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Efficient synthesis of new tricyclic pyrano[3,2-*c*]pyridine derivatives

Ibrahim G. Mamedov, Victor N. Khrustalev, Pavel V. Dorovatovskii,
Farid N. Naghiev and Abel M. Maharramov

NMR experiments have been performed on a BRUKER FT NMR spectrometer AVANCE 300 (300 MHz for ^1H and 75 MHz for ^{13}C) with a BVT 3200 variable-temperature unit in 5 mm sample tubes using Bruker Standard software (TopSpin 3.1). The ^1H and ^{13}C chemical shifts were referenced to internal tetramethylsilane (TMS); the experimental parameters for ^1H : digital resolution = 0.23 Hz, SWH = 7530 Hz, TD = 32 K, SI = 16 K, 90° pulse length = 10 μs , PL1 = 3 dB, ns= 1, ds= 0, d1=1 s; for ^{13}C : digital resolution = 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90° pulse length = 9 μs , PL1 = 1.5 dB, ns= 100, ds= 2, d1= 3 s (Figures S1-S7).

Electrospray mass spectra of **3f** was run with an ion-trap instrument (Esquire 6000 Ion Trap Mass Spectrometer) equipped with an electrospray (ESI) ion source. For electrospray ionization, the drying gas and flow rate were optimized according to the particular sample with 35 p.s.i. nebulizer pressure. Scanning was performed from m/z 100 to 1200 in methanol solution. The compounds were observed in the positive mode (capillary voltage = 80–105 V). MS (ESI): 621.16, 545.12, 476.13 $[\text{M}+\text{H}]^+$.

The progress in reactions was monitored by thin-layer chromatography (TLC) using commercial aluminium-backed plates of silica gel (60 F254). ($R_f=0.42$, $R_f=0.39$, $R_f=0.51$, $R_f=0.48$, $R_f=0.51$, $R_f=0.42$, $R_f=0.48$ respectively)

The single-crystal X-ray diffraction data for **3a** were collected on the ‘Belok’ beamline of the Kurchatov Synchrotron Radiation Source (National Research Center ‘Kurchatov Institute’, Moscow, Russian Federation) using a Rayonix SX165 CCD detector at $\lambda = 0.81182 \text{ \AA}$. A total of 720 images for two different orientations of the crystal were collected using an oscillation range of 1.0° and φ scan mode. The data were indexed and integrated using the utility iMOSFLM from the CCP4 program suite and then scaled and corrected for absorption using the Scala program. For details, see Table. The structure was determined by direct methods and refined by full-matrix least square technique on F^2 in anisotropic approximation for non-hydrogen atoms. The hydrogen atoms of the imino-groups were objectively localized in the difference-Fourier map and included in the refinement within the riding model with isotropic displacement parameters [$U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{N})$]. The other hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters [$U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for the methyl groups and $1.2U_{\text{eq}}(\text{C})$ for the other groups]. All calculations were carried out using the SHELXTL program suite. Crystallographic data for **3a** have been deposited with the Cambridge Crystallographic Data Center, CCDC 1854454.

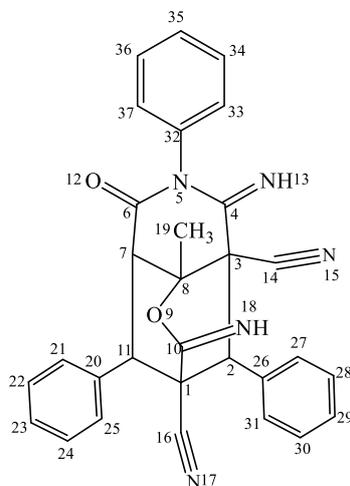
Table S1. Crystal data and structure refinements for **3a**.

Compound	3a
Empirical formula	C ₃₀ H ₂₃ N ₅ O ₂
Formula weight	485.53
Temperature, K	100.0(2)
Crystal system	Triclinic
Space group	<i>P</i> -1
<i>a</i> , Å	12.854(3)
<i>b</i> , Å	13.615(3)
<i>c</i> , Å	14.632(3)
α , deg.	83.49(3)
β , deg.	84.59(3)
γ , deg.	79.26(3)
<i>V</i> , Å ³	2492.6(10)
<i>Z</i>	4
<i>D</i> _{calc} , g·cm ⁻³	1.294
Absorption coefficient, μ	0.111
<i>F</i> (000)	1016
Crystal size, mm	0.07×0.10×0.10
Theta range for data collection	3.18 – 31.02
Index ranges	-16 < <i>h</i> < 16 -17 < <i>k</i> < 17 -18 < <i>l</i> < 18
Reflections collected	42719
Independent reflections, <i>R</i> _{int}	10194, 0.071
Reflections observed with <i>I</i> > 2 σ (<i>I</i>)	7670
Absorption correction	semi-empirical
Data / restraints/ parameters	10194 / 0 / 670
Goodness-of-fit on <i>F</i> ²	1.037
<i>R</i> ₁ [<i>I</i> > 2 σ (<i>I</i>)]	0.061
<i>wR</i> ₂ [all data]	0.163
Extinction coefficient	0.0278(15)
<i>T</i> _{min} / <i>T</i> _{max}	0.980 / 0.990

General procedure for the synthesis of compounds 3a-g:

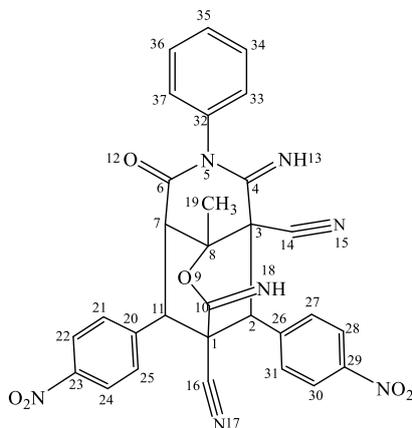
To a stirred mixture of arylidene-malononitrile **1a-g** (8 mmol), acetoacetanilide **2** (0.72 g, 4 mmol) and methanol (20 ml), piperazine hydrate (0.22 g, 7 mol%) was added, and the mixture was left overnight. The resultant mixture was poured into a glass beaker. After evaporation of the solvent, white precipitates were formed. The precipitates were filtered off using a paper filter, washed 4 times with an ethanol-water mixture and dried.

