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Supporting Information

Synthesis and biological evaluation of PET tracers designed for imaging of calcium activated potassium channel 3.1 ($K_{Ca}3.1$) channels *in vivo*

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Contents

1. Purity data (HPLC)

Compd.	Purity [%]	Compd.	Purity [%]
1	99.7	**22**	97.2
5	97.3	**21**	98.9
6	99.7	**24**	95.4
8	99.9	**25**	99.8
10	99.2	**27**	99.5
15	91.3	**28**	95.7
16	96.8	**30**	97.6
17	98.1	**31**	95.1
18	95.3	**36**	98.1
19	93.9	**37**	96.2
20	99.4		

2. Synthesis of [^{19}F]-reference substances

2.1 General considerations

All *chemicals*, *reagents*, and *solvents* for the syntheses of the compounds were analytical grade, purchased from commercial sources and used without further purification unless otherwise specified. Solvents were purified and dried by literature procedures or with silica gel / molecular sieves (3 Å, 8 to 12 mesh, Acros Organics) in dry glassware (Schlenk flask or Schlenk tube sealed with rubber septa) if necessary.

Reaction mixtures were *stirred* with magnetic stirrer MR 3001 K (Heidolph) or RCT CL (IKA).

Temperatures were controlled with dry ice/acetone (-78 °C), ice/water (0 °C), magnetic stirrer MR 3001 K (Heidolph) or RCT CL (IKA®), together with temperature controller EKT HeiCon (Heidolph) or VT-5 (VWR) and PEG or silicone bath.

Chemical structures were generated with ChemDraw (v15.0.0.106).

Chemical yields were calculated relative to the minor reactant.

The *melting points* (mp) are uncorrected and were determined in open capillary tubes on a METTLER TOLEDO MP50 capillary melting point apparatus.

Preparative flash column chromatography was performed with silica gel 60 (40 - 63 µm, Macherey-Nagel) as stationary phase, unless otherwise noted. Pressure was applied with compressed air. In the description of the synthetic procedures diameter of the column (ø), length of the stationary phase (l), fraction size (v) and eluent are given in parentheses. Some samples were chromatographed using the chromatography system Isolera™ One (Biotage®). In the description of the synthetic porcedures the used cartridge-type, eluent, flow rate and fraction volume are given in parentheses.

Thin layer chromatography was conducted with TLC silica gel 60 F_{254} on aluminum sheets (Merck) as stationary phase in a saturated chamber at ambient temperature. Spots were visualized with UV light (254 nm or 365 nm) and with a cerium molybdate dipping bath [$Ce(SO_4)_2$ (1.8 g), $(NH_4)_6Mo_7O_{24}$ x 4 H_2O (45 g), conc. H_2SO_4 (45 g), H_2O (900 mL)] with additional heating using a heat gun. For the visualization of secondary and tertiary amines Dragendorff's reagent [$Bi(NO_3)_3$ (0.85 g), KI (8.0 g) glacial AcOH (10 mL), H_2O (60 mL)] was used as a dipping bath without any heating afterwards.

Compositions of the mobile phase and retention factor (R_f) of the compounds are given in the description of the synthetic procedures. As the retention factor (R_f) values strongly depend on the exact ratio of components of the eluent and some of these are highly volatile, the given retention factor values represent just approximate values.

HPLC was used to determine the *purity* of the synthesized compounds and was carried out at room temperature.

Methods 1 – 3:

DIONEX equipment Ultimate 3000, pump: LPG-3600, degasser: DG-1210, autosampler: WPS-3000 PL, UV detector: VDW-3400 RS; data acquisition: Chromeleon 7 (Thermo Fisher Scientific).

Column: LiChropher® 60 RP-select B (5 µm), LiChroCART® 250-4 mm cartridge

Guard column: LiChropher® 60 RP-select B (5 µm), LiChroCART® 4-4 mm cartridge (No.: 1.50963.0001), manu-CART® NT cartridge holder

Flow rate:	1.0 mL/min
Injection volume:	5.0 µL; method: cut lead and rear
Detection wavelength:	210 nm
Stop time:	30.0 min
Calculation:	manual integration, calculation method: area %, use of blank substraction from the same series

Method 1:

Solvent A:	demineralized water + 0.05 % (V/V) trifluoroacetic acid
Solvent B:	acetonitrile + 0.05 % (V/V) trifluoroacetic acid
Gradient elution (% A):	0 - 4 min: 90 %; 4 - 29 min: gradient from 90 % to 0 %; 29 - 31 min: 0 %; 31 - 31.5 min: gradient from 0 % to 90 %; 31.5 - 40 min: 90 %

Method 2:

Solvent A:	demineralized water + 0.05 % (V/V) trifluoroacetic acid
Solvent B:	acetonitrile + 0.05 % (V/V) trifluoroacetic acid
Gradient elution (% A):	0 - 4 min: 90 %; 4 - 20 min: gradient from 90 % to 0 %; 20 - 31 min: 0 %; 31 - 31.5 min: gradient from 0 % to 90 %; 31.5 - 40 min: 90 %

Method 3:

Merck Hitachi equipment, interface D-7000, pump: L-7100, degasser: L-7614, autosampler: L-7200, UV detector: L-7400, data aquisition: HSM software (Merck-Hitachi)

Column: Phenomenex Gemini C18 110 Å, 250x4.6 mm; 4x3mm security guard

Flow rate:	1.00 mL/min
Injection volume:	5.0 µL
Detection wavelength:	λ = 210 nm
Stop time:	30.0 min
Calculation:	manual integration, calculation method: area %, use of blank substraction from the same series
Solvents: A:	demineralized water + 0.1 % (V/V) ammonia
B:	acetonitrile + 0.1 % (V/V) ammonia
Gradient elution: (A %):	0-4 min: 90 %, 4-29 min: gradient from 90 % to 0 %, 29-31 min: 0 %, 31-31.5 min: gradient from 0 % to 90 %,
31.5-	40 min: 90 %.

NMR spectra were recorded on DD2 400 MHz and DD2 600 MHz spectrometers (Agilent) and Avance II 300 MHz and Avance II 400 MHz spectrometer (Bruker). The frequencies are given in the descriptions of the synthetic procedures. MestReNova software (version 10.0.0 - 14381, © 2014 by Mestrelab Research S.L.) was used for analyzing NMR spectra. Abbreviations for the multiplicities of the signal: s = singulet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, dd = doublet of doublet, etc. The multiplicities are reported as observed in the spectra. ^{1}H NMR spectra were referenced relative to the used deuterated solvents or TMS as the internal standard, ^{13}C NMR spectra were referenced to the undeuterated fraction in the used deuterated solvents and are decoupled. If necessary, ^{1}H and ^{13}C NMR assignments were supported by the following two-dimensional NMR spectroscopy techniques:

COSY (^{1}H, ^{1}H correlation spectroscopy)

gHSQC (gradient heteronuclear single quantum coherence)

gHMBC (gradient heteronuclear multiple bond correlation)

IR spectra were recorded on a FT/IR IRAffinity-1 IR spectrometer (Shimadzu) using ATR technique. All samples were applied to the device without solvent and were directly measured. Absorption bands are characterized by their wave numbers $\tilde{\nu}$ [cm^{-1}].

The *exact mass* of the molecules and adducts was determined with APCI or ESI.

For all samples, the deviations of the found exact masses from the calculated exact masses were 5 mDa or less, unless otherwise stated. All samples were measured in the positive ion mode, so all specified molecules, fragments or adducts represent positively charged ions.

Atmospheric pressure chemical ionization (APCI) mass spectra were recorded with a MicroTOFQII mass spectrometer (Bruker Daltonics). The data were analyzed with DataAnalysis (Bruker). The DirectProbe/APCI-source was operated in the positive ionization mode, scan range 60- 1000 m/z. APCI conditions: The capillary was set to 4.0 kV, the nebulizer was operated at 0.7 bar, the dry gas was set to 3.0 L/min at a temperature of 200 °C. Transfer voltages: The Funnel 1 and 2 were set to 200 Vpp. The hexapole RF voltage was set to 100 Vpp. Mass calibration was done using a Fatty Acid Methyl Ester (FAME) solution (m/z 103 - 383 or 423 - 565) in dichloromethane.

Electrospray ionization (ESI) mass spectra were recorded with a MicroTOFQII mass spectrometer (Bruker Daltonics). The data were analyzed with DataAnalysis (Bruker). The DirectProbe/ESI-source was operated in the positive ionization mode.

Scan range 120- 900 m/z or 800- 1200 m/z. ESI conditions: The capillary was set to 4.5 kV, the nebulizer was operated at 1.6 bar, the dry gas was set to 8.0 L/min at a temperature of 200 °C. Transfer voltages: The Funnel 1 and 2 were set to 200 Vpp. The hexapole RF voltage was set to 100 Vpp. Mass calibration was done using sodium formiate (m/z 90 - 1518 or 770 - 1246).

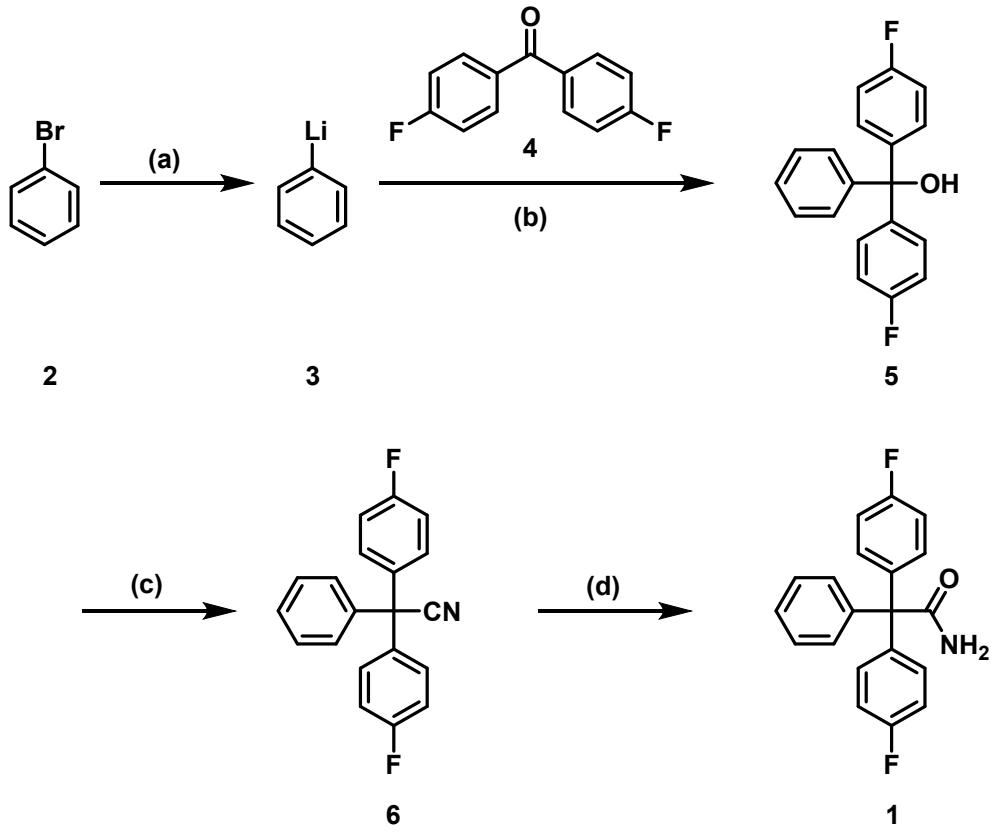
Lyophilisation of compounds which have been purified by reversed-phase HPLC or RP chromatography was performed using an Alpha 1-2 LD plus-freeze-dryer from CHRIST.

2.2 Synthetic procedures

2.2.1 Synthesis of [^{19}F]reference compounds

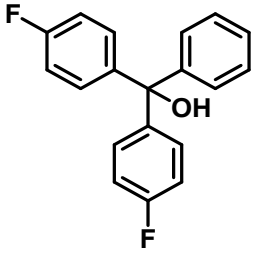
To perform *in vitro* experiments and to identify the labeled compounds by co-injection on the radio-HPLC system, non-radioactive [^{19}F]-containing reference compounds were synthesized.

2.2.1.1 Synthesis of Senicapoc



Scheme S1: Synthesis of senicapoc (**1**). Reagents and reaction conditions: (a) *n*-butyllithium, THF, -78 °C, 1 h. (b) THF, RT, 3 h, 70 %. (c) 1. $InCl_3$, CH_2Cl_2, RT, 30 min. 2. trimethylsilyl cyanide, CH_2Cl_2, 20 - 40 °C, 1 h, 40 - 50 °C, 1.5 h. 3. KOH, KNa-tartrate, H_2O, 12 h, 0 °C – rt, 85 %. (d) KOH (powder), 2-methylbutan-2-ol, 90 °C, 5 h, 74 %.

Bis(4-fluorophenyl)(phenyl)methanol (5)



Under N_2 atmosphere, bromobenzene (**2**, 0.13 mL, 1.20 mmol, 1.0 eq.) was dissolved in dry THF (5 mL). The solution was cooled to -78 °C. *n*-Butlylithium (2.5 M in hexane, 0.62 mL, 1.55 mmol, 1.3 eq.) was added and the mixture was stirred for 1 h. A solution of 4,4'-difluorobenzophenone (**4**, 262 mg, 1.20 mmol, 1.0 eq.) in THF (3.5 mL) was added. The reation mixture was allowed to warm up to room temperature. After stirring for 3 h at room temperature, the mixture was poured into ice-cold water (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 3 cm, h = 30 cm, V = 20 mL, cyclohexane : ethyl acetate = 6:1), R_f = 0.36 (cyclohexane : ethyl acetate = 6:1).

Colorless solid, mp = 99 °C, yield 250 mg (70 %). Purity (HPLC, method 1): 97.3 % (t_R = 18.0 min).

$C_{19}H_{14}F_2O$ (M_r = 296.3).

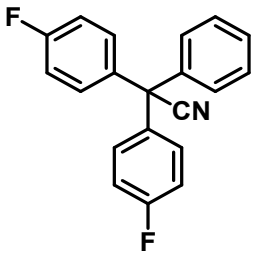
Spectroscopic data

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.79 (s, 1H, O*H*), 6.98 – 7.05 (m, 4H, 3-*H*, 5-*H* $_{(FPh)}$), 7.22 – 7.28 (m, 6H, 2-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 6-*H* $_{(Ph)}$), 7.30 – 7.38 (m, 3H, 3-*H*, 4-*H,* 5-*H* $_{(Ph)}$).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 81.5 (1C, *C*OH),, 115.0 (d, *J* = 21.1 Hz, 4C, C-3, C-5 $_{(FPh)}$), 127.7 (1C, C-4 $_{(Ph)}$), 127.8 (2C, C-2, C-6 $_{(Ph)}$), 128.3 (2C, C-3, C-5 $_{(Ph)}$), 129.8 (d, *J* = 8.1 Hz, 4C, C-2, C-6 $_{(FPh)}$), 142.7 (d, *J* = 3.3 Hz, 2C, C-1 $_{(FPh)}$), 146.7 (1C, C-1 $_{(Ph)}$), 162.1 (d, *J* = 246.6 Hz, 2C, C-4 $_{(FPh)}$).

Exact mass (APCI): (m/z) = 279.0990 (calcd. 279.0980 for $C_{19}H_{13}F_2$ $[M\text{-}OH]^+$).

IR (neat): ṽ (cm^{-1}) = 3458 (O-H), 3067 (C-H, arom), 1606 (C=C, arom), 1507 (C=C, arom)

2,2-bis(4-fluorophenyl)-2-phenylacetonitrile (6)[1]



Under N_2 atmosphere, alcohol **5** (230 mg, 0.78 mmol, 1.0 eq.) and $InCl_3$ (34 mg, 0.16 mmol, 0.2 eq.) were dissolved in dry CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 30 min. Trimethylsillyl cyanide (0.2 mL, 1.60 mmol, 2.1 eq.) was added and the mixture was stirred for 1 h at 20 - 40 °C. Then, the mixture was stirred at 40 – 50 °C for 1.5 h. The mixture was poured into an ice-cold solution of KOH (1.80 g,

31.9 mmol) and KNa-tartrate (1.80 g, 6.40 mmol) in H_2O (20 mL). The mixture was stirred overnight. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 25 cm, V = 20 mL, cyclohexane : ethyl acetate = 6:1 → 4:1), R_f = 0.55 (cyclohexane : ethyl acetate = 4:1) .

Colorless solid, mp = 90 °C, yield 201 mg (85 %). Purity (HPLC, method 1): 99.7 % (t_R = 24.6 min).

$C_{20}H_{13}F_2N$ (M_r = 305.3).

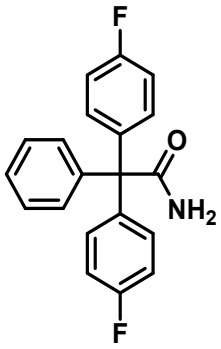
Spectroscopic data

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.03 – 7.07 (m, 4H, 3-*H*, 5-*H* $_{(FPh)}$), 7.16 – 7.21 (m, 6H, 2-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 6-*H* $_{(Ph)}$), 7.34 – 7.40 (m, 3H, 3-*H*, 4-*H,* 5-*H* $_{(Ph)}$).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 56.4 (1C, *C*CN), 115.9 (d, *J* = 22.8 Hz, 4C, C-3, C-5 $_{(FPh)}$), 123.3 (1C, *C*N), 128.6 (1C, C-4 $_{(Ph)}$), 128.7 (2C, C-2, C-6 $_{(Ph)}$), 129.1 (2C, C-3, C-5 $_{(Ph)}$), 130.7 (d, *J* = 8.1 Hz, 4C, C-2, C-6 $_{(FPh)}$), 136.1 (d, *J* = 3.3 Hz, 2C, C-1 $_{(FPh)}$), 140.0 (1C, C-1 $_{(Ph)}$), 162.5 (d, *J* = 249.5 Hz, 2C, C-4 $_{(FPh)}$).

Exact mass (APCI): (m/z) = 306.1101 (calcd. 306.1089 for $C_{20}H_{14}F_2N$ [M+H$^+$])

IR (neat): ṽ (cm^{-1}) = 3073 (C-H, arom), 2240 (C≡N), 1600 (C=C, arom), 1507 (C=C, arom)

2,2-Bis(4-fluorophenyl)-2-phenylacetamide (1, Senicapoc) [1]



Nitrile **6** (190 mg, 0.59 mmol, 1.0 eq.) was dissolved in 2-methylbutan-2-ol (1.9 mL). Crushed KOH (179 mg, 3.19 mmol, 5.4 eq.) was added and the mixture was stirred at 90 °C for 5 h. After cooling down to room temperature, H_2O (48 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 2 cm, h = 20 cm, V = 10 mL, cyclohexane : ethyl acetate = 2:1), R_f = 0.24 (cyclohexane : ethyl acetate = 2:1).

Colorless solid, mp = 189 °C, yield 147 mg (74 %). Purity (HPLC, method 1): 99.7 % (t_R = 21.2 min).

$C_{20}H_{15}F_2NO$ (M_r = 323.3).

Spectroscopic data

^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 6.75 (bs, 1H, NH_2), 7.13 (t, J = 8.9 Hz, 4H, 3-H, 5-H $_{(FPh)}$), 7.18 – 7.23 (m, 6H, 2-H, 6-H $_{(FPh)}$, 2-H, 6-H $_{(Ph)}$), 7.23 – 7.28 (m, 1H, 4-H $_{(Ph)}$), 7.30 – 7.35 (m, 2H, 3-H, 5-H $_{(Ph)}$), 7.57 (bs, 1H, NH_2).

^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 66.0 (1C, CCONH$_2$), 114.4 (d, J = 21.0 Hz, 4C, C-3, C-5 $_{(FPh)}$), 126.7 (1C, C-4 $_{(Ph)}$), 127.9 (2C, C-2, C-6 $_{(Ph)}$), 129.9 (2C, C-3, C-5 $_{(Ph)}$), 132.1 (d, J = 8.1 Hz, 4C, C-2, C-6 $_{(FPh)}$), 140.0 (d, J = 3.3 Hz, 2C, C-1 $_{(FPh)}$), 143.6 (1C, C-1 $_{(Ph)}$), 160.7 (d, J = 243.8 Hz, 2C, C-4 $_{(FPh)}$), 173.8 (1C, CONH$_2$).

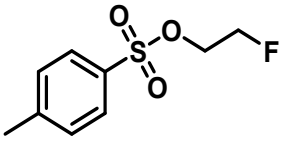
Exact mass (APCI): (m/z) = 324.1208 (calcd. 324.1194 for $C_{20}H_{16}F_2NO$ [M+H]$^+$).

IR (neat): ṽ (cm^{-1}) = 3475 (CON-H), 3120 (C-H, arom), 1673 (C=O), 1599 (C=C, arom), 1504 (C=C, arom).

2.2.1.2 Synthesis of fluoroethoxy derivative 28

The compound was prepared by alkylation of phenol **9** [2] with (2-fluoroethyl) 4-methylbenzenesulfonate (**27**).

2.2.1.2.1 Sythesis of (2-fluoroethyl) 4-methylbenzenesulfonate (27) [3]



Under N_2 atmosphere, 2-fluoroethanol (**26**, 0.45 mL, 7.76 mmol, 1.1 eq.) was dissolved in triethylamine (3.0 mL, 21.5 mmol, 3.0 eq.). The mixture was cooled to 0 °C and a solution of 4-methylbenzenesulfonyl chloride (1.34 g, 7.05 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at room temperature for 24 h. Saturated $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 1.5 cm, h = 20 cm, V = 10 mL, cyclohexane : ethyl acetate = 2:1), R_f = 0.19 (cyclohexane : ethyl acetate = 4:1).

Colorless oil, yield 1.36 g (88 %). Purity (HPLC, method 1): 99.5 % (t_R = 19.0 min).

$C_9H_{11}FO_3S$ (M_r = 218.2).

Spectroscopic data

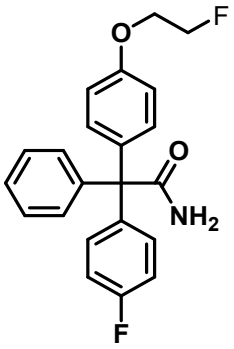
^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 2.43 (s, 3H, CH_3), 4.27 (dt, J = 29.3 / 3.8 Hz, 2H, OCH_2), 4.57 (dt, J = 47.5 / 3.9 Hz, 2H, CH_2F), 7.50 (d, J = 8.3 Hz, 2H, 3-H, 5-H $_{(Ph)}$), 7.80 (d, J = 8.3 Hz, 2H, 2-H, 6-H $_{(Ph)}$).
^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 21.1 (1C, CH$_3$), 69.7 (d, J = 18.6 Hz, 1C, OCH$_2$), 81.0 (d, J = 168.3 Hz, 1C, CH$_2$F), 127.6 (2C, C-2, C-6 $_{(Ph)}$), 130.2 (2C, C-3, C-5 $_{(Ph)}$), 132.1 (1C, C-1 $_{(Ph)}$), 145.13 (1C, C-4 $_{(Ph)}$) .

Exact mass (APCI): (m/z) = 219.0508 (calcd. 219.0486 for $C_9H_{12}FO_3S$ [M+H]$^+$).

IR (neat): ṽ (cm^{-1}) = 1598 (C=C, arom), 1506 (C=C, arom), 1355 (S=O), 1175 (S=O).

2.2.1.2.2 Alkylation of the phenol 9

2-[4-(2-Fluoroethoxy)phenyl]-2-(4-fluorophenyl)-2-phenylacetamide (28)



Amide **9** (158 mg, 0.49 mmol, 1.0 eq.) was dissolved in DMF (3 mL). Cs_2CO_3 (240 mg, 0.74 mmol, 1.5 eq.) and (2-fluoroethyl) 4-methylbenzenesulfonate (**27**, 107 mg, 0.49 mmol, 1.0 eq.) were added. The mixture was stirred and heated up (10 °C/ h) to 100 °C. The mixture was cooled down to room temperature and LiCl solution (5 % wt in H_2O, 10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated and washed with LiCl solution (5 % wt in H_2O, 3 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Ø = 2 cm, h = 25 cm, V = 10 mL, CH_2Cl_2 : CH_3OH = 98:2), R_f = 0.35 (CH_2Cl_2 : CH_3OH = 98:2).

Colorless solid, mp = 131 °C, yield 151 mg (84 %). Purity (HLPC, method 1): 95.7 % (t_R = 21.2 min).

$C_{22}H_{19}F_2NO_2$ (M_r = 367.4).

Spectroscopic data

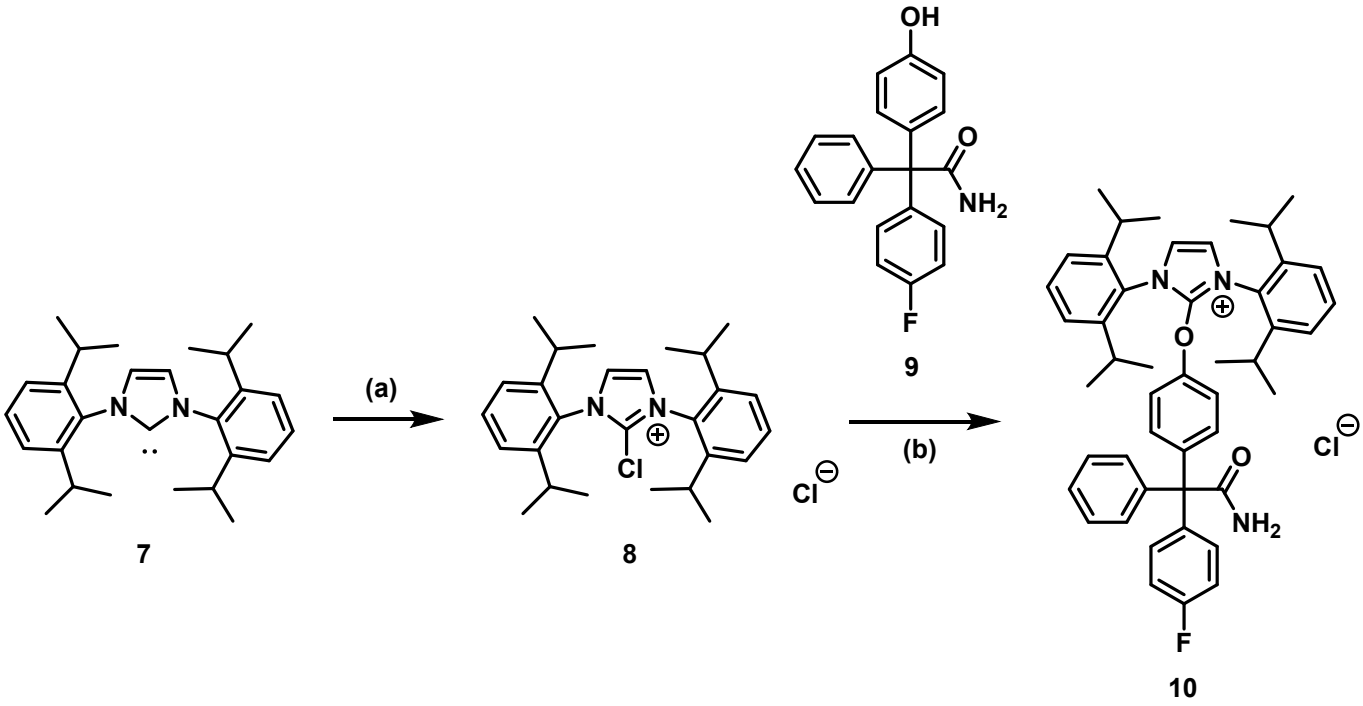
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 4.21 (dt, *J* = 30.1 / 3.9 Hz, 2H, OCH_2CH$_2$F), 4.73 (dt, *J* = 47.8 / 3.9 Hz, 2H, OCH$_2$CH_2F), 6.62 (bs, 1H, NH_2), 6.91 (d, *J* = 9.1 Hz, 2H, 3-*H*, 5-*H* $_{(OPh)}$), 7.06 – 7.15 (m, 4H, 2-*H*, 6-*H* $_{(OPh)}$, 3-*H*, 5-*H* $_{(FPh)}$), 7.15 – 7.27 (m, 5H, 2-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 4-*H*, 6-*H* $_{(Ph)}$), 7.26 – 7.34 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$), 7.52 (bs, 1H, NH_2).
^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) = 65.9 (1C, *C*CONH$_2$), 66.9 (d, *J* = 18.9 Hz, 1C, OCH$_2$CH$_2$F), 82.1 (d, *J* = 166.6 Hz, 1C, OCH$_2$*C*H$_2$F), 113.7 (2C, C-3, C-5 $_{(OPh)}$), 114.2 (d, *J* = 21.1 Hz, 2C, C-3, C-5 $_{(FPh)}$), 126.5 (1C, C-4 $_{(Ph)}$), 127.7 (2C, C-3, C-5 $_{(Ph)}$), 129.9 (2C, C-2, C-6 $_{(Ph)}$), 131.2 (2C, C-2, C-6 $_{(OPh)}$), 132.0 (d, *J* = 8.0 Hz, 2C, C-2, C-6 $_{(FPh)}$), 136.0 (1C, C-1 $_{(OPh)}$), 140.4 (d, *J* = 3.2 Hz, 1C, C-1 $_{(FPh)}$), 144.0 (1C, C-1 $_{(Ph)}$), 156.6(1C, C-4 $_{(OPh)}$), 160.6 (d, *J* = 243.7 Hz, 1C, C-4 $_{(FPh)}$), 174.2 (1C, *C*ONH$_2$).

