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Supporting information for:

Fast and reliable generation of [^{18}F]triflyl fluoride, a gaseous [^{18}F]fluoride source

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1 General methods and materials

Unless otherwise specified, chemicals were obtained from Sigma Aldrich (Zwijndrecht, The Netherlands) and used without further purification. Acetonitrile (MeCN), methanol, ethyl acetate, dichloromethane (DCM), dimethylformamide (DMF), diethylether and hexane were purchased from Biosolve (Valkenswaard, the Netherlands). MeCN, DMF and DCM were dried over molecular sieves (3Å). MeCN used for the labelling of the model compounds was distilled twice, once over P_2O_5 and then over CaH_2, prior to storing it over molecular sieves. Water was distilled and deionised (18 m_cm^{-1}) by means of a Milli-Q water filtration system (Millipore, USA). All air- and moisture-sensitive reactions were performed under argon atmosphere. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 250 (^{1}H = 250.13 MHz, ^{13}C = 62.90 MHz, ^{19}F = 235.33 MHz) instrument at 20°C. Chemical shifts (δ) are given in ppm, internally referenced to residual solvent resonances (^{1}H: δ = 7.26 ppm ($CDCl_3$) and 2.50 ppm (DMSO-d_6); ^{13}C: δ = 77.0 ppm ($CDCl_3$) and 39.5 ppm (DMSO-d_6)). Coupling constants (*J*) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet). High resolution mass spectra (HRMS*, m/z*) analyses were conducted on a Bruker microQTOF MS apparatus (Capillary voltage: -4500V; collision energy: 5eV) using positive (ESI^+) or negative electrospray ionization (ESI^-). Thin-layer chromatography (TLC) was performed using TLC plates from Merck (SiO_2, neutral kieselgel 60 on alumina with a 254 nm fluorescence indicator). Compounds on the TLC plate were visualised by UV light at 254 nm. Flash column chromatography was performed on a Büchi Sepacore® X10 flash system using silica packed cartridges. Aldrich silica gel 60A (230-400 mesh) was used for preparing pre-column cartridges. Optimisation reactions were analysed using a Shimadzu SPD-20A system and LabSolutions 5.85 software (Shimadzu Corporation, Japan). Analysis of the model compounds was performed on a Jasco system consisting of a Jasco PU-1580 pump, a Jasco UV-2075 Plus UV/VIS detector set at a wavelength of 254 nm, a Scionex 51BP 51/2 NaI radioactivity detector and a Raytest Gina data acquisition and control interface. Radiochemical purity and molar activity of [^{18}F]FES and [^{18}F]FET were determined using a Dionex UltiMate 3000 RS HPLC system and Chromeleon 6.8 software. The HPLC analysis of all compounds was performed on a Grace Alltima™ C18 5u 250mm x 4.6mm (Alltech, The Netherlands) using 70:30:0.2 MeCN/H_2O/TFA as eluent at a flow of 1 mL·min^{-1}, unless stated otherwise.

Radiochemical yields and molar activity were defined following the recently published radiochemistry nomenclature guideline.[1]

2 Radiochemistry

2.1 General procedure of the [^{18}F]triflyl fluoride synthesis

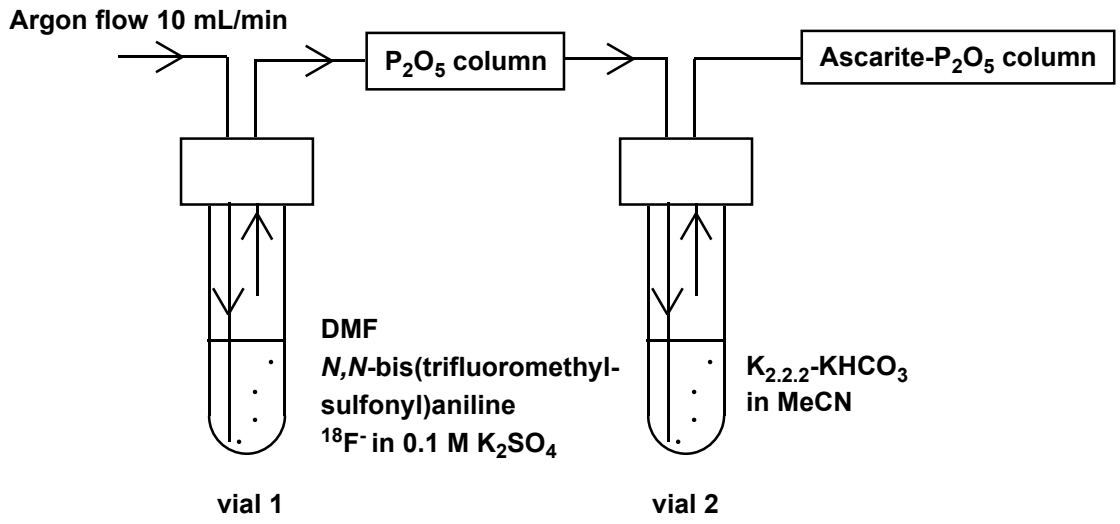


Figure 1 Schematic overview of the reaction set-up.

[^{18}F]fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction on an IBA Cyclone® 18/9 cyclotron using a [^{18}O]H_2O liquid target. After irradiation, the target water was passed through a Chromafix® 30-PS-HCO_3 ^{18}F separation cartridge to trap the [^{18}F]fluoride. The cartridge was eluted with different amounts of aqueous 0.1M potassium sulfate solution depending on the further use of the [^{18}F]fluoride:

- To use the eluate as a stock solution for multiple [^{18}F]fluorination reactions, the [^{18}F]fluoride was eluted with 0.1M potassium sulfate solution (1 mL). 50 µL of this stock solution was combined with 0.1M *N,N*-bis(trifluoromethylsulfonyl)aniline (bistriflate precursor) in DMF (100 µL, 3.5 mg) and DMF (850 µL) (final concentration: 5% H_2O) and reacted at room temperature.
- When the total amount of [^{18}F]fluoride was used for one [^{18}F]fluorination reaction, the [^{18}F]fluoride was eluted from the cartridge with 0.1 M potassium sulfate solution (500 µL). Hereafter the cartridge was eluted with DMF (850 µL) which was then added to the first eluate. 0.1 M *N,N*-bis(trifluoromethylsulfonyl)aniline (150 µL) was added directly to the vessel and the mixture (33% H_2O) was reacted at 40 °C.

Formation and distillation of [^{18}F]triflyl fluoride were carried out simultaneously: while the [^{18}F]fluoride reacted with the *N,N*-bis(trifluoromethylsulfonyl)aniline, the product [^{18}F]triflyl fluoride was continuously blown out of the reaction mixture with a gentle stream of helium (10 mL/min)

over a period of 5 minutes and passed over a phosphorus pentoxide column. The [^{18}F]triflyl fluoride was trapped by conversion to [^{18}F]fluoride in a solution of $K_{2.2.2}$ and $KHCO_3$ in MeCN (100 µL of a 266 mM stock solution of $K_{2.2.2}$/$KHCO_3$-complex in MeCN (800-900 µL)).

2.2 266mM stock solution of $K_{2.2.2}$/$KHCO_3$-complex

Dry acetonitrile (1 mL) was added to potassium bicarbonate (26.6 mg, 0.266 mmol) and kryptofix-$K_{2.2.2.}$ (100 mg, 0.266 mmol). The vial was wrapped in aluminium foil to prevent the solution from degradation by light and the solution was left overnight on a shaking plate.

2.3 Calculation of radiochemical yields

The radiochemical yields of the general procedure were determined as follows: the amount of radioactivity in vial 1 before distillation as well as the amount of radioactivity of the distillate (vial 2) and residue (vial 1) after the distillation were measured in the dose calibrator. The ratio of the amount of decay-corrected radioactivity of the distillate to the amount of radioactivity in vial 1 before distillation is defined as the radiochemical yield. As the [^{18}F]triflyl fluoride was trapped by conversion to free [^{18}F]fluoride, the radiochemical yield does not describe the yield of [^{18}F]triflyl fluoride but the yield of dry [^{18}F]fluoride relative to the starting amount of radioactivity eluted from the cartridge.

The only exception was when trapping in solvent without additives (e.g. THF at -100 °C). In this case [^{18}F]triflyl fluoride was trapped as such and the radiochemical yields refer to [^{18}F]triflyl fluoride.

Table S1 Example of activity calculations of the [^{18}F]fluorotriflate distillation.

	Activity (MBq)	Time	Time difference	Activity dc (MBq)	Yield %
vial 1 before distillation	9420	10:19	0	9420,0	
distillate	8625	10:25	6	8958,0	95
residue	287,3	10:26	7	300,3	3
exhaust	106,6	10:28	9	112,8	1

2.4 Optimisation procedures

2.4.1 Screening of solvents for the [^{18}F]triflyl fluoride formation

To investigate what is the most suitable solvent for the [^{18}F]triflyl fluoride formation and subsequent distillation, the radiofluorination of the bistriflate precursor was carried out in four

different solvents: MeCN, DMF, THF and dioxane. For this, [^{18}F]fluoride was eluted with 0.1 M potassium sulfate solution (1 mL) and 50 µL of the eluate was reacted at room temperature with 0.1 M *N,N*-bis(trifluoromethylsulfonyl)aniline (100 µL, 3.5 mg) and MeCN, DMF, THF or dioxane (860 µL). The product was distilled and trapped according to the procedure described in paragraph 2.1. The radiochemical yields were calculated as described in 2.3.

Table S2. Radiochemical yields obtained with different solvents in vial 1

Solvent	RCY (n=2)
MeCN	94±2%
DMF	98±1%
THF	11±2%
dioxane	62±3%

2.4.2 The influence of water

To determine the influence of water on the [^{18}F]triflyl fluoride formation, 10 µL of a solution of [^{18}F]fluoride in 0.1 M K_2SO_4 was reacted at room temperature with 0.1 M, 0.05 M, 0.01 M or 0.005 M *N,N*-bis(trifluoromethylsulfonyl)aniline solution (100 µL) in DMF (200 - 890 µL) and water (10 - 690 µL) (total volume 1 mL; 0, 1, 2, 5, 10, 15, 20, 40 and 70 % water). Samples were taken of the reaction mixture and analysed by analytical HPLC (Grace Alltima™ C18 5u 250mm x 4.6mm column, MeCN/H_2O/TFA 60:40:0.2; 1 mL/min, 254 nm; t_R([^{18}F]triflyl fluoride) = 6'11).
An overview of the results is given in Table S3. For 40 and 70% of water, too low conversion to [^{18}F]triflyl fluoride was observed to determine the radiochemical purity accurately by HPLC analysis because unreacted [^{18}F]fluoride was sticking to the column.

Table S3 Radiochemical purity (%) of [^{18}F]triflyl fluoride obtained in reactions containing different amounts of water at various concentrations of bistriflate precursor (n=2)

% H_2O	100 mM Precursor	50 mM Precursor	10 mM Precursor	5 mM Precursor
1	98±2	95±3	80±1	78±23
2	98±0	97±2	75±3	85±1
5	96±1	99±0	92±3	95±5
10	85±3	96±1	96±4	91±2
15	73±4	93±2	96±3	93±2
20	49±5	79±19	92±0	91±7

2.4.3 Drying columns

To assess the suitability of different drying materials, [^{18}F]triflyl fluoride was synthesised following the general procedure for small amounts of [^{18}F]fluoride (see 2.1). Distillation was performed for 5 minutes over various drying columns, containing either P_2O_5, $CaSO_4$, $CuSO_4$, $MgSO_4$ or Na_2SO_4, and it was trapped in a solution of kryptofix/$KHCO_3$-complex (100 µL), 0.1 M 1,4-dinitrobenzene (100 µL) and MeCN (850 µL) at 50 °C. After the distillation, the amount of radioactivity on the drying columns was measured and divided by the amount of radioactivity in vessel 1 before distillation to calculate the remaining fraction of triflyl fluoride absorbed by the column material. The conversion of the trapped [^{18}F]triflyl fluoride to 1-fluoro-4-nitrobenzene was monitored by HPLC and reported as radiochemical yield (RCY).

Table S4 Percentage of radioactivity sticking to various drying columns and the RCY of [^{18}F]1-fluoro-4-nitrobenzene using the various drying columns (n=2).

Drying column	Remaining radioactivity on drying column (%)	RCP (HPLC) of 1-fluoro-4-nitrobenzene (%)
$CaSO_4$	15±1	79±3
$CuSO_4$	0.6±0.6	89±8
$MgSO_4$	1±0	85±12
Na_2SO_4	0.7±0.2	85±4
P_2O_5	0.2±0.1	95±0

2.4.4 Trapping

Various solvents and additives were screened to find the most efficient way of trapping the [^{18}F]triflyl fluoride.

For this, [^{18}F]triflyl fluoride was synthesised following the general procedure for small amounts of [^{18}F]fluoride as described above (see 2.1) and the following parameters were varied:

- Solvent in the second reaction vial: [^{18}F]triflyl fluoride was trapped in a mixture of stock solution of $K_{2.2.2}$/$KHCO_3$-complex (100 µL) (see 2.2) and MeCN, DMF, DMA, THF or DMSO (900 µL).
- Base/complex added: $KHCO_3$/$K_{2.2.2}$, K_2CO_3/$K_{2.2.2}$, $K_{2.2.2}$, dibenzo-18-crown-6/K_2CO_3, (n-Bu)$_4NH_4SO_4$/Na_2CO_3, DABCO; 100 µL of a 0.1M solution in MeCN was added to MeCN (850 µL)
- Temperature of the trapping vial: -100 °C – 20 °C

- Precursor for subsequent radiofluorination present in the trapping solution: 100 µL of a 0.1 M solution of 1,4-dinitrobenzene in MeCN was added to the trapping vial containing stock solution of $K_{2.2.2}/KHCO_3$-complex in MeCN (100 µL) (see 2.1) and MeCN (800 µL). The product was trapped in 5 minutes at 50 °C.

The radiochemical yields of the trapping experiments were determined according to chapter 2.2.

Table S5 Radiochemical yields of [^{18}F]fluoride (*=[^{18}F]triflyl fluoride) under different trapping conditions; general: 50 uL K_2SO_4, 5 minutes reaction time, no sicapent column; #=distilled over a distance of 10 m.

solvent	Base complex	temperature	RCY (%)
MeCN	$K_{2.2.2}/KHCO_3$	20 °C	94 ± 1 (n=3)
DMF	$K_{2.2.2}/KHCO_3$	20 °C	95 ± 1% (n=2)
DMA	$K_{2.2.2}/KHCO_3$	20 °C	95 ± 3% (n=2)
THF	$K_{2.2.2}/KHCO_3$	20 °C	90 ± 4% (n=2)
DMSO	$K_{2.2.2}/KHCO_3$	20 °C	62 ± 19% (n=2)
MeCN	$K_{2.2.2}/KHCO_3$	20 °C	99 ± 1 (n=2)#
MeCN	Dibenzo-18-crown-6 /K_2CO_3	20 °C	79 ± 3 (n=2)
MeCN	TBA/HCO_3	-40 °C	86 ± 5 (n=3)
MeCN	$K_{2.2.2}/K_2CO_3$	20 °C	84 ± 8 (n=3)
MeCN	100 µl 0.1M $K_{2.2.2}$	20 °C	2 (n=1)
MeCN	0.1M DABCO	20 °C	15 (n=1)
1.5 mL THF	-	-100 °C	66 ± 35 (n=5)*
1 mL MeCN	-	-40 °C	68 ± 3 (n=2)*

2.5 Radiofluorination with [^{18}F]triflyl fluoride derived fluoride

After trapping of [^{18}F]triflyl fluoride as free [^{18}F]fluoride in a solution of $KHCO_3/K_{2.2.2}$ in MeCN (see 2.1, general procedure), 100 µL of a 0.1 M solution of precursor in MeCN was added to the [^{18}F]fluoride solution. For every precursor, the mixture was reacted at multiple temperatures being RT, 50 °C, 80 °C or 120 °C for either 5 or 15 minutes. Subsequently, a sample (5 µL) was taken to determine the radiochemical purity *via* HPLC (see paragraph 5).

2.6 Analysis of the [^{18}F]fluorinated model compounds

Radioactive products were identified by comparison of the retention times of the radioactivity peak with the UV peak of the injected non-radioactive reference. As the eluent first passed the UV detector followed by the radioactivity detector, the radioactive peaks were delayed for 0.35 - 0.38 min compared to the corresponding UV signals. Radiochemical purity of the monitored reaction was calculated from the integral of the radioactive product peak relative to the total integral of all radioactive peaks.

2.7 [^{18}F]FES synthesis

0.1M potassium sulfate solution (500 µL) was pushed by a stream of helium (10 mL/min) over a HCO_3^- cartridge, eluting the [^{18}F]fluoride (~15 GBq) into a vessel containing DMF (850 µL) and 0.1 M *N,N*-bis(trifluoromethylsulfonyl)aniline (150 µL) which was heated to 40 °C. [^{18}F]Triflyl fluoride was formed instantaneously and distilled for 5 minutes into a second reaction vessel, in which it was trapped in MeCN (900 µL) containing $K_{2.2.2}$ (10 mg) and $KHCO_3$ (2.7 mg). A solution of 3-*O*-methoxymethyl-16,17-*O*-sulfuryl-16-epiestriol (0.4-0.7 mg) in acetonitrile (100 µL) was added to the second vessel, and the reaction mixture was heated for 5 minutes to 100 °C. Subsequently, 2 M H_2SO_4 (250 µL) was added and the mixture was allowed to react for 5 minutes at 100 °C. After addition of water (1 mL), the crude product was purified by semi-preparative HPLC (Phenomenex Luna C18(2) 5 µm 10 mm x 250 mm, ammonium formate buffer pH 4.5/acetonitrile 62/38 v/v, 5 mL/minute). The collected fraction was diluted with water and the product was trapped on a tC18 Plus cartridge. After it was rinsed with water, [^{18}F]FES was eluted with ethanol, formulated in buffered saline and sterile filtrated. The product was obtained with a chemical purity greater than 95%, isolated radiochemical yields of 17 and 57%, and molar activities of 114.3 and 41.3 GBq/µmol.

