Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Further Investigations into the N-Demethylation of Oripavine using Zero-valent Iron as a Redox Catalyst.

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General Experimental		S-2
Synthesis of Oripavine-*N*-oxide		S-2
General N-Demethylation Procedure		S-2
Figure 1	Oripavine-*N*-oxide Hydrochloride (**6**) ^{1}H NMR spectrum in D_2O	S-3
Figure 1A	Oripavine-*N*-oxide Hydrochloride (**6**) ^{1}H NMR spectrum in D_2O (Expansion)	S-4
Figure 1B	Oripavine-*N*-oxide Hydrochloride (**6**) ^{1}H NMR spectrum in D_2O (Expansion)	S-5
Figure 2	*N*-Nororipavine (**7**) Hydrochloride ^{1}H NMR spectrum in D_2O	S-6
Figure 2A	*N*-Nororipavine (**7**) Hydrochloride ^{1}H NMR spectrum in D_2O (Expansion)	S-7
Figure 2B	*N*-Nororipavine (**7**) Hydrochloride ^{1}H NMR spectrum in D_2O (Expansion)	S-8
Figure 3	*N*-Nororipavine (**7**) Hydrochloride ^{1}H NMR spectrum in D_2O+TFA	S-9
Figure 3A	*N*-Nororipavine (**7**) Hydrochloride ^{1}H NMR spectrum in D_2O+TFA (Expansion)	S-10
Figure 3B	*N*-Nororipavine (**7**) Hydrochloride ^{1}H NMR spectrum in D_2O+TFA (Expansion)	S-11
Figure 4	*N*-Nororipavine (**7**) Hydrochloride ^{13}C NMR spectrum in D_2O+TFA	S-12
Figure 4A	*N*-Nororipavine (**7**) Hydrochloride ^{13}C NMR spectrum in D_2O+TFA (Expansion)	S-13
Figure 4B	*N*-Nororipavine (**7**) Hydrochloride ^{13}C NMR spectrum in D_2O+TFA (Expansion)	S-14
Figure 5	*N*-Nororipavine (**7**) Hydrochloride High Resolution MS	S-15
Table A	Specifications for Iron Catalysts used	S-16

General Experimental

Stainless steel powders 303-L and 316-L were purchased from Alfa Aesar. Iron powder was from Höganäs Sweden. *m*-CPBA was purchased from Sigma-Aldrich. All reactions were conducted under an atmosphere of nitrogen. Chloroform and 2-propanol (Merck) were used as supplied. Both solvents were degassed before use: sonicated for 10 minutes under vacuum and then back-filled with nitrogen. Reactions were monitored using thin layer chromatography (TLC) with pre-coated Merck 5554 Kieselgel 60F_{254} aluminum plates using $CHCl_3$/MeOH/NH_4OH (170:30:1) as the mobile phase. The spots were visualized using both UV light and molybdate stain. ^1H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively. Chemical shifts (δ ppm) were referenced using solvent residual peaks.

Synthesis of Oripavine-*N*-oxide hydrochloride (6)

To a stirred solution of oripavine (1.92 g, 6.47 mmol) in $CHCl_3$ (200 mL) and MeOH (1 mL) at -20 °C was added *m*-CPBA (1.54 g of a max 77% reagent) portionwise over 10 min. The solution was then left to stir for a further 20 minutes. Ice-cold H_2O (100 mL) was added; the pH of the aqueous phase was adjusted to 2–3 via the addition of 10% HCl. The layers were separated; the aqueous phase was extracted with $CHCl_3$ (20 mL x 2), saturated with NaCl, and extracted with $CHCl_3$/2-propanol (3:1, 50 mL x 4). The $CHCl_3$/2-propanol (3:1) extracts were combined, dried (Na_2SO_4), filtered and concentrated to give **6** as an off-white solid, 2.43 g. ^1H NMR of the solid was consistent with the desired product **6** with approximately 0.5 molar equivalent of 2-propanol. This material was used in the subsequent step without further purification. ^1H NMR (D_2O) δ 6.80–6.70 (m, 2H), 6.08, 5.98 (each d, *J* = 6.7 Hz, 1H), 5.56, 5.55 (each s, 1H), 5.32, 5.29 (each d, *J* = 6.7 Hz, 1H), 4.79–4.74 (m, 1H), 3.85–3.57 (m, 9H), 3.33, 3.18 (each dd, *J* = 7.2, 1H), 2.70–2.47 (m, 1H), 2.18–1.98 (m, 1H).

