

Facile Synthesis of 1,2,4-Triazoles via a Copper-Catalyzed Tandem Addition-Oxidative Cyclization

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SUPPORTING INFORMATION

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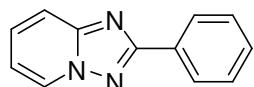
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General Method

¹H and ¹³C NMR spectra were recorded at 400 MHz (¹H NMR) and 100 MHz (¹³C NMR) frequency in CDCl₃, CD₃OD or DMSO-*d*6. Chemical shifts are calibrated to the solvent signals. Melting points were determined without correction. All reagents and solvents were used without further purification from commercial sources. Flash column chromatography was carried out with silica gel (300-350 mesh). MS spectra and High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX102A mass spectrometer.

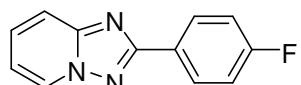
General Procedure for the Synthesis of 1,2,4-Triazolopyridines

To a dried screw-cap vial was added nitrile (0.30 mmol), 2-aminopyridine (0.36 mmol), CuBr (2.2 mg, 0.015 mmol), 1,10-phenanthroline (2.7 mg, 0.015 mmol, 5 mol%) and ZnI₂ (9.6 mg, 0.03 mmol, 10 mol%). 1,2-Dichlorobenzene (0.6 ml) was then added and the vial was sealed under atmospheric air. The reaction mixture was stirred at 130 °C for 24 h in pre-heated oil bath. After cooling to room temperature, the reaction was diluted with EtOAc and filtered over glass filter. The filtrate was concentrated and purified by column chromatography on silica gel.



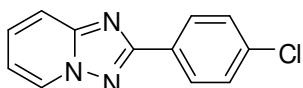
2-Phenyl-[1,2,4]triazolo[1,5-a]pyridine (3a)¹

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (47.4 mg, 81%). m.p. 134-135 °C (lit.¹ m.p. 135-137 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.60 (d, 1H, *J* = 6.8 Hz), 8.31-8.26 (m, 2H), 7.76 (d, 1H, *J* = 9.2 Hz), 7.53-7.45 (m, 4H), 7.03-6.97 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 151.7, 130.8, 130.1, 129.5, 128.7, 128.3, 127.3, 116.4, 113.6; MS (EI), *m/z* 195 (M⁺).



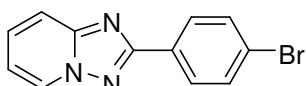
2-(4-Fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridine (3b) (New Compound)

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (51.1 mg, 80%). m.p. 173-174 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.59 (d, 1H, *J* = 6.8 Hz), 8.27 (dd, 2H, *J* = 5.8 Hz, *J* = 9.0 Hz), 7.75 (d, 1H, *J* = 9.6 Hz), 7.55-7.48 (m, 1H), 7.22-7.15 (m, 2H), 7.04-6.99 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 164.4 (d, *J* = 194.3 Hz), 162.8, 151.7, 129.6, 129.2 (d, *J* = 9.0 Hz), 128.3, 127.0 (d, *J* = 33.0 Hz), 116.4, 115.8 (d, *J* = 32.4 Hz), 113.7; HRMS (EI), *m/z* calcd. for C₁₂H₈N₃F (M⁺) 213.0702, found: 213.0708.



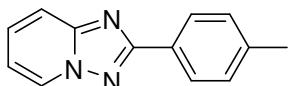
2-(4-Chlorophenyl)-[1,2,4]triazolo[1,5-a]pyridine (3c)²

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (60.5 mg, 80%). m.p. 220-221 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.59 (d, 1H, J = 6.8 Hz), 8.23 (d, 2H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.55-7.45 (m, 3H), 7.05-6.99 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 163.2, 151.7, 136.1, 129.6, 129.3, 128.9, 128.6, 128.3, 116.4, 113.8; MS (EI), *m/z* 229 (M⁺).



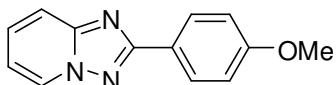
2-(4-Bromophenyl)-[1,2,4]triazolo[1,5-a]pyridine (3d) (New Compound)

The title compound was isolated by column chromatography (hexane-EtOAc 2:1) as a white solid (66.2 mg, 81%). m.p. 229-230 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.59 (d, 1H, J = 6.8 Hz), 8.16 (d, 2H, J = 8.8 Hz), 7.75 (d, 1H, J = 8.0 Hz), 7.63 (d, 2H, J = 8.8 Hz), 7.55-7.47 (m, 1H), 7.05-6.99 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 163.3, 151.7, 131.9, 129.8, 129.7, 128.8, 128.3, 124.5, 116.5, 113.8; HRMS (EI), *m/z* calcd. for C₁₂H₈N₃Br (M⁺) 272.9902, found: 272.9897.



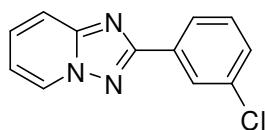
2-p-Tolyl-[1,2,4]triazolo[1,5-a]pyridine (3e)³

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (49.0 mg, 78%). m.p. 167-168 °C (lit.³ m.p. 168-169 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.59 (d, 1H, J = 7.2 Hz), 8.18 (d, 2H, J = 8.4 Hz), 7.74 (d, 1H, J = 9.2 Hz), 7.52-7.45 (m, 1H), 7.31 (d, 2H, J = 8.0 Hz), 7.02-6.95 (m, 1H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 151.7, 140.2, 129.4, 129.4, 128.3, 127.9, 127.2, 116.3, 113.4, 21.5; MS (EI), 209 (M⁺).



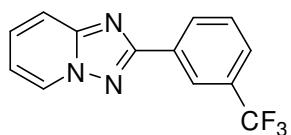
2-(4-Methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine (3f)²

The title compound was isolated by column chromatography (hexane-EtOAc 4:3) as a white solid (47.3 mg, 70%). m.p. 134-135 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, 1H, J = 6.8 Hz), 8.23 (d, 2H, J = 6.8 Hz), 7.72 (d, 1H, J = 7.6 Hz), 7.50-7.44 (m, 1H), 7.01 (d, 2H, J = 8.8 Hz), 7.02-6.95 (dt, 1H, J = 1.2 Hz, J = 6.8 Hz), 3.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 161.2, 151.6, 129.3, 128.7, 128.1, 123.3, 116.0, 114.0, 113.2, 55.3; MS (EI), *m/z* 225 (M⁺).



2-(3-Chlorophenyl)-[1,2,4]triazolo[1,5-a]pyridine (3g) (New Compound)

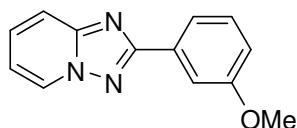
The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (56.3 mg, 82%). m.p. 177-178 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, 1H, *J* = 6.8 Hz), 8.30 (s, 1H), 8.19-8.15 (m, 1H), 7.75 (d, 1H, *J* = 8.2 Hz), 7.55-7.48 (m, 1H), 7.45-7.40 (m, 2H), 7.05-6.99 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 162.9, 151.6, 134.7, 132.6, 130.0, 129.9, 129.7, 128.3, 127.4, 125.3, 116.5, 113.9; HRMS (EI), *m/z* calcd. for C₁₂H₈N₃Cl (M⁺) 229.0407, found: 229.0398.



2-(3-(Trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine (3h)

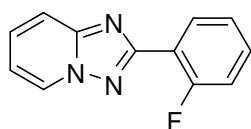
CAS:253328-67-5

The title compound was isolated by column chromatography (hexane-EtOAc 2:1) as a white solid (71.0 mg, 90%). m.p. 164-165 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.62-8.56 (m, 3H), 8.47 (d, 1H, *J* = 8.0 Hz), 7.79-7.69 (m, 2H), 7.64-7.57 (m, 1H), 7.56-7.49 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 162.8, 151.7, 131.7, 131.2 (d, *J* = 32.9 Hz), 130.4, 129.8, 129.2, 128.4, 126.5 (q, *J* = 3.3 Hz), 124.2 (q, *J* = 4.2 Hz), 124.0 (d, *J* = 273.2 Hz), 116.5, 114.0; HRMS (EI), *m/z* calcd. for C₁₃H₈N₃F₃ (M⁺) 263.0670, found: 263.0677.



2-(3-Methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine (3i) (New Compound)

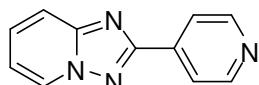
The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (47.8 mg, 71%). m.p. 106-108 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, 1H, *J* = 6.8 Hz), 7.81 (d, 1H, *J* = 7.6 Hz), 7.77-7.74 (m, 1H), 7.67 (d, 1H, *J* = 9.6 Hz), 7.43-7.37 (m, 1H), 7.32 (t, 1H, *J* = 8.0 Hz), 6.96-6.87 (m, 2H), 3.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 159.9, 151.6, 132.0, 129.7, 129.5, 128.3, 119.7, 116.8, 116.3, 113.6, 111.6, 55.4; HRMS (EI), *m/z* calcd. for C₁₃H₁₁N₃O (M⁺) 225.0902, found: 225.0899.



2-(2-Fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridine (3j) (New Compound)

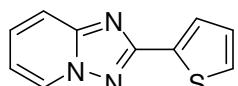
The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white

solid (42.5 mg, 63%). m.p. 171-173 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, 1H, *J* = 6.8 Hz), 8.26 (dt, 1H, *J* = 2.0 Hz, *J* = 7.2 Hz), 7.80 (d, 1H, *J* = 8.8 Hz), 7.57-7.50 (m, 1H), 7.49-7.42 (m, 1H), 7.32-7.22 (m, 2H), 7.04 (dt, 1H, *J* = 1.8 Hz, *J* = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 161.4 (d, *J* = 127.6 Hz), 160.8, 151.1, 131.5 (d, *J* = 9.1 Hz), 130.9 (d, *J* = 2.4 Hz), 129.6, 128.4, 124.3 (d, *J* = 3.3 Hz), 118.8 (d, *J* = 8.7 Hz), 116.8, 116.6, 113.8; HRMS (EI), *m/z* calcd. for C₁₂H₈N₃F (M⁺) 213.0702, found: 213.0707.



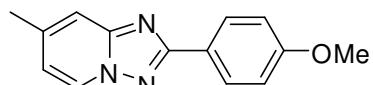
2-(Pyridin-4-yl)-[1,2,4]triazolo[1,5-a]pyridine (3k)⁴

The title compound was isolated by column chromatography (hexane-EtOAc 1:4) as a white solid (42.9 mg, 73%). m.p. 190-192 °C (lit.⁴ m.p. 193 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, 2H, *J* = 6.0 Hz), 8.53 (d, 1H, *J* = 6.8 Hz), 8.05 (d, 2H, *J* = 6.0 Hz), 7.70 (d, 1H, *J* = 9.2 Hz), 7.50-7.44 (m, 1H), 7.00-6.95 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 161.9, 151.7, 150.4, 138.2, 129.9, 128.4, 121.2, 116.7, 114.3; MS (EI), *m/z* 196 (M⁺).



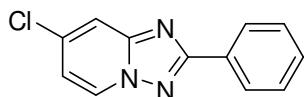
2-(Thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (3l)⁵

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (36.2 mg, 60%). m.p. 155-156 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.57 (d, 1H, *J* = 6.8 Hz), 7.89 (dd, 1H, *J* = 1.2 Hz, *J* = 3.6 Hz), 7.73 (d, 1H, *J* = 8.8 Hz), 7.54-7.47 (m, 1H), 7.45 (dd, 1H, *J* = 3.6 Hz, *J* = 5.2 Hz), 7.17 (dd, 1H, *J* = 3.6 Hz, *J* = 5.2 Hz), 7.03-6.97 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 160.3, 151.5, 133.6, 129.8, 128.2, 128.0, 127.8, 127.6, 116.2, 113.7; MS (EI), *m/z* 201 (M⁺).



