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Graphical Abstract

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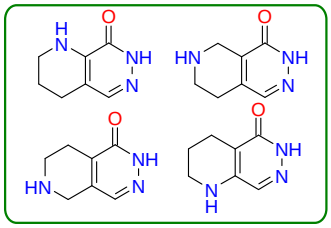

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Tetrahydropyrido[*d*]pyridazinones –promising scaffolds for drug discovery

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ABSTRACT

An approach to the synthesis of all possible tetrahydropyrido[*d*]pyridazinones has been developed. The method relies on the catalytic hydrogenation of the corresponding aromatic counterparts which were obtained by cyclization of the relevant dibromomethyl-substituted pyridinecarboxylates with hydrazine. The synthetic schemes include 4 – 5 steps starting from commercially available materials. The tetrahydropyrido[*d*]pyridazinone scaffolds are combinations of a saturated heterocycle (piperidine) and a privileged aromatic heterocycle (pyridazinone); hence they are promising starting points for the design in medicinal chemistry.

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1. Introduction

Pyridazines are a family of structures which are of top interest to contemporary drug discovery.[1,2] Several hundred papers dealing with biologically active derivatives of this heterocycle belonging to almost all therapeutic classes have been published in the last decade. In a recent review by Wermuth,[3] several arguments justifying largely the status of pyridazines as privileged structures in medicinal chemistry were given. In particular, pyridazine is a classical bioisostere for benzene and pyridine rings which improves significantly both physicochemical properties and interactions with a potential biological target. On the other hand, it can act as a surrogate for a number of functional groups, *e. g.* carboxamide. Recently, pyridazine-based scaffolds were proposed as α-helix mimetics,[4] whereas pyridazinones have attracted attention as possible analogues of nucleobases.[5, 6]

To date, most of the pyridazine derivatives used in medicinal chemistry contain aryl C-3 and/or C-6 substituent; this was related to a higher synthetic feasibility of these compounds. There are also many examples of biologically active compounds containing pyridazine as a part of a fused aromatic heterocyclic system.[3] Recent trends in drug discovery, however, show the tendency of moving away from such sp^2-enriched structures towards their saturated counterparts.[7,8,9,10] On the other hand, it is widely accepted that conformational restriction is one of the essential properties characteristic for drug molecules.[11] In this view, fusion of the piperazine ring with a saturated heterocycle can be a valuable approach to the design of building blocks of enhanced interest to drug discovery. For this reason, saturated heterocyclic amines (*e. g.* piperidine) are especially promising as they allow further functionalization of the molecule using well-established methods of combinatorial chemistry.[12] In the fact, pyridazine (or pyridazinone) moiety can be also used for selective chemical modification of the parent scaffold. Implementation of the ideas discussed above leads to the fused piperazines **1** – **4** as possible targets for the synthesis (Figure 1), which is embodied in this work.

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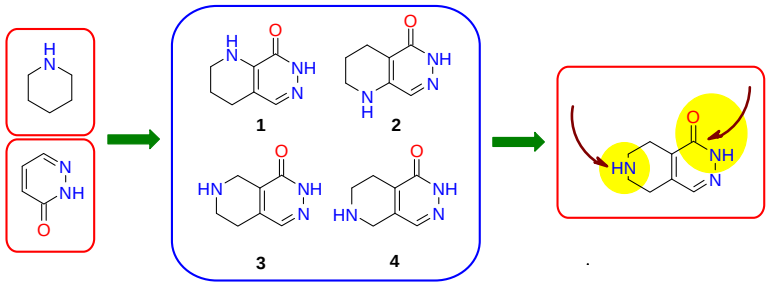
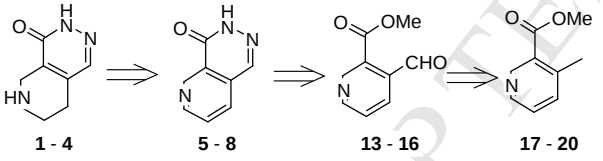


Figure 1. Tetrahydropyrido[*d*]pyridazinone scaffolds

Calculated values of physico-chemical properties of **1** – **4** (MW 151.2; Fsp^3 0.43; cLogP –0.64, –1.19, –1.32 and –0.64, respectively; TPSA 53.49 $Å^2$)[13] fit perfectly into the limits proposed for the molecular fragments in drug discovery, *e. g.* "Rule-of-three".[14] Therefore, heterocycles **1** – **4** are examples of the bifunctional conformationally restricted scaffolds[15] which can be good starting points for the lead-oriented synthesis in drug discovery.[16]

2. Results and discussion

One of is most obvious retrosynthetic approaches to these compounds is from their aromatic counterparts **5** – **8** (Scheme 1). All the compounds **5** – **8** are mentioned in the literature; their reported syntheses relied either on the cyclization of various precursors **9** – **12** with hydrazine (Figure 2).[17, 18, 19, 20] or oxidation of the corresponding dihydropyridopyridazines.[21, 22] Looking for a general approach to the synthesis of **5** – **8**, we have turned our attention to aldehydoesters **13** – **16** as key intermediates. The method for the preparation of these compounds described previously involved partial reduction of the corresponding pyridinedicarboxylates.[23, 24, 25] and was not convenient due to selectivity problems, especially upon scale-up. In this work, we considered bromination of the pyridinecarboxylates **17** – **20** followed by hydrolysis as an alternative approach to **13** – **16**.



Scheme 1 Retrosynthetic analysis of **1** – **4**

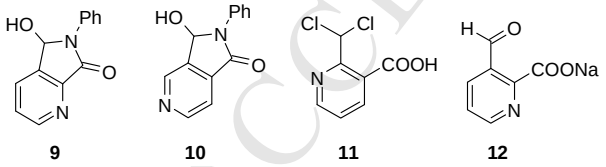
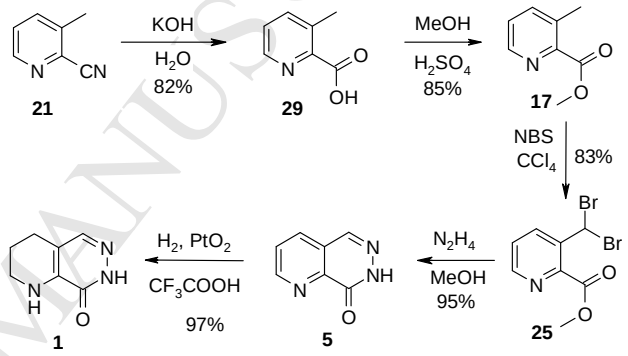
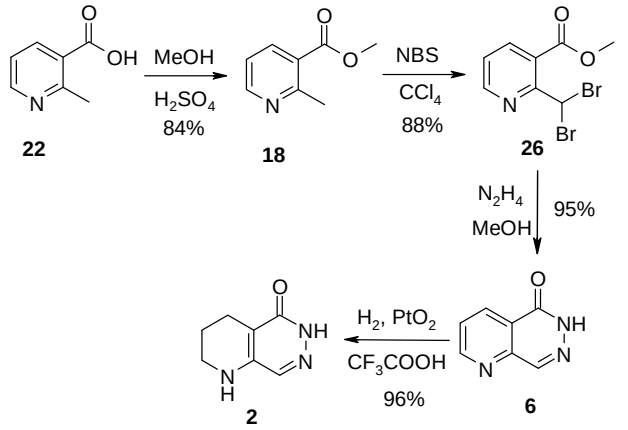


Figure 2 Synthetic precursors of pyrido[*d*]pyridazinones **5** – **8** reported in the literature

The implementation of the retrosynthetic approach discussed above is shown in Schemes 2 – 5. Compounds **21** – **24** which are readily available commercially were used as the starting materials in these syntheses. They were transformed into the esters **17** – **20** in one or two steps. To achieve selective transformation of the methyl groups in **17** – **20** to the aldehydes, two-step reaction sequences were used instead of the methods based on direct oxidation. First, bromination of **17** – **20** was performed, using *N*-bromosuccinimide (NBS) in CCl_4; the corresponding dibromides **25** – **28** were obtained in good yields (82–92%). Unfortunately, hydrolysis of of **25** – **28** by the action of $AgNO_3$ in aqueous methanol failed to produce aldehydes **13** – **16** in pure form; complex mixtures were obtained instead. Nevertheless, dibromides **25** – **28** themselves reacted smoothly with hydrazine and provided the pyrido[*d*]pyridazinones **5** – **8** in excellent yield (95%), making isolation of free aldehydes **13** – **16** unnecessary.



Scheme 2



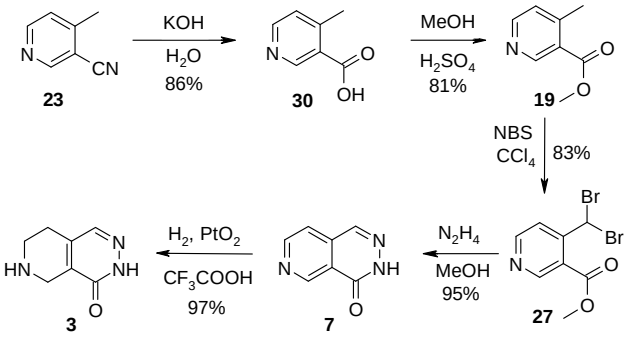
Scheme 3

As the N–N bonds of pyridazines are susceptible to catalytic hydrogenation, some efforts were made to find optimal conditions for the selective reduction of the pyridine ring in **5** – **8**. A number of experimentations showed that using CF_3COOH as a solvent allowed the target compounds **1** – **4** to be obtained in 96–97% yields by catalytic hydrogenation of **5** – **8** in the presence of platinum dioxide in MeOH.

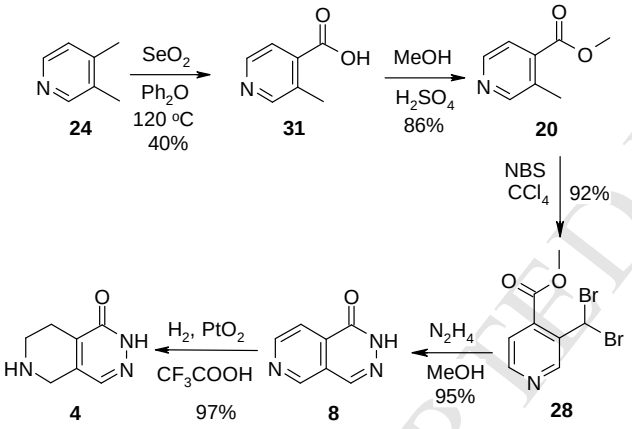
3. Conclusions

Recent tendencies in drug discovery show a great demand for highly hydrophilic, low-molecular-weight molecules with a high

degree of saturation which can be used as the starting points in the search for lead compounds. Combination of a saturated heterocycle (*i. e.* piperidine) and a privileged aromatic heterocycle (such as pyridazinone) into a single molecule provides a good example; the four tetrahydropyrido[*d*]pyridazinone scaffolds thus generated leaves much room for the design of biologically relevant molecules. An approach to the synthesis of these building blocks was developed starting from the properly substituted pyridine derivatives. The methods included 4 – 5 steps starting from commercially available materials and were used for the multigram preparations of the title compounds (~20 g in a single run).



Scheme 4



Scheme 5

4. Experimental part

4.1. General

The solvents were purified according to standard procedures. All the starting materials were purchased from Acros, Merck, Fluka. Analytical TLC was performed using Polychrom SI F254 plates. The IR spectra of all synthesed compounds were recorded on Bruker Vertex 70/70v in KBr pellets, the frequencies are given in cm^{-1}. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for Protons and 125 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons, 100.7 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)).

*4.2. 3-Methylpyridine-2-carboxylic acid (**29**)*

3-Methylpyridine-2-carboxylic acid was prepared in 82% yield starting from **21** according to the procedure described in the literature.[26] For spectral and physical data, ref.[27].

*4.3. 4-Methylnicotinic acid (**30**)*

4-Methylnicotinic acid was prepared in 86% yield starting from **23** according to the procedure described in the literature.[28] For spectral and physical data, see ref. 29.

*4.4. 3-Methylisonicotinic acid (**31**)*

3-Methylisonicotinic acid was prepared in 40% yield starting from **24** according to the procedure described in the literature.[26] For spectral and physical data, ref[30].

*4.5. General procedure for the preparation of **17** – **20***

To a solution of carboxylic acid **22** or **29** – **31** (0.1 mol) in dry methanol (150 mL), conc. H_2SO_4 (20 mL) was added. The mixture was refluxed for 15–20 h (LC–MS control). The solvent was removed in vacuo, and the residue was dissolved in H_2O. The solution was made alkaline with cold saturated aq K_2CO_3 and extracted with CH_2Cl_2 (4×50 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc as eluent) or distilled in vacuo to give **17** – **20**.

*4.5.1. Methyl 3-methylpyridine-2-carboxylate (**17**)*

Yield 12.8 g (85%). For spectral and physical data, see ref. 31, 32.

*4.5.2. Methyl 2-methylnicotinate (**18**)*

Yield 12.7 g (84%). For spectral and physical data, see ref. 33.

*4.5.3. Methyl 4-methylnicotinate (**19**)*

Yield 12.8 g (81%). For spectral and physical data, see ref. 34.

*4.5.4. Methyl 3-methylisonicotinate (**20**)*

Yield 13.0 g (86%). For spectral and physical data, see ref. 32.

*4.6. General procedure for the preparation of **25** – **28***

To a solution of ester **17** – **20** (13.7 g, 0.100 mol) in dry CCl_4 (400 mL), *N*-bromosuccinimide (35.6 g, 0.200 mol) was added. The mixture was slowly heated to reflux, then refluxed for 16 h (monitored by LC–MS), and then cooled to rt. The succinimide was filtered off, and the filtrate was concentrated under reduced pressure to give *gem*-dibromomethyl compound **25** – **28**. Analytical samples were prepared by chromatography (hexanes – EtOAc (1 : 9)).

*4.6.1. Methyl 3-(dibromomethyl)pyridine-2-carboxylate (**25**)*

Yield 12.5 g (83%). Colourless solid. Mp 83–84 °C (CCl_4). IR (KBr): 3413, 3075, 2949, 2844, 1934, 1716, 1580, 1563, 1449, 1427, 1315, 1264, 1197, 1172, 1133, 1080, 957, 854, 807, 718, 673, 652, 592, 529, 483 cm-1. ^{1}H NMR ($CDC1_3$) δ 4.02 (3H, s), 7.59 (1H, dd, J = 8.1 Hz and 4.6 Hz), 7.93 (1H,s), 8.49 (d, 1H, J = 8.1 Hz), 8.64 (1H, d, J = 4.6 Hz). ^{13}C NMR ($CDC1_3$), δ 39.6, 53.1, 120.8, 124.1, 138.9, 153.5, 157.8, 165.2. MS (m/z, APCI): 308 (MH+). Anal. Calcd for $C_8H_7Br_2NO_2$ C 31.10, H 2.28, Br 51.72, N 4.53. Found: C 31.15, H 2.32, Br 51.68, N 4.59.