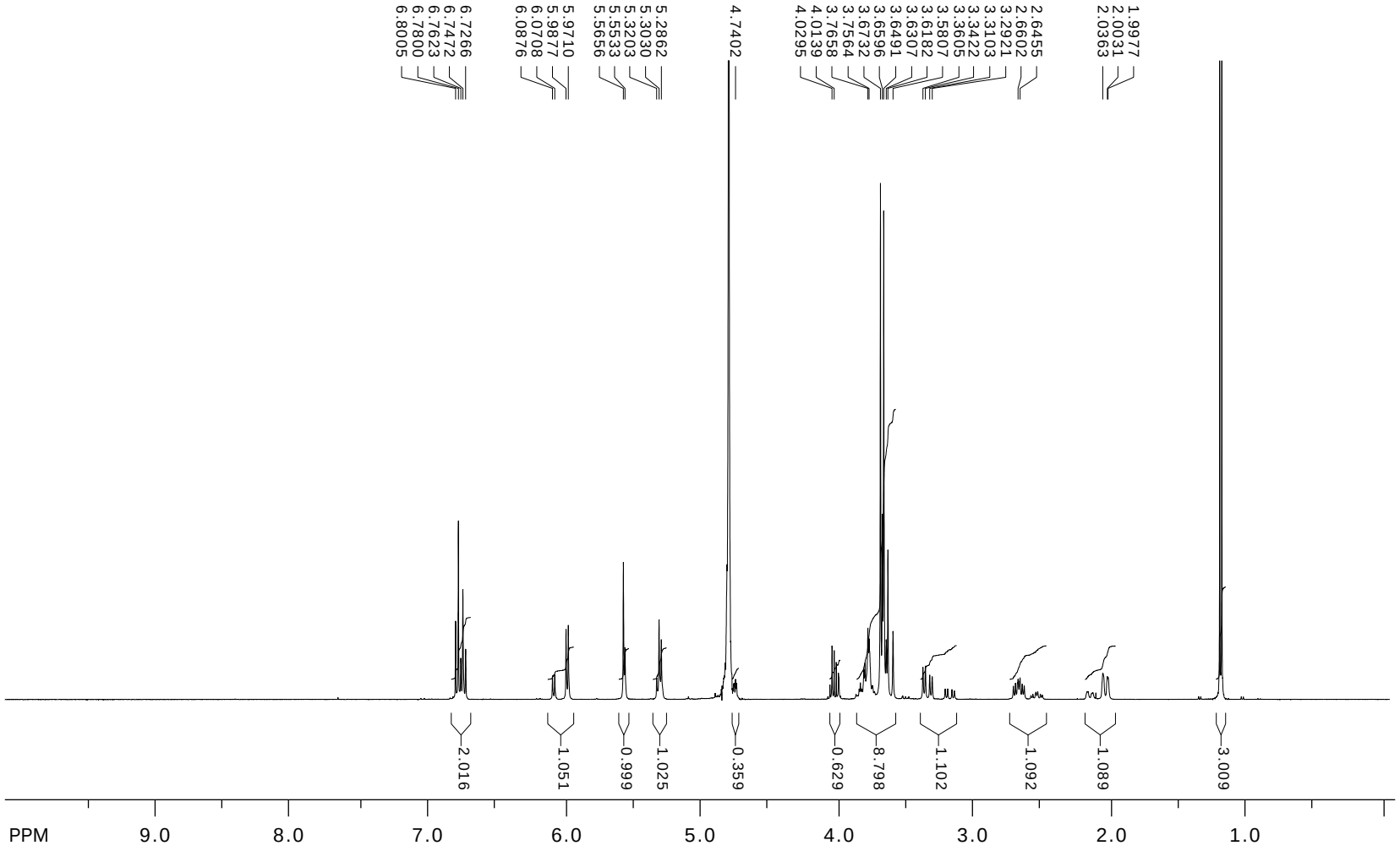
General Procedure for N-Demethylation

To a mixture of oripavine-*N*-oxide hydrochloride (100 mg, 0.263 mmol) and iron powder (varying amounts; see Tables 1 and 2) was added solvent (10 mL). The reaction mixture was then stirred at the specified temperature until complete consumption of **6** (via TLC analysis). The mixture was concentrated to dryness and the remaining residue was subjected to column chromatography on silica gel. Elution with a gradient of $CHCl_3$/MeOH (24:1−17:3) gave oripavine followed by *N*-nororipavine, both as the corresponding hydrochloride.

The above procedure was repeated substituting iron powder with stainless steel powder 303-L or 316-L (see Table 3).

***N*-Nororipavine Hydrochloride (7·HCl)**: Off-white solid, mp >200 °C dec; $[\alpha]_D^{24}$ -188 (*c* 1.0, 10% HOAc); [lit.[1] $[\alpha]_D^{24}$ -194 (*c* 0.83, 10% HOAc)]; ^1H NMR (D_2O) δ 6.79–6.73 (m, 2H), 5.90 (d, *J* = 6.6 Hz, 1H), 5.50 (s, 1H), 5.25 (d, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 6.0, 1H), 3.64 (s, 3 H), 3.46–3.22 (m, 4H), 2.31 (ddd, *J* = 6.0, 13.3 and 13.3 Hz, 1H), 2.08–2.01 (m, 1H); ^{13}C NMR (D_2O/CF_3CO_2D) δ 153.0, 142.8, 138.6, 132.0, 124.4, 124.2, 120.8, 117.3, 117.0, 96.1, 87.7, 55.1, 53.2, 44.6, 37.0, 33.5, 33.1; MS (ESI) *m/z* 284 $[M+H]^+$; HRMS $C_{17}H_{18}NO_3$ calcd for $[M+H]^+$ 284.1281, found 284.1287.

Figure 1. **^{1}H NMR of Oripavine-*N*-oxide Hydrochloride (6) in D_2O**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5.3203
5.3030
5.2862
4.7402
4.0295
4.0139
3.7658
3.7564
3.6732
3.6596
3.6491
3.6307
3.6182
3.5807
3.3605
3.3422
3.3103
3.2921
2.6602
2.6455
2.0363
2.0031
1.9977
2.016
1.051
0.999
1.025
0.359
0.629
8.798
1.102
1.092
1.089
3.009
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

Figure 1A. ^{1}**H NMR of Oripavine-*N*-oxide Hydrochloride (6) in D_2O (Expansion)**

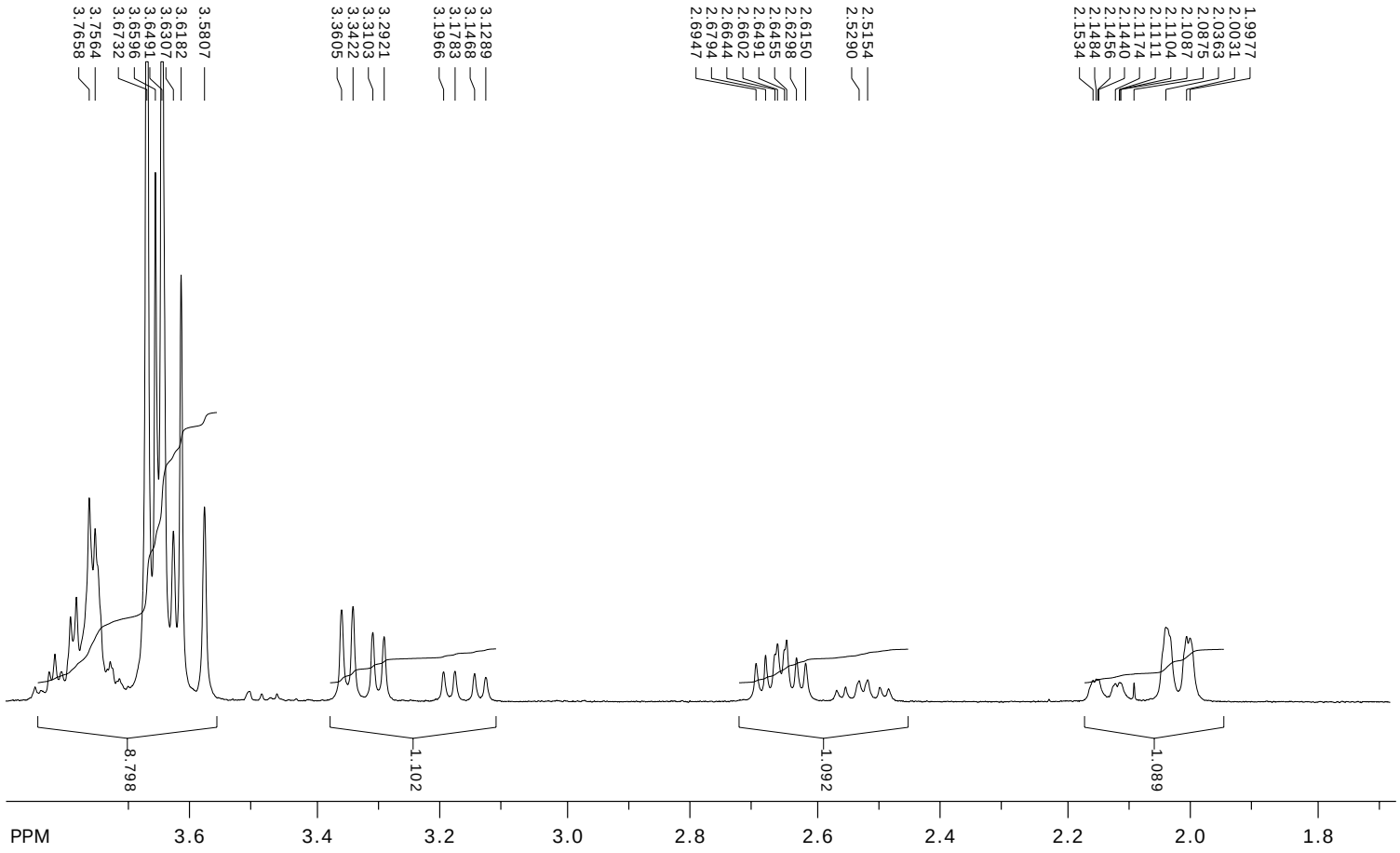

Figure 1B. ^{1}**H NMR of Oripavine-*N*-oxide Hydrochloride (6) in D_2O (Expansion)**

