Supporting Information for

Carbonylation as a novel method for the assembly of pyrazine based oligoamide alpha-helix mimetics

Seger Van Mileghem,[†a] Brecht Egle,[†a] Philippe Gilles,[a] Cedrick Veryser,[a] Luc Van Meervelt[b] and Wim M. De Borggraeve*[a]

(†) Authors contributed equally

(a) Molecular Design and Synthesis, Department of chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Heverlee, Belgium

(b) Biochemistry, Molecular and Structural Biology Section, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Heverlee, Belgium

(*) wim.deborggraeve@kuleuven.be

Table of contents

1 General Considerations

^{1}H NMR spectra

Bruker 300 Avance (300 MHz), Bruker 400 Avance (400 MHz) and Bruker 600 Avance II^{+} (600 MHz) with tetramethylsilane as internal standard with $CDCl_3$ and DMSO. The δ-values are expressed in ppm.

^{13}C NMR spectra

Bruker 300 Avance (operating at 75 MHz), Bruker 400 Avance (operating at 100 MHz) and Bruker 600 Avance II^{+} (operating at 150 MHz) with the deuterated solvent as internal standard ($CDCl_3$: 77.2 ppm, triplet; DMSO: 39.52 ppm, quintet). The δ-values are expressed in ppm.

IR spectra

- Perkin-Elmer 1720 Infrared Fourier Transform Spectrometer and Perkin Elmer 297 grating IR-spectrophotometer. The crystalline products are measured in KBr-pills. The oils are measured between NaCl plates.
- Bruker Alpha-T FT-IR spectrometer with universal sampling module. Data processing using Opus software.

Mass spectra

Spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA).
Samples were infused at 3μL/min and spectra were obtained in positive (or: negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

Melting points

Reichert-Jung Thermovar (the measurements are not corrected).

Chromatography

- TLC plates: pre-coated TLC-plates SIL G-25 (with fluorescence-indicator 254 nm): layer thickness 0.25 mm; average pore diameter 60 Å; 20x20 cm glass plates
- Silica gel for column chromatography: MP Silica 32-63, average pore diameter 60 Å, Ecochron

- MPLC apparatus: Büchi SepacoreTM flash apparatus, consisting of a C-660 Büchi fraction collector, C-615 Pump manager, C-635 UV-photometer, two C-605 pump modules and a Linseis D120S plotter.
- Reverse phase HPLC: Waters Delta 600 analytical/preparative system equipped with Waters 996 Photo Diode Array Detector. Preparative column size: Alltech C18 Prevail 5 µm, 150x22 mm, and Phenomenex Luna C18, 5 µm, 150x22 mm.

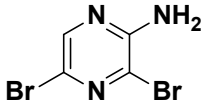
X-ray diffraction experiments

Crystal structures were determined on an Agilent SuperNova diffractometer (single source at offset, Eos detector). Using Olex2[a], the structure was solved with the ShelXS[b] structure solution program using Direct Methods and refined with the ShelXL[c] refinement package using least-squares minimization.

[a] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. *J., Appl. Cryst.* ***2009***, 42, 339-341.
[b] Sheldrick, G.M., *Acta Cryst.* **2008**, A64, 112-122.
[c] Sheldrick, G.M., *Acta Cryst.* **2015**, C71, 3-8.

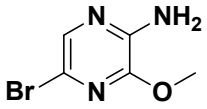
2 Preparation of building blocks

3,5-Dibromo-2-aminopyrazine



Pyrazin-2-amine (5 g, 52.6 mmol) was dissolved in a mixture of DMSO (100 mL) and water (2.5 ml). The solution was subsequently cooled to <15 °C. NBS (20 g, 112 mmol) was added slowly over a period of approx. 50 min. Afterwards the reaction was stirred at RT for 6 hours. The reaction mixture was then poured into 300 mL of ice water. The aqueous phase was extracted with EtOAc. The organic fraction was washed with sat. $NaHCO_3$ solution, water and afterwards dried over $MgSO_4$. The solvent was evaporated *in vacuo* to obtain a brown colored solid. The crude product was purified by column chromatography (heptanes/EtOAc 6:4) to give 3,5-dibromopyrazin-2-amine (11.5 g, 72%) as white-yellow crystals. R_f = 0.42. Melting point: 86-88 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 5.06 (bs, 2H), 8.04 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 123.6, 123.9, 143.1, 151.9. FT-IR (cm^{-1}): 3338, 2953. HR-MS: Calculated mass: 251.8768 Mass found: 251.8779.

5-Bromo-3-methoxypyrazin-2-amine (1a)



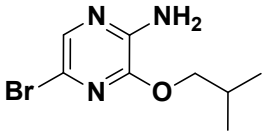
A solution of 3,5-dibromopyrazin-2-amine (1 g, 3.95 mmol) in 3 mL of dry methanol was prepared and cooled to 0 °C. NaOMe (1 mL of a 25% solution in MeOH) was then added dropwise while vigorous stirring the mixture. After addition, the reaction mixture was set to reflux for 16 hours. Afterwards the solution was allowed to cool to RT and left standing overnight. The resulting precipitate was filtered, washed with ice-cold methanol and air-dried to give 5-bromo-3-methoxypyrazin-2-amine **1a** (670 mg, 83%) as a white solid. Melting point: 137-139 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 4.00 (s, 3H), 4.85 (s, 2H), 7.63 (s, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ 54.4, 121.1, 134.4, 144.2, 147.7. FT-IR (cm^{-1}): 3484 (s, -NH_2). HR-MS: Calculated mass: 202.9694 Mass found: 202.9703.

General Procedures for S_NAr with alcohols on 3,5-dibromo-2-aminopyrazine

Procedure A: *with NaH*: The alcohol (1.5 eq.) was dissolved in dry THF (0.25 M) under an argon atmosphere. This solution was then cooled to 0 °C and NaH (1.5 eq.) was slowly added (***Caution:*** *evolution of hydrogen gas!*), keeping the temperature at 0 °C. The suspension was then allowed to stir at 0 °C for 30 min. 3,5-dibromo-2-aminopyrazine (**10**) (1 eq.), dissolved in dry THF (0.4 M), was then slowly added while keeping the temperature at 0 °C. After addition, the reaction mixture is allowed to heat to RT and then heated at 50 °C for 18 hours. The reaction mixture was subsequently cooled to RT and diluted with EtOAc. The organic phase was then washed with water and brine before being dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was then purified using MPLC.

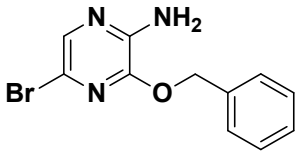
Procedure B: *with NaHMDS*: The alcohol (1.5 eq.) was dissolved in dry THF (0.15 M) under an argon atmosphere. This solution was then cooled to 0 °C and NaHMDS (1.5 eq., 1 M solution in THF) was slowly added, keeping the temperature at 0 °C. The suspension was then allowed to stir at RT for 30 min. 3,5-dibromo-2-aminopyrazine (**10**) (1 eq.), dissolved in dry THF (0.4 M), was then slowly added while keeping the temperature at 0 °C. After addition, the reaction mixture is allowed to heat to RT and then heated at 50 °C for 18 hours. The reaction mixture was subsequently cooled to RT and diluted with EtOAc. The organic phase was then washed with water and brine before being dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was then purified using MPLC.

5-Bromo-3-isobutoxypyrazin-2-amine (1b)



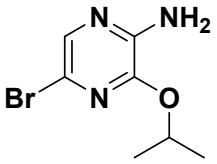
Using **procedure B**, purified by reverse phase HPLC in ACN/water (from 0% to 80% ACN in 30 minutes), **1b** was obtained as a red oil (88%). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.02 (d, J = 6.7 Hz, 6H), 2.12 (m, 1H), 4.13 (d, J = 6.7 Hz, 2H), 4.77 (bs, 2H), 7.62 (s, 1H). ^{13}C-NMR (150MHz, $CDCl_3$, ppm): δ 19.2, 27.8, 73.4, 121.1, 134.1, 144.2, 147.5. HR-MS: Calculated mass: 246.0237 Mass found: 246.0254.

3-(Benzyloxy)-5-bromopyrazin-2-amine (1c)



Using general **procedure A**, purified using MPLC (7/3 heptanes/EtOAc), **1c** was obtained as yellow crystals (81%). $R_f = 0.13$. All analytical data were found to be in accordance with the literature.[2]

5-Bromo-3-isopropoxypyrazin-2-amine (1d)



Using general **procedure A** (10 eq. IPA, 3 eq. NaH), **1d** was obtained as a yellow solid (91%) and was used after extraction ($EtOAc/H_2O$) without further purification. Melting point: 105-106 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.37 (s, 6H), 4.77 (bs, 2H), 5.32 (m, J = 6 Hz, 1H), 7.60 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 21.8, 70.5, 121.0, 133.3, 144.3, 146.9.

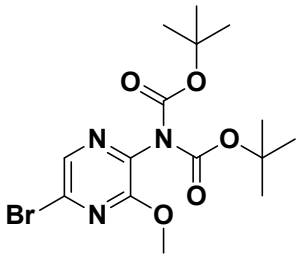
3 Synthesis of multimers

General procedure for diBoc protection

Procedure C: *For diBoc protection of pyrazine building blocks*:

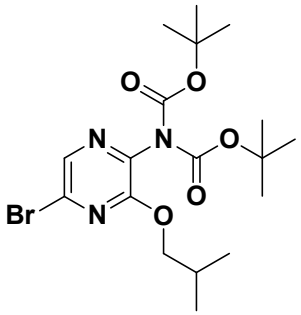
The amine (1 eq.) and DMAP (0.1 eq.) were dissolved in dry DCM (0.2 M) under an argon atmosphere. Boc_2O (2.5 eq.) was then slowly added at RT, while stirring vigorously. Afterwards the reaction was heated to reflux for 16 hours. The mixture was then cooled to RT and the solvent was evaporated *in vacuo*. The residue was suspended in EtOAc and washed with water and brine. The organic phase was then dried over $MgSO_4$, filtered and evaporated *in vacuo.*

di-*tert*-Butyl (5-bromo-3-methoxypyrazin-2-yl)imidodicarbonate (2a)



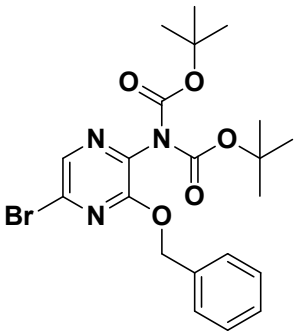
5-Bromo-3-methoxypyrazin-2-amine (**1a**) (1 g, 4.90 mmol) was dissolved in THF (Volume: 20 mL) and cooled to < 5 °C in an ice bath. Boc_2O (2.84 mL, 12.25 mmol) was slowly added and the mixture was stirred for 1 hour in the ice bath. Afterwards the solution was allowed to warm to RT and left stirring overnight. Water was added (20 mL) and the aqueous phase was extracted with EtOAc. The combined EtOAc fractions were washed with sat. $NaHCO_3$, water and subsequently dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give the crude product. Purification was carried out by MPLC (9/1 heptanes/EtOAc) to give **2a** as white crystals (1.8 g, 91%). R_f = 0.19. Melting point: 74-76 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.42 (s, 18H), 4.02 (s, 3H), 8.12 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 27.8, 54.9, 83.6, 134.9, 136.3, 136.9, 149.9, 155.2. FT-IR (cm^{-1}): 1797 (s, carbamate). HR-MS: Calculated mass: 403.0768 Mass found: 403.0743.

di-*tert*-Butyl (5-bromo-3-isobutoxypyrazin-2-yl)imidodicarbonate (2b)



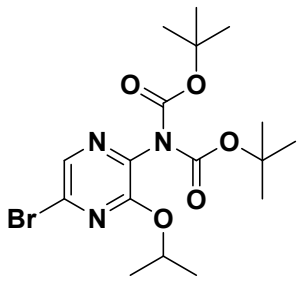
Prepared using **procedure C**, purified using MPLC (8/2 heptanes/EtOAc), **2b** was obtained as an off-white solid (81%). R_f = 0.40. Melting point 73-76 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.00 (d, J = 6.5 Hz, 6H), 1.41 (s, 9H), 2.08 (m, 1H), 4.16 (d, J = 6.5Hz, 2H), 8.09 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 19.1, 27.4, 27.9, 74.0, 83.6, 135.1, 136.0, 136.8, 149.9, 155.4. HR-MS: Calculated mass: 445.1212 Mass found: 445.1246.

di-*tert*-Butyl [3-(benzyloxy)-5-bromopyrazin-2-yl]imidodicarbonate (2c)



Prepared using **procedure C**, purified using MPLC (8/2 heptanes/EtOAc), **2c** was obtained as orange crystals (66%). R_f = 0.16. Melting point: 69-72 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.35 (18H), 5.45 (2H), 7.36 (5H), 8.13 (1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 27.8, 69.3, 83.7, 128.3, 128.4, 134.8, 135.3, 136.5, 136.9, 149.9, 154.7. HR-MS: Calculated mass: 502.0949 Mass found: 502.0949.

di-*tert*-Butyl (5-bromo-3-ispropoxypyrazin-2-yl)imidodicarbonate (2d)



Prepared using **procedure C** (but 4 eq. of Boc_2O), purified using MPLC (8/2 heptanes/EtOAc), **2d** was obtained as yellow crystals (79%). R_f = 0.18. Melting point: 81-83 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.35 (d, J = 6 Hz, 6H), 1.41 (s, 15H), 5.28-5.46 (m, 1H), 8.07 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 21.7, 27.9, 71.3, 83.4, 134.9, 135.7, 137.0, 149.8, 154.7. HR-MS: Calculated mass: 454.0949 Mass found: 454.0939 [M+Na].

General procedures for carbonylative coupling

Procedure D: *Alkoxycarbonylation of monomers.*

All solid reagents ($Pd(OAc)_2$ (5 mol%), the monomer (1 eq.) and Xantphos (10 mol%)) were brought into an oven-dried 2-necked flask with a septum, under an atmosphere of argon. The flask was evacuated and backfilled with argon, this was repeated 2 times. Methanol (10 eq.) and triethylamine (0.2 M) were added with a syringe via the septum. The resulting mixture was purged with carbon monoxide for 2 minutes (***Caution!*** *Carbon monoxide is a highly toxic and flammable gas*). The reaction was then placed under a carbon monoxide atmosphere by means of a balloon and heated to 80 °C in an oil bath for 24 hours. After this time, the mixture was cooled, diluted with EtOAc and filtered over Celite®. The resulting filtrate was evaporated *in vacuo* to obtain the crude product. Purification was carried out by MPLC.

Procedure E: *General procedure for CO precursor two-chamber system*

Chamber A of a flame-dried two-chamber reactor (Figure) was filled with 1 mg palladium(II) acetate (0.005 mmol, 1 mol%), 3 mg Xantphos (0.005 mmol, 1 mol%) and 159 mg sodium carbonate (1.50 mmol, 3 eq.). The reactor was brought under argon atmosphere by two consecutive vacuum-argon cycles. Next, chamber B was filled with 2 mL dry degassed toluene, 51 µL mesyl chloride (0.65 mmol, 1.3 eq.) and 25 µL formic acid (0.65 mmol, 1.3 eq.). In chamber A, 1 mL dry degassed toluene was added, followed by 0.50 mmol aryl bromide (1 eq.) and 0.75 mmol amine/alcohol (1.1 eq.). Then the reactor was placed in an oil-

bath at 100 °C. Finally, 181 µL triethylamine (1.30 mmol, 2.6 eq.) was added by injection through the septum in chamber B and instant gas formation was observed.

*[**Remark:** when the aryl bromide and/or amine are solids at room temperature, they were added to Chamber A after the addition of palladium(II) acetate and Xantphos.]*

After 2 to 24 hours, the reactor was brought to room temperature and the residual pressure was released carefully by removing one of the caps. As carbon monoxide is a highly toxic gas, the reaction was stirred at room temperature for 15 minutes to ensure that all carbon monoxide gas was extracted out of the fume hood. Next, the content of chamber A was transferred to a 100 mL round-bottomed flask. Chamber A was rinsed five times with 2 mL of EtOAc and these fractions were added to the same flask. After the addition of 1 g Celite®, the solvent was removed under reduced pressure. For purification, the crude product was dry-loaded onto the MPLC system.

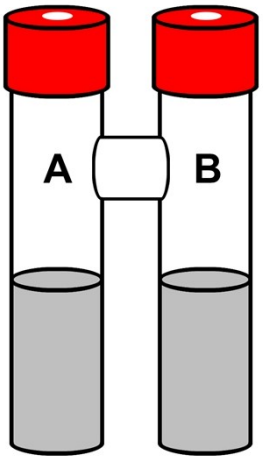
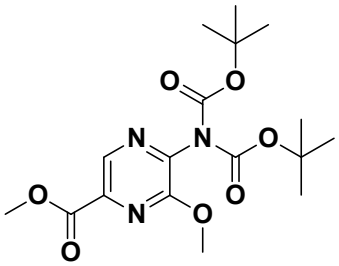


Figure 1. Representation of the two-chamber reactor. Inner volume = 20 mL.

Procedure F: *Aminocarbonylative coupling of monomers*

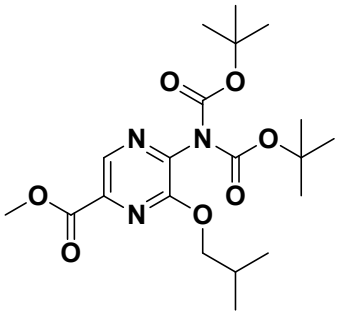
All solid reagents: monomer A (1 eq.), monomer B (1 eq.), $Pd(OAc)_2$ (5 mol%), Na_2CO_3 (3 eq.) and Xantphos (5 mol%) were brought in a dry two-necked flask with a cooler and a septum, under an atmosphere of argon. The flask was evacuated and subsequently purged with argon. This was repeated 2 times. Dry degassed toluene (0.2 M) was added via a syringe. The mixture was purged with carbon monoxide for 2 minutes via a needle through the septum. (***Caution!*** *Carbon monoxide is a highly toxic and flammable gas*). Then a carbon monoxide atmosphere was created by means of a balloon. The mixture was stirred at 80 °C, for 24 hours. Afterwards, the reaction was cooled to room temperature, diluted with EtOAc and filtered over a plug of Celite®. The filtrate was evaporated to afford the crude product which was purified by MPLC.

Methyl 5-[bis(*tert*-butoxycarbonyl)amino]-6-methoxypyrazine-2-carboxylate (3a)



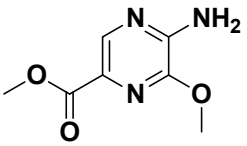
Using **Procedure D**, after purification by MPLC (8/2 heptanes/EtOAc), the product was obtained as white crystals (88%). R_f = 0.18. Melting point: 99-102 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.40 (s, 18H), 4.05 (s, 3H), 4.10 (s, 3H), 8.55 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 52.9, 54.5, 75.5, 83.7, 136.6, 139.0, 141.4, 149.6, 155.4, 164.2. FT-IR (cm^{-1}): 1742, 1705 (carbamate). HR-MS: Calculated mass: 283.1180 Mass found: 283.1182 [M – Boc].

Methyl 5-[bis(*tert*-butoxycarbonyl)amino]-6-isobutoxypyrazine-2-carboxylate (3b)



Using **Procedure D**, after purification by MPLC (8/2 heptanes/EtOAc), the product was obtained as a white solid (89%). R_f = 0.25. Melting point 59-62 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.01 (d, J = 6.8 Hz, 6H), 1.39 (s, 18H), 2.10 (m, 1H), 4.00 (s, 3H), 4.26 (d, J = 6 Hz, 2H), 8.71 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 19.1, 27.8, 27.9, 52.9, 73.5, 83.7, 136.3, 139.1, 141.3, 149.6, 155.6, 164.2. HR-MS: Calculated mass: 425.2162 Mass found: 425.2125.

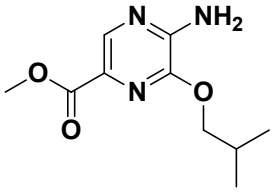
Methyl 5-amino-6-methoxypyrazine-2-carboxylate (4a)



Methyl 5-[bis(tert-butoxycarbonyl)amino]-6-methoxypyrazine-2-carboxylate (**3a**) (800 mg, 2.1 mmol) was dissolved in 10 mL of dry DCM and the solution was cooled in an ice bath. To

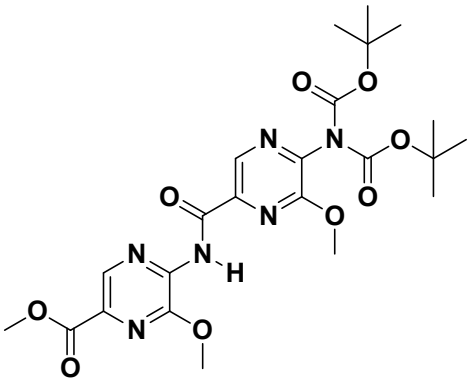
this TFA (3.2 mL, 41.7 mmol) was added dropwise while stirring. After the addition of TFA, the reaction was stirred at RT for 6 hours. Afterwards, the solvent was evaporated *in vacuo*. The residue was purified using MPLC (7/3 EtOAc/heptanes) to obtain the pure product as off-white crystals (350 mg, 92%). R_f = 0,10. Melting point: 87-88 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 3.93 (s, 3H), 4.11 (s, 3H), 5.81 (bs, 2H), 8.35 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 52.2, 54.0, 128.6, 138.1, 147.3, 147.8, 165.3. FT-IR (cm^{-1}): 3338, 3111, 2953, 2876, 1715, 1551, 1447. HR-MS: Calculated mass: 183.0644 Mass found: 183.0650.

Methyl 5-amino-6-isobutoxypyrazine-2-carboxylate (4b)



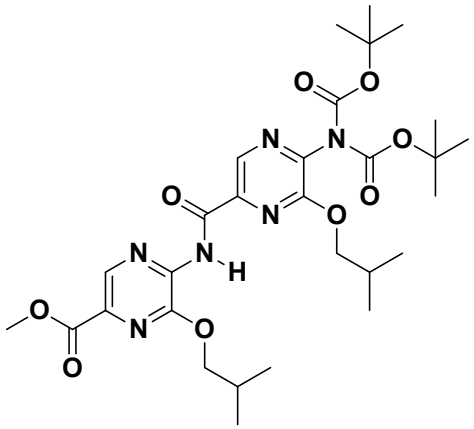
In a sealed vessel under an argon atmosphere, methyl 5-[bis(tert-butoxycarbonyl)amino]-6-isobutoxypyrazine-2-carboxylate (**3b**) (220 mg, 0.517 mmol) was suspended in 15 mL of water. The mixture was stirred vigorously while heating to 100 °C for 24 hours. The suspension was then allowed to cool to RT and extracted three times with EtOAc. The combined organic phases were washed with water, brine and dried over $MgSO_4$. After filtration, the filtrate was evaporated *in vacuo* to give the pure product (**4b**) as white crystals (90 mg, 77%). R_f = 0.11 (heptanes/EtOAc 7:3). Melting point: 115-117 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.04 (d, J = 6.6 Hz), 2.13 (m, 1H), 3.92 (s, 3H), 4.25 (d, J = 6.6 Hz, 2H), 5.33 (bs, 2H), 8.37 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 19.3, 27.9, 29.7, 52.2, 72.9, 128.6, 137.9, 147.2, 147.8, 165.3. HR-MS: Calculated mass: 226.11860 Mass found: 226.1201.

Methyl 5-[((5-[bis(*tert*-butoxycarbonyl)amino]-6-methoxypyrazin-2-yl)11-carbonyl)amino]-6-methoxypyrazine-2-carboxylate (5a)



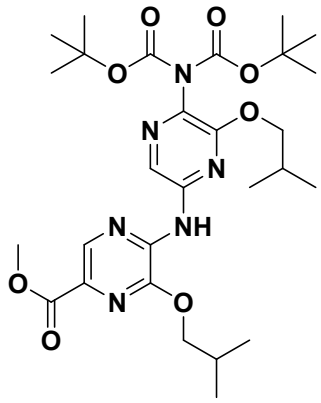
Using **procedure F**, after purification using MPLC (1/1 heptanes/EtOAc), **5a** was obtained as white crystals (60%). R_f = 0.16. Melting point: 242 °C (decomposition). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 2.17 (s, 18H), 3.99 (s, 3H), 4.17 (s, 3H), 4.21 (s, 3H), 8.81 (s, 1H), 8.98 (s, 1H), 10.53 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 27.8, 52.7, 54.2, 55.0, 84.0, 134.0, 135.4, 137.6, 139.1, 140.3, 142.1, 149.1, 149.7, 154.2, 159.7, 164.3. HR-MS: Calculated mass: 534.2074 Mass found: 534.2103.

Methyl 5-[((5-[bis(*tert*-butoxycarbonyl)amino]-6-isobutoxypyrazin-2-yl)carbonyl)amino]-6-isobutoxypyrazine-2-carboxylate (5b)



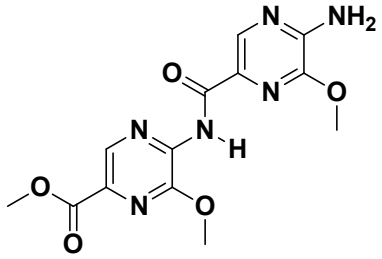
Using **procedure F**, after purification using MPLC (1/1 heptanes/EtOAc), **5b** was obtained as a yellow oil (59%). Rf = 0.37. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.07 (d, J = 7 Hz, 6H), 1.10 (d, J = 7Hz, 6H), 1.43 (s, 18H), 2.18 (bm, 2H), 3.99 (s, 3H), 4.25 (d, J = 6.4 Hz, 2H), 4.37 (d, J = 6.4 Hz, 2H), 8.80 (s, 1H), 8.98 (s, 1H), 10.39 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 19.2, 19.4, 21.1, 28.1, 52.7, 73.5, 73.9, 83.9, 134.0, 135.4, 137.3, 139.4, 140.3, 142.2, 148.9, 149.8, 154.5, 159.9, 164.4. HR-MS: Calculated mass: 618.3013, Mass found: 618.3000.

Methyl-[(5-{bis[(tert-butoxy)carbonyl]amino}-6-(2-methylpropoxy)pyrazin-2-yl)amino]-6-(2-methylpropoxy)pyrazine-2-carboxylate (5b', Buchwald-Hartwig amination product)



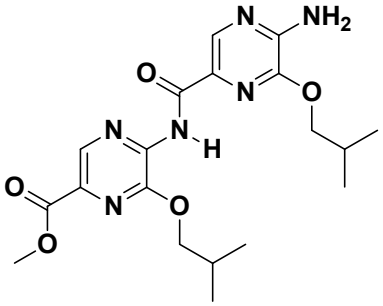
Using **procedure F**, after purification using MPLC (1/1 heptanes/EtOAc), **5b'** was obtained as off-white crystals (59%). Melting point: 130-133 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 9.28 (s, 1H), 8.60 (s, 1H), 7.82 (s, 1H), 4.36 (d, *J* = 6.7 Hz, 2H), 4.12 (d, *J* = 6.5 Hz, 2H), 3.95 (s, 3H), 2.32 – 2.16 (m, 1H), 2.15 – 2.00 (m, *J* = 13.3, 6.7 Hz, 1H), 1.40 (s, 18H), 1.09 (d, *J* = 6.7 Hz, 6H), 1.01 (d, *J* = 6.7 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ 165.1, 154.3, 150.6, 147.5, 145.1, 142.3, 137.1, 132.6, 130.6, 123.8, 83.0, 73.7, 73.1, 52.5, 28.1, 28.0, 19.4, 19.3. HR-MS: Calculated mass: 591.3137 Mass found: 591.3120 [M+H]

Methyl 5-[[(5-amino-6-methoxypyrazin-2-yl)carbonyl]amino]-6-methoxypyrazine-2-carboxylate (6a)



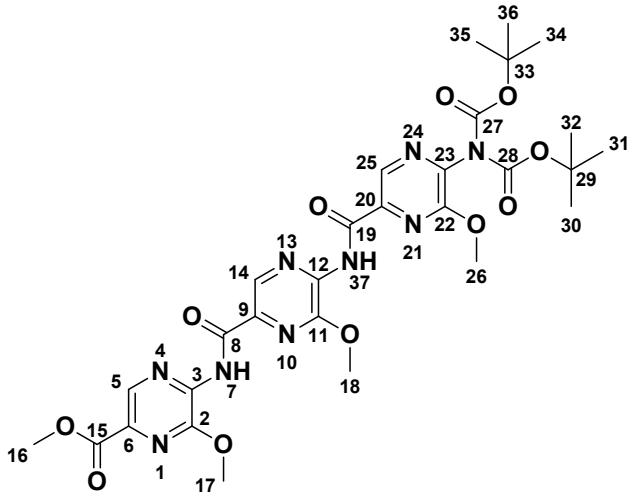
Me thyl-5-[((5-[bis(*tert*-butoxycarbonyl)amino]-6-isobutoxypyrazin-2-yl)carbonyl) amino]-6-isobutoxypyrazine-2-carboxylate (**5a**) (200 mg, 0.374 mmol) was dissolved in 20 mL of DCM under an atmosphere of argon. The solution was cooled to 0 °C in an ice bath and TFA (0.577 mL, 7.48 mmol) was slowly added while stirring. The reaction mixture was then stirred at RT for 4 hours. Afterwards, the solvent was evaporated *in vacuo* to give a white-yellow powder, which was washed with water, MeOH, heptane, EtOAc and DCM to afford **6b** as an off-white powder (125 mg, quant.). Melting point: 290 °C (decomposition). Due to the poor solubility of this product in all solvents tried, analytical data are not available.

Methyl 5-[5-amino-6-(2-methylpropoxy)pyrazine-2-amido]-6-(2-methylpropoxy) pyrazine-2-carboxylate (6b)



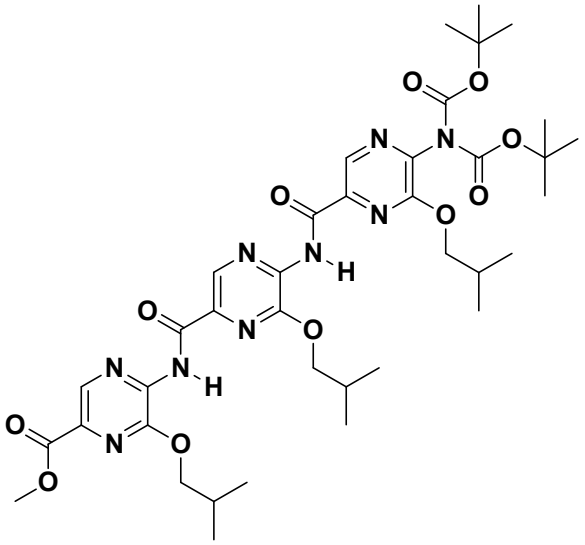
In a sealed vessel under an argon atmosphere, methyl 5-[((5-[bis(*tert*-butoxycarbonyl)amino]-6-isobutoxypyrazin-2-yl)carbonyl) amino]-6-isobutoxypyrazine-2-carboxylate (**5b**) (115 mg, 0.186 mmol) was suspended in 7 mL of water. The mixture was stirred vigorously while heating to 100 °C for 72 hours. The suspension was then allowed to cool to RT and extracted three times with EtOAc. The combined organic phases were washed with water, brine and dried over $MgSO_4$. After filtration, the filtrate was evaporated *in vacuo* to give the pure product as white crystals (72 mg, 92%). R_f = 0.31 (heptanes/EtOAc 2:8). Melting point: 196-198 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.095 (d, J = 6.8 Hz, 6H), 1.10 (d, J = 6.8 Hz, 6H), 2.19 (m, 2H), 3.97 (s, 3H), 4.23 (d, J = 6 Hz, 2H), 4.35 (d, J = 6Hz, 2H), 5.60 (bs, 2H), 8.59 (s, 1H), 8.77 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 19.3, 19.5, 28.0, 28.1, 52.6, 72.9, 73.7, 129.5, 133.0, 136.8, 137.4, 141.0, 146.0, 148.4, 148.8, 161.3, 164.9. HR-MS: Calculated mass: 418.1965 Mass found: 418.1971.

Methyl 5-[((5-[((5-[bis(*tert*-butoxycarbonyl)amino]-6-methoxypyrazin-2-yl)carbonyl)amino]-6-methoxypyrazin-2-yl)carbonyl)amino]-6-methoxypyrazine-2-carboxylate (7a)



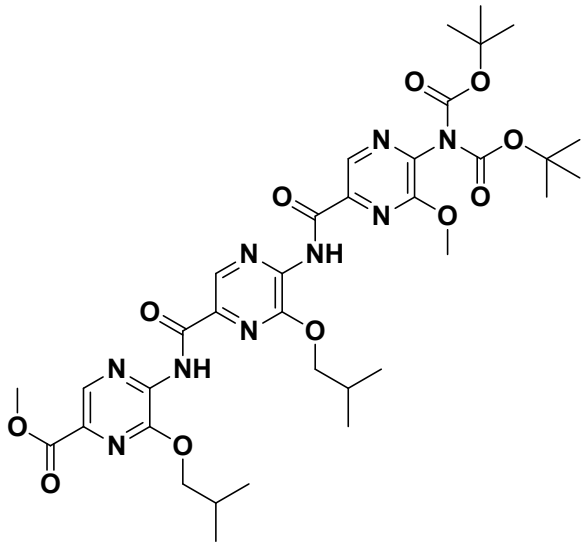
Using **procedure F**, after purification using MPLC (9/1 EtOAc/heptanes), **7a** was obtained as a white solid (17%). R_f = 0.23. Peak assignments of the ^{13}C and ^{1}H NMR spectra were confirmed using 2D NMR experiments. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.44 (s, 18H, $H^{30\text{-}32,\ 34\text{-}37}$), 3.99 (s, 3H, H^{16}), 4.18 (s, 3H, H^{26}), 4.21 (s, 3H, H^{18}), 4.27 (s, 3H, H^{17}), 8.81 (s, 1H, H^{14}), 9.00 (s, 1H, H^{25}), 9.04 (s, 1H, H^{5}), 10.40 (s, 1H, H^{7}), 10.50 (s, 1H, H^{37}). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 27.9 ($C^{30\text{-}32,\ 34\text{-}36}$), 52.7 ($C^{15}$), 54.2 ($C^{18}$), 54.7 ($C^{17}$), 55.0 ($C^{26}$), 84.1 ($C^{29,33}$), 133.8 ($C^{9}$), 134.5 ($C^{6}$), 135.5 ($C^{5}$), 136.3 ($C^{25}$), 137.6 ($C^{14}$), 139.0 ($C^{20}$), 140.5 ($C^{12}$), 140.9 ($C^{3}$), 142.2 ($C^{23}$), 148.0 ($C^{2}$), 149.0 ($C^{11}$), 149.7 ($C^{27,28}$), 154.2 ($C^{22}$), 159.5 ($C^{8}$), 159.8 ($C^{19}$), 164.3 ($C^{15}$). HR-MS: Calculated mass: 483.1266 Mass found: 483.1278 [M-2Boc].

Methyl 5-[((5-[((5-[bis(*tert*-butoxycarbonyl)amino]-6-isobutoxypyrazin-2-yl)carbonyl)amino]-6-isobutoxypyrazin-2-yl)carbonyl)amino]-6-isobutoxypyrazine-2-carboxylate (7b)



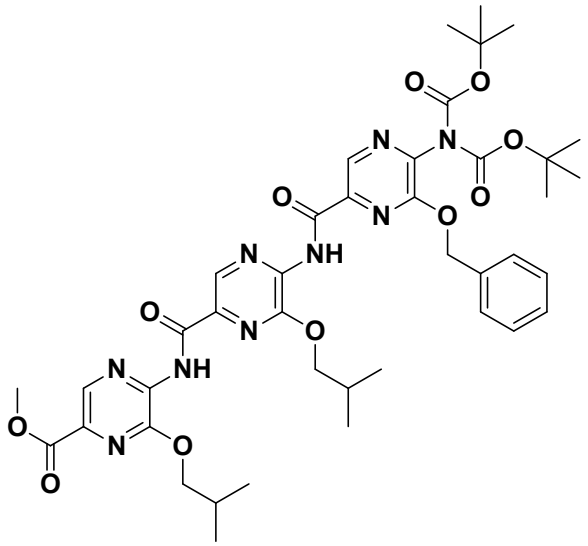
Using **procedure F**, after purification using MPLC (8/2 EtOAc/heptanes), **7b** was obtained as an off-white wax (19%). R_f = 0.4. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.08, 1.11, 1.16, 1.44, 2.19, 3.99, 4.26, 4.35, 4.37, 8.79, 9.00, 9.06, 10.26, 10.37. ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 19.2, 19.48, 19.50, 27.9, 28.06, 28.09, 28.2, 52.7, 73.5, 73.8, 84.0, 133.8, 134.6, 135.5, 136.3, 137.4, 139.3, 140.5, 141.0, 142.3, 147.9, 148.9, 149.8, 154.5, 159.8, 160.0, 164.4.

Methyl-[5-(5-{bis[(tert-butoxy)carbonyl]amino}12-6-methoxypyrazine-2-amido)-6-(2-methylpropoxy)pyrazine-2-amido]-6-(2-methylpropoxy)pyrazine-2-carboxylate (7c)



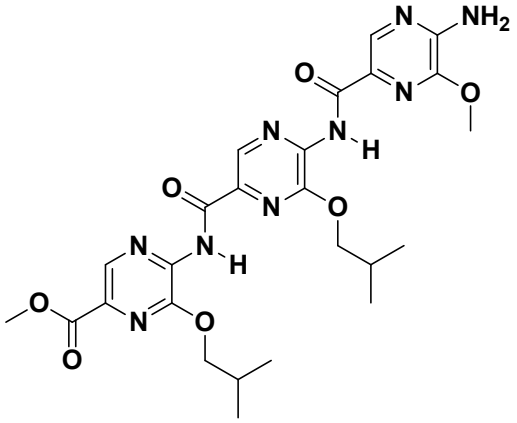
Using **procedure F**, after purification using MPLC (98/2 DCM/MeOH), **7c** was obtained as a yellow solid (23%). R_f = 0.35. Melting point: 215-219 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.6 Hz, 6H), 1.15 (d, *J* = 6.6 Hz, 6H), 1.44 (s, 18H), 3.98 (s, 3H), 4.14 (s, 3H), 4.40 – 4.32 (m, 4H), 8.78 (s, 1H), 9.01 (s, 1H), 9.05 (s, 1H), 10.25 (s, 1H), 10.43 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.4, 19.5, 27.9, 28.1, 28.2, 52.7, 54.2, 73.7, 73.8, 84.1, 133.8, 134.7, 135.8, 136.4, 137.4, 139.1, 140.5, 141.0, 142.3, 147.9, 148.9, 149.8, 154.3, 159.6, 160.0, 164.4. HR-MS: Calculated mass: 770.3468 Mass found: 770.3480 [M+H].

Methyl-{5-[6-(benzyloxy)-5-{bis[(tert-butoxy)carbonyl]amino}pyrazine-2-amido]-6-(2-methylpropoxy)pyrazine-2-amido}-6-(2-methylpropoxy)pyrazine-2-carboxylate (7d)



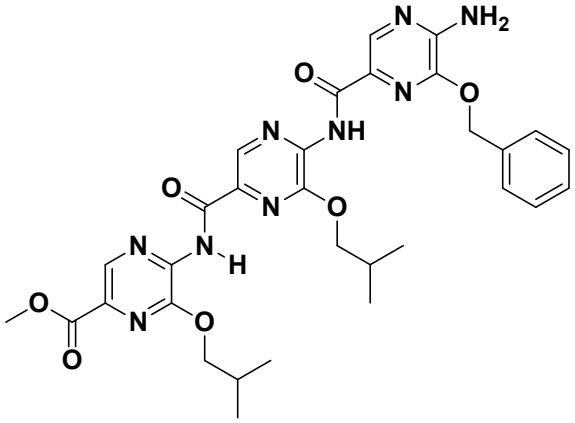
Using **procedure F**, after purification using MPLC (98/2 DCM/MeOH), **7d** was obtained as a yellow solid (24%). R_f = 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 – 1.06 (m, *J* = 6.7, 2.4 Hz, 11H), 1.38 (s, 15H), 2.25 – 2.11 (m, *J* = 13.3, 6.6 Hz, 3H), 3.98 (s, 3H), 4.40 – 4.28 (m, *J* = 10.5, 6.6 Hz, 4H), 5.54 (s, 2H), 7.45 – 7.38 (m, *J* = 5.2, 3.6 Hz, 5H), 8.79 (s, 1H), 9.04 (s, 1H), 9.07 (s, 1H), 10.25 (s, 1H), 10.45 – 10.41 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.4, 19.5, 27.8, 28.1, 28.2, 52.7, 69.1, 73.8, 73.8, 84.1, 128.1, 128.8, 128.9, 133.8, 134.7, 135.9, 136.4, 137.4, 139.1, 140.5, 141.0, 142.3, 147.9, 148.9, 149.8, 153.9, 159.6, 160.0, 164.4. HR-MS: Calculated mass: 846.3781 Mass Found: 846.3801 [M+H].

Methyl-5-[5-(5-amino-6-methoxypyrazine-2-amido)-6-(2-methylpropoxy)pyrazine-2-amido]-6-(2-methylpropoxy)pyrazine-2-carboxylate (8a)



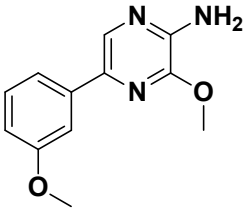
7c was dissolved in dry DCM (0.2 M) and the solution was cooled in an ice bath. Subsequently, TFA (20 eq.) was added dropwise while stirring. After the addition of TFA, the reaction was stirred at RT for 6 hours. Afterwards, the solvent was evaporated *in vacuo* to obtain the pure product as a yellow solid (98%). ^{1}H-NMR (400 MHz, CDCl3) δ 10.31 (s, 1H), 10.26 (s, 1H), 9.03 (s, 1H), 8.79 (s, 1H), 8.63 (s, 1H), 5.38 (s, 2H), 4.36 (d, J = 6.7 Hz, 2H), 4.32 (d, J = 6.5 Hz, 3H), 4.13 (s, 3H), 3.98 (s, 3H), 2.26 – 2.16 (m, 3H), 1.15 (d, J = 6.7 Hz, 6H), 1.10 (d, J = 6.7 Hz, 7H). FT-IR (cm^{-1}): 3499 ($-NH_2$), 3338, 2919, 1719. HR-MS: Calculated mass: 570.2419 Mass found: 570.2416 [M+H].

Methyl-5-{5-[5-amino-6-(benzyloxy)pyrazine-2-amido]-6-(2-methylpropoxy)pyrazine-2-amido}-6-(2-methylpropoxy)pyrazine-2-carboxylate (8b)



7d was dissolved in dry DCM (0.2 M) and the solution was cooled in an ice bath. Subsequently, TFA (20 eq.) was added dropwise while stirring. After the addition of TFA, the reaction was stirred at RT for 6 hours. Afterwards, the solvent was evaporated *in vacuo* to obtain the pure product as a yellow solid (quant.). Melting point: 244-246 °C .^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 – 1.04 (m, *J* = 6.7, 1.9 Hz, 12H), 2.27 – 2.09 (m, 2H), 3.97 (d, *J* = 2.3 Hz, 3H), 4.39 – 4.28 (m, 4H), 5.48 (s, 4H), 7.51 – 7.43 (m, 5H), 8.65 (s, 1H), 8.78 (s, 1H), 9.03 (s, 1H), 10.26 (s, 1H), 10.34 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.5, 19.6, 28.2, 28.3, 52.8, 69.0, 73.8, 73.9, 128.7, 129.1, 129.2, 133.8, 133.9, 135.2, 136.6, 137.5, 137.6, 137.6, 140.8, 141.8, 145.7, 147.8, 148.5, 149.0, 160.4, 161.0, 164.6. HR-MS: Calculated mass: 846.3781 Mass found: 846.3801 [M+H].

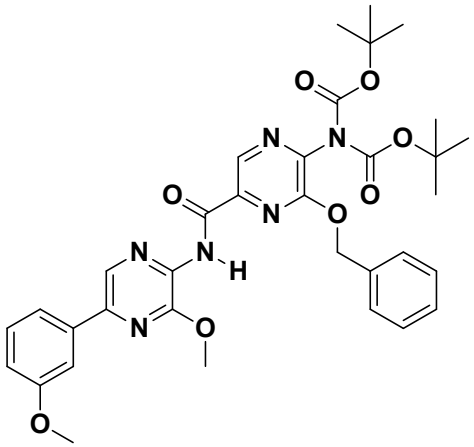
3-methoxy-5-(3-methoxyphenyl)pyrazin-2-amine (9)



5-bromo-3-methoxypyrazin-2-amine (**1a**) (246 mg; 1.21 mmol), (2-methoxyphenyl)boronic acid, (220 mg; 1.45 mmol), SPhos (4 mol%), $Pd(OAc)_2$ (2 mol%) and K_2CO_3 (500 mg; 3.62 mmol) were brought in a dry two-necked flask with a cooler and a septum, under an atmosphere of argon. The flask was evacuated and subsequently purged with argon. This was repeated two times. A degassed mixture of ACN/water (3/2; 6.5 mL; 0.2 M) was added via a syringe. The mixture was stirred at 100 °C, for 24 hours. Afterwards, the reaction was cooled to RT, diluted with EtOAc and filtered over a plug of Celite®. The filtrate was dried over

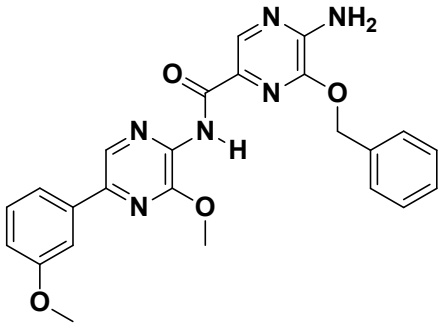
$MgSO_4$, filtered and evaporated *in vacuo*. The reaction mixture was purified using MPLC (75/25 heptanes/EtOAc) to give 3-methoxy-5-(3-methoxyphenyl)pyrazin-2-amine (**9**) as a white solid (203 mg, 73%). R_f = 0.13. Melting point: 92-94 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 3.87 (s, 3H), 4.08 (s, 3H), 4.95 (s, 2H), 6.87 (m, 1H), 7.33 (m, 1H), 7.48 (m, 2H), 8.03 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 53.4, 55.3, 111.3, 112.9, 117.8, 129.7, 130.0, 138.0, 138.7, 144.4, 147.7, 156.0. HR-MS: Calculated mass: 231.1008 Mass found: 231.1007.

di-*tert*-butyl [3-(benzyloxy)-5-([[3-methoxy-5-(3-methoxyphenyl)pyrazin-2-yl]amino]carbonyl)pyrazin-2-yl]imidodicarbonate



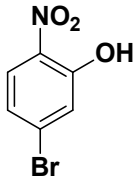
Using **procedure F**, after purification using MPLC (1/1 heptanes/EtOAc), the product was obtained as white crystals (21%). R_f = 0.34. Melting point: 101-103 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.37, 3.90, 4.20, 5.62, 7.37, 7.39, 7.42, 7.50, 7.58, 8.54, 8.98, 10.19. ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 27.8, 54.2, 55.4, 68.9, 83.9, 112.4, 114.4, 118.8, 127.9, 128.6, 128.7, 130.0, 131.2, 135.3, 135.4, 136.0, 137.4, 139.6, 141.7, 144.1, 149.4, 149.7, 153.6, 160.1. HR-MS: Calculated mass: 659.2824 Mass found: 659.2829.

Methyl 5-([[5-amino-6-(benzyloxy)pyrazin-2-yl]carbonyl]amino)-6-methoxypyrazine-2-carboxylate (10)



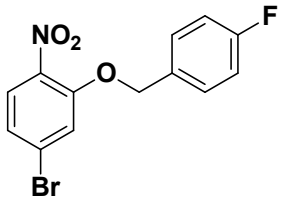
di-*tert*-butyl [3-(benzyloxy)-5-([[3-methoxy-5-(3-methoxyphenyl)pyrazine-2-yl]amino] carbonyl)pyrazin-2-yl]imidodicarbonate (65 mg, 0.01 mmol) was dissolved in 8 mL of DCM under an atmosphere of argon. The solution was cooled to 0 °C in an ice bath and TFA (0.15 mL, 1.97 mmol) was slowly added while stirring. The reaction mixture was then stirred at RT for 4 hours. Afterwards, the solvent was evaporated to give a white-yellow powder, which was dissolved in EtOAc and extracted with $NaHCO_3$. The organic phase was evaporated *in vacuo* to give **10** as a yellow powder (45 mg, quant.). Melting point: 240-243 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 3.89, 4.17, 5.40, 5.55, 6.94, 6.95, 6.97, 6.98, 7.37, 7.40, 7.42, 7.42, 7.44, 7.53, 7.53, 7.55, 7.56, 7.57, 7.58, 7.59, 8.51, 8.60, 10. ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 54.1, 55.4, 68.6, 112.2, 114.1, 118.7, 128.5, 128.77, 128.82, 129.8, 129.9, 131.1, 135.6, 136.5, 136.8, 137.7, 143.1, 145.3, 148.0, 149.2, 160.1, 161.0. HR-MS: Calculated mass: 459.1775 Mass found: 459.1772.

5-bromo-2-nitrophenol (12)



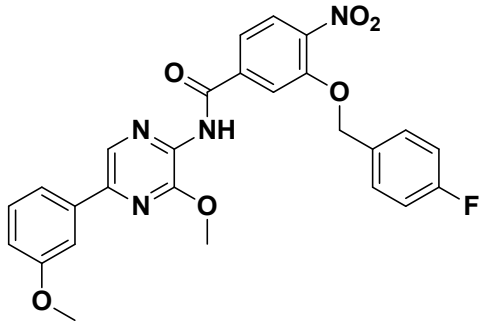
KO*t*Bu (5.54 g, 49.40 mmol) was added to 20 mL of $NH_{3(l)}$ under an argon atmosphere while stirring. A solution of cumene hydroperoxide (1.56 mL, 10.86 mmol) and 1-bromo-4-nitrobenzene (2 g, 9.90 mmol) in 7 mL of dry THF was then added dropwise. The reaction mixture was refluxed at -33 °C for 30 minutes, after which the reaction was quenched by first slowly adding solid NH_4Cl, followed by sat. aqueous NH_4Cl. Aqueous HCl (1 M) was then added until an acidic pH was observed on a pH indicator strip. The mixture was subsequently extracted with EtOAc (3x50 mL), dried and evaporated *in vacuo*. Purification was performed using MPLC (9/1 heptanes/EtOAc) to give **12** as bright yellow crystals (1.23 g, 57%). R_f = 0.42. Melting point: 28-29 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 7.14 (dd, J = 2.9Hz, 1H), 7.38 (d, J = 2Hz, 1H), 7.98 (d, J = 9Hz, 1H), 10.63 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 123.0, 123.9, 126.1, 132.3, 132.7, 155.3. FT-IR (cm^{-1}): 1521, 1310 (s, -NO_2). HR-MS: Calculated mass: 215.9302 Mass found: 215.9294.

