

SUPPORTING INFORMATION

Single-step Syntheses of 2-Amino-7-chlorothiazolo[5,4-*d*]pyrimidines: Intermediates for Bivalent Thiazolopyrimidines

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Contents

Analytical Data	S2
Analytical Data (Table 2, Compounds 7, 18-19)	S2
Analytical Data (Table 3, Compound 20-23)	S3
Analytical Data (Table 3, Compounds 24-28)	S4
Analytical Data (Table 4, Compounds 29-32)	S5
Analytical Data (Table 4, Compounds 33-35)	S6
Crystallographic Data	
Thermal Ellipse Rendering of Compound 6	S7
¹H NMR Spectra (Compounds 4, 6, 7, 18-35)	S8-S28

¹H NMR data were obtained using TMS as an internal standard. HPLC (ELSD) data were obtained using a PrincetonSPHER HTS C18, 5- μ m, 60- \AA , 3 X 50 mm column (Princeton Chromatography, Inc.). Each HPLC (ELSD) run was carried out using a linear gradient of 25-100% CH₃CN/H₂O (0.1% TFA) in 2.4 min, and the retention time (R_t) for the expected (major) product was recorded. Accurate mass values are reported as the averages of 20 measurements.

Analytical Data

(7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)phenylamine (7) as an off-white powder (241 mg, 92%). ¹H NMR (300 MHz, DMSO-d₆): δ 11.22 (s, 1H), 8.65 (s, 1H), 7.78 (d, J =7.5 Hz, 2H), 7.43 (dd, J =7.5, 7.9 Hz, 2H), 7.14(t, J =7.5 Hz, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 163.03, 161.32, 150.17, 145.10, 141.83, 136.94, 132.89, 129.61 (2C), 118.93 (2C); HR-MS m/z (M+H⁺) calcd 263.0158, obsd 263.0167.

(7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)-(2,6-dimethylphenyl)amine (18) as a white powder (262 mg, 90%). ¹H NMR (300 MHz, DMSO-d₆): δ 10.66 (s, 1H), 8.56 (s, 1H), 7.21-7.16 (m, 3H), 2.24 (s, 6H); ¹³C NMR (75 MHz, DMSO-d₆): δ 169.0, 163.5, 149.4, 144.5 (2C), 143.2, 136.1 (2C), 128.8 (3C), 17.6 (2C); HR-MS m/z (M+H⁺) calcd 291.0471, obsd 291.0480.

(7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)-*p*-tolylamine (19) as a yellow powder (258 mg, 93%). ¹H NMR (300 MHz, DMSO-d₆): δ 11.15 (s, 1H), 8.63 (s, 1H), 7.65 (d, J =8.7 Hz, 2H), 7.23 (d, J =8.7 Hz, 2H), 2.30 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 163.6,

161.9, 150.7, 145.6, 142.4, 137.5, 133.4, 130.1 (2C), 119.5 (2C), 21.0; HR-MS m/z (M+H⁺) calcd 277.0315, obsd 277.0321.

(7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)-(4-methoxyphenyl)amine (20) as a white powder (278 mg, 95%). ¹H NMR (300 MHz, DMSO-d₆): δ 11.05 (s, 1H), 8.61 (s, 1H), 7.66 (d, *J*=9.0 Hz, 2H), 7.00 (d, *J*=9.0 Hz, 2H), 3.76 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 163.6, 162.4, 156.5, 150.7, 145.5, 142.7, 133.1, 121.6 (2C), 115.1 (2C), 56.0; HR-MS m/z (M+H⁺) calcd 293.0264, obsd 293.0256.

(7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)-(3-trifluoromethylphenyl)amine (21) as an off-white powder (271 mg, 82%). ¹H NMR (300 MHz, DMSO-d₆): δ 11.55 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.90 (d, *J*=8.4 Hz, 1H), 7.65 (dd, *J*=8.0, 7.9 Hz, 1H), 7.47 (d, *J*=7.5 Hz, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 163.7, 161.6, 151.5, 146.6, 142.1, 140.8, 131.1, 130.7, 130.4, 122.8, 120.4, 115.4; HR-MS m/z (M+H⁺) calcd 331.0032, obsd 331.0048.

(7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)-(4-nitrophenyl)amine (22) as a red solid (154 mg, 50%). ¹H NMR (400 MHz, DMSO-d₆): δ 11.85 (s, 1H), 8.70, (s, 1H), 8.28 (d, *J*=9.2 Hz, 2H), 7.97 (d, *J*=9.2 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 163.6, 161.5, 151.4, 146.8, 146.3, 142.3, 141.8, 125.8 (2C), 118.9 (2C); HR-MS m/z (M+H⁺) calcd 308.0009, obsd 308.0008.

(7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)-pyridin-3-ylamine (23) as a yellow powder (210 mg, 80%). ¹H NMR (300 MHz, DMSO-d₆): δ 12.32 (s, 1H), 9.28 (d, *J*=2.7 Hz, 1H), 8.75 (s, 1H), 8.59-8.53 (m, 2H), 7.86 (dd, *J*=8.6, 5.4 Hz, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 163.7, 161.3, 151.7, 147.0, 141.4, 139.4, 138.4, 134.6, 131.2, 126.9; HR-MS m/z (M⁺) calcd 263.0032, obsd 263.0025.

t-Butyl-(7-chlorothiazolo[5,4-d]pyrimidin-2-yl)amine (24) as a white powder (182 mg, 75%). ^1H NMR (300 MHz, DMSO-d₆): δ 8.71 (s, 1H), 8.49 (s, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 163.9, 163.6, 149.8, 144.3, 143.0, 54.7, 28.8 (3C); HR-MS m/z (M+H⁺) calcd 243.0471, obsd 243.0470.

(7-Chlorothiazolo[5,4-d]pyrimidin-2-yl)isopropylamine (25) as a white powder (153 mg, 67%). ^1H NMR (400 MHz, CDCl₃): δ 8.54 (s, 1H), 5.69 (d, $J=7.2\text{Hz}$, 1H), 3.99-3.90 (m, 1H), 1.36 (d, $J=6.8\text{ Hz}$, 6H); ^{13}C NMR (100 MHz, CDCl₃): δ 165.5, 163.1, 149.6, 146.2, 142.6, 48.3, 22.8 (2C); HR-MS m/z (M+H⁺) calcd 229.0315, obsd 229.0324.

1-(7-Chlorothiazolo[5,4-d]pyrimidin-2-yl)-1,3-dimethylthiourea (26) as a white powder (133 mg, 98% based on isothiocyanate). ^1H NMR (300 MHz, DMSO-d₆): δ 9.41 (s, 1H), 8.81 (s, 1H), 3.89 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d₆): δ 181.9, 164.5, 162.2, 152.1, 149.7, 140.1, 41.9, 33.7; HR-MS m/z (M⁺) calcd 272.9910, obsd 272.9914.

1,3-Dibenzyl-1-(7-chlorothiazolo[5,4-d]pyrimidin-2-yl)thiourea (27) as an off-white powder (200 mg, 94% based on isothiocyanate). ^1H NMR (400 MHz, DMSO-d₆): δ 10.46 (s, 1H), 8.80 (s, 1H), 7.39-7.16 (m, 10H), 5.89 (s, 2H), 4.82 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d₆): δ 182.0, 164.1, 153.6, 152.5, 148.7, 138.4, 137.1, 135.9, 129.3, 129.0 (2C), 128.8 (2C), 128.0 (2C), 127.6, 127.4 (2C), 54.1, 49.9; HR-MS m/z (M+H⁺) calcd 426.0614, obsd 426.0600.

[7-(4-Methylpiperazin-1-yl)-thiazolo[5,4-d]pyrimidin-2-yl]phenylamine (28) as a white powder (52.7 mg, 85%). ^1H NMR (300 MHz, DMSO-d₆): δ 10.61 (s, 1H), 8.22 (s, 1H), 7.61 (dd, $J=8.7, 0.9\text{ Hz}$, 2H), 7.36 (dd, $J=8.7, 7.2\text{ Hz}$, 2H), 7.03 (t, $J=7.2\text{ Hz}$, 1H), 4.22-4.09 (m, 4H), 2.46-2.43 (m, 4H), 2.21 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d₆):

δ 160.8, 156.5, 152.6, 151.7, 140.8, 129.8 (2C), 128.9, 123.1, 118.4 (2C), 55.3 (2C), 46.4, 46.0 (2C); HR-MS m/z (M+H⁺) calcd 327.1392, obsd 327.1398.

N⁷-Butyl-N²-phenylthiazolo[5,4-d]pyrimidine-2,7-diamine (29) as an off-white powder (51.3 mg, 90%). ¹H NMR (300 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.18 (s, 1H), 7.85 (d, *J*=7.8 Hz, 2H), 7.48 (t, *J*=5.4 Hz, 1H), 7.35 (dd, *J*=7.8, 7.2 Hz, 2H), 7.03 (t, *J*=7.2 Hz, 1H), 3.51-3.49 (m, 2H), 1.63-1.58 (m, 2H), 1.39-1.32 (m, 2H), 0.92 (t, *J*=7.2 Hz, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 158.0, 156.3, 153.3, 152.3, 140.8, 129.4 (2C), 129.1, 122.5, 118.2 (2C), 39.1, 31.9, 20.1, 14.3; HR-MS m/z (M+H⁺) calcd 300.1283, obsd 300.1268.

N⁷-*t*-Butyl-N²-phenyl-thiazolo[5,4-d]pyrimidine-2,7-diamine (30) as white powder (11.4 mg, 20%). ¹H NMR (300 MHz, DMSO-d₆): δ 10.60 (s, 1H), 8.21 (s, 1H), 7.76, (dd, *J*=1.2, 8.6 Hz, 2H), 7.36 (dd, *J*=7.5, 8.6 Hz, 2H), 7.04 (t, *J*=7.2 Hz, 1H), 6.16 (s, 1H), 1.53 (s, 9H); ¹³C NMR (75 MHz, DMSO-d₆): δ 158.4, 156.1, 153.0, 151.6, 140.6, 129.6, 129.5 (2C), 122.8, 118.4 (2C), 52.1, 29.2 (3C); HR-MS m/z (M⁺) calcd 299.1205, obsd 299.1193.