*4.6.2. Methyl 2-(dibromomethyl)nicotinate (**26**)*

Yield 2.71 g (88%). Colourless solid. Mp. 95–96 °C (n-hexane). IR (KBr): 3087, 3069, 3043, 3009, 2952, 2841, 1993, 1957, 1712, 1583, 1562, 1427, 1273, 1255, 1190, 1136, 1078, 1056, 957, 858, 833, 809, 791, 737, 696, 668, 638, 599, 488 cm^{-1}.

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^{1}H NMR, δ ($CDC1_3$): 3.96 (3H, s), 7.36 (1H, dd, J = 8.1 Hz and 4.6 Hz), 7.99 (1H, s), 8.25 (1H, dd, J = 8.1 Hz and 1.6 Hz), 8.88 (1H, dd, J = 4.6 Hz and 1.6 Hz). ^{13}C NMR ($CDC1_3$) δ 39.6, 53.1, 124.2, 138.8, 153.4, 157.8, 165.2. MS (m/z, APCI): 308 (MH+). Anal. Calcd. for $C_8H_7Br_2NO_2$.C 31.10, H 2.28, Br 51.72, N 4.53. Found: C 31.18, H 2.34, Br 51.82, N 4.61.

*4.6.3. Methyl 4-(dibromomethyl)nicotinate (**27**)*[35]

Yield 2.56 g (83%). Colourless solid. Mp. 71–72 °C (*n*-hexane). IR(KBr): 3419, 3057, 2957, 2849, 1924, 1723, 1585, 1555, 1488, 1437, 1404, 1277, 1197, 1149, 1107, 1054, 954, 846, 814, 792, 726, 670, 636, 585 cm^{-1}. ^{1}H NMR ($CDC1_3$) δ 3.92 (3H, s), 7.87 (1H, s), 7.94 (1H, d, J = 5.4 Hz), 8.77 (1H, d, J = 5.4 Hz), 9.05 (1H, s). ^{13}C NMR, δ ($CDC1_3$): 35.6, 52.9, 119.7, 124.7, 151.1, 151.5, 153.3, 165.2. MS (*m/z*, APCI): 308 (MH^+). Anal. Calcd for $C_8H_7Br_2NO_2$ C 31.10, H 2.28, Br 51.72, N 4.53. Found: C 31.12, H 2.32, Br 51.80, N 4.60.

*4.6.4. Methyl 3-(dibromomethyl)isonicotinate (**28**)*

Yield 2.84 g (92%). Colourless solid. Mp 79 – 80 °C (*n*-hexane). IR(KBr): 3071, 2956, 1912, 1785, 1718, 1584, 1552, 1483, 1429, 1406, 1310, 1282, 1189, 1157, 1097, 958, 854, 810, 708, 679, 679, 646, 606, 495 cm^{-1}. ^{1}H NMR ($CDC1_3$) δ 3.95 (3H, s), 7.63 (1H, d, J = 4.8 Hz,), 7.84 (1H, s), 8.64 (1H, d, J = 4.8 Hz,), 9.39 (1H, s). ^{13}C NMR ($CDC1_3$) δ 34.1, 53.2, 122.1, 131.4, 136.9, 150.6, 153.8, 165.1. MS (*m/z*, APCI): 308 (MH^+). Anal. Calcd. for $C_8H_7Br_2NO_2$ C 31.10, H 2.28, Br 51.72, N 4.53. Found: C 31.15, H 2.30, Br 51.78, N 4.61.

*4.7. General procedure for the preparation of **5** – **8***

A solution of **25** – **28** (3.08 g, 0.01 mol) and hydrazine hydrate (2.00 g, 0.04 mol) in methanol (50 mL) was stirred under reflux for 5 h. The solvent was evaporated under reduced pressure, and the residue was recrystallized from MeOH – H_2O (9 : 1).

*4.7.1. Pyrido[2,3-d]pyridazin-8(7H)-one (**5**)*[17, 19]

Yield 1.37 g (95%). Light yellow crystals. Mp 285–286 °C (MeOH–H_2O (9 : 1)) (lit.[17] 288–290 °C). IR(KBr): 3170, 3056, 2924, 1678, 1588, 1552, 1458, 1422, 1364, 1343, 1217, 1167, 1136, 1081, 917, 899, 867, 816, 716, 679, 610, 570, 498 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.92 (1H, dd, J = 8.1 Hz and J = 4.8 Hz), 8.39 (1H, dd, J = 8.1 Hz and 1.6 Hz), 8.40 (1H, s), 9.07 (1H, dd, J = 4.8 Hz and J = 1.6 Hz), 12.92 (1H, br. s). ^{13}C NMR (DMSO-d_6) δ 127.1, 128.6, 135.8, 138.1, 144.0, 154.4, 159.5. MS (*m/z*, APCI): 146 (MH^+). Anal. Calcd. for $C_7H_5N_3O$ C 57.14, H 3.43, N 20.56. Found: C 57.37, H 3.25, N 20.51.

*4.7.2. Pyrido[2,3-d]pyridazin-5(6H)-one (**6**)*[20, 36, 37]

Yield 1.38 g (95%). Light yellow crystals. Mp 253–255 °C (MeOH–H_2O (9 : 1)).IR(KBr): 3178, 3118, 3062, 3012, 2956, 2871, 1667, 1602 ,1444, 1360, 1318, 1300, 1220, 1148, 1074, 921, 868, 814, 784, 713, 596, 553, 498, 471 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.84 (1H, dd, J = 8.1 Hz and 4.8 Hz), 8.41 (1H, s), 8.58 (1H, dd, J = 8.1 Hz and 1.2 Hz), 9.13 (1H, dd, J = 4.8 Hz and 1.2 Hz), 12.97 (1H, br, s). ^{13}C NMR (DMSO-d_6), δ 124.5, 127.1, 134.5, 139.8, 146.9, 156.4, 160.3. MS (*m/z*, APCI): 146 (MH^+). Anal. Calcd. for $C_7H_5N_3O$ C 57.14, H 3.43, N 28.56. Found: C 57.40, H 3.49, N 28.77.

*4.7.3. Pyrido[3,4-d]pyridazin-4(3H)-one (**7**)*[22]

Yield 1.36 g (93%). Light yellow crystals. Mp 255–256 °C (MeOH–H_2O (9 : 1)). IR(KBr): 3167, 3101, 3062, 3025, 2846, 1664, 1594, 1554, 1496, 1461, 1408, 1366, 1323, 1285, 1247, 1220, 1168, 1135, 1032, 917, 892, 847, 792, 737, 682, 611, 554, 497, 468 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.83 (1H, d, J = 5.2Hz), 8.43 (1H, s), 9.02 (1H, d, J = 5.2 Hz), 9.43 (1H, s), 13.00 (1H, br. s). ^{13}C NMR (DMSO-d_6) δ 119.4, 122.1, 134.9, 137.4, 149.3, 153.3, 159.2. MS (*m/z*, APCI): 146 (MH^+). Anal. Calcd for $C_7H_5N_3O$ C 57.14, H 3.43, N 20.56. Found: C 57.28, H 3.21, N 20.30.

*4.7.4. Pyrido[3,4-d]pyridazin-1(2H)-one (**8**)*[17, 22]

Yield 1.32 g (90%). Light yellow crystals. Mp 290–292°C (MeOH–H_2O (9 : 1)). IR(KBr): 3453, 3167, 3100, 3061, 3011, 2841, 1666, 1552, 1497, 1461, 1407, 1366, 1322, 1284, 1249, 1218, 1167, 1136, 1031, 917, 891, 848, 792, 738, 682, 611, 553, 497, 466 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 8.06 (1H, d, J = 5.2 Hz), 8.52 (1H, s), 8.98 (1H, d, J = 5.2 Hz), 9.32 (1H, s), 12.99 (1H, br. s). ^{13}C NMR (DMSO-d_6) δ 118.4, 124.8, 133.0, 137.0,150.6, 151.4,159.0. MS (*m/z*, APCI): 146 (MH^+). Anal. Calcd for $C_7H_5N_3O$ C 57.14, H 3.43, N 20.56. Found: C 56.97, H 3.55, N 20.47.

*4.8. General procedure for the preparation of **1** – **4***

Compound **5** – **8** (150 mg, 0.6 mmol) and PtO_2 (30 mg) in CF_3COOH (5 mL) were stirred in a pressure vessel at rt and 50 psi of hydrogen atmosphere for 48 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give compounds **1** – **4** as trifluoroacetates. To obtain the compounds **1** **2** as free bases, the trifluoroacetates were neutralized with saturated aq K_2CO_3, to pH = 7 and then extracted with CH_2Cl_2 (3×50 mL). The combined extracts were dried over Na_2SO_4 and evaporated in vacuo.

*4.8.1. 1,3,4,7-Tetrahydropyrido[2,3-d]pyridazin-8(2H)-one (**1**)*[36, 37]

Yield 1.46 g (97%). Light grey crystals. Mp 236–238 °C (MeOH). IR(KBr): 3320, 3105, 3023, 2956, 2864, 1766, 1633, 1562, 1439, 1366, 1334, 1274, 1239, 1186, 1133, 1096, 1052, 990, 887, 863, 834, 774, 698, 603, 572, 532, 497, 462, 429 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.76 (2H, quint, J = 5.7 Hz), 2.46 (2H, t, J = 5.7 Hz), 3.24 (2H, t, J = 5.7 Hz), 6.56 (1H, s), 7.38 (1H, s), 12.35 (1H, br. s). ^{13}C NMR (DMSO-d_6) δ 20.0, 22.5, 110.0, 139.7, 140.6, 156.6. MS (*m/z*, APCI): 150 (MH^+). Anal. Calcd. for $C_7H_9N_3O$ C 55.62, H 6.00, N 27.80 Found: C 55.76, H 6.13, N 27.90.

*4.8.2. 2,3,4,6-Tetrahydropyrido[2,3-d]pyridazin-5(1H)-one (**2**)*[36, 37]

Yield 1.44 g (96%). Light grey crystals. Mp 234–235 °C. IR(KBr): 3232, 2957, 1676, 1605, 1561, 1410, 1379, 1351, 1316, 1287, 1194, 1138, 992, 834, 797, 749, 721, 635, 566, 513, 439 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.72 (2H, quint, J = 5.5 Hz), 2.34 (2H, t, J = 5.5 Hz), 3.18 (2H, t, J = 5.5 Hz), 7.03 (1H, br. s,), 7.41 (1H, s), 12.12 (1H, br. s). ^{13}C NMR (DMSO-d_6) δ 19.3, 19.7, 105.2, 131.5, 145.8, 161.5. MS (*m/z*, APCI): 150 (MH^+). Anal. Calcd. for $C_7H_9N_3O$ C 55.62, H 6.00, N 27.80. Found: C 55.38, H 5.74, N 27.87.

*4.8.3. 5,6,7,8-Tetrahydropyrido[3,4-d]pyridazin-4(3H)-one (**3**), trifluoroacetate*

Yield 2.57 g (98%). White crystals. Mp 144–146°C. IR(KBr): 3417, 3195, 3049, 2807, 2647, 2538, 1677, 1620, 1568, 1479, 1422, 1372, 1330, 1281, 1189, 1129, 990, 935, 875, 838, 796, 754, 723, 640, 597, 565, 521, 456, 422 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.81 (2H, t, J=5.8 Hz), 3.34 (2H, d, J = 5.8 Hz), 3.97 (2H, t, J = 5.8 Hz), 7.83 (1H, s), 9.24 (2H, br. s), 13.16 (1H, br. s). ^{13}C NMR (D_2O) δ 18.6, 36.1, 36.5, 113.1 (q, J = 292 Hz) 125.6, 135.7, 136.8, 157.1, 159.6 (q, J = 34 Hz). MS (*m/z*, APCI): 150 (MH^+). Anal. Calcd. for $C_9H_{10}F_3N_3O_3$ C 40.76, H 3.80, N 15.85. Found: C 40.79, H 3.94, N 15.98.

*4.8.4. 5,6,7,8-Tetrahydropyrido[3,4-d]pyridazin-1(2H)-one (**4**), trifluoroacetate*

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Yield 2.57 g (97%). White crystals. Mp 178–179 °C. IR (KBr): 3478, 3144, 2982, 2841, 2675, 2500, 1677, 1623, 1566, 1482, 1455, 1425, 1375, 1302, 1208, 1179, 1115, 1040, 989, 945, 892, 836, 792, 752, 721, 640, 608, 564, 540, 517, 478, 460, 442, 426 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.66 (2H, quint, J = 5.6 Hz), 3.36 (2H, t, J = 5.6 Hz), 4.15 (2H, t, J = 5.6 Hz), 7.79 (1H, s), 9.62 (2H, s), 13.07 (1H, br. s). ^{13}C NMR (D_2O) δ 16.9, 37.4, 38.4, 113.7 (q, J = 292 Hz), 130.2, 131.4, 134.6, 158.2, 160.2 (q, J = 35 Hz). MS (*m/z*, APCI): 150 (MH^+). Anal. Calcd. for $C_9H_{10}F_3N_3O_3$. C 40.76, H 3.80, N 15.85. Found: C 40.82, H 3.85, N 15.71.

