

The synthesis and evaluation of fluoro-, trifluoromethyl, and iodo- muscimols as GABA_A receptor agonists.

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Table of Contents

General experimental protocols	2
Experimental section for the synthesis of compounds 3-5 and 7-19	4
References	16
Spectra Data	
Methyl 3-isopropoxyisoxazole-5-carboxylate (7).....	17
5-Hydroxymethyl-3-isopropoxyisoxazole (8)	18
5-Bromomethyl-3-isopropoxyisoxazole (9).....	19
5-Azidomethyl-3-isopropoxyisoxazole (10).....	20
5-Aminomethyl-3-isopropoxyisoxazole (11).....	21
5-(<i>tert</i> -Butyloxycarbonyl)aminomethyl-3-isopropoxyisoxazole (12)	22
5-(<i>tert</i> -Butyloxycarbonyl)aminomethyl-4-fluoro-3-isopropoxyisoxazole (13).....	23
5-Ammoniomethyl-4-fluoro-3-isopropoxyisoxazole trifluoroacetate (14).....	25
5-Aminomethyl-4-fluoro-3-hydroxyisoxazole (3).....	27
5-Azidomethyl-4-iodo-3-isopropoxyisoxazole (15)	29
5-Aminomethyl-4-iodo-3-isopropoxyisoxazole (16).....	30
5-(<i>tert</i> -Butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (17)	31
5-Di(<i>tert</i> -butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (18)	32
5-Di(<i>tert</i> -butyloxycarbonyl)aminomethyl-4-trifluoromethyl-3-isopropoxyisoxazole (19).....	33
5-Aminomethyl-4-trifluoromethyl-3-hydroxyisoxazole (4)	36
5-Aminomethyl-4-iodo-3-hydroxyisoxazole (5)	38
Analytical HPLC of 5-Aminomethyl-4-fluoro-3-hydroxyisoxazole (2).....	39
Analytical HPLC of 5-aminomethyl-4-trifluoromethyl-3-hydroxyisoxazole (4).....	39
Analytical HPLC of 5-aminomethyl-4-iodo-3-hydroxyisoxazole (5)	39
Computational details for the conformational analysis of (1) and (3)	40

General experimental protocol

Reactions were carried out in oven-dried glassware under an inert Ar atmosphere using double vacuum manifold with the inert gas passing through a bed of silica gel and molecular sieves.

NMR spectra were acquired on either Bruker Avance 400 (^1H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) equipped with BBFO probe, Bruker Avance III HD 500 (^1H at 500 MHz, ^{13}C at 125 MHz) equipped with BBFO probe, Bruker Avance III 500 (^1H at 500 MHz, ^{13}C at 125 MHz) equipped with TCI cryoprobe or Bruker Avance III 700 (^{13}C at 176 MHz) equipped with a TCI cryoprobe. The chemical shifts (δ) are reported in parts per million (ppm) and are quoted relative to centre of the residual non-deuterated solvent peak for δ_{H} (CDCl_3 : 7.26 ppm; MeCN: 1.94 ppm; D_2O : 4.79 ppm) and δ_{C} (CDCl_3 : 77.16 ppm; MeCN: 1.32 ppm and 118.26 ppm). Chemical shifts δ_{F} are quoted relative to CFCl_3 (δ_{F} CFCl_3 : 0.00 ppm). ^{13}C NMR spectra were recorded using the DEPT Q or UDEFT pulse sequence with broadband ^1H decoupling. $^{19}\text{F}\{^1\text{H}\}$ spectra were recorded with inverse-gating, to avoid errors on the integrals. Coupling constants (J) are given in Hertz (Hz). Signal splitting patterns are described as: br s (broad singlet), d (doublet), s (singlet), sept (septet), t (triplet). Spectroscopic data were assigned based on the combination of one- and two-dimensional experiments (HSQC and HMBC).

Melting points were determined in Pyrex capillaries on an Electrothermal 9100 melting point apparatus without correction.

High and low resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service, Swansea or at the University of St Andrews by Caroline Horsburgh on a Waters Micromass LCT time of flight mass spectrometer coupled to a Waters 2975 HPLC system. Values are reported as a ratio of mass to charge (m/z).

IR spectra were recorded using the ATR technique on Shimadzu IR Affinity-1S FTIR spectrometer.

Flash Column chromatography was carried out on Merck Geduran silica gel 60 (240-400 mesh), eluting with solvents as supplied, under a positive pressure of compressed air.

Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F₂₅₄ aluminium-supported thin layer chromatography sheets. Visualisation was by absorption of UV light (λ_{max} 254 or 365 nm), or thermal development after dipping in basic aqueous solution of potassium permanganate (KMnO₄) or butanolic solution of ninhydrin and acetic acid.

HPLC analyses were performed using either a Waters 600E Multisolute HPLC system or Shimadzu Prominence with reverse phase column as indicated in individual experiment.

Single crystal X-ray Diffraction analyses were carried out by Dr David B. Cordes and Prof Alexandra M. Z. Slawin at the University of St Andrews. All diffraction data except for (**14**) were collected by using a Rigaku FR-X Ultrahigh brilliance Microfocus RA generator/confocal optics and Rigaku XtaLAB P200 system, with Mo K α radiation ($\lambda = 0.71075 \text{ \AA}$). Data for (**14**) were collected at 125 K by using a Rigaku MM-007HF High brilliance RA generator/confocal optics and Rigaku XtaLAB P200 system, with Cu K α radiation ($\lambda = 1.54187 \text{ \AA}$). Intensity data for all samples were collected using ω steps accumulating area detector images spanning at least a hemisphere of reciprocal space. All data were corrected for Lorentz polarisation effects. A multiscan absorption correction was applied by using CrystalClear¹ or CrysAlisPro.² Structures were solved by Patterson (PATTY³) or direct (SIR2004,⁴ SIR2011⁵) methods and refined by full-matrix least-squares against F² (SHELXL-2013⁶). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the CrystalStructure⁷ interface.

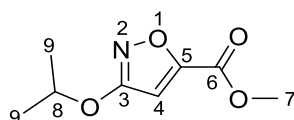
Anhydrous solvents (THF, DCM) were obtained from the MBraun MB SPS-800 solvent purification system, by passage through two drying columns and dispensed under an argon atmosphere. Anhydrous MeOH and MeCN were distilled from calcium hydride in recycling still.⁸ Anhydrous dioxane was available commercially.

Chemicals Muscimol **1** analytical grade was purchased from Sigma Aldrich. Methyl-3-hydroxyisoxazole-5-carboxylate **6** was purchased from Fluorochem UK and used without further purification. *n*-BuLi was purchased from Sigma Aldrich (as a 2.5 M solution in hexanes) and titrated against diphenylacetic acid before use. Other chemicals not specifically

mentioned were purchased from Acros UK, Sigma Aldrich, Fluorochem UK or Alfa Aesar UK and were used without further purification.

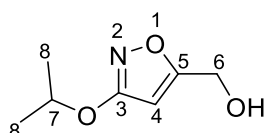
Experimental Section

Methyl 3-isopropoxyisoxazole-5-carboxylate (7)⁹



Isopropyl bromide (3.9 mL, 42.0 mmol, 1.5 eq) was added to a mixture of methyl 3-hydroxyisoxazole-5-carboxylate (**6**) (4.0 g, 28.0 mmol, 1.0 eq) and K₂CO₃ (4.3 g, 31.0 mmol, 1.1 eq) in DMF (50 mL). The mixture was stirred for 1 h at 60 °C then at 55 °C overnight. After cooling down to rt, water (80 mL) was added and the aqueous phase was extracted into Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting yellow residue was purified by silica gel column chromatography (petroleum ether/Et₂O, 90:10) to afford methyl 3-isopropoxyisoxazole-5-carboxylate (**7**) (4.0 g, 77%) as colourless oil: **R_f** 0.61 (petroleum ether/Et₂O, 80:20, UV/KMnO₄); **δ_H** (500 MHz, CDCl₃) 6.48 (1H, s, H-4), 4.93 (1H, sept, ³J_{HH} 6.1, H-8), 3.92 (3H, s, H-7), 1.38 (6H, d, ³J_{HH} 6.1, H-9); **δ_C** (125 MHz, CDCl₃) 170.9 (C-3), 160.0 (C-5), 157.3 (C-6), 101.5 (C-4), 74.2 (C-8), 52.9 (C-7), 21.9 (C-9); **HRMS** *m/z* (NSI⁺), found: [M+H]⁺ 186.0758, C₈H₁₂NO₄ requires [M+H]⁺ 186.0761. The data were in good agreement with the literature values.⁹

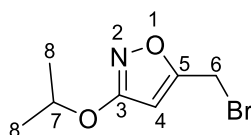
5-Hydroxymethyl-3-isopropoxyisoxazole (8)



NaBH₄ (1.53 g, 40.5 mmol, 2.5 eq) was added to a solution of methyl 3-isopropoxyisoxazole-5-carboxylate (**7**) (3.00 g, 16.2 mmol, 1.0 eq) in MeOH (80 mL) at 0

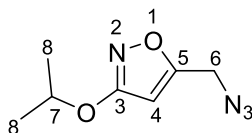
°C. The mixture was stirred at rt overnight and quenched with a saturated solution NH₄Cl (50 mL). The reaction mixture was partitioned between water (60 mL) and EtOAc (60 mL). The aqueous layer was extracted into EtOAc (3 x 80 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to afford a pale yellowish oil, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 80:20) to afford 5-hydroxymethyl-3-isopropoxyisoxazole (**8**) (2.29 g, 90%) as colourless oil: **R_f** 0.79 (petroleum ether/EtOAc, 70:30, KMnO₄); **FT-IR** (ATR, cm⁻¹) 3367 (OH), 2982, 1622, 1504, 1456, 1386, 1375, 1338, 1111; **δ_H** (500 MHz, CDCl₃) 5.83 (1H, s, H-4), 4.85 (1H, sept, ³J_{HH} 6.1, H-7), 4.63 (2H, s, H-6), 2.61 (br s, 1H, -OH), 1.36 (6H, d, ³J_{HH} 6.1, H-8); **δ_C** (125 MHz, CDCl₃) 171.9 (C-5), 171.2 (C-3), 94.1 (C-4), 73.5 (C-7), 56.9 (C-6), 22.0 (C-8); **HRMS** *m/z* (NSI⁺), found: [M+H]⁺ 158.0809, C₇H₁₂NO₃ requires [M+H]⁺ 158.0812.

5-Bromomethyl-3-isopropoxyisoxazole (**9**)



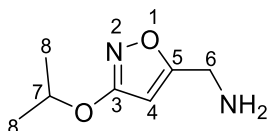
CBr₄ (7.26 g, 21.9 mmol, 2.2 eq) and PPh₃ (7.82 g, 29.8 mmol, 3.0 eq) were added to a solution of 5-hydroxymethyl-3-isopropoxyisoxazole (**8**) (1.56 g, 9.94 mmol, 1.0 eq) in DCM (100 mL) at 0 °C. The reaction mixture was stirred at rt for 12 h and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/Et₂O, 95:5) to afford 5-bromomethyl-3-isopropoxyisoxazole (**9**) (1.27 g, 58%) as a colourless oil: **R_f** 0.66 (petroleum ether/Et₂O, 80:20 UV/KMnO₄); **FT-IR** (ATR, cm⁻¹) 2980, 1618, 1504, 1447, 1387, 1373, 1340, 1287, 1109, 1030, 916, 667; **δ_H** (500 MHz, CDCl₃) 5.90 (1H, s, H-4), 4.89 (1H, sept, ³J_{HH} 6.1, H-7), 4.33 (2H, s, H-6), 1.38 (6H, d, ³J_{HH} 6.1, H-8); **δ_C** (125 MHz, CDCl₃) 171.0 (C-3), 167.8 (C-5), 95.9 (C-4), 73.6 (C-7), 22.0 (C-8), 19.2 (C-6); **HRMS** *m/z* (ESI⁺), found: [M+H]⁺ 219.9969, C₇H₁₁NO₂⁷⁹Br requires [M+H]⁺ 219.9968.

5-Azidomethyl-3-isopropoxyisoxazole (**10**)



NaN₃ (1.6 g, 25.0 mmol, 5.0 eq) was added to a solution of 5-bromomethyl-3-isopropoxyisoxazole (**9**) (1.1 g, 5.0 mmol, 1.0 eq) in DMF (50 mL). After stirring at 80 °C for 3.5 h, the resulting solution was diluted with water (60 mL) and the product was extracted into Et₂O (5 x 60 mL). The combined organic layers were washed with a saturated solution of Na₂CO₃ (60 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting yellowish oil was purified by silica gel column chromatography (petroleum ether/Et₂O, 95:5) to give 5-azidomethyl-3-isopropoxyisoxazole (**10**) (828 mg, 91%) as a colourless oil: **R_f** 0.64 (petroleum ether/Et₂O, 80:20, KMnO₄); **FT-IR** (ATR, cm⁻¹) 2980, 2100 (N₃), 1622, 1506, 1456, 1446, 1339, 1111, 1029; **δ_H** (500 MHz, CDCl₃) 5.87 (1H, s, H-4), 4.89 (1H, sept, ³J_{HH} 6.1, H-7), 4.31 (2H, s, H-6), 1.38 (6H, d, ³J_{HH} 6.1, H-8); **δ_C** (CDCl₃, 125 MHz) 171.1 (C-3), 166.9 (C-5), 95.5 (C-4), 73.7 (C-7), 45.9 (C-6), 22.0 (C-8); **HRMS** *m/z* (NSI⁺), found: [M+H]⁺ 183.0876, C₇H₁₁N₄O₂ requires [M+H]⁺ 183.0877.

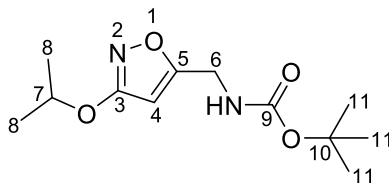
5-Aminomethyl-3-isopropoxyisoxazole (**11**)



PMe₃ (1.0 M solution in THF, 13.2 mL, 13.2 mmol, 3.0 eq) was added to a solution of 5-azidomethyl-3-isopropoxyisoxazole (**10**) (800 mg, 4.40 mmol, 1.0 eq) in THF (30 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and was quenched by slow addition of water (50 mL). The organic phase was separated and the aqueous phase was extracted into EtOAc (3 x 80 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc, 100) affording 5-aminomethyl-3-isopropoxyisoxazole (**11**) (446 mg, 65%) as yellowish oil: **R_f** 0.40 (EtOAc/MeOH, 80:20, ninhydrin); **FT-IR** (ATR, cm⁻¹) 3383, 3315 (NH₂), 2980, 1616, 1499, 1449, 1385, 1373, 1340, 1111, 1028; **δ_H** (500 MHz,

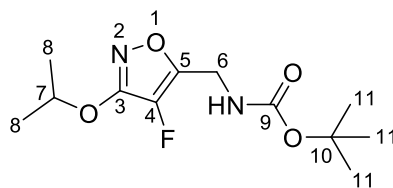
CDCl₃) 5.70 (1H, t, ⁴J_{HH} 0.7, H-4), 4.85 (1H, sept, ³J_{HH} 6.1, H-7), 3.82 (2H, s, H-6), 1.56 (br s, 2H, -NH₂), 1.35 (6H, d, ³J_{HH} 6.1, H-8); δ_C (125 MHz, CDCl₃) 174.3 (C-5), 171.2 (C-3), 92.6 (C-4), 73.2 (C-7), 38.8 (C-6), 22.0 (C-8); **HRMS** *m/z* (NSI⁺), found: [M+H]⁺ 157.0967, C₇H₁₃N₂O₂ requires [M+H]⁺ 157.0972

5-(*tert*-Butyloxycarbonyl)aminomethyl-3-isopropoxyisoxazole (**12**)¹⁰



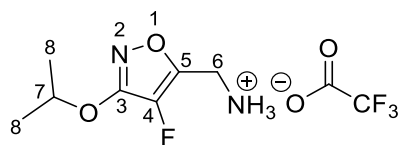
Na₂CO₃ (543 mg, 5.12 mmol, 2.0 eq) was added to a solution of 5-aminomethyl-3-isopropoxyisoxazole (**11**) (400 mg, 2.56 mmol, 1.0 eq) in dioxane/water (3:1 v/v mixture, 8 mL) at 0 °C, followed by dropwise addition of di-*tert*-butyl dicarbonate (0.65 mL, 2.82 mmol, 1.1 eq) in dioxane (2 mL). After stirring at rt overnight, dioxane was removed under reduced pressure and the residue was diluted with Et₂O (30 mL) and washed with water (50 mL). The aqueous layer was extracted into Et₂O (3 x 30 mL). The combined organic layers were combined, dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting yellow residue was purified by silica gel column chromatography (petroleum ether/Et₂O, 70:30) to afford 5-(*tert*-butyloxycarbonyl)aminomethyl-3-isopropoxyisoxazole (**12**) (590 mg, 90%) as a colourless viscous oil that crystallised in time: **R_f** 0.74 (petroleum ether/Et₂O, 50:50, ninhydrin); **mp** 49-50 °C; **FT-IR** (ATR, cm⁻¹) 3306 (NH), 2980, 1712 (C=O), 1616, 1522 (NH), 1497, 1449, 1384, 1366, 1271, 1254, 1138, 1036, 901; δ_H (500 MHz, CDCl₃) 5.74 (1H, s, H-4), 5.00 (br s, 1H, -NH), 4.85 (1H, sept, ³J_{HH} 6.1, H-7), 4.29 (2H, d, ³J_{HH} 5.9, H-6), 1.44 (9H, s, H-11), 1.36 (6H, d, ³J_{HH} 6.1, H-8); δ_C (125 MHz, CDCl₃) 171.2 (C-3), 170.2 (C-5), 155.6 (C-9), 94.0 (C-4), 80.4 (C-10), 73.4 (C-7), 37.1 (C-6), 28.4 (C-11), 22.0 (C-8); **HRMS** *m/z* (NSI⁺), found: [M+H]⁺ 257.1496, C₁₂H₂₁N₂O₄ requires [M+H]⁺ 257.1496.

5-(*tert*-Butyloxycarbonyl)aminomethyl-4-fluoro-3-isopropoxyisoxazole (**13**)



n-BuLi (1.7 mL, 2.5 M in hexanes, 4.29 mmol, 2.2 eq) was added dropwise to a solution of 5-(*tert*-butyloxycarbonyl)aminomethyl-3-isopropoxyisoxazole (**12**) (500 mg, 1.95 mmol, 1.0 eq) at -78 °C. The mixture was stirred for 1.5 h at -78 °C and added a solution of NFSI (676 mg, 2.15 mmol, 1.1 eq) in THF (2 mL). The mixture was stirred for 2 h at -78 °C and the temperature was allowed to warm to rt over 12 h. The reaction mixture was quenched with aqueous NH₄Cl (10 mL) and the organic phase was extracted into EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/Et₂O, 80:20) to afford 5-(*tert*-butyloxycarbonyl)aminomethyl-4-fluoro-3-isopropoxyisoxazole (**13**) (160 mg, 30%) as a colourless viscous oil that crystallised in time: **R_f** 0.67 (petroleum ether/Et₂O, 50:50, ninhydrin); **mp** 63-65 °C; **FT-IR** (ATR, cm⁻¹) 3333 (NH), 2983, 1680 (C=O), 1612, 1526 (NH), 1285, 1269, 1252, 1107, 1078, 916, 907; **δ_H** (400 MHz, CDCl₃) 4.97 (br s, 1H, -NH, overlapped with H-7), 4.92 (1H, sept, ³*J*_{HH} 6.1, H-7), 4.36 (2H, d, ³*J*_{HH} 5.0, H-6), 1.44 (9H, s, H-11), 1.40 (6H, d, ³*J*_{HH} 6.1, H-8); **δ_C** (125 MHz, CDCl₃) 161.5 (d, ²*J*_{CF} 12.5, C-3), 155.5 (C-9), 152.3 (d, ²*J*_{CF} 19.2, C-5), 134.3 (d, ¹*J*_{CF} 254.6, C-4), 80.5 (C-10), 74.6 (C-7), 35.0 (C-6), 28.4 (C-11), 22.0 (C-8); **δ_F** (376 MHz, CDCl₃) -188.0 (1F, s, CF); **HRMS** *m/z* (NSI⁺), found: [M+H]⁺ 275.1404, C₁₂H₂₀N₂O₄F requires [M+H]⁺ 275.1402.