N²,N⁷-Diphenylthiazolo[5,4-d]pyrimidine-2,7-diamine (31) as a white powder (56.4 mg, 93%). ¹H NMR (300 MHz, DMSO-d₆): δ 10.70 (s, 1H), 9.22 (s, 1H), 8.33 (s, 1H), 7.93-7.82 (m, 4H), 7.40-7.35 (m, 4H), 7.12-7.03 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆): δ 158.6, 158.3, 151.5, 150.6, 140.6, 139.7, 130.0, 129.5 (2C), 128.8 (2C), 123.5, 122.8, 122.2 (2C), 118.5 (2C); HR-MS m/z (M⁺) calcd 319.0892, obsd 319.0892.

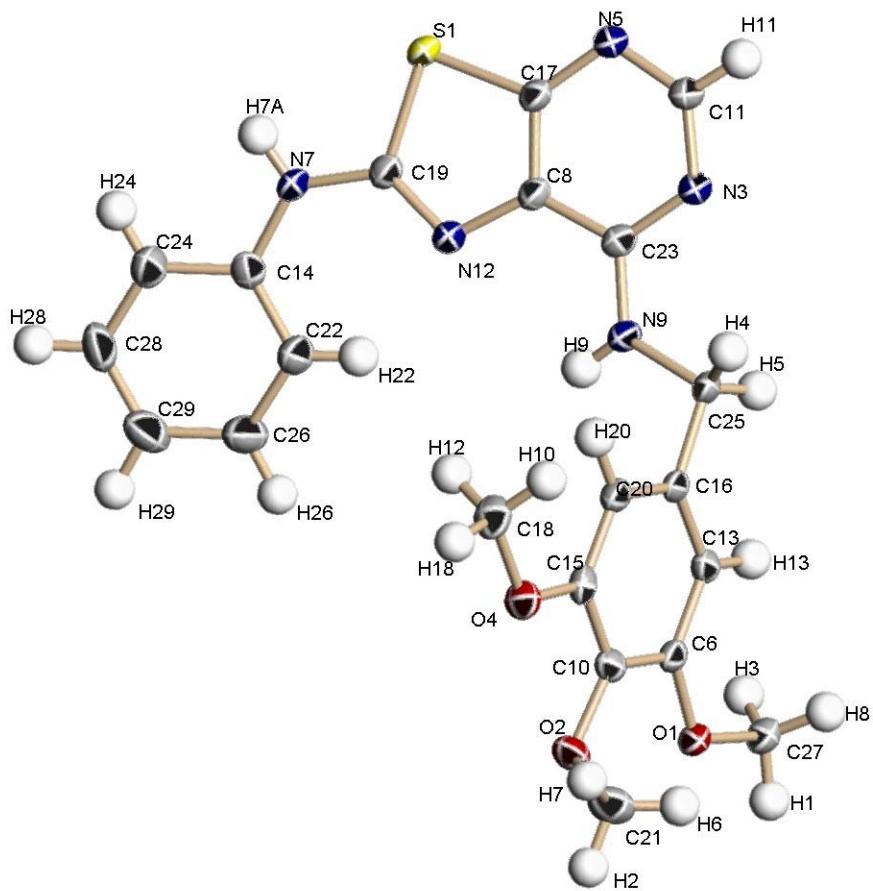
N⁷-(4-Methoxyphenyl)-N²-phenylthiazolo[5,4-d]pyrimidine-2,7-diamine (32) as a reddish-brown powder (57 mg, 86%). ¹H NMR (300 MHz, DMSO-d₆): δ 10.69 (s, 1H), 9.13 (s, 1H), 8.26 (s, 1H), 7.91 (d, *J*=7.5 Hz, 2H), 7.66 (d, *J*=9.0 Hz, 2H), 7.36 (dd,

J=7.8, 8.1 Hz, 2H), 7.05 (t, *J*=7.8 Hz, 1H), 6.95 (d, *J*=8.4 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 158.4, 157.9, 156.0, 151.7, 151.0, 140.6, 132.5, 129.6, 129.4 (2C), 124.5 (2C), 122.7, 118.5 (2C), 114.1 (2C), 55.7; HR-MS m/z (M $^+$) calcd 349.0997, obsd 349.0983.

***N*⁷- (3-Chlorophenyl)-*N*²-phenylthiazolo[5,4-*d*]pyrimidine-2,7-diamine (33)** as a pale brown powder (60.5 mg, 90%). ^1H NMR (300 MHz, DMSO-d₆): δ 10.74 (s, 1H), 9.37 (s, 1H), 8.39 (s, 1H), 8.07-8.06 (m, 1H), 7.90 (d, *J*=5.7 Hz, 2H), 7.84 (dd, *J*=6.3, 0.9 Hz, 1H), 7.39-7.35 (m, 3H), 7.11 (dd, *J*=6.3, 0.9 Hz, 1H), 7.05 (t, *J*=5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 159.0 (2C), 151.6, 150.2, 141.7, 140.7, 133.4, 130.7, 130.5, 129.8 (2C), 123.2, 123.1, 121.2, 120.3, 118.8 (2C); HR-MS m/z (M+H $^+$) calcd 354.0580, obsd 354.0576.

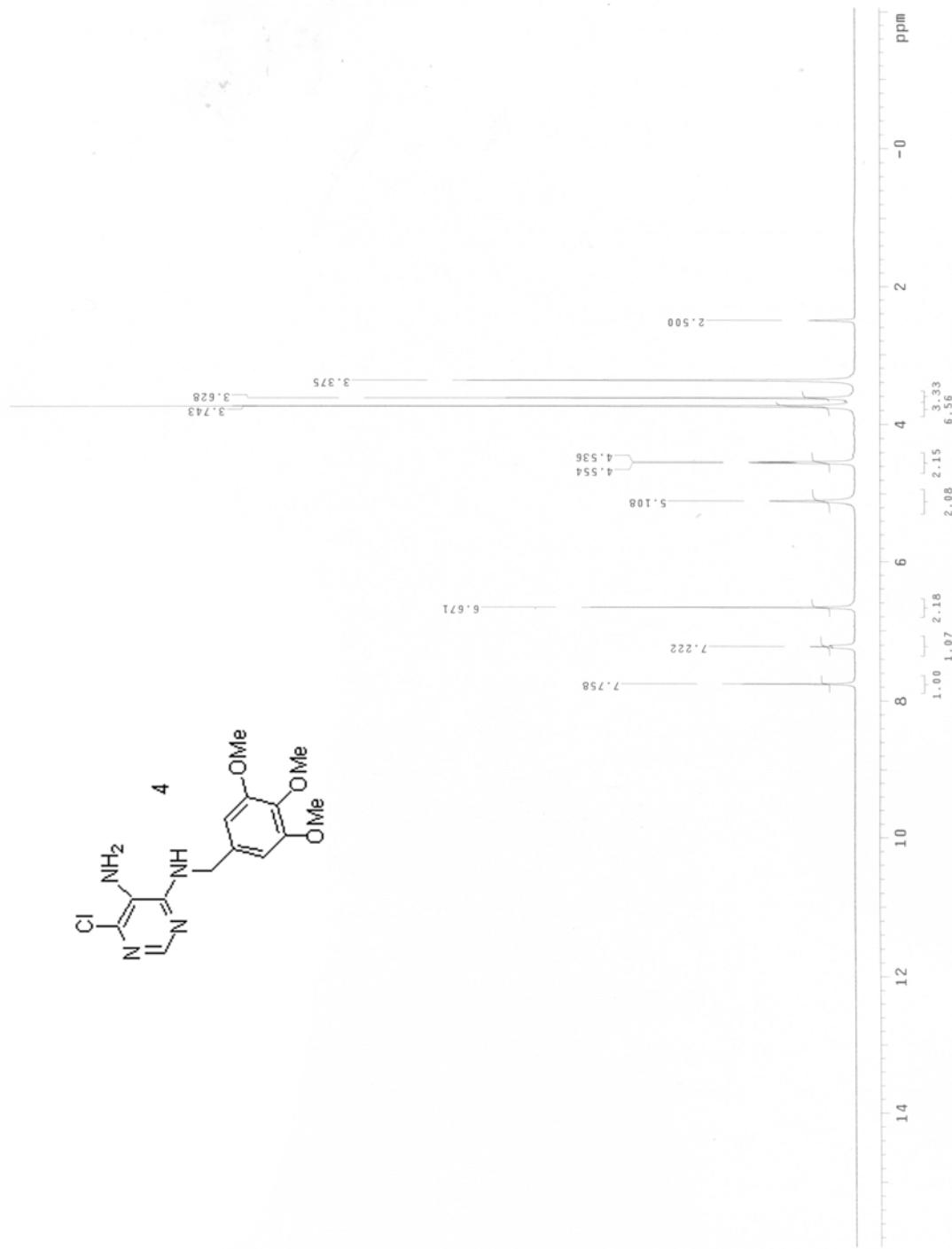
***N*⁷- (4-Nitrophenyl)-*N*²-phenylthiazolo[5,4-*d*]pyrimidine-2,7-diamine (34)** as a yellow-green powder (15.2 mg, 22%). ^1H NMR (300 MHz, DMSO-d₆): δ 10.85 (s, 1H), 9.90 (s, 1H), 8.49 (s, 1H), 8.29-8.20 (m, 3H), 7.91 (d, *J*=7.5 Hz, 2H), 7.41-7.34 (m, 2H), 7.10-7.05 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d₆): δ 159.9, 159.2, 151.0, 149.1, 146.7, 141.7, 140.3, 131.2, 129.5 (2C), 125.1 (2C), 123.1, 120.2 (2C), 118.7 (2C); HR-MS m/z (M+H $^+$) calcd 365.0821, obsd 365.0839.