References

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Supporting information

Tetrahydropyrido[*d*]pyridazinones –promising scaffolds for drug discovery

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Table of contents

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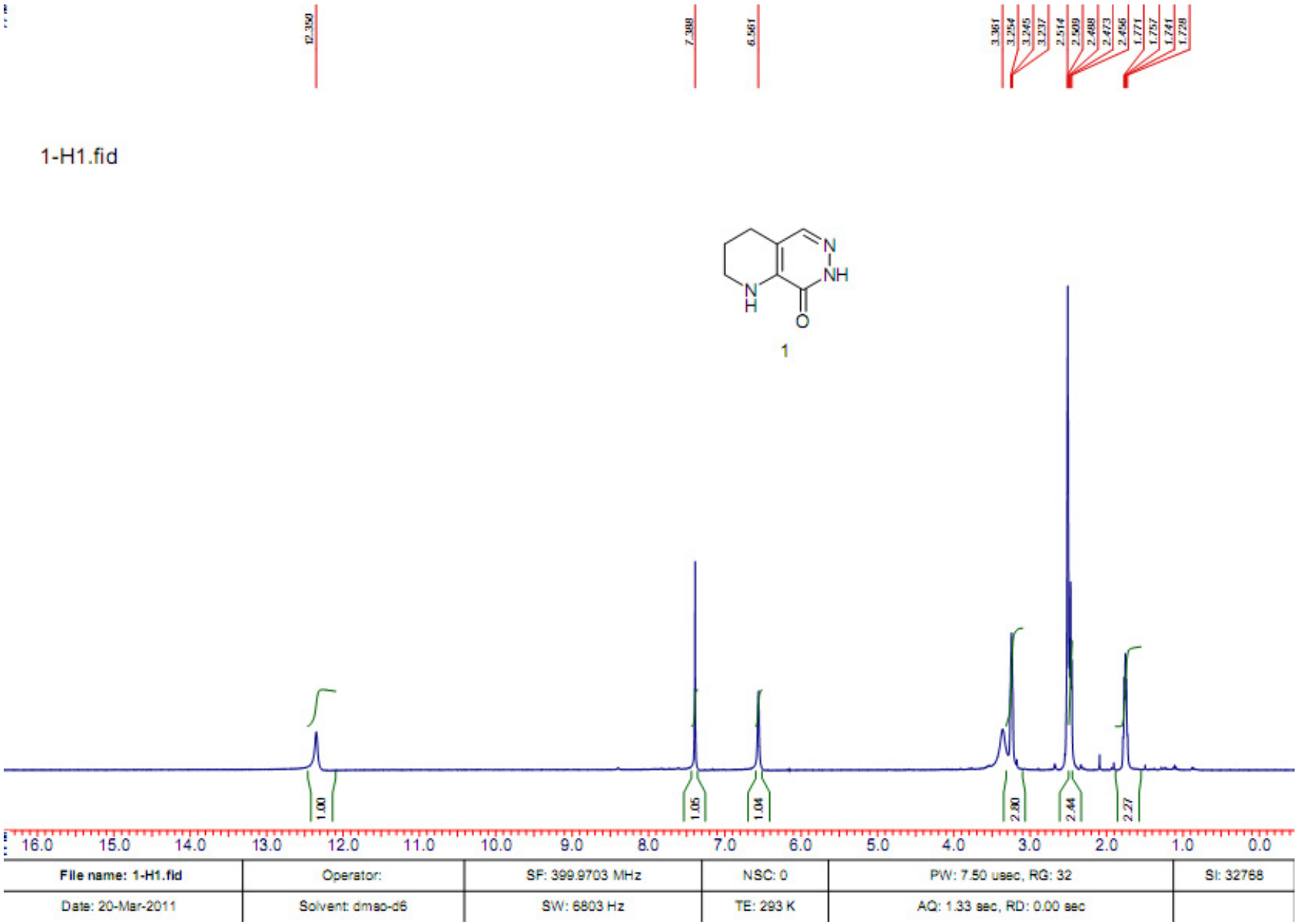
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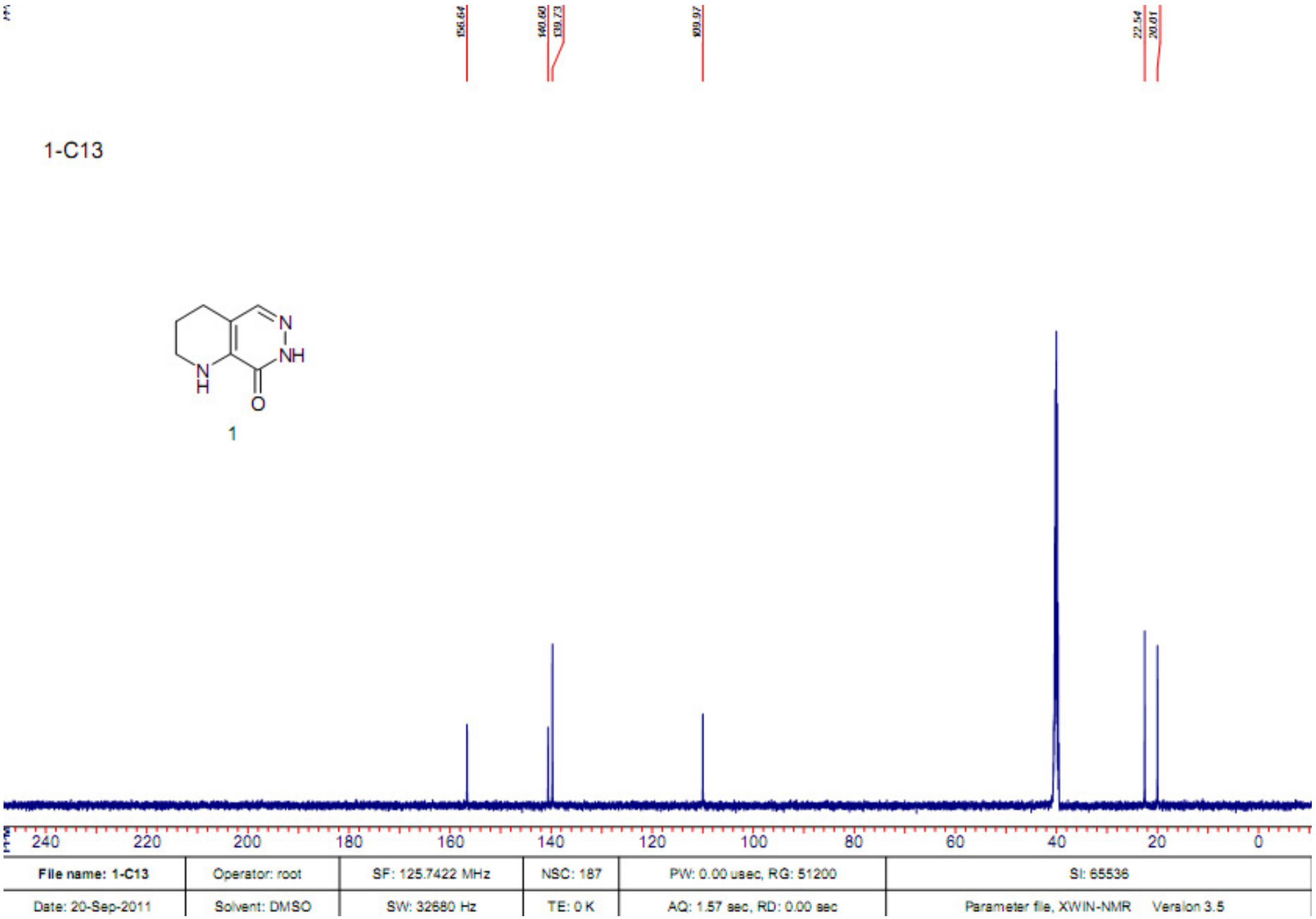
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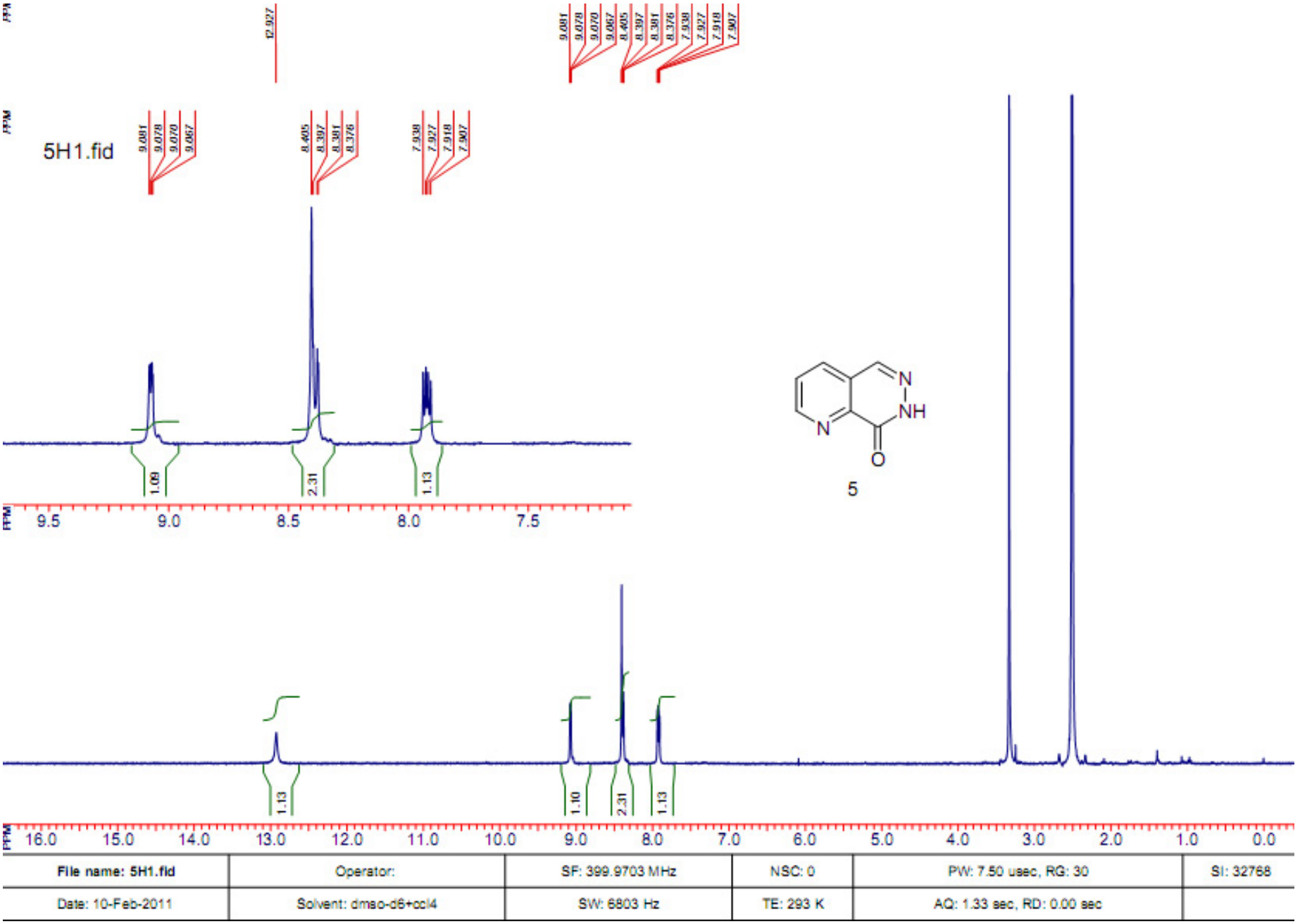

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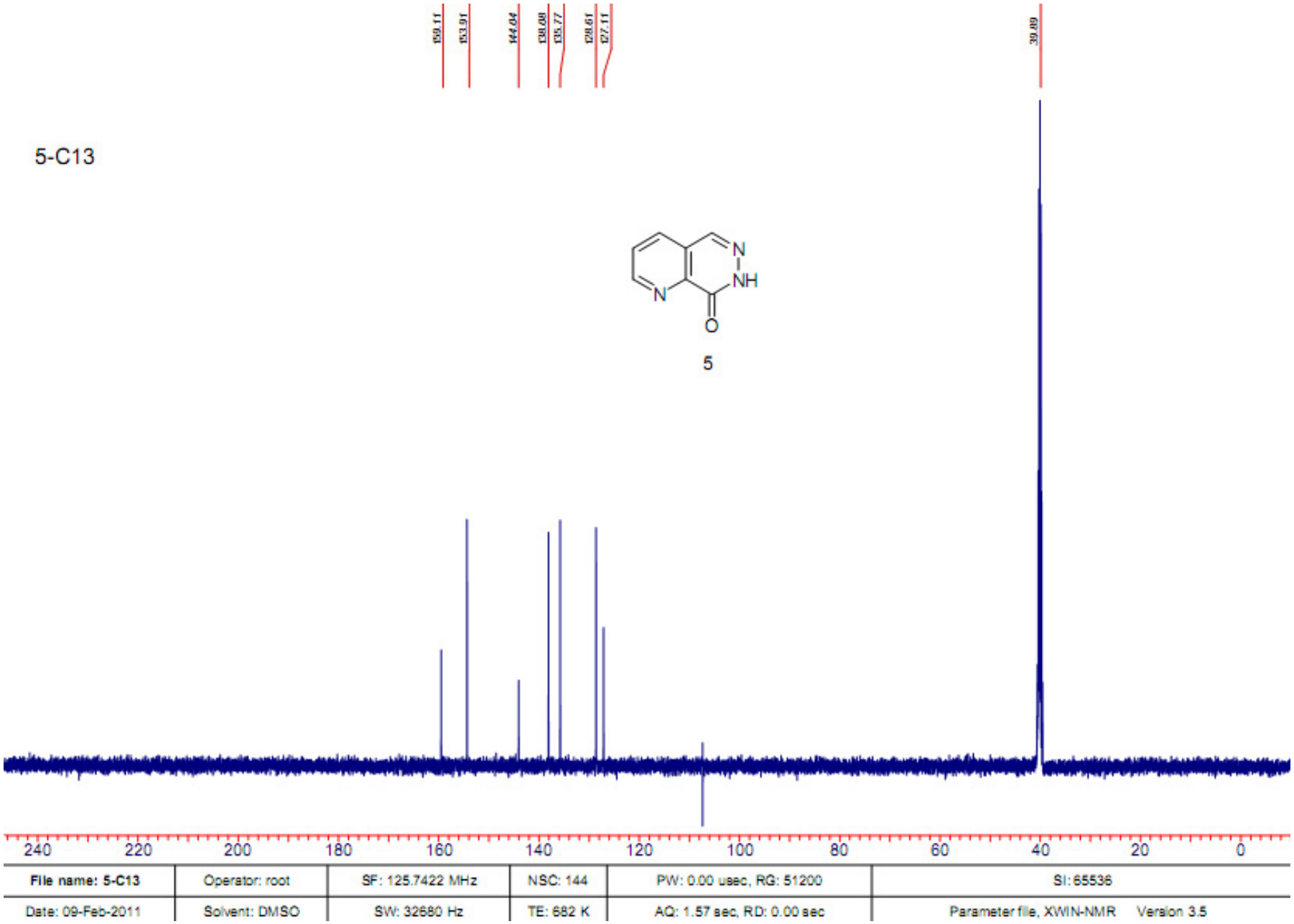
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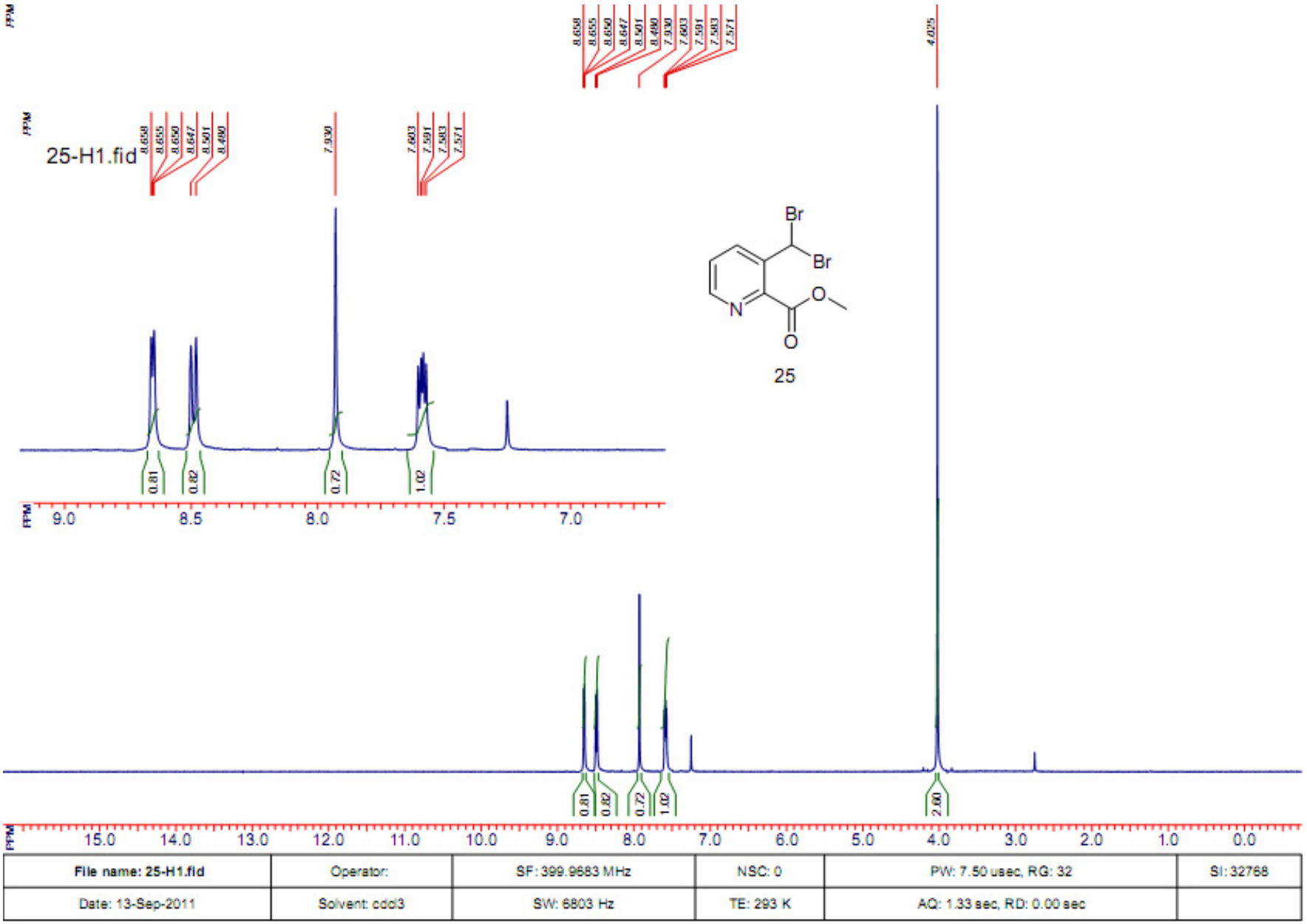

