Concise asymmetric syntheses of novel phenanthroquinolizidines

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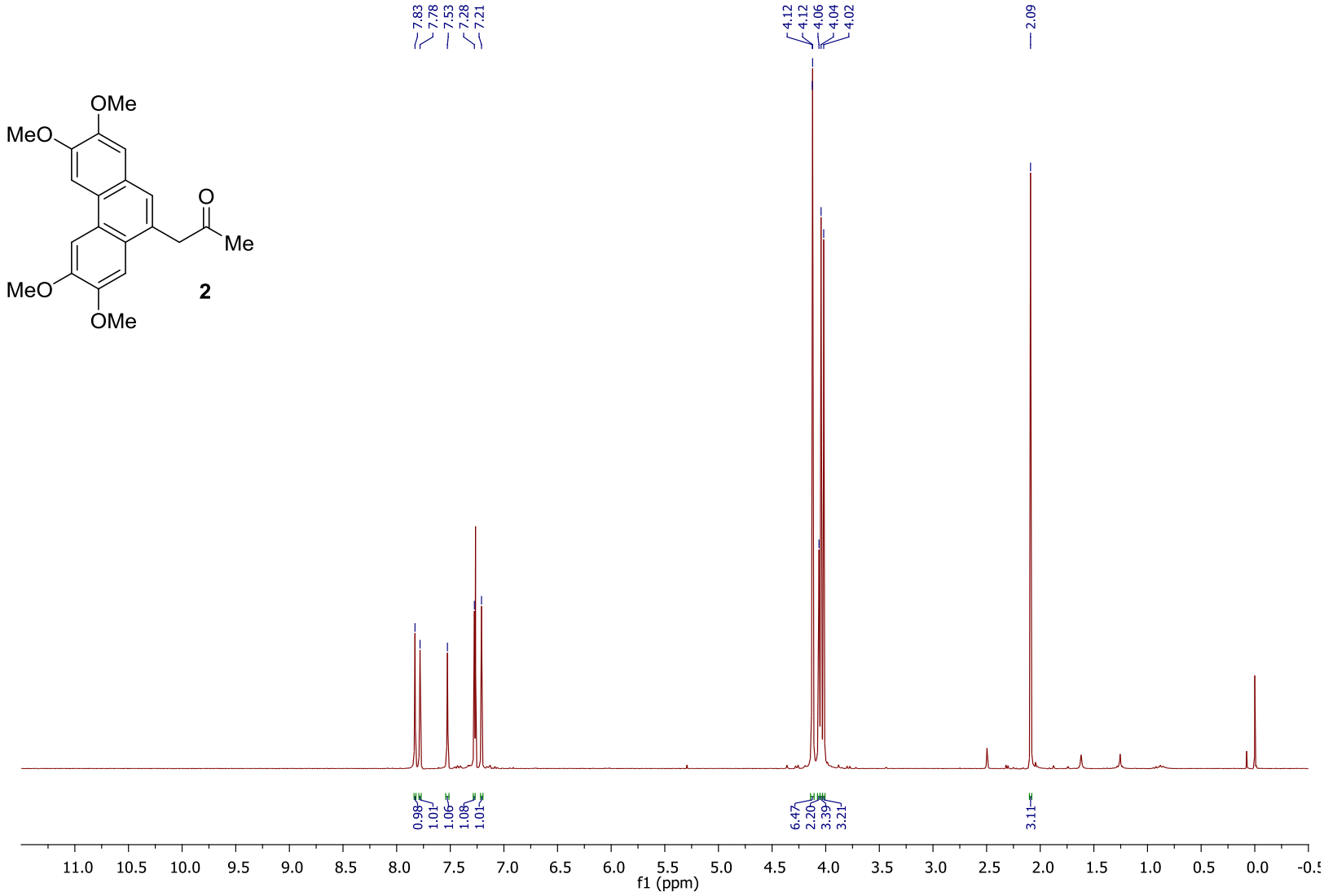
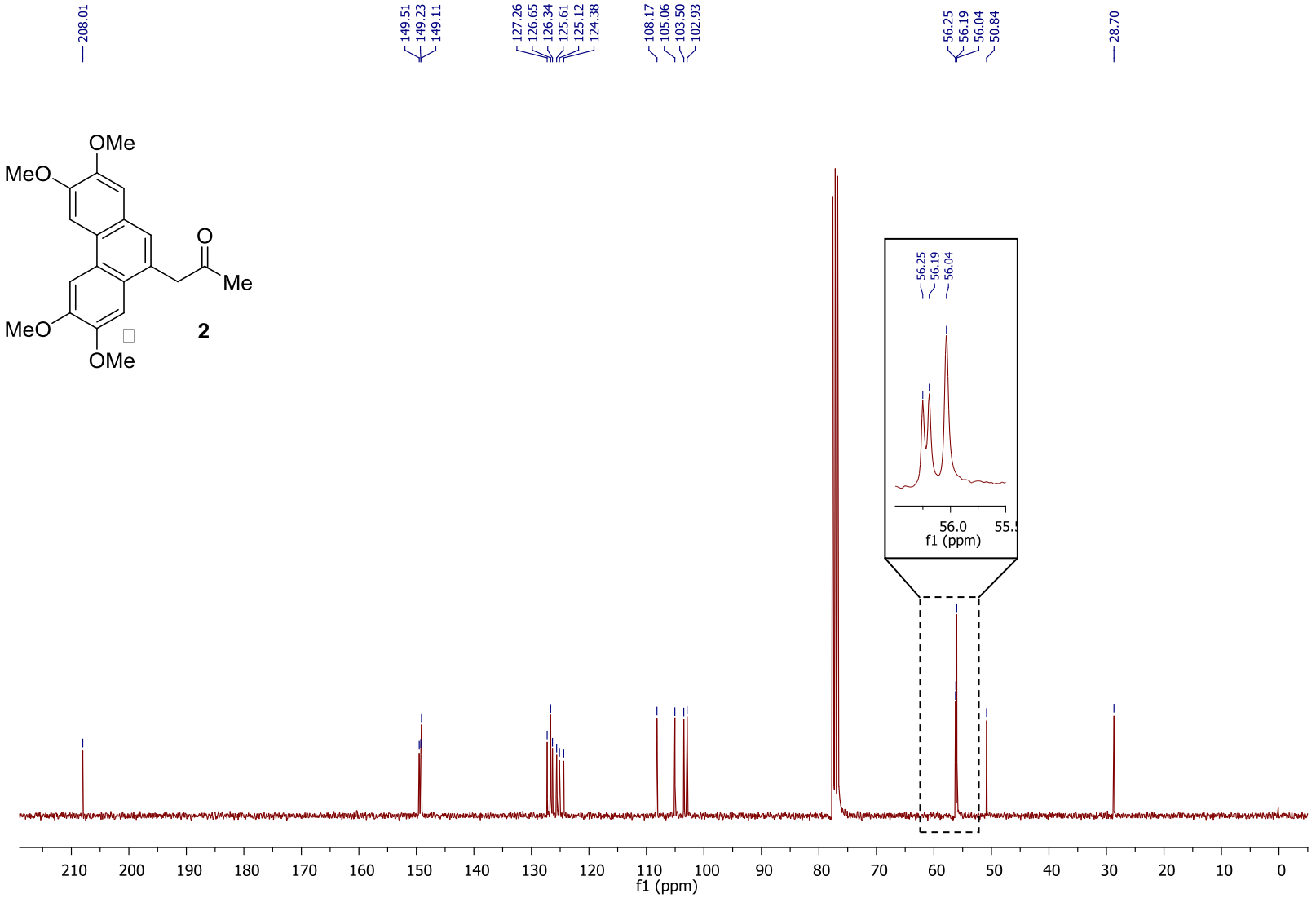
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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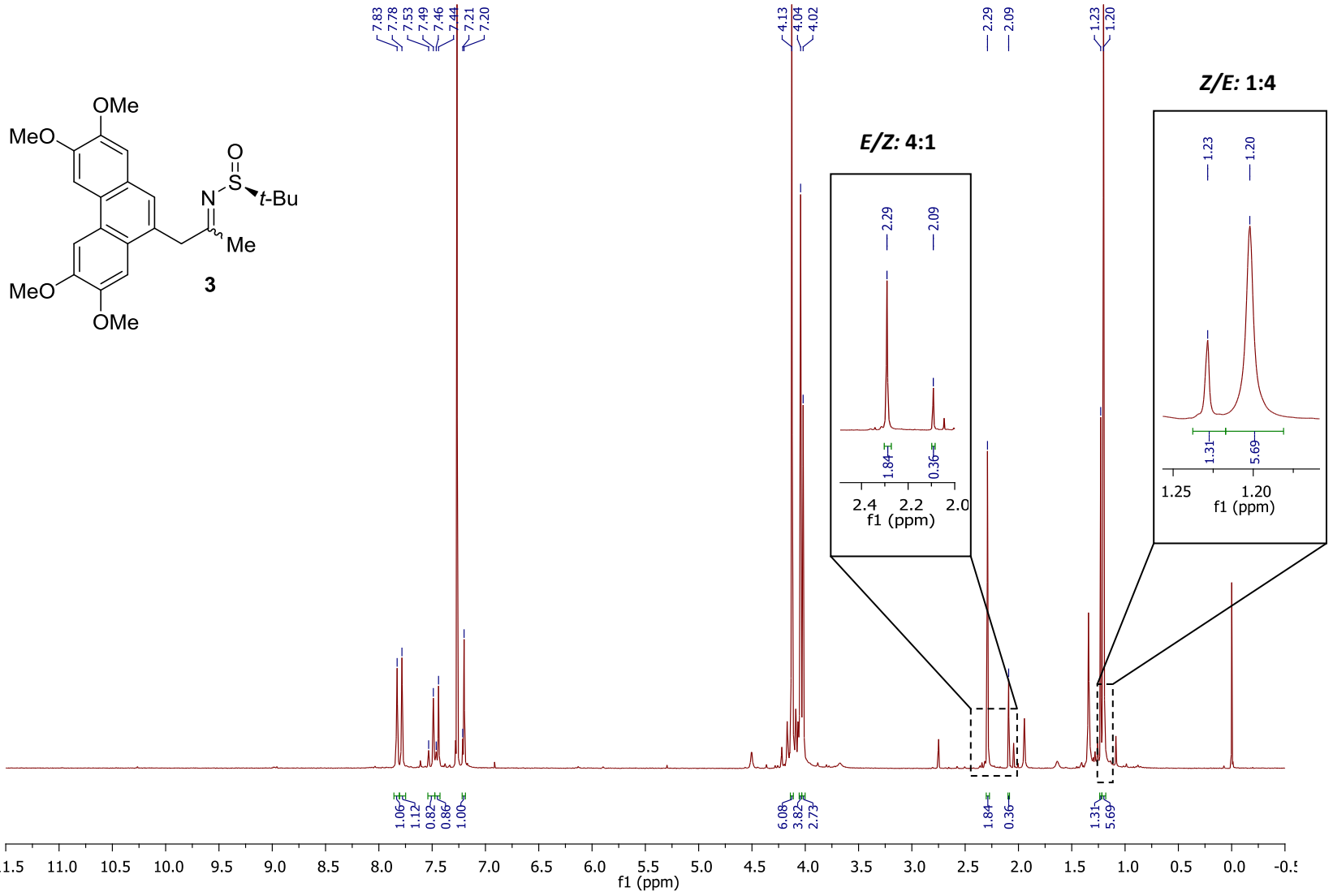

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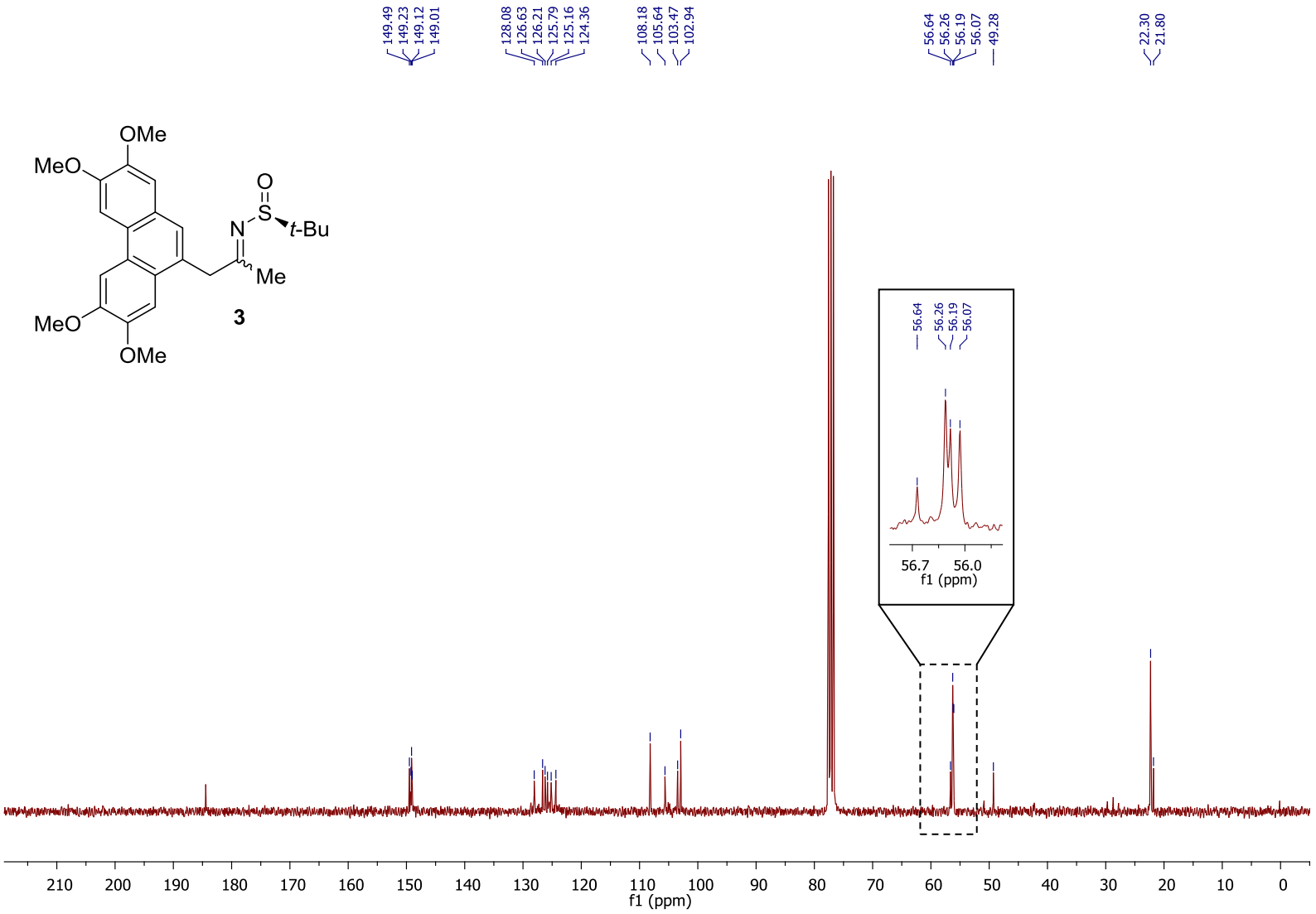