Exact mass (APCI): (m/z) = 368.1465 (calcd. 368.1457 for $C_{22}H_{20}F_2NO_2$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 3476 (CON-H), 2978 (C-H, aliph), 2886 (C-H, aliph), 1674 (C=O), 1601 (C=C, arom), 1504 (C=C, arom).

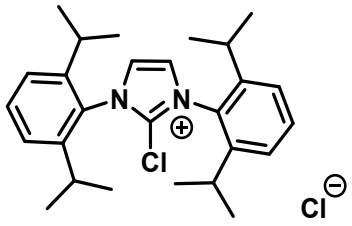
2.2.2 Synthesis of precursors for radiosynthesis

2.2.2.1 Synthesis of uronium-salt 10



Scheme S2: Synthesis of the uronium salt precursor **10**. Reagents and reaction conditions: (a) Cl_3C-CCl_3, THF, -45 °C - RT, 20 h, 90 %. (b) 2-Chloro-1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium chloride (**8**), Ag_2CO_3, CH_2Cl_2, 60 °C, 4 h, 68 %.

2-Chloro-1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride (8) [4]



1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**7**, 250 mg, 0.64 mml, 1.0 eq.) was dissolved in THF (1.5 mL). 1,1,1,2,2,2-Hexachloroethane (167 mg, 0.70 mml, 1.1 eq.) was added at -45 °C. The mixture was allowed to warm up slowly to room temperature and was stirred at room temperature for 20 h. The mixture was filtered and the filter cake was washed with THF (3 x 7.5 mL) and toluene (3 x 7.5 mL). The product was used without further purification.

Colorless solid, mp = 283 °C (decomposition), yield 264 mg (90 %). Purity (HPLC, method 1): 99.9 % (t_R = 24.5 min).

$C_{27}H_{36}Cl_2N_2$ (M_r = 459.5).

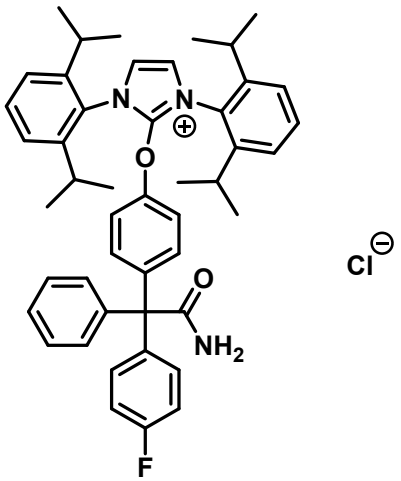
Spectroscopic data

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.20 (d, *J* = 6.9 Hz, 12H, C*H*$_3$), 1.31 (d, *J* = 6.8 Hz, 12H, C*H*$_3$), 2.36 (sept, *J* = 6.9 Hz, 4H, C*H*), 7.40 (d, *J* = 7.8 Hz, 4H, 3-*H*, 5-*H* $_{(Ph)}$), 7.63 (t, *J* = 7.9 Hz, 2H, 4-*H* $_{(Ph)}$), 8.88 (s, 2H, 4-*H*, 5-*H* $_{(imidazole)}$).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 23.7 (4C, *C*H_3), 24.4 (4C, *C*H_3), 29.5 (4C, *C*H), 125.4 (4C, C-3, C-5 $_{(Ph)}$), 128.8 (2C, C-1 $_{(Ph)}$), 129.1 (2C, C-4, C-5 $_{(Imidazole)}$), 133.0 (2C, C-4 $_{(Ph)}$), 145.3 (4C, C-2, C-6 $_{(Ph)}$).

Exact mass (APCI): (m/z) = 423.2615 (calcd. 423.2562 for $C_{27}H_{36}ClN_2$ $[M]^+$).

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2967 (C-H, aliph), 2936 (C-H, aliph), 2780 (C-H, aliph), 1586 (C=C, arom), 1532 (C=C, arom), 1498 (C=C, arom).

{4-[1-Carbamoyl-1-(4-fluorophenyl)1-phenylmethyl]phenoxy}-1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (10)



Imidazolium chloride **8** (100 mg, 0.24 mmol, 1.0 eq.), amide **9** (75.8 mg, 0.24 mmol, 1.0 eq.) and Ag_2CO_3 (32.5 mg, 0.12 mmol, 0.5 eq.) were suspended in CH_2Cl_2 (0.5 mL) and stirred at 60 °C for 4 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 1 cm, h = 20 cm, V = 5 mL, CH_2Cl_2 : CH_3OH = 9:1), R_f = 0.17 (CH_2Cl_2 : CH_3OH = 9:1).

Colorless solid, mp = 144 °C, yield 121 mg (68 %). Purity (HPLC, method 1): 99.2 % (t_R = 25.6 min).

$C_{47}H_{27}ClFN_3O_2$ (M_r = 744.4).

Spectroscopic data

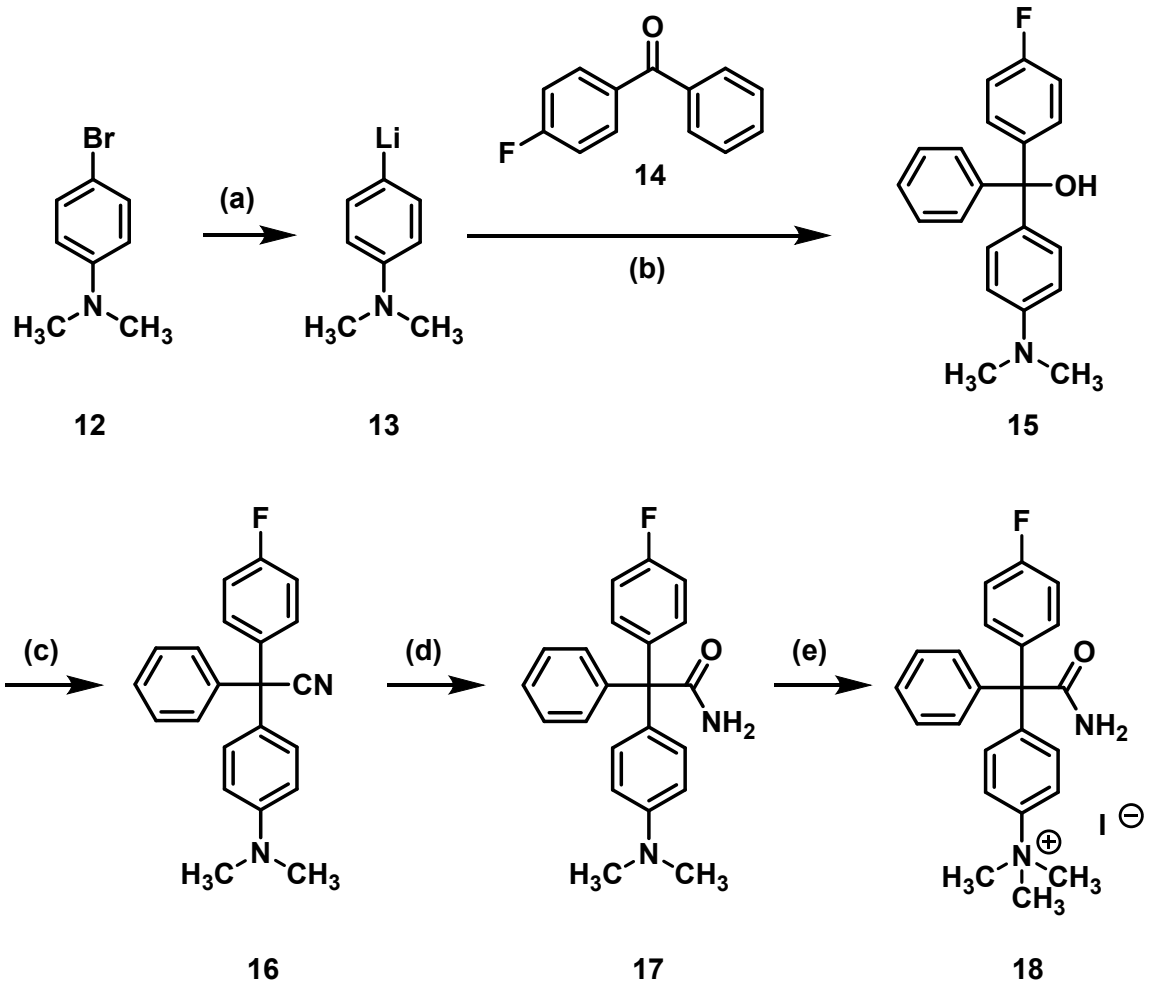
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.16 (d, *J* = 6.8 Hz, 12H, C*H*$_{3\ (iprop)}$), 1.29 (d, *J* = 6.7 Hz, 12H, C*H*$_{3\ (iprop)}$), 2.50 (sept, *J* = 6.6 Hz, 4H, C*H* $_{(iprop)}$), 5.54 (bs, 1H, N*H*$_2$), 5.84 (bs, 1H, N*H*$_2$), 6.37 (d, *J* = 8.8 Hz, 2H, 2-*H*, 6-*H* $_{(OPh)}$), 6.96 (t, *J* = 8.5 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 6.97 – 7.00 (m, 2H, 2-*H*, 6-*H* $_{(Ph)}$), 7.01 – 7.05 (m, 2H, 2-*H*, 6-*H* $_{(FPh)}$), 7.09 (d, *J* = 8.8 Hz, 2H, 3-*H*, 5-*H* $_{(OPh)}$), 7.26 – 7.32 (m, 7H, 3-*H*, 4-*H*, 5-*H* $_{(Ph),}$ 3-*H*, 5-*H* $_{(ipropPh)}$), 7.53 (t, *J* = 7.8 Hz, 2H, 4-*H* $_{(ipropPh)}$), 8.41 (s, 2H, 4-*H*, 5-*H* $_{(imidazole)}$).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 23.0 (4C, *C*$H_{3\ (iroprop)}$), 25.8 (4C, *C*$H_{3\ (iroprop)}$), 29.7 (4C, *C*H $_{(iroprop)}$), 66.3 (1C, *C*$CONH_2$), 115.3 (d, *J* = 21.3 Hz, 2C, C-3, C-5 $_{(FPh)}$), 117.1 (2C, C-2, C-6 $_{(OPh)}$), 123.9 (2C, C-4, C-5 $_{(Imidazole)}$), 125.2 (4C, C-3, C-5 $_{(ipropPh)}$),

127.7 (2C, C-1 $_{(ipropPh)}$), 128.1 (1C, C-4 $_{(Ph)}$), 128.7 (2C, C-3, C-5 $_{(Ph)}$), 130.0 (2C, C-2, C-6 $_{(Ph)}$), 131.9 (d, *J* = 7.9 Hz, 2C, C-2, C-6 $_{(FPh)}$), 132.5 (2C, C-4 $_{(ipropPh)}$), 132.6 (2C, C-3, C-5 $_{(OPh)}$), 138.0 (d, *J* = 3.5 Hz, 1C, C-1 $_{(FPh)}$), 142.0 (1C, C-1 $_{(Ph)}$), 143.0 (1C, C-1 $_{(OPh)}$), 144,0 (1C, C-2 $_{(Imidazole)}$), 145.6 (4C, C-2, C-6 $_{(ipropPh)}$), 151.9 (1C, C-4 $_{(OPh)}$), 162.0 (d, *J* = 248.6 Hz, 1C, C-4 $_{(FPh)}$), 174.4 (1C, *C*$CONH_2$).

Exact mass (APCI): (m/z) = 708.4038 (calcd. 708.3960 for $C_{47}H_{27}FN_3O_2^+$ $[M]^+$).

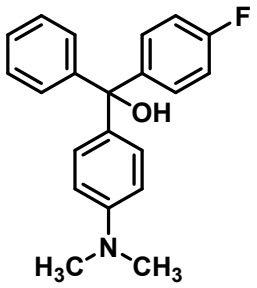
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3476 (CON-H), 2967 (C-H, aliph), 2928 (C-H, aliph), 1674 (C=O), 1597 (C=C, arom), 1562 (C=C, arom), 1497 (C=C, arom).

2.2.2.2 Synthesis of the trimethylammonium precursor 18



Scheme S3: Synthesis of the trimethylammonium precursor **18.** Reagents and reaction conditions: (a) *n*-butyllithium, tetrahydrofurane (THF), -78 °C, 1 h. (b) THF,room temperature (RT), 4 h, 57 %. (c) 1. $InCl_3$, dichloromethane (CH_2Cl_2), RT, 30 min. 2. trimethylsilyl cyanide, CH_2Cl_2, 20 – 40 °C, 1 h, 40 - 50 °C, 2 h; 3. Potassium hydroxide (KOH), potassium sodium tartrate (KNa-tartrate), H_2O, 0 °C – rt, 15 h, 86 %. (d) KOH, 2-methylbutan-2-ol , 70 °C, 48 h, 34 %. (e) iodmethane (CH_3I), CH_2Cl_2, RT, 24 h, 82 %.

1-[4-(Dimethylamino)phenyl]-1-(4-fluorophenyl)-1-phenylmethanol (15)



Under N_2 atmosphere, 4-bromo-*N,N*-dimethylaniline (**12**, 750 mg, 3.75 mmol, 1.0 eq.) was dissolved in dry THF (45 mL). The solution was cooled to -78 °C. *n*-Butlylithium (2.0 M in *n*-hexane, 2.55 mL, 5.10 mmol, 1.4 eq.) was added and the mixture was stirred for 1 h. A solution of 4-fluorobenzophenone (**14**, 749 mg, 3.75 mmol, 1.0 eq.) was added. The reation mixture was allowed to warm up to room temperature. After stirring for 4 h at room temperature, the mixture was poured into ice-cold water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 8 cm, h = 30 cm, V = 20 mL, cyclohexane : ethyl acetate = 6:1 → 4:1 → 2:1), R_f = 0.44 (cyclohexane : ethyl acetate = 2:1).

Colorless solid, mp = 87 °C yield 687 mg (57 %). Purity (HPLC, method 3): 91,3 % (t_R = 21.3 min).

$C_{21}H_{20}FNO$ (M_r = 321.4).

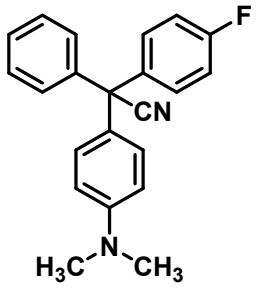
Spectroscopic data

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.86 (s, 6H, N(C*H*$_3$)$_2$), 6.23 (s, 1H, O*H*), 6.64 (d, *J* = 9.2 Hz, 2H, 3-*H*, 5-*H* $_{(NPh)}$), 6.95 (d, *J* = 9.2 Hz, 2H, 2-*H*, 6-*H* $_{(NPh)}$), 7.10 (t, *J* = 8.9 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.18 – 7.24 (m, 5H, 2-*H*, 6-*H* $_{(FPh),}$ 2-*H*, 4-*H*, 6-*H* $_{(Ph)}$), 7.25 – 7.31 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$).
^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) = 40.1 (2C, N(*C*H$_3$)$_2$), 79.9 (1C, *C*OH), 111.4 (2C, C-3, C-5 $_{(NPh)}$), 114.0 (d, *J* = 20.9 Hz, 2C, C-3, C-5 $_{(FPh)}$), 126.5 (1C, C-4 $_{(Ph)}$), 127.4 (2C, C-3, C-5 $_{(Ph)}$), 127.6 (2C, C-2, C-6 $_{(Ph)}$), 128.4 (2C, C-2, C-6 $_{(NPh)}$), 129.7 (d, *J* = 8.1 Hz, 2C, C-2, C-6 $_{(FPh)}$), 135.3 (1C, C-1 $_{(NPh)}$), 144.7 (d, *J* = 2.9 Hz, 1C, C-1 $_{(FPh)}$), 148.3 (1C, C-1 $_{(Ph)}$), 149.1 (1C, C-4 $_{(NPh)}$), 160.8 (d, *J* = 242.7 Hz, 1C, C-4 $_{(FPh)}$).

Exact mass (APCI): (m/z) = 322.1573 (calcd. 322.1602 for $C_{21}H_{21}FNO$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 3325 (O-H), 2978 (C-H, aliph), 1601 (C=C, arom), 1505 (C=C, arom).

2-[4-(Dimethylamino)phenyl]-2-(4-fluorophenyl)-2-phenylacetonitrile (16)



Under N_2 atmosphere, alcohol **15** (300 mg, 0.93 mmol, 1.0 eq.) and $InCl_3$ (42.2 mg, 0.19 mmol, 0.2 eq.) were dissolved in dry CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 30 min. Trimethylsillyl cyanide (0.23 mL, 1.86 mmol, 2.0 eq.) was added and the mixture was stirred for 1 h at 20 - 40 °C. Then, the mixture was stirred at 40 – 50 °C for 2 h. The mixture was poured into an ice-cold solution of KOH (1.80 g, 31.9 mmol) and KNa-tartrate (1.80 g, 6.40 mmol) in H_2O (20 mL). The mixture was stirred for 15 h at room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 5 cm, h = 35 cm, V = 20 mL, cyclohexane : ethyl acetate = 4:1), R_f = 0.42 (cyclohexane : ethyl acetate = 4:1).

Colorless solid, mp = 133 °C, yield 261 mg (86 %). Purity (HPLC, method 2): 96.8 % (t_R = 17.4 min).

$C_{22}H_{19}FN_2$ (M_r = 330.4).

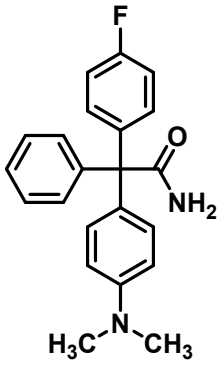
Spectroscopic data

^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 2.90 (s, 6H, N(C*H*$_3$)$_2$), 6.74 (d, *J* = 9.1 Hz, 2H, 3-*H*, 5-*H* $_{(NPh)}$), 6.90 (d, *J* = 9.0 Hz, 2H, 2-*H*, 6-*H* $_{(NPh)}$), 7.12 – 7.20 (m, 4H, 2-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 6-*H* $_{(Ph)}$), 7.27 (t, *J* = 8.7 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.36 – 7.48 (m, 3H, 3-*H*, 4-*H*, 5-*H*, $_{(Ph)}$).
^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 39.8 (2C, N(*C*H$_3$)$_2$), 55.5 (1C, *C*CN), 112.6 (2C, C-3, C-5 $_{(NPh)}$), 115.8 (d, *J* = 22.0 Hz, 2C, C-3, C-5 $_{(FPh)}$), 123.3 (1C, *C*N), 126.2 (1C, C-1 $_{(NPh)}$), 128.0 (2C, C-2, C-6 $_{(Ph)}$), 128.2 (1C, C-4 $_{(Ph)}$), 128.8 (2C, C-2, C-6 $_{(NPh)}$), 128.9 (2C, C-3, C-5 $_{(Ph)}$), 130.3 (d, *J* = 8.7 Hz, 2C, C-2, C-6 $_{(FPh)}$), 136.7 (d, *J* = 3.2 Hz, 1C, C-1 $_{(FPh)}$), 140.3 (1C, C-1 $_{(Ph)}$), 149.9 (1C, C-4 $_{(NPh)}$), 161.5 (d, *J* = 245.9 Hz, 1C, C-4 $_{(FPh)}$).

Exact mass (APCI): (m/z) = 331.1615 (calcd. 331.1605 for $C_{20}H_{20}FN_2$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 2978 (C-H, aliph), 2234 (C≡N), 1609 (C=C, arom), 1505 (C=C, arom).

2-[4-(Dimethylamino)phenyl]-2-(4-fluorophenyl)-2-phenylacetamide (17)



Nitrile **16** (156 mg, 0.47 mmol, 1.0 eq.) was dissolved in 2-methylbutan-2-ol (20 mL). Crushed KOH (146 mg, 2.60 mmol, 5.5 eq.) was added and the mixture was stirred at 70 °C for 48 h. After cooling down to room temperature, CH_2Cl_2 (20 mL) was added. The aquesous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 3 cm, h = 30 cm, V = 10 mL, (CH_2Cl_2 : ethyl acetate : CH_3OH = 40:10:1), R_f = 0.57 (CH_2Cl_2 : ethyl acetate : CH_3OH = 40:10:1).

Colorless solid, mp = 201 °C, yield 55.4 mg (34 %). Purity (HPLC, method 2): 98.1 % (t_R = 13.6 min).

$C_{22}H_{21}FN_2O$ (M_r = 348.4).

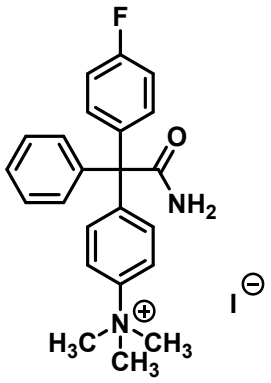
Spectroscopic data

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.88 (s, 6H, N(C*H*$_3$)$_2$), 6.50 (bs, 1H, N*H*$_2$), 6.66 (d, *J* = 8.9 Hz, 2H, 3-*H*, 5-*H* $_{(NPh)}$), 6.97 (d, *J* = 9.0 Hz, 2H, 2-*H*, 6-*H* $_{(NPh)}$), 7.09 (t, *J* = 8.8 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.16 – 7.25 (m, 5H, 2-*H*, 6-*H* $_{(FPh),}$ 2-*H*, 4-*H*, 6-*H* $_{(Ph)}$), 7.25 – 7.32 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$), 7.46 (bs, 1H, N*H*$_2$).
^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) = 40.0 (2C, N(*C*H$_3$)$_2$), 65.7 (1C, *C*CONH$_2$), 111.6 (2C, C-3, C-5 $_{(NPh)}$), 114.0 (d, *J* = 21.0 Hz, 2C, C-3, C-5 $_{(FPh)}$), 126.3 (1C, C-4 $_{(Ph)}$), 127.6 (2C, C-3, C-5 $_{(Ph)}$), 129.9 (2C, C-2, C-6 $_{(Ph)}$), 130.6 (2C, C-2, C-6 $_{(NPh)}$), 130.7 (1C, C-1 $_{(NPh)}$), 132.0 (d, *J* = 7.8 Hz, 2C, C-2, C-6 $_{(FPh)}$), 140.8 (d, *J* = 3.4 Hz, 1C, C-1 $_{(FPh)}$), 144.4 (1C, C-1 $_{(Ph)}$), 148.7 (1C, C-4 $_{(NPh)}$), 160.5 (d, *J* = 243.0 Hz, 1C, C-4 $_{(FPh)}$), 174.5 (1C, *C*ONH$_2$).

Exact mass (APCI): (m/z) = 349.1744 (calcd. 349.1711 for $C_{22}H_{22}FN_2O$ $[M+H]^+$).

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3464 (CON-H), 3120 (C-H, arom), 2978 (C-H, aliph), 1736 (C=O), 1682 (C=O), 1601 (C=C, arom), 1504 (C=C, arom).

***n*-{4-[1-Carbamoyl-1-(4-fluorophenyl)-1-phenylmethyl]phenyl}-(-*N,N,N*-trimethylamonium iodide (18)**



Amide **17** (95 mg, 0.27 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (1.0 mL). CH_3I (0.13 mL, 2.10 mmol, 7.8 eq.) was added dropwise. The mixture was stirred at room temperature for 24 h. A colorless solid precipitated overnight. The mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL) and H_2O (2 mL). The layers were separated and the organic layer was extracted with H_2O (3 x 2 mL). The aqueous layer was lyophilized yielding the desired product.
Colorless solid, mp = 124 °C (lyophilisate), yield 110 mg (82 %). Purity (HPLC, method 1): 95.3 % (t_R = 15.7 min).

$C_{23}H_{24}FIN_2O$ (M_r = 490.4).

Spectroscopic data

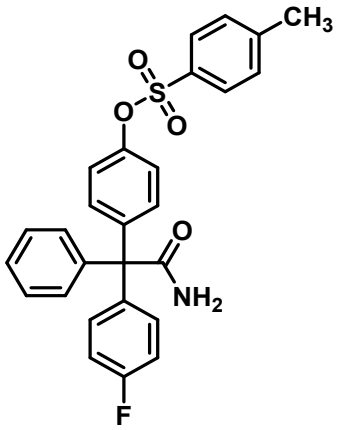
^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 3.58 (s, 9H, N(CH_3)$_3$), 6.90 (bs, 1H, NH_2), 7.19 (t, *J* = 9.1 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.22 – 7.31 (m, 5H, 2-*H*, 6-*H* $_{(FPh),}$ 2-*H*, 4-*H*, 6-*H* $_{(Ph)}$), 7.32 – 7.38 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$), 7.43 (d, *J* = 9.3 Hz, 2H, 3-*H*, 5-*H* $_{(NPh)}$), 7.61 (bs, 1H, NH_2), 7.88 (d, *J* = 9.3 Hz, 2H, 2-*H*, 6-*H* $_{(NPh)}$).
^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 56.3 (3C, N(*C*H_3)$_3$), 66.3 (1C, *C*CONH$_2$), 114.7 (d, *J* = 21.3 Hz, 2C, C-3, C-5 $_{(FPh)}$), 119.7 (2C, C-2, C-6 $_{(NPh)}$), 126.9 (1C, C-4 $_{(Ph)}$), 128.1 (2C, C-3, C-5 $_{(Ph)}$), 129.8 (2C, C-2, C-6 $_{(Ph)}$), 131.4 (2C, C-3, C-5 $_{(NPh)}$), 132.0 (d, *J* = 8.1 Hz, 2C, C-2, C-6 $_{(FPh)}$), 139.2 (d, *J* = 3.3 Hz, 1C, C-1 $_{(FPh)}$), 142.9 (1C, C-1 $_{(Ph)}$), 145.1 (1C, C-1 $_{(NPh)}$), 146.1 (1C, C-4 $_{(NPh)}$), 160.8 (d, *J* = 244.4 Hz, 1C, C-4 $_{(FPh)}$), 173.3 (1C, *C*ONH$_2$).

