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Trapping of the Putative Cationic Intermediate in the Morin Rearrangement with Carbon Nucleophiles

John Freed, David H. Hart*, and Nabi A. Magomedov
Department of Chemistry, The Ohio State University, 100 W. 18th Ave., Columbus, Ohio 43210

Supporting Material

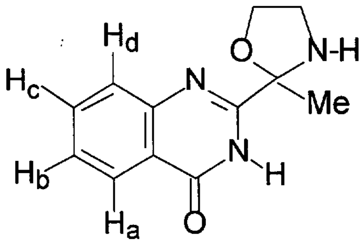
1. General Procedures for Experimental Section of Text and Supporting Material.
2. Procedures for the preparation of selected compounds presented in the text.
3. ^{1}H NMR and ^{13}C NMR spectra of selected compounds (all compounds lacking combustion analysis and many for which combustion analyses were obtained).
4. Selected crystallographic data for compounds **5**, **19** and **31**.

1. General Procedures

All melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were obtained using a Perkin-Elmer 241 polarimeter at the sodium D line (1 mL sample cell, concentration *c* reported in g/100 mL). Infrared spectra were taken using a Perkin-Elmer 1600 (FT-IR) instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-250, Bruker AM-300, Bruker AC-300, or Bruker AC-500 spectrometers and are recorded in parts per million from internal chloroform, benzene, acetonitrile, acetone, or dimethylsulfoxide on the δ scale. ^{1}H NMR spectra are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants in hertz, integration, interpretation]. ^{13}C NMR spectra are reported as follows: chemical shift (multiplicity determined from Distortionless Enhancement by Polarization Transfer (DEPT) spectra). Mass-spectra were obtained on Kratos MS-30 or Kratos VG70-250s instruments at an ionization energy of 70 eV. Compounds for which an exact mass is reported exhibited no significant peaks at *m/z* greater than that of the parent ion. Combustion analyses were performed by *Atlantic Microlab*, Norcross, GA.

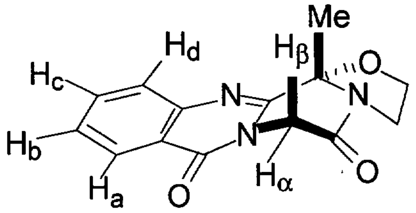
Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether, benzene and triethylamine were distilled from sodium metal; dichloromethane, toluene, acetonitrile, dimethylformamide, and dimethylsulfoxide were distilled from calcium hydride. Reactions requiring an inert atmosphere were run under argon. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM Laboratory or Whatman silica gel (240-400 mesh). The abbreviations used in this dissertation follow the guidelines suggested by the *Journal of Organic Chemistry* (1999). The order of experimental procedures follows their order of appearance in the text. References 28-30 are included at the end of this material. Other references appear in the published text of this article.

2. Procedures for Selected Compounds.

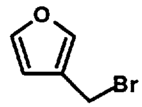


(±)-2-(2-Methyl-2-oxazolidinyl)-4(3*H*)-quinazolinone (ii). To a supension of 1.675 g (8.90 mmol) of 2-acetylquinazolinone in 50 mL of benzene was added, in one portion, 1.07 mL (17.80

mmol) of freshly distilled ethanolamine at room temperature. The reaction mixture was brought to reflux under Dean-Stark conditions. The starting material rapidly dissolved and a product started to precipitate as white needles. After 1 h of reflux, starting material was completely consumed as judged by TLC (silica gel, EtOAc). The reaction mixture was cooled to room temperature. Filtration of the reaction mixture gave 1.30 g (68%) of pure *N*,*O*-acetal as white needles. The mother liquor was washed with four 15-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to provide additional 0.62 g (26%) of pure *N*,*O*-acetal **ii** (by NMR) as a light yellow crystalline solid: mp 190-191 °C (EtOAc); IR (KBr) 3423, 3184, 2948, 2880, 1656, 1604, 1434, 1336, 1081, 1054 cm^{-1}; ^1H NMR (DMSO-d^6, 300 MHz) δ 2.28 (s, 3H, CH_3), 3.52-3.55 (m, 2H, NCH_2), 3.69-3.75 (m, 2H, OCH_2), 5.01 (t, *J* = 6.6 Hz, 1H, $N\underline{H}CH_2$), 7.57 (ddd, *J* = 8.2 Hz, 7.0 Hz, 1.2 Hz, 1H, H_b), 7.77 (ddd, *J* = 8.2 Hz, 1.2 Hz, 0.6 Hz, 1H, H_d), 7.85 (ddd, *J* = 8.2 Hz, 7.0 Hz, 1.4 Hz, 1H, H_c), 8.17 (ddd, *J* = 8.2 Hz, 1.4 Hz, 0.5 Hz, 1H, H_a), 11.69 (bs, 1H, NHCO); ^{13}C NMR (DMSO-d^6, 75.5 MHz) δ 12.9 (q), 54.6 (t), 61.0 (t), 122.4 (s), 126.0 (d), 127.6 (d), 128.0 (d), 134.5 (d), 148.0 (s), 149.8 (s), 160.7 (s), 160.9 (s); mass-spectrum (EI), *m/z* (relative intensity) 231 (M^+, 4), 201 (14), 200 (100), 173 (35), 145 (5), 119 (4), 90 (10), 86 (10), 45 (11), 42 (16); exact mass calcd. for $C_{12}H_{13}N_3O_2$ *m/z* 231.1008, found *m/z* 231.1017. Anal. calcd. for $C_{12}H_{13}N_3O_2$: C, 62.37; H, 5.67. Found: C, 62.37; H, 5.74.



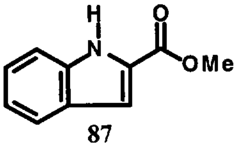
(±)-2,3-Dihydro-13b-methyloxazolo[2',3':3,4]pyrazino[2,1-*b*]quinazoline-5,8(6*H*, 13b*H*)-dione (iii). To a suspension of 0.91 g (3.96 mmol) of *N*,*O*-acetal **195** in 20 mL of dry THF was added 1.00 g (7.25 mmol) of anhydrous K_2CO_3 followed by addition of 380 μL (4.36 mmol) of α-bromoacetyl bromide in one portion at room temperature. The reaction mixture was stirred at room temperature for 25 min, and then 15 mL of water was added followed by the addition of 0.5 mL of 40% aqueous *n*-Bu_4NOH, as a phase-transfer catalyst, in one portion. The reaction mixture was stirred for additional 5 h, and then partitioned between 100 mL of EtOAc and 30 mL of water. The organic layer was separated, washed with two 30-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to give an orange semisolid residue. The residure was flash chromatographed over 80 g of silica gel (EtOAc) to give 0.34 g (45%) of 2-acetylquinazolinone and 0.37 g (35%) of the desired tetracyclic product **iii** as a white crystalline solid: mp 216-216.5 °C ($CHCl_3$/hexane); IR (KBr) 2982, 2887, 1689, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76 (s, 3H, CH_3), 3.60-3.69 (m, 1H, C$\underline{H}$H), 4.06-4.17 (m, 2H, CH_2), 4.21 (d, J = 17.7 Hz, 1H, H_β), 4.31-4.39 (m, 1H, CH$\underline{H}$), 5.37 (d, J = 17.7 Hz, 1H, H_α), 7.51 (ddd, J = 8.0 Hz, 7.0 Hz, 1.3 Hz, 1H, H_b), 7.77 (ddd, J = 8.2 Hz, 7.0 Hz, 1.4 Hz, 1H, H_c), 7.83 (ddd, J = 8.2 Hz, 1.2 Hz, 0.5 Hz, 1H, H_d), 8.26 (dm, J = 8.0 Hz, 1H, H_a); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.1 (q), 43.1 (t), 45.6 (t), 65.4 (t), 90.2 (s), 120.4 (s), 126.8 (d), 127.7 (d), 127.9 (d), 134.9 (d), 146.8 (s), 151.2 (s), 160.2 (s), 160.8 (s); mass-spectrum (EI), *m/z* (relative intensity) 271 (M^+, 16), 257 (13), 256 (100), 229 (8), 228 (58), 158 (6), 145 (9), 76 (8), 56 (15), 43 (10); exact mass calcd. for $C_{14}H_{13}N_3O_3$ *m/z* 271.0957, found *m/z* 271.1016. Anal. calcd. for $C_{14}H_{13}N_3O_3$: C, 61.79; H, 4.83. Found: C, 61.75; H, 4.82.



80

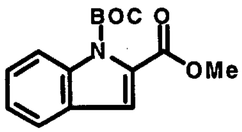
3-(Bromomethyl)furan.[23] A 250 mL round-bottomed flask, fitted with a magnetic stirrer, was charged with 4.25 g (44 mmol) of 3-(hydroxymethyl)furan, 17.5 g (52 mmol) of carbon tetrabromide, and 70 mL of CH_2Cl_2. The resulting solution was cooled to 0 °C in an ice-water bath, and then 17.5 g (68 mmol) of Ph_3P was added as a solid in portions over 2-3 min. A white precipitate formed within several minutes, and then the reaction mixture was stirred at the bath temperature for 6 h. Subsequently, the mixture was concentrated *in vacuo* to give a solid residue, which was rinsed with 250 mL of diethyl ether. The solid was filtered and the ethereal solution was concentrated to give an orange liquid which was chromatographed over 30 g of flash silica gel (hexanes) to provide 3.71 g (54%) of 3-

(bromomethyl)furan as a clear liquid. The liquid was pure by ^{1}H NMR and was capable of being used directly in the next step. (Note: chromatography has to be performed as fast as possible due to the limited stability of the product on silica gel. In addition, due to the volatility of the product, the solvent collected in the evaporator trap must be collected and evaporated multiple times to collect all possible product): ^{1}H NMR (CDCl$_3$, 250 MHz) δ 7.48 (s, 1H), 7.41 (t, J = 1.6 Hz, 1H), 6.45 (s, 1H), 4.38 (s, 2H).



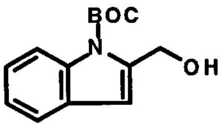
87

Methyl indole-2-carboxylate (iv).[28] Diazomethane was prepared initially, via use of an Aldrich Diazomethane Kit. A solution of 11.2 g (52 mmol) of Diazald in 100 mL of diethyl ether was added dropwise to a heated solution (65 °C) of 10 g (179 mmol) of KOH in 42 mL of EtOH-water (4:3). An ethereal solution of the diazomethane thus generated was distilled into a collecting flask cooled to below -20 °C in a sodium chloride-ice bath. The resulting ethereal solution of diazomethane was added to a stirred solution of 4.50 g (28 mmol) of indole-2-carboxylic acid in 70 mL of diethyl ether, causing immediate gas evolution. Following cessation of gas evolution, AcOH was added dropwise until no additional gas evolved. The reaction mixture was then transferred to a separatory funnel and was washed successively with 75 mL of saturated aqueous NaHCO$_3$ and 75 mL of water. The washes were back-extracted with 60 mL of diethyl ether and the combined extracts were dried (MgSO$_4$), filtered, and evaporated to give 4.87 g (100%) of methyl indole-2-carboxylate (**iv**) as a yellow solid which was pure by ^{1}H NMR: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.99 (s, 3H), 7.18 (t, J = 7.1 Hz, 1H), 7.26 (s, 1H), 7.35 (t, J = 7.2 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 9.18 (bs, 1H).



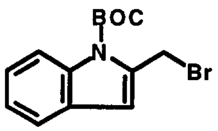
88

Methyl 1-(*tert*-butoxycarbonyl)indole-2-carboxylate (v).[29] A 250-mL round-bottomed flask was fitted with a magnetic stirrer and then charged with 4.87 g (27.7 mmol) of methyl indole-2-carboxylate and 85 mL of freshly distilled acetonitrile. Subsequently, 315 mg (2.8 mmol) of DMAP and 7.6 mL (33 mmol) of di-*t*-butyldicarbonate were added, immediately turning the solution deep red. The reaction mixture was permitted to stir overnight at room temperature. At this time, 1 mL (5 mmol) of 2-amino-5-diethylaminopentane was added to removed excess of BOC anhydride. The mixture was stirred for 15 min and then concentrated *in vacuo* to give an oily residue which was dissolved in 100 mL of CH_2Cl_2 and washed successively with 150 mL of 1 *M* HCl and 75 mL of water. The washes were back-extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 7.55 g (99%) of methyl *N*-Boc-indole-2-carboxylate (v) as a yellow solid which was pure by ^1H NMR and could be used directly in the next step. The solid was recrystallized from hexanes: mp 63-65 °C; IR (KBr) 3117, 2980, 2945, 1742, 1725, 1712, 1555, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.63 (s, 9H), 2.92 (s, 3H), 7.10 (s 1H), 7.26 (t, J = 7.1, 1H), 7.41 (t, J= 7.2, 1H), 7.61 (d, J = 8.5, 1H), 8.10 (d, J = 8.4, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (q, 3C), 52.8 (q), 85.0 (s), 115.3 (d), 122.6 (d), 123.7 (d), 127.2 (d), 129.7 (s), 130.8 (s), 138.3 (s), 149.7 (s), 162.8 (s), one aromatic CH (possibly at δ 115.3) was not observed due to magnetic equivalence; mass-spectrum (EI), *m/z* (relative intensity) 275 (M+, 13), 202 (37), 175 (88), 143 (51), 115 (51), 57 (100), 41 (48); exact mass calcd. for $C_{15}H_{17}NO_4$ *m/z* 275.1157, found *m/z* 275.1154.



89

1-(*tert*-Butoxycarbonyl)-2-hydroxymethylindole (vi).[30] A 250 mL flame-dried round-bottomed flask was fitted with a magnetic stirrer, charged with 6.58 g (24 mmol) of ester **v**, and then flushed with argon. Freshly distilled toluene (50 mL) was added via syringe and the resulting solution was cooled to -40 °C in a dry ice-acetone bath. Subsequently, 57 mL (57 mmol) of 1*M* DIBAL-H in hexanes was added dropwise via syringe over 20 min. The reaction mixture was allowed to stir for an additional 20 min and then 10 mL of MeOH was added dropwise over 3-4 min, followed by dropwise addition of 9 mL of water over 1-2 min. The reaction mixture was removed from the cold bath and allowed to stir for 15 min while warming. The resulting precipitate was filtered and rinsed several times with CH_2Cl_2. The filtrate was transferred to a separatory funnel and washed with 100 mL of water. The aqueous phase was back-extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow oily residue. Chromatography of the residue over 75 g of flash grade silica gel (hexanes-EtOAc, 5:1) afforded 3.95 g (67%) of the desired alcohol **vi** as a clear oil: IR (Neat) 3415, 2976, 2920, 1731, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.73 (s, 9H), 4.81 (s, 2H), 6.59 (s, 1H), 7.22 (t, $J = 7.1$ Hz, 1H), 7.29 (td, $J = 7.4, 1.3$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.99 (d, $J = 8.3$, 1H), OH not observed; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.7 (q, 3C), 59.4 (t), 85.5 (s), 110.1 (d), 116.1 (d), 121.3 (d), 123.5 (d), 124.8 (d), 129.5 (s), 136.7 (s), 140.8 (s), 151.8 (s); mass-spectrum (HREI), *m/z* (relative intensity) 247 (M^+, 5), 57 (100), 41 (72), 129 (67), 130 (55), 147 (42), 39 (39); exact mass calcd. for $C_{14}H_{17}NO_3$ *m/z* 247.1208, found *m/z* 247.1207.



90

1-Bromomethyl-2-(*tert*-butoxycarbonyl)indole (vii).[30] A 50-mL round-bottomed flask was fitted with a magnetic stirrer and charged with 475 mg (1.9 mmol) of the appropriate alcohol, 1.6 g (19 mmol) of LiBr, and 25 mL of CH_2Cl_2. Subsequently, 430 μL (3.1 mmol) of Et_3N and 240 μL (3.1 mmol) of methanesulfonyl chloride were added via syringe. The reaction mixture was stirred for 24 h. The mixture was transferred to a separatory funnel, diluted with 25 mL of CH_2Cl_2, and washed successively with 50 mL of water and 50 mL of saturated aqueous $NaHCO_3$. The washes were back-extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oily residue (bromide:chloride = 2:1 by crude ^{1}H NMR). The residue was dissolved in 20 mL of freshly distilled CH_3CN, and to the resulting solution was added 1.8 g (22 mmol) of LiBr. The suspension was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was partitioned in 60 mL of CH_2Cl_2-water (1:1). The organic phase was washed with 30 mL of water. The combined aqueous phases were back-extracted with CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated to give an oily residue. Chromatography of the residue over flash grade silica gel (hexanes-EtOAc, 20:1) afforded 355 mg (63%) of the desired bromide **vii** as a clear oil. IR (Neat) 3055, 2981, 2951, 1737, 1546, 1476, 1434 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74 (s, 9H), 4.94 (s, 2H), 6.70 (s, 1H), 7.23 (td, J = 7.7, 1.0 Hz, 1H), 7.33 (td, J = 7.3, 1.1 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.0 (t), 28.5 (q, 3C), 85.2 (s), 112.3 (d), 116.3 (d), 121.3 (d), 123.6 (d), 125.7 (d), 128.7 (s), 136.4 (s), 138.0 (s), 150.2 (s); mass-spectrum (HREI), *m/z* (relative intensity) 309 (M^+, 3), 57 (100), 130 (78), 41 (50), 174 (43); exact mass calcd. for $C_{14}H_{16}NO_2{}^{79}Br$ *m/z* 309.0365, found *m/z* 309.0368.