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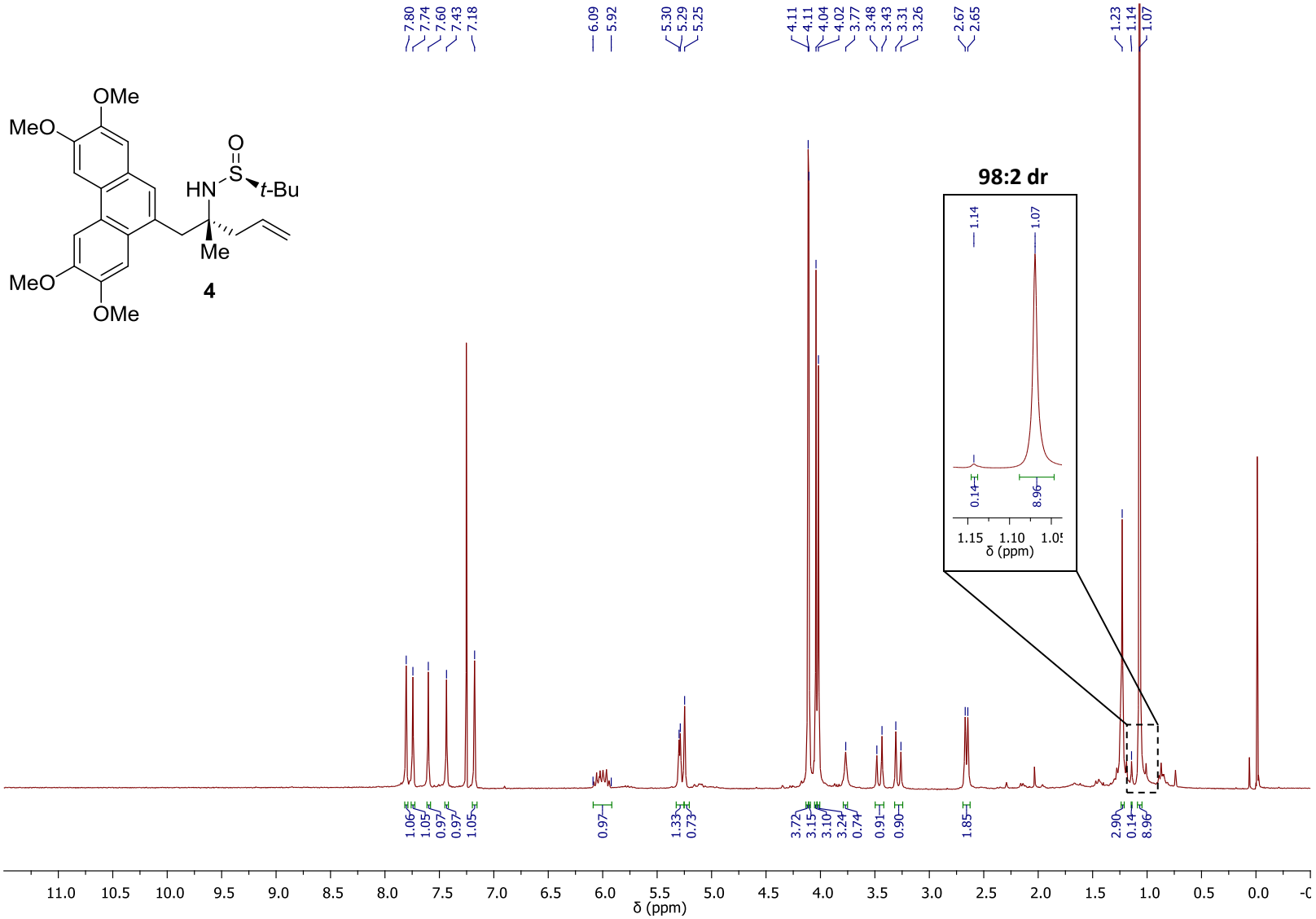

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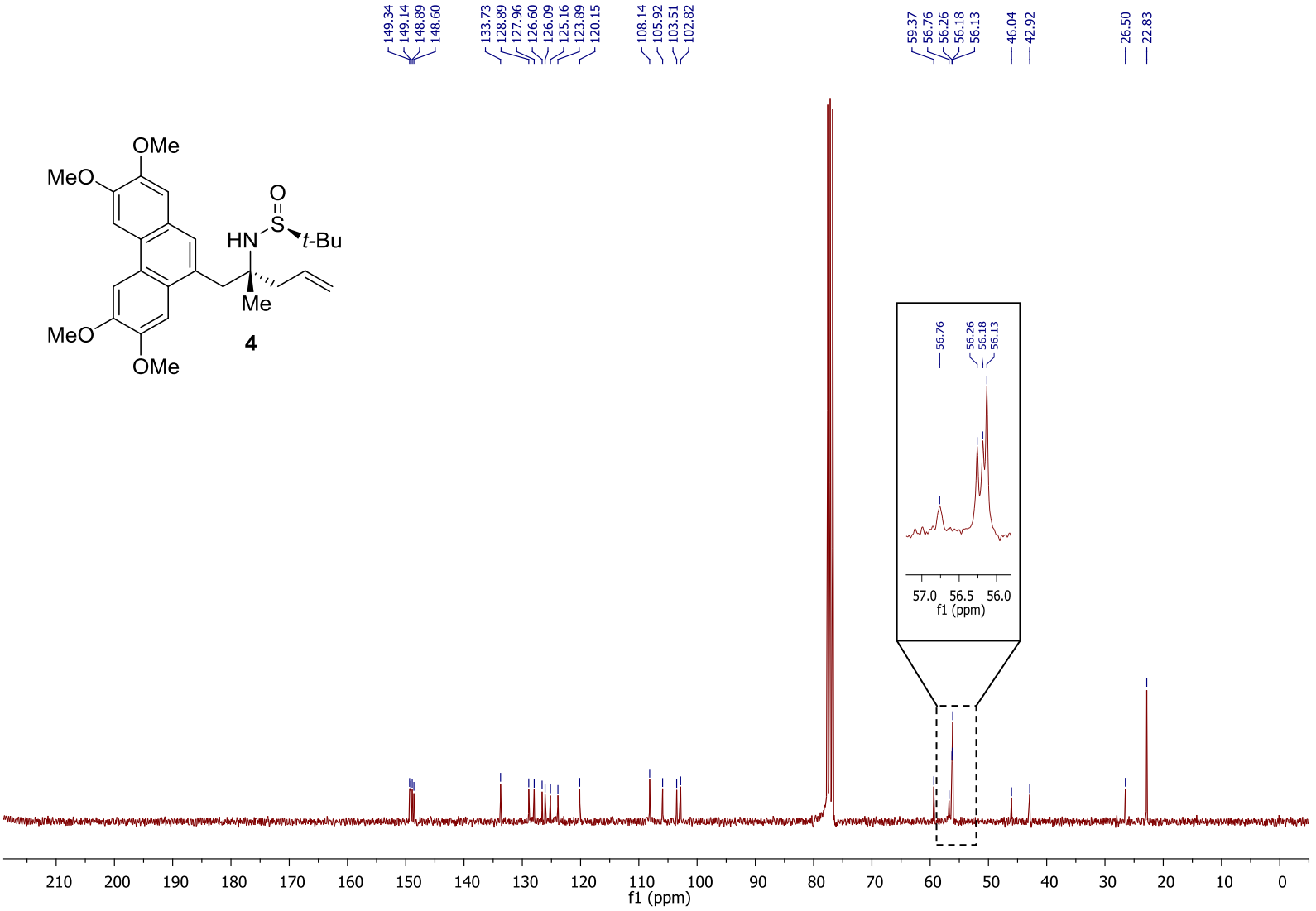

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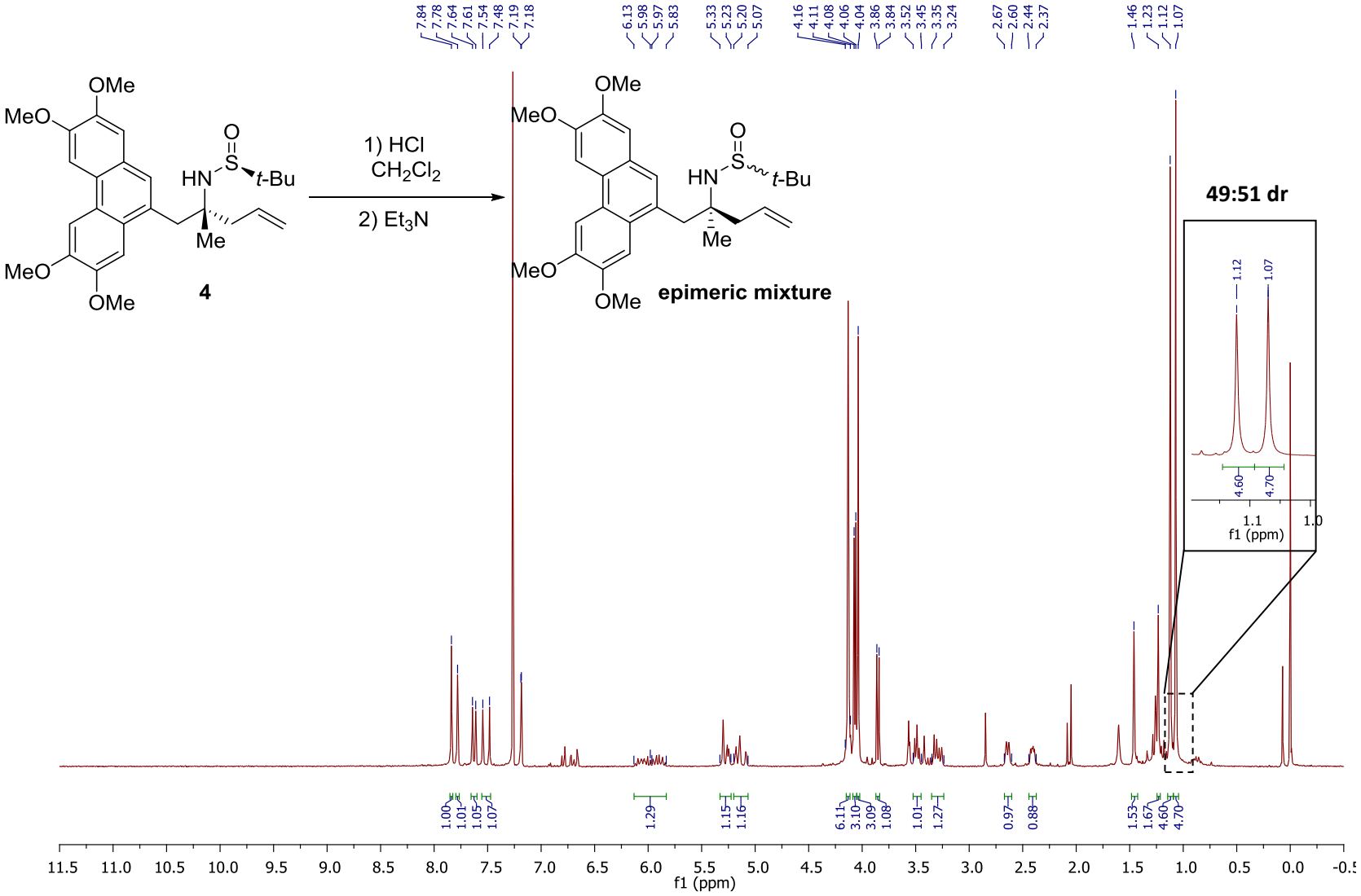

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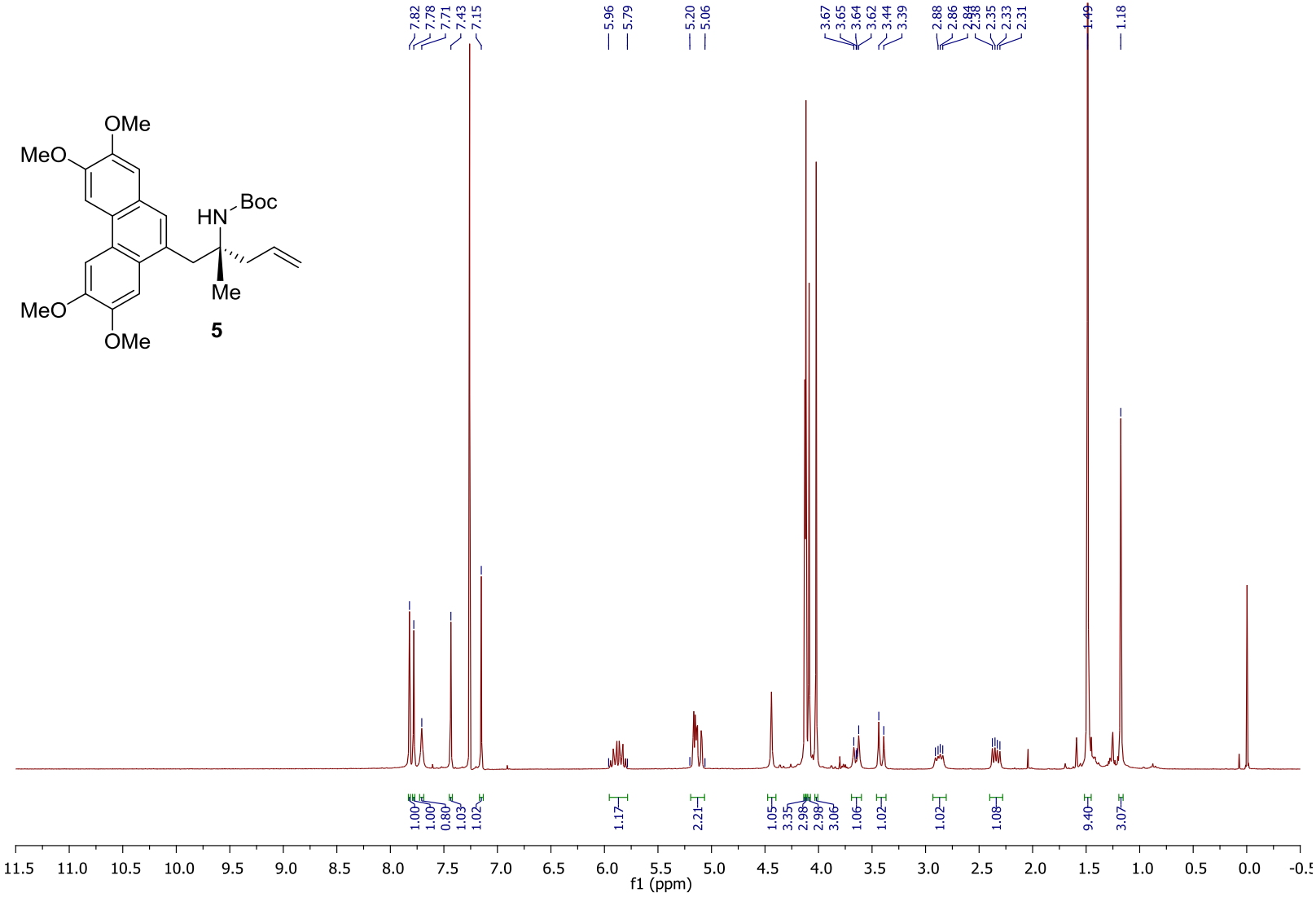

