Supplementary Information

Biomimetic Deiodination of Thyroid Hormones and Iodothyronamines – A Structure-Activity Relationship Study

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General Procedure

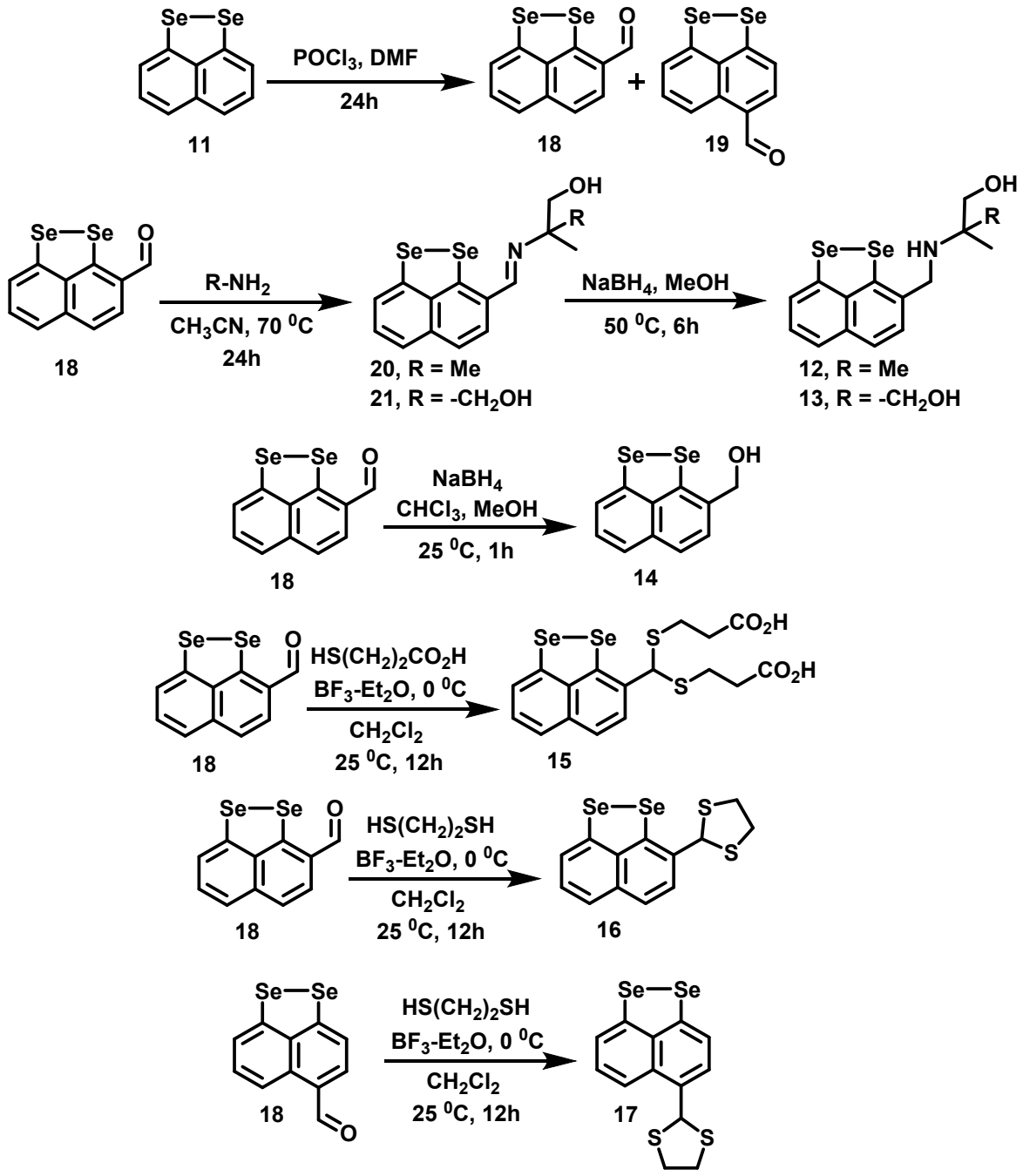
Tyramine, iodine monochloride (ICl), tri-isopropylborate, tetrabutylammonium fluoride (TBAF), borontrifluoride diethyletherate (BF_3-Et_2O), ethane dithiol, selenium powder, T4, rT3, T3, acetonitrile were obtained from Sigma-Aldrich. *n*-Butyllithium (*n*-BuLi) was purchased from Acros Chemical Co. (Belgium). Dithiothreitol (DTT) and anhydrous cupric acetate were bought from Alfa Aesar. 3,5-diodothyronine (3,5-T2) was purchased from TCI Chemicals (India) Private Limited. Trifluroacetic acid (TFA) and precoated silica gel plates were obtained from Merck. Liquid state NMR spectra were recorded in $CDCl_3$ or d_4-MeOH or d_6-DMSO as solvent. ^1H (400 MHz), ^{13}C (100.56 MHz), ^{77}Se (76.29 MHz) NMR spectra were recorded using a Bruker 400 MHz NMR spectrometer. Chemical shift values are cited with respect to $SiMe_4$ as internal (^1H and ^{13}C) and Me_2Se as external (^{77}Se) standard. Column chromatography was carried out in glass columns or in an automated flash chromatography system (Biotage) by using preloaded silica cartridges. HPLC experiments were carried out on a Waters Alliance system (Milford, MA) consisting of a 2695 separation module and a 2996 photodiode-array detector. 1.7 mL HPLC sample vials were used to perform the deiodinase assays and a built in auto-sampler was used for sample injection. The HPLC system was controlled by EMPOWER software (Waters corporation, Milford, MA). Single crystal X-ray diffraction data were obtained by Bruker Kappa Apex II X-ray diffractometer using a CCD detector.

Table S01. The initial rates of deiodination of T4, T3, T3AM, 3,5-T2 and 3,5-T2AM by compounds **3** and **5-10**.

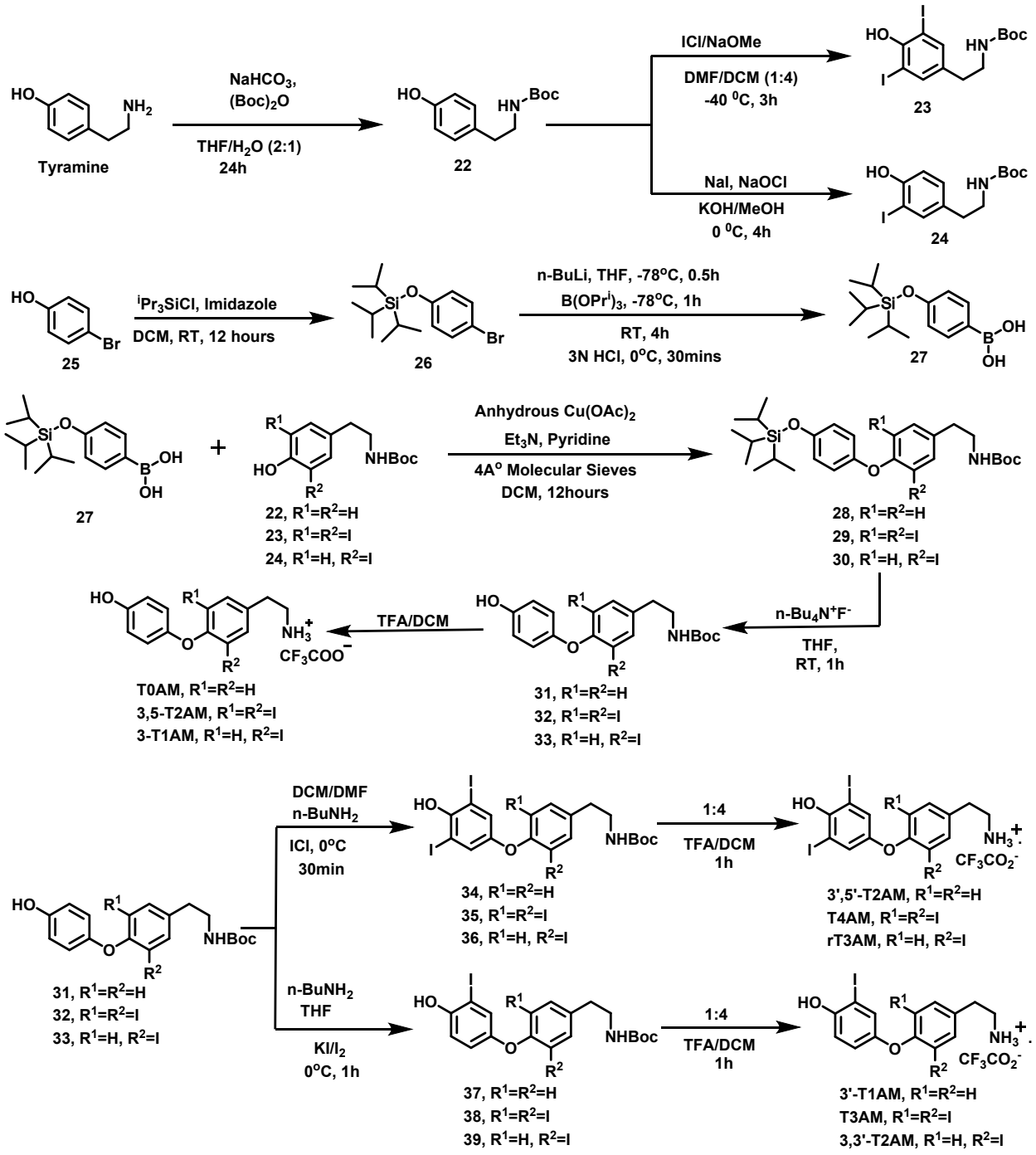
compounds	Initial rates ($\times 10^{-2}$ μM/min)				
	T4	T3	T3AM	3,5-T2	3,5-T2AM
3	38.1 ± 0.9	127.9 ± 4.7	12.0 ± 1.4	54.6 ± 1.6	16.1 ± 0.2
5	97.4 ± 5.2	144.1 ± 5.5	27.9 ± 1.8	170.6 ± 1.5	17.2 ± 0.6
6	70.7 ± 2.5	158.4 ± 4.1	20.4 ± 0.1	141.9 ± 3.0	16.9 ± 0.3
7	70.5 ± 3.0	194.3 ± 6.3	29.1 ± 1.9	119.3 ± 0.9	29.4 ± 0.5
8	117.4 ± 8.3	296.7 ± 3.6	81.1 ± 2.1	165.0 ± 4.4	42.0 ± 0.7
9	83.5 ± 3.1	226.3 ± 12.2	28.5 ± 1.5	158.7 ± 2.0	25.0 ± 0.4
10	79.8 ± 2.0	203.6 ± 4.3	21.6 ± 0.1	142.2 ± 1.0	20.7 ± 0.8

Table S02. The initial rates of deiodination of T3AM and 3,5-T2AM by compound **9** at different pH.

Substrate	Initial rate (μM/min)				
	pH 7.0	pH 8.0	pH 9.0	pH 10.0	pH 11.0
T3AM	0.28 ± 0.015	0.33 ± 0.014	0.39 ± 0.010	0.62 ± 0.010	0.92 ± 0.020
3,5-T2AM	0.25 ± 0.004	1.29 ± 0.050	1.72 ± 0.020	2.01 ± 0.115	2.23 ± 0.092



Scheme S01. Synthesis of **12**-**17**.



Scheme S02. Synthesis of Iodothyronamines.

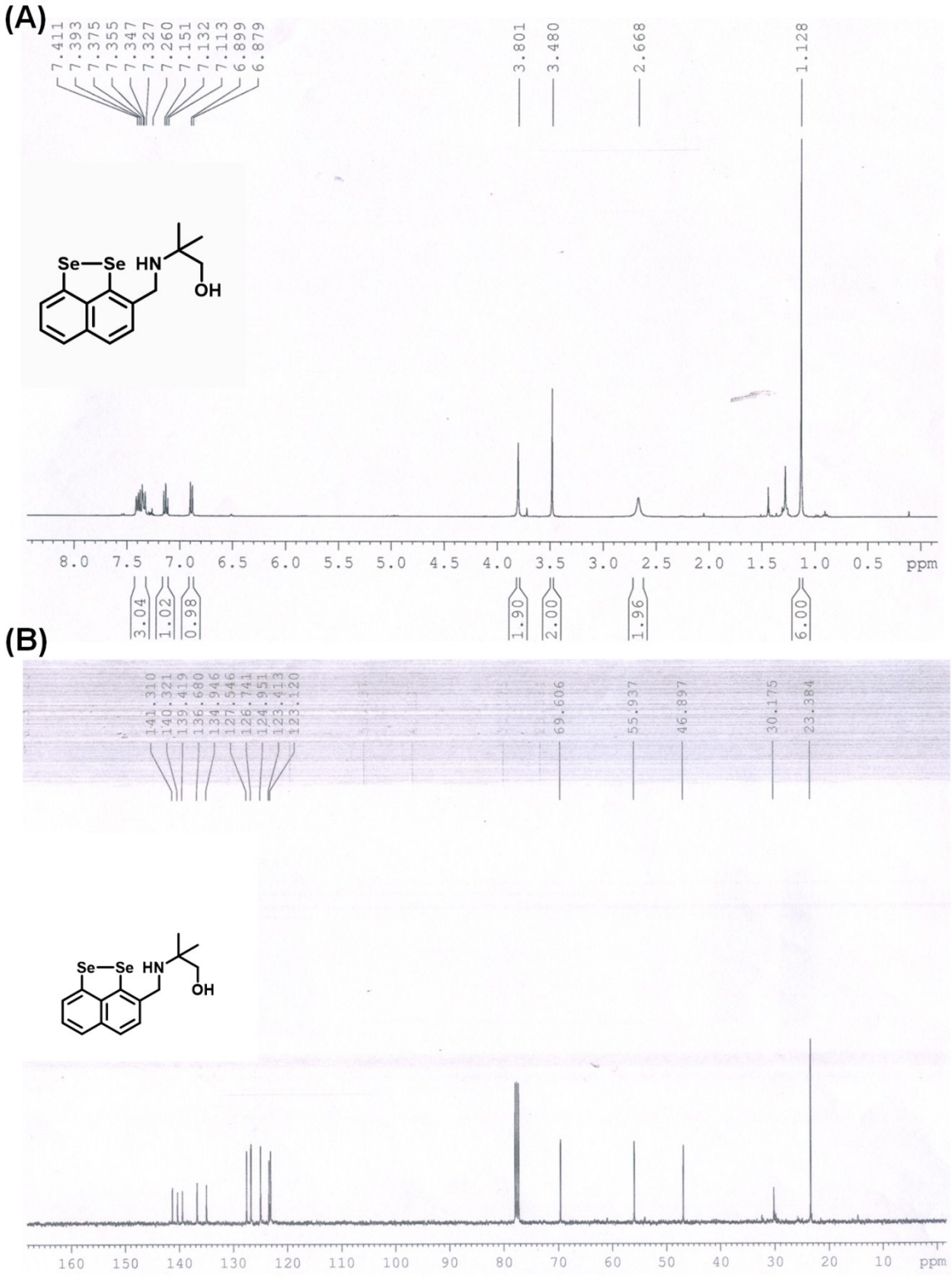


Figure S01. ^{1}H (A) and ^{13}C (B) NMR spectra of **12** in $CDCl_3$.