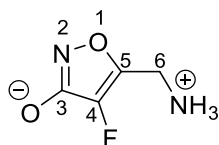
5-Ammoniomethyl-4-fluoro-3-isopropoxyisoxazole trifluoroacetate (**14**)



TFA (1.7 mL, 22.0 mmol, 40.0 eq) was added to a solution of 5-(*tert*-butyloxycarbonyl)aminomethyl-4-fluoro-3-isopropoxyisoxazole (**13**) (150 mg, 0.55 mmol, 1.0 eq) in DCM (8 mL). After stirring at rt overnight, the solvent was removed under reduced

pressure and the resulting residue was purified by silica gel column chromatography (DCM/MeOH, 95:5) to afford 5-ammoniomethyl-4-fluoro-3-isopropoxyisoxazole trifluoroacetate salt (**14**) (155 mg, 98%) as light yellow solid: **R_f** 0.54 (DCM/MeOH, 90:10, ninhydrin); **mp** 116-118 °C; **FT-IR** (ATR, cm⁻¹) 2988, 2926, 2843, 2612, 1670 (C=O), 1541, 1516, 1508, 1435, 1381, 1352, 1339, 1290, 1242, 1120, 1177, 1138, 1103, 1064, 986; **δ_H** (400 MHz, CD₃CN) 6.76 (br s, 3H, -NH₃), 4.91 (1H, sept, ³J_{HH} 6.1, H-7), 4.15 (2H, s, H-6), 1.38 (6H, d, ³J_{HH} 6.1, H-8); **δ_C** (100 MHz, CD₃CN) 162.5 (q, ²J_{CF} 30.5, TFA), 162.3 (d, ²J_{CF} 12.5, C-3), 150.8 (d, ²J_{CF} 20.4, C-5), 136.3 (d, ¹J_{CF} 255.7, C-4), 117.6 (q, ¹J_{CF} 291.9, TFA), 76.0 (C-7), 34.0 (C-6), 21.9 (C-8); **δ_F** (376 MHz, CD₃CN) -76.4 (3F, s, TFA), -186.5 (1F, s, CF); **HRMS** *m/z* (ESI⁺), found: [M-TFA+H]⁺ 175.0876, C₇H₁₂N₂O₂F requires [M-TFA+H]⁺175.0877.

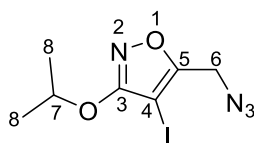
5-Aminomethyl-4-fluoro-3-hydroxyisoxazole (**3**)



A solution of HBr 33% in AcOH (0.79 mL, 4.5 mmol, 25 eq) was added to 5-aminomethyl-4-fluoro-3-isopropoxyisoxazole trifluoroacetate (**14**) (53 mg, 0.18 mmol, 1.0 eq) and stirred at 60 °C for 17 h. The solvent was removed under vacuum and the residue was washed with water (3 x 2 mL). The residue was passed through a reverse phase C18 cartridge (Varian Mega Bond Elut C18, preconditioned with water) and the product was eluted with water (3 x 10 mL). The fractions were combined and concentrated under reduced pressure. The product was further purified by preparative HPLC (Waters system, using a Phenomenex Kingsorb C18 (250 x 21.2 mm, 5 μ) column equipped with security guard cartridge), with an isocratic mobile phase of H₂O at flow rate of 8.0 mL/min detected at 254 nm. Fractions containing product (*t_R* = 7.80 min) were collected and concentrated under reduced pressure. Fluoromuscimol (**3**) was obtained as a colourless solid after freeze drying (11 mg, 36%). Analytical HPLC analysis was performed using Shimadzu system (Phenomenex Kingsorb C18 (150 x 4.6 mm, 5 μ) column), with an isocratic mobile phase of H₂O at flow rate of 0.8 mL/min detected at 254 nm (*t_R* = 1.97 min, purity >99%); **mp** >200

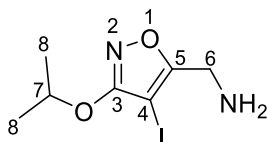
°C (dec.); **FT-IR** (ATR, cm^{-1}) 3429, 2982, 2621 (br), 2237, 2099 (br), 1521, 1458, 1273, 1219, 1144, 1088, 1069, 988; δ_{H} (400 MHz, D_2O) 4.21 (2H, d, $^4J_{\text{HF}}$ 1.5, H-6); $^1\text{H}\{^{19}\text{F}\}$ (400 MHz, D_2O) 4.21 (2H, s, H-6); δ_{C} (176 MHz, D_2O) 167.8 (d, $^2J_{\text{CF}}$ 11.0, C-3), 145.6 (d, $^2J_{\text{CF}}$ 21.8, C-5), 139.1 (d, $^1J_{\text{CF}}$ 257.1, C-4), 32.5 (d, $^3J_{\text{CF}}$ 3.1, C-6); δ_{F} (376 MHz, D_2O) -185.2 (1F, s, CF); **HRMS** m/z (ESI^+), found: $[\text{M}+\text{H}]^+$ 133.0407, $\text{C}_4\text{H}_6\text{N}_2\text{O}_2\text{F}$ requires $[\text{M}+\text{H}]^+$ 133.0413.

5-Azidomethyl-4-iodo-3-isopropoxyisoxazole (15)



NIS (202 mg, 0.90 mmol, 1.5 eq) was added to a solution of 5-azidomethyl-3-isopropoxyisoxazole (**10**) (110 mg, 0.60 mmol, 1.0 eq) in TFA (5 mL) at rt. After stirring at rt overnight, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ Et_2O , 95:5), affording 5-azidomethyl-4-iodo-3-isopropoxyisoxazole (**15**) (159 mg, 86%) as yellowish oil: R_f 0.87 (petroleum ether/ Et_2O , 90:10, UV/ KMnO_4); **FT-IR** (ATR, cm^{-1}) 2980, 2095 (N_3), 1607, 1506, 1427, 1387, 1373, 1333, 1287, 1182, 1109, 1087, 914, 839, 768, 700; δ_{H} (500 MHz, CDCl_3) 4.95 (1H, sept, $^3J_{\text{HH}}$ 6.2, H-7), 4.37 (2H, s, H-6), 1.42 (6H, d, $^3J_{\text{HH}}$ 6.2, H-8); δ_{C} (125 MHz, CDCl_3) 170.3 (C-3), 167.4 (C-5), 74.9 (C-7), 53.2 (C-4), 45.3 (C-6), 21.9 (C-8); **HRMS** m/z (NSI^+), found: $[\text{M}+\text{H}]^+$ 308.9846, $\text{C}_7\text{H}_{10}\text{N}_4\text{O}_2^{127}\text{I}$ requires $[\text{M}+\text{H}]^+$ 308.9843.

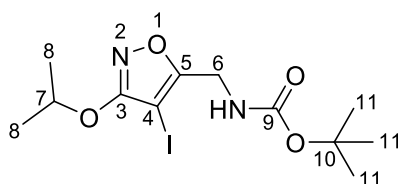
5-Aminomethyl-4-iodo-3-isopropoxyisoxazole (16)



PMe_3 (1.0 M solution in THF, 1.47 mL, 1.47 mmol, 3.0 eq) was added to a solution of 5-azidomethyl-4-iodo-3-isopropoxyisoxazole (**15**) (150 mg, 0.49 mmol, 1.0 eq) in THF (8

mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and was quenched by slow addition of water (10 mL). The organic phase was separated and the aqueous phase was extracted into EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc, 100), affording 5-aminomethyl-4-iodo-3-isopropoxyisoxazole (**16**) (114 mg, 83%) as yellowish oil: **R_f** 0.50 (EtOAc/MeOH, 90:10, UV/ninhydrin); **FT-IR** (ATR, cm⁻¹) 3397, 3377 (NH₂), 2978, 1593, 1502, 1431, 1385, 1373, 1335, 1107, 1084, 916, 837, 754, 721, 691; **δ_H** (500 MHz, CDCl₃) 4.91 (1H, sept, ³J_{HH} 6.2, H-7), 3.85 (2H, s, H-6), 1.53 (br s, 2H, -NH₂), 1.39 (6H, d, ³J_{HH} 6.2, H-8); **δ_C** (125 MHz, CDCl₃) 173.2 (C-5), 170.2 (C-3), 74.4 (C-7), 49.2 (C-4), 38.5 (C-6), 21.9 (C-8); **HRMS** *m/z* (NSI⁺), found: [M+H]⁺ 282.9935, C₇H₁₂N₂O₂¹²⁷I requires [M+H]⁺ 282.9938.

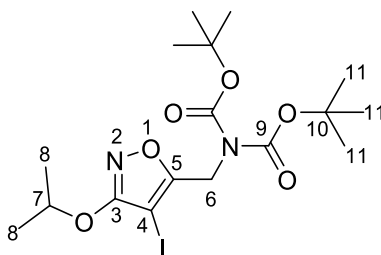
5-(*tert*-Butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (**17**)



Na₂CO₃ (541 mg, 5.10 mmol, 2.0 eq) was added to a solution of 5-aminomethyl-4-iodo-3-isopropoxyisoxazole (**16**) (720 mg, 2.55 mmol, 1.0 eq) in dioxane/water (3:1 v/v mixture, 16 mL) at 0 °C, followed by dropwise addition of di-*tert*-butyl dicarbonate (0.65 mL, 2.81 mmol, 1.1 eq) in dioxane (2 mL). After stirring at rt overnight, dioxane was removed under reduced pressure and the residue was diluted with Et₂O (40 mL) and washed with water (50 mL). The aqueous layer was extracted into Et₂O (3 x 40 mL). The combined organic layers were combined, dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting yellow residue was purified by silica gel column chromatography (petroleum ether/Et₂O, 70:30) to afford 5-(*tert*-butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (**17**) (788 mg, 81%) as a colourless viscous oil: **R_f** 0.53 (petroleum ether/Et₂O, 60:40, UV/ninhydrin); **FT-IR** (ATR, cm⁻¹) 3352 (NH), 2980, 1699 (C=O), 1603, 1506 (NH), 1433, 1387, 1368, 1337, 1281, 1250, 1167, 1090, 916; **δ_H** (500 MHz, CDCl₃) 4.98 (br s, 1H, -NH), 4.90 (1H, sept, ³J_{HH} 6.2, H-7), 4.37 (2H, d, ³J_{HH} 5.9, H-6), 1.44 (9H, s, H-11), 1.39 (6H, d, ³J_{HH} 6.2, H-8); **δ_C** (125

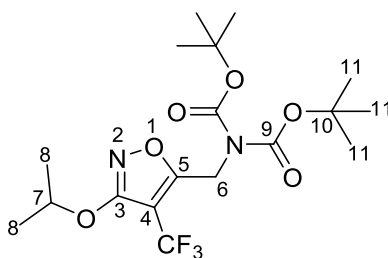
MHz, CDCl₃) 170.3 (C-3), 169.3 (C-5), 155.4 (C-9), 80.4 (C-10), 74.5 (C-7), 50.5 (C-4), 37.1 (C-6), 28.5 (C-11), 21.9 (C-8); **HRMS** *m/z* (ESI⁺), found: [M+Na]⁺ 405.0273, C₁₂H₁₉N₂O₄¹²⁷INa requires [M+Na]⁺ 405.0282.

5-Di(*tert*-butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (**18**)



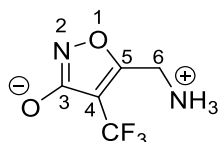
DMAP (34.2 mg, 0.28 mmol, 0.2 eq) and di-*tert*-butyl dicarbonate (0.65 mL, 2.82 mmol, 2.0 eq) were added to a solution of 5-(*tert*-butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (**17**) (540 mg, 1.41 mmol, 1.0 eq) in MeCN (25 mL). The reaction mixture was heated under reflux for 3 h and allowed to cool to rt. The reaction was diluted with DCM (20 mL), and washed with water (30 mL). The aqueous layer was extracted into DCM (3 x 30 mL). The combined organic layers were combined, dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting brown oil was purified by silica gel column chromatography (petroleum ether/Et₂O, 90:10) to afford 5-di(*tert*-butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (**18**) (592 mg, 87%) as a colourless viscous oil: **R_f** 0.68 (petroleum ether/Et₂O, 70:30, UV/ninhydrin); **FT-IR** (ATR, cm⁻¹) 2986, 1730 (C=O), 1688 (C=O), 1601, 1510, 1435, 1416, 1383, 1368, 1337, 1227, 1165, 1140, 1121, 1090, 918, 858, 849, 791, 760; **δ_H** (500 MHz, CDCl₃) 4.90 (1H, sept, ³J_{HH} 6.2, H-7), 4.83 (2H, s, H-6), 1.48 (18H, s, H-11), 1.39 (6H, d, ³J_{HH} 6.2, H-8); **δ_C** (125 MHz, CDCl₃) 171.0 (C-3), 169.7 (C-9), 151.7 (C-5), 83.5 (C-10), 74.4 (C-7), 48.8 (C-4), 42.7 (C-6), 28.2 (C-11), 21.9 (C-8); **HRMS** *m/z* (ESI⁺), found: [M+Na]⁺ 505.0796, C₁₇H₂₇N₂O₆¹²⁷INa requires [M+Na]⁺ 505.0806.

5-Di(*tert*-butyloxycarbonyl)aminomethyl-4-trifluoromethyl-3-isopropoxyisoxazole (**19**)



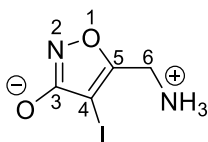
Methyl 2,2-difluoro-2-(fluorosulfonyl) acetate (MFDSA) (945 mg, 4.92 mmol, 4.0 eq) was added to a preformed solution of 5-di(*tert*-butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (**18**) (592 mg, 1.23 mmol, 1.0 eq), copper(I) iodide (47.6 mg, 0.25 mmol, 0.2 eq) and HMPA (1 ml) in DMF (8 ml). The reaction mixture was heated under reflux at 80 °C for 24 h. The clear, dark orange reaction mixture was cooled to room temperature and diluted with Et₂O (10 ml), washed with a saturated aqueous solution of NH₄Cl (15 ml) and brine (15 ml). The aqueous layer was back-extracted into Et₂O (3 x 20 ml) and the combined organic layers were combined, dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting yellowish oil was purified by silica gel column chromatography (petroleum ether/Et₂O, 90:10) to afford 5-di(*tert*-butyloxycarbonyl)aminomethyl-4-trifluoromethyl-3-isopropoxyisoxazole (**19**) (177 mg, 34%) as a colourless viscous oil: **R_f** 0.66 (petroleum ether/Et₂O, 80:20, ninhydrin); **FT-IR** (ATR, cm⁻¹) 2982, 1761 (C=O), 1699 (C=O), 1647, 1516, 1472, 1718, 1369, 1333, 1308, 1260, 1227, 1130, 1109, 1078, 1036, 918, 854, 843.764; **δ_H** (400 MHz, CDCl₃) 4.97 (2H, q, ⁵J_{HF} 1.0, H-6), 4.91 (1H, sept, ³J_{HH} 6.2, H-7), 1.49 (18H, s, H-11), 1.40 (6H, d, ³J_{HH} 6.2, H-8); **¹H{¹⁹F}** (400 MHz, CDCl₃) 4.97 (2H, s, H-6), 4.91 (1H, sept, ³J_{HH} 6.2, H-7), 1.49 (18H, s, H-11), 1.40 (6H, d, ³J_{HH} 6.2, H-8); **δ_C** (176 MHz, CDCl₃) 169.4 (C-9), 167.4 (C-3), 151.6 (C-5), 121.2 (q, ¹J_{CF} 254.6, CF₃), 99.2 (q, ²J_{CF} 39.4, C-4), 83.8 (C-10), 74.9 (C-7), 42.2 (C-6), 28.1 (C-11), 21.8 (C-8); **δ_F** (376 MHz, CDCl₃) -57.7 (3F, t, ⁵J_{HF} 1.0, CF₃); **¹⁹F{¹H}** (376 MHz, CDCl₃) -57.7 (s, CF₃); **HRMS** *m/z* (ESI⁺), found: [M+Na]⁺ 447.1704, C₁₈H₂₇N₂O₆F₃Na requires [M+Na]⁺ 447.1713.

5-Aminomethyl-4-trifluoromethyl-3-hydroxyisoxazole (**4**)



TFA (0.17 mL, 2.2 mmol, 20.0 eq) was added to a solution of 5-di(*tert*-butyloxycarbonyl)aminomethyl-4-trifluoromethyl-3-isopropoxyisoxazole (**19**) (45 mg, 0.11 mmol, 1.0 eq) in DCM (5 mL). After stirring at rt for 6 h, the solvent was removed under reduced pressure to afford a hygroscopic colourless crystalline solid contained (**20**) (35 mg), which was used in the subsequent step without further purification. A solution of HBr 33% in AcOH (0.9 mL, 5.0 mmol, 50 eq) was added to crude (**20**) (35 mg, 0.10 mmol, 1.0 eq) and stirred at 60 °C for 48 h. The solvent was removed under vacuum and the residue was washed with water (3 x 2 mL). The residue was passed through a reverse phase C18 cartridge (Varian Mega Bond Elut C18, preconditioned with water) and the product was eluted with water (3 x 10 mL). The fractions were combined and concentrated under reduced pressure. The product was further purified by preparative HPLC (Waters system, using a Phenomenex Kingsorb C18 (250 x 21.2 mm, 5 μ) column equipped with security guard cartridge) with an isocratic mobile phase of H₂O at flow rate of 8.0 mL/min detected at 254 nm. Fractions containing product (t_R = 9.10 min) were collected and concentrated under reduced pressure. Trifluoromethylmuscimol (**4**) was obtained as a colourless solid after freeze drying (7.2 mg, 36% over 2 steps). Analytical HPLC analysis was performed using Shimadzu system (Phenomenex Kingsorb C18 (150 x 4.6 mm, 5 μ) column), with an isocratic mobile phase of H₂O at flow rate of 0.8 mL/min detected at 254 nm (t_R = 2.27 min, purity >98%); **mp** 165-168 °C (dec); **FT-IR** (ATR, cm⁻¹) 2997, 2891, 2631 (br), 1667, 1491, 1425, 1371, 1344, 1161, 1109, 1042, 978, 745; δ_H (400 MHz, D₂O) 4.38 (s, H-6); δ_C (176 MHz, D₂O) 172.2 (C-3), 163.7 (C-5), 121.6 (q, ¹ J_{CF} 267.8, CF₃), 103.2 (q, ² J_{CF} 39.5, C-4), 34.5 (C-6); δ_F (376 MHz, D₂O) -58.9 (s, CF₃); **HRMS** m/z (ESI⁺), found: [M+H]⁺ 183.0373, C₅H₆N₂O₂F₃ requires [M+H]⁺ 183.0381.