4,10-Diimino-8-methyl-2,5,11-triphenyl-6-oxo-9-oxa-5-azatricyclo[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3a**: White powder, yield 84%, mp 276°C. ¹H NMR (300 MHz, DMSO-*d*₆): 1.91 (s, 3H, CH₃-19), 3.95 (d, 1H, CH-11, ³J_{H,H} = 3.0 Hz), 4.49 (d, 1H, CH-7, ³J_{H,H} = 3.0 Hz), 4.94 (s, 1H, CH-2), 7.37-7.64 (m, 15H, 3Ar), 7.88 (s, 1H, NH-13), 9.20 (s, 1H, NH-18). ¹³C NMR (75 MHz, DMSO-*d*₆): 22.19 (CH₃-19), 48.15 (C_{quat}-3), 49.29 (CH-11), 50.85 (CH-7), 51.30 (CH-2), 55.58 (C_{quat}-1), 76.35 (C_{quat}-8), 115.13 (CN-16), 115.79 (CN-14), 128.88 (CH_{arom}), 129.08 (CH_{arom}), 129.32 (CH_{arom}), 129.53 (CH_{arom}), 129.64 (CH_{arom}), 129.71 (CH_{arom}), 129.85 (CH_{arom}), 130.29 (CH_{arom}), 130.66 (CH_{arom}), 133.76 (C_{arom}), 136.01 (C_{arom}), 137.83 (C_{arom}), 154.63 (N=C-10), 155.59 (N=C-4), 167.62 (C=O-12).



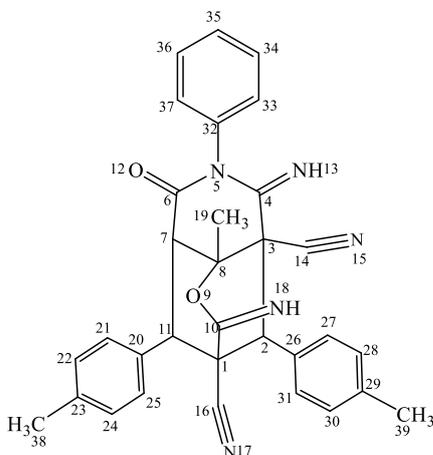
4,10-Diimino-8-methyl-2,11-bis(4-nitrophenyl)-5-phenyl-6-oxo-9-oxa-5-azatricyclo-[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3b**: Brown powder, yield 64%, mp 221°C. ¹H NMR (300 MHz, DMSO-*d*₆): 1.97 (s, 3H, CH₃-19), 4.16 (d, 1H, CH-11, ³J_{H,H} = 3.0 Hz), 4.75 (d, 1H, CH-7, ³J_{H,H} = 3.0 Hz), 5.26 (s, 1H, CH-2), 7.61-7.82 (m, 8H, 2C₆H₄), 8.07 (s, 1H, NH-13), 8.33-8.44 (m, 5H, Ar), 9.48 (s, 1H, NH-18). ¹³C NMR (75 MHz, DMSO-*d*₆): 22.03 (CH₃-19), 47.38 (C_{quat}-3), 48.31 (CH-11), 50.06 (CH-7), 50.51 (CH-2), 55.08 (C_{quat}-1), 76.49 (C_{quat}-8), 114.78 (CN-16), 115.23 (CN-14), 124.25 (CH_{arom}), 129.17 (CH_{arom}), 130.24 (CH_{arom}), 130.39 (CH_{arom}), 130.65

(CH_{arom}), 130.80 (CH_{arom}), 131.18 (CH_{arom}), 133.52 (C_{arom}), 142.66 (C_{arom}), 144.12 (C_{arom}), 148.28 (C_{arom}), 148.49 (C_{arom}), 154.03 (N=C-10), 154.65 (N=C-4), 167.14 (C=O-12).

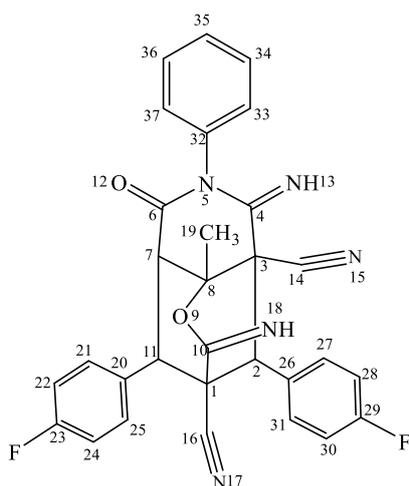


4,10-Diimino-8-methyl-2,11-bis(4-methylphenyl)-5-phenyl-6-oxo-9-oxa-5-azatricyclo-

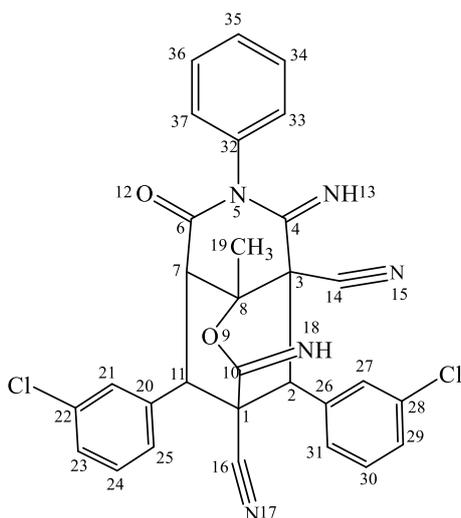
[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3c**: White powder, yield 72%, mp 225°C. ¹H NMR (300 MHz, DMSO-*d*₆): 1.88 (s, 3H, CH₃-19), 2.33 (s, 6H, 2CH₃-19/38/39), 3.86 (d, 1H, CH-11, ³J_{H,H} = 3.0 Hz), 4.40 (d, 1H, CH-7, ³J_{H,H} = 3.0 Hz), 4.84 (s, 1H, CH-2), 7.21-7.63 (m, 13CH_{arom}, 3Ar), 7.82 (s, 1H, NH-13), 9.13 (s, 1H, NH-18). ¹³C NMR (75 MHz, DMSO-*d*₆, δ): 21.16 (CH₃-19), 21.21 (CH₃-38/39), 48.36 (C_{quat}-3), 49.42 (CH-11), 50.56 (CH-7), 51.08 (CH-2), 55.62 (C_{quat}-1), 76.31 (C_{quat}-8), 115.20 (CN-16), 115.86 (CN-14), 129.40 (CH_{arom}), 129.46 (CH_{arom}), 129.57 (CH_{arom}), 129.82 (CH_{arom}), 130.24 (CH_{arom}), 130.63 (CH_{arom}), 130.70 (CH_{arom}), 133.12 (C_{arom}), 133.81 (C_{arom}), 134.99 (C_{arom}), 138.46 (C_{arom}), 138.87 (C_{arom}), 154.70 (N=C-10), 155.64 (N=C-4), 167.63 (C=O-12).



