Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting information

Calcium-mediated *one-pot* preparation of isoxazoles with deuterium incorporation

Maria S. Ledovskaya,[a] Konstantin S. Rodygin,[a] and Valentine P. Ananikov[a,b,*]

[a] Institute of Chemistry, Saint Petersburg State University, Universitetsky prospect 26, Peterhof, 198504, Russia

[b] N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences, Leninsky prospect 47, Moscow,119991, Russia

* e-mail: val@ioc.ac.ru

Contents

S1. Materials and methods

S1.1 General

Reagents were obtained from commercial sources and checked by NMR and GC before use. NMR spectra were recorded on a Bruker Avance III spectrometer (^{1}H 400 MHz; ^{13}C 101 MHz, ^{19}F 376 MHz). Chemical shifts δ are reported in ppm relative to residual $CHCl_3$ (^{1}H, δ = 7.28) and $CDCl_3$ (^{13}C, δ = 77.0) as internal standards. Signals in the ^{13}C NMR-spectra were assigned using DEPT method. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF spectrometer using electrospray ionization (ESI). X-ray diffraction data were registered using a Bruker APEX-II CCD diffractometer with Mo-K X-ray radiation. Reactions were monitored by TLC analysis using Merck UV-254 plates. Preparative thin layer chromatography (PTLC) was performed on Macherey-Nagel silica gel P/UV_{254} with gypsum and eluted with hexane–ethyl acetate. Preparative column chromatography was performed on Merck silica gel 60 (230-400 Mesh) that was previously treated with triethylamine.

S1.2 Optimization of the 4,5-dideuteroisoxazoles synthesis

To optimize the reaction conditions, we chose 2,6-dichlorobenzaldoxime **1u** as a model substrate. First, the established conditions were used, but D_2O was utilized instead of H_2O. By this method, the isoxazole product was isolated in 90% yield, but 80% **5u** and 18% mono-deuterated products were found in the isolated substance (Entry 1, Table 3 in the article). To achieve better deuteration, we investigated the influence of the D_2O quantity (Entries 2-4, Table 3). The result was slightly improved – 86% **5u** was observed in the isolated product. Furthermore, we proposed that the succinimide formed during the *in situ* chlorination of benzaldoxime could influence the quality of the resulting substance. Therefore, the starting aldoxime and *N*-chlorosuccinimide were dissolved in CCl_4. After chloroaldoxime formed (controlled by TLC), the succinimide residue was separated, and calcium carbide (2.0 mmol) and 8.0 mmol of D_2O were added to the resulting solution. However, the quality of the resulting product decreased – the NMR spectrum showed 75% **5u** and 22% mono-deuterated isoxazoles (Entry 5, Table 3).

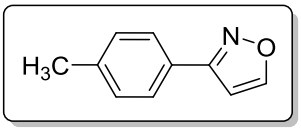
Furthermore, we proposed that a source of protium is in the materials we used. After investigating this assumption, we found two problems. First, the aldoximes we used were crystallized from water or a water-ethanol mixture. Water impurities were detected in the NMR-spectra of aldoximes. Second, to reach a maximal deuterium incorporating the *O*-deuterated oxime was required. To remove residual water and get the *O*-deuterated oxime, the starting oxime **1u** was treated with deuterium oxide before the reaction (Entry 6, Table 3), but the result

was the same as that using the untreated oxime (Entry 3, Table 3). Most likely, this was due to the low solubility of the aldoxime in water (*O*-deuteration was not achieved). Furthermore, we treated the starting oxime by another method: **1u** was dissolved in a small quantity of deuterochloroform, then deuterium oxide was added, and the resulting two-phase solution was stirred for 5 days. The reaction was performed in a sealed tube to preserve the mixture from H_2O. Finally, the desired *O*-deuterated oxime was obtained. The latter was immediately isolated and used in the next step. Using this two-step sequence, 89% **5u** (Entry 7, Table 3) was achieved in the isolated product. We proposed that calcium carbide could also be a source of protium. Next, we decreased the quantity of CaC_2 used, and the **5u** content was slightly improved (Entry 8, 92%). Furthermore, the quantities of the aldoxime and NCS were decreased (Entry 9), resulting in better results – the isotope purity was 96%. So, the overall deuterium incorporation into the product was 98 %.

Using these optimized conditions, the deuteration process was studied for different products (see Table 4). In most cases, ≥97% deuterium incorporation was observed. Synthesized 4,5-dideuteroisoxazoles **5** were stable compounds and were easily isolated by standard procedures. Eight randomly chosen 4,5-dideuteroisoxazoles **5** (Table 4, Entries 2, 3, 6, 7, 9, 10, 12, 13) were treated by preparative TLC to demonstrate their stability on silica. Deuterium enrichment in all studied cases was confirmed by NMR.

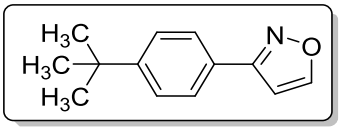
S2. Experimental details and spectral data for 4

3-(*p*-tolyl)isoxazole 4a[1]



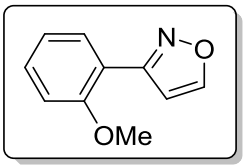
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colorless crystals (48 mg, 81 %); M.p. 53-55 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.7 Hz, $1H_{isox}$), 7.75 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 6.66 (d, J = 1.7 Hz, $1H_{isox}$), 2.43 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5 (C), 158.7 (CH), 140.2 (C), 129.6 (2CH), 126.8 (2CH), 126.0 (C), 102.4 (CH), 21.4 (CH_3); **HRMS** (ESI) Calcd. for $C_{10}H_{10}NO^+$ $[M+H]^+$ 160.0757, found 160.0758.

3-(4-*tert*-butylphenyl)isoxazole 4b



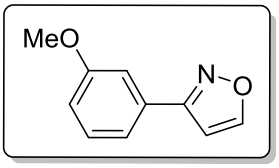
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a yellowish viscous oil (59 mg, 95 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.7 Hz, $1H_{isox}$), 7.80 (d, 2H, J = 8.6 Hz), 7.52 (d, 2H, J = 8.6 Hz), 6.67 (d, J = 1.7 Hz, $1H_{isox}$), 1.39 (s, 9H, *t*-Bu); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4 (C), 158.7 (CH_{isox}), 153.4 (C), 126.7 (2CH), 126.0 (C), 125.9 (2CH), 102.4 (CH_{isox}), 34.8 (C_{tBu}), 31.2 ($3CH_3$); **HRMS** (ESI) Calcd. for $C_{13}H_{16}NO^+$ $[M+H]^+$ 202.1226, found 202.1225.

3-(2-methoxyphenyl)isoxazole 4c[2]



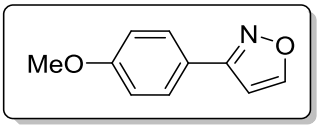
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil (53 mg, 88 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.6 Hz, $1H_{isox}$), 7.93 (dd, J = 7.7, 1.7 Hz, 1H), 7.47-7.43 (m, 1H), 7.09-7.03 (m, 2H), 6.88 (d, J = 1.6 Hz, $1H_{isox}$), 3.93 (s, 3H, OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2 (C), 157.7 (CH), 157.3 (C), 131.2 (CH), 129.7 (CH), 121.0 (CH), 117.8 (C), 111.5 (CH), 105.8 (CH), 55.6 (OMe); **HRMS** (ESI) Calcd. for $C_{10}H_{10}NO_2^+$ $[M+H]^+$ 176.0706, found 176.0701.

3-(3-methoxyphenyl)isoxazole 4d[3]



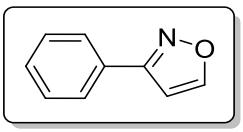
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil (35 mg, 59 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, J = 1.7 Hz, $1H_{isox}$), 7.44-7.39 (m, 3H, 3CH), 7.05-7.00 (m, 1H), 6.67 (d, J = 1.7 Hz, $1H_{isox}$), 3.90 (s, 3H, OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5 (C), 160.0 (C), 158.9 (CH), 130.1 (C), 130.0 (CH), 119.4 (CH), 116.2 (CH), 111.9 (CH), 102.6 (CH), 55.4 (OMe); **HRMS** (ESI) Calcd. for $C_{10}H_{10}NO_2^+$ $[M+H]^+$ 176.0706, found 176.0708.

3-(4-methoxyphenyl)isoxazole 4e[1]



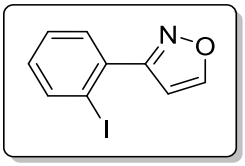
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (53.5 mg, 90 %); M.p. 34-36 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (d, J = 1.6 Hz, $1H_{isox}$), 7.79 (d, 2H, J = 8.8 Hz), 7.00 (d, 2H, J = 8.8 Hz), 6.62 (d, J = 1.6 Hz, $1H_{isox}$), 3.88 (s, 3H, OMe); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.12 (C), 161.05 (C), 158.6 (CH_{isox}), 128.3 (2CH), 121.4 (C), 114.4 (2CH), 102.2 (CH_{isox}), 55.4 (OMe); **HRMS** (ESI) Calcd. for $C_{10}H_{10}NO_2^+$ $[M+H]^+$ 176.0706, found 176.0708.

3-phenylisoxazole 4f[1]



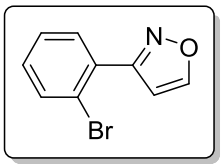
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil (51 mg, 77 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, J = 1.7 Hz, $1H_{isox}$), 7.87-7.84 (m, 2H), 7.52-7.47 (m, 3H), 6.69 (d, J = 1.7 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5 (C), 158.9 (CH), 130.0 (CH), 129.0 (2CH), 128.8 (C), 126.9 (2CH), 102.5 (CH); **HRMS** (ESI) Calcd. for $C_9H_8NO^+$ $[M+H]^+$ 146.0600, found 146.0602.

3-(2-iodophenyl)isoxazole 4g



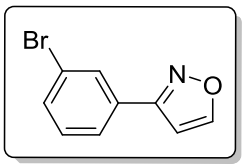
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless viscous oil (63 mg, 95 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.6 Hz, $1H_{isox}$), 8.00 (d, J = 8.0 Hz, 1H), 7.54 (dd, J = 7.7, 1.6 Hz, 1H), 7.46 (td, J = 7.6, 0.8 Hz, 1H), 7.17 (td, J = 7.7, 1.7 Hz, 1H), 6.74 (d, J = 1.6 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (C), 158.0 (CH), 140.2 (CH), 134.4 (C), 131.0 (CH), 130.9 (CH), 128.3 (CH), 105.8 (CH), 96.6 (C); **HRMS** (ESI) Calcd. for $C_9H_6AgINO^+$ $[M+Ag]^+$ 377.8540, found 377.8530.

3-(2-bromophenyl)isoxazole 4h[1]



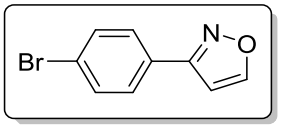
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless viscous oil (62 mg, 92 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.6 Hz, $1H_{isox}$), 7.72 (dd, J = 8.0, 0.9 Hz, 1H), 7.68 (dd, J = 7.7, 1.7 Hz, 1H), 7.43 (td, J = 7.5, 1.0 Hz, 1H), 7.34 (td, J = 7.7, 1.7 Hz, 1H), 6.83 (d, J = 1.6 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5 (C), 158.0 (CH), 133.6 (CH), 131.4 (CH), 131.0 (CH), 130.3 (C), 127.6 (CH), 122.3 (C), 105.9 (CH); **HRMS** (ESI) Calcd. for $C_9H_6BrNONa^+$ $[M+Na]^+$ 245.9525 & 247.9505, found 245.9520 & 247.9501.

3-(3-bromophenyl)isoxazole 4i



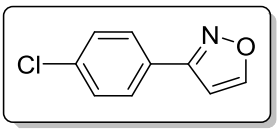
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil (50 mg, 71 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (d, J = 1.7 Hz, $1H_{isox}$), 8.01 (t, J = 1.7 Hz, 1H), 7.80-7.77 (m, 1H), 7.60 (ddd, J = 8.0, 1.9 Hz, 1.0 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 6.67 (d, J = 1.7 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.3 (C), 159.2 (CH), 133.0 (CH), 130.8 (C), 130.5 (CH), 129.9 (CH), 125.5 (CH), 123.0 (C), 102.4 (CH); **HRMS** (ESI) Calcd. for $C_9H_6BrNONa^+$ $[M+Na]^+$ 245.9525 & 247.9505, found 245.9522 & 247.9502.

3-(4-bromophenyl)isoxazole 4j[1]



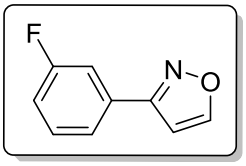
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (58 mg, 84 %); M.p. 102-103 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (d, J = 1.7 Hz, $1H_{isox}$), 7.73 (d, 2H, J = 8.6 Hz), 7.62 (d, 2H, J = 8.6 Hz), 6.66 (d, J = 1.7 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 (C), 159.2 (CH), 132.2 (2CH), 128.4 (2CH), 127.8 (C), 124.4 (C), 102.3 (CH) ; **HRMS** (ESI) Calcd. for $C_9H_6AgBrNO^+$ $[M+Ag]^+$ 331.8658, found 331.8654.

3-(4-chlorophenyl)isoxazole 4k[1]



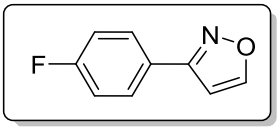
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (43 mg, 72 %); M.p. 76-77 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (d, J = 1.6 Hz, $1H_{isox}$), 7.79 (d, 2H, J = 8.5 Hz), 7.47 (d, 2H, J = 8.5 Hz), 6.66 (d, J = 1.6 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 (C), 159.2 (CH), 136.1 (C), 129.2 (2CH), 128.2 (2CH), 127.3 (C), 102.4 (CH); **HRMS** (ESI) Calcd. for $C_9H_6ClNONa^+$ $[M+Na]^+$ 202.0030, found 202.0023.

3-(3-fluorophenyl)isoxazole 4l[3]



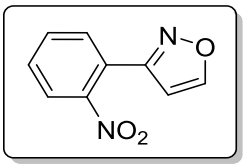
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil (31 mg, 47 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (d, J = 1.7 Hz, 1H), 7.64-7.62 (m, 1H), 7.57 (ddd, J = 9.6, 2.4, 1.5 Hz,1H), 7.46 (td, J = 8.0, 5.9 Hz, 1H), 7.17 (tdd, J = 8.4, 2.6, 0.9 Hz, 1H), 6.68 (d, J = 1.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0 (d, J = 246.8 Hz, C), 160.6 (d, J = 2.6 Hz, C), 159.2 (CH), 130.9 (d, J = 8.2 Hz, C), 130.6 (d, J = 8.2 Hz, CH), 122.6 (d, J = 3.0 Hz, CH), 117.0 (d, J = 21.2 Hz, CH), 113.9 (d, J = 23.0 Hz, CH), 102.5 (CH); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.09 ppm; **HRMS** (ESI) Calcd. for $C_9H_6AgFNO^+$ $[M+Ag]^+$ 269.9479, found 269.9476.

3-(4-fluorophenyl)isoxazole 4m[4]



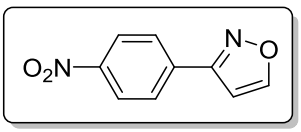
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil (48 mg, 78 %); **^{1}H NMR** (400 MHz, CDCl3) δ 8.47 (d, J = 1.7 Hz, 1H$_{isox}$), 7.86-7.81 (m, 2H), 7.20-7.14 (m, 2H), 6.65 (d, J = 1.7 Hz, 1H$_{isox}$); **^{13}C NMR** (101 MHz, CDCl3) δ 163.8 (d, $J_{C\text{-}F}$ = 249.8 Hz, C), 160.6 (C), 159.1 (CH), 128.8 (d, $J_{C\text{-}F}$ = 8.3 Hz, 2CH), 125.0 (d, $J_{C\text{-}F}$ = 3.5 Hz, C), 116.1 (d, $J_{C\text{-}F}$ = 22.0 Hz, 2CH), 102.4 (CH); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.56 ppm; **HRMS** (ESI) Calcd. for $C_9H_7FNO^+$ $[M+H]^+$ 164.0506, found 164.0512.

3-(2-nitrophenyl)isoxazole 4n[1]



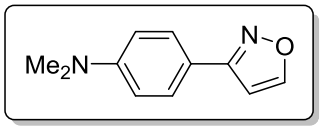
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (30 mg, 50 %); M.p. 81-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (d, J = 1.7 Hz, 1H$_{isox}$), 8.02 (d, J = 8.0 Hz,1H), 7.73-7.72 (m, 2H), 7.69-7.63 (m, 1H), 6.51 (d, J = 1.7 Hz, 1H$_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9 (C), 158.7 (CH), 148.7 (C), 133.0 (CH), 131.7 (CH), 130.7 (CH), 124.5 (CH), 124.1 (C), 104.8 (CH); **HRMS** (ESI) Calcd. for $C_9H_6N_2NaO^+$ $[M+Na]^+$ 213.0271, found 213.0279.

3-(4-nitrophenyl)isoxazole 4o[1]



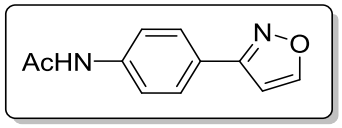
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (41 mg, 72 %); M.p. 179-182 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.7 Hz, 1H$_{isox}$), 8.36 (d, J = 8.9 Hz, 2H), 8.04 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 1.7 Hz, 1H$_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.83 (CH), 159.79 (C), 148.8 (C), 134.9 (C), 127.8 (2CH), 124.3 (2CH), 102.7 (CH); **HRMS** (ESI) Calcd. for $C_9H_6N_2NaO^+$ $[M+Na]^+$ 213.0271, found 213.0272.

3-(4-dimethylaminophenyl)isoxazole 4p[1]



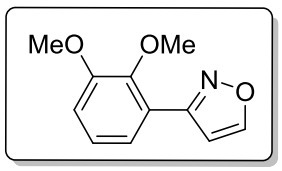
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (36 mg, 63 %); M.p. 125-126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, J = 1.6 Hz, $1H_{isox}$), 7.73 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 1.6 Hz, $1H_{isox}$), 3.04 (s, 6H, NMe_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5 (C), 158.2 (CH_{isox}), 151.5 (C), 127.9 (2CH), 116.4 (C), 112.1 (2CH), 102.0 (CH_{isox}), 40.3 (NMe_2); **HRMS** (ESI) Calcd. for $C_{11}H_{13}N_2O^+$ $[M+H]^+$ 189.1022, found 189.1022.

3-(4-acetamidophenyl)isoxazole 4q



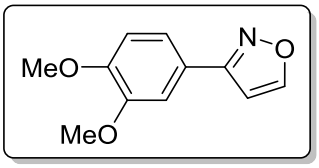
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (28 mg, 44 %); M.p. 143-146 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ δ 8.46 (d, J = 1.7 Hz, $1H_{isox}$), 7.82 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.27 (br s, 1H, NH), 6.66 (d, J = 1.7 Hz, $1H_{isox}$), 2.23 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.4 (C), 161.0 (C), 158.9 (CH), 139.5 (C), 133.3 (CH), 127.7 (CH), 124.6 (C), 119.8 (CH), 102.3 (CH), 24.7 (CH_3); **HRMS** (ESI) Calcd. for $C_{11}H_{11}N_2O_2^+$ $[M+H]^+$ 203.0815, found 203.0821.

3-(2,3-dimethoxyphenyl)isoxazole 4r



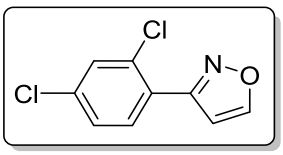
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil (49 mg, 86 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (d, J = 1.6 Hz, $1H_{isox}$), 7.50 (dd, J = 7.9, 1.4 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.03 (dd, J = 8.2, 1.3 Hz, 1H), 6.90 (d, J = 1.6 Hz, $1H_{isox}$), 3.93 (s, 3H, OMe), 3.81 (s, 3H, OMe); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.0 (C), 158.2 (CH), 153.3 (C), 147.6 (C), 124.5 (CH), 123.2 (C), 121.0 (CH), 113.8 (CH), 105.5 (CH), 60.9 (OMe), 55.9 (OMe); **HRMS** (ESI) Calcd. for $C_{11}H_{11}AgNO_3^+$ $[M+Ag]^+$ 311.9784, found 311.9778.

3-(3,4-dimethoxyphenyl)isoxazole 4s[5]



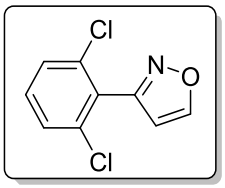
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as light yellow crystals (31 mg, 53 %); M.p. 73-74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (d, J = 1.7 Hz, $1H_{isox}$), 7.47 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 8.3, 2.0 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 1.7 Hz, $1H_{isox}$), 3.97 (s, 3H, OMe), 3.95 (s, 3H, OMe); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2 (C), 158.7 (CH), 150.7 (C), 149.4 (C), 121.6 (C), 120.0 (CH), 111.1 (CH), 109.5 (CH), 102.3 (CH), 56.03 (OMe), 55.96 (OMe); **HRMS** (ESI) Calcd. for $C_{11}H_{11}NNaO_3^+$ $[M+Na]^+$ 228.0631, found 228.0630.

3-(2,4-dichlorophenyl)isoxazole 4t



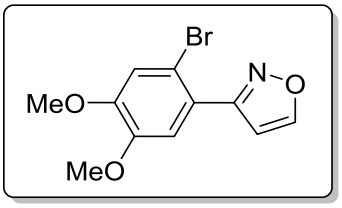
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (52 mg, 93 %); M.p. 77-78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (d, J = 1.7 Hz, $1H_{isox}$), 7.73 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.38 (dd, J = 8.4, 2.1 Hz, 1H), 6.85 (d, J = 1.7 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3 (C), 158.4 (CH), 136.4 (C), 133.7 (C), 131.8 (CH), 130.3 (CH), 127.6 (CH), 126.7 (C), 105.6 (CH); **HRMS** (ESI) Calcd. for $C_9H_5AgCl_2NO^+$ $[M+Ag]^+$ 319.8794, found 319.8781.

3-(2,6-dichlorophenyl)isoxazole 4u[6]



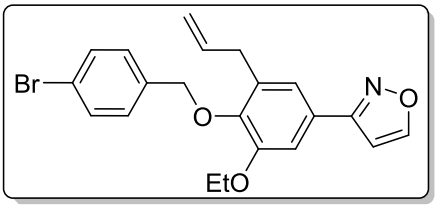
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (54 mg, 96 %); M.p. 53-54 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (d, J = 1.6 Hz, $1H_{isox}$), 7.46-7.43 (m, 2H), 7.35 (dd, J = 8.9, 7.1 Hz, 1H), 6.50 (d, J = 1.6 Hz, $1H_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7 (CH), 157.9 (C), 135.6 (C), 131.1 (CH), 128.3 (2CH+C), 106.1 (CH); **HRMS** (ESI) Calcd. for $C_9H_6Cl_2NO^+$ $[M+H]^+$ 213.9821, found 213.9831.

3-(2-bromo-4,5-dimethoxyphenyl)isoxazole 4v



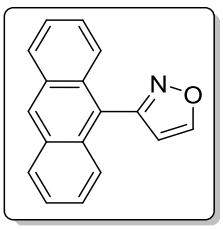
The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (51 mg, 61 %); M.p. 85-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (d, J = 1.7 Hz, $1H_{isox}$), 7.24 (s, 1H), 7.15 (s, 1H), 6.89 (d, J = 1.7 Hz, $1H_{isox}$), 3.95 (s, 3H, OMe), 3.93 (s, 3H, OMe); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4 (C), 157.9 (CH), 150.6 (C), 148.5 (C), 122.1 (C), 116.2 (CH), 113.5 (CH), 112.8 (C), 105.8 (CH), 56.3 (OMe), 56.2 (OMe); **HRMS** (ESI) Calcd. for $C_{11}H_{11}BrNO_3^+$ $[M+H]^+$ 283.9917 found 283.9918.

3-(3-allyl-4-((4-bromobenzyl)oxy)-5-ethoxyphenyl)isoxazole 4w



The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as colourless crystals (46 mg, 60 %); M.p. 94-95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.6 Hz, $1H_{isox}$), 7.53 (d, J = 8.3 Hz, 2H), 7.39-7.36 (m, 3H), 7.18 (d, J = 1.8 Hz, 1H), 6.64 (d, J = 1.6 Hz, $1H_{isox}$), 5.94 (ddt, J = 16.8, 10.3, 6.5 Hz, 1H), 5.09-5.04 (m, 4H), 4.19 (q, J = 7.0 Hz, 2H, O$\underline{CH_2}$$CH_3$), 3.41 (d, J = 6.5 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3 (C), 158.8 (CH), 152.3 (C), 147.3 (C), 136.8 (C), 136.7 (CH), 134.6 (C), 131.5 (2CH), 129.8 (2CH), 124.5 (C), 121.9 (C), 121.0 (CH), 116.1 (=CH_2), 109.8 (CH), 102.5 (CH), 73.8 (CH_2), 64.4 (CH_2), 34.3 (CH_2), 14.9 (CH_3); **HRMS** (ESI) Calcd. for $C_{21}H_{20}AgBrNO_3^+$ $[M+Ag]^+$ 519.9672, found 519.9669.

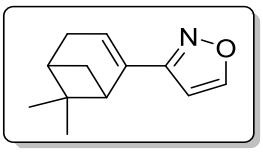
3-(antrace*n*-9-yl)isoxazole 4x



The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as yellow crystals (68 mg, 85 %); M.p. 111-112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.77

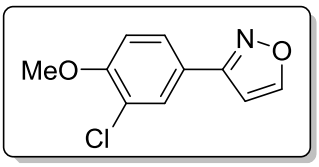
(d, J = 1.4 Hz, 1H$_{isox}$), 8.61 (s, 1H), 8.09-8.07 (m, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.54-7.47 (m, 4H), 6.65 (d, J = 1.4 Hz, 1H$_{isox}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9 (C), 158.8 (CH), 131.2 (2C), 130.71 (2C), 129.0 (CH), 128.6 (2CH), 126.6 (2CH), 125.6 (2CH), 125.4 (2CH), 122.9 (C), 108.0 (CH); **HRMS** (ESI) Calcd. for $C_{17}H_{12}NO^+$ $[M+H]^+$ 246.0913, found 246.0920.

3-(6,6-dimethylbicyclo[3.1.1]hept-2-e*n*-2-yl)isoxazole 4y

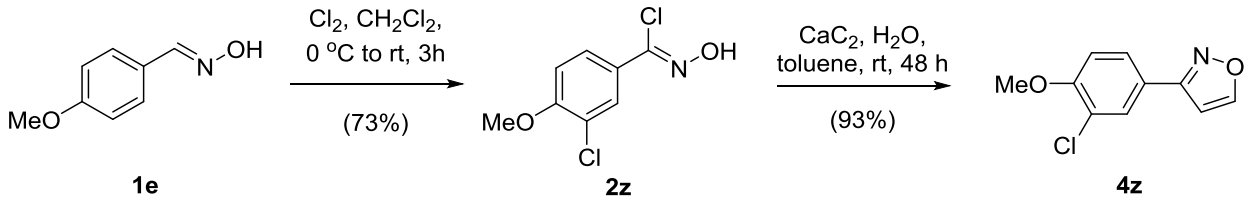


The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a yellowish oil (47 mg, 81 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, J = 1.7 Hz, 1H$_{isox}$), 6.45 (d, J = 1.7 Hz, 1H$_{isox}$), 6.23 (ddd, J = 4.7, 3.2, 1.4 Hz, 1H, CH=), 3.03 (td, J = 5.7, 1.4 Hz, 1H), 2.57-2.47 (m, 3H), 2.24-2.19 (m, 1H), 1.39 (s, 3H, CH_3), 1.30 (d, J = 9.0 Hz, 1H), 0.89 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5 (C), 157.8 (=CH), 137.7 (C), 126.6 (=CH), 101.1 (=CH), 42.8 (CH), 40.6 (CH), 37.9 (C), 32.2 (CH_2), 31.3 (CH_2), 26.0 (CH_3), 20.9 (CH_3); **HRMS** (ESI) Calcd. for $C_{12}H_{16}NO^+$ $[M+H]^+$ 190.1226, found 190.1222.

3-(3-chloro-4-methoxyphenyl)isoxazole 4z



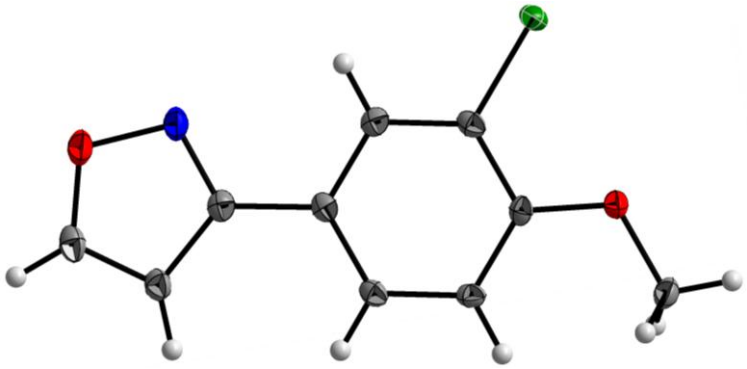
Synthesized from 3-chloro-*N*-hydroxy-4-methoxybenzimidoyl chloride (chloroaldoxime **2z**). The corresponding chloroaldoxime **2z** was obtained by direct chlorination of 4-methoxybenzaldoxime **1e** with chlorine,[7] which also led to Cl insertion into the aromatic ring.



The crude material was purified by column chromatography (*n*-hexane/EtOAc 10:1) to give the product as a colourless crystals (56 mg, 93 %); M.p. 100-101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (d, J = 1.6 Hz, 1H$_{isox}$), 7.87 (d, J = 2.1 Hz, 1H), 7.73 (dd, J = 8.6, 2.1 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H$_{isox}$), 3.97 (s, 3H, OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2 (C), 159.0 (CH$_{isox}$), 156.4 (C), 128.8 (CH), 126.5 (CH), 123.1 (C), 122.2 (C), 112.2 (CH),

102.2 (CH), 56.3 (OMe); **HRMS** (ESI) Calcd. for $C_{10}H_8ClNNaO_2^+$ $[M+Na]^+$ 232.0136 found 232.0138.

The position of the chlorine atom was additionally confirmed with single crystal X-ray diffraction. The single crystal of **4z** was obtained by slow crystallization from the methanol – dichloromethane mixture.



X-ray diffraction structure of **4z**

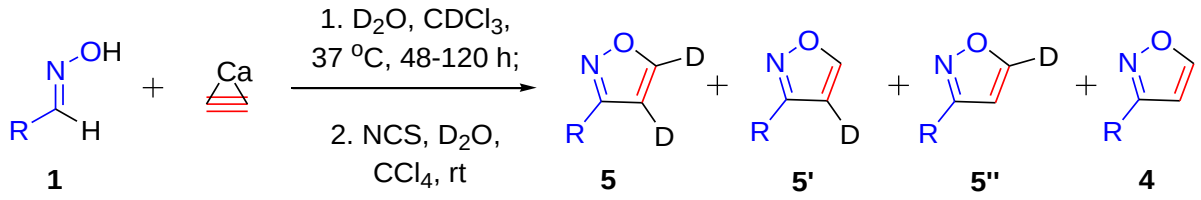
Phase data:

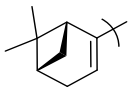
Space group	Monoclinic $P2_1/c$ (14)
Cell parameters	a=3.8516(2)Å; b=11.2844(4)Å; c=21.4208(8)Å; β=89.074(3)°; V=930.89(10) $Å^3$; Z=4

Crystallographic data for **4z** was deposited at the Cambridge Crystallographic Data Centre (Deposition № CCDC-1541266) and can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

S3. Experimental details and spectral data for 4,5-dideuteroisoxazoles 5

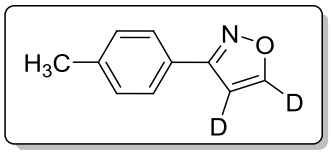
Table S1. The details of the aldoximes reaction with CaC_2, D_2O and NCS[a]



Entry	R	**5**, %[b]	**5'**+**5''**, %[b,c]	**4**, %[b]	**Deuterium incorporation**, %[d]
1	4-MeC_6H_4	96	4	*Trace*	98
2	2-$MeOC_6H_4$	96	4	*Trace*	98
3	3-$MeOC_6H_4$	93	6	1	96
4	4-$MeOC_6H_4$	92	7	1	96
5	Ph	90	8	2	94
6	2-IC_6H_4	95	5	*Trace*	98
7	2-BrC_6H_4	95	5	*Trace*	98
8	3-BrC_6H_4	93	6	1	96
9	4-BrC_6H_4	96	4	*Trace*	98
10	4-ClC_6H_4	96	4	*Trace*	98
11	3-FC_6H_4	92	7	< 1	96
12	4-FC_6H_4	96	4	*Trace*	98
13	2,3-$(MeO)_2C_6H_3$	94	5	1	97
14	3,4-$(MeO)_2C_6H_3$	95	5	*Trace*	98
15	2,4-$Cl_2C_6H_3$	94	6	*Trace*	97
16	2,6-$Cl_2C_6H_3$	96	4	*Trace*	98
17	Antracene-9-yl	94	6	*Trace*	97
18		93	7	*Trace*	97

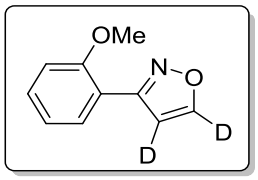
[a] Reaction conditions: 1. Aldoxime (100 mg), D_2O (1.0 ml), $CDCl_3$ (0.75 ml), 37 °C, 120 h; 2. Aldoxime (0.25 mmol), CaC_2 (1.5 mmol), D_2O (8.0 mmol), *N*-chlorosuccinimide (0.3 mmol), CCl_4 (1.5 ml), 20 °C, 48 h; [b] The percentage of isoxazoles by 1H NMR (determined by the residual signals of **5'**, **5"** and **4** isoxazole protons); [c] The percentage of **5'** and **5''** are equal; [d] Deuterium incorporation into the product = 5+(5'+5")/2.