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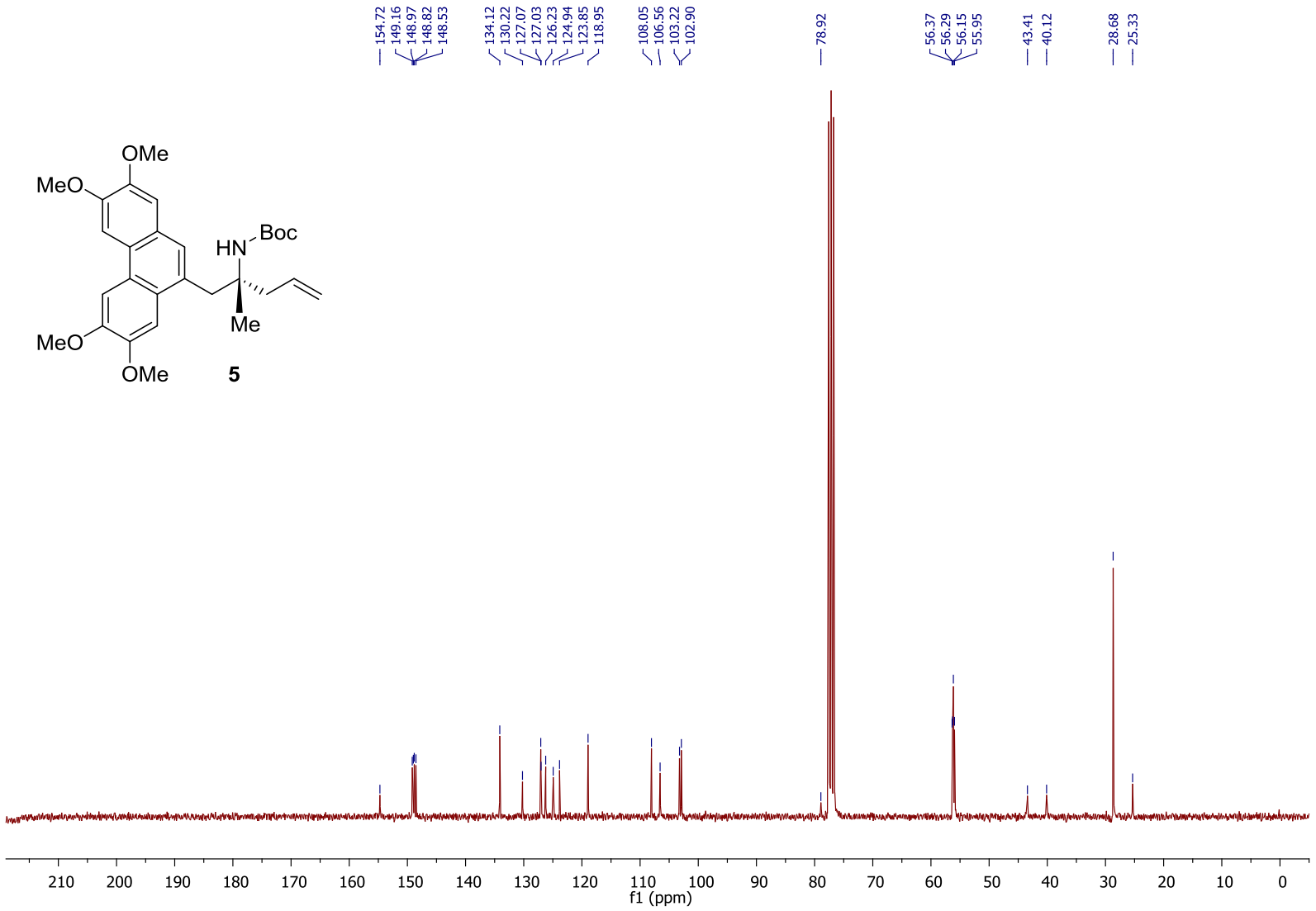

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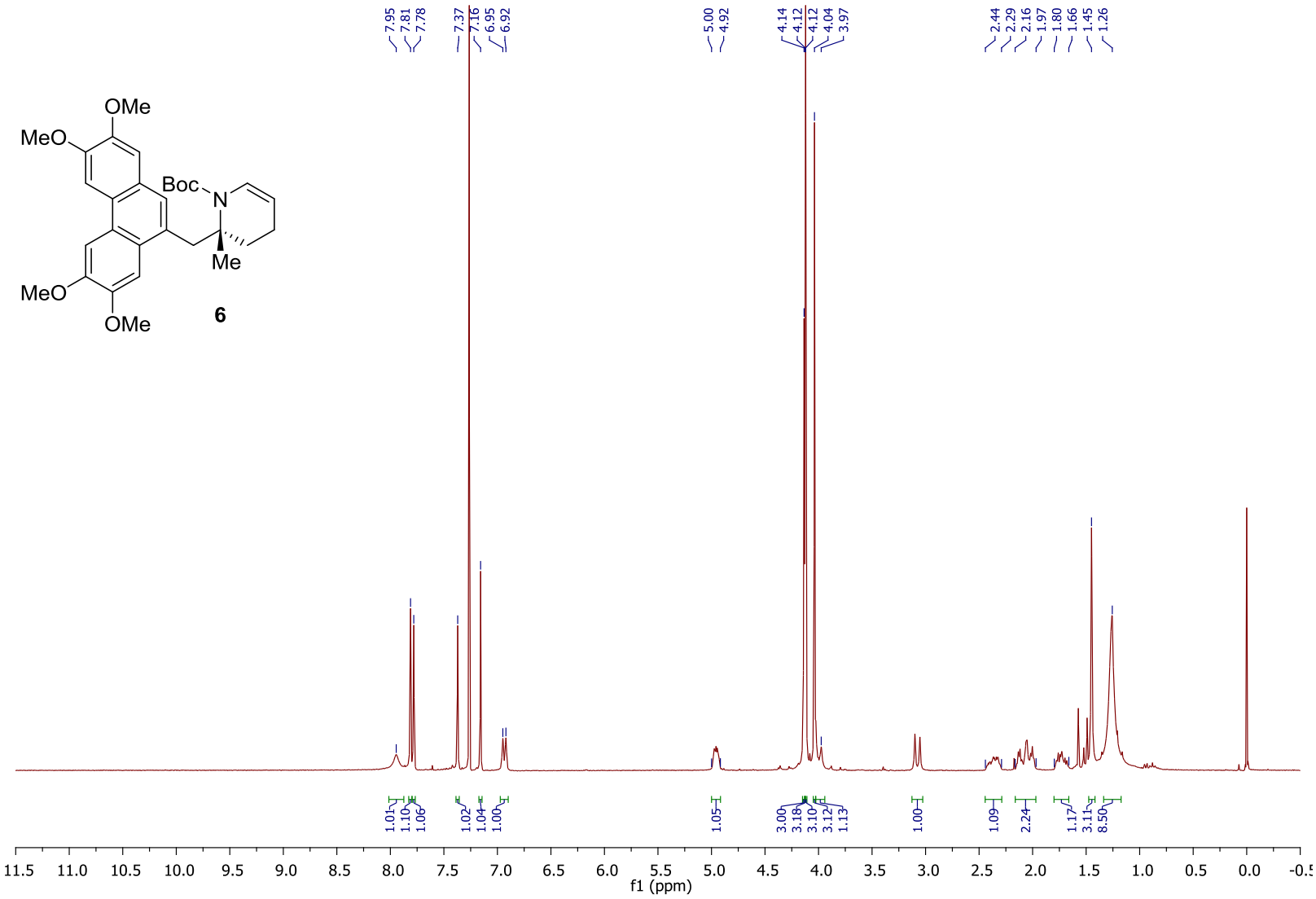

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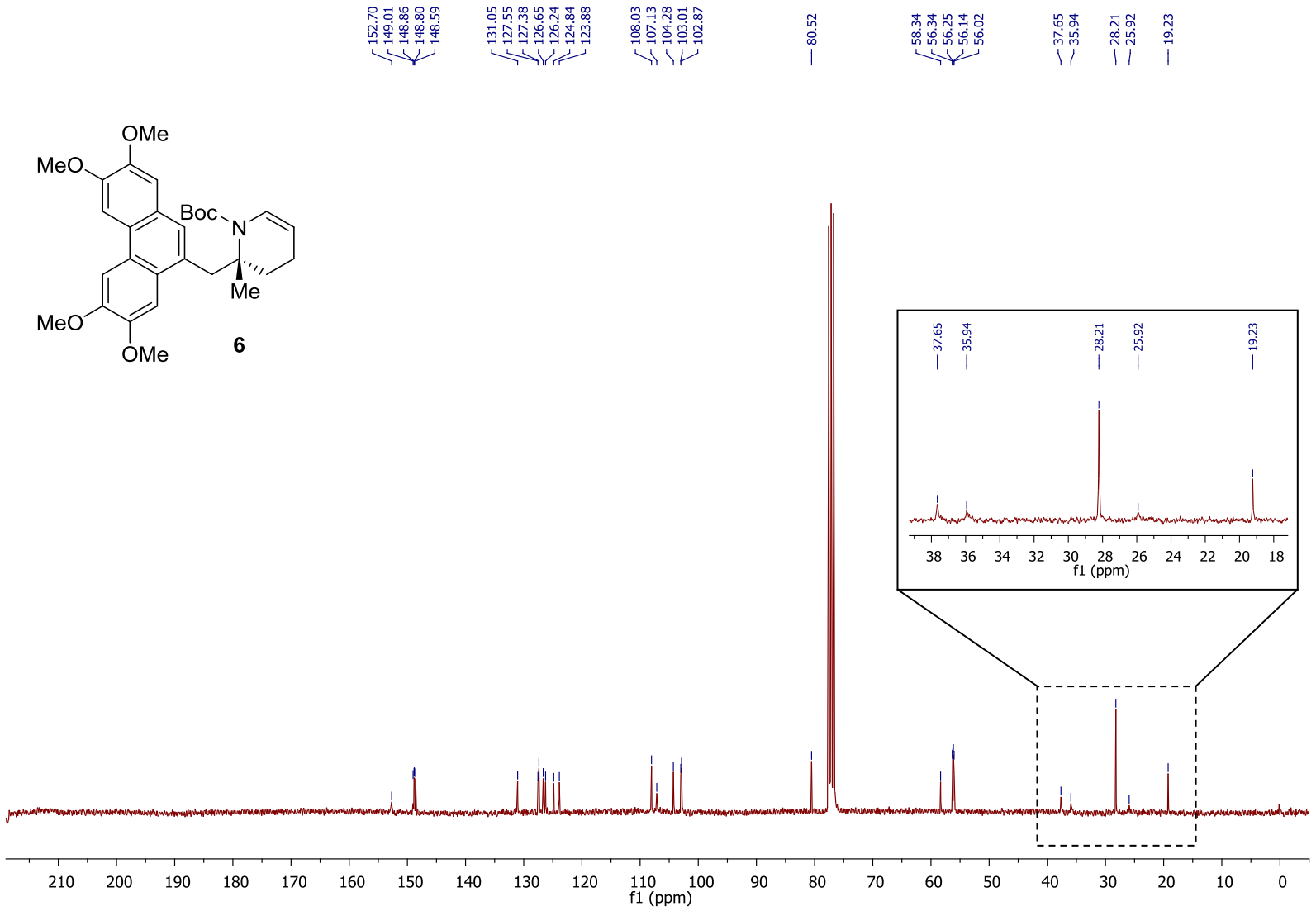

