Supporting information to

Alcohol-supported Cu-mediated ^{18}F-fluorination of iodonium salts under "minimalist" conditions

Victoriya V. Orlovskaya [1,†], Daniel J. Modemann [2,†], Olga F. Kuznetsova [1], Olga S. Fedorova [1], Elizaveta A. Urusova [2,3], Niklas Kolks [2,3], Bernd Neumaier [2,3,4,*], Raisa N. Krasikova [1,5,*] and Boris D. Zlatopolskiy [2,3,4]

[1] N.P. Bechtereva Institute of the Human Brain, 197376 St.-Petersburg, Russia; vikaorl@list.ru (V.V.O.); kuznetsova@ihb.spb.ru (O.F.K.); fedorova@ihb.spb.ru (O.S.F.);

[2] Institute of Neuroscience and Medicine, INM-5: Nuclear Chemistry, Forschungszentrum Jülich GmbH, 52425 Jülich, Germany; daniel.modemann@med.uni-goettingen.de (D.J.M.); e.urusova@fz-juelich.de (E.A.U.); niklas.kolks@uk-koeln.de (N.K.); boris.zlatopolskiy@uk-koeln.de (B.D.Z.)

[3] Institute of Radiochemistry and Experimental Molecular Imaging, University Clinic Cologne, 50937 Cologne, Germany

[4] Max Planck Institute for Metabolism Research, 50931 Cologne, Germany;

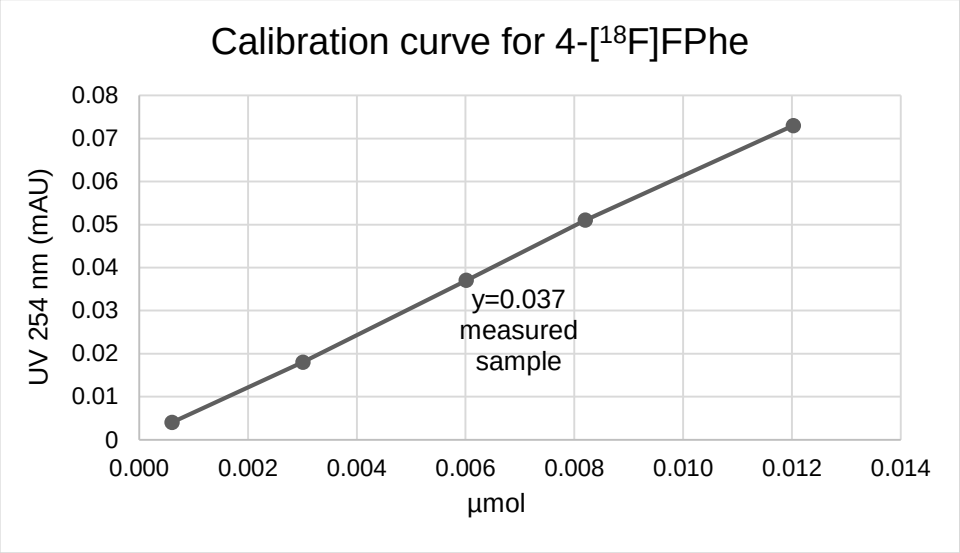
[5] St.-Petersburg State University, 199034 St.-Petersburg, Russia

* Correspondence: b.neumaier@fz-juelich.de (B.N.); raisa_krasikova@inbox.ru (R.N.K.)

† Contributed equally

Molar activity calculation: The molar activity (GBq/µmol) was calculated by dividing the radioactivity of the ^{18}F-labeled product by the amount of the unlabeled tracer determined from the peak area in a UV-HPLC chromatograms (λ=254 nm). The solution of 4-[^{18}F]FPhe obtained after HPLC purification was concentrated under reduced pressure, the residue was dissolved in a small amount of the HPLC eluent. The resulting solution was completely injected into the HPLC system. The peak area was determined and the amount of 4-FPhe was calculated according to the calibration curve. The molar activity of 4-[^{18}F]FPhe (2.22 GBq) was determined to 207 GBq/µmol.

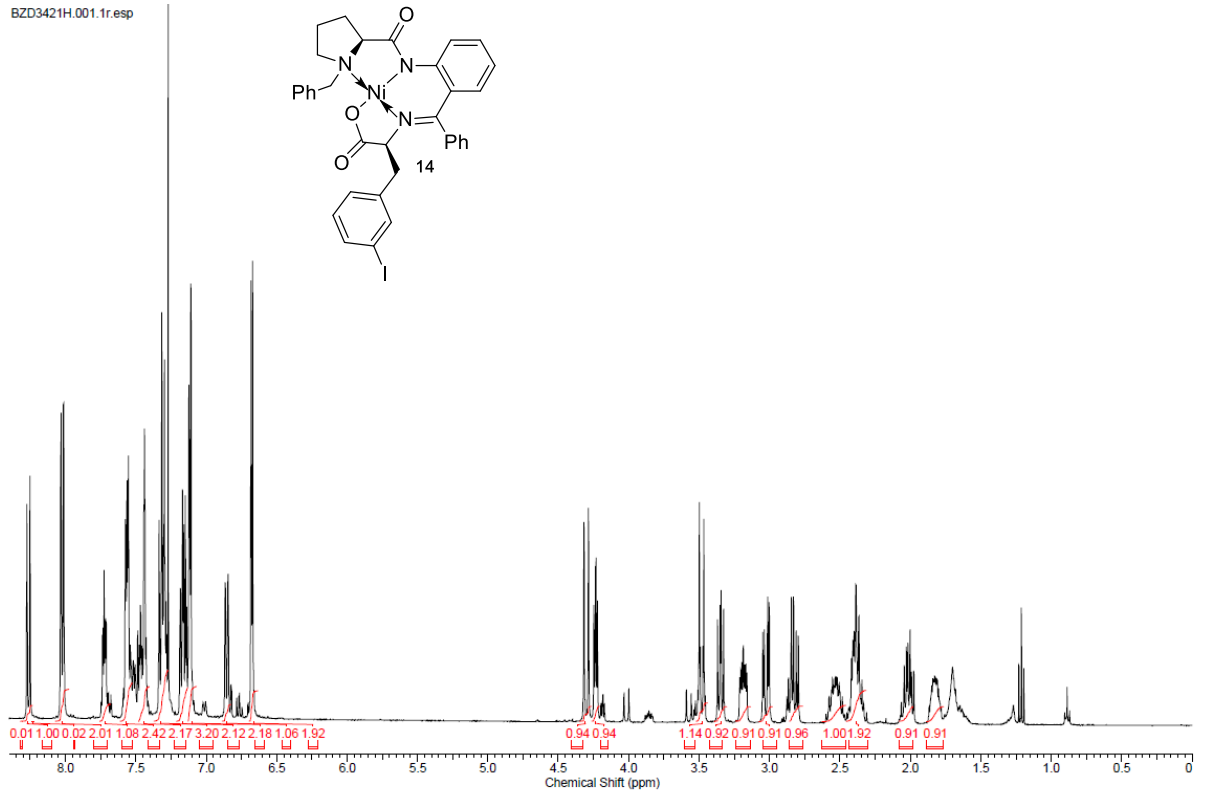
Calibration curve for 4-[^{18}F]FPhe:

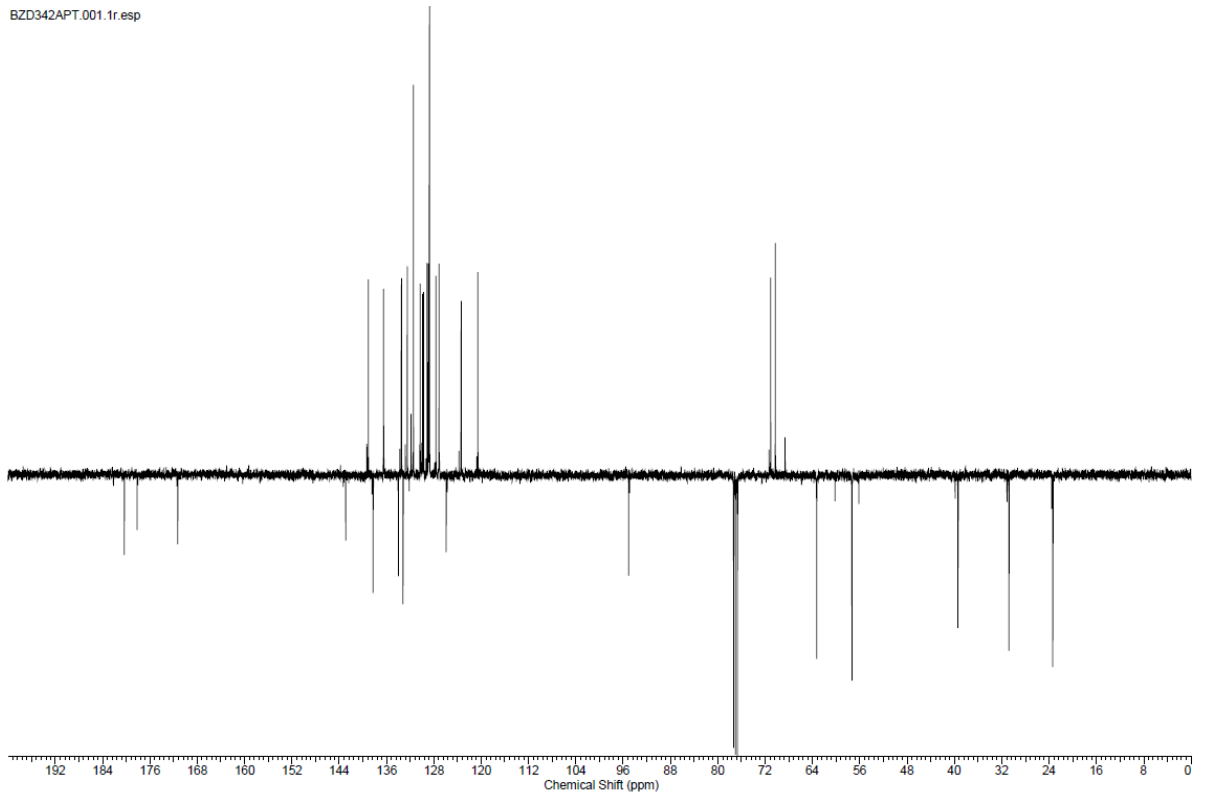


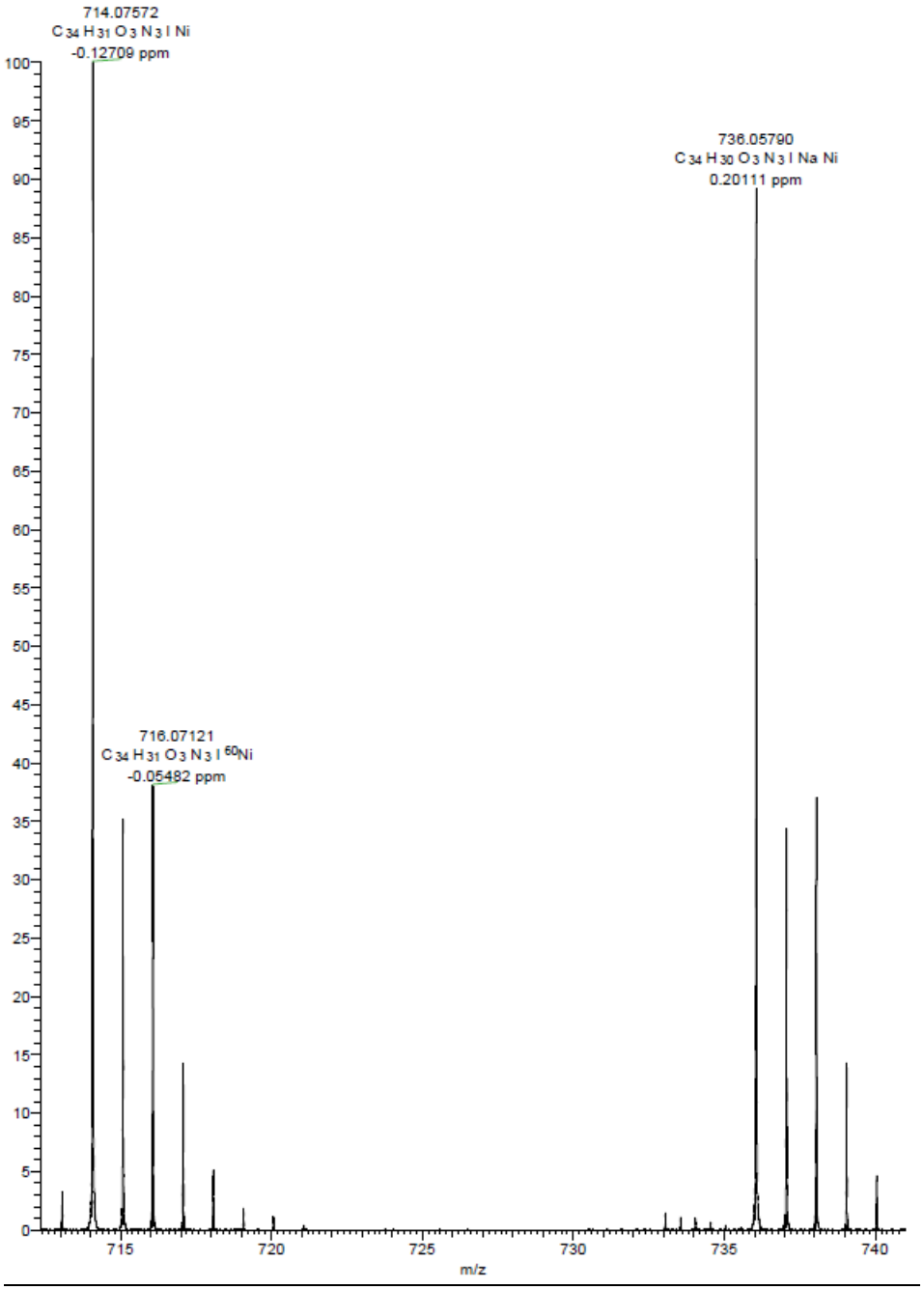
C, µmol	Peak area (mAU)
0.012	0.073
0.008	0.051
0.006	0.037
0.003	0.018
0.001	0.004

