Supporting Information

Discovery of AD258 as a Sigma Receptor Ligand with Potent Antiallodynic Activity

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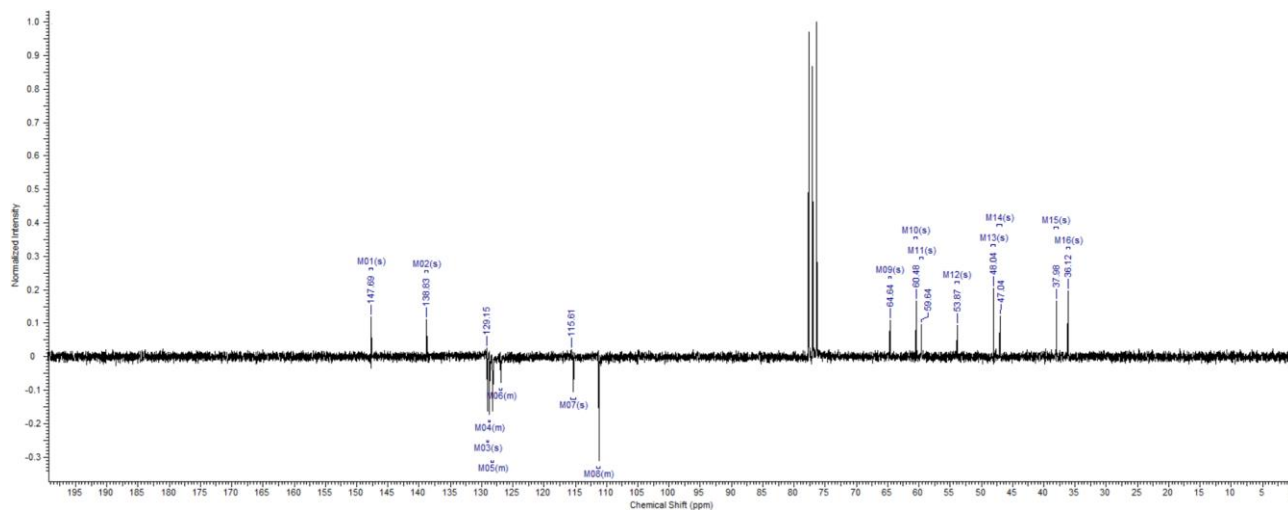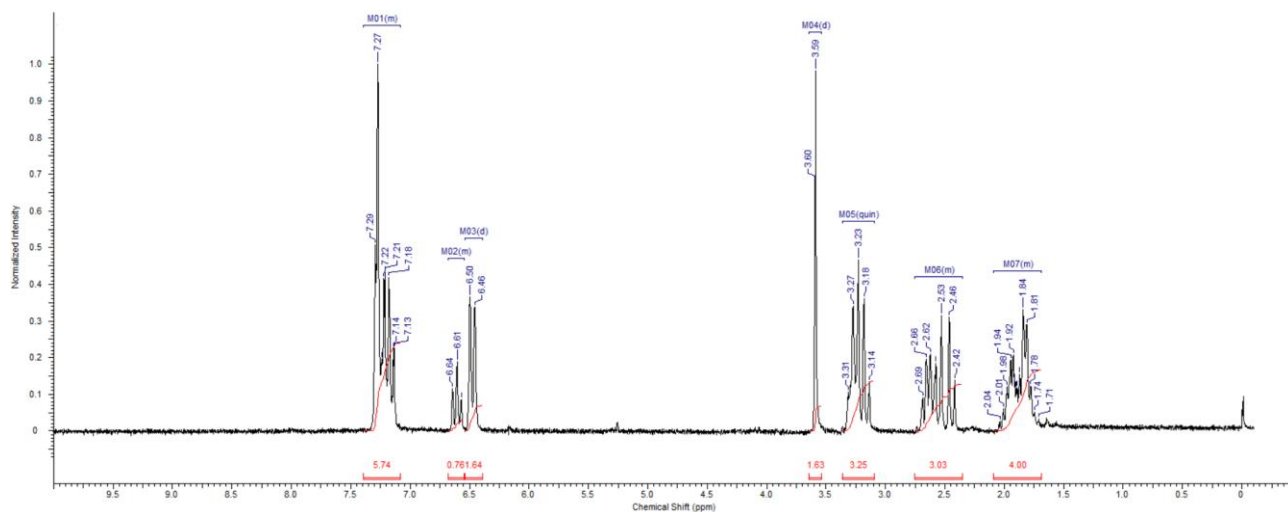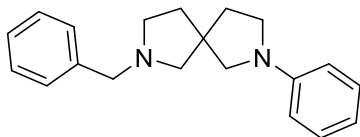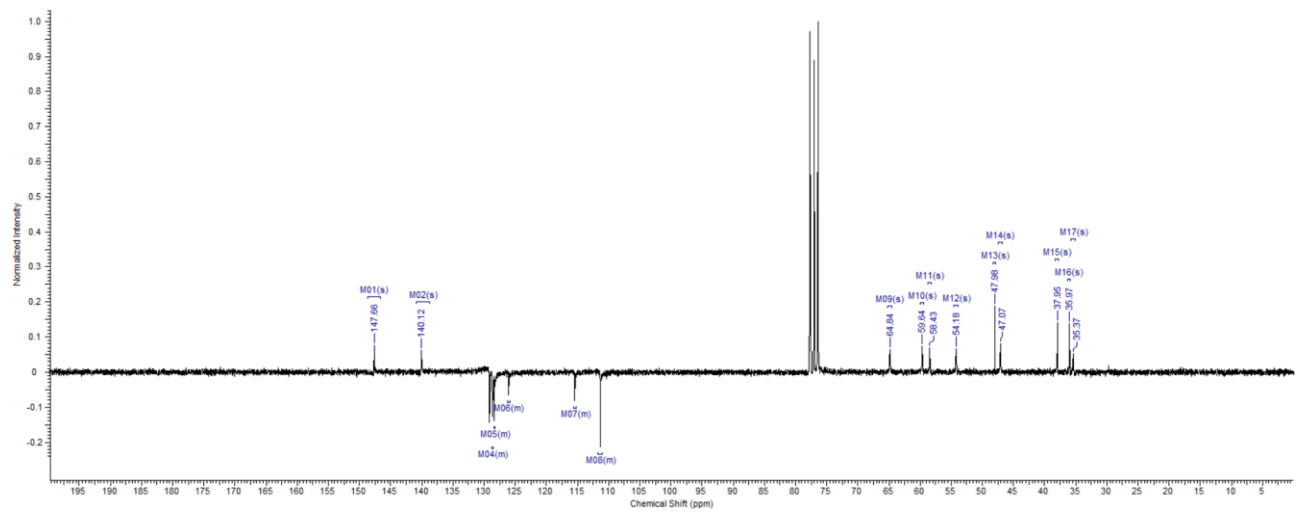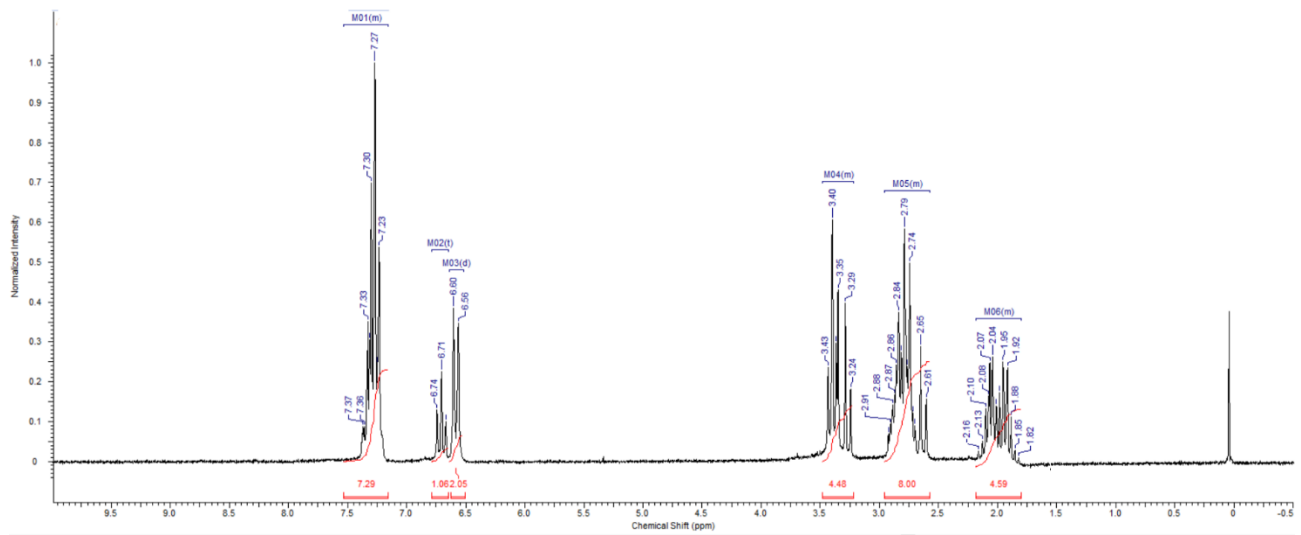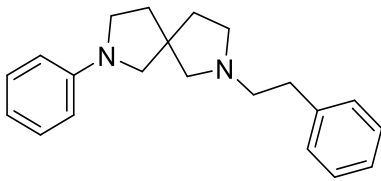*Stefano Alcaro: phone, (+39) 09613694198; email, alcaro@unicz.it

^{1}H and ^{13}C NMR spectra

NMR spectra in CDCl$_3$ from final compounds synthesized by the authors are included.