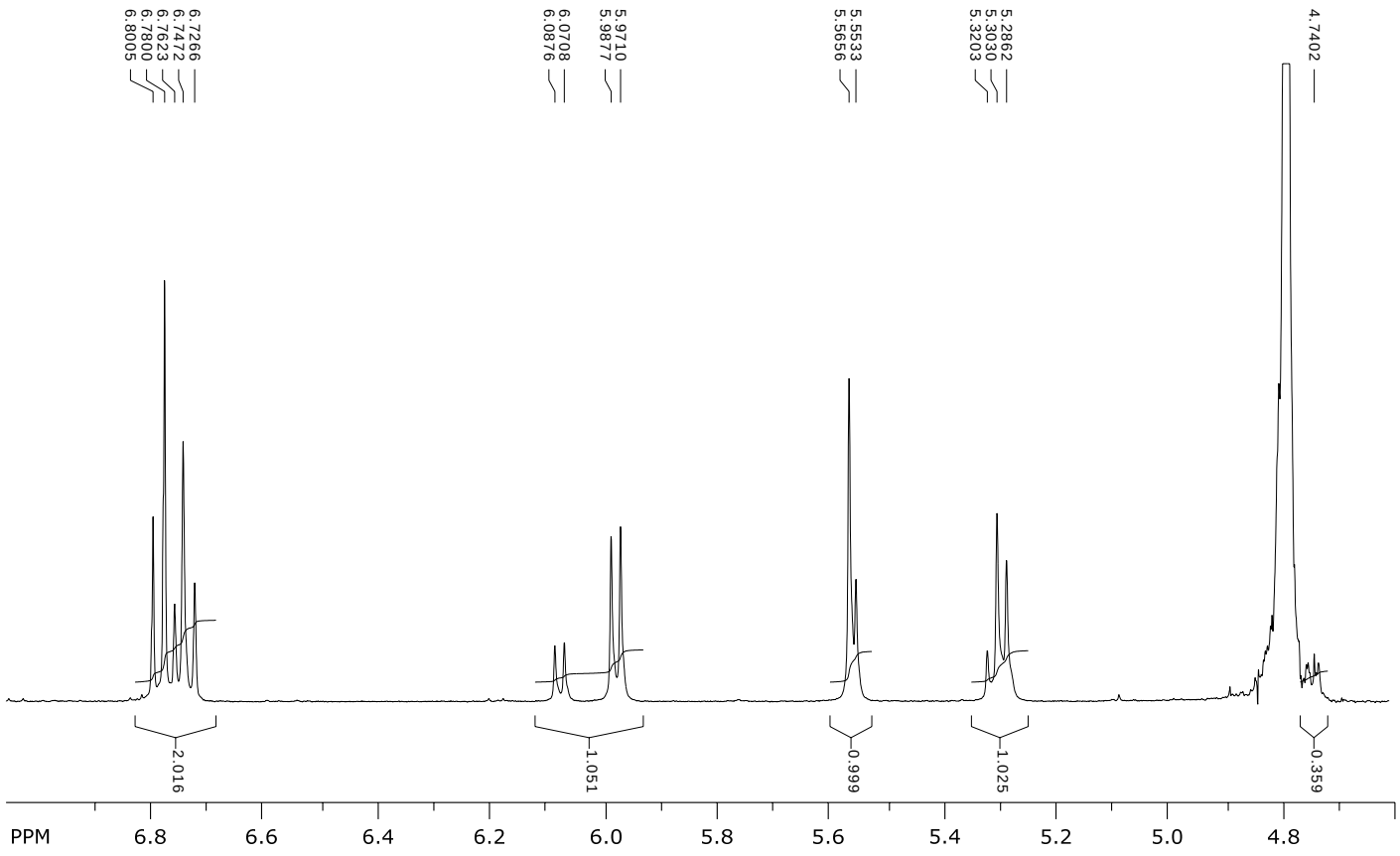

Figure 2. **^{1}H NMR of *N*-Nororipavine (6) Hydrochloride in D_2O**

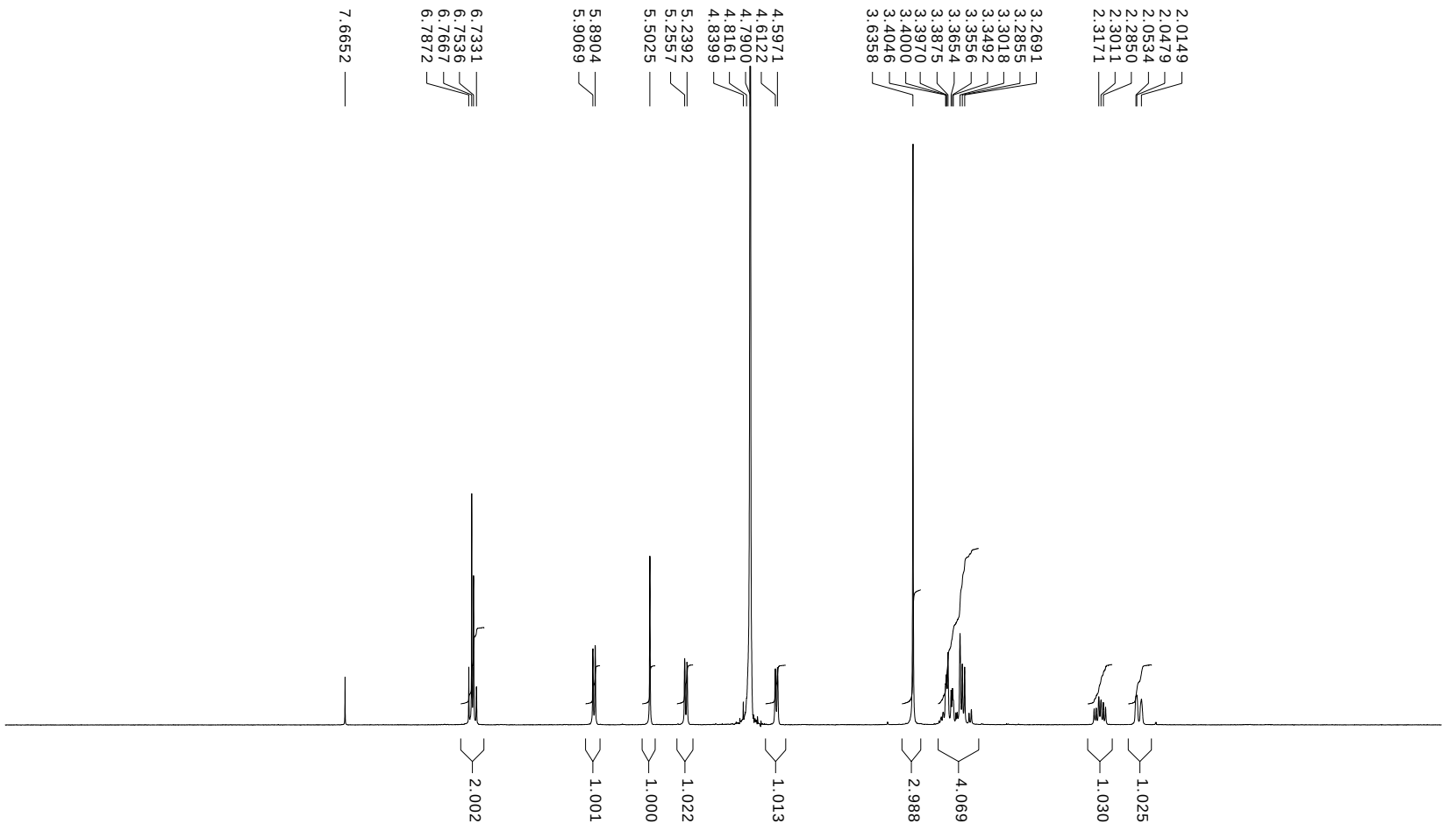

Figure 2A. **^{1}H NMR of *N*-Nororipavine (7) Hydrochloride in D_2O (Expansion)**

