

Supplementary Information

Synthesis of meta-substituted phenols and 1-estradiol conjugated analogues of suberoylanilide hydroxamic acid (SAHA)

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Characterization of synthetic compounds

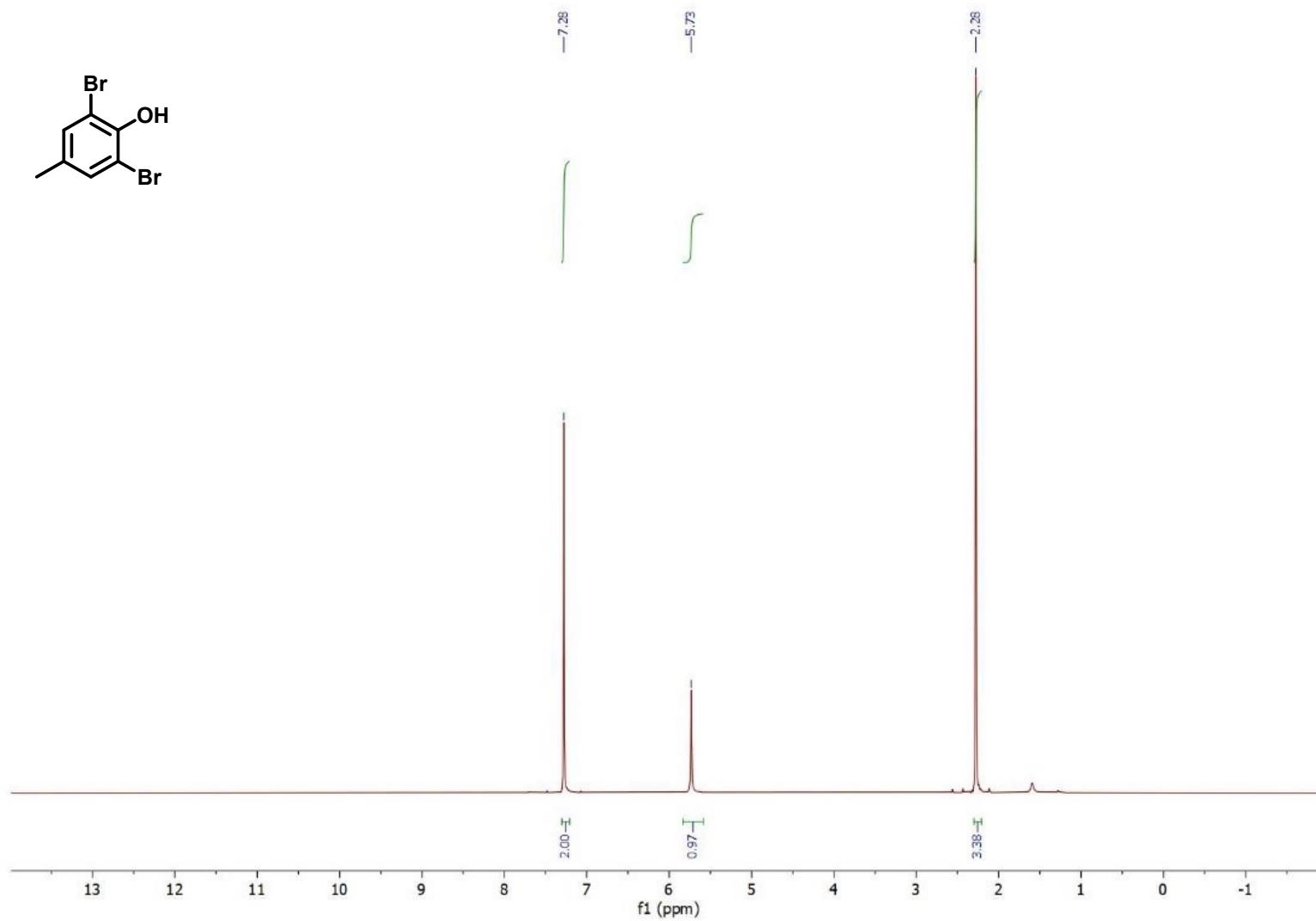


Figure S1. ¹H-NMR spectrum of compound 1

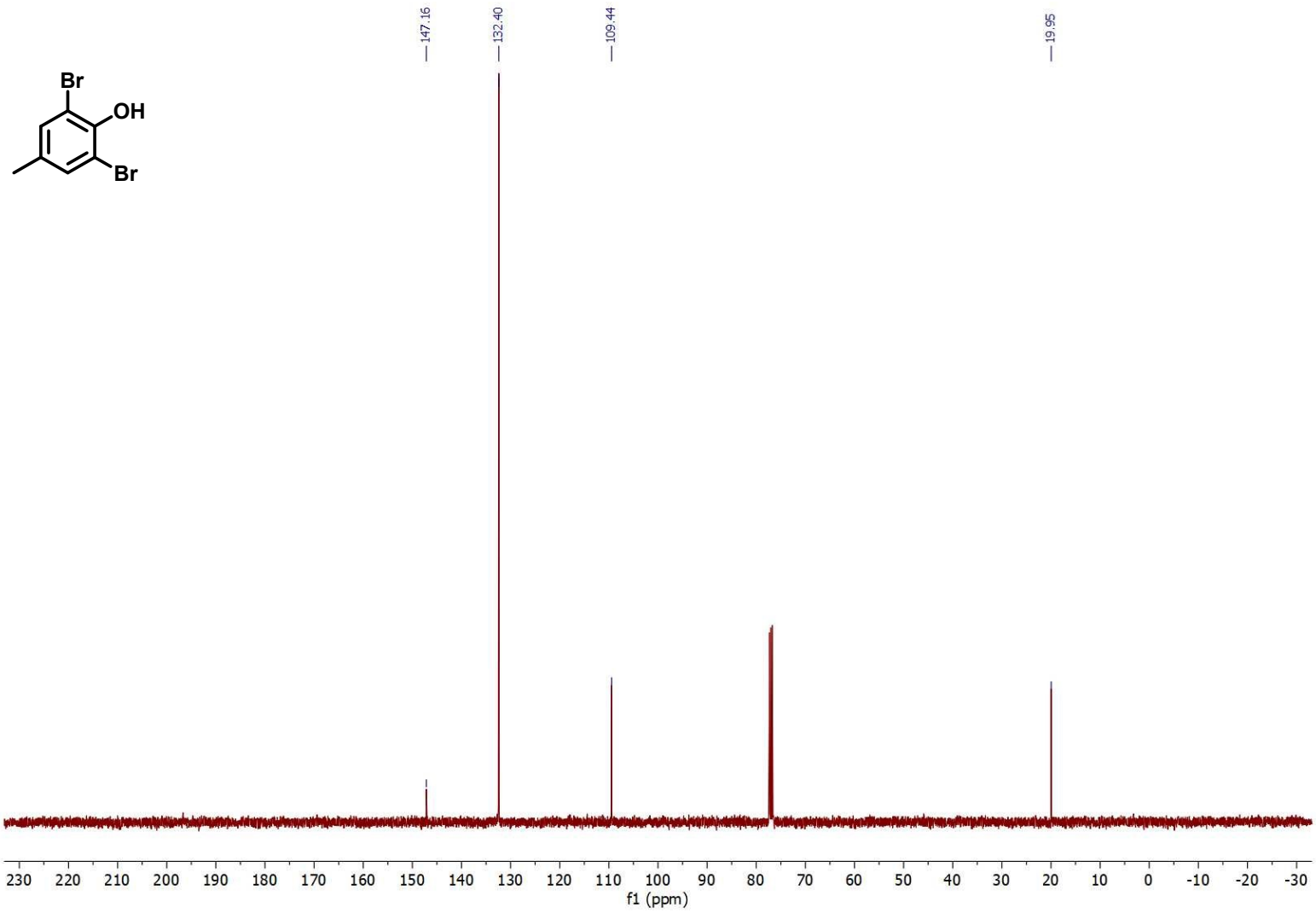


Figure S2. ¹³C-NMR spectrum of **compound 1**

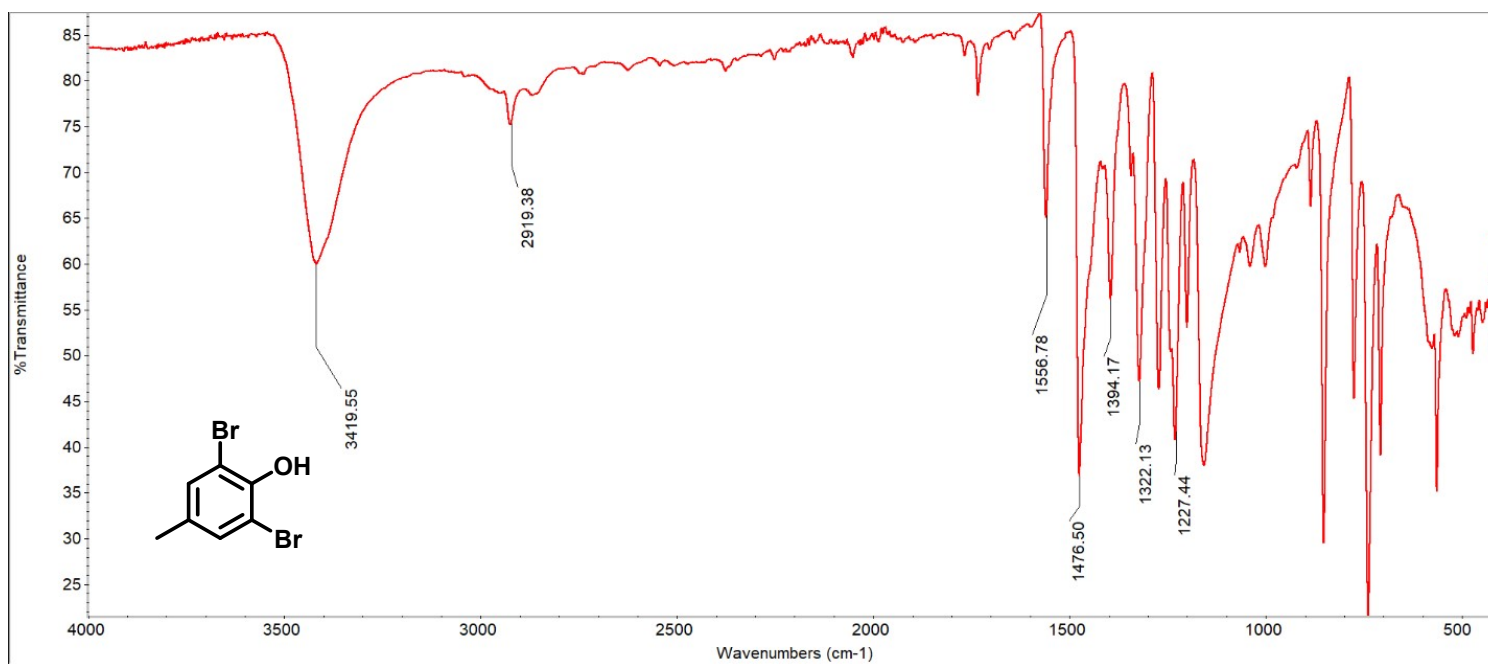


Figure S3. FTIR-spectrum of compound 1

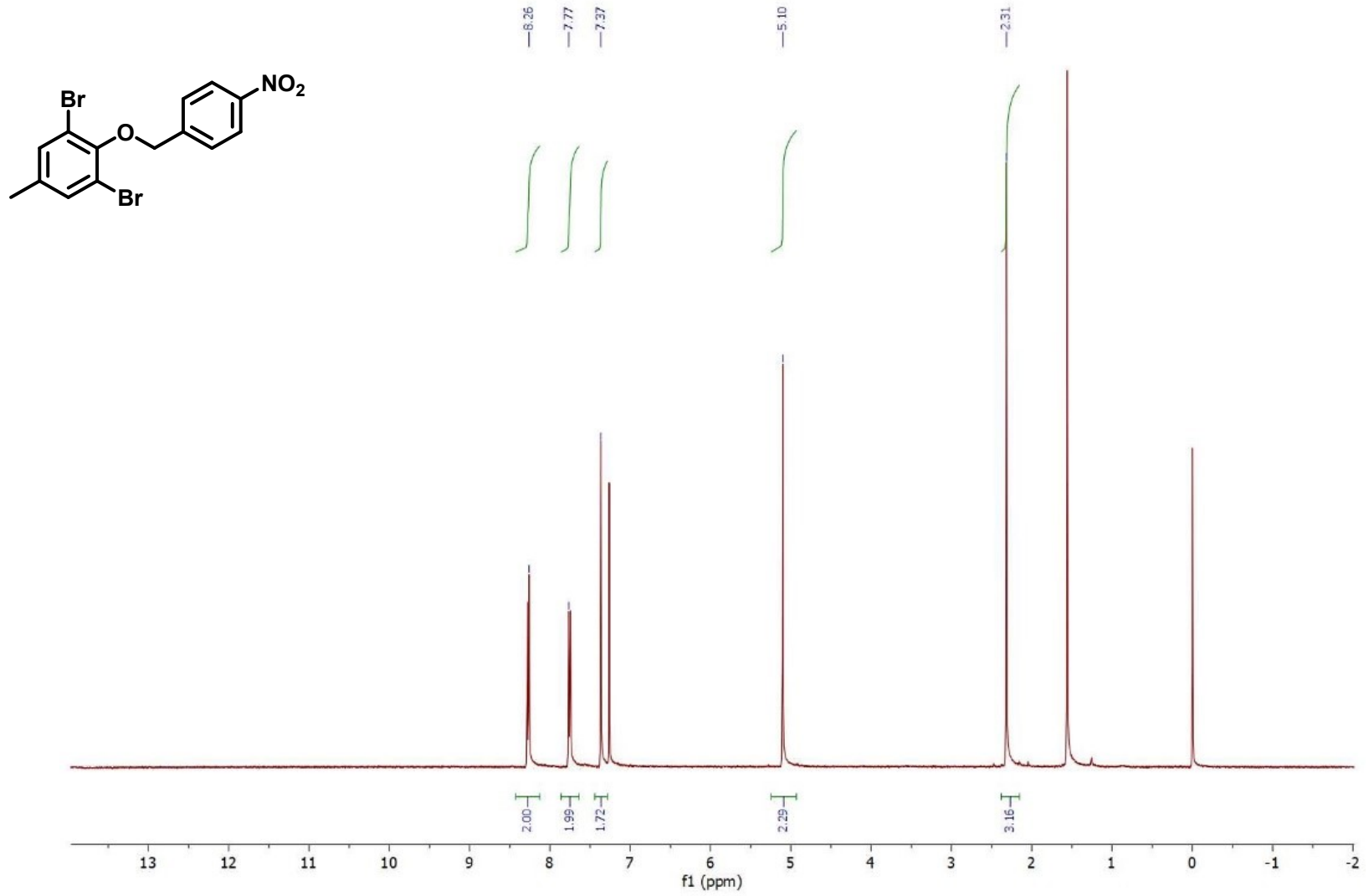


Figure S4. ¹H-NMR spectrum of compound 2

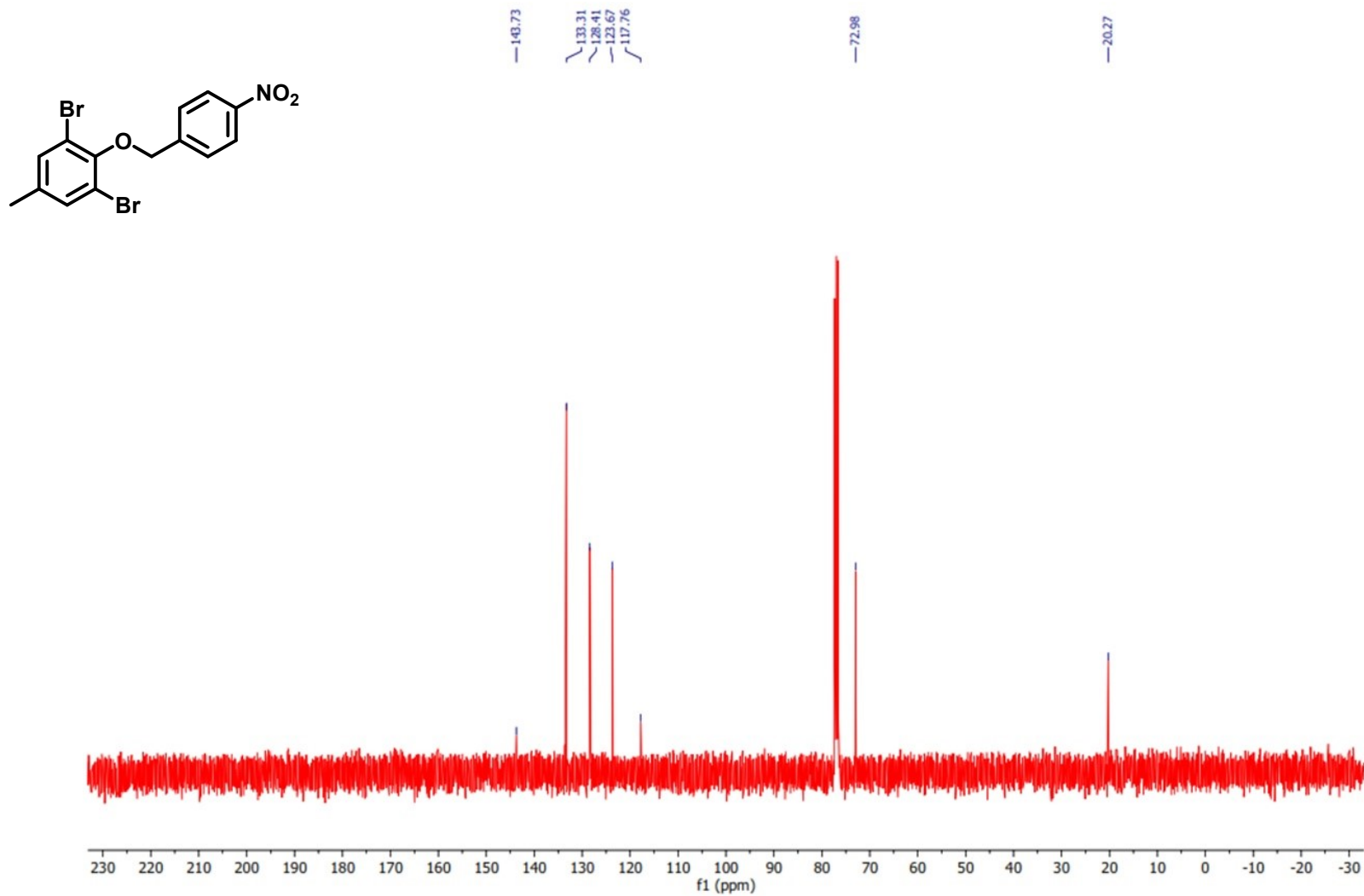


Figure S5. ¹³C-NMR spectrum of **compound 2**

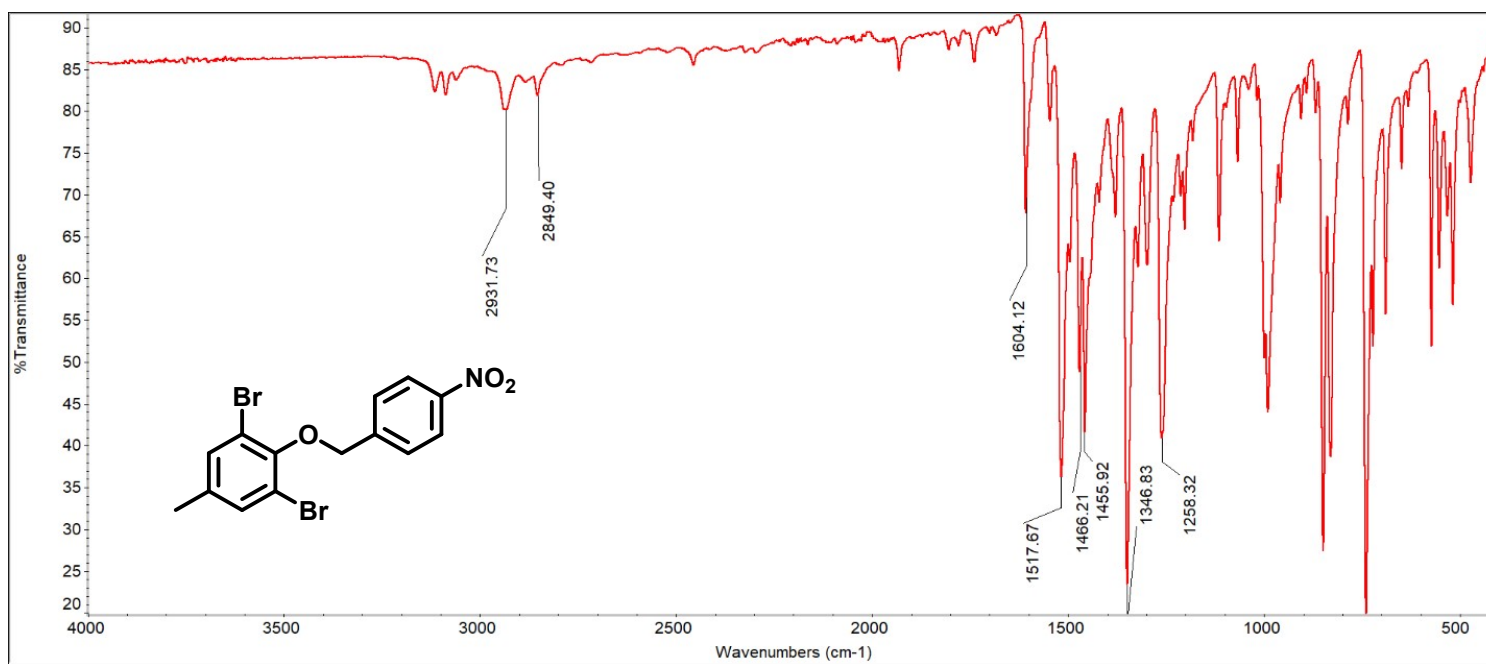


Figure S6. FTIR-spectrum of compound 2

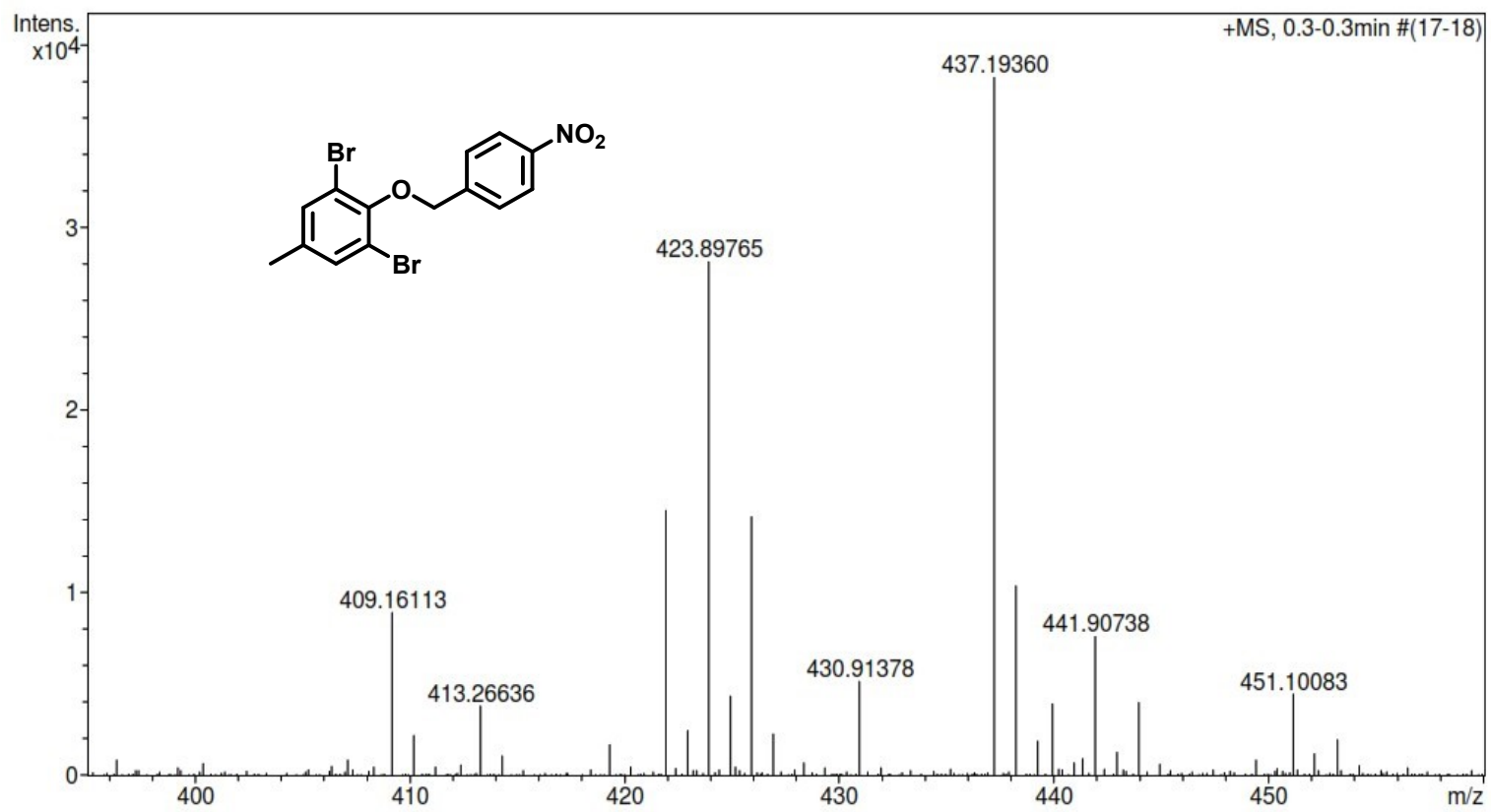


Figure S7 Mass spectrum of compound 2

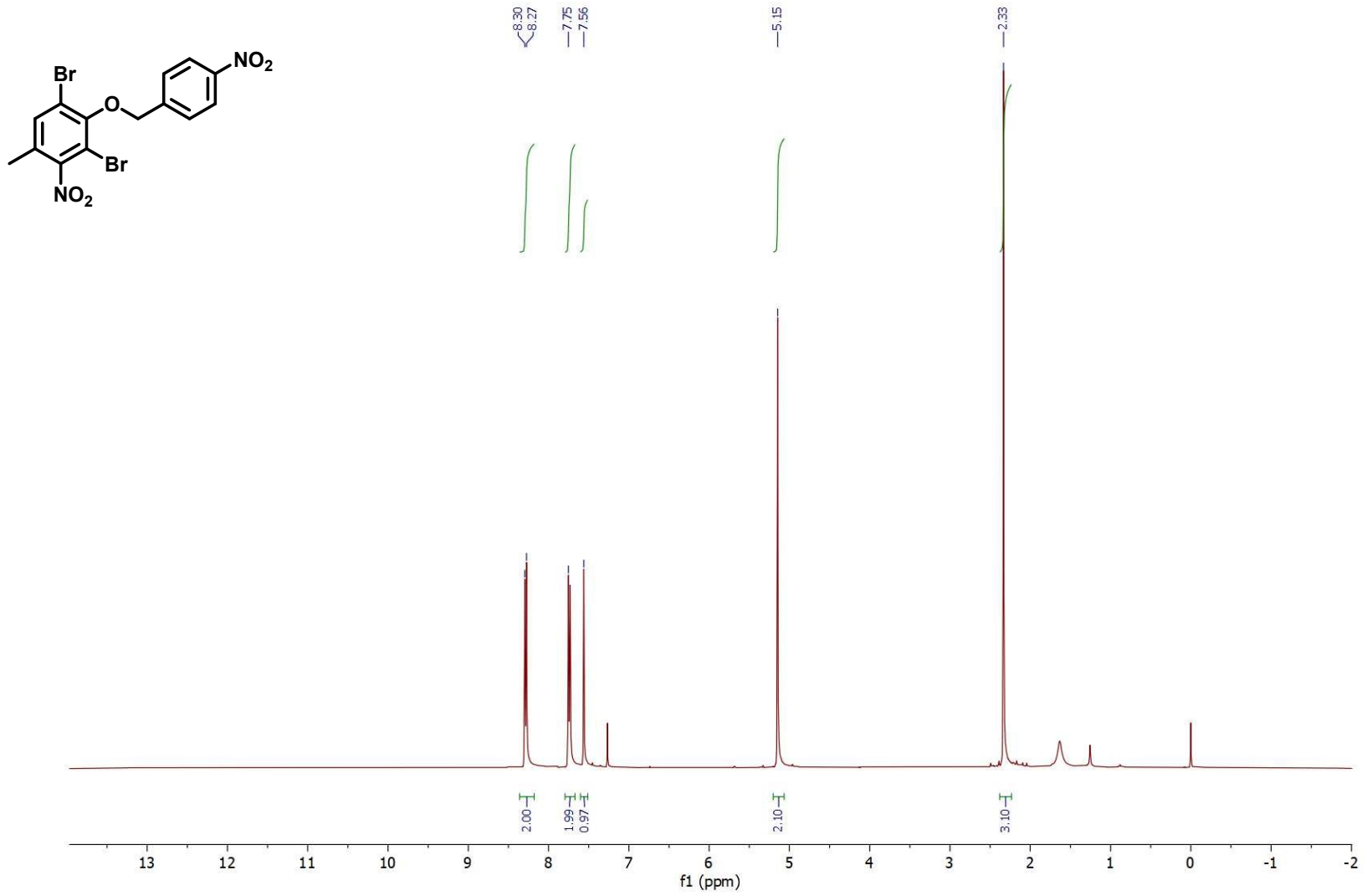


Figure S8 ¹H-NMR spectrum of compound 3

