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Labeling of highly reactive tetrazines using [^{18}F]SuFEx

Umberto M. Battisti[#a], Marius Müller[#a,b], Rocío García-Vázquez[a,b], Matthias Manfred Herth*[a,b]

[a]Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Jagtvej 160, 2100 Copenhagen; [b]Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark

*Corresponding Author: matthias.herth@sund.ku.dk; Phone: +45 35 33 66 24

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Synthesis

General

Materials. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. All solvents were analytical or HPLC grade and used as received. NMR spectra were acquired on a 600 MHz Bruker Avance III HD (600 MHz for ^{1}H and 151 MHz for ^{13}C) and a 400 MHz Bruker Avance UltraShield (400 MHz for ^{1}H, 376 MHz for ^{19}F and 101 MHz for ^{13}C), using $CDCl_3$, MeOD or DMSO-d_6 as deuterated solvent and with the residual solvent as the internal reference. NMR spectra of all compounds were reprocessed in MestReNova software (version 12.0.22023) from original FID's files. Yields refer to isolated compounds estimated to be >90% pure as determined by ^{1}H NMR (25 °C) and analytical HPLC. Analytical HPLC method: Thermo Fisher UltiMate 3000 with a C-18 column (Luna 5 µm C18(2) 100 Å, 150 mm × 4.6 mm). Eluents: A, H_2O with 0.1% TFA; B, MeCN with 0.1% TFA. Gradient from 100% A to 100% B over 12 min, back to 100% A over 3 min, flow rate 2 mL/min. Detection by UV absorption at $\lambda = 254$ nm on a UVD 170U detector. Thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates from Merck (Germany). Visualization was accomplished by UV lamp (254 nm). Data were acquired and processed using Chromeleon Software v. 6.80. Semi-preparative HPLC was performed on the same system using a Luna 5µ C18 column (250 × 10 mm) with a flow rate of 3 mL/min. Automated Flash Column Chromatography was performed on a CombiFlash NextGen 300+ system supplied by TeleDyne ISCO, equipped with RediSep silica packed columns. Mass spectra analysis was completed using MS-Acquity-A: Waters Acquity UPLC with QDa-detector.

*Synthesis of 4-(1,2,4,5-tetrazin-3-yl)phenyl sulfurofluoridate (**1**)*

The first step was performed following the literature procedure.[1] 4-Hydroxybenzonitrile (0.71 g, 6.00 mmol), CH_2Cl_2 (6.00 mmol, 0.38 mL), sulfur (0.38 g, 1.50 mmol) and ethanol (4.0 mL) were mixed together in a 20 ml microwave reaction tube. Hydrazine monohydrate (2.3 mL, 48.00 mmol) was added slowly with stirring afterwards. The vessel was sealed, and the reaction mixture was heated to 50 °C for 24 hours. Then 3 mL of CH_2Cl_2 and sodium nitrite (4.13 g, 60.00 mmol) in 50 ml of H_2O were added to the mixture. Excess acetic acid (21 mL) was then added slowly during which the solution turned bright red in color. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified using flash chromatography (75/25 Heptane/EtOAc) to yield 0.35 g (33%) of 4-(1,2,4,5-tetrazin-3-

yl)phenol (**3**) as a red solid. Rf = 0.28 (n-Heptane/EtOAc 70/30); ^{1}H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 10.42 (s, 1H), 8.38 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ 165.8, 162.5, 158.0, 130.3, 122.8, 116.9; HPLC-MS [M+H]+ m/z calc. for $[C_8H_7N_4O]^+$: 175.0; found: 175.1.

The second step was performed following the literature procedure.[2] Compound **3** (0.1 g, 0.57 mmol) and TEA (0.39 mL, 2.87 mmol) were solubilized in CH_2Cl_2/methanol (V/V=10:1, 10.0 mL). The flask was sealed by a rubber septum, evacuated to vacuum, and backfilled with sulfuryl fluoride gas (ABCR chemicals) via a balloon. The resulting mixture was stirred at room temperature for 3 days. All the volatiles were then removed under reduced pressure. The resulting residue was purified using flash chromatography (95/5 Heptane/EtOAc) to yield 0.035 g (24%) of 4-(1,2,4,5-tetrazin-3-yl)phenyl sulfurofluoridate (**1**) as a red solid. Rf = 0.32 (n-Heptane/EtOAc 90/10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.80 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.0, 159.9, 154.9, 133.9, 132.4, 123.8; HPLC-MS [M+H]+ m/z calc. for $[C_8H_6FN_4O_3S]^+$: 257.0; found: 257.0.

*Synthesis of 6-(6-(pyridin-2-yl)-1,2,4,5-tetrazin-3-yl)pyridin-3-yl sulfurofluoridate (**2**)*

The first step was performed following the literature procedure.[3] 5-Hydroxypicolinonitrile (0.50 g, 4.16 mmol), 2-pyridinecarbonitrile (2.17 g, 20.81 mmol), and sulfur (0.27 g, 1.04 mmol) were suspended in EtOH (10 mL), followed by the addition of hydrazine hydrate (3.04 mL, 62.44 mmol). The reaction was heated to 90 °C for 3 h. The volatiles were then removed under reduced pressure. The residue was solubilized in CH_2Cl_2 followed by an addition of a solution of $NaNO_2$ (1.0 g, 14.62 mmol) in 20 mL of water. The mixture was then cautiously acidified to pH 2 by addition of glacial AcOH. After stirring for 10 minutes at room temperature the suspension was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated under reduce pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 95/5) to give 0.26 g (25%) of 6-(6-(pyridin-2-yl)-1,2,4,5-tetrazin-3-yl)pyridin-3-ol (**4**) as a pink solid. Rf = 0.24 (CH_2Cl_2/MeOH 97/3); ^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 8.93 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.58 (d, *J* = 7.9 Hz, 1H), 8.53 (d, *J* = 8.7 Hz, 1H), 8.47 (d, *J* = 2.8 Hz, 1H), 8.15 (td, *J* = 7.8, 1.8 Hz, 1H), 7.72 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.47 (dd, *J* = 8.7, 2.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 163.4, 163.3, 157.0, 151.0, 150.7, 141.1, 140.0, 138.2, 126.9, 126.3, 124.5, 123.3; HPLC-MS [M+H]+ m/z calc. for $[C_{12}H_9N_6O]^+$: 253.2; found: 253.1.

The second step was performed following the literature procedure.[2] Compound **4** (0.1 g, 0.39 mmol) and TEA (0.27 mL, 1.98 mmol) were solubilized in CH_2Cl_2/MeOH (V/V=10:1, 10.0

mL). The flask was sealed by a rubber septum, evacuated to vacuum, and backfilled with sulfuryl fluoride gas (ABCR chemicals) via a balloon. The resulting mixture was stirred at room temperature for 1 day. All the volatiles were then removed under reduced pressure. The resulting residue was purified using flash chromatography (CH_2Cl/MeOH 99/1) to yield 0.045 g (34%) of 6-(6-(pyridin-2-yl)-1,2,4,5-tetrazin-3-yl)pyridin-3-yl sulfurofluoridate (**2**) as a red solid. Rf = 0.44 (CH_2Cl_2/MeOH 99/1); ^1H NMR (600 MHz, $CDCl_3$) δ 9.01 – 8.89 (m, 2H), 8.86 (d, *J* = 8.7 Hz, 1H), 8.71 (d, *J* = 7.7 Hz, 1H), 8.03 – 7.92 (m, 2H), 7.59 – 7.49 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.9, 162.9, 151.2, 150.2, 149.7, 148.7, 143.8, 137.6, 130.1, 126.9, 125.8, 124.8; HPLC-MS [M+H]+ m/z calc. for $[C_{12}H_8FN_6O_3S]^+$: 335.0; found: 335.0.

Synthesis of TCO-PNB carbonate

The compound was synthesized as previously described.[4] Trans-Cyclooct-4-enol (1.00 g, 7.92 mmol, 1.0 eq.) and DIPEA (3.07 g, 4.14 ml, 23.8 mmol, 3.0 eq.) were dissolved in dry THF (0.3 M, 26 ml). The resulting solution was added dropwise at 0 °C to a solution of 4-nitrophenyl chloroformate (4.79 g, 23.8 mmol, 3.0 eq.) in dry THF (0.3 M, 26 ml) over a period of 2 h. The reaction mixture was allowed to warm up to RT and stirred overnight. EtOAc (50 ml) was added and insoluble components were filtered off over a celite pad 545. The filtrate was then washed with H_2O (50 ml), and saturated NaCl solution (50 ml). Subsequently, the remaining organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (n-heptane/EtoAc 95/5) to give 0.41 g (19%) of a white solid (major isomer). ^1H NMR (600 MHz, $CDCl_3$) δ 8.24 – 8.14 (m, 2H), 7.33 – 7.26 (m, 2H), 5.55 (ddd, *J* = 15.2, 10.9, 3.8 Hz, 1H), 5.43 (ddd, *J* = 16.1, 11.0, 3.6 Hz, 1H), 4.39 (ddd, *J* = 11.0, 4.5, 1.9 Hz, 1H), 2.33 (tdq, *J* = 17.4, 11.8, 5.6 Hz, 3H), 2.15 – 2.00 (m, 2H), 1.92 (dtt, *J* = 16.6, 11.3, 5.6 Hz, 2H), 1.86 – 1.79 (m, 1H), 1.74 – 1.60 (m, 2H), ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.7, 150.9, 133.8, 132.0, 124.2, 120.8, 85.4, 39.7, 37.3, 33.1, 31.4, 30.1.