References

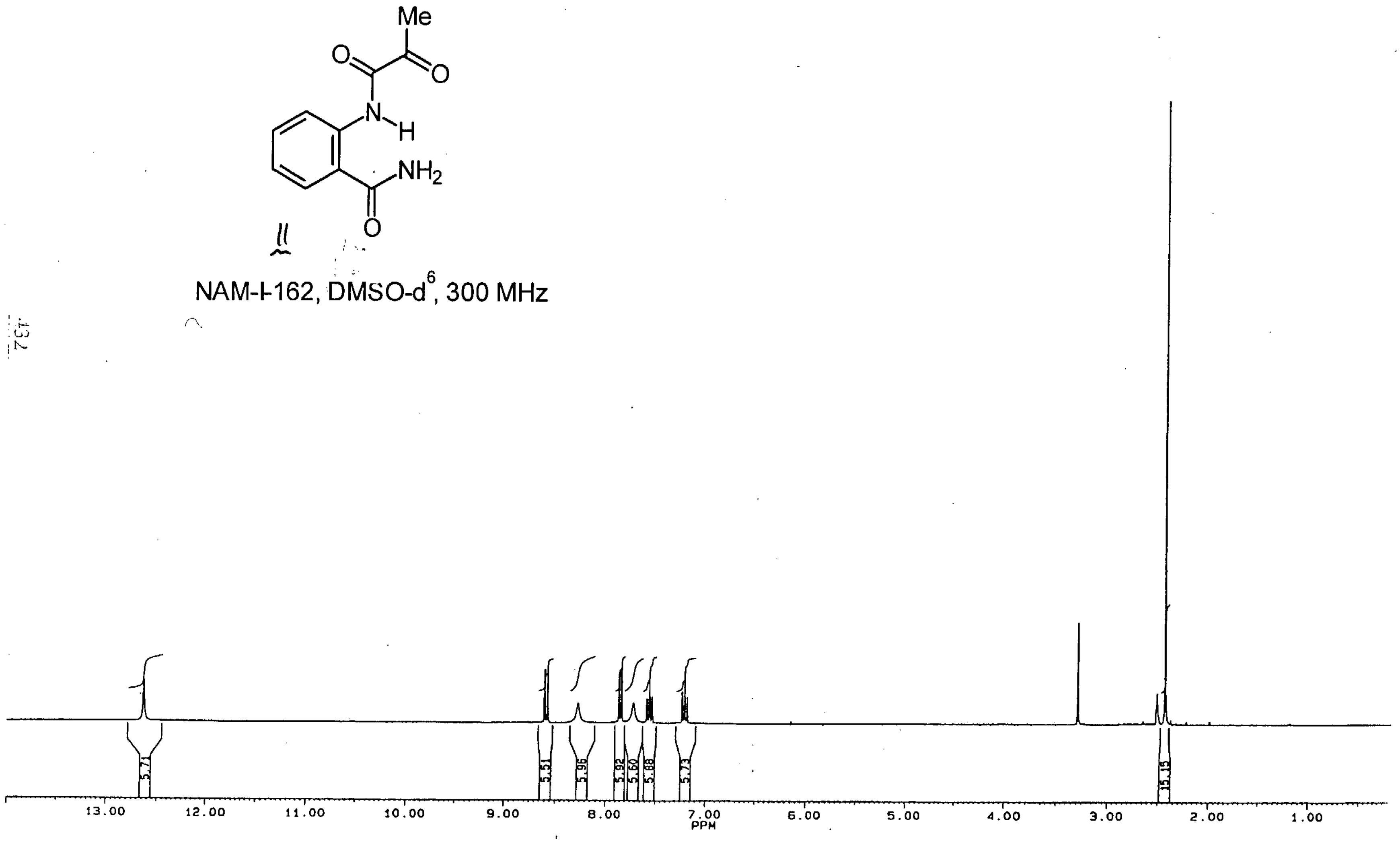
28. For other procedures for the preparation of this material see: Ciamician, G. *Chem. Ber.* **1888**, *21*, 1929. Also see reference 29b.

29. For other procedures for the preparation of this material see: (a) Coulton, S.; Gilchrist, T. L.; Graham, K. Tetrahedron 1997, 53, 791. (b) Boger, D. L.; Nishi, T. Bioorg. *Med. Chem.* **1995**, *3*, 67.

30. These materials have been described in a patent application. See Aquino, C. J.; Dezube, M.; Henke, B. R.; Brackeen, M.; Jeffs, P. W.; Suh, E. M.; Hirst, G. C.; Sugg, E. E.; Willson, T. M.; Momtahen, T. *Chem. Abstracts 124*:202316.

3. **^{1}H NMR and ^{13}C NMR Spectra** (see following pages)

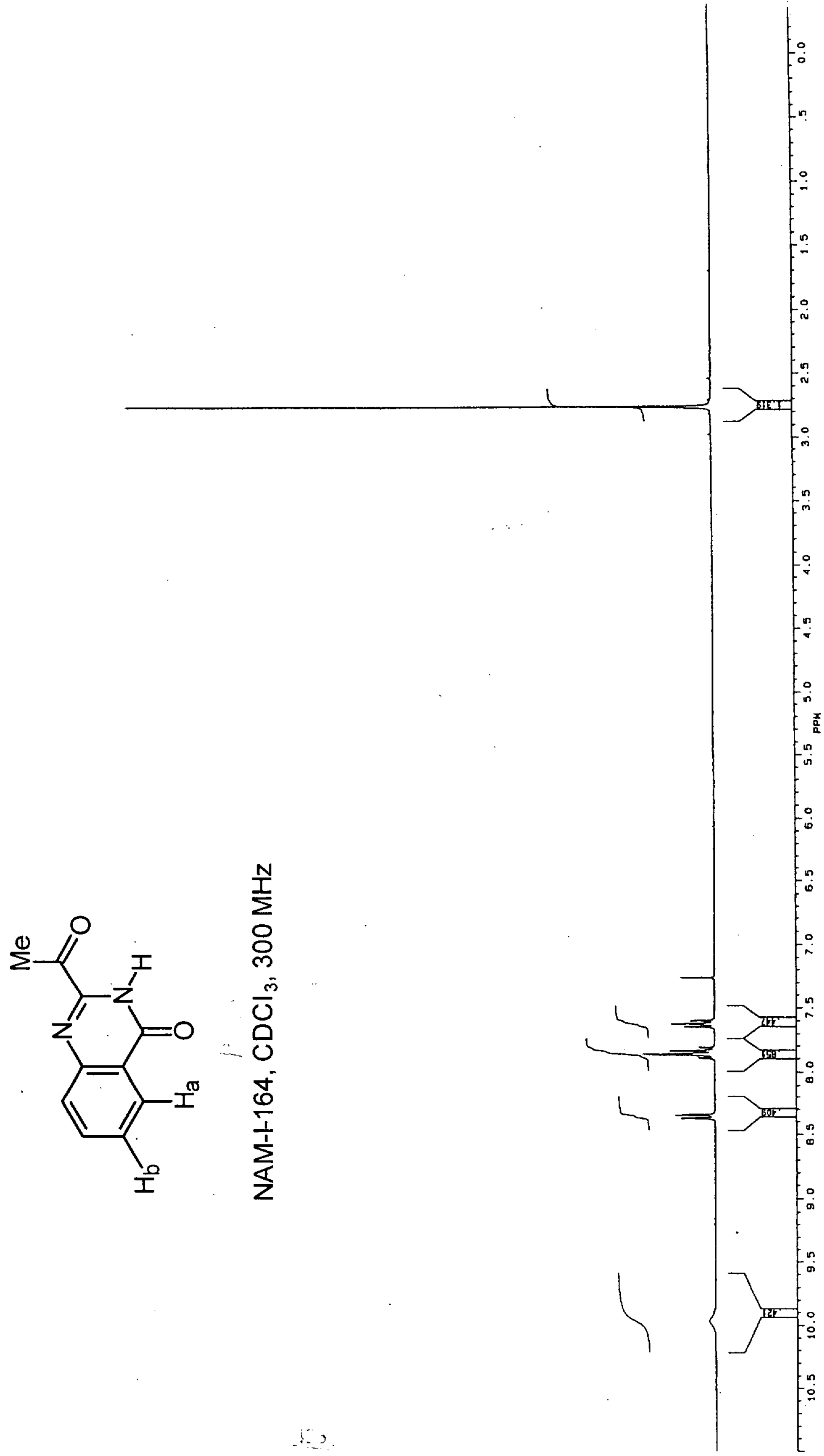
4. **X-Ray Crystallographic Data** (see following pages)



11

NAM-I-162, DMSO-d6, 300 MHz

432



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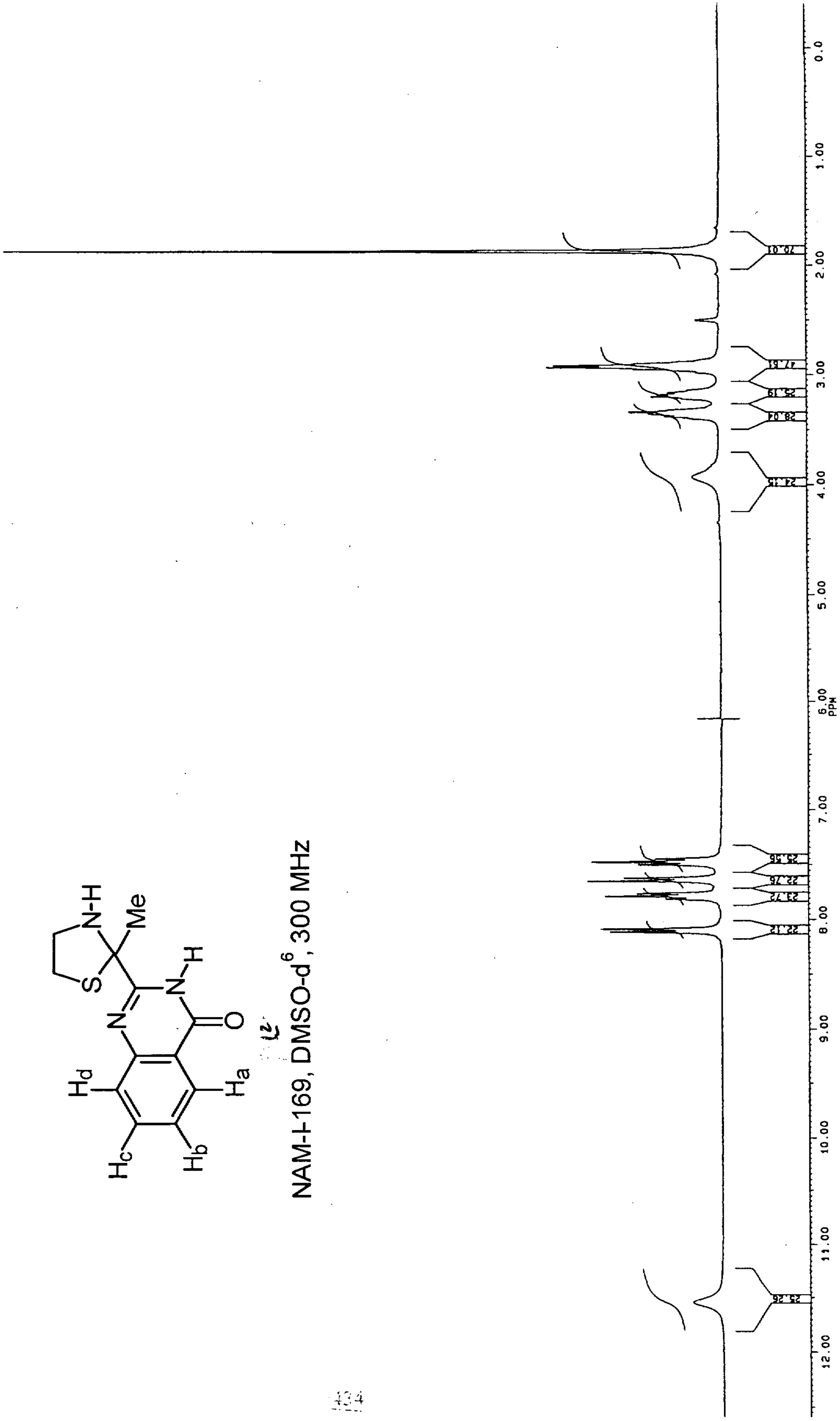
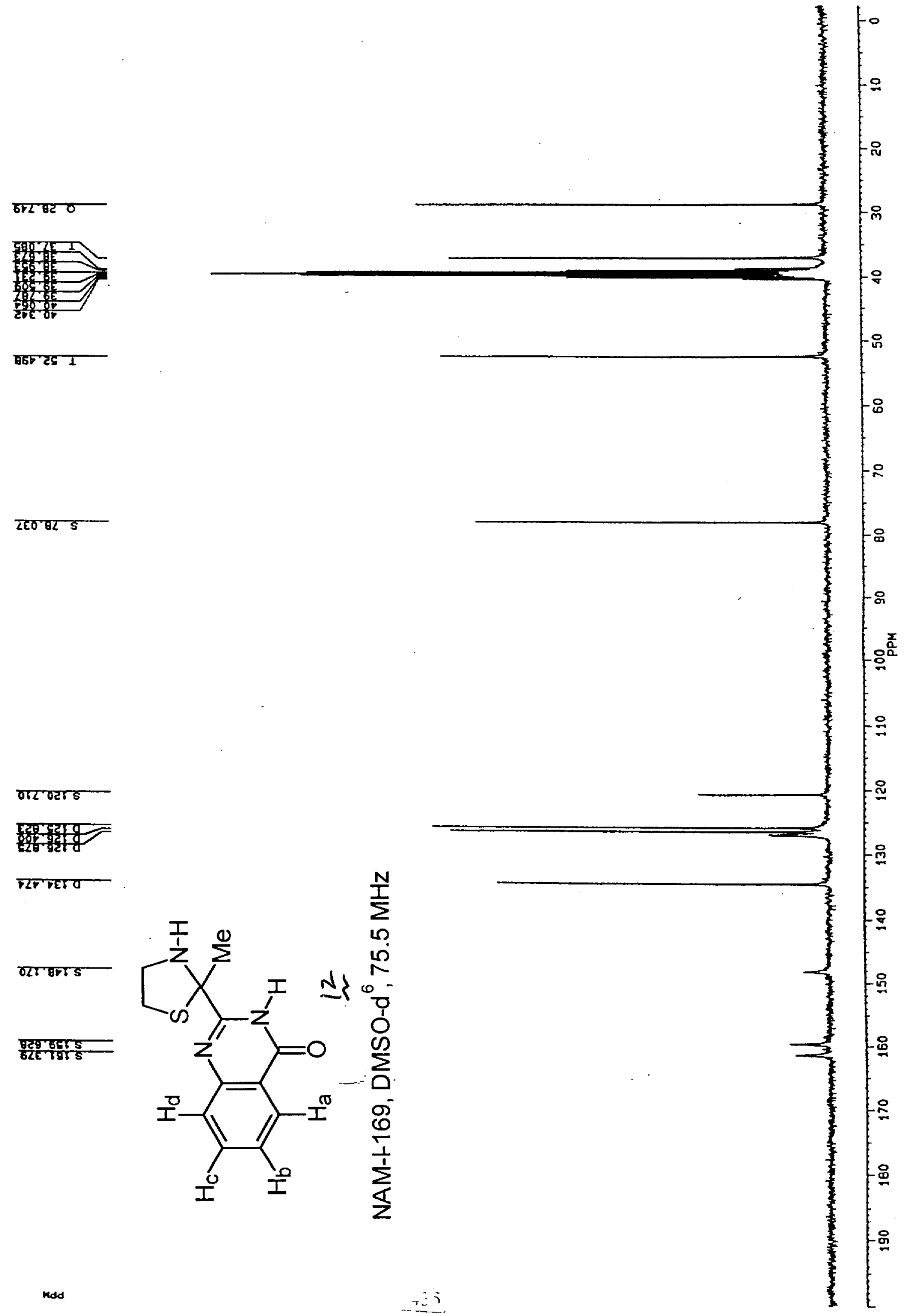


