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Supplementary Information

[^{18}F]Fluoro-benziodoxole: A no-carrier-added electrophilic fluorinating reagent. Rapid, simple radiosynthesis, purification and application for fluorine-18 labeling

Miguel A. Cortés González,[a] Patrik Nordeman,[b] Antonio Bermejo Gómez,[a,c] Denise N. Meyer,[a] Gunnar Antoni,[b] Magnus Schou[c] and Kálmán J. Szabó*[a].

[a] Department of Organic Chemistry Stockholm University, SE-106 91, Stockholm, Sweden. E-mail: kalman.j.szabo@su.se

[b] Department of Medicinal Chemistry, Uppsala University, SE-751 23, Uppsala, Sweden.

[c] AstraZeneca PET Centre at Karolinska Institutet Solna, SE-171 76, Stockholm, Sweden.

Email: kalman.j.szabo@su.se

Table of Contents

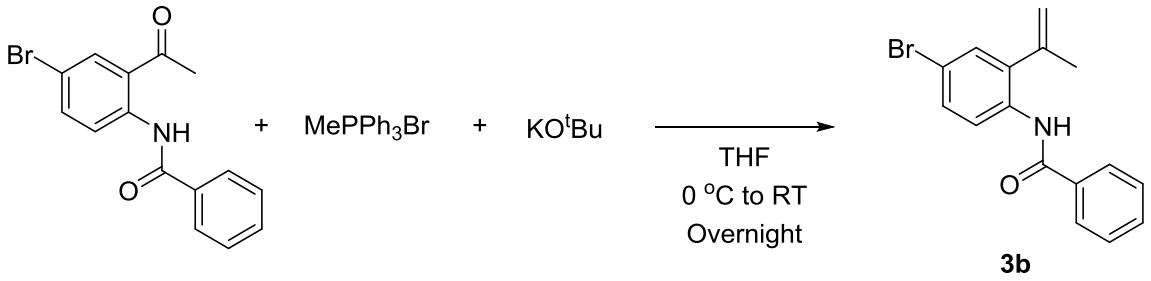
General Information

The reagents were used as obtained from commercial suppliers without further purification. Solvents were obtained from commercial suppliers and dried using a Vacuum Atmospheres Solvent Purifier system. IST Phase Separators® were obtained from Biotage. Flash chromatography purifications were carried out on 60 Å (35-70 µm) silica gel (Acros Kieselgel 60) using or *n*-pentane / EtOAc or *n*-pentane / Et_2O mixtures as eluent.

Fluorine-19 experiments. All reactions were carried out in dry closed glass reaction vessels using dry solvents under an atmosphere of dry Ar. Reagent **1** was prepared following the reported literature procedure.[1] The synthesis of reference compounds **4a**, **4d**, **4f** and **4g** was performed following the reported procedure by Gulder.[2] Additional reference compounds **4b**, **4c** and **4e** were synthesized using a similar methodology (see below). Analytical TLC was carried out on aluminum-backed plates (1.5 Å, ~ 5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized by exposure to UV light (λ = 254 nm) or by dipping the plates in a solution of 0.75% $KMnO_4$ (w/v) in an aqueous solution of K_2CO_3 0.36 M. Melting points were recorded in a metal block and are uncorrected. ^1H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz and ^{19}F NMR spectra were recorded at 377 MHz with a Bruker Advance spectrometer. ^1H and ^{13}C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane, using the residual solvent resonance ($CHCl_3$: δ_H 7.26 and $CDCl_3$: δ_C 77.0) as an internal reference. Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF ESI-TOF mass spectrometer.

Fluorine-18 experiments. The labeling reactions were carried out in dry conical glass vials under an atmosphere of dry N_2. Dry CH_2Cl_2 for the labeling reactions was obtained from commercial suppliers and dried using a Vacuum Atmospheres Solvent Purifier system. Dry MeCN for the labeling reactions was obtained from a commercial supplier.

Synthesis and Characterization of *N*-(4-bromo-2-(prop-2'-ene)phenyl)benzamide (3b)



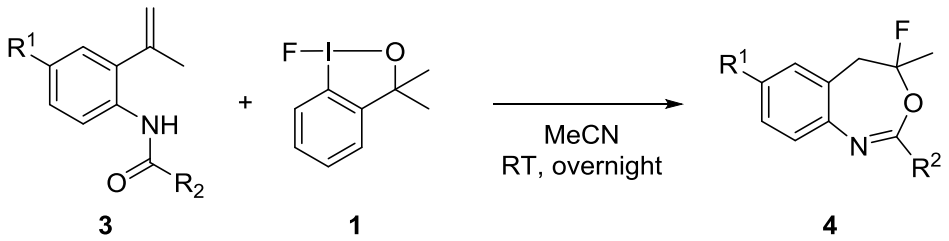
Synthesis of **3b** was carried out with reported procedure[2] with modifications. To a suspension of methyltriphenylphosphonium bromide in THF (2.1 equiv., 0.5 M) at 0 °C was added potassium *tert*-butoxide portionwise (2.2 equiv.). The suspension was stirred at 0 °C for 1 h before adding *N*-(2-acetyl-4-bromophenyl)benzamide (761 mg, 2.39 mmol, 1.0 equiv., 0.4 M) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of water (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (25 mL) and sat. aq. NaCl (25 mL) before being dried by filtration through an ISP Phase Separator® and concentrated under reduced pressure. Purification by column chromatography (SiO_2; Et_2O / *n*-pentane 4:10 to pure Et_2O) afforded the title compound as a white solid (739 mg, 98%). M.p.: 132-133 °C.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.42-8.13 (m, 2H), 7.82-7.79 (m, 2H), 7.58-7.54 (m, 1H), 7.51-7.47 (m, 2H), 7.43 (dd, *J*(H,H) = 8.8, 2.4 Hz, 1H), 7.32 (d, *J*(H,H) = 2.4 Hz, 1H), 5.51-5.50 (m, 1H), 5.14-5.13 (m, 1H), 2.11-2.10 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 165.1, 142.2, 135.5, 134.8, 133.3, 132.1, 131.0, 130.6, 129.0, 127.0, 122.4, 117.9, 116.8, 24.5.

HRMS (ESI): m/z calcd for $C_{16}H_{14}{}^{79}BrNO-H^+$: 134.0186 $[M-H]^-$; found: 314.0173

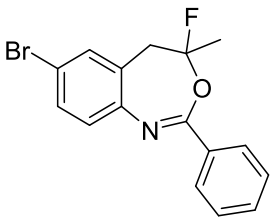
Synthesis and characterization of fluorobenzoxazepines (4)



3 **1** **4**

The synthesis of these compounds were carried out by reported literature procedures[2] with minor modifications. The corresponding *o*-styrilamide (1 equiv.) and 1-fluoro-3,3-dimethyl-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodoxole (**1**, 1.2 equiv.) were dissolved in MeCN (0.2 M) and stirred at room temperature overnight. Purification by column chromatography afforded the desired 4-fluoro-4-methyl-4,5-dihydrobenzo[d][1,3]oxazepines.

2-phenyl-4-fluoro-4-methyl-7-bromo-4,5-dihydrobenzo[*d*][1,3]oxazepine (4b)



From *N*-(4-bromo-2-(prop-2'-ene)phenyl)benzamide **3b** (32 mg, 0.1 mmol). Purification by column chromatography (SiO_2; Et_2O / *n*-pentane 1:15) afforded the title compound as a white solid (19 mg, 48%). M.p.: 79-80 °C.

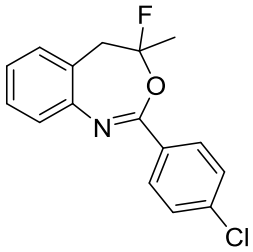
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.19-8.16 (m, 2H), 7.54-7.52 (m, 1H), 7.47-7.43 (m, 3H), 7.37 (d, *J*(H,H) = 2.2 Hz, 1H), 7.17 (d, *J*(H,H) = 8.4 Hz, 1H), 3.19 (dd, *J*(H,F) = 14.2, Hz, *J*(H,H) = 8.7 Hz, 1H), 3.06 (dd, *J*(H,H) = 14.2 Hz, *J*(H,H) = 3.4 Hz, 1H), 1.72 (dd, *J*(H,F) = 17.7 Hz, *J*(H,H) = 0.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 153.7 (d, *J*(C,F) = 2.2 Hz), 143.5, 133.6, 131.9 (d, *J*(C,F) = 0.8 Hz), 131.8, 131.6, 129.5 (d, *J*(C,F) = 9.6 Hz), 129.1, 128.5, 127.5, 122.4 (d, *J*(C,F) = 228.7 Hz), 118.8, 42.2 (d, *J*(C,F) = 31.4 Hz), 24.9 (d, *J*(C,F) = 29.7 Hz).

^{19}F NMR (377 MHz, CDCl3): δ = −73 01 (qdd, *J*(F,H) = 17.7, 8.9, 3.4 Hz).

HRMS (ESI): m/z calcd for $C_{16}H_{13}{}^{79}BrFNO-H^+$: 332.0092 $[M-H]^-$; found: 332.0098.

2-(4-chlorophenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]33oxazepine (4c)



From 4-chloro-*N*-(2-(prop-2'-ene)phenyl)benzamide **3c** (27 mg, 0.1 mmol). Purification by column chromatography (SiO_2; Et_2O / *n*-pentane 1:20) afforded the title compound as a white solid (18 mg, 62%). M.p.: 113-115 °C.

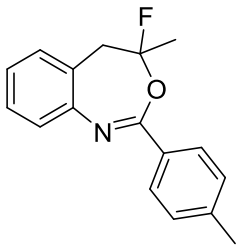
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.15-8.11 (m, 2H), 7.44-7.43 (m, 3H), 7.29-7.28 (m, 1H), 7.24-7.17 (m, 2H), 3.20 (dd, *J*(H,F) = 14.2 Hz, *J*(H,H) = 9.0 Hz, 1H), 3.09 (dd, *J*(H,F) = 14.2 Hz, *J*(H,H) = 2.9 Hz, 1H), 1.69 (dd, *J*(H,F) = 17.7 Hz, *J*(H,H) = 0.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 152.4 (d, *J*(C,F) = 2.2 Hz), 144.2, 137.9, 132.4, 130.4, 129.2, 128.7, 128.6, 127.5 (d, *J*(C,F) = 9.6 Hz), 126.1, 125.7, 123.1 (d, *J*(C,F) = 228.5 Hz), 42.5 (d, 30.7 Hz), 24.7 (d, 29.8 Hz).

^{19}F NMR (377 MHz, CDCl3): δ = −72.29 (qdd, *J*(F,H) = 17.7, 9.2, 2.9 Hz).

HRMS (ESI): m/z calcd for $C_{16}H_{15}ClFNO{-}H^+$: 290.0742 [*M*−H]$^-$; found: 290.0757.

2-(4-methylphenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]oxazepine (4e)



From 4-methyl-*N*-(2-(prop-2'-ene)phenyl)benzamide **3f** (25 mg, 0.1 mmol). Purification by column chromatography (SiO_2; Et_2O / *n*-pentane 1:15) afforded the title compound as a white solid (20 mg, 76%). M.p.: 124-125 °C.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): □ = 8.09 (d, *J*(H,H) = 8.3 Hz, 2H), 7.37 (td, *J*(H,H) = 7.5, 1.77 Hz, 1H), 7.30-7.25 (m, 3H), 7.23 (d, *J*(H,H) = 7.0, 1.6 Hz, 1H), 7.17 (td, *J*(H,H) = 7.3, 1.4 Hz, 1H), 3.22 (dd, *J*(H,F) =

14.1 Hz, *J*(H,H) = 9.5 Hz, 1H), 3.08 (dd, *J*(H,F) = 14.1 Hz, *J*(H,H) = 2.1 Hz, 1H), 2.43 (s, 3H), 1.69 (dd, *J*(H,F) = 17.6 Hz, *J*(H,H) = 1.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 153.8 (d, *J*(C,F) = 2.2 Hz), 144.6, 142.1, 131.0, 129.2, 129.1, 129.0, 128.5, 127.6 (d, *J*(C,F) = 9.7 Hz), 125.6, 125.5, 123.2 (d, *J*(C,F) = 228.2 Hz), 42.4 (d, 31.1 Hz), 24.7 (d, 29.9 Hz), 21.7.

^{19}F NMR (377 MHz, CDCl3): δ = −72.12 (qdd, *J*(F,H) = 17.7, 9.4, 1.0 Hz).

HRMS (ESI): m/z calcd for $C_{17}H_{16}FNO+H^+$: 270.1289 $[M+H]^-$; found: 270.1288.

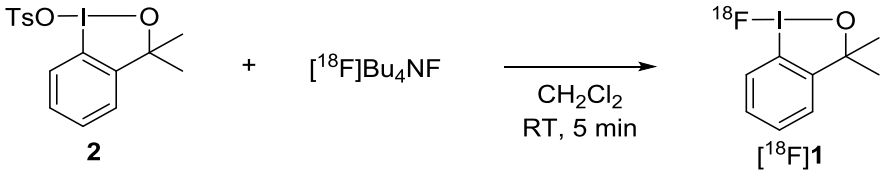
Radiochemistry

Preparation of [^{18}F]Bu_4NF

[^{18}F]Fluoride was produced by the nuclear reaction $^{18}O(p,n)^{18}F$ using [^{18}O]H_2O as target in a GE PETtrace 800 or a Scanditronix MC-17 cyclotron and was separated from [^{18}O]H_2O using anion exchange Sep-PAK® Accell Plus QMA Light cartridges (Waters Corporation, Milford, Massachusetts USA) pretreated with K_2CO_3 (aq. 0.5 M, 10 mL) and later with H_2O (10 mL). [^{18}F]Fluoride was released from the cartridge as [^{18}F]Bu_4NF using a solution of Bu_4NHCO_3 (0.0375 M) in a 1:1 mixture acetonitrile / H_2O (450 μL). Acetonitrile was added (200 μL) and the [^{18}F]Bu_4NF was dried at 120 °C under a flow of N_2 for 4 minutes. The drying process was repeated (x2) using 200 μL of acetonitrile for 3 and 2 minutes, respectively. The obtained [^{18}F]Bu_4NF was dissolved in dry CH_2Cl_2 and used in the next step.

The activity in the vials was determined using a CRC-15R (Capintec) detector calibrated for fluorine-18.

Synthesis and characterization of [^{18}F]-1-fluoro-3,3-dimethyl-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole ([^{18}F]1)

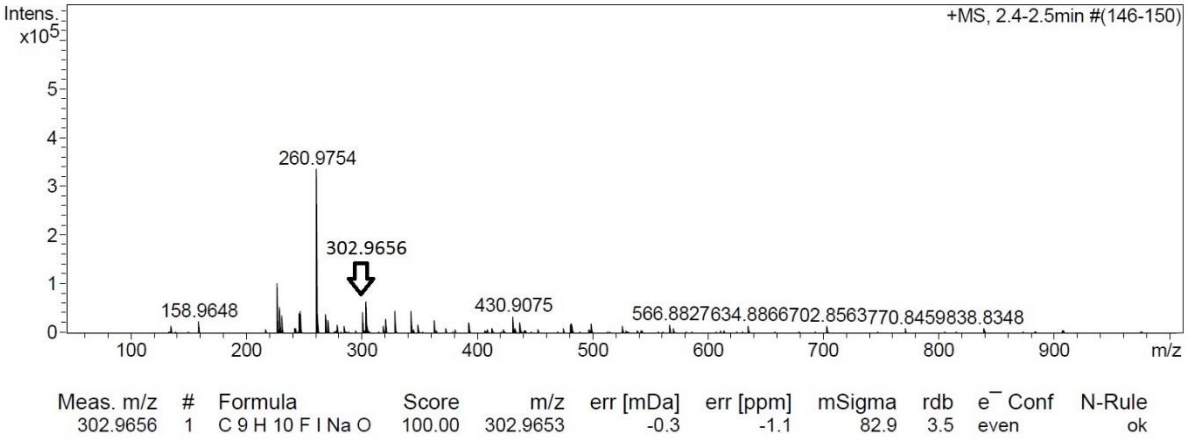


2 [^{18}F]**1**

A 0.5 mL conical glass vial containing a magnetic stirrer was loaded with 1-tosyloxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **2** (5 mg, 0.012 mmol). [^{18}F]Bu_4NF in CH_2Cl_2 was added (500 μL, 100-1000 MBq) and the reaction was stirred at room temperature for 5 minutes. After that time, the solvent was evaporated under a stream of N_2 for 10 minutes at room temperature until a solid formed. To ensure the formation of the solid, *n*-hexane (300 μL) was added before the CH_2Cl_2 evaporated completely. To the remaining solid was added *n*-hexane (500 μL) and stirred at 70 °C for 1 minute. The *n*-hexane supernatant was extracted by means of a syringe, filtered through a 1 mL IST Phase Separator® (Biotage, Part No. 120-1901-A) and used as such in the radiolabeling reactions.