NMR and MS-spectra

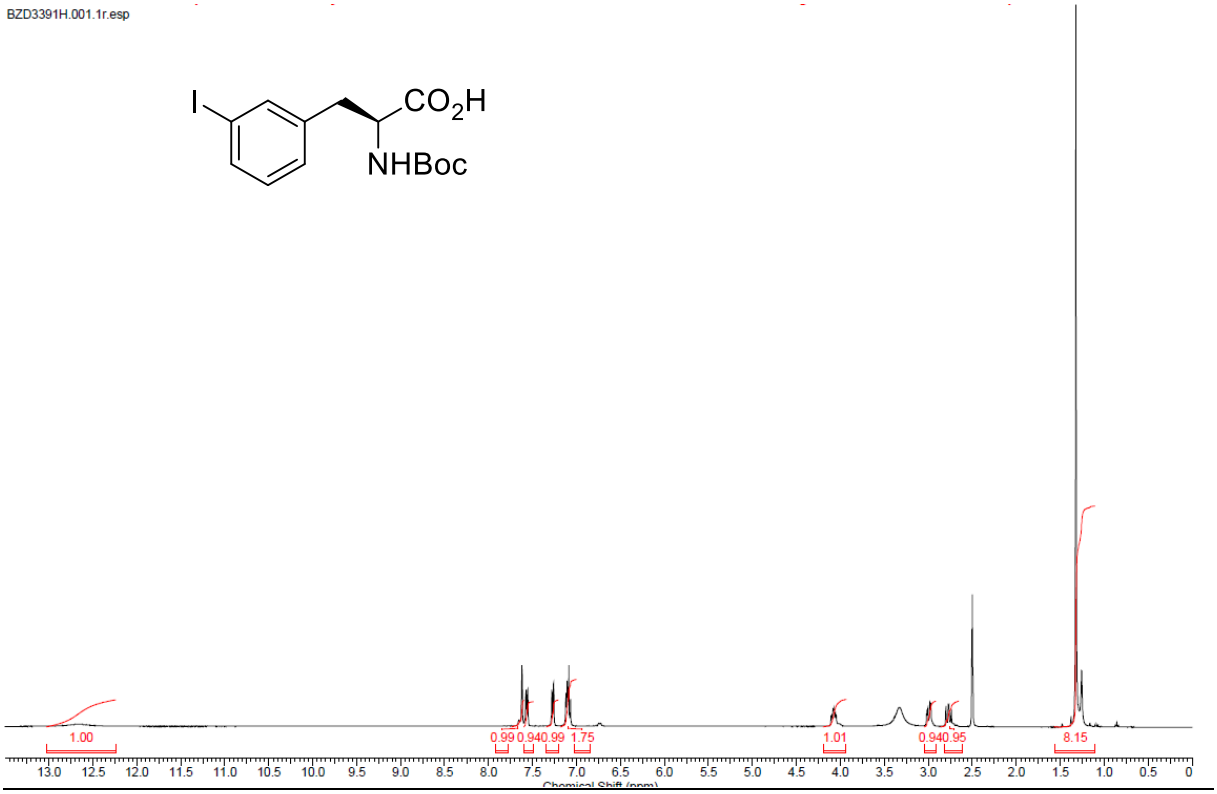
(*S*,*S*)-Ni-BPB-3-IPhe (**14**):



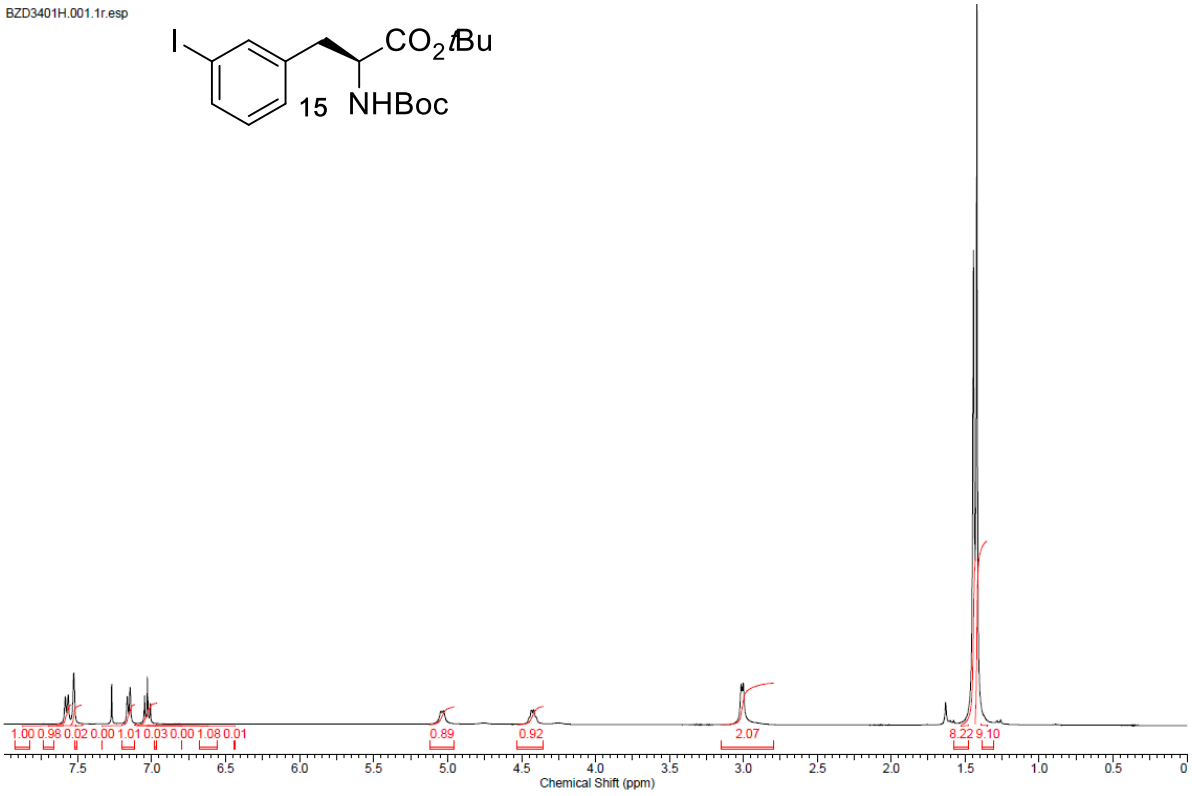


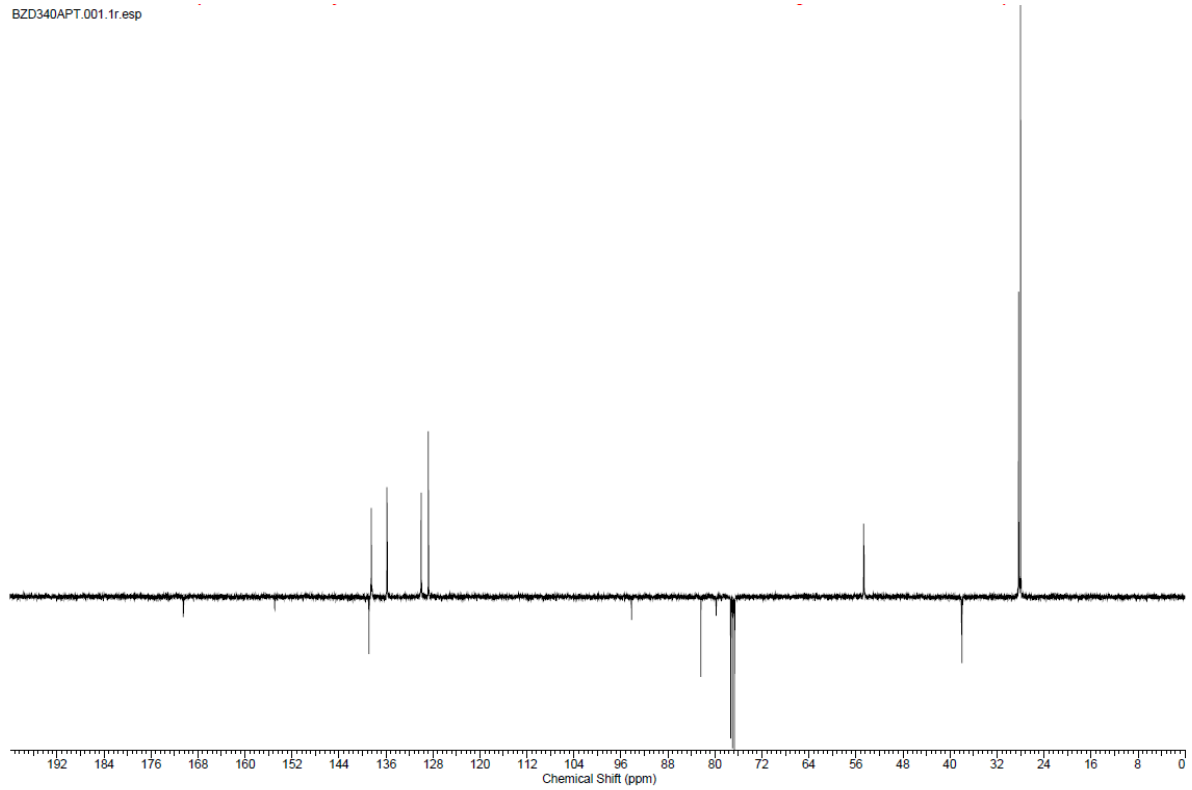

714.07572
C34 H31 O3 N3 I Ni
-0.12709 ppm
736.05790
C34 H30 O3 N3 I Na Ni
0.20111 ppm
716.07121
C34 H31 O3 N3 I 60Ni
-0.05482 ppm
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
715
720
725
730
735
740
m/z

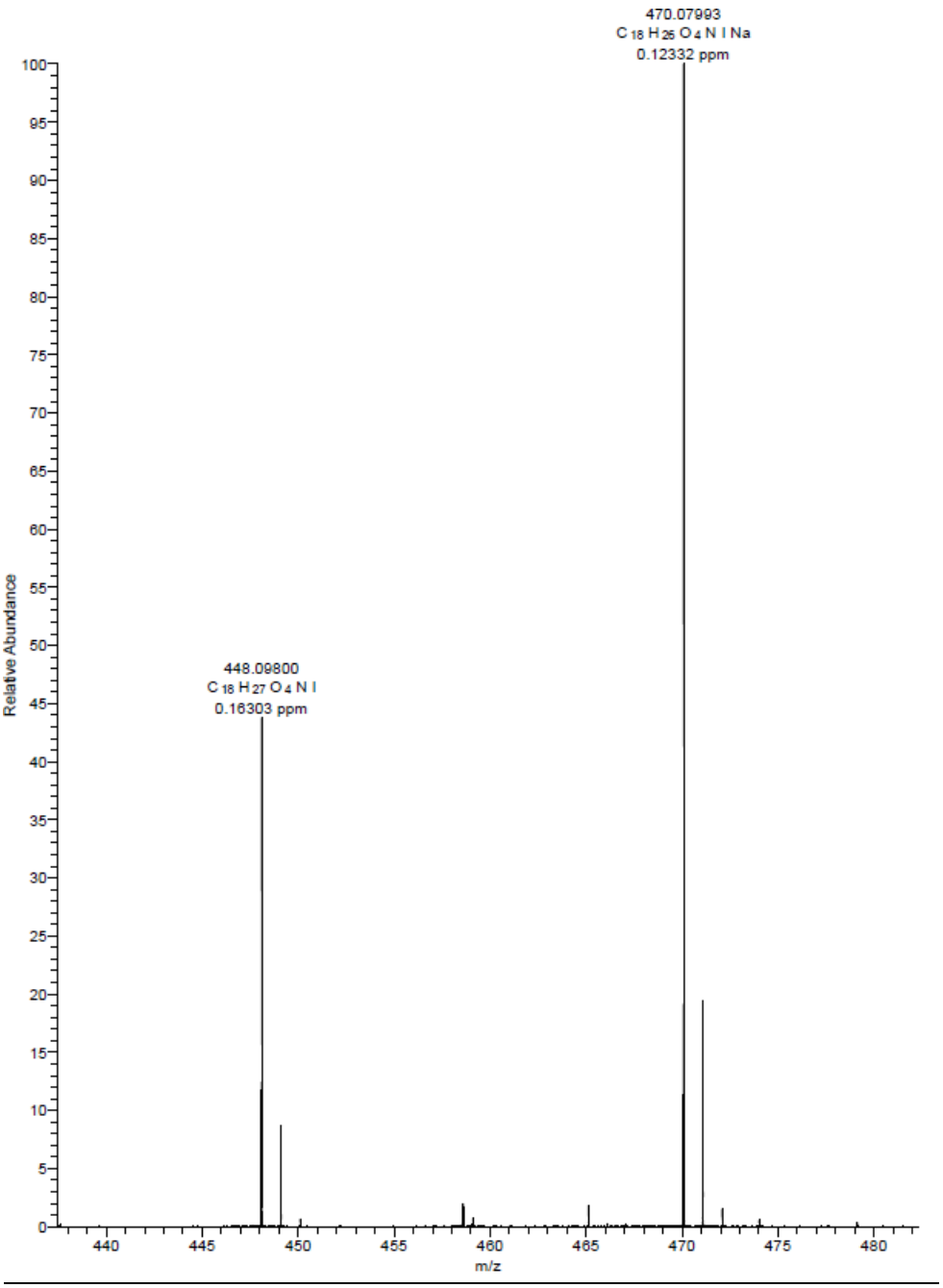
Boc-3IPhe-OH:


BZD3391H.001.1r.esp
I
CO2H
NHBoc
1.00
0.99
0.94
0.99
1.75
1.01
0.94
0.95
8.15
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

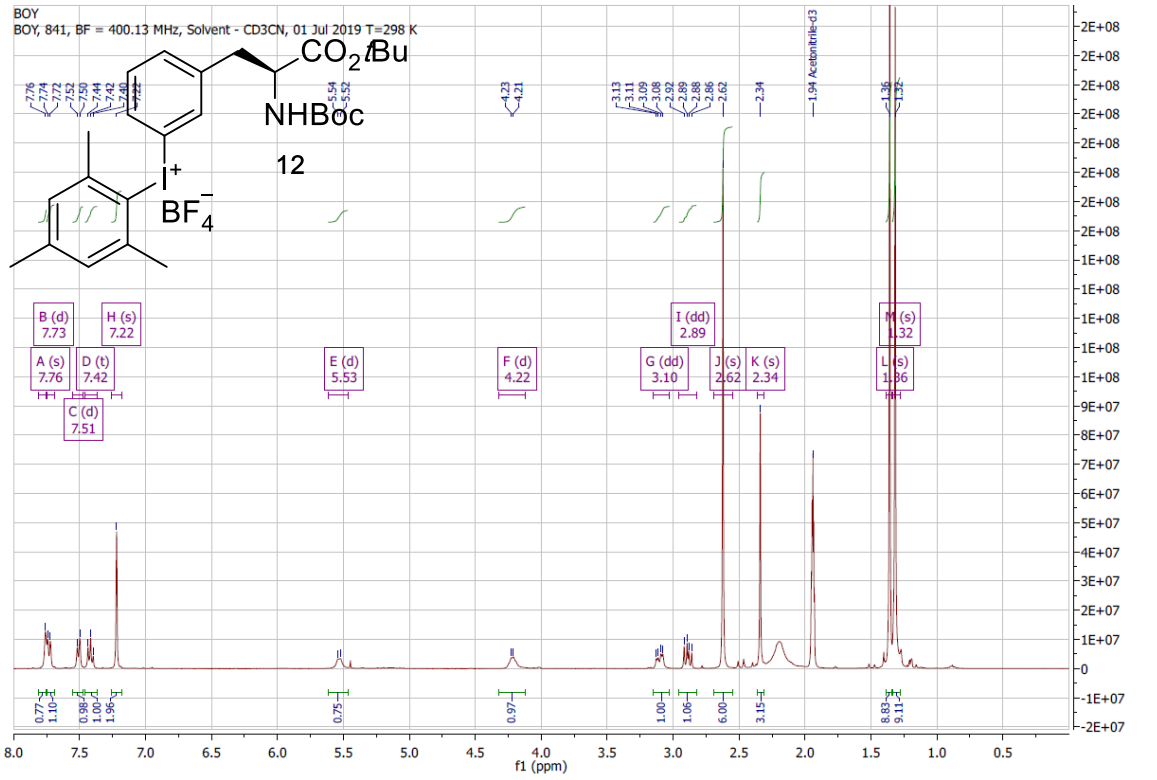
Boc-3-IPhe-O*t*Bu (**15**):

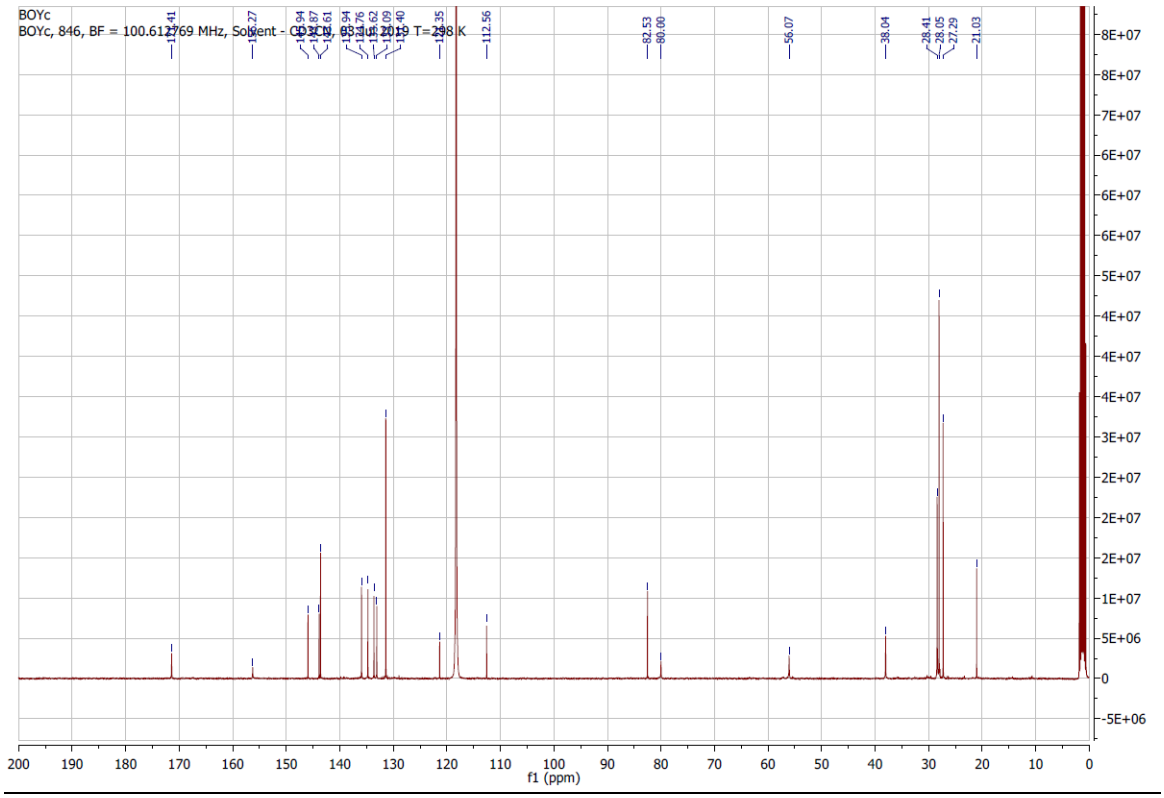


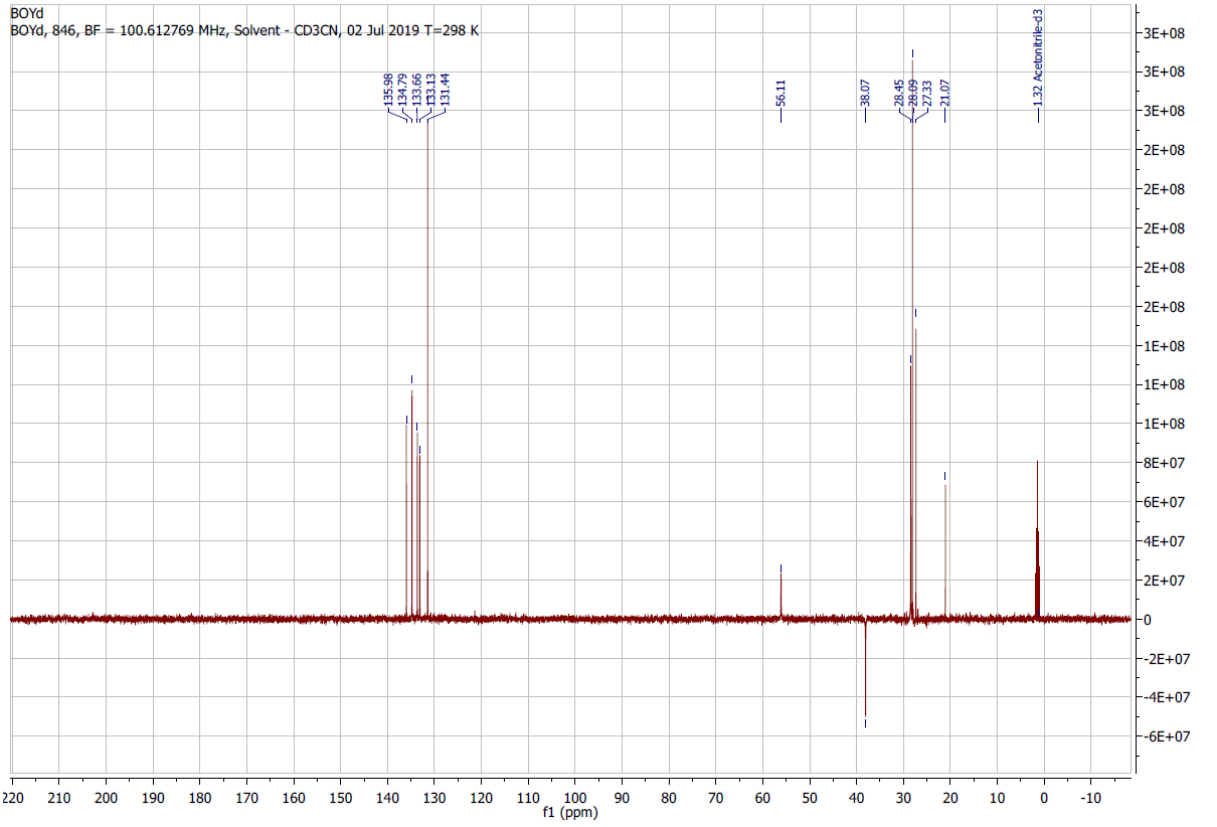


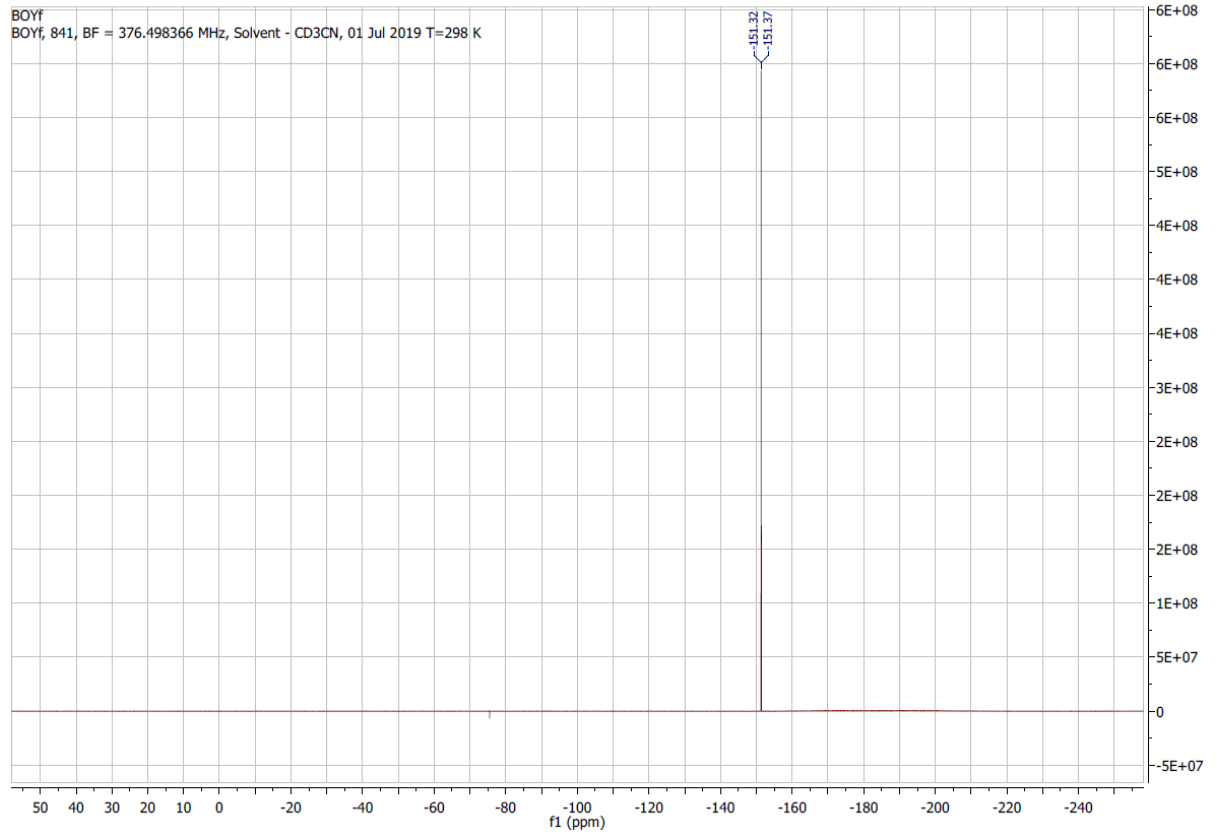

470.07993
C 18 H 26 O 4 N I Na
0.12332 ppm
448.09800
C 18 H 27 O 4 N I
0.16303 ppm
Relative Abundance
m/z
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
440
445
450
455
460
465
470
475
480