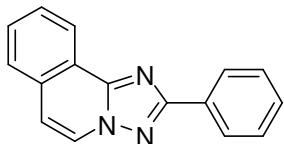
2-(4-Methoxyphenyl)-7-methyl-[1,2,4]triazolo[1,5-a]pyridine (3m)⁶

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (50.9 mg, 82%). m.p. 165-166 °C (lit.⁶ 167.5-168 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, 1H, *J* = 6.8 Hz), 8.20 (d, 2H, *J* = 7.6 Hz), 7.45 (s, 1H), 7.00 (d, 2H, *J* = 7.6 Hz), 6.75 (dd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz), 3.86 (s, 3H), 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 161.0, 151.8, 140.7, 128.6, 127.1, 123.5, 115.7, 114.6, 114.0, 55.2, 21.5; MS (EI), *m/z* 239 (M⁺).



7-Chloro-2-phenyl-[1,2,4]triazolo[1,5-a]pyridine (3n) (New Compound)

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (43.3 mg, 63%). m.p. 189-190 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.48 (d, 1H, *J* = 8.0 Hz), 8.28-8.23 (m, 2H), 7.73 (d, 1H, *J* = 2.0 Hz), 7.52-7.45 (m, 3H), 6.96 (dd, 1H, *J* = 2.0 Hz, *J* = 7.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 165.2, 151.8, 136.1, 130.3, 130.3, 128.7, 128.4, 127.3, 115.4, 115.1; HRMS (EI), *m/z* calcd. for C₁₂H₈N₃ Cl (M⁺) 229.0407, found: 229.0414.

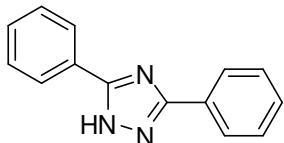


2-Phenyl-[1,2,4]triazolo[5,1-a]isoquinoline (3o)⁷

The title compound was isolated by column chromatography (hexane-EtOAc 2:1) as a white solid (63.9 mg, 87%). m.p. 152-154 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.71-8.67 (m, 1H), 8.37-8.29 (m, 3H), 7.80-7.75 (m, 1H), 7.71-7.65 (m, 2H), 7.54-7.44 (m, 3H), 7.18 (d, 1H, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 163.2, 150.1, 131.3, 131.0, 129.8, 129.7, 128.6, 128.3, 127.1, 124.5, 124.3, 122.2, 113.9; MS (EI), *m/z* 245 (M⁺).

General Procedure for the Preparation of 1*H*-1,2,4-Triazoles.

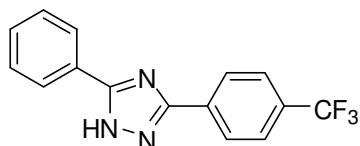
To a dried screw-cap vial was added nitrile (0.3 mmol), amidine (0.45 mmol), Cs₂CO₃ (293 mg, 0.9 mmol), CuBr (2.2 mg, 0.015 mmol, 5 mol%). DMSO (0.8 ml) was added and the vial was sealed. The reaction mixture was stirred under atmospheric air at 120 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and successively washed with 5% aqueous NaHCO₃ and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel.



3,5-Diphenyl-1*H*-1,2,4-triazole (5a)⁸

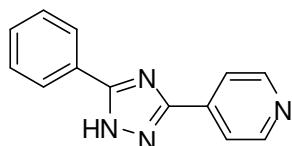
The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (50.4 mg, 76%). m.p. 190-191 °C (lit.⁸ 191-192 °C); ¹H NMR (400 MHz, CD₃OD) δ

7.97-7.91 (m, 4H), 7.39-7.32 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.6, 131.0, 130.2, 129.9, 127.6; MS (EI), m/z 221 (M^+).



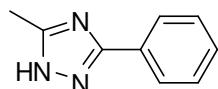
5-Phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazole (5b)⁹

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (71.1 mg, 82%). m.p. 214-216 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.34 (d, 2H, J = 8.4 Hz), 8.17-8.12 (m, 2H), 7.90 (d, 2H, J = 8.4 Hz), 7.62-7.51 (m, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 158.9, 156.5, 130.0, 129.4 (d, J = 31.2 Hz), 129.0, 128.9, 126.6, 126.2, 126.0, 125.8 (d, J = 3.3 Hz), 124.2 (d, J = 273.2 Hz); MS (EI), m/z 289 (M^+).



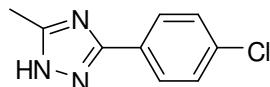
4-(5-Phenyl-1*H*-1,2,4-triazol-3-yl)pyridine (5c)¹⁰

The title compound was isolated by column chromatography (hexane-EtOAc 1:4) as a white solid (46.5 mg, 70%). m.p. 248-251 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.76 (br, 2H), 8.15-8.10 (m, 2H), 8.04 (d, 2H, J = 5.2 Hz), 7.62-7.53 (m, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 159.6, 155.7, 150.4, 138.2, 131.2, 130.3, 129.0, 126.2, 120.1; MS (EI), m/z 222 (M^+).



5-Methyl-3-phenyl-1*H*-1,2,4-triazole (5d)¹¹

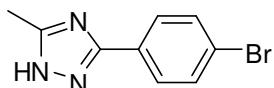
The title compound was isolated by column chromatography (hexane-EtOAc 2:3) as a white solid (37.2 mg, 78%). m.p. 163-165 °C (lit.¹¹ 162-164) ^1H NMR (400 MHz, CD_3OD) δ 7.87-7.82 (m, 2H), 7.34-7.27 (m, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.8, 156.5, 132.9, 130.7, 129.8, 127.3, 12.0; MS (EI), m/z 159 (M^+).



3-(4-Chlorophenyl)-5-methyl-1*H*-1,2,4-triazole (5e)¹²

The title compound was isolated by column chromatography (hexane-EtOAc 2:3) as a white solid (48.0 mg, 83%). m.p. 174-175 °C (lit.¹² 173-175); ^1H NMR (400 MHz, CD_3OD) δ 7.93

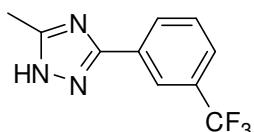
(d, 2H, $J = 8.4$ Hz), 7.44 (d, 2H, $J = 8.4$ Hz), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 162.1, 155.7, 136.4, 130.3, 130.0, 128.8, 11.7; MS (EI), m/z 193 (M^+).



3-(4-Bromophenyl)-5-methyl-1*H*-1,2,4-triazole (5f)

CAS: 170230-86-1

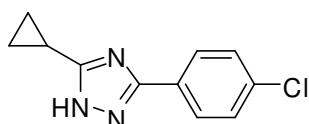
The title compound was isolated by column chromatography (hexane-EtOAc 2:3) as a white solid (51.7 mg, 73%). m.p. 183-185 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.78 (d, 2H, $J = 8.0$ Hz), 7.50 (d, 2H, $J = 8.4$ Hz), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.4, 156.1, 132.9, 132.7, 128.9, 124.5, 11.8; HRMS (EI), m/z calcd. for $\text{C}_9\text{H}_8\text{N}_3\text{Br}$ (M^+) 236.9902, found: 236.9906.



5-Methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazole (5g)

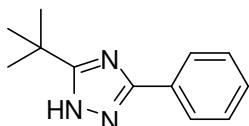
CAS: 1094688-10-4

The title compound was isolated by column chromatography (hexane-EtOAc 2:3) as a white solid (57.9 mg, 85%). m.p. 170-171 °C; ^1H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 8.19 (d, 1H, $J = 7.6$ Hz), 7.67 (d, 1H, $J = 8.0$ Hz), 7.63-7.57 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.8, 156.5, 132.7, 132.2 (d, $J = 33.2$ Hz), 130.7, 130.6, 126.8 (d, $J = 2.5$ Hz), 123.8 (d, $J = 4.1$ Hz), 122.8 (d, $J = 273.2$ Hz), 11.7; HRMS (EI), m/z calcd. for $\text{C}_{10}\text{H}_8\text{N}_3\text{F}_3$ (M^+) 227.0670, found: 227.0663.



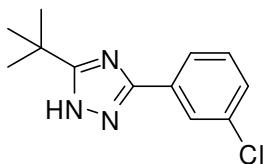
3-(4-Chlorophenyl)-5-cyclopropyl-1*H*-1,2,4-triazole (5h) (New Compound)

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (45.4 mg, 69%). m.p. 202-203 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.83 (d, 2H, $J = 8.8$ Hz), 7.34 (d, 2H, $J = 8.8$ Hz), 2.03-1.97 (m, 1H), 1.03-0.92 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 162.8, 160.6, 136.4, 130.3, 130.0, 128.9, 8.5, 8.2; HRMS (EI), m/z calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_3\text{Cl}$ (M^+) 219.0563, found: 219.0569.



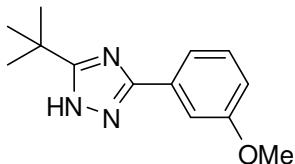
5-*tert*-Butyl-3-phenyl-1*H*-1,2,4-triazole (5i) (New Compound)

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (38.0 mg, 63%). m.p. 145-146 °C; ¹H NMR (400 MHz, CD₃OD) δ 7.90-7.85 (m, 2H), 7.35-7.29 (m, 3H), 1.33 (s, 9H); ¹³C NMR (100 MHz, CD₃OD) δ 167.1, 163.0, 132.1, 130.4, 129.7, 127.6, 33.4, 29.6; HRMS (EI), *m/z* calcd. for C₁₂H₁₅N₃ (M⁺) 201.1262, found: 201.1266.



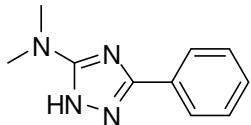
5-*tert*-Butyl-3-(3-chlorophenyl)-1*H*-1,2,4-triazole (5j) (New Compound)

The title compound was isolated by column chromatography (hexane-EtOAc 3:2) as a white solid (50.0 mg, 71%). m.p. 119-121 °C; ¹H NMR (400 MHz, CD₃OD) δ 8.02-7.99 (m, 1H), 7.93-7.88 (m, 1H), 7.40-7.36 (m, 2H), 1.41 (s, 9H); ¹³C NMR (100 MHz, CD₃OD) δ 167.9, 161.0, 135.7, 133.9, 131.2, 130.2, 127.4, 125.7, 33.3, 29.5; HRMS (EI), *m/z* calcd. for C₁₂H₁₄N₃Cl (M⁺) 235.0876, found: 235.0870.



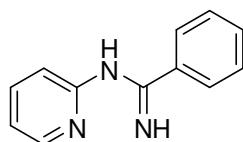
5-*tert*-Butyl-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (5k) (New Compound)

The title compound was isolated by column chromatography (hexane-EtOAc 1:1) as colorless oil (38.1 mg, 71%). ¹H NMR (400 MHz, CD₃OD) δ 7.48-7.44 (m, 2H), 7.21 (t, 1H, *J* = 8.0 Hz), 6.86-6.82 (m, 1H), 3.71 (s, 3H), 1.31 (s, 9H); ¹³C NMR (100 MHz, CD₃OD) δ 168.4, 161.7, 161.4, 132.4, 130.8, 119.9, 116.6, 112.7, 55.7, 33.3, 29.6; HRMS (EI), *m/z* calcd. for C₁₃H₁₇N₃O (M⁺) 231.1372, found: 231.1366.



N,N-Dimethyl-3-phenyl-1*H*-1,2,4-triazol-5-amine (5l)¹³

The title compound was isolated by column chromatography (hexane-EtOAc 1:4) as a white solid (37.2 mg, 66%). m.p. 209-210 °C (lit.¹³ 203-204); ¹H NMR (400 MHz, CD₃OD) δ 7.84-7.80 (m, 2H), 7.34-7.27 (m, 3H), 2.94 (s, 6H); ¹³C NMR (100 MHz, CD₃OD) δ 161.5, 161.1, 132.7, 130.1, 129.5, 127.4, 38.9; MS (EI): *m/z* 188 (M⁺).