4,5-dideutero-3-(*p*-tolyl)isoxazole 5a



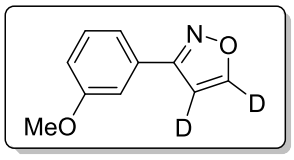
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 96 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 2.43 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4 (C), 158.4 (t, $J_{C\text{-}D}$ = 30.5 Hz, CD), 140.2 (C), 129.6 (2CH), 126.8 (2CH), 126.0 (C), 102.0 (t, $J_{C\text{-}D}$ = 29.2 Hz, CD), 21.4 (CH_3); **HRMS** (ESI) Calcd. for $C_{10}H_8D_2NO^+$ $[M+H]^+$ 162.0882, found 162.0892.

4,5-dideutero-3-(2-methoxyphenyl)isoxazole 5c



The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 96 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.7, 1.7 Hz, 1H), 7.45 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H, OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.1 (C), 157.3 (C), 131.2 (CH), 129.6 (CH), 121.0 (CH), 117.8 (C), 111.5 (CH), 55.6 (OMe), CD signals were not observed; **HRMS** (ESI) Calcd. for $C_{10}H_7D_2NNaO_2^+$ $[M+Na]^+$ 200.0651, found 200.0645.

4,5-dideutero-3-(3-methoxyphenyl)isoxazole 5d

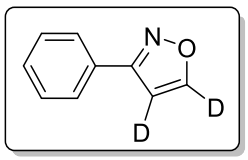


The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 3H, 3CH), 7.04-6.99 (m, 1H), 3.89 (s, 3H, OCH_3); **HRMS** (ESI) Calcd. for $C_{10}H_8D_2NO_2^+$ $[M+H]^+$ 178.0832, found 178.0830.

4,5-dideutero-3-(4-methoxyphenyl)isoxazole 5e

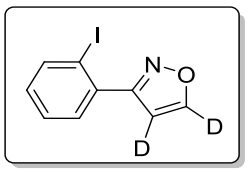
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80-7.76 (m, 2H), 7.02-6.98 (m, 2H), 3.87 (s, 3H, OMe); **HRMS** (ESI) Calcd. for $C_{10}H_7D_2NNaO_2^+$ $[M+H]^+$ 200.0651, found 200.0659.

4,5-dideutero-3-phenylisoxazole 5f



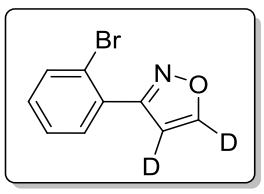
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.50-7.46 (m, 3H); **HRMS** (ESI) Calcd. for $C_9H_6D_2NO^+$ $[M+H]^+$ 146.0726, found 148.0730.

4,5-dideutero-3-(2-iodophenyl)isoxazole 5g



The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 95 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.0, 0.9 Hz, 1H), 7.54 (dd, J = 7.7, 1.7 Hz, 1H), 7.46 (td, J = 7.5, 1.1 Hz, 1H), 7.16 (td, J = 7.7, 1.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (C), 157.7 (t, $J_{C\text{-}D}$ = 31.4 Hz, CD), 140.2 (CH), 134.3 (C), 131.0 (CH), 130.9 (CH), 128.3 (CH), 105.5 (t, $J_{C\text{-}D}$ = 28.0 Hz, CD), 96.6 (C); **HRMS** (ESI) Calcd. for $C_9H_5D_2INO^+$ $[M+H]^+$ 273.9692, found 273.9694.

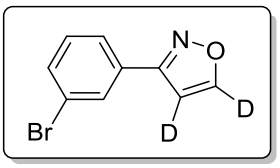
3-(2-bromophenyl)-4,5-dideuteroisoxazole 5h



The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 95 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.0, 1.1 Hz, 1H), 7.68

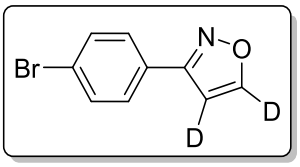
(dd, *J* = 7.7, 1.7 Hz, 1H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.34 (td, J = 7.7, 1.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5 (C), 133.7 (CH), 131.4 (CH), 131.0 (CH), 130.3 (C), 127.6 (CH), 122.3 (C), CD signals were not observed; **HRMS** (ESI) Calcd. for $C_9H_5D_2BrNO^+$ $[M+H]^+$ 225.9831 & 227.9811, found 225.9840 & 227.9832.

3-(3-bromophenyl)-4,5-dideuteroisoxazole 5i



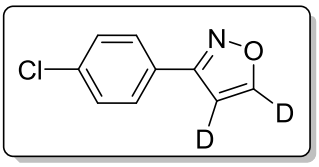
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.8 Hz, 1H), 7.79-7.76 (m, 1H), 7.59 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H); **HRMS** (ESI) $C_9H_4D_2BrNNaO^+$ $[M+H]^+$ 247.9651 & 249.9630, found 247.9651 & 249.9643.

3-(4-bromophenyl)-4,5-dideuteroisoxazole 5j



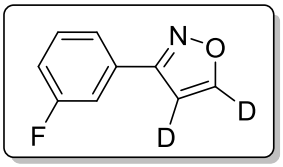
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 96 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74-7.71 (m, 2H), 7.64-7.61 (m, 2H), **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 (C), 132.2 (2CH), 128.4 (2CH), 127.8 (C), 124.4 (C), CD signals were not observed; **HRMS** (ESI) $C_9H_5D_2BrNO^+$ $[M+H]^+$ 225.9831 & 227.9811, found 225.9834 & 227.9814.

3-(4-chlorophenyl)-4,5-dideuteroisoxazole 5k



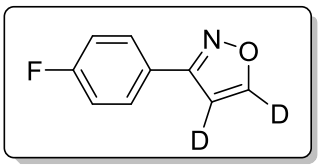
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 96 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 (C), 158.9 (t, $J_{C\text{-}D}$ = 30.1 Hz, CD), 136.1 (C), 129.2 (2CH), 128.2 (2CH), 127.3 (C), 102.9 (t, $J_{C\text{-}D}$ = 20.8 Hz, CD); **HRMS** (ESI) Calcd. for $C_9H_5D_2ClNO^+$ $[M+H]^+$ 182.0336, found 182.0446.

4,5-dideutero-3-(3-fluorophenyl)isoxazole 5l



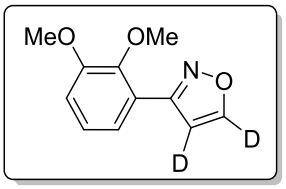
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 1H), 7.57 (ddd, J = 9.6, 2.5, 1.7 Hz, 1H), 7.46 (td, J = 8.0, 5.8 Hz, 1H), 7.17 (tdd, J = 8.4, 2.6, 0.9 Hz, 1H); **HRMS** (ESI) Calcd. for $C_9H_5D_2FNO^+$ $[M+H]^+$ 166.0632, found 166.0634.

4,5-dideutero-3-(4-fluorophenyl)isoxazole 5m



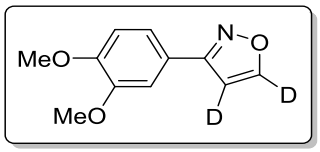
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 96 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87-7.82 (m, 2H), 7.22-7.15 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (d, $J_{C\text{-}F}$ = 250.0 Hz, C), 160.6 (C), 158.8 (t, $J_{C\text{-}D}$ = 31.3 Hz, CD), 128.8 (d, $J_{C\text{-}F}$ = 8.6 Hz, 2CH), 125.1 (d, $J_{C\text{-}F}$ = 3.2 Hz, C), 116.1 (d, $J_{C\text{-}F}$ = 21.9 Hz, 2CH), 102.0 (t, $J_{C\text{-}D}$ = 27.7 Hz, CD); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.57 ppm; **HRMS** (ESI) Calcd. for $C_9H_5D_2FNO^+$ $[M+H]^+$ 166.0632, found 166.0648.

4,5-dideutero-3-(2,3-dimethoxyphenyl)isoxazole 5r



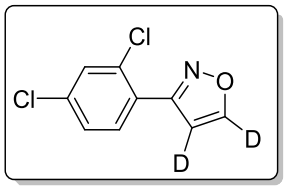
The crude material was purified by PTLC (*n*-hexane/EtOAc 10:1) to give the product as a colourless oil, 94 % 4,5-D_2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 7.9, 1.5 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.03 (dd, J = 8.2, 1.5 Hz, 1H), 3.93 (s, 3H, OMe), 3.81 (s, 3H, OMe); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.0 (C), 157.9 (t, $J_{C\text{-}D}$ = 30.3 Hz, CD), 153.3 (C), 147.6 (C), 124.5 (CH), 123.2 (C), 121.0 (CH), 113.8 (CH), 105.1 (t, $J_{C\text{-}D}$ = 27.9 Hz, CD), 60.9 (OMe), 55.9 (OMe); **HRMS** (ESI) Calcd. for $C_{11}H_{10}D_2NO_3^+$ $[M+H]^+$ 208.0937, found 208.0929.

3-(3,4-dimethoxyphenyl)-4,5-dideuteroisoxazole 5s



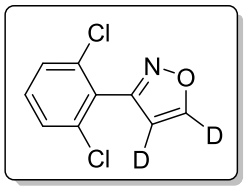
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, J = 1.9 Hz, 1H), 7.34 (dd, J = 8.3, 2.0 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 3.98 (s, 3H, OMe), 3.96 (s, 3H, OMe); **HRMS** (ESI) Calcd. for $C_{11}H_9D_2NNaO_3^+$ $[M+Na]^+$ 230.0757, found 230.0753.

4,5-dideutero-3-(2,4-dichlorophenyl)isoxazole 5t



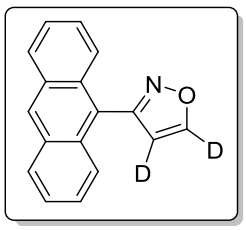
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.37 (dd, J = 8.4, 2.1 Hz, 1H); HRMS (ESI) Calcd. for $C_9H_4D_2Cl_2NO^+$ $[M+H]^+$ 215.9946, found 215.9952.

4,5-dideutero-3-(2,6-dichlorophenyl)isoxazole 5u



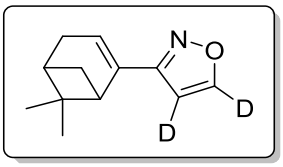
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.36 (dd, J = 8.9, 7.2 Hz, 1H); HRMS (ESI) Calcd. for $C_9H_3D_2Cl_2NNaO^+$ $[M+Na]^+$ 237.9766, found 237.9775.

4,5-dideutero-3-(antrace*n*-9-yl)isoxazole 5x



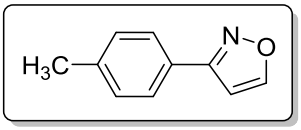
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.09-8.07 (m, 2H), 7.86-7.84 (m, 2H), 7.54-7.46 (m, 4H); **HRMS** (ESI) Calcd. for $C_{17}H_{10}D_2NO^+$ $[M+H]^+$ 248.1039, found 248.1048.

4,5-dideutero-3-(6,6-dimethylbicyclo[3.1.1]hept-2-e*n*-2-yl)isoxazole 5y

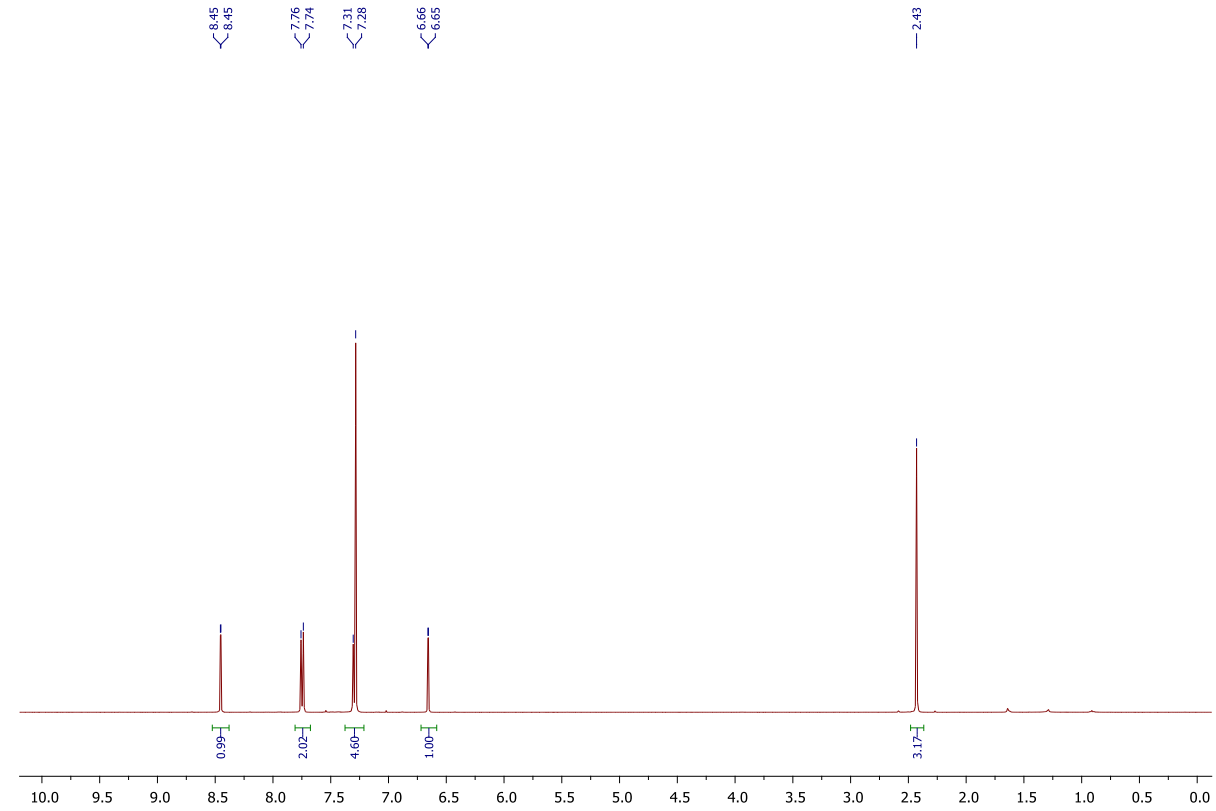


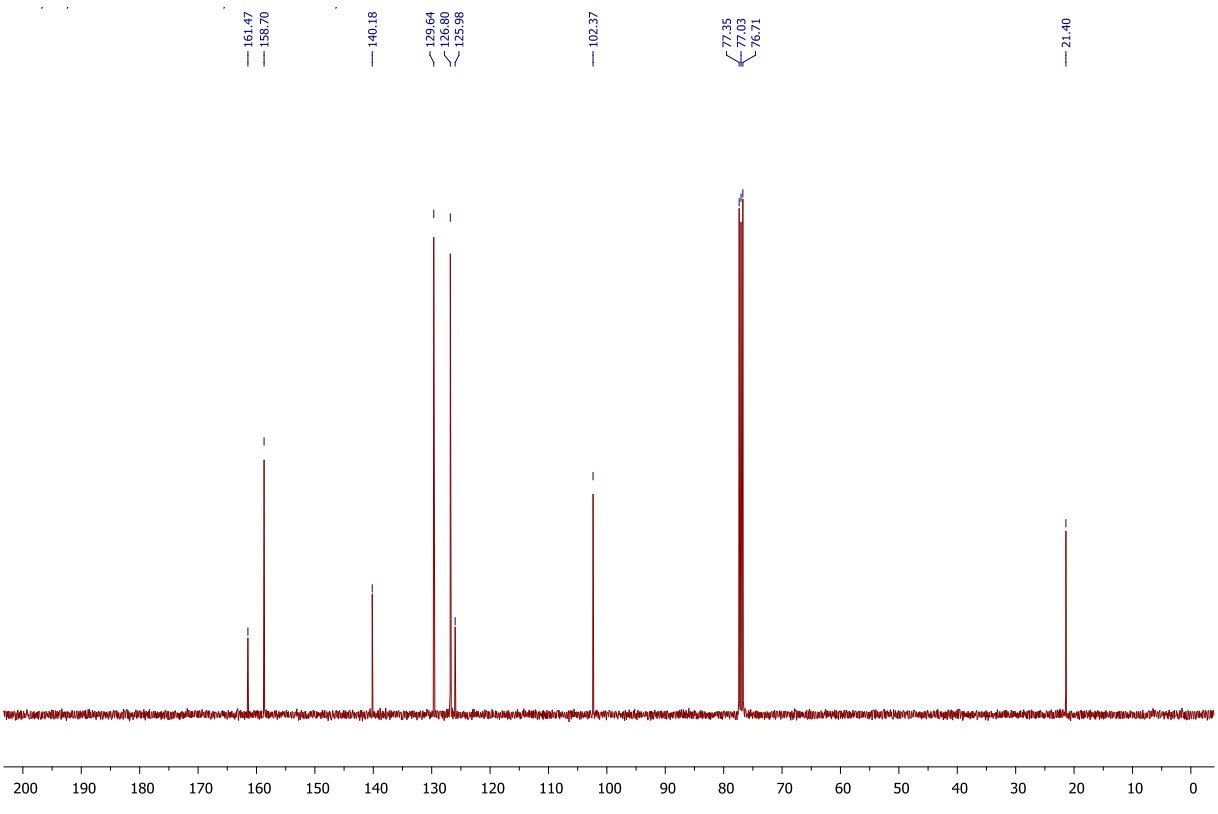
The data was obtained from the spectrum of the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.22 (ddd, J = 4.7, 3.2, 1.4 Hz, 1H, CH=), 3.02 (td, J = 5.7, 1.5 Hz, 1H), 2.56-2.46 (m, 3H), 2.23-2.19 (m, 1H), 1.39 (s, 3H, CH_3), 1.29 (d, J = 9.0 Hz, 1H), 0.88 (s, 3H, CH_3); **HRMS** (ESI) Calcd. for $C_{12}H_{14}D_2NO^+$ $[M+H]^+$ 192.1352, found 192.1346.

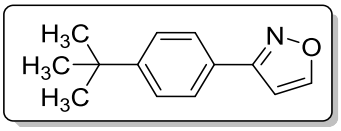
S4. NMR-spectra



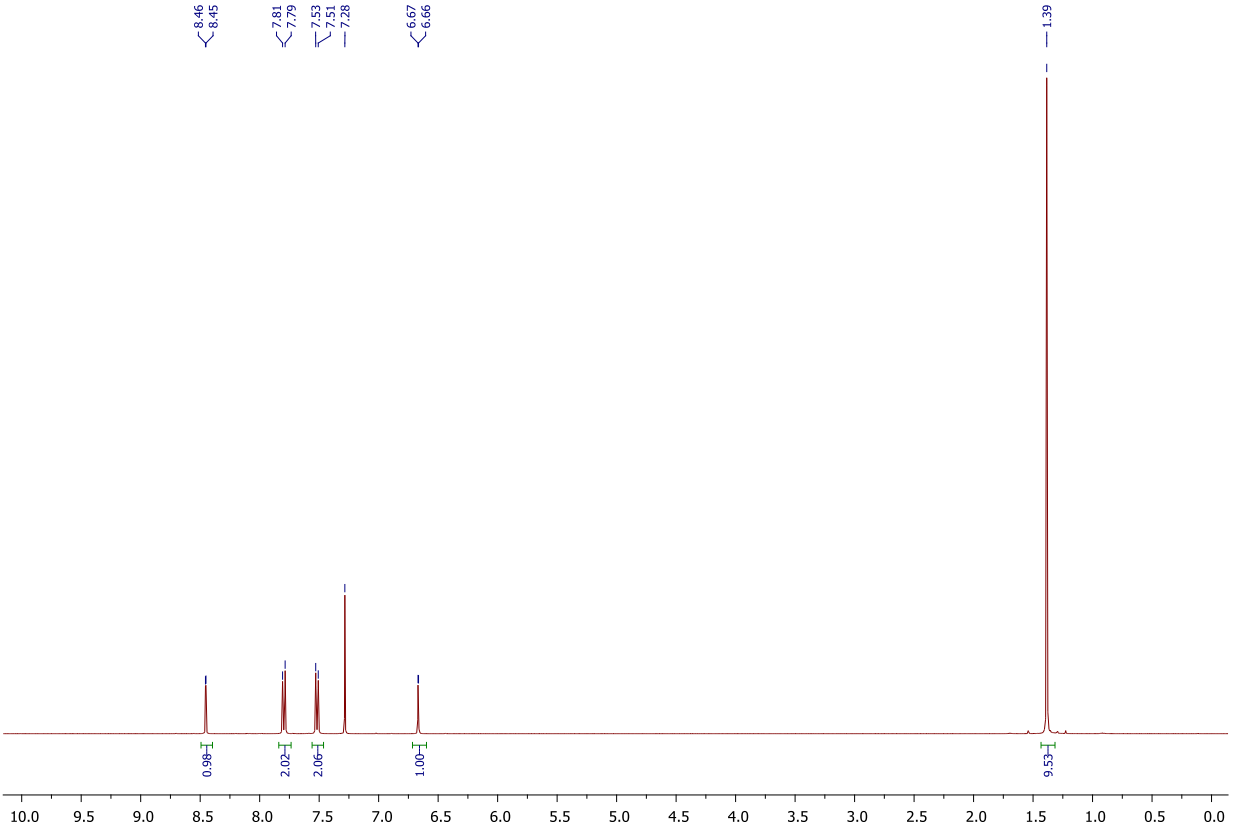
3-(4-Tolyl)isoxazole **4a** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

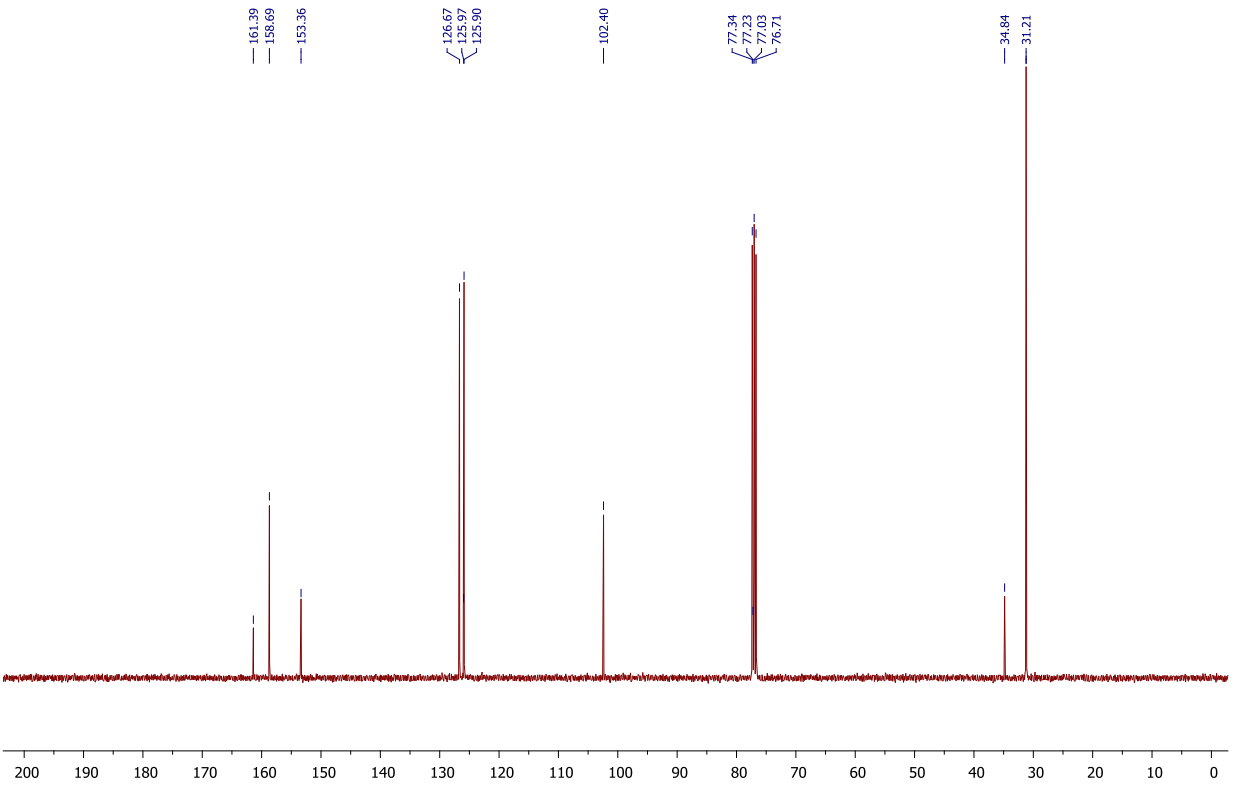


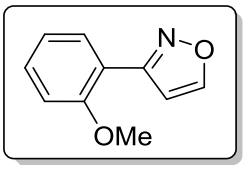




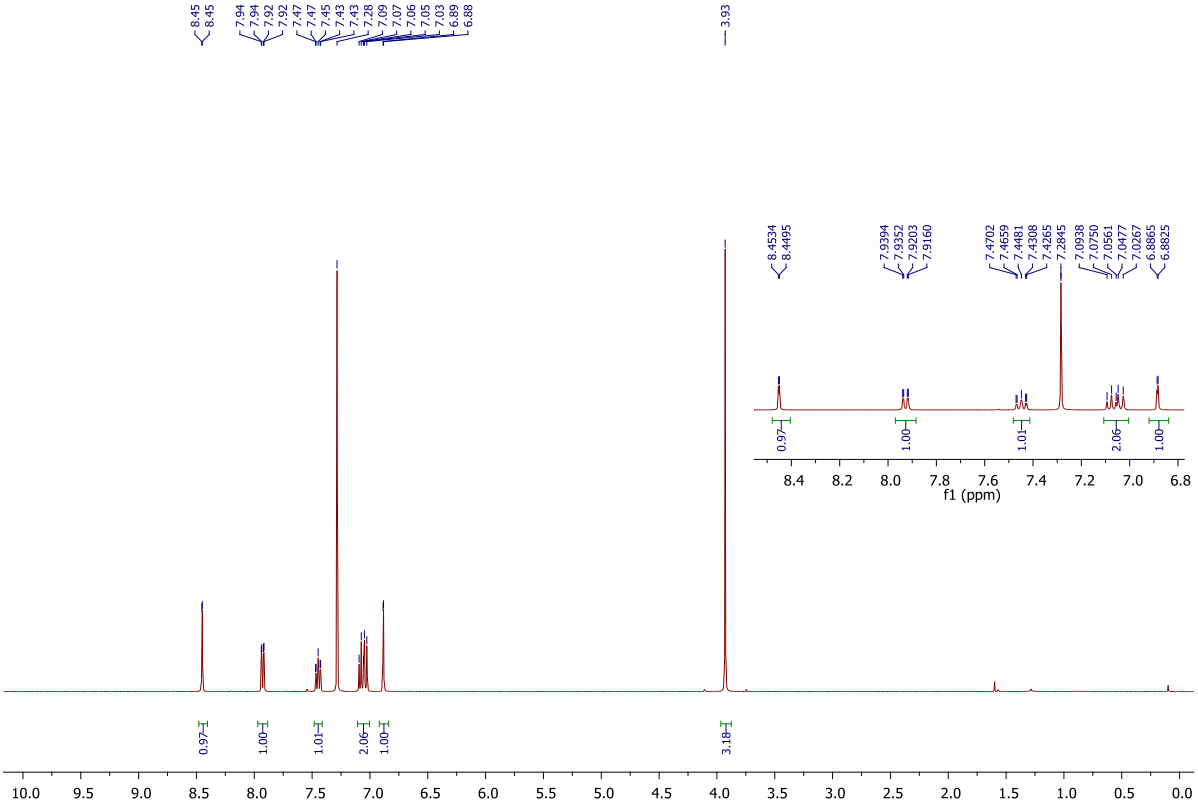
3-(4-*Tert*-butylphenyl)isoxazole **4b** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

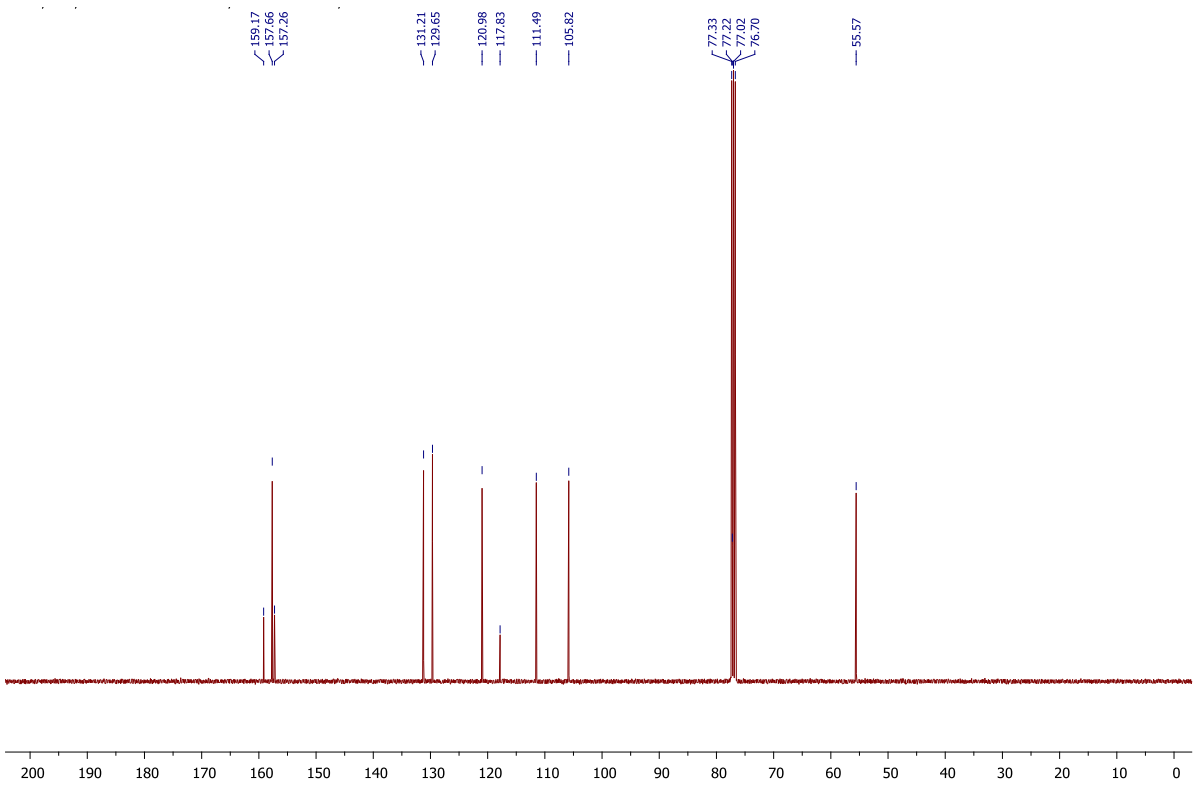


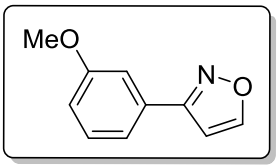




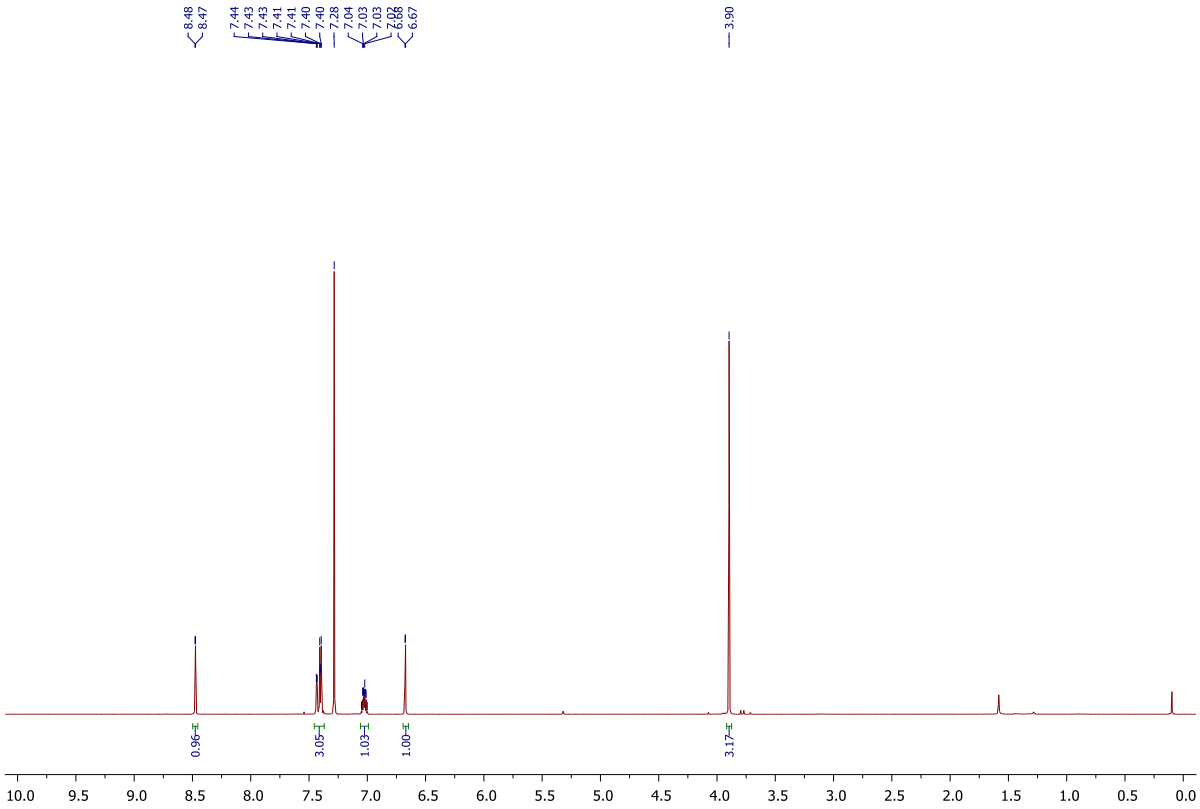
3-(2-Methoxyphenyl)isoxazole **4c** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