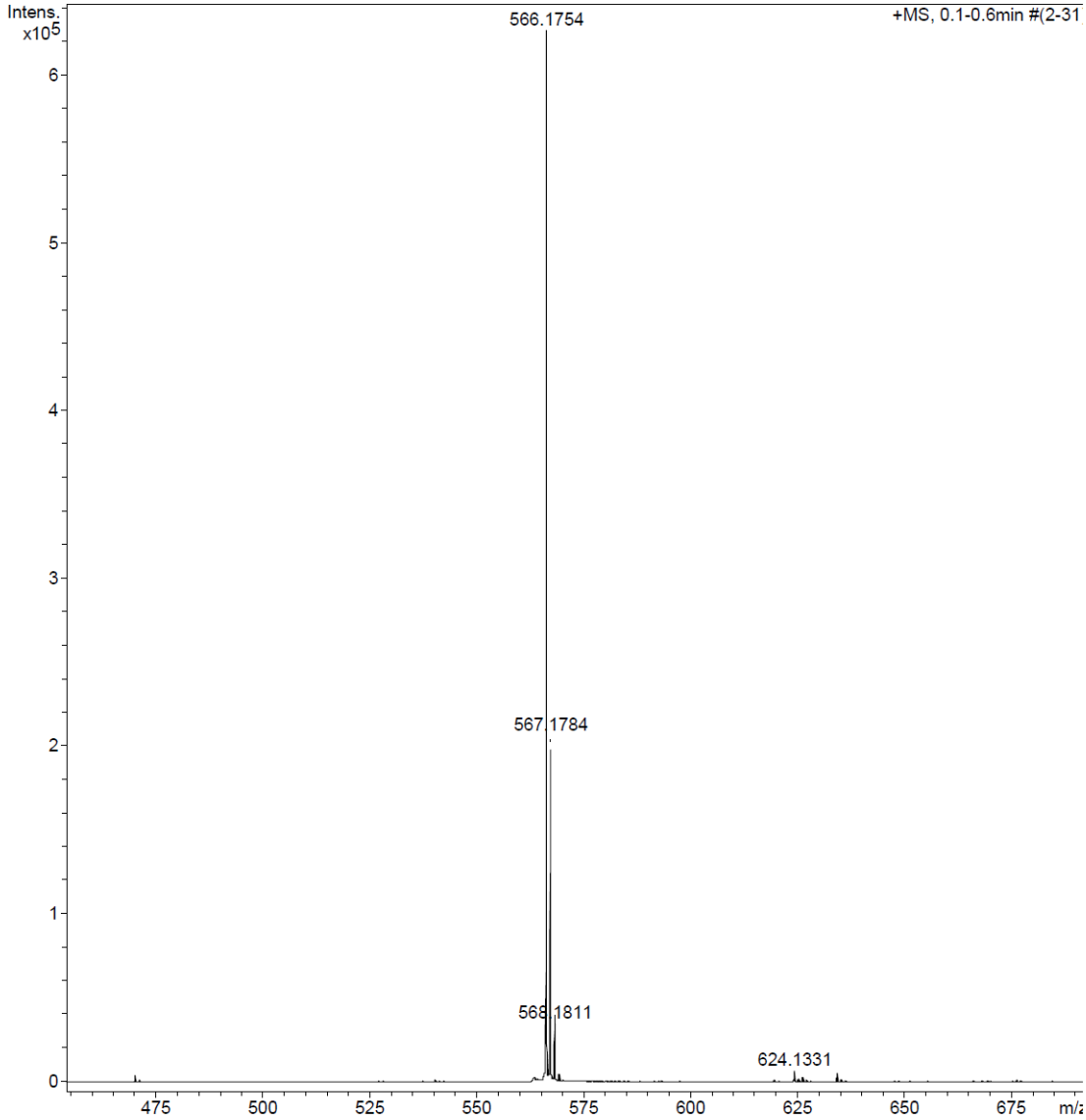
3-{2-[(2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(*tert*-butoxy)-3-oxopropyl]phenyl}(2,4,6-trimethylphenyl)iodonium tetrafluoroborate (**12**):





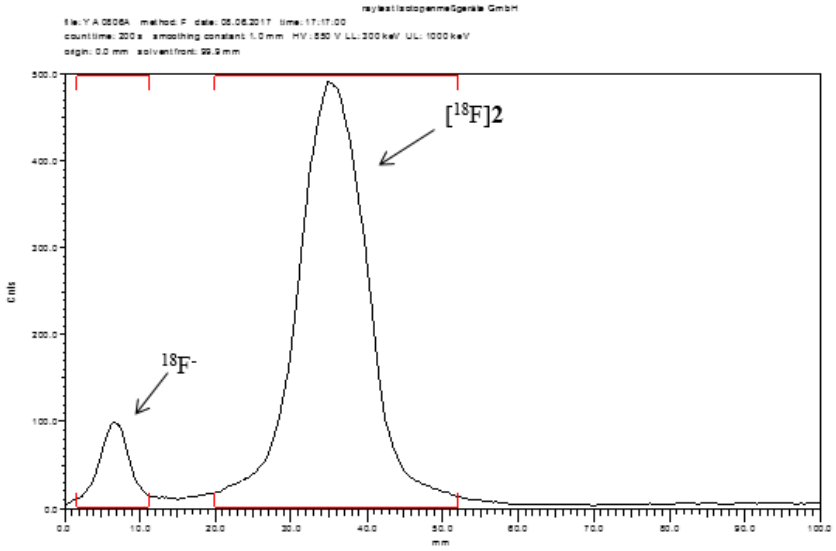

BOYd
BOYd, 846, BF = 100.612769 MHz, Solvent - CD3CN, 02 Jul 2019 T=298 K
135.98
134.79
133.66
133.13
131.44
56.11
38.07
28.45
28.09
27.33
21.07
1.32 Acetonitrile-d3
f1 (ppm)


BOYf
BOYf, 841, BF = 376.498366 MHz, Solvent - CD3CN, 01 Jul 2019 T=298 K
151.32
151.37
f1 (ppm)

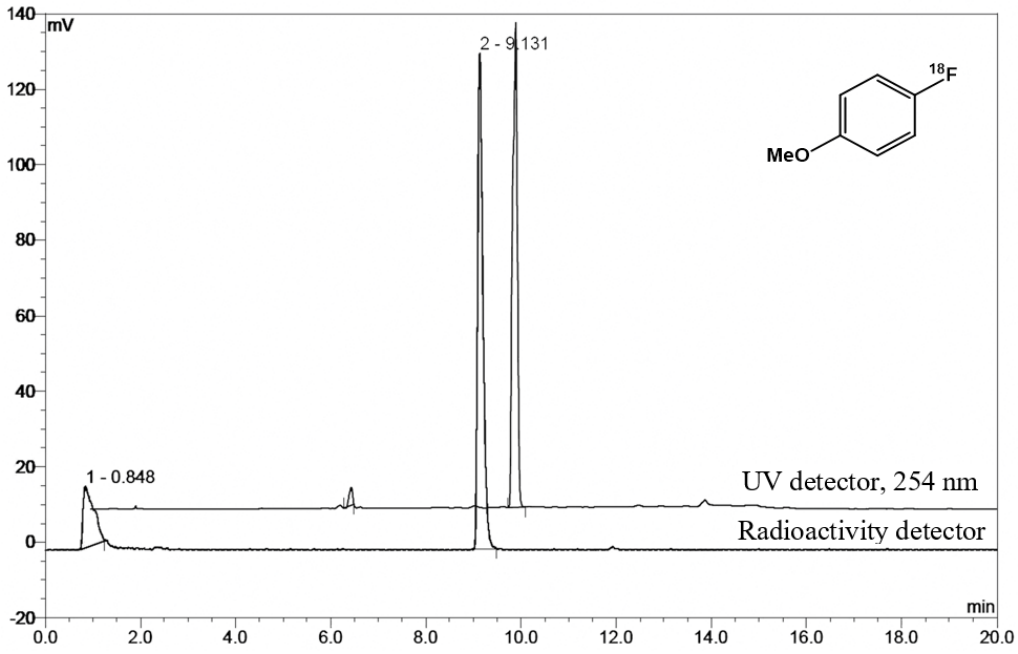

Intens.
x10^5
+MS, 0.1-0.6min #(2-31
566.1754
567.1784
568.1811
624.1331
6
5
4
3
2
1
0
475
500
525
550
575
600
625
650
675
m/z

Chromatograms (TLC and HPLC)

4-[^{18}F]Fluoroanisole ([^{18}F]**2**):



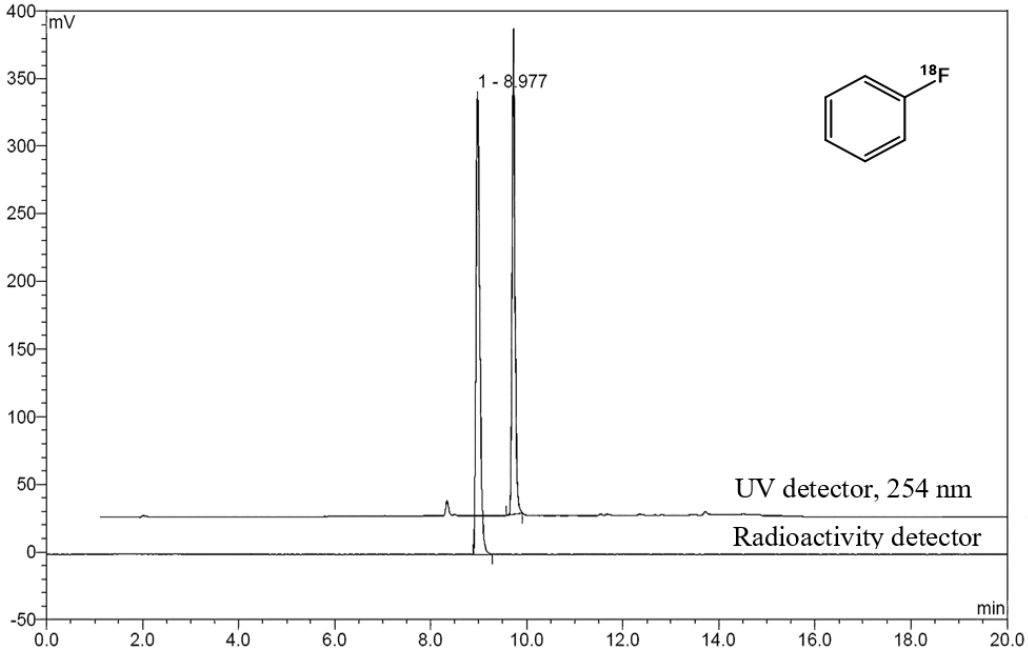
4-[^{18}F]Fluoroanisole, TLC in hexane/ethylacetate (1/4)



4-[^{18}F]Fluoroanisole and the reference compound, HPLC on X-Bridge C18 column 5 µm, 150×4.6 mm (Waters), 0–2 min: 5% MeCN, 2–13 min: 5→90% MeCN (2.0 mL/min), injection loop: 20 µL.