Compound 7b (AD214)
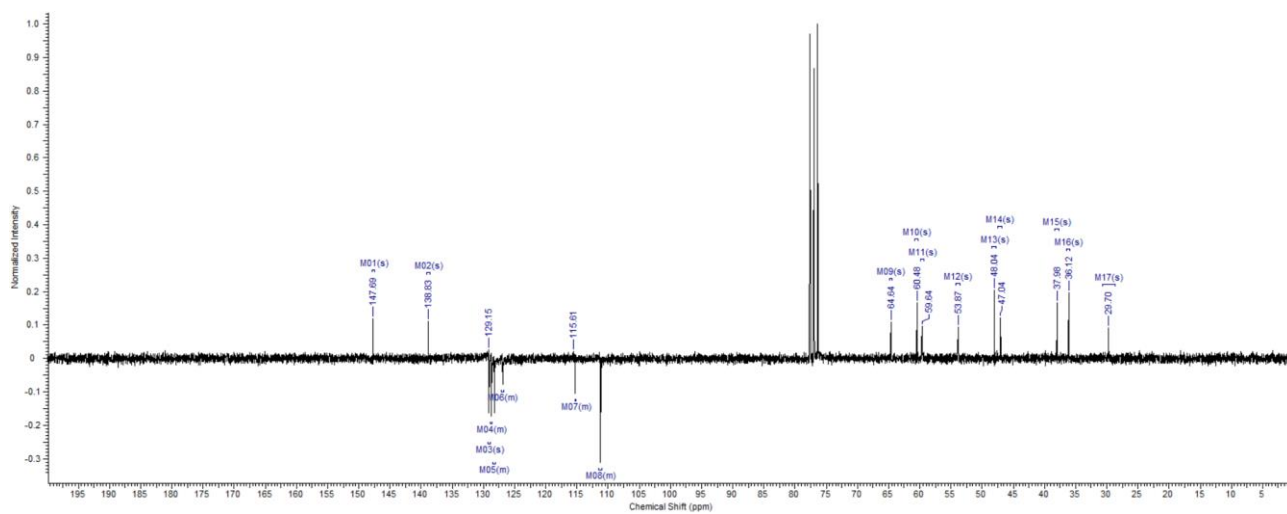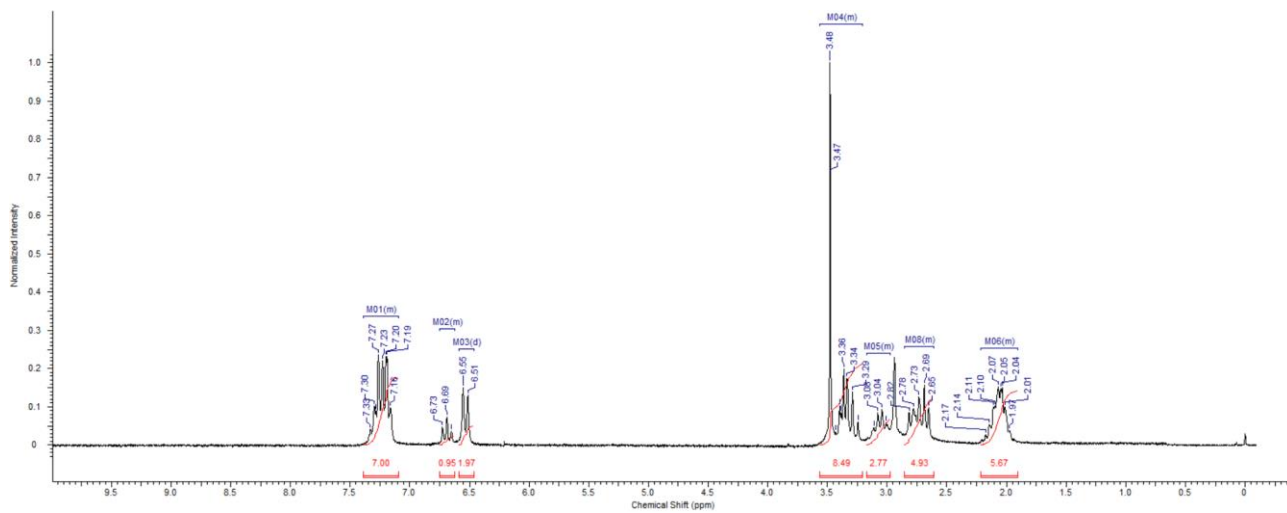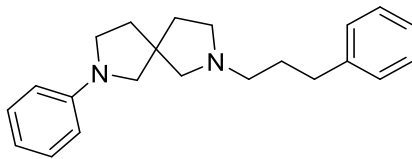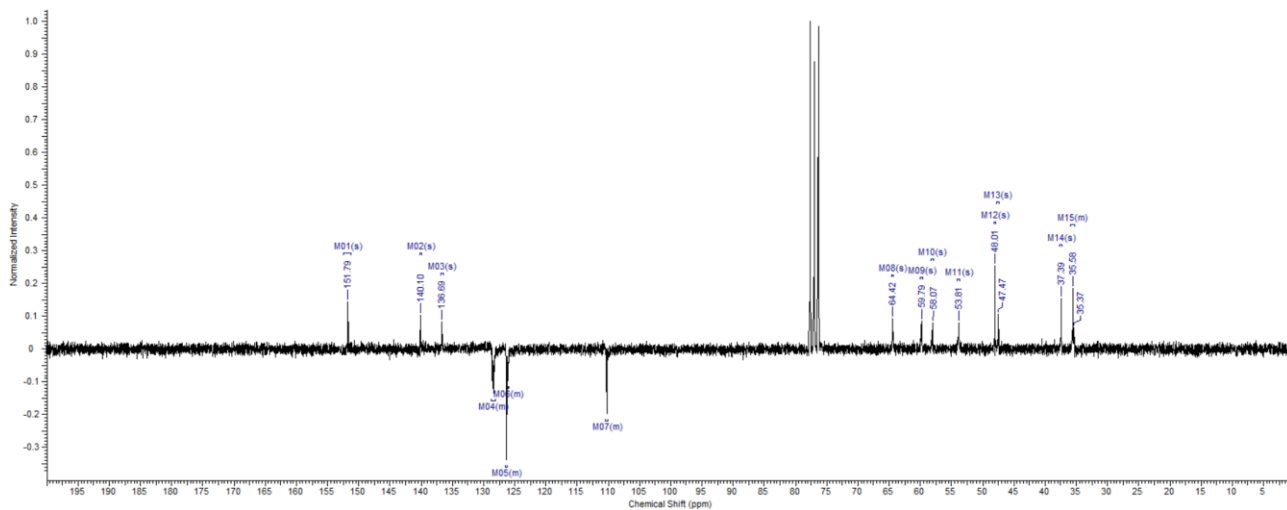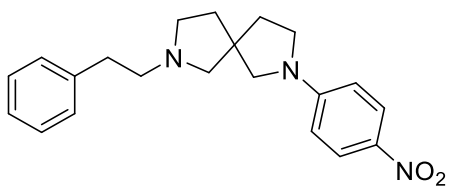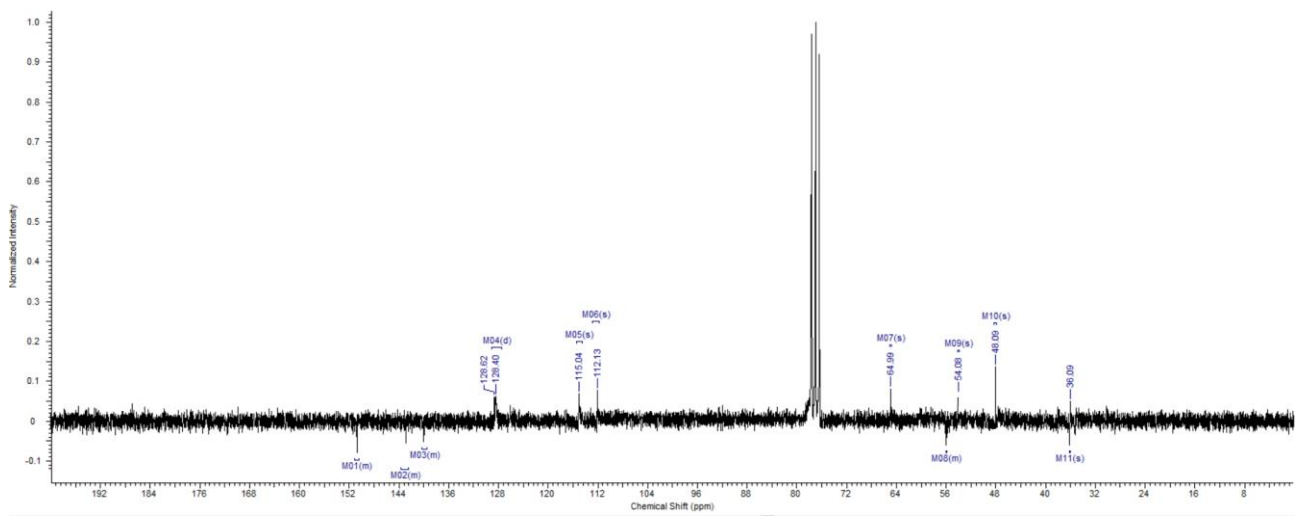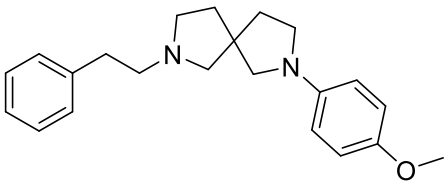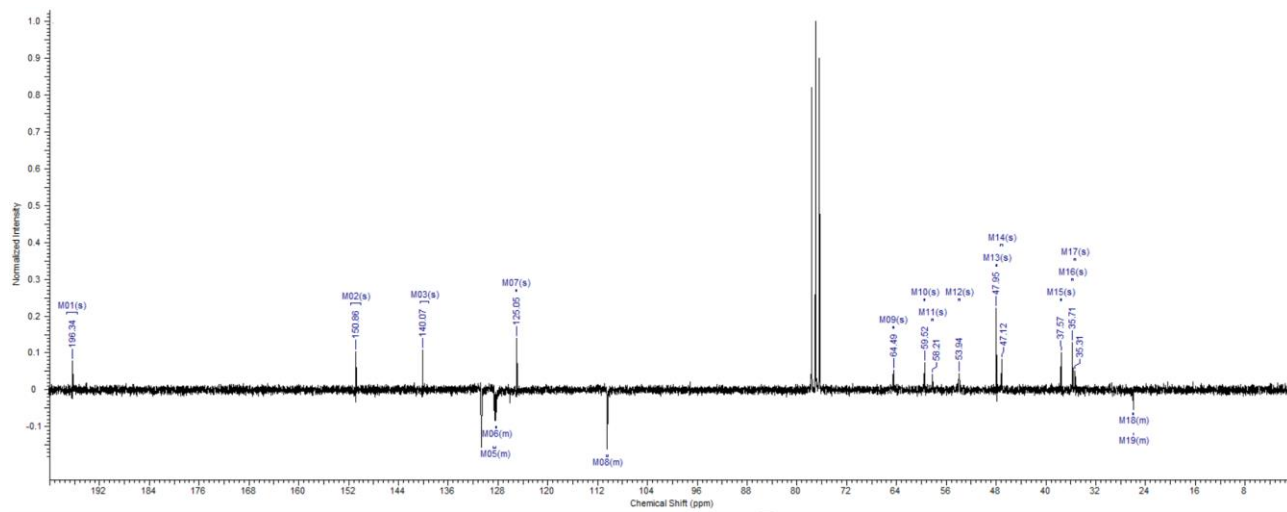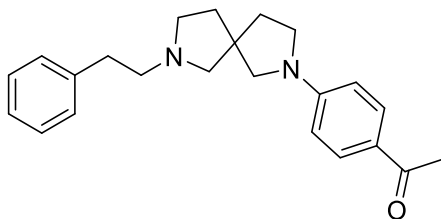
Compound 8a (AD174)

Compound 8b (AD157)

