Discovery of Highly Potent and Selective Inhibitors of Neuronal Nitric Oxide Synthase by Fragment Hopping

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(*R*)-N^1-{(±)-4-[(6'-aminopyridin-2'-yl)methyl]pyrrolidin-3-yl}-3-phenylpropane-1,2-diamine tetrachloride (8). The procedure to prepare **8** is the same as that to prepare **7** except using **37b** (0.125 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.0943 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.843-3.800 (m, 1H), 7.446-7.346 (m, 5H), 6.899 (d, 1H, J=9Hz), 6.818-6.778 (m, 1H), 4.119-4.064 (m, 1H), 3.976-3.967 (m, 1H), 3.841-3.800 (m, 1H), 3.758-3.718 (m, 1H), 3.627-3.575 (m, 1H), 3.532-3.494 (m, 1H), 3.427-3.004 (m, 6H), 2.926-2.815 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ (154.754+154.735) (1C), (144.962+144.912) (1C), 144.819 (1C), (134.409+134.316) (1C), (129.607+129.584) (2C), (129.495+129.476) (2C), (128.180+128.110) (1C), (112.624+112.535) (1C), 112.380 (1C), (58.798+58.535) (1C), (51.107+50.964) (1C), (48.790+48.604) (1C), 47.517 (1C), (46.604+46.461) (1C), (39.018+38.952) (1C), (36.654+36.611) (1C), (29.462+29.350) (1C). MS (ESI, CH_3OH): [$C_{19}H_{27}N_5$] *m/z* 326.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 326.2339, Found: 326.2334.

(*S*)-N^1-{(±)--4-[(6'-aminopyridin-2'-yl)methyl]pyrrolidin-3'-yl}-3-phenylpropane-1,2-diamine tetrachloride (9). The procedure to prepare **9** is the same as that to prepare **7** except using **37c** (0.125 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.0943 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.813-3.804 (m, 1H), 7.419-7.337 (m, 5H), 6.889 (d, 1H, J=9Hz), 6.810-6.767 (m, 1H), 4.233-4.144 (m, 1H), 4.021-4.016 (m, 1H), 3.883-3.763 (m, 1H), 3.700-3.618 (m, 1H), 3.514-3.340 (m, 4H), 3.286-3.004 (m, 4H), 2.927-2.809 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.739 (1C), 144.812 (1C), (144.676+144.610) (1C), (134.231+134.142) (1C), (129.627+129.611) (2C), 129.503 (2C), (128.234+128.168) (1C), (112.678+112.593) (1C), 112.465 (1C), (58.880+58.601) (1C), (50.798+50.705) (1C), (48.867+48.635) (1C), 47.529 (1C), (46.148+46.059) (1C), (38.867+38.731) (1C), (36.677+36.654) (1C), (29.447+29.311) (1C). MS (ESI, CH_3OH): [$C_{19}H_{27}N_5$] *m/z* 326.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 326.2339, Found: 326.2333. Anal. ($C_{19}H_{27}N_5 \cdot 4HCl \cdot 1.56H_2O$), Calcd: C, 45.70; H, 6.89; N, 14.02; Found: C, 46.09; H, 6.99; N, 13.61.

N^1-{(±)-4-[(6-aminopyridin-2-yl)methyl]pyrrolidin-3-yl}-N^2,N^2-dimethylethane-1,2-diamine tetrachloride (10). The procedure to prepare **10** is the same as that to prepare **7** except using **37d** (0.093 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.082 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.836 (t, 1H, J=7.5Hz), 6.9165 (d, 1H, J=8.5Hz), 6.838 (d, 1H, J=7Hz), 4.375-4.326 (m, 1H), 3.992-3.939 (m, 1H), 3.809-3.756 (m, 1H), 3.687-3.619 (m, 4H), 3.576-3.537 (m, 1H), 3.403-3.254 (m, 3H), 3.002 (s, 6H), 2.944-2.857 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.816 (1C), 144.846 (1C), 144.320 (1C), (112.782+112.748) (1C), 112.585 (1C), 58.764 (1C), 52.620 (1C), 47.475 (1C), 45.556 (1C), 43.656 (2C), 42. 039 (1C), 38.793 (1C), 29.327 (1C). MS(ESI, CH_3OH): [$C_{14}H_{25}N_5$] *m/z* 264.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 264.2183, Found: 264.2177.

6-{[(±)-4'-((*R*)-pyrrolidin-3"-ylamino)pyrrolidin-3'-yl]methyl}pyridin-2-amine tetrachloride (11). The procedure to prepare **11** is the same as that to prepare **7** except using **37e** (0.112 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.082 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.834 (t, 1H, J=8.5Hz), 6.910 (d, 1H, J=9Hz), 6.832 (d, 1H, J=7Hz), 4.293-4.174 (m, 2H), 3.954-3.833 (m, 2H), 3.700-3.600 (m, 2H), 3.553-3.490 (m, 2H), 3.459-3.403 (m, 1H), 3.376-3.339 (m, 1H), 3.254-3.224 (m, 2H), 2.921-2.841 (m, 1H), 2.666-2.572 (m, 1H), 2.304-2.189 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.812 (1C), 144.796 (1C), (144.641+144.572) (1C), (112.840+112.713) (1C), 112.516 (1C), (57.023+56.651) (1C), (55.506+55.193) (1C), (47.452+47.393+46.894) (2C), (45.664+45.598) (1C), 44.736 (1C), (38.666+38.542) (1C), 29.303 (1C), (28.383+27.466+27.346) (1C). MS (ESI, CH_3OH): [$C_{14}H_{23}N_5$] *m/z* 262.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 262.2026, Found: 262.2019. Anal. ($C_{14}H_{23}N_5 \cdot 4HCl \cdot 2H_2O$), Calcd: C, 37.94; H, 7.05; N, 15.80; Found: C, 38.04; H, 7.20; N, 15.52.

6-{[(±)-4'-((*S*)-pyrrolidin-3"-ylamino)pyrrolidin-3'-yl]methyl}pyridin-2-amine tetrachloride (12). The procedure to prepare **12** is the same as that to prepare **7** except using **37f** (0.112 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.082 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.853 (t, 1H, J=8.5Hz), 6.9305 (d, 1H, J=8.5Hz), 6.857 (d, 1H, J=7Hz), 4.340-4.222 (m, 2H), 3.990-3.866 (m, 2H), 3.727-3.644 (m, 2H), 3.600-3.514 (m, 2H), 3.500-3.429 (m, 1H), 3.403-3.367 (m, 1H), 3.280-3.258 (m, 2H), 2.947-2.869 (m, 1H), 2.687-2.608 (m, 1H), 2.341-2.232 (m, 1H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.816 (1C), 144.827 (1C), (144.564+144.498) (1C), (112.899+112.771) (1C), 112.539 (1C), (57.065+56.709) (1C), (55.576+55.262) (1C), (47.482+47.424) (1C), (47.335+46.805) (1C), (45.548+45.486) (1C), 44.782 (1C), (38.639+38.511) (1C), 29.327 (1C), (28.321+27.396) (1C). MS (ESI, CH_3OH): [$C_{14}H_{23}N_5$] *m/z* 262.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 262.2026, Found: 262.2020.

6-{[(±)-4'-((*R*)-1-benzylpyrrolidin-3"-ylamino)pyrrolidin-3'-yl]methyl}pyridin-2-amine (13). The procedure to prepare **13** is the same as that to prepare **7** except using **37g** (0.110 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.099 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.780 (t, 1H, J=8.5Hz), 7.487-7.458 (m, 5H), 6.861 (d, 1H, J=9Hz), 6.7995 (d, 1H, J=7.5Hz), 4.470-4.455 (m, 2H), 4.337-4.079 (m, 2H), 3.967-3.845 (m, 2H), 3.719-3.661 (m, 2H), 3.614-3.486 (m, 2H), 3.359-3.320 (m, 2H), 3.233 (m, 2H), 2.901-2.845 (m, 1H), 2.815-2.769 (m, 0.5H), 2.557 (m, 0.5H), 2.457 (m, 0.5H), 2.251 (m, 0.5H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.700 (1C), 144.773 (1C), 144.254 (1C), 130.575 (2C), 130.459 (1C), 129.592 (2C), 129.375 (1C), 112.736 (1C), 112.550 (1C), 58.721 (1C), 56.609 (1C), (54.462+54.407) (2C), (52.864+51.931) (1C), 47.428 (1C), 45.242 (1C), 38.550 (1C), 29.296 (1C), (27.226+25.984) (1C). MS (ESI, CH_3OH): [$C_{21}H_{29}N_5$] *m/z* 352.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 352.2496, Found: 352.2489.

6-{[(±)-4'-((*S*)-1-benzylpyrrolidin-3"-ylamino)pyrrolidin-3'-yl]methyl}pyridin-2-amine (14). The procedure to prepare **14** is the same as that to prepare **7** except using **37h** (0.110 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.099 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.786 (m, 1H), 7.494-7.442 (m, 5H), 6.876 (d, 1H, J=9Hz), 6.800-6.790 (m, 1H), 4.477 (s, 2H), 4.321-4.178 (m, 2H), 3.906-3.866 (m, 1H), 3.765-3.576 (m, 3H), 3.516-3.479 (m, 2H), 3.350-3.299 (m, 2H), 3.212-3.l91 (m, 2H), 2.887-2.830 (m, 1H), 2.770-2.703 (m, 0.5H), 2.659-2.603 (m, 0.5H), 2.404-2.391 (m, 0.5H), 2.245 (m, 0.5H). ^{13}C NMR (D_2O, 125.7 MHz): δ 154.746 (1C), 144.765 (1C), 144.545 (1C), 130.590 (2C), 130.474 (1C), 129.607 (2C), 129.484 (1C), 112.701 (1C), 112.481 (1C), 58.783 (1C), 56.934 (1C), (54.558+54.392) (2C), (52.903+52.100) (1C), 47.413 (1C), 45.734 (1C), 38.561 (1C), 29.272 (1C), (28.537+27. 377) (1C). MS (ESI, CH_3OH): [$C_{21}H_{29}N_5$] *m/z* 352.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 352.2496, Found: 352.2495. Anal. ($C_{21}H_{29}N_5$·4HCl·1.45H_2O), Calcd: C, 48.19; H, 6.91; N, 13.38; Found: C, 48.43; H, 7.19; N, 13.11.

***N*^{1}-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}ethane-1,2-diamine tetrahydrochloride (15).** The procedure to prepare **15** is the same as that to prepare **7** except using **47a** (0.110 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.079 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 6.746 (s, 1H), 6.732 (s, 1H), 4.372-4.300 (m, 1H), 4.002-3.929 (m, 1H), 3.789-3.723 (m, 1H), 3.603-3.472 (m, 5H), 3.414-3.353 (m, 1H), 3.303-3.240 (m, 2H), 2.905-2.838 (m, 1H), 2.351 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.396 (1C), 154.349 (1C), 143.424 (1C), 114.903 (1C), 111.305 (1C), 58.519 (1C), 47.532 (1C), 45.717 (1C), 44.398 (1C), 38.812 (1C), 35.848 (1C), 29.190 (1C), 21.375 (1C). MS (ESI, CH_3OH-H_2O): [$C_{13}H_{23}N_5$] *m/z* 250.2 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 250.2026, Found: 250.2026. Anal. ($C_{13}H_{23}N_5$·4HCl·1.1H_2O), Calcd: C, 37.62; H, 7.09; N, 16.87; Found: C, 37.98; H, 7.14; N, 16.50.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(4'-chloro benzyl)ethane-1,2-diamine tetrahydrochloride (16). The procedure to prepare 16 is the same as that to prepare 7 except using 47b (0.135 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.104 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.463-7.453 (m, 4H), 6.685 (s, 2H), 4.306-4.281 (m, 3H), 3.961-3.905 (m, 1H), 3.747-3.709 (m, 1H), 3.575-3.511 (m, 3H), 3.463-3.416 (m, 2H), 3.377-3.336 (m, 1H), 3.253-3.195 (m, 2H), 2.862-2.807 (m, 1H), 2.304-2.297 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.327 (1C), 154.272 (1C), 143.374 (1C), 135.517 (1C), (131.638+131.583) (2C), 129.501 (2C), 128.809 (1C), 114.826 (1C), 111.268 (1C), 58.569 (1C), 51.047 (1C), 47.495 (1C), 45.728 (1C), 43.020 (1C), 42.959 (1C), 38.831 (1C), 29.190 (1C), 21.339 (1C). MS (ESI, CH_3OH): [$C_{20}H_{28}ClN_5$] *m/z* 374.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 374.2101, Found: 374.2101. Anal. ($C_{20}H_{28}ClN_5$·4HCl·1.75H_2O), Calcd: C, 43.57; H, 6.49; N, 12.70; Found: C, 44.03; H, 6.33; N, 12.30.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-(3'-chloro

benzyl)ethane-1,2-diamine tetrahydrochloride (17). The procedure to prepare 17 is the same as that to prepare 7 except using 47c (0.135 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.104 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.532-7.427 (m, 4H), 6.691 (s, 2H), 4.321 (s, 2H), 4.278-4.211 (m, 1H), 3.894-3.853 (m, 1H), 3.712-3.675 (m, 1H), 3.602-3.427 (m, 5H), 3.371-3.315 (m, 1H), 3.240-3.176 (m, 2H), 2.866-2.815 (m, 1H), 2.315 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.315 (1C), 154.241 (1C), 143.677 (1C), 134.461 (1C), 132.123 (1C), 130.970 (1C), 130.090 (1C), 129.895 (1C), 128.426 (1C), 114.778 (1C), 111.189 (1C), 58.466 (1C), 51.028 (1C), 47.477 (1C), 45.983 (1C), 43.251 (2C), 38.934 (1C), 29.202 (1C), 21.309 (1C). MS (ESI, CH_3OH): [$C_{20}H_{28}ClN_5$] *m/z* 374.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 374.2106, Found: 374.2105. Anal. ($C_{20}H_{28}ClN_5$·4HCl·0.75H_2O), Calcd: C, 45.05; H, 6.33; N, 13.13; Found: C, 45.41; H, 6.21; N, 12.87.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl)pyrrolidin-3'-yl)-*N*^{2}-[4'-(trifluoromethyl)benzyl]ethane-1,2-diamine tetrahydrochloride (18). The procedure to prepare 18 is the same as that to prepare 7 except using 47d (0.142 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.111 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.783 (s, 2H), 7.682 (s, 2H), 6.710 (s, 2H), 4.438-4.434 (s, 2H) 4.349-4.337 (m, 1H), 3.980-3.939 (m, 1H), 3.789-3.762 (m, 1H), 3.640-3.540 (m, 5H), 3.397-3.364 (m, 1H), 3.287-3.236 (m, 2H), 2.890-2.838 (m, 1H), 2.324-2.310 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.372 (1C), 154.279 (1C), 143.421 (1C), 134.268 (1C), (131.595+131.335+131.078+130.800) (1C), 130.576 (2C), 126.391 (2C), (127.250+125.083+122.920+120.749) (1C), 114.858 (1C), 111.267 (1C), 58.612 (1C), 51.189 (1C), 47.517 (1C), 45.784 (1C), 43.384 (1C), 43.308 (1C), 38.870 (1C), 29.215 (1C), 21.354 (1C). ^{19}F NMR (D_2O, 376.5 MHz): δ -62.943 (CF_3). MS (ESI, CH_3OH): [$C_{21}H_{28}F_3N_5$] *m/z* 408.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 408.2370, Found: 408.2366.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(4'-fluorobenzyl)ethane-1,2-diamine tetrahydrochloride (19). The procedure to prepare 19 is the same as that to prepare 7 except using 47e (0.132 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.100 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.542-7.515 (m, 2H), 7.222-7.187 (m, 2H), 6.710 (s, 2H), 4.333 (s, 2H), 4.298-4.286 (m, 1H), 3.945-3.907 (m, 1H), 3.752-3.725 (m, 1H), 3.572-3.530 (m, 5H), 3.390-3.349 (m, 1H), 3.264-3.210 (m, 2H), 2.885-2.834 (m, 1H), 2.327-2.312 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ (164.391+162.429) (1C), 158.356 (1C), 154.259 (1C), 143.573 (1C), (132.366+132.294) (2C), 126.263 (1C), (116.423+116.247) (2C), 114.814 (1C), 111.223 (1C), 58.540 (1C), 51.068 (1C), 47.509 (1C), (45.984+45.912) (1C), 43.360 (1C), 43.179 (1C), 38.930 (1C), 29.215 (1C), 21.354 (1C). ^{19}F NMR(D_2O, 376.5 MHz): δ -112.202 (Ar-F). MS (ESI, CH_3OH): [$C_{20}H_{28}FN_5$] *m/z* 358.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 358.2402, Found: 358.2406.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-[3'-(trifluoromethyl)benzyl]ethane-1,2-diamine (20). The procedure to prepare 20 is the same as

that to prepare 7 except using 47f (0.142 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.111 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.858 (m, 1H), 7.788-7.763 (m, 2H), 7.665-7.636 (m, 1H), 6.717 (s, 1H), 6.700 (s, 1H), 4.442 (s, 2H), 4.356-4.344 (m, 1H), 3.990-3.949 (m, 1H), 3.805-3.768 (m, 1H), 3.648-3.544 (m, 5H), 3.413-3.372 (m, 1H), 3.294-3.240 (m, 2H), 2.906-2.854 (m, 1H), 2.320 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.388 (1C), 154.263 (1C), 143.457 (1C), 133.457 (1C), 131.130 (1C), (131.215+130.953+130.693+130.436) (1C), 130.299 (1C), 126.905 (2C), (127.194+125.031+122.868+120.705) (1C), 114.891 (1C), 111.275 (1C), 58.648 (1C), 51.245 (1C), 47.553 (1C), 45.836 (1C), 43.436 (1C), 43.304 (1C), 38.922 (1C), 29.263 (1C), 21.406 (1C). ^{19}F NMR (D_2O, 376.5 MHz): δ -62.826 (CF_3). MS (ESI, CH_3OH): [$C_{21}H_{28}F_3N_5$] *m/z* 408.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 408.2370, Found: 408.2364.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(3'-methylbenzyl)ethane-1,2-diamine tetrahydrochloride (21). The procedure to prepare 21 is the same as that to prepare 7 except using 47g (0.131 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.0995 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.374-7.305 (m, 4H), 6.707-6.698 (m, 2H), 4.297-4.287 (m, 3H), 3.947-3.907 (m, 1H), 3.756-3.718 (m, 1H), 3.644-3.542 (m, 5H), 3.376-3.341 (m, 1H), 3.258-3.223 (m, 2H), 2.872-2.822 (m, 1H), 2.342-2.328 (s, 6H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.360 (1C), 154.267 (1C), 143.505 (1C), 139.777 (1C), 130.693 (1C), 130.600 (1C), 130.175 (1C), 129.437 (1C), 126.965 (1C), 114.842 (1C), 111.263 (1C), 58.564 (1C), 51.811 (1C), 47.529 (1C), 45.896 (1C), 43.396(1C), 43.071 (1C), 38.906 (1C), 29.227 (1C), 21.382 (1C), 20.584 (1C). MS (ESI, CH_3OH): [$C_{21}H_{31}N_5$] *m/z* 354.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 354.2652, Found: 354.2650.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(3',4'-dichlorobenzyl)ethane-1,2-diamine tetrahydrochloride (22). The procedure to prepare 22 is the same as that to prepare 7 except using 47h (0.142 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.111 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.649-7.635 (m, 1H), 7.582-7.545 (m, 1H), 7.401-7.371 (m, 1H), 6.670 (s, 2H), 4.345-4.271 (m, 2H), 4.244-4.219 (m, 1H), 3.898-3.885 (m, 1H), 3.720-3.683 (m, 1H), 3.541-3.423 (m, 5H), 3.355-3.314 (m, 1H), 3.225-3.154 (m, 2H), 2.849-2.787 (m, 1H), 2.296-2.279 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.341 (1C), 154.261 (1C), 143.672 (1C), 133.727 (1C), 132.658 (1C), 131.966 (1C), 131.407 (1C), 130.557 (1C), 129.811 (1C), 114.790 (1C), 111.189 (1C), 58.544 (1C), 50.487 (1C), 47.512 (1C), 46.146 (1C), 43.547 (1C), 43.316 (1C), 39.030 (1C), 29.261 (1C), (21.386+21.356) (1C). MS (ESI, CH_3OH): [$C_{20}H_{27}Cl_2N_5$] *m/z* 408.5 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 408.1716, Found: 408.1708; [$C_{20}H_{28}Cl^{37}ClN_5$] Calcd: 410.1687, Found: 410.1682.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(2',4'-dichlorobenzyl)ethane-1,2-diamine tetrahydrochloride (23). The procedure to prepare 23 is the same as that to prepare 7 except using 47i (0.142 g, 0.2 mmol) instead of 37a,

affording a hygroscopic white solid (0.111 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.566-7.516 (m, 2H), 7.406-7.379 (m, 1H), 6.674-6.653 (m, 2H), 4.449 (m, 2H), 4.273-4.262 (m, 1H), 3.915-3.879 (m, 1H), 3.731-3.704 (m, 1H), 3.606-3.499 (m, 5H), 3.355-3.316 (m, 1H), 3.237-3.171 (m, 2H), 2.856-2.805 (m, 1H), 2.284 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.322 (1C), 154.212 (1C), 143.538 (1C), 136.568 (1C), 135.324 (1C), 133.332 (1C), 129.944 (1C), 128.293 (1C), 126.860 (1C), 114.796 (1C), 111.196 (1C), 58.562 (1C), 48.538 (1C), 47.518 (1C), 45.982 (1C), 43.681 (1C), 43.286 (1C), 38.969 (1C), 29.249 (1C), (21.416+21.380) (1C). MS (ESI, CH_3OH): [$C_{20}H_{27}Cl_2N_5$] *m/z* 408.5 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 408.1716, Found: 408.1703; [$C_{20}H_{28}Cl^{37}ClN_5$] Calcd: 410.1687, Found: 410.1699. Anal. ($C_{20}H_{27}Cl_2N_5$·4HCl·1.665H_2O), Calcd: C, 41.12; H, 5.92; N, 11.99; Found: C, 41.52; H, 5.98; N, 11.47.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-phenethyl ethane-1,2-diamine tetrahydrochloride (24). The procedure to prepare 24 is the same as that to prepare 7 except using 47k (0.131 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.0995 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.390-7.308 (m, 5H), 6.686-6.678 (m, 2H), 4.333-4.321 (m, 1H), 3.968-3.927 (m, 1H), 3.774-3.736 (m, 1H), 3.600-3.506 (m, 5H), 3.426-3.334 (m, 3H), 3.250-3.223 (m, 2H), 3.055-3.031 (m, 2H), 2.859-2.804 (m, 1H), 2.308-2.300 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.341 (1C), 154.254 (1C), 143.338 (1C), 136.113 (1C), 129.301 (2C), 129.137 (2C), 127.686 (1C), 114.911 (1C), 111.317 (1C), 58.629 (1C), 49.576 (1C), 47.530 (1C), 45.654 (1C), 43.596 (1C), 43.420 (1C), 38.854 (1C), 31.950 (1C), 29.237 (1C), (21.453+21.423) (1C). MS (ESI, CH_3OH): [$C_{21}H_{31}N_5$] *m/z* 354.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 354.2652, Found: 354.2651. Anal. ($C_{21}H_{31}N_5$·4HCl·1.5H_2O), Calcd: C, 47.92; H, 7.28; N, 13.30; Found: C, 47.99; H, 7.18; N, 13.06.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(4'-fluoro phenethyl)ethane-1,2-diamine tetrahydrochloride (25). The procedure to prepare 25 is the same as that to prepare 7 except using 47l (0.134 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.103 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.257-7.230 (m, 2H), 7.042-7.007 (m, 2H), 6.631 (m, 2H), 4.325-4.287 (m, 1H), 3.935-3.893 (m, 1H), 3.733-3.694 (m, 1H), 3.585-3.458 (m, 5H), 3.359-3.291 (m, 3H), 3.220-3.187 (m, 2H), 2.983-2.955 (m, 2H), 2.813-2.760 (m, 1H), 2.247 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ (162.900+160.970) (1C), 158.274 (1C), 154.212 (1C), 143.144 (1C), (131.796+131.772) (1C), (130.800+130.734) (2C), (115.877+115.707) (2C), 114.844 (1C), 111.262 (1C), 58.586 (1C), 49.558 (1C), 47.457 (1C), 45.411 (1C), 43.395 (1C), 43.377 (1C), 38.708 (1C), 31.113 (1C), 29.139 (1C), (21.344+21.313) (1C). ^{19}F NMR (D_2O, 376.5 MH_Z): δ -116.141 (Ar-F). MS (ESI, CH_3OH): [$C_{21}H_{30}FN_5$] *m/z* 372.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 372.2558, Found: 372.2555. Anal. ($C_{21}H_{30}FN_5$·4HCl·2.3H_2O), Calcd: C, 45.14; H, 6.96; N, 12.53; Found: C, 45.59; H, 6.84; N, 12.17.

***N*^{1}-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3-yl}-*N*^{2}-(3'-fluorophenethyl)ethane-1,2-diamine (26).** The procedure to prepare **26** is the same as that to prepare **7** except using **47m** (0.134 g, 0.2 mmol) instead of **37a**, affording a hygroscopic white solid (0.103 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.337-7.309 (m, 1H), 7.082-6.963 (m, 3H), 6.653-6.641 (m, 2H), 4.344-4.333 (m, 1H), 3.965-3.917 (m, 1H), 3.769-3.723 (m, 1H), 3.662-3.486 (m, 5H), 3.403-3.313 (m, 3H), 3.241-3.211 (m, 2H), 3.029-3.008 (m, 2H), 2.843-2.787 (m, 1H), 2.263-2.256 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ (163.769+161.832) (1C), 158.286 (1C), 154.182 (1C), 143.156 (1C), (138.493+138.432) (1C), (130.916+130.849) (1C), 124.947 (1C), (115.877+115.707) (1C), 114.869 (1C), (114.438+114.274) (1C), 111.274 (1C), 58.635 (1C), 49.260 (1C), 47.487 (1C), 45.447 (1C), 43.468 (1C), 43.420 (1C), 38.738 (1C), 31.604 (1C), 29.182 (1C), (21.404+21.362) (1C). ^{19}F NMR (D_2O, 376.5 MH_Z): δ -113.592. MS (ESI, CH_3OH): [$C_{21}H_{30}FN_5$] *m/z* 372.3 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 372.2558, Found: 372.2550. Anal. ($C_{21}H_{30}FN_5$·4HCl·1.5H_2O), Calcd: C, 46.33; H, 6.85; N, 12.87; Found: C, 46.59; H, 6.71; N, 12.68.

(*S*)-*N*^{1}-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(4'-chlorobenzyl)propane-1,2-diamine tetrahydrochloride (29). The procedure to prepare 29 is the same as that to prepare 7 except using 47j (0.138 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.106 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.466-7.403 (m, 4H), 6.661 (s, 1H), 6.648 (s, 1H), 4.386-4.353 (m, 1H), 4.268-4.190 (m, 2H), 3.922-3.842 (m, 2H), 3.722-3.666 (m, 1H), 3.552-3.404 (m, 3H), 3.377-3.283 (m, 1H), 3.242-3.131 (m, 2H), 2.857-2.775 (m, 1H), 2.275 (s, 3H), 1.585-1.506 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.335 (1C), 154.224 (1C), (143.642+143.557) (1C), 135.378 (1C), (131.650+131.571) (2C), 129.483 (2C), 129.112 (1C), (114.899+114.869) (1C), 111.232 (1C), (59.120+58.871) (1C), (52.029+51.841+51.762) (1C), 49.540 (1C), (48.538+48.489) (1C), 47.591 (1C), 45.921 (1C), 38.757 (1C), 29.309 (1C), (21.453+21.410) (1C), (14.629+14.531+14.416) (1C). MS (ESI, CH_3OH): [$C_{21}H_{30}ClN_5$] *m/z* 388.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 388.2263, Found: 388.2267. Anal. ($C_{21}H_{30}ClN_5$·4HCl·2H_2O), Calcd: C, 44.26; H, 6.72; N, 12.29; Found: C, 44.27; H, 6.63; N, 12.12.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-*N*^{2}-(4'-chlorobenzyl)-*N*^{1}-methylethane-1,2-diamine (30). The procedure to prepare 30 is the same as that to prepare 7 except using 54a (0.138 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.106 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.450-7.430 (m, 4H), 6.707 (s, 1H), 6.664 (s, 1H), 4.315 (s, 2H), 4.196 (m, 1H), 3.961-3.924 (m, 1H), 3.637-3.552 (m, 4H), 3.507-3.450 (m, 2H), 3.370-3.344 (m, 1H), 3.256 (m, 1H), 3.080-3.051 (m, 1H), 2.928 (s, 3H), 2.766-2.710 (m, 1H), 2.294 (m, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ 158.231 (1C), 154.297 (1C), 143.156 (1C), 135.524 (1C), 131.772 (2C), 129.507 (2C), 128.839 (1C), 115.537 (1C), 111.262 (1C), 65.465 (1C), 51.501 (1C), 51.130 (1C), 47.408 (1C), 43.505 (1C), 41.574 (1C), 40.505 (1C), 37.281 (1C), 28.575 (1C), (21.471+21.435) (1C). MS (ESI, CH_3OH): [$C_{21}H_{30}ClN_5$] *m/z*

388.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 388.2263, Found: 388.2260. Anal. ($C_{21}H_{30}ClN_5 \cdot 4HCl \cdot 0.6H_2O$), Calcd: C, 46.31; H, 6.51; N, 12.86; Found: C, 46.34; H, 6.43; N, 12.65.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-N^2-(3'-fluoro phenethyl)-N^1-methylethane-1,2-diamine (31). The procedure to prepare 31 is the same as that to prepare 7 except using 54b (0.137 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.106 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.335-7.307 (m, 1H), 7.098-7.083 (m, 1H), 7.052-7.033 (m, 1H), 6.983-6.949 (m, 1H), 6.689 (s, 1H), 6.670 (s, 1H), 4.185-4.156 (m, 1H), 3.942-3.902 (m, 1H), 3.607-3.519 (m, 4H), 3.444-3.319 (m, 4H), 3.345-3.319 (m, 1H), 3.241-3.223 (m, 1H), 3.050-2.955 (m, 3H), 2.915 (s, 3H), 2.713-2.656 (m, 1H), 2.290 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ (163.811+161.868) (1C), 158.195 (1C), 154.303 (1C), 143.028 (1C), (138.566+138.505) (1C), (130.928+130.861) (1C), 124.905 (1C), (115.877+115.822) (1C), (115.625+115.543) (1C), (114.419+114.256) (1C), 111.244 (1C), 65.429 (1C), 51.349 (1C), 49.115 (1C), 47.281 (1C), (43.426+43.377) (1C), 42.047 (1C), 40.390 (1C), 37.208 (1C), 31.525 (1C), 28.472 (1C), (21.386+21.350) (1C). ^{19}F NMR (D_2O, 376.5 MHZ): -113.578 (Ar-F). MS (ESI, CH_3OH): [$C_{22}H_{32}FN_5$] *m/z* 386.5 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 386.2720, Found: 386.2717. Anal. ($C_{22}H_{32}FN_5 \cdot 4HCl \cdot 1.5H_2O$), Calcd: C, 47.32; H, 7.04; N, 12.54; Found: C, 47.53; H, 7.00; N, 12.59.

N^1-{(±)-4'-[(6"-amino-4"-methylpyridin-2"-yl)methyl]pyrrolidin-3'-yl}-N^2-(3'-fluoro phenethyl)-N^1,N^2-dimethylethane-1,2-diamine (32). The procedure to prepare 32 is the same as that to prepare 7 except using 55b (0.120 g, 0.2 mmol) instead of 37a, affording a hygroscopic white solid (0.109 g, quantitative yield). ^{1}H NMR (D_2O, 500 MHz): δ 7.280-7.236 (m, 1H), 7.074-7.060 (m, 1H), 7.030-7.011 (m, 1H), 6.927-6.893 (m, 1H), 6.679 (s, 1H), 6.622 (s, 1H), 4.271 (m, 1H), 3.983-3.943 (m, 1H), 3.743 (m, 3H), 3.648-3.602 (m, 2H), 3.582-3.520 (m, 2H), 3.448-3.411 (m, 1H), 3.331-3.255 (m, 2H), 3.066 (m, 3H), 2.987-2.966 (m, 6H), 2.752-2.696 (m, 1H), 2.248 (s, 3H). ^{13}C NMR (D_2O, 125.7 MHz): δ (163.684+161.747) (1C), 158.146 (1C), 154.200 (1C), 142.707 (1C), (138.171+138.110) (1C), (130.922+130.855) (1C), 124.881 (1C), 115.828 (1C), (115.786+115.664) (1C), (114.383+114.213) (1C), (111.287+112.262) (1C), 65.696 (1C), 57.554 (1C), 50.317 (1C), 50.019 (1C), 47.251 (1C), 43.219 (1C), 40.614 (2C), 37.117 (1C), 29.607 (1C), 28.569 (1C), (21.447+21.398) (1C). ^{19}F NMR (D_2O, 376.5 MHZ): -113.455 (Ar-F). MS (ESI, CH_3OH): [$C_{23}H_{34}FN_5$] *m/z* 400.4 ([M+H]$^+$). HRMS (CI+, CH_3OH) Calcd: 400.2876, Found: 400.2881.

(±)-*tert*-Butyl
3-[(*R*)-2'-(*tert*-butoxycarbonylamino)-3'-phenylpropylamino]-4-{[6'-(*tert*-butoxycarb onylamino)pyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (37b). The procedure to prepare 37b is the same as that to prepare 37a except using 42 (0.138 g, 0.55 mmol) instead of N^1-benzyl N^1-Boc-ethane-1,2-diamine. The desired product was purified by

column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5) to afford a pale-yellow oil (0.192 g, 82%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.758-7.745 (m, 1H), 7.564-7.533 (m, 1H), 7.288-7.161 (m, 6H), 6.801-6.779 (m, 1H), 5.074-4.973 (m, 1H), 3.874 (m, 1H), 3.450-2.333 (m, 12H), 1.527-1.422 (s, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.775 (1C), 155.839 (1C), 154.929 (1C), 152.542 (1C), 151.598 (1C), (138.661+138.584) (1C), (138.189+138.097) (1C), (129.454+129,384) (2C), (128.614+128.533) (2C), (126.533+126.506) (1C), 117.925 (1C), 109.778 (1C), 80.913 (1C), 79.323 (2C), (59.589+59.519+58.560) (1C), (51.952+51.782) (1C), 51.000-49.077 (3C), (42.856+41.843) (1C), 39.158 (1C), 35.239 (1C), 28.654 (3C), 28.531 (3C), 28.418 (3C). MS (APCI, CH_2Cl_2): [$C_{34}H_{51}N_5O_6$] *m/z* 626.3 ([M+H]$^+$)

(±)-*tert*-Butyl
3-[(*S*)-2'-(*tert*-butoxycarbonylamino)-3'-phenylpropylamino]-4-{[6'-(*tert*-butoxycarbonylamino)pyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (37c). The procedure to prepare 37c is the same as that to prepare 37a except using 43 (0.138 g, 0.55 mmol) instead of N^1-benzyl N^1-Boc-ethane-1,2-diamine. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5) to afford a pale-yellow oil (0.206 g, 88%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.762-7.749 (m, 1H), 7.546-7.399 (m, 1H), 7.286 (brs, 1H), 7.274-7.161 (m, 5H), 6.803-6.779 (m, 1H), 5.121 (m, 1H), 3.884 (m, 1H), 3.446-2.339 (m, 12H), 1.526-1.439 (s, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.767 (1C), 155.815 (1C), 154.910 (1C), 152.531 (1C), 151.587 (1C), (138.646+138.569) (1C), (138.189+138.093) (1C), (129.442+129,373) (2C), (128.603+128.518) (2C), (126.518+126.487) (1C), 117.913 (1C), 109.758 (1C), 80.898 (1C), 79.292 (2C), (59.573+59.507+58.548) (1C), (51.952+51.774) (1C), 50.992-49.070 (3C), (42.825+41.816) (1C), 39.185 (1C), 35.227 (1C), 28.643 (3C), 28.515 (3C), 28.407 (3C). MS (ESI, CH_3OH): [$C_{34}H_{51}N_5O_6$] *m/z* 626.6 ([M+H]$^+$).

(±)-*tert*-Butyl
3-{[6'-(*tert*-butoxycarbonylamino)pyridin-2'-yl]methyl}-4-[2'-(dimethylamino)ethylamino]pyrrolidine-1-carboxylate (37d). The procedure to prepare 37d is the same as that to prepare 37a except using N^1, N^1-dimethylethane-1,2-diamine (0.049 g, 0.55 mmol) instead of 41. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 4 : 6 : 0.5) to afford a pale-yellow oil (0.084 g, 80%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (8.015+7.879) (brs, 1H), 7.792-7.753 (m, 1H), 7.579-7.532 (m, 1H), 6.824-6.801 (m, 1H), 3.480-3.197 (m, 4H), 3.133-3.091 (m, 1H), 2.901-2.857 (m, 1H), 2.777-2.666 (m, 2H), 2.572-2.502 (m, 3H), 2.426-2.413 (m, 1H), 2.265 (s, 6H), 1.534 (s, 9H), 1.441 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.632+158.489) (1C), (154.833+154.755) (1C), (152.689+152.647) (1C), (151.726+151.622) (1C), 138.681 (1C), (117.964+117.774) (1C), (109.975+109.839) (1C), (80.994+80.928) (1C), (79.153+79.122) (1C), (59.825+59.790) (1C), (59.651+58.575) (1C), (50.536+49.944) (1C), (49.770+49.426) (1C), (46.280+46.187) (1C), 45.835 (2C), (43.305+42.214) (1C), 35.425 (1C), 28.666

(3C), 28.465 (3C). MS (ESI, CH_3OH): [$C_{24}H_{41}N_5O_4$] *m/z* 464.6 ([M+H]$^+$).

(±)-*tert*-Butyl
3-[(*R*)-1'-(*tert*-butoxycarbonyl)pyrrolidin-3'-ylamino]-4-{[6'-(*tert*-butoxycarbonylamino)pyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (37e). The procedure to prepare 37e is the same as that to prepare 37a except using (*R*)-(+)-1-Boc-3-aminopyrrolidine (0.103 g, 0.55 mmol) instead of 41. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8 : 2 : 0.5) to afford a pale-yellow oil (0.194 g, 92%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.762-7.734 (m, 1H), 7.586-7.556 (m, 1H), 7.321-7.294 (m, 1H), 6.8155 (d, 1H, J=7.5Hz), 3.552-3.027 (m, 10H), 2.882-2.848 (m, 1H), 2.705-2.557 (m, 2H), 2.100-2.005 (m, 0.5H), 1.936-1.900 (m, 0.5H), 1.699-1.646 (m, 1H), 1.521 (s, 9H), 1.467 (s, 9H), 1.452 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.667+158.520) (1C), (154.926+154.806+154.678) (2C), (152.566+152.380) (1C), (151.641+151.475) (1C), 138.592 (1C), (118.103+117.995) (1C), (109.770+109.661) (1C), (80.990+80.936+80.762) (1C), 79.362(1C), 79.215 (1C), (57.766+57.457+56.896+56.745+56.378) (1C), (55.867+55.786+55.376+55.252+55.159) (1C), (52.760+52.656+52.292+52.122+51.963+51.762+51.565) (1C), (51.046+50.903+50.702+50.474) (1C), (49.344+49.058) (1C), (44.516+44.392+44.203+44.017) (1C), (42.736+42.071+41.785+41.266+41.027) (1C), (35.270+35.146+35.053+34.991) (1C), (33.150+33.011+32.310+32.136+32.009+31.521+31.138+30.860) (1C), 28.604 (6C), 28.337 (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]$^+$).

