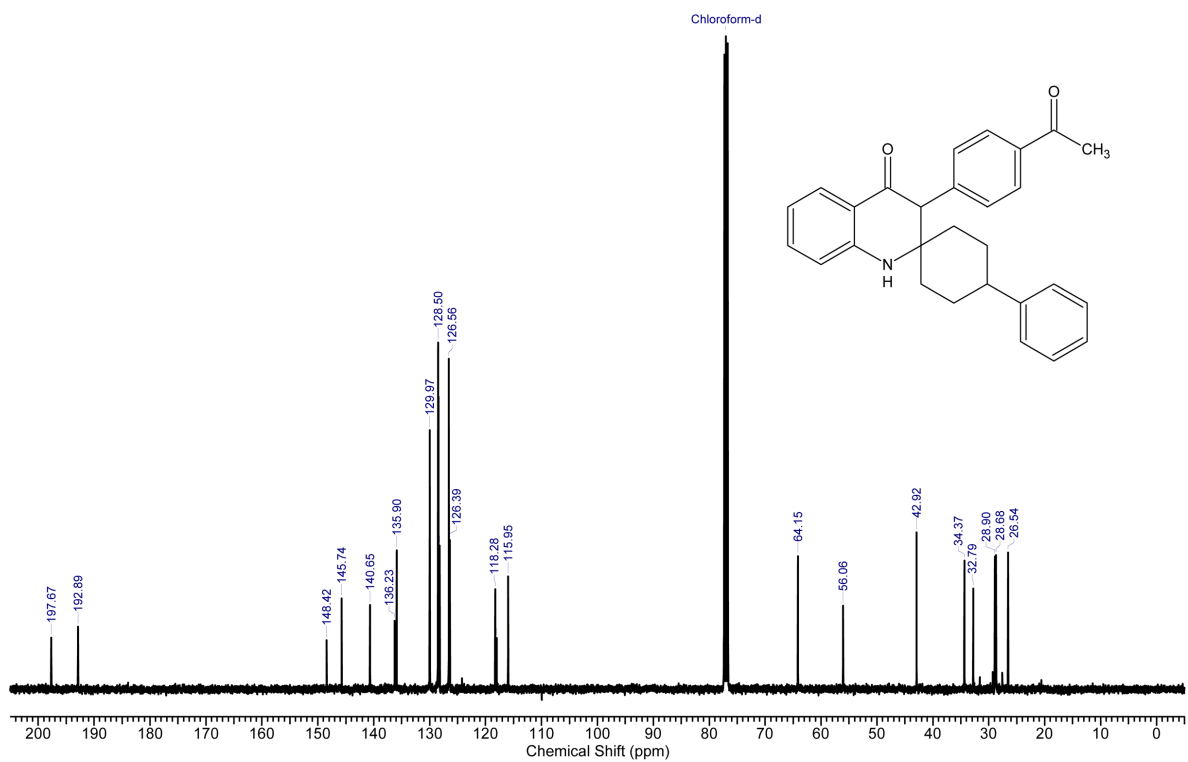
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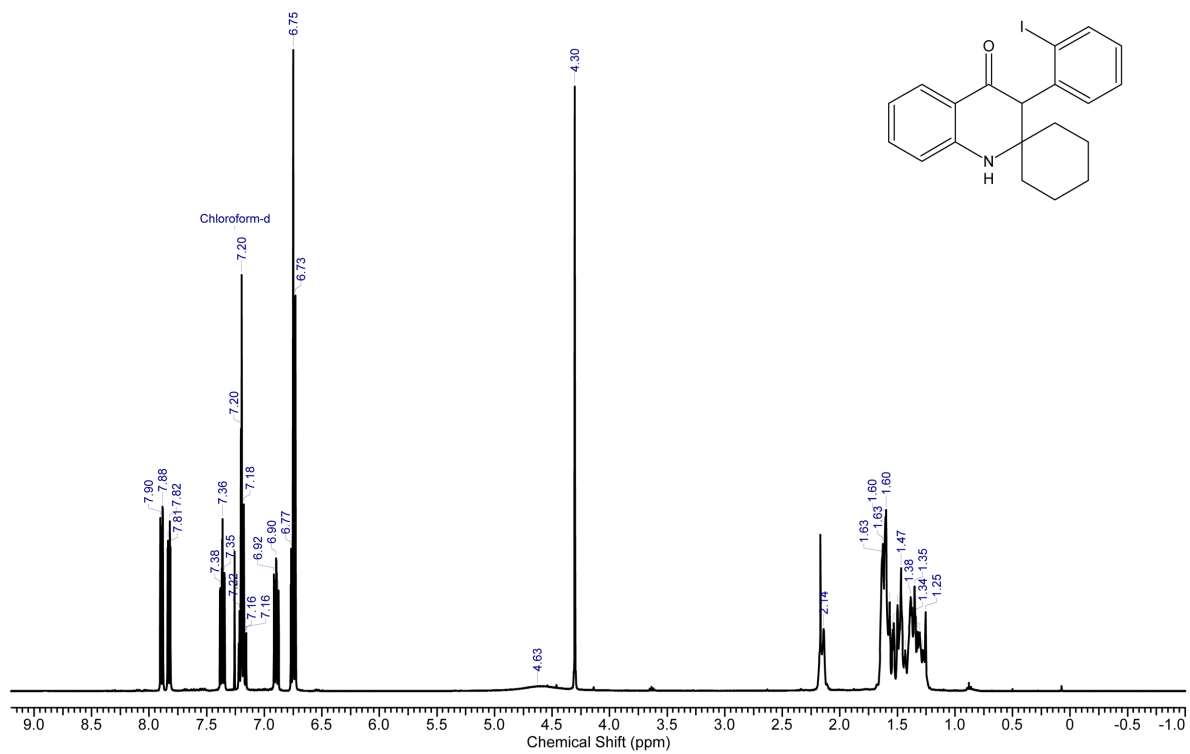
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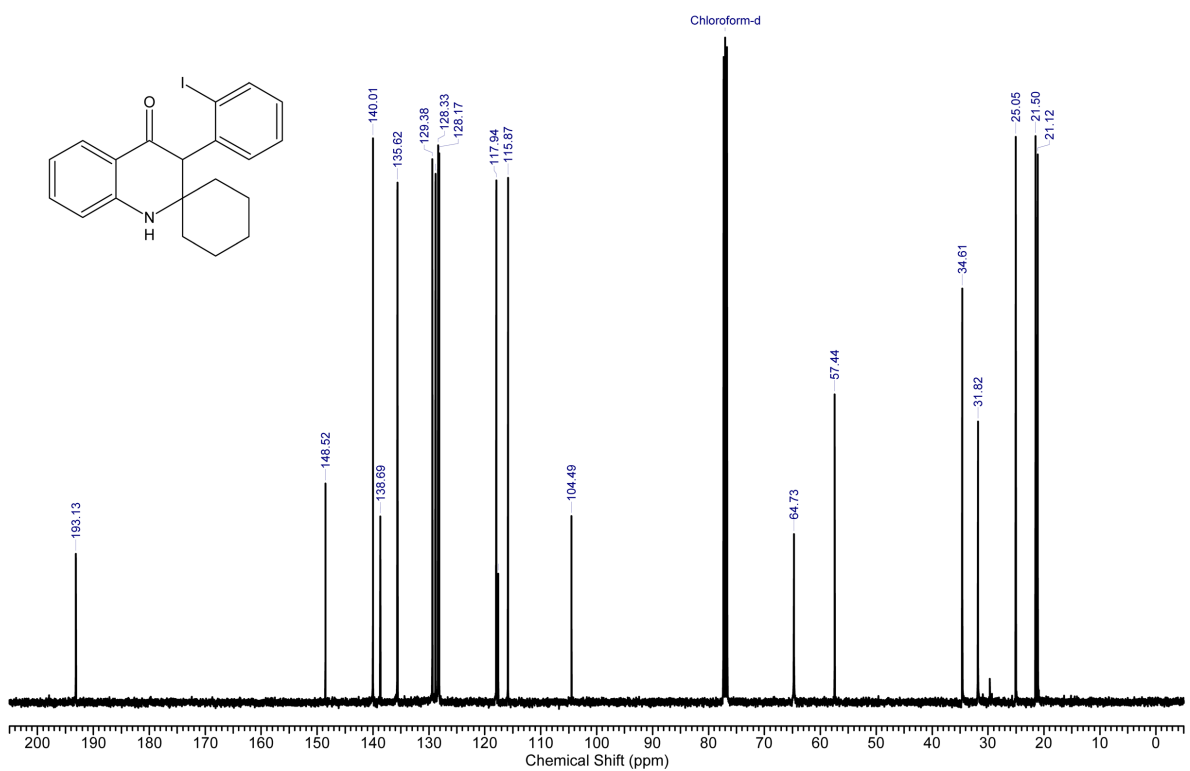
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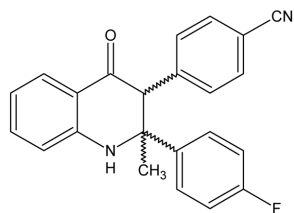
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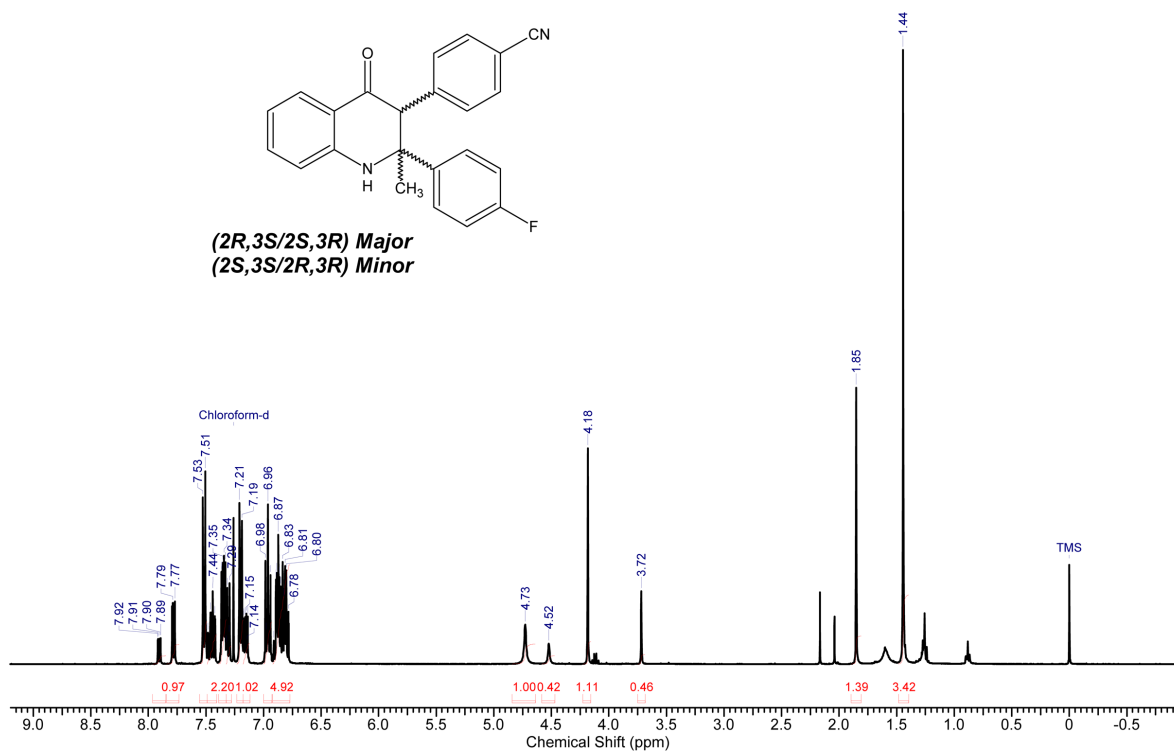
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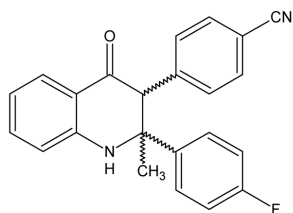
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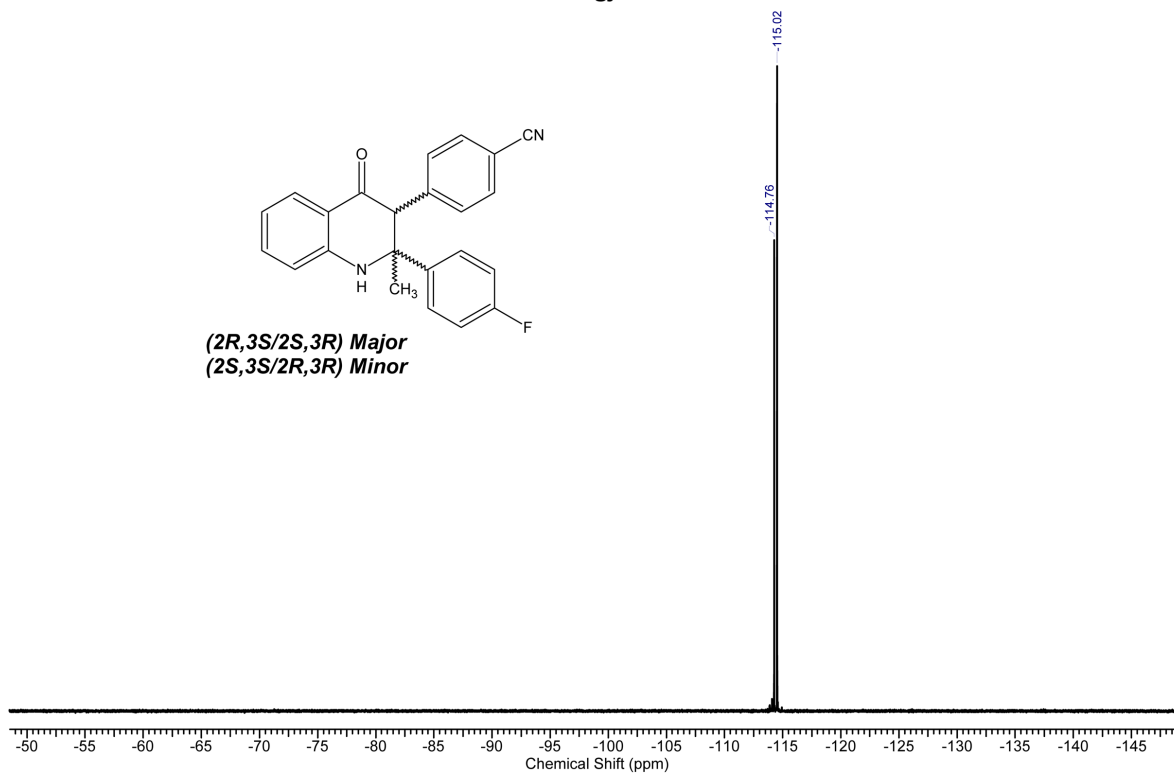
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(2S,3S/2R,3R) Minor

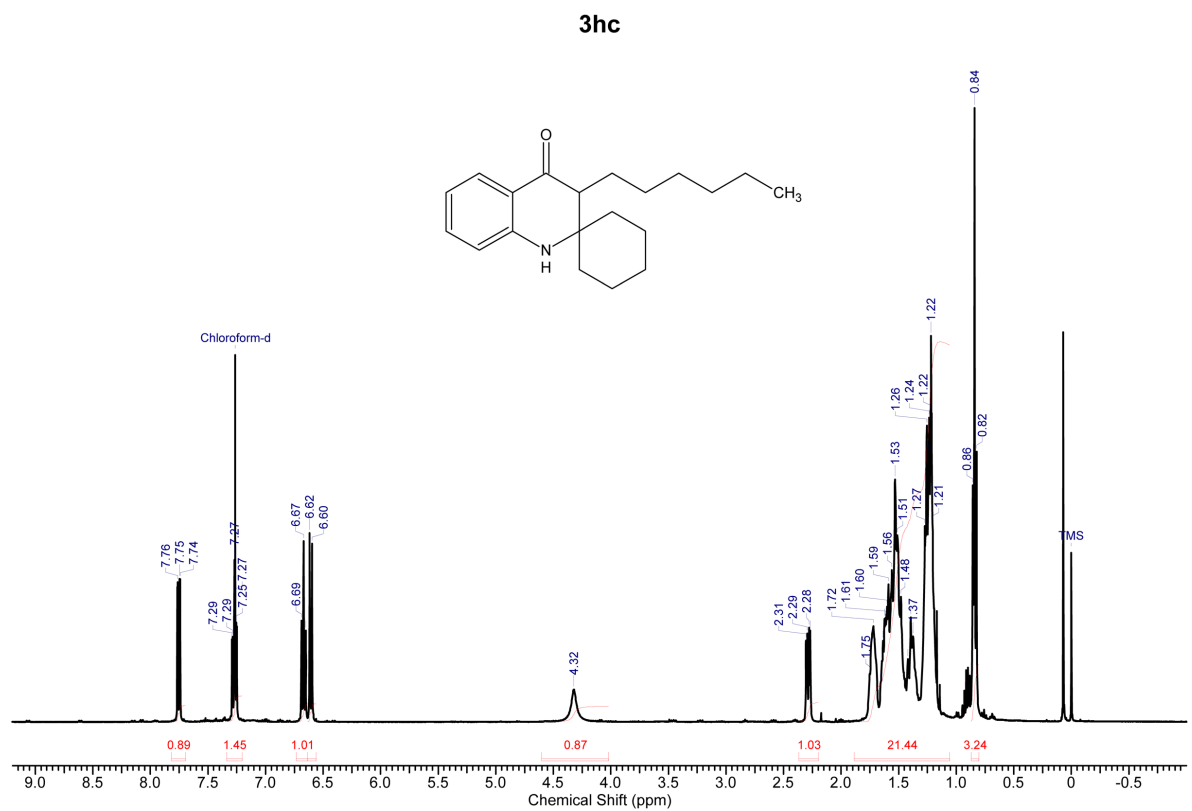
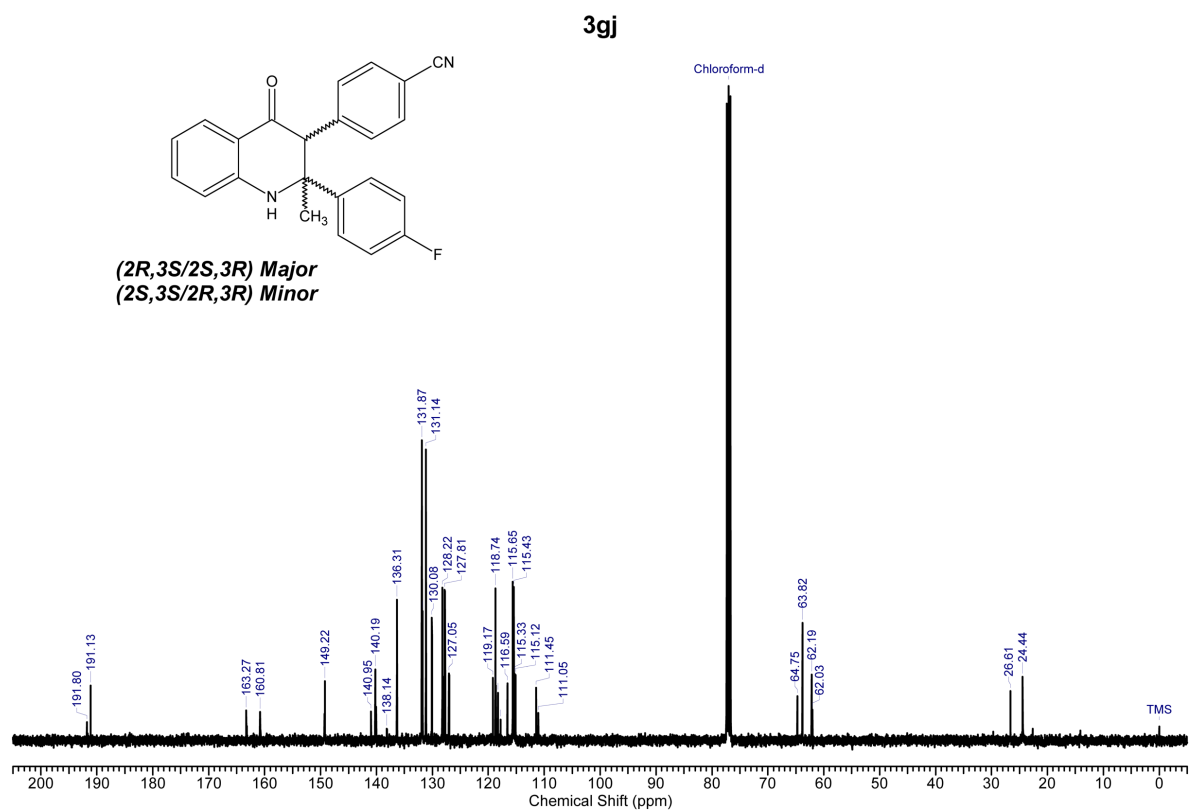


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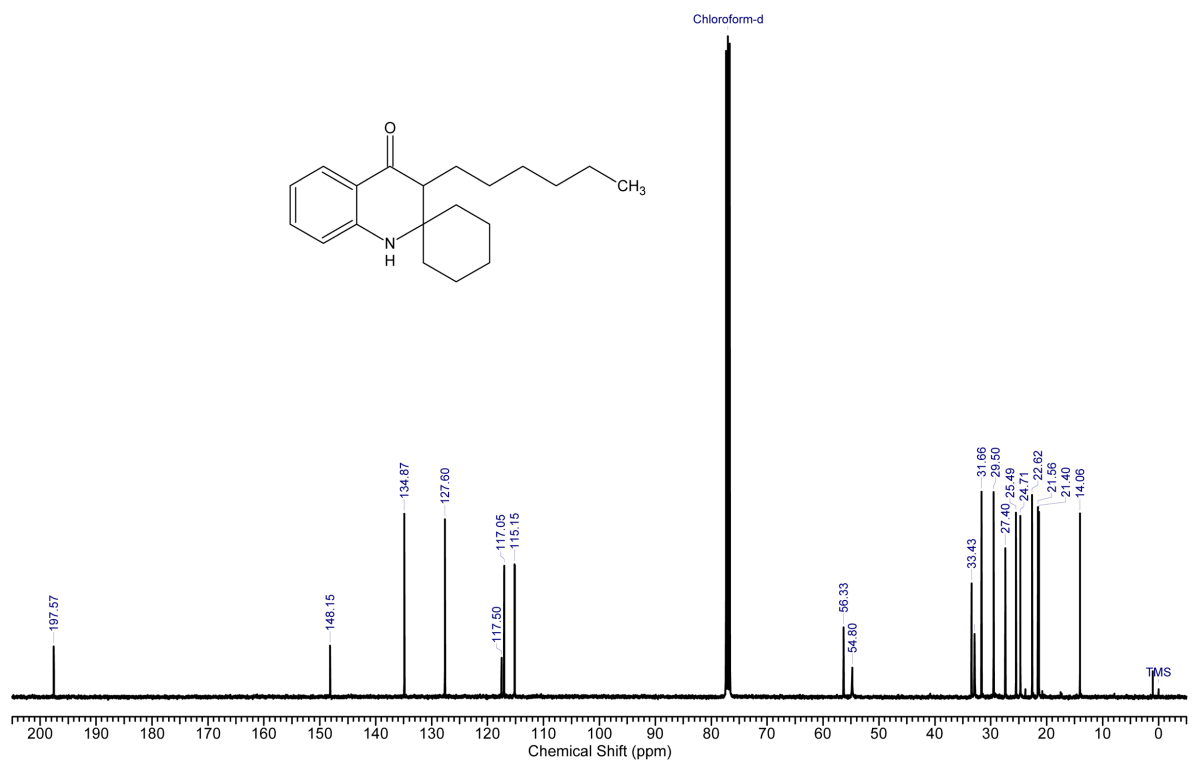


(2R,3S/2S,3R) Major
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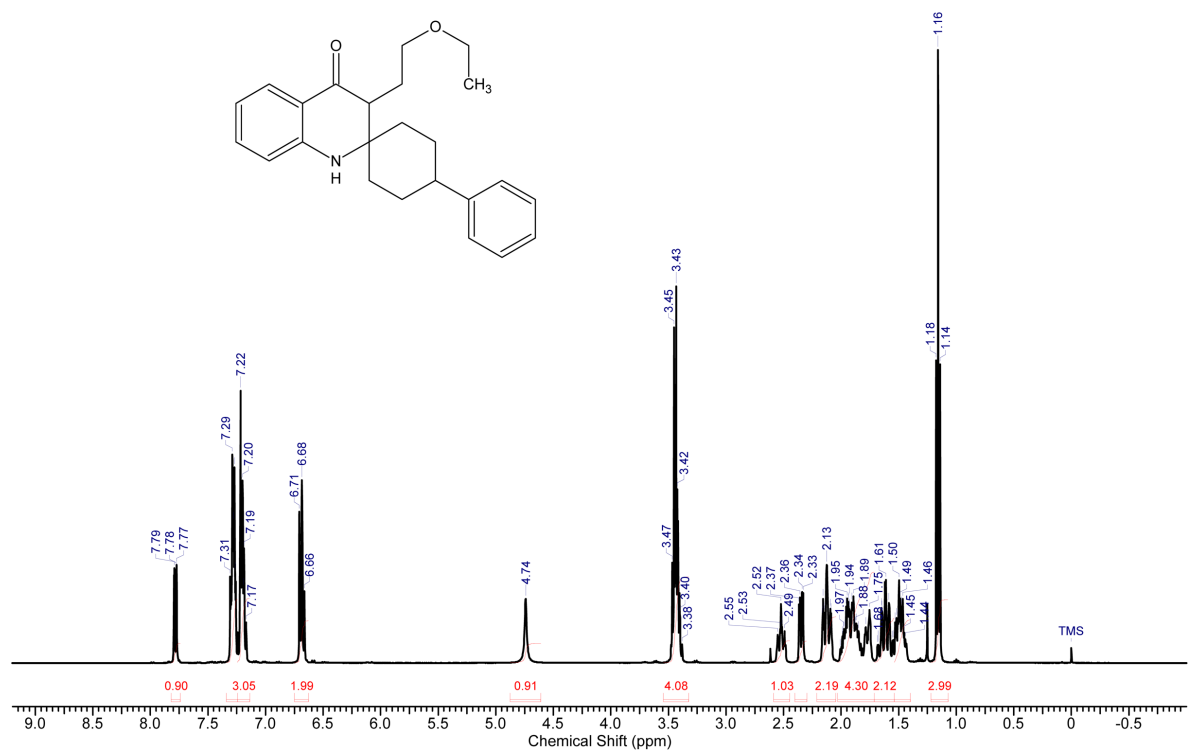