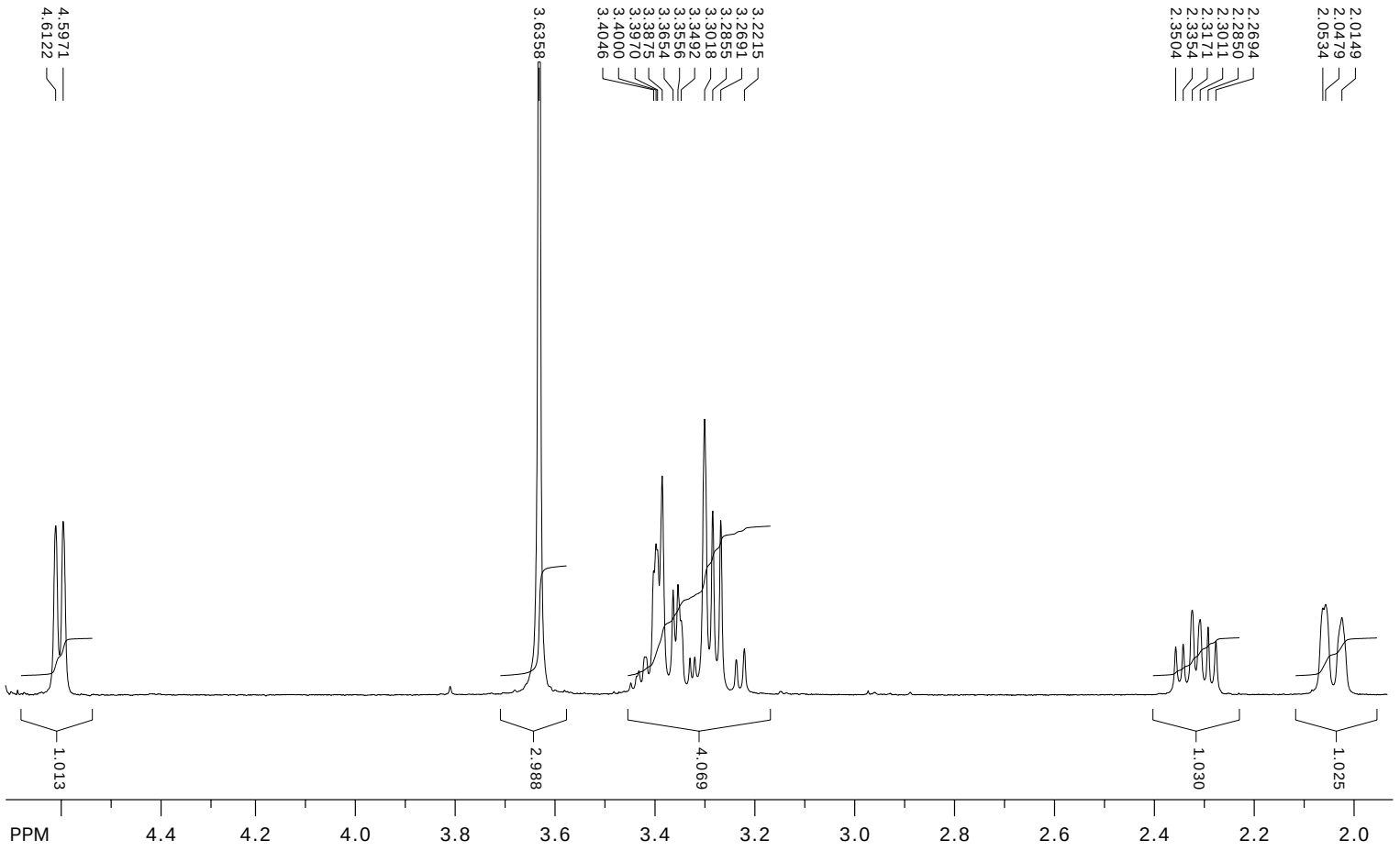

Figure 2B. **^{1}H NMR of *N*-Nororipavine (7) Hydrochloride in D_2O (Expansion)**

