Exploration of the Active Site of Neuronal Nitric Oxide Synthase by the Design and Synthesis of Pyrrolidinomethyl 2-Aminopyridine Derivatives

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Table S1. Crystallographic data collection and refinement statistics (1)

Data set[1]	nNOS[3]-**(3S,4S)-4**	nNOS-**(3R,4R)-4**	nNOS[3]-**(3R,4S)-4**	nNOS[3]-**(3S,4R)-4**
PDB code	3NLK	3NLM	3NLN	3NLO
Data collection				
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions				
a, *b*, *c* (Å)	52.1,112.1,164.7	52.1,111.1,164.2	52.0,112.2,164.8	51.4,112.0,164.3
Resolution (Å)	2.02 (2.05-2.02)	1.85 (1.88-1.85)	2.00 (2.03-2.00)	2.30(2.34 -2.30)
R_{sym} or R_{merge}	0.043 (0.63)	0.052 (0.56)	0.051 (0.64)	0.070 (0.59)
$I / \sigma I$	29.1 (2.3)	31.1 (1.8)	27.3 (2.2)	20.3 (1.6)
No. unique reflections	62,972	80,355	65,190	42,244
Completeness (%)	99.1 (98.0)	95.8 (89.1)	98.8 (99.0)	97.0 (98.2)
Redundancy	4.0 (3.7)	3.9 (3.9)	3.9 (3.9)	3.2 (3.4)
Refinement				
Resolution (Å)	2.02	1.85	2.00	2.29
No. reflections	59,732	76,329	61,889	40,091
R_{work} / R_{free} [2]	0.174/0.211	0.189/0.222	0.189/0.225	0.196/0.262
No. atoms				
Protein	6653	6703	6653	6653
Ligand/ion	183	188	183	183
Water	375	381	306	105
Mean *B*-factor	51.83	44.88	53.34	69.04
R.m.s. deviations				
Bond lengths (Å)	0.014	0.014	0.014	0.019
Bond angles (°)	1.388	1.400	1.399	1.718

Data set[1]	eNOS-**(3S,4S)-4**	eNOS-**(3R,4R)-4**	eNOS-**(3R,4S)-4**	eNOS-**(3S,4R)-4**
PDB code	3NLD	3NLE	3NLF	3NLG
Data collection				
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions				
a, *b*, *c* (Å)	57.4,106.9,157.4	58.5,107.6, 158.3	58.1,107.1,157.3	57.9,106.9,157.0
Resolution (Å)	2.28 (2.32-2.28)	1.95 (1.98-1.95)	2.32 (2.36-2.32)	2.38 (2.42-2.38)
R_{sym} or R_{merge}	0.118 (0.571)	0.056 (0.552)	0.052 (0.331)	0.091 (0.611)
I / σ	14.7 (2.0)	20.9 (2.0)	23.6 (4.5)	13.4 (1.9)
No. unique reflections	44,220	72,238	43,117	39,666
Completeness (%)	98.9 (96.0)	98.3 (99.5)	99.4 (100.0)	98.7 (99.6)
Redundancy	4.7 (3.0)	3.6 (3.6)	3.8 (3.8)	3.7 (3.7)
Refinement				
Resolution (Å)	2.28	1.95	2.32	2.38
No. reflections	41,942	69,838	40,909	37,644
R_{work} / R_{free}[2]	0.222/0.292	0.184/0.206	0.174/0.224	0.171/0.231
No. atoms				
Protein	6511	6418	6418	6425
Ligand/ion	201	201	201	201
Water	138	292	333	361
Mean *B*-factor	60.21	53.11	37.67	33.33
R.m.s. deviations				
Bond lengths (Å)	0.021	0.012	0.012	0.012
Bond angles (°)	1.930	1.280	1.349	1.429

[1] See Fig. 3 for chemical formula of inhibitors.

[2] R_{free} was calculated with the 5% of reflections set aside throughout the refinement. The set of reflections for the R_{free} calculation was kept the same for all data sets of each NOS isoform according to that used in the starting model.

[3] The nNOS R349A mutant used.

Table S2. Crystallographic data collection and refinement statistics (2)

Data set[1]	DMnNOS-**(3S,4S)-4**	DMnNOS-**(3R,4R)-4**	DMnNOS-**(3R,4S)-4**	TMnNOS-**(3R,4R)-4**
PDB code	3NLP	3NLQ	3NLR	3NLJ
Data collection				
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions				
a, *b*, *c* (Å)	51.8, 111.0, 164.6	51.6, 111.2, 164.0	51.5, 110.6, 164.1	51.8, 111.1, 163.9
Resolution (Å)	2.03 (2.07-2.03)	2.15 (2.19-2.15)	2.10 (2.14-2.10)	2.20 (2.24-2.20)
R_{sym} or R_{merge}	0.049 (0.689)	0.048 (0.595)	0.060 (0.383)	0.066(0.625)
$I / \sigma I$	28.0(2.3)	24.8 (2.3)	21.4 (1.6)	21.4(1.9)
No. unique reflections	62,123	52,037	52,286	48,289
Completeness (%)	98.8 (97.1)	99.3 (99.4)	93.6 (68.7)	98.7 (92.0)
Redundancy	3.9 (3.5)	3.6 (3.6)	3.7 (2.7)	3.9 (3.5)
Refinement				
Resolution (Å)	2.03	2.15	2.10	2.20
No. reflections	59,003	49,387	49,547	45,803
R_{work} / R_{free}[2]	0.187/0.228	0.204/0.259	0.186/0.235	0.201/0.268
No. atoms				
Protein	6669	6663	6657	6642
Ligand/ion	183	187	183	183
Water	284	215	201	226
Mean *B*-factor	56.97	61.82	63.07	49.50
R.m.s. deviations				
Bond lengths (Å)	0.017	0.018	0.018	0.014
Bond angles (°)	1.493	1.742	1.794	1.546

Data set[1]	SMeNOS-**(3S,4S)-4**	SMeNOS-**(3R,3R)-4**
PDB code	3NLH	3NLL
Data collection		
Space group	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions		
a, *b*, *c* (Å)	57.8, 106.8, 156.9	58.0, 106.8, 156.6
Resolution (Å)	2.10 (2.14-2.10)	1.98 (2.01-1.98)
R_{sym} or R_{merge}	0.092 (0.771)	0.077 (0.730)
I / σ	13.86 (1.74)	18.08 (1.86)
No. unique reflections	57,492	68,424
Completeness (%)	99.4 (100.0)	99.5 (98.3)
Redundancy	4.0 (4.0)	4.0 (3.9)
Refinement		
Resolution (Å)	2.10	1.98
No. reflections	54,574	64,937
R_{work} / R_{free}[2]	0.173/0.212	0.169/0.203
No. atoms		
Protein	6410	6429
Ligand/ion	201	201
Water	516	626
Mean *B*-factor	29.82	30.67
R.m.s. deviations		
Bond lengths (Å)	0.010	0.009
Bond angles (°)	1.310	1.313

[1] See Fig. 3 for chemical formula of inhibitors. DMnNOS: nNOS D597N/M336V mutant; TMnNOS: nNOS D597N/M336V/Y706A mutant; SMeNOS: eNOS N368D mutant.

[2] R_{free} was calculated with the 5% of reflections set aside throughout the refinement. The set of reflections for the R_{free} calculation was kept the same for all data sets of each NOS isoform according to that used in the starting model.

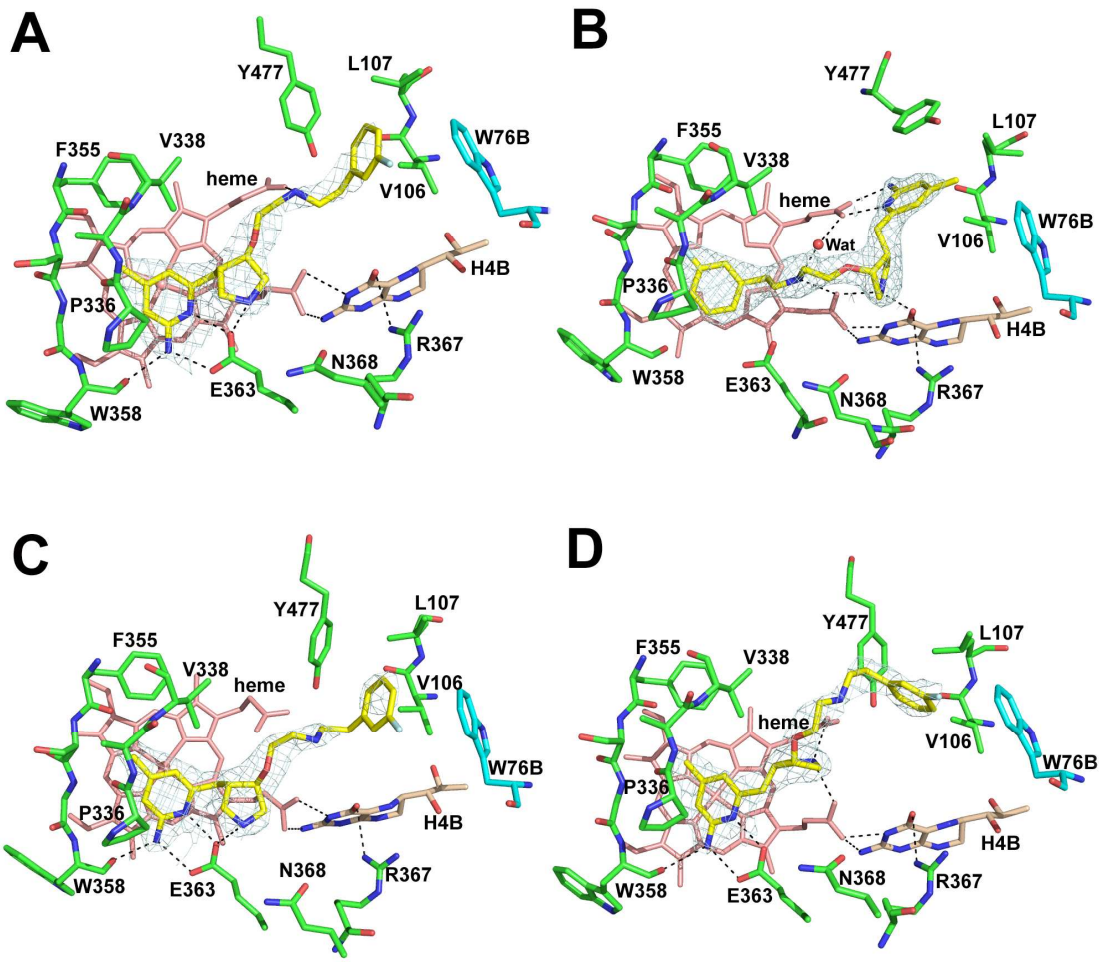
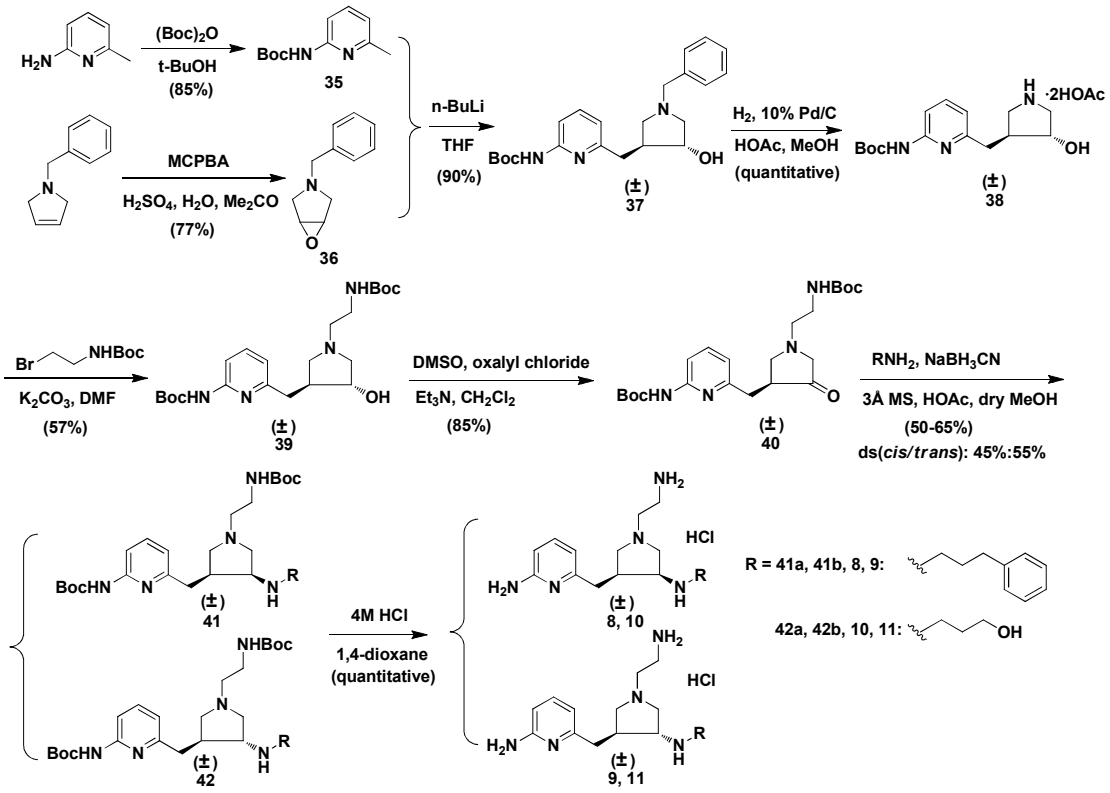


Figure S1. Crystallographic binding conformations of four enantiomerically pure isomers of **4** [A: (3′*S*, 4′*S*)-**4**, B: (3′*R*, 4′*R*)-**4**, C: (3′*R*, 4′*S*)-**4**, D: (3′*S*, 4′*R*)-**4**] with bovine eNOS. Shown also the 2Fo – Fc electron density for the ligands contoured at 1 σ. The active site residues and ligands are represented in an atom-type style (carbons in green or cyan (chain B), nitrogens in blue, oxygen in red, and sulfur in yellow). The important H-bonds between the residues, structural water, cofactors, and inhibitors are depicted with dashed lines.

AutoDock Analysis. AutoDock 3.0.5 was employed to perform the docking calculations.[1] For the protein structure (PDB id: 1P6I), polar hydrogen atoms were added, and Kollman united atom charges were assigned.[2] Hydrogens were also added to the heme and H_4B, and charges were calculated by the Gasteiger–Marsili method.[3] The nonpolar hydrogen atoms of heme and H_4B were removed manually, and their charges were united with the bonded carbon atoms. Atomic solvation parameters and fragmental volumes were assigned using the AddSol utility. The 3D structures of the

ligands were built and partial atomic charges were also calculated using the Gasteiger–Marsili method. The rotatable bonds in the ligands were defined using another AutoDock 3.0 auxiliary program, AutoTors, which also unites the nonpolar hydrogens and partial atomic charges to the bonded carbon atoms. The grid maps were calculated using AutoGrid. The dimensions of the grid box was 27 × 26 × 31 Å, and the grid spacing was set to 0.375 Å. Docking was performed using the Lamarckian genetic algorithm (LGA), and the pseudo-Solis and Wets method were applied for the local search. The procedure in detail used was that previously described.[4-6]

Scheme 1.



(±)-*tert*-Butyl {6-{[cis-1′-(2″-*tert*-butoxycarbonylaminoethyl)-4′-(3″-hydroxypropylamino)--pyrrolidin-3′-yl]methyl}pyridin-2-yl}-carbamate (41b) and (±)-*tert*-Butyl {6-{[trans-1′-(2″-*tert*-butoxycarbonylaminoethyl)-4′-(3″-hydroxypropylamino)-pyrrolidin-3′-yl]methyl}pyridin-2-yl}-carbamate (42b)

The procedure to prepare **41b** and **42b** is the same as that to prepare **41a** and **42a** except using 3-amino-1-propanol (0.113 g, 0.0015 mol) instead of 3-phenyl-1-propylamine. The yield was 55% (0.271 g). The *cis* isomer (**41b**) and the *trans* isomer (**42b**) can be separated by silica gel column chromatography (CH_2Cl_2 : EtOAc : MeOH : Et_3N = 7.6 : 2 : 0.4 : 0.5). The ratio of the *cis* isomer to the *trans* isomer was 45 : 55.

41b: (R_f = 0.25, pale-yellow oil, 0.122 g): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.737 (d, 1H, J=8Hz), 7.556 (t, 2H, J=8Hz), 6.7955 (d, 1H, J=7.5Hz), 5.163 (brs, 1H), 3.865-3.798 (m, 2H), 3.660-3.616 (q, 2H), 3.175 (m, 2H), 2.891-2.870 (m, 2H), 2.819-2.790 (m, 1H), 2.759-2.715 (m, 1H), 2.660-2.645 (m, 3H) 2.584-2.558 (m, 4H), 2.456 (m, 1H), 1.751-1.731 (m, 2H), 1.523 (s, 9H), 1.453 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 159.306 (1C), 156.300 (1C), 152.656 (1C), 151.572 (1C), 138.802 (1C), 117.951 (1C), 109.726 (1C), 81.006 (1C), 79.276 (1C), 64.707 (1C), 59.377 (1C), 59.110 (1C), 57.694 (1C), 55.276 (1C), 48.370 (1C), 41.883 (1C), 39.159 (1C), 36.625 (1C), 31.264 (1C), 28.648 (3C), 28.486 (3C). MS (ESI, CH_3OH): [$C_{25}H_{43}N_5O_5$] *m/z* 494.4 ([M+H]$^+$).

42b: (R_f = 0.2, pale-yellow oil, 0.149 g): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.338 (brs, 1H), 7.784 (d, 1H, J=8Hz), 7.566 (t, 1H, J=8Hz), 6.7995 (d, 1H, J=7.5Hz), 5.247 (brs, 1H), 3.906-3.815 (m, 2H), 3.628-3.585 (q, 1H) 3.224 (m, 2H), 3.064 (m, 1H), 2.987-2.797 (m, 6H), 2.691-2.514 (m, 4H), 2.217-2.186 (m, 1H), 1.887-1.881 (m, 1H), 1.786 (m, 1H), 1.524 (s, 9H), 1.453 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.203 (1C), 156.319 (1C), 152.961 (1C), 152.056 (1C), 138.748 (1C), 118.198 (1C), 110.233 (1C), 80.886 (1C), 79.250 (1C), 63.535 (1C), 63.110 (1C), 58.990 (1C), 57.968 (1C), 54.808 (1C), 47.794 (1C), 42.885 (1C), 41.453 (1C), 38.900 (1C), 29.937 (1C), 28.652 (3C), 28.482 (3C). MS (ESI, CH_3OH): [$C_{25}H_{43}N_5O_5$] *m/z* 494.4 ([M+H]$^+$).

(±)-6-{{cis-1′-(2″-aminoethyl)-4′-[(3″-phenylpropyl)amino]pyrrolidin-3'-yl}methyl}pyridin-2-amine tetrahydrochloride (8). The procedure to prepare **8** is the same as that to prepare **9** except using **41a** (0.111 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.100 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.842 (t, 1H, J=8.5Hz), 7.406-7.283 (m, 5H), 6.928 (d, 1H, J=9Hz), 6.808 (d, 1H, J=7Hz), 4.354-4.311 (m, 1H), 4.102-4.061 (m, 1H), 3.743-3.580 (m, 5H), 3.447-3.357 (m, 3H), 3.291-3.111 (m, 3H), 2.936-2.883 (m, 1H), 2.786-2.748 (m, 2H), 2.125-2.097 (m, 2H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.876 (1C), 144.744 (1C), 144.164 (1C), 140.516 (1C), 128.995 (2C), 128.663 (2C), 126.748 (1C), 112.666 (1C), 112.558 (1C), 56.788 (1C), 56.405 (1C), 54.359 (1C), 52.042 (1C), 47.442 (1C), 37.848 (1C), 35.148 (1C), 31.856 (1C), 29.395 (1C), 27.120 (1C). MS (ESI, CH_3CN-H_2O): [$C_{21}H_{31}N_5$] *m/z* 354.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 354.2652, Found: 354.2651.

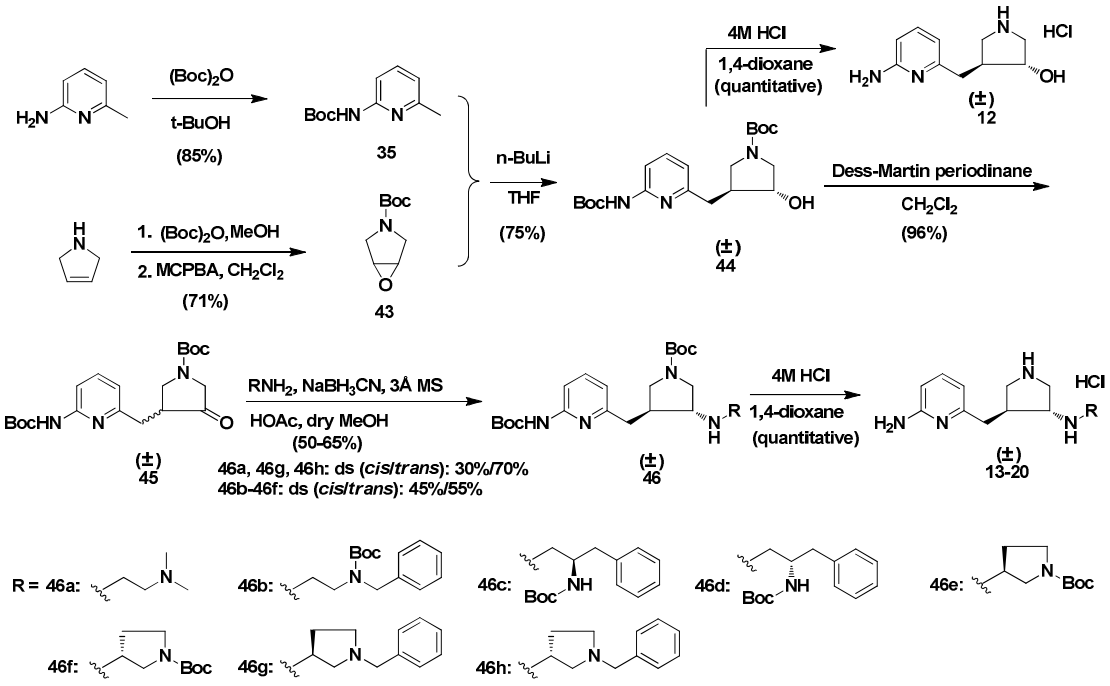
(±)-3-{{cis-1′-(2″-aminoethyl)-4′-[(6″-aminopyridin-2″-yl)methyl]pyrrolidin-3′-yl}amino}propan-1-ol tetrahydrochloride (10). The procedure to prepare **10** is the same as that to prepare **8** except using **41b** (0.097 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.087 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.847 (t, 1H, J=8Hz), 6.931 (d, 1H, J=9Hz), 6.835 (d, 1H, J=7Hz), 4.421 (m, 1H),

4.202 (m, 1H), 3.801-3.665 (m, 6H), 3.453-3.410 (m, 4H), 3.353-3.284(m, 3H), 2.976-2.922 (m, 1H), 2.031-1.982 (m, 2H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.899 (1C), 144.756 (1C), 144.032 (1C), 112.701 (1C), 112.608 (1C), 56.804 (1C), 56.436 (1C), 54.344 (1C), 52.366 (1C), 52.084 (1C), 46.092 (1C), 37.921 (1C), 35.008 (1C), 29.360 (1C), 27.817 (1C). MS (ESI, CH_3OH-H_2O): [$C_{15}H_{27}N_5O$] *m/z* 294.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 294.2288, Found: 294.2288.

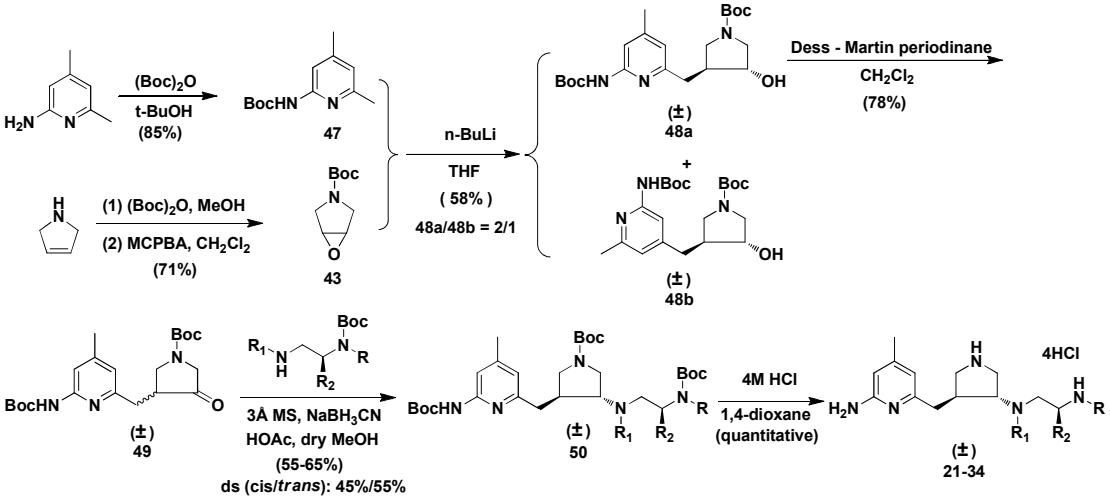
(±)-3-{{trans-1′-(2″-aminoethyl)-4′-[(6″-aminopyridin-2″-yl)methyl]pyrrolidin-3′-yl}amino}propan-1-ol tetrahydrochloride (11). The procedure to prepare **11** is the same as that to prepare **8** except using **42b** (0.097 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.087 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.846 (t, 1H, J=8.5Hz), 6.9215 (d, 1H, J=8.5Hz), 6.813 (d, 1H, J=7Hz), 4.154-2.954 (m, 16H), 2.062-1.932 (m, 2H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.799 (1C), 144.771 (2C), 112.770 (1C), 112.550 (1C), 59.678 (1C), 57.346 (1C), 55.187 (1C), 52.324 (1C), 51.461 (1C), 45.082 (1C), 39.952 (1C), 35.306 (1C), 34.212 (1C), 28.010 (1C). MS (ESI, CH_3OH-H_2O): [$C_{15}H_{27}N_5O$] *m/z* 294.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 294.2288, Found: 294.2283.

Scheme 2.

A.



B.



50a: R_1 = H, R_2 = H, R = Boc
50b: R_1 = H, R_2 = H, R = 4-chlorobenzyl
50c: R_1 = H, R_2 = H, R = 3-chlorobenzyl
50d: R_1 = H, R_2 = H, R = 4-trifluoromethylbenzyl
50e: R_1 = H, R_2 = H, R = 4-fluorobenzyl
50f: R_1 = H, R_2 = H, R = 3-trifluoromethylbenzyl
50g: R_1 = H, R_2 = H, R = 3-methylbenzyl
50h: R_1 = H, R_2 = H, R = 3,4-dichlorobenzyl
50i: R_1 = H, R_2 = H, R = 2,4-dichlorobenzyl
50j: R_1 = H, R_2 = CH_3, R = 4-chlorobenzyl
50k: R_1 = CH_3, R_2 = H, R = 4-chlorobenzyl
50l: R_1 = H, R_2 = H, R = phenethyl
50m: R_1 = H, R_2 = H, R = 4-fluorophenethyl
50n: R_1 = H, R_2 = H, R = 3-fluorophenethyl

(±)-trans-*tert*-Butyl 3-{[6′-(*tert*-butoxycarbonylamino)pyridin-2′-yl]methyl}-4-[2′-(dimethylamino)ethylamino]pyrrolidine-1-carboxylate (46a). The procedure to prepare **46a** is the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol) which was prepared in the previous study[5,6] and N^1, N^1-dimethylethane-1,2-diamine (0.049 g, 0.55 mmol) instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 4 : 6 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.

097 g, 60%, diastereomer ratio: *cis* : *trans* = 30 : 70). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (7.891+7.826) (brs, 1H), 7.764-7.736 (m, 1H), 7.567-7.538 (m, 1H), 6.775 (d, 1H, J=6Hz), 3.782-3.748 (m, 0.5H), 3.693-3.610 (m, 1H), 3.574-3.537 (m, 0.5 H), 3.147-3.035 (m, 2H), 2.990-2.980 (m, 1H), 2.873-2.837 (m, 1H), 2.770-2.605 (m, 3H), 2.529-2.311 (m, 3H), 2.220 (m, 6H), 1.521 (s, 9H), 1.449 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.233 (1C), 154.674 (1C), 152.767 (1C), (151.807+151.742) (1C), 138.646 (1C), 117.983 (1C), (110.315+110.219) (1C), 80.967 (1C), 79.237 (1C), (63.624+62.993) (1C), (59.403+59.360) (1C), (52.509+52.037) (1C), (50.536+50.172) (1C), 46.091 (1C), 45.541 (2C), (43.684+42.984) (1C), (40.199+40.110) (1C), 28.670 (3C), 28.469 (3C). MS (ESI, CH_3OH): $[C_{24}H_{41}N_5O_4]$ *m/z* 464.6 ($[M+H]^+$).

(±)-trans-*tert*-Butyl 3-{2′-[benzyl(*tert*-butoxycarbonyl)amino]ethylamino}-4-{[6′-(*tert*-butoxycarbonyl amino)pyridin-2′-yl]methyl}pyrrolidine-1-carboxylate (46b). The procedure to prepare **46b** is the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol)[1,2] and N^1-benzyl N^1-Boc-ethane-1,2-diamine (0.138 g, 0.55 mmol) which was prepared in the previous study[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.107 g, 62%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.756-7.745 (m, 1H), 7.555-7.514 (m, 1H), 7.407-7.234 (m, 6H), 6.788-6.773 (m, 1H), 4.570-4.448 (m, 2H), 3.764-3.674 (m, 0.5H), 3.660-3.643 (m, 0.5H), 3.622-3.586 (m, 0.5H), 3.546-3.511 (m, 0.5H), 3.297-2.935 (m, 7H), 2.888-2.831 (m, 1H), 2.673 (m, 1H), 2.424-2.356 (m, 0.5H), 2.314-2.300 (m, 0.5H), 1.506-1.454 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.067 (1C), 154.554 (1C), (152.604+152.569) (1C), (151.784+151.703) (1C), (138.765+138.680) (1C), 138.630 (1C), 128.460 (2C), 127.945 (1C), 127.048 (2C), (117.786+117.755) (1C), (109.855+109.793) (1C), 80.646 (1C), 80.106 (1C), 79.211 (1C), (62.943+62.374) (1C), (52.408+51.963) (1C), (50.680+50.192) (1C), (50.304+49.971) (1C), (48.291+48.177) (1C), (46.287+46.250) (1C), (43.824+43.205) (1C), (39.843+39.738) (1C), 28.662 (3C), 28.577 (3C), 28.337 (3C). MS (ESI, CH_3OH): $[C_{34}H_{51}N_5O_6]$ *m/z* 626.3 ($[M+H]^+$).

(±)-trans-*tert*-Butyl 3-[(*R*)-2′-(*tert*-butoxycarbonylamino)-3′-phenylpropylamino]-4-{[6′-(*tert*-butoxyc arbonylamino)pyridin-2′-yl]methyl}pyrrolidine-1-carboxylate (46c). The procedure to prepare **46c** is the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol)[1,2] and (*R*)-*tert*-butyl 1-amino-3-phenylpropan-2-ylcarbamate (0.138 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.095 g, 55%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.756 (m, 1H), 7.555-7.538 (m, 1H), 7.406-7.161 (m, 6H), 6.7575 (d, 1H, J=7.5 Hz), 4.829-4.776 (m, 1H), 3.878-3.839 (m, 1H), 3.660-3.642 (m, 0.5H), 3.660-3.554 (m, 1H), 3.476-3.442 (m, 0.5H), 3.135-2.531 (m, 9H), 2.406-2.397 (m, 0.5H), 2.322-2.269 (m, 0.5H), 1.514 (s, 9H), 1.443 (s, 9H), 1.410 (m, 9H). ^{13}C NMR($CDCl_3$, 125.7 MHz): δ (158.318+158.109) (1C), (155.777+155.715) (1C) 154.686 (1C), 152.461 (1C), 151.610 (1C), 138.634 (1C), (138.592+138.178) (1C), (129.423+129.392) (2C), (128.781+128.572) (2C), 126.525 (1C), 118.002 (1C),

109.836 (1C), 80.909 (1C), 79.358 (2C), (62.308+62.154+61.504+61.326) (1C), (51.952-51.422) (2C), 50.133-49.627 (1C), (44.110+44.002+43.576+43.464) (1C), (40.071-38.876) (2C), 28.631 (3C), 28.507 (3C), 28.395 (3C). MS (APCI, CH_2Cl_2): $[C_{34}H_{51}N_5O_6]$ *m/z* 626.2 ($[M+H]^+$).

(±)-trans-*tert*-Butyl 3-[(*S*)-2′-(*tert*-butoxycarbonylamino)-3′-phenylpropylamino]-4-{[6′-(*tert*-butoxycarbonylamino)pyridin-2′-yl]methyl}pyrrolidine-1-carboxylate (46d). The procedure to prepare **46d** is the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol)[1,2] and (*S*)-*tert*-butyl 1-amino-3-phenylpropan-2-ylcarbamate (0.138 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.103 g, 60%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.764 (m, 1H), 7.549-7.544 (m, 2H), 7.276-7.161 (m, 5H), 6.751 (d, 1H, J = 7 Hz), 4.923 (m, 1H), 3.888-3.838 (m, 1H), 3.661 (m, 0.5H), 3.598-3.553 (m, 1H), 3.473-3.460 (m, 0.5H), 3.133-2.537 (m, 9H), 2.399 (m, 0.5H), 2.311 (m, 0.5H), 1.511 (s, 9H), 1.443 (s, 9H), 1.405 (m, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.218+158.036) (1C), (155.703+155.645) (1C) 154.566 (1C, 19), (152.461+152.403) (1C), 151.591 (1C), 138.530 (1C), (138.483+138.139) (1C), (129.334+129.303) (2C), 128.460 (2C), 126.413 (1C), 117.879 (1C), 109.770 (1C), 80.762 (1C), 79.222 (2C), (62.208+62.007+61.399+60.382) (1C), (51.820-51.313) (2C), 50.056-49.538 (1C), (43.986+43.874+43.475+43.359) (1C), (39.564-38.787) (2C), 28.546 (3C), 28.418 (3C), 28.306 (3C). MS (ESI, CH_3OH): $[C_{34}H_{51}N_5O_6]$ *m/z* 626.6 ($[M+H]^+$).

(±)-trans-*tert*-Butyl 3-{{6′-[(*tert*-butoxycarbonyl)amino]pyridin-2′-yl}methyl}-4-{[(*S*)-1′-(*tert*-butoxycarbonyl)pyrrolidin-3′-yl]amino}pyrrolidine-1-carboxylate (46e). The procedure to prepare **46e** is the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol)[1,2] and (*S*)-(-)-1-Boc-3-aminopyrrolidine (0.103 g, 0.55 mmol) instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8 : 2 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.093 g, 60%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.753-7.737 (m, 1H), 7.564-7.552 (m, 1H), 7.431-7.291 (m, 1H), 6.780 (m, 1H), 3.774 (m, 0.5H), 3.711-3.698 (m, 0.5H), 3.581 (m, 1H), 3.474-3.298 (m, 5H), 3.117-2.897 (m, 5H), 2.619-2.598 (m, 1H), 2.414 (m, 0.5H), 2.325 (m, 0.5H), 1.986 (m, 1H), 1.521 (s, 9H), 1.461-1.450 (m, 18H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.144 (1C), (154.717+154.647+154.566) (2C), 152.392 (1C), 151.567 (1C), 138.661 (1C), (118.103+117.960) (1C), 109.828 (1C), 80.990 (1C), 79.439 (1C), 79.308 (1C), (61.055+60.927+60.711+60.111+59.681) (1C), (56.544+56.378+55.743+55.476+55.120) (1C), (52.726+52.555+52.029+51.453) (2C), (49.928+49.677) (1C), (44.404+44.121+44.005+43.769) (2C), (40.063+39.773+39.676) (1C), (33.138+32.376+32.032+31.444) (1C), 28.620 (6C), 28.376 (3C). MS (ESI, CH_3OH): $[C_{29}H_{47}N_5O_6]$ *m/z* 562.7 ($[M+H]^+$); *m/z* 584.6 ($[M+Na]^+$); *m/z* 1123.6 ($[2M+H]^+$); *m/z* 1145.3 ($[2M+Na]^+$).

(±)-trans-*tert*-Butyl

3-{{6′-[(*tert*-butoxycarbonyl)amino]pyridin-2′-yl}methyl}-4-{[(*R*)-1′-(*tert*-butoxycarbonyl)pyrrolidin-3′-yl]amino}pyrrolidine-1-carboxylate (46f). The procedure to prepare **46f** is the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol)[1,2] and (*R*)-(+)-1-Boc-3-aminopyrrolidine (0.103 g, 0.55 mmol) instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8 : 2 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.100 g, 65%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.752-7.736 (m, 1H), 7.563-7.550 (m, 1H), 7.449-7.314 (m, 1H), 6.789-6.778 (m, 1H), 3.773 (m, 0.5H), 3.709-3.697 (m, 0.5H), 3.592-3.560 (m, 1H), 3.473-3.296 (m, 5H), 3.113-2.898 (m, 5H), 2.618 (m, 1H), 2.411 (m, 0.5H), 2.325 (m, 0.5H), 1.984-1.974 (m, 1H), 1.520 (s, 9H), 1.461-1.449 (m, 18H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.137 (1C), (154.682+154.616) (2C), 152.380 (1C), 151.552 (1C), 138.634 (1C), (118.084+117.937) (1C), 109.801 (1C), 80.956 (1C), 79.400 (1C), 79.273 (1C), (61.036+60.896+60.691+60.099+59.654) (1C), (56.532+56.358+55.735+55.453+55.093) (1C), (52.710+52.536+52.006+51.851+51.437) (2C), (49.913+49.658) (1C), (44.385+44.102+43.986+43.746) (2C), (40.032+39.754+39.657) (1C), (33.119+32.357+32.009+31.428) (1C), 28.600 (6C), 28.356 (3C). MS(ESI, CH_3OH): [$C_{29}H_{47}N_5O_6$] *m/z* 562.7 ([M+H]$^+$); *m/z* 584.6 ([M+Na]$^+$); *m/z* 1123.6 ([2M+H]$^+$); *m/z* 1145.3 ([2M+Na]$^+$).

(±)-trans-*tert*-Butyl 3-[((*S*)-1′-benzylpyrrolidin-3′-yl)amino]-4-{{6′-[(*tert*-butoxycarbonyl)amino]pyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (46g). The procedure to prepare **46g** is the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol)[1,2] and (*S*)-(+)-1-benzyl-3-aminopyrrolidine (0.097 g, 0.55 mmol) instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 7 : 3 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.096 g, 50%, diastereomer ratio: *cis* : *trans* = 30 : 70). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (8.807+8.763) (brs, 1H), 7.803-7.736 (m, 1H), 7.568-7.536 (m, 1H), 7.364-7.223 (m, 5H), 6.777-6.747 (m, 1H), 4.006-3.402 (m, 4H), 3.364-3.255 (m, 1H), 3.160-2.899 (m, 4H), 2.838-2.818 (m, 1H), 2.775-2.617 (m, 3H), 2.574-2.196 (m, 4H), (1.523+1.503) (s, 9H), 1.436 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.191+158.140) (1C), (154.616+154.484) (1C), (152.894+152.484) (1C), (151.896+151.846+151.525) (1C), 138.905 (1C), (138.669+138.553) (1C), (128.990+128.935) (2C), 128.347 (2C), 127.059 (1C), (118.064+117.886+117.844) (1C), (110.199+110.13+110.056+109.971) (1C), 80.983-80.913 (1C), (79.323+79.292) (1C), (61.929+61.643+61.531+61.279) (1C), 60.614 (1C), (60.498+60.347+59.956) (1C) (58.594+58.471) (1C), (56.022+55.968+55.875) (1C), (53.329+53.143+53.085) (1C), (52.973+52.479+51.956) (1C), (50.865+50.509+50.087+49.805) (1C), (44.094+43.812+43.491+43.154) (1C), (40.651+40.524+39.738) (1C), (33.363+31.927+31.846) (1C), 28.627 (3C), (28.519+28.384) (3C). MS (ESI, CH_3OH): [$C_{31}H_{45}N_5O_4$] *m/z* 552.5 ([M+H]$^+$).