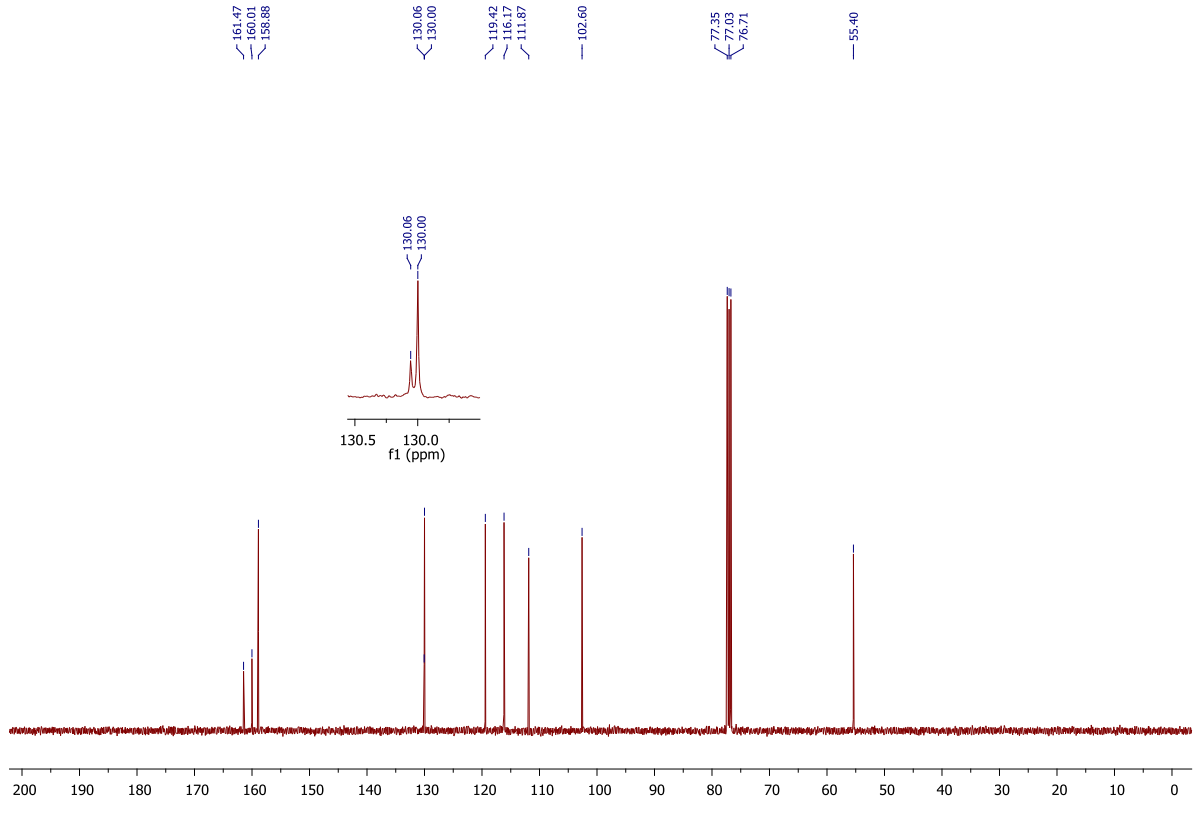


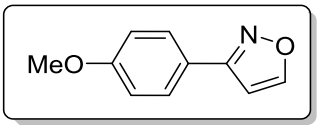




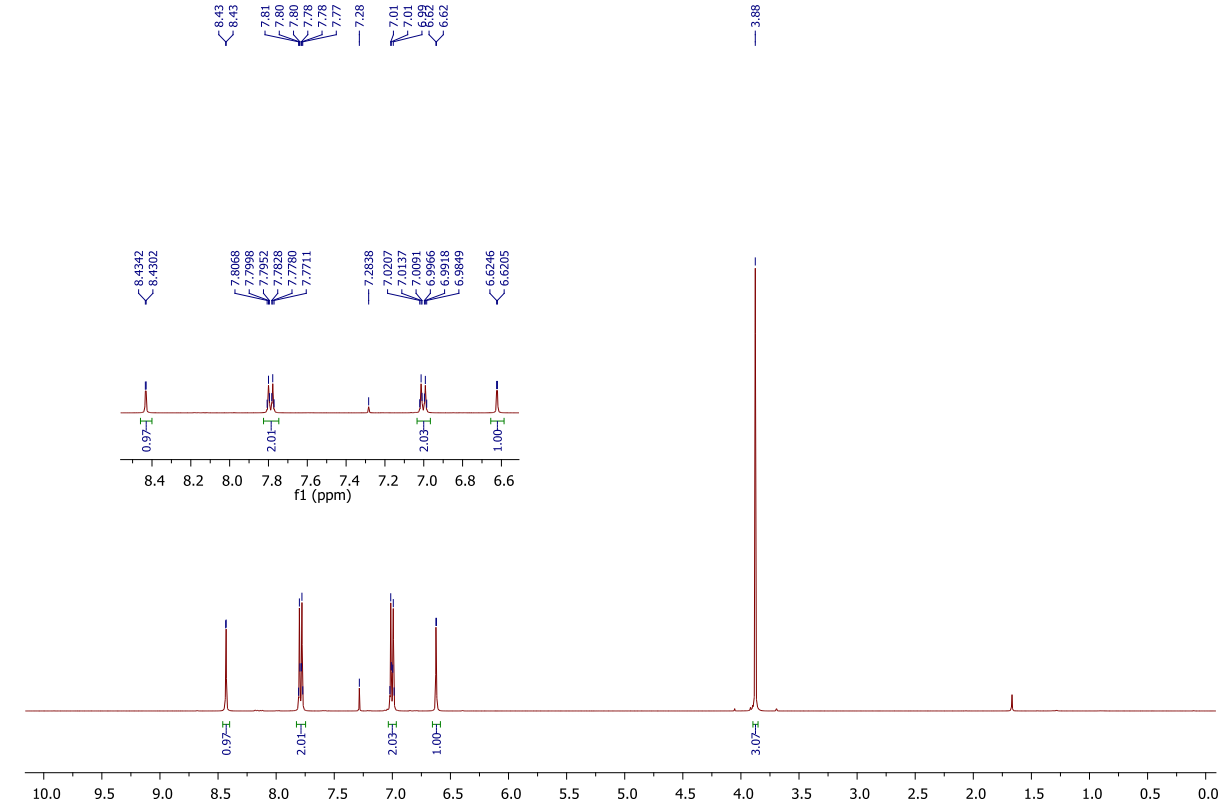
3-(3-Methoxyphenyl)isoxazole **4d** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

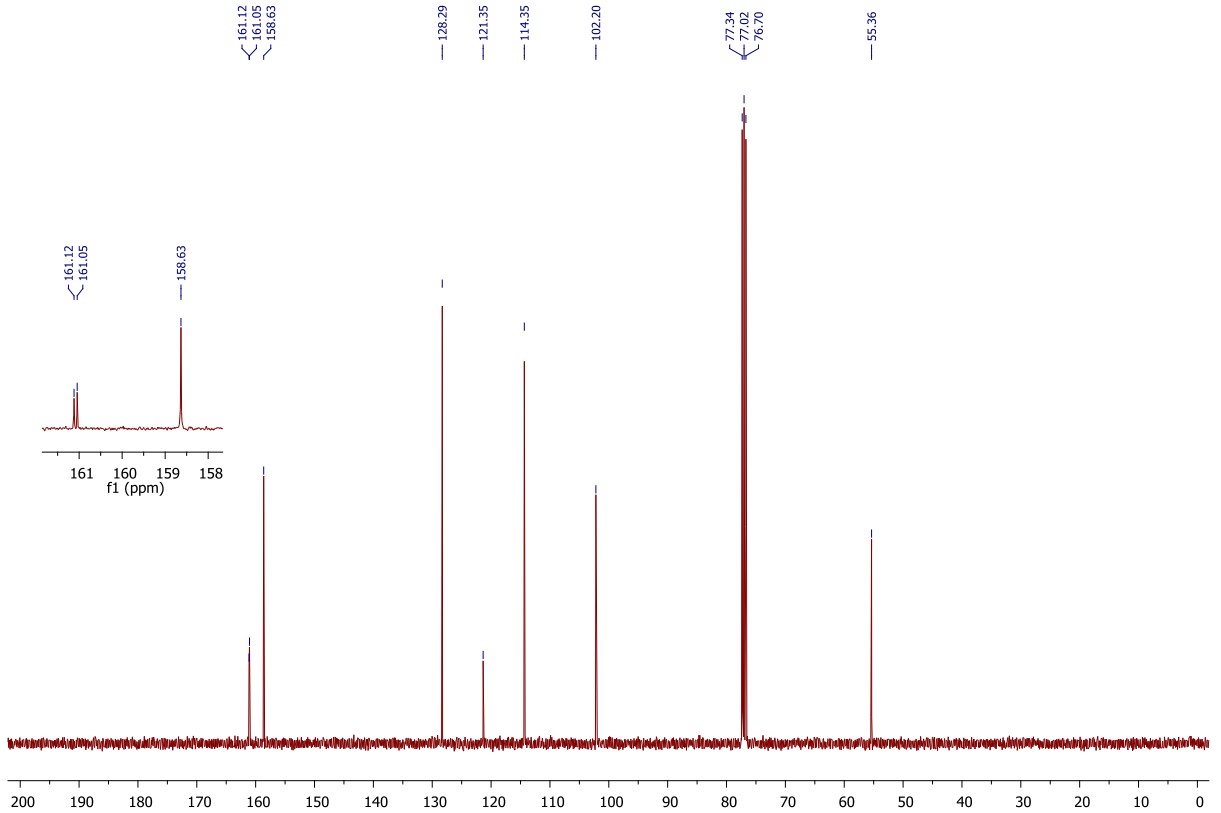


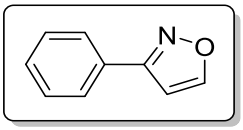




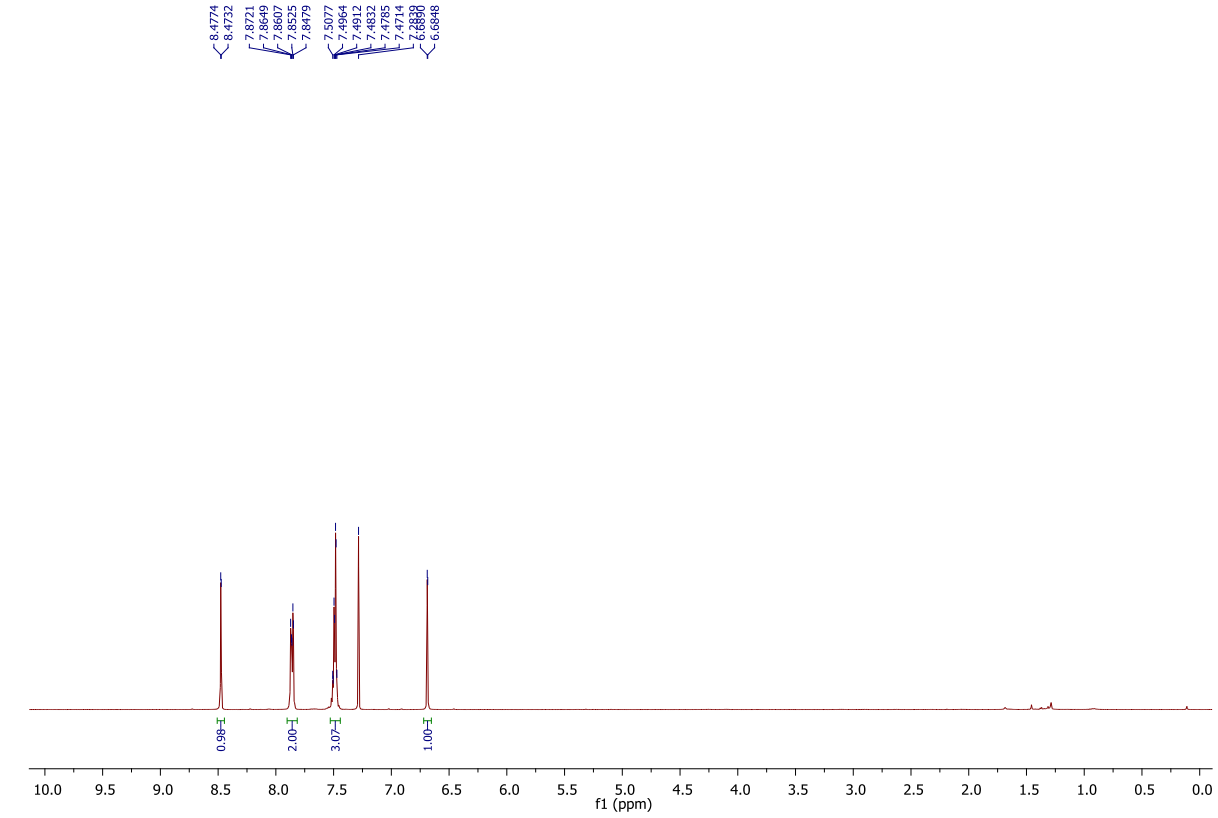
3-(4-Methoxyphenyl)isoxazole **4e** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

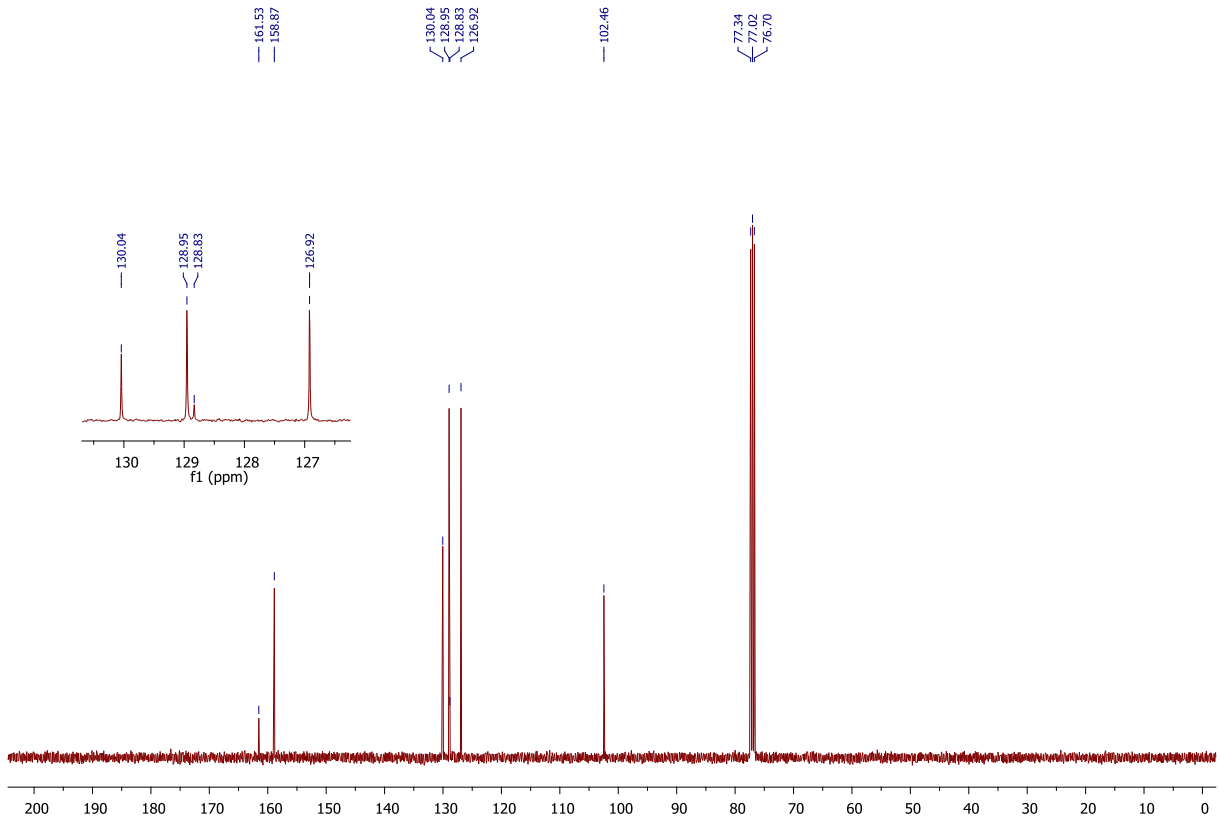


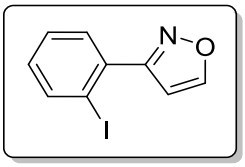




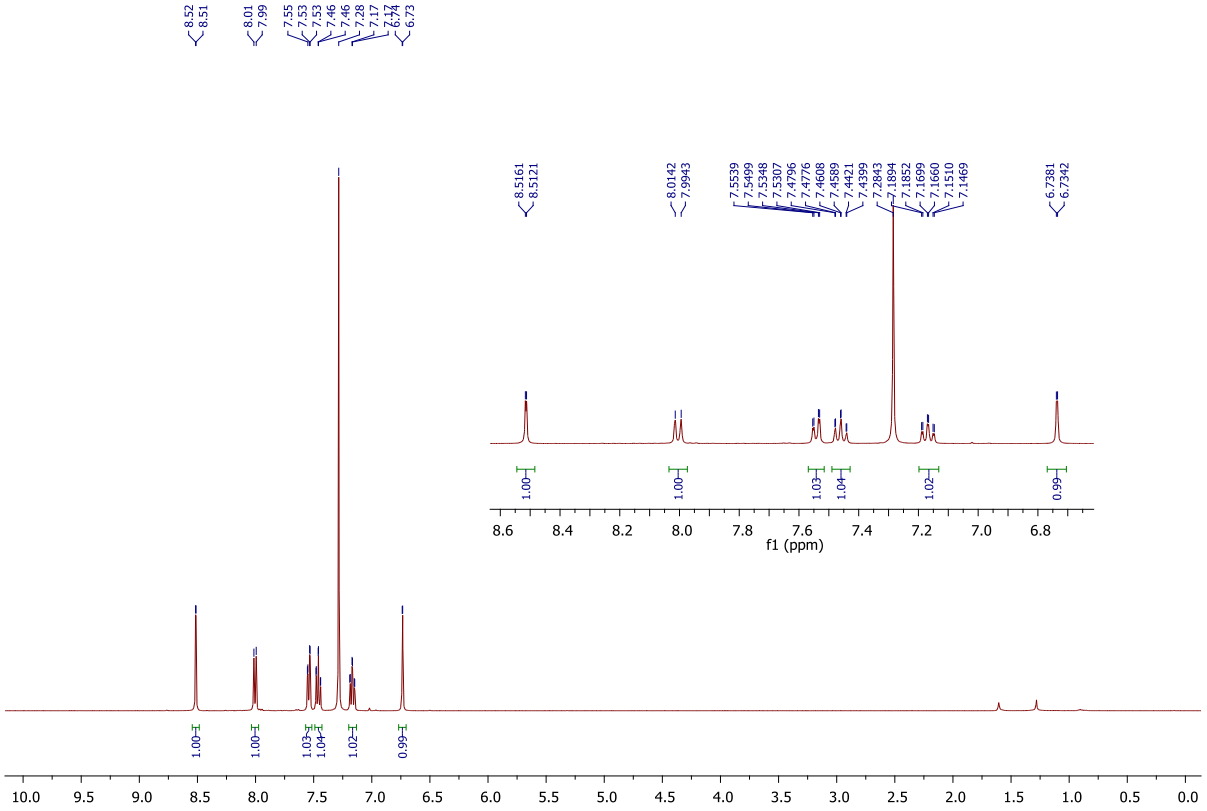
3-Phenylisoxazole **4f** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

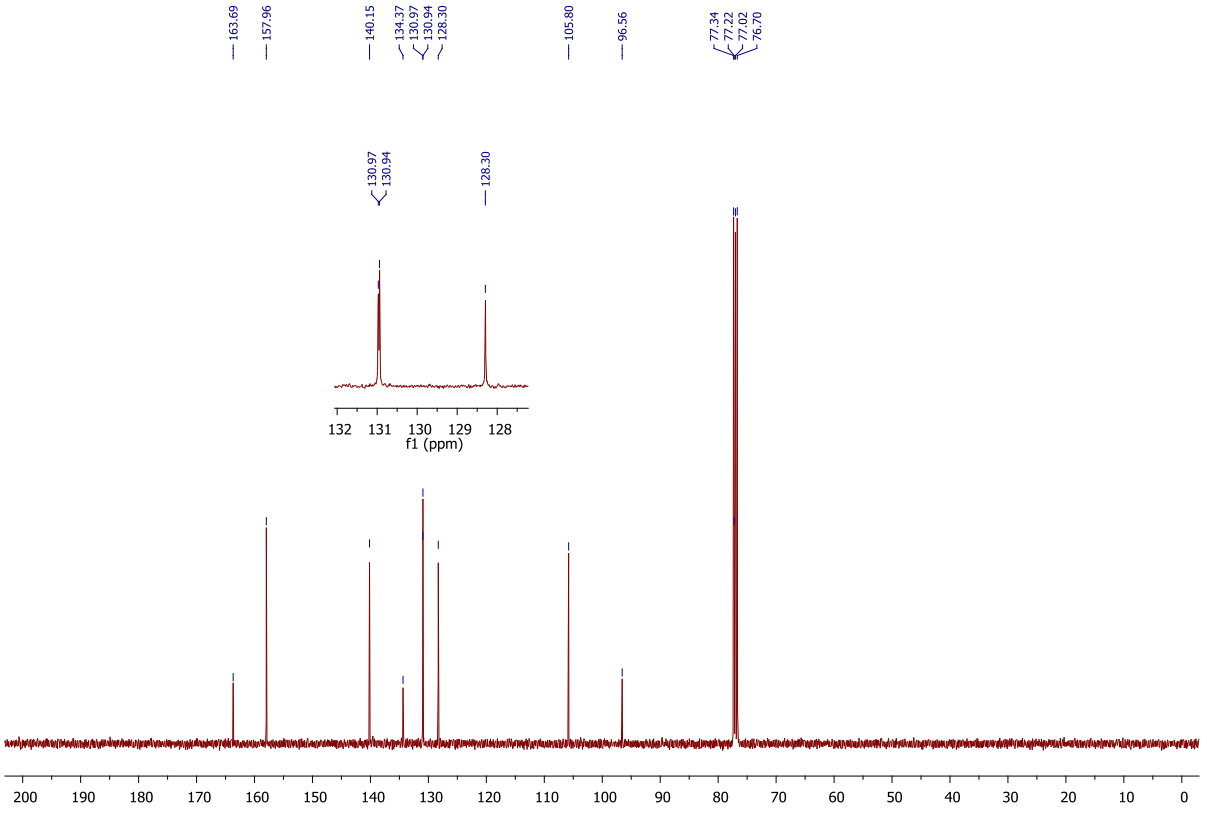


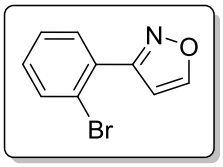




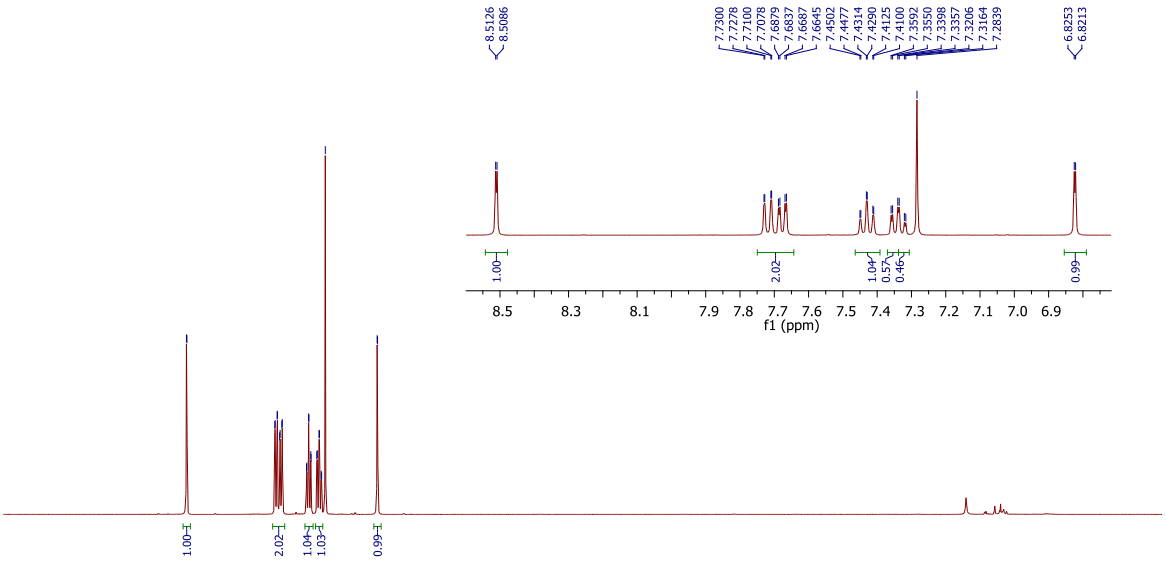
3-(2-Iodophenyl)isoxazole **4g** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

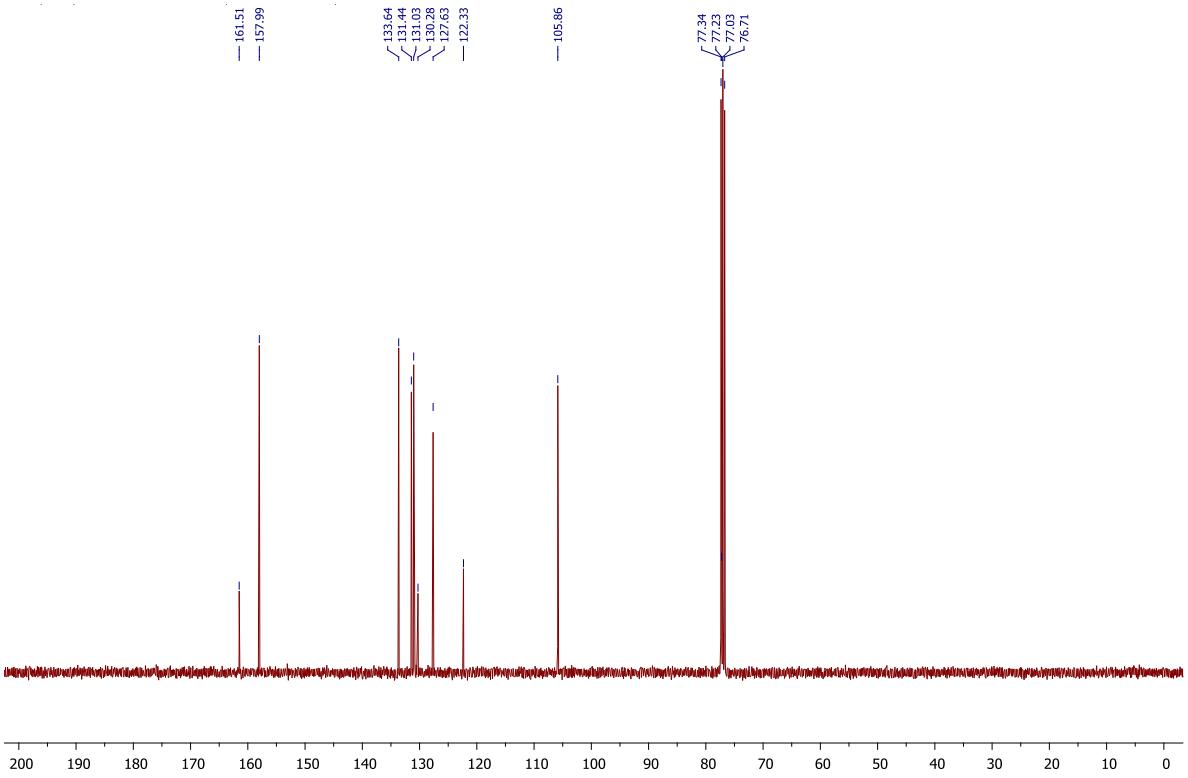


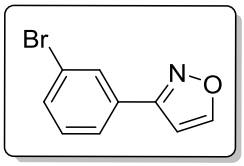




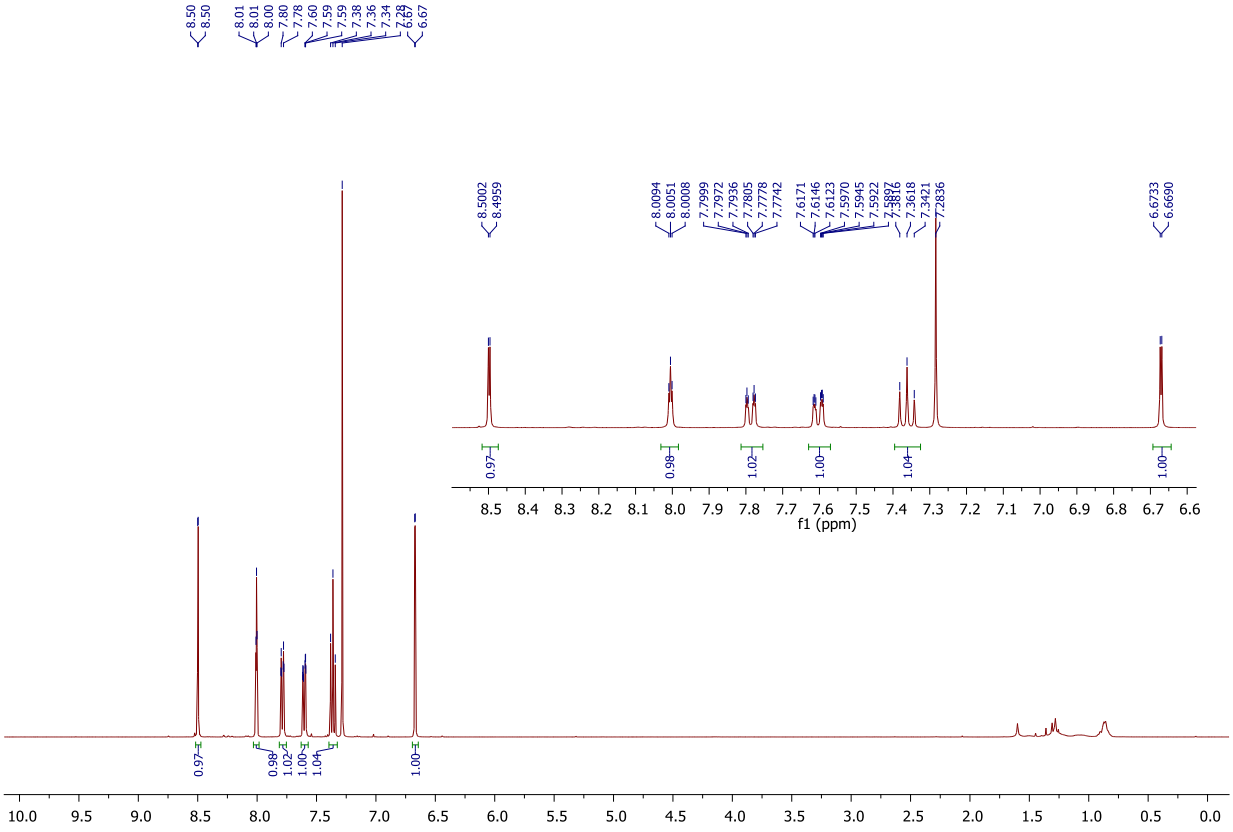
3-(2-Bromophenyl)isoxazole **4h** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