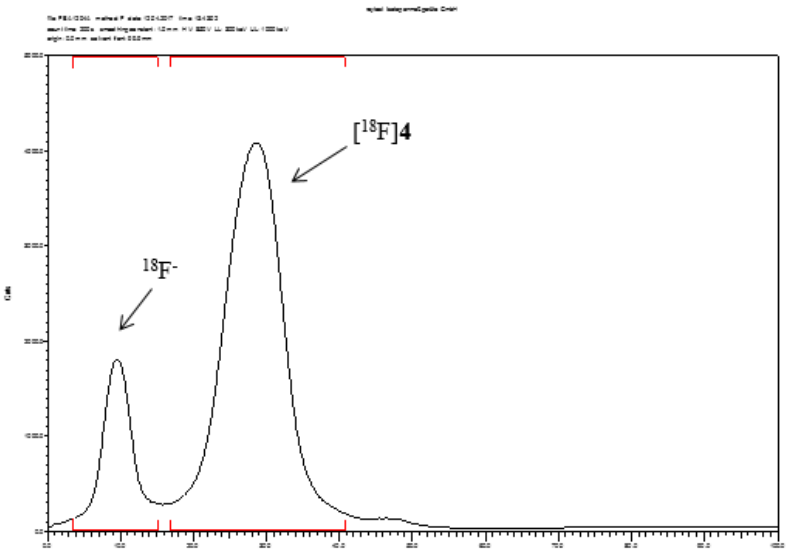
[^{18}F]Fluorobenzene ([^{18}F]**3**):

TLC was not applicable for [^{18}F]fluorobenzene because of volatility of the substance

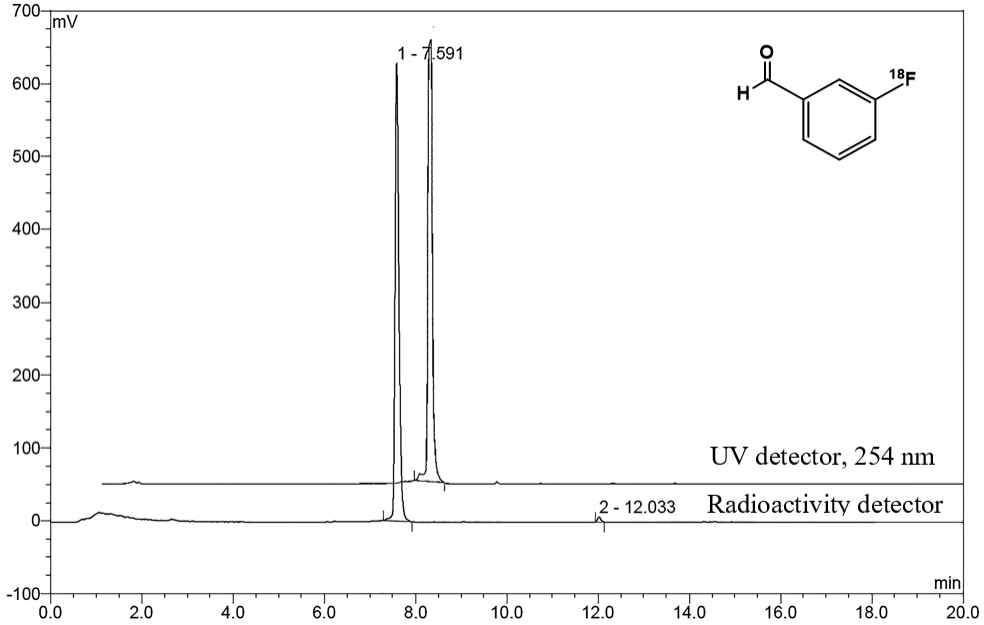


[^{18}F]Fluorobenzene and the reference compound, HPLC on X-Bridge C18 column 5 µm, 150×4.6 mm (Waters), 0–2 min: 5% MeCN, 2–13 min: 5→90% MeCN (2.0 mL/min), injection loop: 20 µL.

3-[^{18}F]Fluorobenzaldehyde ([^{18}F]**4**):



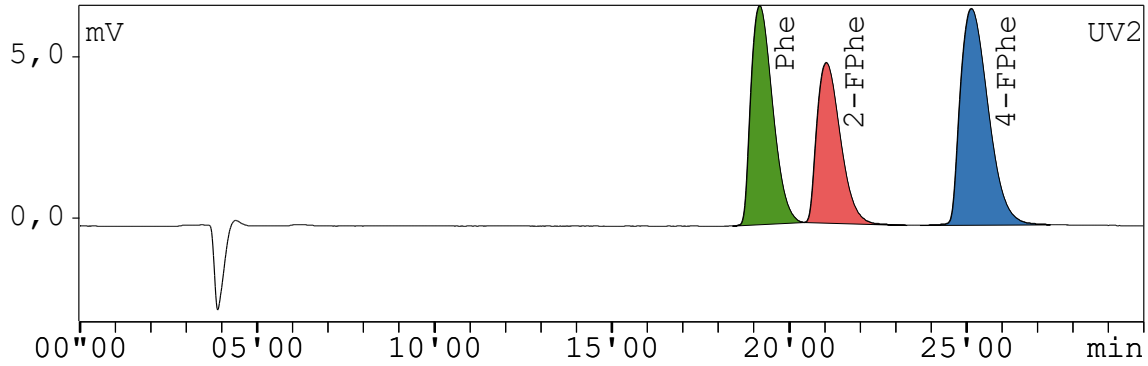
3-[^{18}F]Fluorobenzaldehyde ([^{18}F]**4**), TLC in hexane/ethylacetate (1/4)



3-[^{18}F]Fluorobenzaldehyde ([^{18}F]**4**) and the reference compound, HPLC on X-Bridge C18 column 5 µm, 150×4.6 mm (Waters), 0–2 min: 5% MeCN, 2–13 min: 5→90% MeCN (2.0 mL/min), UV detection: 254 nm, injection loop: 20 µL.

Compound	k	R_t
[^{18}F]**2**	9.8	00:09:06
[^{18}F]**3**	9.6	00:08:52
[^{18}F]**4**	8.0	00:07:36
Dead time		00:00:50

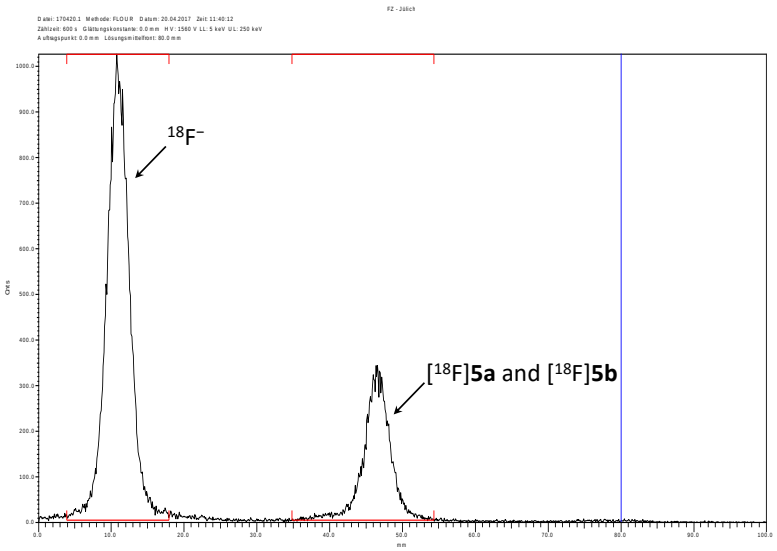
Reference compounds: Phe, 2- and 4-FPhe:



Synergy Hydro-RP (4.6×250 mm), 6% EtOH (1.0 mL/min), 210 nm, 20 µL loop

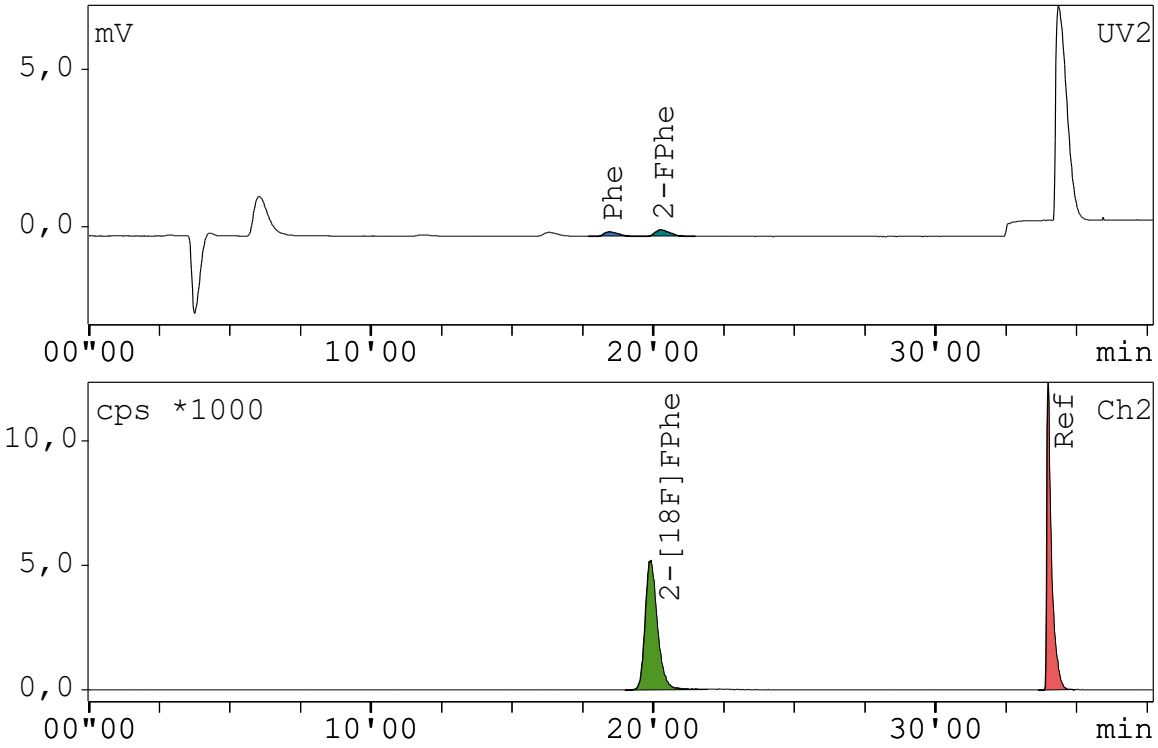
Compound	k'	R_t
Phe	4.6	00:19:19
2-FPhe	5.1	00:21:02
4-FPhe	6.3	00:25:08
Dead time		00:03:28

Boc$_2$-2-[^{18}F]FPhe-O*t*Bu ([^{18}F]**5a**) and Boc-2-[^{18}F]FPhe-O*t*Bu ([^{18}F]**5b**):



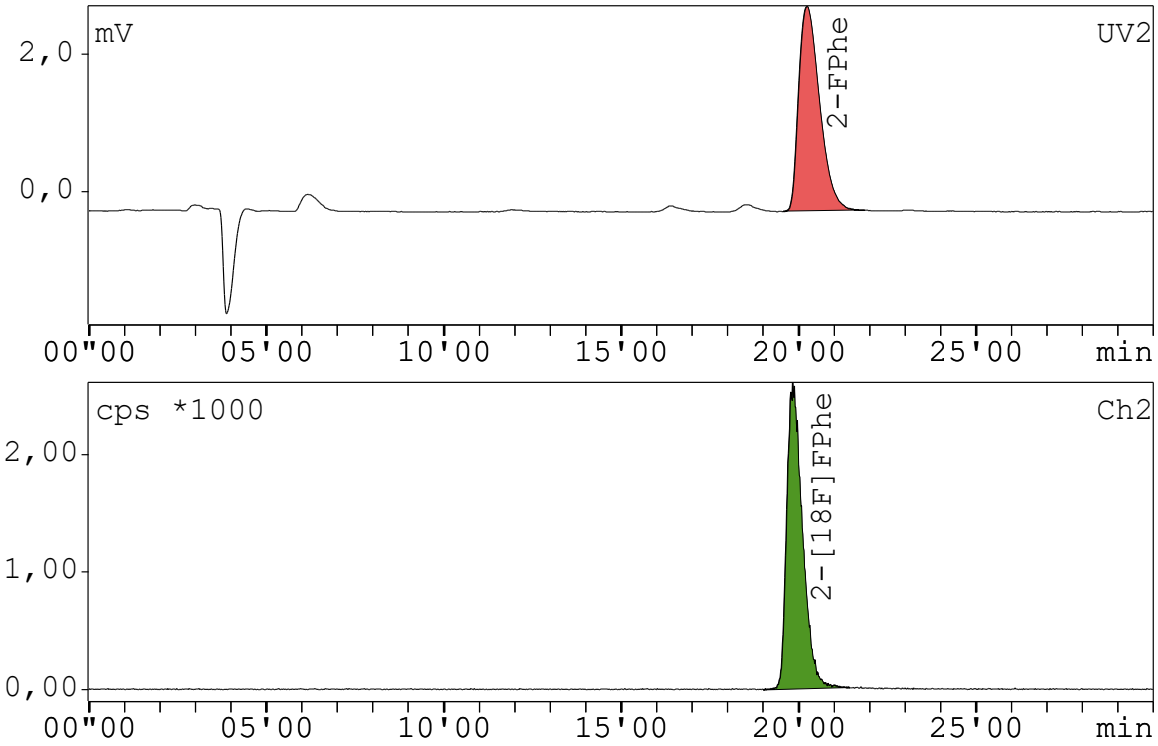
TLC in hexane/ethylacetate (9/1)

2-[^{18}F]FPhe after HPLC purification: Quality control:



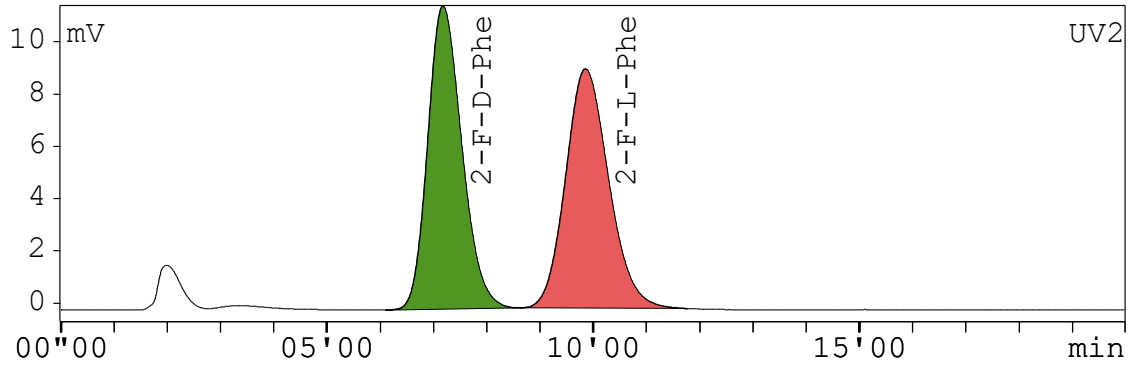
Synergy Hydro-RP (4.6×250 mm), 6% EtOH (1.0 mL/min), 210 nm, 20 µL loop.