Analysis of the decayed sample of [^{18}F]1

Fluoro-benziodoxole [^{18}F]**1** cannot be analyzed by chromatography, because of decomposition on silica gel (see below). Therefore, we choose another analytical method for observation based the analysis of the decayed sample. A decayed extracted sample was analyzed by means of HRMS (ESI+) (Figure S1) and ^{19}F-NMR (Figure S2). The recording conditions for this ^{19}F-NMR (Figure S2, blue spectrum) were the following: solvent: $CDCl_3$; temperature: 25.1 °C; NS (number of scans): 47652; D1 (delay): 1.0 s (the total time for recording of the ^{19}F NMR spectrum was about 13 hours). Both analyses indicated the presence of non-radioactive 1-fluoro-3,3-dimethyl-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole **1**. Fluoro benziodoxole with the natural fluorine-19 isotope was formed from the residual fluorine-19 present in the hot-lab environment. The intense signal m/z = 260.9754 corresponds to the loss of fluorine due to the thermal lability of the F–I bond. Only one signal was observed by ^{19}F-NMR.



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
302.9656	1	C 9 H 10 F I Na O	100.00	302.9653	-0.3	-1.1	82.9	3.5	even	ok

Figure S1. HRMS of decayed [^{18}F]**1** after extraction. The arrow indicates the presence of 1, i.e. the reagent with the natural fluorine isotope.

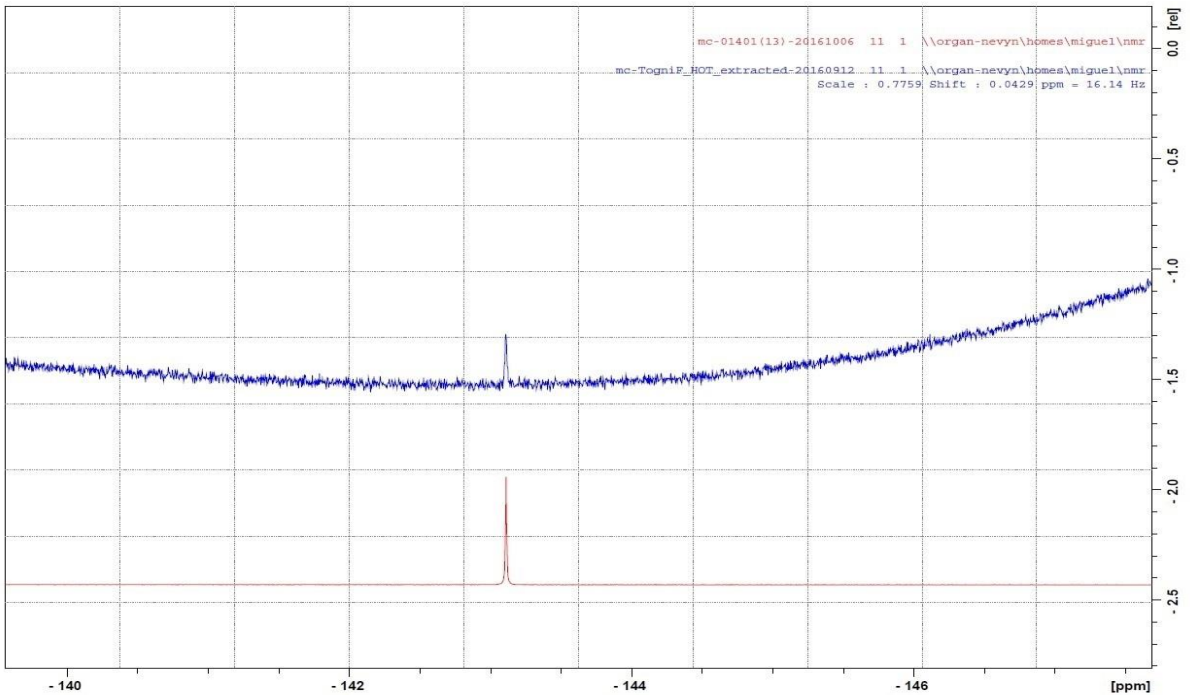


Figure S2. ^{19}F NMR of decayed [^{18}F]1 after extraction. Blue: decayed extracted sample. Red: reference sample.

In order to confirm the above findings with the decayed sample, we made two control experiments. In Figure S3 and Figure S4 the HRMS spectra of fluoro-benziodoxole **1** and tosylate **2** are depicted. In the spectrum of fluoro-benziodoxole **1** (Figure S3), in the region of m/z=250-310, we observed the molecular ion peak of fluoro benziodoxole **1** at m/z=302.9657 m.u. as well as the benziodoxole fragment at 260.9797 m.u. However, in the spectrum of tosylate **2** (Figure S4) solely the benziodoxole fragment at 260.9765 m.u. was observed (the peak at 302.9657 m.u. is clearly absent). This indicates that the decayed sample (Figure S1) did contain **1,** as both the peak of benziodoxole fragment at 260.9754 and the peak at 302.9656 (molecular ion for **1**) are appearing in the HMRS spectrum.

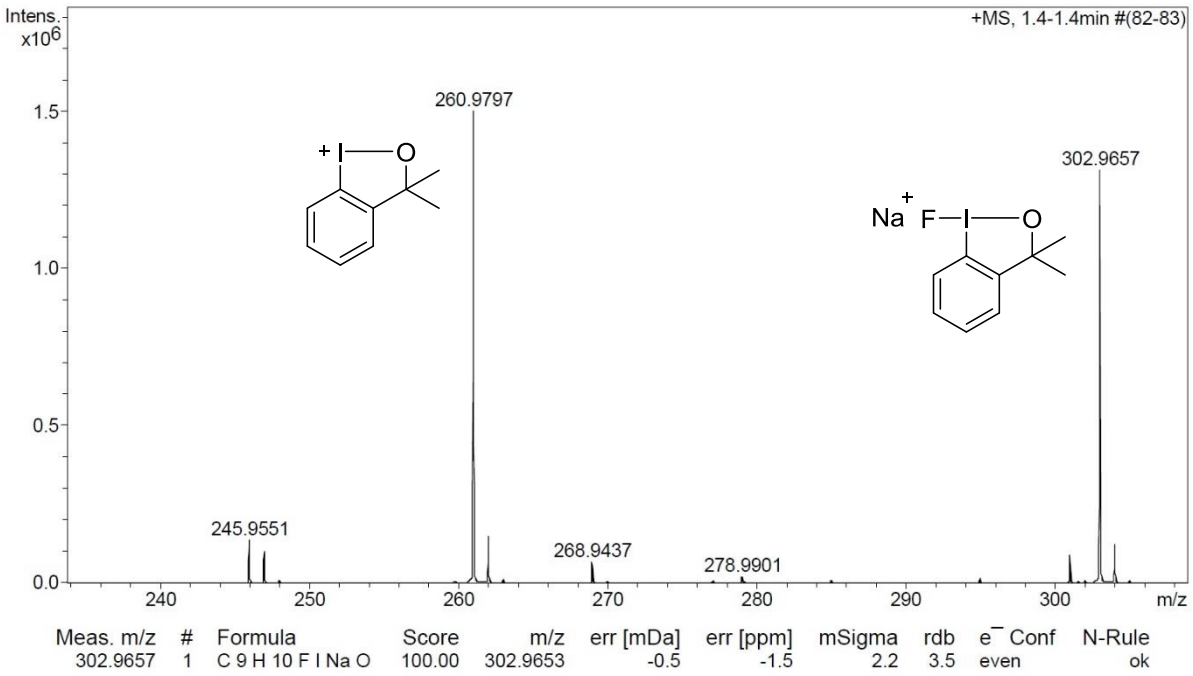


Figure S3. Expansion of the HRMS spectrum of fluoro-benziodoxole **1**, showing the $[M+Na]^+$ molecular peak at m/z=302.9657 and the $[M-F]^+$ peak at m/z=260.9797.

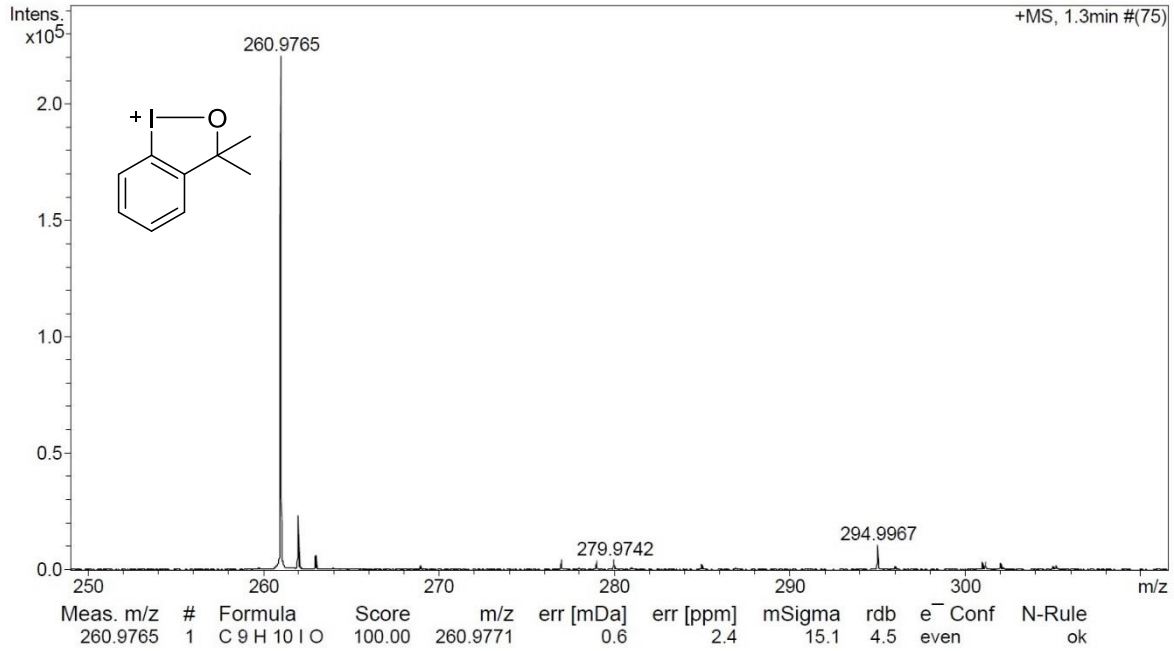


Figure S4. Expansion of the HRMS spectrum of tosyl-benziodoxole **2**, showing the benziodoxole peak at m/z=260.9765. The molecular peak at 454.9780 is excluded from this window for clarity.

In addition, we made a control experiment of the ^{19}F-NMR samples as well. Figure S5 shows the comparison of the decayed sample of **1**, the reference sample of **1** and the reference sample of Bu_4NF in the region of -120 to -145 ppm. It clearly shows that **1** gives a single peak at -143.1 ppm in both the decayed and the reference sample. However, fluoride in Bu_4NF resonates at -122.9 ppm. This peak is

absent in the decayed sample confirming that the hexane extracted sample did not contain significant amounts of Bu_4NF contamination.

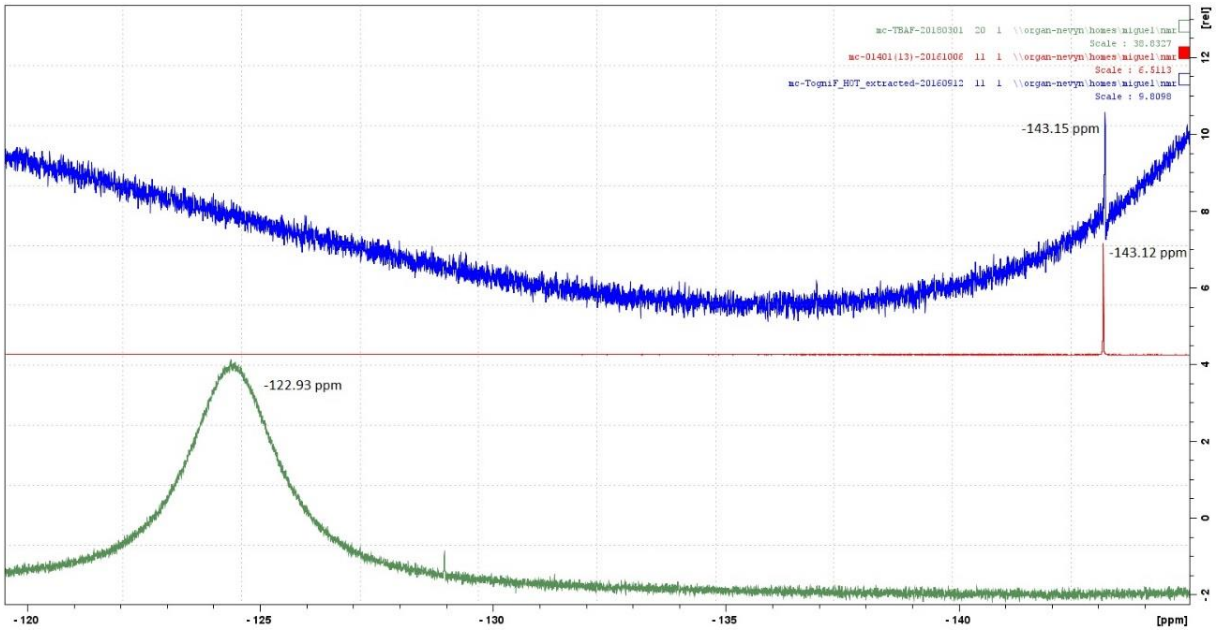


Figure S5. Comparison of the ^{19}F-NMR spectrum of the decayed extracted sample (blue), reference sample (red) of **1** and reference sample of Bu_4NF (green).

Attempts for chromatographic purification of [^{18}F]**1**

As mentioned above [^{18}F]**1** cannot be purified by chromatography, preventing even the radio-TLC detection of the RCC. Here below, we demonstrate that silica, alumina and other adsorbents react with [^{18}F]**1** leading to its substantial or complete decomposition.

We studied the behavior of both [^{18}F]**1** and [^{18}F]Bu_4NF with different solid-phase extraction cartridges: Sep-Pak Silica Plus Light (120 mg, Waters, Part No. WAT023537); Sep-Pak Alumina N Plus Light (280 mg, Waters, Part No. WAT023561); hand-packed Celite® plug (77 mg in a cotton-plugged glass pipette). In the first experiment the crude reaction mixture of [^{18}F]**1** was filtered through the silica and alumina cartridges. We found that 97% of the total activity was retained on the corresponding adsorbent after rinsing with 1.0 mL of CH_2Cl_2 (Figure S6). In case of Celite® 38% of [^{18}F]**1** was eluted but 62% was still retained on the adsorbent. Notably, the retained activity could not be eluted when the adsorbents were rinsed with 1.0 mL of MeCN. This indicates that the retained [^{18}F]**1** was completely decomposed on the adsorbent. In fact the decomposition of [^{18}F]**1** was expected because of the high affinity of the fluorine in hypervalent iodines to silicon, aluminium and alkali ions (in particular to Mg and Ca).