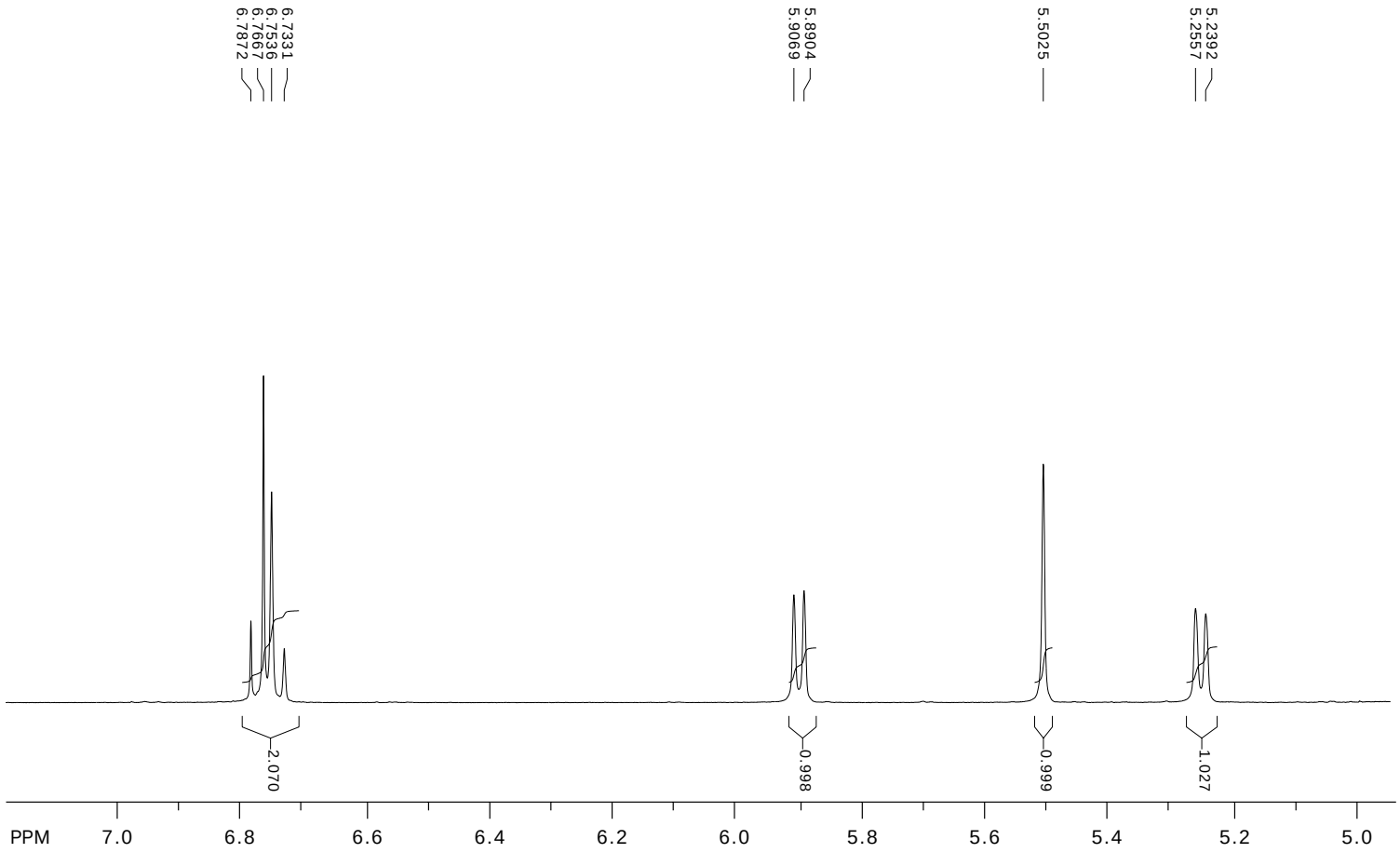

Figure 3. **^{1}H NMR of *N*-Nororipavine (7) Hydrochloride in D_2O +TFA**

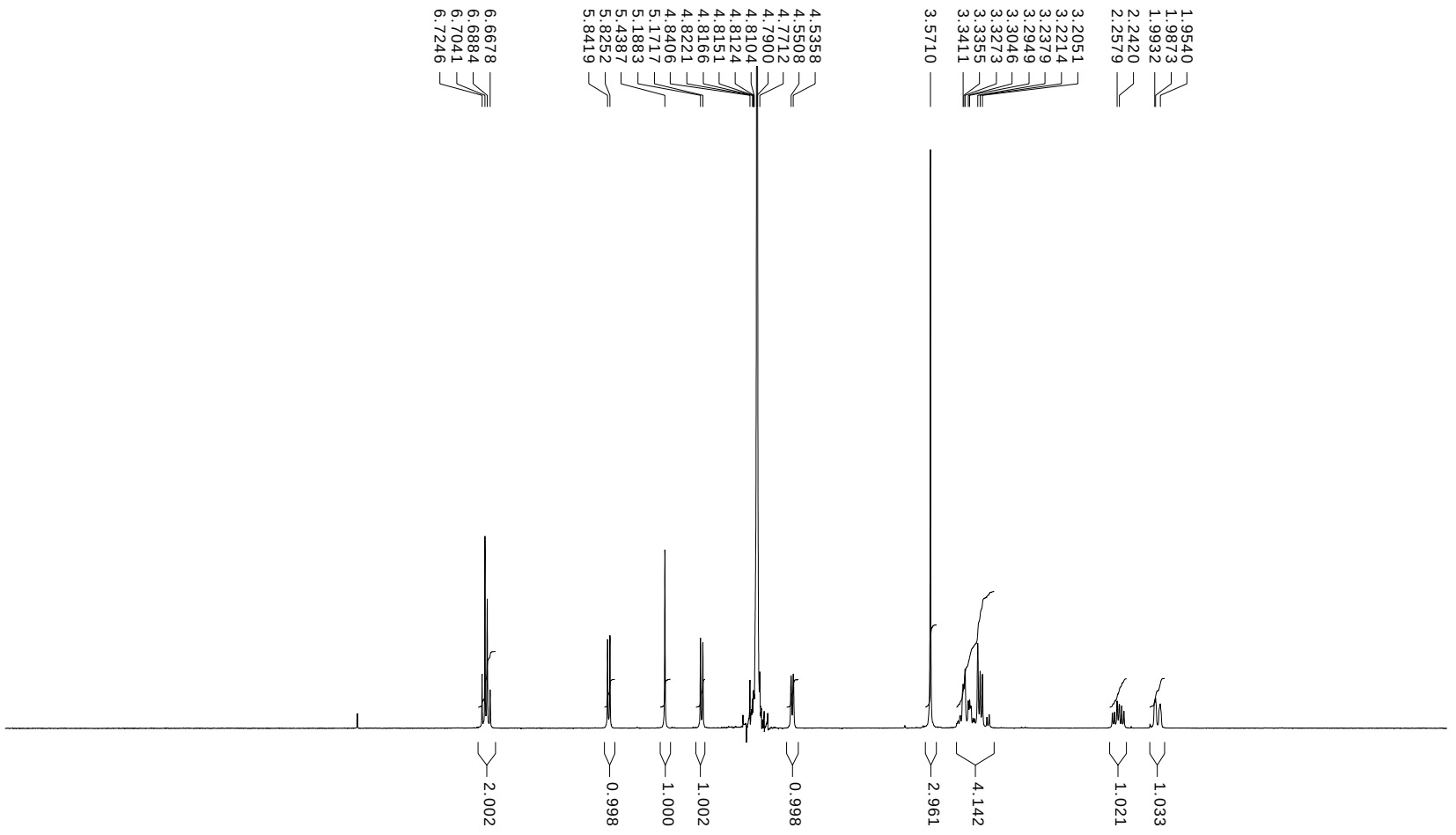

Figure 3A. ^{1}H NMR of *N*-Nororipavine (7) Hydrochloride in D_2O +TFA (Expansion)