2-[^{18}F]FPhe after HPLC purification: Spiking with the reference compound:



Synergy Hydro-RP (4.6×250 mm), 6% EtOH (1.0 mL/min), 210 nm, 20 µL loop.

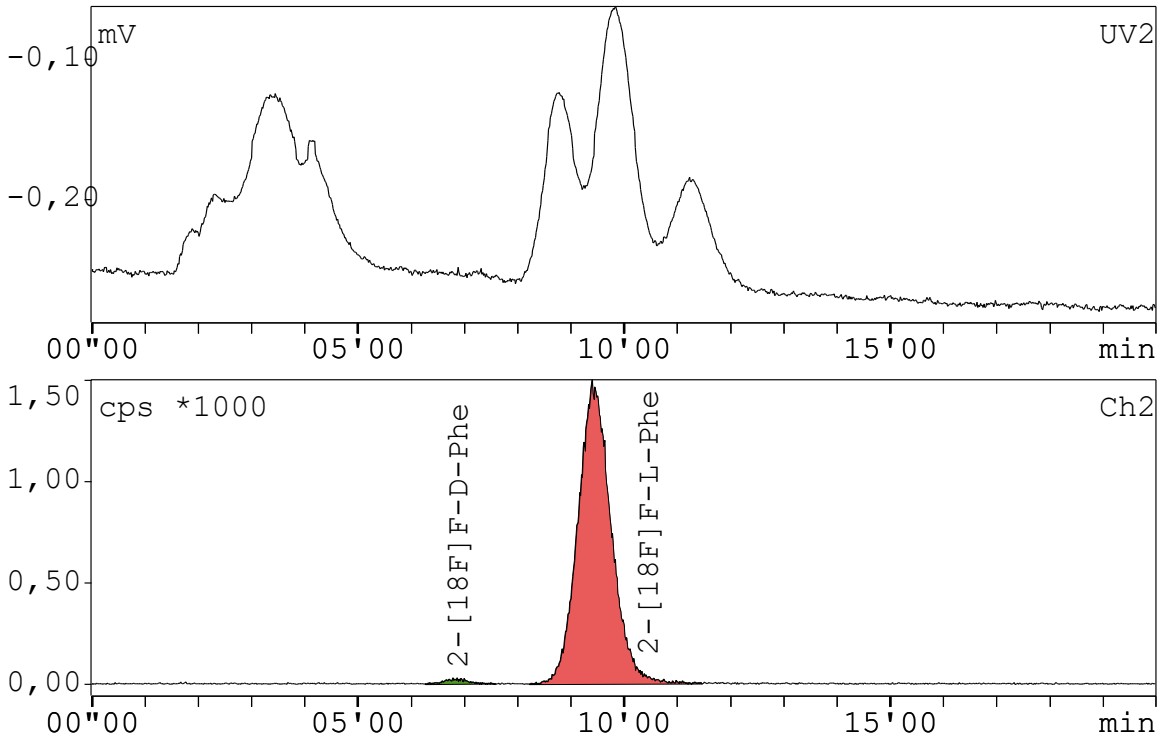
Reference compounds: (*S*)- and (*R*)-2-FPhes:



Crownpak (+) (4.6×150 mm), 0.025 M $HClO_4$ (1.0 mL/min), 210 nm, 20 µL loop.

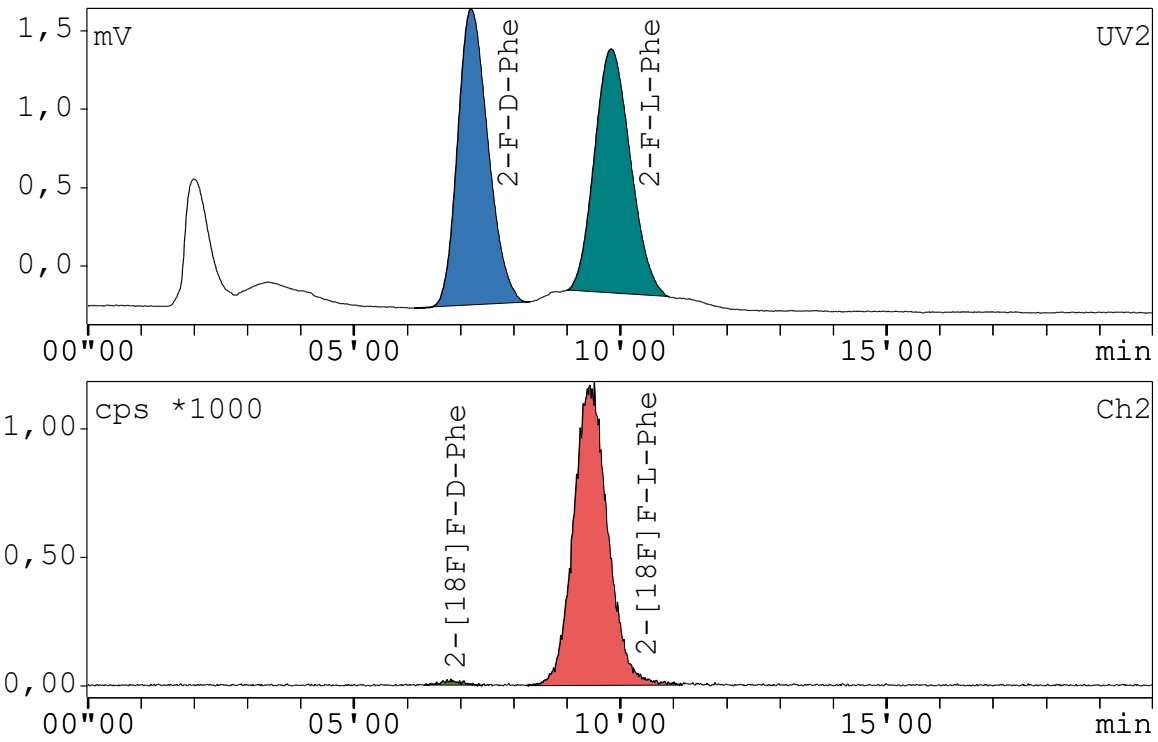
Compound	K'	R_t
(*R*)-2-FPhe	2.5	00:07:11
(*S*)-2-FPhe	3.7	00:09:51
Dead time		00:02:05

2-[^{18}F]FPhe after HPLC purification: Determination of enantiomeric purity, quality control:



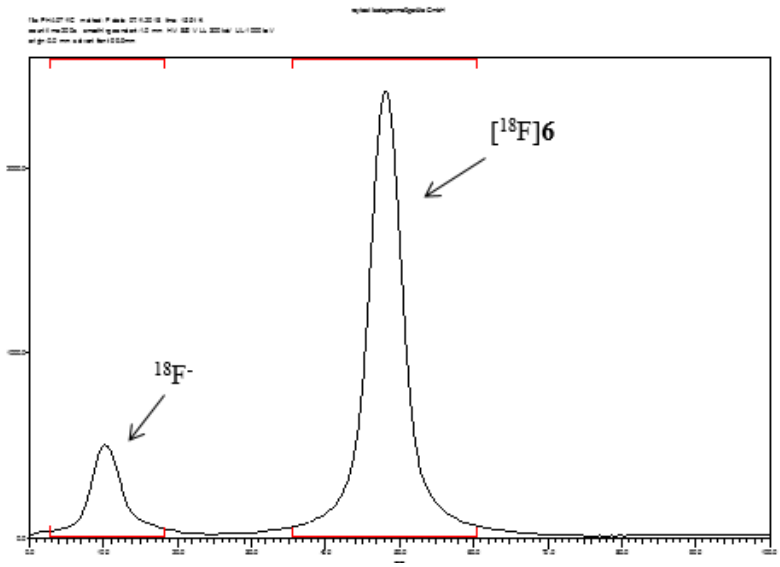
Crownpak (+) (4.6×150 mm), 0.025 M $HClO_4$ (1.0 mL/min), 210 nm, 20 µL loop.

2-[^{18}F]FPhe after HPLC purification: Determination of enantiomeric purity, spiking with (*S*)- and (*R*)-2-FPhes:



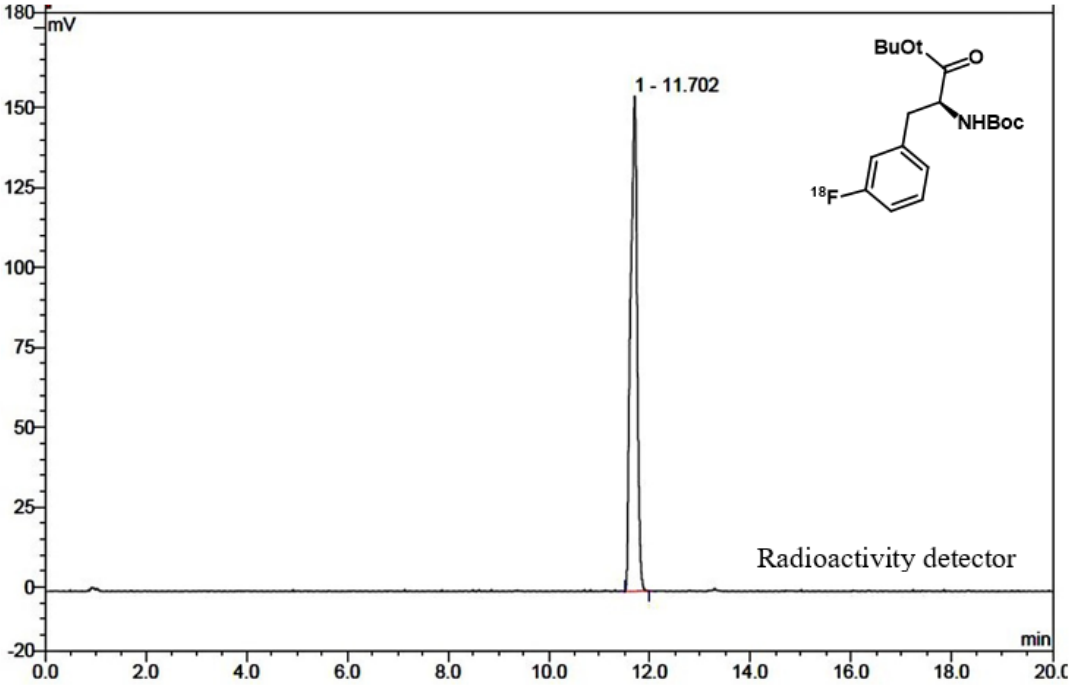
Crownpak (+) (4.6×150 mm), 0.025 M $HClO_4$ (1.0 mL/min), 210 nm, 20 µL loop.

Boc-3-[^{18}F]FPhe-O*t*Bu ([^{18}F]**6**) (TLC):



EtOAc/$CHCl_3$/AcOH (4/1/1)

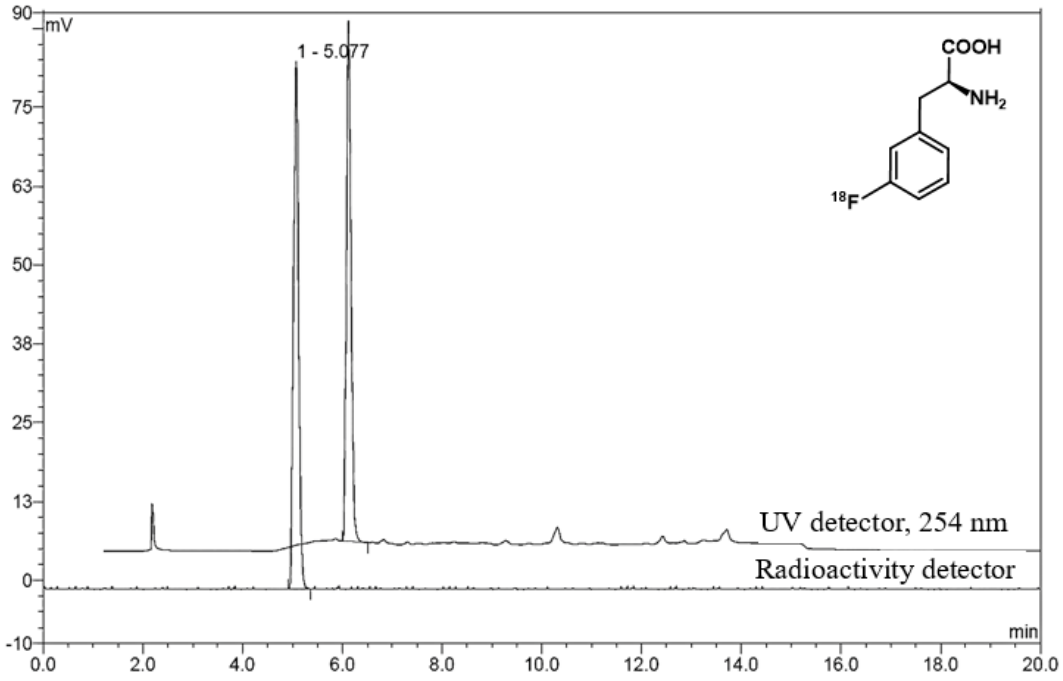
Boc-3-[^{18}F]FPhe-O*t*Bu ([^{18}F]**6**) (HPLC):



Boc-3-[^{18}F]FPhe-O*t*Bu ([^{18}F]**6**), X-Bridge C18 column 5 µm, 150×4.6 mm (Waters), 0–2 min: 5% MeCN, 2–13 min: 5→90% MeCN (2.0 mL/min).