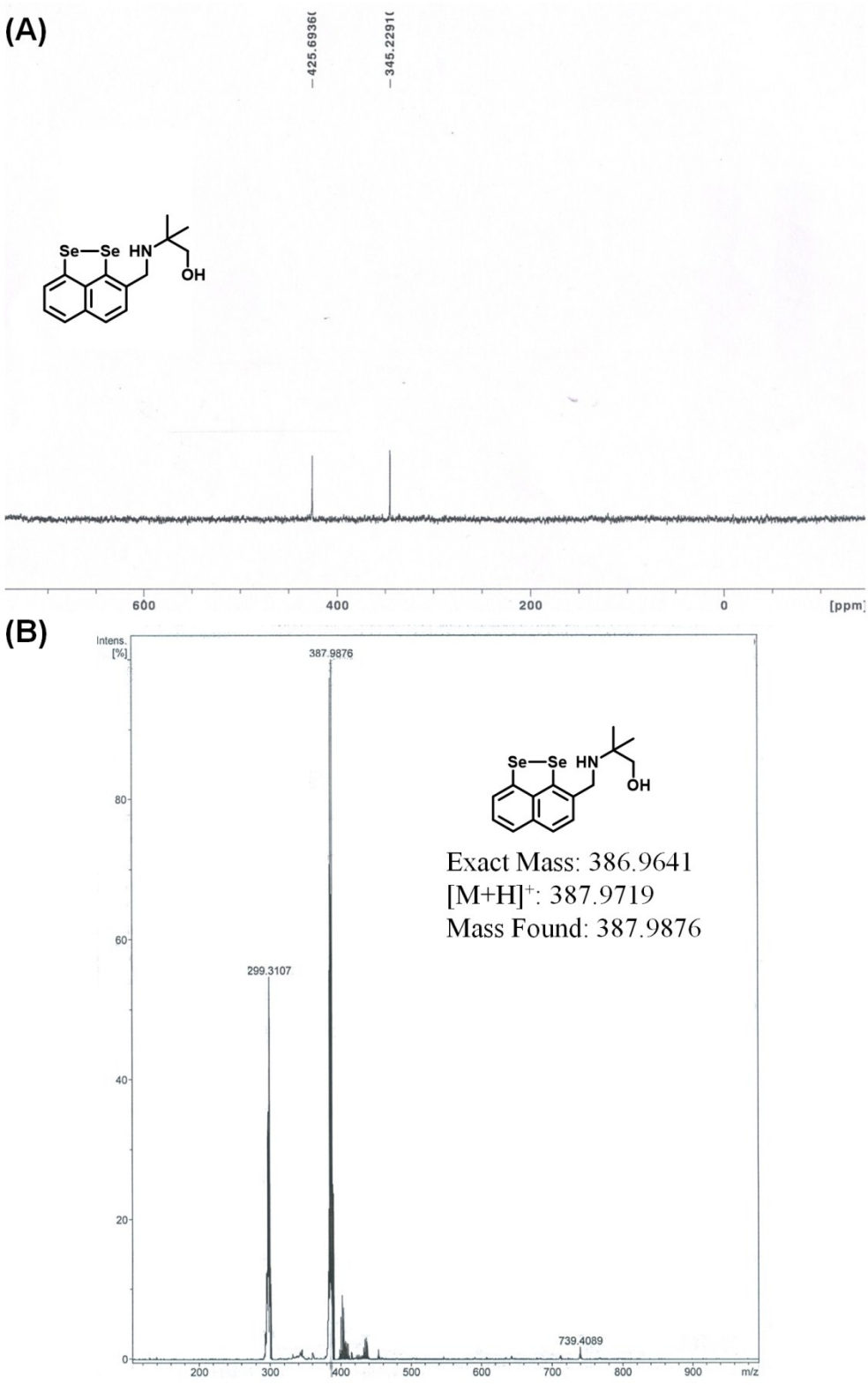


Figure S02. ^{77}Se NMR in $CHCl_3$ (A) and ESI-Mass spectra (B) of **12**.

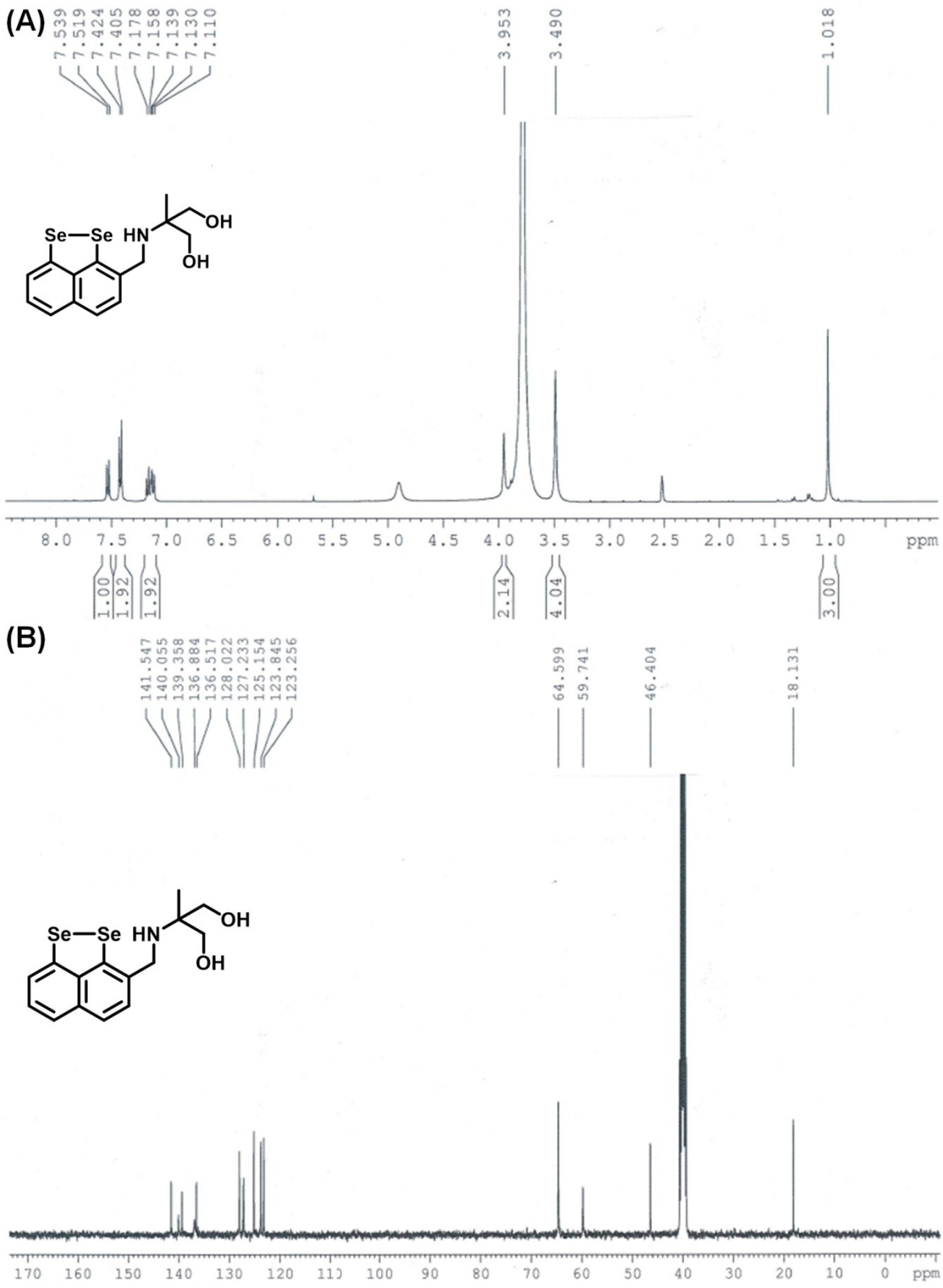


Figure S03. ^{1}H (A) and ^{13}C (B) NMR spectra of **13** in DMSO-d_6.

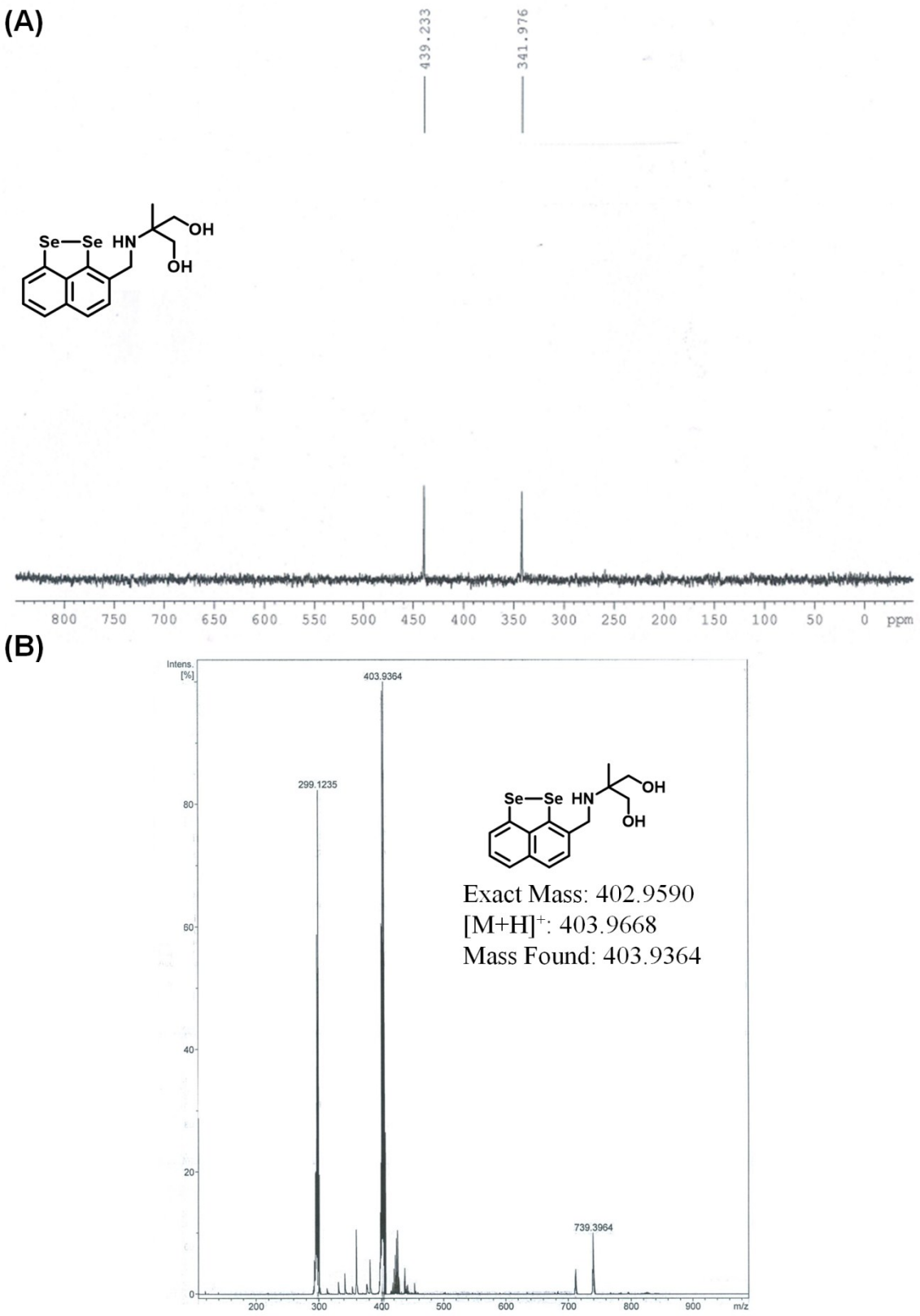


Figure S04. ^{77}Se NMR in DMSO-d_6 (A) and ESI-Mass spectra (B) of **13**.

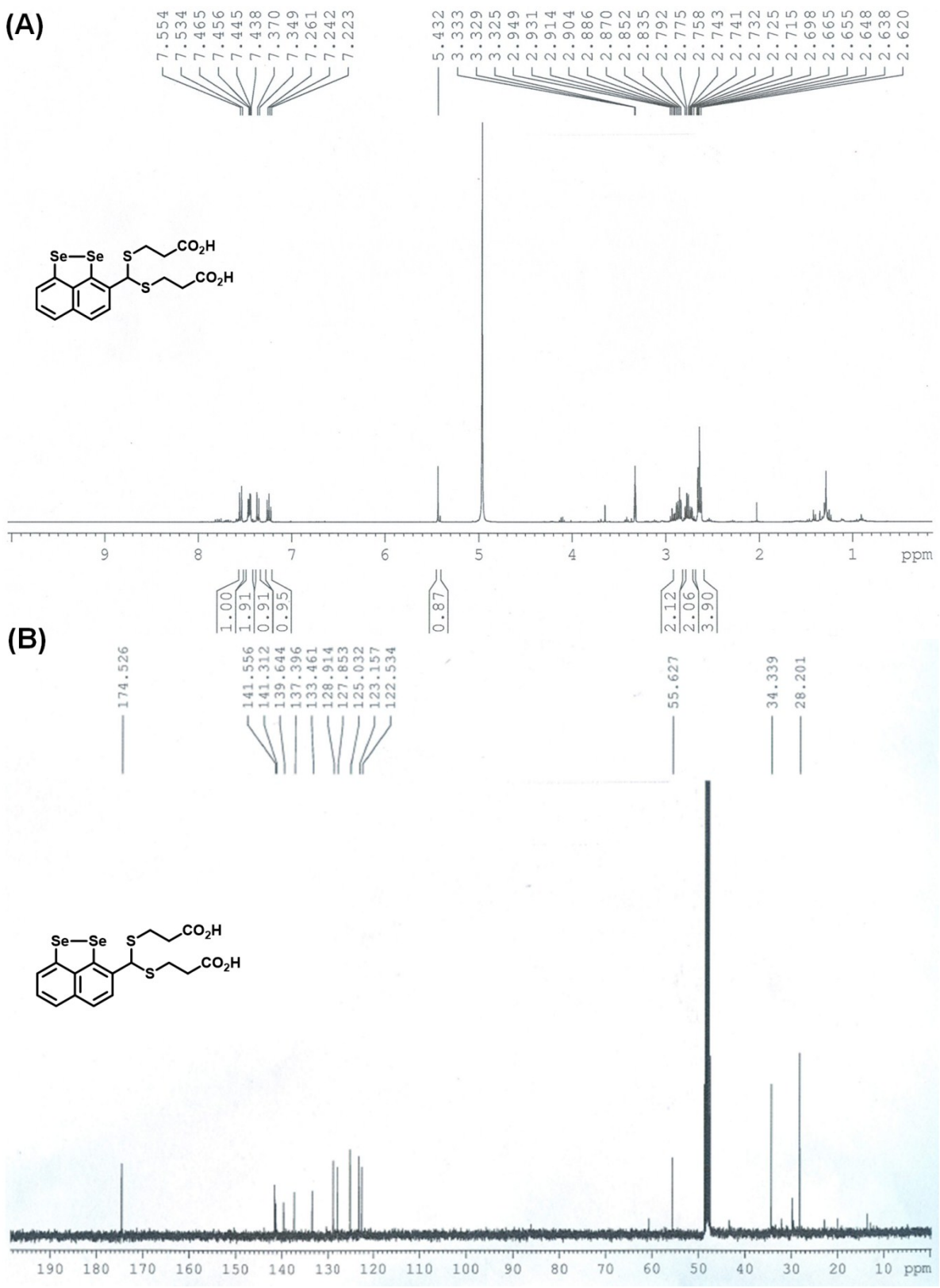


Figure S05. ^{1}H (A) and ^{13}C (B) NMR spectra of **15** in d_4-MeOH.

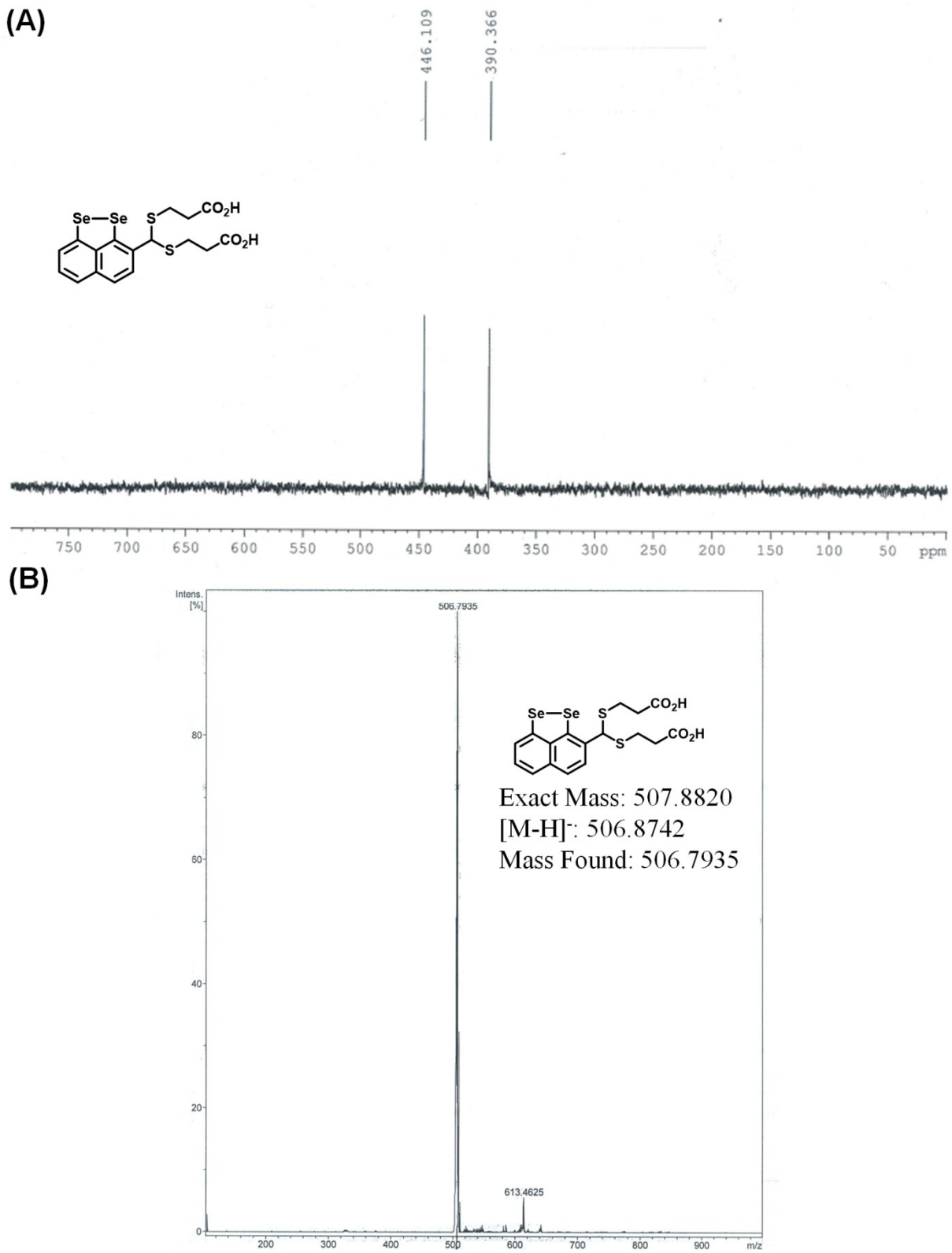


Figure S06. ^{77}Se NMR in $CDCl_3$ (A) and ESI-Mass spectra (B) of **15**.