N-(2-Pyridyl)benzamidine (**8**)¹⁴

To a stirred solution of 2-aminopyridine (941 mg, 10 mmol) in DMF (5.0 ml), were added NaH (60% dispersion in mineral oil, 400 mg, 10 mmol) at 0 °C and stirred at the same temperature for 15 min. Benzonitrile (1.31 ml, 12 mmol) was then added to the reaction mixture and stirred at room temperature for 5 h. The reaction was quenched by the addition of 5% aqueous NaHCO₃ (10 ml) and extracted with EtOAc. The extract was washed with brine and dried over MgSO₄. Concentration under reduced pressure and recrystallization from Et₂O-hexane afforded title compound as pale white crystals (1.38 g, 70%). m.p. 96-97 °C (lit.¹⁴ 96-97 °C); ¹H NMR (400 MHz, CD₃OD) δ 8.35-8.31 (m, 1H), 7.86 (d, 2H, *J* = 8.0 Hz), 7.72-7.67 (m, 1H), 7.51-7.44 (m, 3H), 7.15 (d, 1H, *J* = 8.4 Hz), 7.01-6.96 (m, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 163.7, 162.7, 147.5, 139.0, 138.3, 131.8, 129.5, 128.6, 121.7, 119.2; MS (EI): *m/z* 197 (M⁺).

Gram-Scale Preparation of **3a**

To a dried round-bottom flask were added benzonitrile (1.03 g, 10.0 mmol), 2-aminopyridine benzanilide (1.13 g, 12.0 mmol), CuBr (71.7 mg, 0.5 mmol), 1,10-phenanthroline (90.1 mg, 0.5 mmol), ZnI₂ (319 mg, 1.0 mmol) and 1,2-dichlorobenzene (20 ml). The reaction mixture was stirred at 130 °C for 24 h air atmosphere (balloon). After cooling to room temperature, small amount of methanol was added to dissolve insoluble materials and the residue was purified by column chromatography on silica gel (hexane-AcOEt; 3:2). The product (**3a**) was isolated as white solid (1.35 g, 70%).

Effect of Ligand and Water on the Reaction

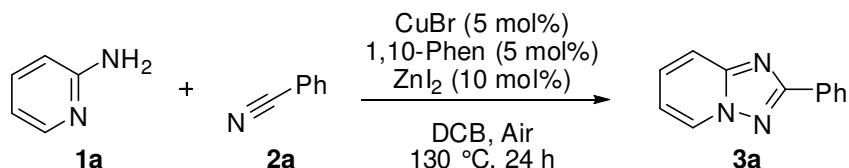


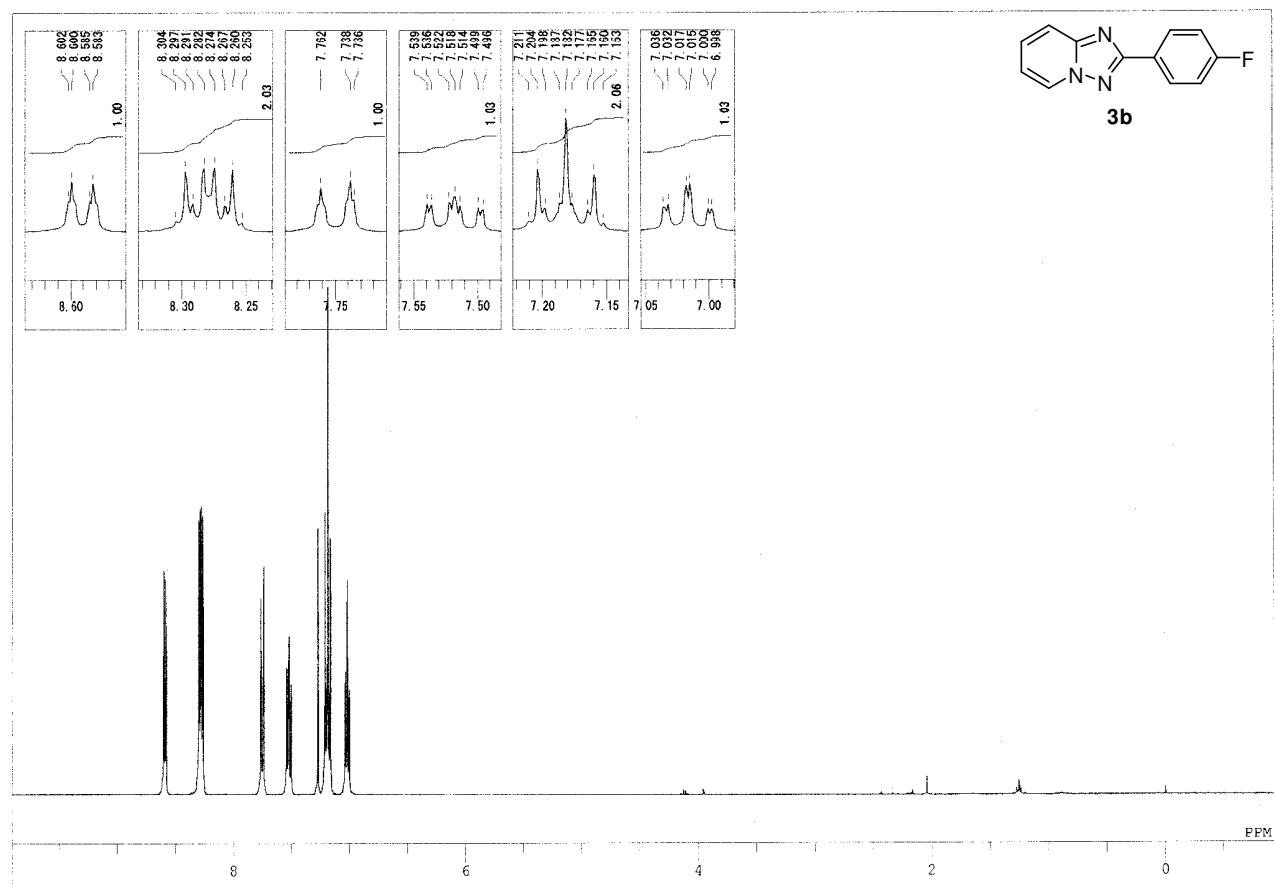
Table S1

entry	change from standard condition	yield (%)
1	none (standard condition)	81
2	2,2'-bipyridine , instead of 1,10-phen	74
3	N,N'-dimethylethylenediamine , instead of 1,10-phen	38
4	D,L-proline , instead of 1,10-phen	47
5	no ligand	70
6	10 mol% H₂O added	75
7	200 mol% H₂O added	60

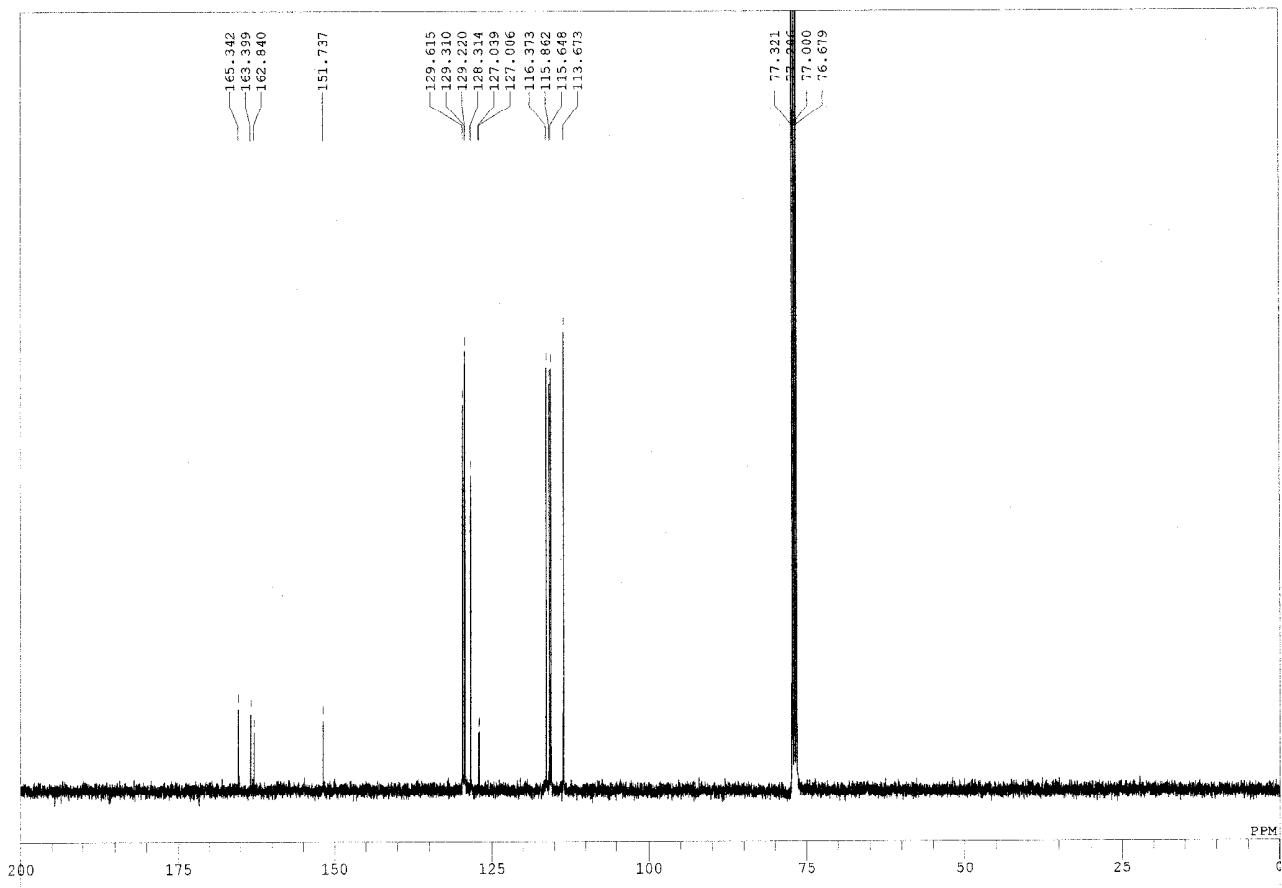
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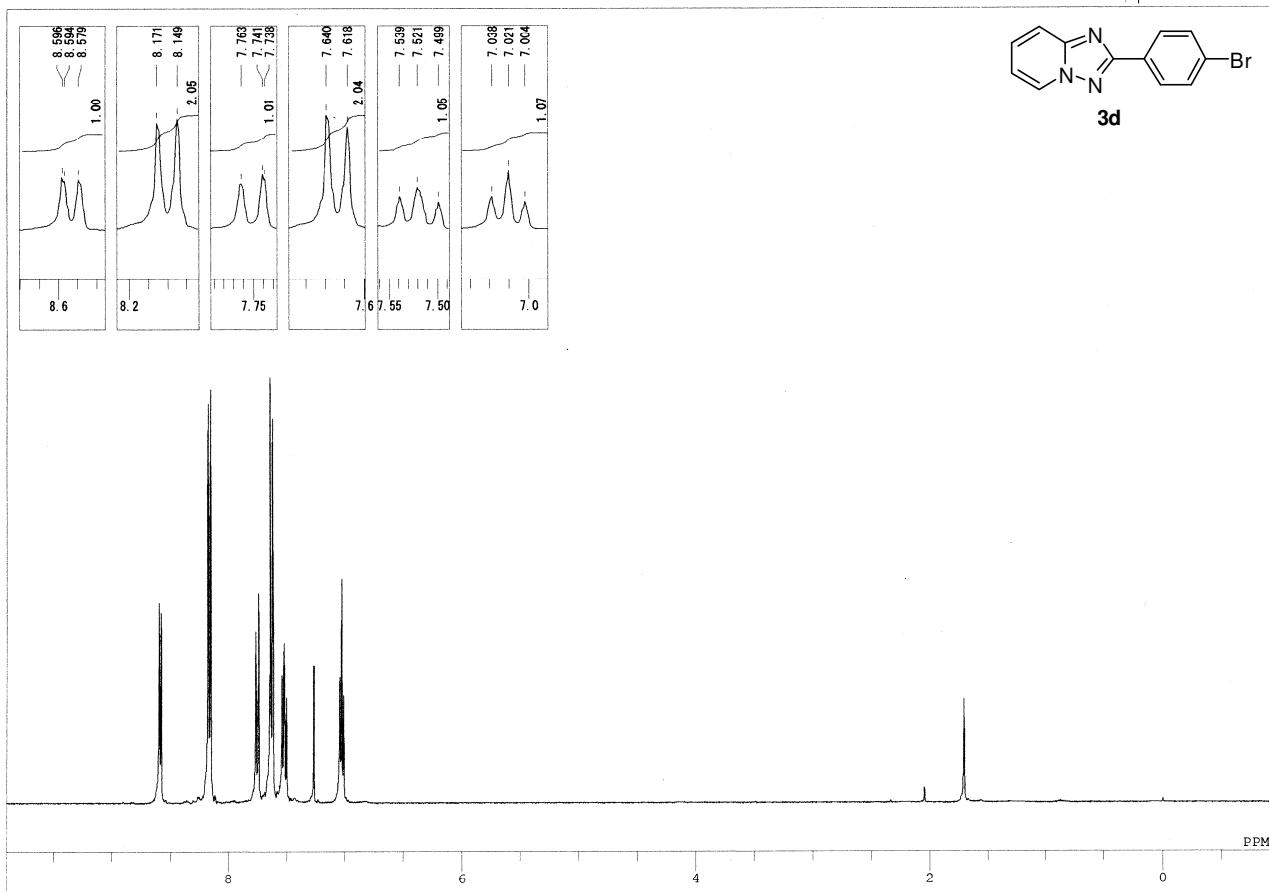
¹H NMR (3b)