(±)-trans-*tert*-Butyl 3-[((*R*)-1′-benzylpyrrolidin-3′-yl)amino]-4-{{6′-[(*tert*-butoxycarbonyl)amino]pyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (46h). The procedure to prepare **46h** is

the same as that to prepare **42a** except using **45** (0.196 g, 0.5 mmol)[1,2] and (*R*)-(-)-1-benzyl-3-aminopyrrolidine (0.097 g, 0.55 mmol) instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 7 : 3 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.096 g, 50%, diastereomer ratio: *cis* : *trans* = 30 : 70). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (8.814+8.770) (brs, 1H), 7.803-7.736 (m, 1H), 7.568-7.520 (m, 1H), 7.364-7.222 (m, 5H), 6.776-6.747 (m, 1H), 4.007-3.401 (m, 4H), 3.364-3.225 (m, 1H), 3.159-2.935 (m, 4H), 2.856-2.819 (m, 1H), 2.775-2.616 (m, 3H), 2.576-2.163 (m, 4H), (1.523+1.502) (s, 9H), 1.436 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.187+158.117) (1C), (154.616+154.473) (1C), (152.887+152.496) (1C), (151.892+151.842+151.517) (1C), 138.901 (1C), (138.661+138.541) (1C), (128.986+128.932) (2C), 128.340 (2C), 127.051 (1C), (118.057+117.879+117.836) (1C), (110.192+110.130+110.052+109.967) (1C), 80.971-80.905 (1C), (79.311+79.280) (1C), (61.933+61.631+61.519+61.279) (1C), 60.606 (1C), (60.490+60.339+59.960) (1C) (58.575+58.459) (1C), (56.018+55.964+55.871) (1C), (53.321+53.132+53.074) (1C), (52.965+52.455+51.956) (1C), (50.861+50.725+50.083+49.801) (1C), (44.087+43.804+43.483+43.139) (1C), (40.651+40.524+39.734) (1C), (33.351+31.952+31.844) (1C), 28.620 (3C), (28.511+28.376) (3C). MS (ESI, CH_3OH): [$C_{31}H_{45}N_5O_4$] *m/z* 552.6 ([M+H]$^+$).

N^1-{(±)-trans-4-[(6-aminopyridin-2-yl)methyl]pyrrolidin-3-yl}-N^2,N^2-dimethyleth ane-1,2-diamine tetrahydrochloride (13). The procedure to prepare **13** is the same as that to prepare **8** except using **46a** (0.093 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.081 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.848 (t, 1H, J=8.5Hz), 6.927 (d, 1H, J=9Hz), 6.8295 (d, 1H, J=7.5Hz), 4.113-4.018 (m, 2H), 3.777-3.679 (m, 2H), 3.654-3.612 (m, 4H), 3.374-3.328 (m, 2H), 3.174-3.133 (m, 1H), 2.997 (s, 6H), 2.962-2.932 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.793 (1C), 144.835 (1C), 144.595 (1C), 112.860 (1C), 112.612 (1C), 60.926 (1C), 52.558 (1C), 48.562 (1C), 46.492 (1C), 43.637 (2C), 41.606 (1C), 40.538 (1C), 33.590 (1C). MS (ESI, CH_3OH): [$C_{14}H_{25}N_5$] *m/z* 264.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 264.2183, Found: 264.2179.

N^1-{(±)-trans-4-[(6-aminopyridin-2-yl)methyl]pyrrolidin-3-yl}-N^2-benzylethane-1 ,2-diamine tetrahydrochloride (14). The procedure to prepare **14** is the same as that to prepare **8** except using **46b** (0.125 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.094 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.855 (t, 1H, J=8Hz), 7.548-7.496 (m, 5H), 6.932 (d, 1H, J=9Hz), 6.829 (d, 1H, J=7Hz), 4.350 (s, 2H), 4.034-3.997 (m, 2H), 3.725-3.683 (m, 2H), 3.535 (m, 4H), 3.370-3.301 (m, 2H), 3.116-3.111 (m, 1H), 2.976-2.926 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.793 (1C), 144.827 (1C), 144.699 (1C), 130.180 (1C), 130.134 (1C), 130.041 (2C), 129.542 (2C), 112.794 (1C), 112.574 (1C), 60.775 (1C), 51.862 (1C), 48.566 (1C), 46.620 (1C), 42.937 (2C), 40.627 (1C), 33.605 (1C). MS (ESI, CH_3OH): [$C_{19}H_{27}N_5$] *m/z* 326.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 326.2339, Found: 326.2331.

(*R*)-N^1-{(±)-trans-4′-[(6″-aminopyridin-2″-yl)methyl]pyrrolidin-3′-yl}-3-phenylpr opane-1,2-diamine tetrahydrochloride (15). The procedure to prepare **15** is the same as that to prepare **8** except using **46c** (0.125 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.094 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ

7.834 (t, 1H, J=8.5 Hz), 7.436-7.342 (m, 5H), 6.917 (d, 1H, J=9Hz), 6.799 (m, 1H), 3.998-3.933 (m, 3H), 3.715-3.657 (m, 2H), 3.531-3.011 (m, 7H), 2.958-2.886 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.704 (1C), 144.839 (1C), (144.750+144.726) (1C), (134.006+133.971) (1C), 129.561 (4C), 128.281 (1C), 112.806 (1C), 112.535 (1C), (61.197+61.046) (1C), (50.554+50.388) (1C), (48.728+48.690) (1C), (48.264+48.156) (1C), (46.929+46.898) (1C), (40.619+40.453) (1C), (36.549+36.522) (1C), (33.857+33.749) (1C). MS (ESI, CH_3OH): [$C_{19}H_{27}N_5$] *m/z* 326.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 326.2339, Found: 326.2334. Comb. Anal. ($C_{19}H_{31}Cl_4N_5 \cdot 1.065\ H_2O$), Calcld: C, 46.53; H, 6.81; N, 14.28; Found: C, 46.93; H, 7.01; N, 13.72.

(*S*)-*N*^{1}-{(±)-trans-4′-[(6″-aminopyridin-2″-yl)methyl]pyrrolidin-3′-yl}-3-phenylpropane-1,2-diamine tetrahydrochloride (16). The procedure to prepare **16** is the same as that to prepare **8** except using **46d** (0.125 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.094 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.815 (t, 1H, J=8.5 Hz), 7.418-7.332 (m, 5H), 6.901 (d, 1H, J=9Hz), 6.801-6.780 (m, 1H), 4.031-3.945 (m, 3H), 3.766-3.695 (m, 2H), 3.599-3.412 (m, 2H), 3.352-3.130 (m, 4H), 3.070-3.010 (m, 1H), 2.958-2.886 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.626 (1C), 144.827 (1C), 144.525 (1C), 133.832 (1C), (129.619+129.592) (2C) 129.553 (2C), 128.296 (1C), 112.868 (1C), 112.574 (1C), (61.189+61.042) (1C), (50.341+50.218) (1C), (48.751+48.717) (1C), (48.260+48.167) (1C), 46.697 (1C), (40.441+40.310) (1C), (36.553+36.526) (1C), (33.803+33.710) (1C). MS (ESI, CH_3OH): [$C_{19}H_{27}N_5$] *m/z* 326.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 326.2339, Found: 326.2336.

6-{[(±)-trans-4′-((*S*)-pyrrolidin-3″-ylamino)pyrrolidin-3′-yl]methyl}pyridin-2-amine tetrahydrochloride (17). The procedure to prepare **17** is the same as that to prepare **8** except using **46e** (0.112 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.081 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.840 (t, 1H, J=8.5Hz), 6.921 (d, 1H, J=9Hz), 6.833 (d, 1H, J=7Hz), 4.289-4.251 (m, 1H), 4.133-4.042 (m, 2H), 3.941-3.864 (m, 1H), 3.776-3.630 (m, 3H), 3.590-3.543 (m, 1H), 3.489-3.436 (m, 1H), 3.378-3.340 (m, 2H), 3.181-3.151 (m, 1H), 2.990-2.940 (m, 1H), 2.694-2.560 (m, 1H), 2.331-2.228 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.781 (1C), 144.831 (1C), 144.541 (1C), (112.837+112.790) (1C), 112.666 (1C), (59.634+59.321) (1C), (55.433+55.278) (1C), (48.573+48.523) (1C), 46.771 (1C), (46.589+46.484) (1C), 44.809 (1C), (40.639+40.503) (1C), (33.687+33.590) (1C), (27.771+27.249) (1C). MS (ESI, CH_3OH): [$C_{14}H_{23}N_5$] *m/z* 262.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 262.2026, Found: 262.2022.

6-{[(±)-trans-4′-((*R*)-pyrrolidin-3″-ylamino)pyrrolidin-3′-yl]methyl}pyridin-2-amine tetrahydrochloride (18). The procedure to prepare **18** is the same as that to prepare **8** except using **46f** (0.112 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.081 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.845-7.815 (m, 1H), 6.918-6.902 (m, 1H), 6.825-6.814 (m, 1H), 4.260-4.249 (m, 1H), 4.082-4.045 (m, 2H), 3.927-3.852 (m, 1H), 3.754-3.632 (m, 3H), 3.564-3.539 (m, 1H), 3.460-3.441 (m, 1H), 3.364-3.330 (m, 2H), 3.149 (m, 1H), 2.975-2.926 (m, 1H), 2.653-2.564 (m, 1H), 2.299-2.258 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.777 (1C), 144.804 (1C), 144.529 (1C), (112.802+112.752) (1C), 112.647 (1C), (59.615+59.298) (1C), (55.409+55.255) (1C), (48.546+48.492) (1C), 46.747 (1C), (46.566+46.461) (1C), 44.782 (1C), (40.623+40.492) (1C), (33.660+33.567) (1C), (27.756+27.230) (1C).

MS (ESI, CH_3OH): [$C_{14}H_{23}N_5$] *m/z* 262.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 262.2026, Found: 262.2023.

6-{{(±)-trans-4′-[((*S*)-1″-benzylpyrrolidin-3″-yl)amino]pyrrolidin-3′-yl}methyl}pyridin-2-amine tetrahydrochloride (19). The procedure to prepare **19** is the same as that to prepare **8** except using **46g** (0.110 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.099 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.805 (t, 1H, J=7.5Hz), 7.518 (m, 5H), 6.912-6.879 (m, 1H), 6.818-6.795 (m, 1H), 4.487 (m, 2H), 4.222 (m, 1H), 4.021-3.841 (m, 3H), 3.713-3.458 (m, 5H), 3.350-3.256 (m, 2H), 3.076-3.069 (m, 1H), 2.971-2.904 (m, 1H), 2.638 (m, 1H), 2.285 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.731 (1C), 144.773 (2C), (130.590+130.571) (2C), 130.501 (1C), 129.627 (2C), (129.472+129.449) (1C), (112.748+112.713) (1C), 112.546 (1C), (59.518+59.147) (1C), (58.810+55.779) (1C), (54.524+54.411+54.202) (2C), 52.454 (1C), (48.570+48.477) (1C), (47.061+46.914) (1C), (40.832+40.786) (1C), (33.698+33.652) (1C), 26.971 (1C). MS (ESI, CH_3OH): [$C_{21}H_{29}N_5$] *m/z* 352.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 352.2496, Found: 352.2497.

6-{{(±)-trans-4′-[((*R*)-1″-benzylpyrrolidin-3″-yl)amino]pyrrolidin-3′-yl}methyl}pyridin-2-amine tetrahydrochloride (20). The procedure to prepare **20** is the same as that to prepare **8** except using **46h**(0.110 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.099 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.809 (t, 1H, J=7.5Hz), 7.521 (m, 5H), 6.9025 (d, 1H, J=8.5Hz), 6.811-6.788 (m, 1H), 4.515-4.450 (m, 2H), 4.154-4.105 (m, 1H), 3.979-3.801 (m, 3H), 3.731-3.505 (m, 5H), 3.324-3.226 (m, 2H), 3.076-2.890 (m, 2H), 2.600 (m, 1H), 2.238 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.742 (1C), 145.009 (1C), 144.769 (1C), 130.571 (2C), 130.486 (1C), 129.619 (2C), 129.546 (1C), 112.697 (1C), 112.469 (1C), (59.534+59.143) (1C), 58.798 (1C), (54.876+54.779) (1C), (54.365+54.152) (1C), 52.500 (1C), (48.535+48.434) (1C), (47.328+47.185) (1C), (41.022+40.964) (1C), 33.725 (1C), 27.694 (1C). MS (ESI, CH_3OH): [$C_{21}H_{29}N_5$] *m/z* 352.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 352.2496, Found: 352.2493.

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(4″-chlorobenzyl)amino]ethyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50b). The procedure to prepare **50b** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(4-chlorobenzyl)carbamate (0.156 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.120 g, 65%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.616-7.600 (m, 1H), 7.292-7.279 (s, 3H), 7.162 (s, 2H), 6.603 (s, 1H), 4.402 (s, 2H), 3.669-3.658 (m, 0.5H), 3.606 (m, 0.5H), 3.553-3.518 (m, 0.5H), 3.464-3.430 (m, 0.5H), 3.379-2.946 (m, 5H), 2.791-2.682 (m, 3H), 2.521-2.501 (m, 1H), 2.409-2.283 (m, 4H), 1.514-1.448 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.791 (1C), 155.927 (1C), (154.749+154.658) (1C), 152.533 (1C), 151.531 (1C), 150.032 (1C), 137.179 (1C), 133.038 (1C), (129.110+128.758+128.491) (4C), (119.292+119.226) (1C), (110.386+110.325) (1C), 80.861 (1C), 80.241 (1C), 79.349 (1C), (62.149+61.299) (1C), (51.882+51.330) (1C), 50.407 (1C), (49.915+49.702) (1C), 47.310 (1C), 46.290 (1C), (44.153+43.169) (1C), (39.691+39.594) (1C), 28.598

(3C), 28.556 (3C), 28.374 (3C), 21.398 (1C). MS (ESI, CH_3OH): [$C_{35}H_{52}ClN_5O_6$] *m/z* 674.3 ([M+H]$^+$).

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(4″-(trifluoromethyl)benzyl)amino]ethyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50d). The procedure to prepare **50d** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(4-(trifluoromethyl)benzyl)carbamate (0.175 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.110 g, 57%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.615-7.574 (m, 3H), 7.337 (s, 2H), 7.228-7.196 (brs, 1H), 6.601 (s, 1H), 4.497 (s, 2H), 3.700-3.666 (m, 0.5H), 3.621 (m, 0.5H), 3.563-3.527 (m, 0.5H), 3.470-3.434 (m, 0.5H), 3.395-3.214 (m, 2H), 3.133-3.097 (m, 1H), 3.069-3.018 (m, 1H), 2.968-2.955 (m, 1H), 2.800-2.718 (m, 3H), 2.553-2.509 (m, 1H), 2.411-2.247 (m, 4H), 1.513-1.447 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.870 (1C), 155.860 (1C), (154.804+154.701) (1C), 152.564 (1C), 151.556 (1C), 150.080 (1C), 142.995 (1C), (130.021+129.760+129.492+129.240) (1C), (127.859+127.264) (2C), (125.643+125.613) (2C), (127.531+125.370+123.202+121.041) (1C), (119.347+119.280) (1C), (110.416+110.349) (1C), 80.940 (1C), 80.430 (1C), 79.410 (1C), (62.246+61.408) (1C), (51.955+51.402) (1C), 50.570 (1C), (49.976+49.769) (1C), (47.681+47.583) (1C), 46.381 (1C), (44.226+43.667) (1C), (39.764+39.679) (1C), 28.653 (3C), 28.544 (3C), 28.410 (3C), 21.428 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ -62.875 (CF_3). MS (ESI, CH_3OH): [$C_{36}H_{52}F_3N_5O_6$] *m/z* 708.3 ([M+H]$^+$), 730.2([M+Na]$^+$).

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(4″-fluorobenzyl)amino]ethyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50e). The procedure to prepare **50e** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(4-fluorobenzyl)carbamate (0.147 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.099 g, 55%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.615-7.598 (m, 1H), 7.199 (m, 3H), 7.003 (m, 2H), 6.602 (s, 1H), 4.404 (s, 2H), 3.668-3.657 (m, 0.5H), 3.600 (m, 0.5H), 3.554-3.519 (m, 0.5H), 3.462-3.442 (m, 0.5H), 3.381-3.197 (m, 2H), 3.125-3.091 (m, 1H), 3.047-3.036 (m, 1H), 2.949-2.938 (m, 1H), 2.818-2.677 (m, 3H), 2.523-2.503 (m, 1H), 2.409-2.283 (m, 4H), 1.514-1.449 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.116+161.161) (1C), 157.858 (1C), 155.939 (1C), (154.737+154.646) (1C), 152.527 (1C), 151.519 (1C), 149.995 (1C), 134.337 (1C), (129.420+128.812) (2C), (119.286+119.220) (1C), (115.540+115.370) (2C), (110.361+110.295) (1C), 80.849 (1C), 80.138 (1C), 79.312 (1C), (62.149+61.329) (1C), (51.900+51.354) (1C), 50.285 (1C), (49.921+49.721) (1C), 47.201 (1C), 46.278 (1C), (44.153+43.607) (1C), (39.709+39.624) (1C), 28.617 (3C), 28.556 (3C), 28.368 (3C), 21.385 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ -115.902 (F). MS (ESI, CH_3OH): [$C_{35}H_{52}FN_5O_6$] *m/z* 658.3 ([M+H]$^+$).

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(3″-(trifluoromethyl)benzyl)amino]ethyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50f). The procedure to prepare **50f** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(3-(trifluoromethyl)benzyl)carbamate (0.175 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.107 g, 55%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.611-7.592 (m, 1H), 7.511-7.430 (m, 4H), 7.217 (brs, 1H), 6.600 (s, 1H), 4.436(s, 2H), 3.692-3.659 (m, 0.5H), 3.607 (m, 0.5H), 3.556-3.520 (m, 0.5H), 3.466-3.430 (m, 0.5H), 3.396-3.217 (m, 2H), 3.130-3.093 (m, 1H), 3.048-3.031 (m, 1H), 2.957-2.906(m, 1H), 2.818-2.719 (m, 3H), 2.575-2.477 (m, 1H), 2.411-2.199 (m, 4H), 1.513-1.447 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.919 (1C), 155.848 (1C), (154.792+154.701) (1C), 152.570 (1C), 151.544 (1C), 150.062 (1C), 139.959 (1C), (131.393+131.138+130.883+130.628+130.482) (2C), 129.158 (1C), 124.204 (2C), (127.477+125.309+123.142+120.980) (1C), (119.341+119.268) (1C), (110.404+110.337) (1C), 80.909 (1C), 80.466 (1C), 79.379 (1C), (62.240+61.426) (1C), (51.937+51.773) (1C), 50.800 (1C), (49.957+49.757) (1C), (47.693+47.420) (1C), 46.400 (1C), (44.208+43.661) (1C), (39.757+39.672) (1C), 28.653 (3C), 28.513 (3C), 28.404 (3C), 21.416 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ -63.069 (CF_3). MS (ESI, CH_3OH): [$C_{36}H_{52}F_3N_5O_6$] *m/z* 708.3 ([M+H]$^+$).

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(3″-methylbenzyl)amino]ethyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50g). The procedure to prepare **50g** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(3-methylbenzyl)carbamate (0.145 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.75 : 0.25 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.117 g, 65%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.611-7.593 (m, 1H), 7.203-7.190 (m, 2H), 7.069-7.029 (m, 3H), 6.597 (s, 1H), 4.410 (s, 2H), 3.663-3.656 (m, 0.5H), 3.593 (m, 0.5H), 3.544-3.508 (m, 0.5H), 3.453-3.418 (m, 0.5H), 3.379-3.212 (m, 2H), 3.120-3.084 (m, 1H), 3.028-3.009 (m, 1H), 2.942-2.923 (m, 1H), 2.790-2.678 (m, 3H), 2.529-2.484 (m, 1H), 2.408-2.281 (m, 4H), 1.513-1.450 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.925 (1C), 156.109 (1C), (154.749+154.670) (1C), 152.545 (1C), 151.501 (1C), 149.983 (1C), 138.490 (1C), 138.247 (1C), (128.557+128.090) (3C), (124.933+124.320) (1C), (119.305+119.226) (1C), (110.355+110.276) (1C), 80.855 (1C), 80.005 (1C), 79.294 (1C), (62.118+61.293) (1C), (51.937+51.390) (1C), 50.880 (1C), (49.921+49.727) (1C), (47.098+46.946) (1C), 46.260 (1C), (44.159+43.637) (1C), (39.709+39.618) (1C), 28.647 (6C), 28.398 (3C), 21.562 (1C), 21.410 (1C). MS (ESI, CH_3OH): [$C_{36}H_{55}N_5O_6$] *m/z* 654.5 ([M+H]$^+$).

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(3″, 4″-dichlorobenzyl)amino]ethyl}amino}

-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50h). The procedure to prepare **50h** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(3,4-dichlorobenzyl)carbamate (0.175 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8.5 : 1.5 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.126 g, 65%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.615-7.597 (m, 1H), 7.393-7.317 (s, 3H), 7.072 (s, 1H), 6.605 (s, 1H), 4.387 (s, 2H), 3.701-3.668 (m, 0.5H), 3.628-3.606 (m, 0.5H), 3.544-3.523 (m, 0.5H), 3.473-3.437 (m, 0.5H), 3.380-3.133 (m, 2H), 3.117-3.096 (m, 1H), 3.074-3.022 (m, 1H), 2.973-2.960 (m, 1H), 2.838-2.713 (m, 3H), 2.552-2.508 (m, 1H), 2.408-2.284 (m, 4H), 1.514-1.449 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.829 (1C), 155.722 (1C), (154.702+154.599) (1C), 152.498 (1C), 151.527 (1C), 149.961 (1C), 139.141 (1C), (132.608+131.181) (1C), 130.544 (1C), (129.493+129.099) (1C), (127.059+126.403) (1C), (119.257+119.184) (1C), (110.350+110.277) (1C), (80.879+80.806) (1C), 80.411 (1C), 79.288 (1C), (62.167+61.347) (1C), (51.869+51.317) (1C), 50.200 (1C), (49.884+49.690) (1C), (47.534+47.332) (1C), 46.332 (1C), (44.128+43.588) (1C), (39.684+39.599) (1C), 28.585 (3C), 28.470 (3C), 28.336 (3C), 21.360 (1C). MS (ESI, CH_3OH): $[C_{35}H_{51}Cl_2N_5O_6]$ *m/z* 708.5 ($[M+H]^+$).

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(2″, 4″-dichlorobenzyl)amino]ethyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50i). The procedure to prepare **50i** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(2,4-dichlorobenzyl)carbamate (0.175 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.126 g, 65%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.615-7.597 (m, 1H), 7.361-7.192 (s, 4H), 6.604 (s, 1H), 4.534-4.510 (s, 2H), 3.705-3.671 (m, 0.5H), 3.632-3.624 (m, 0.5H), 3.565-3.529 (m, 0.5H), 3.475-3.439 (m, 0.5H), 3.394-3.249 (m, 2H), 3.135-3.098 (m, 1H), 3.059-3.024 (m, 1H), 2.978-2.965 (m, 1H), 2.842-2.725 (m, 3H), 2.553-2.511 (m, 1H), 2.438-2.283 (m, 4H), 1.516-1.394 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.823 (1C), 155.850 (1C), (154.696+154.599) (1C), 152.504 (1C), 151.503 (1C), 149.936 (1C), (134.745+133.829) (1C), 133.379 (1C), (129.524+129.287+128.728) (2C), 127.259 (1C), (119.245+119.166) (1C), (110.332+110.259) (1C), 80.782 (1C), 80.345 (1C), 79.270 (1C), (62.124+61.317) (1C), (51.869+51.329) (1C), (49.884+49.690) (1C), (48.670+47.990) (1C), 47.601 (1C), 46.308 (1C), (44.146+43.612) (1C), (39.660+39.562) (1C), (28.591+28.342) (9C), 21.360 (1C). MS (ESI, CH_3OH): $[C_{35}H_{51}Cl_2N_5O_6]$ *m/z* 708.5 ($[M+H]^+$).

(±)-trans-*tert*-Butyl 3-{{(*S*)-2′-[(*tert*-butoxycarbonyl)(4″-chlorobenzyl)amino]propyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50j). The procedure to prepare **50j** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and (S)-*tert*-butyl

(1-aminopropan-2-yl)(4-chlorobenzyl)carbamate (0.164 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8.5 : 1.5 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.115 g, 61%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.613-7.592 (m, 1H), 7.285-7.215 (m, 5H), 6.595 (s, 1H), 4.298-3.789 (s, 3H), 3.653-3.501 (m, 1.5H), 3.427-3.353 (m, 0.5H), 3.110-2.617 (m, 5H), 2.563-2.411 (m, 3H), 2.311-2.288 (m, 3H), 1.514-1.447 (m, 27H), 1.132-1.015 (m, 3H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.987 (1C), 156.311 (1C), (154.830+154.708) (1C), 152.602 (1C), 151.551 (1C), 150.027 (1C), 138.759 (1C), 132.560 (1C), (129.068+128.577+128.261) (4C), (119.342+119.257) (1C), (110.362+110.289) (1C), 80.891 (1C), 80.156 (1C), 79.349 (1C), (62.112+61.500) (1C), 51.784 (3C), 49.708 (1C), (46.939+45.950) (1C), (44.019+43.527) (1C), 39.690 (1C), (28.676+28.421) (9C), 21.445 (1C), 17.007 (1C). MS (ESI, CH_3OH): [$C_{36}H_{54}ClN_5O_6$] *m/z* 688.5 ([M+H]$^+$).

(±)-trans-*tert*-Butyl 3-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}-4-{{2′-[(4″-chlorobenzyl)amino]ethyl}(methyl)amino}pyrrolidine-1-carboxylate (50k). The procedure to prepare **50k** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl 4-chlorobenzyl[2′-(methylamino)ethyl]carbamate (0.164 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.102 g, 63%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.604-7.583 (m, 1H), 7.343-7.159 (s, 5H), 6.596 (s, 1H), 4.574-4.417 (m, 2H), 3.549-3.515 (m, 0.5H), 3.471-3.123 (m, 4.5H), 2.998-2.943 (m, 3H), 2.626-2.425 (m, 4H), 2.229-2.273 (m, 6H), 1.520-1.414 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.145 (1C), (155.977+155.558) (1C), 154.806 (1C), 152.583 (1C), 151.491 (1C), 149.857 (1C), (137.405+137.186) (1C), 133.009 (1C), (129.208+128.753+128.516) (4C), 119.105 (1C), (110.259+110.144) (1C), 80.794 (1C), 80.011 (1C), 79.404 (1C), (68.554+68.256+67.953+67.358) (1C), 52.325 (1C), (50.910+50.364) (1C), (50.090+49.860) (1C), 45.112 (1C), (44.183+43.958+43.679) (1C), (40.595+40.121+39.811+39.520) (2C), (39.119+38.998+38.281+38.117) (1C), (28.628+28.397) (9C), 21.390 (1C). MS (ESI, CH_3OH): [$C_{36}H_{54}ClN_5O_6$] *m/z* 688.4 ([M+H]$^+$).

(±)-trans-*tert*-Butyl 3-{{2′-[(*tert*-butoxycarbonyl)(4″-fluorophenethyl)amino]ethyl}amino}-4-{{6′-[(*tert*-butoxycarbonyl)amino]-4′-methylpyridin-2′-yl}methyl}pyrrolidine-1-carboxylate (50m). The procedure to prepare **50m** is the same as that to prepare **42a** except using **49** (0.203 g, 0.5 mmol)[2] and *tert*-butyl (2-aminoethyl)(4-fluorophenethyl)carbamate (0.155 g, 0.55 mmol)[2] instead of **40** (0.434 g, 0.001 mol) and 3-phenyl-1-propylamine (0.203 g, 0.0015 mol). The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.25 : 0.75 : 0.5, the isomer with lower R_f value, R_f = 0.1) to afford a pale-yellow oil (0.118 g, 64%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.616-7.600 (m, 1H), 7.426 (brs, 1H), 7.119 (m, 2H), 6.982-6.950 (m, 2H), 6.603 (s, 1H), 3.706-3.672 (m, 0.5H), 3.637-3.615 (m, 0.5H), 3.559-3.523 (m, 0.5H), 3.478-3.442 (m, 0.5H), 3.365 (m, 2H), 3.217-2.983 (m, 5H),

2.853-2.776 (m, 3H), 2.689 (m, 2H), 2.553-2.510 (m, 1H), 2.406-2.384 (m, 0.5H), 2.294-2.274 (m, 3.5H), 1.511-1.445 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (162.504+160.561) (1C), 157.775 (1C), 155.577 (1C), (154.617+154.526) (1C), 152.450 (1C), 151.472 (1C), 149.857 (1C), (134.849+134.824) (1C), (130.295+130.234) (2C), (119.166+119.087) (1C), (115.341+115.171) (2C), (110.283+110.204) (1C), 80.679 (1C), 79.586 (1C), 79.167 (1C), (62.124+61.292) (1C), (51.815+51.250) (1C), (49.878+49.828) (1C), (49.714+49.635) (1C), (48.287+47.559+47.261) (1C), 46.344 (1C), (44.037+43.527) (1C), 39.538 (1C), (34.408+33.734) (1C), 28.500 (3C), 28.415 (3C), 28.257 (3C), 21.275 (1C). ^{19}F NMR (CDCl3, 376.5 MH_Z): δ -117.349. MS (ESI, CH_3OH): [$C_{36}H_{54}FN_5O_6$] *m/z* 672.4 ([M+H]$^+$).

***N*^{1}-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-(4-chlorobenzyl)ethane-1,2-diamine tetrahydrochloride (22).** The procedure to prepare **22** is the same as that to prepare **8** except using **50b** (0.135 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.103 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.456-7.430 (m, 4H), 6.692 (s, 1H), 6.673 (s, 1H), 4.306 (s, 2H), 4.102-3.990 (m, 2H), 3.749-3.713 (m, 1H), 3.688-3.648 (m, 1H), 3.548-3.542 (m, 4H), 3.341-3.243 (m, 2H), 3.118-3.088 (m, 1H), 2.898-2.848 (m, 1H), 2.307 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.334 (1C), 154.229 (1C), 143.495 (1C), 135.542 (1C), 131.620 (2C), 129.501 (2C), 128.754 (1C), 114.996 (1C), 111.311 (1C), 60.749 (1C), 51.132 (1C), 48.569 (1C), 46.384 (1C), 42.917 (1C), 42.735 (1C), 40.452 (1C), 33.397 (1C), 21.333 (1C). MS (ESI, CH_3OH): [$C_{20}H_{28}ClN_5$] *m/z* 374.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 374.2106, Found: 374.2102.

***N*^{1}-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-[4′-(trifluoromethyl)benzyl]ethane-1,2-diamine tetrahydrochloride (24).** The procedure to prepare **24** is the same as that to prepare **8** except using **50d** (0.141 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.110 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.792 (s, 2H), 7.679 (s, 2H), 6.707 (s, 2H), 4.435 (s, 2H), 4.081-4.022 (m, 2H), 3.770-3.684 (m, 2H), 3.598 (m, 4H), 3.356-3.277 (m, 2H), 3.134 (m, 1H), 2.930-2.883 (m, 1H), 2.333 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.392 (1C), 154.251 (1C), 143.589 (1C), (131.625+131.379+131.118+130.861) (1C), 130.576 (2C), 126.387 (2C), (127.258+125.095+122.932+120.800) (1C), 115.039 (1C), 111.319 (1C), 60.815 (1C), 51.221 (1C), 48.604 (1C), 46.526 (1C), 43.123 (1C), 42.955 (1C), 40.559 (1C), 33.448 (1C), 21.370 (1C). ^{19}F NMR (D_2O, 376.5 MHz): δ -62.988 (CF_3). MS (ESI, CH_3OH): [$C_{21}H_{28}F_3N_5$] *m/z* 408.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 408.2370, Found: 408.2363.

***N*^{1}-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-(4′-fluorobenzyl)ethane-1,2-diamine tetrahydrochloride (25).** The procedure to prepare **25** is the same as that to prepare **8** except using **50e** (0.131 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.100 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.509 (m, 2H), 7.207-7.173 (m, 2H), 6.705 (s, 1H), 6.686 (s, 1H), 4.316 (s, 2H), 4.083-4.004 (m, 2H), 3.765-3.731 (m, 1H), 3.702-3.662 (m, 1H), 3.589-3.550 (m, 4H), 3.354-3.262 (m, 2H), 3.129 (m, 1H), 2.913-2.863 (m, 1H), 2.317 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ (164.432+162.465) (1C), 158.380 (1C), 154.251 (1C), 143.517 (1C), (132.366+132.298) (2C), 126.198 (1C), (116.447+116.275) (2C), 115.035 (1C), 111.335 (1C), 60.775 (1C), 51.165 (1C),

48.608 (1C), 46.418 (1C), 42.955 (1C), 42.650 (1C), 40.471 (1C), 33.420 (1C), 21.362 (1C). ^{19}F NMR (D_2O, 376.5 MHz): δ -112.169 (F). MS (ESI, CH_3OH): [$C_{20}H_{28}FN_5$] *m/z* 358.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 358.2402, Found: 358.2400.

N^1-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-N^2-[3′-(trifluoromethyl)benzyl]ethane-1,2-diamine tetrahydrochloride (26). The procedure to prepare **26** is the same as that to prepare **8** except using **50f** (0.141 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.110 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.855 (m, 1H), 7.821-7.806 (m, 1H), 7.771-7.756 (m, 1H), 7.682-7.652 (m, 1H), 6.724 (s, 1H), 6.704 (s, 1H), 4.436 (s, 2H), 4.071-4.013 (m, 2H), 3.761-3.678 (m, 2H), 3.588 (m, 4H), 3.367-3.273 (m, 2H), 3.127-3.119 (m, 1H), 2.927-2.877 (m, 1H), 2.337 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.380 (1C), 154.255 (1C), 143.605 (1C), 133.766 (1C), 131.073 (1C), (131.270+131.013+130.752+130.490) (1C), 130.275 (1C), 126.904 (2C), (127.170+125.010+122.843+120.680) (1C), 115.007 (1C), 111.307 (1C), 60.799 (1C), 51.253 (1C), 48.584 (1C), 46.530 (1C), 43.043 (1C), 42.938 (1C), 40.559 (1C), 33.436 (1C), 21.342 (1C). ^{19}F NMR (D_2O, 376.5 MHz): δ -62.879 (CF_3). MS (ESI, CH_3OH): [$C_{21}H_{28}F_3N_5$] *m/z* 408.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 408.2370, Found: 408.2361.

N^1-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-N^2-(3′-methylbenzyl)ethane-1,2-diamine tetrahydrochloride (27). The procedure to prepare **27** is the same as that to prepare **8** except using **50g** (0.131 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.099 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.366-7.297 (m, 4H), 6.705-6.692 (m, 2H), 4.286 (s, 2H), 4.077-4.002 (m, 2H), 3.761-3.666 (m, 2H), 3.550-3.544 (m, 4H), 3.371-3.320 (m, 2H), 3.126-3.117 (m, 1H), 2.913-2.863 (m, 1H), 2.335-2.324 (s, 6H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.372 (1C), 154.235 (1C), 143.553 (1C), 139.793 (1C), 130.721 (1C), 130.592 (1C), 130.115 (1C), 129.445 (1C), 126.961 (1C), 115.039 (1C), 111.331 (1C), 60.771 (1C), 51.859 (1C), 48.617 (1C), 46.494 (1C), 42.971 (1C), 42.730 (1C), 40.519 (1C), 33.444 (1C), 21.386 (1C), 20.576 (1C). MS (ESI, CH_3OH): [$C_{21}H_{31}N_5$] *m/z* 354.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 354.2652, Found: 354.2652.

N^1-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-N^2-(3,4-dichlorobenzyl)ethane-1,2-diamine tetrahydrochloride (28). The procedure to prepare **28** is the same as that to prepare **8** except using **50h** (0.141 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.110 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.630 (s, 1H), 7.551-7.535 (m, 1H), 7.387-7.371 (m, 1H), 6.658 (s, 2H), 4.300 (s, 2H), 4.077-3.996 (m, 2H), 3.753-3.726 (m, 1H), 3.689-3.652 (m, 1H), 3.593-3.557 (m, 4H), 3.340-3.247 (m, 2H), 3.109-3.102 (m, 1H), 2.895-2.845 (m, 1H), 2.284 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.328 (1C), 154.188 (1C), 143.490 (1C), 133.733 (1C), 132.634 (1C), 131.960 (1C), 131.407 (1C), 130.436 (1C), 129.805 (1C), 115.051 (1C), 111.311 (1C), 60.796 (1C), 50.590 (1C), 48.605 (1C), 46.449 (1C), 42.946 (2C), 40.523 (1C), 33.444 (1C), (21.429+21.392) (1C). MS (ESI, CH_3OH): [$C_{20}H_{27}Cl_2N_5$] *m/z* 408.5 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 408.1716, Found: 408.1704; [$C_{20}H_{28}Cl^{37}ClN_5$] Calc.: 410.1687, Found: 410.1679.