2,11-Bis(4-Fluorophenyl)-4,10-diimino-8-methyl-5-phenyl-6-oxo-9-oxa-5-azatricyclo-[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3d**: Yellow powder, yield 55%, mp 195°C. ¹H NMR (300 MHz, DMSO-*d*₆): 1.91 (s, 3H, CH₃-19), 3.98 (d, 1H, CH-11, ³J_{H,H} = 3.0 Hz), 4.51 (d, 1H, CH-7, ³J_{H,H} = 3.0 Hz), 4.97 (s, 1H, CH-2), 7.28-7.64 (m, 13CH_{arom}, 3Ar), 7.91 (s, 1H, NH-13), 9.25 (s, 1H, NH-18). ¹³C NMR (75 MHz, DMSO-*d*₆): 22.13 (CH₃-19), 48.25 (C_{quat}.-3), 49.08 (CH-11), 50.08 (CH-7), 50.46 (CH-2), 55.55 (C_{quat}.-1), 76.39 (C_{quat}.-8), 115.04 (CN-16), 115.66 (CN-14), 115.98 d (CH_{arom}, ²J_{CF} = 22 Hz), 129.79 (CH_{arom}), 130.47 d (CH_{arom}, ²J_{CF} = 22 Hz), 131.15 d (CH_{arom}, ³J_{CF} = 7 Hz), 131.73 d (C_{arom}, ⁴J_{CF} = 3.5 Hz), 133.67 (CH_{arom}), 133.89 (CH_{arom}), 133.92 (C_{arom}), 154.49 (N=C-10), 155.33 (N=C-4), 162.67 (F-C_{arom}, ¹J_{CF} = 243 Hz), 162.90 (F-C_{arom}, ¹J_{CF} = 243 Hz), 167.49 (N=C=O).

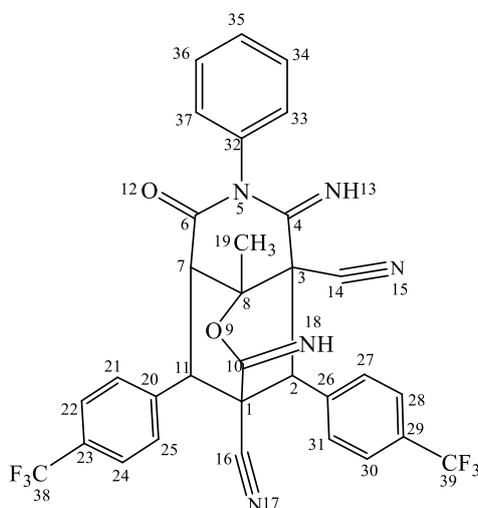


2,11-Bis(3-Chlorophenyl)-4,10-diimino-8-methyl-5-phenyl-6-oxo-9-oxa-5-azatricyclo-[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3e**: White powder, yield 75%, mp 200°C. ¹H NMR (DMSO-*d*₆): 1.89 (s, 3H, CH₃-19), 3.96 (d, 1H, CH-11, ³J_{H,H} = 3.0 Hz), 4.46 (d, 1H, CH-7, ³J_{H,H} = 3.0 Hz), 4.91 (s, 1H, CH-2), 7.33-7.62 (m, 13CH_{arom}, 3Ar), 7.97 (s, 1H, NH-13), 9.27 (s, 1H, NH-18). ¹³C NMR (75 MHz, DMSO-*d*₆): 22.04 (CH₃-19), 47.82 (C_{quat}.-3), 48.74 (CH-11), 50.07 (CH-7), 50.75 (CH-2), 55.21 (C_{quat}.-1), 76.32 (C_{quat}.-8), 114.98 (CN-16), 115.32 (CN-14), 128.33 (CH_{arom}), 129.33 (CH_{arom}), 129.43 (CH_{arom}), 129.56 (C_{arom}), 129.88 (CH_{arom}), 130.49 (CH_{arom}), 130.78 (CH_{arom}), 130.98 (CH_{arom}), 131.08 (CH_{arom}), 133.58 (C_{arom}), 133.61 (C_{arom}), 137.98 (C_{arom}), 139.82 (C_{arom}), 154.37 (N=C-10), 155.24 (N=C-4), 167.33 (C=O-12).