5-Aminomethyl-4-iodo-3-hydroxyisoxazole (**5**)



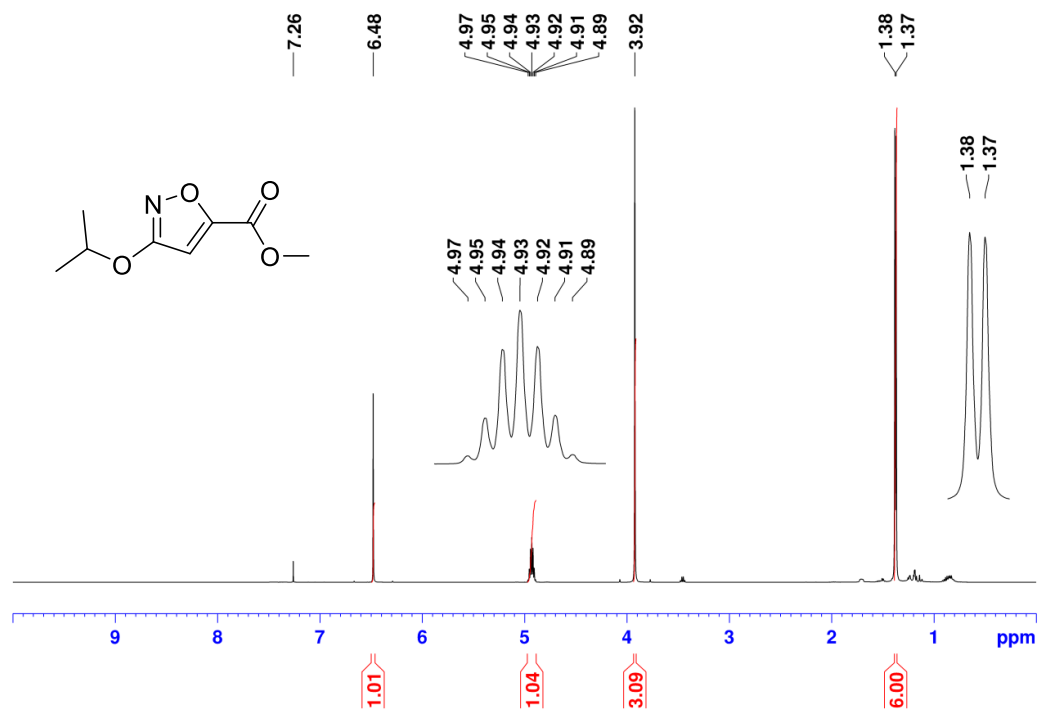
A solution of HBr 33% in AcOH (1.7 mL, 9.5 mmol, 25 eq) was added to 5-aminomethyl-4-iodo-3-isopropoxyisoxazole (**16**) (107 mg, 0.38 mmol, 1.0 eq) and stirred at 60 °C for 17 h. The solvent was removed under vacuum and the residue was washed with water (3 x 2 mL). The residue was passed through a reverse phase C18 cartridge (Varian Mega Bond Elut C18, preconditioned with water) and the product was eluted with water (3 x 10 mL). The fractions were combined and concentrated under reduced pressure. The product was further purified by preparative HPLC (Waters system, using a Phenomenex Kingsorb C18 (250 x 21.2 mm, 5 μ) column equipped with security guard cartridge), with an isocratic mobile phase of H₂O at flow rate of 8.0 mL/min detected at 254 nm. Fractions containing product (*t_R* = 8.97 min) were collected and concentrated under reduced pressure. Iodomuscimol (**5**) was obtained as a colourless solid after freeze drying (17.3 mg, 19%). Analytical HPLC analysis was performed using Shimadzu system (Phenomenex Kingsorb C18 (150 x 4.6 mm, 5 μ) column), with an isocratic mobile phase of H₂O at flow rate of 0.8 mL/min detected at 254 nm (*t_R* = 2.19 min, purity >99%); **mp** 161-162 °C; **FT-IR** (ATR, cm⁻¹) 3350, 2990, 2637 (br), 2363, 1616, 1487, 1358, 1254, 1077, 1037, 968; **δ_H** (400 MHz, D₂O) 4.21 (s, 2H, H-6); **δ_C** (176 MHz, D₂O) 176.4 (C-3), 163.2 (C-5), 61.6 (C-4), 35.3 (C-6); **HRMS** *m/z* (ESI⁺), found: [M+H]⁺ 240.9466, C₄H₆N₂O₂¹²⁷I requires [M+H]⁺ 240.9474.

References

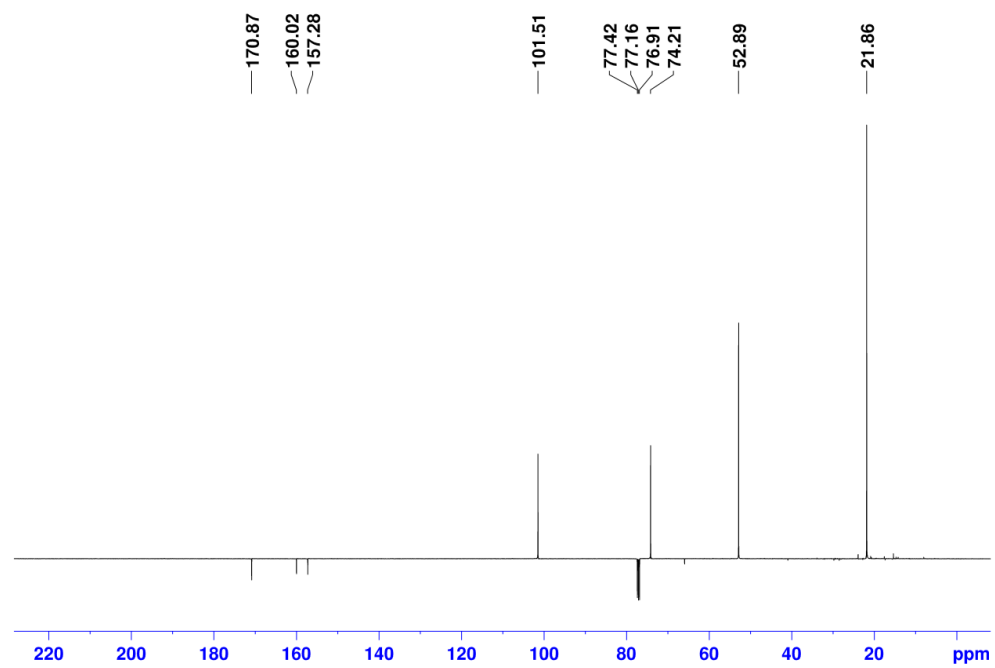
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Methyl 3-isopropoxyisoxazole-5-carboxylate (7)

¹H-NMR

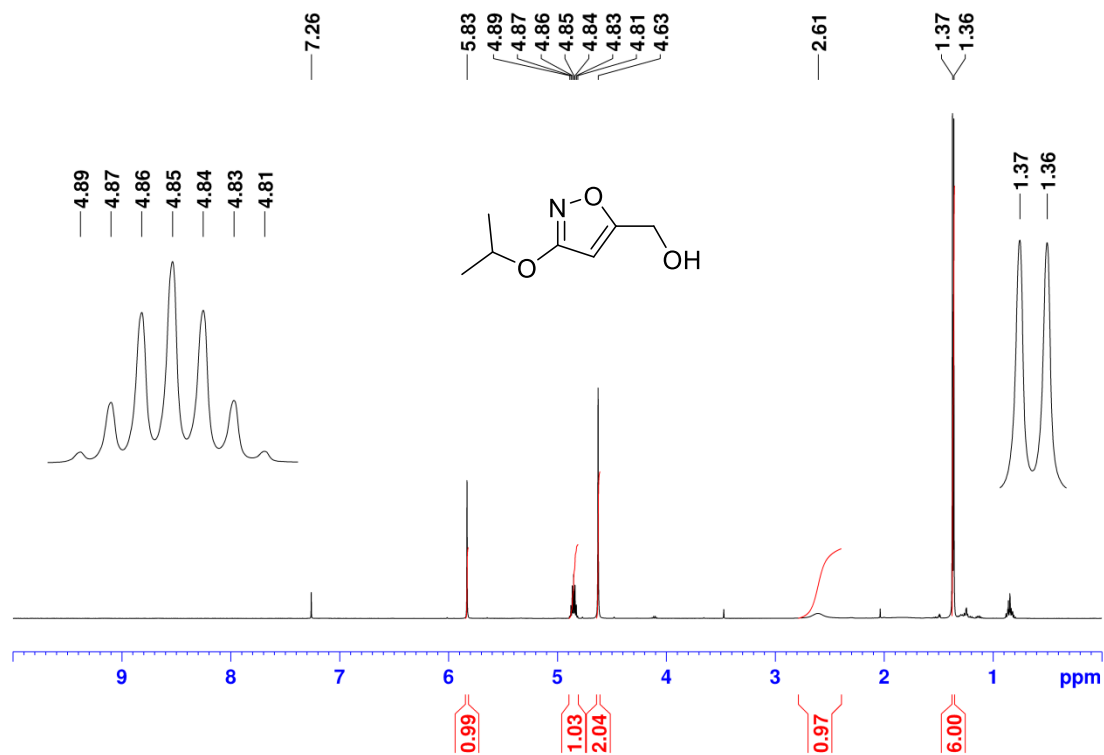


¹³C-NMR

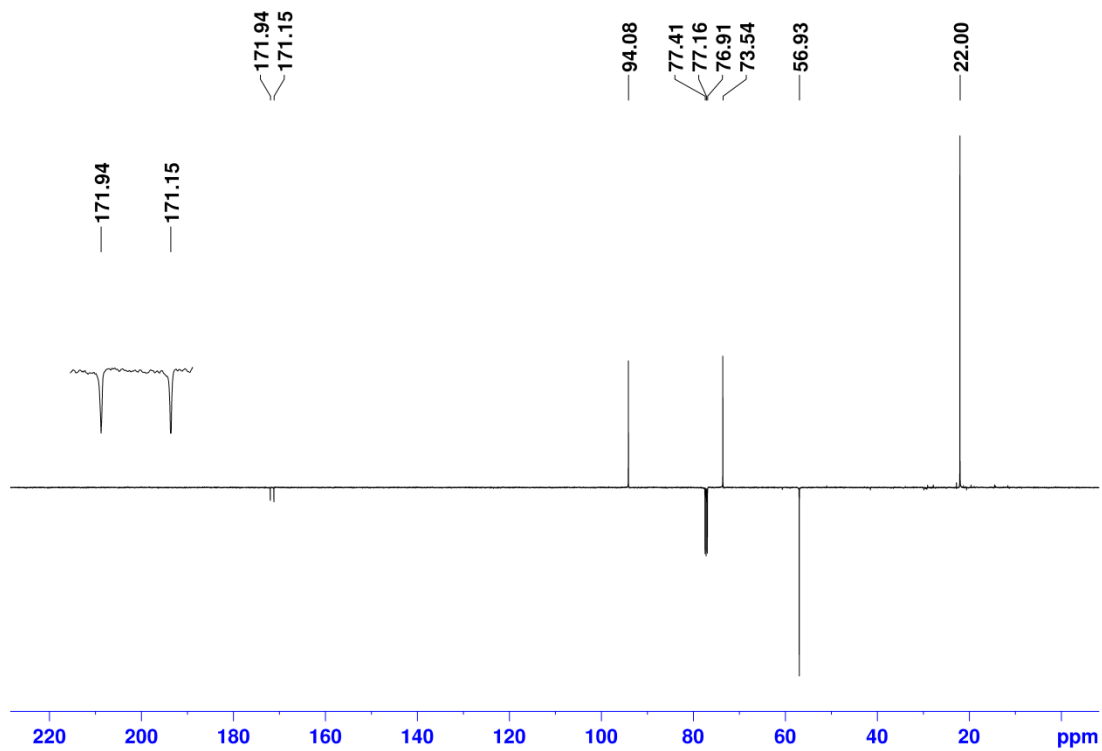


5-Hydroxymethyl-3-isopropoxyisoxazole (8)

¹H-NMR

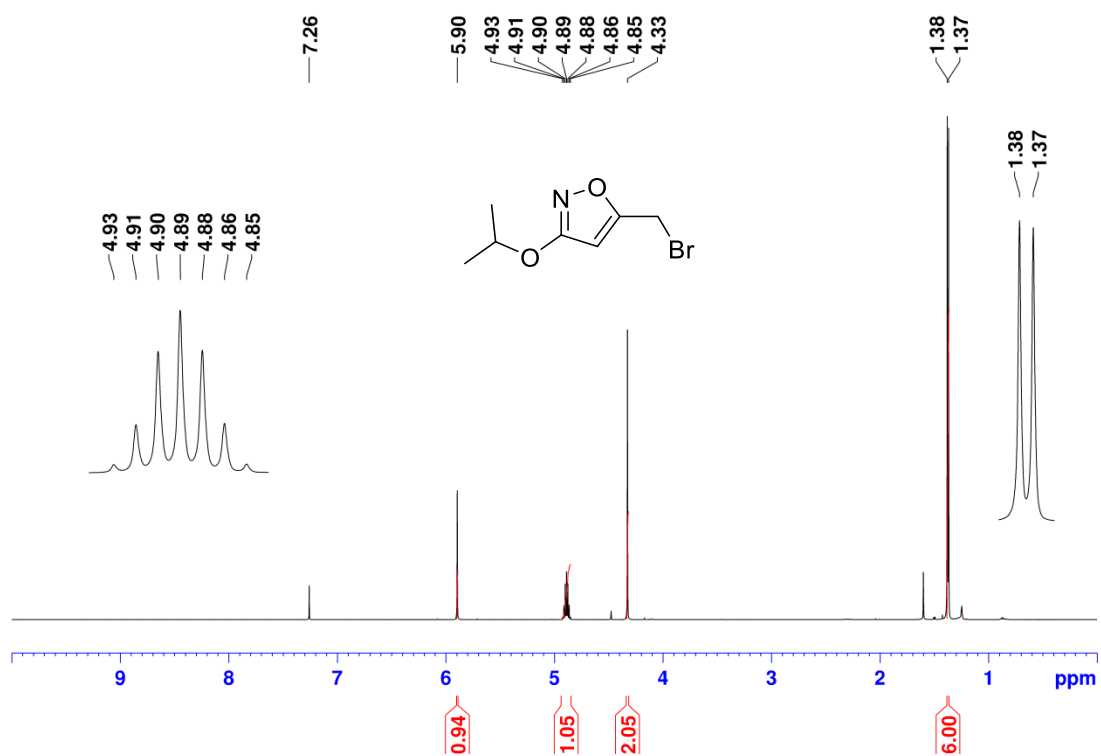


¹³C-NMR

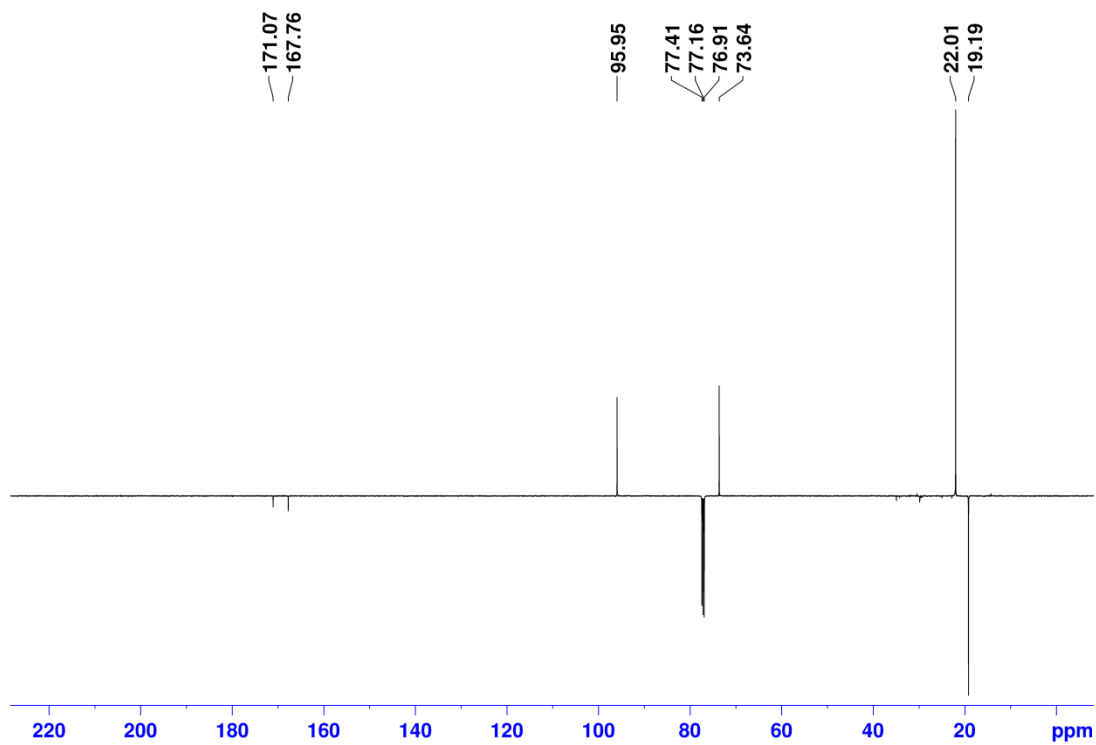


5-Bromomethyl-3-isopropoxyisoxazole (9)

$^1\text{H-NMR}$

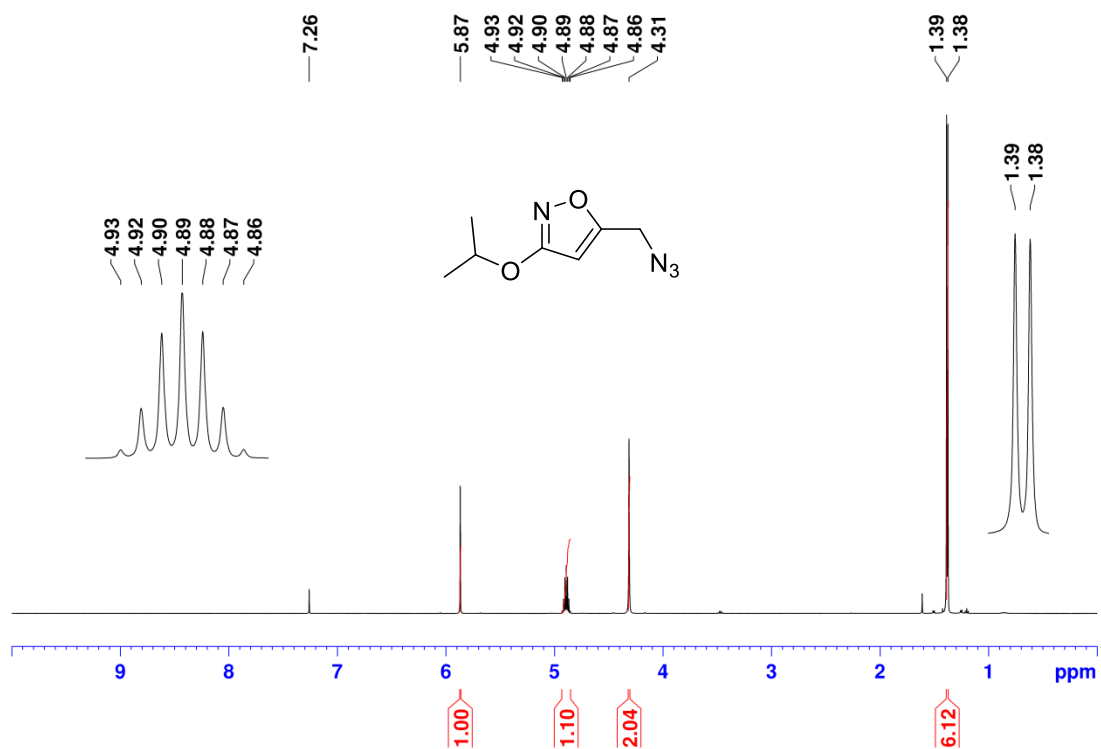


$^{13}\text{C-NMR}$

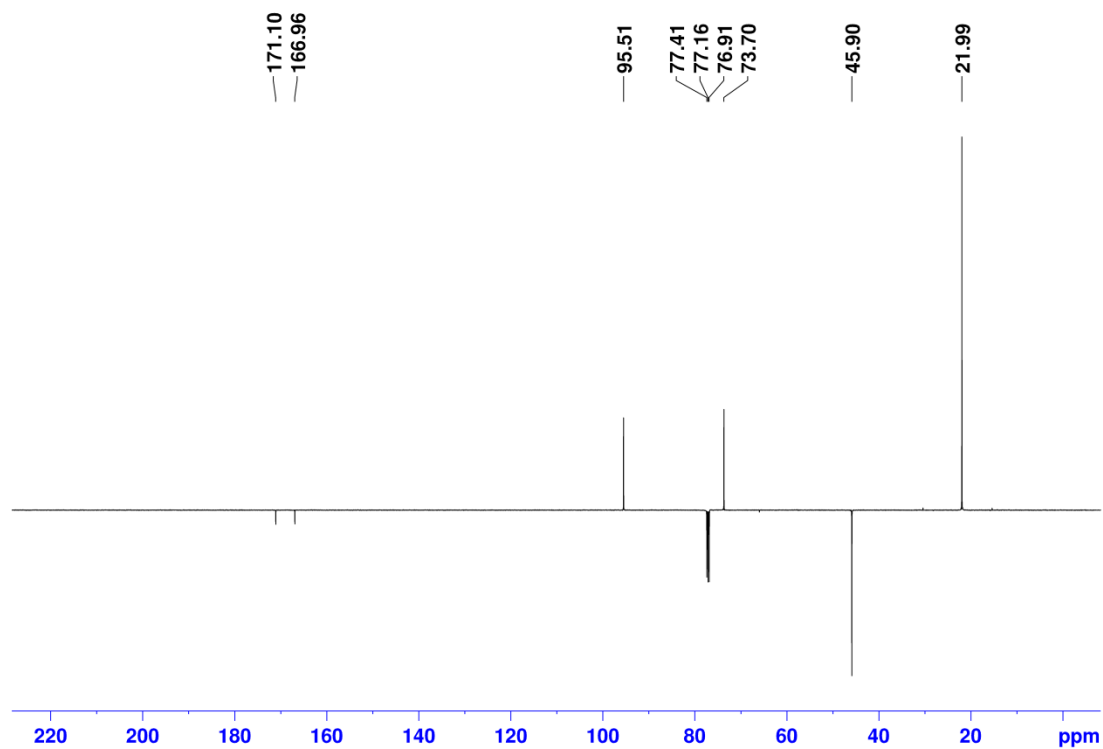


5-Azidomethyl-3-isopropoxyisoxazole (10)