N^1-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-N^2-(2,4-dichlorobenzyl)ethane-1,2-diamine tetrahydrochloride (29). The procedure to

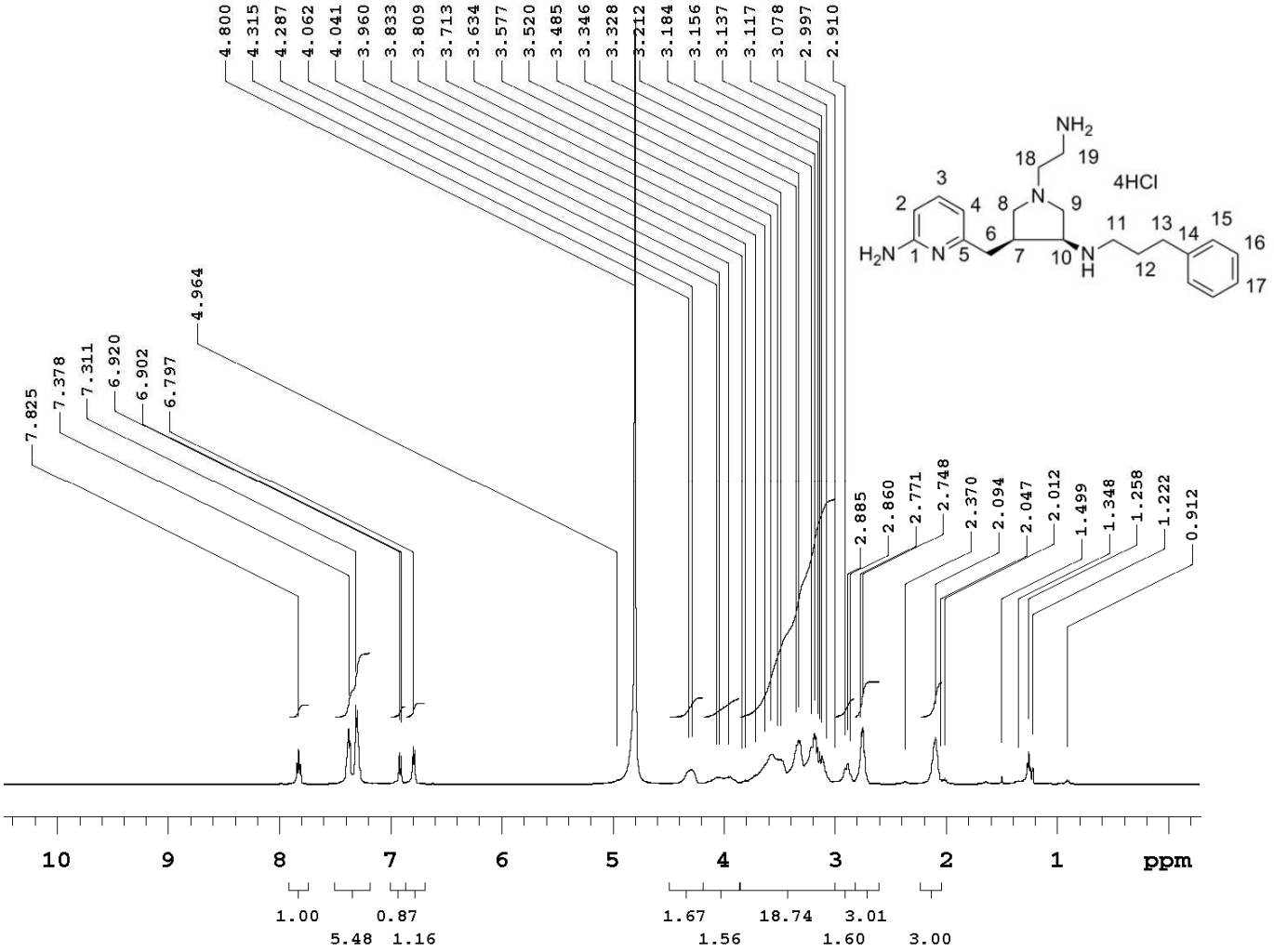
prepare **29** is the same as that to prepare **8** except using **50i** (0.141 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.110 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.546 (s, 1H), 7.4805 (d, 1H, J=8.5Hz), 7.366 (d, 1H, J=8Hz), 6.641 (s, 1H), 6.627(s, 1H), 4.411 (s, 2H), 4.042-3.951 (m, 2H), 3.714-3.677 (m, 1H), 3.643-3.603 (m, 1H), 3.585-3.506 (m, 4H), 3.299-3.204 (m, 2H), 3.080-3.060 (m, 1H), 2.857-2.806 (m, 1H), 2.256 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.328 (1C), 154.230 (1C), 143.465 (1C), 136.611 (1C), 135.311 (1C), 133.302 (1C), (129.987+129.956) (1C), 128.281 (1C), 126.757 (1C), 115.014 (1C), 111.317 (1C), 60.760 (1C), 48.623 (1C), 48.586 (1C), 46.370 (1C), 43.067 (1C), 42.861(1C), 40.469 (1C), 33.389 (1C), (21.368+21.325) (1C). MS (ESI, CH_3OH): [$C_{20}H_{27}Cl_2N_5$] *m/z* 408.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 408.1716, Found: 408.1703; [$C_{20}H_{28}Cl^{37}ClN_5$] Calc.: 410.1687, Found: 410.1681.

(*S*)-*N*^{1}-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-(3,4-dichlorobenzyl)propane-1,2-diamine tetrahydrochloride (30). The procedure to prepare **30** is the same as that to prepare **8** except using **50j** (0.137 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.113 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.425 (m, 4H), 6.651 (s, 2H), 4.350-4.224 (m, 2H), 3.995-3.945 (m, 2H), 3.883-3.781 (m, 1H), 3.661-3.635 (m, 2H), 3.555-3.245 (m, 3H), 3.161-3.132 (m, 1H), 3.051 (m, 1H), 2.871-2.789 (m, 1H), 2.276 (s, 3H), 1.520-1.509 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.341 (1C), 154.206 (1C), 143.757 (1C), 135.427 (1C), (131.590+131.541) (2C), 129.489 (2C), 129.009 (1C), (115.075+114.984) (1C), 111.256 (1C), (61.385+61.318) (1C), (51.640+51.452) (1C), (48.696+48.647+48.544) (2C), (47.129+46.813+46.680) (1C), (40.566+40.536) (1C), (33.796+33.559) (1C), (21.380+21.350) (1C), (14.398+14.337) (1C). MS (ESI, CH_3OH): [$C_{21}H_{30}ClN_5$] *m/z* 388.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 388.2263, Found: 388.2258.

***N*^{1}-{(±)-trans-4-[(6-amino-4-methylpyridin-2-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-(4-chlorobenzyl)-*N*^{1}-methylethane-1,2-diamine tetrahydrochloride (31).** The procedure to prepare **31** is the same as that to prepare **8** except using **50k** (0.137 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.113 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.429-7.403 (m, 4H), 6.658 (s, 1H), 6.638 (s, 1H), 4.306 (s, 2H), 4.247-4.236 (m, 1H), 4.017-3.973 (m, 1H), 3.819-3.781 (m, 1H), 3.630-3.563 (m, 5H), 3.282-3.203 (m, 3H), 3.002 (s, 3H), 2.904-2.855 (m, 1H), 2.266 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.304 (1C), 154.151 (1C), 143.417 (1C), 135.524 (1C), 131.747 (2C), 129.501 (2C), 128.760 (1C), 115.136 (1C), 111.335 (1C), 68.124 (1C), 51.185 (1C), 50.887 (1C), 48.793 (1C), 44.561 (1C), 41.683 (1C), 38.004 (1C), 37.512 (1C), 34.118 (1C), (21.465+21.429) (1C). MS (ESI, CH_3OH): [$C_{21}H_{30}ClN_5$] *m/z* 388.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 388.2263, Found: 388.2261.

***N*^{1}-{(±)-trans-4-[(6′-amino-4′-methylpyridin-2′-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-(4-fluorophenethyl)ethane-1,2-diamine tetrahydrochloride (33).** The procedure to prepare **33** is the same as that to prepare **8** except using **50m** (0.134 g, 0.2 mmol) instead of **42a**, affording a hygroscopic white solid (0.103 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.285-7.258 (m, 2H), 7.073-7.037 (m, 2H), 6.660-6.630 (s, 2H), 4.078-3.996 (m, 2H), 3.762-3.736 (m, 1H), 3.687-3.648 (m, 1H), 3.554-3.511 (m, 4H), 3.384-3.239 (m, 4H), 3.107 (m, 1H), 3.011-2.982 (m, 2H), 2.895-2.845 (m, 1H), 2.284-2.264 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ

(162.894+162.858+160.963+160.921) (1C), (158.236+158.268) (1C), (154.139+154.084) (1C), (143.423+143.387) (1C), (131.826+131.808) (1C), (130.819+130.725) (2C), (115.889+115.719) (2C), 115.051 (1C), 111.293 (1C), 60.748 (1C), 49.552 (1C), 48.592 (1C), 46.395 (1C), 43.371 (1C), 42.952 (1C), 40.475 (1C), 33.402 (1C), 31.125 (1C), (21.410+21.398) (1C). ^{19}F NMR (D_2O, 376.5 MH_Z): δ -116.242. MS (ESI, CH_3OH): [$C_{21}H_{30}FN_5$] *m/z* 372.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calc.: 372.2558, Found: 372.2557.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3.346
3.328
3.212
3.184
3.156
3.137
3.117
3.078
2.997
2.910
4.964
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7.311
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6.902
6.797
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2.860
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1.499
1.348
1.258
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4
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6
11
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14
15
16
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N
5
7
10
N
H
12
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10
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7
6
5
4
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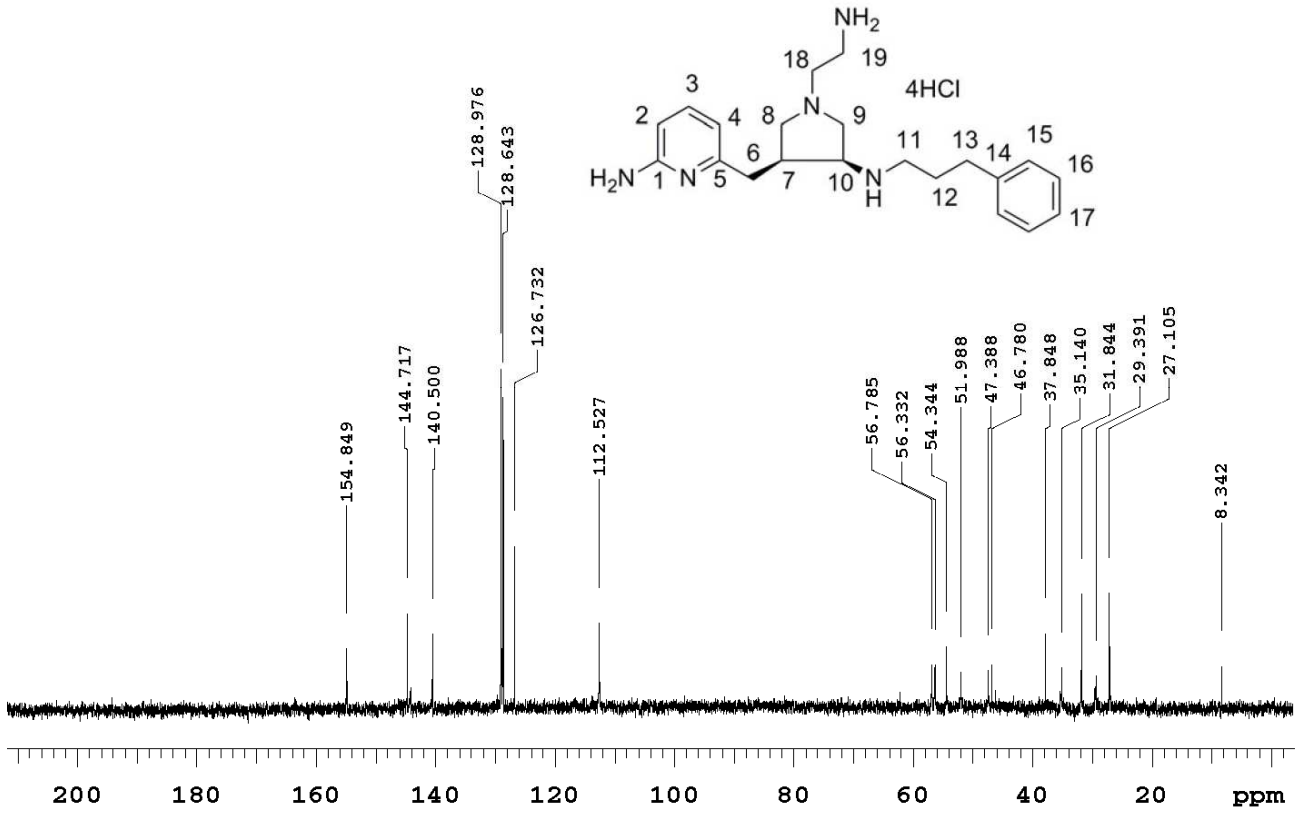
3.00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N
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7
10
N
H
12
17
128.976
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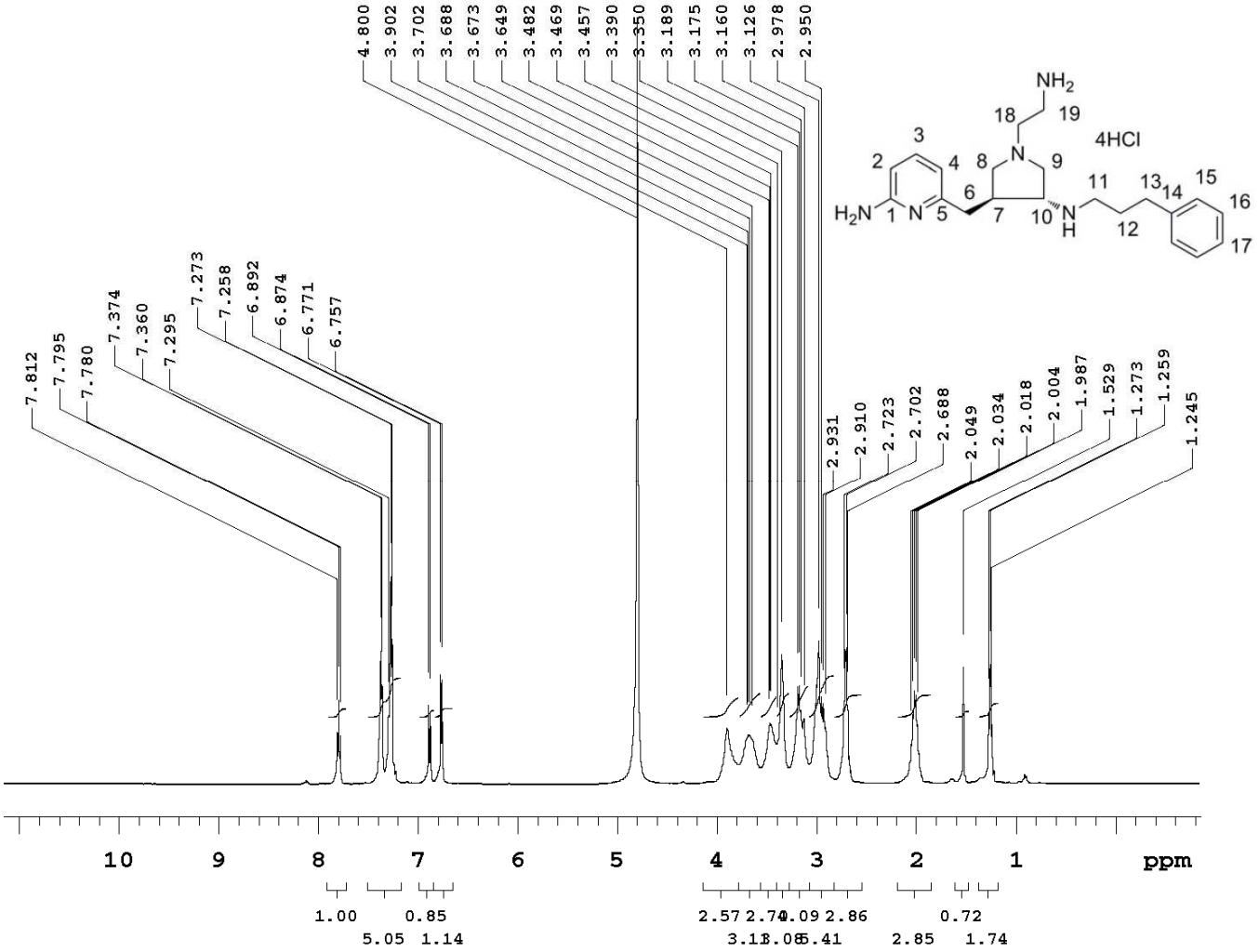
ppm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3.160
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7.780
7.374
7.360
7.295
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2.034
2.018
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1.529
1.273
1.259
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13
14
15
16
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N
5
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10
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H
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7
6
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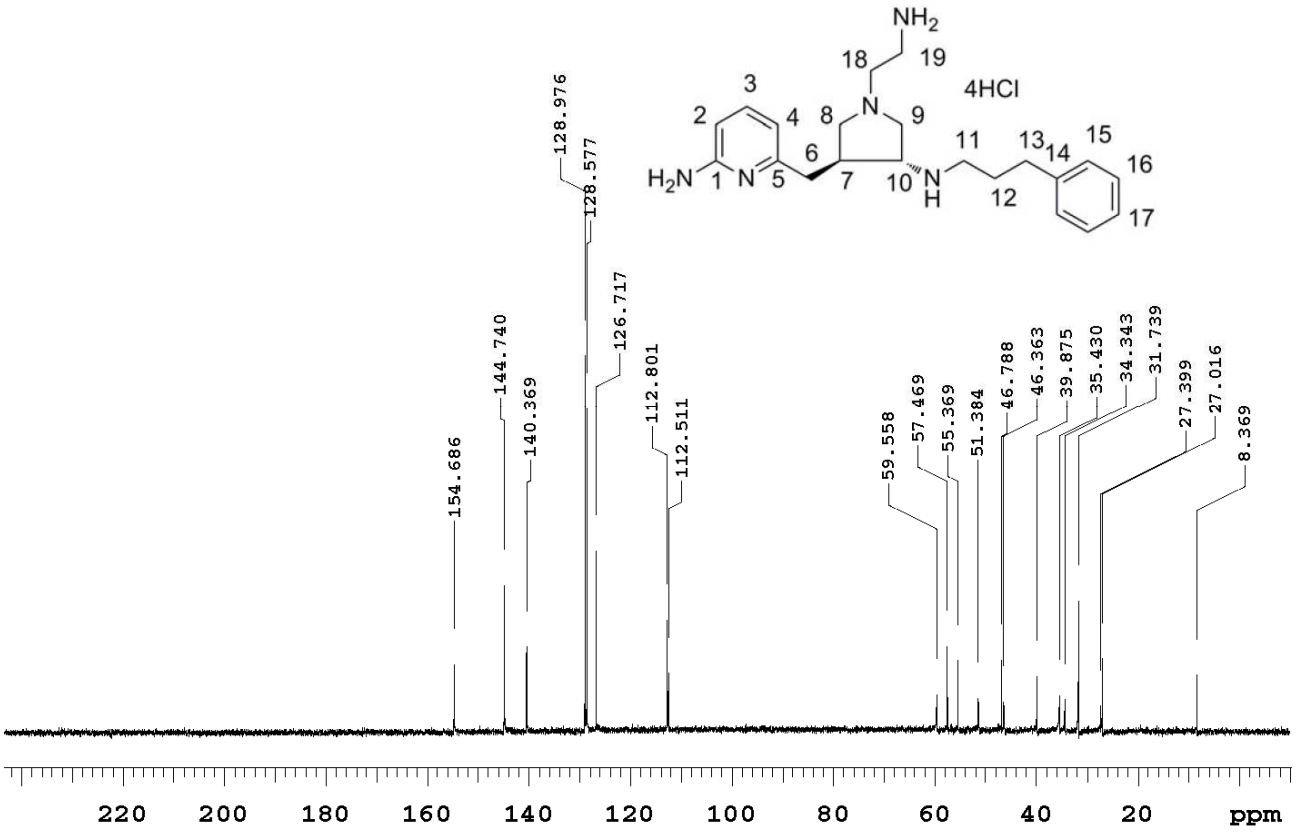
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7
10
N
H
12
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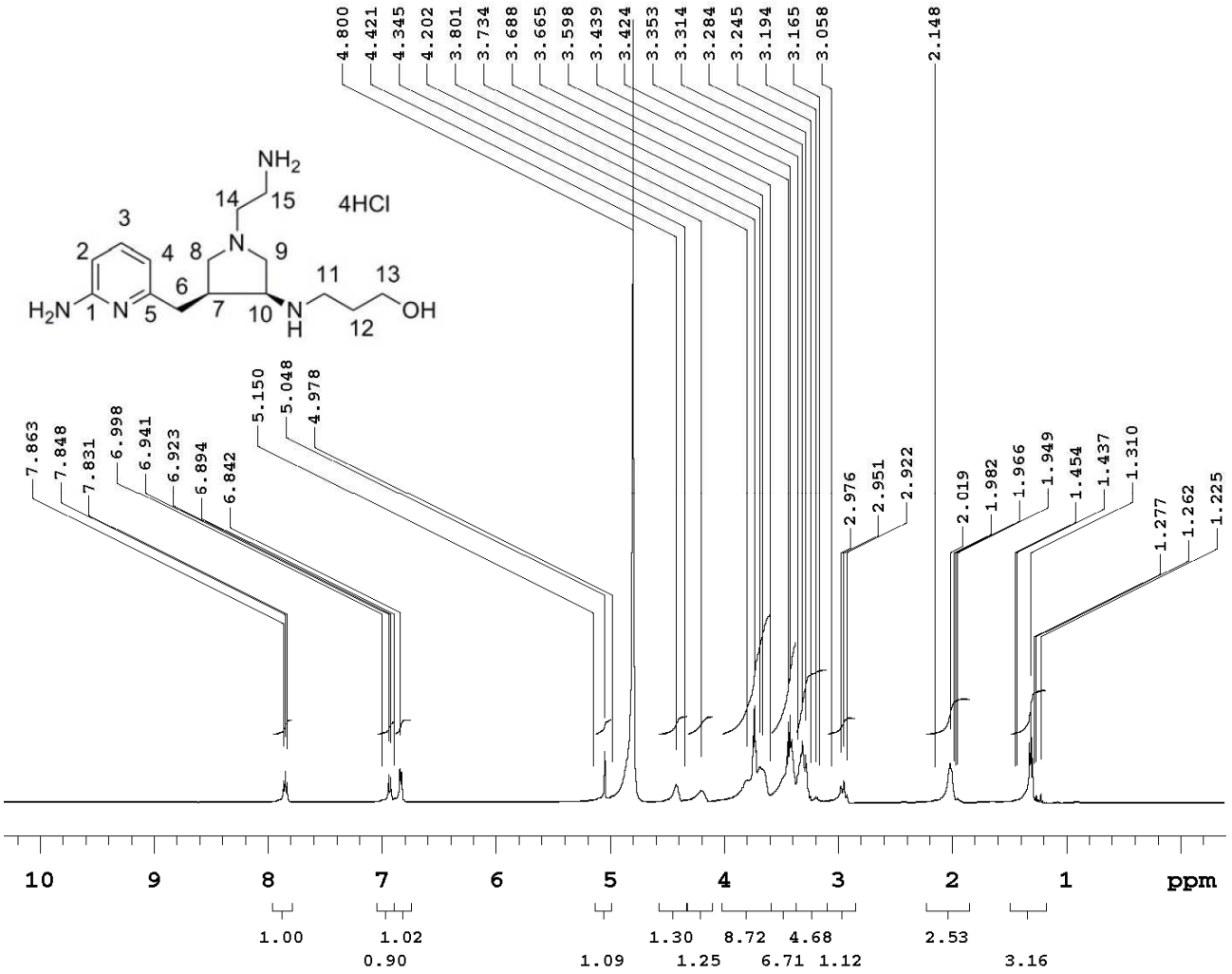
ppm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3.245
3.194
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3.058
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2
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8
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9
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11
13
H2N
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N
5
7
10
N
H
12
OH
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7.848
7.831
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6.923
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2.922
2.019
1.982
1.966
1.949
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1.262
1.225
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7
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5
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3
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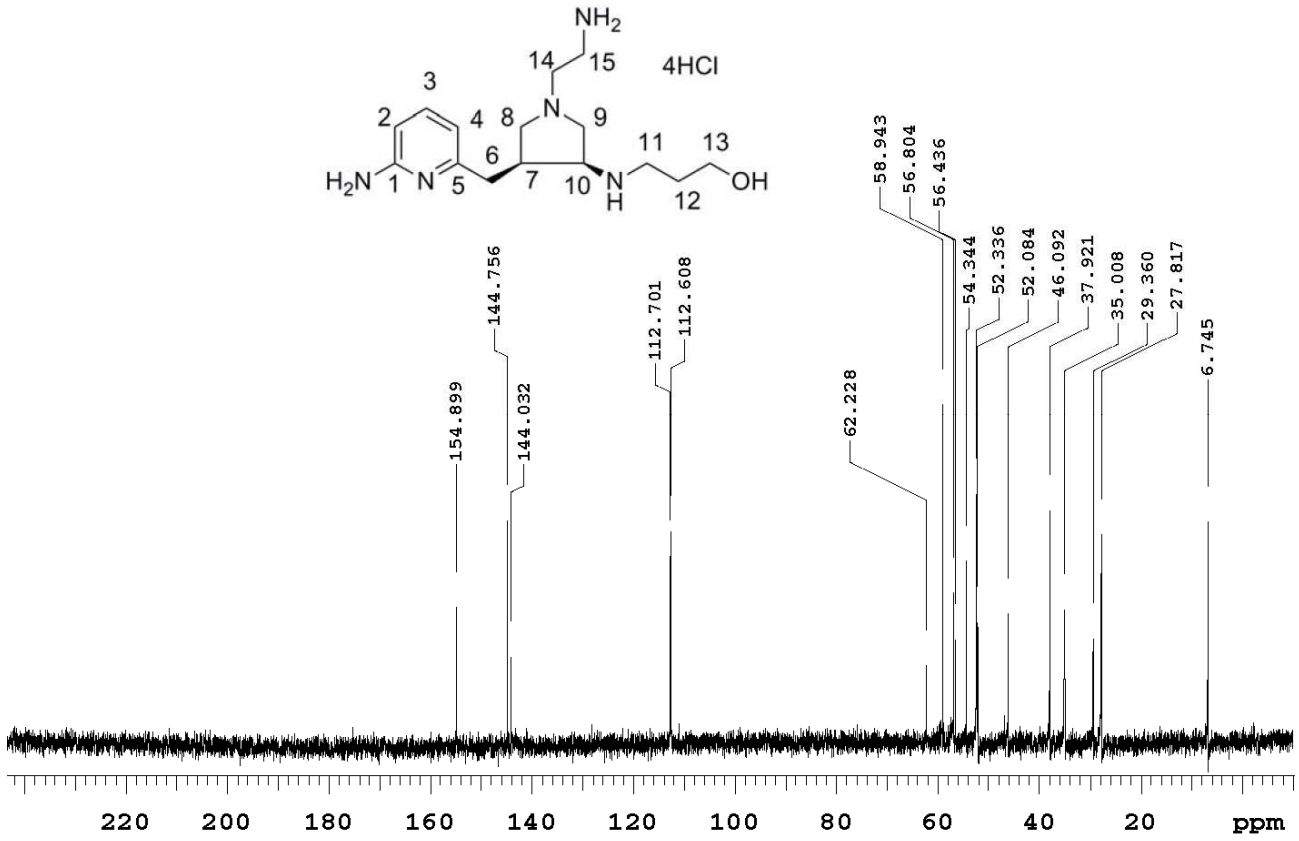
3.16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12
OH
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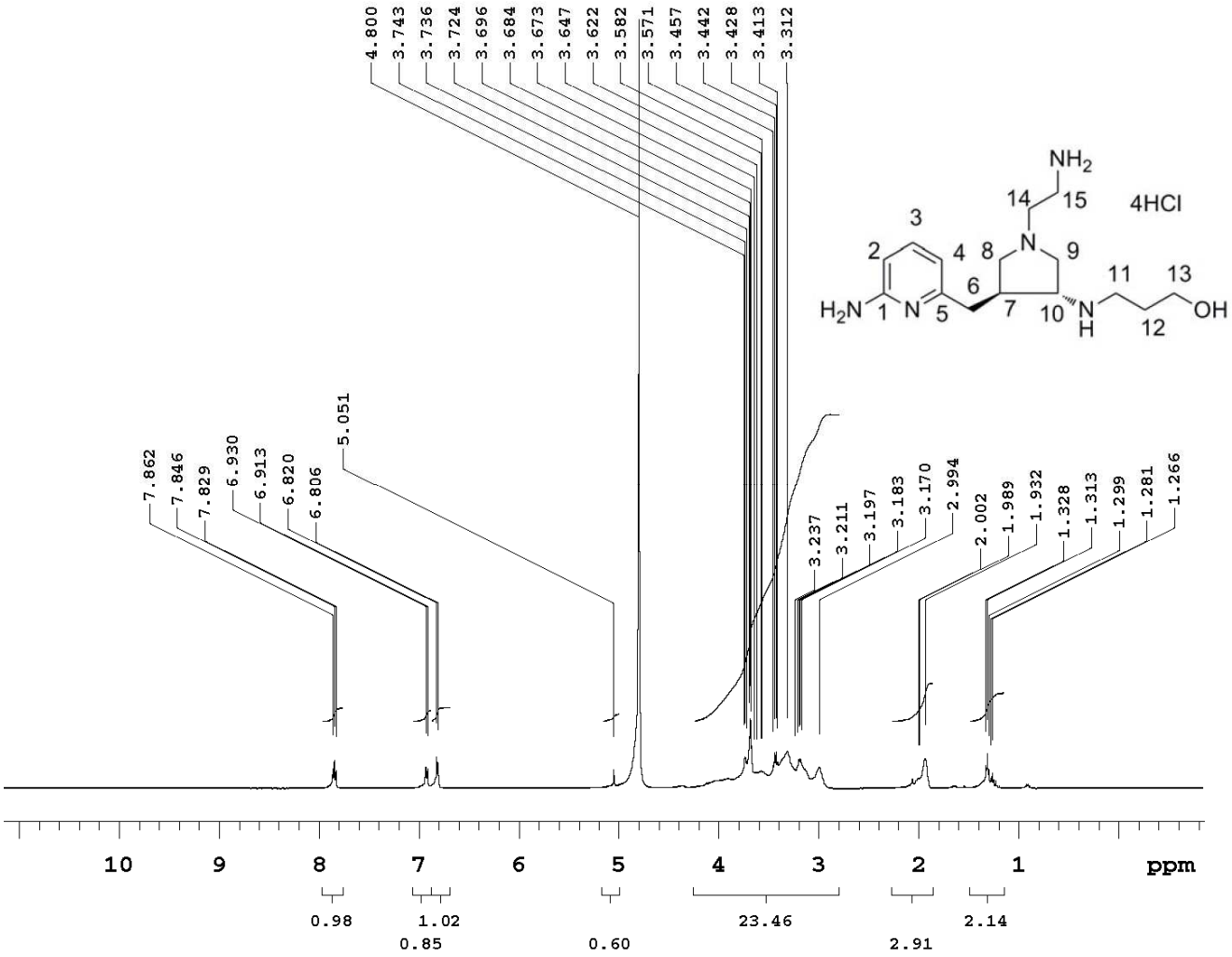
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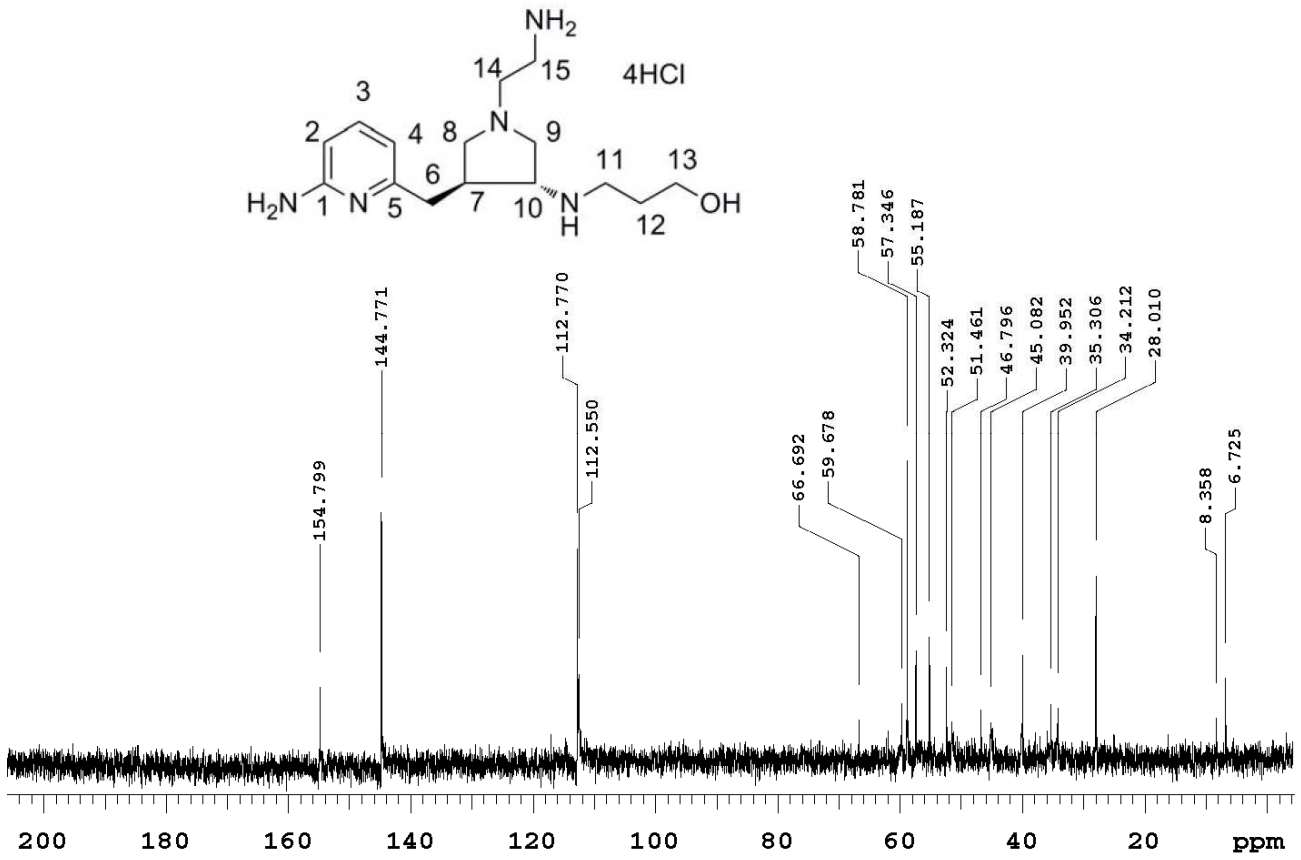
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H
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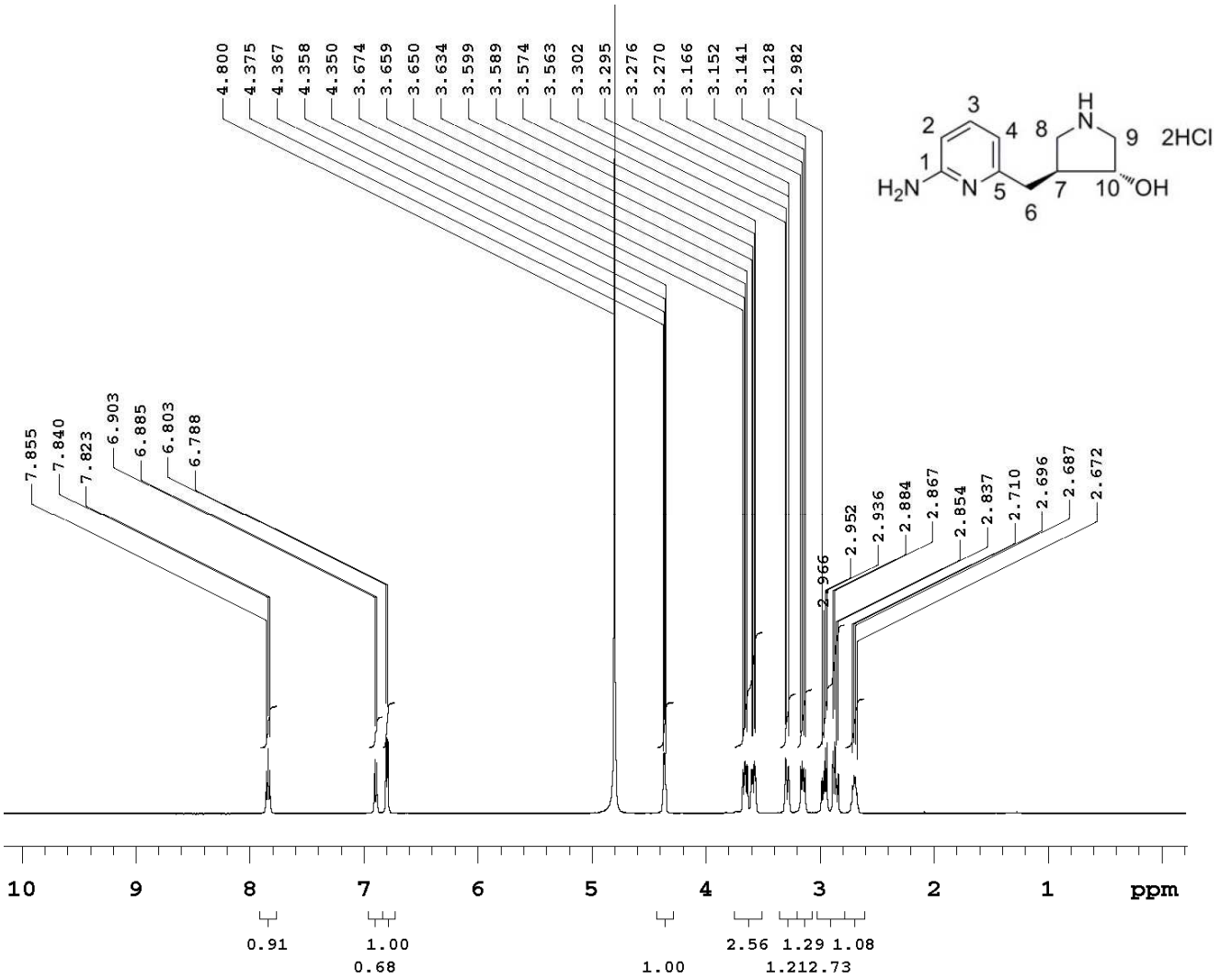
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7.823
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6.803
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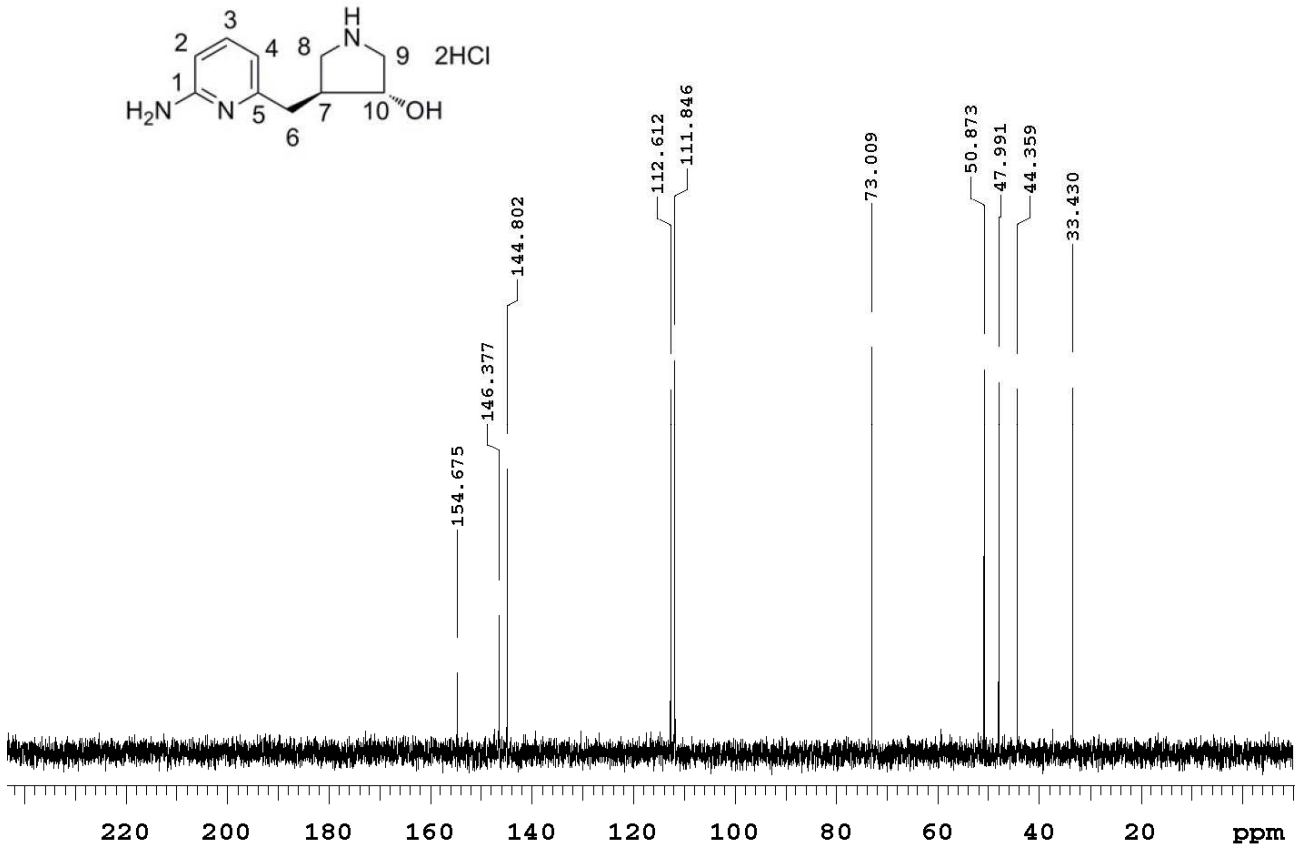
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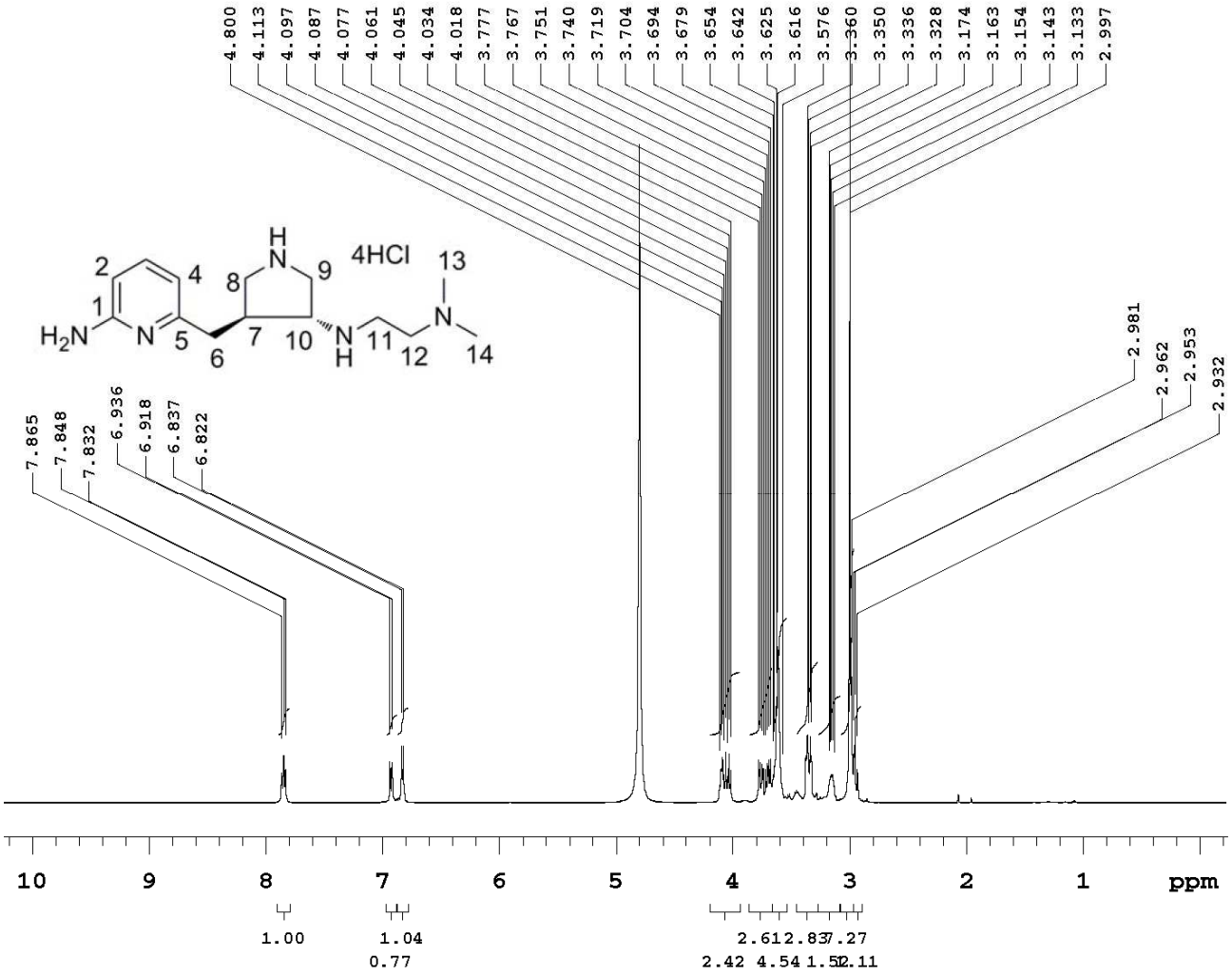
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3.740
3.719
3.704
3.694
3.679
3.654
3.642
3.625
3.616
3.576
3.360
3.350
3.336
3.328
3.174
3.163
3.154
3.143
3.133
2.997
2.981
2.962
2.953
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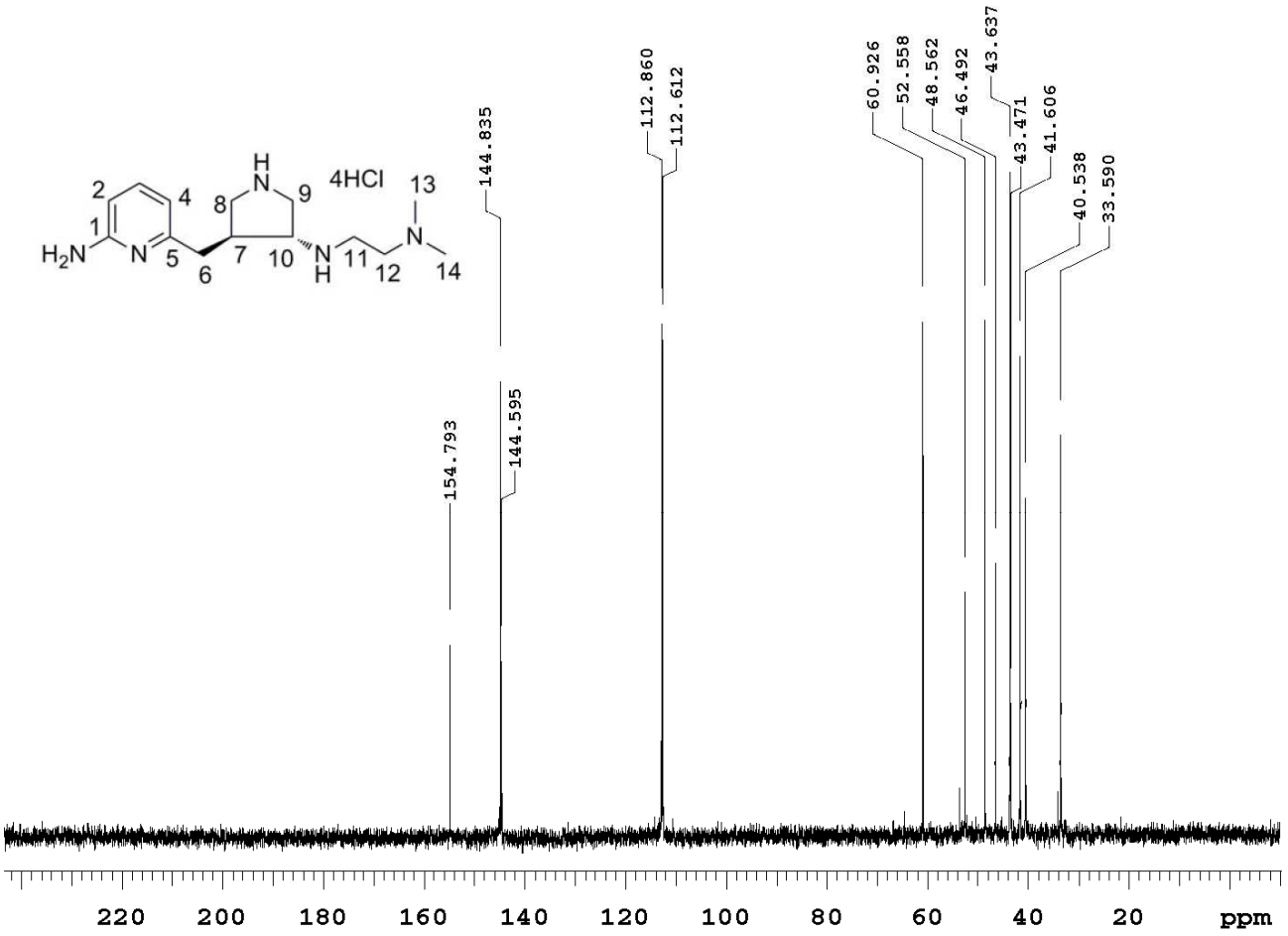
2.11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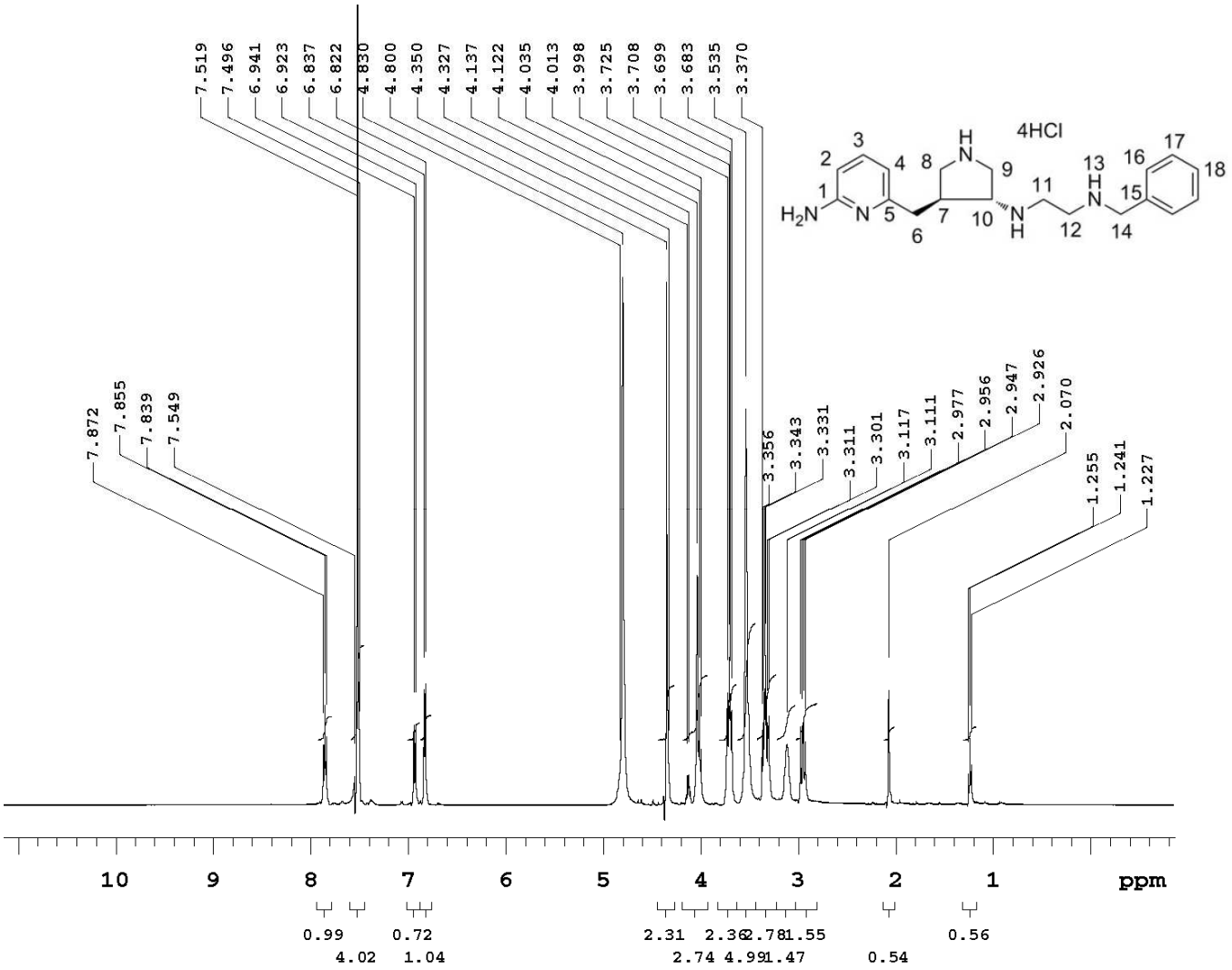
ppm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3.725
3.708
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3.683
3.535
3.370
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7.855
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7.549
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3.343
3.331
3.311
3.301
3.117
3.111
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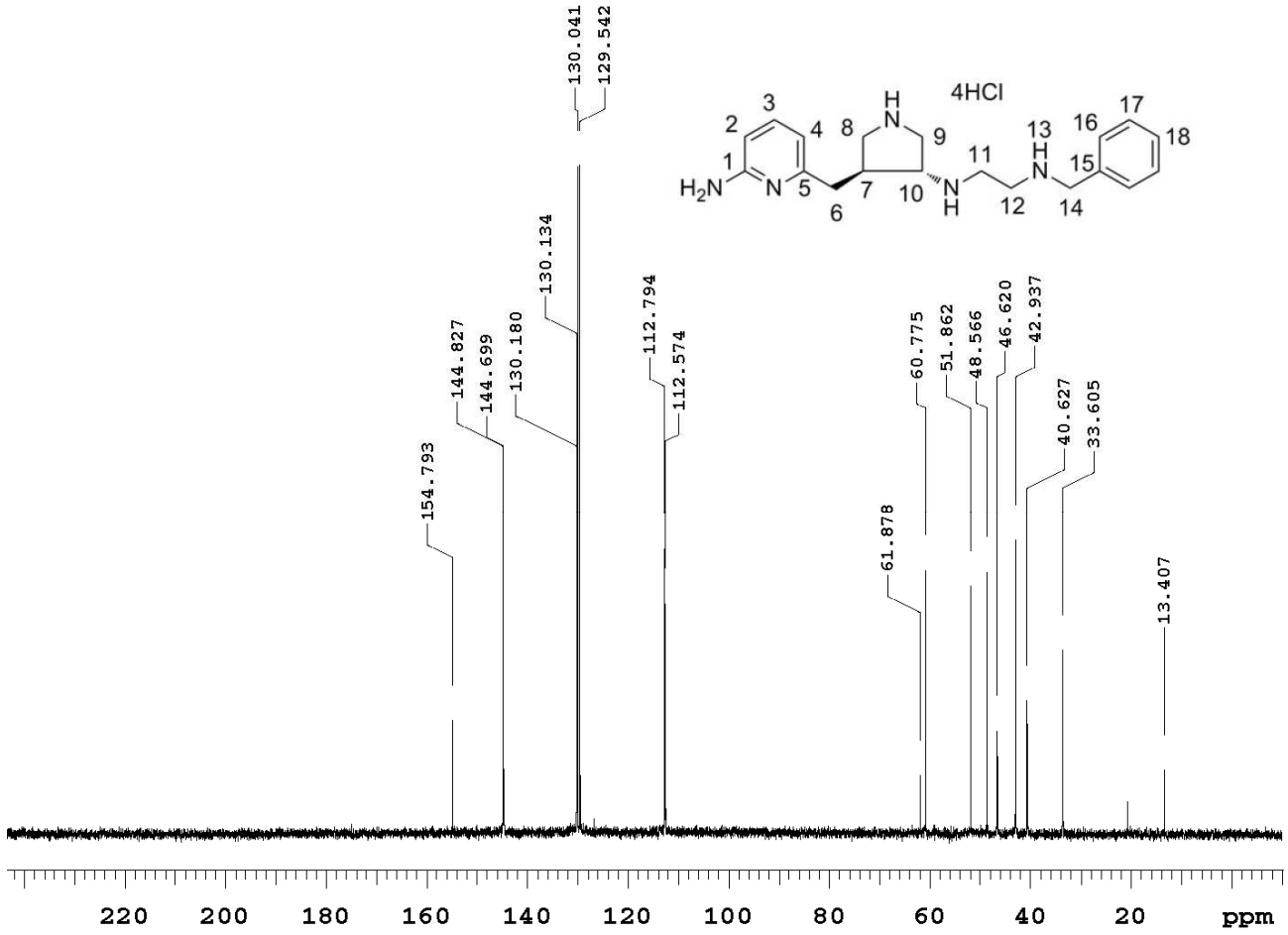
0.56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42.937
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20
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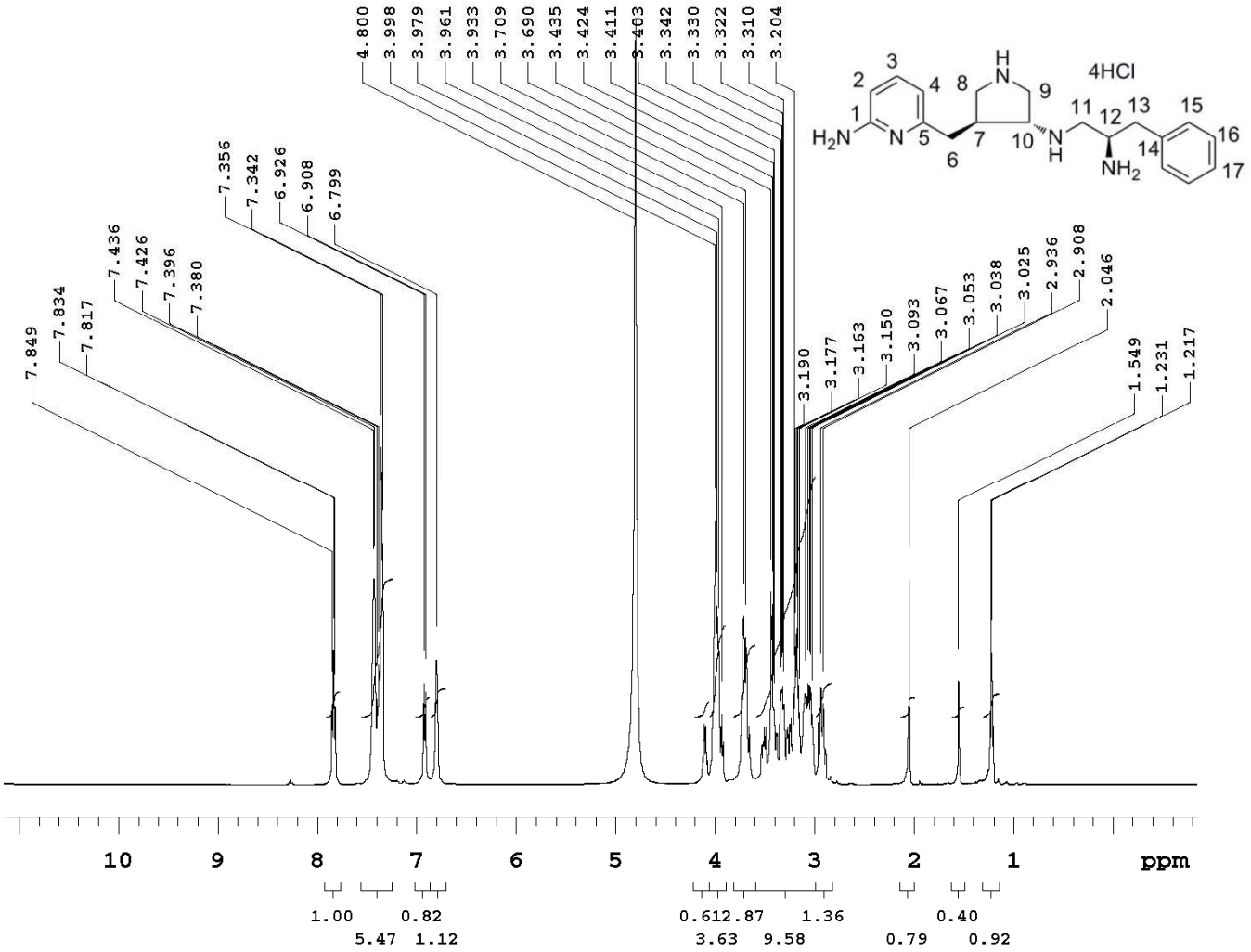
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3.979