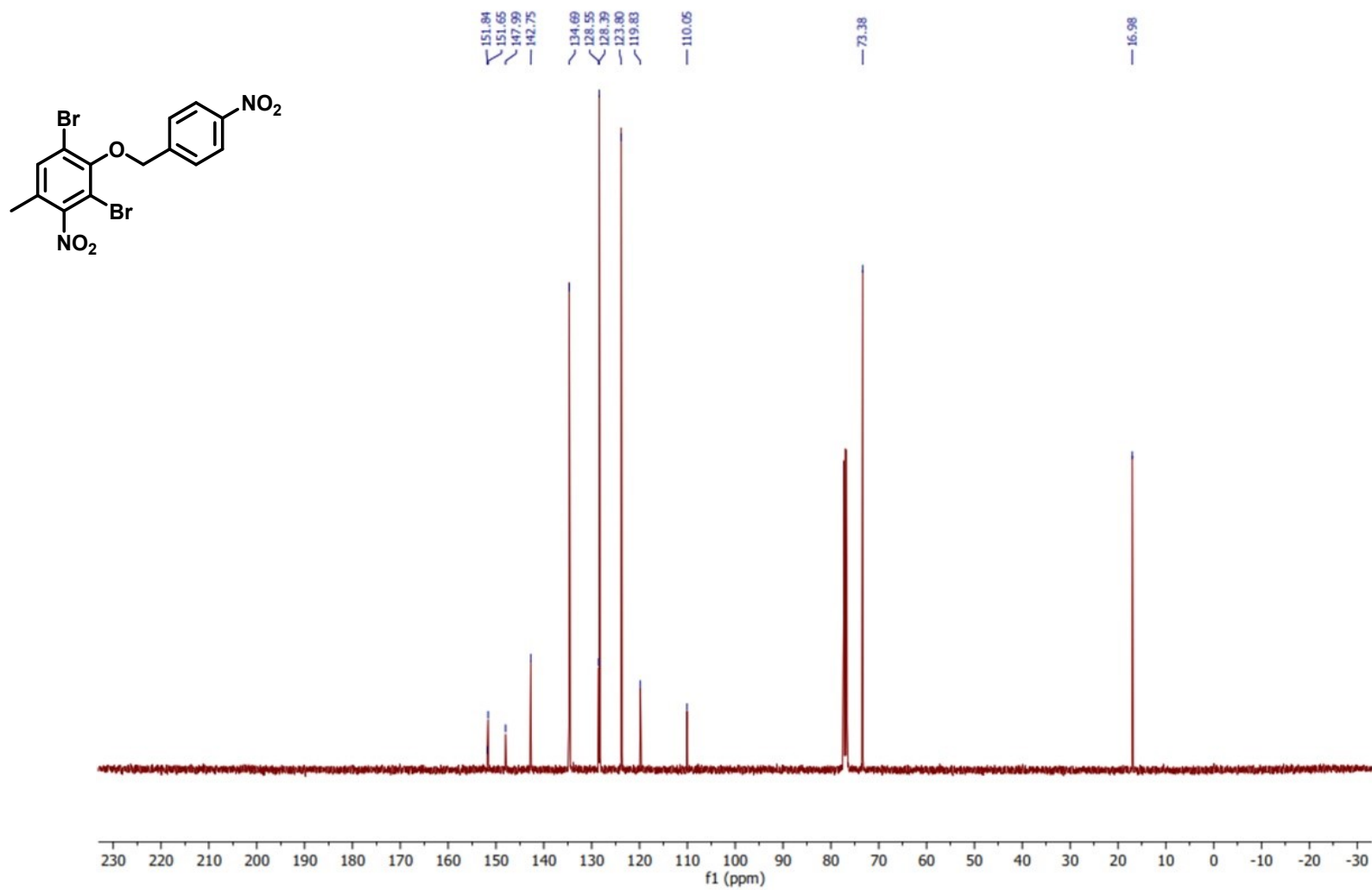


Figure S9 ¹³C-NMR spectrum of compound 3

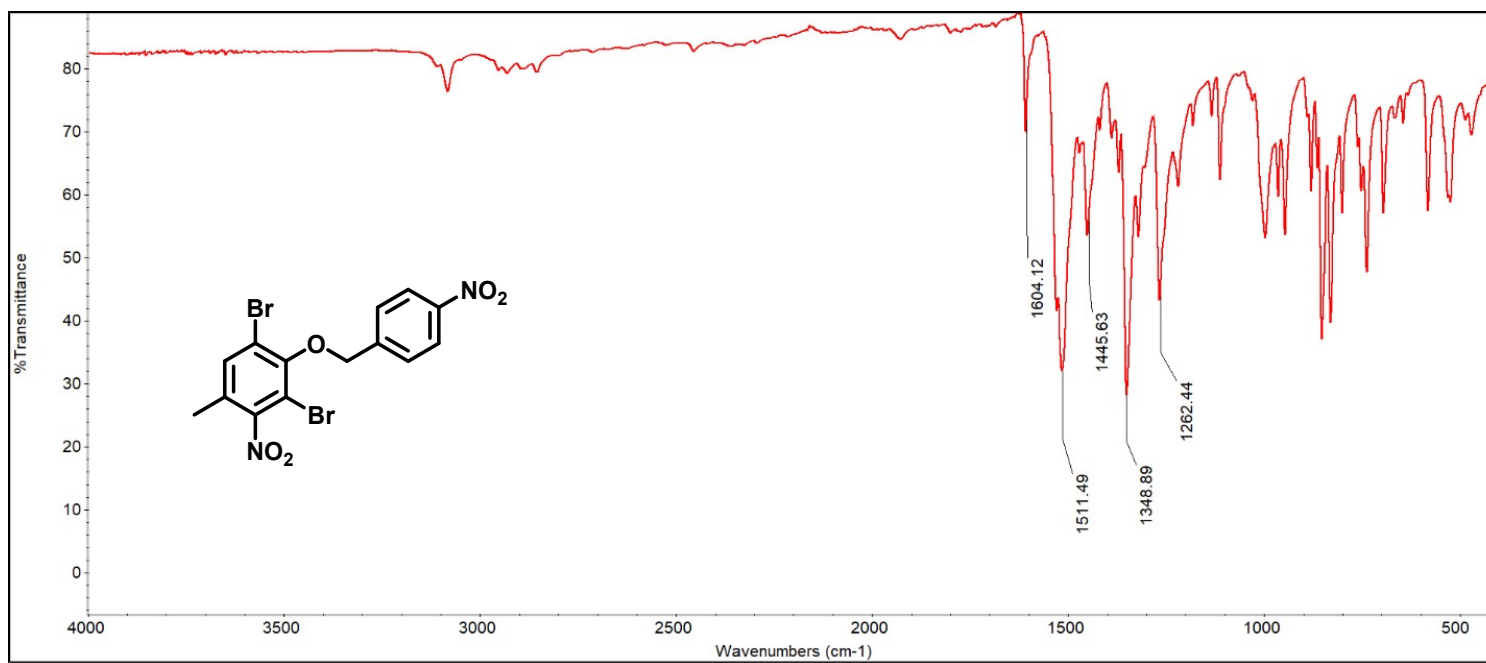


Figure S10 FTIR-spectrum of **compound 3**

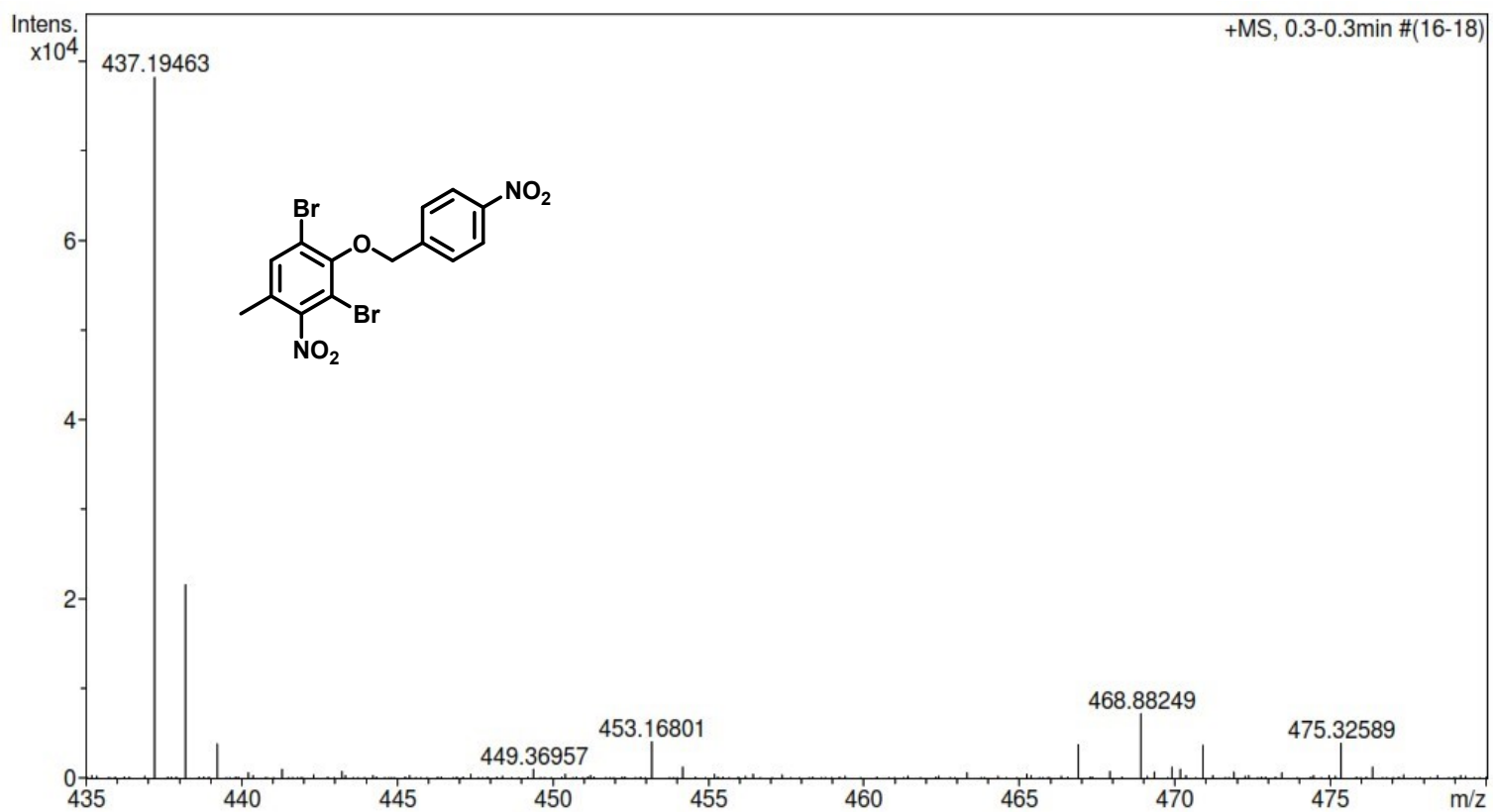


Figure S11 Mass spectrum of **compound 3**

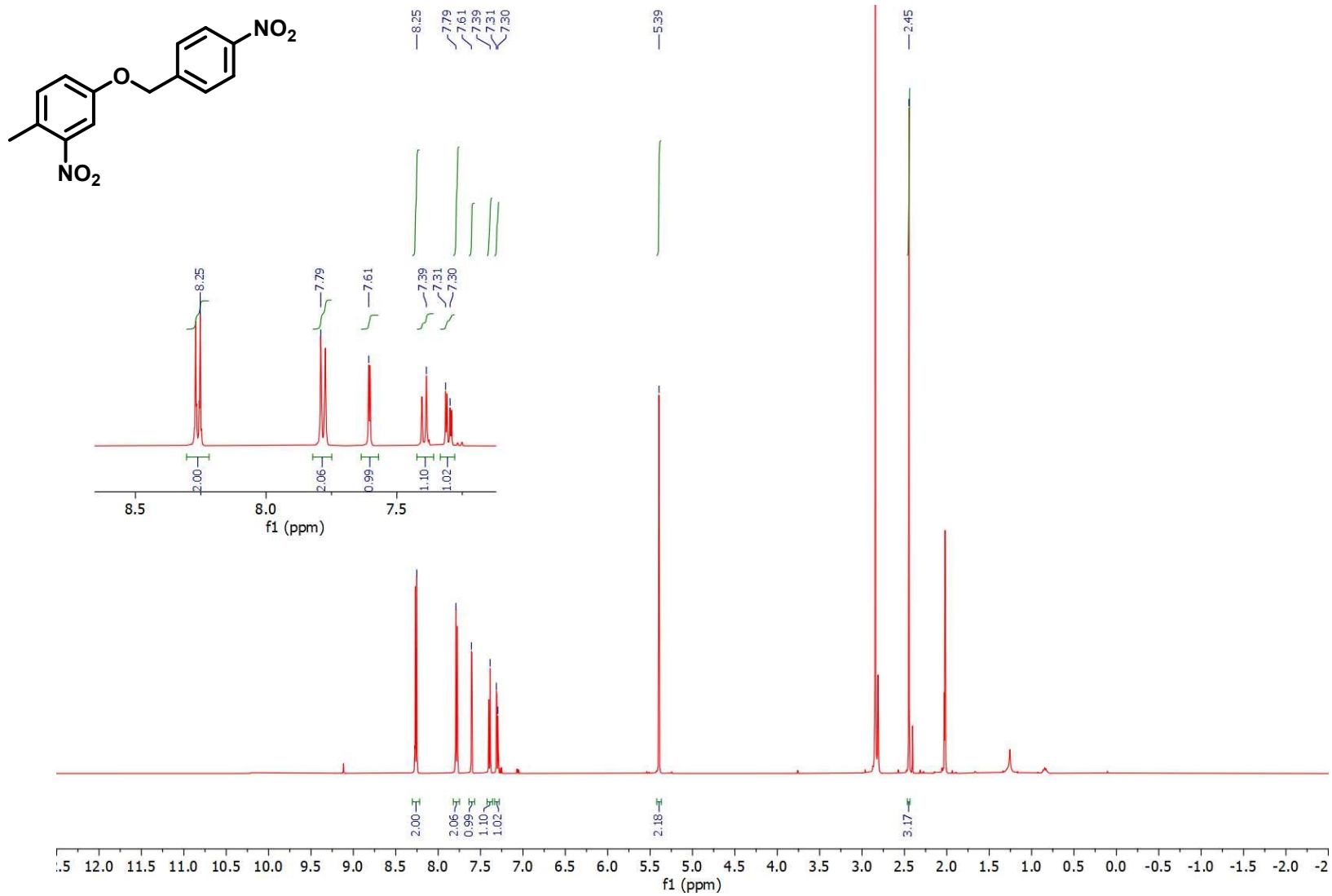


Figure S12 ¹H-NMR spectrum of compound 4

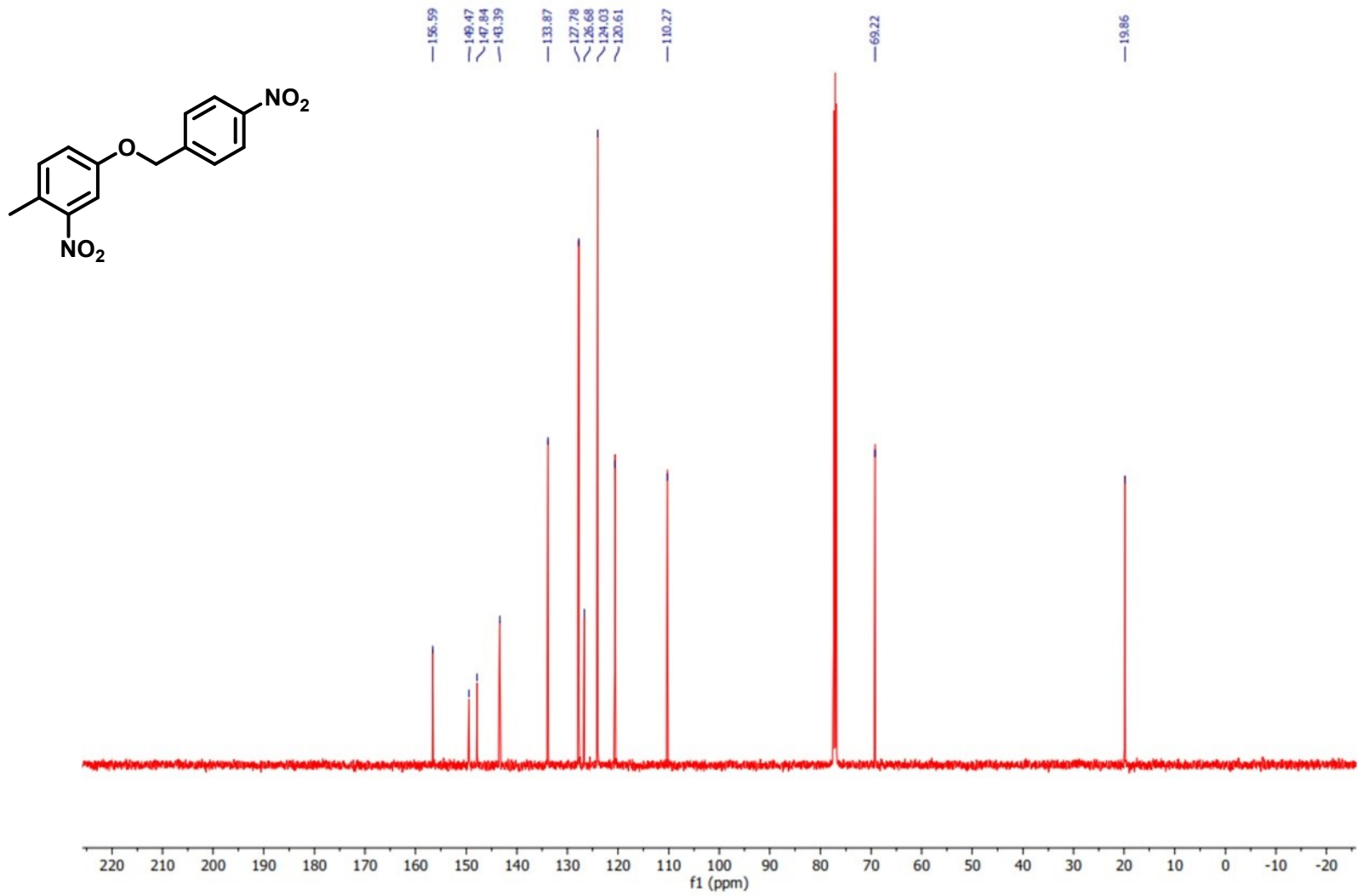


Figure S13 ¹³C-NMR spectrum of compound 4

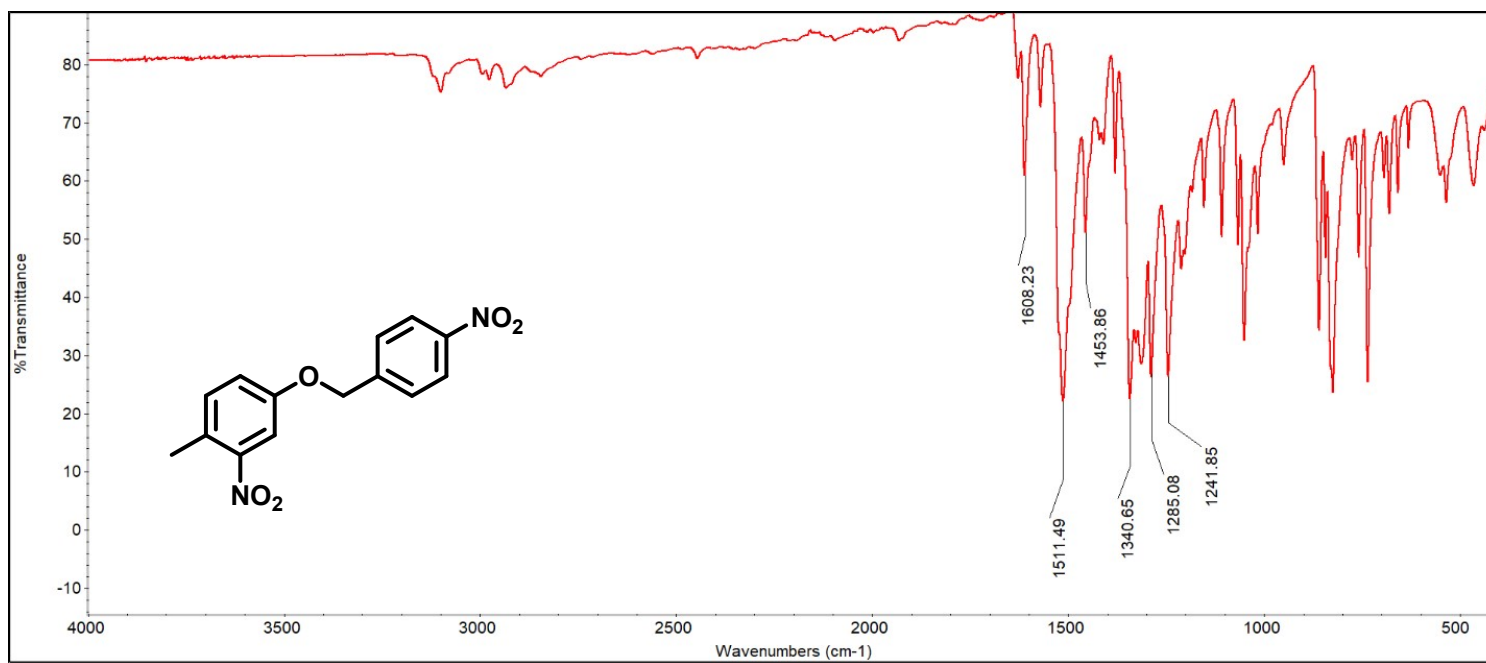


Figure S14 FTIR-spectrum of **compound 4**

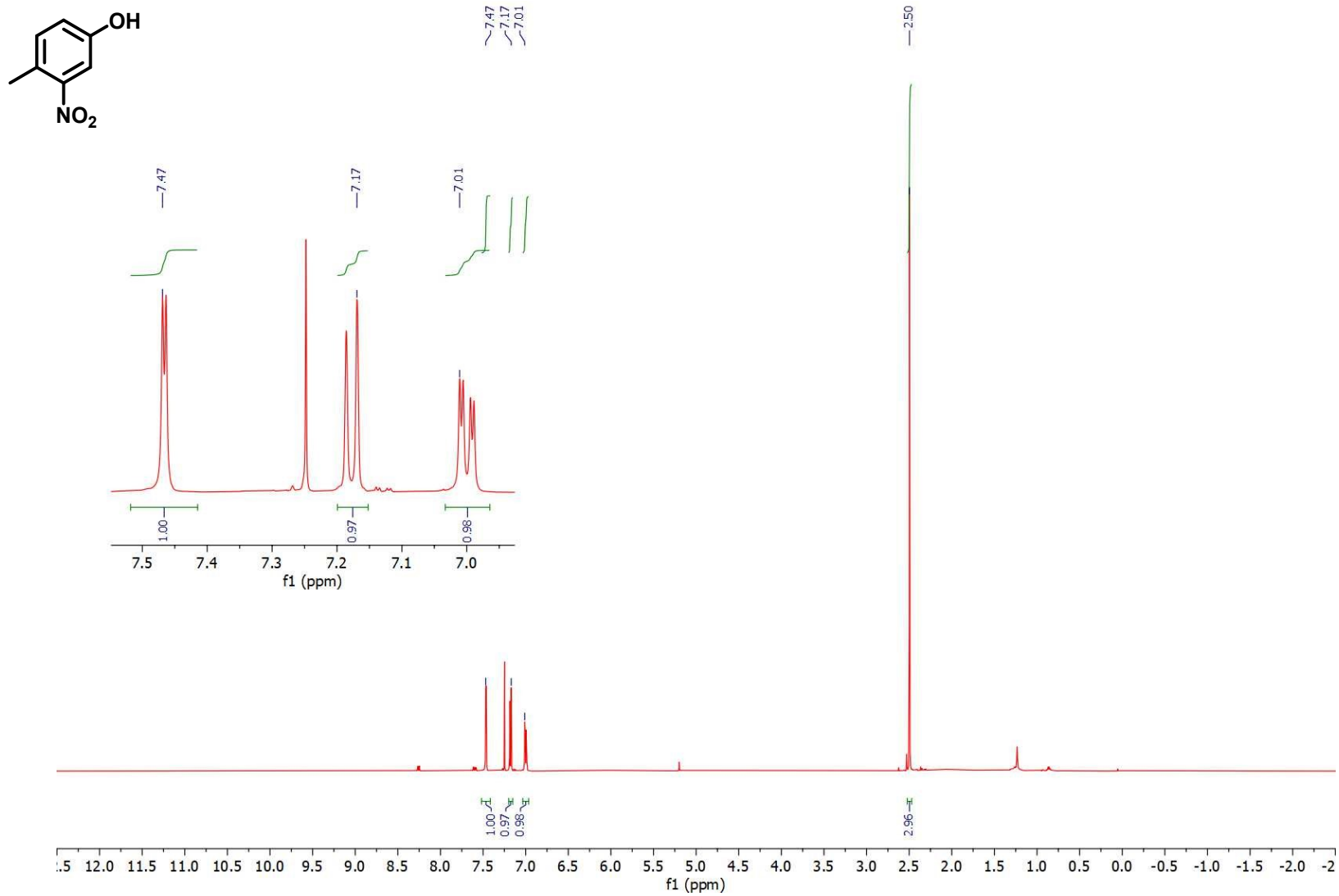


Figure S15 ¹H NMR (CDCl₃) spectrum of compound 5

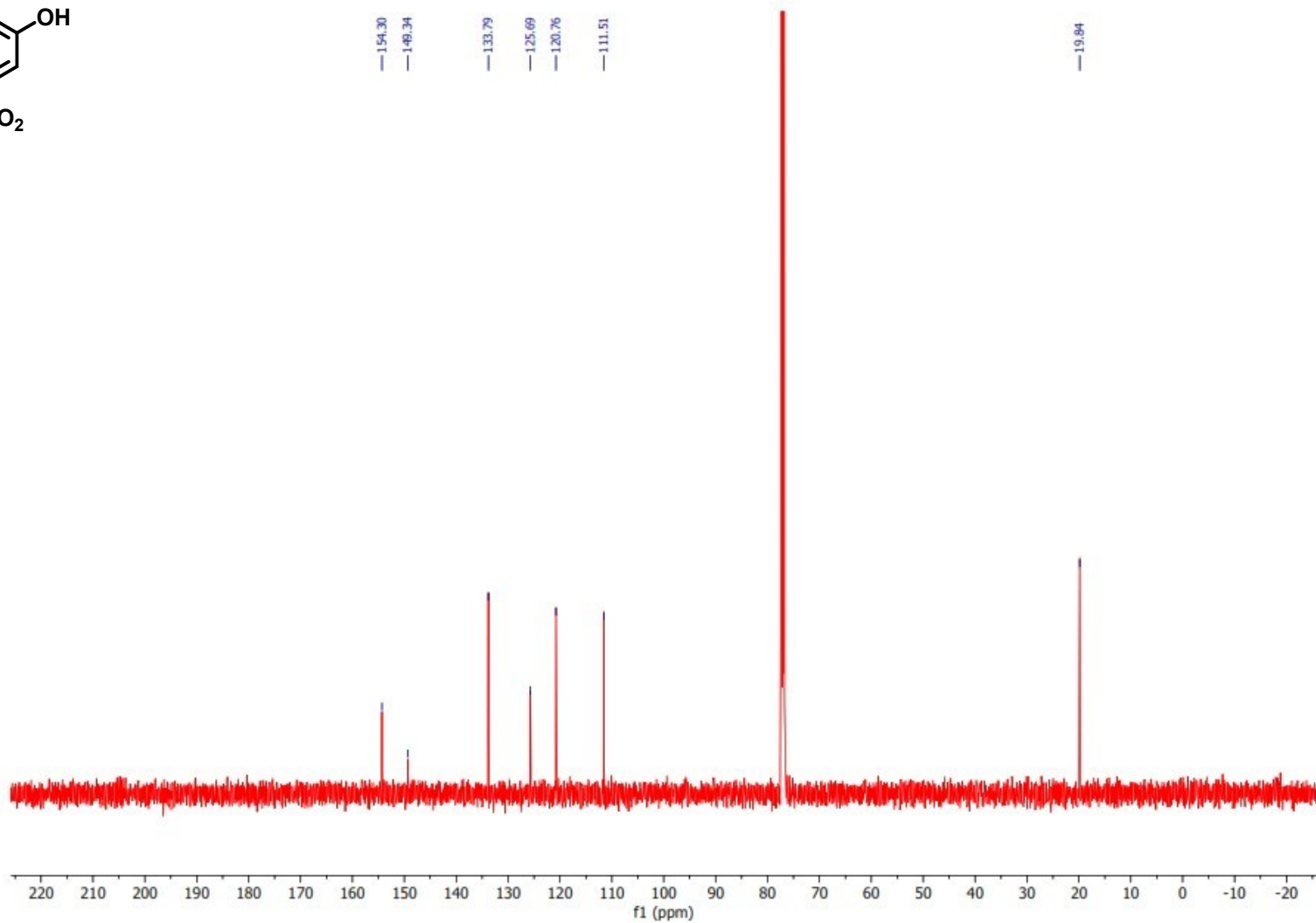
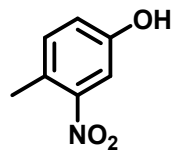


Figure S16 ¹³C NMR (CDCl₃) spectrum of compound 5

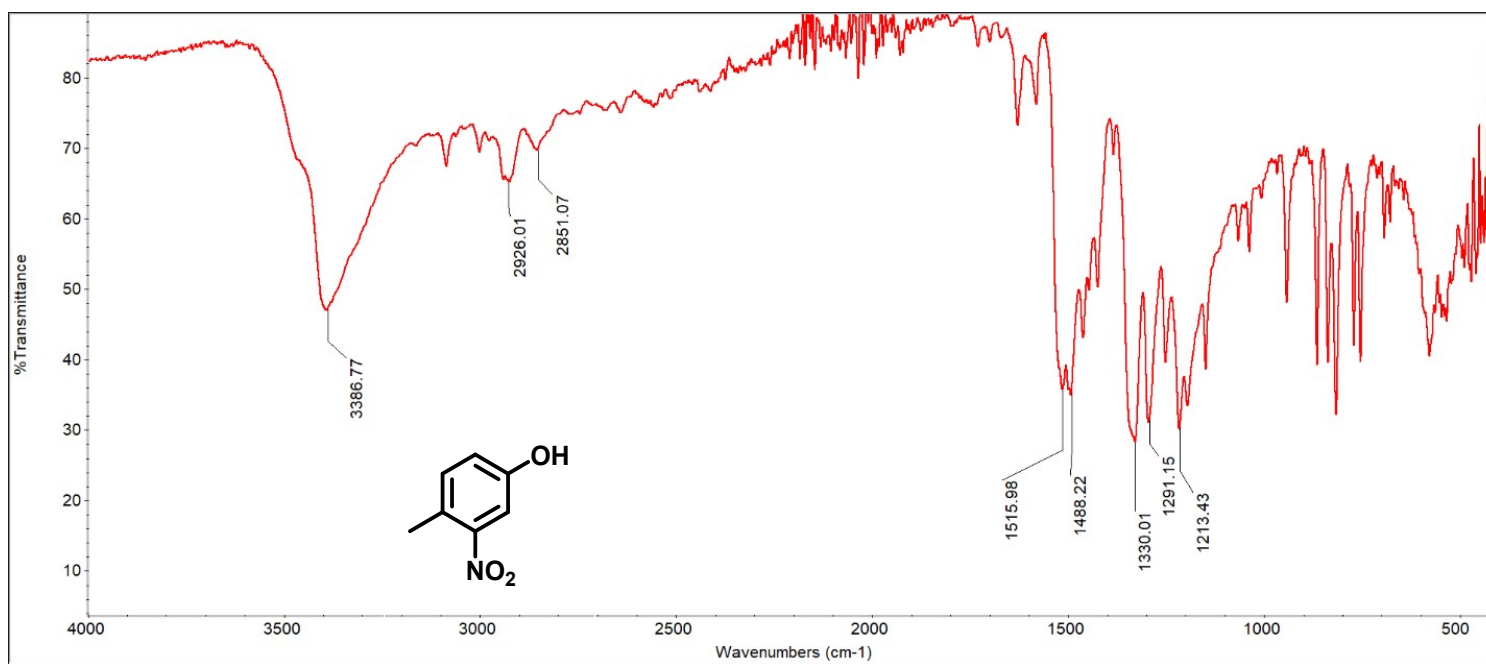


Figure S17 IR spectrum of compound 5

Functionalization on estradiol

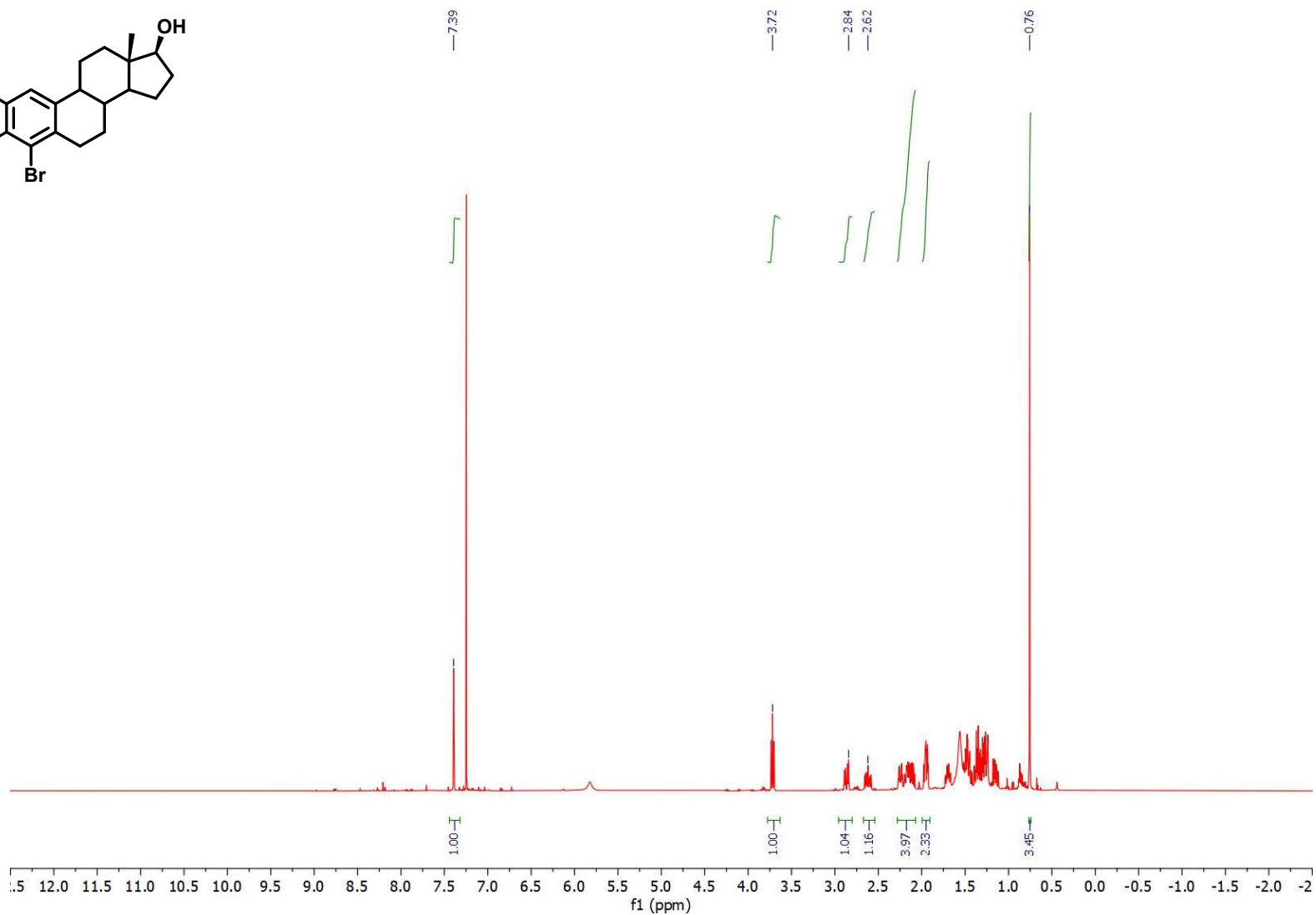
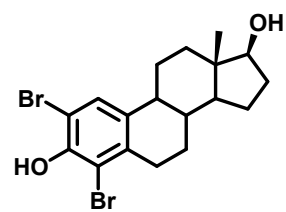