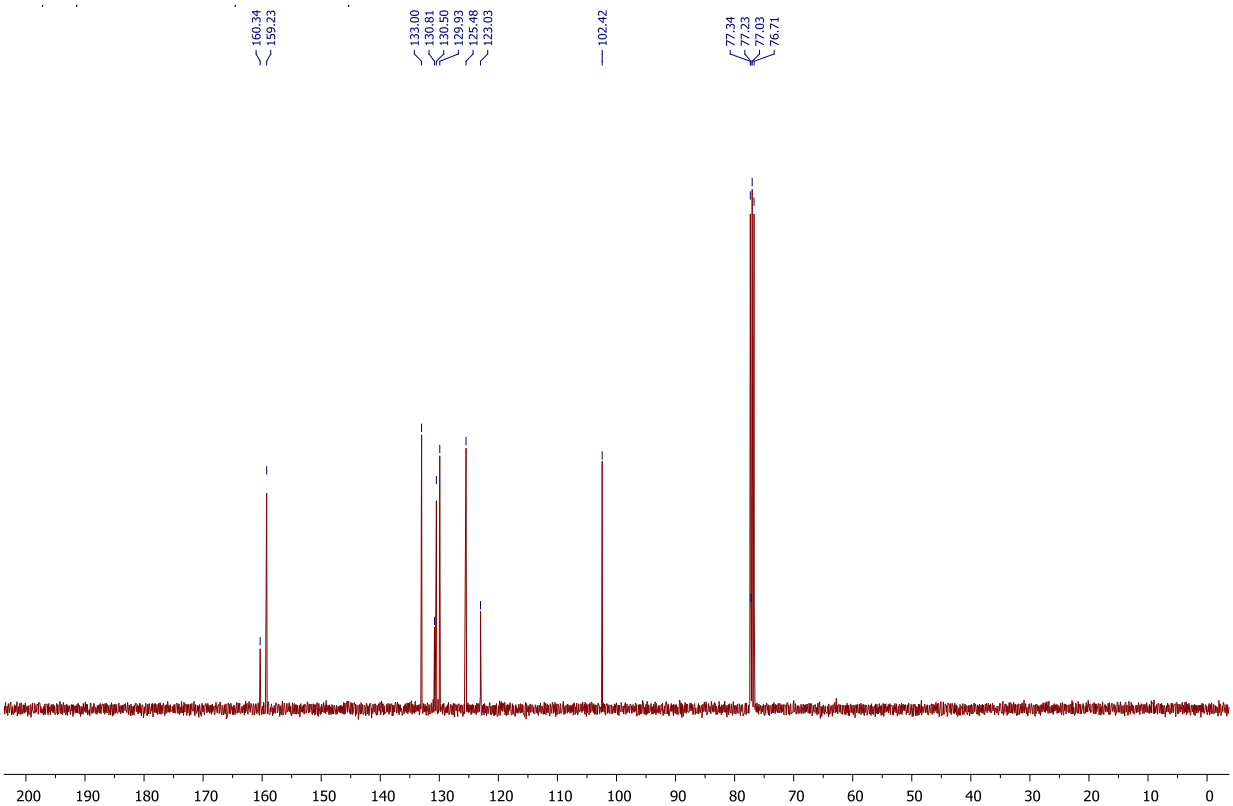


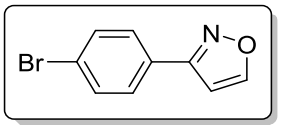




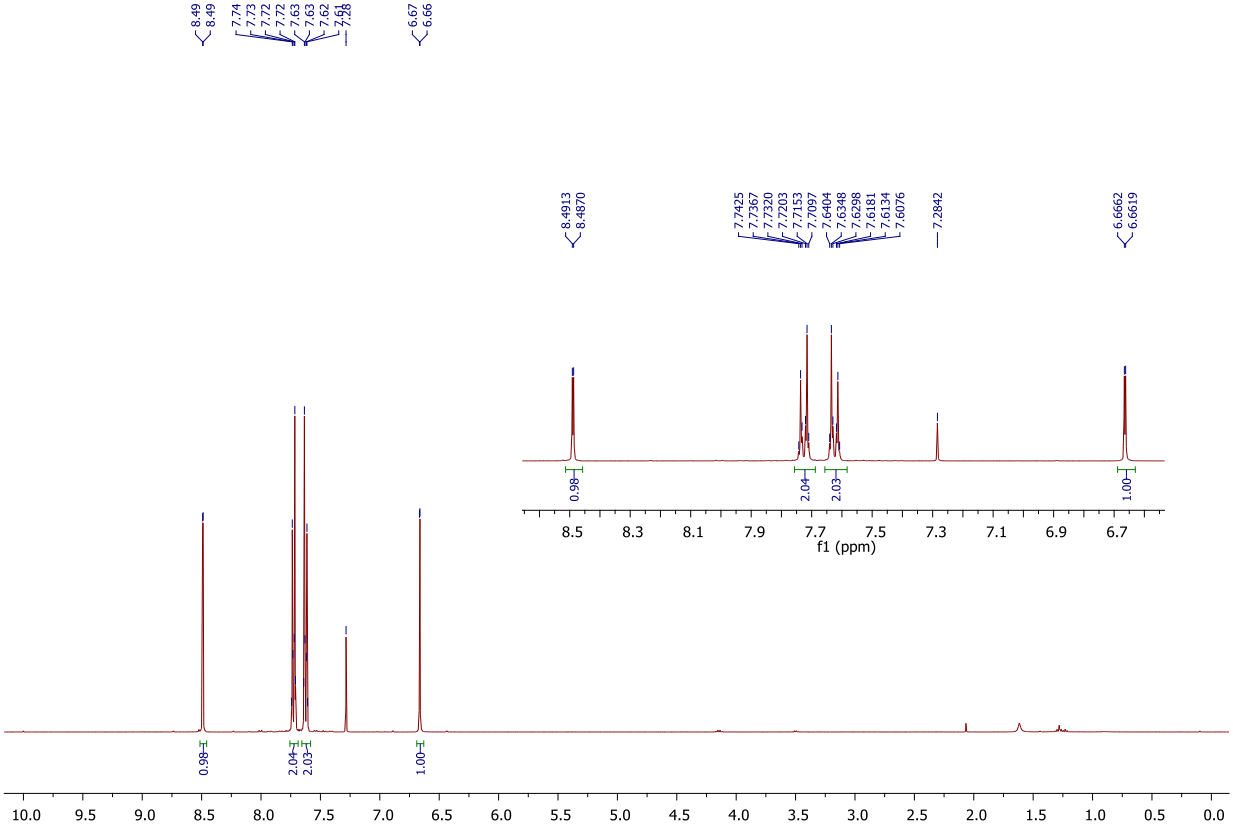
3-(3-Bromophenyl)isoxazole **4i** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

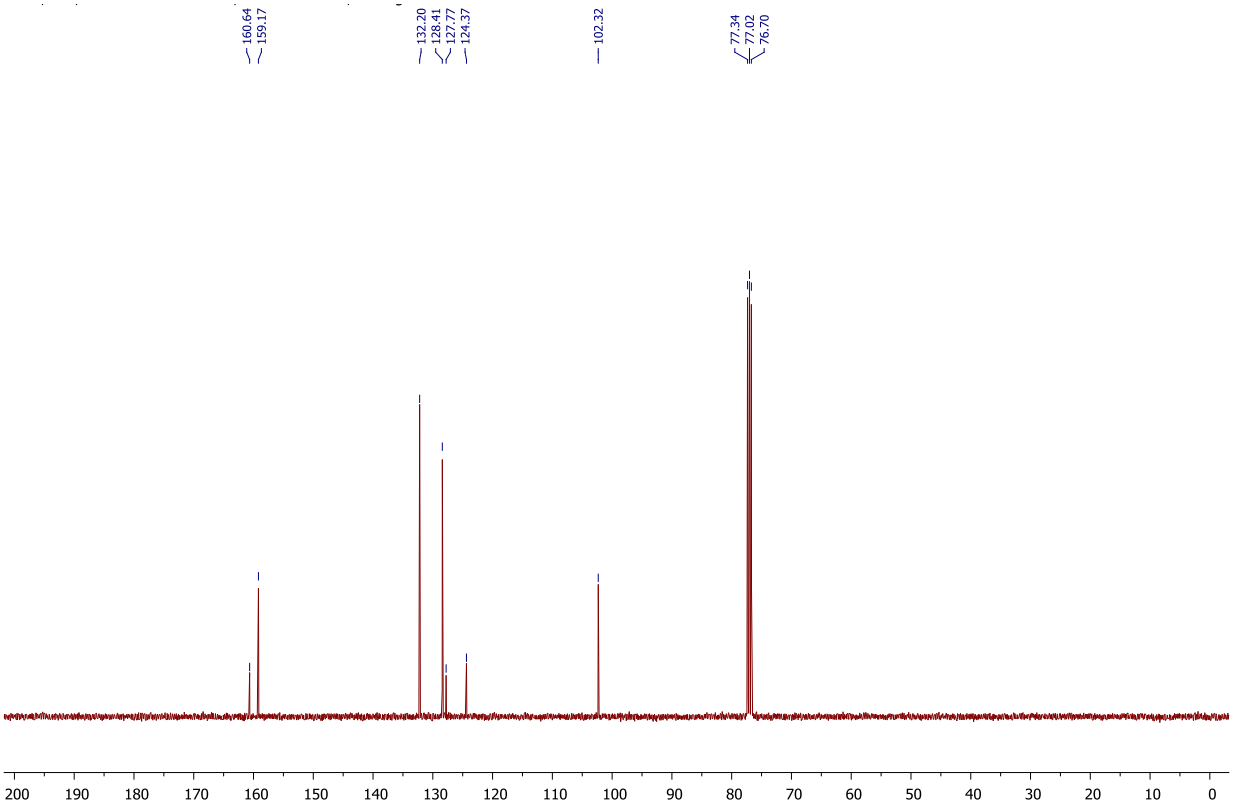


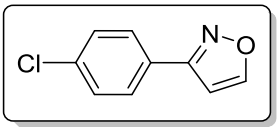




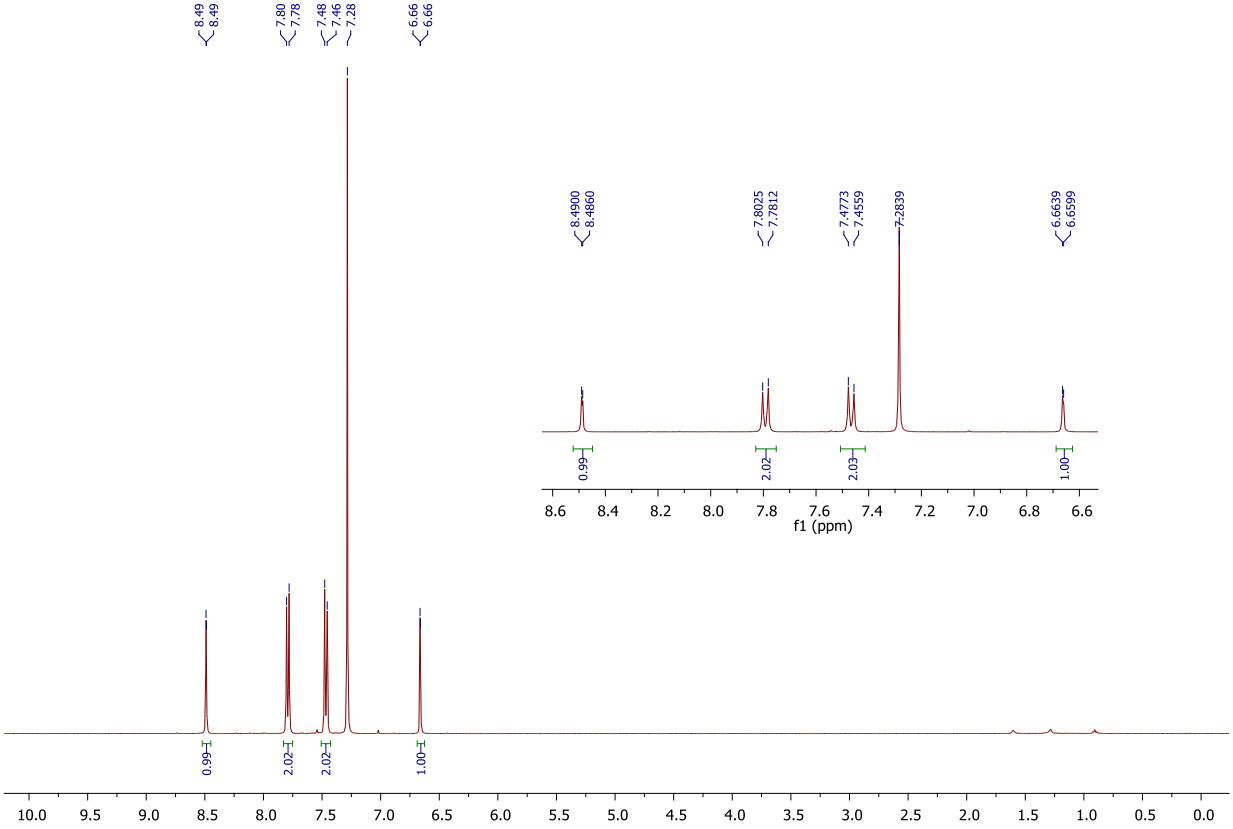
3-(4-Bromophenyl)isoxazole **4j** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

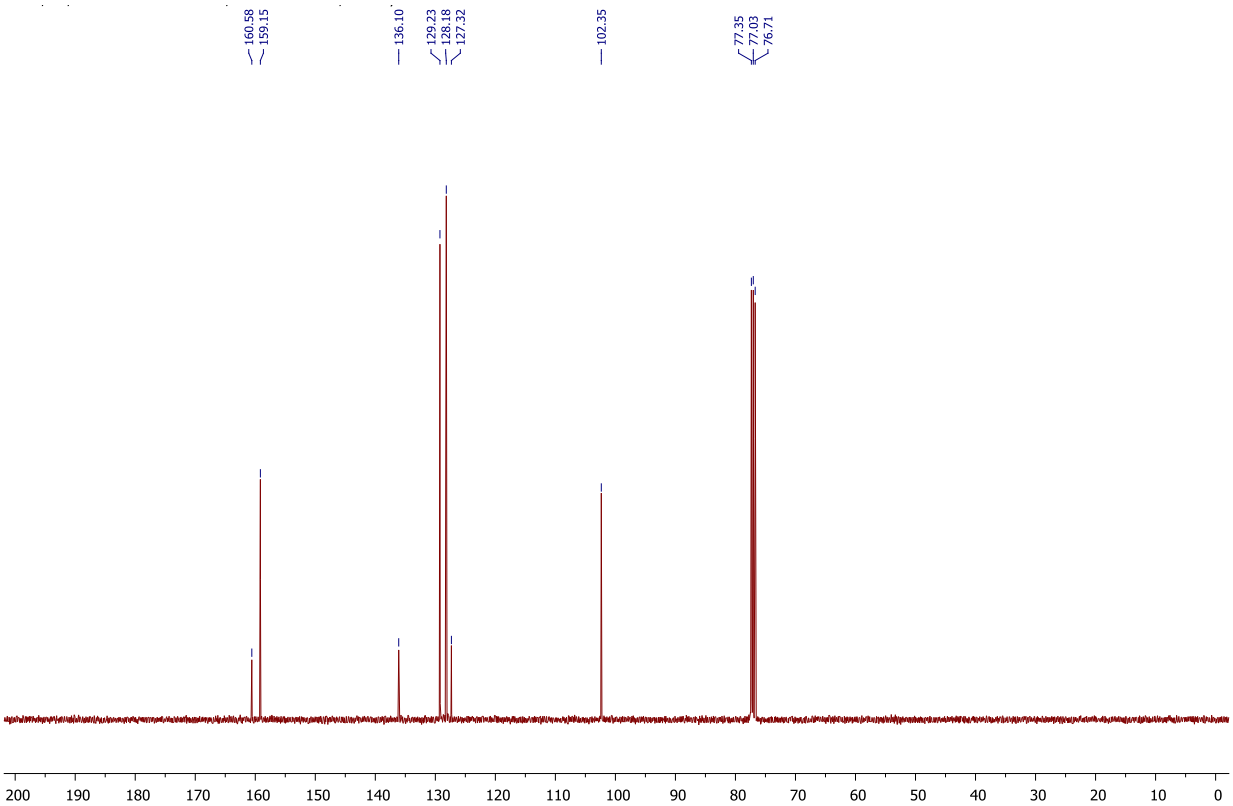


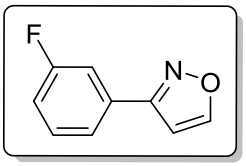




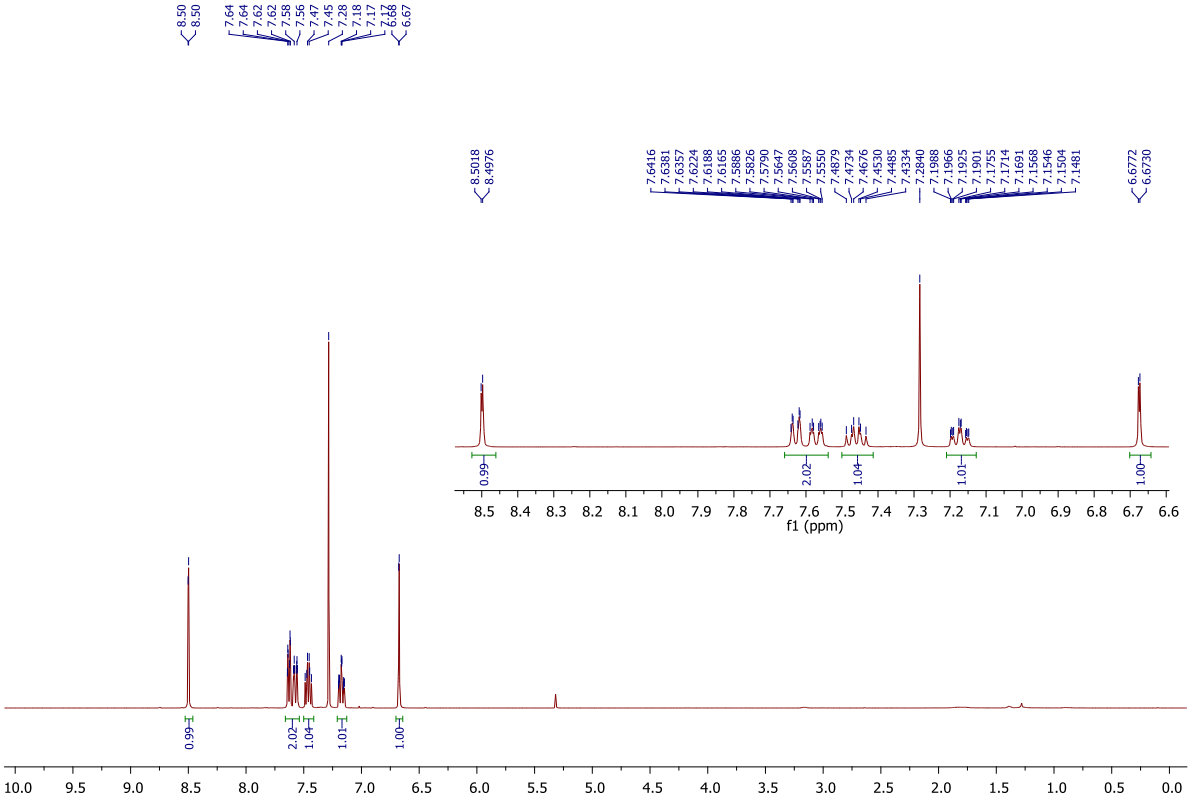
3-(4-Chlorophenyl)isoxazole **4k** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

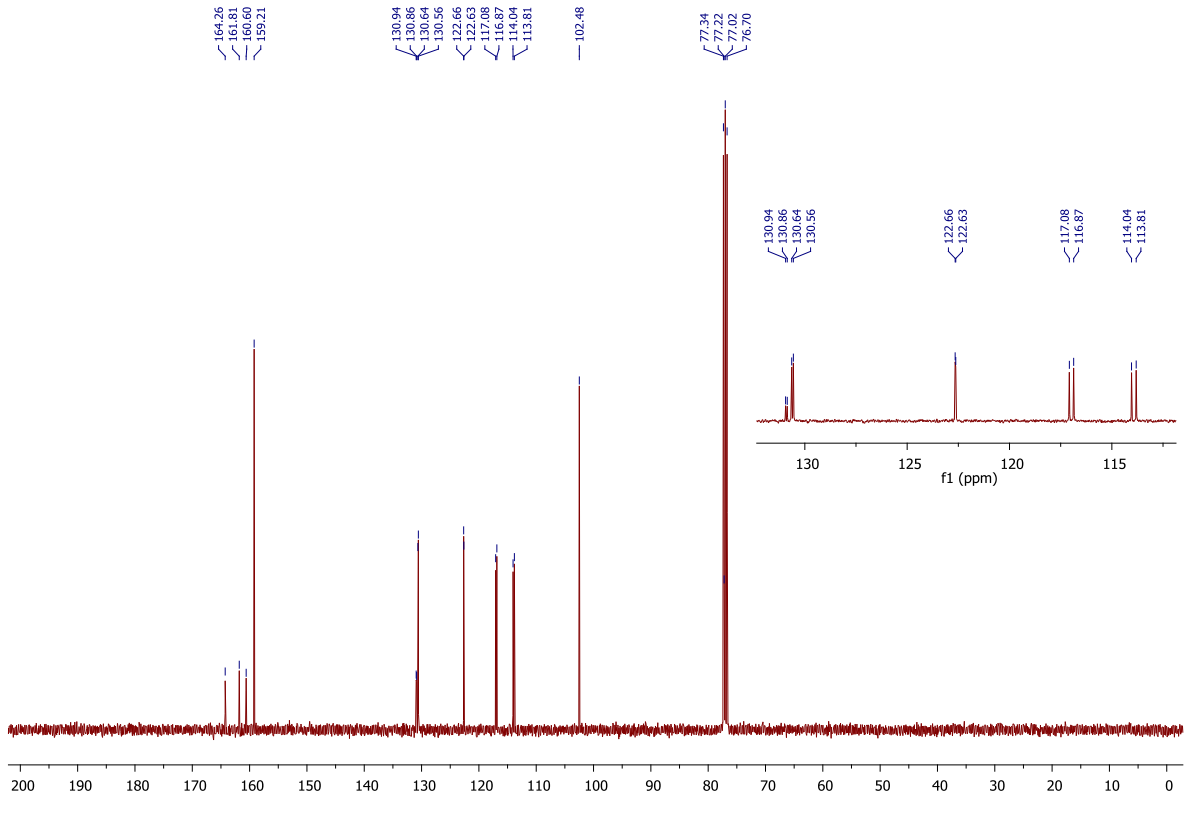


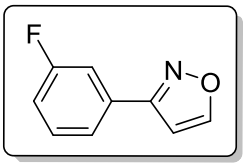




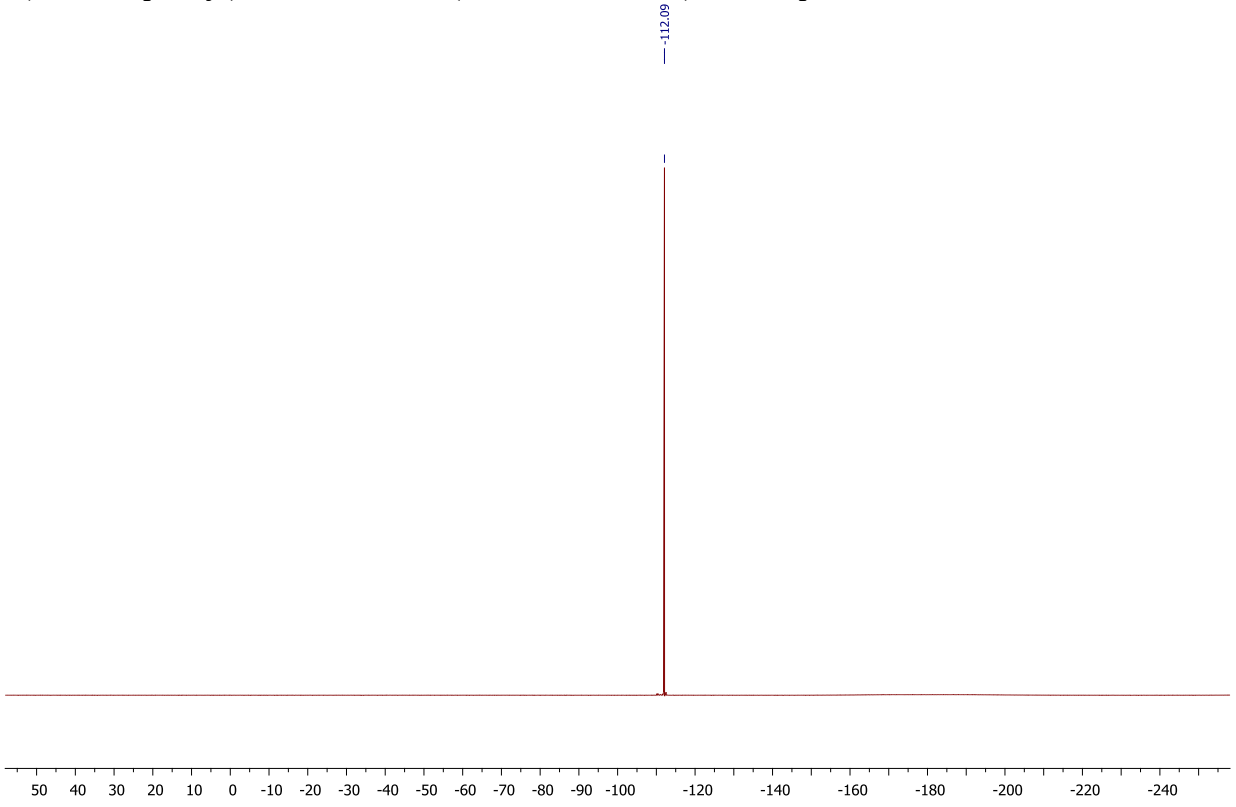
3-(3-Fluorophenyl)isoxazole **4l** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

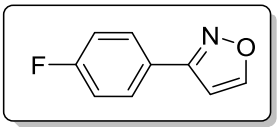




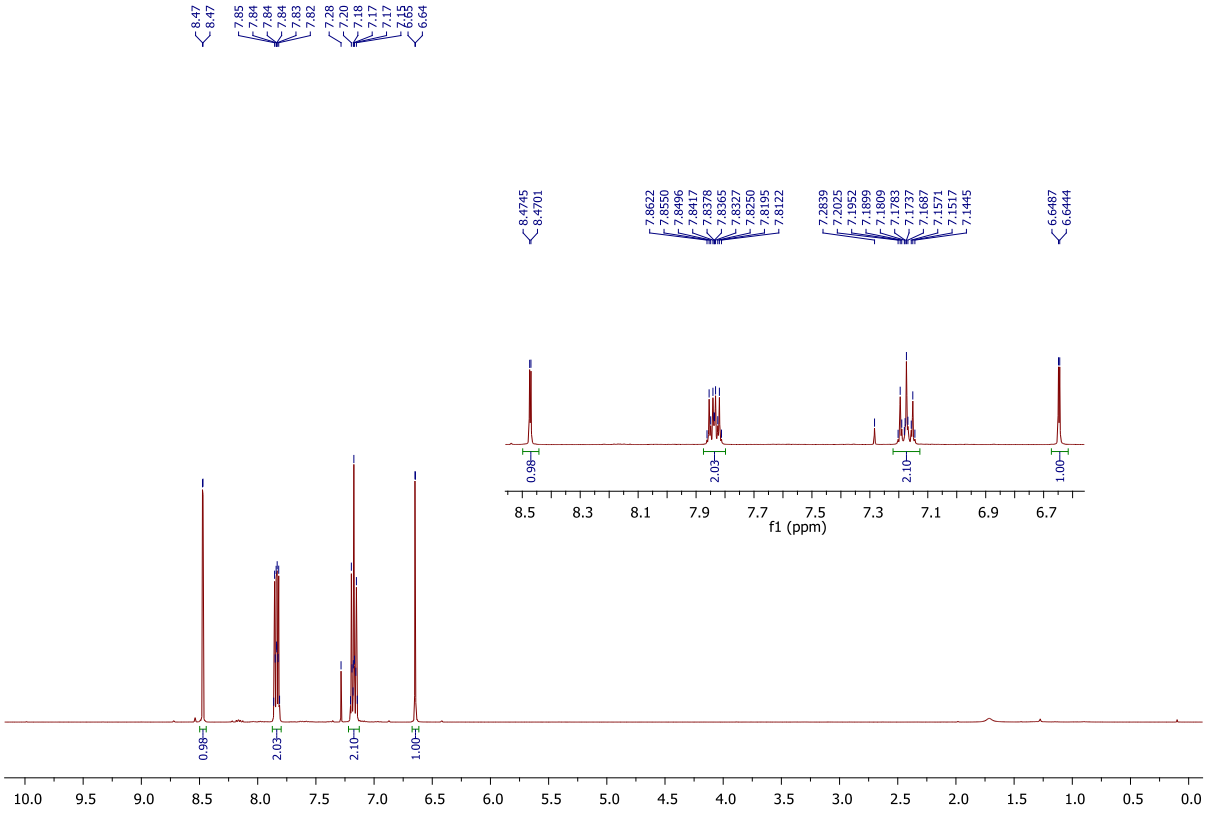


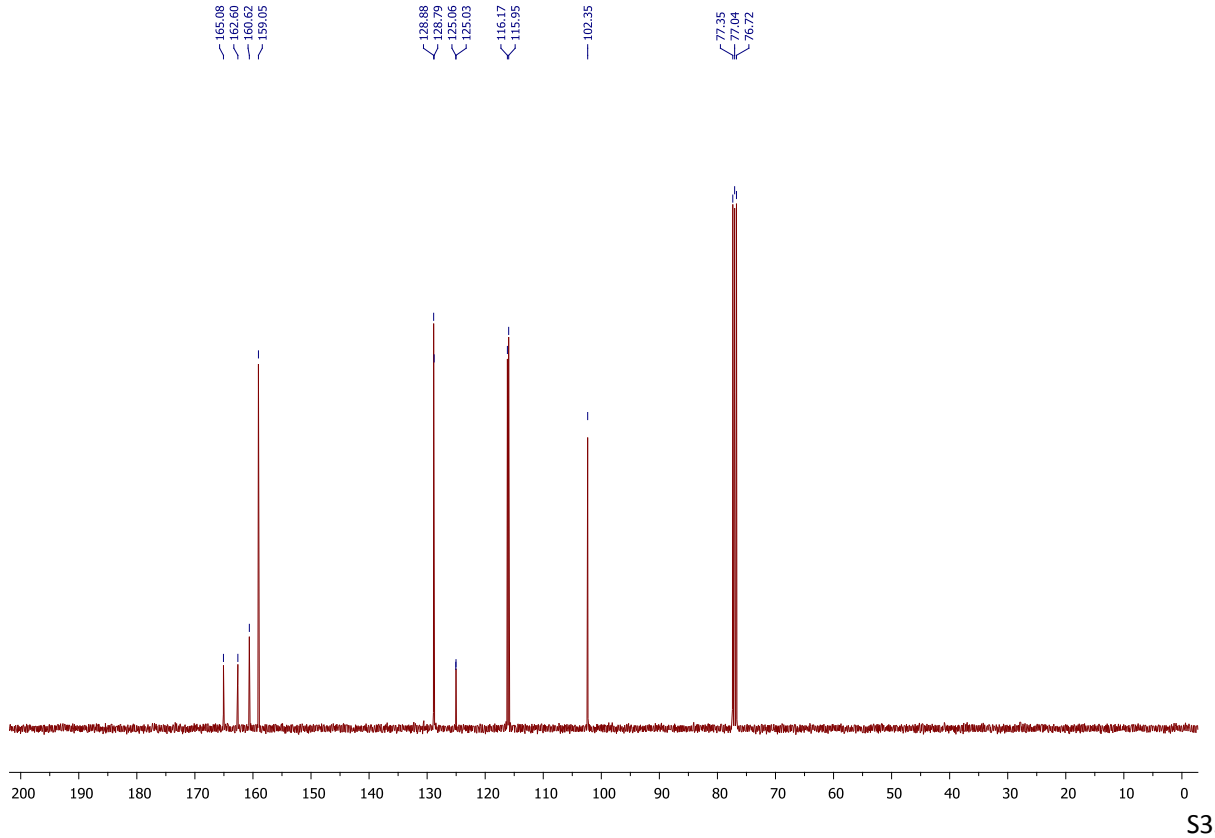
3-(3-Fluorophenyl)isoxazole **4l** ^{19}F (376 MHz, $CDCl_3$) NMR-spectra.