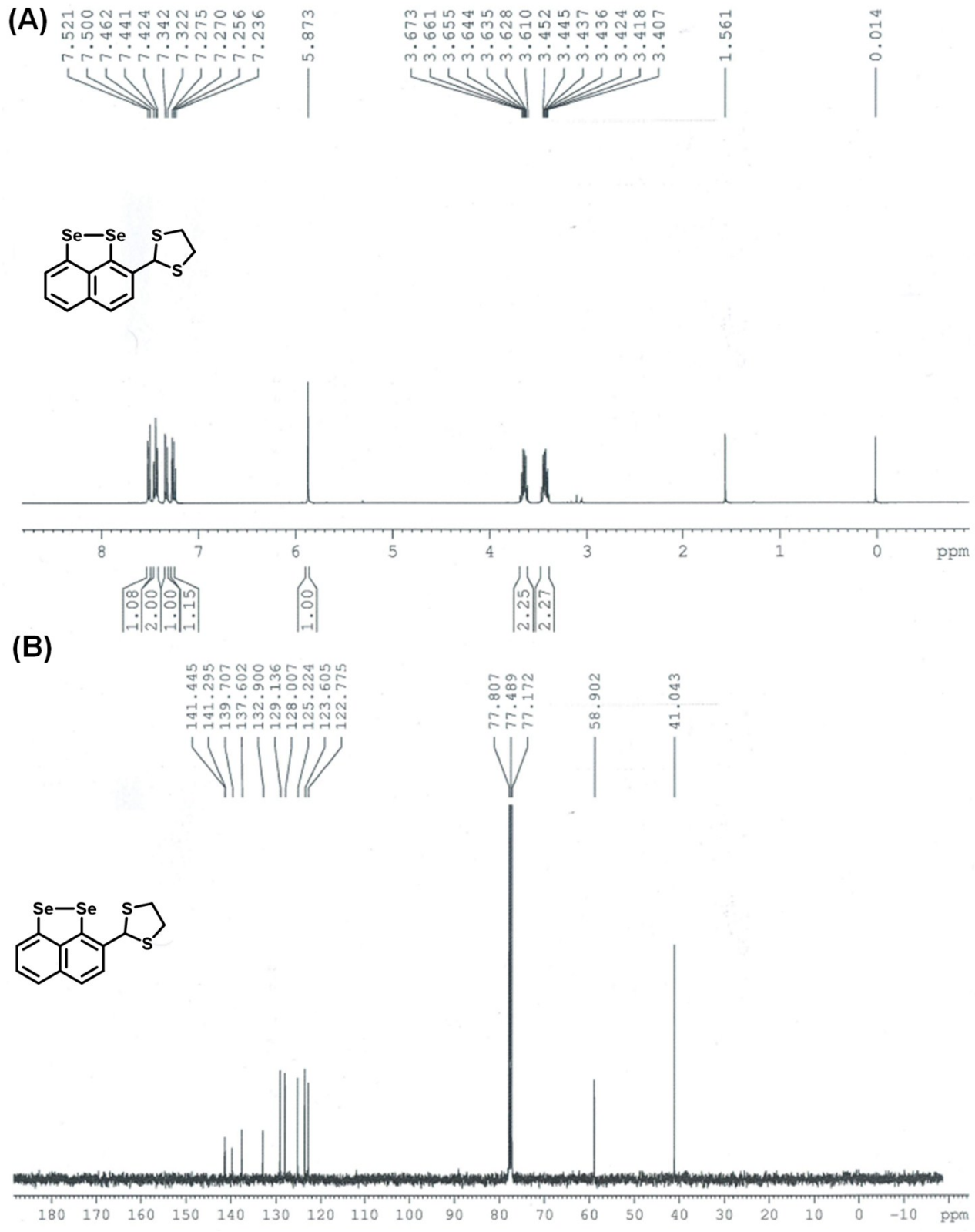


Figure S07. ^{1}H (A) and ^{13}C (B) NMR spectra of **16** in $CDCl_3$.

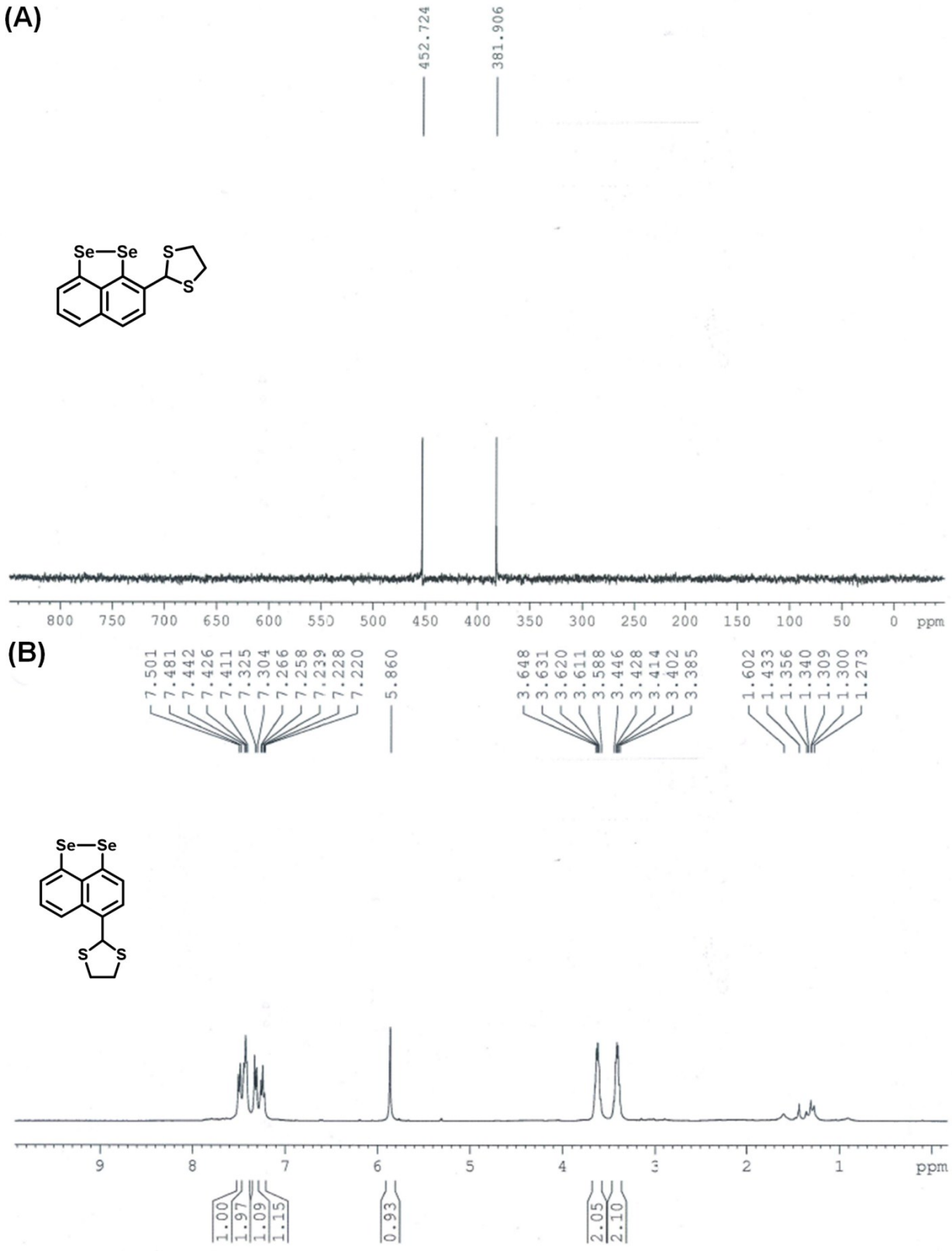


Figure S08. ^{77}Se NMR of **16** (A) and ^{1}H NMR spectra of **17** (B) in $CDCl_3$.

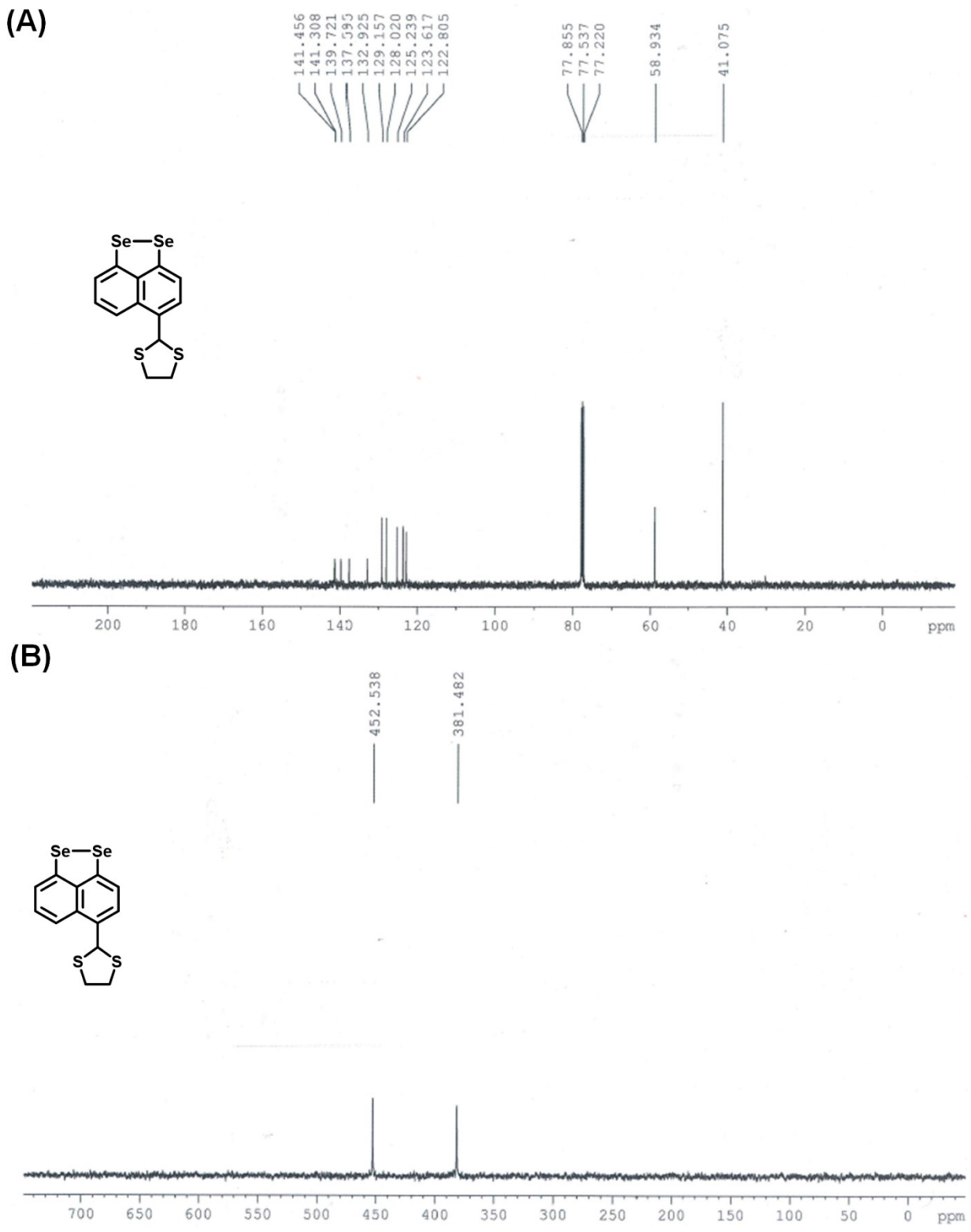


Figure S09. ^{13}C NMR (A) and ^{77}Se NMR (B) spectra of **17** in $CDCl_3$.

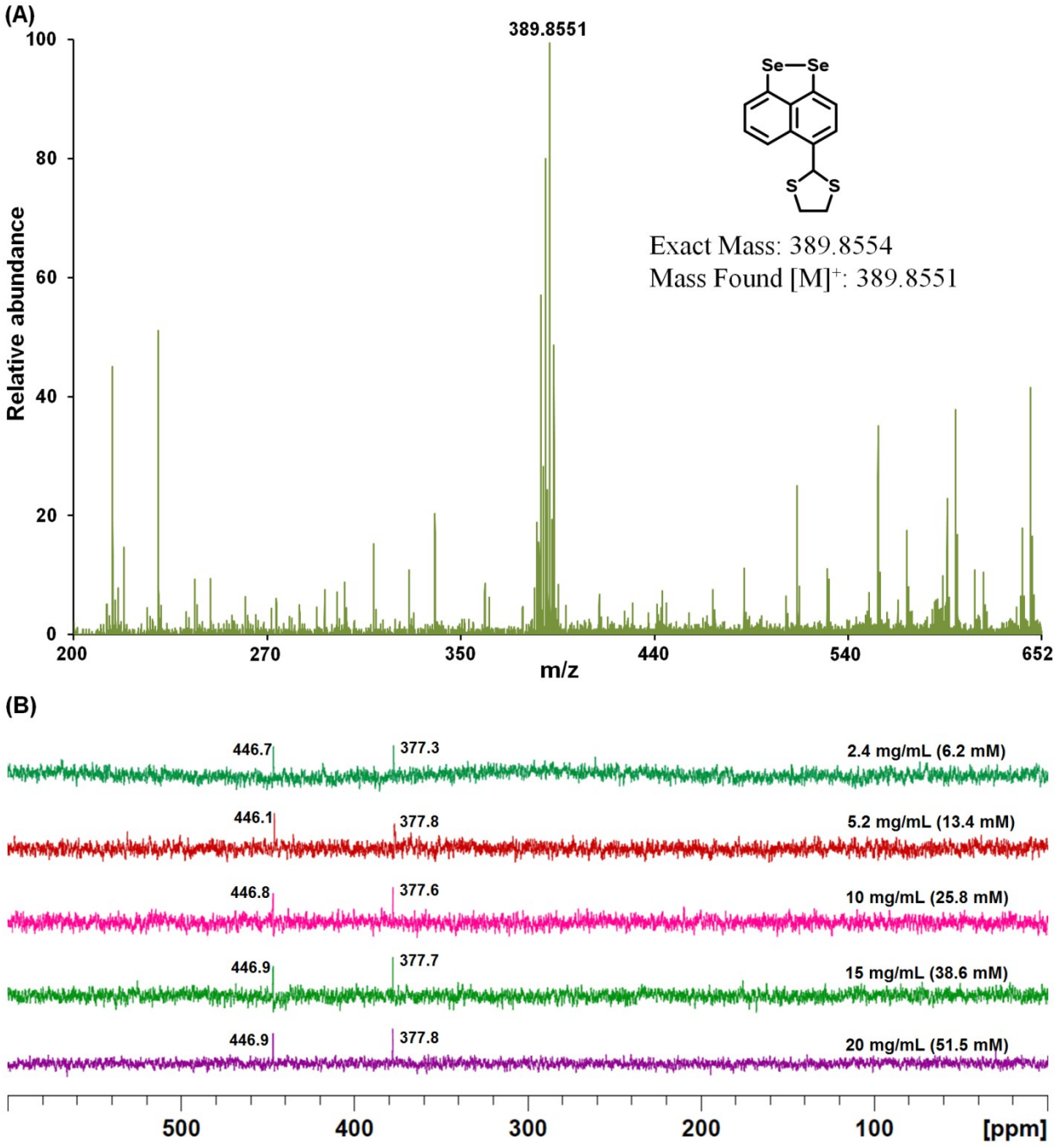


Figure S10. (A) ESI-Mass spectrum of **17**. (B) ^{77}Se NMR spectra of **17** in dichloromethane recorded at different concentrations. Although **17** is expected to exhibit two ^{77}Se signals due to its unsymmetrical structure, in comparison to compounds **15** and **16**, the almost identical chemical shifts in the ^{77}Se NMR spectra of **17** suggests that there may be intermolecular Se···S interactions, which may not break at 6.2 mM concentration. Unfortunately, the ^{77}Se NMR of **17** could not be recorded at further low concentrations due to low natural abundance of ^{77}Se nuclei.