(±)-*tert*-Butyl
3-[(*S*)-1'-(*tert*-butoxycarbonyl)pyrrolidin-3'-ylamino]-4-{[6'-(*tert*-butoxycarbonylamino)pyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (37f). The procedure to prepare 37f is the same as that to prepare 37a except using (*S*)-(-)-1-Boc-3-aminopyrrolidine (0.103 g, 0.55 mmol) instead of 41. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8 : 2 : 0.5) to afford a pale-yellow oil (0.2 g, 95%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.760-7.731 (m, 1H), 7.588-7.538 (m, 1H), 7.301-7.233 (m, 1H), 6.822-6.791 (m, 1H), 3.552-3.014 (m, 10H), 2.900-2.849 (m, 1H), 2.703-2.554 (m, 2H), 2.100-2.020 (m, 0.5H), 1.948-1.912 (m, 0.5H), 1.696-1.647 (m, 1H), 1.521 (s, 9H), 1.466 (s, 9H), 1.452 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.655+158.547) (1C), (154.991+154.871+154.740) (2C), (152.608+152.422) (1C), (151.656+151.482) (1C), 138.642 (1C), (118.250+118.153+118.060) (1C), (109.812+109.700) (1C), (81.021+80.851) (1C), 79.447 (1C), 79.296 (1C), (57.813+57.496+56.942+56.788+56.412+56.316) (1C), (55.906+55.820+55.418+55.290+55.198+54.760) (1C), (52.818+52.710+52.354+52.168+52.010+51.809+51.565) (1C,), (51.089+50.946+50.749+50.516) (1C), (49.387+49.104) (1C),

(44.563+44.443+44.249+44.063) (1C), (42.783+42.148+41.831+41.317+41.061) (1C), (35.328+35.208+35.111) (1C), (33.204+33.065+32.372+32.198+32.055+31.564+31.181+30.902) (1C), 28.654 (6C), 28.391 (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 ($[2M+Na]^+$).

(±)-*tert*-Butyl 3-[(*R*)-1'-benzylpyrrolidin-3'-ylamino]-4-{[6'-(*tert*-butoxycarbonylamino)pyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (37g). The procedure to prepare 37g is the same as that to prepare 37a except using (*R*)-(+)-1-benzyl-3-aminopyrrolidine (0.097 g, 0.55 mmol) instead of 41. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 7 : 3 : 0.5) to afford a pale-yellow oil (0.112 g, 90%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.761-7.728(m, 1H), 7.551-7.505 (m, 2H), 7.313-7.231 (m, 5H), 6.805 (d, 1H, J=7Hz), 3.679-3.539 (m, 2H), 3.427-3.109 (m, 6H), 2.929-2.840 (m, 2H), 2.738-2.665 (m, 1H), 2.646-2.488 (m, 4H), 2.341-2.292 (m, 1H), 2.227-2.144 (m, 1H), 1.509 (s, 9H), 1.437 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.721+158.686) (1C), (154.972+154.883) (1C), (152.558+152.531) (1C), (151.529+151.475) (1C), 138.936 (1C), 138.661 (1C), 128.993 (2C), 128.378 (2C), 127.086 (1C), (118.258+118.204) (1C), (109.959+109.859) (1C), (81.029+80.975) (1C), 79.277 (1C), 60.656 (1C), (60.119+59.821) (1C), (57.585+56.606) (1C), (55.391+55.368) (1C), 53.244 (1C), (50.756+50.362) (1C), (49.607+49.317) (1C), (42.446+41.595) (1C), (35.394+35.305) (1C), (32.987+32.879) (1C), 28.685 (3C), 28.434 (3C). MS (ESI, CH_3OH): $[C_{31}H_{45}N_5O_4]$ *m/z* 552.5 ($[M+H]^+$).

(±)-*tert*-Butyl 3-[(*S*)-1'-benzylpyrrolidin-3'-ylamino]-4-{[6'-(*tert*-butoxycarbonylamino)pyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (37h). The procedure to prepare 37h is the same as that to prepare 37a except using (*S*)-(-)-1-benzyl-3-aminopyrrolidine (0.097 g, 0.55 mmol) instead of 41. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 7 : 3 : 0.5) to afford a pale-yellow oil (0.100 g, 86%, diastereomer ratio: *cis* : *trans* = 45 : 55). ^1H NMR ($CDCl_3$, 500 MHz): δ (8.425+8.214) (brs, 1H), 7.851-7.807 (m, 1H), 7.587-7.543 (m, 1H), 7.363-7.229 (m, 5H), 6.815-6.787 (m, 1H), 4.137-3.983 (m, 2H), 3.508-3.415 (m, 2H), 3.372-3.151 (m, 4H), 3.066-2.890 (m, 2H), 2.824-2.767 (m, 1H), 2.695-2.462 (m, 4H), 2.418-2.312 (m, 1H), 1.906-1.843 (m, 1H), 1.513 (s, 9H), 1.434 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (158.411+158.264) (1C), (154.802+154.678) (1C), (152.840+152.747) (1C), (151.629+151.552) (1C), (138.990+138.924) (1C), 138.774 (1C), 128.854 (2C), 128.382 (2C), (127.040+126.993) (1C), (117.844+117.685) (1C), (110.141+110.006) (1C), (81.099+81.021) (1C), 79.087 (C), (61.585+61.511) (1C), (60.521+60.447) (1C), (55.654+54.606) (1C), (54.447+54.377) (1C), (54.273+54.203) (1C), (50.126+49.874) (1C), 49.460 (1C), (43.669+42.582) (1C), (35.293+35.262) (1C), (30.535+30.039) (1C), 28.627 (3C), 28.445 (3C). MS (ESI, CH_3OH): $[C_{31}H_{45}N_5O_4]$ *m/z* 552.5 ($[M+H]^+$).

(*R*)-*tert*-Butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate (39). The procedure to prepare **39** is the same as that to prepare **38** except using (*R*)-(+)-2-amino-3-phenyl-1-propanol (0.756 g, 0.005 mol) instead of 2-benzylaminoethanol. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 8 : 2) to afford a colorless oil (1.256 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.316-7.207 (m, 5H), 4.755 (brs, 1H), 3.872 (m, 1H), 3.664-3.655 (m, 1H), 3.563-3.542 (m, 1H), 2.848-2.835 (m, 2H), 1.413 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.386 (1C), 137.991 (1C), 129.495 (1C), 128.772 (2C), 126.745 (1C), 79.930 (1C), 64.622 (1C), 53.933 (1C), 37.634 (1C), 28.543 (3C). MS(ESI, CH_3OH): [$C_{14}H_{21}NO_3$] *m/z* 252.3 ([M+H]$^+$); *m/z* 274.4 ([M+Na]$^+$); *m/z* 525.1 ([2M+Na]$^+$).

(*S*)-*tert*-Butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate (40). The procedure to prepare **40** is the same as that to prepare **38** except using (*S*)-(-)-2-amino-3-phenyl-1-propanol (0.756 g, 0.005 mol) instead of 2-benzylaminoethanol. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 8 : 2) to afford a colorless oil (1.256 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.319-7.206 (m, 5H), 4.732 (brs, 1H), 3.871 (m, 1H), 3.680-3.661 (m, 1H), 3.576-3.546 (m, 1H), 2.849-2.836 (m, 2H), 1.415 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.380 (1C), 137.992 (1C), 129.496 (1C), 128.788 (2C), 126.765 (1C), 79.938 (1C), 64.688 (1C), 53.952 (1C), 37.649 (1C), 28.550 (3C). MS (ESI, CH_3OH): [$C_{14}H_{21}NO_3$] *m/z* 252.3 ([M+H]$^+$); *m/z* 274.4 ([M+Na]$^+$); *m/z* 525.1 ([2M+Na]$^+$).

(*R*)-*tert*-Butyl 1-amino-3-phenylpropan-2-ylcarbamate (42). The procedure to prepare **42** is the same as that to prepare **41** except using **39** (1.256 g, 0.005 mol) instead of **38**. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.851 g, 68%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.282-7.172 (m, 5H), 5.080 (brs, 1H), 3.774 (m, 1H), 2.801-2.557 (m, 4H), 1.400 (s, 9H), 1.142 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 155.823 (1C), 138.143 (1C), 129.253 (2C), 128.359 (2C), 126.274 (1C), 78.975 (1C), 54.072 (1C), 44.535 (1C), 38.775 (1C), 28.353 (3C). MS (ESI, CH_3OH): [$C_{14}H_{22}N_2O_2$] *m/z* 251.3 ([M+H]$^+$); *m/z* 501.1 ([2M+H]$^+$).

(*S*)-*tert*-Butyl 1-amino-3-phenylpropan-2-ylcarbamate (43). The procedure to prepare **43** is the same as that to prepare **41** except using **40** (1.256 g, 0.005 mol) instead of **38**. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.776 g, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.302-7.184 (m, 5H), 4.743 (brs, 1H), 3.794 (m, 1H), 2.820-2.590 (m, 4H), 1.408 (s, 9H), 1.100 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 155.951 (1C), 138.251 (1C), 129.473 (2C), 128.610 (2C), 126.537 (1C), 79.362 (1C), 54.169 (1C), 44.756 (1C), 38.999 (1C), 28.538 (3C). MS (ESI, CH_3OH): [$C_{14}H_{22}N_2O_2$] *m/z* 251.3 ([M+H]$^+$); *m/z* 501.1 ([2M+H]$^+$).

(±)-*tert*-Butyl
3-{2'-[*tert*-butoxycarbonyl(4"-chlorobenzyl)amino]ethylamino}-4-{[6'-(*tert*-butoxyc arbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47b). The procedure to prepare 47b is the same as that to prepare 47a except using 53b (0.103 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5) to afford a pale-green oil (0.215 g, 85%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.625-7.608 (m, 1H), 7.478 (brs, 1H), 7.281 (s, 2H), 7.187 (s, 2H), 6.642 (s, 1H), 4.569-4.339 (m, 2H), 3.339-3.110 (m, 7H), 2.764-2.567 (m, 5H), 2.300-2.286 (m, 3H), 1.508-1.452 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.210 (1C), 155.818 (1C), (154.792+154.695) (1C), (152.539+152.503) (1C), 151.453 (1C), 149.819 (1C), 137.191 (1C), 132.892 (1C), (129.073+128.655+128.618+128.412) (4C), 119.159 (1C), 110.264 (1C), 80.691 (1C), (80.108+79.986) (1C), 79.106 (1C), (59.295+58.245) (1C), (50.686+50.182) (2C), (49.326+49.022) (1C), (47.310+46.873) (1C), (46.236+46.114) (1C), (42.538+41.646) (1C), (35.034+34.882) (1C), 28.519 (3C), 28.422 (3C), 28.264 (3C), 21.288 (1C). MS (ESI, CH_3OH): [$C_{35}H_{52}ClN_5O_6$] *m/z* 674.3 ([M+H]$^+$).

(±)-*tert*-Butyl
3-{2'-[*tert*-butoxycarbonyl(3"-chlorobenzyl)amino]ethylamino}-4-{[6'-(*tert*-butoxyc arbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47c). The procedure to prepare 47c is the same as that to prepare 47a except using 53a (0.103 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5) to afford a pale-green oil (0.207 g, 82%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.614-7.594 (m, 1H), 7.373-7.120 (m, 5H), 6.638 (s, 1H), 4.581-4.346 (m, 2H), 3.395-3.103 (m, 7H), 2.764-2.550 (m, 5H), 2.302-2.284 (m, 3H), 1.510-1.449 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.337 (1C), 155.885 (1C), (154.901+154.804) (1C), (152.624+152.588) (1C), 151.489 (1C), (149.935+149.904) (1C), 140.919 (1C), 134.495 (1C), 129.923 (1C), (127.762+127.434) (2C), (125.862+125.236) (1C), (119.286+119.268) (1C), 110.325 (1C), (80.849+80.788) (1C), (80.320+80.217) (1C), 79.215 (1C), (59.447+58.391) (1C), (51.044+50.777+50.285) (2C), (49.417+49.126) (1C), 47.043 (1C), (46.321+46.211) (1C), (42.569+41.706) (1C), (35.161+34.991) (1C), 28.629 (3C), 28.513 (3C), 28.368 (3C), 21.392 (1C). MS (ESI, CH_3OH): [$C_{35}H_{52}ClN_5O_6$] *m/z* 674.3 ([M+H]$^+$).

(±)-*tert*-Butyl
3-{2'-{*tert*-butoxycarbonyl[4"-(trifluoromethyl)benzyl]amino}ethylamino}-4-{[6'-(*te rt*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47d). The procedure to prepare 47d is the same as that to prepare 47a except using 53c (0.175 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5) to afford a pale-green oil (0.212 g, 80%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.616-7.577 (m, 3H), 7.359-7.285 (m, 3H), 6.634 (s, 1H),

4.645-4.433 (m, 2H), 3.406-3.097 (m, 7H), 2.770-2.557 (m, 5H), 2.298-2.281 (m, 3H), 1.509-1.447 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.331 (1C), 155.970 (1C), (154.992+154.877) (1C), (152.667+152.630) (1C), 151.538 (1C), (150.056+150.026) (1C), 143.050 (1C), (130.040+129.766+129.505+129.260) (1C), (127.926+127.295) (2C), 125.637 (2C), (127.543+125.382+123.221+121.065) (1C), (119.335+119.305) (1C), 110.392 (1C), (80.958+80.909) (1C), 80.466 (1C), 79.337 (1C), (59.538+58.451) (1C), (50.844+50.352) (2C), (49.484+49.198) (1C), (47.705+47.207) (1C), (46.412+46.272) (1C), (42.672+41.816) (1C), (35.259+35.095) (1C), 28.677 (3C), 28.556 (3C), 28.422 (3C), 21.434 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ -62.863 (CF_3). MS (ESI, CH_3OH): [$C_{36}H_{52}F_3N_5O_6$] *m/z* 708.3 ([M+H]$^+$), 730.3([M+Na]$^+$).

(±)-*tert*-Butyl
3-{2-[*tert*-butoxycarbonyl(4-fluorobenzyl)amino]ethylamino}-4-{[6-(*tert*-butoxycarb onylamino)-4-methylpyridin-2-yl]methyl}pyrrolidine-1-carboxylate (47e). The procedure to prepare 47e is the same as that to prepare 47a except using 53d (0.148 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5) to afford a pale-green oil (0.223 g, 88%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.613-7.593 (m, 1H), 7.351-3.313 (brs, 1H), 7.207 (m, 2H), 7.018-6.988 (m, 2H), 6.634 (s, 1H), 4.563-4.329 (m, 2H), 3.397-3.099 (m, 7H), 2.758-2.474 (m, 5H), 2.300-2.283 (m, 3H), 1.508-1.448 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.128+161.179) (1C), 158.337 (1C), 155.970 (1C), (154.925+154.822) (1C), 152.636 (1C), 151.550 (1C), (149.965+149.929) (1C), 134.404 (1C), (129.462+129.843) (2C), 119.292 (1C), (115.559+115.389) (2C), 110.349 (1C), (80.873+80.818) (1C), 80.181 (1C), 79.240 (1C), (59.362+59.366) (1C), (50.807+50.310) (1C), 49.800 (1C), (49.435+49.132) (1C), 46.782 (1C), (46.327+46.211) (1C), (42.635+41.779) (1C), (35.168+35.004) (1C), 28.635 (6C), 28.374 (3C), 21.392 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ -115.882 (Ar-F). MS (ESI, CH_3OH): [$C_{35}H_{52}FN_5O_6$] *m/z* 658.3 ([M+H]$^+$).

(±)-*tert*-Butyl
3-{2'-{*tert*-butoxycarbonyl[3"-(trifluoromethyl)benzyl]amino}ethylamino}-4-{[6'-(*te rt*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47f). The procedure to prepare 47f is the same as that to prepare 47a except using 53e (0.175 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5) to afford a pale-green oil (0.228 g, 86%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.615-7.596 (m, 1H), 7.505-7.440 (m, 4H), 7.312 (brs, 1H), 6.637 (s, 1H), 4.651-4.424 (m, 2H), 3.335-3.106 (m, 7H), 2.764-2.556 (m, 5H), 2.298-2.282 (m, 3H), 1.508-1.448 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.344 (1C), 155.958 (1C), (154.956+154.859) (1C), (152.655+152.618) (1C), (151.574+151.525) (1C), 150.001 (1C), 139.966 (1C), (131.120+130.871+130.610+130.494) (2C), 129.158 (1C), 124.174 (2C), (127.471+125.303+123.136+120.968) (1C), 119.311 (1C), 110.368 (1C),

(80.903+80.855) (1C), 80.472 (1C), 79.282 (1C), (59.471+58.445) (1C), (51.317+50.813+50.328) (2C), (49.460+49.168) (1C), (47.723+47.590+47.250) (1C), (46.406+46.296) (1C), (42.605+41.799) (1C), (35.210+35.034) (1C), 28.647 (3C), 28.489 (3C), 28.392 (3C), 21.398 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ -63.081 (CF_3). MS (ESI, CH_3OH): [$C_{36}H_{52}F_3N_5O_6$] *m/z* 708.3 ([M+H]$^+$), 730.2([M+Na]$^+$).

(±)-*tert*-Butyl
3-{2'-[*tert*-butoxycarbonyl(3"-methylbenzyl)amino]ethylamino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47g). The procedure to prepare 47g is the same as that to prepare 47a except using 53f (0.146 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.75 : 0.25 : 0.5) to afford a pale-green oil (0.223 g, 91%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.611-7.592 (m, 1H), 7.360-7.286 (brs, 1H), 7.208-7.195 (m, 1H), 7.072-7.042 (m, 3H), 6.634 (s, 1H), 4.591-4.334 (m, 2H), 3.379-3.098 (m, 7H), 2.761-2.545 (m, 5H), 2.332-2.283 (m, 3H), 1.508-1.447 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.453 (1C), 156.170 (1C), (154.925+154.840) (1C), 152.655 (1C), 151.501 (1C), 149.935 (1C), 138.241 (2C), (128.557+128.078) (3C), (124.957+124.350) (1C), 119.323 (1C), 110.325 (1C), (80.861+80.800) (1C), 80.023 (1C), 79.215 (1C), (59.441+58.372) (1C), (51.293+50.850+50.334) (2C), (49.423+49.107) (1C), 46.606 (1C), (46.290+46.193) (1C), (42.617+41.737) (1C), (35.125+34.967) (1C), 28.659 (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]$^+$).

(±)-*tert*-Butyl
3-{2'-[*tert*-butoxycarbonyl(3",4"-dichlorobenzyl)amino]ethylamino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47h). The procedure to prepare 47h is the same as that to prepare 47a except using 53g (0.175 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8.5 : 1.5 : 0.5) to afford a pale-green oil (0.247 g, 93%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.619-7.600 (m, 1H), 7.399-7.341 (m, 3H), 7.102-7.087 (m, 1H), 6.641 (s, 1H), 4.536-4.328 (m, 2H), 3.404-3.108 (m, 7H), 2.768-2.561 (m, 5H), 2.305-2.287 (m, 3H), 1.512-1.451 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.224 (1C), (156.141+155.734) (1C), (154.860+154.751) (1C), (152.571+152.535) (1C), (151.521+151.472) (1C), (149.912+149.882) (1C), 139.178 (1C), (132.590+131.145) (1C), 130.545 (1C), (129.542+129.068) (1C), (127.035+126.421) (1C), (119.233+119.190) (1C), 110.314 (1C), (80.800+80.745) (1C), (80.424+80.314) (1C), 79.197 (1C), (59.398+58.372) (1C), (50.722+50.242) (2C), (49.392+49.101) (1C), 47.146 (1C), (46.320+46.192) (1C), (42.531+41.657) (1C), (35.130+34.966) (1C), 28.585 (3C), 28.464 (3C), 28.330 (3C), 21.348 (1C). MS (ESI, CH_3OH): [$C_{35}H_{51}Cl_2N_5O_6$] *m/z* 708.5 ([M+H]$^+$).

(±)-*tert*-Butyl

3-{2'-[*tert*-butoxycarbonyl(2",4"-dichlorobenzyl)amino]ethylamino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47i). The procedure to prepare 47i is the same as that to prepare 47a except using 53h (0.175 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.5 : 0.5 : 0.5) to afford a pale-green oil (0.228 g, 86%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.616-7.596 (m, 1H), 7.366-7.228 (m, 4H), 6.639 (s, 1H), 4.650-4.543 (m, 2H), 3.382-3.310 (m, 4H), 3.233-3.100 (m, 3H), 2.788 (m, 1H), 2.640-2.491 (m, 4H), 2.304-2.285 (m, 3H), 1.512-1.448 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.345 (1C), 155.965 (1C), (154.933+154.830) (1C), (152.626+152.596) (1C), 151.509 (1C), (149.973+149.948) (1C), (134.842+134.484+133.914) (1C), 133.404(1C), (129.712+129.336+128.832) (2C), 127.302 (1C), 119.281 (1C), 110.332 (1C), (80.873+80.812) (1C), 80.430 (1C), 79.264 (1C), (59.532+58.390) (1C), (50.813+50.321) (1C), (49.423+49.131) (1C), 48.815 (1C), 47.413 (1C), (46.429+46.350) (1C), (42.604+41.748) (1C), (35.197+35.027) (1C), (28.646+28.391) (9C), 21.409 (1C). MS (ESI, CH_3OH): [$C_{35}H_{51}Cl_2N_5O_6$] *m/z* 708.3 ([M+H]$^+$)

(±)-*tert*-Butyl
3-{(*S*)-2'-[*tert*-butoxycarbonyl(4"-chlorobenzyl)amino]propylamino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47j). The procedure to prepare 47j is the same as that to prepare 47a except using 53i (0.164 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 8.5 : 1.5 : 0.5) to afford a pale-green oil (0.235 g, 91%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.621-7.587(m, 1H), 7.432-7.182(m, 5H), 6.626(s, 1H), 4.345-3.856(m, 3H), 3.394-3.264(m, 3H), 3.209-3.035(m, 2H), 2.747-2.394(m, 5H), 2.309-2.290(m, 3H), 1.515-1.452(m, 27H), 1.109-1.077(m, 3H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.345 (1C), 156.317 (1C), (154.994+154.927+154.842) (1C), (152.681+152.626) (1C), (151.600+151.545+151.478) (1C), 149.967 (1C), 138.850 (1C), 132.438 (1C), 128.540 (4C), (119.275+119.196) (1C), (110.283+110.223) (1C), (80.812+80.770) (1C), 80.084 (1C), 79.270 (1C), (59.544+59.390+58.244) (1C), (53.229+52.713+52.235+51.845) (2C), (50.667+50.333+50.078) (1C), (49.325+49.192+49.076) (1C), (46.933+46.308) (1C), (42.568+41.675) (1C), 34.954 (1C), (28.652+28.385) (9C), 21.427 (1C), 17.195 (1C). MS (ESI, CH_3OH): [$C_{36}H_{54}ClN_5O_6$] *m/z* 688.5 ([M+H]$^+$).

(±)-*tert*-Butyl
3-{2'-[*tert*-butoxycarbonyl(phenethyl)amino]ethylamino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47k). The procedure to prepare 47k is the same as that to prepare 47a except using 53j (0.146 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5) to afford a pale-green oil (0.221 g, 90%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$,

500 MHz): δ 7.603-7.587 (m, 1H), 7.299-7.177 (s, 6H), 6.628 (s, 1H), 3.409-3.108 (m, 9H), 2.818-2.779 (m, 4H), 2.604-2.544 (m, 3H), 2.289-2.274 (m, 3H), 1.509-1.440 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 158.370 (1C), 155.832 (1C), (154.921+154.824) (1C), (152.632+152.583) (1C), 151.478 (1C), (149.942+149.906) (1C), 139.293 (1C), 128.983 (2C), 128.601 (2C), 126.391 (1C), 119.312 (1C), (110.320+110.259) (1C), (80.849+80.788) (1C), 79.665 (1C), 79.203 (1C), (59.495+58.433) (1C), (50.910+50.376) (1C), 49.817 (1C), (49.416+49.113) (1C), (48.597+47.589) (1C), (46.569+45.834) (1C), (42.507+41.663) (1C), (35.367+35.142) (1C), (34.954+34.663) (1C), 28.634 (3C), 28.549 (3C), 28.385 (3C), 21.396 (1C). MS (ESI, CH_3OH): [$C_{36}H_{55}N_5O_6$] *m/z* 654.4 ([M+H]$^+$).

(±)-*tert*-Butyl
3-{2'-[*tert*-butoxycarbonyl(4'-fluorophenethyl)amino]ethylamino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47l). The procedure to prepare 47l is the same as that to prepare 47a except using 53k (0.156 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.25 : 0.75 : 0.5) to afford a pale-green oil (0.224 g, 89%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.609-7.592 (m, 1H), 7.324 (brs, 1H), 7.123 (m, 2H), 6.988-6.956 (m, 2H), 6.632 (s, 1H), 3.392-3.111 (m, 9H), 2.794 (m, 4H), 2.614-2.534 (m, 3H), 2.295-2.279 (m, 3H), 1.512-1.441 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (162.607+160.665) (1C), 158.327 (1C), 155.747 (1C), (154.909+154.812) (1C), (152.614+152.571) (1C), 151.472 (1C), 149.918 (1C), (134.940+134.915) (1C), (130.386+130.325) (2C), (119.287+119.257) (1C), (115.444+115.280) (2C), (110.326+110.259) (1C), (80.855+80.800) (1C), 79.731 (1C), 79.215 (1C), (59.495+58.420) (1C), (50.868+50.333) (1C), 49.720 (1C), (49.410+49.101) (1C), 47.395 (1C), (46.903+46.502+46.277) (1C), (42.501+41.651) (1C), (35.130+34.960) (1C), (34.511+33.782) (1C), 28.615 (3C), 28.530 (3C), 28.360 (3C), 21.390 (1C). ^{19}F NMR (CDCl3, 376.5 MH_Z): δ -117.401 (Ar-F). MS (ESI, CH_3OH): [$C_{36}H_{54}FN_5O_6$] *m/z* 672.4 ([M+H]$^+$).

(±)-*tert*-Butyl
3-{2'-[*tert*-butoxycarbonyl(3''-fluorophenethyl)amino]ethylamino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (47m). The procedure to prepare 47m is the same as that to prepare 47a except using 53l (0.156 g, 0.55 mmol) instead of *N*-Boc-1,2-diaminoethane. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9.25 : 0.75 : 0.5) to afford a pale-green oil (0.227 g, 90%, diastereomer ratio: *cis* : *trans* = 75 : 25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.611-7.596 (m, 1H), 7.376 (brs, 1H), 7.266-7.223 (m, 1H), 6.945-6.902 (m, 3H), 6.636 (s, 1H), 3.424-3.115 (m, 9H), 2.819-2.785 (m, 4H), 2.619-2.523 (m, 3H), 2.295-2.280 (m, 3H), 1.511-1.441 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ), (163.907+161.952) (1C), 158.272 (1C), 155.656 (1C), (154.866+154.769) (1C), (152.589+152.547) (1C), 151.466 (1C), (149.900+149.869) (1C), (141.825+141.770) (1C), 129.961 (1C), (124.636+124.618) (1C),

(119.239+119.202) (1C), (115.857+115.693) (1C), (113.337+113.167) (1C), (110.295+110.235) (1C), (80.788+80.727) (1C), 79.744 (1C), 79.161 (1C), (59.465+58.384) (1C), (50.801+50.303) (1C), (49.372+49.064) (2C), 47.486 (1C), (46.879+46.551+46.253) (1C), (42.483+41.621) (1C), (35.088+34.918+34.329) (2C), 28.567 (3C), 28.464 (3C), 28.318 (3C), 21.342 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -113.945 (Ar-F). MS (ESI, CH_3OH): [$C_{36}H_{54}FN_5O_6$] *m/z* 672.4 ([M+H]$^+$).

2-(4'-chlorobenzylamino)ethanol (48b). The procedure to prepare **48b** is the same as that to prepare **48a** except using 4-chlorobenzaldehyde (0.14 g, 0.01 mmol) instead of 3-chlorobenzaldehyde. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a pale-green oil (1.83 g, 99%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.2905 (d, 2H, J= 8.5Hz), 7.244 (d, 2H, J= 8Hz), 3.764 (s, 2H), 3.645 (t, 2H, J=5Hz), 2.768 (t, 2H, J=5Hz), 2.236 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 138.654 (1C), 132.980 (1C), 129.642 (2C), 128.763 (2C), 61.120 (1C), 53.002 (1C), 50.727 (1C). MS (ESI, CH_3OH): [$C_9H_{12}ClNO$] *m/z* 186.4 ([M+H]$^+$); *m/z* 371.1 ([2M+H]$^+$).

2-[4'-(trifluoromethyl)benzylamino]ethanol (48c). The procedure to prepare **48c** is the same as that to prepare **48a** except using 4-(trifluoromethyl)benzaldehyde (1.741 g, 0.01 mmol) instead of 4-chlorobenzaldehyde. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a pale-green oil (2.126 g, 97%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.582 (d, 2H, J= 8Hz), 7.439 (d, 2H, J= 8Hz), 3.867 (s, 2H), 3.670 (t, 2H, J=5Hz), 2.794 (t, 2H, J=5Hz), 2.173 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 144.300 (1C), (129.960+129.702+129.445+129.189) (1C), 128.486 (2C), (125.593+125.565) (2C), (127.118+125.477+123.310+121.147) (1C), 61.120 (1C), 53.002 (1C), 50.727 (1C). MS (ESI, CH_3OH): [$C_{10}H_{12}F_3NO$] *m/z* 220.5 ([M+H]$^+$).

2-(4'-fluorobenzylamino)ethanol (48d). The procedure to prepare **48d** is the same as that to prepare **48a** except using 4-fluorobenzaldehyde (1.241 g, 0.01 mmol) instead of 4-chlorobenzaldehyde. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9.25 : 0.75) to afford a pale-green oil (1.623 g, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.276-7.249 (m, 2H), 7.014-6.890 (m, 2H), 3.745 (s, 2H), 3.632 (t, 2H, J=5Hz), 2.747 (t, 2H, J=4Hz), 2.623 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.079+161.130) (1C), (135.709+135.691) (1C), (129.905+129.845) (2C), (115.461+115.298) (2C), 60.922 (1C), 52.987 (1C), 50.759 (1C). MS (ESI, CH_3OH): [$C_9H_{12}FNO$] *m/z* 170.5 ([M+H]$^+$); *m/z* 361.6 ([2M+Na]$^+$).

2-[3'-(trifluoromethyl)benzylamino]ethanol (48e). The procedure to prepare **48e** is the same as that to prepare **48a** except using 3-(trifluoromethyl)benzaldehyde (1.741 g, 0.01 mmol) instead of 4-chlorobenzaldehyde. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a pale-green oil (2.103 g, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.668-7.410 (m, 4H), 3.847 (s, 2H),

3.663 (t, 2H, J=4.5Hz), 2.777 (t, 2H, J=5.5Hz), 2.498 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 141.064 (1C), 131.660 (1C), (131.302+131.047+130.792+130.531) (1C), 129.080 (1C), (124.994+124.969) (1C), (124.180+124.150+124.119+124.089) (1C), (127.586+125.419+123.251+121.084) (1C), 61.050 (1C), 53.272 (1C), 50.886 (1C). MS (ESI, CH_3OH): [$C_{10}H_{12}F_3NO$] *m/z* 220.5 ([M+H]$^+$); *m/z* 439.2 ([2M+H]$^+$).

2-(3-methylbenzylamino)ethanol (48f). The procedure to prepare **48f** is the same as that to prepare **48a** except using 3-methylbenzaldehyde (1.202 g, 0.01 mmol) instead of 4-chlorobenzaldehyde. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9.25 : 0.75) to afford a pale-green oil (1.569 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.256-7.196 (m, 1H), 7.117-7.061 (m, 3H), 3.744 (s, 2H), 3.639 (t, 2H, J=5Hz), 2.769 (t, 2H, J=5Hz), 2.501 (brs, 2H), 2.339 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 139.953 (1C), 138.259 (1C), 129.104 (1C), 128.533 (1C), 128.005 (1C), 125.346 (1C), 60.995 (1C), 53.673 (1C), 50.801 (1C), 21.549 (1C). MS (ESI, CH_3OH): [$C_{10}H_{15}NO$] *m/z* 166.5 ([M+H]$^+$); *m/z* 331.3 ([2M+H]$^+$); *m/z* 353.5 ([2M+Na]$^+$).

2-(3,4-dichlorobenzylamino)ethanol (48g). The procedure to prepare **48g** is the same as that to prepare **48a** except using 3,4-dichlorobenzaldehyde (1.75 g, 0.01 mmol) instead of 4-chlorobenzaldehyde. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a pale-green oil (2.103 g, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.433 (s, 1H), 7.389 (d, 1H, J= 8Hz), 7.1605 (d, 1H, J=8.5Hz), 3.767 (s, 2H), 3.668 (t, 2H, J=5Hz), 2.777 (t, 2H, J=5Hz), 2.150 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 140.562 (1C), 132.620 (1C), 131.121 (1C), 130.562 (1C), 130.155 (1C), 127.587 (1C), 61.189 (1C), 52.568 (1C), 50.710 (1C). MS (ESI, CH_3CN): [$C_9H_{11}C_{l2}NO$] *m/z* 220.1 ([M+H]$^+$).

2-(2,4-dichlorobenzylamino)ethanol (48h). The procedure to prepare **48h** is the same as that to prepare **48a** except using 2,4-dichlorobenzaldehyde (1.75 g, 0.01 mmol) instead of 4-chlorobenzaldehyde. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a pale-green oil (2.113 g, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.362 (s, 1H), 7.303 (d, 1H, J= 8Hz), 7.209 (d, 1H, J=8Hz), 3.836 (s, 2H), 3.640 (t, 2H, J=4.5Hz), 2.736 (t, 2H, J=4.5Hz). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 135.929 (1C), 134.460 (1C), 133.543 (1C), 130.969 (1C), 129.421 (1C), 127.211 (1C), 60.879 (1C), 50.613 (1C), 50.412 (1C). MS (ESI, CH_3OH): [$C_9H_{11}C_{l2}NO$] *m/z* 220.0 ([M+H]$^+$).

(*S*)-2-(4-chlorobenzylamino)propan-1-ol (48i). The procedure to prepare **48i** is the same as that to prepare **48a** except using (*S*)-(+)-2-amino-1-propanol (0.75 g, 0.01 mmol) instead of ethanolamine. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a white solid (1.891 g, 95%). mp: 84.9-85.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.2795 (d, 2H, J= 8.5Hz), 7.2415 (d, 2H, J= 8.5Hz), 3.820 (d, 1H, J=13Hz), 3.6735 (d, 1H, J=13.5Hz), 3.571-3.543 (m, 1H), 3.296-3.261 (m, 1H), 2.811-2.777 (m, 1H), 2.357 (brs, 2H),

1.068-1.051 (m, 3H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 138.825 (1C), 132.900 (1C), 129.609 (2C), 128.722 (2C), 65.688 (1C), 53.922 (1C), 50.509 (1C), (17.098+17.055) (1C). MS (ESI, CH_3CN): [$C_{10}H_{14}ClNO$] *m/z* 200.4 ([M+H]$^+$).

2-(3'-fluorophenyl)acetaldehyde (49b). The procedure to prepare **49b** is the same as that to prepare **49a** except using 3-fluorophenethyl alcohol (0.56 g, 0.5 mL, 0.004 mol) instead of 4-fluorophenethyl alcohol. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 8 : 2) to afford a pale-yellow volatile oil (0.47 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.726-9.710 (m, 1H), 7.331-7.288 (m, 1H) 6.996-6.920 (m, 3H), 3.687-3.637 (m, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (198.514+198.466) (1C), (163.980+162.019) (1C), (134.405+134.345) (1C), (130.447+130.386) (1C), (125.347+125.328) (1C), (116.664+116.494) (1C), (114.363+114.193) (1C), 49.975 (1C).

2-[benzyl(4'-fluorophenethyl)amino]ethanol (50b). The procedure to prepare **50b** is the same as that to prepare **50a** except using **49a** (0.414 g, 0.003 mol) instead of phenylacetaldehyde. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 5 : 5) to afford a pale-yellow oil (0.820 g, quantitative). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.313-7.206 (m, 5H), 7.061-7.033 (m, 2H), 6.956-6.921 (m, 2H), 3.668 (s, 2H), 3.533 (t, 2H, J=5.5Hz), 2.740 (m, 4H), 2.690 (t, 2H, J=5.5Hz), 2.493 (brs, 1H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (162.516+160.580) (1C), 138.831 (1C), (135.850+135.826) (1C), (130.228+130.167) (2C), 129.044 (2C), 128.595 (2C), 127.405 (1C), (115.420+115.250) (2C), 58.645 (1C), 58.451 (1C), 55.391 (1C), 55.306 (1C), 32.986 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -117.681 (Ar-F). MS (ESI, CH_3OH): [$C_{17}H_{20}FNO$] *m/z* 274.3 ([M+H]$^+$).

2-[benzyl(3'-fluorophenethyl)amino]ethanol (50c). The procedure to prepare **50c** is the same as that to prepare **50a** except using **49b** (0.414 g, 0.003 mol) instead of phenylacetaldehyde. The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 6 : 4) to afford a pale-yellow oil (0.820 g, quantitative). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.301-7.170 (m, 6H), 6.880-6.841 (m, 2H), 6.787-6.768 (m, 1H), 3.652 (s, 2H), 3.523 (t, 2H, J=5.5Hz), 2.740 (m, 4H), 2.674 (t, 2H, J=5Hz), 2.591 (brs, 1H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.919+161.964) (1C), (142.820+142.766) (1C), 138.722 (1C), (129.906+129.840) (1C), 128.959 (2C), 128.504 (2C), 127.332 (1C), (124.491+124.466) (1C), (115.687+115.517) (1C), (113.125+112.955) (1C), 58.645 (1C), 58.402 (1C), 55.360 (1C), 54.923(1C), 33.333 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -113.997. MS (ESI, CH_3OH): [$C_{17}H_{20}FNO$] *m/z* 274.3 ([M+H]$^+$).

2-(4'-fluorophenethylamino)ethanol (51b). The procedure to prepare **51b** is the same as that to prepare **51a** except using **50b** (0.820 g, 0.003 mol) instead of **50a**. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 8.5 : 1.5) to afford a pale-green oil (0.456 g, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.168-7.141 (m, 2H), 6.994-6.960 (m, 2H), 3.628 (t, 2H, J=5Hz), 2.870 (t, 2H, J=7.5Hz),

2.788-2.761 (m, 4H), 2.544 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (162.620+160.677) (1C), (135.516+135.492) (1C), (130.234+130.173) (2C), (115.523+115.353) (2C), 60.843 (1C), 51.177 (1C), 50.898 (1C), 35.622 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -117.511 (Ar-F). MS (ESI, CH_3CN): [$C_{10}H_{14}FNO$] *m/z* 184.3 ([M+H]$^+$).

2-(3'-Fluorophenethylamino)ethanol (51c). The procedure to prepare **51c** is the same as that to prepare **51a** except using **50c** (0.820 g, 0.003 mol) instead of **50a**. The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 8.5 : 1.5) to afford a pale-green oil (0.45 g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.271-7.226 (m, 1H), 6.985-6.970 (m, 1H), 6.920-6.887 (m, 2H), 3.633 (t, 2H, J=5Hz), 2.893 (t, 2H, J=7.5Hz), 2.815-2.762 (m, 4H), 2.560 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (164.071+162.116) (1C), (142.511+142.450) (1C), (130.131+130.070) (1C), (124.533+124.509) (1C), (115.748+115.584) (1C), (113.404+113.234) (1C), 60.849 (1C), 51.165 (1C), 50.521 (1C), (36.175+36.162) (1C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -113.900 (Ar-F). MS (ESI, CH_3CN): [$C_{10}H_{14}FNO$] *m/z* 184.3 ([M+H]$^+$); *m/z* 367.1 ([2M+H]$^+$).