Radiochemistry

General

$[^{18}F]$Fluoride was produced via the (p,n)-reaction in a cyclotron (60 mikroA CTI Siemens or 40 mikroA Scanditronix) by irradiating $[^{18}O]H_2O$ with a 11 MeV (CTI siemens) or 16 MeV (Scanditronix) proton beam. Analytical HPLC was performed on a Dionex system connected to a P680A pump, a UVD 170U detector and a Scansys radiodetector. The system was controlled by Chromeleon software. Analytical HPLC method: Thermo Fisher Ultimate with a C-18 column (Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm and Luna 5 µm PFP(2) 90 Å 150 x 4.6 mm. Eluents: A, H_2O with 0.1 % TFA; B, MeCN with 0.1 % TFA. Gradient from 100 % A to 100 % B over 12 min, back to 100 % A over 3 min, flowrate 2 mL/min. Detection by UV absorption at delta = 254 nm on a UVD 170 U detector.

Radiochemical conversion (RCC) of all radiolabeled compounds was determined by analyzing a labelled aliquot of the reaction mixture by radio-HPLC and analyzed by integrating the radioactive peaks from the reaction solution. The products were characterized by comparing the radio-HPLC trace of the reaction mixture with the HPLC UV traces of the authentic ^{19}F-reference samples, respectively.

The radiochemical yield (RCY) was determined using the activity of $[^{18}F]$fluoride received from the cyclotron at the beginning of the synthesis and that of the formulated product at the end of the synthesis, the decomposition was corrected and have been decay corrected (d.c.). The molar activity (A_m) was determined by integrating the area of the UV absorbance peak corresponding to the radiolabeled product on the HPLC chromatogram. This area was converted into a molar mass by comparison with an average of integrated areas (triplet) of a known concentration for the corresponding reference compounds. The values for radiochemical yield (RCY), radiochemical purity (RCP) and molar activity (A_m) are given as mean values. This applies for all radiolabeled compounds described below.

Preparation of anhydrous $[^{18}F]F$ fluoride for radiolabeling:

QMA anion exchange cartridge (Sep-Pak Accel Plus QMA Plus Light, chloride form, Waters) was washed with EtOH (10 mL), 0.5 M K_3PO_4 (10 mL), H_2O (10 mL), and dried with air (10 mL) before use. Irradiated $[^{18}O]H_2O$ containing $[^{18}F]F^-$ was passed through the preconditioned QMA anion exchange cartridge. $[^{18}F]F$ trapped on the QMA anion exchange cartridge was then eluted with a mixture of 20 nM tetrabutyl ammonium salt (Bu_4NOMs or Bu_4NOTf) in MeOH (1 mL). The resulting mixture was then concentrated to dryness at 100 degrees under a continuous stream of nitrogen for 15 min to give $[^{18}F]Bu_4NF$ as a colourless oil. The

[^{18}F]Bu_4NF was then cooled to room temperature under a continuous stream of nitrogen for 5 min.

*Manual Synthesis of [^{18}F]-4-(1,2,4,5-tetrazin-3-yl)phenyl sulfurofluoridate ([^{18}F]**1**)*

To the dry [^{18}F]fluoride was added a mixture of compound **1** (0.0027 g and 0.0099 mmol) in dry MeCN (0.5 mL). The reaction was left at room temperature, and quenched with H_2O (0.1 mL) after 5 min. Aliquots of the reaction were taken after 1 and 5 min. The aliquots were added to H_2O + 0.1 % TFA (0.1 mL) and analyzed by radio-HPLC.

*Manual Synthesis of [^{18}F]-6-(6-(pyridin-2-yl)-1,2,4,5-tetrazin-3-yl)pyridin-3-yl sulfurofluoridate ([^{18}F]**2**)*

To the dry [^{18}F]fluoride was added a mixture of compound **2** (0.0033 g and 0.0099 mmol) in dry DMF (0.5 mL). The reaction was left at room temperature, and quenched with H_2O (0.1 mL) after 10 min. Aliquots of the reaction were taken after 1 and 5 min. The aliquots were added to H_2O + 0.1 % TFA (0.1 mL) and analyzed via radio-HPLC.

*General procedure for automated synthesis of [^{18}F]**1** and [^{18}F]**2***

Automated synthesis was performed on a Scansys Laboratorieteknik synthesis module. The same procedure was used as in the manual synthesis with minor differences. A solution of either **1** (0.5 µmol, 0.13 mg) in dry MeCN (0.5 mL) or **2** (0.5 µmol, 0.17 mg) in dry DMF (0.5 mL) was added to the reaction vial containing the dried [^{18}F]Bu_4NF (5.0 – 6.0 GBq), after being cooled with compressed air to room temperature for 8 min. The reaction was left at room temperature for 30 sec, before being immediately quenched with 0.3 mL of H_2O + 0.1 % TFA. The crude reaction was then purified via semi-preparative HPLC (Thermo Fisher UltiMate 300) with a C-18 column (Luna 5 µm C18(2) 100 Å, 250 mm x 10 mm) used an isocratic method (for [^{18}F]**1**: 60 % MeCN in H_2O + 0.1 % TFA; for [^{18}F]**2**: 40 % MeCN in H_2O + 0.1 % TFA; flowrate 4 mL/min, R_t = 550 sec ([^{18}F]**1**), 708 sec ([^{18}F]**2**) (Figure S1, Figure S2).

Formulation of [^{18}F]**1** and [^{18}F]**2** proceeded by diluting the collected fraction with Milli-Q H_2O (1:20) and trapping the resulting solution on a C18 Solid Phase Extraction catridge (Sep-Pak® Light C18 Cartridges, Waters). Subsequently, the C18 Solid Phase Extraction cartridge was was washed with Milli-Q H_2O (7 mL), and [^{18}F]**1** and [^{18}F]**2** were eluted with EtOH (1 mL), followed by the concentration under continuous N_2 flow at r.t. for 12 min. The resulting dry [^{18}F]**1** and [^{18}F]**2** was dissolved in Phosphate buffer (pH = 7.2, 17.8 mg/mL disodium hydrogenphosphate dehydrate, 10.15 mg/ml hydrogen chloride RAP, in water) resulting in activity concentration of 100 MBq/mL.

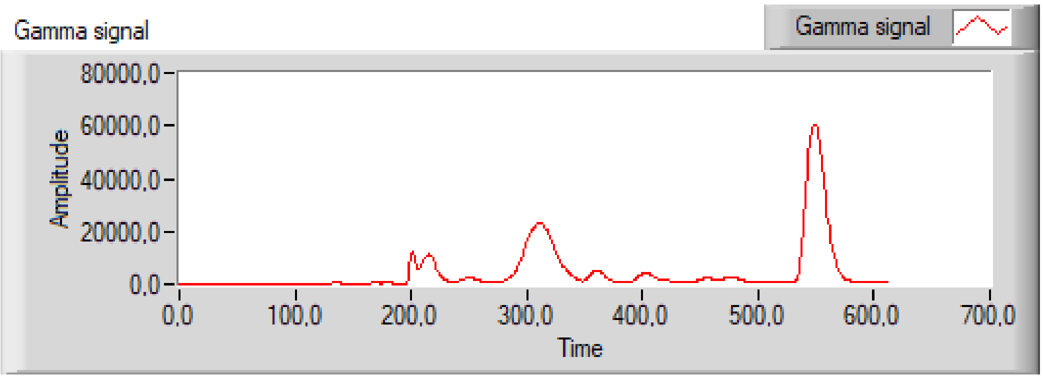


Figure S1. Radiotrace chromatogram from semipreparative HPLC purification of [^{18}F]**1** with a C-18 column (Luna 5 µm C18(2) 100 Å, 250 mm x 10 mm) using an isocratic method (60 % MeCN in H_2O + 0.1 % TFA) and a flow rate of 4 mL/min (R_t = 550 sec).