The above experiment clearly shows that [^{18}F]**1** (similarly to its fluor-19 analog) cannot be purified by silica or alumina chromatography or filtration through Celite® unless substantial purification losses. In addition extensive decomposition of [^{18}F]**1** prevents its analysis on silica or alumina based adsorbents.

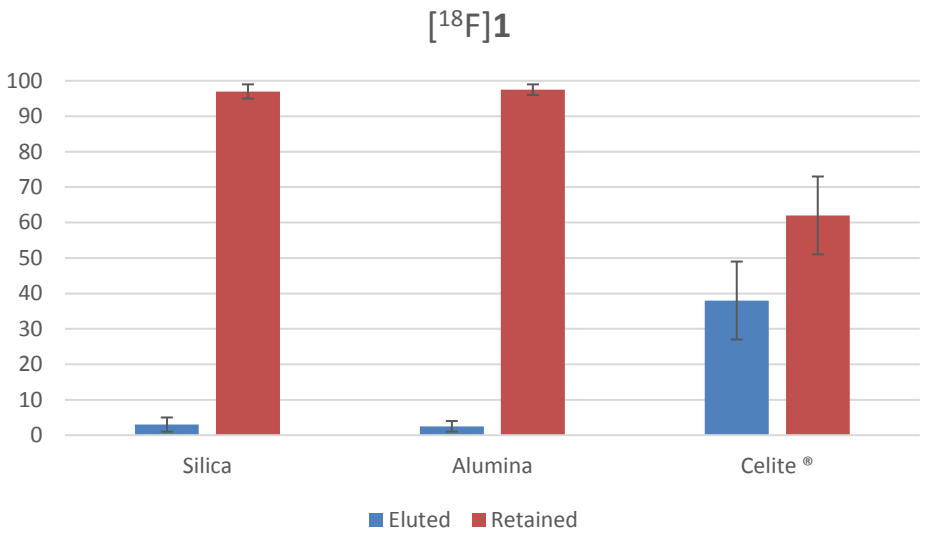


Figure S6. Elution of [^{18}F]**1** using diverse adsorbents.

In a subsequent control experiment a solution of [^{18}F]Bu_4NF in 500 μL of CH_2Cl_2 was filtered through the corresponding silica, alumina and celite cartridges, and then the adsorbents were rinsed with 1 mL CH_2Cl_2. The activity in the combined collected eluate was measured and compared to the activity that was retained in the adsorbent (Figure S7). It was found that silica, alumina and Celite® failed to fully retain [^{18}F]Bu_4NF. In all three cases, only 74-81% of the total activity was retained by the adsorbents. This indicates that quick filtration by silica, alumina and Celite® is not suitable for efficient removal of the unreacted [^{18}F]Bu_4NF. Fortunatly, the purification of [^{18}F]**1** can be achived by extraction with hexane at 70 ^{o}C (see Table 1 in the article). Figures S2 and S5 show that the purified, and subsequently decayed sample does contain **1** but not Bu_4NF.

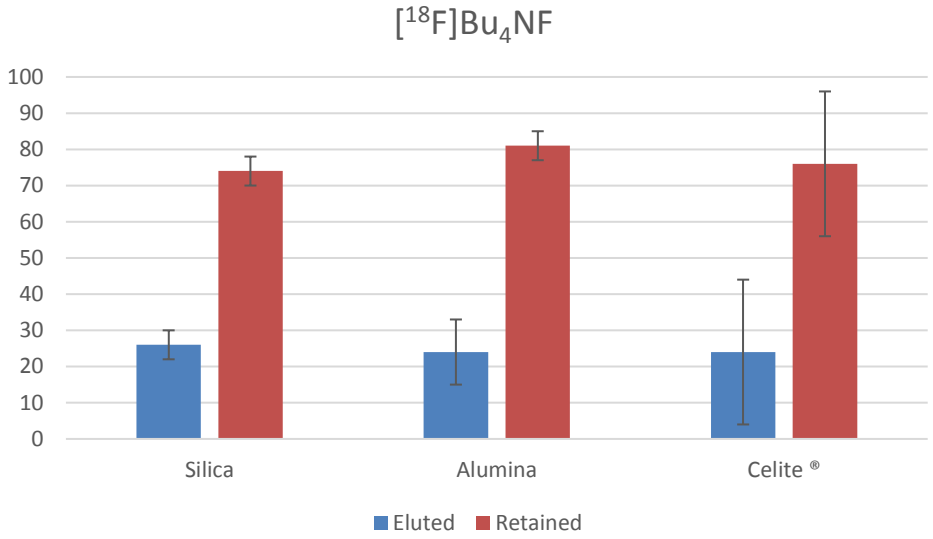
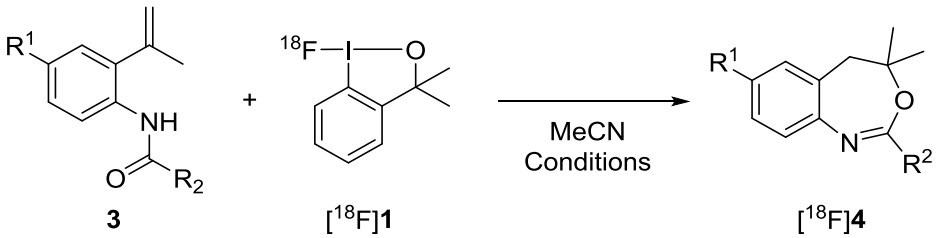


Figure S7. Elution of [^{18}F]Bu$_4$NF using diverse adsobents.

Radiolabeling of [^{18}F]4a–g



To a 0.5 mL conical glass vial containing a magnetic stirrer and a solution of the corresponding *o*-styrilamide **3** in MeCN (25 μL, 16 μmol/mL) was added the labeling reagent [^{18}F]**1** in *n*-hexane solution (50-100 μL, 2-30 MBq). The solvents were then removed under a stream of N_2 at room temperature for 3 minutes. The resulting material was dissolved in MeCN (500 μL) and stirred at the indicated temperatures and times. An aliquot was analyzed by radio-HPLC in order to estimate the radiochemical conversion to fluorobenzoxazepines [^{18}F]**4**.

Compound	Temperature [°C]	Time [min]	RCC [%] (n = 2)
[^{18}F]**4a**	90	7	76 ± 2
[^{18}F]**4b**	90	7	57 ± 1
[^{18}F]**4c**	90	7	88 ± 6
[^{18}F]**4d**	70	7	50 ± 6
[^{18}F]**4e**	90	2	90 ± 1
[^{18}F]**4f**	70	2	74 ± 3
[^{18}F]**4g**	70	2	80 ± 1

Analysis and Radiochemical Conversion (RCC) Determination.

Radiochemical conversions (RCC) were determined by radio-HPLC analysis of the crude reaction mixtures. High pressure liquid chromatography (HPLC) analyses were performed using a VWR LaChrom ELITE system (L-2130, L-2200, L-2400) with a built-in UV-detector (λ = 254 nm), in series with a Bioscan Flow-Count PMT radioactivity detector using a Chromolith Performance RP-18 end-capped column (2 μm, 100 x 4.6 mm) and eluted with a linear increase gradient (mobile phase A: acetonitrile, mobile phase B: $HCOONH_4$ 0.05 M) at a flow of 4 mL/min.

Time (min)	Phase A [%]	Phase B [%]
0	30	70
10	90	10

The ^{18}F-labelled compounds were identified by comparison of the retention times with the corresponding references **4a-g**.

Compound	Retention time (^{18}F-labelled) β^+-flow detector [min]	Retention time (^{19}F-reference) UV detector [min]
[^{18}F]**4a**	6.22	6.06
[^{18}F]**4b**	6.38	6.19
[^{18}F]**4c**	5.87	5.59
[^{18}F]**4d**	4.93	4.60
[^{18}F]**4e**	5.82	5.41
[^{18}F]**4f**	5.75	5.53
[^{18}F]**4g**	5.17	4.99

Determination of the radiochemical yield and molar activity for [^{18}F]4a

A 0.5 mL conical glass vial containing a magnetic stirrer was loaded with 3,3-dimethyl-1λ^3-benzo[*d*][1,2]iodaoxole-1(3H)-yl 4-methylbenzenesulfonate **2** (5 mg, 12 μmol). The [^{18}F]Bu_4NF solution in CH_2Cl_2 was added (500 μL, 3.93 GBq) and the mixture was stirred at room temperature for 5 minutes. The solvent was evaporated under a stream of N_2 at room temperature for 10 minutes, adding *n*-hexane (300 μL) before the solvent evaporated completely. To the obtained solid residue was added *n*-hexane (500 μL) and stirred at 70 °C for 1 minute. The *n*-hexane supernatant was extracted by means of a syringe and filtered through a 1 mL IST Phase Separator® obtaining 1.32 GBq of extracted activity (RCC = 34%).

To a 0.5 mL conical vial containing a magnetic stirrer and a solution of *N*-(4-chloro-2-(prop-1-en-2-yl)phenyl)benzamide **3a** in MeCN (25 μL, 16 μmol/mL) was added the hexane solution containing [^{18}F]**1** (904 MBq). The solvents were evaporated under a stream of N_2 for 5 minutes. The resulting material was dissolved in MeCN (500 μL) and stirred at 90 °C for 7 minutes. The labeled compound [^{18}F]**4a** was purified by semi-preparative HPLC. The activity of the isolated sample of [^{18}F]**4a** was 93 MBq, corresponding to 10% radiochemical yield (RCY) based on [^{18}F]**1**. This value was measured two hours after the end of the bombardment and it was non-decay corrected.

Details of the purification procedure. Semi-preparative HPLC was performed using a VWR LaPrep HPLC system (LP1200) with a in-series UV-detector (λ = 212 nm), in series with a Bioscan Flow-Count PMT radioactivity detector using a reverse phase column (Kinetex 5 μm, C18, 100 Å, 10 × 250 mm) and eluted with a linear increase gradient (mobile phase A: acetonitrile, mobile phase B: $HCOONH_4$ 0.05 M) at a flow of 6 mL/min.

Time [min]	Phase A [%]	Phase B [%]
0	60	40
7	100	0
20	100	0

The product was collected in a fraction over 60 seconds with a retention time of 8.9 minutes.

Analysis of the purified sample was performed using a VWR LaChrom ELITE system (L-2200, L-2300, L-2450) with a built-in variable wavelength PDA detector, in series with a Bioscan Flow-Count PMT radioactivity detector using a Chromolith Performance RP-18 end-capped column (2 μm, 100 x 4.6 mm) and eluted with a linear increase gradient (mobile phase A: acetonitrile, mobile phase B: $(NH_4)_2CO_3$ 0.008 M) at a flow of 4 mL/min.

Time [min]	Phase A [%]	Phase B [%]
0	30	70
10	90	10

The product [^{18}F]**4a** was obtained with >99% radiochemical purity. The identity of the purified product [^{18}F]**4a** was confirmed by co-injection with true product **4a** (Figure S8). The molar activity (M.A.) of the purified product [^{18}F]**4a** was calculated using a calibration curve (Figure S9) giving a value of 396.83 GBq·μmol^{-1} 2 hours after the end of the bombardment.

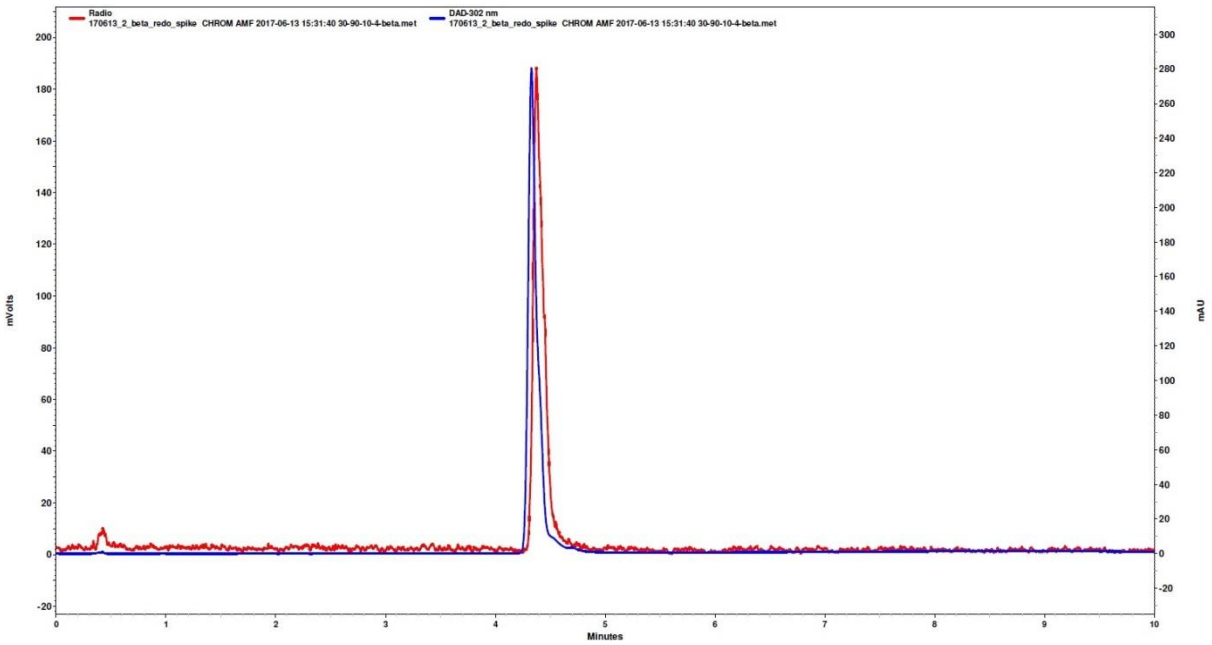


Figure S8. Co-injection of the purified product [^{18}F]**4a** and true **4a**.