$^1\text{H-NMR}$

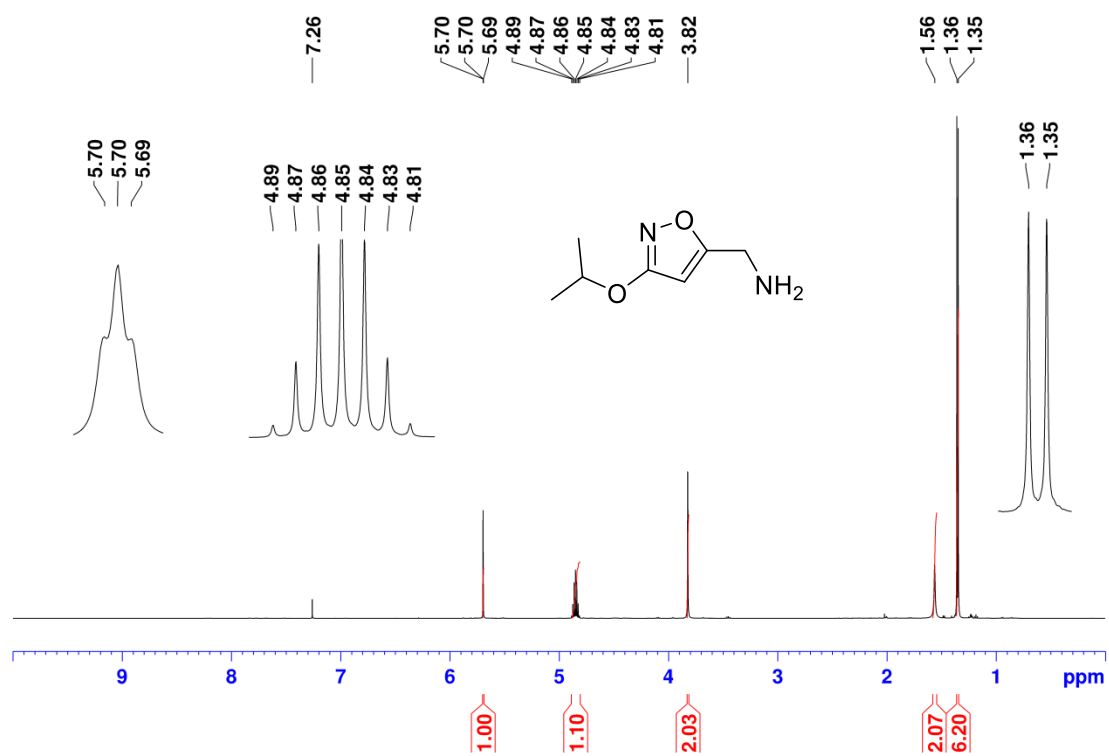


$^{13}\text{C-NMR}$

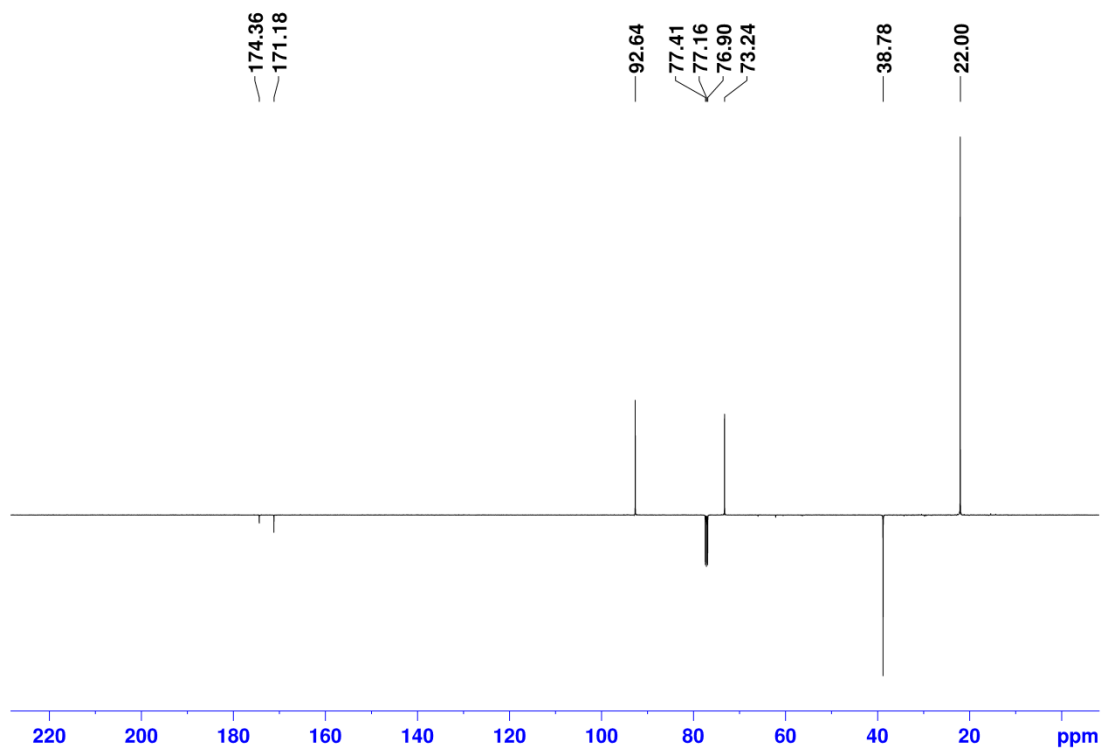


5-Aminomethyl-3-isopropoxyisoxazole (11)

$^1\text{H-NMR}$

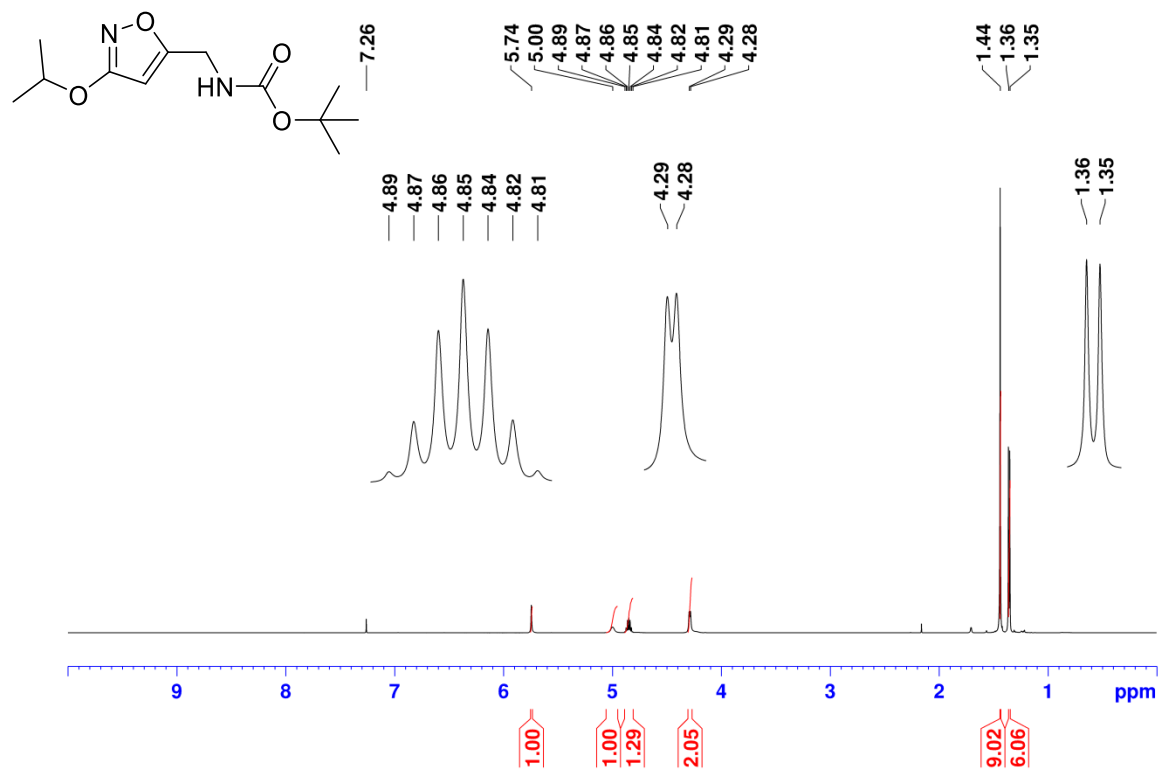


$^{13}\text{C-NMR}$

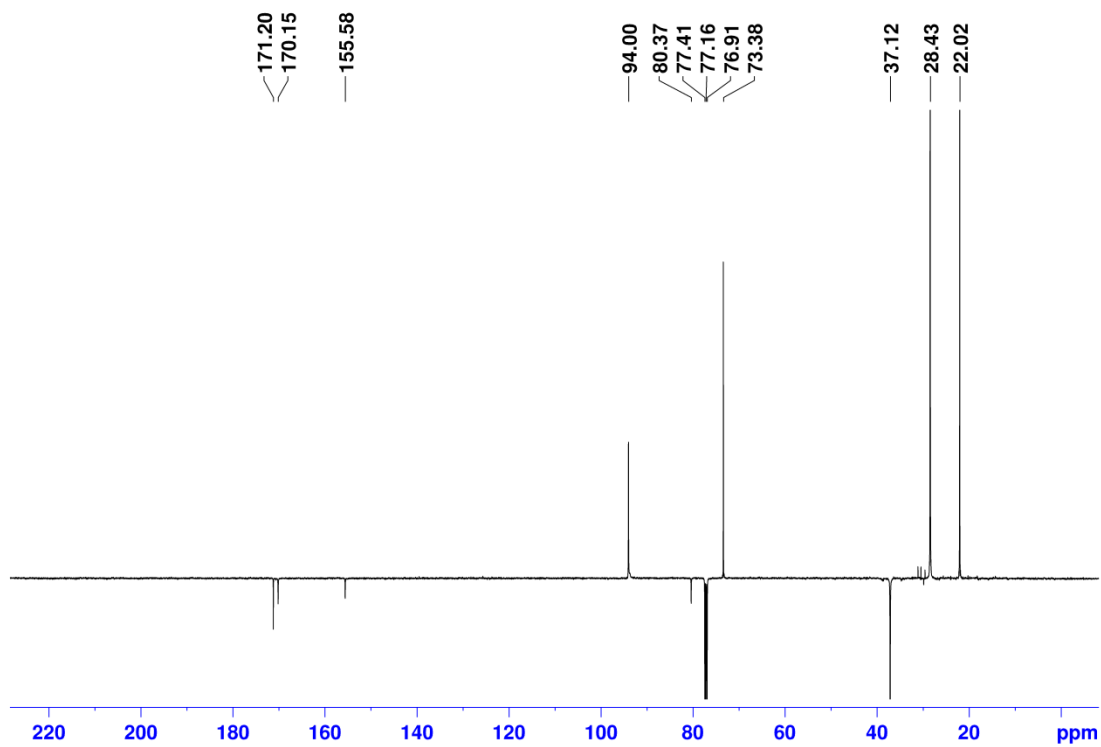


5-(*tert*-Butyloxycarbonyl)aminomethyl-3-isopropoxyisoxazole (12)

$^1\text{H-NMR}$

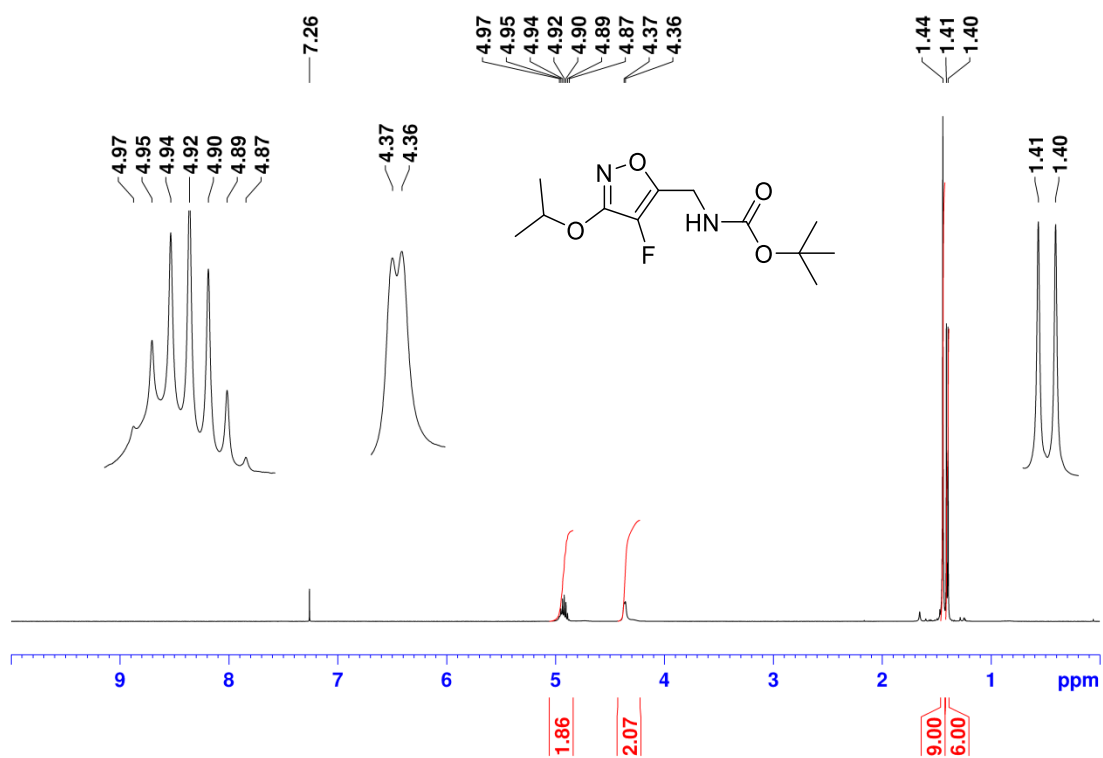


$^{13}\text{C-NMR}$

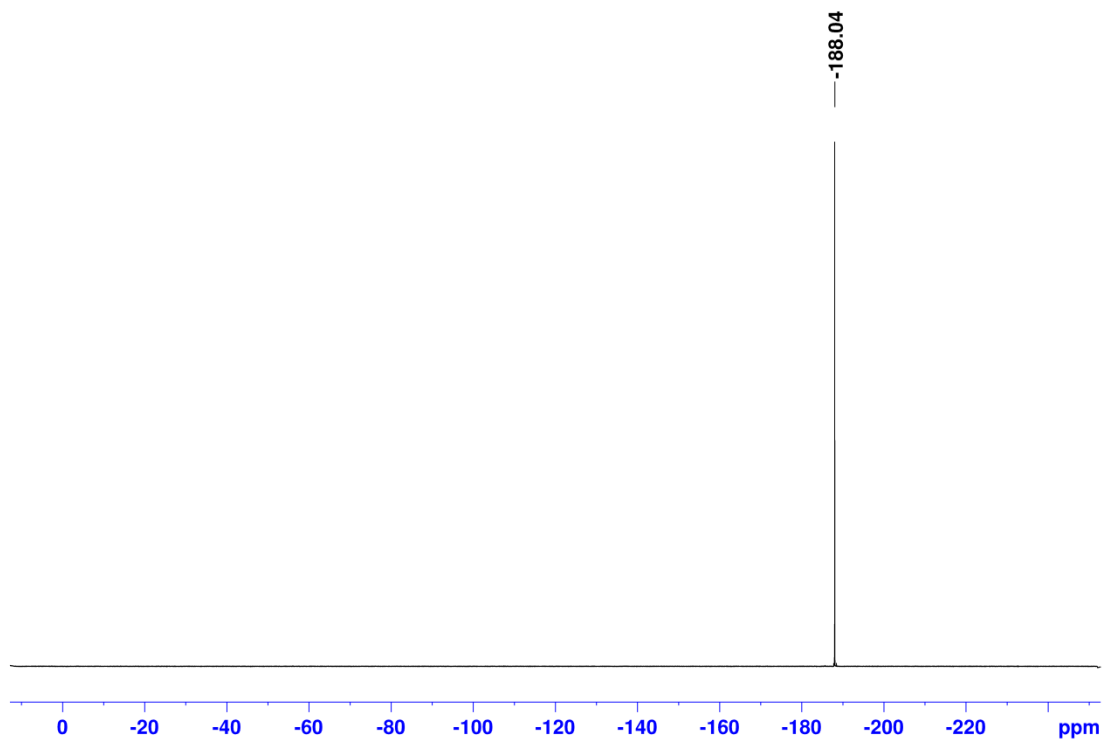


5-(*tert*-Butyloxycarbonyl)aminomethyl-4-fluoro-3-isopropoxyisoxazole (13)