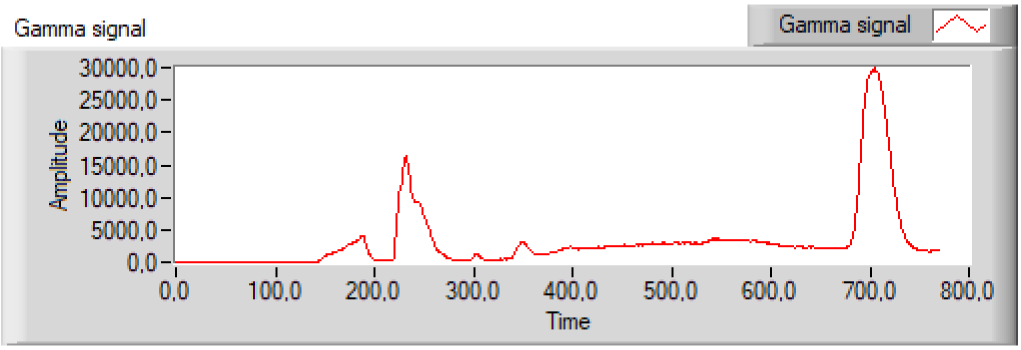


Figure S2. Radiotrace chromatogram from semipreparative HPLC purification of [^{18}F]**2** with a C-18 column (Luna 5 µm C18(2) 100 Å, 250 mm x 10 mm) using an isocratic method (40 % MeCN in H_2O + 0.1 % TFA) and a flow rate of 4 mL/min (R_t = 708 sec).

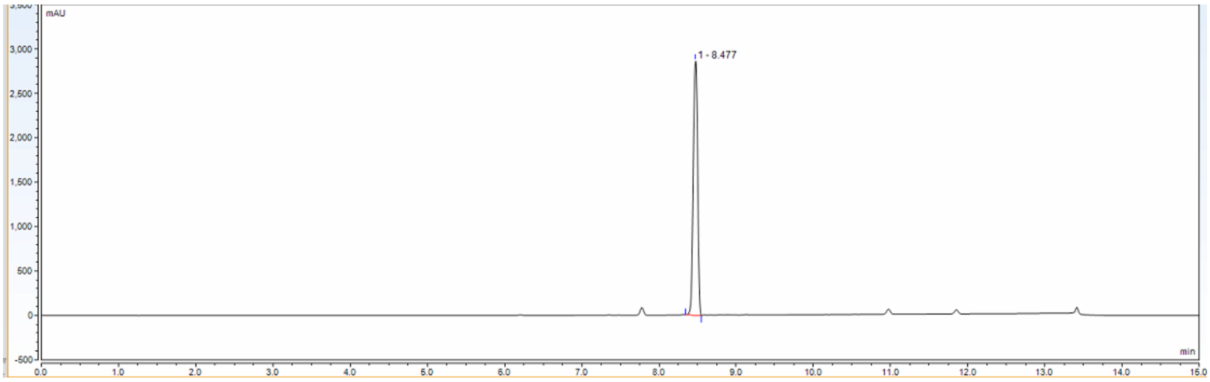


Figure S3. Analytical HPLC of reference compound **1** (UV/Vis 254 nm). HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.

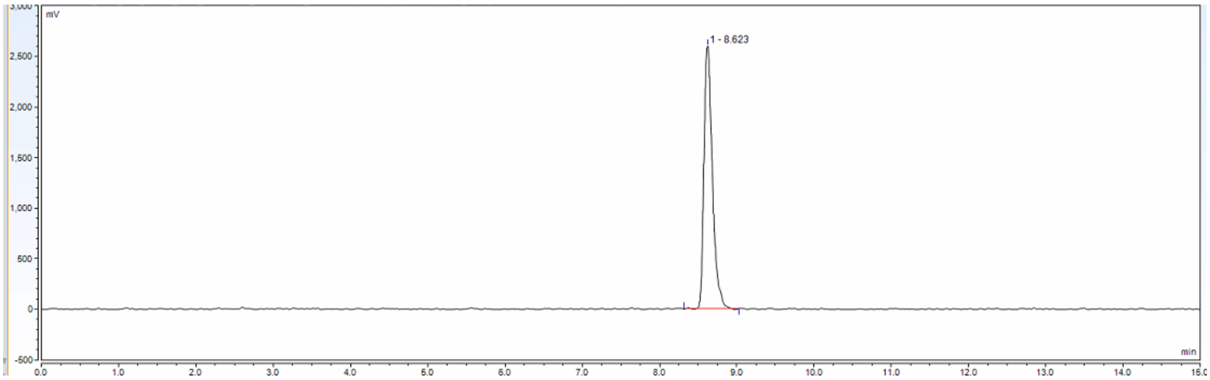
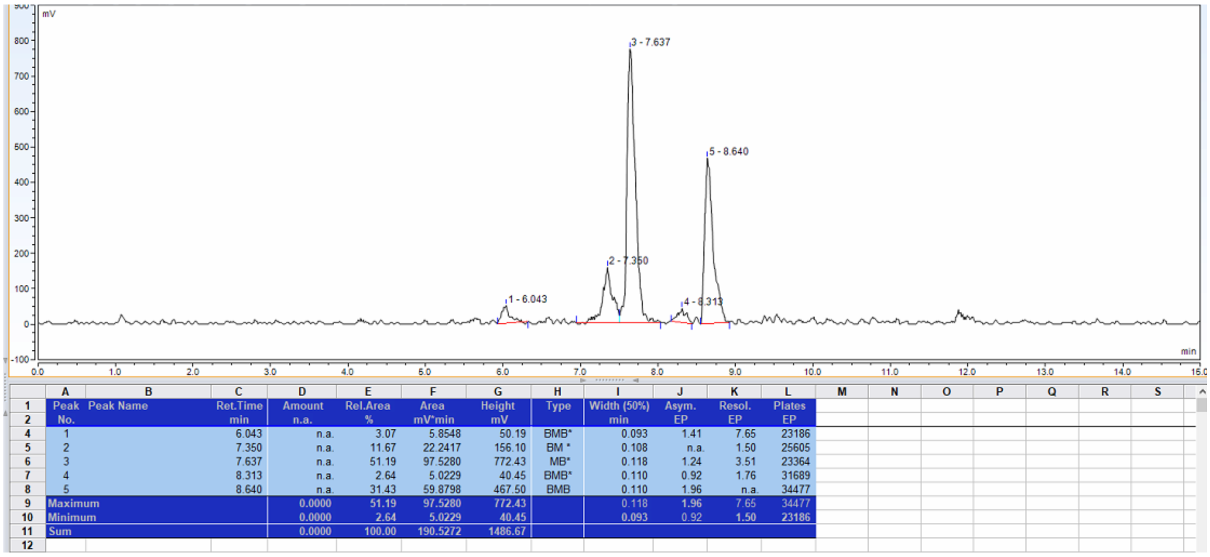


Figure S4. Radio-HPLC of purified [^{18}F]**1**. HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.



	A	B	C	D	E	F	G	H	I	J	K	L
1–2	Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
4	1		6.043	n.a.	3.07	5.8548	50.19	BMB*	0.093	1.41	7.65	23186
5	2		7.350	n.a.	11.67	22.2417	156.10	BM *	0.108	n.a.	1.50	25605
6	3		7.637	n.a.	51.19	97.5280	772.43	MB*	0.118	1.24	3.51	23364
7	4		8.313	n.a.	2.64	5.0229	40.45	BMB*	0.110	0.92	1.76	31689
8	5		8.640	n.a.	31.43	59.8798	467.50	BMB	0.110	1.96	n.a.	34477
9	Maximum			0.0000	51.19	97.5280	772.43		0.118	1.96	7.65	34477
10	Minimum			0.0000	2.64	5.0229	40.45		0.093	0.92	1.50	23186
11	Sum			0.0000	100.00	190.5272	1486.67					
12												

Figure S5. Radio-HPLC of the stability analysis of purified and in phosphate buffer (pH = 7.2) formulated [^{18}F]**1** after 4 h (R_t = 8.640 min; RCP = 31.43 %). HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.

