Crystal structures of 8-arylethynyl substituted guanosine derivatives: are hydrogen-bonded ribbons a surprise?

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Supporting Information

General Methods

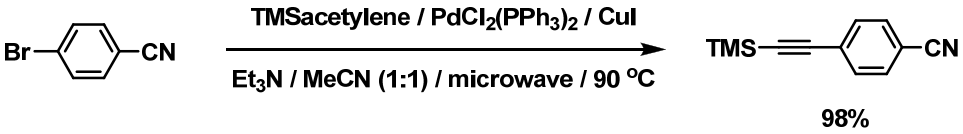
All reactions were performed under nitrogen atmosphere in oven-dried glassware. Reagents and solvents were purchased from commercial suppliers and used without further purification. Compounds 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine[1] and $PdCl_2(PPh_3)_2$[2] were prepared according to literature procedures. Microwave-assisted reactions were performed in a Biotage Initiator 2.0 microwave reactor, producing monochromatic microwave radiation with the frequency of 2.45 GHz.

Mass spectral measurements were performed by the Mass Spectrometry Facility of the Department of Chemistry and Biochemistry at the University of Texas at Austin. NMR spectra were obtained on JEOL ECX-400 and ECA-500 spectrometers, with working frequencies (for ^{1}H nuclei) of 400 and 500 MHz, respectively. All ^{13}C-NMR spectra were recorded with simultaneous decoupling of ^{1}H nuclei. ^{1}H-NMR chemical shifts are reported in ppm units relative to the residual signal of the solvent ($CDCl_3$: 7.26 ppm, DMSO-d_6: 2.50 ppm). All NMR spectra were recorded at 25 °C. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer using Pike MIRacle Micrometer pressure clamp. Microanalyses were conducted by Intertek USA, Inc. Melting points measurements were performed in open capillary tubes using Mel-Temp Thermo Scientific apparatus, and are uncorrected.

Column chromatography was carried out on silica gel 60, 32–63 mesh. Analytical TLC was performed on Merck aluminum-backed silica gel plates.

Experiments are presented in the order that follows the discussion of the manuscript.
Compound numbers are identical to those in the main text of the manuscript.

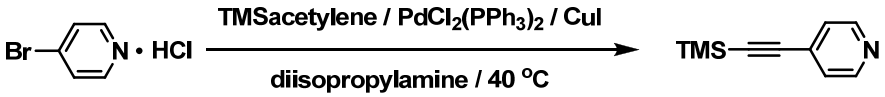
Synthesis of 4-[(Trimethylsilyl)ethynyl]benzonitrile



A mixture of 4-bromobenzonitrile (500 mg, 2.75 mmol), (trimethylsilyl)acetylene (1.98 mL, 13.7 mmol), $PdCl_2(PPh_3)_2$ (193 mg, 0.28 mmol), CuI (52 mg, 0.28 mmol), Et_3N (1 mL, 7.17 mmol), and MeCN (9.0 mL) was sealed in a thick-walled microwave pressure vial and exposed to microwave irradiation for 3 h at 90 °C. After cooling, solvents were removed under reduced pressure and the crude solid was purified by column chromatography, eluting with a hexane/ethyl acetate (91:9) mixture to collect the product. After removal of the solvent, the product was obtained as a yellow solid in 98% yield (538 mg, 2.70 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, $^3J_{H–H}$ = 8.2 Hz, 2H), 7.51 (d, $^3J_{H–H}$ = 8.2 Hz, 2H), 0.25 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 132.58, 132.08, 128.13, 118.57, 111.92, 103.13, 99.70, −0.11. This data agrees with a previous literature report.[3]

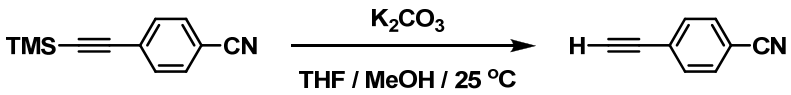
Synthesis of 4-[(Trimethylsilyl)ethynyl]pyridine



A mixture of 4-bromopyridine hydrochloride (3.00 g, 15.4 mmol), $PdCl_2(PPh_3)_2$ (271 mg, 0.39 mmol), and CuI (74 mg, 0.39 mmol) was placed in a 100 mL three-neck round-bottom flask. The flask was flushed with nitrogen gas, and degassed diisopropylamine (30 mL) was added into the flask while stirring at 40 °C, followed by the addition of (trimethylsilyl)acetylene (4.44 mL, 30.9 mmol). After 12 h, the reaction mixture was diluted with water (1 mL), extracted with CH_2Cl_2, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude oil was purified by column chromatography, eluting with a hexane/ethyl acetate (89:11) mixture to collect the product. After removal of the solvent, the product was obtained as a dark brown oil in 96% yield (2.60 g, 14.9 mmol).

