Iron-catalyzed direct amination of azoles using formamides or amines as nitrogen sources in air

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General information:

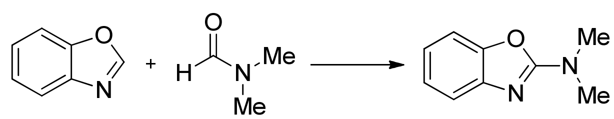
^{1}H-NMR, ^{13}C-NMR spectra were measured on a Bruker AM400 NMR spectrometer (400 MHz or 100MHz, respectively) with $CDCl_3$ as solvent and recorded in ppm relative to internal tetramethylsilane standard. Mass spectroscopy data of the product was collected on an Agilent 6890-5973N GCMS-EI instrument.

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. Formamide was distilled under high vacuum. Benzoxazole derivatives[1] and 1, 3, 4-oxadiazole derivatives[2] are prepared according to the literature.

Optimization studies of direct amination of benzoxazoles with formamides

For initial optimization of the reaction conditions, we selected benzoxazole (**1a**) and N, N-dimethylformamide (DMF) as model substrates, and the results are summarized in Table S1.

Table S1: Optimization of direct amination of benzoxazoles with formamides[a]



1a **2a**

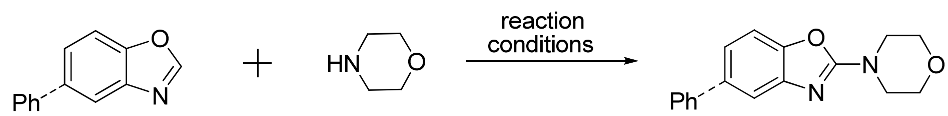
Entry	[M] (equiv)	Additive	Temp(℃)	Yield (%)[b]
1	$CuCl_2 \cdot 2H_2O$(0.5)	None	130	0
2	$CuCl_2 \cdot 2H_2O$(0.5)	Pyrazole	130	trace
3	$CuCl_2 \cdot 2H_2O$(0.5)	Imidazole	130	54
4	None	Imidazole	130	0
5	$NiCl_2 \cdot 6H_2O$(0.5)	Imidazole	130	0
6	$FeSO_4 \cdot 7H_2O$(0.5)	Imidazole	130	0
7	$Fe(CO)_9$(0.5)	Imidazole	130	0
8	$FeCl_3 \cdot 6H_2O$(0.5)	Imidazole	130	52
9	$FeCl_3 \cdot 4H_2O$(0.5)	Imidazole	130	58
10	$FeCl_3 \cdot 6H_2O$(0.5)	None	130	11
11	$FeCl_3$(1.0)	Imidazole	130	74
12	$FeCl_3$(0.5)	1-Methylimidazole	130	56
13	$FeCl_3$(0.5)	2-Methylimidazole	130	37
14	$FeCl_3$(0.5)	Pyrazole	130	8
15	$FeCl_3$(0.5)	Et_3N	130	trace
16	$FeCl_3$(0.25)	o-Phen	130	0
17[c]	$FeCl_3$(0.5)	Imidazole	130	30
18	$FeCl_3$(0.5)	Imidazole	110	45
19[d]	$FeCl_3$(0.25)	Imidazole	130	82

[a] Conditions: **1a** (0.2 mmol), DMF (2 mL), additive(2.0 equiv), 12 h, under air. [b] Isolated yields. [c] Reaction under nitrogen with a balloon. [d] **1a** (0.5 mmol). Et3N = Triethylamine; o-Phen = 1, 10-Phenanthroline.

Optimization studies of direct amination of benzoxazoles with amines

For initial optimization of the reaction conditions, we selected benzoxazole (**1a**) and morpholine (**7a**) as model substrates, and the results are summarized in Table S2.

Table S2: Optimization of direct amination of benzoxazoles with amines[a]



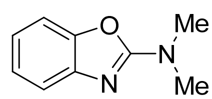
Entry	[Fe] (equiv)	Additive	Solvent	Temp(℃)	Yield (%)[b]
1	none	imidazole	CH_3CN	60	0
2	$FeCl_3$(0.5)	none	CH_3CN	60	trace
3	$FeCl_3$(0.25)	imidazole	CH_3CN	60	<5
4	$FeCl_3$(0.5)	imidazole	CH_3CN	60	42
5	$FeCl_3$(1.0)	imidazole	CH_3CN	60	43
6[c]	$FeCl_3$(0.5)	imidazole	CH_3CN	60	15.8
7	$FeCl_3$(0.5)	imidazole	DMF	60	35
8	$FeCl_3$(0.5)	imidazole	DMSO	60	20
9	$FeCl_3$(0.5)	imidazole	1,4-doxane	60	<5
10	$FeCl_3$(0.5)	imidazole	DCE	60	<5
11	$FeCl_3$(0.5)	imidazole	THF	60	<5
12	$FeCl_3$(0.5)	imidazole	Toluene	60	<5
13	$FeCl_3$(0.5)	imidazole	CH_3CN	40	14
14	$FeCl_3$(0.5)	imidazole	CH_3CN	80	28
15[d]	$FeCl_3$(0.5)	imidazole	CH_3CN	60	75
16[e]	$FeCl_3$(0.5)	imidazole	CH_3CN	60	14
17[f]	$FeCl_3$(0.5)	imidazole	CH_3CN	60	57

[a] Conditions: **1a** (1.5 equiv), morpholine (0.5 mmol), imidazole (2.0 equiv), solvent (2 mL), 60℃, 12 h. [b] Yield of isolated. [c] **1a** (1.2 equiv). [d] **1d** (1.5 equiv) was used instead of **1a**. [e] Reaction under nitrogen with a balloon. [f] Reaction under oxgen with a balloon.

General procedure for amination of benzoxazoles with formamides(I)

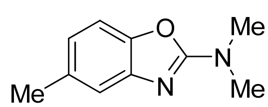
A dried reflux tube equipped with a magnetic stir bar charged with benzoxazole derivative (0.5 mmol 1.0equiv), $FeCl_3$ (0.25equiv), imidazole (2.0 equiv), formamide derivative (2 mL) and the reaction vessel was placed in a 130℃ oil bath. After stirring at this temperature for 12 h under air, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was directly filtered through a pad of celite and washed with water. The aqueous layer was extracted again with EtOAc. The combined organic layer was concentrated under reduced pressure after had been dried over $MgSO_4$. The crude product was purified by column chromatography using the indicated eluent. The identity and purity of the known product was confirmed by GC-MC, ^{1}H-NMR and ^{13}C-NMR.

2-(*N*,*N*-Dimethylamino)benzoxazole (2a).



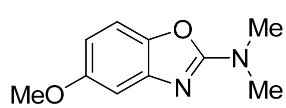
EtOAc/*n*-hexane (1:5); orange solid (67mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.24 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.17-7.13 (m, 1H), 7.01-6.97 (m, 1H), 3.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.1, 149.1, 143.6, 123.9, 120.2, 116.0, 108.6, 37.7; MS (EI) *m/z* (%) 162 (M^+,100), 147 (40), 133 (17).

2-(*N*,*N*-Dimethylamino)-5-methylbenzoxazole (2b).



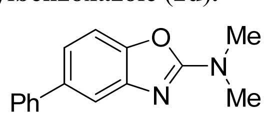
EtOAc/*n*-hexane (1:5); yellow solid (77mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.15 (s, 1H), 7.11 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 7.6 Hz , 1H), 3.19 (s, 6H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.3, 147.2, 143.7, 133.5, 120.8, 116.4, 107.9, 37.7, 21.5; MS (EI) *m/z* (%) 176 (M^+,100), 161 (85), 147 (24), 133 (12), 44 (27).

2-(*N*,*N*-Dimethylamnio)-5-methoxybenzoxazole (2c).



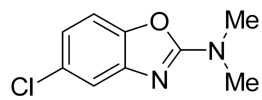
EtOAc/*n*-hexane (1:5); yellow solid (68mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.11 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 8.8 2.4Hz, 1H), 3.80 (s, 3H), 3.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.8, 157.0, 144.5, 143.6, 108.4, 106.5, 101.2, 55.8, 37.6; MS (EI) *m/z* (%) 192 (M^+,100), 177 (55), 163 (12), 149 (54), 44 (15).

2-(*N*,*N*-Dimethylamino)-5-phenylbenzoxazole (2d).



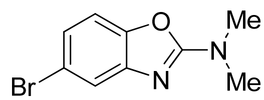
EtOAc/*n*-hexane (1:5); pale yellow solid (104mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.60-7.57 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34-7.21 (m, 3H), 3.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.3, 148.5, 1440, 141.5, 137.4, 128.5, 127.1, 126.6, 119.4, 114.5, 108.3, 37.5; MS (EI) *m/z* (%) 238 (M^+,100), 223 (21), 195 (14).

5-Chloro-2-(*N*,*N*-dimethylamino)benzoxazole (2e).



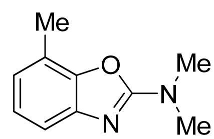
EtOAc/*n*-hexane (1:5); light yellow solid (63mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.30 (d, *J* = 1.2 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.91 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.9, 147.8, 145.1, 129.4, 120.2, 116.3, 109.1, 37.8; MS (EI) *m/z* (%) 197 (M^+,100), 181 (58), 167 (22), 153 (19), 44 (21).

5-Bromo-2-(*N*,*N*-dimethylamino)benzoxazole (2f).



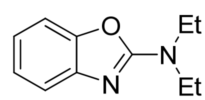
EtOAc/*n*-hexane (1:5); brown solid (93mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.45 (s, 1H), 7.10 (brs, 2H), 3.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.6, 148.1, 145.5, 122.8, 119.0, 116.6, 109.7, 37.7; MS (EI) *m/z* (%) 241 (M^+,100), 227 (39), 213 (15), 199 (12), 44 (22).

2-(*N*,*N*-Dimethylamino)-7-methylbenzoxazole (2h).



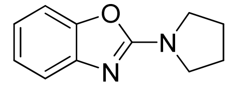
EtOAc/*n*-hexane (1:5); orange oil (70mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.18 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.6 Hz , 1H), 3.20 (s, 6H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.0, 148.0, 143.1, 123.7, 121.8, 119.0, 113.4, 38.2, 14.9; MS (EI) *m/z* (%) 176 (M^+,100), 161 (65), 147 (21), 44 (16).

2-(*N*,*N*-Diethylamino)benzoxazole (5a).



0.5 equiv of $FeCl_3$ used; stirring for 24h; EtOAc/*n*-hexane (1:5); orange solid (11mg, 12%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.28 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.09-7.05 (m, 1H), 6.93-6.89 (m, 1H), 3.52 (q, *J* = 7.12 4H), 1.21 (t, *J* = 7.1, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.1, 149.1, 143.6, 123.9, 120.2, 116.0, 108.6, 37.7; MS (EI) *m/z* (%) 190 (M^+,100), 175 (24), 161 (55), 147 (98).

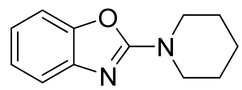
2-(1-Pyrrolidinyl)benzoxazole (5b).



0.5 equiv of $FeCl_3$ used; stirring for 24h; EtOAc/*n*-hexane (1:5); yellow solid (64mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.36 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.17-7.12 (m, 1H), 7.01-6.97 (m, 1H), 3.65 (t, *J* = 7.12 4H), 2.06-2.02 (m, 4H); ^{13}C NMR (100 MHz,

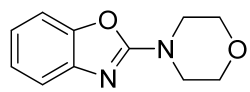
$CDCl_3$) d=161.0, 149.0, 143.7, 123.8, 120.0, 116.0, 108.6, 47.4, 25.6; MS (EI) *m/z* (%) 188 (M^+,100), 160 (33), 133 (35).

2-(1-Piperidinyl)benzoxazole (5c).



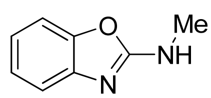
EtOAc/*n*-hexane (1:5); yellow solid (96mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.34 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 3.66 (m, 4H), 1.69 (brs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=162.5, 148.7, 143.4, 123.8, 120.3, 116.0, 108.5, 46.6, 25.2, 24.1; MS (EI) *m/z* (%) 202 (M^+,100), 187 (11), 173 (18), 147 (16), 134 (36).

2-(4-Morpholinyl)benzoxazole (5d).



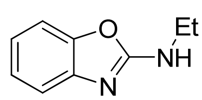
EtOAc/*n*-hexane (1:5); yellow solid (64mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.38 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 3.83-3.81 (m, 4H), 3.71-3.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) d=161.9, 148.5, 142.6, 123.9, 120.7, 116.3, 108.6, 46.0, 45.5, 24.1; MS (EI) *m/z* (%) 204 (M^+,100), 147 (61).

2-(*N*-Methylamino)benzoxazole (5e).



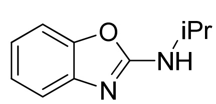
0.75 equiv of $FeCl_3$ used; stirring for 24h; EtOAc/*n*-hexane (1:5); orange solid (10mg, 13%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.31 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.11-7.07 (m, 1H), 6.98-6.94 (m, 1H), 5.02 (brs, 1H), 3.06 (s, 3H), 2.06-2.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) d=162.1, 148.6, 143.2, 123.9, 120.9, 116.4, 108.7, 29.6; MS (EI) *m/z* (%) 148 (M^+,100), 119 (25).

2-(*N*-Ethylamino)benzoxazole (5f).



EtOAc/*n*-hexane (1:5); orange solid (29mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.36 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 5.38 (s, 1H), 3.54 (q, *J* = 6.7 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=162.1, 148.5, 143.0, 123.9, 120.7, 116.2, 108.7, 38.0, 15.2; MS (EI) *m/z* (%) 162 (M^+,71), 147 (26), 134 (100).

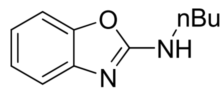
2-(*N*-Isopropylamino)benzoxazole (5g).



EtOAc/*n*-hexane (1:5); yellow solid (59mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.36 (d, *J*

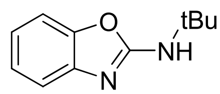
= 7.8 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.18-7.14 (m, 1H), 7.04-7.00 (m, 1H), 5.14 (br, 1H), 4.13-4.05 (m, 1H), 1.32 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=161.5, 148.4, 143.1, 123.8, 120.7, 116.2, 108.7, 45.4, 23.1; MS (EI) *m/z* (%) 176 (M^+,60), 161 (17), 134 (100).

2-(*N*-n-Butylamino)benzoxazole (5h).



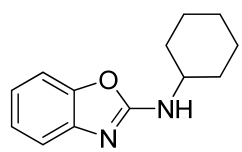
EtOAc/*n*-hexane (1:5); yellow solid (49mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.36 (dd, *J* = 7.8, 0.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.18-7.13 (m, 1H), 7.04-7.00 (m, 1H), 5.26 (s, 1H), 3.51-3.46(m, 2H), 1.71-1.63 (m, 2H), 1.49-1.39 (m, 2H), 0.96 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=162.2, 148.5, 143.1, 123.8, 120.7, 116.2, 108.6, 42.9, 31.8, 19.9, 13.7; MS (EI) *m/z* (%) 190 (M^+,100), 173 (30), 160 (18), 147 (44), 134 (84), 120 (16).

2-(*N*-*tert*-Butylamino)benzoxazole (5i).