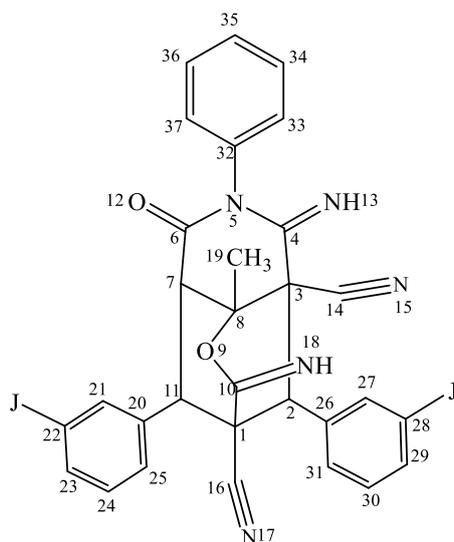


4,10-Diimino-8-methyl-2,11-bis(4-trifluoromethylphenyl)-5-phenyl-6-oxo-9-oxa-5-

azatricyclo[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3f**: Pink powder, yield 69.3%, mp 187°C. ¹H NMR (300 MHz, DMSO-*d*₆): 1.91 (s, 3H, CH₃-19), 4.02 (d, 1H, CH-11, ³J_{H,H} = 3.0 Hz), 4.62 (d, 1H, CH-7, ³J_{H,H} = 3.0 Hz), 5.10 (s, 1H, CH-2), 7.59-7.86 (m, 13CH_{arom}, 3Ar), 7.99 (s, 1H, NH-13), 9.27 (s, 1H, NH-18). ¹³C NMR (75 MHz, DMSO-*d*₆): 22.03 (CH₃-19), 47.57 (C_{quat}-3), 48.67 (CH-11), 50.22 (CH-7), 50.70 (CH-2), 55.18 (C_{quat}-1), 76.39 (C_{quat}), 114.87 (CN-16), 115.28 (CN-14), 126.02 (CH_{arom}), 126.06 (CH_{arom}), 126.12 (CH_{arom}), 126.19 (CH_{arom}), 129.51 (C_{arom}), 129.58 (CH_{arom}), 129.65 (CH_{arom}) 129.74 (CH_{arom}), 130.03 (CF₃, ¹J_{C-F} = 278.0 Hz), 133.63 (C_{arom}), 140.50 (C_{arom}), 141.67 (C_{arom}), 154.20 (N=C-10), 155.12 (N=C-4), 167.28 (C=O-12), (other C-F coupling values identification failed due to signals overlaps), MS (ESI): 621.16, 545.12, 476.13 [M+H]⁺



4,10-Diimino-2,11-bis(3-iodophenyl)-8-methyl-5-phenyl-6-oxo-9-oxa-5-azatricyclo-[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3g**: Pink powder, yield 69%, mp 163°C. ¹H NMR (300 MHz, DMSO-*d*₆): 1.87 (s, 3H, CH₃-19), 4.09 (d, 1H, CH-11, ³J_{H,H} = 3.0 Hz), 4.40 (d, 1H, CH-7, ³J_{H,H} = 3.0 Hz), 4.83 (s, 1H, CH-2), 7.23-7.77 (m, 13CH_{arom}, 3Ar), 7.94 (s, 1H, NH-13), 9.23 (s, 1H, NH-18). ¹³C NMR (75 MHz, DMSO-*d*₆): 22.12 (CH₃-19), 47.87 (C_{quat}.-3), 48.77 (CH-11), 49.92 (CH-7), 50.62 (CH-2), 55.24 (C_{quat}.-1), 76.29 (C_{quat}.-8), 95.02 (C_{arom}.-22), 95.29 (C_{arom}.-28), 115.09 (CN-16), 115.38 (CN-14), 121.30 (CH_{arom}), 128.85 (CH_{arom}), 129.54 (CH_{arom}), 129.58 (CH_{arom}), 130.53 (CH_{arom}), 130.82 (CH_{arom}), 130.90 (CH_{arom}), 130.96 (CH_{arom}), 133.30 (CH_{arom}), 137.85 (C_{arom}), 138.13 (CH_{arom}), 138.16 (C_{arom}), 139.65 (CH_{arom}), 154.42 (H=C-10), 155.20 (N=C-4), 167.33 (C=O-12).