2.8 [^{18}F]FET synthesis

0.1M potassium sulfate solution (500 µL) was pushed by a stream of helium (10 mL/min) over a HCO_3^- cartridge, eluting the [^{18}F]fluoride (~15 GBq) into a vessel containing DMF (850 µL) and 0.1 M *N,N*-bis(trifluoromethylsulfonyl)aniline (150 µL) which was heated to 40 °C. [^{18}F]Triflyl fluoride was formed instantaneously and distilled for 5 minutes into a second reaction vessel, in which it was trapped in MeCN (500 µL) containing $K_{2.2.2}$ (5 mg) and $KHCO_3$ (1.35 mg). A solution of precursor (6 mg) in acetonitrile (100 µL) was added and the mixture was reacted for 10 minutes at 100 °C. Subsequently, 1 M HCl (0.5 mL) was added and the intermediate was hydrolysed at 100 °C for 5 minutes. After evaporation of the solvent with a stream of helium at

room temperature under vacuum, the reaction mixture was neutralised with 0.5 M sodium acetate (2 mL) and purified by semi-preparative HPLC (Phenomenex Luna C18 5 µm 10 x 250 mm, phosphate buffer pH 3.0/acetonitrile 92/8 v/v, 4 mL/min, 280 nm, RT ~18 min). After the collected fraction was diluted with water (10 mL), the product was trapped on a LiChrolut SCX ion exchange cartridge and it was rinsed with water. Finally, [^{18}F]FET was eluted, formulated in buffered saline (10 mL) and sterile filtrated. The product was obtained with a chemical purity greater than 95%, isolated radiochemical yields of 55 and 10%, and molar activities of 33.8 and 123.4 GBq/µmol.

2.9 Comparison with routine production

[^{18}F]FES and [^{18}F]FET were synthesized following the procedure described in 2.7 and 2.8 and the products were compared with those obtained in routine production with regard to yield, purity and molar activity. An overview is given in Table S6.

In routine production a similar procedure was applied as described in 2.7 and 2.8, but the [^{18}F]fluoride was eluted and dried according to conventional methods (elution with K_2CO_3 /K_{222}, azeotropic drying with MeCN).

Table S6 [^{18}F]FES and [^{18}F]FET: comparison of the [^{18}F]triflyl fluoride method with routine production (EOS).

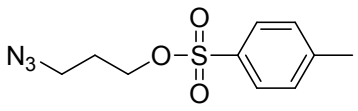
tracer	method	Yield (MBq)	Purity (%)	Molar activity (GBq/µmol)	n
[^{18}F]FES	[^{18}F]triflyl fluoride	4095±2463	99±2	78±52	2
	azeotrop.drying	3284±1163	97±2	75±29	5
[^{18}F]FET	[^{18}F]triflyl fluoride	3945±3777	100±0	79±63	2
	azeotrop.drying	4000±1163	99±1	121±33	5

The yield, purity and molar activity of [^{18}F]triflyl fluoride derived [^{18}F]FES and [^{18}F]FET is within the usual range observed in routine production.

3 Synthesis of precursors and reference compounds

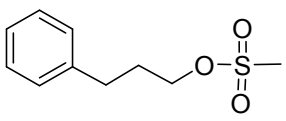
3.1 Precursors

3.1.1 3-Azidopropyl 4-methylbenzenesulfonate[2]



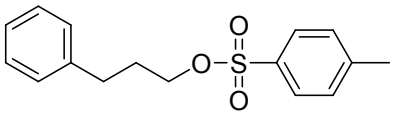
To a solution of propane-1,3-diyl bis(4-methylbenzenesulfonate) (3.7 g; 9.62 mmol) in DMF (20 mL), sodium azide (626 mg; 9.62 mmol) was added in small portions of each 100 mg. The mixture instantaneously coloured brown. After stirring overnight at room temperature, the reaction mixture was colourless and a white precipitate was formed. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over anhydrous sodium sulfate. The crude mixture was concentrated *in vacuo* to give a colourless oil which turned into white crystals (probably non removed sodium azide) after standing overnight at room temperature. Purification of the crude product was performed by column chromatography (silica; petroleum ether/EtOAc 75:25) resulting in a yellow oil (310 mg; 1.21 mmol; 12.6%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm)**:** 1.83 – 1.96 (m, 2H, $N_3CH_2C\underline{H}_2CH_2$), 2.47 (s, 3H, $PhC\underline{H}_3$), 3.39 (t, *J*=6.5 Hz, 2H, $N_3C\underline{H}_2CH_2CH_2$), 4.12 (t, *J*=5.9 Hz, 2H, $N_3CH_2CH_2C\underline{H}_2O$), 7.33 – 7.41 (m, 2 H, Ph-*H*), 7.76 – 7.85 (m, 2H, Ph-*H*); HRMS (ESI$^+$, *m/z*) *calc.* for $C_{10}H_{10}N_3O_3S$ 255.0678 (M^+) *found* 255.0460

3.1.2 3-Phenylpropyl methanesulfonate[3,4]



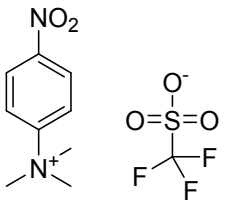
To a vigorously stirred solution of 3-phenylpropan-1-ol (501 mg, 3.67 mmol) and triethylamine (3.72 mg, 3.67 mmol) in dichloromethane (10 mL) was slowly added methylsulfonylchloride (379 mg, 3.31 mmol) at 0°C under argon atmosphere. The reaction was stirred at room temperature for two hours and diluted with water (40 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. A pale yellow oil (620 mg; 2.89 mmol; 79%) was obtained, which was not further purified. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm)**:** 2.01 – 2.18 (m, 2 H, $PhCH_2C\underline{H}_2CH_2$), 2.77 (t, *J*=7.5 Hz, 2 H, $PhC\underline{H}_2CH_2CH_2$), 3.00 (s, 3 H, $SO_2C\underline{H}_3$), 4.24 (t, *J*=6.3 Hz, 2 H, $PhCH_2CH_2C\underline{H}_2$), 7.15 – 7.38 (m, 5 H, Ph-*H*); HRMS (ESI$^+$, *m/z*) *calc.* for $C_{10}H_{14}O_3S$ 214.0664 (M^+) found 214.0230

3.1.3 3-Phenylpropyl 4-methylbenzenesulfonate[4]



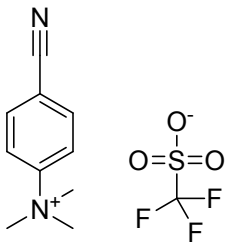
The preparation was analogous to 3-phenylpropyl methanesulfonate (see section 3.1.2). *p*-Toluenesulfonyl chloride (631 mg, 3.31 mmol) was used instead of methylsufonyl chloride and after evaporation of the organic solvent a colourless oil (326 mg; 1.13 mmol; 30%) was obtained, which was not further purified. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm)**:** 1.89 – 2.04 (m, 2 H, $PhCH_2C\underline{H}_2CH_2O$), 2.47 (s, 3 H, $C\underline{H}_3$), 2.66 (t, *J*=7.6 Hz, 2 H, $PhC\underline{H}_2CH_2CH_2O$), 4.04 (t, *J*=6.2 Hz, 2 H, $PhCH_2CH_2C\underline{H}_2O$), 7.03 – 7.11 (m, 2 H, Ph-*H*), 7.14 – 7.30 (m, 3 H, Ph-*H*), 7.36 (d, *J*=8.3 Hz, 2 H, Ph-*H; tosylate*), 7.80 (d, *J*=8.3 Hz, 2 H, Ph-*H; tosylate*); HRMS (ESI$^+$, *m/z)* calc for $C_{16}H_{18}O_3S$ 290.0977 (M+ Na^+) found 313.0862

3.1.4 4-Trimethylammonium-nitrobenzene trifluoromethanesulfonate[5a]



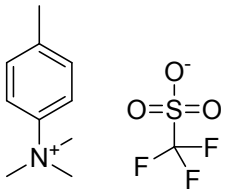
Methyltrifluoromethanesulfonate (691 mg, 4.21 mmol) was added to a solution of *N,N*-dimethyl-4-nitroaniline (500 mg, 3.01 mmol) in dry dichloromethane (7 mL) under argon atmosphere. The reaction mixture was stirred overnight at room temperature. Subsequently, it was heated to 50°C and dichloromethane (20 mL) was added to dissolve the formed precipitate Next, diethylether (20 mL) was added, resulting in precipitate formation. After filtration, the product was obtained as pale yellow powder (619 mg; 1.87 mmol; 62%). ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm)**:** 3.36 (s, 9 H, $N(C\underline{H}_3)_3$), 7.80 – 8.00 (m, 4 H, Ph-*H*); HRMS (ESI$^+$, *m/z)* calc. for $C_9H_{13}N_2O_2^+$ 181.0972 (M^+) found 181.0975

3.1.5 4-Trimethylammonium-cyanobenzene trifluoromethanesulfonate[5b]



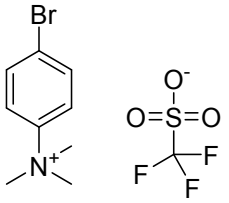
The preparation was analogous to *N,N,N*-trimethyl-4-nitrobenzenaminium trifluoromethanesulfonate (see section 3.1.4). Methyl trifluoromethane-sulfonate (786 mg, 4.79 mmol) and 4-cyano-*N,N*-dimethylaniline (500 mg, 3.42 mmol) were used as starting materials. The product was obtained as light yellow powder (910 mg; 2.93 mmol; 86%). ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm)**:** 3.36 (s, 9 H, $N(C\underline{H}_3)_3$), 7.80 – 8.00 (m, 4 H, Ph-*H*); HRMS (ESI$^+$, *m/z*) calc. for $C_{10}H_{13}N_2^+$ 161.1073 (M^+) found 161.1079

3.1.6 4-Trimethylammonium-toluene trifluoromethanesulfonate[5c]



The preparation was analogous to *N,N,N*-trimethyl-4-nitrobenzenaminium trifluoromethanesulfonate (see section 3.1.4). Methyl trifluoromethanesulfonate (850 mg, 5.18 mmol) and 4,*N,N*-trimethylaniline (500 mg, 3.70 mmol) were used as starting materials. The product was obtained as white precipitate (1.07 gram; 3.75 mmol; 97%). ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm)[5c] **:** 2.37 (s, 3 H, Ph-C<u>H</u>$_3$), 3.57 (s, 9 H, N (C<u>H</u>$_3$)$_3$), 7.42 (d, *J*= 8.9 Hz, 2 H, Ph-<u>*H*</u>), 7.83 (d, *J*= 8.9 Hz, 2 H, Ph-<u>*H*</u>); HRMS (ESI$^+$, *m/z*)calc. for $C_{10}H_{16}N^+$ 150.1277 (M^+) found 150.1290

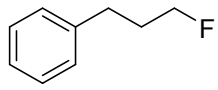
3.1.7 4-Trimethylammonium-bromobenzene trifluoromethanesulfonate[5c]



The preparation was analogous to *N,N,N*-trimethyl-4-nitrobenzenaminium trifluoromethanesulfonate (see section 3.1.4). Methyl trifluoromethanesulfonate (574 mg, 3.50 mmol) and 4-bromo-*N,N*-dimethylaniline (500 mg, 2.50 mmol) were used as starting materials. The product was obtained as a white solid (740 mg; 2.03 mmol; 81%). ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm)**:** 3.67 (s, 9 H, N (C<u>H</u>$_3$)$_3$), 8.27 (d, *J*=9.4 Hz, 2 H, Ph-<u>*H*</u>), 8.47 (d, *J*=9.4 Hz, 2 H, Ph-<u>*H*</u>); HRMS (ESI$^+$, *m/z*) calc. for $C_9H_{13}BrN^+$ 214.0226 (M^+ (^{79}Br)) found 214.0230

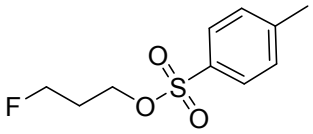
3.2 Reference compounds

3.2.1 3-Phenylpropylfluoride[6a,b]



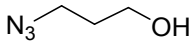
A solution of 3-phenylpropan-1-ol (1.00 g, 7.34 mmol) in dichloromethane (10 mL) was cooled to -78 °C, after which diethylaminosulfur trifluoride (1.07 mL, 8.08 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 3 days. The crude reaction mixture was concentrated *in vacuo* and purified by column chromatography (Hexane/EtOAc (90:10-75:25)) resulting in a colourless oil (498 mg; 3.61 mmol; 49%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.99-2.18 (m, 2H, $FCH_2C\underline{H}_2CH_2$), 2.76 – 2.86 (m, 2H, $FCH_2CH_2C\underline{H}_2$), 4.43 – 4.61 (dt, J= 47.2 Hz 2 H, $FC\underline{H}_2CH_2CH_2$), 7.21 – 7.41 (m, 5H, Ph-H);

3.2.2 3-Fluoropropyl 4-methylbenzenesulfonate[7]



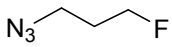
Tetrabutylammonium fluoride (2.50 mL; 2.50 mmol) was slowly added to a refluxing solution of propane-1,3-diyl bis(4-methylbenzene-sulfonate) (1.00 g, 2.60 mmol) in acetonitrile (5 mL). The mixture was stirred overnight at 80 °C. After evaporation of the solvent, the crude product was purified by column chromatography (Hexane/EtOAc (90:10-75:25)) resulting in a colourless oil (93 mg; 0.40 mmol; 16%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm)**:** 1.91 – 2.19 (m, 2 H, $FCH_2C\underline{H_2}CH_2$), 2.46 (s, 3 H, CH_3), 4.17 (t, *J*=6.2 Hz, 2 H, $FCH_2CH_2C\underline{H_2}$), 4.40 – 4.59 (dt, *J*=46.8 Hz, 2 H, $FC\underline{H_2}CH_2CH_2$), 7.36 (d, *J*= 8.3 Hz, 2 H, Ph-*H*), 7.81 (d, *J*= 8.3 Hz, 2 H, Ph-*H*);

3.2.3 3-Azidopropan-1-ol [8]



A solution of 3-bromopropan-1-ol (1.00 g, 7.20 mmol) and NaN_3 (1.20 g, 18.0 mmol) in water (5 mL) was stirred overnight at 80 °C. After cooling down the reaction mixture to room temperature, it was extracted with dichloromethane (20 mL). The organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The product was obtained as a colourless oil (595 mg; 5.90 mmol; 82%) and was not further purified. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm)**:** 1.68 (s, 1 H, $N_3CH_2CH_2CH_2O\underline{H}$), 1.84 (m, 2 H, $N_3CH_2C\underline{H_2}CH_2OH$), 3.46 (t, *J*=6.6 Hz, 2 H, $N_3C\underline{H_2}CH_2CH_2OH$), 3.70 – 3.82 (m, 2 H, $N_3CH_2CH_2C\underline{H_2}OH$);