Exact mass (APCI): (m/z) = 363.1876 (calcd. 363.1867 for $C_{23}H_{24}FN_2O^+$ $[M]^+$).

IR (neat): ṽ (cm^{-1}) = 3472 (CON-H), 2889 (C-H, aliph), 1670 (C=O), 1597 (C=C, arom), 1505 (C=C, arom).

2.2.2.3 Synthesis of aryltosylate precursor 20

4-[1-Carbamoyl-1-(4-fluorophenyl)-1-phenylmethyl]phenyl 4-methylbenzenesulfonate (20)



Under N_2 atmosphere, amide **9** (125 mg, 0.39 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (0.5 mL). Triethylamine (0.11 mL, 0.79 mmol, 2.0 eq.) was added and the mixture was stirred at room temperature for 5 min. 4-Methylbenzenesulfonyl chloride (49 mg, 0.78 mmol, 2.0 eq.) was added slowly. After stirring for 2 h at room temperature, H_2O (1 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Ø = 2 cm, h = 30 cm, V = 10 mL, CH_2Cl_2 : CH_3OH = 30:1), R_f = 0.27 (CH_2Cl_2 : CH_3OH = 35:1) .

Colorless solid, mp = 195 °C, yield 180 mg (98 %). Purity (HLPC, method 1): 99.4 % (t_R = 23.2 min).

$C_{27}H_{22}FNO_4S$ (M_r = 475.5).

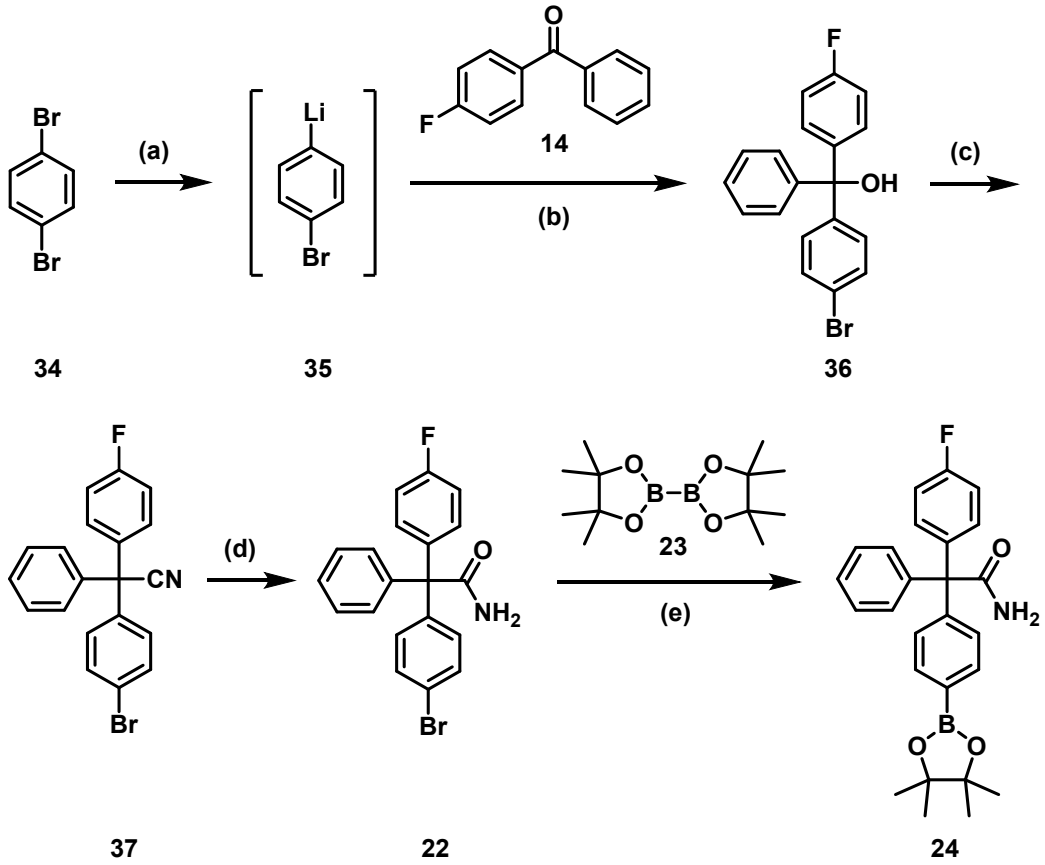
Spectroscopic data

^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 2.42 (s, 3H, CH_3), 6.74 (bs, 1H, NH_2), 6.97 (d, *J* = 8.7 Hz, 2H, 2-*H*, 6-*H* $_{(OPh)}$), 7.10 – 7.16 (m, 6H, 2-*H*, 3-*H*, 5-*H*, 6-*H* $_{(FPh),}$ 2-*H*, 6-*H* $_{(Ph}$), 7.18 (d, *J* = 8.9 Hz, 2H, 3-*H*, 5-*H* $_{(OPh)}$), 7.24 – 7.27 (m, 1H, 4-*H* $_{(Ph)}$), 7.29 – 7.34 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$), 7.46 (d, *J* = 8.4 Hz, 2H, 3-*H*, 5-*H* $_{(OTs)}$), 7.58 (bs, 1H, NH_2), 7.73 (d, *J* = 8.4 Hz, 2H, 2-*H*, 6-*H* $_{(OTs)}$).
^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 21.2 (1C, *C*H_3), 66.2 (1C, *C*CONH$_2$), 114.5 (d, *J* = 21.3 Hz, , 2C, C-3, C-5 $_{(FPh)}$), 121.1 (2C, C-2, C-6 $_{(OPh)}$), 126.7 (1C, C-4 $_{(Ph)}$), 127.9 (2C, C-3, C-5 $_{(Ph)}$), 128.2 (2C, C-2, C-6 $_{(OTs)}$), 129.9 (2C, C-2, C-6 $_{(Ph)}$), 130.2 (2C, C-3, C-5 $_{(OTs)}$), 131.5 (1C, C-1 $_{(OTs)}$), 131.7 (2C, C-3, C-5 $_{(OPh)}$), 132.0 (d, *J* = 8.0 Hz, 2C, C-2, C-6 $_{(FPh)}$), 139.6 (d, *J* = 3.3 Hz, 1C, C-1 $_{(FPh)}$), 143.0 (1C, C-4 $_{(OPh)}$), 143.3 (1C, C-1 $_{(Ph)}$), 145.8 (1C, C-4 $_{(OTs)}$),, 147.4 (1C, C-1 $_{(OPh)}$), 160.7 (d, *J* = 244.4 Hz, (1C, C-4 $_{(FPh)}$), 173.6 (1C, *C*CONH$_2$).

Exact mass (APCI): (m/z) = 476.1426 (calcd. 476.1326 for $C_{27}H_{23}FNO_4S$ $[M+H]^+$).

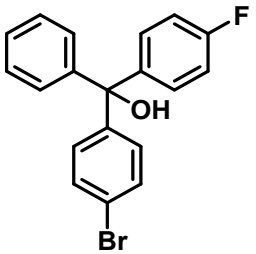
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3483 (CON-H), 3198 (C-H, arom), 2978 (C-H, aliph), 1678 (C=O), 1597 (C=C, arom), 1497 (C=C, arom), 1369 (S=O), 1157 (S=O).

2.2.2.4 Synthesis of the boronic ester precursor 40



Scheme S4: Synthesis of the pinacol boronic ester **24**. Reagents and reaction conditions: (a) n-butlylithium, THF, -78 °C, 1 h. (b) THF, RT. 3 h. (c) 1. $InCl_3$, CH_2Cl_2, RT, 30 min. 2. trimethylsilyl cyanide, CH_2Cl_2, 20 – 40 °C, 1 h, 40 - 50 °C, 2 h; 3. KOH, KNa-tartrate, H_2O, 0 °C – rt, 12 h, 56 %. (d) KOH (powder), 2-methylbutan-2-ol, 70 °C, 48 h, 46 %. (e) Pd(dppf)Cl_2, KOAc, dioxane, RT- 50 °C, 5 h, 15 %.

1-(4-Bromophenyl)-1-(4-fluorophenyl)-1-(phenyl)methanol (36)



Under N_2 atmosphere, 1,4-dibromobenzene (**34**, 5.10 g, 21.6 mmol, 1.0 eq.) was dissolved in dry THF (100 mL). The solution was cooled to -78 °C. *n*-Butlylithium (2.5 M in *n*-hexane, 7.35 mL, 18.4 mmol, 0.85 eq.) was added and the mixture was stirred for 1 h. A solution of 4-fluorobenzophenone (**14**, 4.23 g, 21.6 mmol, 1.0 eq.) was added. The reation mixture was allowed to warm up to room temperature. After stirring for 3 h at room temperature, the mixture was poured into ice-cold water (200 mL). The mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried

(Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø= 8 cm, h = 15 cm, V = 40 mL, cyclohexane: ethyl acetate = 4:1) yielding 7.89 g (>100 %) product with a purity (HPLC, method 2): 82.5 % (t_R = 19.1 min). The impure product was used without further purification for the next synthetic step.

For the characterization of the compound, 100 mg were further purified by automatic flash column chromatography 1: (cartridge: SNAP KP-Sil, 25 g (Biotage®), 15 % → 66 % ethylacetate in cyclohexane, 25 mL/min, V = 20 mL); automatic flash column chromatography 2: (cartridge: SNAP KP-Sil, 25 g (Biotage®), 0 % → 33 % ethyl acetate in cyclohexane, 25 mL/min, V = 20 mL).

Colorless oli. Purity (HPLC, method 1): 98.1 % (t_R = 23.7 min).

$C_{19}H_{14}BrFO$ (M_r = 357.2).

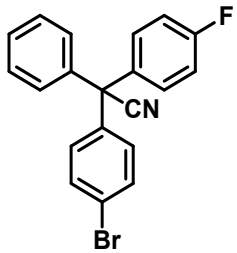
Spectroscopic data

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.78 (s, 1H, O*H*), 7.00 (t, *J* = 8.7 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.17 (d, *J* = 8.5 Hz, 2H, 2-*H*, 6-*H* $_{(BrPh)}$), 7.20 – 7.26 (m, 4H, 2-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 6-*H* $_{(Ph)}$), 7.28 – 7.35 (m, 3H, 3-*H*, 4-*H*, 5-*H* $_{(Ph)}$), 7.45 (d, *J* = 8.6 Hz, 2H, 3-*H*, 5-*H* $_{(BrPh)}$).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 81.5 (1C, *C*OH), 115.0 (d, *J* = 21.2 Hz, 2C, C-3, C-5 $_{(FPh)}$), 121.7 (1C, C-4 $_{(BrPh)}$), 127.8 (3C, C-2, C-4, C-6 $_{(Ph)}$), 128.3 (2C, C-3, C-5 $_{(Ph)}$), 129.7 (2C, C-2, C-6 $_{(BrPh)}$), 129.8 (d, *J* = 7.7 Hz, C-2, C-6 $_{(FPh)}$), 131.2 (2C, C-3, C-5 $_{(BrPh)}$), 142.3 (d, *J* = 3.0 Hz, 1C, C-1 $_{(FPh)}$), 145.8 (1C, C-1 $_{(BrPh)}$), 146.4 (1C, C-1 $_{(Ph)}$), 162.2 (d, *J* = 246.8 Hz, 1C, C-4 $_{(FPh)}$).

Exact mass (APCI): (m/z) = 357.0165 (calcd. 357.0285 for $C_{19}H_{15}BrFO$ $[M+H]^+$).

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3449 (O-H), 1597 (C=C, arom), 1505 (C=C, arom).

2-(4-Bromophenyl)-2-(4-fluorophenyl)-2-phenylacetonitrile (37)



Under N_2 atmosphere, alcohol **36** (6.52 g, 18.3 mmol, 1.0 eq.) and $InCl_3$ (806 mg, 3.65 mmol, 0.2 eq.) were dissolved in dry CH_2Cl_2 (80 mL). The mixture was stirred at room temperature for 30 min. Trimethylsillyl cyanide (4.56 ml, 36.7 mmol, 2.0 eq.) was added and the mixture was stirred for 1 h at 20 - 40 °C. Then, the mixture was stirred at 40 - 50°C for 2 h. The mixture was poured into an ice-cold solution of KOH (1.80 g, 31.9 mmol) and KNa-tartrate (1.80 g, 6.40 mmol) in H_2O (100 mL). The mixture was stirred overnight at room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 8 cm, h = 20 cm, V = 60 mL, cyclohexane : CH_2Cl_2 = 3:1 → 1:1),

R_f = 0.40 (cyclohexane : CH_2Cl_2 = 2:1) followed by recrystallization from EtOH: H_2O = 4:1.

Colorless solid, mp = 105 °C, yield 3.76 g (56 %). Purity (HPLC, method 1): 96.2 % (t_R = 25.3 min).

$C_{20}H_{13}BrFN$ (M_r = 366.2).

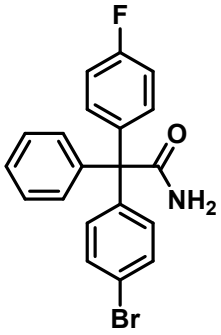
Spectroscopic data

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.02 – 7.12 (m, 4H, 2-*H*, 6-*H* $_{(BrPh),}$ 3-*H*, 5-*H* $_{(FPh)}$), 7.14 – 7.23 (m, 4H, 2-*H*, 6-*H* $_{(FPh),}$ 2-*H*, 6-*H* $_{(Ph)}$), 7.34 – 7.42 (m, 3H, 3-*H*, 4-*H*, 5-*H* $_{(Ph)}$), 7.50 (d, *J* = 8.7 Hz, 2H, 3-*H*, 5-*H* $_{(BrPh)}$).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 56.6 (1C, *C*CN), 116.0 (d, *J* = 22.0 Hz, 2C, C-3, C-5 $_{(FPh)}$), 122.9 (1C, C-4 $_{(BrPh)}$), 123.0 (1C, *C*N), 128.7 (1C, C-4 $_{(Ph)}$), 128.7 (2C, C-2, C-6 $_{(Ph)}$), 129.1 (2C, C-3, C-5 $_{(Ph)}$), 130.5 (2C, C-2, C-6 $_{(BrPh)}$), 130.7 (d, *J* = 8.4 Hz, 2C, C-2, C-6 $_{(FPh)}$), 132.1 (2C, C-3, C-5 $_{(BrPh)}$), 135.7 (d, *J* = 3.4 Hz, 1C, C-1 $_{(FPh)}$), 139.4 (1C, C-1 $_{(BrPh)}$), 139.6 (1C, C-1 $_{(Ph)}$), 162.6 (d, *J* = 249.1 Hz, 1C, C-4 $_{(FPh)}$).

Exact mass (APCI): (m/z) = 366.0244 (calcd. 366.0288 for $C_{20}H_{14}BrFN$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 2234 (C≡N), 1601 (C=C, arom), 1505 (C=C, arom).

2-(4-Bromophenyl)-2-(4-fluorophenyl)-2-phenylacetamide (22)



Nitrile **37** (276 mg, 0.75 mmol, 1.0 eq.) was dissolved in 2-methylbutan-2-ol (5 mL). Crushed KOH (233 mg, 4.15 mmol, 5.5 eq.) was added and the mixture was stirred at 70 °C for 48 h. After cooling down to room temperature, the pH was adjusted to 6.5-7.5 with HCl (1 M) and CH_2Cl_2 (10 mL) was added.The aquesous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography; column 1: (Ø = 3 cm, h = 25 cm, V = 10 mL, (CH_2Cl_2: ethyl acetate : CH_3OH = 40:10:1), column 2: (Ø = 2 cm, h = 30 cm, V = 10 mL, cyclohexane : ethyl acetate = 2:1), R_f = 0.20 (cyclohexane : ethyl acetate = 2:1).

Colorless solid, mp = 198 °C, yield 134 mg (46 %). Purity (HPLC, method 2): 97.2 % (t_R = 17.5 min).

$C_{20}H_{15}BrFNO$ (M_r = 384.3).

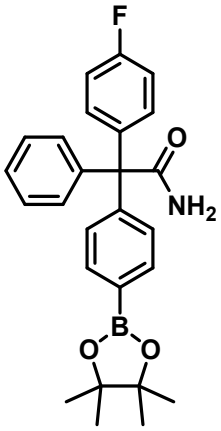
Spectroscopic data

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.70 (bs, 1H, N*H*$_2$), 5.96 (bs, 1H, N*H*$_2$), 7.00 (t, *J* = 8.7 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.17 (d, *J* = 8.7 Hz, 2H, 2-*H*, 6-*H* $_{(FPh)}$), 7.20 – 7.27 (m, 4H, 2-*H*, 6-*H* $_{(BrPh),}$ 2-*H*, 6-*H* $_{(Ph)}$), 7.29 – 7.36 (m, 3H, 3-*H*, 4-*H,* 5-*H* $_{(Ph)}$), 7.44 (d, *J* = 8.8 Hz, 2H, 3-*H*, 5-*H* $_{(BrPh)}$).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 66.7 (1C, *C*CNH_2), 115.1 (d, *J* = 21.3 Hz, 2C, C-3, C-5 $_{(FPh)}$), 121.7 (1C, C-4 $_{(BrPh)}$), 127.8 (1C, C-4 $_{(Ph)}$), 128.5 (2C, C-2, C-6 $_{(Ph)}$), 130.3 (2C, C-3, C-5 $_{(Ph)}$), 131.3 (2C, C-3, C-5 $_{(BrPh)}$), 132.2 (d, *J* = 8.0 Hz, 2C, C-2, C-6 $_{(FPh)}$), 132.2 (2C, C-2, C-6 $_{(BrPh)}$), 138.6 (d, *J* = 3.5 Hz, 1C, C-1 $_{(FPh)}$), 142.4 (1C, C-1 $_{(BrPh)}$), 142.7 (1C, C-1 $_{(Ph)}$), 161.9 (d, *J* = 247.9 Hz, 1C, C-4 $_{(FPh)}$), 175.5 (1C, *C*ONH_2).

Exact mass (APCI): (m/z) = 384.0400 (calcd. 384.0394 for $C_{20}H_{16}BrFNO$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 3468 (CON-H), 3140 (C-H, arom), 1735 (C=O), 1682 (C=O), 1601 (C=C, arom), 1505 (C=C, arom).

2-(4-Fluorophenyl)-2-phenyl-2-[4-(4,4,5,5-tatramethyl-1,2-dioxa-3-borolan-2-yl)phenyl]acetamide (24)



Under N_2 atmosphere, amide **22** (134 mg, 0.35 mmol, 1.0 eq.), bis(pinacolato)dibor (**23**, 135 mg, 0.53 mmol, 1.5 eq.), potassium acetate (104 mg, 1.10 mmol, 3.0 eq.) and Pd(dppf)Cl_2 (76.3 mg, 0.10 mmol, 0.3 eq.) were dissolved in 1,4-dioxane (5.0 mL) and stirred at room temperature for 3 h and at 50 °C for 2 h. After cooling down to room temperature, H_2O (10 mL) and CH_2Cl_2 (20 mL) was added. The layers were separated and the aquesous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography; column 1: (Ø 4 cm, h = 35 cm, V = 20 mL, (cyclohexane : ethyl acetate = 1:1), column 2: (Ø 3 cm, h = 35 cm, V = 10 mL, CH_2Cl_2: CH_3OH = 97:3), automatic flash column chromatography (cartridge: SNAP HP-Sil, 50g (Biotage®), 33 % ethylacetate in cyclohexane, 50 mL/min, V = 20 mL) and semi-preperative HPLC (method F), R_f = 0.18 (CH_2Cl_2: CH_3OH = 97:3).

Colorless solid, mp = 90 °C, yield 21.9 mg (15 %). Purity (HPLC, method 1): 95.4 % (t_R = 23.6 min).

$C_{26}H_{27}BFNO_3$ (M_r = 431.3).

Spectroscopic data

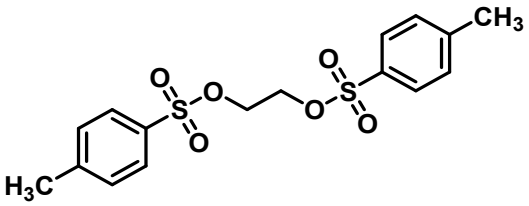
^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 1.28 (s, 12H, CH_3), 6.70 (bs,1H, NH_2), 7.12 (t, *J* = 9.1 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.18 – 7.28 (m, 7H, 2-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 6-*H* $_{(BPh)}$, 2-*H*, 4-*H*, 6-*H* $_{(Ph)}$), 7.28 – 7.33 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$), 7.54 (bs, 1H, NH_2), 7.61 (d, *J* = 8.3 Hz, 2H, 3-*H*, 5-*H* $_{(BPh)}$).
^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 24.6 (4C, *C*H_3), 66.8 (1C, *C*CNH_2), 83.6 (2C, O*C*CH_3), 114.3 (d, *J* = 21.1 Hz, 2C, C-3, C-5 $_{(FPh)}$), 126.6 (1C, C-4 $_{(Ph)}$), 127.8 (2C, C-3, C-5 $_{(FPh)}$), 129.6 (2C, C-2, C-6 $_{(BPh)}$), 130.0 (2C, C-2, C-6 $_{(Ph)}$), 132.1 (d, *J* = 8.0 Hz, 2C, C-2, C-6 $_{(FPh)}$), 133.9 (C-3, C-5 $_{(BPh)}$), 139.9 (d, *J* = 3.4 Hz, 1C, C-1 $_{(FPh)}$), 143.5 (1C, C-1 $_{(Ph)}$), 147.2 (1C, C-1 $_{(BPh)}$), 160.6 (d, *J* = 243.6 Hz, 1C, C-4 $_{(FPh)}$), 173.7 (1C, *C*ONH_2).

Exact mass (APCI): (m/z) = 432.2173 (calcd. for 432.2145 $C_{26}H_{28}BFNO_3$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 3476 (CON-H), 2978 (C-H, aliph), 1678 (C=O), 1605 (C=C, arom), 1505 (C=C, arom), 1358 (C-H, geminal $(CH_3)_2$).

2.2.2.5 Synthesis of tosylate precursor 31 for the preparation of [^{18}F]28

Ethane-1,2-diyl bis(4-methylbenzenesulfonate) (30) [5]



Under N_2 atmosphere, ethane-1,2-diol (**29**, 0.33 mL, 5.90 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (5 mL) and triethylamine (2.48 mL, 18.0 mmol, 3.1 eq.) was added. The mixture was cooled to 0 °C and stirred for 5 min. 4-Methylbenzenesulfonyl chloride (2.56 g, 13.4 mmol, 2.3 eq.) was added. The mixture was stirred for 12 h at room temperature. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 25 cm, V = 20 mL, CH_2Cl_2 : CH_3OH = 20:1), R_f = 0.83 (CH_2Cl_2 : CH_3OH = 20:1).

Colorless soild, mp = 127 °C, yield 2.11 g (97 %). Purity (HPLC, method 1): 97.6 % (t_R = 21.9 min).

$C_{16}H_{18}O_6S_2$ (M_r = 370.4).

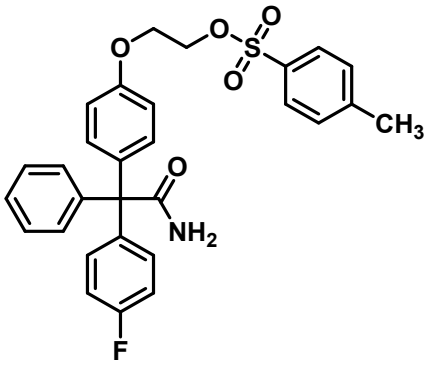
Spectroscopic data

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.45 (s, 6H, CH_3), 4.18 (s, 4H, CH_2), 7.31 – 7.36 (m, 4H, 3-*H*, 5-*H* $_{(Ph)}$), 7.70 – 7.76 (m, 4H, 2-*H*, 6-*H* $_{(Ph)}$).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 21.8 (2C, *C*H_3), 66.8 (2C, *C*H_2), 128.1 (4C, C-2, C-6 $_{(Ph)}$), 130.1 (4C, C-3, C-5 $_{(Ph)}$), 132.5 (2C, C-1 $_{(Ph)}$), 145.4 (2C, C-4 $_{(Ph)}$).

Exact mass (APCI): (m/z) = 371.0581 (calcd. 371.0618 for $C_{16}H_{19}O_6S_2$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 1597 (C=C, arom), 1492 (C=C, arom), 1358 (S=O), 1177 (S=O).

2-{4-[1-Carbamoyl-1-(4-fluorophenyl)phenylmethyl]phenoxy}ethyl 4-methylbenzenesulfonate (31)



Amide **9** (100 mg, 0.311 mmol, 1.0 eq.) and Cs_2CO_3 (122 mg, 0.374 mmol, 1.2 eq.) were dissolved in DMF (2 mL). The mixture was stirred for 10 min. Ethylene bis(4-methylbenzenesulfonate) (**30**, 138 mg, 0.373 mmol, 1.2 eq.) was added and the mixture was stirred at room temperature for 24 h. LiCl solution (5% wt in H_2O, 5 mL) and ethyl acetate (5 mL) were added. The organic layer was separated and washed with LiCl solution (5% wt in H_2O, 3 x 5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Ø = 2 cm, h = 30 cm, V = 10 mL, cyclohexane : ethyl acetate = 1:1), R_f = 0.4 (cyclohexane : ethyl acetate = 2:1) .

Colorless solid, mp = 177 °C, yield 79.0 mg (49 %). Purity (HLPC, method 1): 95.1 % (t_R = 22.9 min).

$C_{29}H_{26}FNO_5S$ (M_r 519.6).

Spectroscopic data

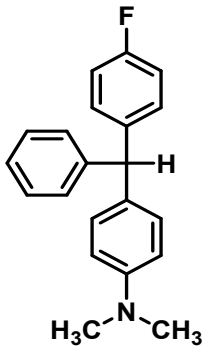
^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 2.41 (s, 3H, C*H*$_3$), 4.11 – 4.15 (m, 2H, PhOC*H*$_2$), 4.31 – 4.35 (m, 2H, TsOC*H*$_2$), 6.62 (bs, 1H, N*H*$_2$), 6.78 (d, *J* = 9.0 Hz, 2H, 2H, 2-*H*, 6-*H* $_{(OPh)}$), 7.06 (d, *J* = 8.9 Hz, 2H, 3-*H*, 5-*H* $_{(OPh)}$), 7.11 (t, *J* = 8.8 Hz, 2H, 3-*H*, 5-*H* $_{(FPh)}$), 7.15 – 7.21 (m, 4H, 2-*H*, 6-*H* $_{(FPh),}$ 2-*H*, 6-*H* $_{(Ph)}$), 7.21 – 7.26 (m, 1H, 4-*H* $_{(Ph)}$), 7.27 – 7.33 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$), 7.48 (d, *J* = 8.4 Hz, 2H, 3-*H*, 5-*H* $_{(OTs)}$), 7.53 (bs, 1H, N*H*$_2$), 7.80 (d, *J* = 8.5 Hz, 2H, 2-*H*, 6-*H* $_{(OTs)}$).
^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 21.1 (1C, *C*H$_3$), 65.3 (1C, PhO*C*H$_2$), 65.9 (1C, *C*CONH$_2$), 69.2 (1C, TsO*C*H$_2$), 113.6 (2C, C-2, C-6 $_{(OPh)}$), 114.2 (d, *J* = 21.0 Hz, 2C, C-3, C-5 $_{(FPh)}$), 126.5 (1C, C-4 $_{(Ph)}$), 127.7 (2C, C-2, C-6 $_{(OTs)}$), 127.7 (2C, C-3, C-5 $_{(Ph)}$), 129.9 (2C, C-2, C-6 $_{(Ph)}$), 130.2 (2C, C-3, C-5 $_{(OTs)}$), 131.2 (2C, C-3, C-5 $_{(OPh)}$), 132.0 (d, *J* = 8.0 Hz, 2C, C-2, C-6 $_{(FPh)}$), 132.2 (1C, C-4 $_{(OTs)}$), 136.1 (1C, C-4 $_{(OPh)}$), 140.3 (d, *J* = 3.3 Hz, 1C, C-1 $_{(FPh)}$), 144.0 (1C, C-1 $_{(Ph)}$), 145.0 (1C, C-1 $_{(OTs)}$), 156.2 (1C, C-1 $_{(OPh)}$, 160.6 (d, *J* = 243.4 Hz, 1C, C-4 $_{(FPh)}$), 174.1 (1C, *C*ONH$_2$).