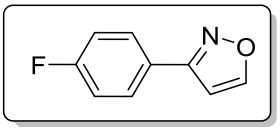




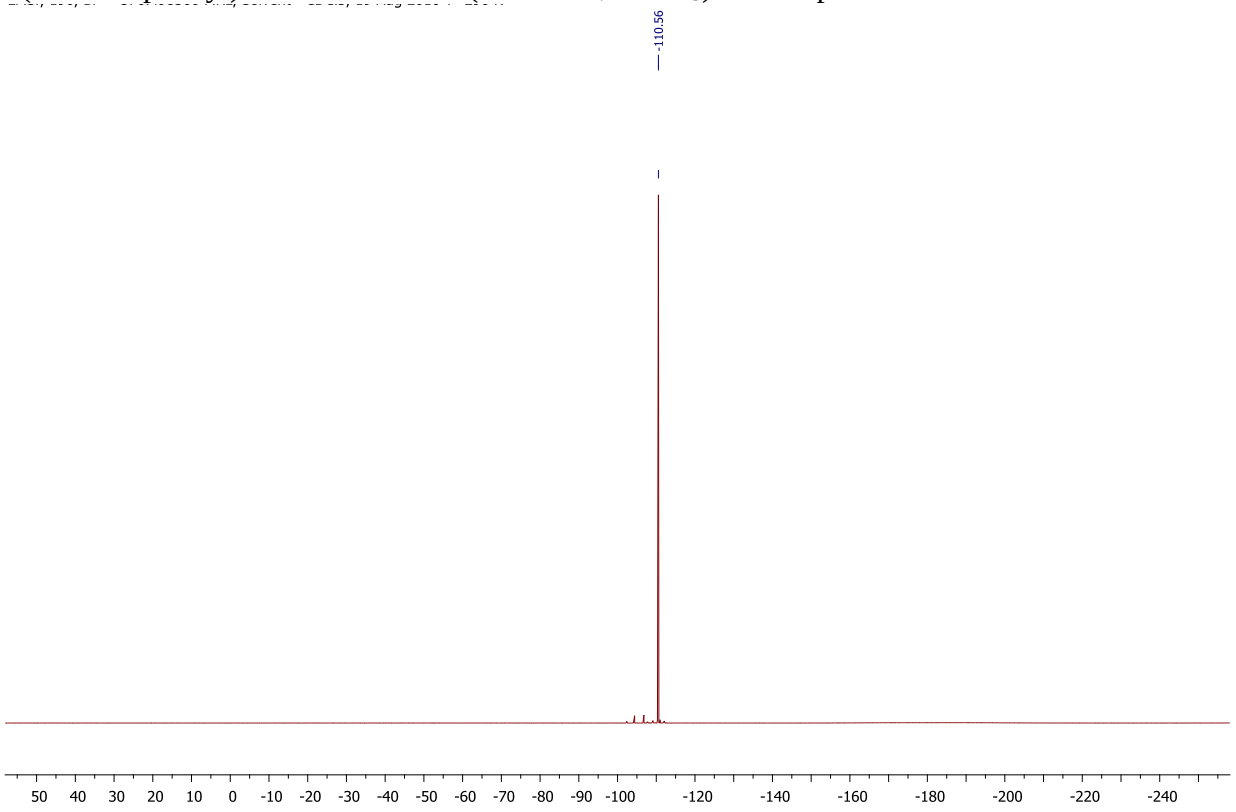
3-(4-Fluorophenyl)isoxazole **4m** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

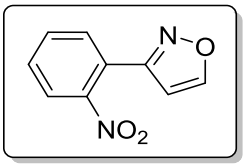




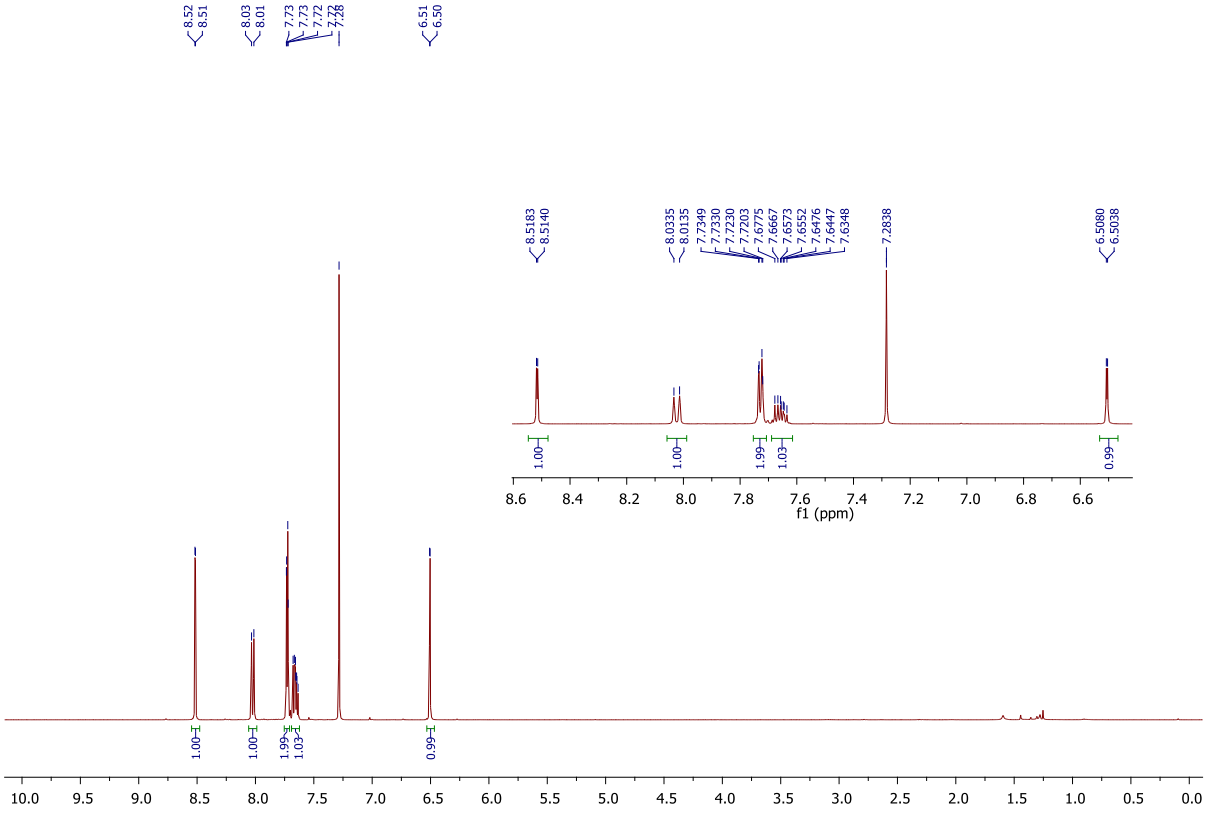


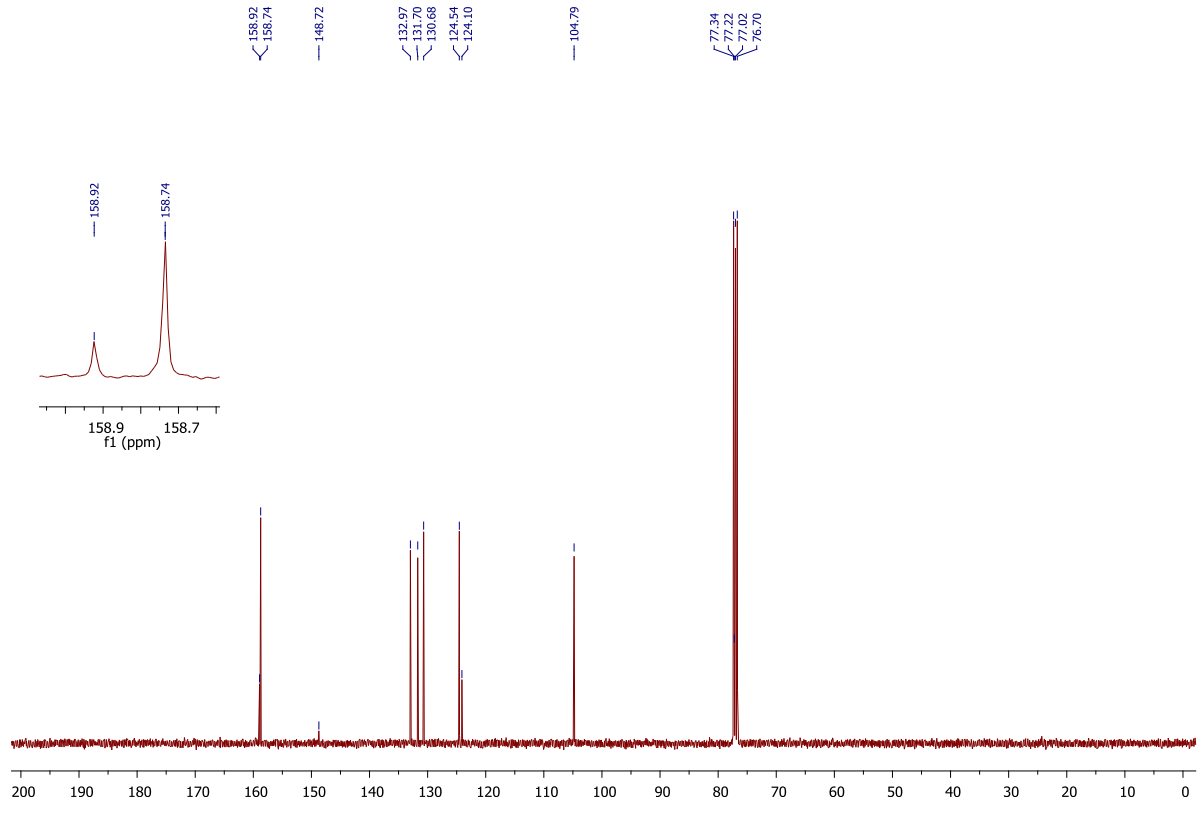
3-(4-Fluorophenyl)isoxazole **4m** ^{19}F (376 MHz, $CDCl_3$) NMR-spectra.

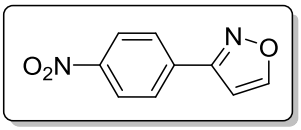




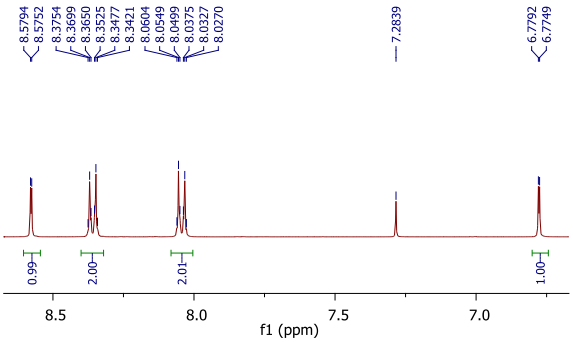
3-(2-Nitrophenyl)isoxazole **4n** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

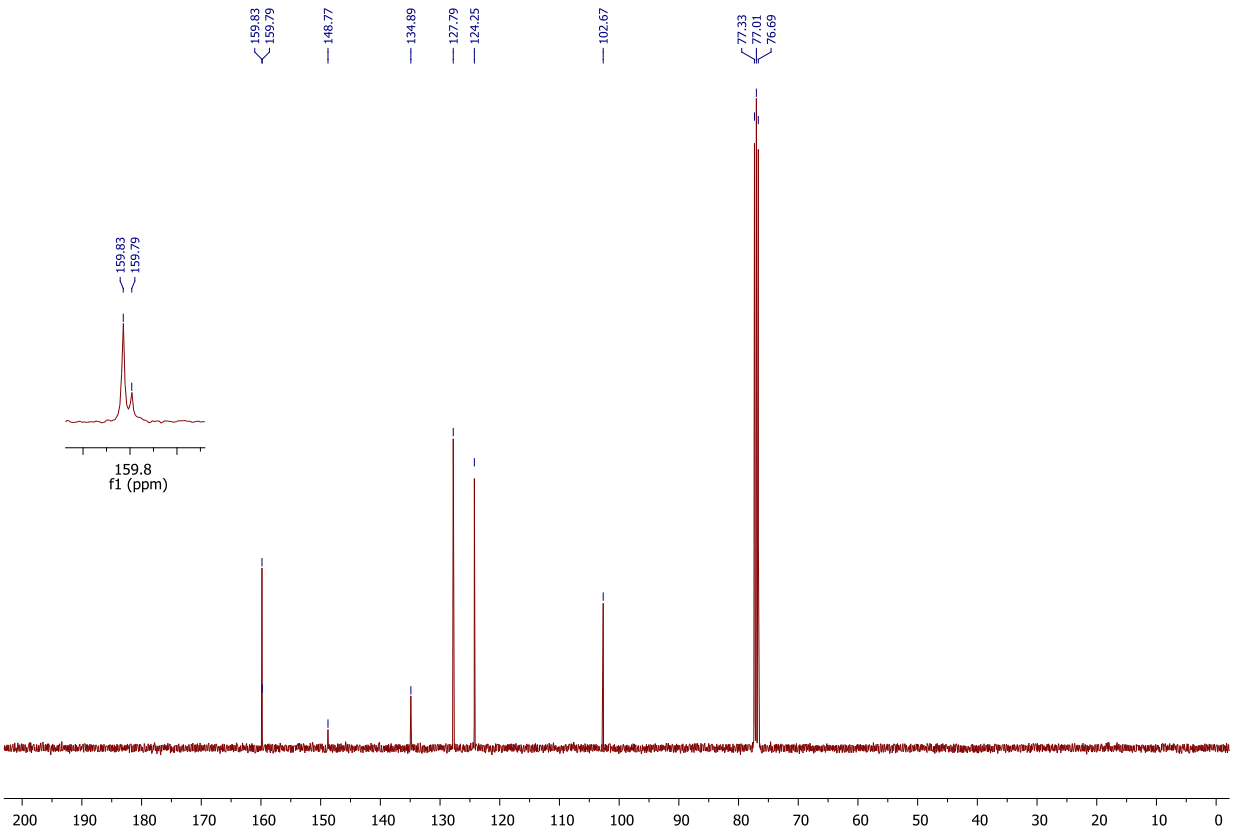


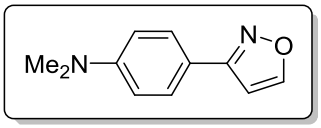




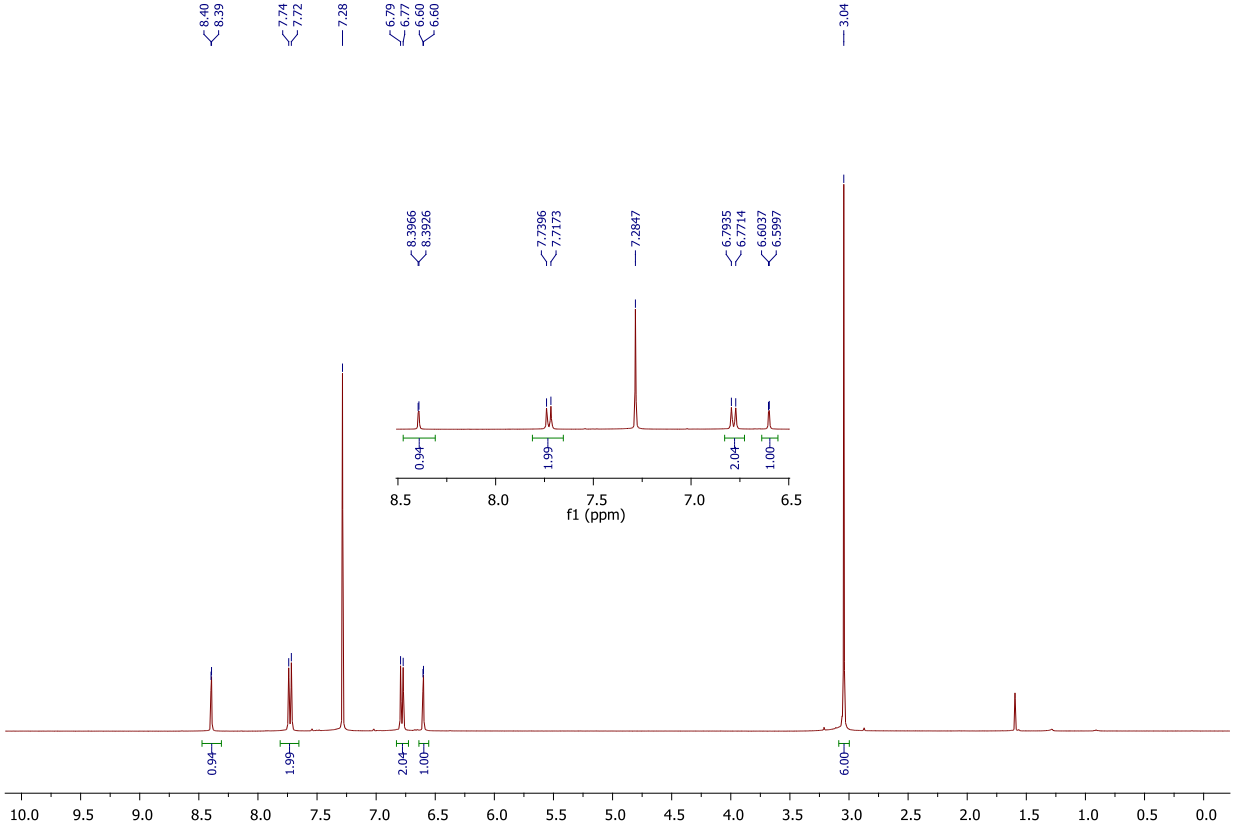
3-(4-Nitrophenyl)isoxazole **4o** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

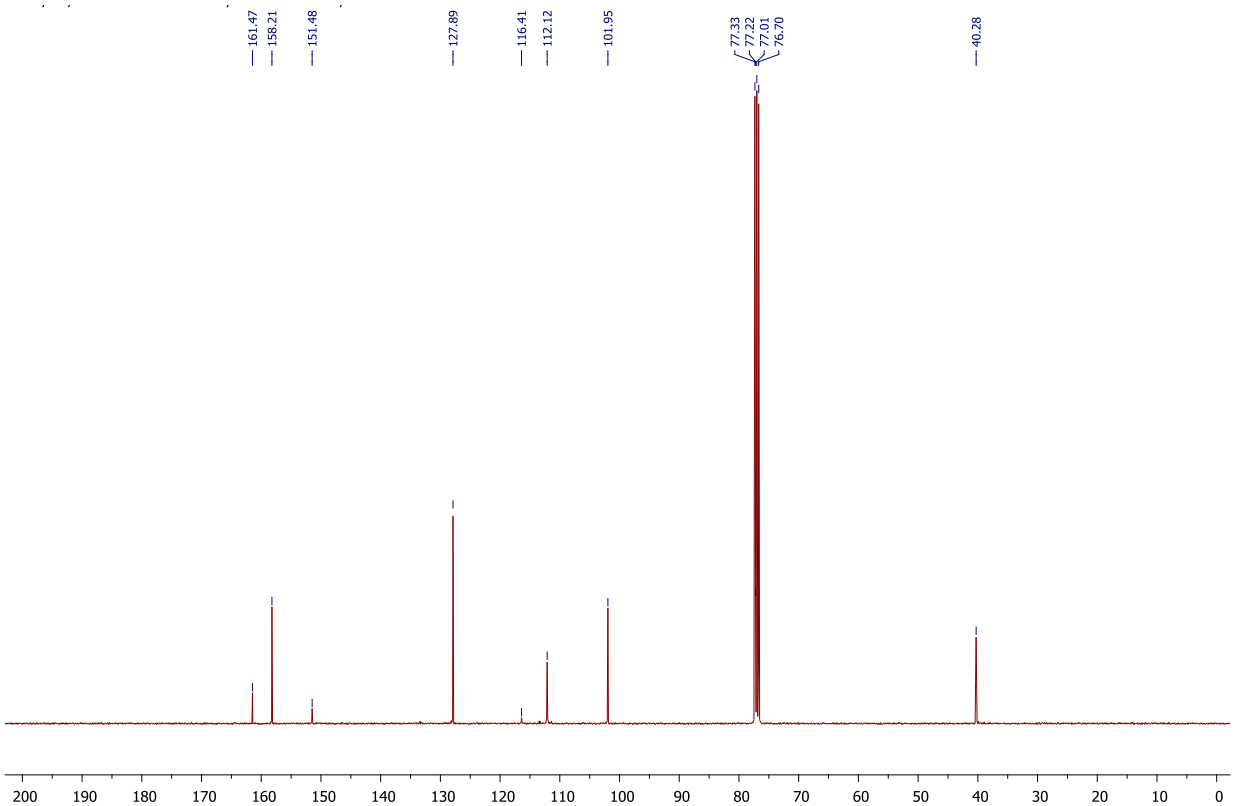


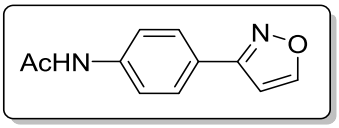




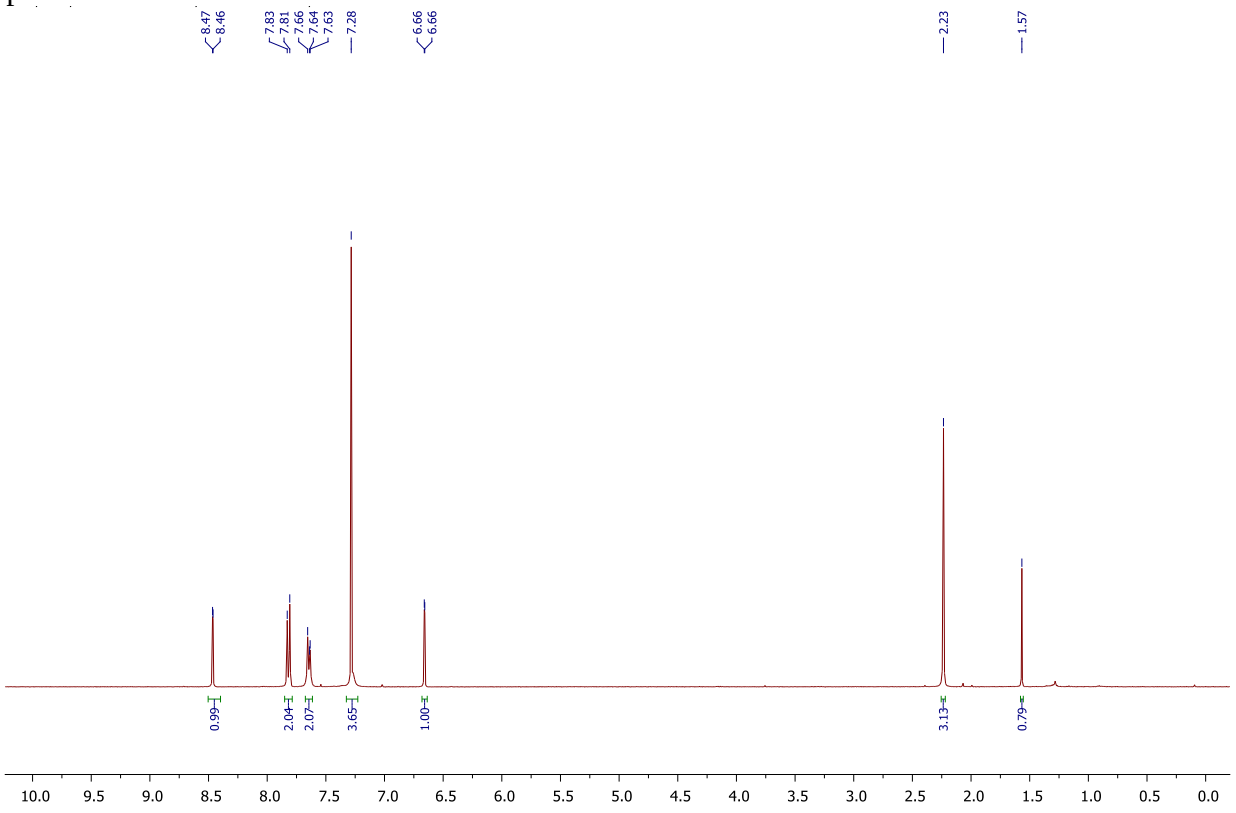
3-(4-Dimethylaminophenyl)isoxazole **4p** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

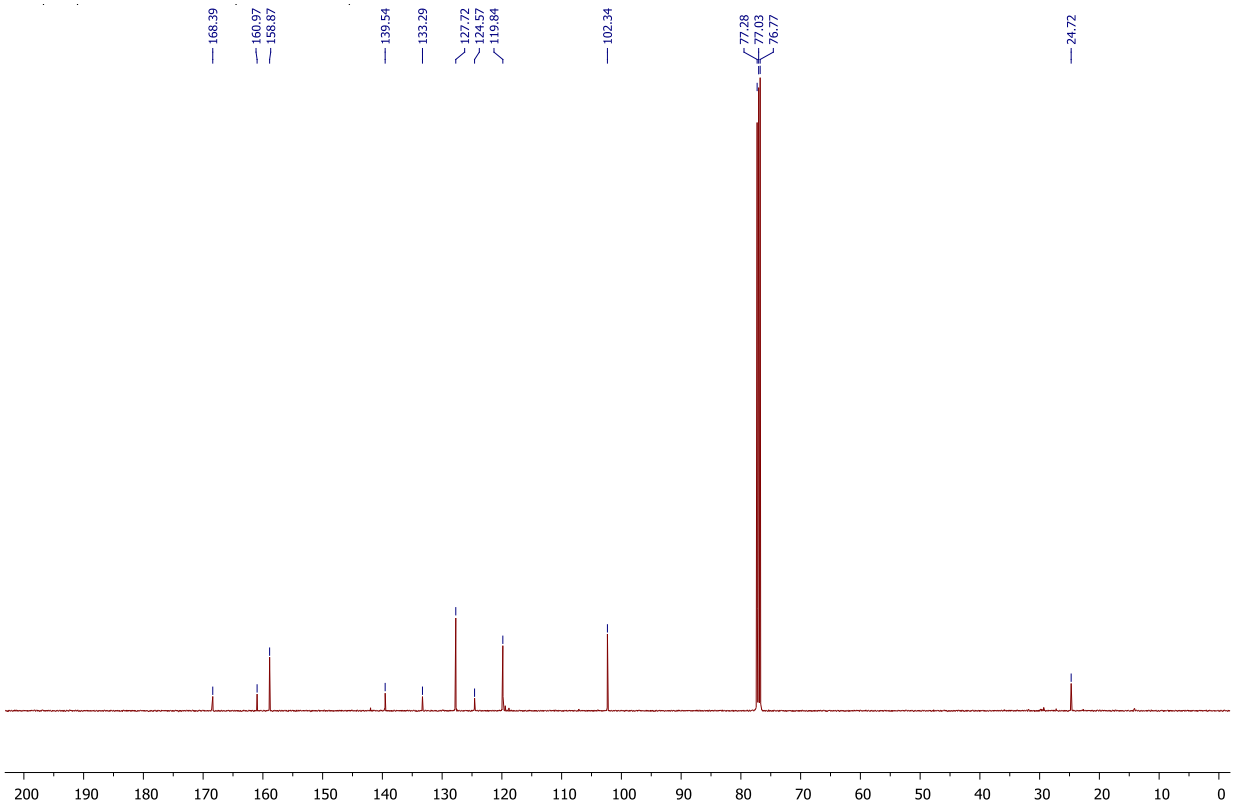


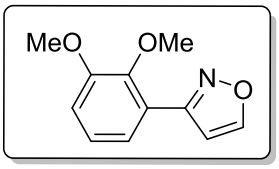




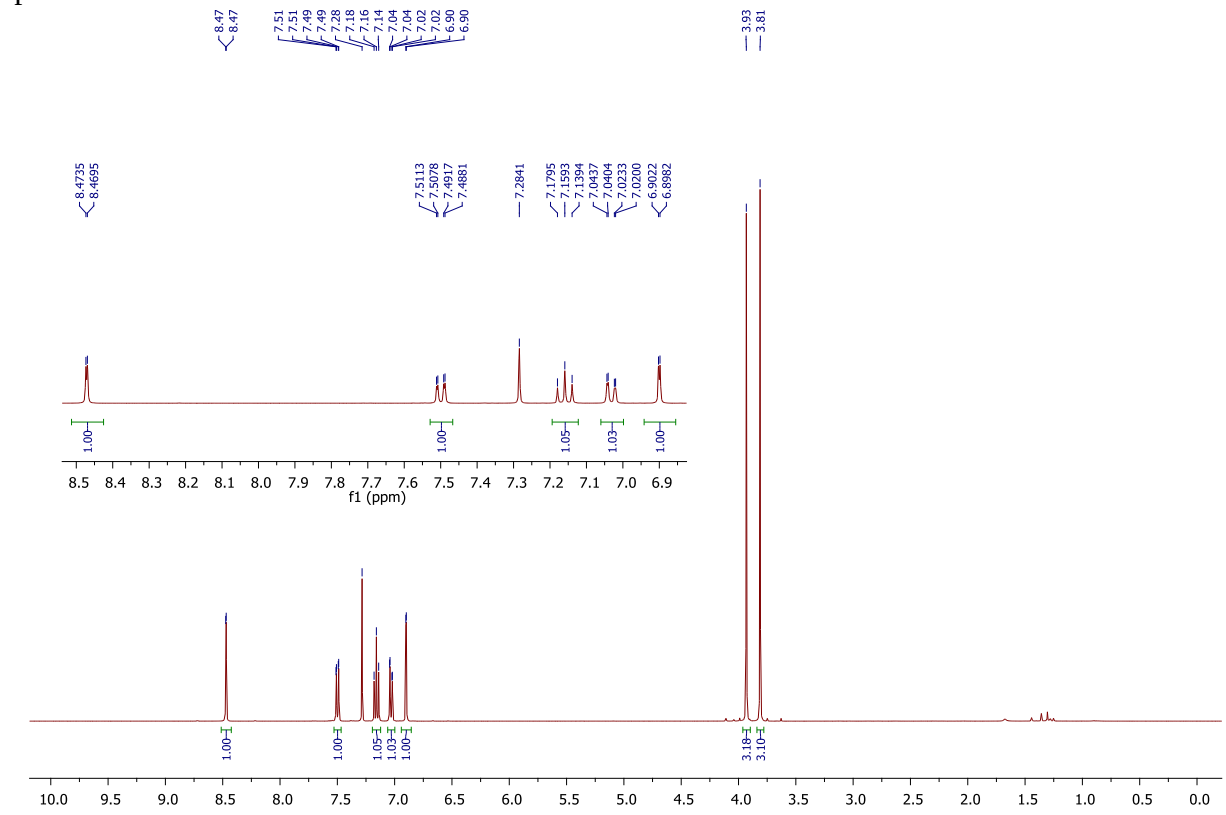
3-(4-Acetamidophenyl)isoxazole **4q** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