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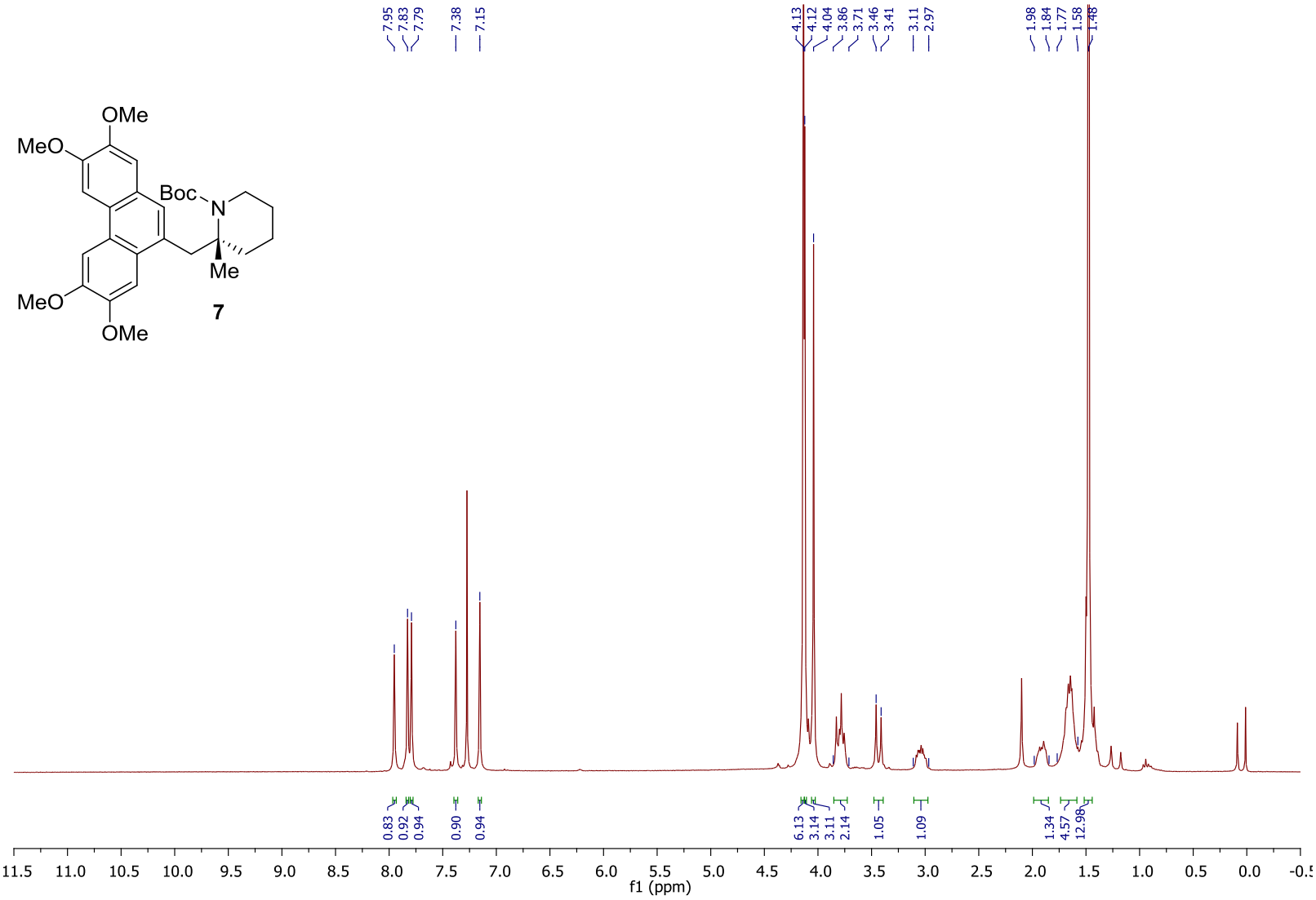

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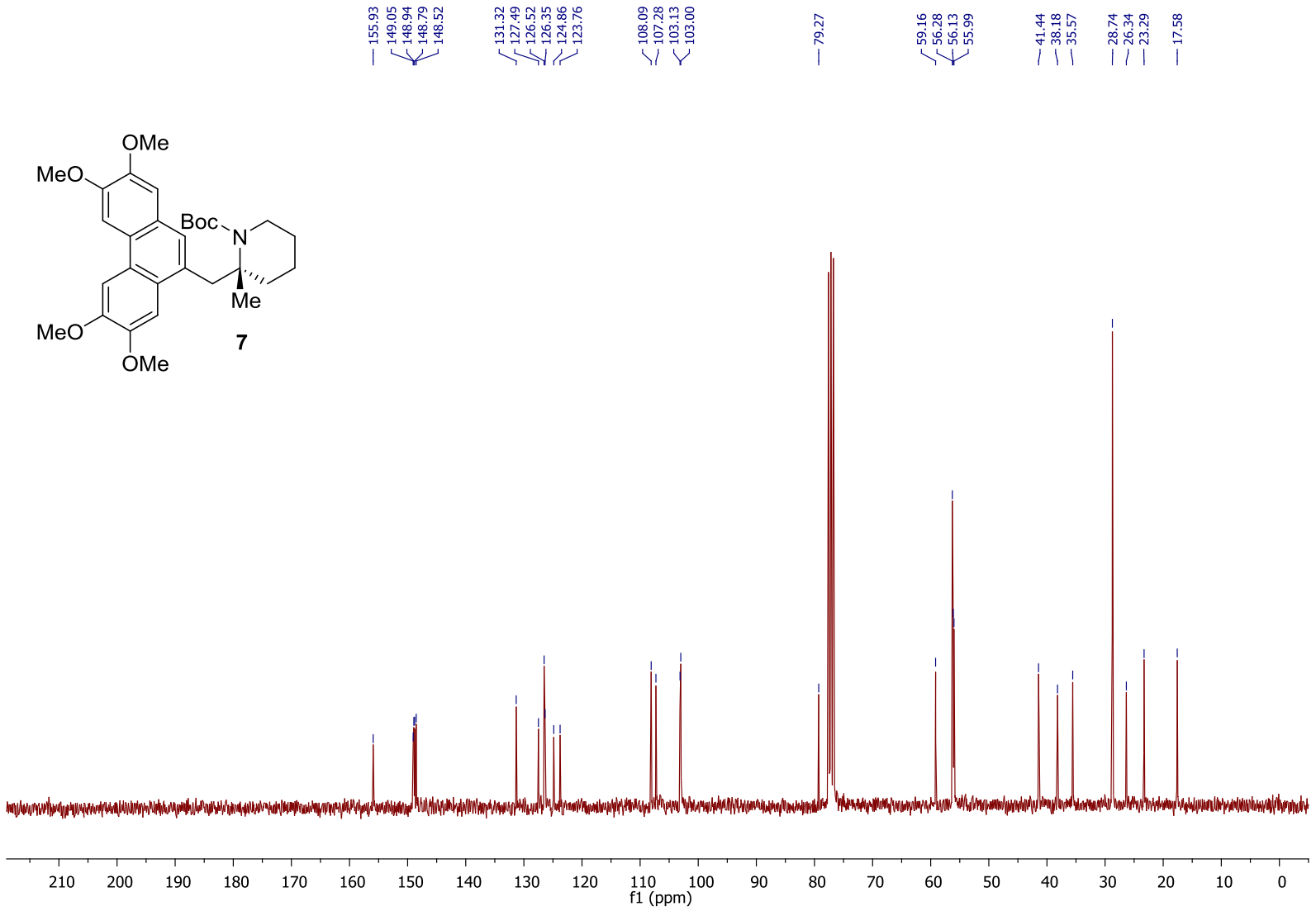

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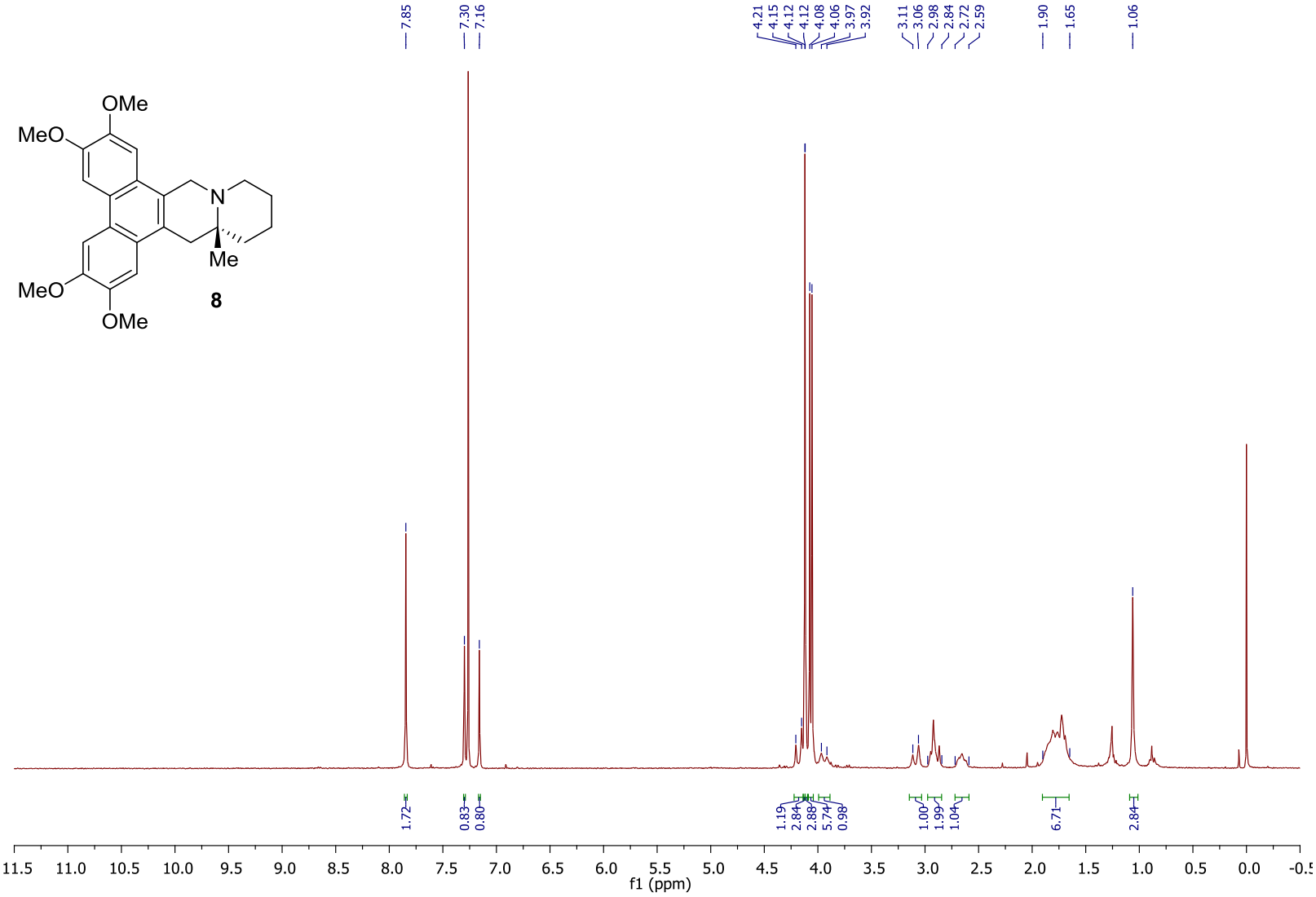