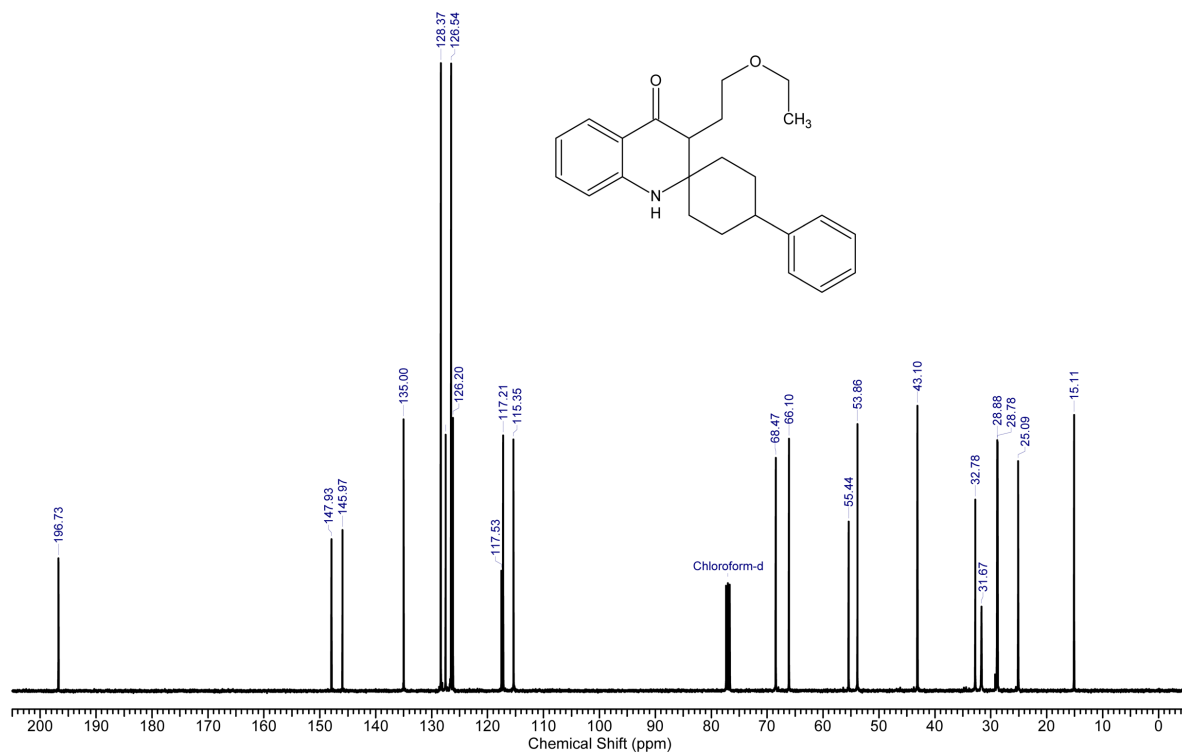
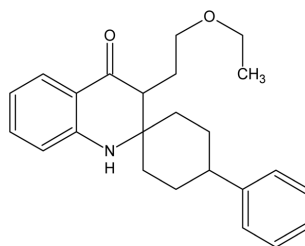
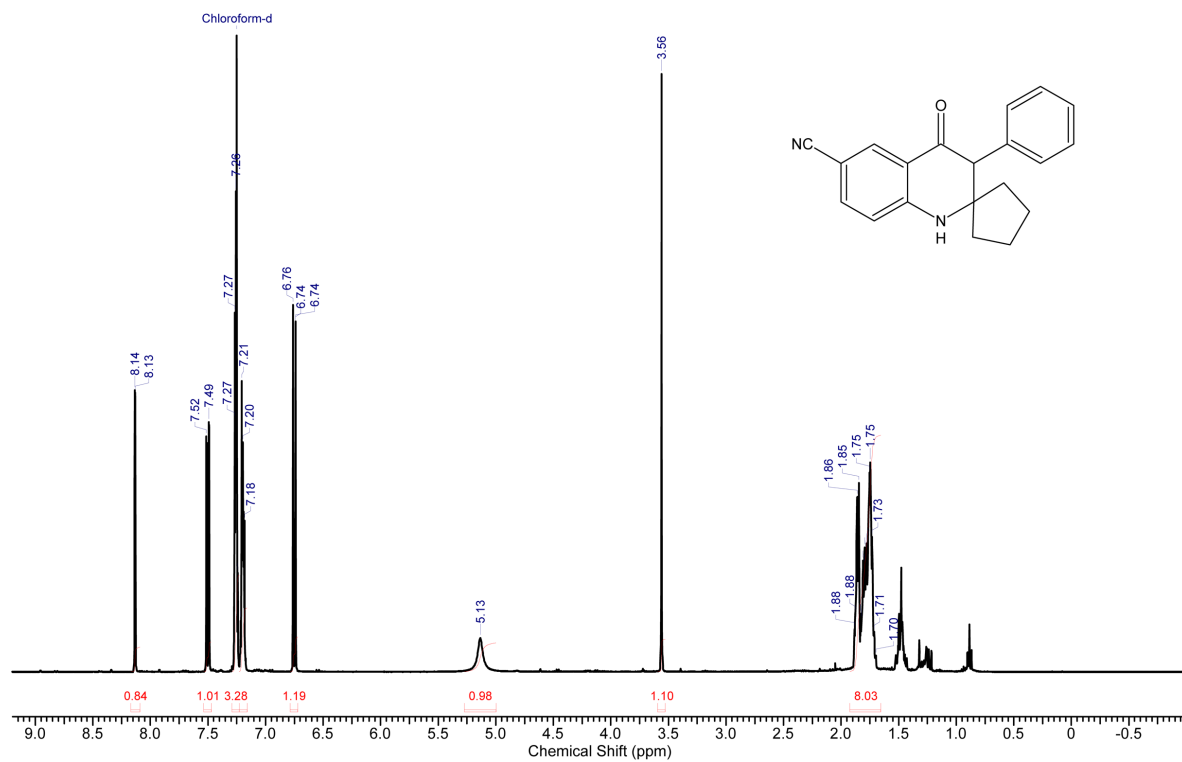
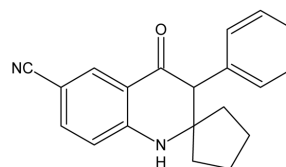


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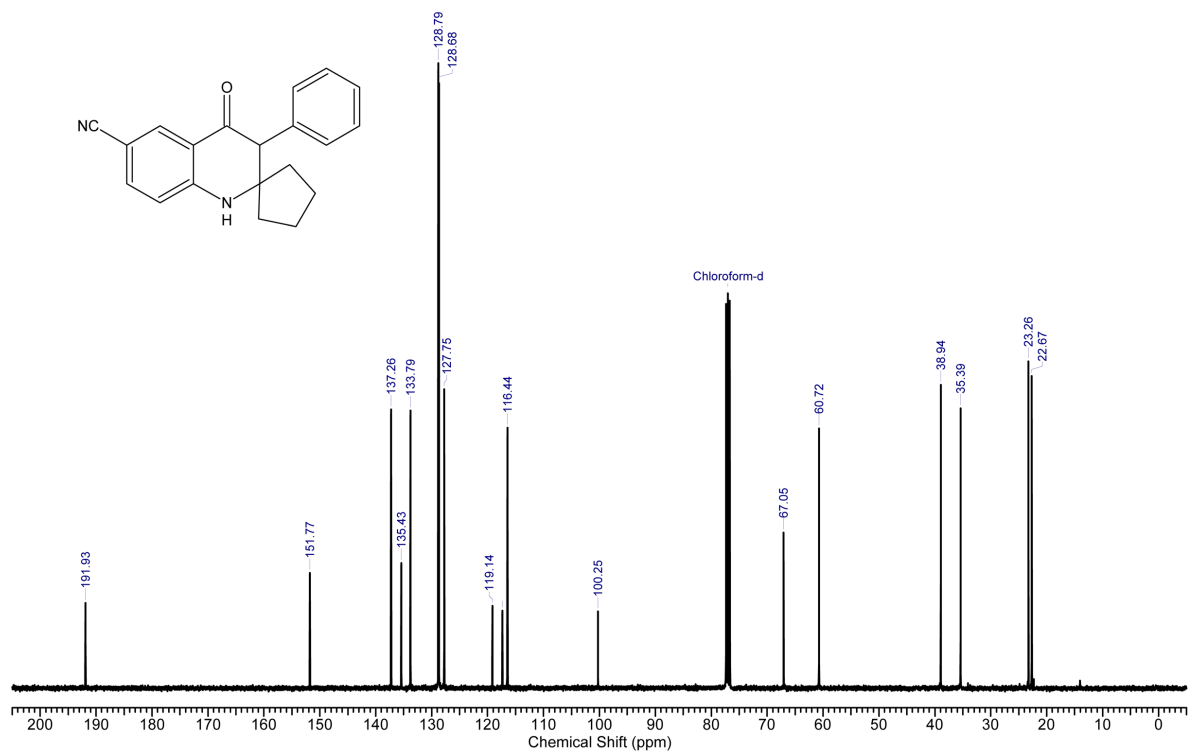


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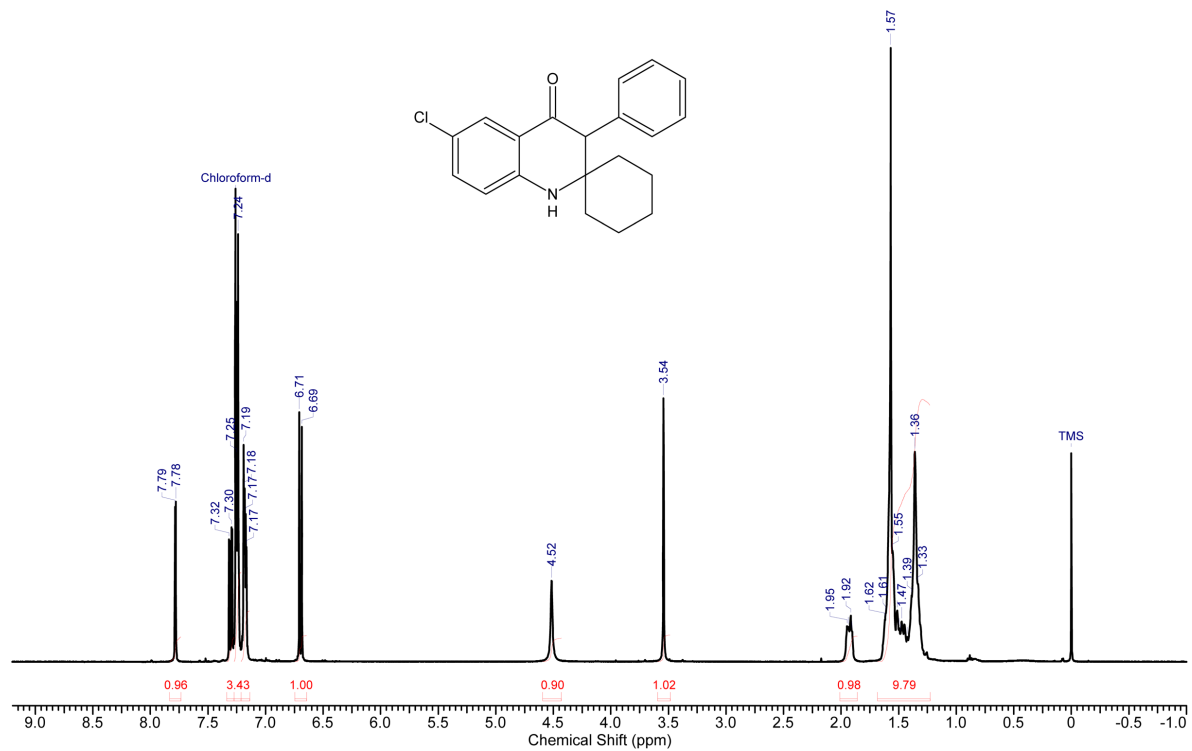


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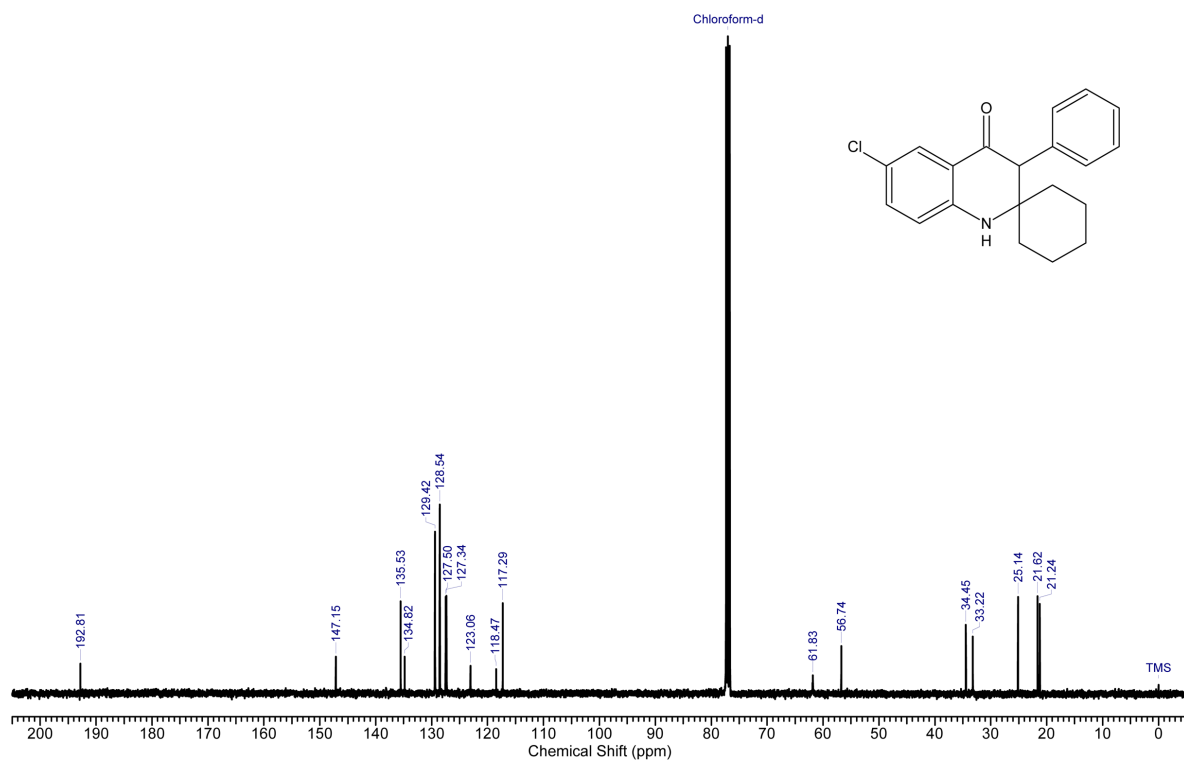
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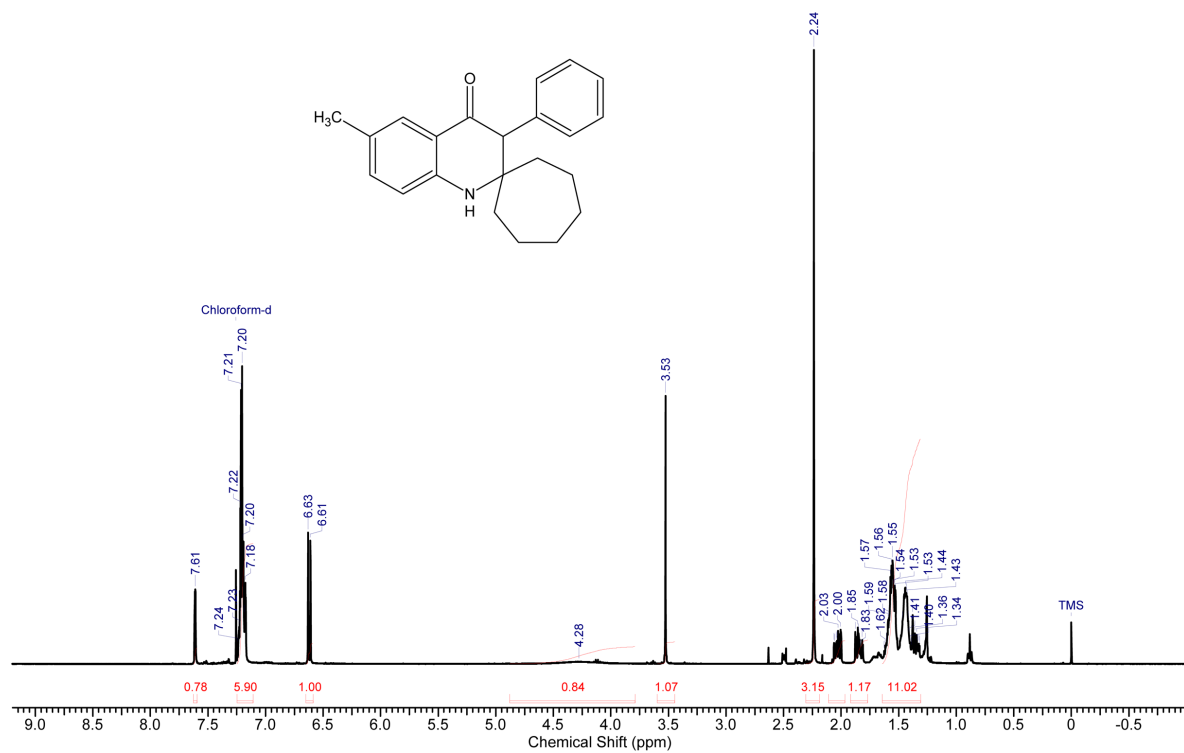
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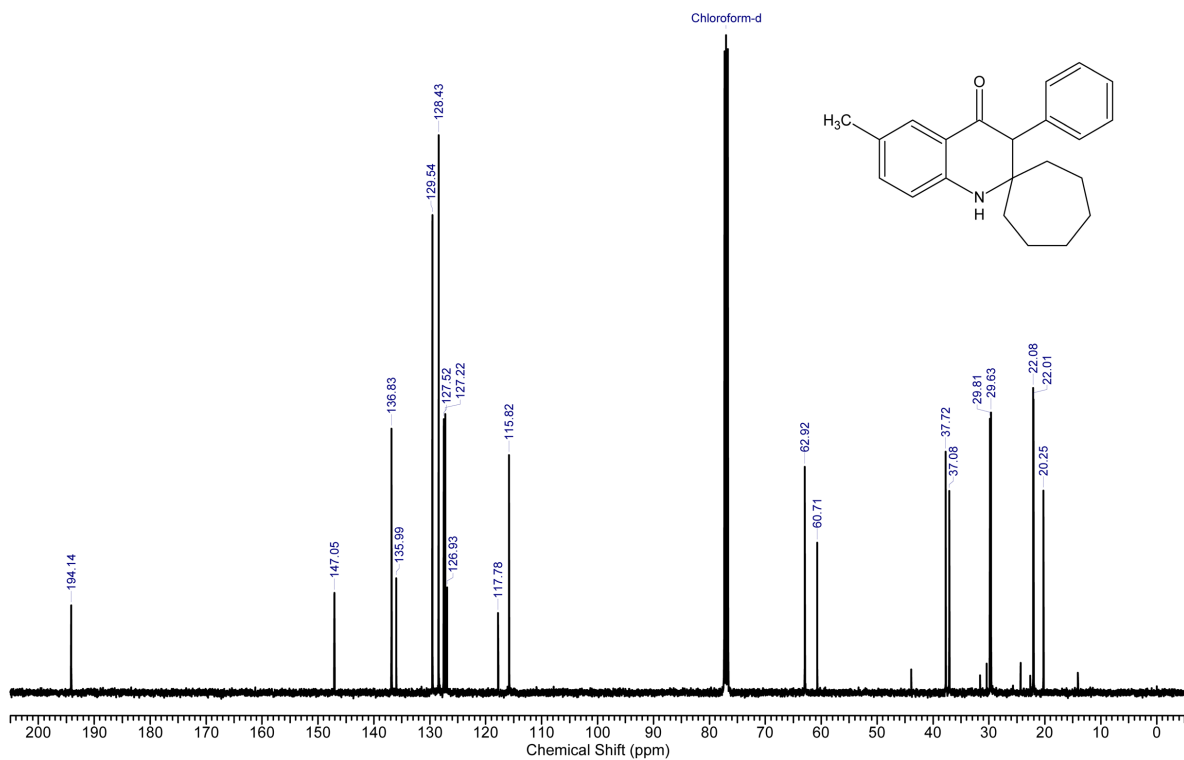
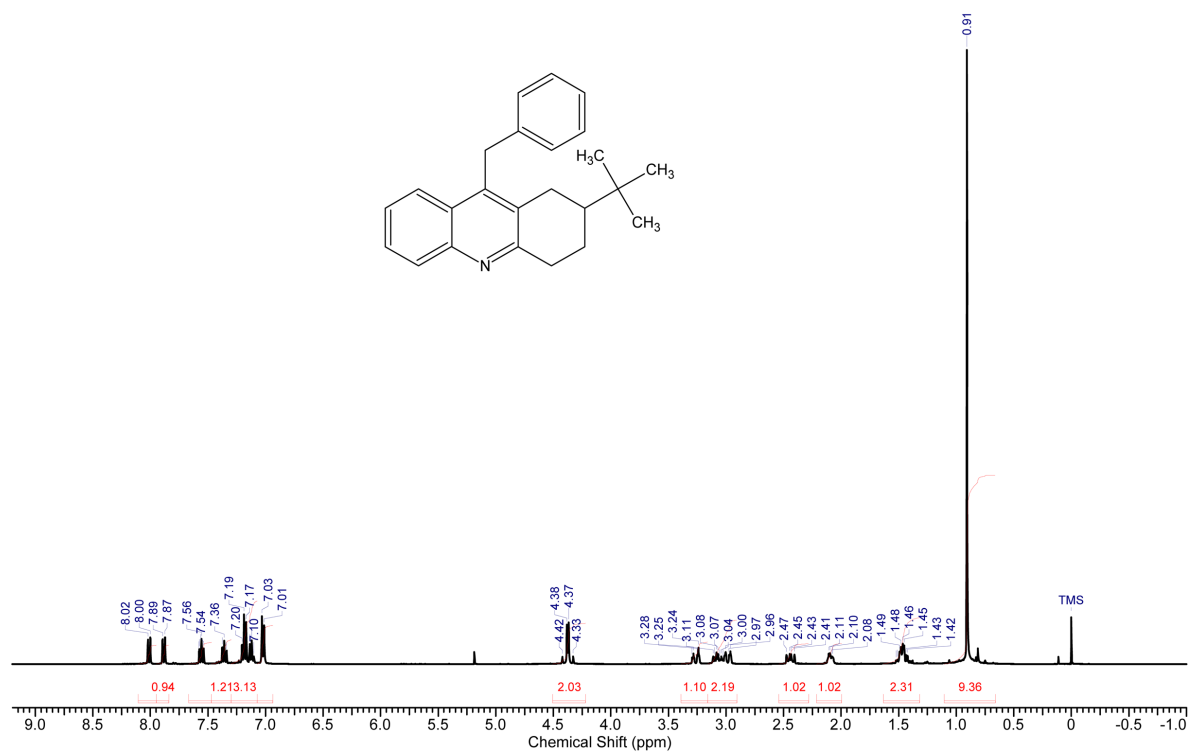


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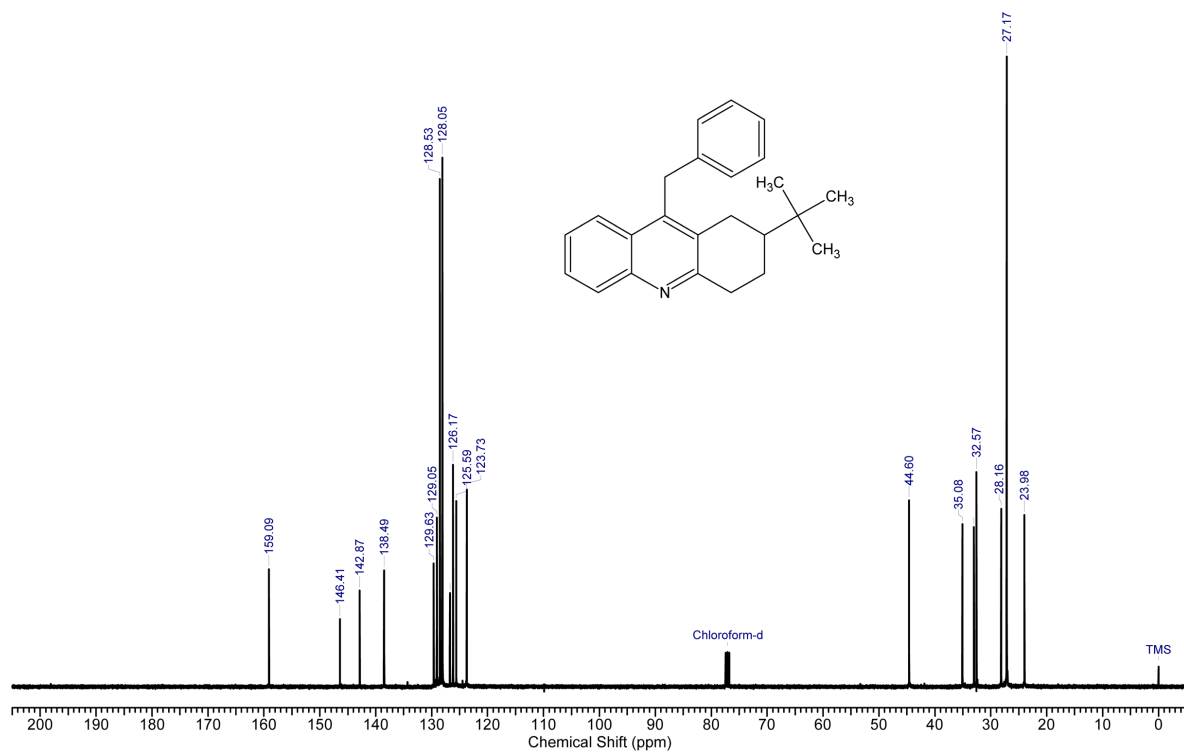