Exact mass (APCI): (m/z) = 520.1570 (calcd. 520.1589 for $C_{29}H_{27}FNO_5S$ $[M+H]^+$)

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3453 (CON-H), 3129 (C-H, arom), 2928 (C-H, aliph), 1678 (C=O), 1597 (C=C, arom), 1504 (C=C, arom), 1354 (S=O), 1177 (S=O).

2.2.2.6 Decomposition products

4-[1-(4-Fluorophenyl)-1-phenylmethyl]-*N,N*-dimethylaniline (19)



Trimethylammonium iodide **18** (20.0 mg, 0.04 mmol, 1.0 eq.) was dissolved in dry DMF (1 mL). Tetrabutylammonium fluoride (55.0 mg, 0.21 mmol, 5.3 eq.) was added and the mixture was stirred at 155 °C for 10 min. After cooling down to room temperature, LiCl solution (5 % wt in H_2O, 5 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was separated and washed with LiCl solution (5 % wt in H_2O, 3 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 2 cm, h = 30 cm, V = 10 mL, cyclohexane : ethyl acetate = 2:1), R_f = 0.61 (cyclohexane : ethyl acetate = 2:1).

Pale yellow oil, yield 9.7 mg (78 %). Purity (HPLC, method 1): 93.9 % (t_R = 19.6 min).

$C_{21}H_{20}FN$ (M_r = 305.4).

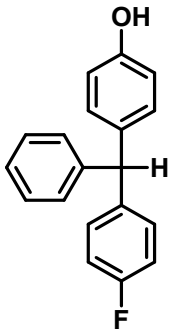
Spectroscopic data

^{1}H NMR (4600 MHz, DMSO-d_6): δ (ppm) = 2.85 (s, 6H, N(C*H*$_3$)$_2$), 5.48 (s, 1H, C*H*), 6.66 (d, *J* = 8.7 Hz, 2H, 2-*H*, 6-*H* $_{(NPh)}$), 6.91 (d, *J* = 8.7 Hz, 2H, 3-*H*, 5-*H* $_{(NPh)}$), 7.05 – 7.14 (m, 6H, 2-*H*, 3-*H*, 5-*H*, 6-*H* $_{(FPh)}$), 2-*H*, 6-*H* $_{(Ph)}$)), 7.17 – 7.22 (m, 1H, 4-*H* $_{(Ph)}$), 7.25 – 7.31 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 40.2 (2C, N(*C*H$_3$)$_2$), 54.1 (1C, *C*H), 112.5 (2C, C-2, C-6 $_{(NPh)}$), 114.9 (d, *J* = 21.3 Hz, 2C, C-3, C-5 $_{(FPh)}$), 126.1 (1C, C-4 $_{(Ph)}$), 128.3 (2C, C-3, C-5 $_{(Ph)}$), 128.9 (2C, C-2, C-6 $_{(Ph)}$), 129.4 (2C, C-3, C-5 $_{(NPh)}$), 130.7 (d, *J* = 8.9 Hz, 2C, C-2, C-6 $_{(FPh)}$), 140.8 (d, *J* = 3.2 Hz, 1C, C-1 $_{(FPh)}$), 144.5 (1C, C-1 $_{(Ph)}$), 148.9 (1C, C-1 $_{(NPh)}$), 160.6 (d, *J* = 242.2 Hz, 1C, C-4 $_{(FPh)}$).
The signal for C-4 $_{(NPh)}$ cannot be observed in the spectrum.

Exact mass (APCI): (m/z) = 306.1653 (calcd. 306.1653 for $C_{21}H_{21}FN$ $[M+H]^+$).

IR (neat): ṽ (cm^{-1}) = 2959 (C-H, aliph), 1612 (C=C, arom), 1505 (C=C, arom).

4-[1-(4-Fluorophenyl)-1-phenylmethyl]phenol (21)



Tosylate **20** (10.0 mg, 0.02 mmol, 1.0 eq.) was dissolved in DMF (3 mL). Tetrabutylammonium fluoride (86.1 mg, 0.33 mmol, 15.7 eq.) was added and the mixture was stirred at 130 °C for 20 min. After cooling down to room temperature, LiCl solution (5 % wt in H_2O, 5 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was separated and washed with LiCl solution (5 % wt in H_2O, 3 x 5 mL).The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 2 cm, h = 25 cm, V = 10 mL, cyclohexane : ethyl acetate = 2:1), R_f = 0.63 (cyclohexane : ethyl acetate = 2:1).

Pale yellow oil, yield 4.7 mg (80 %). Purity (HPLC, method 1): 98.9 % (t_R = 22.0 min).

$C_{19}H_{15}FO$ (M_r = 278.3).

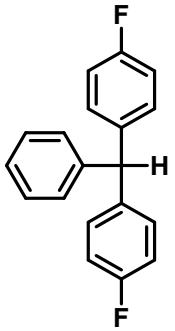
Spectroscopic data

^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 5.50 (s, 1H, C*H*), 6.69 (d, *J* = 8.8 Hz, 2H, 2-*H*, 6-*H* $_{(OPh)}$), 6.88 (d, *J* = 8.8 Hz, 2H, 3-*H*, 5-*H* $_{(OPh)}$), 7.06 – 7.14 (m, 6H, 2-*H*, 3-*H*, 5-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 6-*H* $_{(Ph)}$), 7.18 – 7.22 (m, 1H, 4-*H* $_{(Ph)}$), 7.26 – 7.32 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$), 9.29 (s, 1H, O*H*).
^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 54.2 (1C, *C*H), 115.0 (d, *J* = 21.3 Hz, 2C, C-3, C-5 $_{(FPh)}$), 115.1 (2C, C-2, C-6 $_{(OPh)}$), 126.2 (1C, C-4 $_{(Ph)}$), 128.3 (2C, C-3, C-5 $_{(Ph)}$), 128.9 (2C, C-2, C-6 $_{(Ph)}$), 129.9 (2C, C-3, C-5 $_{(OPh)}$), 130.7 (d, *J* = 8.1 Hz, 2C, C-2, C-6 $_{(FPh)}$), 133.9 (1C, C-4 $_{(OPh)}$), 140.6 (d, *J* = 2.9 Hz, 1C, C-1 $_{(FPh)}$), 144.3 (1C, C-1 $_{(Ph)}$), 155.7 (1C, C-1 $_{(OPh)}$), 160.6 (d, *J* = 242.2 Hz, 1C, C-4 $_{(FPh)}$).

Exact mass (APCI): (m/z) = 277.1015 (calcd. 277.1023 for $C_{19}H_{14}FO$ $[M-H]^+$).

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 1601 (C=C, arom), 1508 (C=C, arom).

4,4‘-Difluorotriphenylmethane (25)



Senicapoc (**1**, 100 mg, 0.31 mmol, 1.0 eq.) was dissolved in DMF (8 mL). Tetrabutylammonium fluoride (405 mg, 1.55 mmol, 5.0 eq.) was added and the mixture was stirred at 130 °C for 10 min. After cooling down to room temperature, LiCl solution (5 % wt in H_2O, 10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated and washed with LiCl solution (5 % wt in H_2O, 3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 3 cm, h = 25 cm, V = 20 mL, cyclohexane : CH_2Cl_2 = 1:1), R_f = 0.71 (cyclohexane : CH_2Cl_2 = 1:1).

Colorless oil, yield 65.2 mg (75 %). Purity (HPLC, method 1): 99.8 % (t_R = 24.8 min).

$C_{19}H_{14}F_2$ (M_r = 280.3).

Spectroscopic data

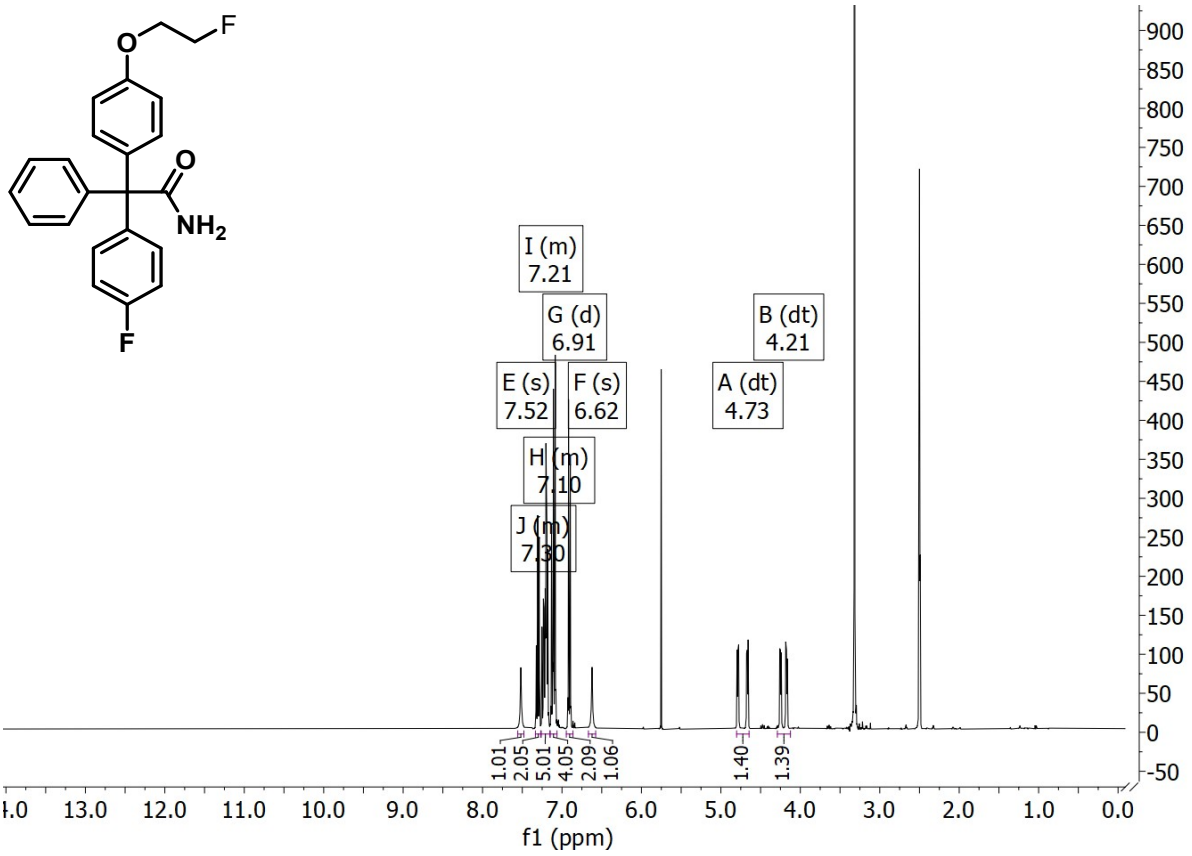
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.52 (s, 1H, C*H*), 6.98 (t, *J* = 8.6 Hz, 4H, 3-*H*, 5-*H* $_{(FPh)}$), 7.02 – 7.10 (m, 6H, 2-*H*, 6-*H* $_{(FPh)}$, 2-*H*, 6-*H* $_{(Ph)}$), 7.20 – 7.26 (m, 1H, 4-*H* $_{(Ph)}$), 7.27 – 7.33 (m, 2H, 3-*H*, 5-*H* $_{(Ph)}$).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 55.4 (1C, *C*H), 115.3 (d, *J* = 21.3 Hz, 4C, C-3, C-5 $_{(FPh)}$), 126.7 (1C, C-4 $_{(Ph)}$), 128.6 (2C, C-3, C-5 $_{(Ph)}$), 129.4 (2C, C-2, C-6 $_{(Ph)}$), 130.9 (d, *J* = 8.0 Hz, 4C, C-2, C-6 $_{(FPh)}$), 139.6 (d, *J* = 3.1 Hz, 2C, C-1 $_{(FPh)}$), 143.7 (1C, C-1 $_{(Ph)}$), 161.6 (d, *J* = 245.2 Hz, 2C, C-4 $_{(FPh)}$).

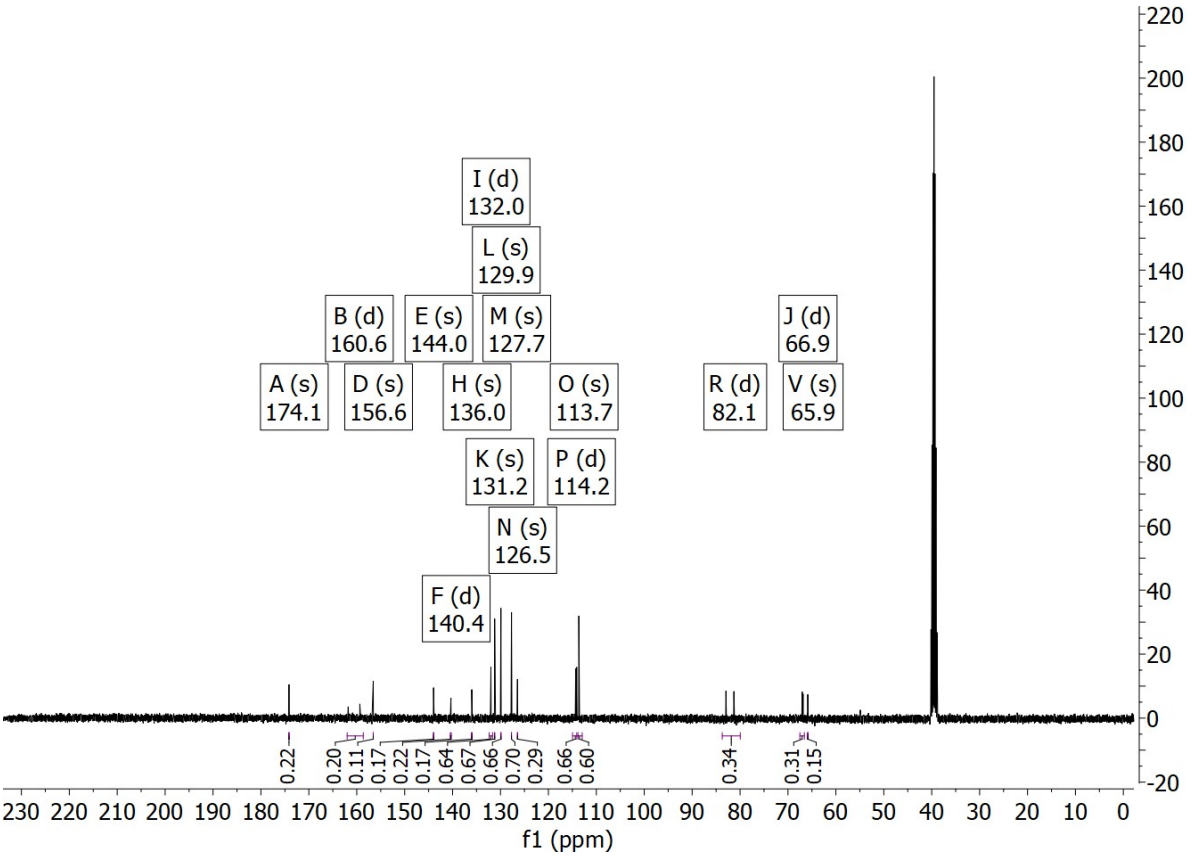
Exact mass (APCI): (m/z) = 279.0980 (calcd. 279.0980 for $C_{19}H_{13}F_2$ $[M-H]^+$).

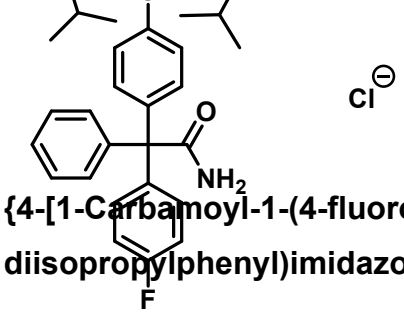
IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3028 (C-H, arom), 1601 (C=C, arom), 1505 (C=C, arom).

3. ^{1}H and ^{13}C NMR spectra of new compounds

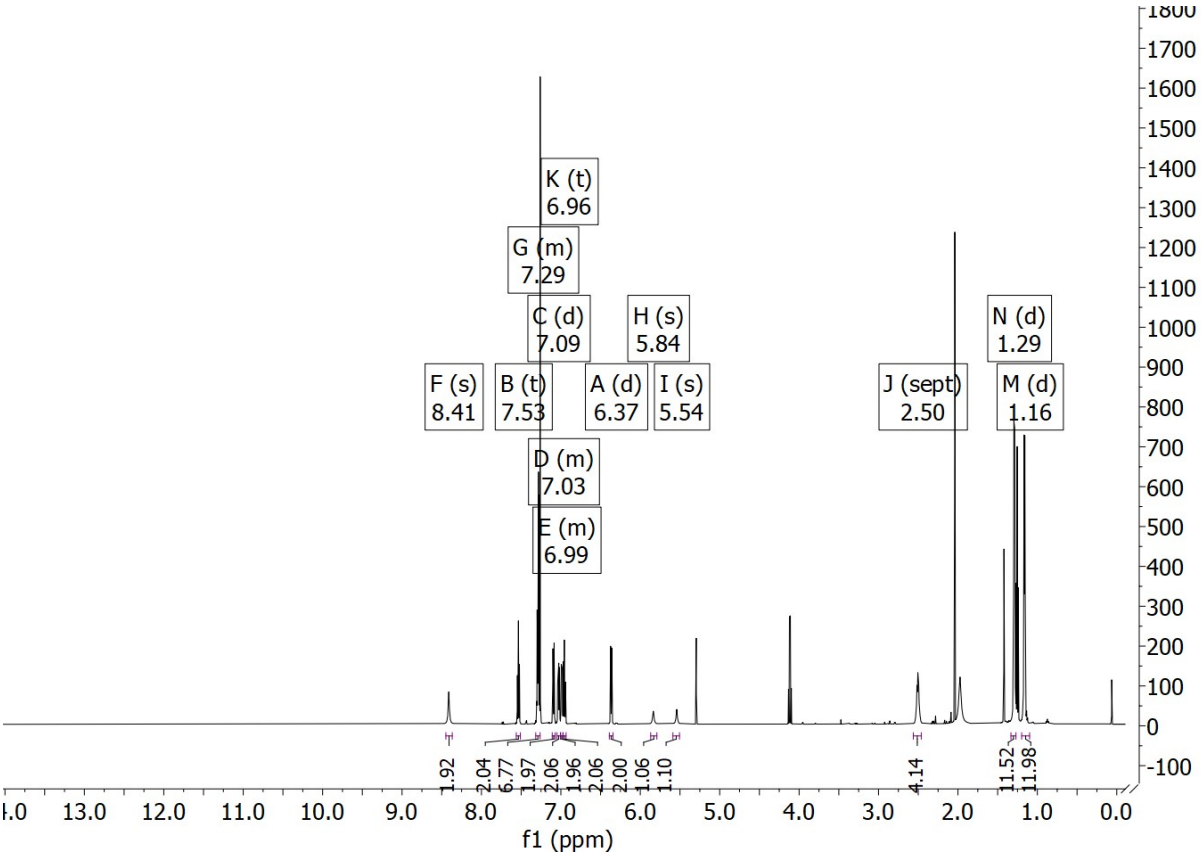
2-[4-(2-Fluoroethoxy)phenyl]-2-(4-fluorophenyl)-2-phenylacetamide (28)

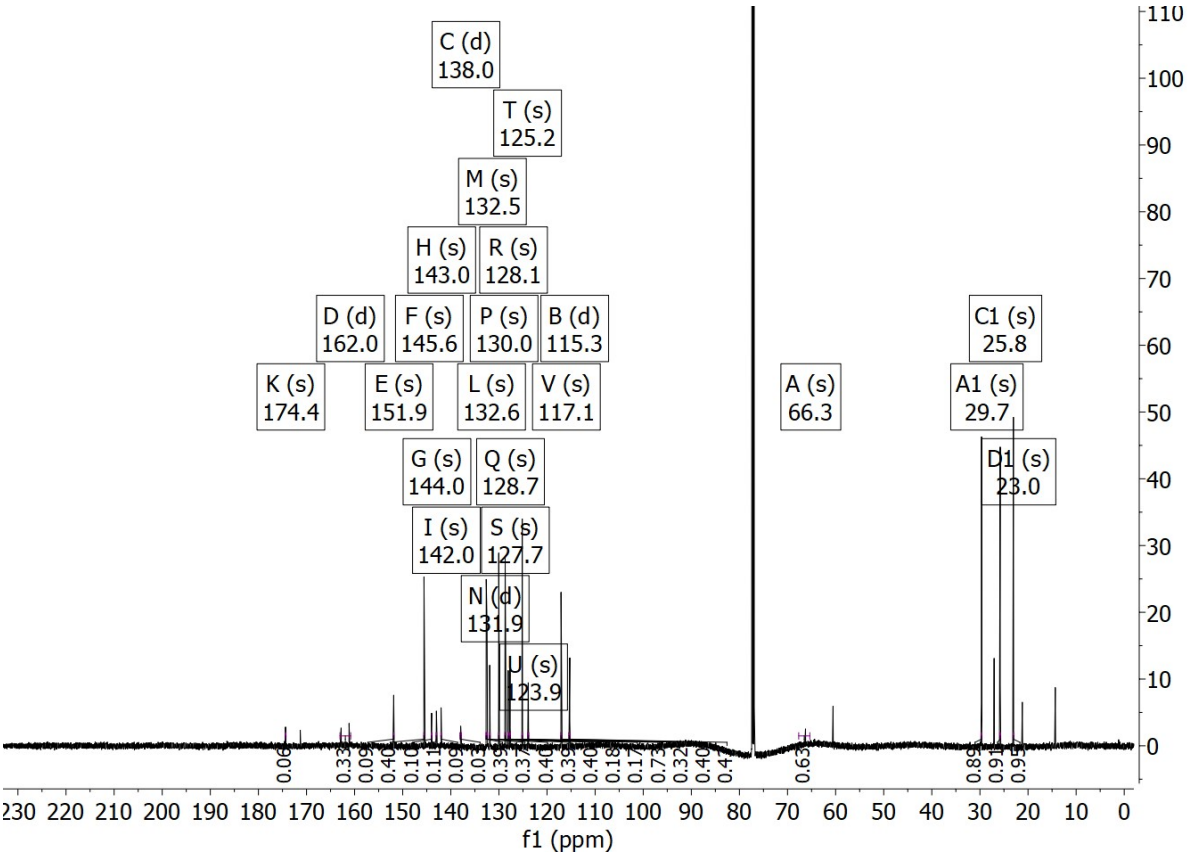




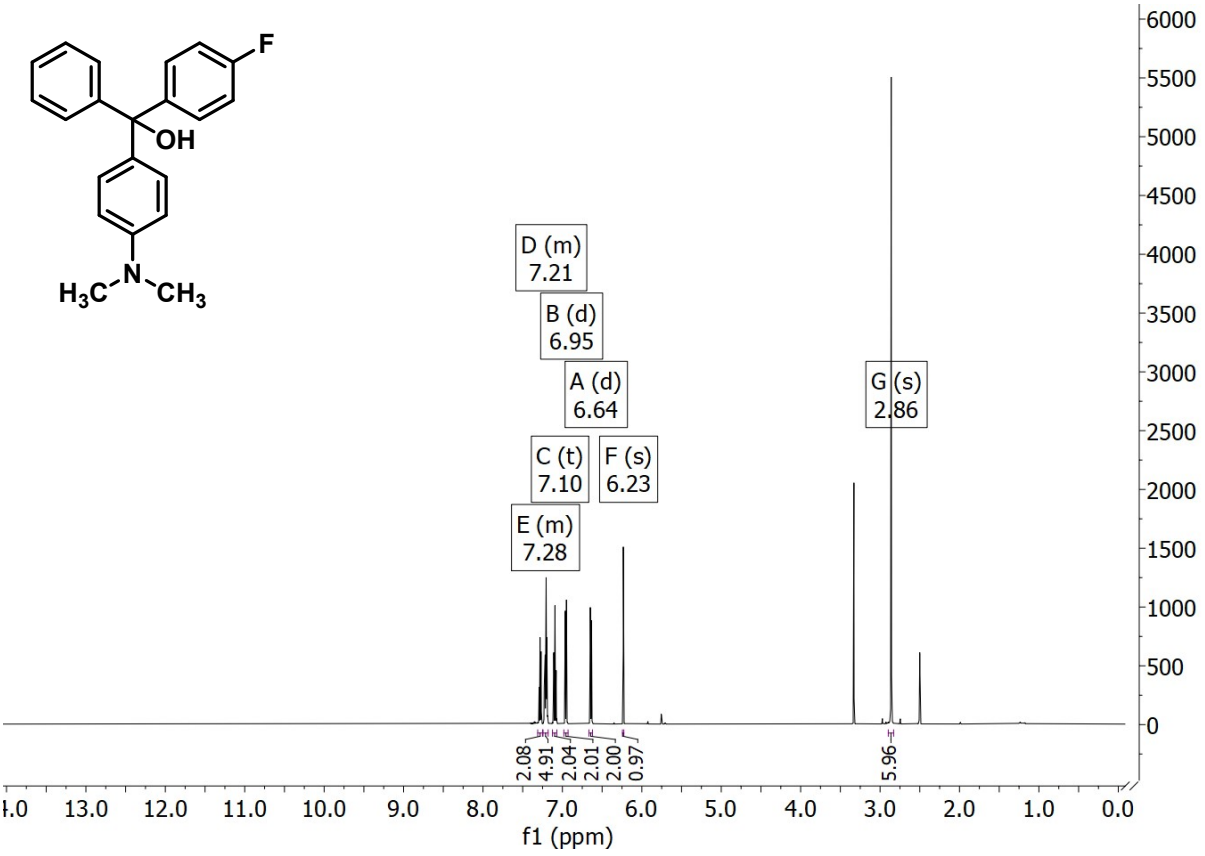


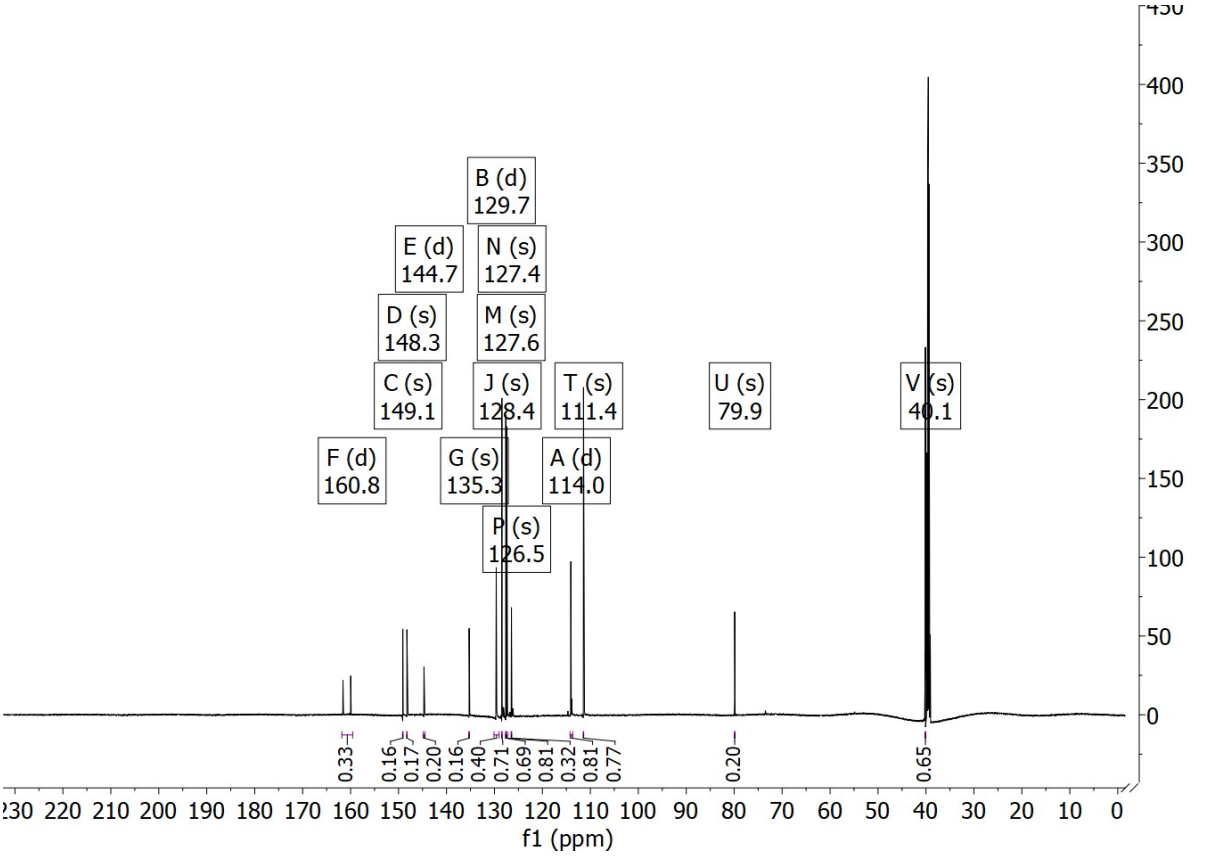
{4-[1-Carbamoyl-1-(4-fluorophenyl)1-phenylmethyl]phenoxy}-1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (10)