3.2.4 1-Azido-3-fluoropropane

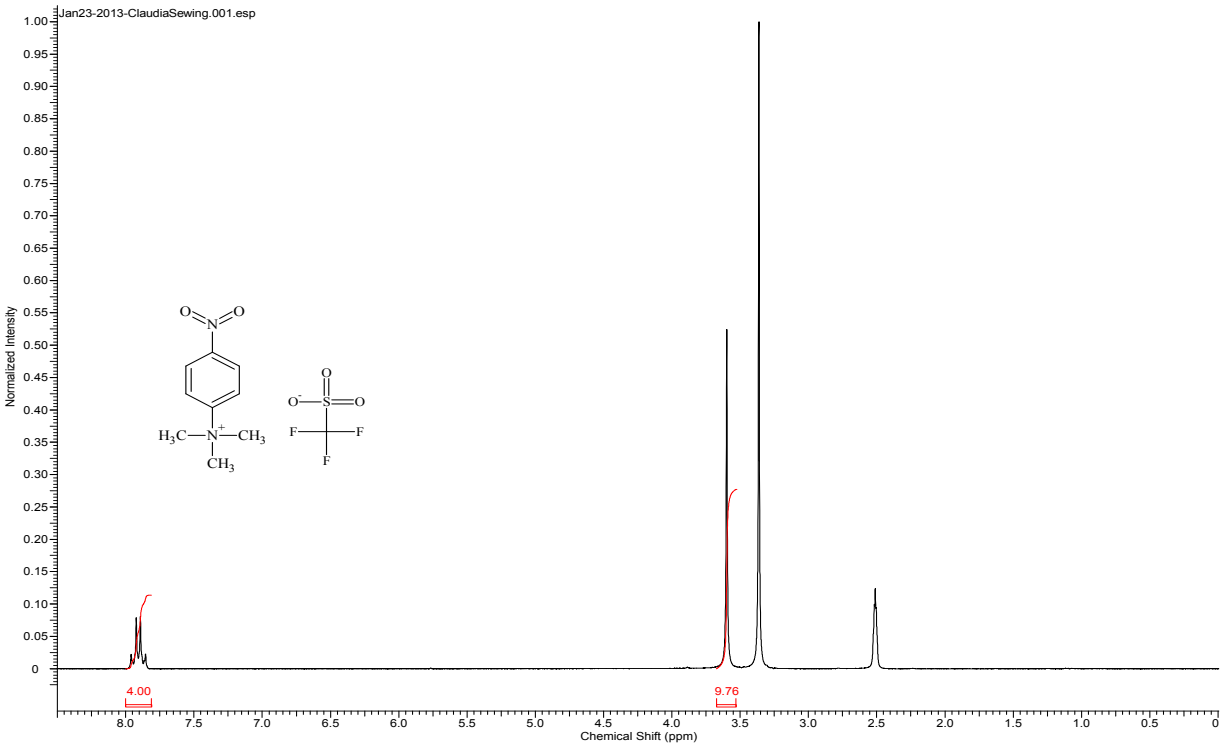


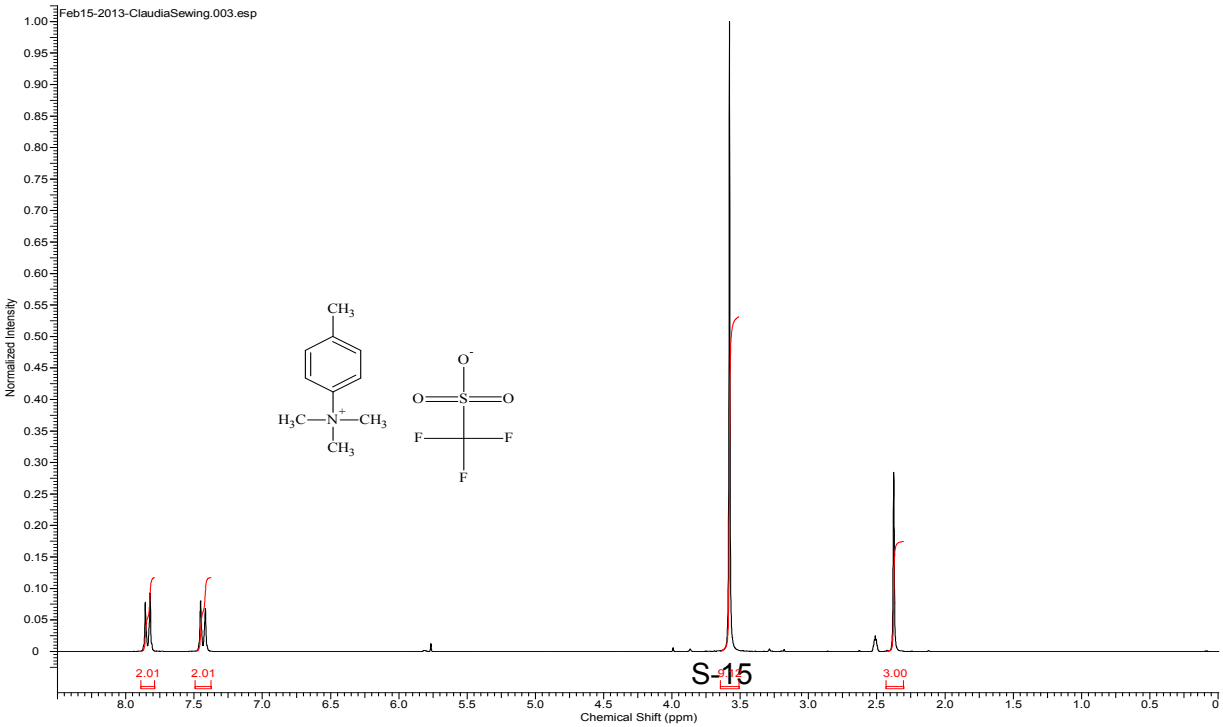
Diethylaminosulfur trifluoride (1.04 g, 6.47 mmol) was added to a solution of 3-azidopropan-1-ol (595 mg, 5.89 mmol) in dichloromethane (10 mL) at -78 °C. The reaction mixture was allowed to warm up to room temperature and stirred overnight. Hereafter it was concentrated *in vacuo* and purified by column chromatography (Hexane/ EtOAc (85:15->0:100)) resulting in a yellow oil (66 mg; 0.64 mmol; 11%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm)**:** 1.95 (quin, *J*=6.3 Hz, 2 H, $N_3CH_2C\underline{H_2}CH_2F$), 3.46 (t, *J*=6.56 Hz, 2 H, $N_3C\underline{H_2}CH_2CH_2F$), 3.98 – 4.22 (m, 2 H, $N_3CH_2CH_2C\underline{H_2}F$); ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: -73.96 (s, 1F).

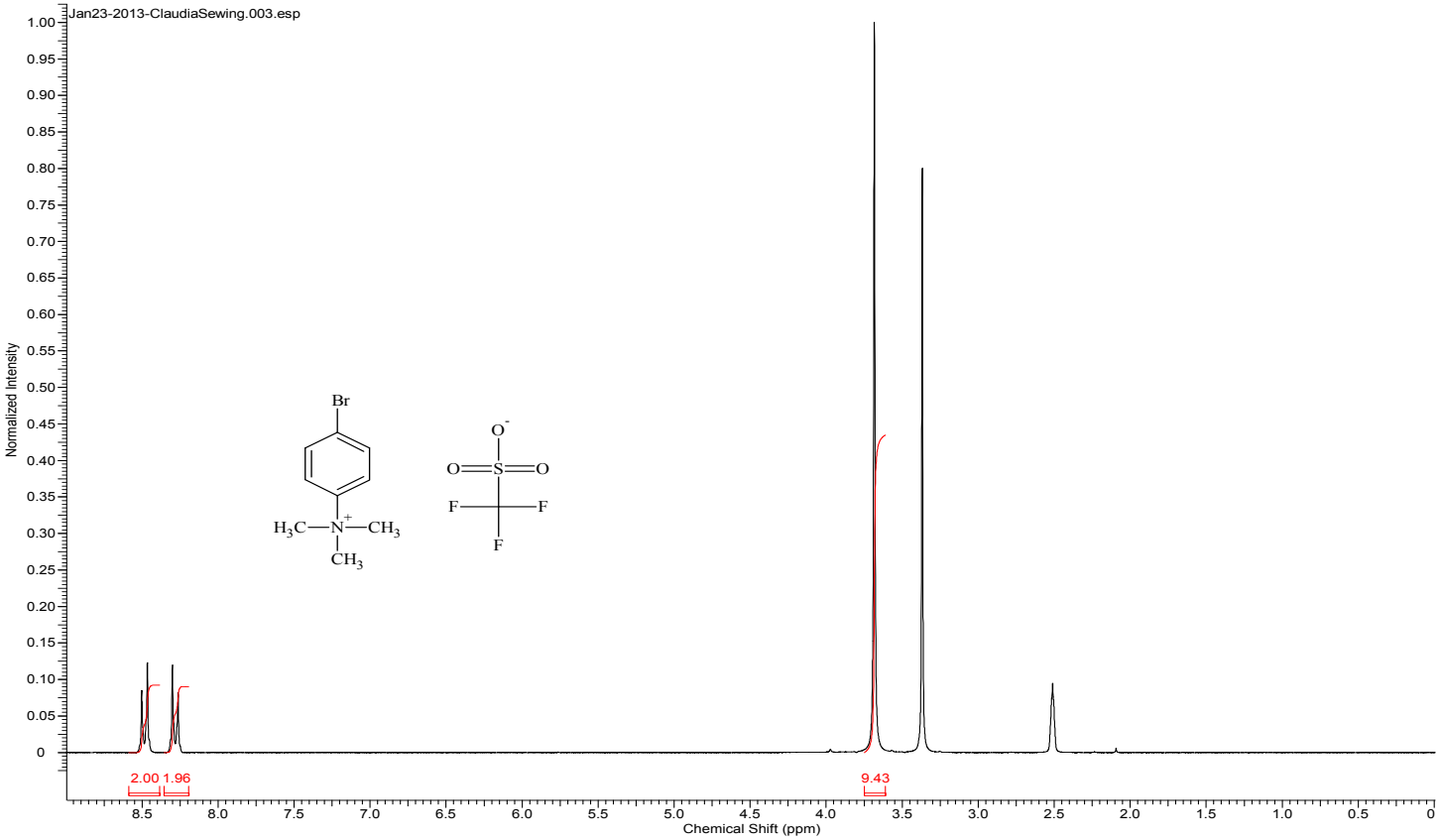
4 NMR spectra

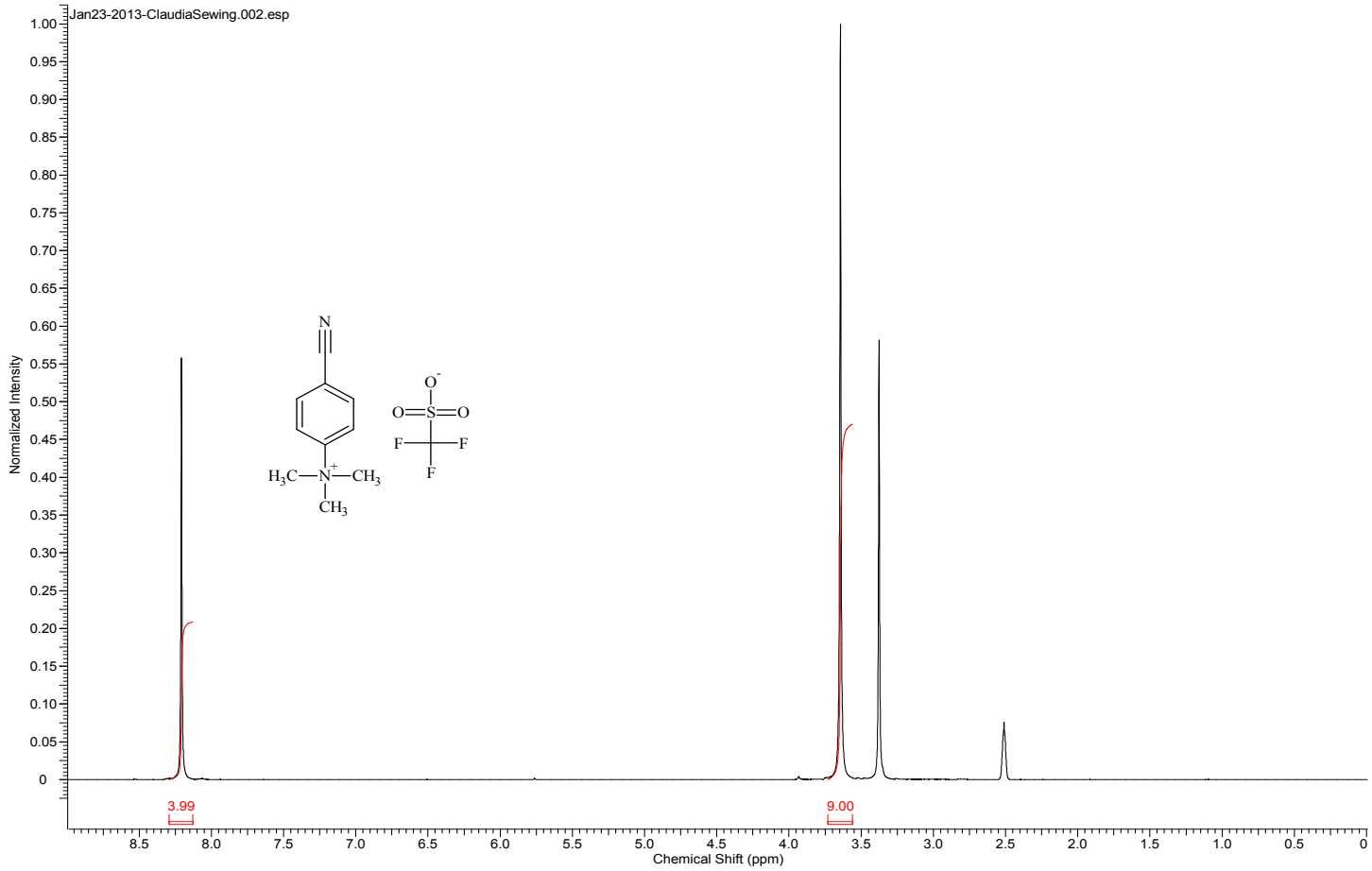
General remark about residual solvent peaks: Peaks at 2.50 ppm and 3.33 ppm originate from DMSO und water, peaks at 7.26 ppm and 1.56 ppm originate from chloroform and water.