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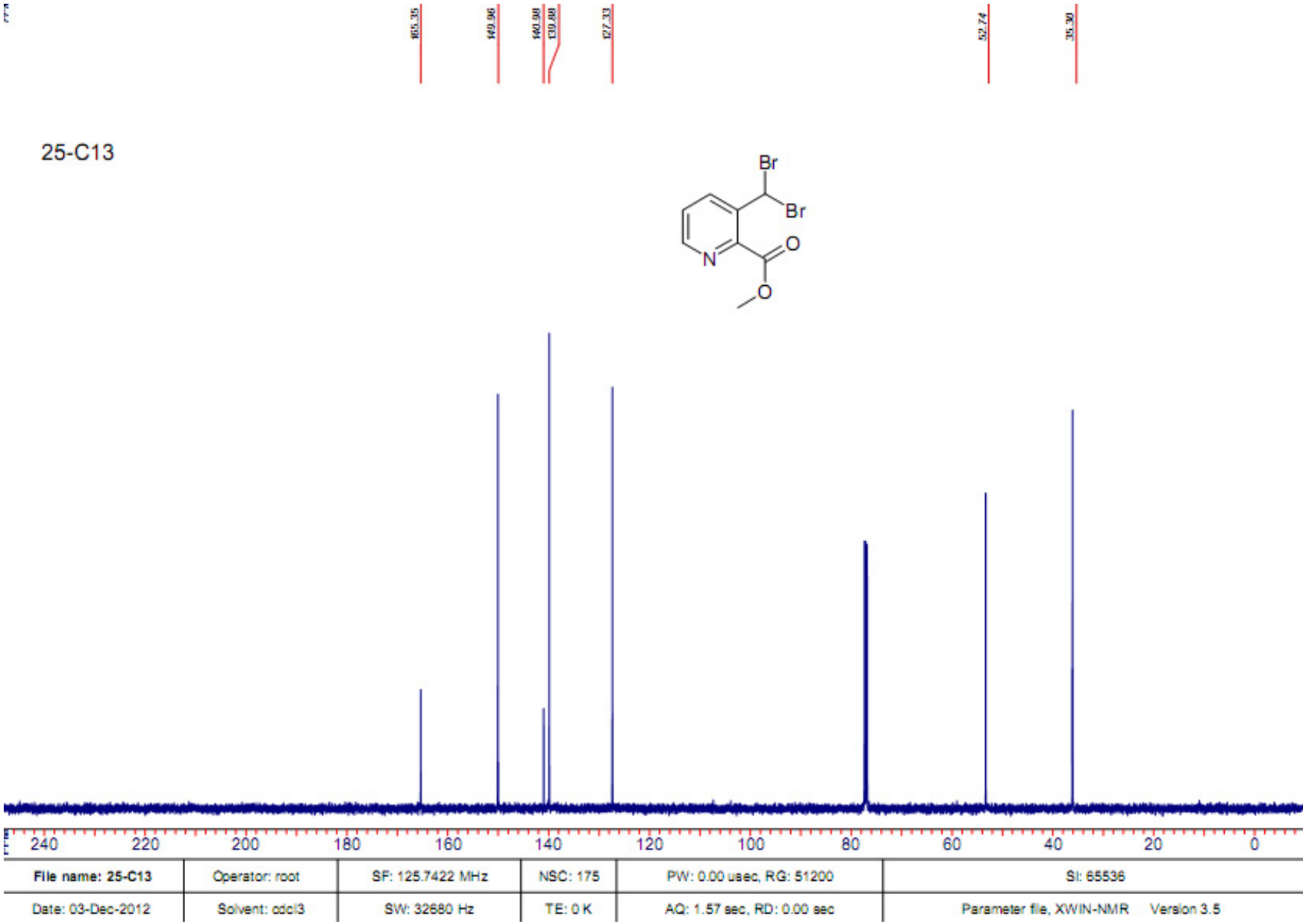
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140
120
100
80
60
40
20
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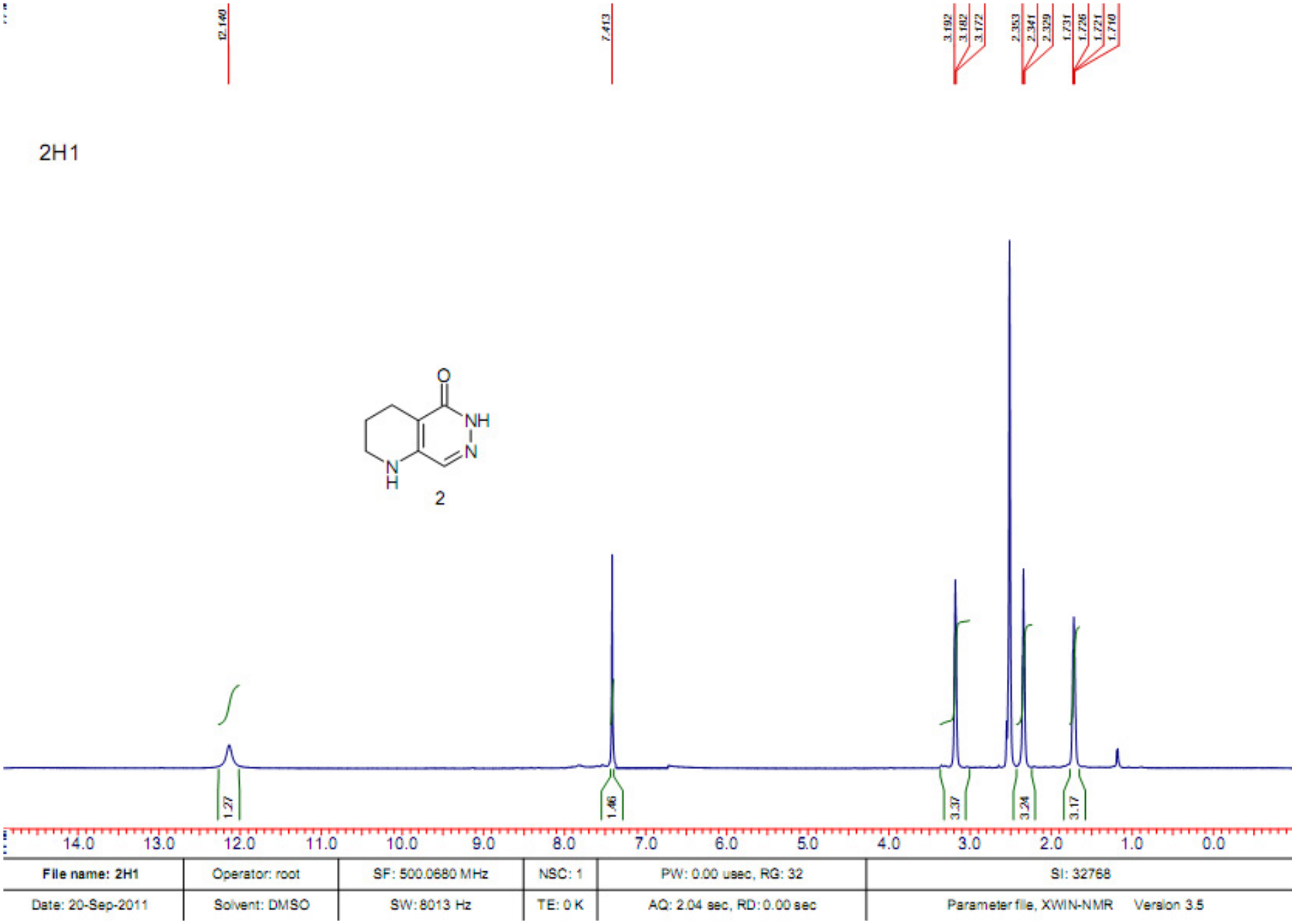
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N
N
H
2
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1.46
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3.24
3.17
14.0
13.0
12.0
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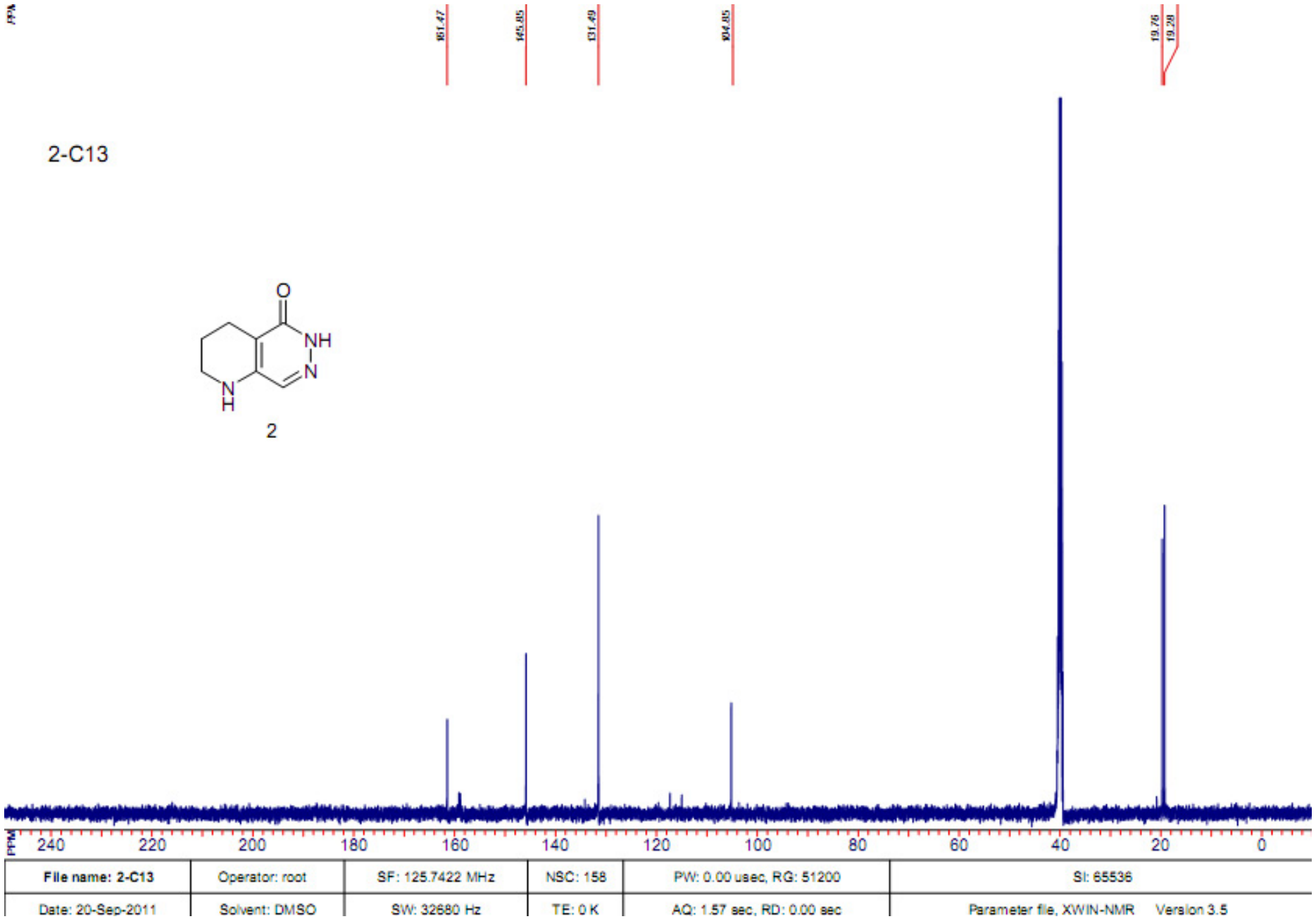
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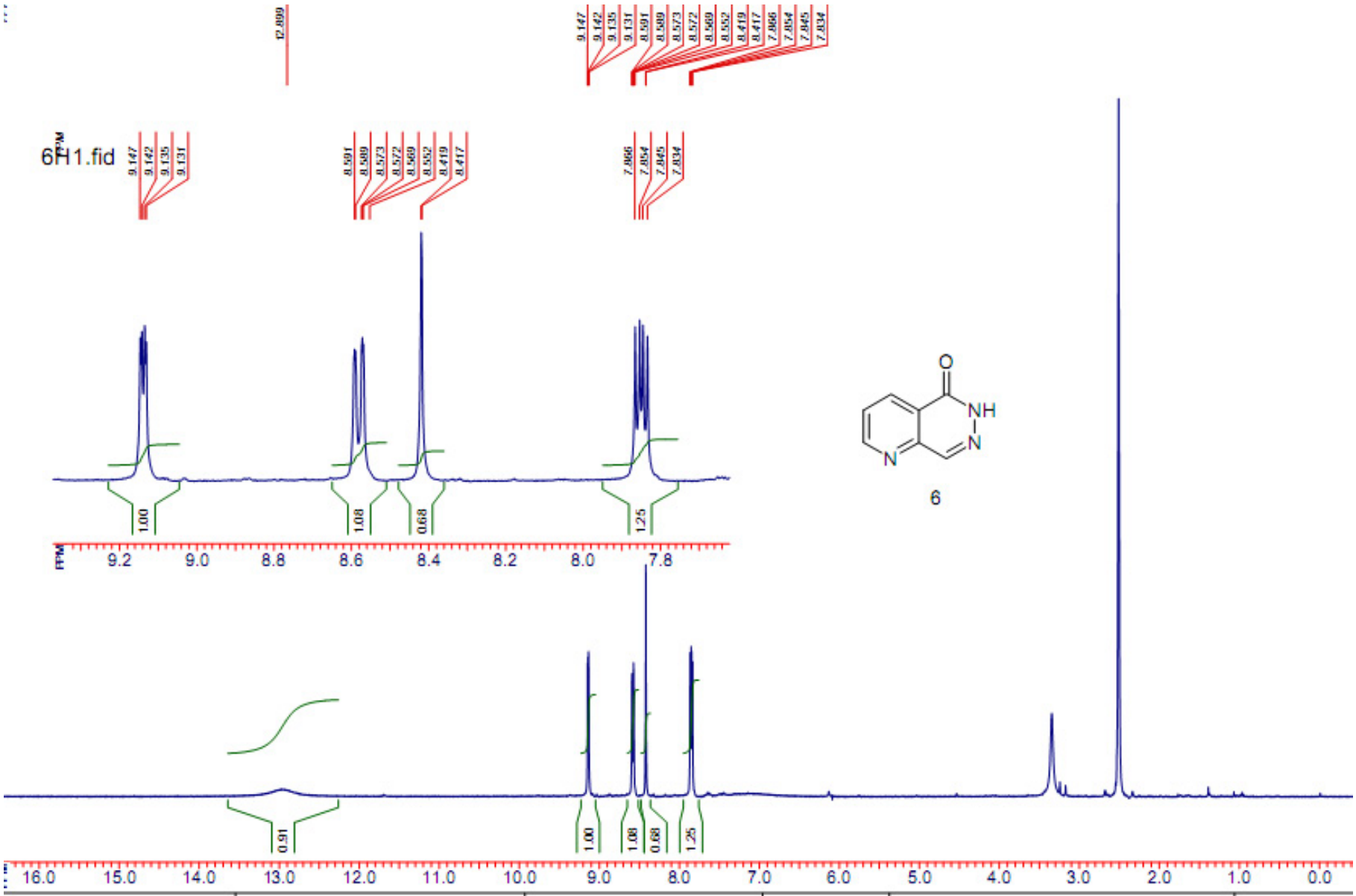