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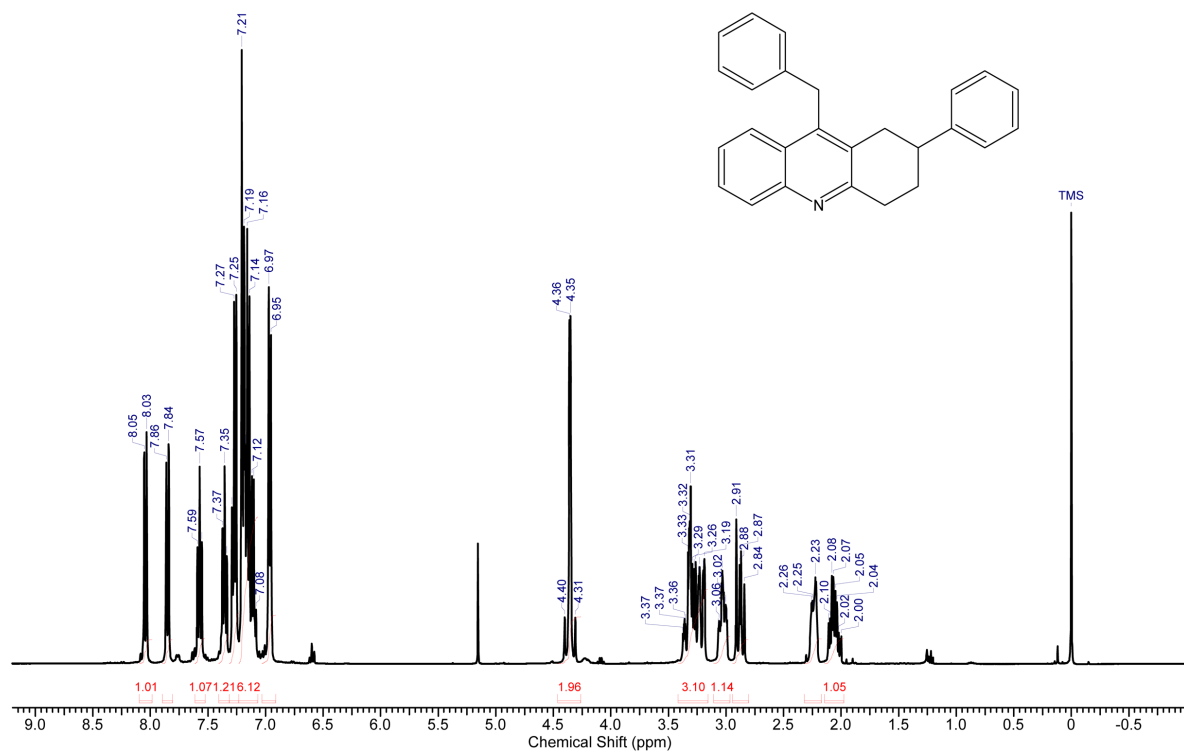