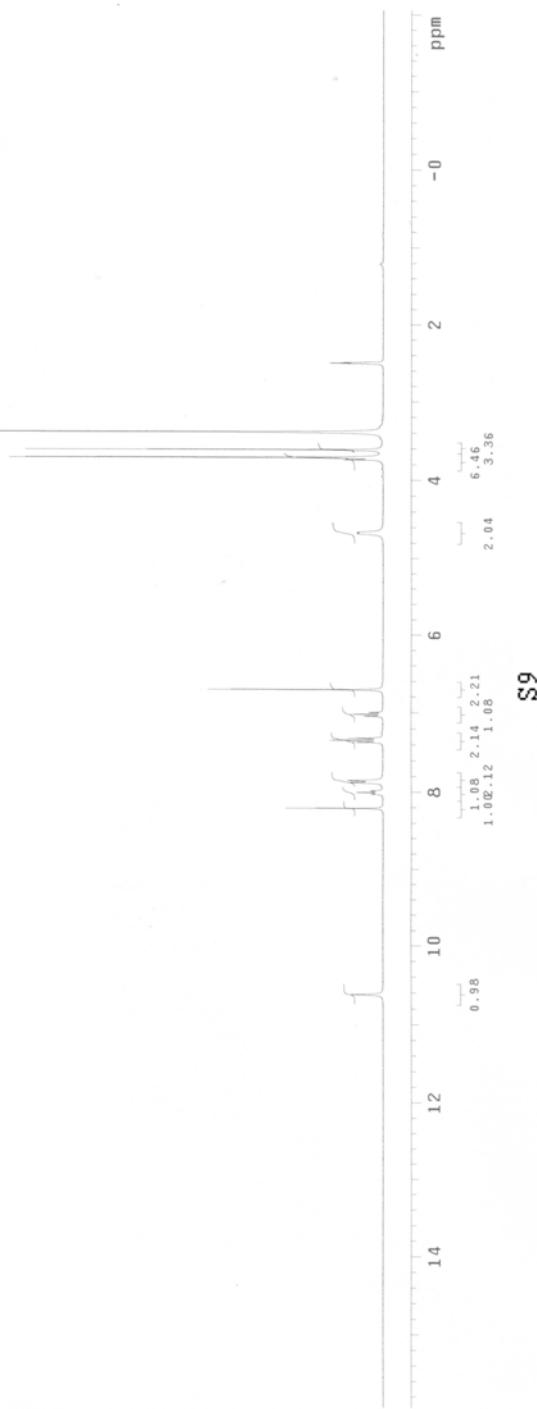
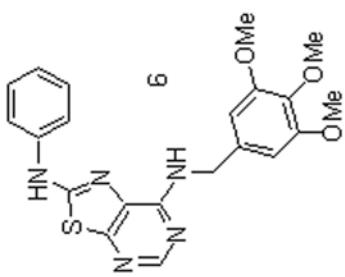
***N*⁷-Methyl-*N*²,*N*⁷-diphenylthiazolo[5,4-*d*]pyrimidine-2,7-diamine (35)** as a white powder (38 mg, 60%). ^1H NMR (400 MHz, DMSO-d₆): δ 10.40 (s, 1H), 8.38 (s, 1H), 7.44-7.41 (m, 2H), 7.35-7.28 (m, 3H), 7.08 (dd, *J*=7.2, 8.4 Hz, 2H), 6.97 (d, *J*=7.6 Hz, 2H), 6.87 (t, *J*=7.6 Hz, 1H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d₆): δ 160.5, 155.8, 152.5, 151.5, 147.0, 140.3, 130.3, 129.4 (2C), 129.0 (2C), 126.6 (2C), 126.1, 122.1, 117.5 (2C), 40.7; HR-MS m/z (M+H $^+$) calcd 334.1126, obsd 334.1129.



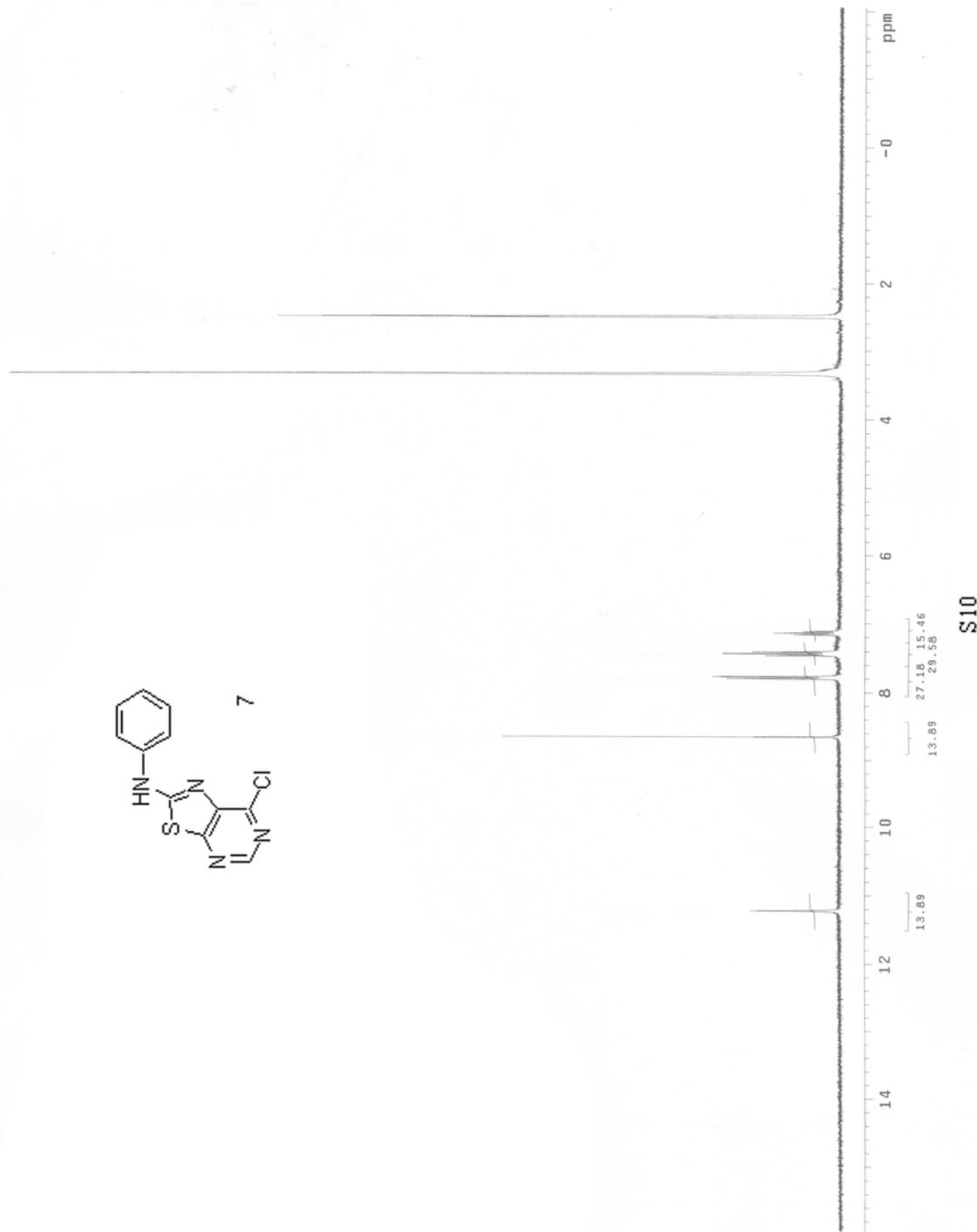
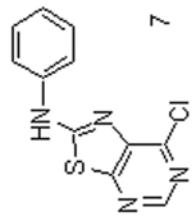
Thermal Ellipse Rendering of Compound 6

S8

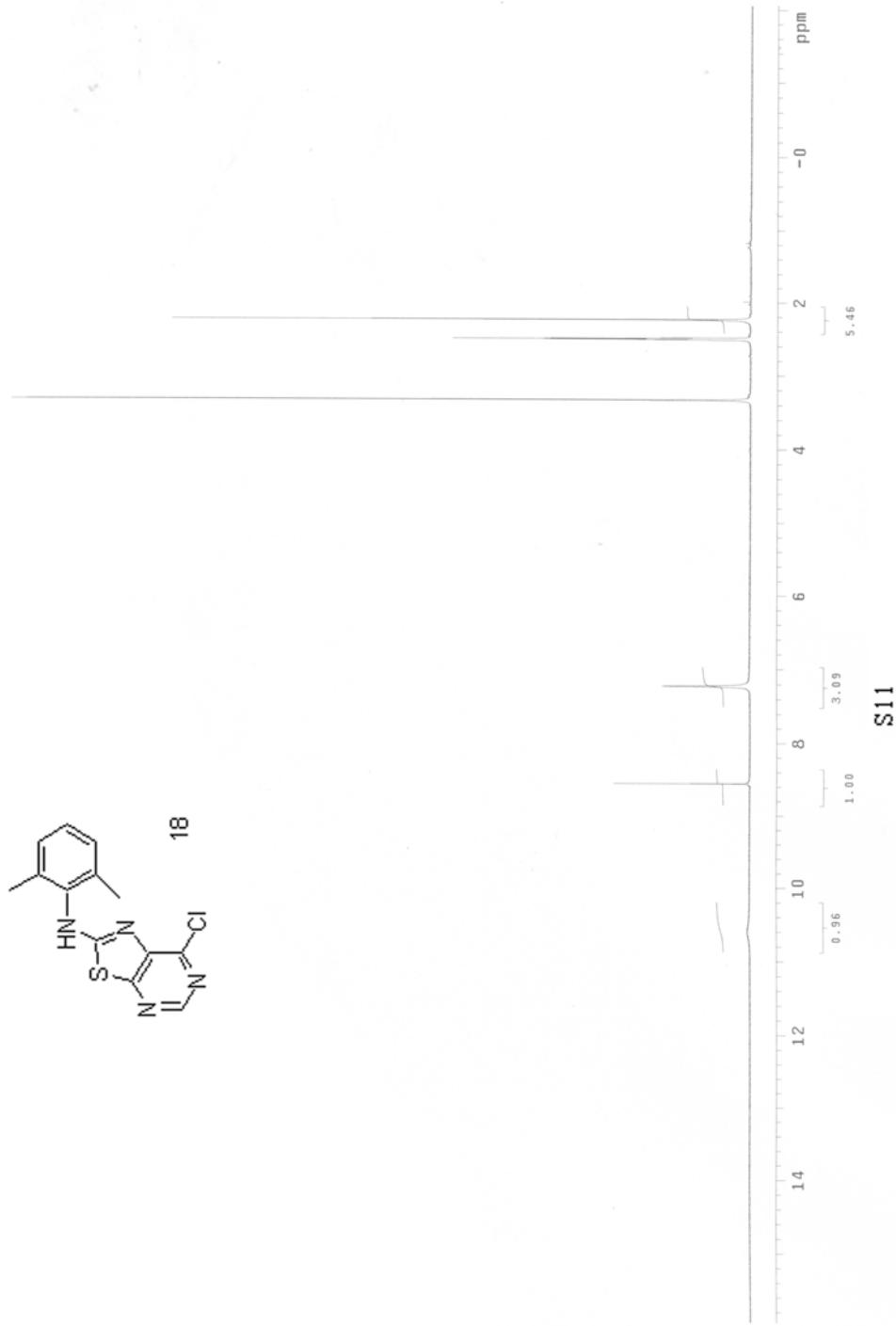
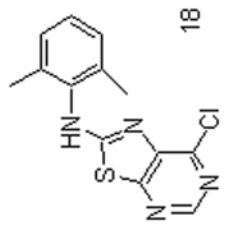