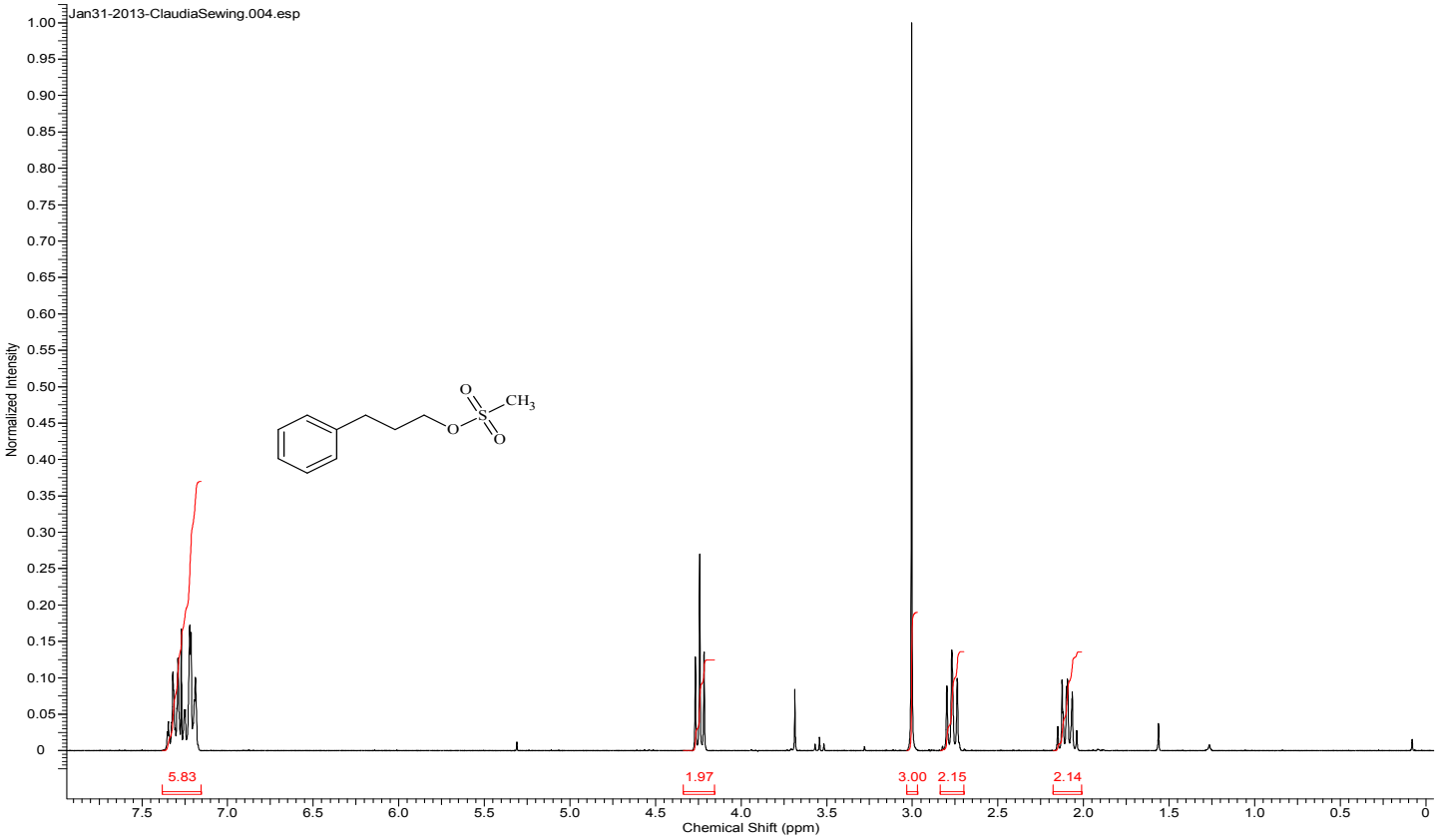
^{1}H-NMR

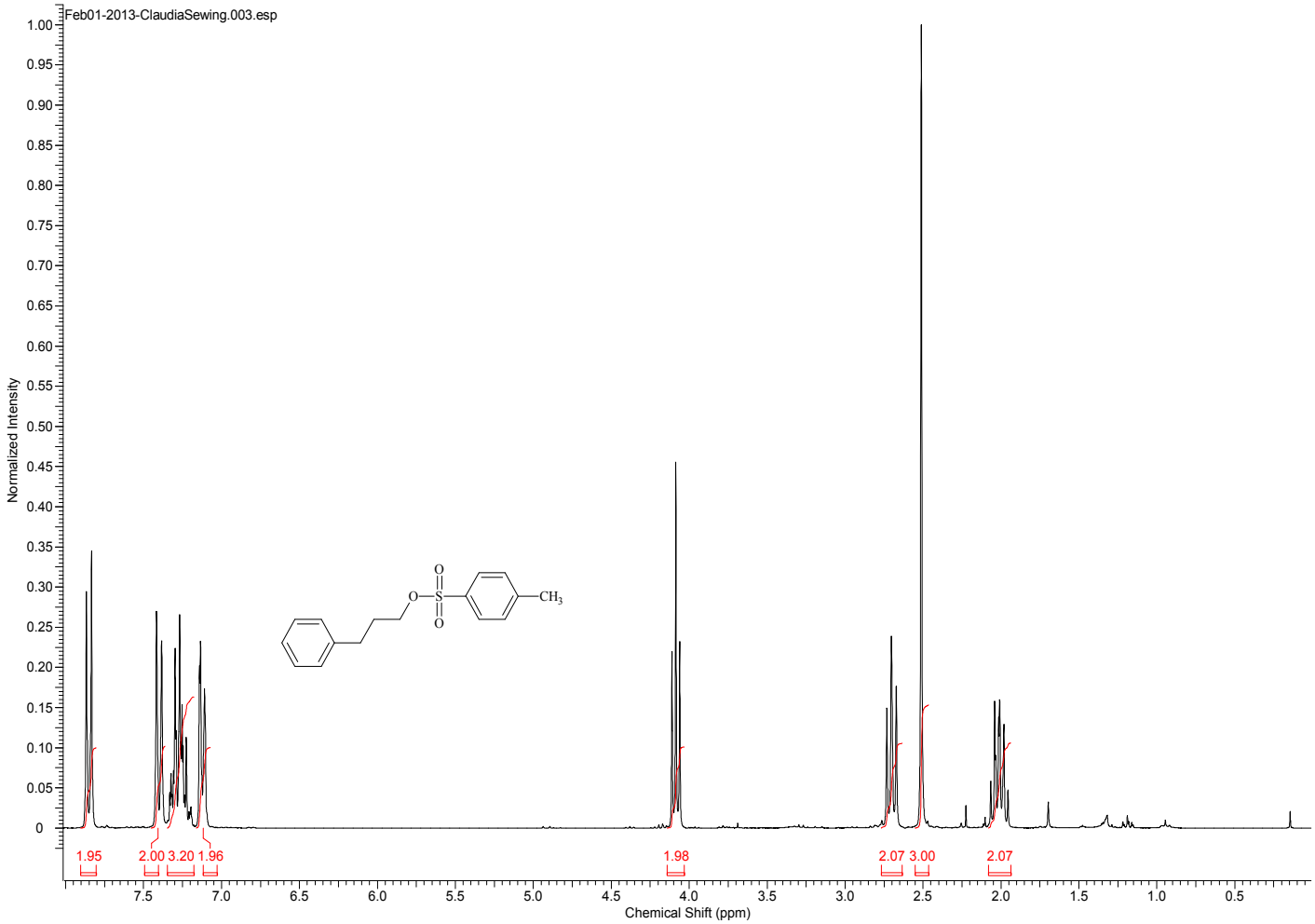


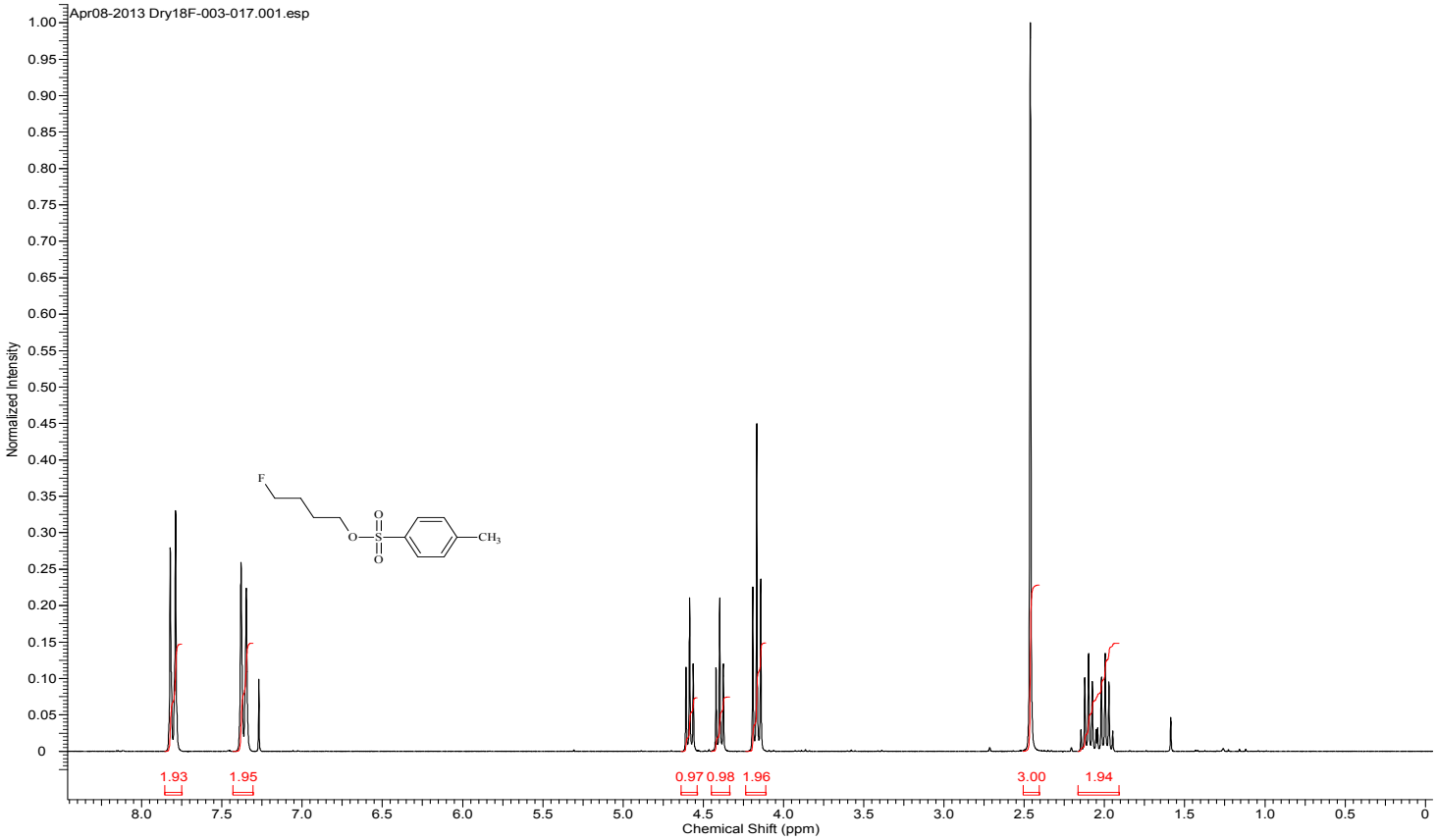


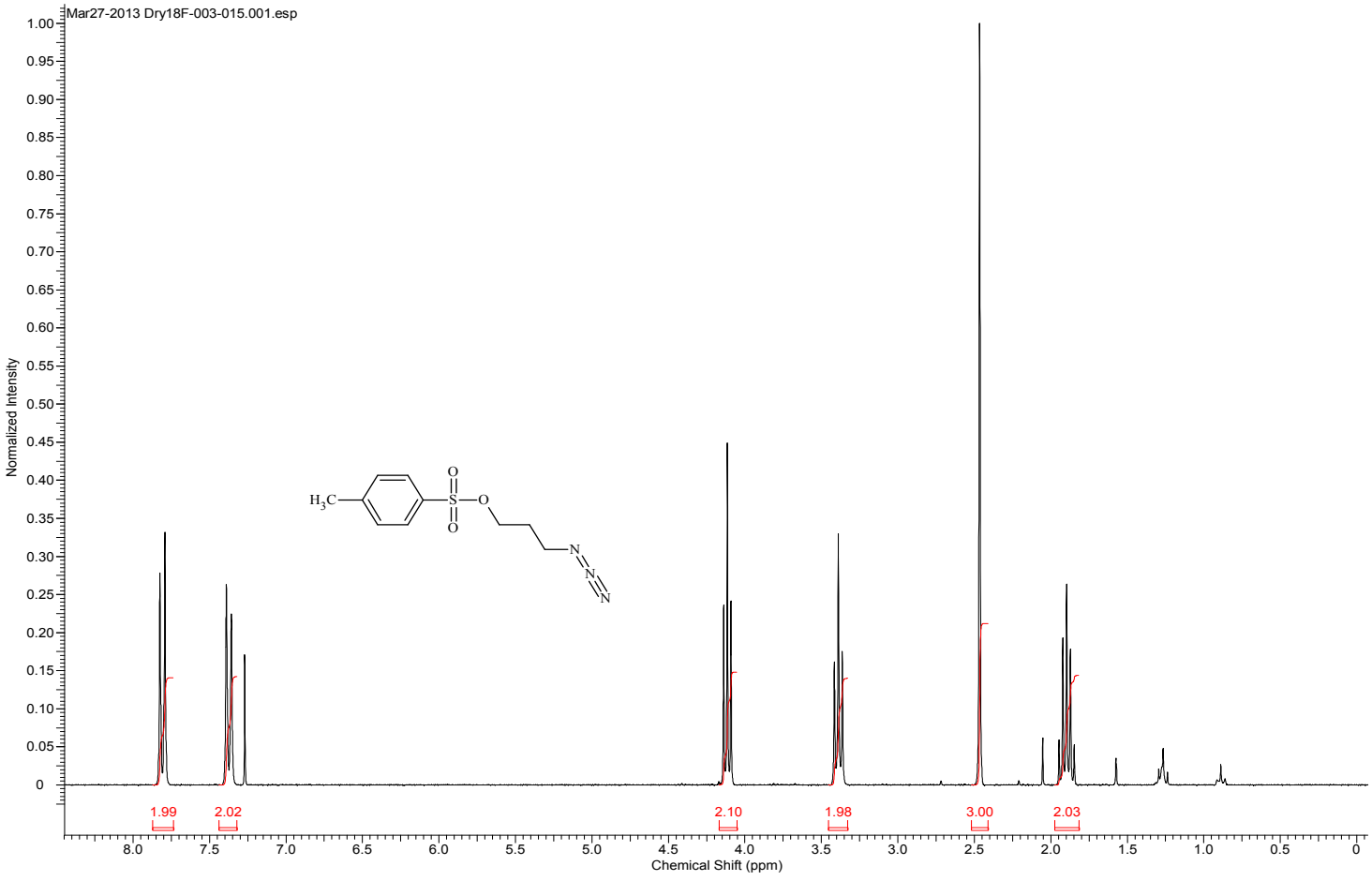

Jan23-2013-ClaudiaSewing.003.esp
Normalized Intensity
Chemical Shift (ppm)
2.00
1.96
9.43
Br
$H_3C-N^+-CH_3$
CH_3
O
O=S=O
F
F
F

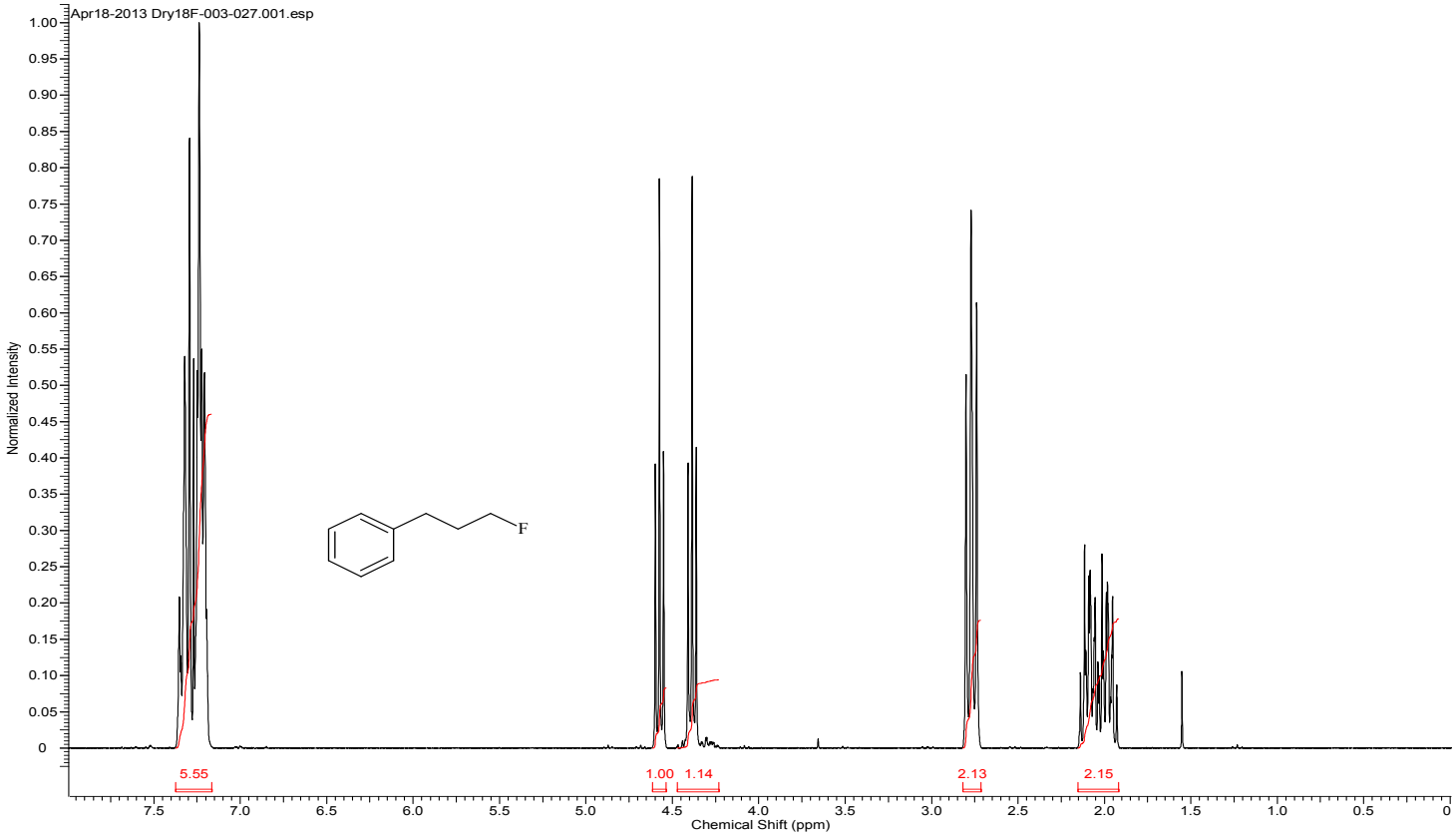

Jan23-2013-ClaudiaSewing.002.esp
Normalized Intensity
Chemical Shift (ppm)
3.99
9.00
N
$H_3C-N^+-CH_3$
CH_3
O
O=S=O
F
F
F

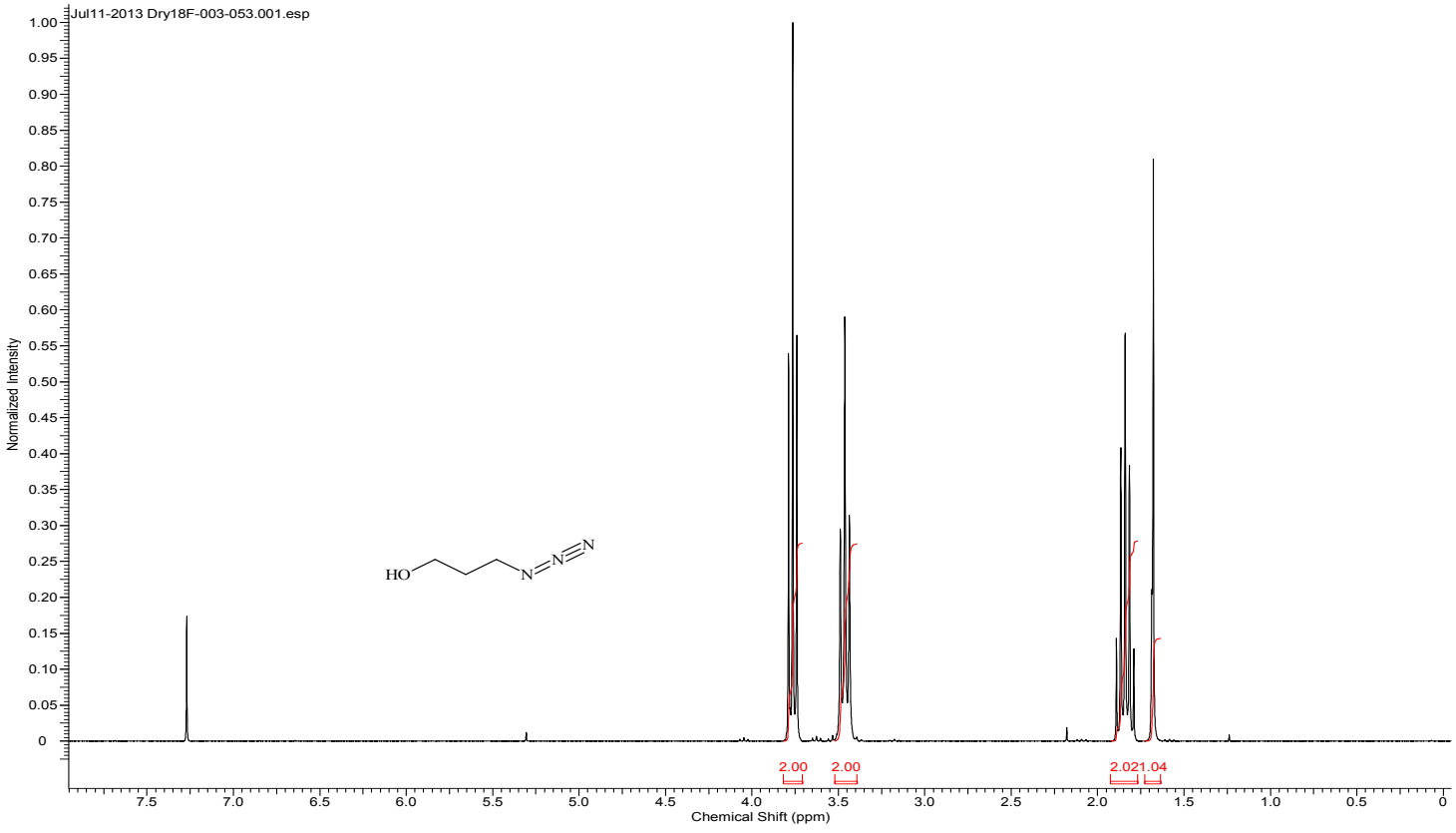

Jan31-2013-ClaudiaSewing.004.esp
Normalized Intensity
Chemical Shift (ppm)
5.83
1.97
3.00
2.15
2.14