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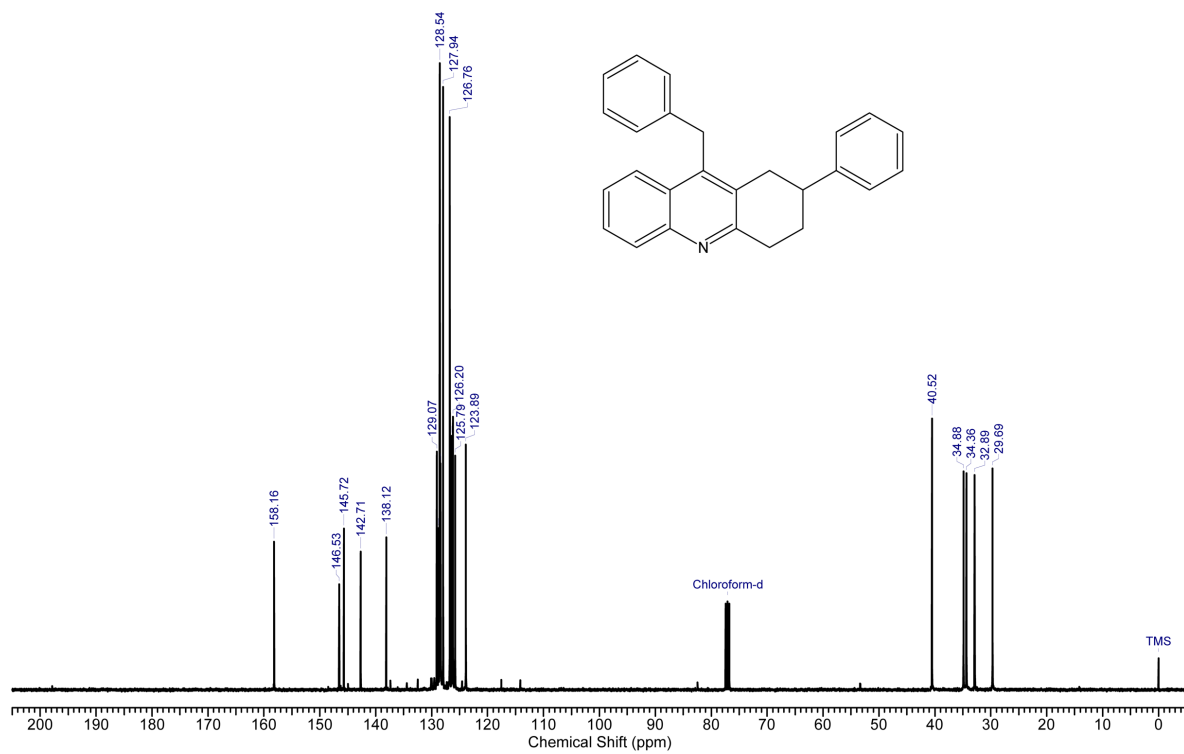
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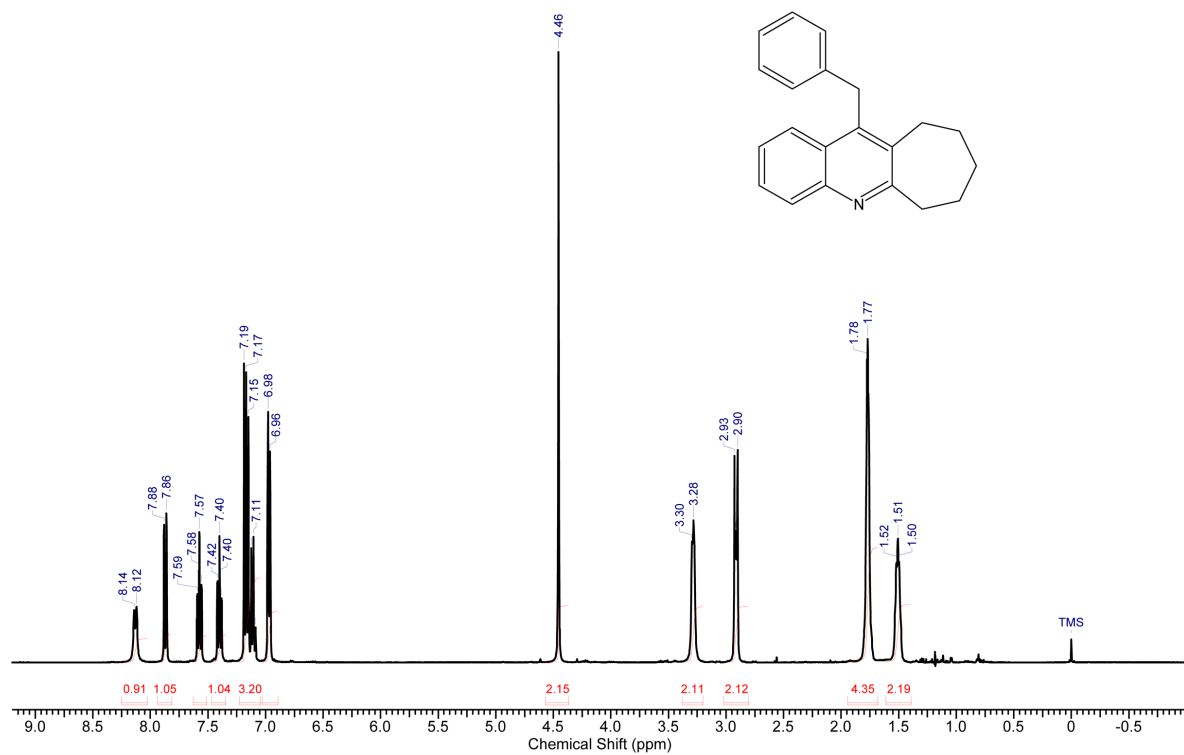
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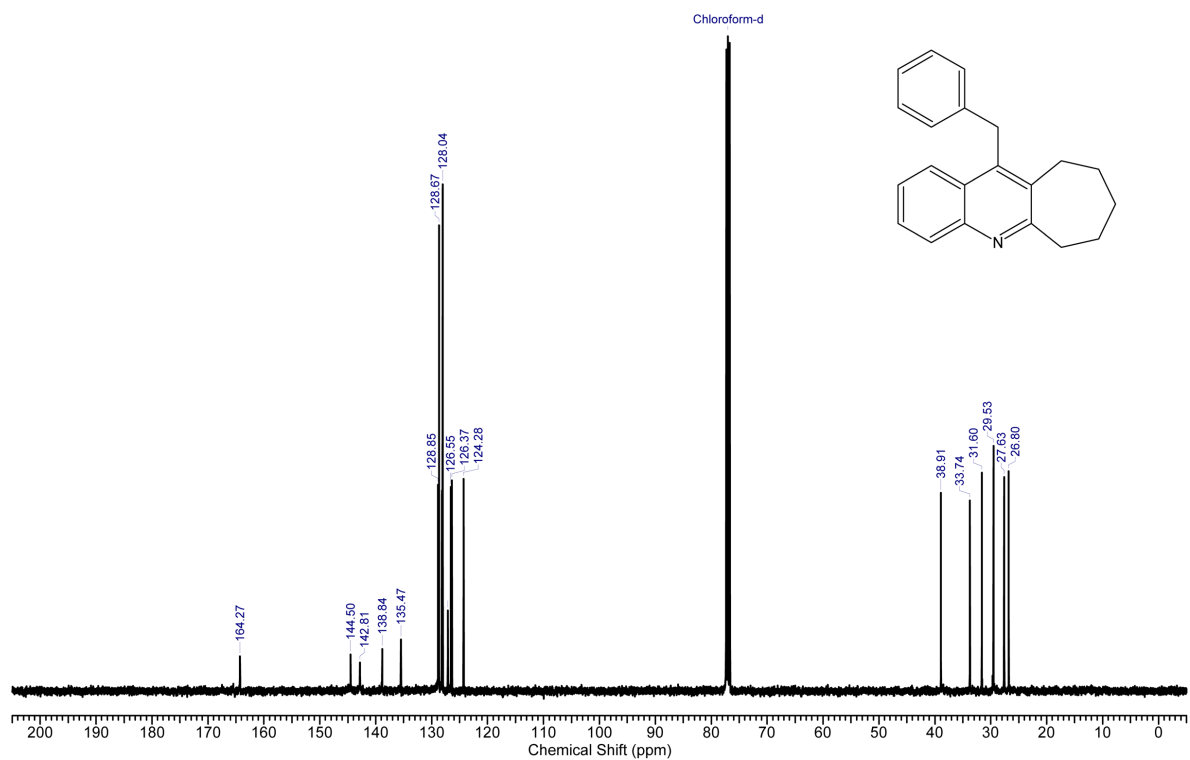
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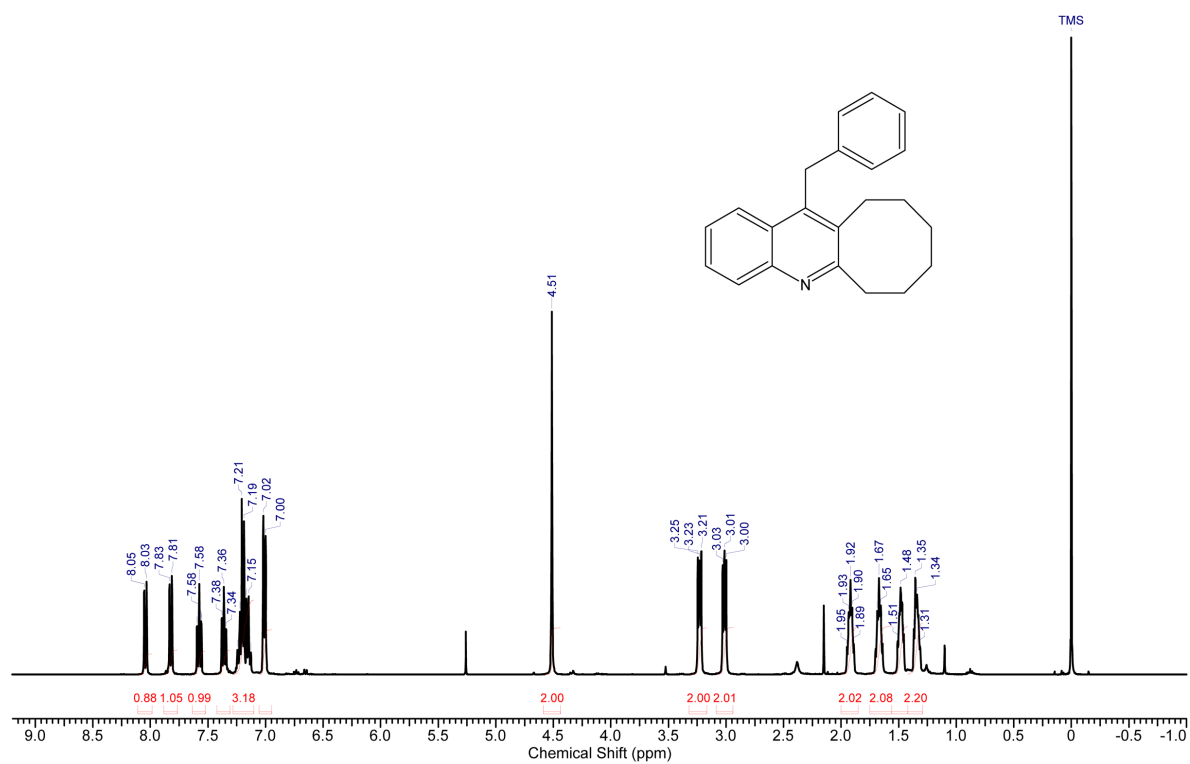
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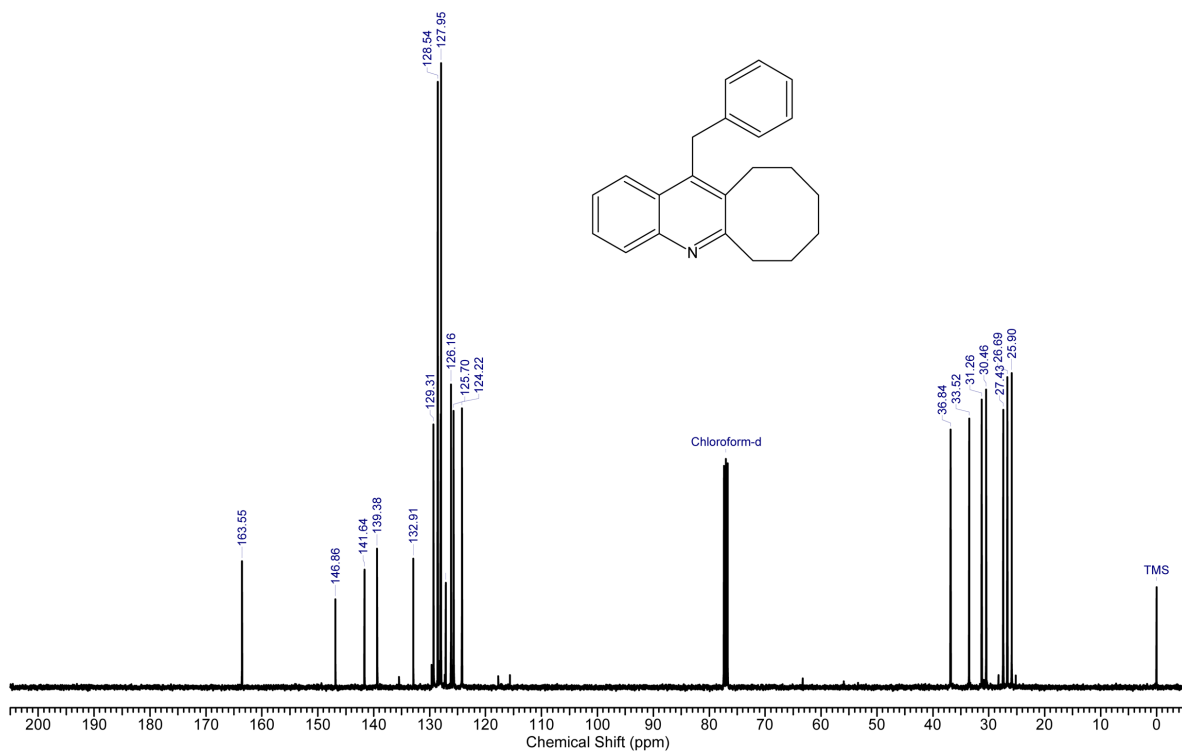
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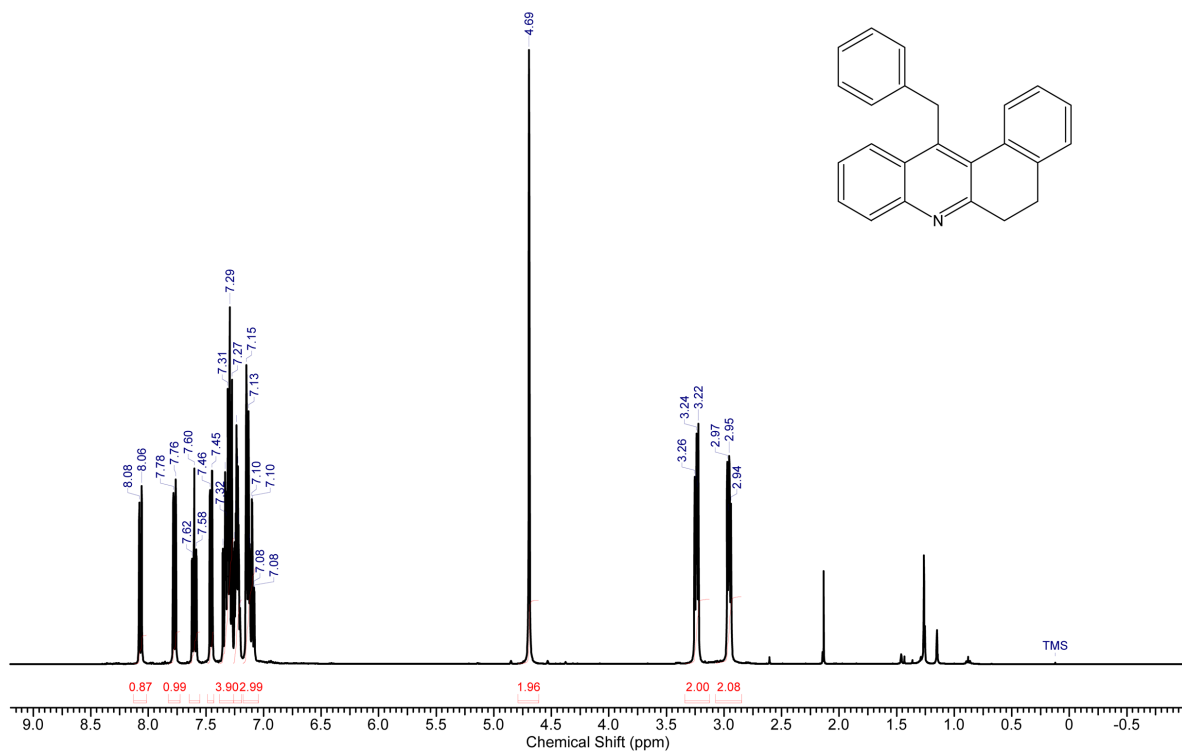
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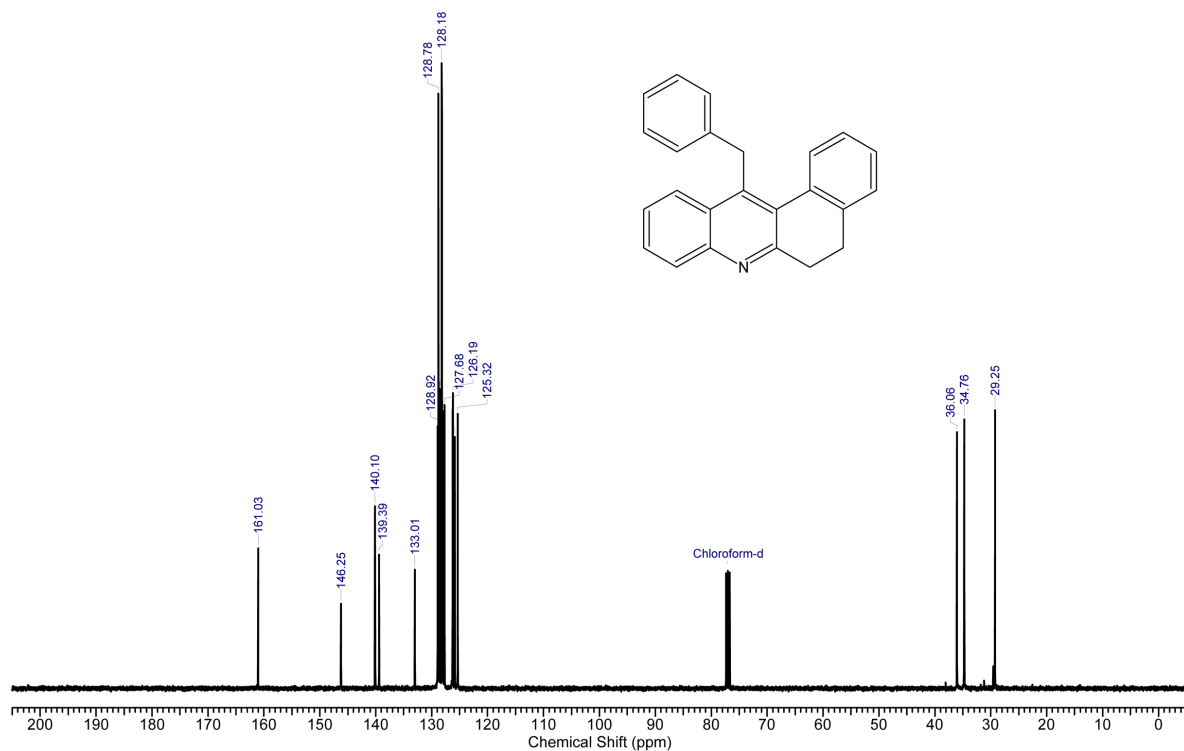
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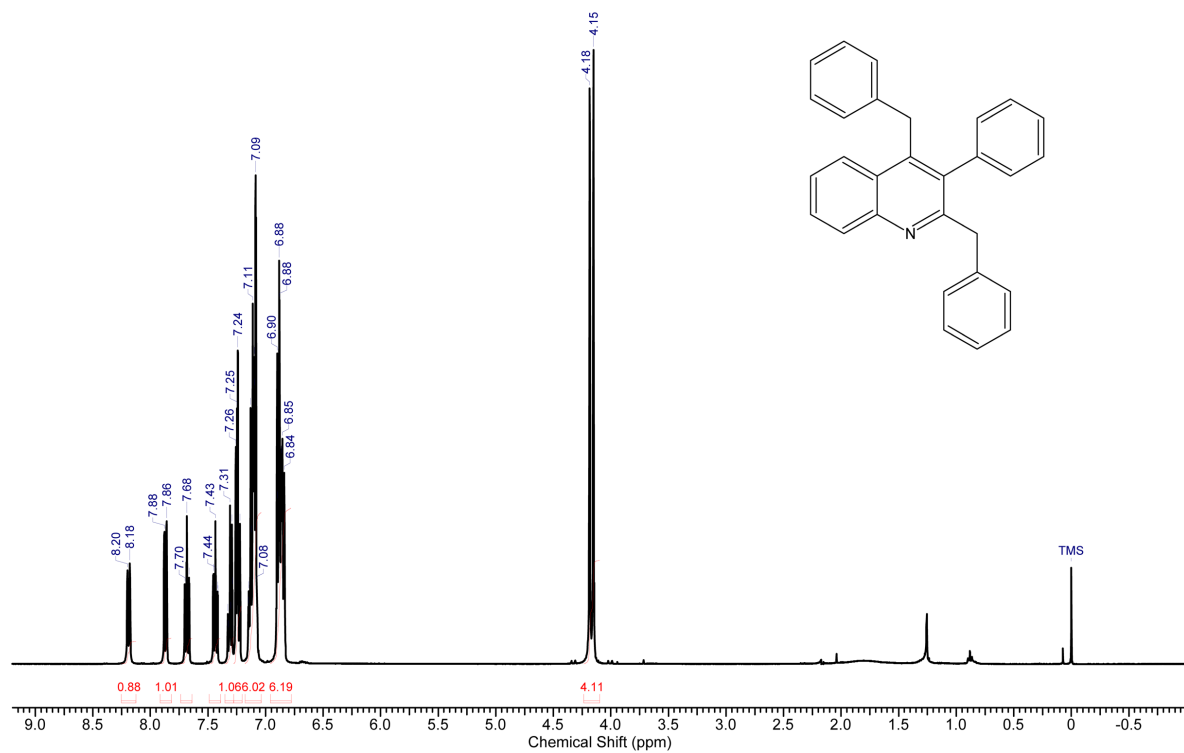
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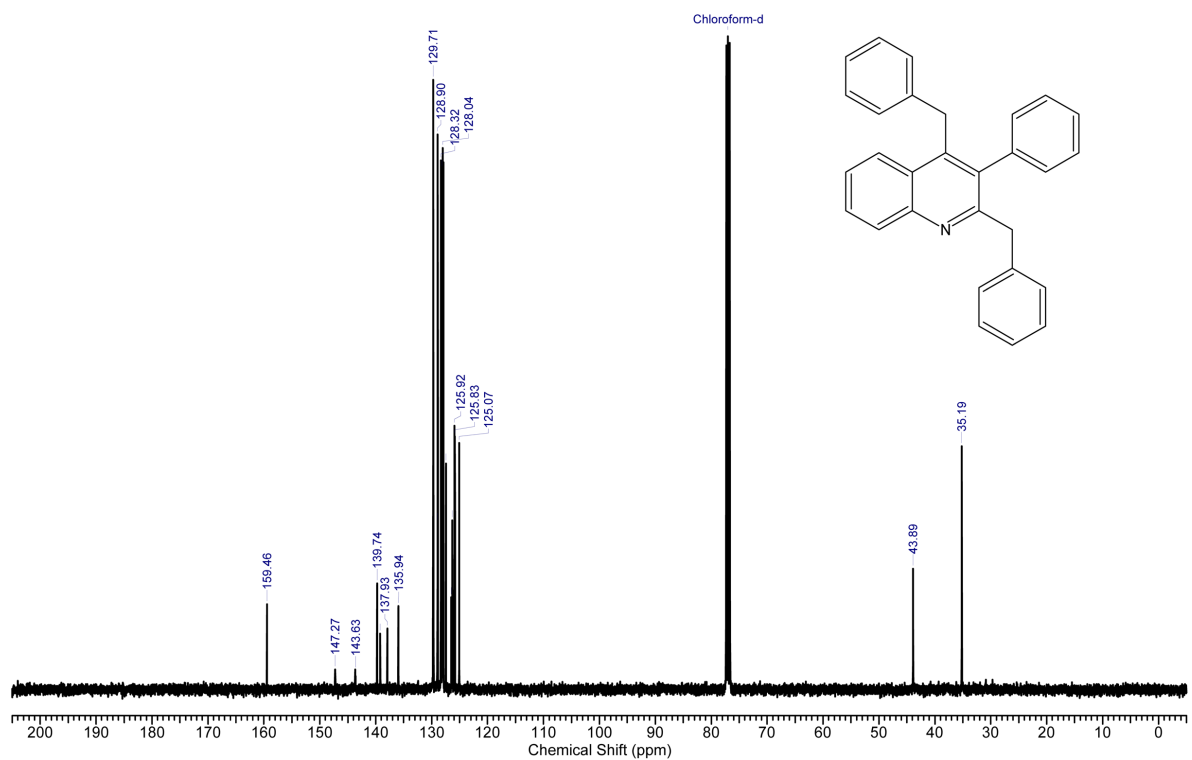
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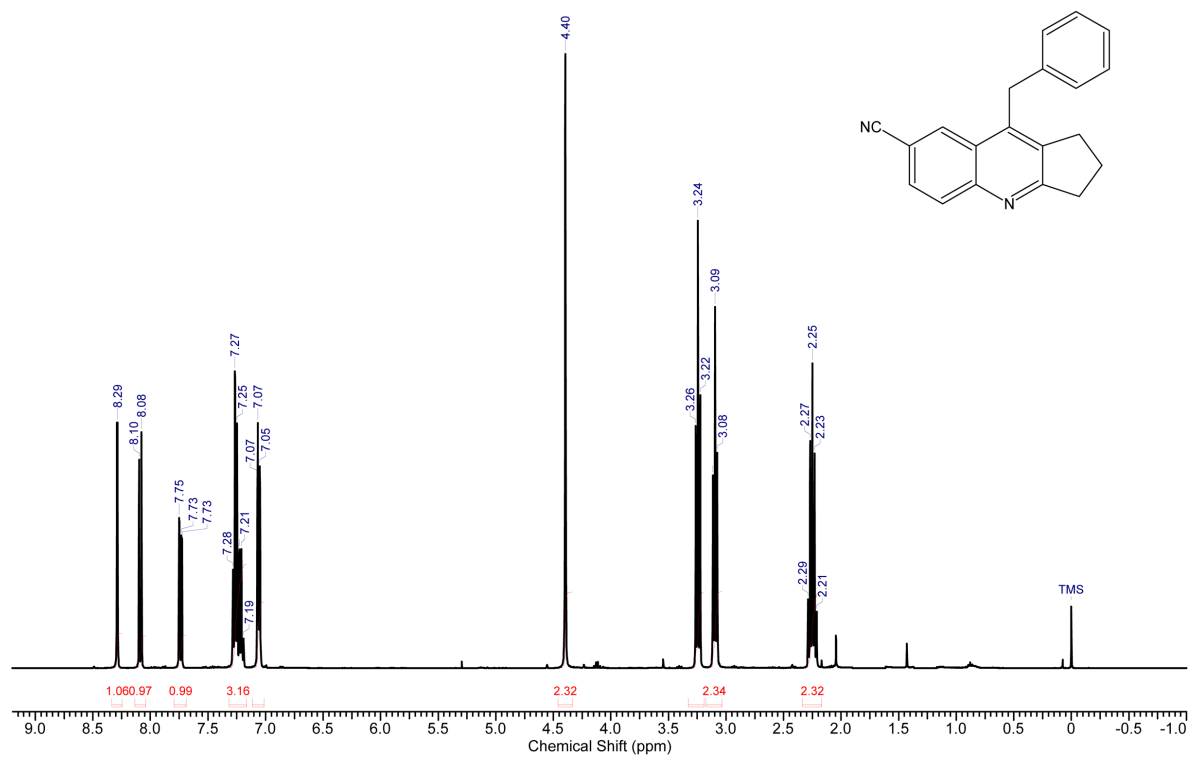
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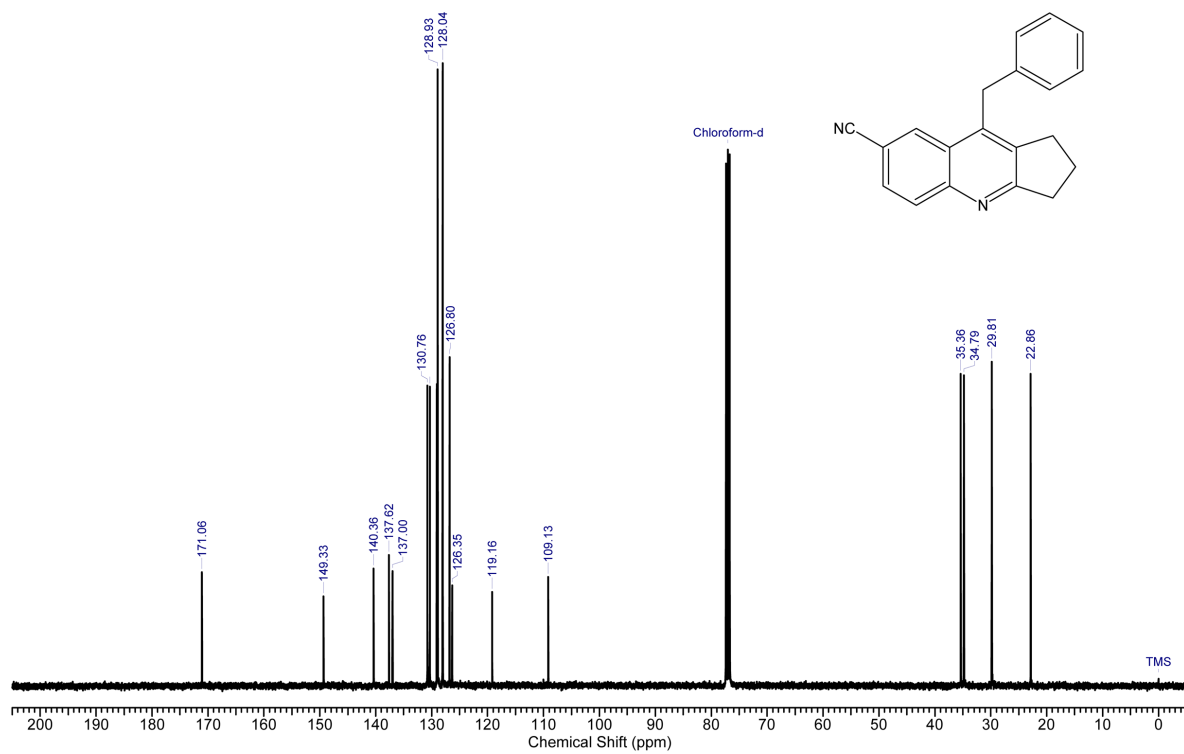
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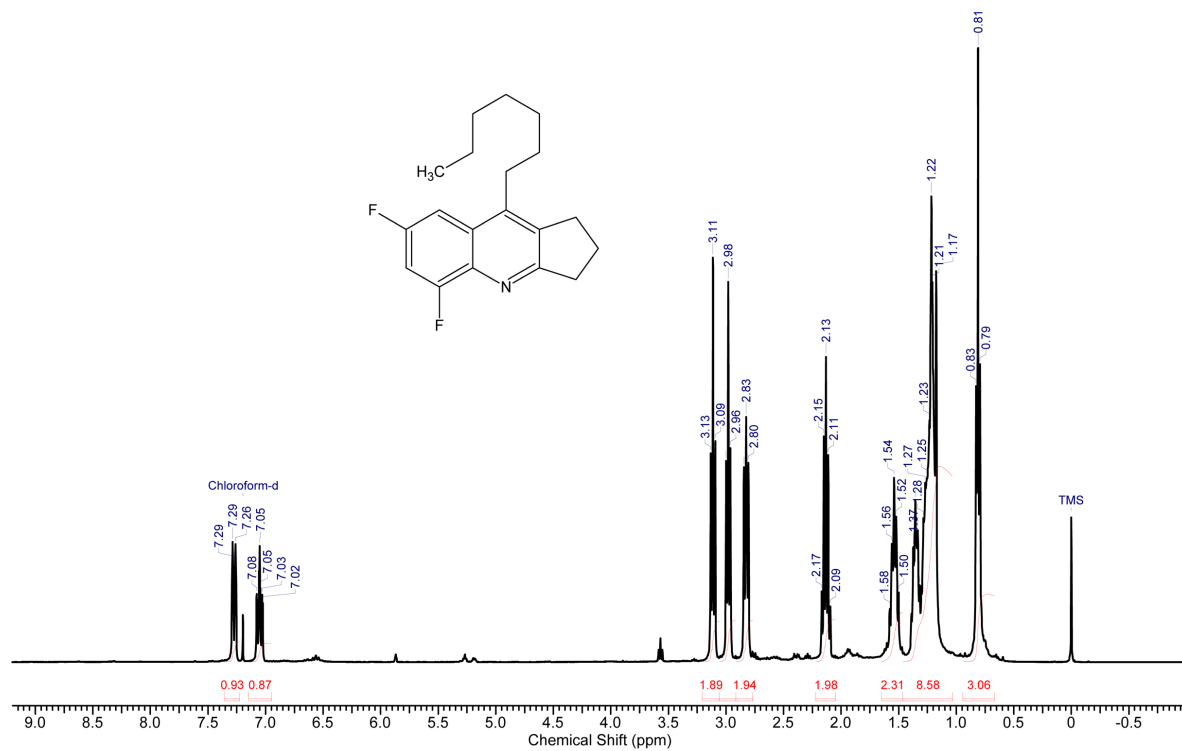
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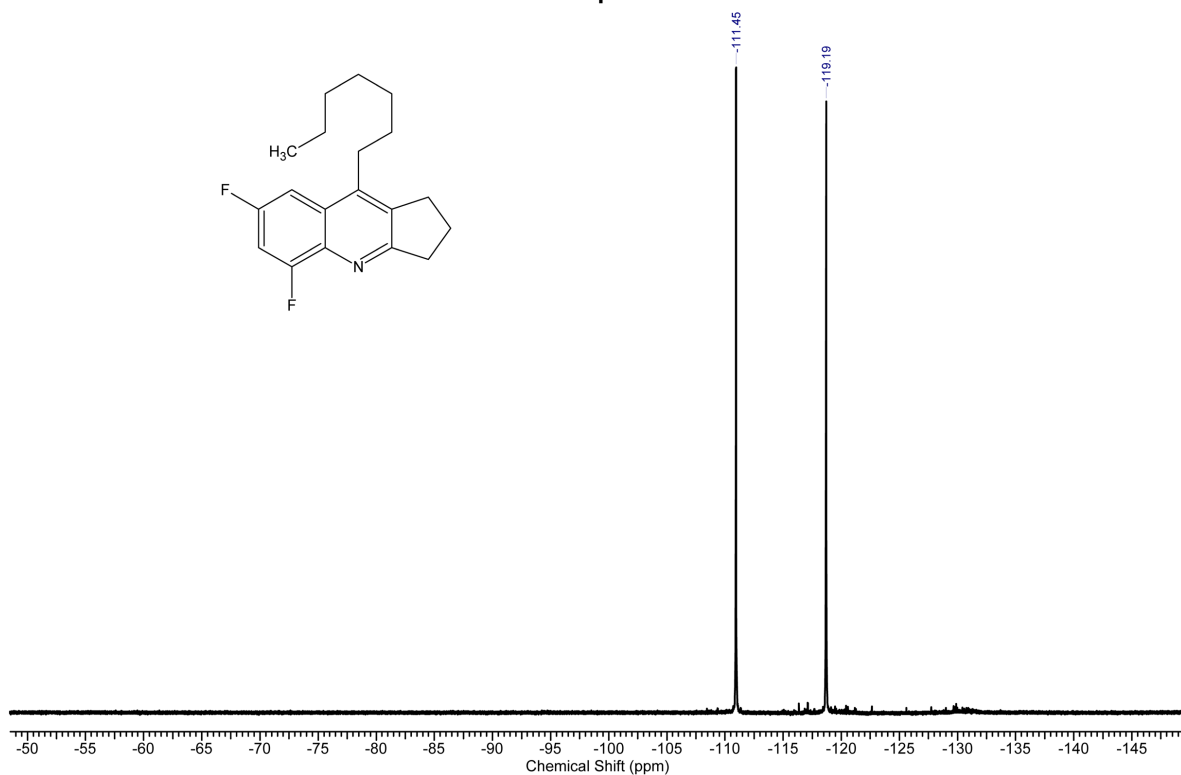
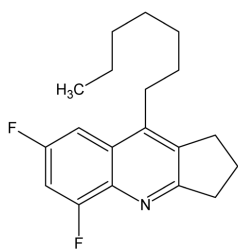
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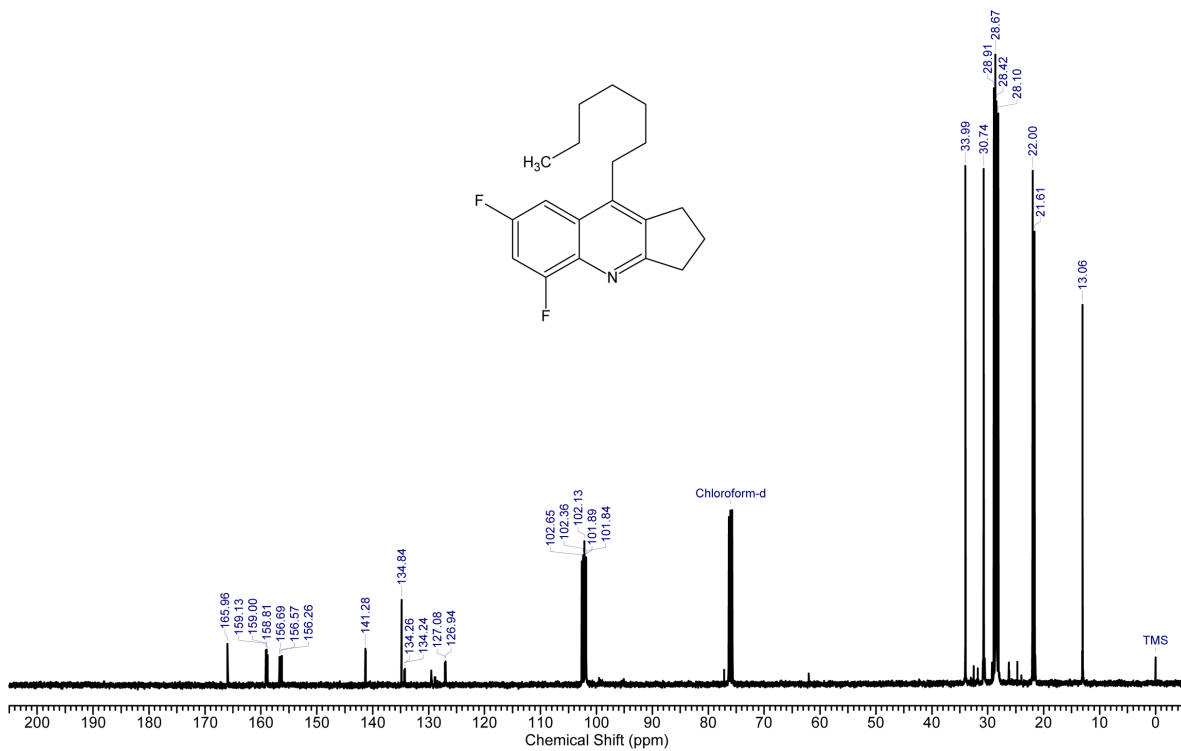
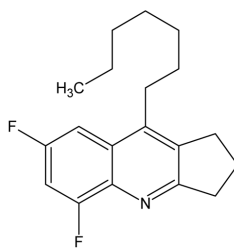
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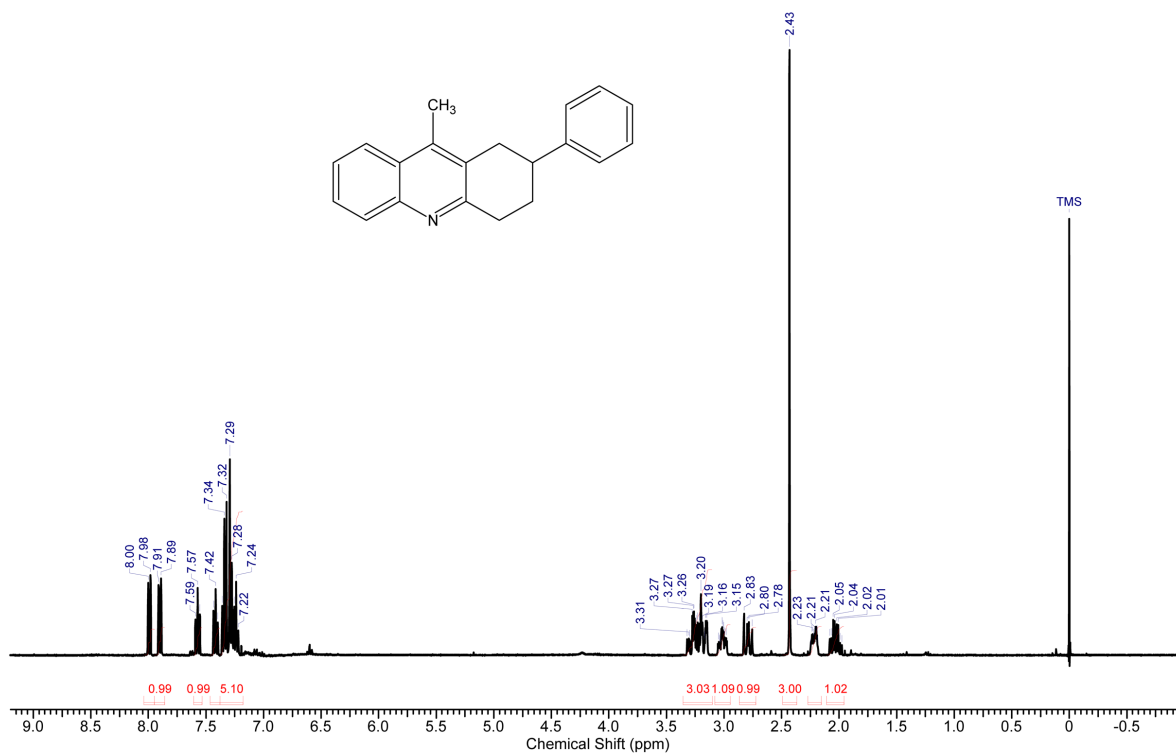
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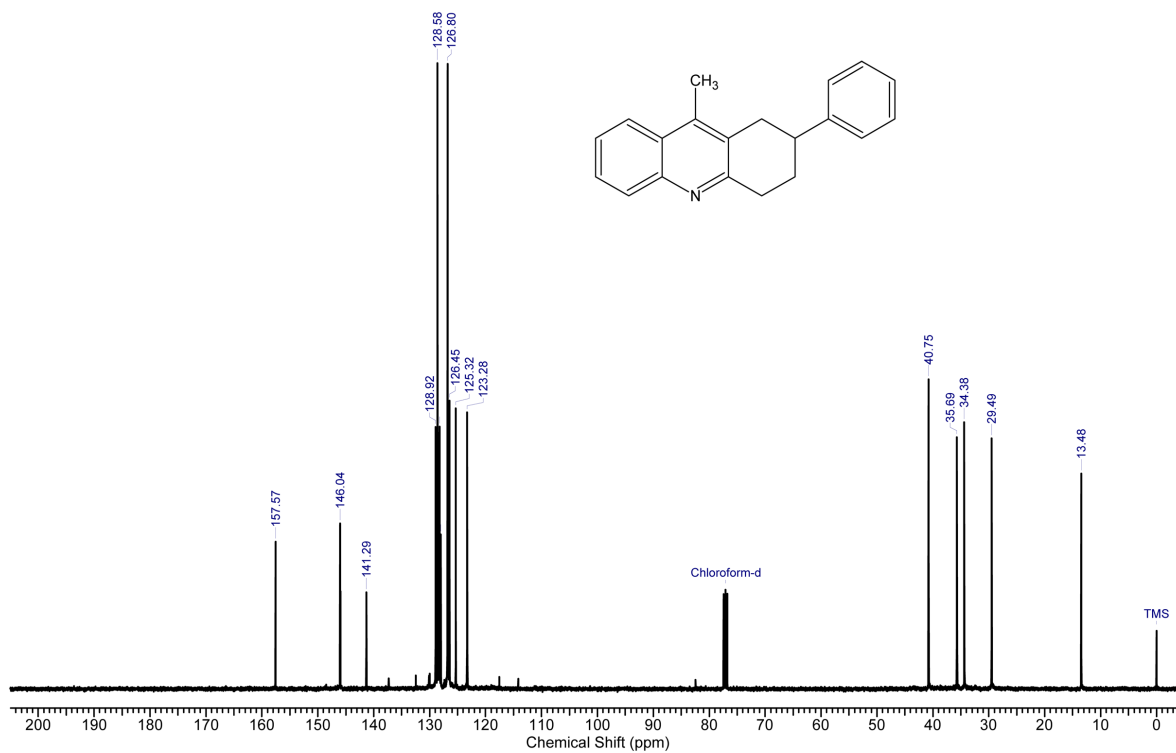
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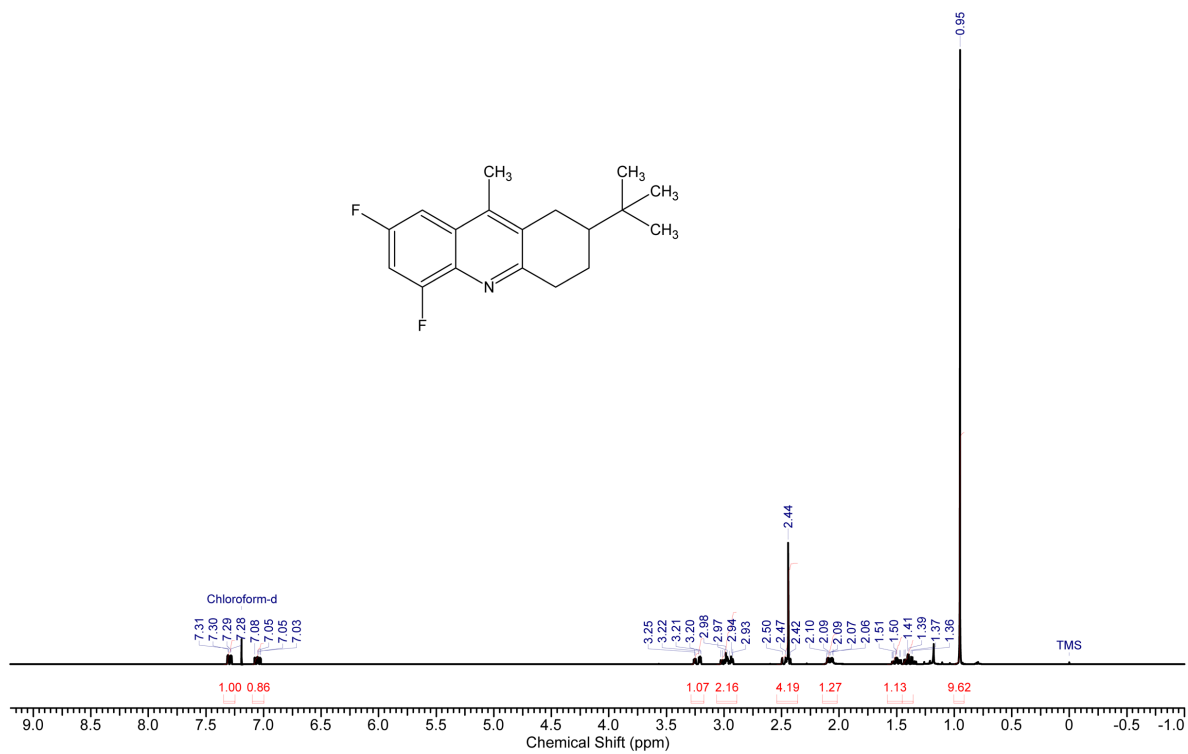
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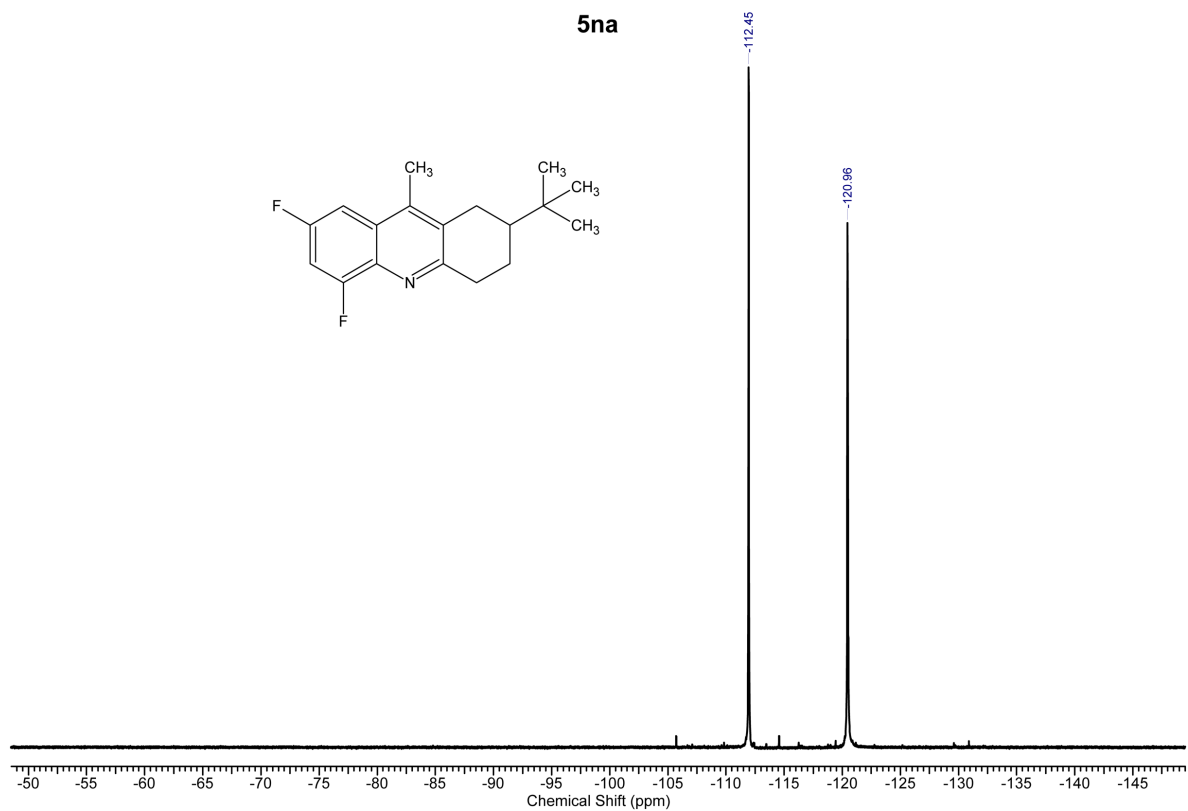
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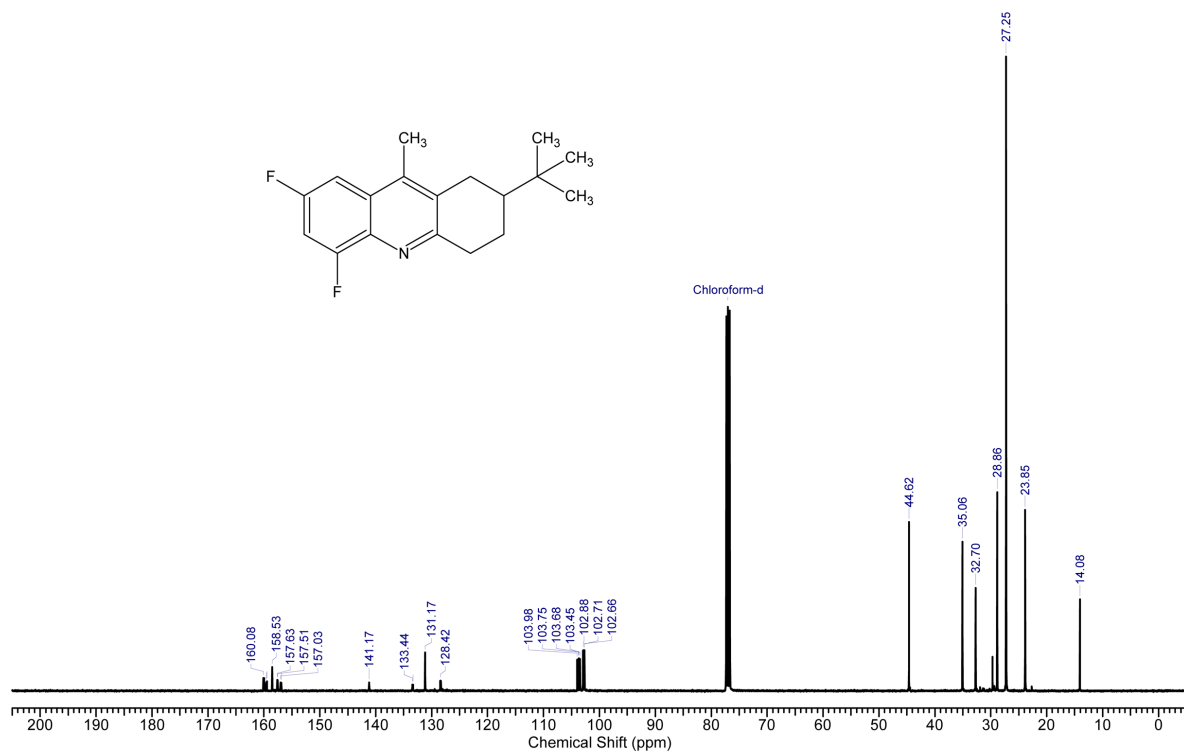
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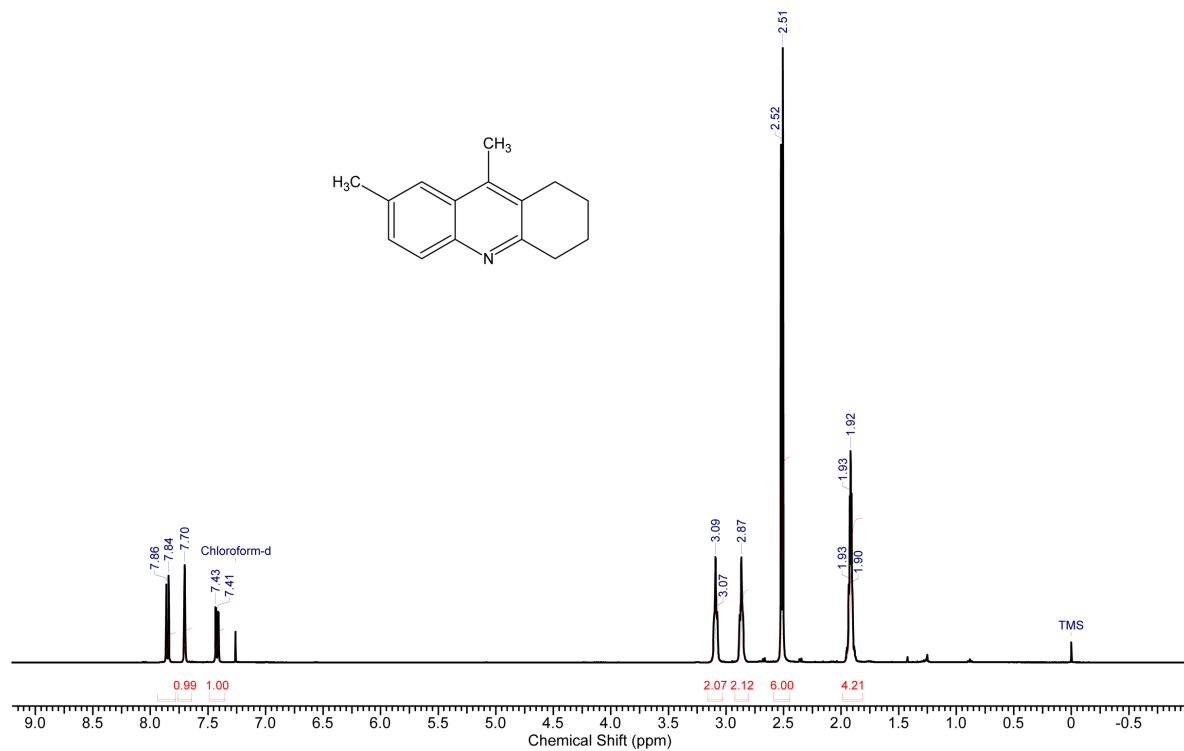
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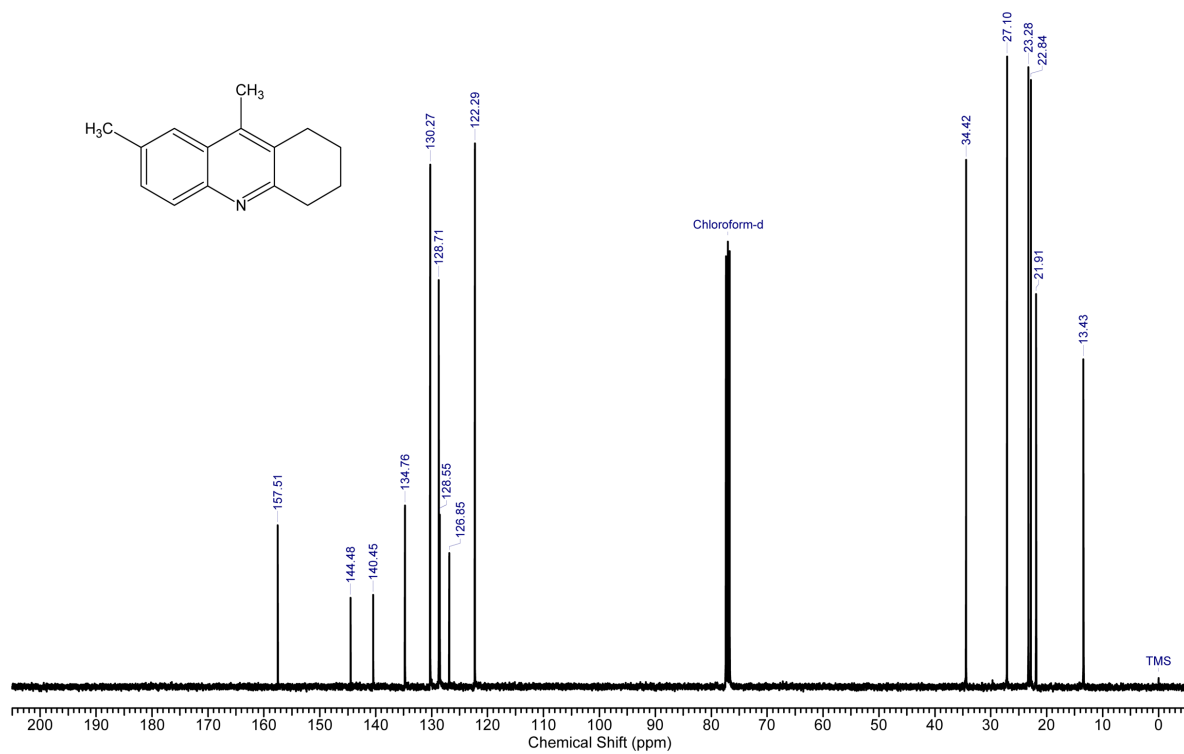
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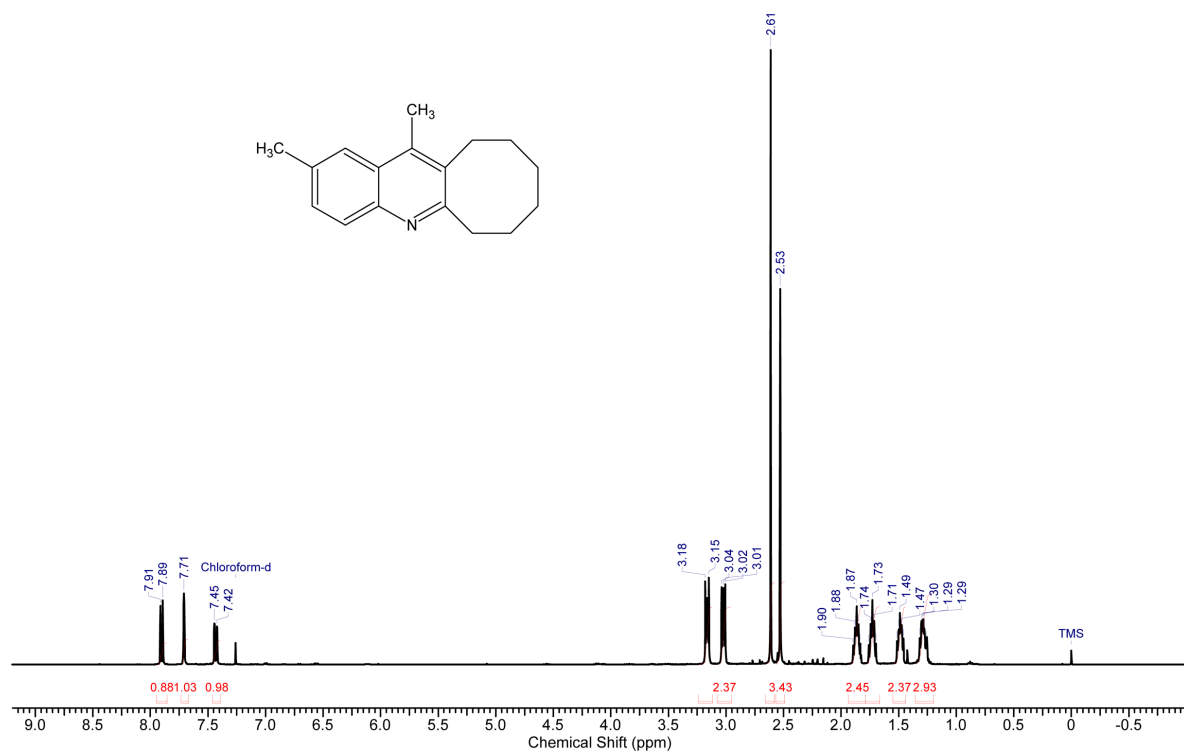
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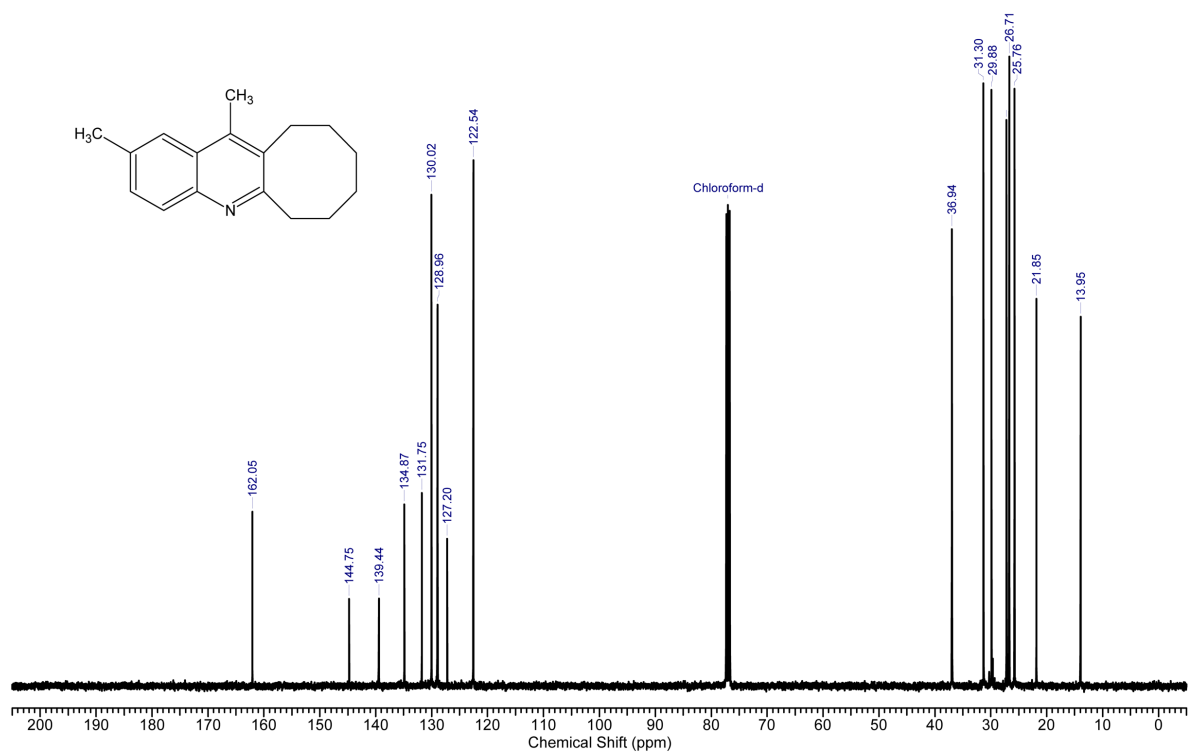
50c