Figure S18 ¹H-NMR spectrum of 2,4-dibromo-estradiol

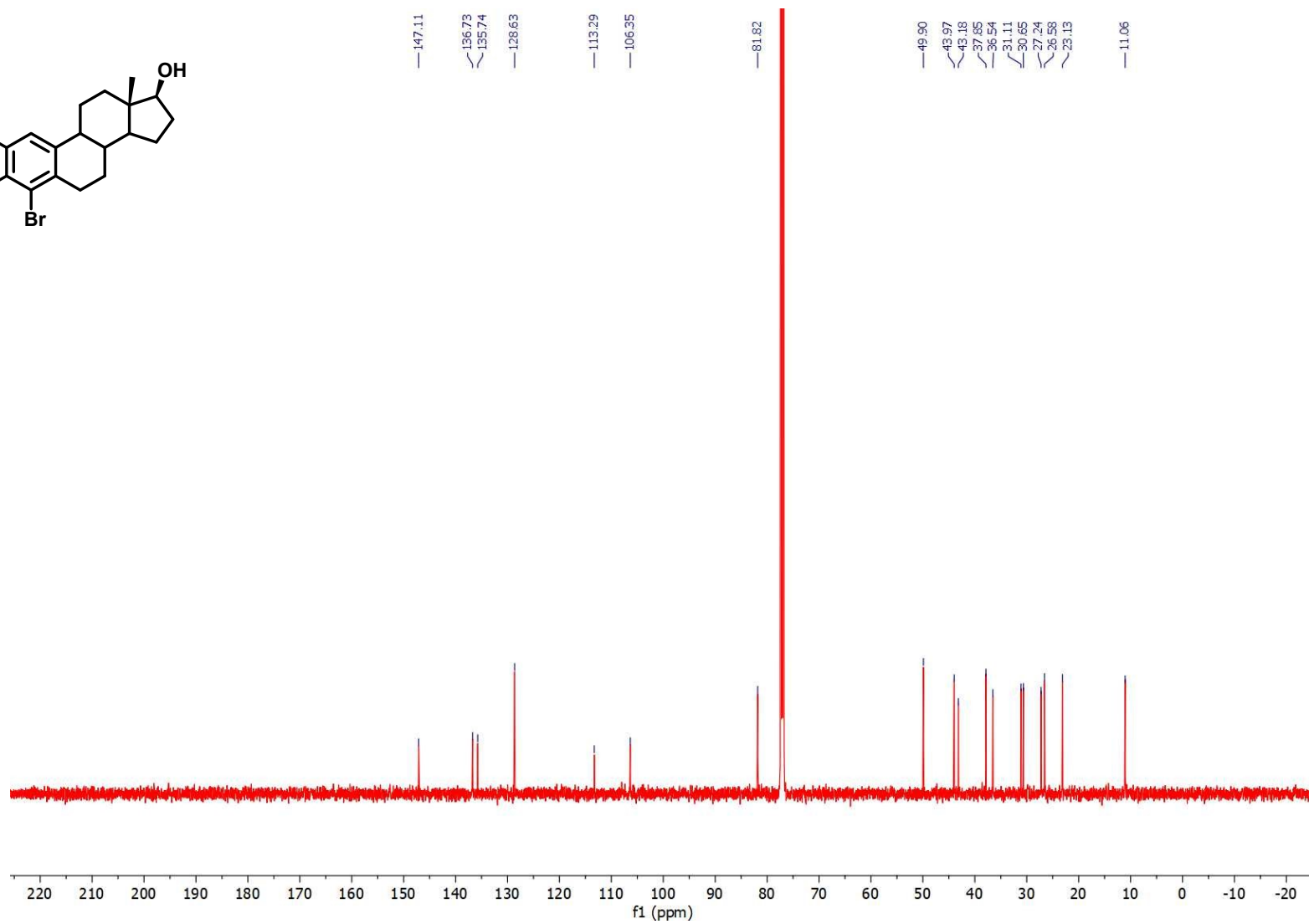
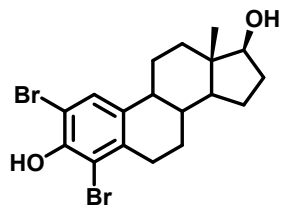