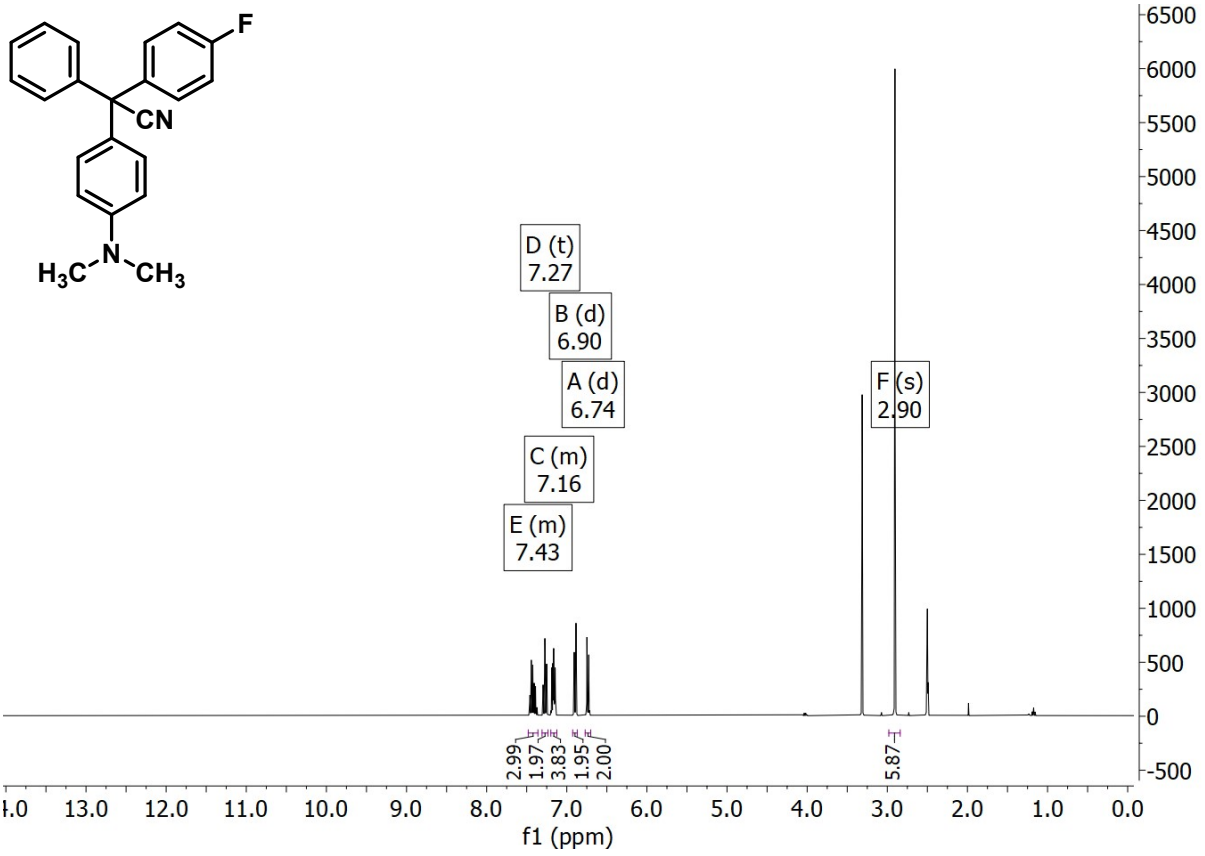


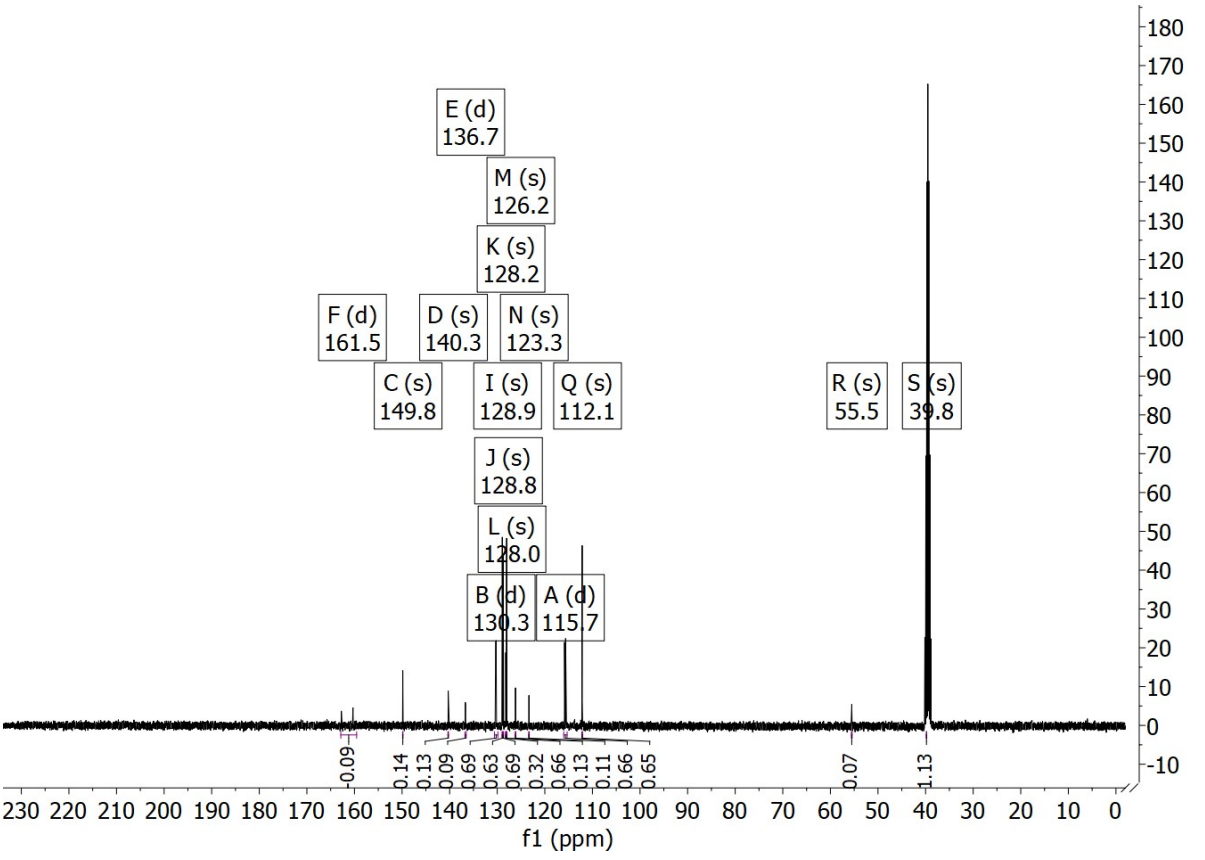
1-[4-(Dimethylamino)phenyl]-1-(4-fluorophenyl)-1-phenylmethanol (15)



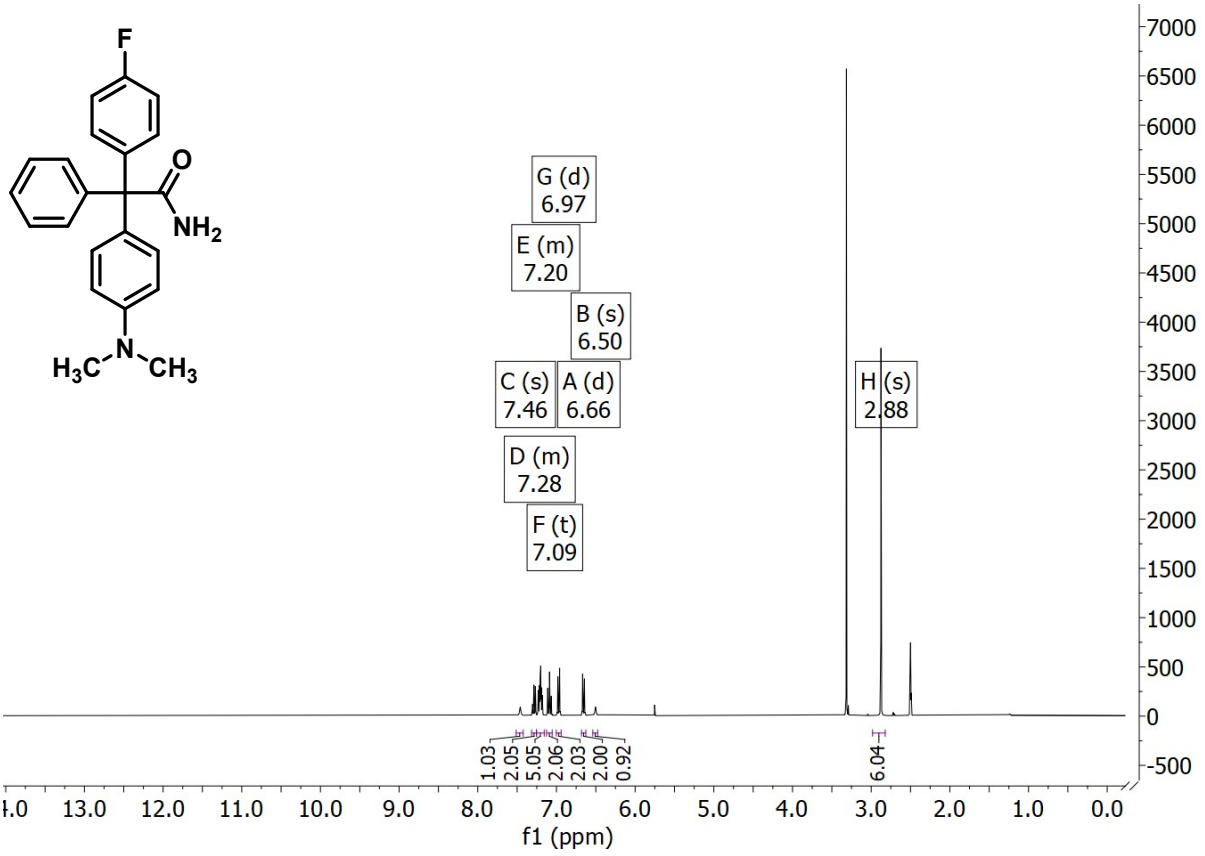


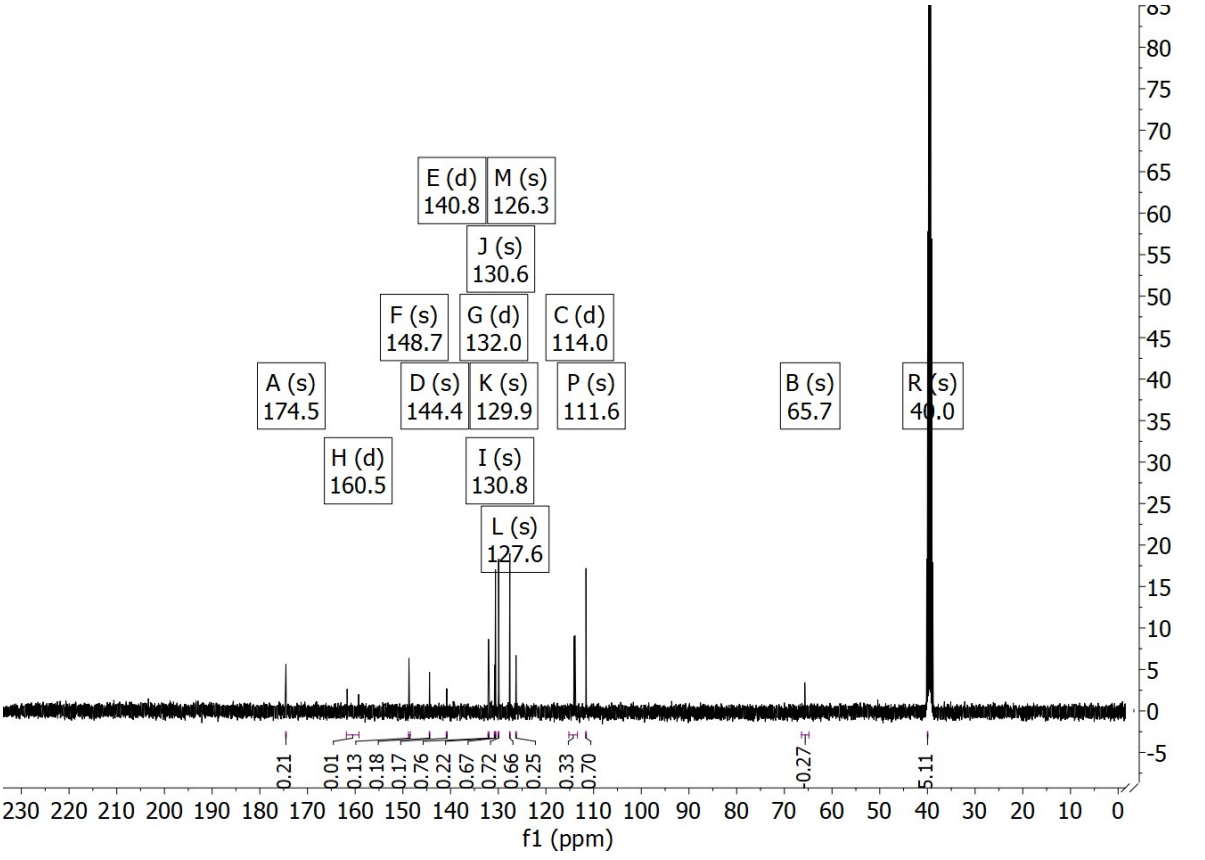
2-[4-(Dimethylamino)phenyl]-2-(4-fluorophenyl)-2-phenylacetonitrile (16)

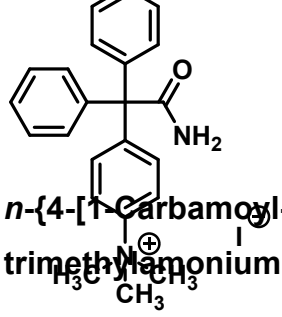




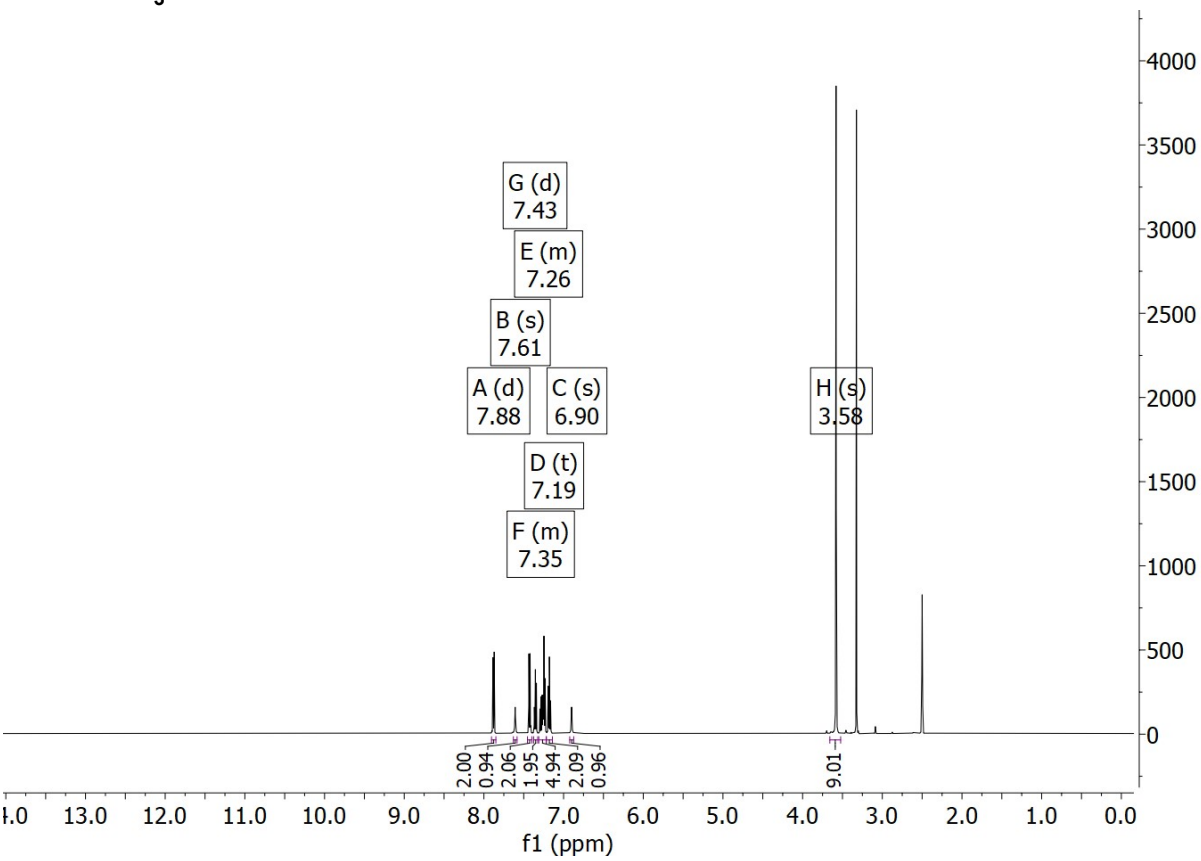
2-[4-(Dimethylamino)phenyl]-2-(4-fluorophenyl)-2-phenylacetamide (17)

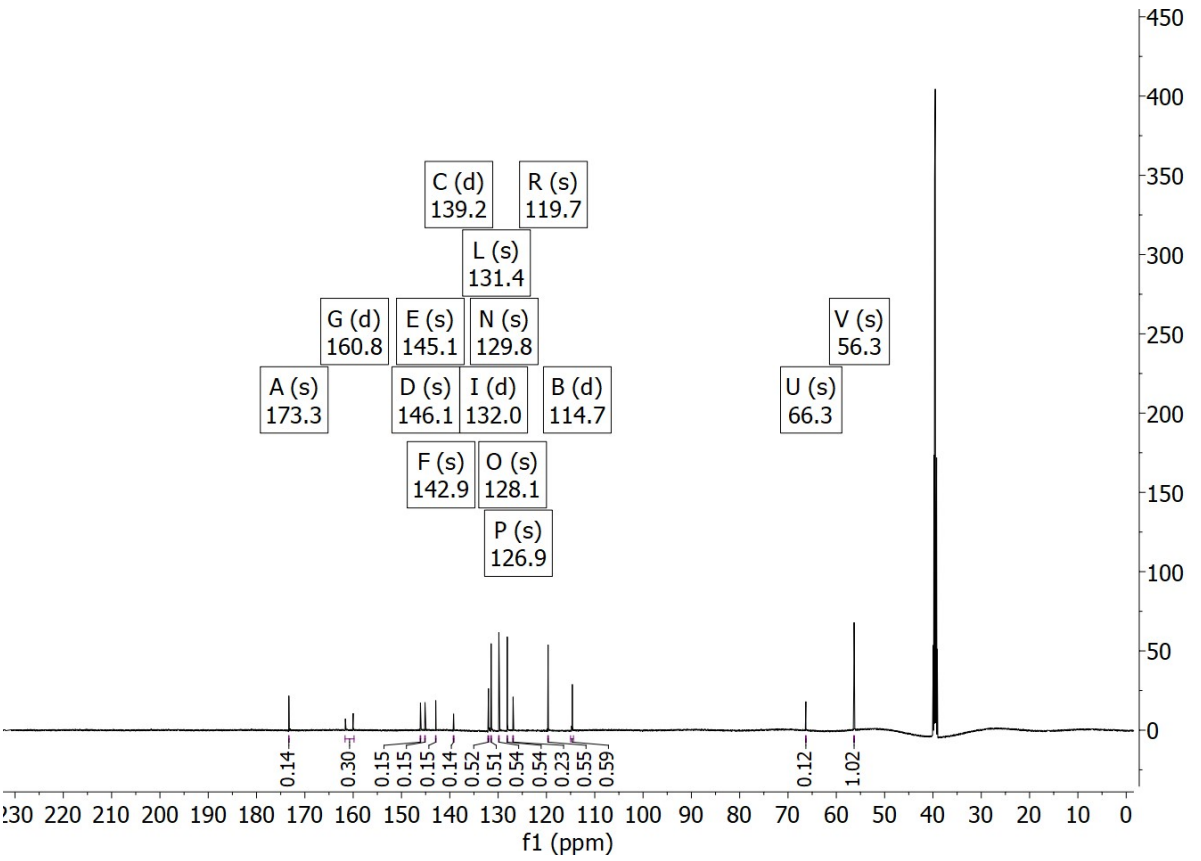




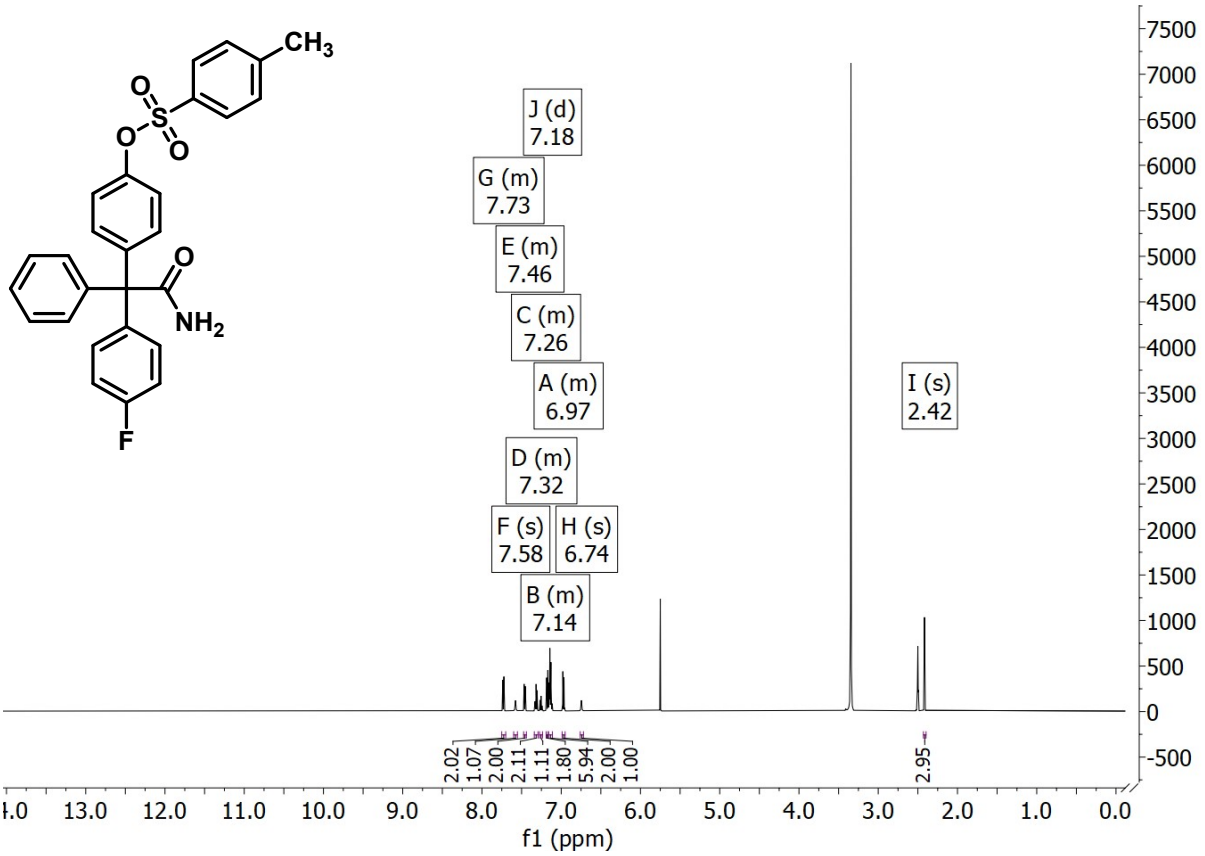


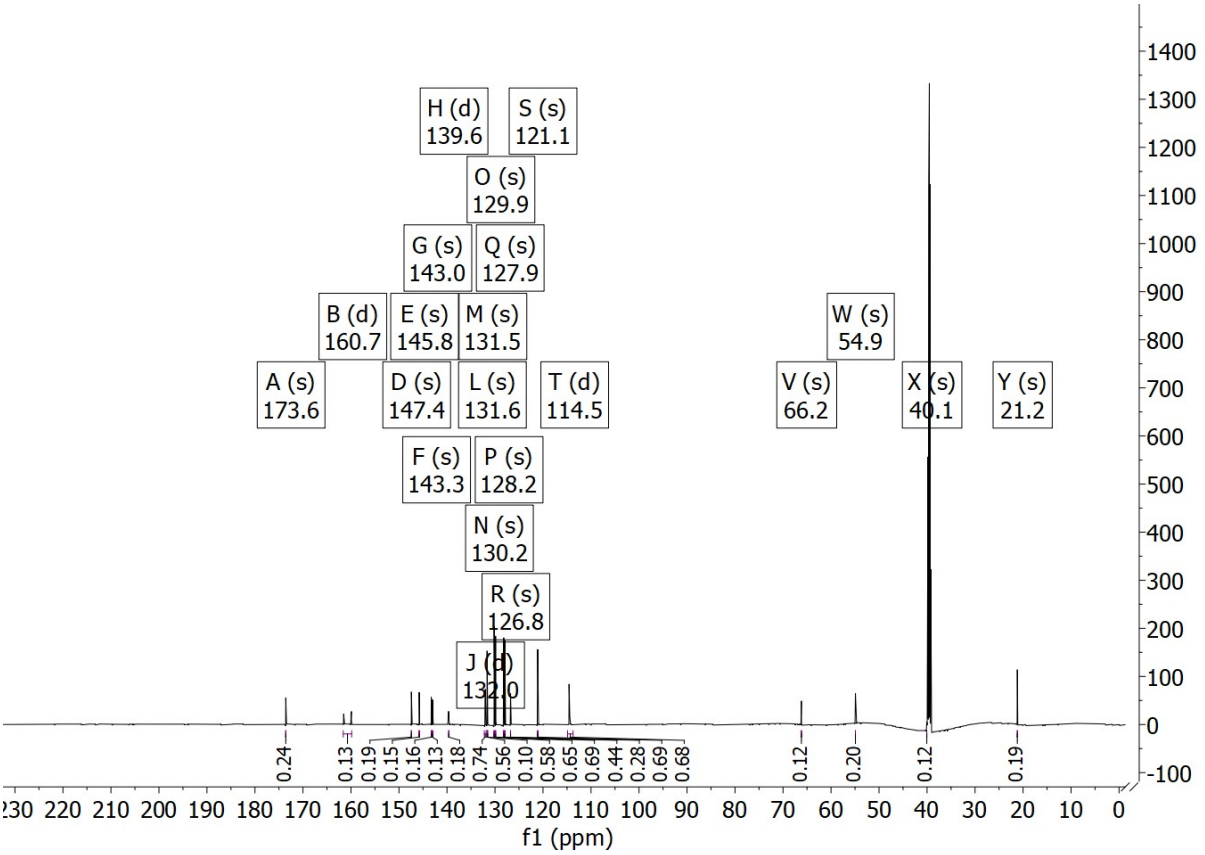
***n*-{4-[1-Carbamoyl-1-(4-fluorophenyl)-1-phenylmethyl]phenyl}-(-*N,N,N*-trimethyl)ammonium iodide (18)**