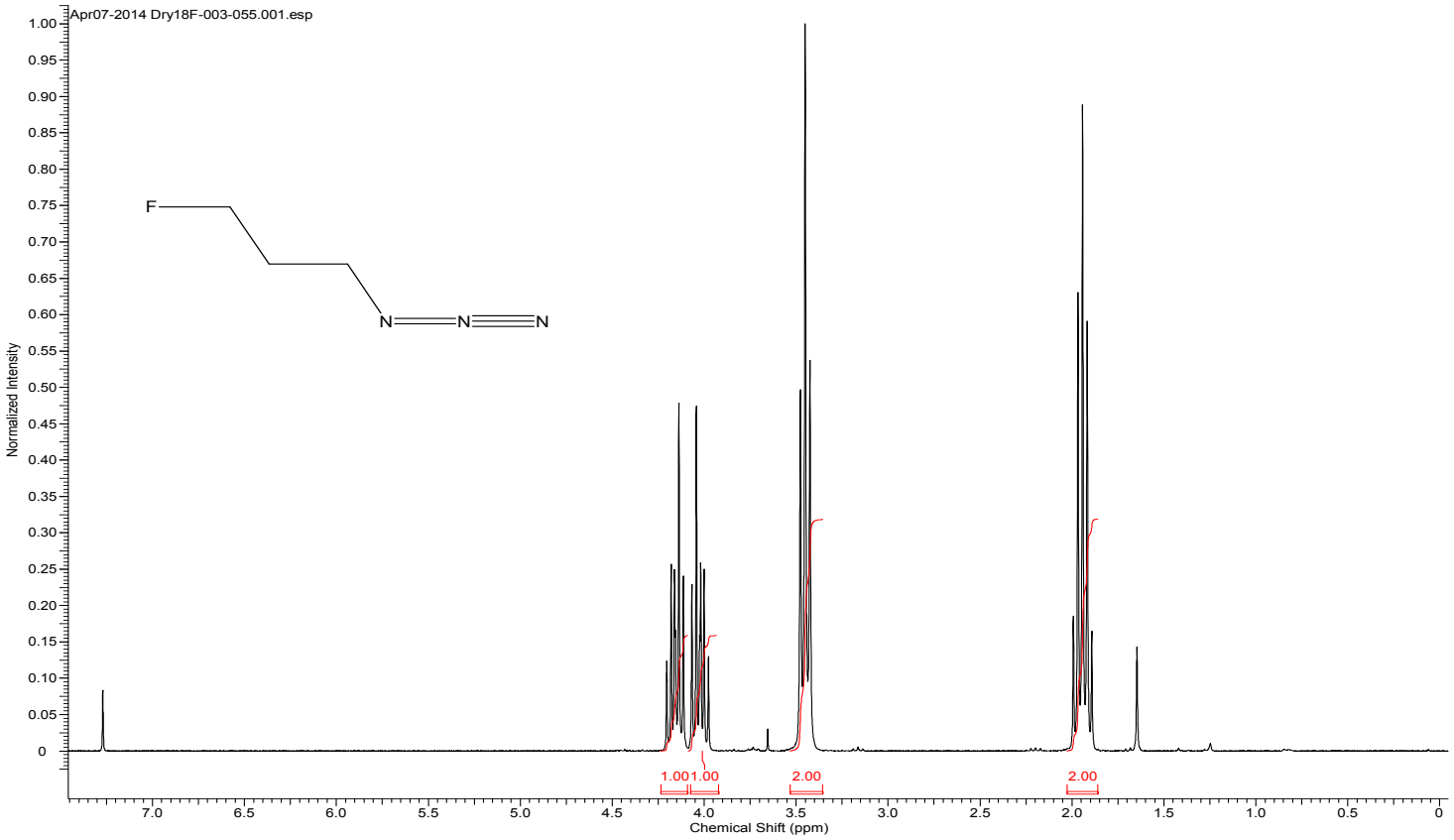

Feb01-2013-ClaudiaSewing.003.esp
Normalized Intensity
Chemical Shift (ppm)
1.95
2.00
3.20
1.96
1.98
2.07
3.00
2.07


Apr08-2013 Dry18F-003-017.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.93
1.95
0.97
0.98
1.96
3.00
1.94

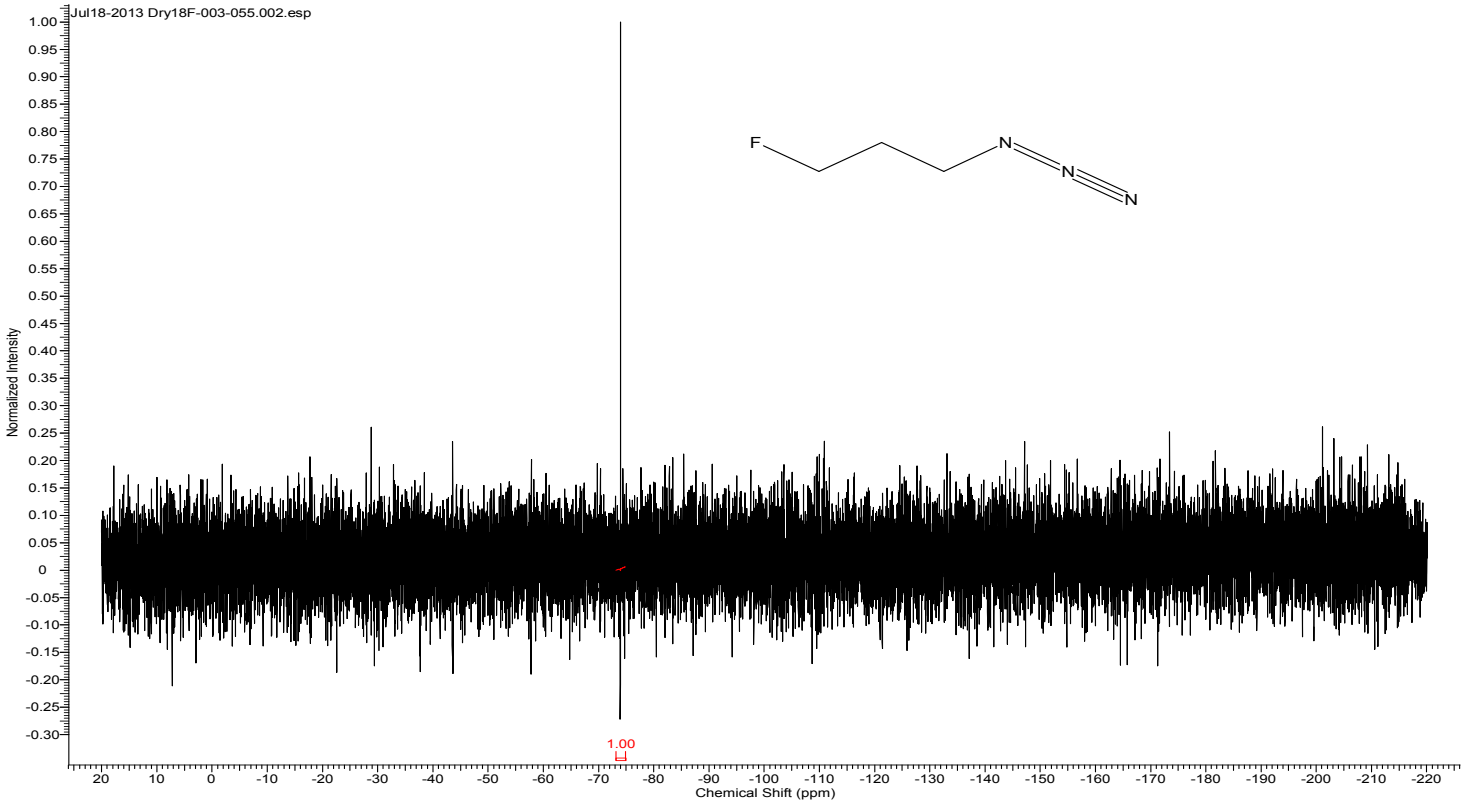

Mar27-2013 Dry18F-003-015.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.99
2.02
2.10
1.98
3.00
2.03


Apr18-2013 Dry18F-003-027.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.55
1.00
1.14
2.13
2.15
F

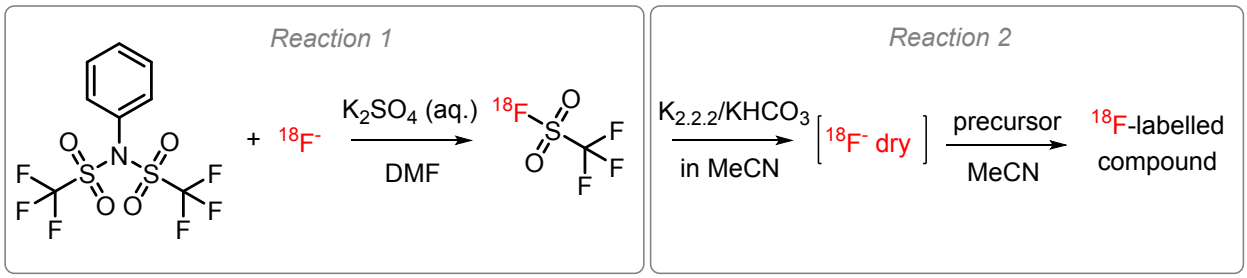

Jul11-2013 Dry18F-003-053.001.esp
Normalized Intensity
Chemical Shift (ppm)
2.00
2.00
2.02
1.04
HO
N
N
N


Apr07-2014 Dry18F-003-055.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.00
2.00
2.00

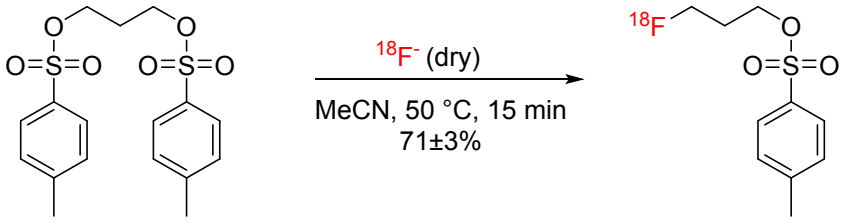
^{19}F-NMR

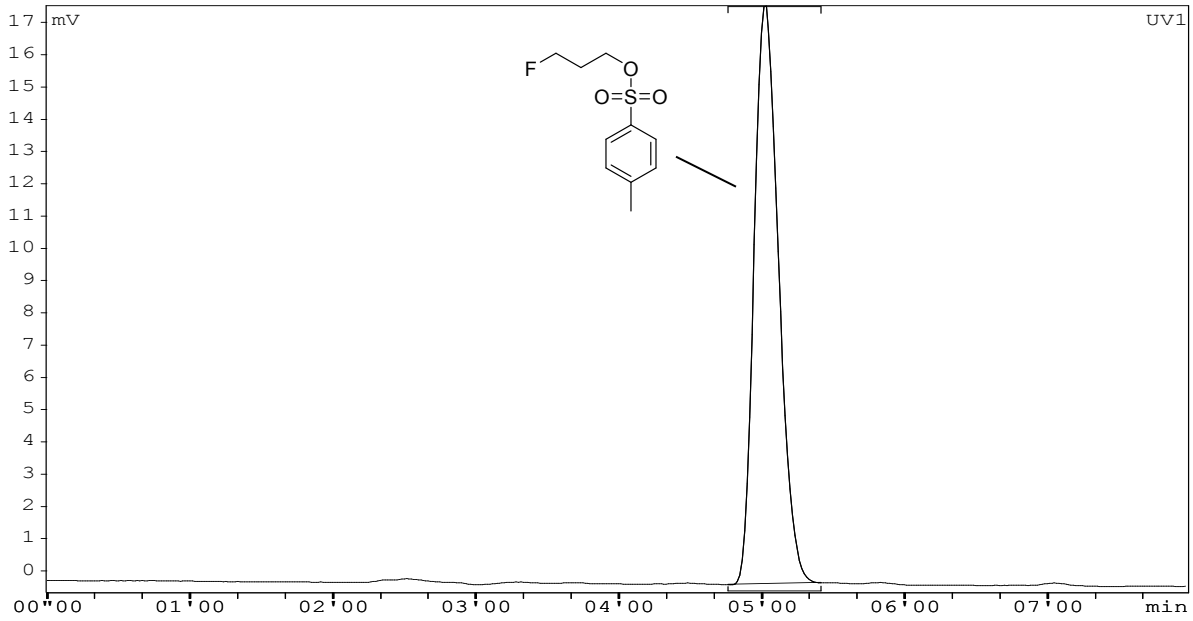

Jul18-2013 Dry18F-003-055.002.esp
Normalized Intensity
Chemical Shift (ppm)
1.00

5 HPLC chromatograms of the [^{18}F]fluorination reactions

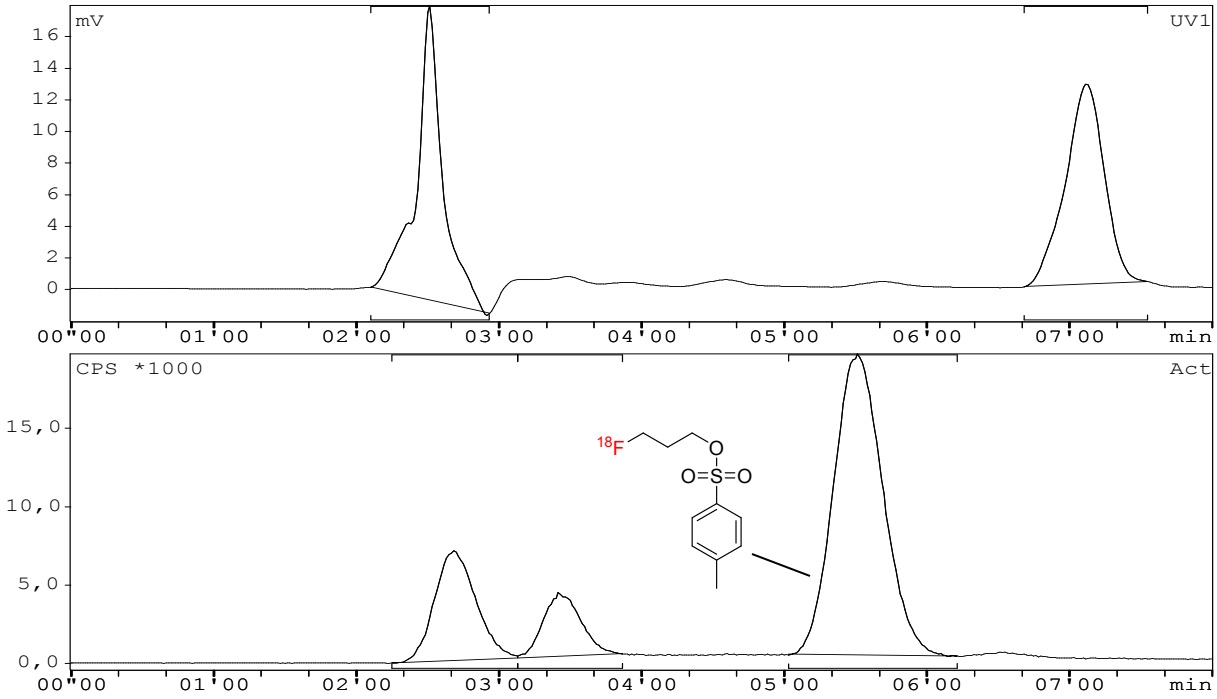


5.1 Synthesis of 3-[^{18}F]fluoropropyl tosylate



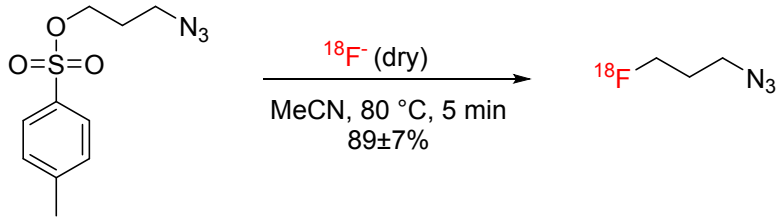


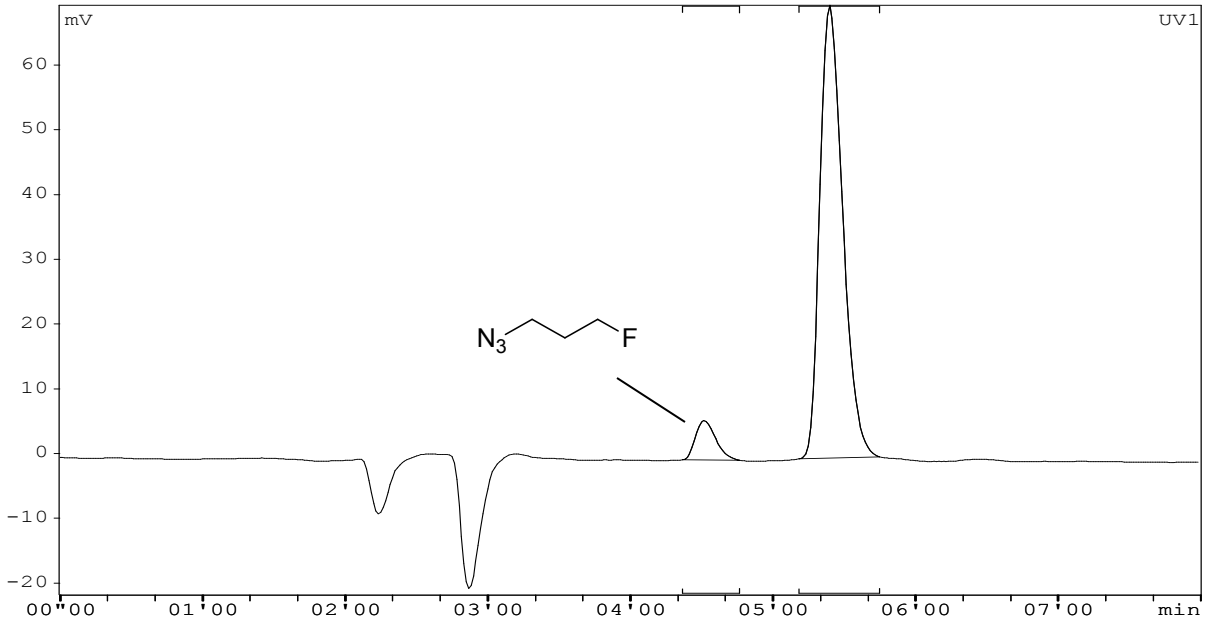
UV at 254 nm; 3-[^{19}F]fluorotosyloxypropanol; Eluent: 70:30:0.2 MeCN/H_2O/TFA