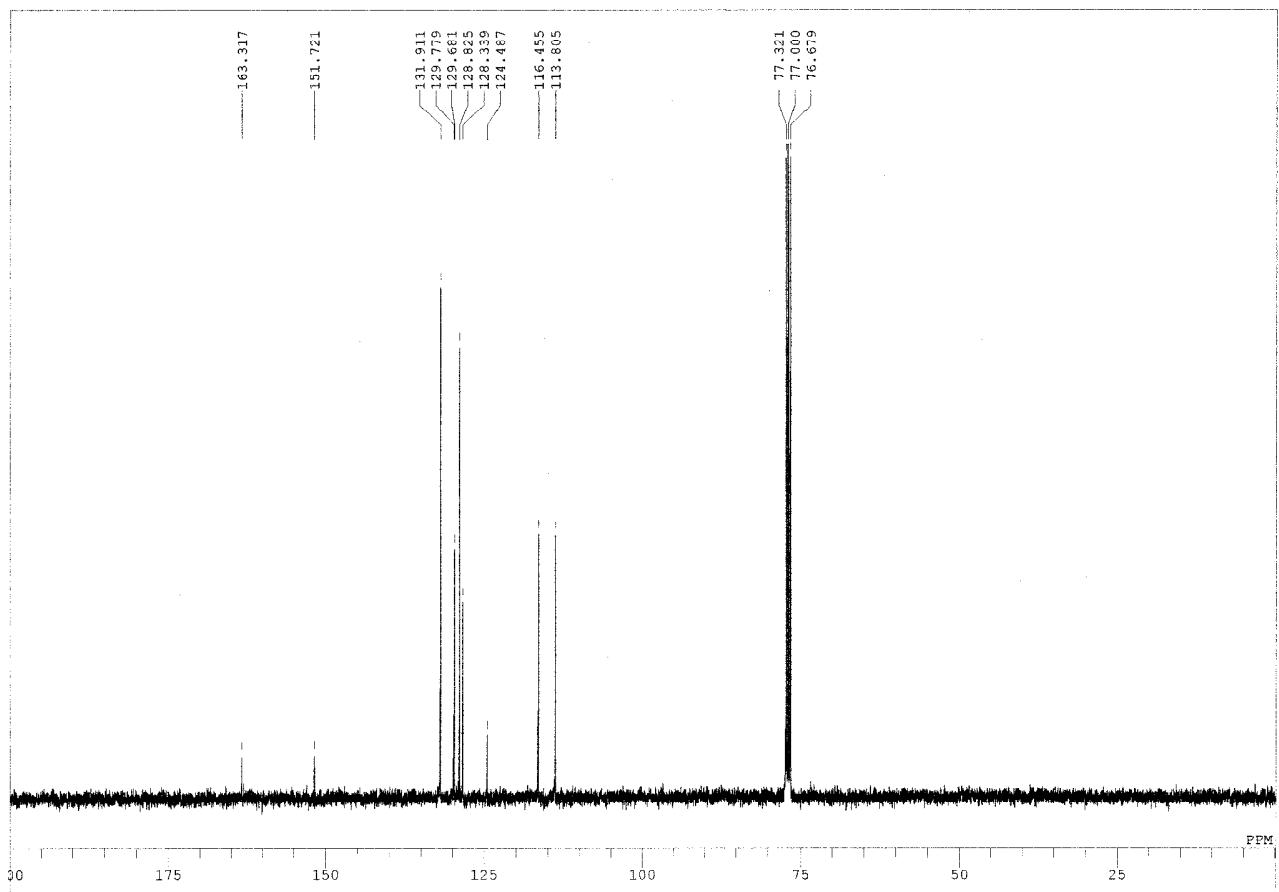
¹³C NMR (3b)



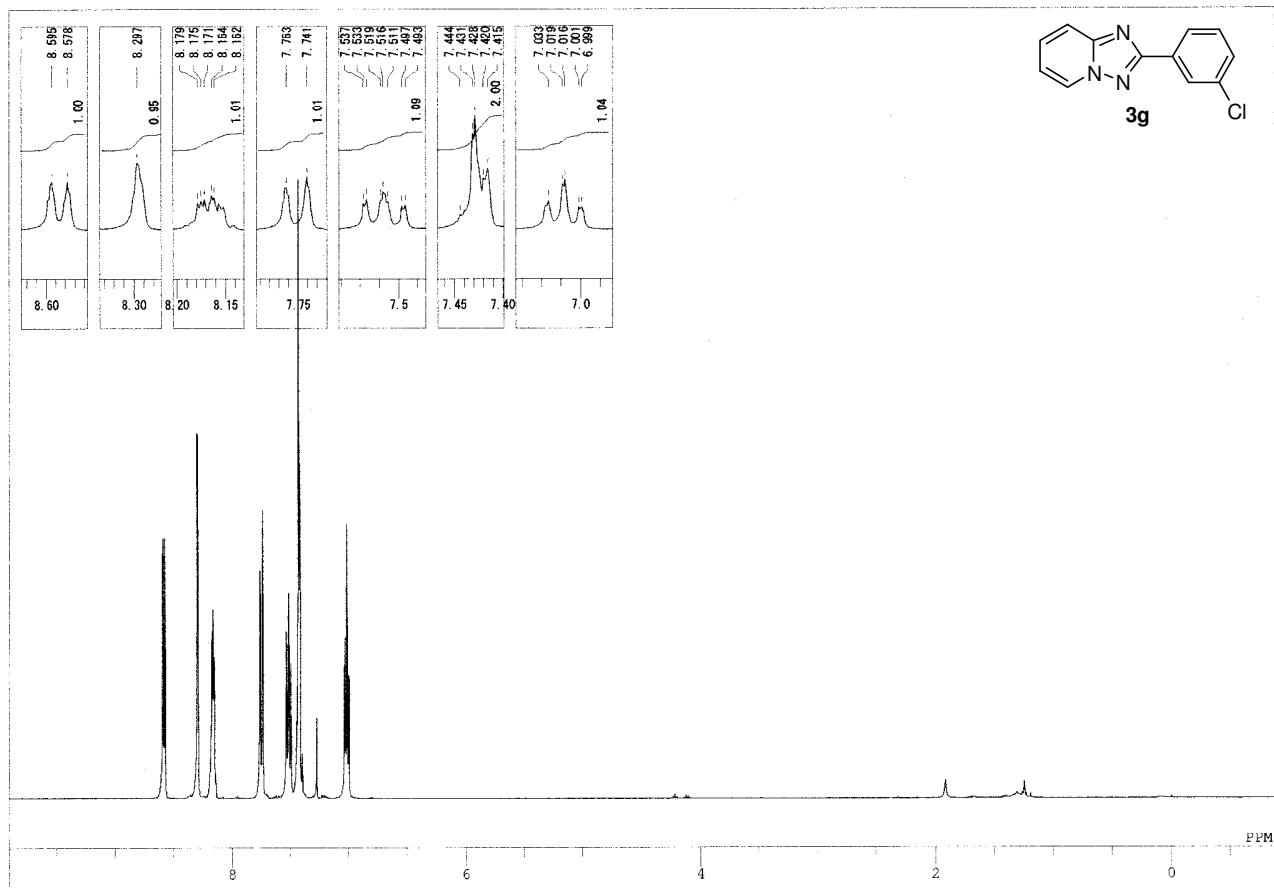
¹H NMR (3d)



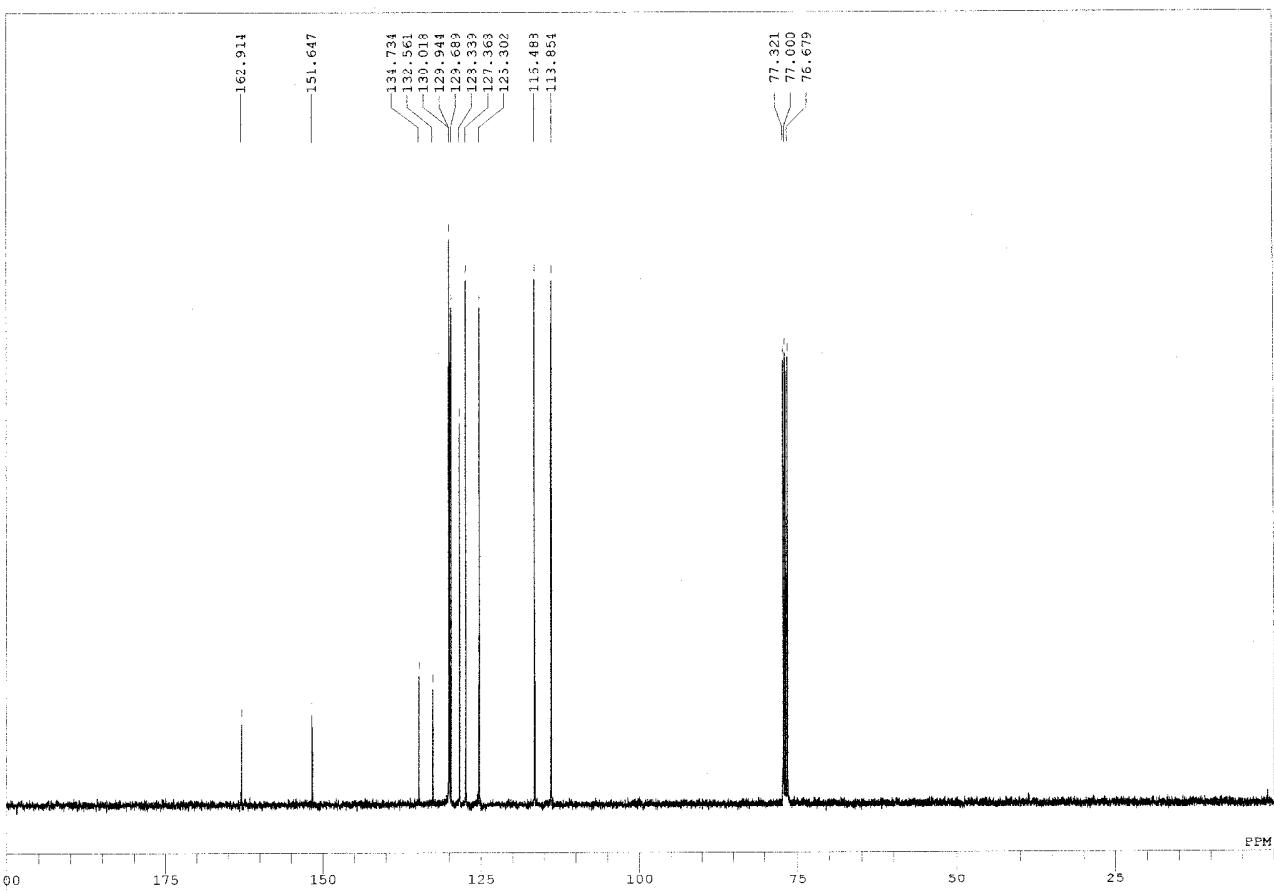
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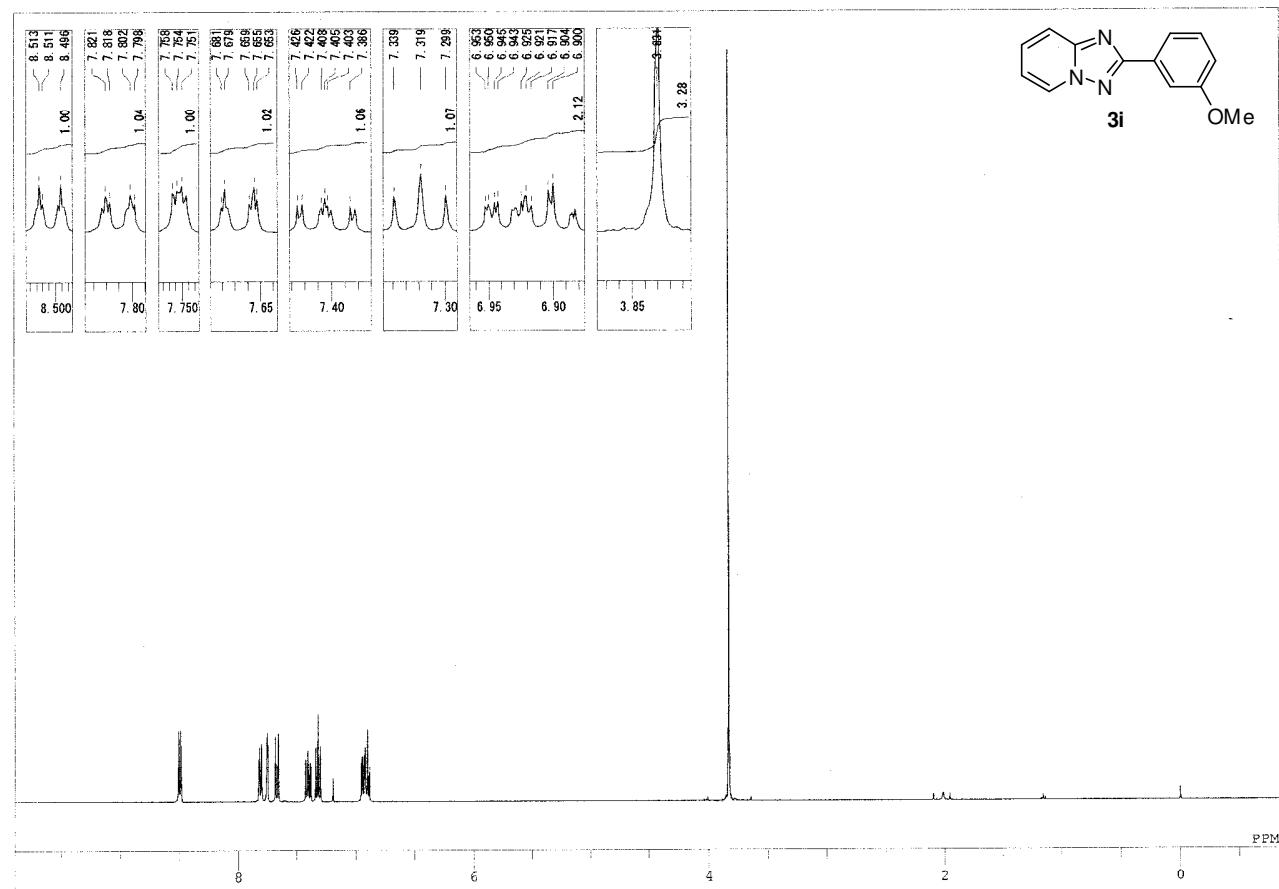
¹H NMR (3g)