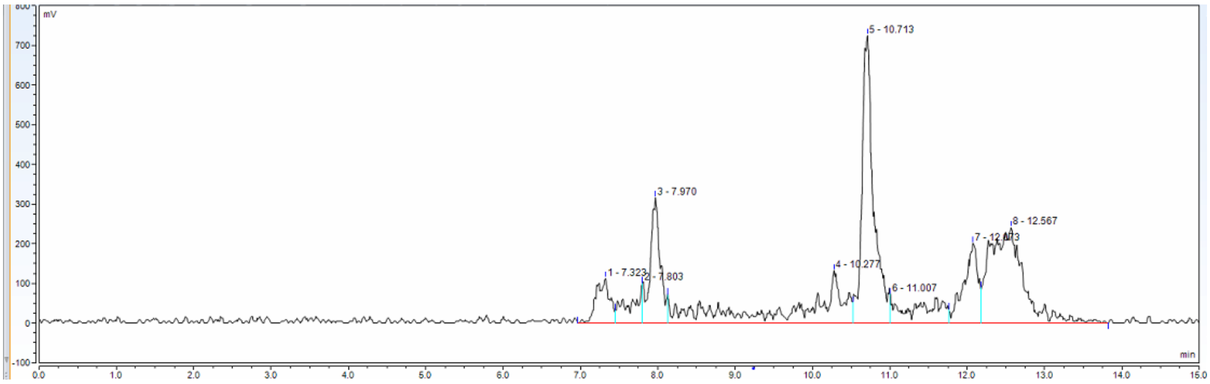


Figure S6. Radio-HPLC of the click-reaction of purified [^{18}F]**1** with the TCO-PNB ester (NMR shown below) after 0 h. HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.

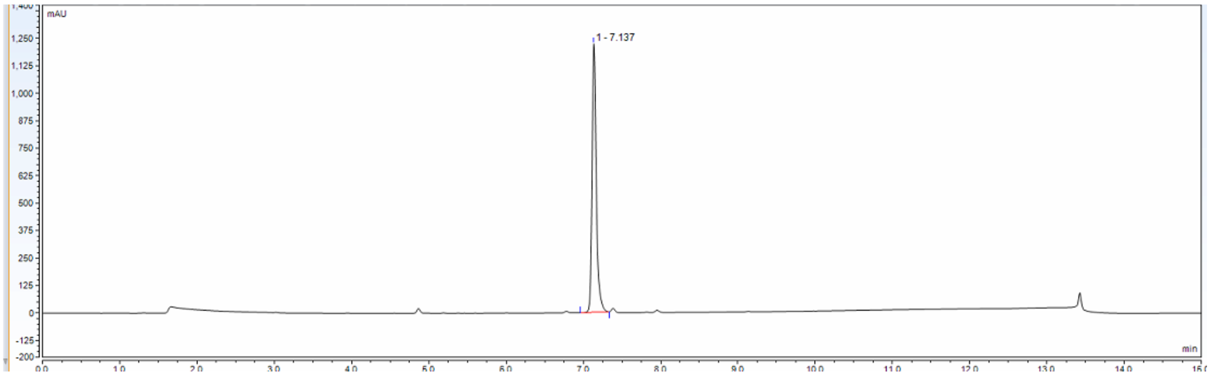


Figure S7. Analytical HPLC of reference compound **2** (UV/Vis 254 nm). HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.

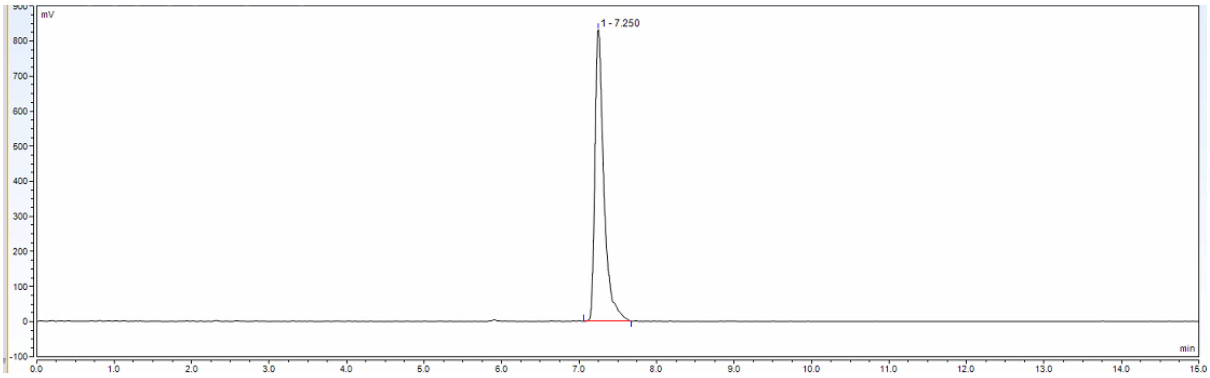
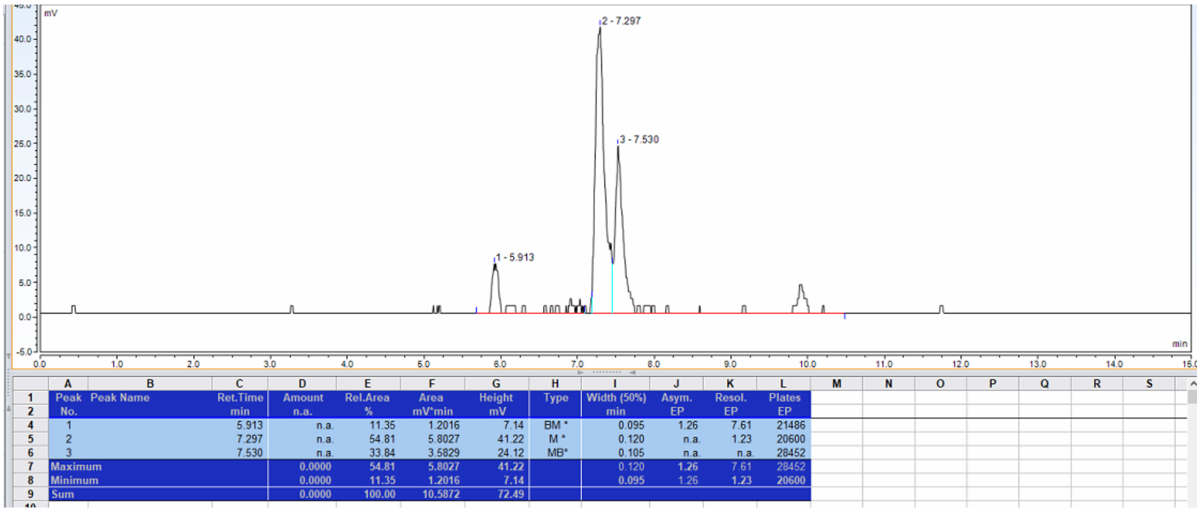


Figure S8. Radio-HPLC of purified [^{18}F]**2**. HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.



	A	B	C	D	E	F	G	H	I	J	K	L
1 2	Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
4	1		5.913	n.a.	11.35	1.2016	7.14	BM *	0.095	1.26	7.61	21486
5	2		7.297	n.a.	54.81	5.8027	41.22	M *	0.120	n.a.	1.23	20600
6	3		7.530	n.a.	33.84	3.5829	24.12	MB*	0.105	n.a.	n.a.	28452
7	Maximum			0.0000	54.81	5.8027	41.22		0.120	1.26	7.61	28452
8	Minimum			0.0000	11.35	1.2016	7.14		0.095	1.26	1.23	20600
9	Sum			0.0000	100.00	10.5872	72.49					

Figure S9. Radio-HPLC of the stability analysis of purified and in phosphate buffer (pH = 7.2) formulated [^{18}F]**2** after 4 h (R_t = 7.297 min; RCP = 54.81 %). HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.