4-bromo-2-[(4-fluorobenzyl)oxy]-1-nitrobenzene (13)



5-Bromo-2-nitrophenol (**12**) (500 mg, 2.29 mmol), *p*-fluorobenzylalcohol (318 mg, 2.52 mmol) and PPh_3 (902 mg, 3.44 mmol) were dissolved in 4 mL of dry THF under an argon atmosphere. The solution was then cooled to 0 °C and DIAD (696 mg, 3.44 mmol) was slowly added while keeping the temperature at 0 °C. Afterwards the reaction mixture was allowed to warm to RT and stirred for an additional 18 hours. Then the solvent was evaporated and the residue was redissolved in EtOAc and filtered over silica gel. The filtrate was once again evaporated *in vacuo* to deliver the crude product. Purification was performed using MPLC (9/1 heptanes/EtOAc) to give product **13** as a yellow solid (462 mg, 62%). R_f = 0.25. Melting point: 80-82 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 5.18 (s, 2H), 7.10 (t, *J* = 8.7 Hz, 2H), 7.21 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 7.44 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 71.0 (s), 115.8 (d, *J* = 21.7 Hz), 118.5 (s), 124.1 (s), 127.0 (s), 128.4 (s), 129.0 (d, *J* = 8.3 Hz), 130.6 (d, *J* = 3.2 Hz), 139.0 (s), 152.4 (s), 162.8 (d, *J* = 247.2 Hz). HR-MS: Several ionization methods tried. Suspicion that compound is not ionisable.

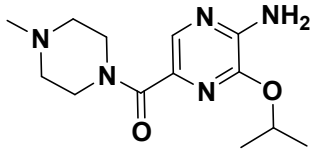
3-[(4-fluorobenzyl)oxy]-*N*-(3-methoxy-5-morpholin-4-ylpyrazin-2-yl)-4-nitrobenzamide (14)



Using **procedure F**, after purification using reverse phase HPLC in ACN/water (from 0% to 80% ACN in 30 minutes), **14** was obtained as yellow crystals (65%). Melting point: 83-85 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 3.90 (s, 3H), 4.18 (s, 3H), 5.30 (s, 2H), 6.99 (d, J = 9Hz, 1H), 7.09 (t, J = 9Hz, 2H), 7.37-7.51 (m, 3H), 7.54-7.60 (m, 2H), 7.79 (s, 1H), 7.94 (d, J = 9Hz, 1H), 8.45 (s, 1H), 8.50 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 54.2 (s), 55.4 (s),

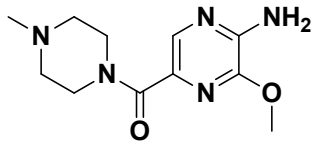
70.9 (s), 112.4 (s), 114.6 (s), 115.3 (s), 115.8 (d, *J* = 21.7 Hz), 118.4 (s), 118.8 (s), 125.9 (s), 129.2 (d, *J* = 8.3 Hz), 130.0 (s), 130.7 (d, *J* = 3.3 Hz), 131.0 (s), 135.8 (s), 137.2 (s), 139.2 (s), 142.3 (s), 144.9 (s), 149.6 (s), 151.9 (s), 160.1 (s), 162.68 (s), 162.73 (d, *J* = 123.7 Hz). HR-MS: Calculated mass: 505.1518 Mass found: 505.1520.

(5-amino-6-isopropoxypyrazin-2-yl)(4-methylpiperazin-1-yl)methanone (15a)



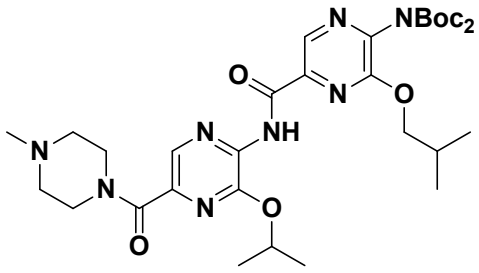
Using **procedure E**, after purification using MPLC (95/5 DCM/MeOH), **15a** was obtained as yellow crystals (62%). R_f = 0.15. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.38 (d, *J* = 6.2 Hz, 6H), 2.32 (s, 4H), 2.46 (s, 5H), 3.76 (s, 4H), 5.04 (s, 2H), 5.30 – 5.21 (m, 1H), 8.02 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 22.0, 46.1, 69.6, 77.0, 77.2, 133.6, 135.7, 145.0, 146.2, 166.2.

(5-amino-6-methoxypyrazin-2-yl)(4-methylpiperazin-1-yl)methanone (15b)



Using **procedure E**, after purification using MPLC (95/5 DCM/MeOH), **15b** was obtained as a yellow solid (53%). R_f = 0.12. Melting point: 167-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.46 (bs, 4H), 3.76 (bs, 4H), 3.94 (s, 3H), 5.32 (bs, 2H), 8.01 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 42.6, 46.0, 47.2, 53.7, 54.6, 55.0, 133.3, 136.2, 145.8, 146.2, 166.1, FT-IR (cm^{-1}): 3394 (-NH_2), 2996, 2805, 1611. HR-MS: Calculated mass: 252.1455 Mass found: 252.1453 [M+H].

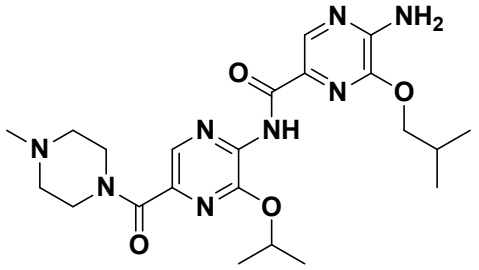
***tert*-butyl *N*-[(tert-butoxy)carbonyl]-N-(5-{[5-(4-methylpiperazine-1-carbonyl)-3-(propan-2-yloxy)pyrazin-2-yl]carbamoyl}-3-(2-methylpropoxy)pyrazin-2-yl)carbamate**



Using procedure E, after purification using MPLC (95/5 DCM/MeOH), the product was obtained as yellow crystals (16% (43% with recovery of starting material)). R_f = 0.13. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 1.07 (d, *J* = 6.7 Hz, 6H), 1.42 (s, 18H), 1.45 (d, *J* = 6.2 Hz, 6H), 1.79 (s, 2H), 2.23 – 2.10 (m, 1H), 2.33 (s, 4H), 2.41 (s, 2H), 2.52 (s, 2H), 3.61 (s, 2H), 3.81 (s, 2H), 4.26 (d, *J* = 6.5 Hz, 2H), 5.46 – 5.35 (m, 1H), 8.36 (s, 1H), 8.95 (s, 1H), 10.33 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 19.3, 22.1, 27.9, 28.1, 46.1, 70.9, 73.5, 83.9, 134.7, 135.2, 138.3, 139.5, 139.6, 141.9, 147.3, 149.8, 154.4, 159.7, 165.2. HR-MS: Calculated mass: 673.3668 Mass found: 673.3690 [M+H].

5-amino-6-isobutoxy-*N*-(3-isopropoxy-5-(4-methylpiperazine-1-carbonyl)pyrazin-2-yl)pyrazine-2-carboxamide (16)



tert-butyl *N*-[(tert-butoxy)carbonyl]-N-(5-{[5-(4-methylpiperazine-1-carbonyl)-3-(propan-2-yloxy)pyrazin-2-yl]carbamoyl}-3-(2-methylpropoxy)pyrazin-2-yl)carbamate (20 mg, 0.030 mmol) was dissolved in 1 mL of DCM under an atmosphere of argon. The solution was cooled to 0 °C in an ice bath and TFA (46 µL, 0.60 mmol) was slowly added while stirring. The reaction mixture was then stirred at RT for 4 hours. After evaporation, **16** was diluted in saturated Na_2CO_3-solution and extracted with DCM. Afterwards, the organic phase was dried and evaporated *in vacuo* to give **16** as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.7 Hz, 6H), 1.45 (d, *J* = 6.2 Hz, 6H), 2.26 – 2.16 (m, 1H), 2.34 (s, 3H), 2.42 (s, 1H), 2.52 (s, 2H), 3.64 (s, 2H), 3.82 (s, 2H), 4.25 (d, *J* = 6.6 Hz, 2H), 5.42 – 5.31 (m, 1H),

5.43 (s, 2H), 8.34 (s, 1H), 8.57 (s, 1H), 10.19 (s, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 19.4, 22.1, 28.0, 29.7, 46.0, 54.7, 55.3, 70.6, 72.9, 129.8, 134.8, 136.4, 138.4, 139.1, 145.9, 147.1, 148.2, 161.1, 165.4. HR-MS: Calculated mass: 473.2619 Mass found: 473.2617 [M+H].

4 X-ray structure determination

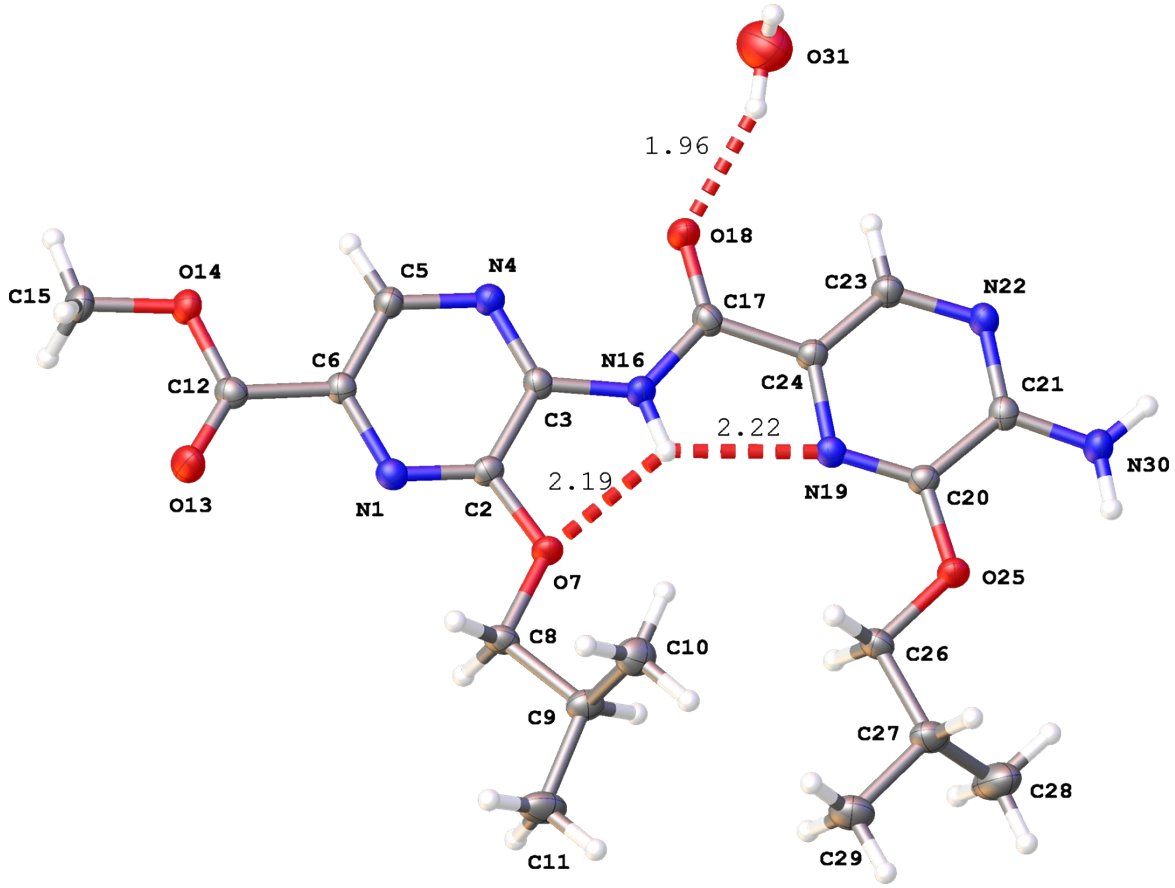


Figure S1: Molecular structure of **6b (CCDC 1512413)** with ellipsoids drawn at the 50% probability level. Dashed lines represent hydrogen bonds.

Table S1: Crystal data and structure refinement for 6b.

Empirical formula	$C_{19}H_{28}N_6O_6$
Formula weight	436.47
Temperature/K	120.0
Crystal system	orthorhombic
Space group	Pbca
a/Å	17.7469(6)
b/Å	8.5054(3)
c/Å	28.7562(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4340.6(3)

Z	8
ρ_{calc}g/cm^3	1.336
μ/mm^{-1}	0.101
F(000)	1856.0
Crystal size/mm^3	0.5 × 0.15 × 0.15
Radiation	MoKα (λ = 0.71073 Å)
2Θ range for data collection/°	5.496 to 52.742
Index ranges	-22 ≤ h ≤ 22, -9 ≤ k ≤ 10, -34 ≤ l ≤ 35
Reflections collected	28743
Independent reflections	4434 [R_{int} = 0.0375, R_{sigma} = 0.0257]
Data/restraints/parameters	4434/0/288
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0530, wR_2 = 0.1498
Final R indexes [all data]	R_1 = 0.0652, wR_2 = 0.1607
Largest diff. peak/hole / e Å^{-3}	0.35/-0.74

Table S2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 6b. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
N1	3539.3(9)	3645.0(19)	3564.6(5)	19.5(4)
C2	2898.8(10)	4087(2)	3740.9(6)	18.2(4)
C3	2842.9(10)	5093(2)	4137.6(6)	18.4(4)
N4	3450.1(9)	5637(2)	4345.2(6)	21.5(4)
C5	4121(1)	5175(2)	4161.2(7)	20.5(4)
C6	4164.8(10)	4199(2)	3780.1(6)	18.2(4)
O7	2236.3(7)	3649.7(16)	3553.4(5)	21.6(3)
C8	2257.7(11)	2724(2)	3131.4(7)	21.7(4)
C9	1480.4(11)	2797(2)	2914.2(7)	23.6(4)
C10	1309.4(13)	4450(3)	2740.1(8)	30.6(5)
C11	1434.5(14)	1593(3)	2522.0(8)	34.6(5)
C12	4896.7(11)	3681(2)	3575.8(7)	20.8(4)
O13	4958.3(8)	2900.0(19)	3228.6(5)	33.2(4)
O14	5480.0(7)	4189.0(17)	3831.8(5)	24.5(3)
C15	6216.9(11)	3736(3)	3663.9(8)	26.6(5)
N16	2121.2(9)	5472(2)	4282.1(6)	20.6(4)
C17	1899.5(11)	6423(2)	4642.2(7)	20.8(4)
O18	2342.2(8)	7075.5(18)	4906.1(5)	30.1(4)
N19	632.0(9)	5808.2(19)	4372.0(5)	18.8(3)
C20	-86.1(10)	5993(2)	4418.3(6)	18.4(4)

C21	-415.9(10)	6962(2)	4780.5(7)	19.7(4)
N22	27.1(9)	7708(2)	5078.6(6)	22.0(4)
C23	771.5(11)	7516(3)	5026.6(7)	22.0(4)
C24	1078.3(10)	6589(2)	4685.0(7)	19.8(4)
O25	-591.7(7)	5311.9(17)	4130.8(5)	22.6(3)
C26	-305.8(11)	4299(2)	3767.1(7)	23.9(4)
C27	-964.5(12)	3855(3)	3459.2(8)	29.1(5)
C28	-1573.9(15)	3026(4)	3729.7(10)	48.4(7)
C29	-681.2(14)	2837(3)	3056.4(8)	35.4(5)
N30	-1163.0(9)	7103(2)	4811.6(6)	24.0(4)
O31	2410.0(14)	9499(3)	5543.9(8)	62.3(6)

Table S3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 6b. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	21.5(8)	20.5(8)	16.4(8)	-0.5(6)	-0.5(6)	1.0(6)
C2	18.8(9)	20.4(10)	15.3(9)	0.6(8)	-2.9(7)	0.0(7)
C3	19.2(9)	20.3(9)	15.6(9)	-0.2(8)	-0.2(7)	2.5(7)
N4	19.3(8)	25.4(9)	19.9(8)	-4.2(7)	-0.2(6)	0.3(6)
C5	17.3(9)	24.1(10)	20(1)	-2.0(8)	0.0(7)	0.5(7)
C6	18.9(9)	20(1)	15.6(9)	0.5(7)	0.2(7)	1.0(7)
O7	18.5(6)	28.9(8)	17.4(7)	-7.6(6)	-3.4(5)	0.2(5)
C8	25.8(10)	23.1(10)	16.3(9)	-4.6(8)	-2.7(8)	-0.1(8)
C9	25.2(10)	25.6(11)	20(1)	-0.7(8)	-5.5(8)	-2.2(8)
C10	32.3(11)	29.3(12)	30.0(12)	0.6(9)	-7.8(9)	3.2(9)
C11	41.9(13)	30.1(12)	31.7(12)	-7.1(10)	-17.3(10)	0.8(10)
C12	22.8(9)	22.1(10)	17.4(10)	-1.3(8)	1.2(7)	-0.4(8)
O13	23.9(7)	47.3(10)	28.4(8)	-16.5(7)	2.5(6)	0.9(7)
O14	17.5(7)	32.3(8)	23.8(7)	-5.7(6)	2.3(5)	-0.3(6)
C15	17.8(9)	32.7(12)	29.2(11)	-5.1(9)	4.3(8)	0.6(8)
N16	17.1(8)	26.5(9)	18.2(8)	-5.1(7)	-2.2(6)	1.6(6)
C17	21.6(9)	22.9(10)	17.8(9)	-2.6(8)	0.1(7)	3.3(8)
O18	19.6(7)	41.5(9)	29.2(8)	-16.6(7)	-2.6(6)	0.5(6)
N19	20.0(8)	21.6(8)	14.7(8)	-1.0(6)	-1.2(6)	1.3(6)
C20	19.3(9)	20.7(9)	15.2(9)	-0.8(7)	-1.1(7)	-0.7(7)
C21	19.9(9)	22.6(10)	16.5(9)	1.2(8)	0.7(7)	2.3(7)
N22	19.9(8)	27.7(9)	18.4(8)	-4.4(7)	0.9(6)	2.2(7)
C23	21.0(9)	27.4(10)	17.7(10)	-3.8(8)	-2.2(7)	1.5(8)
C24	19.3(9)	23.5(10)	16.7(9)	-1.5(8)	-1.3(7)	0.1(8)
O25	19.5(6)	28.4(8)	20.0(7)	-6.9(6)	-3.7(5)	0.7(6)
C26	25(1)	25.7(11)	21.1(10)	-7.4(8)	-0.8(8)	1.3(8)
C27	30.2(11)	30.2(11)	27.0(11)	-8.0(9)	-6.9(9)	-0.3(9)
C28	37.3(14)	61.6(18)	46.2(15)	-22.3(13)	3.8(12)	-15.8(12)
C29	39.2(12)	38.7(13)	28.5(12)	-10.3(10)	-5.6(10)	-2.8(10)

N30	18.3(8)	31.8(10)	21.8(9)	-5.5(7)	0.4(7)	2.0(7)
O31	61.5(14)	62.2(14)	63.2(14)	-15.4(11)	7.0(11)	-5.6(12)

Table S4 Bond Lengths for 6b.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C2	1.300(2)	N16	C17	1.372(3)
N1	C6	1.356(2)	C17	O18	1.225(2)
C2	C3	1.429(3)	C17	C24	1.469(3)
C2	O7	1.346(2)	N19	C20	1.291(2)
C3	N4	1.316(2)	N19	C24	1.371(2)
C3	N16	1.385(2)	C20	C21	1.451(3)
N4	C5	1.361(2)	C20	O25	1.351(2)
C5	C6	1.377(3)	C21	N22	1.325(3)
C6	C12	1.492(3)	C21	N30	1.334(2)
O7	C8	1.447(2)	N22	C23	1.339(2)
C8	C9	1.516(3)	C23	C24	1.372(3)
C9	C10	1.523(3)	O25	C26	1.447(2)
C9	C11	1.525(3)	C26	C27	1.515(3)
C12	O13	1.204(2)	C27	C28	1.507(3)
C12	O14	1.342(2)	C27	C29	1.531(3)
O14	C15	1.446(2)			

Table S5 Bond Angles for 6b.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	N1	C6	115.92(16)	C17	N16	C3	129.01(16)
N1	C2	C3	123.01(17)	N16	C17	C24	113.85(16)
N1	C2	O7	121.85(17)	O18	C17	N16	123.41(17)
O7	C2	C3	115.12(16)	O18	C17	C24	122.74(17)
N4	C3	C2	121.05(17)	C20	N19	C24	116.34(16)
N4	C3	N16	122.63(17)	N19	C20	C21	122.77(17)
N16	C3	C2	116.32(16)	N19	C20	O25	122.71(17)
C3	N4	C5	116.01(17)	O25	C20	C21	114.51(16)
N4	C5	C6	122.20(17)	N22	C21	C20	119.80(17)
N1	C6	C5	121.81(17)	N22	C21	N30	120.21(17)
N1	C6	C12	115.48(16)	N30	C21	C20	119.99(17)
C5	C6	C12	122.71(17)	C21	N22	C23	117.02(17)
C2	O7	C8	117.60(14)	N22	C23	C24	122.80(18)
O7	C8	C9	107.43(15)	N19	C24	C17	118.15(17)
C8	C9	C10	110.76(17)	N19	C24	C23	121.27(17)
C8	C9	C11	109.02(17)	C23	C24	C17	120.58(17)
C10	C9	C11	111.46(17)	C20	O25	C26	117.70(15)
O13	C12	C6	124.62(18)	O25	C26	C27	107.49(16)

O13	C12	O14	124.23(18)	C26	C27	C29	109.26(18)
O14	C12	C6	111.14(16)	C28	C27	C26	111.6(2)
C12	O14	C15	115.39(15)	C28	C27	C29	111.21(19)

Table S6 Torsion Angles for 6b.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N1	C2	C3	N4	0.4(3)	O7	C8	C9	C11	−169.26(17)
N1	C2	C3	N16	179.39(17)	O13	C12	O14	C15	0.0(3)
N1	C2	O7	C8	-2.9(3)	N16	C3	N4	C5	−179.33(17)
N1	C6	C12	O13	4.2(3)	N16	C17	C24	N19	-0.1(3)
N1	C6	C12	O14	−175.34(16)	N16	C17	C24	C23	−179.41(18)
C2	N1	C6	C5	-0.2(3)	O18	C17	C24	N19	−179.93(19)
C2	N1	C6	C12	179.81(16)	O18	C17	C24	C23	0.7(3)
C2	C3	N4	C5	-0.4(3)	N19	C20	C21	N22	0.5(3)
C2	C3	N16	C17	−178.75(18)	N19	C20	C21	N30	−179.76(18)
C2	O7	C8	C9	−163.40(16)	N19	C20	O25	C26	1.9(3)
C3	C2	O7	C8	175.65(16)	C20	N19	C24	C17	−179.44(17)
C3	N4	C5	C6	0.1(3)	C20	N19	C24	C23	-0.1(3)
C3	N16	C17	O18	-1.7(3)	C20	C21	N22	C23	-0.2(3)
C3	N16	C17	C24	178.42(18)	C20	O25	C26	C27	−172.94(17)
N4	C3	N16	C17	0.2(3)	C21	C20	O25	C26	−178.62(16)
N4	C5	C6	N1	0.2(3)	C21	N22	C23	C24	-0.3(3)
N4	C5	C6	C12	−179.84(18)	N22	C23	C24	C17	179.76(19)
C5	C6	C12	O13	-175.8(2)	N22	C23	C24	N19	0.4(3)
C5	C6	C12	O14	4.7(3)	C24	N19	C20	C21	-0.3(3)
C6	N1	C2	C3	-0.1(3)	C24	N19	C20	O25	179.06(17)
C6	N1	C2	O7	178.41(16)	O25	C20	C21	N22	−178.94(17)
C6	C12	O14	C15	179.56(16)	O25	C20	C21	N30	0.8(3)
O7	C2	C3	N4	−178.15(17)	O25	C26	C27	C28	-59.0(2)
O7	C2	C3	N16	0.8(3)	O25	C26	C27	C29	177.60(17)
O7	C8	C9	C10	67.7(2)	N30	C21	N22	C23	−179.91(18)

Table S7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 6b.

Atom	*x*	*y*	*z*	U(eq)
H5	4574	5538	4300	25
H8A	2393	1622	3204	26
H8B	2638	3155	2914	26
H9	1100	2513	3157	28
H10A	1323	5187	3002	46
H10B	808	4468	2597	46
H10C	1688	4758	2509	46
H11A	1828	1813	2292	52
H11B	939	1659	2373	52
H11C	1507	535	2649	52
H15A	6297	4181	3353	40
H15B	6249	2587	3648	40
H15C	6604	4134	3877	40
H16	1754	5044	4120	25
H23	1101	8043	5235	26
H26A	-76	3345	3904	29
H26B	83	4856	3583	29
H27	-1182	4842	3326	35
H28A	-1977	2704	3517	73
H28B	-1779	3739	3966	73
H28C	-1362	2095	3882	73
H29A	-305	3425	2877	53
H29B	-1105	2560	2854	53
H29C	-452	1876	3180	53
H30A	-1363	7693	5031	29
H30B	-1456	6605	4613	29
H31A	2265	8840	5340	93
H31B	2463	10397	5418	93

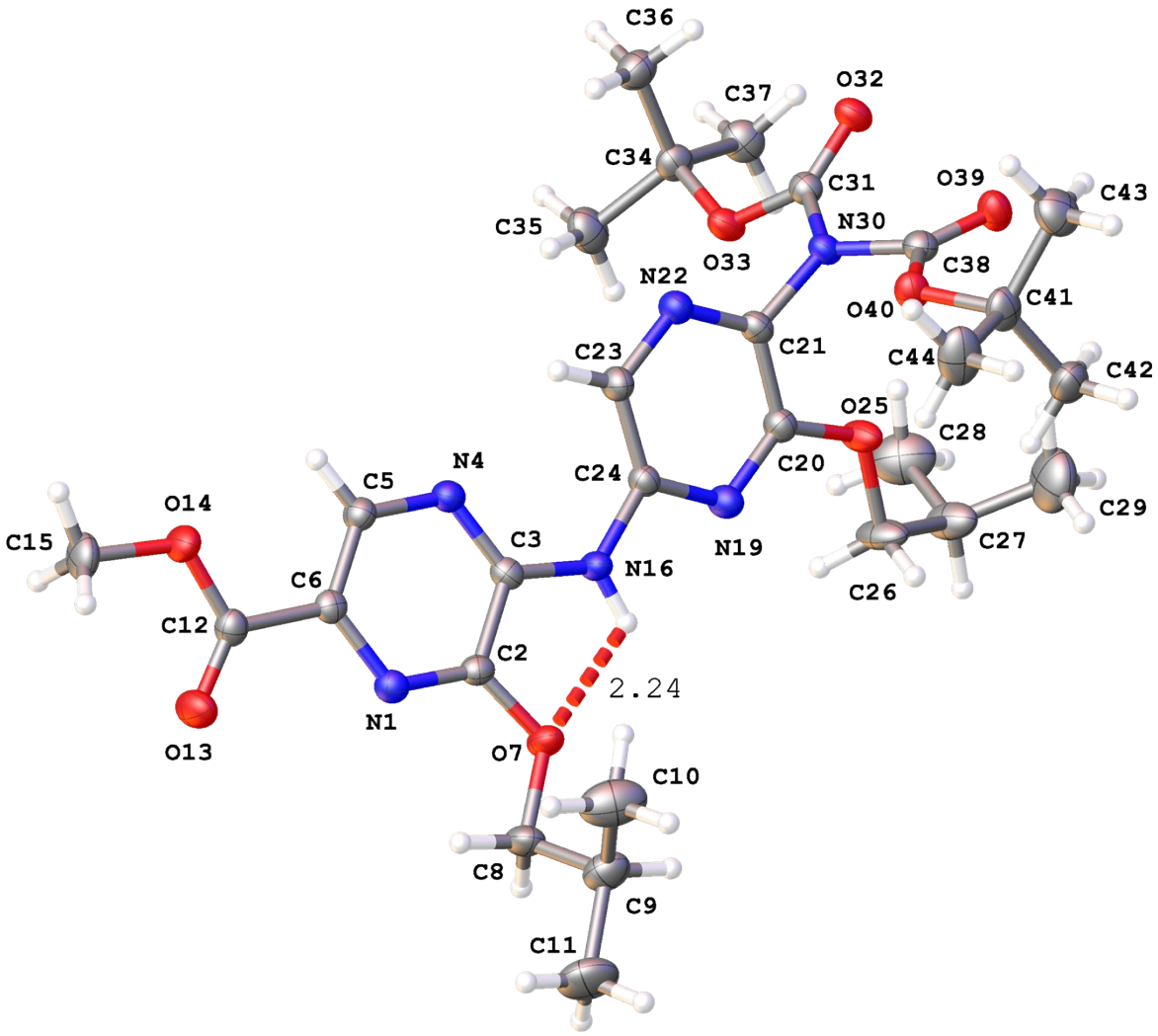


Figure S2: Molecular structure of **5b' (CCDC 1512412)** with ellipsoids drawn at the 50% probability level. Dashed lines represent hydrogen bonds.

Table S8: Crystal data and structure refinement for 5b' (Buchwald-Hartwig amination product)

Empirical formula	$C_{28}H_{42}N_6O_8$
Formula weight	590.67
Temperature/K	110.02(13)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.6767(4)
b/Å	13.4665(5)
c/Å	25.2462(7)
α/°	90
β/°	100.061(3)
γ/°	90
Volume/Å^3	3239.3(2)
Z	4
ρ_{calc}g/cm^3	1.211

μ/mm^{-1}	0.090
F(000)	1264.0
Crystal size/mm^3	0.5 × 0.3 × 0.3
Radiation	MoKα (λ = 0.71073 Å)
2Θ range for data collection/°	4.912 to 52.744
Index ranges	-11 ≤ h ≤ 12, -16 ≤ k ≤ 11, -31 ≤ l ≤ 31
Reflections collected	17986
Independent reflections	6598 [R_{int} = 0.0307, R_{sigma} = 0.0440]
Data/restraints/parameters	6598/0/390
Goodness-of-fit on F^2	1.095
Final R indexes [I>=2σ (I)]	R_1 = 0.0618, wR_2 = 0.1284
Final R indexes [all data]	R_1 = 0.0904, wR_2 = 0.1448
Largest diff. peak/hole / e Å^{-3}	0.45/-0.27

Table S9 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 5b'. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
N1	-560(2)	6686.0(15)	254.6(7)	22.1(4)
C2	553(2)	6698.9(17)	641.4(9)	20.9(5)
C3	941(2)	5872.9(17)	1004.1(9)	20.5(5)
N4	193(2)	5047.6(15)	935.0(8)	22.9(4)
C5	-952(2)	5036.8(18)	521.9(9)	23.1(5)
C6	-1340(2)	5834.8(18)	194.8(9)	21.0(5)
O7	1432.2(18)	7474.3(13)	735.9(6)	27.6(4)
C8	1166(3)	8340(2)	392.6(11)	32.7(6)
C9	2427(3)	8523(2)	143.9(11)	38.2(7)
C10	2728(4)	7651(3)	-189.0(13)	59.1(10)
C11	2175(4)	9472(2)	-191.8(14)	57.5(9)
C12	-2642(3)	5850.3(19)	-234.0(9)	24.5(5)
O13	-3141(2)	6578.5(14)	-474.2(7)	38.1(5)
O14	-3228.3(18)	4947.4(13)	-313.1(7)	31.5(4)
C15	-4547(3)	4897(2)	-702.0(11)	36.7(7)
N16	2081(2)	5993.4(15)	1417.8(7)	22.3(4)
N19	3730(2)	5695.3(15)	2188.6(8)	24.8(5)
C20	4470(3)	5070.6(18)	2535.2(9)	23.6(5)
C21	4245(2)	4040.8(18)	2496.4(9)	22.2(5)
N22	3236(2)	3659.0(15)	2129.4(8)	24.7(5)
C23	2441(3)	4281.3(18)	1777(1)	25.3(5)
C24	2724(2)	5292.4(17)	1797.9(9)	20.8(5)
O25	5480.3(19)	5376.6(13)	2944.7(7)	31.3(4)
C26	5640(3)	6440.1(19)	3039.0(11)	40.4(7)
C27	6434(3)	6578(2)	3614.9(11)	41.2(7)
C28	5633(4)	6132(3)	4010.8(12)	57.1(9)
C29	7927(4)	6191(3)	3702.6(14)	64.4(11)
N30	5182(2)	3401.3(14)	2857.0(7)	21.2(4)

C31	4779(2)	2997.5(18)	3310.8(9)	22.2(5)
O32	5438.7(18)	2372.2(13)	3595.3(6)	26.9(4)
O33	3557.8(18)	3406.3(12)	3360.5(6)	25.8(4)
C34	2720(3)	2949(2)	3723.4(10)	27.2(6)
C35	1422(3)	3613(2)	3628.5(11)	38.0(7)
C36	2336(3)	1900(2)	3536.0(11)	34.0(6)
C37	3508(3)	3008(2)	4304.9(10)	33.5(6)
C38	6600(3)	3334.7(18)	2802.9(9)	23.8(5)
O39	7580.8(18)	3134.6(14)	3158.8(7)	30.2(4)
O40	6638.7(17)	3539.8(13)	2291.4(6)	26.5(4)
C41	8023(3)	3644(2)	2130.8(10)	31.7(6)
C42	8785(3)	4538(2)	2416.1(12)	39.7(7)
C43	8863(3)	2689(2)	2234.4(12)	42.9(7)
C44	7574(3)	3838(3)	1531.8(11)	47.4(8)

Table S10 Anisotropic Displacement Parameters ($Å^2×10^3$) for 5b'. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	24.6(11)	22.6(11)	18.9(9)	0.3(8)	3.2(8)	0.3(9)
C2	23.6(12)	18.7(12)	20.9(11)	-0.5(9)	5.1(9)	0.1(10)
C3	22.5(12)	21.4(12)	17.6(11)	-0.2(9)	3.6(9)	2.9(10)
N4	23.6(11)	20.4(10)	24(1)	1.0(8)	2.6(8)	0.7(8)
C5	23.3(13)	22.1(12)	23.0(12)	-1.1(10)	1.9(10)	-1.9(10)
C6	20.8(12)	22.6(12)	20.1(11)	-1.4(9)	5.2(9)	1.1(10)
O7	30(1)	22.8(9)	27.4(9)	6.2(7)	-1.7(7)	-5.5(8)
C8	35.8(15)	23.0(13)	36.8(15)	9.2(11)	-0.2(12)	-1.3(12)
C9	44.7(18)	34.0(16)	36.4(15)	4.6(12)	8.8(13)	-7.8(13)
C10	90(3)	44(2)	50(2)	-1.9(16)	31.3(19)	-5.6(19)
C11	76(3)	43.6(19)	55(2)	17.0(16)	18.9(18)	-9.8(18)
C12	22.8(13)	29.2(14)	21.3(12)	0.7(10)	3.2(10)	-1.4(11)
O13	39.2(11)	31.9(11)	37.1(10)	6.6(9)	-9.9(9)	-0.6(9)
O14	29(1)	26.4(10)	34.9(10)	-0.9(8)	-6.1(8)	-5.0(8)
C15	25.9(14)	44.4(17)	35.2(15)	-4.4(13)	-7.2(11)	-5.0(13)
N16	23.5(11)	18.2(10)	23.4(10)	2.6(8)	-1.5(8)	-1.7(8)
N19	27.7(11)	22.5(11)	22.4(10)	0.7(8)	-0.6(8)	0.3(9)
C20	23.4(13)	24.6(13)	22.0(12)	1.5(10)	2(1)	0.2(10)
C21	22.8(12)	23.6(12)	20.0(11)	3.4(10)	2.9(9)	3.2(10)
N22	24.9(11)	23.3(11)	24.6(10)	1.9(9)	0.9(8)	0.3(9)
C23	23.9(13)	24.6(13)	25.2(12)	0.2(10)	-1.9(10)	-0.4(10)
C24	20.6(12)	21.6(12)	19.7(11)	1.4(9)	2.2(9)	0.6(10)
O25	39.6(11)	20.1(9)	28.7(9)	0.1(7)	-9.4(8)	-0.7(8)
C26	62(2)	17.8(14)	34.4(15)	-0.3(11)	-11.9(14)	-4.8(13)
C27	60(2)	28.2(15)	29.3(14)	-0.6(12)	-10.3(13)	-7.2(14)
C28	84(3)	51(2)	37.4(17)	-7.5(15)	12.5(17)	-3.7(19)

C29	51(2)	83(3)	51(2)	-6(2)	-13.1(17)	-12(2)
N30	21.6(10)	20.6(10)	21.4(10)	3.1(8)	3.2(8)	3.2(8)
C31	23.1(12)	21.2(12)	21.9(12)	-1.3(10)	2.6(9)	0.7(10)
O32	27.1(9)	26.3(9)	27.4(9)	6.9(7)	4.9(7)	5.6(8)
O33	26.6(9)	24.5(9)	27.5(9)	5.9(7)	8.0(7)	5.4(7)
C34	26.8(14)	29.8(14)	26.2(12)	4.1(11)	8.4(10)	-0.6(11)
C35	30.3(15)	45.8(17)	39.8(15)	4.0(13)	11.3(12)	7.6(13)
C36	32.8(15)	31.9(15)	38.1(15)	-0.4(12)	8.5(12)	-4.9(12)
C37	36.6(16)	38.1(16)	26.7(13)	1.7(12)	8.3(11)	1.9(13)
C38	25.2(13)	20.7(12)	25.3(12)	1.1(10)	3.9(10)	0.8(10)
O39	23.9(9)	38.2(11)	27.2(9)	8.2(8)	1.0(7)	0.8(8)
O40	24.1(9)	32.6(10)	23.1(8)	4.2(7)	5.2(7)	-0.1(8)
C41	22.9(13)	42.3(16)	32.1(14)	4.8(12)	10.6(11)	-0.9(12)
C42	30.3(15)	40.4(17)	47.7(17)	11.4(14)	5.0(13)	-6.2(13)
C43	37.1(17)	46.0(18)	48.2(17)	0.8(14)	14.9(13)	9.0(14)
C44	37.4(17)	77(2)	30.1(15)	9.3(15)	11.8(13)	-5.2(16)

Table S11 Bond Lengths for 5b'.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C2	1.322(3)	C21	N30	1.451(3)
N1	C6	1.366(3)	N22	C23	1.359(3)
C2	C3	1.448(3)	C23	C24	1.388(3)
C2	O7	1.342(3)	O25	C26	1.456(3)
C3	N4	1.321(3)	C26	C27	1.533(4)
C3	N16	1.390(3)	C27	C28	1.494(4)
N4	C5	1.383(3)	C27	C29	1.515(5)
C5	C6	1.367(3)	N30	C31	1.384(3)
C6	C12	1.511(3)	N30	C38	1.405(3)
O7	C8	1.449(3)	C31	O32	1.213(3)
C8	C9	1.487(4)	C31	O33	1.330(3)
C9	C10	1.502(4)	O33	C34	1.461(3)
C9	C11	1.529(4)	C34	C35	1.527(4)
C12	O13	1.209(3)	C34	C36	1.516(4)
C12	O14	1.342(3)	C34	C37	1.533(3)
O14	C15	1.469(3)	C38	O39	1.218(3)
N16	C24	1.411(3)	C38	O40	1.327(3)
N19	C20	1.329(3)	O40	C41	1.472(3)
N19	C24	1.371(3)	C41	C42	1.526(4)
C20	C21	1.405(3)	C41	C43	1.520(4)
C20	O25	1.357(3)	C41	C44	1.521(4)
C21	N22	1.327(3)			

Table S12 Bond Angles for 5b'.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	N1	C6	117.1(2)	N19	C24	N16	113.4(2)
N1	C2	C3	123.0(2)	N19	C24	C23	121.7(2)
N1	C2	O7	123.5(2)	C23	C24	N16	124.7(2)
O7	C2	C3	113.5(2)	C20	O25	C26	117.73(19)
N4	C3	C2	119.2(2)	O25	C26	C27	107.2(2)
N4	C3	N16	122.8(2)	C28	C27	C26	110.7(3)
N16	C3	C2	118.0(2)	C28	C27	C29	110.9(3)
C3	N4	C5	117.2(2)	C29	C27	C26	113.8(3)
C6	C5	N4	123.1(2)	C31	N30	C21	121.12(19)
N1	C6	C5	120.3(2)	C31	N30	C38	118.45(19)
N1	C6	C12	116.3(2)	C38	N30	C21	119.40(19)
C5	C6	C12	123.4(2)	O32	C31	N30	124.6(2)
C2	O7	C8	118.63(18)	O32	C31	O33	128.0(2)
O7	C8	C9	108.2(2)	O33	C31	N30	107.40(19)
C8	C9	C10	111.2(3)	C31	O33	C34	118.98(18)
C8	C9	C11	108.0(3)	O33	C34	C35	100.7(2)
C10	C9	C11	111.8(3)	O33	C34	C36	109.2(2)
O13	C12	C6	125.5(2)	O33	C34	C37	109.9(2)
O13	C12	O14	122.6(2)	C35	C34	C37	112.2(2)
O14	C12	C6	111.8(2)	C36	C34	C35	110.3(2)
C12	O14	C15	115.9(2)	C36	C34	C37	113.6(2)
C3	N16	C24	129.1(2)	O39	C38	N30	126.2(2)
C20	N19	C24	117.2(2)	O39	C38	O40	127.8(2)
N19	C20	C21	121.3(2)	O40	C38	N30	105.98(19)
N19	C20	O25	122.9(2)	C38	O40	C41	118.00(18)
O25	C20	C21	115.8(2)	O40	C41	C42	109.5(2)
C20	C21	N30	118.0(2)	O40	C41	C43	110.9(2)
N22	C21	C20	121.2(2)	O40	C41	C44	100.1(2)
N22	C21	N30	120.8(2)	C43	C41	C42	112.8(2)
C21	N22	C23	118.8(2)	C43	C41	C44	111.6(3)
N22	C23	C24	119.7(2)	C44	C41	C42	111.4(2)

Table S13 Torsion Angles for 5b'.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N1	C2	C3	N4	3.1(3)	C20	C21	N30	C31	101.5(3)
N1	C2	C3	N16	-175.9(2)	C20	C21	N30	C38	-66.8(3)
N1	C2	O7	C8	-0.9(3)	C20	O25	C26	C27	160.5(2)
N1	C6	C12	O13	-10.3(4)	C21	C20	O25	C26	-173.1(2)
N1	C6	C12	O14	171.5(2)	C21	N22	C23	C24	1.8(3)
C2	N1	C6	C5	-0.8(3)	C21	N30	C31	O32	171.3(2)
C2	N1	C6	C12	177.5(2)	C21	N30	C31	O33	-7.5(3)

C2	C3	N4	C5	-1.7(3)	C21	N30	C38 O39	152.9(2)
C2	C3	N16	C24	-175.3(2)	C21	N30	C38 O40	-26.7(3)
C2	O7	C8	C9	-122.3(2)	N22	C21	N30 C31	-80.8(3)
C3	C2	O7	C8	179.0(2)	N22	C21	N30 C38	111.0(3)
C3	N4	C5	C6	-0.8(3)	N22	C23	C24 N16	172.5(2)
C3	N16	C24	N19	-173.0(2)	N22	C23	C24 N19	-4.3(4)
C3	N16	C24	C23	10.0(4)	C24	N19	C20 C21	1.1(3)
N4	C3	N16	C24	5.7(4)	C24	N19	C20 O25	-179.0(2)
N4	C5	C6	N1	2.2(4)	O25	C20	C21 N22	176.5(2)
N4	C5	C6	C12	-176.0(2)	O25	C20	C21 N30	-5.7(3)
C5	C6	C12	O13	168.0(2)	O25	C26	C27 C28	-60.3(3)
C5	C6	C12	O14	-10.2(3)	O25	C26	C27 C29	65.4(3)
C6	N1	C2	C3	-1.8(3)	N30	C21	N22 C23	-175.7(2)
C6	N1	C2	O7	178.1(2)	N30	C31	O33 C34	165.14(19)
C6	C12	O14	C15	176.7(2)	N30	C38	O40 C41	172.8(2)
O7	C2	C3	N4	-176.8(2)	C31	N30	C38 O39	-15.7(4)
O7	C2	C3	N16	4.2(3)	C31	N30	C38 O40	164.8(2)
O7	C8	C9	C10	60.3(3)	C31	O33	C34 C35	-177.0(2)
O7	C8	C9	C11	-176.7(2)	C31	O33	C34 C36	-60.9(3)
O13	C12	O14	C15	-1.6(4)	C31	O33	C34 C37	64.4(3)
N16	C3	N4	C5	177.3(2)	O32	C31	O33 C34	-13.6(4)
N19	C20	C21	N22	-3.5(4)	C38	N30	C31 O32	-20.4(3)
N19	C20	C21	N30	174.2(2)	C38	N30	C31 O33	160.8(2)
N19	C20	O25	C26	7.0(4)	C38	O40	C41 C42	-64.5(3)
C20	N19	C24	N16	-174.4(2)	C38	O40	C41 C43	60.5(3)
C20	N19	C24	C23	2.8(3)	C38	O40	C41 C44	178.4(2)
C20	C21	N22	C23	2.0(3)	O39	C38	O40 C41	-6.8(4)

Table S14 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 5b'.

Atom	*x*	*y*	*z*	U(eq)
H5	-1496	4447	463	28
H8A	978	8925	607	39
H8B	336	8225	109	39
H9	3252	8630	437	46
H10A	2860	7055	37	89
H10B	3583	7780	-336	89
H10C	1939	7550	-485	89
H11A	1393	9367	-490	86
H11B	3024	9639	-335	86
H11C	1945	10017	35	86
H15A	-4423	5225	-1037	55
H15B	-5292	5232	-553	55
H15C	-4804	4200	-776	55

H16	2454	6591	1447	27
H23	1696	4026	1518	30
H26A	4709	6764	2996	49
H26B	6174	6741	2779	49
H27	6490	7309	3686	49
H28A	4665	6378	3940	86
H28B	6077	6319	4376	86
H28C	5632	5407	3976	86
H29A	7915	5469	3654	97
H29B	8396	6354	4068	97
H29C	8435	6499	3442	97
H35A	1688	4292	3743	57
H35B	731	3362	3837	57
H35C	1012	3612	3245	57
H36A	1872	1912	3159	51
H36B	1700	1613	3757	51
H36C	3190	1496	3571	51
H37A	4302	2546	4353	50
H37B	2871	2830	4552	50
H37C	3854	3686	4382	50
H42A	8195	5131	2340	60
H42B	9672	4641	2286	60
H42C	8978	4417	2805	60
H43A	9122	2580	2623	64
H43B	9716	2740	2076	64
H43C	8294	2130	2071	64
H44A	6999	3283	1367	71
H44B	8409	3903	1363	71
H44C	7026	4453	1479	71

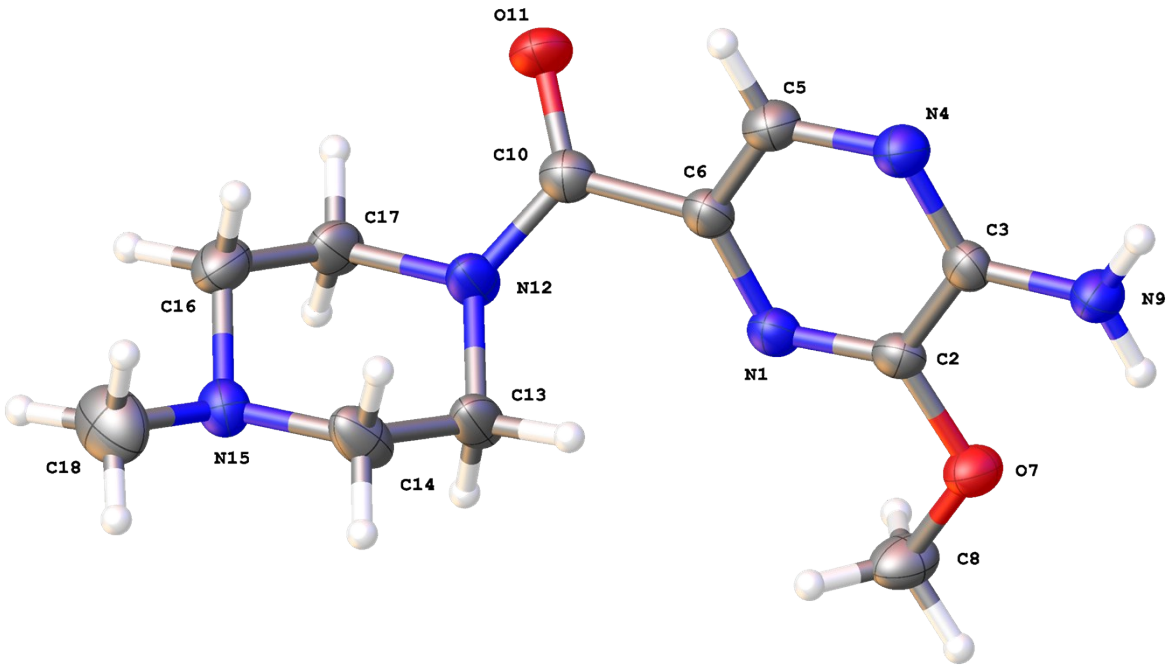


Figure S3: Molecular structure of **15b (CCDC 1512414)** with ellipsoids drawn at the 50% probability level.