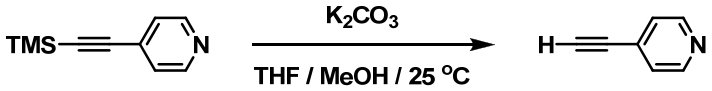
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (dd, $^3J_{H–H}$ = 4.6 Hz, $^5J_{H–H}$ = 1.8 Hz, 2H), 7.30 (dd, $^3J_{H–H}$ = 4.6 Hz, $^5J_{H–H}$ = 1.8 Hz, 2H), 0.26 (s, 9H). This data agrees with a previous literature report.[4]

Synthesis of 4-Ethynylbenzonitrile



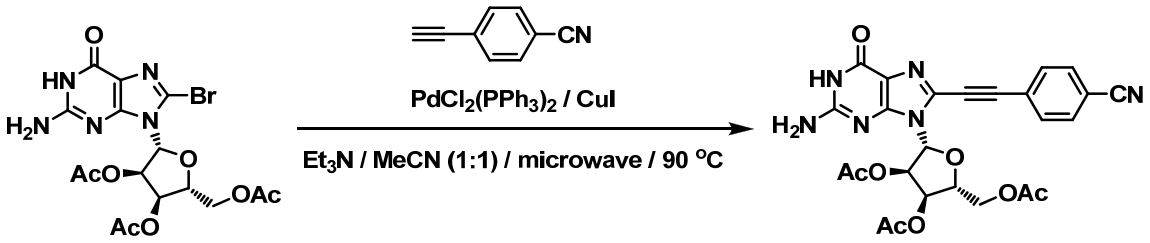
In a nitrogen-flushed round-bottom flask, anhydrous K_2CO_3 (423 mg, 3.07 mmol) was added to a solution of 4-[(trimethylsilyl)ethynyl]benzonitrile (306 mg, 1.54 mmol) in a mixture of MeOH (3 mL) and THF (3 mL). After stirring for 30 min, the reaction mixture was filtered through celite. The solvent was removed under reduced pressure, to yield crude 4-ethynylbenzonitrile, which was used without purification in the next step. To minimize manipulations of this somewhat sensitive compound, we assumed a 95% yield for this reaction.

Synthesis of 4-Ethynylpyridine



In a nitrogen-flushed round-bottom flask, anhydrous K_2CO_3 (1.15 g, 8.30 mmol) was added to a solution of 4-[(trimethylsilyl)ethynyl]pyridine (64 mg, 3.69 mmol) in a mixture of MeOH (5 mL) and THF (5 mL). After stirring for 30 min, the reaction mixture was filtered through celite. The solvent was removed under reduced pressure, to yield crude 4-ethynylpyridine, which was used without purification in the next step. To minimize manipulations of this somewhat sensitive compound, we assumed a 95% yield for this reaction.

Synthesis of Compound **3**



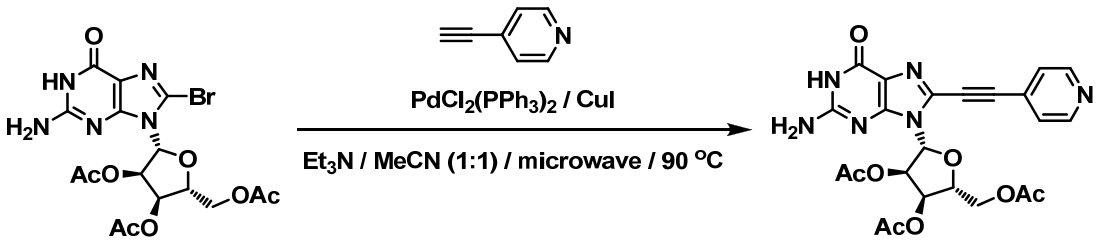
2 **3, 83%**

The entire amount of crude 4-ethynylbenzonitrile (prepared as above described) was added to a thick-walled microwave pressure vial containing a mixture of 8-bromo-2′,3′,5′-tri-*O*-