Figure S19 ¹³C-NMR spectrum of 2,4-dibromo-estradiol

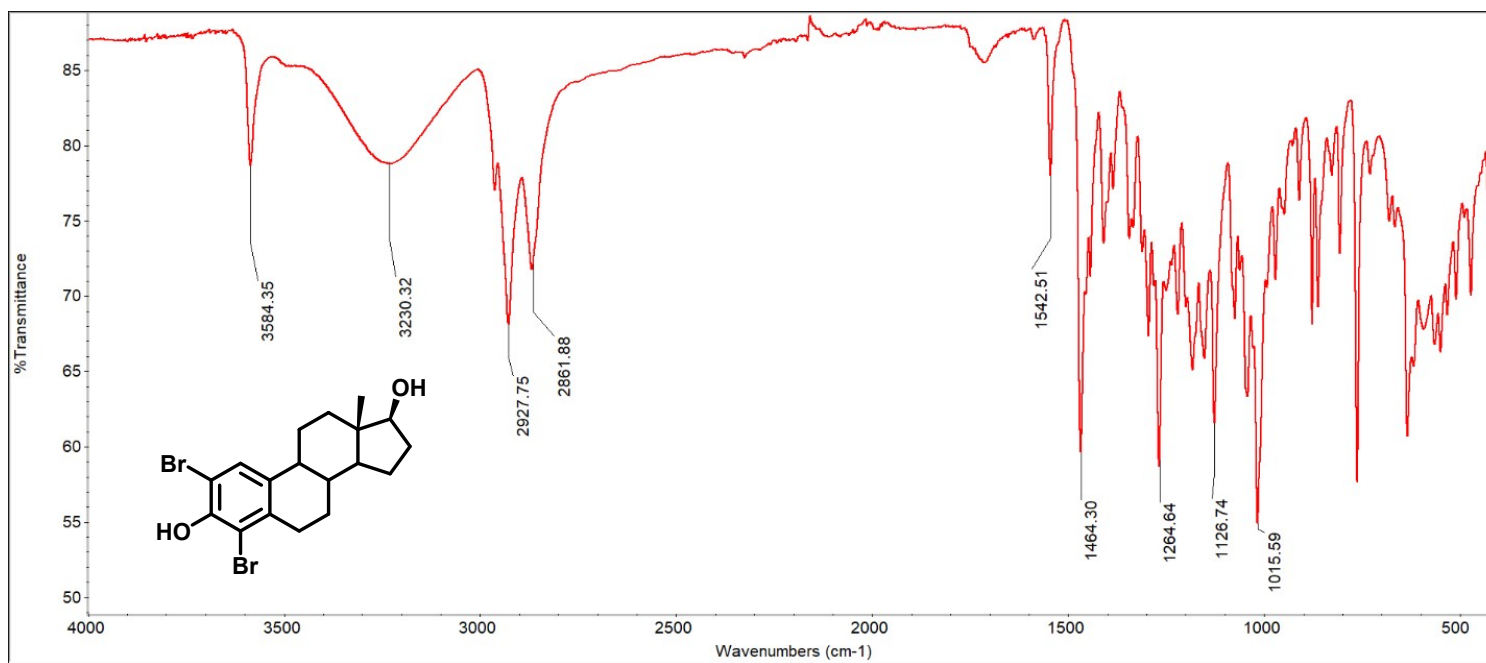


Figure S20 FTIR-spectrum of 2,4-dibromo-estradiol

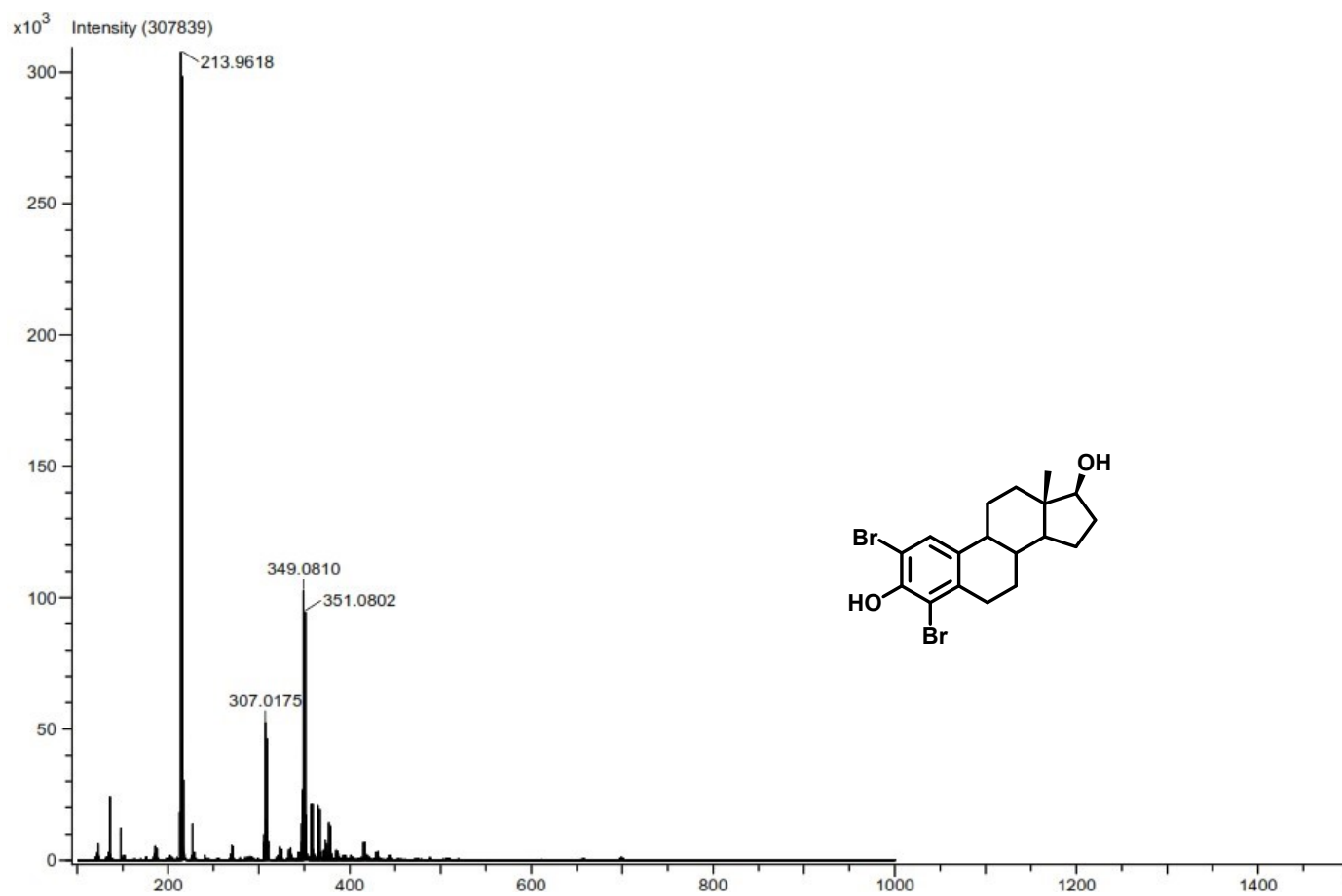


Figure S21 Mass spectrum of 2,4-dibromo-estradiol

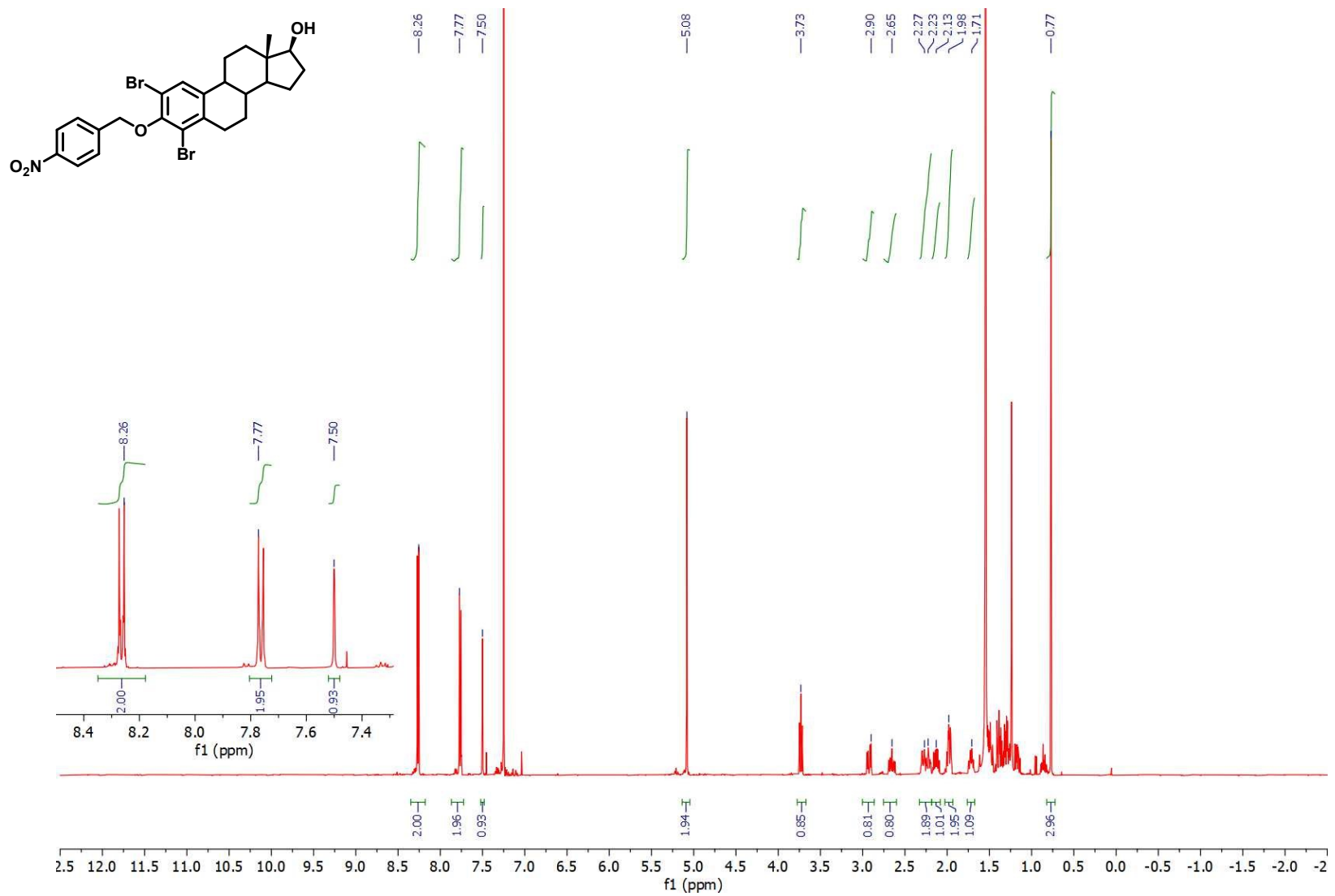


Figure S22 ¹H-NMR spectrum of compound 6

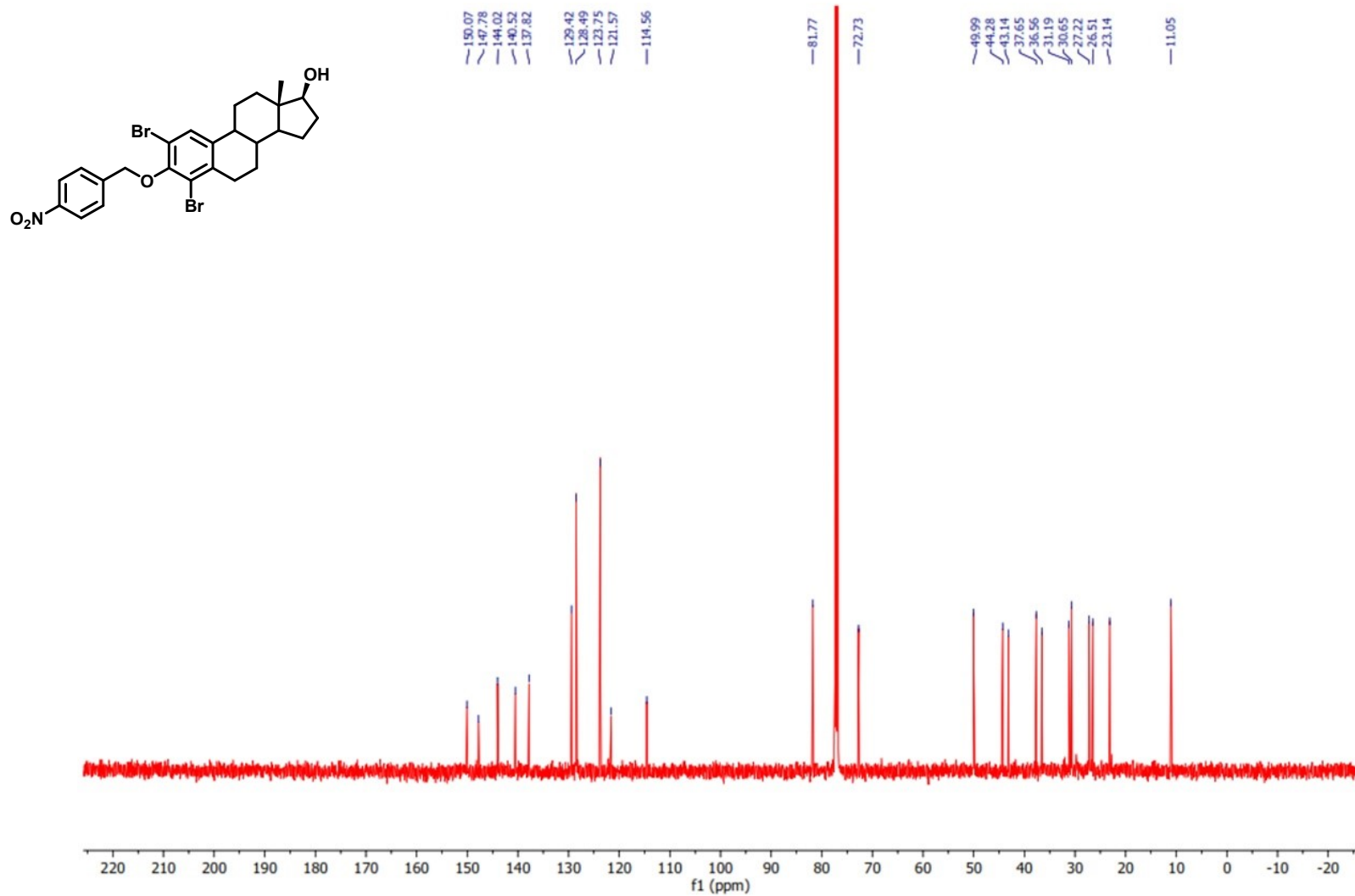


Figure S23 ¹³C-NMR spectrum of compound 6

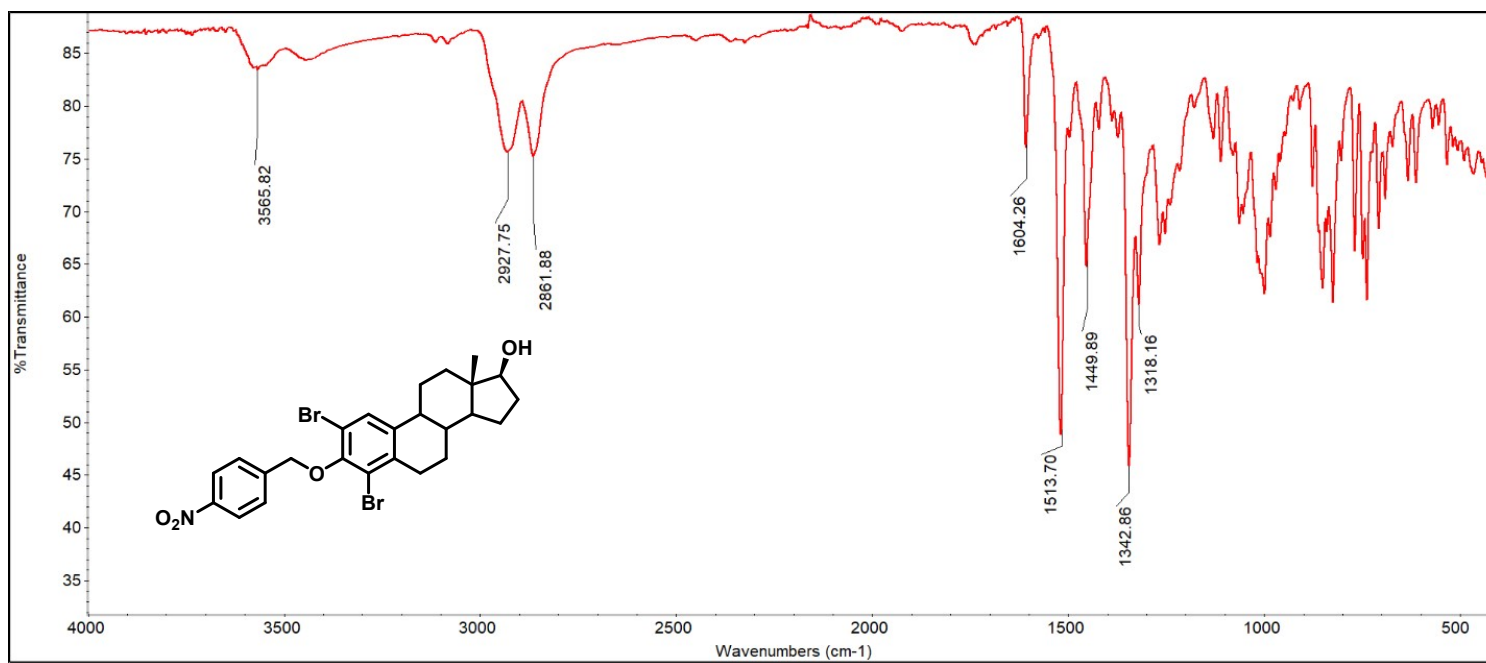


Figure S24 FTIR-spectrum of **compound 6**

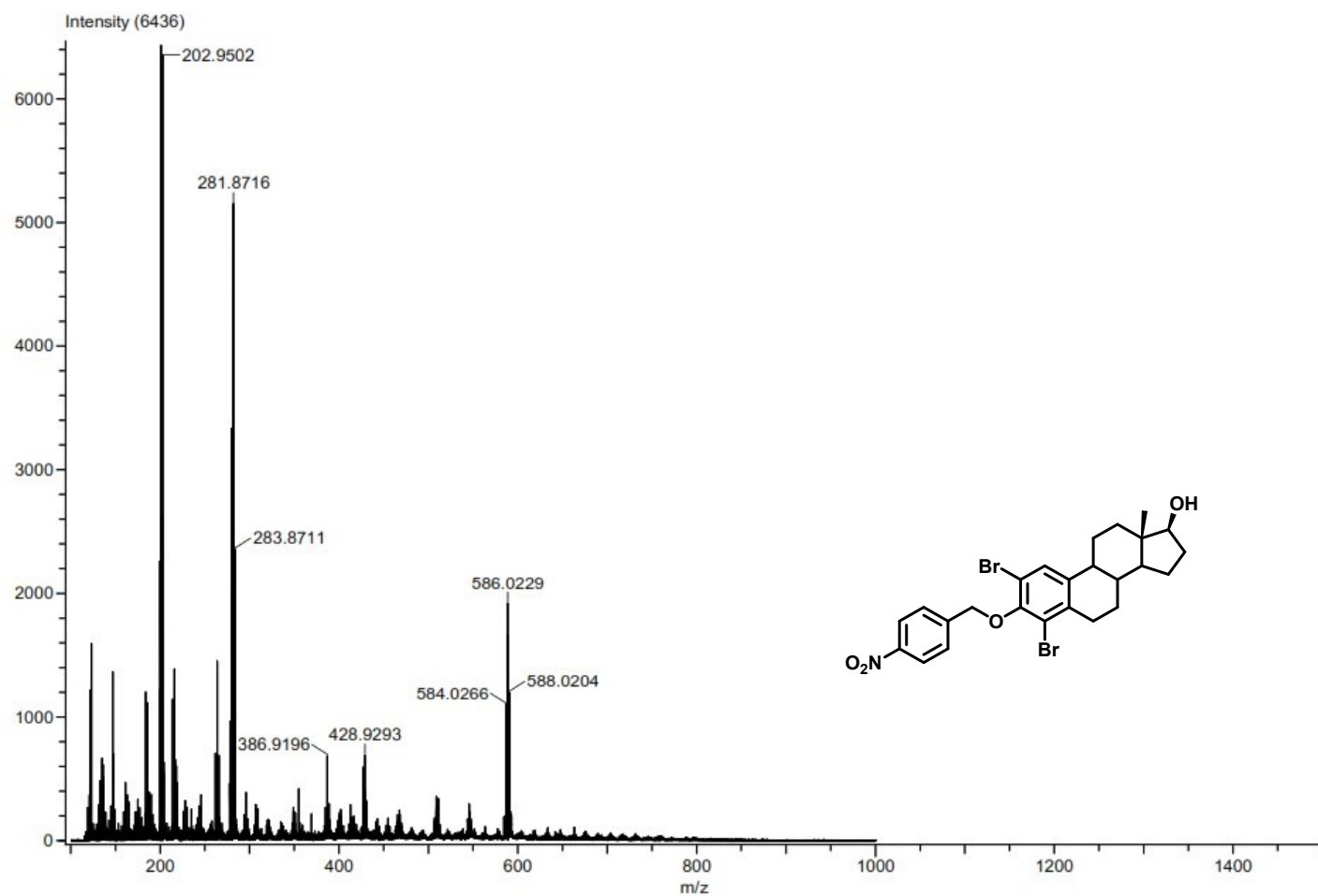


Figure S25 Mass spectrum of compound 6

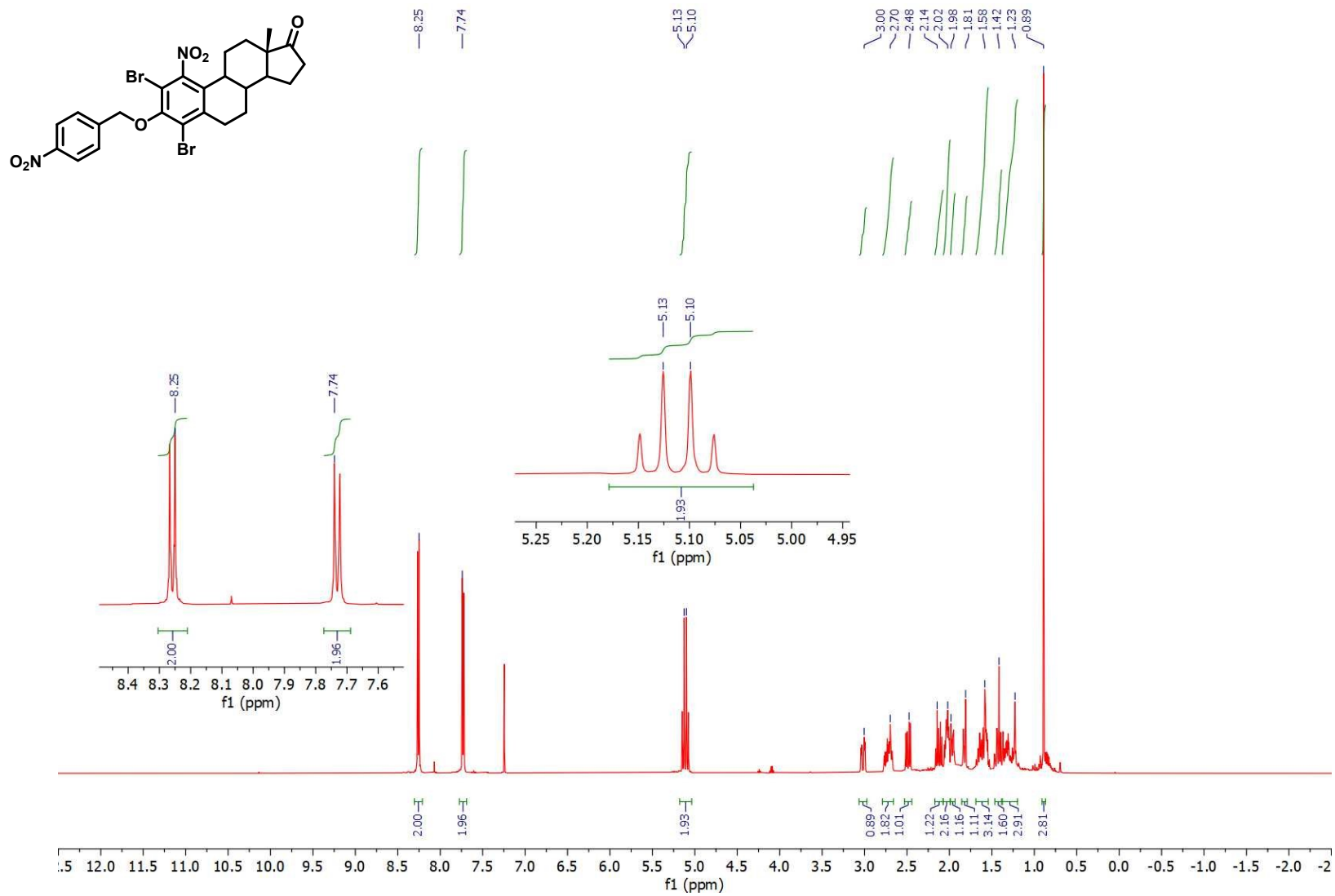


Figure S26 ¹H-NMR spectrum of compound 7

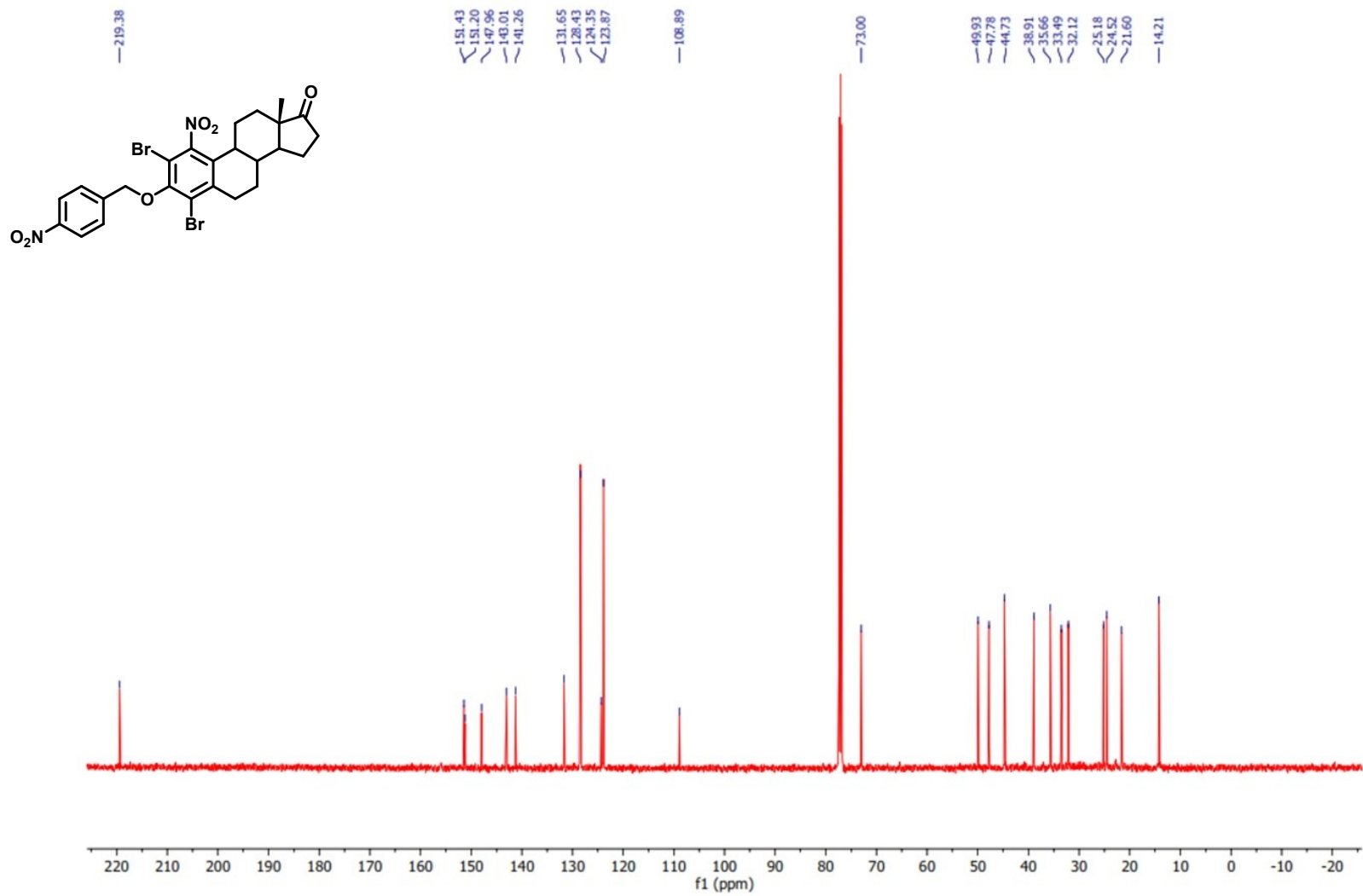


Figure S27 ¹³C-NMR spectrum of compound 7

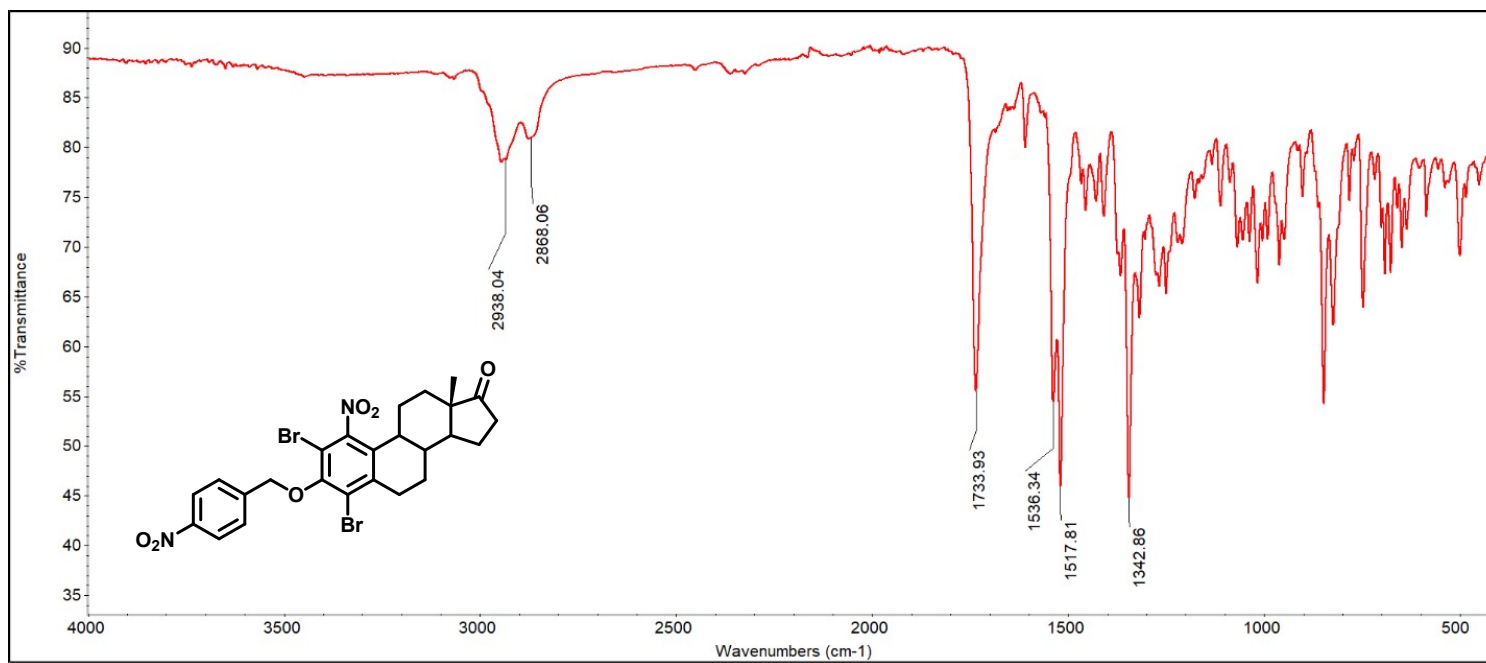


Figure S28 FTIR-spectrum of compound 7

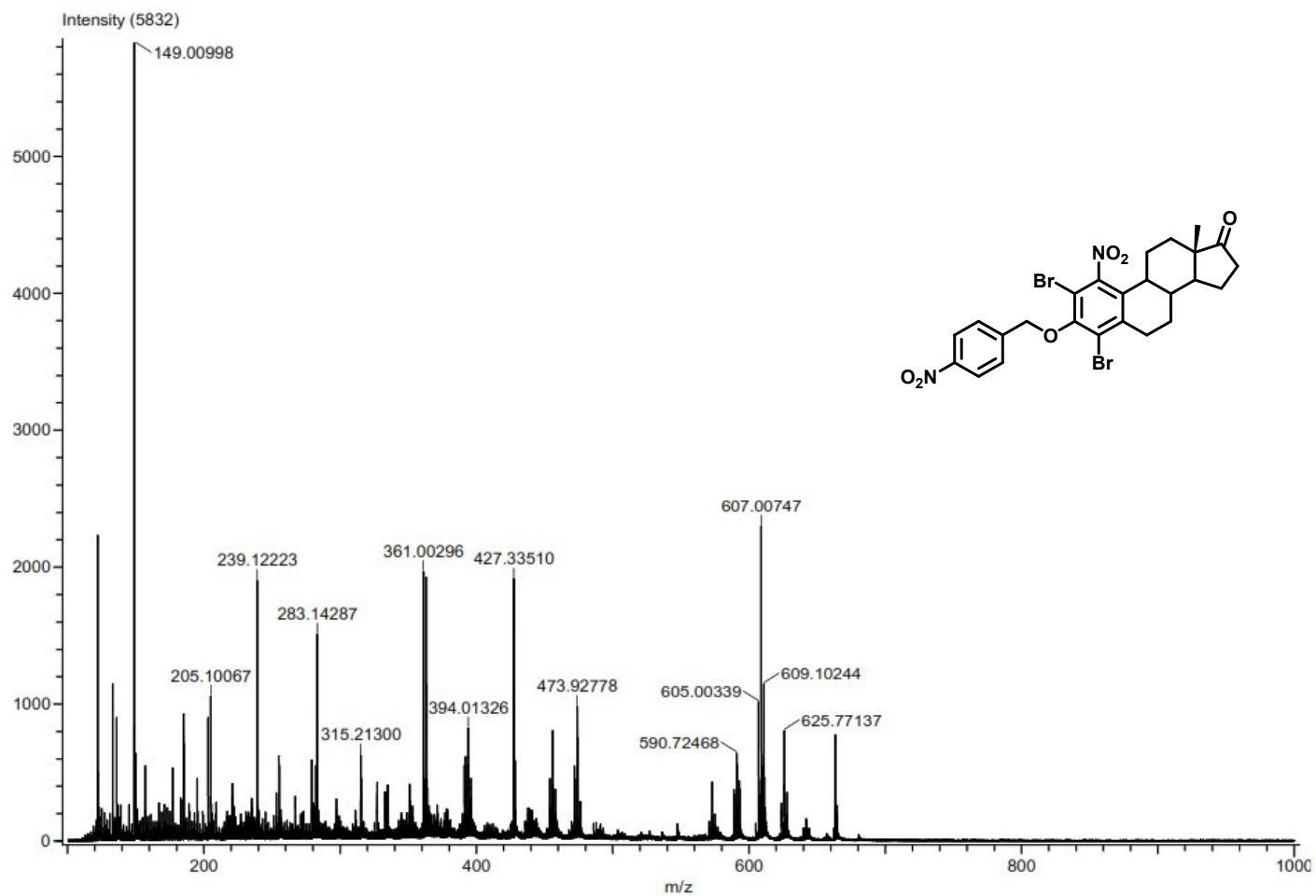


Figure S29 Mass spectrum of compound 7

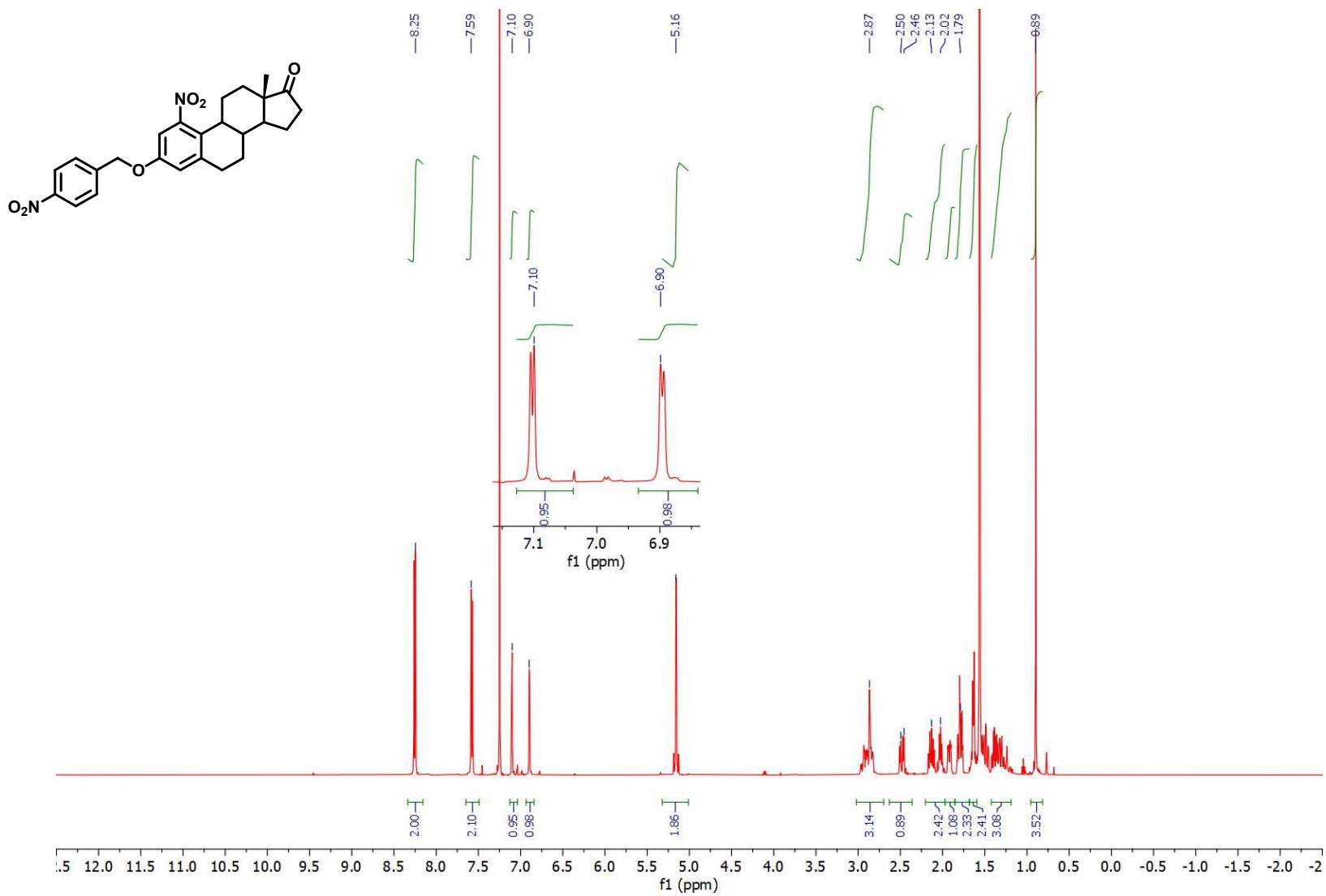


Figure S30 ¹H-NMR spectrum of **compound 8**