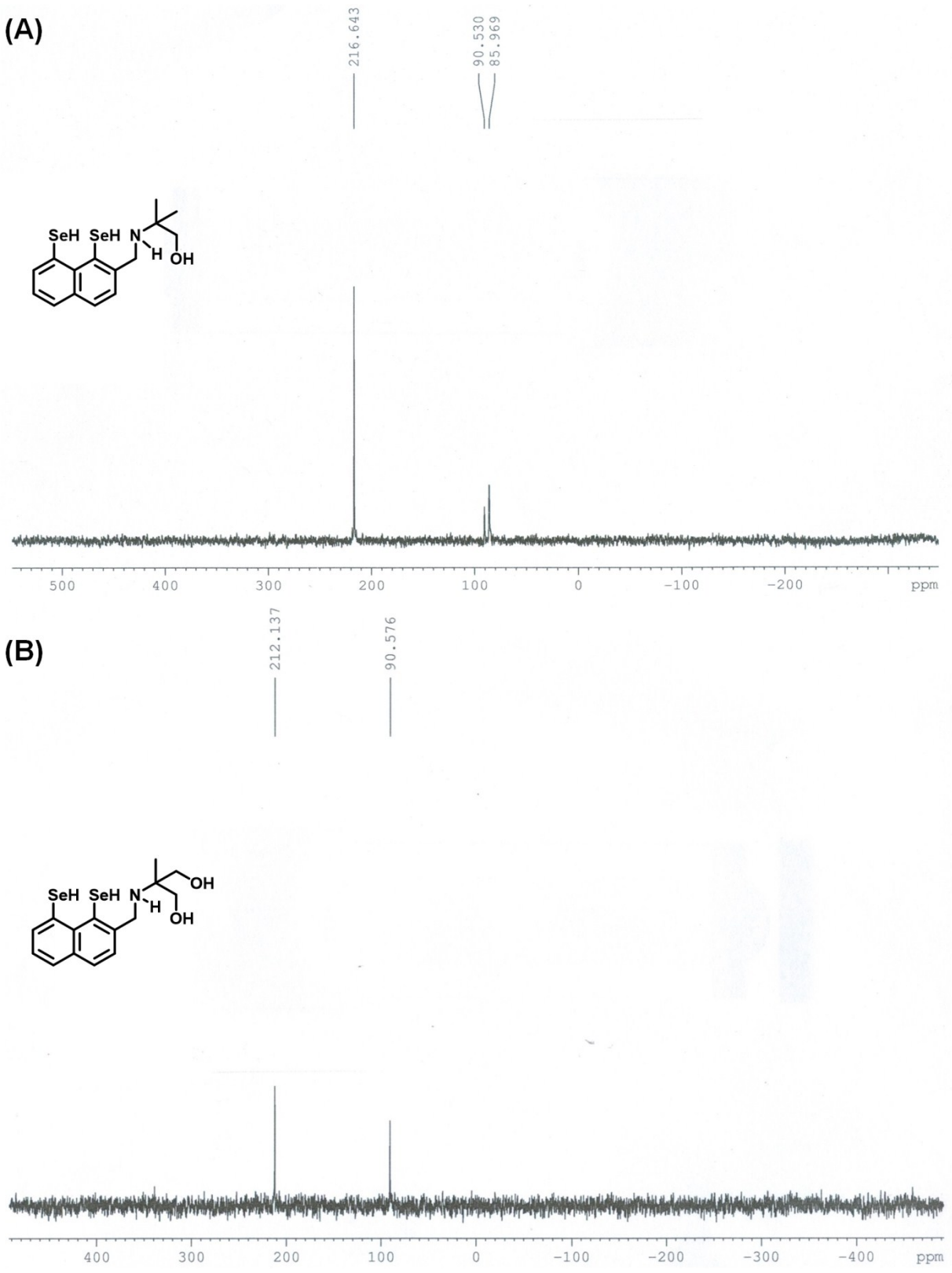


Figure S11. ^{77}Se NMR spectra of **5** (A) and **6** (B) in a mixture of 1:1 $CHCl_3$ and MeOH.

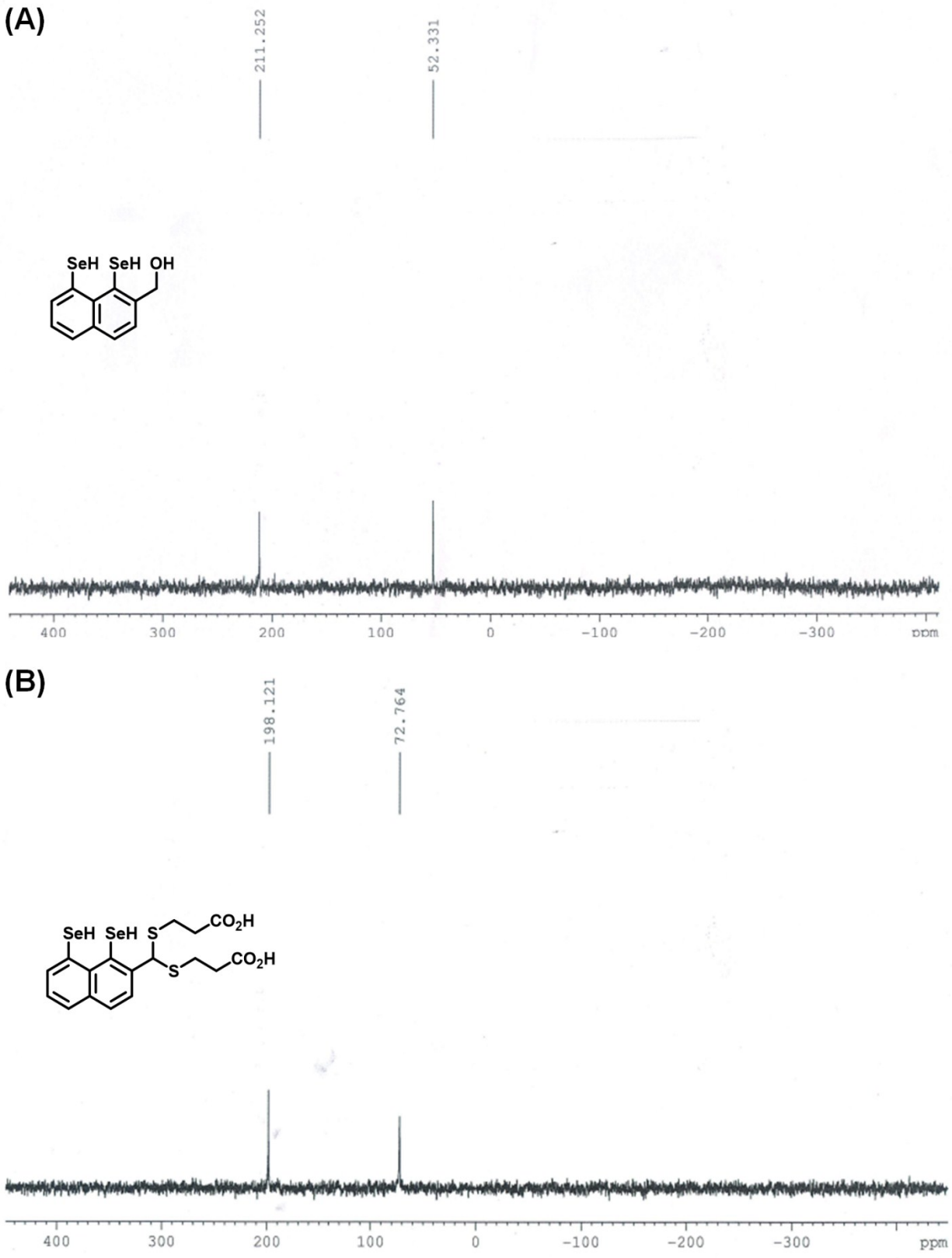


Figure S12. ^{77}Se NMR spectra of **7** (A) and **8** (B) in a mixture of 1:1 $CHCl_3$ and MeOH.

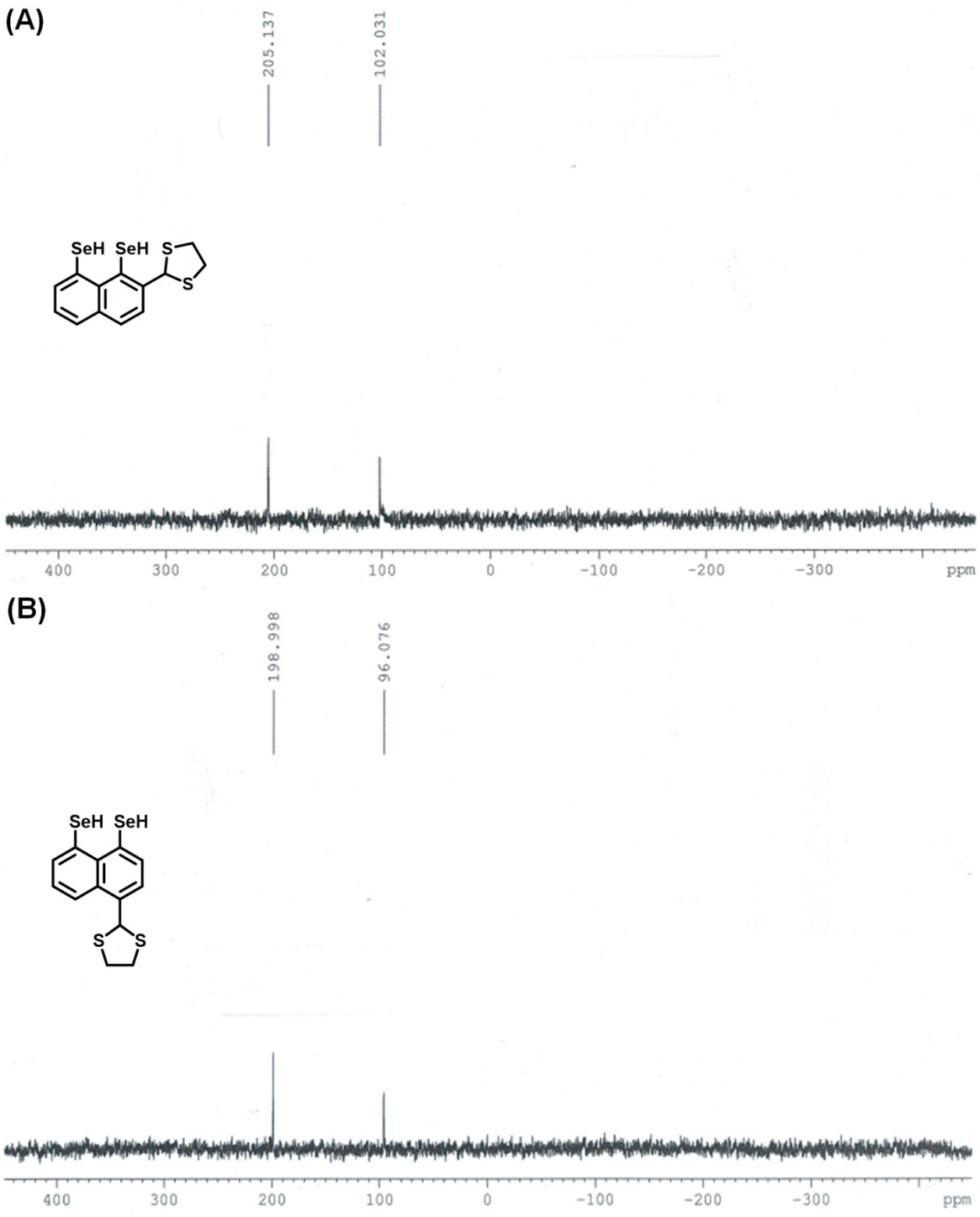


Figure S13. ^{77}Se NMR spectra of **9** (A) and **10** (B) in a mixture of 1:1 $CHCl_3$ and MeOH.

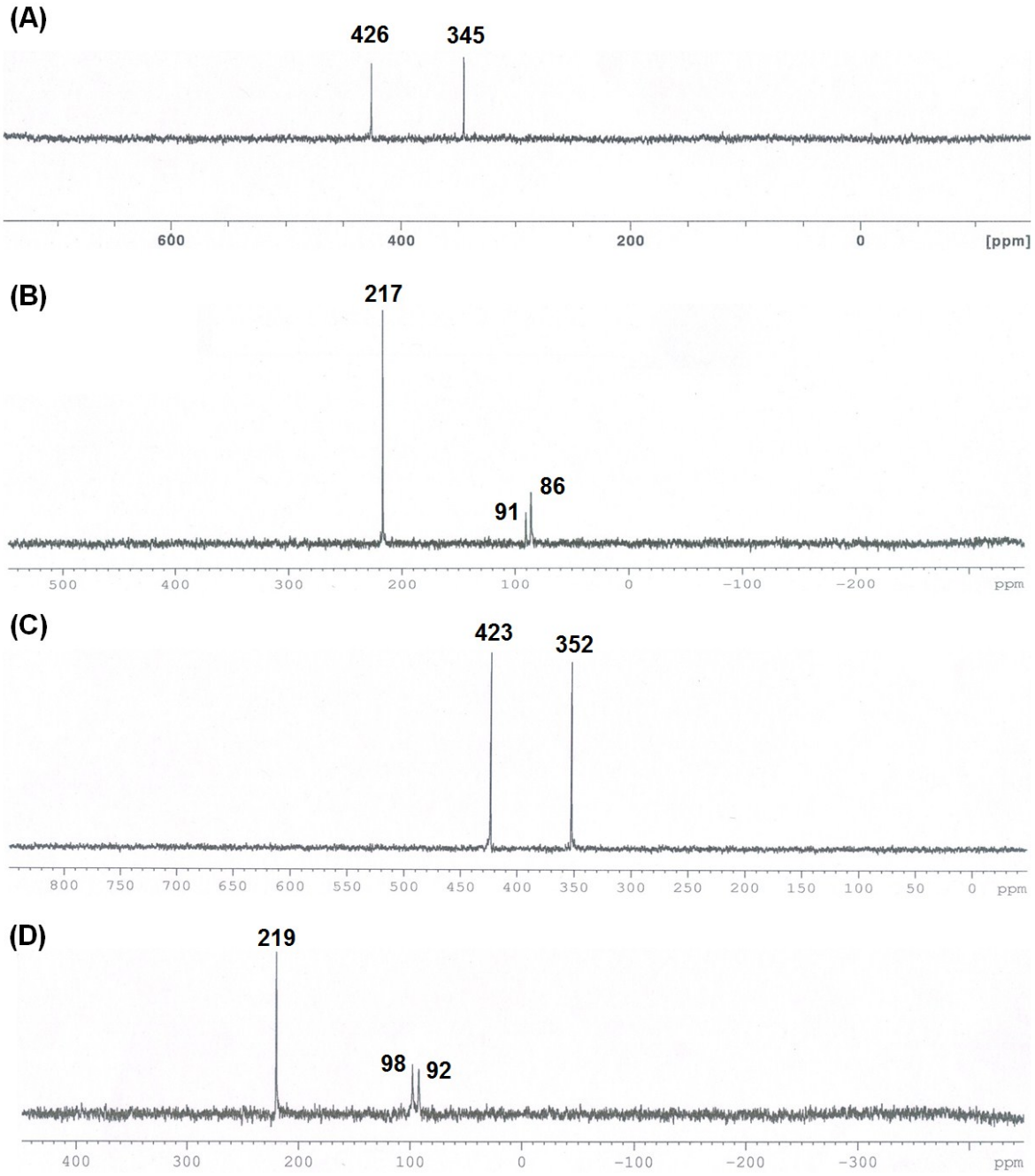


Figure S14. Reproducibility of the ^{77}Se NMR of compounds **5** and **12**. (A) ^{77}Se NMR spectra of compound **12** (A), and compound **5** (B) generated from compound **12** by reduction with sodium borohydride. (C) Compound **5** was then left in the NMR tube for aerial oxidation and this quantitatively regenerated compound **12** as indicated by the appearance of two peaks in the ^{77}Se NMR spectra at 352 and 423 ppm corresponding to the oxidized diselenide. (D) The reaction mixture was again reduced with sodium borohydride to regenerate compound **5** and ^{77}Se NMR spectra of the mixture exhibited three peaks at 219, 92 and 98 ppm, which is quite similar to that observed earlier, that is, in B.