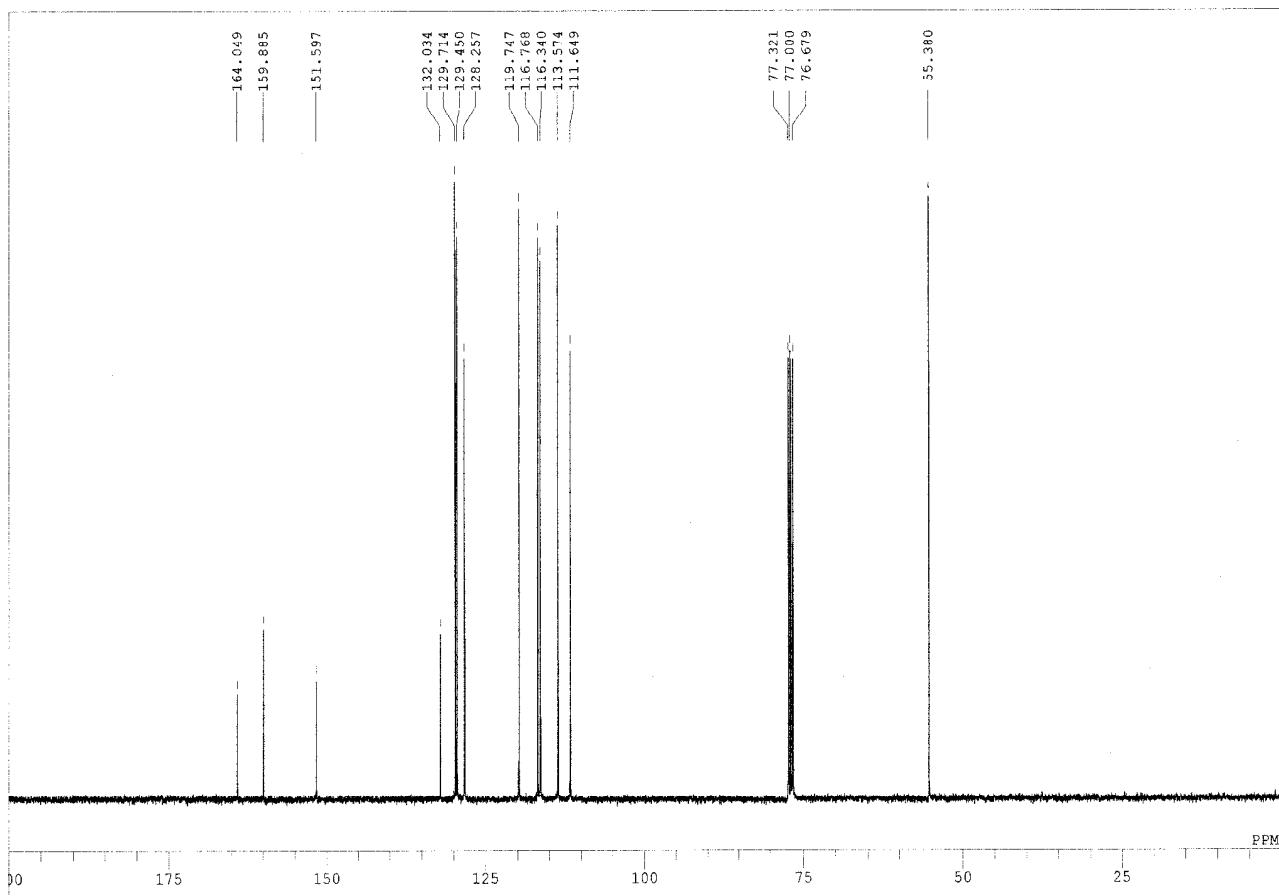
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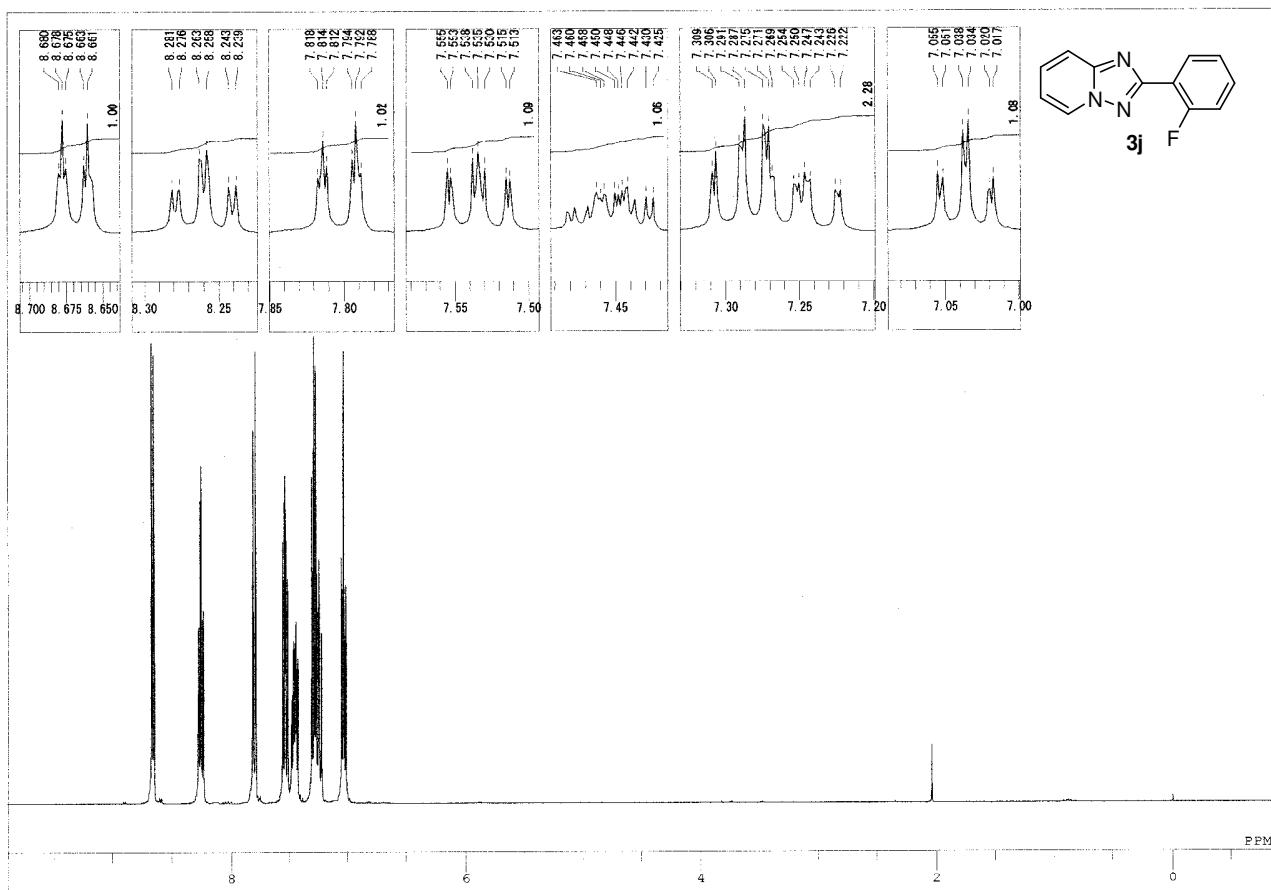
¹H NMR (**3i**)