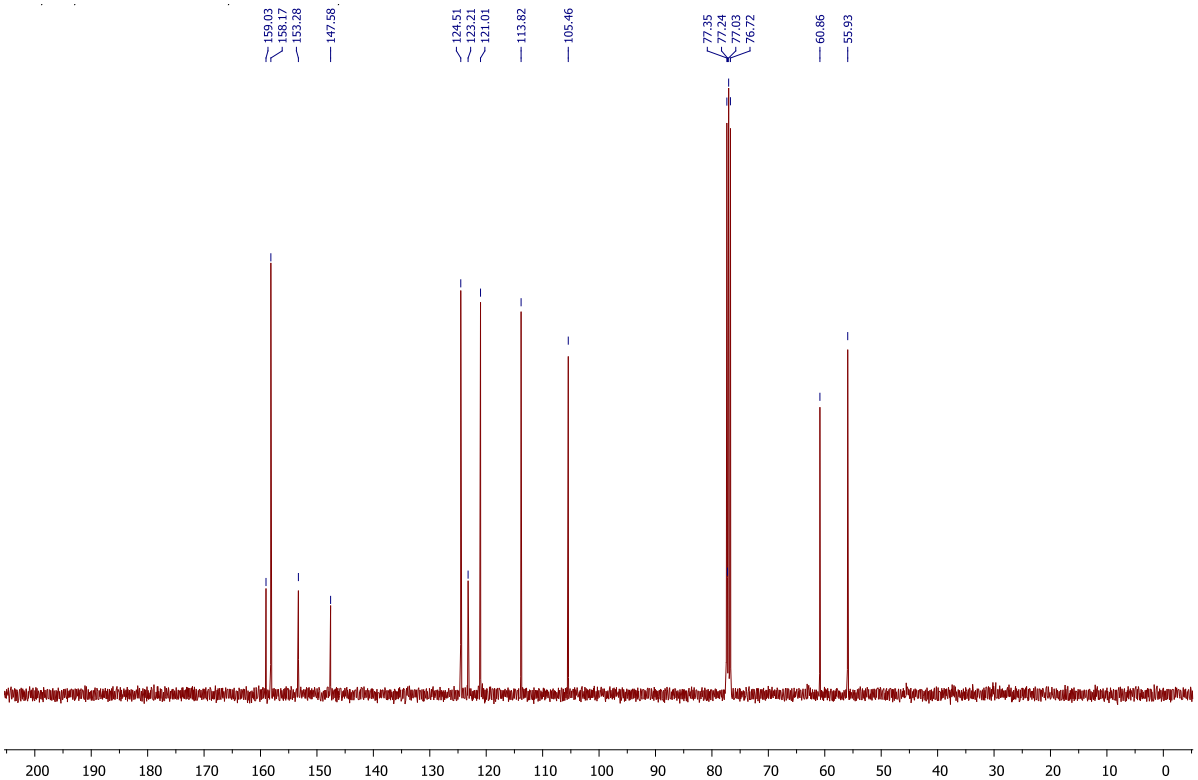


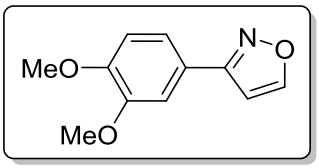




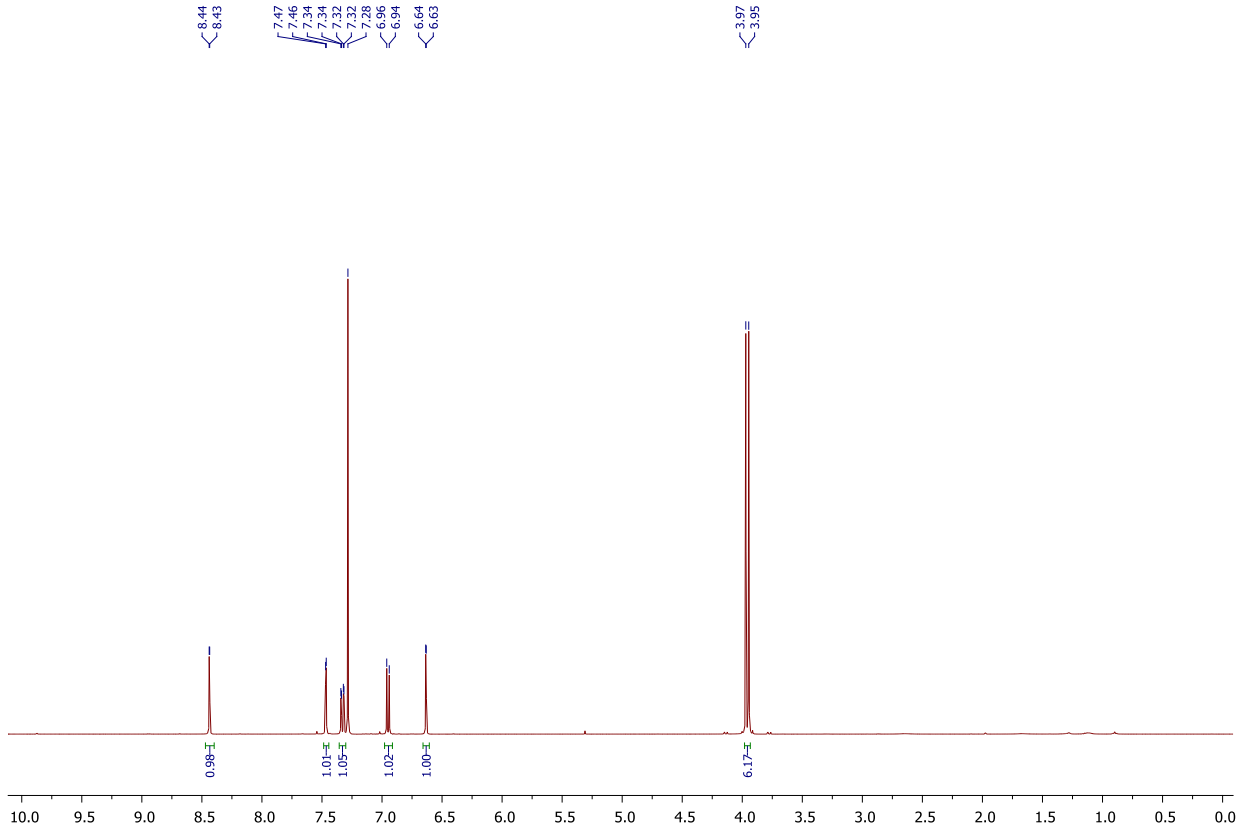
3-(2,3-Dimethoxyphenyl)isoxazole **4r** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

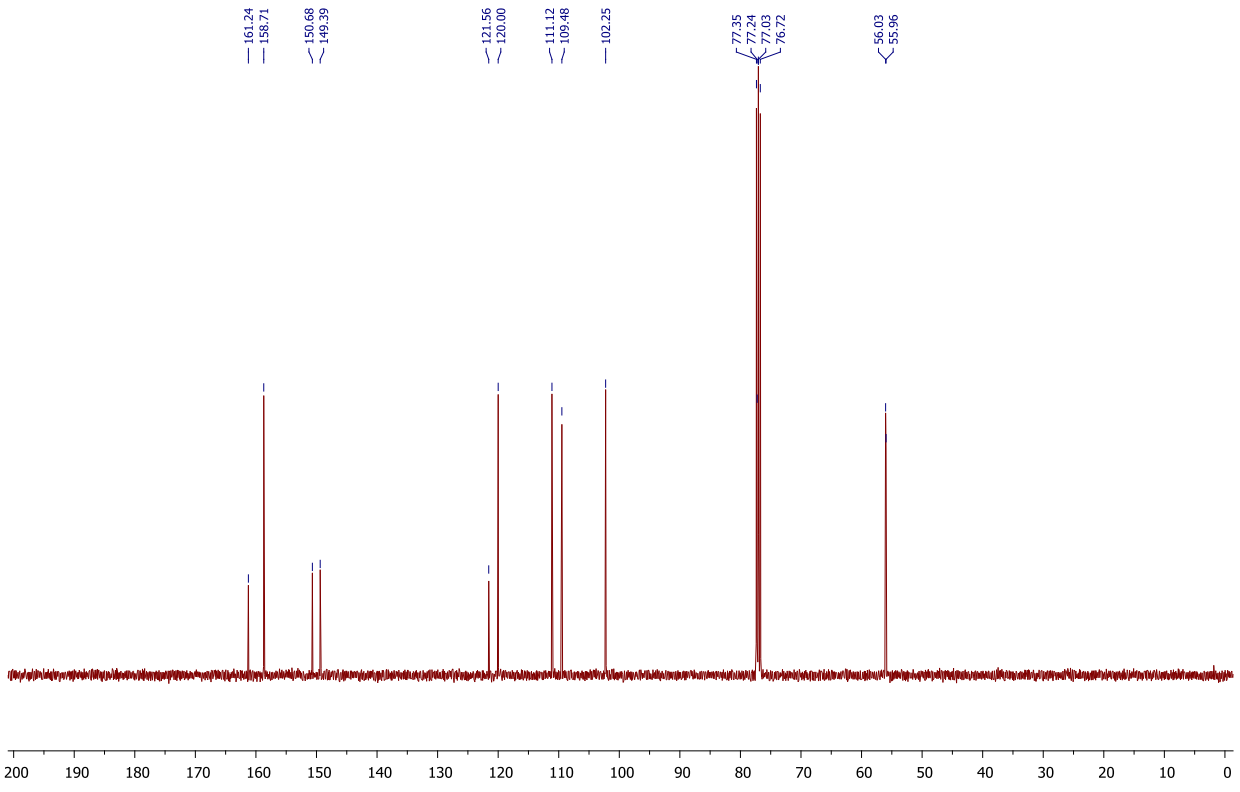


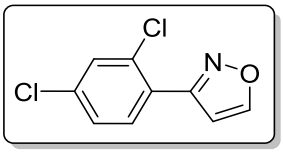




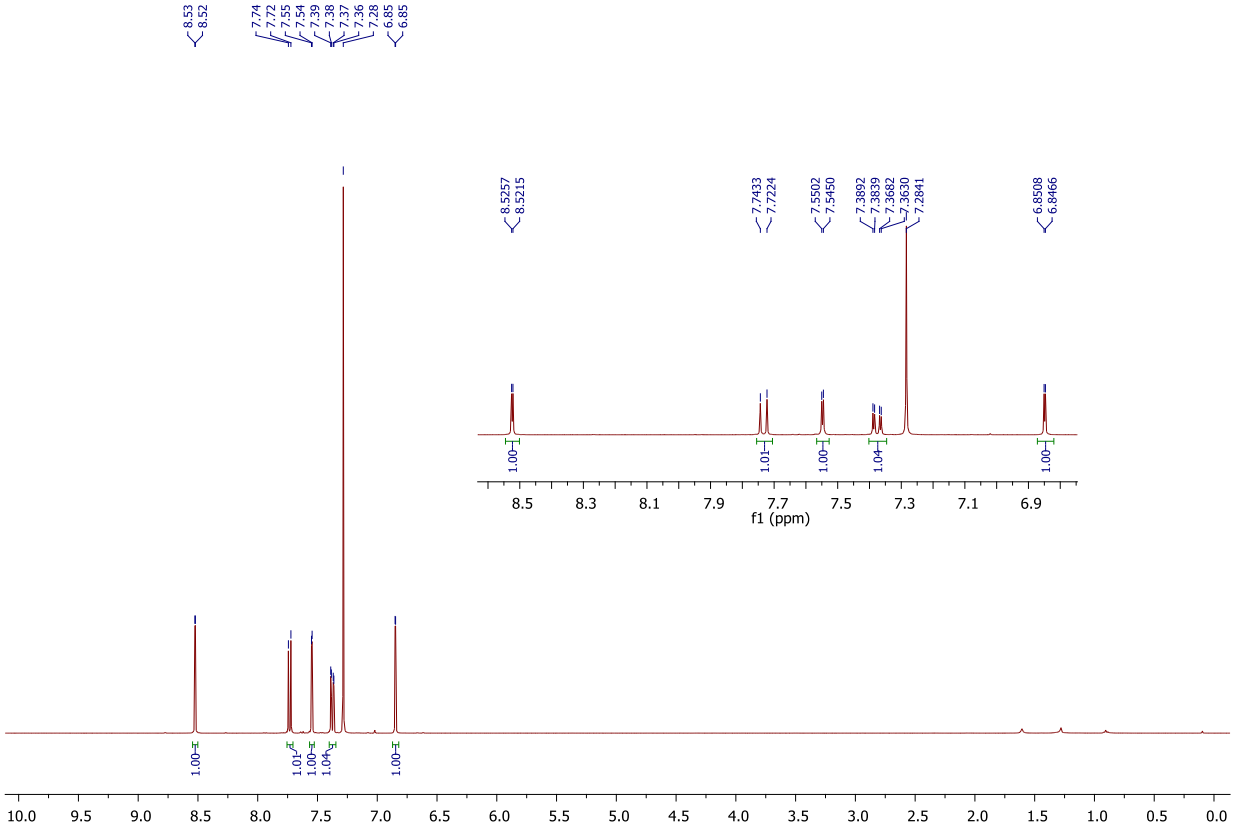
3-(3,4-Dimethoxyphenyl)isoxazole **4s** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

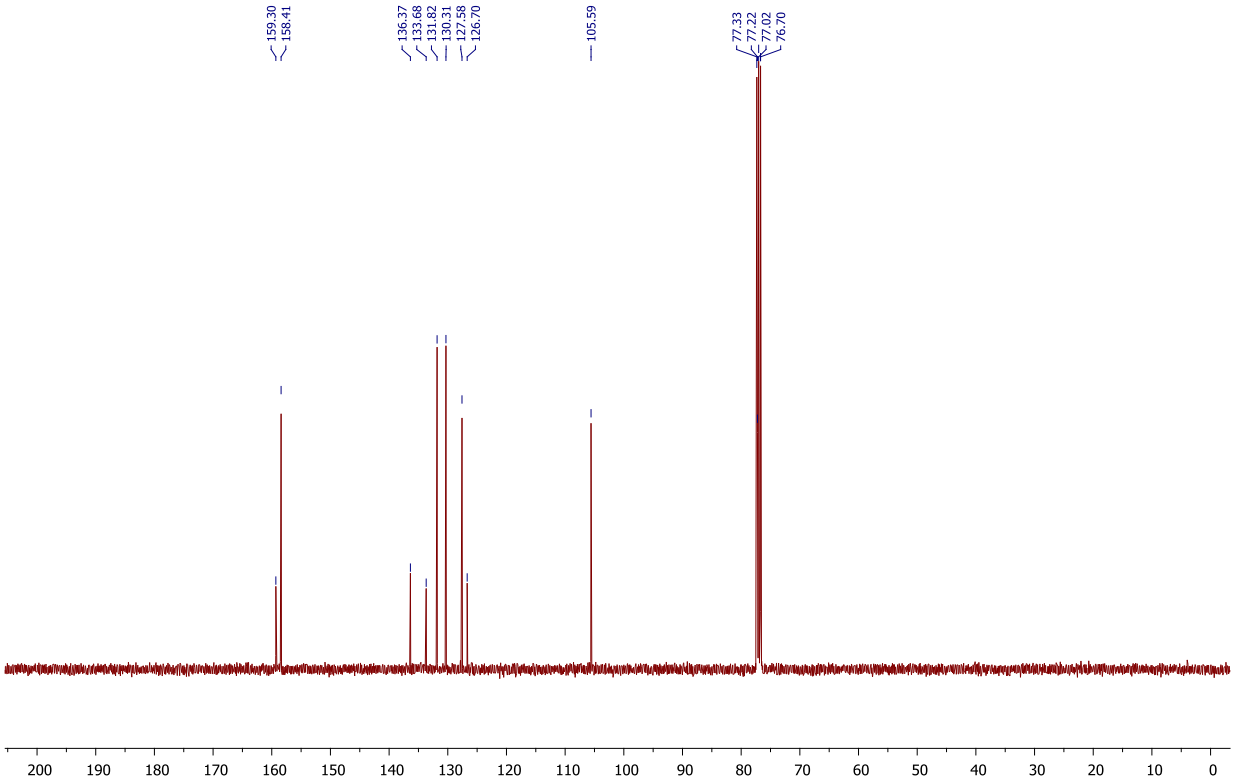


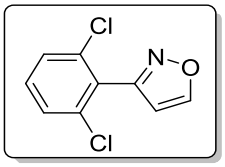




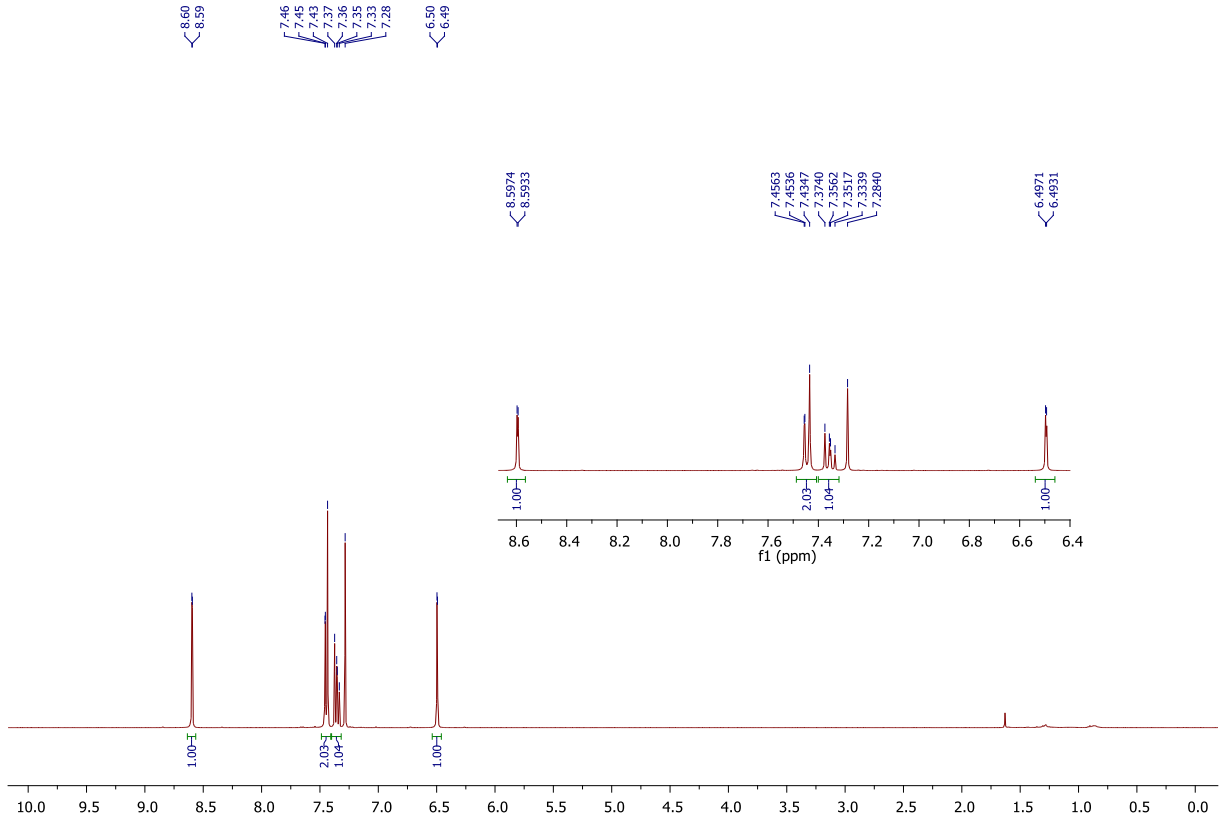
3-(2,4-Dichlorophenyl)isoxazole **4t** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

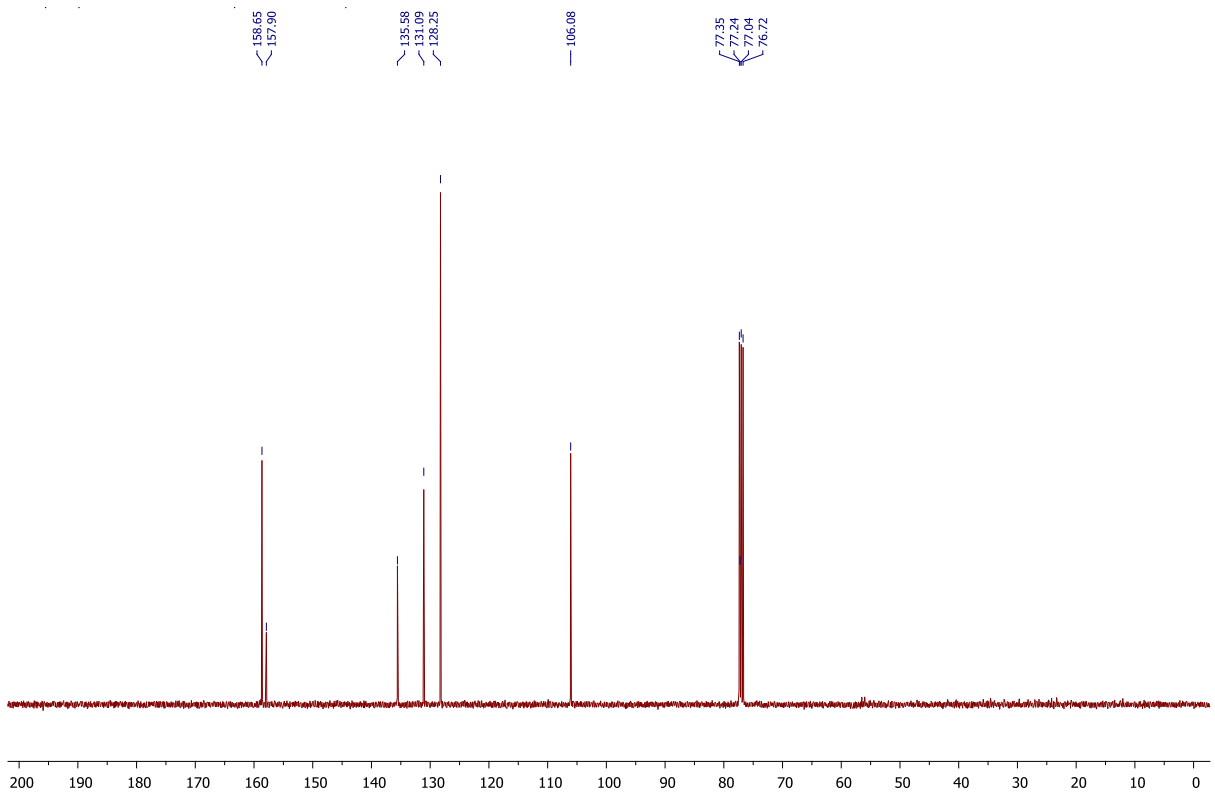


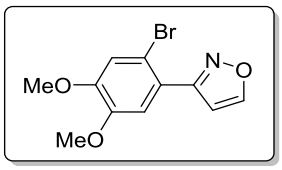




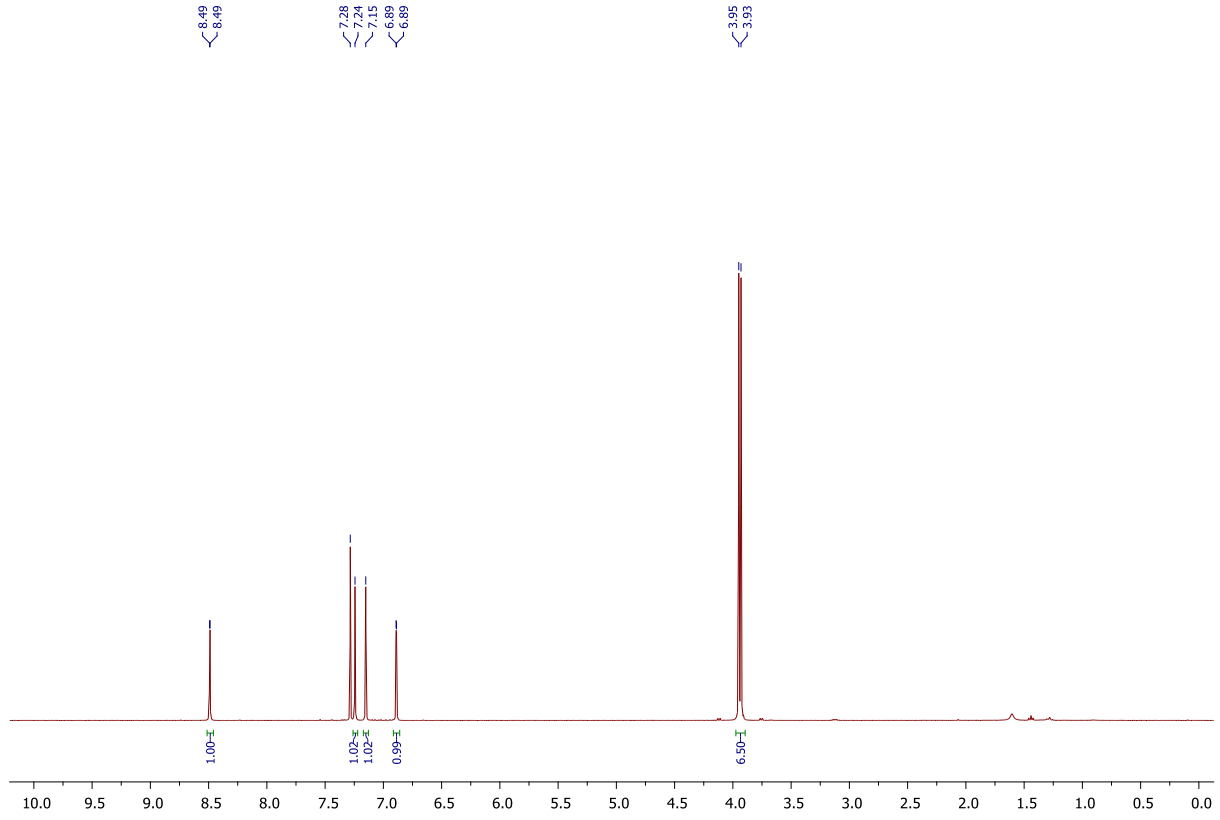
3-(2,6-Dichlorophenyl)isoxazole **4u** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

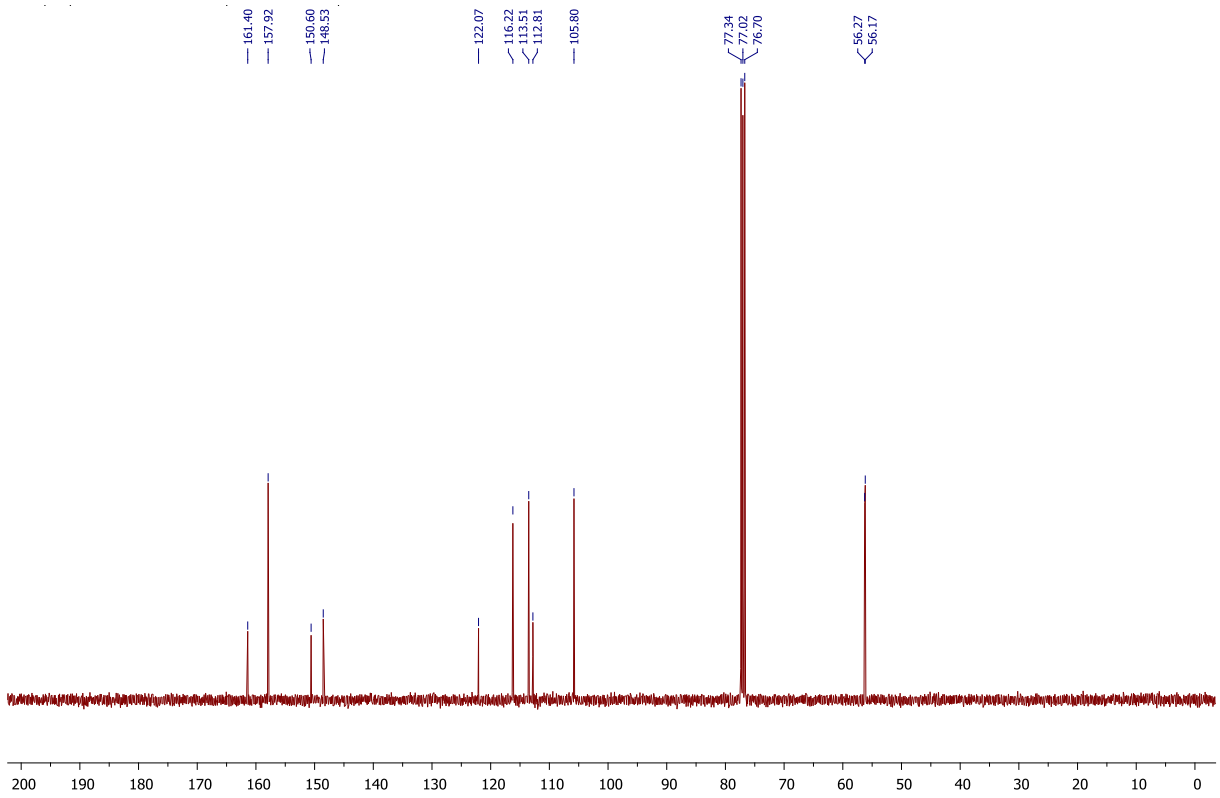


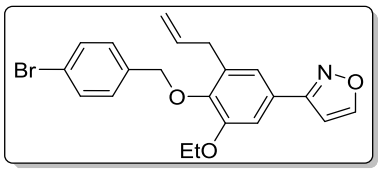




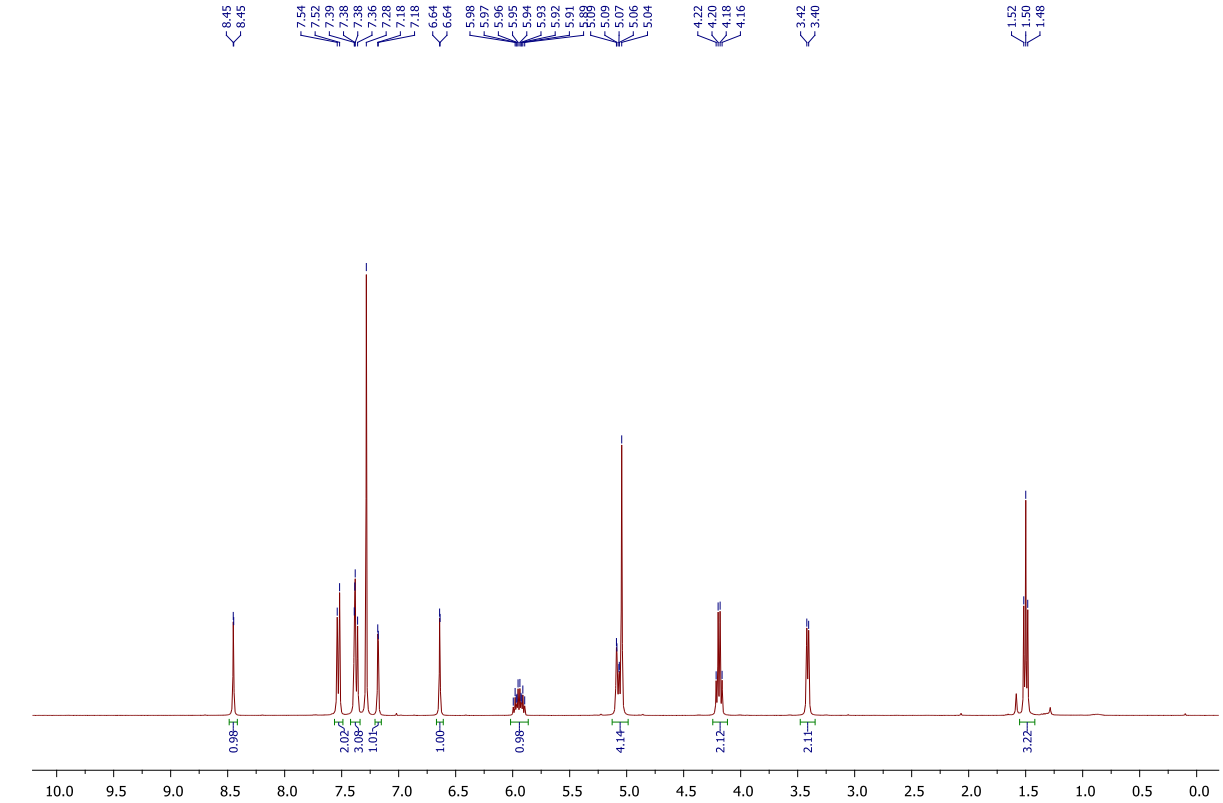
3-(2-Bromo-4,5-dimethoxyphenyl)isoxazole **4v** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