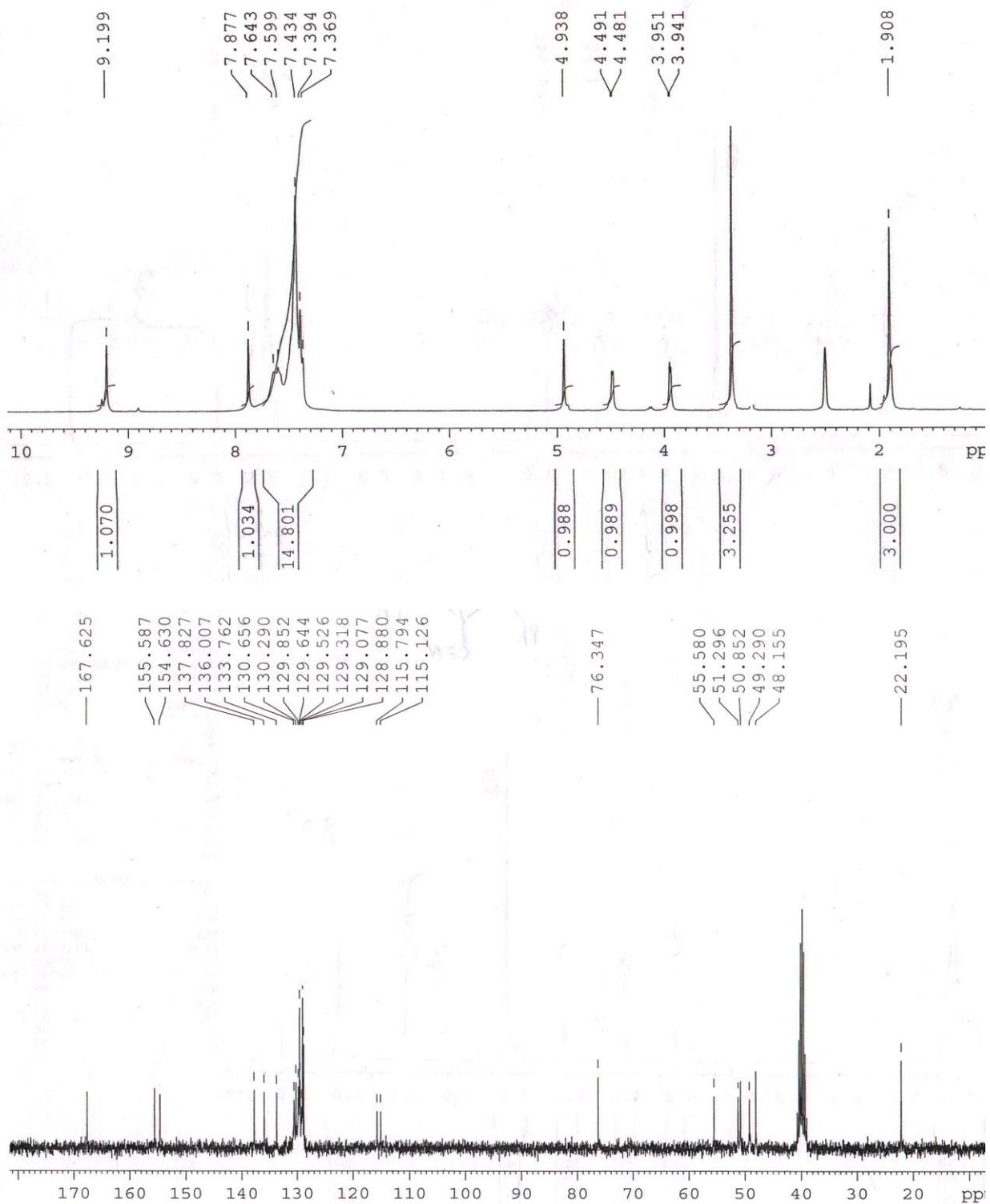


Figure S1. ^1H and ^{13}C NMR spectra of **3a**

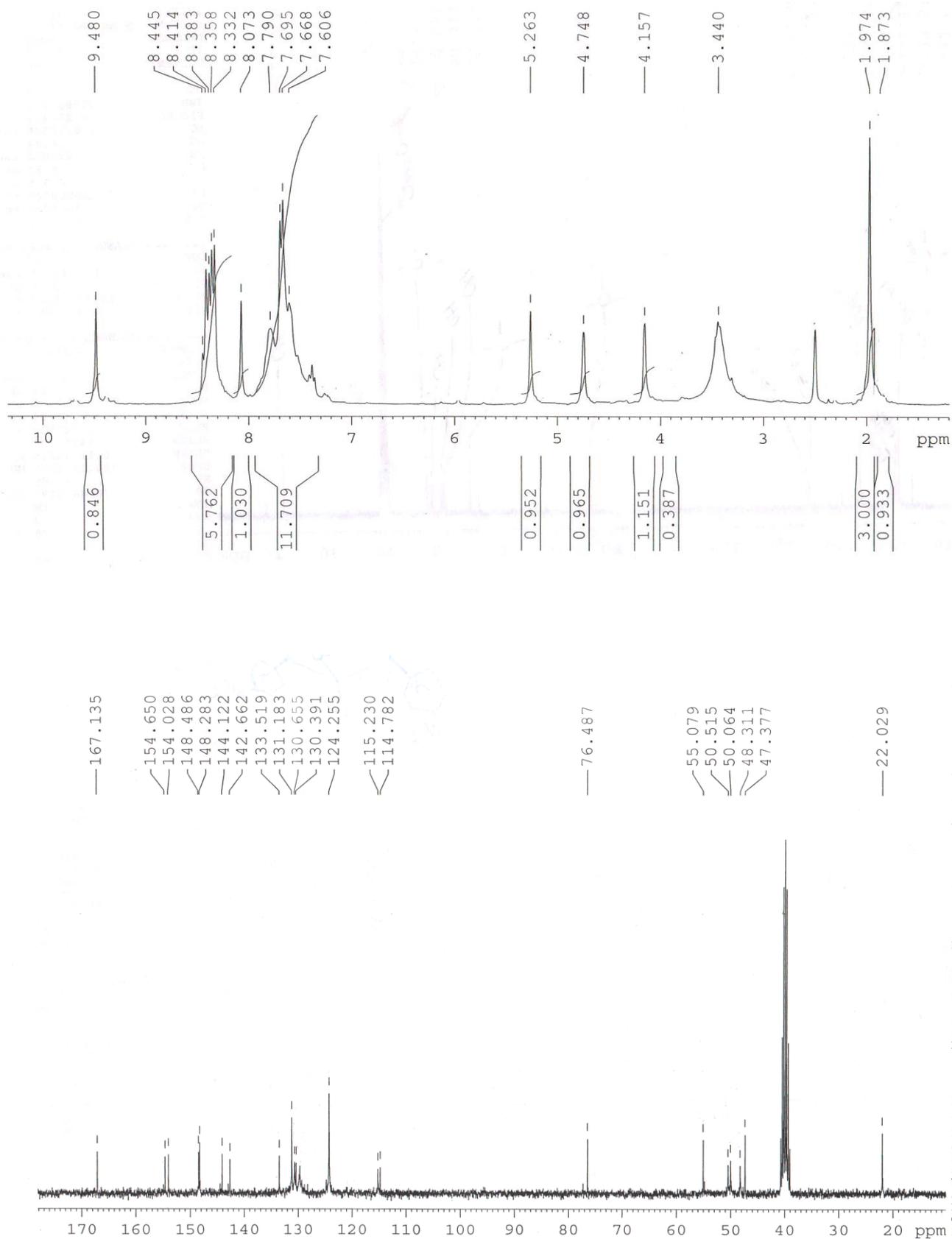


Figure S2. ^1H and ^{13}C