Table S15: Crystal data and structure refinement for 15b

Empirical formula	$C_{11}H_{17}N_5O_2$
Formula weight	251.29
Temperature/K	150
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	12.7749(11)
b/Å	10.4901(10)
c/Å	9.5080(13)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1274.2(2)
Z	4
ρ_{calc}g/cm^3	1.310
μ/mm^{-1}	0.094
F(000)	536.0
Crystal size/mm^3	0.5 × 0.35 × 0.25
Radiation	MoKα (λ = 0.71073Å)
2Θ range for data collection/°	5.024 to 52.734
Index ranges	$-15 \leq h \leq 15$, $-13 \leq k \leq 11$, $-11 \leq l \leq 11$
Reflections collected	7542
Independent reflections	2589 [R_{int} = 0.0267, R_{sigma} = 0.0346]
Data/restraints/parameters	2589/0/165
Goodness-of-fit on F^2	1.064

Final R indexes [I>=2σ (I)] $R_1 = 0.0393$, $wR_2 = 0.0869$
Final R indexes [all data] $R_1 = 0.0511$, $wR_2 = 0.0945$
Largest diff. peak/hole / e $Å^{-3}$ 0.13/-0.18
Flack parameter 0.8(7)

Table S16 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 15b. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
N1	3756.1(15)	9096.6(19)	518(2)	29.4(5)
C2	4203.0(17)	7981(2)	529(3)	27.4(5)
C3	3852.1(18)	6923(2)	-287(3)	28.2(5)
N4	3025.2(16)	7055.6(19)	-1115(3)	33.5(5)
C5	2551(2)	8220(2)	-1120(3)	35.1(6)
C6	2902.6(17)	9220(2)	-325(3)	29.8(6)
O7	5057.6(13)	7762.9(16)	1336(2)	34.4(4)
C8	5413(2)	8833(3)	2151(3)	41.0(7)
N9	4344.4(15)	5792(2)	-201(2)	33.8(5)
C10	2319.5(18)	10460(2)	-332(3)	31.9(6)
O11	1354.1(13)	10453.9(16)	-354(2)	43.3(5)
N12	2869.6(15)	11562.3(18)	-295(3)	36.4(6)
C13	3982.5(19)	11709(2)	-627(4)	42.9(8)
C14	4114(2)	12406(2)	-2000(3)	42.4(8)
N15	3590.8(17)	13638.3(19)	-1968(2)	32.6(5)
C16	2476(2)	13468(3)	-1658(3)	39.6(7)
C17	2328.8(19)	12785(2)	-287(3)	36.2(6)
C18	3728(3)	14315(3)	-3294(3)	54.9(9)

Table S17 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 15b. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	23.8(10)	27(1)	37.4(13)	1.3(10)	2.2(10)	-1.9(8)
C2	21.2(11)	29.9(13)	31.1(13)	2.2(11)	1.7(11)	-4.1(10)
C3	26.2(12)	25.3(12)	33.1(14)	4.9(11)	2.1(11)	-1.9(10)
N4	28.8(11)	29.8(11)	42.0(13)	-1.2(11)	-3.8(11)	0.0(9)
C5	27.7(13)	34.9(14)	42.8(16)	2.0(13)	-5.7(13)	-1.0(11)
C6	23.4(12)	26.6(12)	39.4(15)	2.5(12)	2.6(12)	-2(1)
O7	28.8(9)	32.2(9)	42.0(11)	-4.3(9)	-7.3(8)	1.4(8)
C8	33.2(14)	42.5(17)	47.5(17)	-12.0(14)	-10.2(13)	1.2(12)
N9	30.1(11)	27.4(11)	44.0(13)	-1.1(11)	-6.9(11)	0.4(9)
C10	27.1(12)	31.9(13)	36.8(15)	2.0(13)	0.9(12)	-0.6(11)
O11	21.9(9)	39.6(10)	68.5(14)	4.0(11)	-1.5(10)	0.5(8)
N12	23(1)	25.7(11)	60.5(15)	1.6(12)	9.0(11)	3.0(8)
C13	23.6(13)	26.1(12)	79(2)	5.1(15)	8.6(14)	3.0(11)

C14	34.5(15)	27.5(14)	65(2)	-9.0(15)	18.4(15)	-3.4(12)
N15	33.5(11)	28.3(11)	35.9(12)	2.8(10)	-0.3(10)	-0.3(10)
C16	32.3(14)	36.4(15)	50.2(18)	-1.4(14)	-9.4(13)	3.5(12)
C17	24.0(12)	29.7(14)	54.7(18)	-3.3(14)	5.3(13)	5.4(10)
C18	68(2)	58(2)	39.0(18)	7.5(16)	1.3(16)	-8.3(18)

Table S18 Bond Lengths for 15b.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C2	1.302(3)	C10	O11	1.234(3)
N1	C6	1.359(3)	C10	N12	1.353(3)
C2	C3	1.426(3)	N12	C13	1.464(3)
C2	O7	1.354(3)	N12	C17	1.457(3)
C3	N4	1.325(3)	C13	C14	1.506(4)
C3	N9	1.345(3)	C14	N15	1.455(3)
N4	C5	1.363(3)	N15	C16	1.465(3)
C5	C6	1.369(4)	N15	C18	1.458(4)
C6	C10	1.499(3)	C16	C17	1.499(4)
O7	C8	1.437(3)			

Table S19 Bond Angles for 15b.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	N1	C6	116.2(2)	O11	C10	C6	119.5(2)
N1	C2	C3	123.9(2)	O11	C10	N12	121.6(2)
N1	C2	O7	120.7(2)	N12	C10	C6	118.90(19)
O7	C2	C3	115.5(2)	C10	N12	C13	126.1(2)
N4	C3	C2	119.5(2)	C10	N12	C17	120.39(19)
N4	C3	N9	120.1(2)	C17	N12	C13	111.64(19)
N9	C3	C2	120.4(2)	N12	C13	C14	110.2(2)
C3	N4	C5	116.8(2)	N15	C14	C13	111.2(2)
N4	C5	C6	122.6(2)	C14	N15	C16	110.00(19)
N1	C6	C5	121.0(2)	C14	N15	C18	111.0(2)
N1	C6	C10	118.9(2)	C18	N15	C16	110.5(2)
C5	C6	C10	120.0(2)	N15	C16	C17	110.8(2)
C2	O7	C8	115.35(19)	N12	C17	C16	110.9(2)

Table S20 Torsion Angles for 15b.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N1	C2	C3	N4	0.1(4)	C6	C10	N12	C17	-179.4(3)
N1	C2	C3	N9	-178.8(2)	O7	C2	C3	N4	-179.5(2)
N1	C2	O7	C8	0.0(3)	O7	C2	C3	N9	1.6(3)

N1	C6	C10	O11	-138.8(3)	N9	C3	N4	C5	178.3(2)
N1	C6	C10	N12	40.3(4)	C10	N12	C13	C14	109.0(3)
C2	N1	C6	C5	-0.6(4)	C10	N12	C17	C16	-109.6(3)
C2	N1	C6	C10	177.0(2)	O11	C10	N12	C13	-163.2(3)
C2	C3	N4	C5	-0.6(4)	O11	C10	N12	C17	-0.3(4)
C3	C2	O7	C8	179.7(2)	N12	C13	C14	N15	56.6(3)
C3	N4	C5	C6	0.5(4)	C13	N12	C17	C16	55.6(3)
N4	C5	C6	N1	0.1(4)	C13	C14	N15	C16	-57.9(3)
N4	C5	C6	C10	-177.5(2)	C13	C14	N15	C18	179.4(2)
C5	C6	C10	O11	38.8(4)	C14	N15	C16	C17	57.6(3)
C5	C6	C10	N12	-142.1(3)	N15	C16	C17	N12	-56.6(3)
C6	N1	C2	C3	0.5(3)	C17	N12	C13	C14	-55.2(3)
C6	N1	C2	O7	-179.9(2)	C18	N15	C16	C17	-179.4(2)
C6	C10	N12	C13	17.7(4)					

Table S21 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 15b.

Atom	*x*	*y*	*z*	U(eq)
H5	1952	8341	-1697	42
H8A	5507	9572	1533	62
H8B	6082	8622	2600	62
H8C	4893	9035	2875	62
H9A	4117	5139	-695	41
H9B	4894	5705	350	41
H13A	4315	10859	-692	51
H13B	4333	12191	134	51
H14A	4869	12533	-2190	51
H14B	3819	11884	-2772	51
H16A	2144	12972	-2422	48
H16B	2130	14311	-1612	48
H17A	2604	13318	489	43
H17B	1573	12645	-120	43
H18A	4477	14404	-3496	82
H18B	3409	15162	-3225	82
H18C	3392	13835	-4053	82

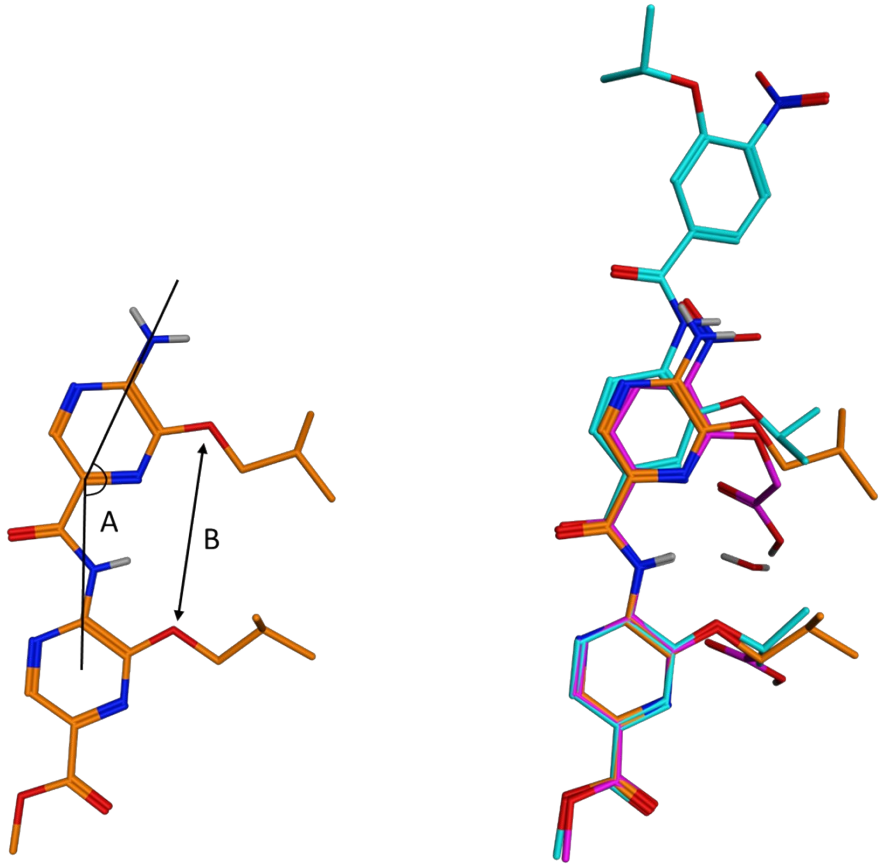


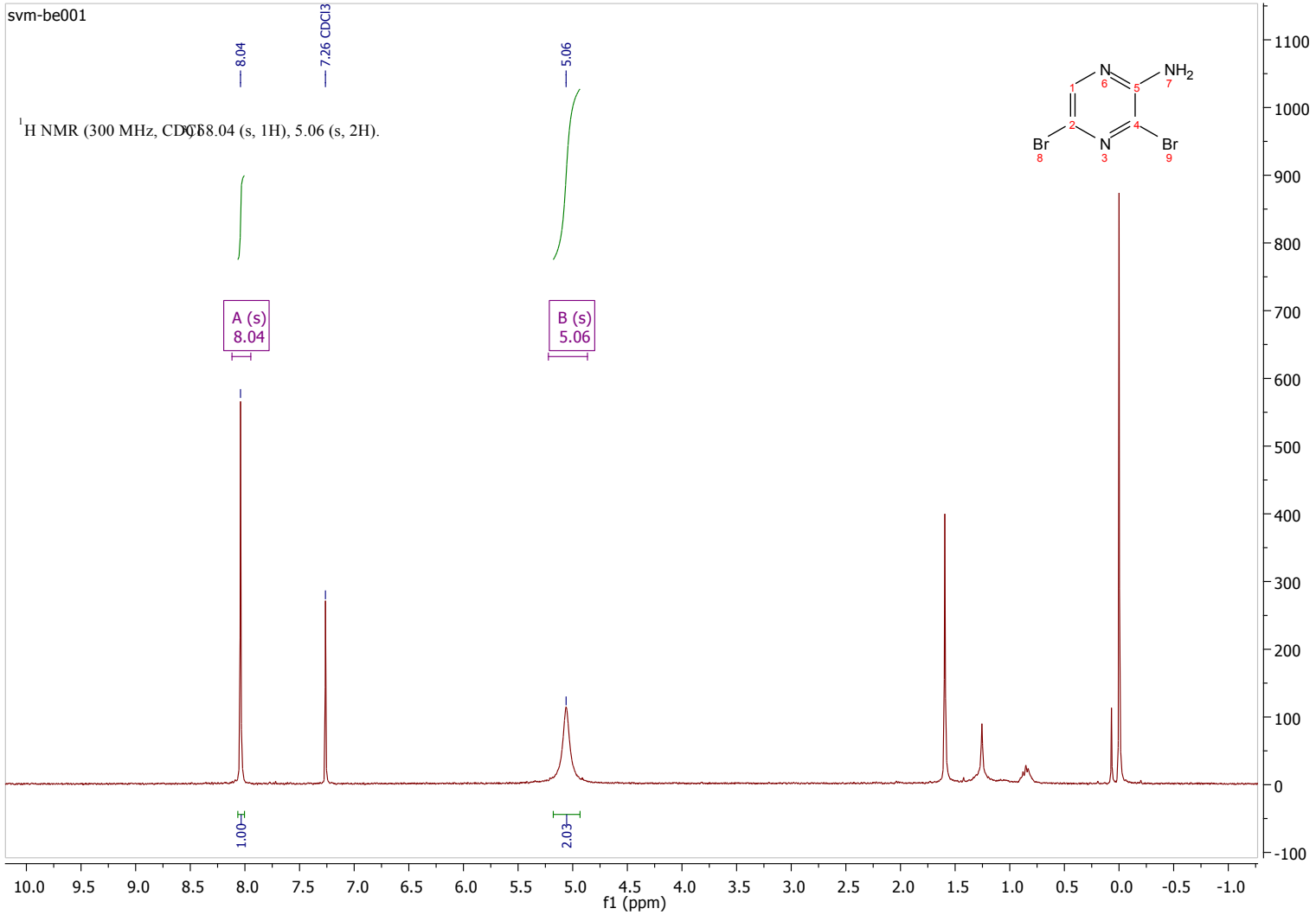
Figure S4 Angle of inclination and overlay analysis of Wilson's benzamide crystal, Hamilton's pyridine crystal and our pyrazine crystal

Compound	Angle of inclination (A)	Distance between side chains (B)
Benzamide[a]	159.6 °	5.9 Å
Pyridinyl amide[b]	152.0 °	5.2 Å
Pyrazinyl amide[c]	155.9 °	5.5 Å

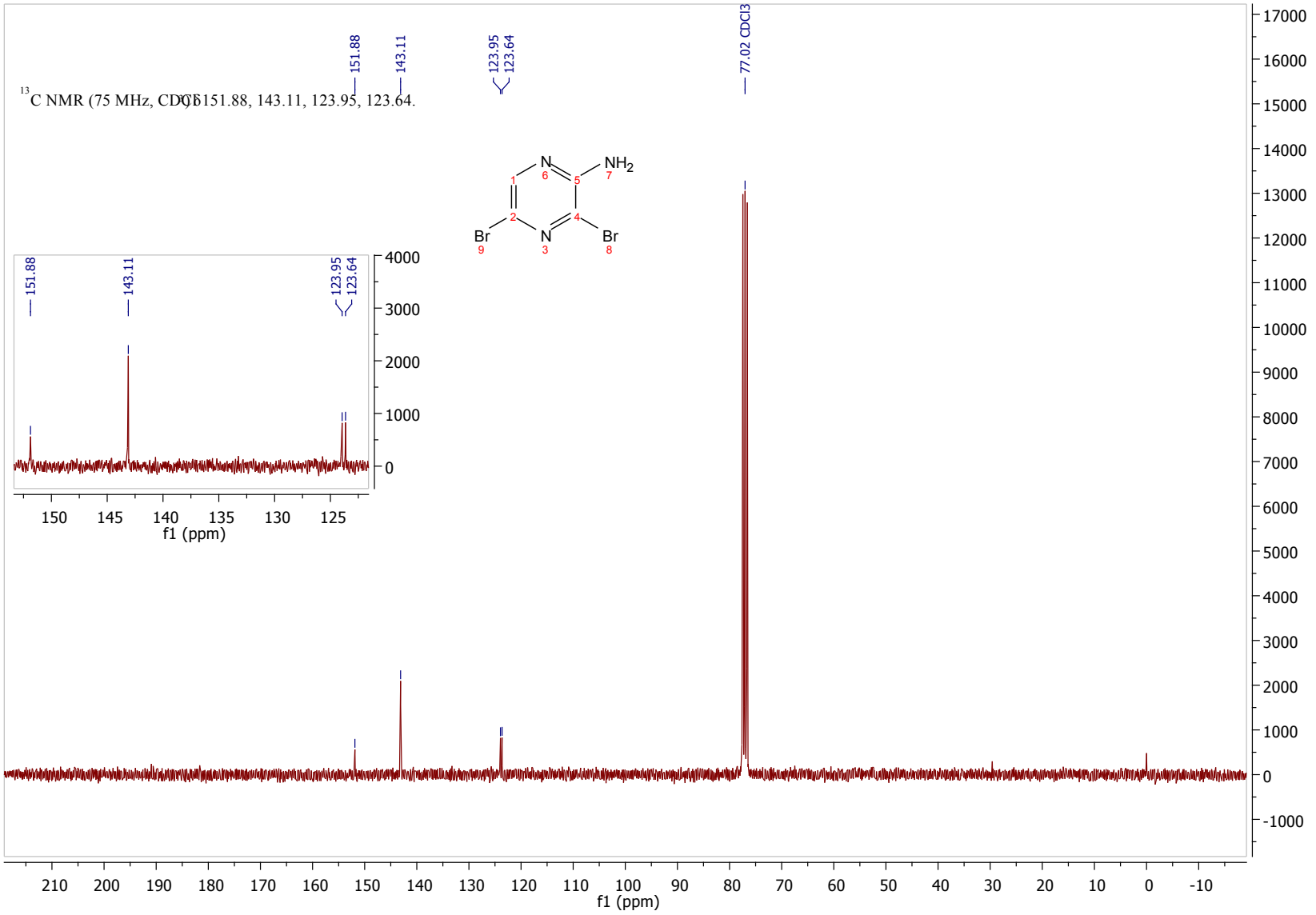
[a] CCDC 870274, [b] CCDC 697087, [c] CCDC 1512413

5 NMR Spectra

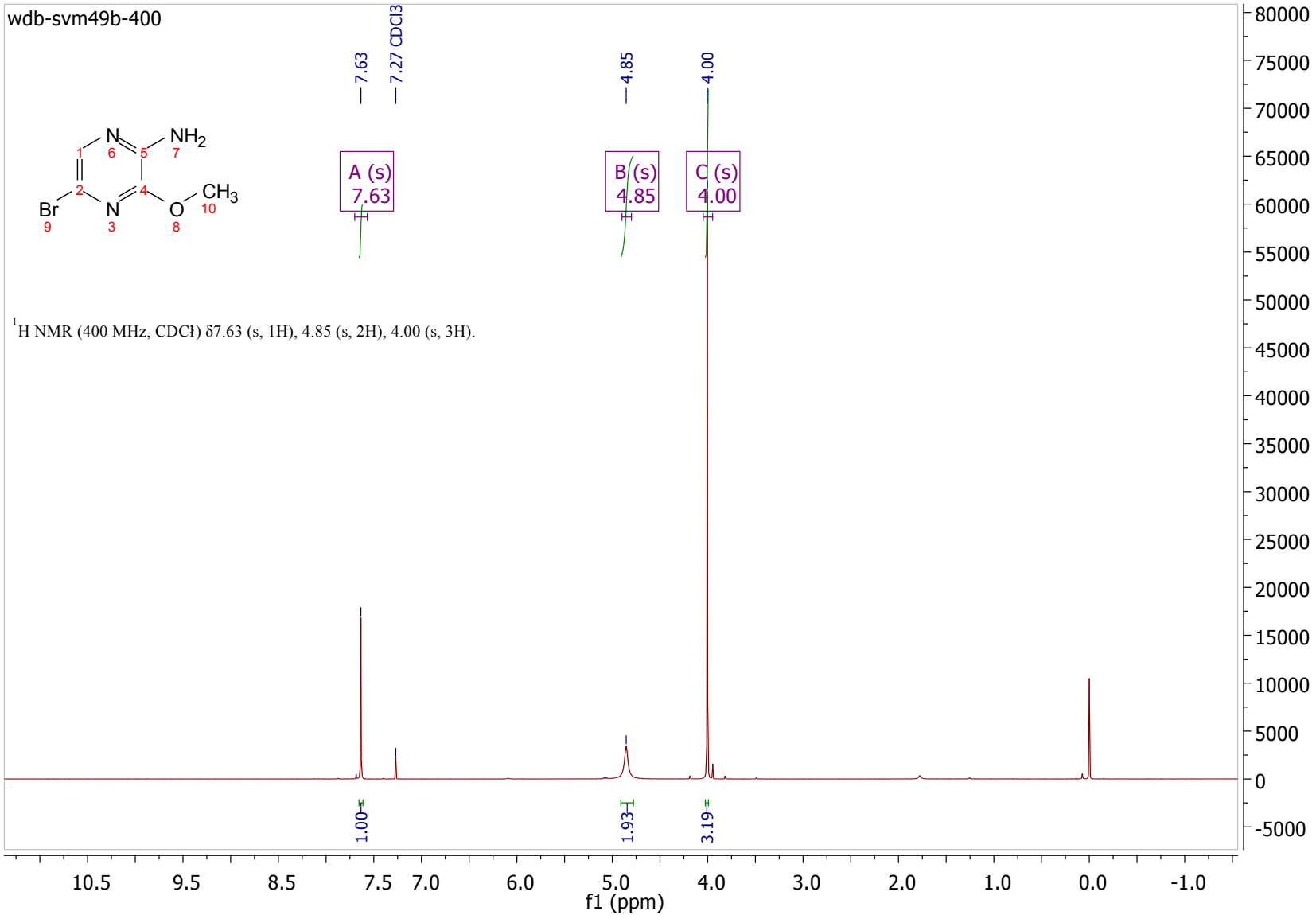
3,5-dibromo-2-aminopyrazine



3,5-dibromo-2-aminopyrazine

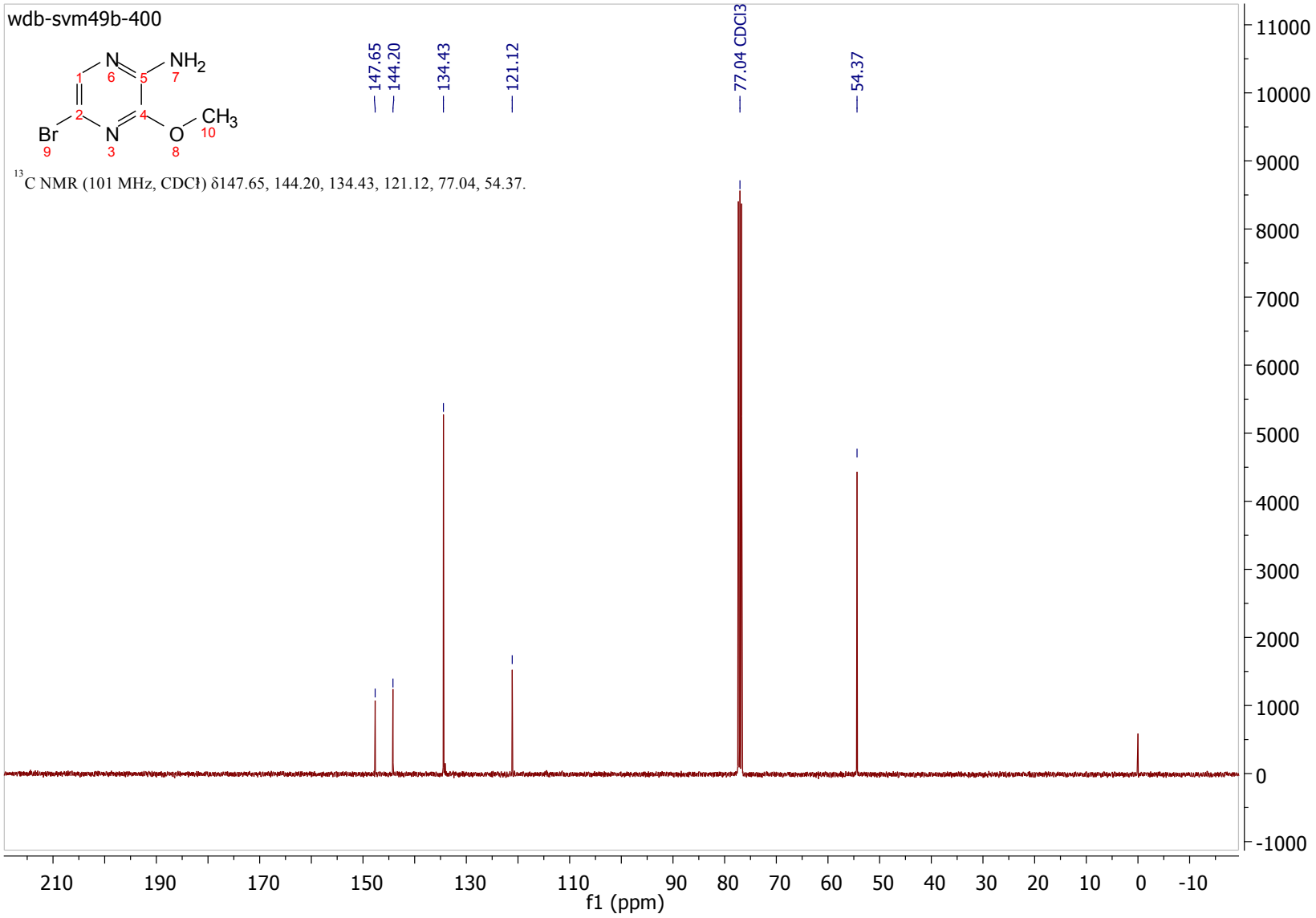


1a

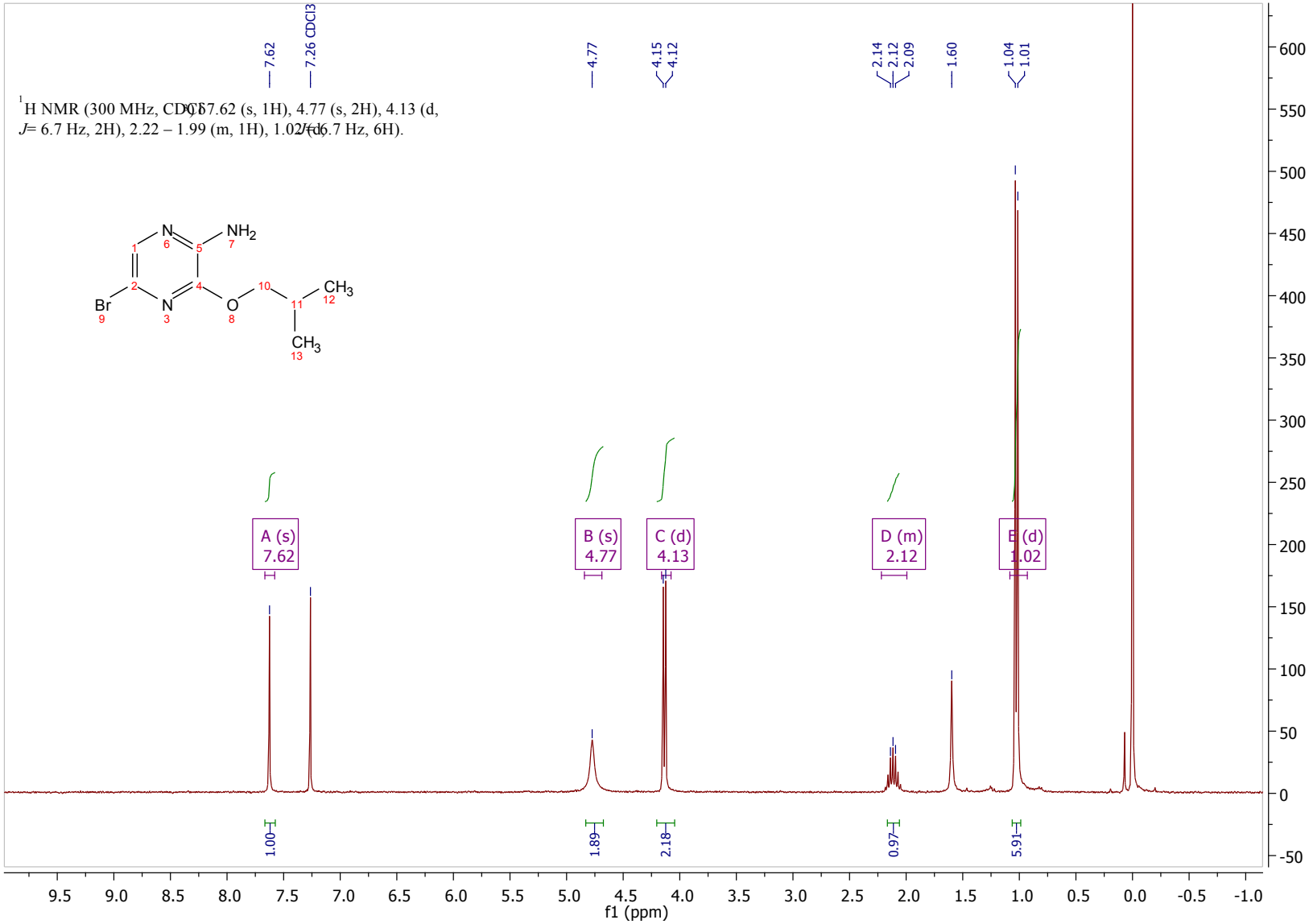


^{1}H NMR (400 MHz, CDCł) δ7.63 (s, 1H), 4.85 (s, 2H), 4.00 (s, 3H).

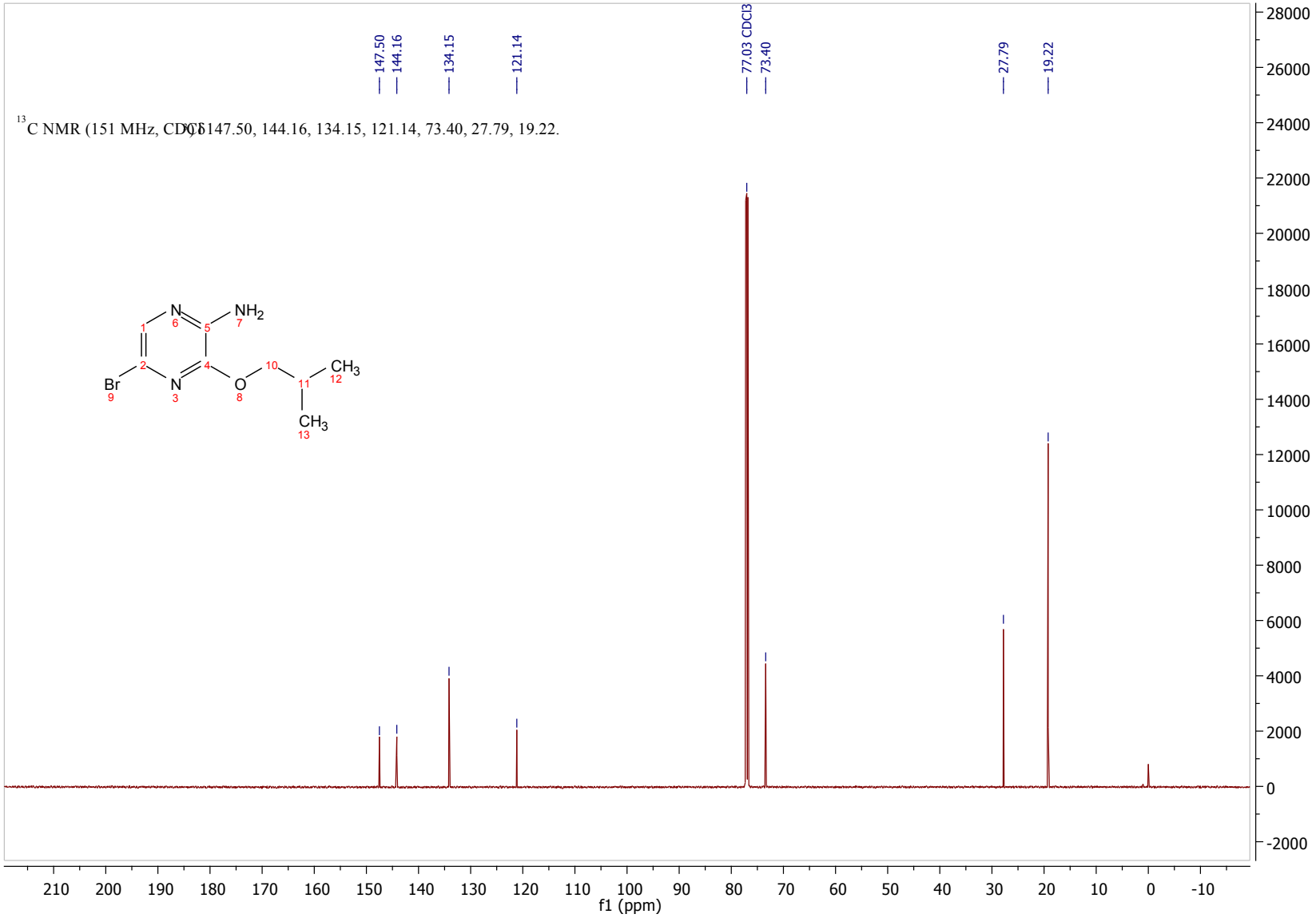
1a


wdb-svm49b-400
147.65
144.20
134.43
121.12
77.04 CDCl3
54.37
^{13}C NMR (101 MHz, CDCl) δ147.65, 144.20, 134.43, 121.12, 77.04, 54.37.
f1 (ppm)

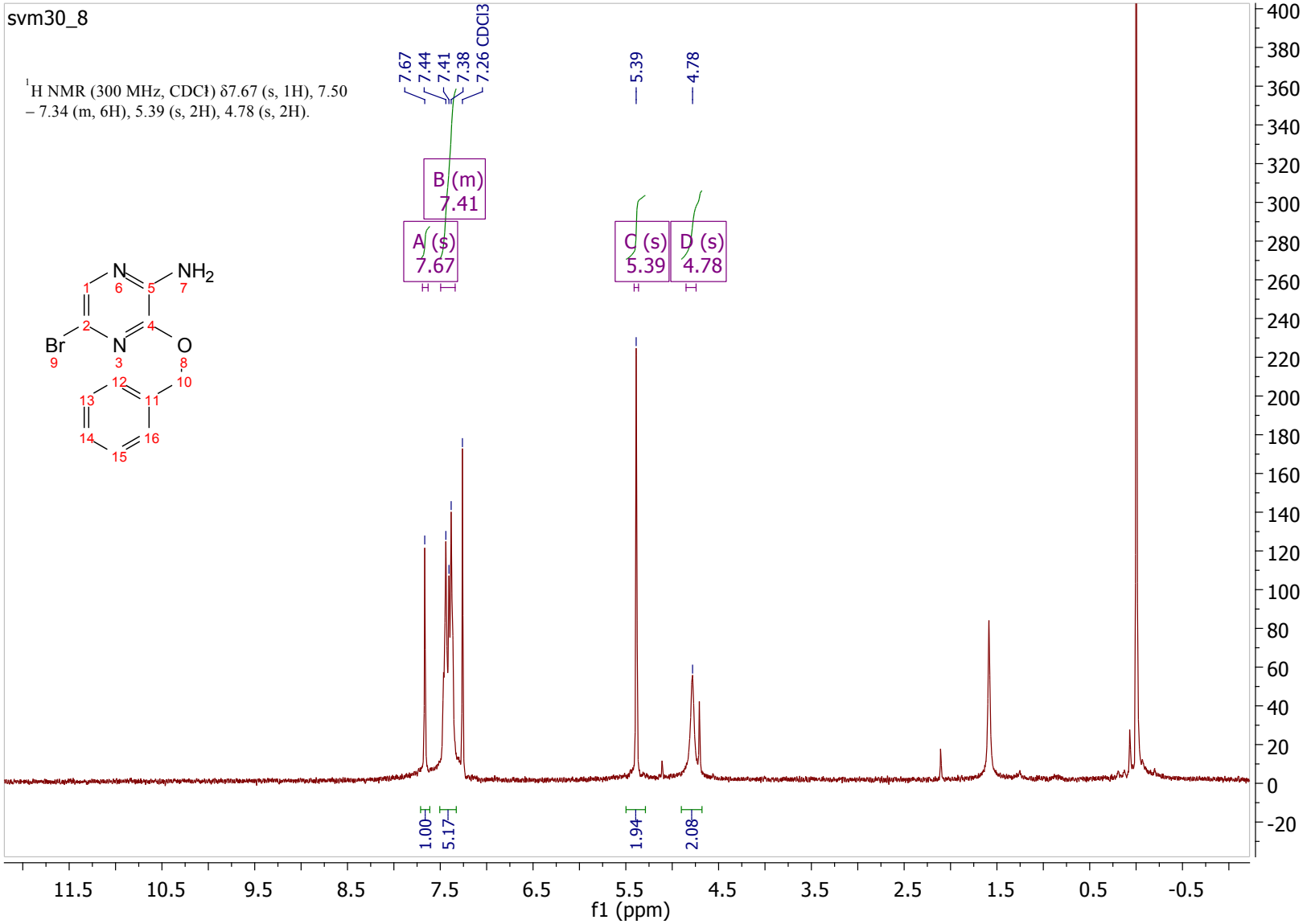
1b


7.62
7.26 CDCl3
4.77
4.15
4.12
2.14
2.12
2.09
1.60
1.04
1.01
1H NMR (300 MHz, CDCl3) δ 7.62 (s, 1H), 4.77 (s, 2H), 4.13 (d, J= 6.7 Hz, 2H), 2.22 – 1.99 (m, 1H), 1.02 (d, J= 6.7 Hz, 6H).
NH2
Br
CH3
CH3
A (s) 7.62
B (s) 4.77
C (d) 4.13
D (m) 2.12
E (d) 1.02
1.00
1.89
2.18
0.97
5.91
f1 (ppm)

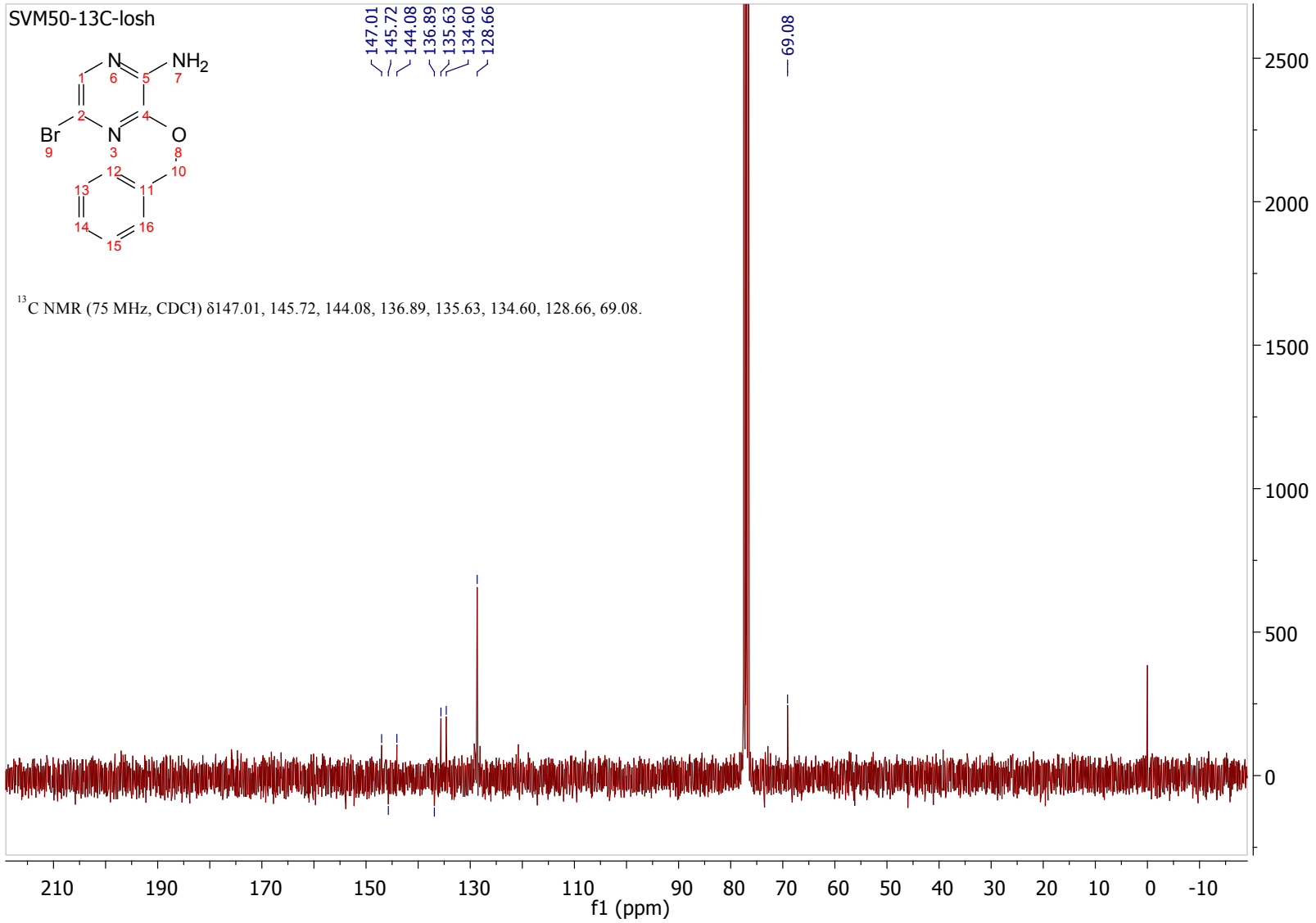
1b


147.50
144.16
134.15
121.14
77.03 CDCl3
73.40
27.79
19.22
13C NMR (151 MHz, CDCl3) δ 147.50, 144.16, 134.15, 121.14, 73.40, 27.79, 19.22.
N
NH2
Br
N
O
CH3
CH3
f1 (ppm)

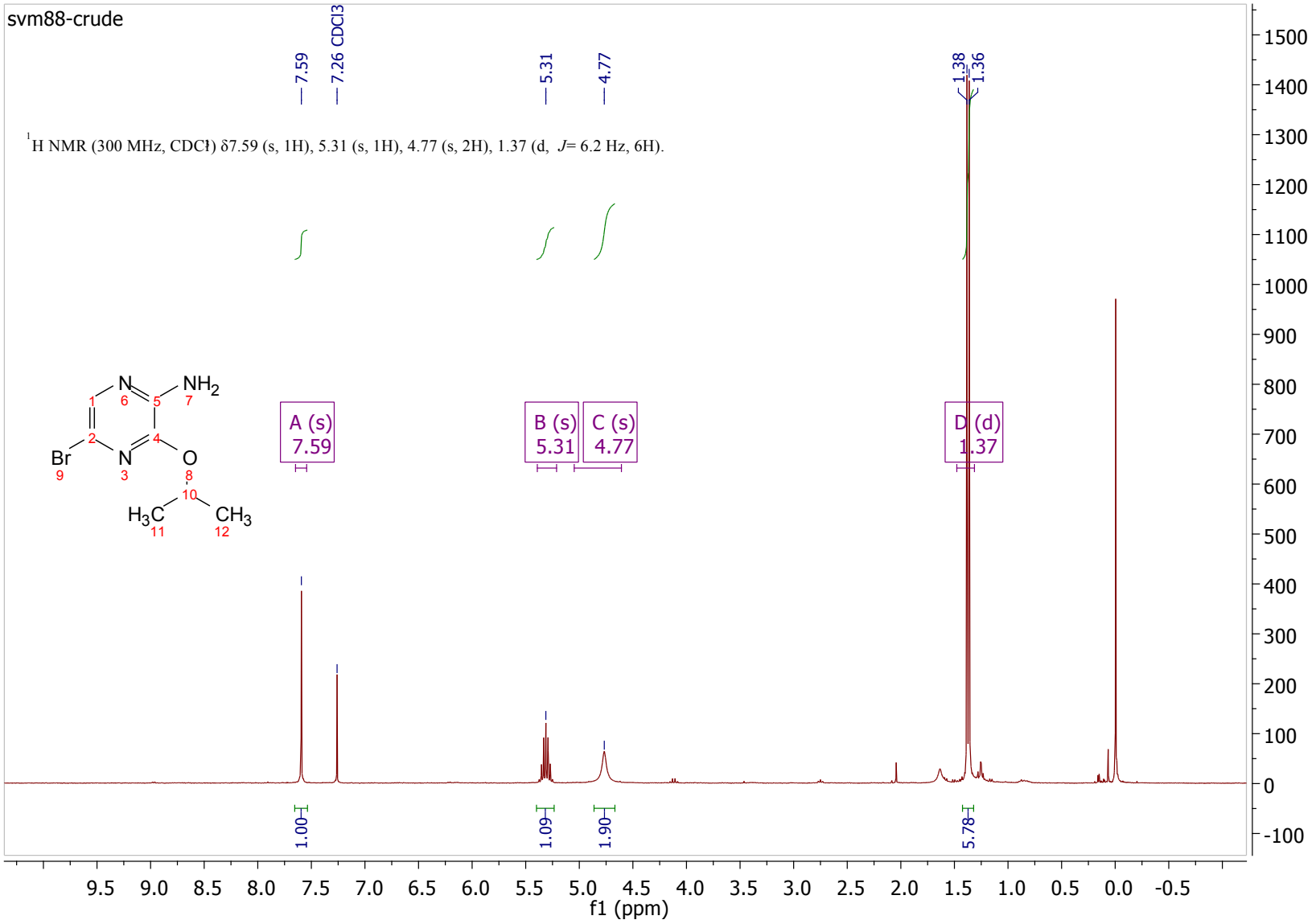
1c


svm30_8
^{1}H NMR (300 MHz, CDCl) δ7.67 (s, 1H), 7.50 – 7.34 (m, 6H), 5.39 (s, 2H), 4.78 (s, 2H).
7.67
7.44
7.41
7.38
7.26 CDCl3
5.39
4.78
B (m) 7.41
A (s) 7.67
C (s) 5.39
D (s) 4.78
1.00
5.17
1.94
2.08
f1 (ppm)

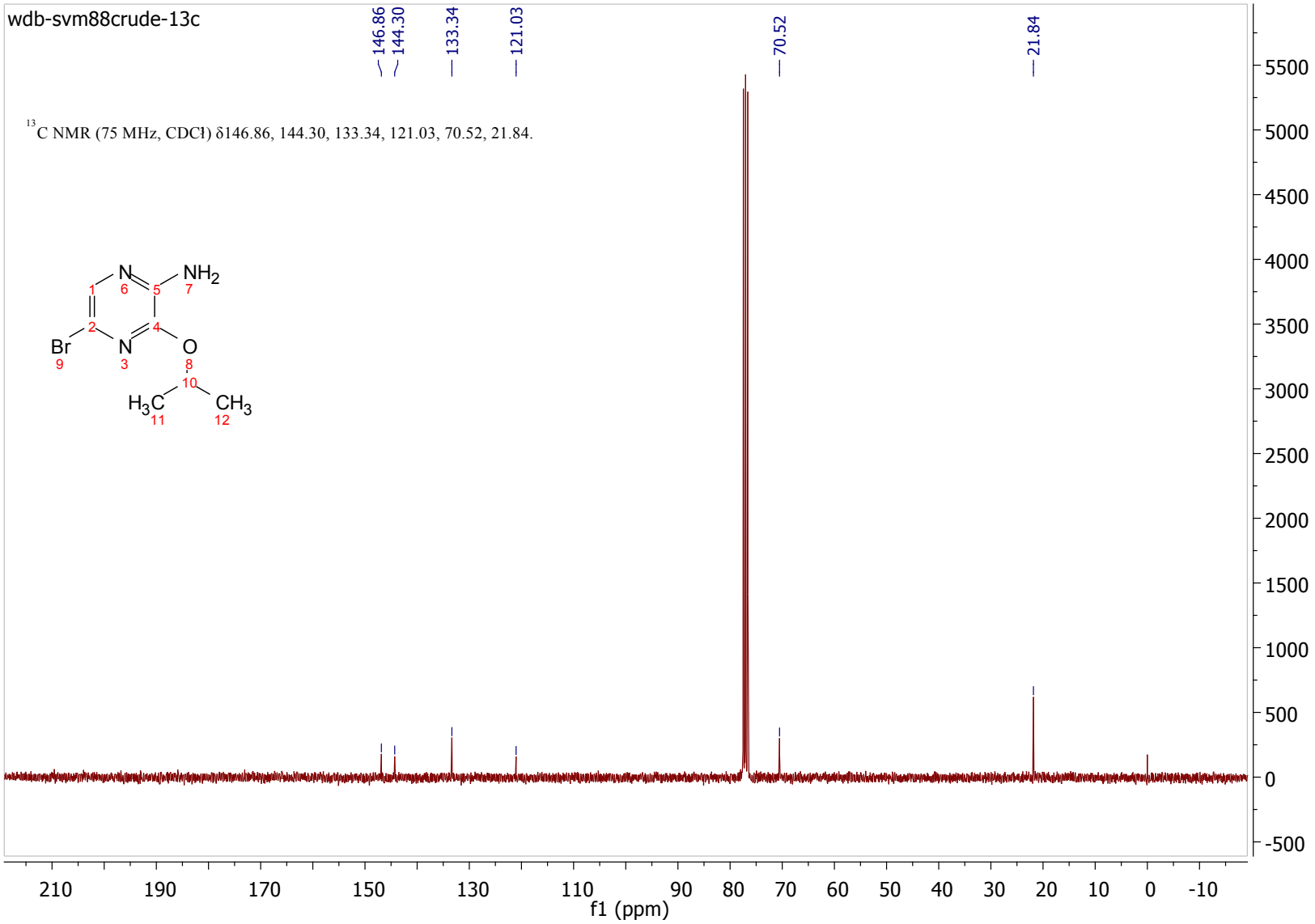
1c


SVM50-13C-losh
147.01
145.72
144.08
136.89
135.63
134.60
128.66
69.08
NH2
Br
O
N
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
13C NMR (75 MHz, CDCl3) δ147.01, 145.72, 144.08, 136.89, 135.63, 134.60, 128.66, 69.08.
2500
2000
1500
1000
500
0
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