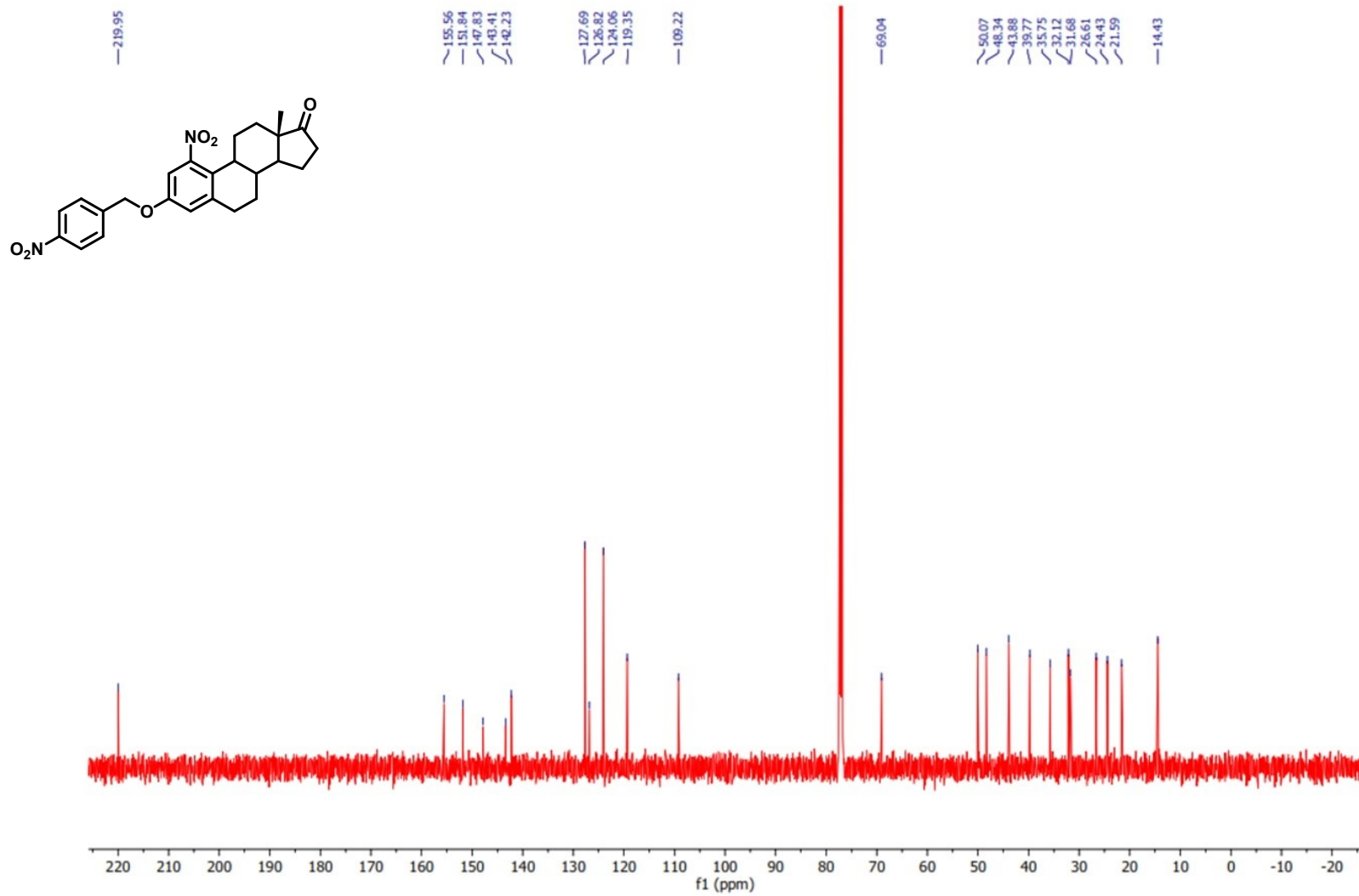


Figure S31 ¹³C-NMR spectrum of compound 8

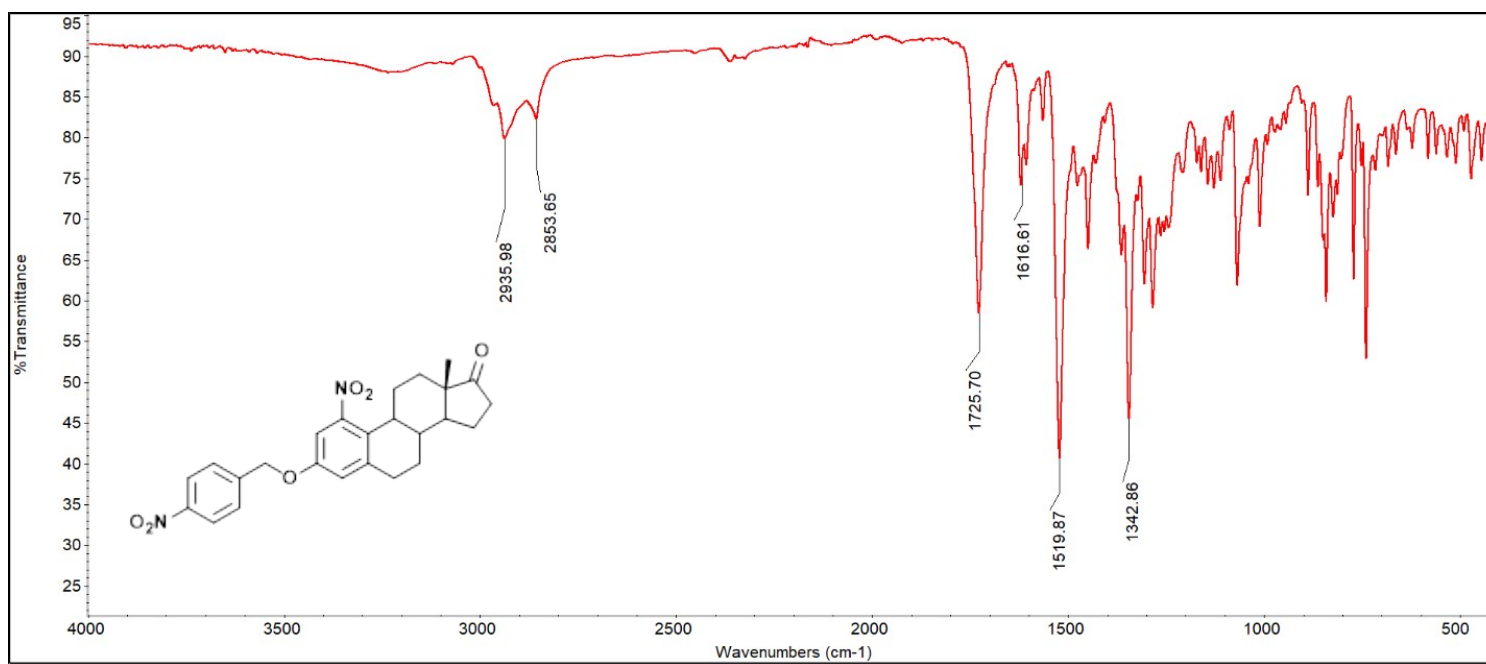


Figure S32 FTIR-spectrum of **compound 8**

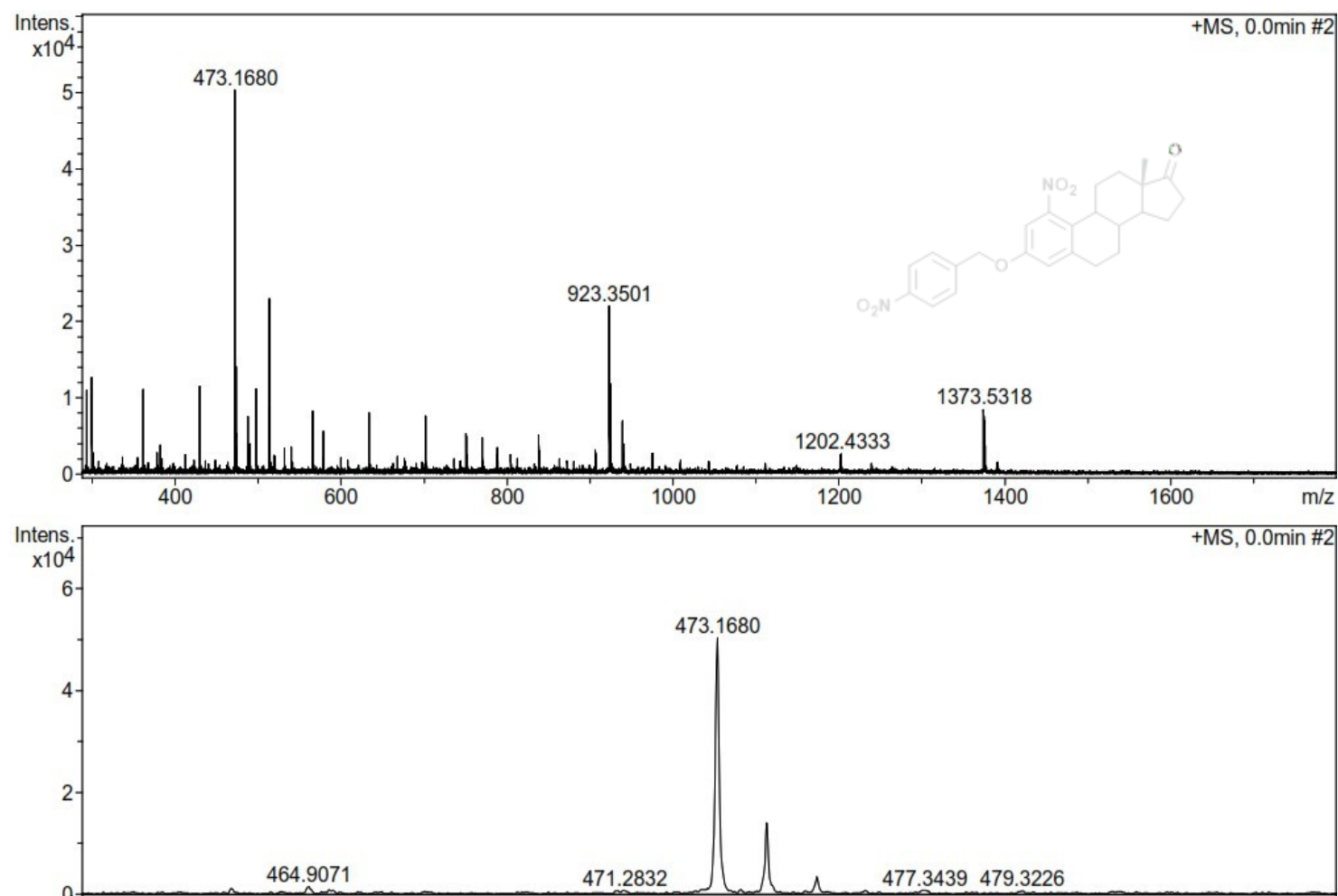


Figure S33 Mass spectrum of compound 8

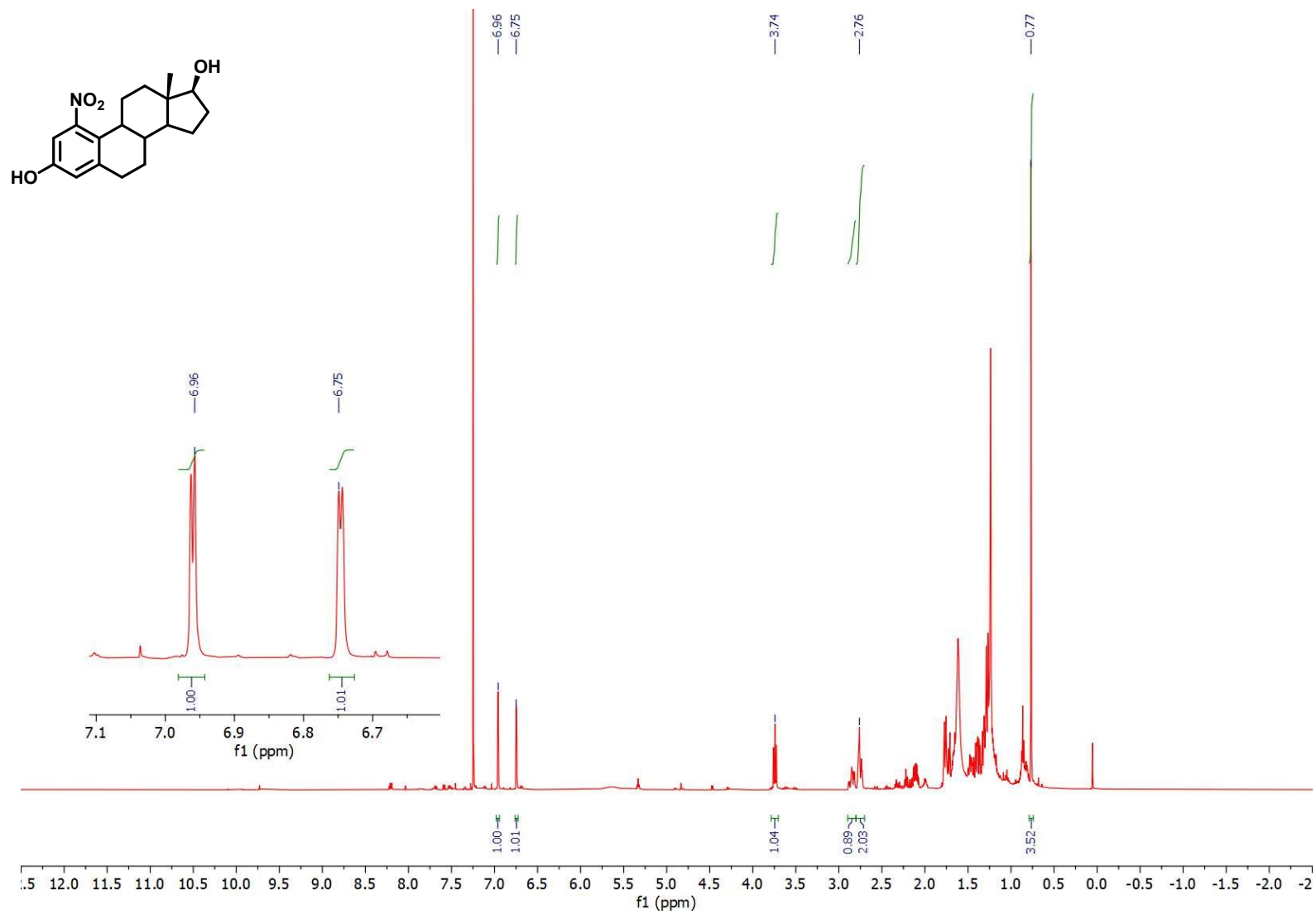


Figure S34 ¹H-NMR spectrum of compound 9

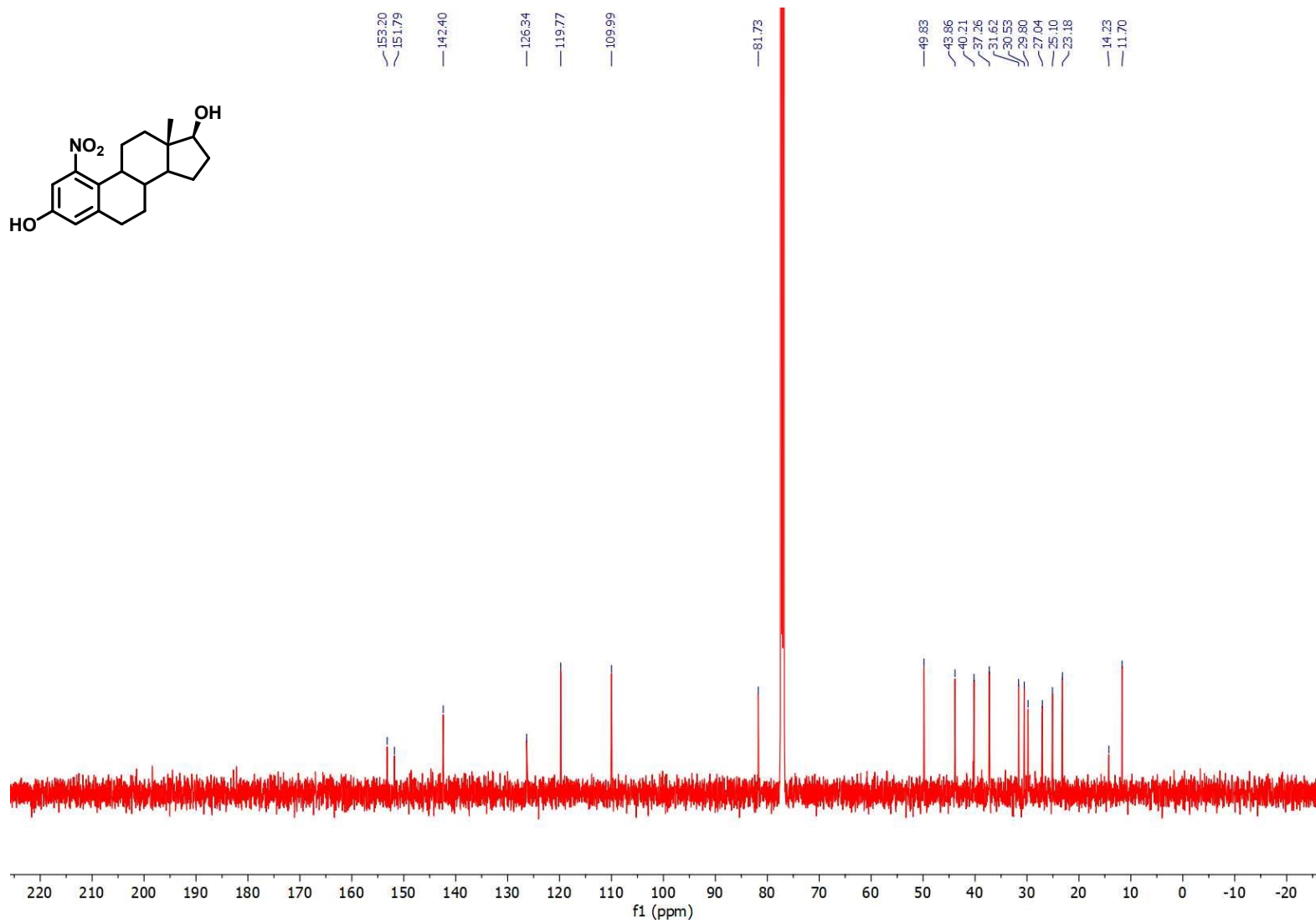


Figure S35 ¹³C-NMR spectrum of compound 9

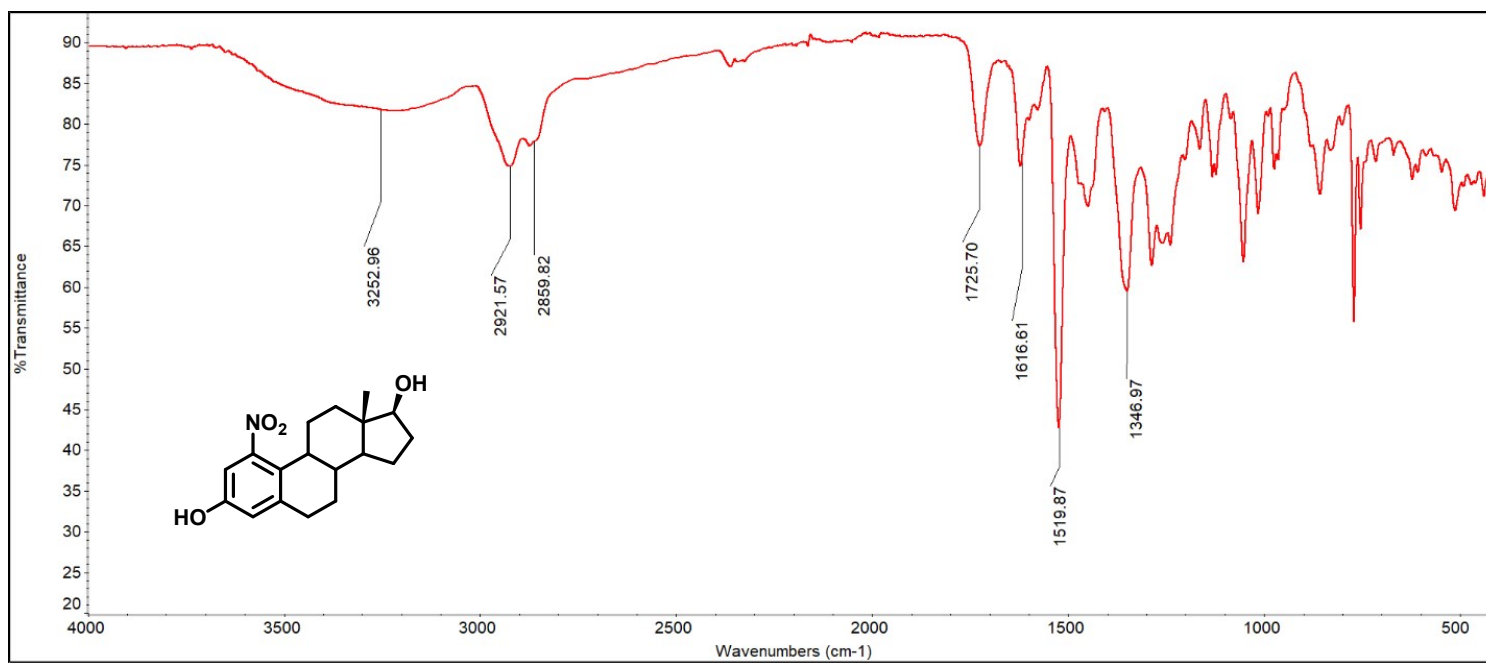


Figure S36 FTIR-spectrum of **compound 9**

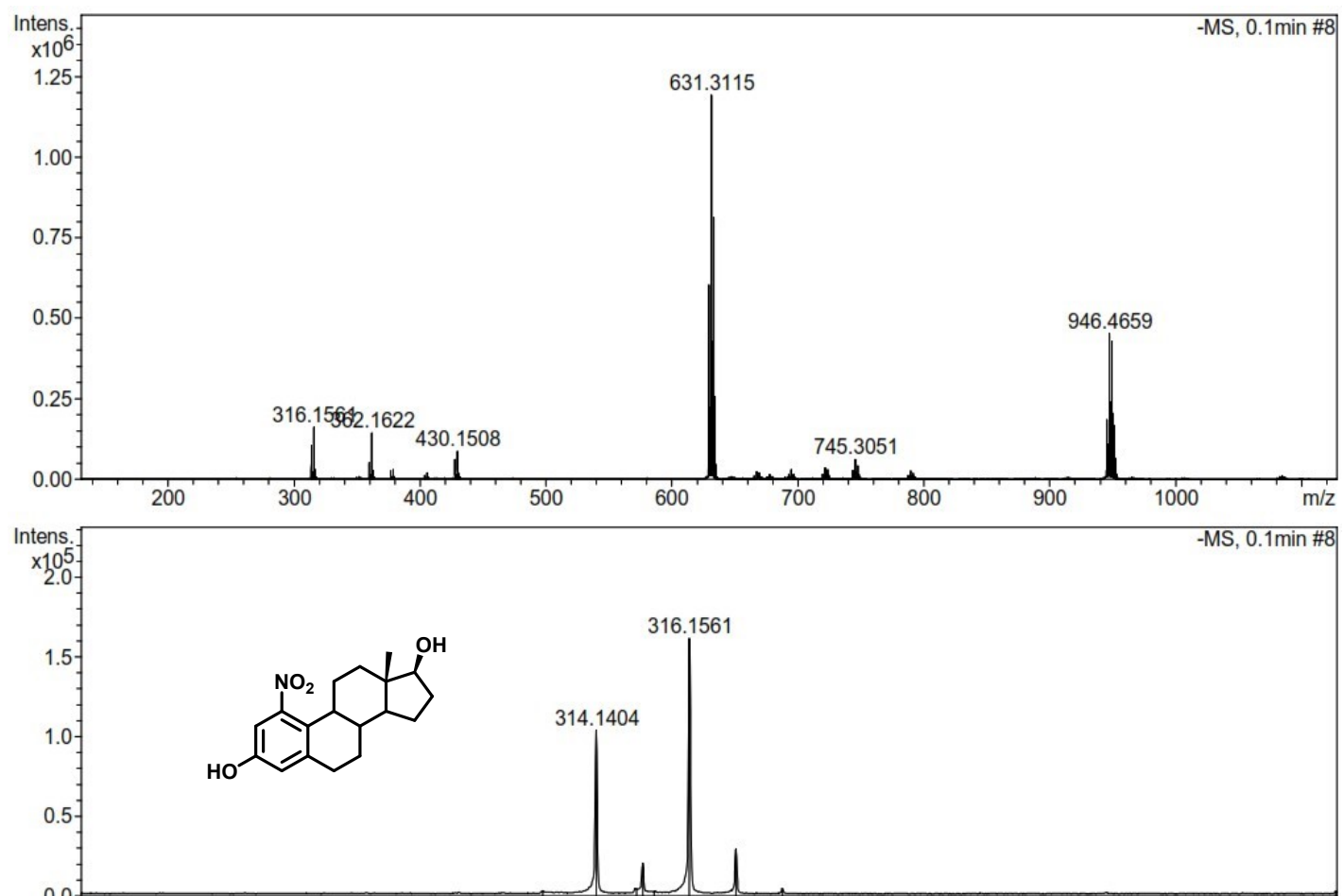


Figure S37 Mass spectrum of compound 9

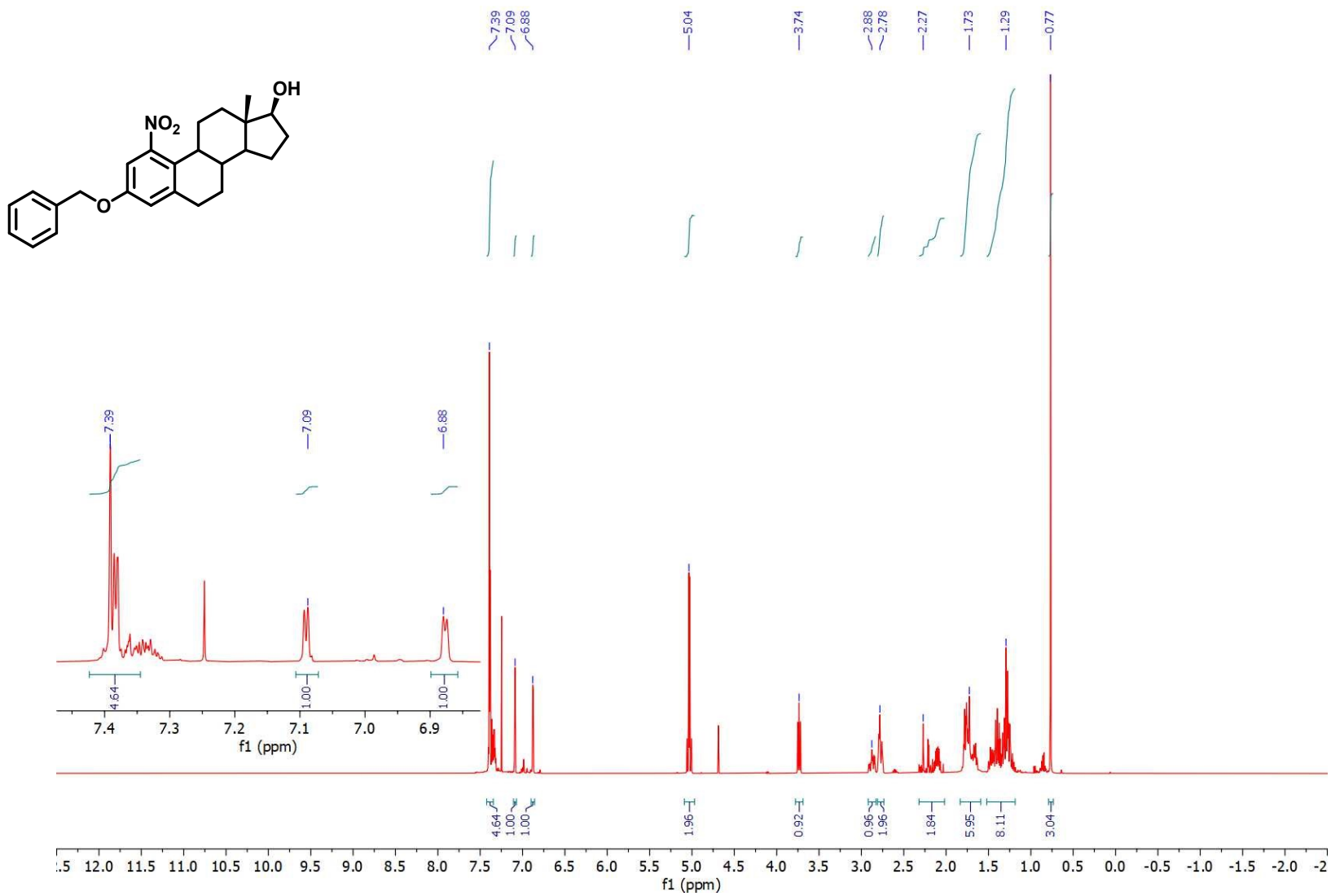


Figure S38 ¹H-NMR spectrum of **3-(benzyloxy)-1-nitro-esradiol**

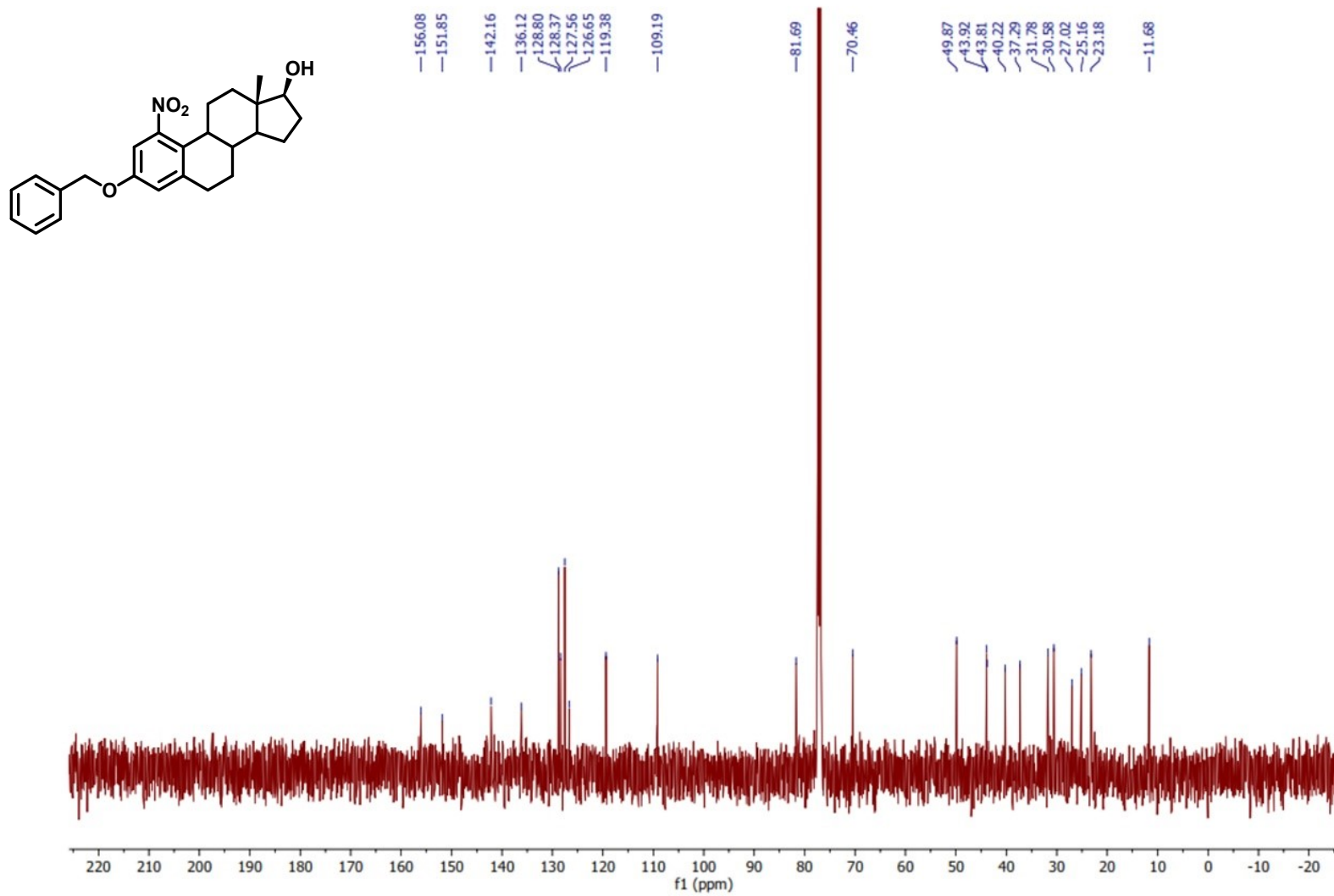


Figure S39 ^{13}C -NMR spectrum of 3-(benzyloxy)-1-nitro-esradiol

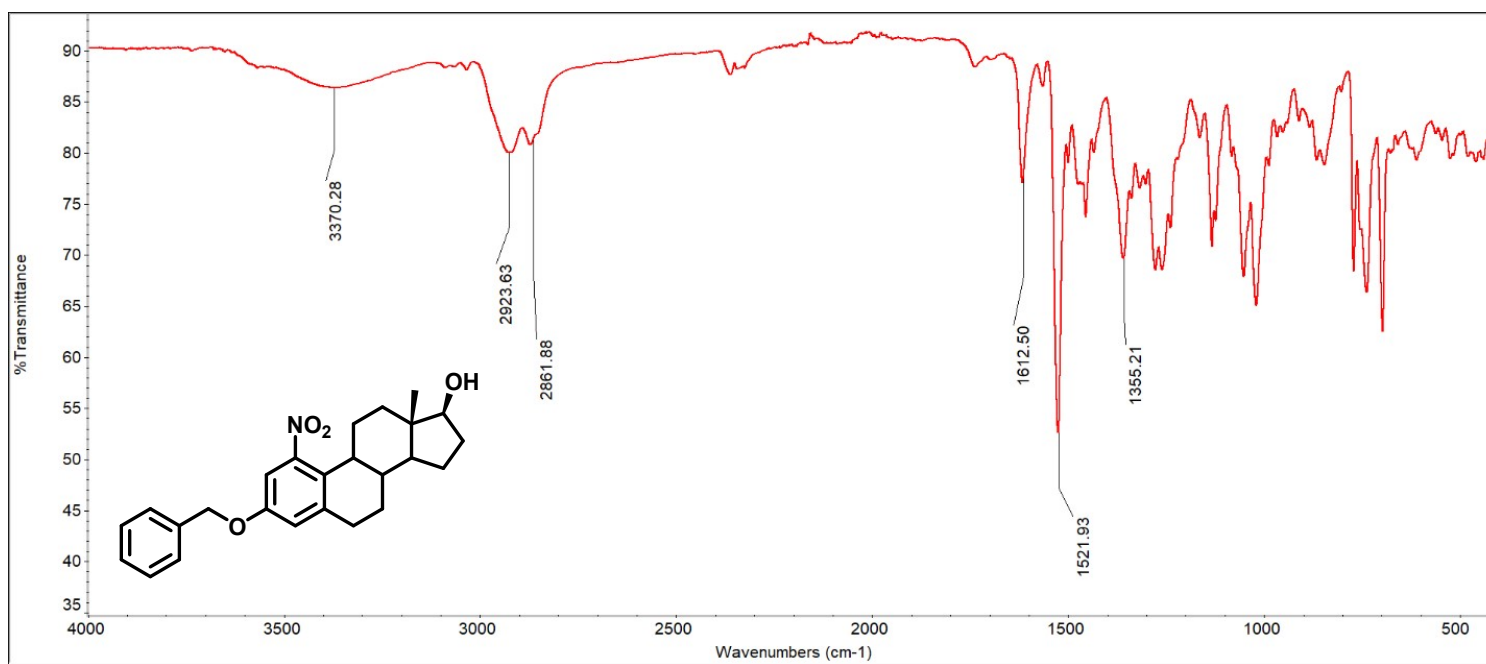


Figure S40 FTIR-spectrum of **3-(benzyloxy)-1-nitro-esradiol**

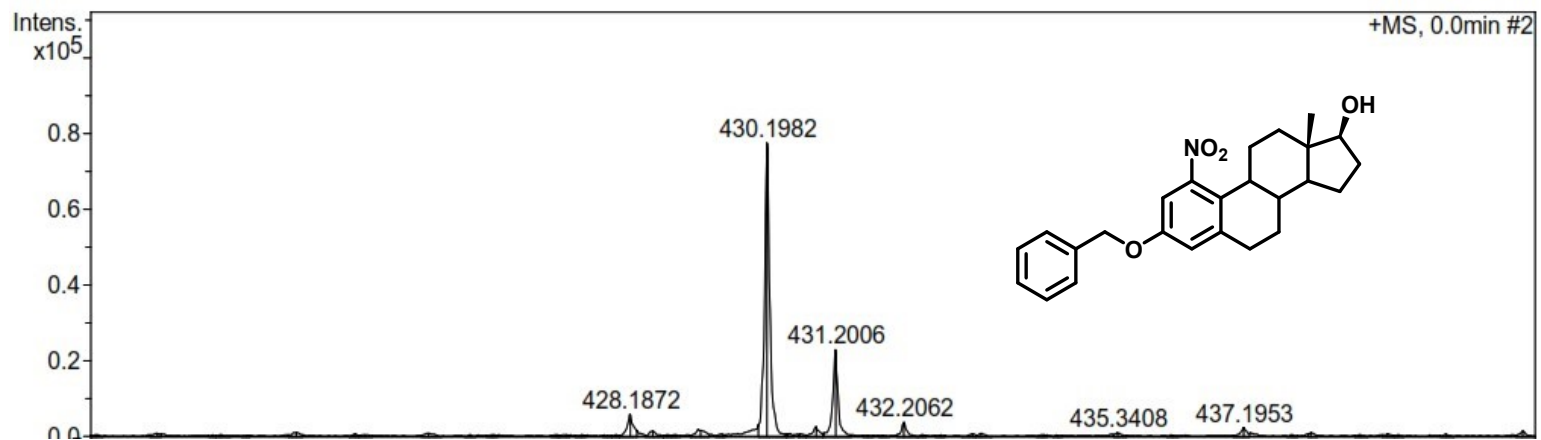
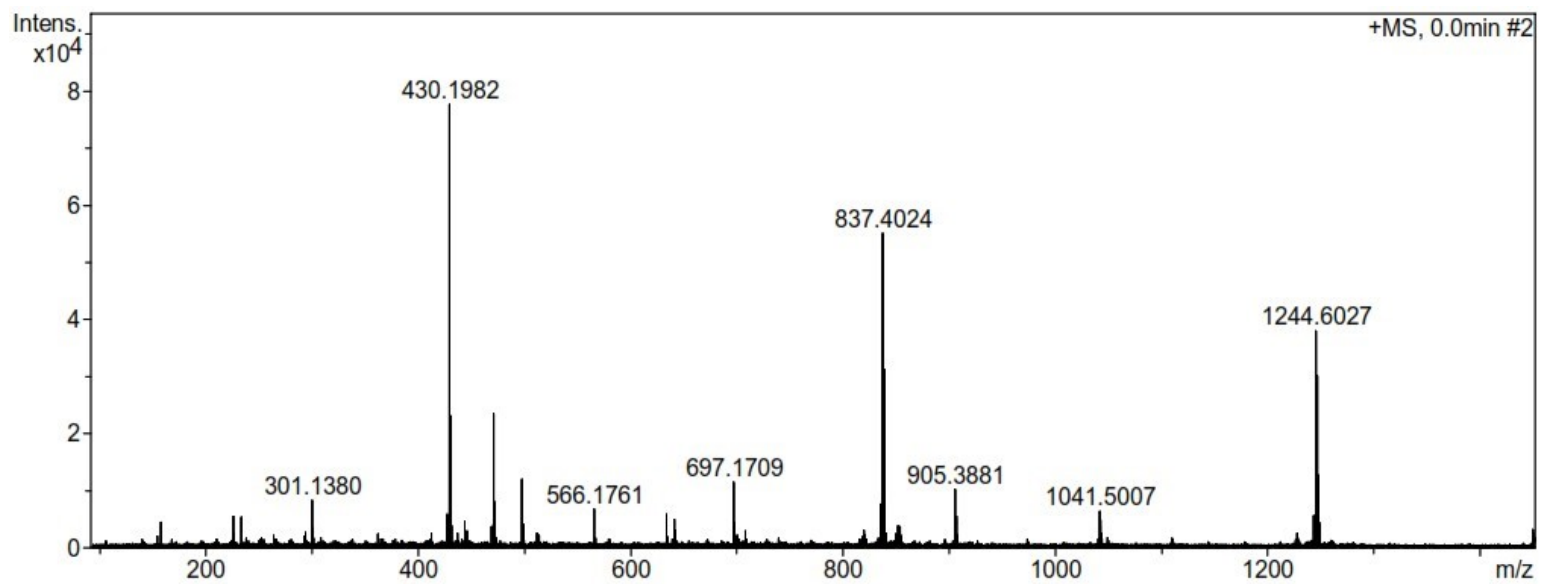