Compound 9a (AD242)
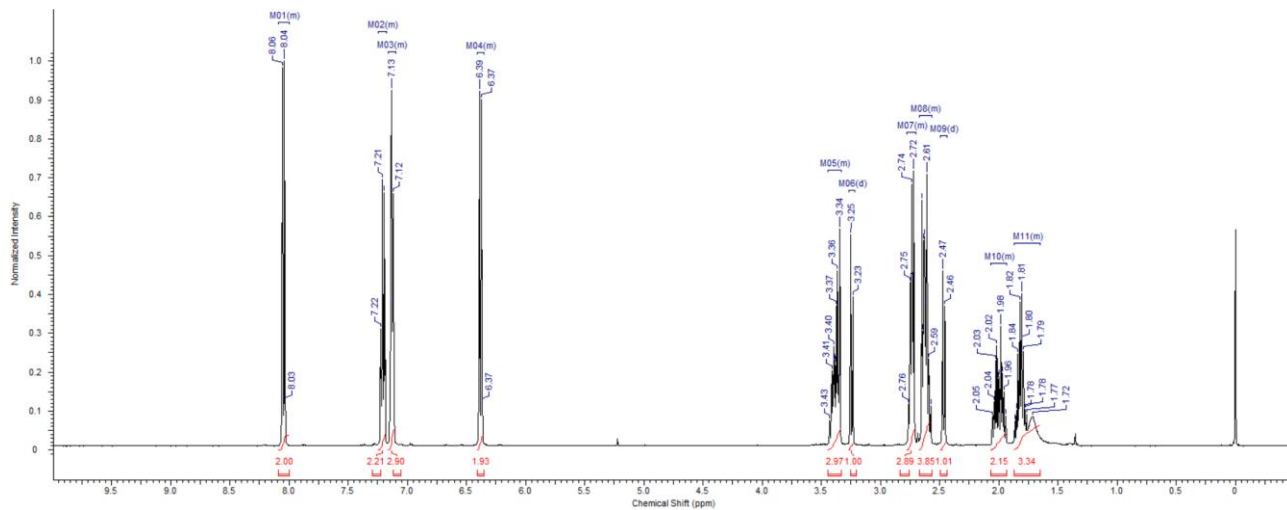
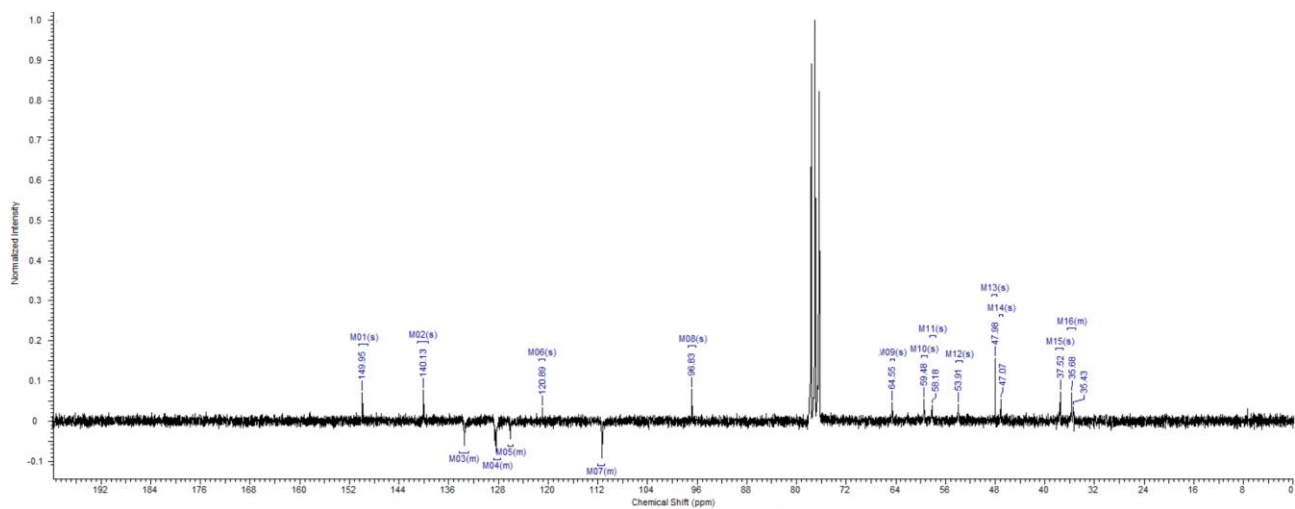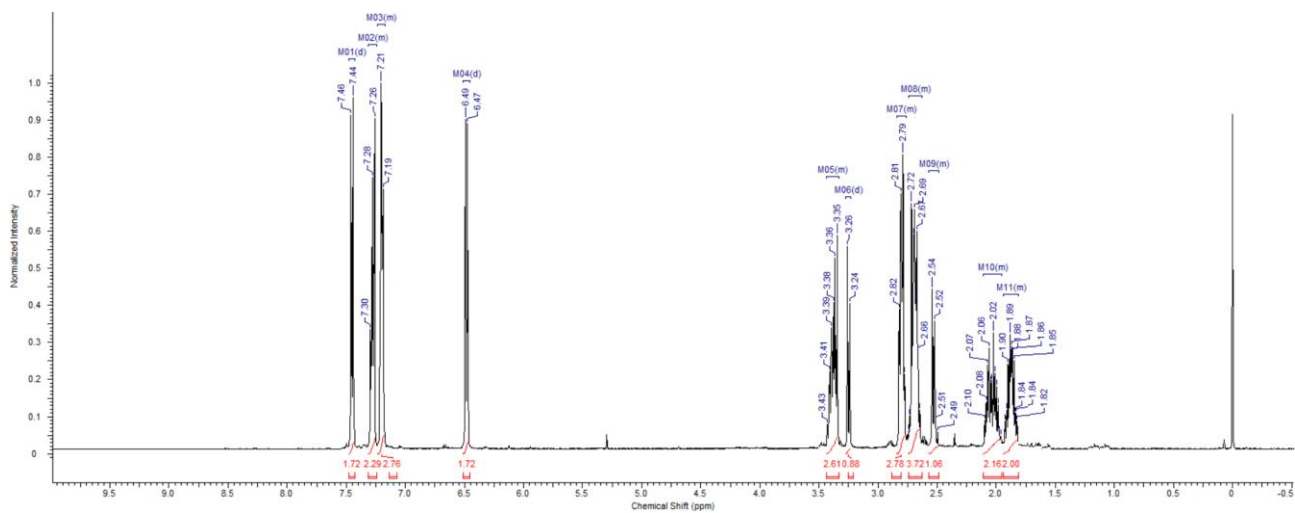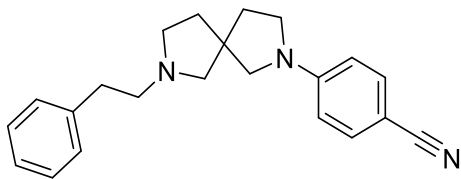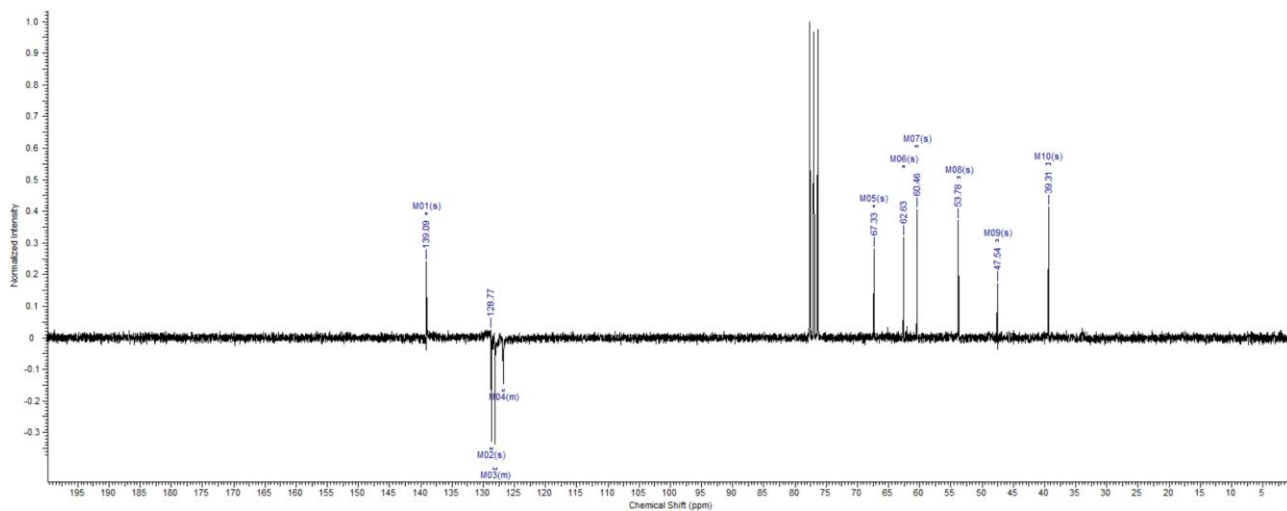**Compound 9b (AD239)**
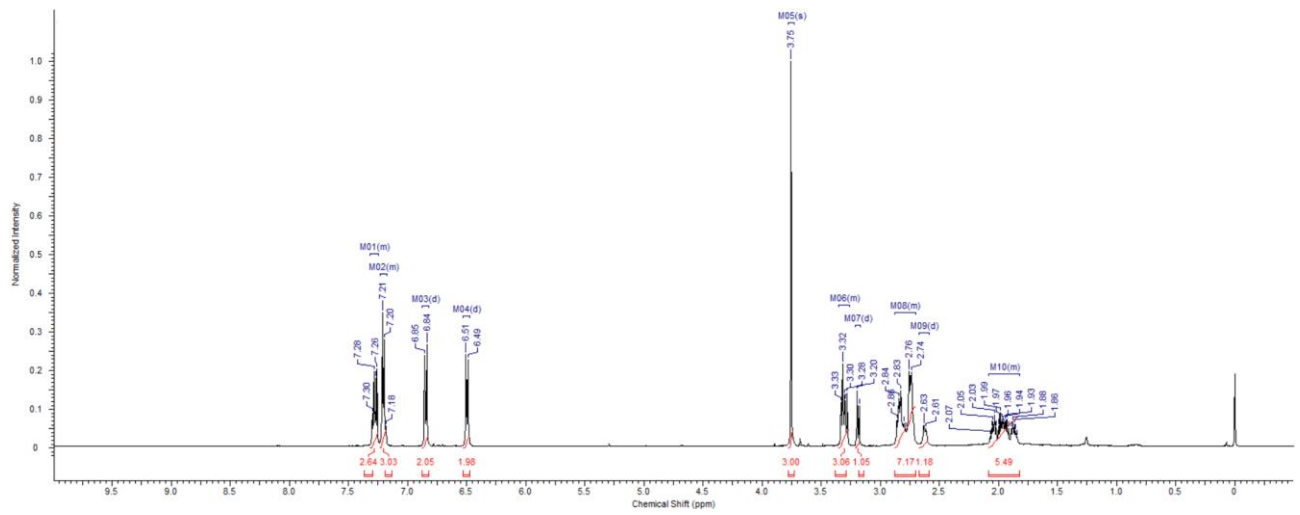
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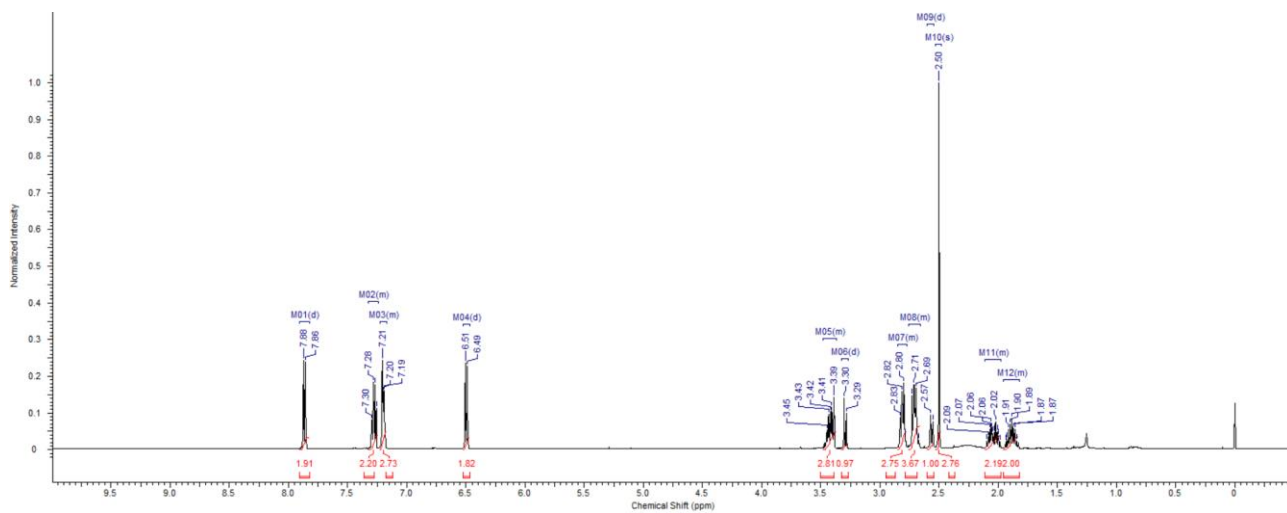
Compound 9d (AD258)