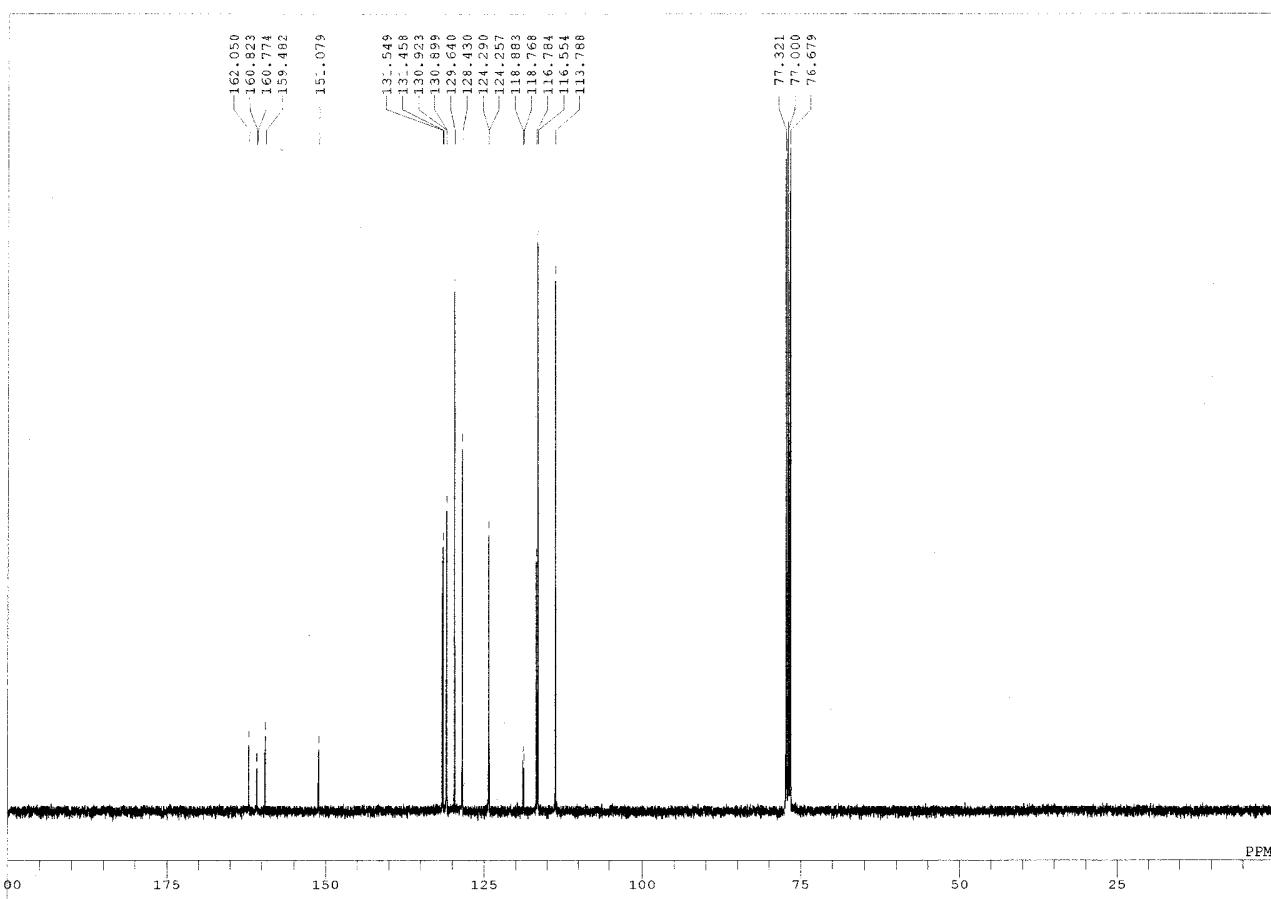
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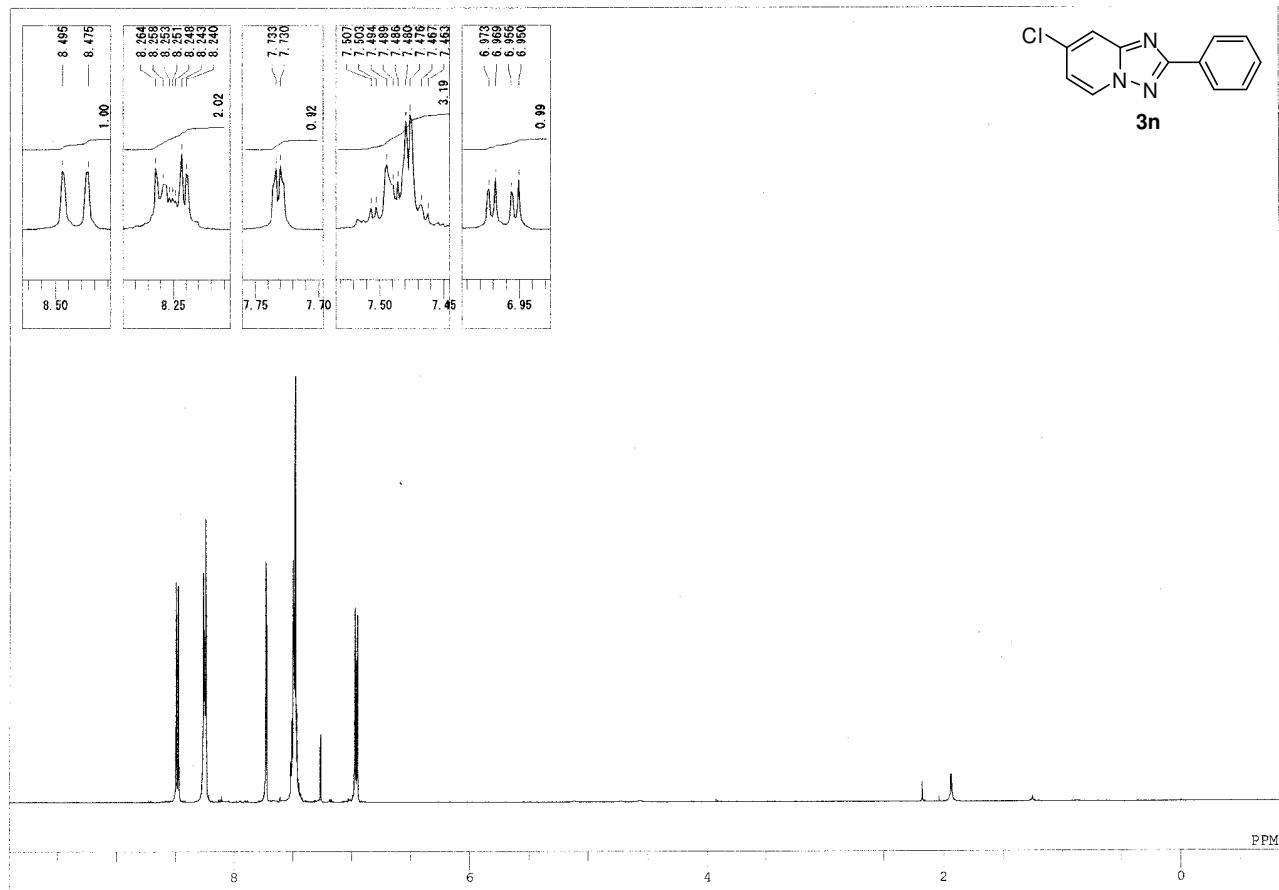
¹H NMR (**3j**)



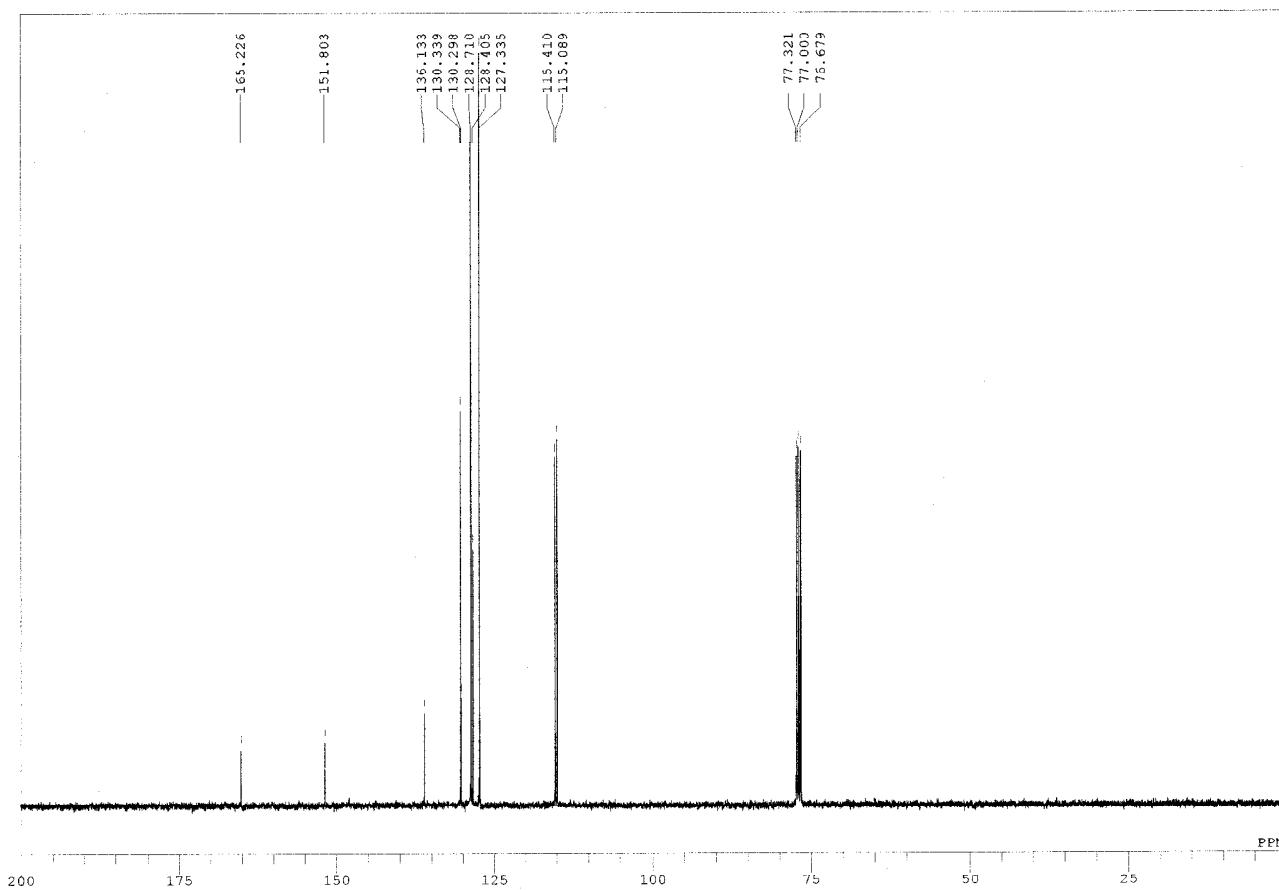
¹³C NMR (**3j**)



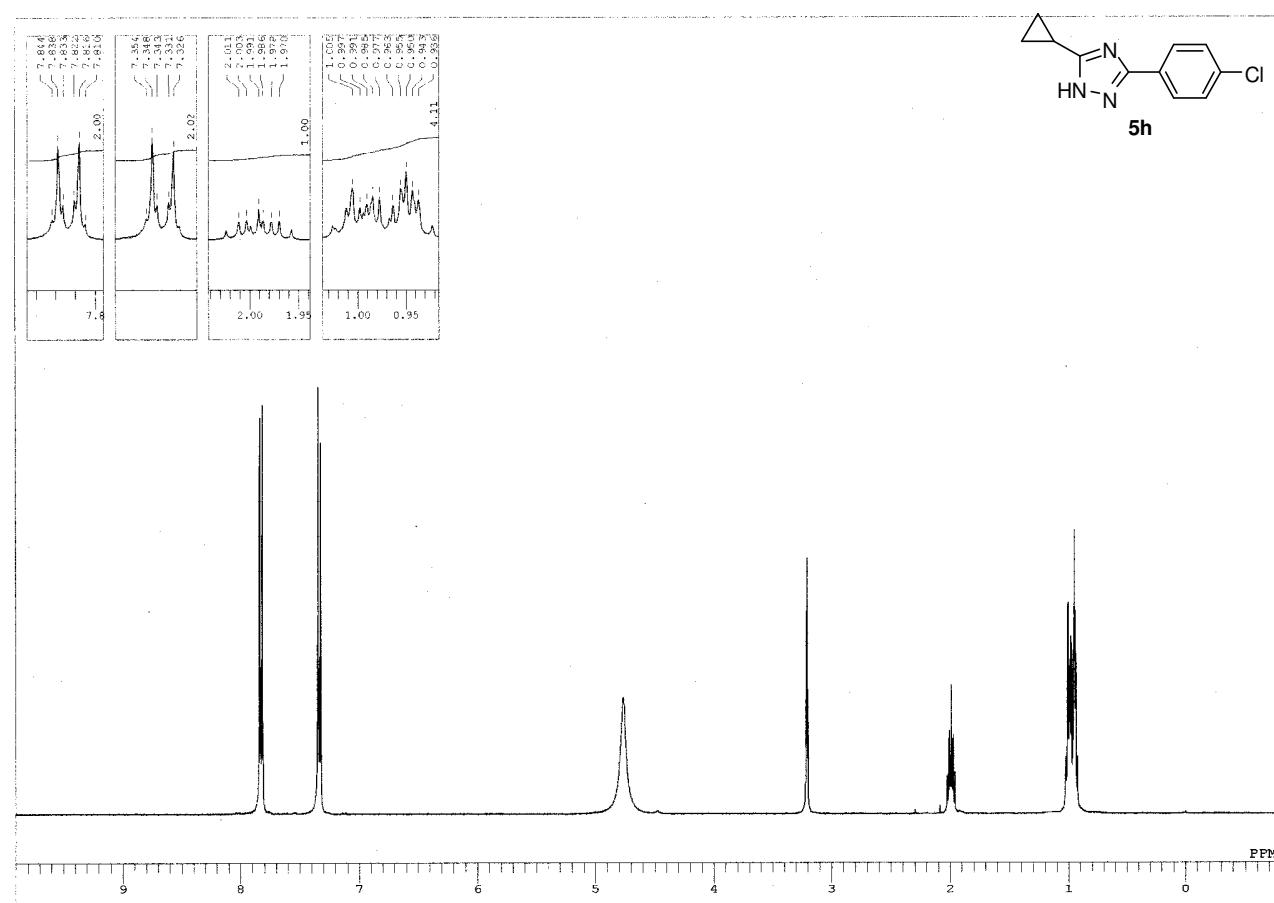
¹H NMR (**3n**)