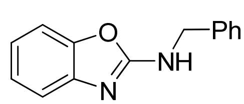
EtOAc/*n*-hexane (1:5); yellow solid (68mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.37 (d, *J* = 7.4, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.17-7.13 (m, 1H), 7.04-7.00 (m, 1H), 5.05 (s, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) d=160.7, 148.1, 143.2, 123.7, 120.6, 116.4, 108.5, 52.0, 29.2; MS (EI) *m/z* (%) 190 (M^+,24), 134 (100).

2-(*N*-Cyclohexylamino)benzoxazole (5j).



0.5 equiv of $FeCl_3$ used; stirring for 24h; EtOAc/*n*-hexane (1:5); yellow solid (51mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.36 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.17-7.13 (m, 1H), 7.03-7.00 (m, 1H), 4.98 (d, *J* = 7.4 Hz, 1H), 3.81-3.71 (m, 1H), 2.15-2.11 (m, 2H), 1.80-1.75 (m, 2H), 1.68-1.63 (m, 1H), 1.50-1.39 (m, 2H), 1.34-1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=161.4, 148.40, 143.2, 123.8, 120.6, 116.2, 108.6, 52.0, 33.4, 25.5, 24.7; MS (EI) *m/z* (%) 216 (M^+,36), 134 (100).

2-(*N*-Benzylamino)benzoxazole (5k).

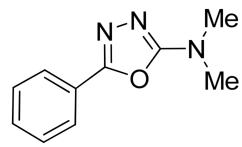


0.5 equiv of $FeCl_3$ used; stirring for 24h; EtOAc/*n*-hexane (1:5); yellow solid (95mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.40-7.29 (m, 6H), 7.21-7.16 (m, 4H), 4.41 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) d=162.9, 136.0, 135.6, 128.9, 128.8, 128.7, 128.5, 128.1, 127.8, 127.7, 50.3; MS (EI) *m/z* (%) 225 (M^+,16), 134 (100), 106 (27), 91 (30), 79 (15).

General procedure for amination of 1,3,4-oxadiazole with formamides(II)

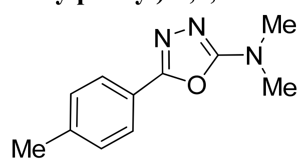
A dried reflux tube equipped with a magnetic stir bar charged with 1,3,4-oxadiazole derivative (0.5 mmol 1.0equiv), $FeCl_3$ (0.5equiv), imidazole (2.0 equiv), DMF (2 mL) and the reaction vessel was placed in a 130℃ oil bath. After stirring at this temperature for 36 h under air, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was directly filtered through a pad of celite and washed with water. The aqueous layer was extracted again with EtOAc. The combined organic layer was concentrated under reduced pressure after had been dried over $MgSO_4$. The crude product was purified by column chromatography using the indicated eluent. The identity and purity of the known product was confirmed by GC-MC, ^{1}H-NMR and ^{13}C-NMR.

2-(*N*,*N*-Dimethylamino)-5-phenyl-1,3,4-oxadiazole (4a).



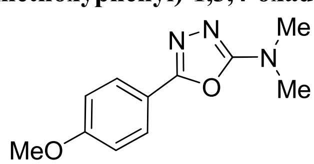
EtOAc/*n*-hexane (1:5); light yellow solid (65mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.92-7.90 (m, 2H), 7.46-7.44 (m, 3H), 3.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=164.8, 159.2, 130.3, 128.8, 125.7, 124.8, 38.1; MS (EI) *m/z* (%) 189 (M^+,100), 105 (38), 72 (17).

2-(*N*,*N*-Dimethylamino)-5-(4-methylphenyl)-1,3,4-oxadiazole (4b).



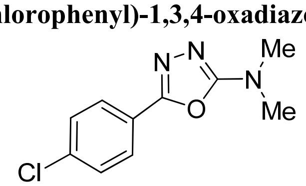
EtOAc/*n*-hexane (1:5); yellow solid (72mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.80 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.15 (s, 6H), 2.40(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=164.7, 159.4, 140.6, 129.5, 125.7, 38.1, 21.5; MS (EI) *m/z* (%) 203 (M^+,100), 119(32), 72(12).

2-(*N*,*N*-Dimethylamino)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (4c).



EtOAc/*n*-hexane (1:5); yellow solid (76mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.85 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 3.14(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=164.6, 161.2, 159.2, 127.4, 117.5, 114.2, 55.4, 38.2, 30.9; MS (EI) *m/z* (%) 219 (M^+,100), 135 (49), 72 (11).

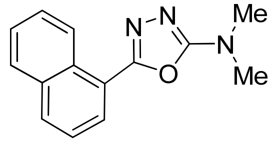
2-(*N*,*N*-Dimethylamino)-5-(4-chlorophenyl)-1,3,4-oxadiazole (4d).



EtOAc/*n*-hexane (1:5); pale yellow solid (69mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.85 (d, *J* = 5.7 Hz, 2H), 7.42 (d, *J* = 5.7 Hz, 2H), 3.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=165.1, 158.5, 136.4, 129.2, 127.0, 123.3, 38.3; MS (EI) *m/z* (%) 224 (M^+,100), 139 (44), 72

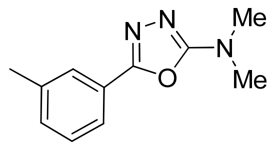
(34).

2-(*N*,*N*-Dimethylamino)-5-(1-naphthyl)-1,3,4-oxadiazole (4f).



EtOAc/*n*-hexane (1:5); yellow solid (75mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) d=9.24 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.58-7.51 (m, 1H), 3.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d=164.5, 159.1, 133.8, 131.2, 129.8, 128.5, 127.7, 126.7, 126.6, 126.5, 124.8, 121.3, 38.2, 30.9; MS (EI) *m/z* (%) 239 (M^+,100), 155 (21), 127 (12), 72 (15).

2-(*N*,*N*-Dimethylamino)-5-(3-methylphenyl)-1,3,4-oxadiazole (4h).

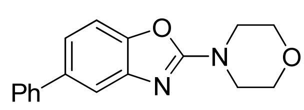


EtOAc/*n*-hexane (1:5); yellow solid (72mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.74 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 3.16(s, 6H), 2.41(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=164.8, 159.3, 138.6, 131.1, 128.7, 126.2, 124.6, 122.8, 38.2, 30.9, 21.3; MS (EI) *m/z* (%) 203 (M^+,100), 119 (43), 91 (14), 72 (15).

General procedure for direct amination of benzoxazoles with amines(III)

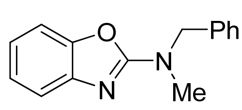
A dried reflux tube equipped with a magnetic stir bar charged with amine (0.5 mmol 1.0equiv), benzoxazole derivative (1.5 equiv), $FeCl_3$ (1.0 equiv), imidazole (2.0 equiv), acetonitrile (2 mL) and the reaction vessel was placed in a 60℃ oil bath. After stirring at this temperature for 12 h under air, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was directly filtered through a pad of celite and washed with water. The aqueous layer was extracted again with EtOAc. The combined organic layer was concentrated under reduced pressure after had been dried over $MgSO_4$. The crude product was purified by column chromatography using the indicated eluent. The identity and purity of the known product was confirmed by GC-MC, ^{1}H-NMR and ^{13}C-NMR

2-(4-Morpholinyl)-5-phenylbenzoxazole (6).



EtOAc/*n*-hexane (1:5); yellow solid (105mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.60-7.58 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.35-7.26 (m, 3H), 3.85-3.82 (m, 4H), 3.73-3.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) d=162.6, 148.4, 143.5, 141.6, 137.9, 128.8, 127.4, 127.0, 120.4, 115.2, 108.8, 66.2, 45.8; MS (EI) *m/z* (%) 280 (M^+,100), 223 (41).

2-(*N*-Benzyl-*N*-methylamino)benzoxazole (5l).



EtOAc/*n*-hexane (1:5); yellow solid (46mg, 39%); ^{1}H NMR (400 MHz, $CDCl_3$) d=7.39-7.26 (m, 7H), 7.19-7.15 (m, 1H), 7.04-7.00 (m, 1H), 4.76 (s, 2H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d=163.0, 149.0, 143.6, 136.4, 128.8, 127.8, 127.7, 127.0, 124.0, 120.4, 116.2, 108.7, 53.9, 35.2; MS (EI) *m/z* (%) 238 (M^+,100), 223 (50), 147 (35), 119 (11), 91 (31).

Investigation of radical scavenger effect

Different equivalent amounts of TEMPO were mixed into reaction systems about the direct amination of benzoxazole with representative nitrogen sources, and the results are summarized in Table S2. Radical scavenger reduced the yield of amination using amides but didn't affect the yield of amination using amines.

Table S2*:* Investigation of radical scavenger effect

Entry	Nitrogen Sources	TEMPO (equiv) [a]	General procedure	Yield(%)	Yield(%)[b]
1	DMF	1.0	I	27	82
2	DMF	2.0	I	19	82
3	4-Formylmorpholine	2.0	I	34	63
4	Morpholine	2.0	III	44	42

[a] TEMPO = 2,2,6,6-Tetramethyl-1-piperidinyloxy. [b] No TEMPO was mixed.

References:

(1) S. H. Cho, J. Y. Kim, S. Y. Lee and S. Chang, *Angew. Chem.* 2009, **121**, 9291; *Angew. Chem. Int. Ed.* 2009, **48**, 9127.

(2) (a) C. Ainsworth, *J. Am. Chem. Soc.* 1955, **77**, 1148; (b) T. Mukai, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.* 2009, **74**, 6410.

Certification of the purity of 99.99+% anhydrous $FeCl_3$

SIGMA-ALDRICH

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Saint Louis, Missouri 63103 USA
Telephone (800)-521-8956 • (314) 771-5765
Fax (800)-325-5052 • (314) 771-5757
sigma-aldrich.com

Certificate of Analysis

Iron(III) chloride, anhydrous, powder, 99.99+%

FeCl3

Product Number	45164-9	Batch No.	MKBC5308
Appearance	Dark Greenish Black Powder		

ICP-MS Full Trace Analysis (ppm)

Element	Results	DL
As	N/A	0.1
Ag	0.1	0.1
Al	0.9	0.1
Au		0.1
B		0.1
Ba	0.8	0.1
Be		0.1
Bi	0.1	0.1
Ca	0.7	0.1
Cd		0.1
Ce	0.2	0.1
Co	<9.2	0.1
Cr	0.8	0.1
Cs	1.7	0.1
Cu	5.3	0.1
Dy	0.3	0.1
Er	0.1	0.1
Eu		0.1
Fe	Major	0.1
Ga	0.1	0.1
Gd		0.1
Ge		0.1
Hf		0.1

Element	Results	DL
Hg		0.1
Ho		0.1
In	0.2	0.1
Ir		0.1
K		0.1
La	0.1	0.1
Li	0.2	0.1
Lu		0.1
Mg	0.3	0.1
Mn	0.7	0.1
Mo		0.1
Na	0.9	0.1
Nb		0.1
Nd		0.1
Ni	10.5	0.1
Os		0.1
Pb	0.2	0.1
Pd		0.1
Pr		0.1
Pt		0.1
Rb		0.1
Re		0.1
Rh		0.1

Element	Results	DL
Ru		0.1
Sb		0.1
Sc		0.1
Se		0.1
Si	7.8	0.1
Sm		0.1
Sn		0.1
Sr		0.1
Ta		0.1
Tb		0.1
Te		0.1
Th		0.1
Ti		0.1
Tl	0.2	0.1
Tm		0.1
U		0.1
V		0.1
W		0.1
Y		0.1
Yb		0.1
Zn	7.5	0.1
Zr		0.1
Total :	48.9	

Elements not reported were below detection limits. N/A = Not analyzed due to interference(s). DL = Detection limit.

Additional Testing	Results	Method
Assay	34.65% Fe	Perchloric Acid Titration

Deepika Pilla

QUALITY SERVICES DEPARTMENT

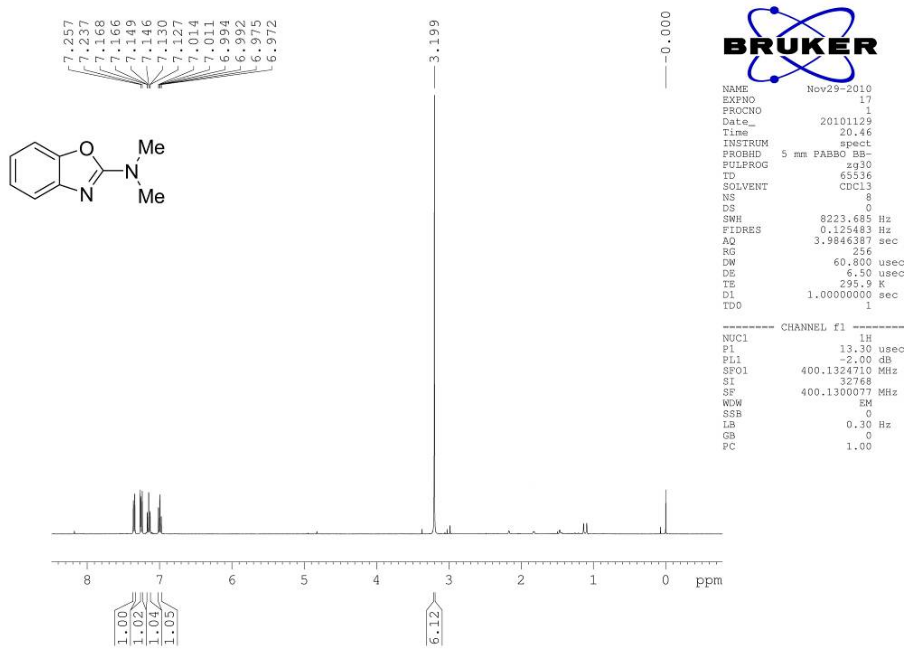
Thursday, November 19, 2009

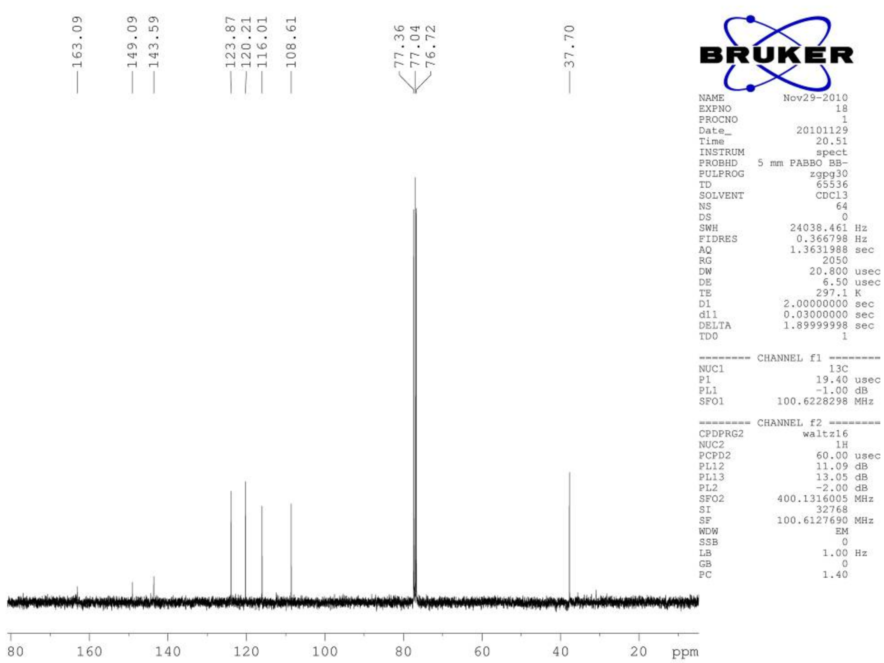
APPROVAL DATE

Accelerating Customers' Success through Leadership in ***Life Science, High Technology*** *and* ***Service***