Compound 11b (AD206)
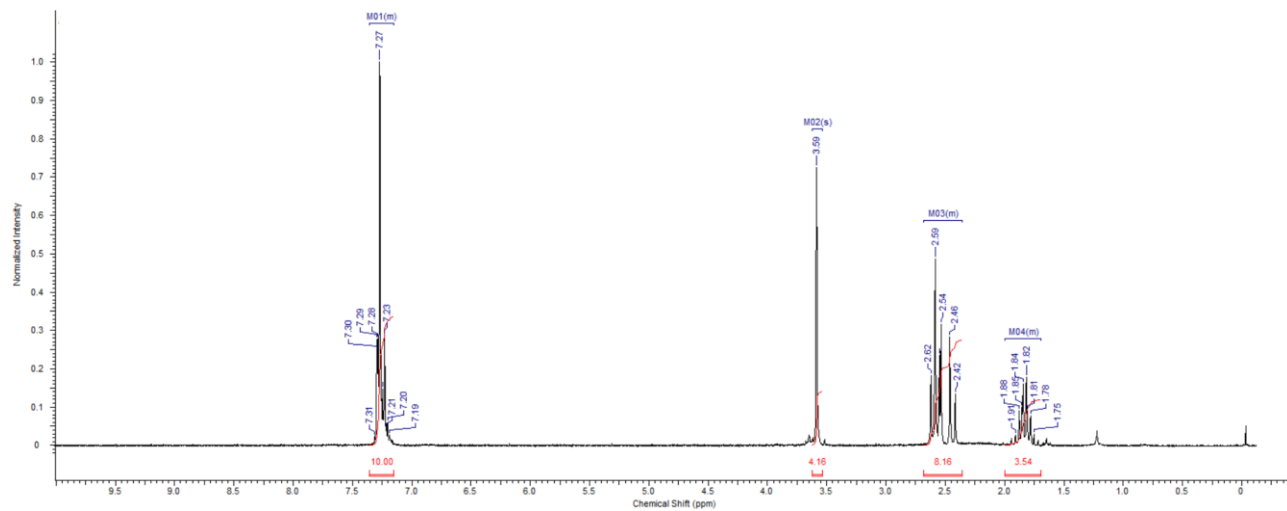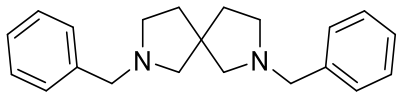
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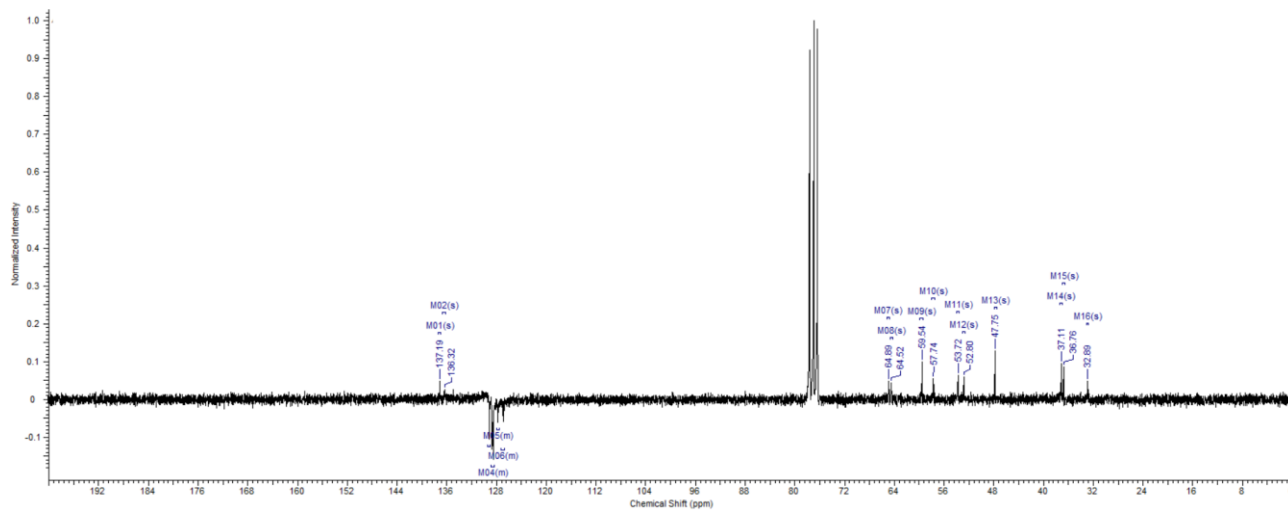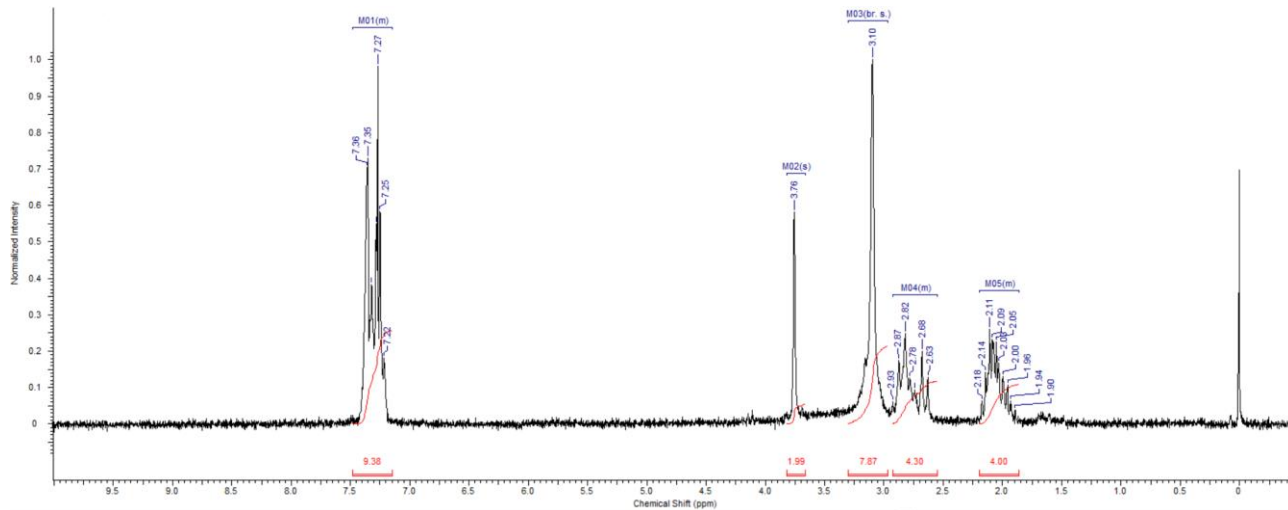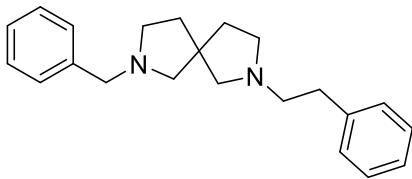
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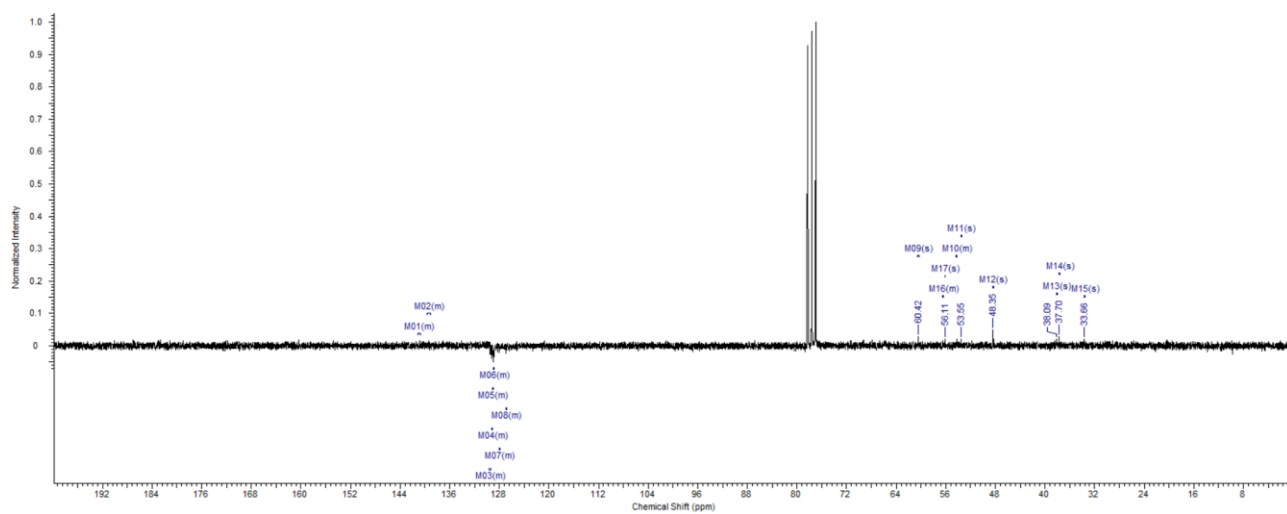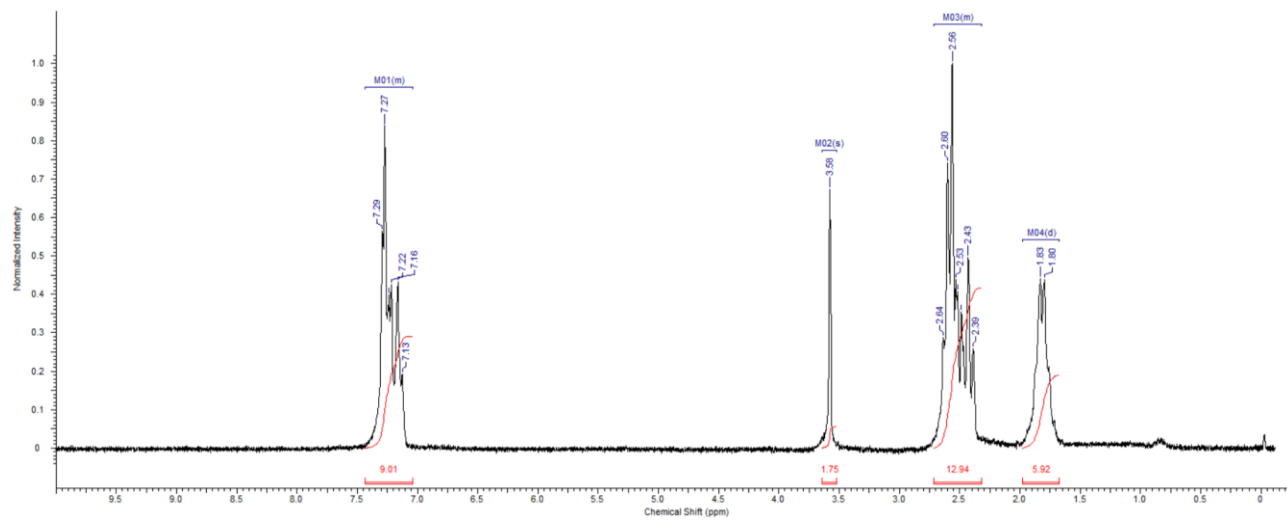
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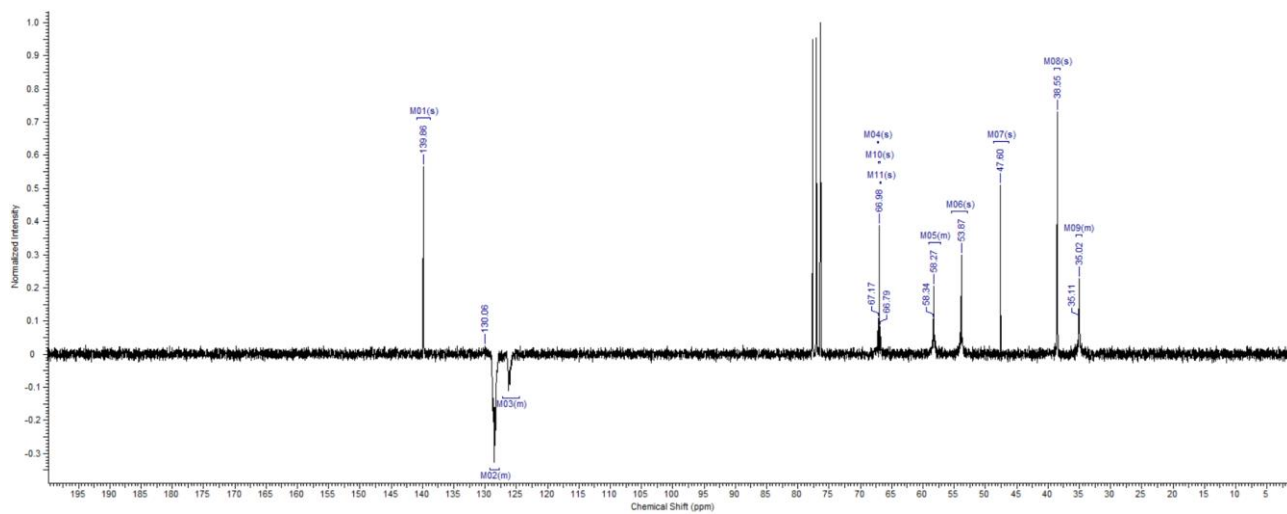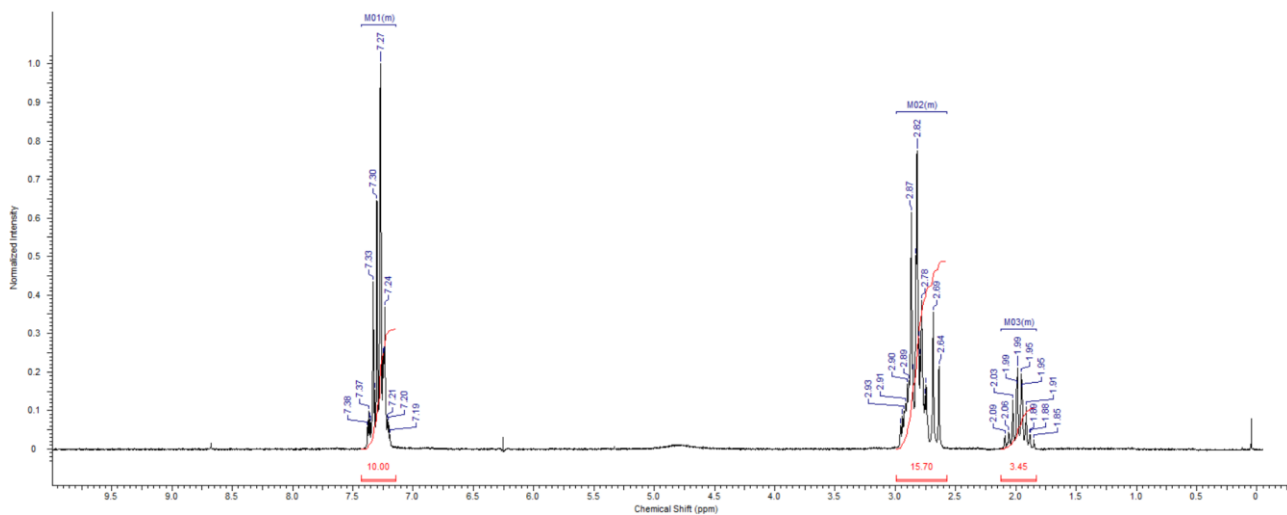
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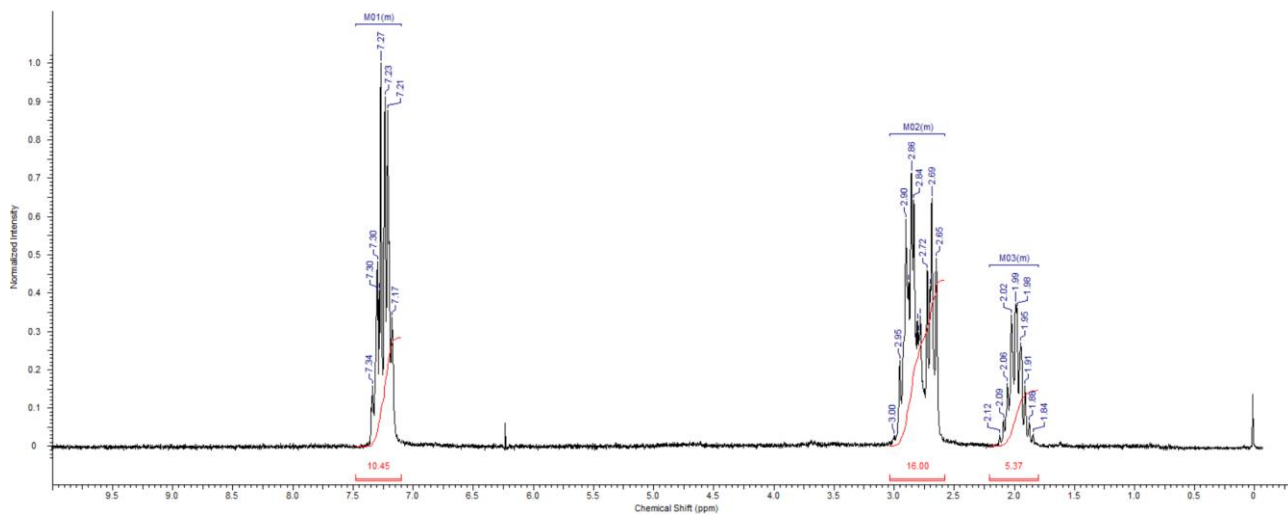
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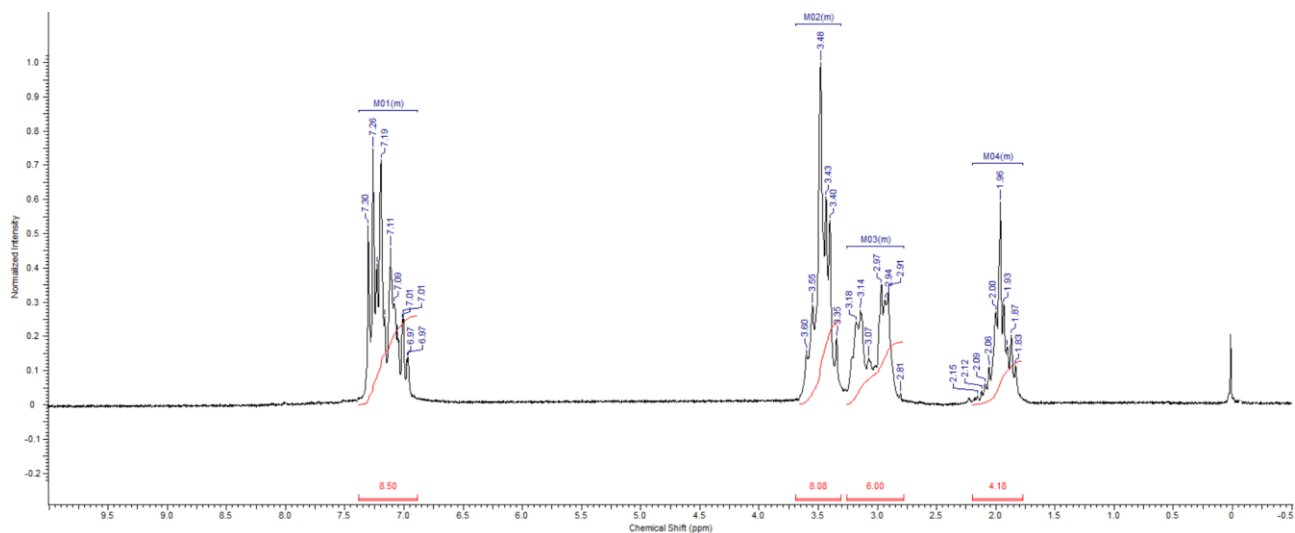
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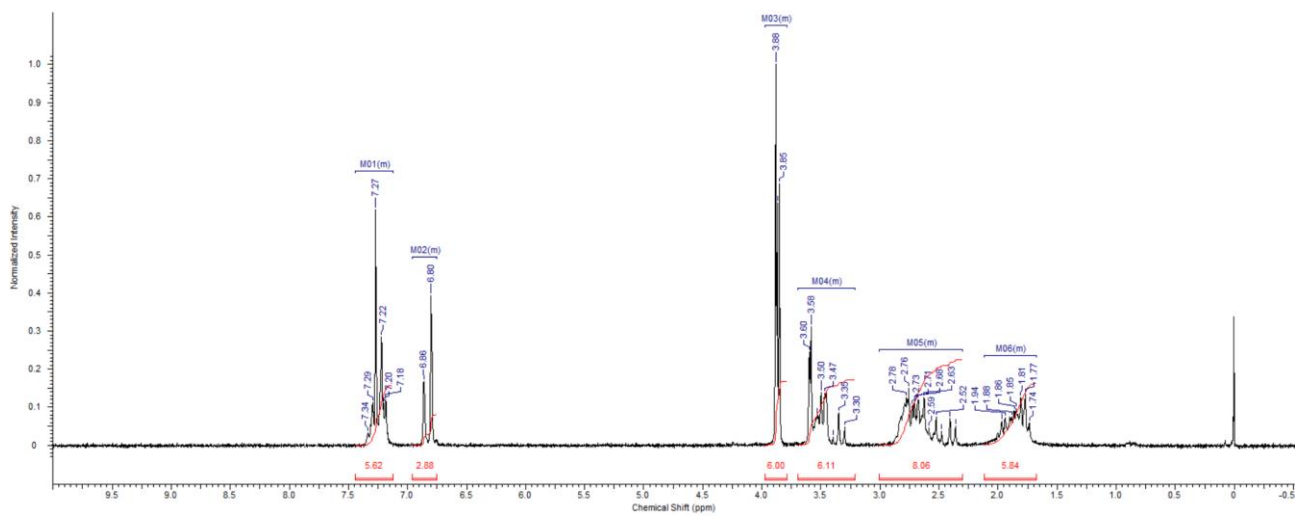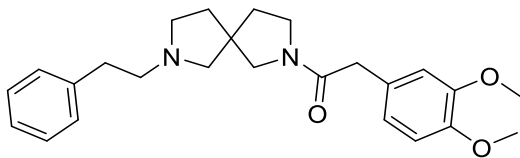