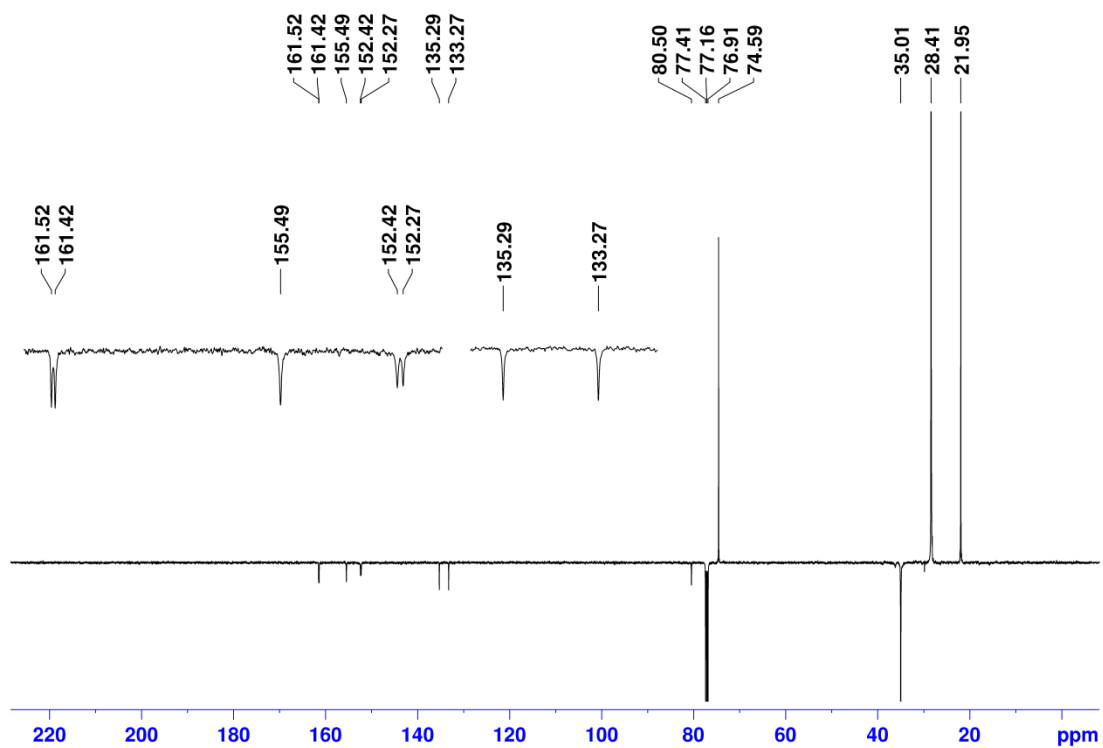
¹H-NMR



¹⁹F-NMR

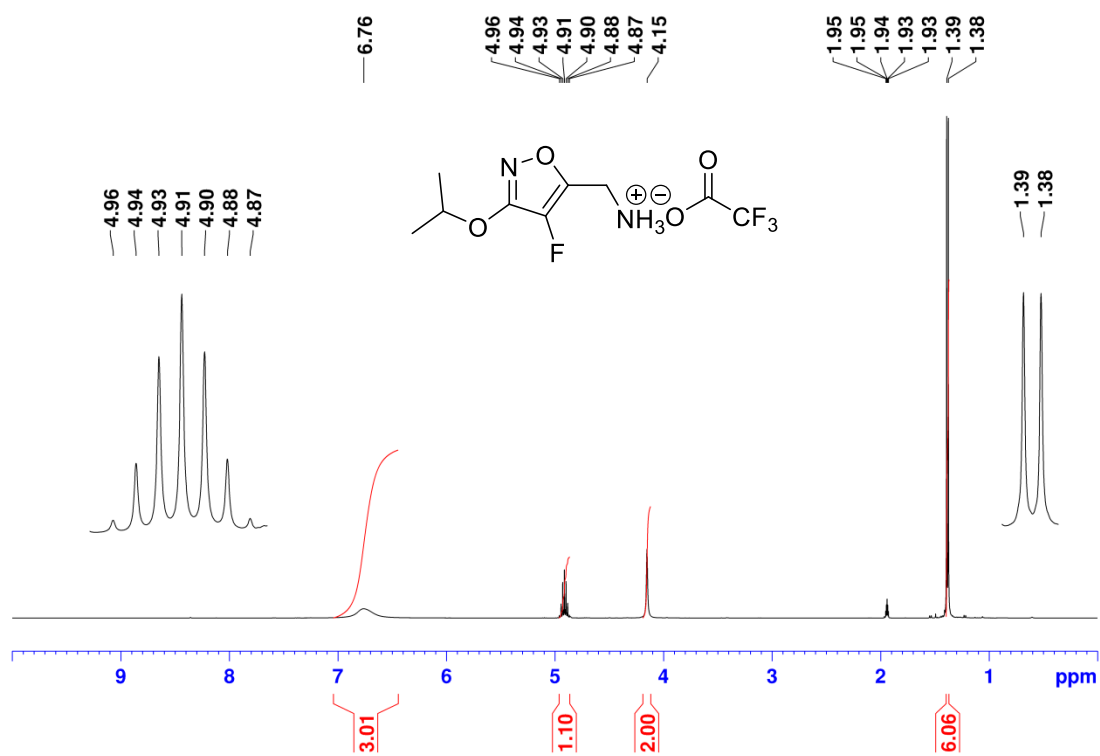


$^{13}\text{C-NMR}$

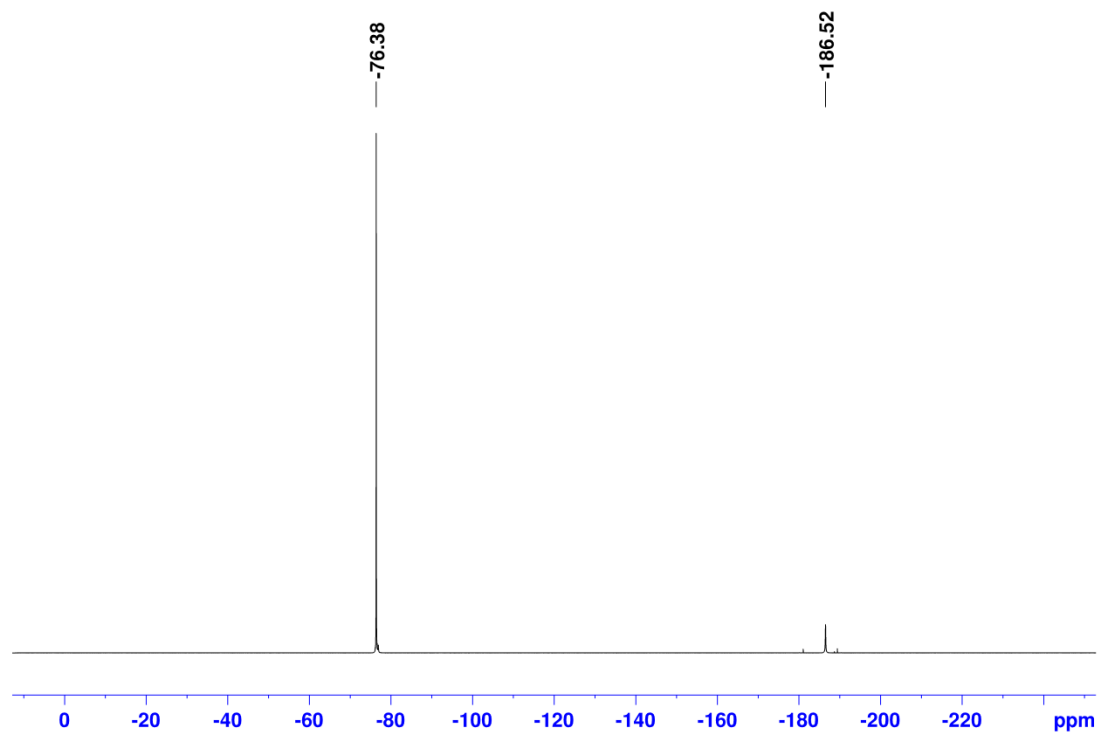


5-Ammoniomethyl -4-fluoro-3-isopropoxyisoxazole trifluoroacetate (14)

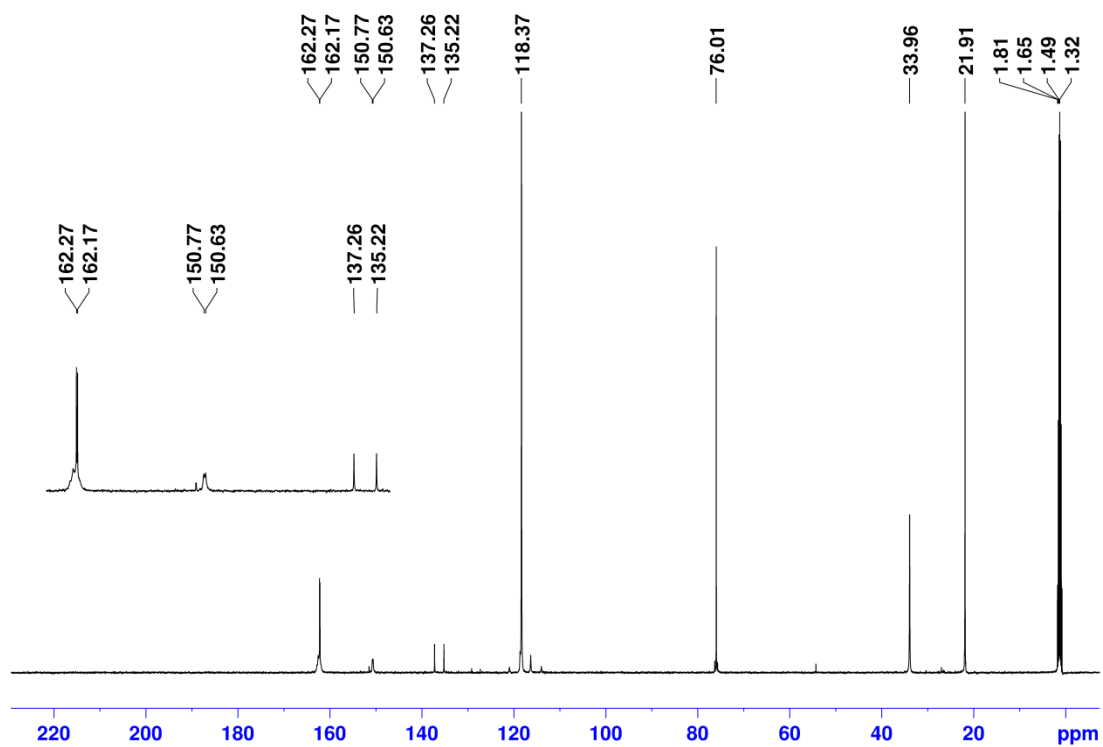
¹H-NMR



¹⁹F-NMR

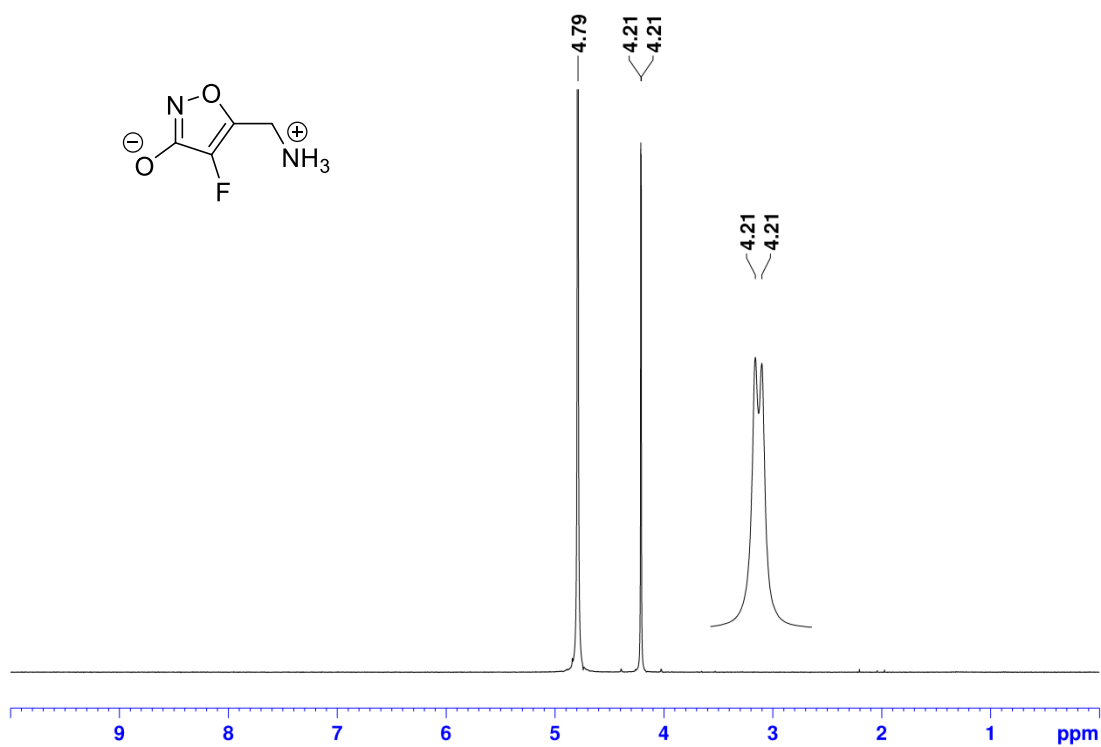


^{13}C -NMR

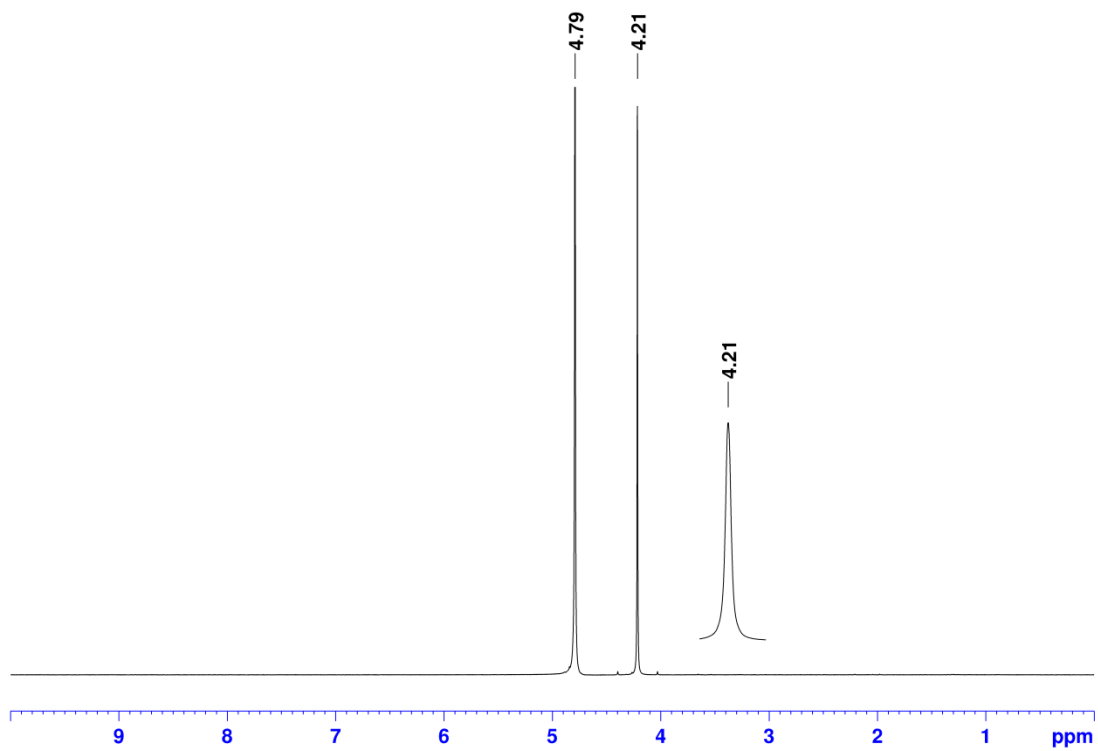


5-Aminomethyl-4-fluoro-3-hydroxyisoxazole (3)