12

NAM-I-169, DMSO-d^6, 300 MHz

434



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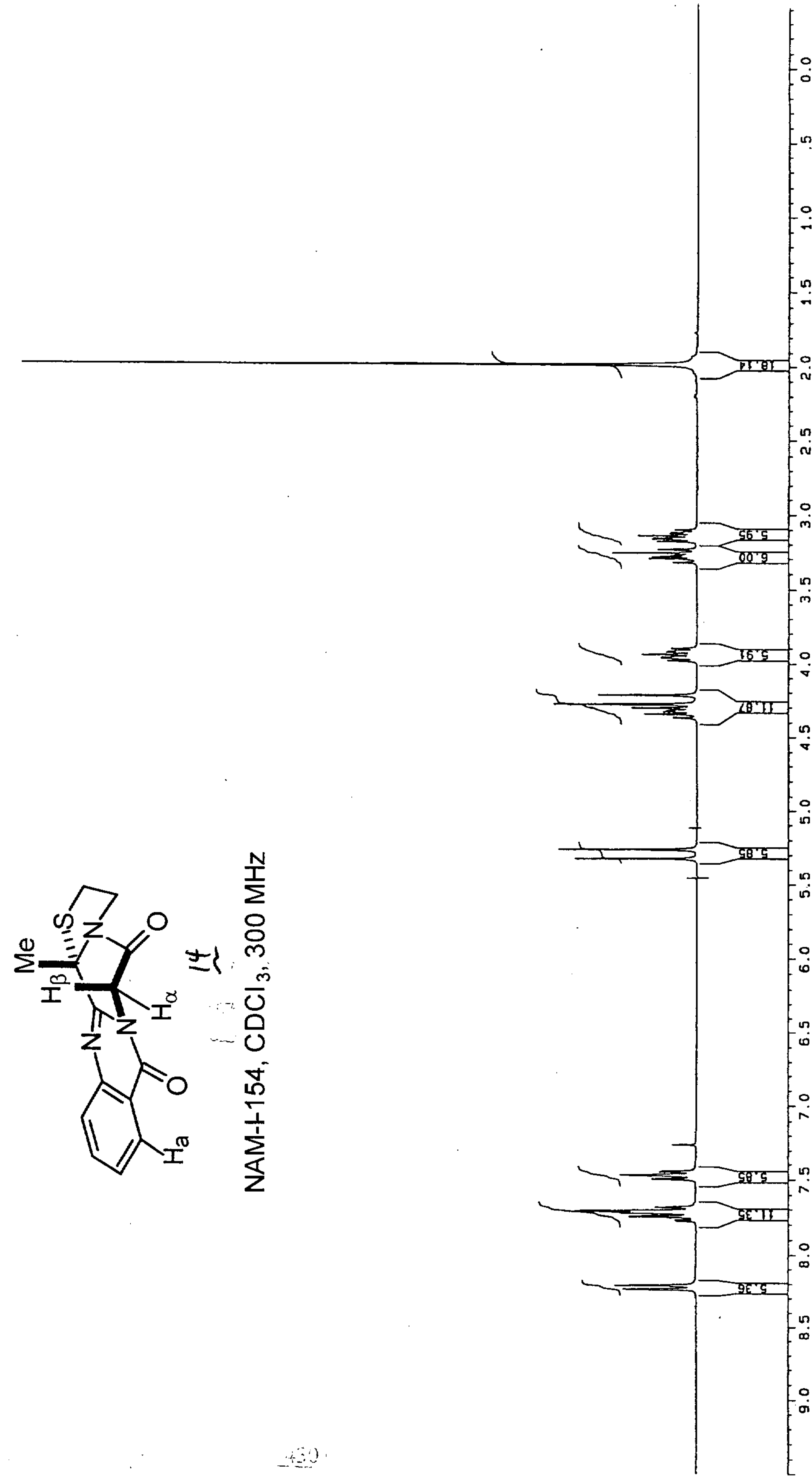

14

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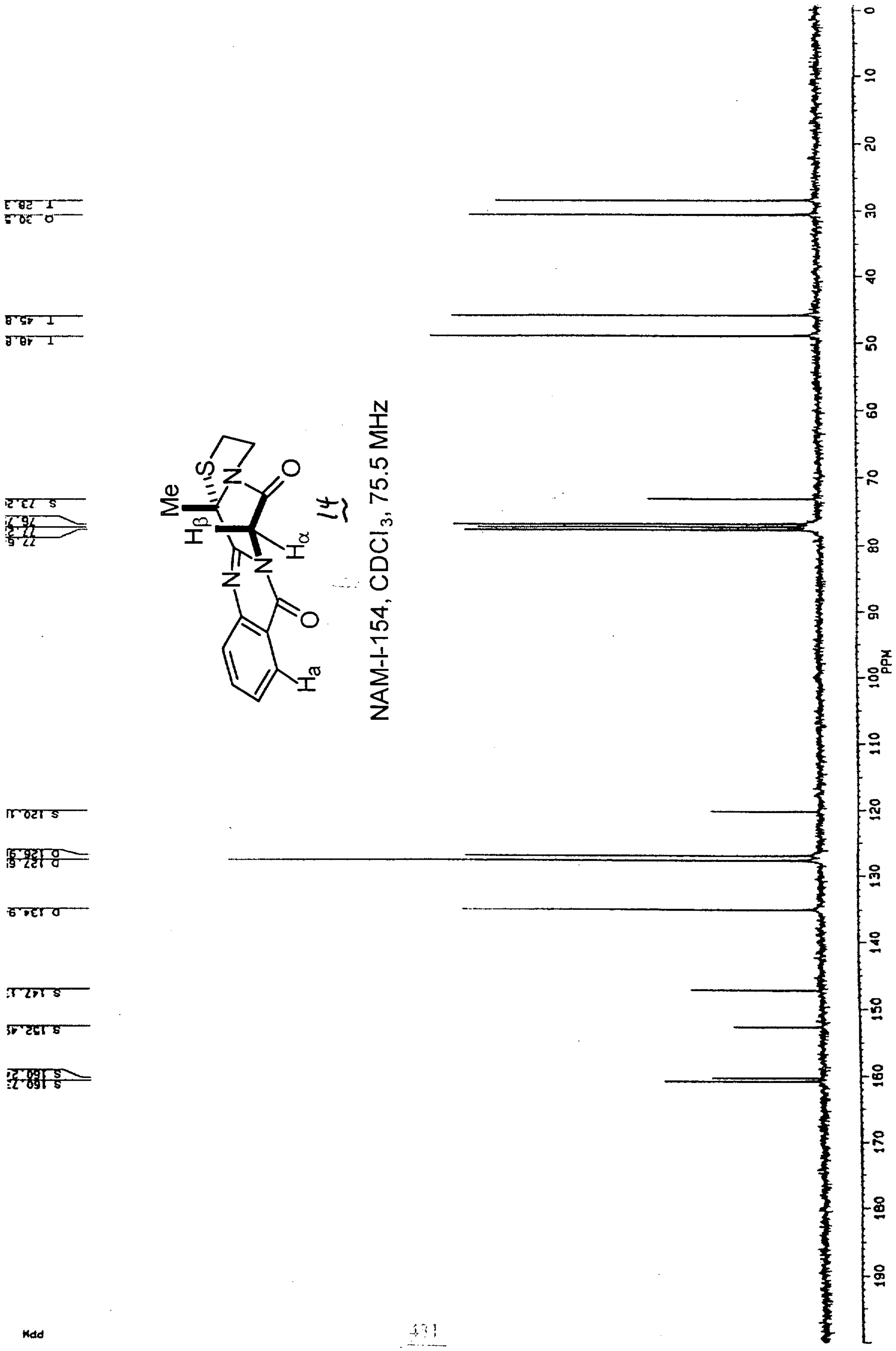
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77.1
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D 134.9
S 147.1
S 152.4
S 160.2
S 160.7
PPM
Me
S
N
O
H$_\beta$
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N
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O
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14
NAM-I-154, CDCl$_3$, 75.5 MHz
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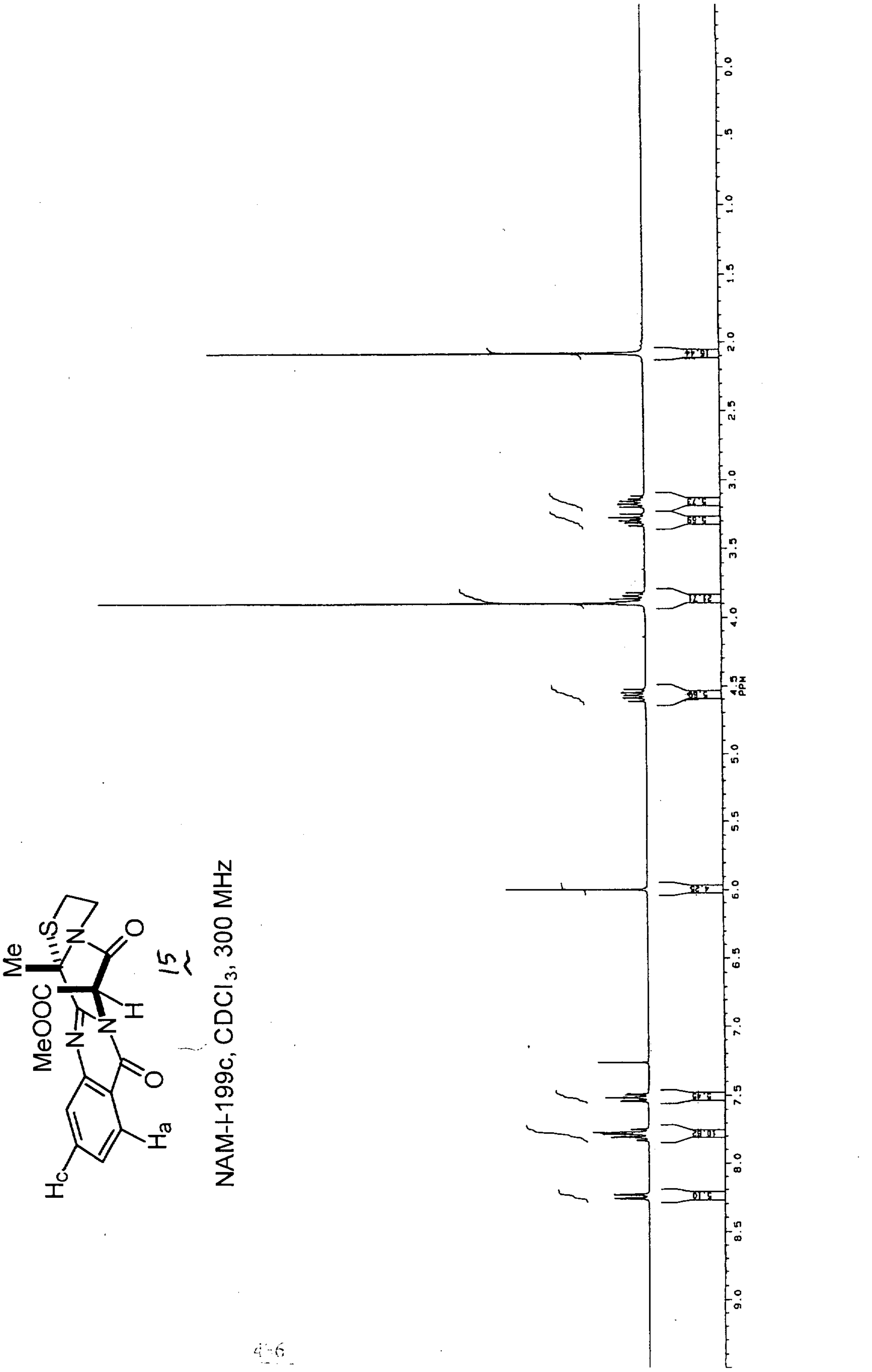
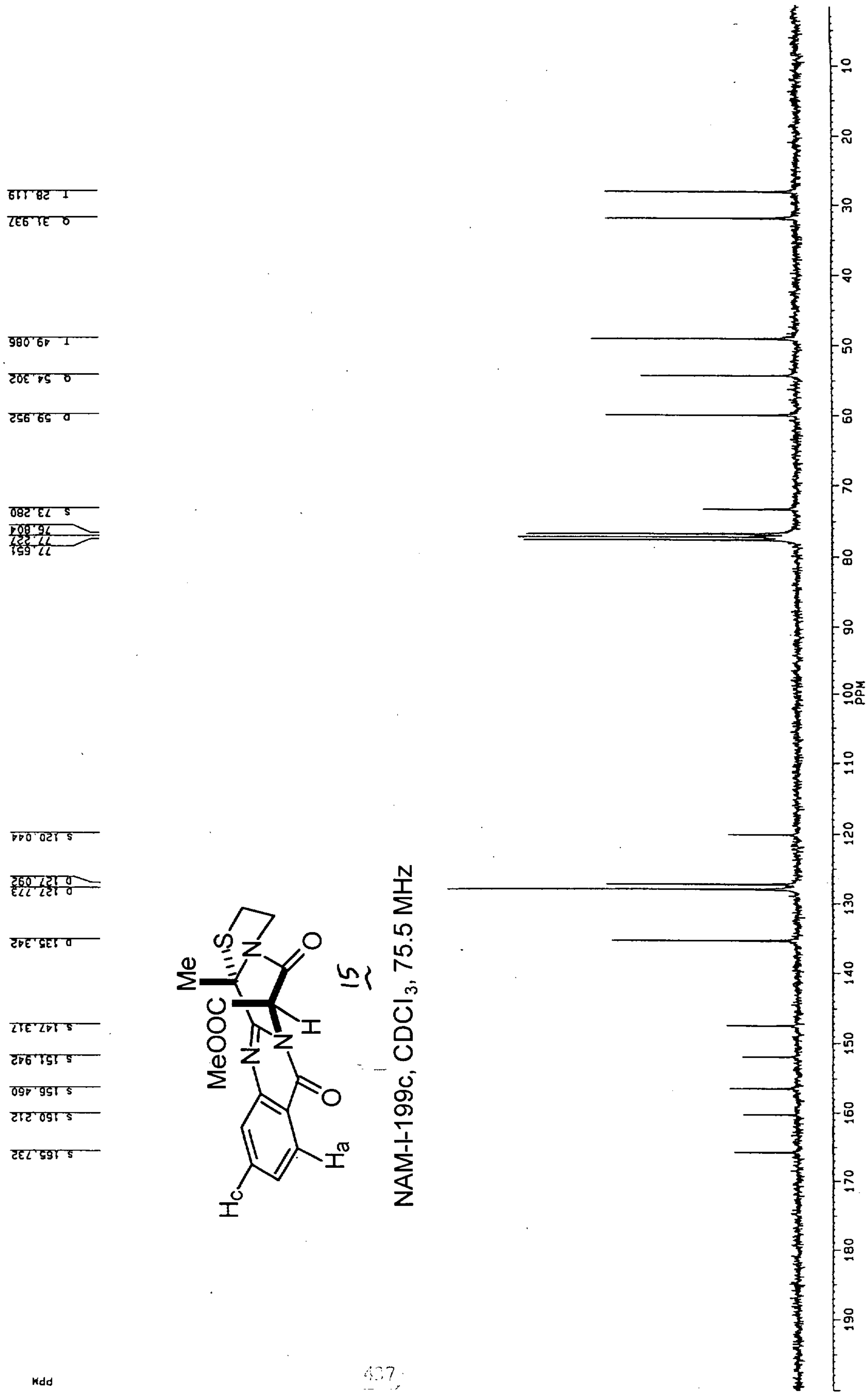