Figure S41 Mass spectrum of 3-(benzyloxy)-1-nitro-esradiol

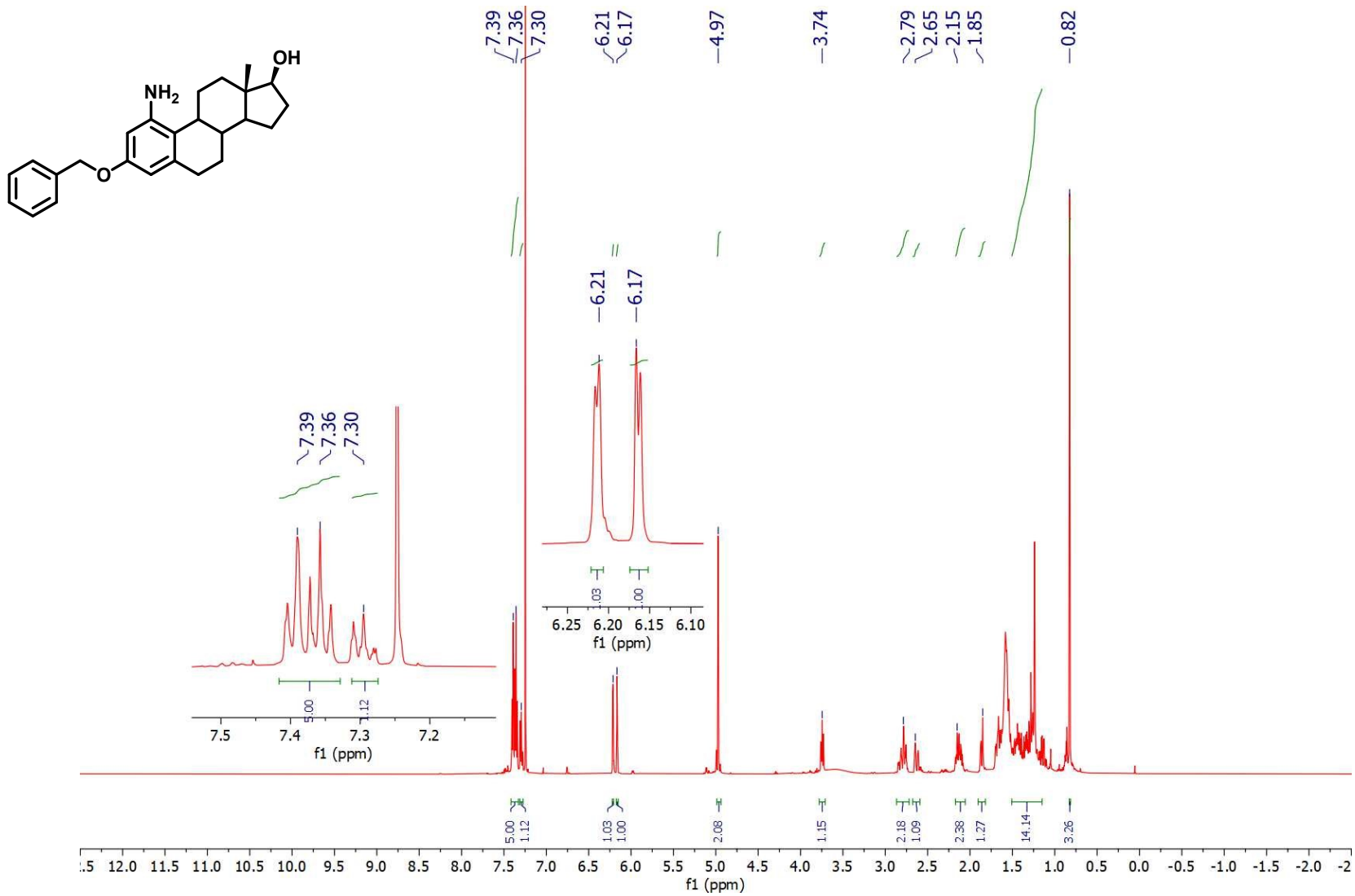


Figure S42 ¹H-NMR spectrum of compound 10

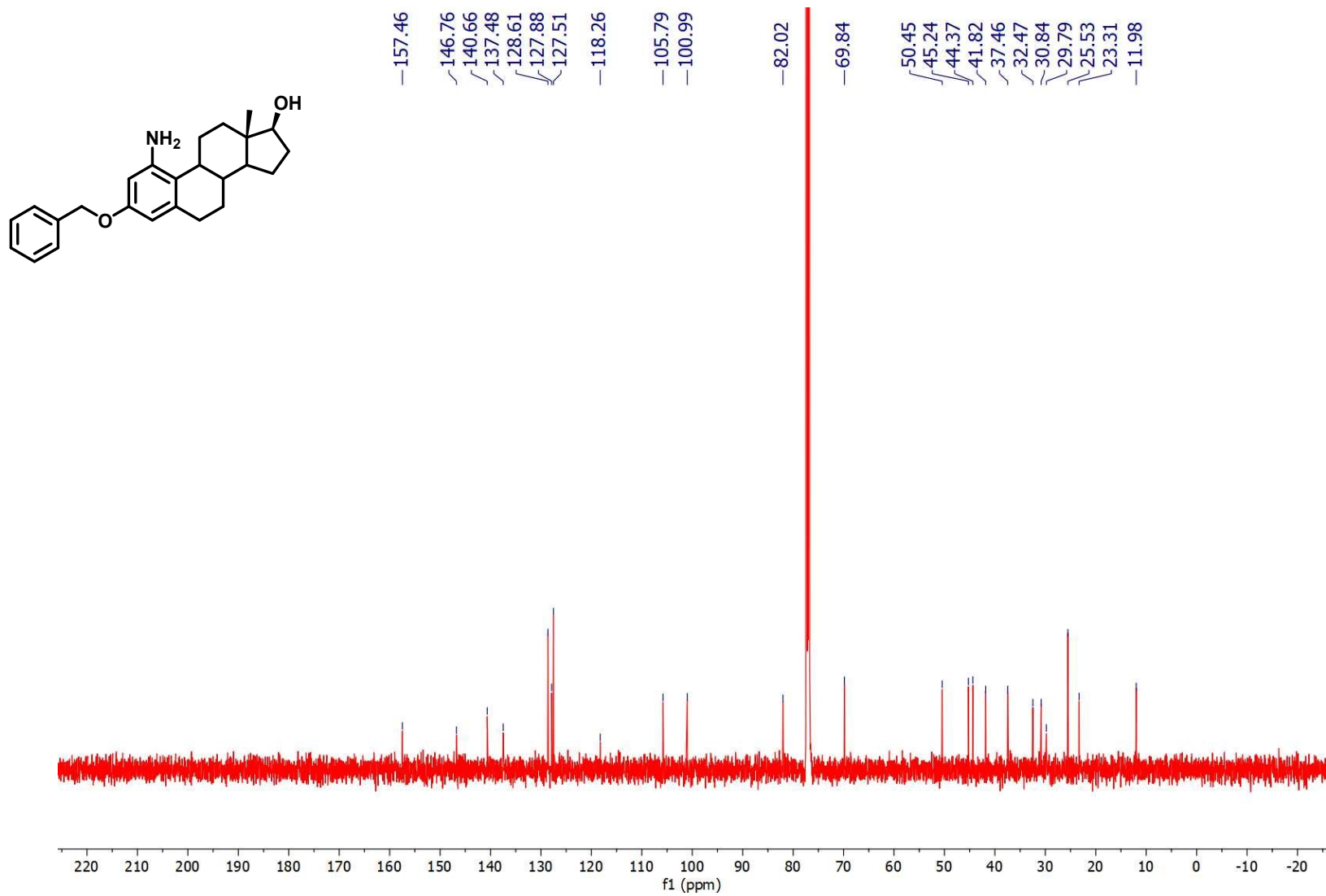


Figure S43 ¹³C-NMR spectrum of compound 10

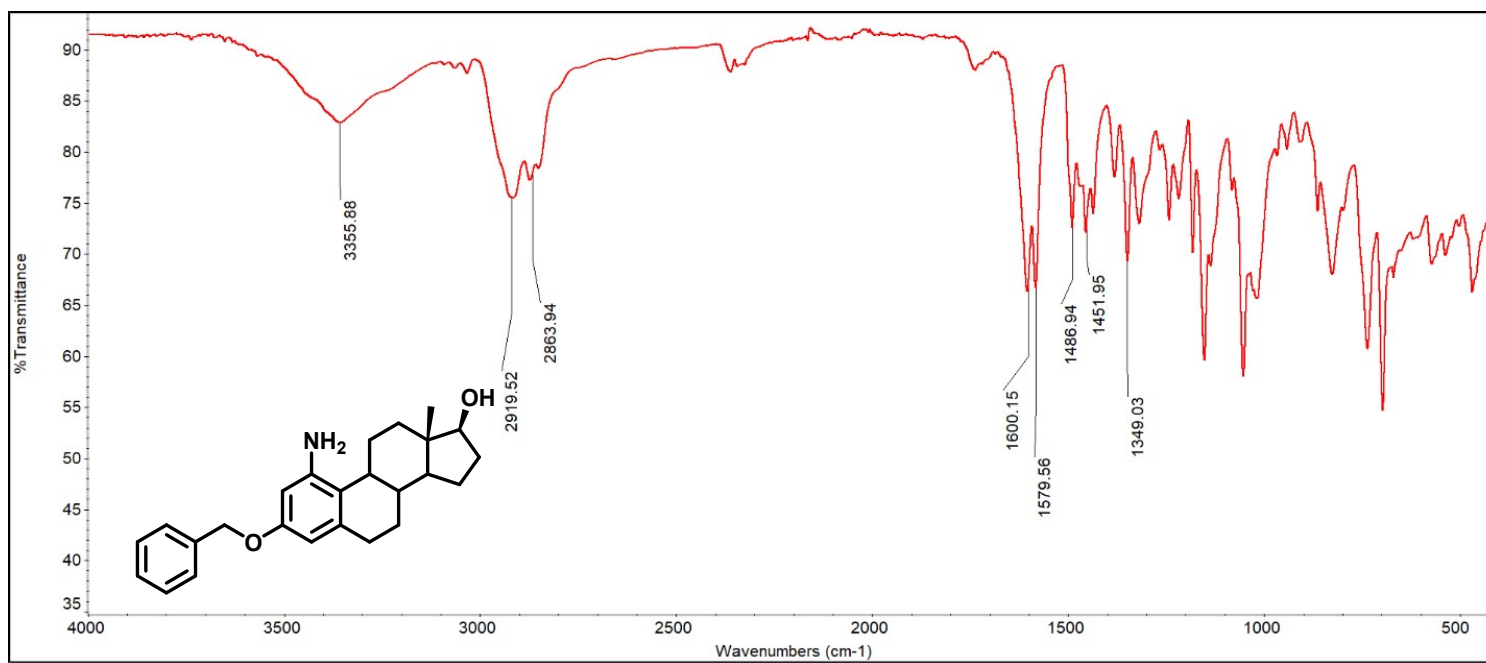


Figure S44 FTIR-spectrum of **compound 10**

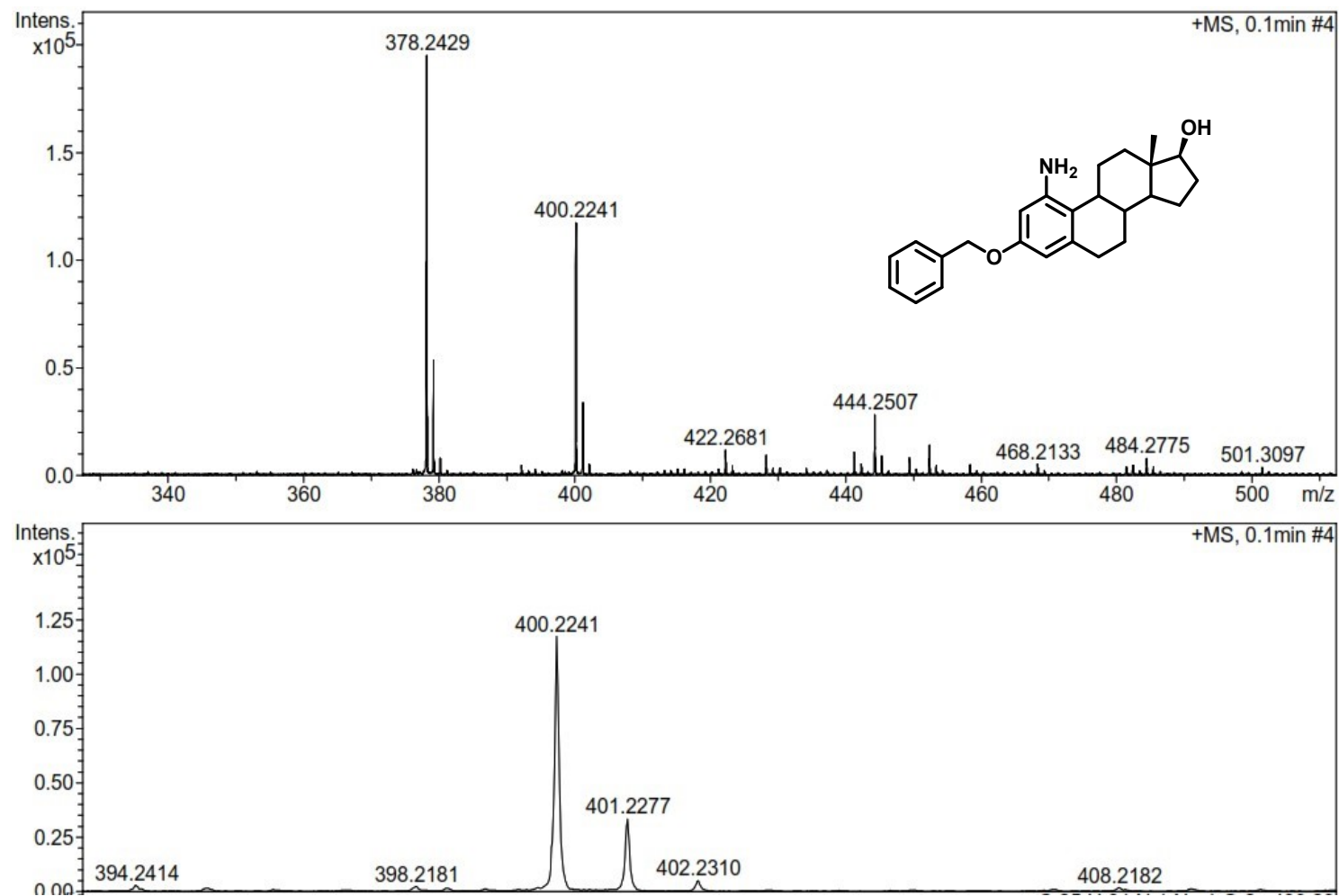


Figure S45 Mass spectrum of compound 10

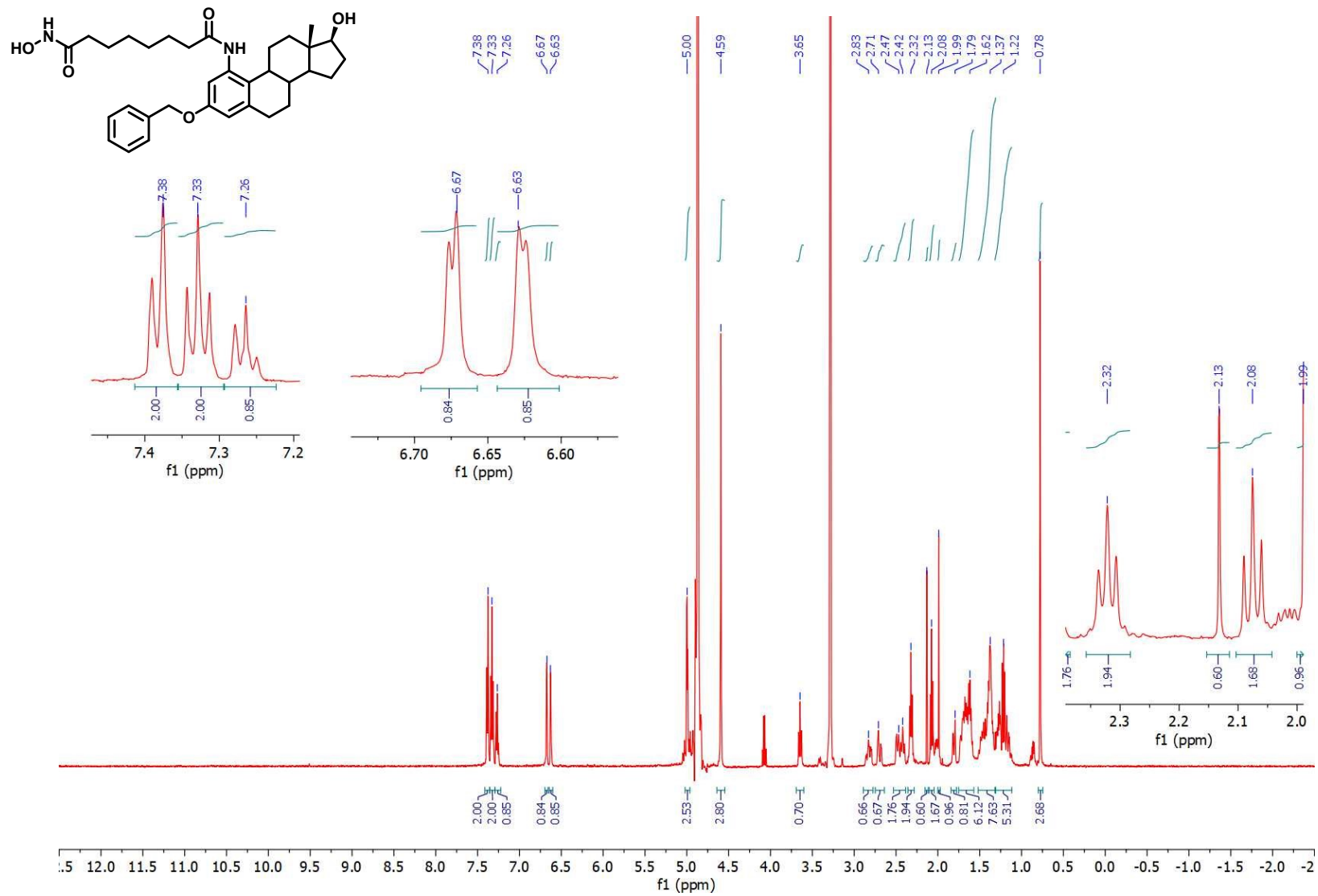


Figure S46 ¹H-NMR spectrum of compound 11

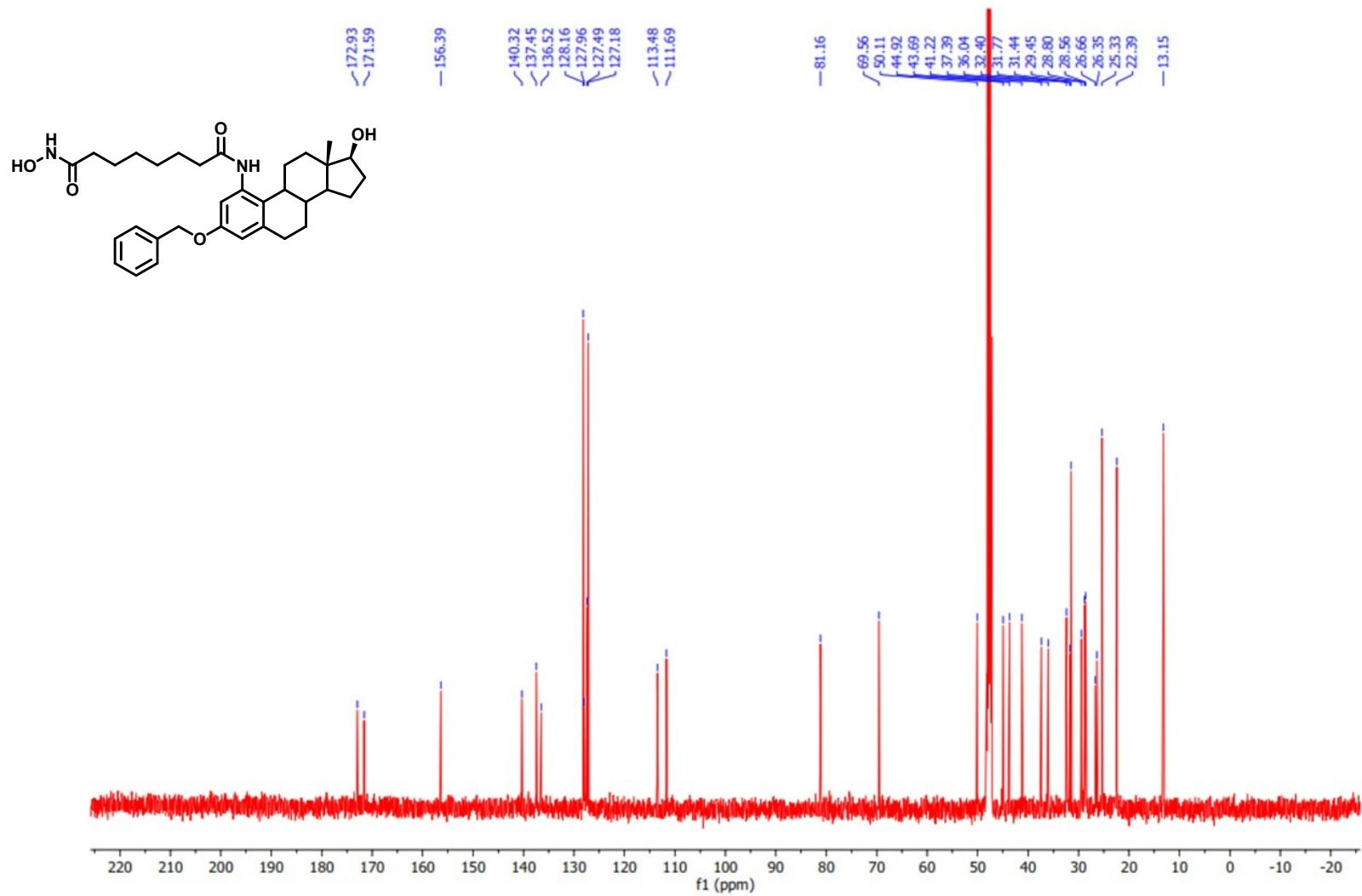


Figure S47 ¹³C-NMR spectrum of compound 11

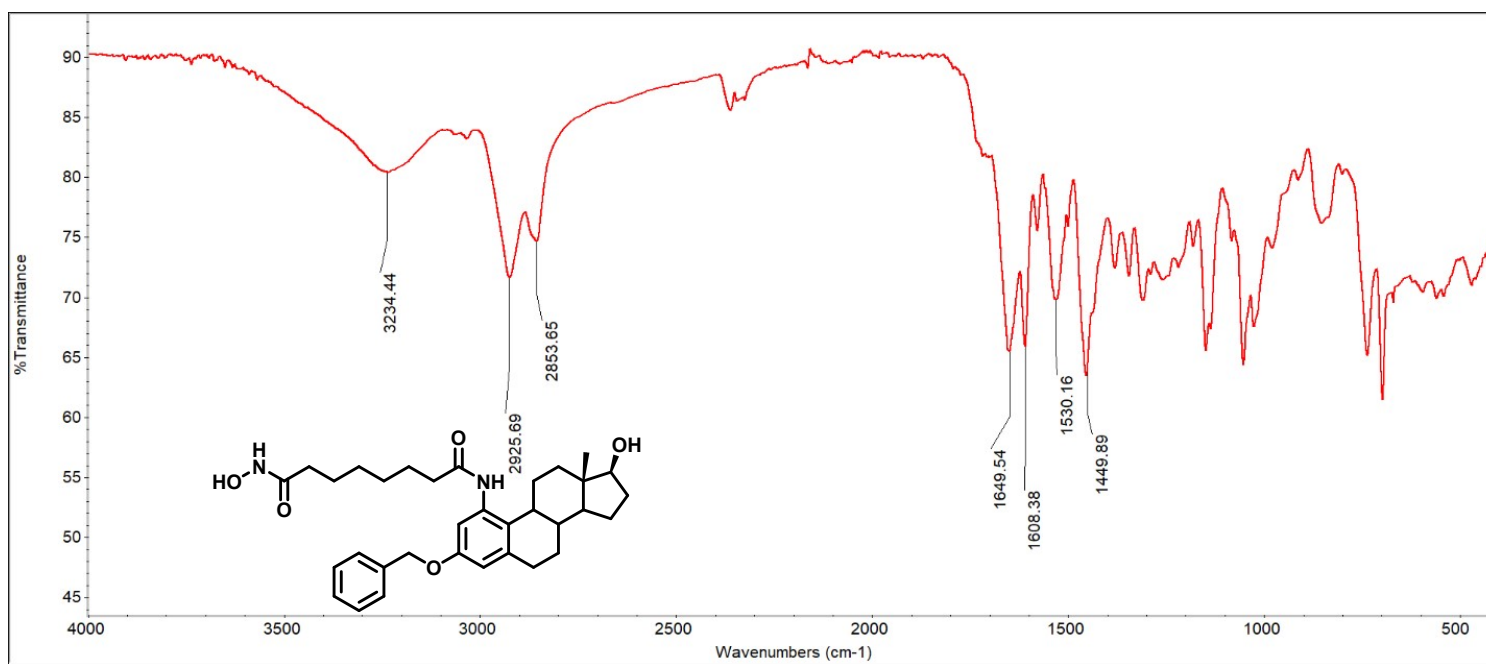


Figure S48 FTIR-spectrum of **compound 11**

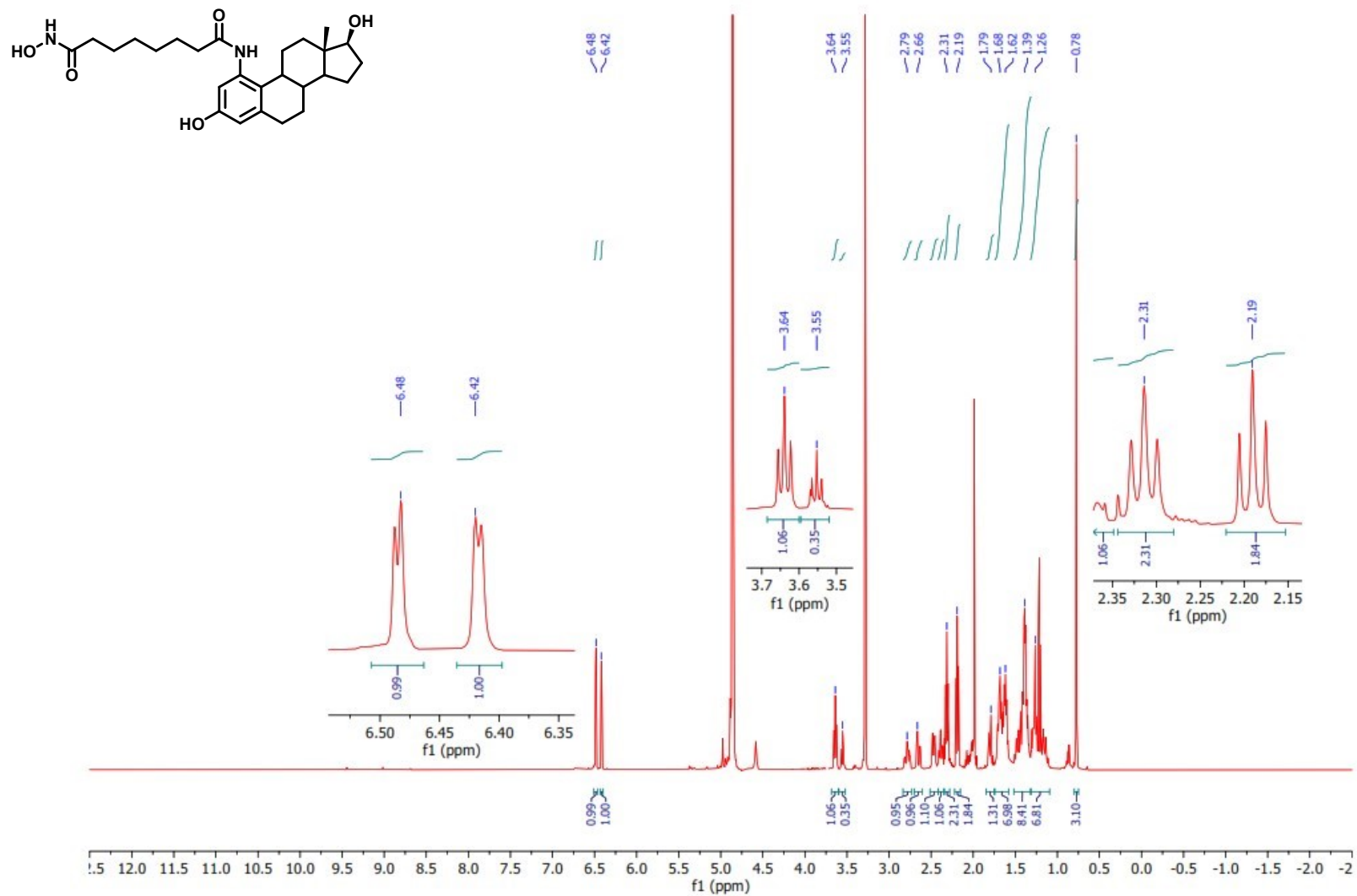