Compound	k'	R_t
[^{18}F]**6**	13.5	00:11:40
Dead time		00:00:50

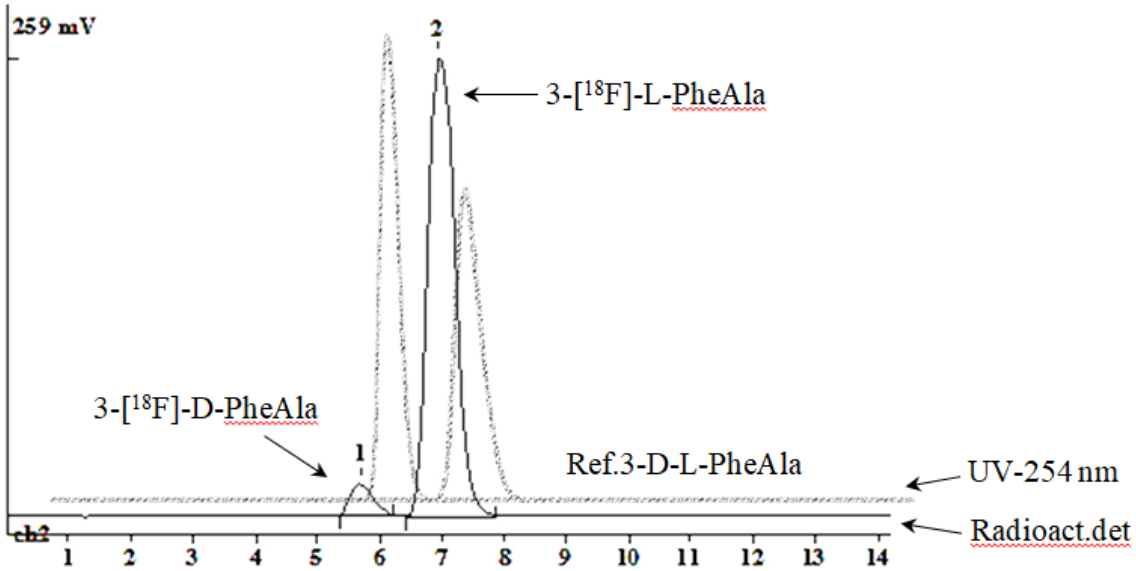
3-[^{18}F]FPhe after HPLC purification: Quality control. Spiking with the reference compound:



(HPLC):

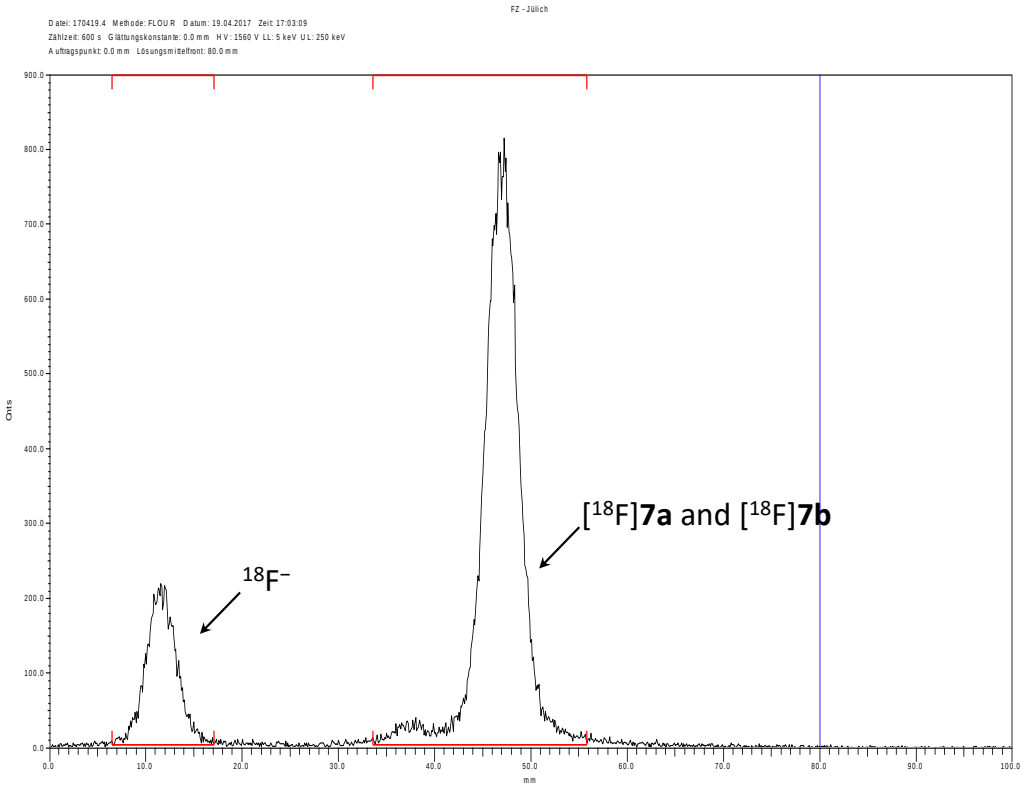
3-[^{18}F]FPhe and the reference compound, X-Bridge C18 column 5 µm, 150×4.6 mm (Waters), 0–2 min: 5% MeCN, 2–13 min: 5→90% MeCN (2.0 mL/min), UV detection: 254 nm, injection loop: 20 µL.

3-[^{18}F]FPhe after HPLC purification: Determination of enantiomeric purity, spiking with (*S*)- and (*R*)-3-FPhes:

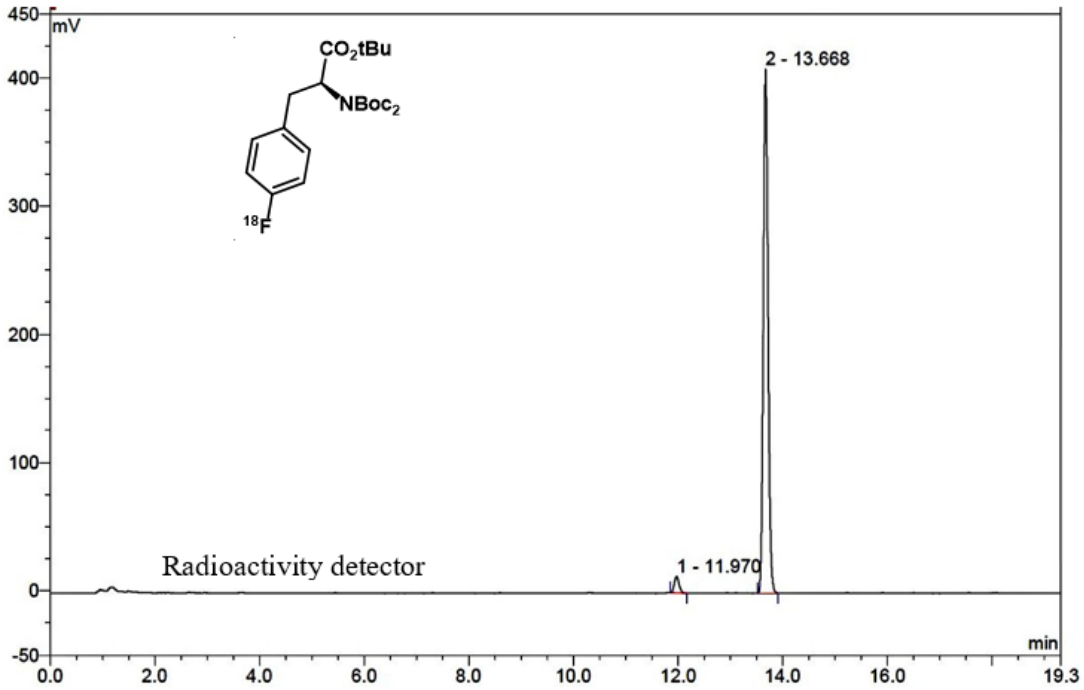


Crownpak (+) (4.6×150 mm) (Daicel) column, an aqueous 10% MeOH in $HClO_4$ (pH 2) (0.8 mL/min), 254 nm, 20 µL loop; 94.7% purity.

Boc$_2$-4-[^{18}F]FPhe-O*t*Bu ([^{18}F]**7a**) and Boc-4-[^{18}F]FPhe-O*t*Bu ([^{18}F]**7b**) (TLC):

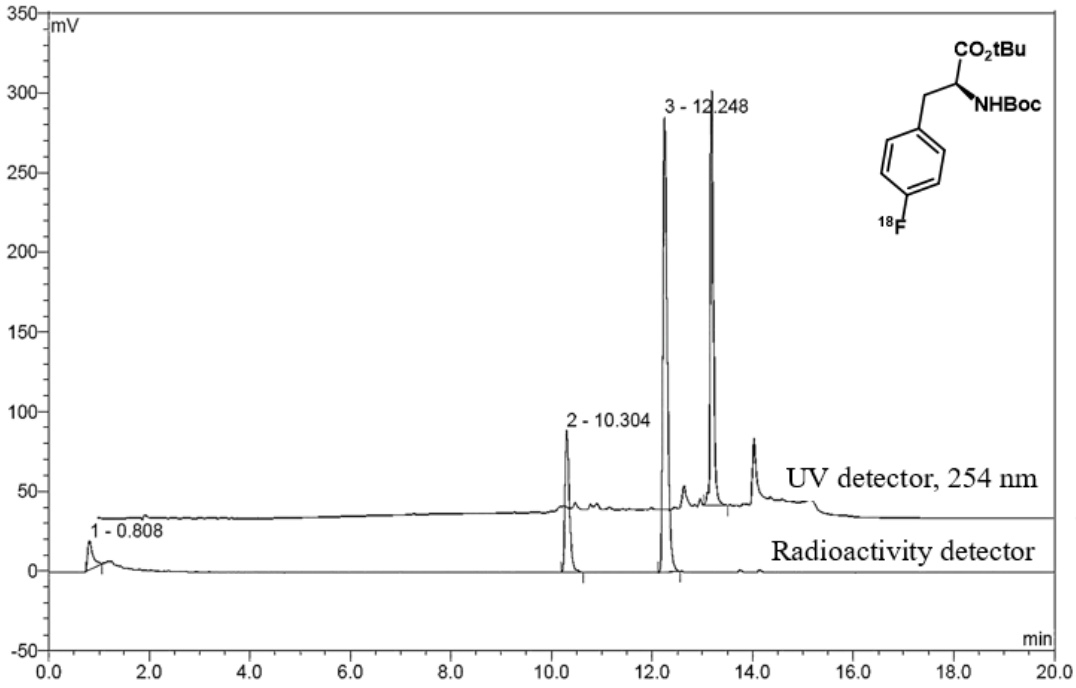


Boc$_2$-4-[^{18}F]FPhe-O*t*Bu ([^{18}F]**7a**) (HPLC):



Boc$_2$-4-[^{18}F]FPhe-O*t*Bu ([^{18}F]**7a**), X-Bridge C18 column 5 µm, 150×4.6 mm (Waters), 0–2 min: 5% MeCN, 2–13 min: 5→90% MeCN (2.0 mL/min).

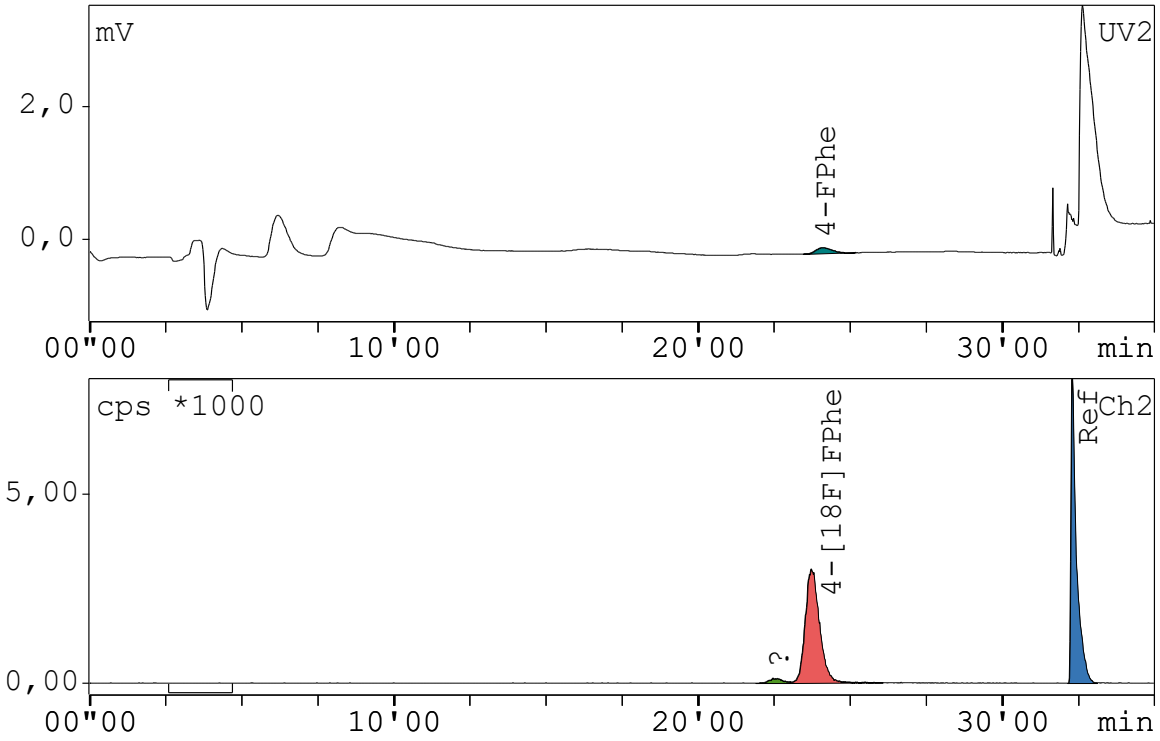
Boc-4-[^{18}F]FPhe-O*t*Bu ([^{18}F]**7b**) (HPLC):



Boc-4-[^{18}F]FPhe-O*t*Bu ([^{18}F]**7b**) and the reference compound, HPLC on X-Bridge C18 column 5 µm, 150×4.6 mm (Waters), 0–2 min: 5% MeCN, 2–13 min: 5→90% MeCN (2.0 mL/min), UV detection: 254 nm, injection loop: 20 µL.