***tert*-Butyl 3-chlorobenzyl(2'-hydroxyethyl)carbamate (52a).** The procedure to prepare **52a** is the same as that to prepare **38** except using **48a** (0.925 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.426 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.277-7.223 (m, 3H), 7.118 (m, 1H), 4.449 (s, 2H), 3.720 (m, 2H), 3.407 (m, 2H), 1.456 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.313 (1C), 140.612 (1C), 134.658 (1C), 130.063 (1C), 127.660 (2C), 125.413 (1C), 81.062 (1C), 62.279 (1C), 51.802 (1C), 50.157 (1C), 28.554 (3C). MS (ESI, CH_3OH): [$C_{14}H_{20}ClNO_3$] *m/z* 308.5 ([M+Na]$^+$); *m/z* 593.3 ([2M+Na]$^+$).

***tert*-Butyl 4-chlorobenzyl(2'-hydroxyethyl)carbamate (52b).** The procedure to prepare **52b** is the same as that to prepare **38** except using **48b** (0.925 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.426 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.297-7.284 (m, 2H, 3, 5), 7.169 (m, 2H, 2, 6), 4.442 (s, 2H, 7), 3.695 (m, 2H, 9), 3.387 (m, 2H, 8), 1.448 (s, 9H, 12). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.357 (1C, 10), 137.001 (1C, 1), 133.217 (1C, 4), 128.892 (4C, 3, 5, 2, 6), 80.934 (1C, 11), 62.199 (1C, 9), 51.646 (1C, 7), 50.065 (1C, 8), 28.546 (3C, 12). MS (ESI, CH_3OH): [$C_{14}H_{20}ClNO_3$] *m/z* 308.5 ([M+Na]$^+$); *m/z* 593.2 ([2M+Na]$^+$).

***tert*-Butyl 2-hydroxyethyl[4'-(trifluoromethyl)benzyl]carbamate (52c).** The procedure to prepare **52c** is the same as that to prepare **38a** except using **48c** (1.096 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.596 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.590 (d, 2H, J=8Hz),

7.3485 (d, 2H, J=7.5Hz), 4.542 (s, 2H), 3.726 (m, 2H), 3.424-3.348 (m, 2H), 1.434 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.240 (1C), 142.707 (1C), (130.144+129.879+129.622+129.365) (1C), (127.855+127.383) (2C), (125.726+125.698) (2C), (127.383+125.393+123.230+121.063) (1C), 81.078(1C), (62.167+61.485) (1C), (51.979+51.092) (1C), (50.254+49.435) (1C), 28.505(3C). MS (ESI, CH_3OH): [$C_{15}H_{20}F_3NO_3$] *m/z* 320.3 ([M+H]$^+$); *m/z* 342.4 ([M+Na]$^+$); *m/z* 661.0 ([M+Na]$^+$).

***tert*-Butyl 4-fluorobenzyl(2'-hydroxyethyl)carbamate (52d).** The procedure to prepare **52d** is the same as that to prepare **38** except using **48d** (0.846 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.346 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.203 (m, 2H), 7.025-6.995 (m, 2H), 4.440 (s, 2H), 3.693 (m, 2H), 3.387-3.304 (m, 2H), 1.457 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.201+161.246) (1C), 157.324 (1C), 134.161 (1C), (129.468+128.958) (2C), (115.650+115.480) (2C), 80.855 (1C), (62.130+61.317) (1C), (51.506+50.565) (1C), (49.854+49.041) (1C), 28.525 (3C). MS (ESI, CH_3OH): [$C_{14}H_{20}FNO_3$] *m/z* 292.5 ([M+Na]$^+$); *m/z* 561.1 ([2M+Na]$^+$).

***tert*-Butyl 2-hydroxyethyl[3'-(trifluoromethyl)benzyl]carbamate (52e).** The procedure to prepare **52e** is the same as that to prepare **38** except using **48e** (1.096 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.596 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.524-7.441 (m, 4H), 4.526 (s, 2H), 3.738 (m, 2H), 3.433-3.344 (m, 2H), 1.437 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (157.160+156.213) (1C), 139.644 (1C), (131.447+131.198+130.937) (1C) 130.531 (1C), 129.225 (1C), (124.301+124.271+124.107) (2C), (127.477+125.309+123.148+120.980) (1C), 81.085 (1C), (62.088+61.438) (1C), (51.925+51.002) (1C), (50.212+49.338) (1C), 28.459 (3C). MS (ESI, CH_3OH): [$C_{15}H_{20}F_3NO_3$] *m/z* 342.5 ([M+Na]$^+$); *m/z* 661.0 ([2M+Na]$^+$).

***tert*-Butyl 2-hydroxyethyl(3'-methylbenzyl)carbamate (52f).** The procedure to prepare **52f** is the same as that to prepare **38** except using **48f** (0.826 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.326 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.263-7.202 (m, 1H), 7.085-7.032 (m, 3H), 4.435 (s, 2H), 3.696 (m, 2H), 3.392 (m, 2H), 2.339 (s, 3H), 1.471 (s, 9H). ^{13}C NMR($CDCl_3$, 125.7 MHz): δ 157.724 (1C), 138.423 (1C), 138.259 (1C), 128.697 (1C), 128.254 (2C), (124.945+124.447) (1C), (62.422+61.463) (1C), (52.137+51.117) (1C), (49.963+49.168) (1C), 28.586 (3C), 21.622 (1C). MS (ESI, CH_3OH): [$C_{15}H_{23}NO_3$] *m/z* 288.5 ([M+Na]$^+$); *m/z* 553.2 ([2M+Na]$^+$).

***tert*-Butyl 3,4-dichlorobenzyl(2-hydroxyethyl)carbamate (52g).** The procedure to prepare **52g** is the same as that to prepare **38** except using **48g** (1.095 g, 0.005 mol)

instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 6.5 : 3.5) to afford a colorless oil (1.596 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.401 (d, 1H, J=8Hz), 7.330 (s, 1H), 7.085 (s, 1H), 4.427 (s, 2H), 3.733 (m, 2H), 3.411 (m, 2H), 1.453 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.198 (1C), 138.880 (1C), 134.821 (1C), 131.442 (1C), 130.750 (1C), 129.299 (1C), (127.126+126.537) (1C), 81.225 (1C), (62.306+61.590) (1C), 51.347 (1C), 50.206 (1C), 28.549 (3C). MS (ESI, CH_3CN): [$C_{14}H_{19}Cl_2NO_3$] *m/z* 342.4, 344.4 ([M+Na]$^+$); *m/z* 661.4, 662.9, 664.8 ([2M+Na]$^+$).

***tert*-Butyl 2,4-dichlorobenzyl(2-hydroxyethyl)carbamate (52h).** The procedure to prepare **52h** is the same as that to prepare **38** except using **48h** (1.095 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.596 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.373 (s, 1H), 7.2435 (d, 1H, J=8.5Hz), 7.1775 (d, 1H, J=8.5Hz), (4.593+4.534) (m, 2H), 3.726 (m, 2H), (3.438+3.365) (m, 2H), 1.493-1.404 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.277 (1C), 134.496 (1C), 133.543 (1C), 129.469 (2C), 128.838 (1C), 127.435 (1C), 81.079 (1C), (62.136+61.371) (1C), (50.406+49.544+48.457) (2C), 28.427 (3C). MS (ESI, CH_3CN): [$C_{14}H_{19}Cl_2NO_3$] *m/z* 342.5, 344.5 ([M+Na]$^+$); *m/z* 661.4, 662.9, 664.9 ([2M+Na]$^+$).

(*S*)-*tert*-Butyl 4-chlorobenzyl(1-hydroxypropan-2-yl)carbamate (52i). The procedure to prepare **52i** is the same as that to prepare **38** except using **48i** (0.996 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.496 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.2855 (d, 2H, J=8.5Hz), 7.205 (d, 2H, J=7Hz), 4.387-4.321 (m, 2H), 4.038 (m, 1H), 3.580 (m, 2H), 1.401 (s, 9H), 1.122 (m, 3H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.864 (1C), 138.315 (1C), 132.833 (1C), (128.759+128.303) (4C), 80.715 (1C), 65.882 (1C), 54.905 (1C), 48.202 (1C), 28.555 (3C), (14.785+14.396) (1C). MS (ESI, CH_3CN): [$C_{15}H_{22}ClNO_3$] *m/z* 322.5 ([M+Na]$^+$); *m/z* 621.4 ([2M+Na]$^+$).

***tert*-Butyl 2-hydroxyethyl(phenethyl)carbamate (52j).** The procedure to prepare **52j** is the same as that to prepare **38** except using **51a** (0.826 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.326 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.306-7.169 (m, 5H), 3.701 (m, 2H), 3.437 (m, 2H), 3.337 (m, 2H), 2.818 (m, 2H), 1.436-1.398 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 157.489 (1C), 139.178 (1C), 129.050 (2C), 128.716 (2C), 126.549 (1C), 80.369 (1C), (62.713+61.693) (1C), (50.940+50.752) (2C), (35.422+34.760) (1C), 28.524 (3C). MS (ESI, CH_3CN): [$C_{15}H_{23}NO_3$] *m/z* 288.5 ([M+Na]$^+$); *m/z* 553.2 ([2M+Na]$^+$).

***tert*-Butyl 4-fluorophenethyl(2'-hydroxyethyl)carbamate (52k).** The procedure to prepare **52k** is the same as that to prepare **38** except using **51b** (0.916 g, 0.005 mol)

instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.416 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.115 (m, 2H), 6.994-6.962 (m, 2H), 3.709 (m, 2H), 3.414 (m, 2H), 3.331 (m, 2H), 2.791 (m, 2H), 1.432 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (162.753+160.810) (1C), 157.459 (1C), 134.885 (1C), (130.483+130.416) (2C), (115.596+115.426) (2C), 80.448 (1C), 62.768 (1C), 50.928 (1C), 50.740 (1C), 34.596 (1C), 28.543 (3C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -117.268 (Ar-F). MS (ESI, CH_3OH): [$C_{15}H_{22}FNO_3$] *m/z* 306.3 ([M+Na]$^+$); *m/z* 589.1 ([2M+Na]$^+$).

***tert*-Butyl 3-fluorophenethyl(2'-hydroxyethyl)carbamate (52l).** The procedure to prepare **52l** is the same as that to prepare **38** except using **51c** (0.916 g, 0.005 mol) instead of 2-benzylaminoethanol, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7 : 3) to afford a colorless oil (1.416 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.274-7.226 (m, 1H), 6.928-6.891 (m, 3H), 3.712 (m, 2H), 3.447 (m, 2H), 3.344-3.214 (m, 2H), 2.818 (m, 2H), 1.431 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (164.034+162.079) (1C), 152.258 (1C), 141.758 (1C), 130.107 (1C), (124.746+124.727) (1C), (115.960+115.796) (1C), (113.525+113.368) (1C), 80.448 (1C), 62.543 (1C), 50.582 (2C), 35.118 (1C), 28.494 (3C). ^{19}F NMR (CDCl3, 376.5 MH_Z): δ -113.904. MS (ESI, CH_3OH): [$C_{15}H_{22}FNO_3$] *m/z* 306.4 ([M+Na]$^+$); *m/z* 589.2 ([2M+Na]$^+$).

***tert*-Butyl 2-aminoethyl(3'-chlorobenzyl)carbamate (53a).** The procedure to prepare **53a** is the same as that to prepare **51a** except using **52a** (1.426 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9.5 : 0.5) to afford a pale-green oil (0.725 g, 51%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.270-7.221 (m, 3H), 7.109 (s, 1H), 4.422 (s, 2H), 3.298-3.207 (m, 2H), 2.803 (m, 2H), 1.496-1.444 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.152 (1C), 140.901 (1C), 134.611 (1C), 130.021 (1C), 127.586 (2C), (125.886+125.303) (1C), 80.387 (1C), (50.874+50.261) (2C), 40.644 (1C), 28.604 (3C). MS (ESI, CH_3OH): [$C_{14}H_{21}ClN_2O_2$] *m/z* 285.4 ([M+H]$^+$).

***tert*-Butyl 2-aminoethyl(4'-chlorobenzyl)carbamate (53b).** The procedure to prepare **53b** is the same as that to prepare **51a** except using **52b** (1.426 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a pale-green oil (0.852 g, 60%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.299-7.283 (m, 2H, 3, 5), 7.172 (m, 2H, 2, 6), 4.427 (s, 2H, 7), 3.280-3.201 (m, 2H, 8), 2.788 (m, 2H, 9), 1.476 (s, 9H, 12); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.140 (1C, 10), 137.246 (1C, 1), 133.160 (1C, 4), (129.237+128.873+128.582) (4C, 3, 5, 2, 6), 80.290 (1C, 11), (50.753+50.212) (2C, 7, 8), 40.579 (1C, 9), 28.604 (3C, 12). MS (ESI, CH_2Cl_2): [$C_{14}H_{21}ClN_2O_2$] *m/z* 285.2 ([M+H]$^+$).

***tert*-Butyl 2-aminoethyl[4'-(trifluoromethyl)benzyl]carbamate (53c).** The procedure to prepare **53c** is the same as that to prepare **51a** except using **52c** (1.596 g,

0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9.5 : 0.5) to afford a colorless oil (0.795 g, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.593-7.578 (m, 2H), 7.346 (m, 2H), 4.524 (s, 2H), 3.313-3.225 (m, 2H), 2.812 (m, 2H), 1.501-1.427 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.018 (1C), 142.874 (1C), (130.039+129.778+129.523+129.450) (1C), (127.877+127.288) (2C), (125.680+125.649) (2C), (127.600+125.388+123.221+121.059) (1C), 80.417 (1C), (51.062+50.382) (2C), 40.620 (1C), 28.538 (3C). MS (ESI, CH_3OH): [$C_{15}H_{21}F_3N_2O_2$] *m/z* 319.3 ([M+H]$^+$); *m/z* 637.2 ([2M+H]$^+$).

***tert*-Butyl 2-aminoethyl(4'-fluorobenzyl)carbamate (53d).** The procedure to prepare **53d** is the same as that to prepare **51a** except using **52d** (1.346 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.791 g, 59%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.205 (m, 2H), 7.023-6.991 (m, 2H), 4.429 (s, 2H), 3.277-3.197 (m, 2H), 2.784 (m, 2H), 1.474 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.170+161.215) (1C), 156.103 (1C), 134.368 (1C), (129.438+128.891) (2C), (115.601+115.431) (2C), 80.162 (1C), (50.589+50.042) (2C), 40.595 (1C), 28.574 (3C). MS (ESI, CH_3OH): [$C_{14}H_{21}FN_2O_2$] *m/z* 269.4 ([M+H]$^+$); *m/z* 537.5 ([2M+H]$^+$).

***tert*-Butyl 2-aminoethyl[3'-(trifluoromethyl)benzyl]carbamate (53e).** The procedure to prepare **53e** is the same as that to prepare **51a** except using **52e** (1.596 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.795 g, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.534-7.437 (m, 4H), 4.533 (s, 2H), 3.326-3.233 (m, 2H), 2.827 (m, 2H), 1.502-1.439 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.061 (1C), 139.966 (1C), (132.971+132.261) (1C) (130.992+130.488) (1C), 129.219 (1C), 124.283 (2C), (127.180+125.352+123.190+120.250) (1C), 80.496 (1C), (51.105+50.449) (2C), 40.753 (1C), 28.562 (3C). MS (ESI, CH_3OH): [$C_{15}H_{21}F_3N_2O_2$] *m/z* 319.4 ([M+Na]$^+$); *m/z* 637.3 ([2M+H]$^+$).

***tert*-Butyl 2-aminoethyl(3'-methylbenzyl)carbamate (53f).** The procedure to prepare **53f** is the same as that to prepare **51a** except using **52f** (1.326 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.845 g, 64%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.222-7.192 (m, 1H), 7.076-7.035 (m, 3H), 4.441-4.419 (m, 2H), 3.282-3.195 (m, 2H), 2.785 (m, 2H), 2.335 (s, 3H) 1.496-1.459 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.346 (1C), 138.326 (2C), (128.612+128.126) (3C), (124.969+124.362) (1C), 80.011 (1C), (51.147+50.662) (1C), 50.036 (1C), 40.577 (1C), 28.629 (3C), 21.616 (1C). MS (ESI, CH_3OH): [$C_{15}H_{24}N_2O_2$] *m/z* 265.4 ([M+H]$^+$); *m/z* 529.6 ([2M+H]$^+$).

***tert*-Butyl 2-aminoethyl(3',4'-dichlorobenzyl)carbamate (53g).** The procedure to prepare **53g** is the same as that to prepare **51a** except using **52g** (1.596 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (1.066 g, 67%). ^{1}H NMR ($CDCl_3$, 500

MHz): δ 7.3925 (d, 1H, J=8.5Hz), 7.329 (s, 1H), 7.081 (s, 1H), 4.411 (s, 2H), 3.301-3.216 (m, 2H), 2.812 (m, 2H), 1.489-1.451 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.141 (1C), 139.044 (1C), 132.669 (1C), 131.254 (1C), 130.629 (1C), (129.572+129.166) (1C), (127.071+126.433) (1C), 80.503 (1C), (50.333+50.163+49.866) (2C), 40.601 (1C), 28.488 (3C). MS (ESI, CH_3CN): [$C_{14}H_{20}Cl_2N_2O_2$] *m/z* 319.4, 321.3 ([M+H]$^+$); 637.5, 639.2, 641.0([2M+H]$^+$).

***tert*-Butyl 2-aminoethyl(2',4'-dichlorobenzyl)carbamate (53h).** The procedure to prepare **53h** is the same as that to prepare **51a** except using **52h** (1.596 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (1.018 g, 64%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.370 (s, 1H), 7.2345 (d, 1H, J=8.5Hz), 7.201-7.152 (m, 1H), 4.564-4.506 (m, 2H), 3.315-3.234 (m, 2H), 2.829 (m, 2H), 1.498-1.399 (s, 9H), 1.147 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.081 (1C), 134.745 (1C), 133.501 (1C), (129.615+129.427) (2C), 128.692 (1C), 127.362 (1C), 80.430 (1C), 50.479 (1C), (48.566+47.820) (1C), (40.856+40.667) (1C), 28.488 (3C). MS (ESI, CH_3OH): [$C_{14}H_{20}Cl_2N_2O_2$] *m/z* 319.1, 321.0 ([M+H]$^+$).

(*S*)-*tert*-Butyl 1-aminopropan-2-yl(4'-chlorobenzyl)carbamate (53i). The procedure to prepare **53i** is the same as that to prepare **51a** except using **52i** (1.496 g, 0.005 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (1.014 g, 68%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.276 (d, 2H, J=8Hz), 7.227-7.219 (m, 2H), 4.355-4.323 (m, 2H), 4.190 (m, 0.5H), 3.760-3.754 (m, 0.5H), 2.755-2.641 (m, 2H), 1.503-1.382 (s, 9H), 1.102-1.066 (m, 3H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.141 (1C), 138.686 (1C), 132.517 (1C), (128.947+128.565+128.115) (4C), 80.156 (1C), (56.356+54.650) (1C), (47.455+46.095) (2C), 28.476 (3C), (16.940+16.521) (1C). MS (ESI, CH_2Cl_2): [$C_{15}H_{23}ClN_2O_2$] *m/z* 299.2 ([M+H]$^+$).

tert-Butyl 2-aminoethyl(phenethyl)carbamate (53j). The procedure to prepare **53j** is the same as that to prepare **51a** except using **52j** (0.663 g, 0.0025 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.337 g, 51%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.301-7.168 (m, 5H), 3.438-3.400 (m, 2H), 3.235-3.154 (m, 2H), 2.809 (m, 2H), 2.036 (m, 2H), 1.446 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 156.123 (1C), 139.226 (1C), 129.008 (2C), 128.656 (2C), 126.470 (1C), 79.780 (1C), (50.989+49.987) (2C), (40.995+40.649) (1C), (35.385+34.736) (1C), 28.555 (3C). MS (ESI, CH_3OH): [$C_{15}H_{24}N_2O_2$] *m/z* 265.3 ([M+H]$^+$); *m/z* 279.3 ([M+Na]$^+$).

tert-Butyl 2-aminoethyl(4'-fluorophenethyl)carbamate (53k). The procedure to prepare **53k** is the same as that to prepare **51a** except using **52k** (0.708 g, 0.0025 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.501 g, 71%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.121 (m, 2H), 6.988-6.955 (m, 2H), 3.387 (m, 2H), 3.211-3.143 (m, 2H),

2.793 (m, 4H), 1.447 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (162.650+160.707) (1C), 155.935 (1C), 134.952 (1C), (130.404+130.343) (2C), (115.487+115.317) (2C), 79.756 (1C), (51.135+50.436) (1C), 49.866 (1C), (41.062+40.722) (1C), (34.541+33.843) (1C), 28.543 (3C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -117.349 (Ar-F). MS (ESI, CH_3OH): [$C_{15}H_{23}FN_2O_2$] *m/z* 283.2 ([M+H]$^+$); *m/z* 565.1 ([2M+H]$^+$.

***tert*-Butyl 2-aminoethyl(3'-fluorophenethyl)carbamate (53l).** The procedure to prepare **53l** is the same as that to prepare **51a** except using **52l** (0.708 g, 0.0025 mol) instead of **38**, The desired product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 9 : 1) to afford a colorless oil (0.494 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.291-7.223 (m, 1H), 6.921-6.889 (m, 3H), 3.413 (m, 2H), 3.226-3.140 (m, 2H), 2.807 (m, 4H), 1.448 (s, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.986+162.031) (1C), 155.892 (1C), 141.825 (1C), 130.046 (1C), (124.691+124.667) (1C), (115.918+115.748) (1C), (113.434+113.270) (1C), 79.816 (1C), (51.220+50.400) (1C), 49.550 (1C), (41.032+40.704) (1C), (35.106+34.438) (1C), 28.524 (3C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -113.969. MS (ESI, CH_3CN): [$C_{15}H_{23}FN_2O_2$] *m/z* 283.2 ([M+H]$^+$); *m/z* 565.1 ([2M+H]$^+$).

(±)-*tert*-Butyl 3-{{2'-[*tert*-butoxycarbonyl(3"-fluorophenethyl)amino]ethyl}(methyl)amino}-4-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}pyrrolidine-1-carboxylate (54b). The procedure to prepare 54b is the same as that to prepare 54a except using 47m (0.336 g, 0.5 mmol) instead of 47b, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 6 : 4) to afford a colorless oil (0.316 g, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.583-7.570 (m, 1H), 7.266-7.186 (m, 2H), 6.950-6.897 (m, 3H), 6.653-6.614 (m, 1H), 3.639-3.544 (m, 1H), 3.460-3.409 (m, 3H), 3.221-3.094 (m, 4H), 2.950-2.818 (m, 4H), 2.695-2.588 (m, 2H), 2.454-2.242 (m, 8H), 1.506-1.395 (m, 27H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ), (163.925+161.970) (1C), (159.104+158.995+158.764) (1C), 155.328 (1C), (154.963+154.884) (1C), 152.498 (1C), 151.484 (1C), (149.809+149.712) (1C), 141.867 (1C), 130.003 (1C), 124.594 (1C), 119.767 (1C), (115.845+115.681) (1C), (113.380+113.216+113.119) (1C), 110.022 (1C), (80.782+80.697) (1C), (79.731+79.598) (1C), (79.398+79.306) (1C), (66.392+65.779) (1C), (54.286+54.061+53.837) (1C), (49.878+49.599+49.429) (2C), (49.180+48.724+48.390) (1C), (45.670+45.537+44.936+44.760) (1C), (40.831+40.655+40.212+39.927) (2C), (35.094+34.559) (1C), 33.873 (1C), (28.646+28.597) (3C), 28.458 (3C), 28.342 (3C), 21.342 (1C). MS (ESI, CH_3OH): [$C_{37}H_{56}FN_5O_6$] *m/z* 686.7 ([M+H]$^+$); *m/z* 708.4 ([M+Na]$^+$).

(±)-*tert*-Butyl 3-{[6'-(*tert*-butoxycarbonylamino)-4'-methylpyridin-2'-yl]methyl}-4-{{2'-[(3"-fluorophenethyl)(methyl)amino]ethyl}(methyl)amino}pyrrolidine-1-carboxylate (55b). The procedure to prepare 55b is the same as that to prepare 55a except using 60a (0.105 g, 0.5 mmol) instead of 57a, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 6 : 4) to afford a colorless oil (0.228 g,

76%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.596-7.580 (m, 1H), 7.493 (brs, 1H), 7.225-7.182 (m, 2H), 6.949-6.934 (m, 1H), 6.899-6.846 (m, 2H), 6.619-6.605 (m, 1H), 3.657-3.622 (m, 0.5H), 3.564-3.530 (m, 0.5H), 3.434-3.412 (m, 1H), 3.255-3.145 (m, 2H), 3.016-2.987 (m, 1H), 2.834-2.572 (m, 9H), 2.411-2.245 (m, 11H), 1.504 (s, 9H), 1.479-1.448 (m, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (163.852+161.897) (1C), (159.135+159.025) (1C), (154.945+154.860) (1C), (152.559+152.541) (1C), (151.642+151.600) (1C), (149.730+149.633) (1C), (143.045+143.009+142.990+142.954) (1C), (129.833+129.767) (1C), 124.375 (1C), 119.658 (1C), (115.632+115.462) (1C), (112.997+112.967+112.833+112.797) (1C), 109.961 (1C), (80.679+80.600) (1C), (79.325+79.240) (1C), (66.781+66.113) (1C), (59.702+59.653) (1C), (55.075+54.960) (1C), (53.837+53.624) (1C), (49.829+49.356) (1C), (48.658+48.305) (1C), (42.871+42.732) (1C), (40.904+40.850) (1C), (40.497+40.091) (1C), (34.080+34.031) (1C), 33.479 (1C), (28.628+28.573) (3C), 28.324 (3C), 21.330 (1C). MS (ESI, CH_3OH): [$C_{33}H_{50}FN_5O_4$] *m/z* 600.4 ([M+H]$^+$); *m/z* 622.3 ([M+Na]$^+$).

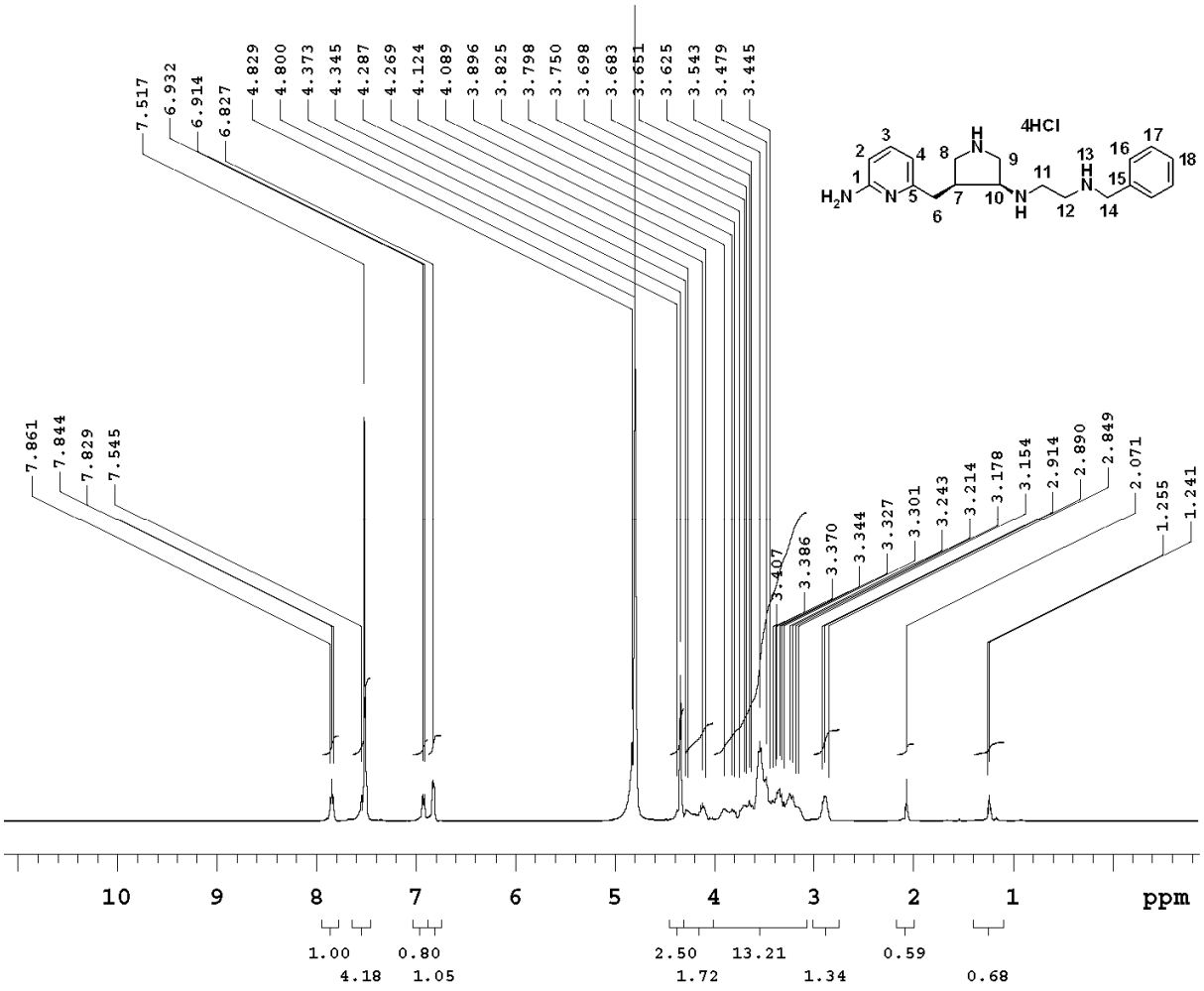
***tert*-Butyl 3-fluorophenethyl(2'-oxoethyl)carbamate (56b).** The procedure to prepare **56b** is the same as that to prepare **56a** except using **52l** (0.283 g, 0.001 mol) instead of **52b**, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc = 7.5 : 2.5) to afford a colorless oil (0.234 g, 83%). ^{1}H NMR ($CDCl_3$, 500MHz): δ (9.511+9.424) (s, 1H), 7.276-7.234 (m, 1H), 6.986-6.864 (m, 3H), 3.875 (s, 1H), 3.724 (s, 1H), 3.558-3.475 (m, 2H), 2.876-2.799 (m, 2H), 1.443-1.390 (m, 9H). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ (199.468+199.352+198.951+198.502) (1C), (164.089+162.128) (1C), (155.777+154.994) (1C), 141.363 (1C), (130.277+130.240) (1C), (124.727+124.691) (1C), (115.972+115.802) (1C), (113.744+113.689+113.574+113.519) (1C), (81.176+80.921) (1C), (58.499+57.813) (1C), (50.631+50.546) (1C), (35.191+34.723) (1C), (28.415+28.373) (3C). MS (ESI, CH_3OH): [$C_{15}H_{20}FNO_3$] *m/z* 282.1([M+H]$^+$); *m/z* 585.2([2M+Na]$^+$).

(±)-*tert*-Butyl 3-{2-[*tert*-butoxycarbonyl(3-fluorophenethyl)amino]ethylamino}-4-{[2-(*tert*-butoxycarbonylamino)-6-methylpyridin-4-yl]methyl}pyrrolidine-1-carboxylate (66b). The procedure to prepare **66b** is the same as that to prepare **66a** except using **56b** (0.141 g, 0.5 mmol) instead of **56a**, The desired product was purified by column chromatography (silica gel, hexanes : EtOAc : Et_3N = 9 : 1 : 0.5) to afford a colorless oil (0.265 g, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (8.419+8.354) (s, 1H), 7.645 (s, 1H), 7.250-7.222 (m, 1H), 6.948-6.901 (m, 3H), 6.647 (s, 1H), 3.452-3.108 (m, 9H), 2.839-2.825 (m, 4H), 2.672 (m, 1H), 2.468-2.449 (m, 2H), (2.412+2.393) (s, 3H), 1.479-1.449 (m, 27H). ^{13}C NMR ($CDCl_3$, 100.7 MHz): δ (164.036+161.597) (1C), 156.606 (1C), (155.621+155.348) (1C), (154.705+154.667) (1C), 152.644 (1C), 152.205 (1C), (151.895+151.811) (1C), (141.745+141.677) (1C), (129.915+129.839) (1C), (124.552+124.522) (1C), 118.546 (1C), (115.774+115.562) (1C), (113.222+113.010) (1C), (109.382+109.306) (1C), 80.396 (1C), 79.578 (1C), 79.184 (1C), (59.280+58.439) (1C), (50.819+50.160) (1C), (49.502+49.358) (1C),

(48.820+48.608) (1C), (48.176+47.214) (1C), 46.487 (1C), (43.109+42.458) (1C), (34.952+34.278) (1C), (32.824+32.604) (1C), 28.423 (3C), 28.340 (3C), 28.181 (3C), 23.742 (1C). ^{19}F NMR ($CDCl_3$, 376.5 MH_Z): δ -113.911 (Ar-F). MS (ESI, CH_3OH): [$C_{36}H_{54}FN_5O_6$] *m/z* 672.8 ([M+H]$^+$); *m/z* 694.8 ([M+Na]$^+$); *m/z* 1365.4 ([2M+Na]$^+$).

Supplementary Table. Elemental analysis data of highly potent and selective nNOS inhibitors.

		Calcd.			Found		
Compd	Formula	C	H	N	C	H	N
7	$C_{19}H_{31}Cl_4N_5 + 1.75\ H_2O$	45.39	6.92	13.93	45.38	6.78	13.66
9	$C_{19}H_{31}Cl_4N_5 + 1.56\ H_2O$	45.70	6.89	14.02	46.09	6.99	13.61
11	$C_{14}H_{27}Cl_4N_5 + 2\ H_2O$	37.94	7.05	15.80	38.04	7.20	15.52
14	$C_{21}H_{33}Cl_4N_5 + 1.45\ H_2O$	48.19	6.91	13.38	48.43	7.19	13.11
16	$C_{20}H_{32}Cl_5N_5 + 1.75\ H_2O$	43.57	6.49	12.70	44.03	6.33	12.30
17	$C_{20}H_{32}Cl_5N_5 + 0.75\ H_2O$	45.05	6.33	13.13	45.41	6.21	12.87
23	$C_{20}H_{31}Cl_6N_5 + 1.665\ H_2O$	41.12	5.92	11.99	41.52	5.98	11.47
24	$C_{21}H_{35}Cl_4N_5 + 1.5\ H_2O$	47.92	7.28	13.30	47.99	7.18	13.06
25	$C_{21}H_{34}Cl_4FN_5 + 2.3\ H_2O$	45.14	6.96	12.53	45.59	6.84	12.17
26	$C_{21}H_{34}Cl_4FN_5 + 1.5\ H_2O$	46.33	6.85	12.87	46.59	6.71	12.68
29	$C_{21}H_{34}Cl_5N_5 + 2\ H_2O$	44.26	6.72	12.29	44.27	6.63	12.12
30	$C_{21}H_{34}Cl_5N_5 + 0.6\ H_2O$	46.31	6.51	12.86	46.34	6.43	12.65
31	$C_{22}H_{36}Cl_4FN_5 + 1.5\ H_2O$	47.32	7.04	12.54	47.53	7.00	12.59



Supplementary Figure

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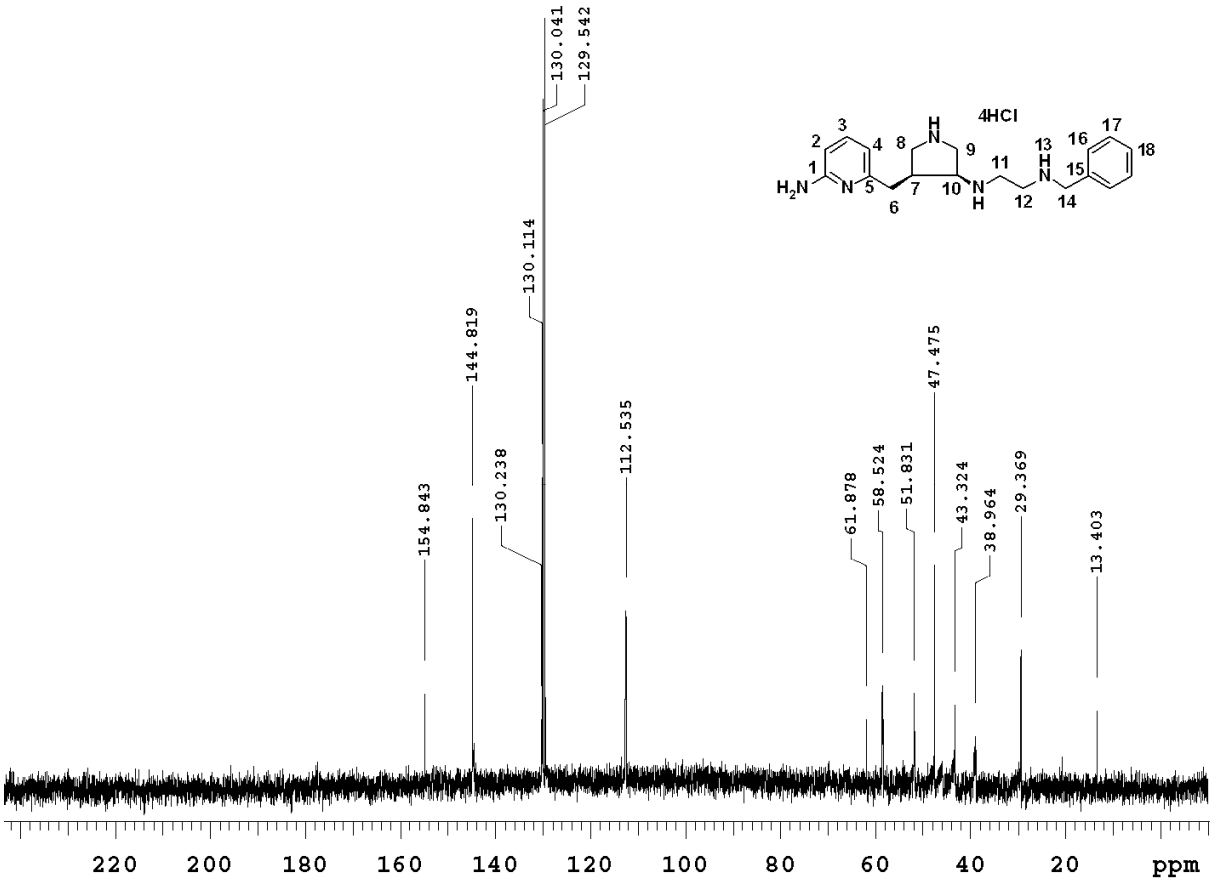