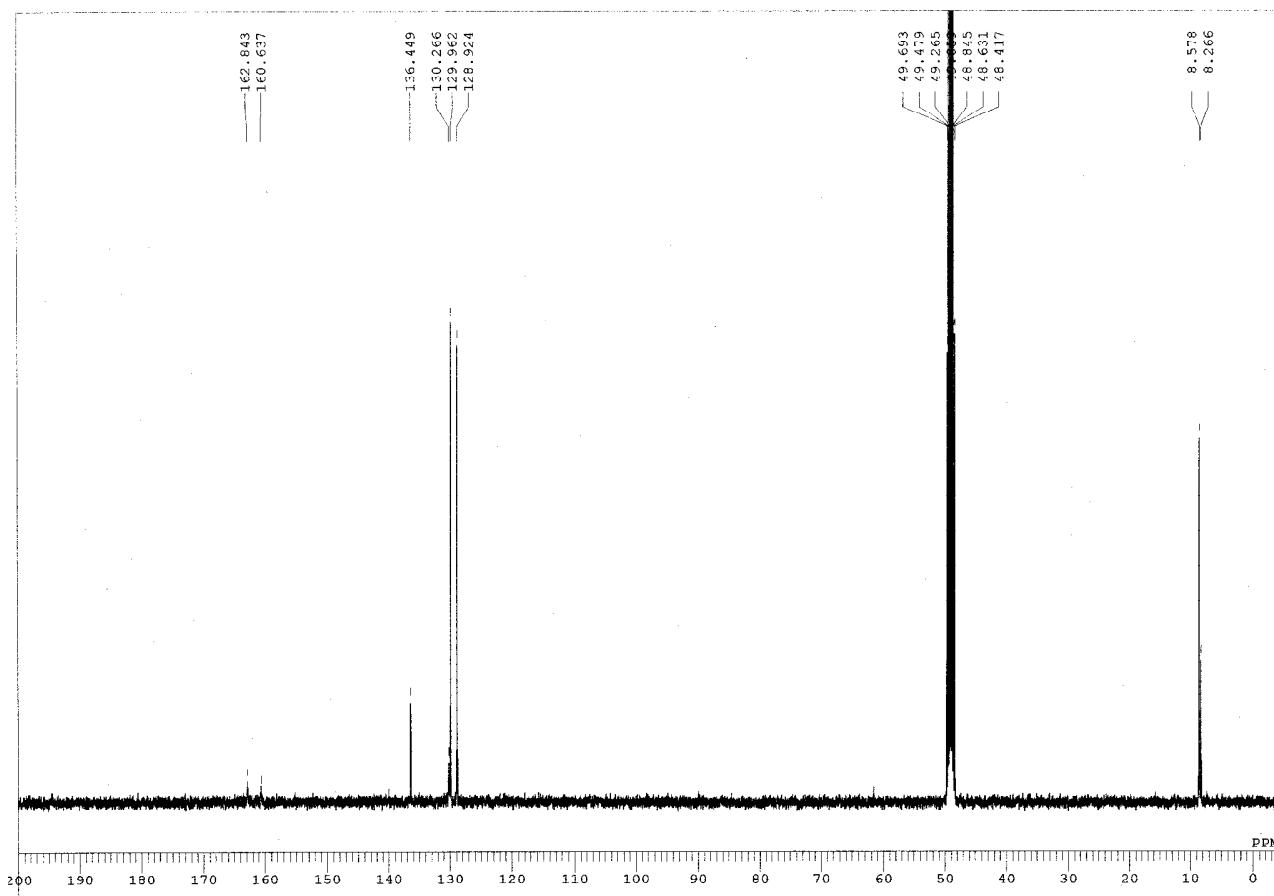
¹³C NMR (**3n**)



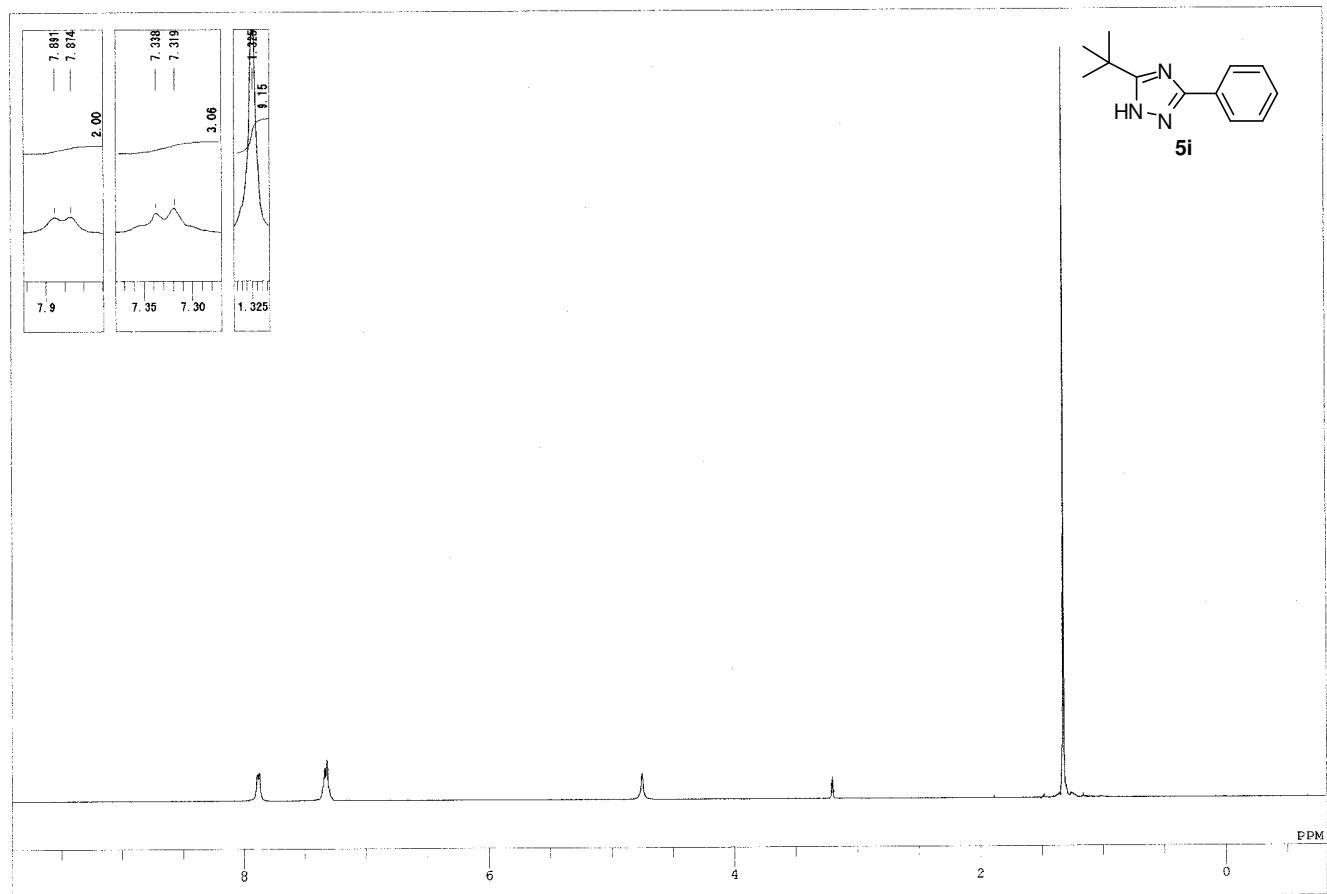
¹H NMR (**5h**)



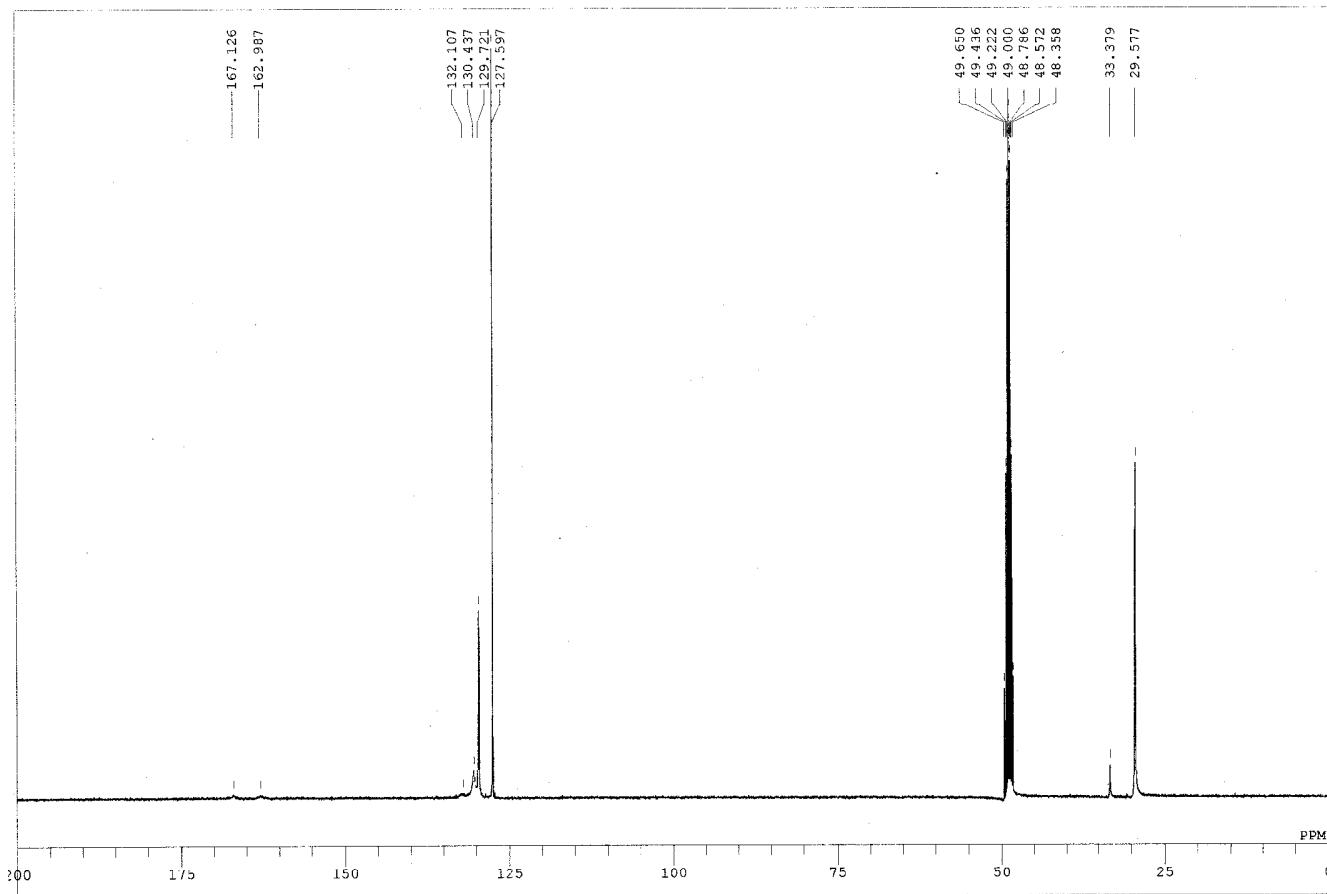
¹³C NMR (**5h**)