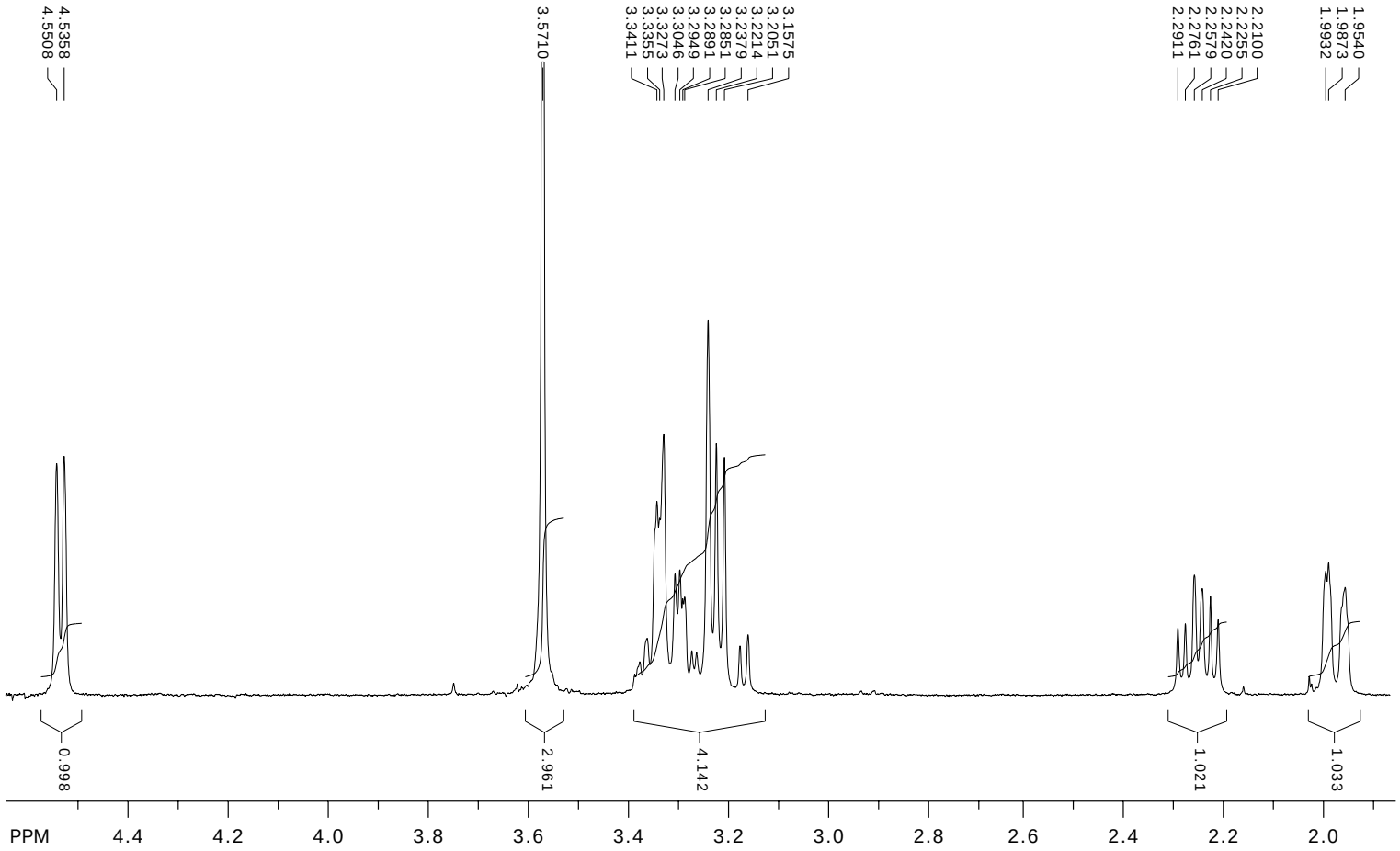

Figure 3B. ^{1}H NMR of *N*-Nororipavine (7) Hydrochloride in D_2O +TFA (Expansion)