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3.709
3.690
3.435
3.424
3.411
3.403
3.342
3.330
3.322
3.310
3.204
7.356
7.342
6.926
6.908
6.799
7.436
7.426
7.396
7.380
7.849
7.834
7.817
3.190
3.177
3.163
3.150
3.093
3.067
3.053
3.038
3.025
2.936
2.908
2.046
1.549
1.231
1.217
4HCl
10
9
8
7
6
5
4
3
2
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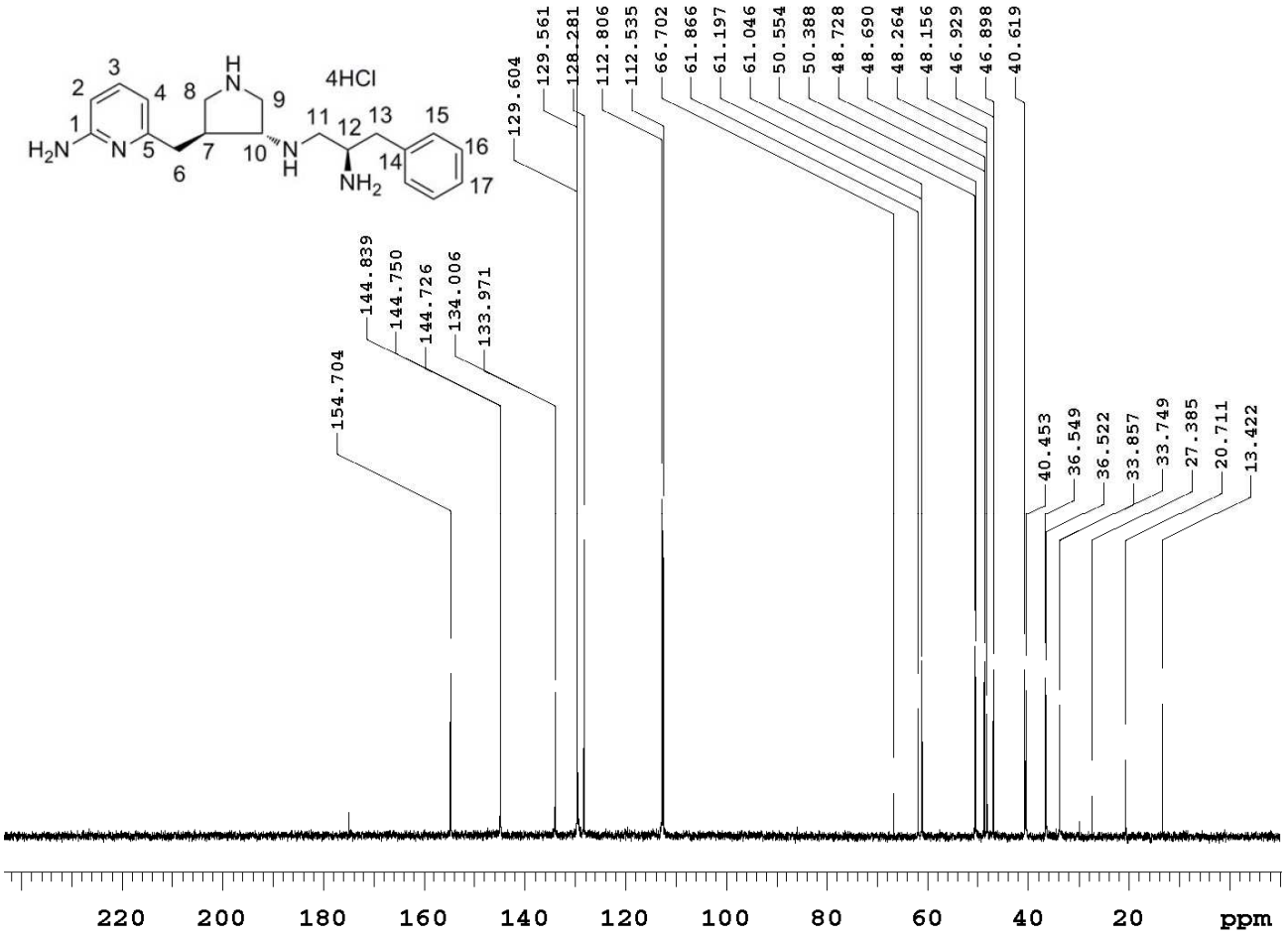
0.92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48.728
48.690
48.264
48.156
46.929
46.898
40.619
144.839
144.750
144.726
134.006
133.971
154.704
40.453
36.549
36.522
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20.711
13.422
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200
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140
120
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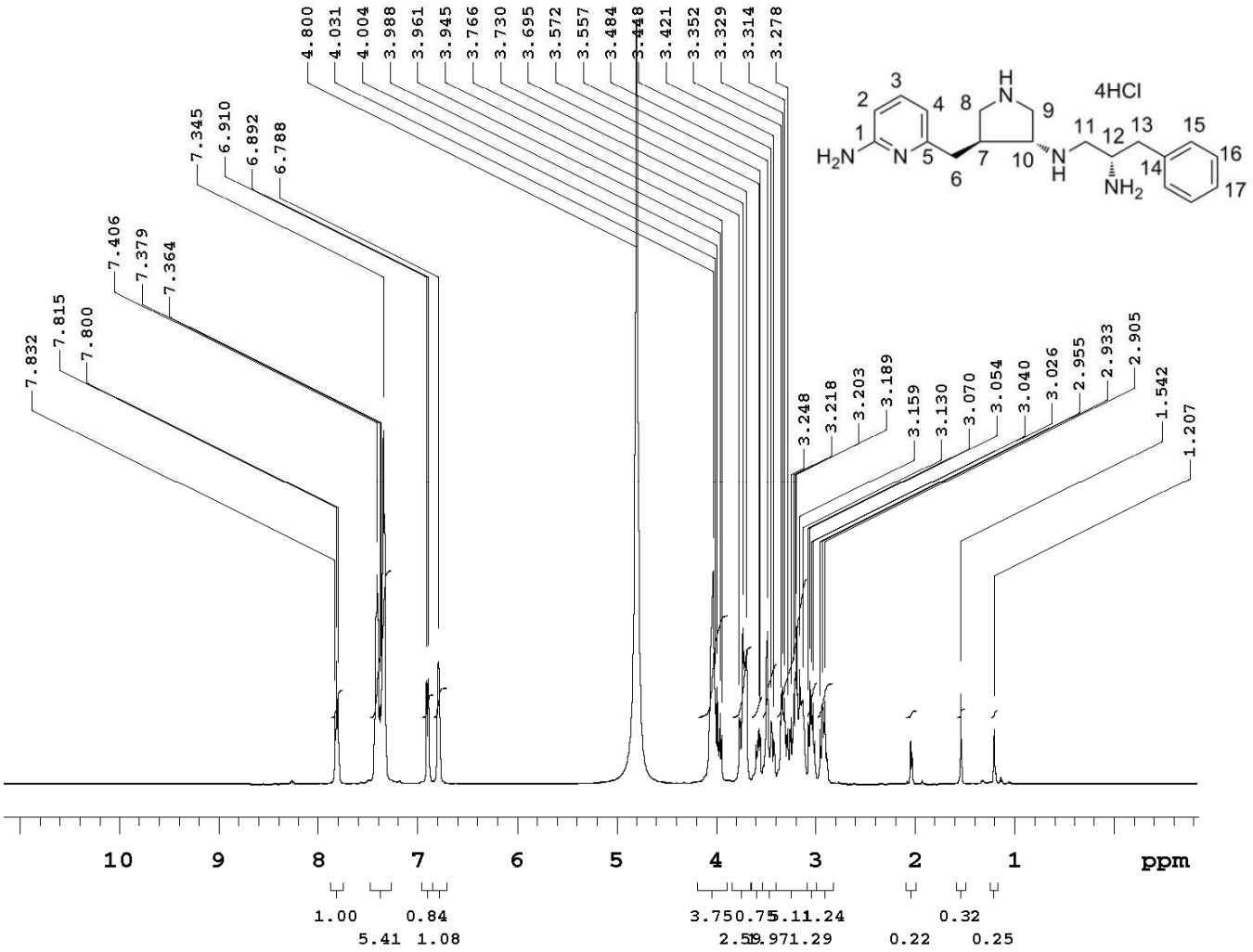
80
60
40
20
ppm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3.945
3.766
3.730
3.695
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3.484
3.448
3.421
3.352
3.329
3.314
3.278
7.345
6.910
6.892
6.788
7.406
7.379
7.364
7.832
7.815
7.800
3.248
3.218
3.203
3.189
3.159
3.130
3.070
3.054
3.040
3.026
2.955
2.933
2.905
1.542
1.207
4HCl
10
9
8
7
6
5
4
3
2
1
ppm
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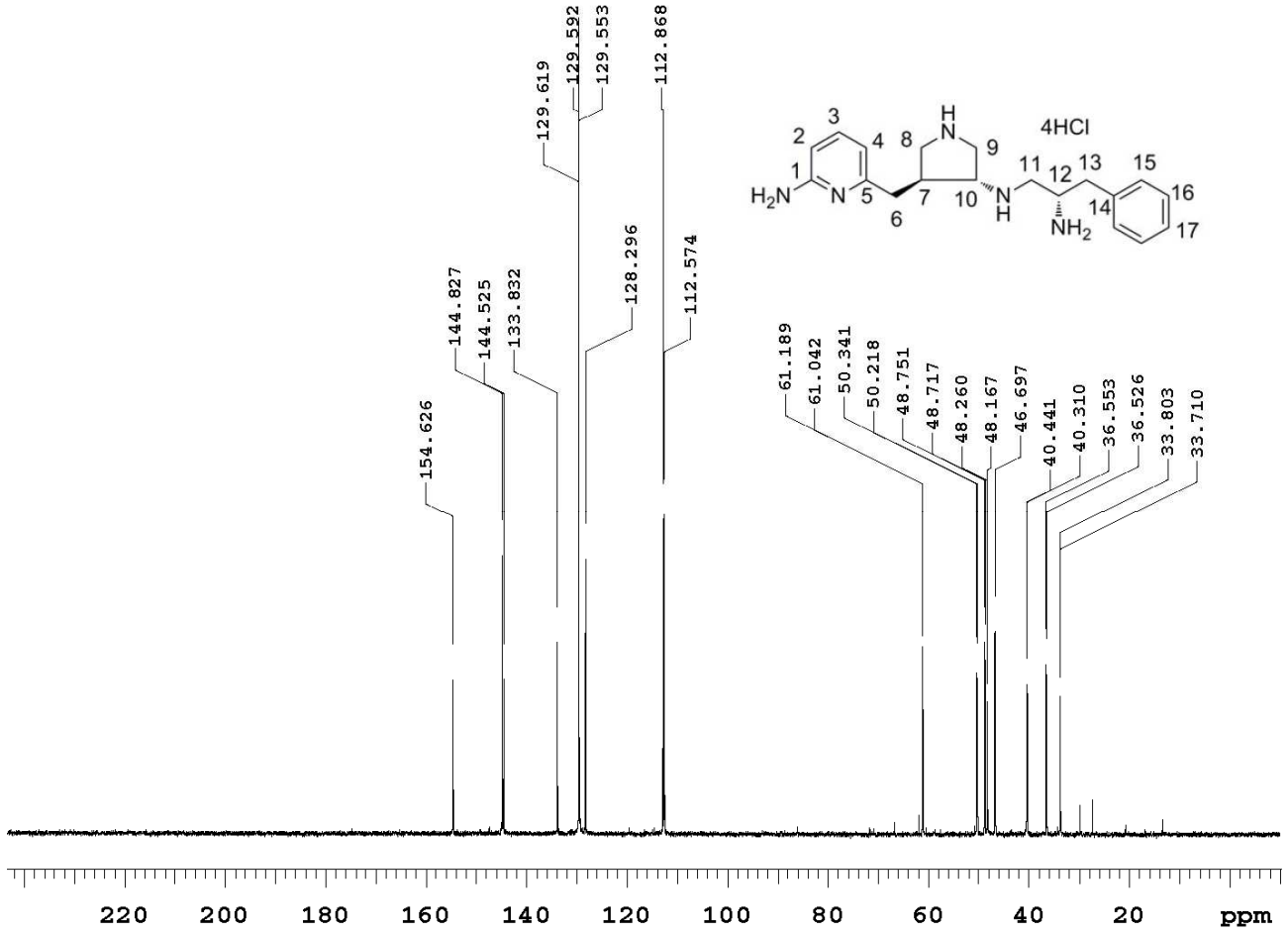
0.25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61.042
50.341
50.218
48.751
48.717
48.260
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40.441
40.310
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33.710
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40
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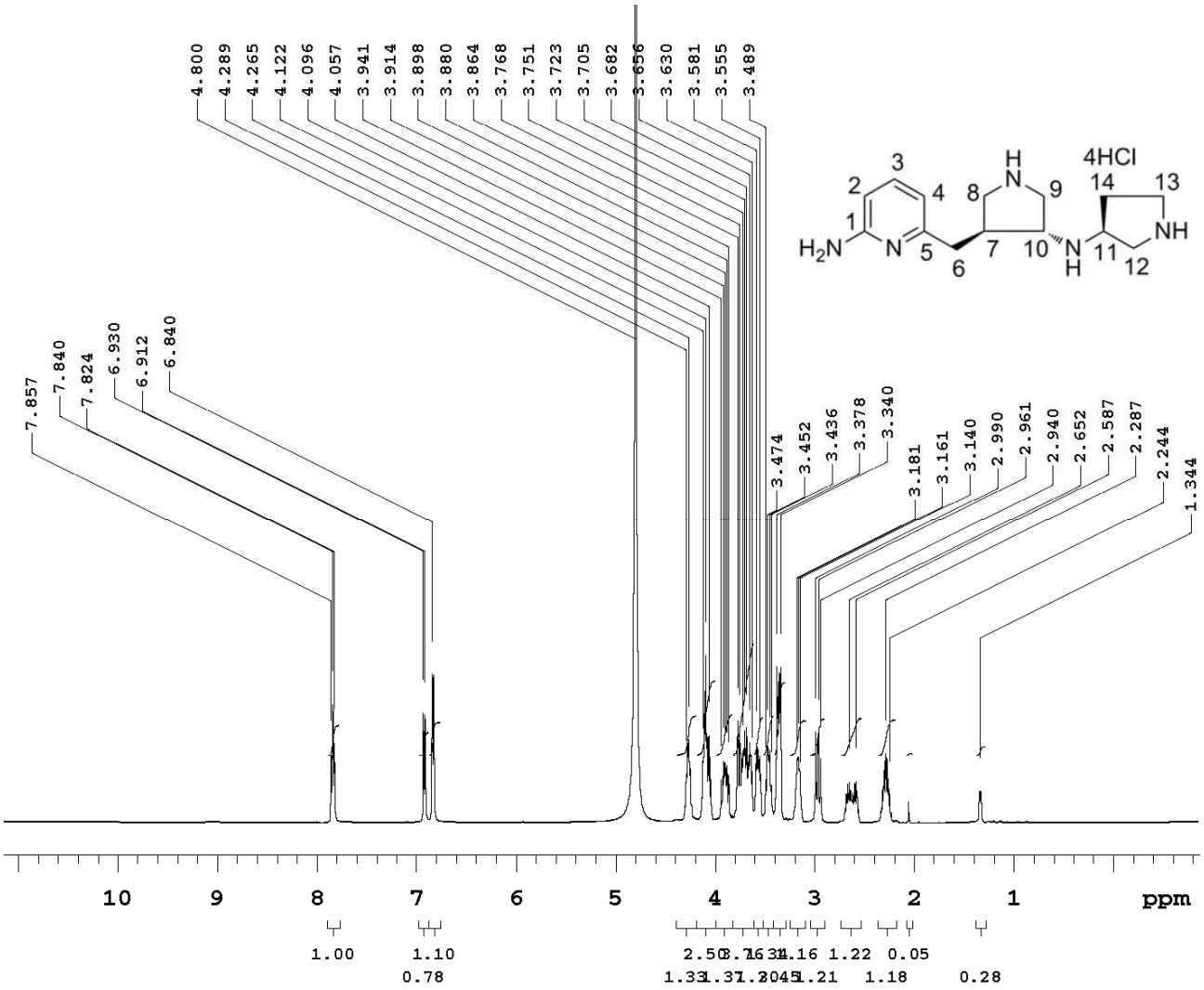
ppm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4.096
4.057
3.941
3.914
3.898
3.880
3.864
3.768
3.751
3.723
3.705
3.682
3.656
3.630
3.581
3.555
3.489
7.857
7.840
7.824
6.930
6.912
6.840
3.474
3.452
3.436
3.378
3.340
3.181
3.161
3.140
2.990
2.961
2.940
2.652
2.587
2.287
2.244
1.344
4HCl
10
9
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3
2
1
ppm
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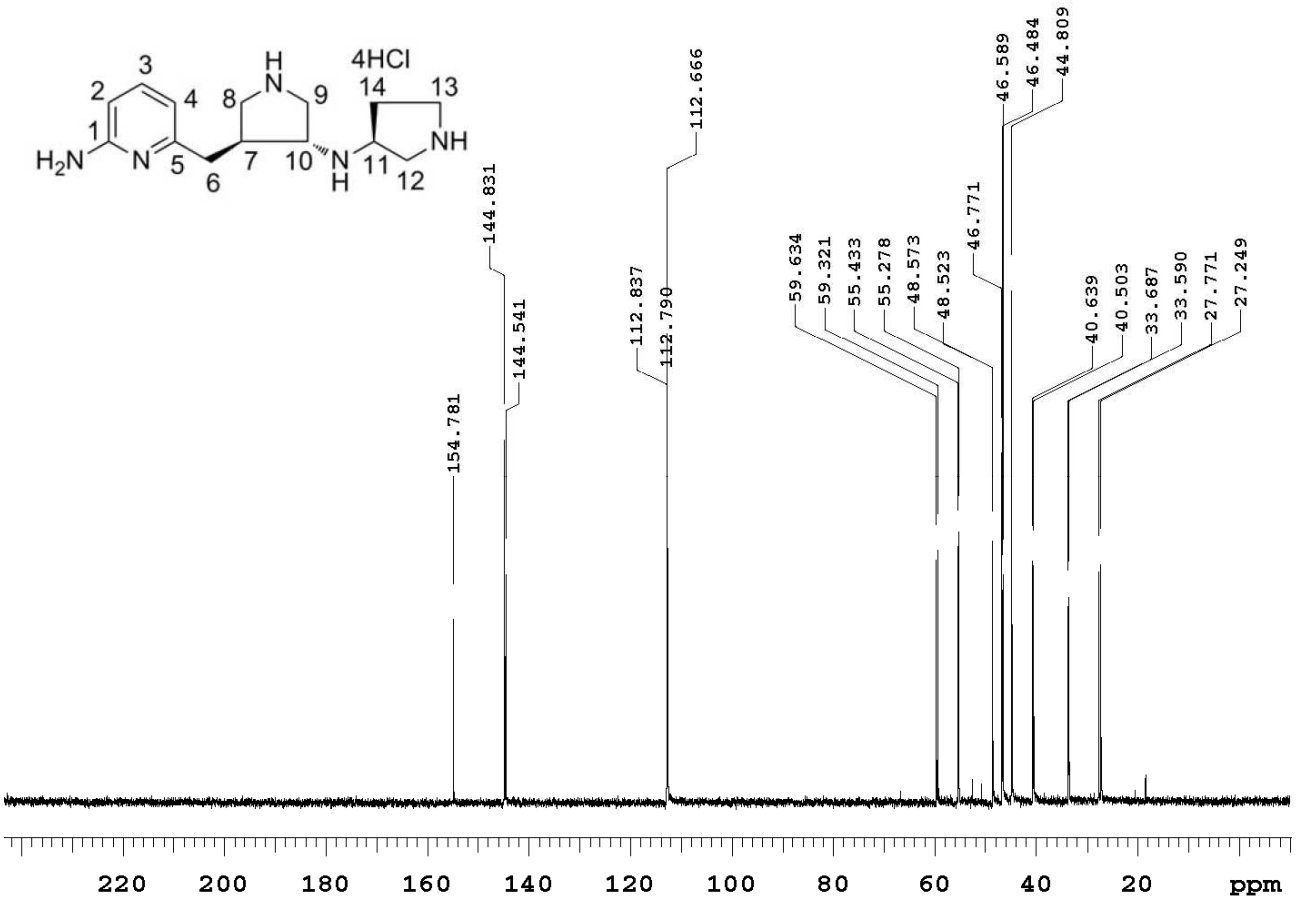
0.78
1.22
0.05
1.18
0.28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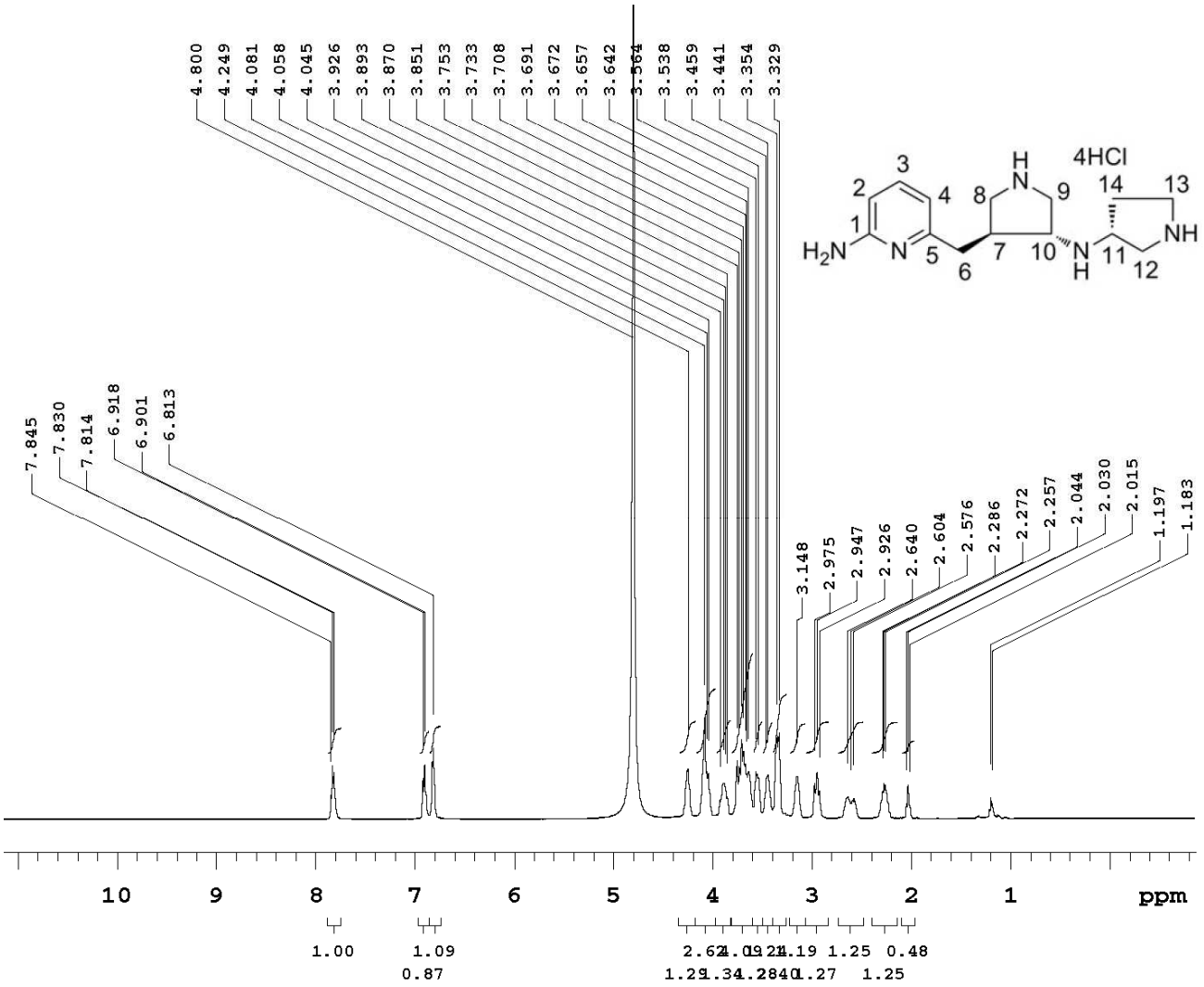
144.541
112.837
112.790
112.666
59.634
59.321
55.433
55.278
48.573
48.523
46.771
46.589
46.484
44.809
40.639
40.503
33.687
33.590
27.771
27.249
220
200
180
160
140
120
100
80
60
40
20
ppm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4.249
4.081
4.058
4.045
3.926
3.893
3.870
3.851
3.753
3.733
3.708
3.691
3.672
3.657
3.642
3.564
3.538
3.459
3.441
3.354
3.329
7.845
7.830
7.814
6.918
6.901
6.813
3.148
2.975
2.947
2.926
2.640
2.604
2.576
2.286
2.272
2.257
2.044
2.030
2.015
1.197
1.183
4HCl
10
9
8
7
6
5
4
3
2
1
ppm
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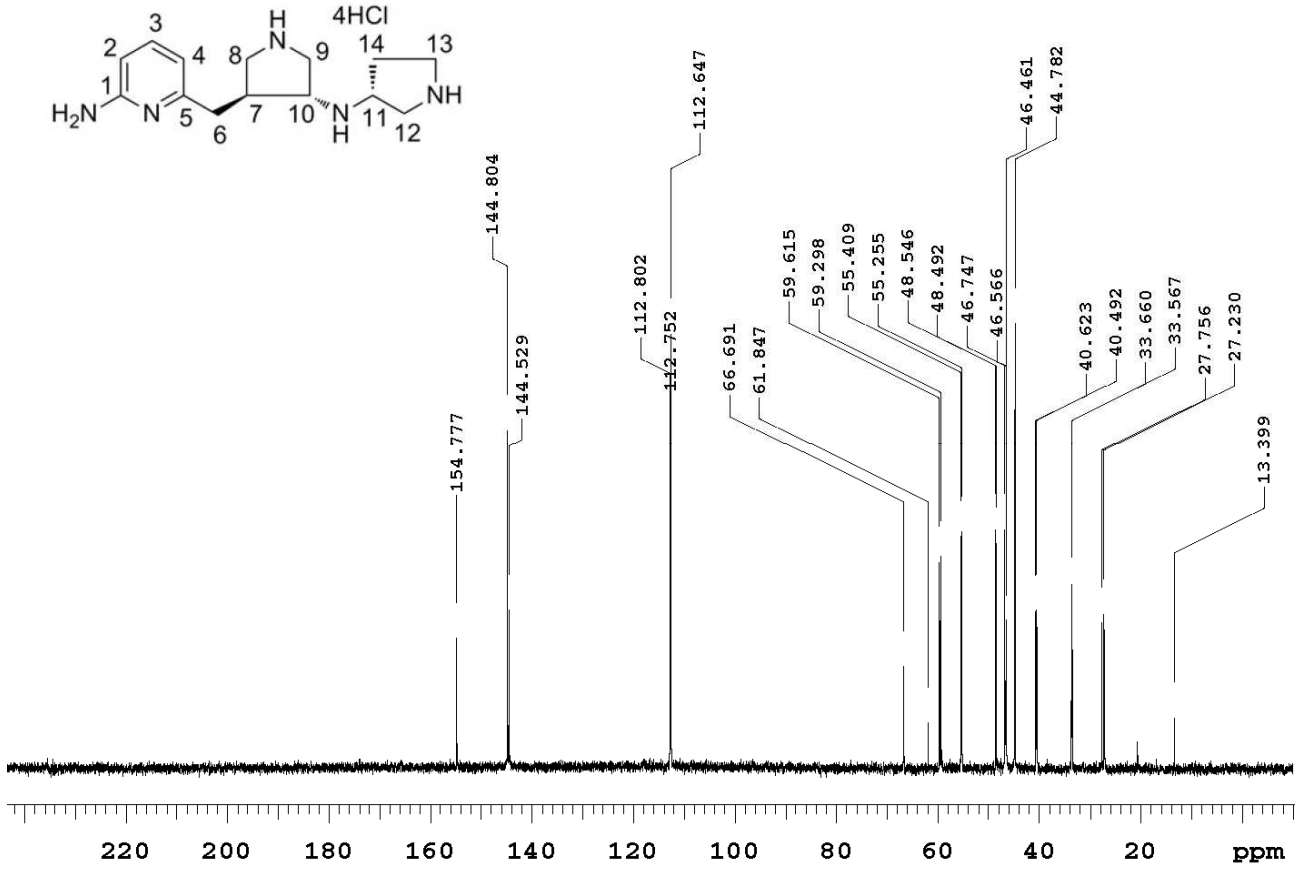
1.09
0.87
1.25
0.48
1.27
1.25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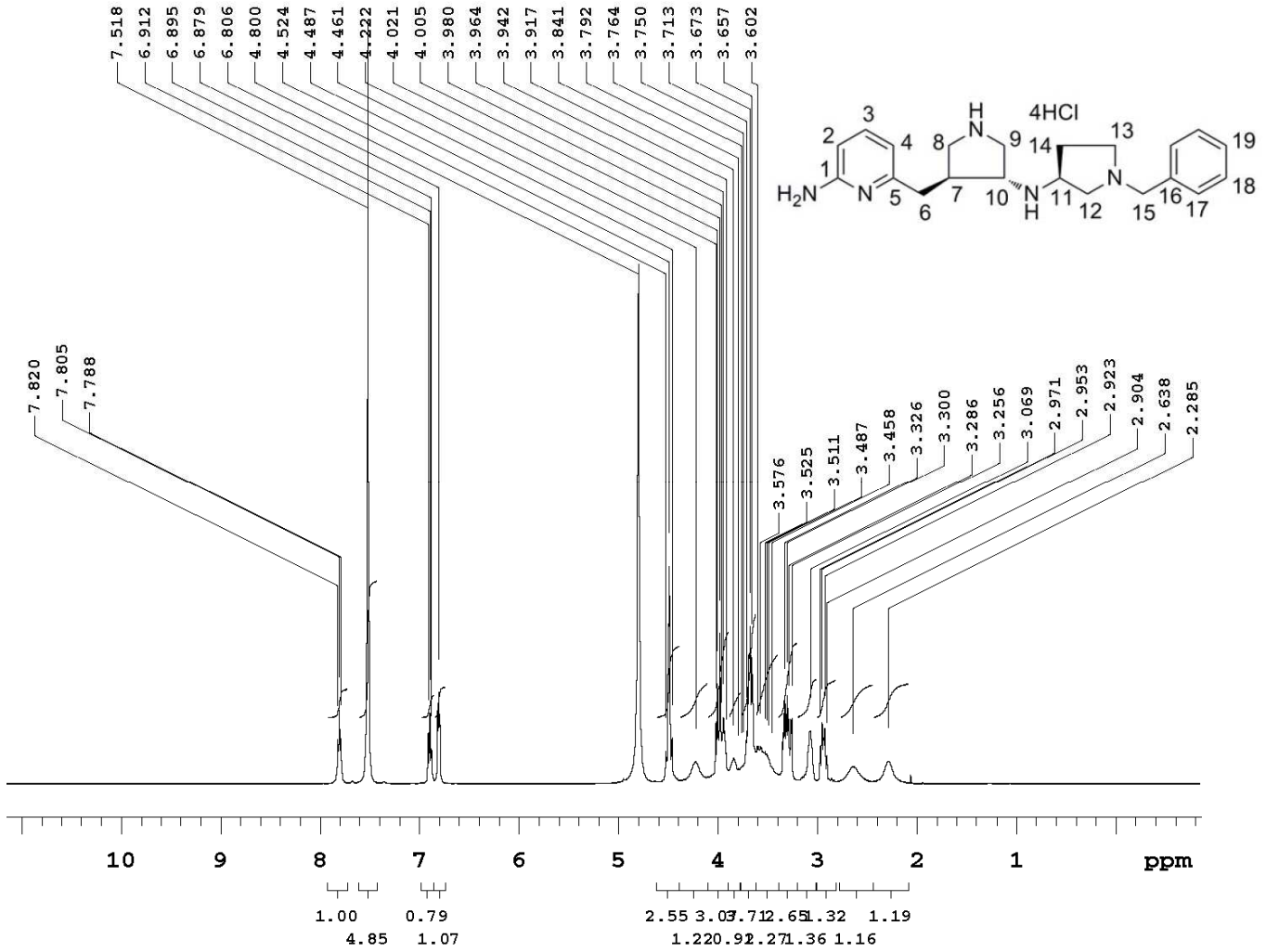
H2N
N
H
NH
1
2
3
4
5
6
7
8
9
10
11
12
13
14
154.777
144.804
144.529
112.802
112.752
112.647
66.691
61.847
59.615
59.298
55.409
55.255
48.546
48.492
46.747
46.566
46.461
44.782
40.623
40.492
33.660
33.567
27.756
27.230
13.399
220
200
180
160
140
120
100
80
60
40
20
ppm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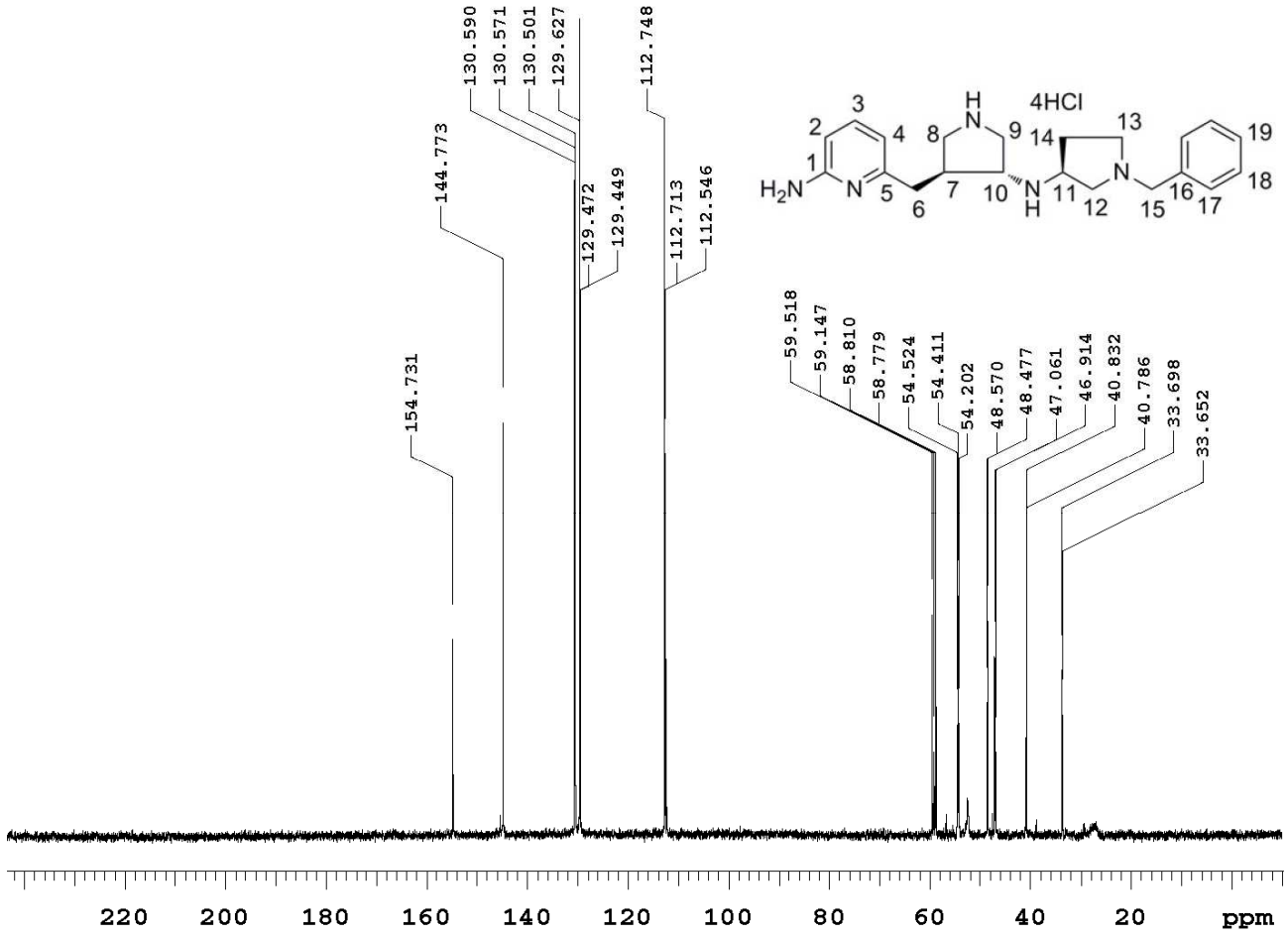
6.912
6.895
6.879
6.806
4.800
4.524
4.487
4.461
4.222
4.021
4.005
3.980
3.964
3.942
3.917
3.841
3.792
3.764
3.750
3.713
3.673
3.657
3.602
7.820
7.805
7.788
3.576
3.525
3.511
3.487
3.458
3.326
3.300
3.286
3.256
3.069
2.971
2.953
2.923
2.904
2.638
2.285
4HCl
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.79
4.85
1.07
2.55
3.03
3.71
2.65
1.32
1.19
1.22
0.92
1.27
1.36
1.16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130.571
130.501
129.627
112.748
144.773
129.472
129.449
112.713
112.546
154.731
59.518
59.147
58.810
58.779
54.524
54.411
54.202
48.570
48.477
47.061
46.914
40.832
40.786
33.698
33.652
4HCl
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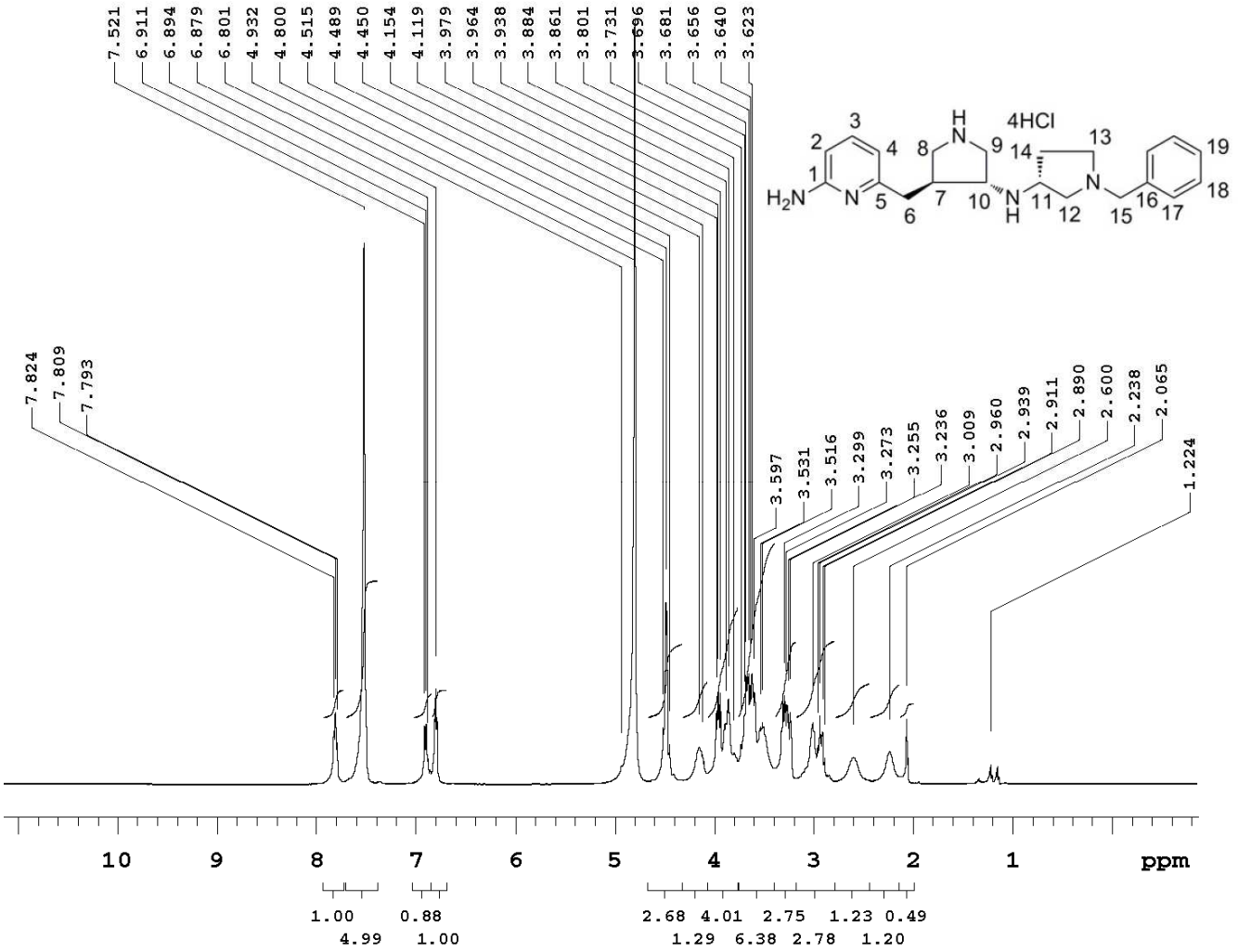
200
180
160
140
120
100
80
60
40
20
ppm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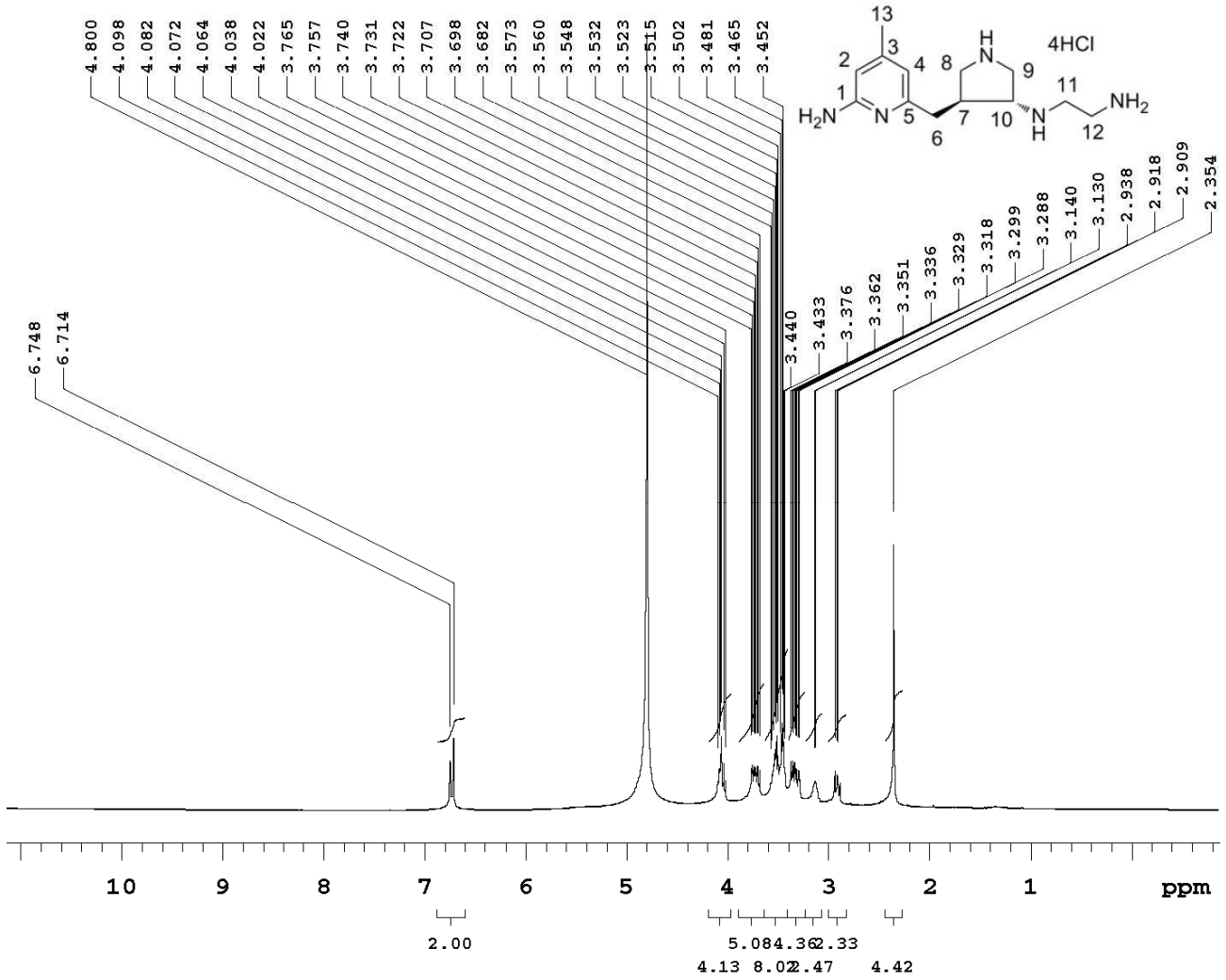
6.911
6.894
6.879
6.801
4.932
4.800
4.515
4.489
4.450
4.154
4.119
3.979
3.964
3.938
3.884
3.861
3.801
3.731
3.696
3.681
3.656
3.640
3.623
7.824
7.809
7.793
3.597
3.531
3.516
3.299
3.273
3.255
3.236
3.009
2.960
2.939
2.911
2.890
2.600
2.238
2.065
1.224
4HCl
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.88
2.68
4.01
2.75
1.23
0.49
4.99
1.00
1.29
6.38
2.78
1.20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4.098
4.082
4.072
4.064
4.038
4.022
3.765
3.757
3.740
3.731
3.722
3.707
3.698
3.682
3.573
3.560
3.548
3.532
3.523
3.515
3.502
3.481
3.465
3.452
6.748
6.714
3.440
3.433
3.376
3.362
3.351
3.336
3.329
3.318
3.299
3.288
3.140
3.130
2.938
2.918
2.909
2.354
4HCl
10
9
8
7
6
5
4
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2
1
ppm
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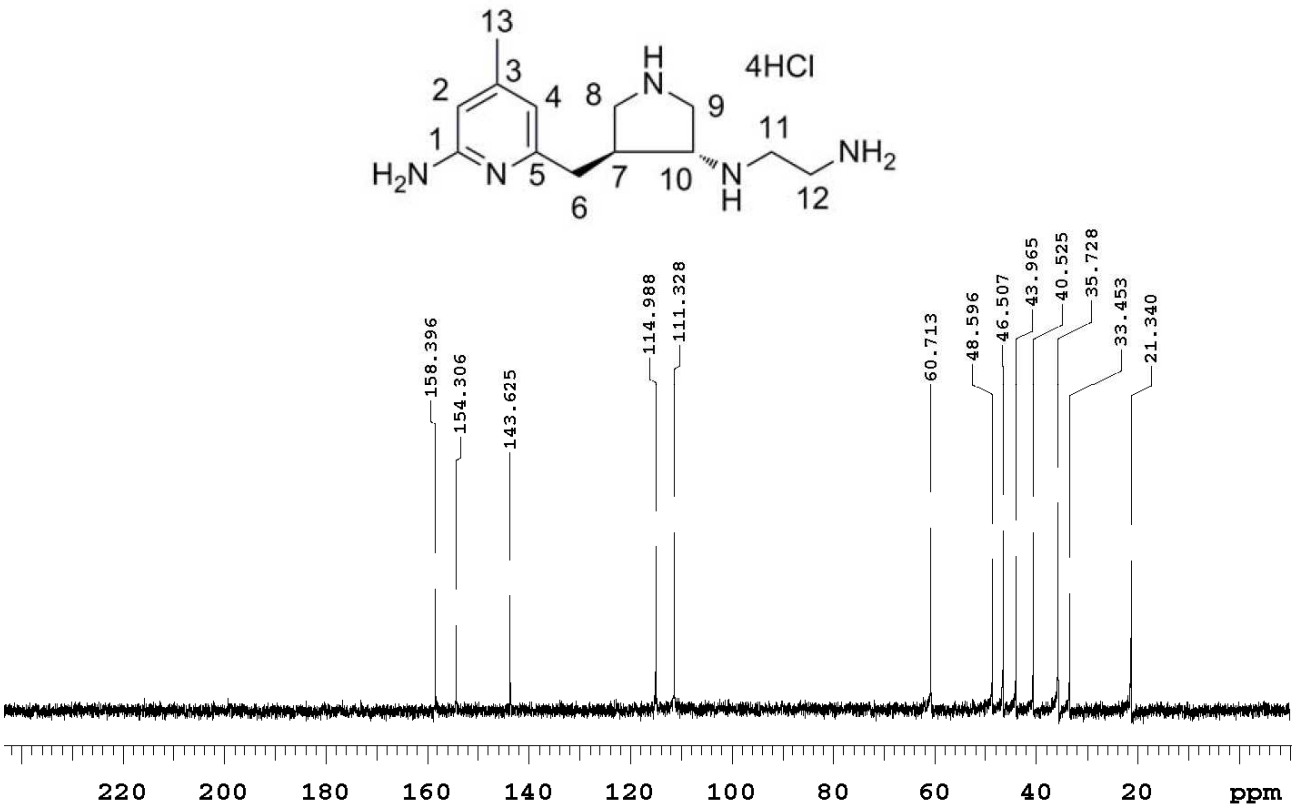
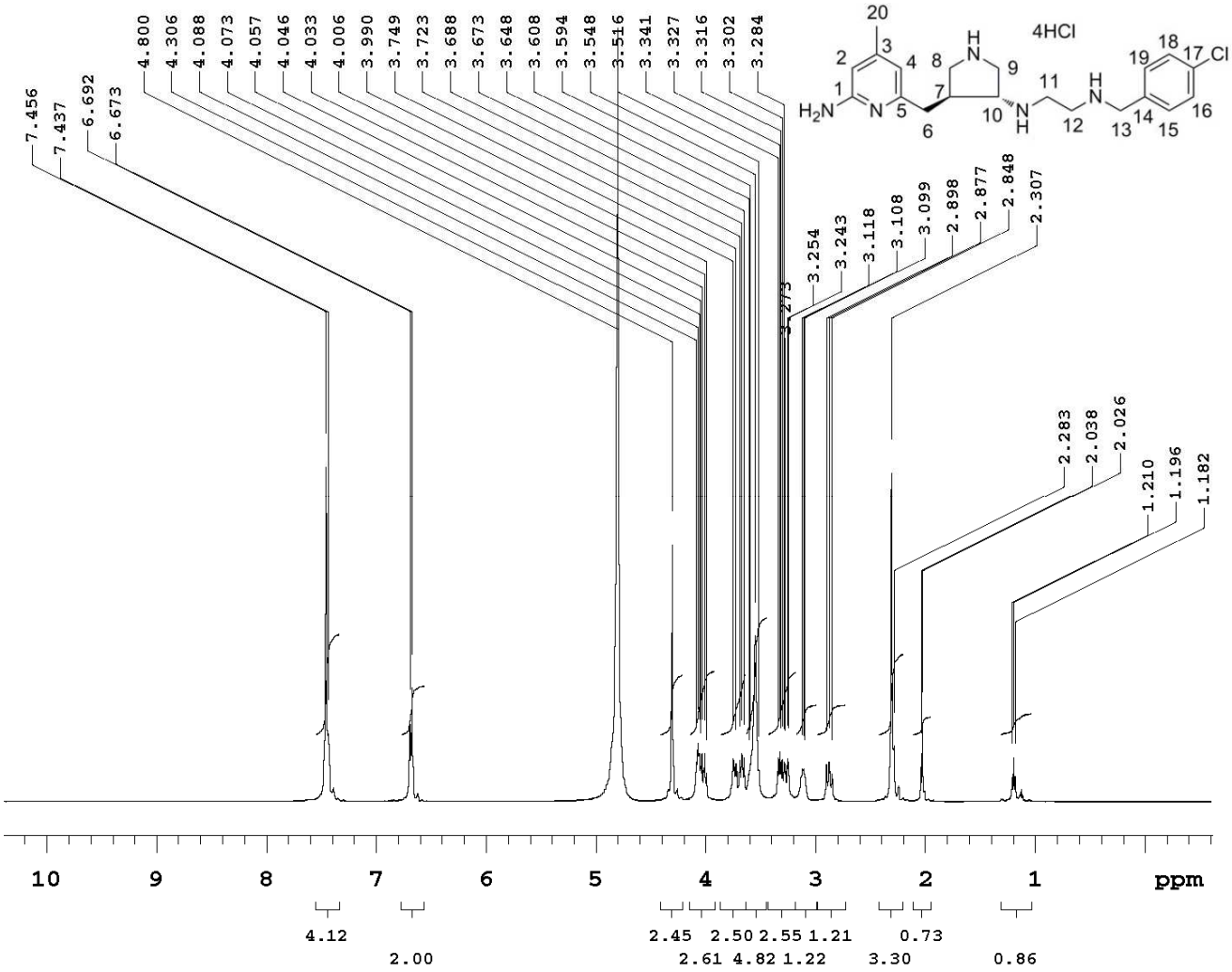
5.08
4.36
2.33
4.13
8.02
2.47
4.42