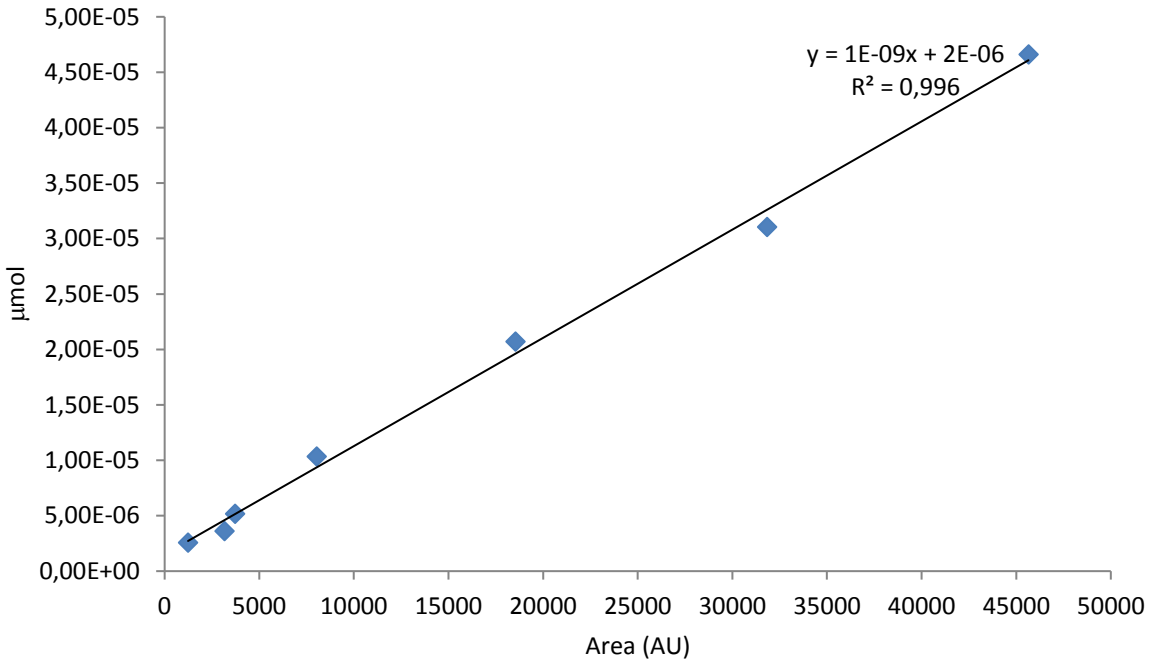
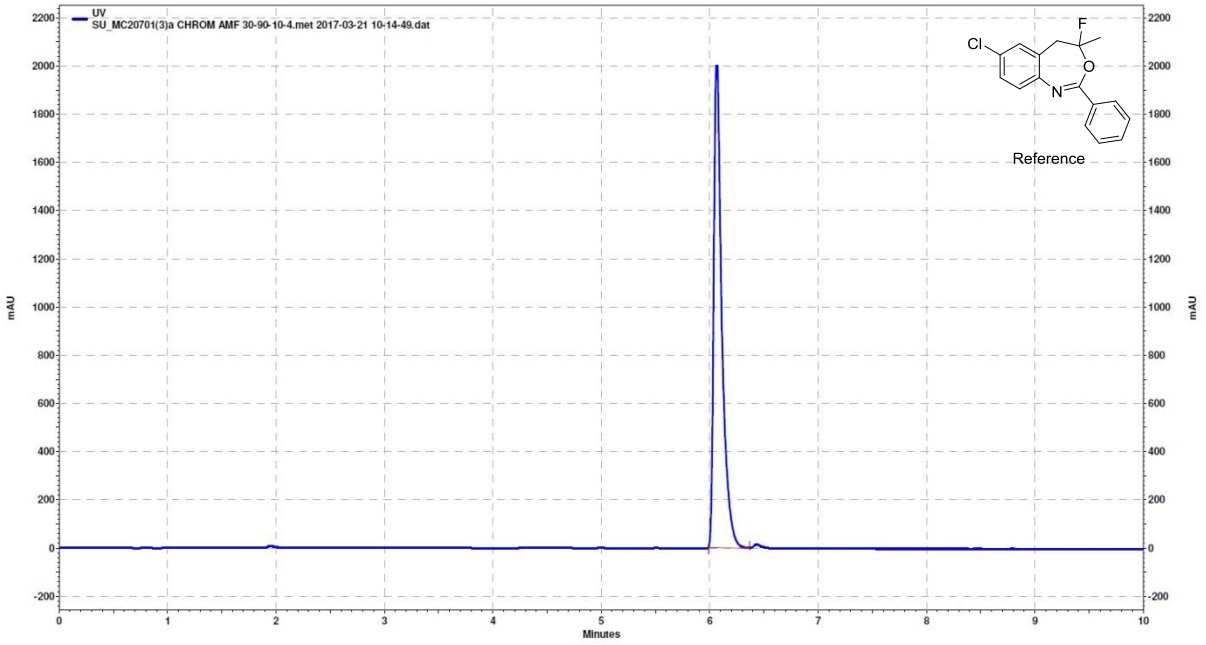
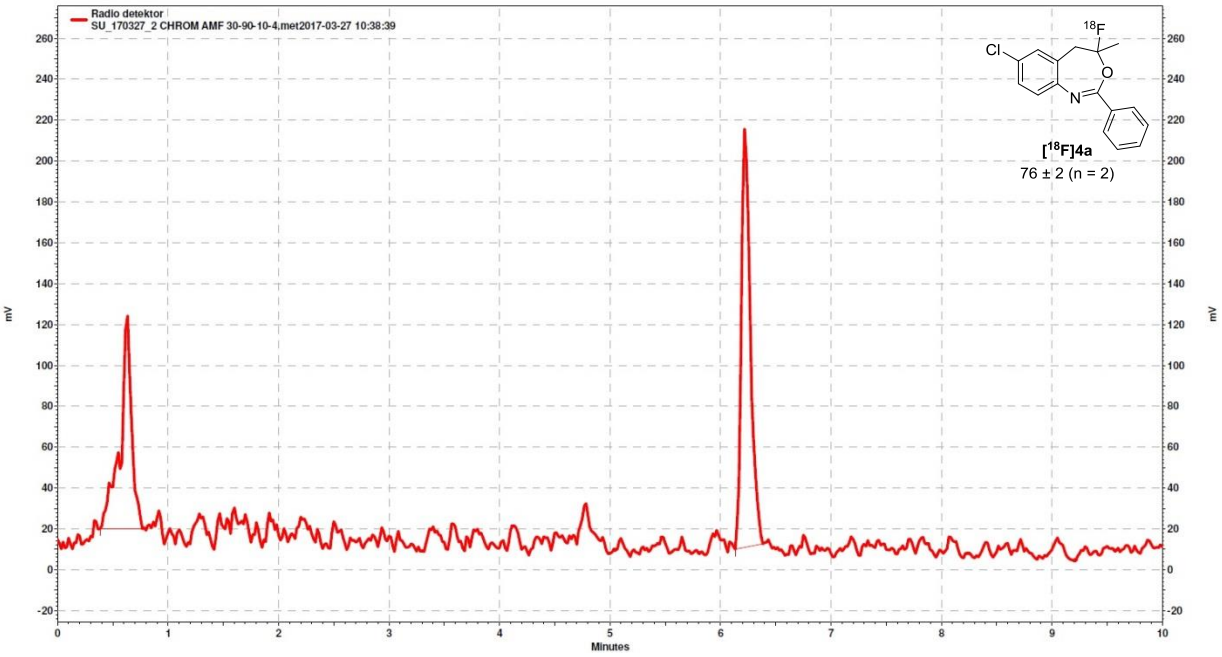
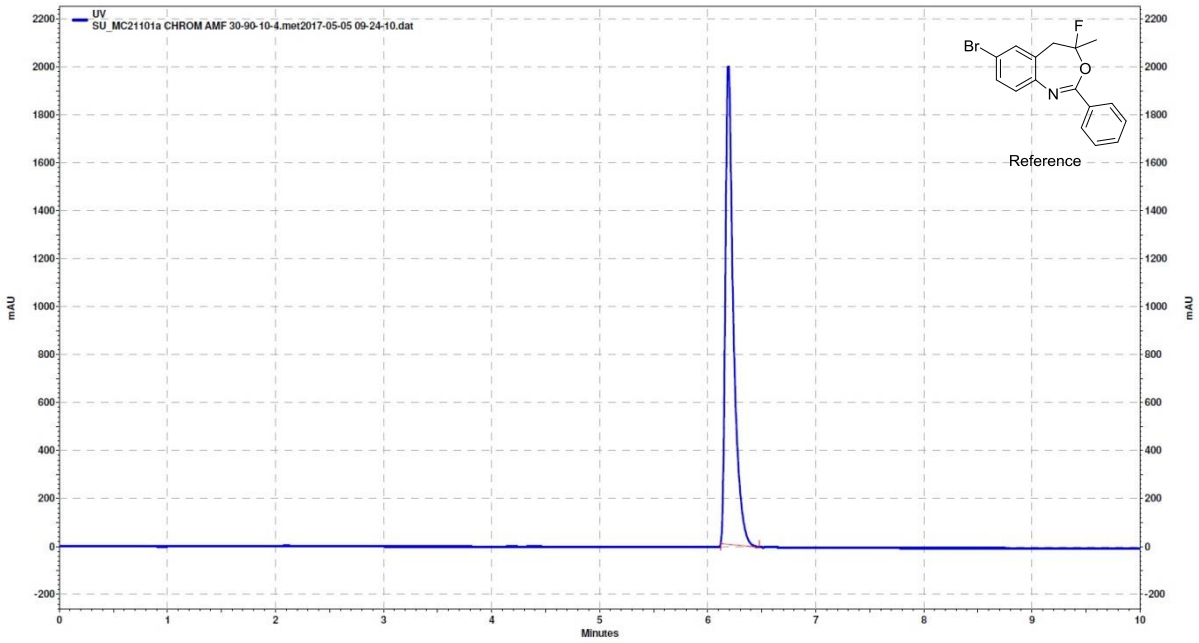


Figure S9. Calibration curve of **4a** for the determination of the molar activity.

Radio-HPLC Chromatograms






UV
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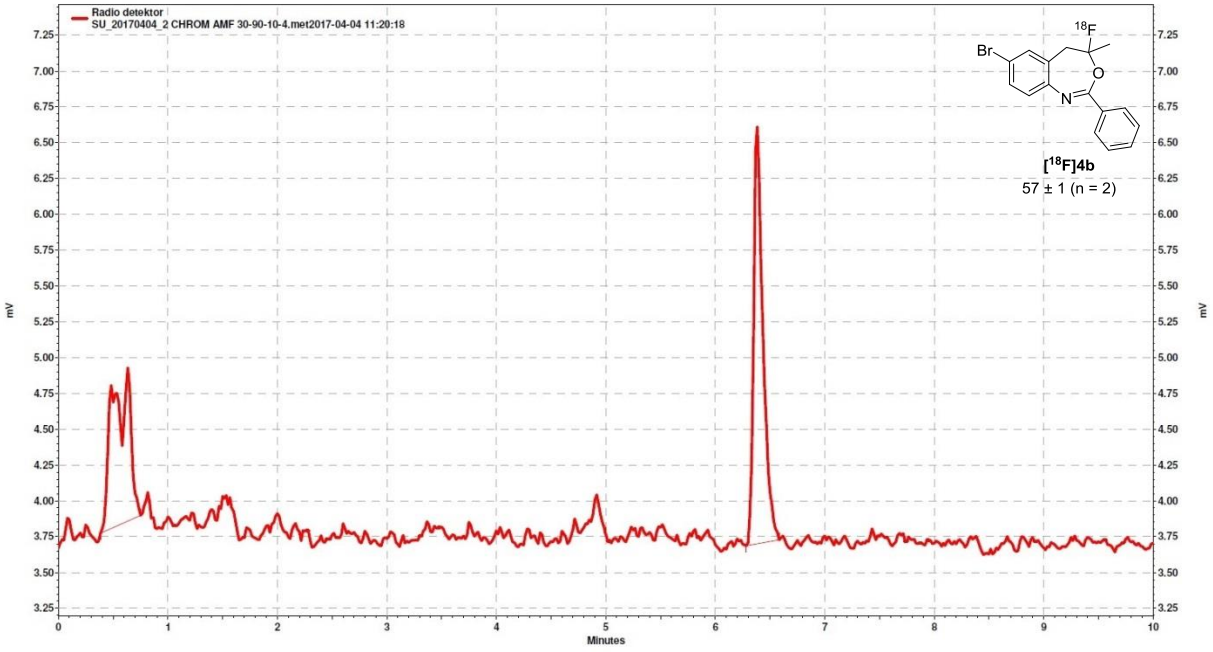
mAU
Minutes
Br
F
O
N
Reference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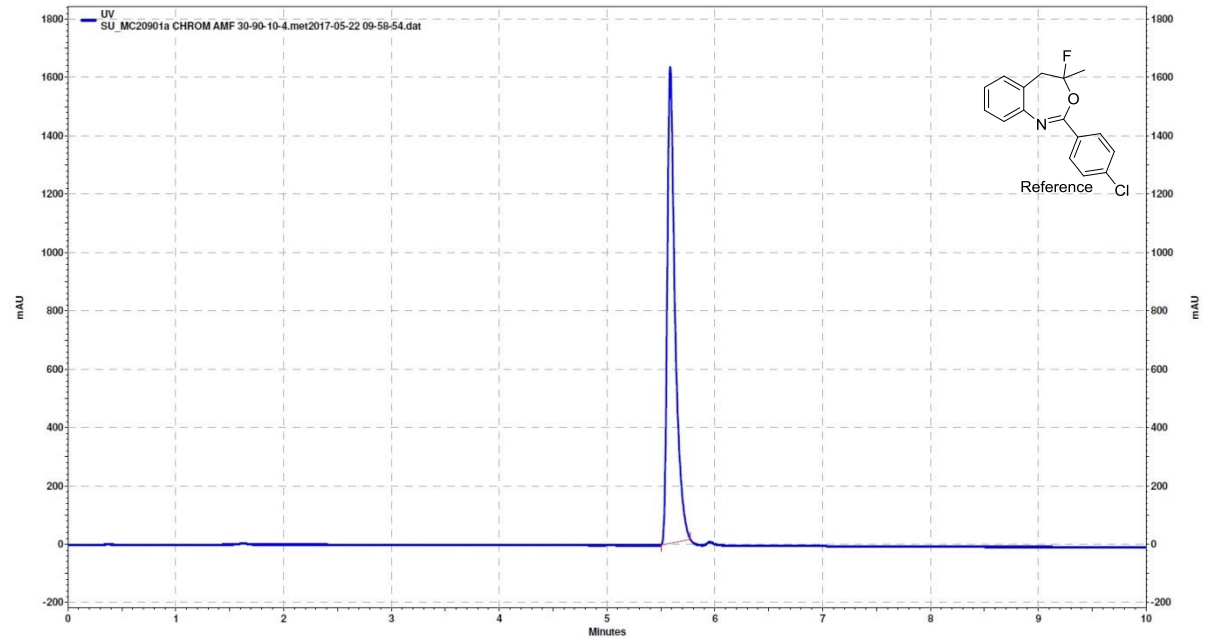
mV
Minutes
Br
18F
O
N
[18F]4b
57 ± 1 (n = 2)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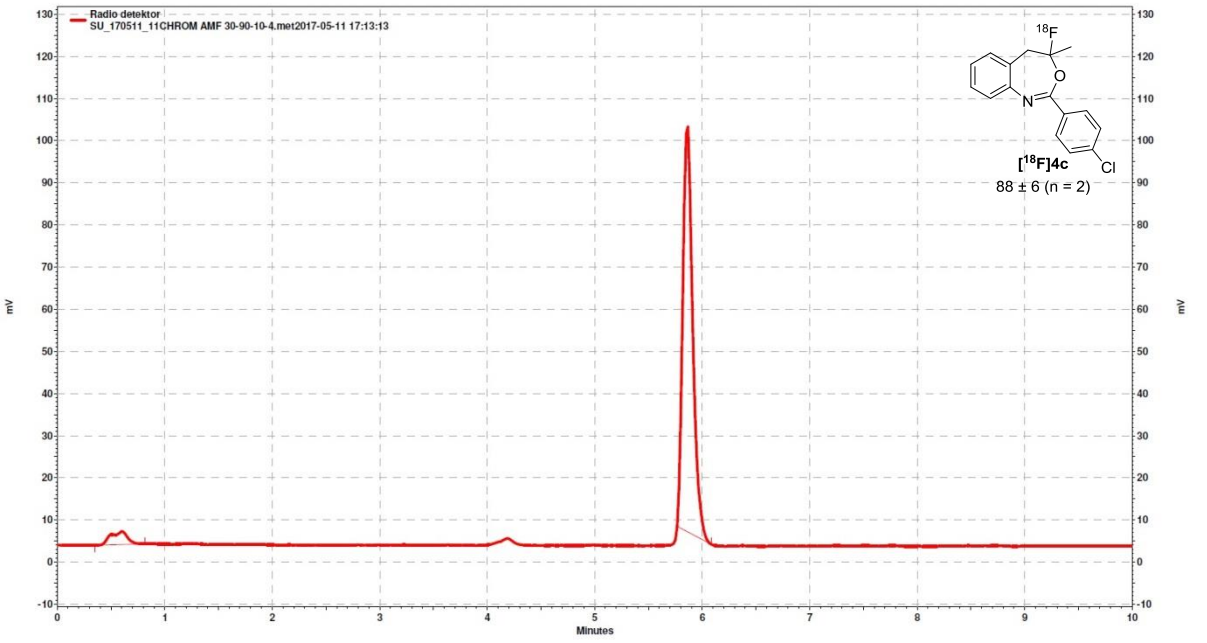
mAU
Minutes
F
O
N
Reference
Cl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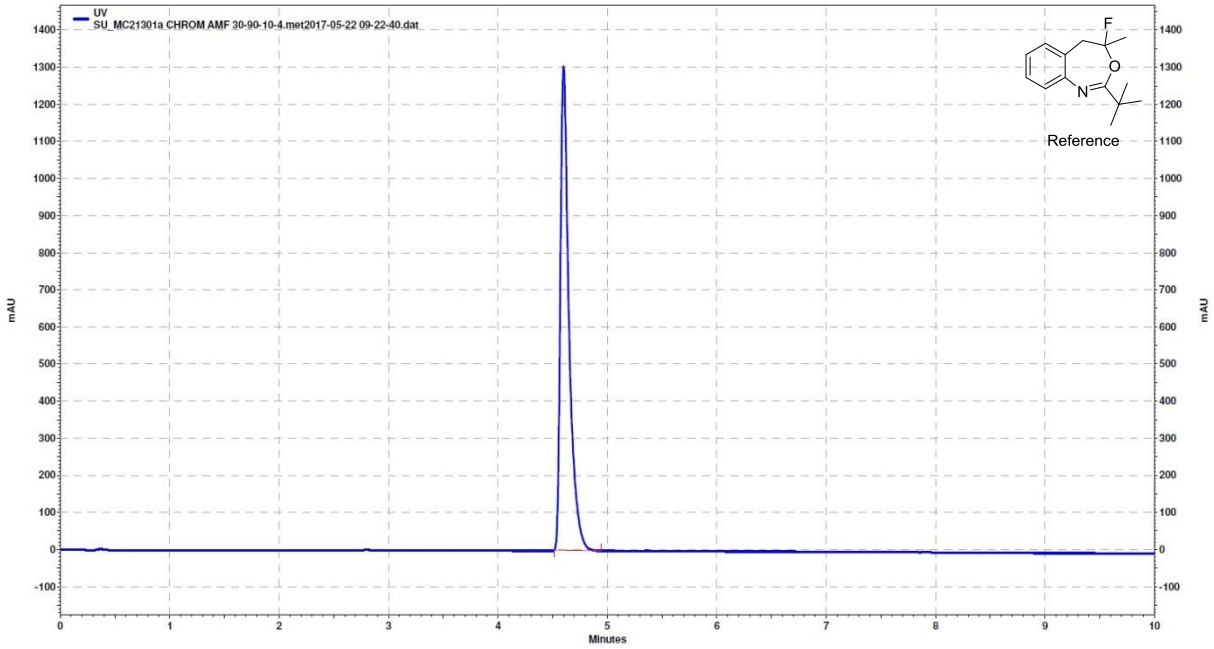
mV
Minutes
18F
O
N
[18F]4c
Cl
88 ± 6 (n = 2)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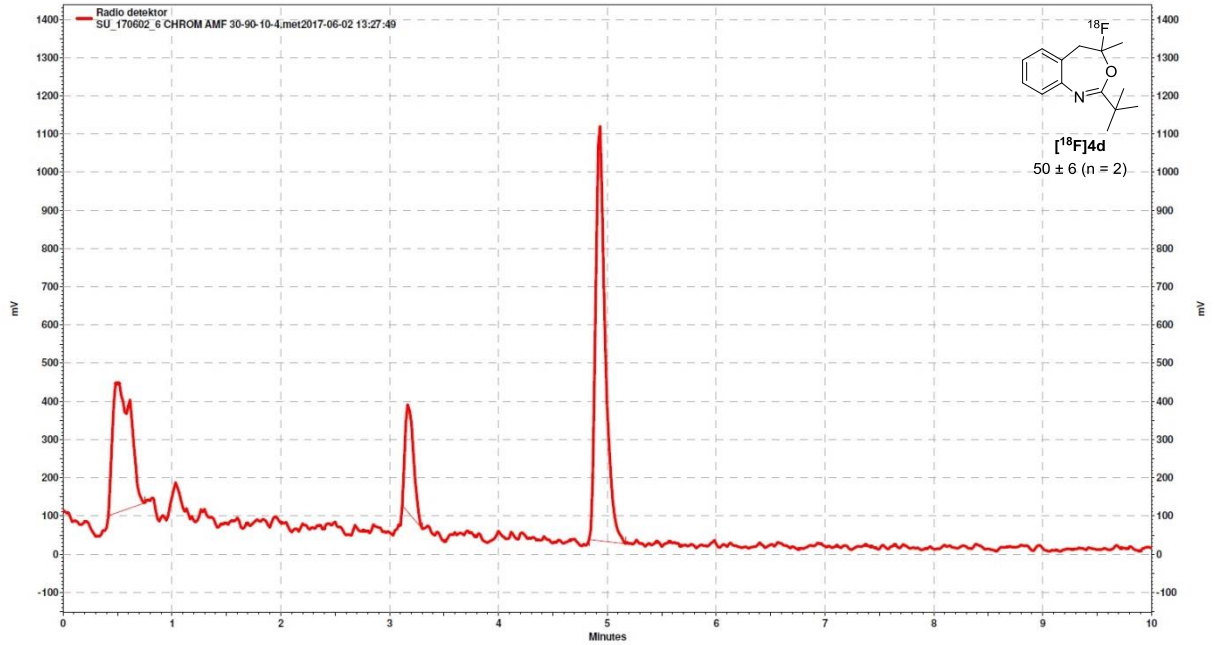
mAU
Minutes
F
O
N
Reference