15

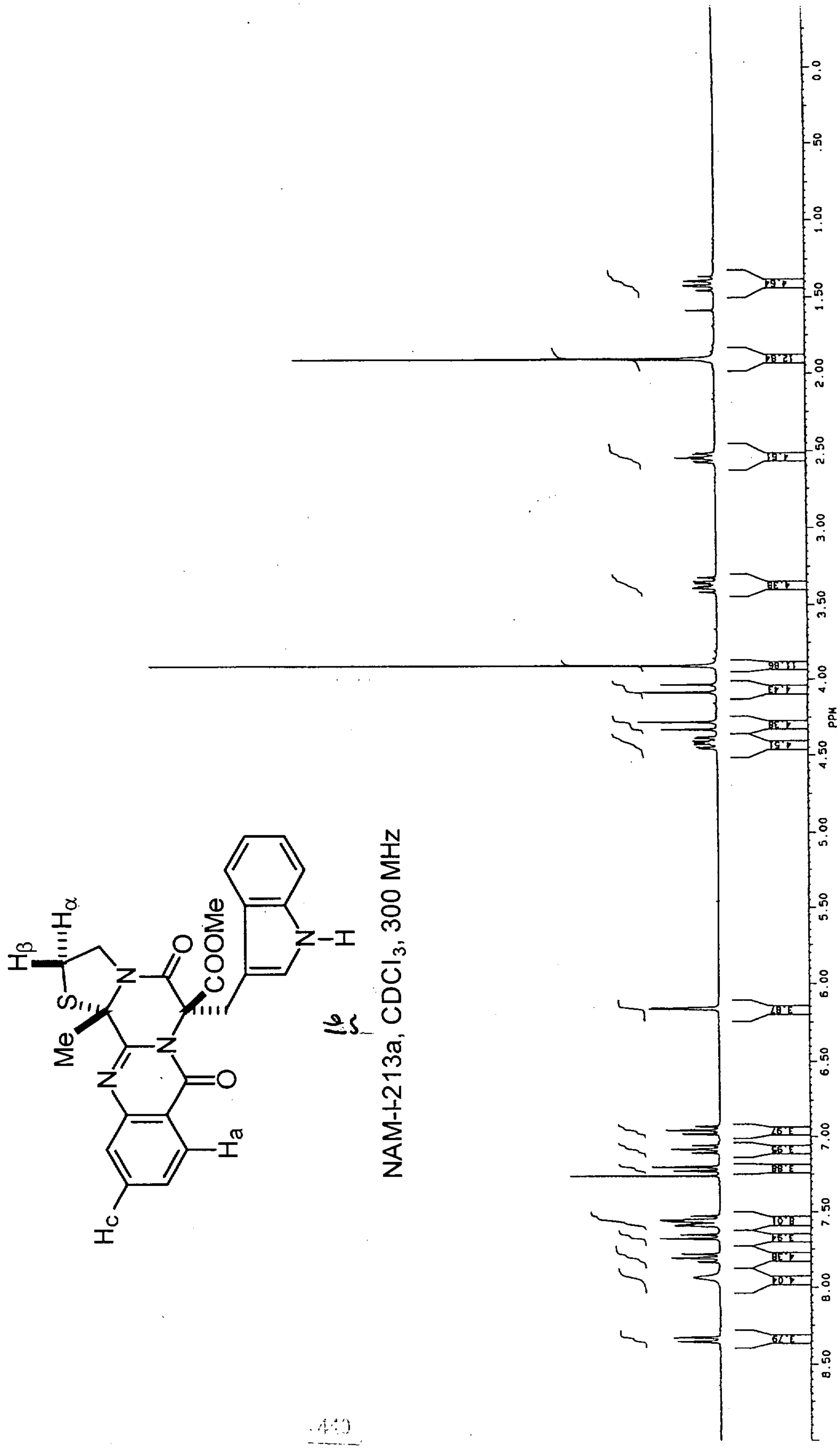
NAM-I-199c, $CDCl_3$, 300 MHz



15

NAM-I-199c, $CDCl_3$, 75.5 MHz

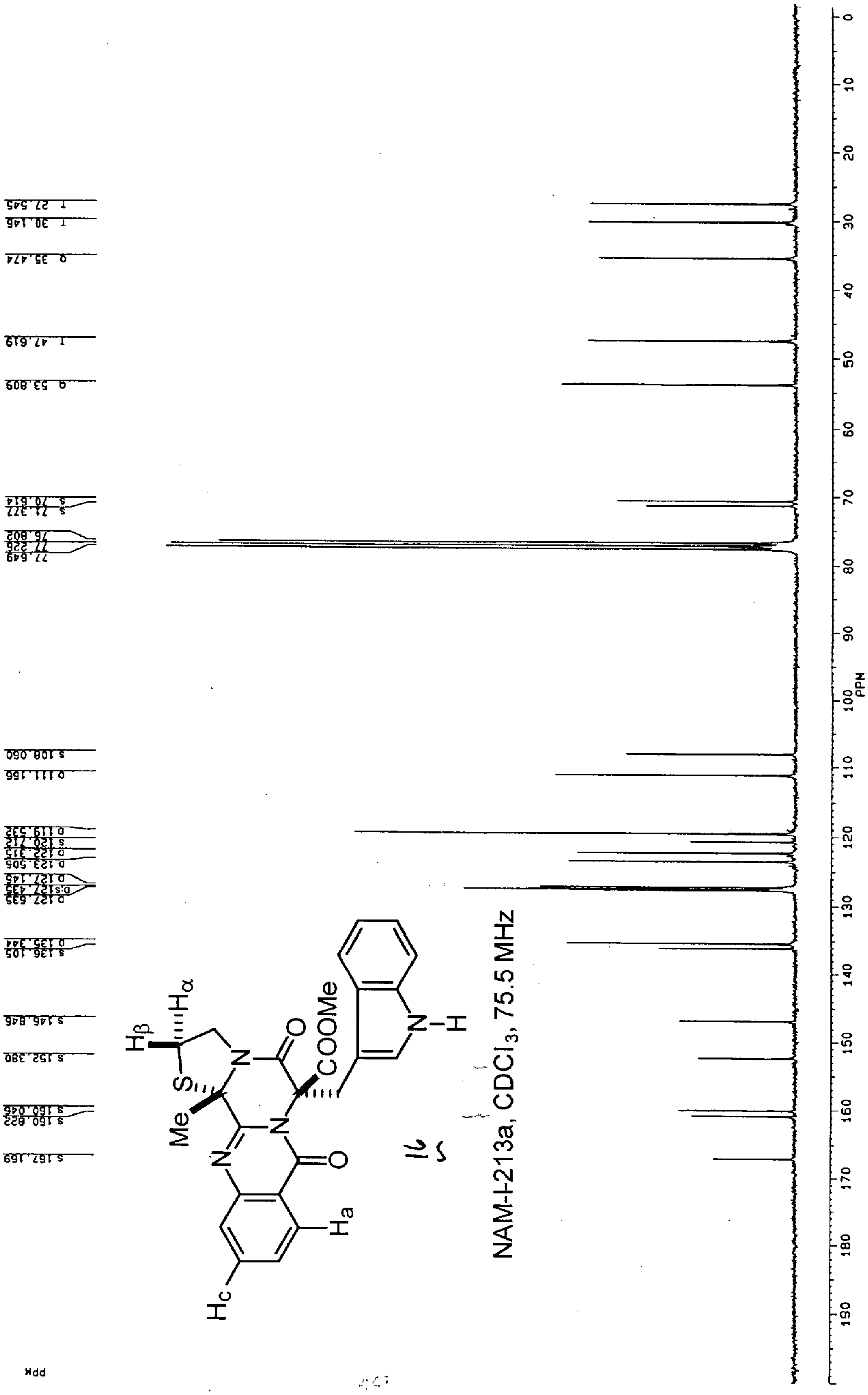
437



16

NAM-I-213a, $CDCl_3$, 300 MHz

440



16

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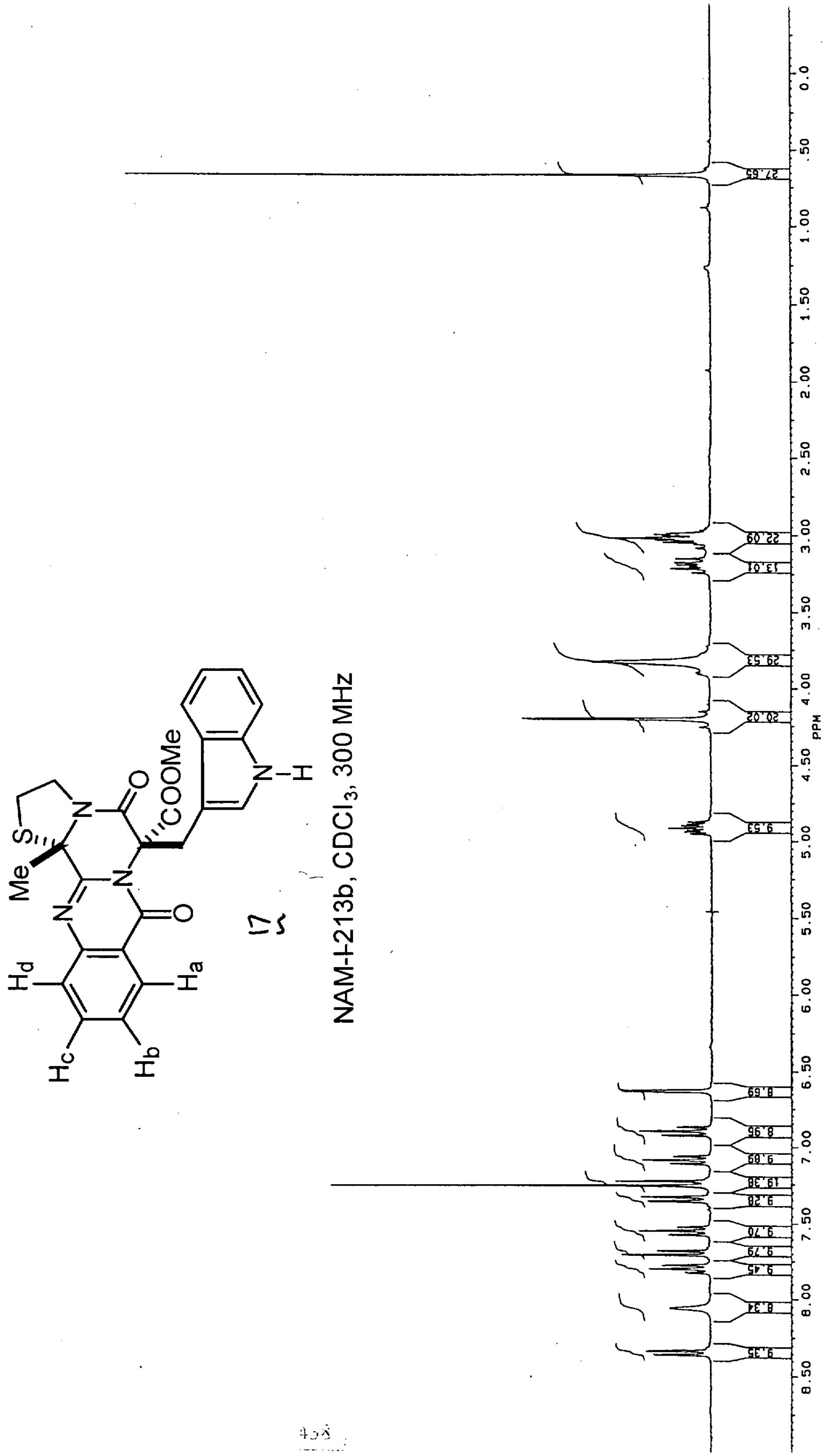

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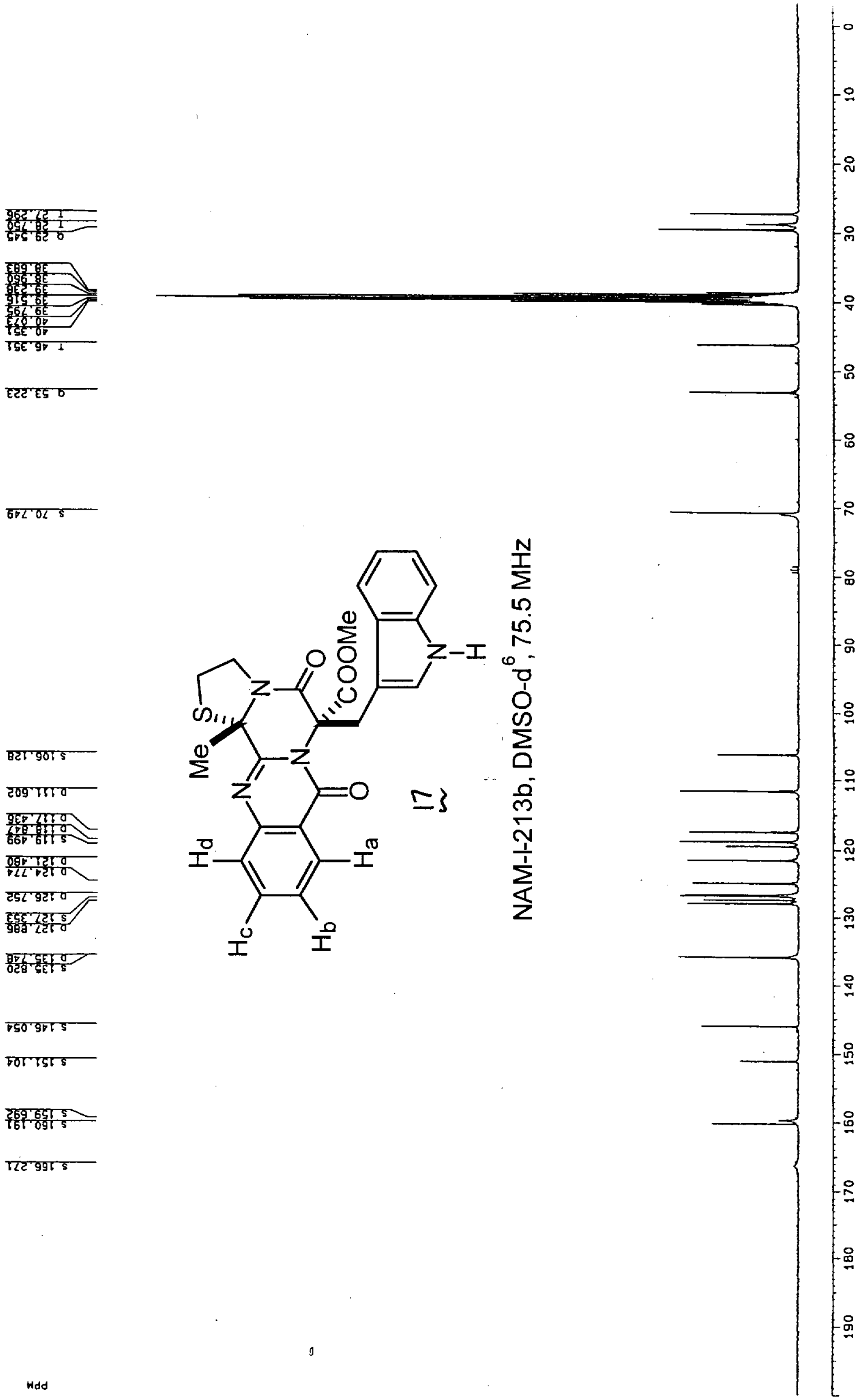
438



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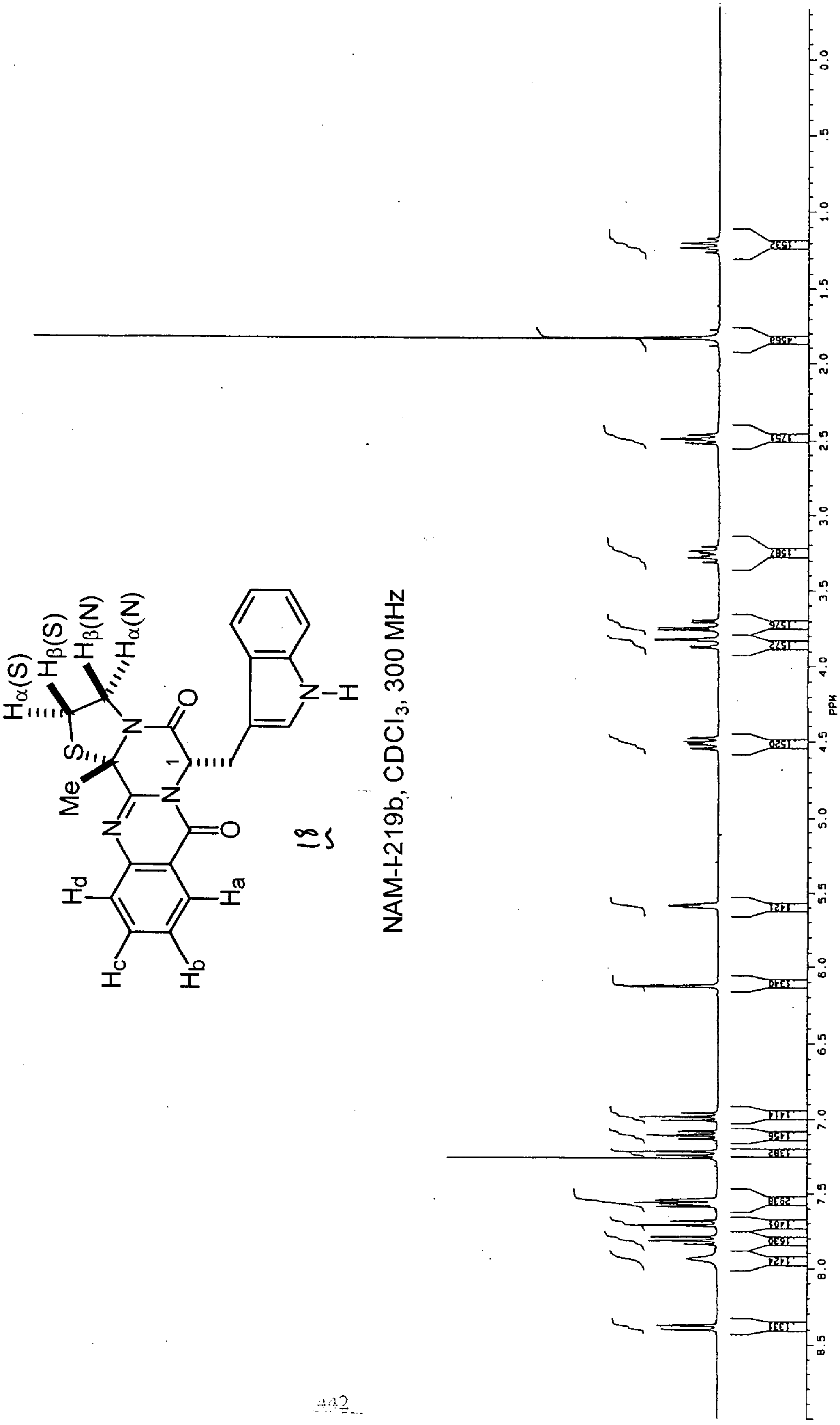
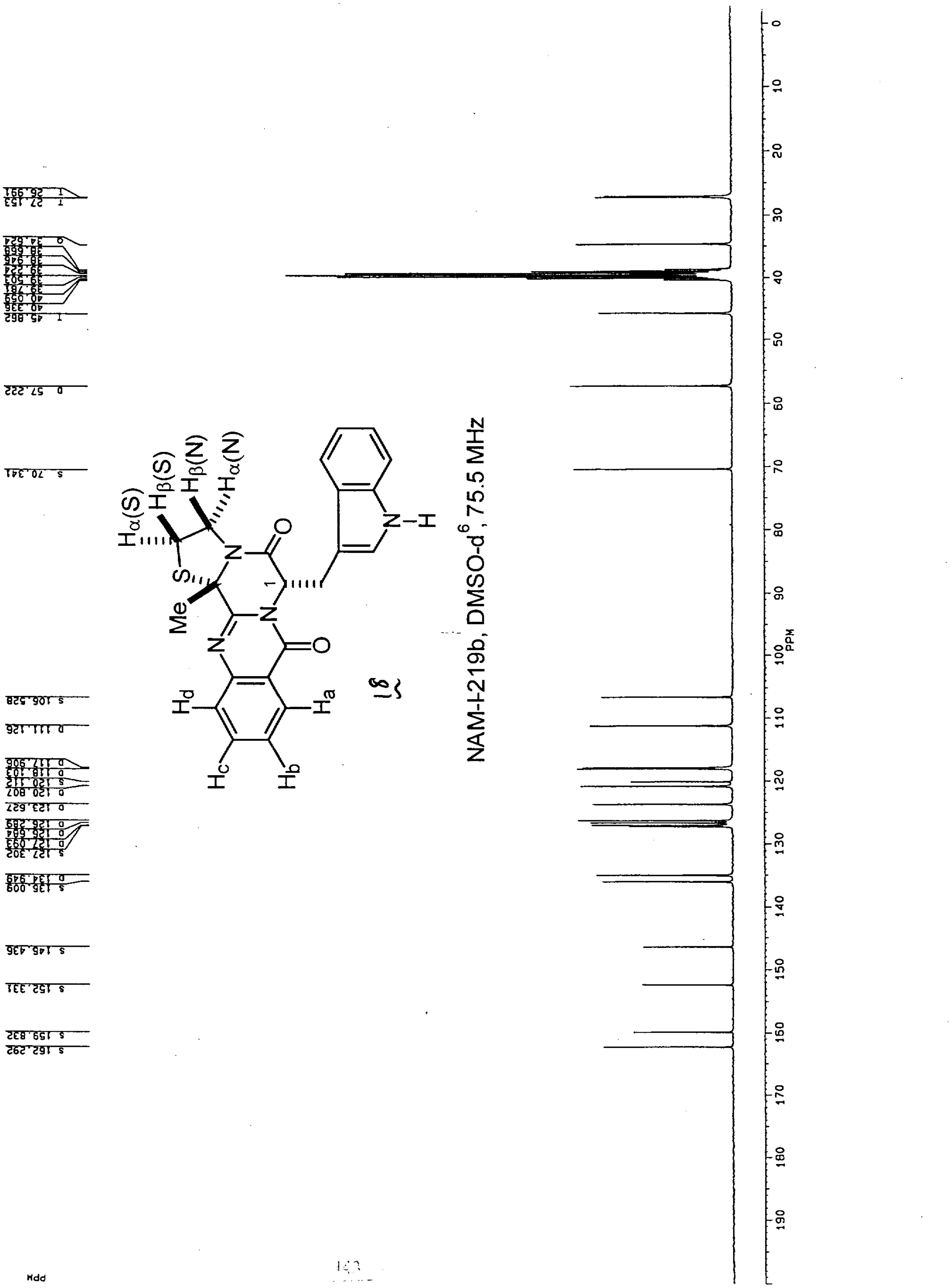