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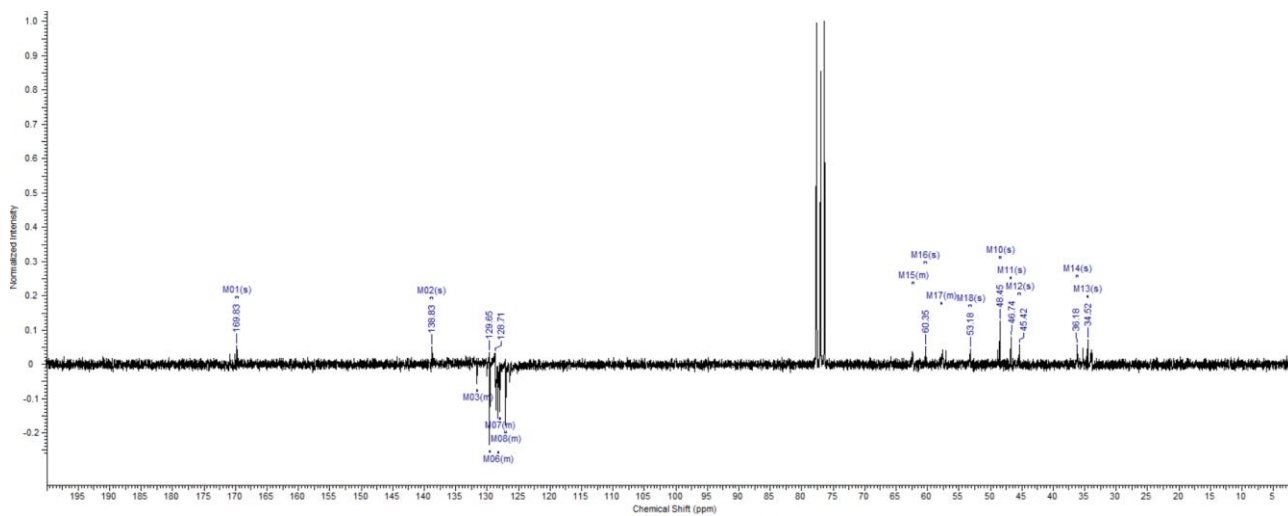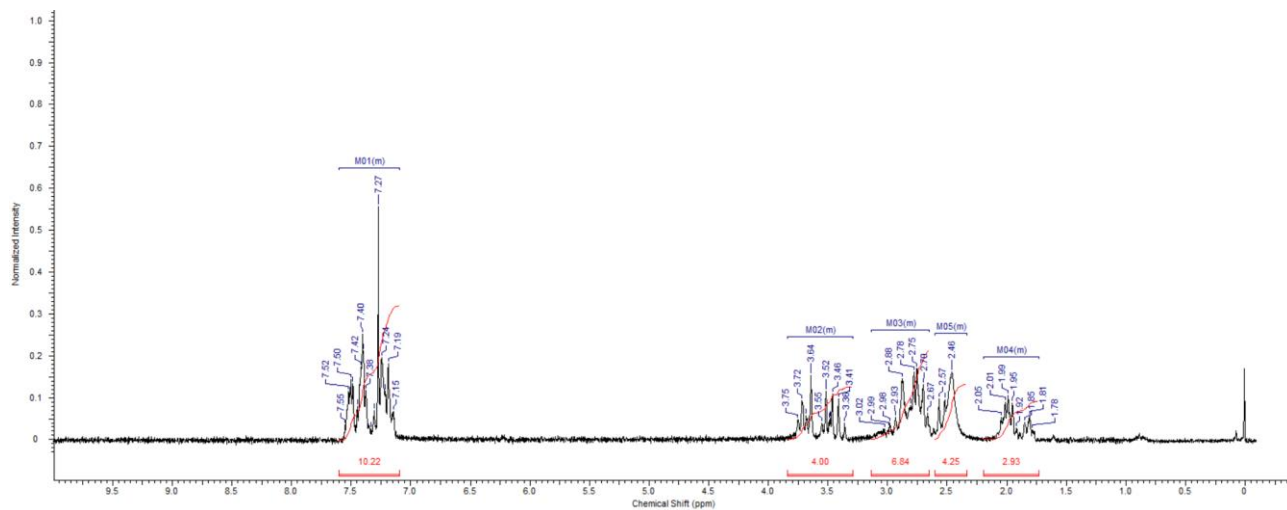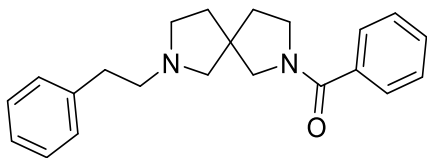
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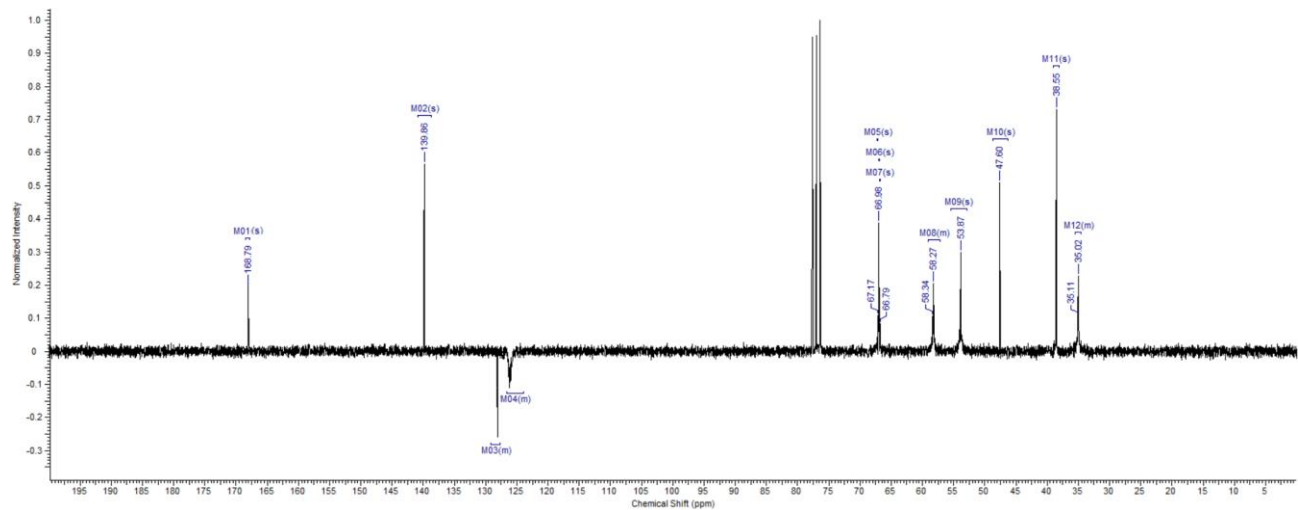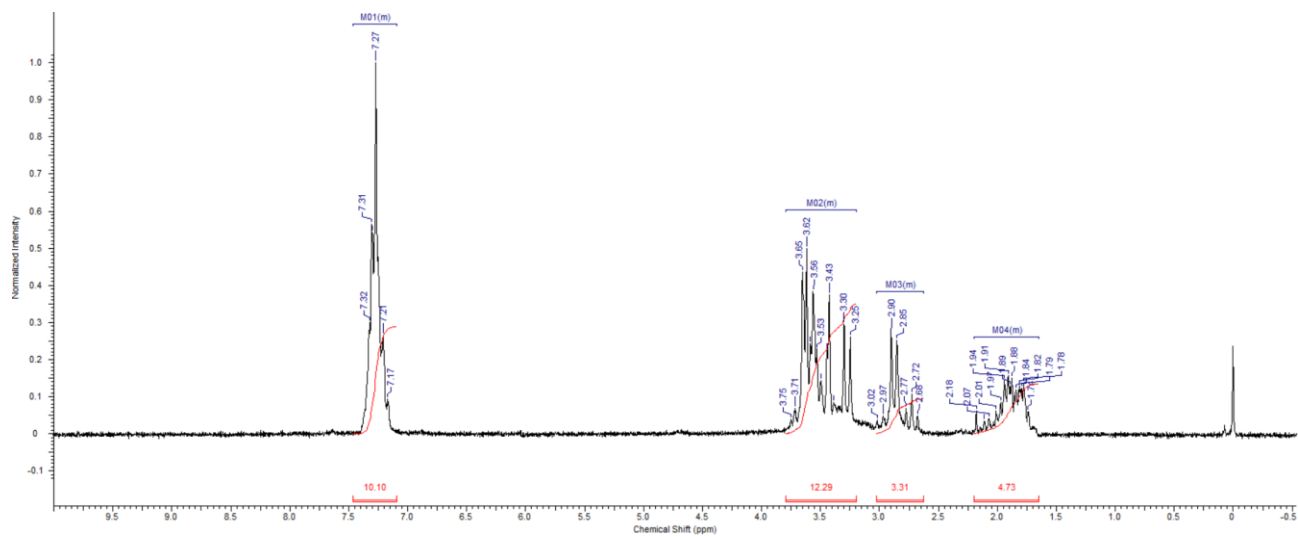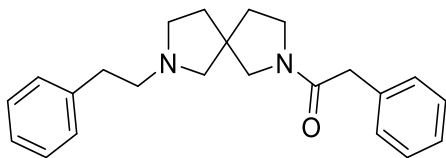
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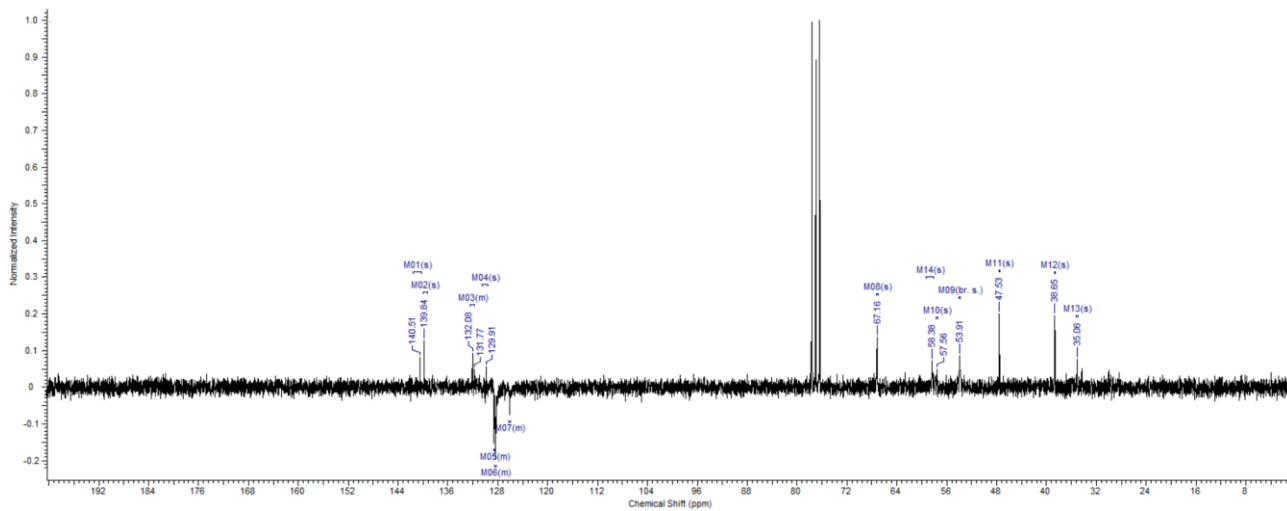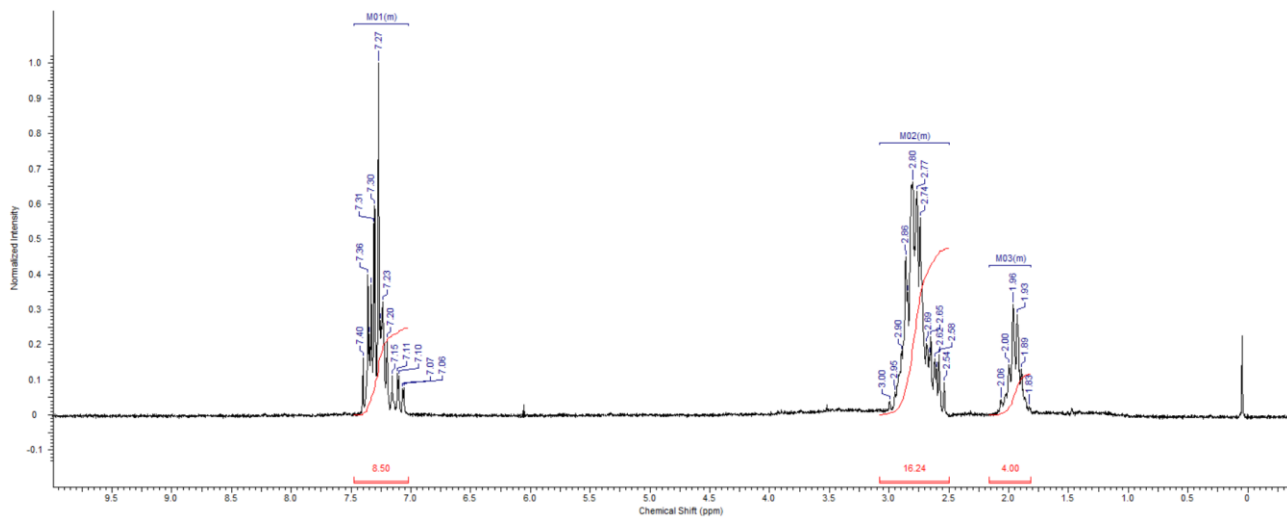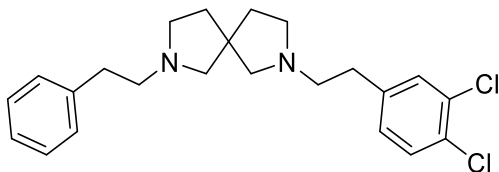
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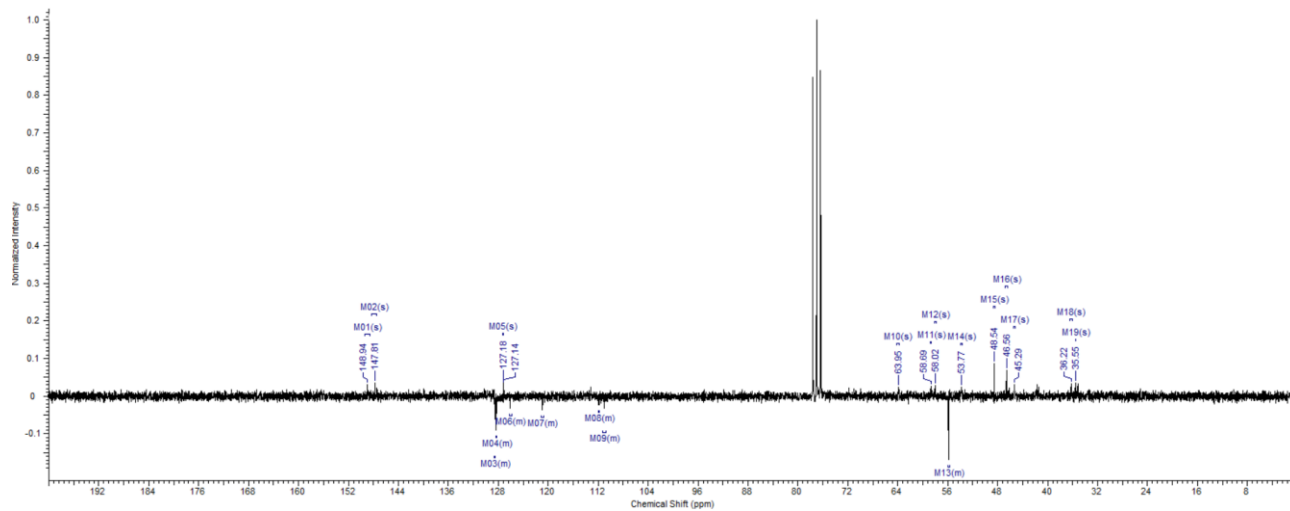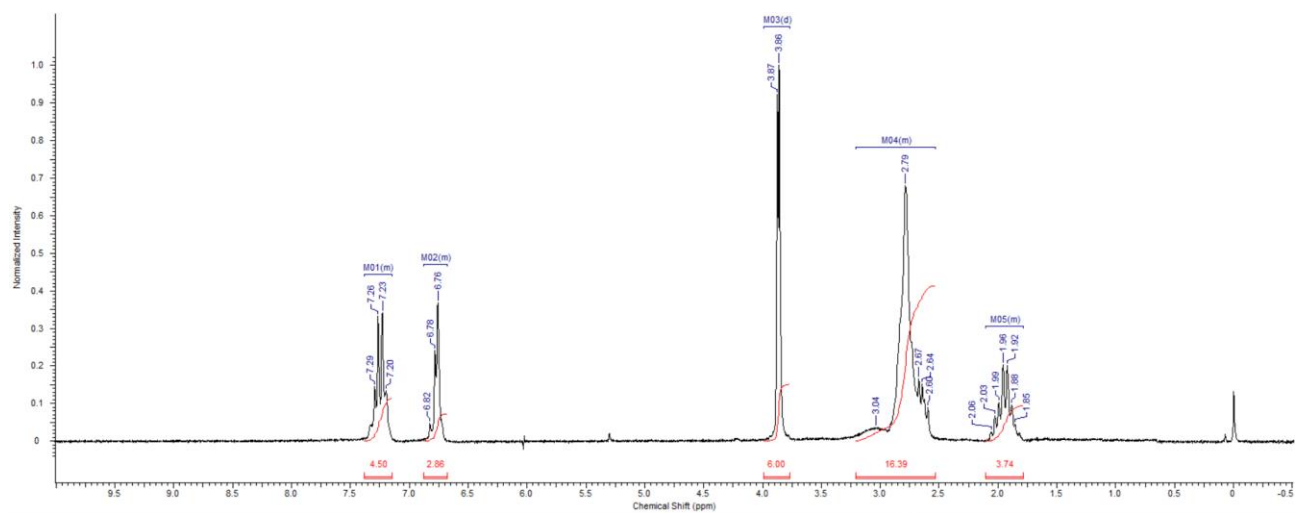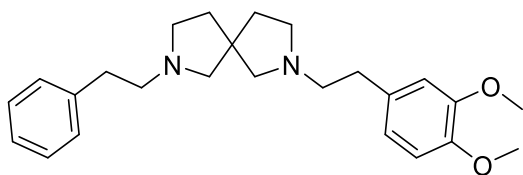
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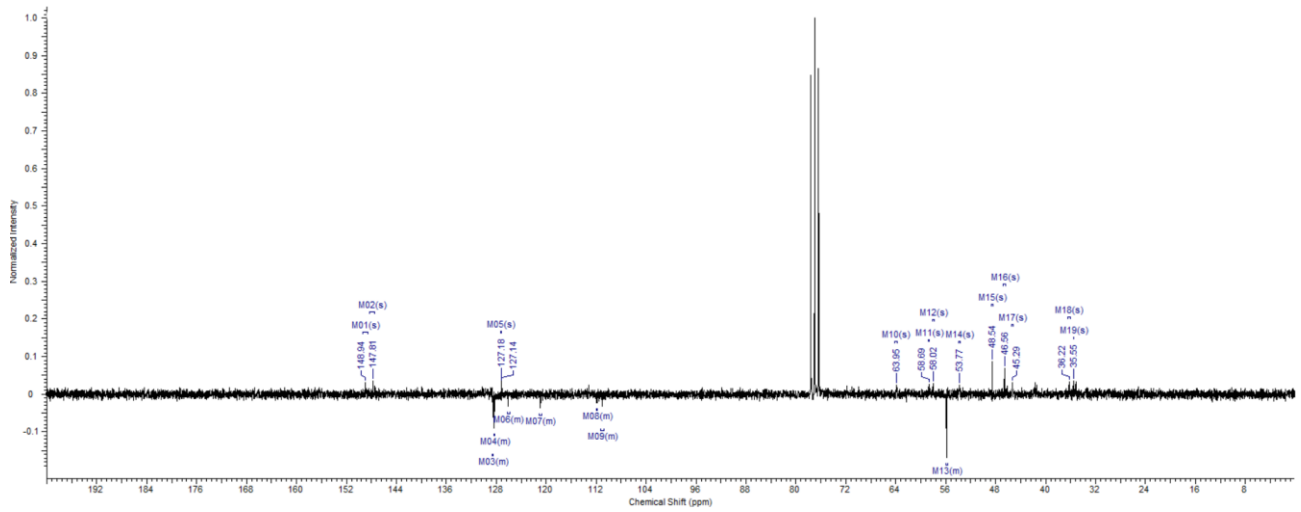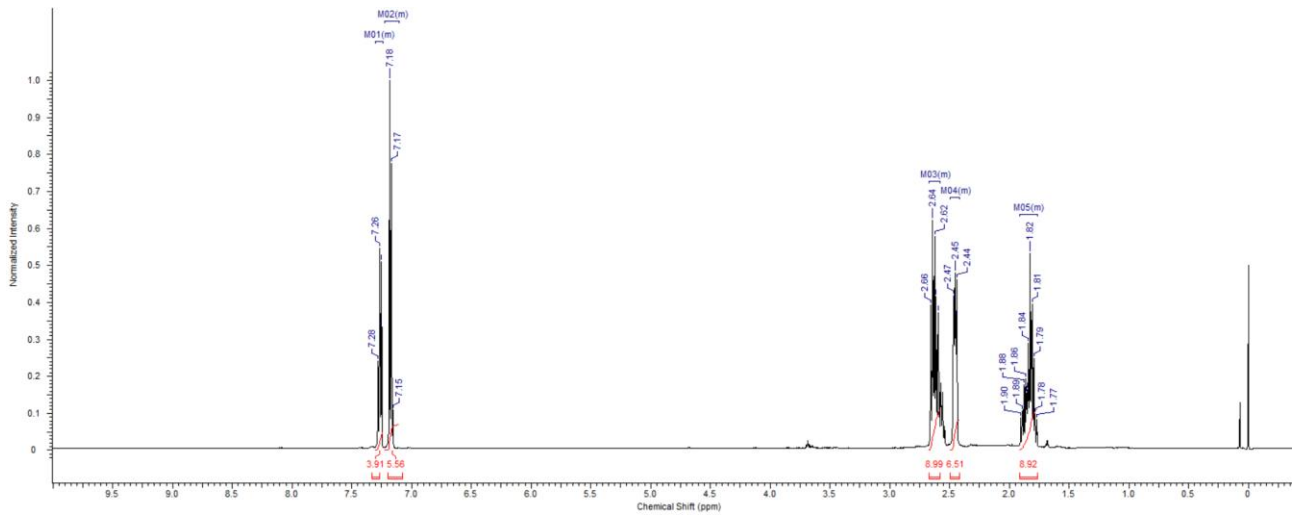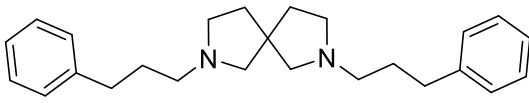
Molecular modeling analysis