acetylguanosine (**2**, 500 mg, 1.02 mmol), $PdCl_2(PPh_3)_2$ (144 mg, 0.21 mmol), CuI (39 mg, 0.21 mmol), Et_3N (5 mL), and MeCN (5 mL). The vial was sealed and exposed to microwave irradiation for 3 h at 90 °C. After cooling, solvents were removed under reduced pressure and the crude solid was purified by column chromatography, eluting first with pure CH_2Cl_2, then with a CH_2Cl_2/MeOH (97:3) mixture, and finally with a 19:1 CH_2Cl_2/MeOH mixture. After removal of the solvent, the product was obtained as a yellow solid (mp >150 °C, with decomposition) in 83% yield (452 mg, 0.85 mmol). Single crystals of **3** were obtained by layering a chloroform solution of **3** (8 mg/mL) with pentane (crystals formed in 2 days).

UV-Vis (CH_2Cl_2): λ_{max} (logε) = 266 (6.23), 348 (6.30) nm. IR (neat): 3710 (w, $\tilde{\nu}_{N-H\cdots N}$), 3461 (w, $\tilde{\nu}_{N-H}$), 2968 (w, $\tilde{\nu}_{C-H}$), 2230 (w, $\tilde{\nu}_{C\equiv N}$), 2130 (w, $\tilde{\nu}_{C\equiv C}$), 1739 (s, $\tilde{\nu}_{C=O}$), 1367 (s, $\tilde{\nu}_{C-N}$), 1229 (s, $\tilde{\nu}_{C-O}$), 1033 (w, $\tilde{\nu}_{N-C=N}$) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 11.90 (br s, 1H), 7.74 (d, $^3J_{H-H}$ = 8.0 Hz, 2H), 7.68 (d, $^3J_{H-H}$ = 8.0 Hz, 2H), 6.90 (br s, 2H), 6.19 (dd, $^3J_{H-H}$ = 5.7 Hz, $^3J_{HH}$ = 3.4 Hz, 1H), 6.13 (d, $^3J_{H-H}$ = 3.4 Hz, 1H), 6.08 (dd, $^3J_{H-H}$ = 6.3 Hz, $^3J_{H-H}$ = 5.7 Hz, 1H), 4.50 (dd, $^2J_{H-H}$ = 12.0 Hz, $^3J_{H-H}$ = 4.0 Hz, 1H), 4.38 (m, 1H), 4.30 (dd, $^2J_{H-H}$ = 12.0 Hz, $^3J_{H-H}$ = 5.7 Hz, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.87, 169.64 (2C), 158.44, 154.49, 151.22, 132.73, 132.36, 130.27, 125.92, 118.32, 118.16, 113.05, 93.09, 87.43, 81.80, 79.50, 72.90, 70.28, 62.92, 20.81, 20.75 (2C). HRMS (ESI): Calcd for $C_{25}H_{23}N_6O_8^+$: 535.1572. Found: 535.1566. Anal. calcd for $C_{25}H_{22}N_6O_8$: C, 56.18; H, 4.15; N, 15.72. Found: C, 55.67; H, 4.67; N, 12.97.

Synthesis of Compound **4**



2 **4, 58%**

The entire amount of 4-ethynylpyridine (prepared as above described) was added to a thick-walled microwave pressure vial that contained a mixture of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine (**2**, 900 mg, 1.84 mmol), $PdCl_2(PPh_3)_2$ (259 mg, 0.37 mmol), CuI (70 mg, 0.37 mmol), Et_3N (5 mL), and MeCN (5 mL). The vial was sealed and exposed to microwave irradiation for 3 h at 90 °C. After cooling, solvents were removed under reduced pressure, and the crude solid was purified by column chromatography, eluting first with pure CH_2Cl_2, and then successively with CH_2Cl_2/MeOH mixtures in 97:3, 19:1, and 9:1 ratios. After removal of the

solvent, the product was obtained as a yellow solid (mp >127 °C, with decomposition) in 58% yield (546 mg, 1.07 mmol). Single crystals of **4** were obtained by layering a chloroform solution of **4** (4 mg/mL) with hexane (crystals formed in 7 days).