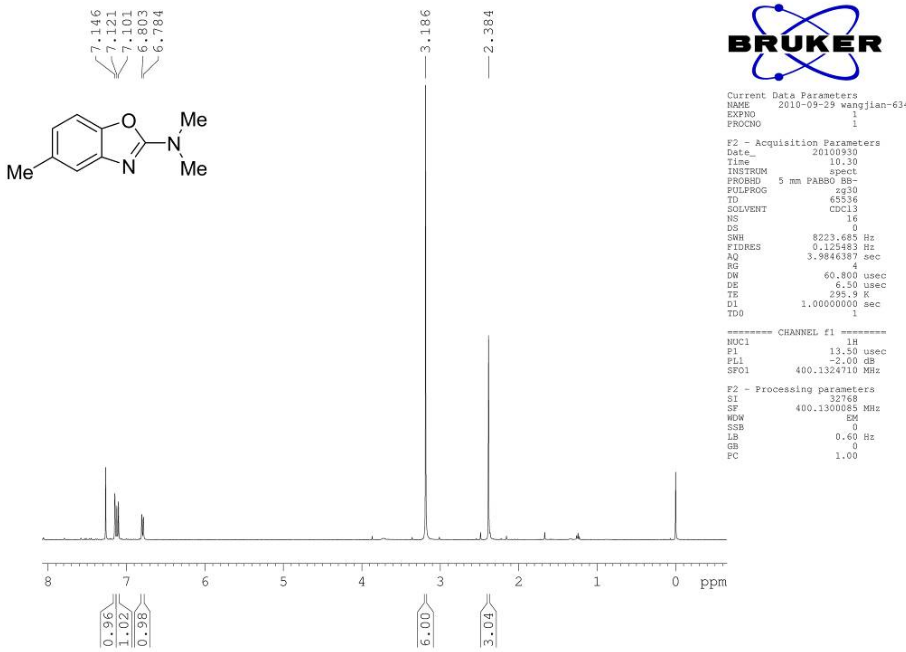
Copies of products' ^{1}H NMR and ^{13}C NMR spectra

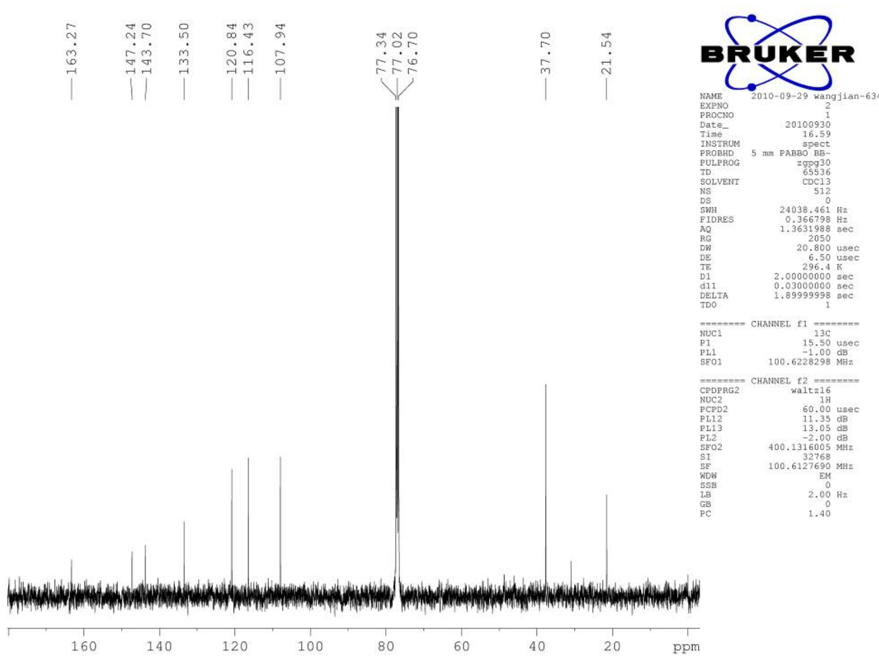
2-(*N*,*N*-Dimethylamino)benzoxazole (2a)



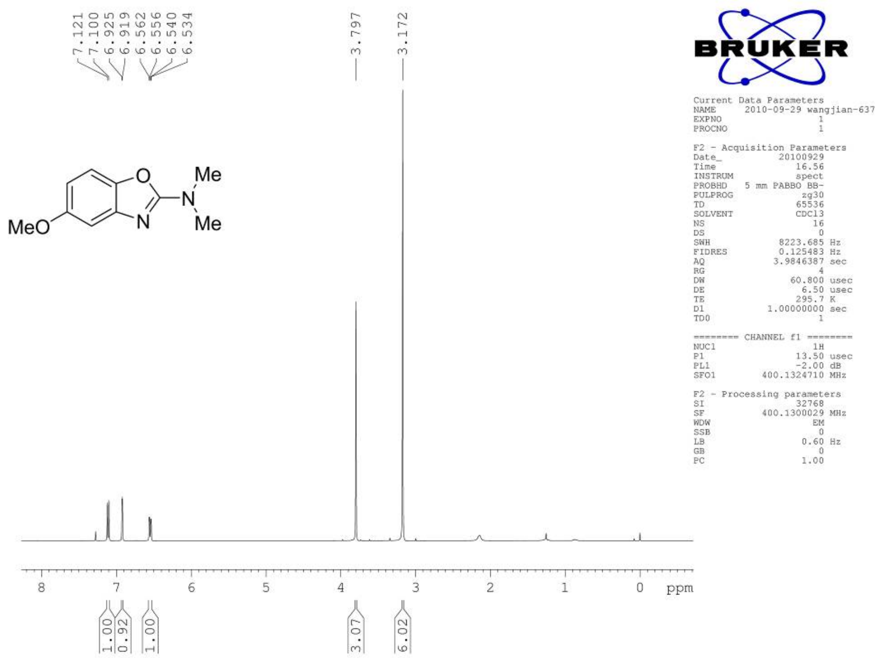


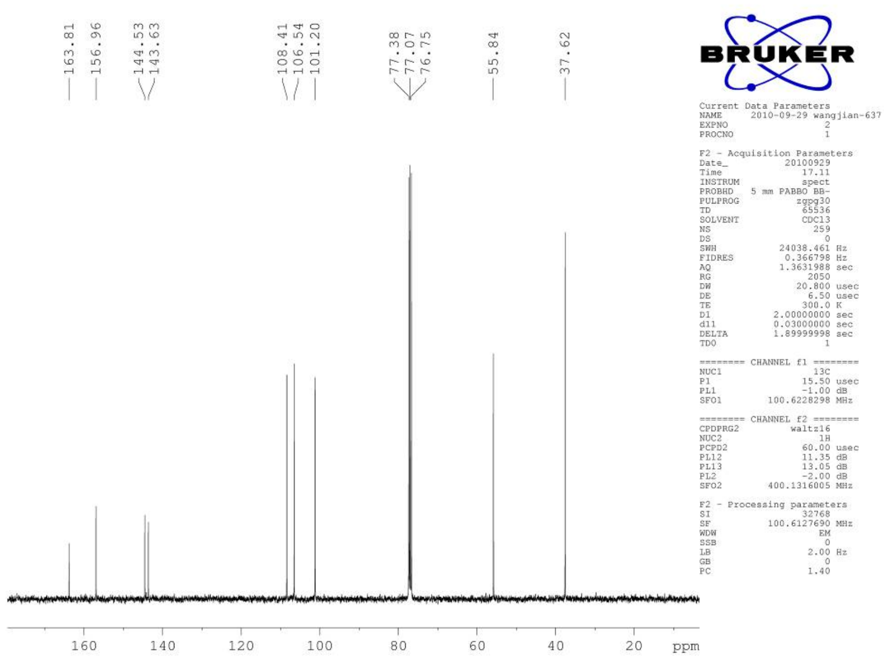
2-(*N*,*N*-Dimethylamino)-5-methylbenzoxazole (2b)



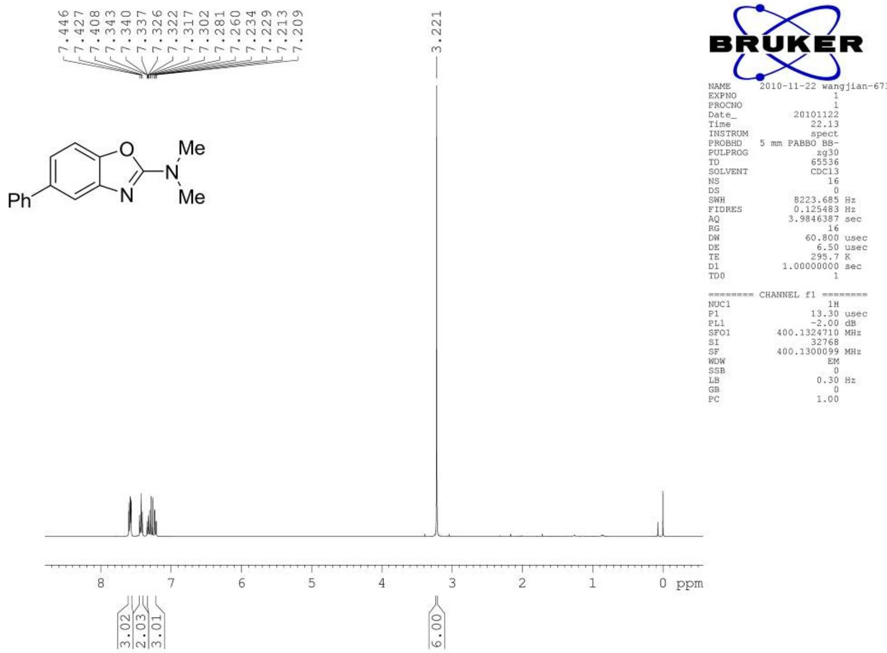


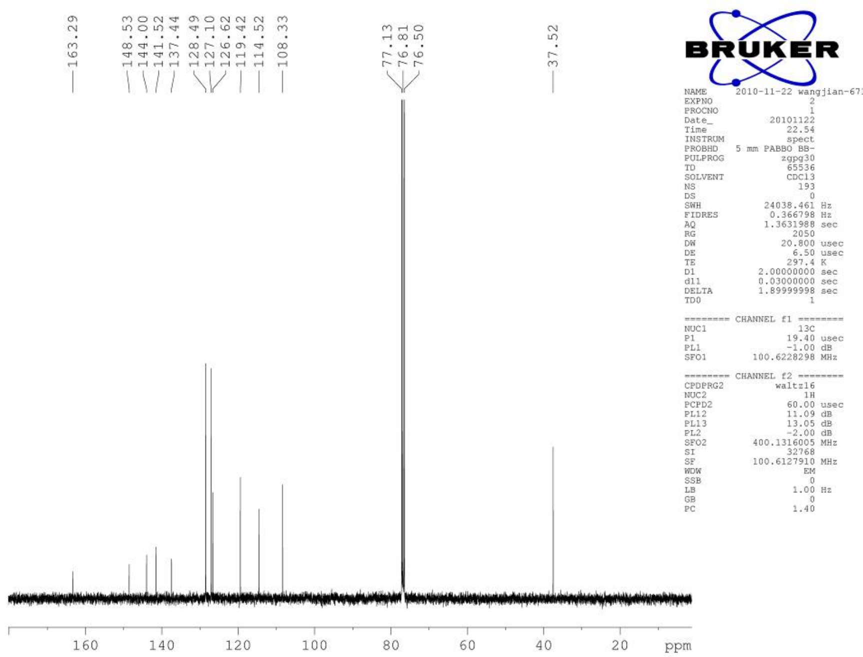
2-(*N*,*N*-Dimethylamnio)-5-methoxybenzoxazole (2c)



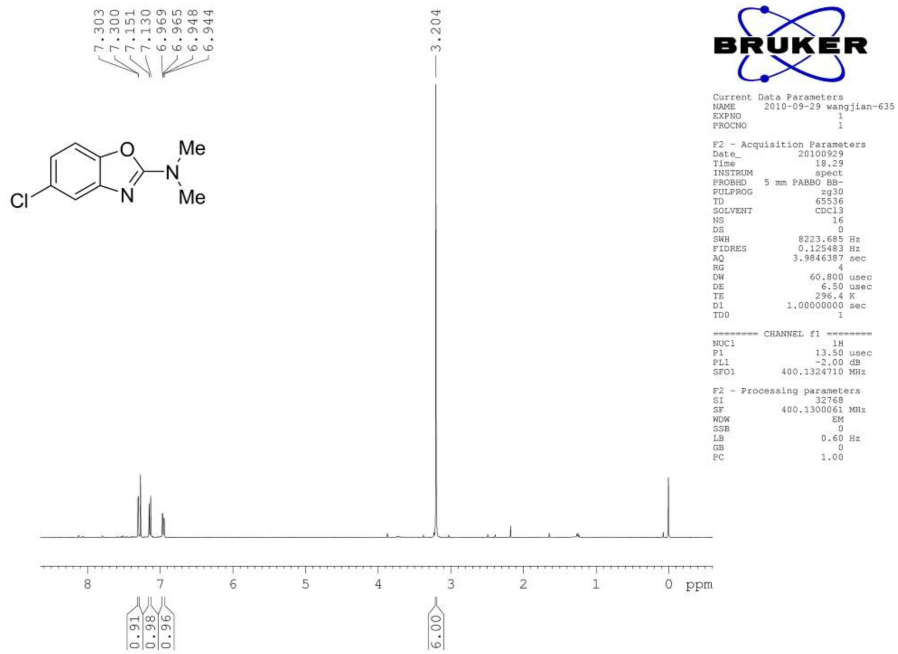


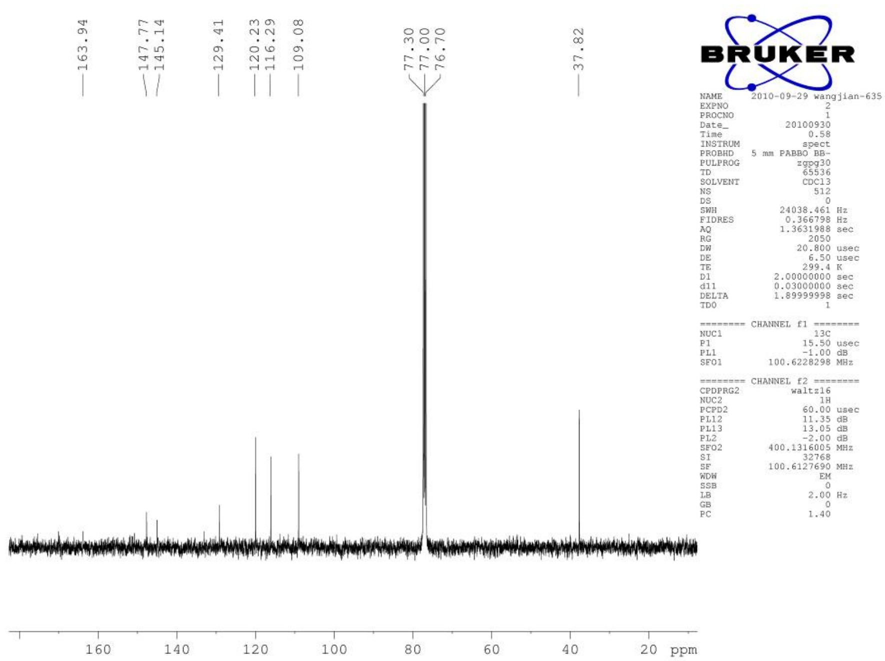
2-(*N*,*N*-Dimethylamino)-5-phenylbenzoxazole (2d)