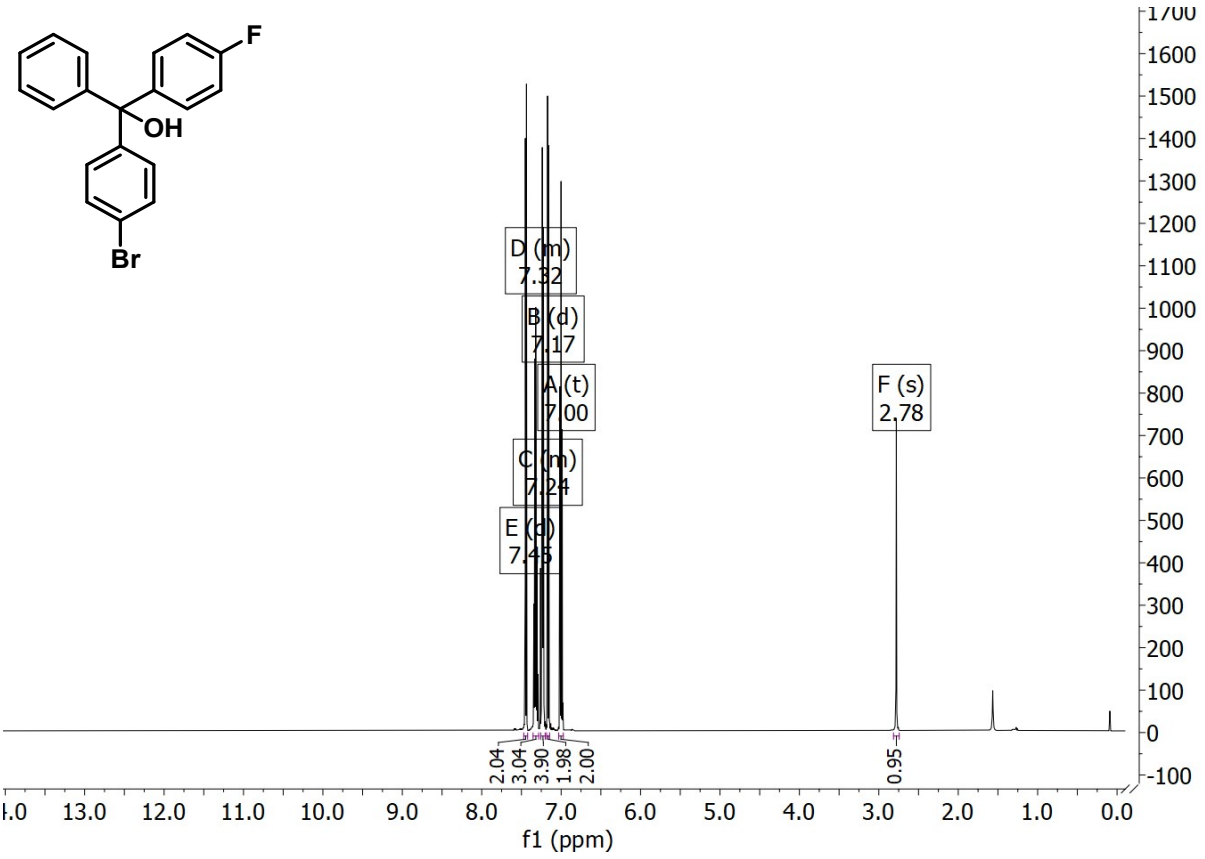


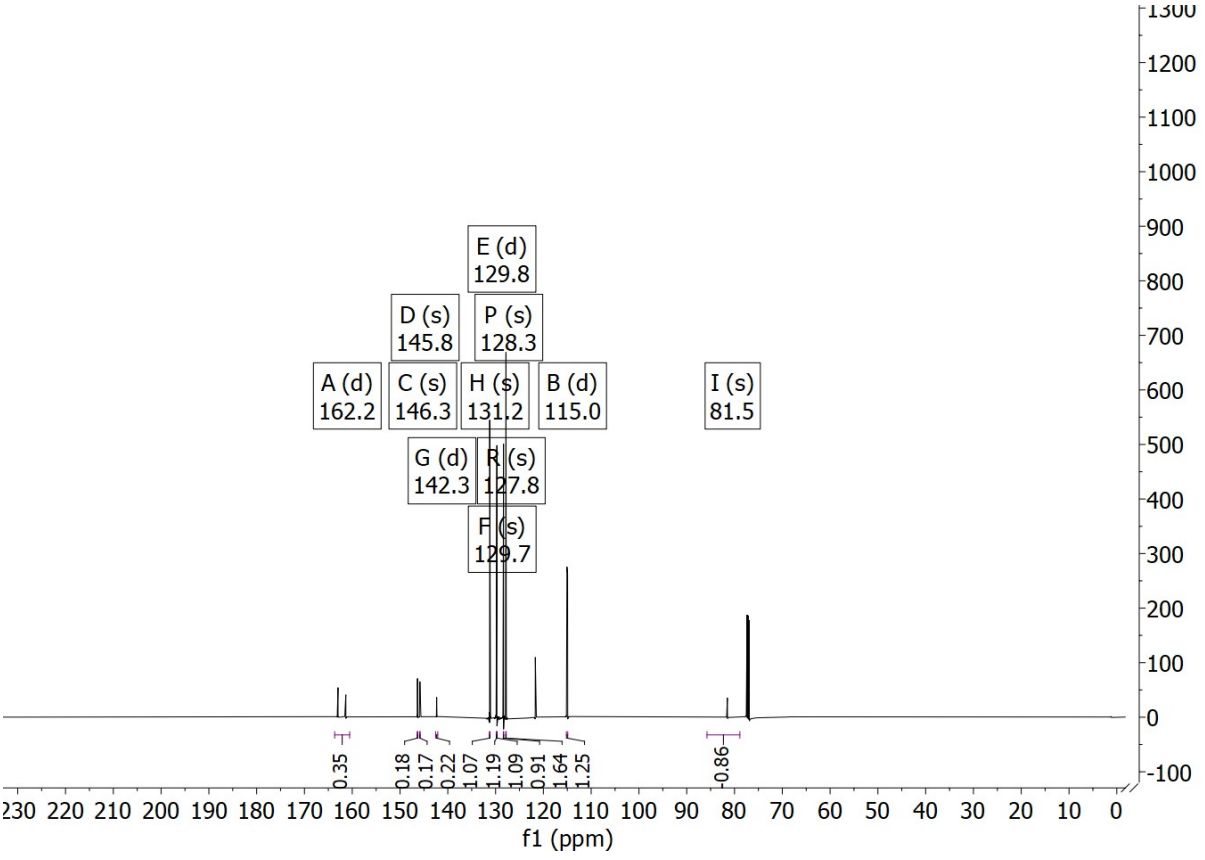
4-[1-Carbamoyl-1-(4-fluorophenyl)-1-phenylmethyl]phenyl 4-methylbenzenesulfonate (20)



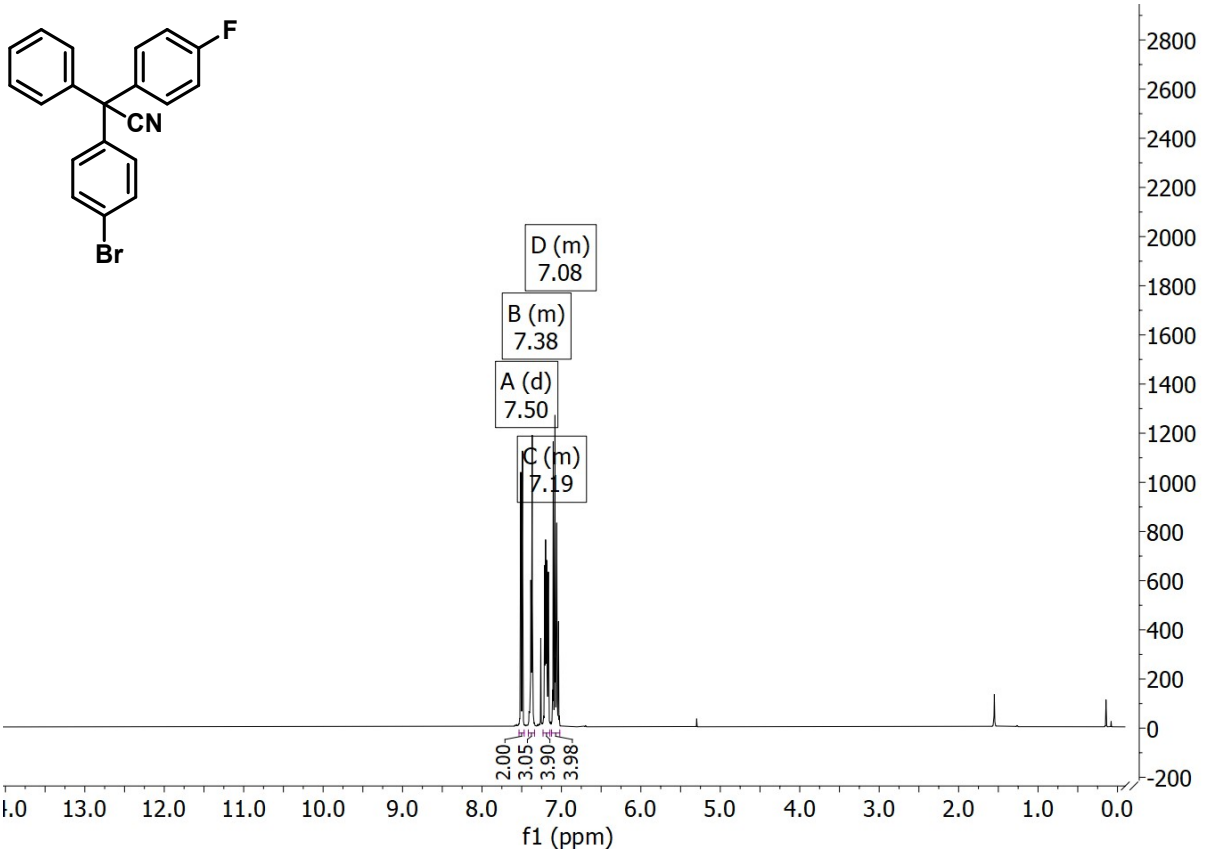


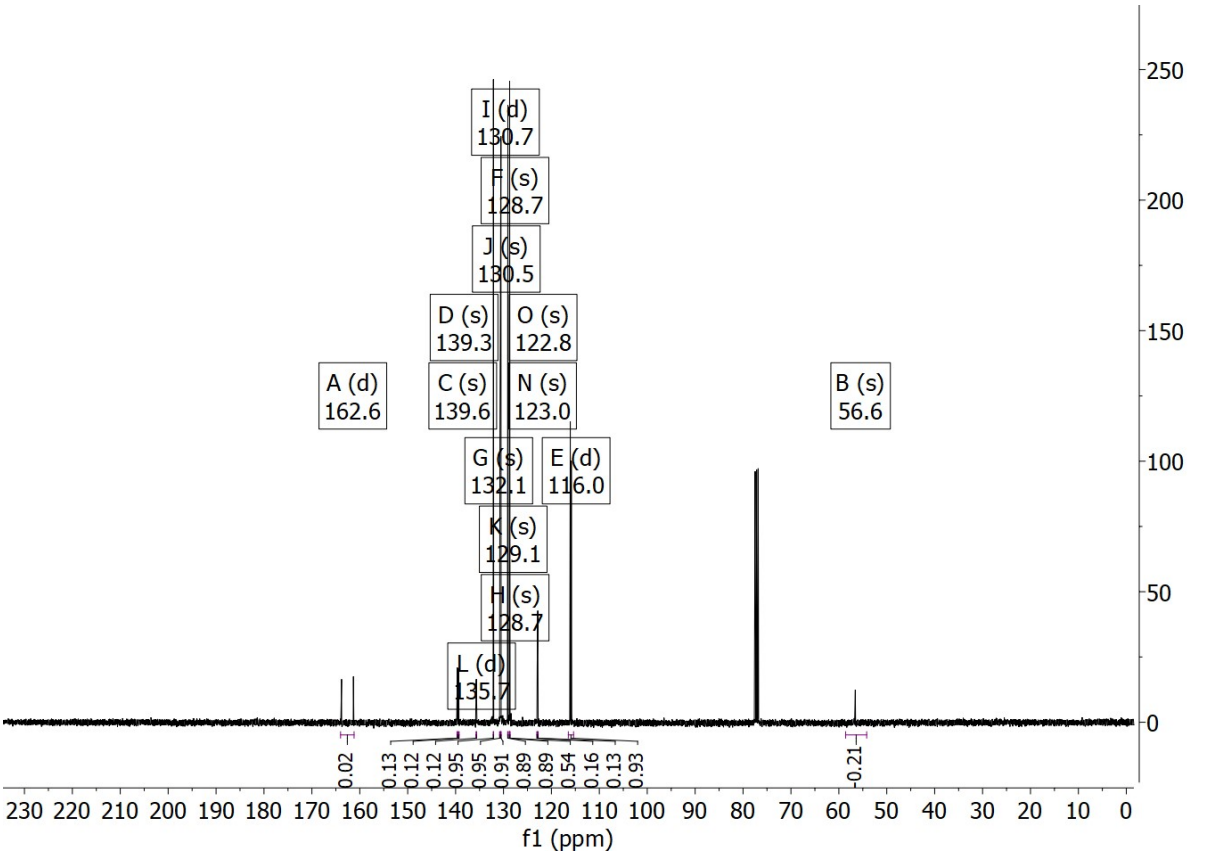
1-(4-Bromophenyl)-1-(4-fluorophenyl)-1-(phenyl)methanol (36)



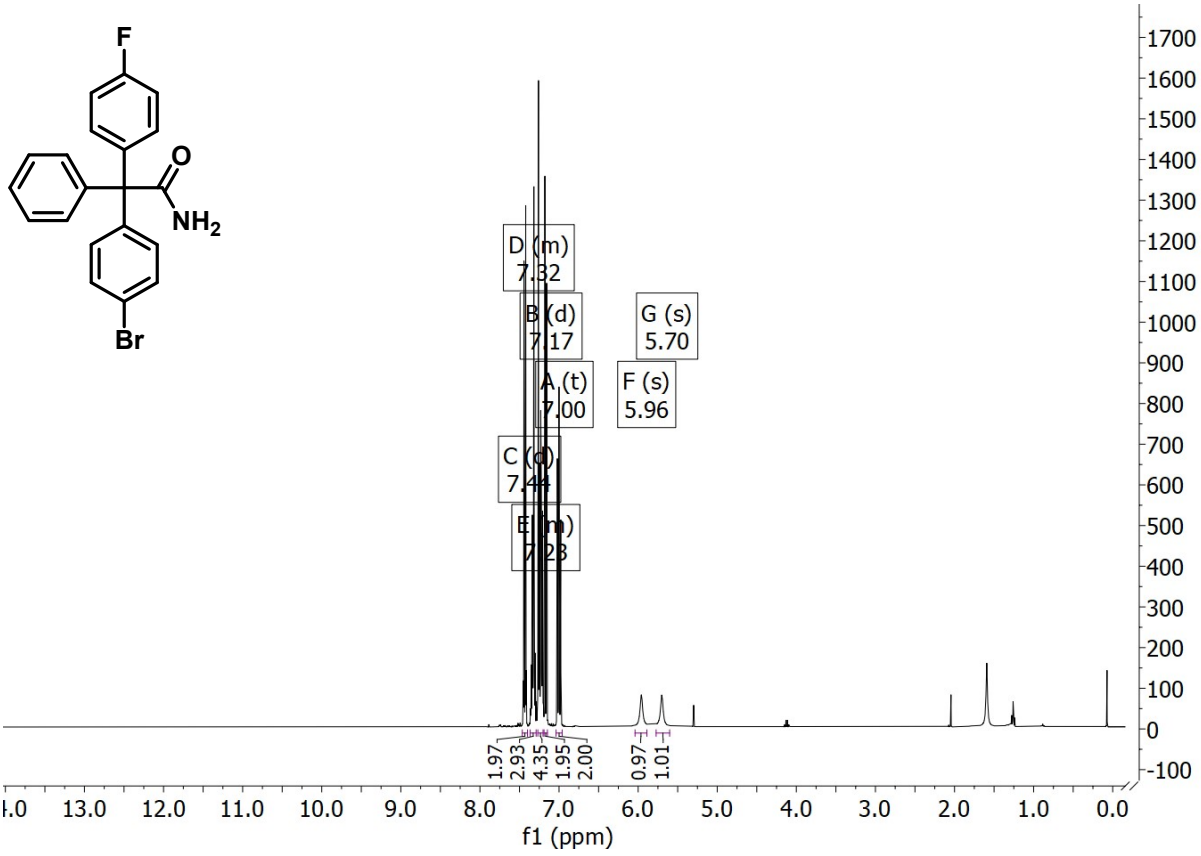


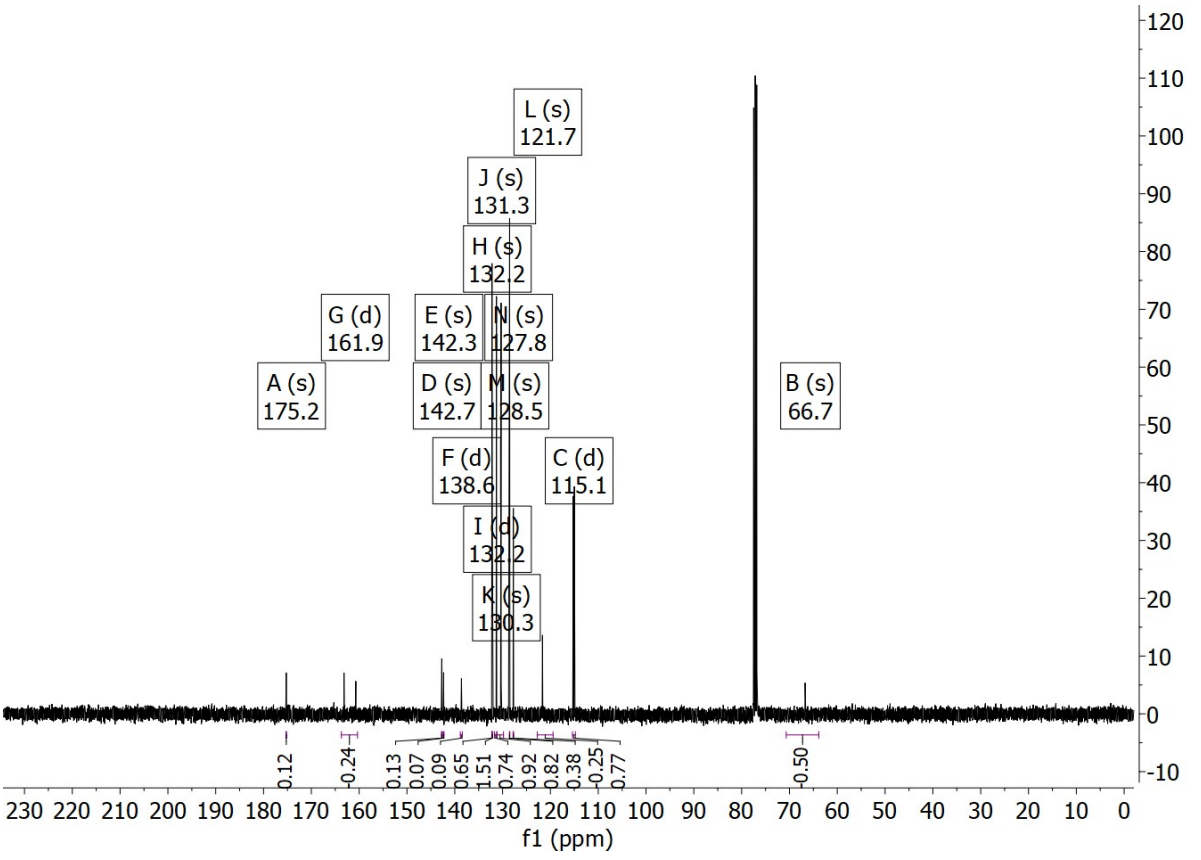
2-(4-Bromophenyl)-2-(4-fluorophenyl)-2-phenylacetonitrile (37)



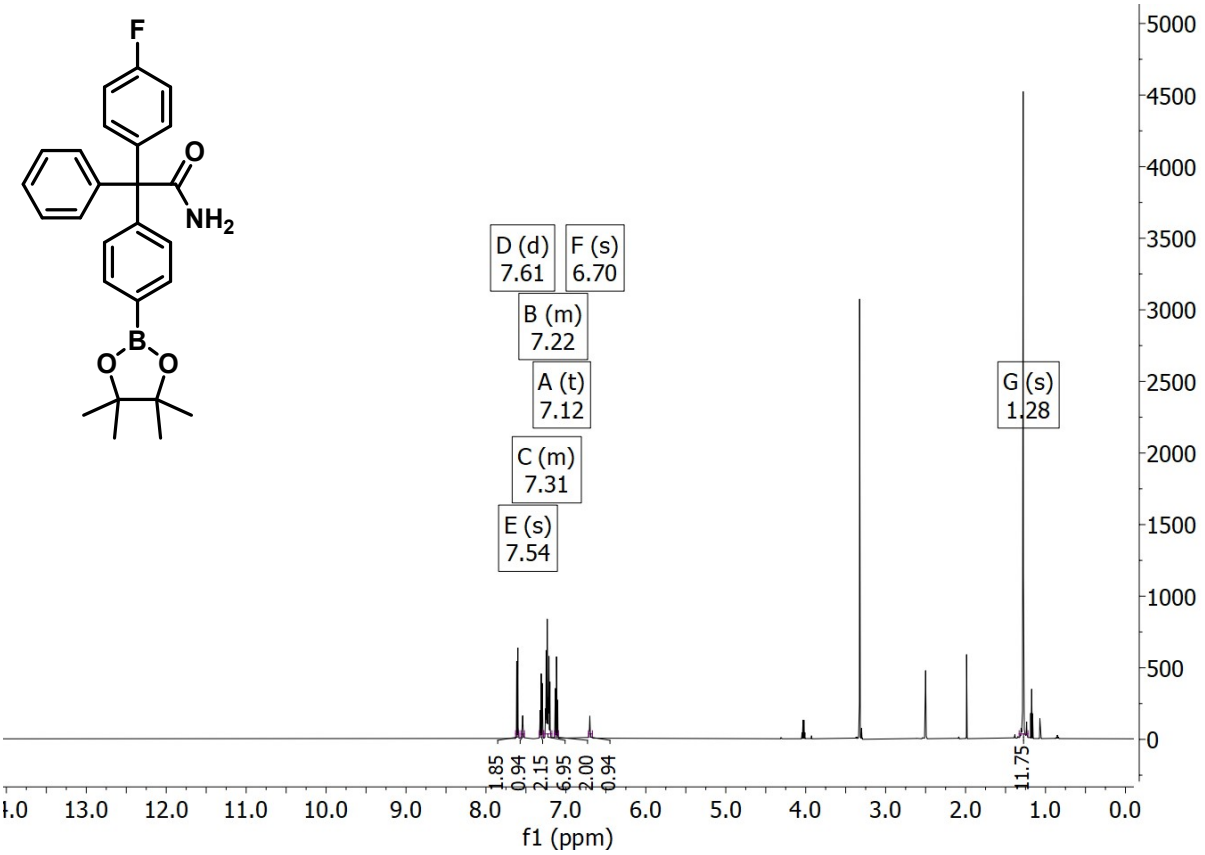


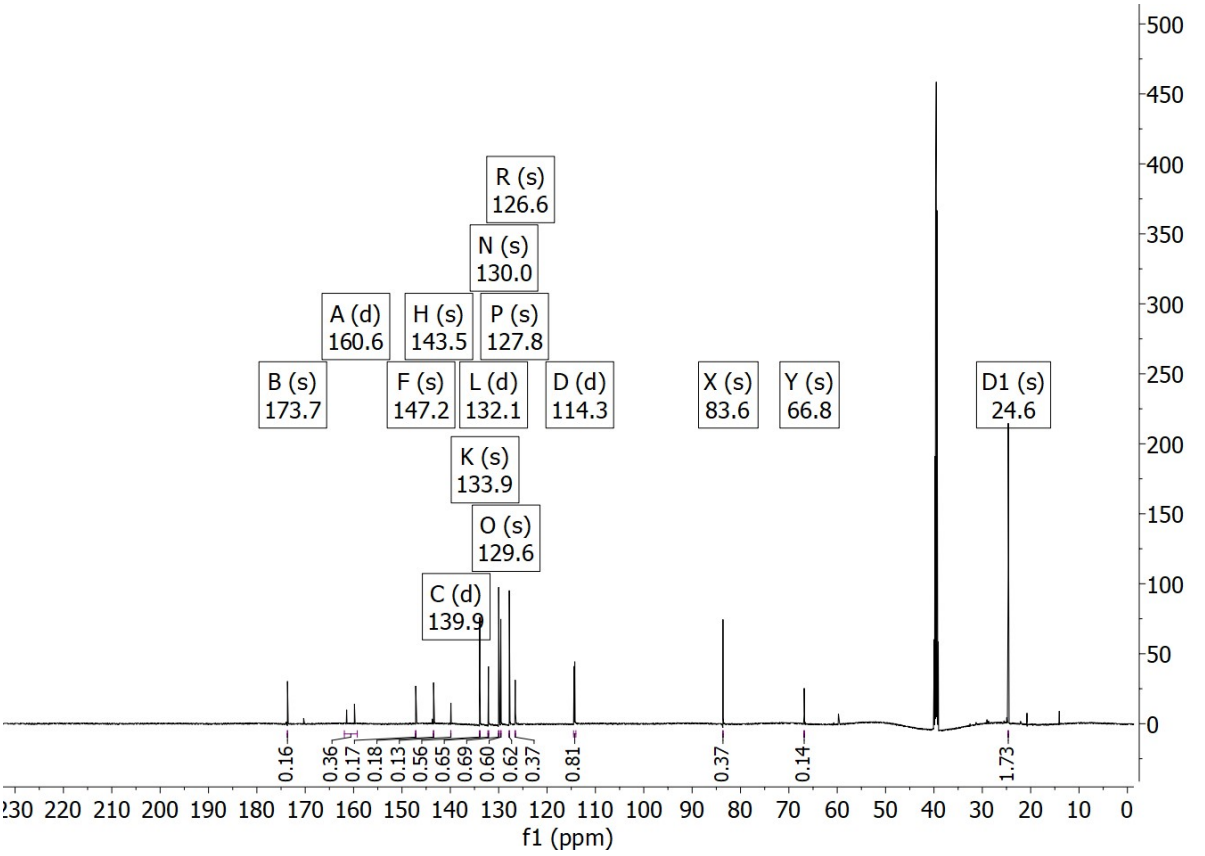
2-(4-Bromophenyl)-2-(4-fluorophenyl)-2-phenylacetamide (22)