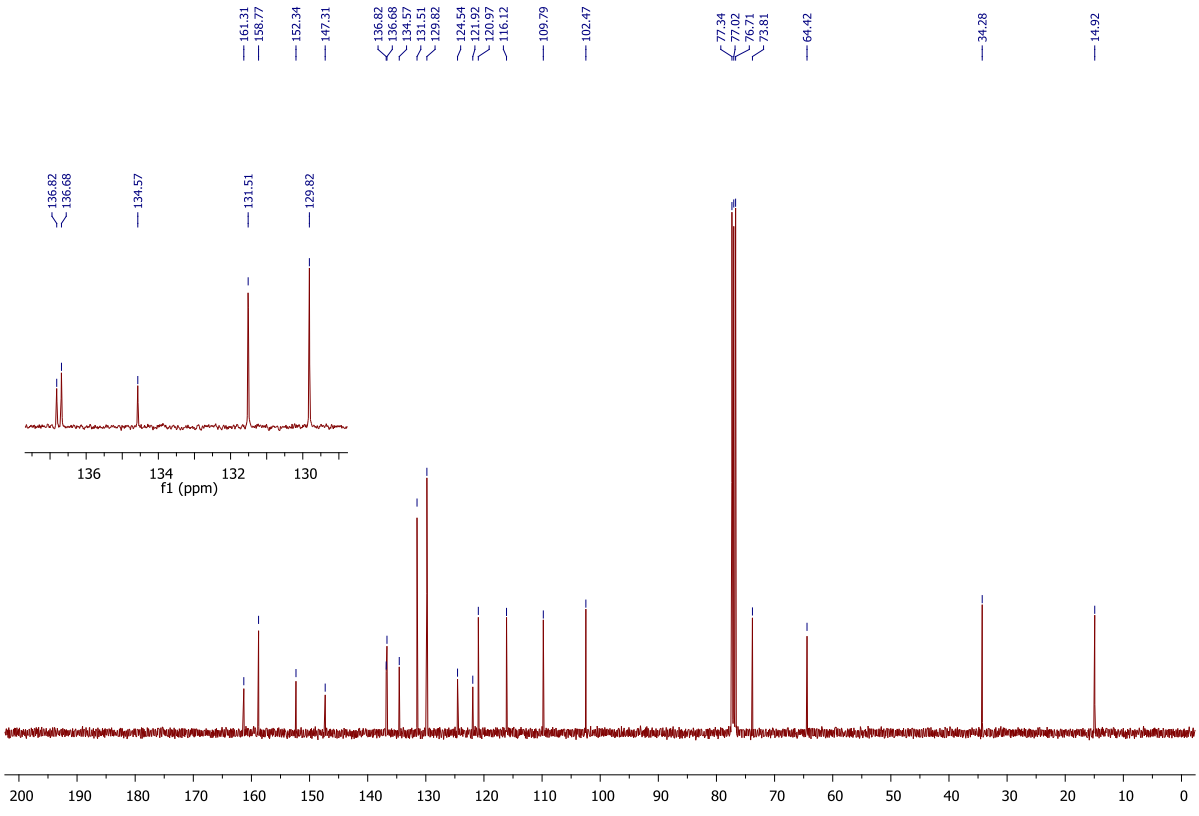


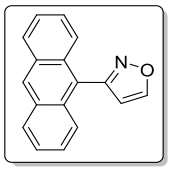




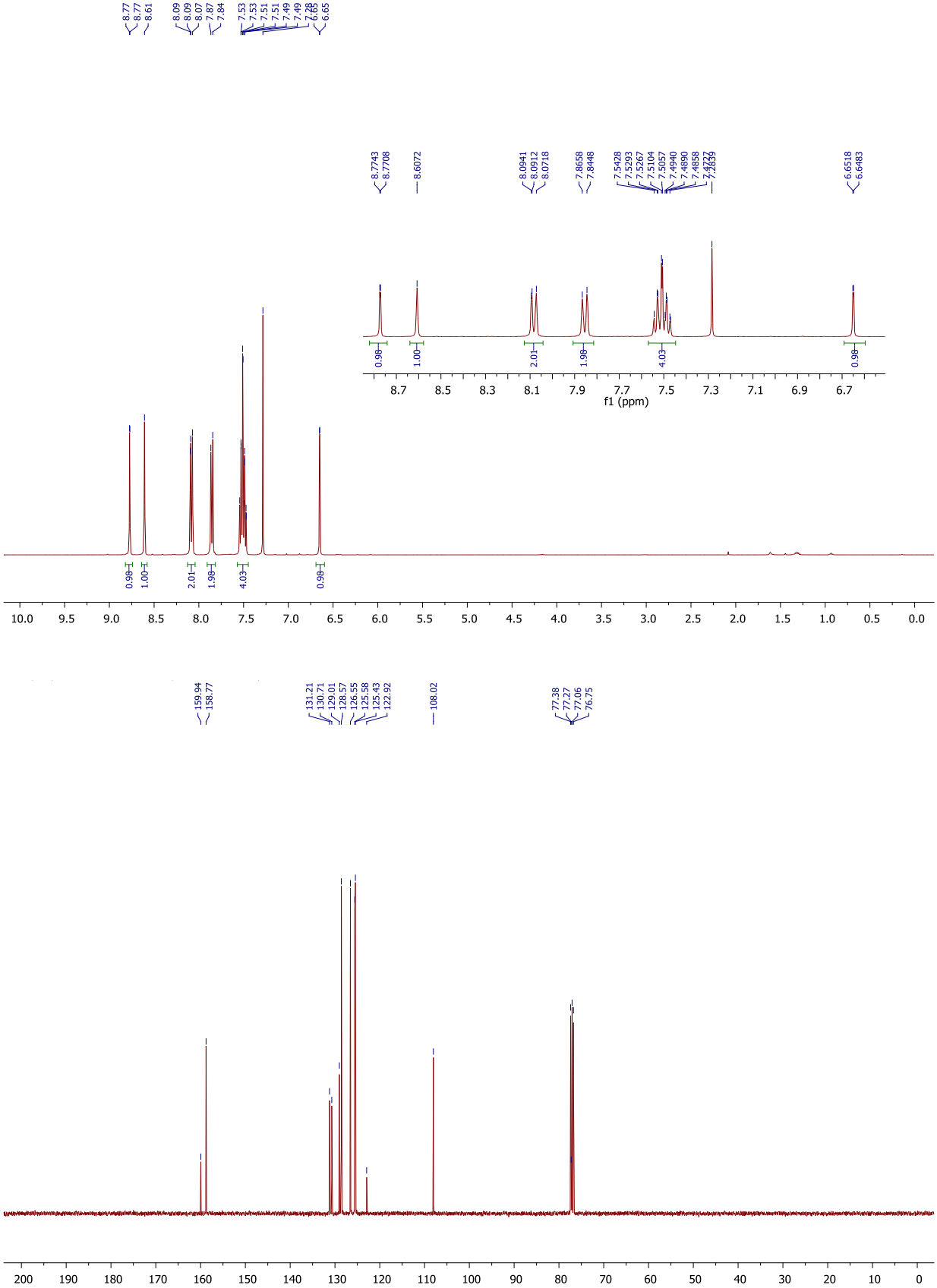
3-(3-Allyl-4-((4-bromobenzyl)oxy)-5-ethoxyphenyl)isoxazole **4w** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

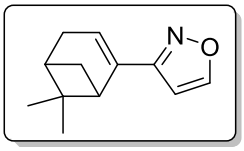




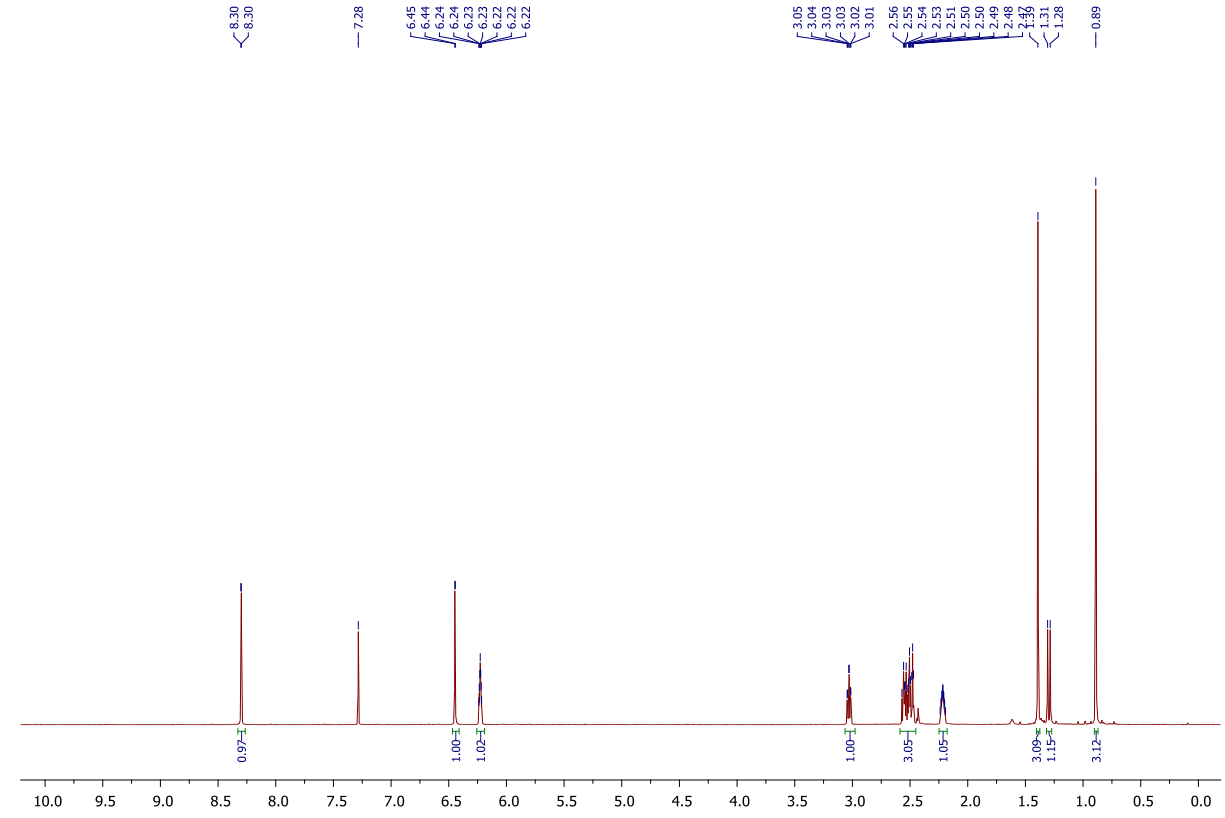


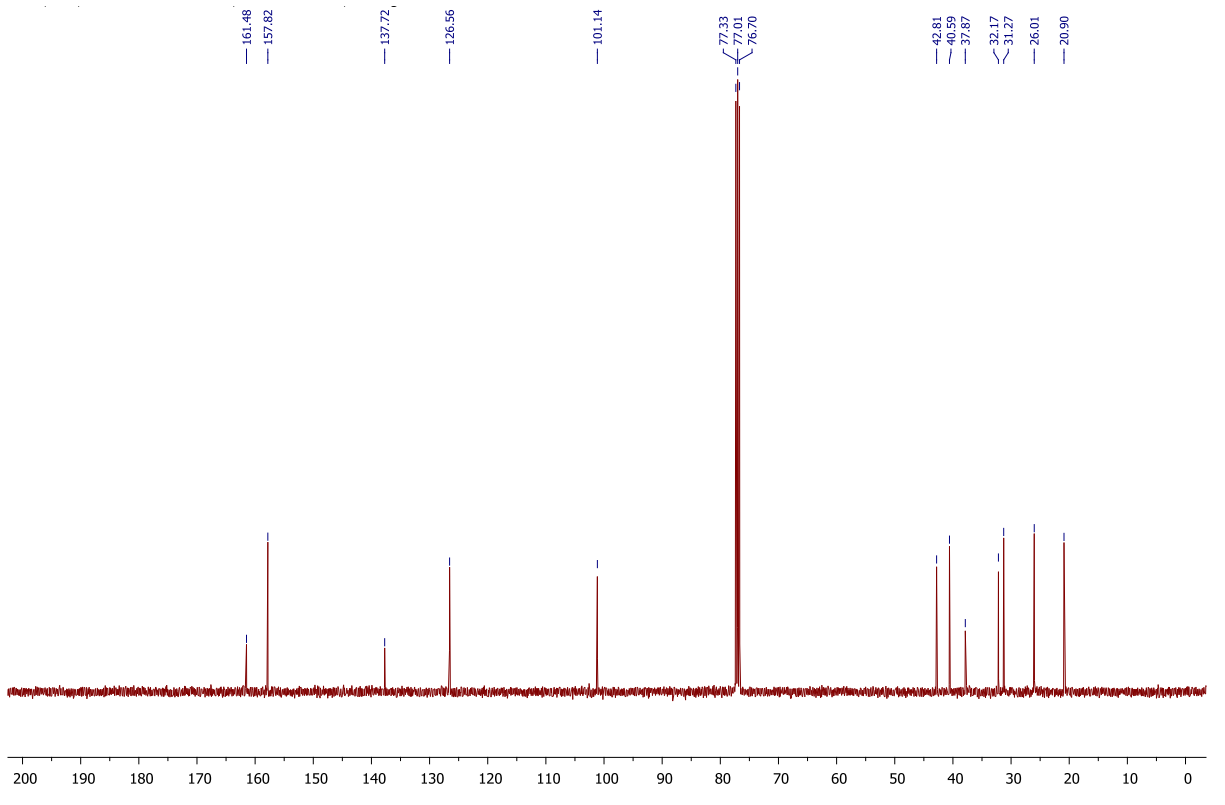
3-(Antracen-9-yl)isoxazole **4x** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

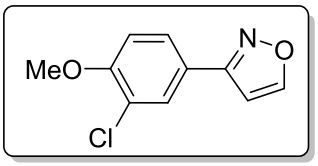




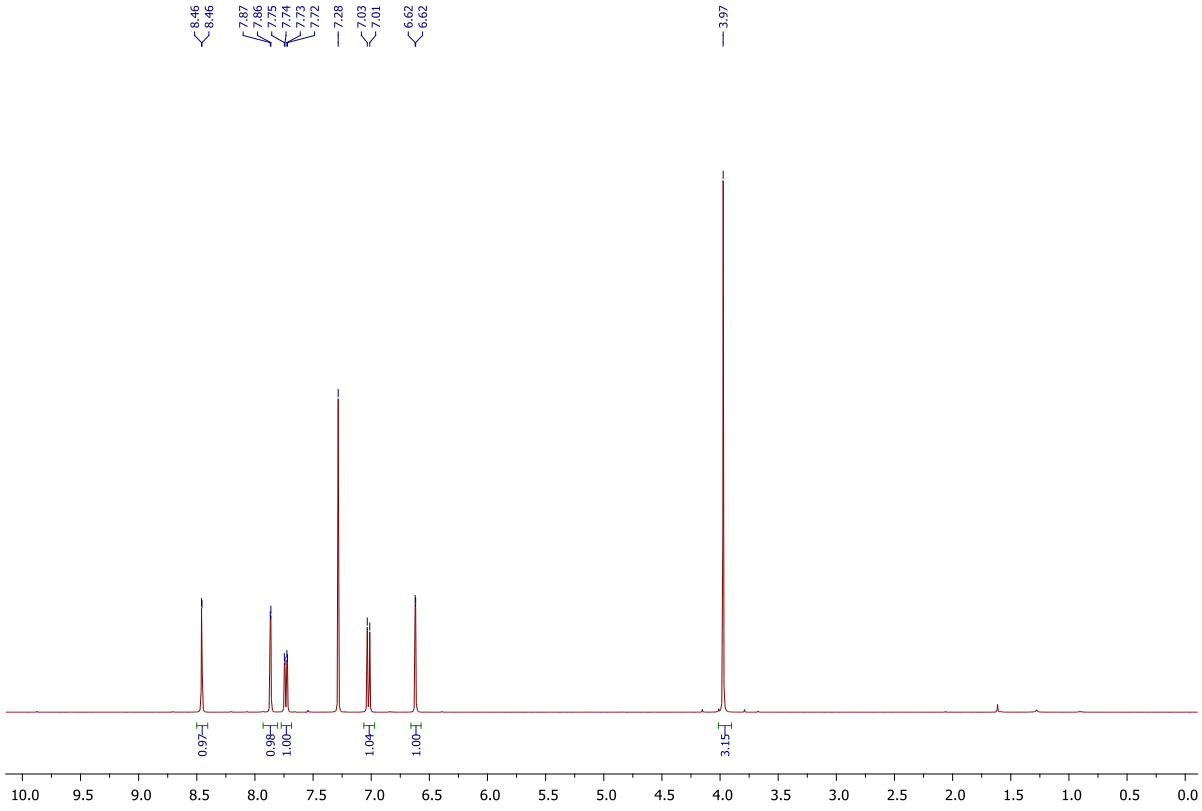
3-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)isoxazole **4y** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

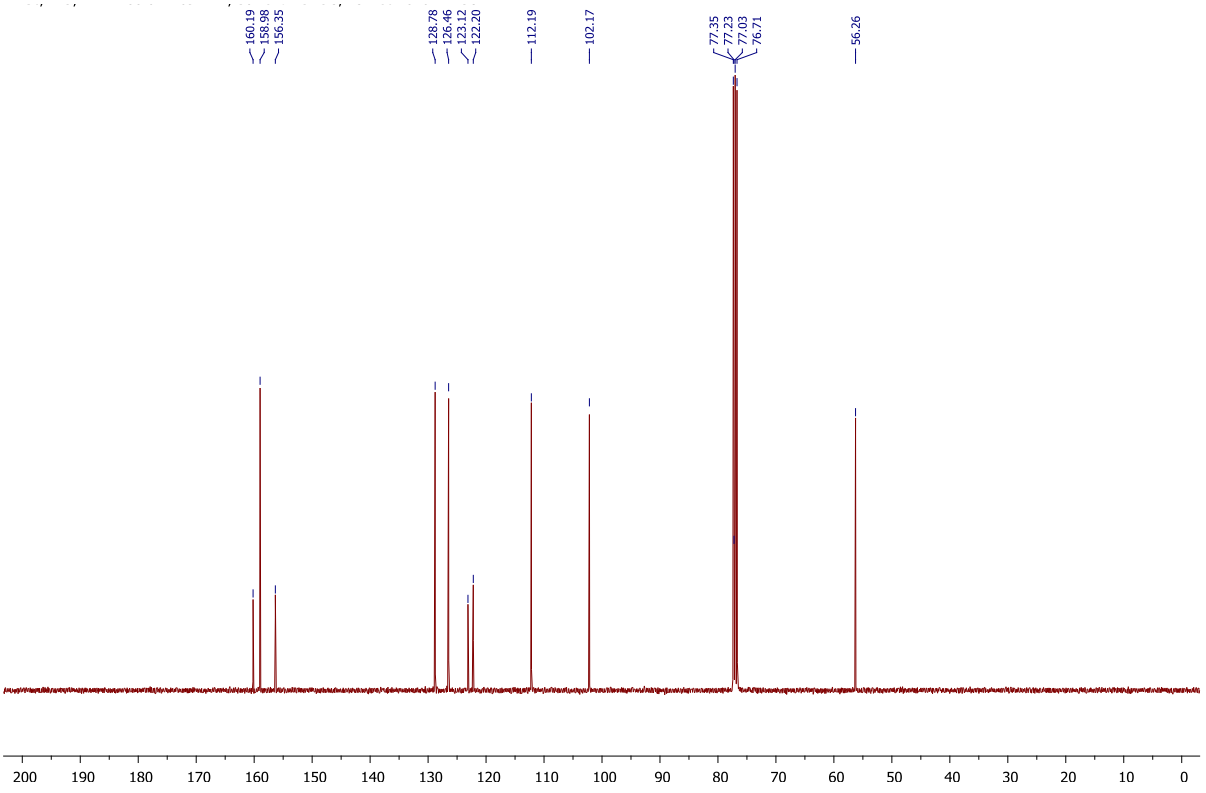


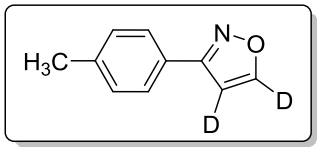




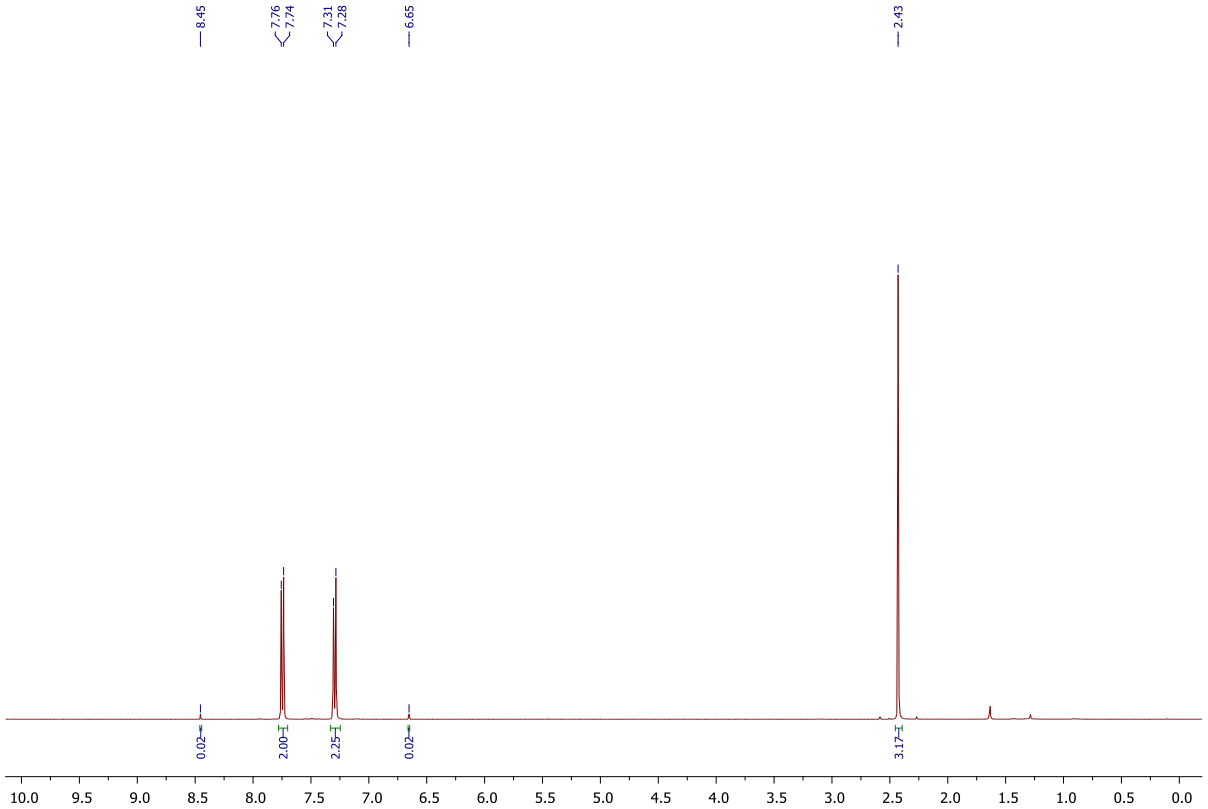
3-(3-Chloro-4-methoxyphenyl)isoxazole **4z** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

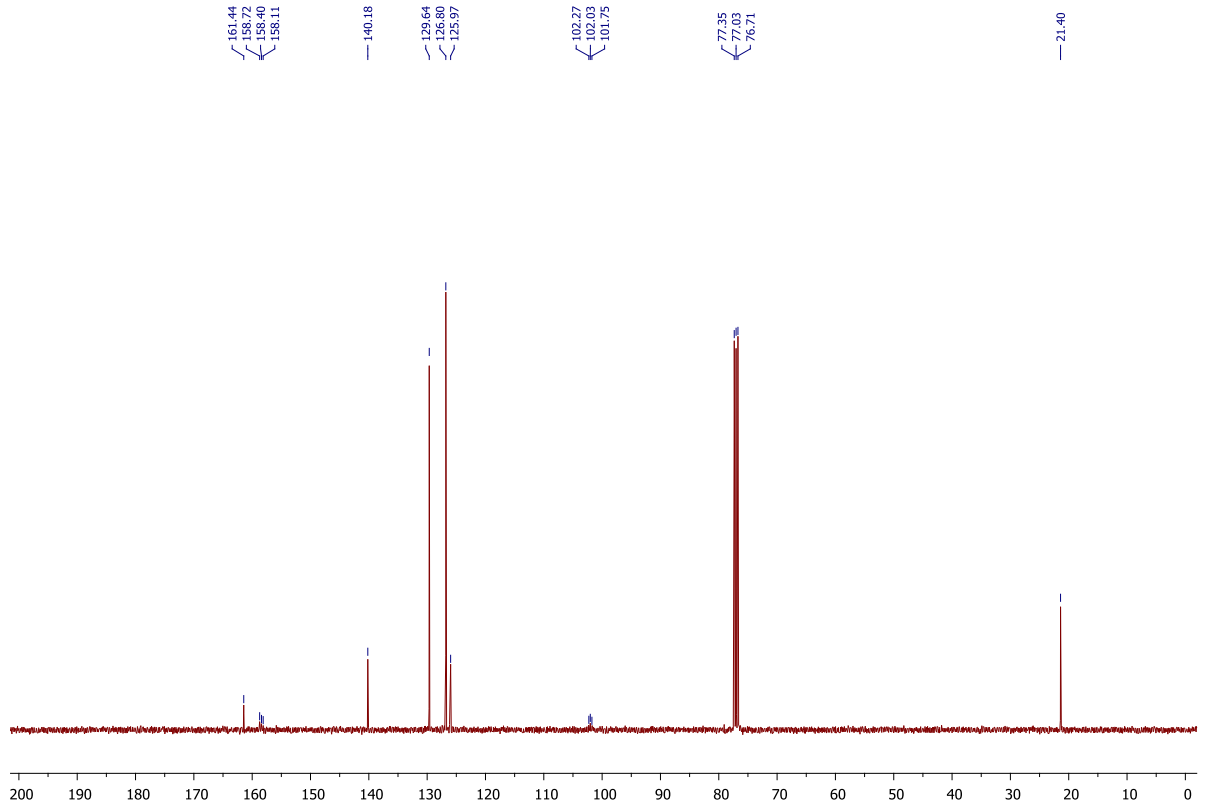


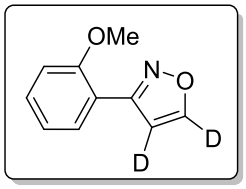




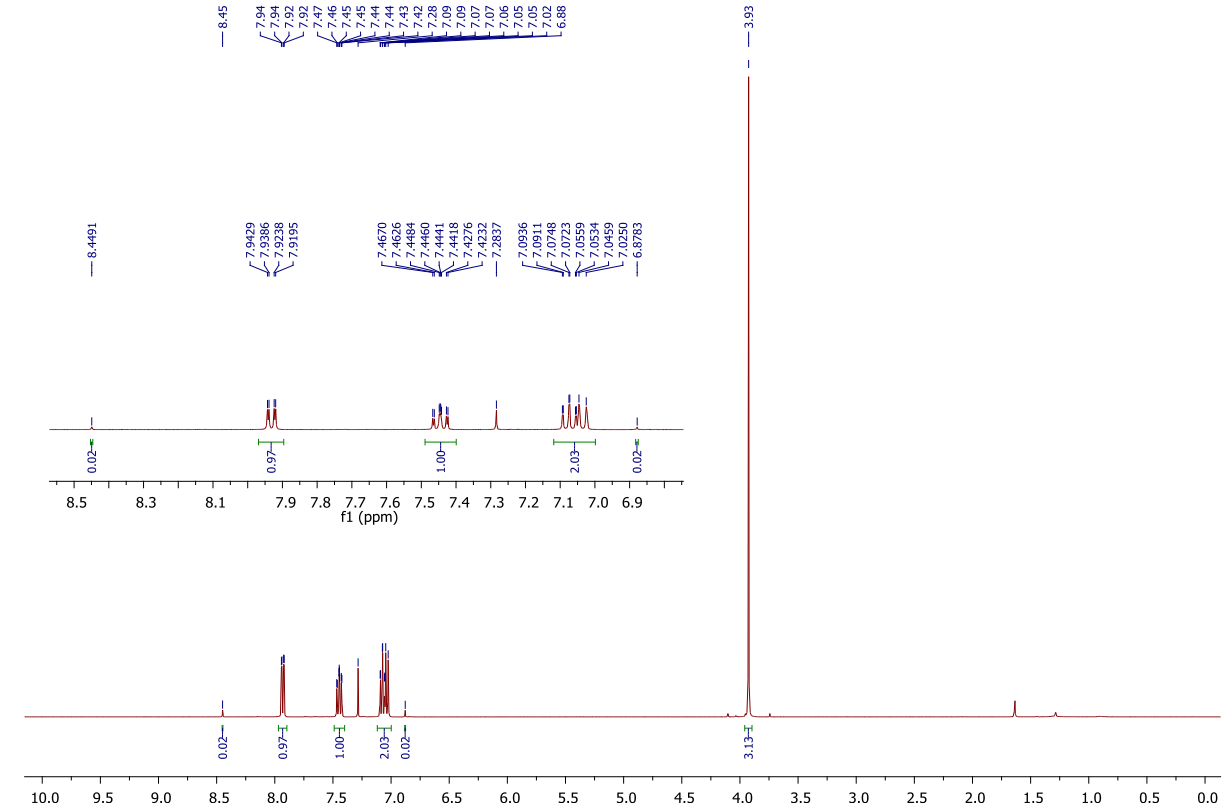
4,5-Dideutero-3-(4-tolyl)isoxazole **5a** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

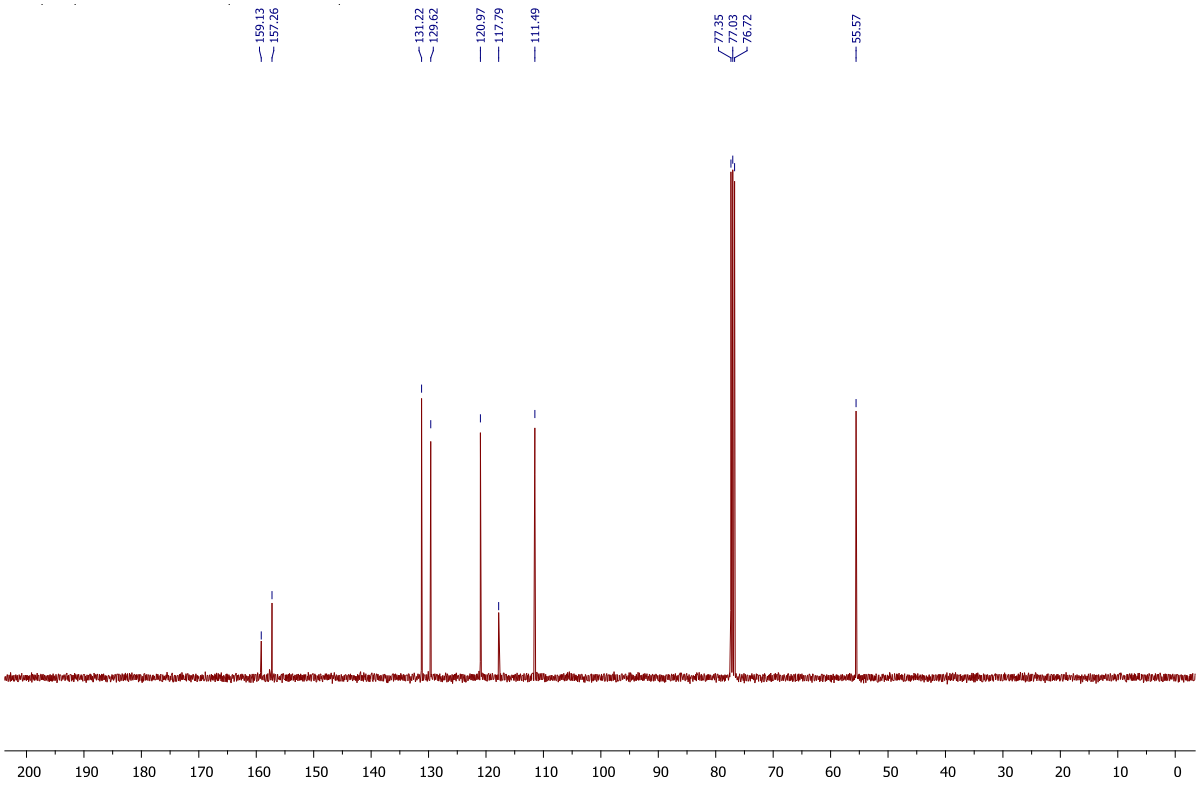


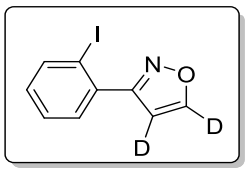




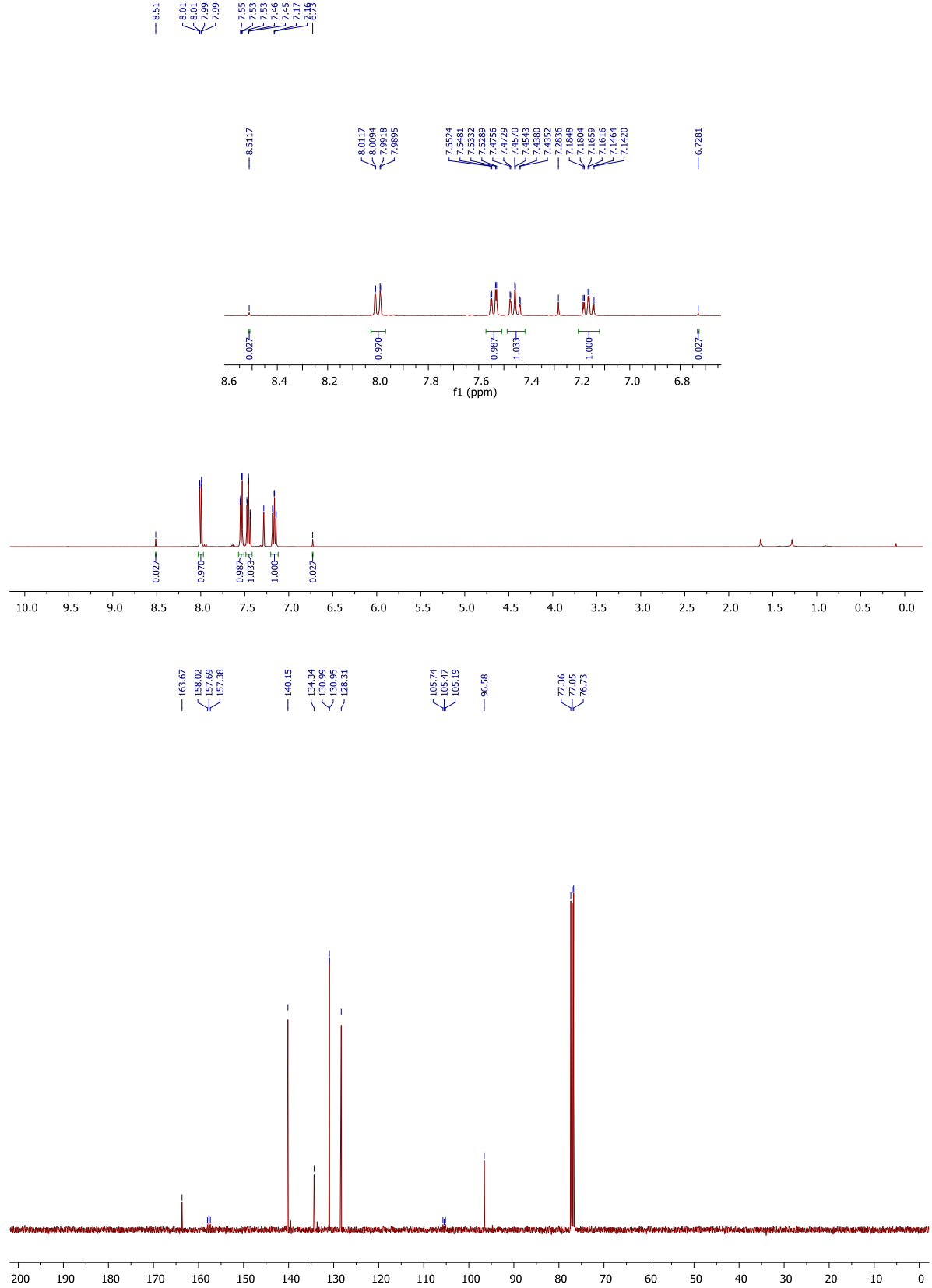
4,5-Dideutero-3-(2-methoxyphenyl)isoxazole **5c** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