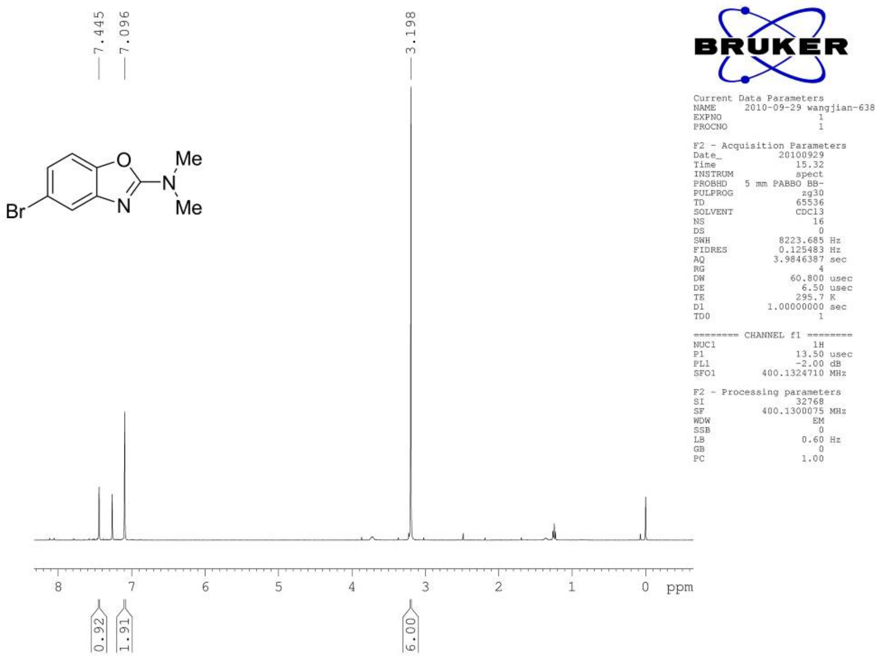


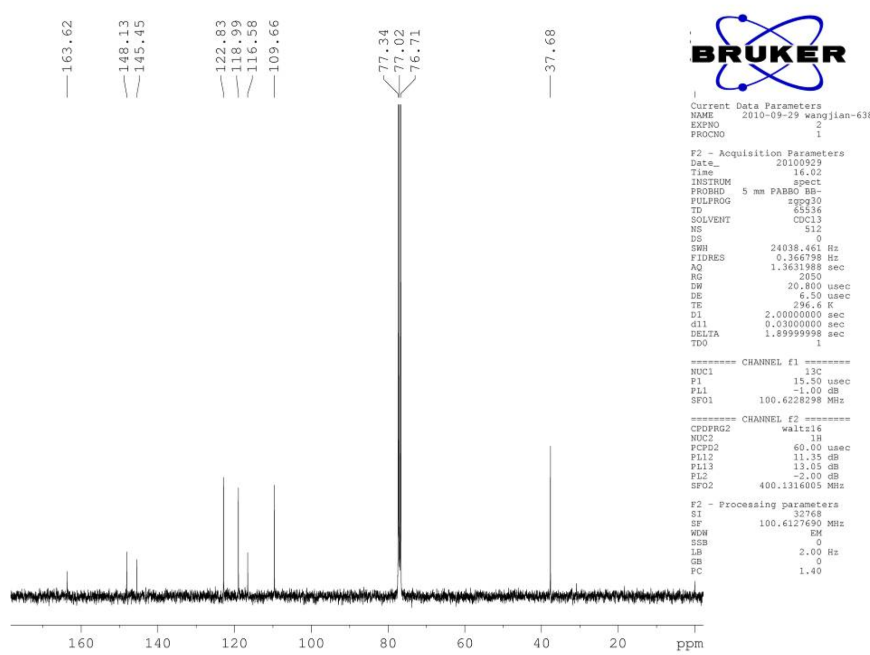
5-Chloro-2-(*N*,*N*-dimethylamino)benzoxazole (2e)



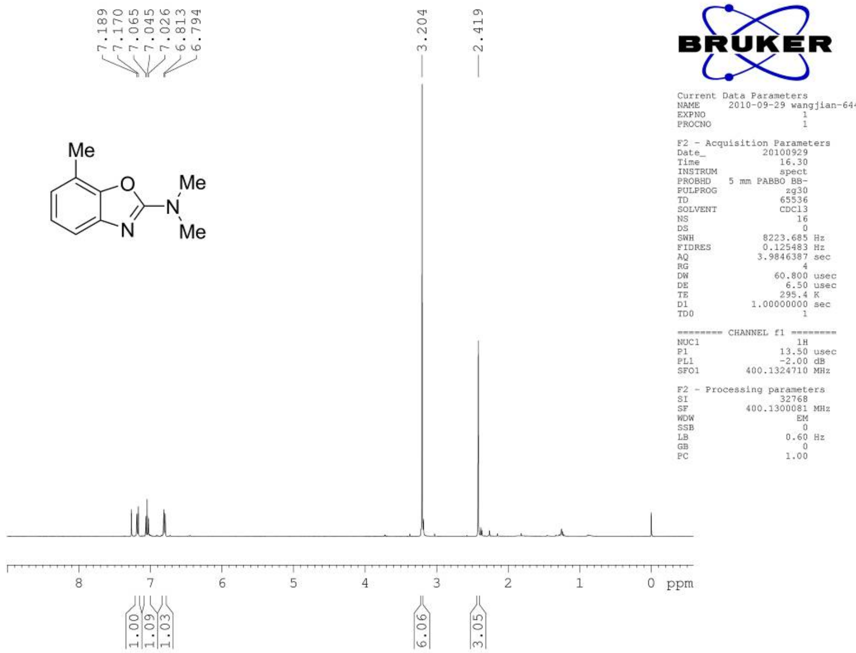


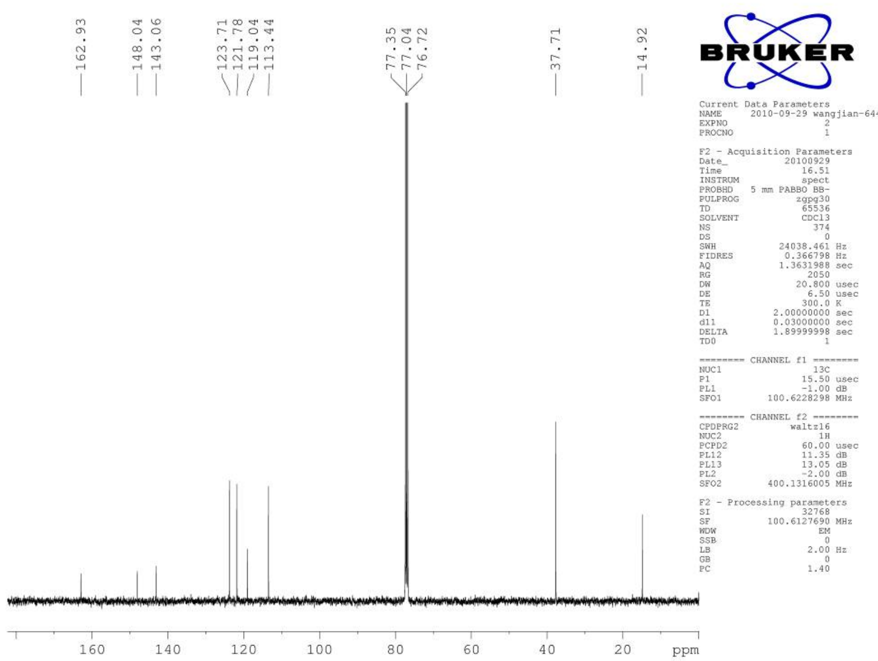
5-Bromo-2-(*N*,*N*-dimethylamino)benzoxazole (2f)



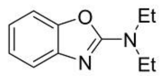


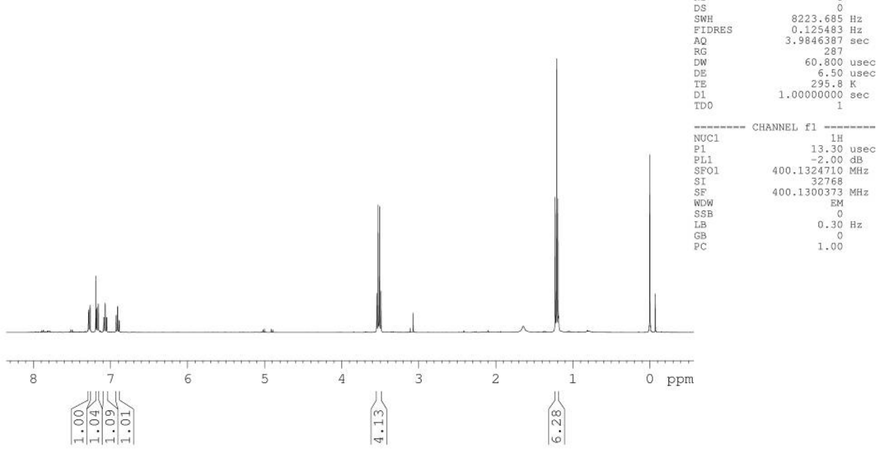
2-(*N,N*-Dimethylamino)-7-methylbenzoxazole (**2h**)

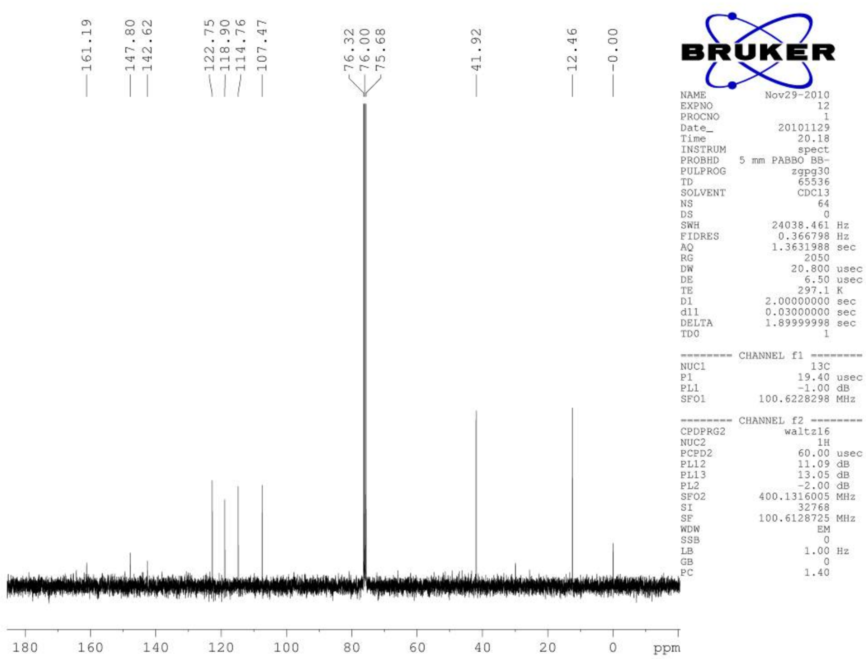




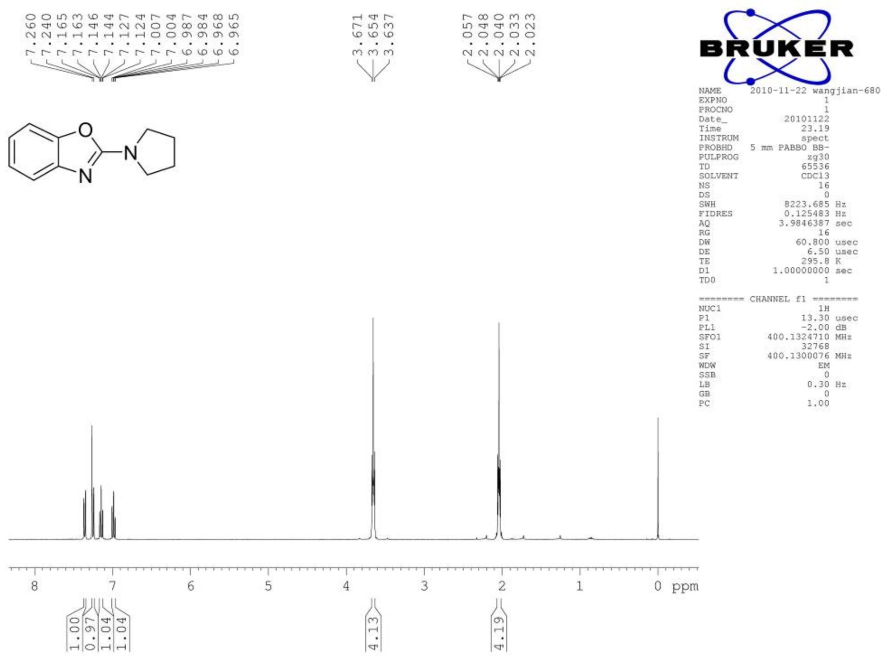
2-(*N*,*N*-Diethylamino)benzoxazole (5a)