Radio detektor
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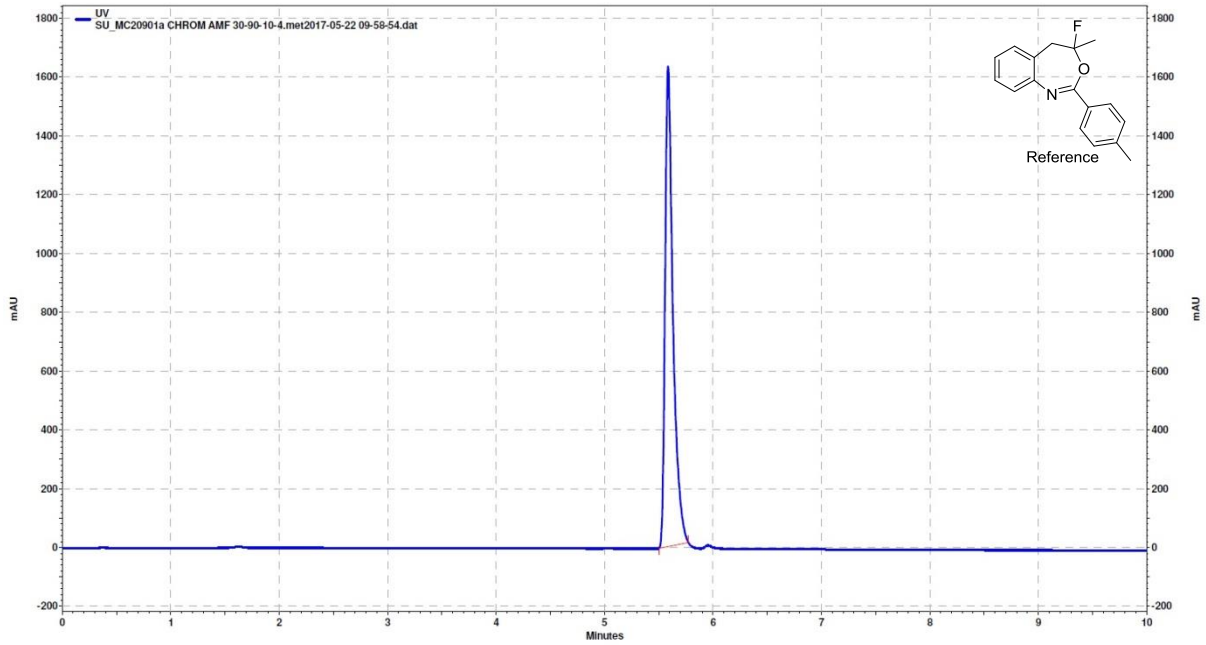
mV
Minutes
18F
O
N
[18F]4d
50 ± 6 (n = 2)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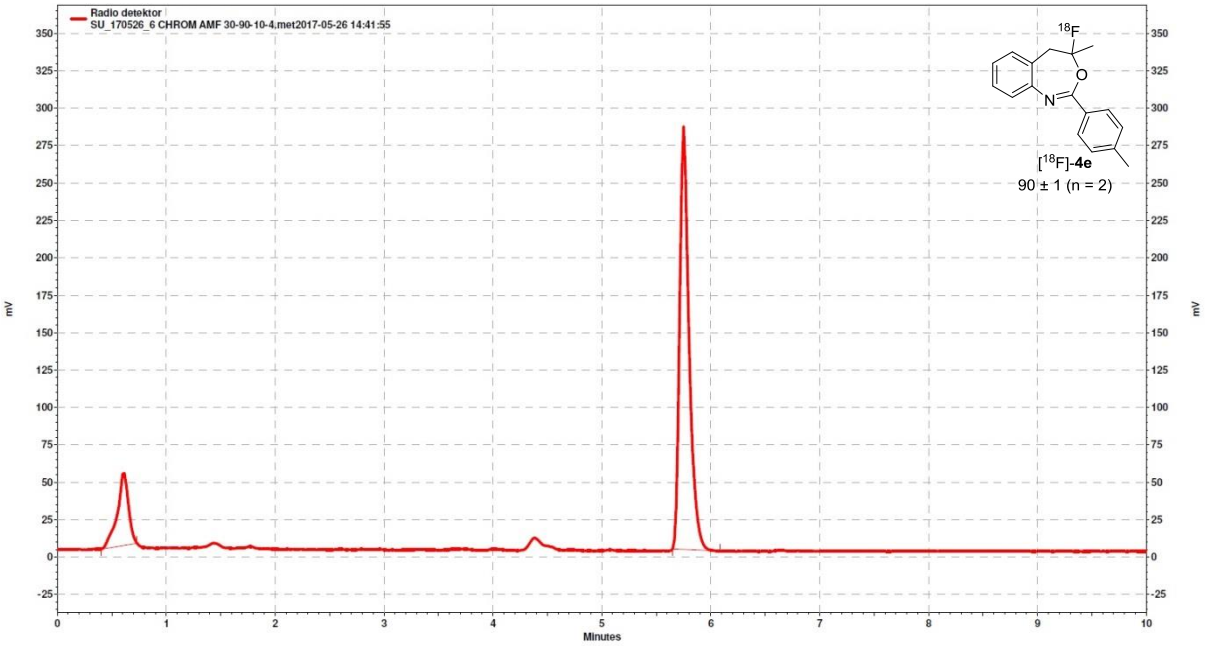
mAU
Minutes
Reference