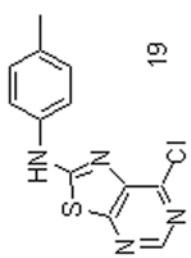
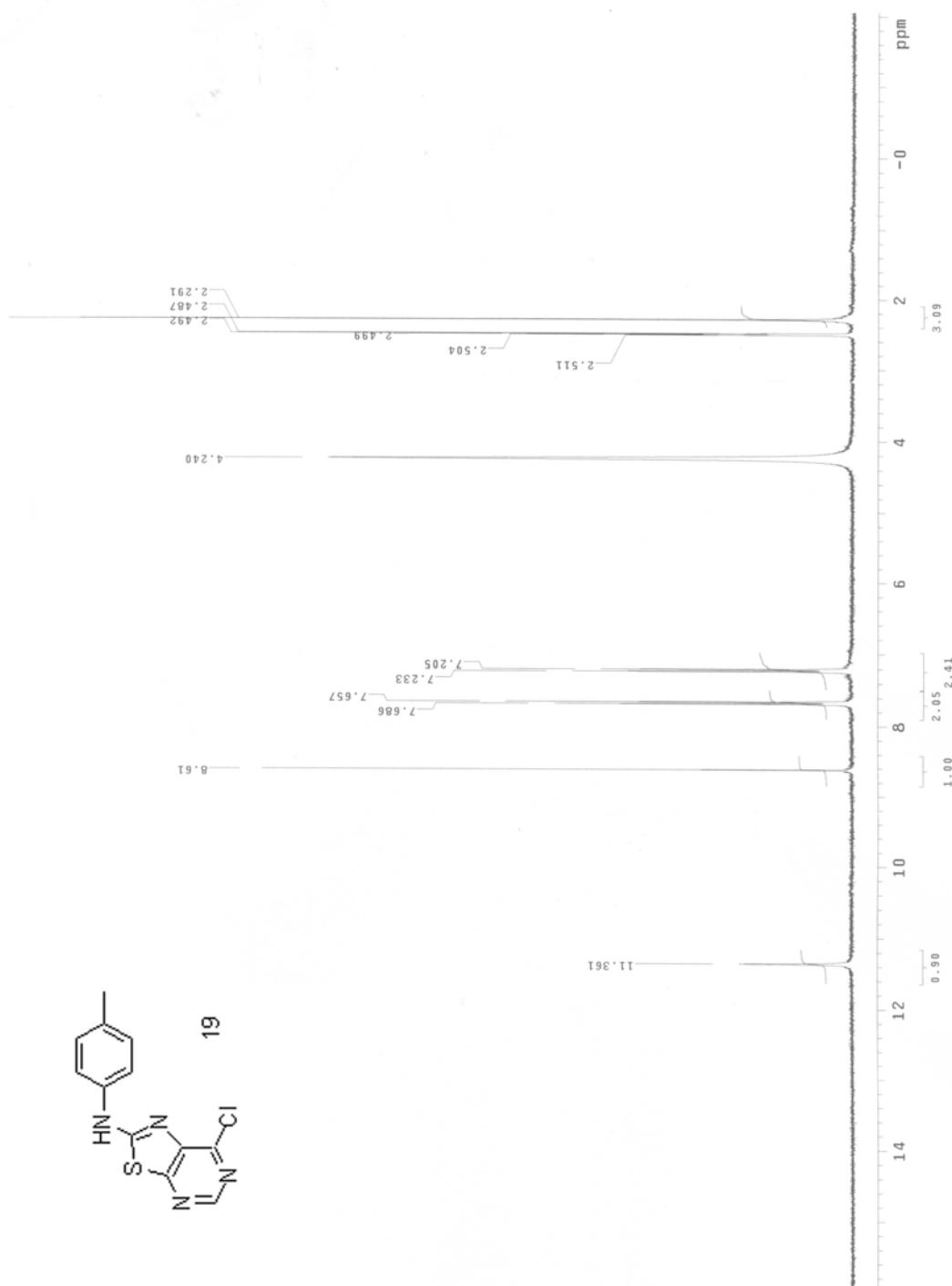
S9