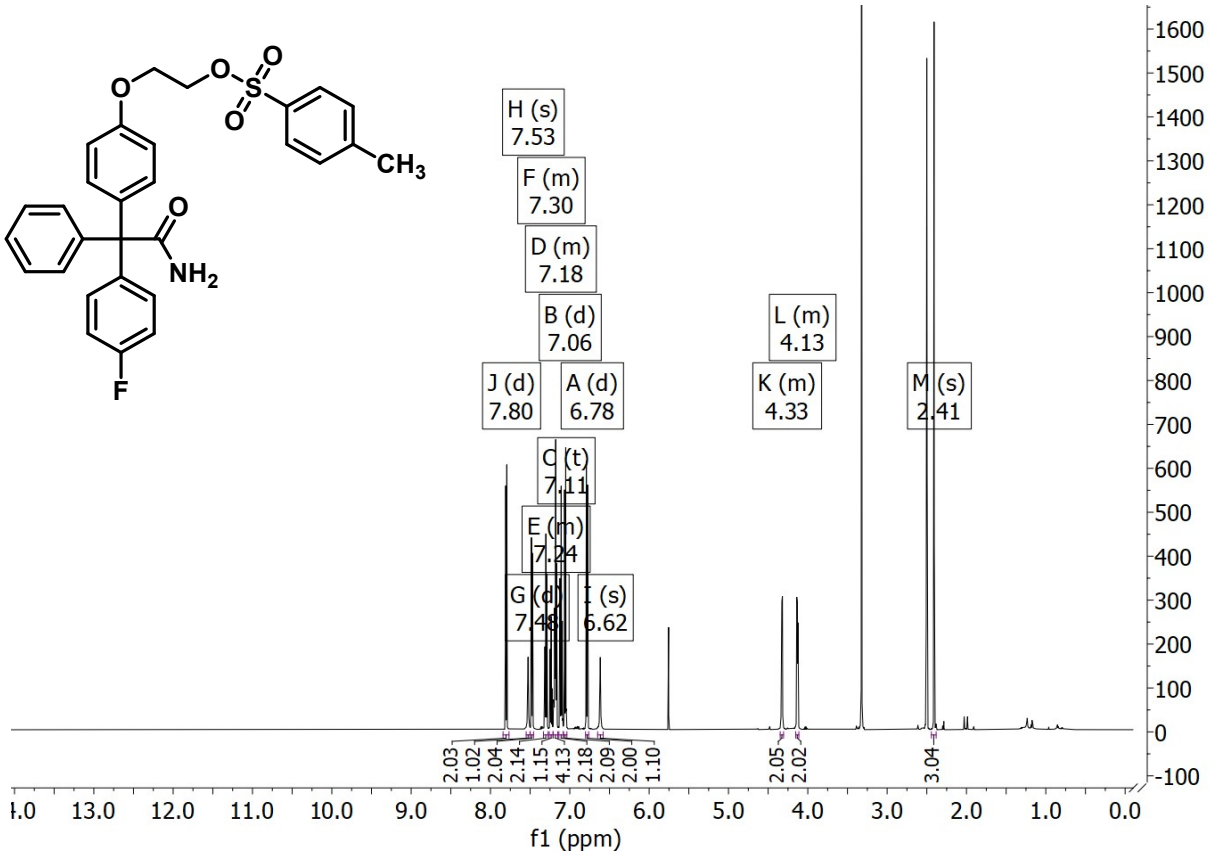


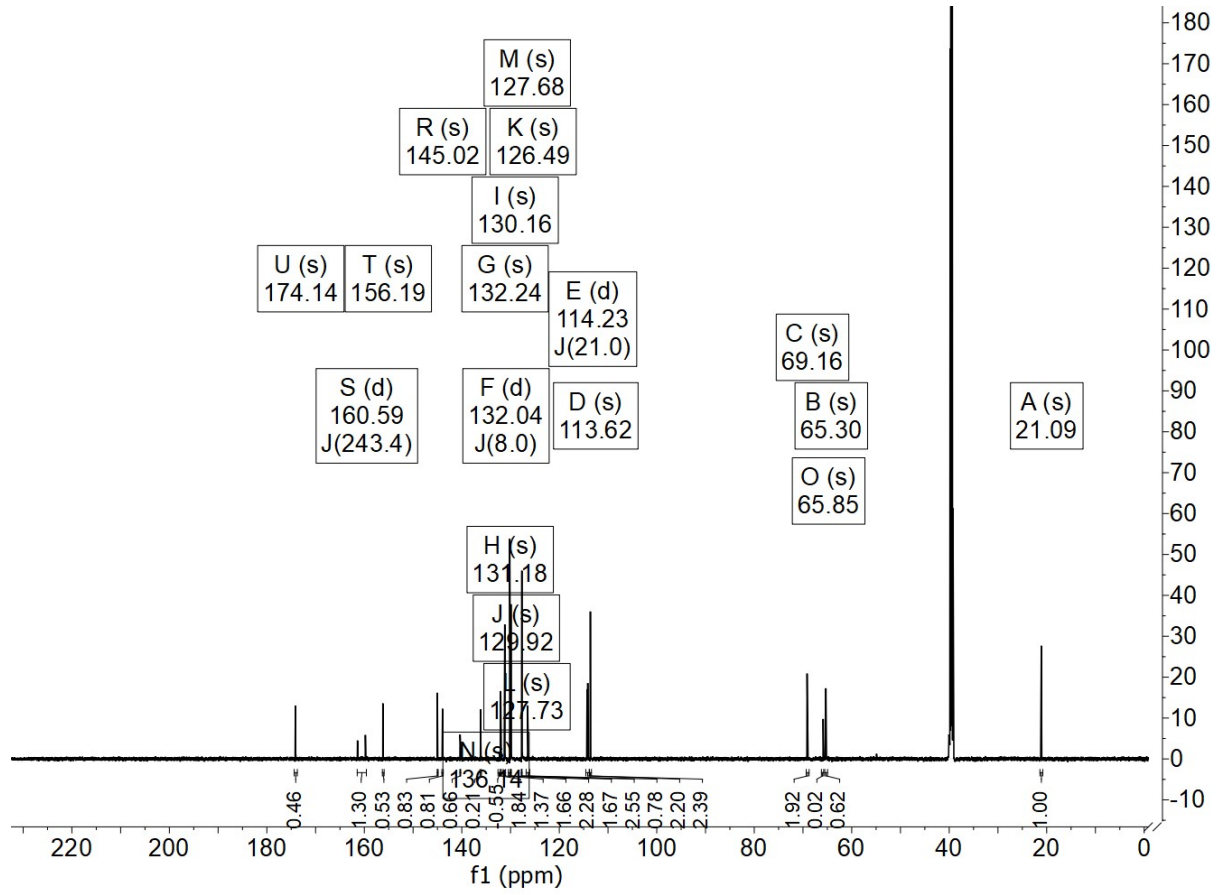
2-(4-Fluorophenyl)-2-phenyl-2-[4-(4,4,5,5-tatramethyl-1,2-dioxa-3-borolan-2-yl)phenyl]acetamide (24)



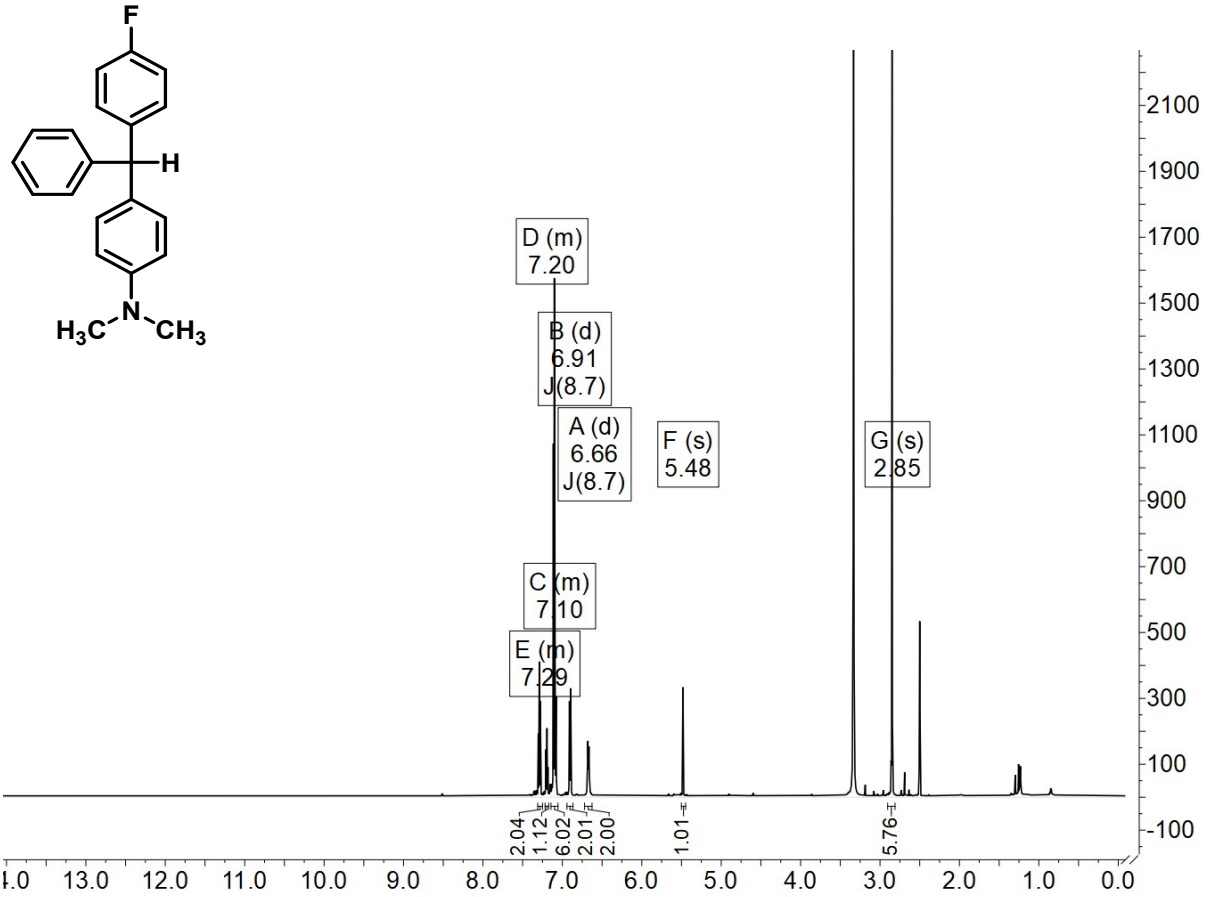


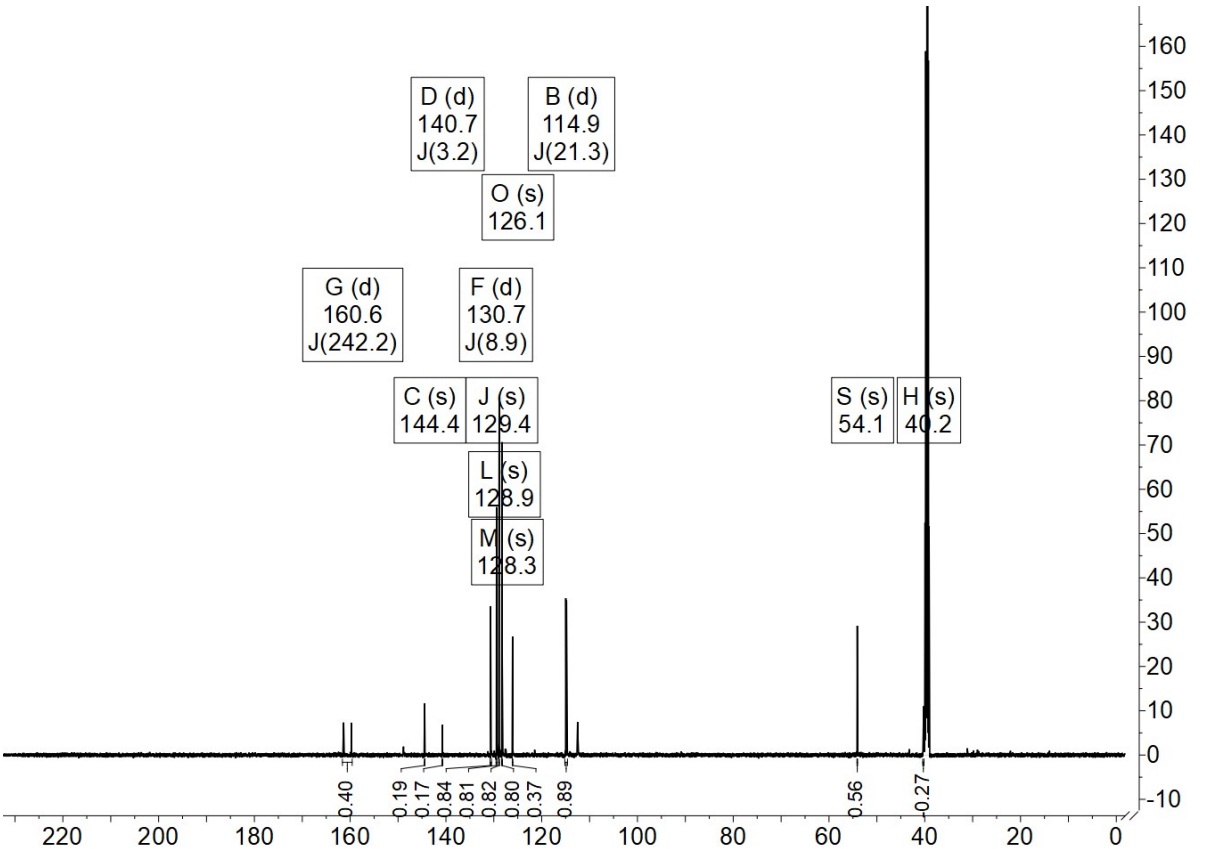
2-{4-[1-Carbamoyl-1-(4-fluorophenyl)phenylmethyl]phenoxy}ethyl 4-methylbenzenesulfonate (31)



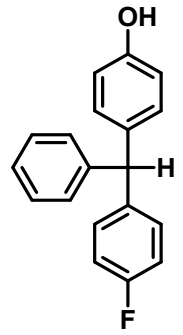


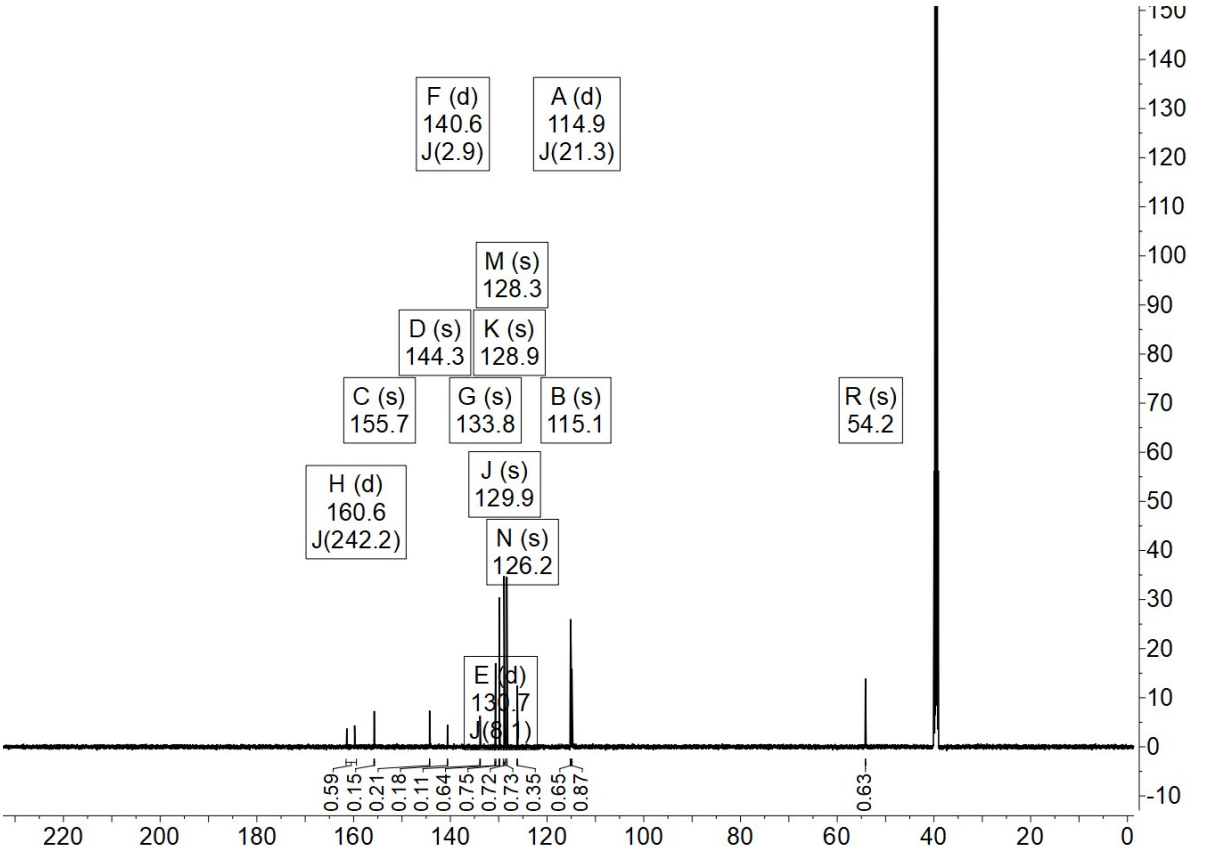
4-[1-(4-Fluorophenyl)-1-phenylmethyl]-*N,N*-dimethylaniline (19)



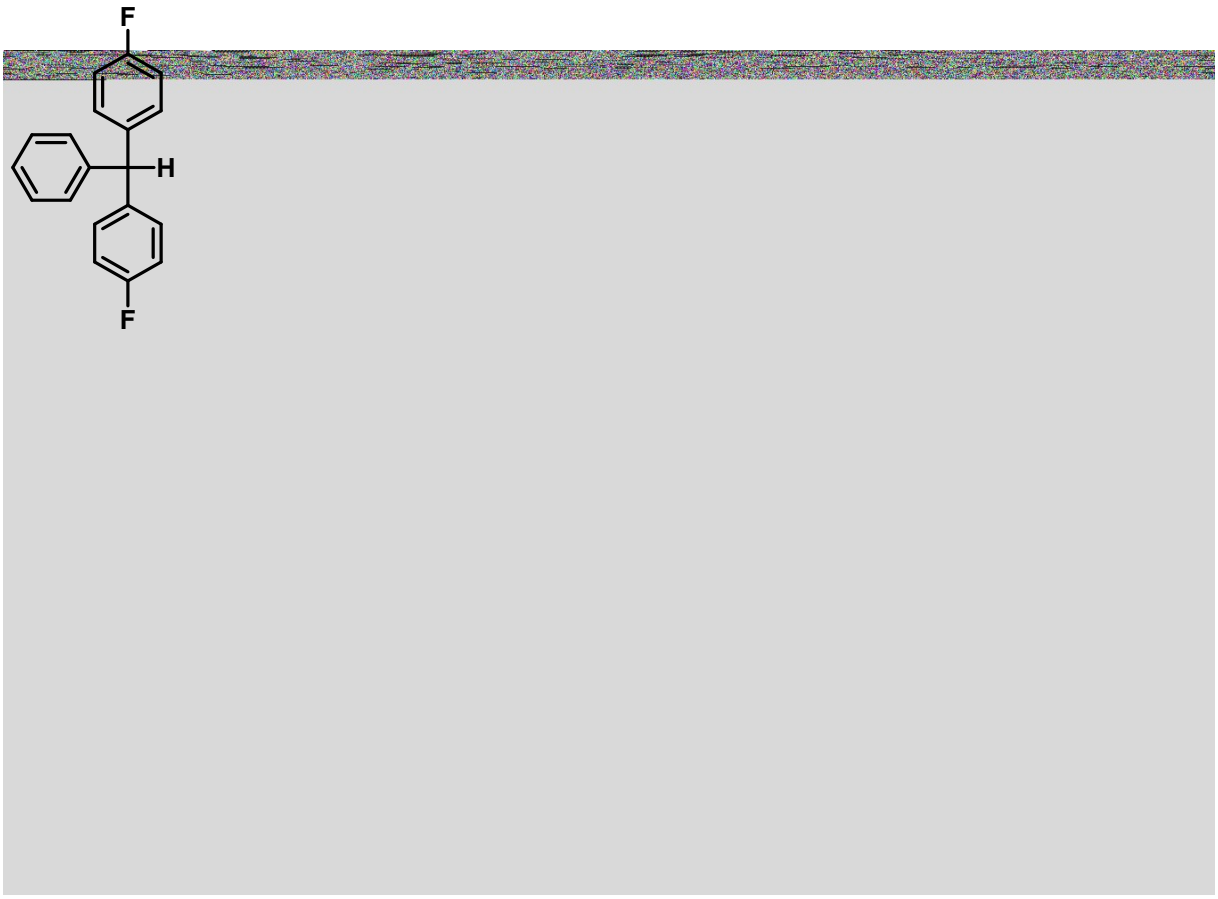


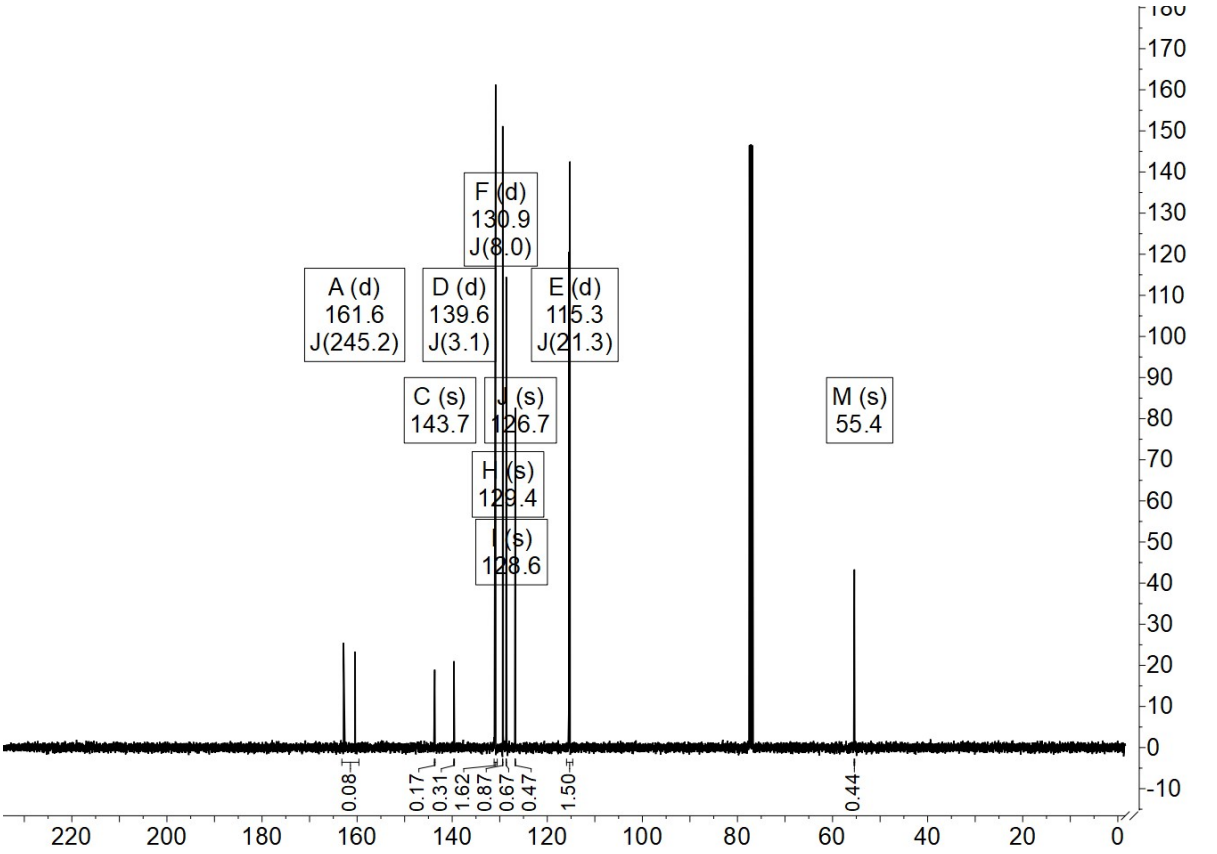
4-[1-(4-Fluorophenyl)-1-phenylmethyl]phenol (21)





4,4‘-Difluorotriphenylmethane (25)





4. Radiosynthesis

4.1 General considerations

All *chemicals*, *reagents*, and *solvents* for the radiosynthesis of tracers were analytical grade, purchased from commercial sources and used without further purification unless otherwise specified. Only solvents of pharmaceutical purity from ABX and Milli-Q®-water or water for injection from B. BRAUN were used for radiosynthesis.

All *radiosynthesis* were carried out semiautomated on a modified PET tracer radiosynthesizer (TRACERLab Fx_{FDG}, GE Healthcare). The recorded data was processed by the TRACERLab Fx software (GE Healthcare).

Sep-Pak® C-18 Plus cartridges from WATERS were used for the *purification* of radiolabeled compounds. The cartriges were conditioned with ethanol (5 mL) followed by water (10 mL) prior to use.

In some cases vessels were *coated on the surface* using Sigmacote® from SIGMA-ALDRICH.

Identification of labeled compounds was performed by co-injection of a non-radioactive [^{19}F]-containing reference compound on HPLC system C.

Radiochemical yields are based on the initially used activity and are generally decay corrected.

Radiochemical purity is the ratio of the fraction of product radioactivity and total radioactivity and was determined by analytical HPLC system C.

The *time of radiosynthesis* is given as the time between measurement of the starting activity and reconstitution of the tracer for application.

Measurements of total radioactivity for the determination of experimental log*D*-values were performed using a gamma-counter Wizard^2 2480 from PERKINELMER.