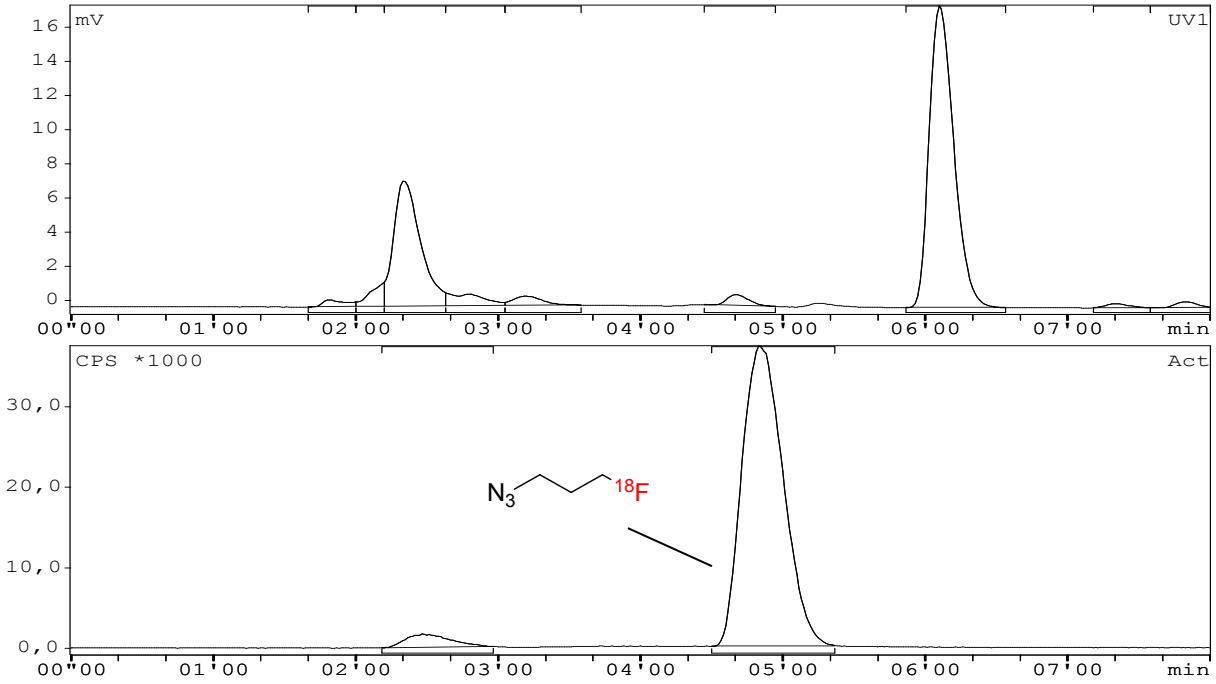
Top panel: UV at 254 nm, peak at 7 min is precursor 1,3-Bistosyloxypropanediol; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$ and at 3.5 min is $^{18}F/K_{2.2.2}$-complex; Eluent: 70:30:0.2 MeCN/H_2O/TFA

5.2 3-[^{18}F]Fluoropropyl azide



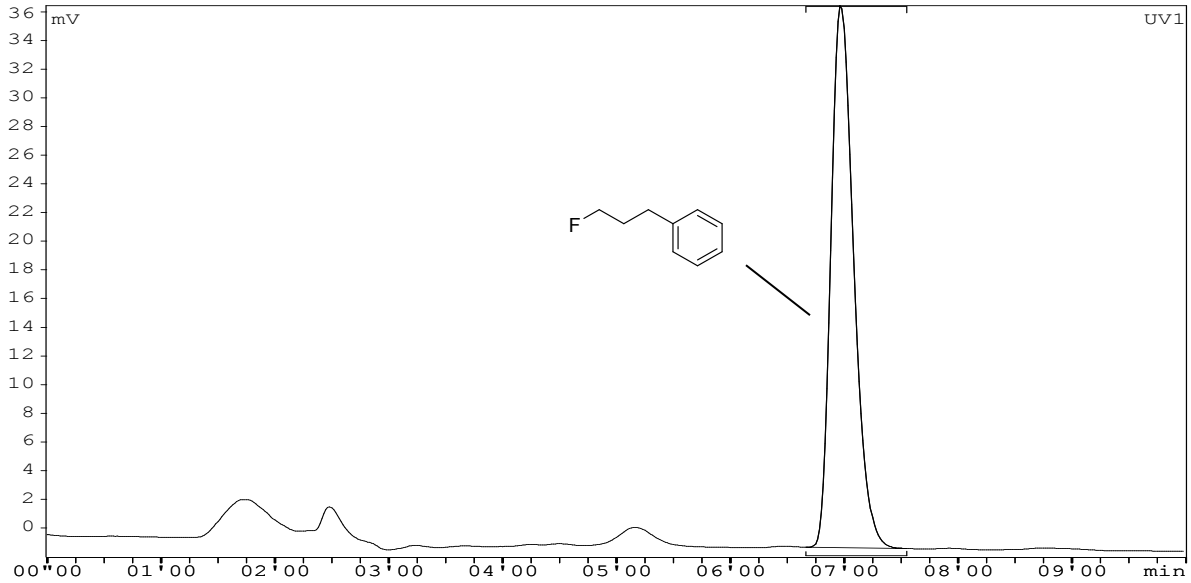


UV at 254 nm; reference compound of 3-azidofluoropropane solved in chloroform (peak at 5.5 min); Eluent: 70:30:0.2 MeCN/H_2O/TFA



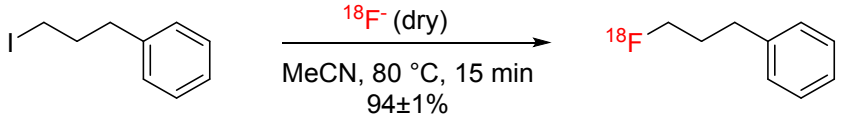
Top panel: UV at 254 nm, peak at 6.1 min is precursor 1-azido-3-tosyloxypropanol; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$; Eluent 70:30:0.2 MeCN/H_2O/TFA

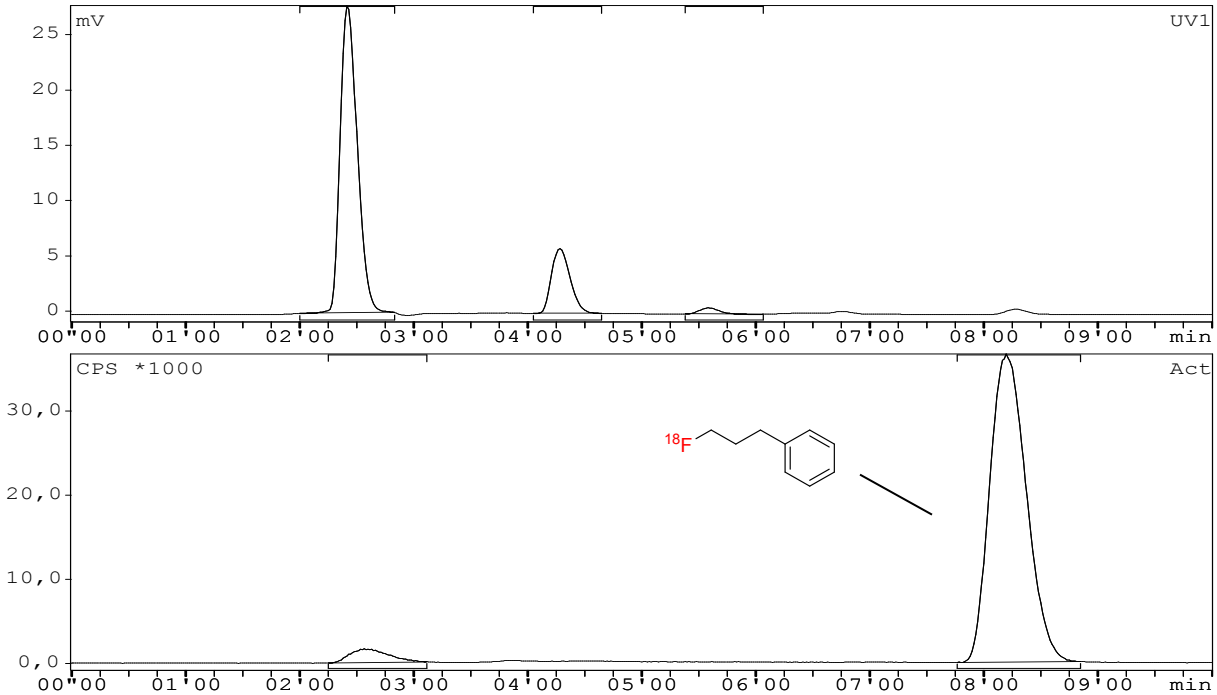
5.3 (3-[^{18}F]Fluoropropyl)benzene



UV at 254 nm; reference chromatogram; Eluent: 70:30:0.2 MeCN/H_2O/TFA

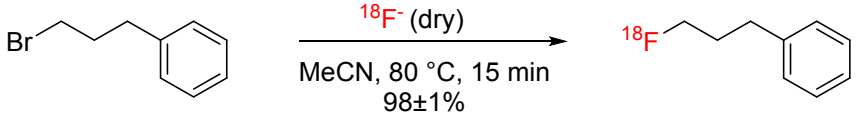
5.3.1 Radiofluorination of (3-iodopropyl)benzene

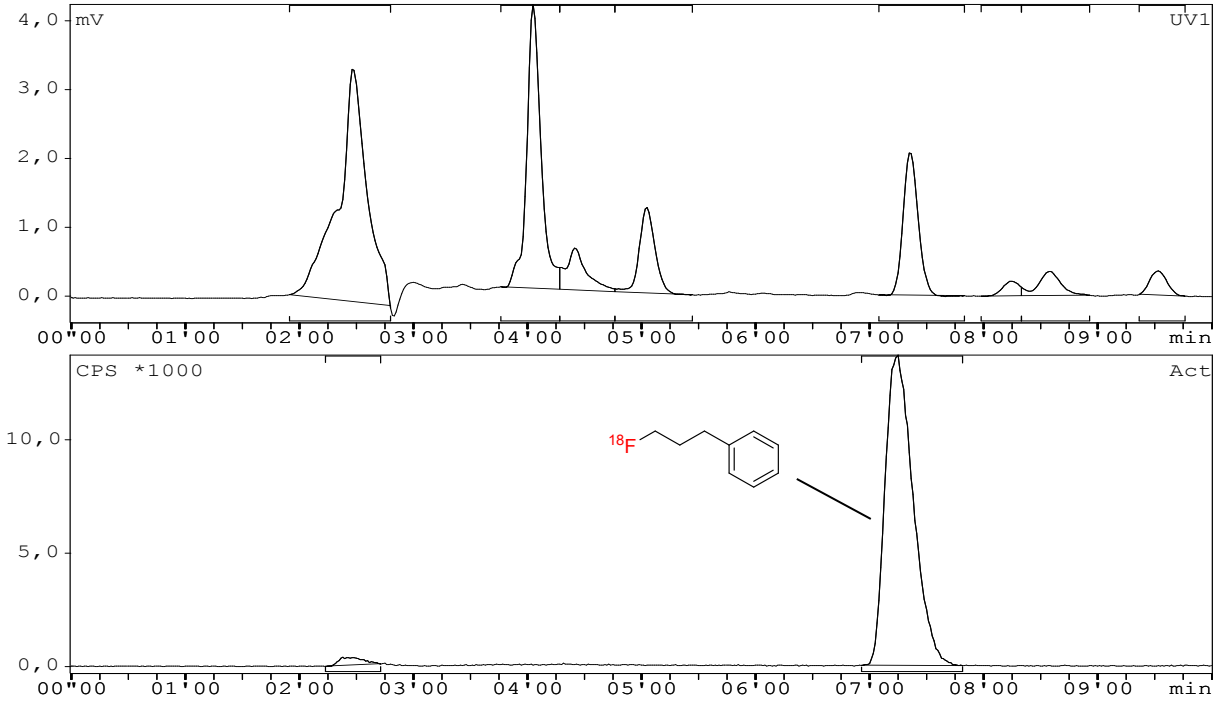




Top panel: UV at 254 nm, peak at 2.5 min is injection peak; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$; Eluent 70:30:0.2 MeCN/H_2O/TFA

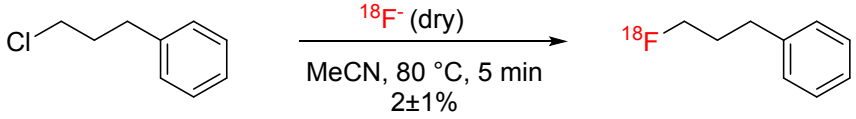
5.3.2 Radiofluorination of (3-bromopropyl)benzene

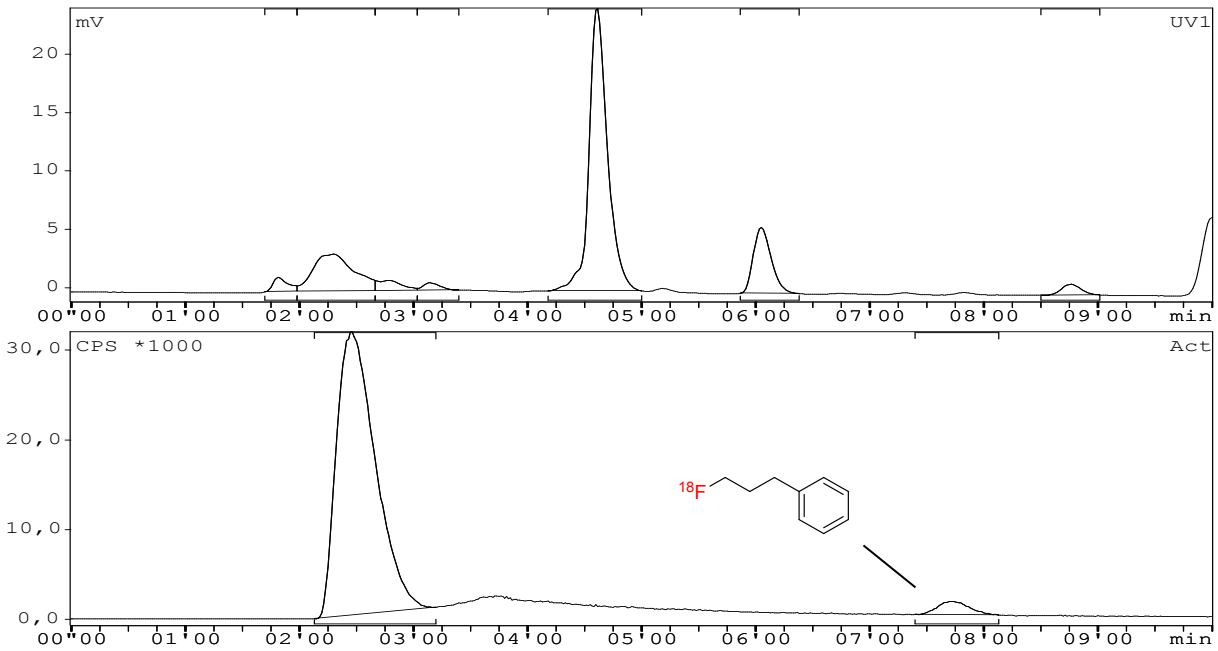




Top panel: UV at 254 nm, peak at 2.5 min is injection peak; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$; Eluent 70:30:0.2 MeCN/H_2O/TFA

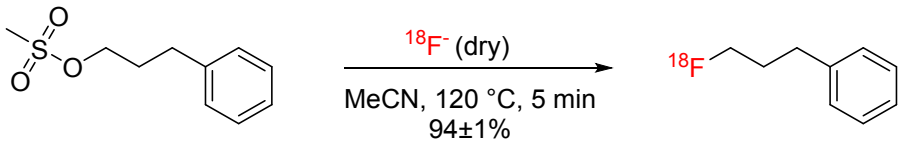
5.3.3 Radiofluorination of (3-chloropropyl)benzene

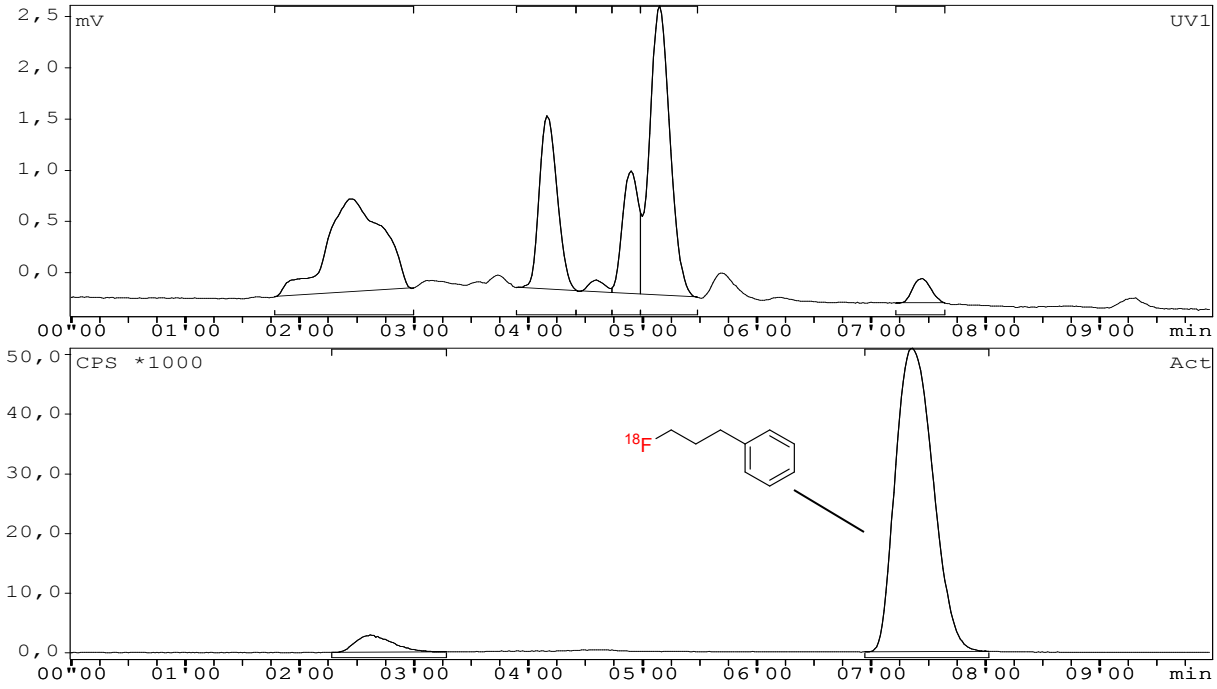




Top panel: UV at 254 nm; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$; Eluent 70:30:0.2 MeCN/H_2O/TFA

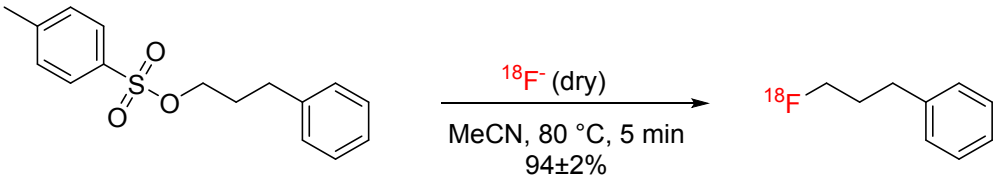
5.3.4 Radiofluorination of (3-mesylpropyl)benzene