S10

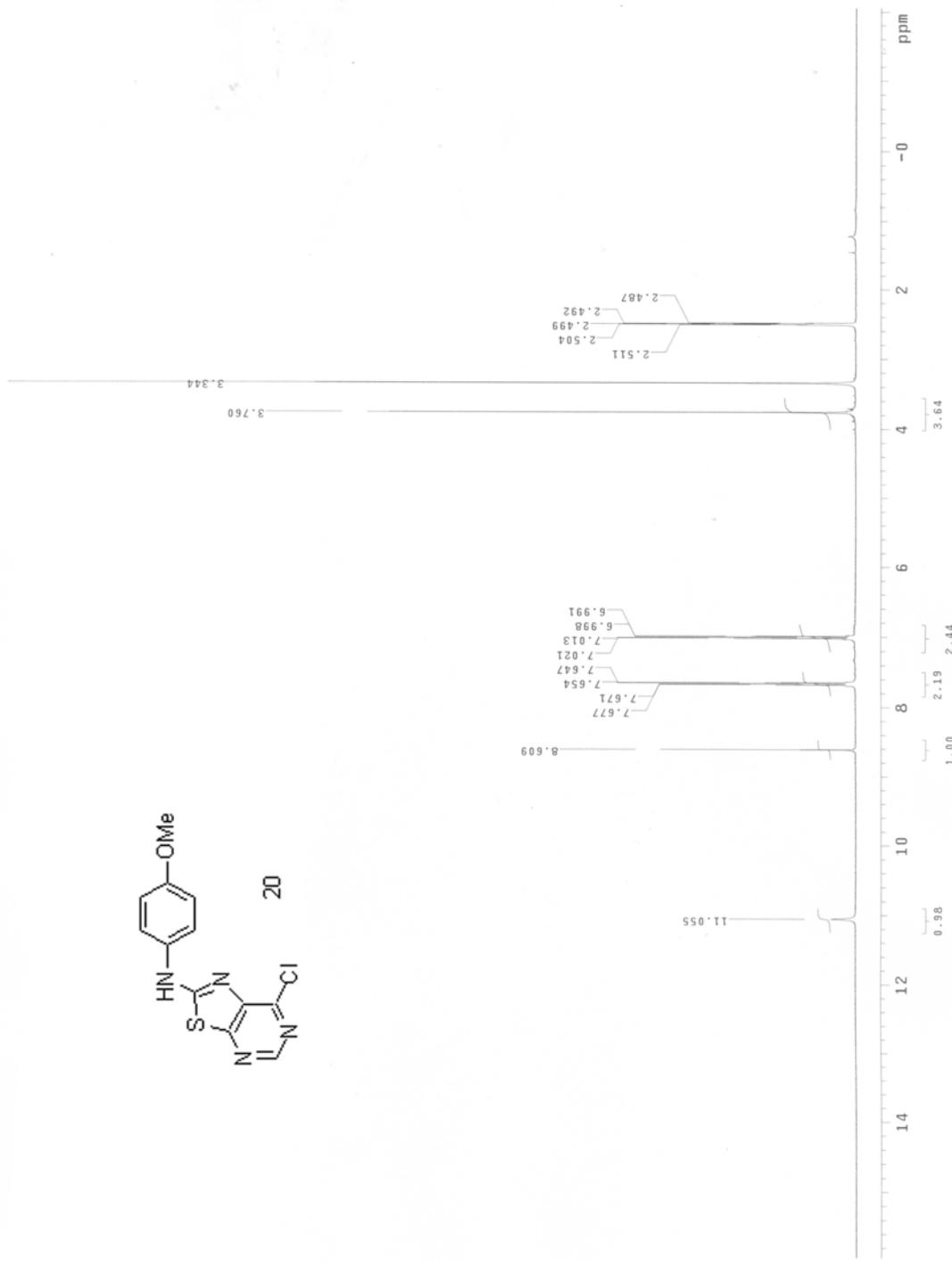


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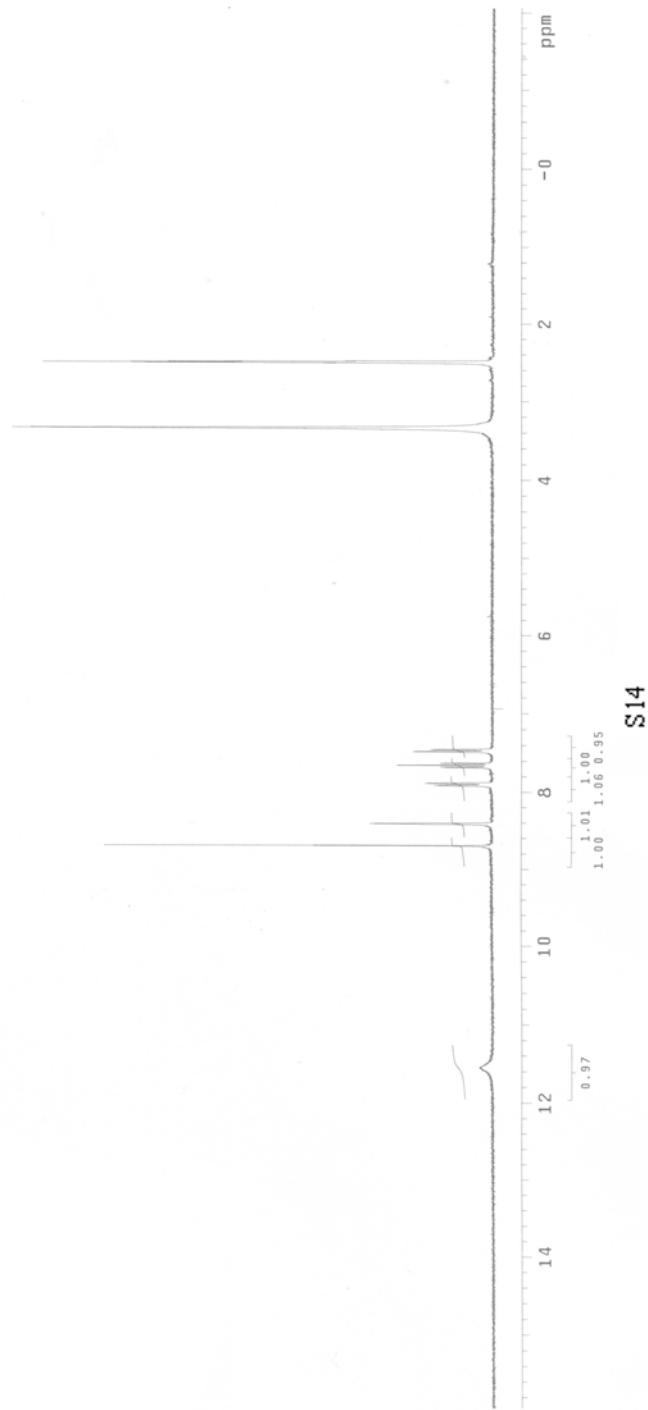
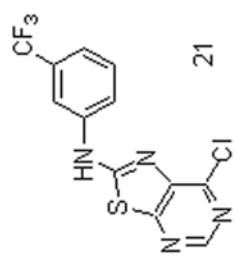


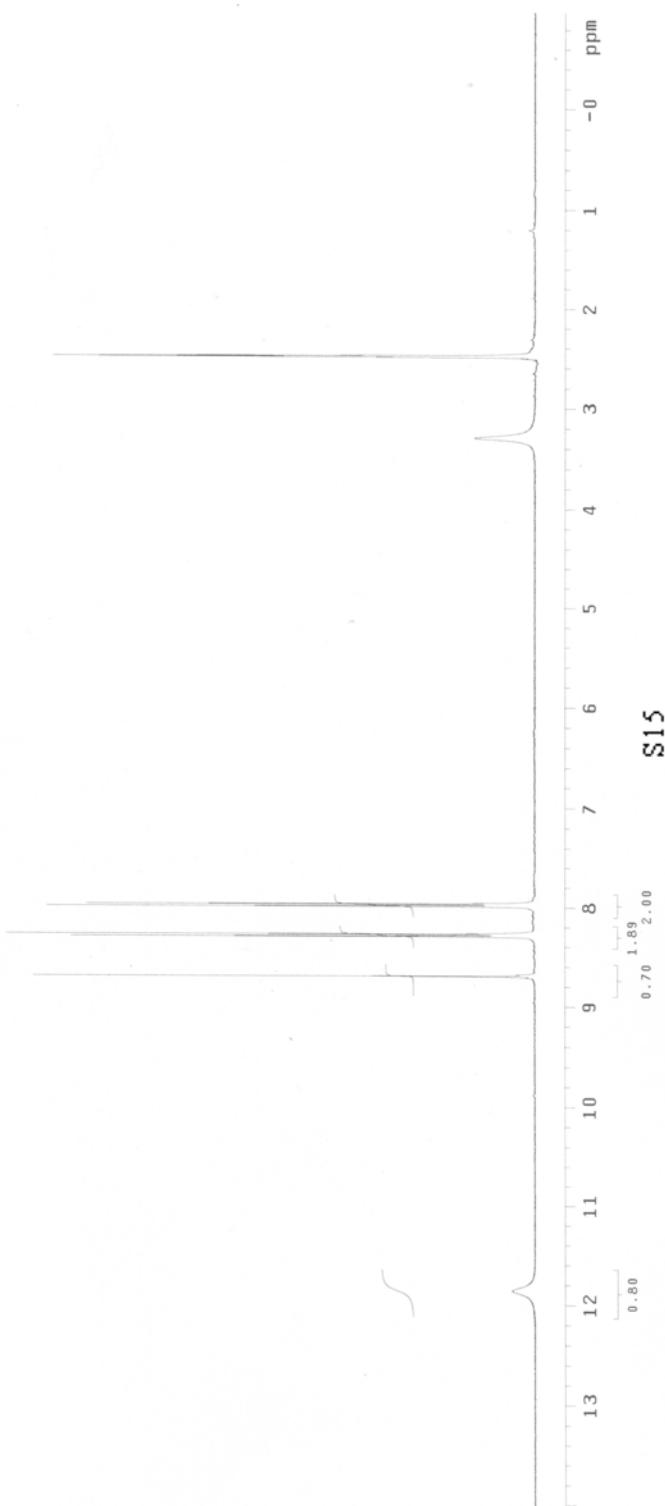
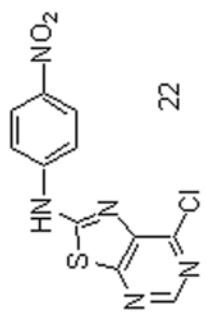
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S13