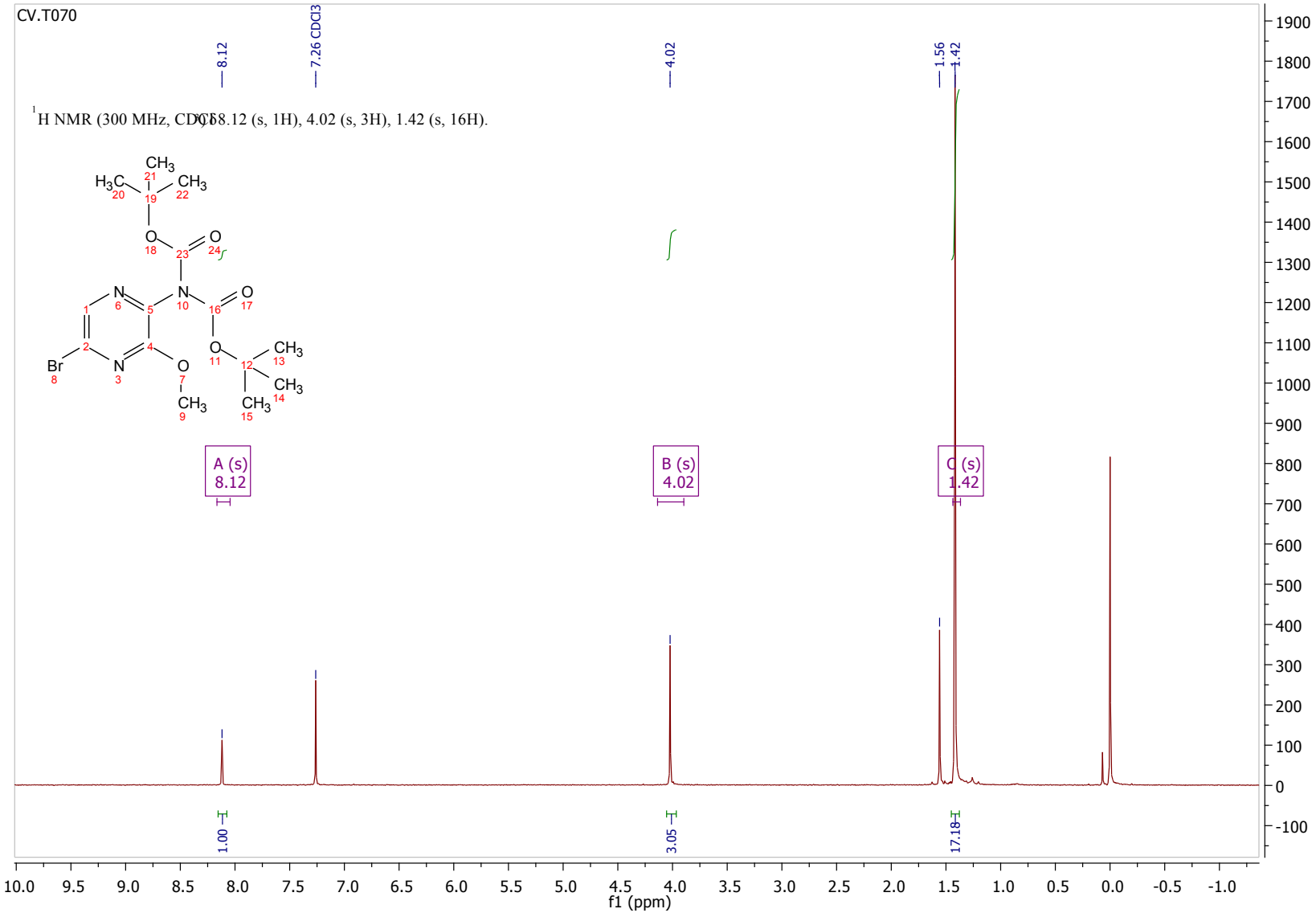
1d


svm88-crude
7.59
7.26 CDCl3
5.31
4.77
1.38
1.36
^{1}H NMR (300 MHz, CDCł) δ7.59 (s, 1H), 5.31 (s, 1H), 4.77 (s, 2H), 1.37 (d, J= 6.2 Hz, 6H).
A (s) 7.59
B (s) 5.31
C (s) 4.77
D (d) 1.37
1.00
1.09
1.90
5.78
f1 (ppm)

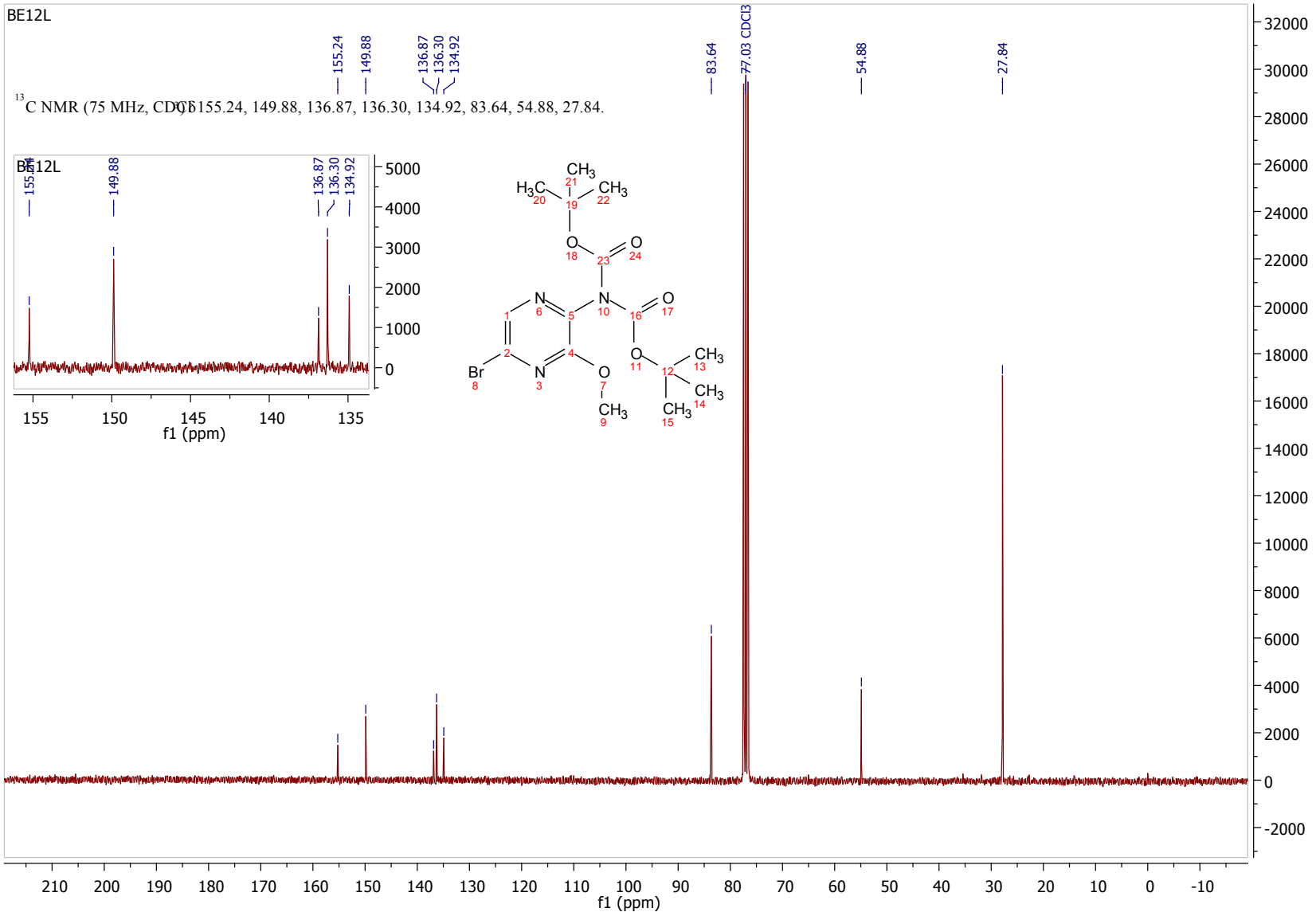
1d


wdb-svm88crude-13c
146.86
144.30
133.34
121.03
70.52
21.84
13C NMR (75 MHz, CDCl3) δ146.86, 144.30, 133.34, 121.03, 70.52, 21.84.
N
NH2
Br
N
O
H3C
CH3
f1 (ppm)

2a

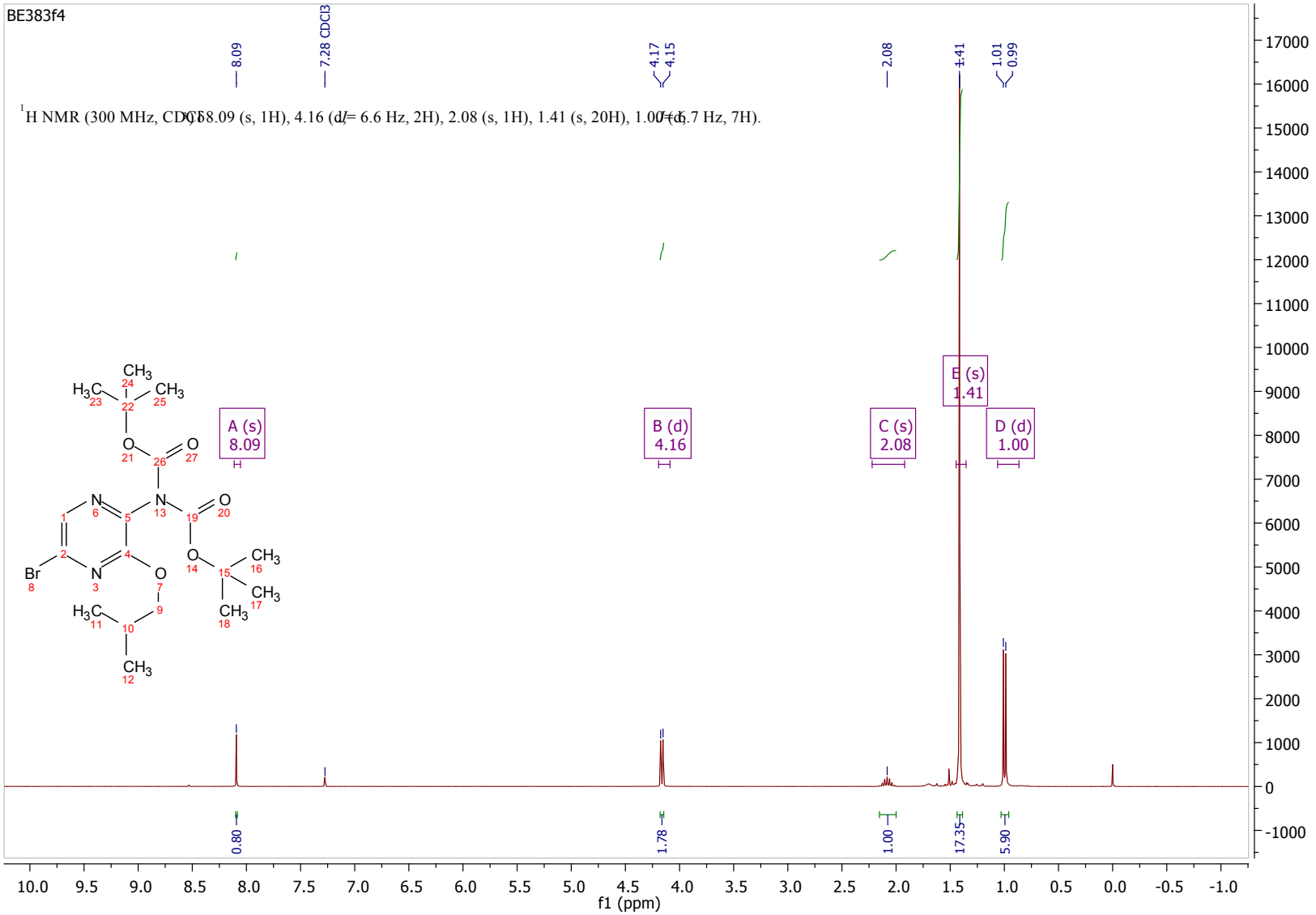

CV.T070
8.12
7.26 CDCl3
4.02
1.56
1.42
^{1}H NMR (300 MHz, CDCl3) δ 8.12 (s, 1H), 4.02 (s, 3H), 1.42 (s, 16H).
A (s) 8.12
B (s) 4.02
C (s) 1.42
1.00
3.05
17.18
f1 (ppm)

2a



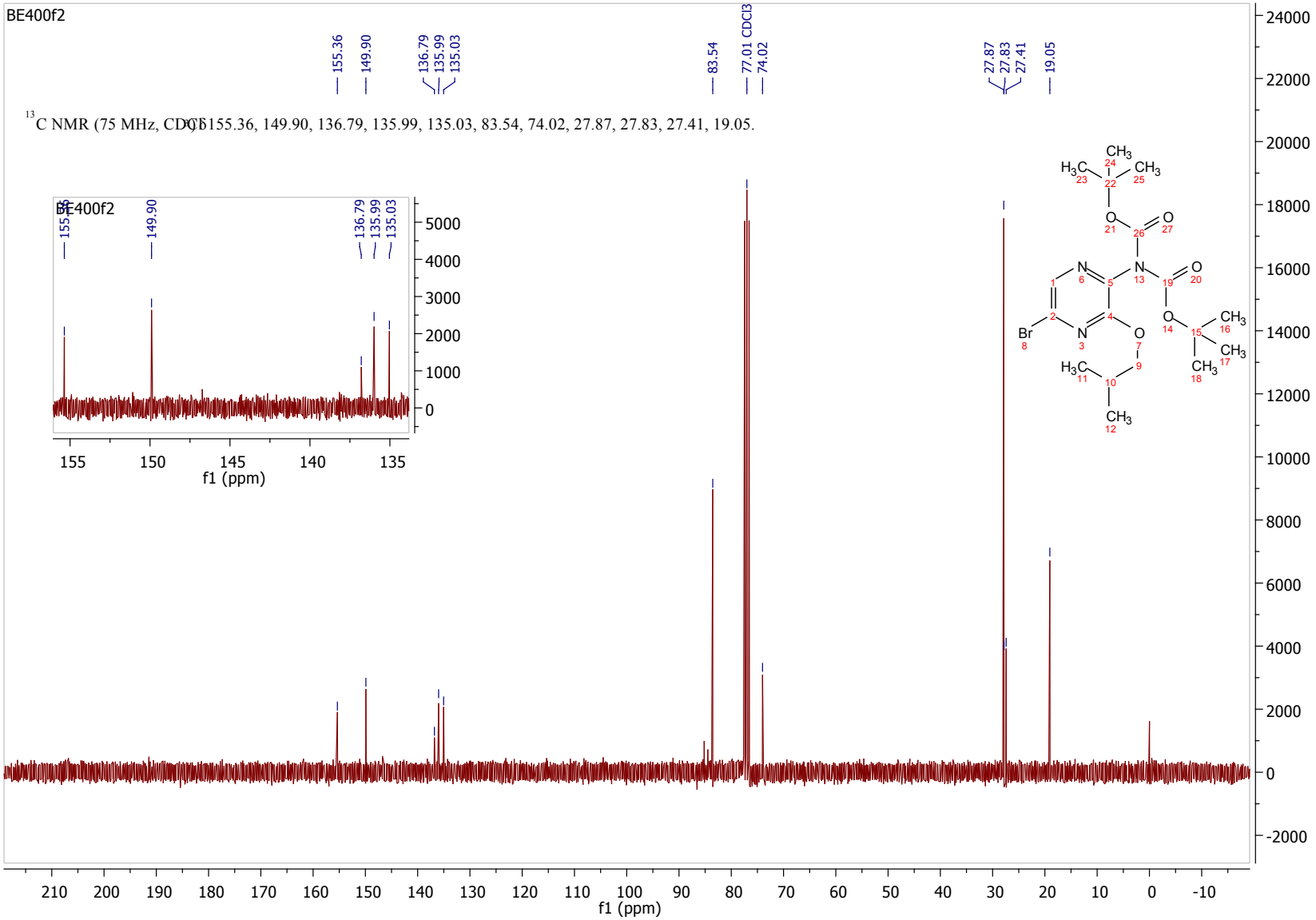
^{13}C NMR (75 MHz, CDCl$_3$) δ 155.24, 149.88, 136.87, 136.30, 134.92, 83.64, 54.88, 27.84.

2b

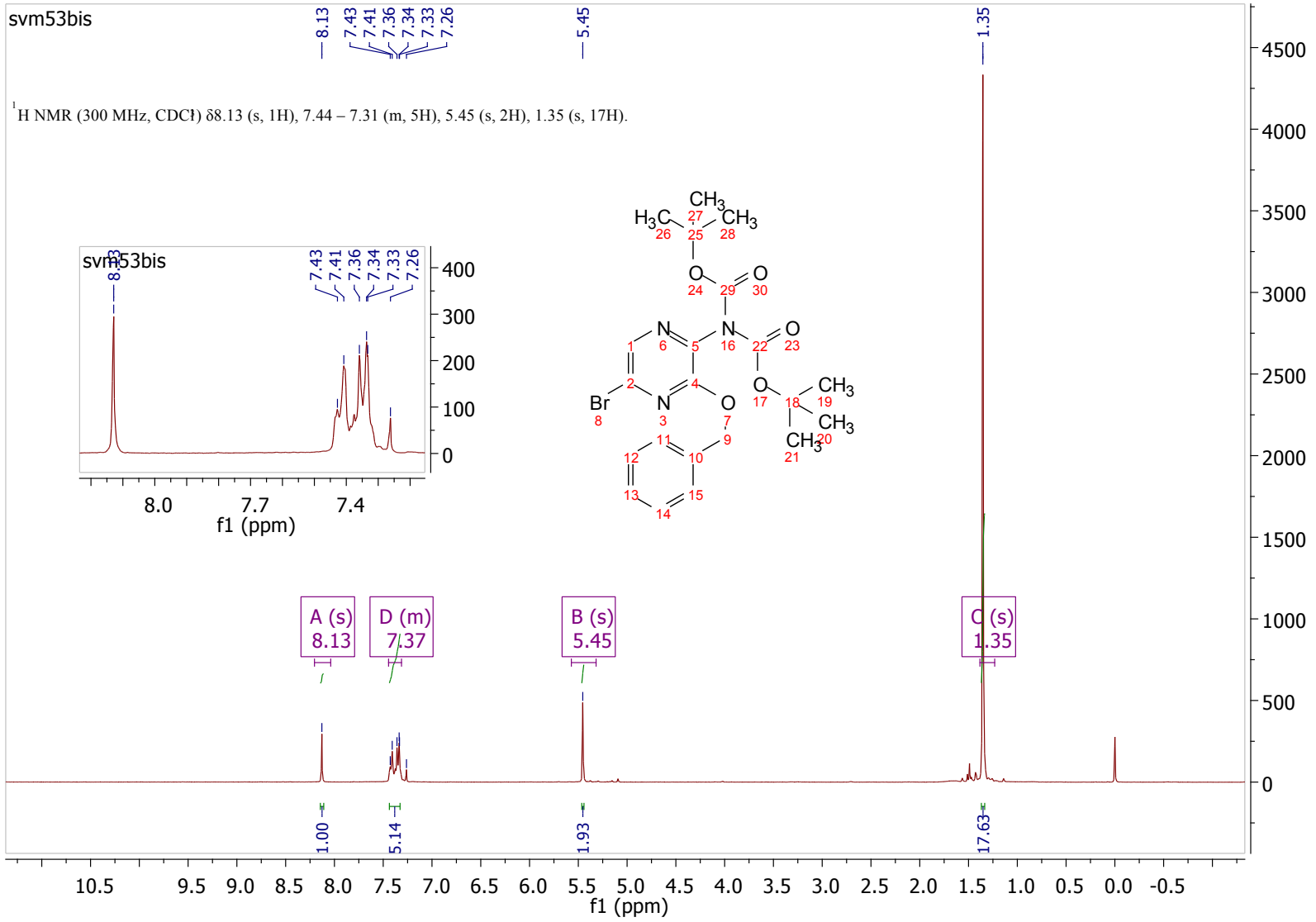


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 4.16 (d, *J* = 6.6 Hz, 2H), 2.08 (s, 1H), 1.41 (s, 20H), 1.00 (d, *J* = 6.7 Hz, 7H).

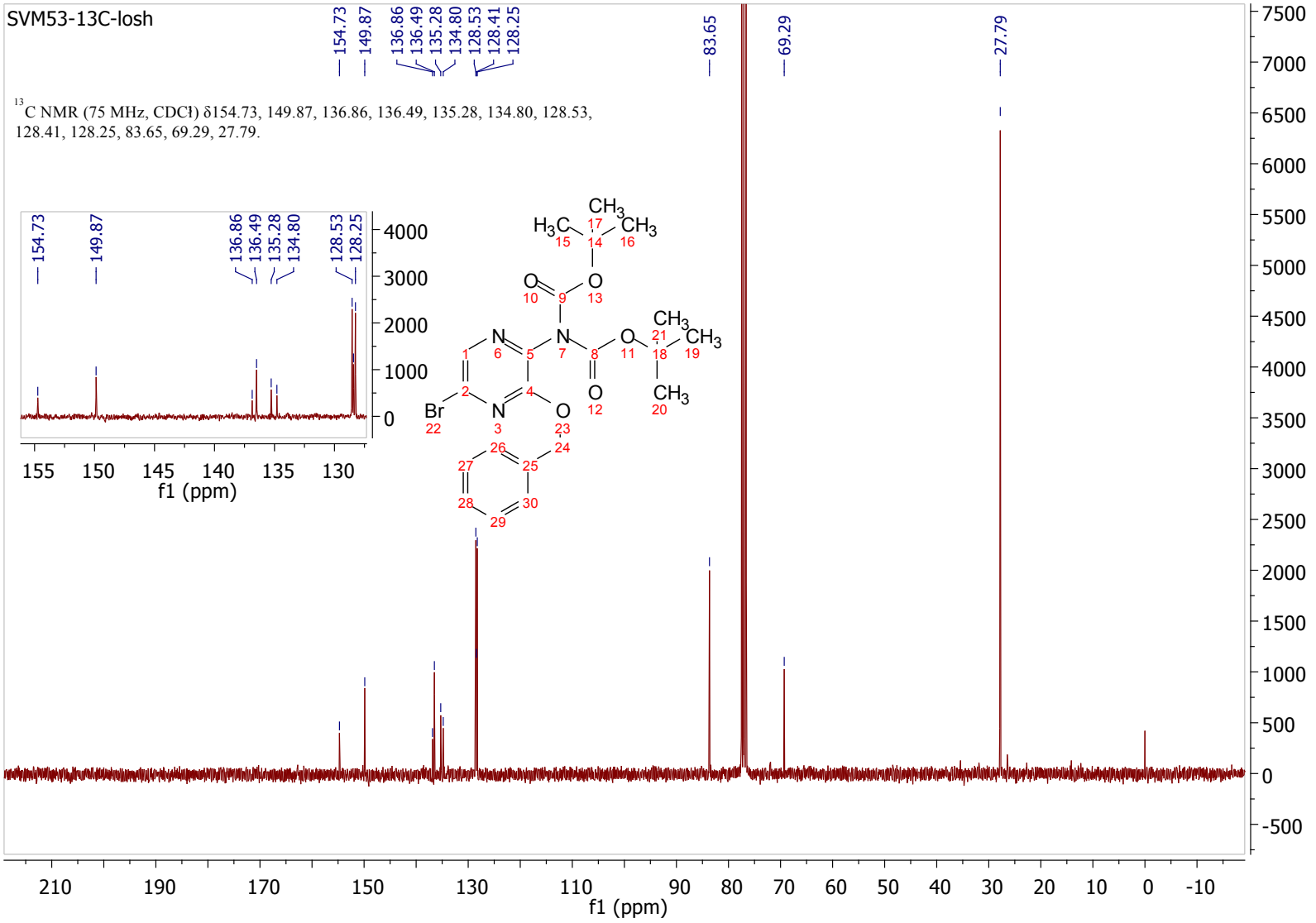
2b


BE400f2
155.36
149.90
136.79
135.99
135.03
83.54
77.01 CDCl3
74.02
27.87
27.83
27.41
19.05
13C NMR (75 MHz, CDCl3) δ 155.36, 149.90, 136.79, 135.99, 135.03, 83.54, 74.02, 27.87, 27.83, 27.41, 19.05.
f1 (ppm)

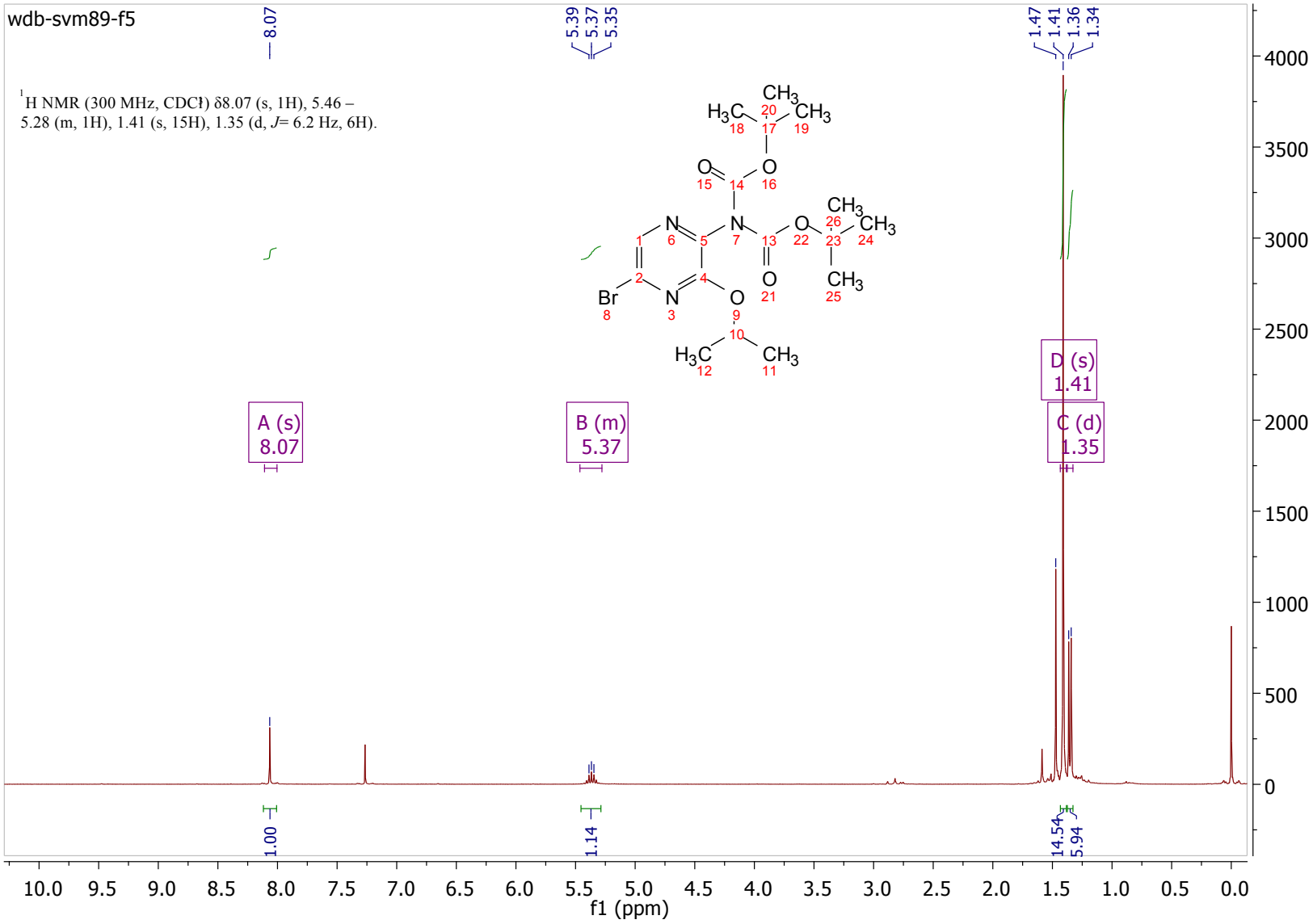
2c


svm53bis
8.13
7.43
7.41
7.36
7.34
7.33
7.26
5.45
1.35
^{1}H NMR (300 MHz, CDCl) δ8.13 (s, 1H), 7.44 – 7.31 (m, 5H), 5.45 (s, 2H), 1.35 (s, 17H).
f1 (ppm)
A (s) 8.13
D (m) 7.37
B (s) 5.45
C (s) 1.35
1.00
5.14
1.93
17.63

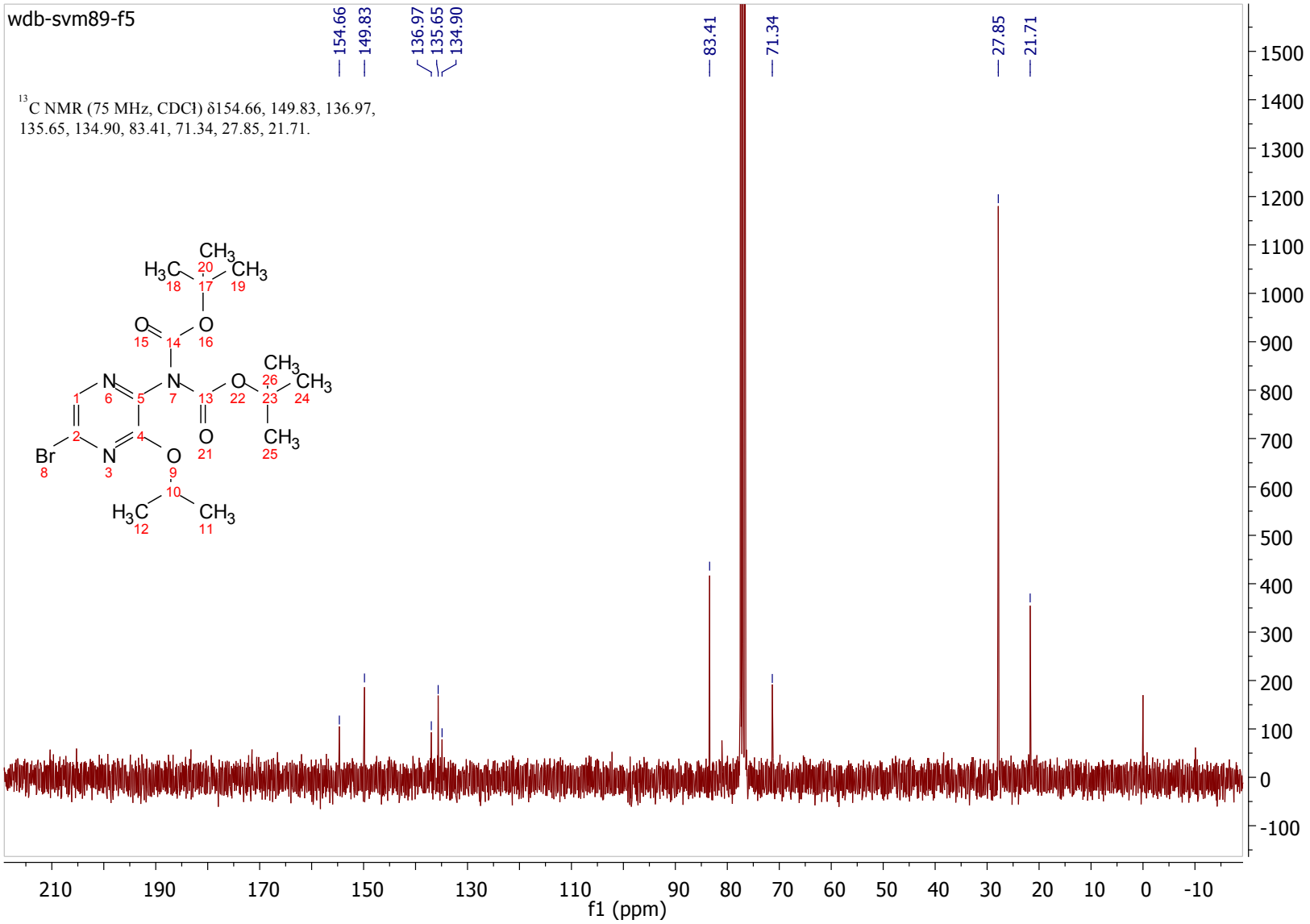
2c


SVM53-13C-losh
154.73
149.87
136.86
136.49
135.28
134.80
128.53
128.41
128.25
83.65
69.29
27.79
13C NMR (75 MHz, CDCl) δ154.73, 149.87, 136.86, 136.49, 135.28, 134.80, 128.53, 128.41, 128.25, 83.65, 69.29, 27.79.
f1 (ppm)

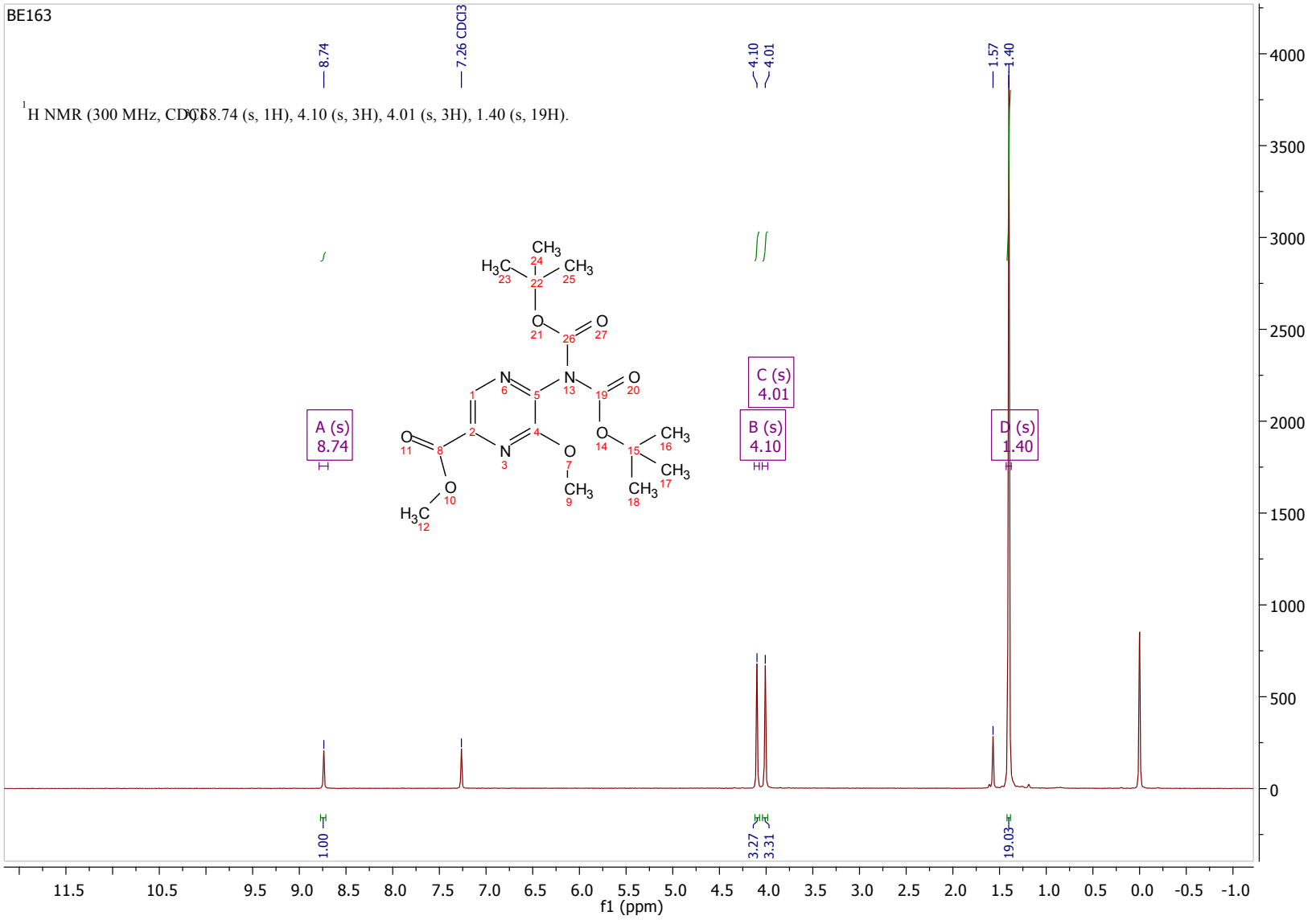
2d


wdb-svm89-f5
8.07
5.39
5.37
5.35
1.47
1.41
1.36
1.34
^{1}H NMR (300 MHz, CDCł) δ8.07 (s, 1H), 5.46 – 5.28 (m, 1H), 1.41 (s, 15H), 1.35 (d, J= 6.2 Hz, 6H).
A (s) 8.07
B (m) 5.37
D (s) 1.41
C (d) 1.35
1.00
1.14
14.54
5.94
f1 (ppm)

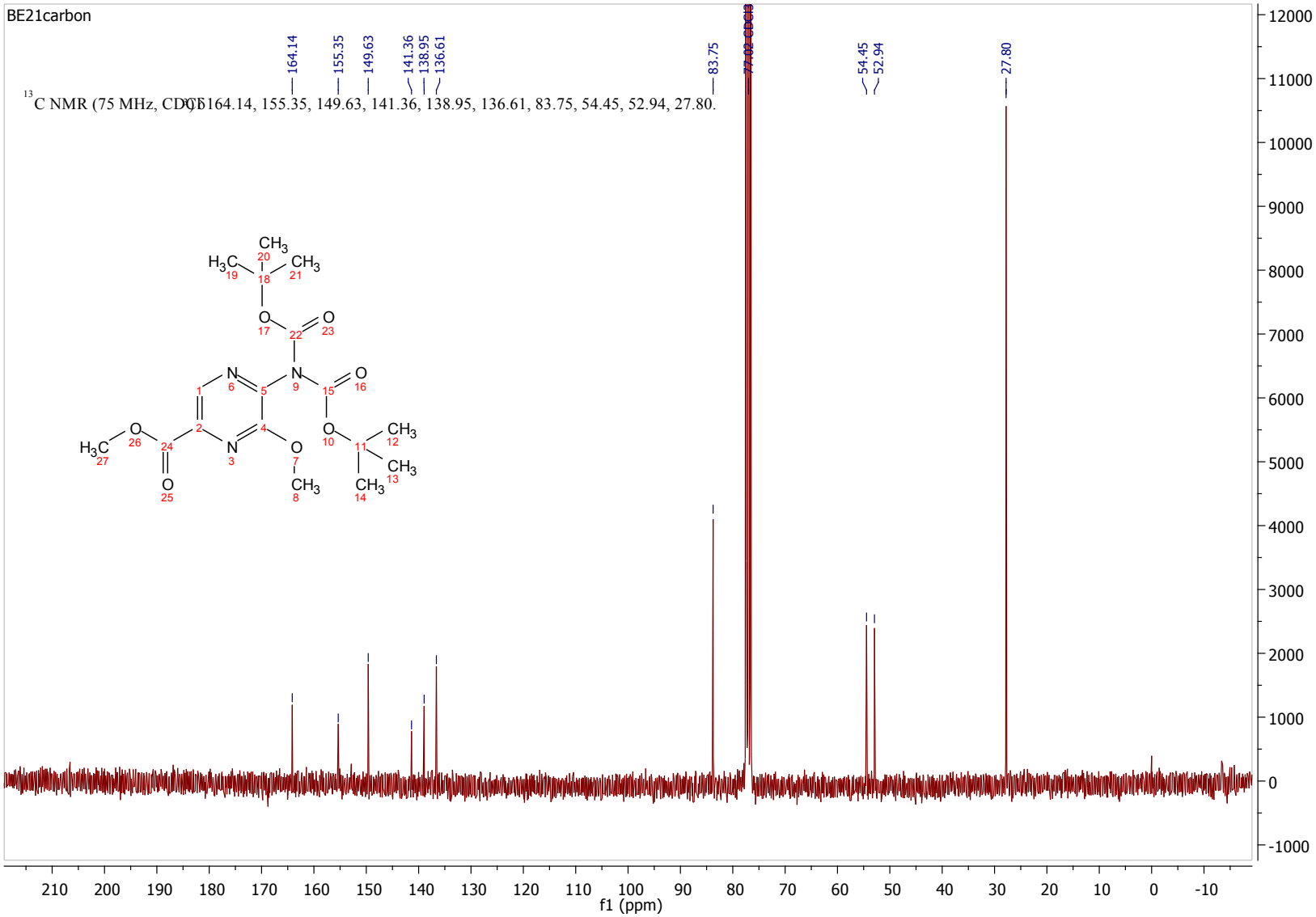
2d


wdb-svm89-f5
154.66
149.83
136.97
135.65
134.90
83.41
71.34
27.85
21.71
13C NMR (75 MHz, CDCl) δ154.66, 149.83, 136.97, 135.65, 134.90, 83.41, 71.34, 27.85, 21.71.
f1 (ppm)

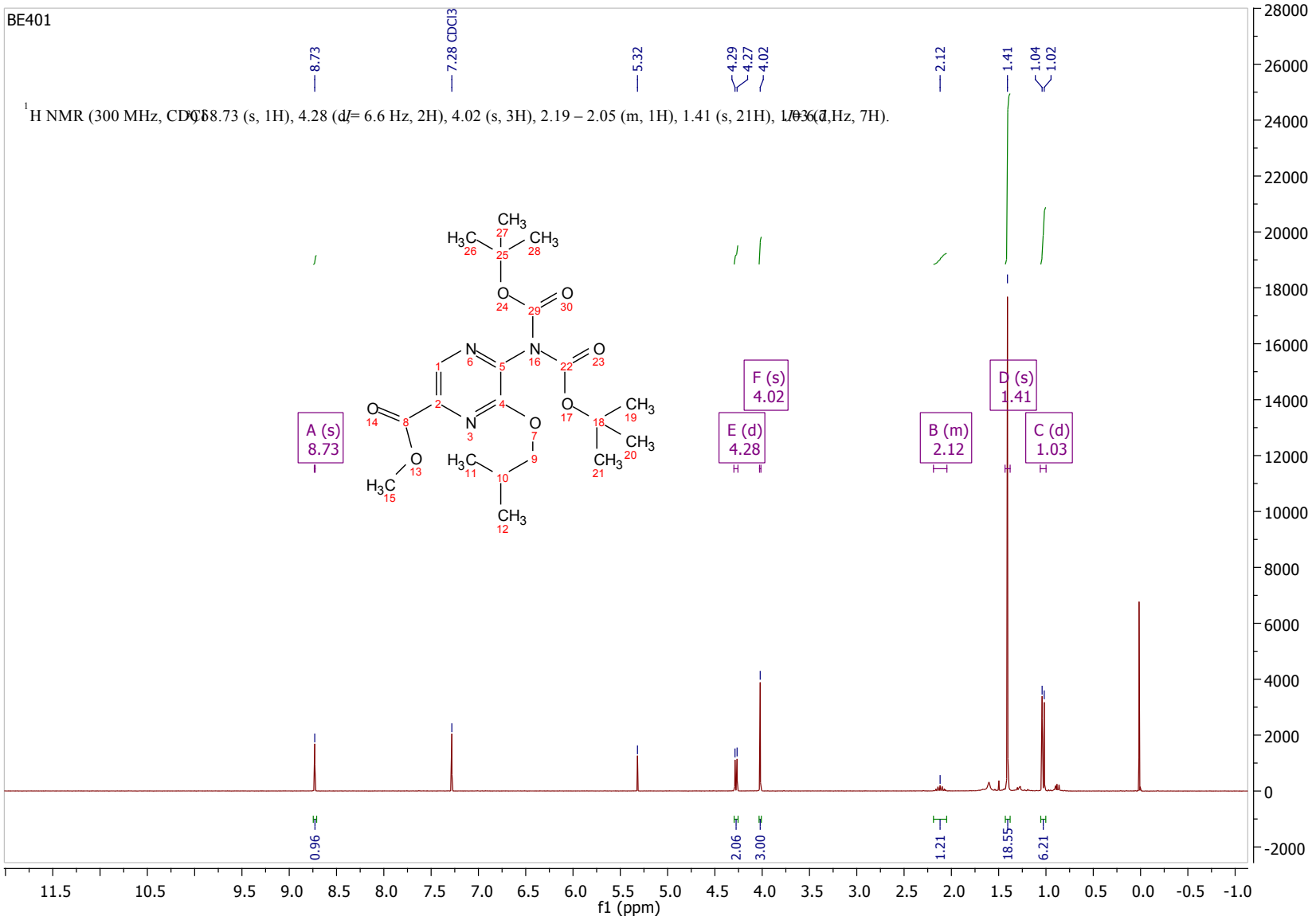
3a


BE163
8.74
7.26 CDCl3
4.10
4.01
1.57
1.40
^{1}H NMR (300 MHz, CDCl$_3$) δ 8.74 (s, 1H), 4.10 (s, 3H), 4.01 (s, 3H), 1.40 (s, 19H).
A (s) 8.74
B (s) 4.10
C (s) 4.01
D (s) 1.40
1.00
3.27
3.31
19.03
f1 (ppm)

3a

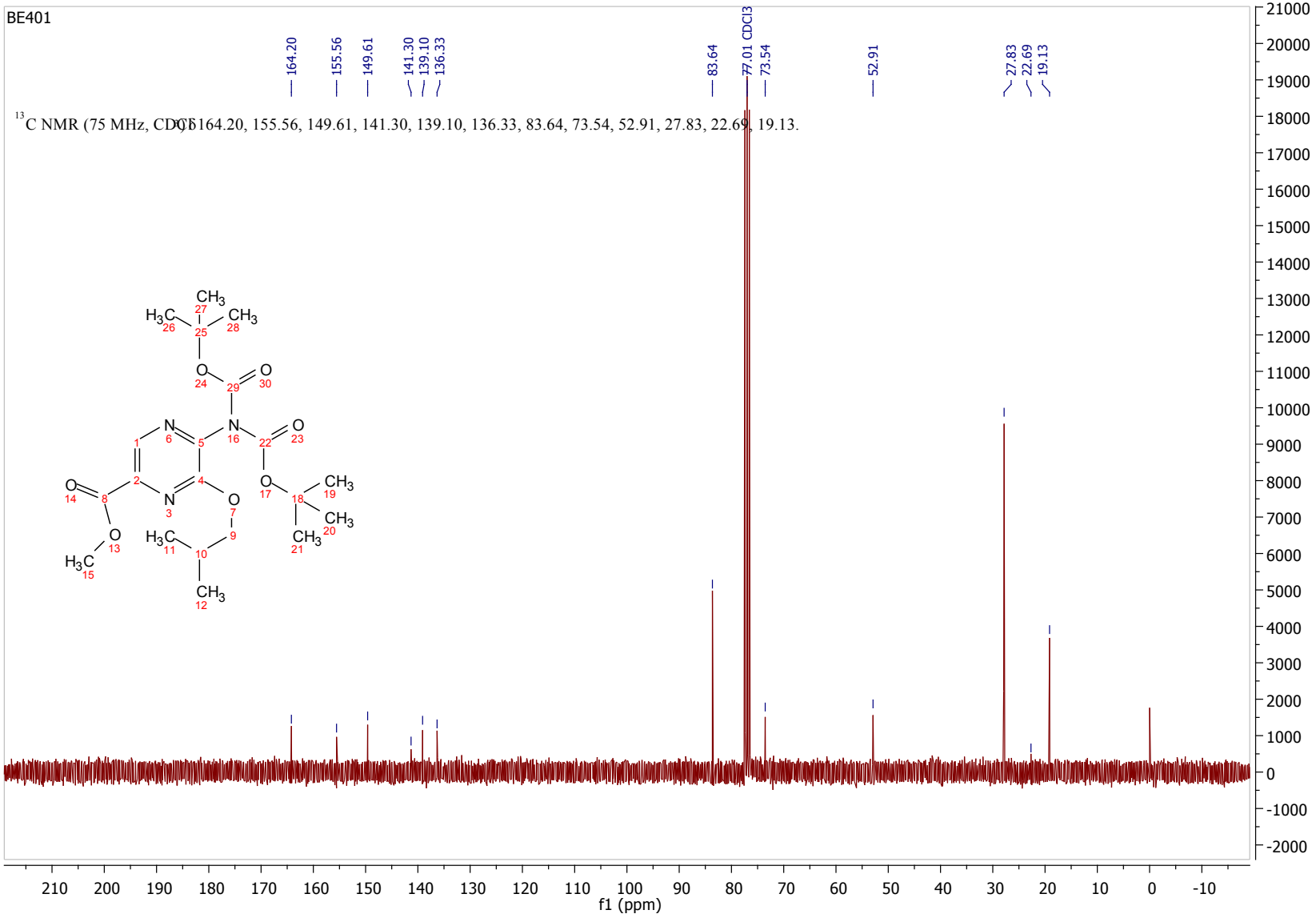

BE21carbon
164.14
155.35
149.63
141.36
138.95
136.61
83.75
77.03
54.45
52.94
27.80
13C NMR (75 MHz, CDCl3) δ 164.14, 155.35, 149.63, 141.36, 138.95, 136.61, 83.75, 54.45, 52.94, 27.80.
f1 (ppm)

3b

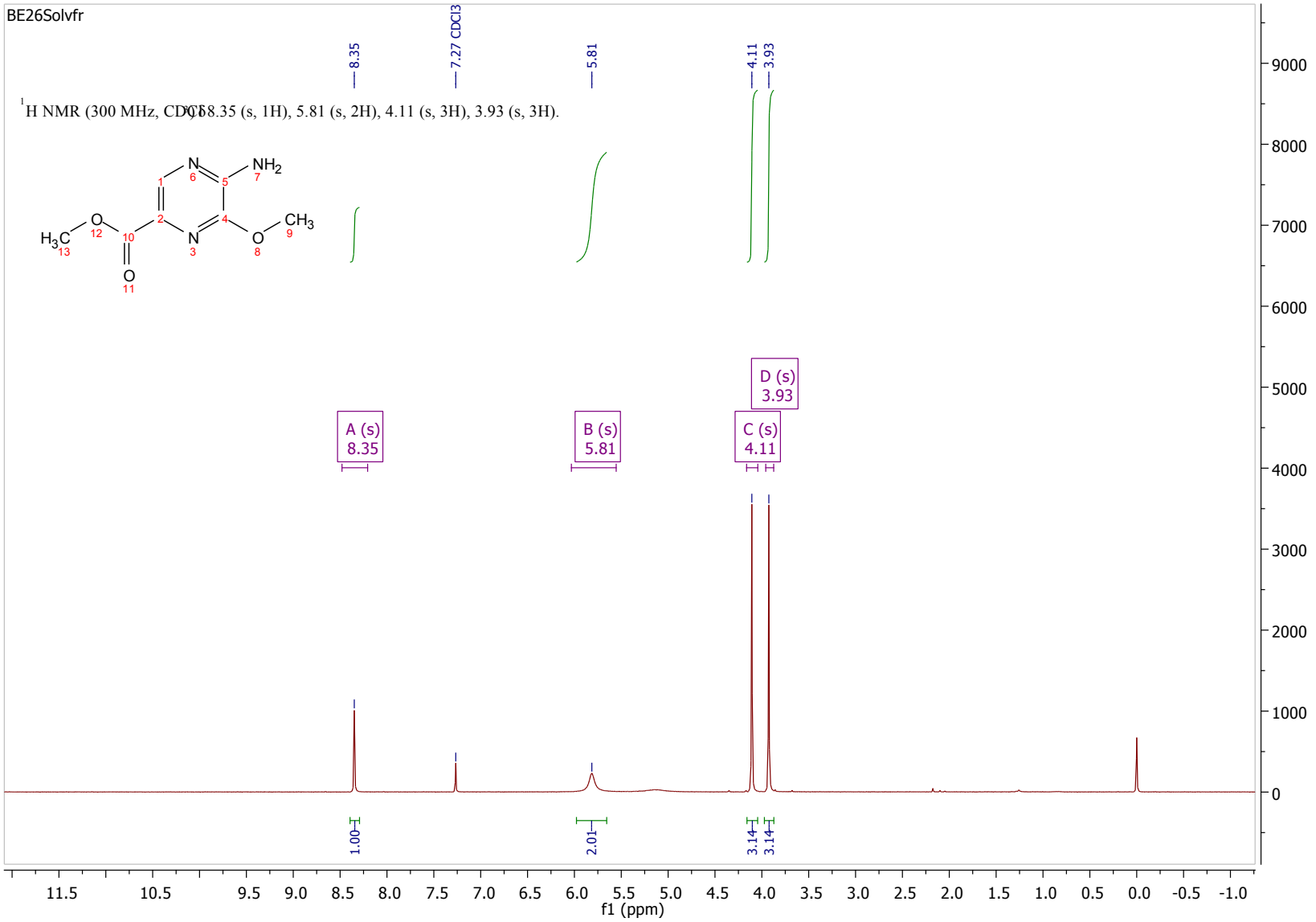


^{1}H NMR (300 MHz, CDCl$_3$) δ 8.73 (s, 1H), 4.28 (d, J = 6.6 Hz, 2H), 4.02 (s, 3H), 2.19 – 2.05 (m, 1H), 1.41 (s, 21H), 1.03 (d, J = 6.7 Hz, 7H).