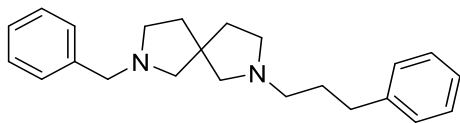**Table S1.** Docking Score values of the 19 compounds in the presence of S1R and S2R. The Docking score values correspond to the average values of the compounds' stereoisomers.

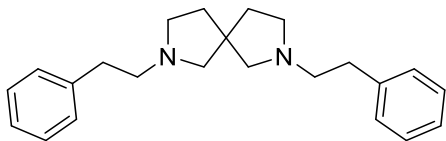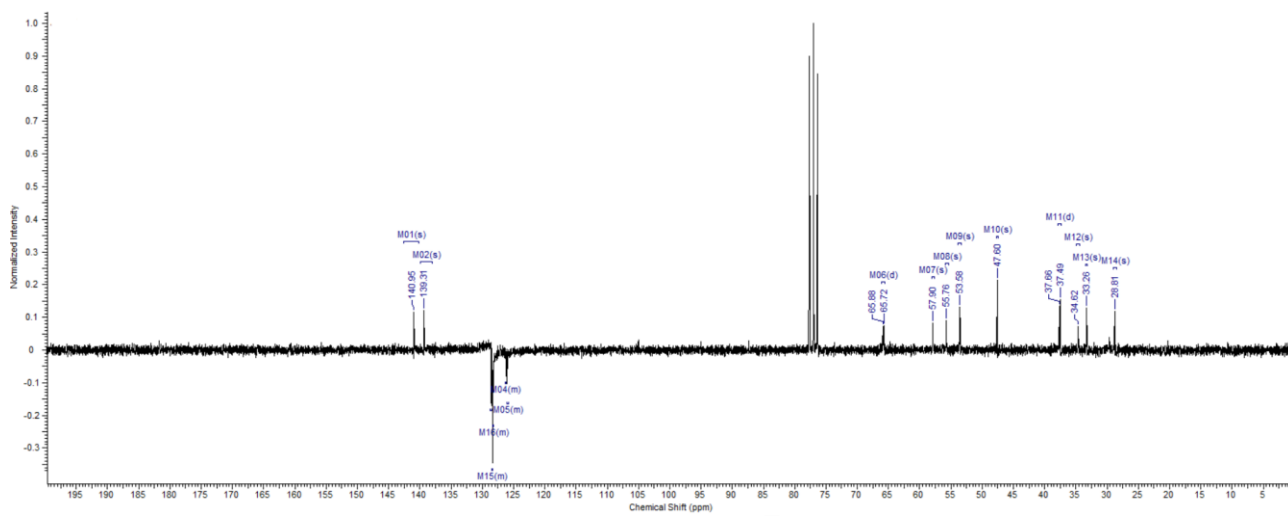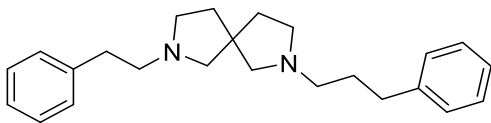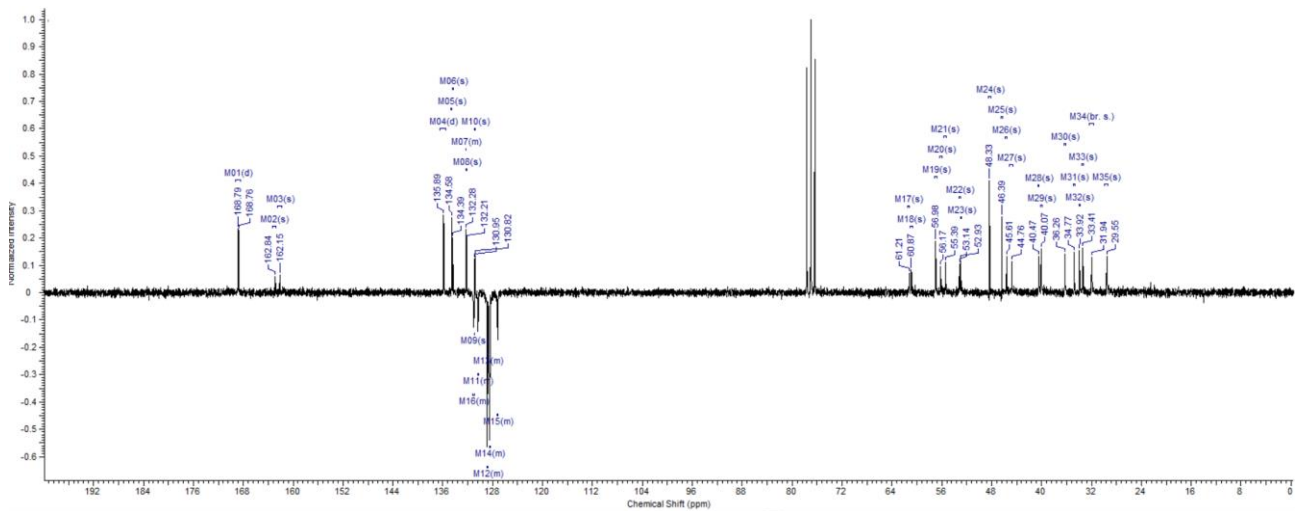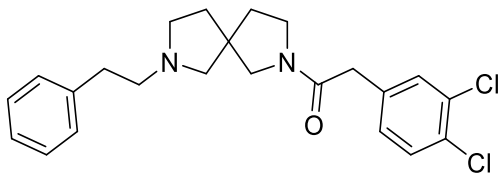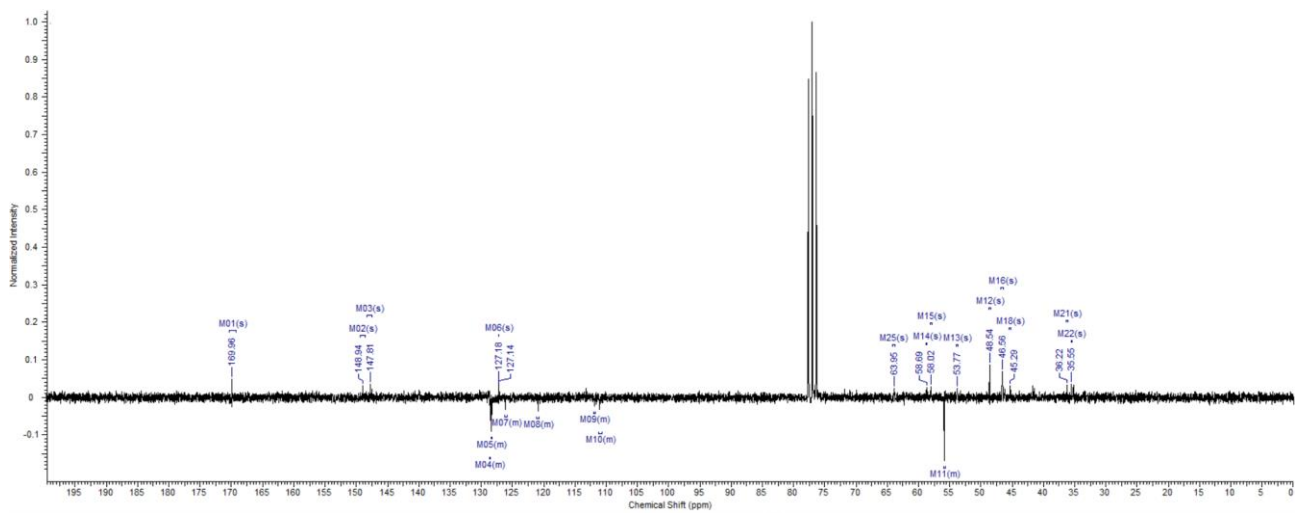| Compound	D-Score* S1R	D-Score* S2R
7b	-8.78	-8.10
8a	-8.53	-8.02
8b	-9.41	-8.24
9a	-9.47	-7.50
9b	-9.29	-8.05
9c	-10.07	-8.35
9d	-9.63	-8.05
11b	-8.91	-9.04
13a	-9.13	-8.44
13b	-9.77	-8.88
14a	-9.75	-8.76
14b	-9.82	-9.18
15a	-11.16	-7.74
15b	-10.19	-7.42
15d	-10.10	-8.36
15e	-10.42	-8.60
16a	-9.81	-8.93
16b	-10.37	-8.92
16c	-10.25	-8.39