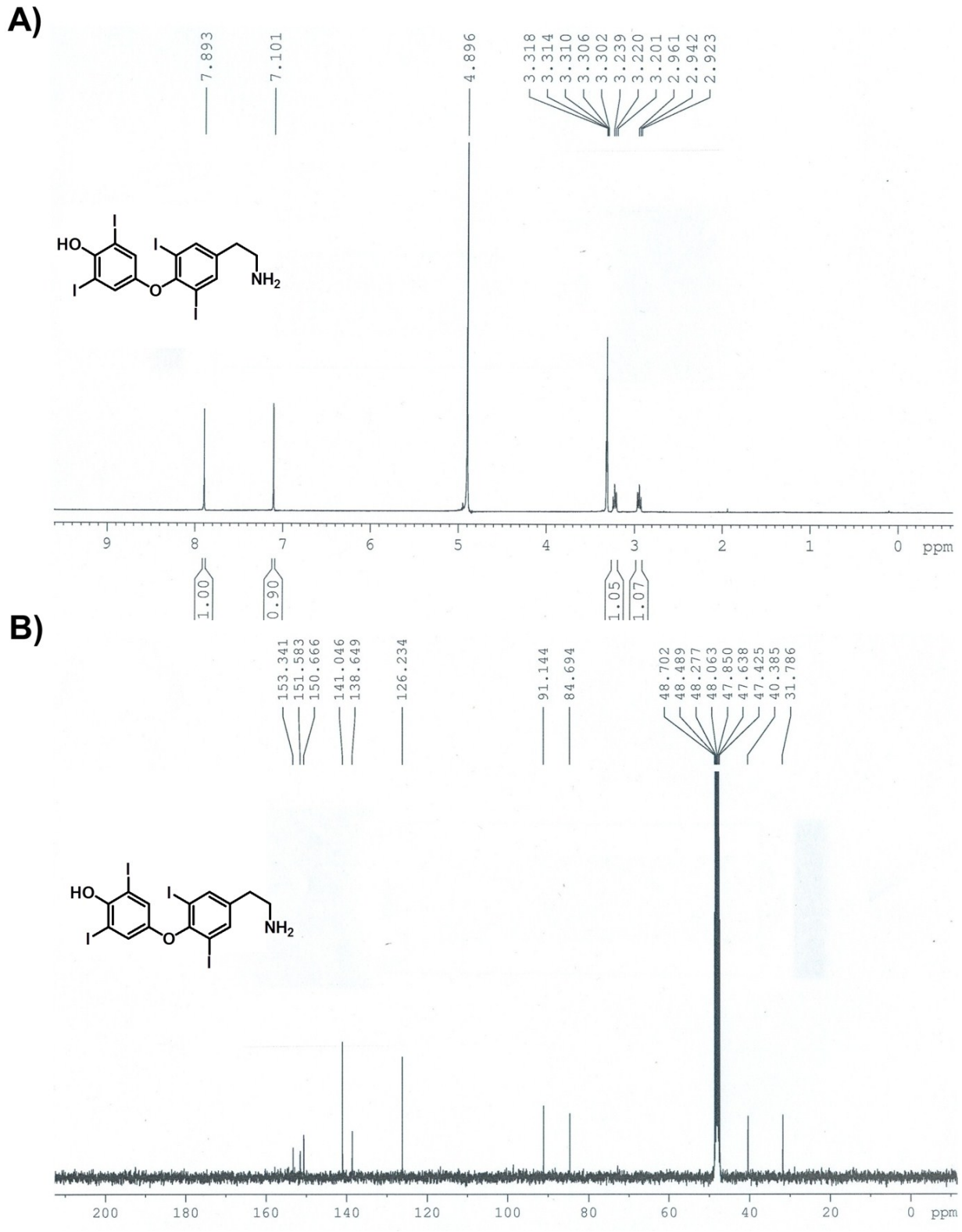


Figure S15. ^{1}H (A) and ^{13}C (B) NMR spectra of T4AM in d_4-MeOH.

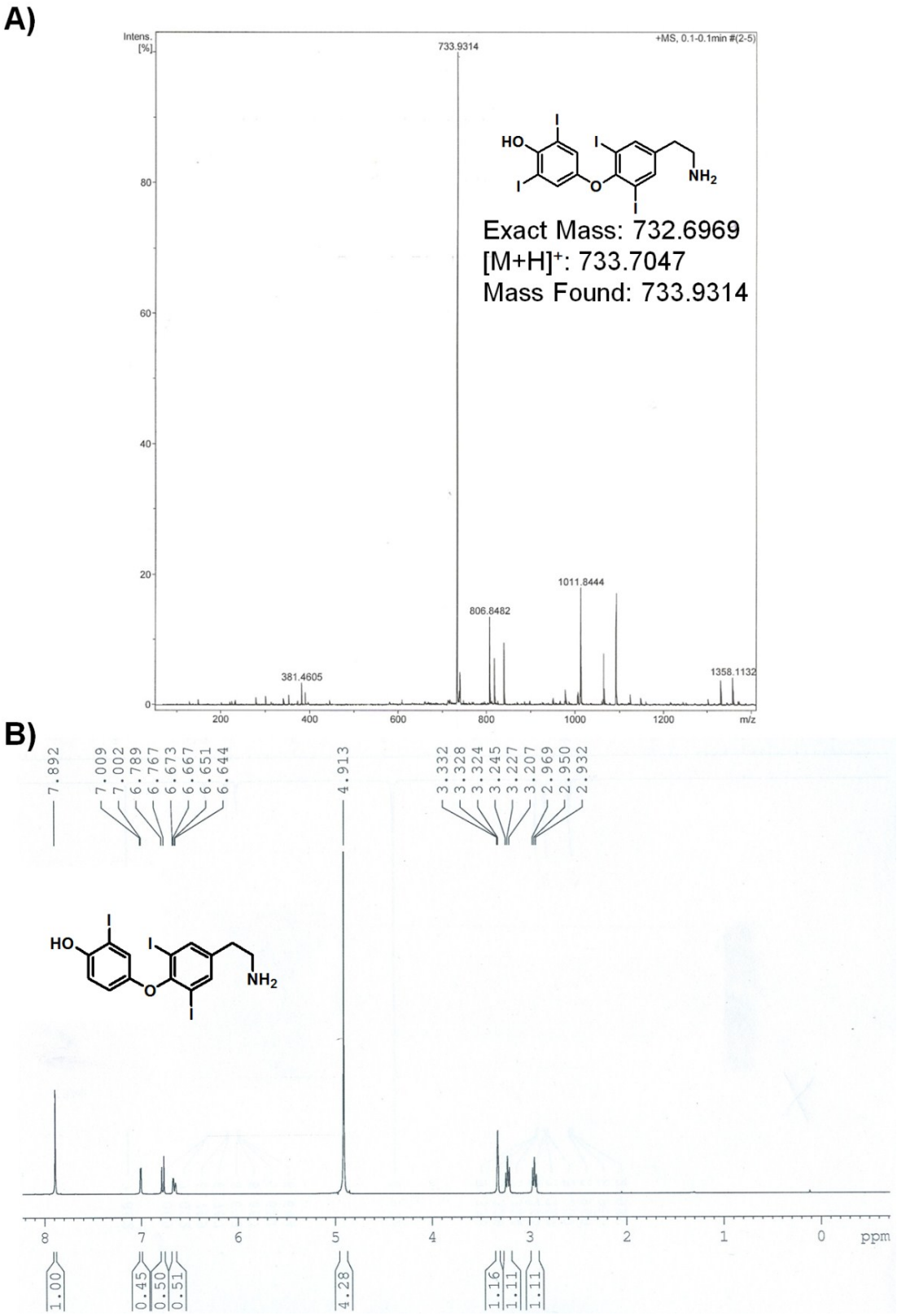


Figure S16. ESI Mass spectrum of T4AM (A) and ^{1}H NMR spectrum of T3AM in d_4-MeOH (B).

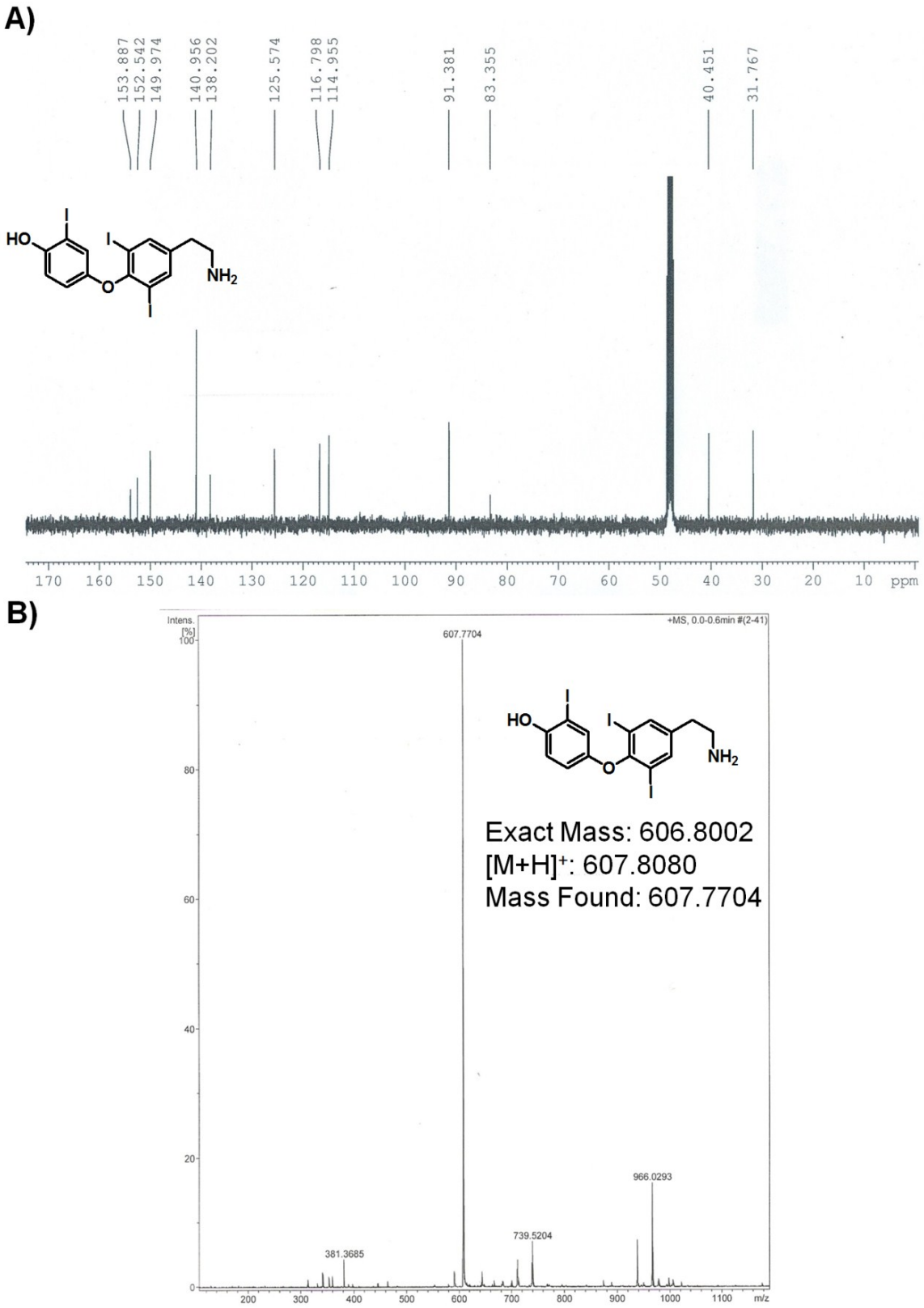


Figure S17. ^{13}C NMR spectrum in d_4-MeOH (A) and ESI Mass spectrum (B) of T3AM.

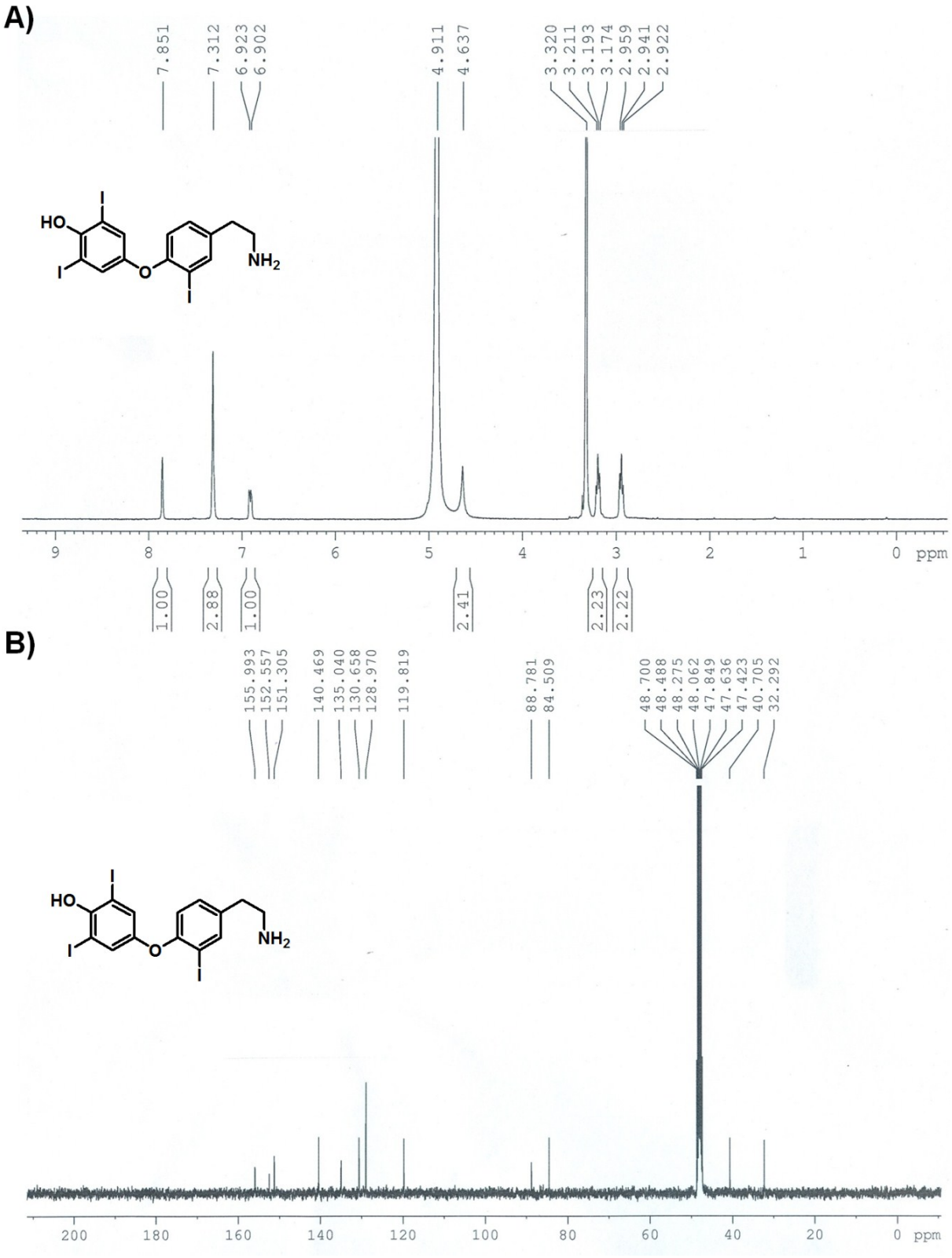


Figure S18. ^{1}H (A) and ^{13}C (B) NMR spectra of rT3AM in d_4-MeOH.

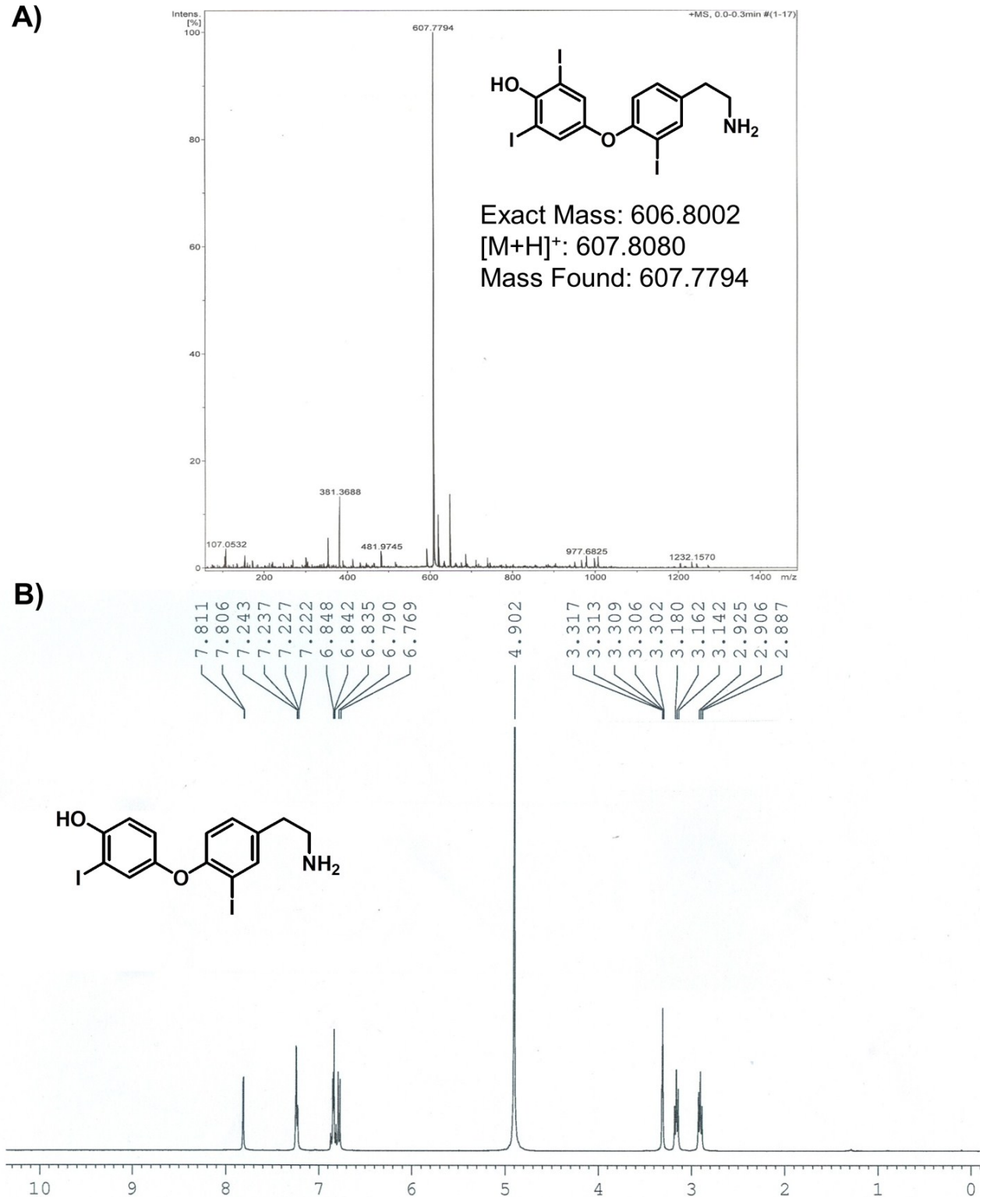


Figure S19. ESI Mass spectrum of rT3AM (A) and ^{1}H NMR spectrum of 3,3′-T2AM in d_4-MeOH (B).