NMR spectra of **3b**

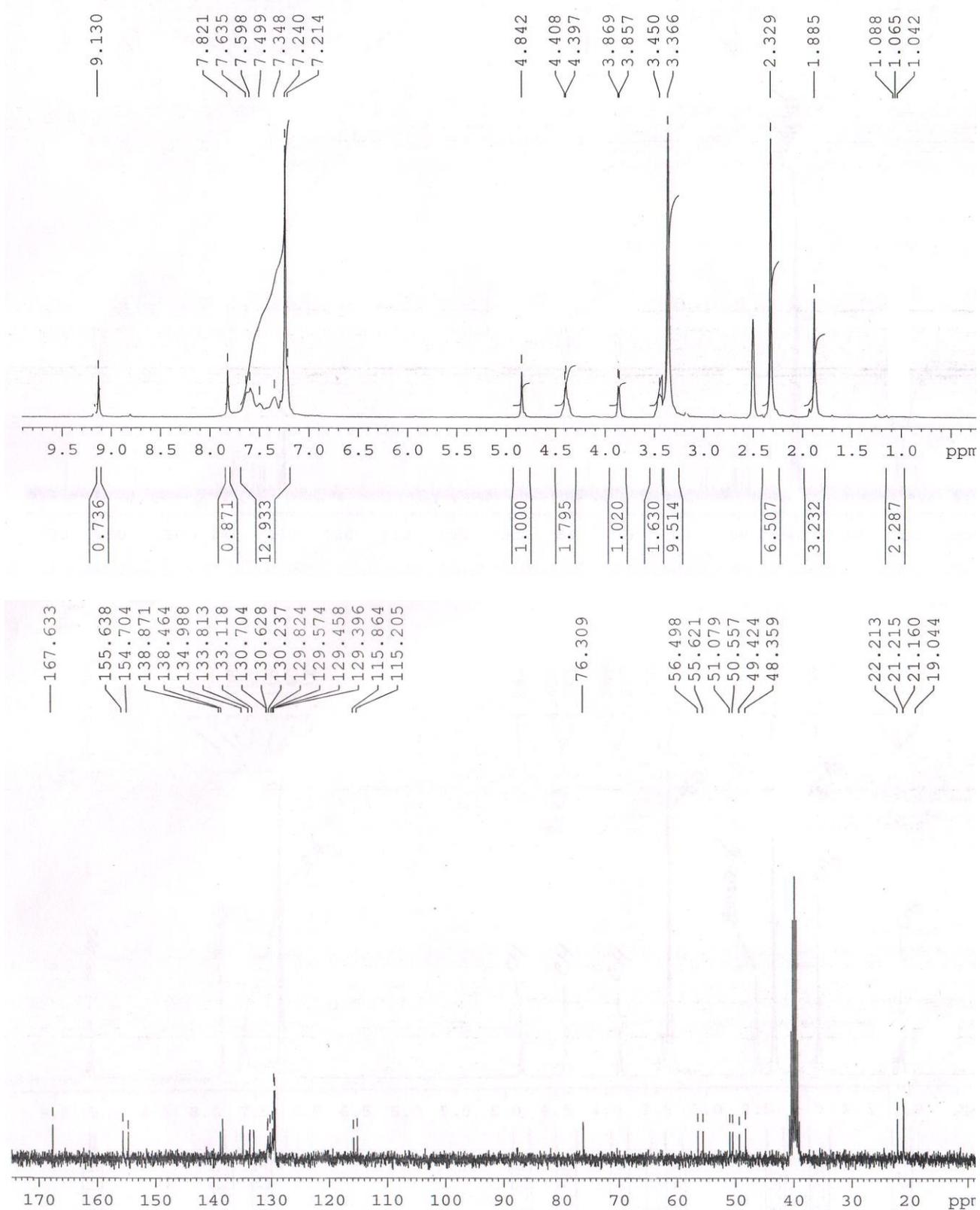


Figure S3. ^1H and ^{13}C NMR spectra of **3c**

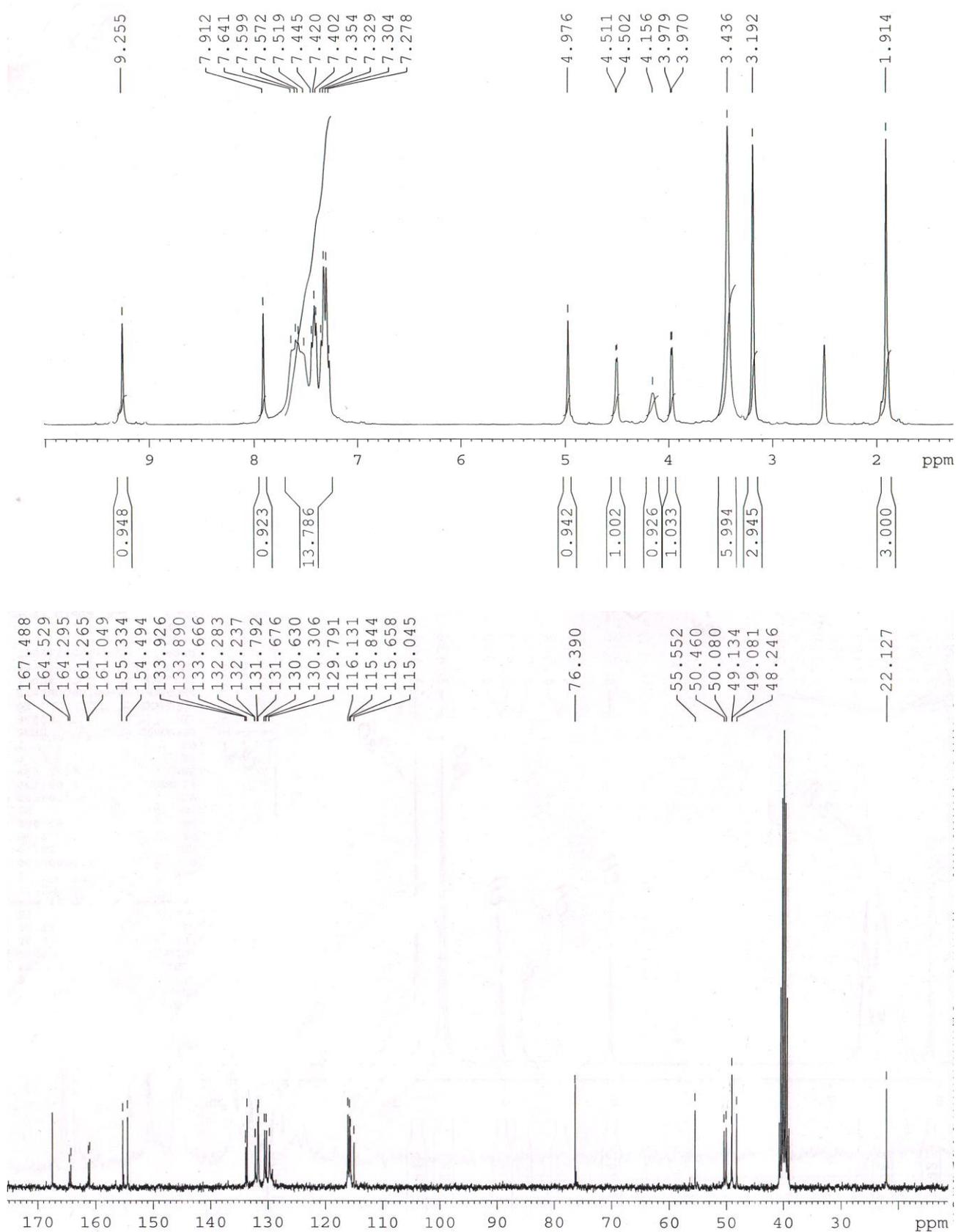