Radio detektor
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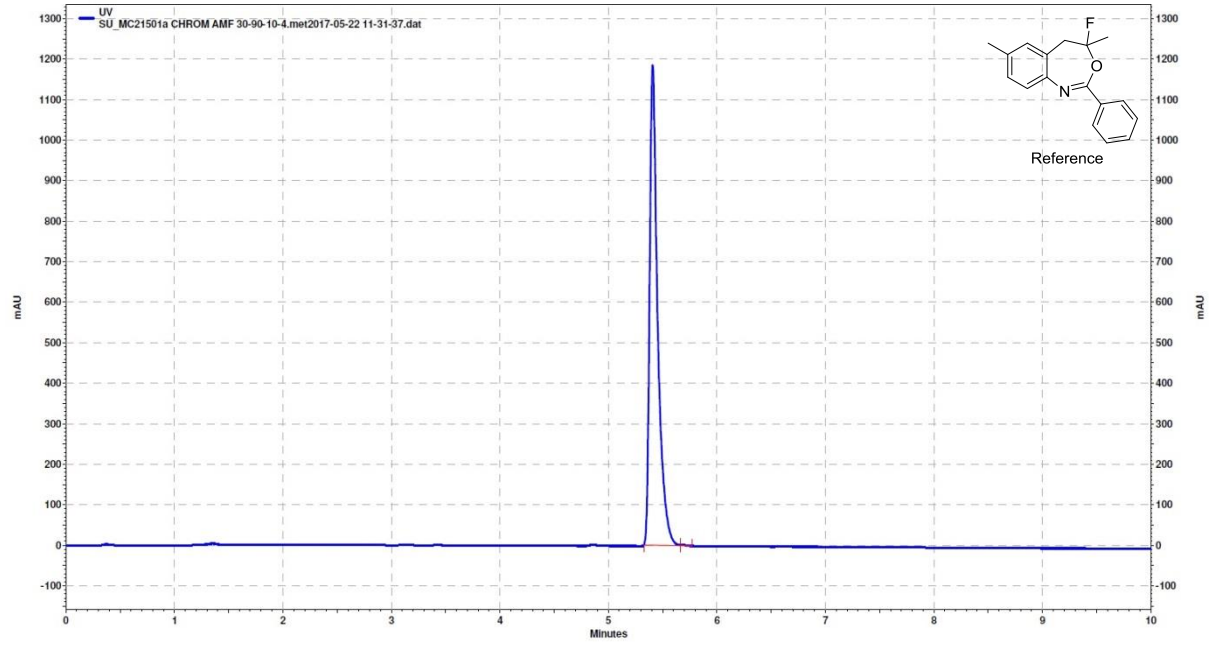
mV
Minutes
[18F]-4e
90 ± 1 (n = 2)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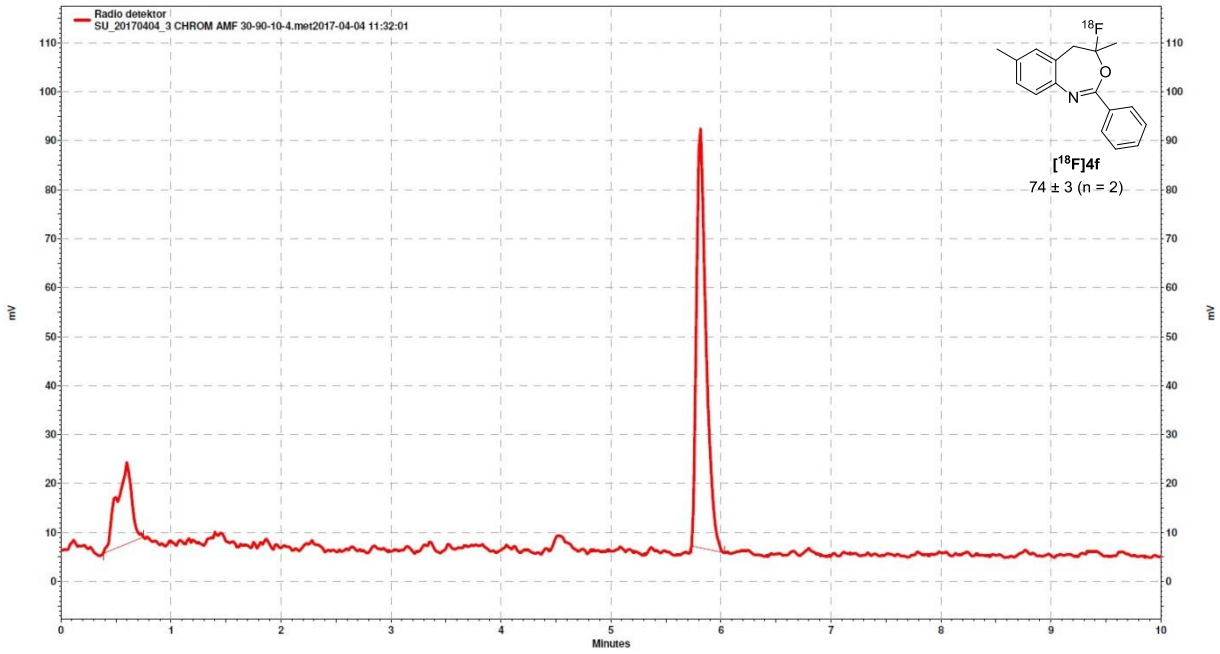
mAU
Minutes
F
O
N
Reference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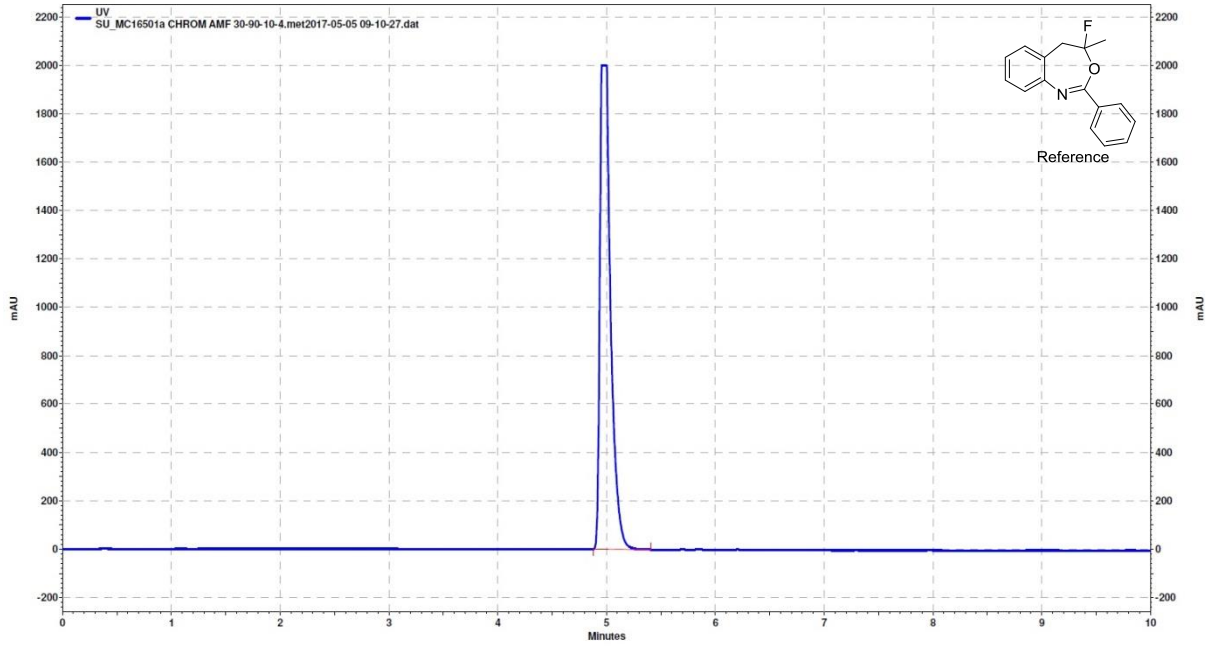
mV
Minutes
18F
O
N
[18F]4f
74 ± 3 (n = 2)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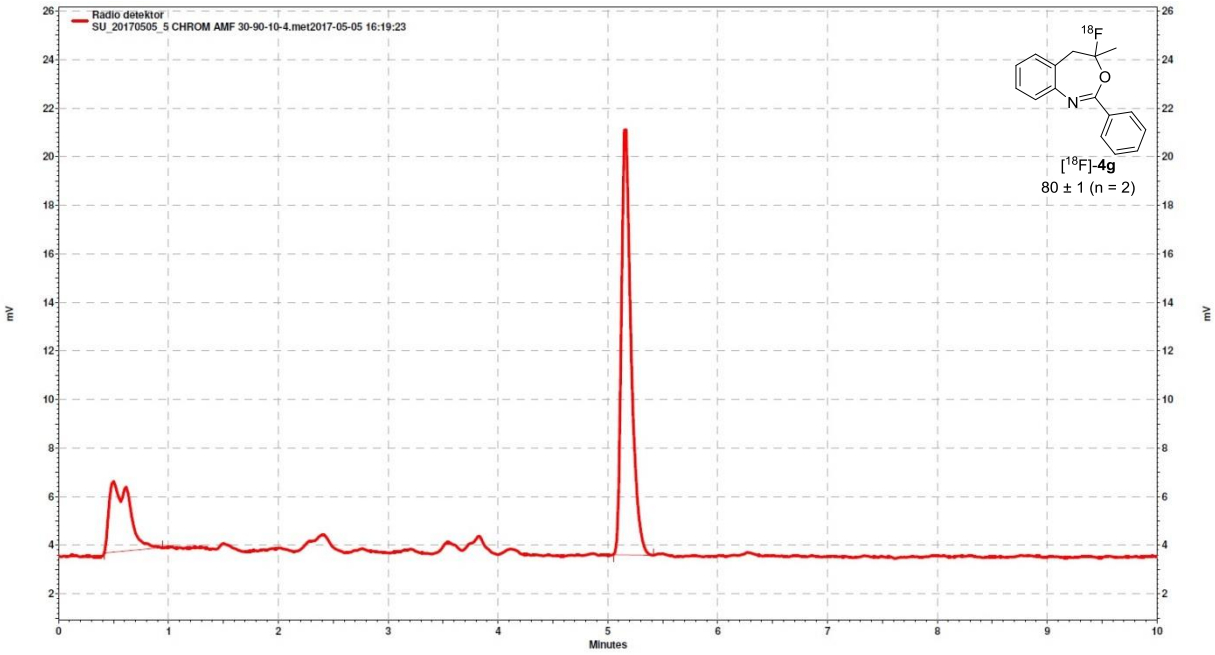
Minutes
F
O
N
Reference


Radio detektor
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mV
Minutes
18F
O
N
[18F]-4g
80 ± 1 (n = 2)

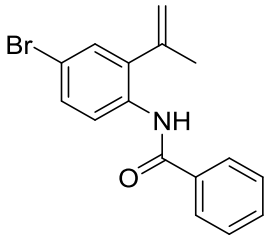
References

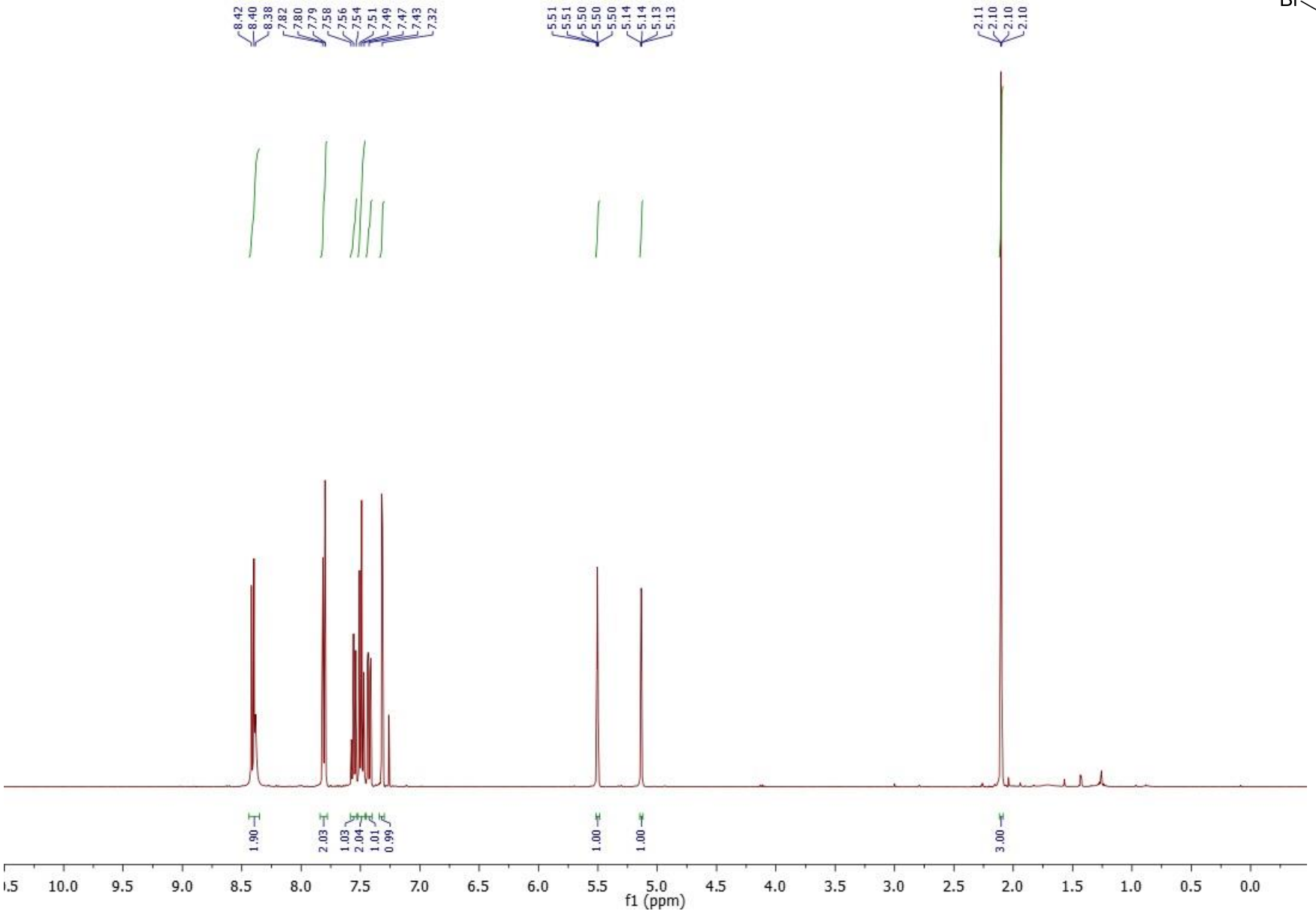
[1] G. C. Geary, E. G. Hope, K. Singh, A. M. Stuart, *Chem. Commun.* **2013**, *49*, 9263-9265.

[2] A. Ulmer, C. Brunner, A. M. Arnold, A. Pothig, T. Gulder, *Chem. Eur. J.* **2016**, *22*, 3660-3664.

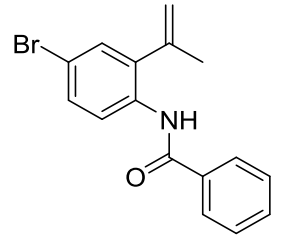
Copies of ^{1}H-, ^{13}C- and ^{19}F-NMR of compounds

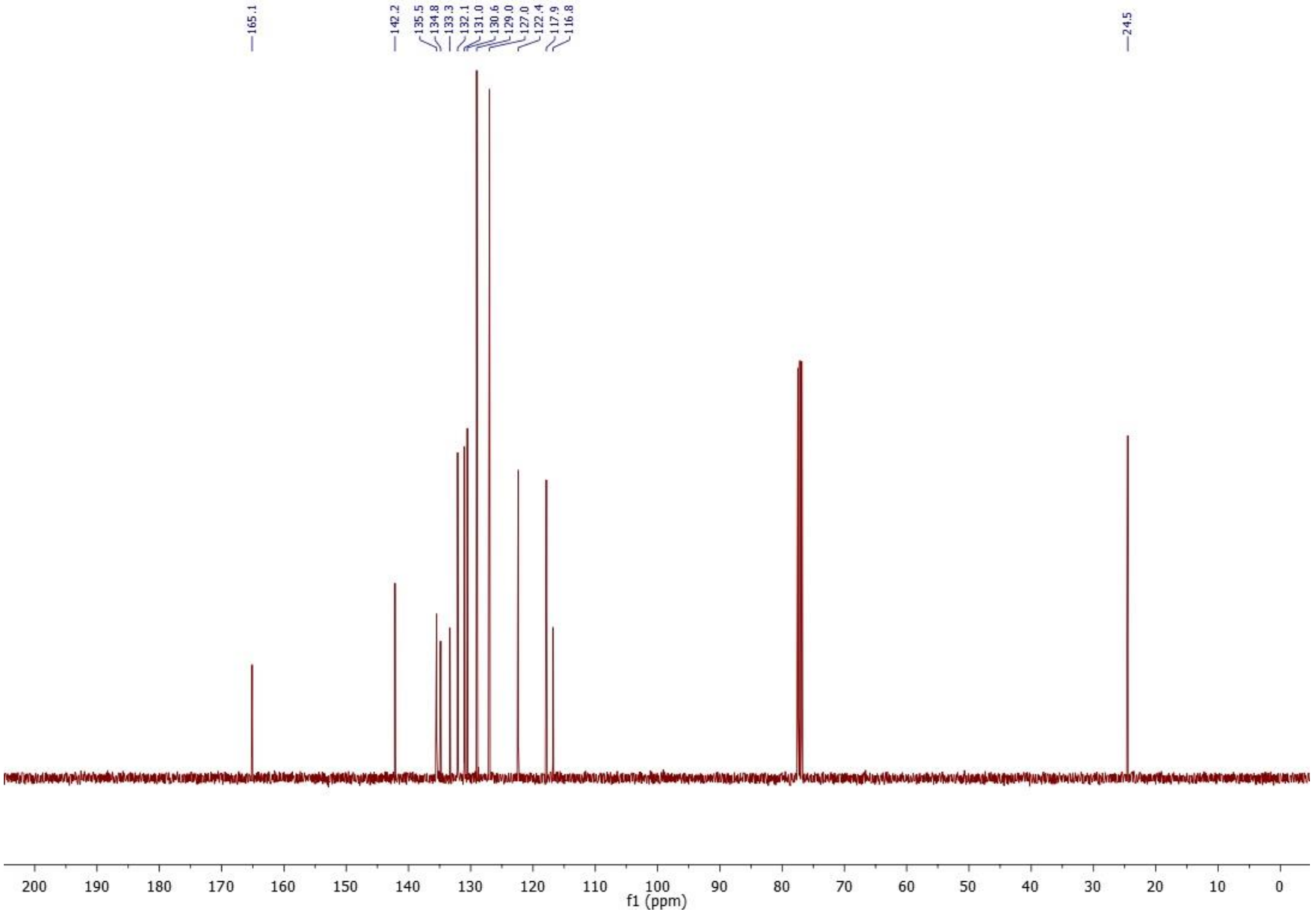
^{1}H NMR ($CDCl_3$, 400 MHz) *N*-(4-bromo-2-(prop-1-en-2-yl)phenyl)benzamide (**3b**)