UV-Vis (CH_2Cl_2): λ_{max} (logε) = 267 (5.90), 336 (6.15) nm. IR (neat): 3467 (w, $\tilde{\nu}_{N-H}$), 3155 (w, $\tilde{\nu}_{C-H}$), 2227 (w, $\tilde{\nu}_{C\equiv C}$), 1754 (s, $\tilde{\nu}_{C=O}$), 1729 (s, $\tilde{\nu}_{C=O}$), 1705 (s, $\tilde{\nu}_{C=O}$), 1366 (s, $\tilde{\nu}_{C-N}$), 1244 (s, $\tilde{\nu}_{C-O}$) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 12.03 (br s, 1H), 8.69 (d, $^3J_{H-H}$ = 5.9 Hz, 2H), 7.52 (d, $^3J_{H-H}$ = 5.9 Hz, 2H), 6.69 (br s, 2H), 6.21 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 3.7 Hz, 1H), 6.15 (d, $^3J_{H-H}$ = 3.7 Hz, 1H), 6.12 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 5.9 Hz, 1H), 4.54 (dd, $^2J_{H-H}$ = 11.9 Hz, $^3J_{H-H}$ = 3.7 Hz, 1H), 4.41 (ddd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 3.7 Hz , 1H), 4.33 (dd, $^2J_{H-H}$ = 11.9 Hz, $^3J_{H-H}$ = 5.9 Hz, 1H), 2.14 (s, 3H), 2.14 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.10, 169.62, 169.53, 156.06, 154.54, 151.07, 150.17, 128.27, 127.76, 125.33, 117.76, 90.63, 86.59, 82.46, 79.21, 78.92, 71.78, 69.76, 62.83, 20.42, 20.32. HRMS (ESI): Calcd for $C_{23}H_{23}N_6O_8^+$: 511.1572. Anal. calcd for $C_{23}H_{22}N_6O_8$: C, 54.12; H, 4.34; N, 16.46. Found: C, 53.20; H, 4.03; N, 16.04.

Crystal Data for Compound **3**

Empirical formula	$C_{27}H_{24}Cl_6N_6O_8$	
Formula weight	773.22	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.726(8) Å	α = 90.00°
	b = 10.525(2) Å	β = 90.00°
	c = 34.007(2) Å	γ = 90.00°
Volume	3481.5(4) Å^3	
Z	4	
Density (calculated)	1.475 Mg/m^3	
Absorption coefficient	0.548 mm^{-1}	
F(000)	1576	
Crystal size	0.45 × 0.30 × 0.08 mm	
Theta range for data collection	1.20 to 23.54 °	
Index ranges	$-10 \le h \le 11$, $0 \le k \le 11$, $0 \le l \le 38$	
Reflections collected	15676	
Independent reflections	5190 [R_{int} = 0.062]	
Completeness to theta = 23.54 °	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9892 and 0.7299	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3072 / 0 / 389	
Goodnees-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R_1 = 0.059, wR_2 = 0.169	
R indices (all data)	R_1 = 0.096, wR_2 = 0.206	
Largest diff. peak and hole	+0.61 and −0.33 e$^-$/Å^3	

Crystal Data for Compound **4**

Empirical formula	$C_{25}H_{24}Cl_6N_6O_8$	
Formula weight	749.20	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.754(1) Å	α = 90.00°
	b = 10.353(1) Å	β = 90.00°
	c = 31.859(3) Å	γ = 90.00°
Volume	3217.4(6) Å^3	
Z	4	
Density (calculated)	1.547 Mg/m^3	
Absorption coefficient	0.590 mm^{-1}	
F(000)	1528	
Crystal size	0.45 × 0.20 × 0.05 mm	
Theta range for data collection	1.28 to 23.64 °	
Index ranges	$-10 \le h \le 11$, $0 \le k \le 11$, $0 \le l \le 35$	
Reflections collected	13581	
Independent reflections	4782 [R_{int} = 0.079]	
Completeness to theta = 23.64 °	99.3 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9957 and 0.7244	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2814 / 0 / 415	
Goodnees-of-fit on F^2	1.218	
Final R indices [I>2sigma(I)]	R_1 = 0.058, wR_2 = 0.124	
R indices (all data)	R_1 = 0.120, wR_2 = 0.169	
Largest diff. peak and hole	+0.44 and −0.41 e$^-$/Å^3	