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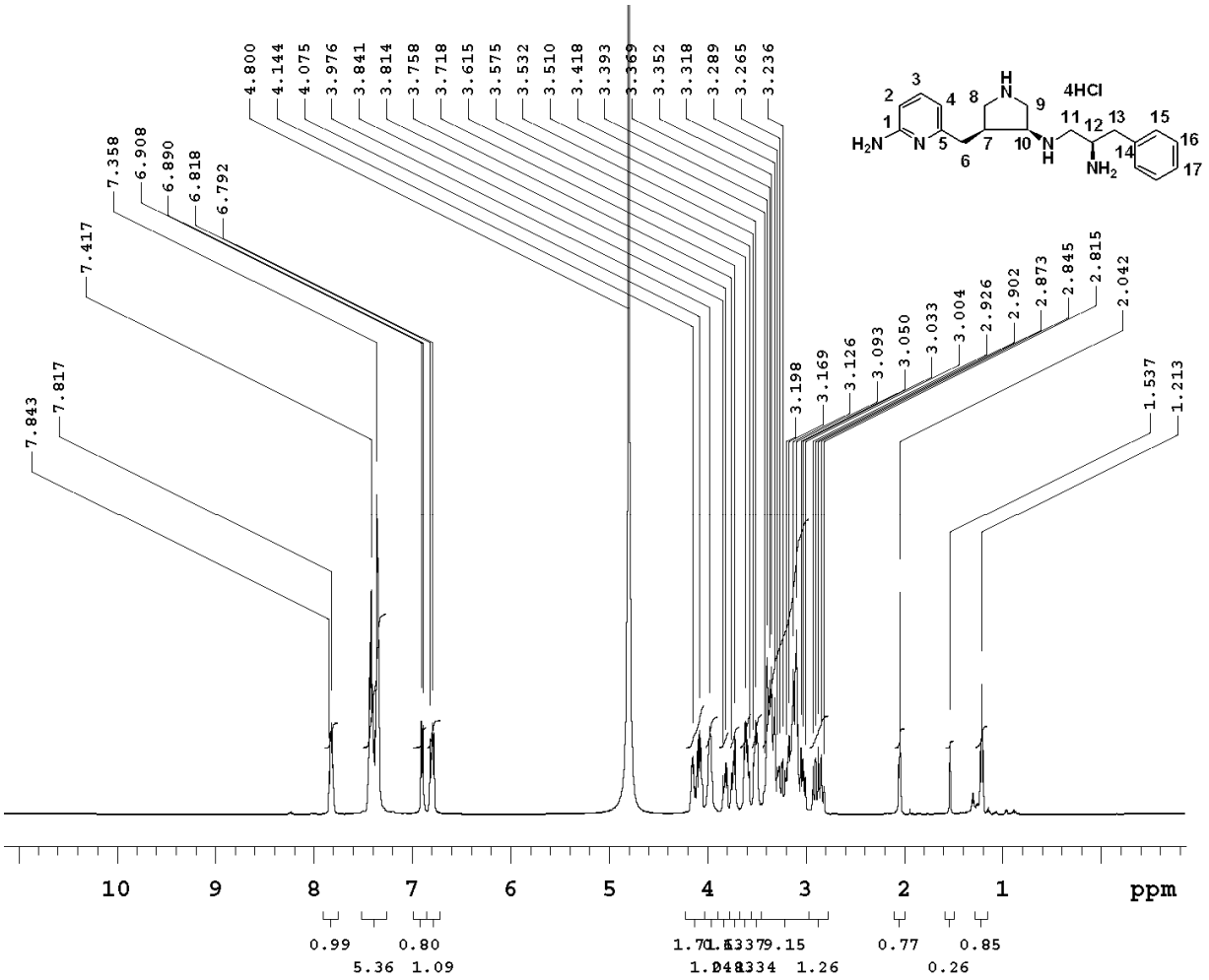

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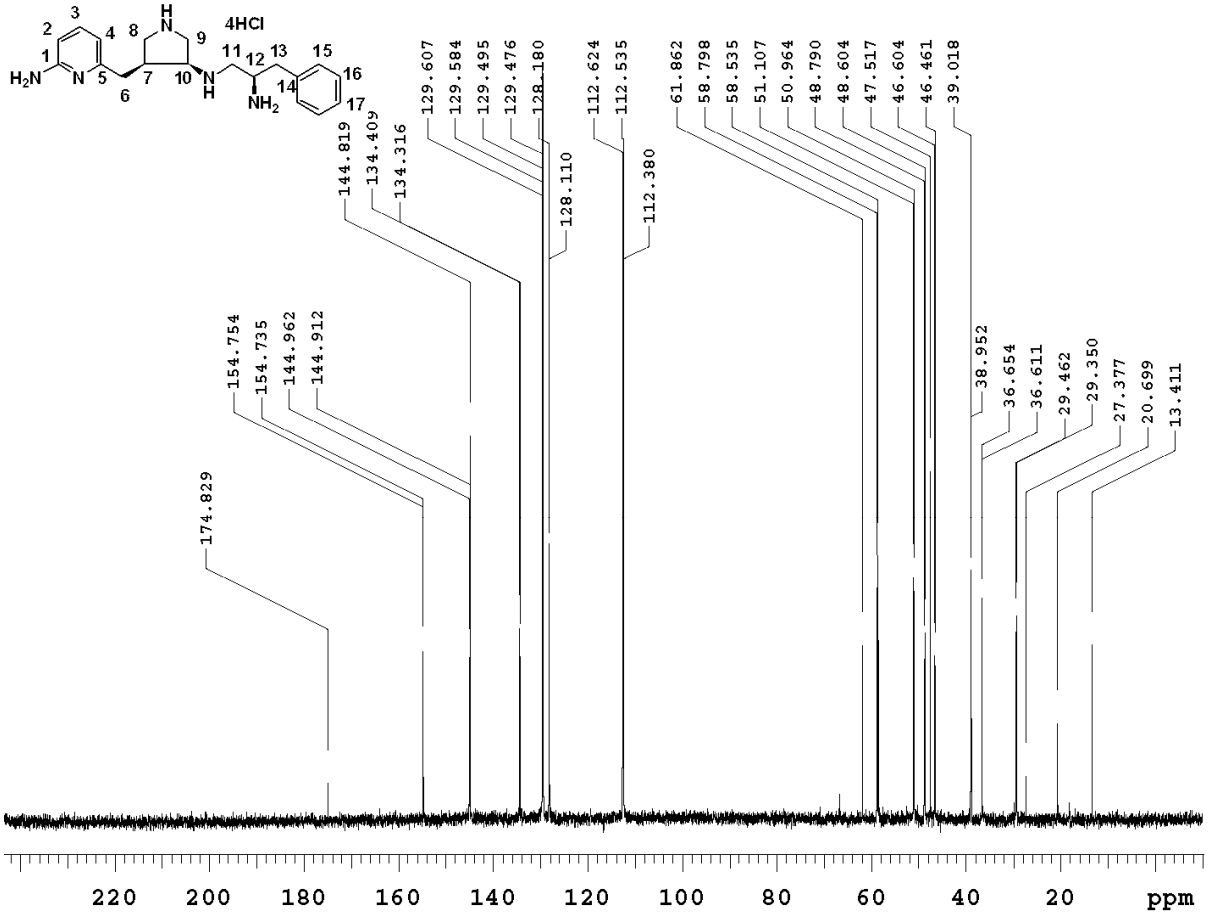

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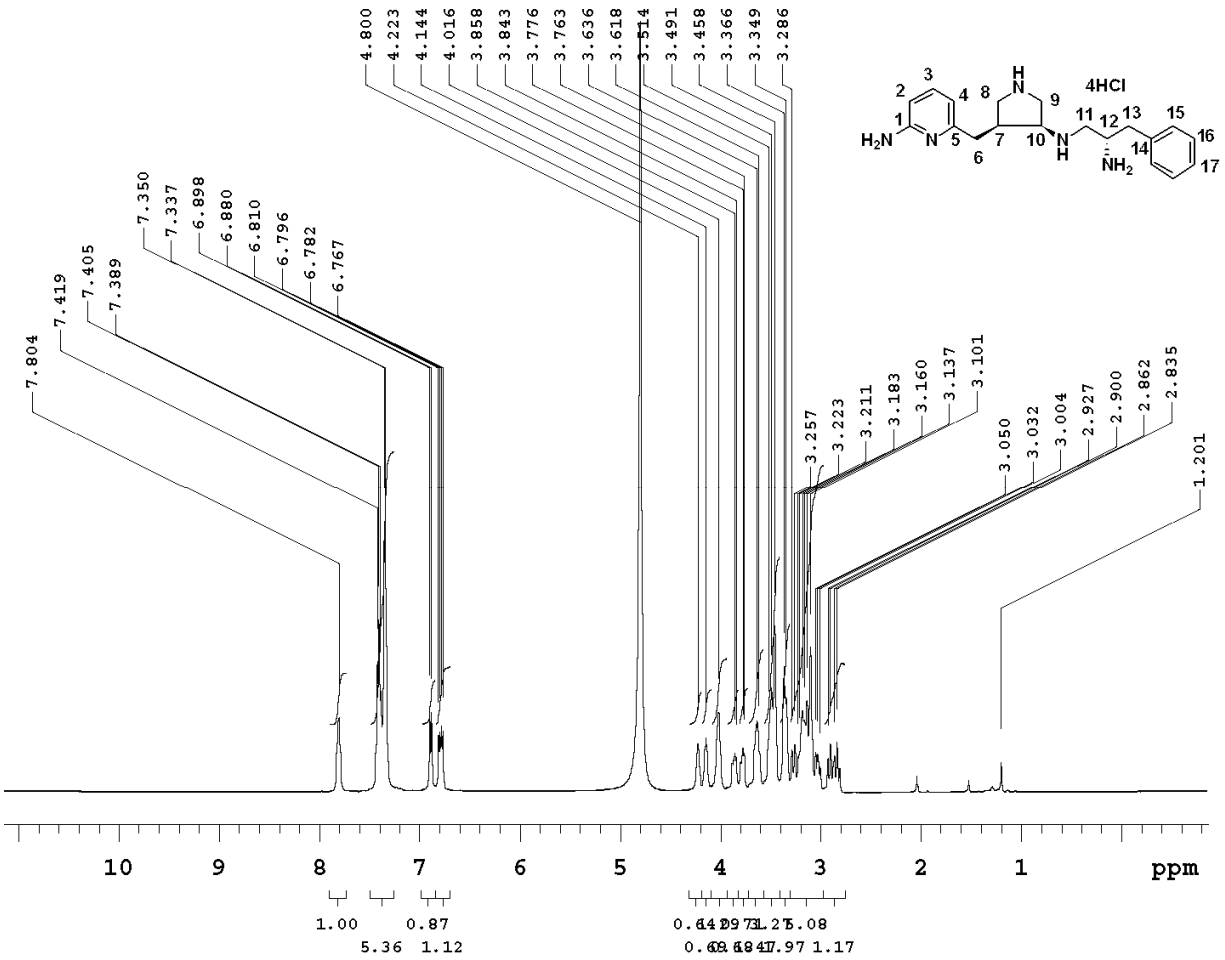

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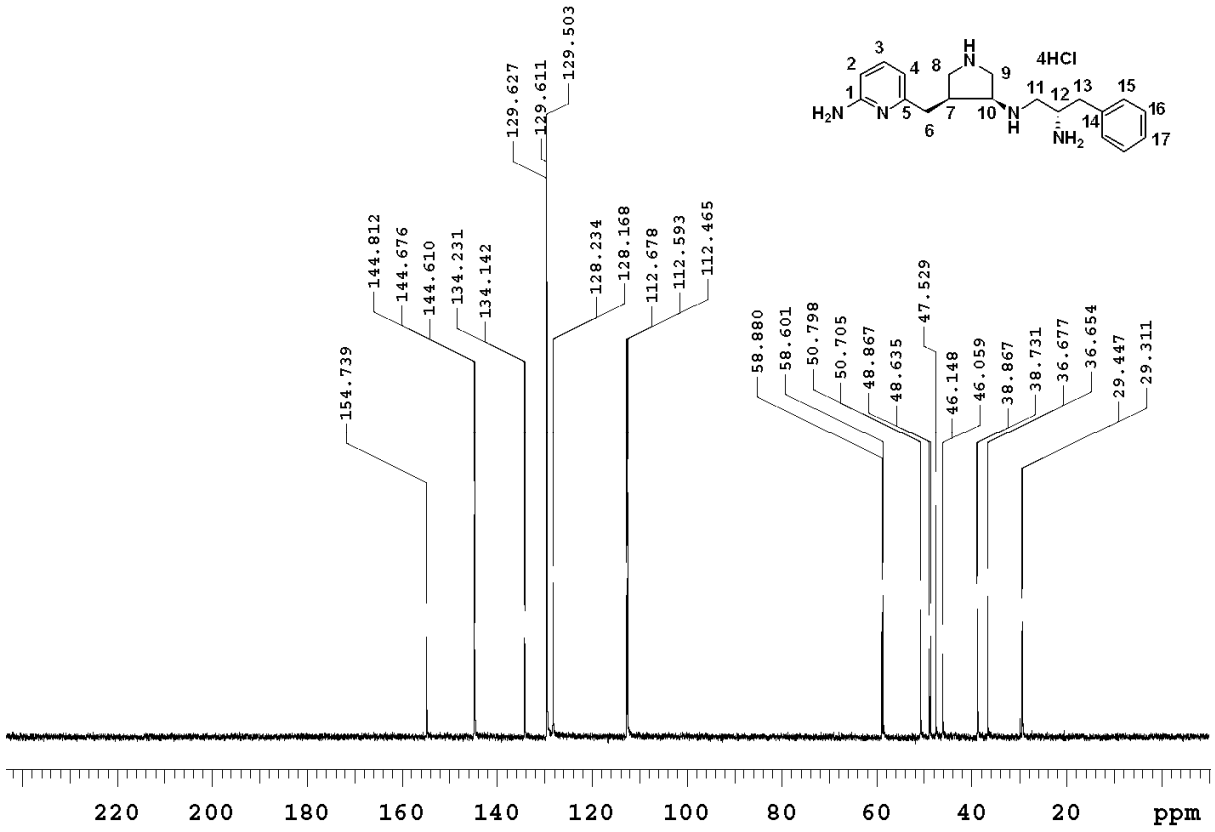

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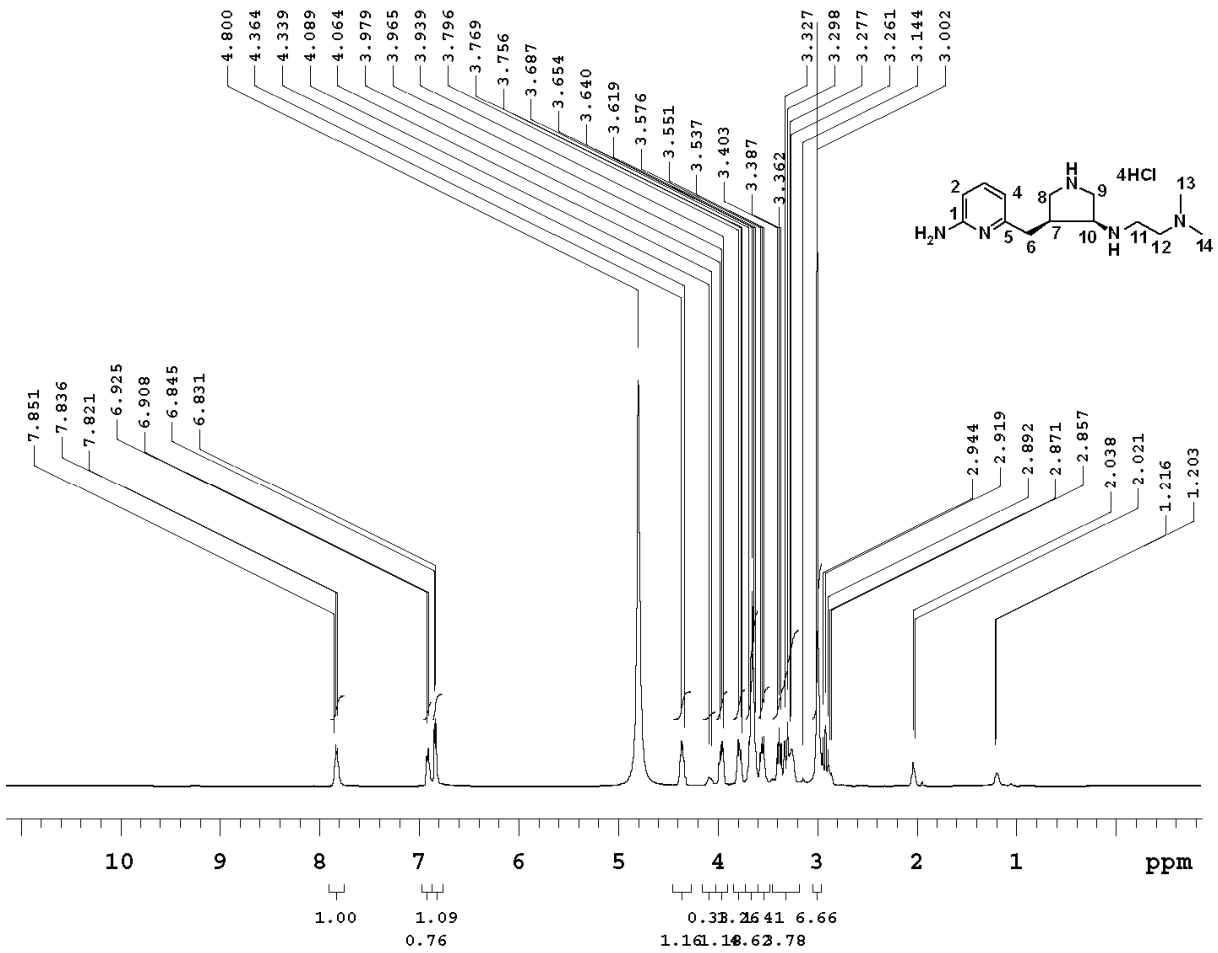

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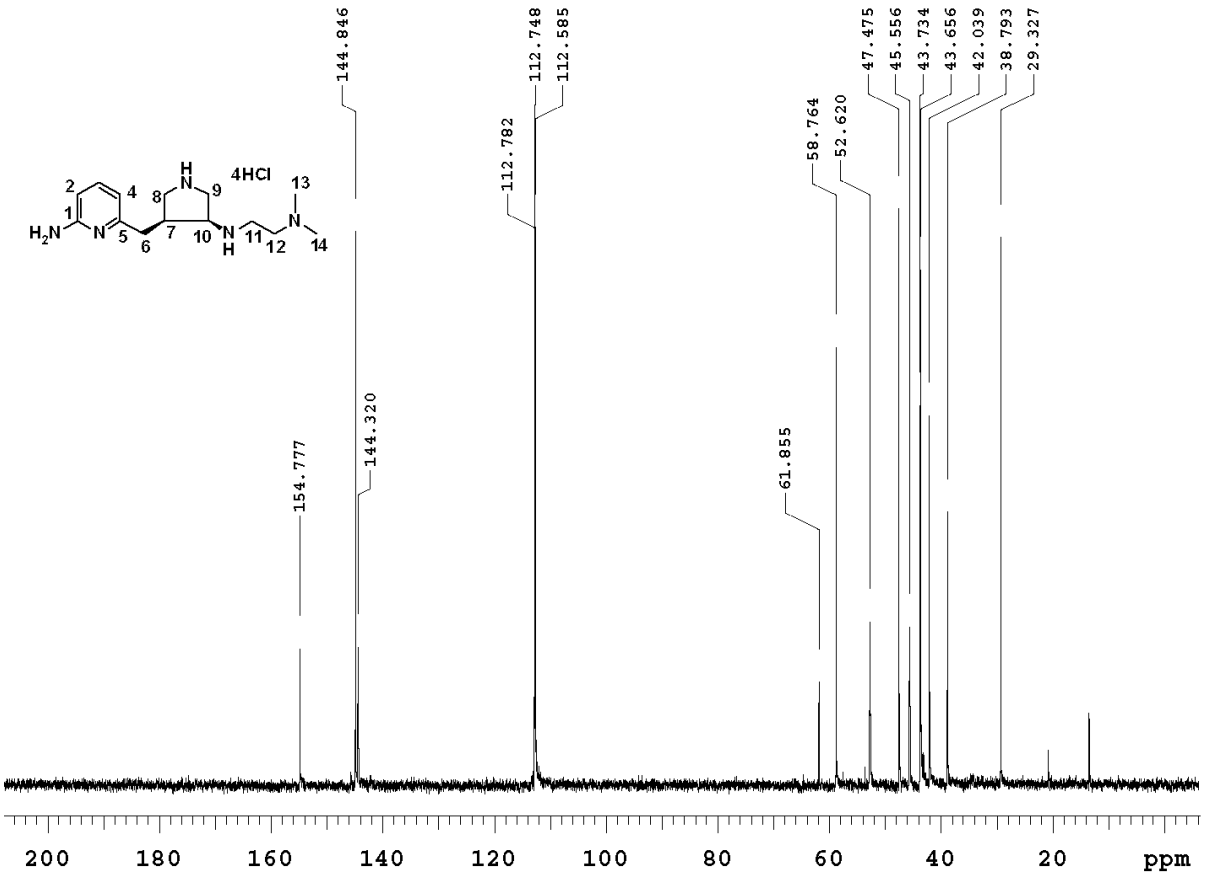

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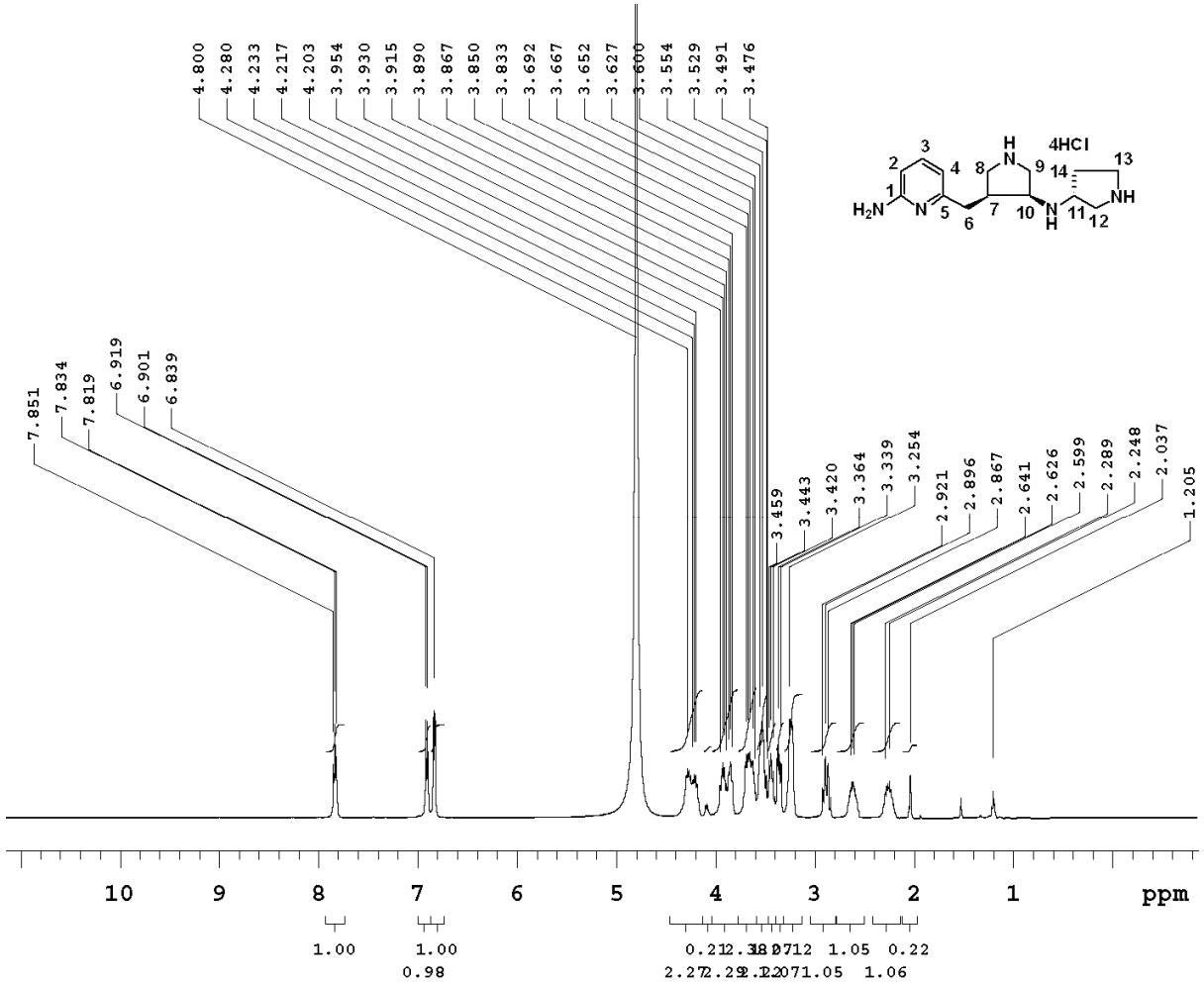

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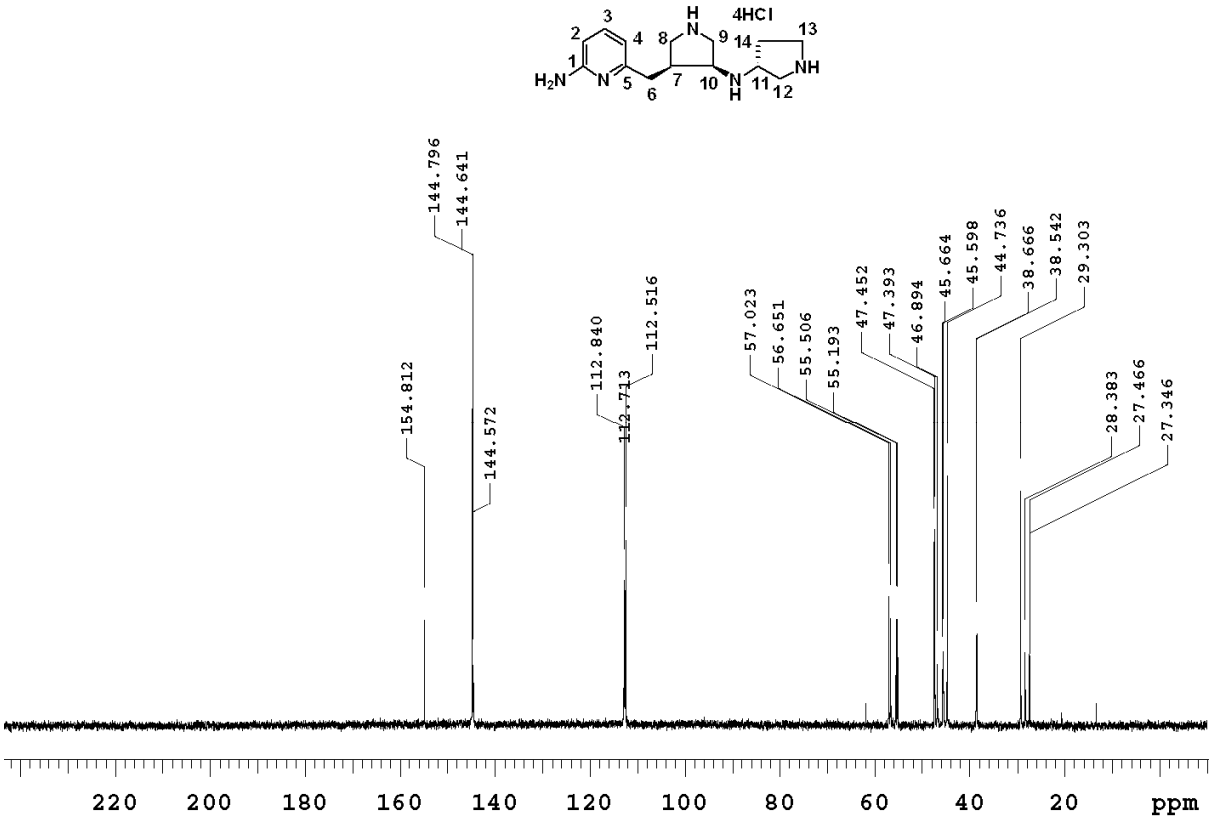

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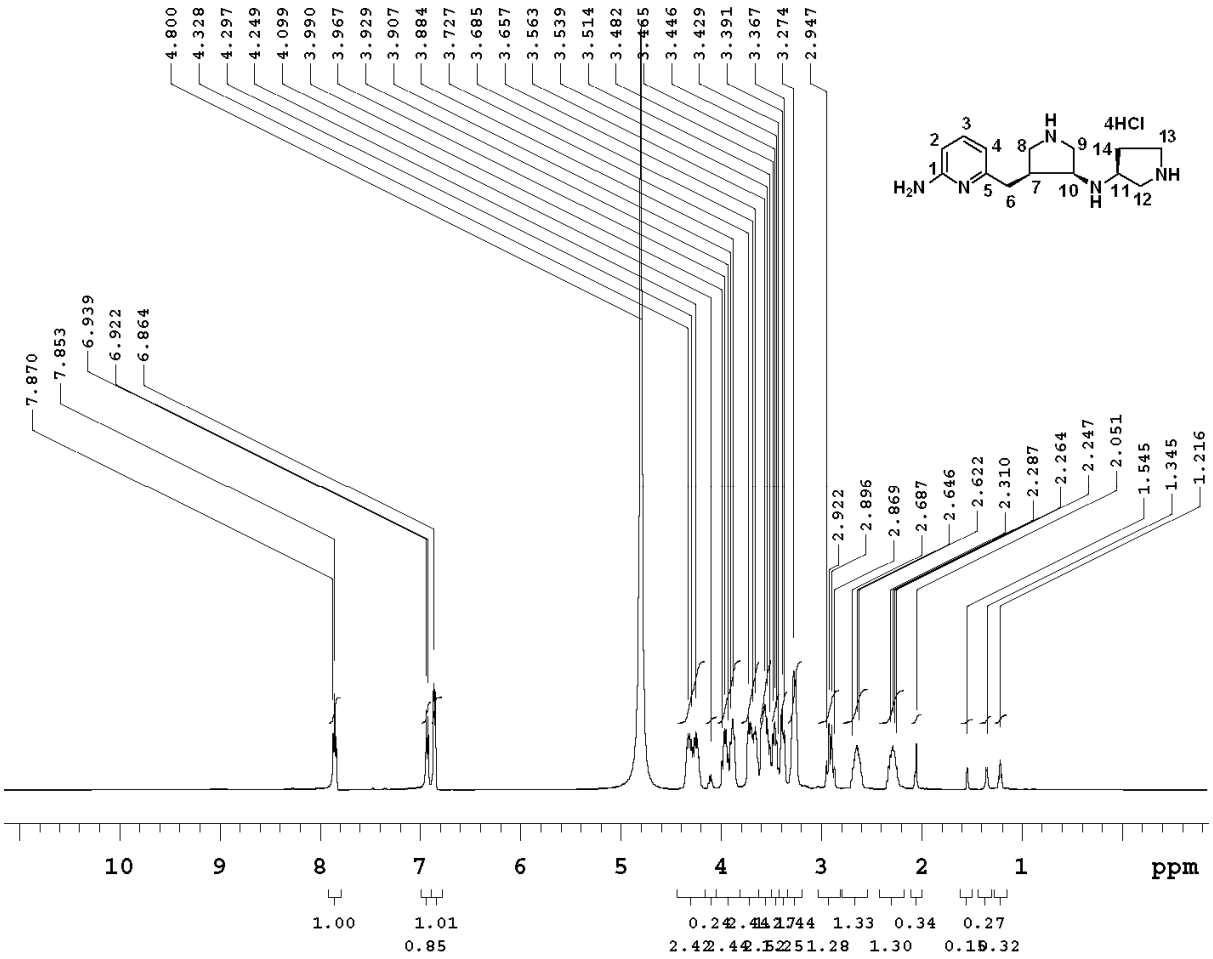

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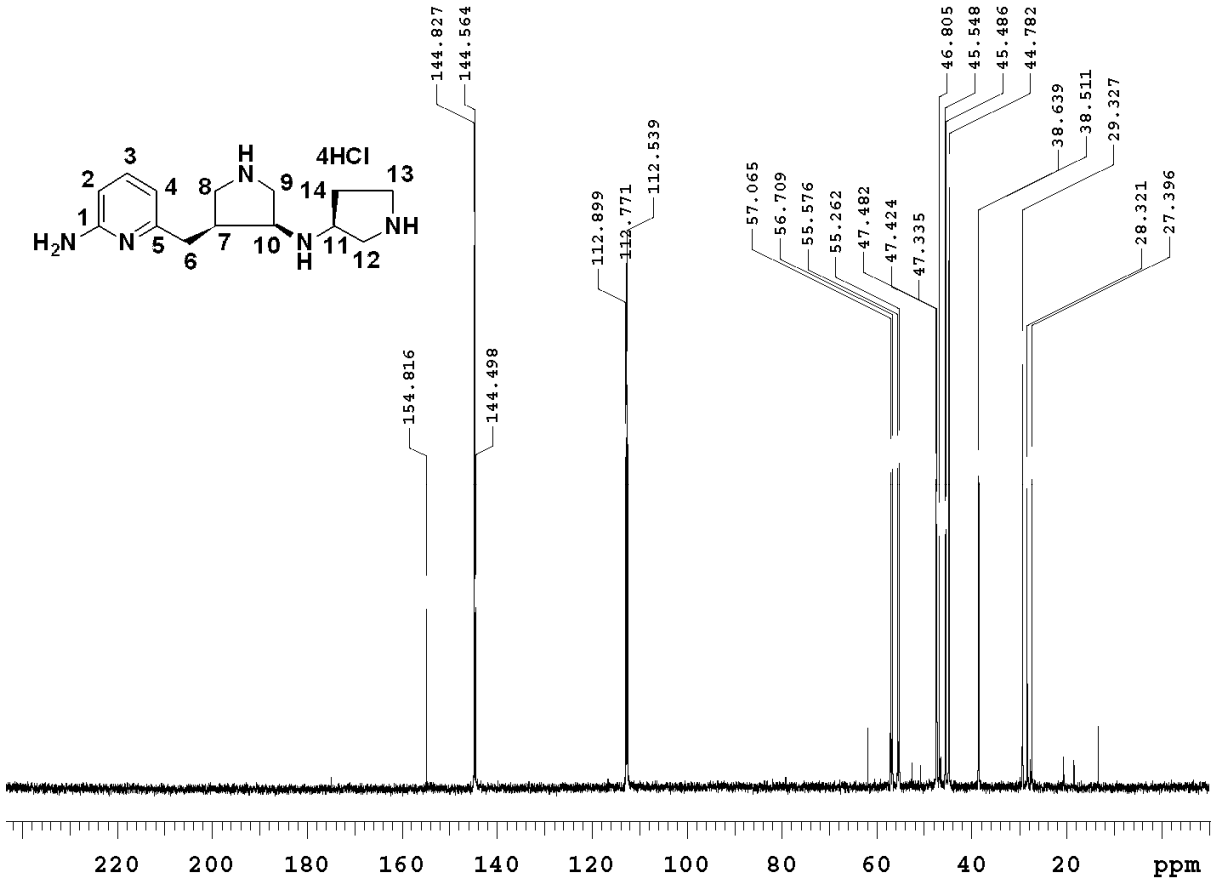

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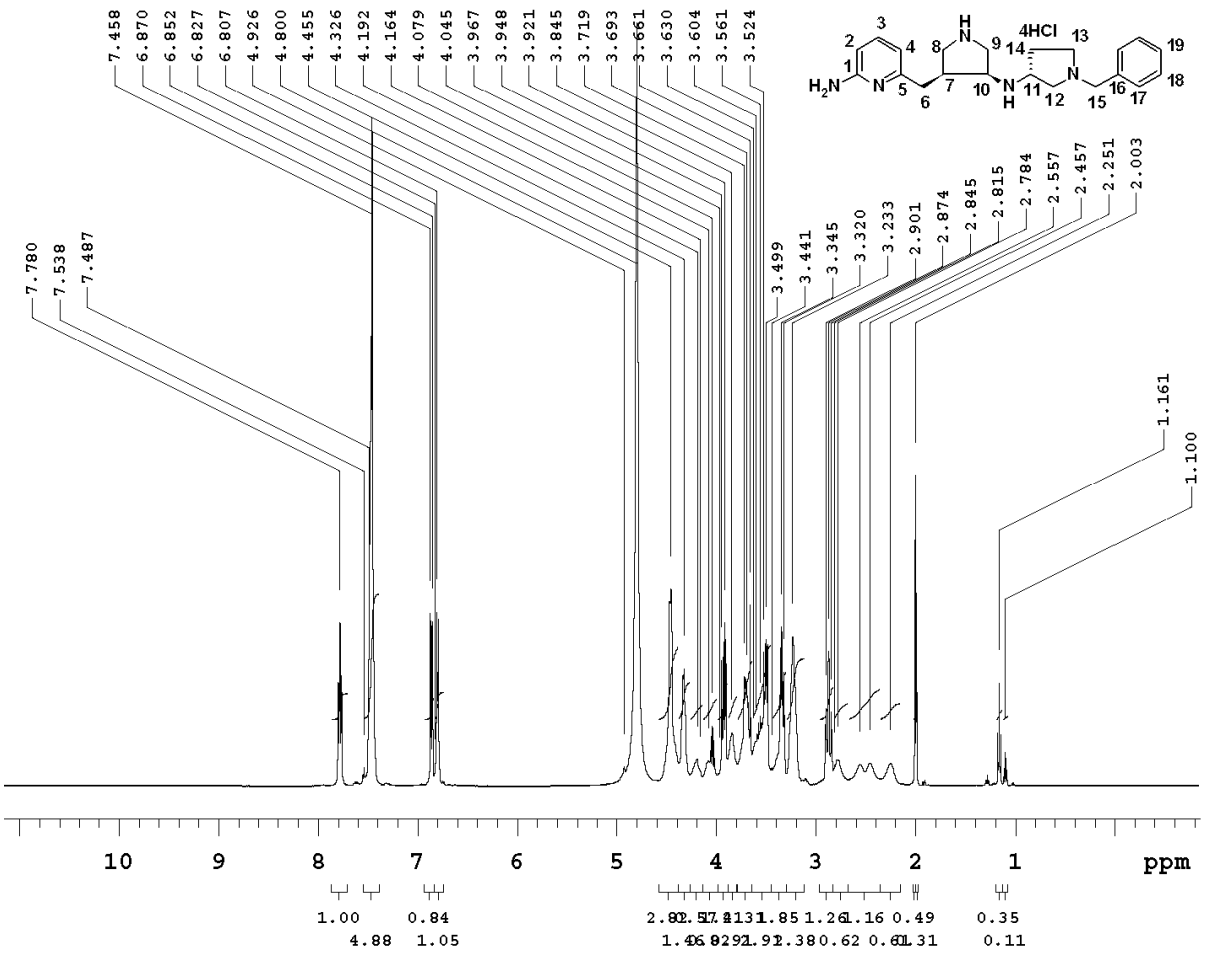