18

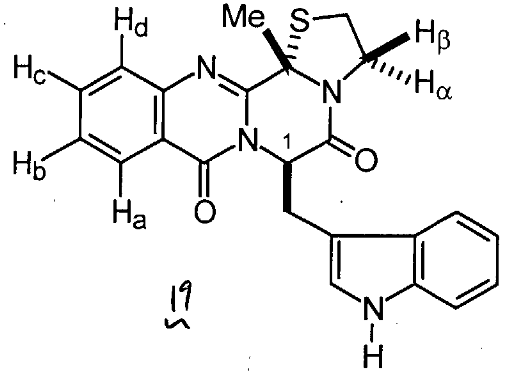
NAM-I-219b, CDCl$_3$, 300 MHz

442



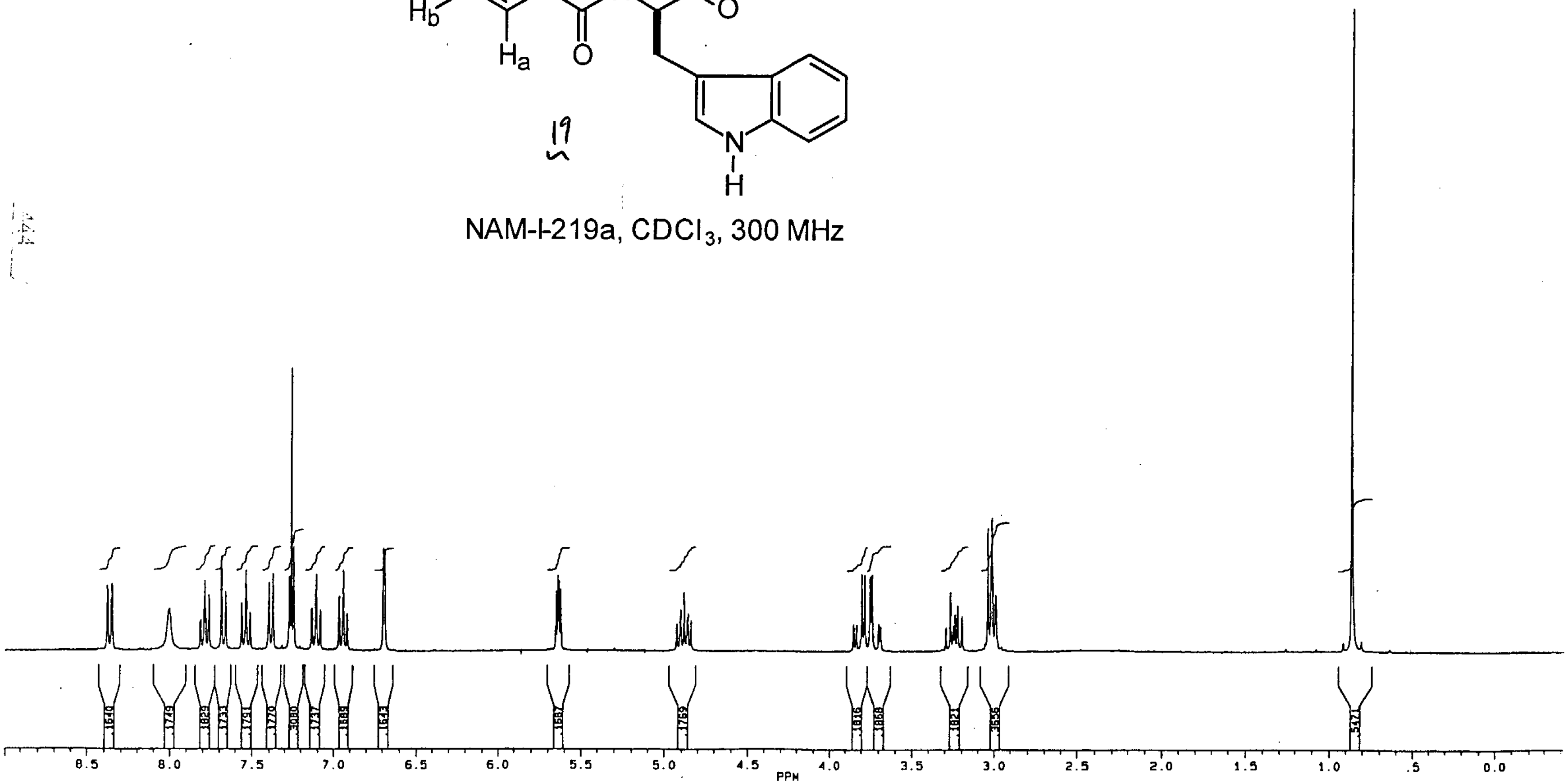
18

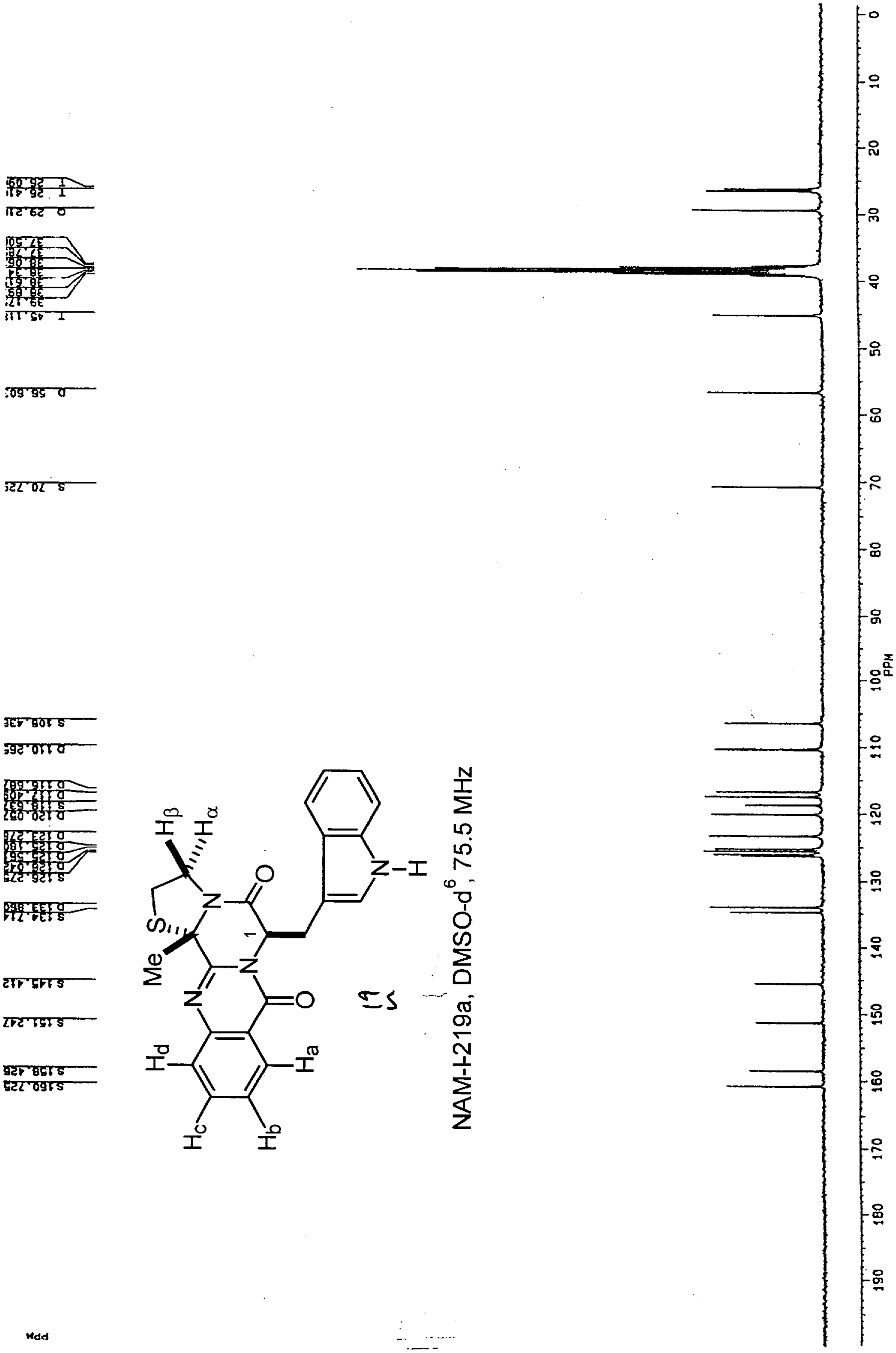
NAM-I-219b, DMSO-d^6, 75.5 MHz



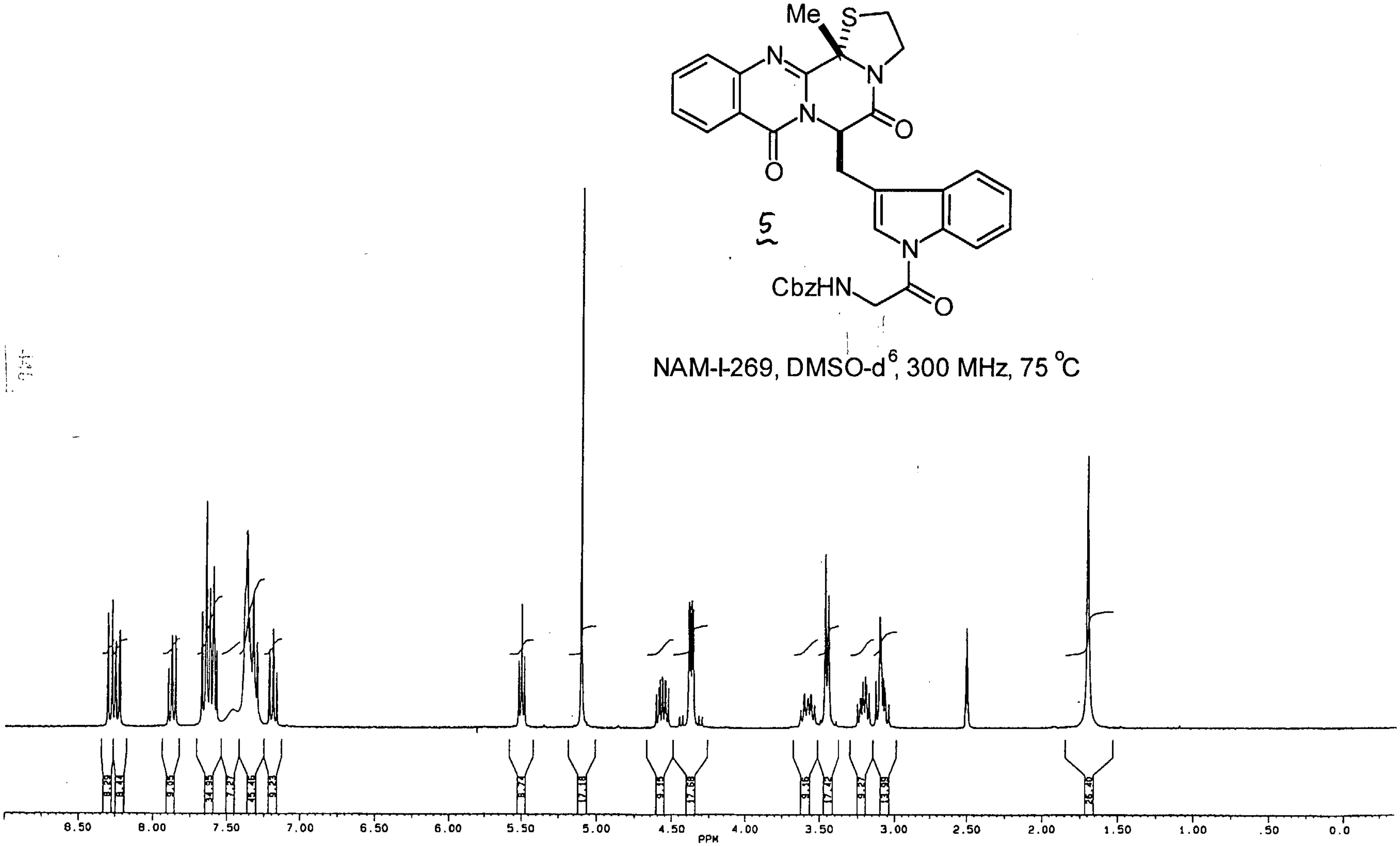
19

NAM-I-219a, CDCl$_3$, 300 MHz



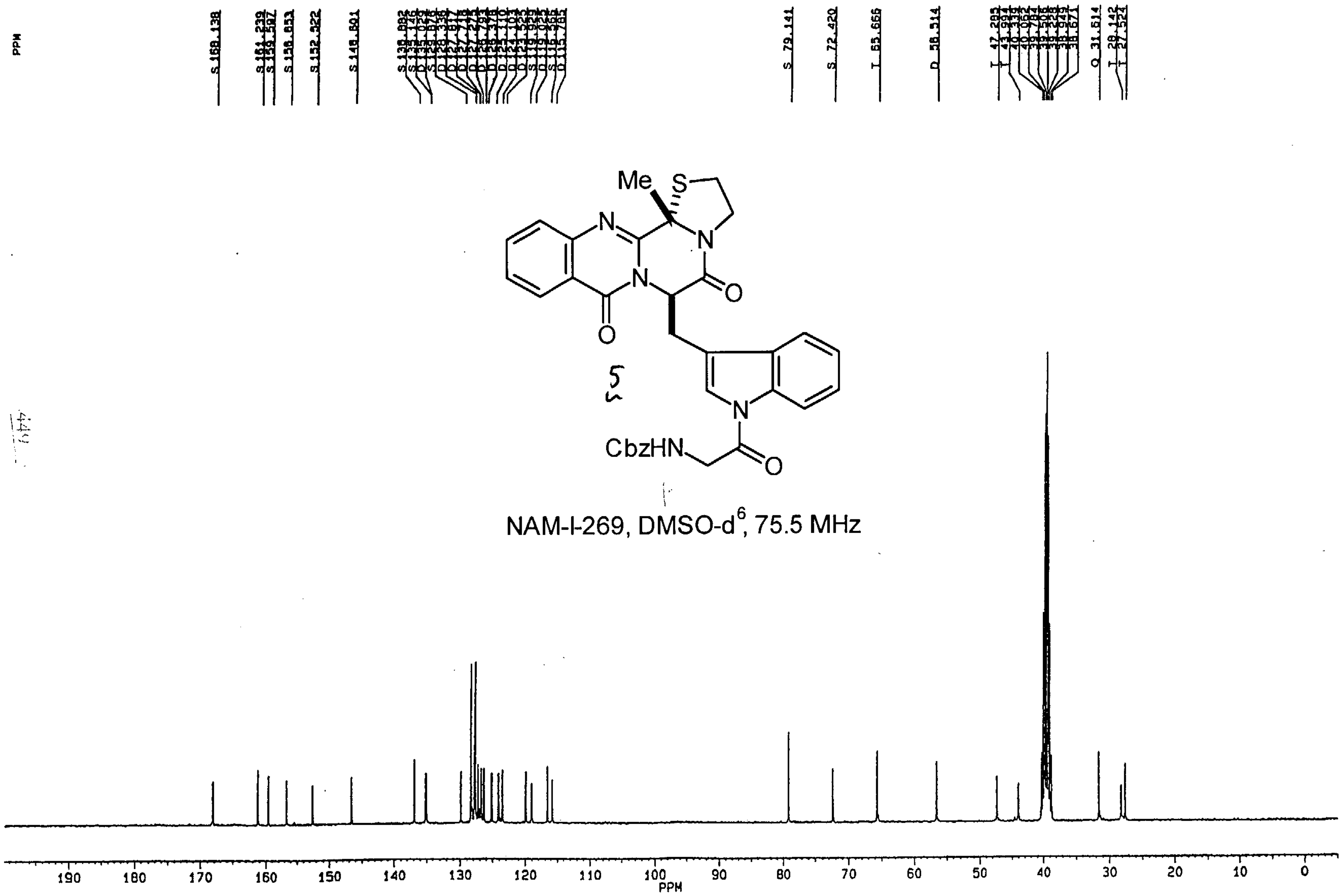


NAM-I-219a, DMSO-d^6, 75.5 MHz



5

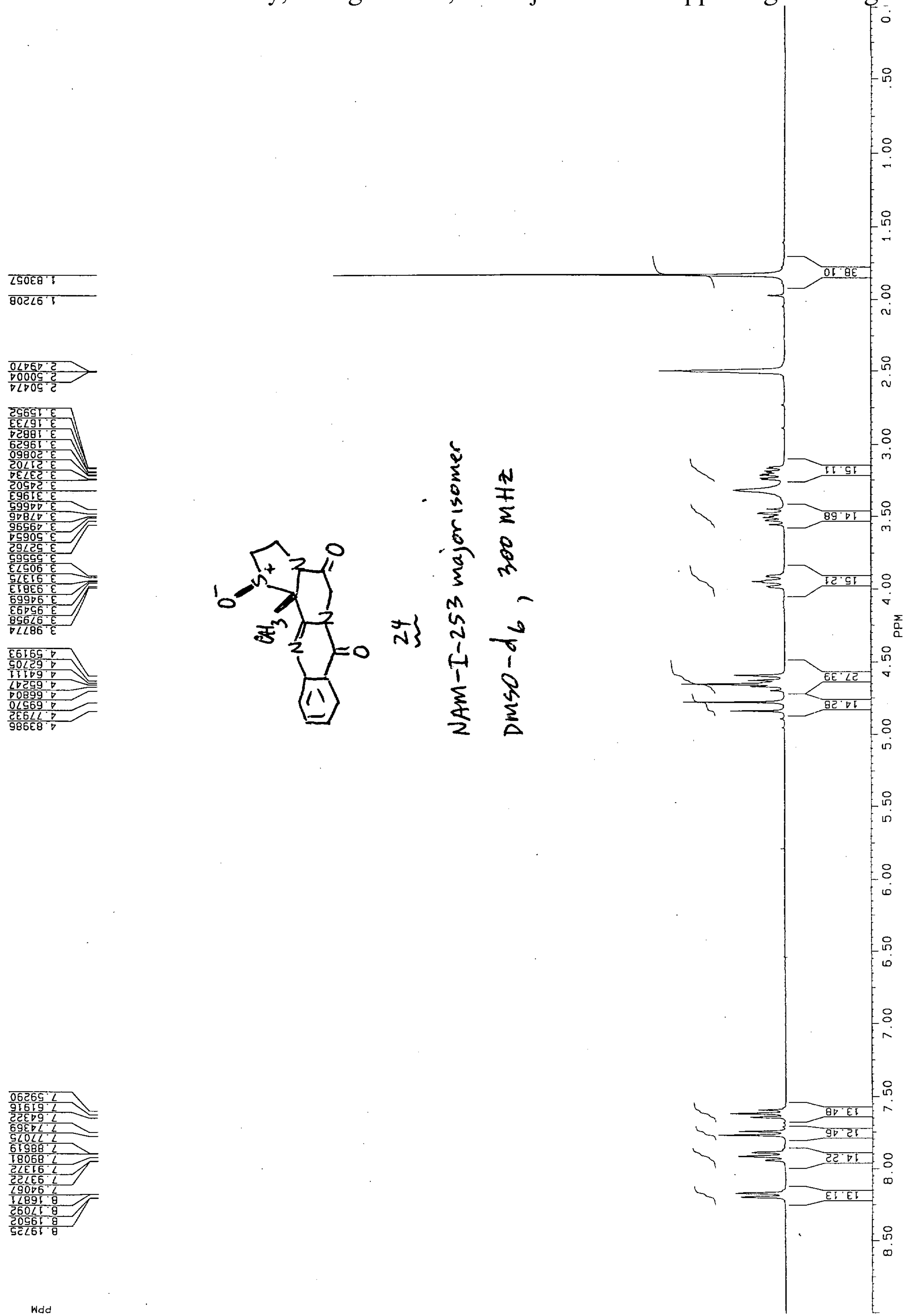