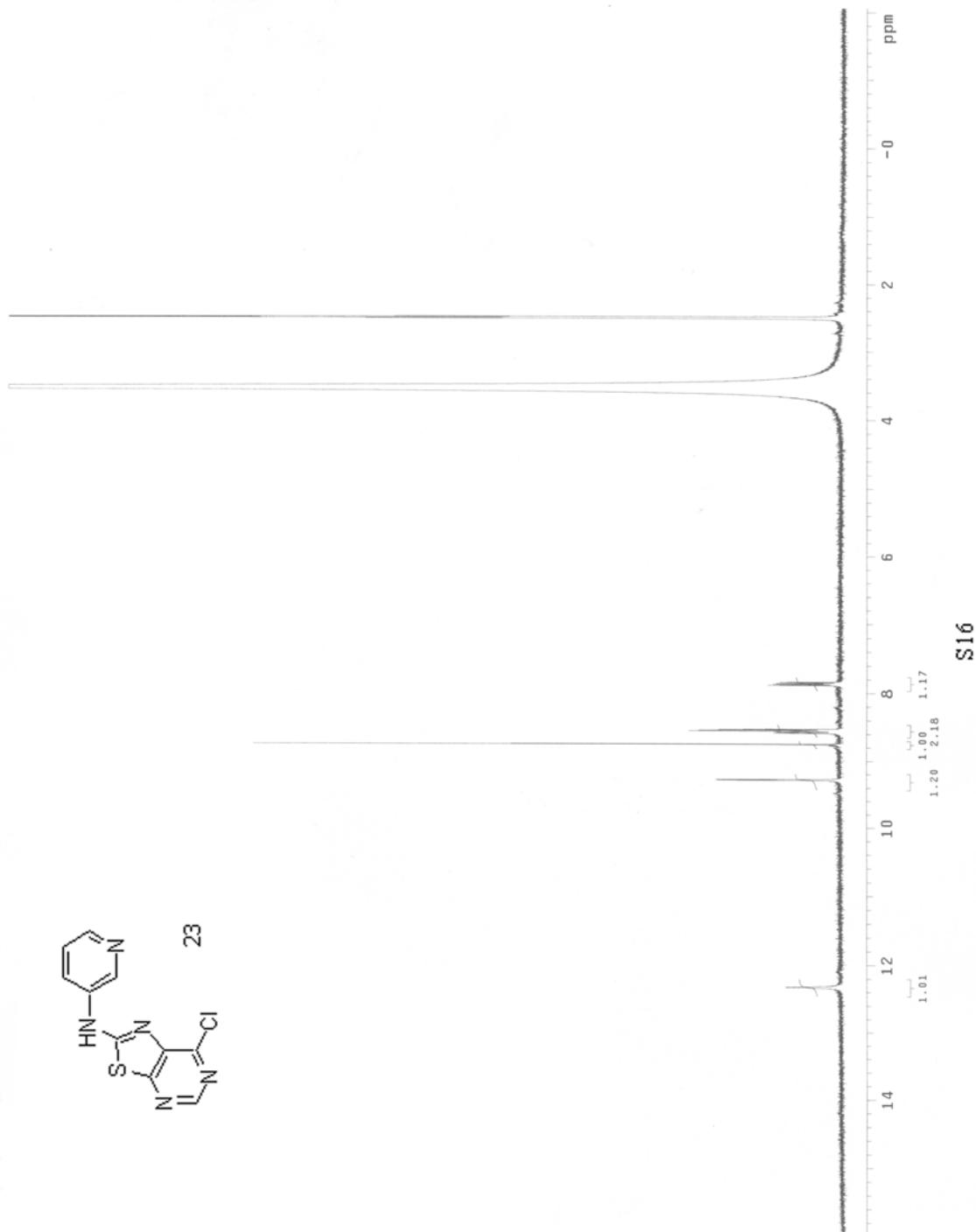


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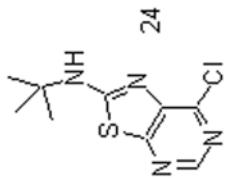
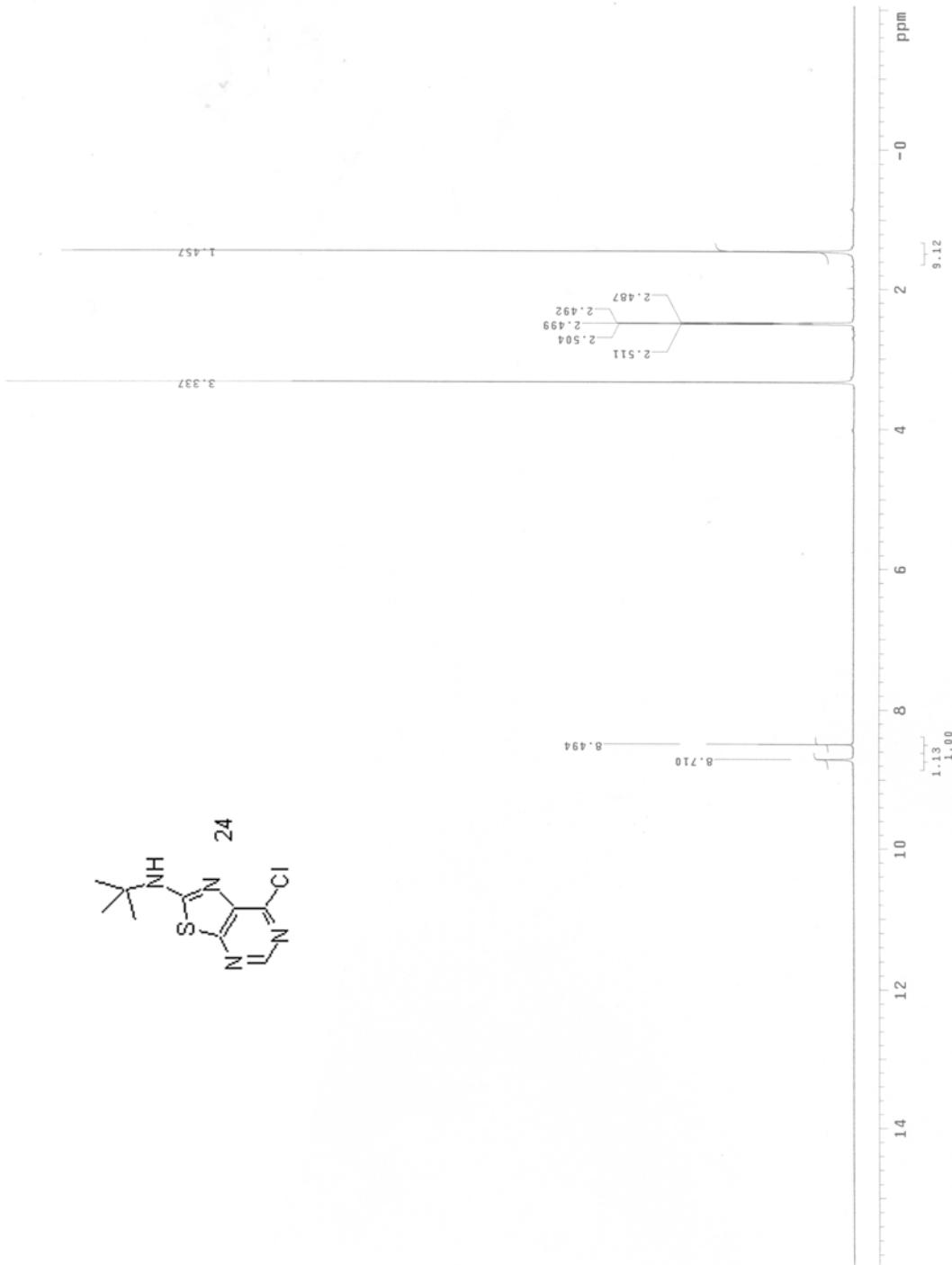




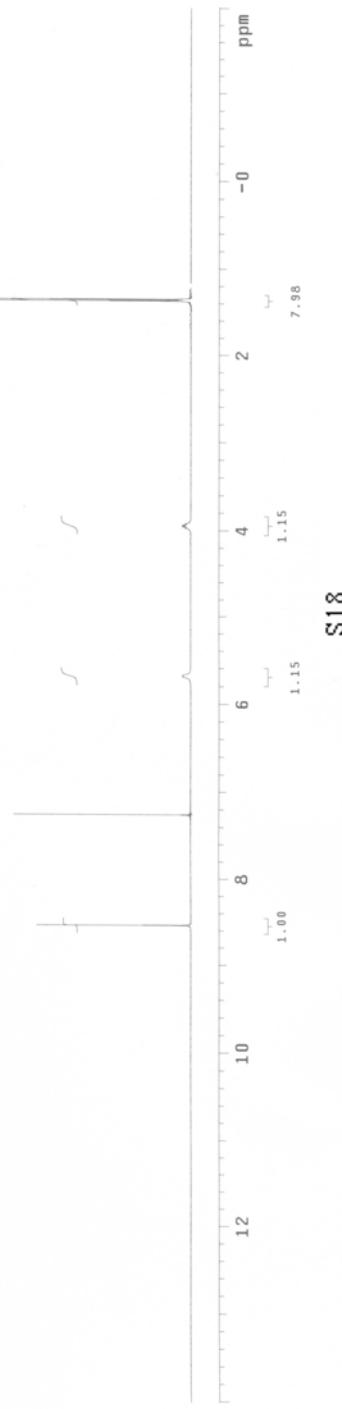
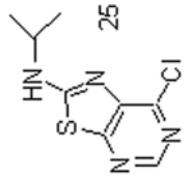
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S17



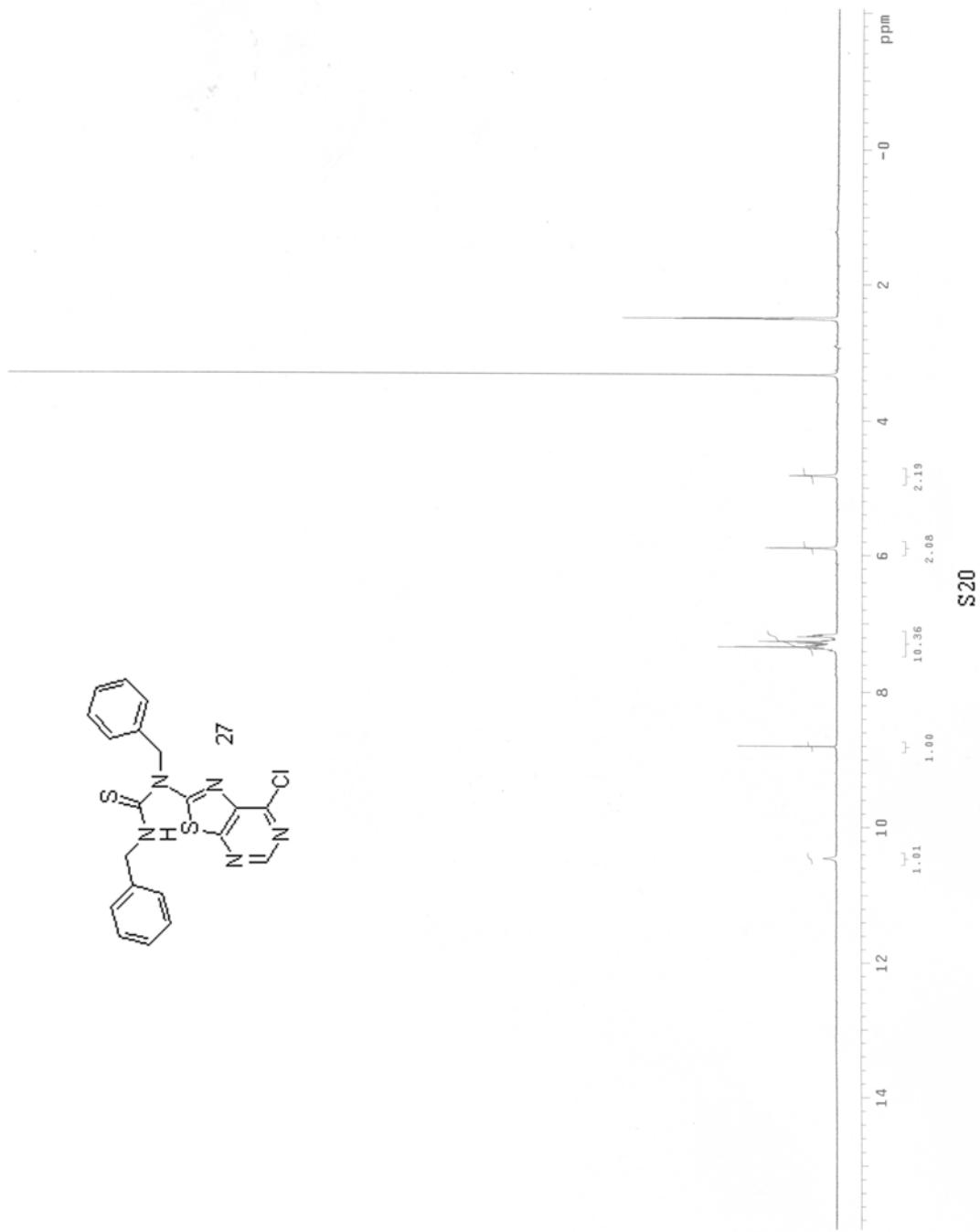
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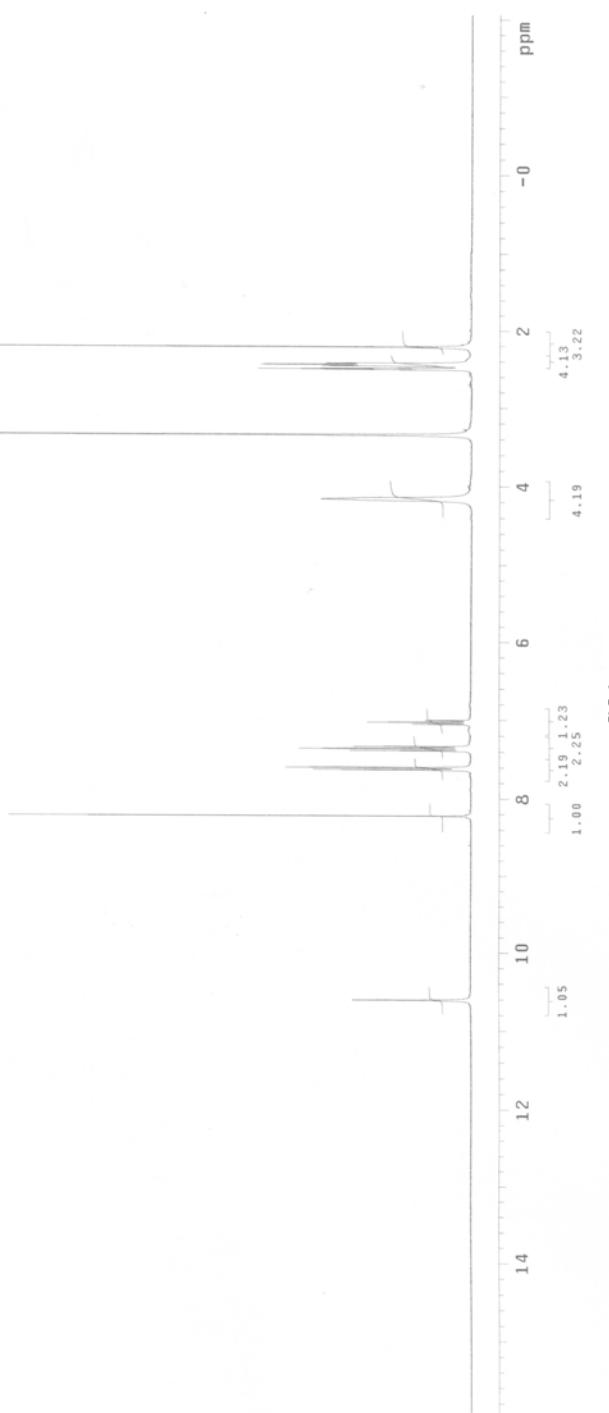
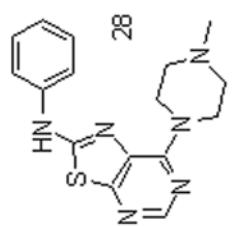