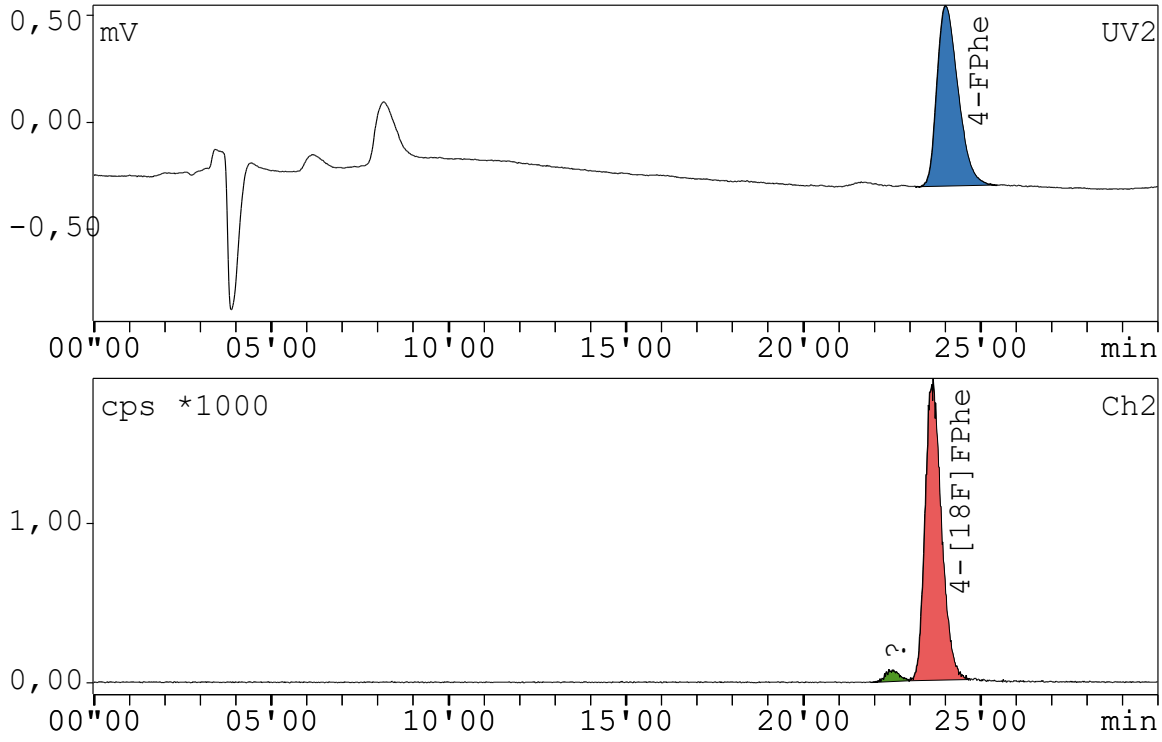
Compound	k'	R_t
[^{18}F]**7a**	16.1	00:13:42
[^{18}F]**7b**	14.3	00:12:12
Dead time		00:00:50

4-[^{18}F]FPhe after HPLC purification: Quality control:



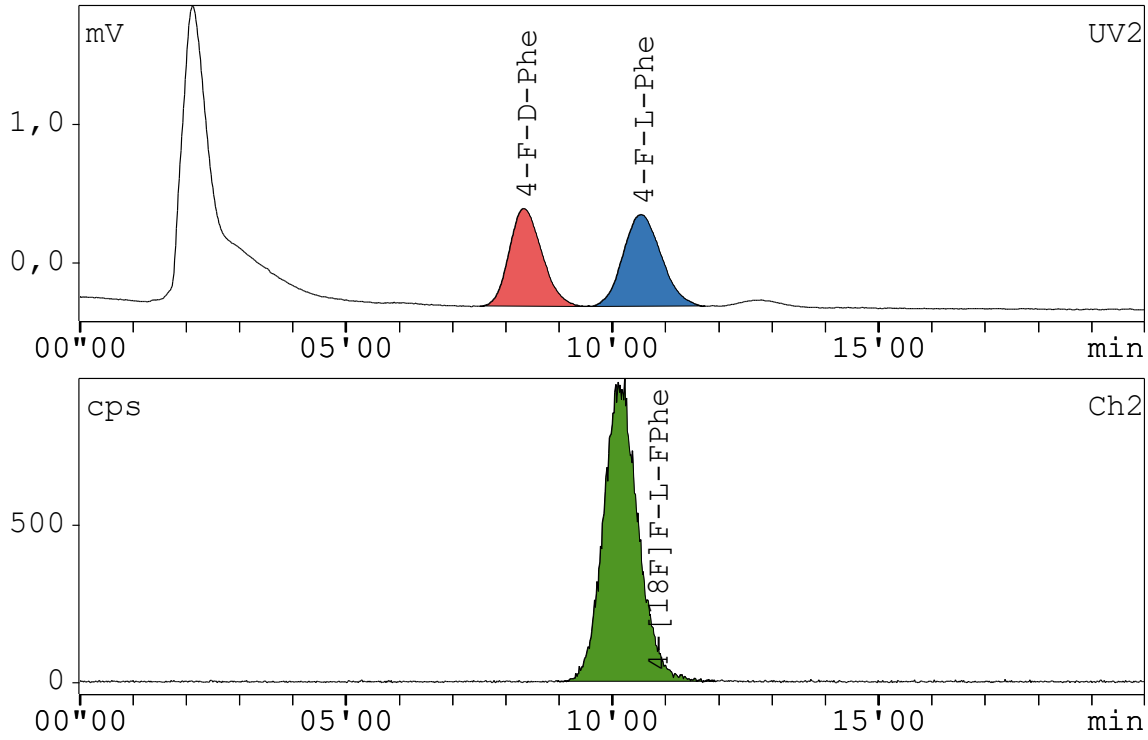
Synergy Hydro-RP (4.6×250 mm), 6% EtOH (1.0 mL/min), 210 nm, 20 µL loop.

4-[^{18}F]FPhe after HPLC purification: Spiking with the reference compound:



Synergy Hydro-RP (4.6×250 mm), 6% EtOH (1.0 mL/min), 210 nm, 20 µL loop.

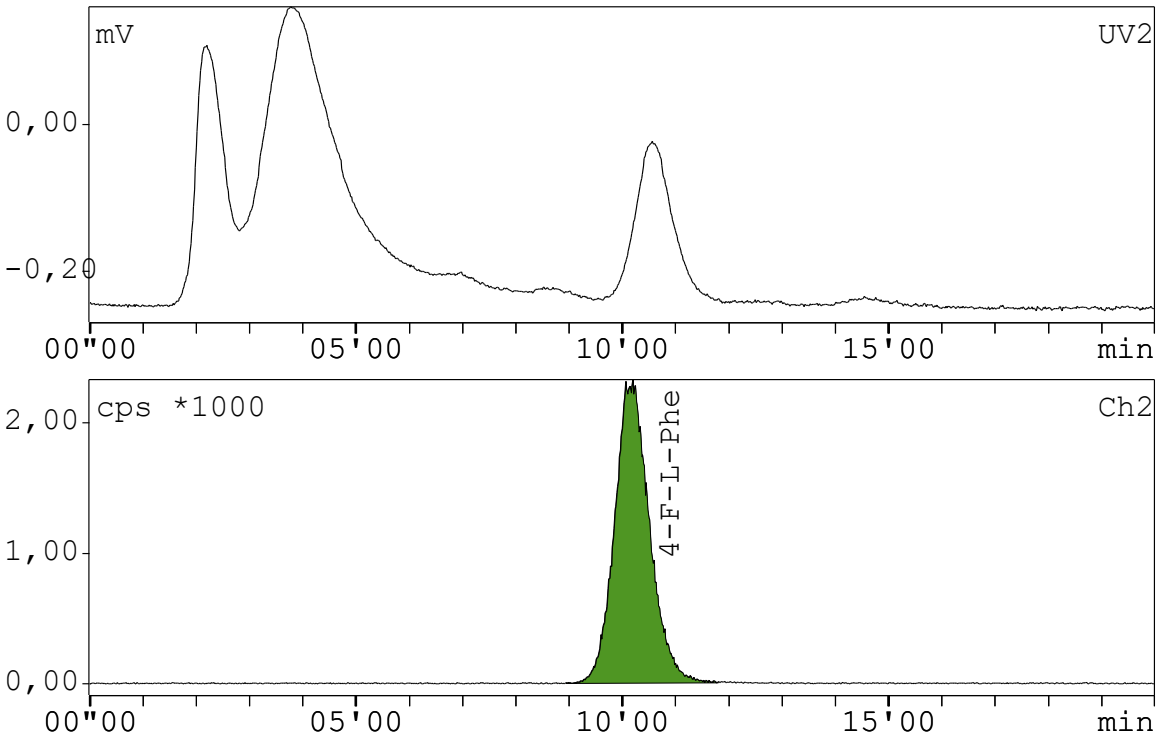
Reference compounds: (*S*)- and (*R*)-4-FPhes:



Crownpak (+) (4.6×150 mm), 0.025 M $HClO_4$ (1.0 mL/min), 210 nm, 20 µL loop.

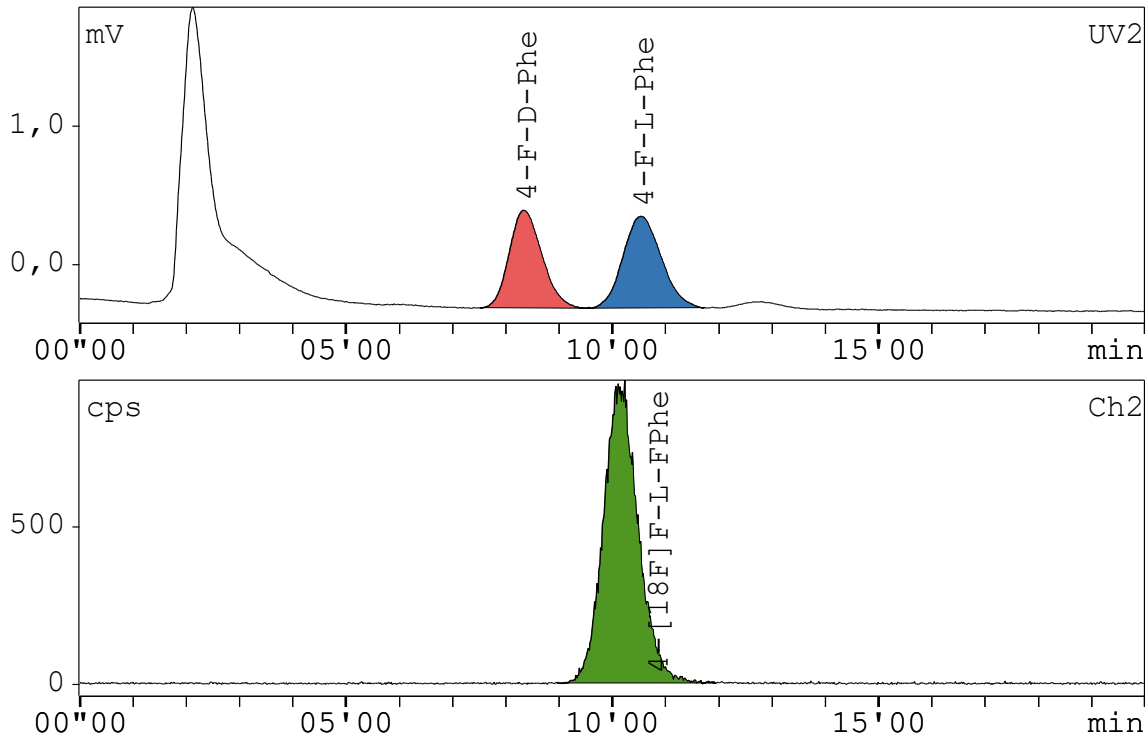
Compound	K'	R_t
(*R*)-4-FPhe	3.0	00:08:16
(*S*)-4-FPhe	4.1	00:10:30
Dead time		00:02:05

4-[^{18}F]FPhe after HPLC purification: Determination of enantiomeric purity, quality control:



Crownpak (+) (4.6×150 mm), 0.025 M $HClO_4$ (1.0 mL/min), 210 nm, 20 µL loop.

4-[^{18}F]FPhe after HPLC purification: Determination of enantiomeric purity, spiking with (*S*)- and (*R*)-4-FPhes:



Crownpak (+) (4.6×150 mm), 0.025 M $HClO_4$ (1.0 mL/min), 210 nm, 20 µL loop.