References

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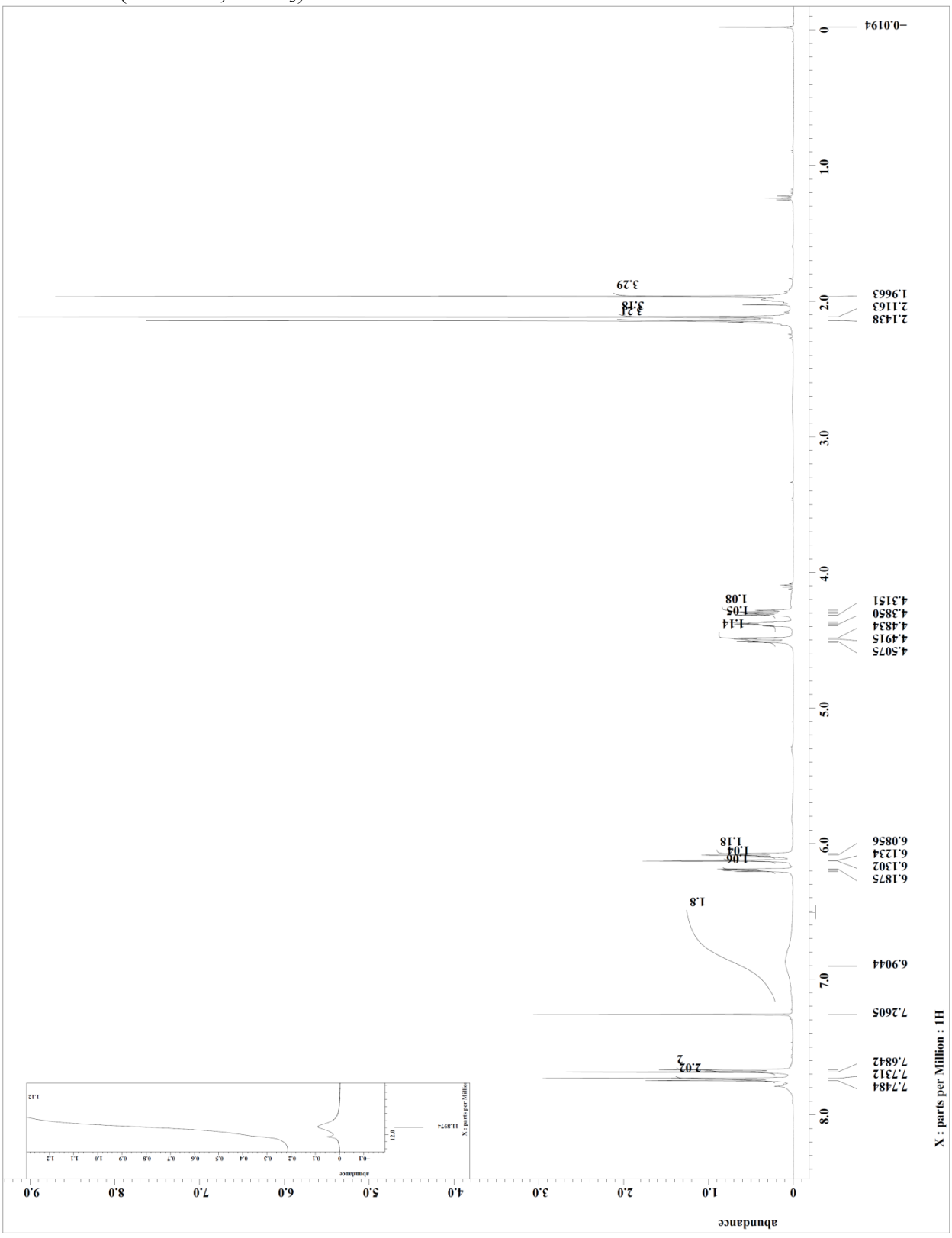
(2) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London/Orlando, 1985; pp. 18.