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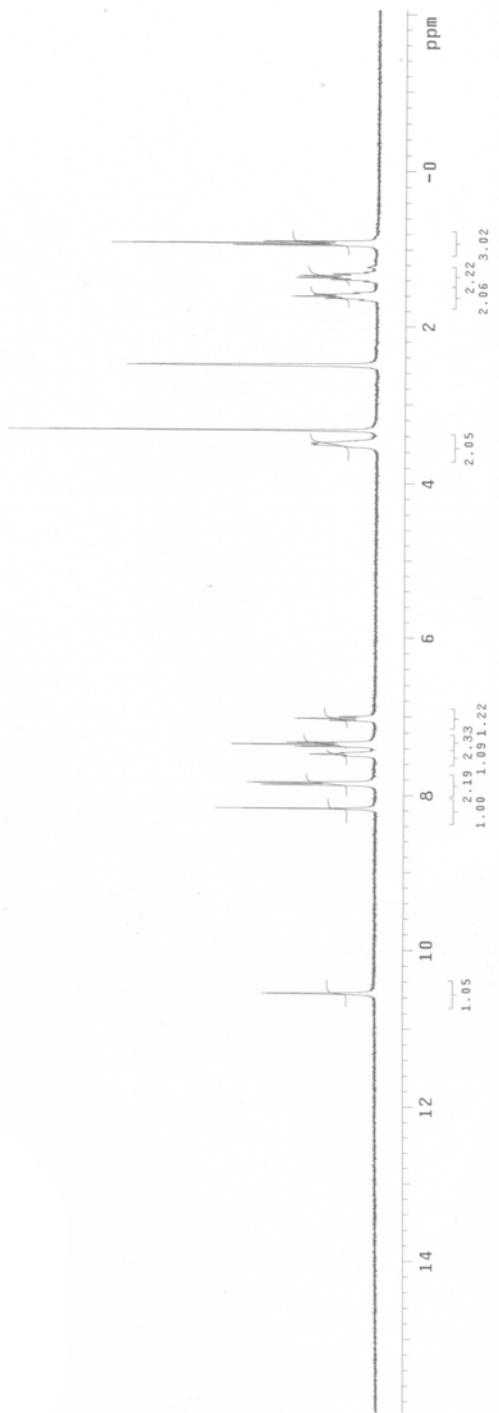
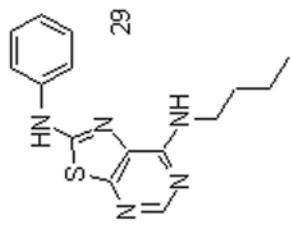
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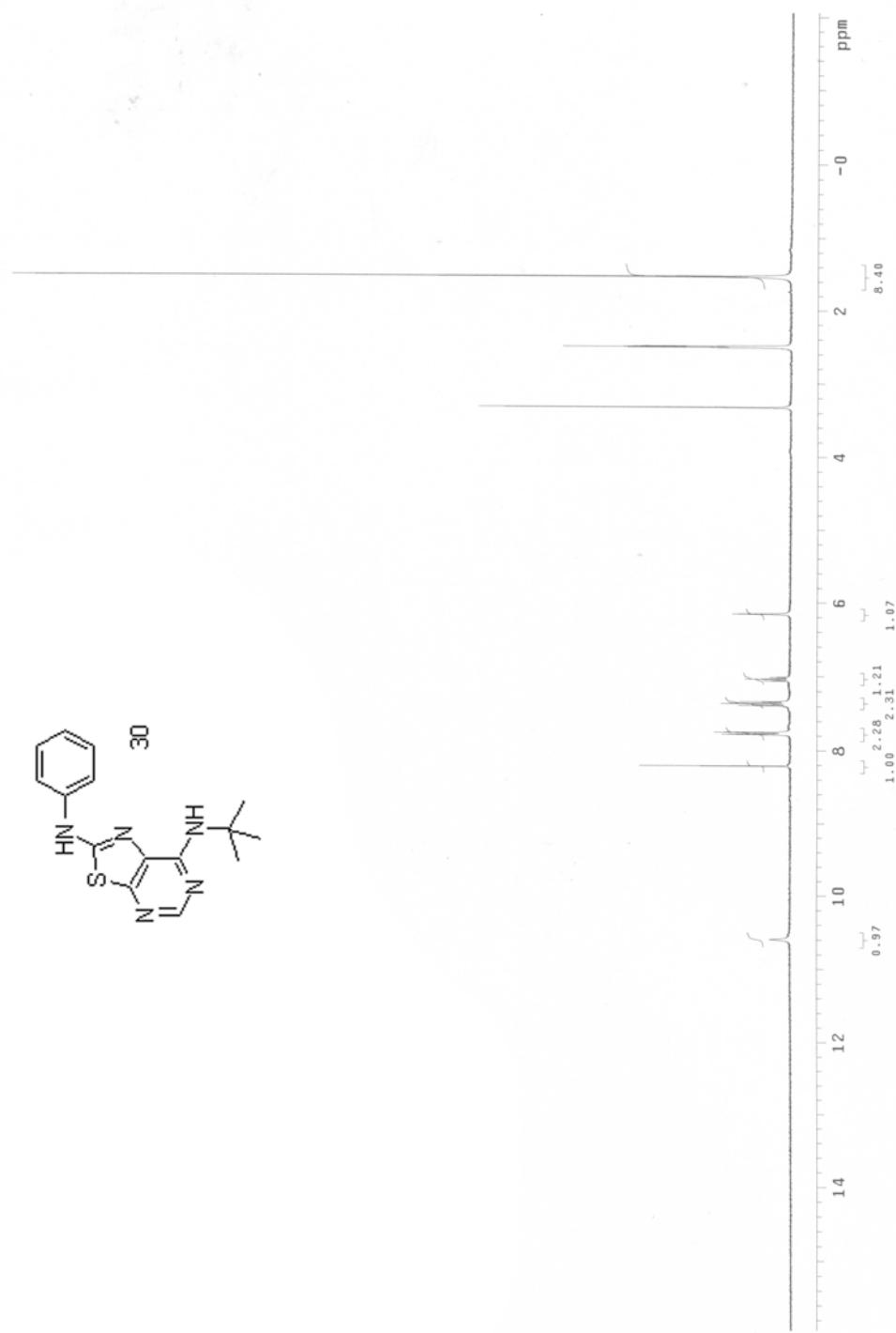
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S21

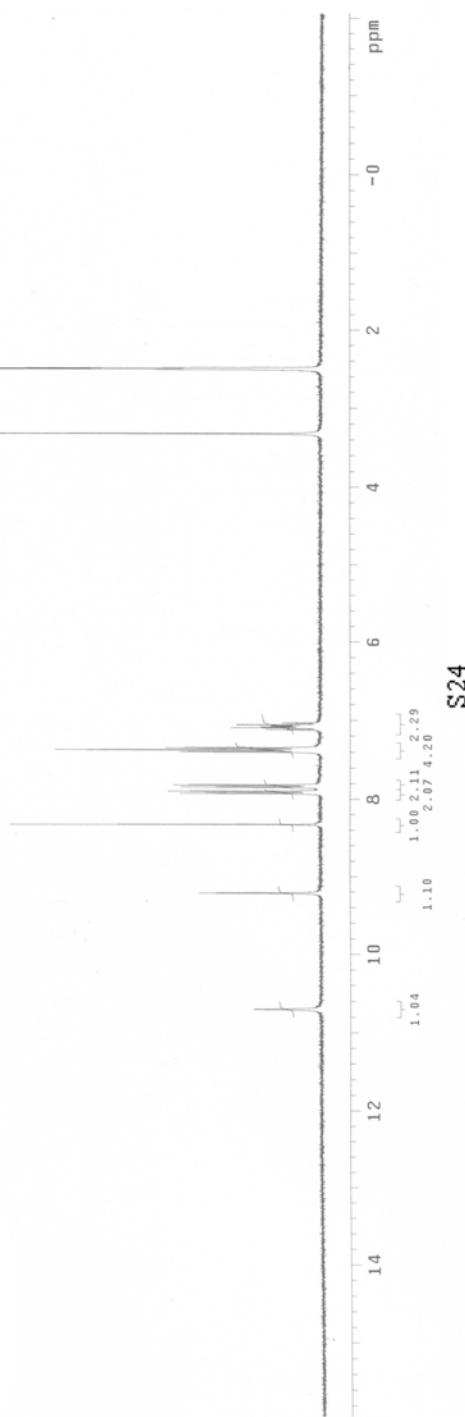
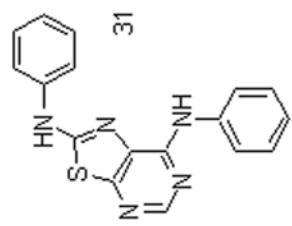