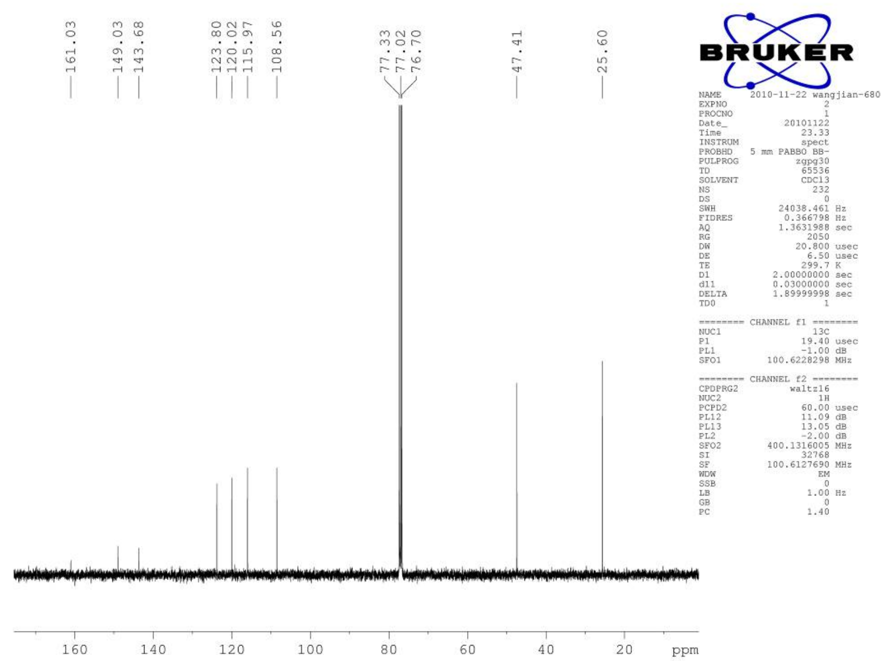




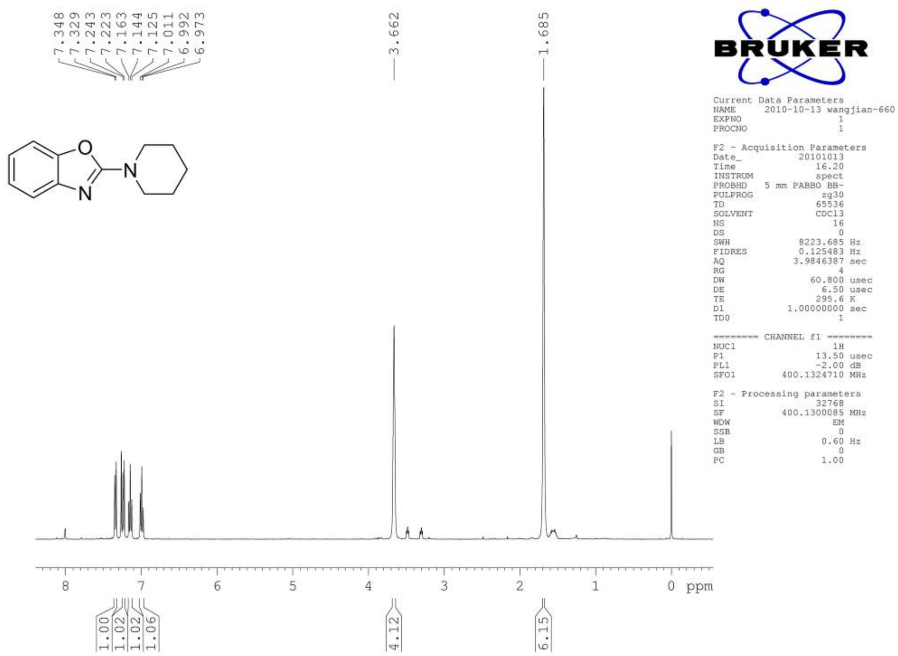


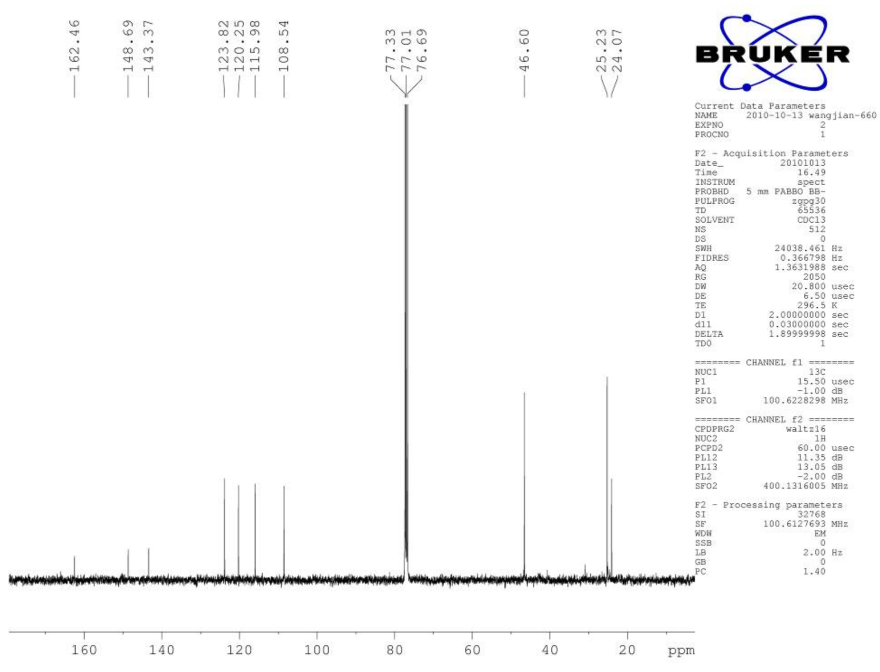
2-(1-Pyrrolidinyl)benzoxazole (5b)



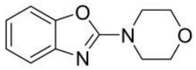


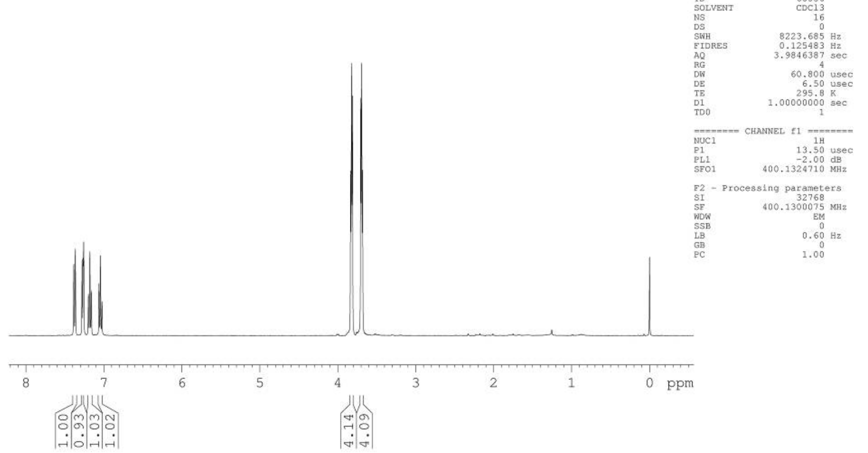
2-(1-Piperidinyl)benzoxazole (5c)

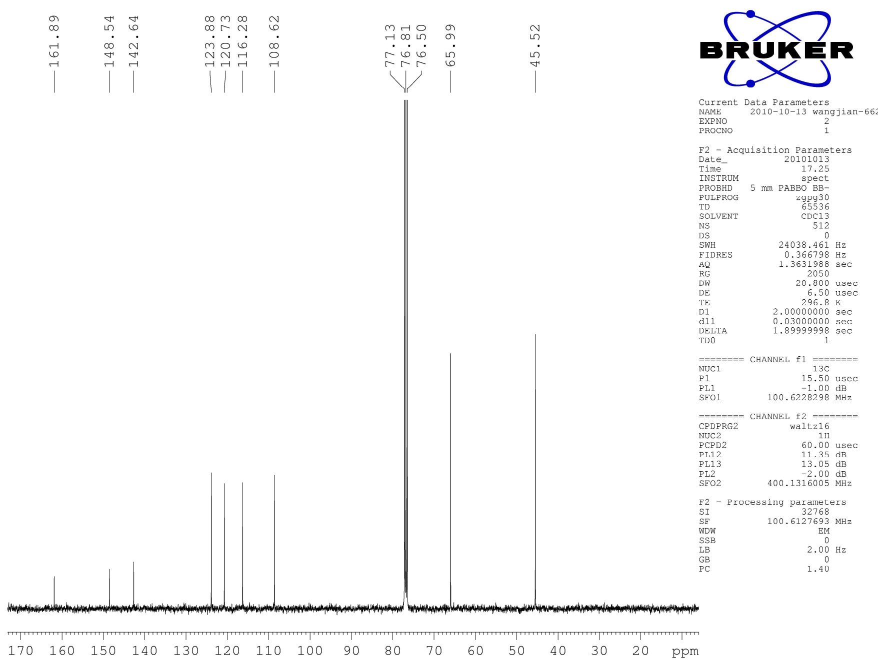




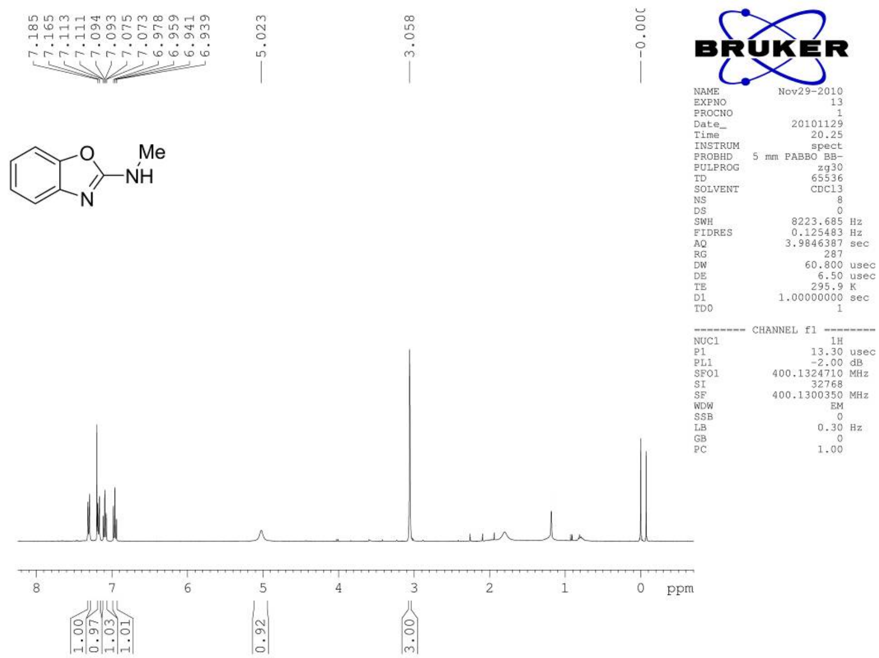
2-(4-Morpholinyl)benzoxazole (5d)

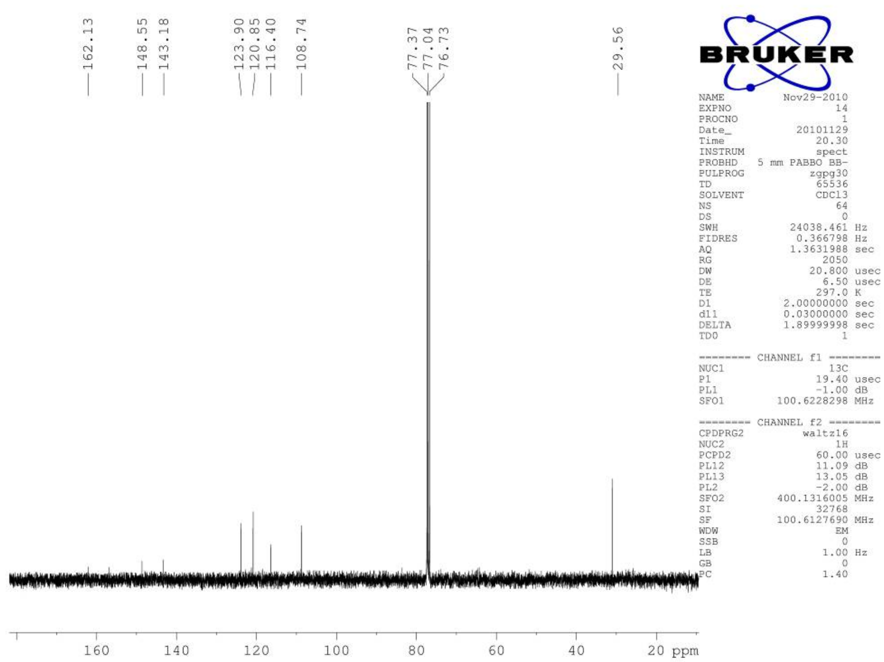




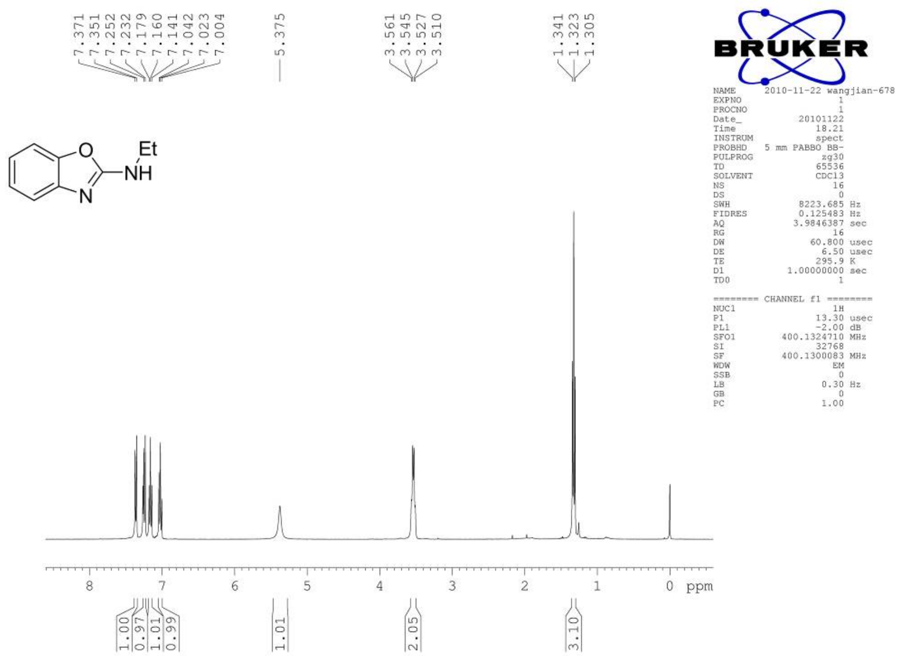


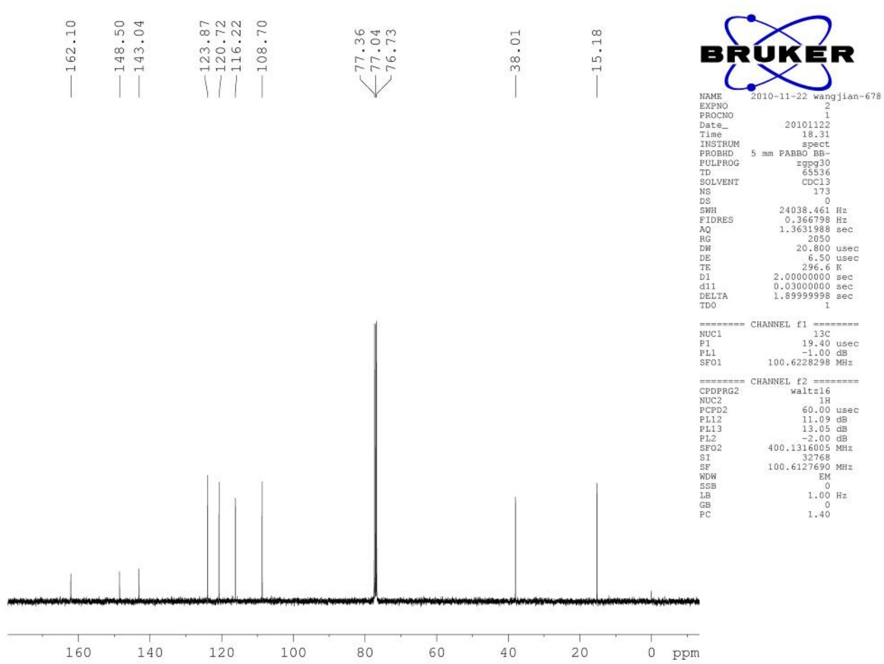
2-(*N*-Methylamino)benzoxazole (5e)