NAM-I-269, DMSO-d^6, 300 MHz, 75 °C



5

NAM-I-269, DMSO-d^6, 75.5 MHz

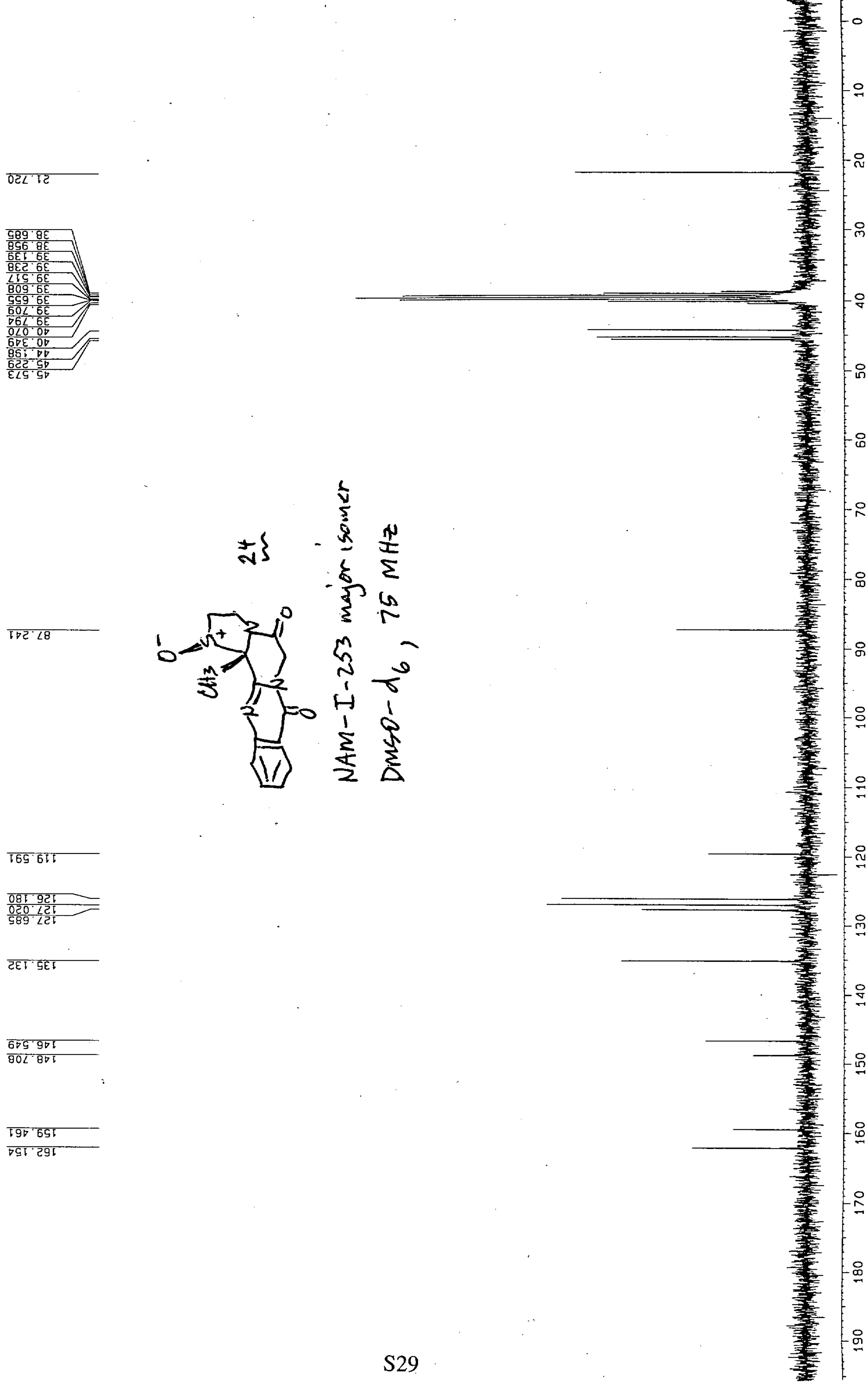
449



24

NAM-I-253 major isomer

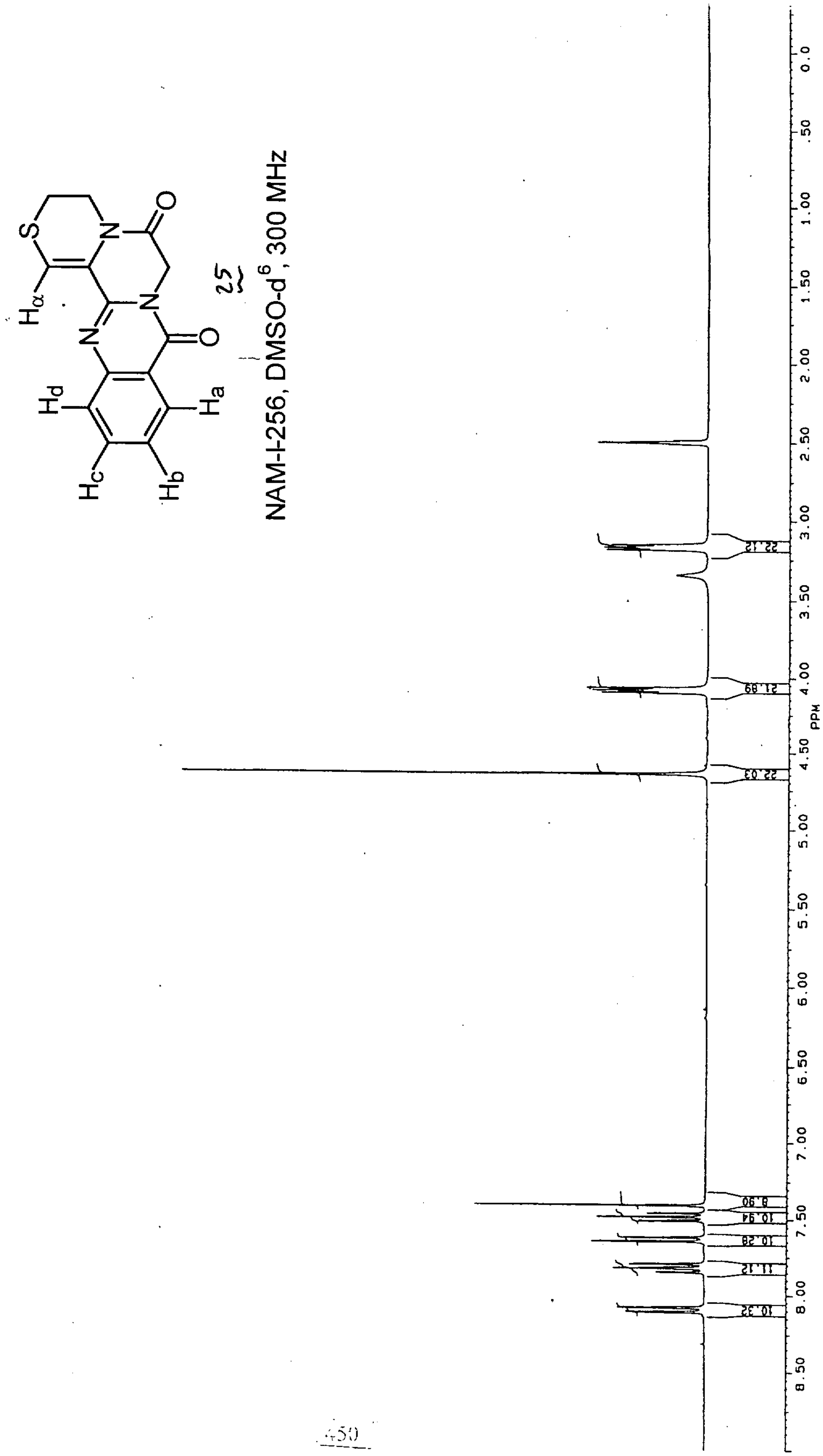
DMSO-d_6, 300 MHz



24

NAM-I-253 major isomer

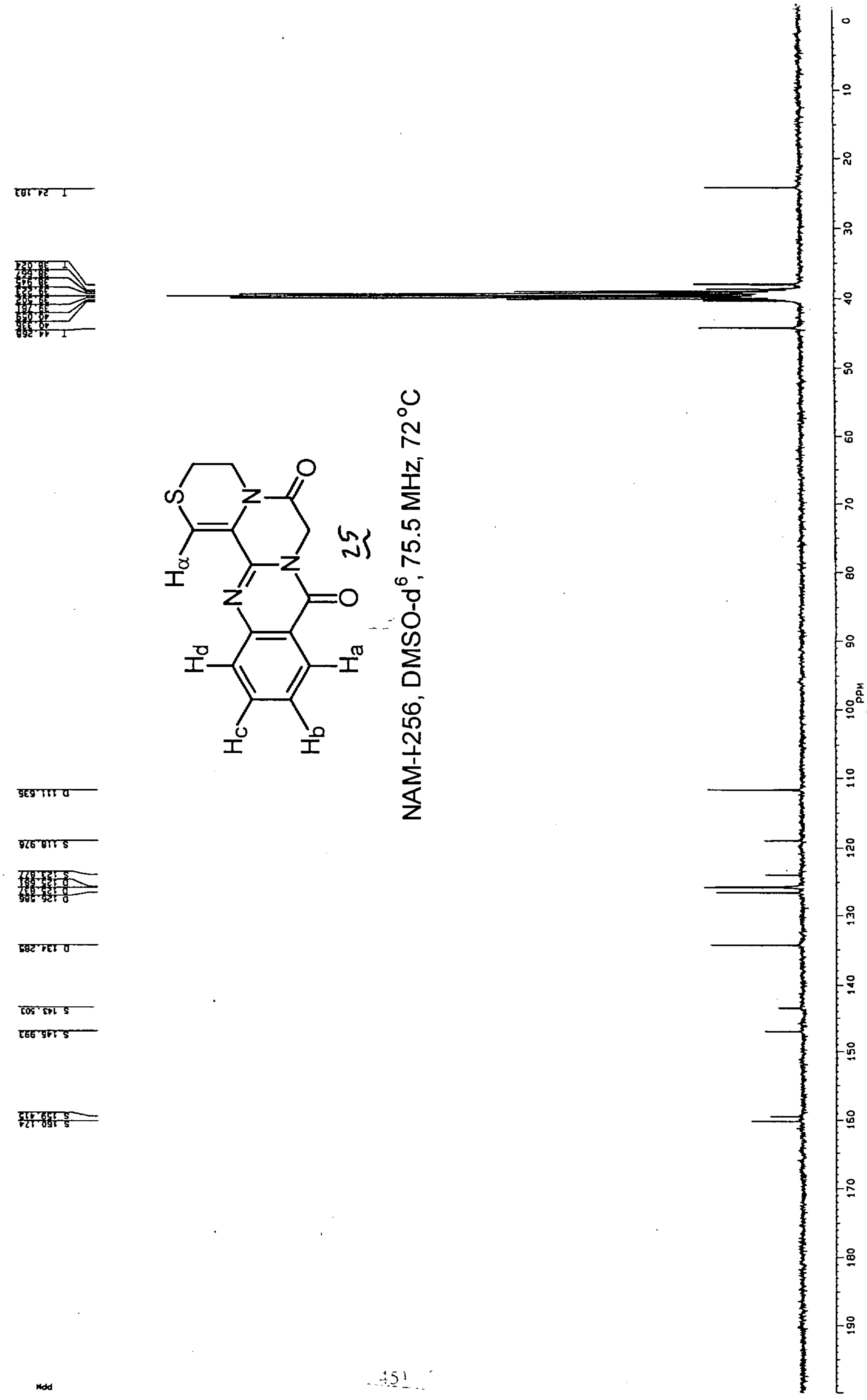
DMSO-d_6, 75 MHz



25

NAM-I-256, DMSO-d^6, 300 MHz

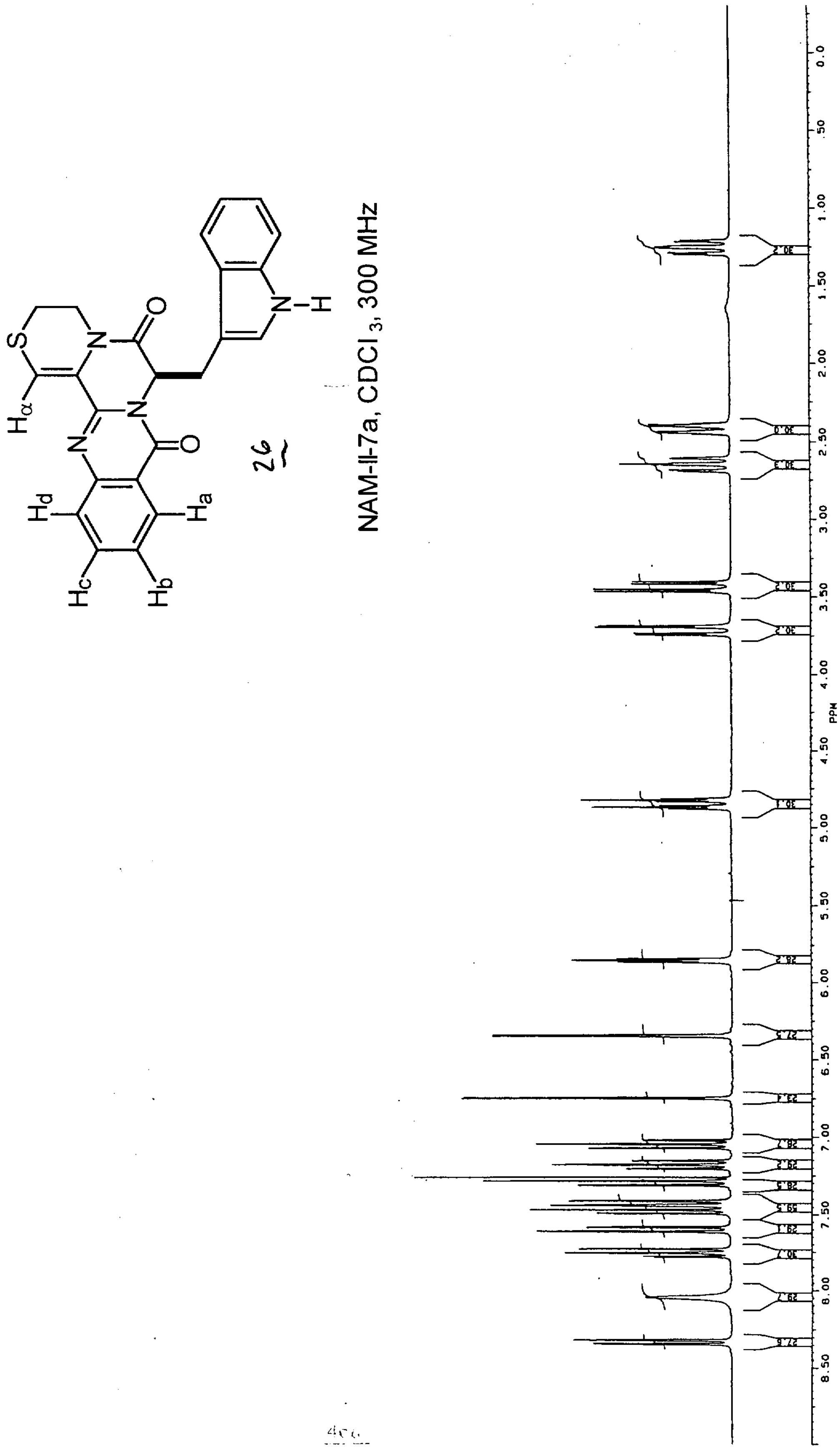
450



NAM-I-256, DMSO-d^6, 75.5 MHz, 72 °C