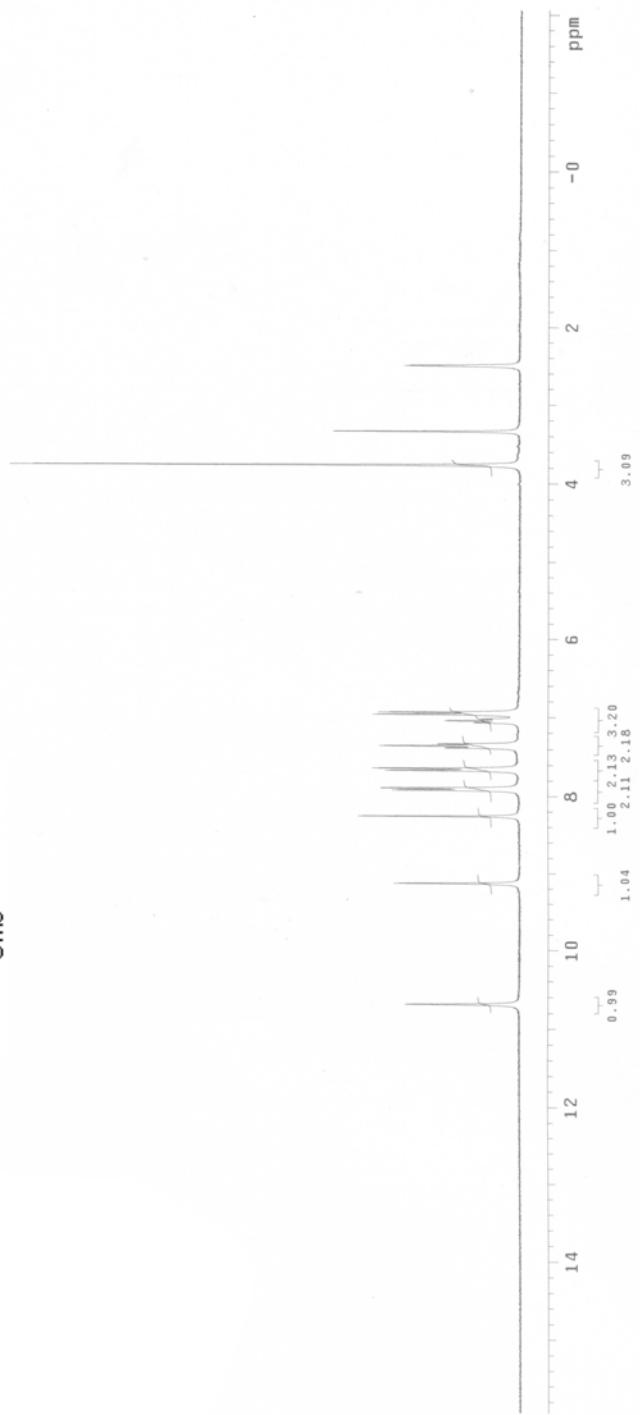
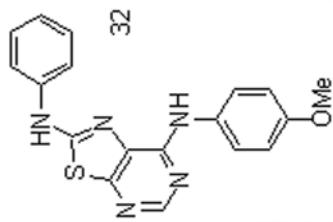
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S23

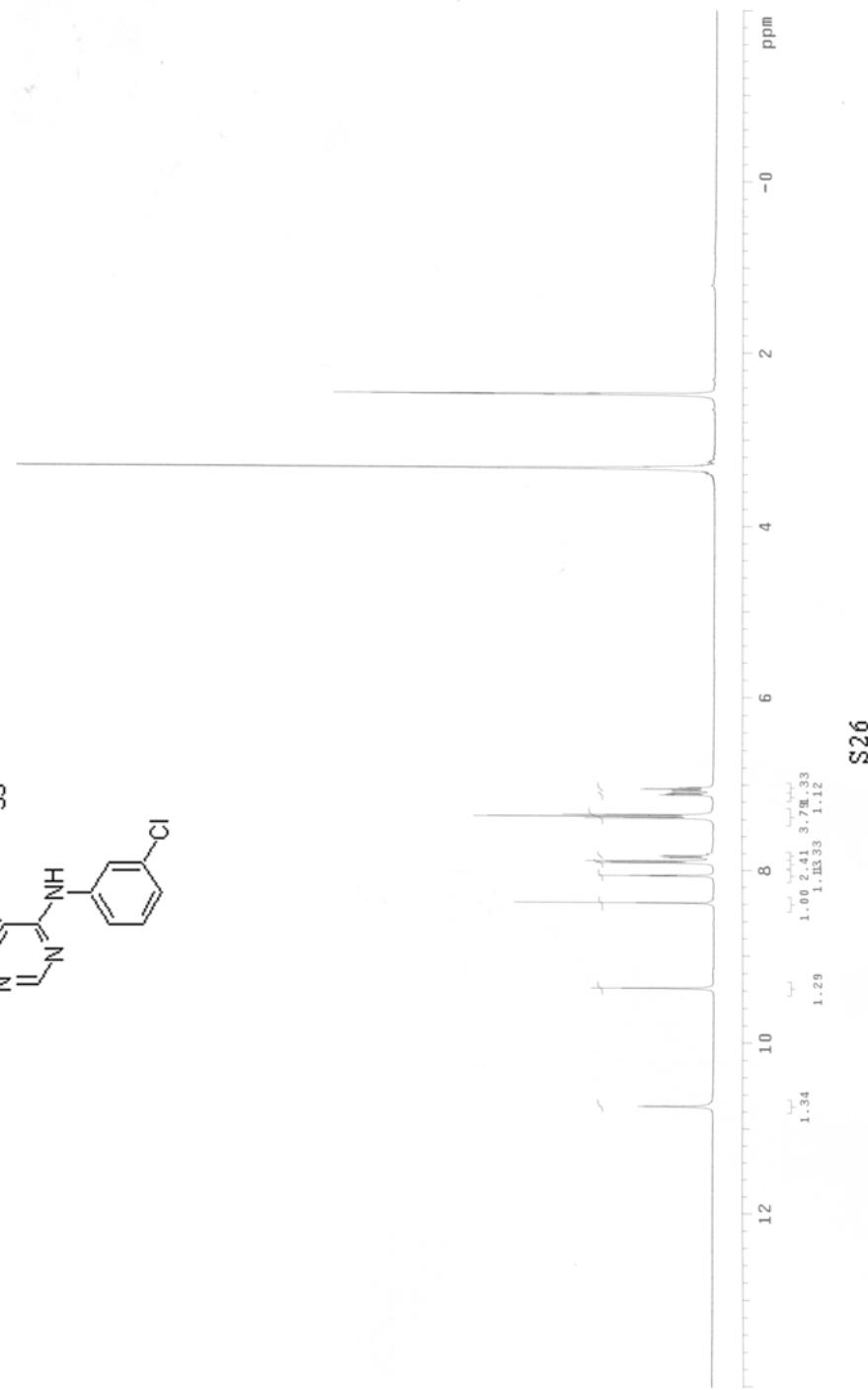
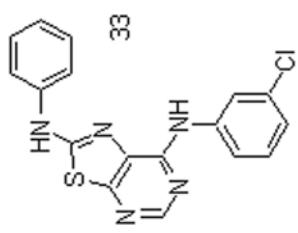


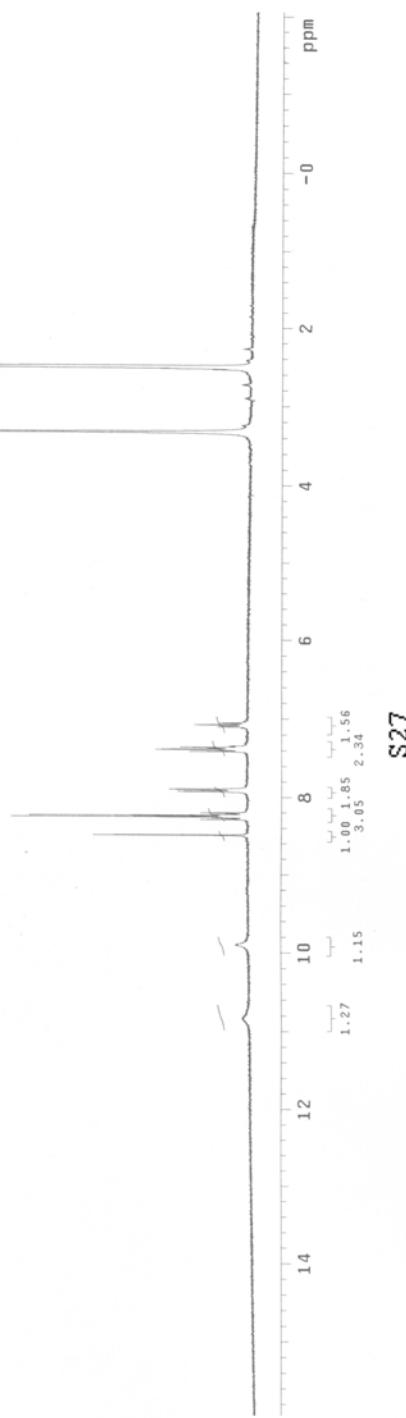
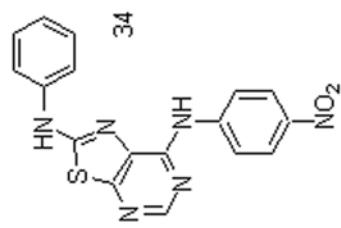
S23





S25





S27