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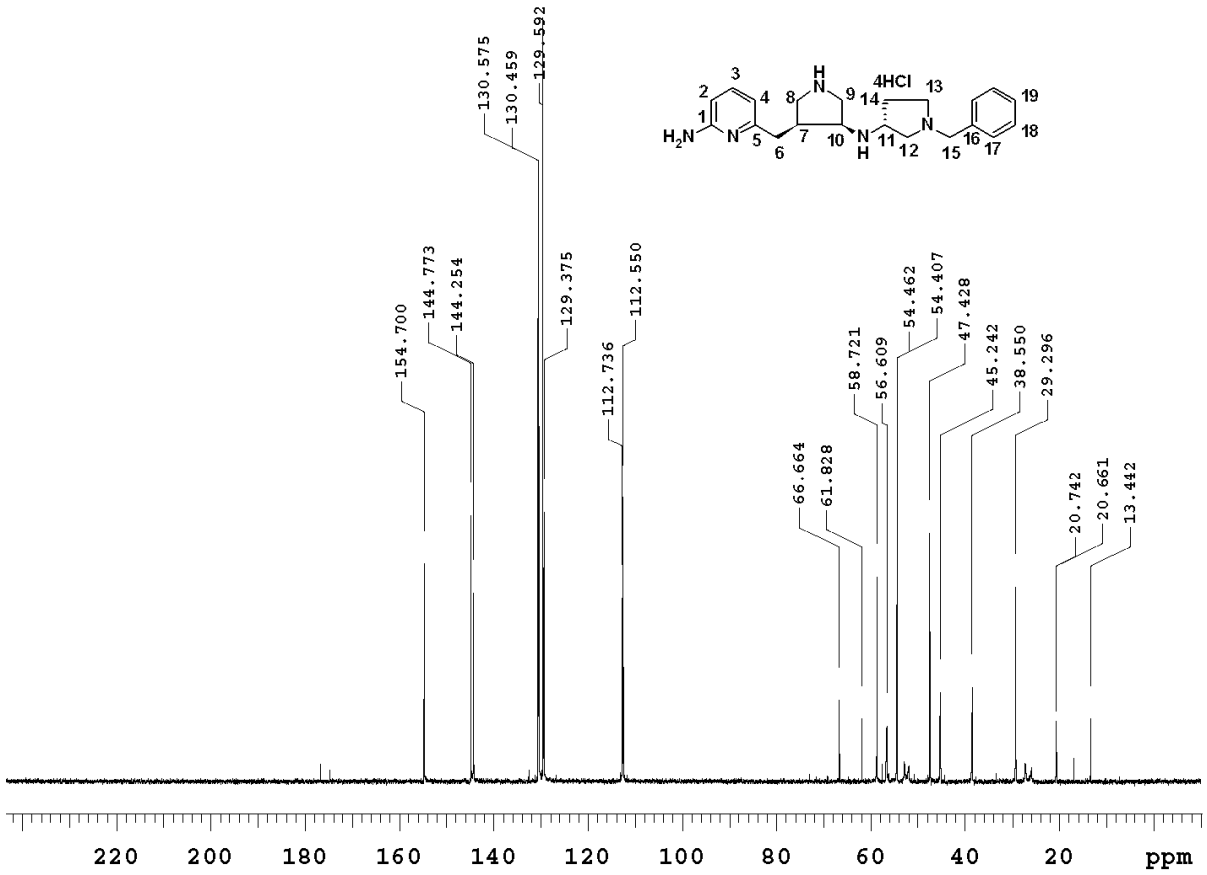

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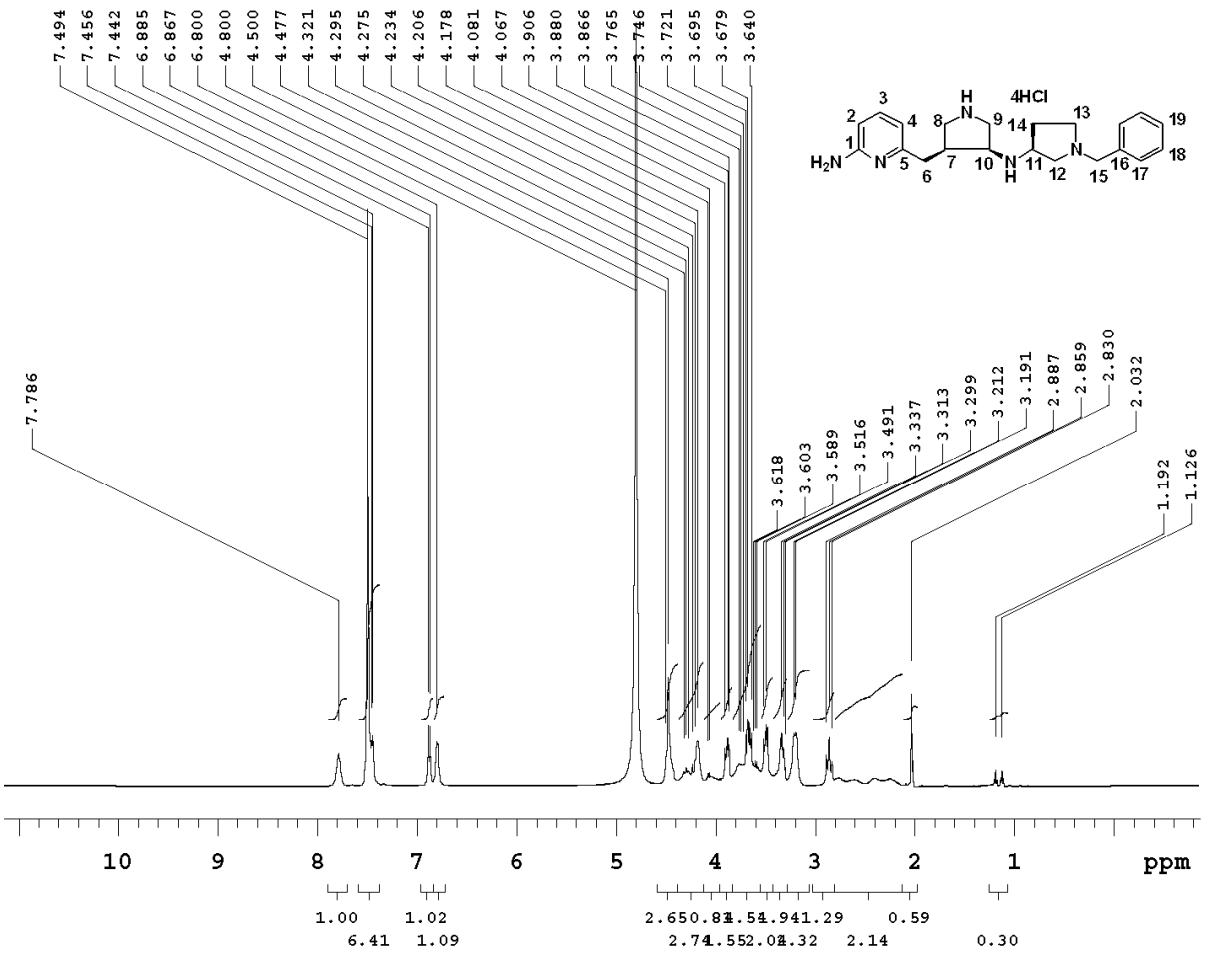

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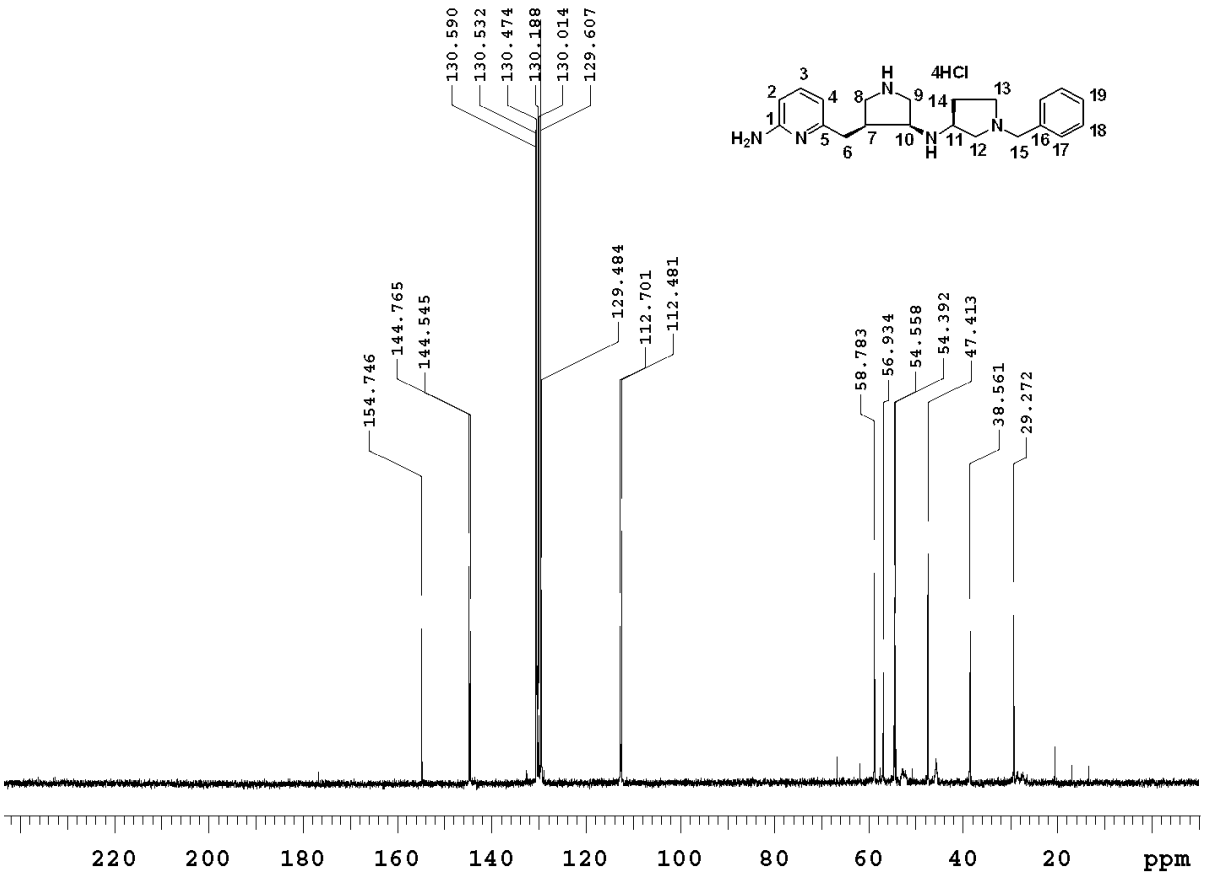

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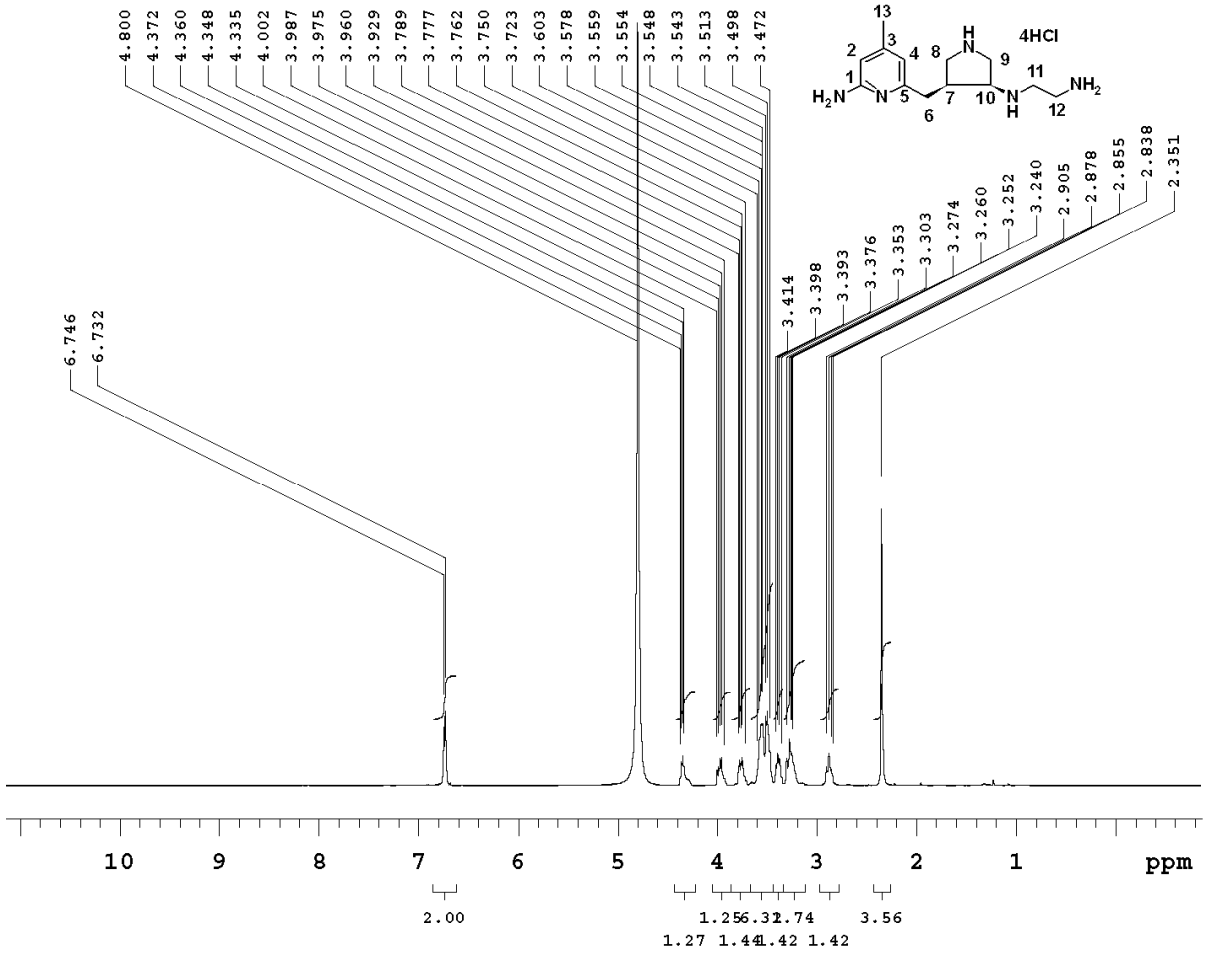

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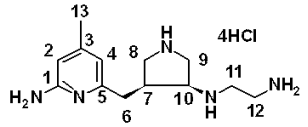

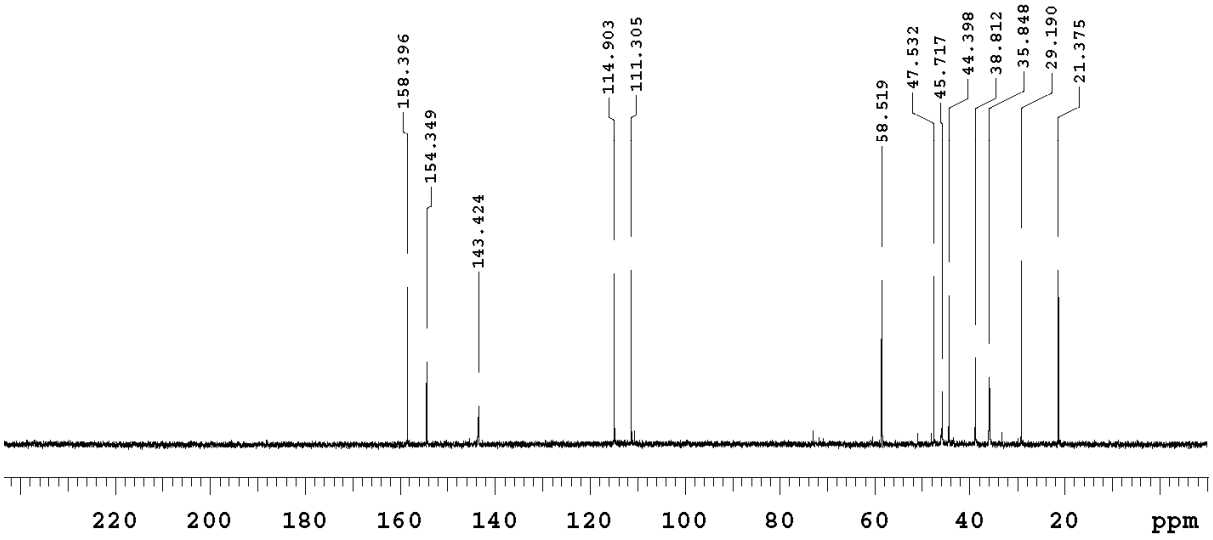

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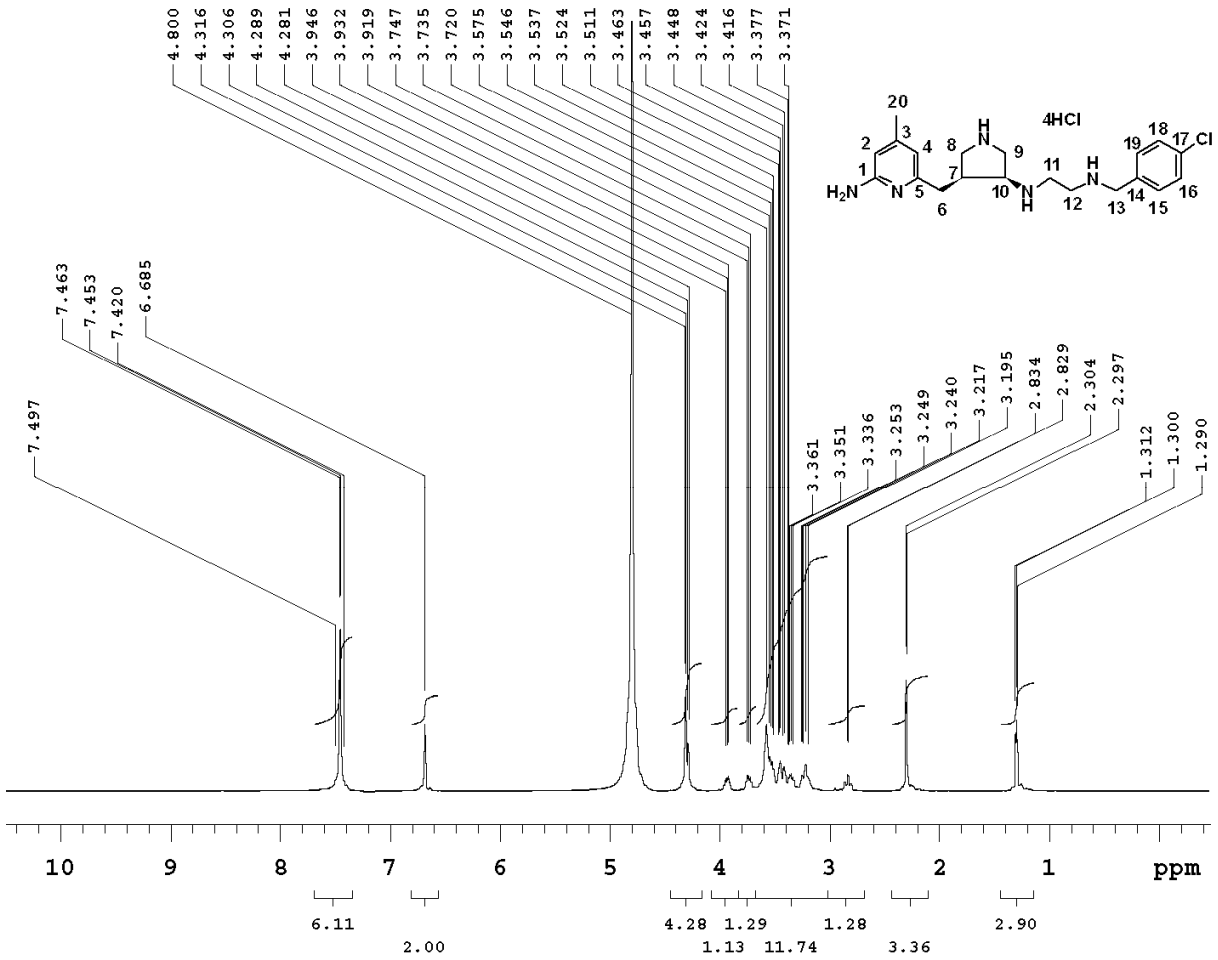

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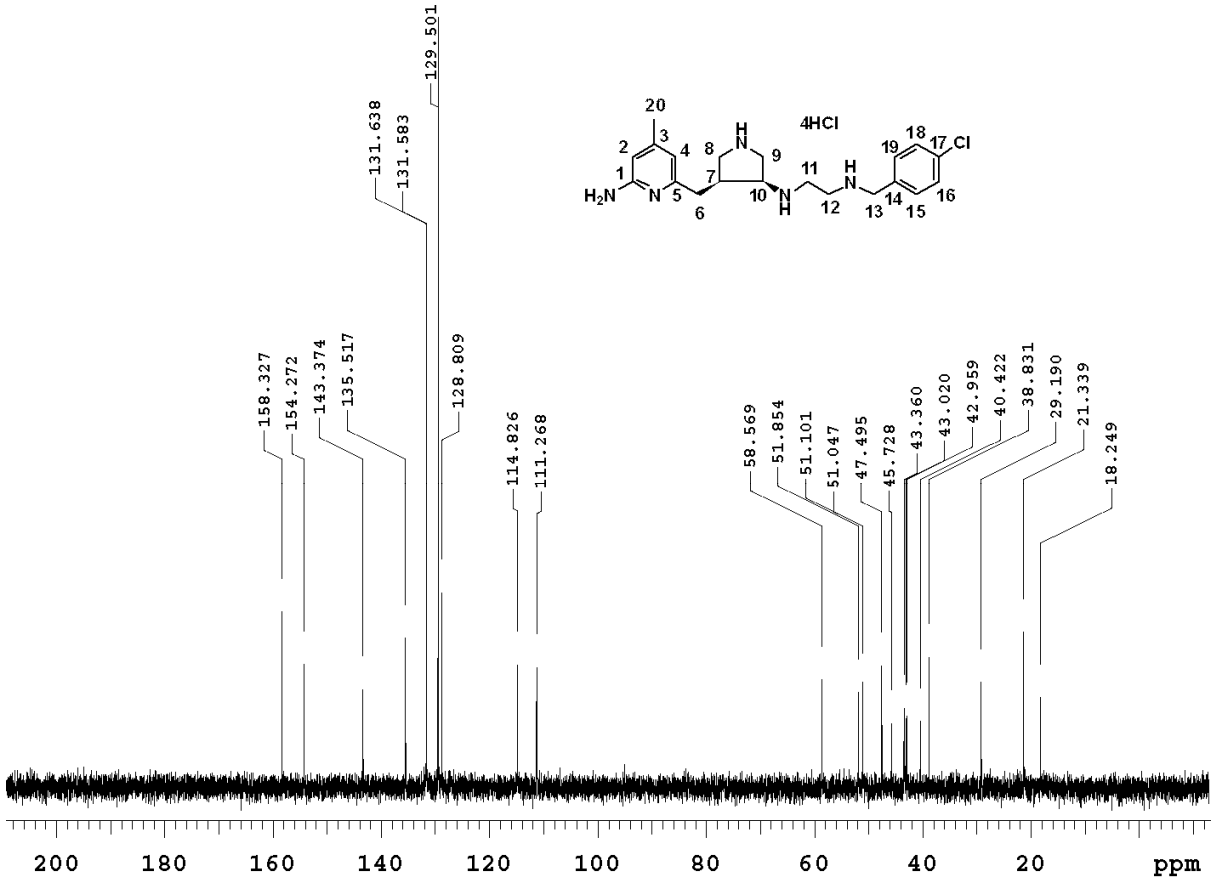

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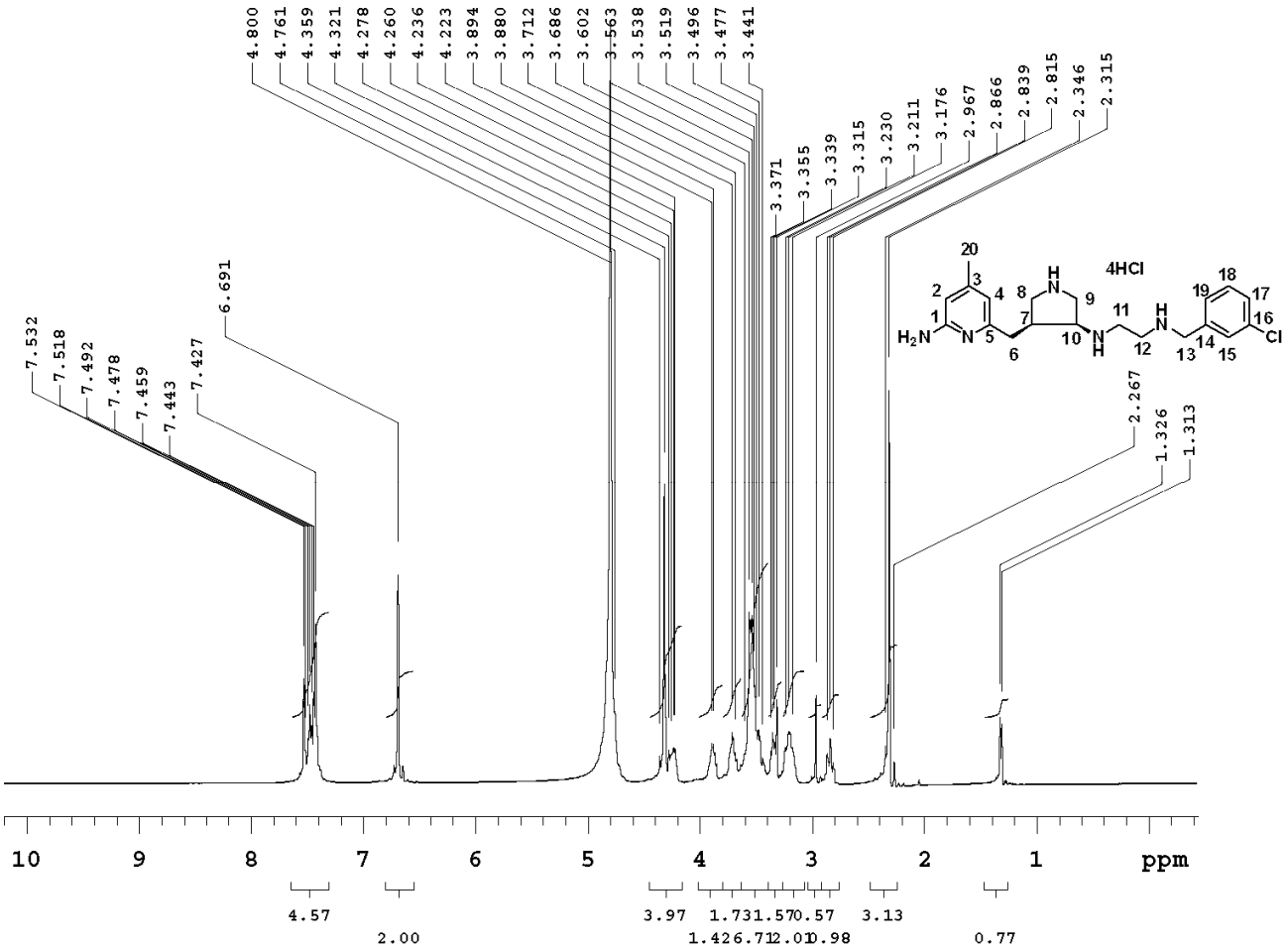

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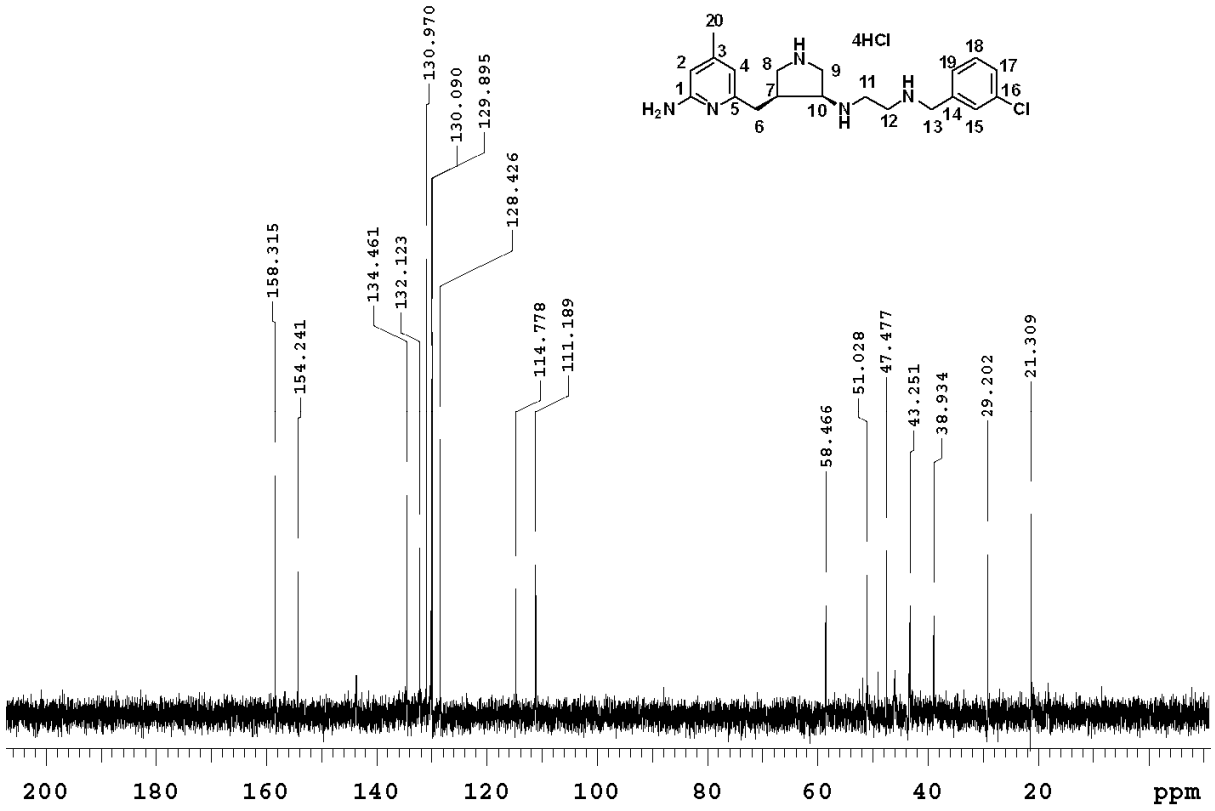

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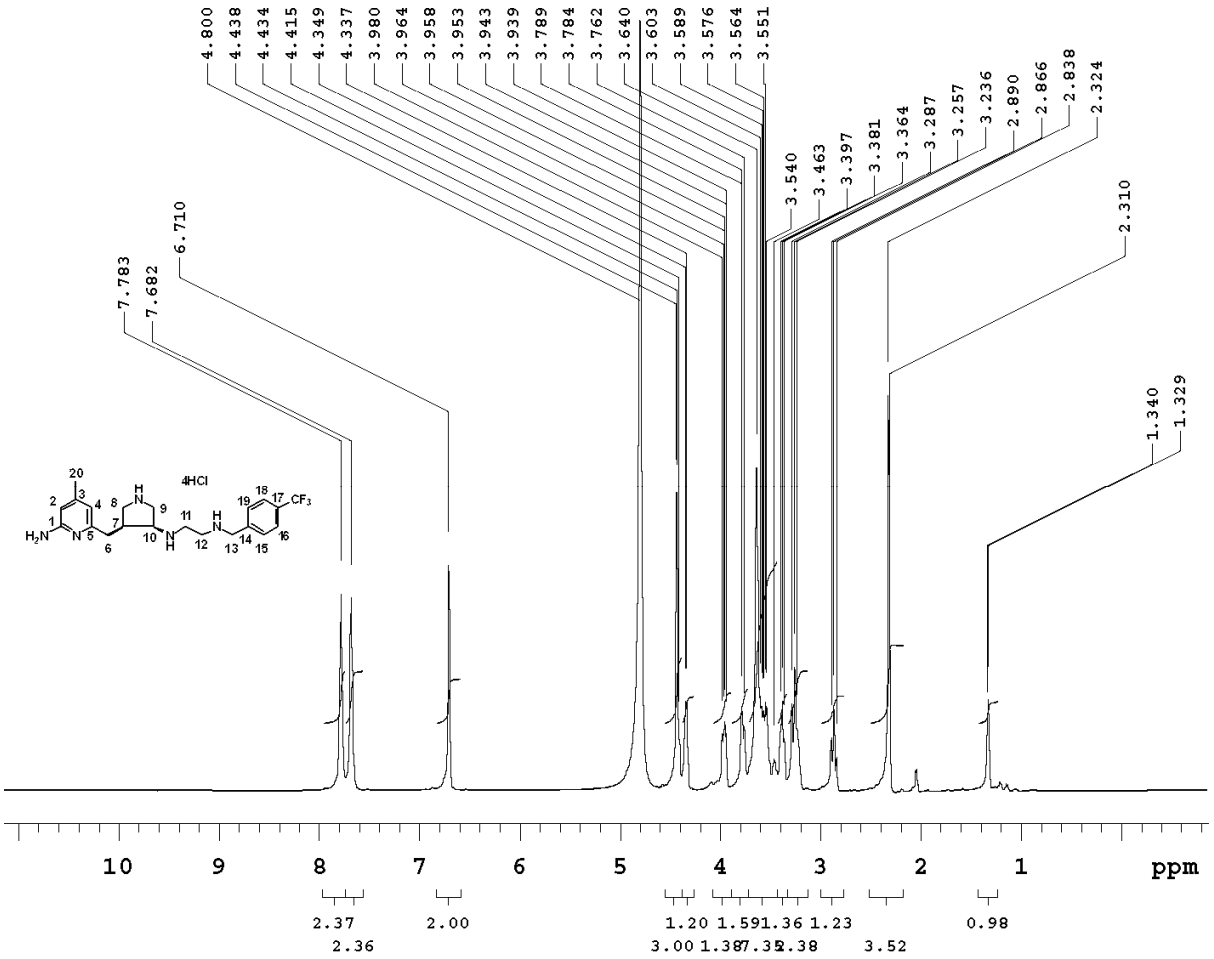

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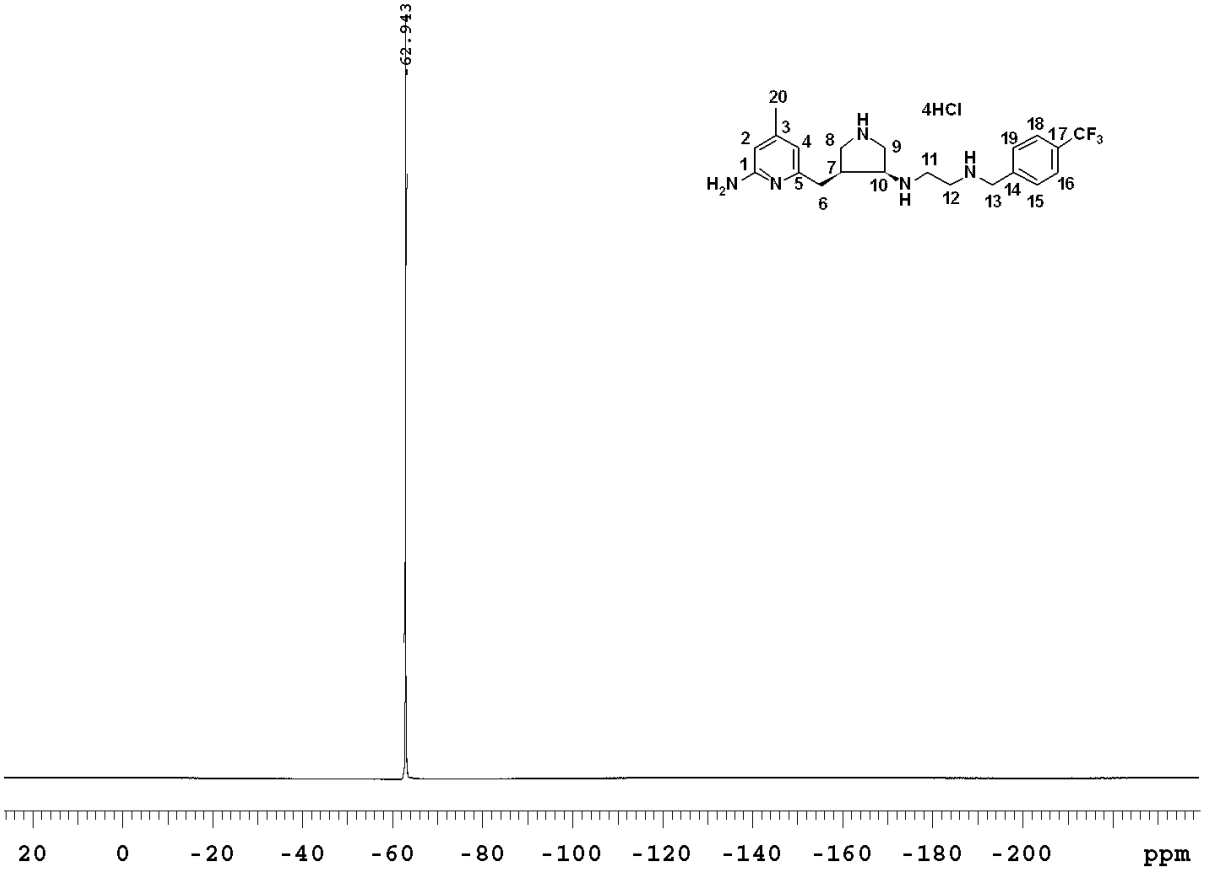

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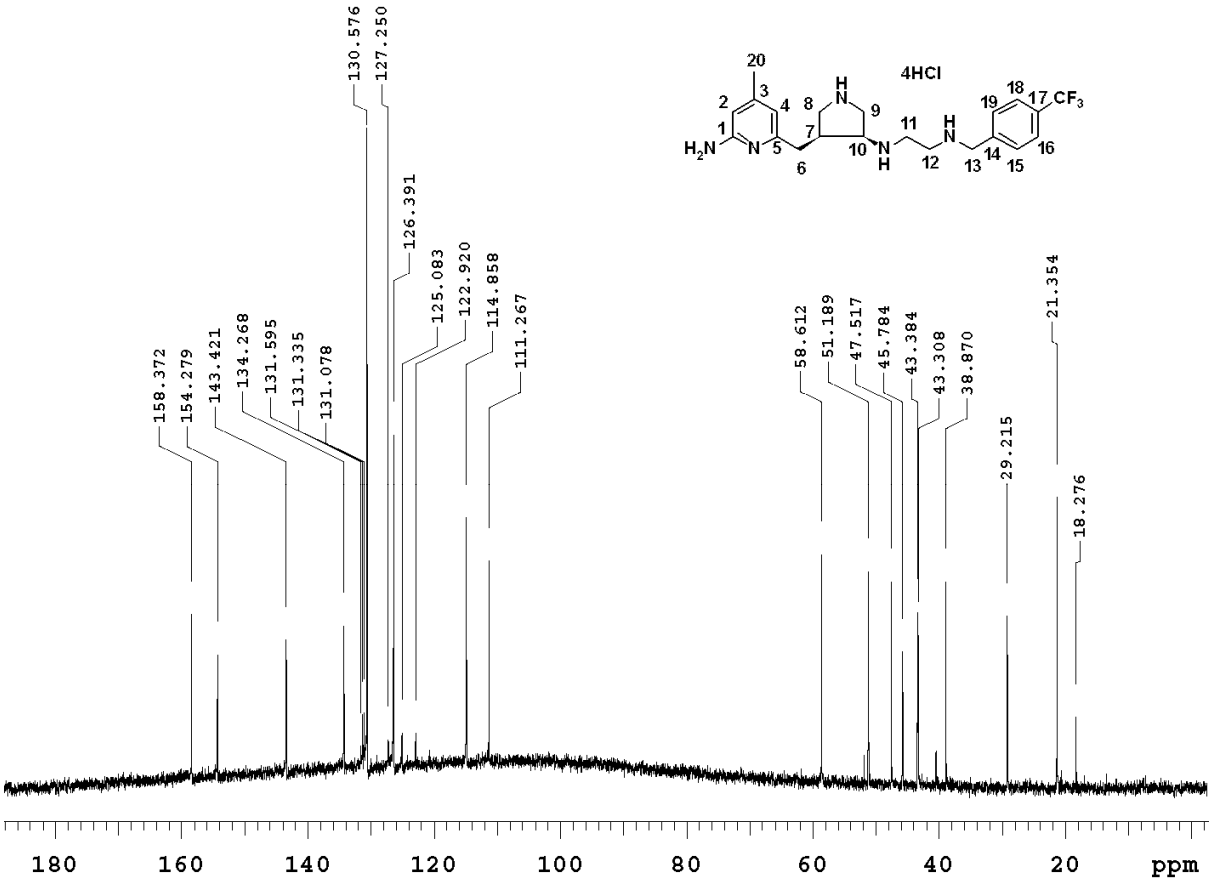