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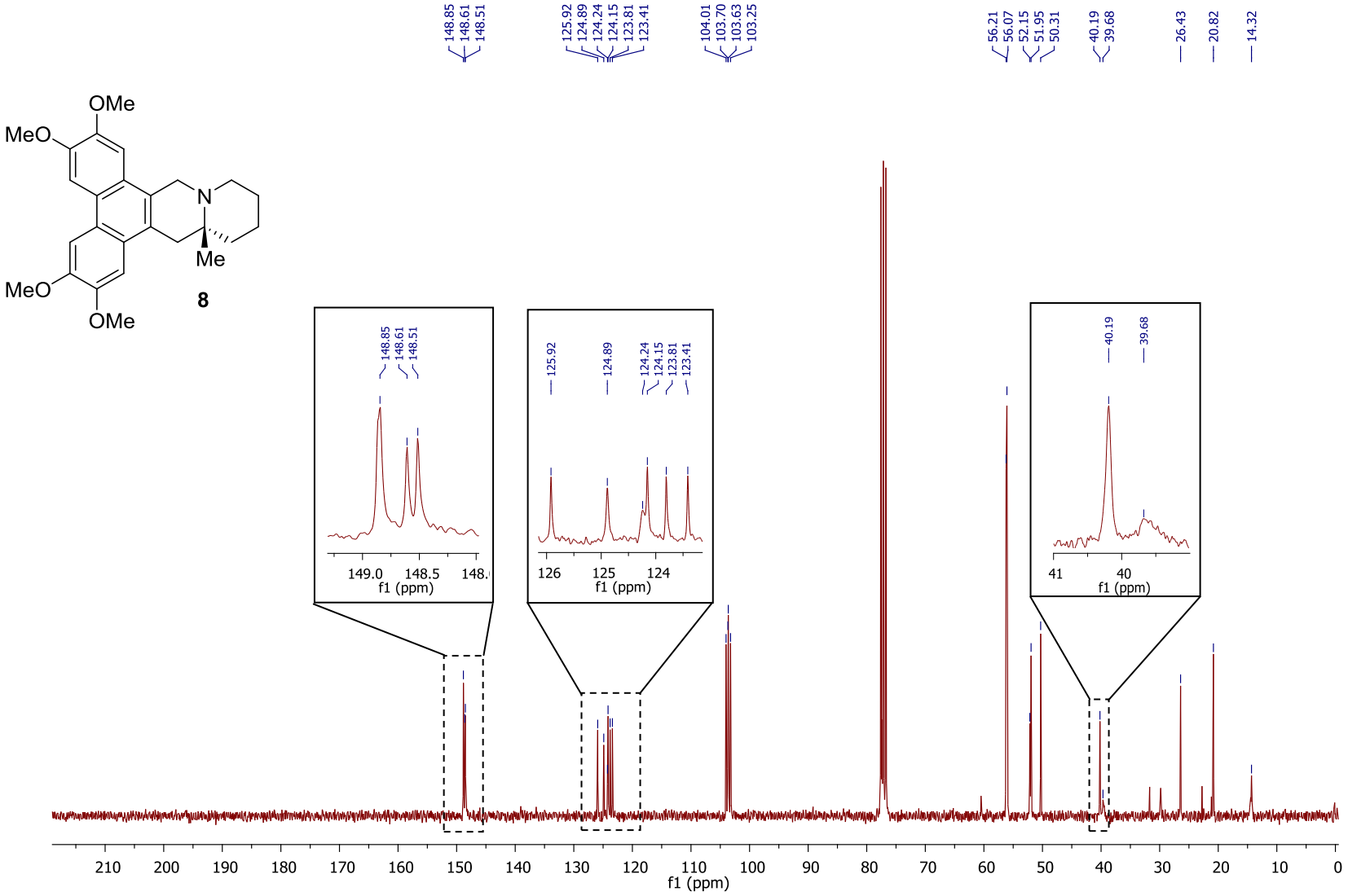
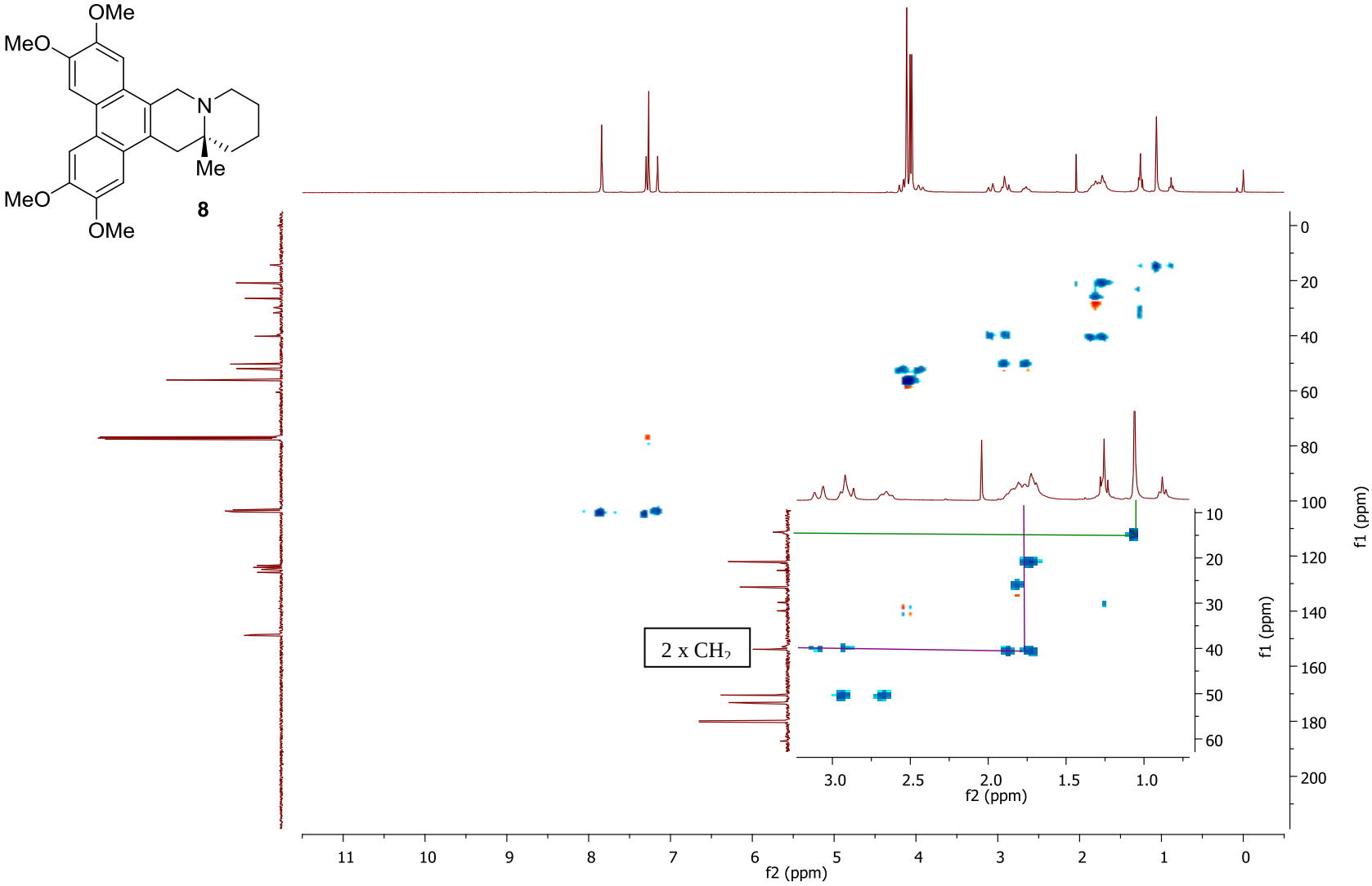
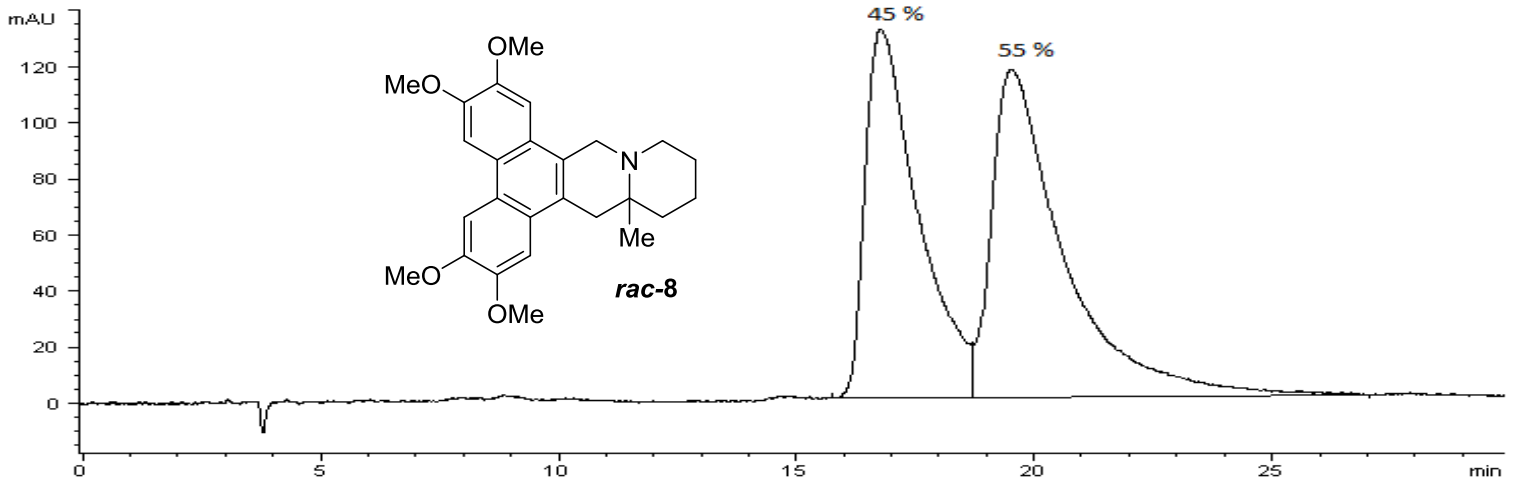


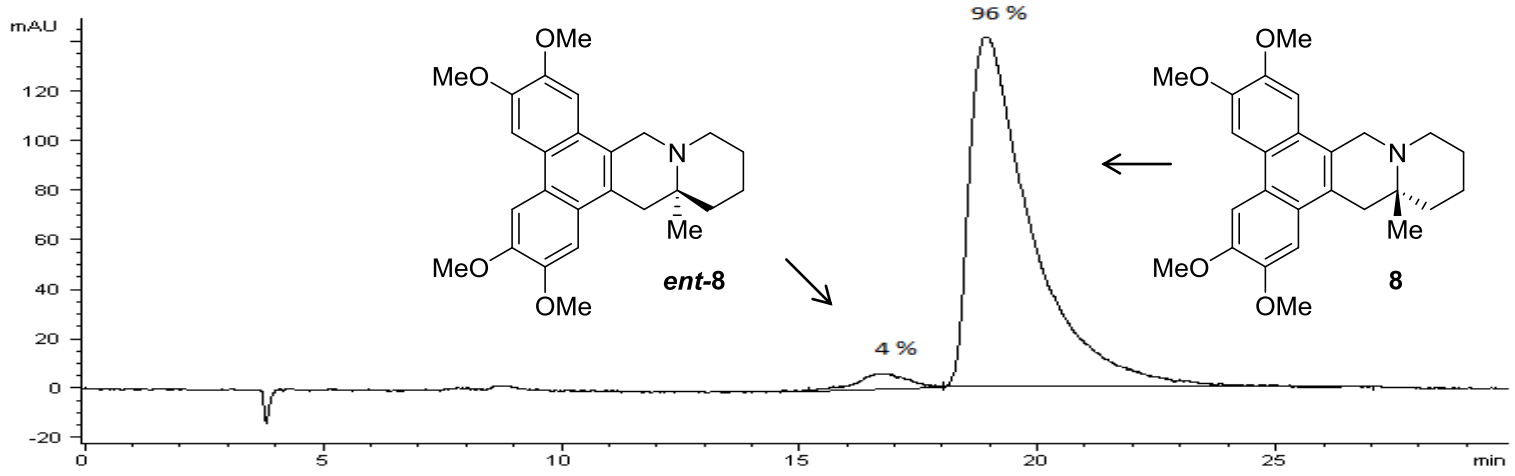
COSY (300 MHz, $CDCl_3$)



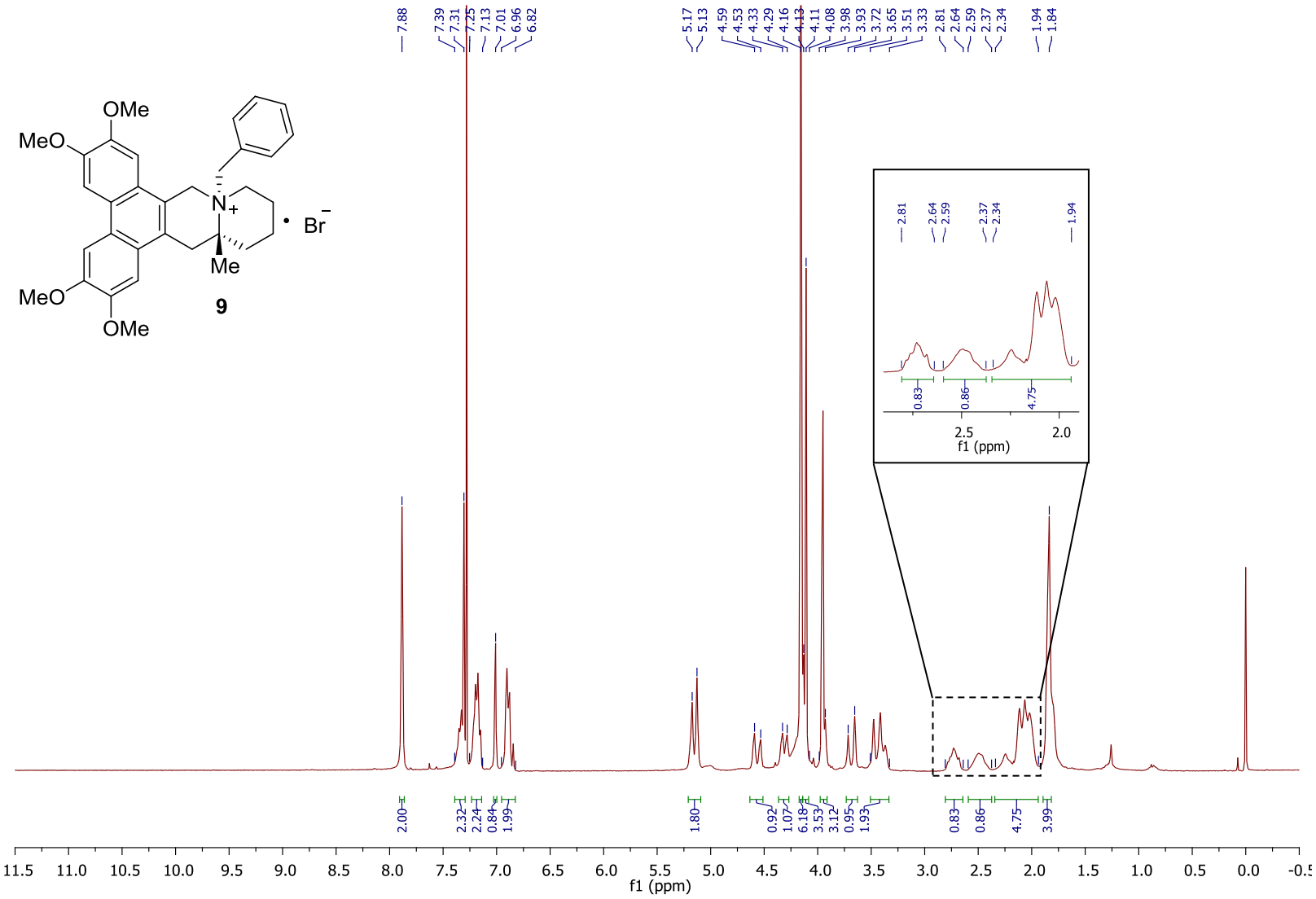
HPLC traces of compounds ***rac*-8** and***ent*-8/ 8**

CHIRALPAK IB column 4.6 mm x 250 mL; isocratic elution with 75:25:0.3, *n*-hexane/*i*-PrOH/TEA, 1.0 mL·min^{-1}; UV detection at 254 nm.

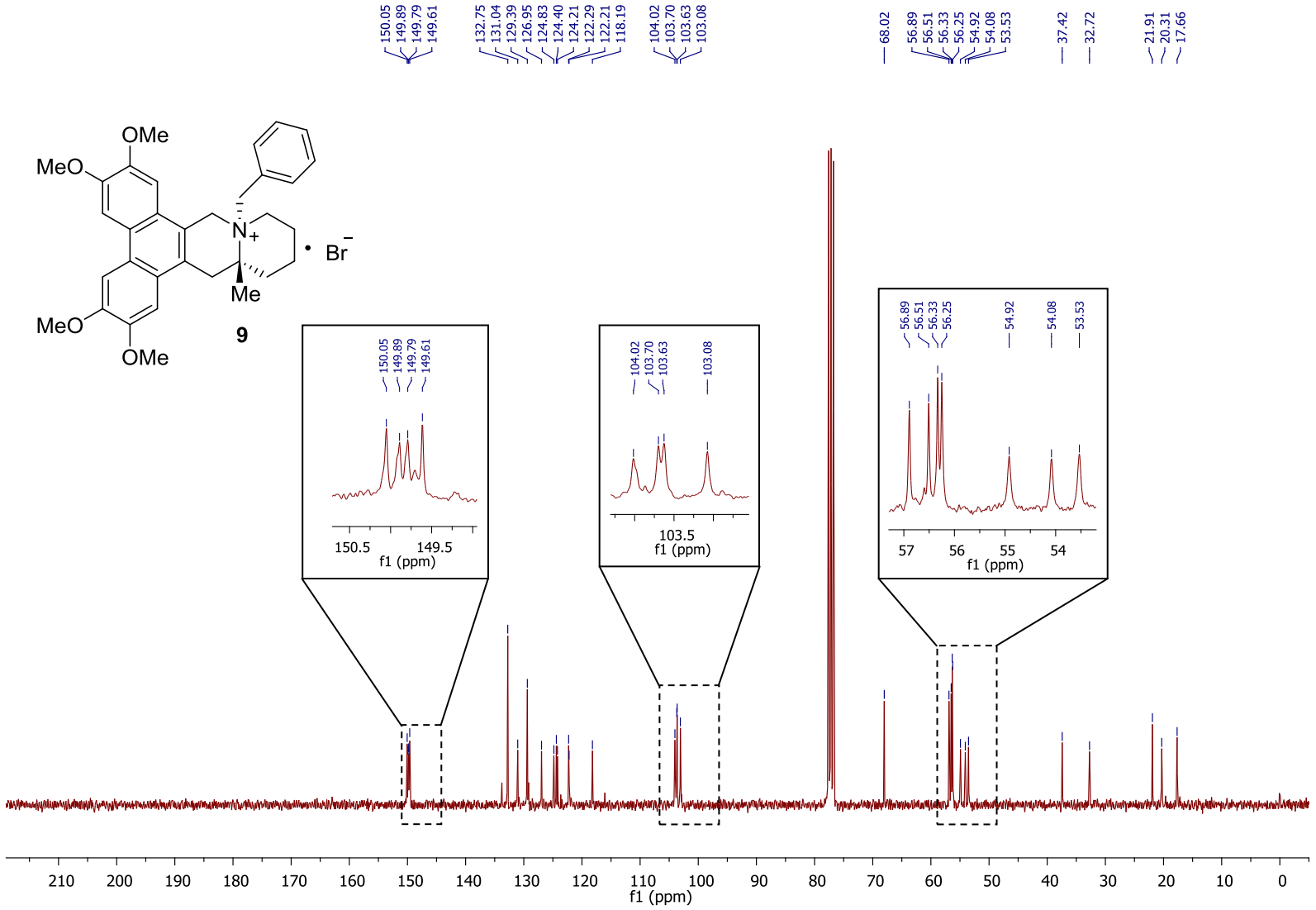


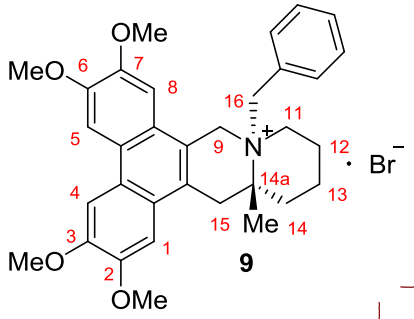


^{1}H NMR (300 MHz, $CDCl_3$)