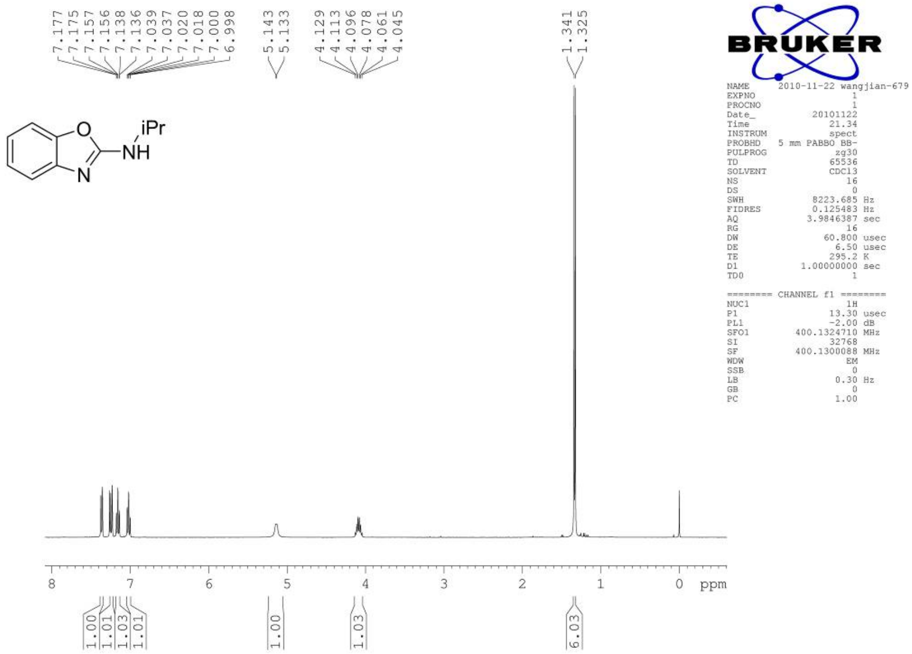


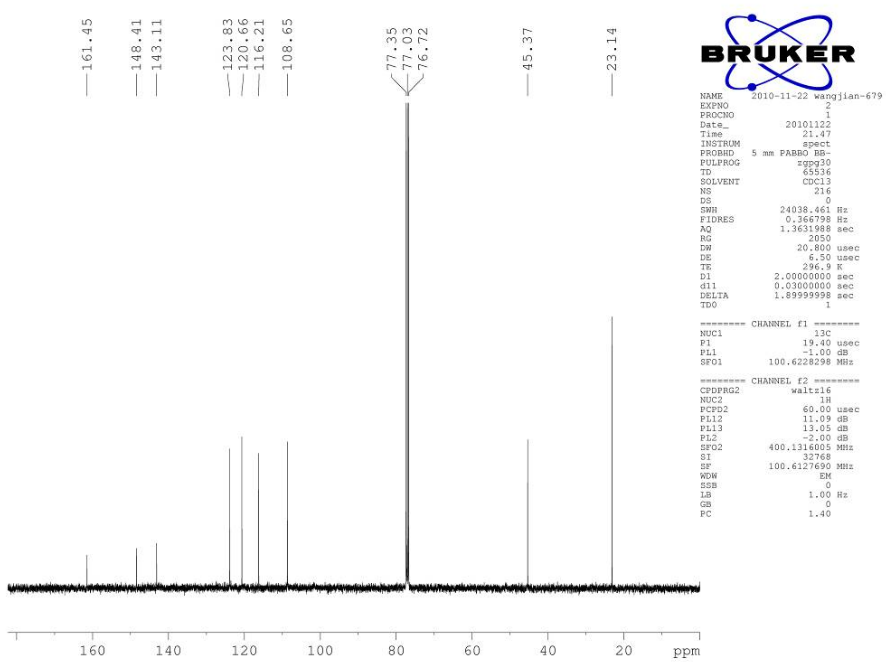
2-(*N*-Ethylamino)benzoxazole (5f)



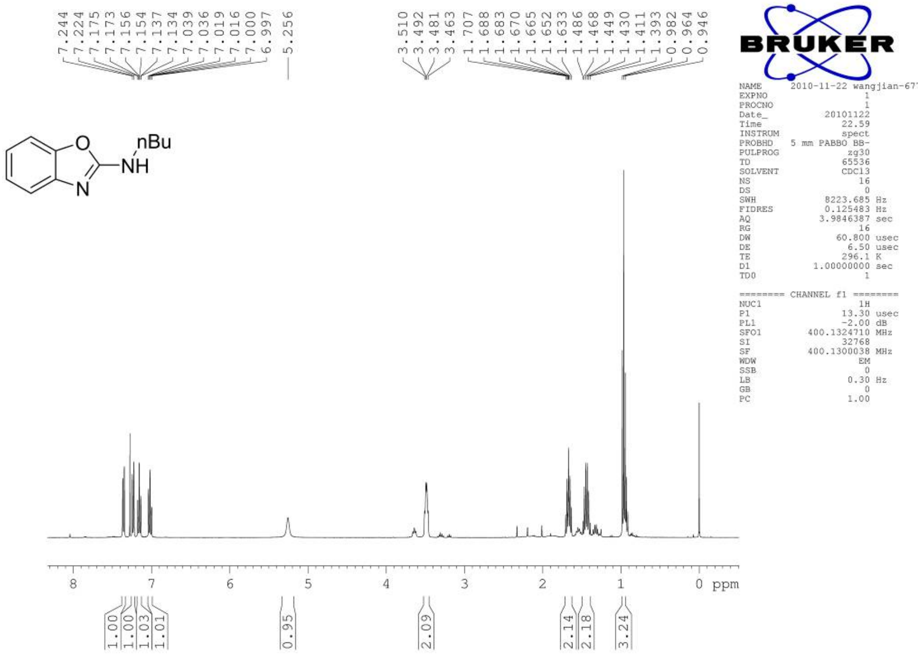


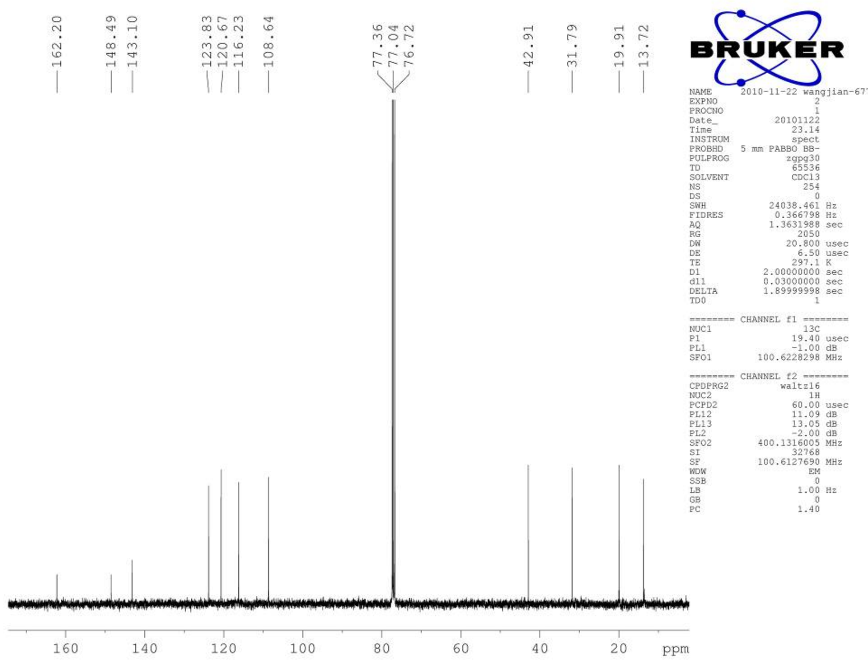
2-(*N*-Isopropylamino)benzoxazole (5g)



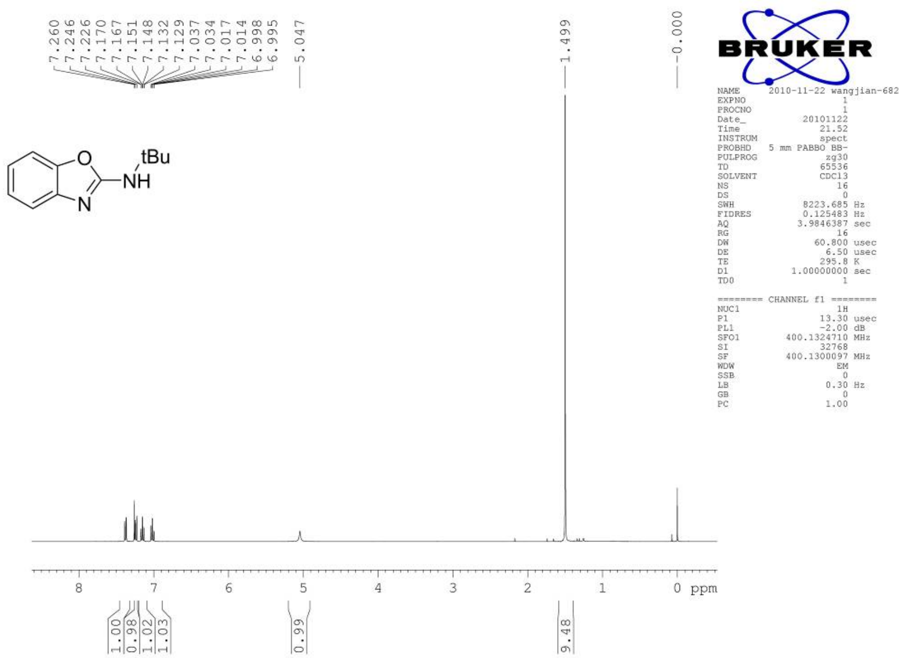


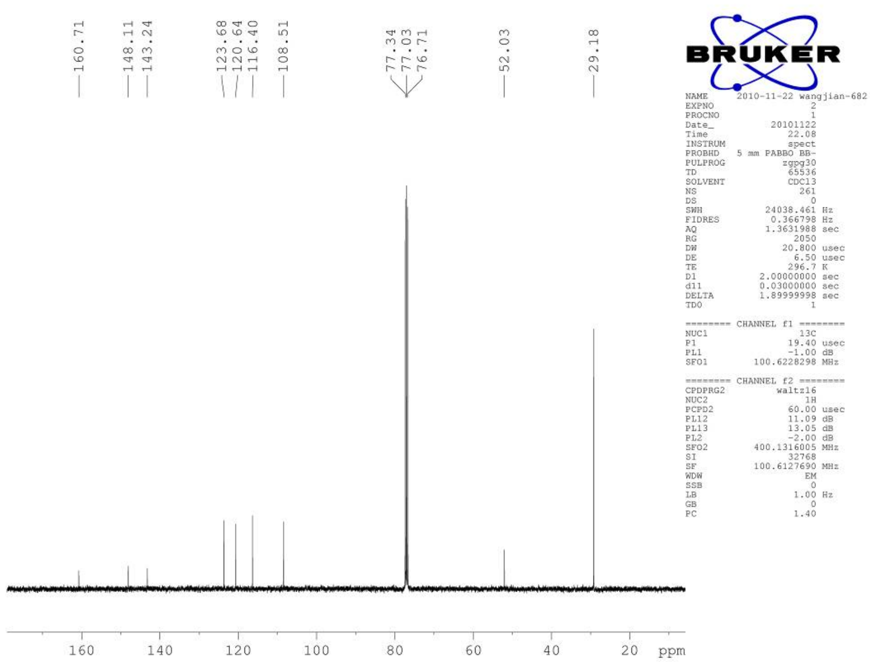
2-(*N*-n-Butylamino)benzoxazole (5h)



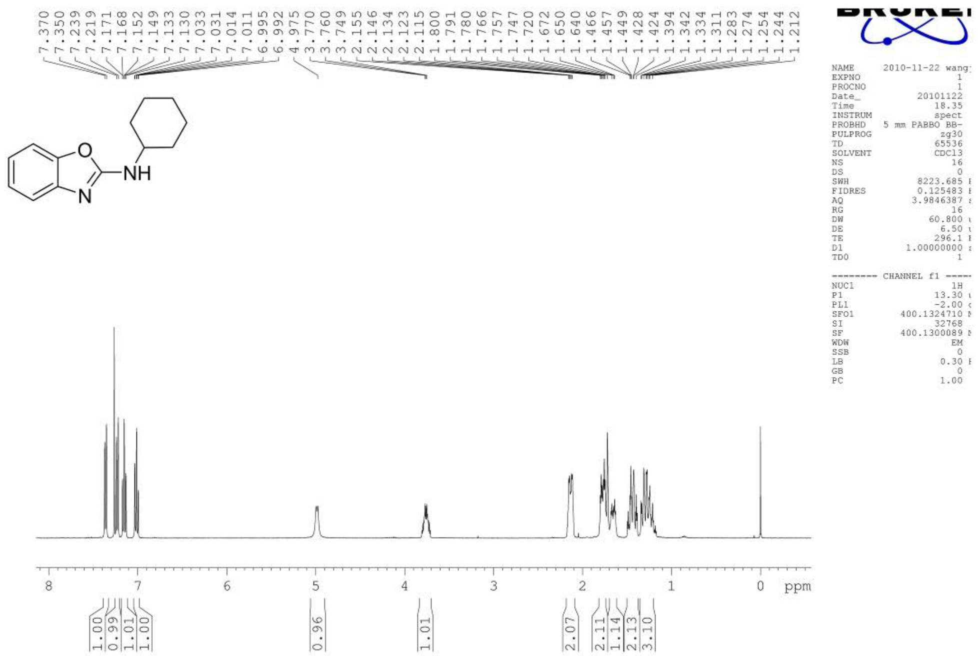


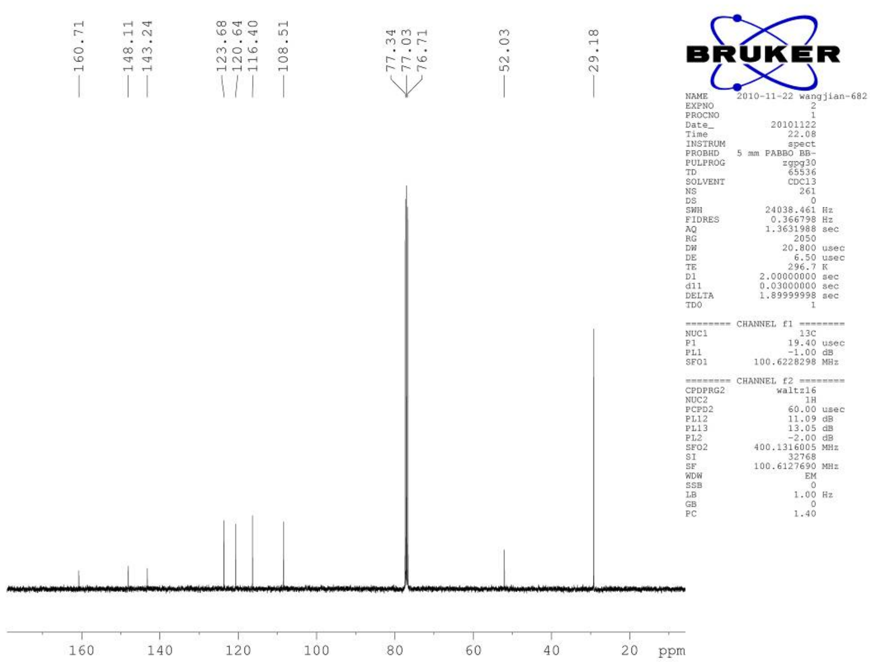
2-(*N-tert*-Butylamino)benzoxazole (5i)