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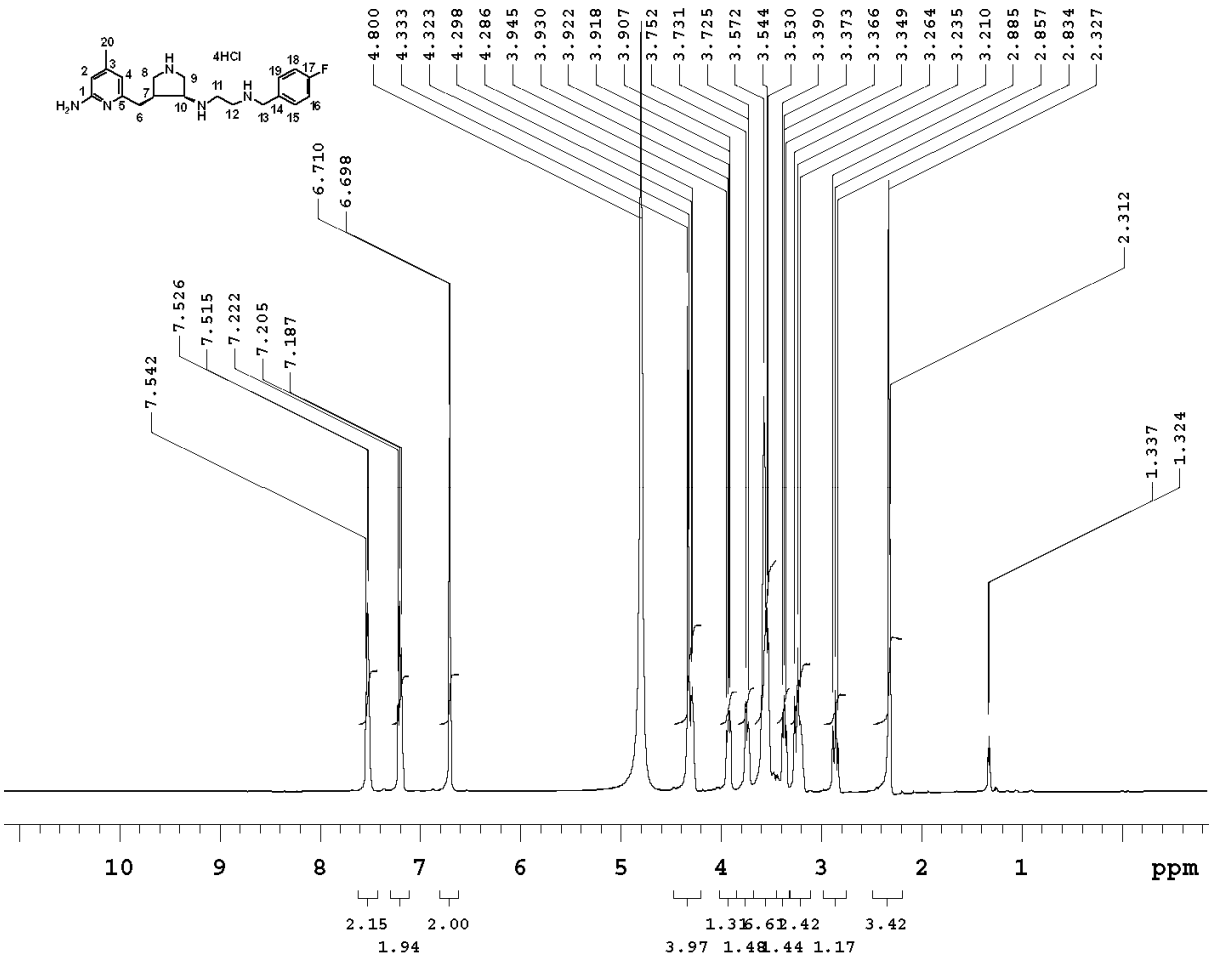

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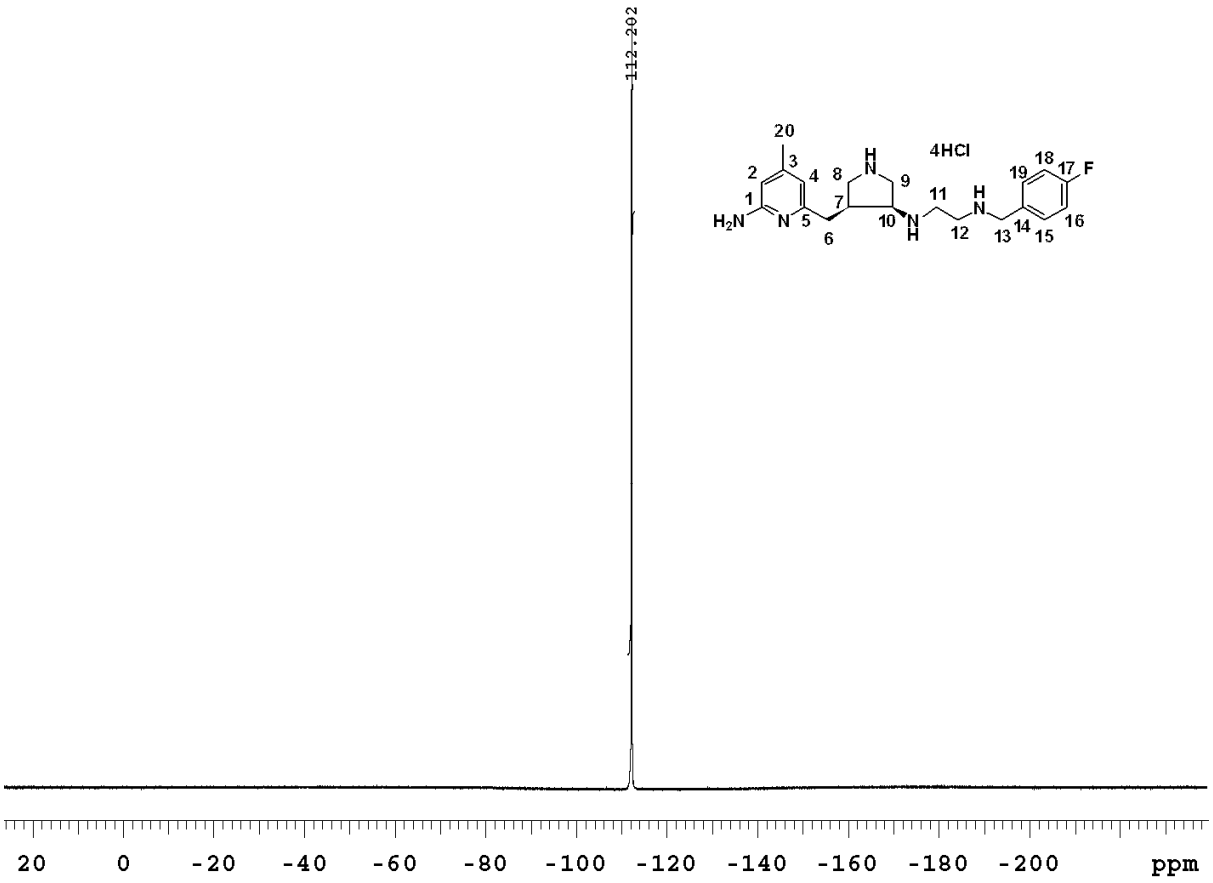

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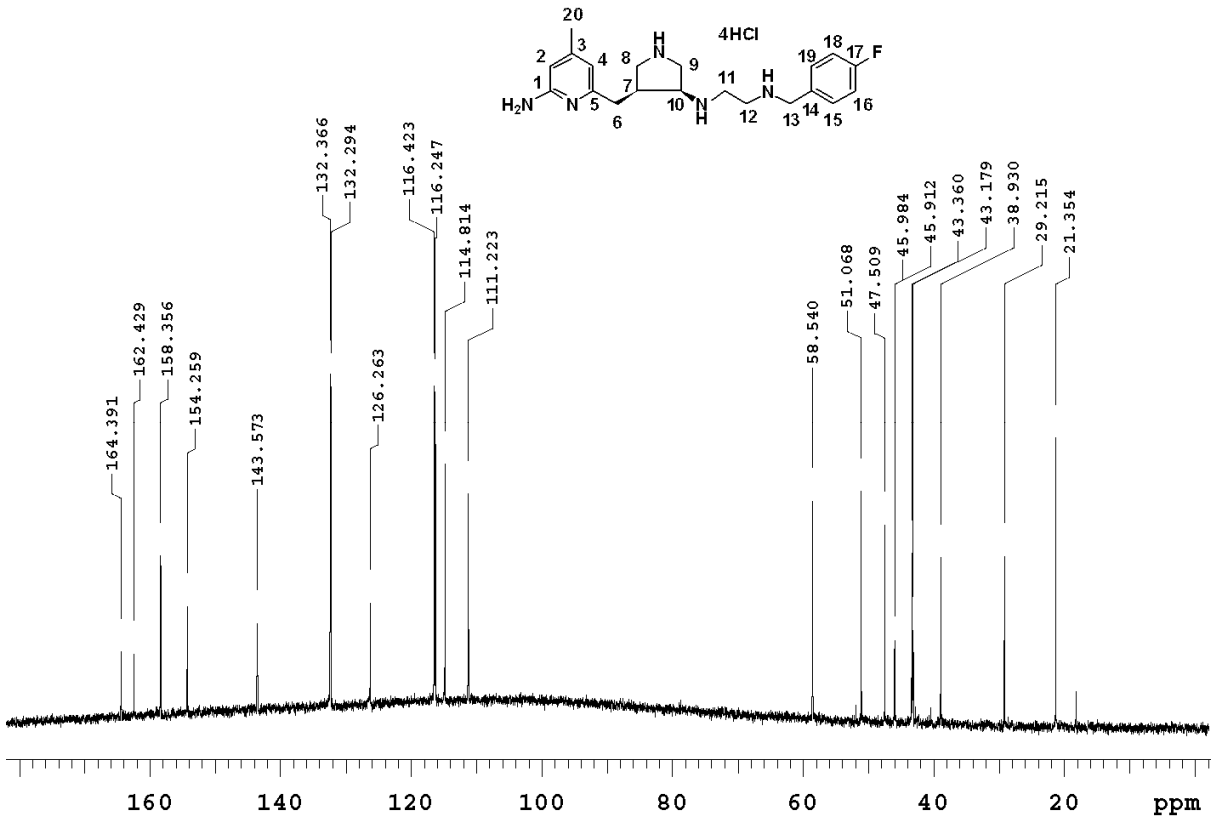

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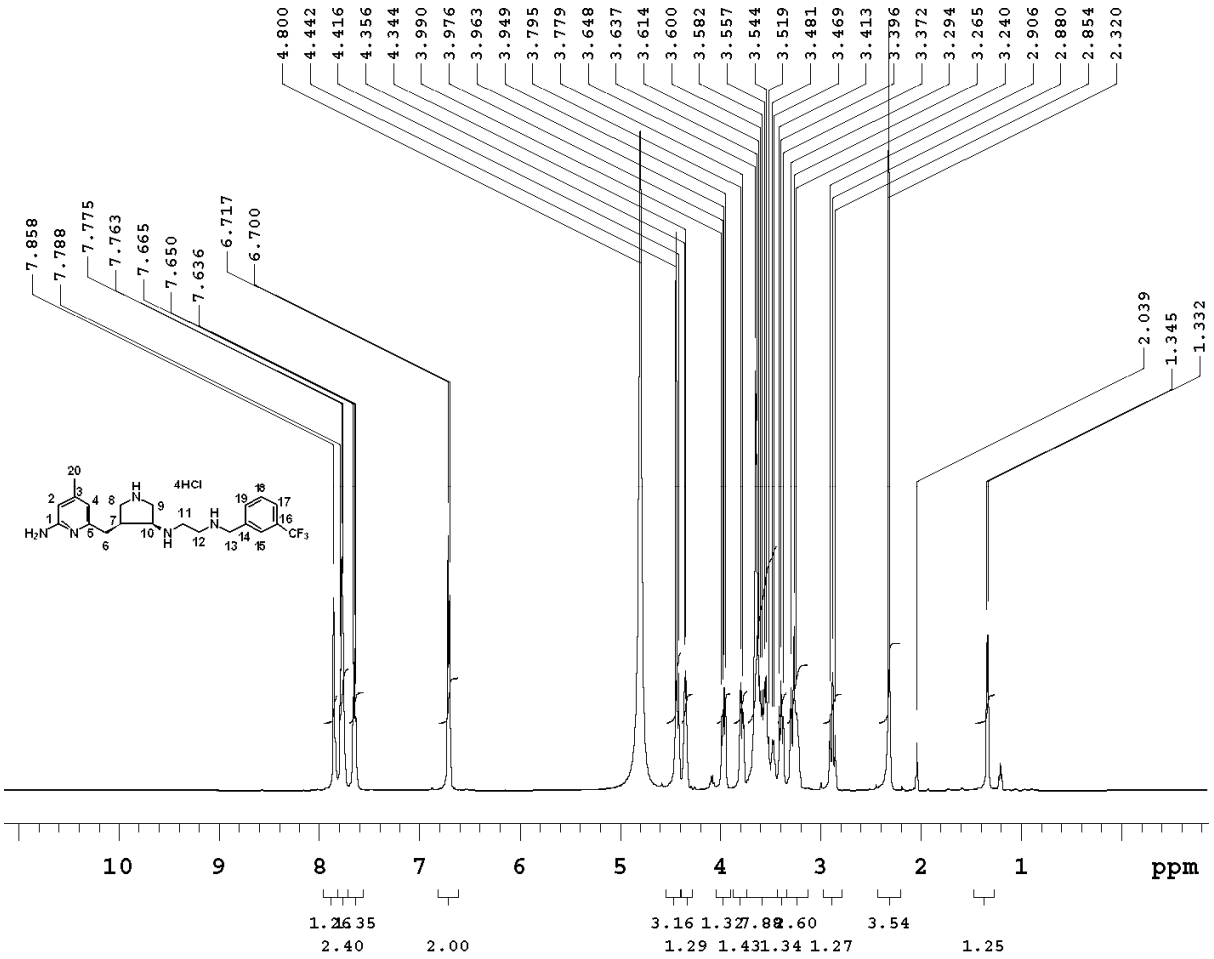

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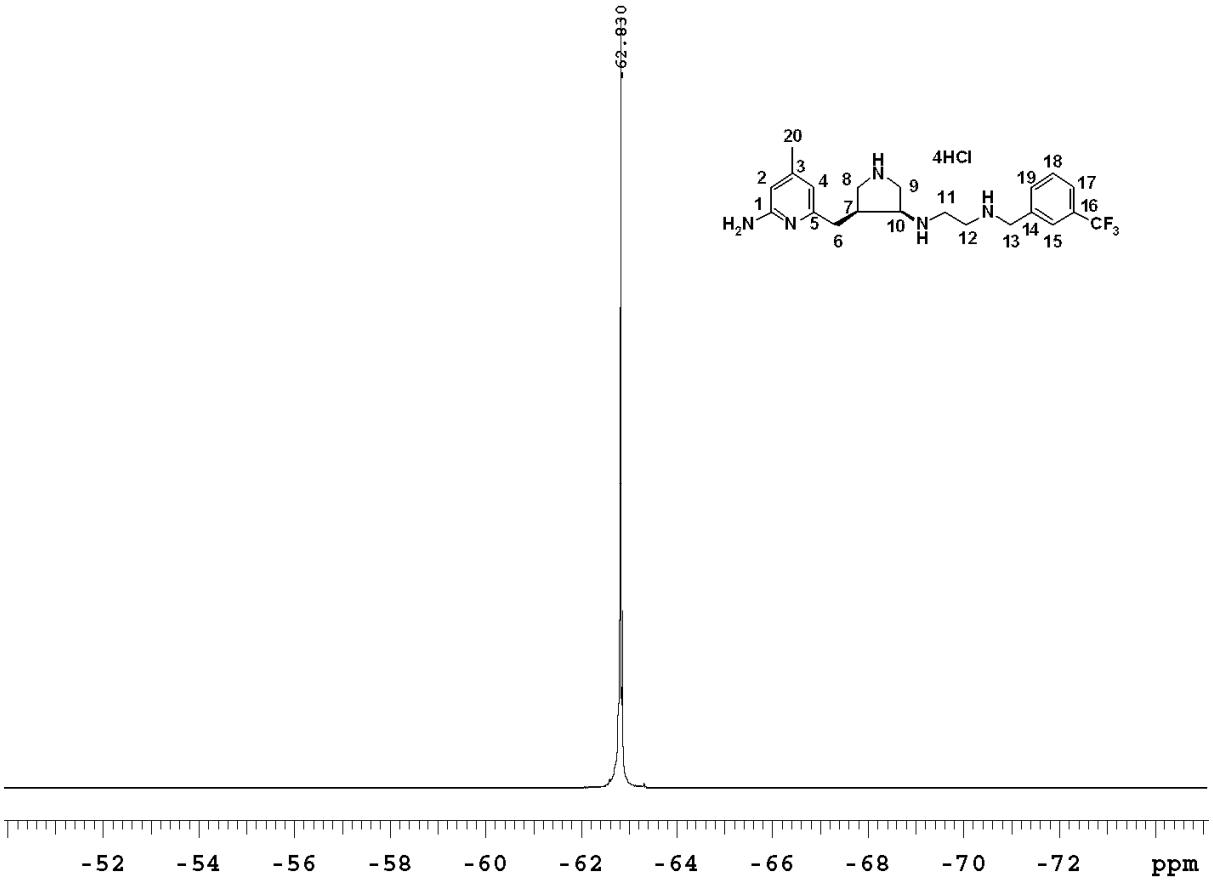

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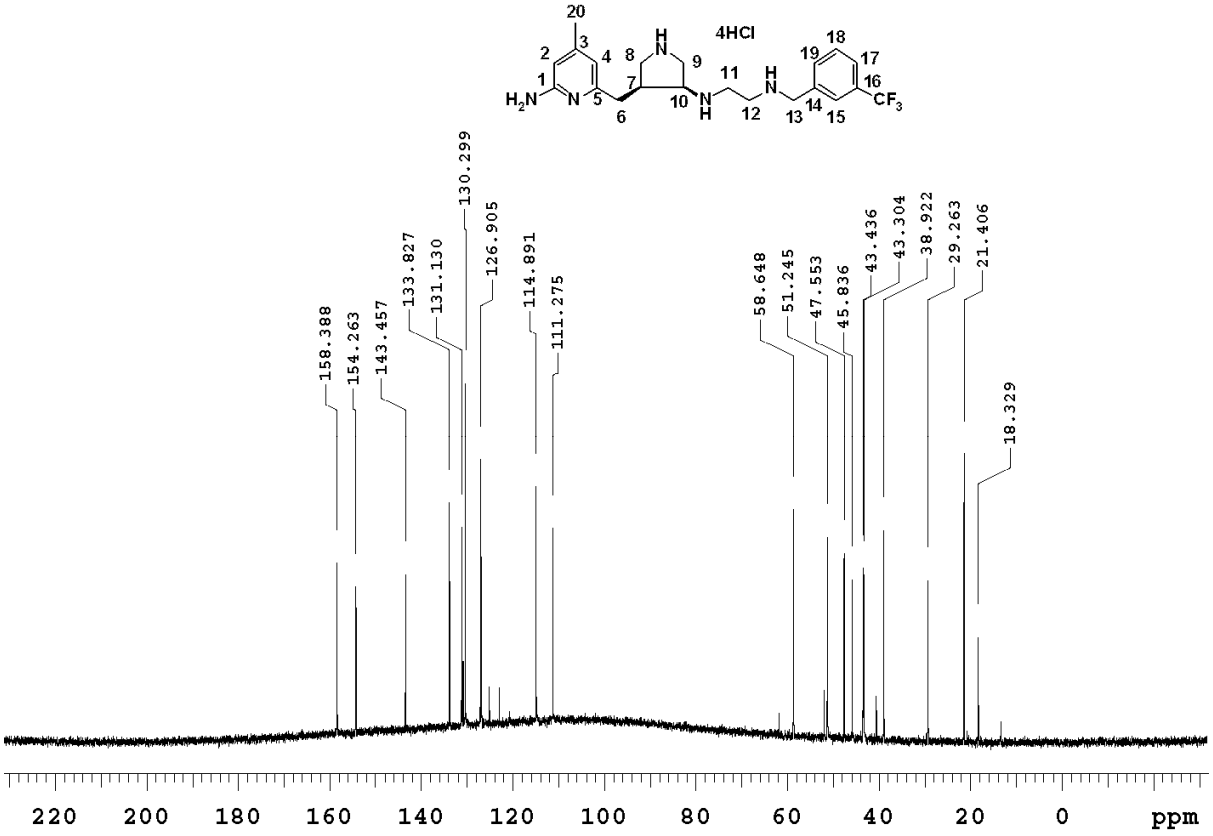

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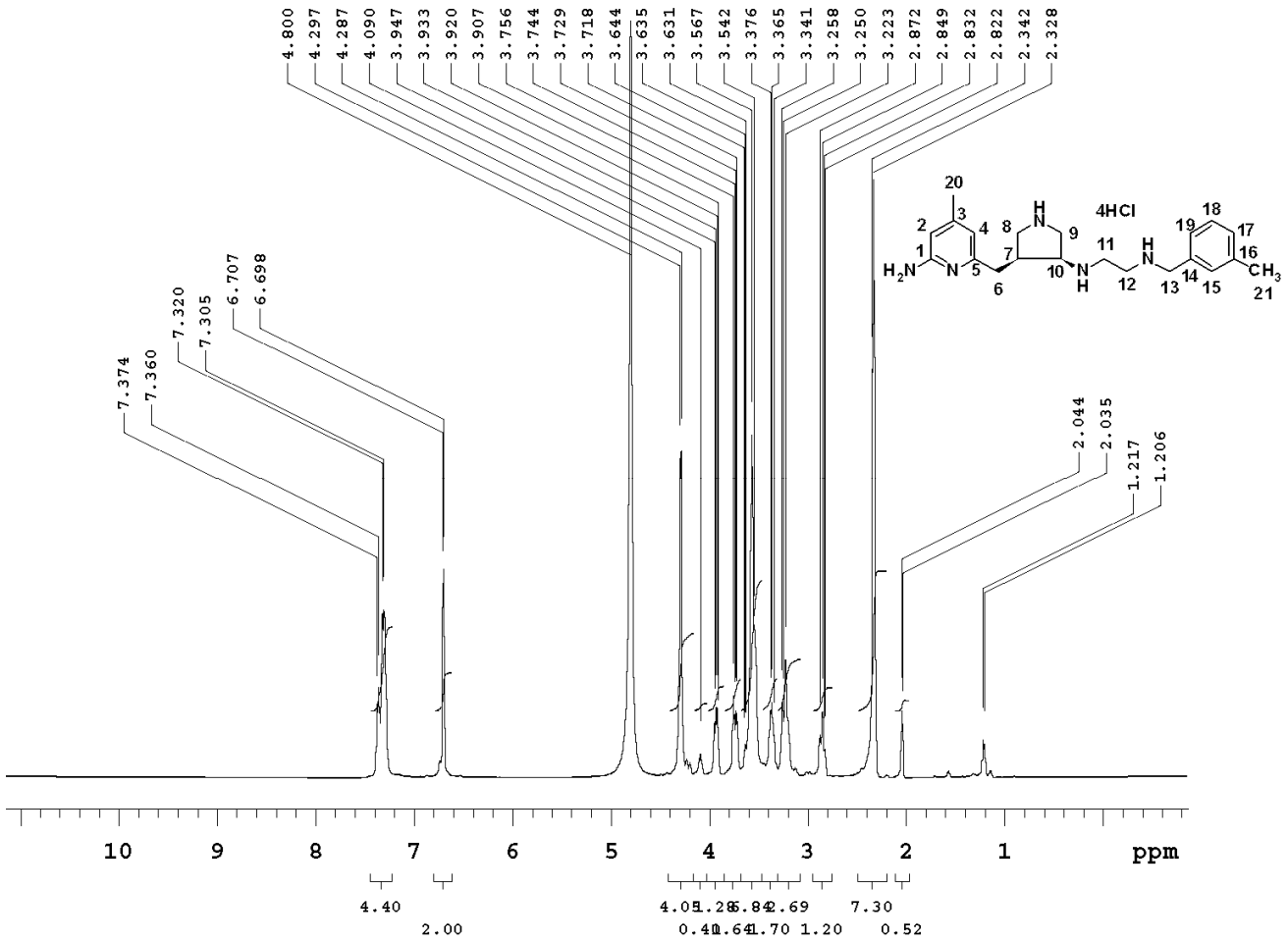

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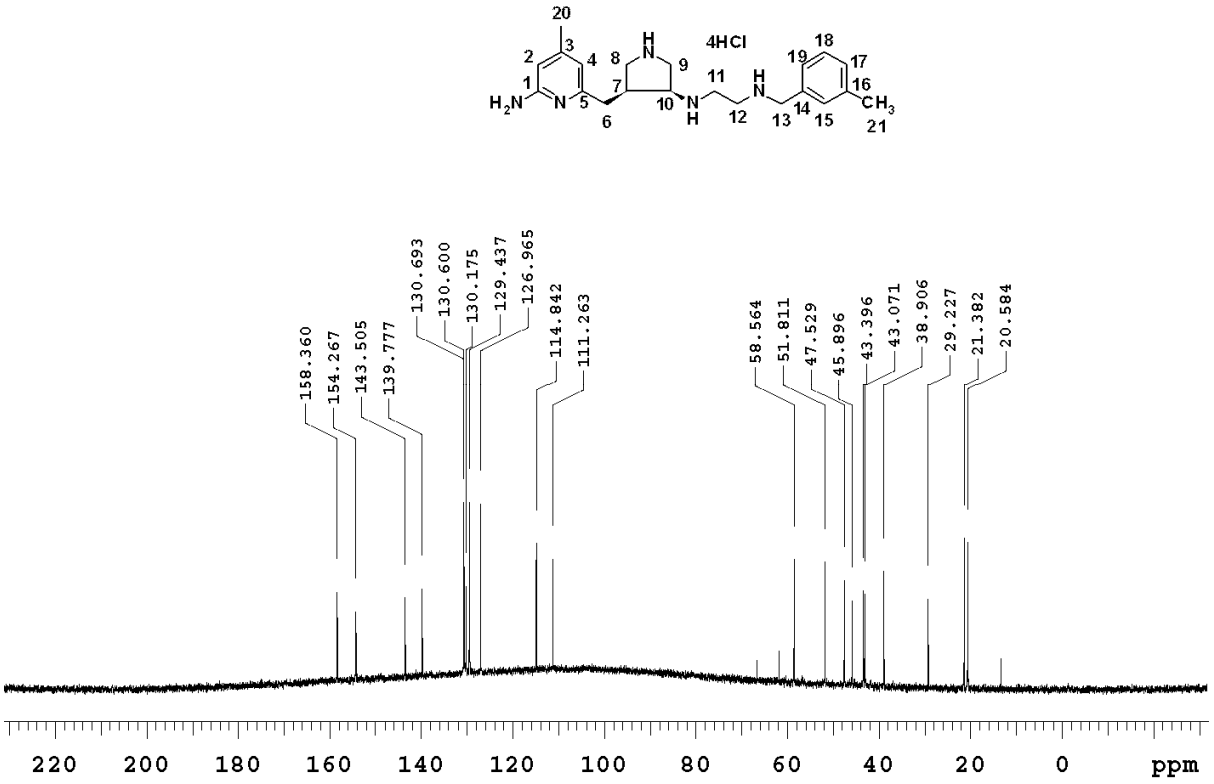

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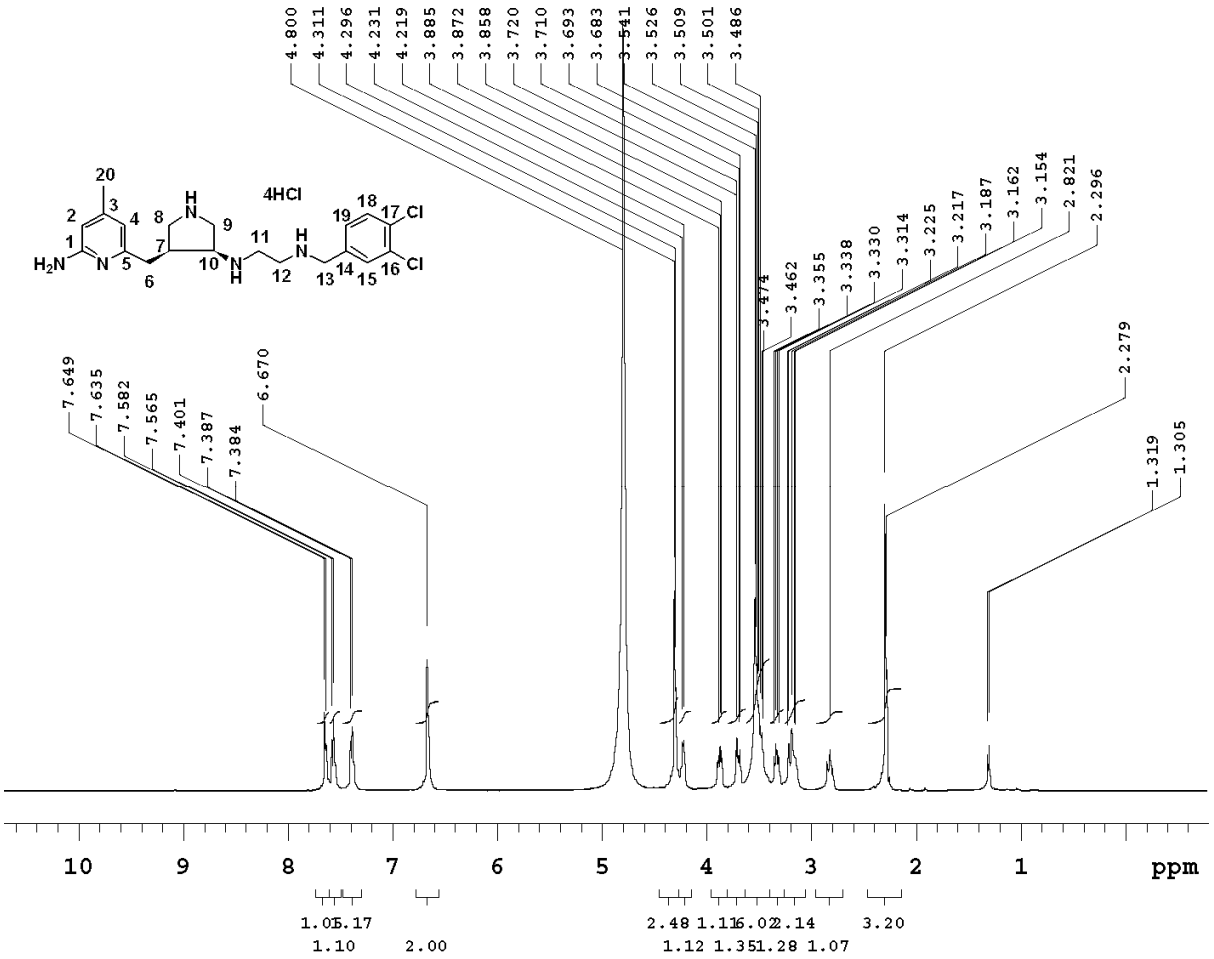

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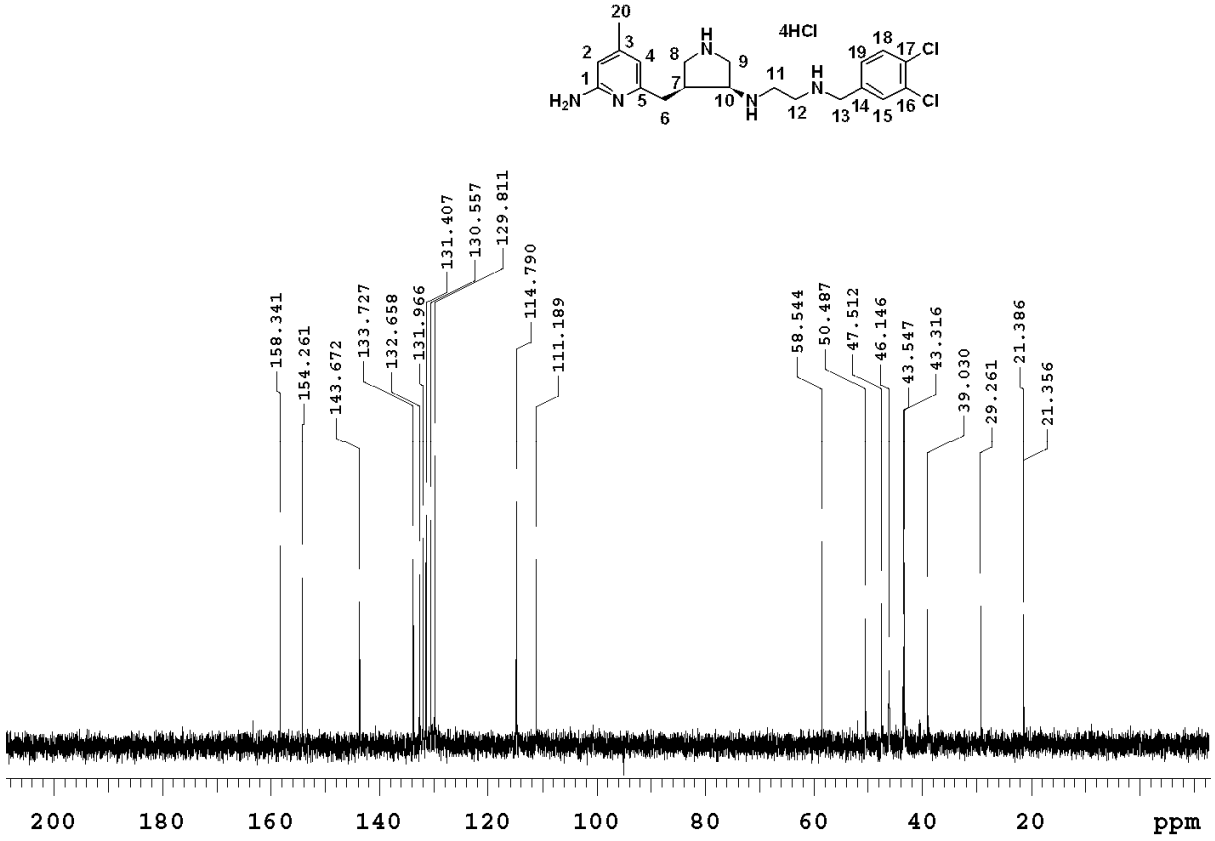

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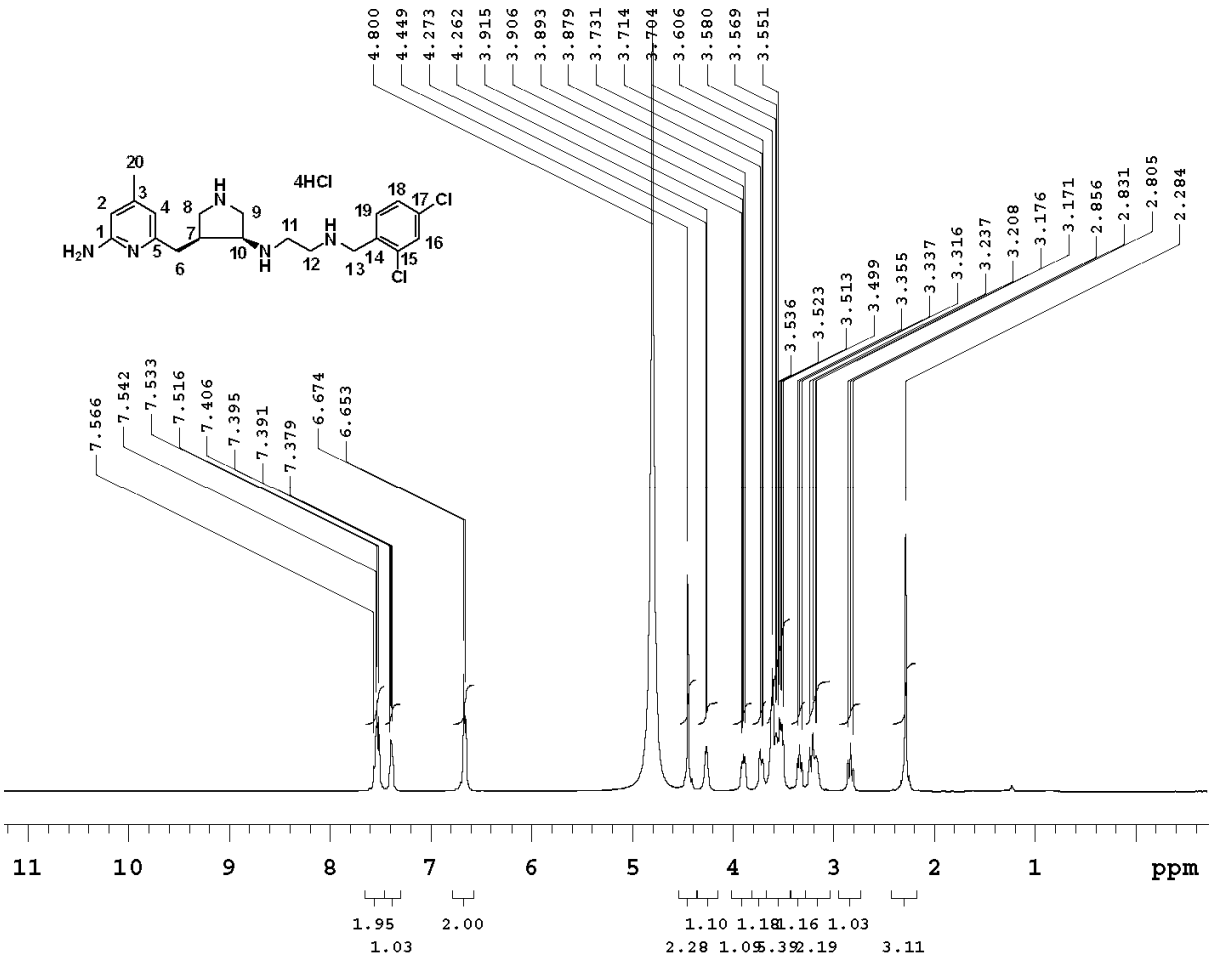

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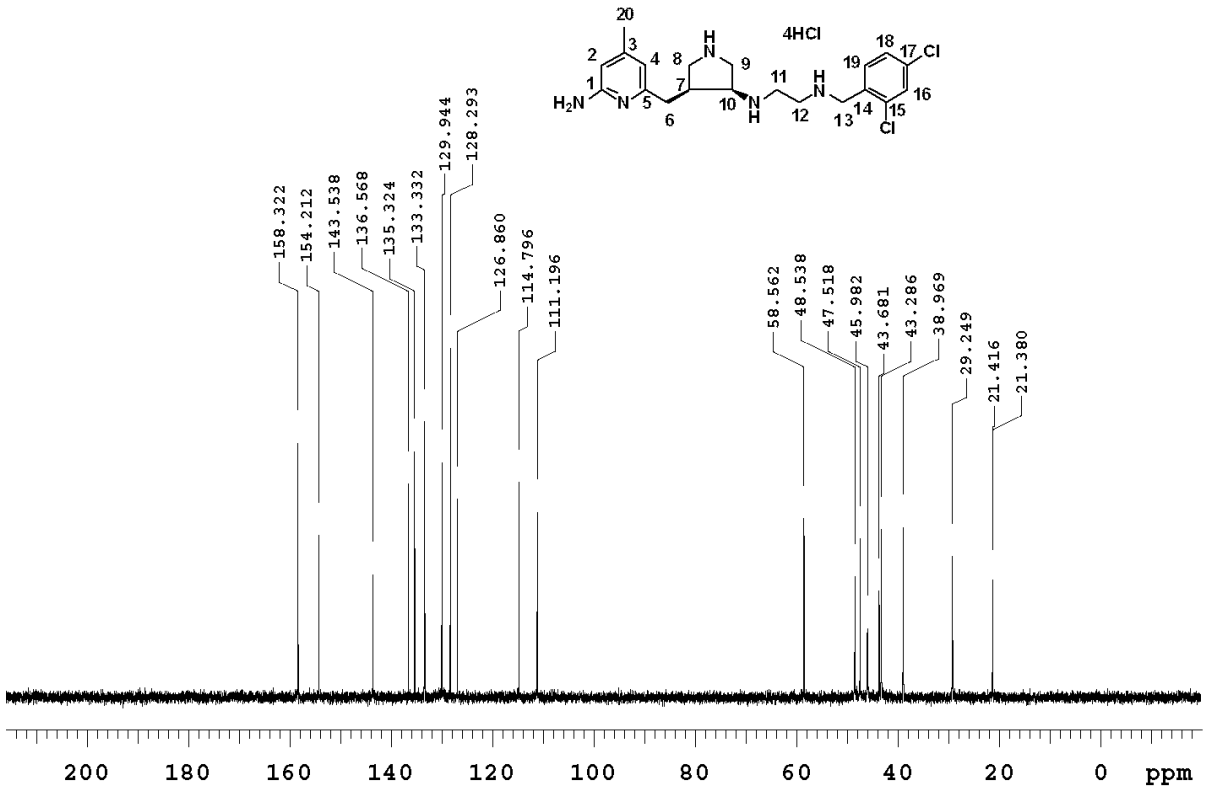