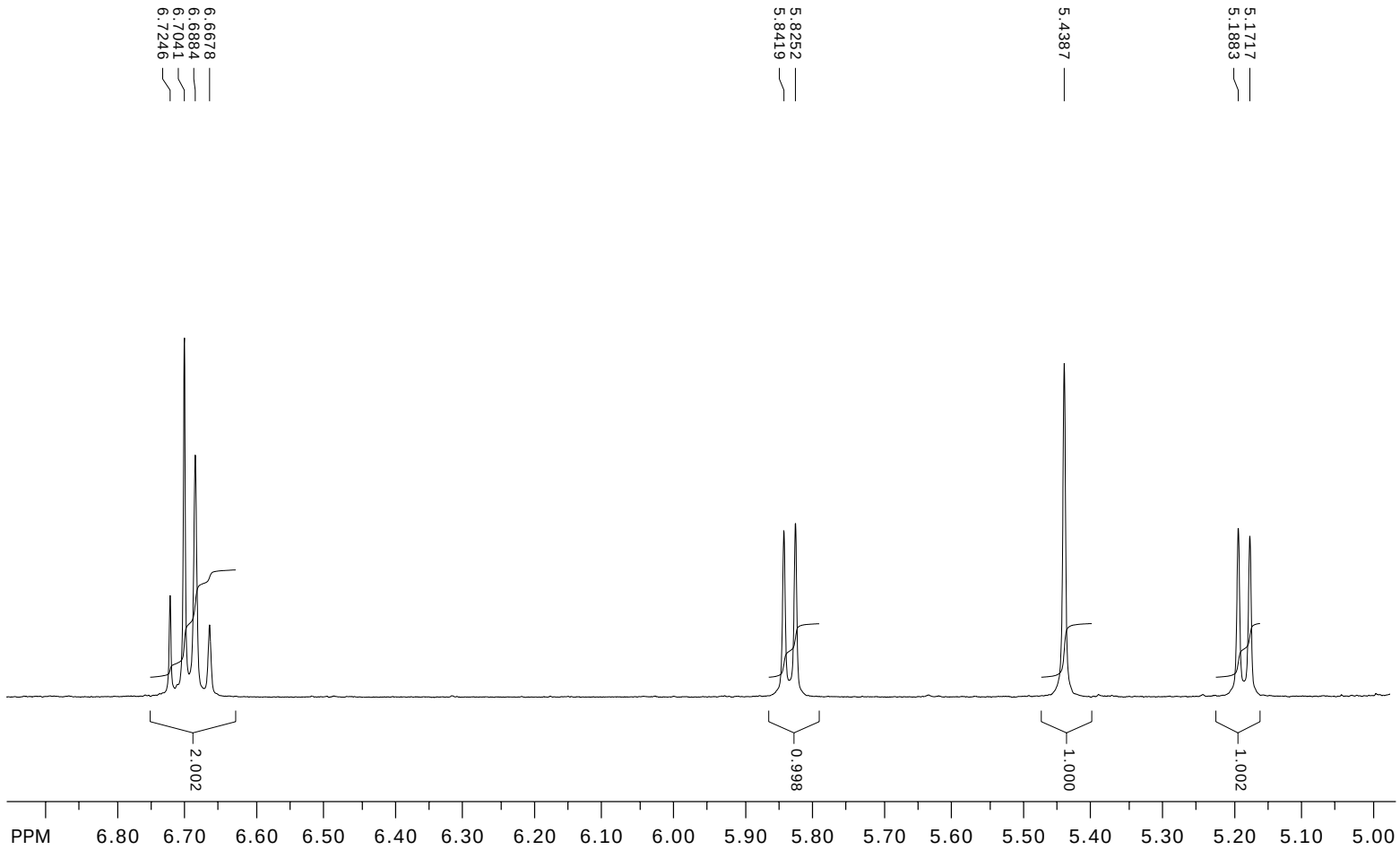

Figure 4. **^{13}C NMR of *N*-Nororipavine (7) Hydrochloride in D_2O + TFA**

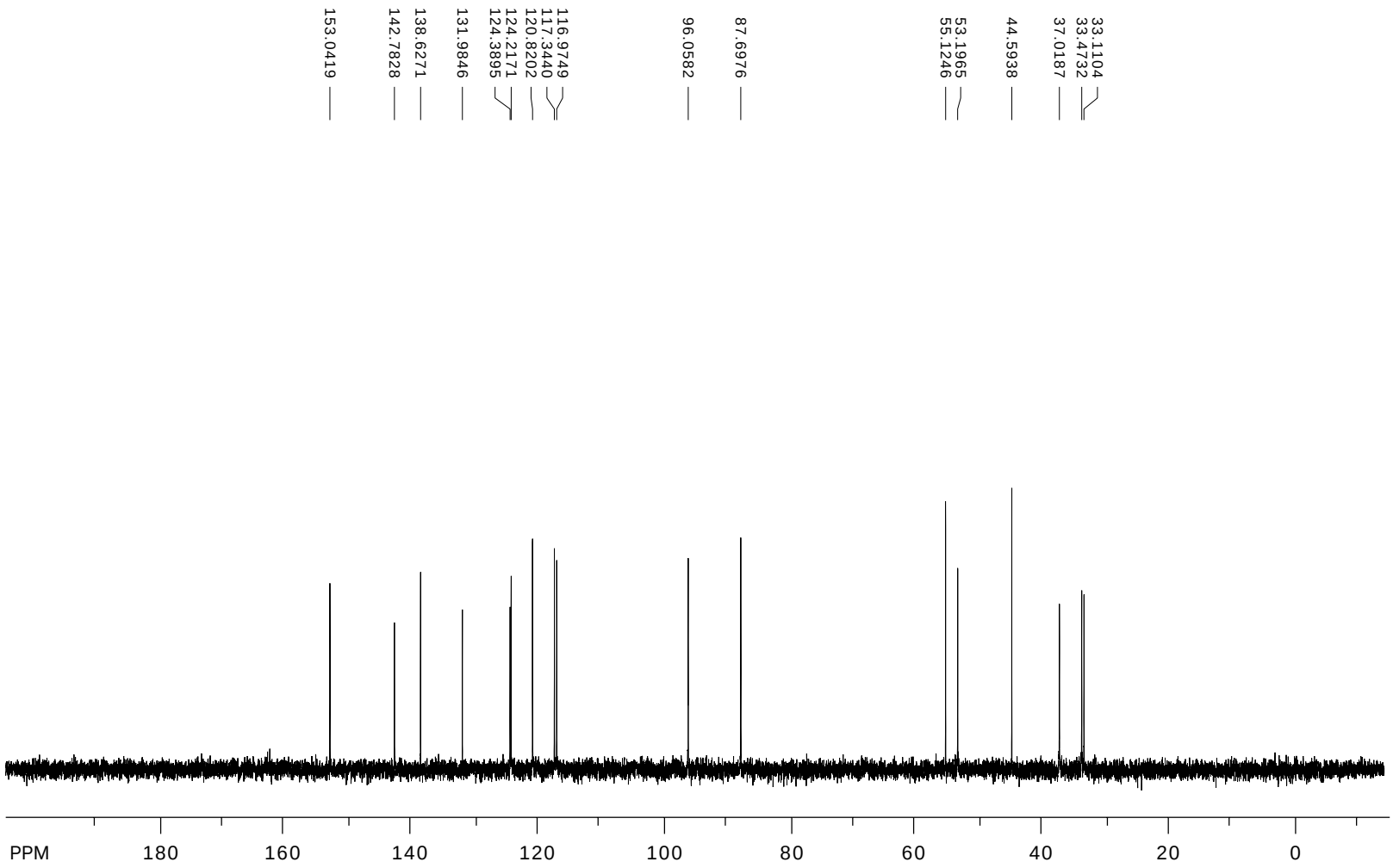

Figure 4A. ^{13}C NMR of *N*-Nororipavine (7) Hydrochloride in D_2O + TFA (Expansion)

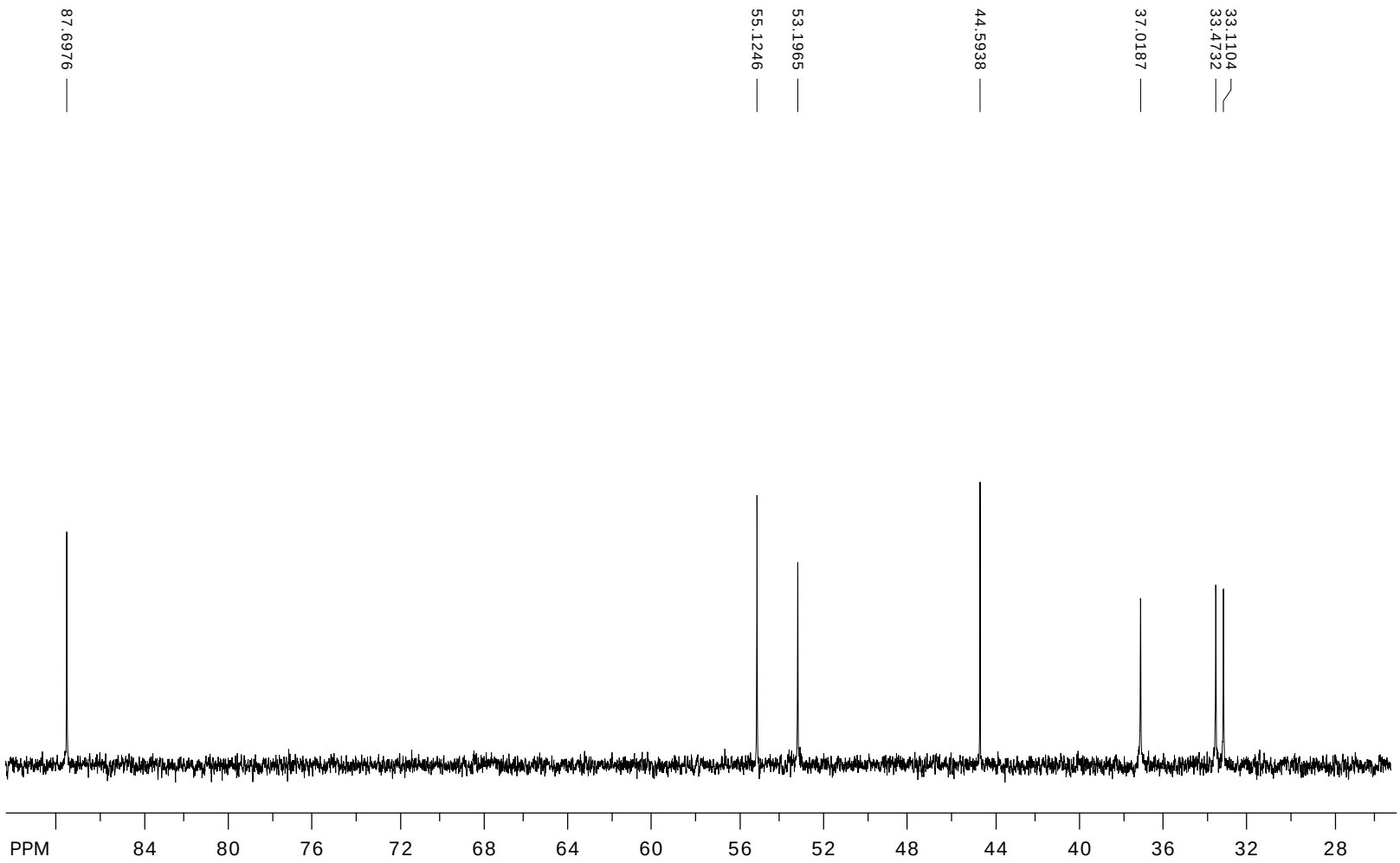

Figure 4B. ^{13}C NMR of *N*-Nororipavine (7) Hydrochloride in D_2O + TFA (Expansion)