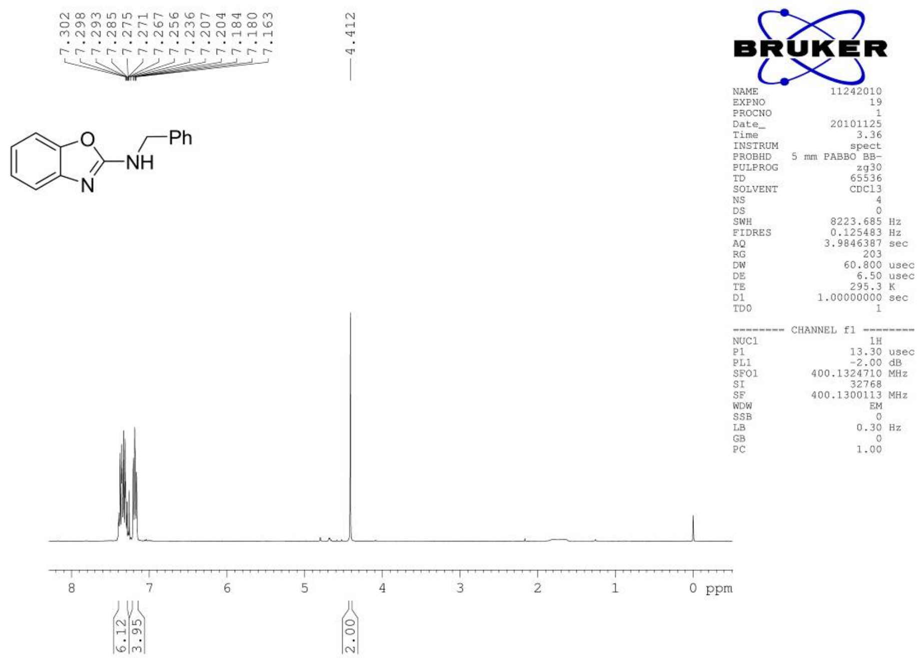


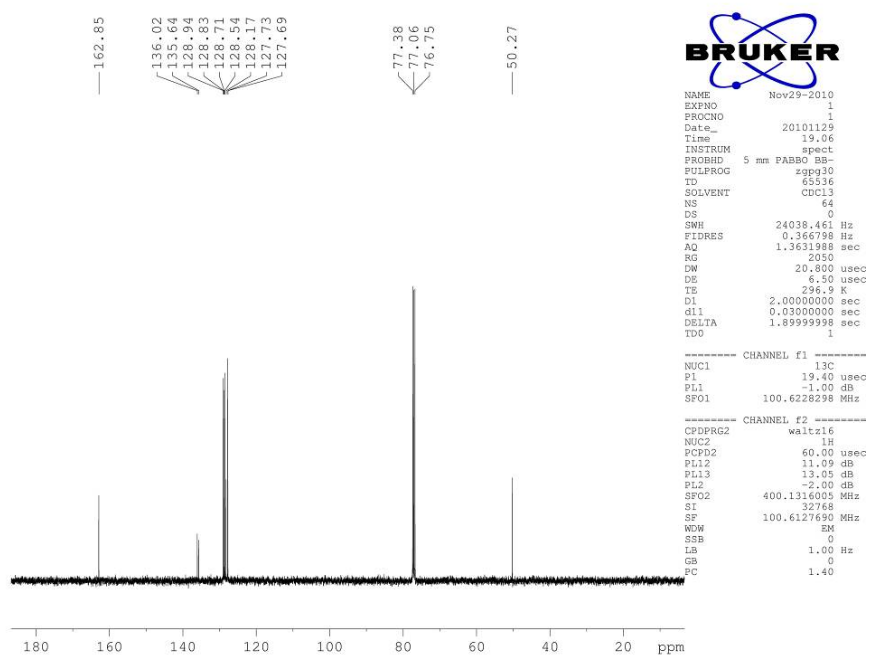
2-(*N*-Cyclohexylamino)benzoxazole (5j)



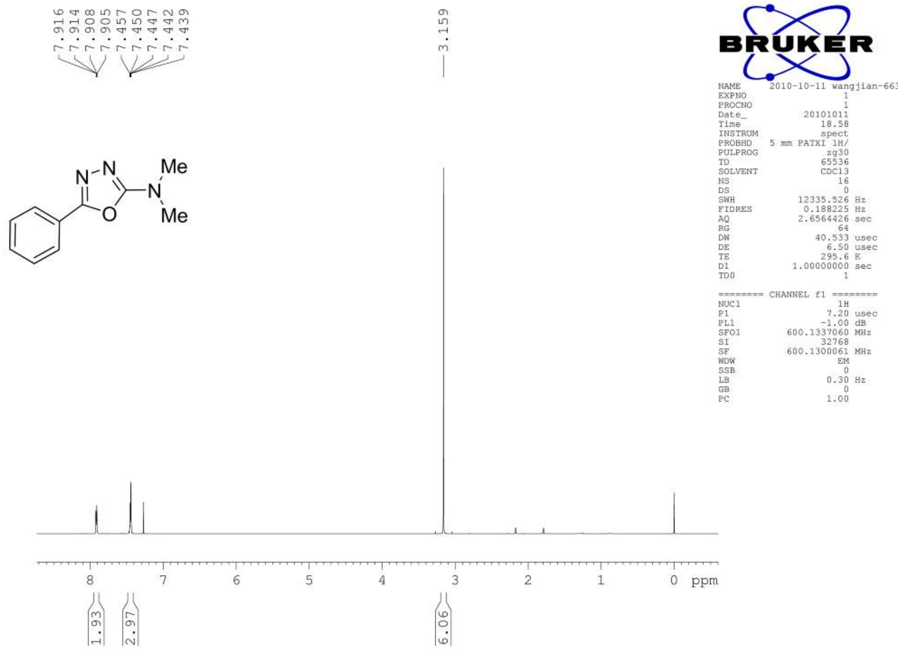


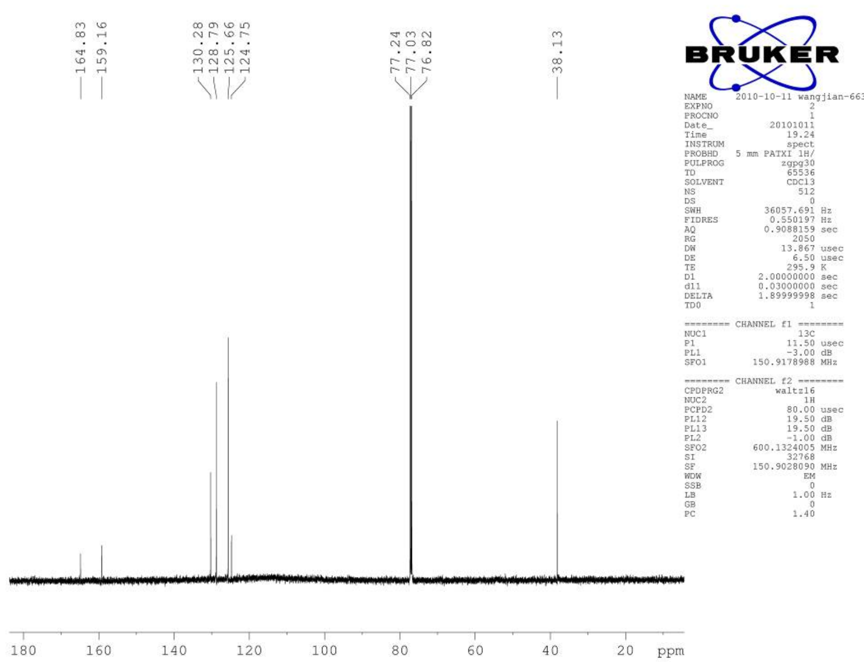
2-(*N*-Benzylamino)benzoxazole (5k)



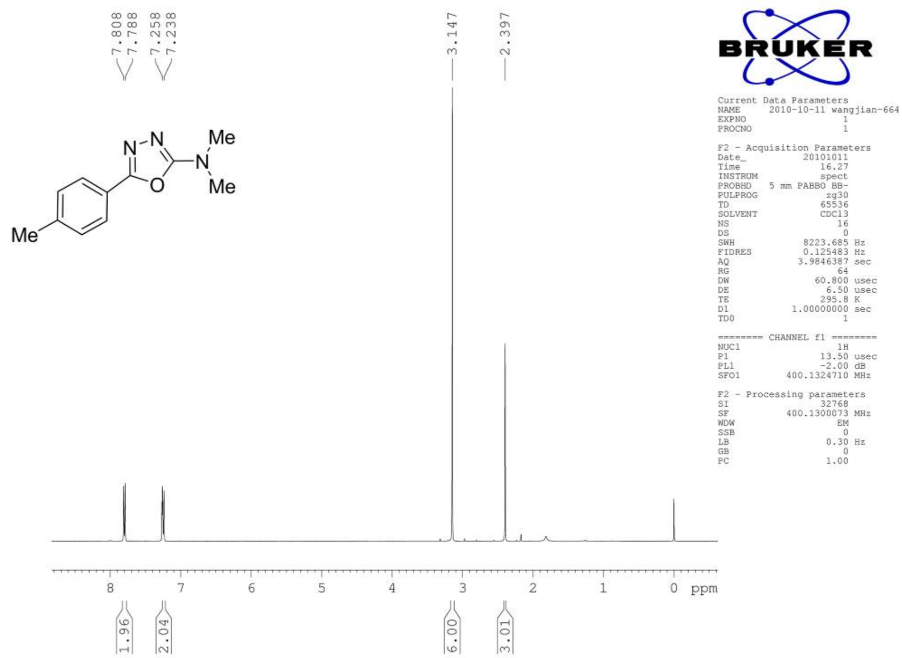


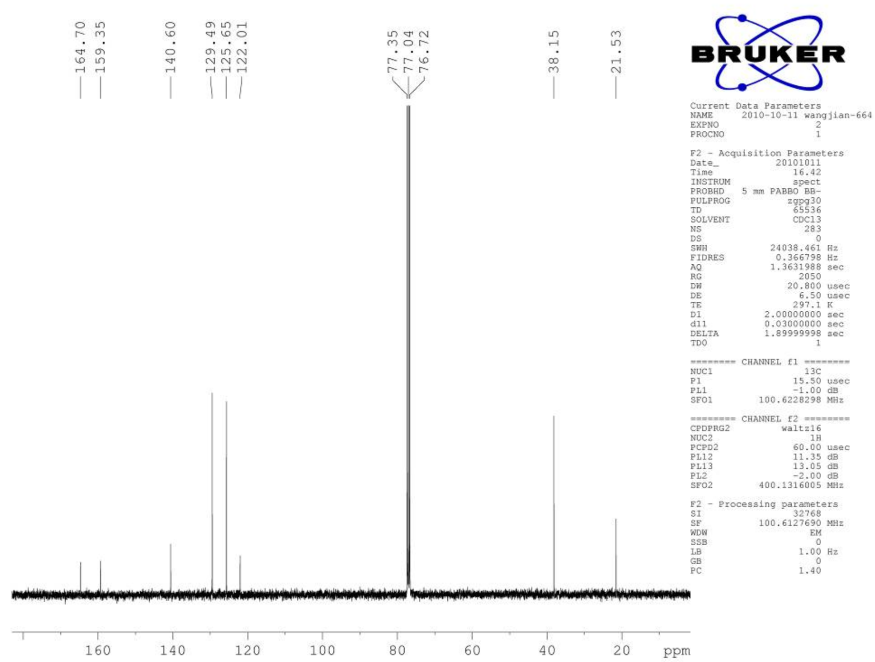
2-(*N*,*N*-Dimethylamino)-5-phenyl-1,3,4-oxadiazole (4a)



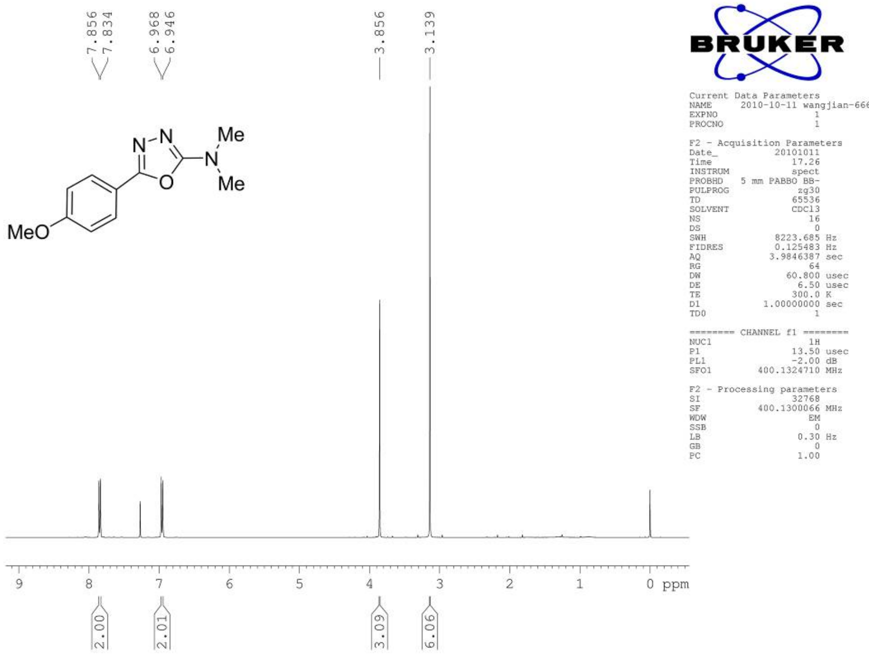


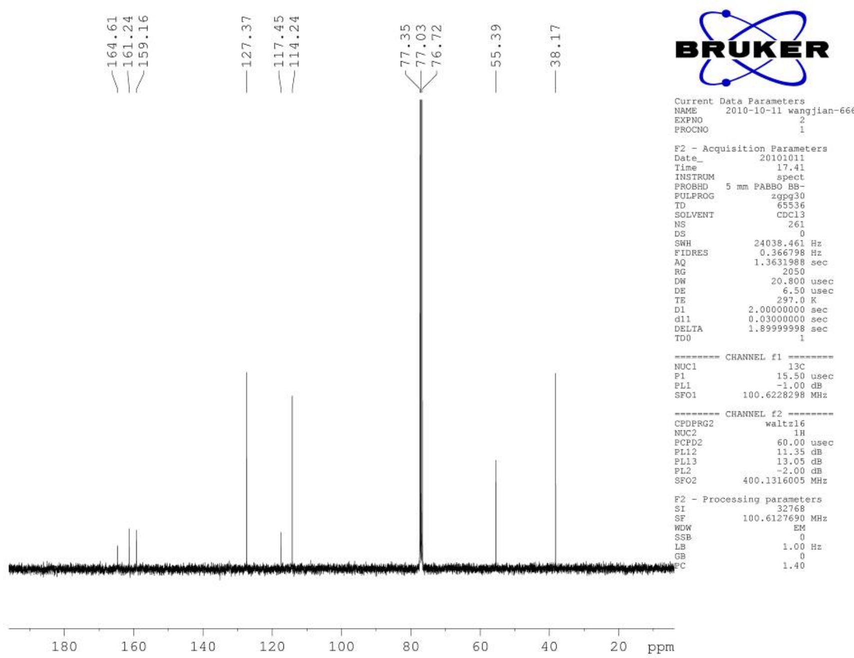
2-(*N*,*N*-Dimethylamino)-5-(4-methylphenyl)-1,3,4-oxadiazole (4b)