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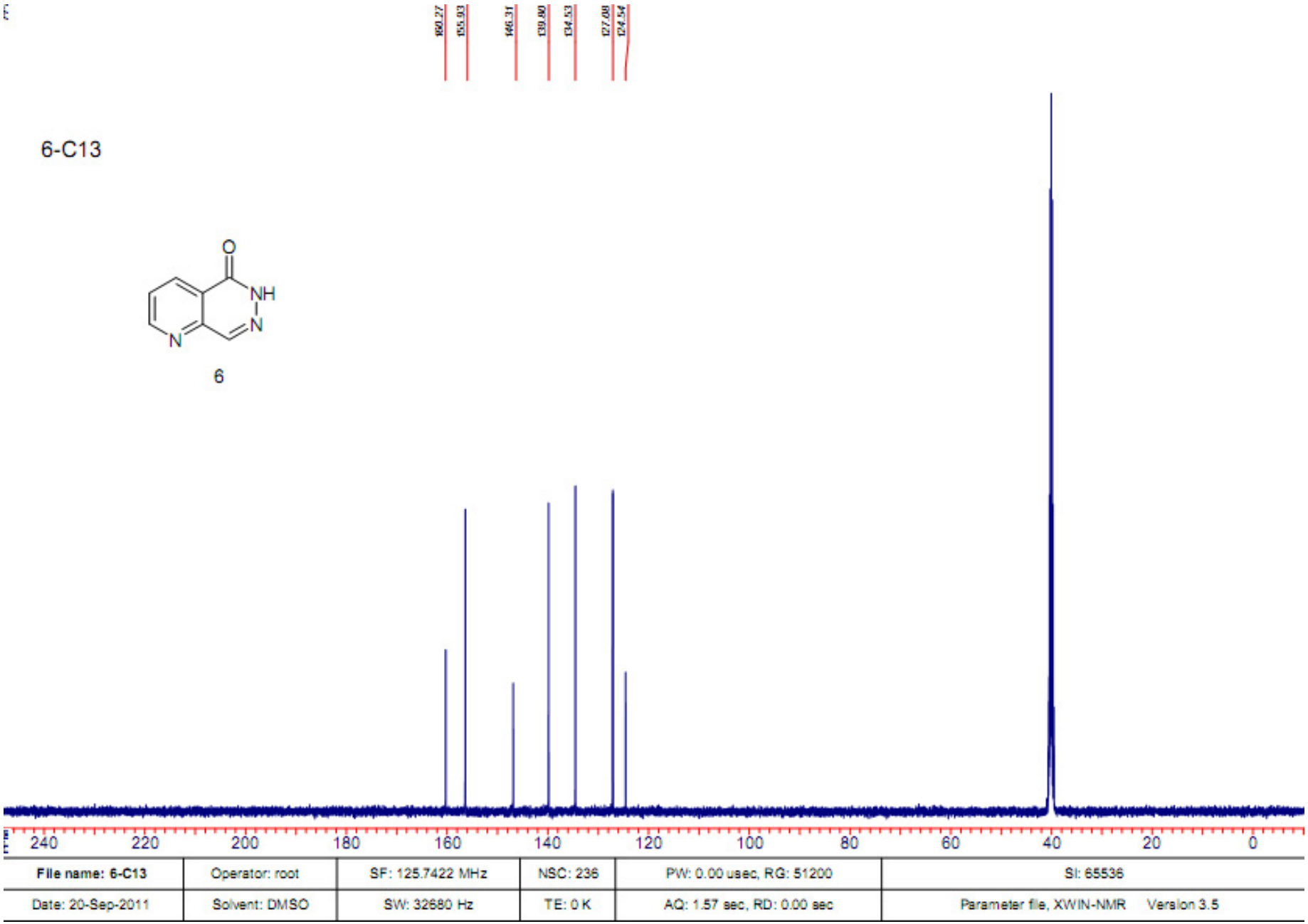

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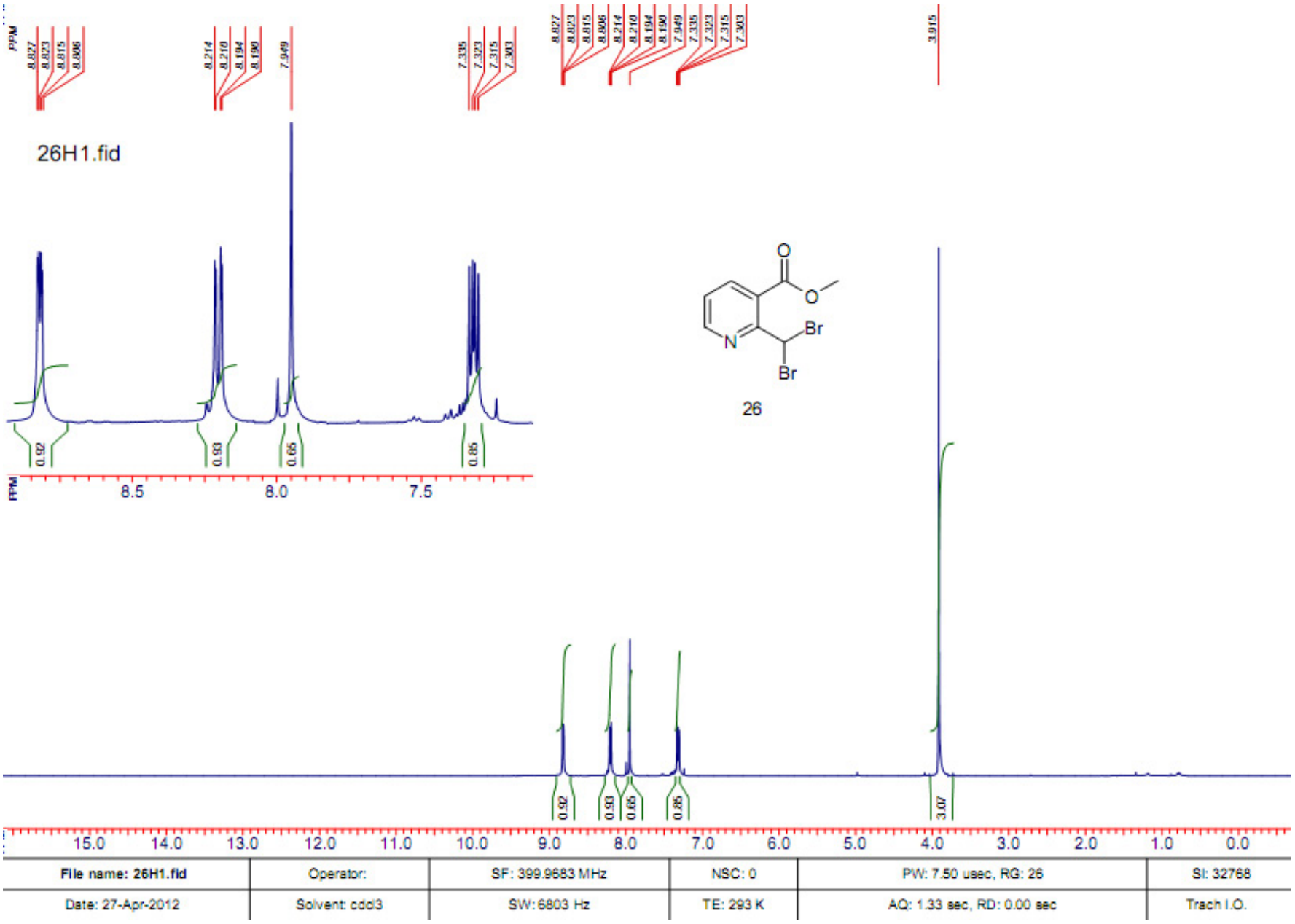