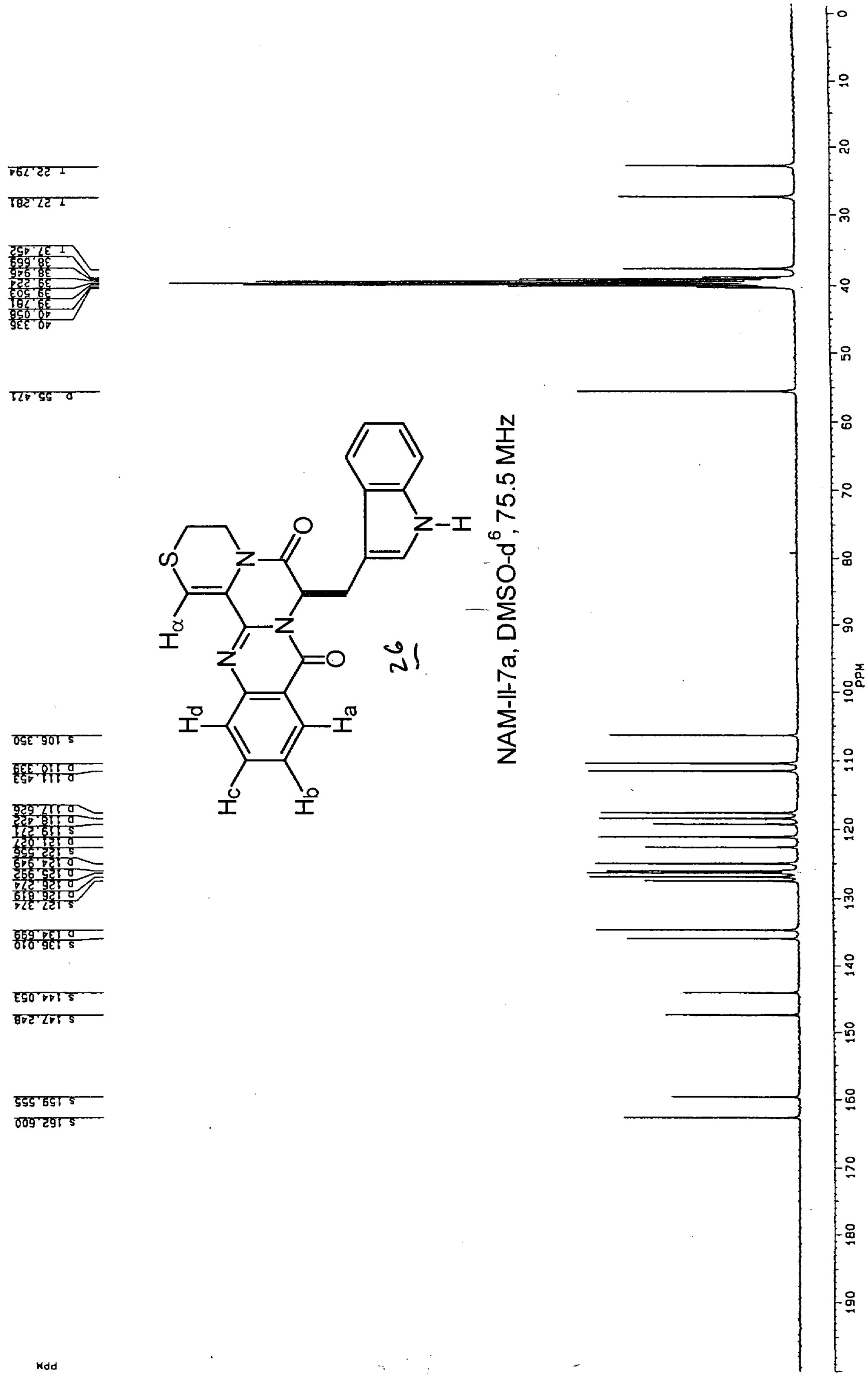
25

451

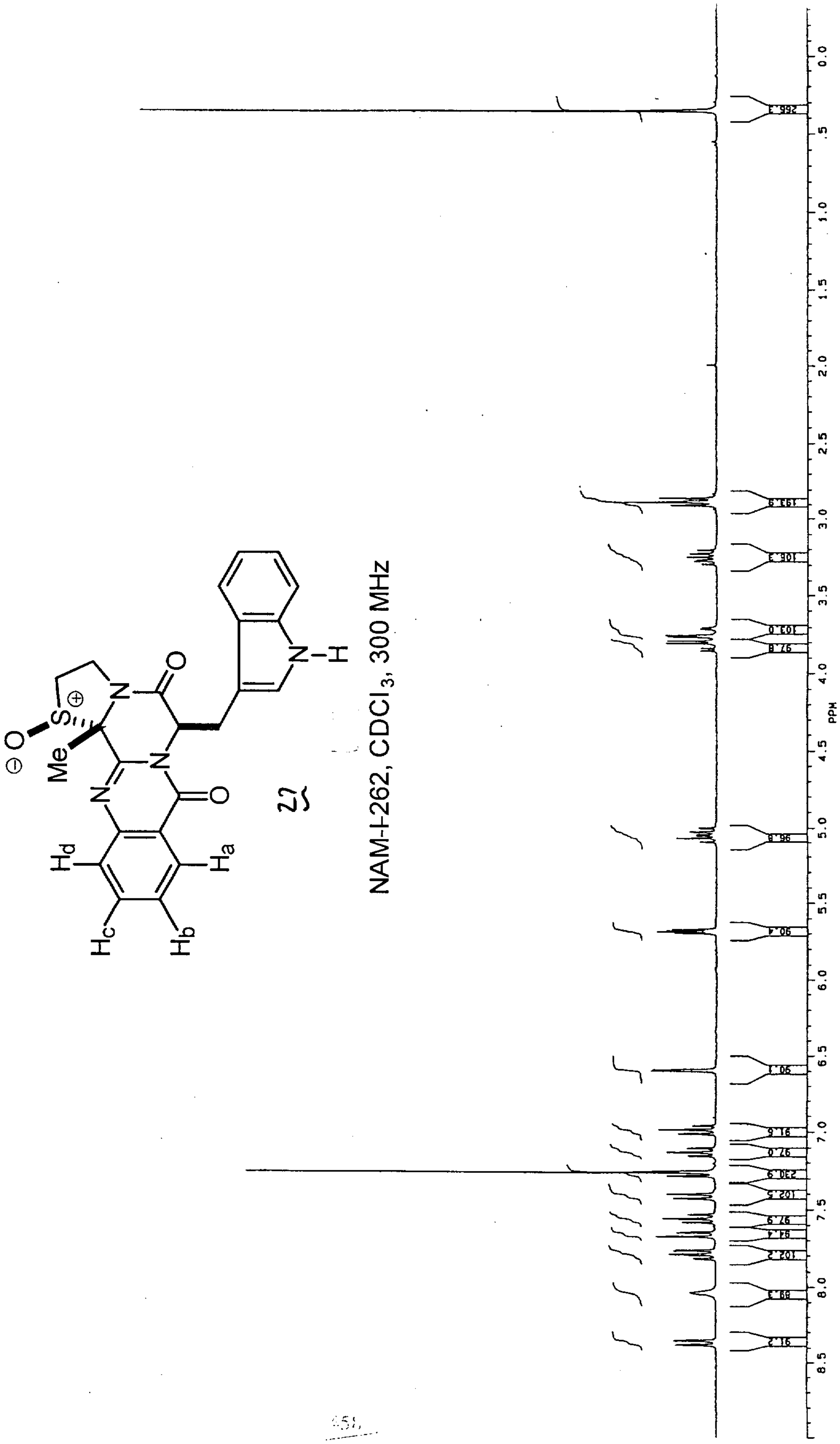


26

NAM-II-7a, $CDCl_3$, 300 MHz

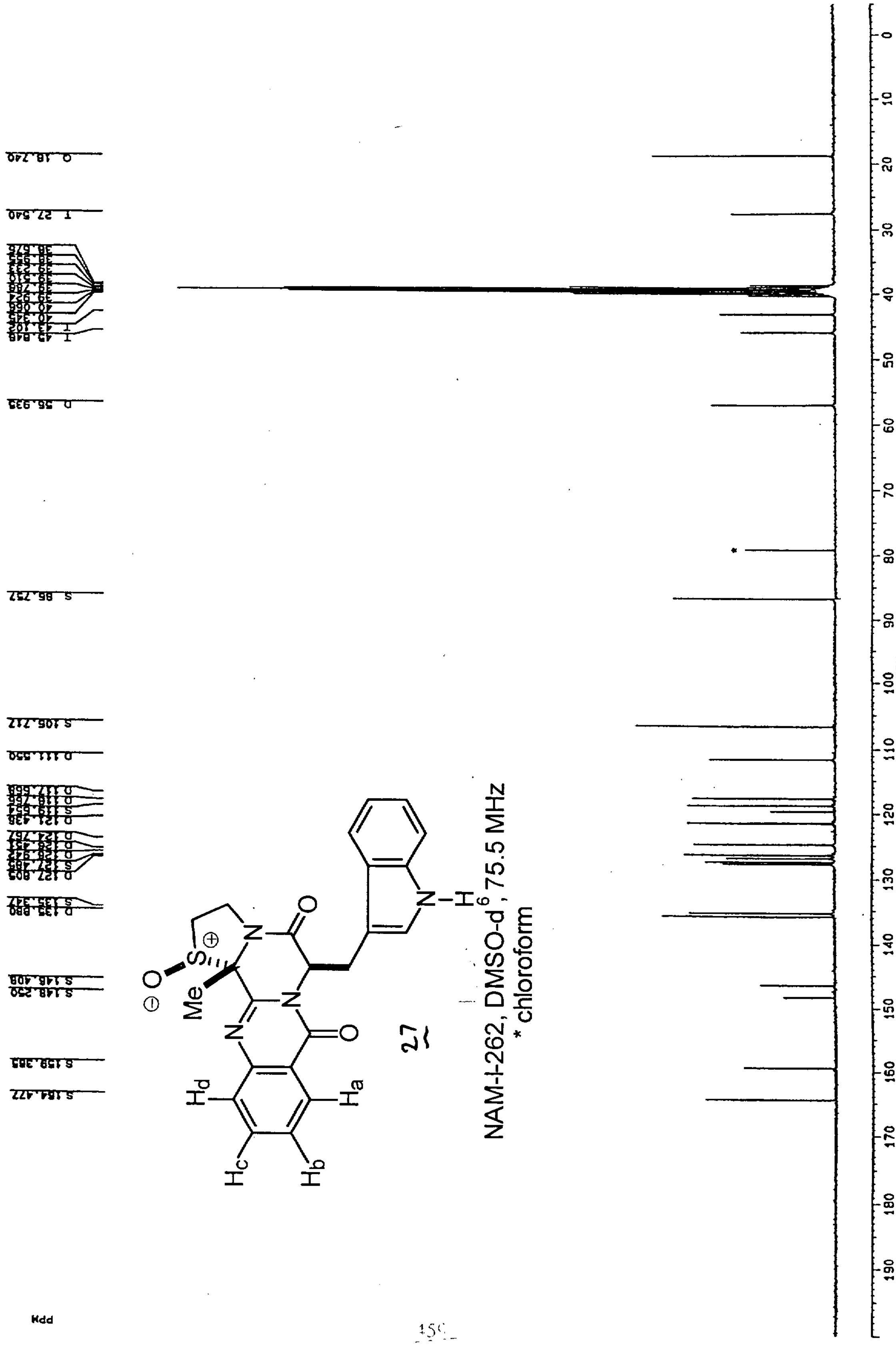


NAM-II-7a, DMSO-d^6, 75.5 MHz



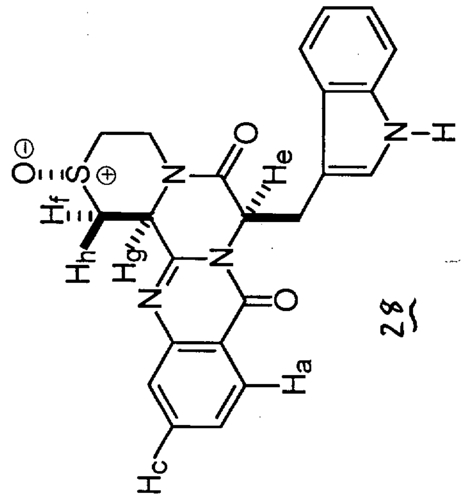
22

NAM-I-262, $CDCl_3$, 300 MHz



27

NAM-I-262, DMSO-d^6, 75.5 MHz
* chloroform



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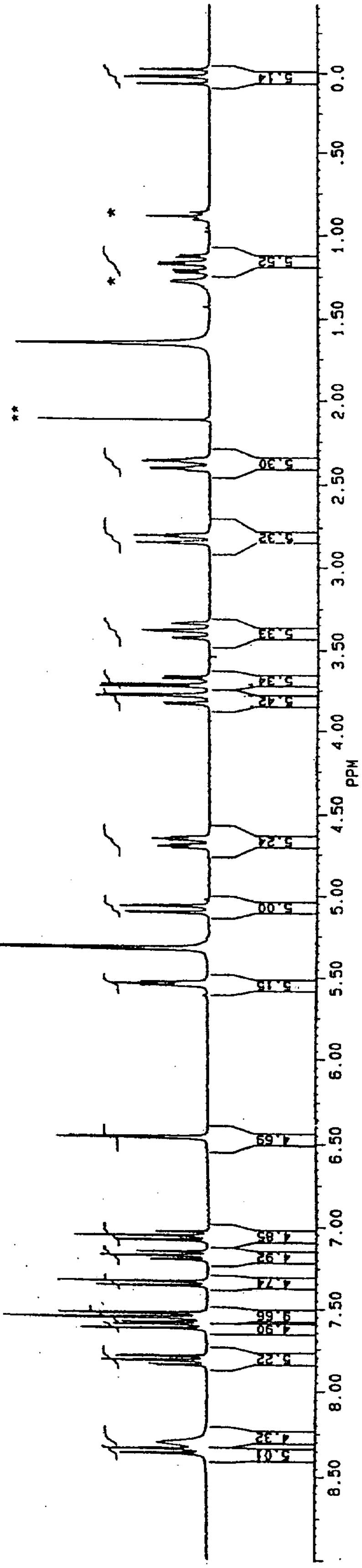