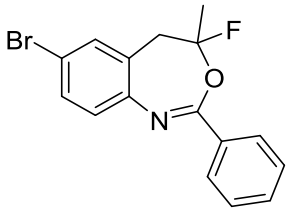


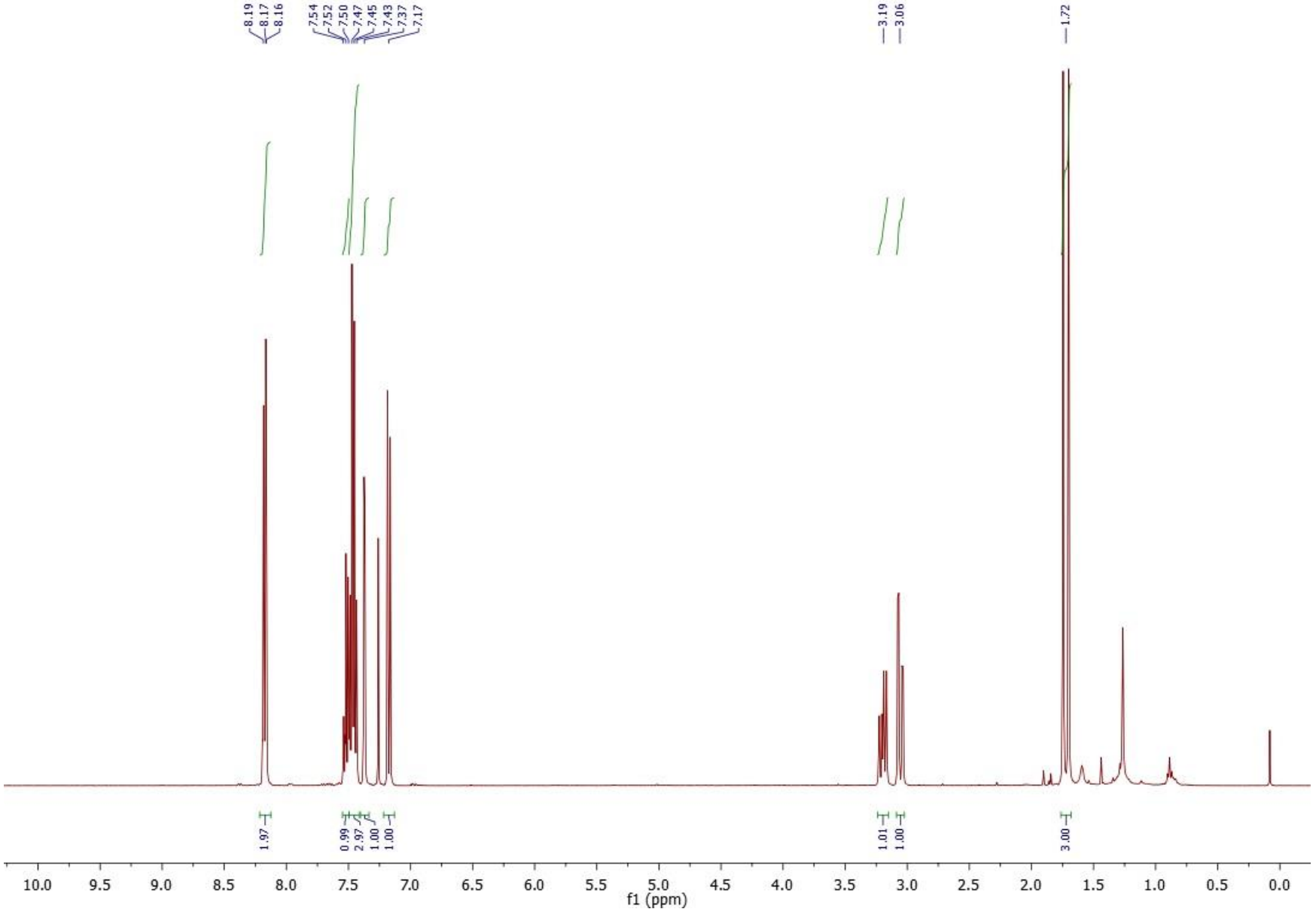
^{13}C NMR ($CDCl_3$, 100 MHz) *N*-(4-bromo-2-(prop-1-en-2-yl)phenyl)benzamide (**3b**)



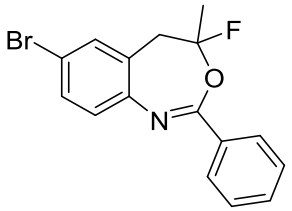


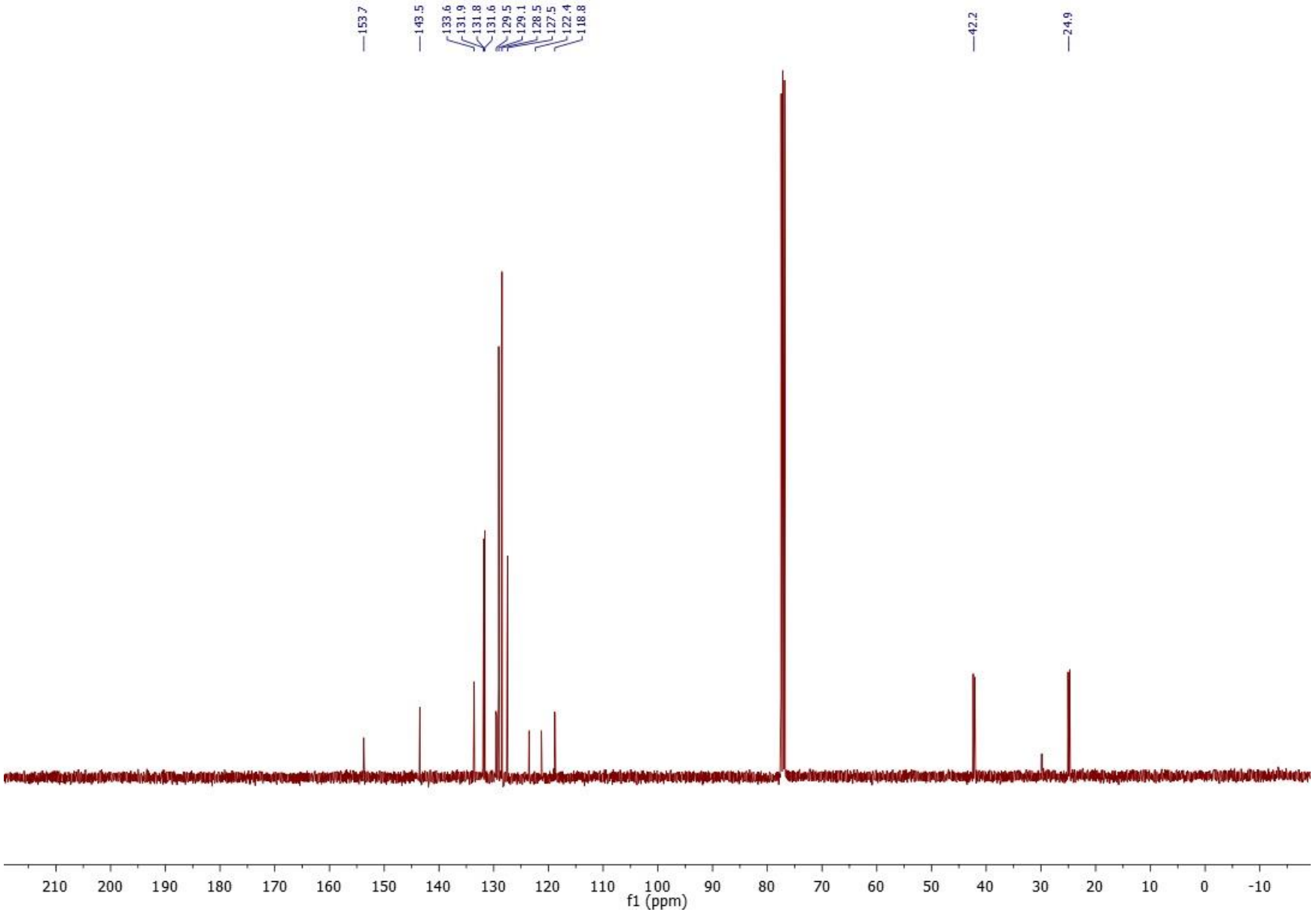
^{1}H NMR ($CDCl_3$, 400 MHz) 2-phenyl-4-fluoro-4-methyl-7-bromo-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4b**)



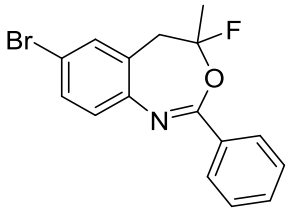


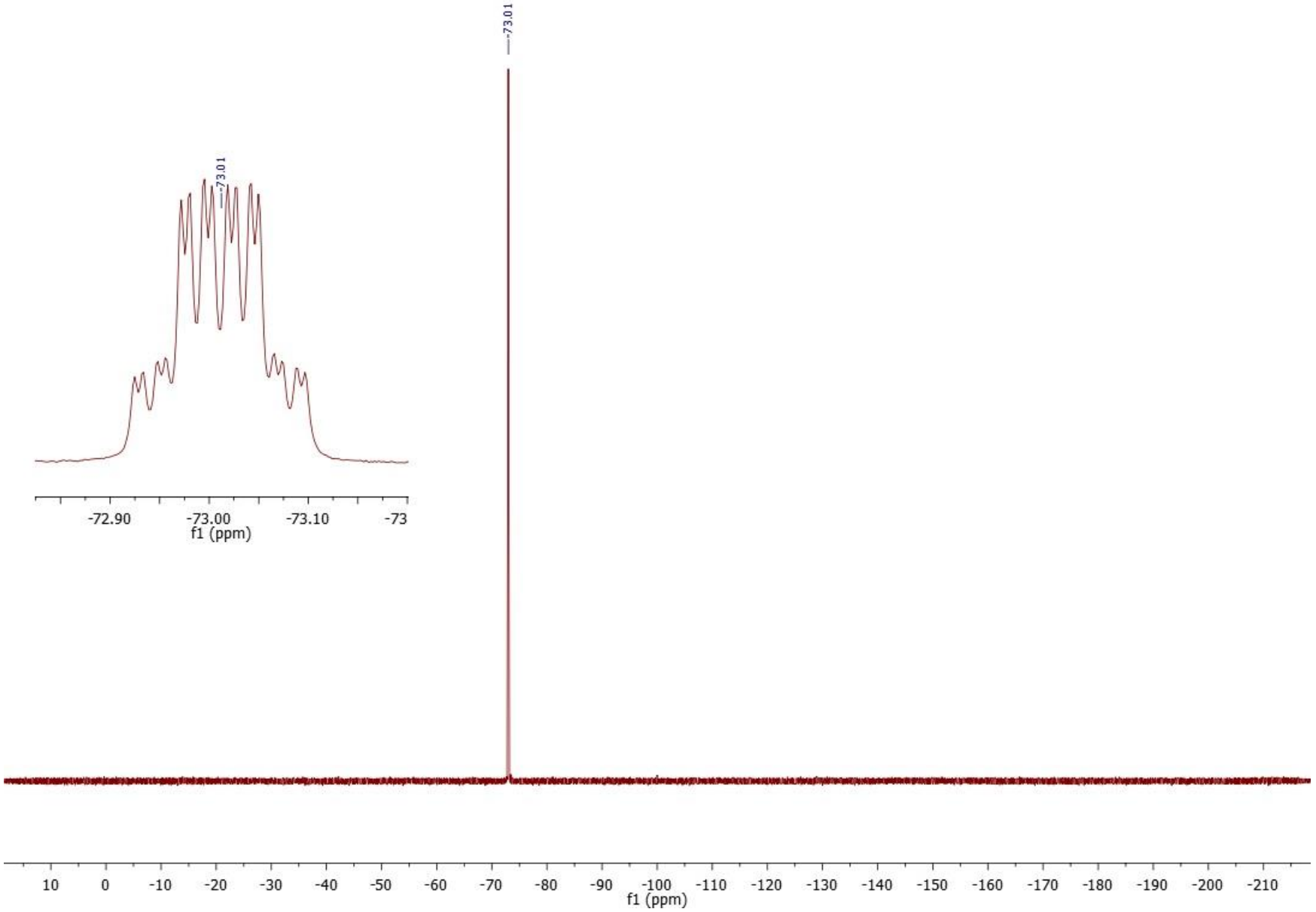
^{13}'C NMR ($CDCl_3$, 100 MHz) 2-phenyl-4-fluoro-4-methyl-7-bromo-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4b**)



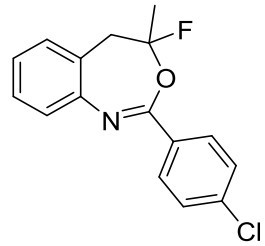


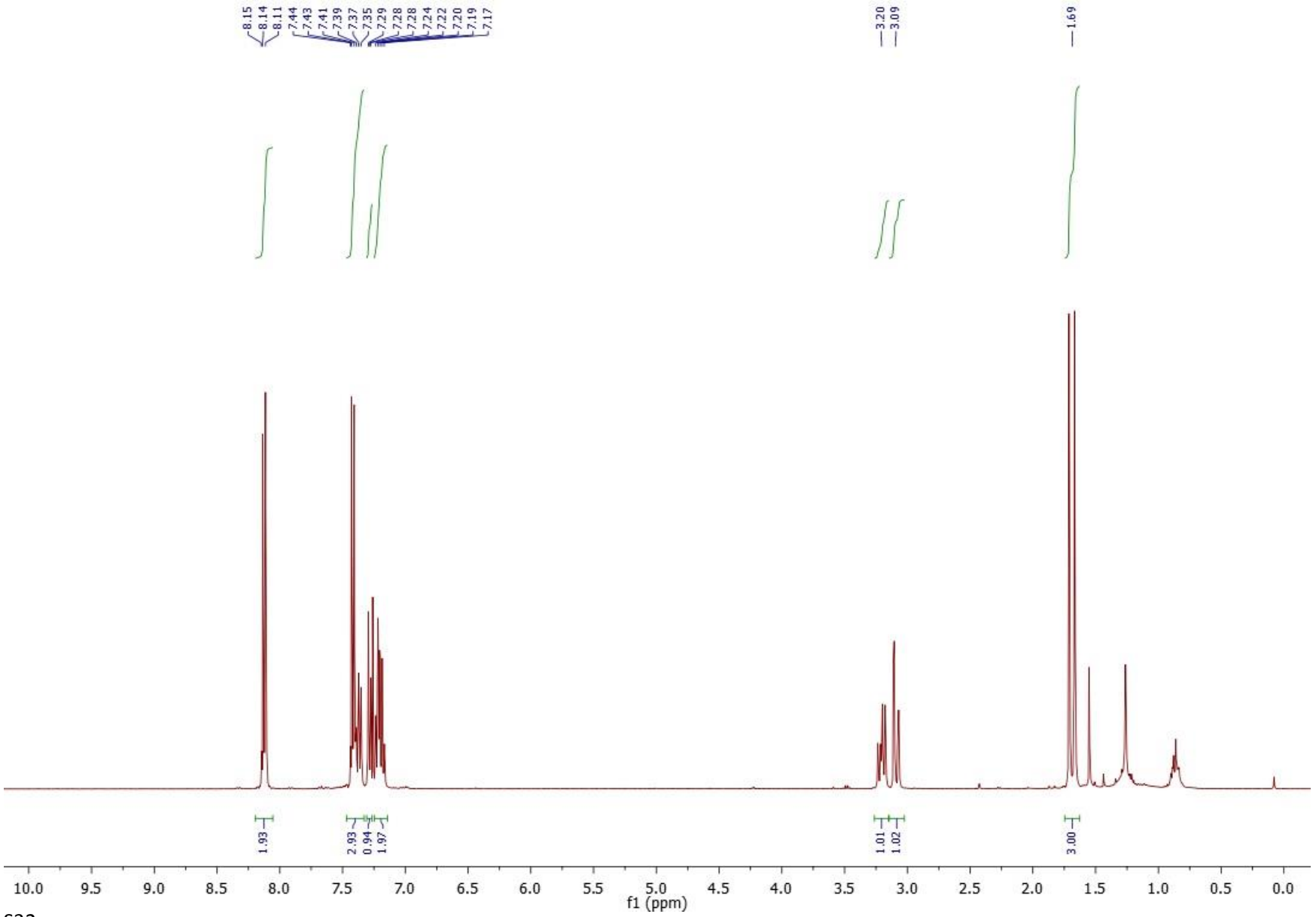
^{19}F NMR ($CDCl_3$, 377 MHz) 2-phenyl-4-fluoro-4-methyl-7-bromo-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4b**)