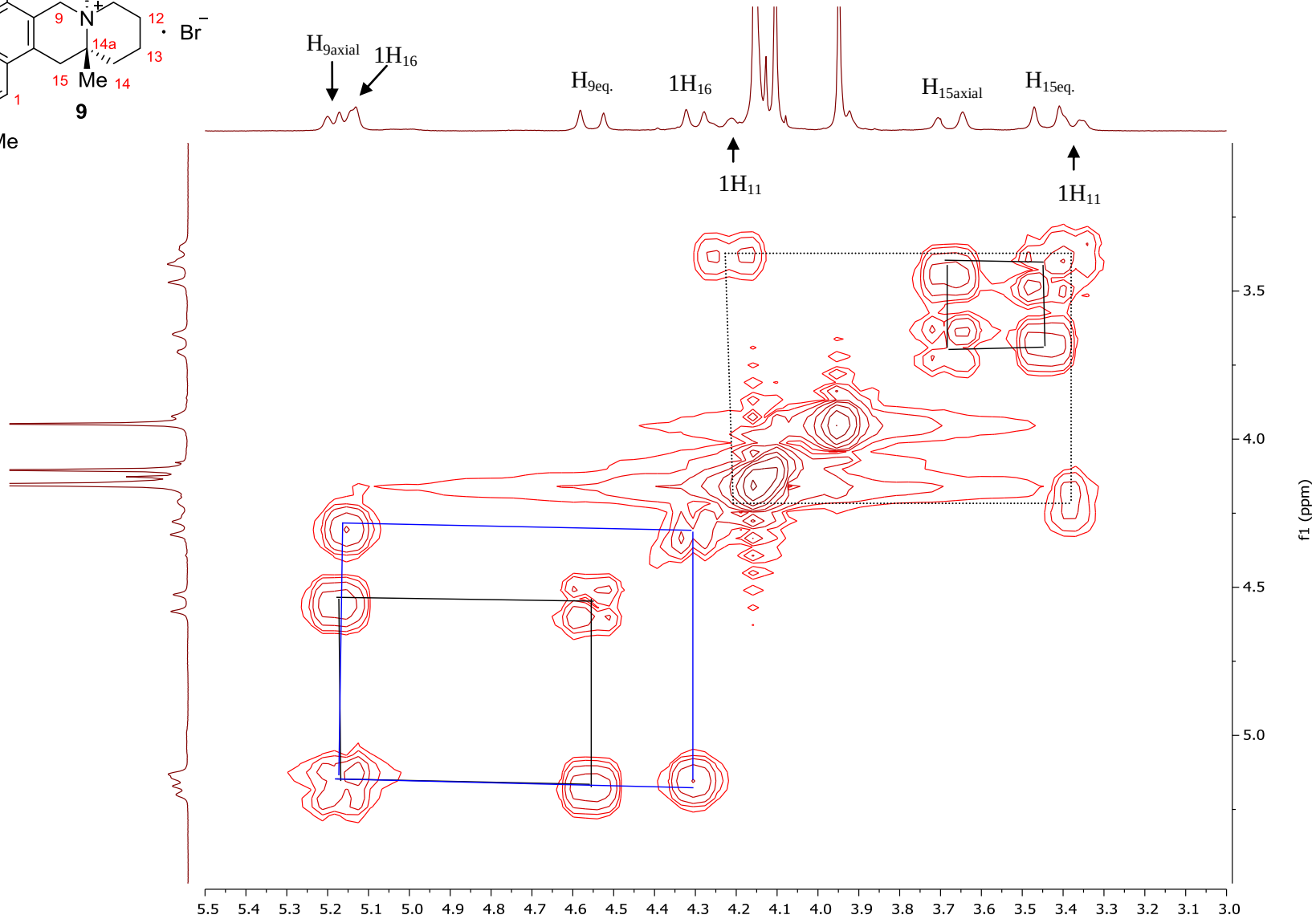


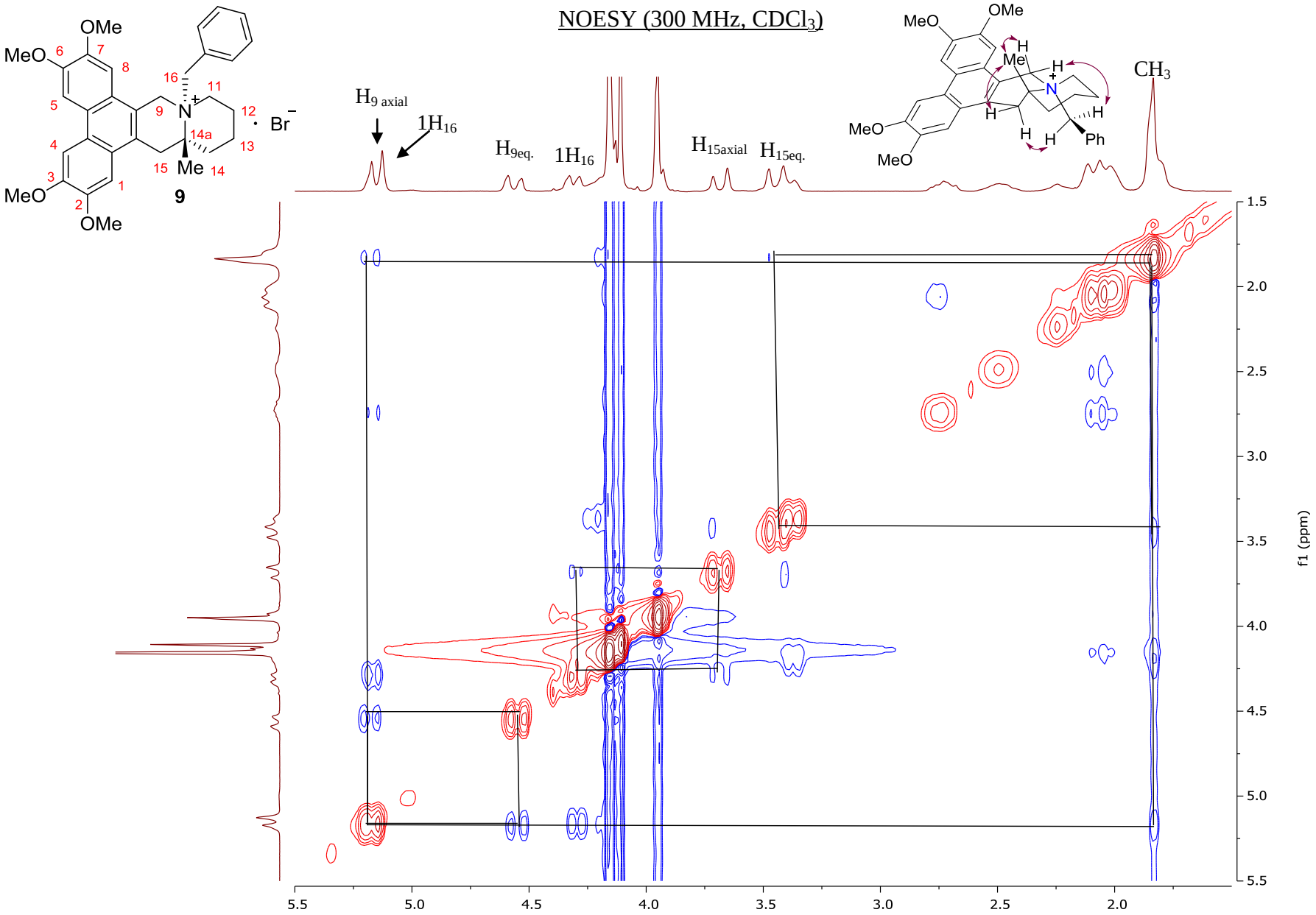
^{13}C NMR (75 MHz, $CDCl_3$)



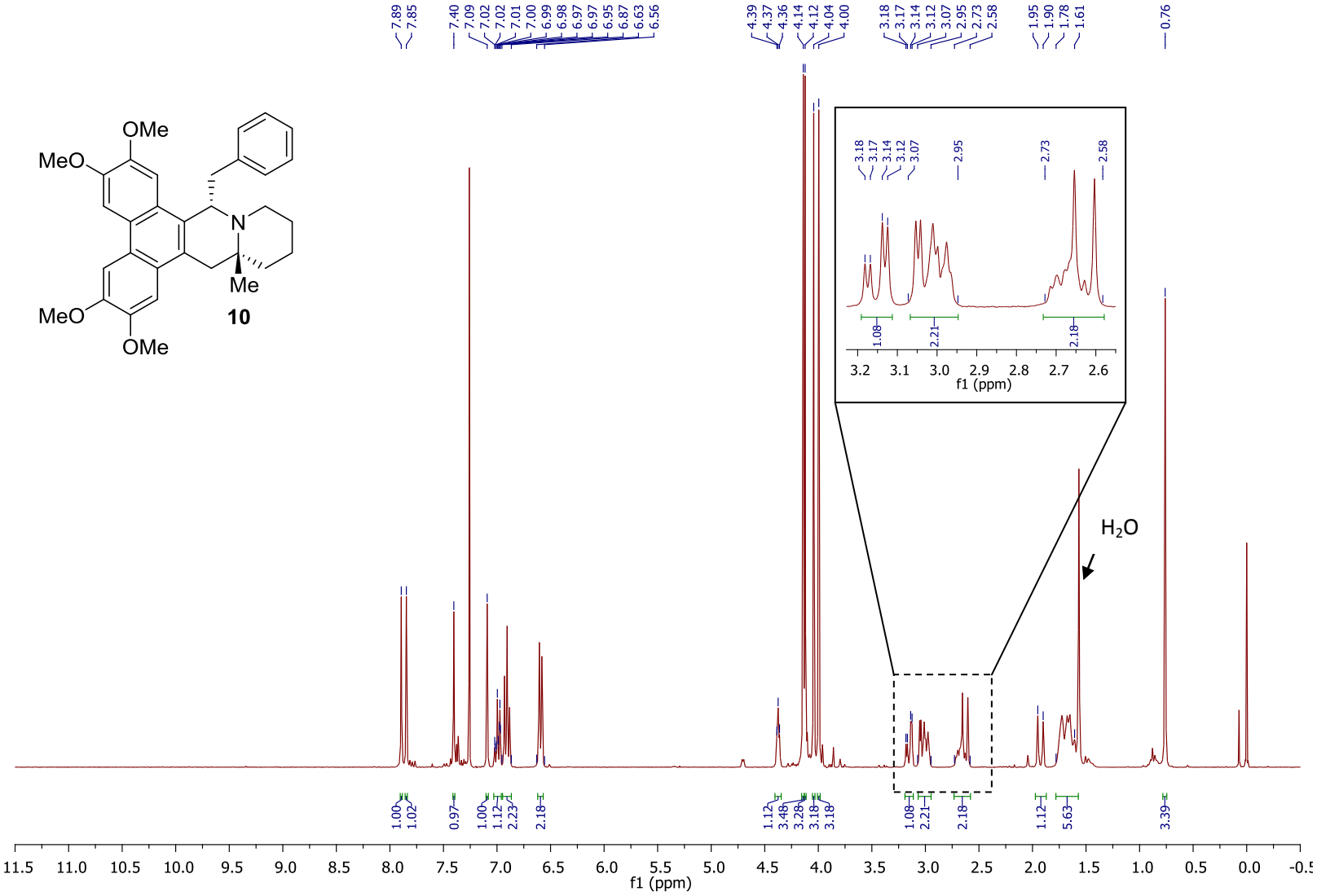


COSY (300 MHz, $CDCl_3$)