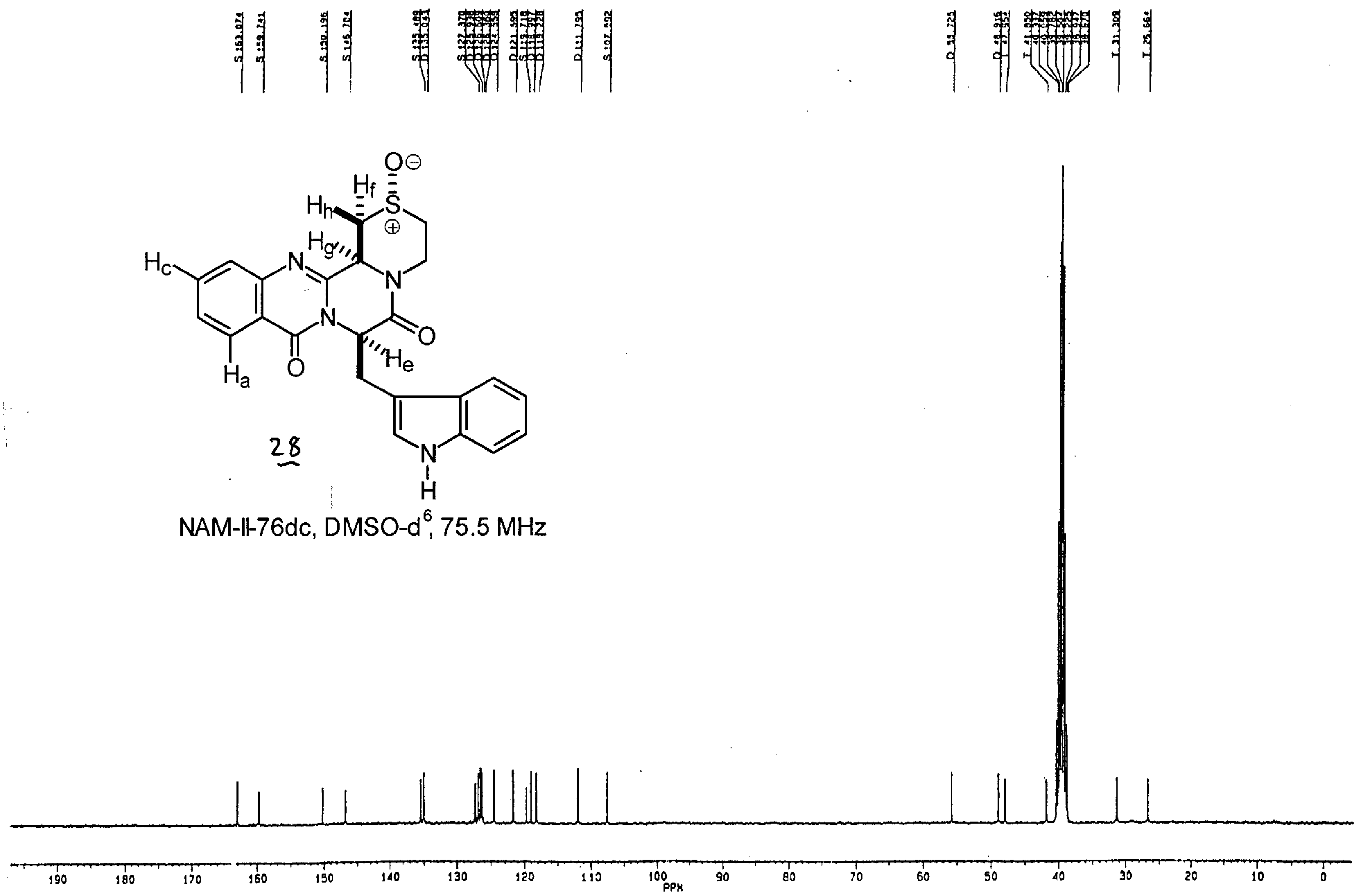
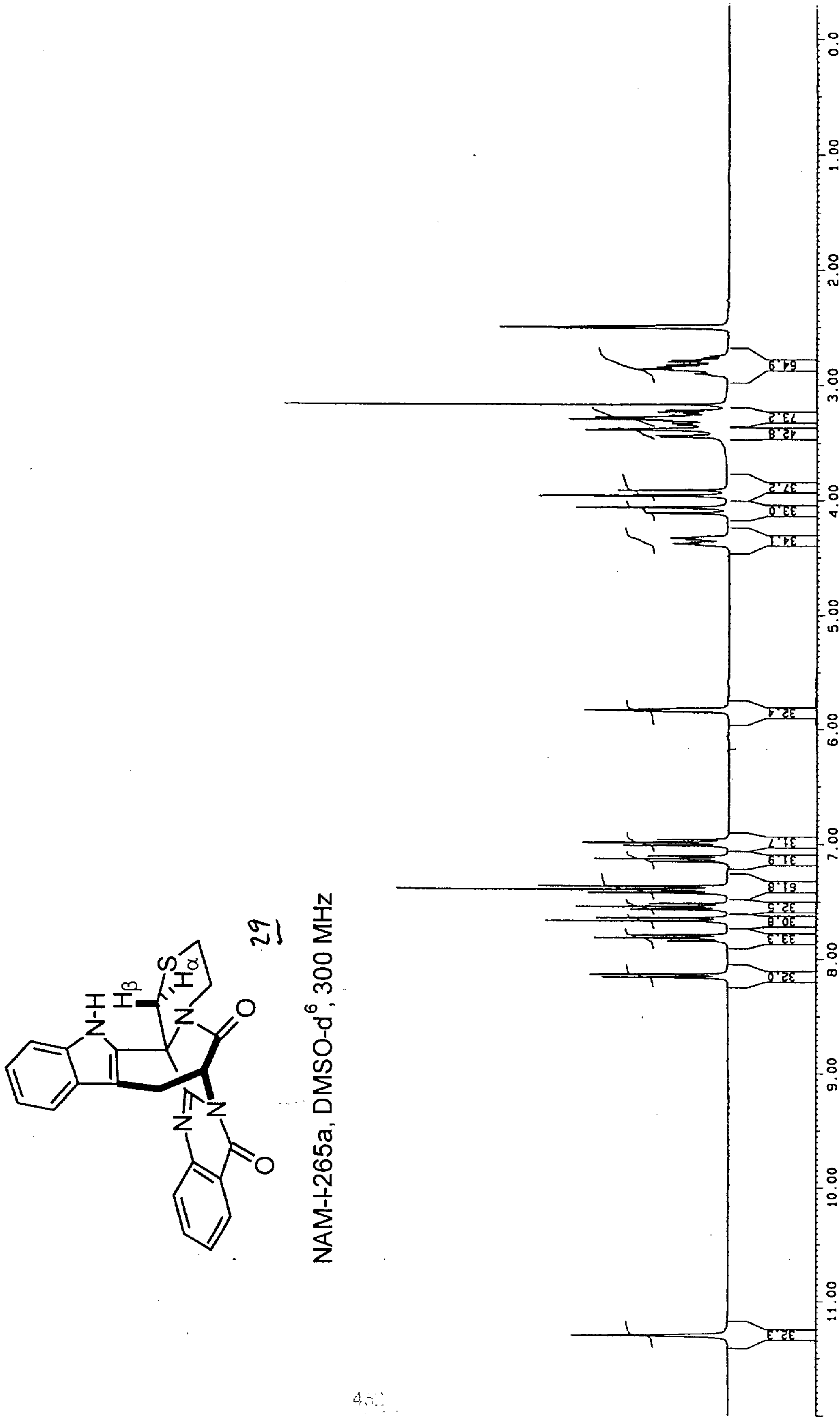
NAM-II-76dc, CD_2Cl_2, 300 MHz
* impurity, ** acetone





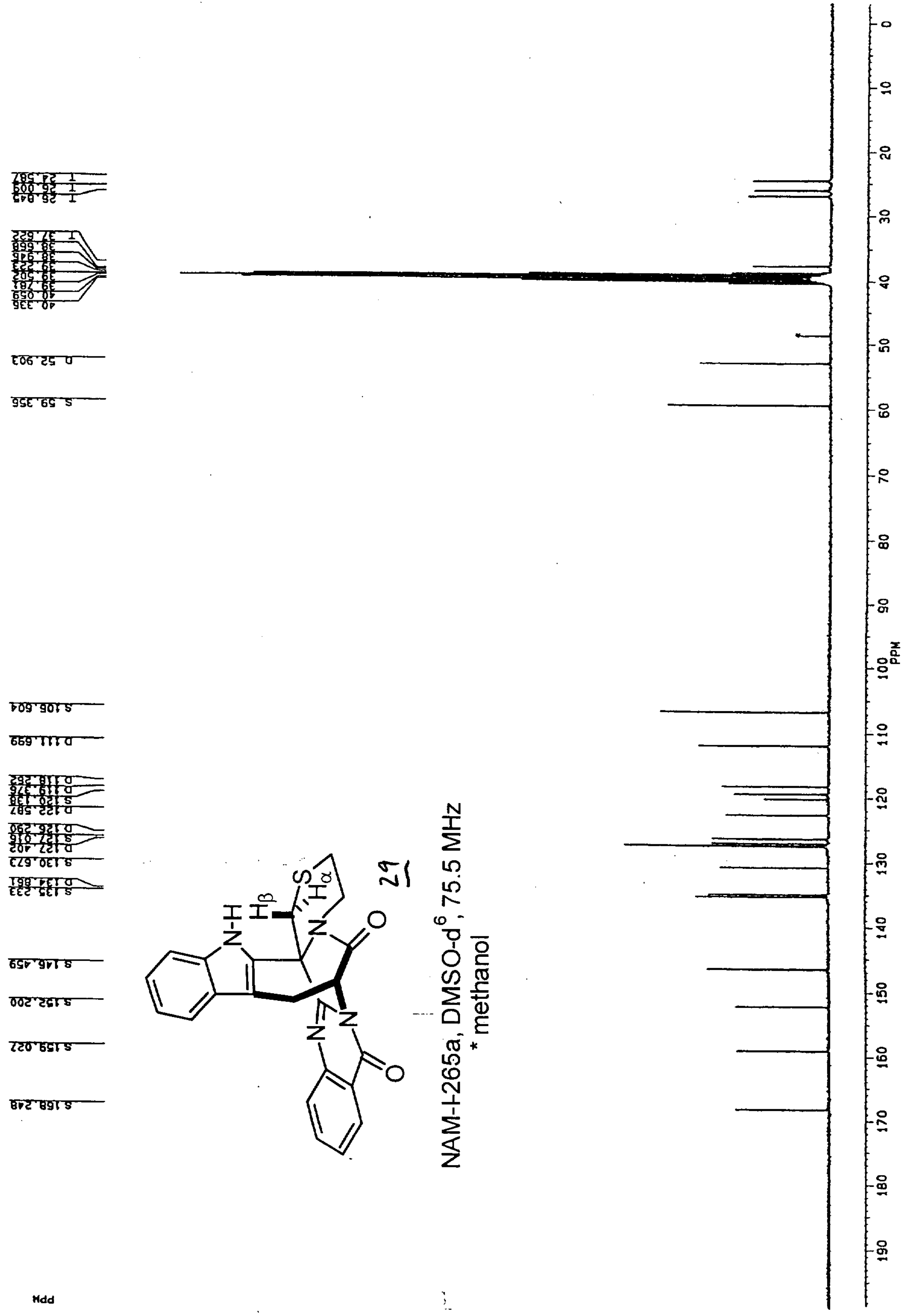
28

NAM-II-76dc, DMSO-d^6, 75.5 MHz



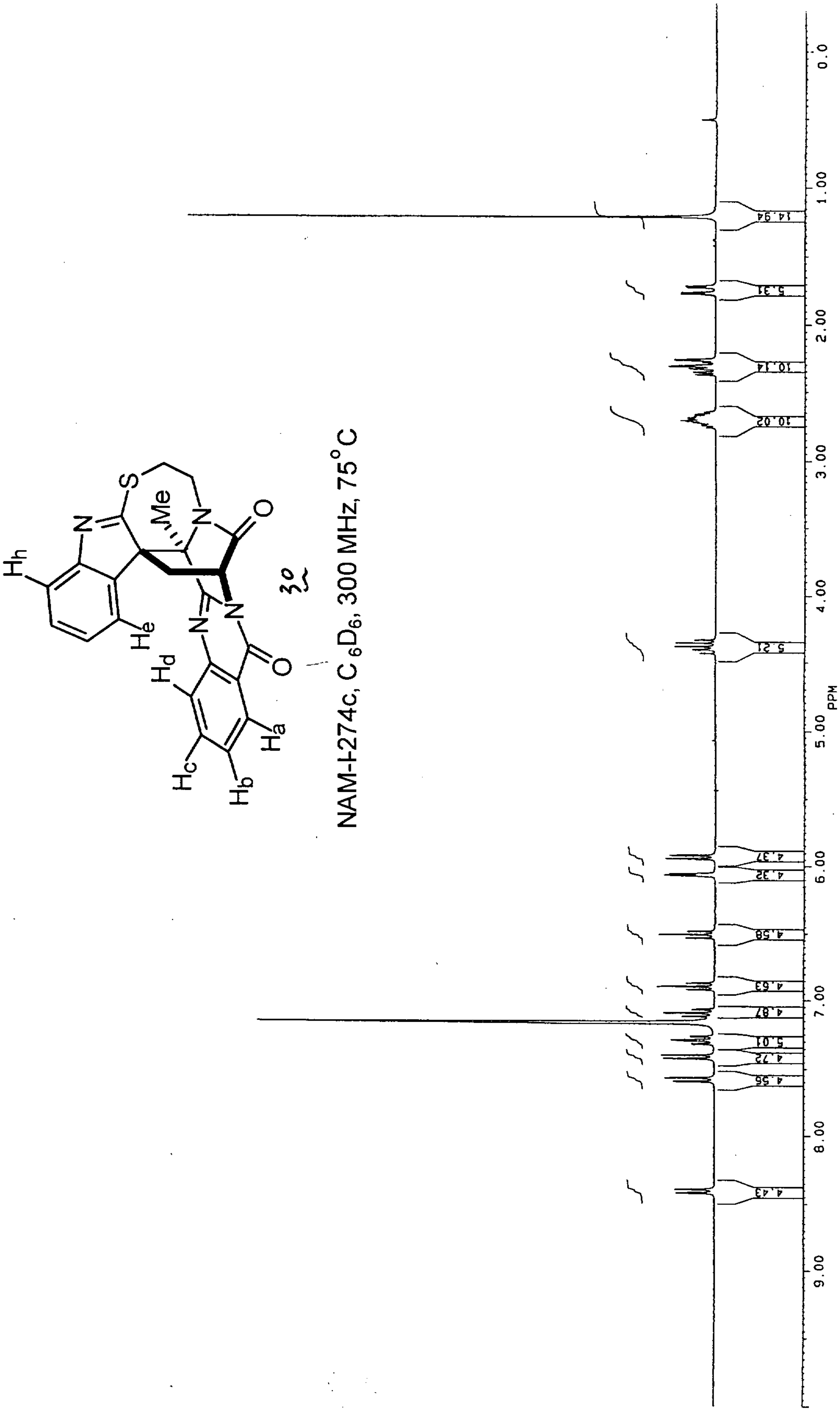
29

NAM-I-265a, DMSO-d^6, 300 MHz



29

NAM-I-265a, DMSO-d^6, 75.5 MHz
* methanol



30

NAM-I-274c, C_6D_6, 300 MHz, 75 °C