Docking Scores values are expressed in kcal/mol.

```
PDB 7M95      7 MGTLGARRGLEWFLGFYFLSHIPITLLMDLQGVLPRDLYPVELRNLQQWY    56
                ||....||.:||.||.||||||||||.||||.||||:|||||.|||.:||
SIGMA 2 human 1 MGAPATRRCVEWLLGLYFLSHIPITLFMDLQAVLPRELYPVEFRNLLKWY    50

PDB 7M95     57 IEEFKDPLLQTPPAWFKSFLFCELVFQLPFFPIAAYAFFKGGCKWIRTPA   106
                .:|||||||||.|||||||||||||||||||||.|||.||.|||||||||
SIGMA 2 human 51 AKEFKDPLLQEPPAWFKSFLFCELVFQLPFFPIATYAFLKGSCKWIRTPA  100

PDB 7M95    107 IIYSVHTMTTLIPILSTLLLDDFSKASHFRGQGPKTFQERLFLISVYIPY   156
                |||||||||||||||||.|.:|||||||.|:||.|:|..|||.|:|||.||
SIGMA 2 human 101 IIYSVHTMTTLIPILSTFLFEDFSKASGFKGQRPETLHERLTLVSVYAPY  150

PDB 7M95    157 FLIPLILLLFMVRNPYYK      174
                .|||.|||:||:|:||||
SIGMA 2 human 151 LLIPFILLIFMLRSPYYK      168
```