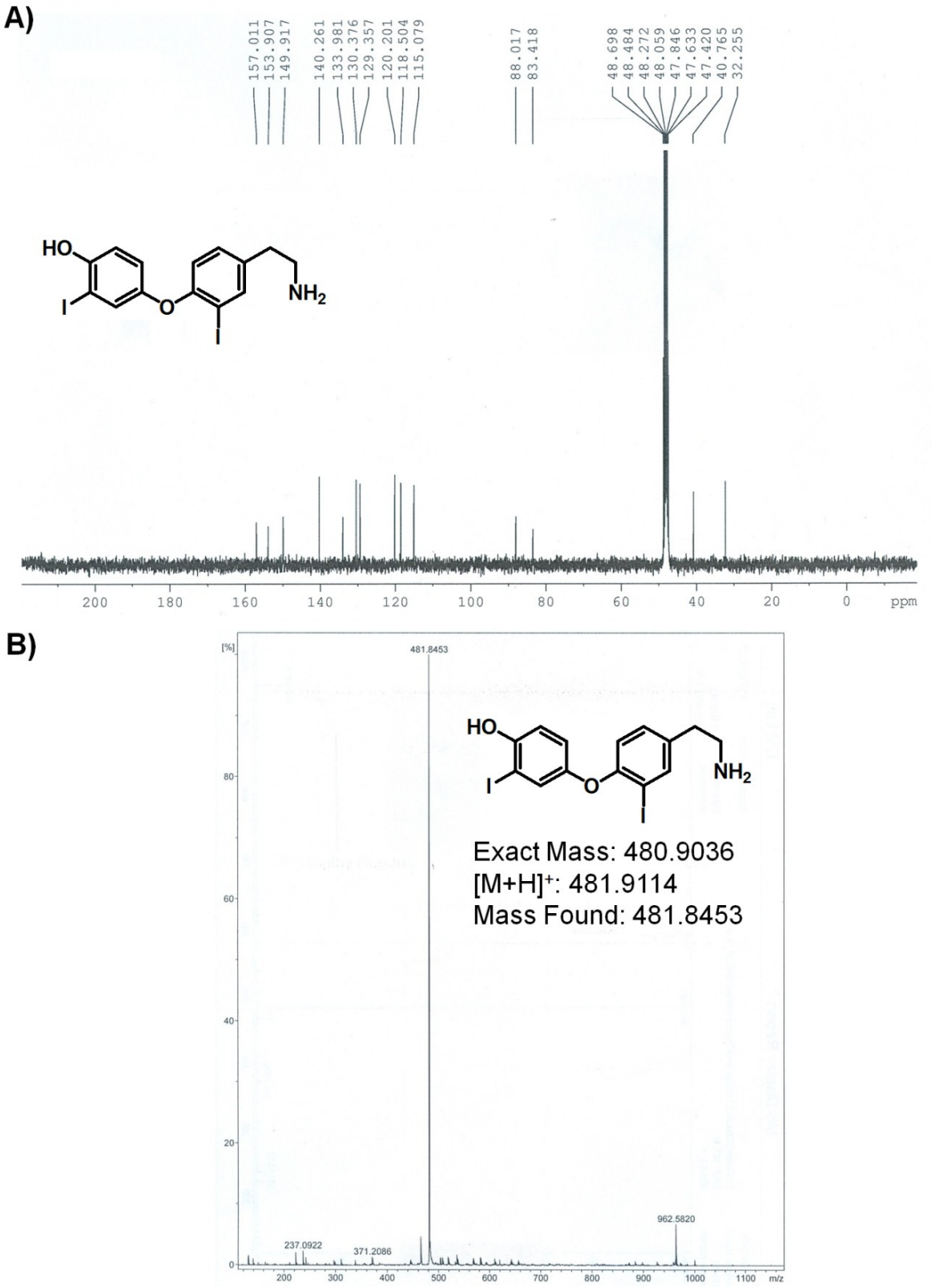


Figure S20. ^{13}C NMR in d_4-MeOH (A) and ESI Mass spectra (B) of 3,3′-T2AM.

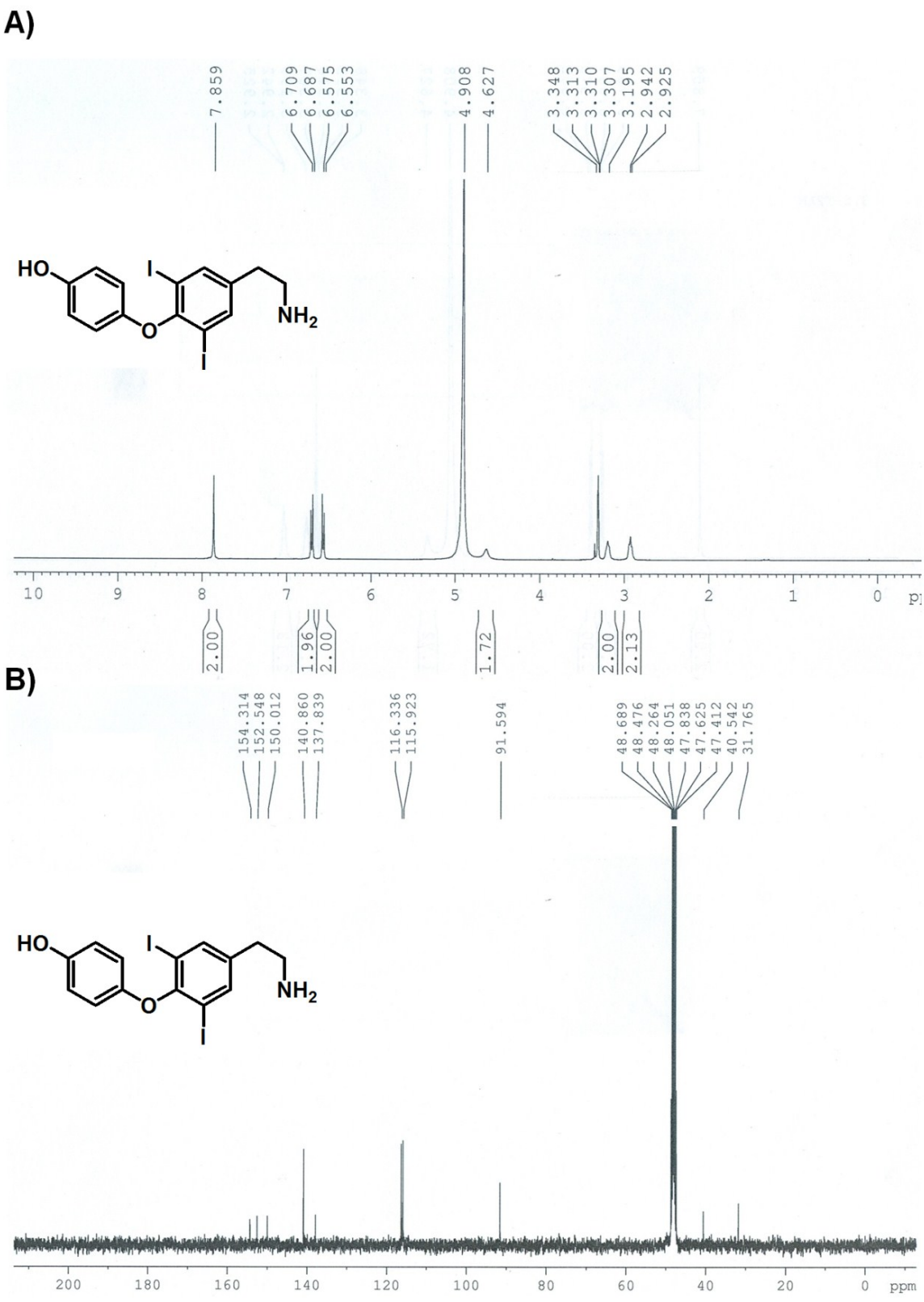


Figure S21. ^{1}H (A) and ^{13}C (B) NMR spectra of 3,5-T2AM in d_4-MeOH.

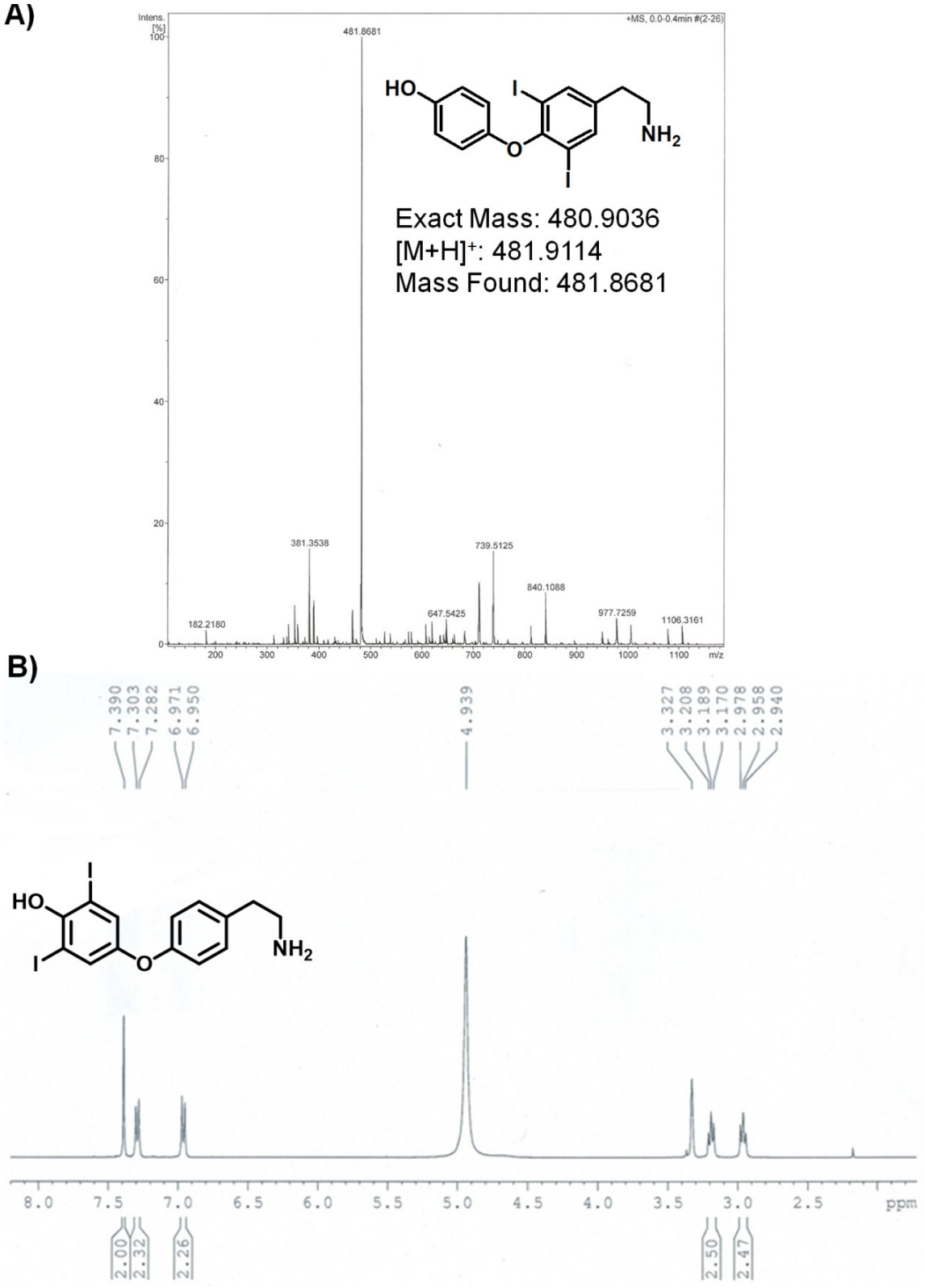


Figure S22. ESI Mass spectrum of 3,5-T2AM (A) and ^{1}H NMR spectrum of 3′,5′-T2AM in d_4-MeOH (B).

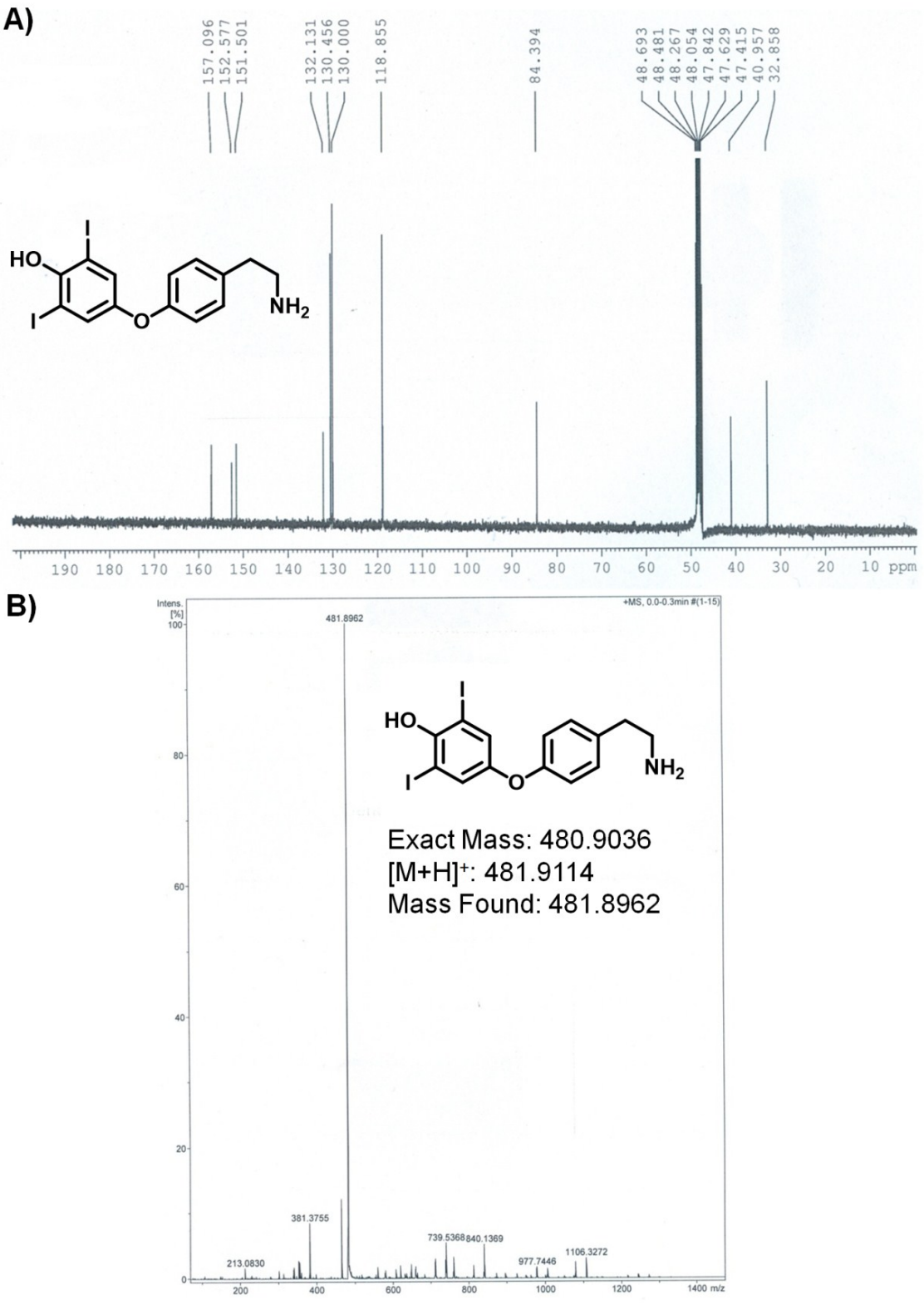


Figure S23. ^{13}C NMR spectrum in d_4-MeOH (A) and ESI Mass spectrum (B) of 3′,5′-T2AM.