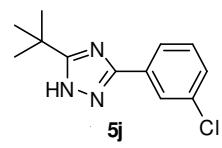
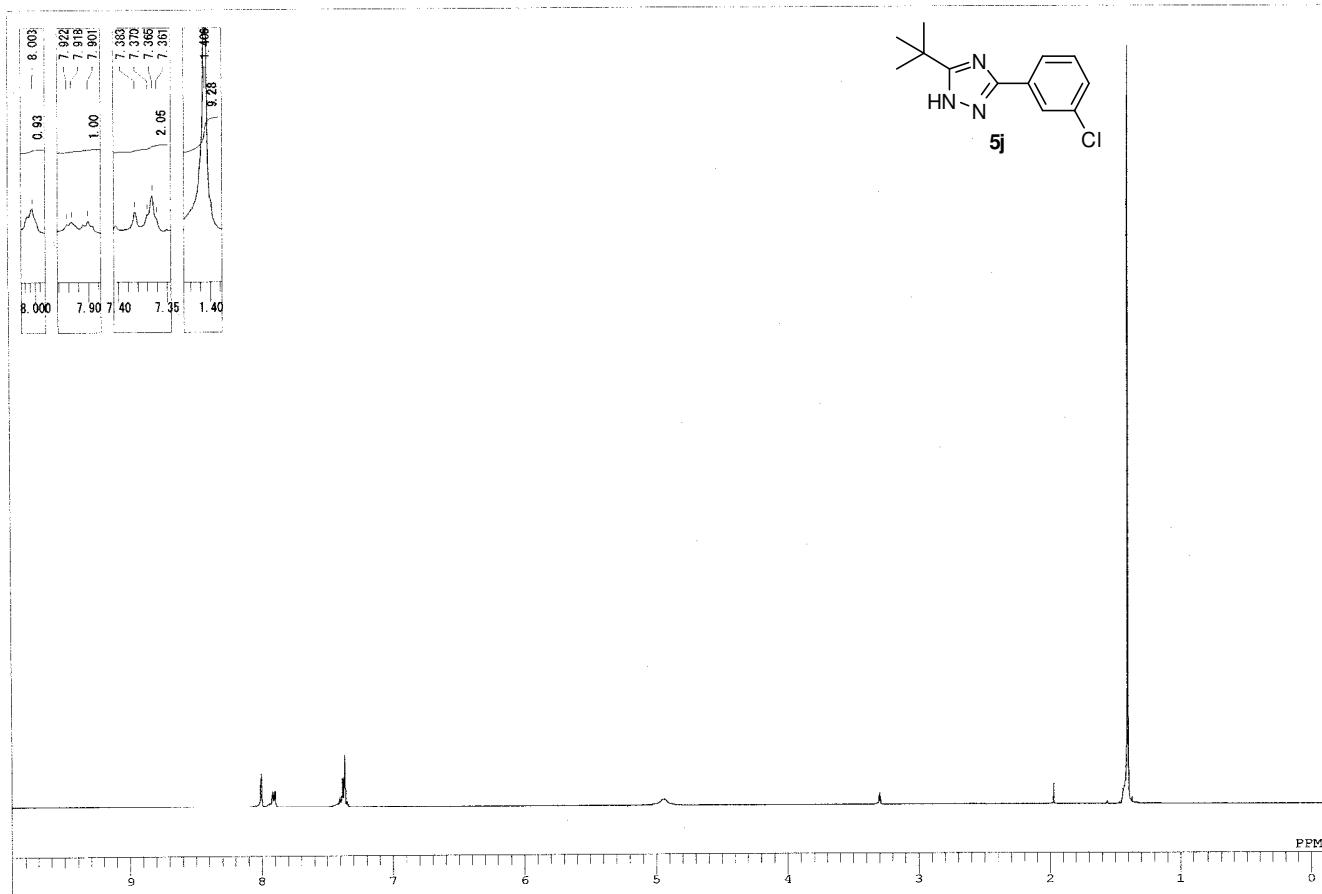
¹H NMR (**5i**)



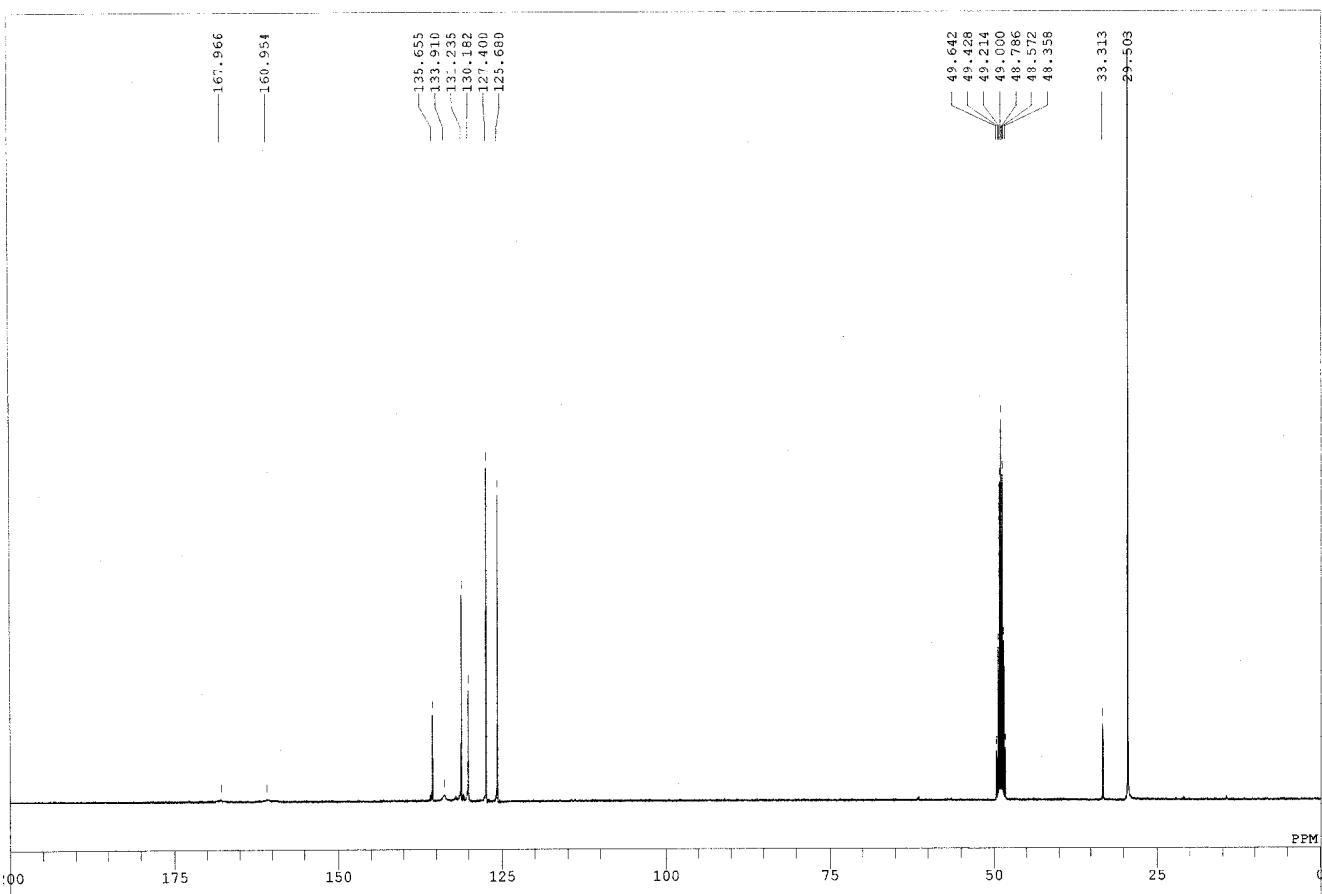
¹³C NMR (**5i**)



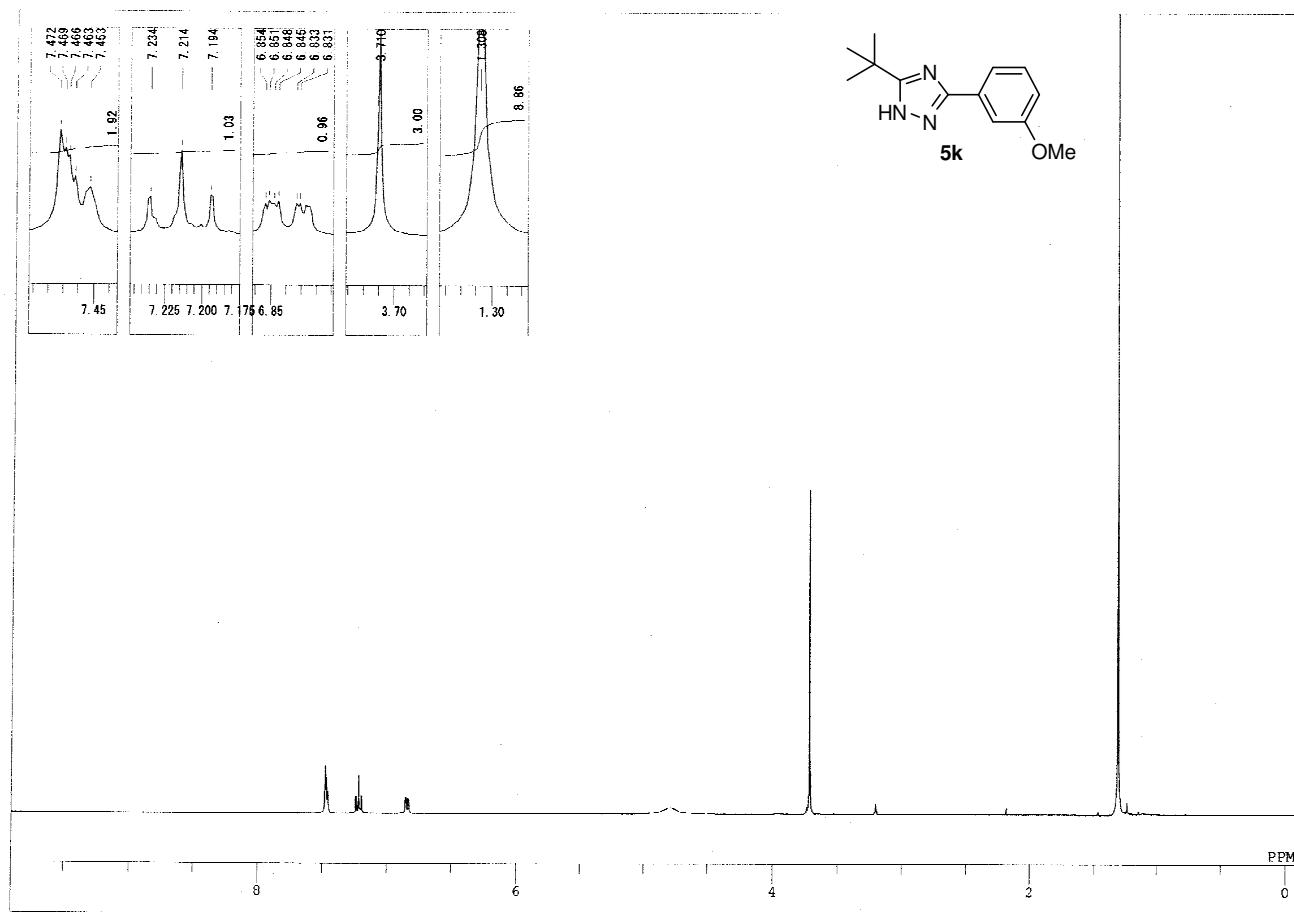
¹H NMR (**5j**)



¹³C NMR (**5j**)



¹H NMR (5k)



¹³C NMR (5k)