13
3
2
4
8
H
N
9
4HCl
1
11
H_2N
N
5
7
10
N
H
NH_2
6
12
158.396
154.306
143.625
114.988
111.328
60.713
48.596
46.507
43.965
40.525
35.728
33.453
21.340
220
200
180
160
140
120
100
80
60
40
20
ppm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4.800
4.306
4.088
4.073
4.057
4.046
4.033
4.006
3.990
3.749
3.723
3.688
3.673
3.648
3.608
3.594
3.548
3.516
3.341
3.327
3.316
3.302
3.284
3.273
3.254
3.243
3.118
3.108
3.099
2.898
2.877
2.848
2.307
2.283
2.038
2.026
1.210
1.196
1.182
10
9
8
7
6
5
4
3
2
1
ppm
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2.61
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1.22
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3.30
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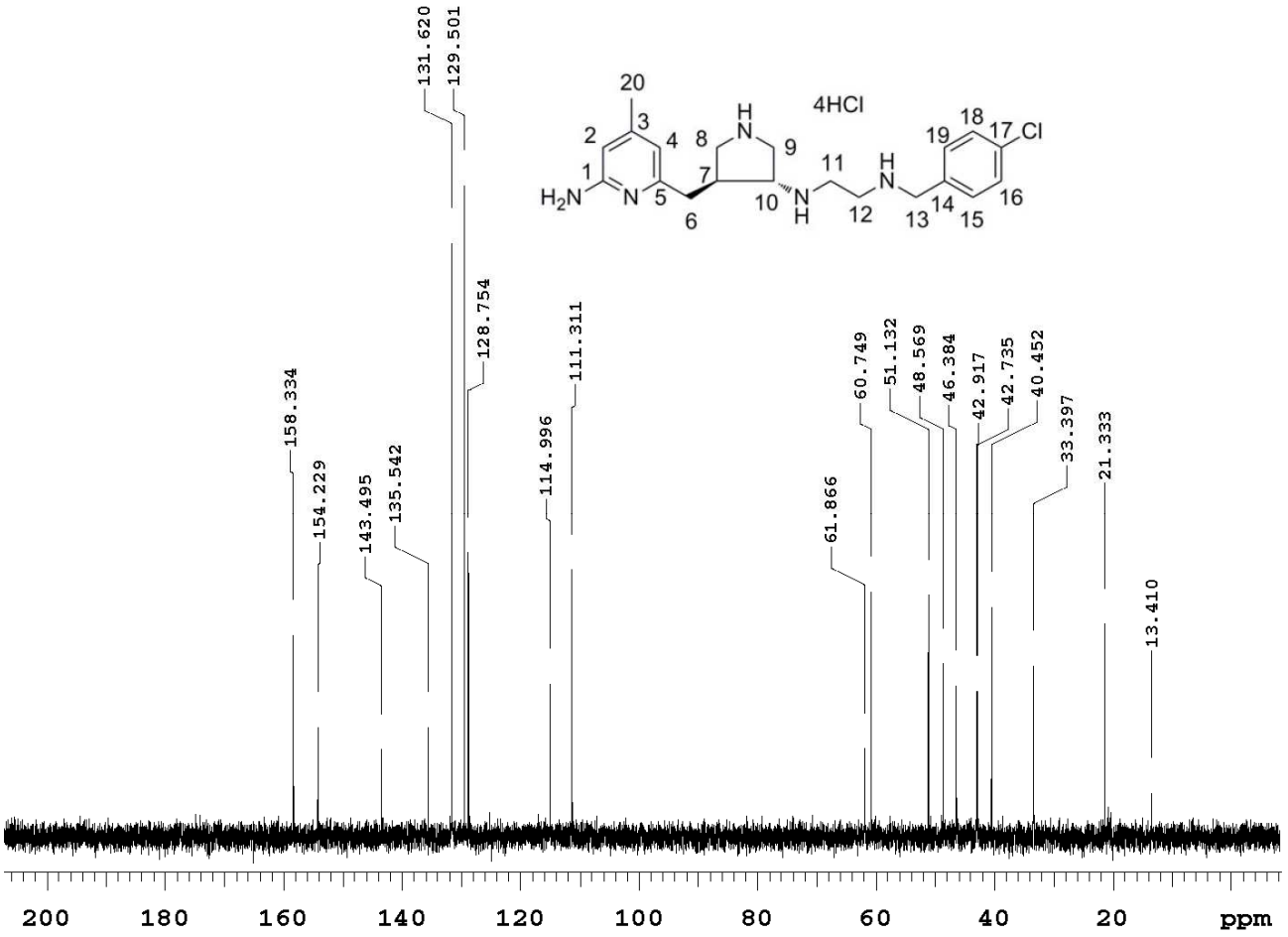
0.86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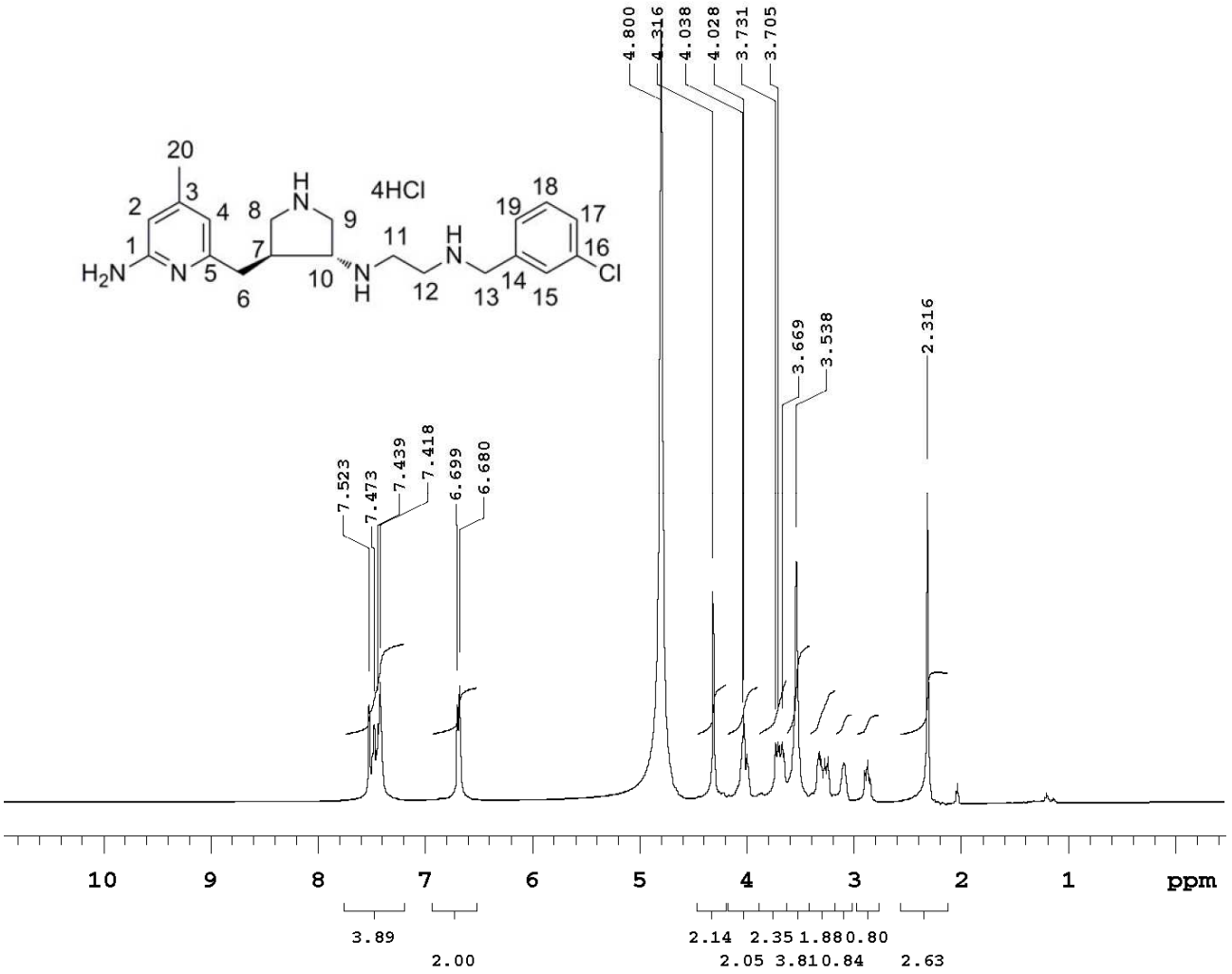
129.501
158.334
154.229
143.495
135.542
128.754
114.996
111.311
61.866
60.749
51.132
48.569
46.384
42.917
42.735
40.452
33.397
21.333
13.410
4HCl
200
180
160
140
120
100
80
60
40
20
ppm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4.028
3.731
3.705
3.669
3.538
2.316
7.523
7.473
7.439
7.418
6.699
6.680
10
9
8
7
6
5
4
3
2
1
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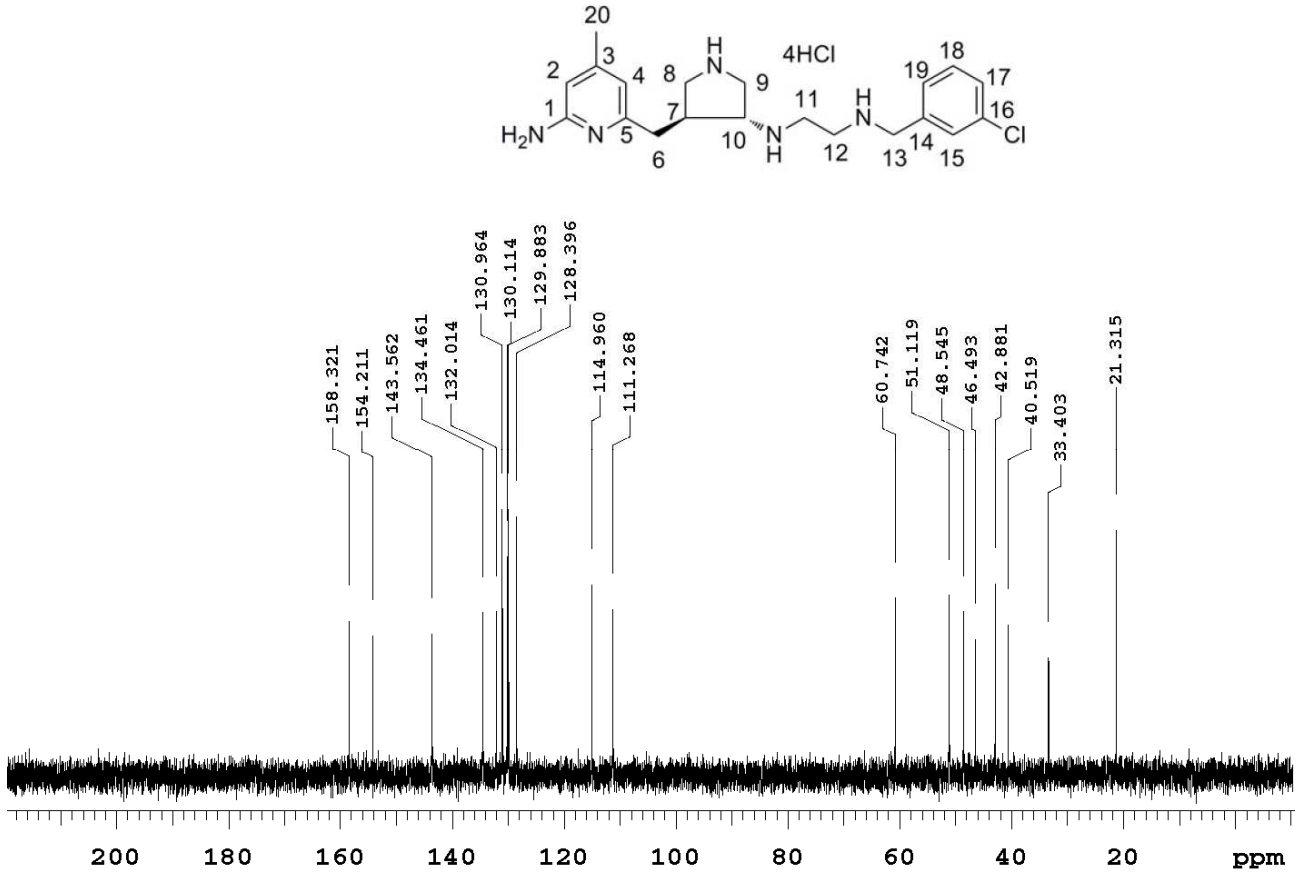
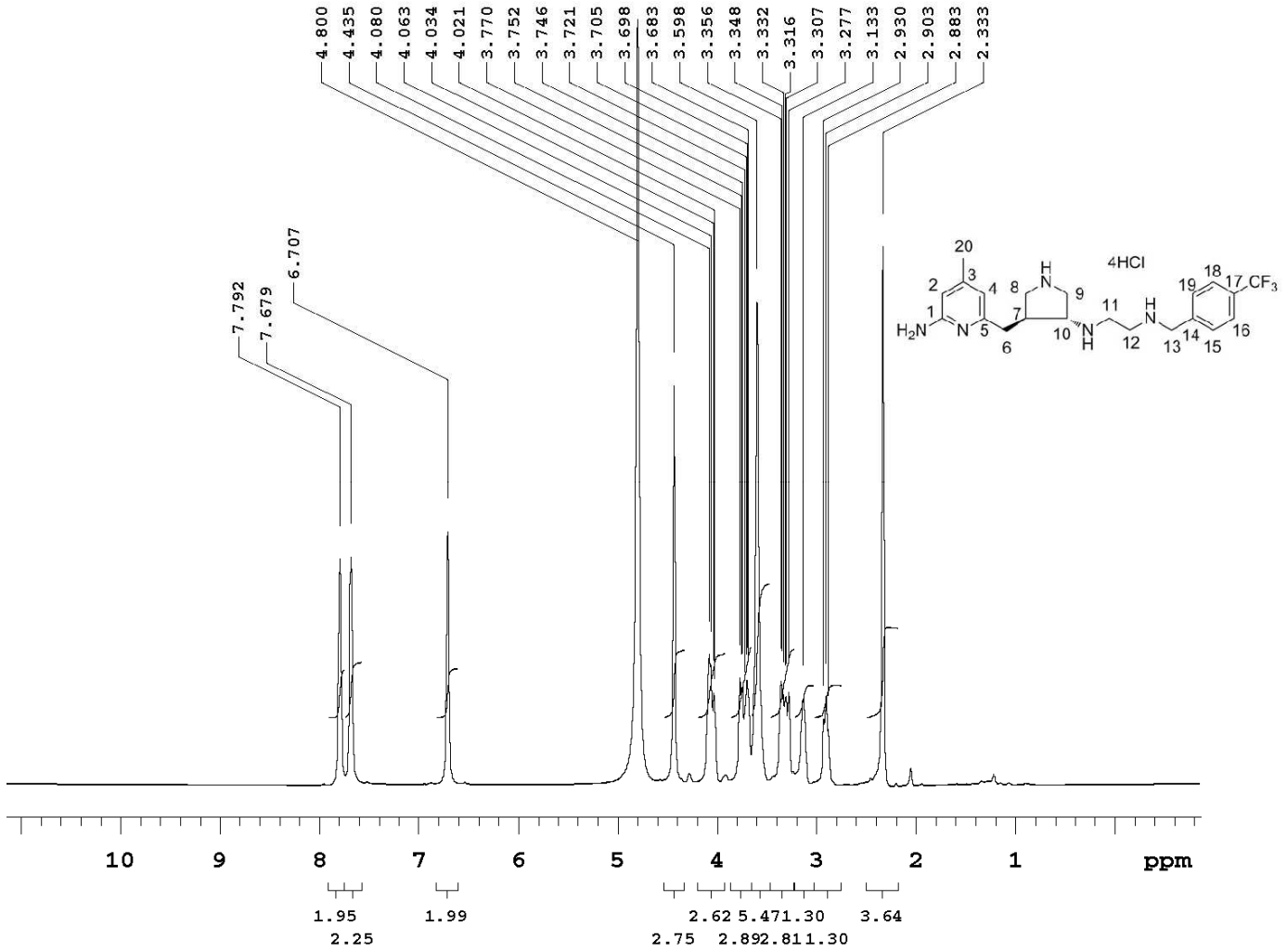
1.88
0.80
2.05
3.81
0.84
2.63