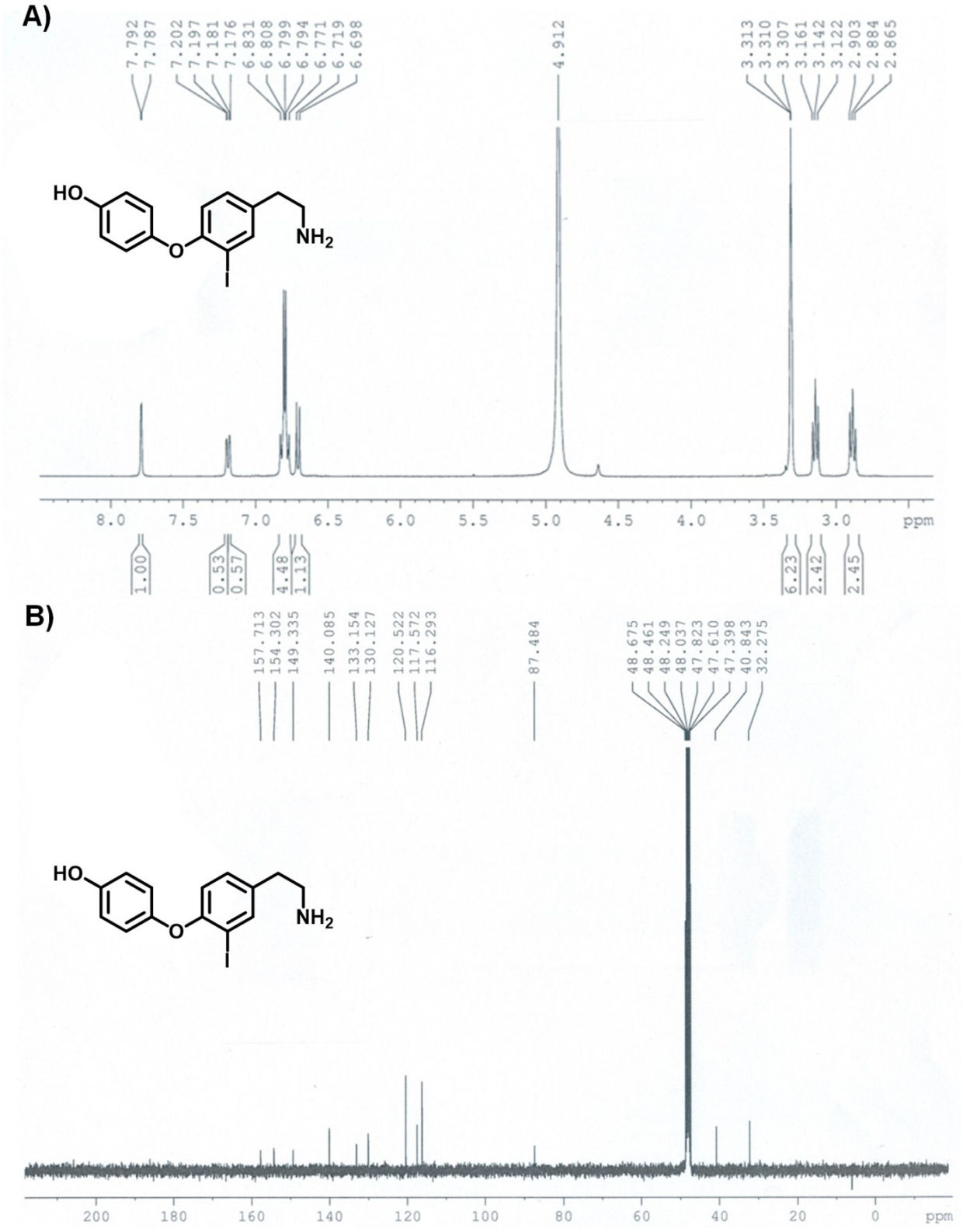


Figure S24. ^{1}H (A) and ^{13}C NMR (B) spectra of 3-T1AM in d_4-MeOH.

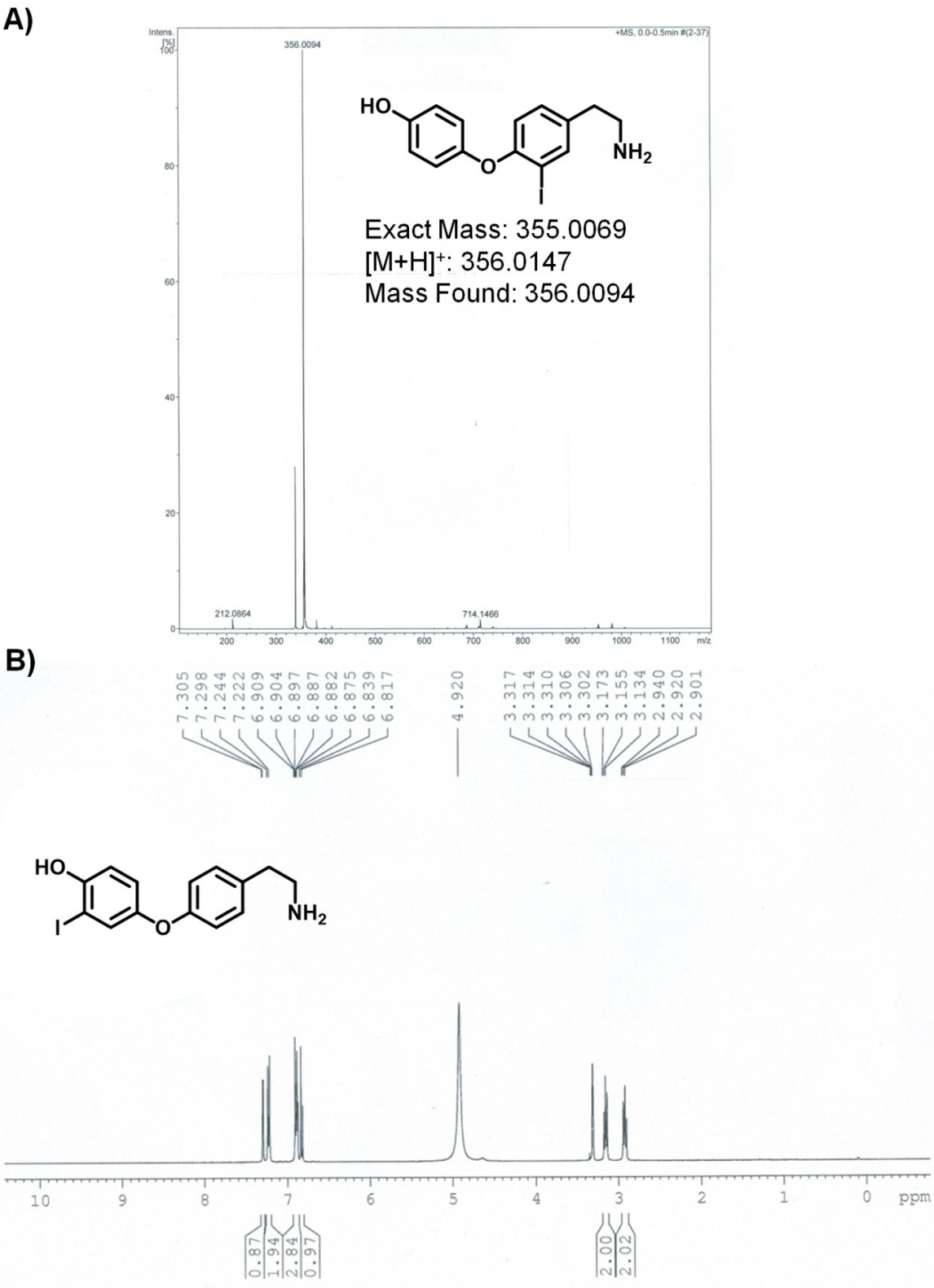


Figure S25. ESI Mass spectrum of 3-T1AM (A) and ^{1}H NMR spectrum of 3′-T1AM in d_4-MeOH (B).

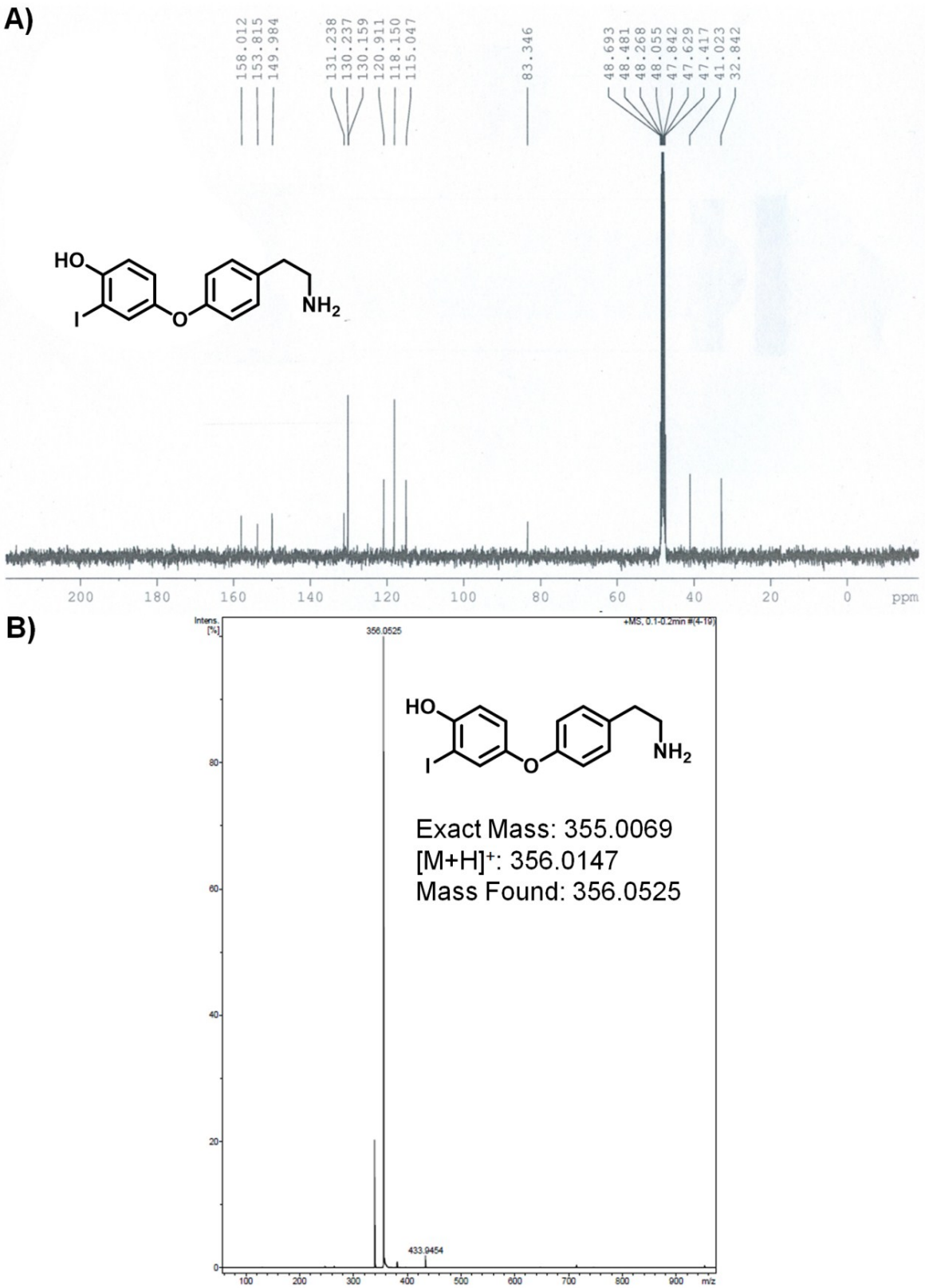


Figure S26. ^{13}C NMR spectrum in d_4-MeOH (A) and ESI Mass spectrum (B) of 3′-T1AM.

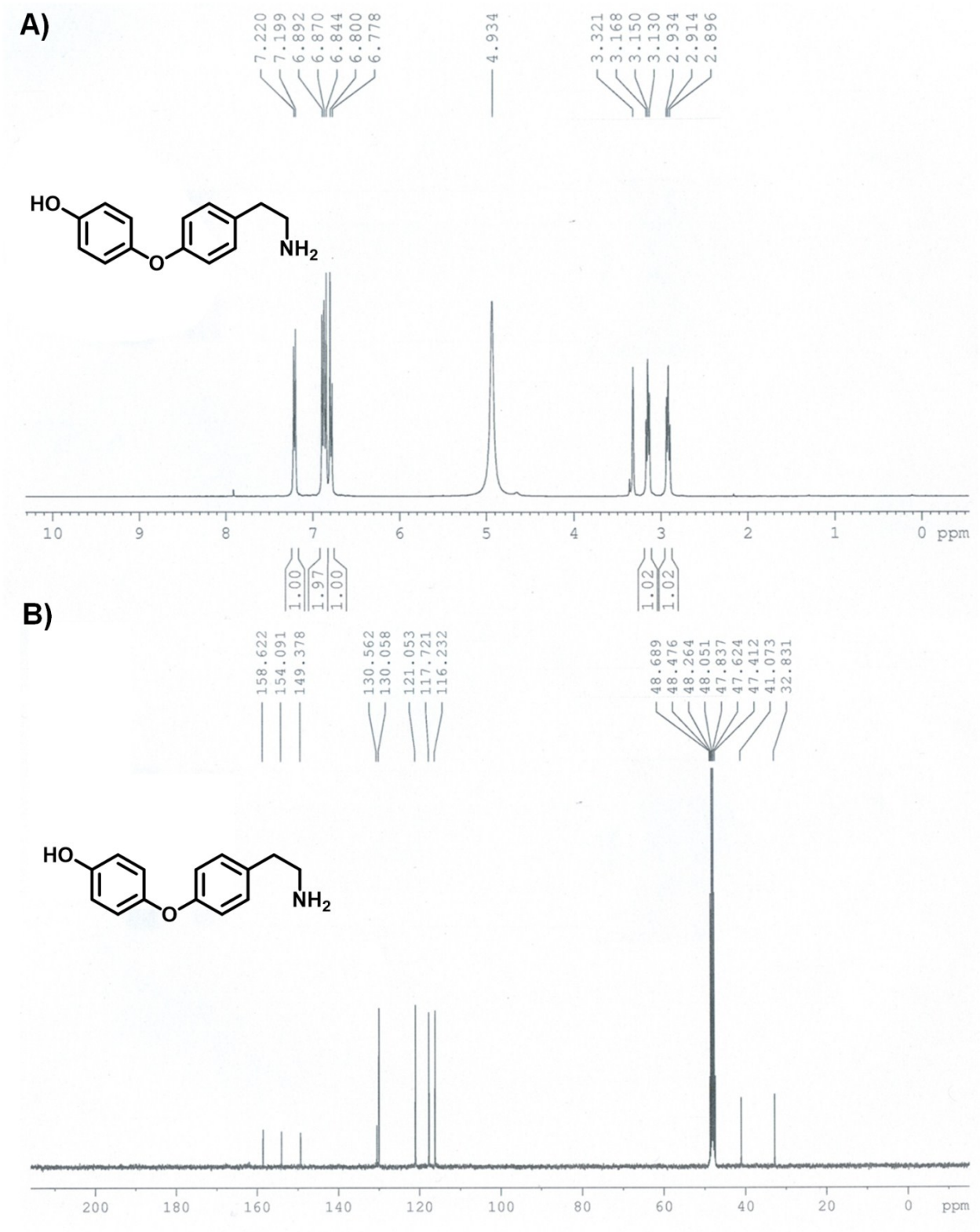


Figure S27. ^{1}H (A) and ^{13}C (B) NMR spectrum of T0AM in d_4-MeOH.

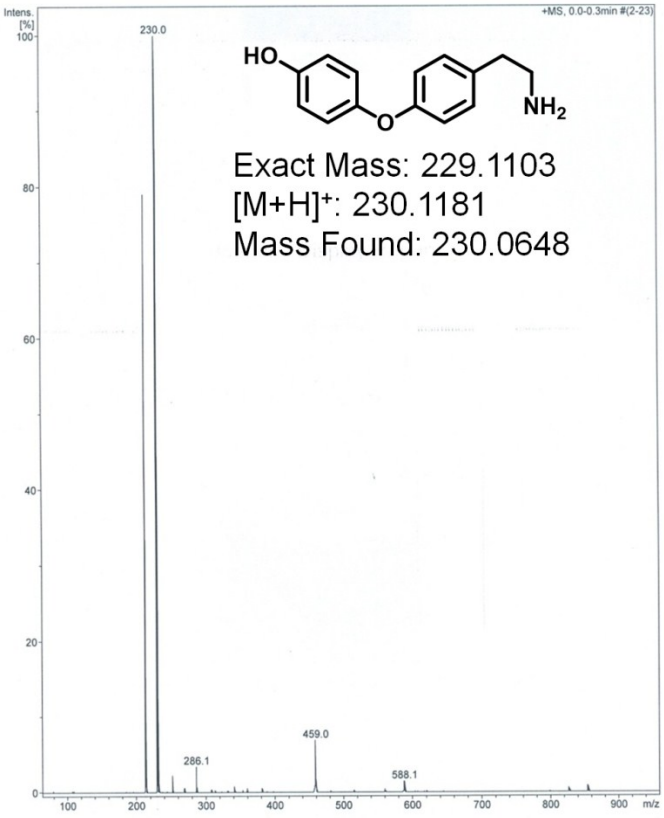


Figure S28. ESI Mass spectrum of T0AM.