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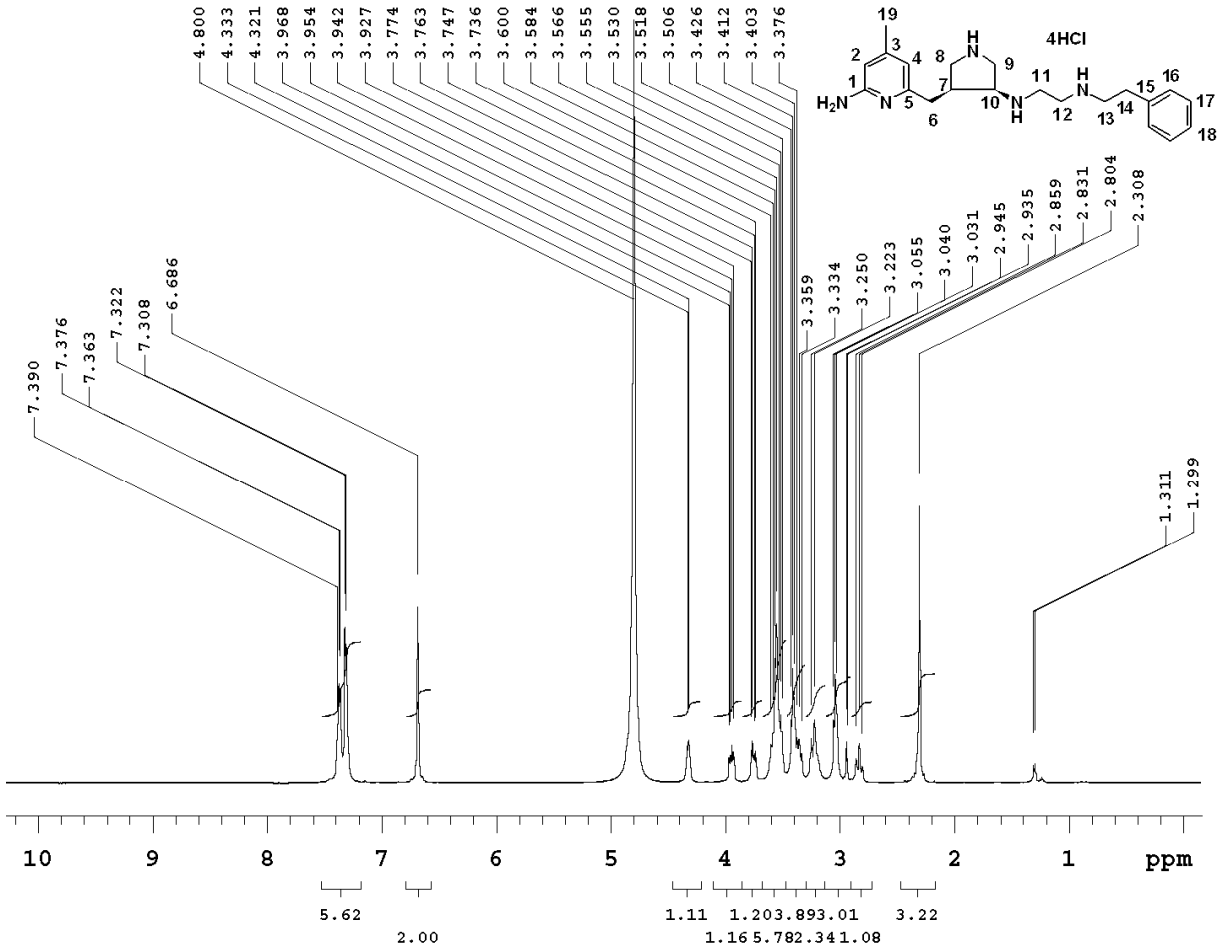

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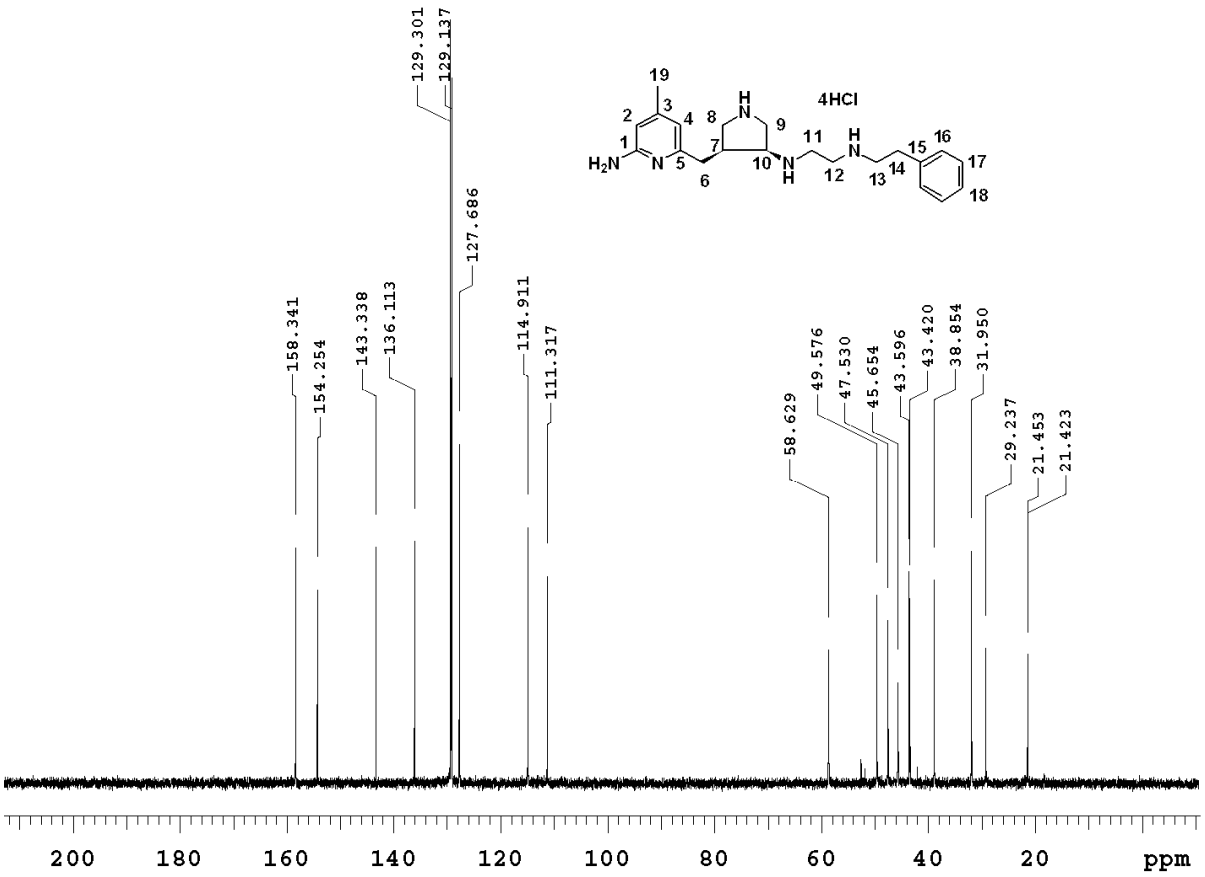

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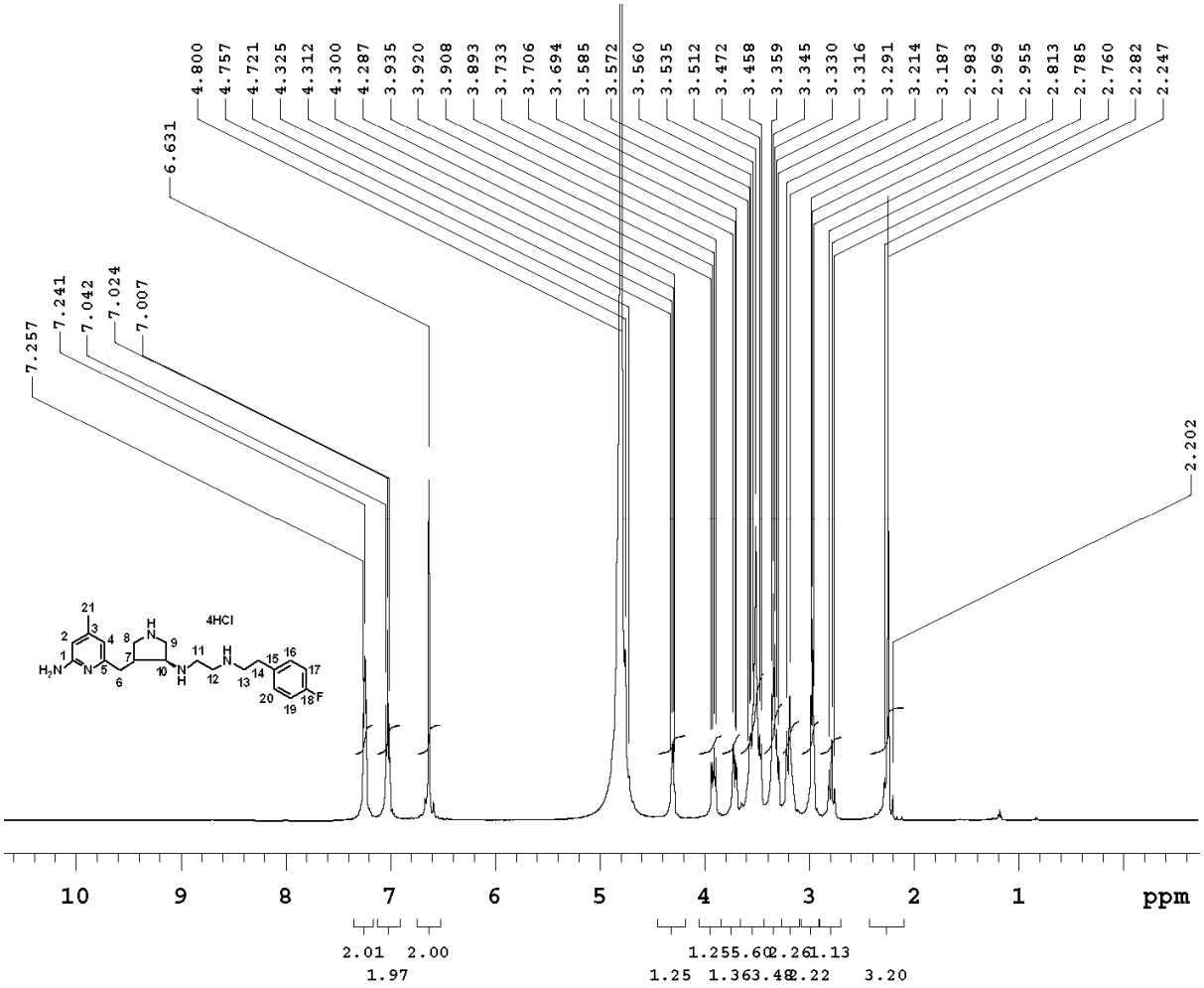

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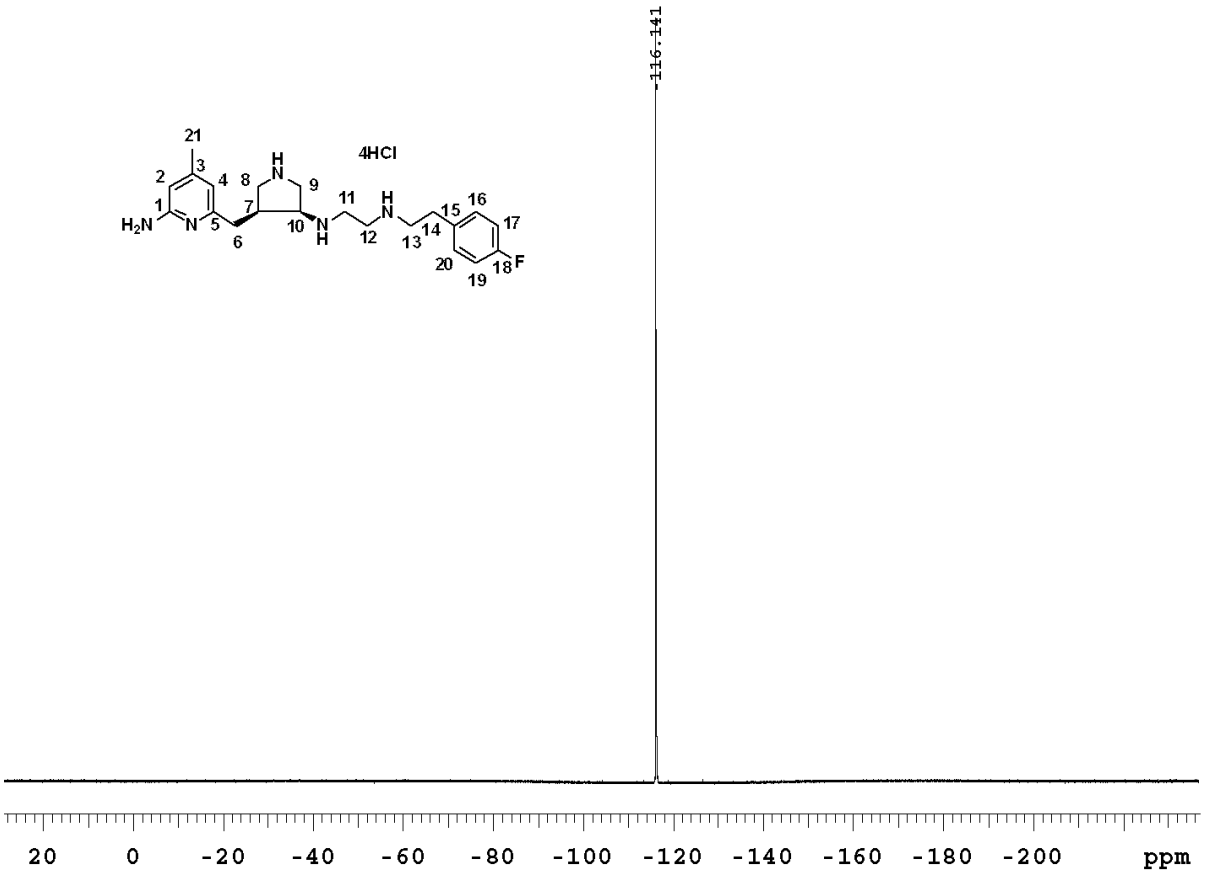

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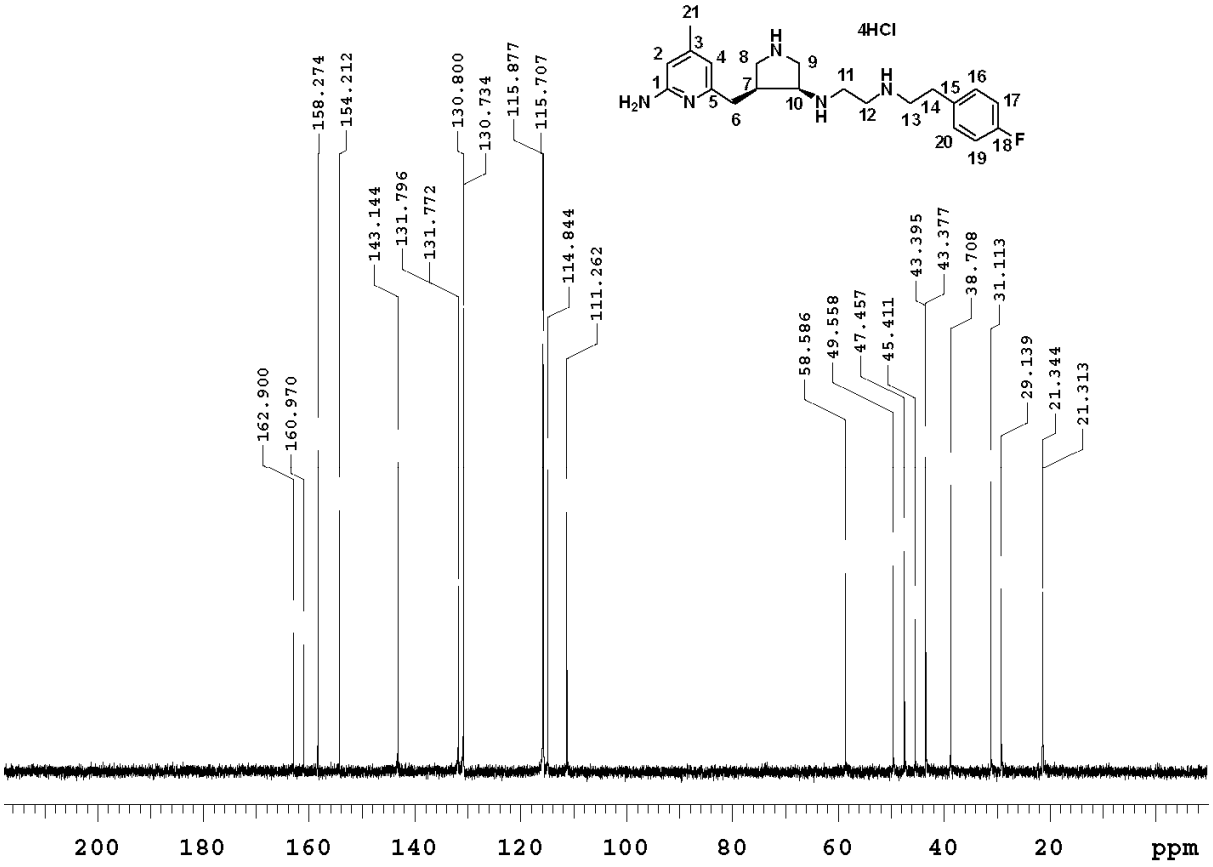

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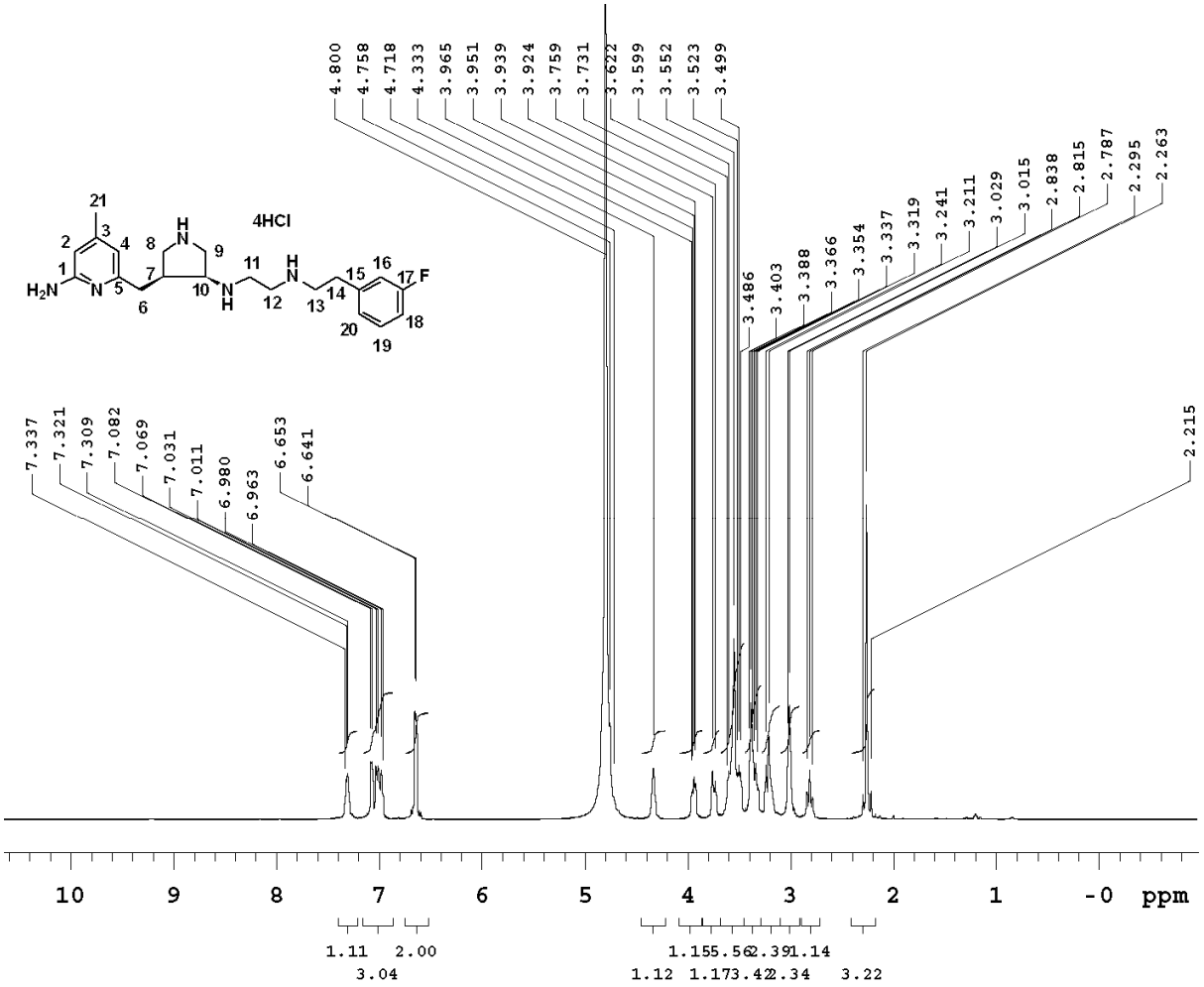

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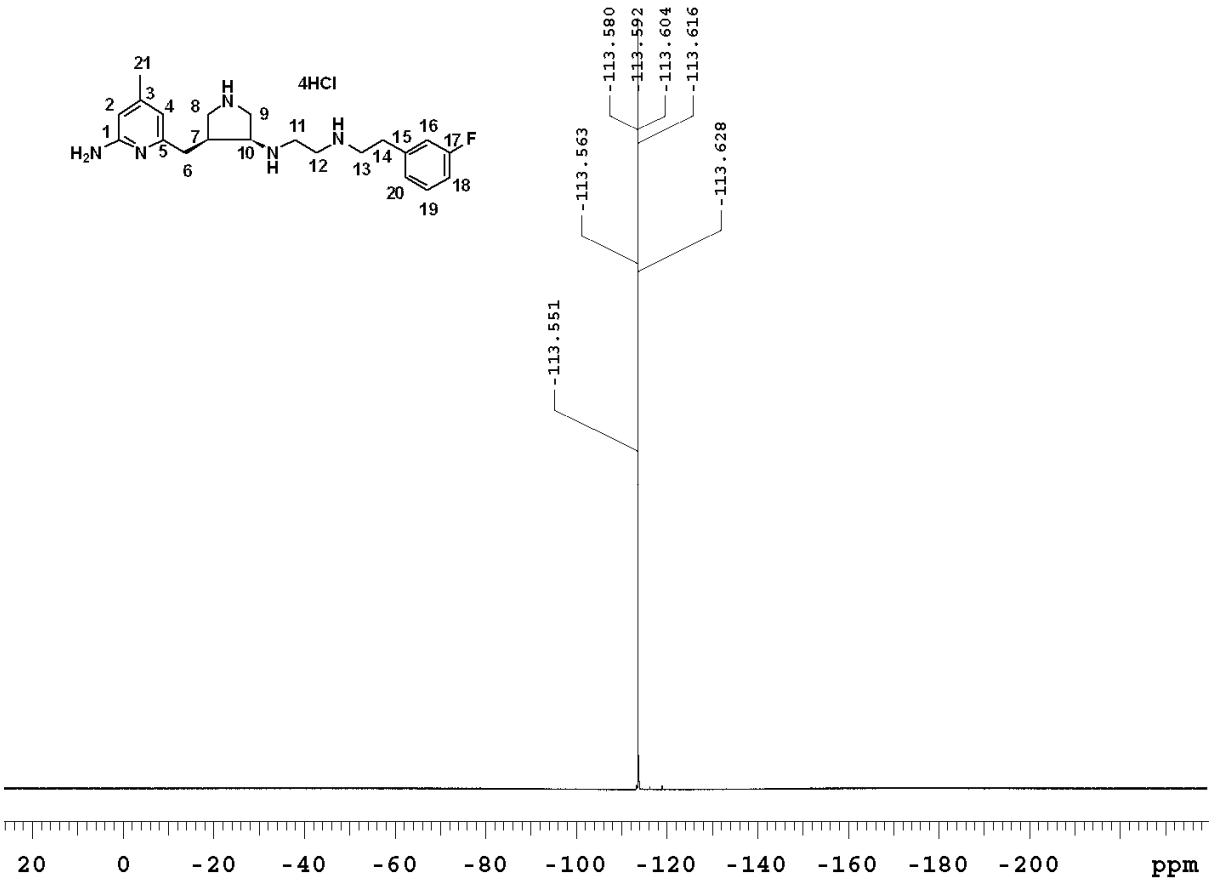

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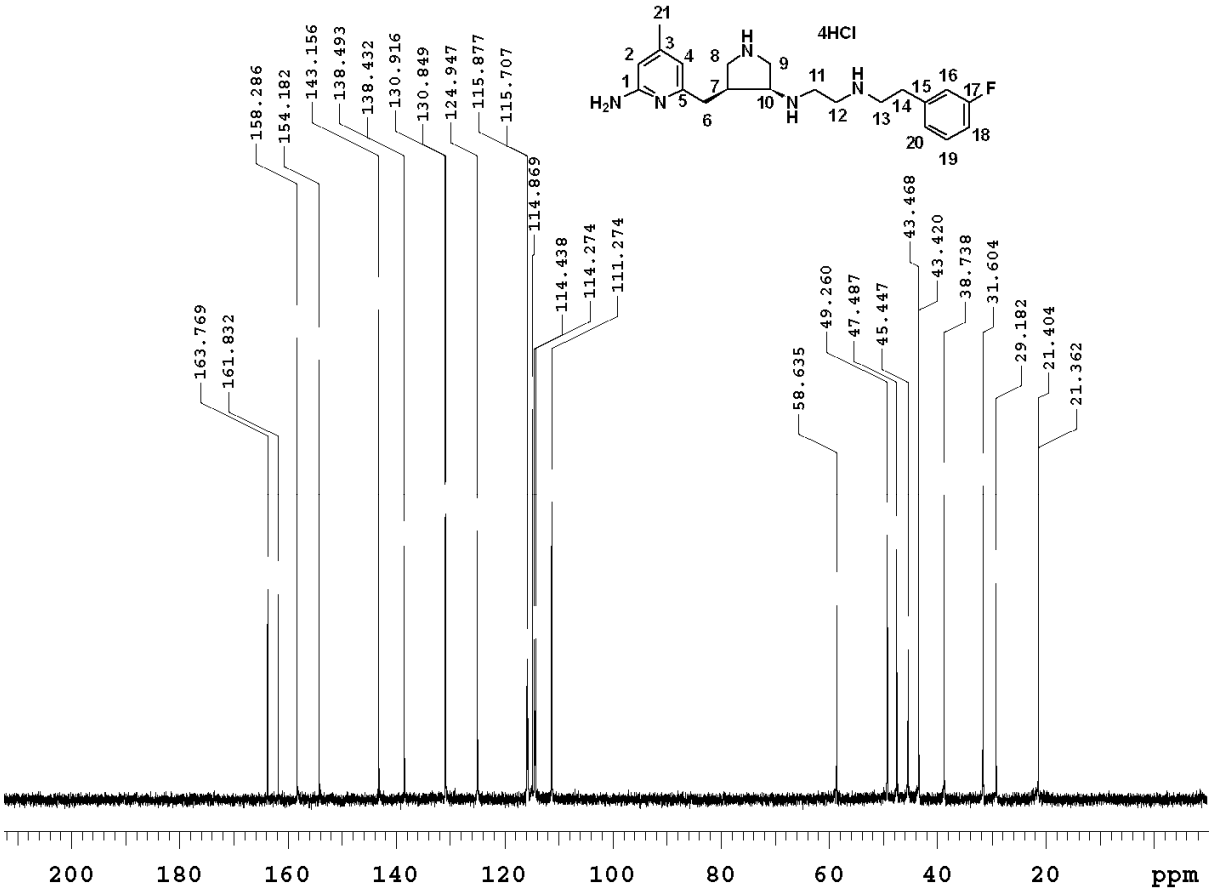

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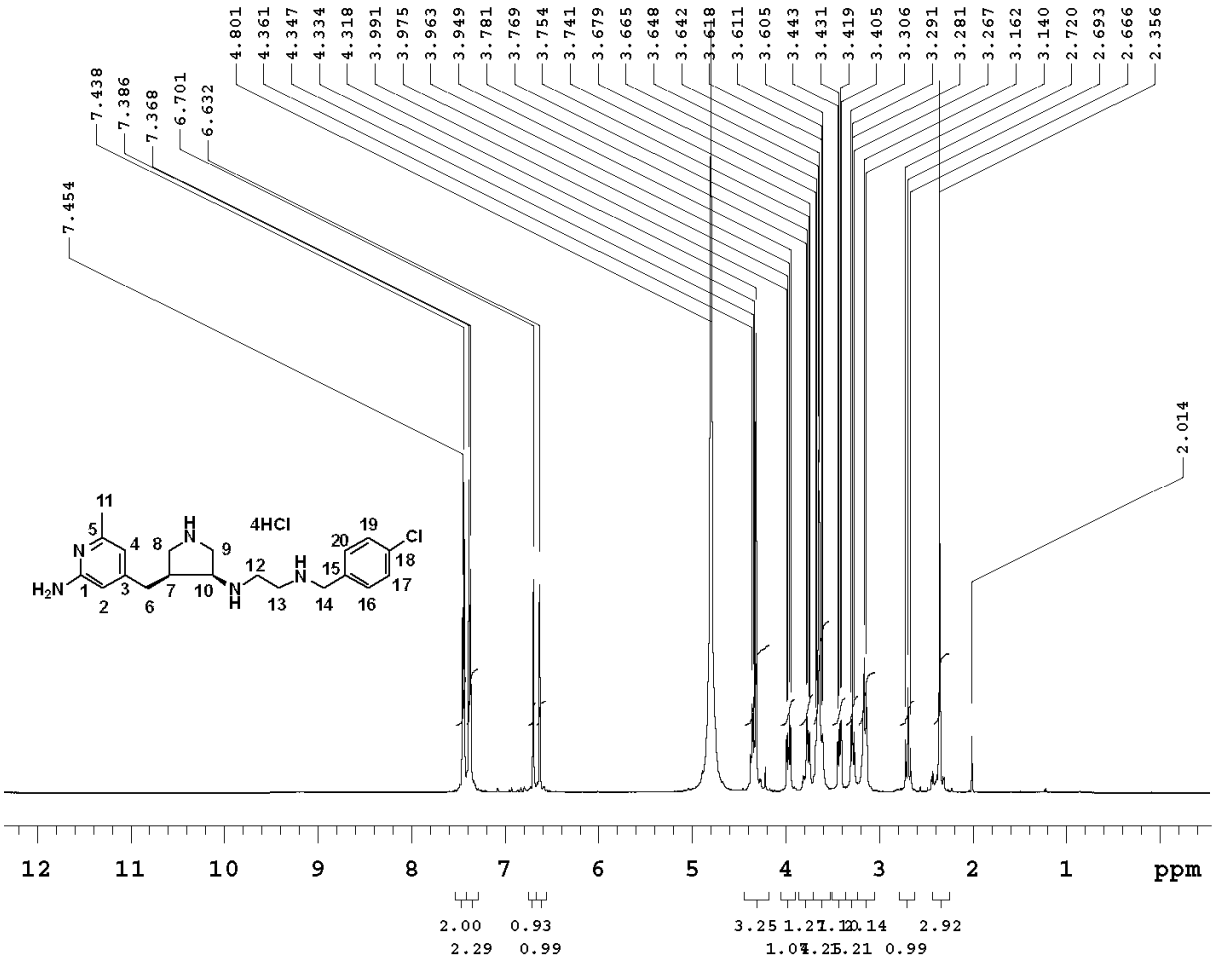

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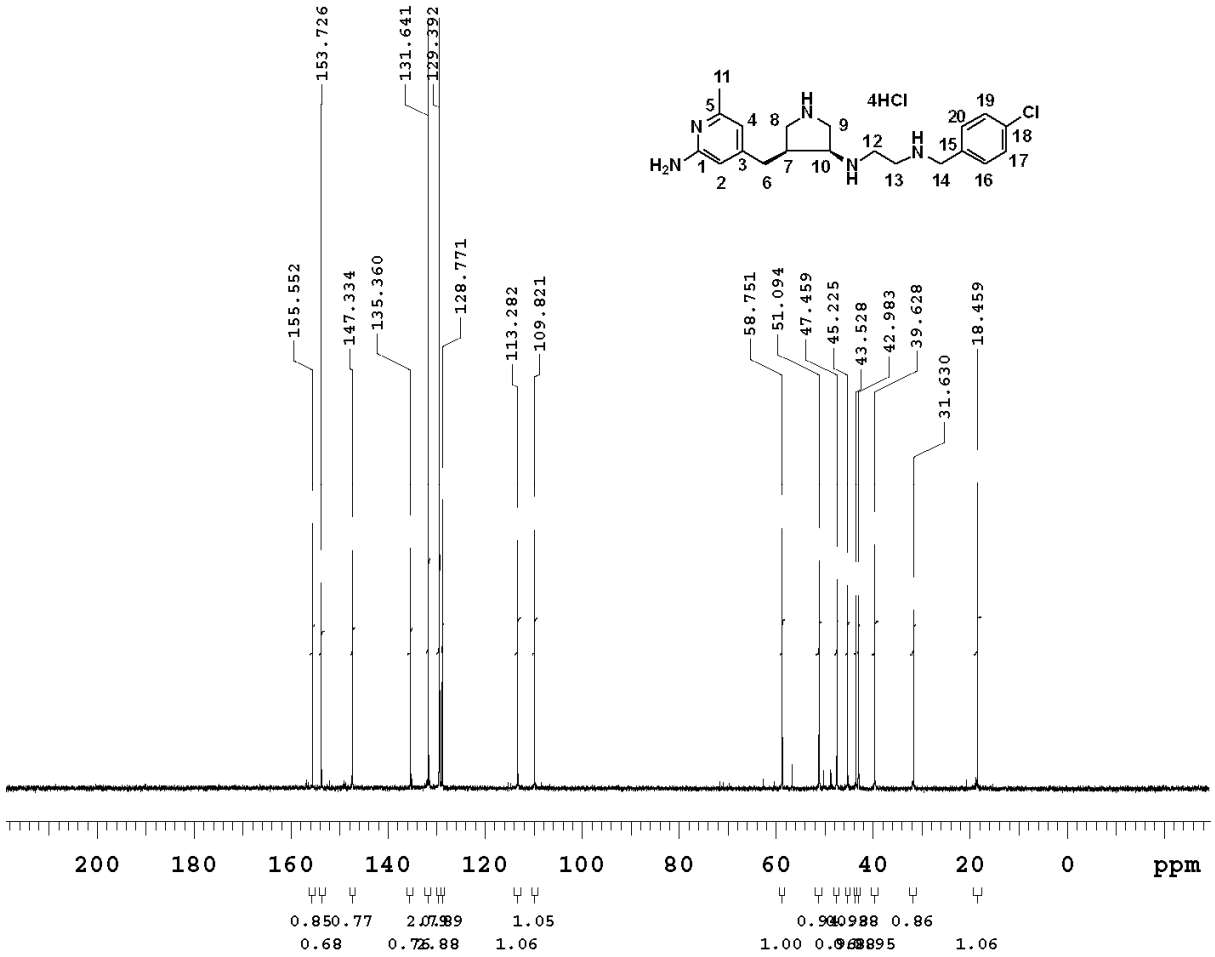

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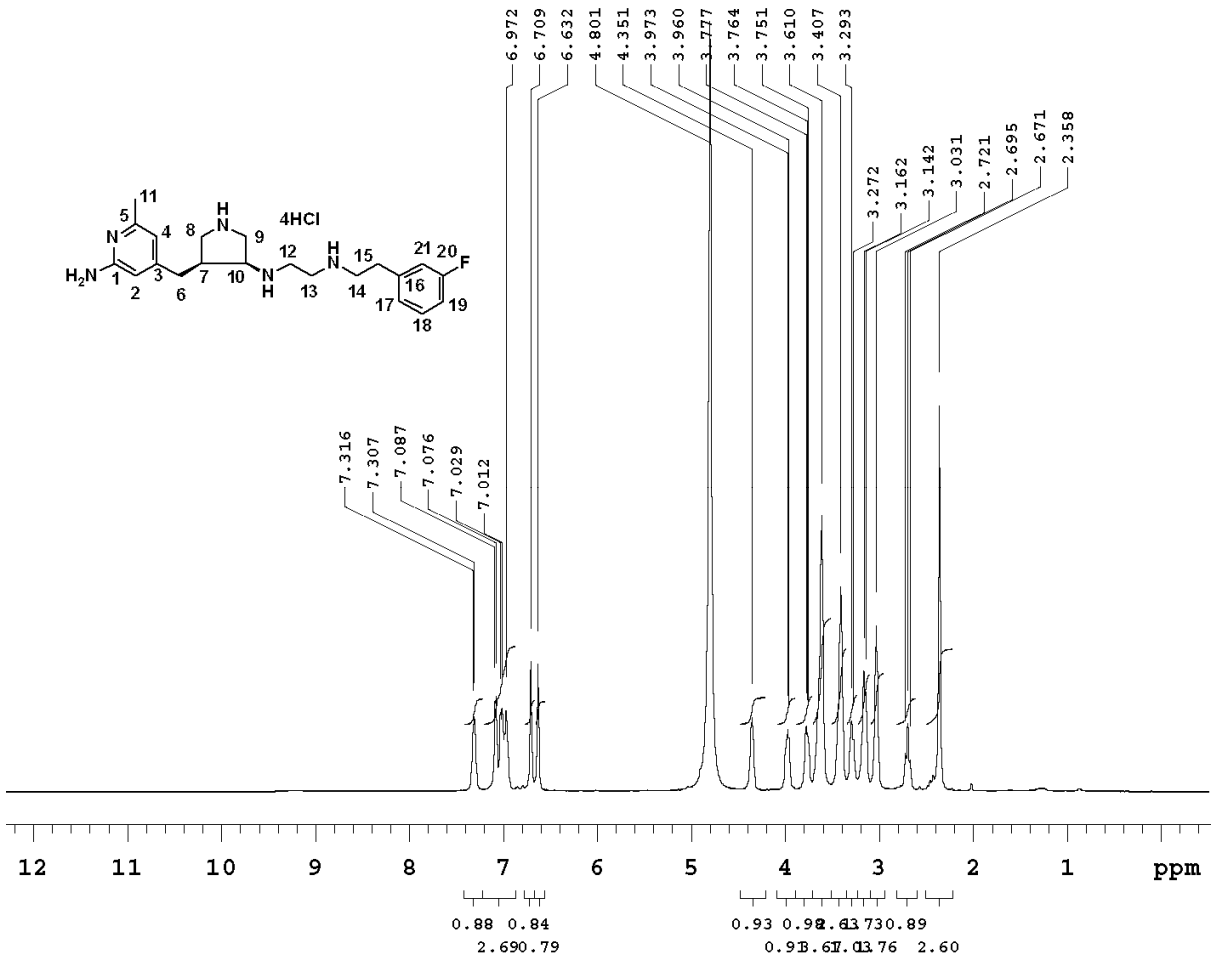