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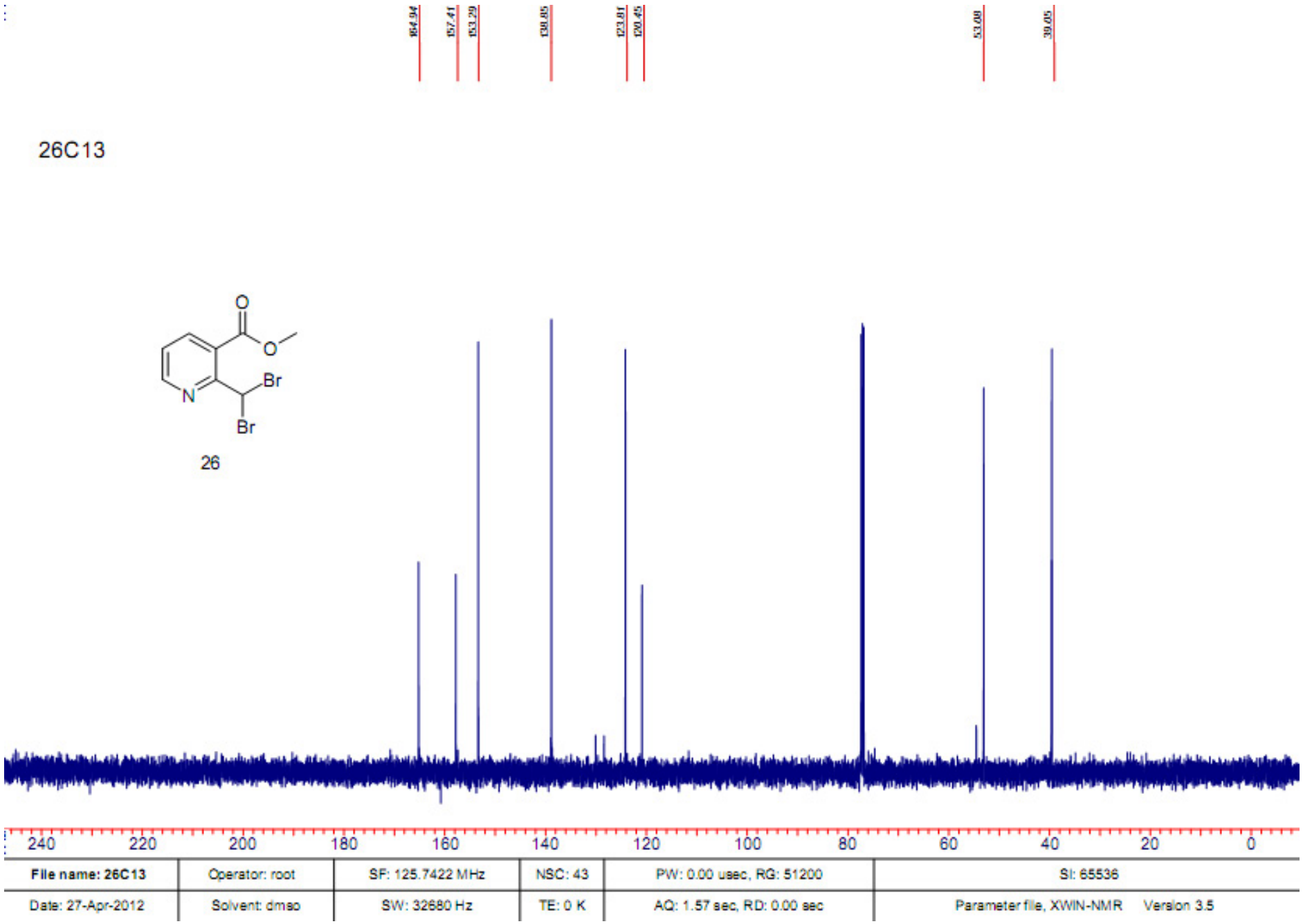
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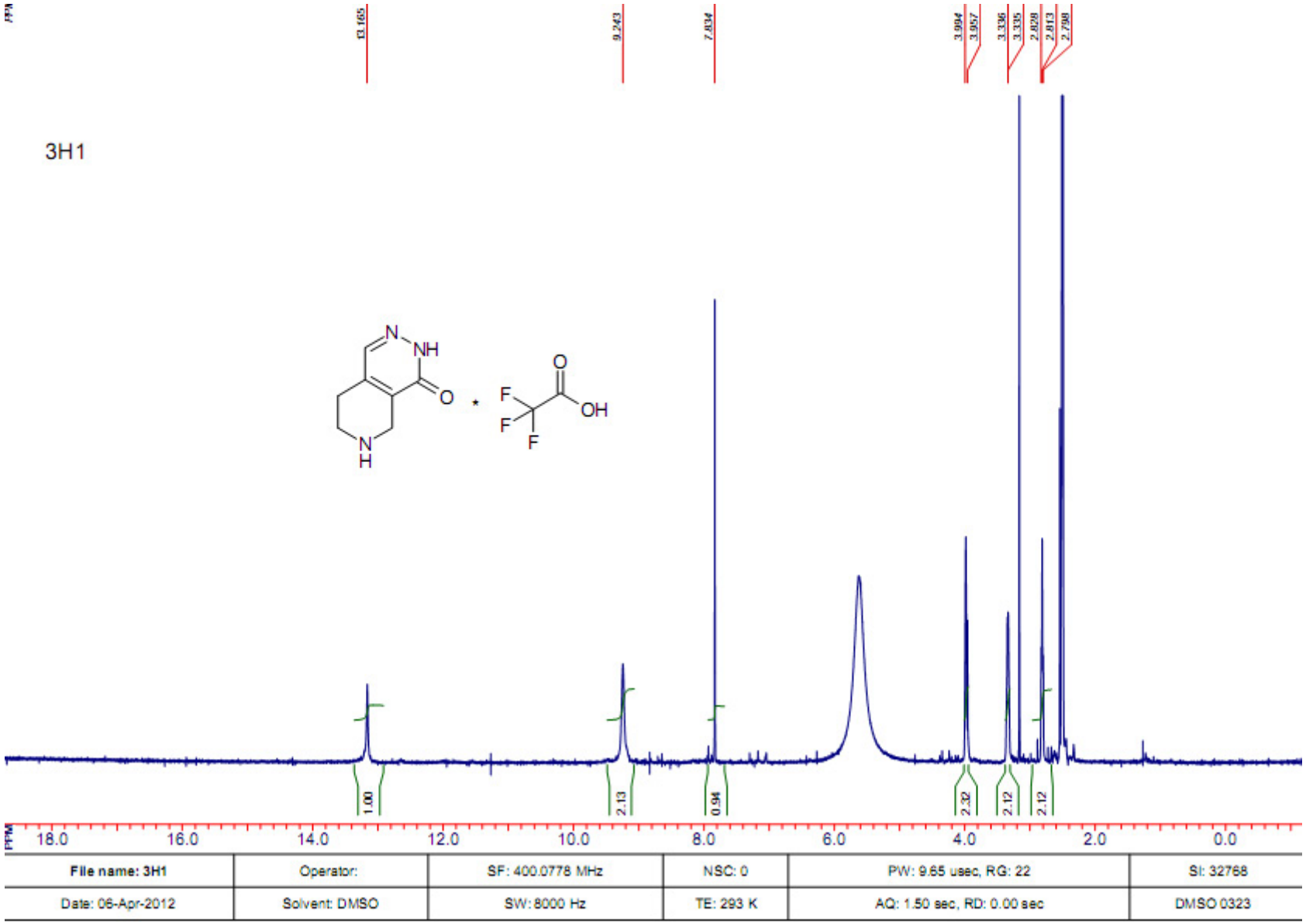
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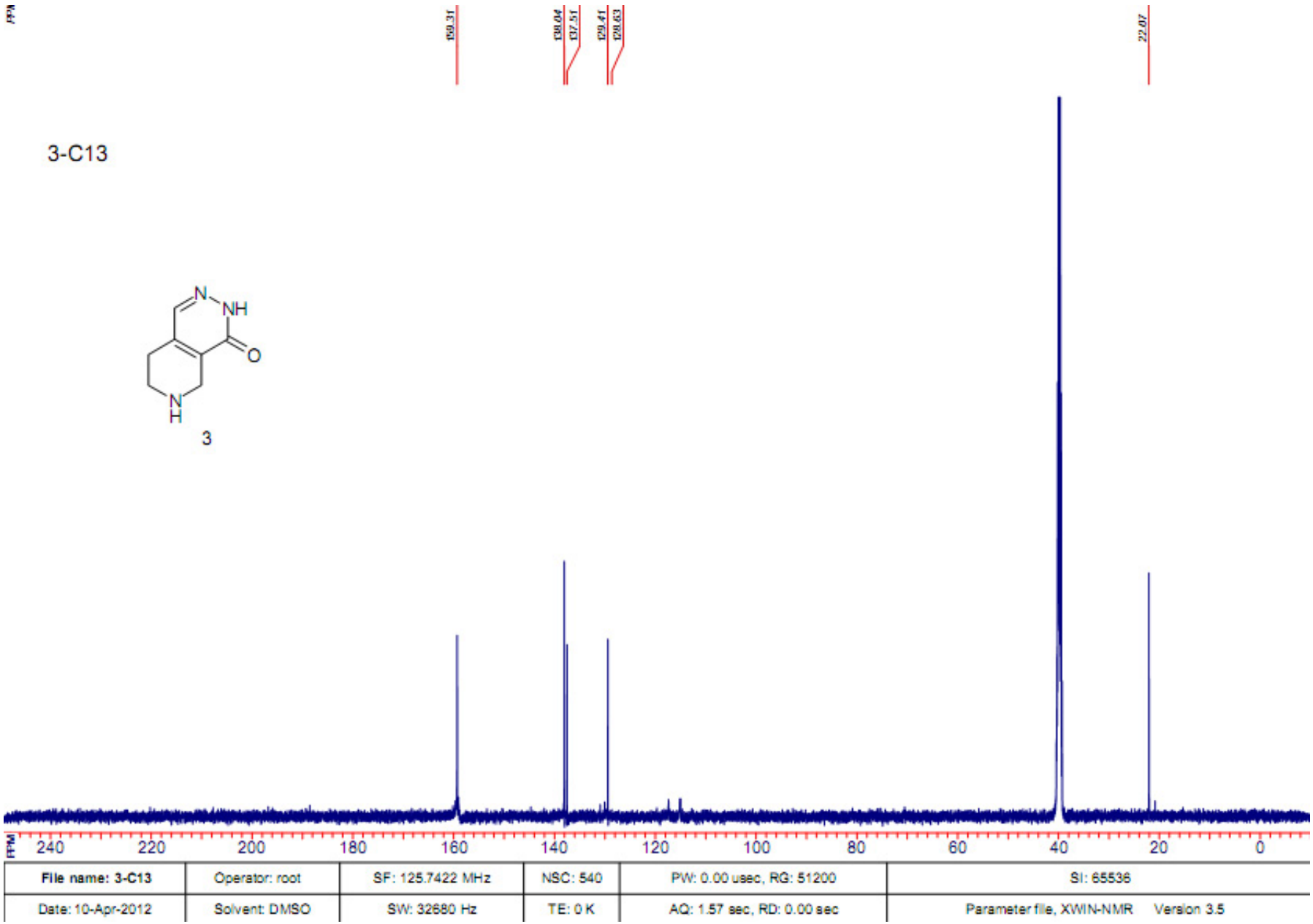
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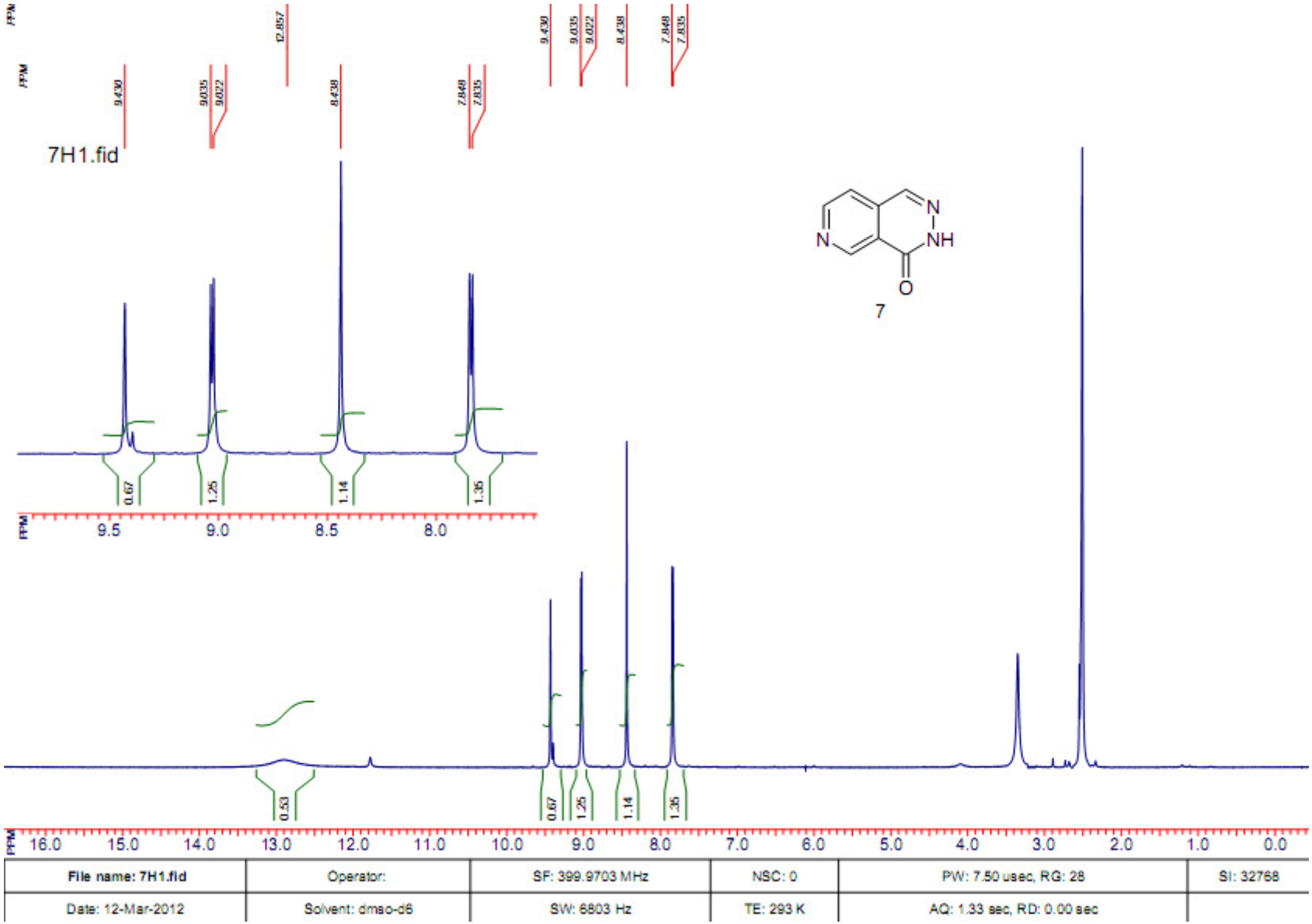
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12.0
11.0
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0.0
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SI: 32768
Date: 12-Mar-2012
Solvent: dmso-d6
SW: 6803 Hz
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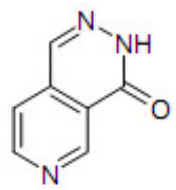
119.43