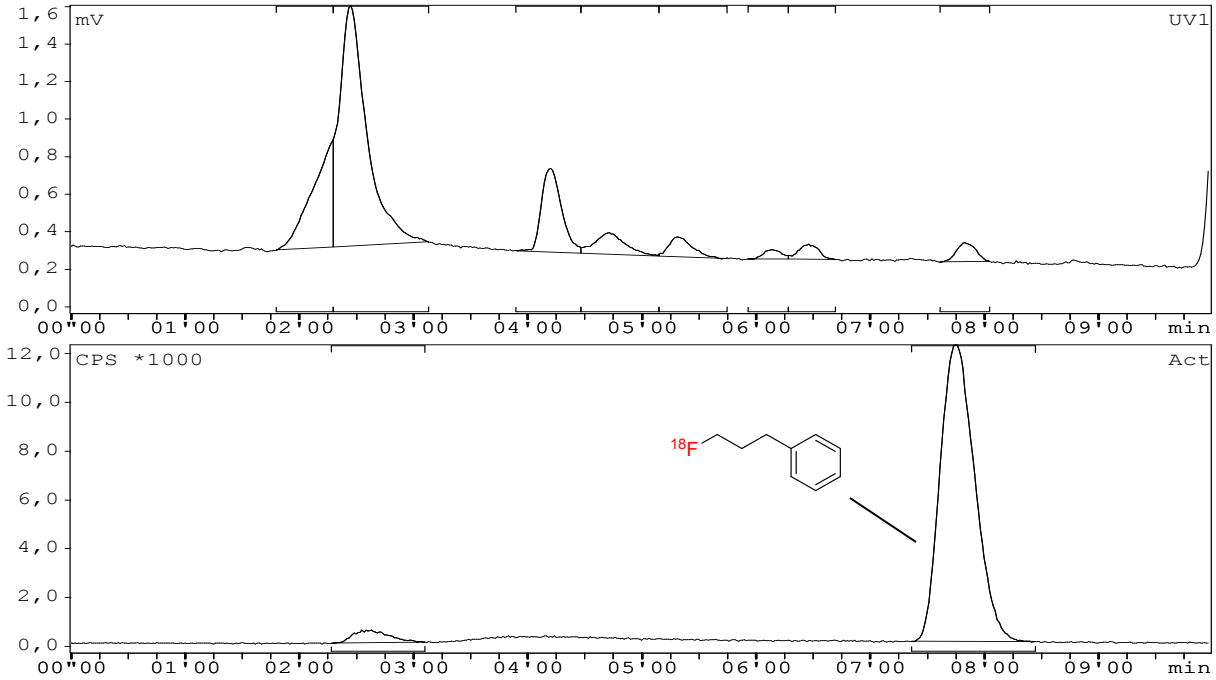




Top panel: UV at 254 nm, peak at 5.1 min is precursor (3-mesylpropyl)benzene; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$; Eluent 70:30:0.2 MeCN/H_2O/TFA

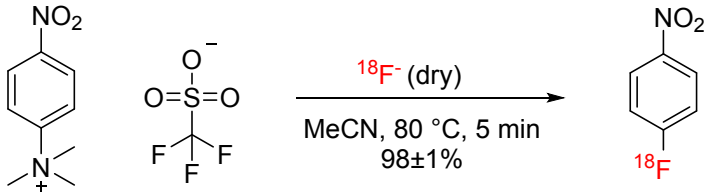
5.3.5 Radiofluorination of (3-tosylpropyl)benzene

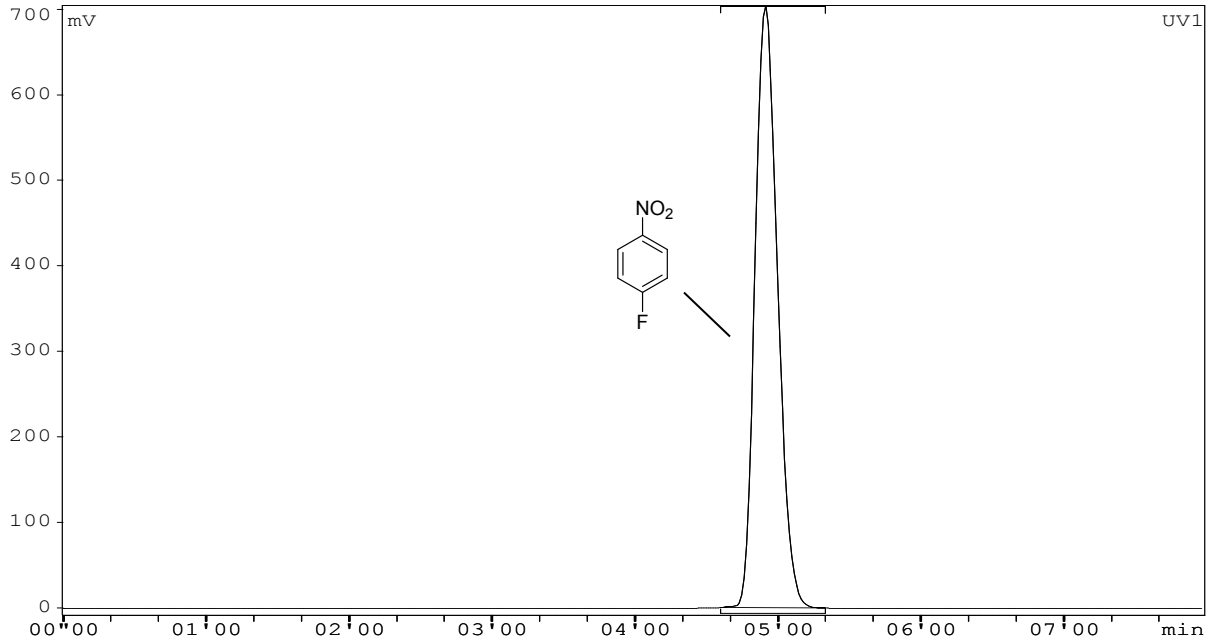




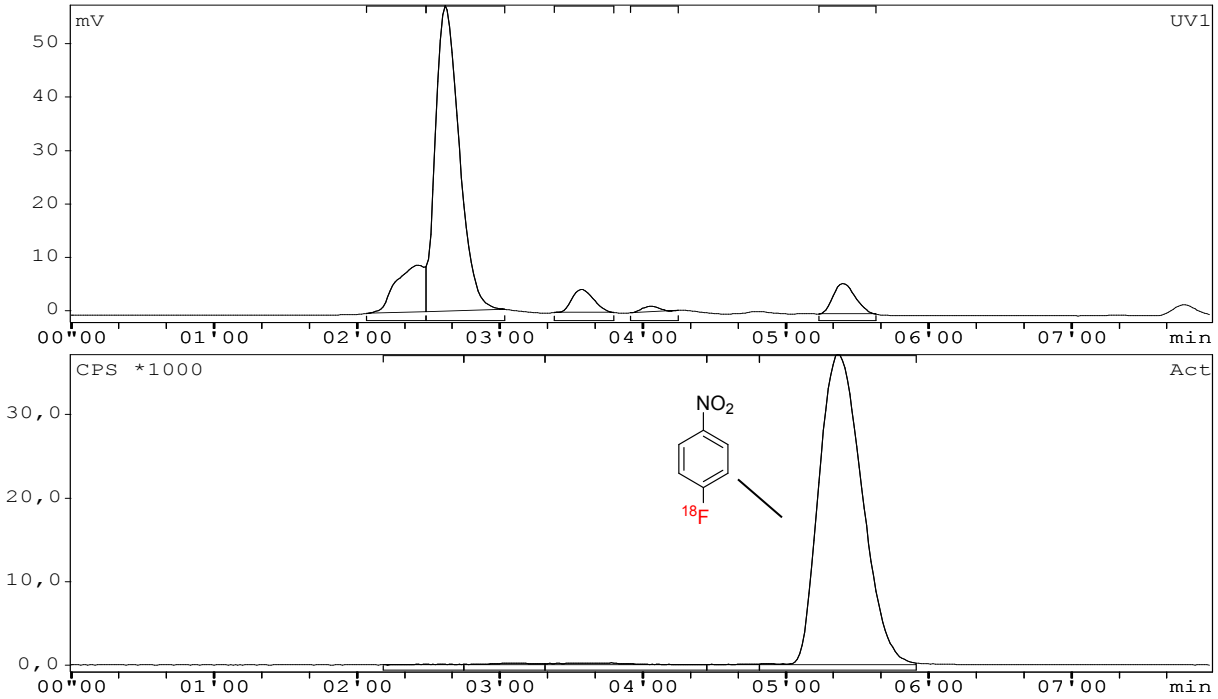
Top panel: UV at 254 nm; peak at 2.5 min is injection peak; bottom panel: radioactivity measurement; peak at 2.5 min is $^{18}F^-$; Eluent 70:30:0.2 MeCN/H_2O/TFA

5.4 1-[^{18}F]Fluoro-4-nitrobenzene



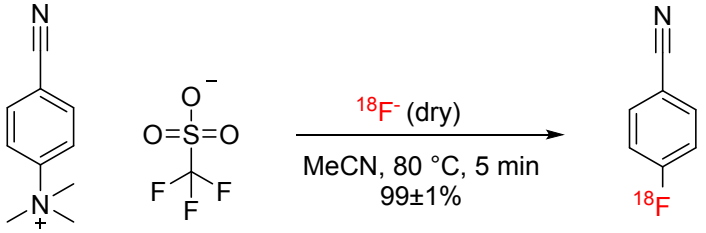


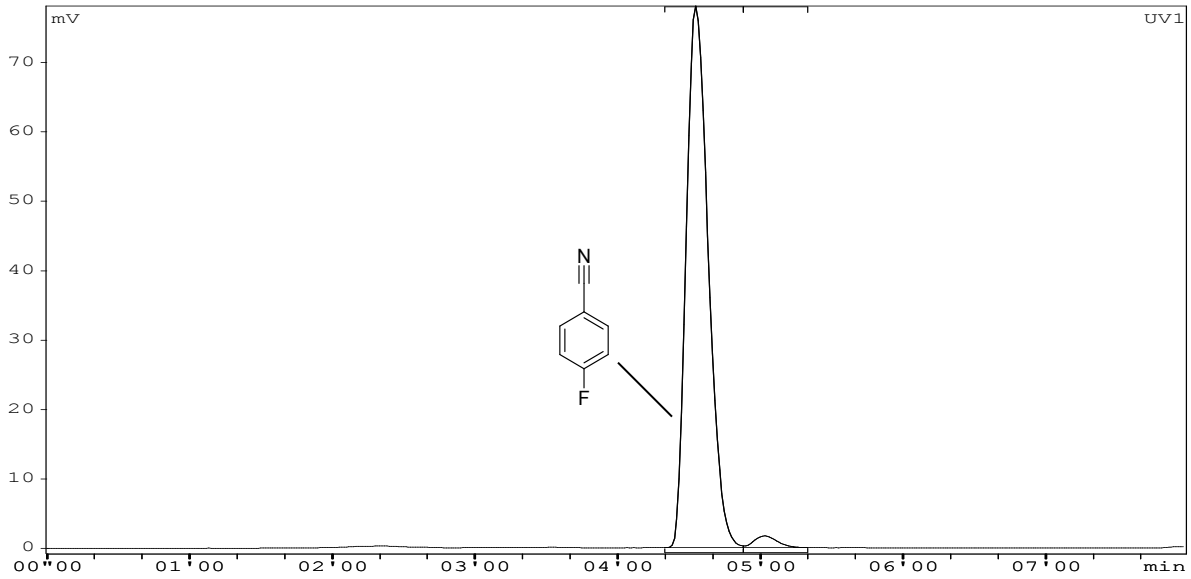
UV at 254 nm; reference chromatogram of 4-fluoronitrobenzene; Eluent: 70:30:0.2 MeCN/H_2O/TFA



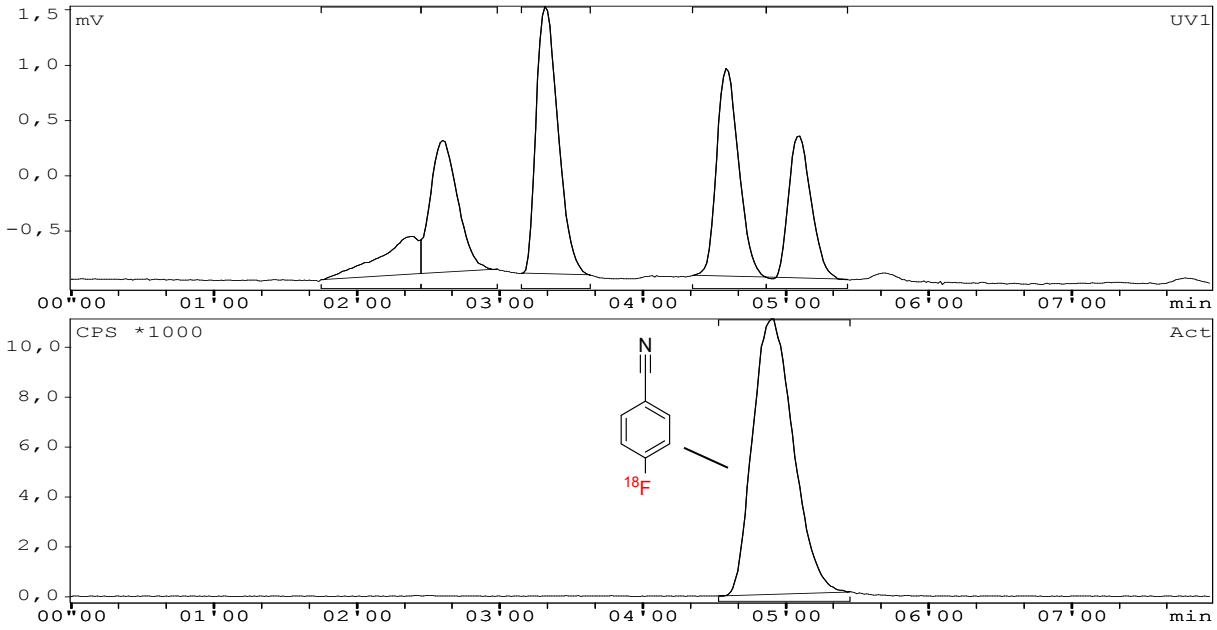
Top panel: UV at 254 nm, peak at 2.5 min is precursor *N,N*,N-trimethyl-4-nitrobenzenaminium trifluoromethanesulfonate; bottom panel: radioactivity measurement; Eluent 70:30:0.2 MeCN/H_2O/TFA

5.5 1-[^{18}F]Fluoro-4-cyanobenzene



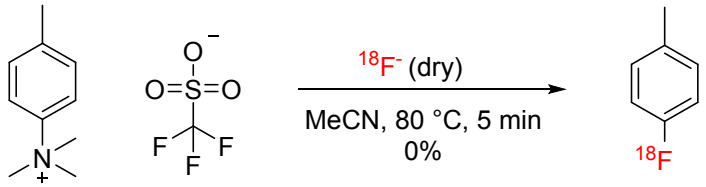


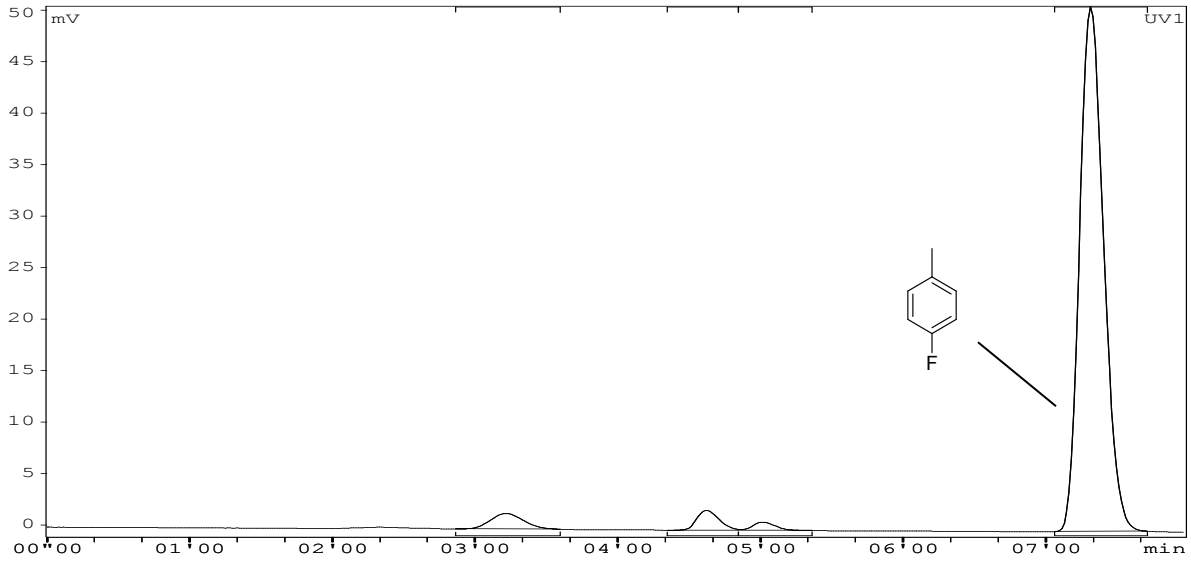
UV at 254 nm; reference chromatogram of 4-fluorobenzonitrile; Eluent: 70:30:0.2 MeCN/H_2O/TFA