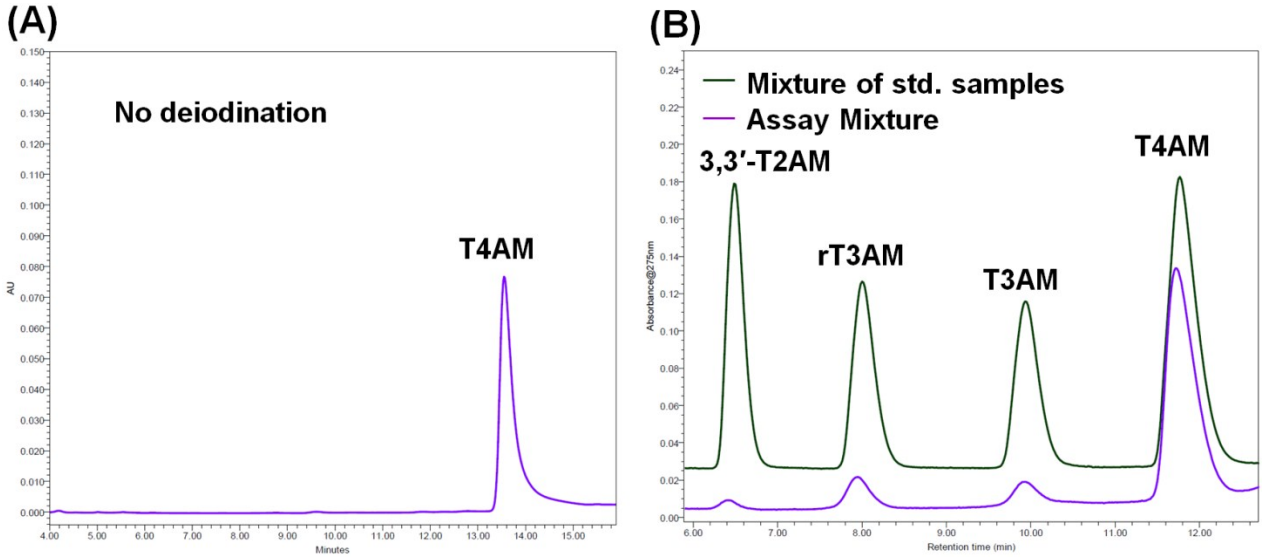


Figure S29. HPLC chromatogram for the deiodination of T4AM in a mixture of phosphate buffer and 20% (v/v) acetonitrile (A), and in acetonitrile (B) by compound **3**. In acetonitrile, T4AM undergoes both the tyrosyl and phenolic ring deiodination to produce rT3AM and T3AM, respectively, by **3**.

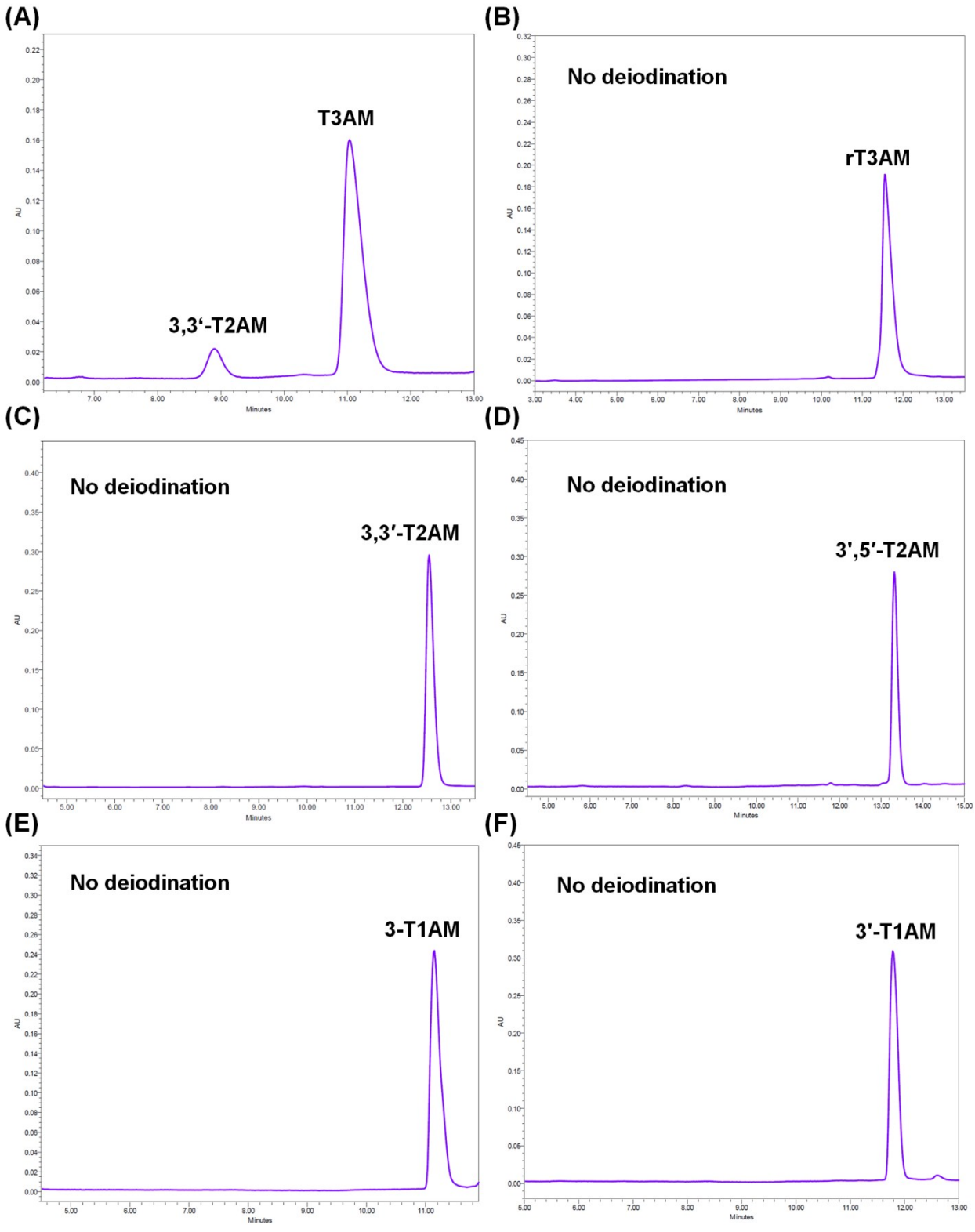
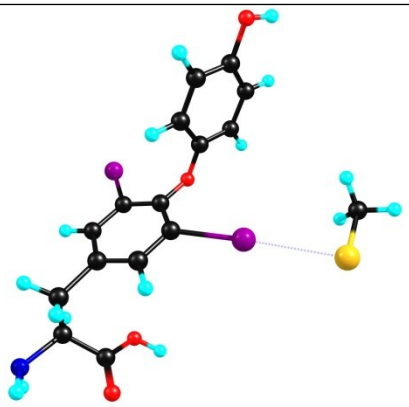
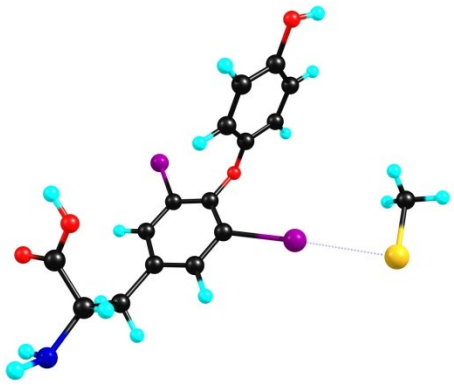


Figure S30. HPLC chromatograms of deiodination of T3AM (A), rT3AM (B), 3,3'-T2AM (C), 3',5'-T2AM (D), 3-T1AM (E), 3'-T1AM (F) by compound **8**.

Table S03. Coordinates of optimized geometries discussed in this paper.



3,5-T2·MeSe$^-$_trans



3,5-T2·MeSe$^-$_cis

6	-2.763251000	-0.867107000	0.980146000	6	-2.403106000	-1.791351000	-0.553834000
6	-1.431644000	-1.287868000	0.907290000	6	-1.017190000	-1.919820000	-0.409672000
6	-0.428769000	-0.504099000	0.336242000	6	-0.150523000	-0.832466000	-0.500534000
53	1.666302000	-1.475592000	0.062453000	53	2.130871000	-1.278635000	-0.403593000
6	-0.768979000	0.760225000	-0.147762000	6	-0.695911000	0.433704000	-0.730046000
8	0.161437000	1.563947000	-0.786630000	8	0.110380000	1.548698000	-0.891993000
6	-2.095399000	1.194705000	-0.076250000	6	-2.075204000	0.572209000	-0.898870000
6	-3.091062000	0.395582000	0.476913000	6	-2.930393000	-0.524329000	-0.817517000
6	-3.845057000	-1.761887000	1.544755000	6	-3.310268000	-2.995438000	-0.421526000
6	-4.618384000	-2.600322000	0.492028000	6	-3.662108000	-3.388947000	1.035257000
1	-5.037985000	-1.923063000	-0.255177000	1	-2.736322000	-3.573402000	1.583425000
6	1.104143000	2.246715000	-0.048972000	6	0.702821000	2.132143000	0.206733000
6	2.156964000	2.808740000	-0.767717000	6	1.730359000	3.035350000	-0.055844000
6	3.131159000	3.553340000	-0.110795000	6	2.354762000	3.705178000	0.991170000
1	3.952518000	3.983077000	-0.677848000	1	3.160252000	4.402896000	0.778635000
6	3.063184000	3.734147000	1.270419000	6	1.961799000	3.468916000	2.308296000
8	4.005931000	4.463622000	1.969816000	8	2.551636000	4.106368000	3.383393000
6	2.012906000	3.170345000	1.987024000	6	0.937511000	2.564790000	2.569175000
6	1.031589000	2.430498000	1.330922000	6	0.304585000	1.898720000	1.522065000
1	-1.166597000	-2.270857000	1.289645000	1	-0.593573000	-2.907154000	-0.240558000
53	-2.651447000	3.125297000	-0.851238000	53	-2.935128000	2.502425000	-1.318835000
1	-4.112700000	0.753978000	0.517127000	1	-3.995993000	-0.392829000	-0.959931000
1	-4.600815000	-1.169894000	2.067559000	1	-2.838727000	-3.876489000	-0.863889000
1	-3.413462000	-2.454039000	2.275473000	1	-4.248639000	-2.823828000	-0.959601000
1	2.208176000	2.643805000	-1.836651000	1	2.039841000	3.191536000	-1.081594000
1	1.973636000	3.305524000	3.061352000	1	0.647324000	2.377481000	3.596187000
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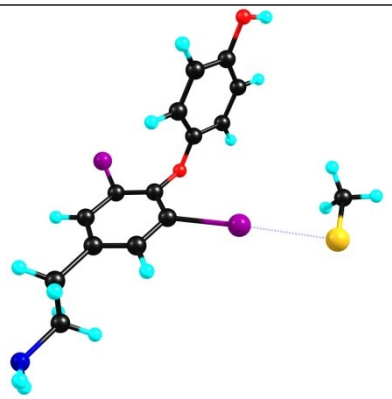
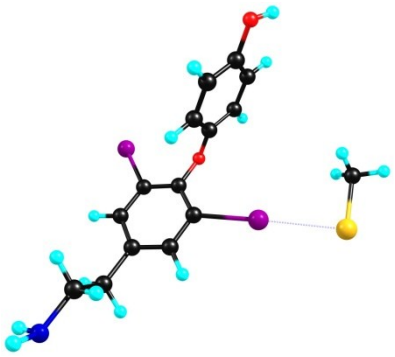
 **3,5-T2AM·MeSe¯_trans**				 **3,5-T2AM·MeSe¯_cis**			
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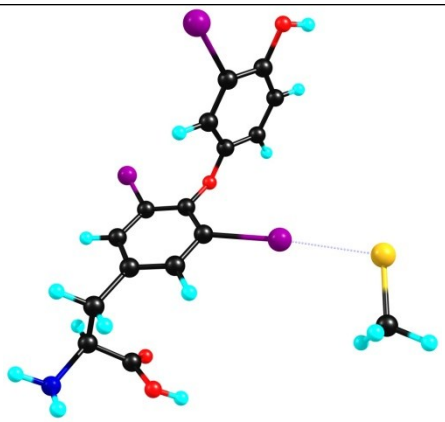				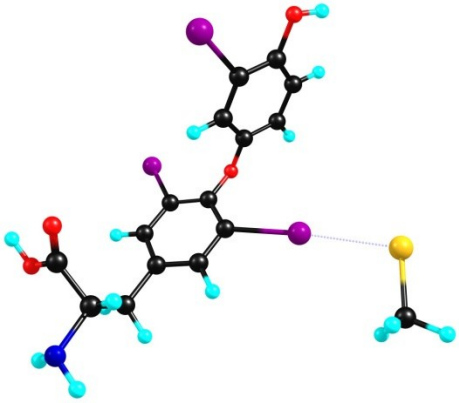			
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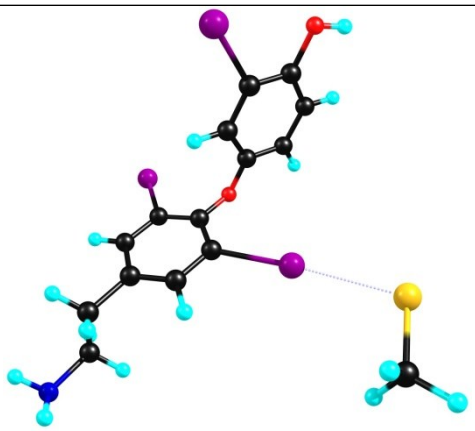
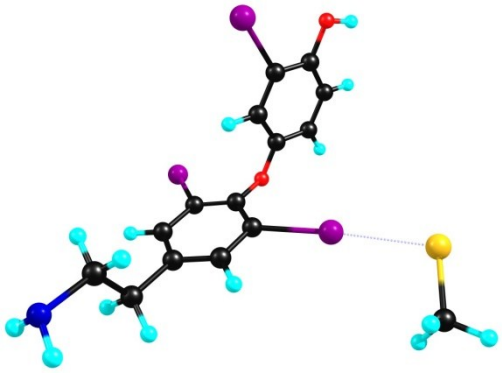
 **T3AM·MeSe$^-$_trans**				 **T3AM·MeSe$^-$_cis**			
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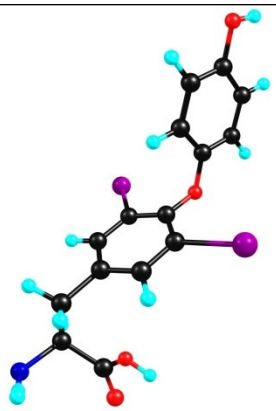

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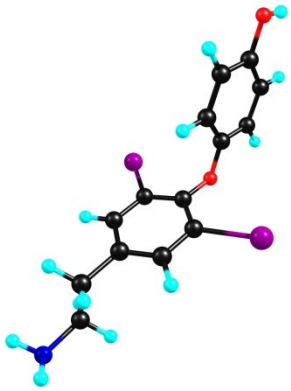

3,5-T2AM

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8	-0.981570000	0.015137000	-0.967673000
6	0.901747000	-1.186360000	-0.063096000
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6	4.222769000	0.014297000	1.369766000
6	5.314783000	-0.055622000	0.272827000
7	6.694497000	-0.061311000	0.748787000
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6	-3.338792000	-0.014898000	-0.941812000
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1	-5.482640000	-0.042453000	-0.845922000
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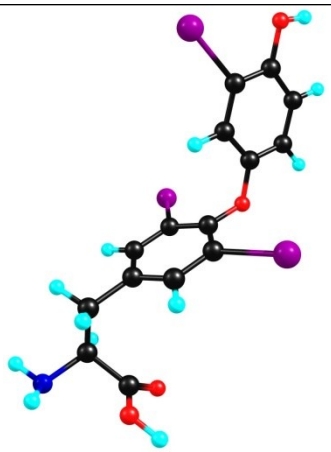

T3

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1	-3.693099000	1.103799000	2.870102000
1	-3.998649000	-0.617214000	2.664914000
1	2.116919000	-0.011909000	-3.494395000
53	4.104029000	-0.223486000	2.153477000
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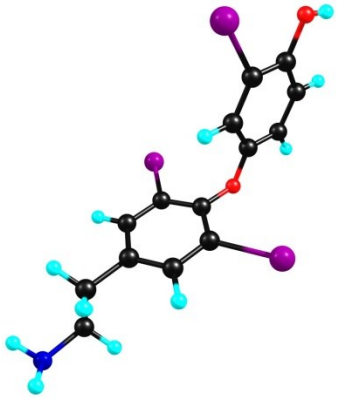

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6	1.191203000	0.000095000	-0.726066000
8	0.255751000	-0.000588000	-1.729082000
6	1.719400000	-1.201038000	-0.236926000
6	2.714102000	-1.200278000	0.736901000
6	4.330730000	0.001508000	2.265241000
6	5.739211000	0.003657000	1.619275000
7	6.864268000	0.003893000	2.548648000
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6	-3.338936000	0.005358000	-2.276197000
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6	-2.967434000	-0.000521000	0.097077000
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1	3.096042000	2.144757000	1.107280000
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1	3.100672000	-2.142879000	1.104418000
1	4.239567000	-0.878339000	2.910957000
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1	6.857472000	0.822898000	3.147561000
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1	-1.568809000	0.006191000	-3.507190000
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1	-0.912724000	-0.004528000	0.726746000
1	-5.686718000	0.006878000	-1.557703000
1	5.835983000	-0.870920000	0.968528000

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