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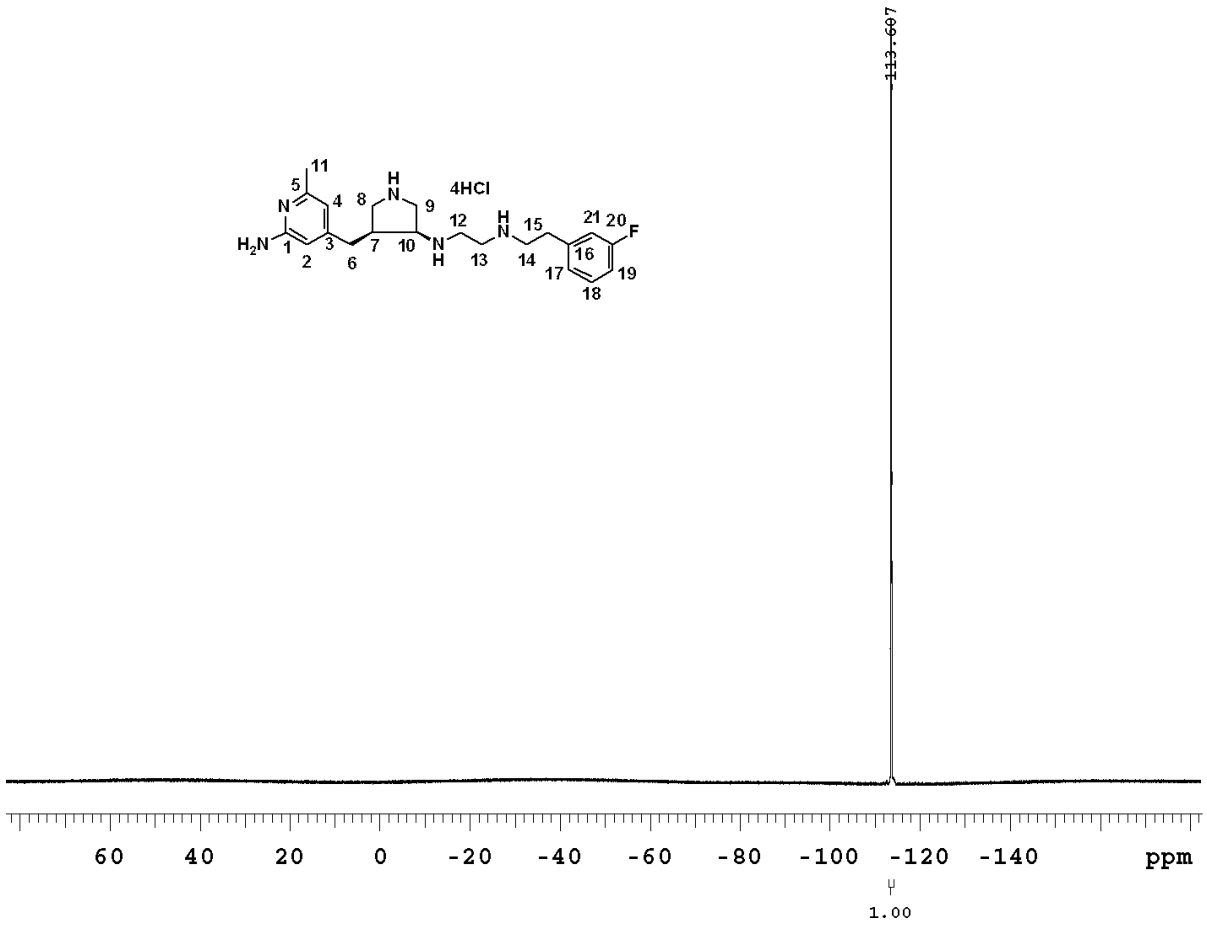

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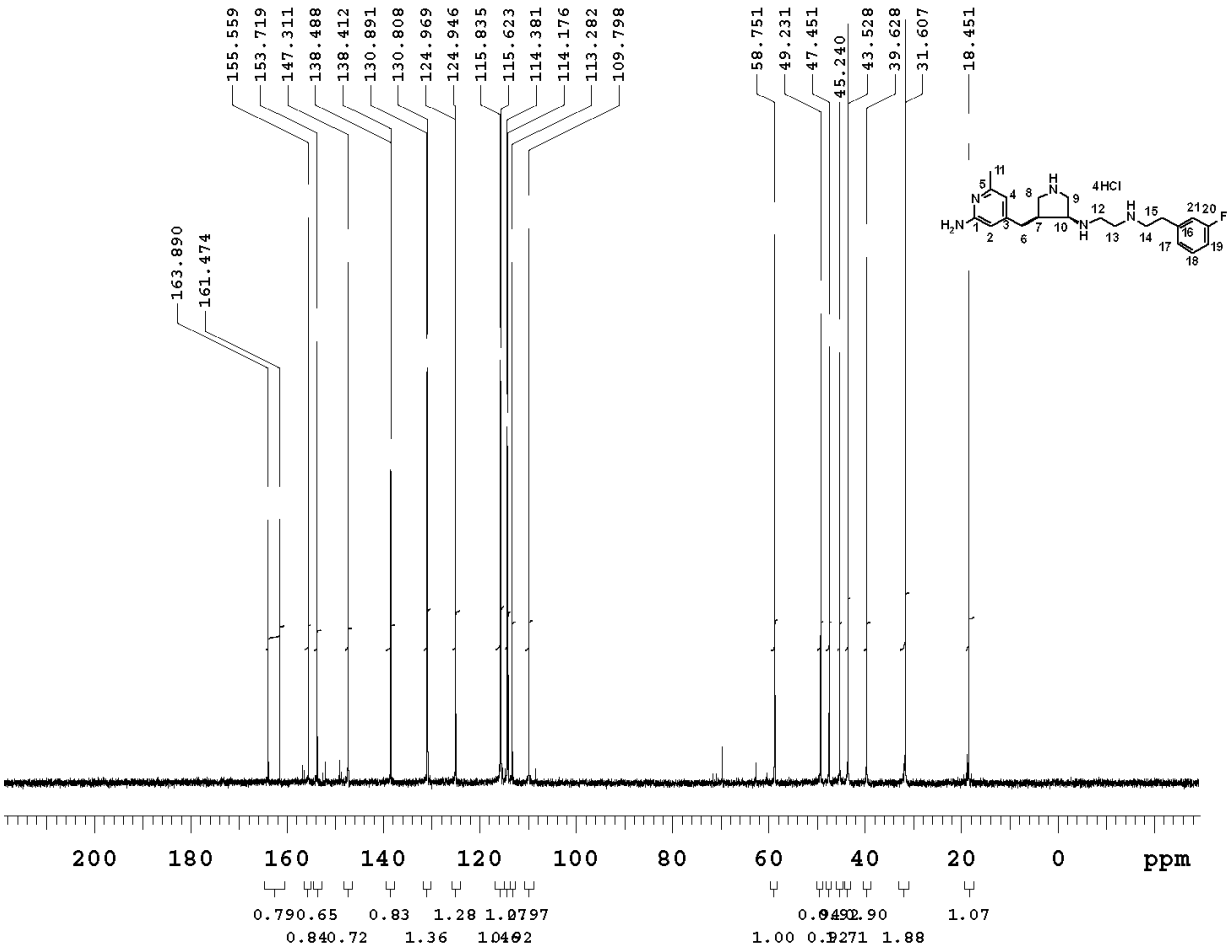

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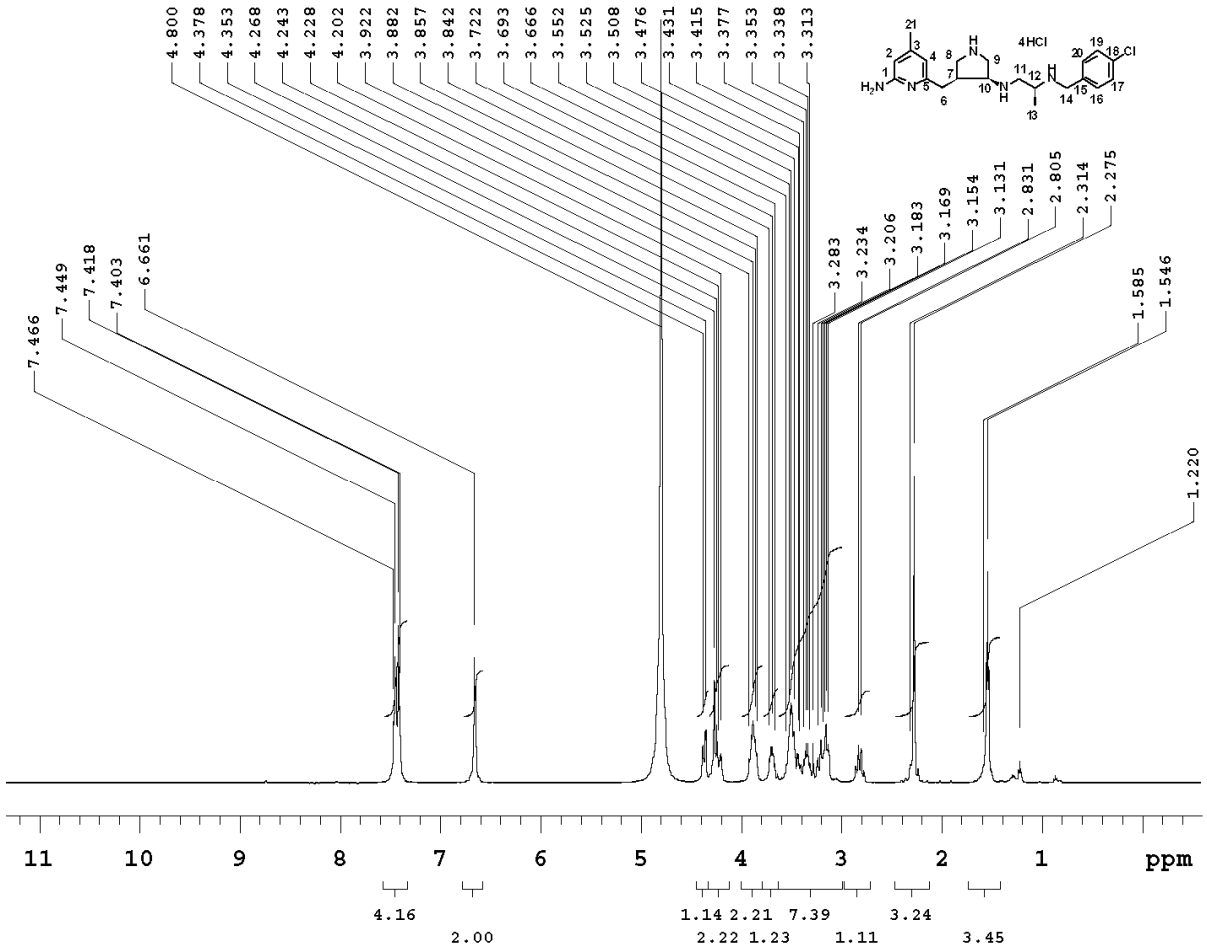

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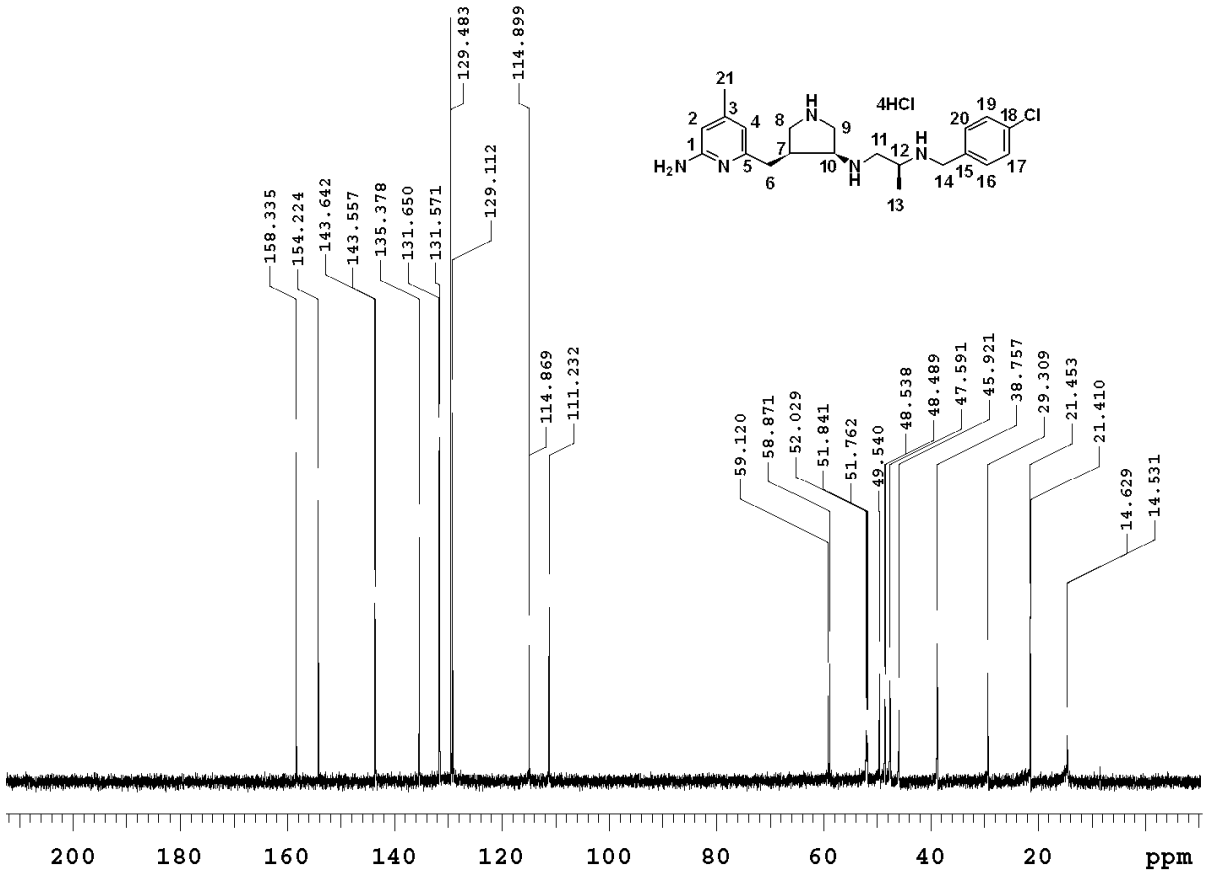

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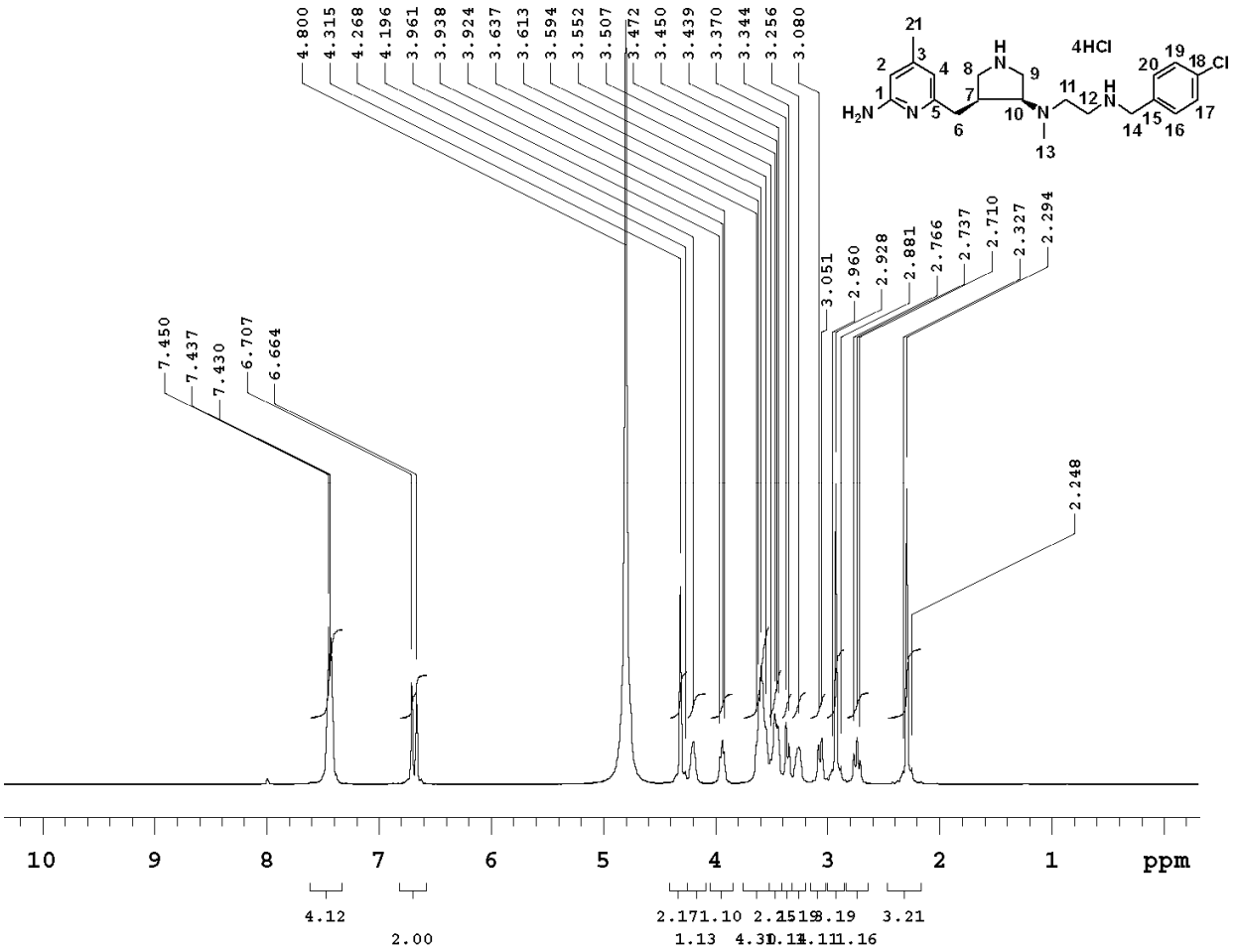

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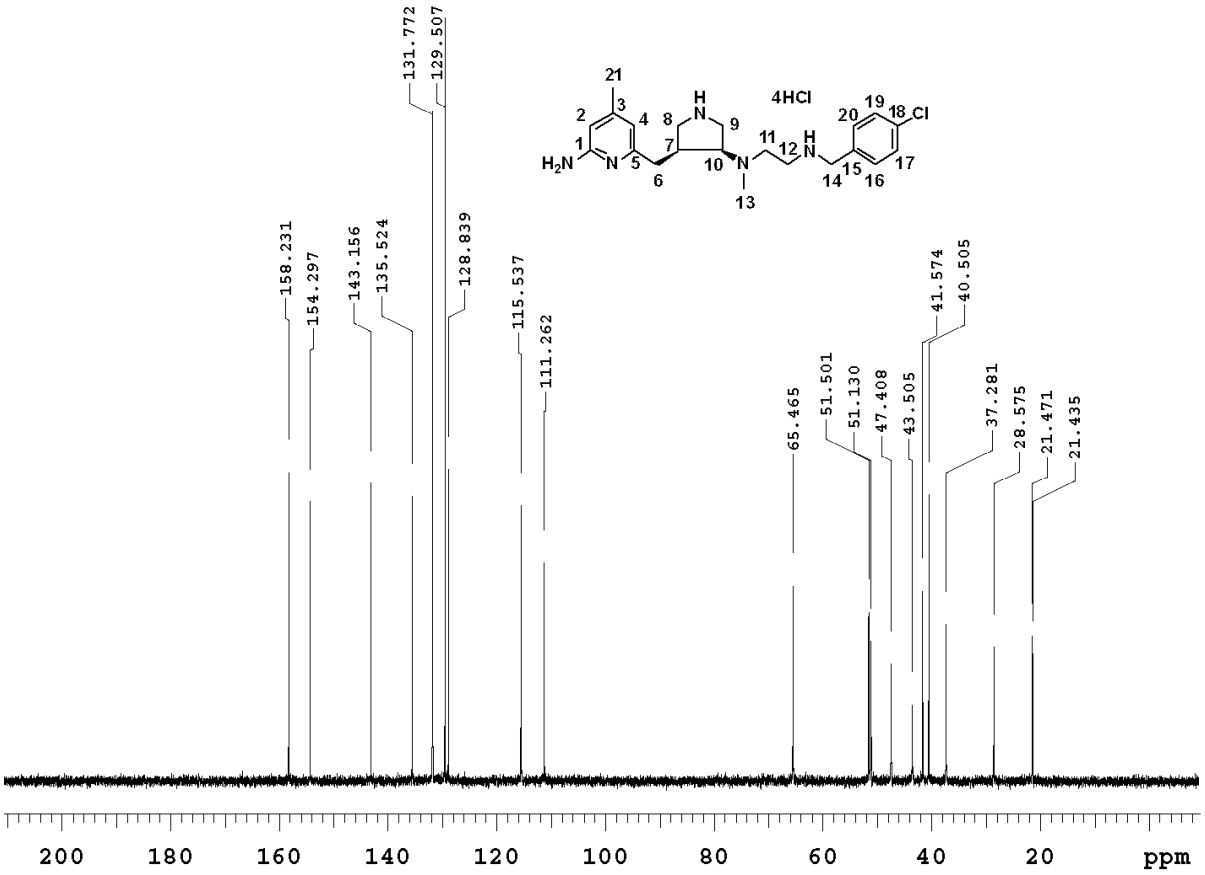

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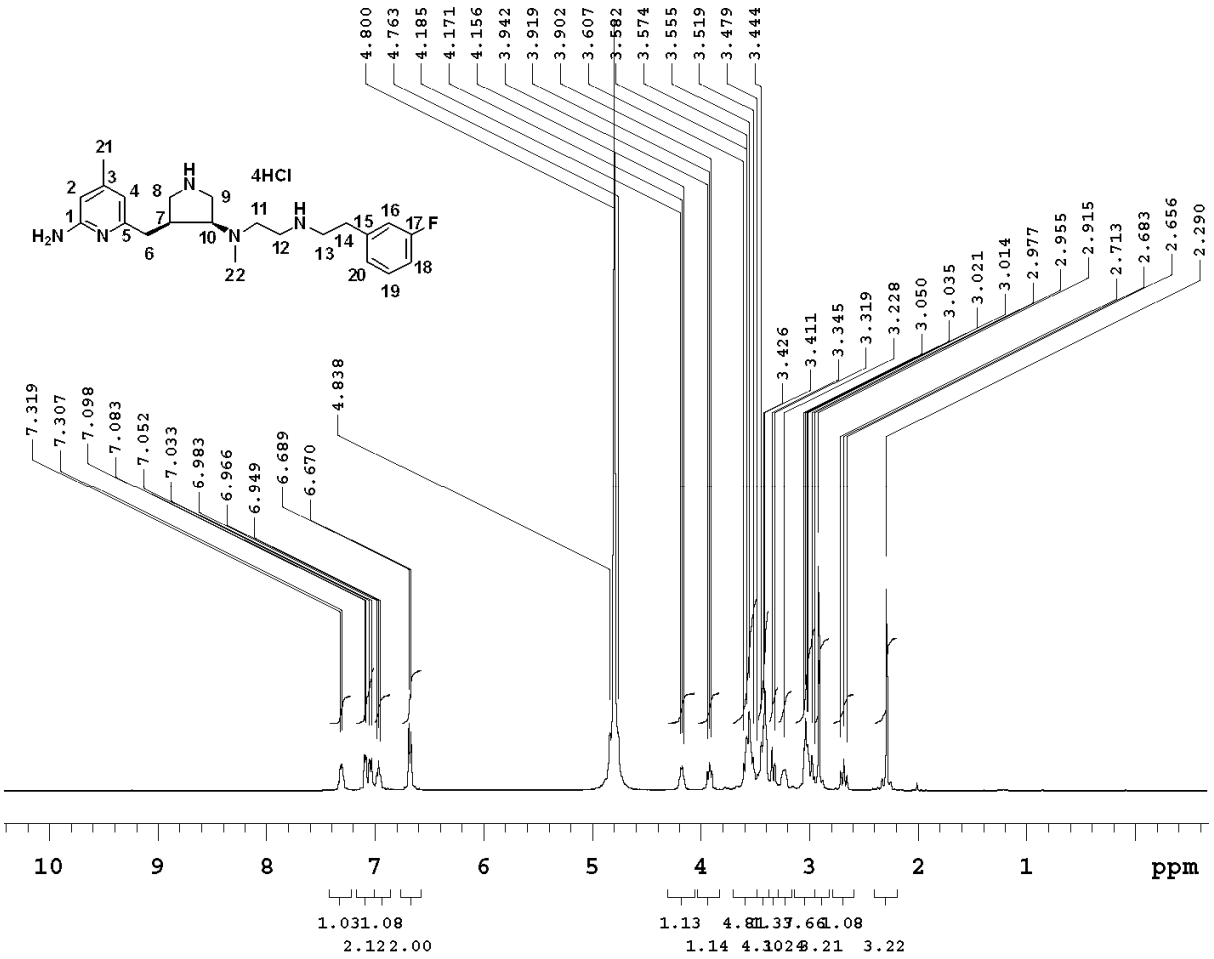
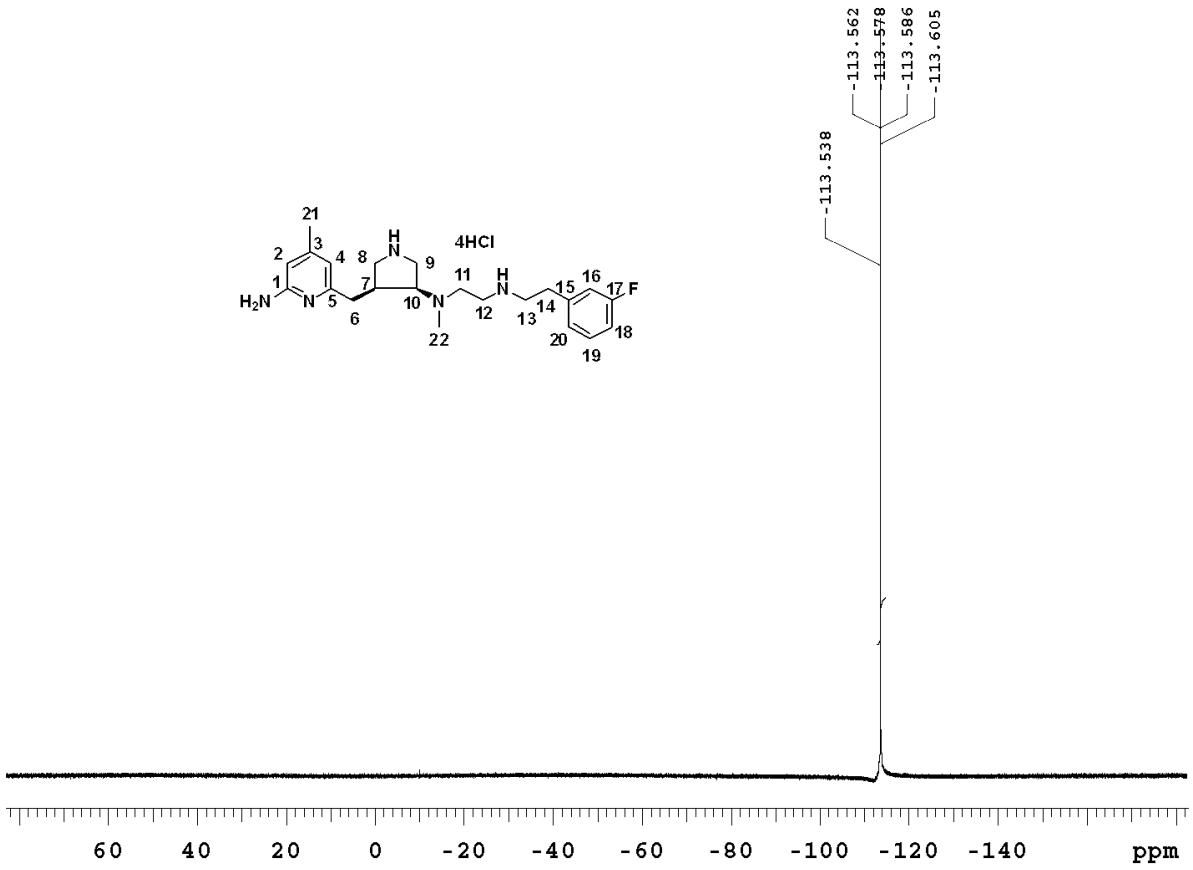
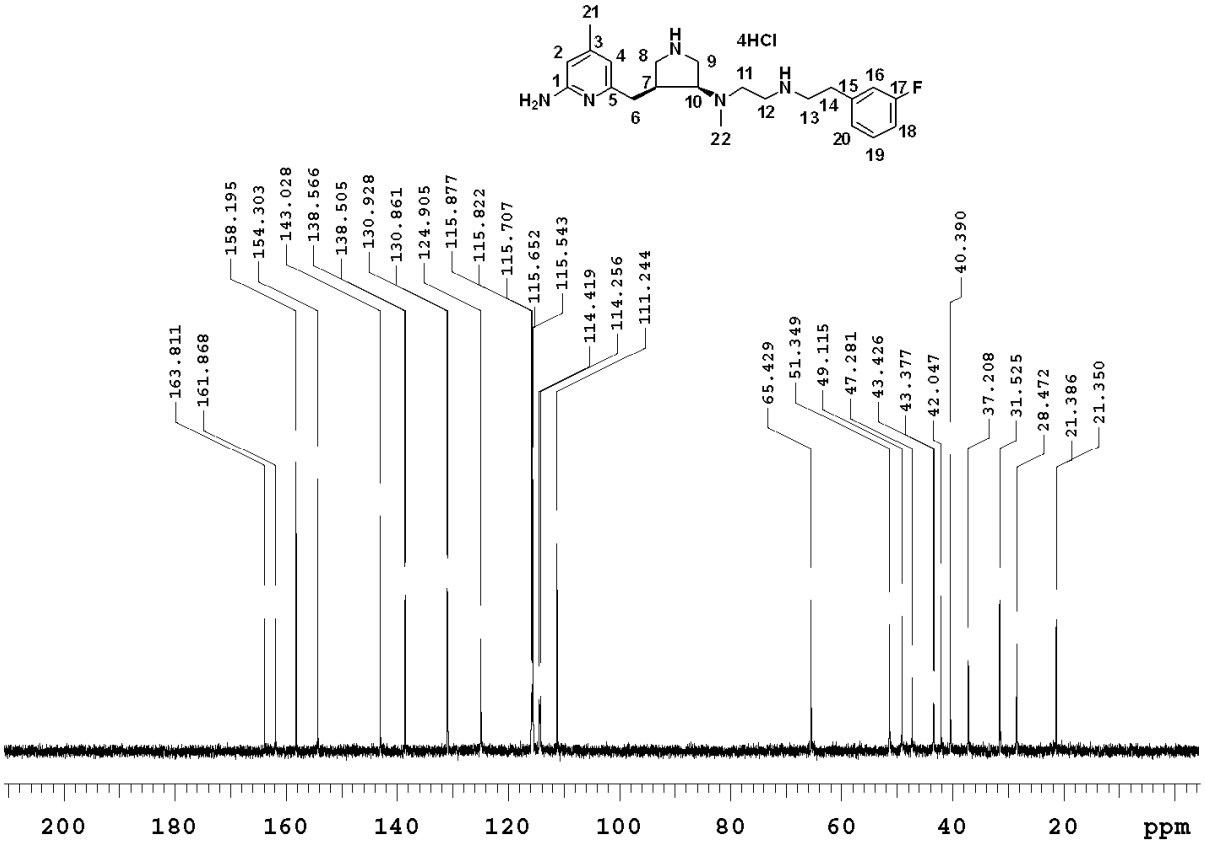


Supplementary Figure continued



Supplementary Figure continued



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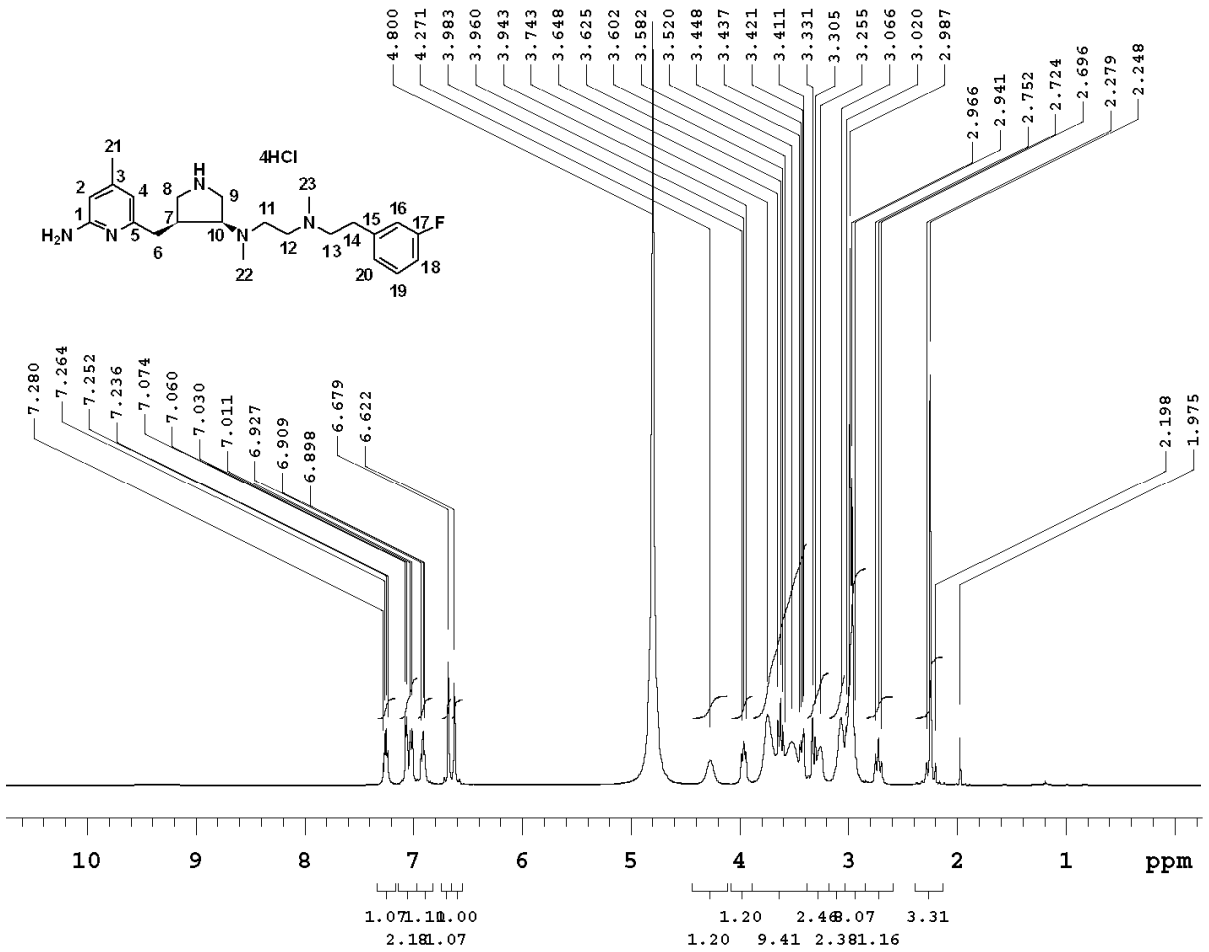

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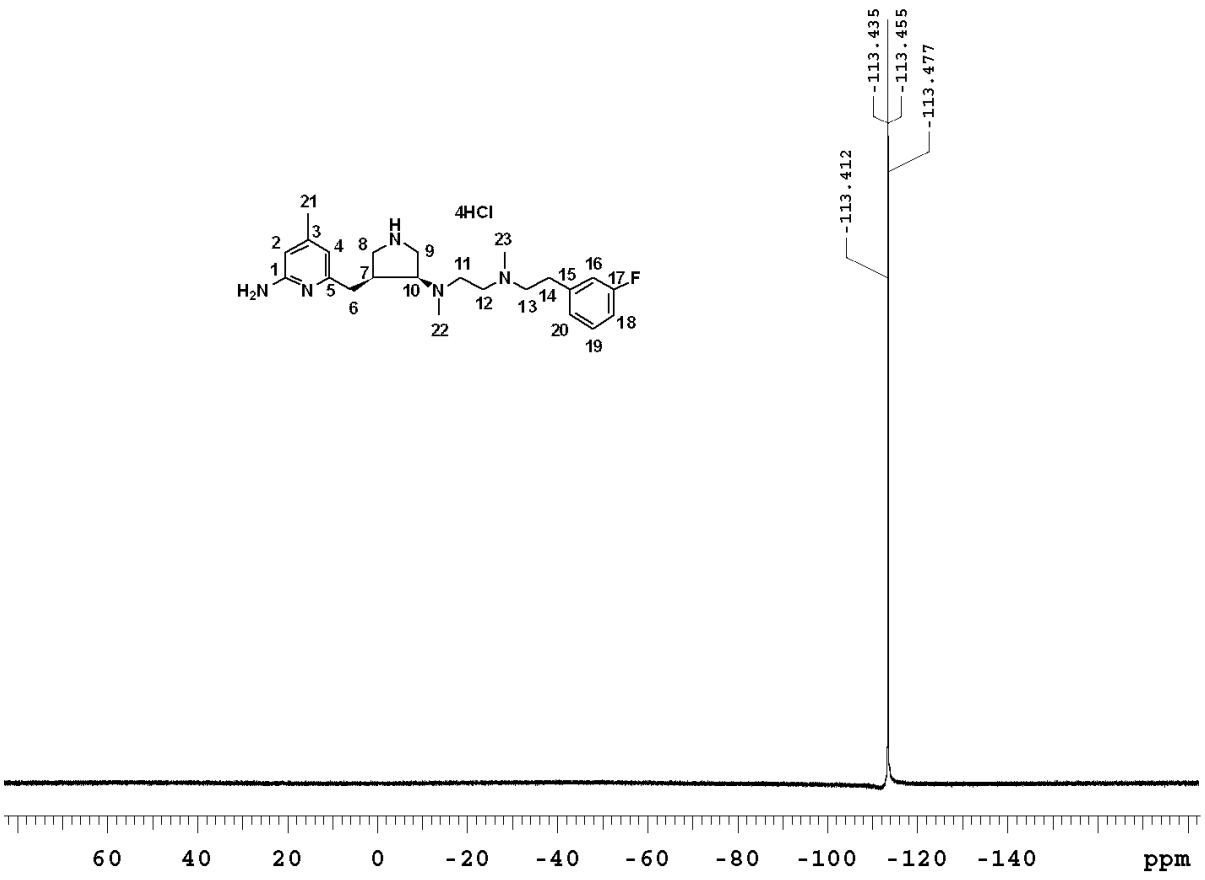

Supplementary Figure continued