Figure S49 ¹H-NMR spectrum of 1-SEHA

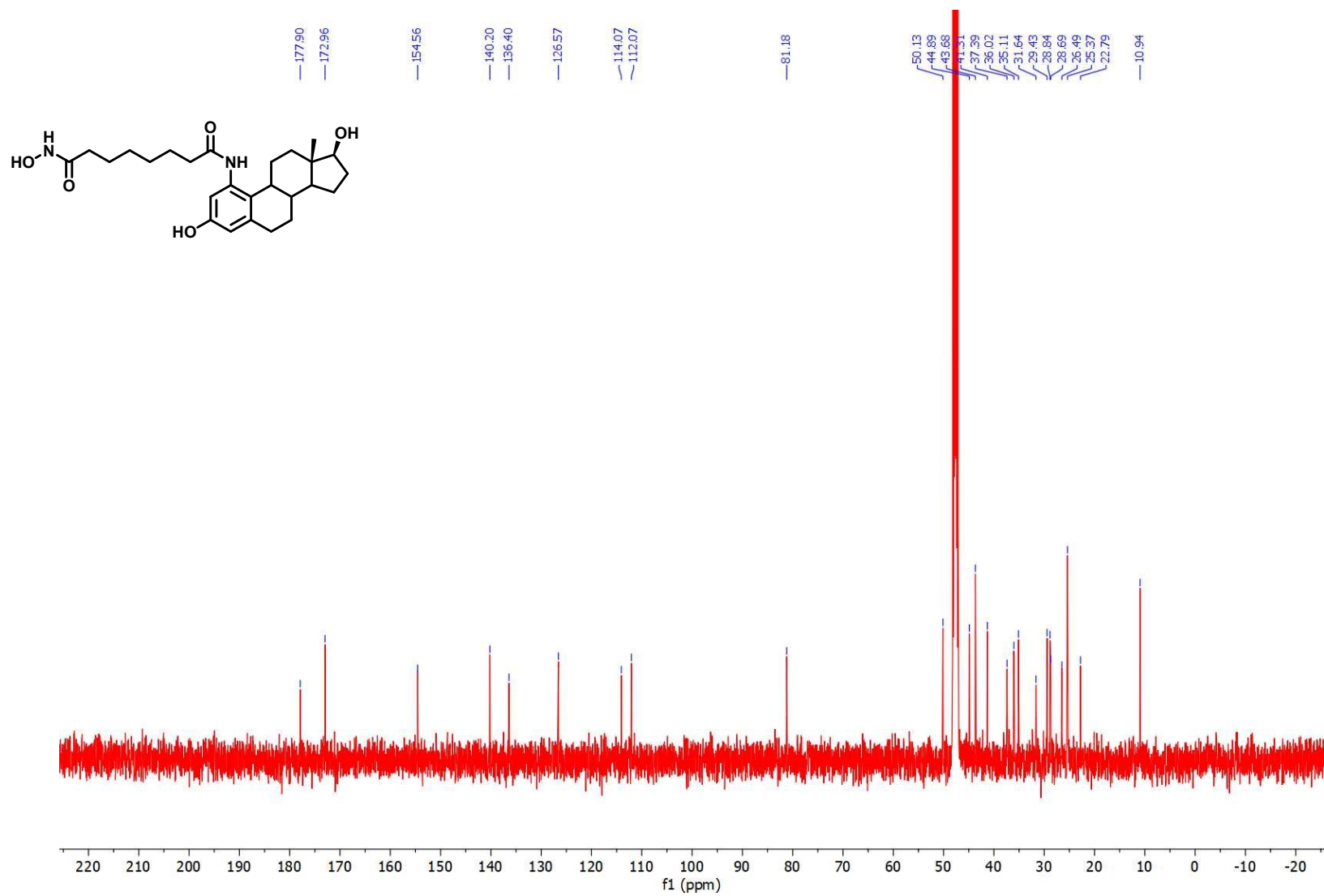


Figure S50 ¹³C-NMR spectrum of 1-SEHA

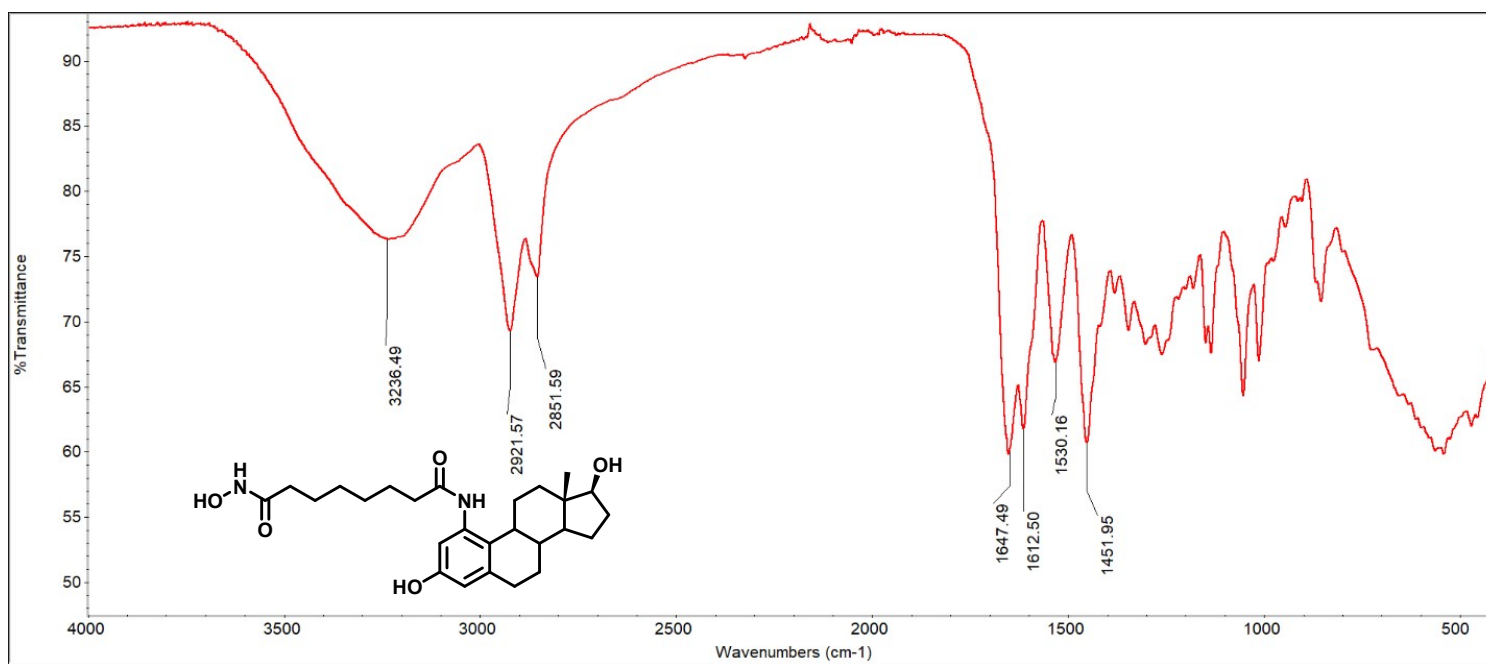


Figure S51 FTIR-spectrum of **1-SEHA**

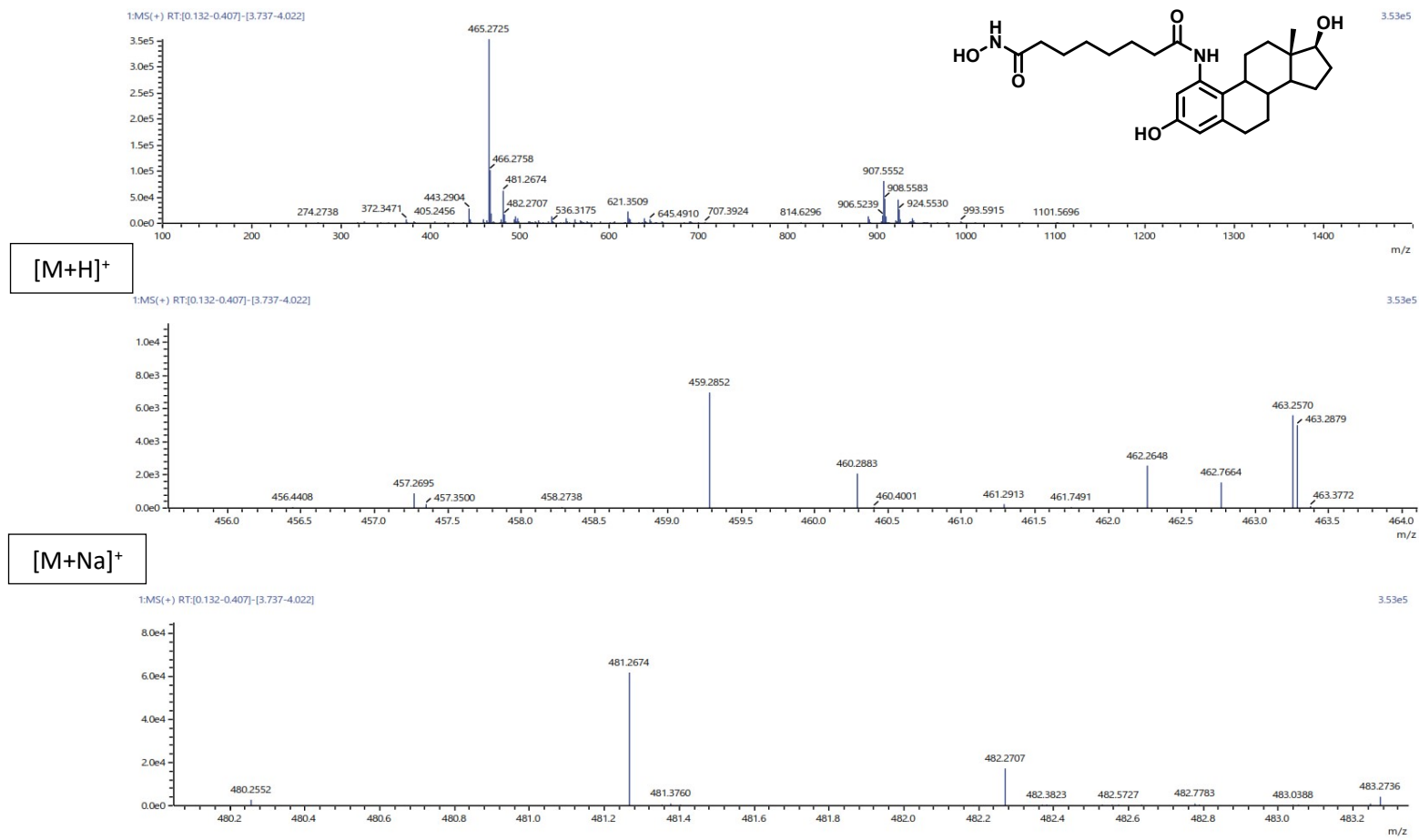


Figure S52 HRMS spectrum of 1-SEHA

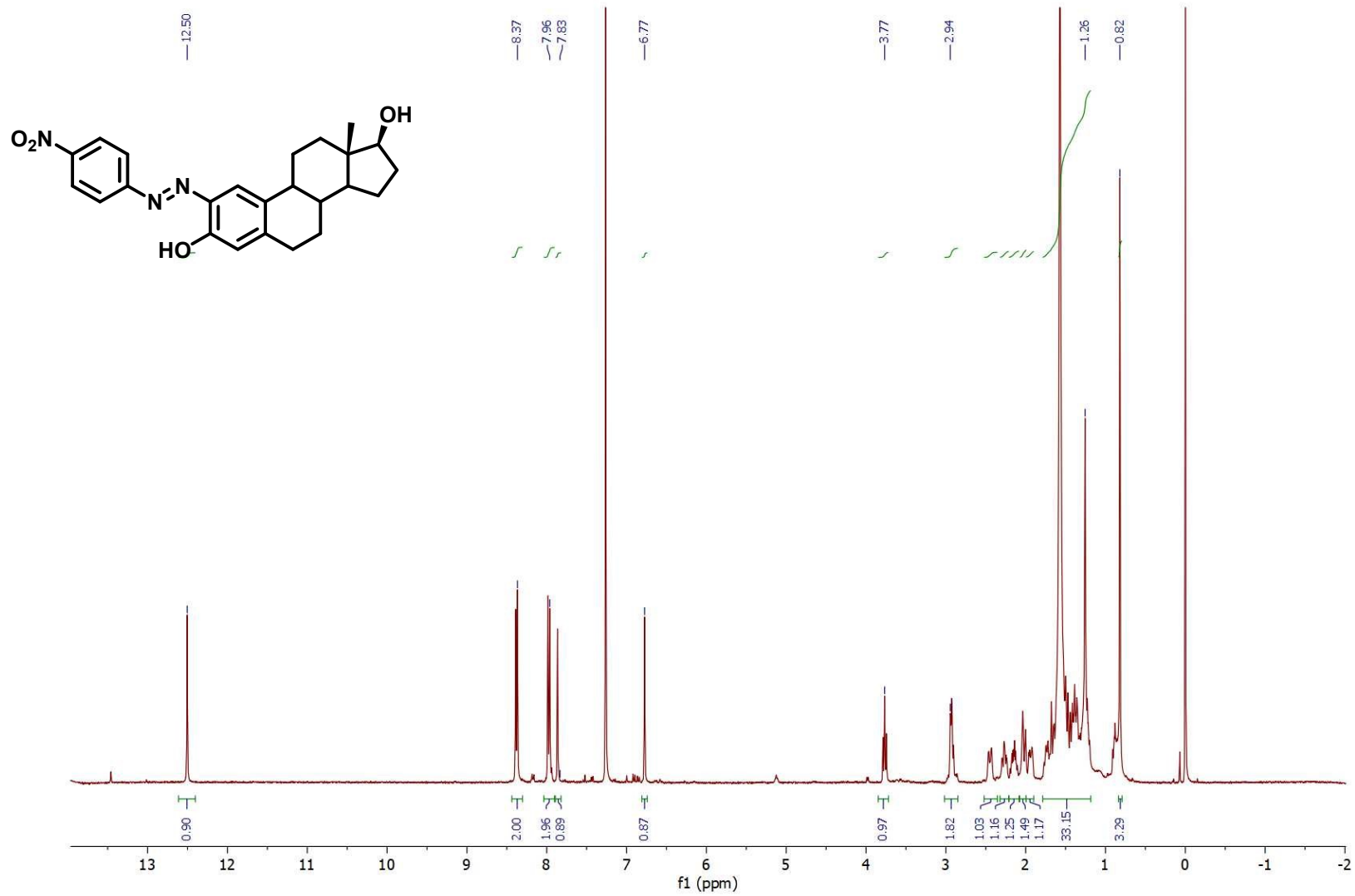


Figure S53 ¹H-NMR spectrum of compound 12a

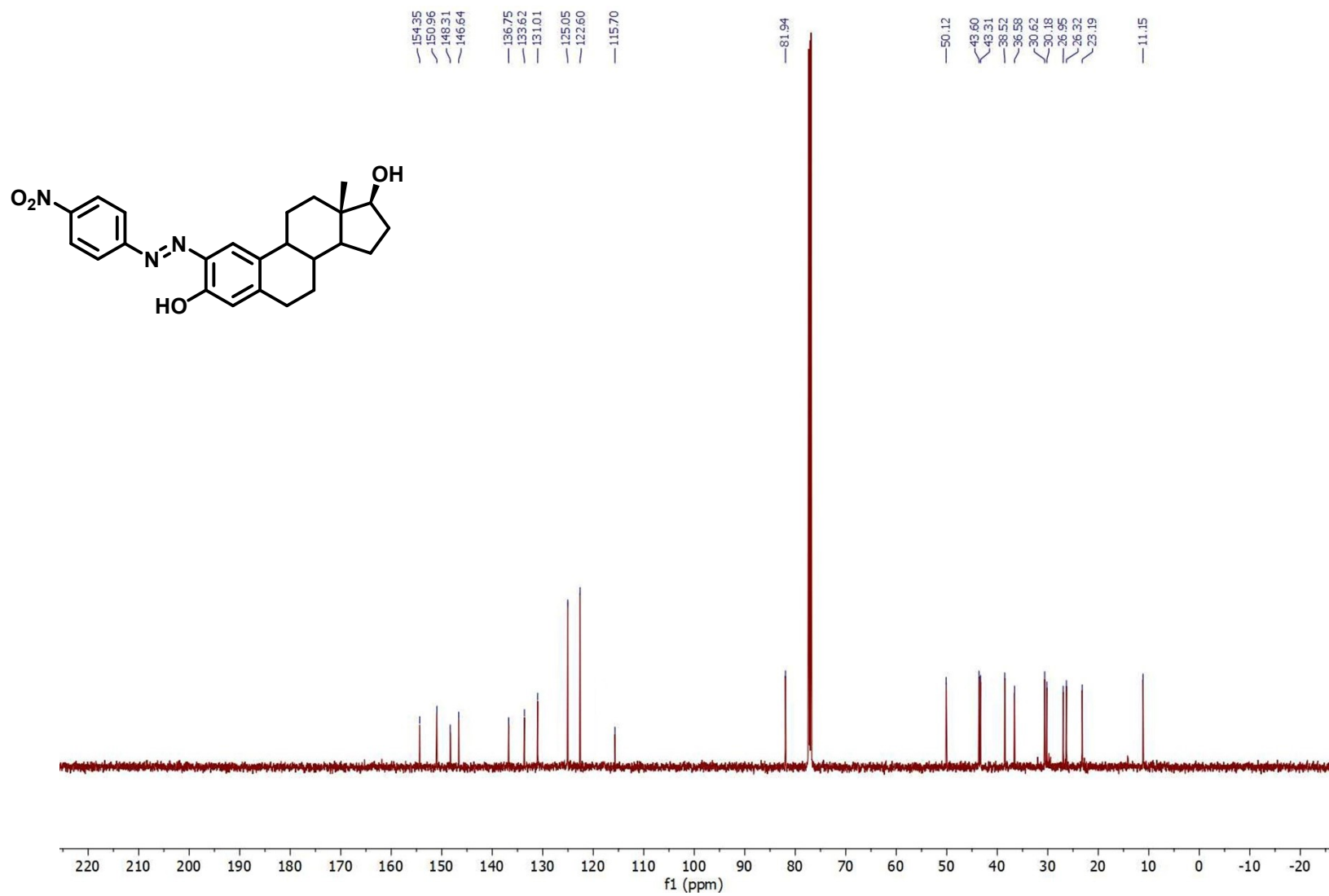


Figure S54 ¹³C-NMR spectrum of compound 12a

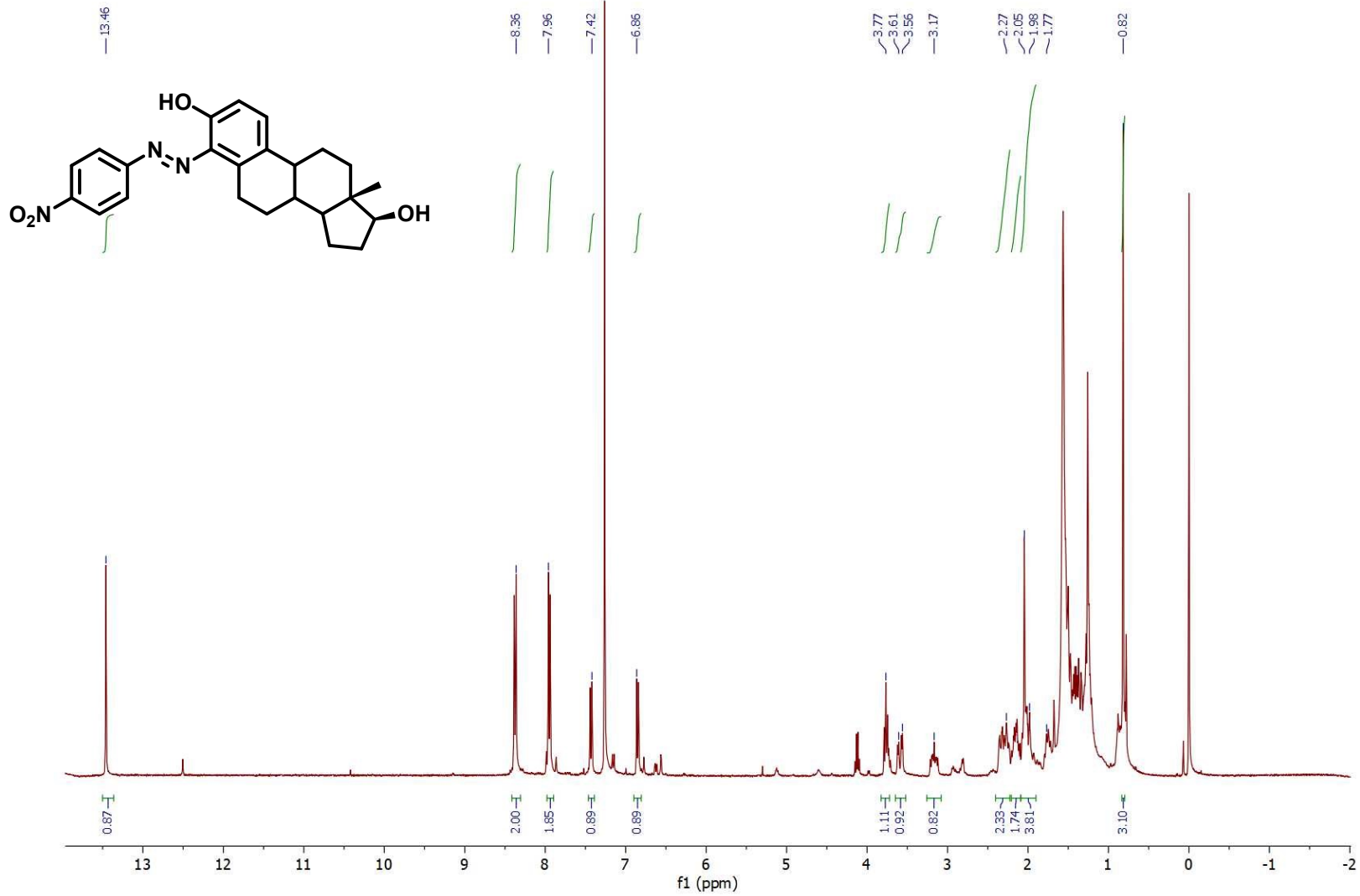


Figure S55 ¹H-NMR spectrum of compound 12b

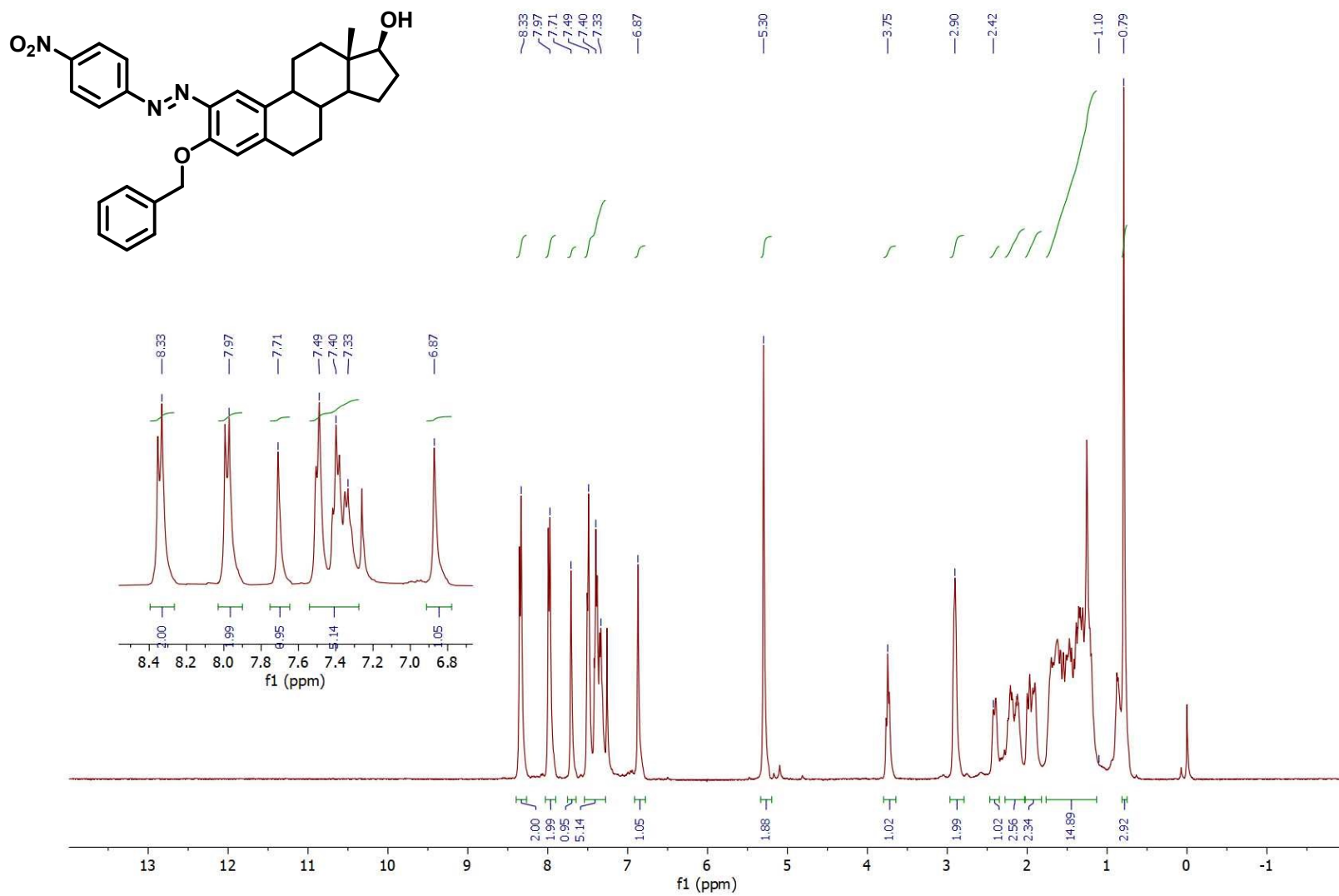


Figure S56 $^1\text{H-NMR}$ spectrum of 3-(Benzyloxy)-2-(4-nitrophenyl)diazinyloestradiol