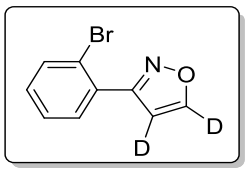




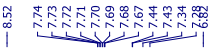


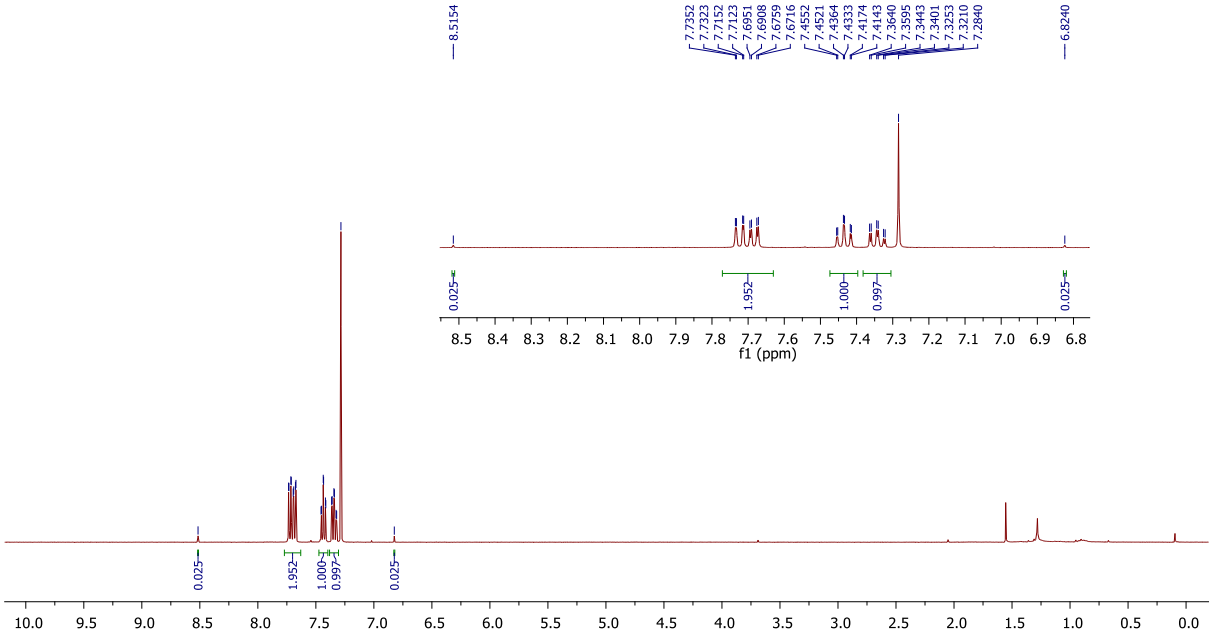
4,5-Dideutero-3-(2-iodophenyl)isoxazole **5g** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

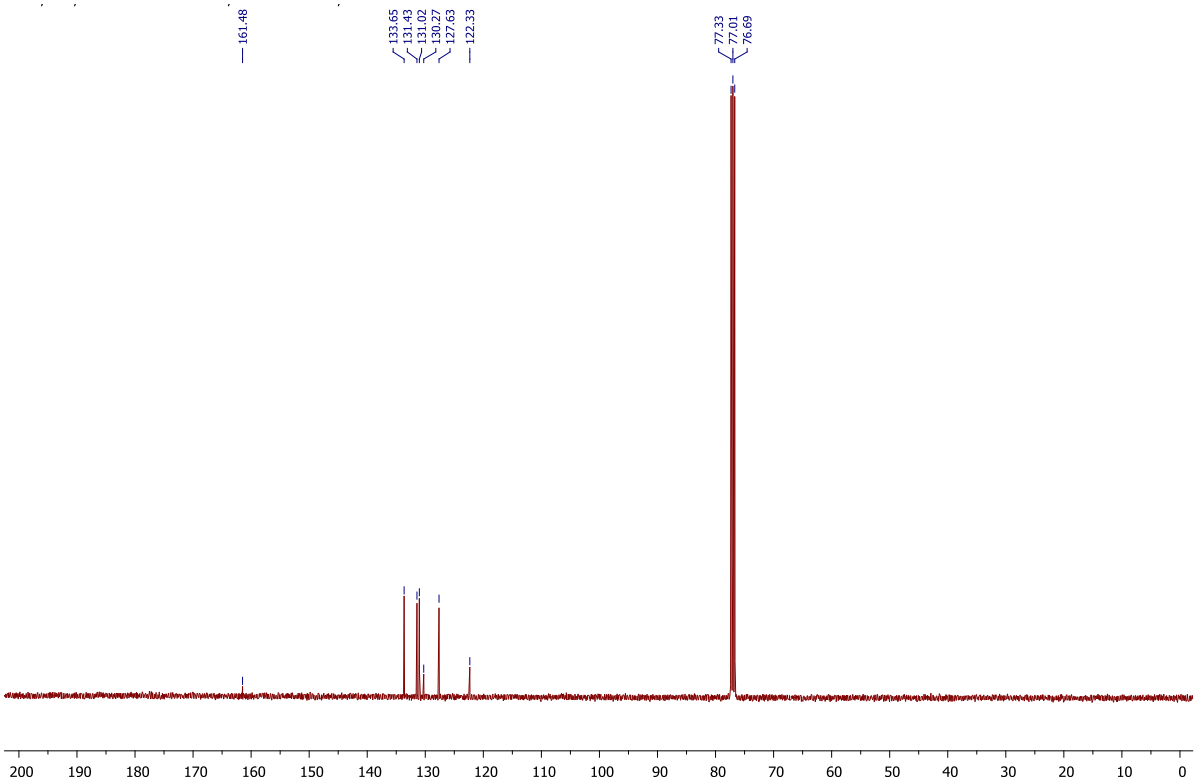


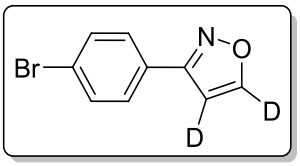


4,5-Dideutero-3-(2-bromophenyl)isoxazole **5h** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

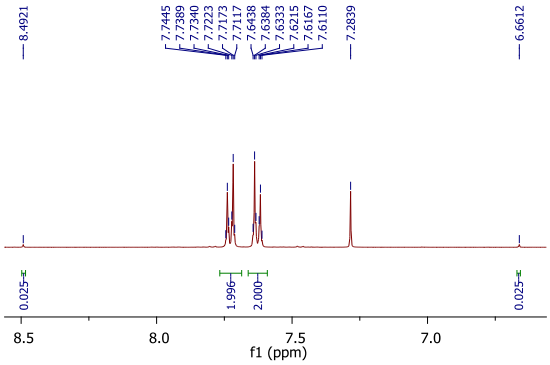


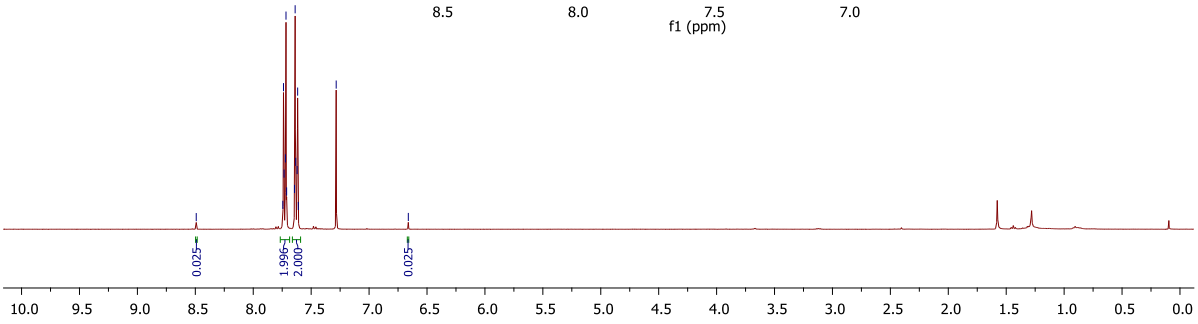


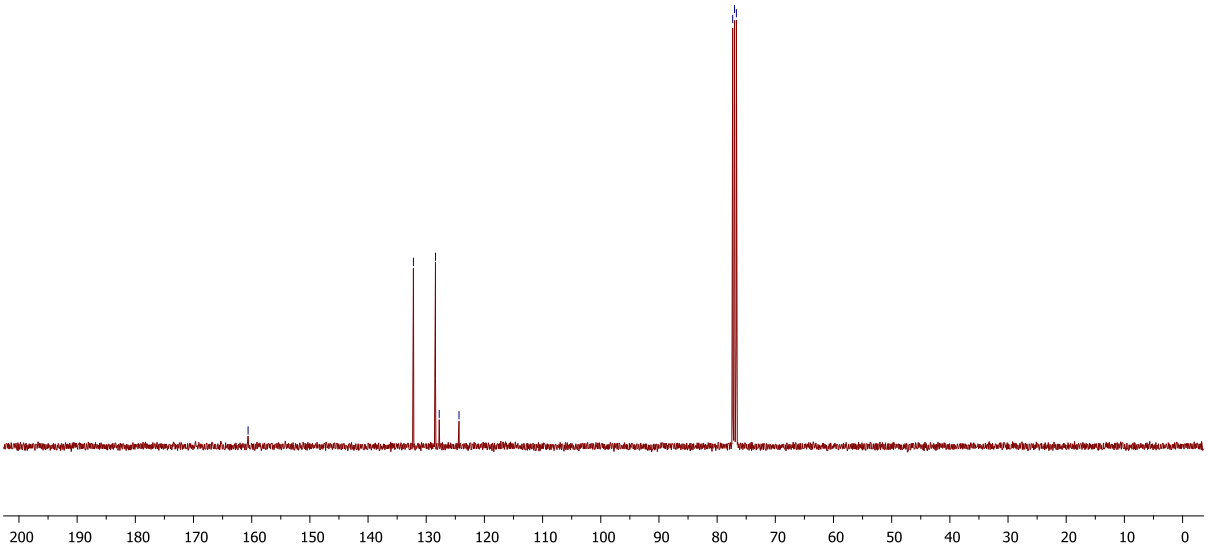


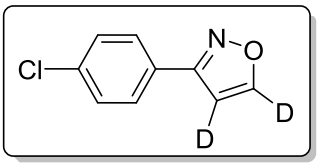


4,5-Dideutero-3-(4-bromophenyl)isoxazole **5j** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

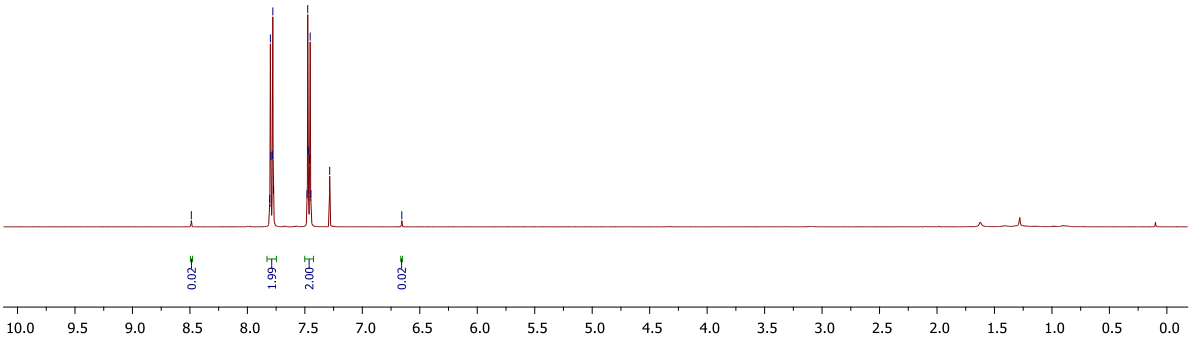


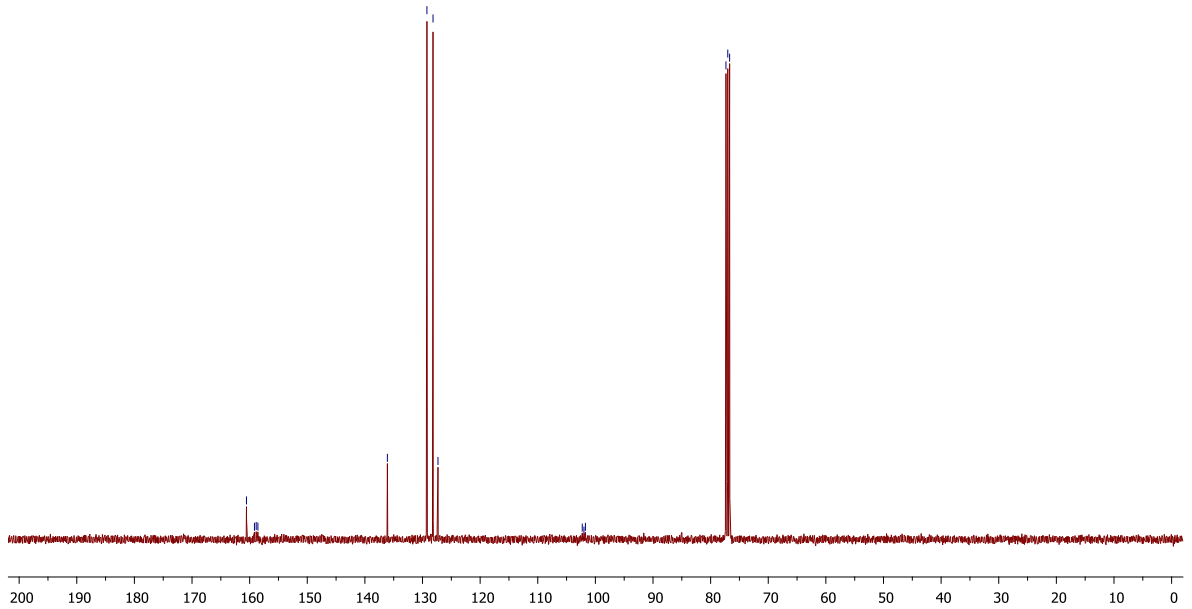


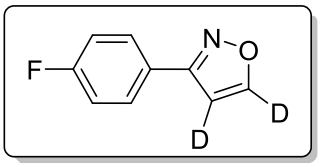




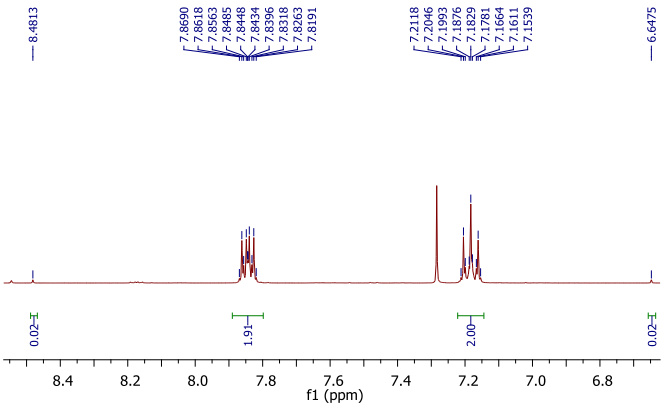
4,5-Dideutero-3-(4-chlorophenyl)isoxazole **5k** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

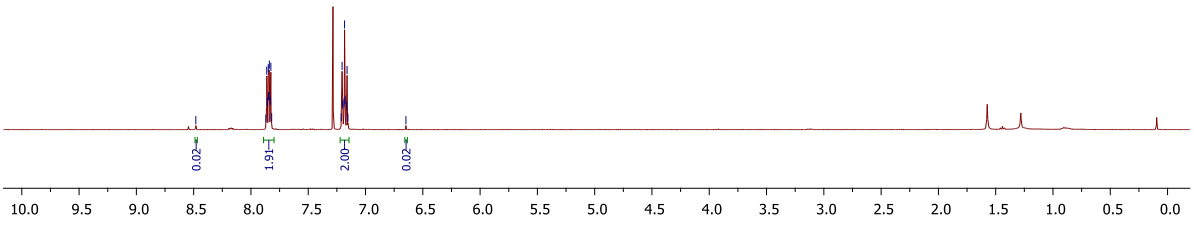


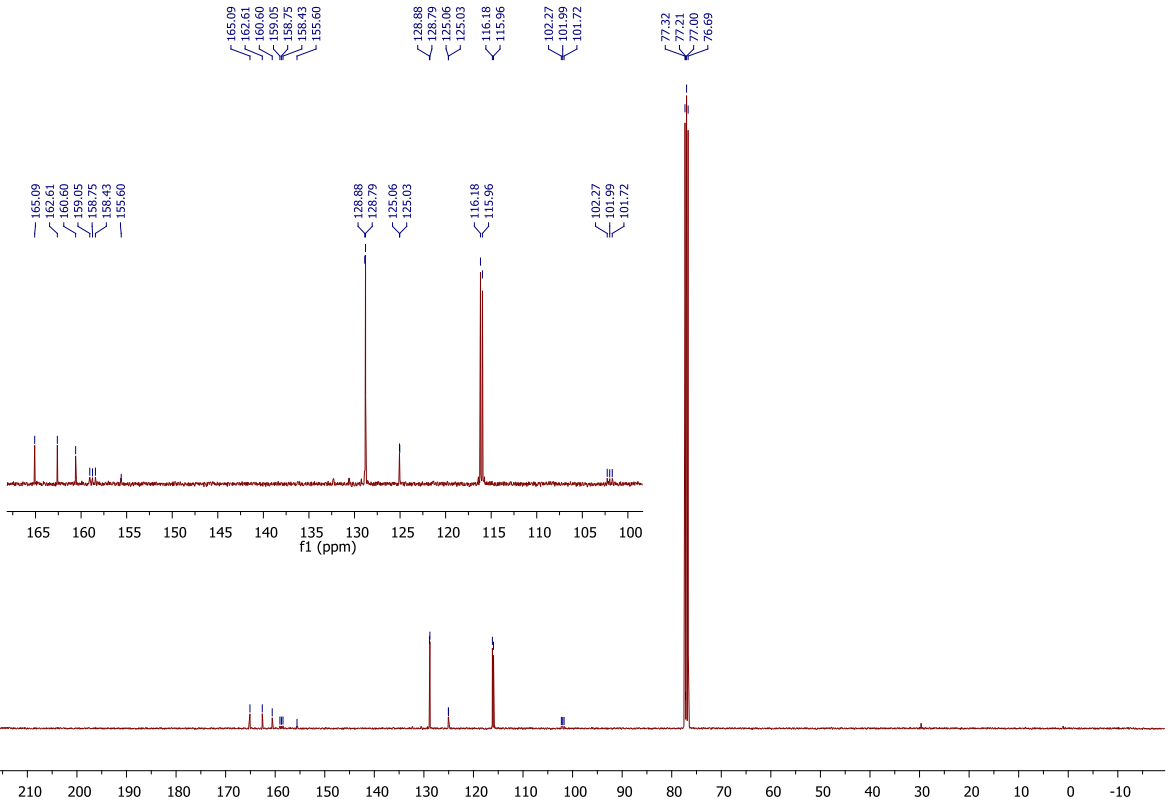


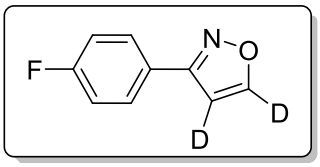


4,5-Dideutero-3-(4-fluorophenyl)isoxazole **5m** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.

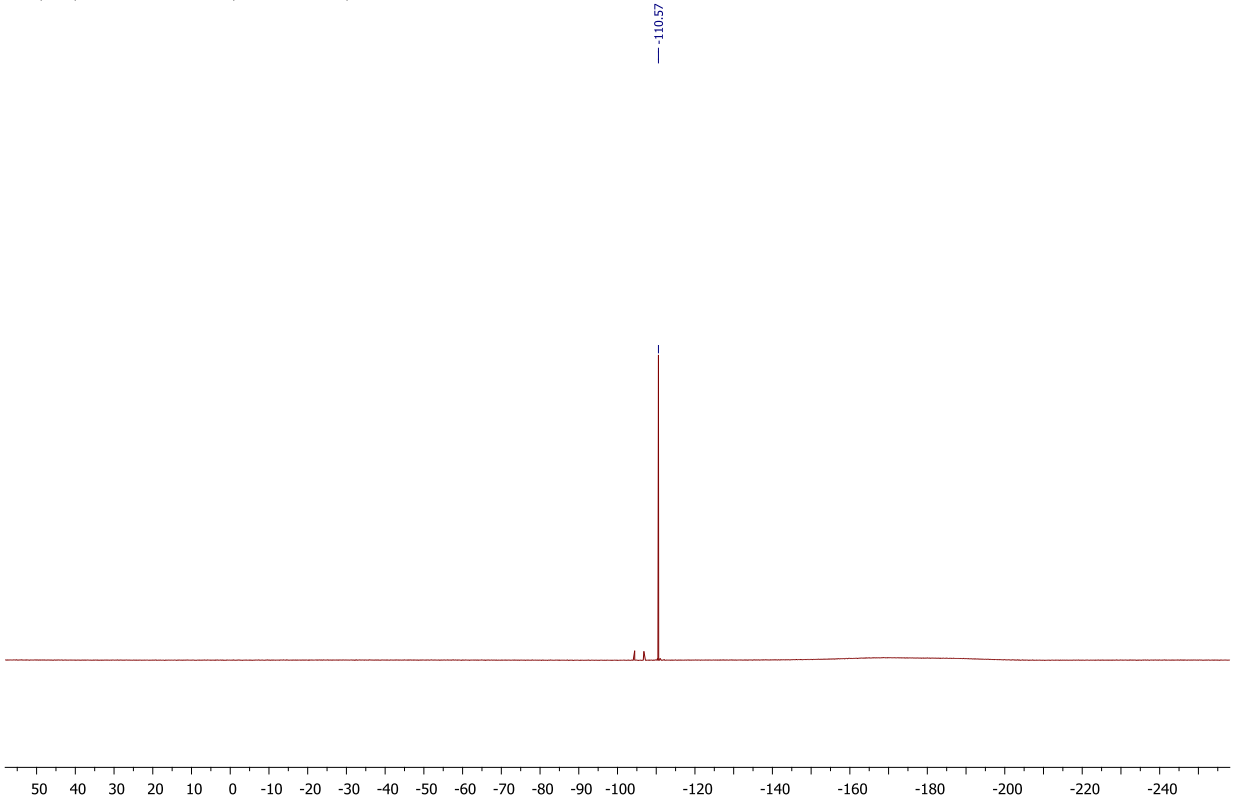


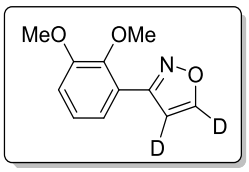




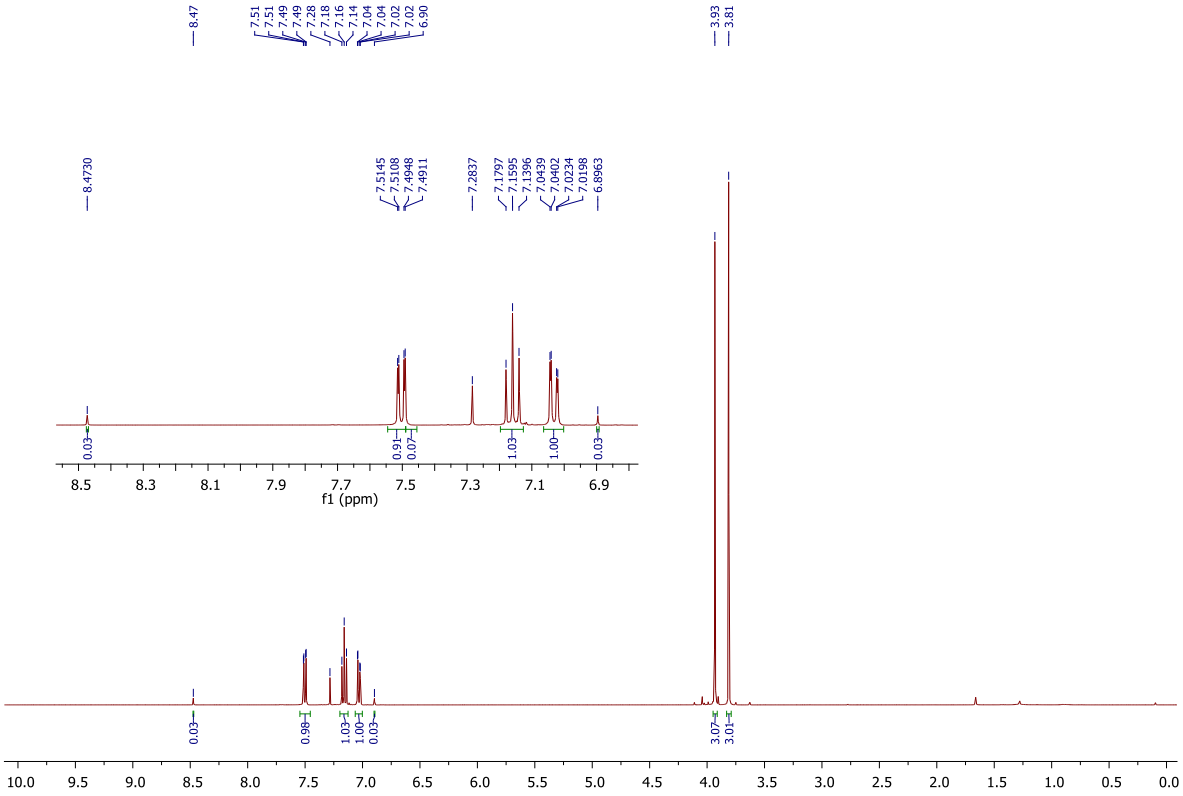


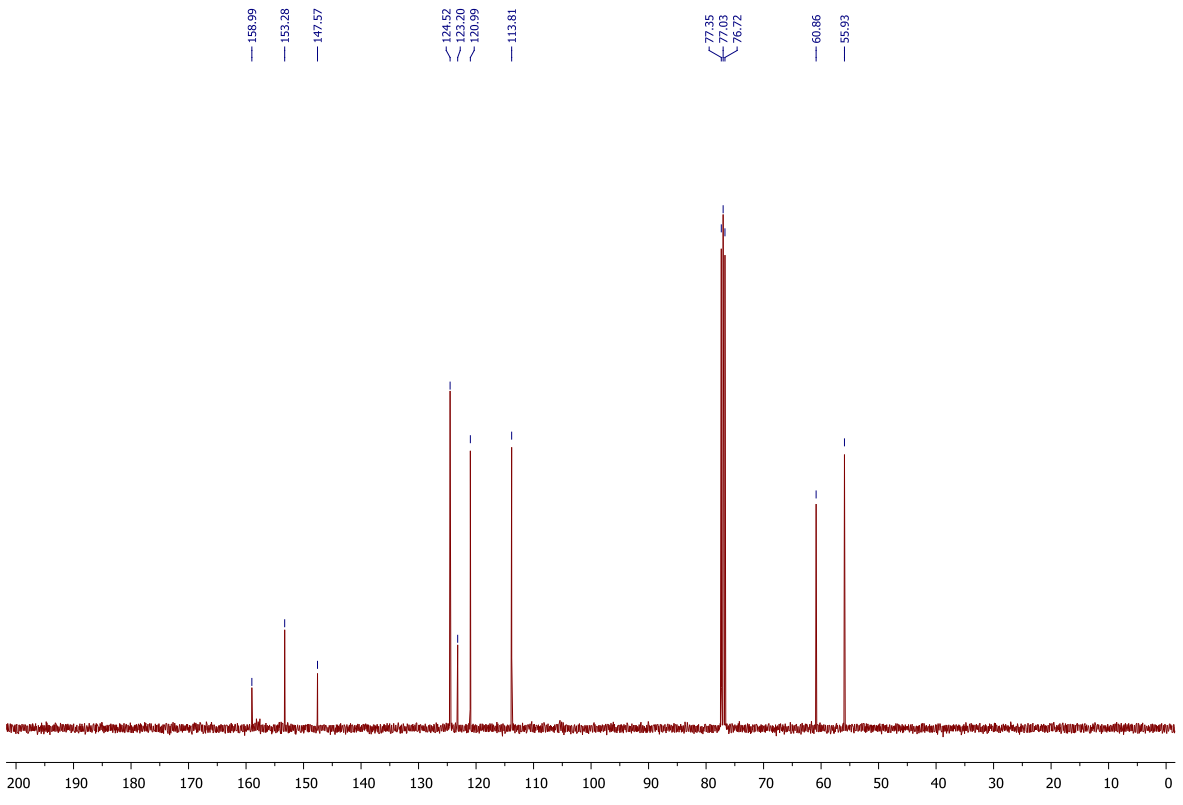
4,5-Dideutero-3-(4-fluorophenyl)isoxazole **5m** ^{19}F (376 MHz, $CDCl_3$) NMR-spectra.





4,5-Dideutero-3-(2,3-dimethoxyphenyl)isoxazole **5r** ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (101 MHz, $CDCl_3$) NMR-spectra.





S5. References

1. Tang, S.; He, J.; Sun, Y.; He, L.; She, X. *Org. Lett*. **2009**, *11*, 3982-3985;
2. Gołbiewski, W. M.; Gucma, M. *J. Heterocyclic Chem*. **2006**, *43*, 509-513;
3. Di Nunno, L.; Vitale, P.; Scilimati, A. *Tetrahedron* **2008**, *64*, 11198-11204;
4. Vitale, P.; Di Nunno, L.; Scilimati, A. *Synthesis* **2010**, *18*, 3195-3203;
5. Koroleva, E. V.; Bondar, N. F.; Katok, Ya. M.; Chekanov, N. A.; Chernikhova, T. V. *Chem.Het. Comp.* **2007**, *43*, 362-369;
6. Sheng, S.-R.; Xin, Q.; Liu, X.-L.; Sun, W.-K.; Guo, R.; Huang, X. *Synthesis* **2006**, *14*, 2293-2296;
7. Demina, O. V.; Khodonov, A. A.; Sinauridze, E. I.; Shvets, V. I.; Varfolomeeva, S. D. *Russ. Chem. Bull*. **2014**, *63*, 2092-2113.