20
3
2
4
8
H
N
9
4HCl
19
18
17
16
Cl
1
7
11
H
N
H_2N
N
5
10
N
H
12
13
14
15
6
158.321
154.211
143.562
134.461
132.014
130.964
130.114
129.883
128.396
114.960
111.268
60.742
51.119
48.545
46.493
42.881
40.519
33.403
21.315
200
180
160
140
120
100
80
60
40
20
ppm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4.063
4.034
4.021
3.770
3.752
3.746
3.721
3.705
3.698
3.683
3.598
3.356
3.348
3.332
3.316
3.307
3.277
3.133
2.930
2.903
2.883
2.333
7.792
7.679
6.707
4HCl
10
9
8
7
6
5
4
3
2
1
ppm
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1.99
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2.62
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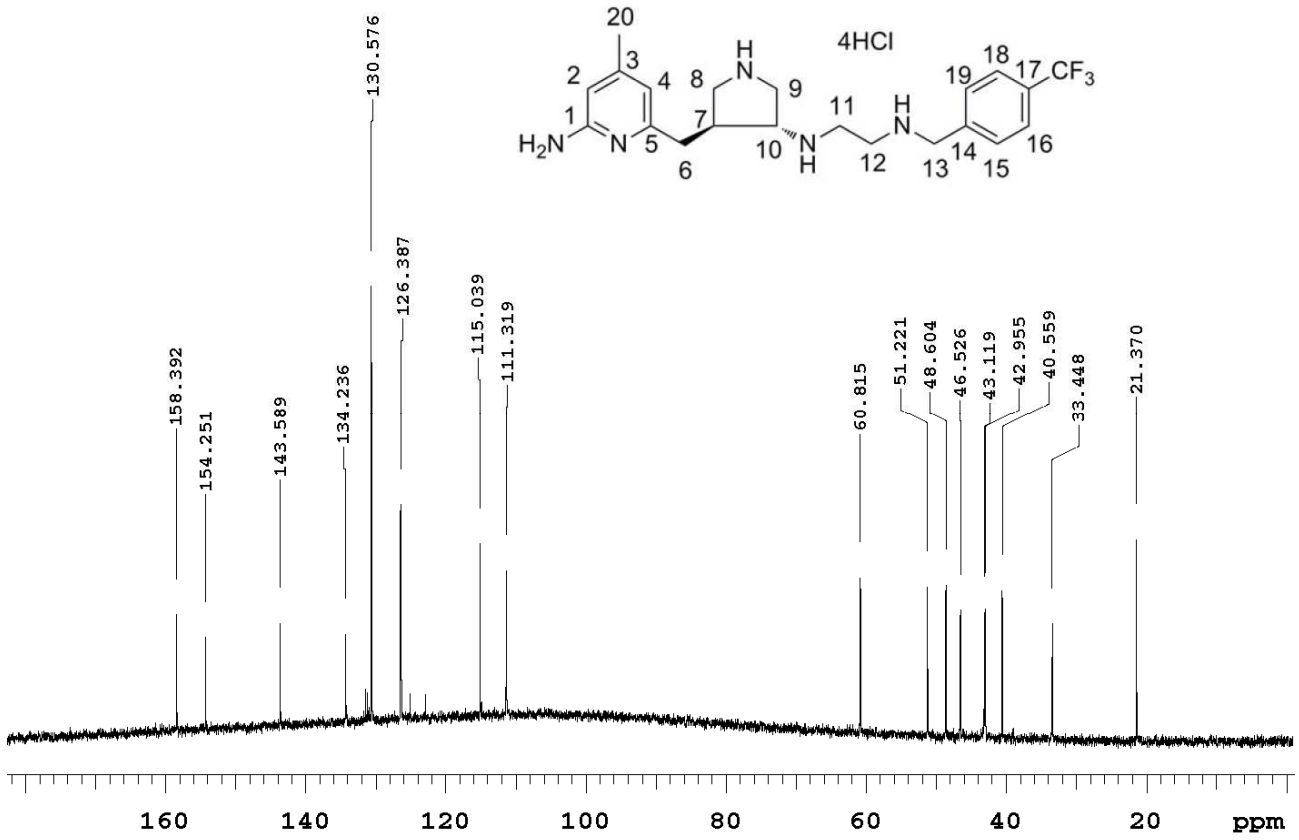
5.47
2.81
1.30
1.30
3.64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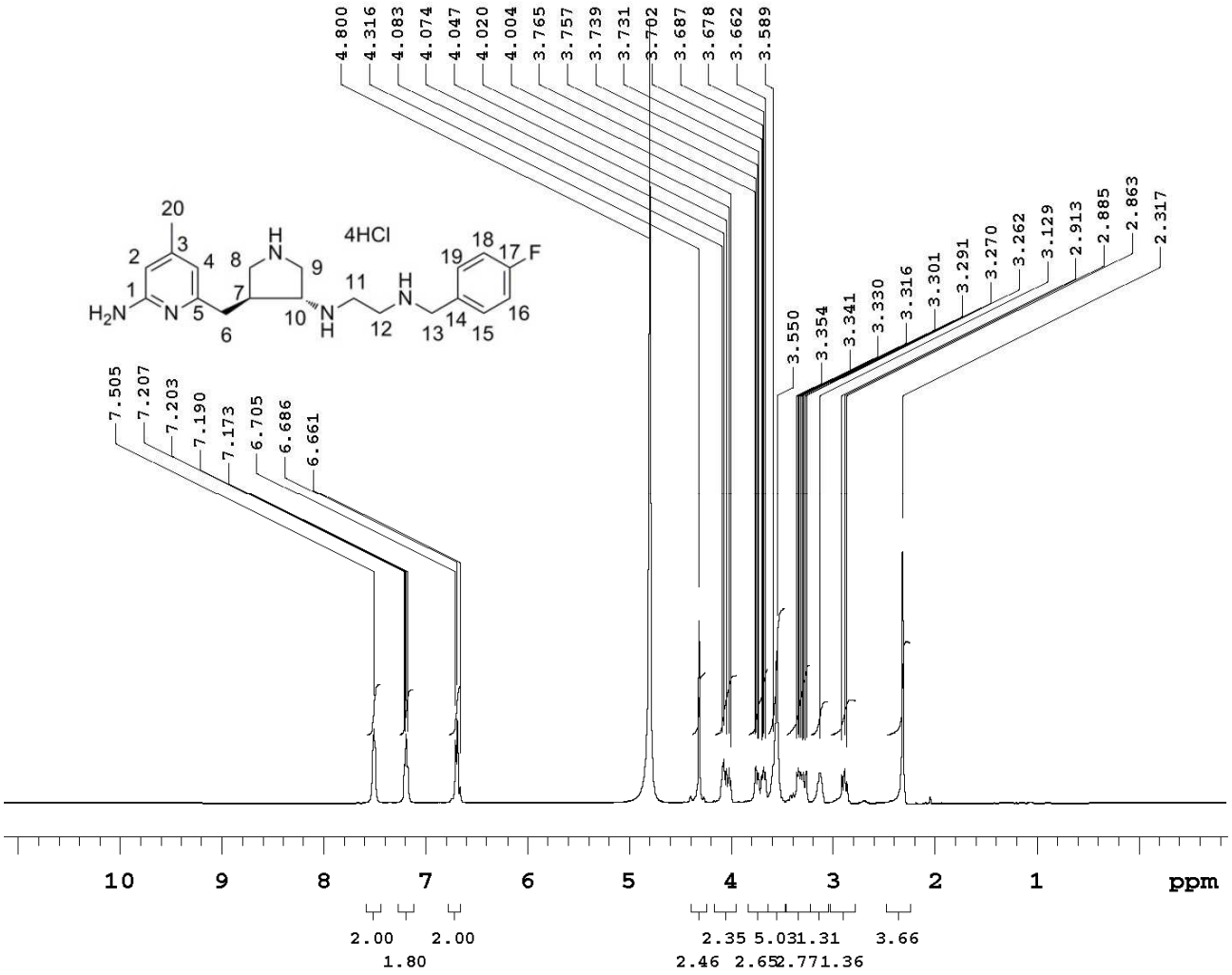
134.236
130.576
126.387
115.039
111.319
60.815
51.221
48.604
46.526
43.119
42.955
40.559
33.448
21.370
160
140
120
100
80
60
40
20
ppm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4.316
4.083
4.074
4.047
4.020
4.004
3.765
3.757
3.739
3.731
3.702
3.687
3.678
3.662
3.589
3.550
3.354
3.341
3.330
3.316
3.301
3.291
3.270
3.262
3.129
2.913
2.885
2.863
2.317
7.505
7.207
7.203
7.190
7.173
6.705
6.686
6.661
4HCl
10
9
8
7
6
5
4
3
2
1
ppm
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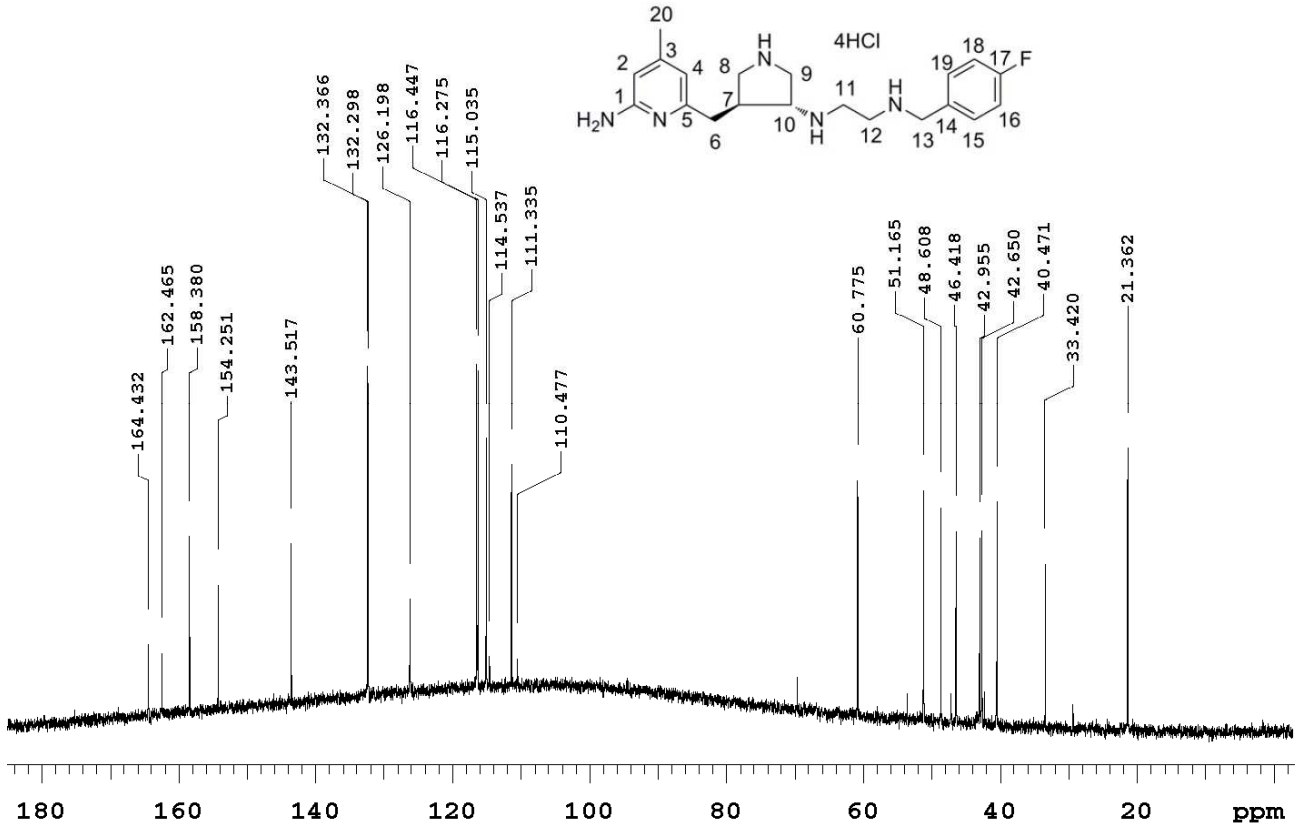
2.65
2.77
1.36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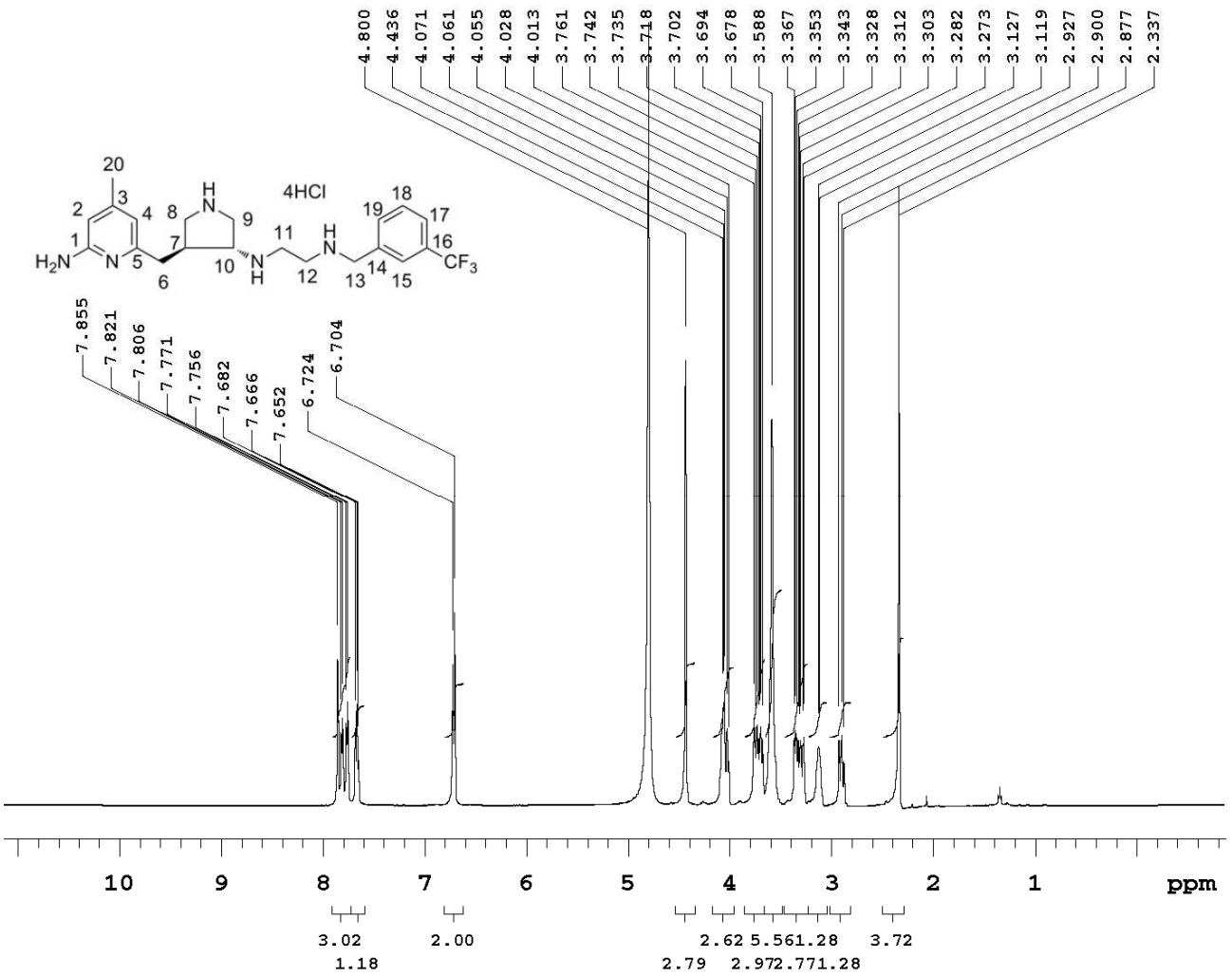
154.251
143.517
132.366
132.298
126.198
116.447
116.275
115.035
114.537
111.335
110.477
60.775
51.165
48.608
46.418
42.955
42.650
40.471
33.420
21.362
180
160
140
120
100
80
60
40
20
ppm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4.436
4.071
4.061
4.055
4.028
4.013
3.761
3.742
3.735
3.718
3.702
3.694
3.678
3.588
3.367
3.353
3.343
3.328
3.312
3.303
3.282
3.273
3.127
3.119
2.927
2.900
2.877
2.337
4HCl
7.855
7.821
7.806
7.771
7.756
7.682
7.666
7.652
6.724
6.704
10
9
8
7
6
5
4
3
2
1
ppm
3.02
1.18
2.00
2.79
2.62
2.97
5.56
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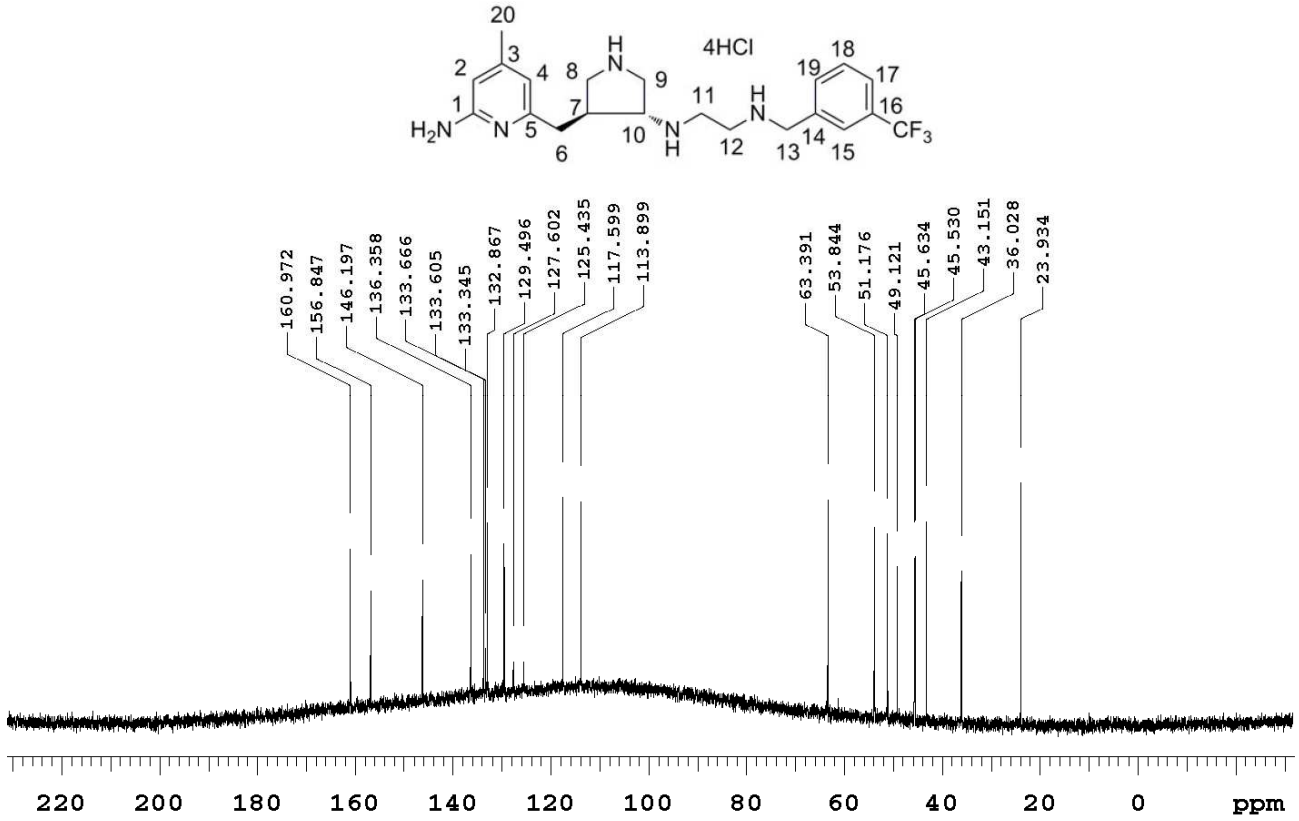
1.28
1.28
3.72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117.599
113.899
63.391
53.844
51.176
49.121
45.634
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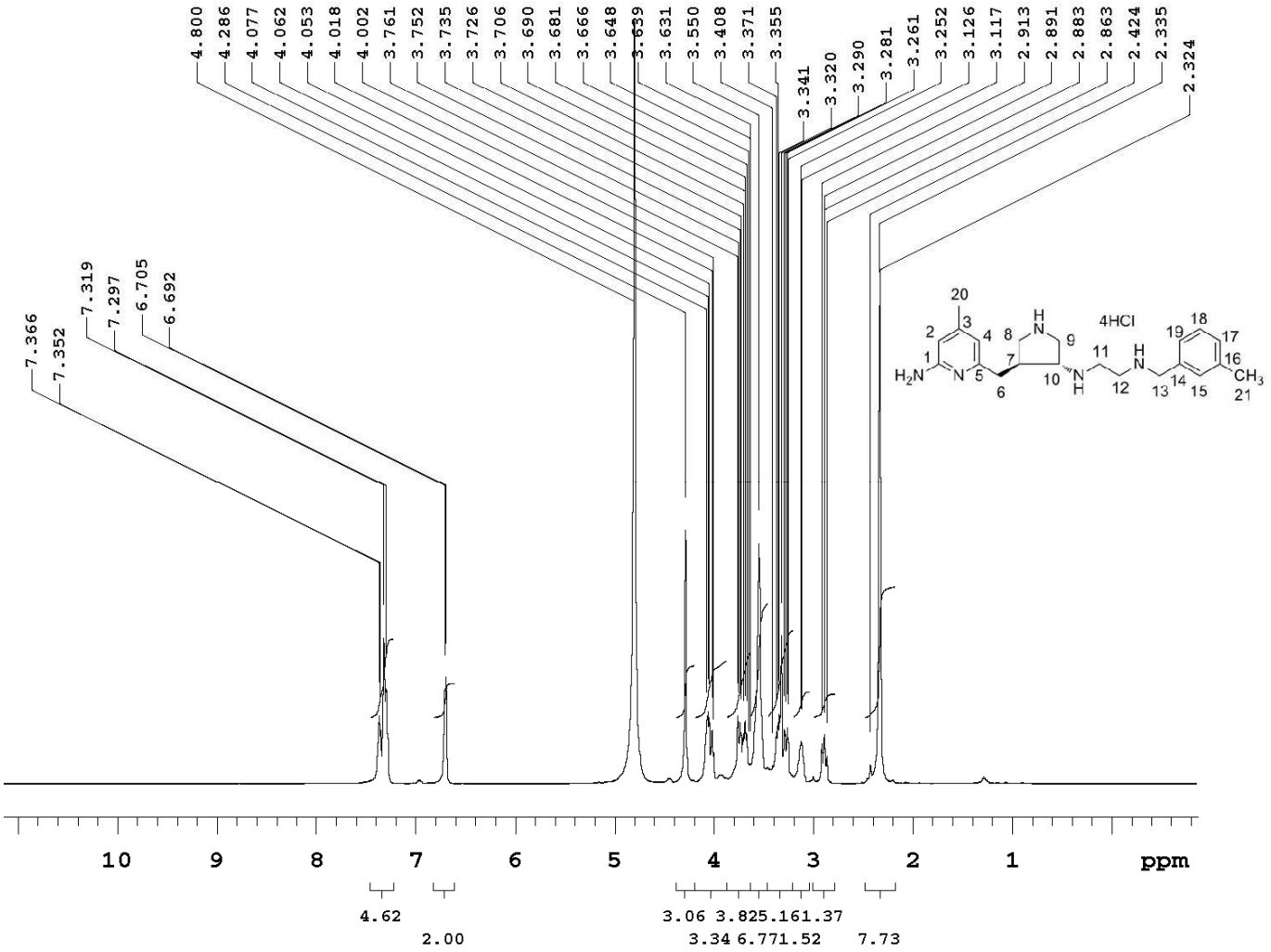
20
0
ppm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3.690
3.681
3.666
3.648
3.639
3.631
3.550
3.408
3.371
3.355
3.341
3.320
3.290
3.281
3.261
3.252
3.126
3.117
2.913
2.891
2.883
2.863
2.424
2.335
2.324
7.366
7.352
7.319
7.297
6.705
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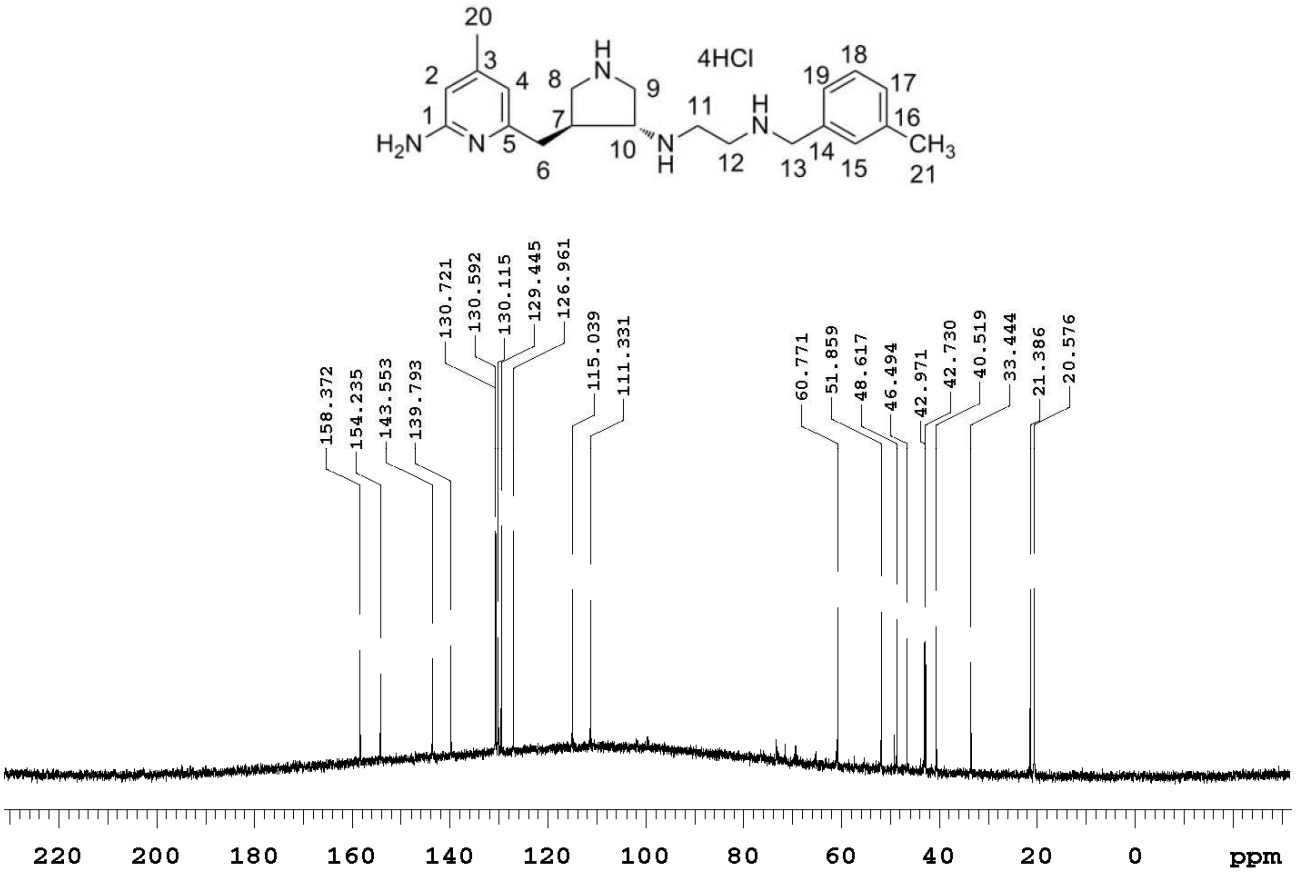
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130.115
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111.331
60.771
51.859
48.617
46.494
42.971
42.730
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20.576
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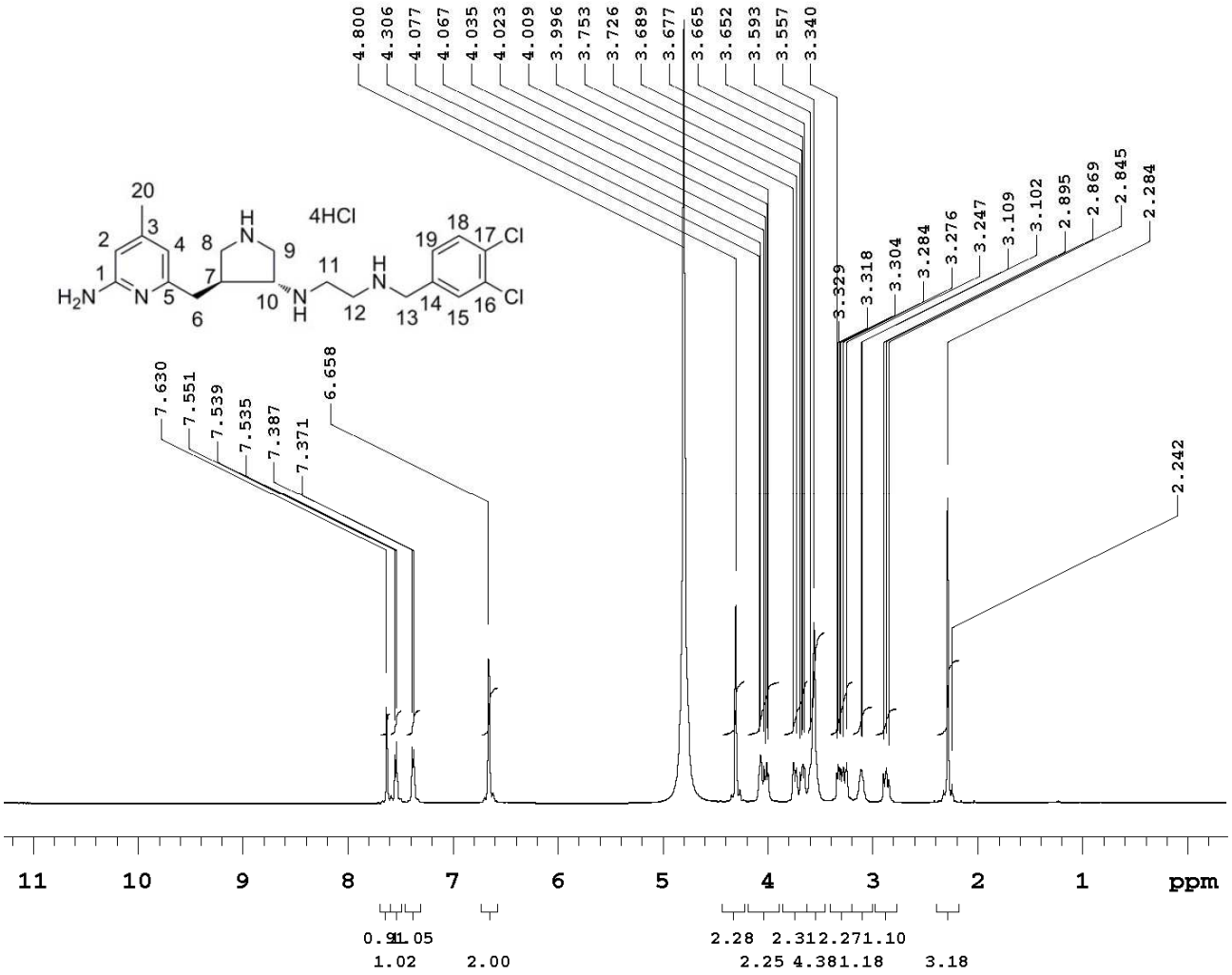
20
0
ppm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3.996
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3.665
3.652
3.593
3.557
3.340
3.329
3.318
3.304
3.284
3.276
3.247
3.109
3.102
2.895
2.869
2.845
2.284
2.242
7.630
7.551
7.539
7.535
7.387
7.371
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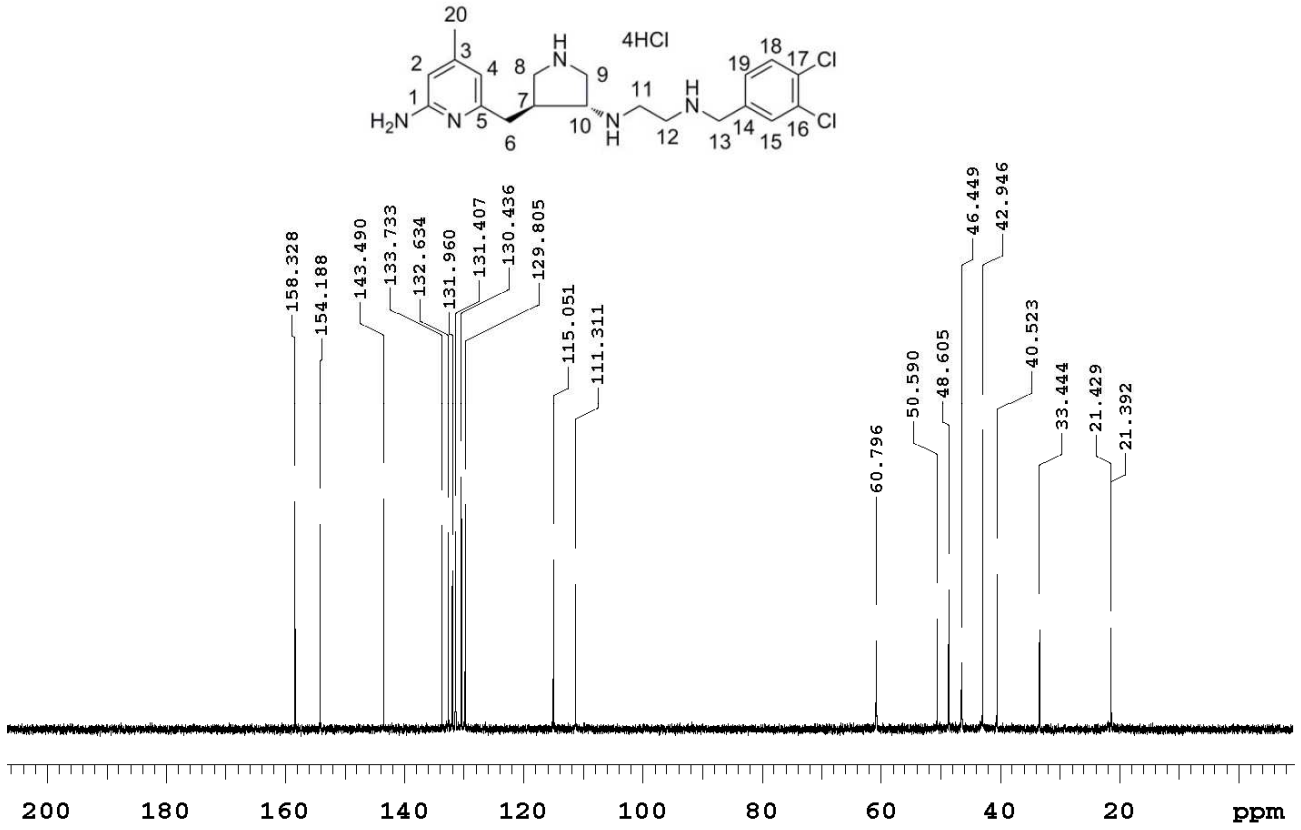
1.02 2.25 4.38 1.18 3.18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131.960
131.407
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115.051
111.311
60.796
50.590
48.605
46.449
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33.444
21.429
21.392
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140
120
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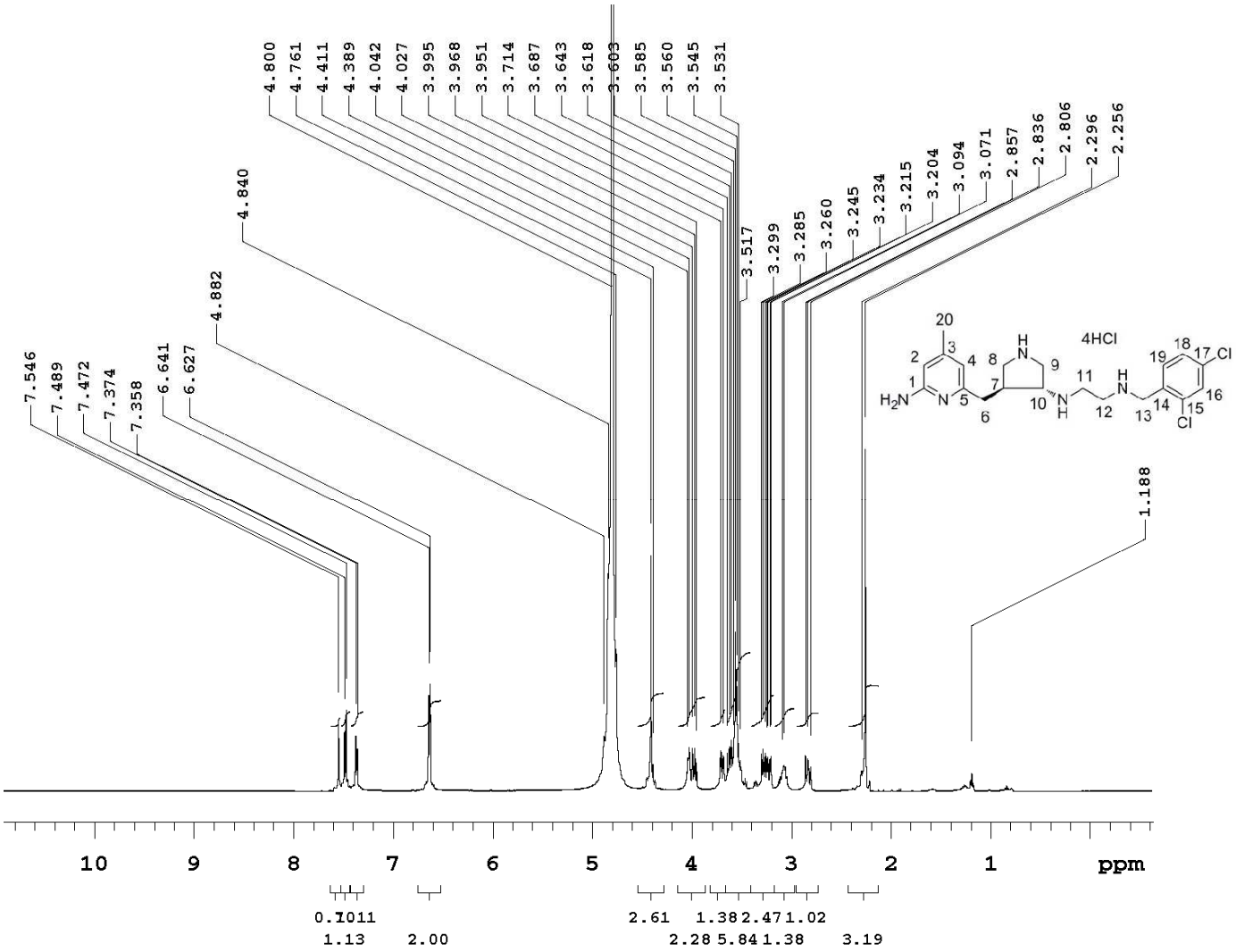
80
60
40
20
ppm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3.714
3.687
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3.618
3.603
3.585
3.560
3.545
3.531
4.840
4.882
3.517
3.299
3.285
3.260
3.245
3.234
3.215
3.204
3.094
3.071
2.857
2.836
2.806
2.296
2.256
7.546
7.489
7.472
7.374
7.358
6.641
6.627
1.188
4HCl
10
9
8
7
6
5
4
3
2
1
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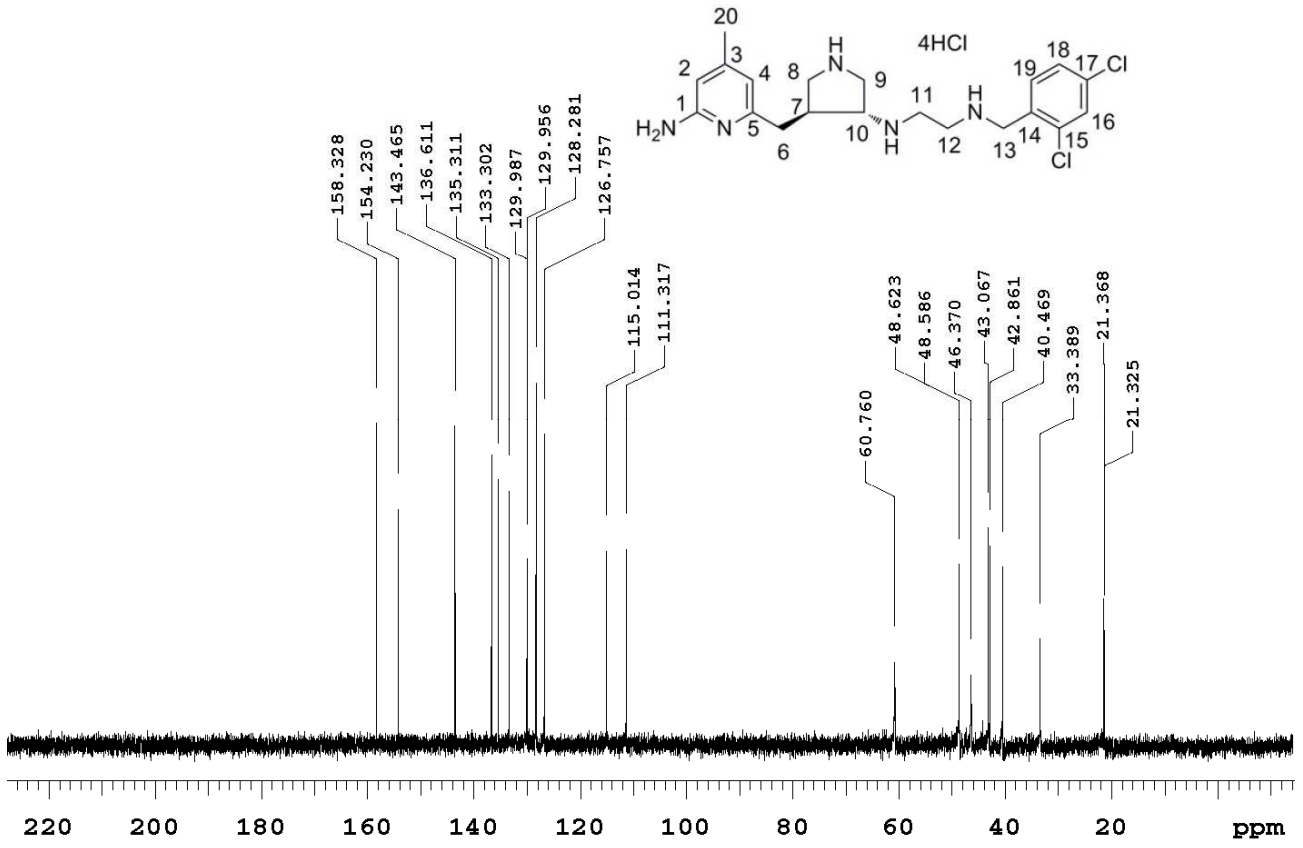
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115.014
111.317
60.760
48.623
48.586
46.370
43.067
42.861
40.469
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21.368
21.325
4HCl
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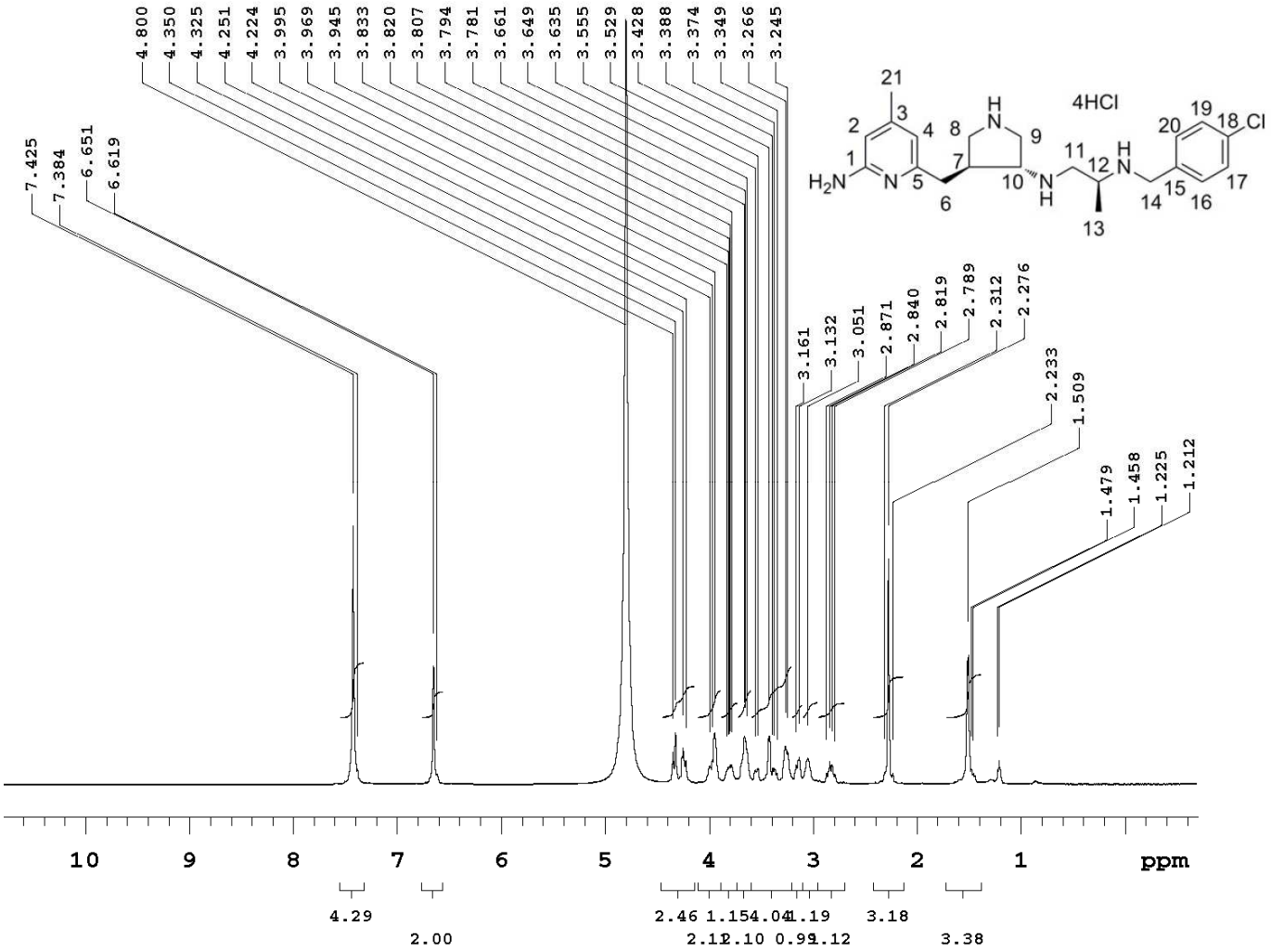
200
180
160
140
120
100
80
60
40
20
ppm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3.794
3.781
3.661
3.649
3.635
3.555
3.529
3.428
3.388
3.374
3.349
3.266
3.245
7.425
7.384
6.651
6.619
3.161
3.132
3.051
2.871
2.840
2.819
2.789
2.312
2.276
2.233
1.509
1.479
1.458
1.225
1.212
4HCl
Cl
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9
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7
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5
4
3
2
1
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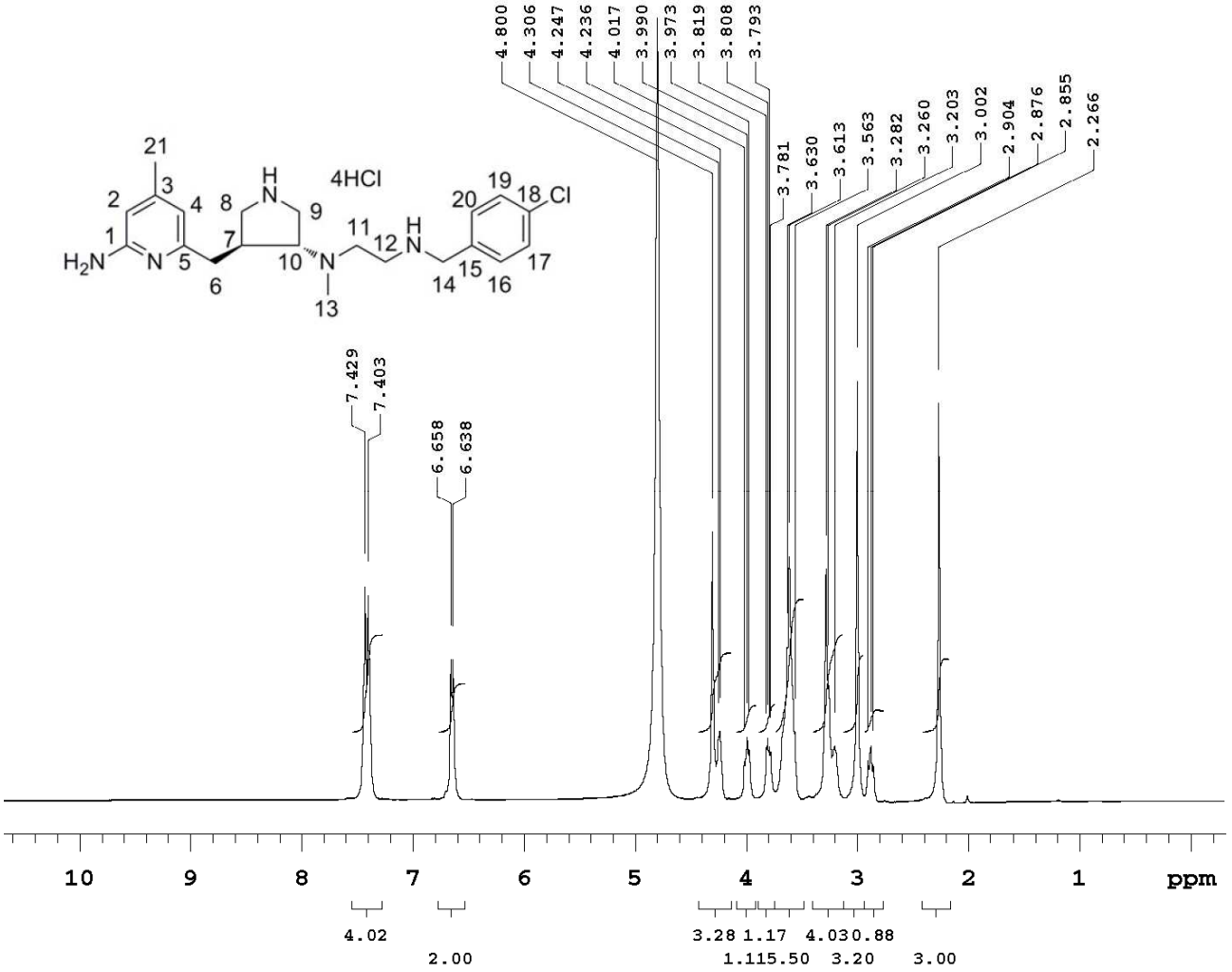
3.38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3.630
3.613
3.563
3.282
3.260
3.203
3.002
2.904
2.876
2.855
2.266
7.429
7.403
6.658
6.638
4HCl
Cl
10
9
8
7
6
5
4
3
2
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2.00
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1.17
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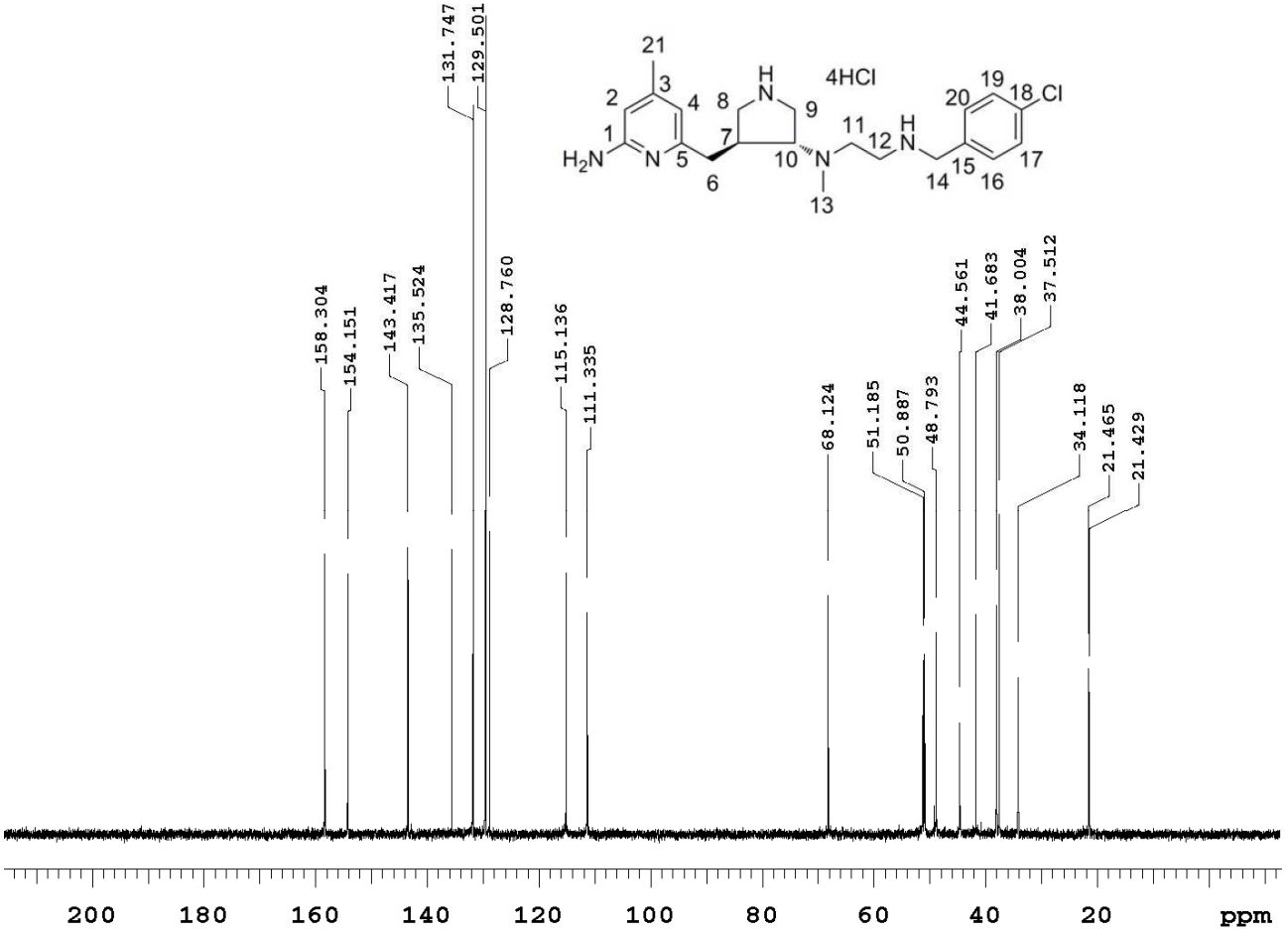
3.00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51.185
50.887
48.793
44.561
41.683
38.004
37.512
34.118
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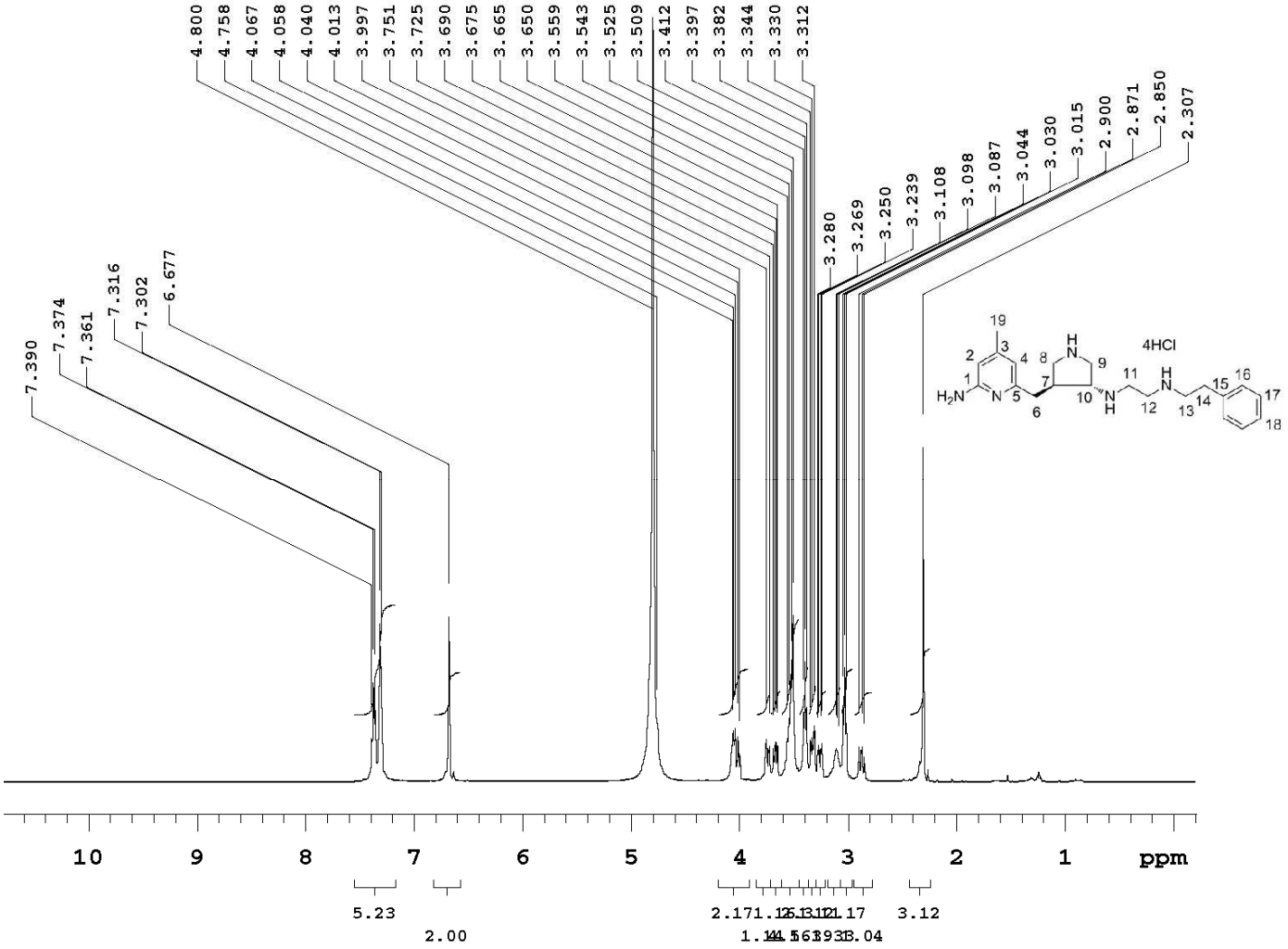
21.429
4HCl
Cl
200
180
160
140
120
100
80
60
40
20
ppm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3.650
3.559
3.543
3.525
3.509
3.412
3.397
3.382
3.344
3.330
3.312
3.280
3.269
3.250
3.239
3.108
3.098
3.087
3.044
3.030
3.015
2.900
2.871
2.850
2.307
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7.374
7.361
7.316
7.302
6.677
4HCl