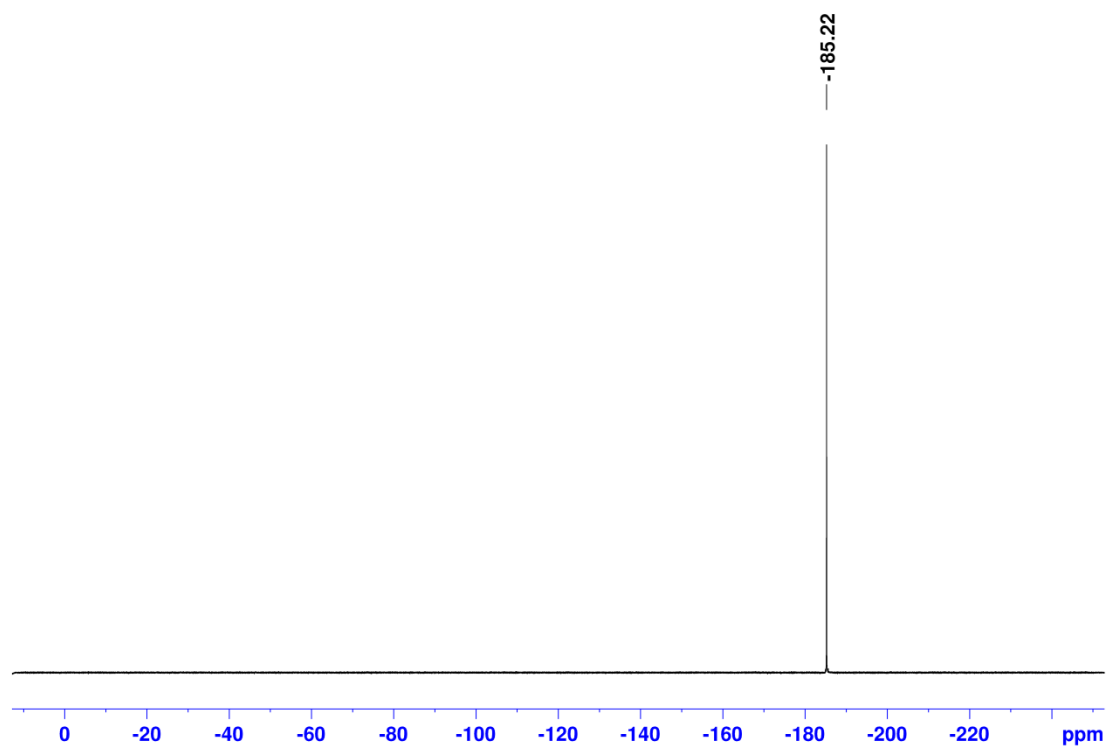
^1H -NMR



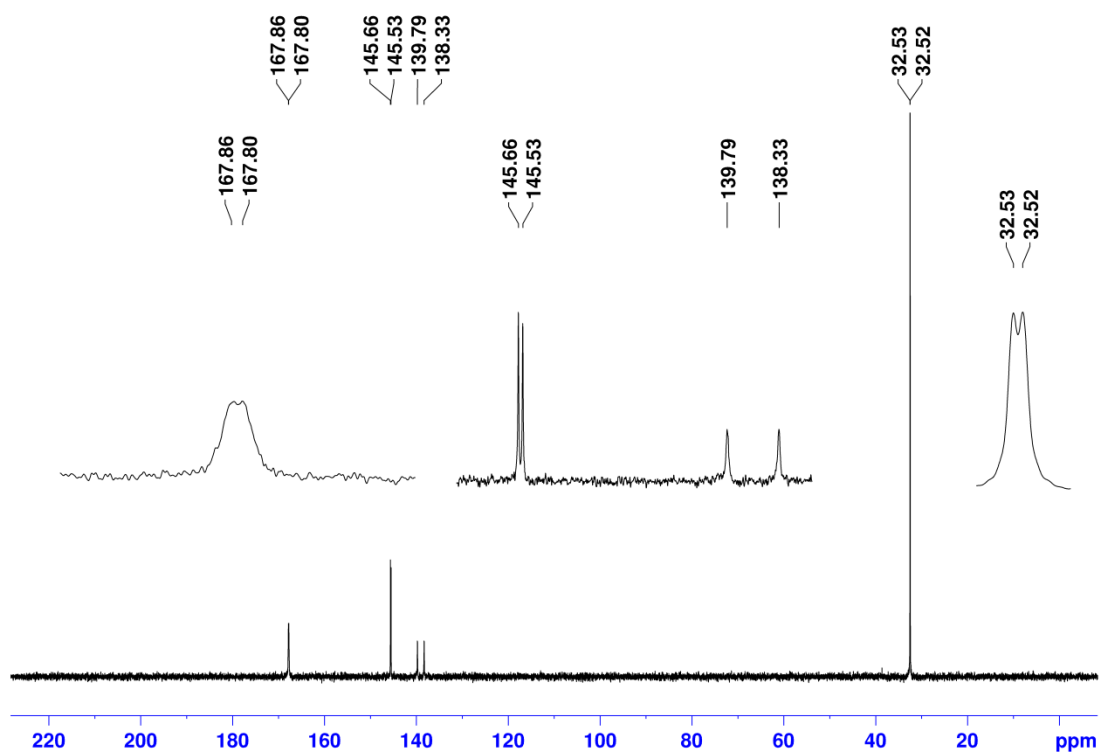
$^1\text{H}\{^{19}\text{F}\}$ -NMR



¹⁹F-NMR

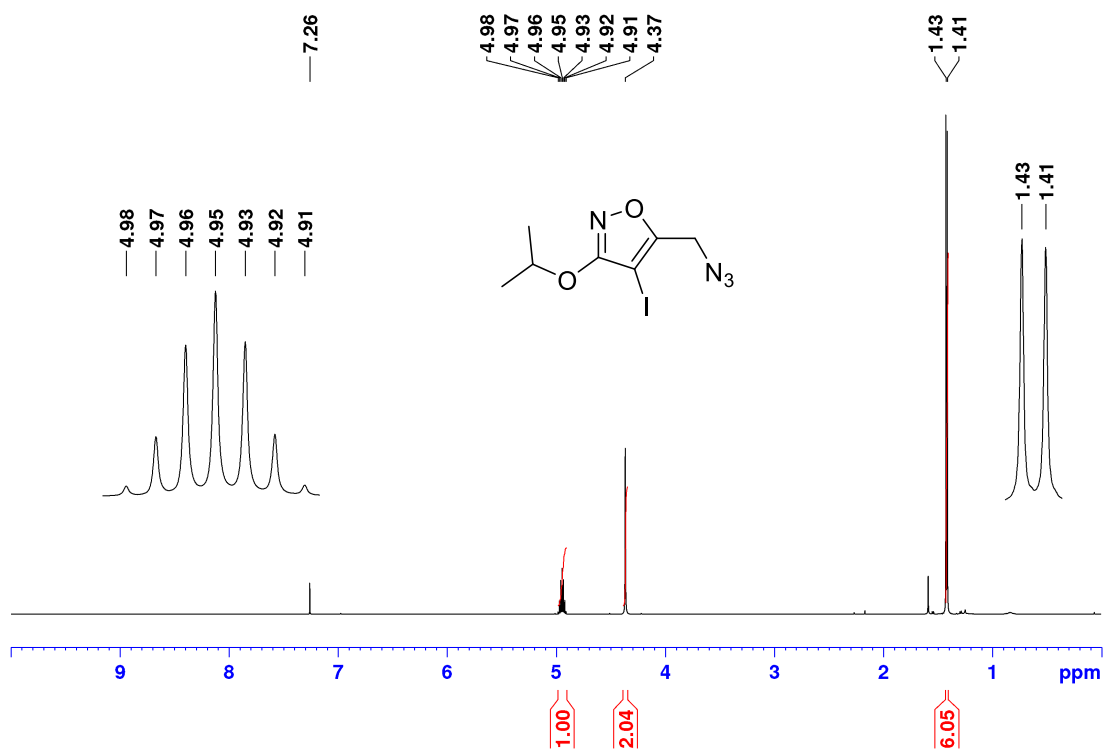


¹³C-NMR

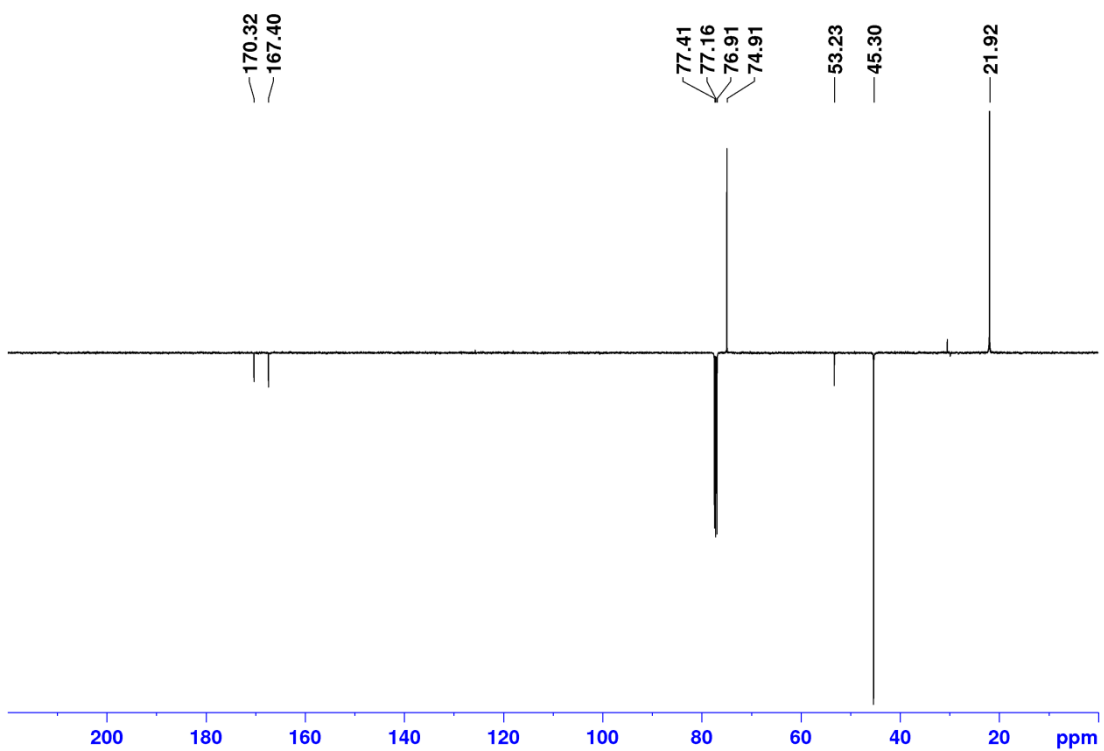


5-Azidomethyl-4-iodo-3-isopropoxyisoxazole (15)

¹H-NMR

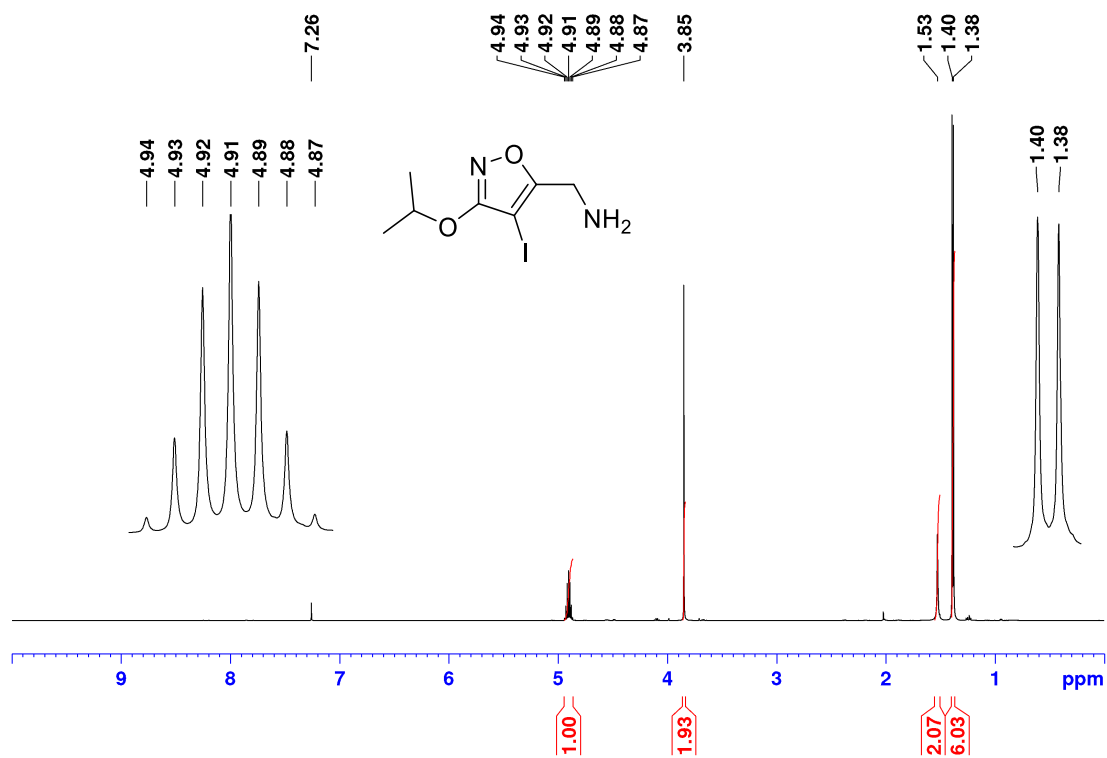


¹³C-NMR

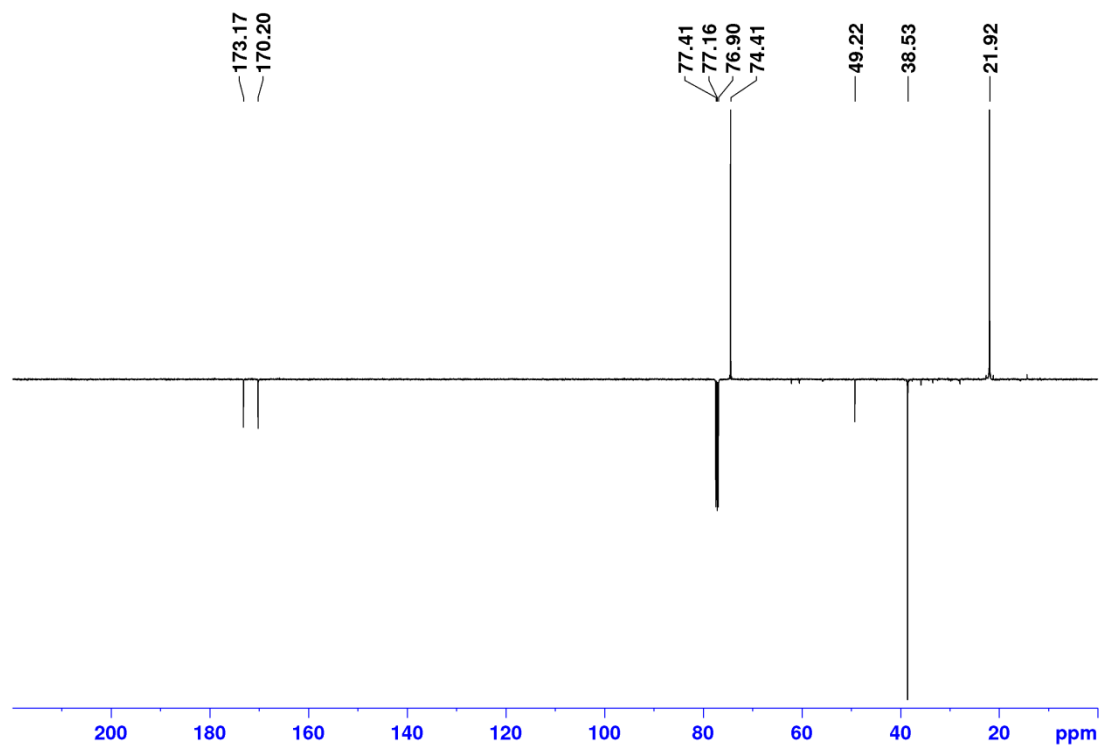


5-Aminomethyl-4-iodo-3-isopropoxyisoxazole (16)

$^1\text{H-NMR}$

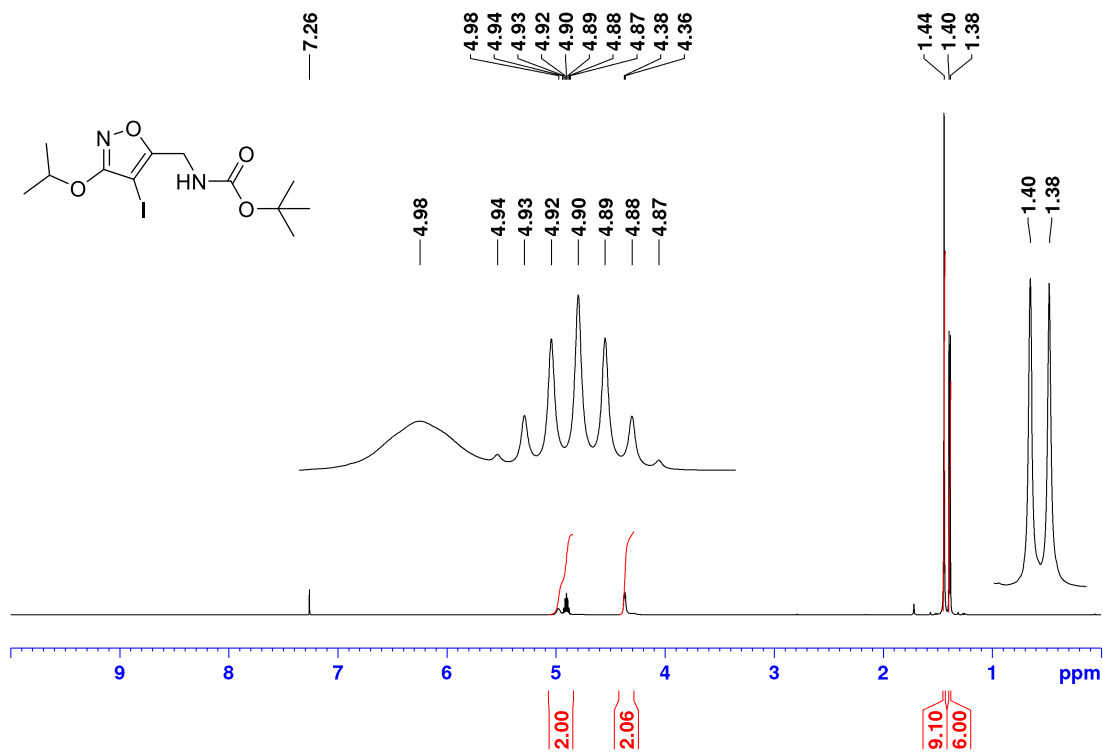


$^{13}\text{C-NMR}$

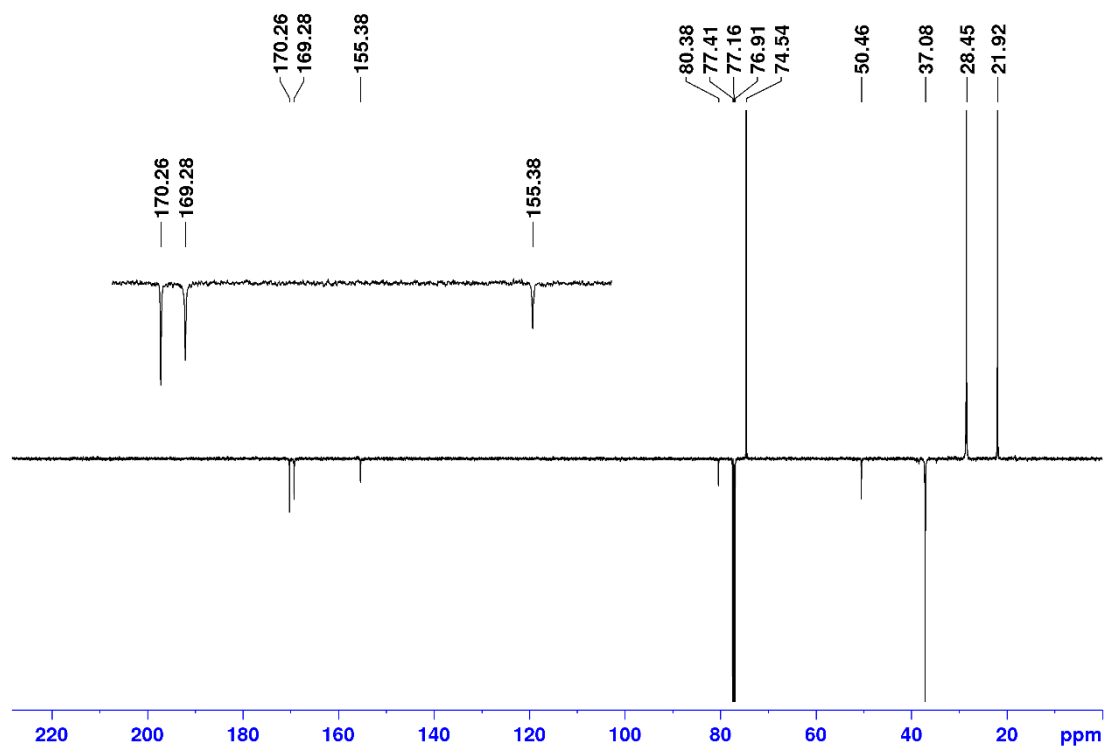


5-(*tert*-Butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (17)

¹H-NMR

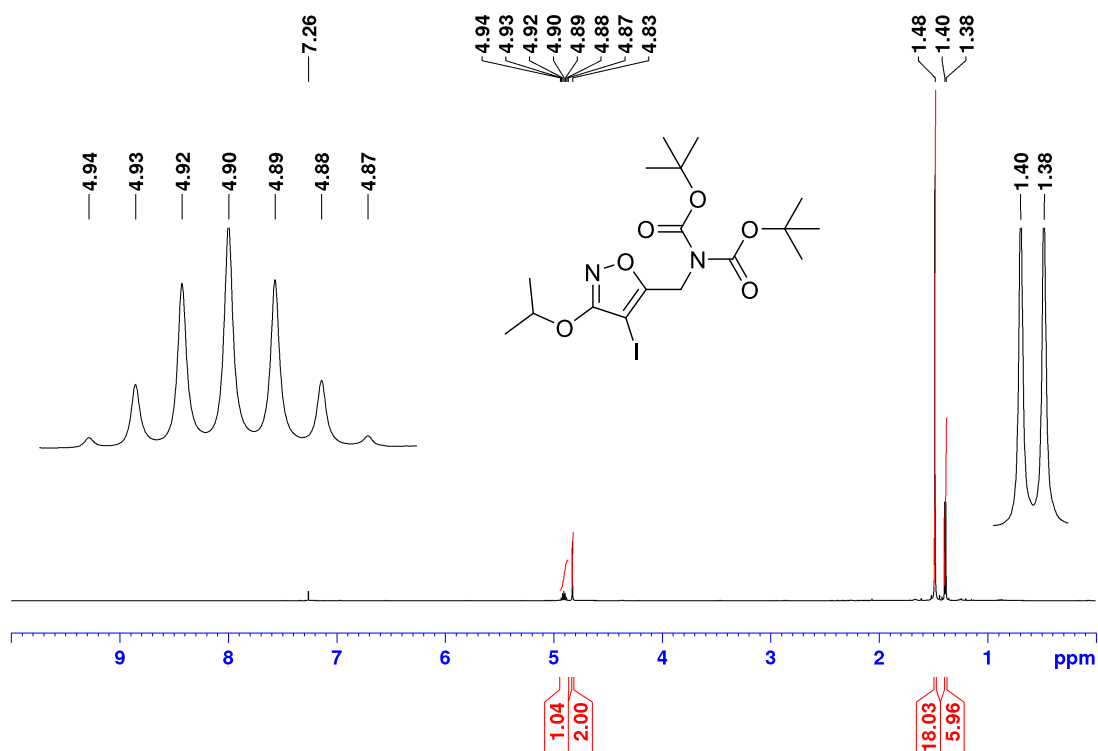


¹³C-NMR

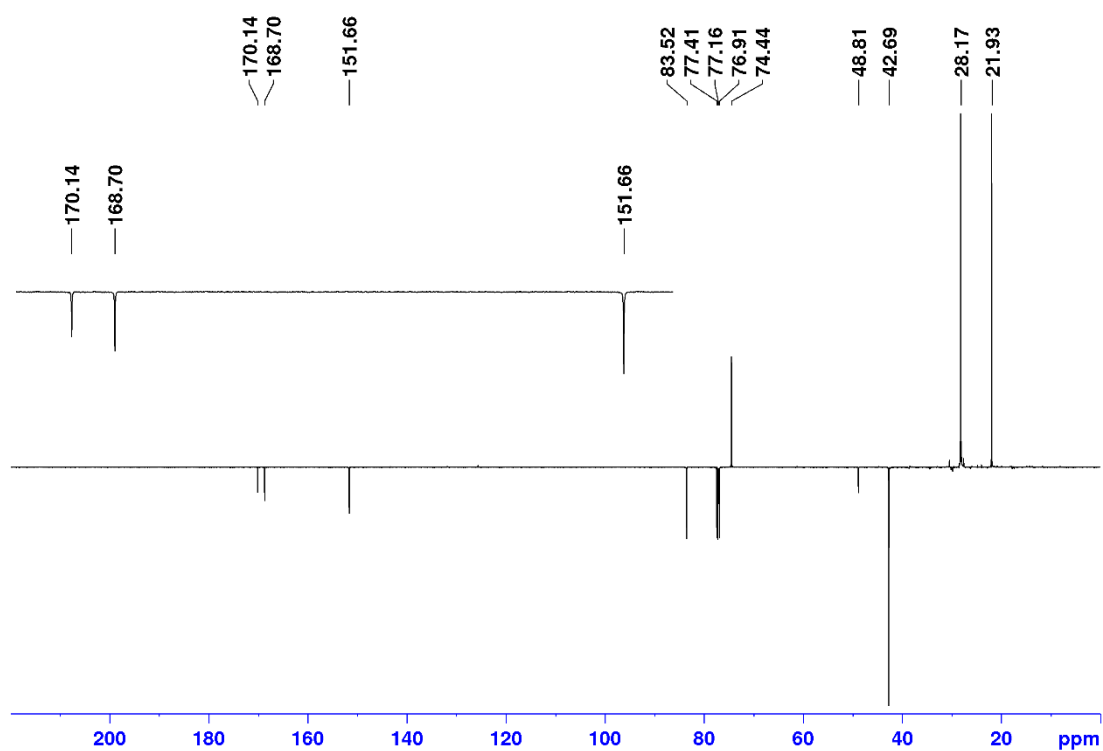


5-Di(*tert*-butyloxycarbonyl)aminomethyl-4-iodo-3-isopropoxyisoxazole (18)