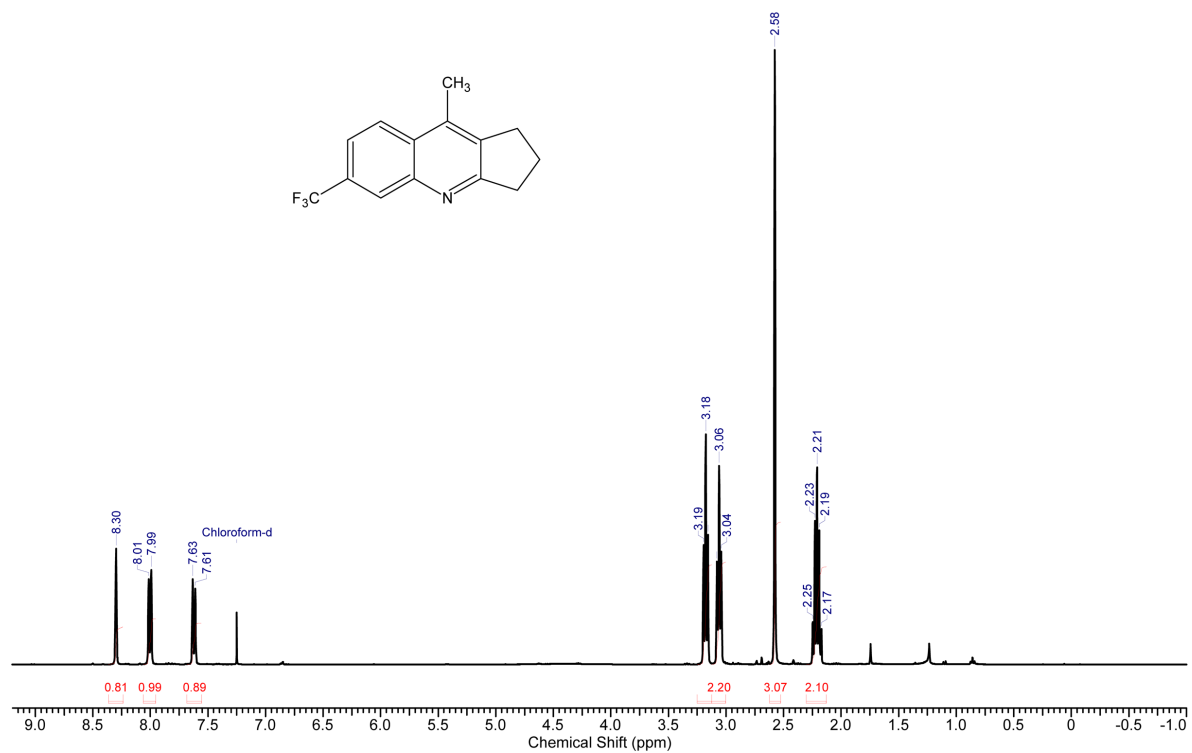
50g



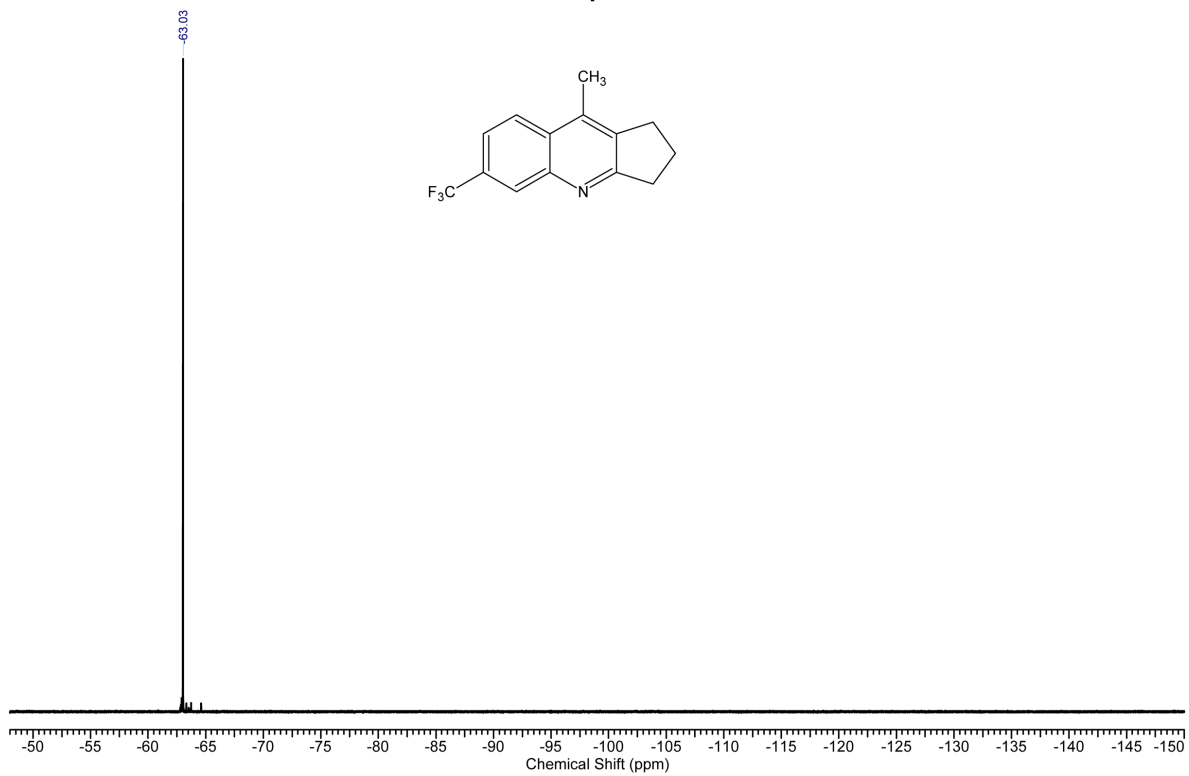
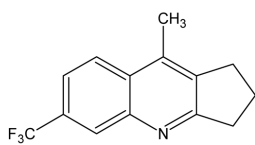
5og