3b

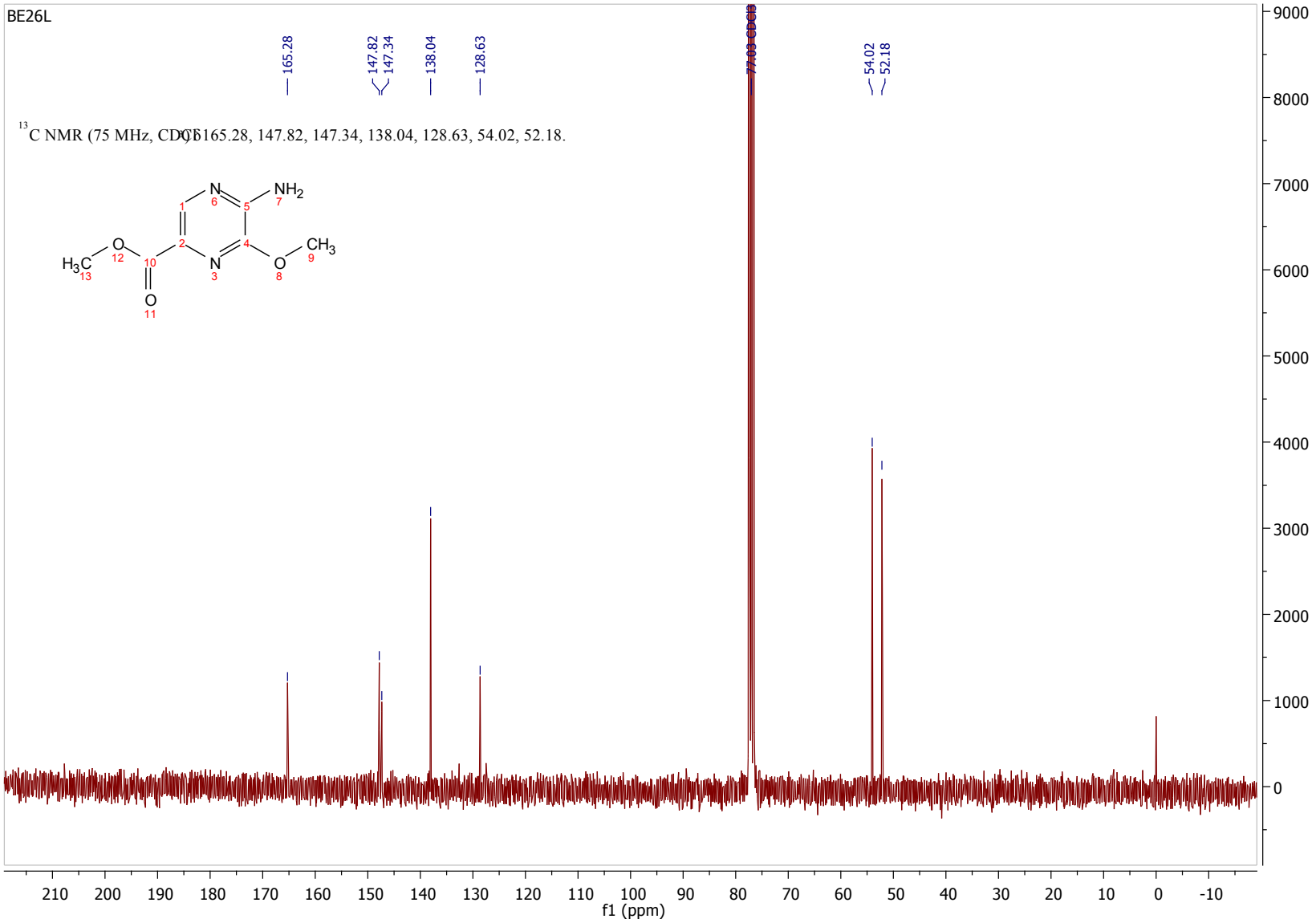

BE401
164.20
155.56
149.61
141.30
139.10
136.33
83.64
77.01 CDCl3
73.54
52.91
27.83
22.69
19.13
13C NMR (75 MHz, CDCl3) δ 164.20, 155.56, 149.61, 141.30, 139.10, 136.33, 83.64, 73.54, 52.91, 27.83, 22.69, 19.13.
f1 (ppm)

4a

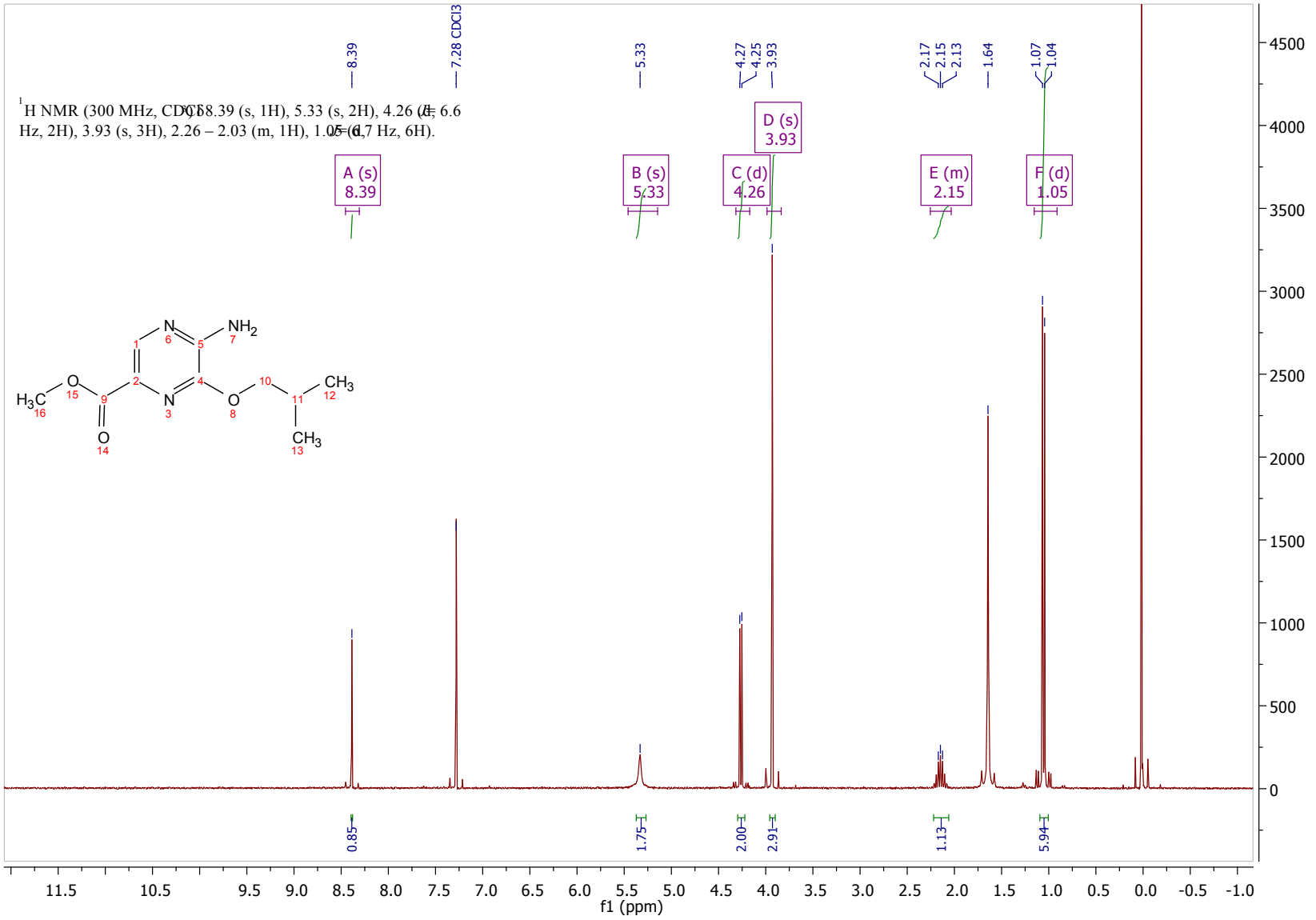


^{1}H NMR (300 MHz, CDCl$_3$) δ 8.35 (s, 1H), 5.81 (s, 2H), 4.11 (s, 3H), 3.93 (s, 3H).

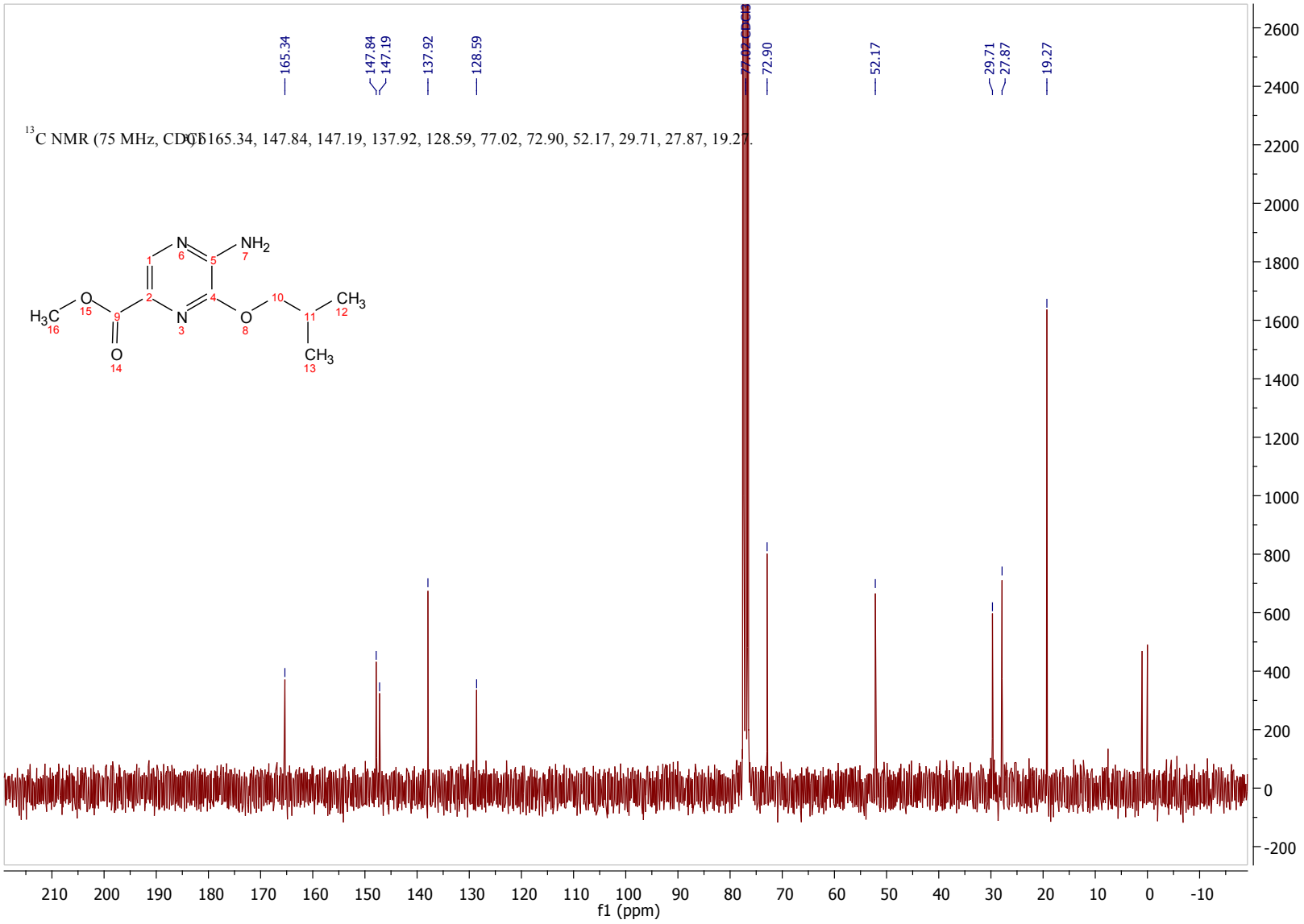
4a


BE26L
165.28
147.82
147.34
138.04
128.63
77.03
54.02
52.18
13C NMR (75 MHz, CDCl3) δ 165.28, 147.82, 147.34, 138.04, 128.63, 54.02, 52.18.
N
NH2
O
CH3
H3C
O
O
1
2
3
4
5
6
7
8
9
10
11
12
13
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

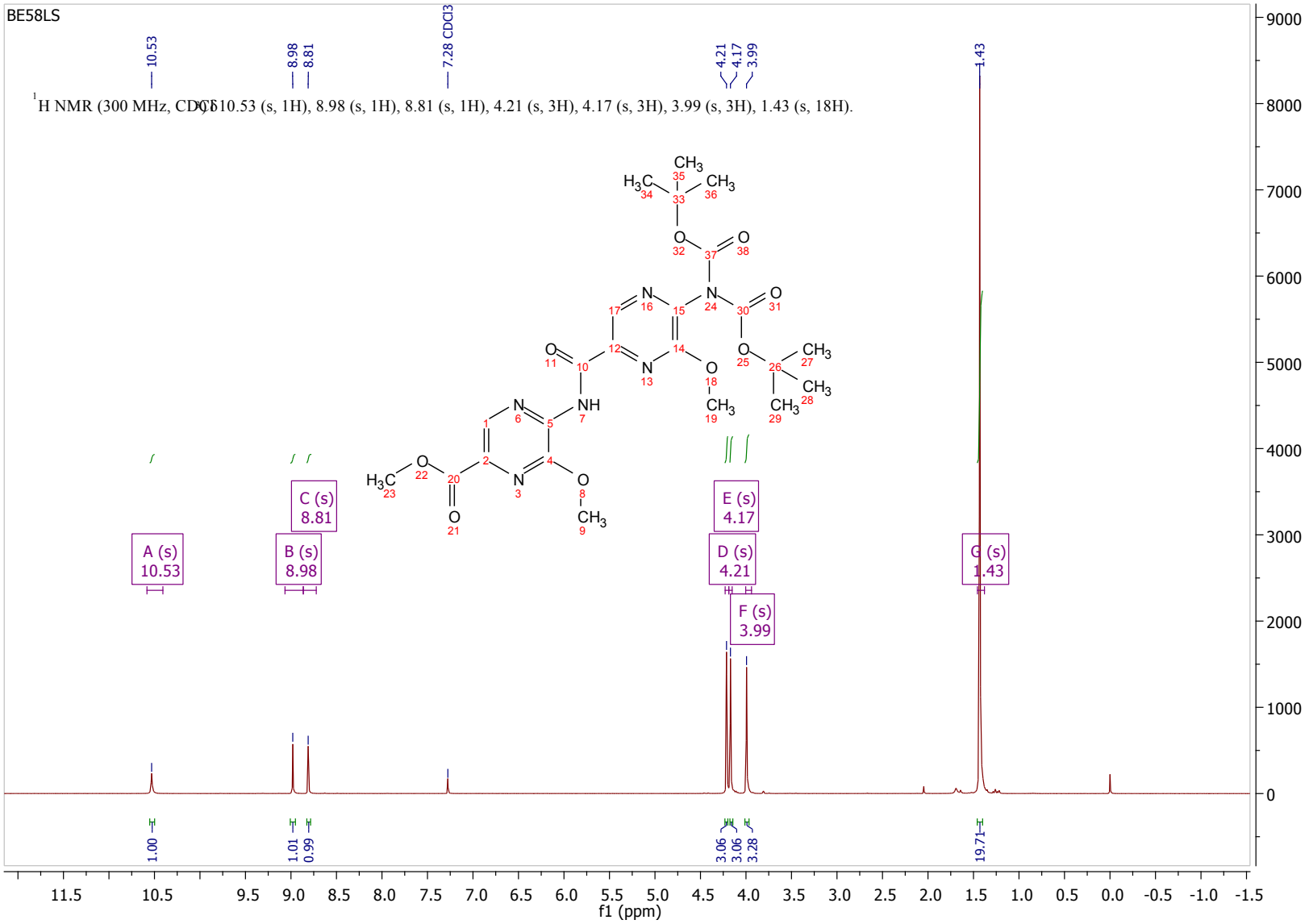
4b


1H NMR (300 MHz, CDCl3) δ 8.39 (s, 1H), 5.33 (s, 2H), 4.26 (d, J = 6.6 Hz, 2H), 3.93 (s, 3H), 2.26 – 2.03 (m, 1H), 1.05 (d, J = 6.7 Hz, 6H).
8.39
7.28 CDCl3
5.33
4.27
4.25
3.93
2.17
2.15
2.13
1.64
1.07
1.04
A (s) 8.39
B (s) 5.33
C (d) 4.26
D (s) 3.93
E (m) 2.15
F (d) 1.05
0.85
1.75
2.00
2.91
1.13
5.94
f1 (ppm)

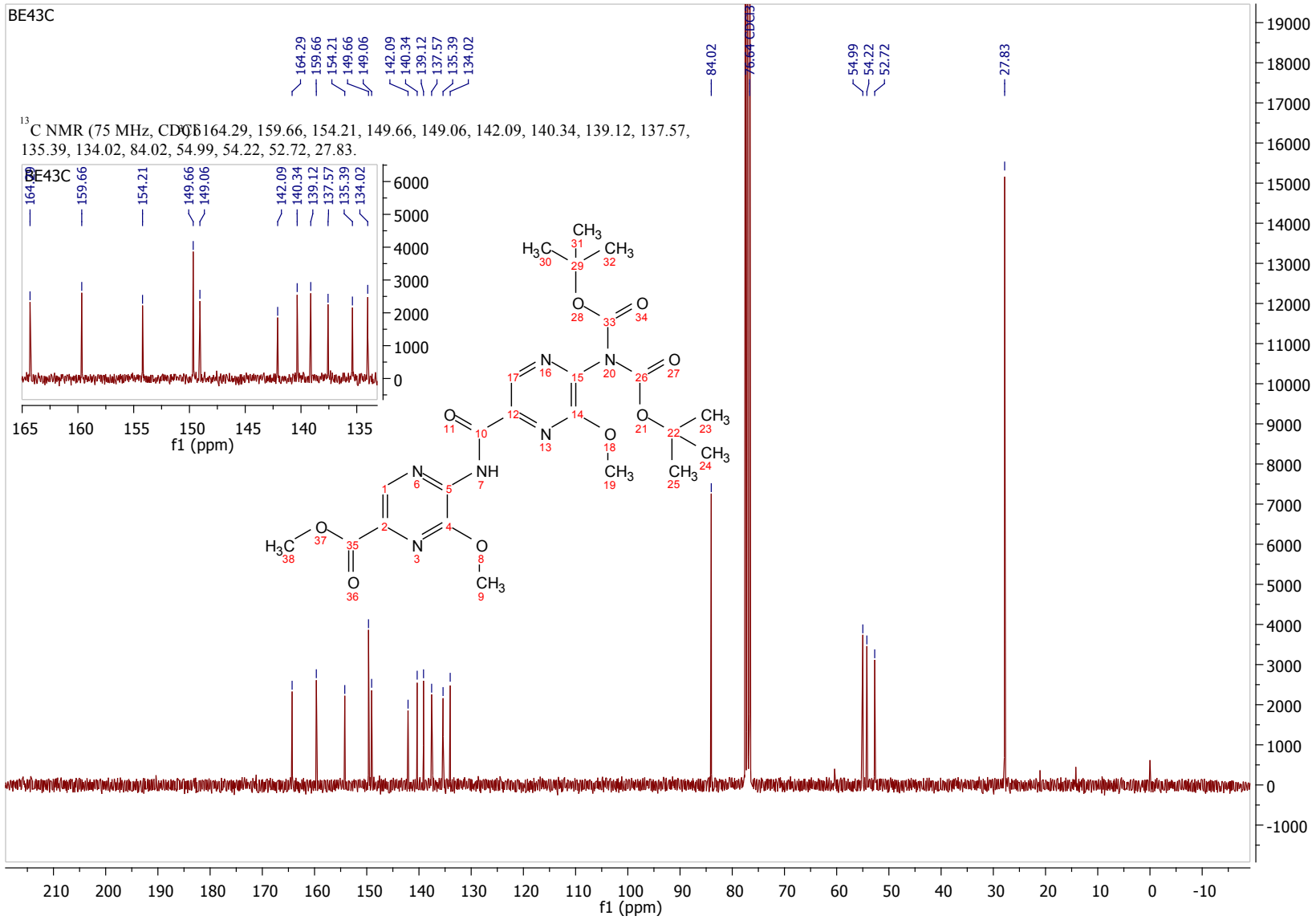
4b


165.34
147.84
147.19
137.92
128.59
77.02
72.90
52.17
29.71
27.87
19.27
13C NMR (75 MHz, CDCl3) δ 165.34, 147.84, 147.19, 137.92, 128.59, 77.02, 72.90, 52.17, 29.71, 27.87, 19.27.
NH2
CH3
CH3
H3C
O
N
f1 (ppm)

5a

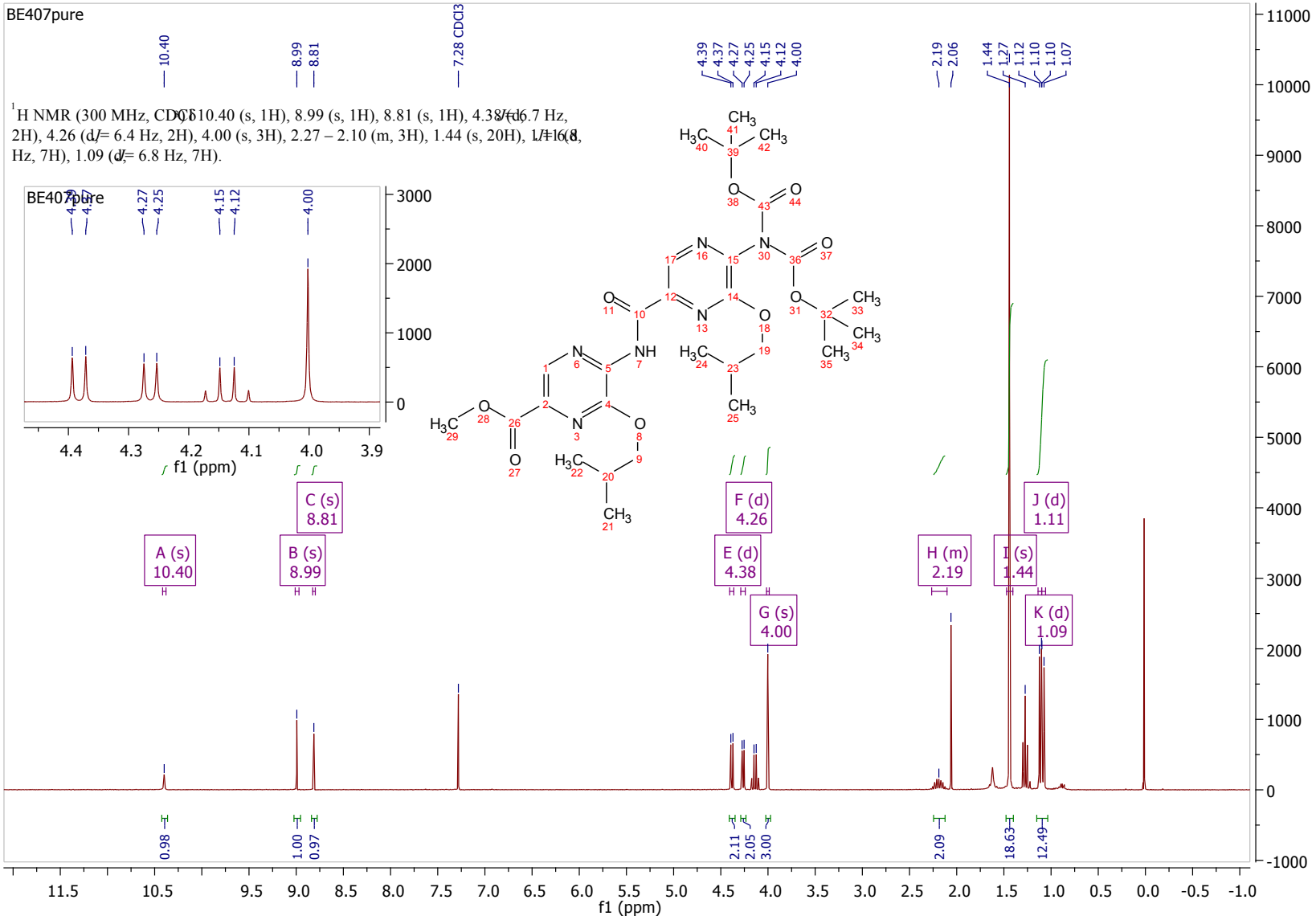

BE58LS
10.53
8.98
8.81
7.28 CDCl3
4.21
4.17
3.99
1.43
^{1}H NMR (300 MHz, CDCl3) δ 10.53 (s, 1H), 8.98 (s, 1H), 8.81 (s, 1H), 4.21 (s, 3H), 4.17 (s, 3H), 3.99 (s, 3H), 1.43 (s, 18H).
A (s) 10.53
B (s) 8.98
C (s) 8.81
D (s) 4.21
E (s) 4.17
F (s) 3.99
G (s) 1.43
1.00
1.01
0.99
3.06
3.06
3.28
19.71
f1 (ppm)

5a

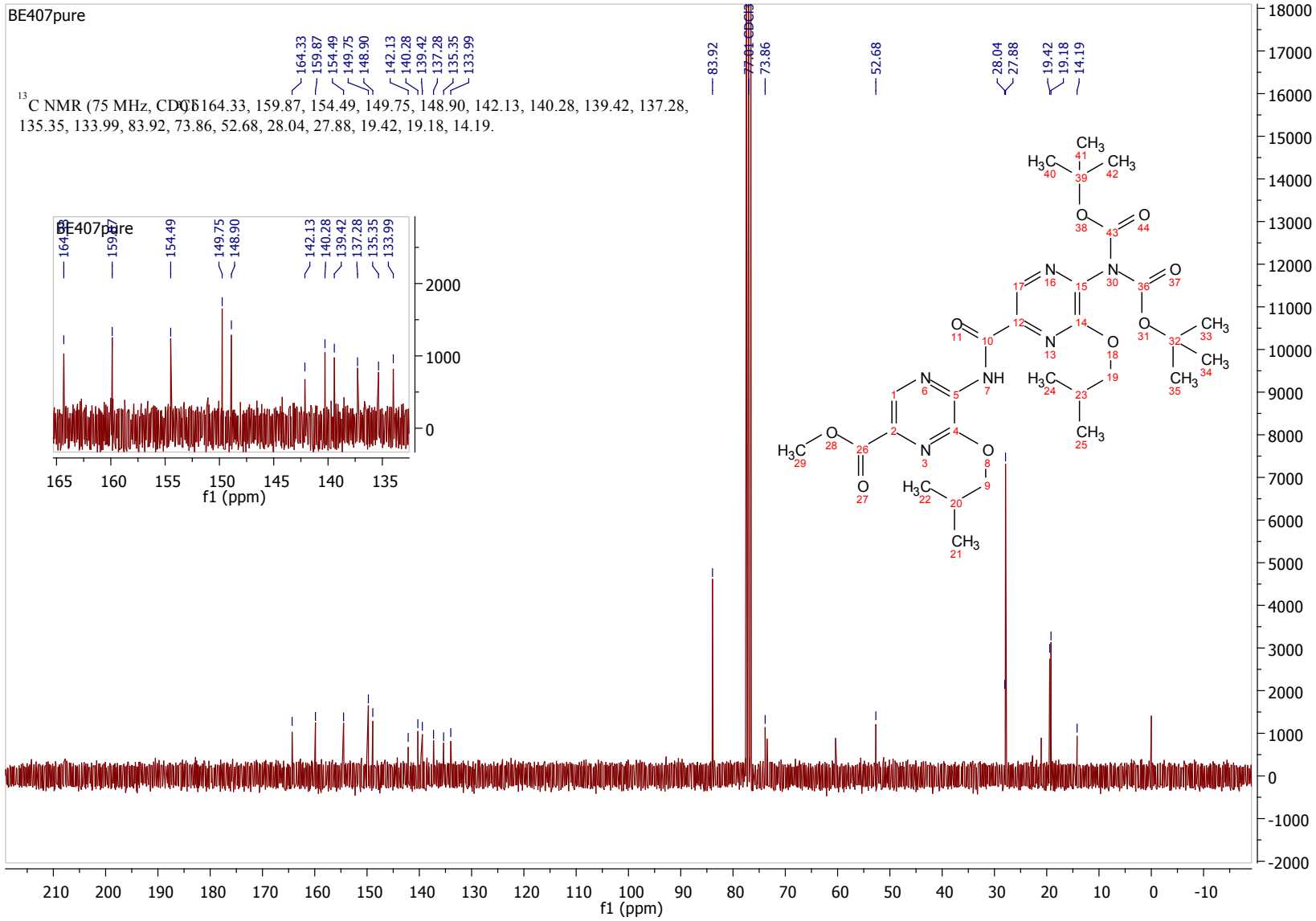


^{13}C NMR (75 MHz, CDCl$_3$) δ 164.29, 159.66, 154.21, 149.66, 149.06, 142.09, 140.34, 139.12, 137.57, 135.39, 134.02, 84.02, 54.99, 54.22, 52.72, 27.83.

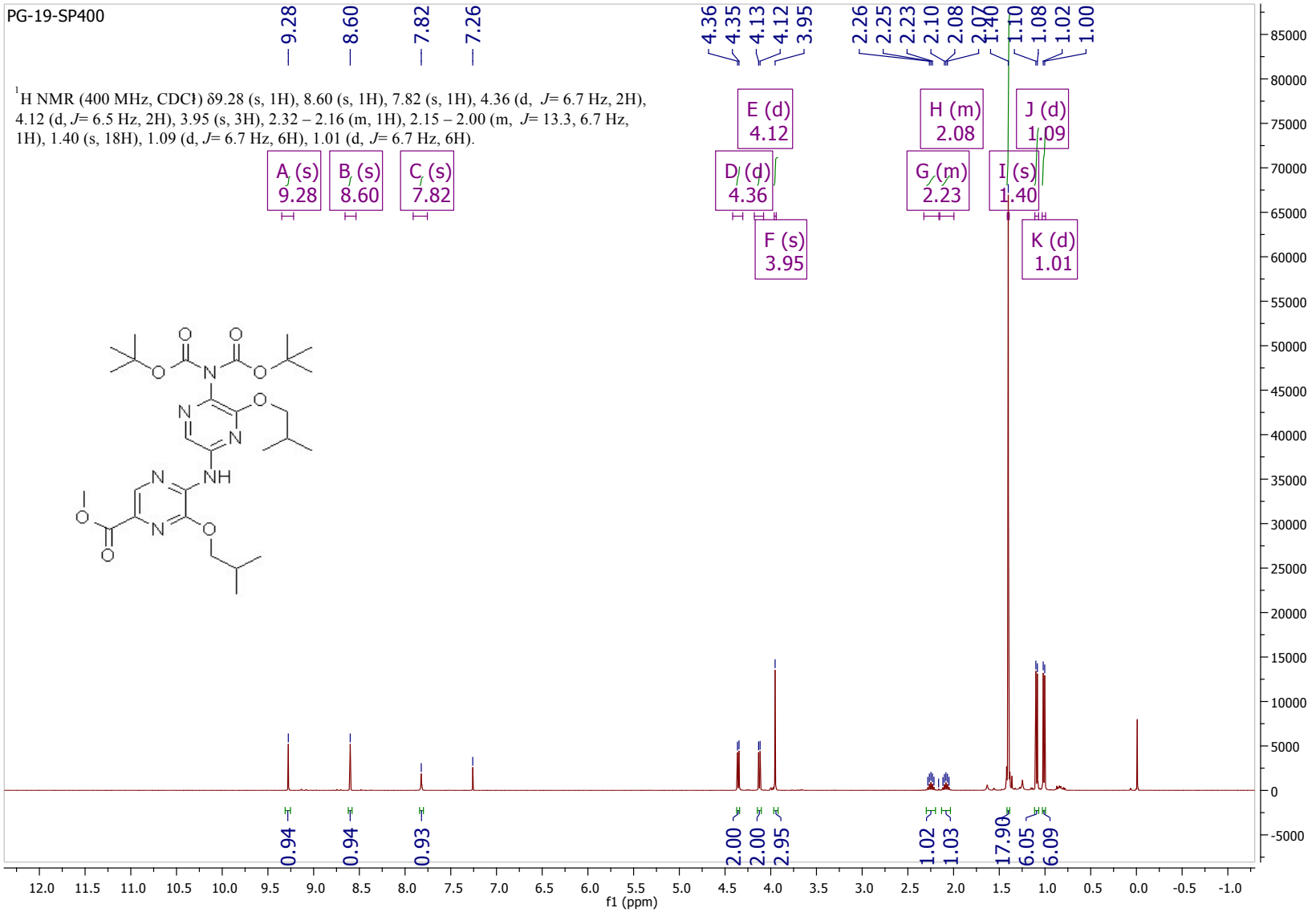
5b


BE407pure
10.40
8.99
8.81
7.28 CDCl3
4.39
4.37
4.27
4.25
4.15
4.12
4.00
2.19
2.06
1.44
1.27
1.12
1.10
1.10
1.07
A (s) 10.40
B (s) 8.99
C (s) 8.81
E (d) 4.38
F (d) 4.26
G (s) 4.00
H (m) 2.19
I (s) 1.44
J (d) 1.11
K (d) 1.09
0.98
1.00
0.97
2.11
2.05
3.00
2.09
18.63
12.49
f1 (ppm)

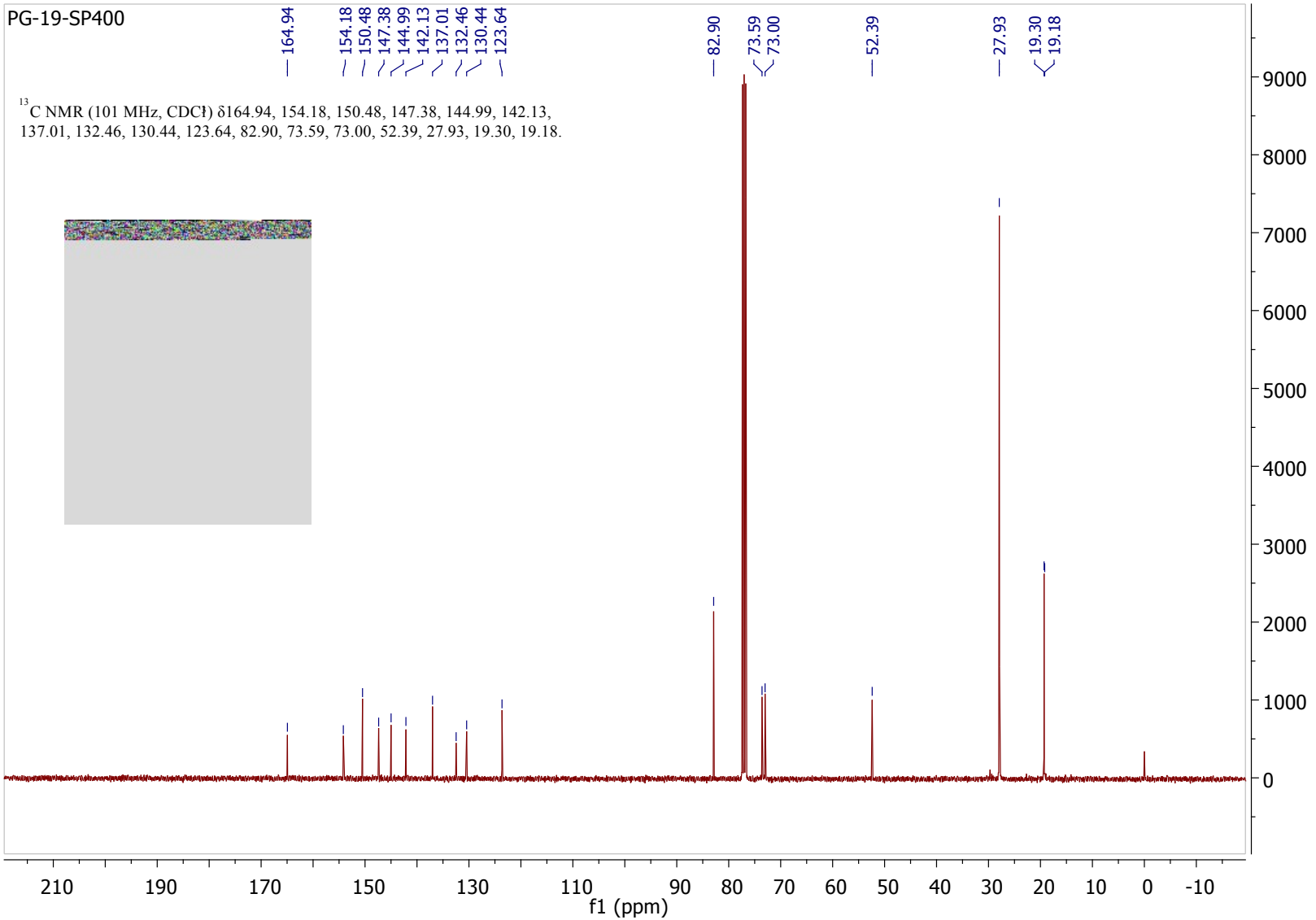
5b


BE407pure
164.33
159.87
154.49
149.75
148.90
142.13
140.28
139.42
137.28
135.35
133.99
83.92
77.01
73.86
52.68
28.04
27.88
19.42
19.18
14.19
13C NMR (75 MHz, CDCl3) δ 164.33, 159.87, 154.49, 149.75, 148.90, 142.13, 140.28, 139.42, 137.28, 135.35, 133.99, 83.92, 73.86, 52.68, 28.04, 27.88, 19.42, 19.18, 14.19.
f1 (ppm)

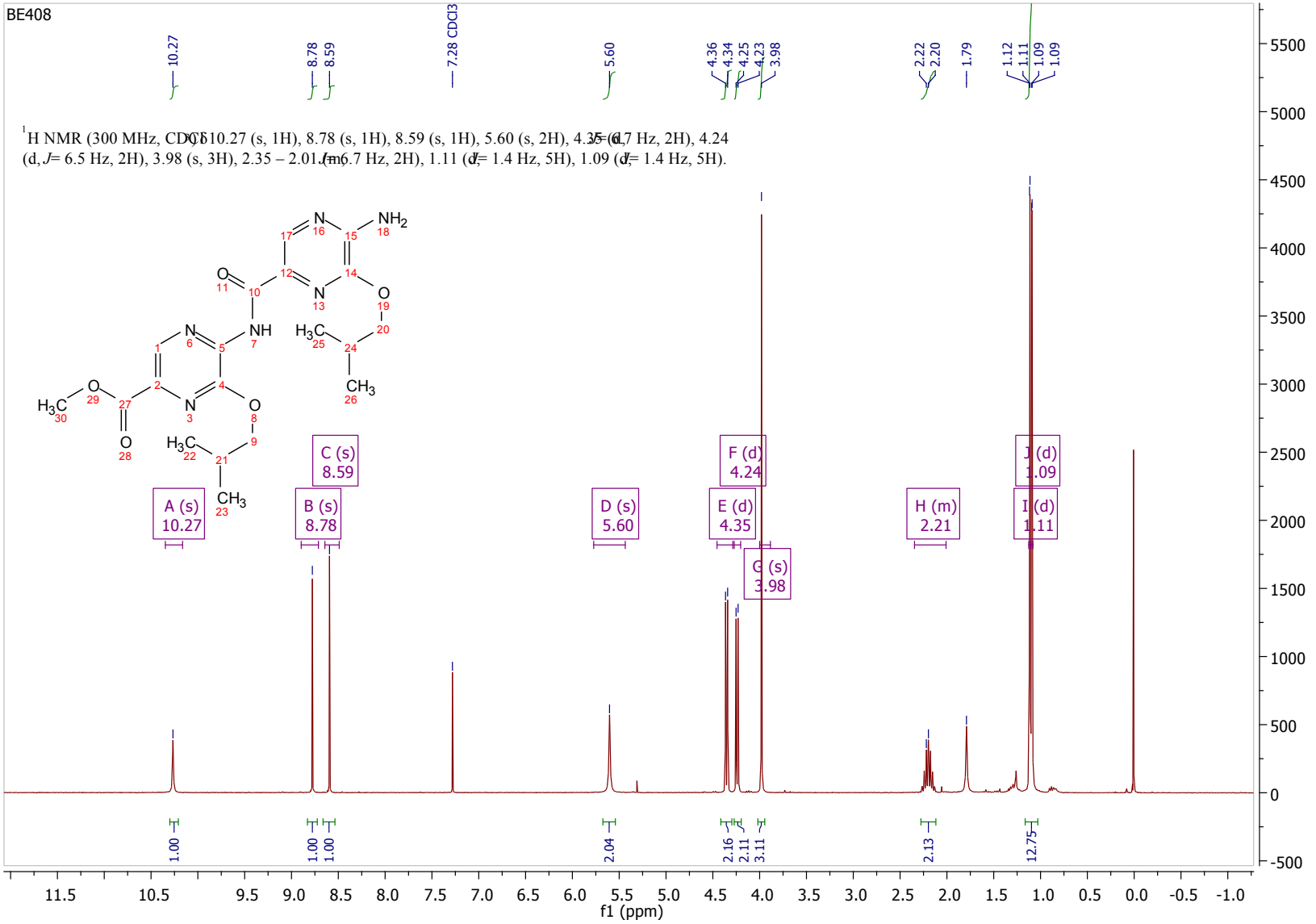
5b’ (Buchwald-Hartwig aminated product)



5b’ (Buchwald-Hartwig aminated product)

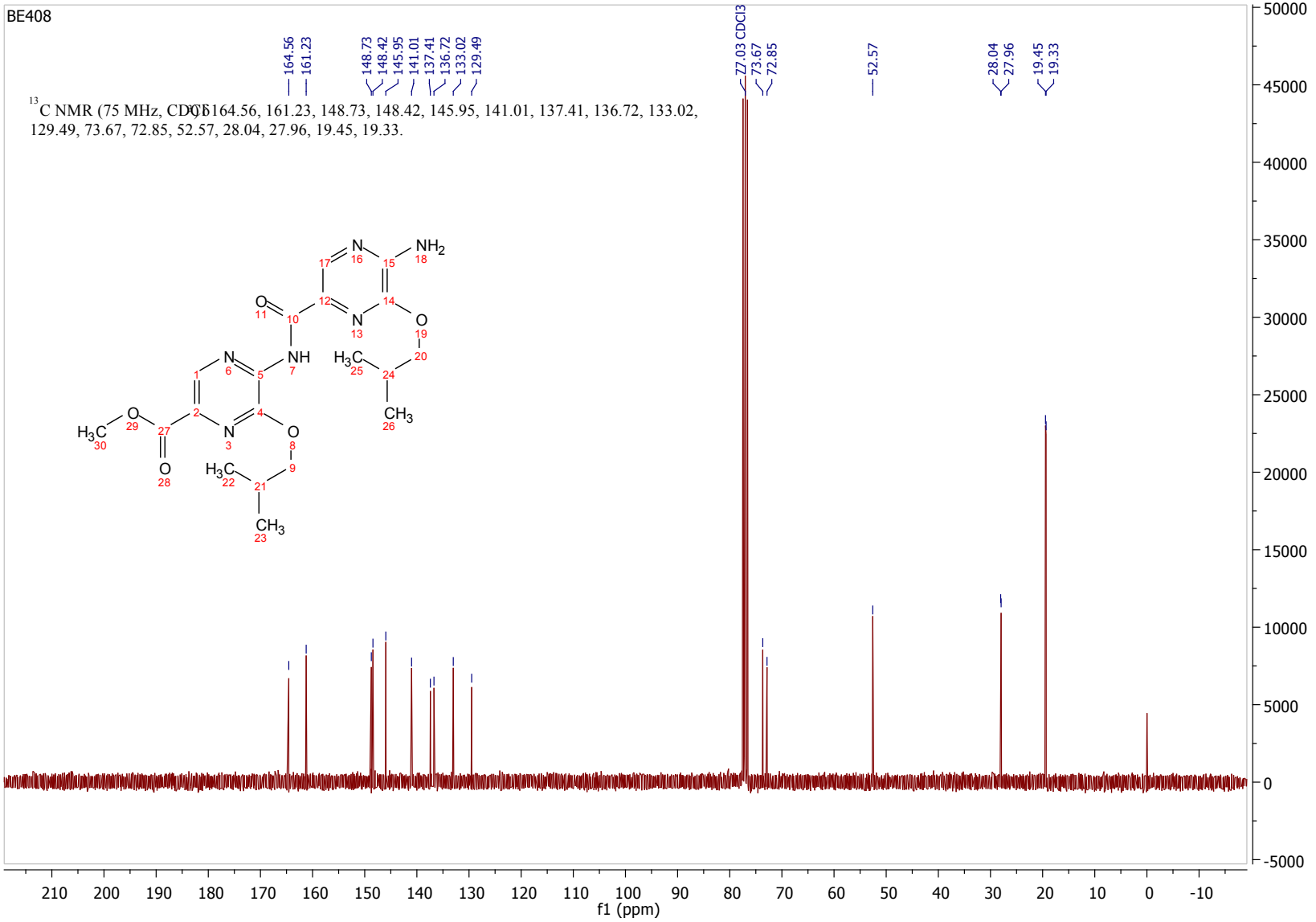


6b

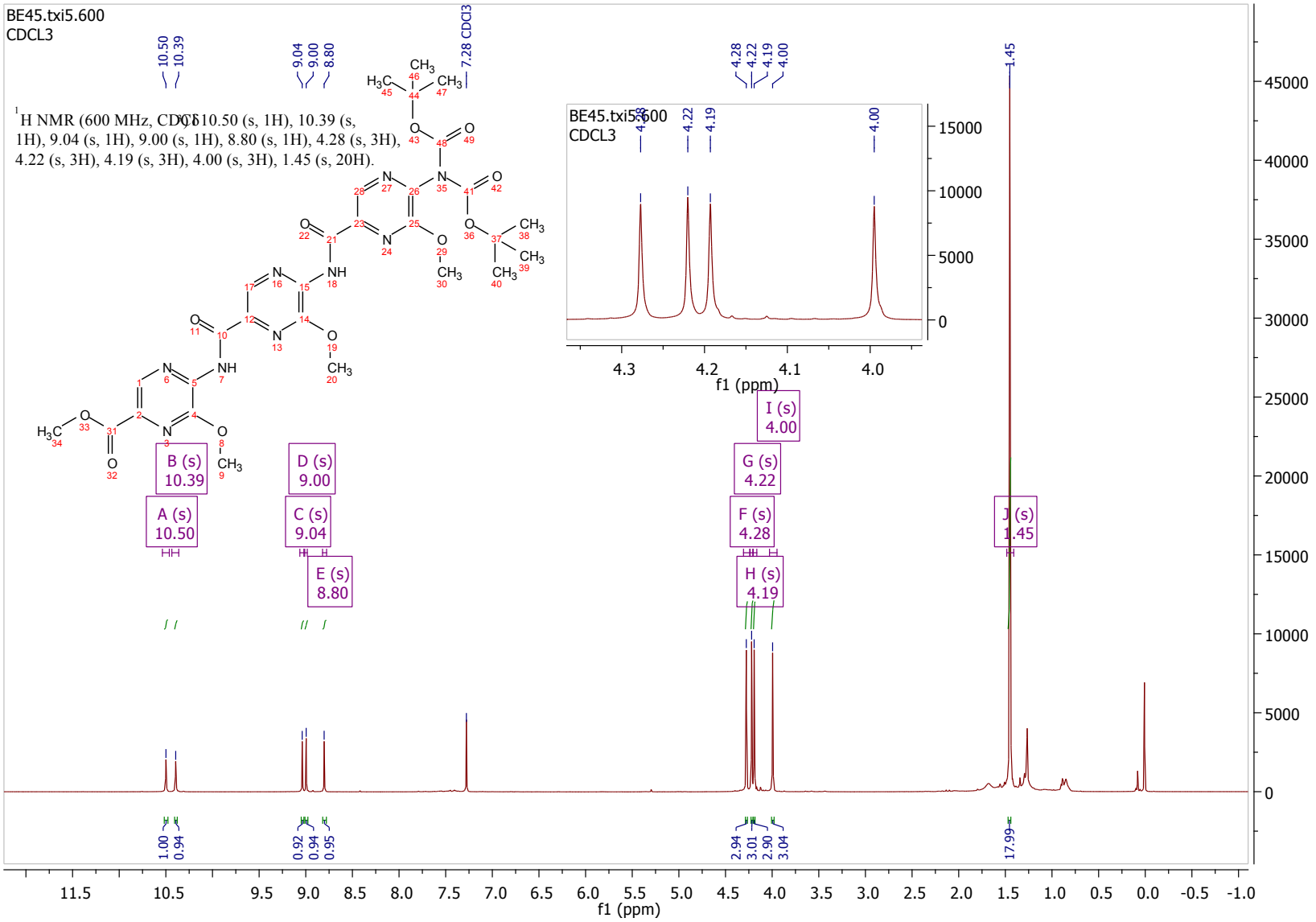


^{1}H NMR (300 MHz, CDCl$_3$) δ 10.27 (s, 1H), 8.78 (s, 1H), 8.59 (s, 1H), 5.60 (s, 2H), 4.35 (d, *J* = 6.7 Hz, 2H), 4.24 (d, *J* = 6.5 Hz, 2H), 3.98 (s, 3H), 2.35 – 2.01 (m, 2H), 1.11 (d, *J* = 6.7 Hz, 2H), 1.09 (d, *J* = 1.4 Hz, 5H), 1.09 (d, *J* = 1.4 Hz, 5H).