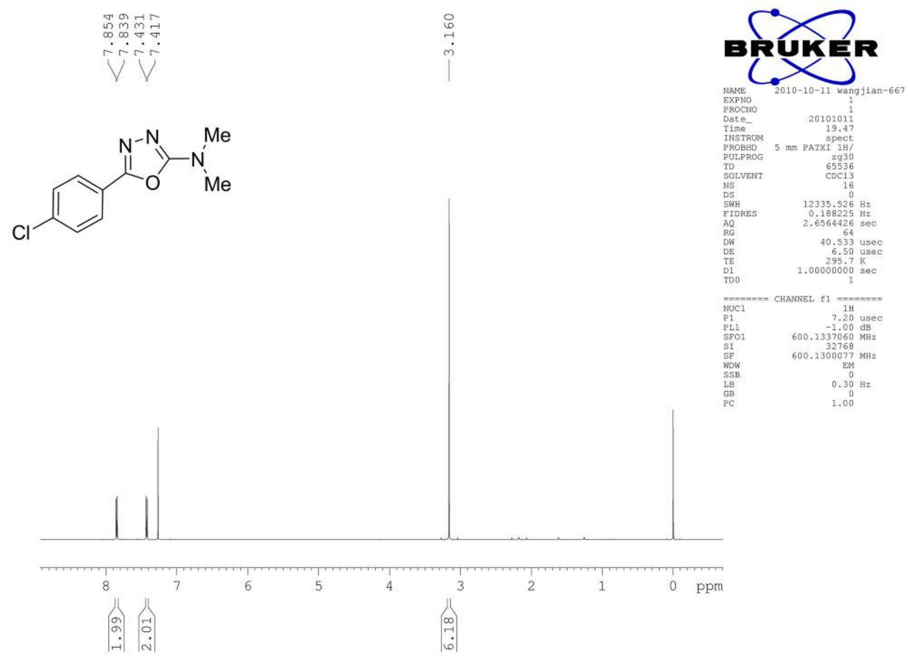


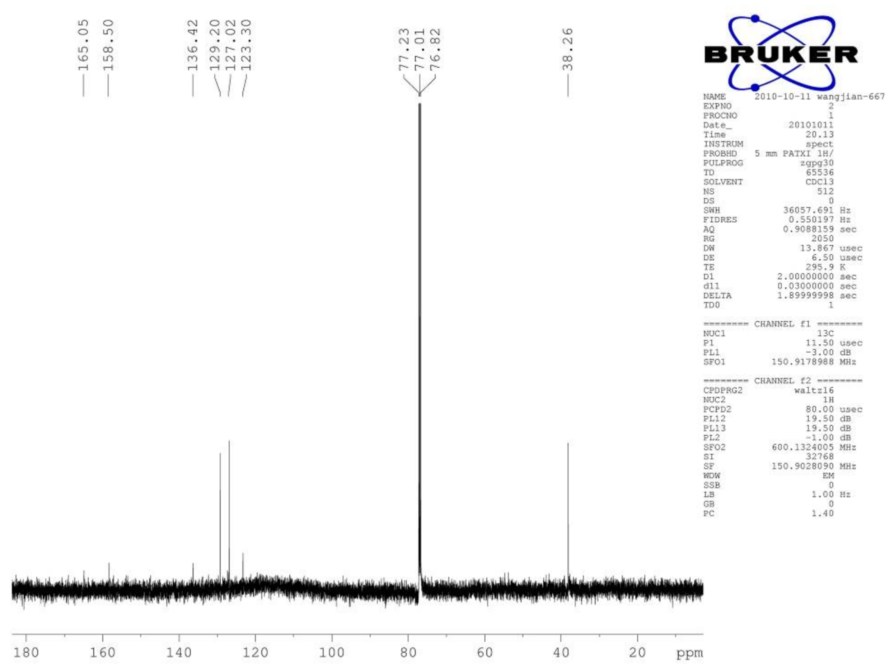
2-(*N*,*N*-Dimethylamino)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (4c)



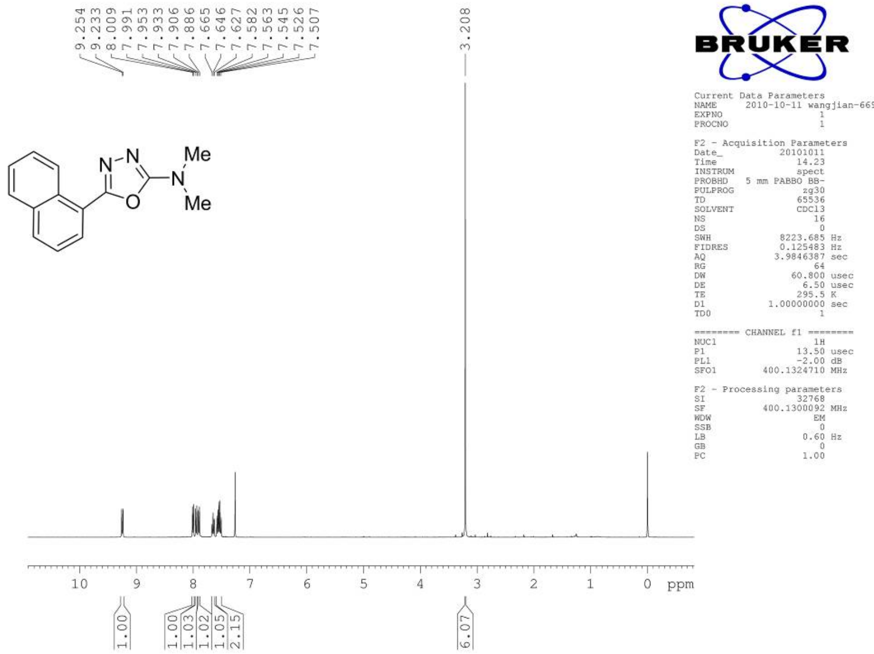


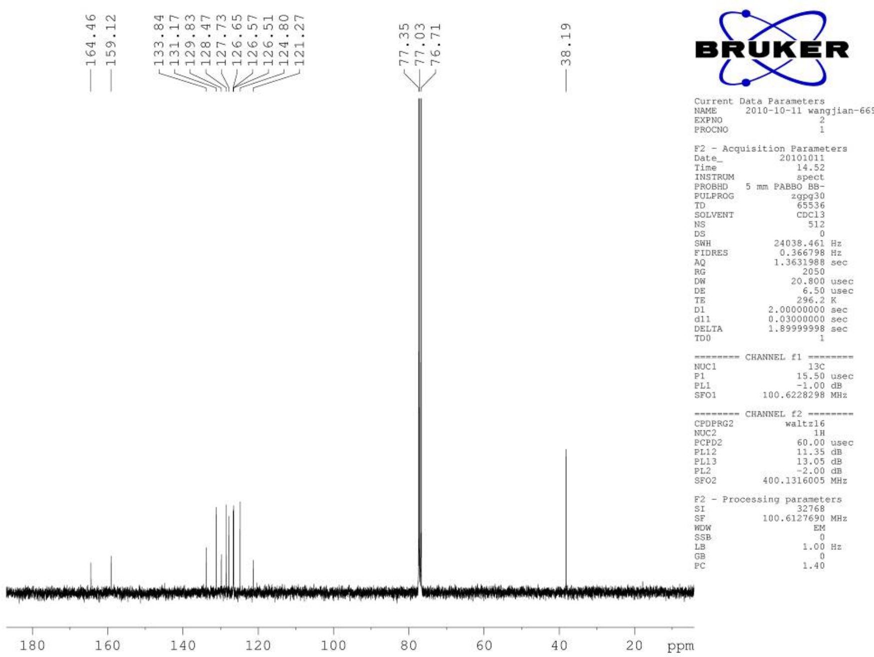
2-(*N*,*N*-Dimethylamino)-5-(4-chlorophenyl)-1,3,4-oxadiazole (4d)



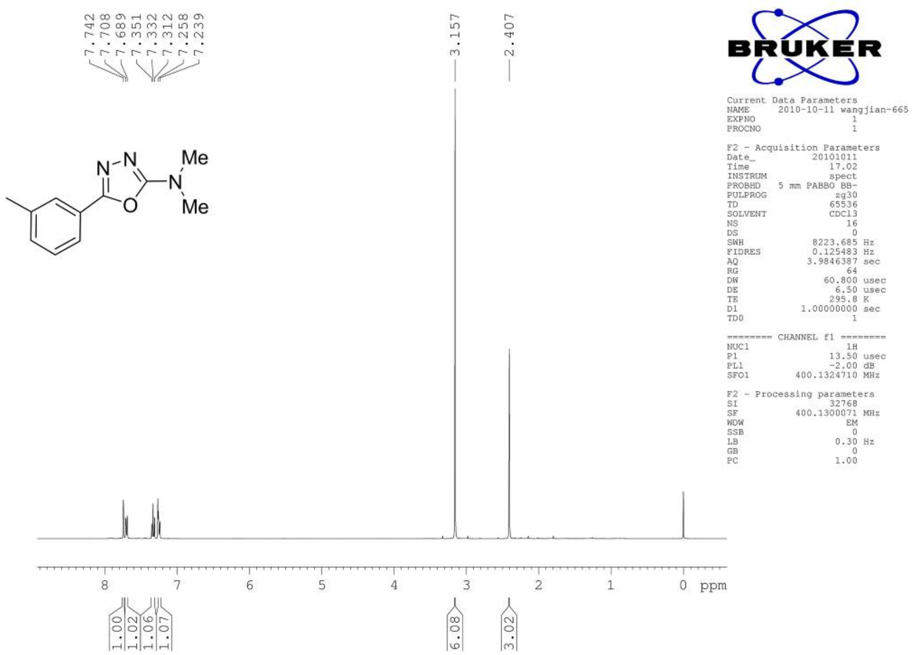


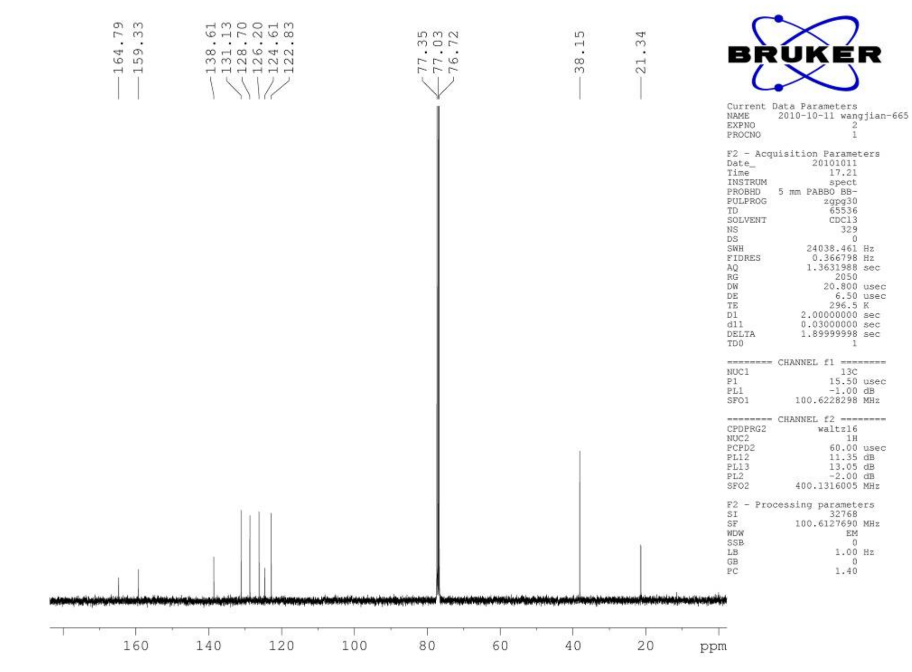
2-(*N*,*N*-Dimethylamino)-5-(1-naphthyl)-1,3,4-oxadiazole (4f)



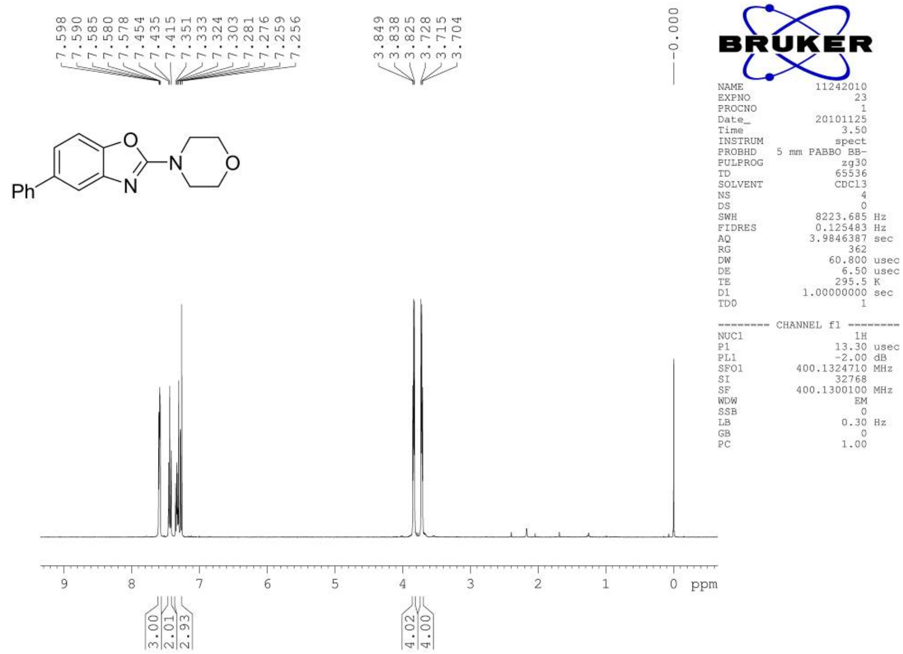


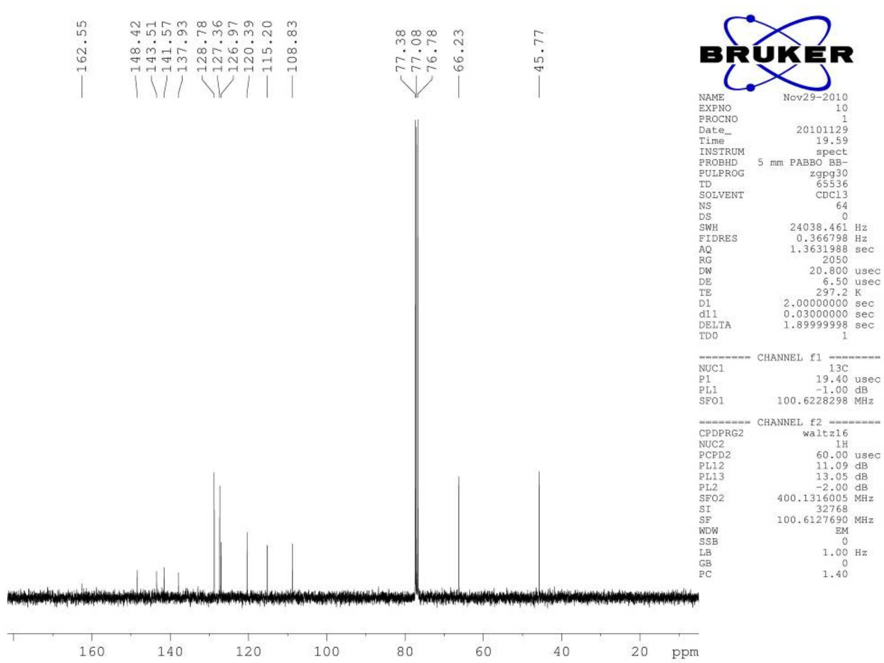
2-(*N*,*N*-Dimethylamino)-5-(3-methylphenyl)-1,3,4-oxadiazole (4h)





2-(4-Morpholinyl)-5-phenylbenzoxazole (6)





2-(*N*-Benzyl-*N*-methylamino)benzoxazole (5l)