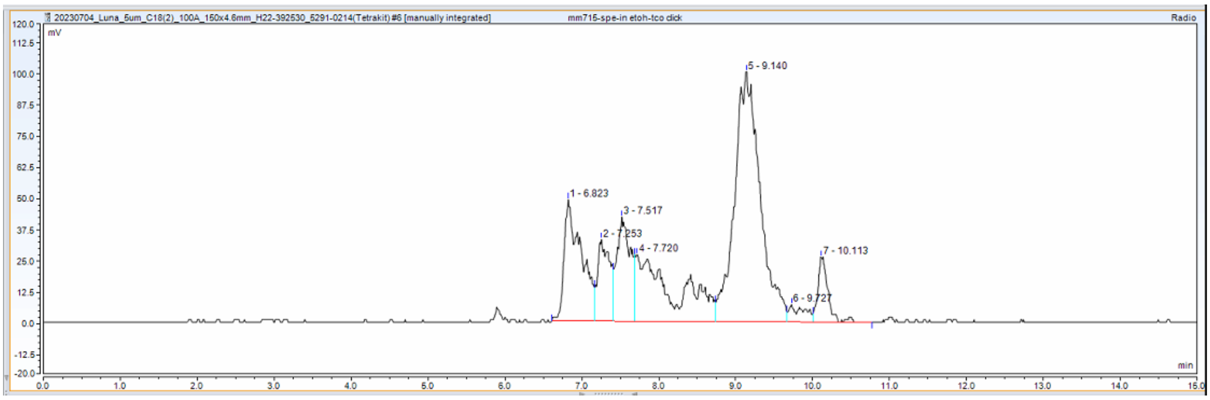
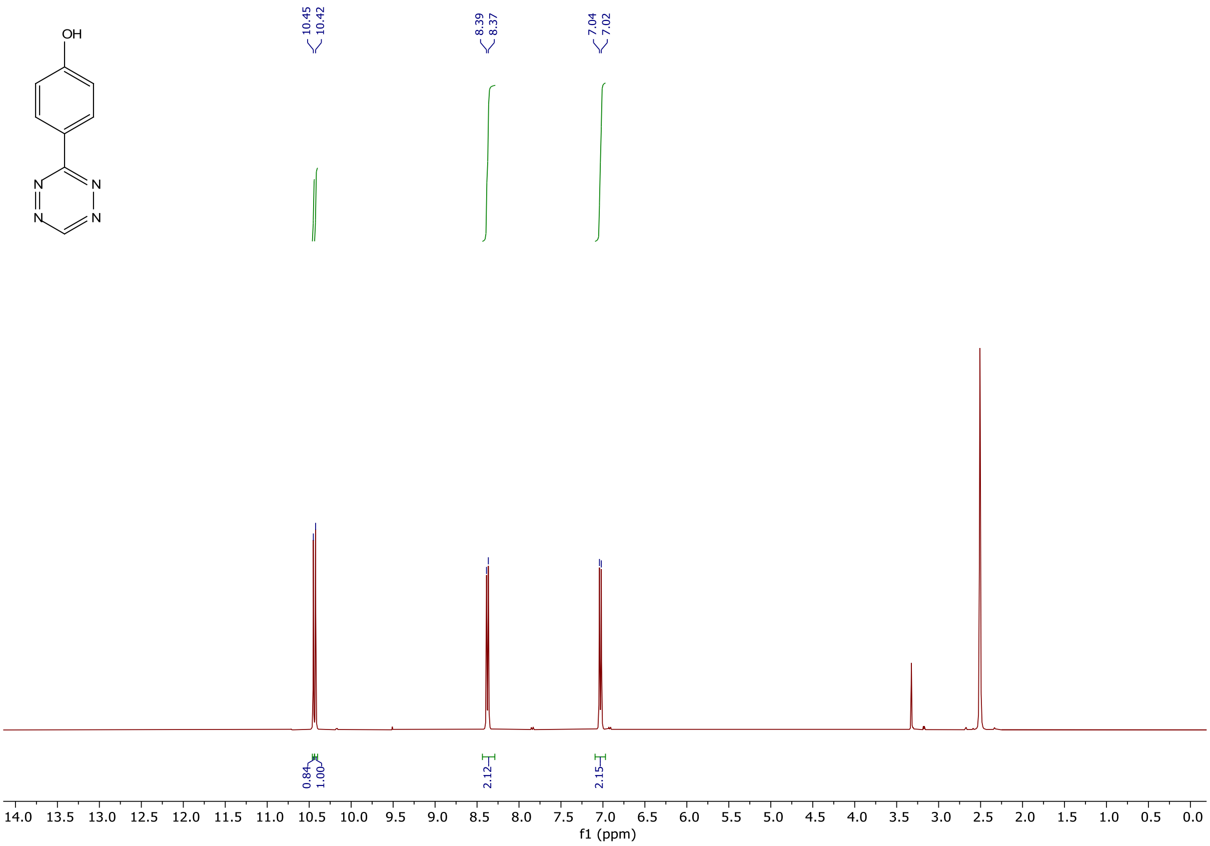
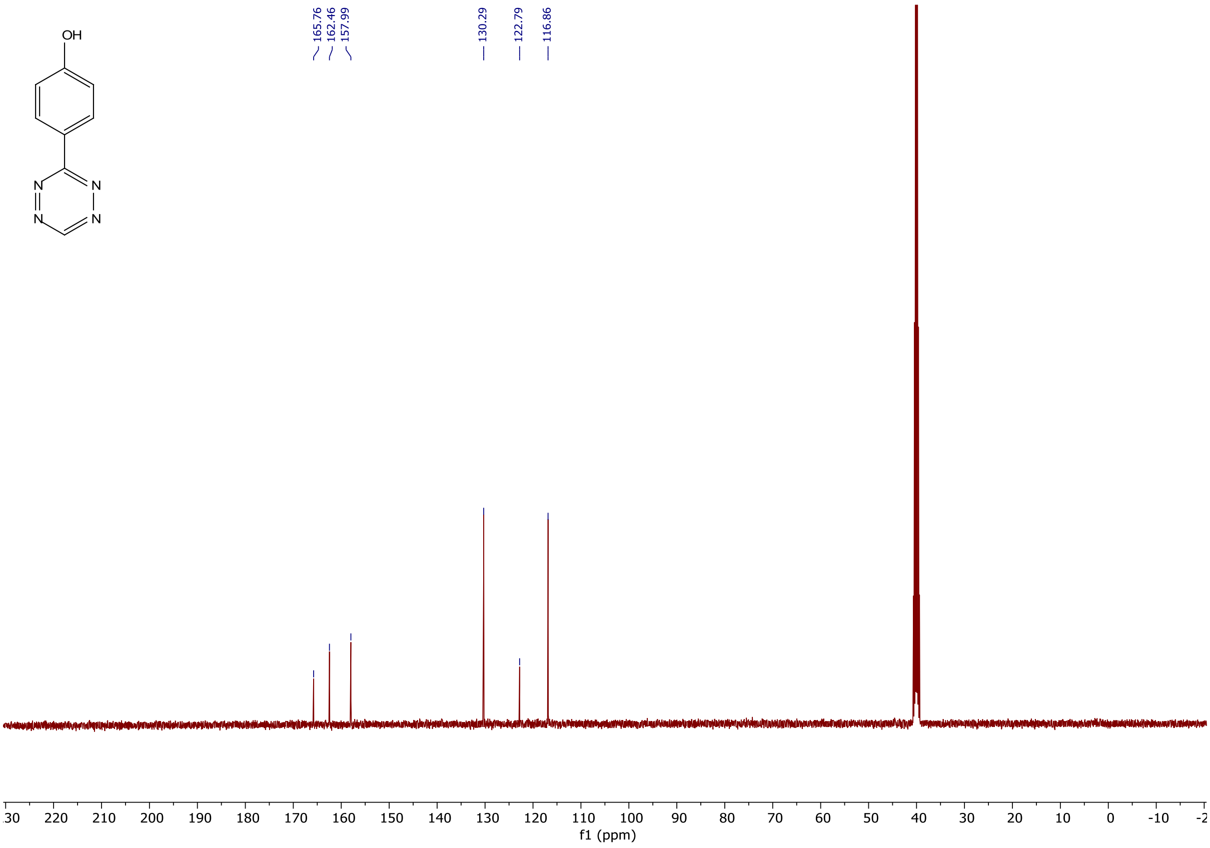