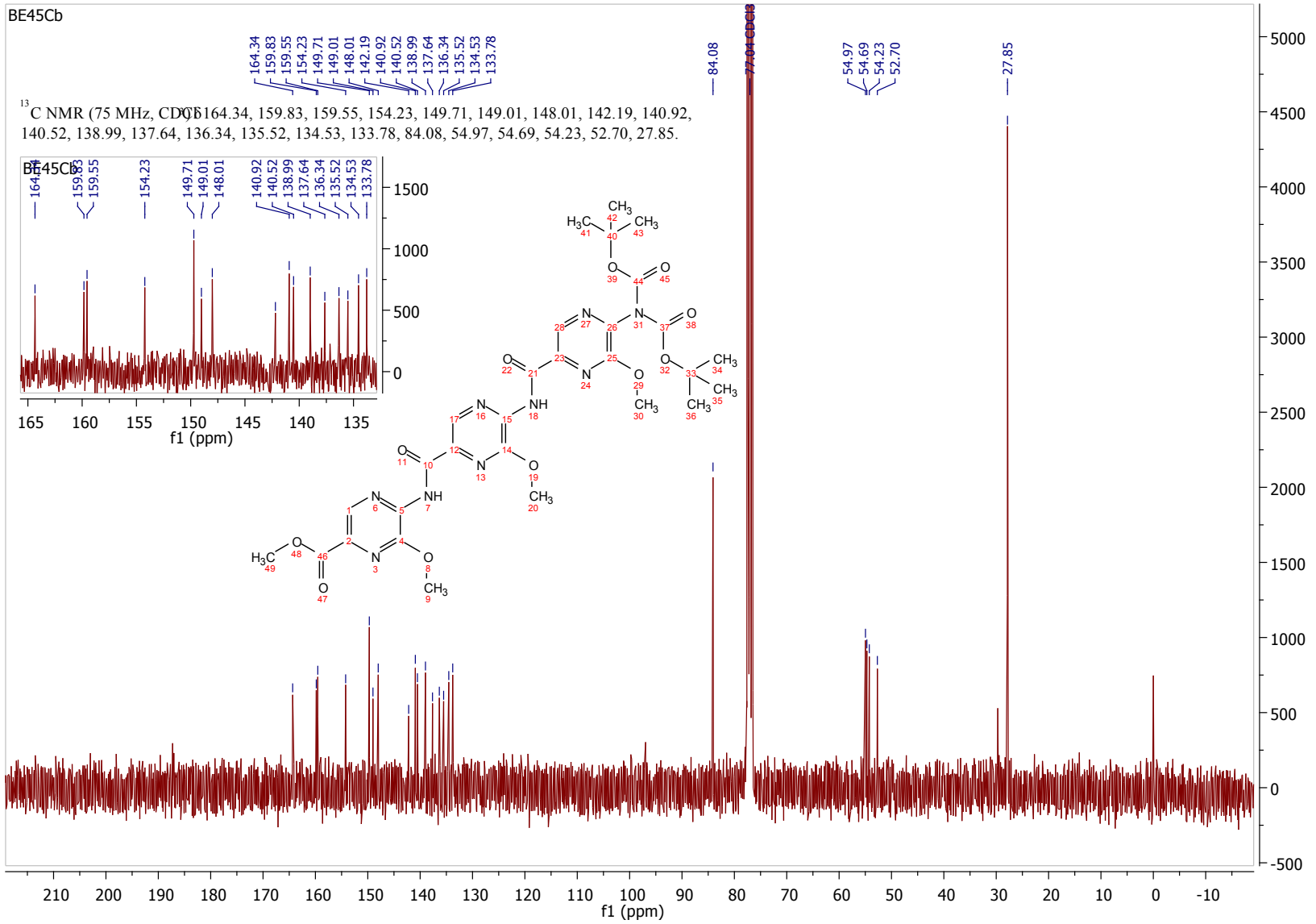
6b


BE408
164.56
161.23
148.73
148.42
145.95
141.01
137.41
136.72
133.02
129.49
77.03 CDCl3
73.67
72.85
52.57
28.04
27.96
19.45
19.33
13C NMR (75 MHz, CDCl3) δ 164.56, 161.23, 148.73, 148.42, 145.95, 141.01, 137.41, 136.72, 133.02, 129.49, 73.67, 72.85, 52.57, 28.04, 27.96, 19.45, 19.33.
f1 (ppm)

7a

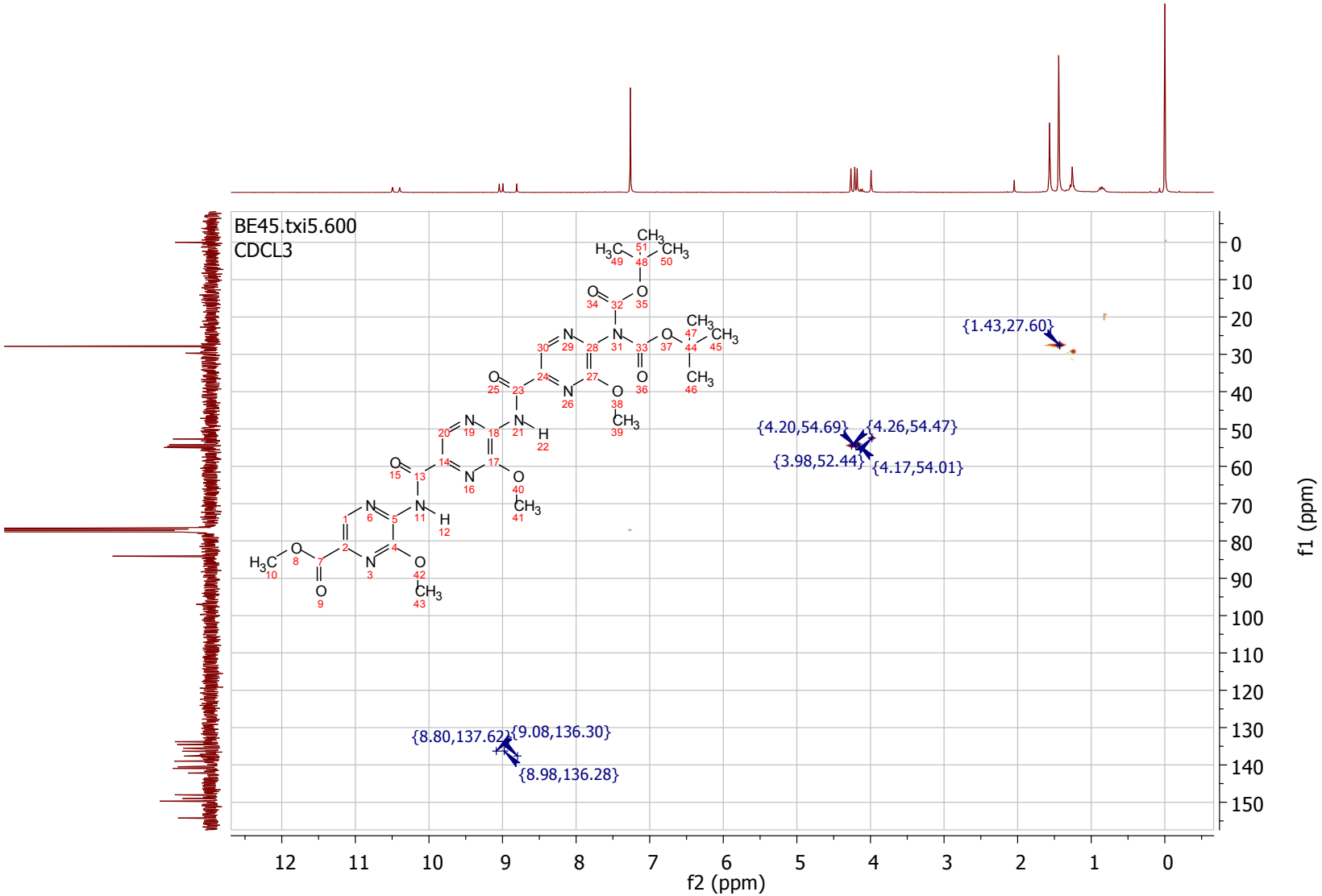

BE45.txi5.600
CDCL3
^{1}H NMR (600 MHz, CDCl$_3$) δ 10.50 (s, 1H), 10.39 (s, 1H), 9.04 (s, 1H), 9.00 (s, 1H), 8.80 (s, 1H), 4.28 (s, 3H), 4.22 (s, 3H), 4.19 (s, 3H), 4.00 (s, 3H), 1.45 (s, 20H).
A (s) 10.50
B (s) 10.39
C (s) 9.04
D (s) 9.00
E (s) 8.80
F (s) 4.28
G (s) 4.22
H (s) 4.19
I (s) 4.00
J (s) 1.45
f1 (ppm)

7a

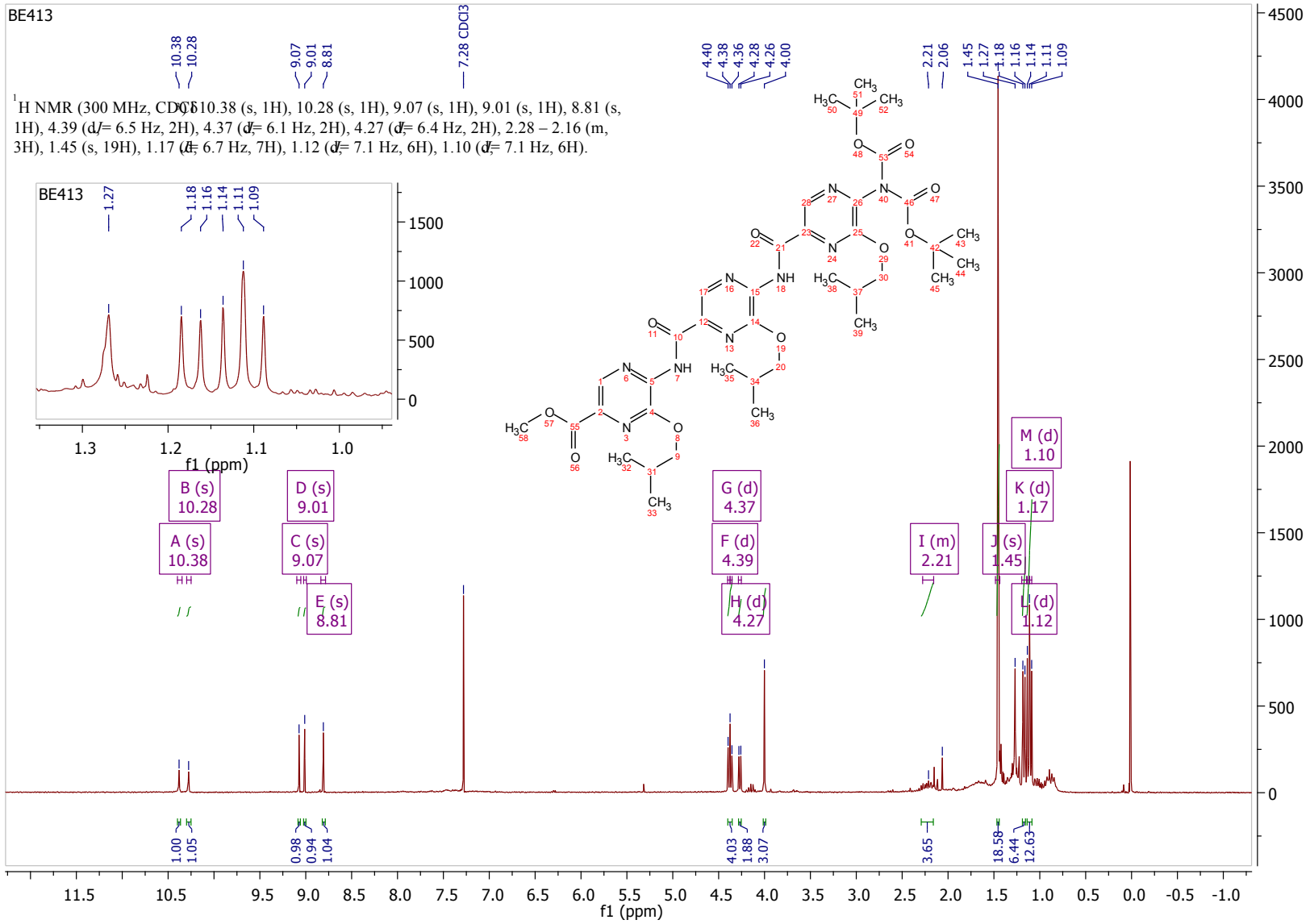


^{13}C NMR (75 MHz, CDCl$_3$) δ 164.34, 159.83, 159.55, 154.23, 149.71, 149.01, 148.01, 142.19, 140.92, 140.52, 138.99, 137.64, 136.34, 135.52, 134.53, 133.78, 84.08, 54.97, 54.69, 54.23, 52.70, 27.85.

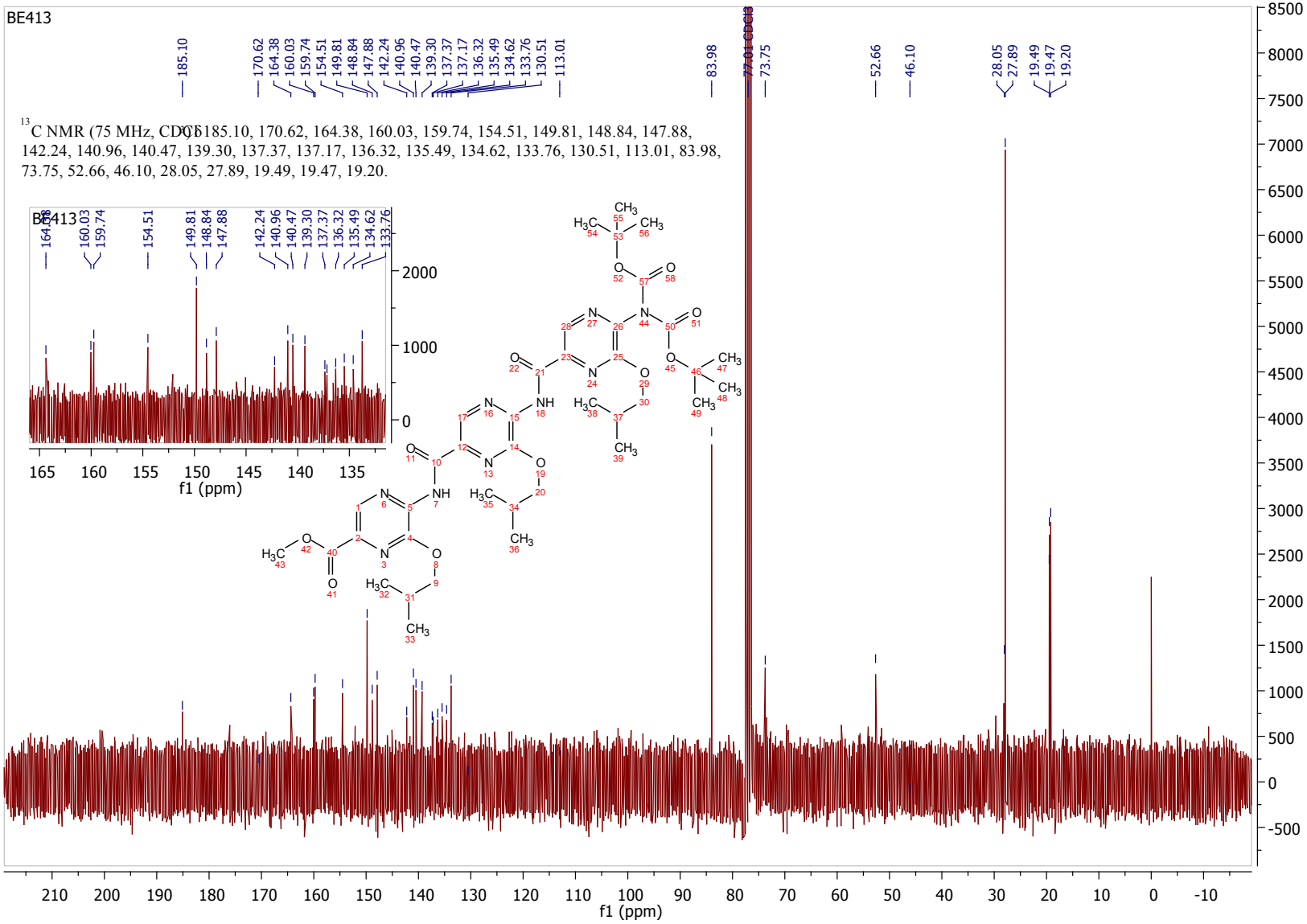
7a


BE45.txi5.600
CDCL3
{1.43,27.60}
{4.20,54.69}
{4.26,54.47}
{3.98,52.44}
{4.17,54.01}
{8.80,137.62}
{9.08,136.30}
{8.98,136.28}
f2 (ppm)
f1 (ppm)

7b

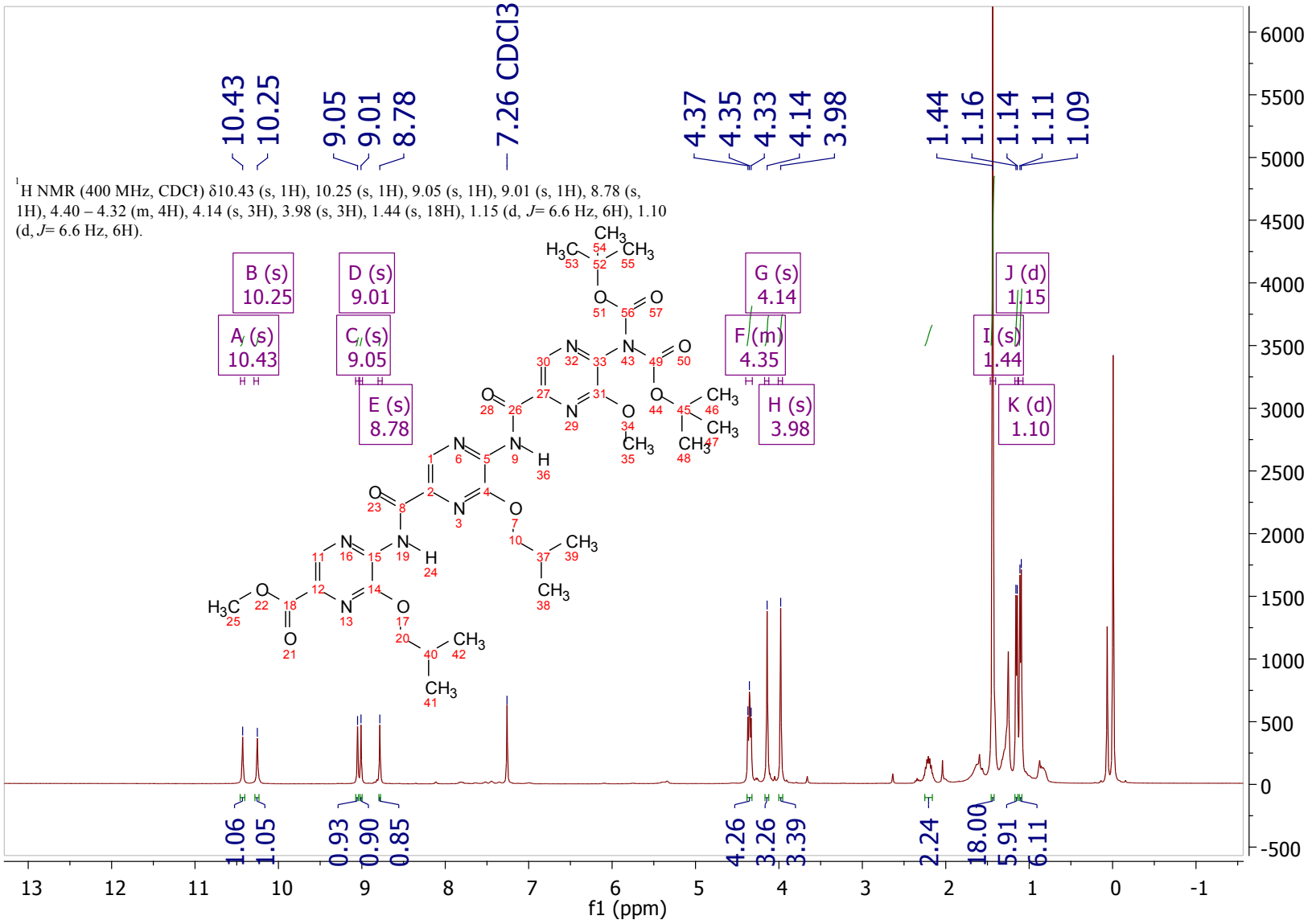

BE413
10.38
10.28
9.07
9.01
8.81
7.28 CDCl3
4.40
4.38
4.36
4.28
4.26
4.00
2.21
2.06
1.45
1.27
1.18
1.16
1.14
1.11
1.09
¹H NMR (300 MHz, CDCl3) δ 10.38 (s, 1H), 10.28 (s, 1H), 9.07 (s, 1H), 9.01 (s, 1H), 8.81 (s, 1H), 4.39 (d, J = 6.5 Hz, 2H), 4.37 (d, J = 6.1 Hz, 2H), 4.27 (d, J = 6.4 Hz, 2H), 2.28 – 2.16 (m, 3H), 1.45 (s, 19H), 1.17 (d, J = 6.7 Hz, 7H), 1.12 (d, J = 7.1 Hz, 6H), 1.10 (d, J = 7.1 Hz, 6H).
BE413
1.27
1.18
1.16
1.14
1.11
1.09
f1 (ppm)
A (s) 10.38
B (s) 10.28
C (s) 9.07
D (s) 9.01
E (s) 8.81
F (d) 4.39
G (d) 4.37
H (d) 4.27
I (m) 2.21
J (s) 1.45
K (d) 1.17
L (d) 1.12
M (d) 1.10
1.00
1.05
0.98
0.94
1.04
4.03
1.88
3.07
3.65
18.58
6.44
12.63
f1 (ppm)

7b

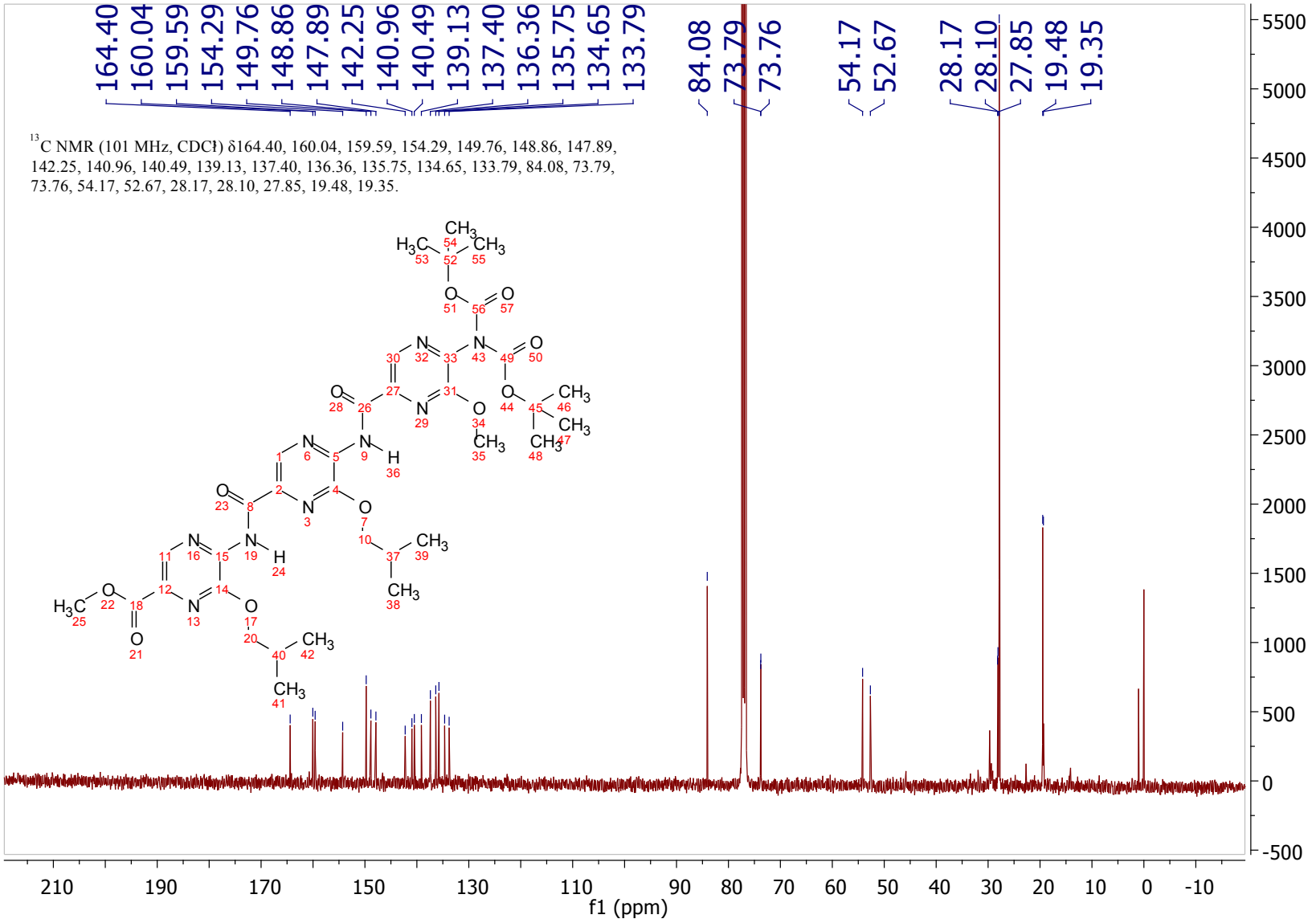


^{13}C NMR (75 MHz, CDCl$_3$) δ 185.10, 170.62, 164.38, 160.03, 159.74, 154.51, 149.81, 148.84, 147.88, 142.24, 140.96, 140.47, 139.30, 137.37, 137.17, 136.32, 135.49, 134.62, 133.76, 130.51, 113.01, 83.98, 73.75, 52.66, 46.10, 28.05, 27.89, 19.49, 19.47, 19.20.

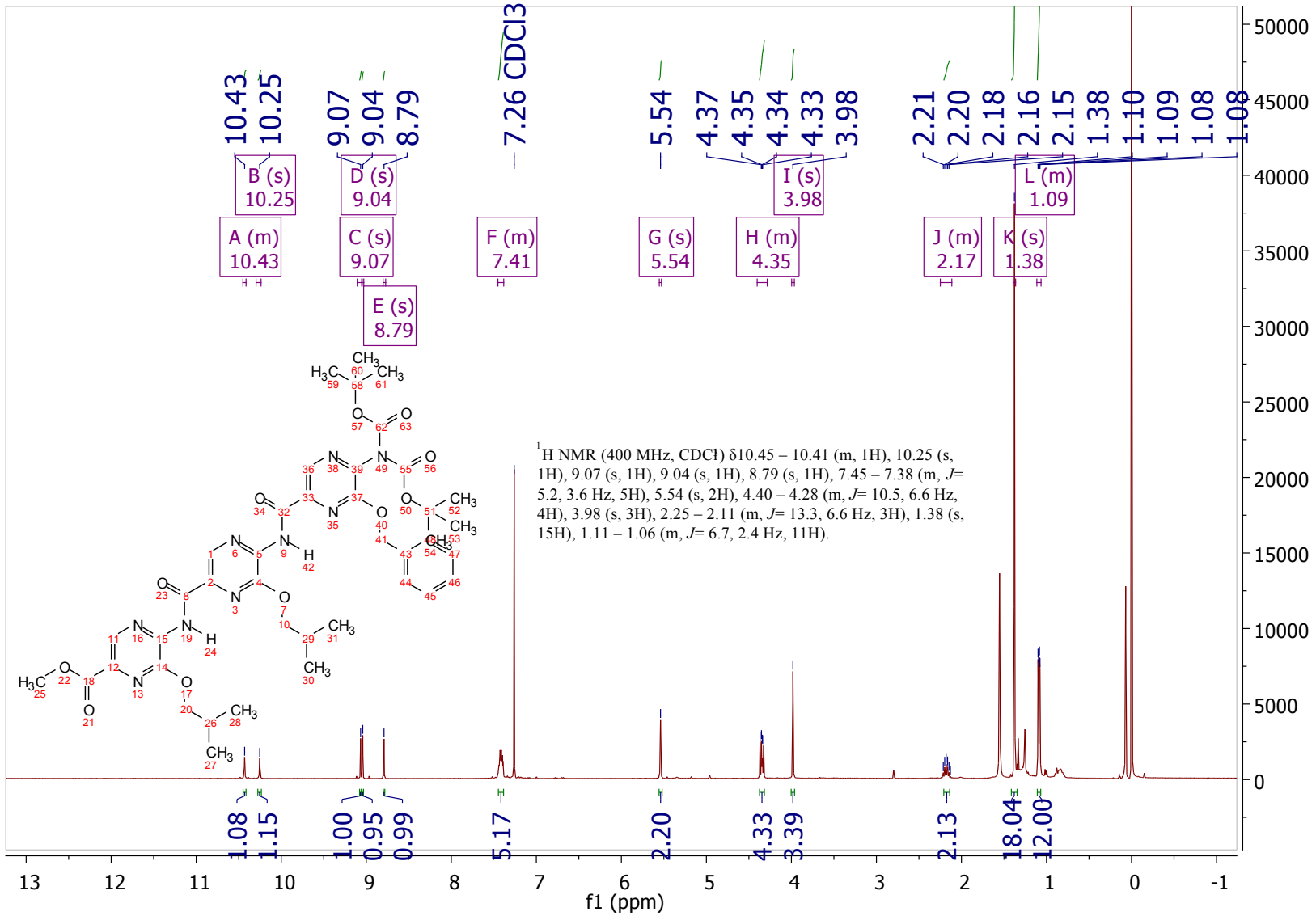
7c


10.43
10.25
9.05
9.01
8.78
7.26 CDCl3
4.37
4.35
4.33
4.14
3.98
1.44
1.16
1.14
1.11
1.09
1H NMR (400 MHz, CDCl3) δ10.43 (s, 1H), 10.25 (s, 1H), 9.05 (s, 1H), 9.01 (s, 1H), 8.78 (s, 1H), 4.40 – 4.32 (m, 4H), 4.14 (s, 3H), 3.98 (s, 3H), 1.44 (s, 18H), 1.15 (d, J= 6.6 Hz, 6H), 1.10 (d, J= 6.6 Hz, 6H).
B (s) 10.25
A (s) 10.43
D (s) 9.01
C (s) 9.05
E (s) 8.78
G (s) 4.14
F (m) 4.35
H (s) 3.98
J (d) 1.15
I (s) 1.44
K (d) 1.10
1.06
1.05
0.93
0.90
0.85
4.26
3.26
3.39
2.24
18.00
5.91
6.11
f1 (ppm)

7c

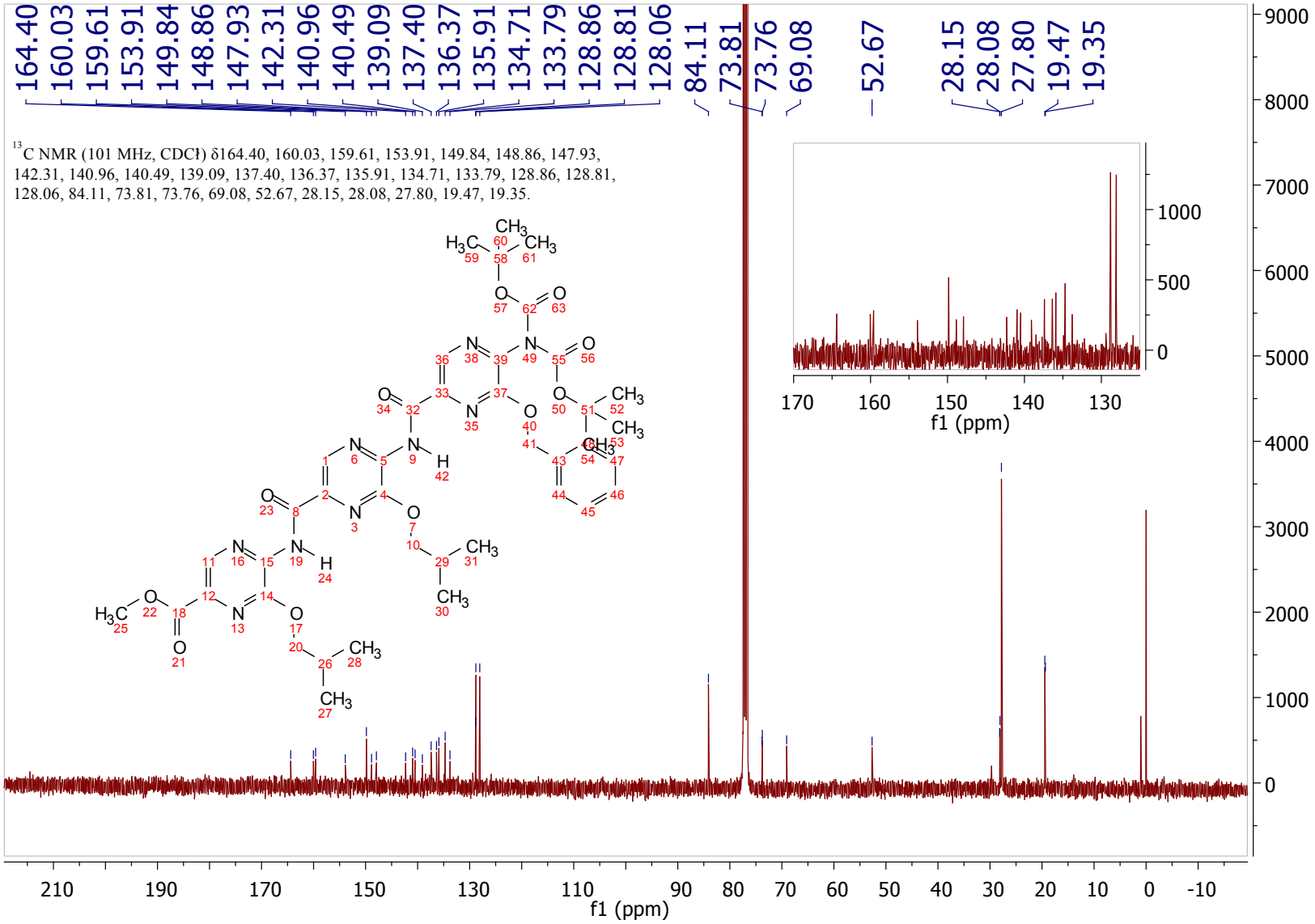

164.40
160.04
159.59
154.29
149.76
148.86
147.89
142.25
140.96
140.49
139.13
137.40
136.36
135.75
134.65
133.79
84.08
73.79
73.76
54.17
52.67
28.17
28.10
27.85
19.48
19.35
13C NMR (101 MHz, CDCl3) δ164.40, 160.04, 159.59, 154.29, 149.76, 148.86, 147.89, 142.25, 140.96, 140.49, 139.13, 137.40, 136.36, 135.75, 134.65, 133.79, 84.08, 73.79, 73.76, 54.17, 52.67, 28.17, 28.10, 27.85, 19.48, 19.35.
f1 (ppm)

7d

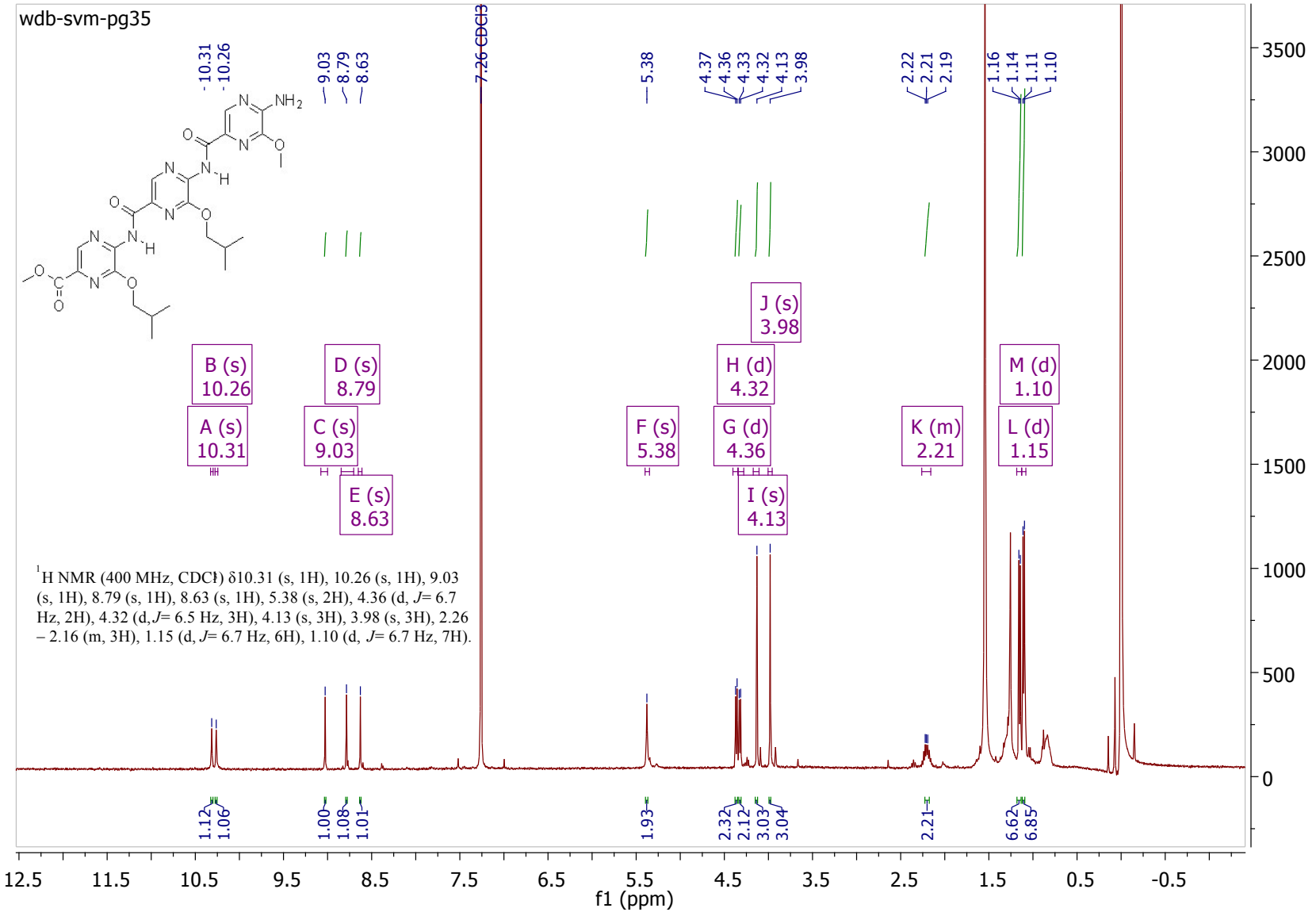


^{1}H NMR (400 MHz, CDCl$_3$) δ10.45 – 10.41 (m, 1H), 10.25 (s, 1H), 9.07 (s, 1H), 9.04 (s, 1H), 8.79 (s, 1H), 7.45 – 7.38 (m, *J*= 5.2, 3.6 Hz, 5H), 5.54 (s, 2H), 4.40 – 4.28 (m, *J*= 10.5, 6.6 Hz, 4H), 3.98 (s, 3H), 2.25 – 2.11 (m, *J*= 13.3, 6.6 Hz, 3H), 1.38 (s, 15H), 1.11 – 1.06 (m, *J*= 6.7, 2.4 Hz, 11H).

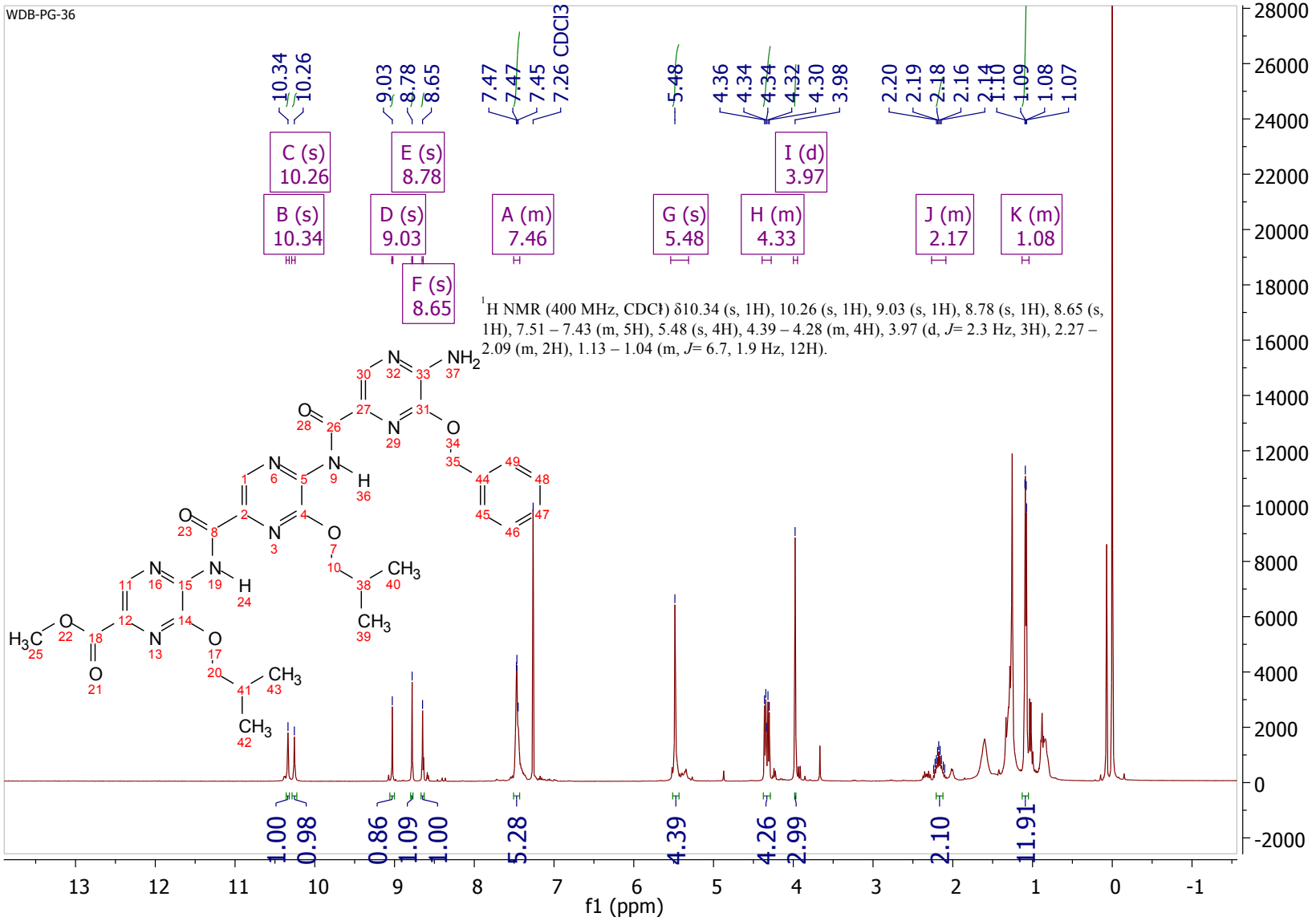
7d


164.40
160.03
159.61
153.91
149.84
148.86
147.93
142.31
140.96
140.49
139.09
137.40
136.37
135.91
134.71
133.79
128.86
128.81
128.06
84.11
73.81
73.76
69.08
52.67
28.15
28.08
27.80
19.47
19.35
13C NMR (101 MHz, CDCl3) δ164.40, 160.03, 159.61, 153.91, 149.84, 148.86, 147.93, 142.31, 140.96, 140.49, 139.09, 137.40, 136.37, 135.91, 134.71, 133.79, 128.86, 128.81, 128.06, 84.11, 73.81, 73.76, 69.08, 52.67, 28.15, 28.08, 27.80, 19.47, 19.35.
f1 (ppm)
f1 (ppm)

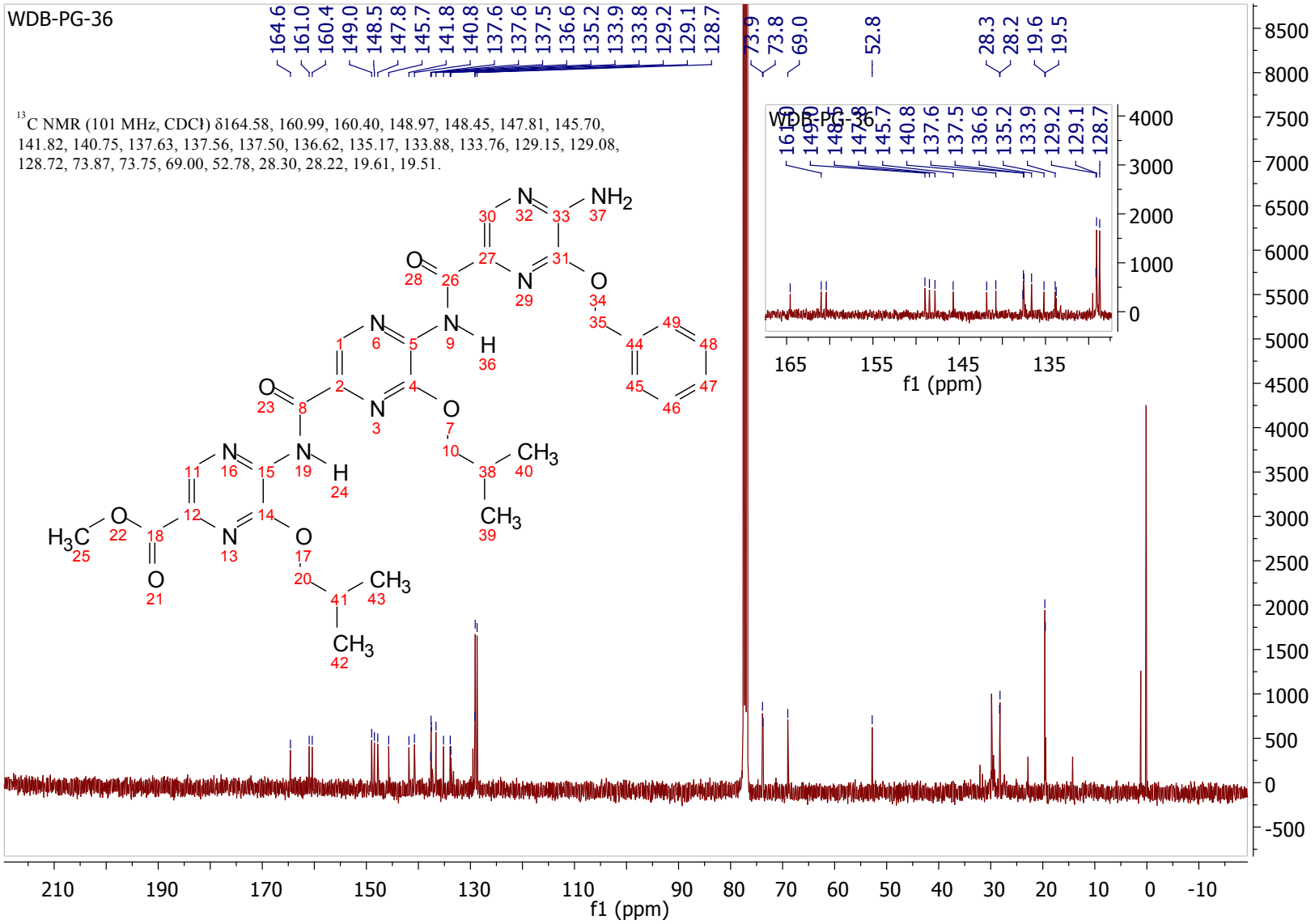
8a


wdb-svm-pg35
10.31
10.26
9.03
8.79
8.63
7.26 CDCl3
5.38
4.37
4.36
4.33
4.32
4.13
3.98
2.22
2.21
2.19
1.16
1.14
1.11
1.10
B (s) 10.26
A (s) 10.31
D (s) 8.79
C (s) 9.03
E (s) 8.63
F (s) 5.38
J (s) 3.98
H (d) 4.32
G (d) 4.36
I (s) 4.13
K (m) 2.21
M (d) 1.10
L (d) 1.15
1H NMR (400 MHz, CDCl3) δ10.31 (s, 1H), 10.26 (s, 1H), 9.03 (s, 1H), 8.79 (s, 1H), 8.63 (s, 1H), 5.38 (s, 2H), 4.36 (d, J= 6.7 Hz, 2H), 4.32 (d, J= 6.5 Hz, 3H), 4.13 (s, 3H), 3.98 (s, 3H), 2.26 – 2.16 (m, 3H), 1.15 (d, J= 6.7 Hz, 6H), 1.10 (d, J= 6.7 Hz, 7H).
1.12
1.06
1.00
1.08
1.01
1.93
2.32
2.12
3.03
3.04
2.21
6.62
6.85
3500
3000
2500
2000
1500
1000
500
0
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