Figure S4. ^1H and ^{13}C NMR spectra of **3d**

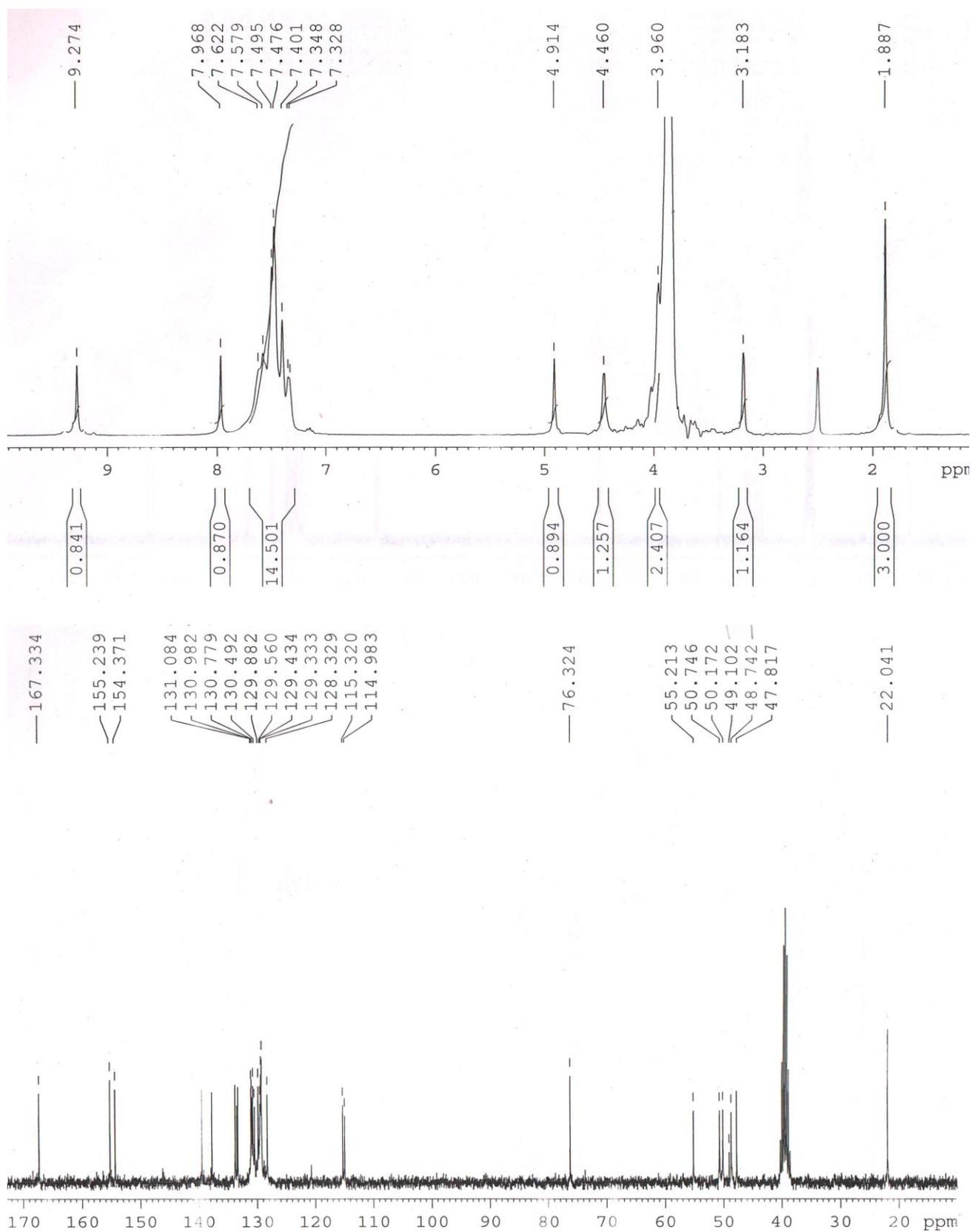


Figure S5. ^1H and ^{13}C NMR spectra of **3e**