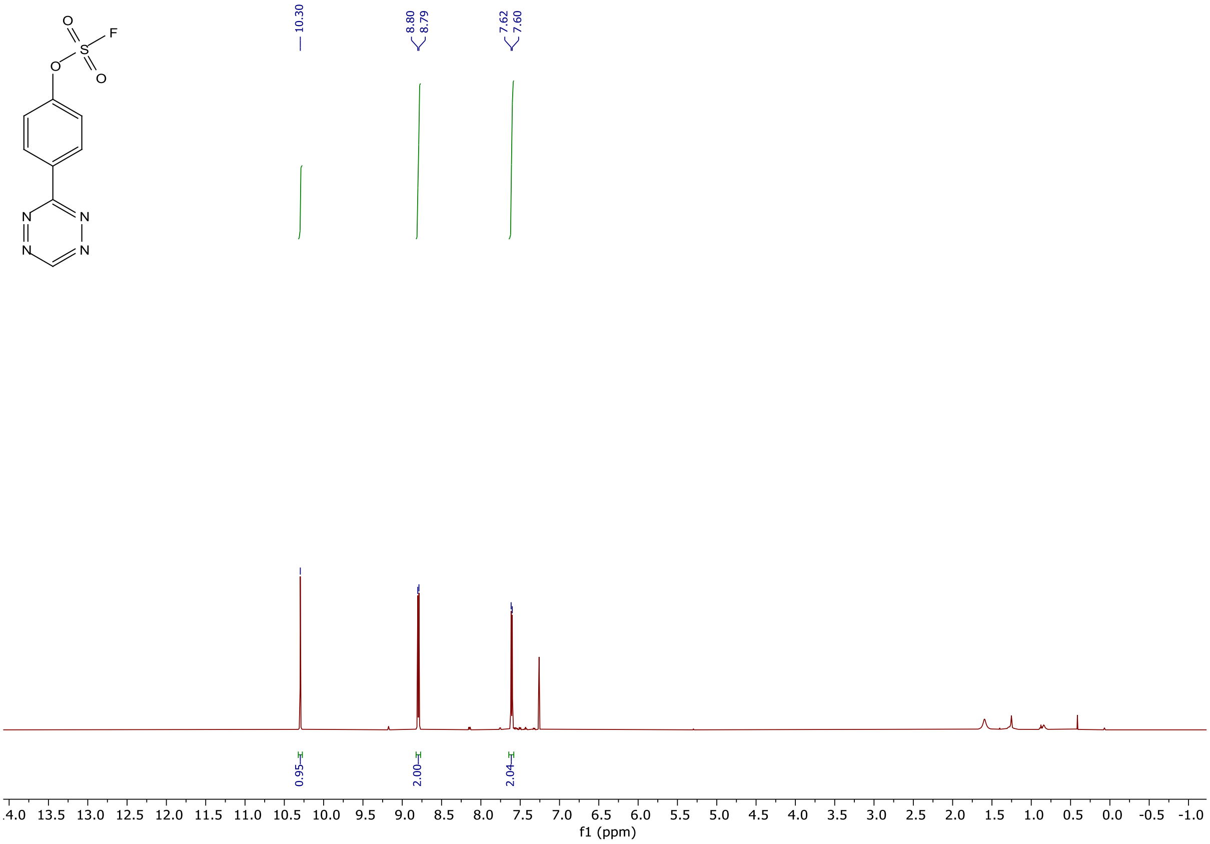
Figure S10. Radio-HPLC of the click-reaction of purified [^{18}F]**2** with the TCO-PNB ester (NMR shown below) after 0 h. HPLC conditions: Luna 5 µm C18(2) 100 Å, 150 mm x 4.6 mm eluted with a gradient of MeCN: with 0.1 % v/v TFA (solvent B) in water with 0.1 % TFA (solvent B) at 2 mL/min. Gradient: 0-1 min – 0 %B, 1-11 min – 100 % B, 12-13 min – 100 %, 13-15 min – 0 % B.

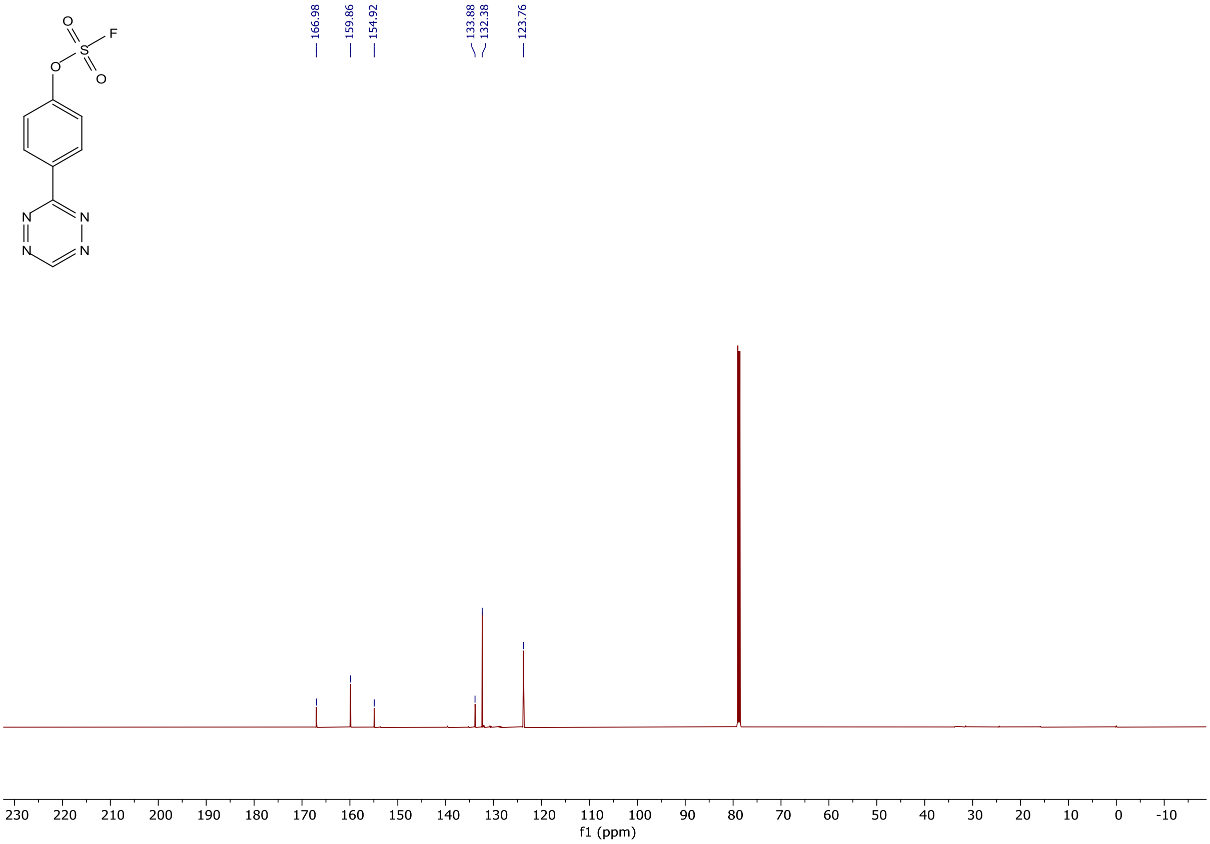
4-(1,2,4,5-tetrazin-3-yl)phenol (**3**)