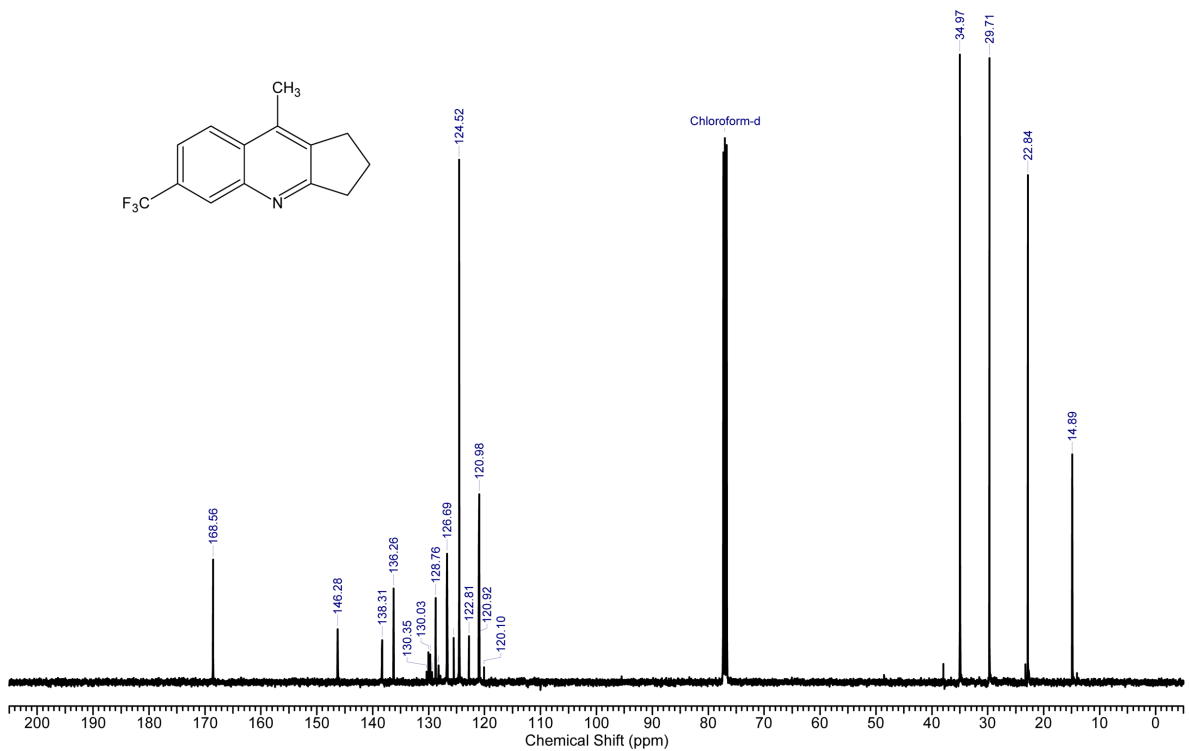
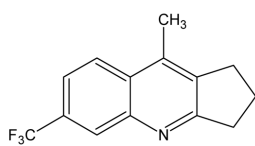
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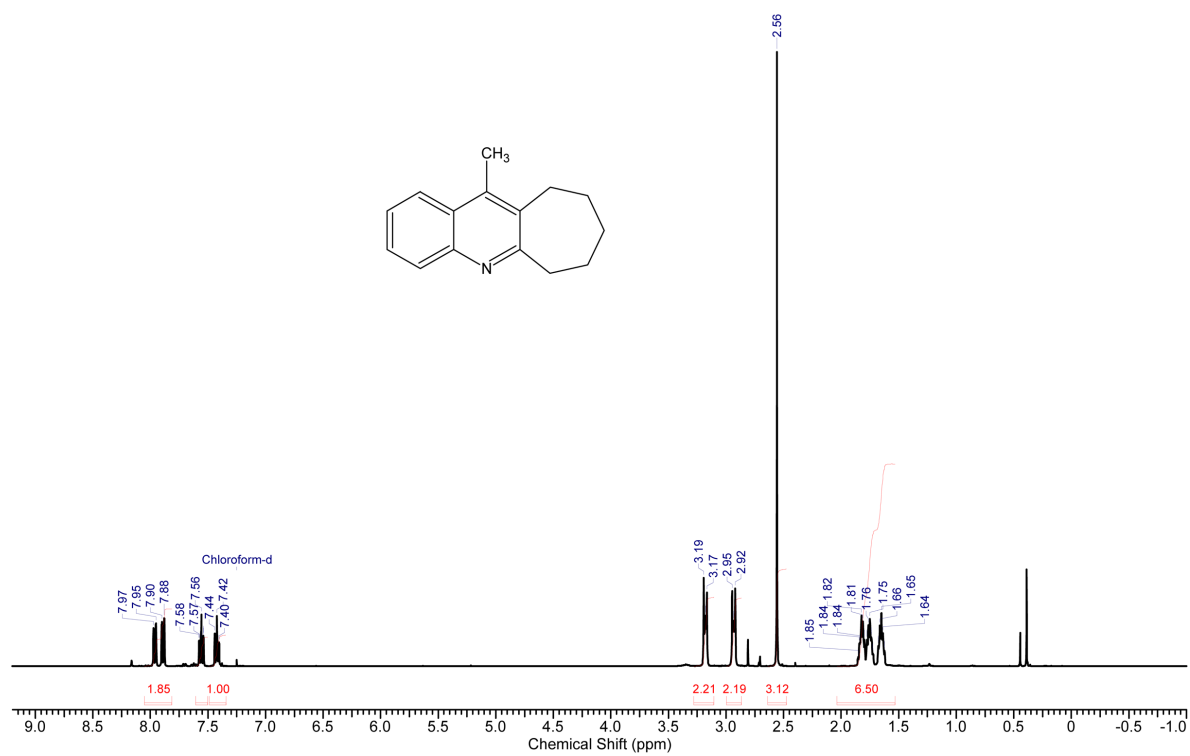
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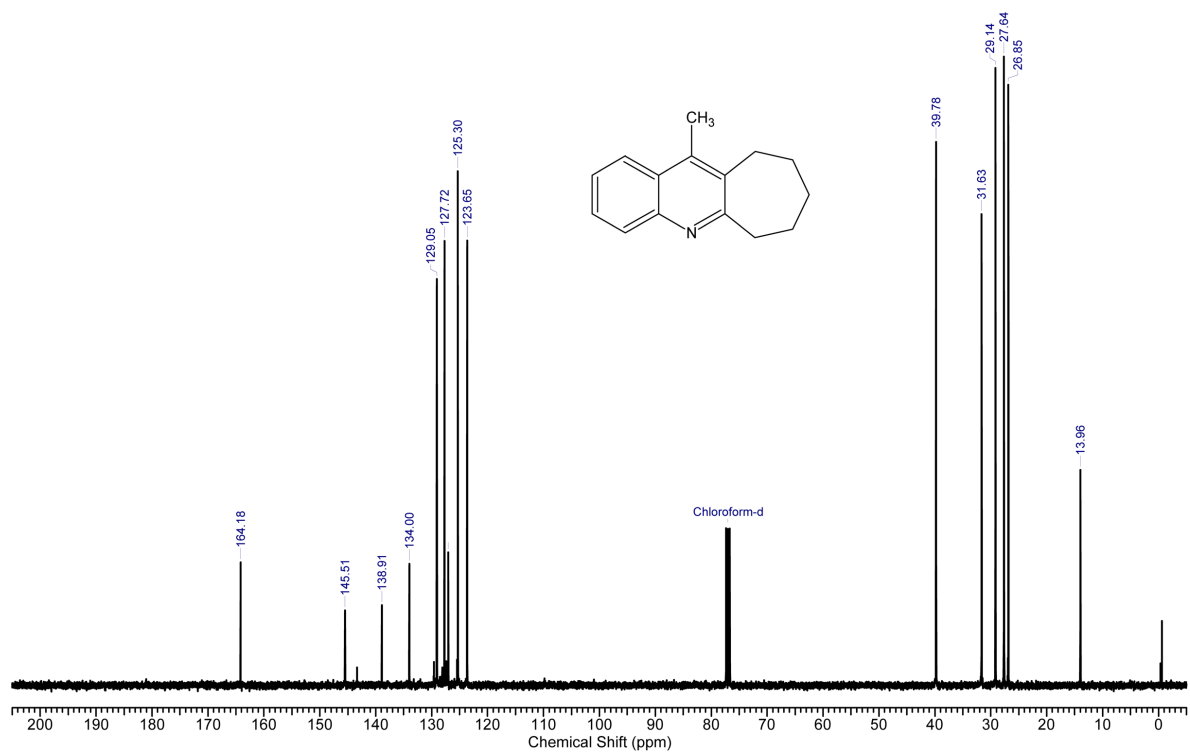
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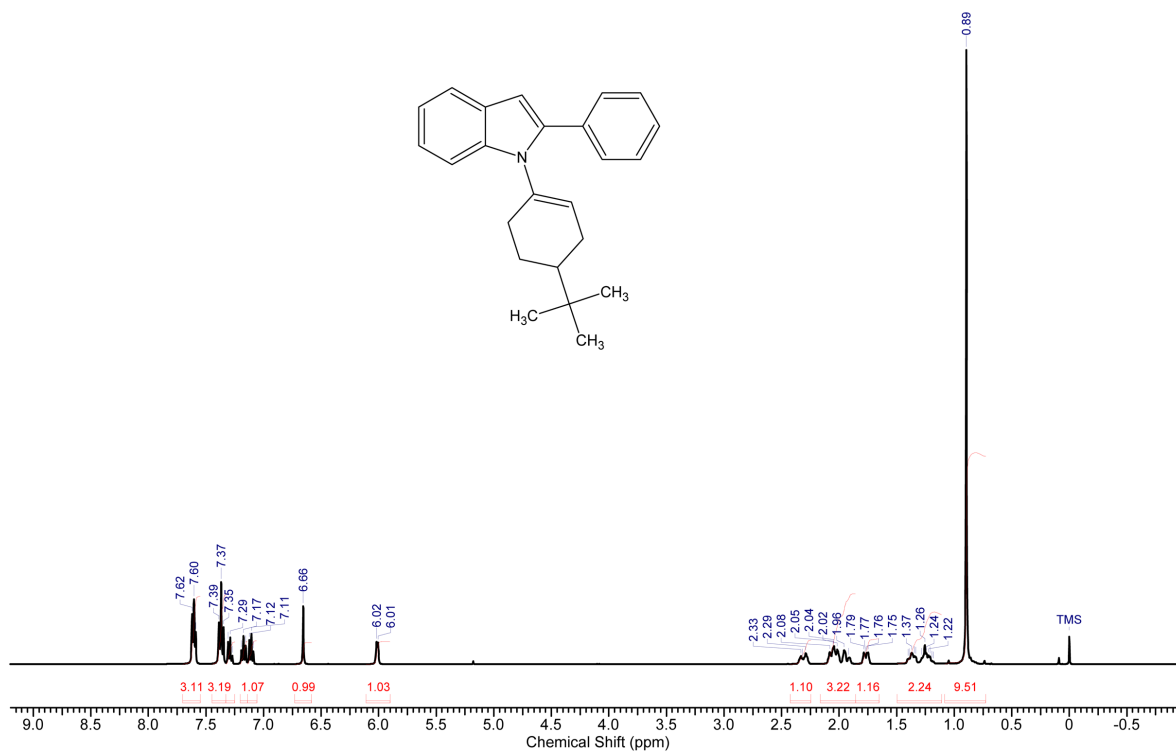
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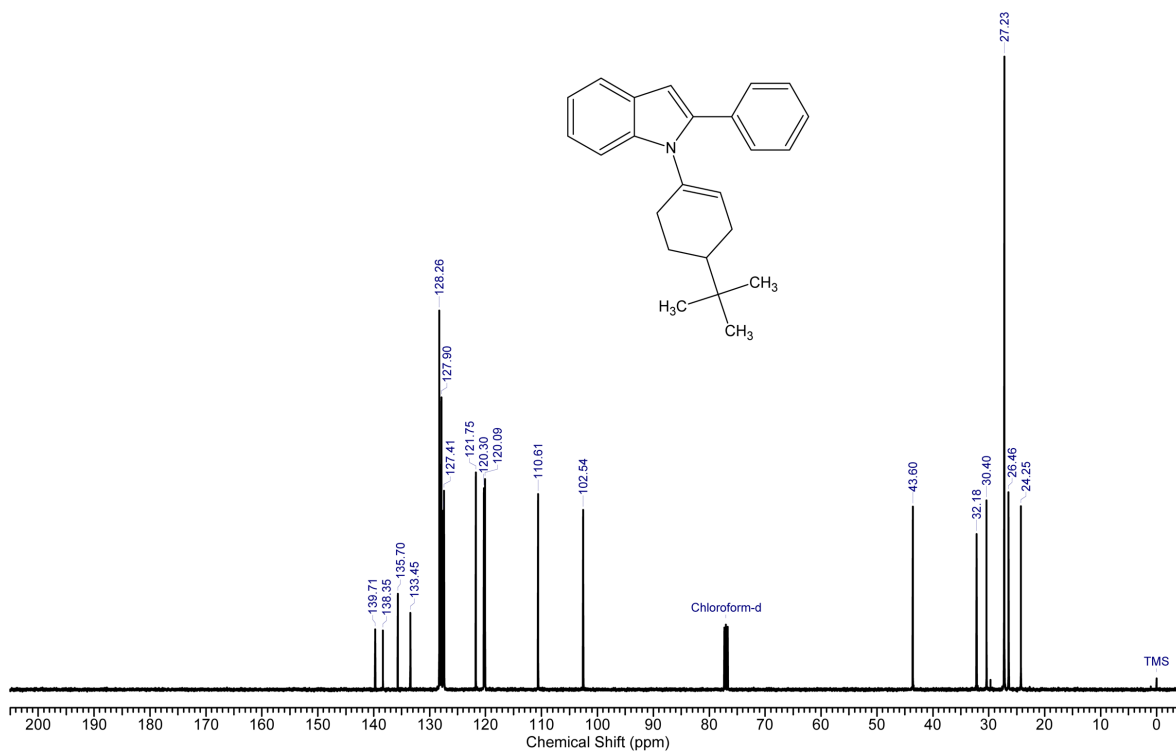
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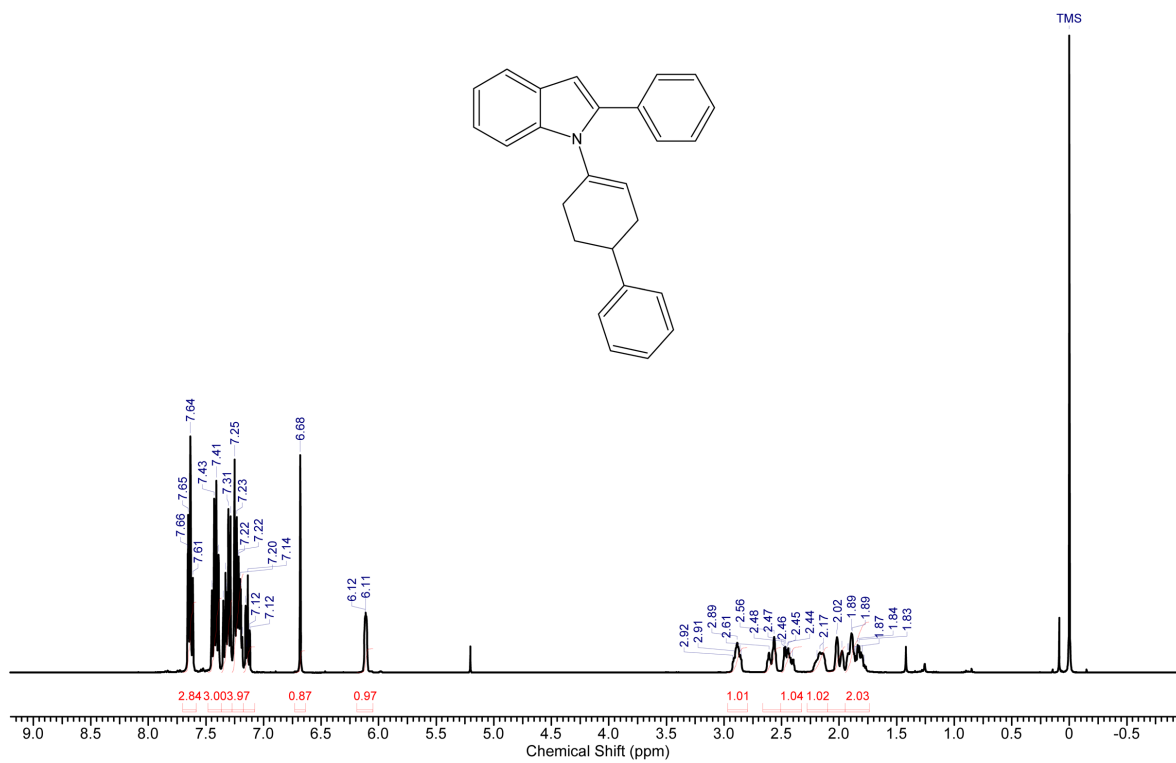
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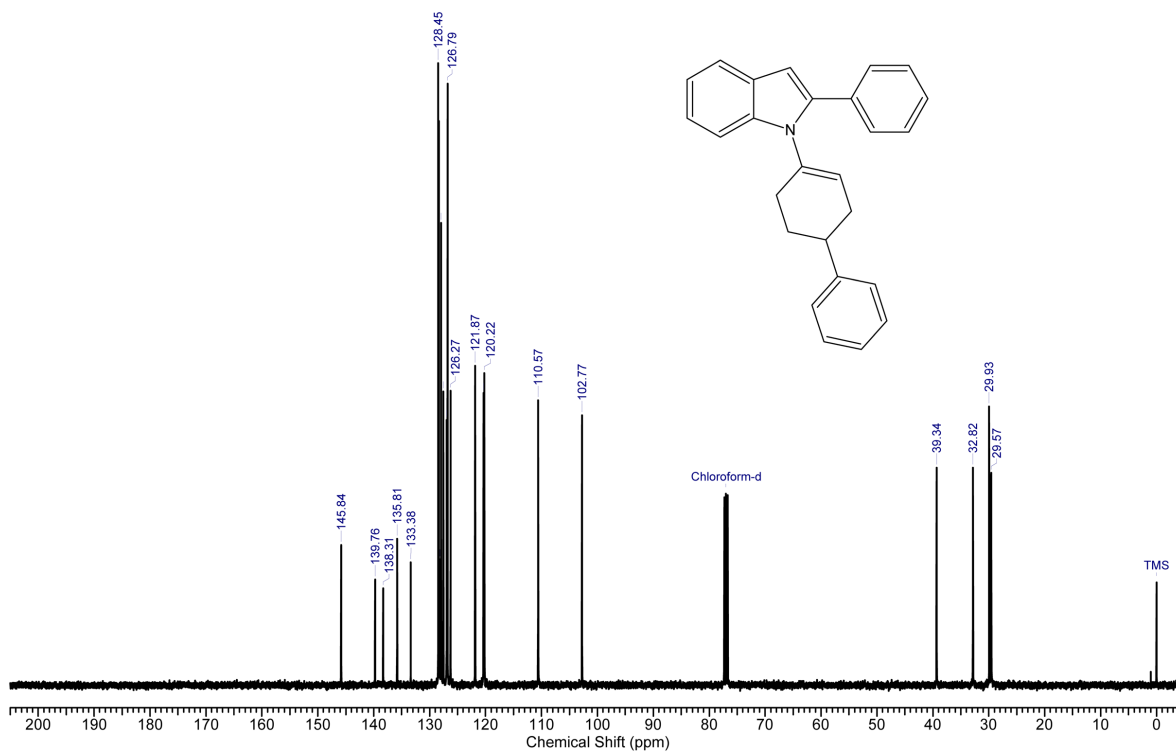
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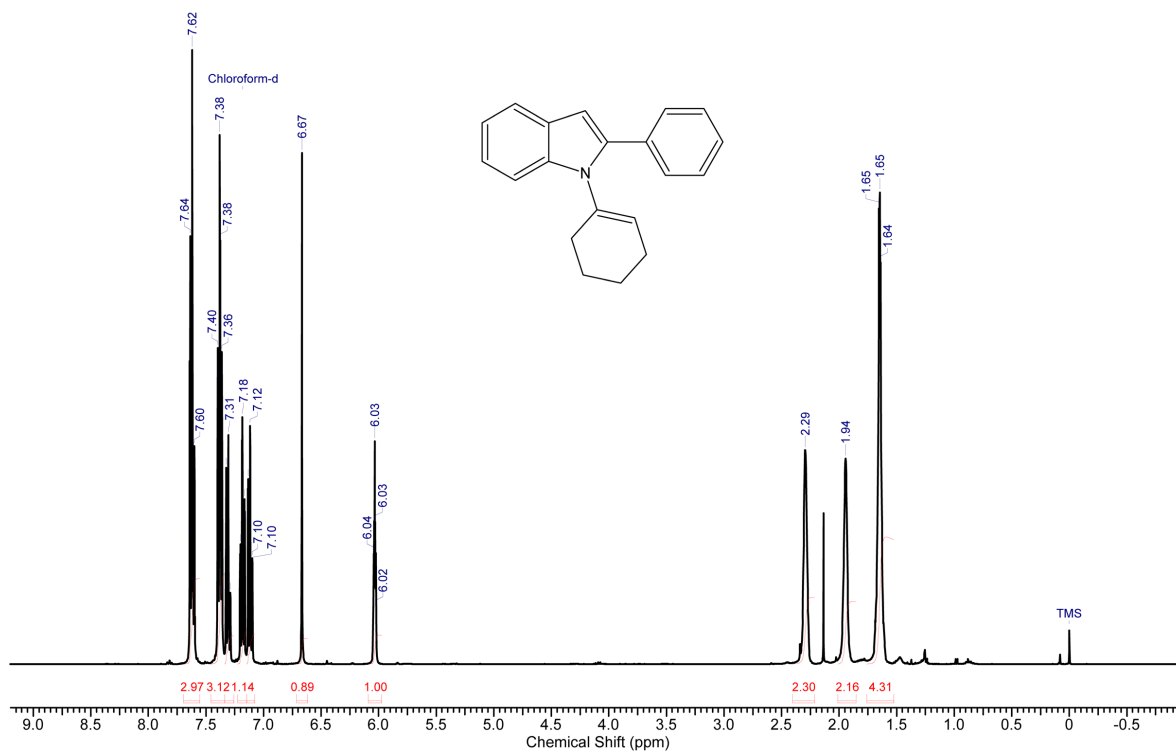
6ab