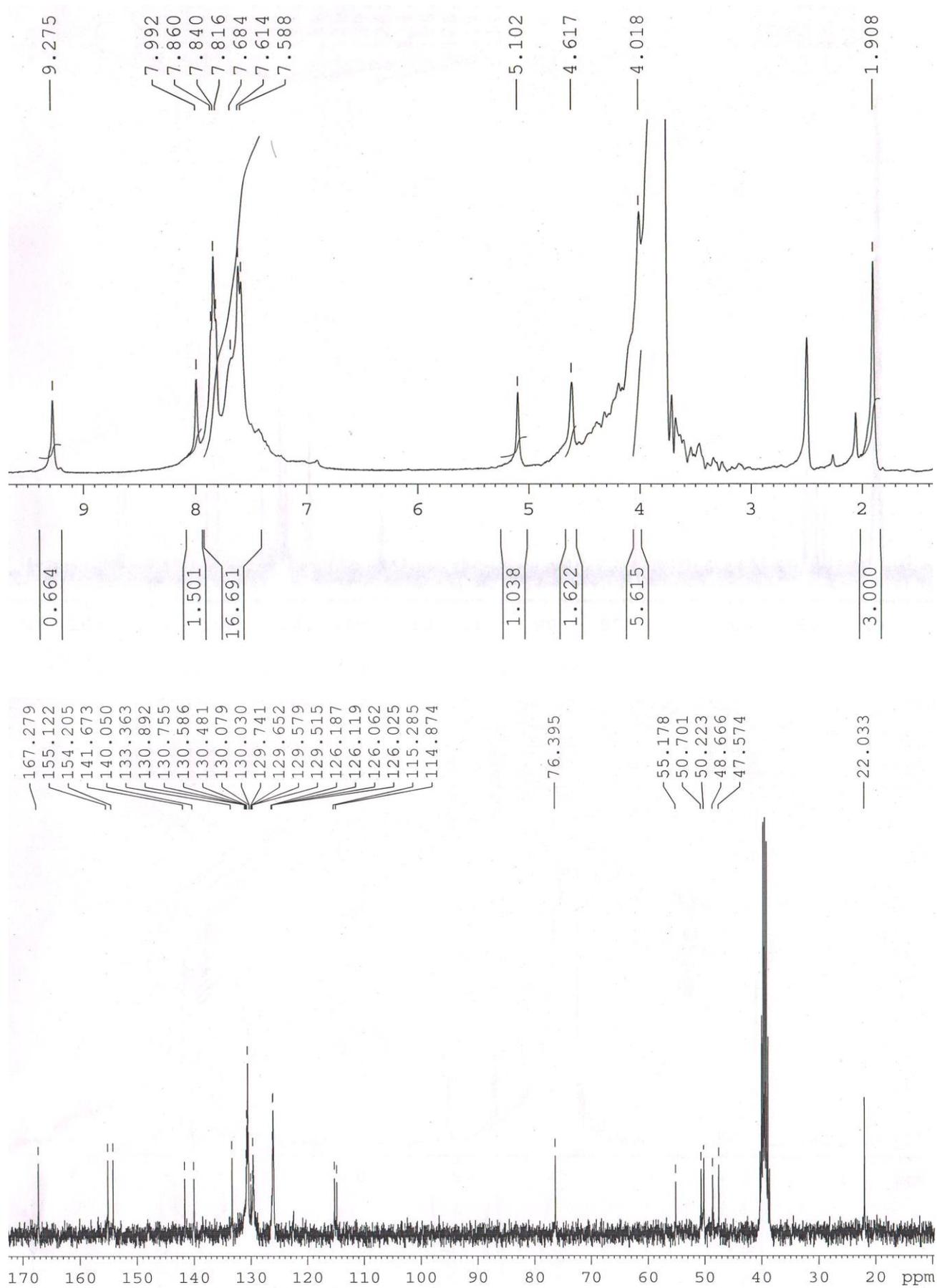


Figure S6. ^1H and ^{13}C NMR spectra of **3f**

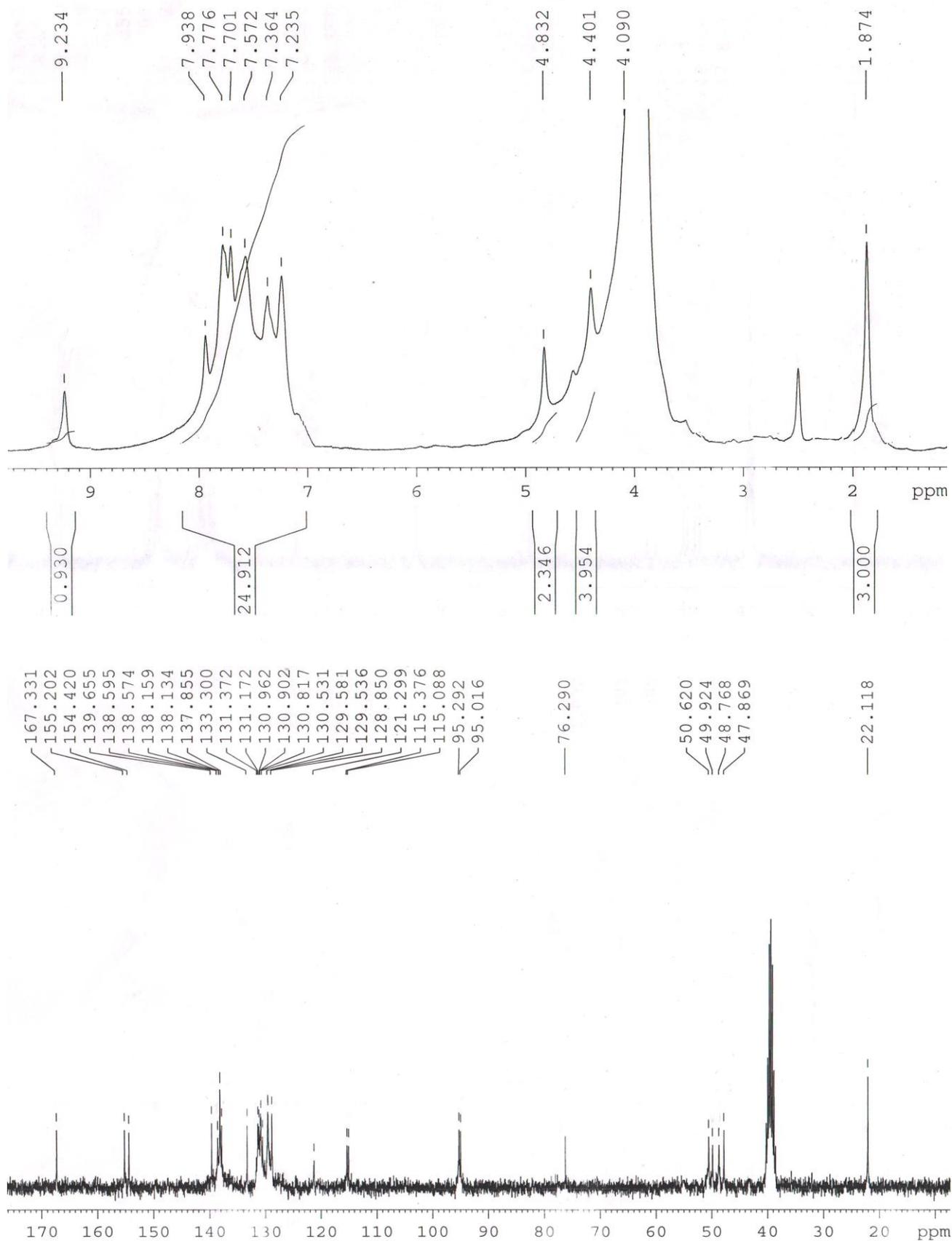


Figure S7. ¹H and ¹³C NMR spectra of **3g**