Figure S1. Sequence alignment between human and bovine S2R (PDB model 7M95). The single and the double dots indicate the different and similar residues between the human and bovine S2R sequences, respectively.
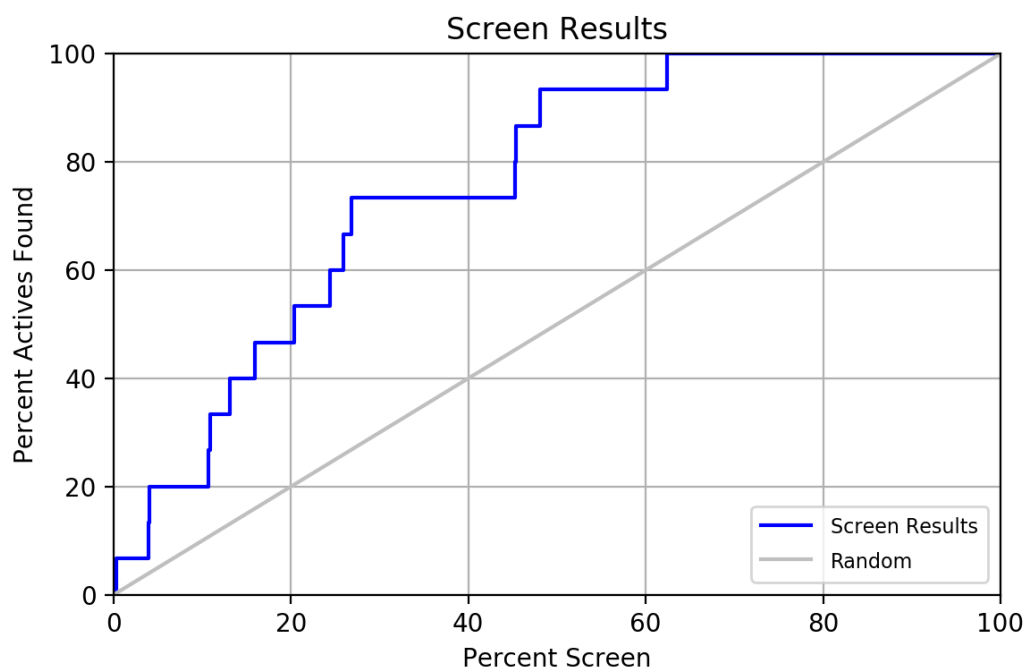
Table S2. Count and percentage of actives in top N% of results for S1R.

% Results	1	2	5	10	20
# Actives	1	1	3	3	7
% Actives	6.7	6.7	20.0	20.0	46.7

Figure S2. Percent screen plot for S1R. The percentage of the processed compounds and the percentage of the identified active compounds are reported on the abscissa and on the ordinate axes, respectively.

Table S3. Count and percentage of actives in top N% of results for S2R.

% Results	1	2	5	10	20
# Actives	5	7	11	13	15
% Actives	33.3	46.7	73.3	86.7	100.0
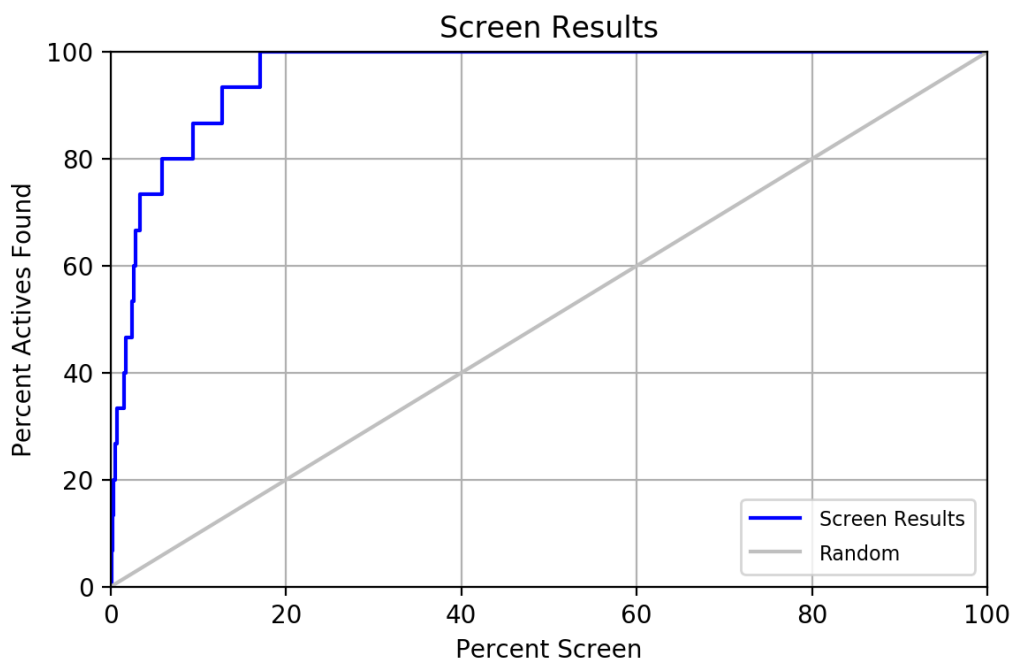
Figure S3. Percent screen plot for S2R. The percentage of the processed compounds and the percentage of the identified active compounds are reported on the abscissa and on the ordinate axes, respectively.