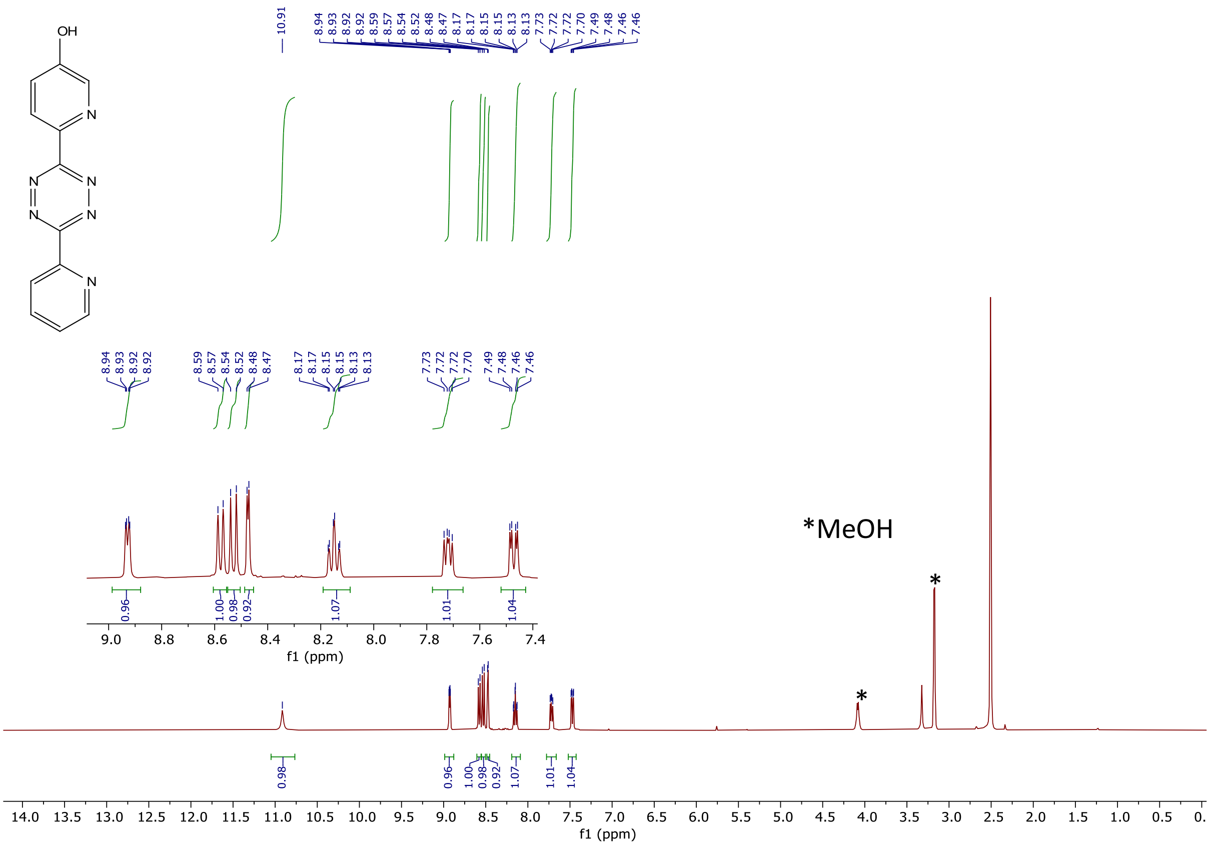


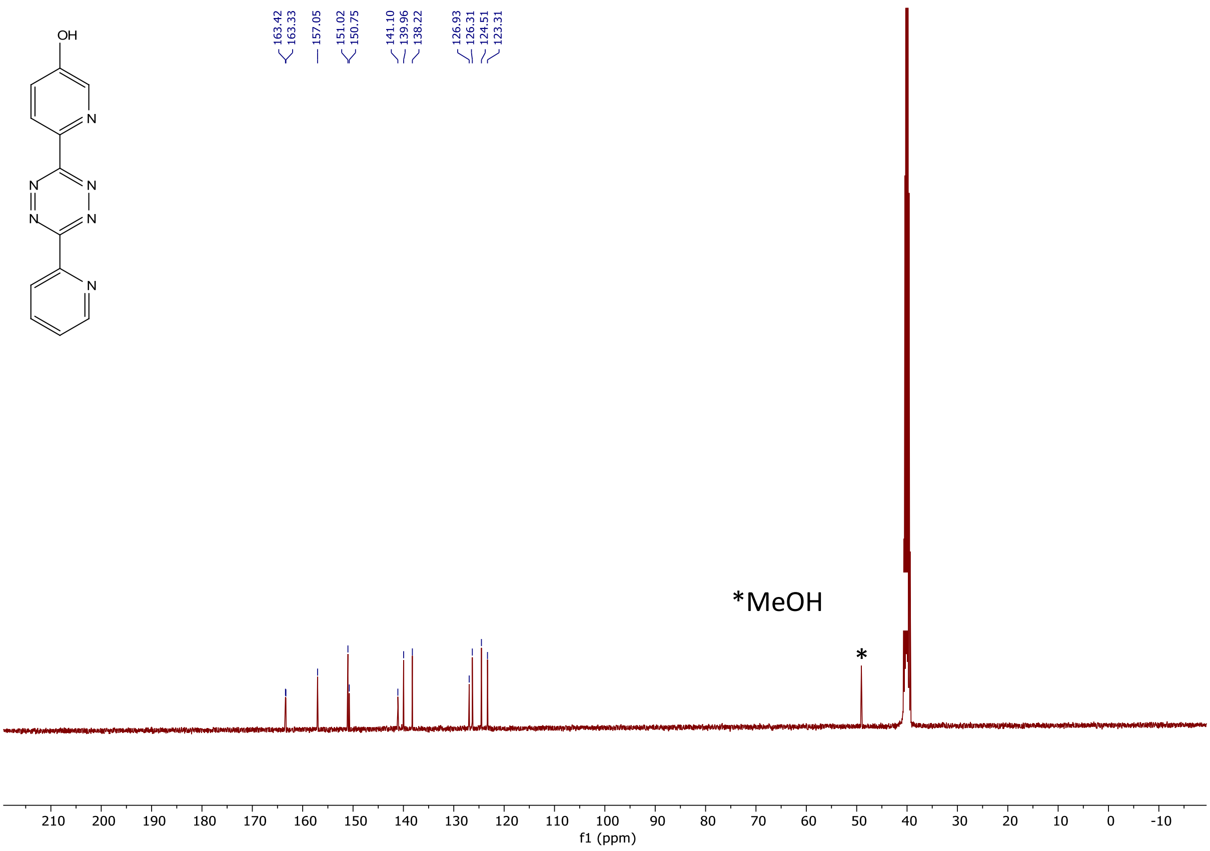
4-(1,2,4,5-Tetrazin-3-yl)phenyl sulfurofluoridate (**1**)