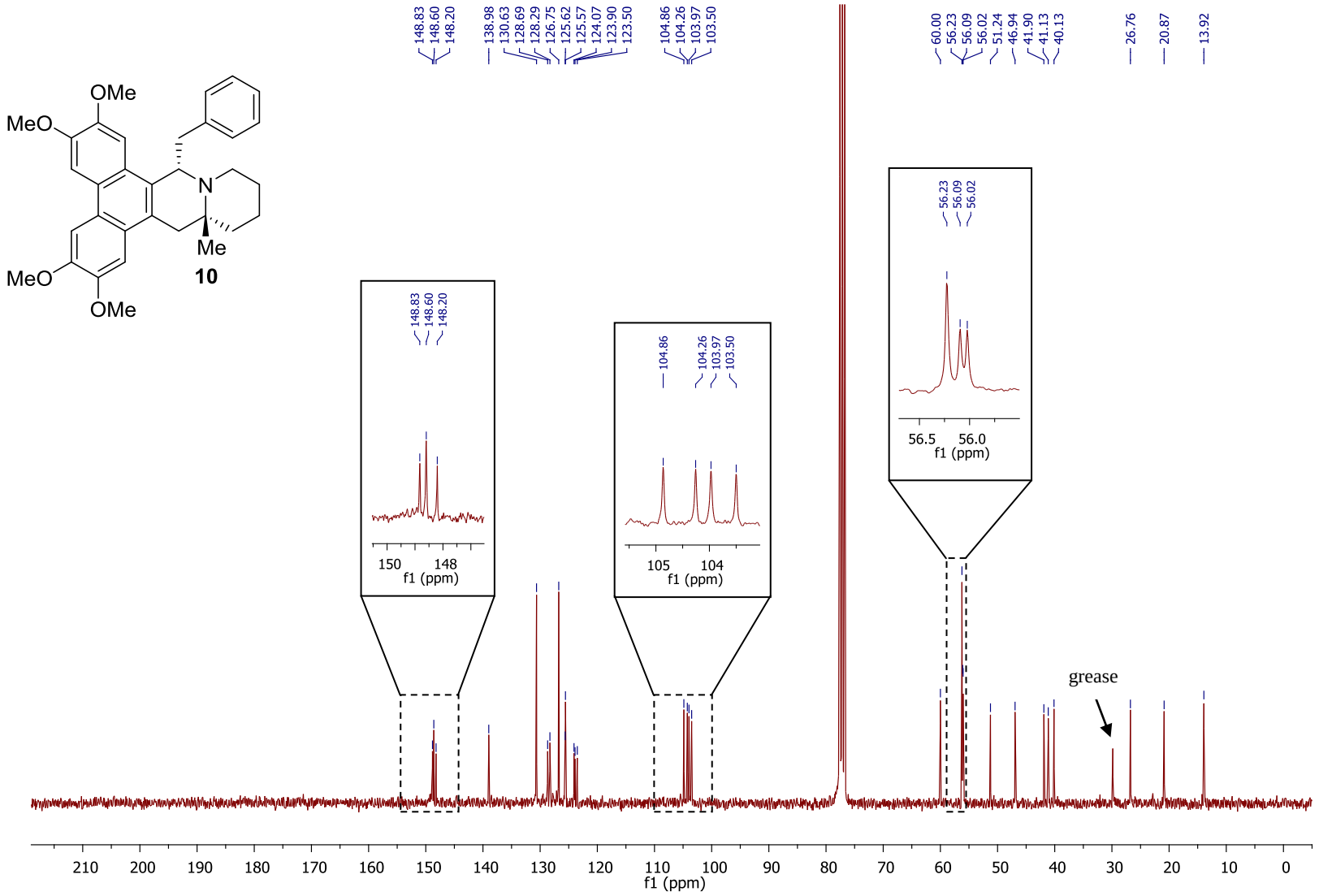



NOESY (300 MHz, CDCl3)
OMe
MeO
MeO
OMe
Br⁻
9
H9 axial
1H16
H9eq.
1H16
H15axial
H15eq.
CH3
MeO
OMe
MeO
Me
Ph
f1 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

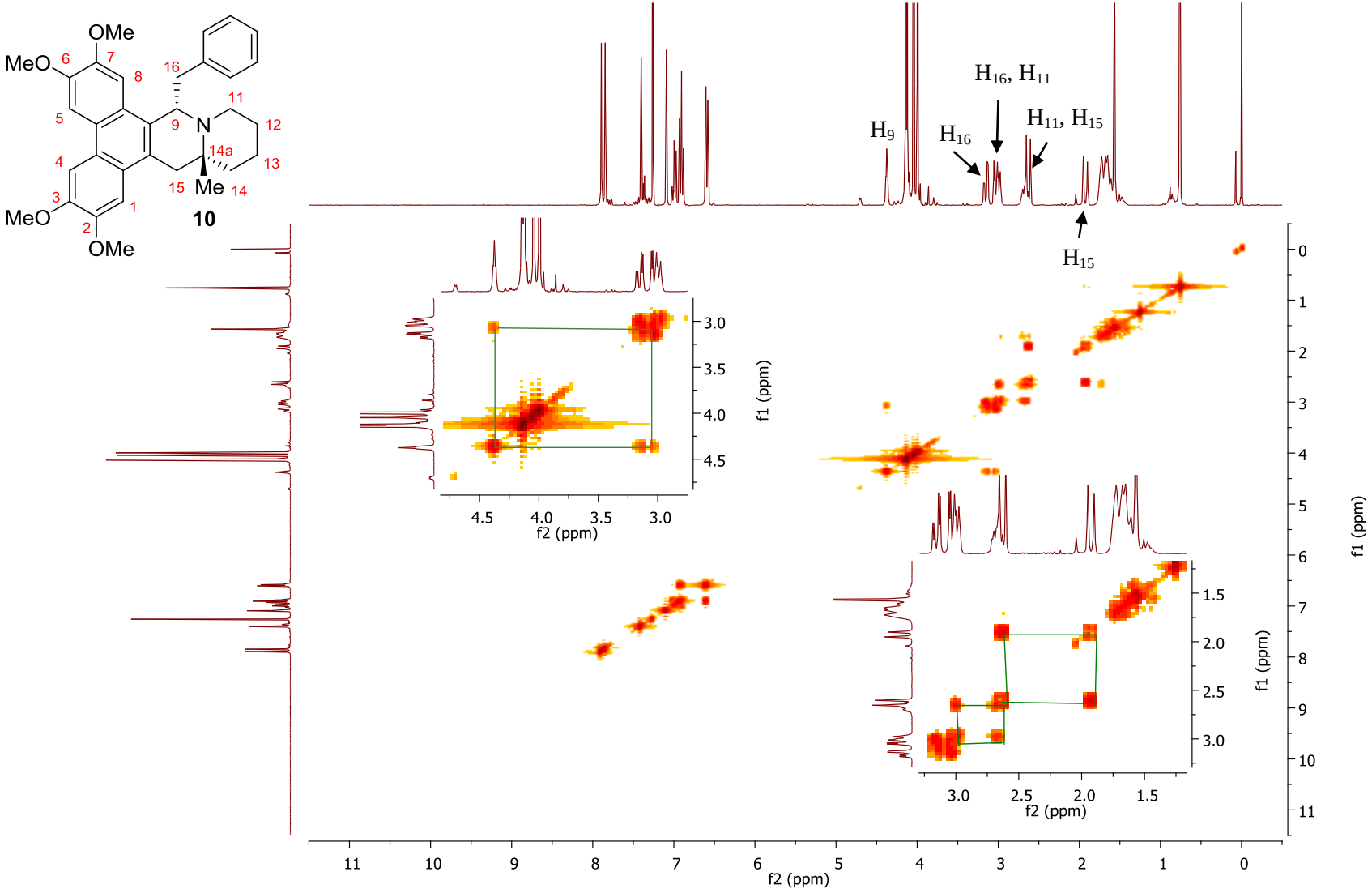
^{1}H NMR (300 MHz, $CDCl_3$)



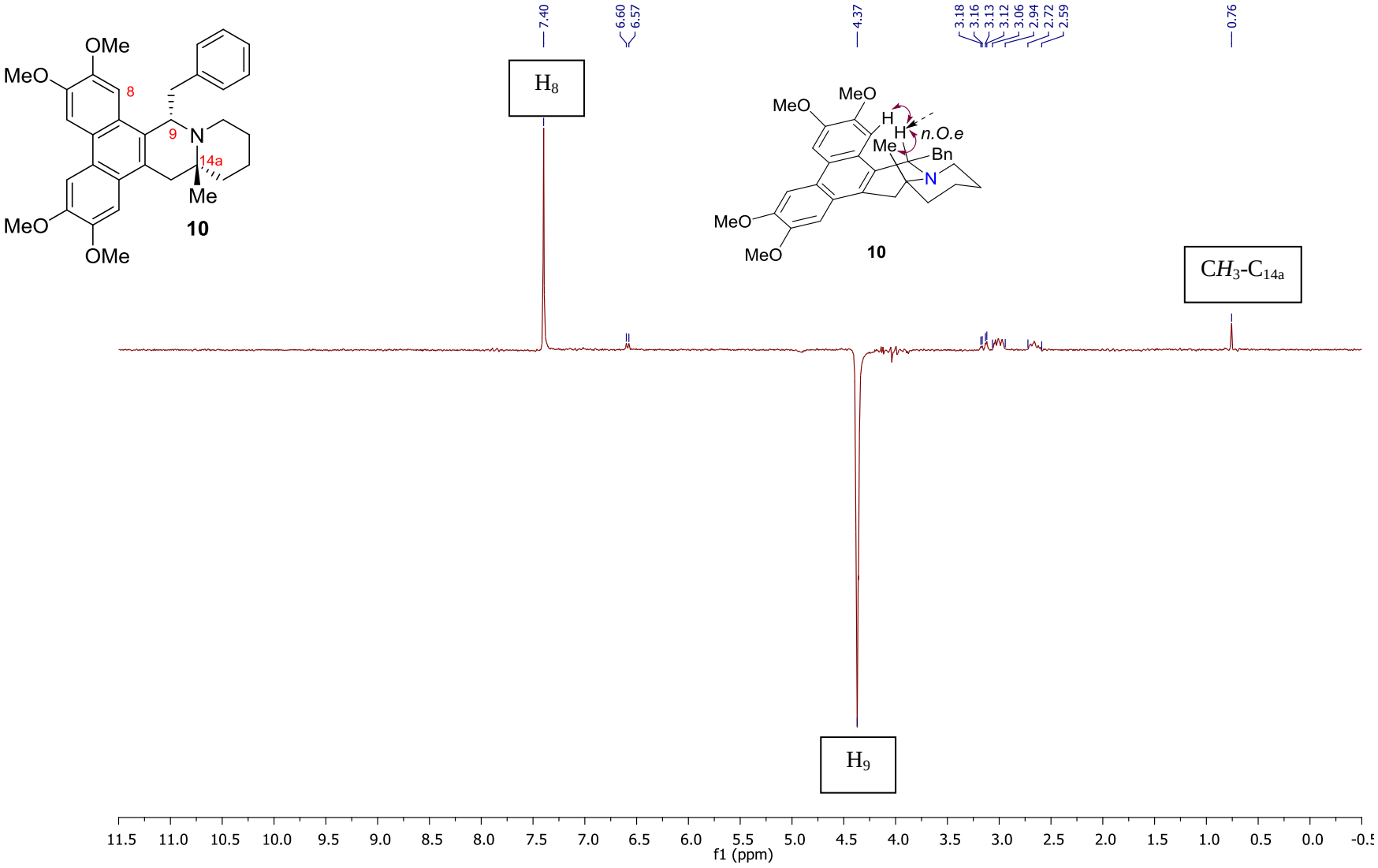
^{13}C NMR (75 MHz, $CDCl_3$)



COSY (300 MHz, $CDCl_3$)

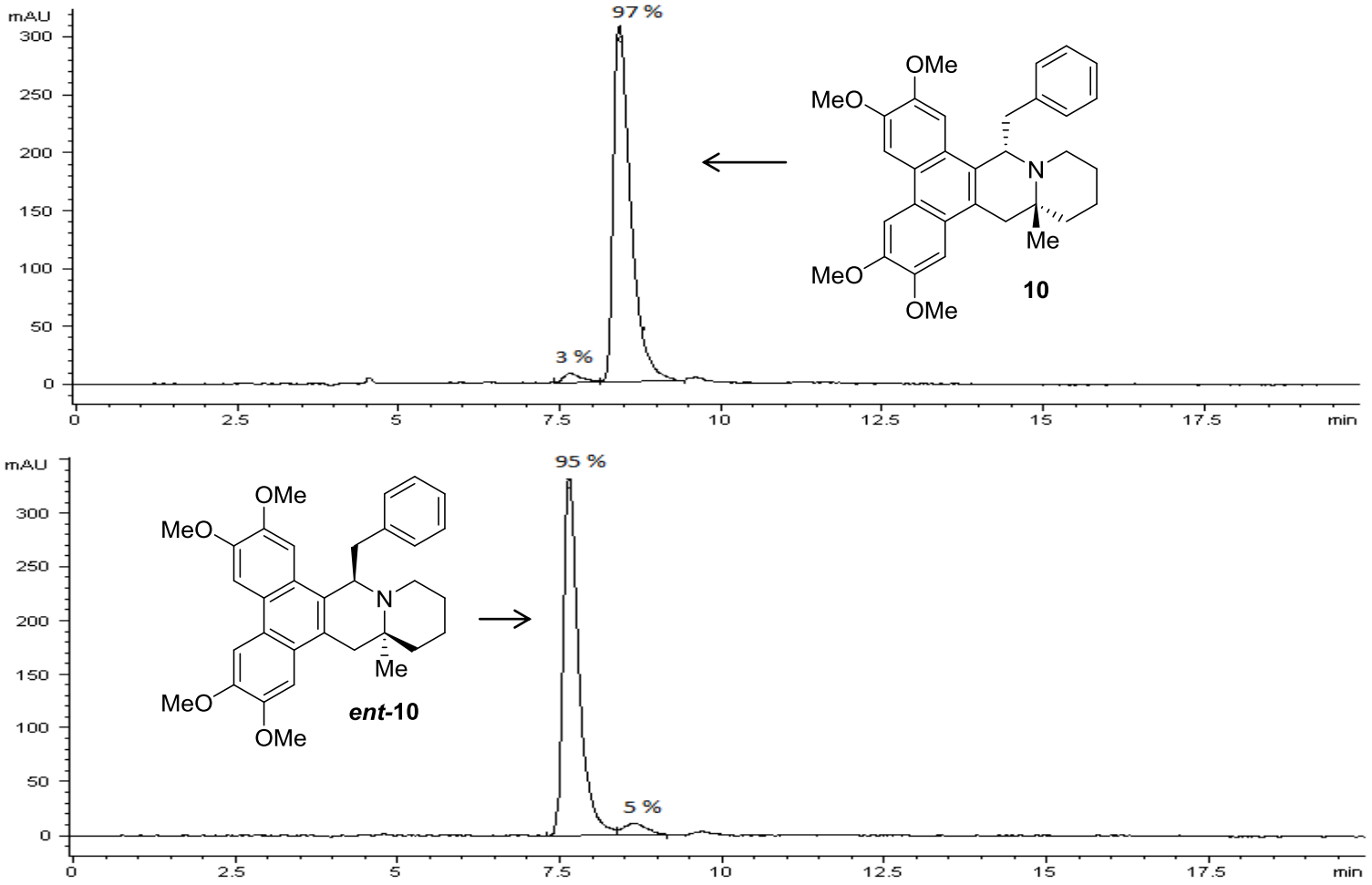


DPFGSE-NOE when H_9 is irradiated (300 MHz, $CDCl_3$)



HPLC traces of compounds**10/ *ent*-10**

CHIRALPAK IB column 4.6 mm x 250 mL; isocratic elution with 75:25:0.3, *n*-hexane/*i*-PrOH/TEA1.0 mL·min^{-1}; UV detection at 254 nm.