8b

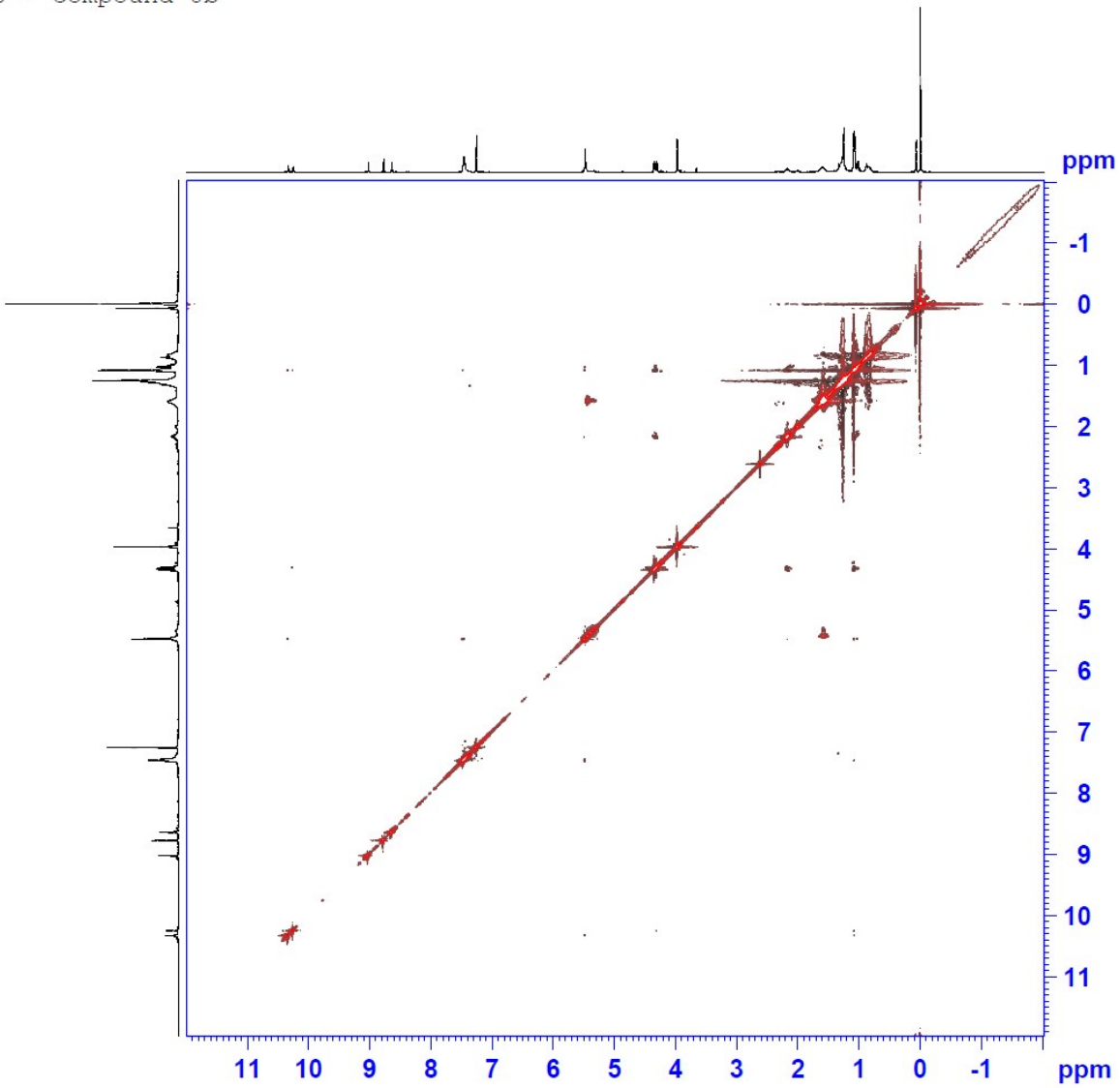

WDB-PG-36
10.34
10.26
9.03
8.78
8.65
7.47
7.47
7.45
7.26 CDCl3
5.48
4.36
4.34
4.34
4.32
4.30
3.98
2.20
2.19
2.18
2.16
2.14
2.10
1.09
1.08
1.07
C (s) 10.26
E (s) 8.78
I (d) 3.97
B (s) 10.34
D (s) 9.03
A (m) 7.46
G (s) 5.48
H (m) 4.33
J (m) 2.17
K (m) 1.08
F (s) 8.65
1H NMR (400 MHz, CDCl) δ10.34 (s, 1H), 10.26 (s, 1H), 9.03 (s, 1H), 8.78 (s, 1H), 8.65 (s, 1H), 7.51 – 7.43 (m, 5H), 5.48 (s, 4H), 4.39 – 4.28 (m, 4H), 3.97 (d, J= 2.3 Hz, 3H), 2.27 – 2.09 (m, 2H), 1.13 – 1.04 (m, J= 6.7, 1.9 Hz, 12H).
1.00
0.98
0.86
1.09
1.00
5.28
4.39
4.26
2.99
2.10
11.91
f1 (ppm)

8b


WDB-PG-36
164.6
161.0
160.4
149.0
148.5
147.8
145.7
141.8
140.8
137.6
137.6
137.5
136.6
135.2
133.9
133.8
129.2
129.1
128.7
73.9
73.8
69.0
52.8
28.3
28.2
19.6
19.5
13C NMR (101 MHz, CDCł) δ164.58, 160.99, 160.40, 148.97, 148.45, 147.81, 145.70, 141.82, 140.75, 137.63, 137.56, 137.50, 136.62, 135.17, 133.88, 133.76, 129.15, 129.08, 128.72, 73.87, 73.75, 69.00, 52.78, 28.30, 28.22, 19.61, 19.51.
WDB-PG-36
f1 (ppm)
f1 (ppm)

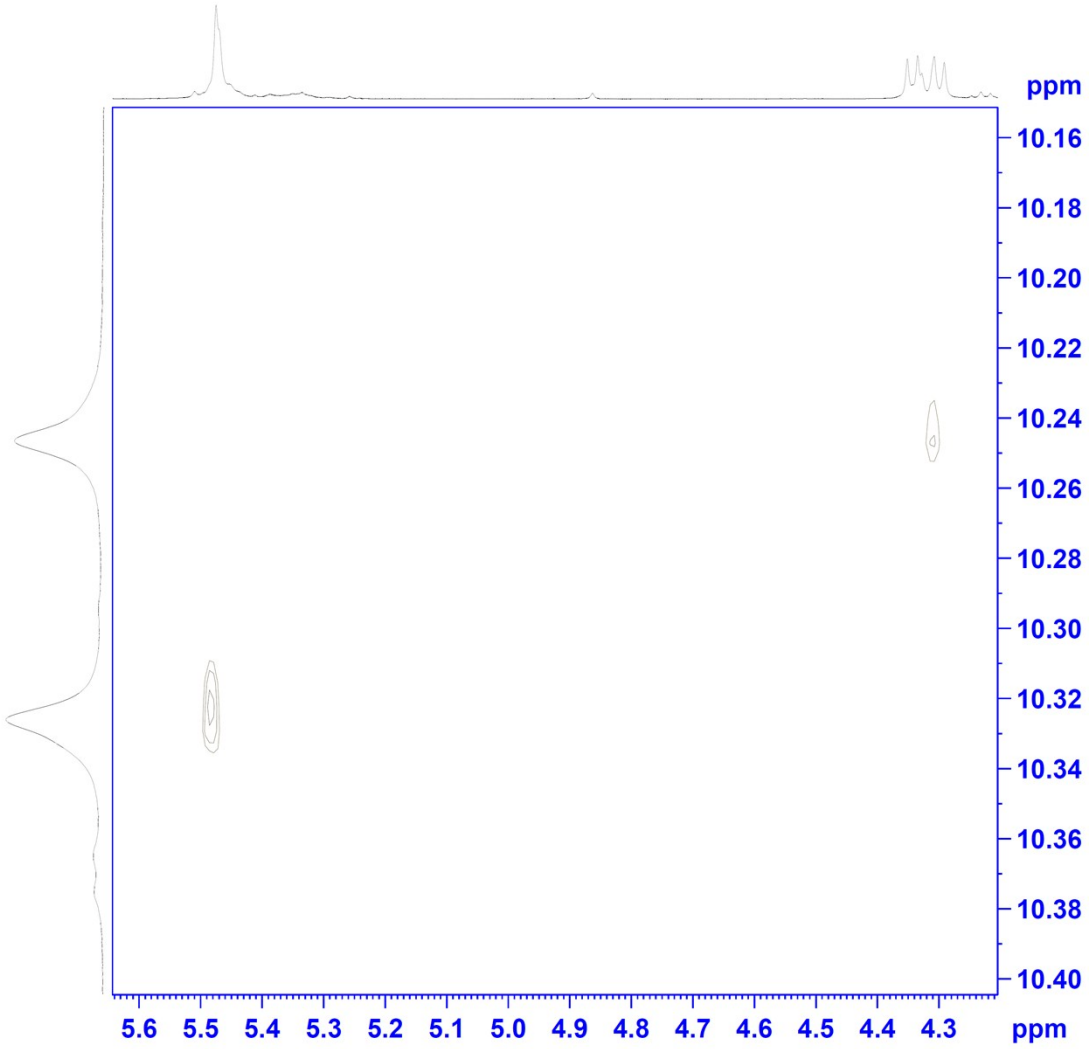
8b - NOESY

PG36 - Compound 8b

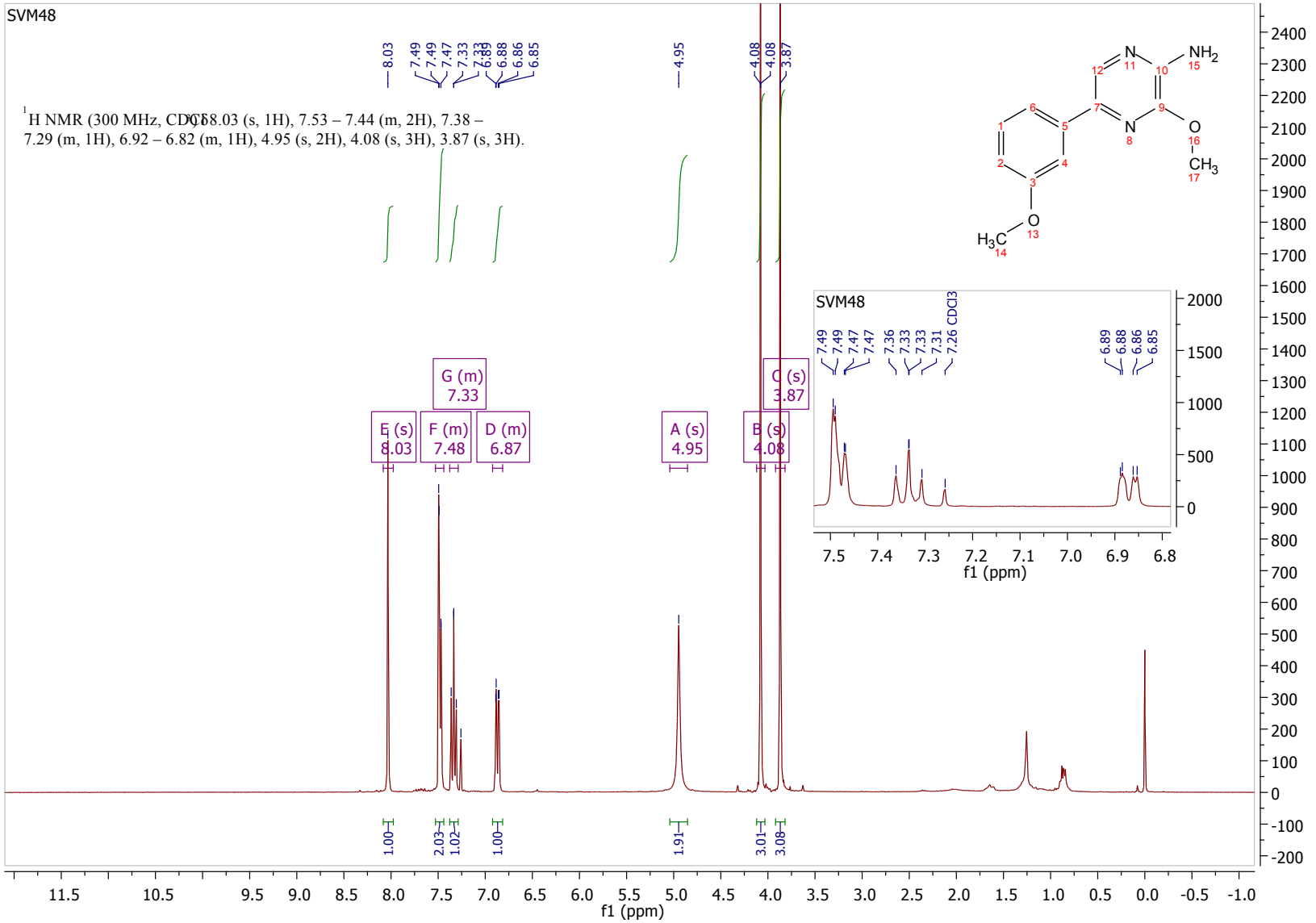


8b – NOESY

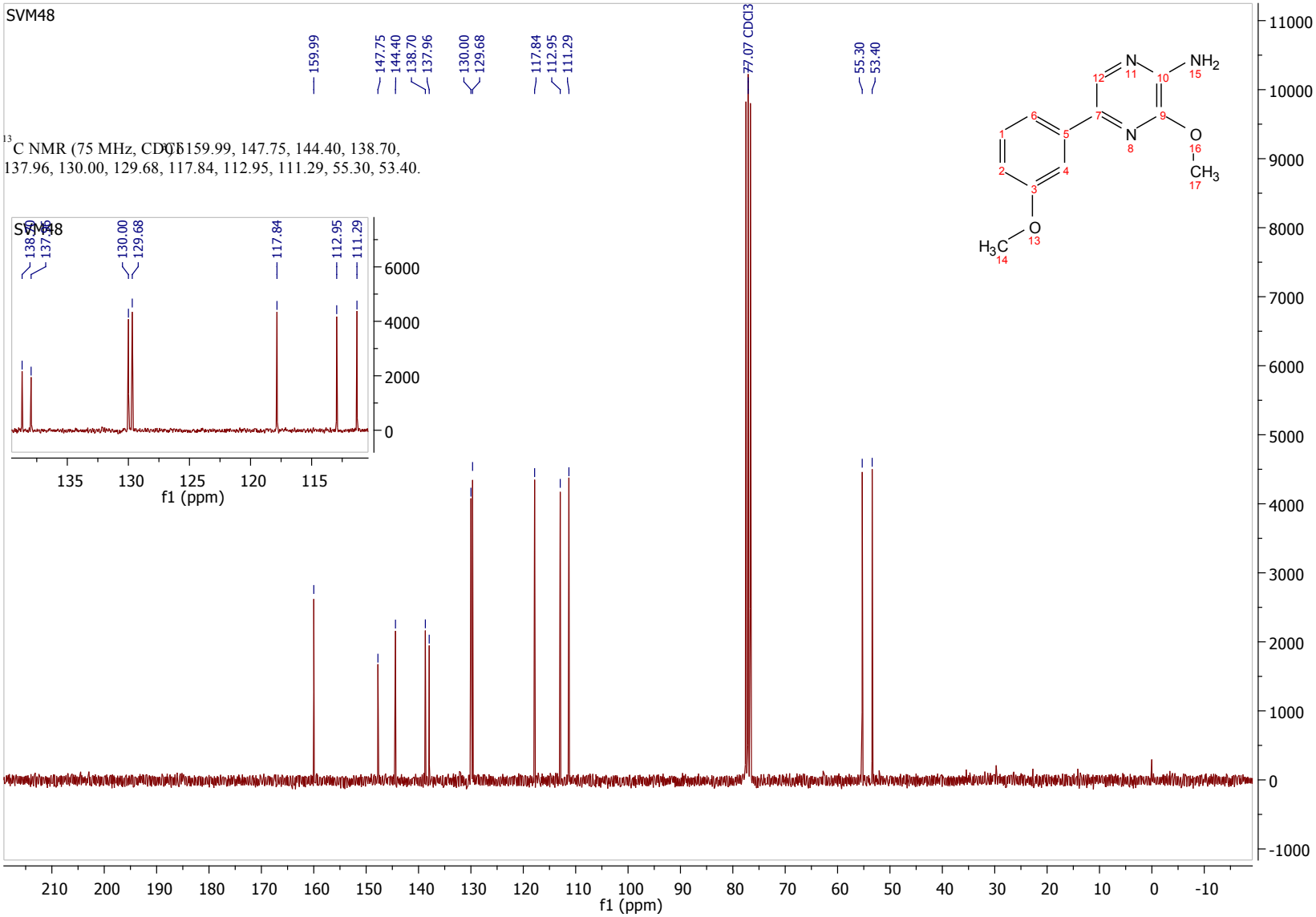
PG36 - Compound 8b



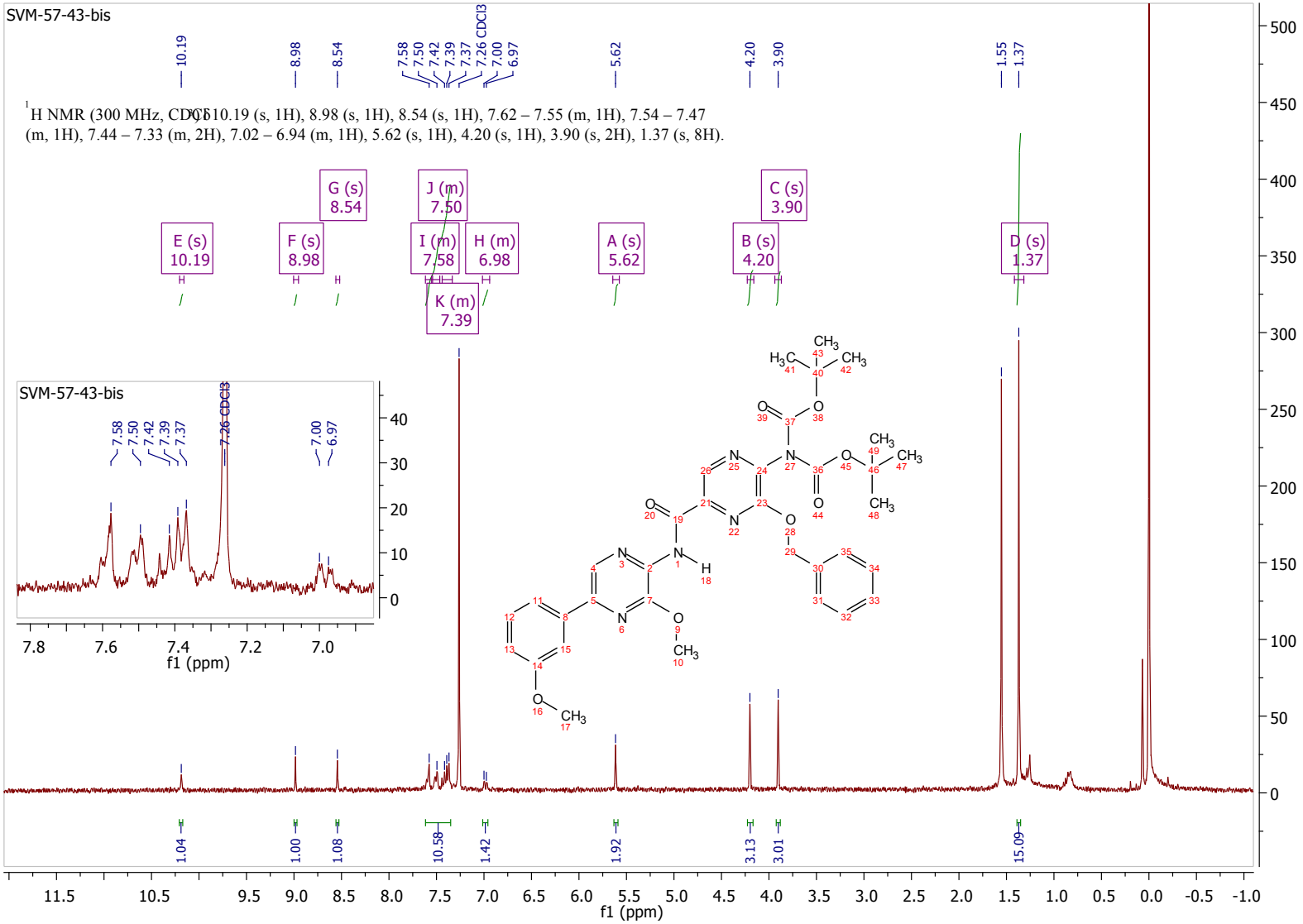
9


SVM48
^{1}H NMR (300 MHz, CDCl3) δ 8.03 (s, 1H), 7.53 – 7.44 (m, 2H), 7.38 – 7.29 (m, 1H), 6.92 – 6.82 (m, 1H), 4.95 (s, 2H), 4.08 (s, 3H), 3.87 (s, 3H).
8.03
7.49
7.49
7.47
7.33
6.89
6.88
6.86
6.85
4.95
4.08
4.08
3.87
G (m) 7.33
E (s) 8.03
F (m) 7.48
D (m) 6.87
A (s) 4.95
B (s) 4.08
C (s) 3.87
1.00
2.03
1.02
1.00
1.91
3.01
3.08
f1 (ppm)
SVM48
7.49
7.49
7.47
7.47
7.36
7.33
7.33
7.31
7.26 CDCl3
6.89
6.88
6.86
6.85
f1 (ppm)

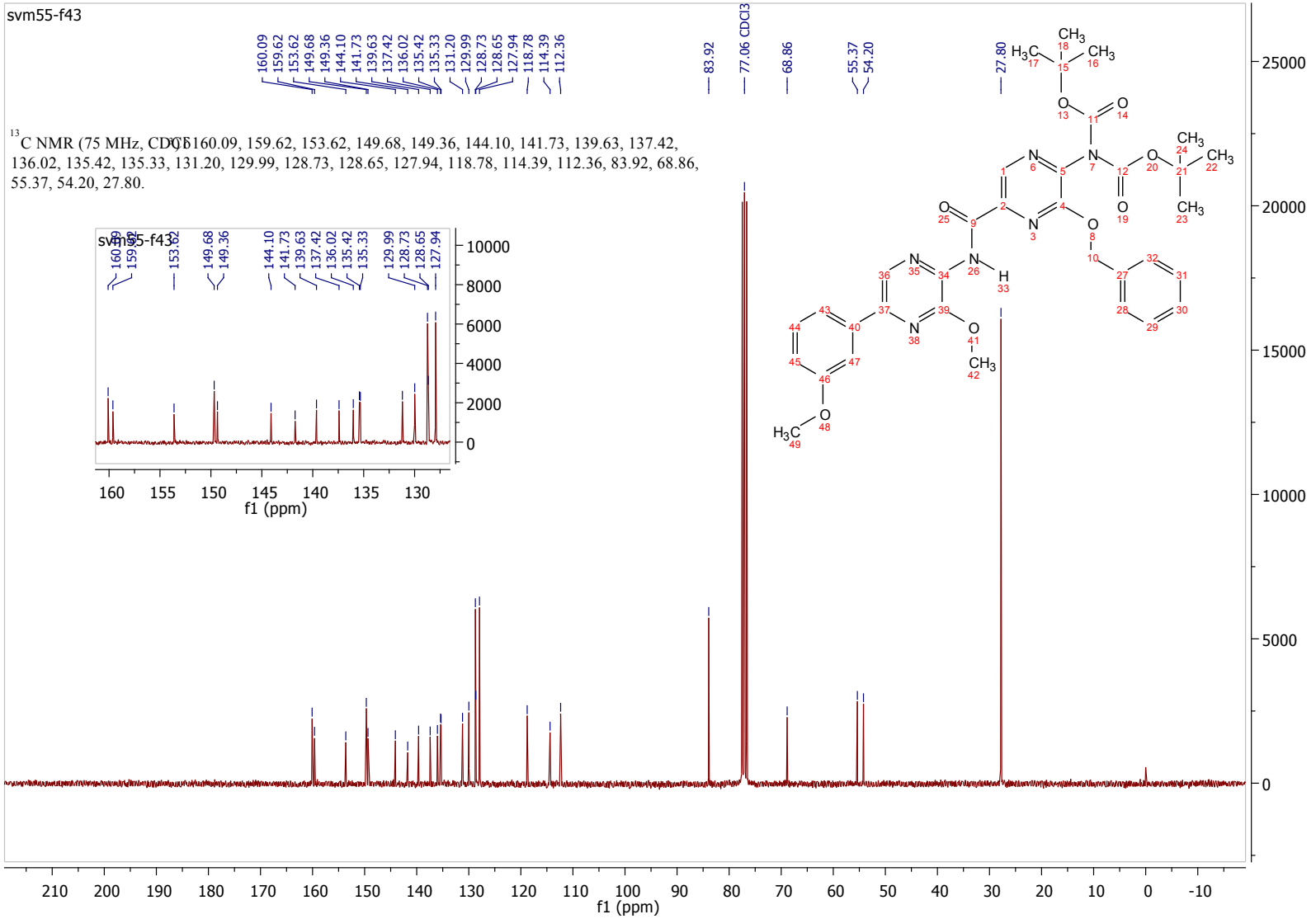
9

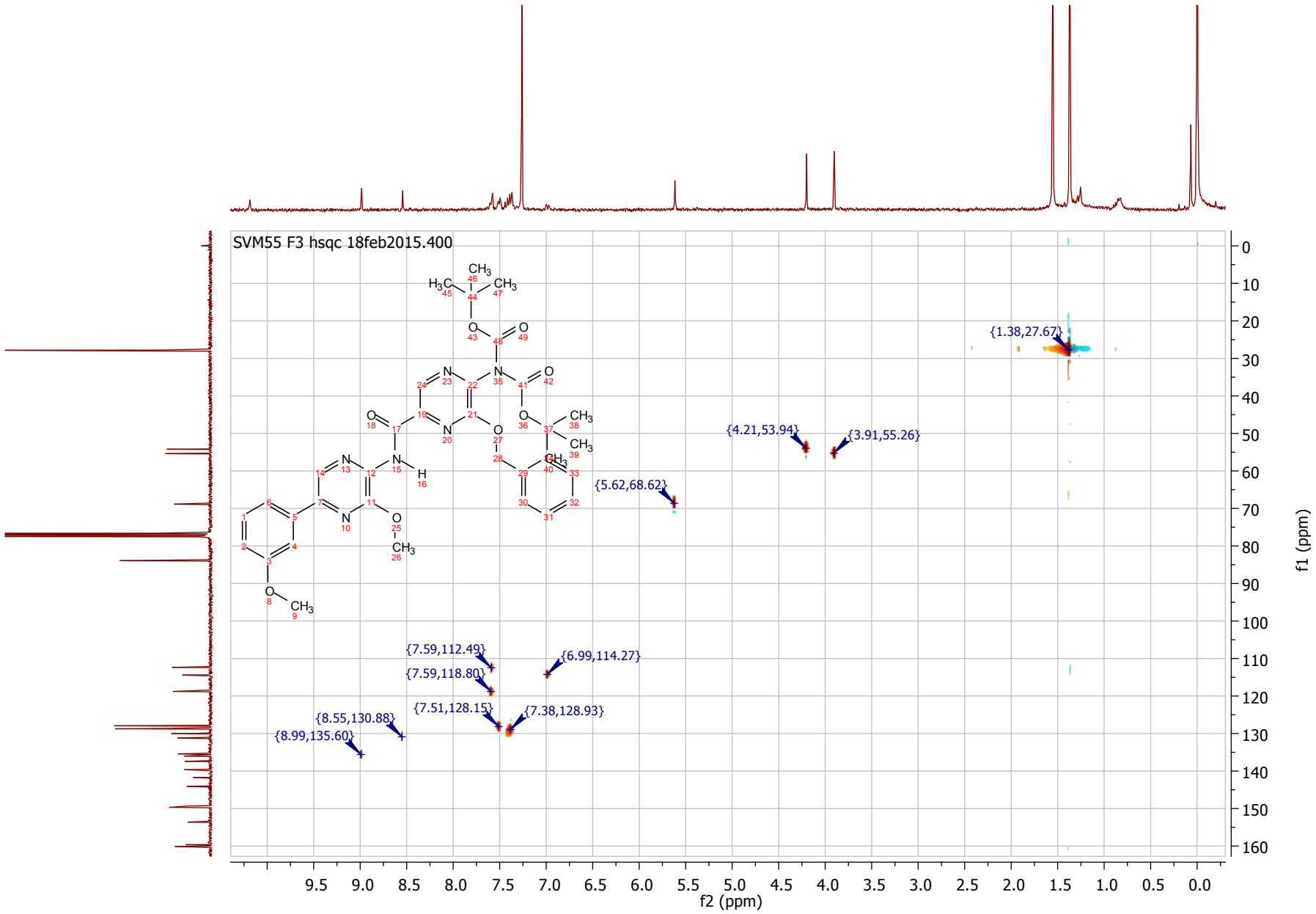

SVM48
159.99
147.75
144.40
138.70
137.96
130.00
129.68
117.84
112.95
111.29
77.07 CDCl3
55.30
53.40
13C NMR (75 MHz, CDCl3) δ 159.99, 147.75, 144.40, 138.70, 137.96, 130.00, 129.68, 117.84, 112.95, 111.29, 55.30, 53.40.
f1 (ppm)

di-*tert*-butyl [3-(benzyloxy)-5-([[3-methoxy-5-(3-methoxyphenyl)pyrazin-2-yl]amino]carbonyl)pyrazin-2-yl]imidodicarbonate

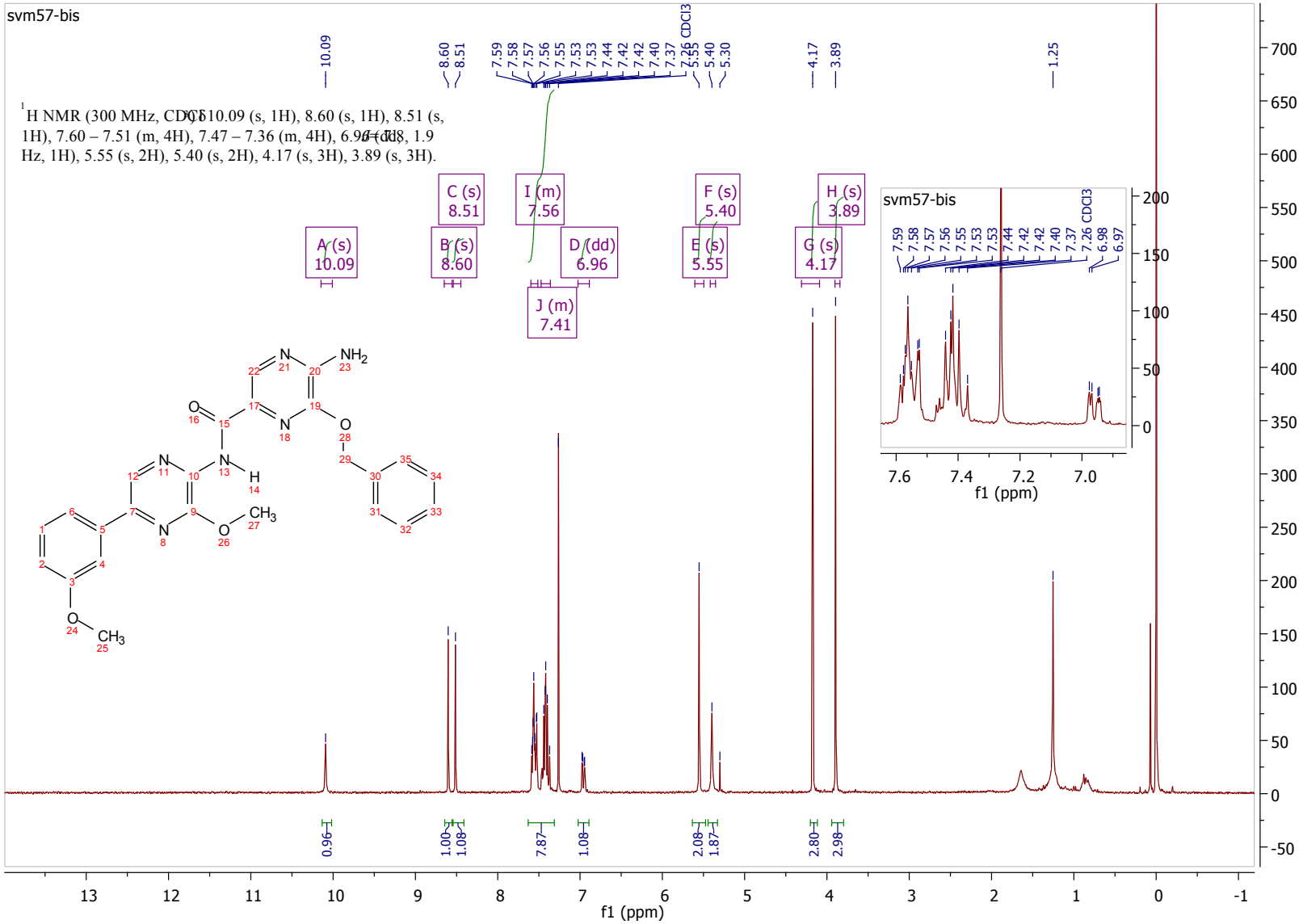


di-*tert*-butyl [3-(benzyloxy)-5-([[3-methoxy-5-(3-methoxyphenyl)pyrazin-2-yl]amino]carbonyl)pyrazin-2-yl]imidodicarbonate

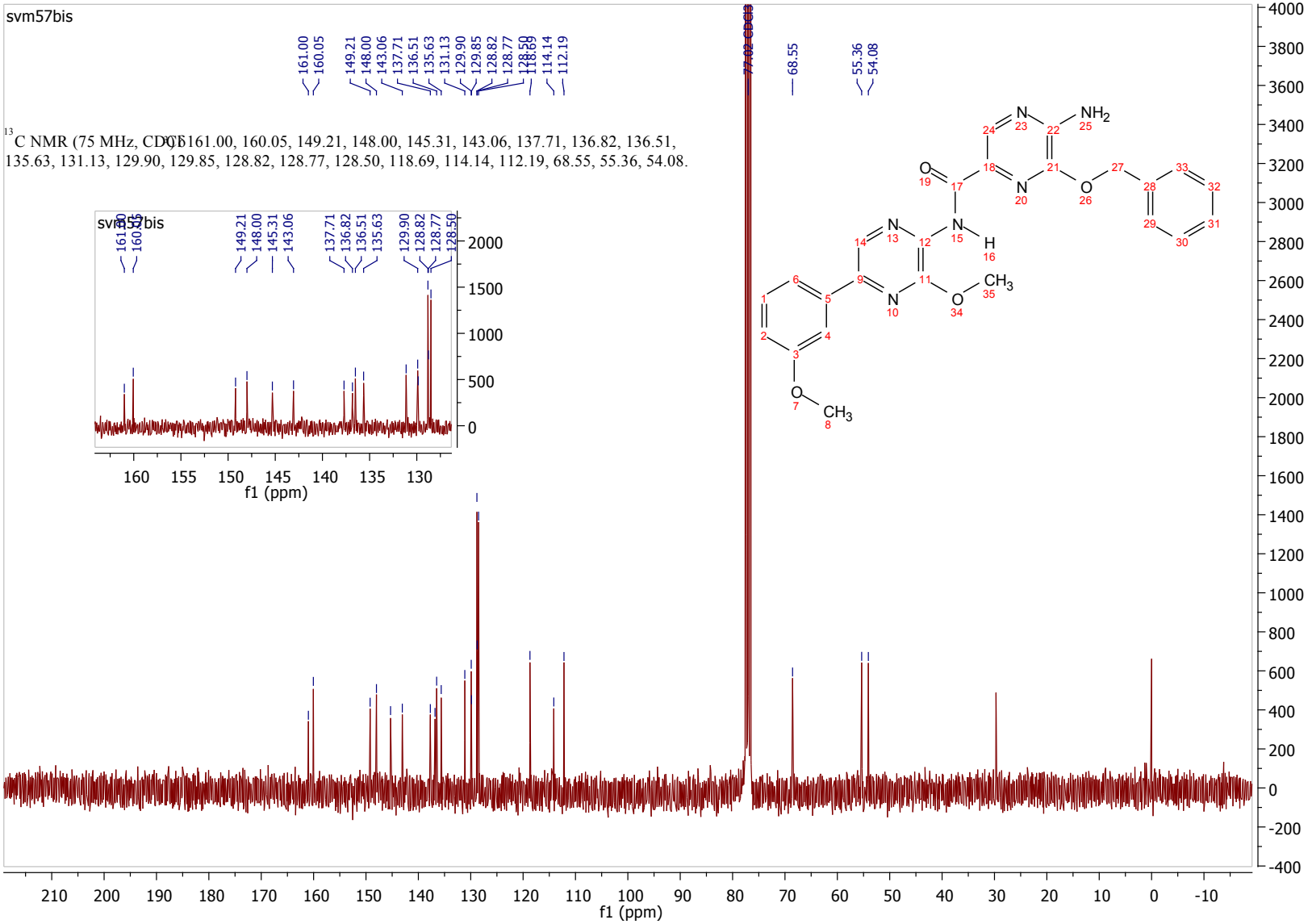



SVM55 F3 hsqc 18feb2015.400
{1.38,27.67}
{4.21,53.94}
{3.91,55.26}
{5.62,68.62}
{7.59,112.49}
{7.59,118.80}
{6.99,114.27}
{7.51,128.15}
{7.38,128.93}
{8.55,130.88}
{8.99,135.60}
f2 (ppm)
f1 (ppm)

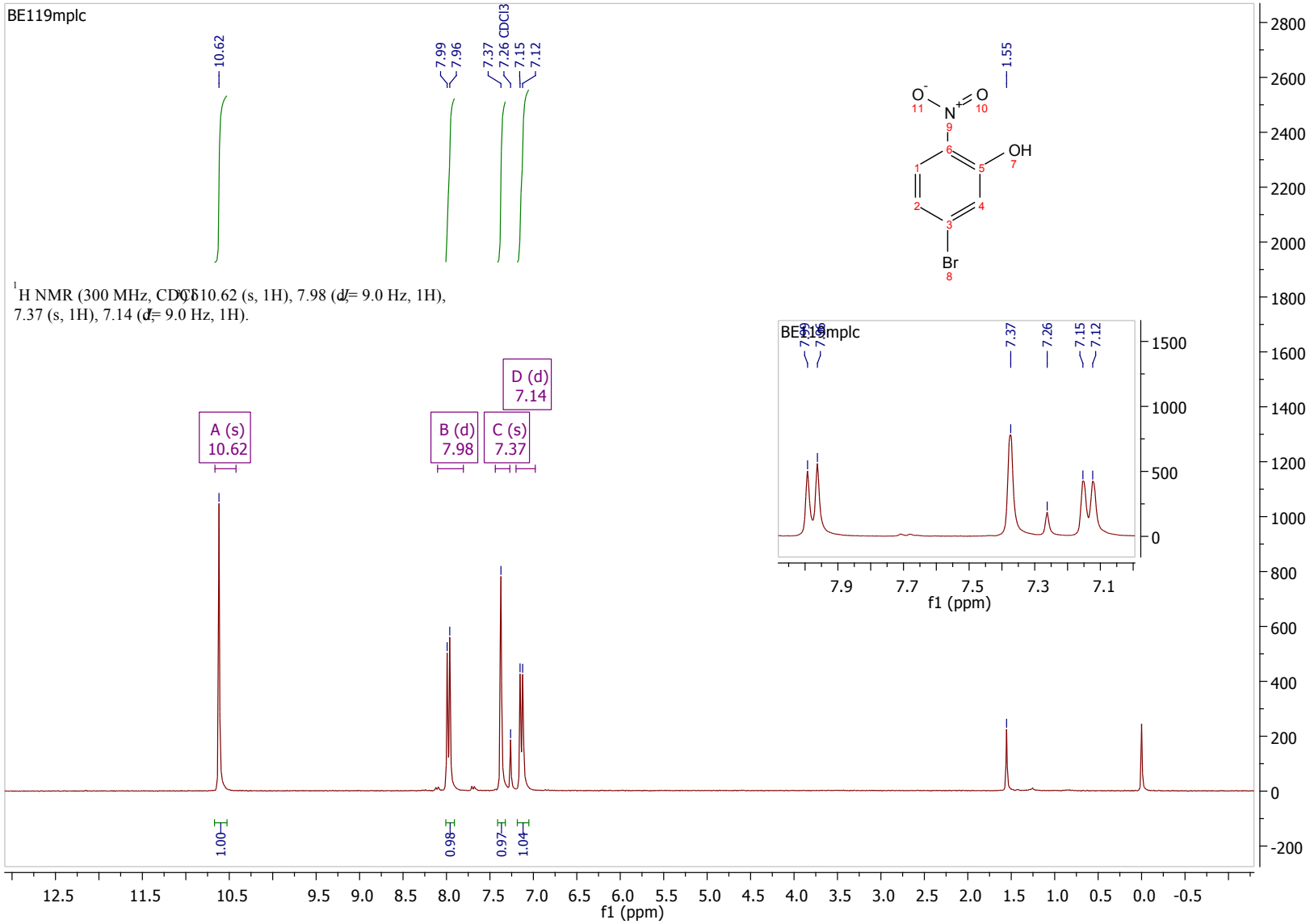
10


svm57-bis
^{1}H NMR (300 MHz, CDCl3) δ 10.09 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 7.60 – 7.51 (m, 4H), 7.47 – 7.36 (m, 4H), 6.96 (dd, J = 7.8, 1.9 Hz, 1H), 5.55 (s, 2H), 5.40 (s, 2H), 4.17 (s, 3H), 3.89 (s, 3H).
A (s) 10.09
B (s) 8.60
C (s) 8.51
D (dd) 6.96
I (m) 7.56
J (m) 7.41
E (s) 5.55
F (s) 5.40
G (s) 4.17
H (s) 3.89
f1 (ppm)

10

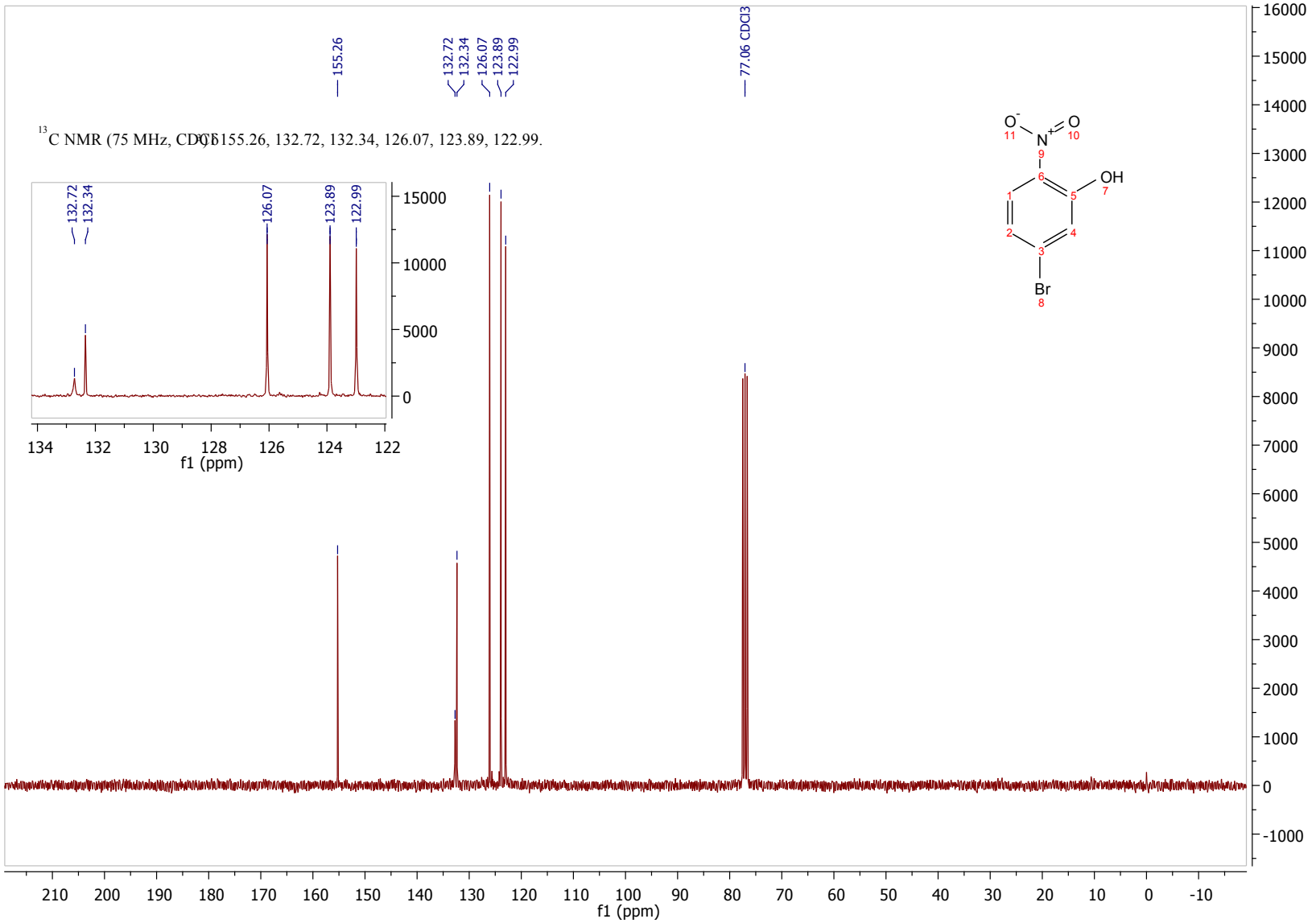

svm57bis
161.00
160.05
149.21
148.00
143.06
137.71
136.51
135.63
131.13
129.90
129.85
128.82
128.77
128.50
118.69
114.14
112.19
77.00 CDCl3
68.55
55.36
54.08
13C NMR (75 MHz, CDCl3) 161.00, 160.05, 149.21, 148.00, 145.31, 143.06, 137.71, 136.82, 136.51, 135.63, 131.13, 129.90, 129.85, 128.82, 128.77, 128.50, 118.69, 114.14, 112.19, 68.55, 55.36, 54.08.
svm57bis
149.21
148.00
145.31
143.06
137.71
136.82
136.51
135.63
129.90
128.82
128.77
128.50
f1 (ppm)
f1 (ppm)

12

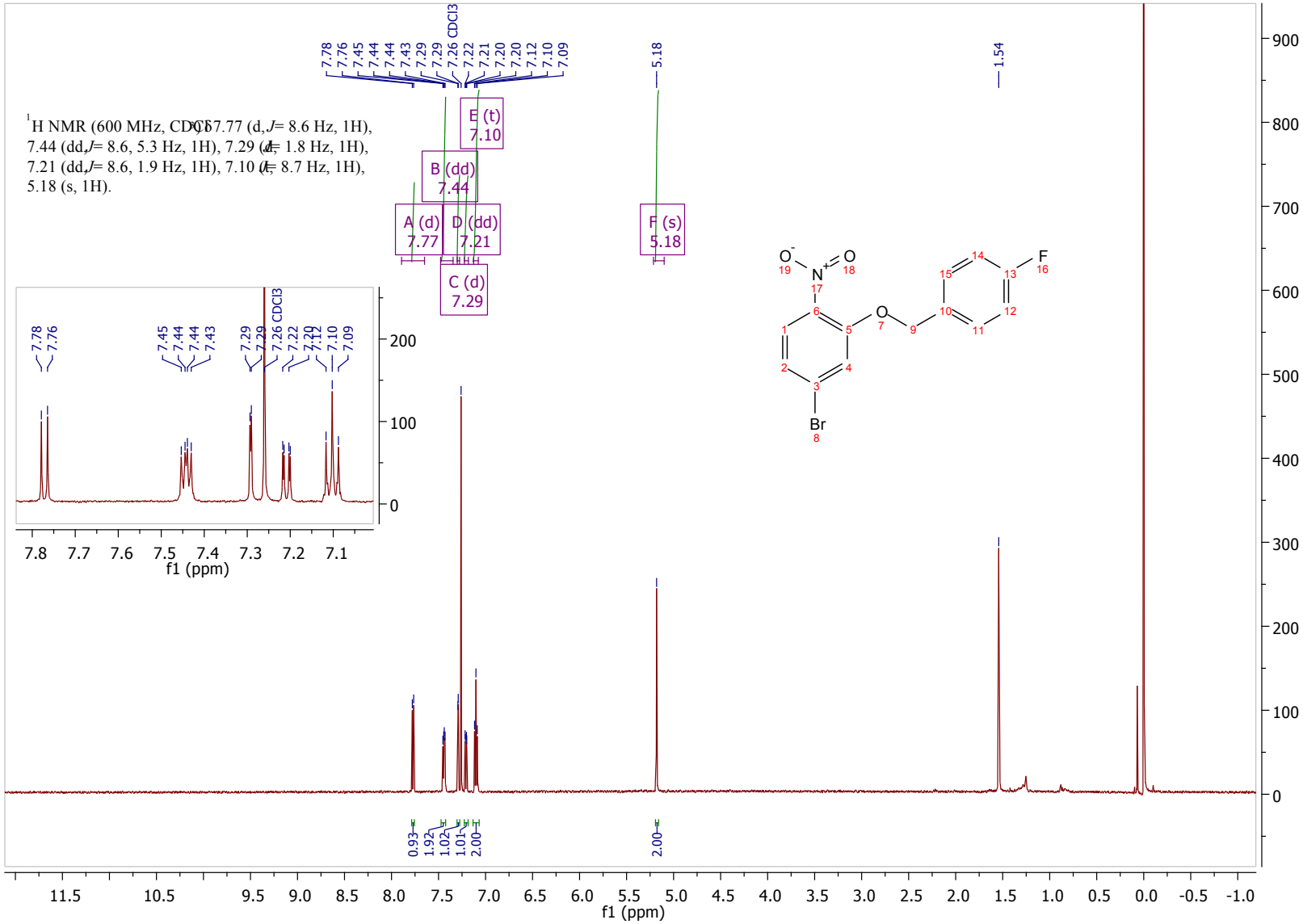


^{1}H NMR (300 MHz, CDCl$_3$) δ 10.62 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.37 (s, 1H), 7.14 (d, J = 9.0 Hz, 1H).