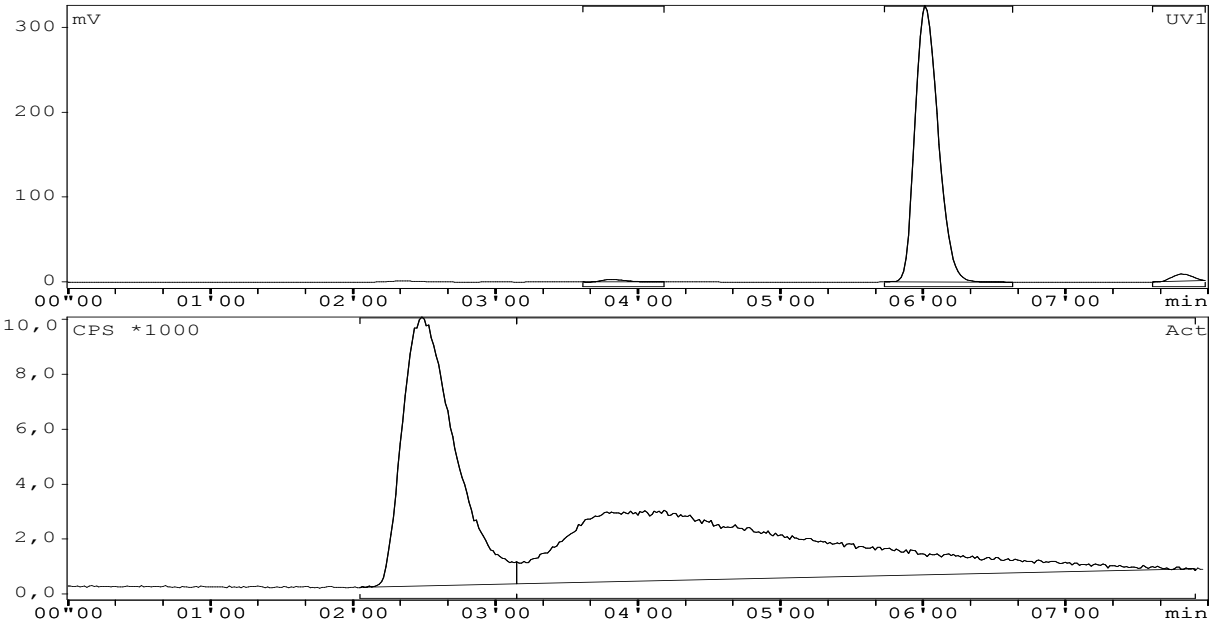
Top panel: UV at 254 nm, peak at 2.6 min is precursor *N,N,N*-trimethyl-4-cyanobenzenaminium trifluoromethanesulfonate; bottom panel: radioactivity measurement; Eluent 70:30:0.2 MeCN/H_2O/TFA

5.6 4-[^{18}F]Fluorotoluene



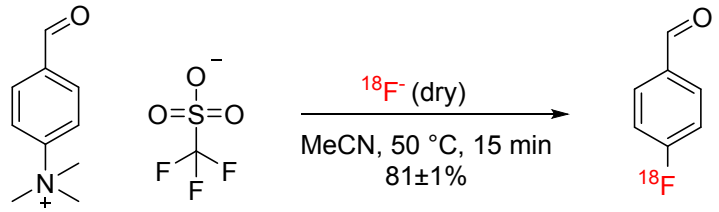


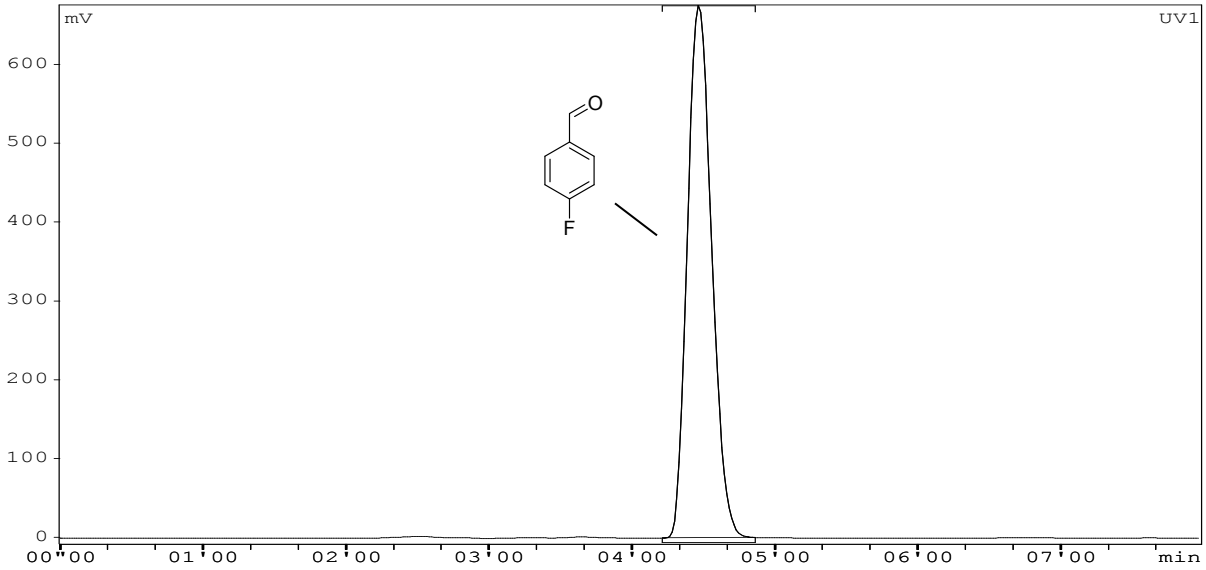
UV at 254 nm; reference chromatogram of 4-fluorotoluene; Eluent: 70:30:0.2 MeCN/H_2O/TFA



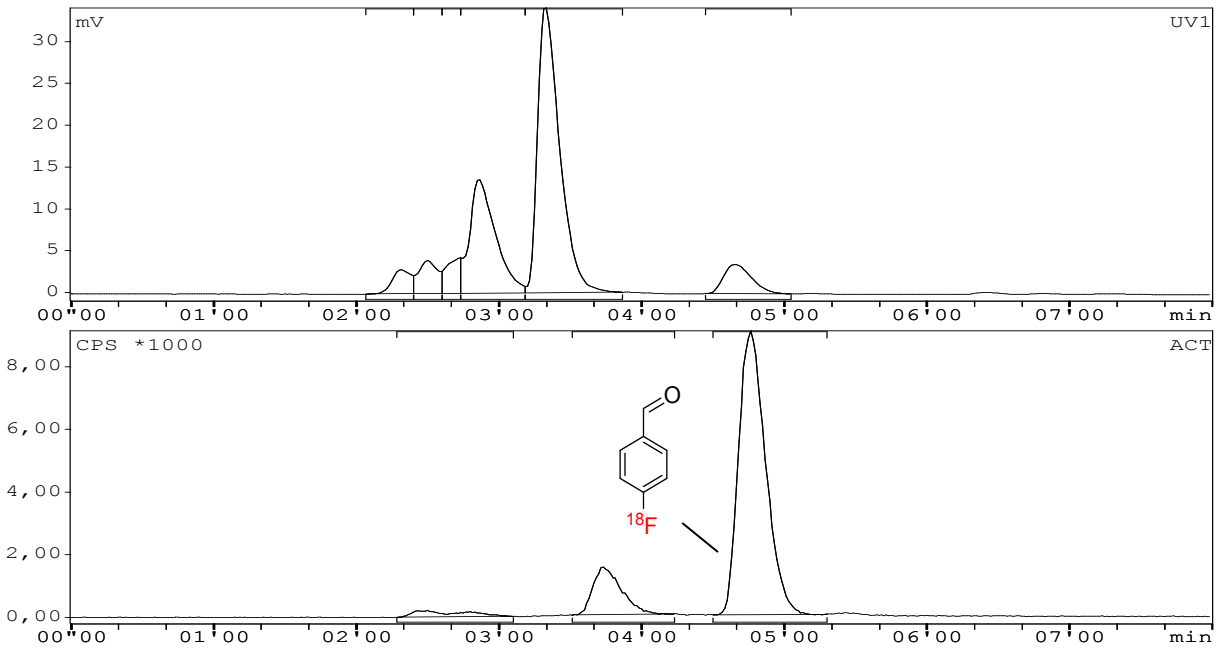
Top panel: UV at 254 nm, Peak at 6 min is 4-methyl-*N,N,N*-trimethylbenzenaminium trifluoromethanesulfonate; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$ and the broad peak at 4 min is $^{18}F^-/K_{2.2.2}$-complex ; Eluent: 70:30:0.2 MeCN/H_2O/TFA

5.7 4-[^{18}F]Fluorobenzaldehyde



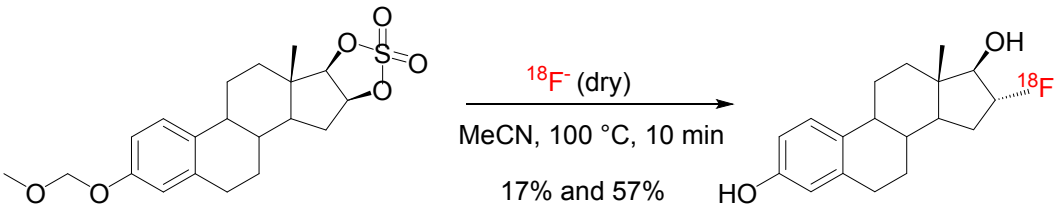


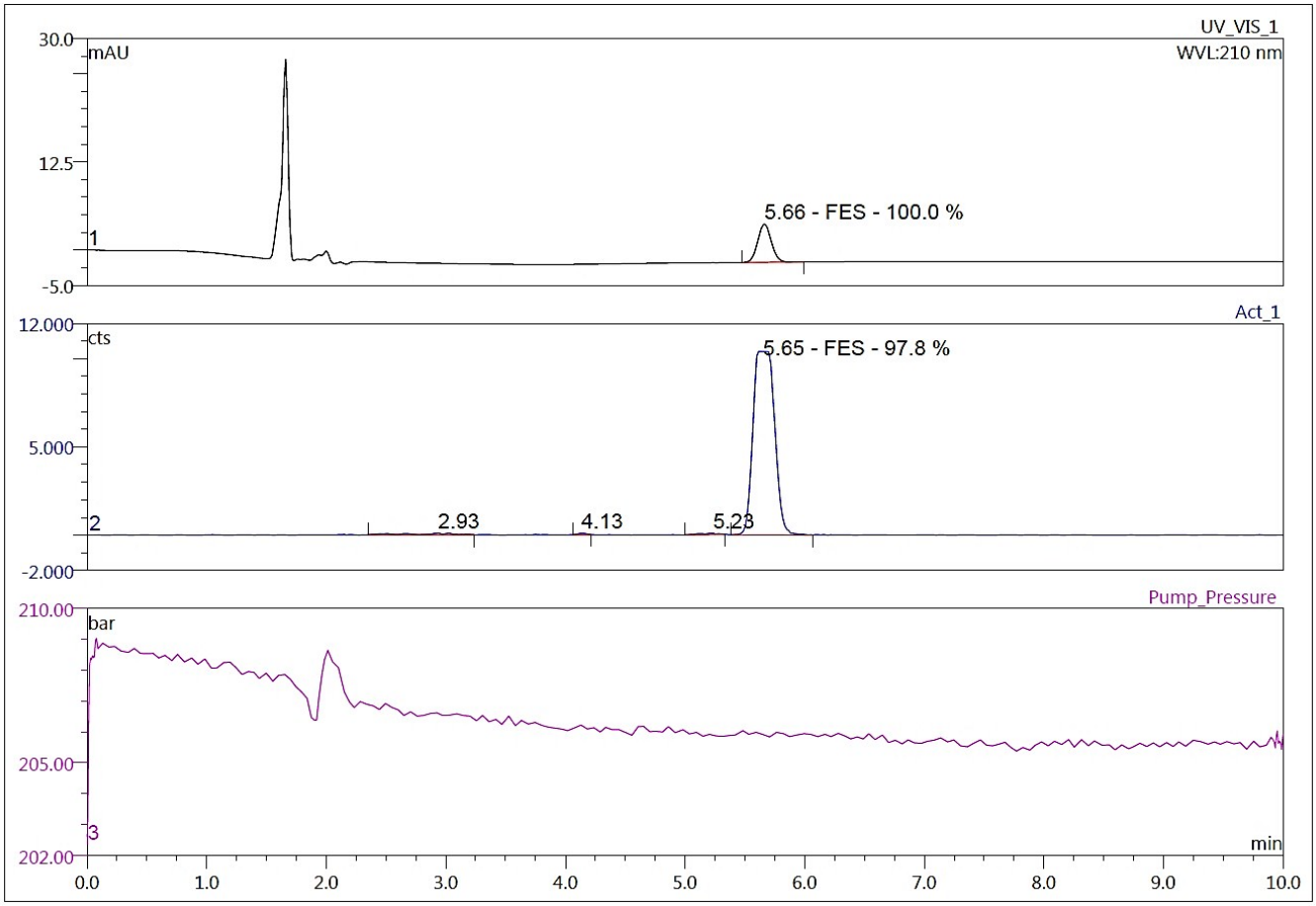
UV at 254 nm; reference chromatogram of 4-fluorobenzaldehyde; Eluent: 70:30:0.2 MeCN/H_2O/TFA



Top panel: UV at 254 nm, Peak at 4.5 min is *N,N,N*-trimethyl-4-benzaldehydeaminium trifluoromethanesulfonate; bottom panel: radioactivity measurement, peak at 2.5 min is $^{18}F^-$ and the peak at 3.8 min is $^{18}F^-/K_{2.2.2}$-complex; Eluent 70:30:0.2 MeCN/H_2O/TFA

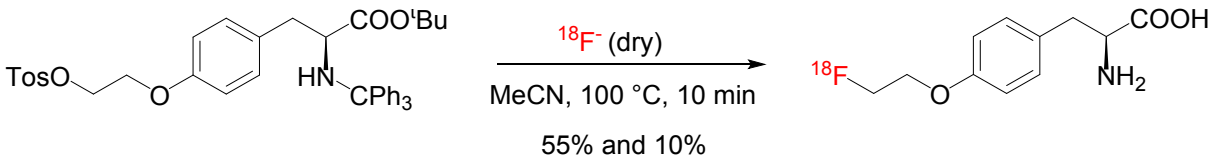
5.8 [^{18}F]FES

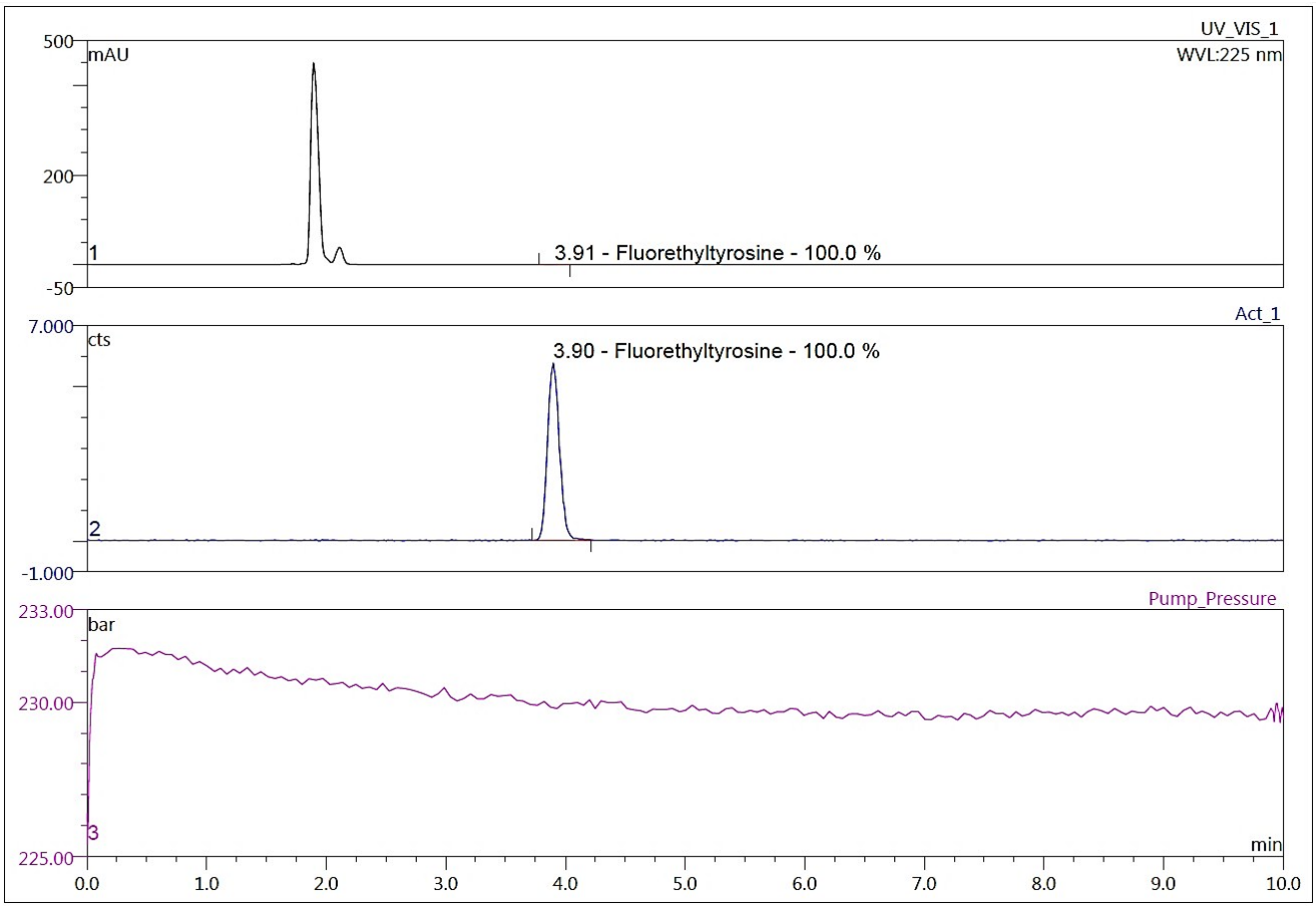




Top panel: UV at 210 nm, Peak at 5.66 min is fluoroestradiol; middle panel: radioactivity measurement, peak at 5.65 min is [^{18}F]fluoroestradiol; bottom panel: pump pressure of HPLC; column: Platinum C18 5µ, 250 x 4.6 mm; eluent: 42:58 MeCN/Phosphate buffer pH 2.5; flow: 1.5 mL/min

5.9 [^{18}F]FET





Top panel: UV at 210 nm, Peak at 3.91 min is fluoroethyltyrosine; middle panel: radioactivity measurement, peak at 3.90 min is [^{18}F]fluoroethylthyrosine; bottom panel: pump pressure of HPLC;

Column: Platinum C18 5µ, 250 x 4.6 mm; eluent: 42:58 MeCN/Phosphate buffer pH 2.5; flow: 1.5 mL/min

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