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9
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3
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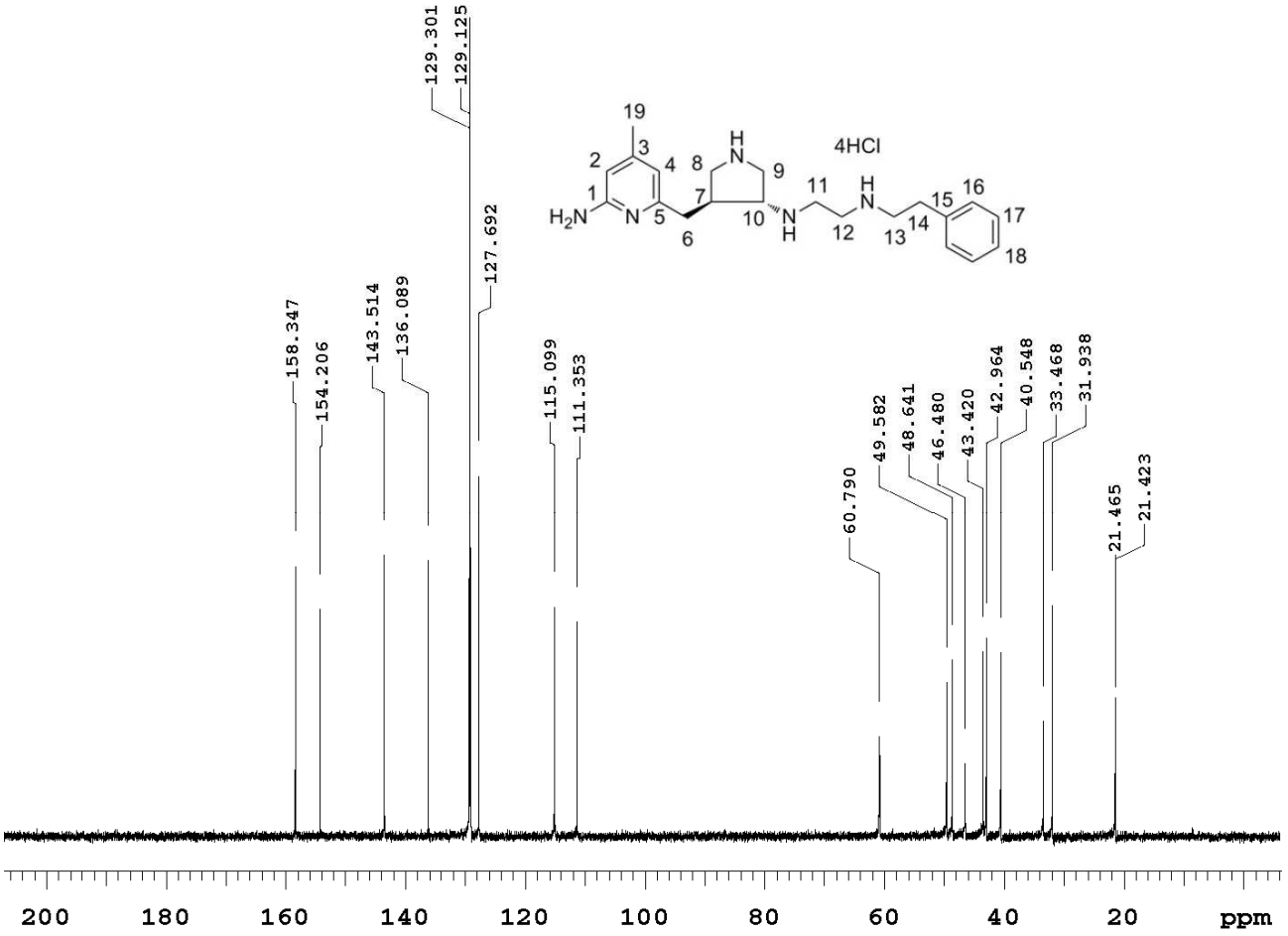
3.04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49.582
48.641
46.480
43.420
42.964
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21.465
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4HCl
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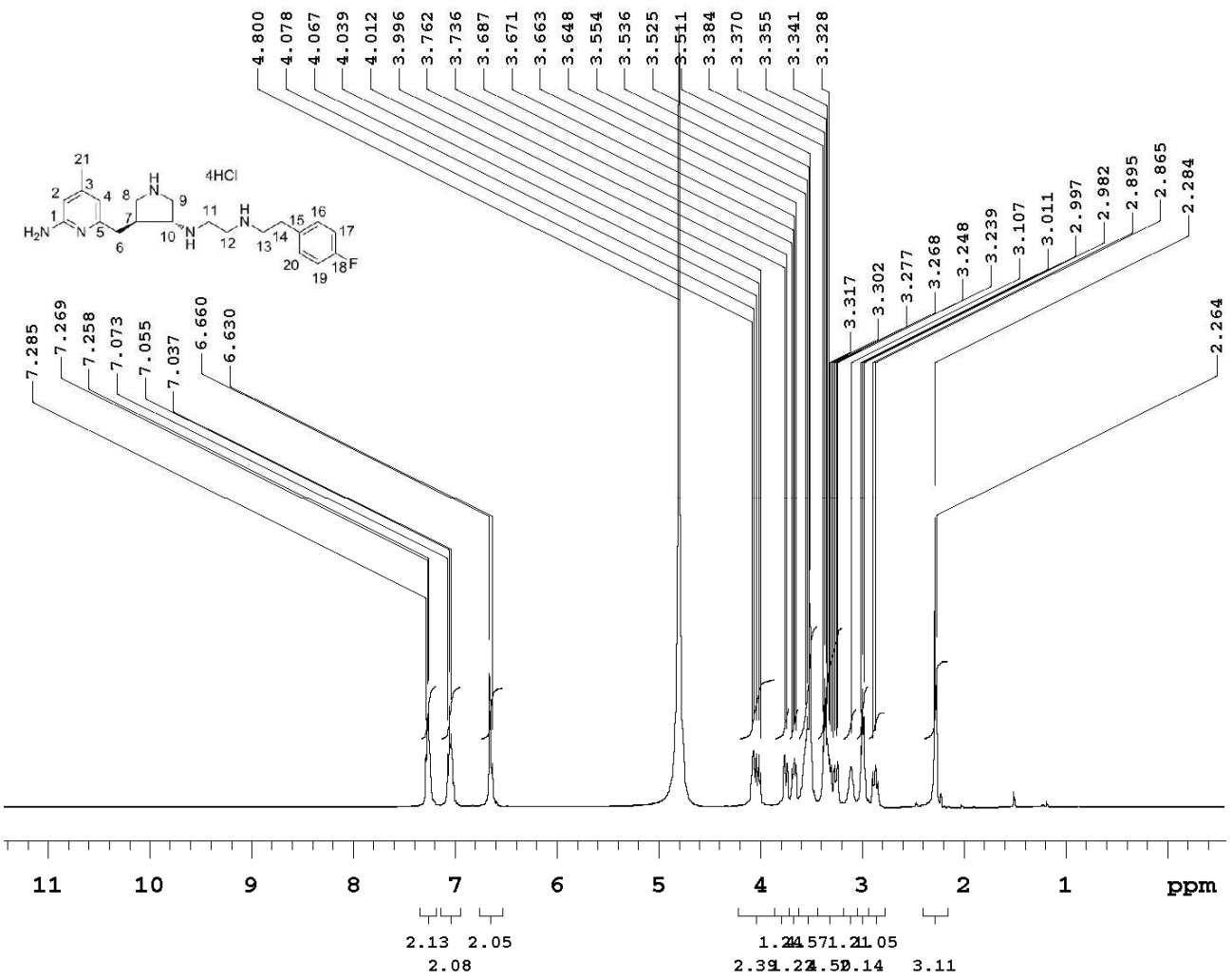
160
140
120
100
80
60
40
20
ppm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3.736
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3.648
3.554
3.536
3.525
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3.384
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3.355
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3.107
3.011
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2.895
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7.285
7.269
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7.073
7.055
7.037
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ppm
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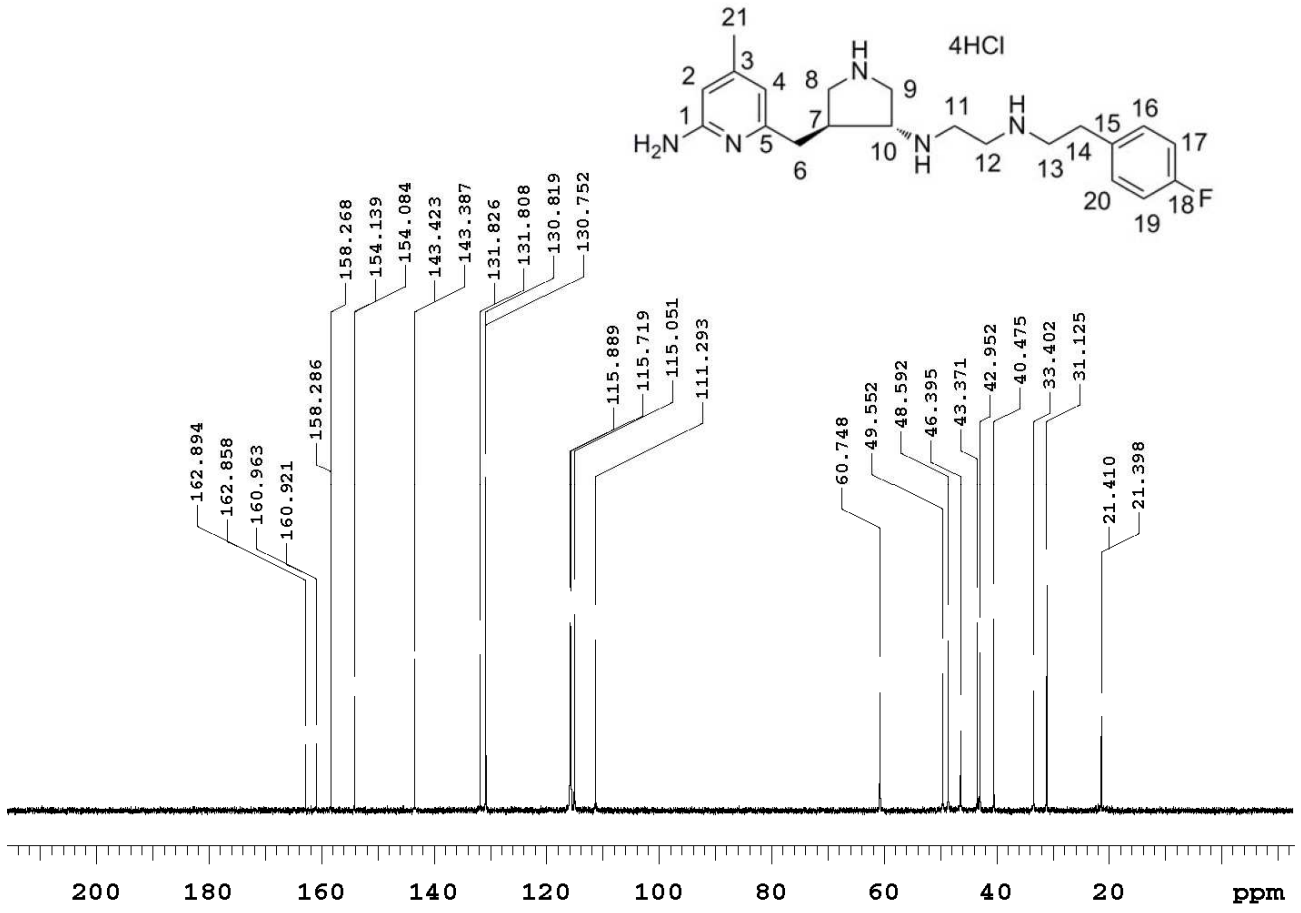
2.08
3.11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131.808
130.819
130.752
115.889
115.719
115.051
111.293
60.748
49.552
48.592
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43.371
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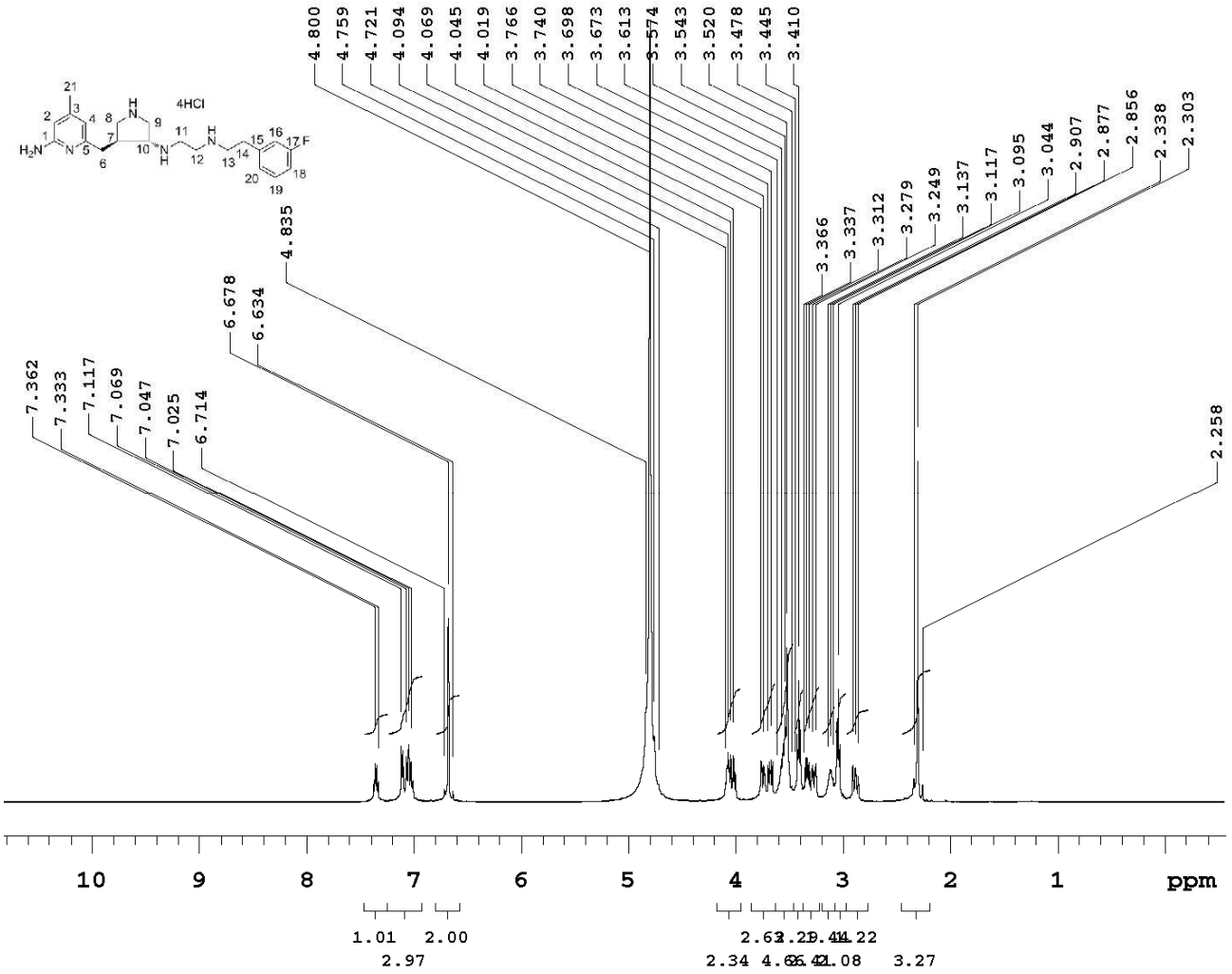
20
ppm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3.543
3.520
3.478
3.445
3.410
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6.634
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7.333
7.117
7.069
7.047
7.025
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3.337
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3.137
3.117
3.095
3.044
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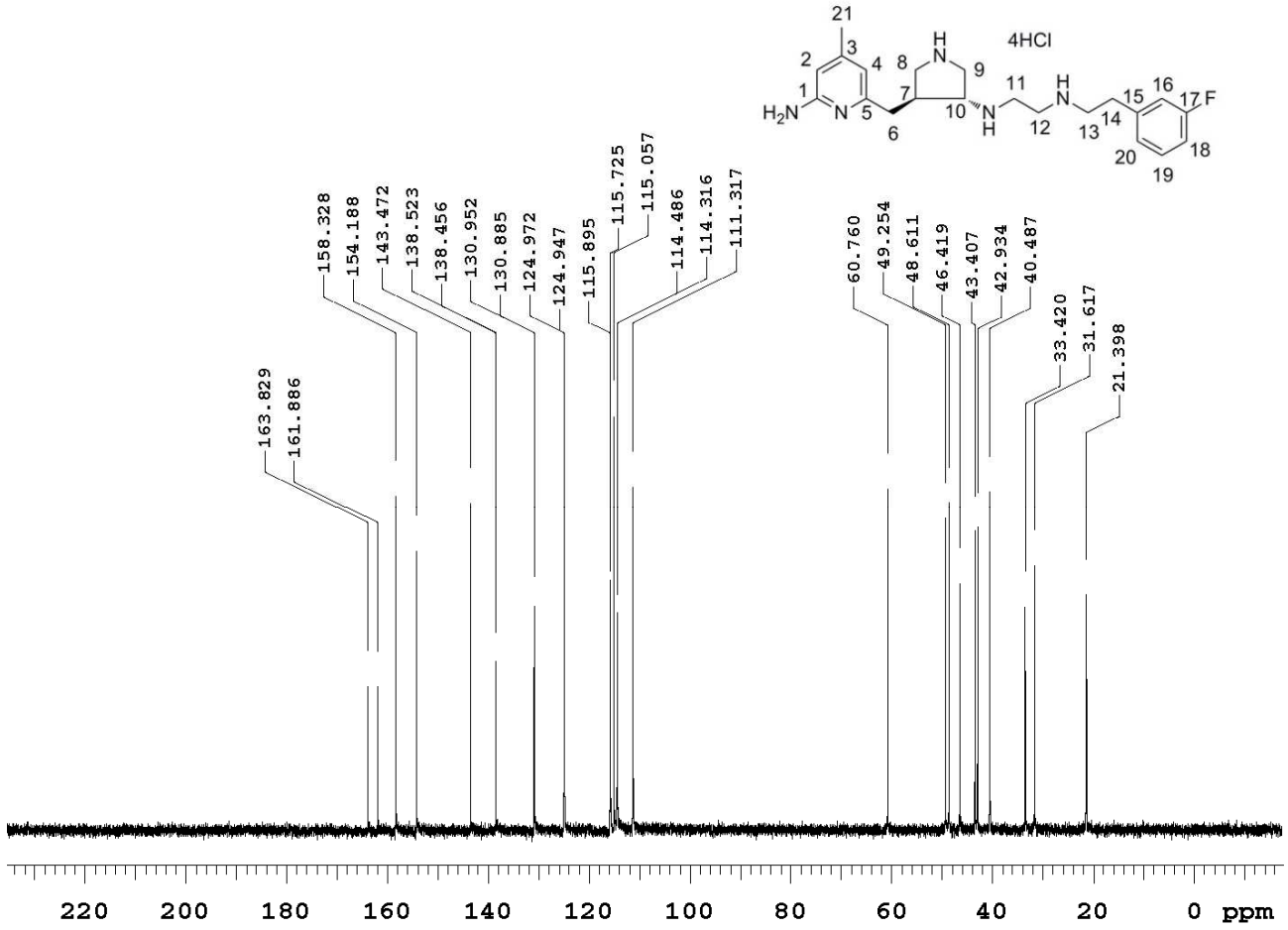
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115.725
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114.486
114.316
111.317
60.760
49.254
48.611
46.419
43.407
42.934
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31.617
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140
120
100
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40
20
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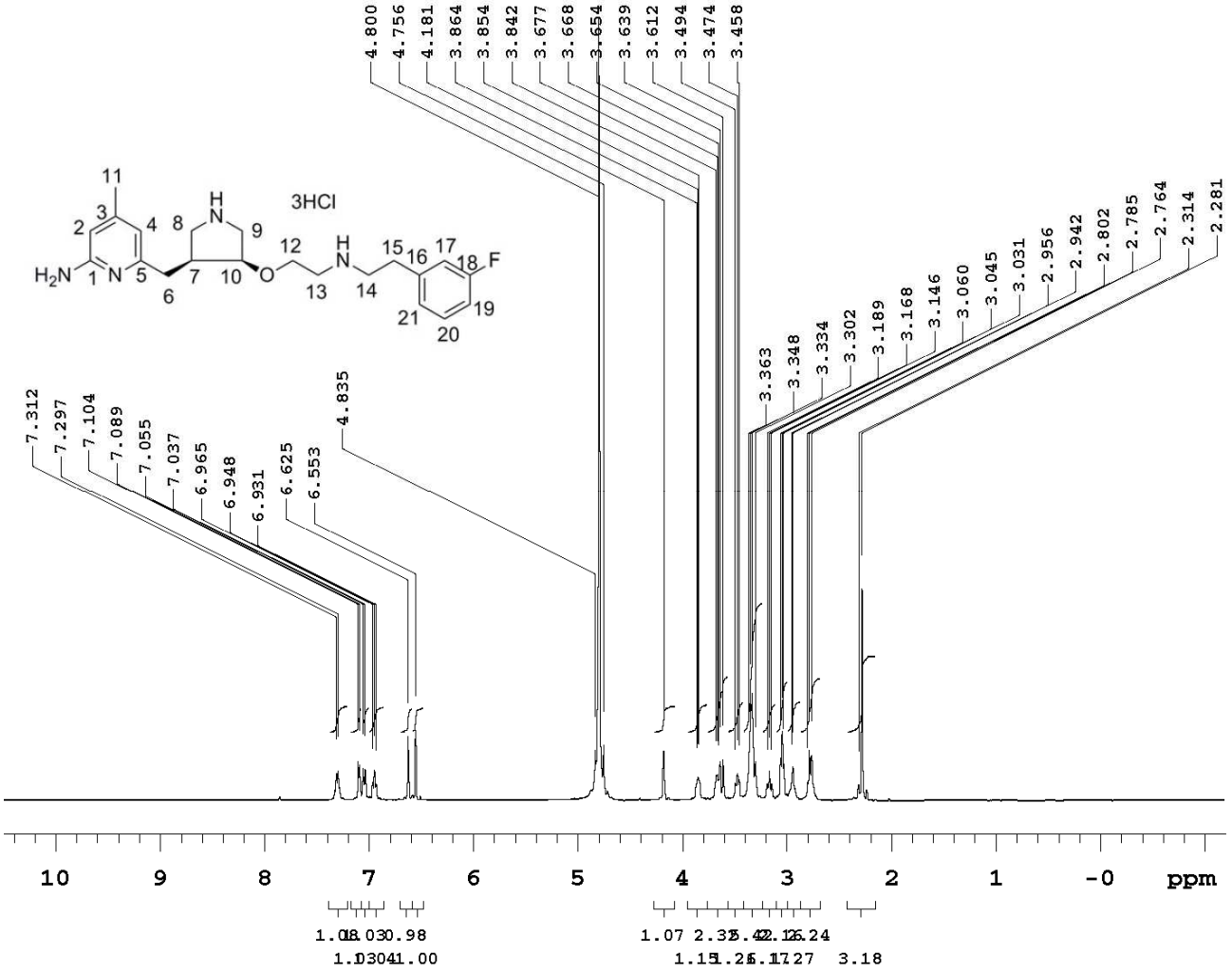
ppm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3HCl
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7.055
7.037
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6.931
6.625
6.553
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3.334
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3.189
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3.045
3.031
2.956
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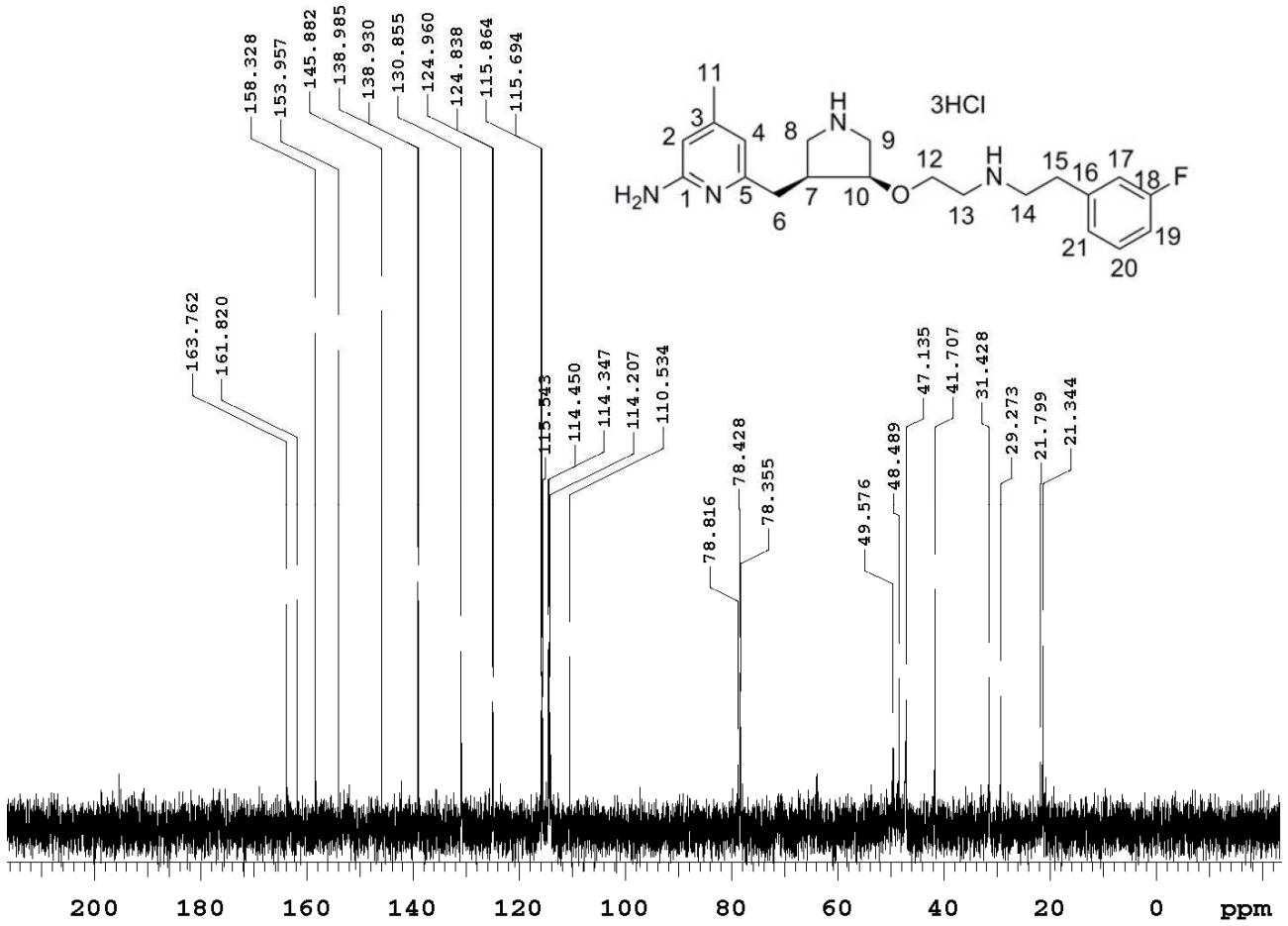
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115.543
114.450
114.347
114.207
110.534
78.816
78.428
78.355
49.576
48.489
47.135
41.707
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21.344
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200
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120
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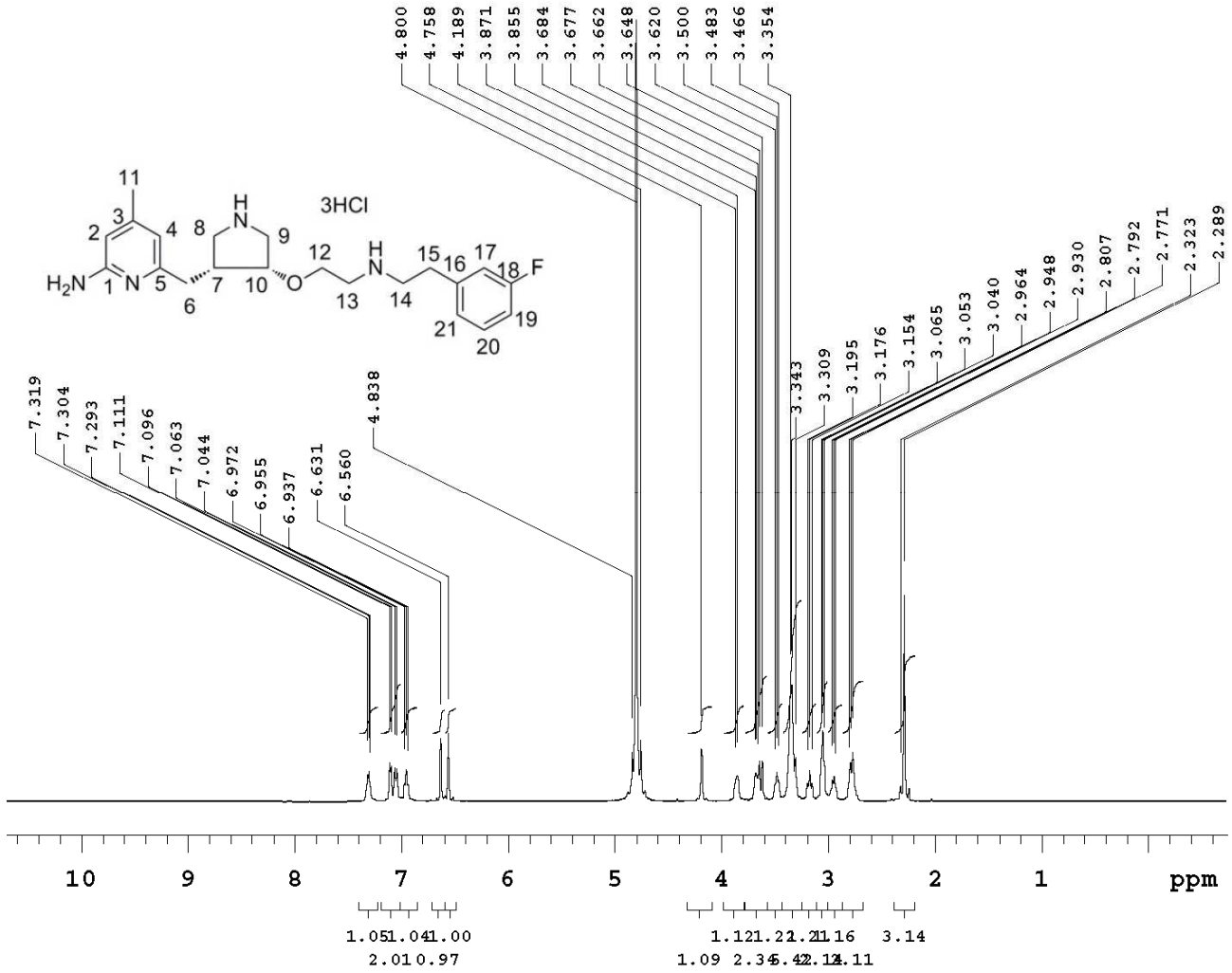
20
0
ppm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3.466
3.354
3HCl
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7.304
7.293
7.111
7.096
7.063
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6.937
6.631
6.560
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3.053
3.040
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2.948
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2.771
2.323
2.289
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8
7
6
5
4
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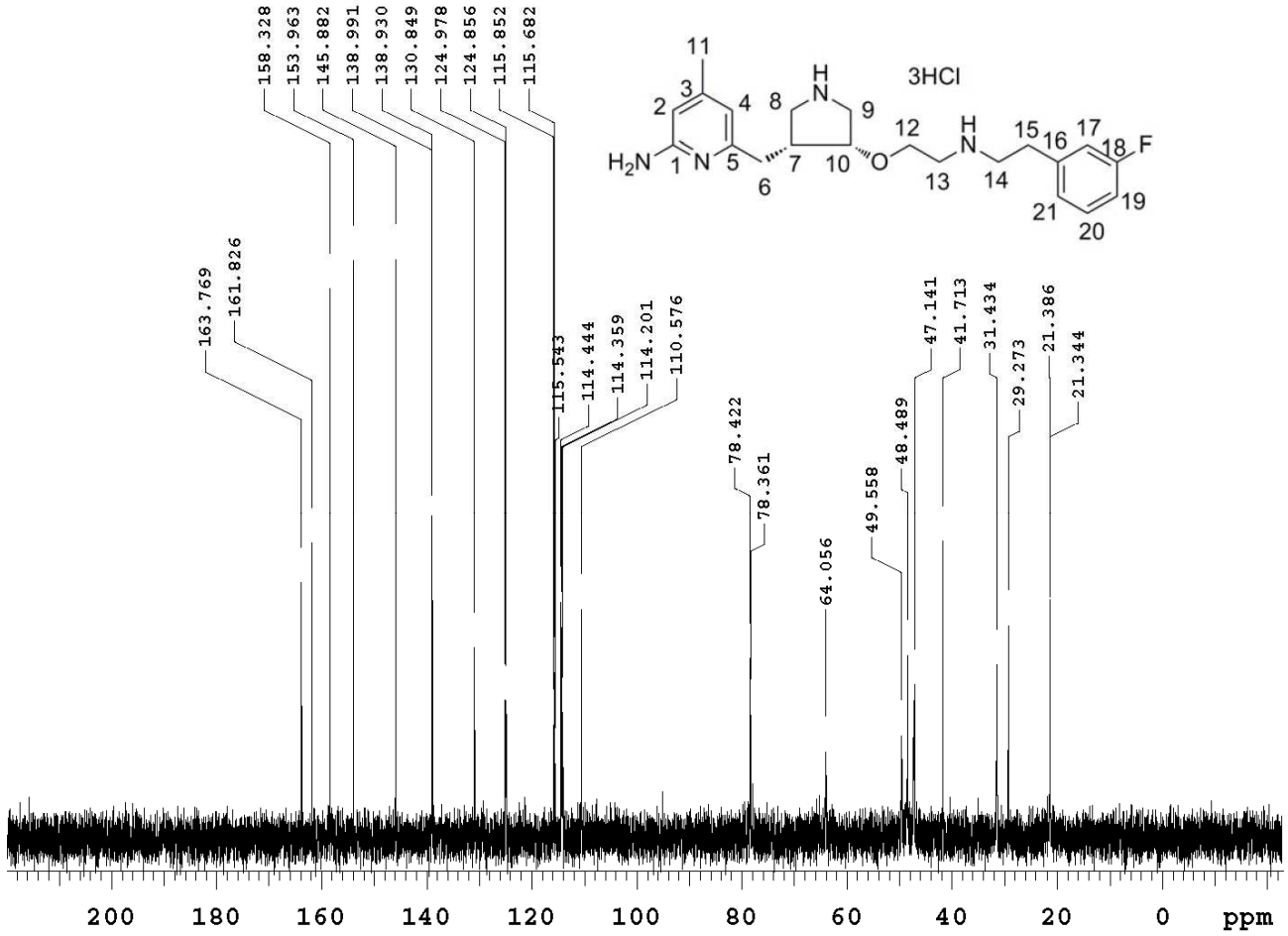
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114.444
114.359
114.201
110.576
78.422
78.361
64.056
49.558
48.489
47.141
41.713
31.434
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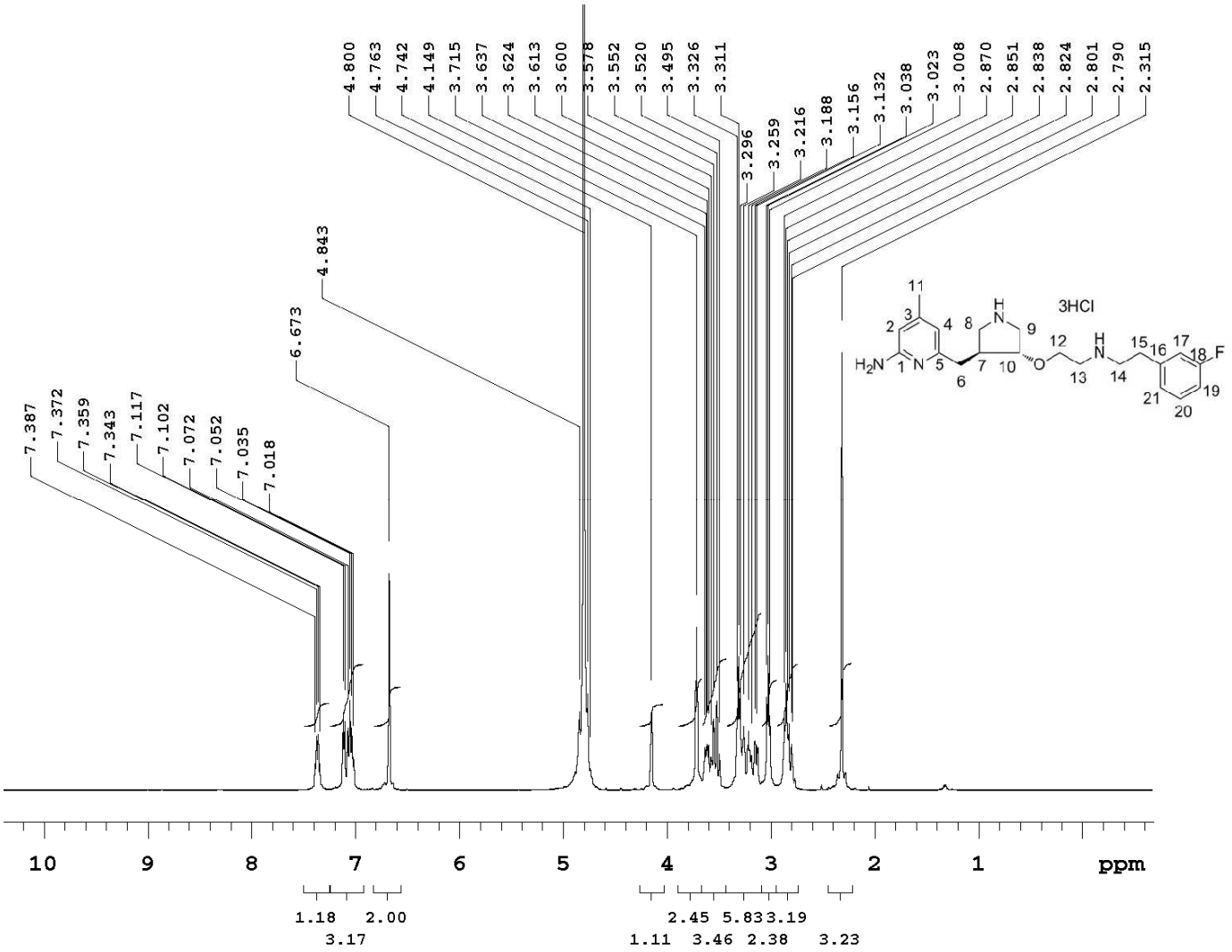
21.386
21.344
3HCl
200
180
160
140
120
100
80
60
40
20
0
ppm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3.495
3.326
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3.188
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3.023
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4.843
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7.372
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7.052
7.035
7.018
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7
6
5
4
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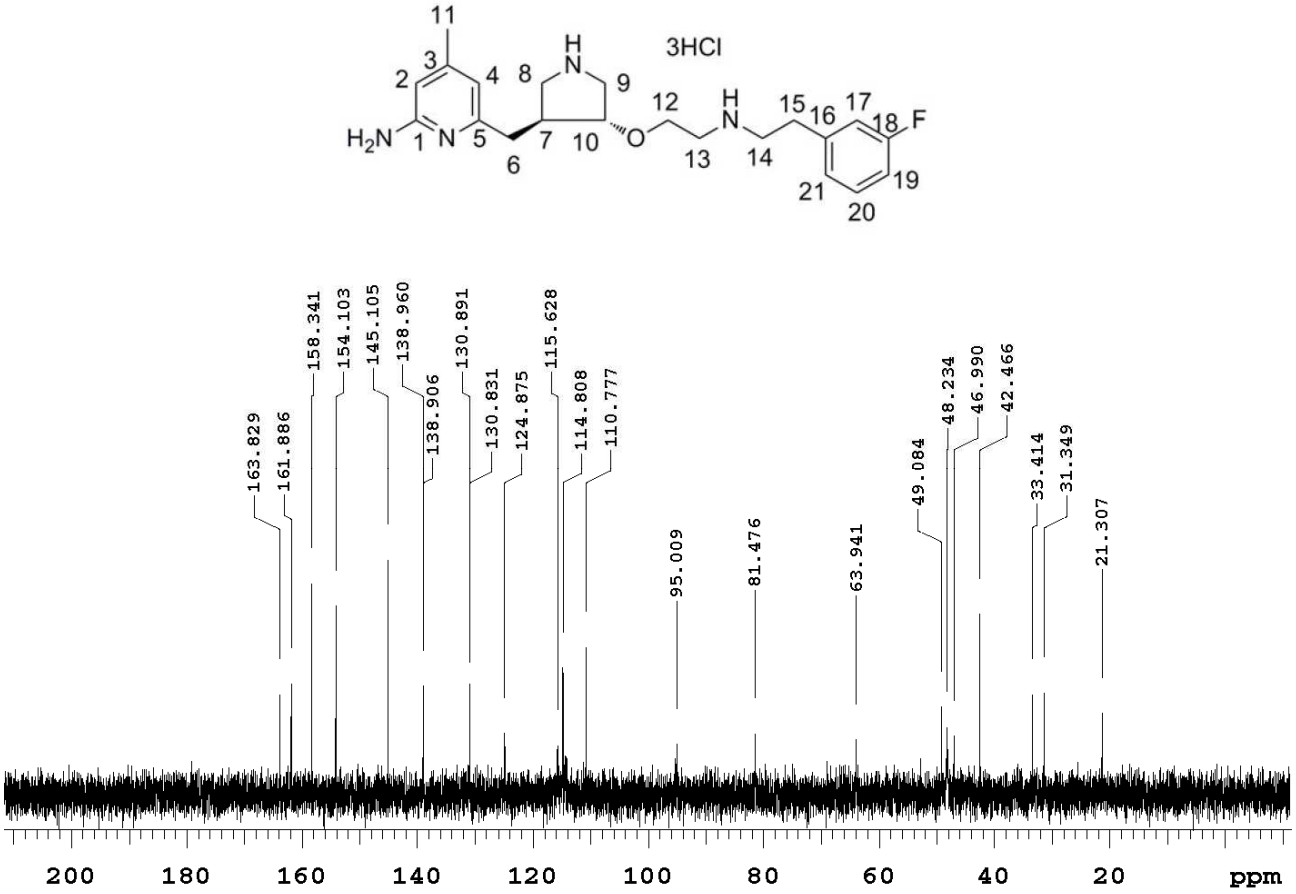
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O
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H
N
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F
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20
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8
9
2
3
4
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130.831
124.875
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114.808
110.777
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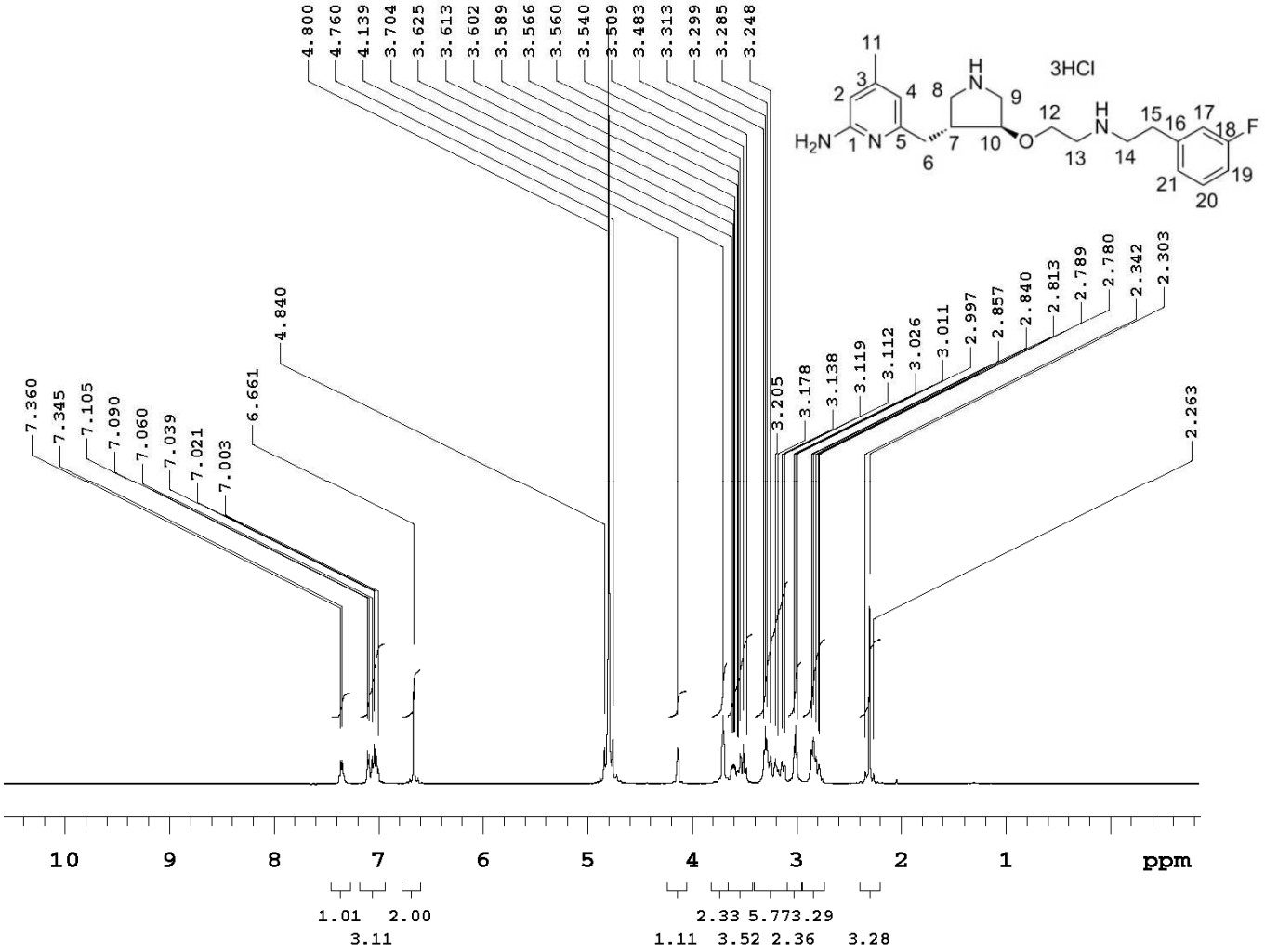
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3.248
4.840
6.661
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7.039
7.021
7.003
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3.178
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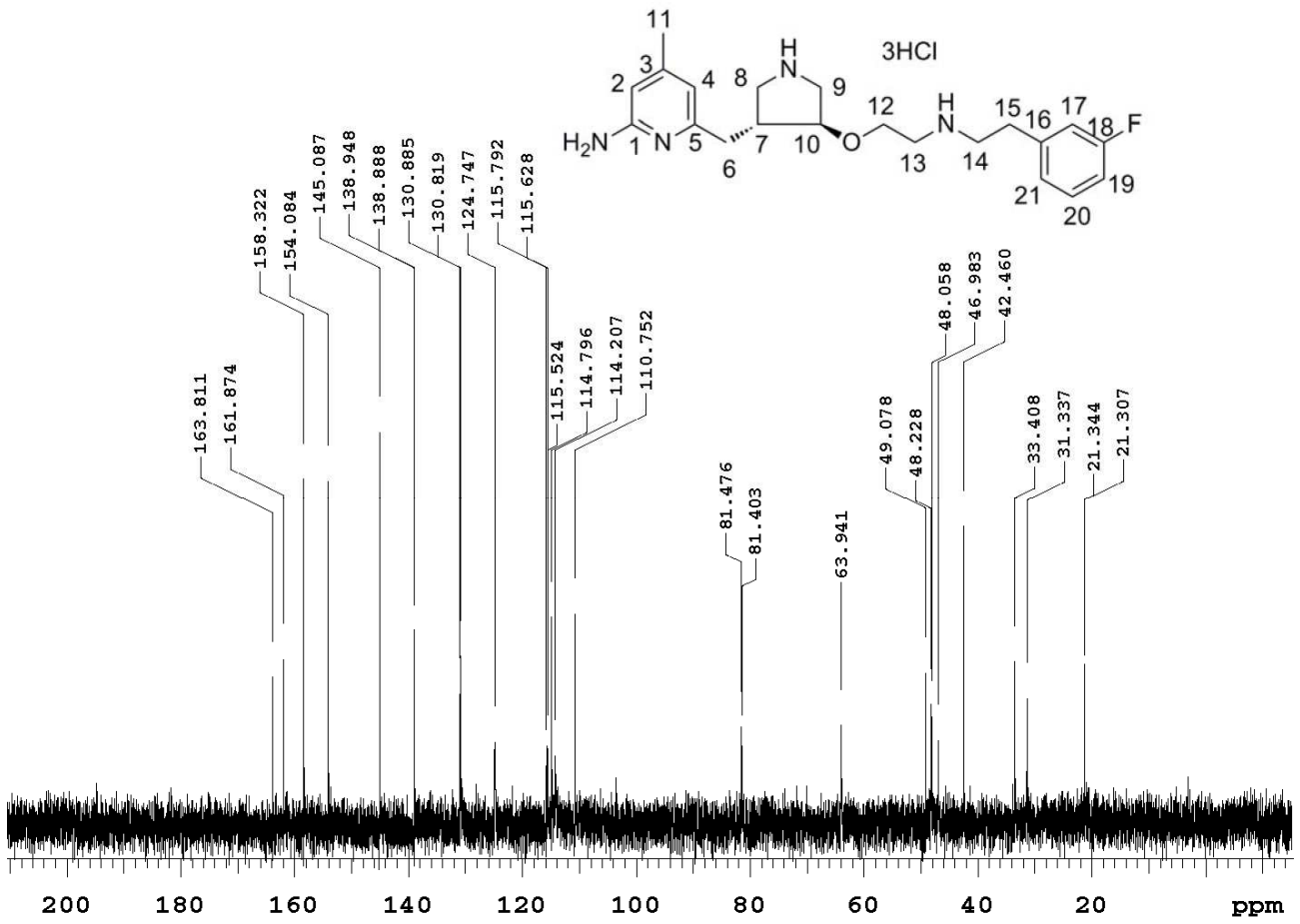
3.112
3.026
3.011
2.997
2.857
2.840
2.813
2.789
2.780
2.342
2.303
2.263
3HCl
10
9
8
7
6
5
4
3
2
1
ppm
1.01
2.00
3.11
2.33
5.77
3.29
1.11
3.52
2.36
3.28


3HCl
163.811
161.874
158.322
154.084
145.087
138.948
138.888
130.885
130.819
124.747
115.792
115.628
115.524
114.796
114.207
110.752
81.476
81.403
63.941
49.078
48.228
48.058
46.983
42.460
33.408
31.337
21.344
21.307
200
180
160
140
120
100
80
60
40
20
ppm

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