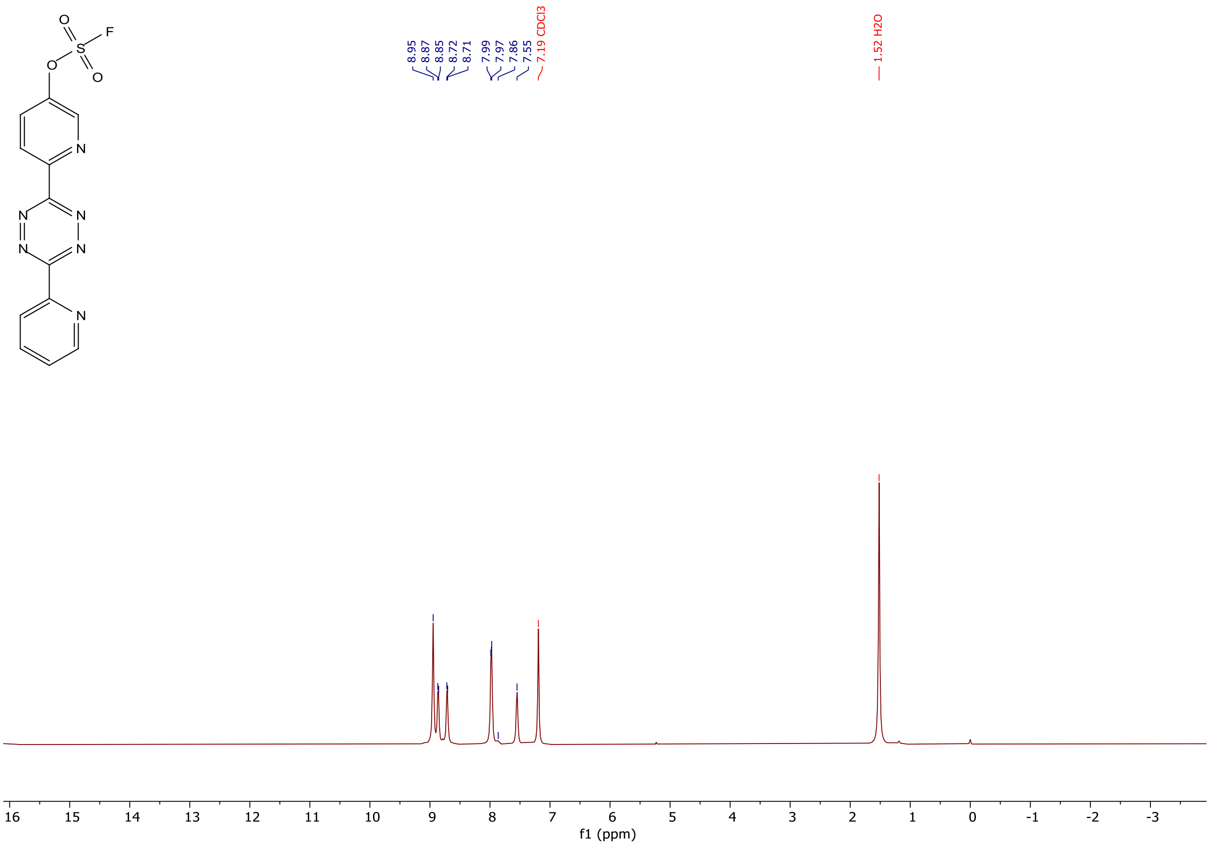


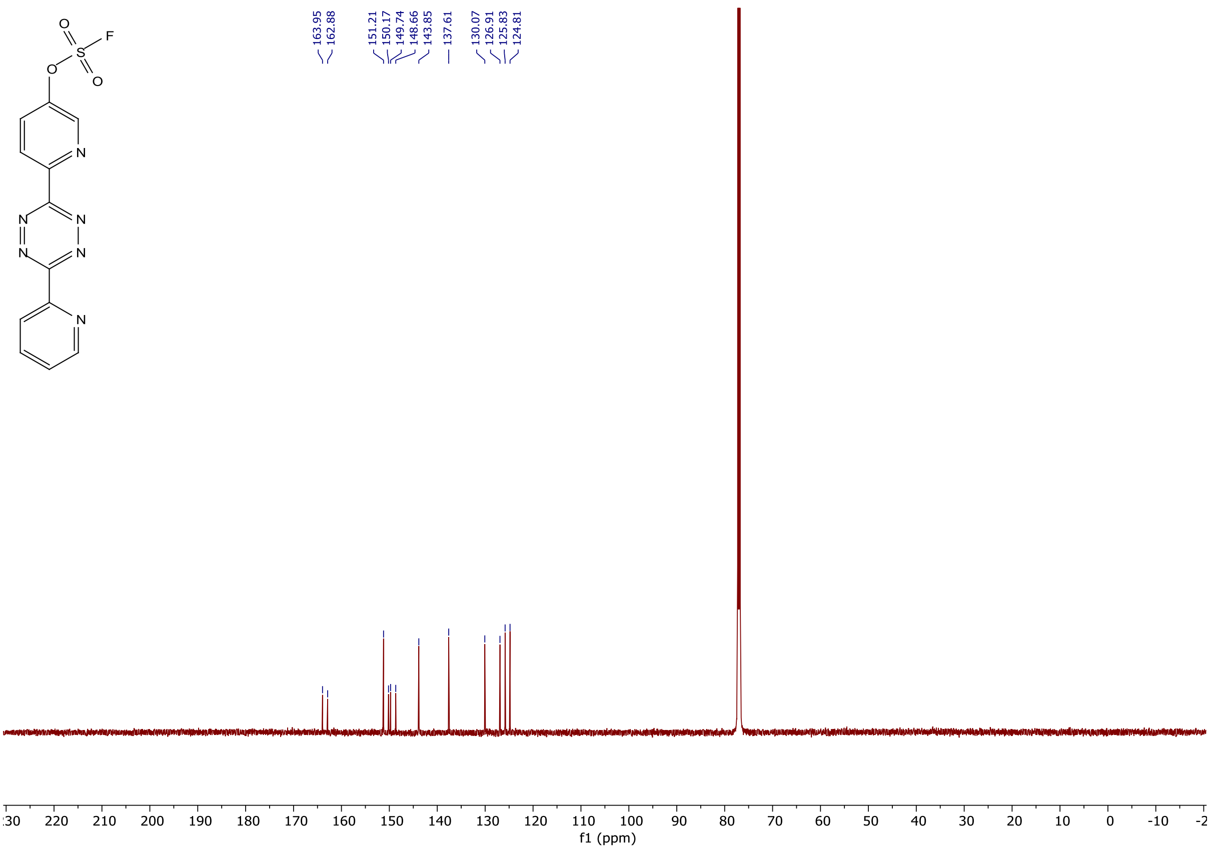
6-(6-(pyridin-2-yl)-1,2,4,5-tetrazin-3-yl)pyridin-3-ol (**4**)



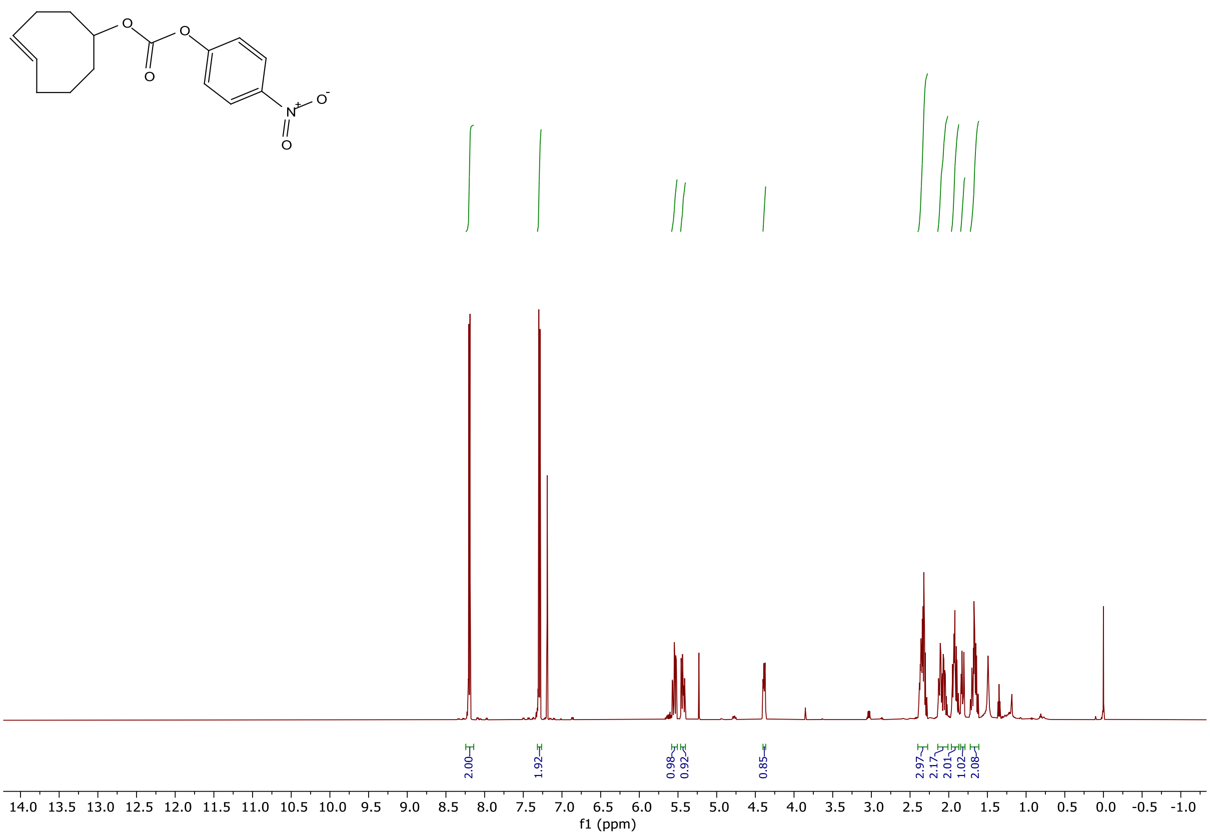


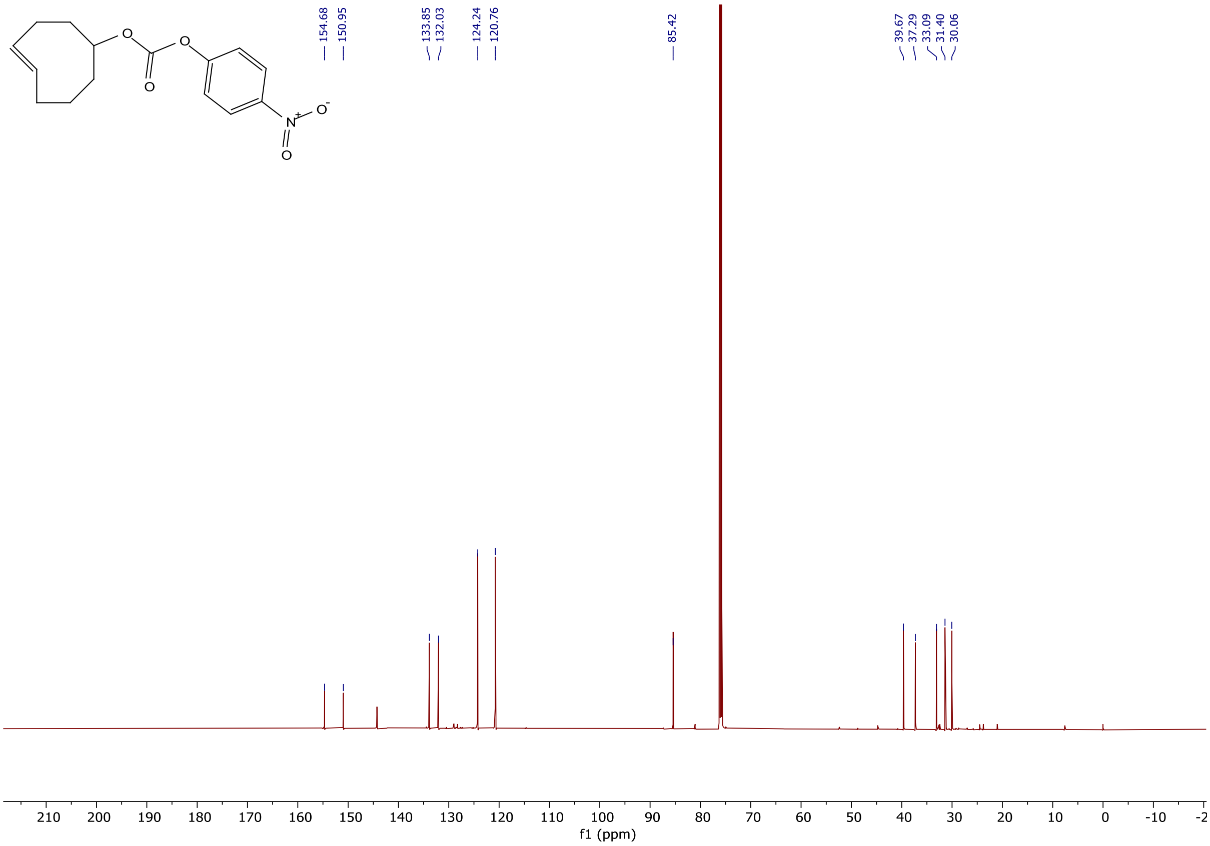
6-(6-(pyridin-2-yl)-1,2,4,5-tetrazin-3-yl)pyridin-3-yl sulfurofluoridate (**2**)





TCO-PNB carbonate





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