7-C13



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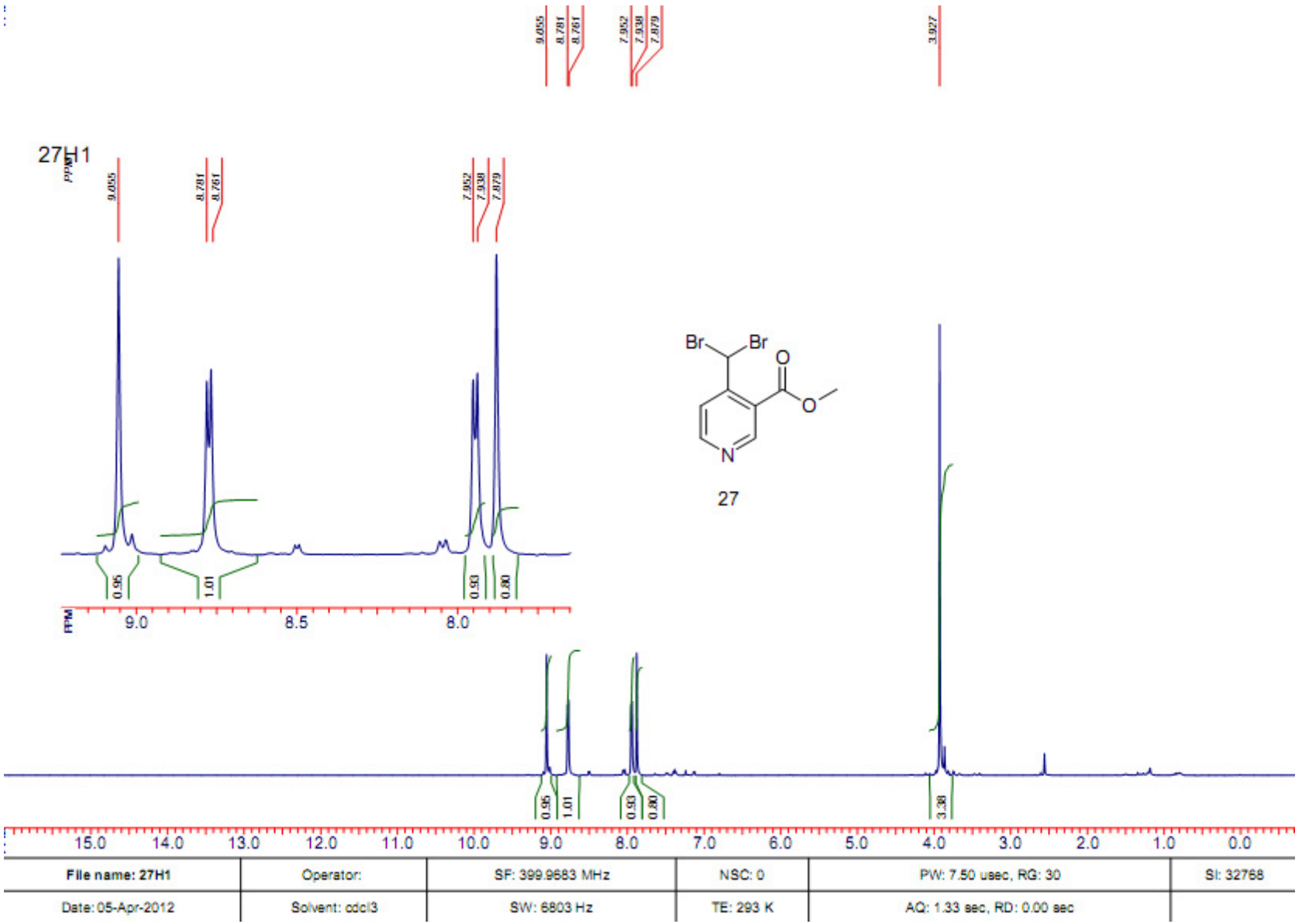
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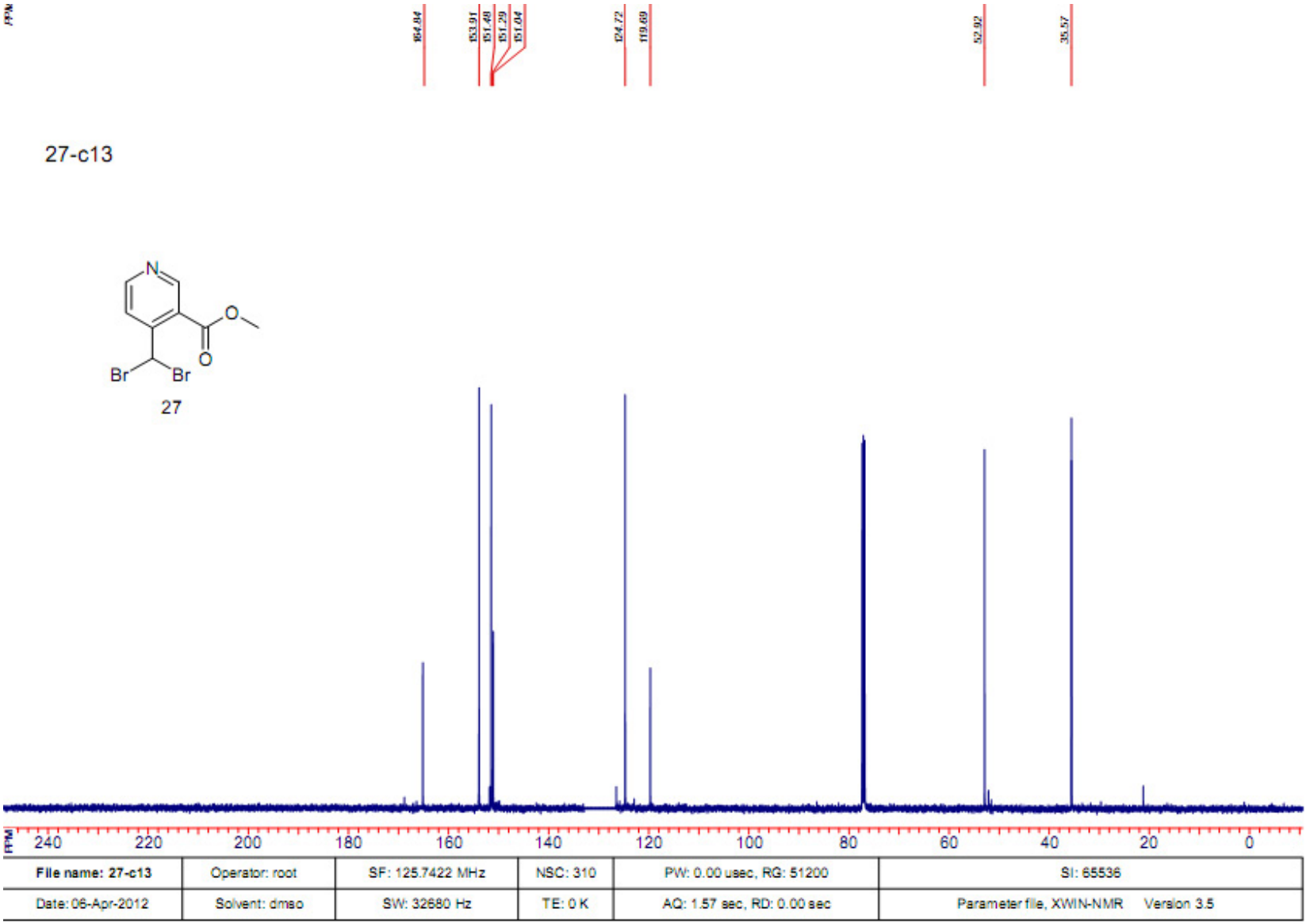
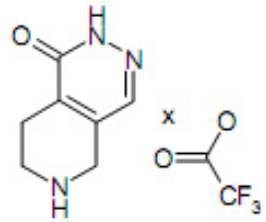
Br
Br
O
O
N
27
0.95
1.01
0.93
0.80
3.38
PPM
9.0
8.5
8.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
File name: 27H1
Operator:
SF: 399.9683 MHz
NSC: 0
PW: 7.50 usec, RG: 30
SI: 32768
Date: 05-Apr-2012
Solvent: cdcl3
SW: 6803 Hz
TE: 293 K
AQ: 1.33 sec, RD: 0.00 sec

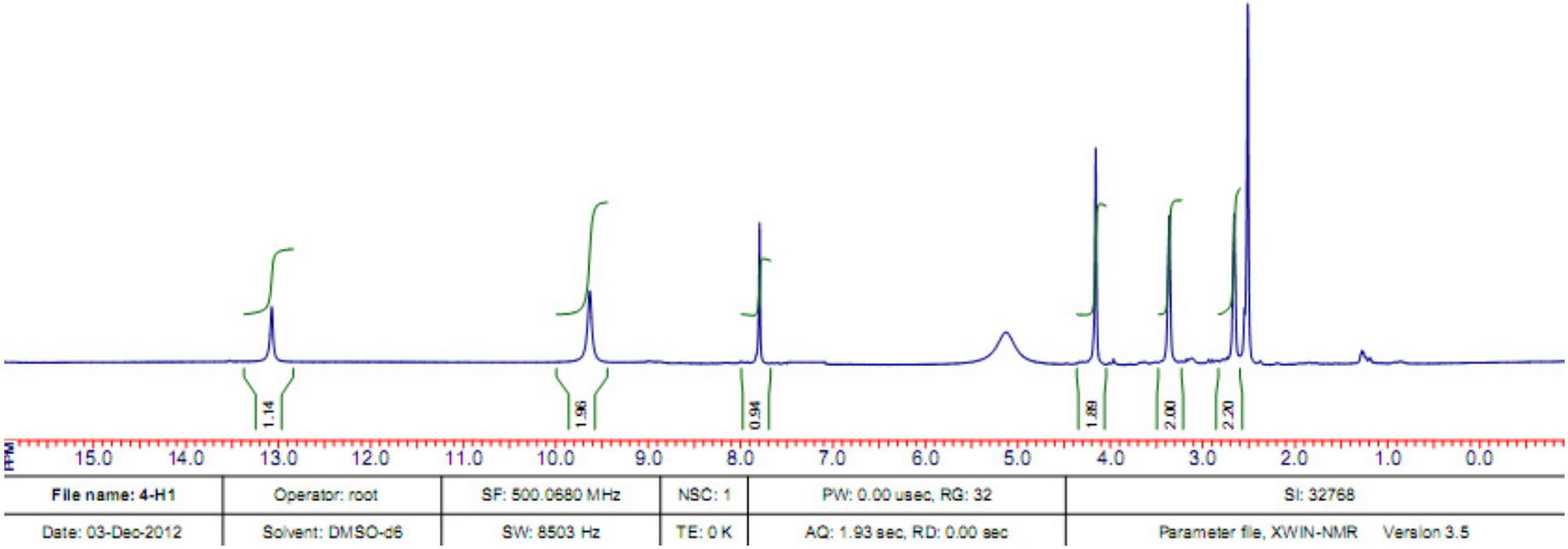

164.84
153.91
151.48
151.29
151.04
124.72
119.69
52.92
35.57
27-c13
N
O
O
Br
Br
27
240
220
200
180
160
140
120
100
80
60
40
20
0
File name: 27-c13
Operator: root
SF: 125.7422 MHz
NSC: 310
PW: 0.00 usec, RG: 51200
SI: 65536
Date: 06-Apr-2012
Solvent: dmso
SW: 32680 Hz
TE: 0 K
AQ: 1.57 sec, RD: 0.00 sec
Parameter file, XWIN-NMR Version 3.5