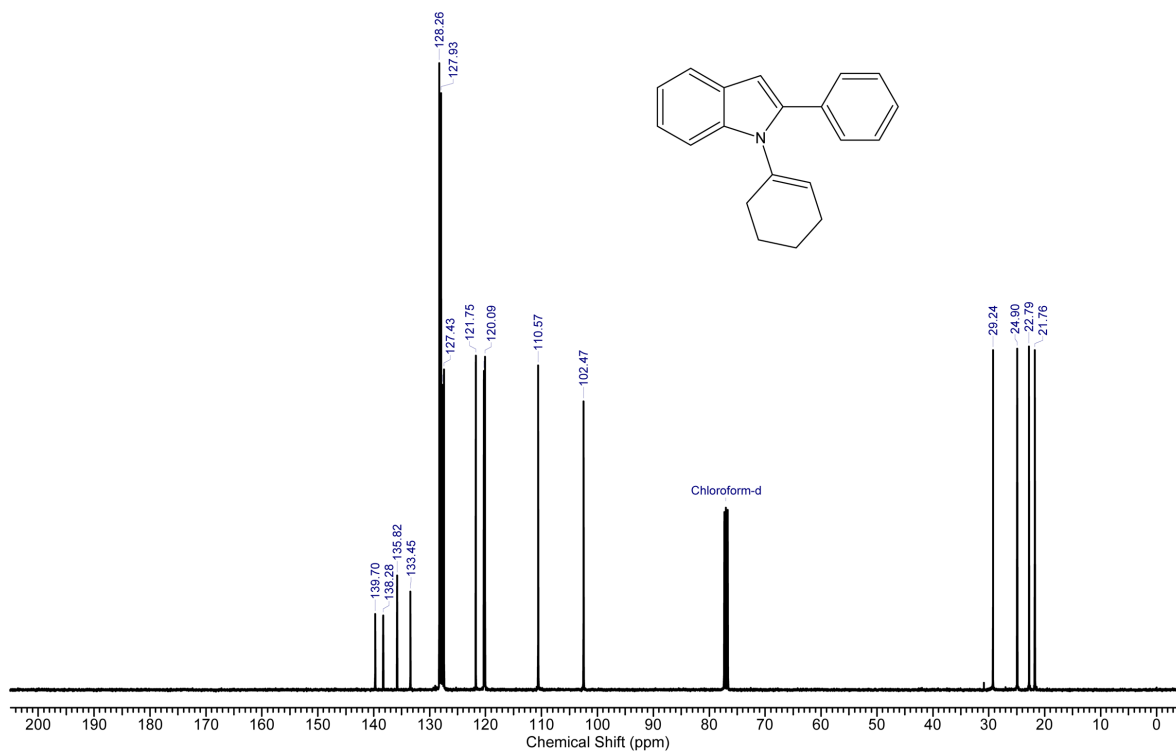
6ab



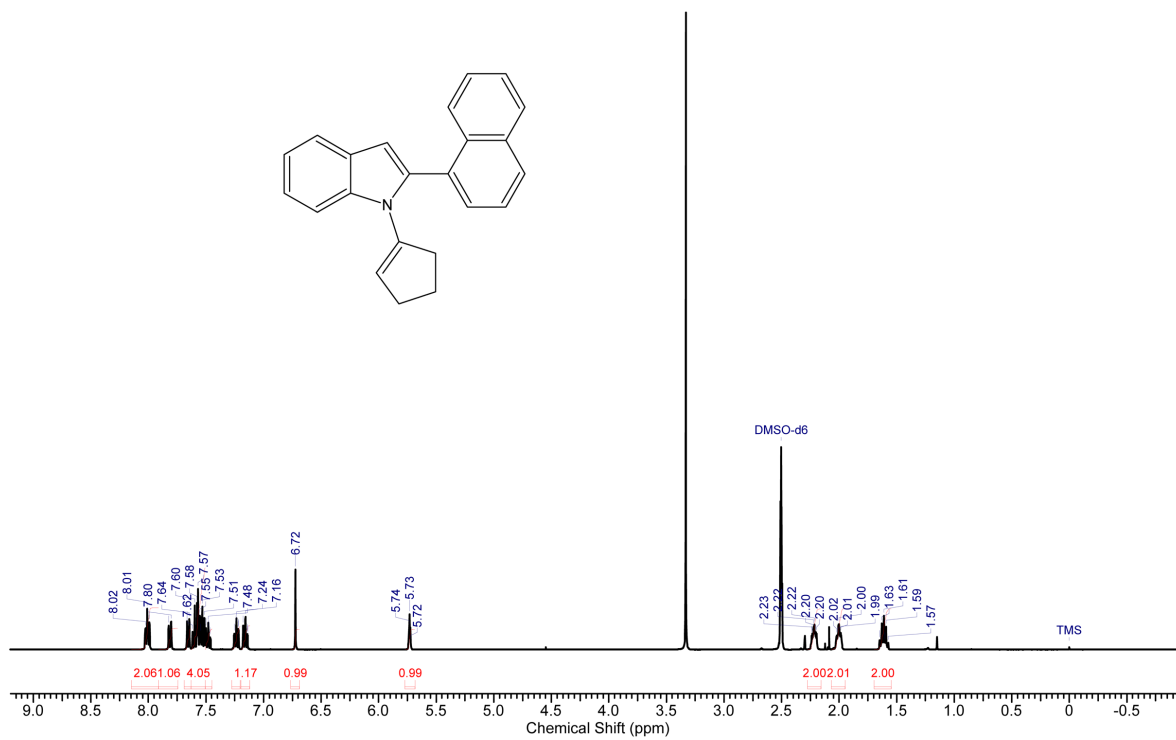
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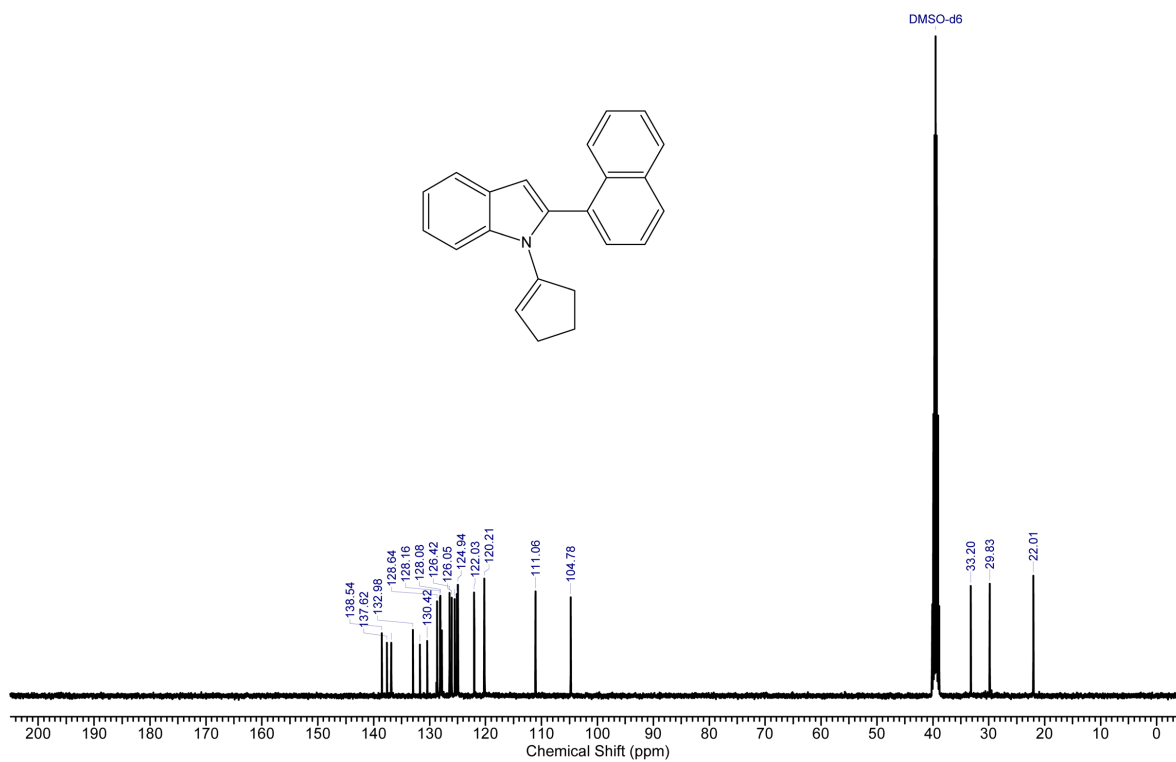
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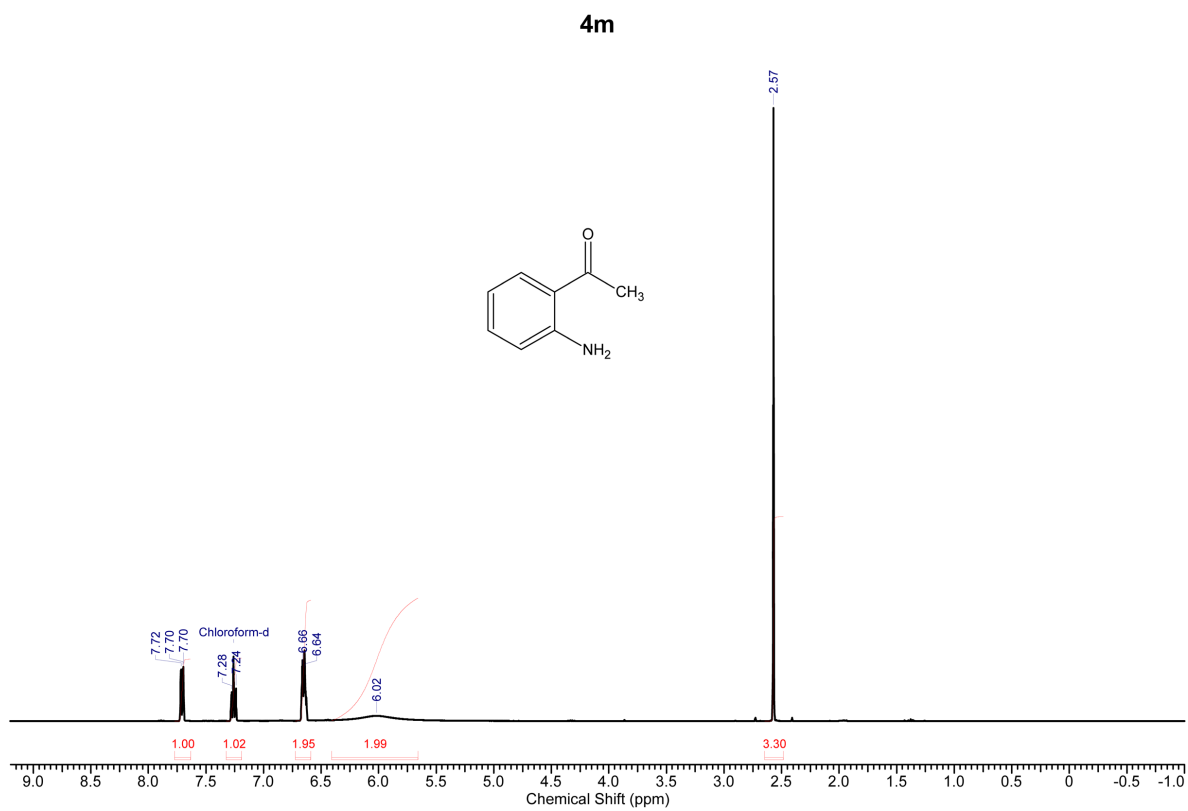
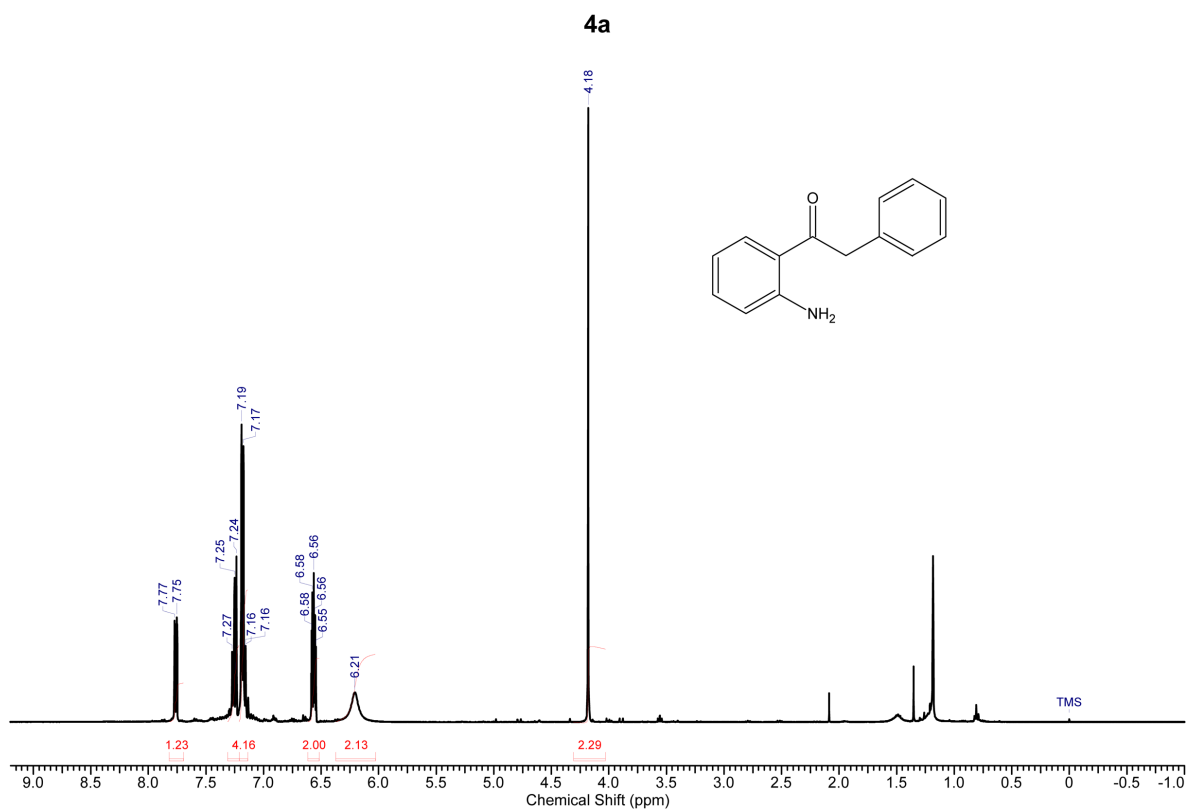


6re

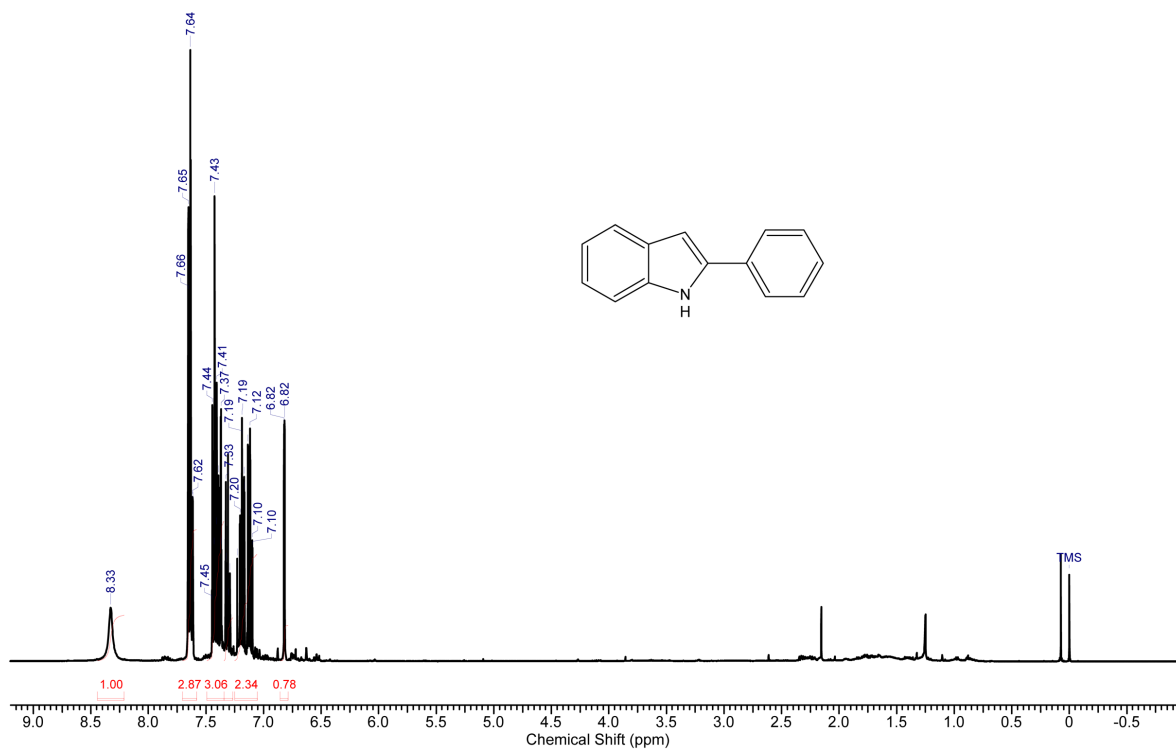


6re

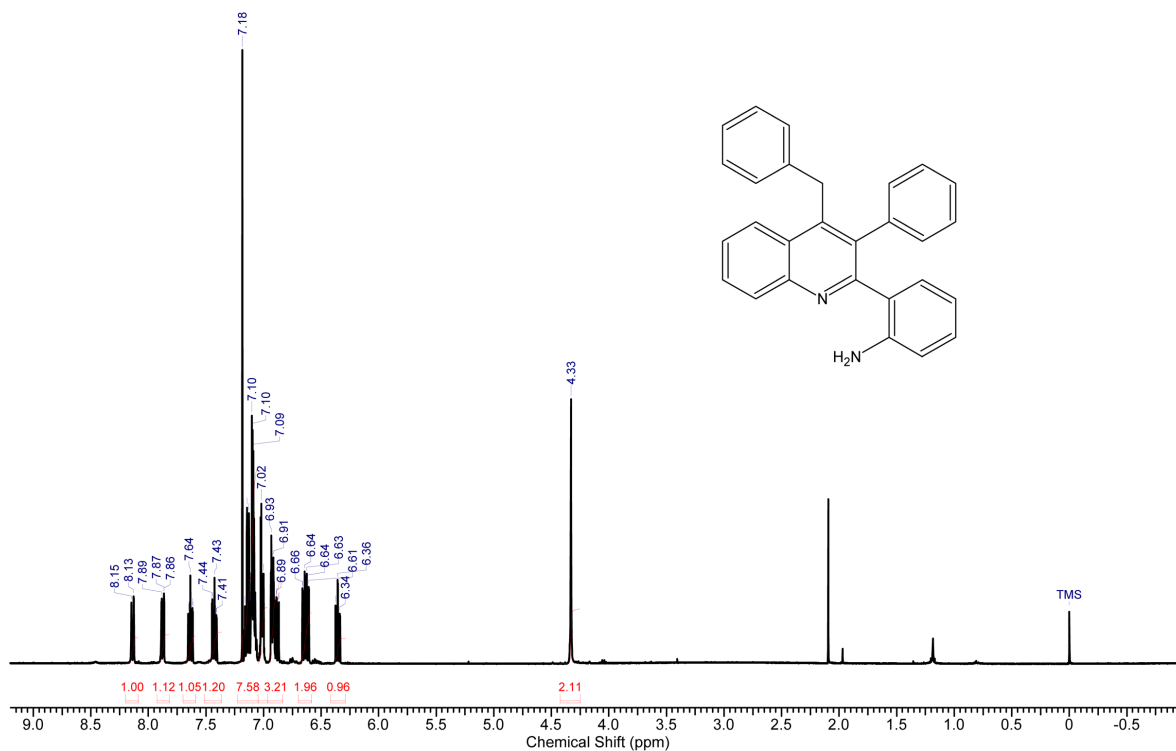




7a



8a



NMR - Structural characterization in solution

Compounds **3ai-3an** and **3gj** were isolated as diastereoisomers mixture, in order to assign correctly NMR spectral picks, H–H Noesy correlation spectra were analysed. Noesy experiments were acquired using standard “noesygpshz” Bruker sequence with 512 increments in the t1 dimension, 16 scans for each increment and mixing time of 700 ms.

2-(4-chlorophenyl)-2-methyl-3-phenyl-2,3-dihydroquinolin-4(1H)-one (3ai)

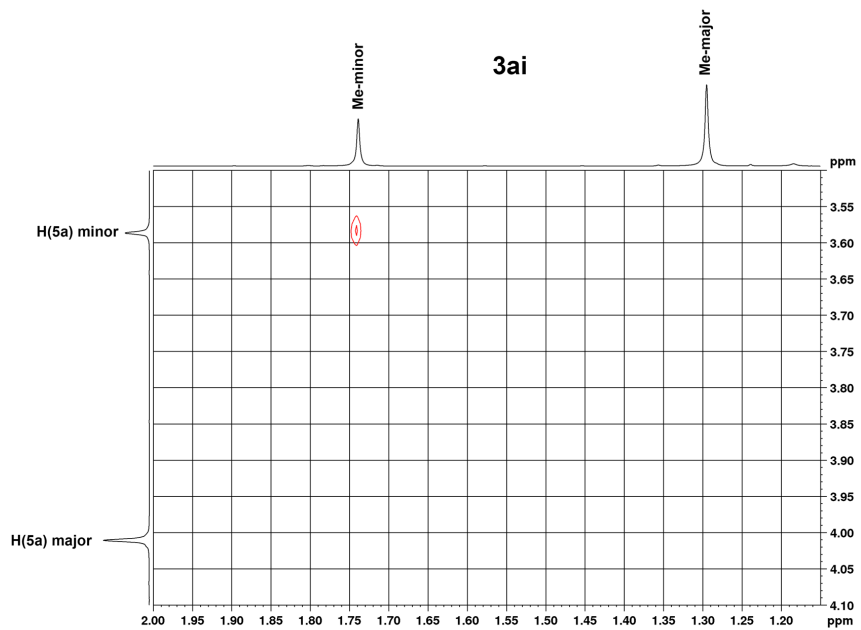
The key NOE interactions to be considered for assigning NMR peaks to diastereomers are those of methyl(18) and of proton H(5a) with phenyl and *p*-Cl-phenyl groups and the interactions between methyl(18) and proton H(5a).

Analysis of Noesy spectrum (Figure S01A) showed proximity between the methyl(18) and proton H(5a) for the minor isomer, whereas there are not interaction between the same protons for the major isomer. This allows to assign the structure for the two diastereomers as shown in the Figure S01B. The assignment was confirmed by the interaction between the methyl(18) and both protons H(13,17) and H(20,24) for the major isomer, whereas there are not interaction between methyl(18) and the protons H(13,17), for the minor isomer (Figure S01C).

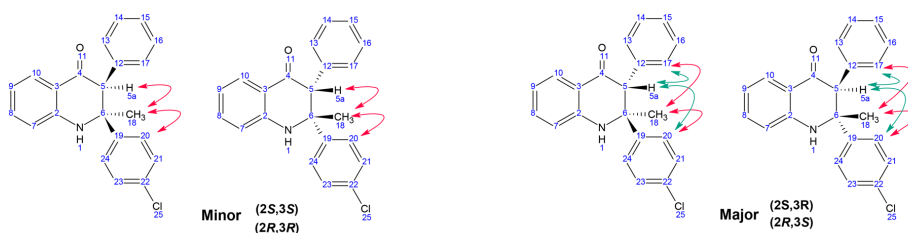
2-(4-fluorophenyl)-2-methyl-3-phenyl-2,3-dihydroquinolin-4(1H)-one 3aj

The key NOE interactions to be considered for assigning NMR peaks to diastereomers are those of methyl(18) and of proton H(5a) with phenyl and *p*-F-phenyl groups and the interactions between methyl(18) and proton H(5a).

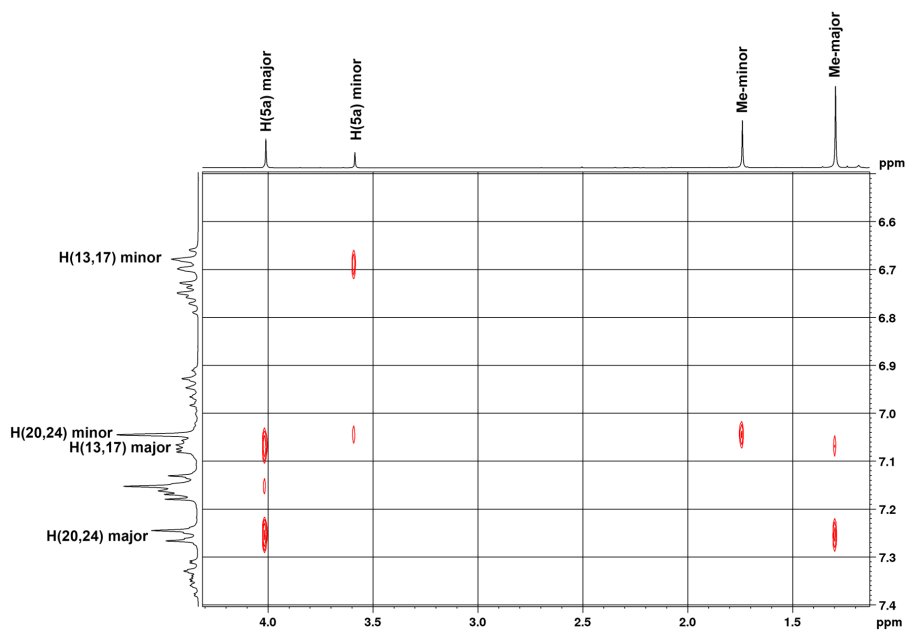
Analysis of Noesy spectrum (Figure S02A) showed interaction between the methyl(18) and proton H(5a) for both the minor and major isomer, but because the intensity was very similar the methyl(18) was closer to proton H(5a) in the minor isomer than in the major one, allowing to assign the structure for the two diastereomers as shown in the Figure S02B. The assignment was confirmed by the interaction between the methyl(18) and both protons H(13,17) and H(20,24) for the major isomer, whereas there are not interaction between methyl(18) and the protons H(13,17), for the minor isomer (Figure S02C). Moreover, the proton H(5a), for the minor isomer, showed only interaction with the protons H(13,17), and not with protons H(20,24) (Figure S02C).



A

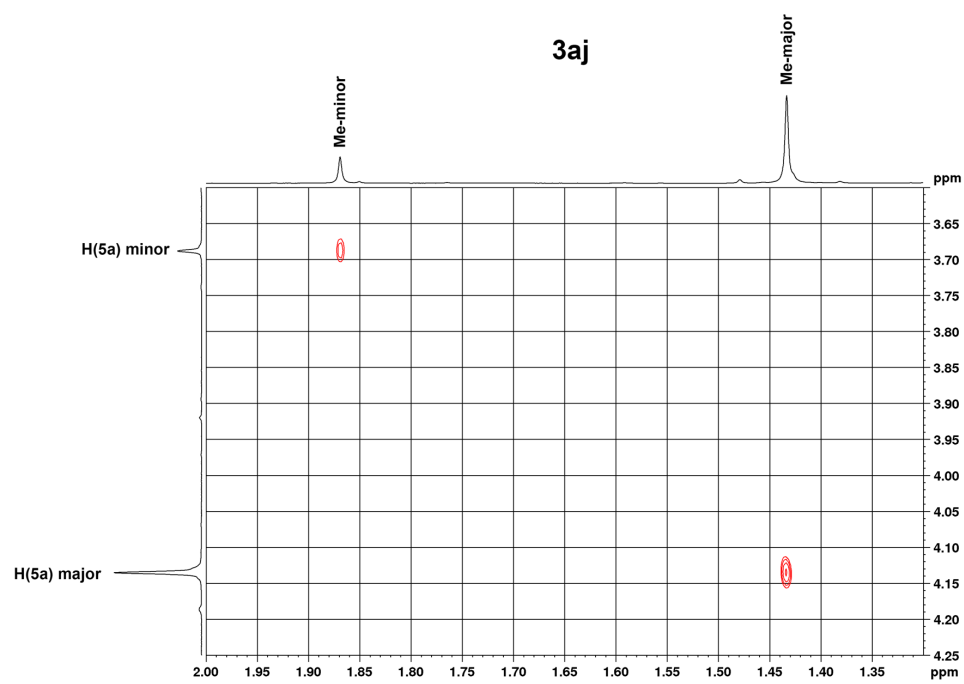


B

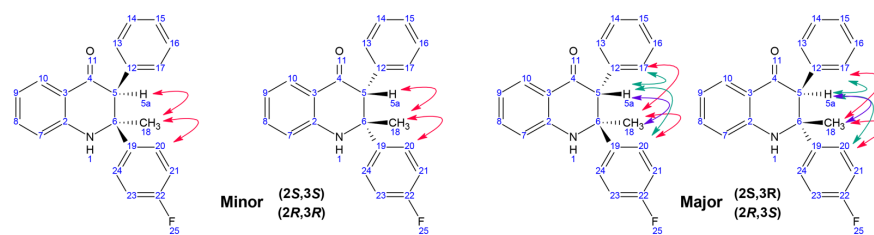


C

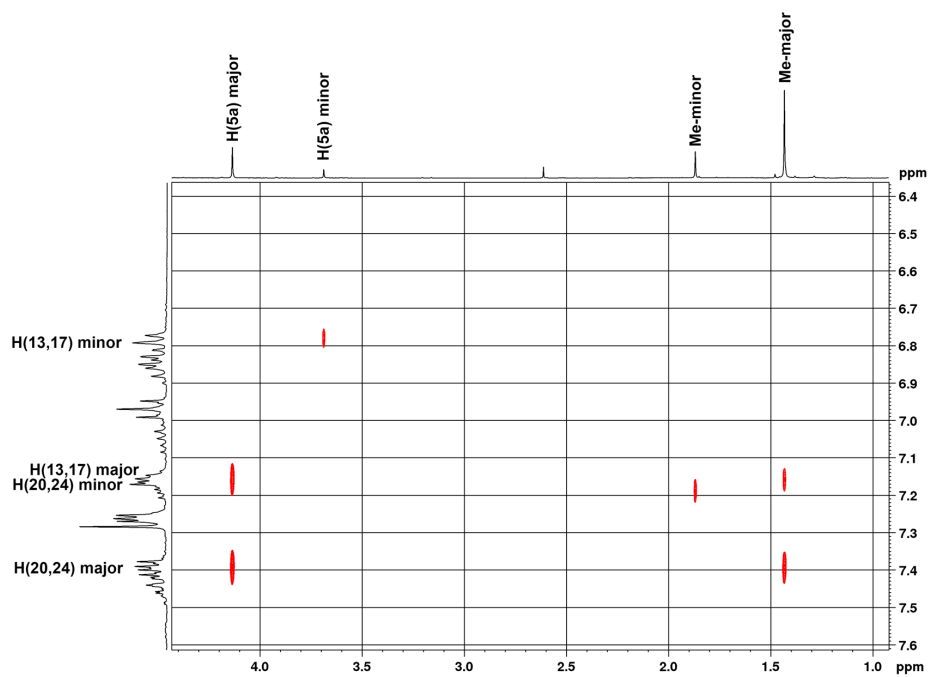
Figure S01. NOESY spectrum for **3ai**; A) Relevant Noesy interactions; B) diastereomers Assignment C) Relevant Noesy interactions.