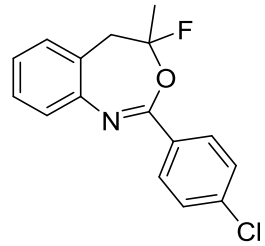


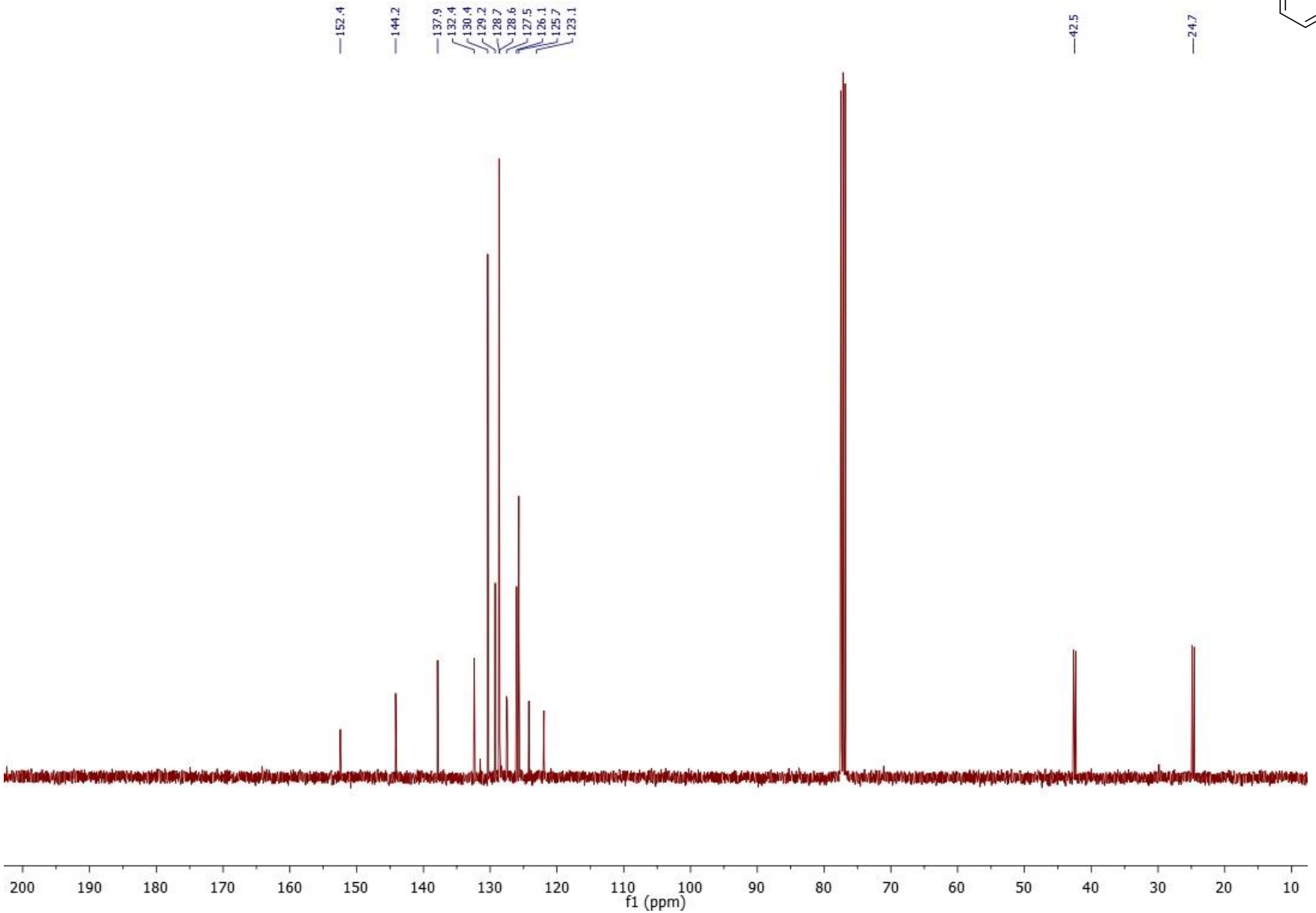
^{1}H NMR ($CDCl_3$, 400 MHz) 2-(4-chlorophenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4c**)



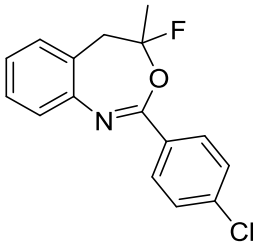


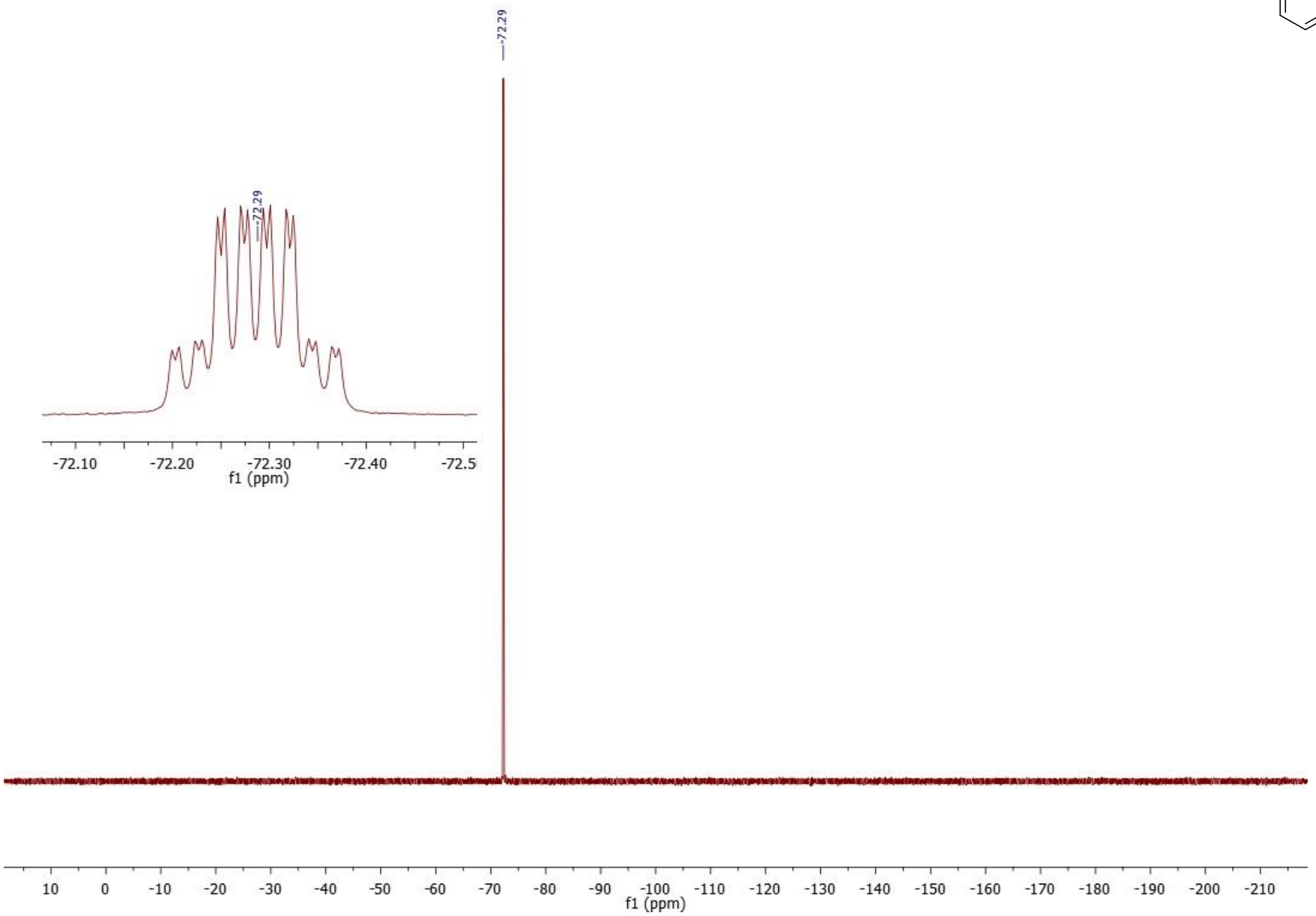
^{13}C NMR ($CDCl_3$, 100 MHz) 2-(4-chlorophenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4c**)



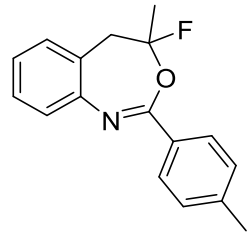


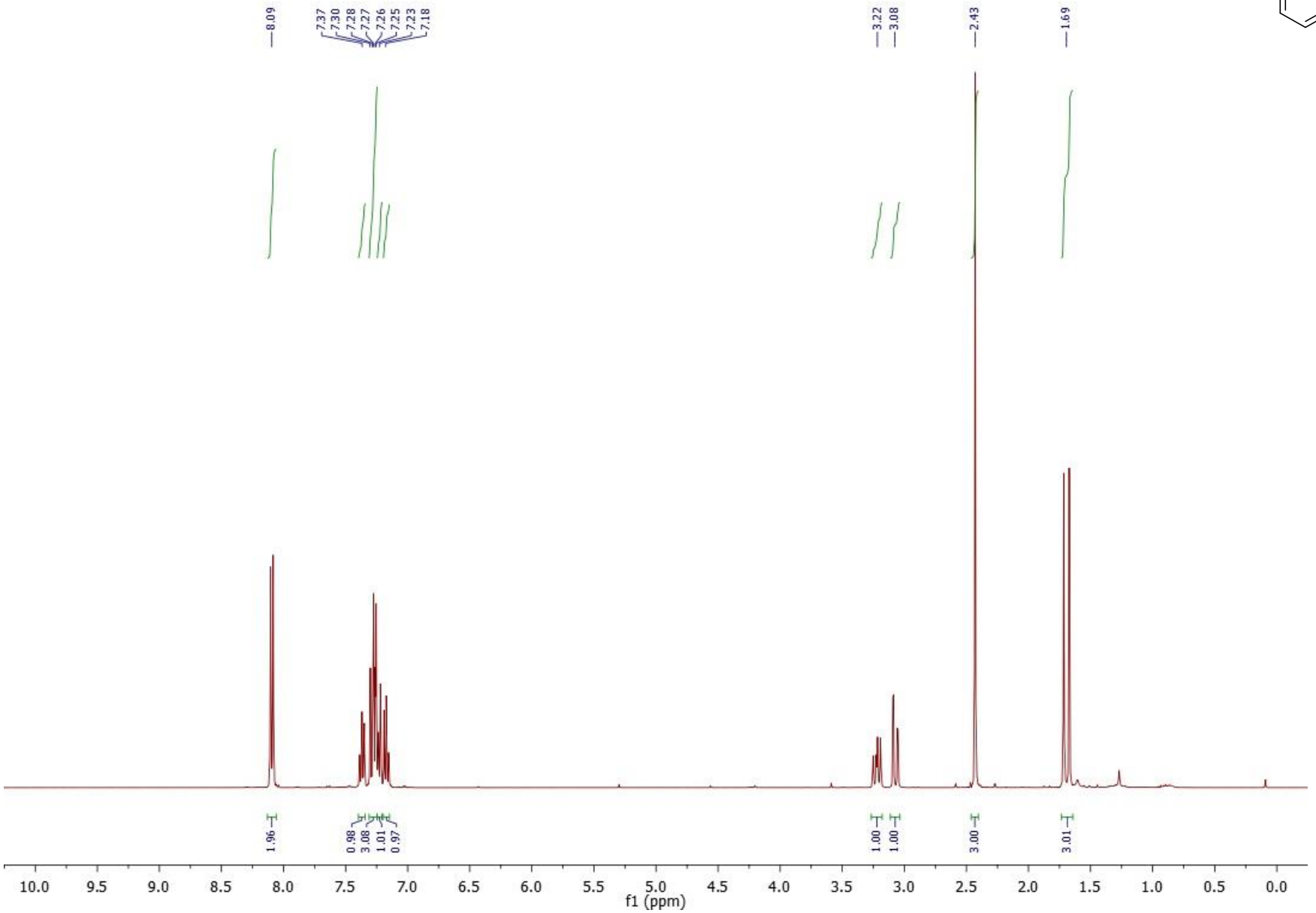
^{19}F NMR ($CDCl_3$, 377 MHz) 2-(4-chlorophenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4c**)



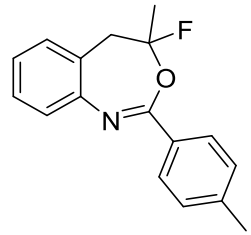


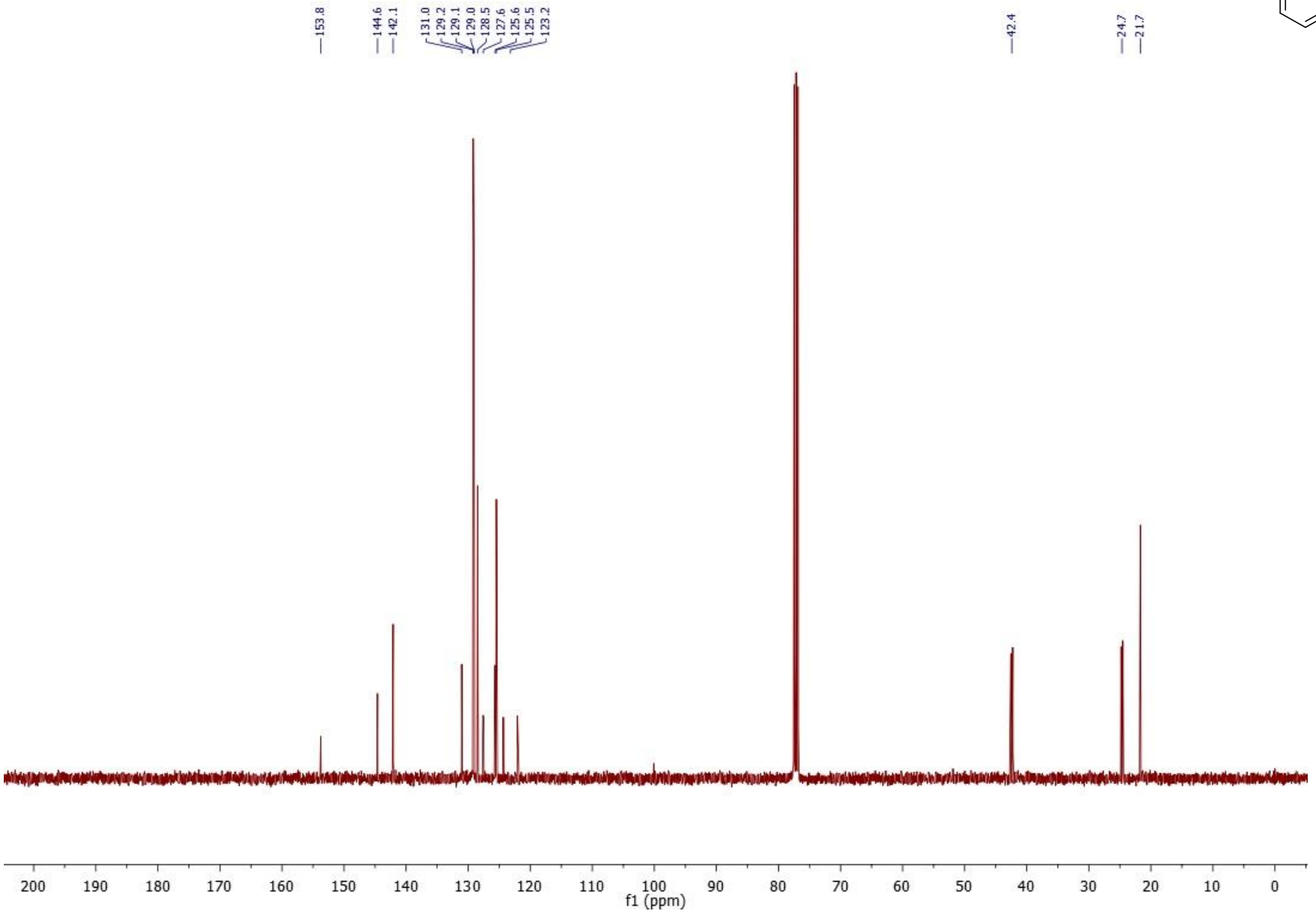
^{1}H NMR ($CDCl_3$, 400 MHz) 2-(4-methylphenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4e**)





^{13}C NMR ($CDCl_3$, 100 MHz) 2-(4-methylphenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4e**)





^{19}F NMR ($CDCl_3$, 377 MHz) 2-(4-methylphenyl)-4-fluoro-4-methyl-4,5-dihydrobenzo[*d*][1,3]oxazepine (**4e**)