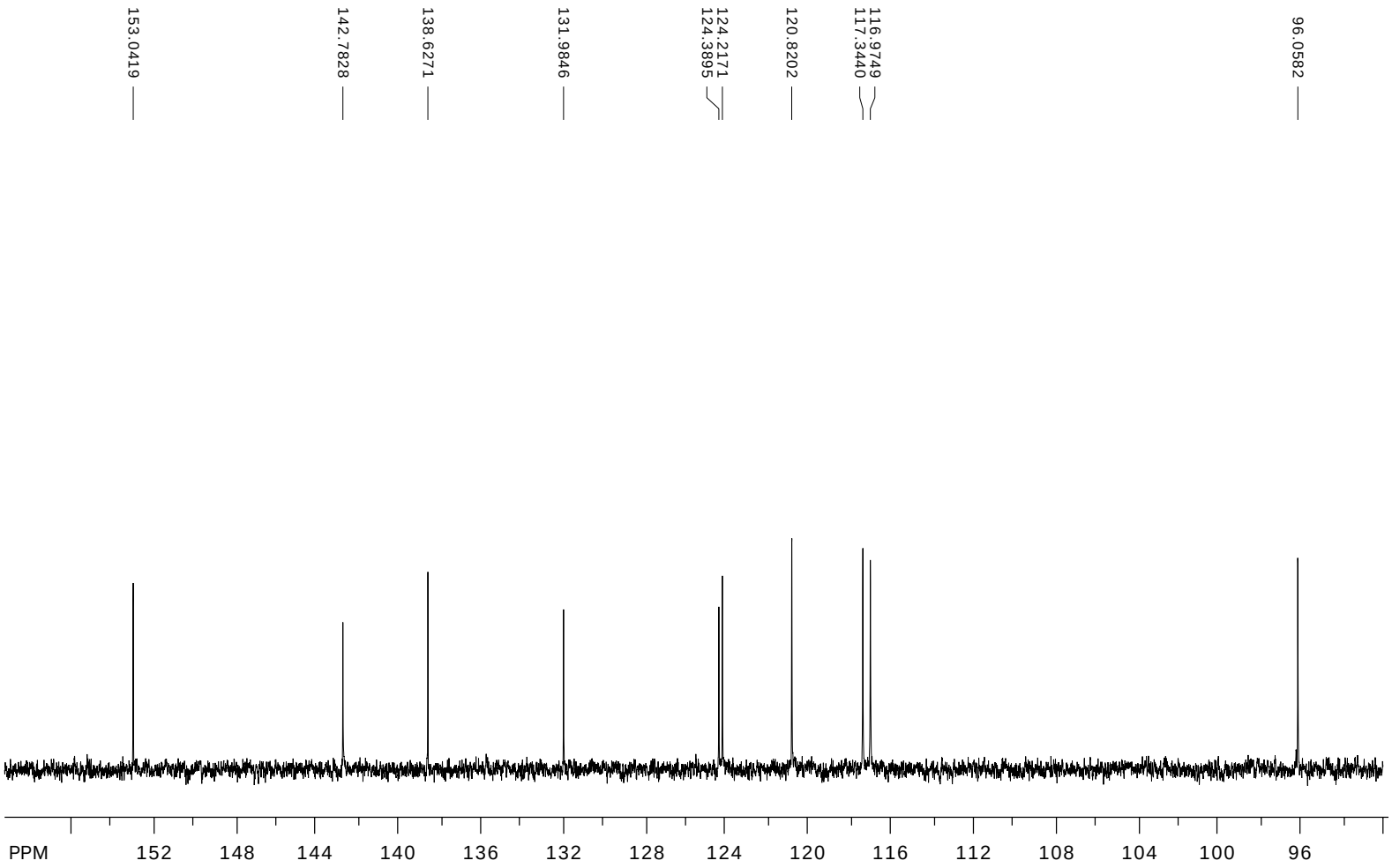

Figure 5. High Resolution MS of *N*-Nororipavine (7)

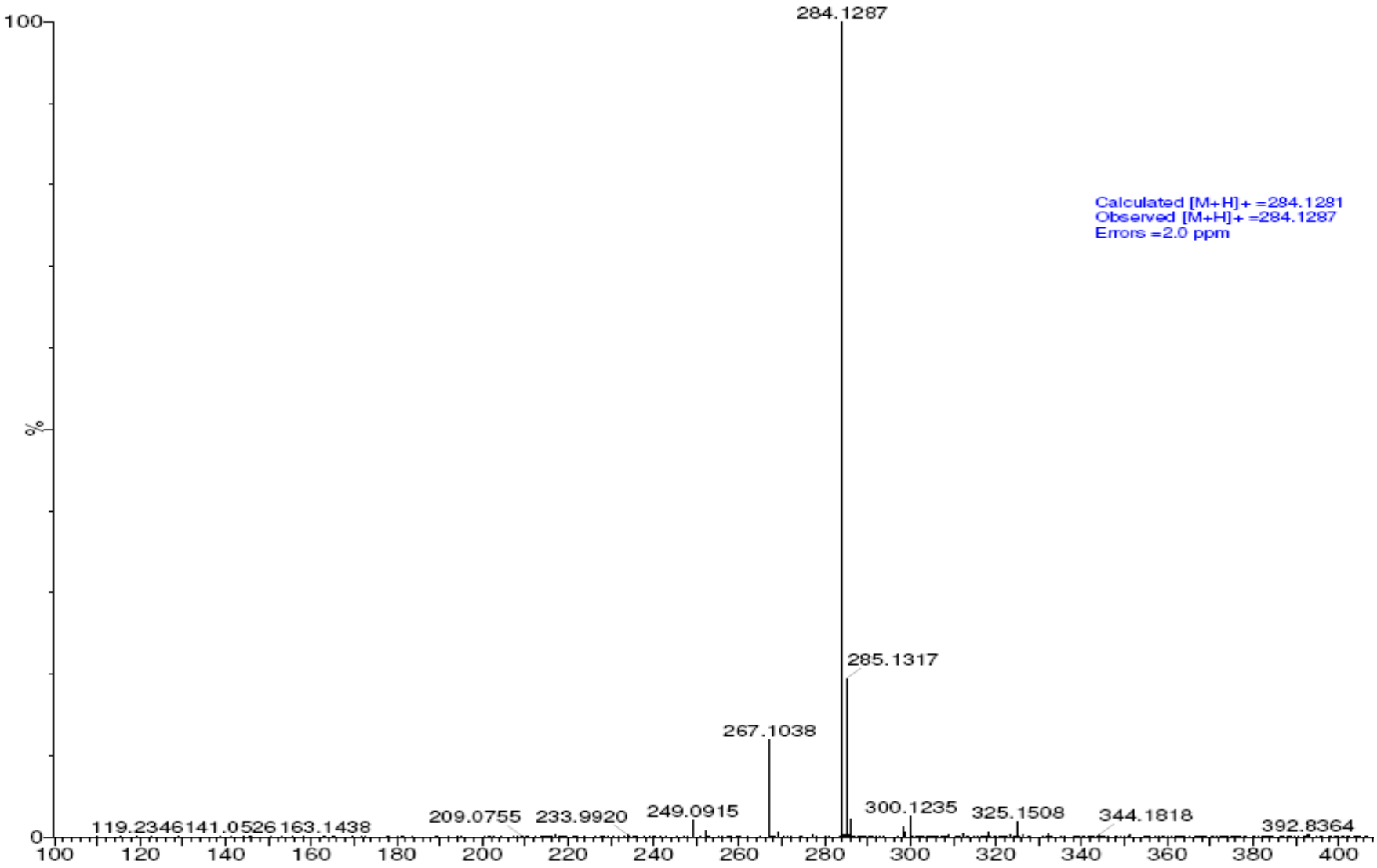

Table A. Specifications for Iron and Stainless Steel Catalysts

Catalyst	**Supplier**	**Physical properties**	**Chemical analysis (%)**						
			Fe	**Cr**	**Ni**	**Mo**	**Mn**	**Si**	**Other**
Iron(0)	Höganäs Sweden	Powder, +212 to -45 microns	99	0.002	0.01	<5 ppm	0.04 (MnO)	0.13 (SiO_2)	Bal
303-L	Alfa Aesar	Powder, -140 mesh	70	17	13				
316-L	Alfa Aesar	Powder, -100 mesh	67.5	17	13	2.5			