¹H-NMR

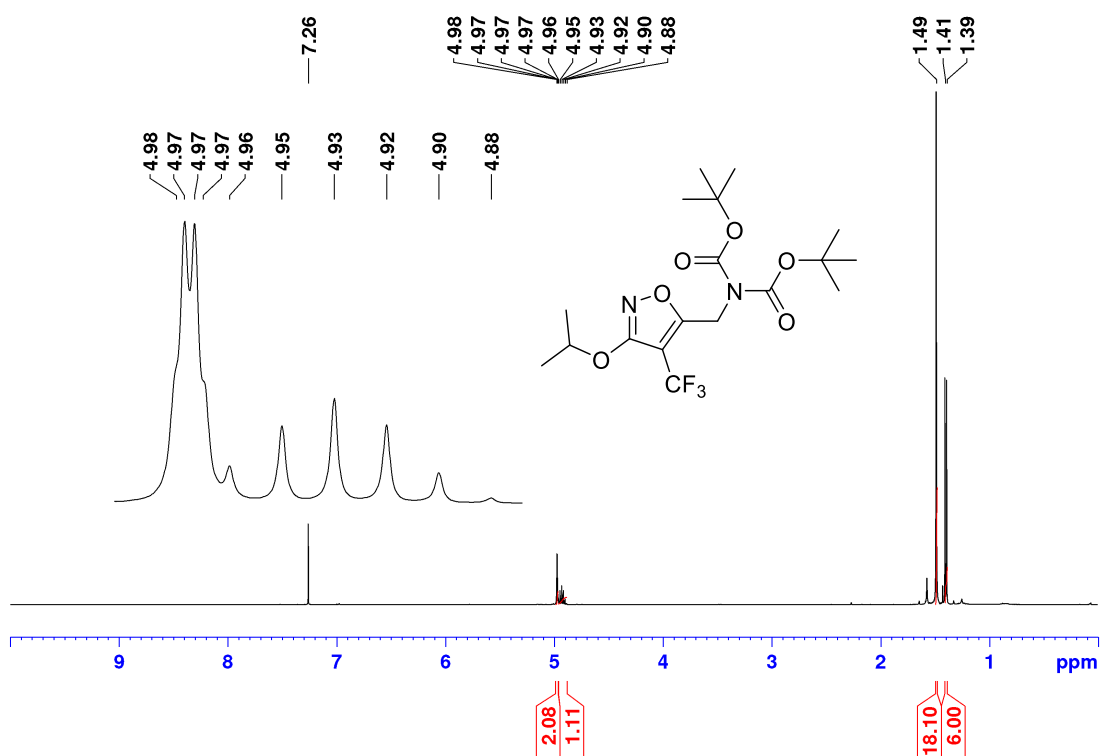


¹³C-NMR

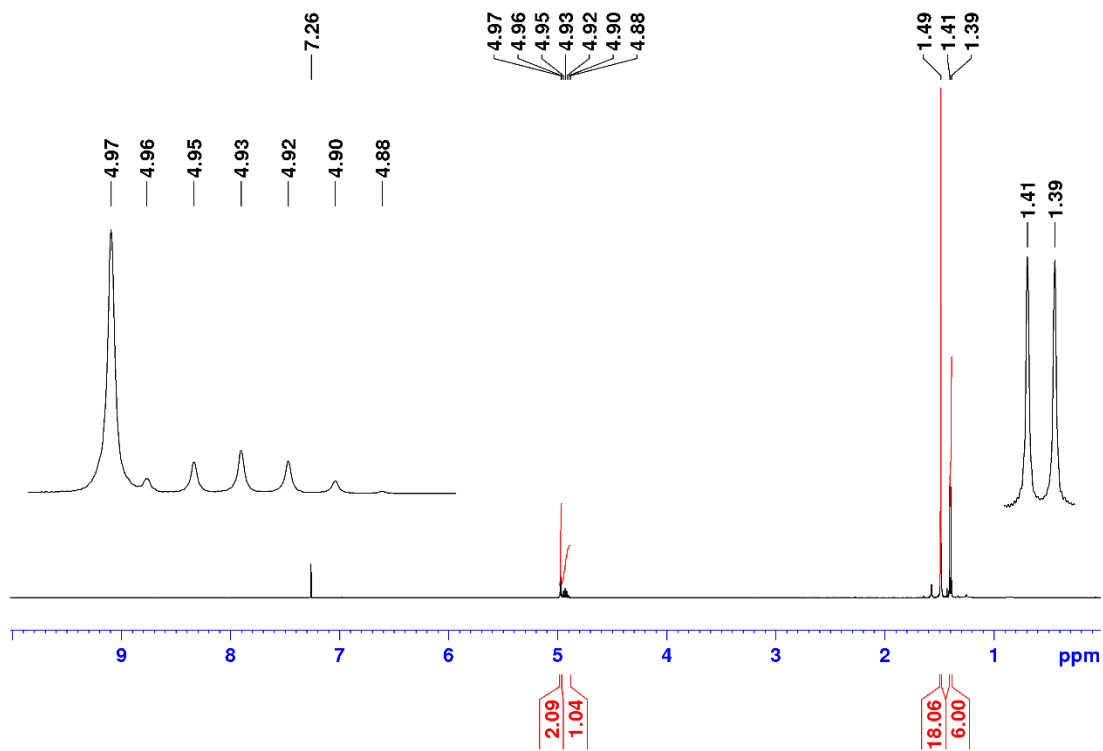


5-Di(*tert*-butyloxycarbonyl)aminomethyl-4-trifluoromethyl-3-isopropoxyisoxazole (19)

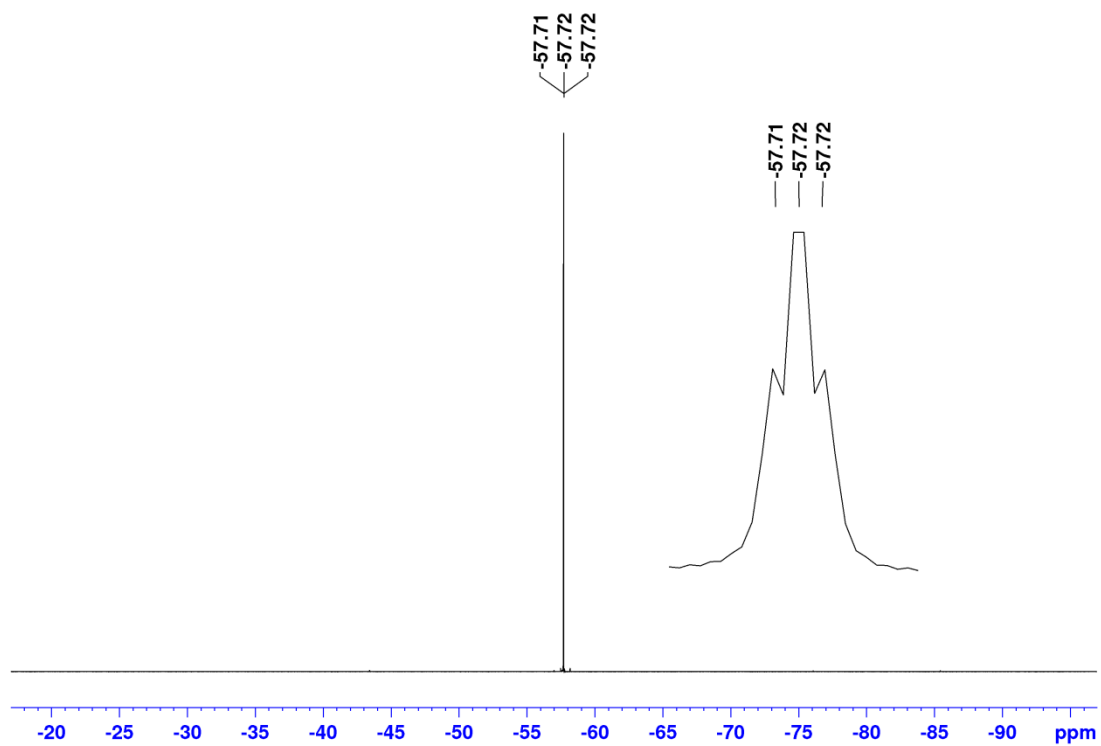
^1H -NMR



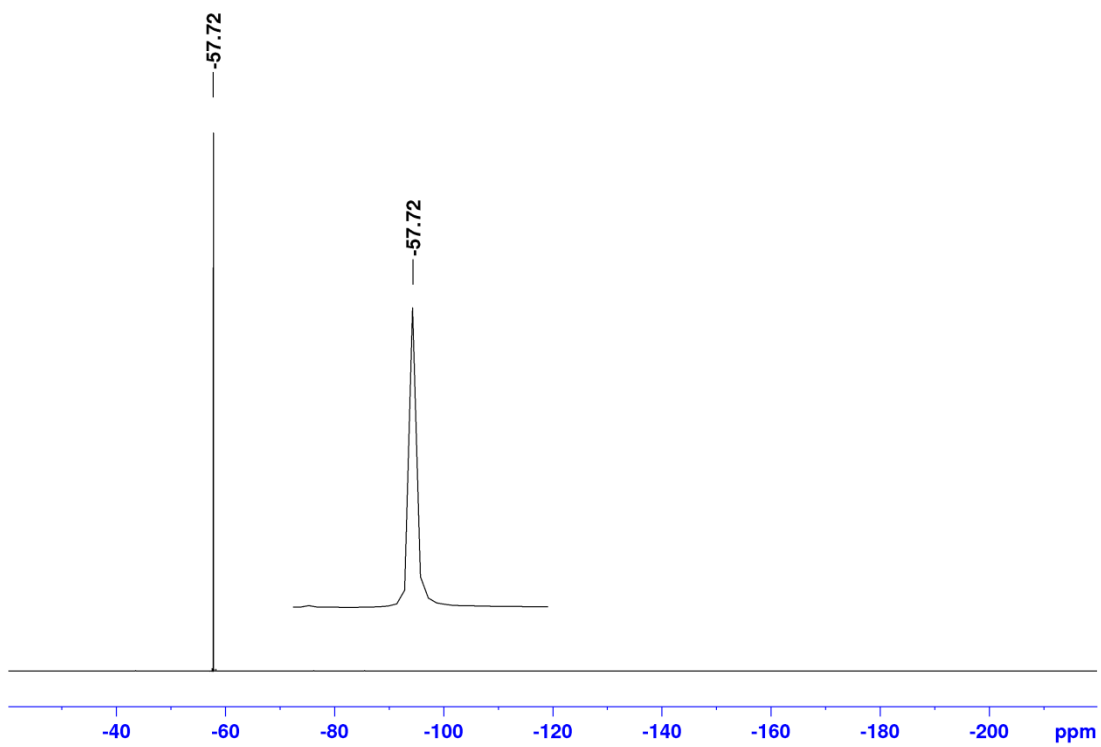
$^1\text{H}\{^{19}\text{F}\}$ -NMR



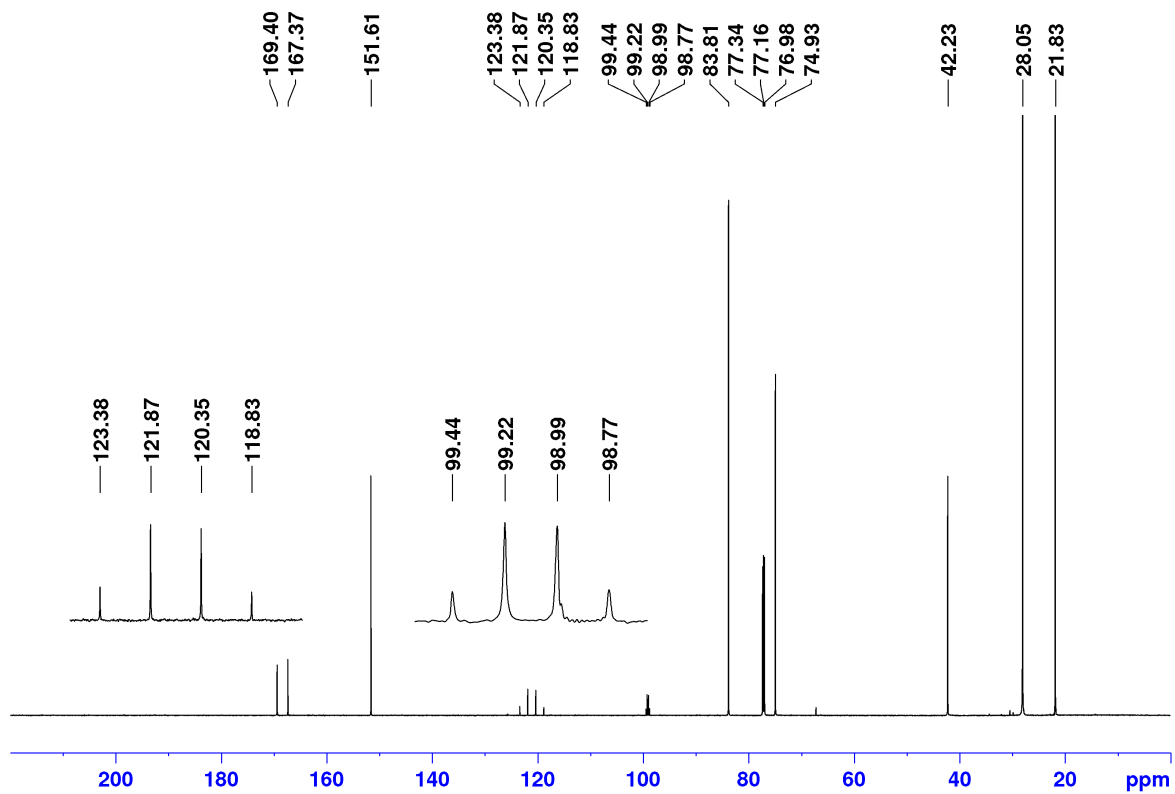
^{19}F -NMR



$^{19}\text{F}\{^1\text{H}\}$ -NMR

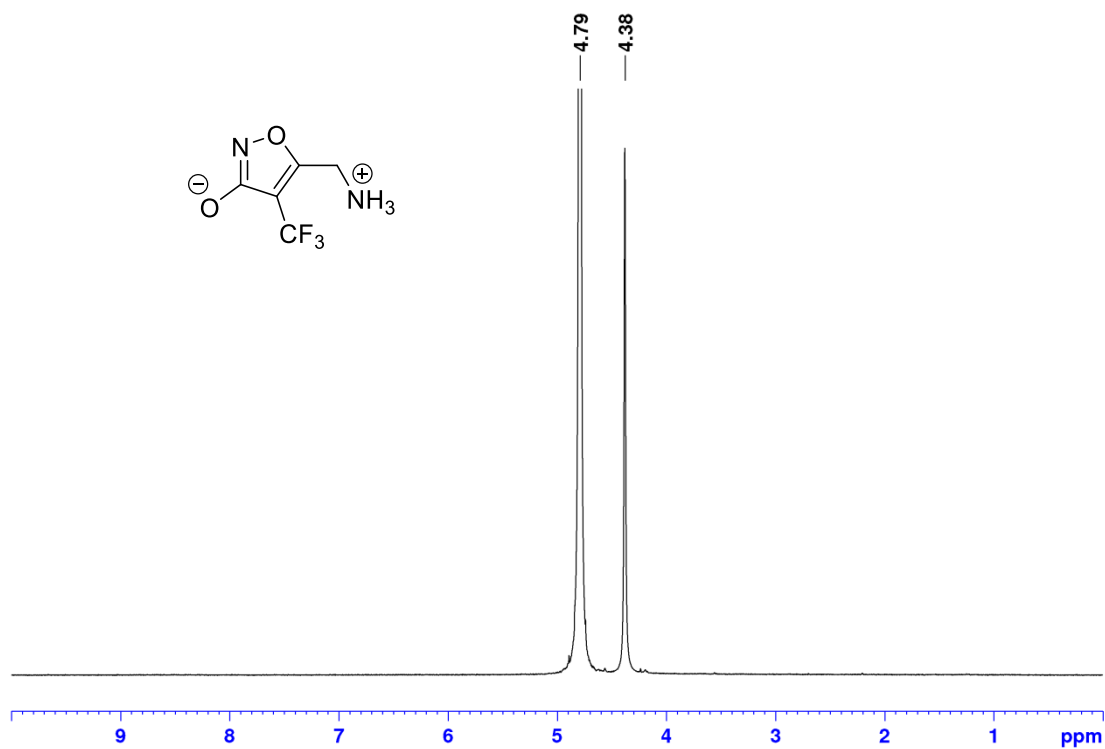


¹³C-NMR

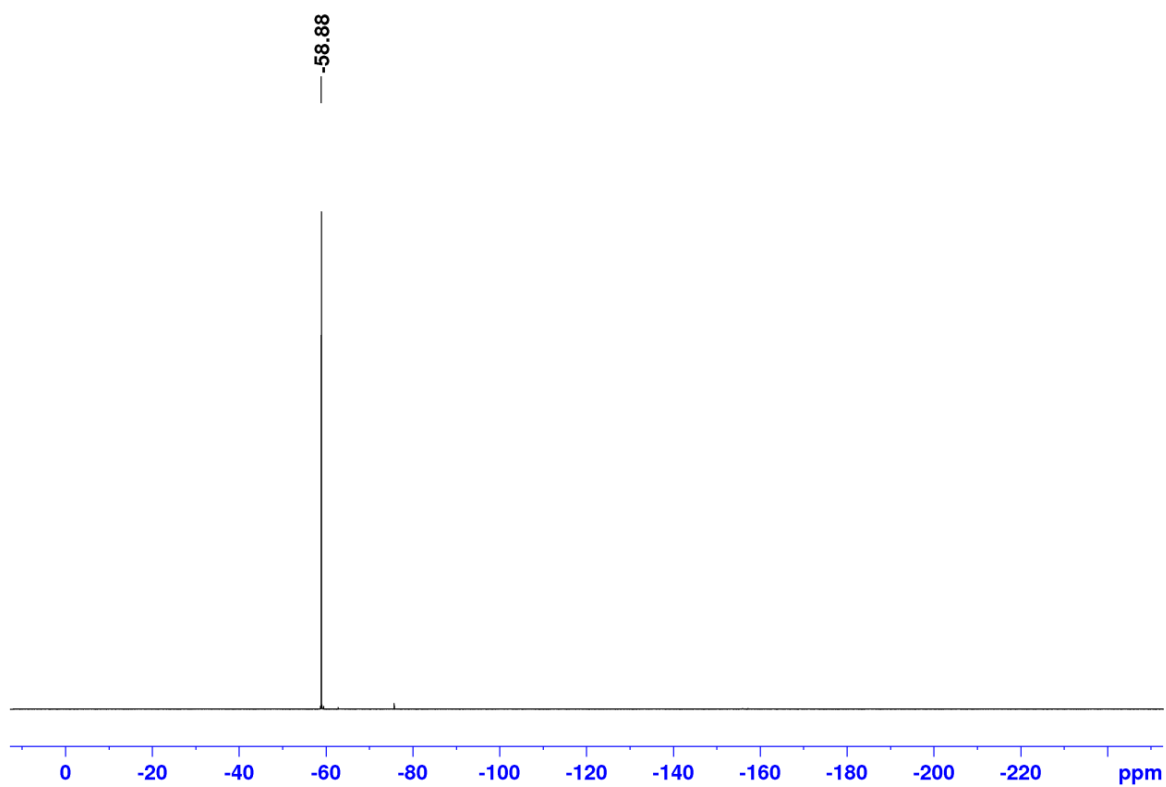


5-Aminomethyl-4-trifluoromethyl-3-hydroxyisoxazole (4)