(3) Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717–729.

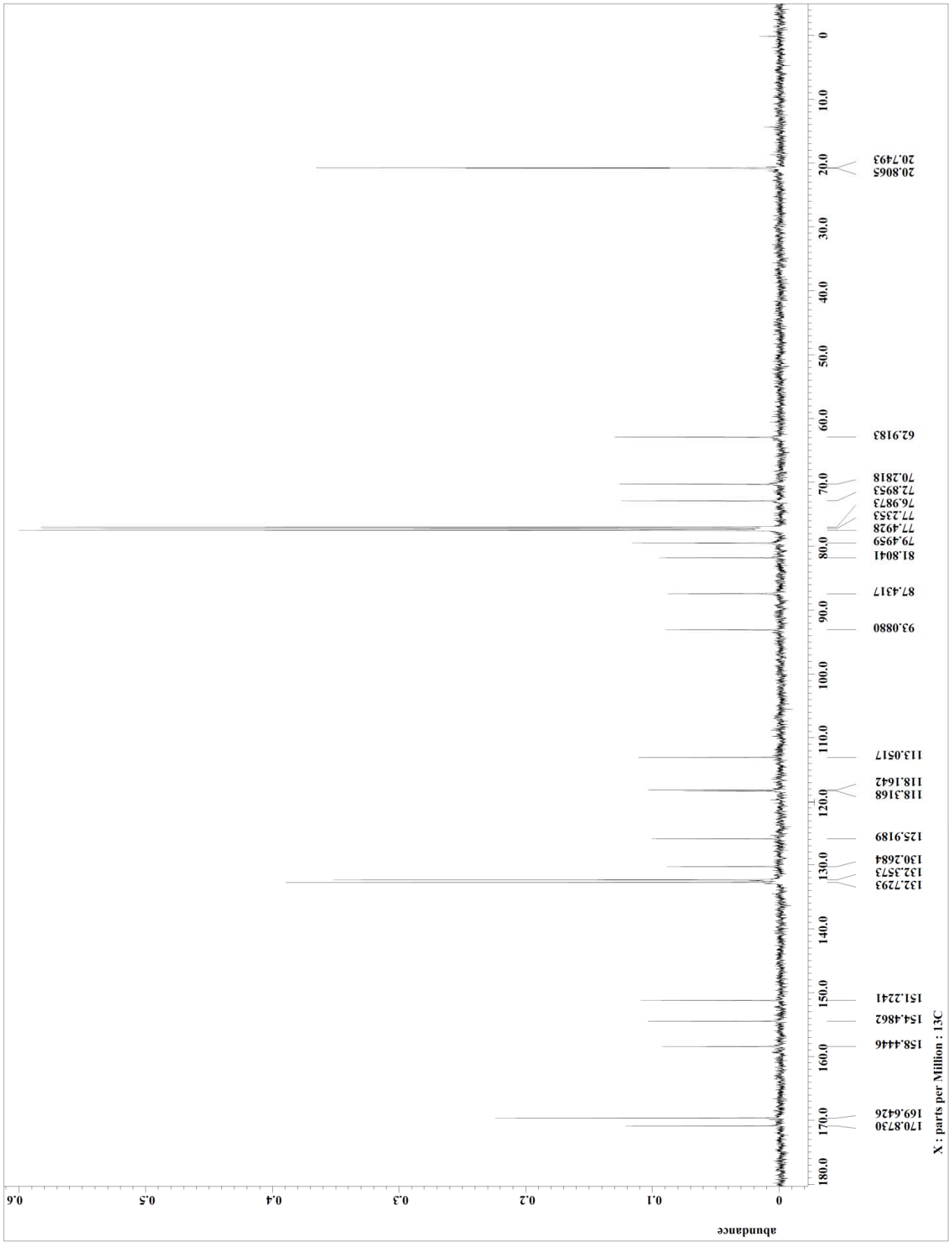
(4) Ziessel, R.; Suffert, J.; Youinou, M.-T. *J. Org. Chem.* **1996**, *6*, 6535–6546.