Cytotoxic Studies

All the cell lines employed were purchased to the American Tissue Culture Collection (ATCC) and grown following the instructions and media from the provider.

Cells were seeded in 96-well culture microplates and kept at 37^{o}C in a 5% CO_2 atmosphere for 24 h. Solutions of test compounds in MeOHwere then added to each microplate, keeping 1% of MeOH, and incubated for different times depending on the cell line studied. After the incubation time cell viability was measured by using the tetrazolium dye assay (MTT method). Experiments were repeated three times.

Data was expressed as a percentage of inhibition in basis of the cell viability observed in vehicle-treated well following the formula:
%inhibition=100-((AO*100)/AT); where AO is the absorbance observed in the test well and AT is the absorbance observed in the vehicle-treated wells (with 1% of MeOH to consider the effect of the solvent).Concentration-% inhibitionwerefitted by using GraphPad Prism (v2.1) following the equation:

$$y = \frac{E_{max}}{1 + \left(\frac{IC_{50}}{x}\right)^{n}}$$

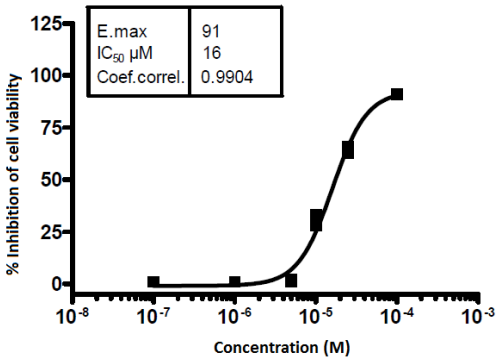
where Emax is the inhibition observed at the maximum concentration examined for each compound (100 μM), IC_{50} is the concentration that inhibits cell viability in a 50% and n is the Hill slope.
The seeding numbers and incubation times for each cell lines, as well as the concentration-response curves obtained for the compounds examined (including CDDP as a control experiment) were the following:

MCF-7

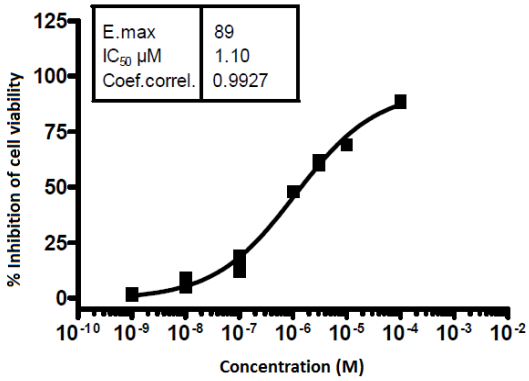
Seeding number: 10000

Incubation time with test compound:96 h

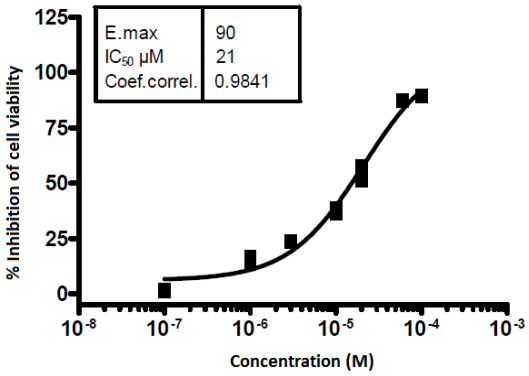
CDDP



8·HCl



***ent*-8·HCl**



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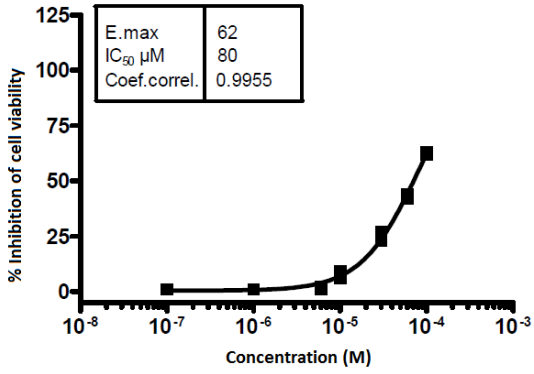
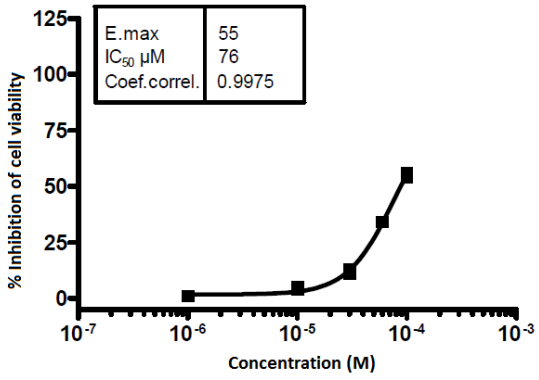


***ent*- 9**



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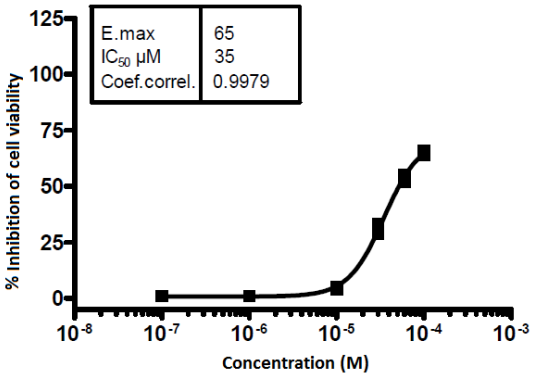
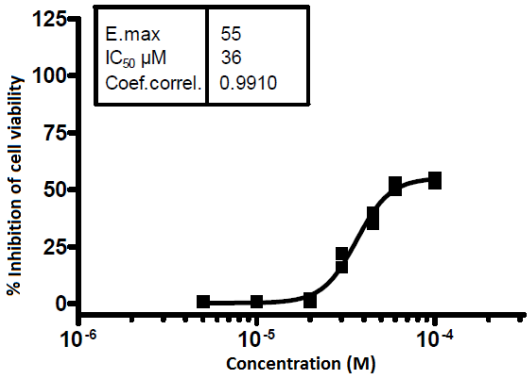


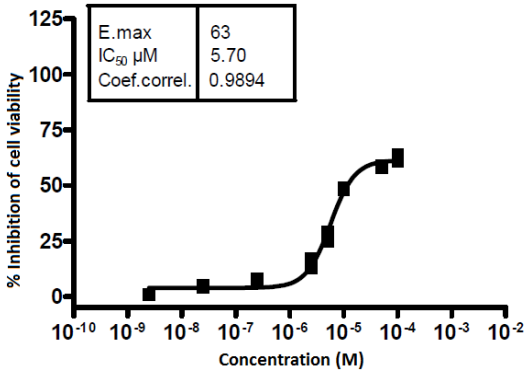
***ent*-10**



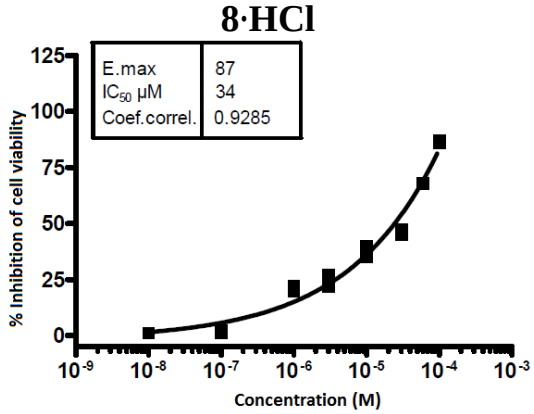
NCI-H460

Seeding number: 15000
Incubation time with test compound:48 h

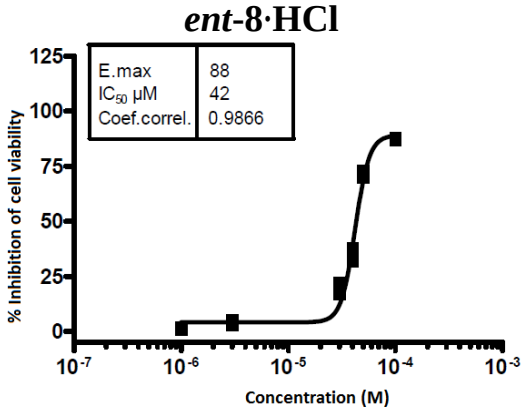
CDDP



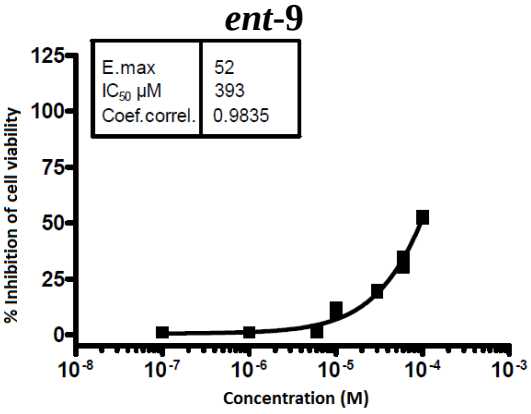
8·HCl



***ent*-8·HCl**



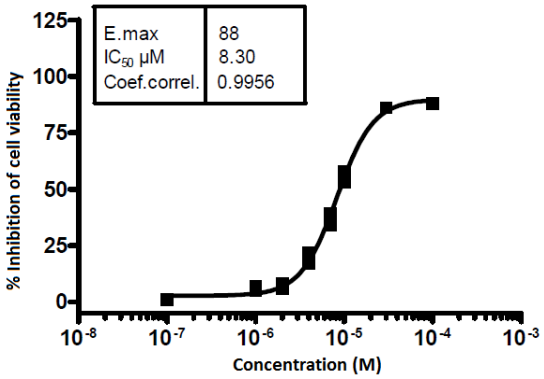
***ent*-9**



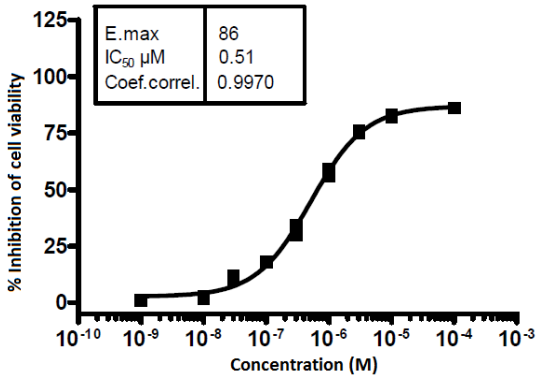
HL-60

Seeding number: 10000
Incubation time with test compound: 24 h

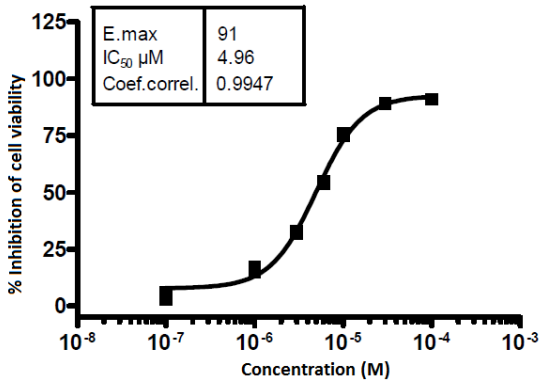
CDDP



8·HCl



***ent*-8·HCl**



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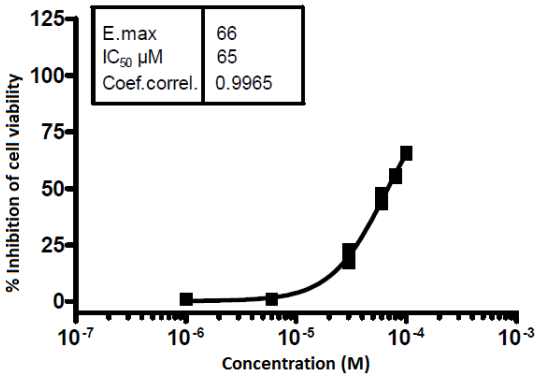

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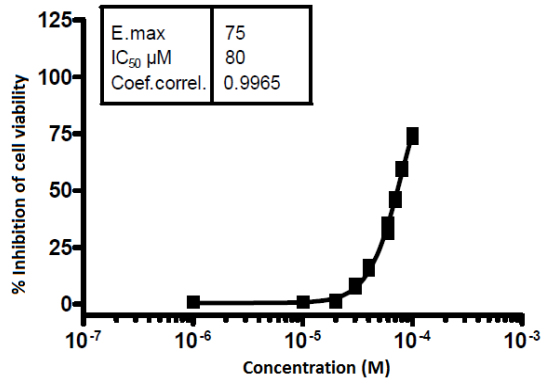
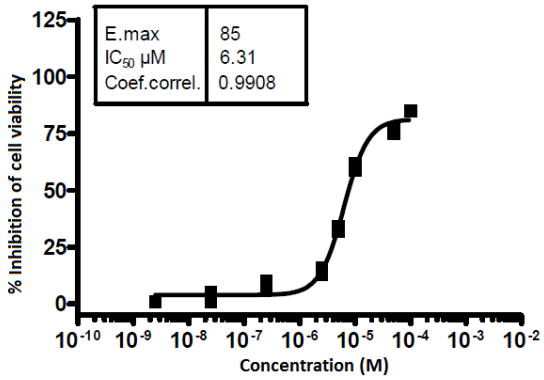


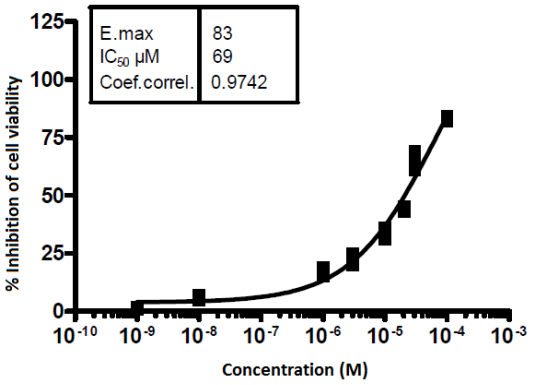
NCI/ADR-RES

Seeding number: 15000
Incubation time with test compound: 48 h

CDDP



8·HCl



***ent*-8·HCl**