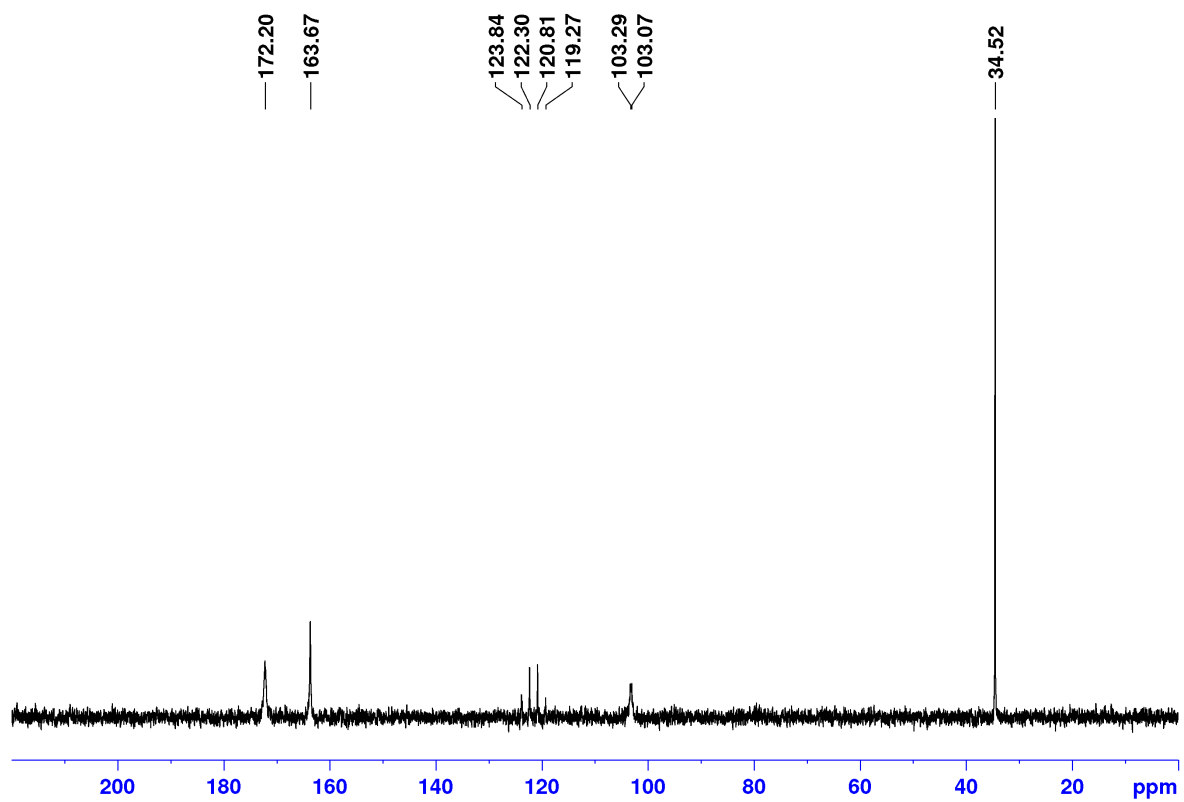
¹H-NMR



¹⁹F-NMR

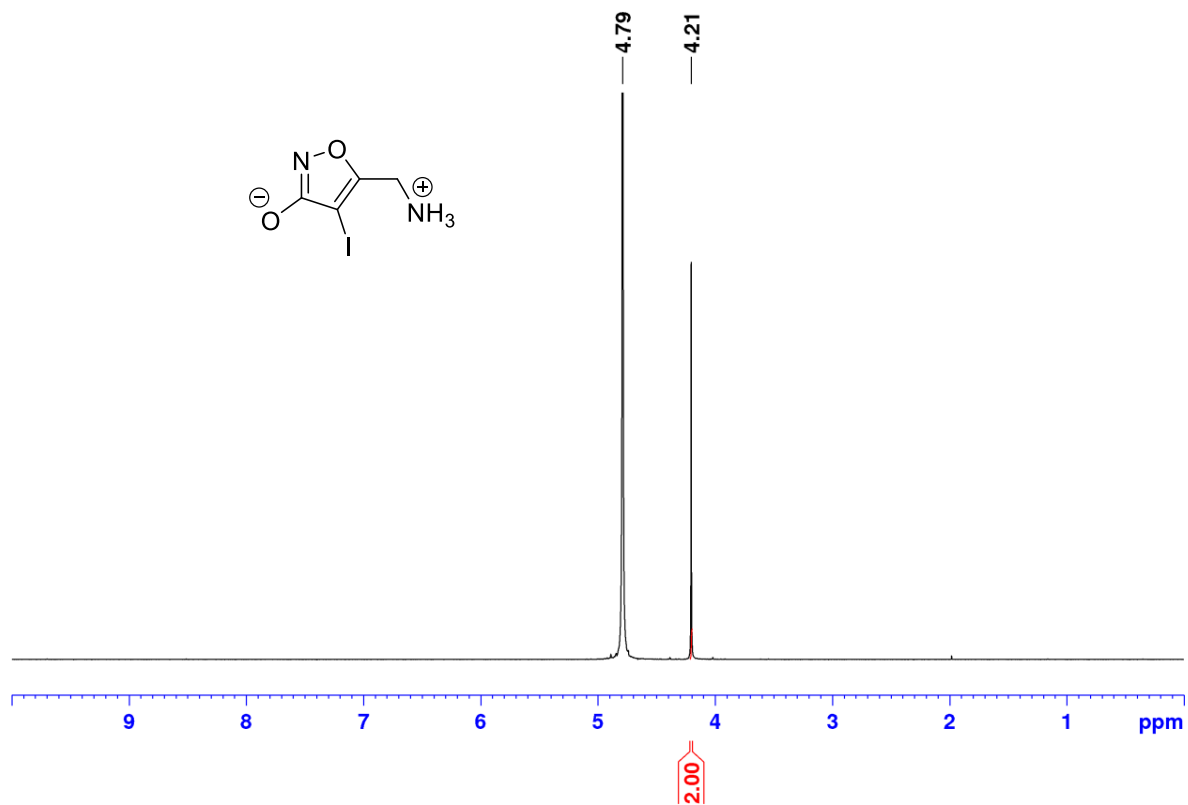


^{13}C -NMR

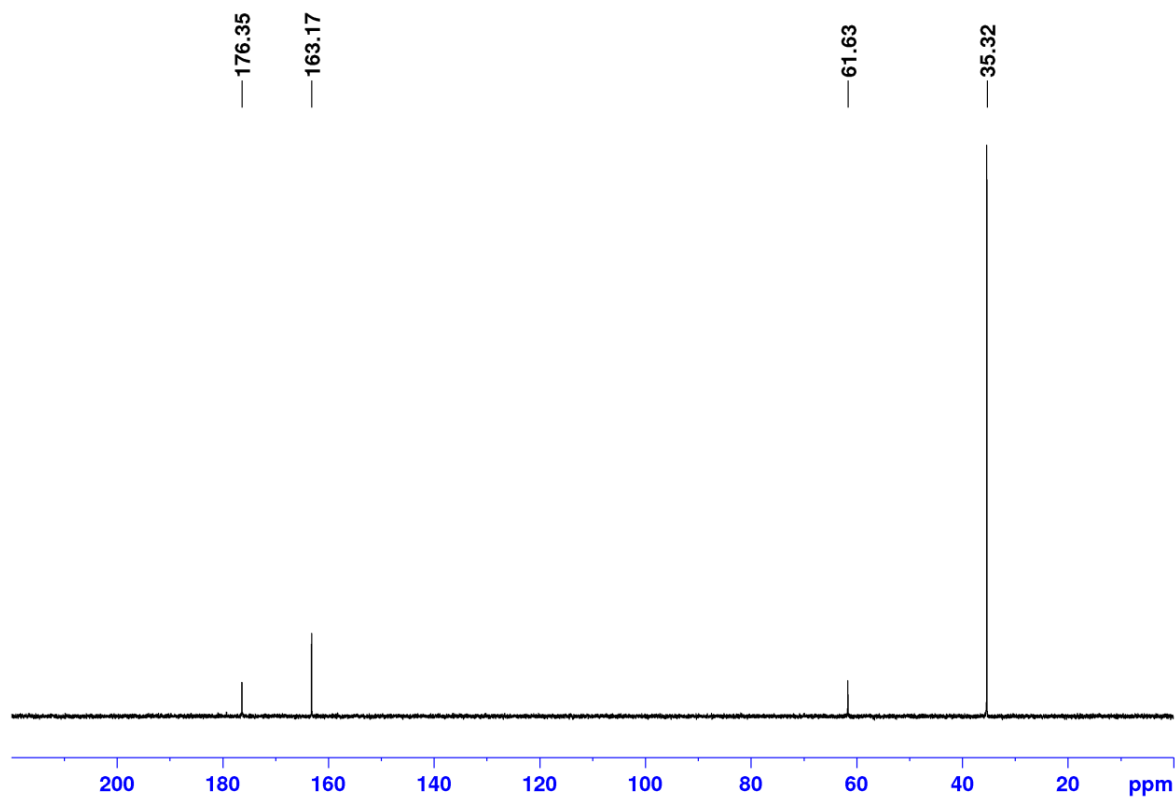


5-Aminomethyl-4-iodo-3-hydroxyisoxazole (5)

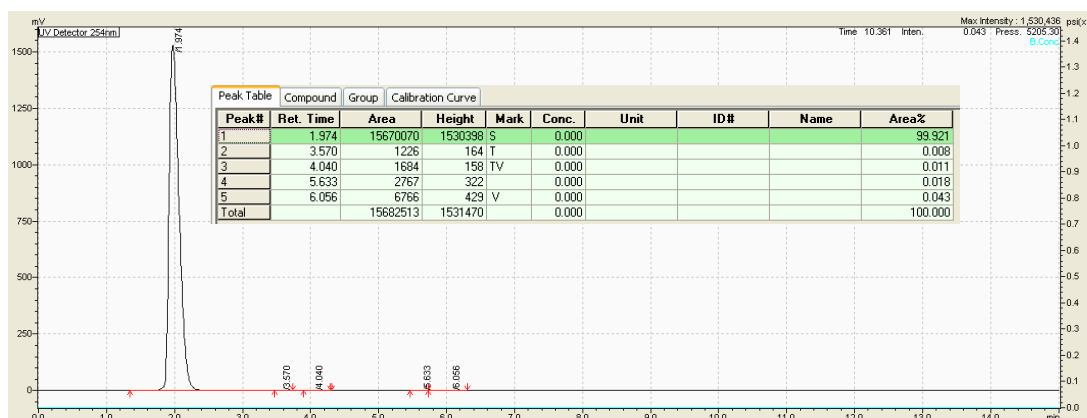
$^1\text{H-NMR}$



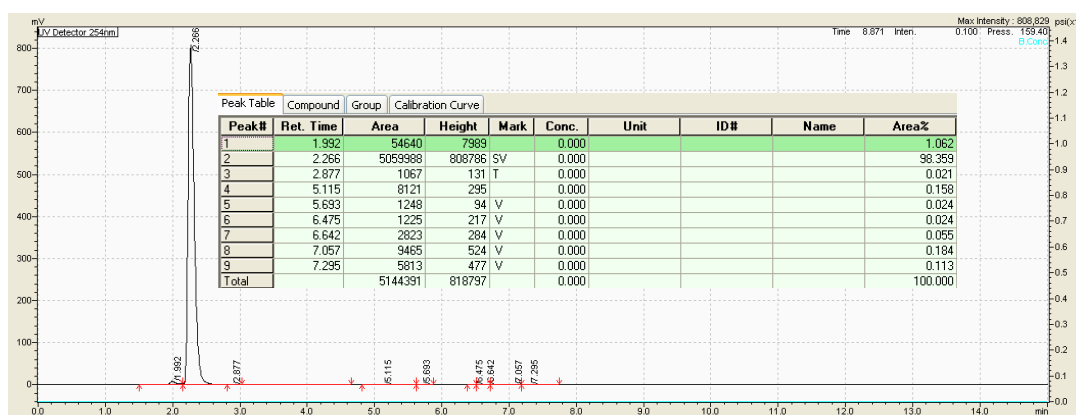
$^{13}\text{C-NMR}$



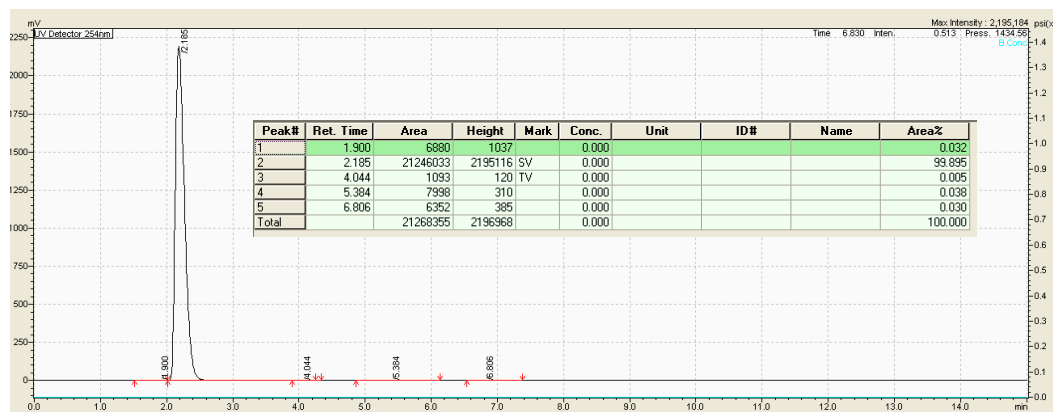
Analytical HPLC of 5-aminomethyl-4-fluoro-3-hydroxyisoxazole (3)



Analytical HPLC of 5-aminomethyl-4-trifluoromethyl-3-hydroxyisoxazole (4)



Analytical HPLC of 5-aminomethyl-4-iodo-3-hydroxyisoxazole (5)



Computational Details for the conformational analysis of **1** and **3**

Conformational analyses of muscimol and its fluoro derivative were performed (employing the Gaussian09 suite of programs)¹¹ at the B3LYP¹²/6-311+G** level of density functional theory, using an implicit solvent model, namely the polarizable conductor variant of the polarizable continuum model (CPCM),¹³ with the default settings in Gaussian 09.

Assuming zwitterionic structures throughout, initial relaxed scans of the rotational profiles for the ammonium side group (using the C-C-C-NH₃ dihedral as coordinate in steps of 10°, see Figure S1) revealed the existence of only one minimum each for muscimol and fluoromuscimol (or rather, enantiomeric pairs of minima) with an out-of-plane orientation of the ammonium side group. After full optimisation the C-C-C-NH₃ dihedral angles were 113.9° and 106.7° for muscimol and fluoromuscimol, respectively (the latter value in fair agreement with the structure in the solid, where this angle is 120.8°). Two transition states each were located, where this ammonium group passes either the O atom from the heterocycle or the F/H substituent (fully optimised in C_s symmetry and characterised by the presence of single imaginary frequencies). The resulting energy barriers are collected in Table S1.

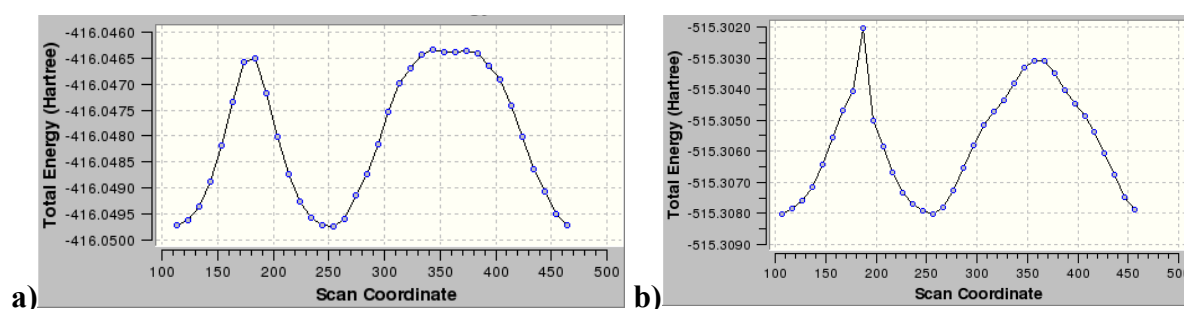


Figure S1: Relaxed scans of muscimole (**1**, left) and fluoromuscimole (**3**, right) at the B3LYP/6-311+G**/CPCM(H₂O) level using the C-C-C-NH₃ dihedral angle as scan coordinate (in degrees); energies given in atomic units (see text and Table S1 for fully optimised values).

Table S1: Energy barriers (ΔE^\ddagger , kJ mol⁻¹) relative to the respective minimum, B3LYP/6-311+G**/CPCM(H₂O) level.

transition state		
X = H 1	8.7	8.8
X = F 3	10.6	13.2

Coordinates of the DFT-optimised structures

Cartesian coordinates in Å, B3LYP/6-311+G** optimised (xyz format)

14

muscimol **1** minimum

H 5.5915505642 1.4762840606 4.5905737316
O 3.4415453294 0.8926122252 2.1961969565
O 6.8841890636 1.2158073377 2.0279188197
N 4.669558058 0.9115626414 1.4404813864
N 1.6835841968 2.3219503264 4.1362873194
H 1.3372287762 2.288319156 3.1741345623
H 0.8720190045 2.3352536855 4.7587910332
H 2.1823379243 3.2072522973 4.2551517672
C 5.6580315391 1.1396241463 2.3346440189
C 5.0655654957 1.2812596792 3.6697155352
C 3.7403613413 1.1172250097 3.4940504793
C 2.5873192326 1.1392952651 4.4320088318
H 2.9213913709 1.239622063 5.4614351954
H 1.9648646934 0.2499081266 4.3352853331

14

fluoromuscimol **3** minimum

F 5.6731525095 1.6386612459 4.763524858
O 3.4710381457 0.7881704137 2.1742273284
O 6.9116307994 1.2513437833 2.0777613999
N 4.718025713 0.8183765467 1.4454044061
N 1.6971281701 2.3448051183 4.1764436787
H 1.3369118056 2.3714257524 3.2192148226
H 0.8919391713 2.3497265327 4.80753171
H 2.2200028985 3.210040816 4.3344024464
C 5.6818799197 1.1337457805 2.3341111611
C 5.0317521443 1.3119034794 3.6288665897
C 3.7140015633 1.0903228431 3.4712438011
C 2.5651464691 1.1175199876 4.4051362591
H 2.9047551473 1.1571182282 5.4374134193
H 1.9142955434 0.2545994723 4.2695381197

14

fluoromuscimol **3** TS1

C -0.0007103118 0. -0.0468448822
C -0.0755759354 0. 1.4112808795
C 1.177659792 0. 1.8922162321
C 1.7447526642 0. 3.2756137343
O -0.967485039 0. -0.8569120705
N 1.3056083067 0. -0.3862286216
F -1.223419747 0. 2.1171497966
N 3.2468319193 0. 3.2213570699
H 1.443509216 0.8850731144 3.8356852436
H 1.443509216 -0.8850731144 3.8356852436
H 3.6412699264 0. 4.1648235276
H 3.6076826095 -0.8235159619 2.7322246547
H 3.6076826095 0.8235159619 2.7322246547
O 2.0486587691 0. 0.8590725009

14

fluoromuscimol **3** TS2

C 0.0092884634 0. -0.1377261004
C -0.0842555962 0. 1.3195205877
C 1.1627557521 0. 1.8208435349
C 1.7501984651 0. 3.1927902959
O -0.9486918938 0. -0.9585143506

N 1.318861783 0. -0.4538703908
F -1.2439322083 0. 2.015836441
N 0.6820400919 0. 4.2507333565
H 2.3653595894 -0.884910198 3.3579203392
H 2.3653595894 0.884910198 3.3579203392
H 1.108473892 0. 5.1808114402
H 0.080767727 0.8264047657 4.1931712498
H 0.080767727 -0.8264047657 4.1931712498
O 2.0467150874 0. 0.8034486344

14

muscimol 1 TS1

C 0.0145026071 0. -0.033540476
C -0.1033754135 0. 1.4292967073
C 1.1609589512 0. 1.8880770335
C 1.7388005897 0. 3.2713377105
O -0.9295994434 0. -0.8771721742
N 1.324352449 0. -0.3728937648
H -1.0187514162 0. 1.9988847445
N 3.2423231631 0. 3.2117828712
H 1.4418368723 0.8853384793 3.8325253889
H 1.4418368723 -0.8853384793 3.8325253889
H 3.6437261039 0. 4.1520061115
H 3.5976246574 -0.8221717606 2.7172547163
H 3.5976246574 0.8221717606 2.7172547163
O 2.0529013568 0. 0.8766148802

14

muscimol 1 TS2

C 0.0177947465 0. -0.1176283838
C -0.1144751452 0. 1.3461519882
C 1.1482720261 0. 1.8162843311
C 1.7508066046 0. 3.1841777456
O -0.9213252504 0. -0.9670479347
N 1.3284313924 0. -0.4401145902
H -1.0460151907 0. 1.8895550531
N 0.6848627022 0. 4.241051218
H 2.3660859893 -0.8851127187 3.3485767692
H 2.3660859893 0.8851127187 3.3485767692
H 1.1007661998 0. 5.1753329942
H 0.0849689772 0.8266954327 4.1757382533
H 0.0849689772 -0.8266954327 4.1757382533
O 2.0472684624 0. 0.816270051

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