NMR Spectra of New Compounds

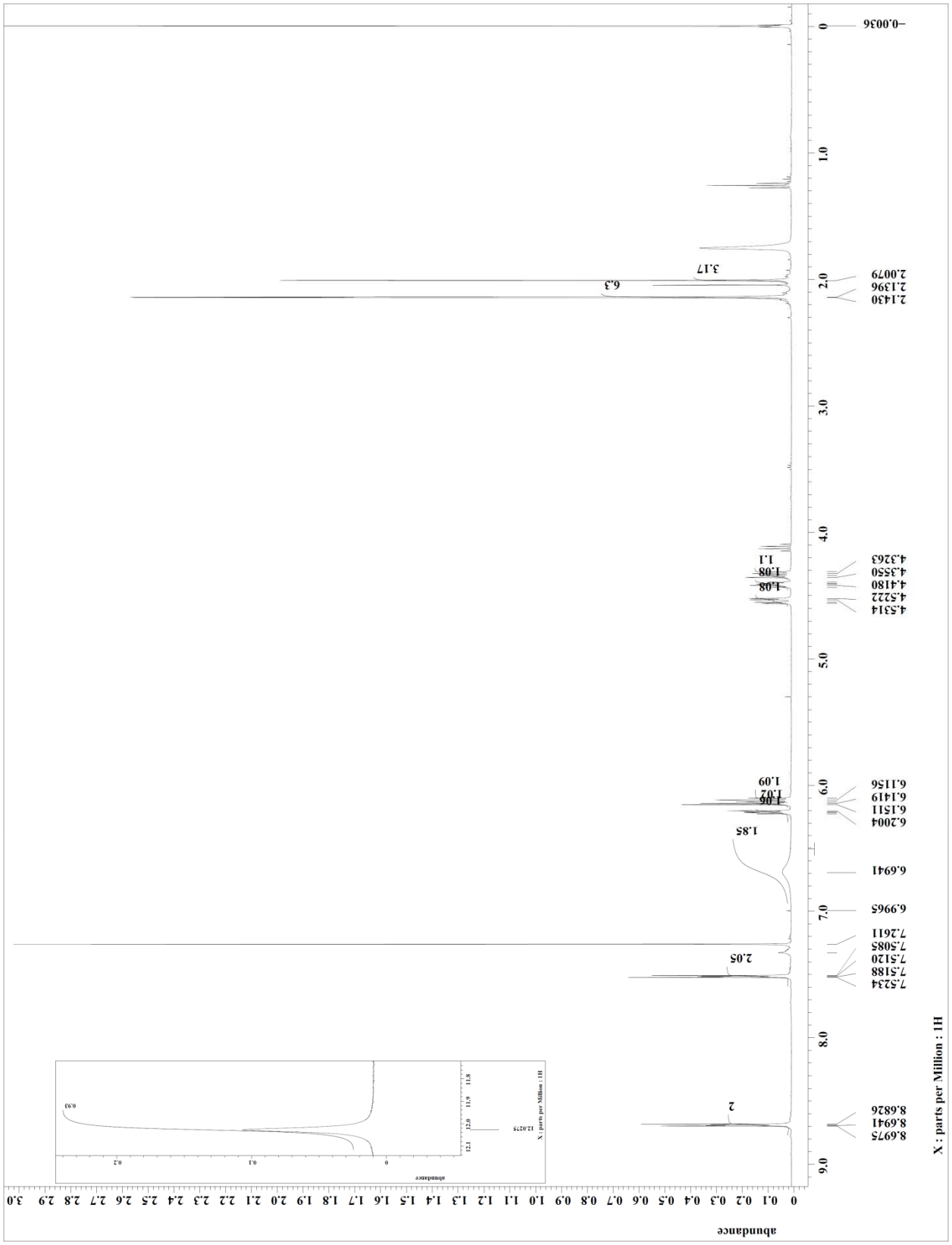
3: ^{1}H NMR (500 MHz, $CDCl_3$)



3: ^{13}C NMR (125 MHz, $CDCl_3$)



4: ^{1}H NMR (400 MHz, $CDCl_3$)



4: ^{13}C NMR (125 MHz, DMSO-d_6)