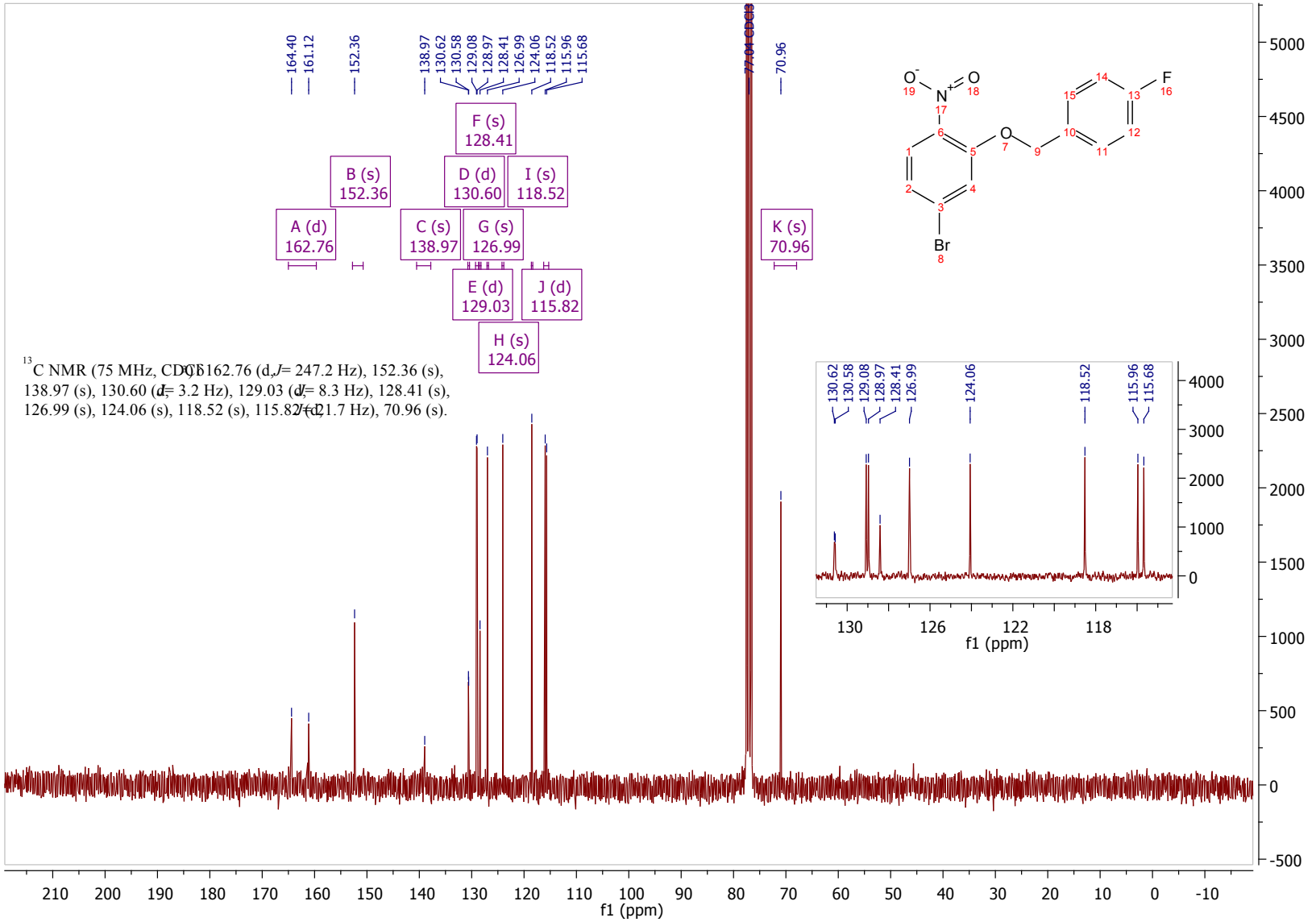
12


155.26
132.72
132.34
126.07
123.89
122.99
77.06 CDCl3
13C NMR (75 MHz, CDCl3) δ 155.26, 132.72, 132.34, 126.07, 123.89, 122.99.
OH
Br
f1 (ppm)

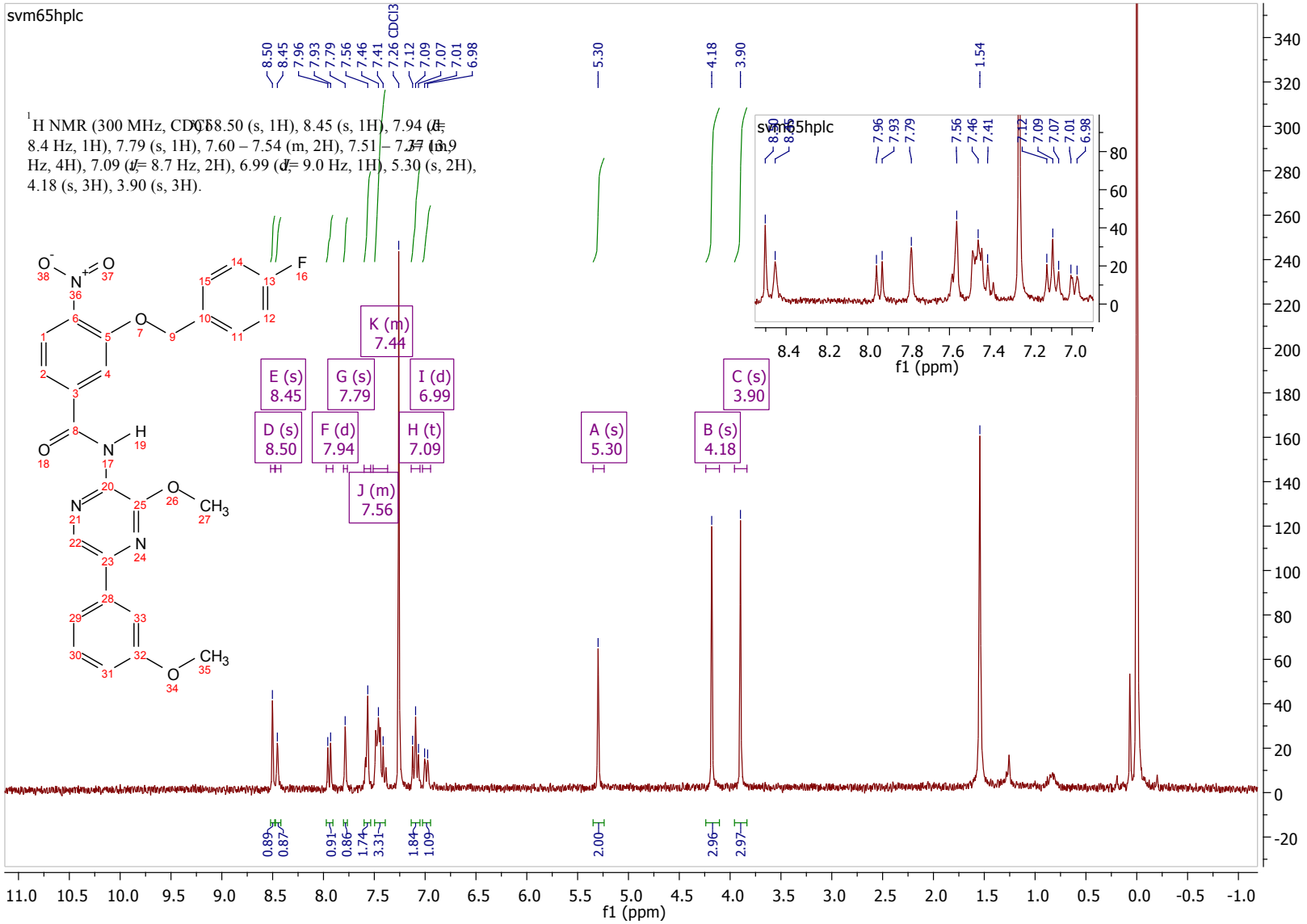
13


^{1}H NMR (600 MHz, CDCl$_3$) δ 7.77 (d, J= 8.6 Hz, 1H), 7.44 (dd, J= 8.6, 5.3 Hz, 1H), 7.29 (d, J= 1.8 Hz, 1H), 7.21 (dd, J= 8.6, 1.9 Hz, 1H), 7.10 (t, J= 8.7 Hz, 1H), 5.18 (s, 1H).
A (d) 7.77
B (dd) 7.44
C (d) 7.29
D (dd) 7.21
E (t) 7.10
F (s) 5.18
CDCl3
f1 (ppm)

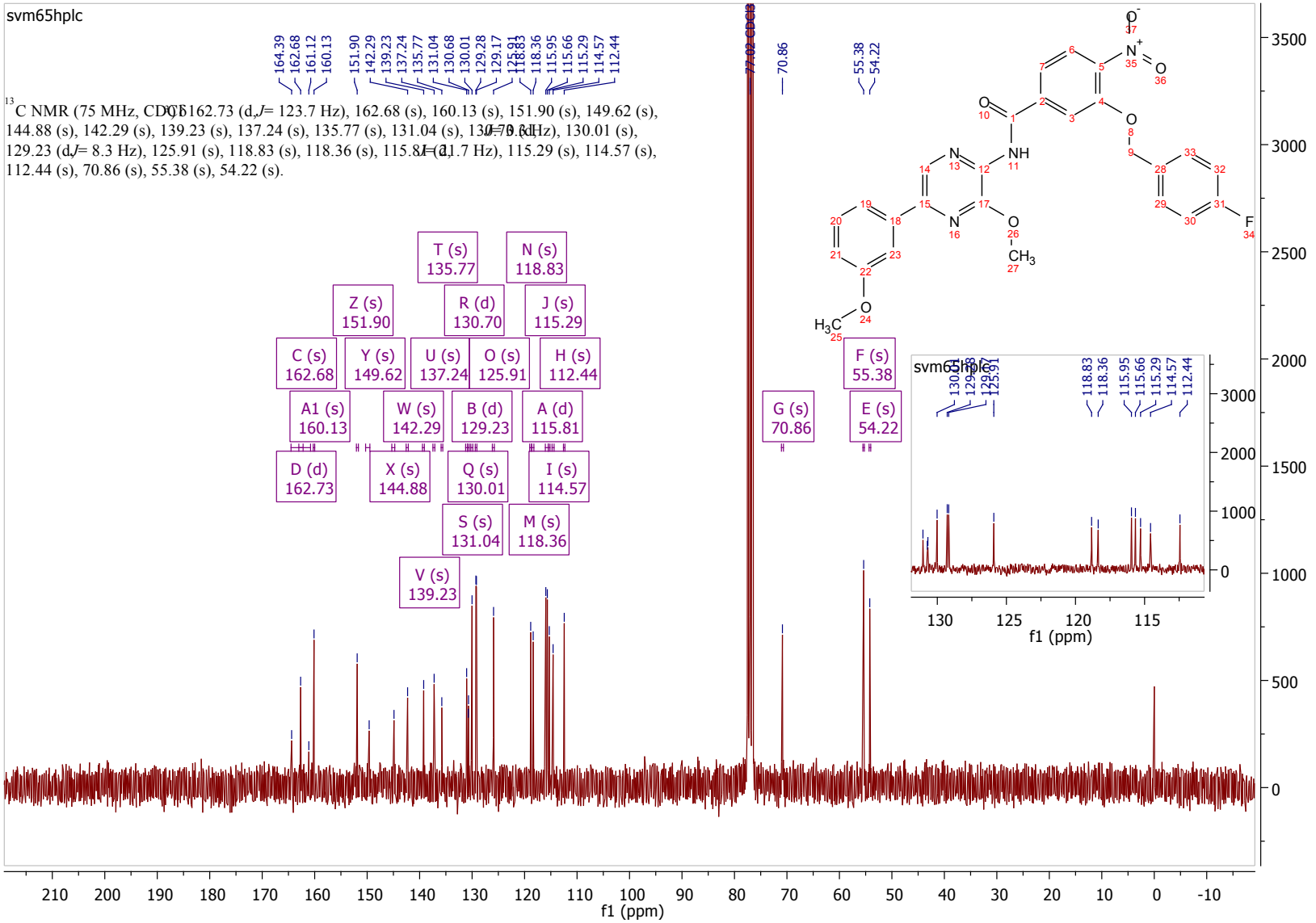
13


164.40
161.12
152.36
138.97
130.62
130.58
129.08
128.97
128.41
126.99
124.06
118.52
115.96
115.68
77.04
70.96
F (s) 128.41
B (s) 152.36
D (d) 130.60
I (s) 118.52
A (d) 162.76
C (s) 138.97
G (s) 126.99
K (s) 70.96
E (d) 129.03
J (d) 115.82
H (s) 124.06
13C NMR (75 MHz, CDCl3) δ 162.76 (d, J = 247.2 Hz), 152.36 (s), 138.97 (s), 130.60 (d, J = 3.2 Hz), 129.03 (d, J = 8.3 Hz), 128.41 (s), 126.99 (s), 124.06 (s), 118.52 (s), 115.82 (d, J = 21.7 Hz), 70.96 (s).
f1 (ppm)

14

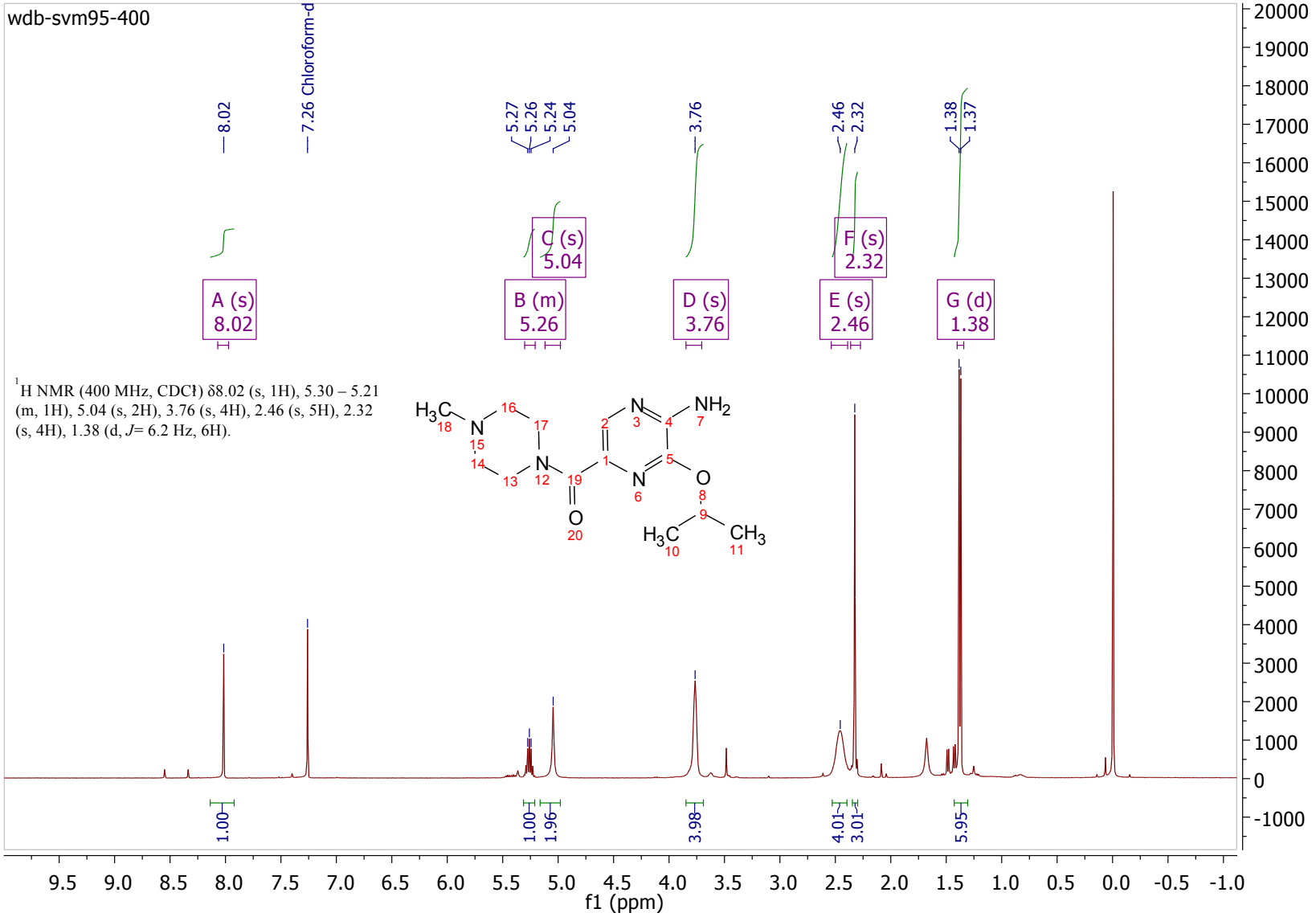

svm65hplc
8.50
8.45
7.96
7.93
7.79
7.56
7.46
7.41
7.26 CDCl3
7.12
7.09
7.07
7.01
6.98
5.30
4.18
3.90
1.54
1H NMR (300 MHz, CDCl3) δ 8.50 (s, 1H), 8.45 (s, 1H), 7.94 (d, J= 8.4 Hz, 1H), 7.79 (s, 1H), 7.60 – 7.54 (m, 2H), 7.51 – 7.37 (m, 4H), 7.09 (t, J= 8.7 Hz, 2H), 6.99 (d, J= 9.0 Hz, 1H), 5.30 (s, 2H), 4.18 (s, 3H), 3.90 (s, 3H).
K (m) 7.44
E (s) 8.45
G (s) 7.79
I (d) 6.99
C (s) 3.90
D (s) 8.50
F (d) 7.94
H (t) 7.09
A (s) 5.30
B (s) 4.18
J (m) 7.56
0.89
0.87
0.91
0.86
1.74
3.31
1.84
1.09
2.00
2.96
2.97
f1 (ppm)

14

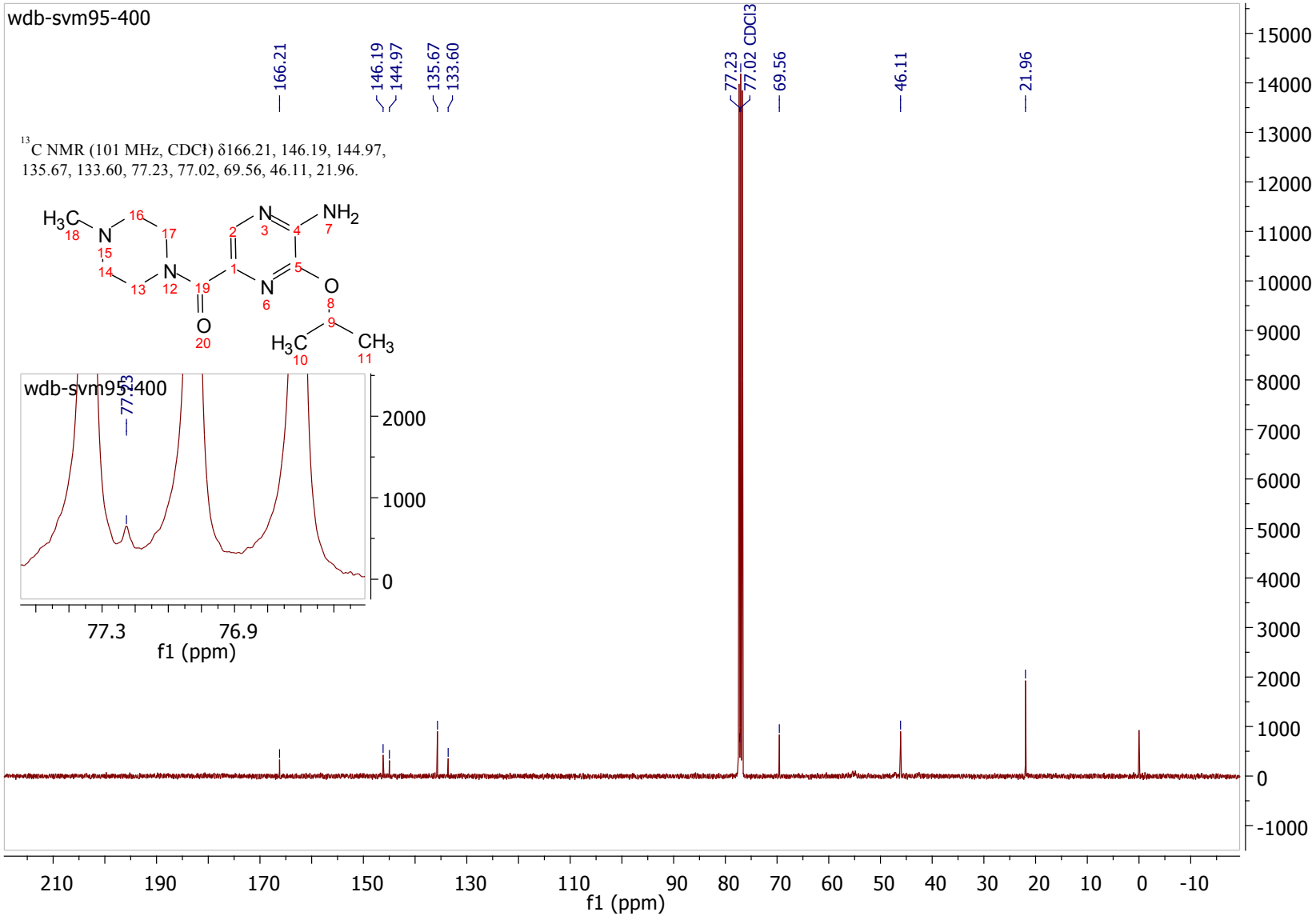


^{13}C NMR (75 MHz, CDCl$_3$) δ 162.73 (d, J = 123.7 Hz), 162.68 (s), 160.13 (s), 151.90 (s), 149.62 (s), 144.88 (s), 142.29 (s), 139.23 (s), 137.24 (s), 135.77 (s), 131.04 (s), 130.68 (s), 130.01 (s), 129.23 (d, J = 8.3 Hz), 125.91 (s), 118.83 (s), 118.36 (s), 115.81 (d, J = 21.7 Hz), 115.29 (s), 114.57 (s), 112.44 (s), 70.86 (s), 55.38 (s), 54.22 (s).

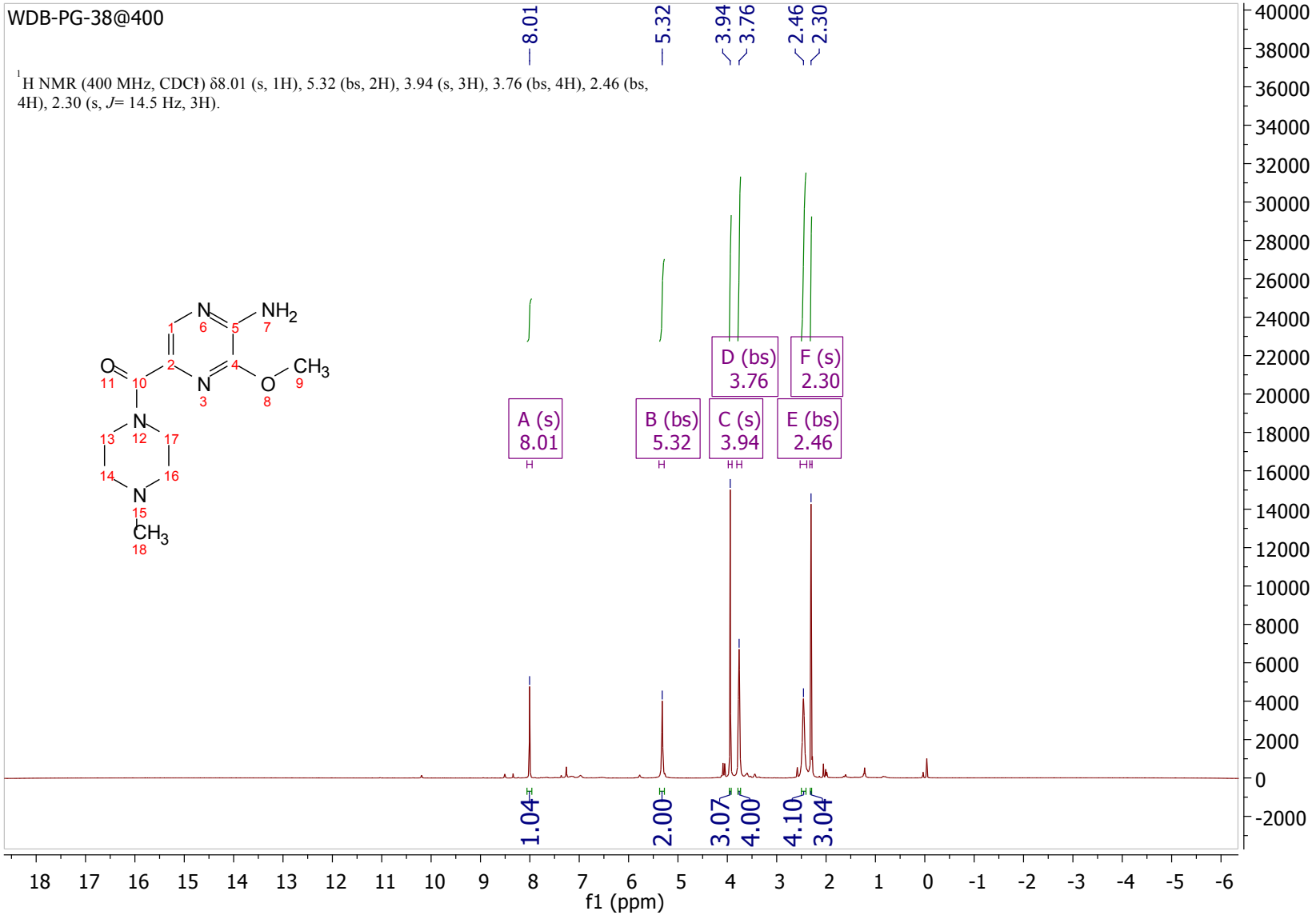
15a


wdb-svm95-400
8.02
7.26 Chloroform-d
5.27
5.26
5.24
5.04
3.76
2.46
2.32
1.38
1.37
A (s) 8.02
B (m) 5.26
C (s) 5.04
D (s) 3.76
E (s) 2.46
F (s) 2.32
G (d) 1.38
1H NMR (400 MHz, CDCł) δ8.02 (s, 1H), 5.30 – 5.21 (m, 1H), 5.04 (s, 2H), 3.76 (s, 4H), 2.46 (s, 5H), 2.32 (s, 4H), 1.38 (d, J= 6.2 Hz, 6H).
1.00
1.00
1.96
3.98
4.01
3.01
5.95
f1 (ppm)

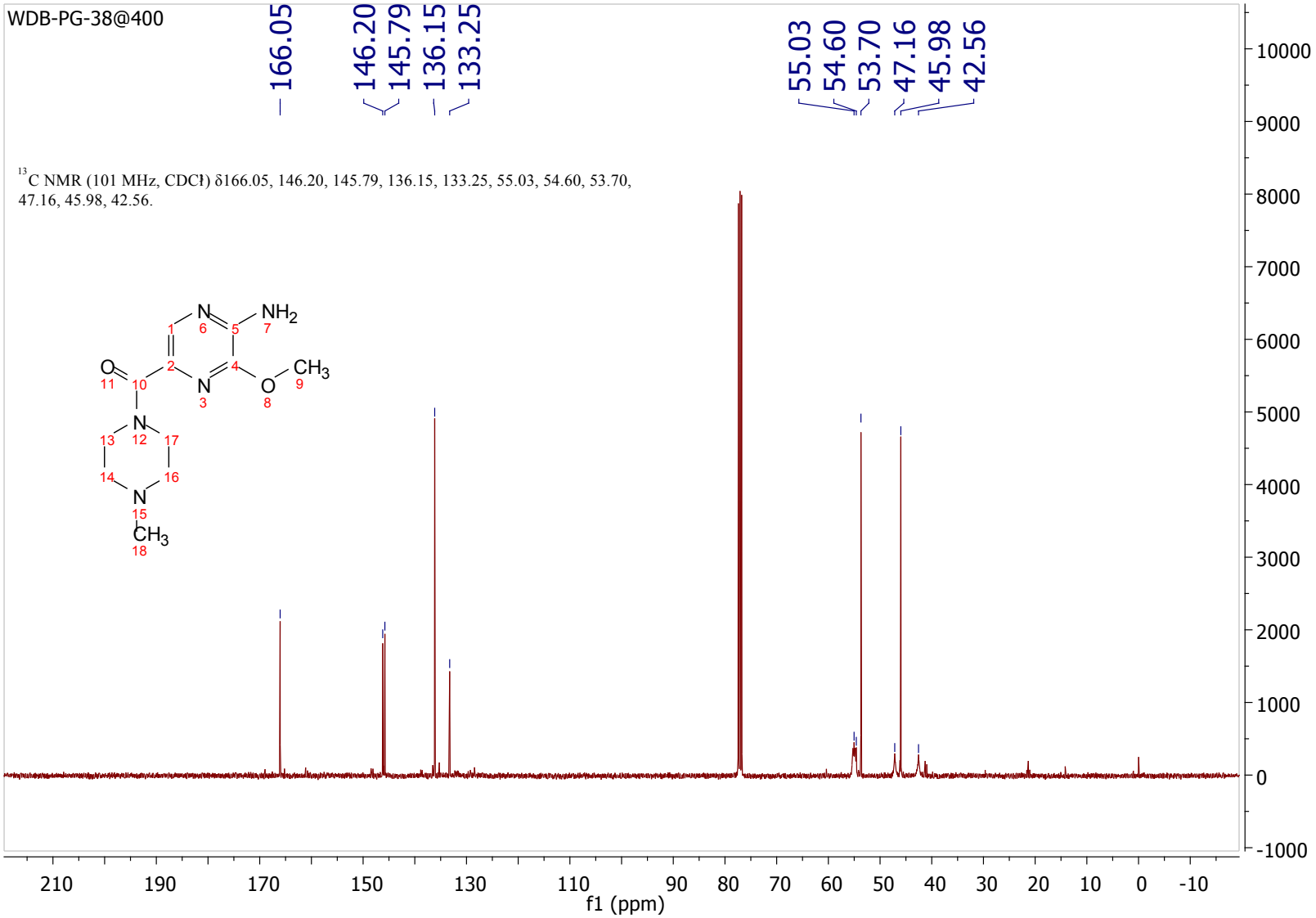
15a


wdb-svm95-400
166.21
146.19
144.97
135.67
133.60
77.23
77.02 CDCl3
69.56
46.11
21.96
13C NMR (101 MHz, CDCl3) δ166.21, 146.19, 144.97, 135.67, 133.60, 77.23, 77.02, 69.56, 46.11, 21.96.
wdb-svm95-400
77.23
77.3
76.9
f1 (ppm)
f1 (ppm)

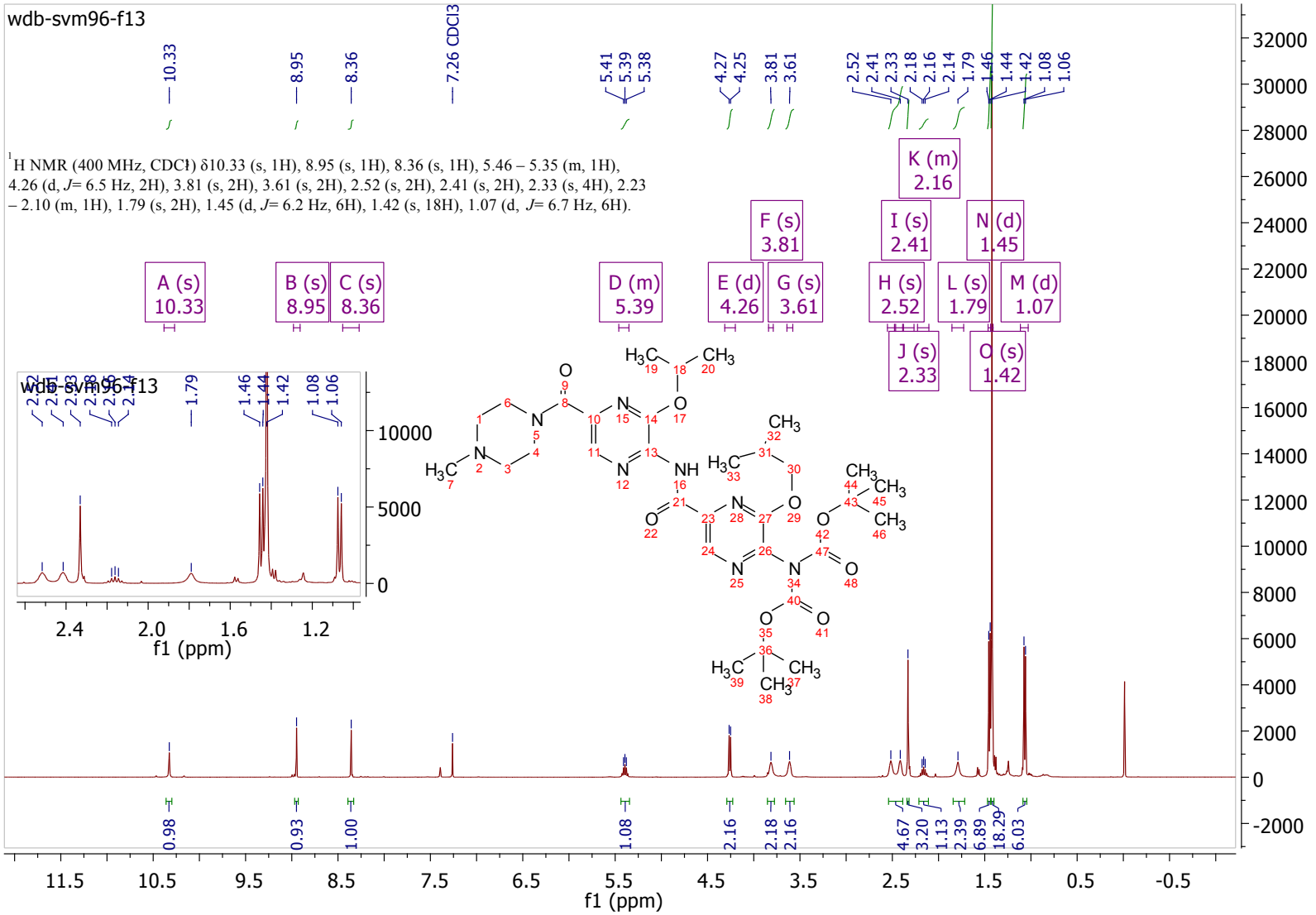
15b


WDB-PG-38@400
8.01
5.32
3.94
3.76
2.46
2.30
^{1}H NMR (400 MHz, CDCl) δ8.01 (s, 1H), 5.32 (bs, 2H), 3.94 (s, 3H), 3.76 (bs, 4H), 2.46 (bs, 4H), 2.30 (s, J= 14.5 Hz, 3H).
A (s) 8.01
B (bs) 5.32
C (s) 3.94
D (bs) 3.76
E (bs) 2.46
F (s) 2.30
1.04
2.00
3.07
4.00
4.10
3.04
f1 (ppm)

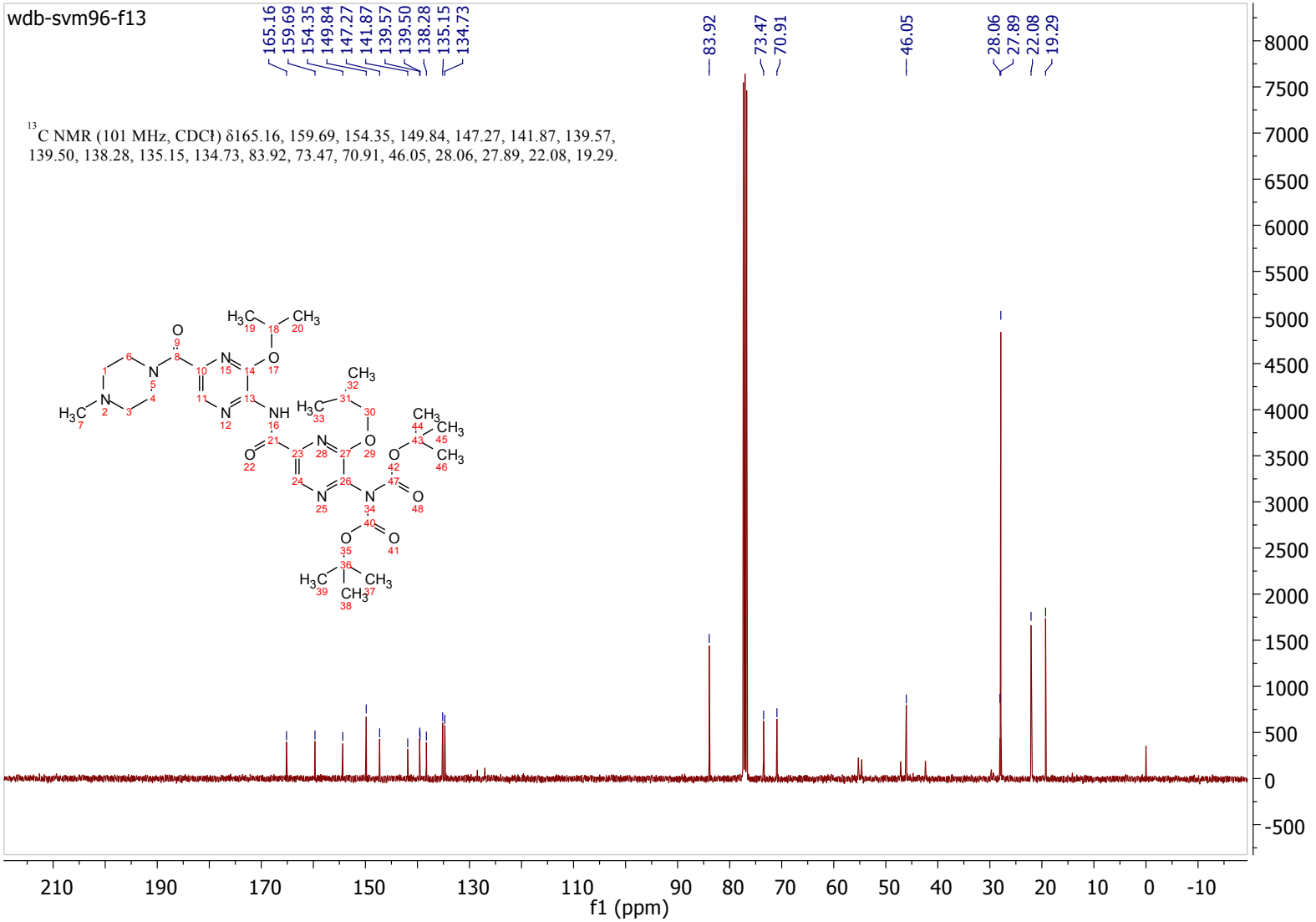
15b


WDB-PG-38@400
166.05
146.20
145.79
136.15
133.25
55.03
54.60
53.70
47.16
45.98
42.56
13C NMR (101 MHz, CDCl) δ166.05, 146.20, 145.79, 136.15, 133.25, 55.03, 54.60, 53.70, 47.16, 45.98, 42.56.
f1 (ppm)

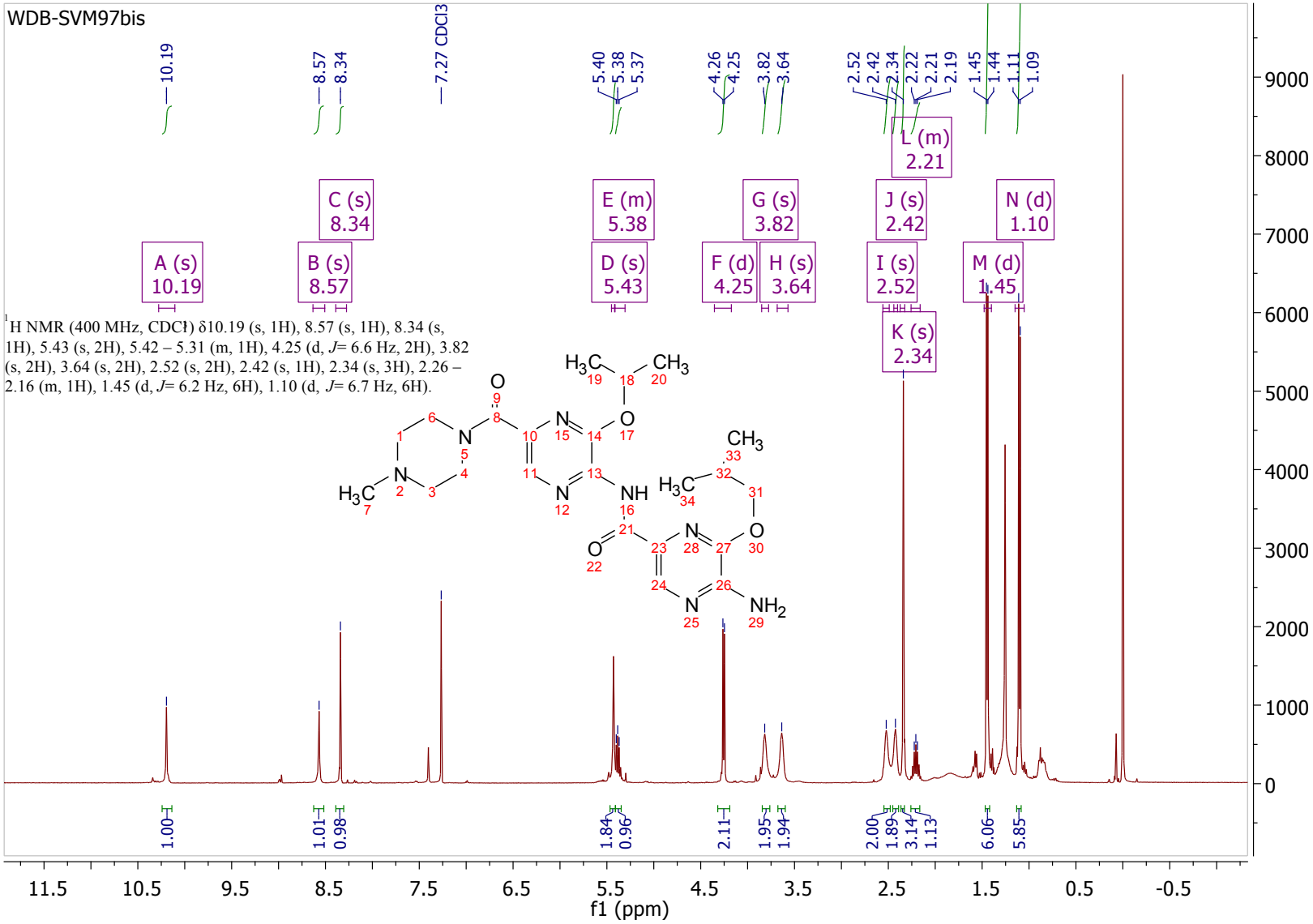
***tert*-butyl *N*-[(tert-butoxy)carbonyl]-N-(5-{[5-(4-methylpiperazine-1-carbonyl)-3-(propan-2-yloxy)pyrazin-2-yl]carbamoyl}-3-(2-methylpropoxy)pyrazin-2-yl)carbamate**



***tert*-butyl *N*-[(tert-butoxy)carbonyl]-N-(5-{[5-(4-methylpiperazine-1-carbonyl)-3-(propan-2-yloxy)pyrazin-2-yl]carbamoyl}-3-(2-methylpropoxy)pyrazin-2-yl)carbamate**

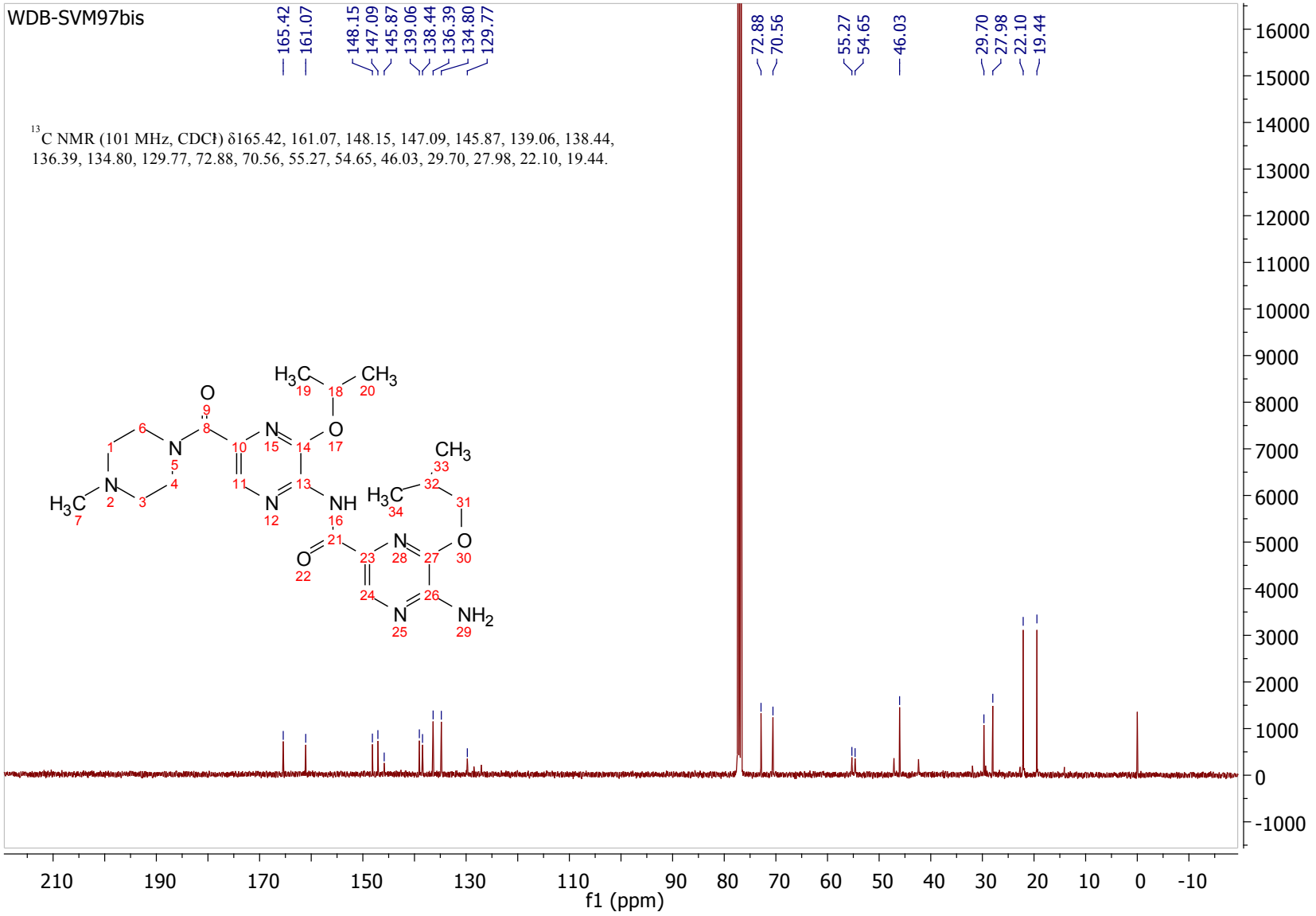


16



^{1}H NMR (400 MHz, CDCł) δ10.19 (s, 1H), 8.57 (s, 1H), 8.34 (s, 1H), 5.43 (s, 2H), 5.42 – 5.31 (m, 1H), 4.25 (d, *J*= 6.6 Hz, 2H), 3.82 (s, 2H), 3.64 (s, 2H), 2.52 (s, 2H), 2.42 (s, 1H), 2.34 (s, 3H), 2.26 – 2.16 (m, 1H), 1.45 (d, *J*= 6.2 Hz, 6H), 1.10 (d, *J*= 6.7 Hz, 6H).

16


WDB-SVM97bis
165.42
161.07
148.15
147.09
145.87
139.06
138.44
136.39
134.80
129.77
72.88
70.56
55.27
54.65
46.03
29.70
27.98
22.10
19.44
13C NMR (101 MHz, CDCl) δ165.42, 161.07, 148.15, 147.09, 145.87, 139.06, 138.44, 136.39, 134.80, 129.77, 72.88, 70.56, 55.27, 54.65, 46.03, 29.70, 27.98, 22.10, 19.44.
f1 (ppm)

6 References

1. Millet, R.; Domarkas, J.; Houssin, R.; Gilleron, P.; Goossens, J. F.; Chavatte, P.; Loge, C.; Pommery, N.; Pommery, J.; Henichart, J. P., Potent and selective farnesyl transferase inhibitors. *J. Med. Chem.* **2004,** *47* (27), 6812-6820.
2. Caldwell, J. J.; Veillard, N.; Collins, I., Design and synthesis of 2(1H)-pyrazinones as inhibitors of protein kinases. *Tetrahedron* **2012,** *68* (47), 9713-9728.