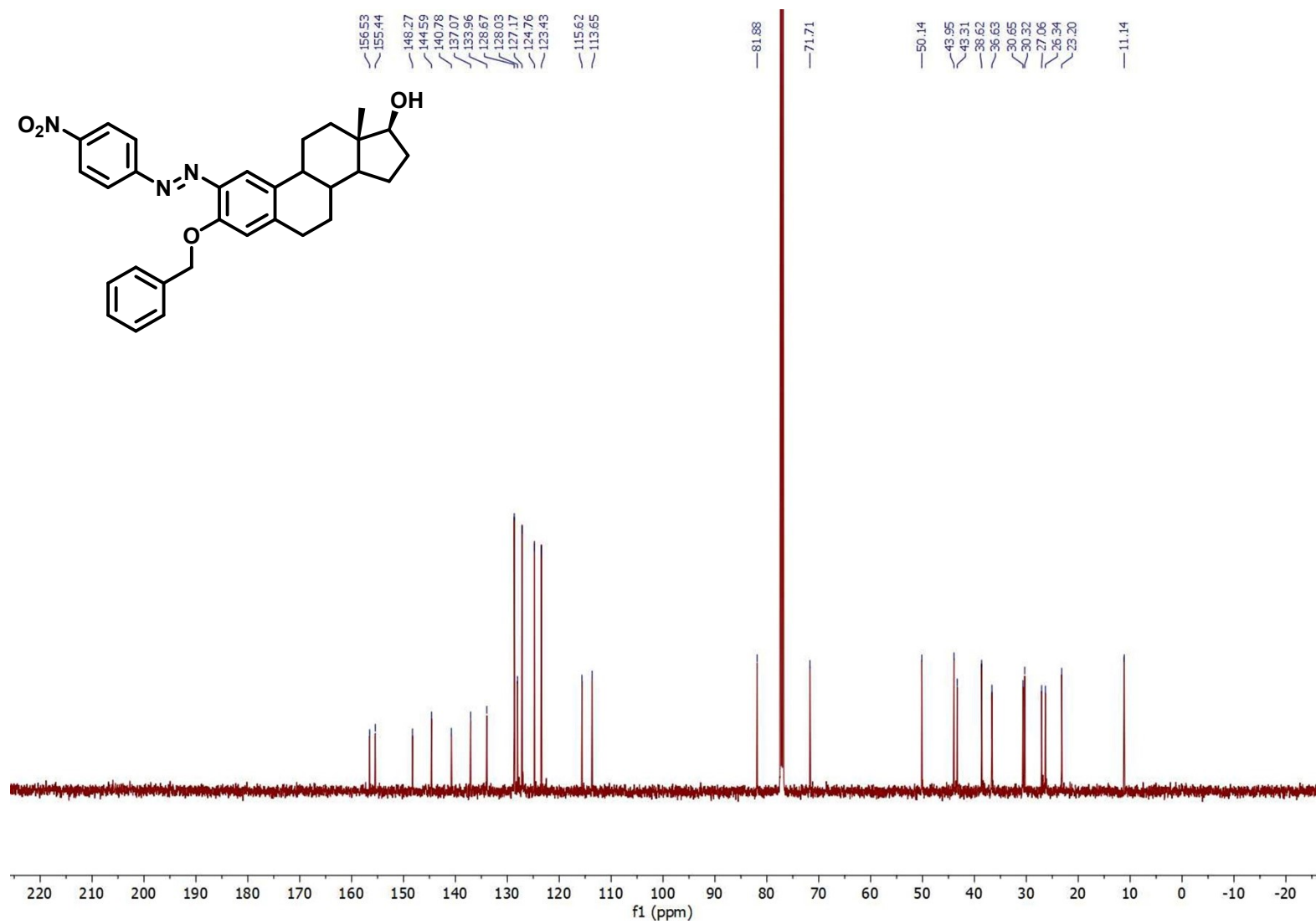


Figure S57 ¹³C-NMR spectrum of 3-(Benzyloxy)-2-(4-nitrophenyl)diazinyl)estradiol

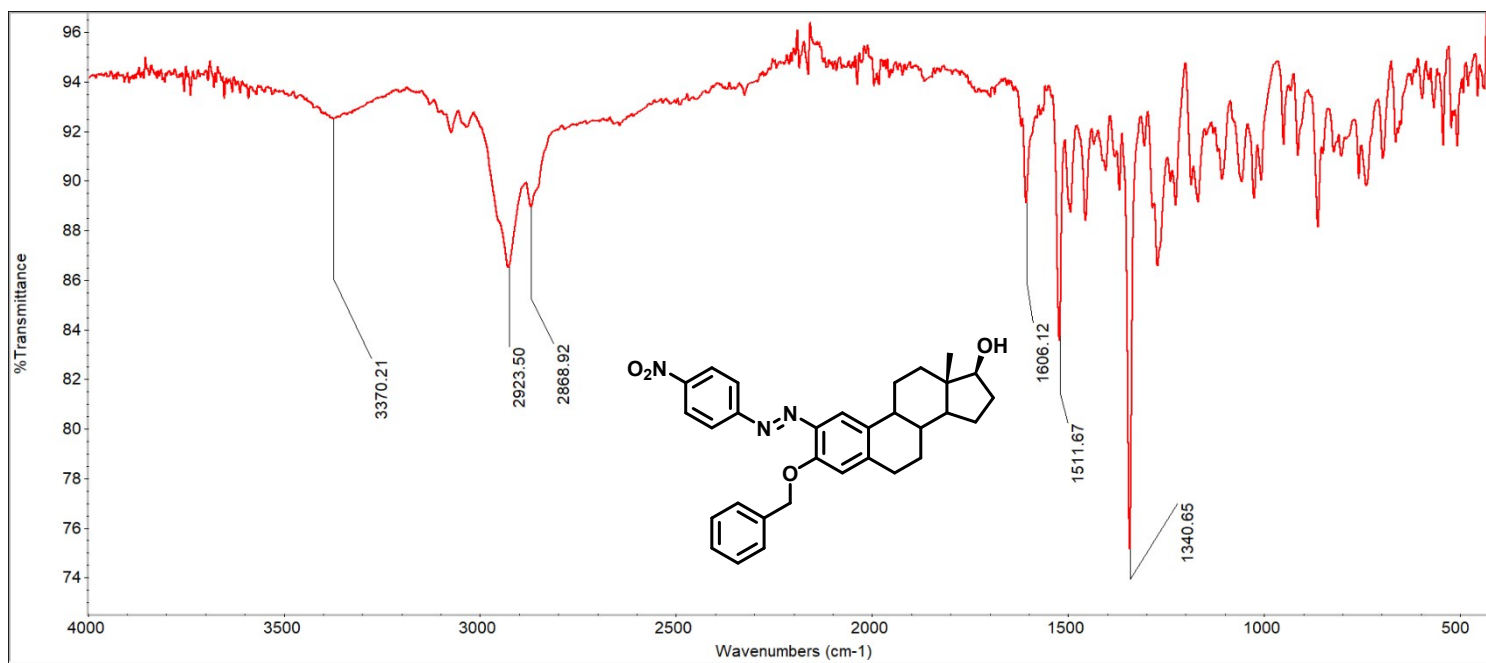


Figure S58 FTIR-spectrum of 3-(Benzyloxy)-2-(4-nitrophenyl)diazinylestrodiol

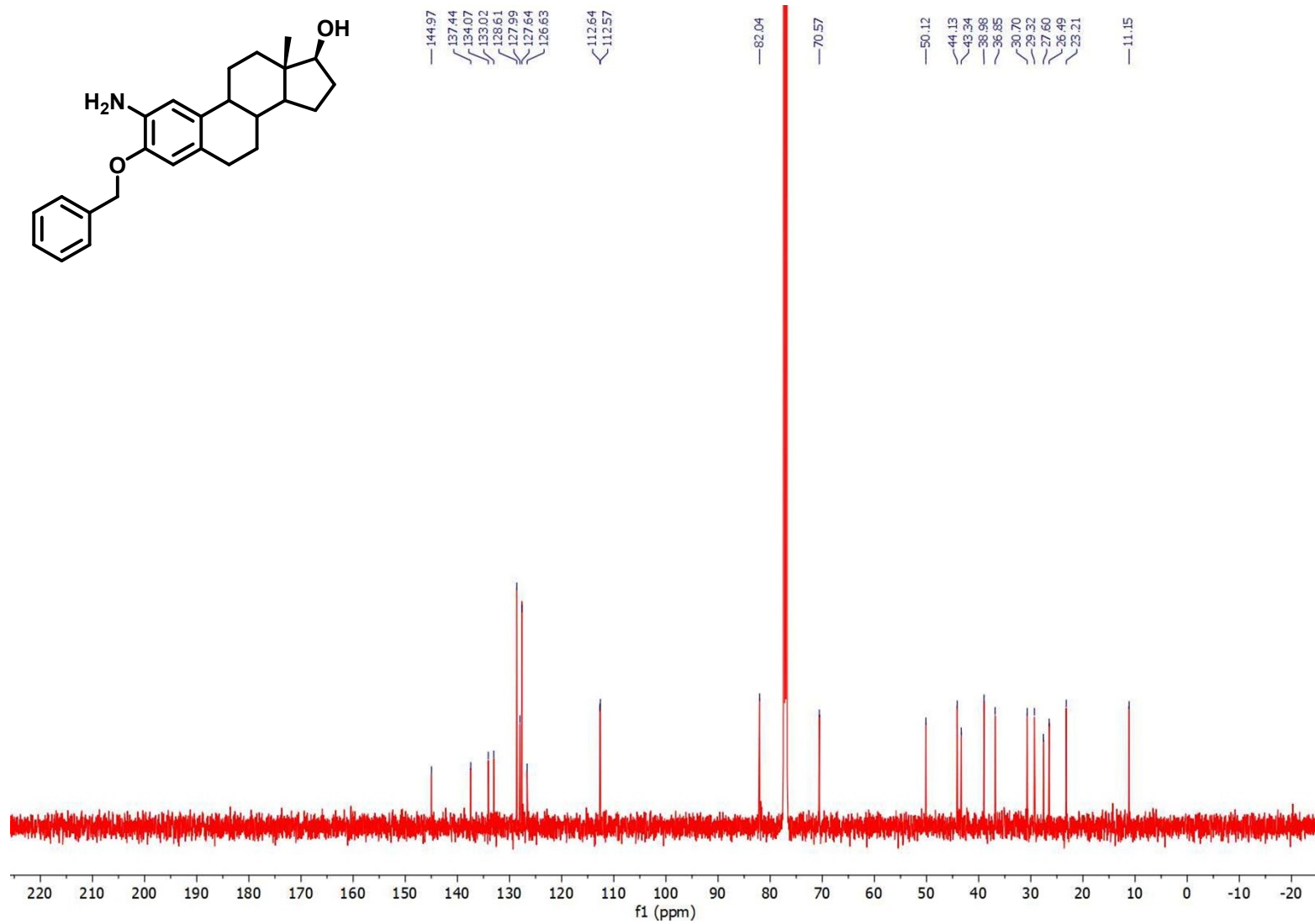


Figure S60 ¹³C-NMR spectrum of compound 13

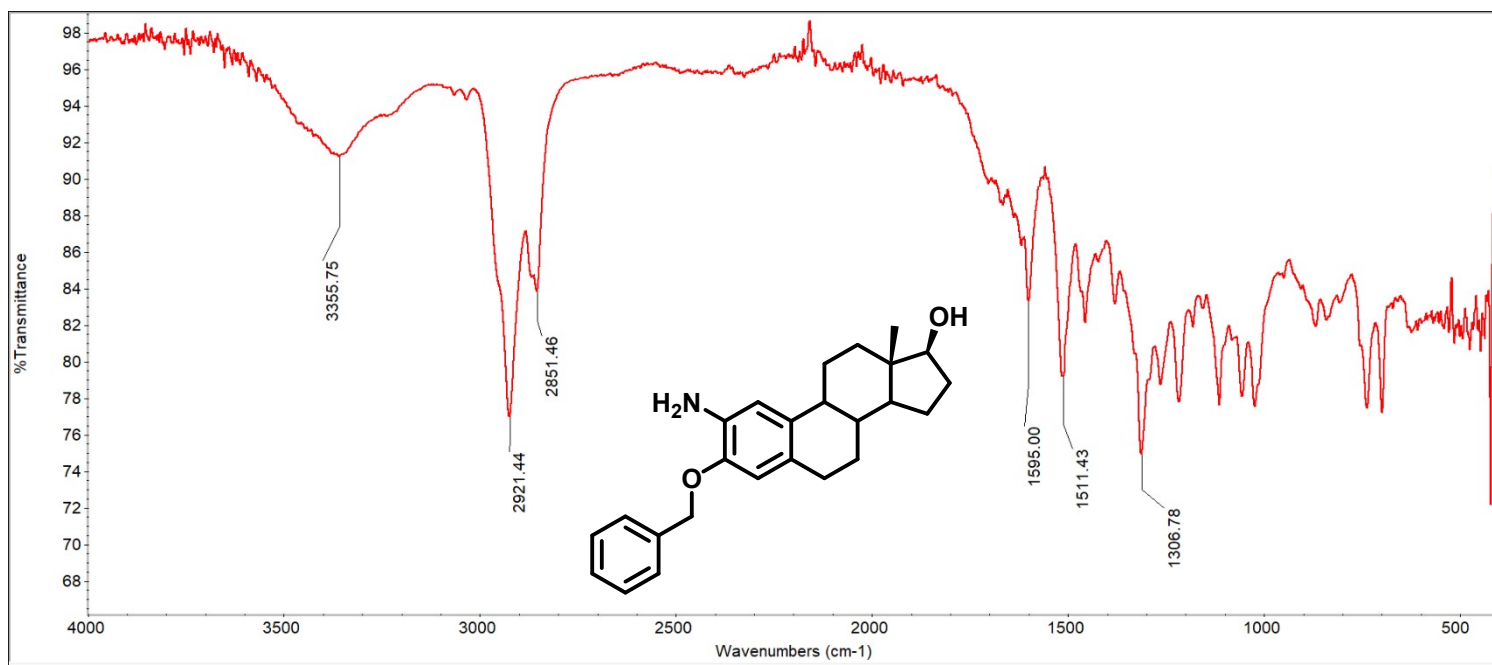


Figure S61 FTIR-spectrum of **compound 13**

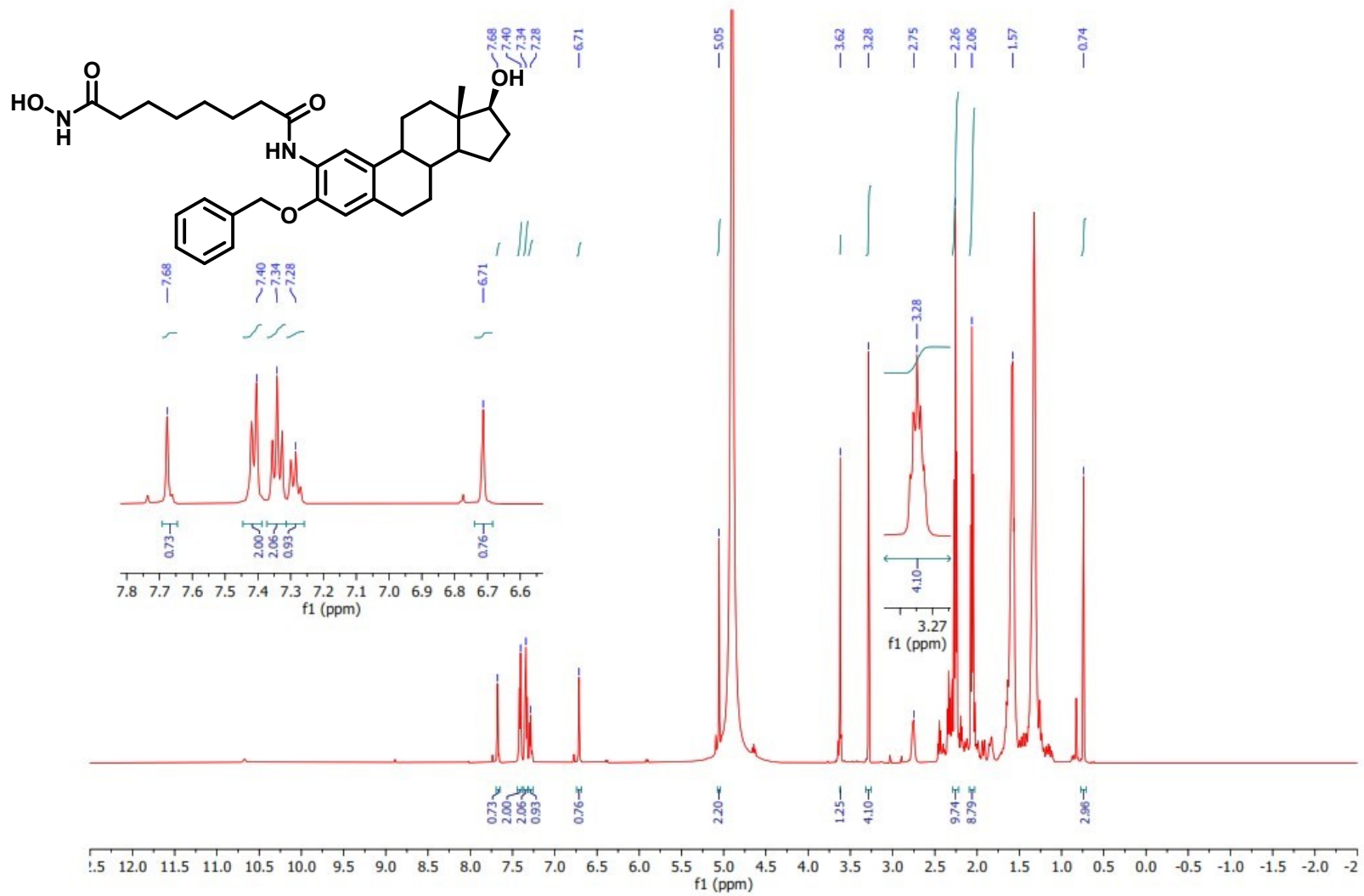


Figure S62 $^1\text{H-NMR}$ spectrum of compound 14

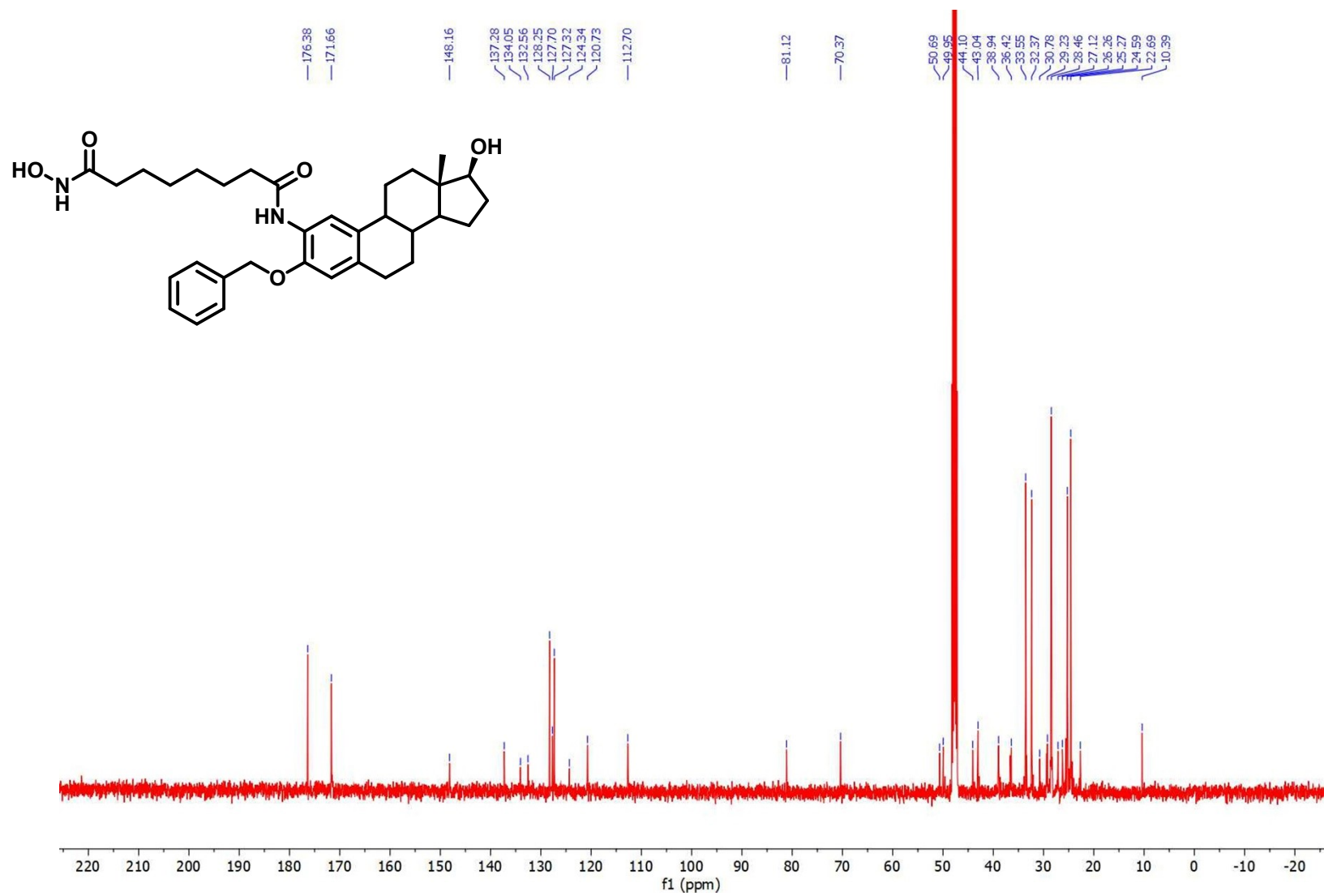


Figure S63 ¹³C-NMR spectrum of compound 14

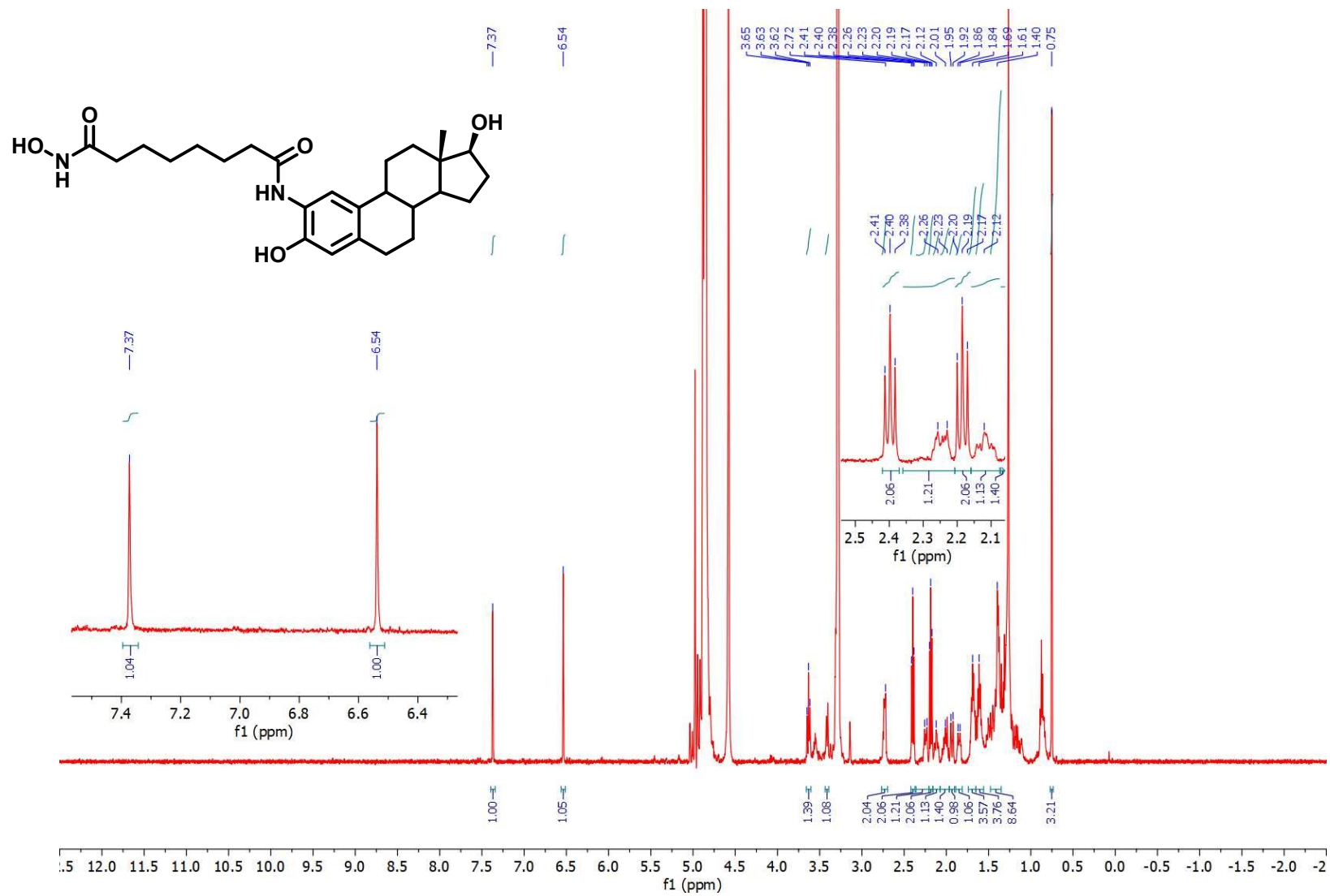


Figure S64 ¹H-NMR spectrum of 2-SEHA

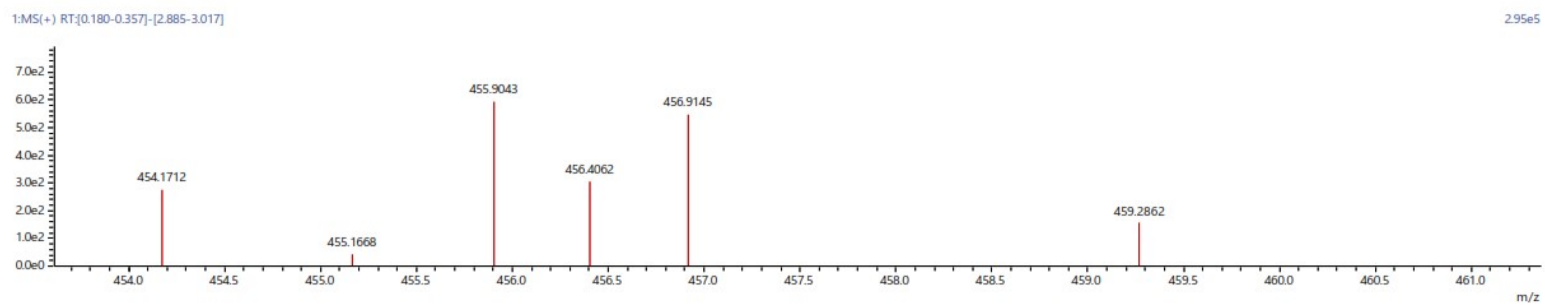
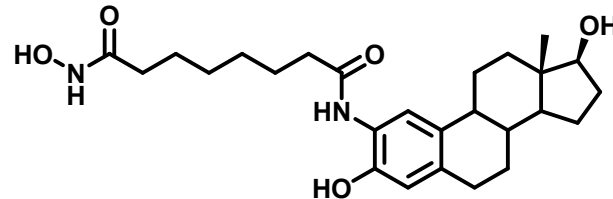
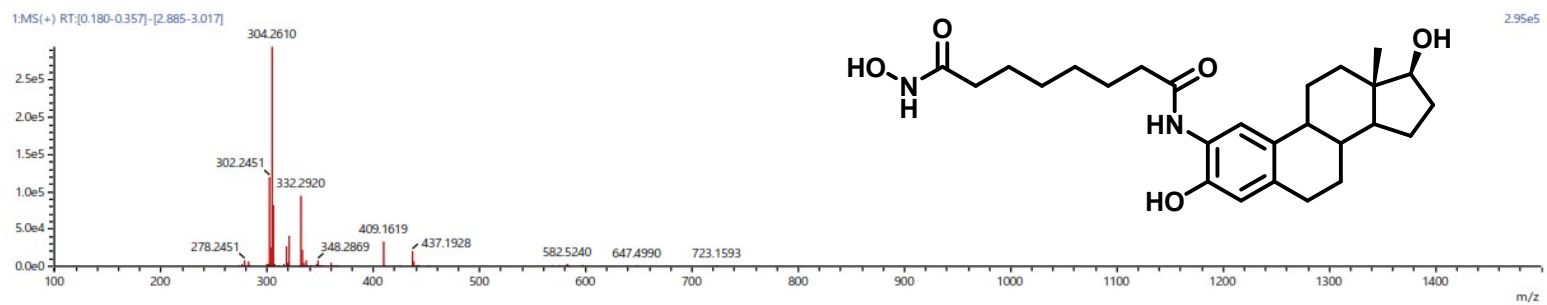
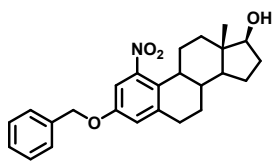
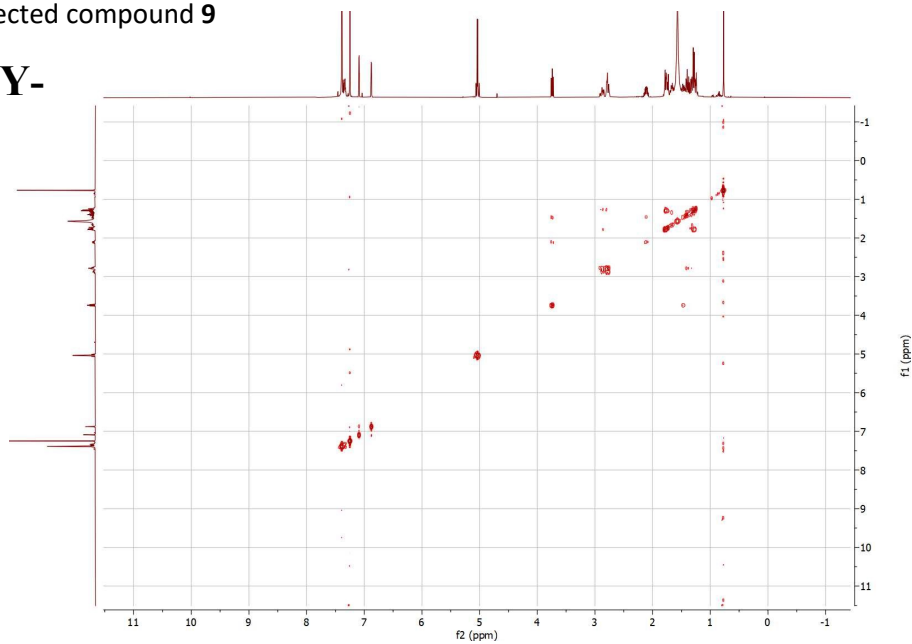


Figure S65 HRMS spectrum of 2-SEHA



Benzyl-protected compound **9**

A) COSY-



B)

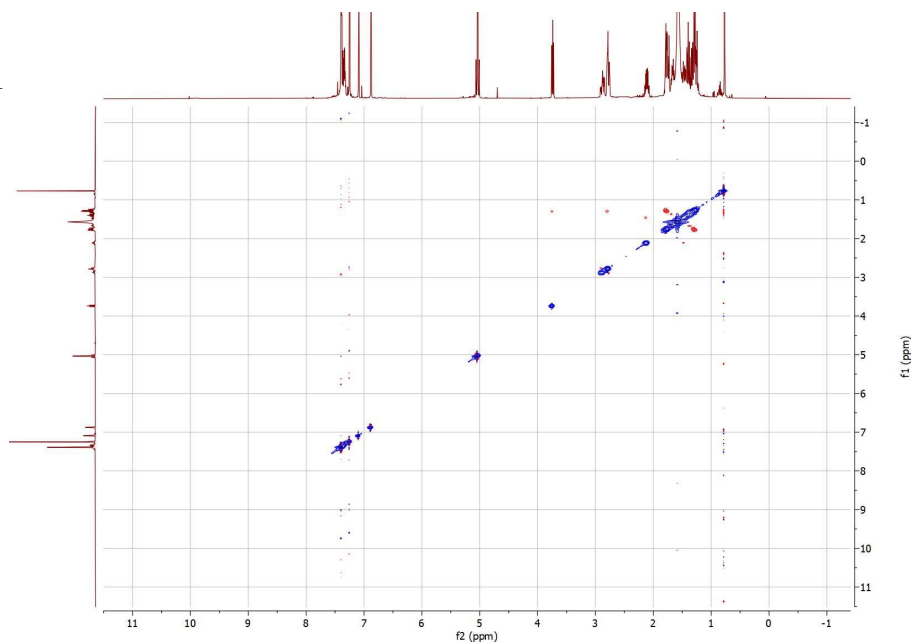
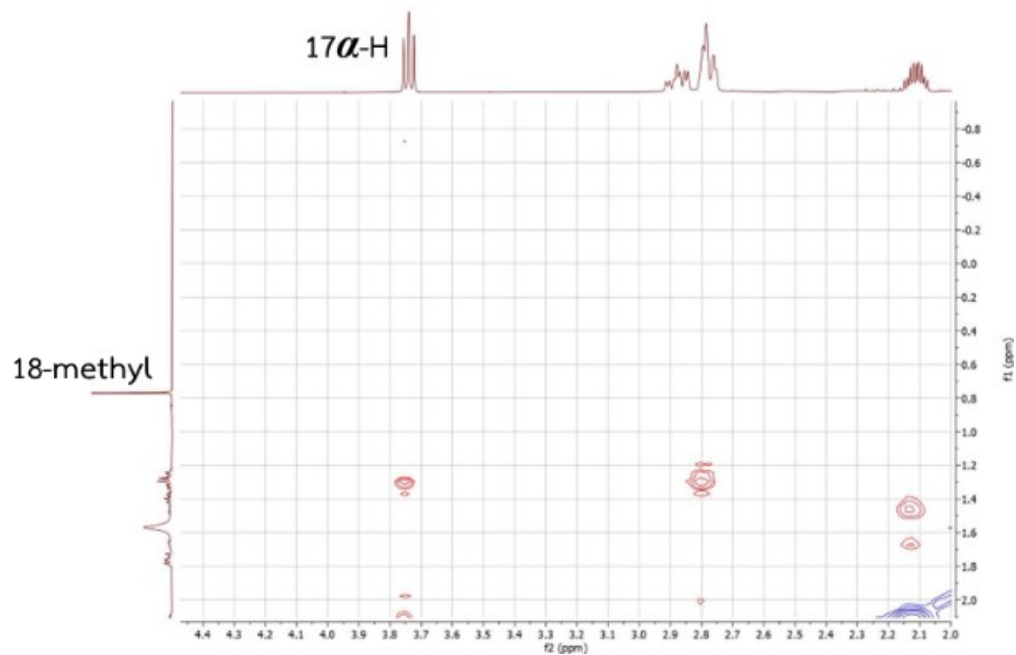


Figure S66 2D-NMR of benzyl-protected compound **9** A) COSY B) NOESY

A)



B)

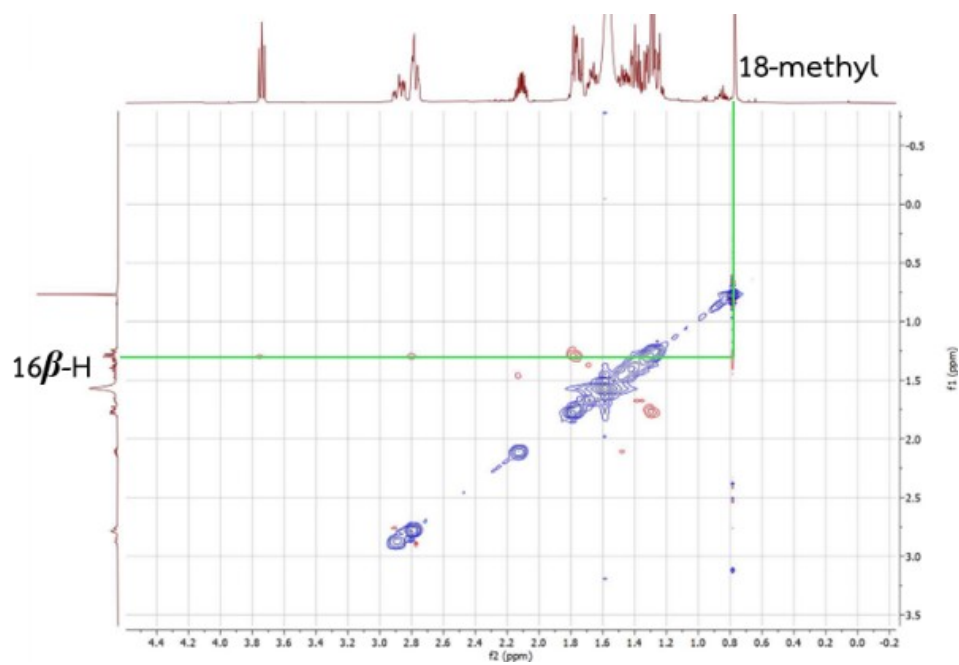


Figure S67 NOESY spectrum of benzyl-protected compound **9** showing NOE correlations between **A)** 18-methyl group and 17-H **B)** 18-methyl group with 16 β -H

Molecular Docking

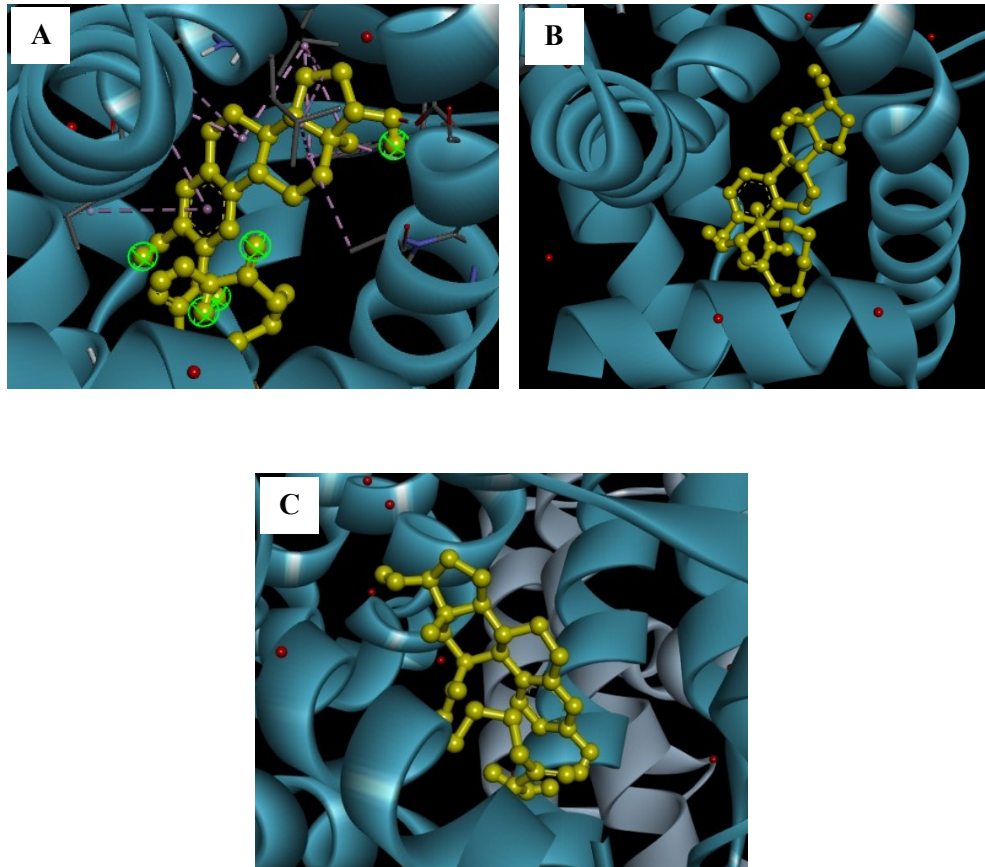


Figure S68 3D complex of A) 2-SEHA B) 4-SEHA C) 11-SEHA with ER

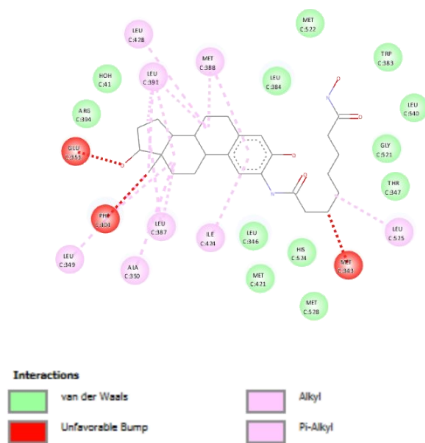
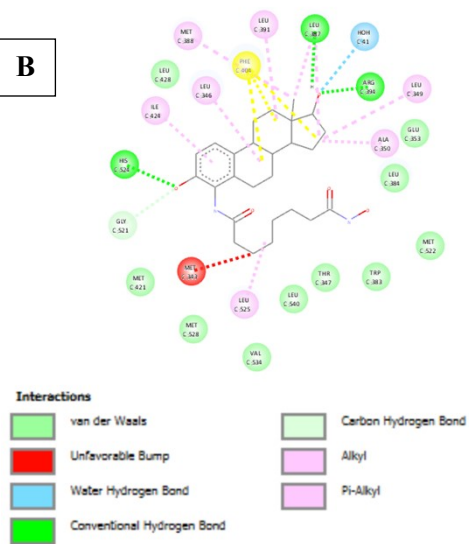
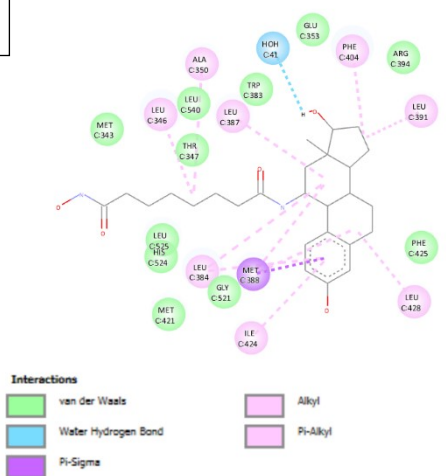
A**B****C**

Figure S69 Interaction of the ligand **A) 2-SEHA B) 4-SEHA C) 11-SEHA** with ER

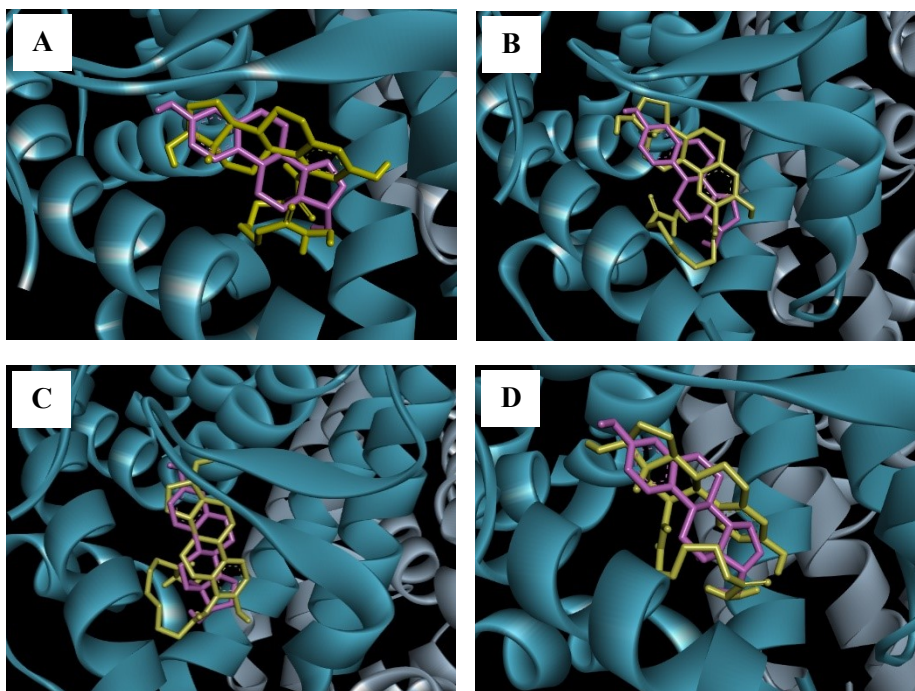


Figure S70 The orientation of target ligand (yellow structure) **A) 1-SEHA B) 2-SEHA** compared with unmodified estradiol (pink structure)

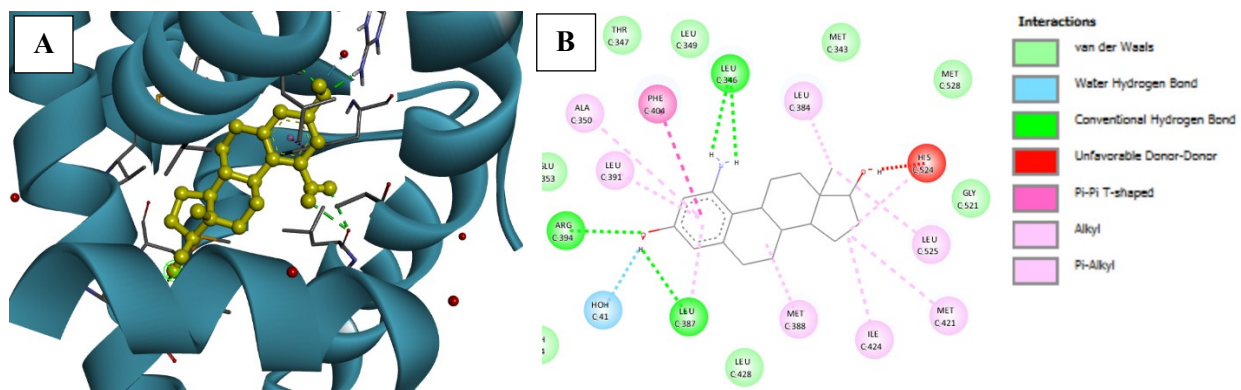


Figure S71 The orientation of target ligand **A)** 3D complex of 1-NH₂-E2 with ER **B)** the interaction of 1-NH₂-E2 with ER

Table S1 The relative binding affinity (RBA) of the ligands complex with ER

ligand	Affinity(kcal/mol)	RBA (calculated)	RBA (experiment)
estradiol	-10.6	100	100
1-NH ₂ -estradiol	-10.7	100	-

The bioactivity test

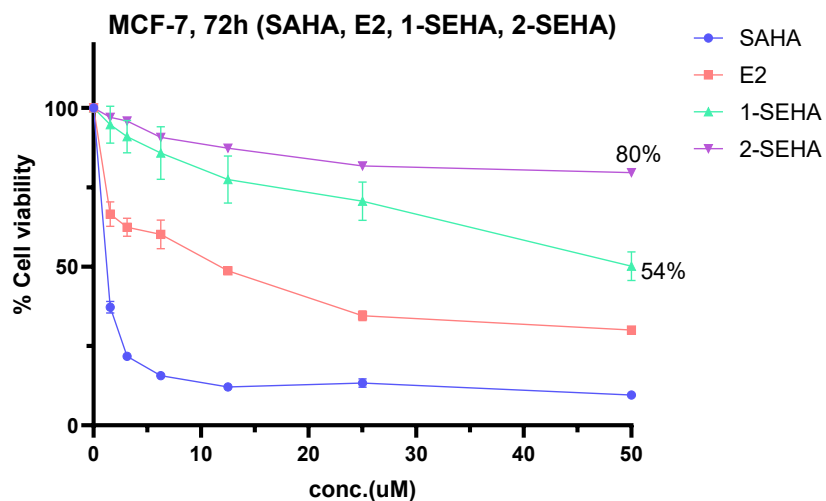


Figure S72 %cell viability of compound **SAHA** (blue), **E2** (pink), **1-SEHA** (green), **2-SEHA** (purple) against MCF-7 for 72h

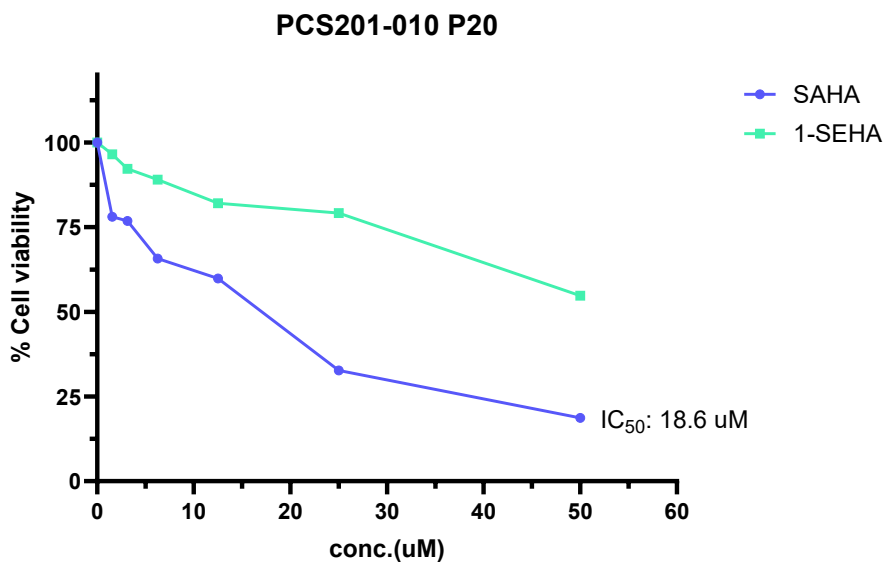
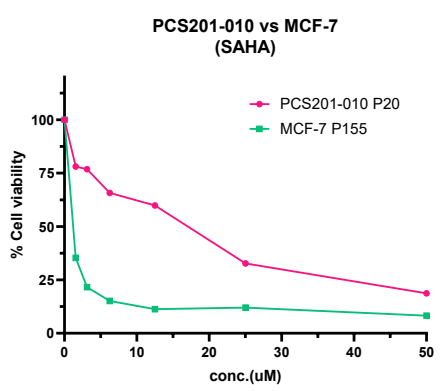
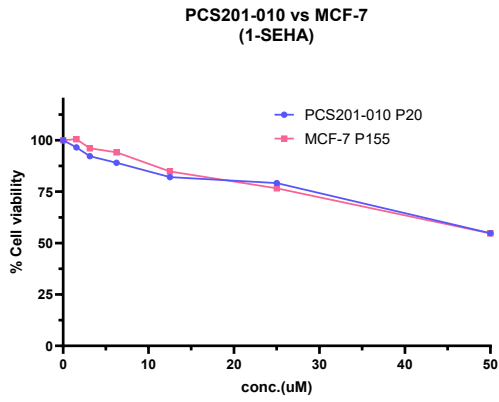


Figure S73 %cell viability of compound **SAHA** (blue) and **1-SEHA** (green) against PCS201-010 (normal cells)



A



B

Figure S74 %cell viability of PCS201-010 compared to MCF-7 (A) SAHA, (B) 1-SEHA

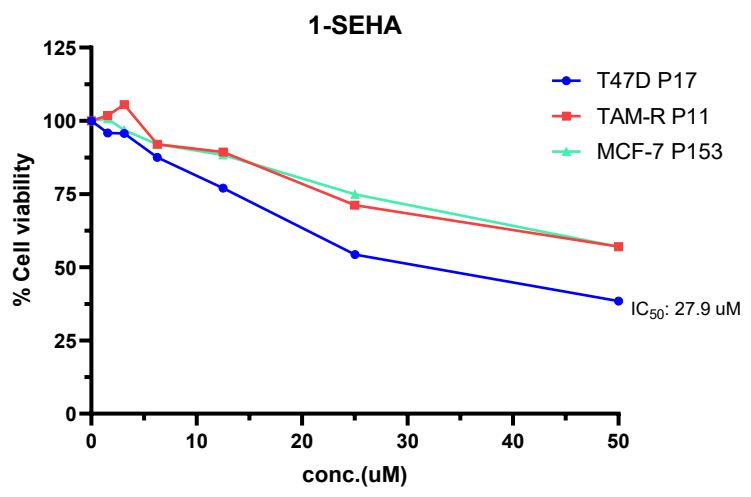


Figure S75 %cell viability of 1-SEHA against 2 cells: T47D (blue line) and TAM-R (red line) at 24h