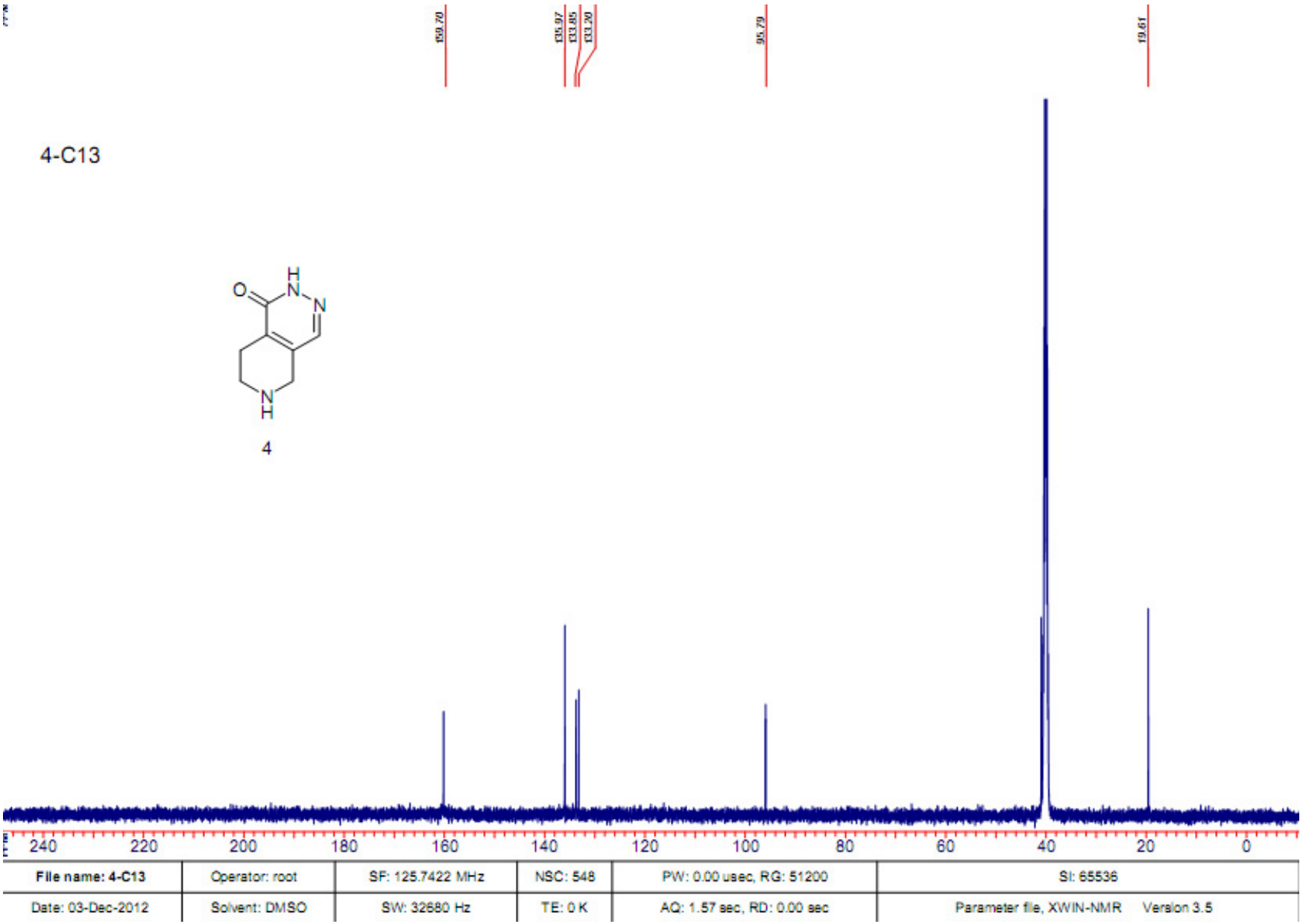

13.071
9.624
7.794
4.158
3.377
3.363
3.355
2.673
2.659
2.650

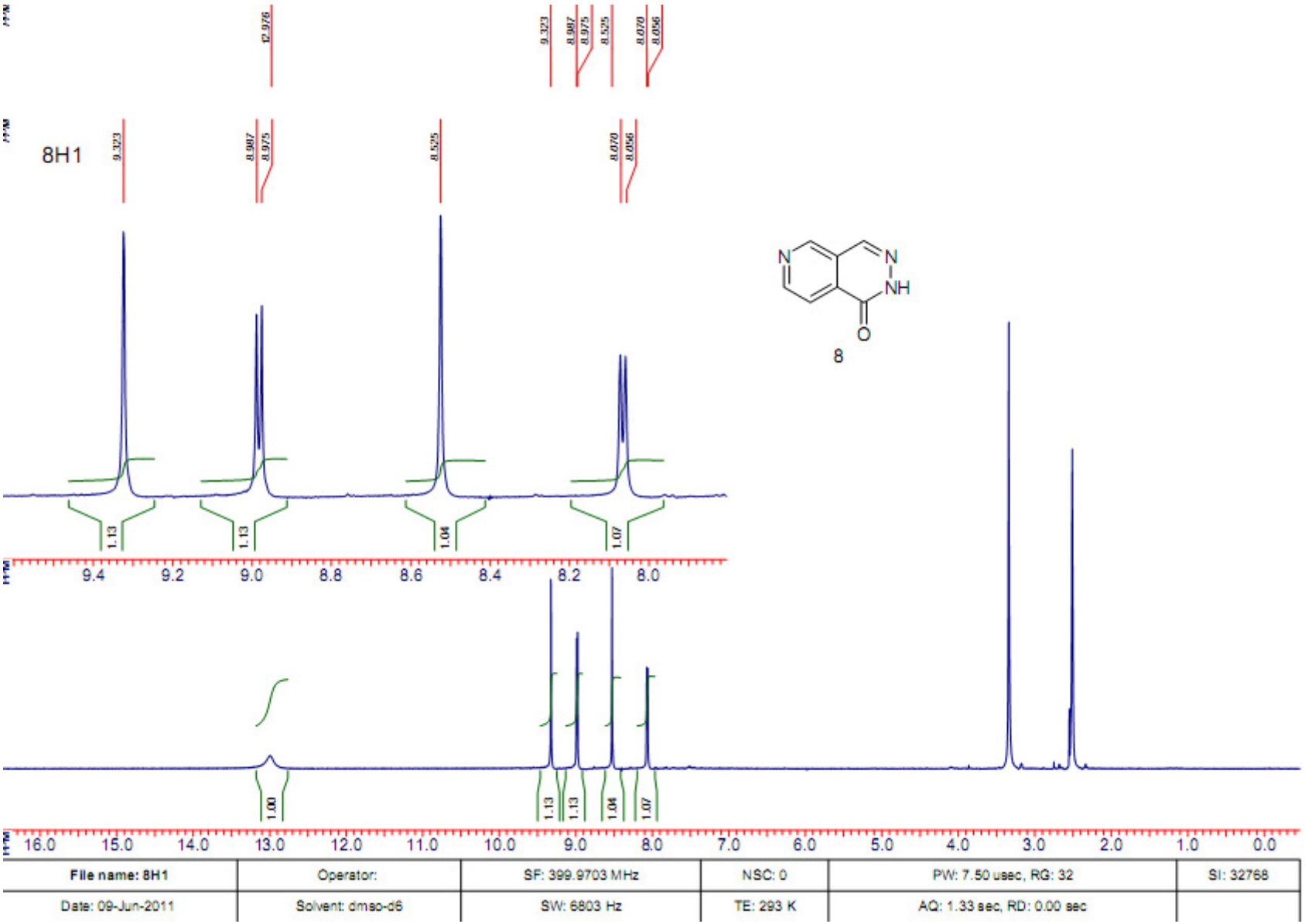
4-H1

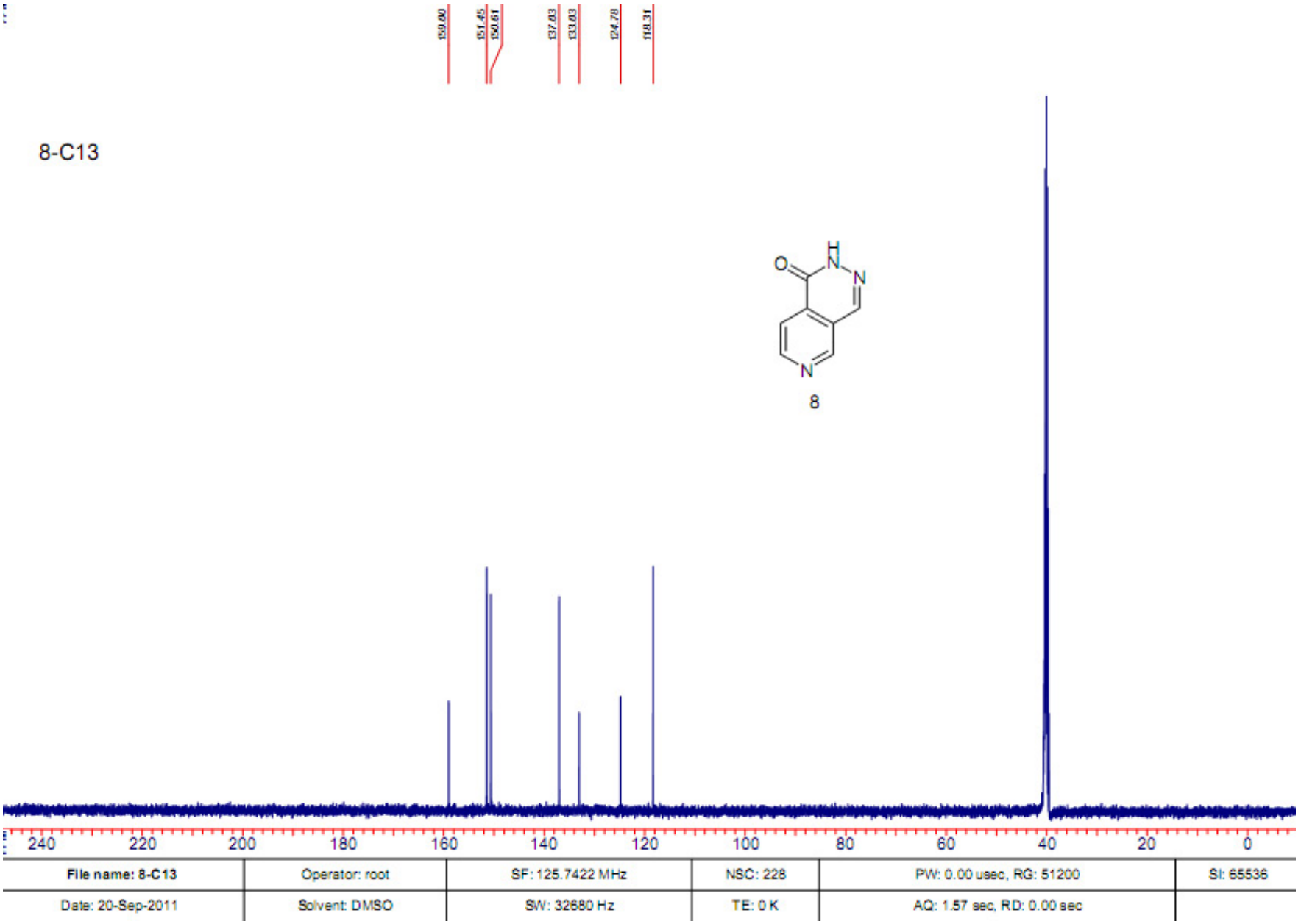

O
H
N
N
N
H
x
O
O
CF3

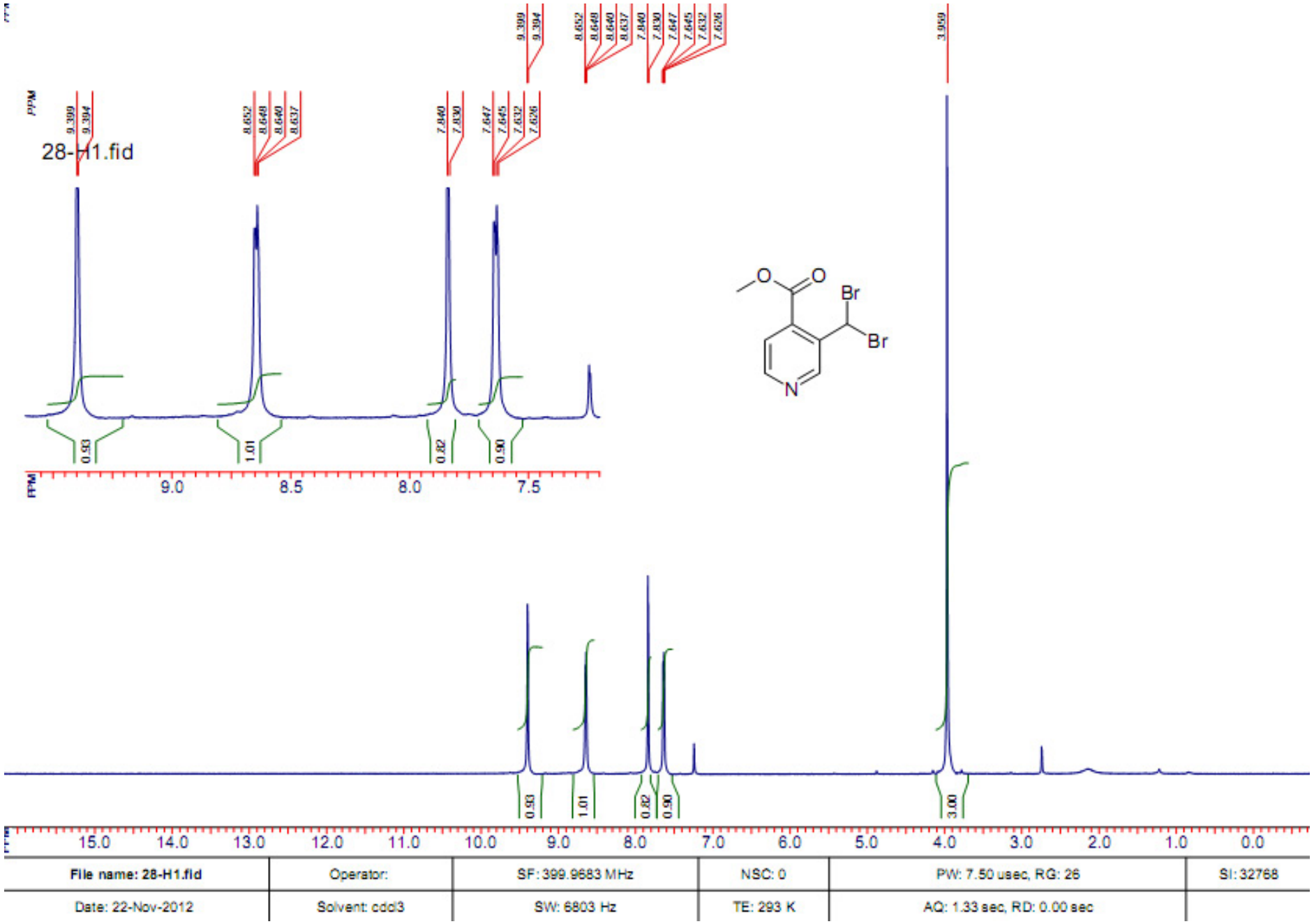
4

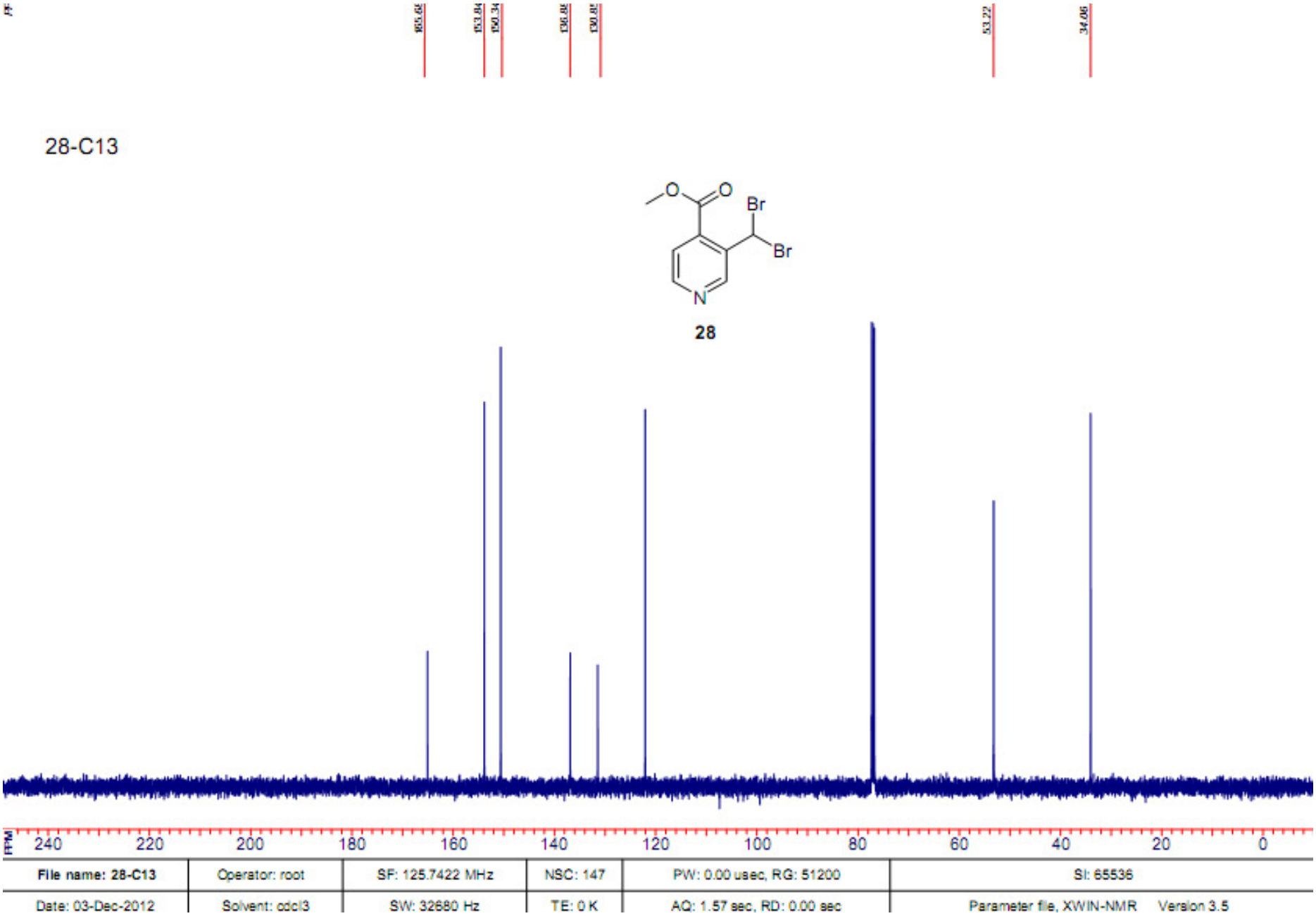

1.14
1.96
0.94
1.89
2.00
2.20
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
File name: 4-H1
Operator: root
SF: 500.0680 MHz
NSC: 1
PW: 0.00 usec, RG: 32
SI: 32768
Date: 03-Dec-2012
Solvent: DMSO-d6
SW: 8503 Hz
TE: 0 K
AQ: 1.93 sec, RD: 0.00 sec
Parameter file, XWIN-NMR Version 3.5


159.70
135.97
133.85
133.20
95.79
19.61
4-C13
O
H
N
N
N
H
4
240
220
200
180
160
140
120
100
80
60
40
20
0
File name: 4-C13
Operator: root
SF: 125.7422 MHz
NSC: 548
PW: 0.00 usec, RG: 51200
SI: 65536
Date: 03-Dec-2012
Solvent: DMSO
SW: 32680 Hz
TE: 0 K
AQ: 1.57 sec, RD: 0.00 sec
Parameter file, XWIN-NMR Version 3.5


8H1
12.976
9.323
8.987
8.975
8.525
8.070
8.056
N
N
NH
O
8
1.13
1.13
1.04
1.07
1.00
1.13
1.13
1.04
1.07
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
File name: 8H1
Operator:
SF: 399.9703 MHz
NSC: 0
PW: 7.50 usec, RG: 32
SI: 32768
Date: 09-Jun-2011
Solvent: dmso-d6
SW: 6803 Hz
TE: 293 K
AQ: 1.33 sec, RD: 0.00 sec


159.00
151.45
150.61
137.03
133.03
124.78
118.31
8-C13
O
H
N
N
N
8
240
220
200
180
160
140
120
100
80
60
40
20
0
File name: 8-C13
Operator: root
SF: 125.7422 MHz
NSC: 228
PW: 0.00 usec, RG: 51200
SI: 65536
Date: 20-Sep-2011
Solvent: DMSO
SW: 32680 Hz
TE: 0 K
AQ: 1.57 sec, RD: 0.00 sec


28-H1.fid
9.399
9.394
8.652
8.648
8.640
8.637
7.840
7.830
7.647
7.645
7.632
7.626
3.959
O
O
Br
Br
N
0.93
1.01
0.82
0.90
3.00
PPM
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
File name: 28-H1.fid
Operator:
SF: 399.9683 MHz
NSC: 0
PW: 7.50 usec, RG: 26
SI: 32768
Date: 22-Nov-2012
Solvent: cdcl3
SW: 6803 Hz
TE: 293 K
AQ: 1.33 sec, RD: 0.00 sec


165.68
153.84
150.34
136.88
130.85
53.22
34.06
28-C13
O
O
Br
Br
N
28
240
220
200
180
160
140
120
100
80
60
40
20
0
File name: 28-C13
Operator: root
SF: 125.7422 MHz
NSC: 147
PW: 0.00 usec, RG: 51200
SI: 65536
Date: 03-Dec-2012
Solvent: cdcl3
SW: 32680 Hz
TE: 0 K
AQ: 1.57 sec, RD: 0.00 sec
Parameter file, XWIN-NMR Version 3.5