A



B



C

Figure S02. NOESY spectrum for **3aj**; A) Relevant Noesy interactions; B) diastereomers Assignment C) Relevant Noesy interactions.

2-methyl-(4-nitrophenyl)-3-phenyl-2,3-dihydroquinolin-4(1H)-one (3ak)

The key NOE interactions to be considered for assigning NMR peaks to diastereomers are those of methyl(18) and of proton H(5a) with phenyl and *p*-NO₂-phenyl groups and the interactions between methyl(18) and proton H(5a).

Analysis of Noesy spectrum (Figure S03A) showed interaction between the methyl(18) and proton H(5a) for both the minor and major isomer, but because the intensity was very similar the methyl(18) was closer to proton H(5a) in the minor isomer than in the major one, allowing to assign the structure for the two diastereomers as shown in the Figure S03B. The assignment was confirmed by the interaction between the methyl(18) and both protons H(13,17) and H(20,24) for the major isomer, whereas there are not interaction between methyl(18) and the protons H(13,17), for the minor isomer (Figure S02C). Moreover, the proton H(5a), for the minor isomer, showed only interaction with the protons H(13,17), and not with protons H(20,24) (Figure S03C).

2-(2-bromophenyl)-3-phenyl-2,3-dihydroquinolin-4(1H)-one (3al)

The key NOE interactions to be considered for assigning NMR peaks to diastereomers are those of methyl(18) and of proton H(5a) with phenyl and *o*-Br-phenyl groups and the interactions between methyl(18) and proton H(5a).

Analysis of Noesy spectrum (Figure S04A) showed, for the major isomer, a greater interaction between the methyl(18) and phenyl(H13,17) than between methyl(18) and the *o*-Br-phenyl group(H24), moreover the Noe interactions between the proton H(5a) and the proton H(24) was greater than between the proton H(5a) and the protons H(13,17) allowing to assign the structure for the two diastereomers as shown in the Figure S04B

(2S,3S / 2R,3R)-2,3-Diphenyl-2-propyl-2,3-dihydroquinolin-4(1H)-one and (2S, 3R / 2R, 3S)-2,3-Diphenyl-2-propyl-2,3-dihydroquinolin-4(1H)-one (3am)

The key NOE interactions to be considered for assigning NMR peaks to diastereomers are those between the propyl group and phenyl's ones.

Analysis of Noesy spectrum (Figure S05) showed different interactions for the diastereomers, in fact, for the 2S,3S / 2R,3R couple the propyl chain interact only with the H(22,26) phenyl protons (Figure S05A), while for the 2S,3R / 2R,3S couple all the protons of propyl chain interacts with both phenyl groups (Figure S05B).

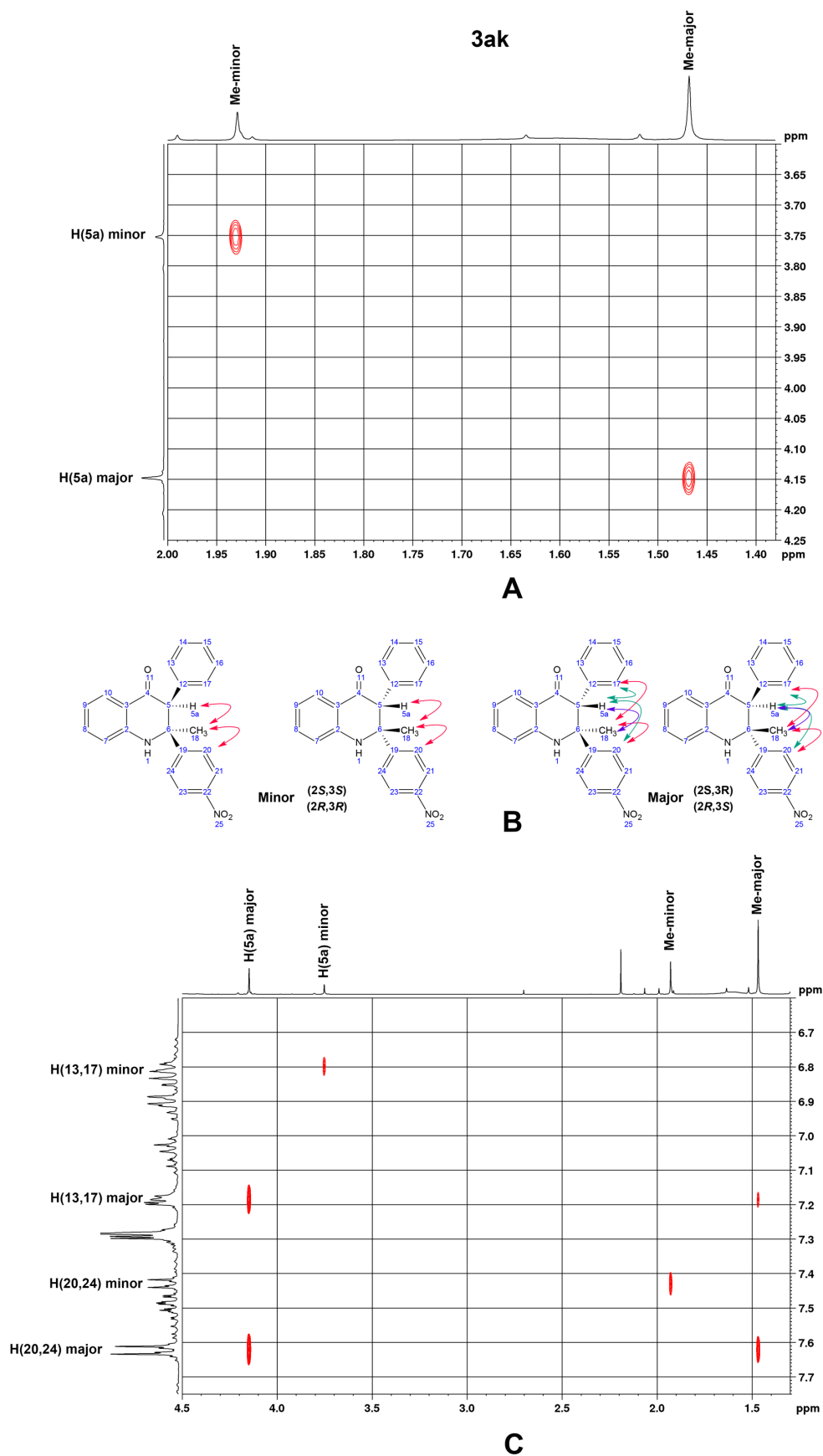


Figure S03. NOESY spectrum for **3ak**; A) Relevant Noesy interactions; B) diastereomers Assignment C) Relevant Noesy interactions;

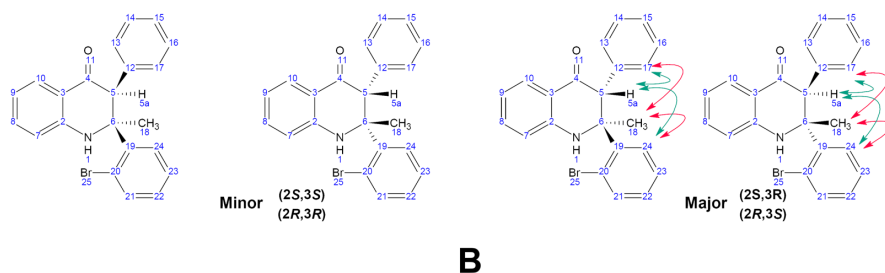
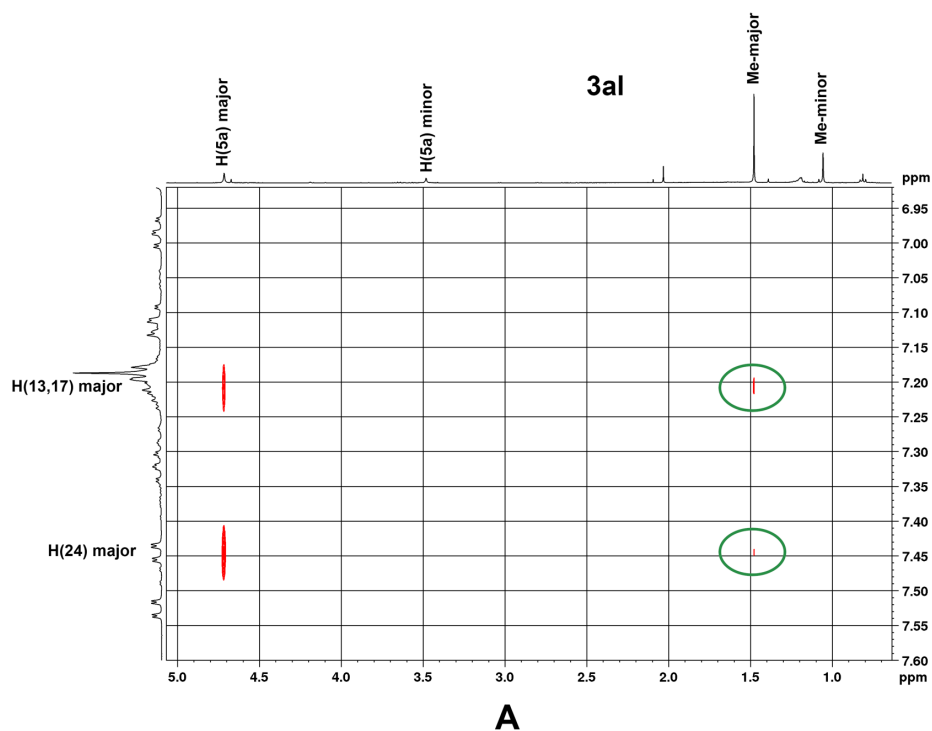


Figure S04. NOESY spectrum for **3al**; A) Relevant Noesy interactions; B) diastereomers Assignment.

2-butyl-2-methyl-3-phenyl-2,3-dihydroquinolin-4(1H)-one (**3an**)

The key NOE interactions to be considered for assigning NMR peaks to diastereomers are those of the methyl(15) and of proton H(3a) with phenyl and buthyl groups and the interactions between methyl(15) and proton H(3a).

Analysis of Noesy spectrum (Figure S06A) showed proximity between the methyl(15) and the proton H(3a) for both the major and the minor isomer, but because for the minor isomer the intensity was greater than in the major one, the methyl(15) was closer to proton H(3a) in the minor isomer than in the major one, allowing to assign the structure for the two diastereomers as shown in the Figure S06B; moreover the proton H(3a), for the major isomer, interacted with all the methylenes of butyl chain whereas the minor not.

The assignment was confirmed by the interaction between the methyl(15) and protons H(17,21) for the major isomer, whereas there were not interaction between the methyl(15) and the protons H(17,21) for the minor isomer (Figure S06C).

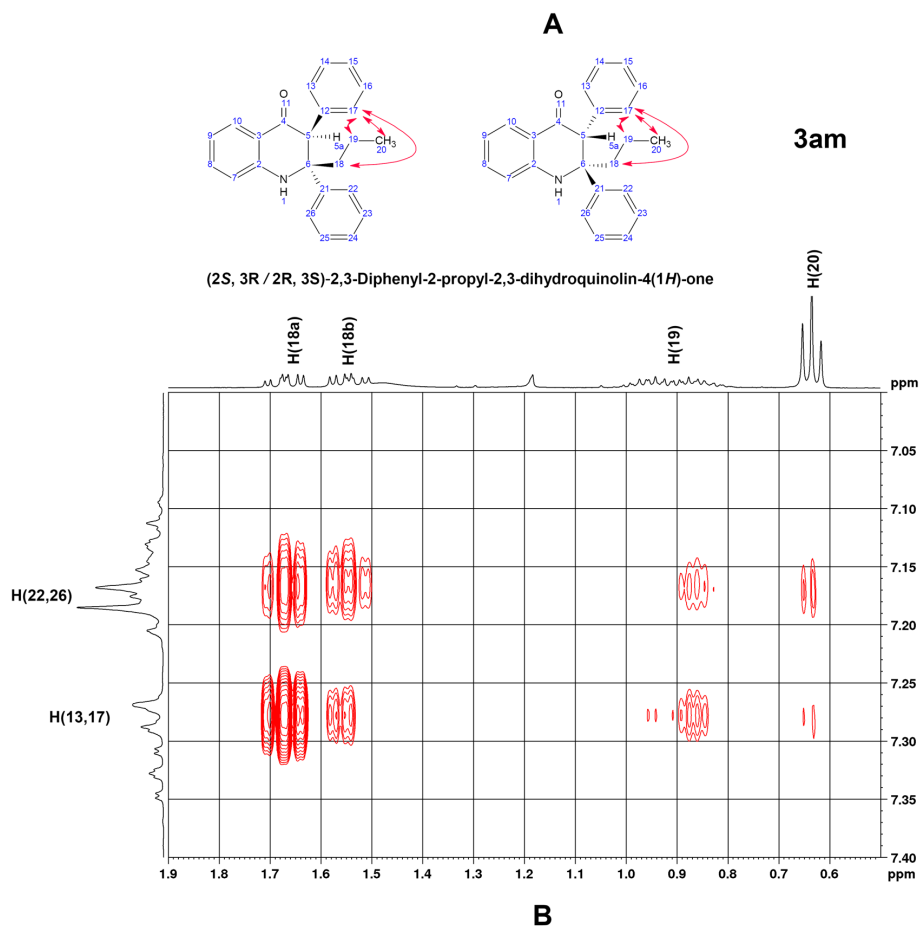
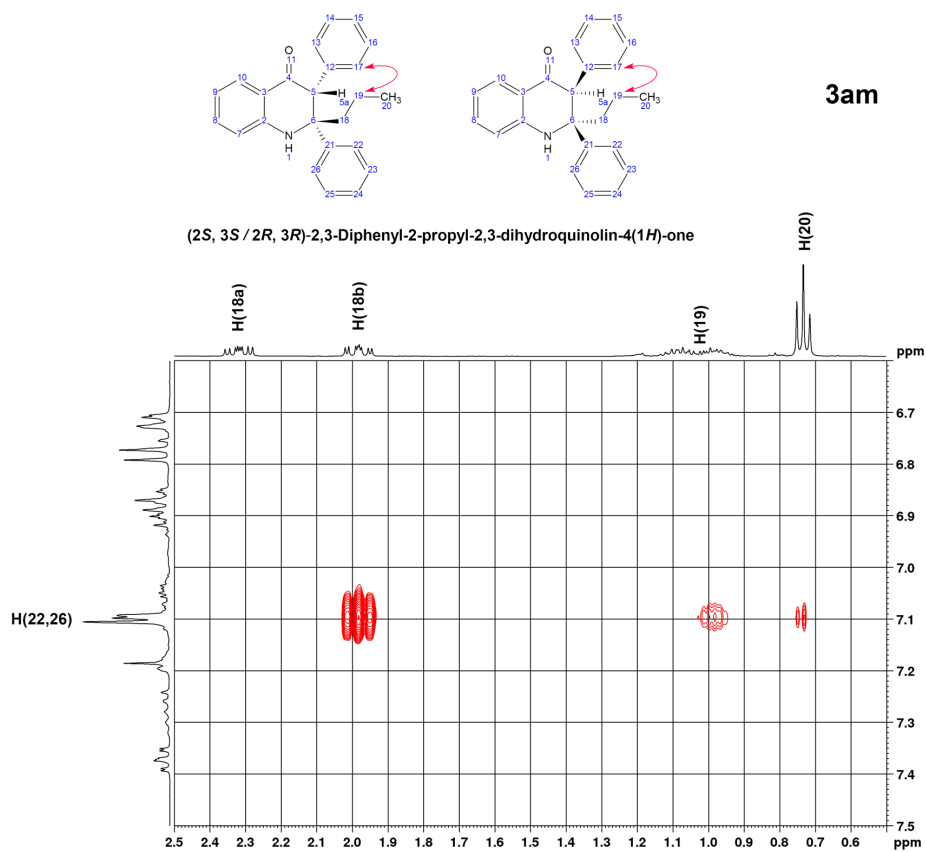


Figure S05. NOESY spectrum for **3am**; A) Relevant Noesy interactions for 2S,3S / 2R,3R enantiomeric couple; B) Relevant Noesy interactions for 2S,3R / 2R,3S enantiomeric couple.

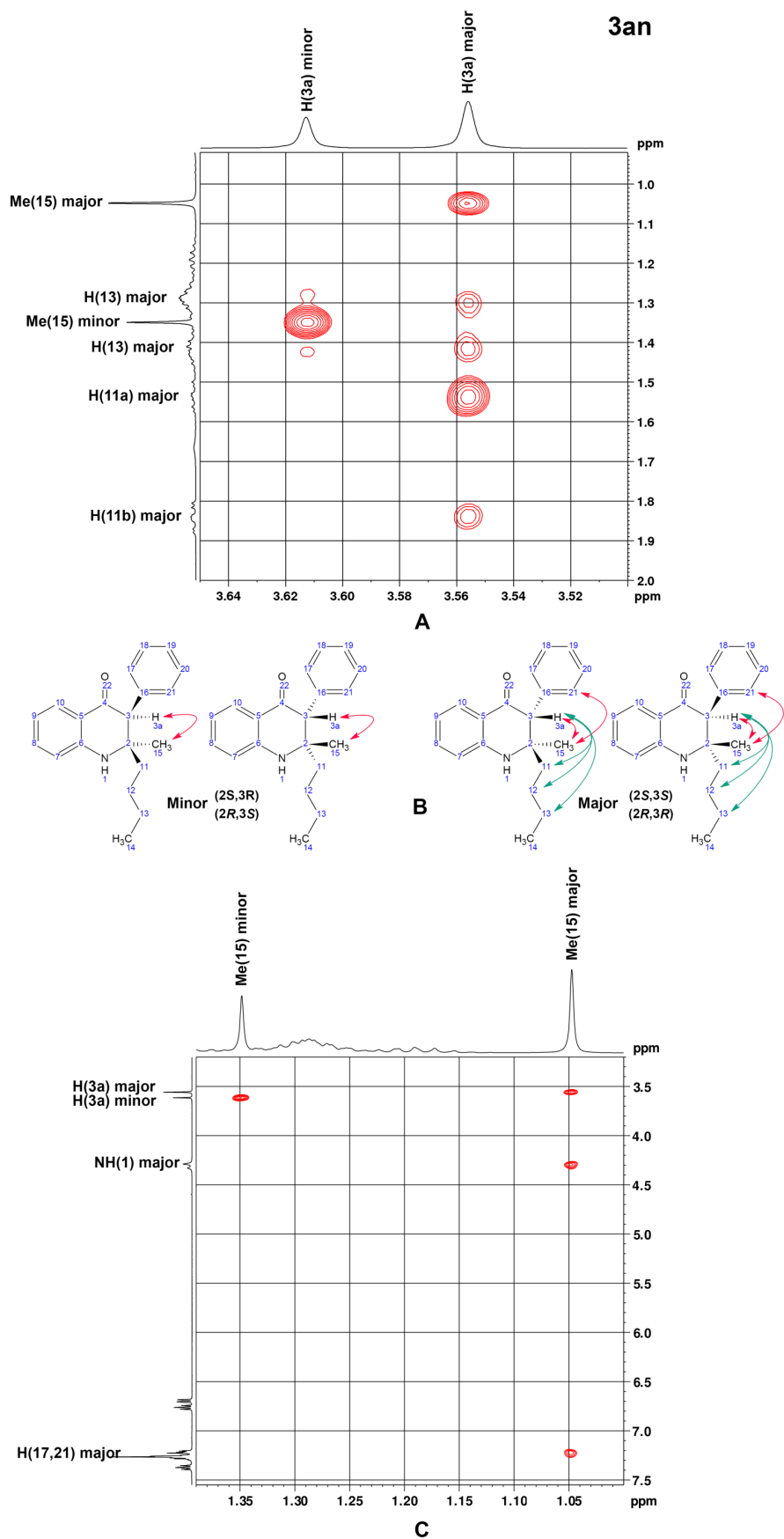
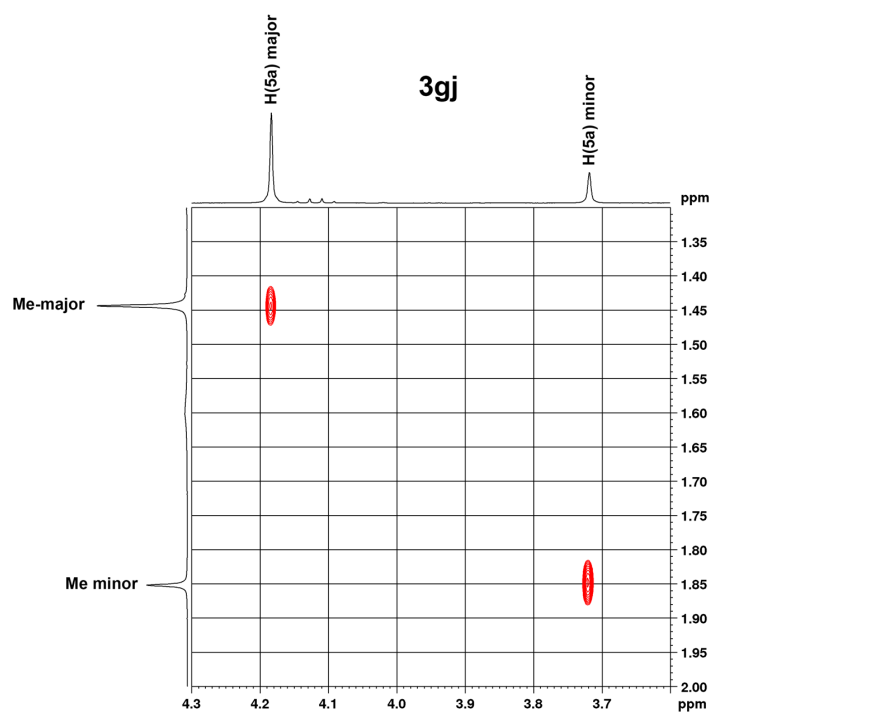


Figure S06. NOESY spectrum for **3an**; A) Relevant Noesy interactions; B) diastereomers Assignment C) Relevant Noesy interactions.

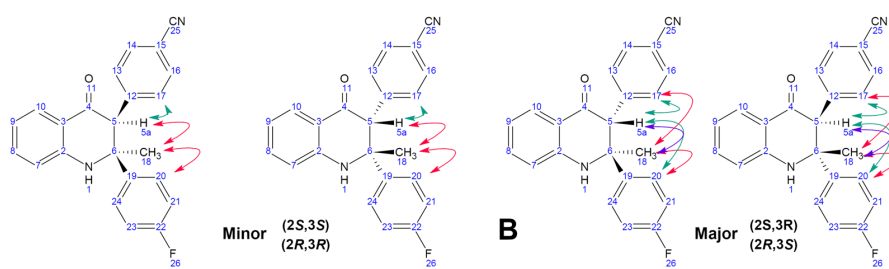
4-(2-(4-fluorophenyl)-2-methyl-4-oxo-1,2,3,4-tetrahydroquinolin-3-yl)benzotrile (3gj)

The key NOE interactions to be considered for assigning NMR peaks to diastereomers are those of methyl(18) and of proton H(5a) with benzonitrile and *p*-F-phenyl groups and the interactions between methyl(18) and proton H(5a).

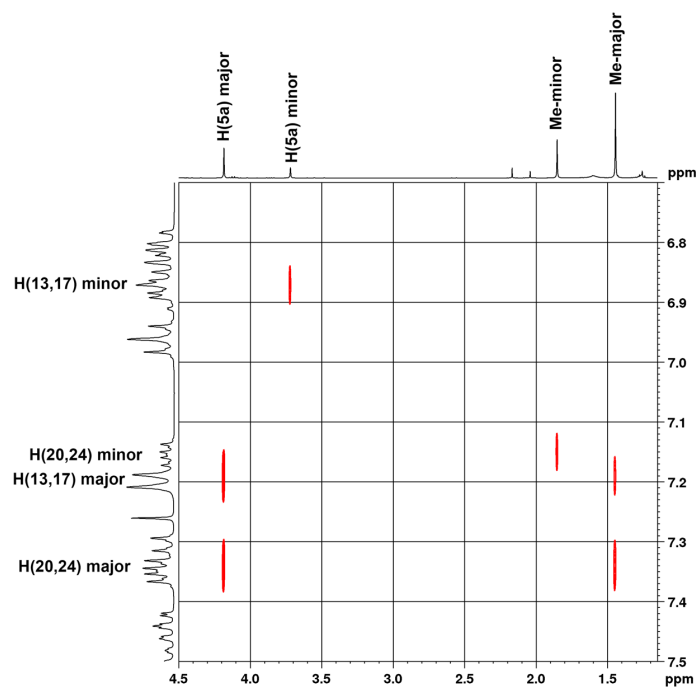
Analysis of Noesy spectrum (Figure S07A) showed interaction between the methyl(18) and proton H(5a) for both the minor and major isomer, but because the intensity was very similar the methyl(18) was closer to proton H(5a) in the minor isomer than in the major one, allowing to assign the structure for the two diastereomers as shown in the Figure S07B. The assignment was confirmed by the interaction between the methyl(18) and both protons H(13,17) and H(20,24) for the major isomer, whereas there are not interaction between the methyl(18) and the protons H(13,17), for the minor isomer (Figure S07C). Moreover, the proton H(5a), for the minor isomer, showed only interaction with the protons H(13,17), and not with protons H(20,24) (Figure S07C).



A



B



C

Figure S07. NOESY spectrum for **3gj**; A) Relevant Noesy interactions; B) diastereomers Assignment C) Relevant Noesy interactions;