General measurements of radioactivity were done on an *Isomed 2010*-activimeter from MED Nuklearmedizintechnik.

Centrifugation was done in Eppendorf vessels (1.5 mL) in a MCF-2360 centrifuge from LMS Consult GmbH & Co. KG.

Incubation of samples for the determination of *serum stability* was performed using a PST-60 HL plus thermo shaker from KISKER Biotech GmbH & Co. KG.

Separation, *purification* and determination of *radiochemical purity* of the compounds were performed by using semipreparative and analytical reversed-phase HPLC systems A and B.

Semipreparative HPLC A: A WELLCHROME K-500 pump and a WELLCHROME K-501 pump, a K-2000 UV detector (HERBERT KNAUER GMBH), a NaI(Tl) Scintibloc 51 SP51 γ-detector (CRISMATEC), and a ACE 5 AQ column (10 mm × 250 mm). The recorded data was processed by the GINA Star software (RAYTEST ISOTOPENMESSGERÄTE GMBH).

Method:

Solvent A:	purified water (MilliQ®) + 0.1 % (V/V) trifluoroacetic acid
Solvent B:	acetonitrile + 0.1 % (V/V) trifluoroacetic acid
Gradient elution (% A):	0 - 2 min: 95 %; 2 - 16 min: gradient from 95 % to 5 %; 16 - 24 min: 5 %; 24 - 32 min: gradient from 5 % to 95 %.
Flow rate:	5,5 mL/min
Injection volume:	100- 1000 µL
Detection:	UV: 254 nm
	γ-Counter: cpm

Analytical HPLC B: Two Smartline 1000 pumps and a Smartline UV detector 2500 (HERBERT KNAUER GMBH), a GabiStar γ-detector (RAYTEST ISOTOPENMESSGERÄTE GMBH) and a Nucleosil 100-5 C–18 column (4 mm × 250 mm). The recorded data was processed by the GINA Star software (RAYTEST ISOTOPENMESSGERÄTE GMBH).

Method:

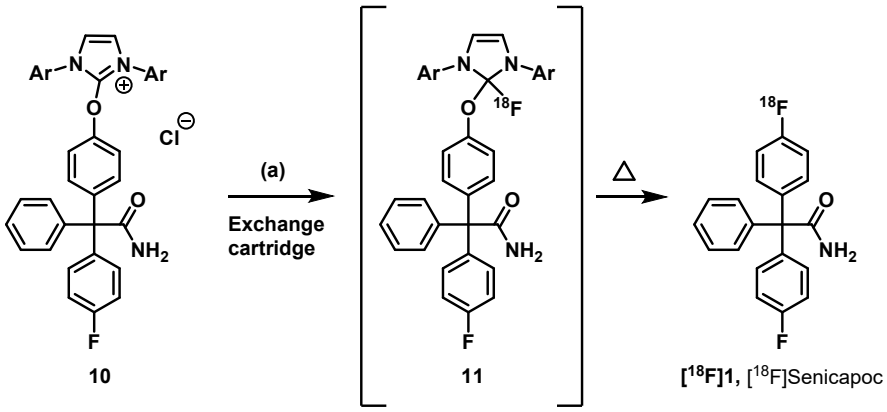
Solvent A:	purified water (MilliQ®) + 0.1 % (V/V) trifluoroacetic acid
Solvent B:	acetonitrile + 0.1 % (V/V) trifluoroacetic acid
Gradient elution (% A):	0 - 9 min: gradient from 90 % to 10 %; 9 - 15 min: gradient from 10 % to 90 %.
Flow rate:	1,0 mL/min
Injection volume:	10 - 20 µL
Detection:	UV: 254 nm
	γ-Counter: cpm

4.2 Radiosynthesis, special considerations

The introduction of [^{18}F]fluorine was performed by direct nucleophilic substitution. In case of the synthesis of [^{18}F]senicapoc the label would be authentic. In this chapter we will introduce the different strategies, synthesis of suitable precursors as well as advantages and disadvantages of the chosen routes.

4.3 Radiosynthesis of [^{18}F]senicapoc ([^{18}F]1)

4.3.1 Uronium salt precursor 10



Scheme S5: Radiosythesis of [^{18}F]senicapoc ([^{18}F]**1**). Reagents and reaction conditions: (a) [^{18}F]F$^-$, butan-2-on : EtOH : Bu_3N (100:10:1), 130 °C, 20 min. RCY (d.c.) = 0,4 % (n = 1).

The semiautomated radiosyntheziser was used (program: FDGBasicMS).

Radiosynthesis was performed semiautomatically according to Neumann *et al.* [6]

An aqueous solution of [^{18}F]fluoride was received from a Siemens RD111 cyclotron. The activity was flushed through an anionic exchange cartridge (Chromabond® PS-HCO_3 cartridges, 45 mg). After fixation of the [^{18}F]fluoride, the cartridge was flushed with butan-2-on:ethanol (1:1, 1 mL). The cartridge was reversed using a luerlock® system as suggested in the original procedure. [6] After reversing the cartridge it was eluted with 5±1 mg of the uroniumsalt **10** in butan-2-on:ethanol:tributylamine (100:10:1, 1 mL). The mixture was reacted at 130 °C for 20 min in the closed reactor vial. After cooling down to rt, the mixture was eluted into the product vial. The reactor vial was rinsed with a mixture of acetone and water (1:1; 8 mL) followed by elution into the waste vial. The mixture containing the product was purified by semi-preparative radio- HPLC (t_R = 13.8 min). RCY: 0.4 % (d.c., n = 1, Yield calculated based on isolated activity after HPLC without reconstitution). Synthesis time (start - HPLC isolation of product): 72 min (n=1). RCP: 87 % by analytical radio-HPLC (t_R = 11.1 min).

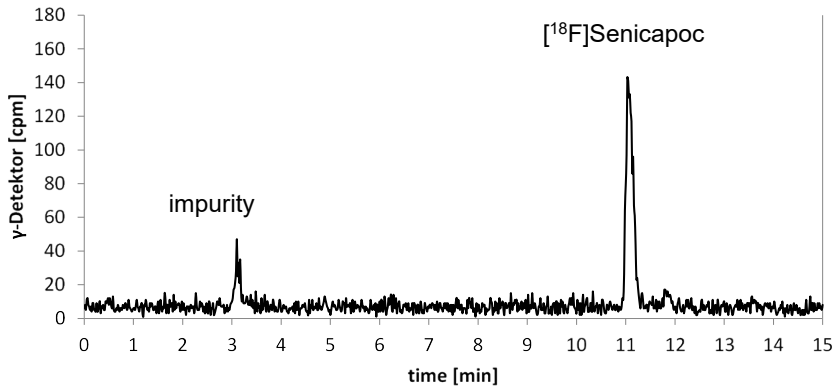


Figure S1: Chromatogram of the analytical radio-HPLC.

4.3.2 Trimethylammonium precursor 18

Chromatograms of the analytical radio-HPLC of the samples taken during the removal of the solvent and radio-TLC:

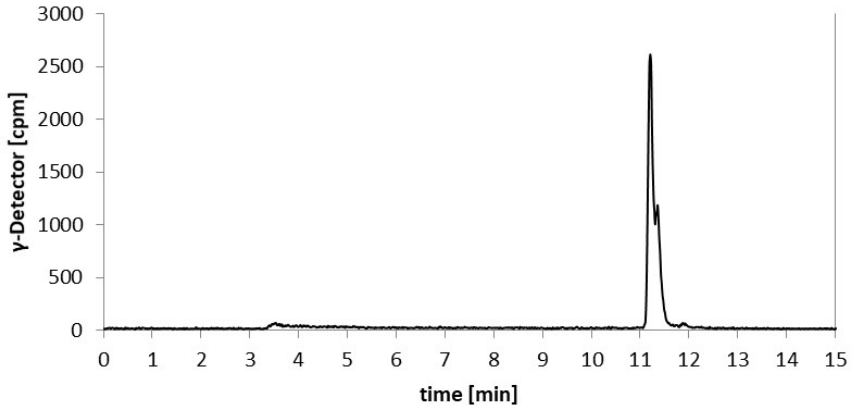


Figure S2: Chromatogram of the analytical radio-HPLC of the sample taken after 10 min.

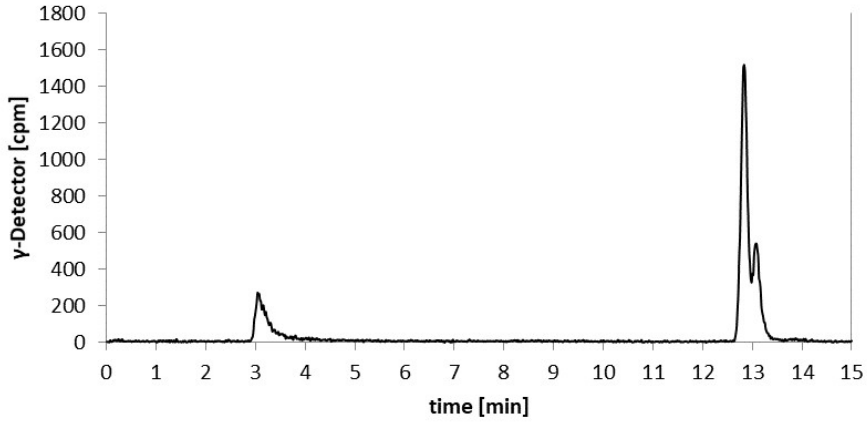


Figure S3: Chromatogram of the analytical radio-HPLC of the sample taken after 20 min.

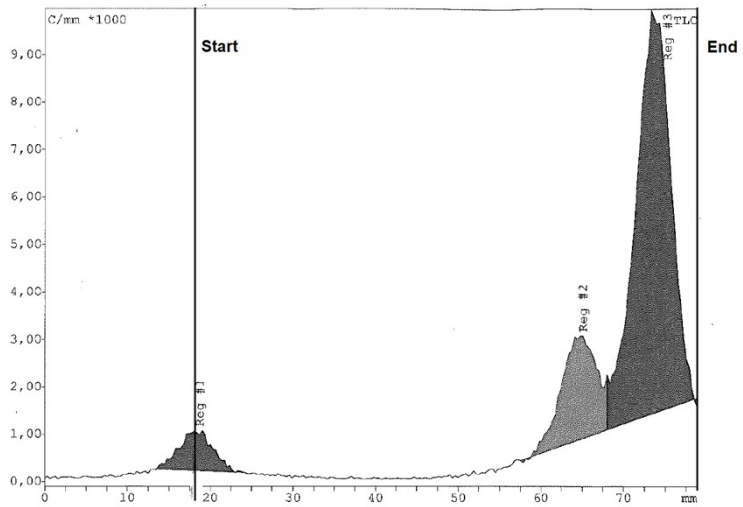
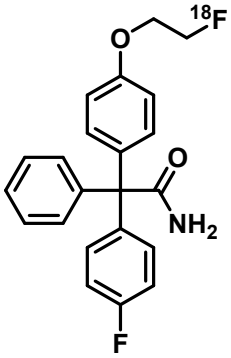


Figure S4: Radio-TLC of the sample taken after 20 min.
Solvent: CH_2Cl_2 :MeOH (98:2).

4.4 Radiosynthesis of [^{18}F]28

[^{18}F]2-[4-(2-Fluoroethoxy)phenyl]-2-(4-fluorophenyl)-2-phenylacetamide ([^{18}F]28)



The semiautomated radiosynthesizer was used (program: FDGBasicMS).

The aqueous [^{18}F]fluoride ions were trapped on a QMA-light cartridge (Waters®), preconditioned with 5 mL aq. K_2CO_3 solution (1 M) und 10 mL H_2O. [^{18}F]Fluoride was eluted with a solution of CH_3CN (800 µL), H_2O (200 µL), K_{222} (20 mg), aq. K_2CO_3 solution (1M, 40 µL). Azeotropic drying was performed following the standard FDGBasicMS-procedure (deviation: 10 min at 84 °C). A solution of the precursor **31** (3.0 mg, 5.77 µmol) in DMF (500 µL) was added to the reactor vial of the radiosynthesiser. The mixture was reacted at 90 °C for 15 min in the closed reactor vial. After cooling down to rt, the mixture was eluted into the product vial. The reactor vial was rinsed with 500 µL CH_3CN followed by elution into the product vial. The reactor vial was rinsed with a mixture of 4 mL EtOH and 4 mL H_2O followed by elution into the waste vial. The mixture containing the product was purified by semi-preparative radio-HPLC (t_R = 13.6 - 13.8 min). RCY: 4 ± 1.5 % (d.c., n = 4). Synthesis time (start - reconstituted product): 106 ± 11.5 min (n=4). RCP: > 96 % by analytical radio-HPLC (t_R = 10.8 min) and radio-TCL. A_M = 0,1 - 5,2 GBq/µmol (n = 4). The purified product was reconstituted in PBS-buffer and EtOH (9:1) to give the injectable solution.

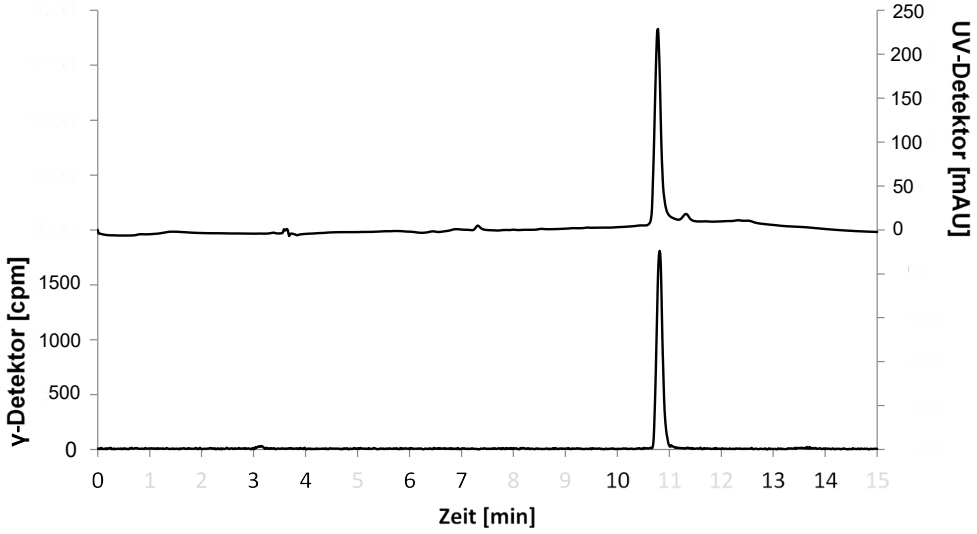


Figure S5: Chromatograms of the analytical radio-HPLC. Traces for ^{18}F-labelled [^{18}F]**28** (γ-detector [cpm], bottom) and co-injection of [^{19}F]**28** as reference compound (UV-detector [mAu], top).

5. *in vitro* and *in vivo* data

5.1 Cell culture for patch clamp experiments and biodistribution

Cells were cultured and prepared for the experiments by Sandra Schimmelpfennig and Sarah Sargin from the Institute of Physiology II.

The A549-3R cell line, used for all experiments, is a hypotriploid epithelial cell line from a pulmonary adenocarcinoma taken from a 58-year-old Caucasian in 1972. The suffix "3R" refers to the repeated process of intravenous administration of parental cells (also initially "0R") in immunocompromised mice to obtain lung metastases, isolation and *in vitro* culture of cells from metastases followed by another round of reinjection to select for tumor cells with high metastatic potential.[7]
Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) with 4.5 g/L glucose and supplemented with 10 % fetal calf serum (FCS Superior) at 37 °C and 5 % CO_2 in cell culture dishes (Ø = 10 cm).

5.2 Patch clamp experiments

Patch clamp experiments were performed by Elke Naß from the Institute for Physiology I.
Whole cell recordings were performed at room temperature using borosilicate glass pipettes (GC150TF-10, Havard Ltd., USA) connected to an EPC-10 amplifier (HEKA Electronics, Lambrecht, Germany). The typical electrode resistance was 3 - 4 MOhm, while series resistance was in the range of 5 – 15 MOhm. Series resistance compensation of > 30% was routinely used. Voltage-clamp experiments on cultured cells were controlled by PatchMaster software (HEKA Electronics, Germany). Current density was calculated by dividing the current amplitude determined at the end of the depolarizing voltage ramp to +60 mV by the membrane capacitance obtained from slow capacitance compensation. The following recording solutions wer used: 1) Extracellular solution (in mmol/l): 140 NaCl, 5 KCl, 10 HEPES, 1 $MgCl_2$, and 1 $CaCl_2$, pH 7.4 with NaOH. 2) Intracellular solution (in mmol/l): 140 KCl, 10 HEPES, 1.3 EGTA, 1.217 $CaCl_2$, and 1 $MgCl_2$, pH 7.4 with KOH. The calculated free Ca^{2+} concentration of the internal solution was 1 µmol/l in order to obtain full activation of the K_{Ca} channels during the patch clamp experiments. Test compounds (**28** and **1**) were dissolved in DMSO and added to the standard extracellular solution and applied for a time period of 2-5 min. The final DMSO concentration was ≤ 0.15 %. A multibarrel application pipette with a tip diameter of about 100 µm was used for test substance application close to the recorded cell. Recordings were analyzed using FitMaster and Excel software. Statistical analysis: ANOVA and t-test were performed using Excel software.

5.3 Determination of plasma protein binding (PPB)

Determination of plasma protein binding (PPB) was done with the [^{19}F]reference compounds **1** and **28** by using an in-house protocol.[8]

The PPB was determined as HSA binding using HPAC with MS detection (HPAC-MS). HSA immobilized on silica was used as stationary phase and aqueous ammonium acetate (50 mM, pH 7.4) and *i*-propanol (isocratic) served as mobile phase.

The buffer solution for the mobile phase was prepared by adjusting the pH value of a 50 mM ammonium acetate solution with ammonia (25% (v/v) to pH 7.4. For preparation of the samples, the 10 mM DMSO stock solutions of the reference compounds and the test compounds were diluted with DMSO to obtain a concentration of 2 mM, which was further diluted with the corresponding mobile phase (4% (v/v) *i*-propanol in 50 mM ammonium acetate solution pH 7.4) to a final concentration of 20 µM. The resulting solutions were analyzed via LC-MS. The dead time of the system was determined with D-glucose (*m/z* (SIM negative ion polarity) = 179). The calibration curve was generated by plotting the *k'*/(*k'*+1) values of all reference compounds (metronidazole, paracetamol, salbutamol, ramipril, propranolol, phenytoin, haloperidol, imipramine, chlorpromazine) against their PPB values known from literature.[9] The correlation between the PPB and the *k*'/(*k*'+1) value obtained from the retention time (t_R) in HPAC is well known in the literature.[10]

$$k' = \frac{t_R - t_D}{t_D}$$

t_R: Retention time [min]

t_D: Dead time [min]

Method:

The LC system was coupled with a single quadrupole (SQ) mass spectrometer.

UPLC-UV/MS (Agilent, Waldbronn, Germany): pump: 1260 Bin Pump (G1212B); degasser: 1260 HiP (G4225A); column oven: 1290 TCC (G1316C), 30 °C; autosampler: 1260 HiP ALS (G1367E); UV/vis detector: 1260 VWD (G1314F); MS source: multimode source (G1978B); MS-Detector: 6120 Quadrupole (G1978B).

MS parameters: Vaporizer temperature: 250 °C; drying gas: 10 L/min; nebulizer pressure: 40 psi; capillary voltage: 3000 V; fragmentor voltage: 100 V; drying gas temperature: 350 °C.

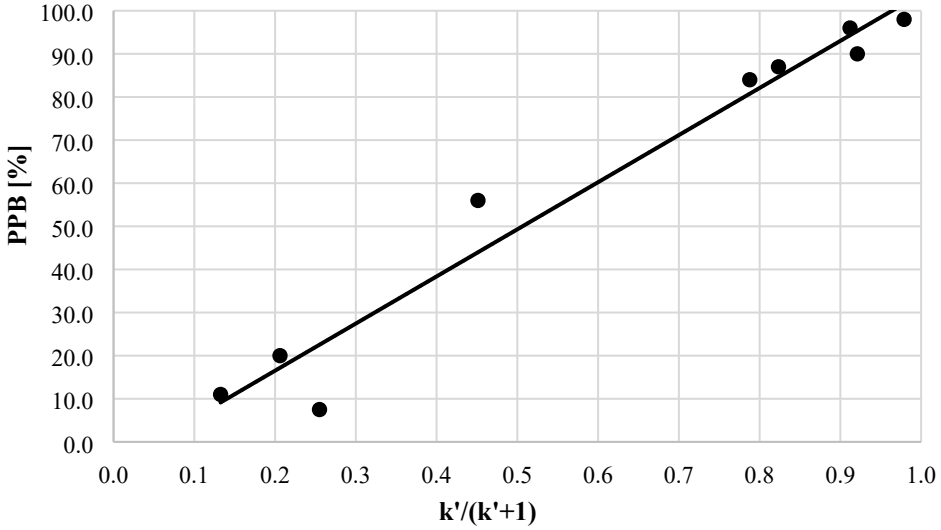
LC parameters: precolumn: Chiralpak® HSA HPLC Guard Column (2.0 x 10 mm, 5 µm particle size); main column: Chiralpak® HSA HPLC Column (2.0 x 50 mm, 5 µm particle size, Daicel, Eschborn, Germany); temperature: 25 °C; mobile phase A: aqueous ammonium acetate solution (50 mM, pH 7.4) / *i*-propanol 96:4; flow rate: 0.3 mL/min; isocratic.

Taking the wide PPB range and the diversity of the reference compounds into account, the obtained correlation coefficient r^2 of 0.9622 is acceptable. The PPB values of the tested compounds (**1** and **28**) were determined as *k*'/(*k*'+1) values and the equation resulting from external calibration.

Table S1: Data for the external calibration.

Compound	t_R [min] (Ø, n=3)	*k'*	*k'*/(*k'*+1)	PPB* [%]
Glucose	0,79	-	-	-
Metronidazole	0,91	0,15	0,132	11,0
Paracetamol	1,00	0,26	0,206	20,0
Salbutamol	1,06	0,34	0,255	7,5
Ramipril	1,44	0,82	0,451	56,0
Propanolol	4,47	4,66	0,823	87,0
Phenytoin	3,72	3,71	0,788	84,0
Haloperidol	8,97	10,4	0,912	96,0
Imipramine	10,0	11,7	0,921	90,0
Chlorpromazine	37,4	46,4	0,979	98,0

* values according to literature [9]



Graph S1: External calibration. Average values of 3 independent measurements (n = 3).

Table S2: PPB of Senicapoc (**1**) and **28**.

compound	t_R [min] (Ø, n=3)	*k'*	*k'*/(*k'*+1)	PPB* [%]
Senicapoc	19,7	23,9	0,960	> 99
28	20,5	25,0	0,962	> 99

* calculated using the equation resulting from the external calibration

5.4 Determination of the distribution coefficient ($logD_{exp}$)

Following a method described by Prante *et al.* [11], the *distribution coefficient ($logD_{exp}$)* of [^{18}F]**28** was determined in a two-phase system consisting of 1-octanol and PBS-buffer (pH = 7.4) to determine the lipophilicity. For this purpose, the corresponding ligand (~ 20 kBq) was dissolved in buffer (500 µL). 1-Octanol (500 µL) was added and the mixture was shaken at room temperature for 1 min. To achieve phase separation, the system was centrifuged for 2 min at 3000 rpm. Subsequently a part of the octanol phase (400 µL) was removed and buffer (400 µL) was added. The combined phases were shaken and layers were separated according to the description above. Aliquots of the buffer and octanol layers (3 × 100 µL from every layer) were taken to measure radioactivity in a γ-counter. The measurement provided the activity in counts per minute (cpm), the values were decay corrected. By calculating the quotient of $\frac{cpm\ (1-Octanol)}{cpm\ (PBS)}$ the *$logD_{exp}$* can be determined as $log\frac{cpm\ (1-Octanol)}{cpm\ (PBS)}$.

5.5 Serum stability

The *serum stability* of [^{18}F]**28** was evaluated by incubation in human and murine serum at 37 °C for up to 120 min. An aliquot of radioactive product (20 µL, ~5 MBq) in PBS-buffer was added to a sample of serum (200 µL), and the mixture was incubated at 37 °C. Samples of 20 µL each were taken after periods of 10, 30, 60, 90 and 120 min and quenched in MeOH/CH_2Cl_2 (1:1 (v/v), 100 µL) followed by centrifugation at 3000 rpm for 2 min. The clear solution was analyzed by analytical radio-HPLC system B (see chapter 3.1).

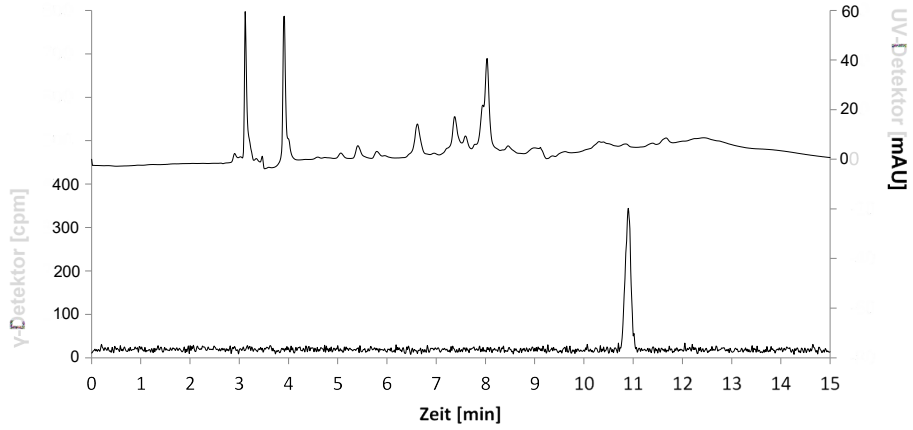


Figure S6: Chromatogram of the analytical radio-HPLC after 120 min incubation of [^{18}F]**28** in human serum.

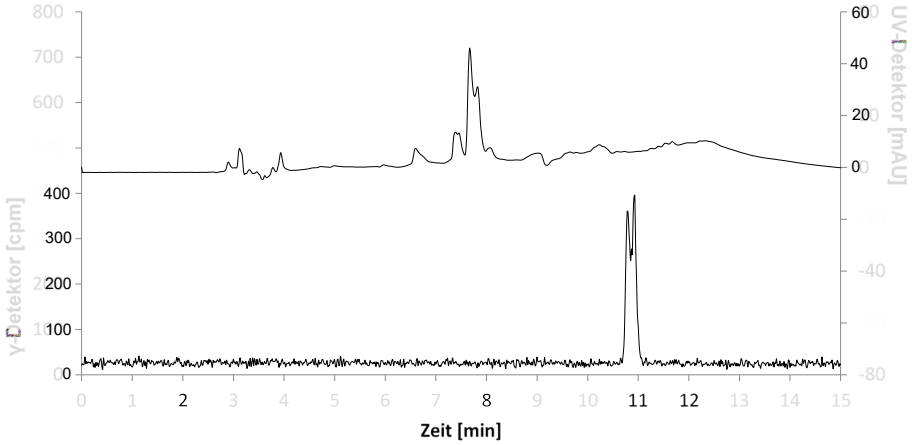


Figure S7: Chromatogram of the analytical radio-HPLC after 120 min incubation of [^{18}F]**28** in murine serum. (double peak is device related)

5.6 Biodistribution

For PET-CT studies, the mice ([^{18}F]**28**: n = 3;) were anesthetized with 4 % isoflurane in air in an anesthesia chamber. The mice were then transferred to a heated PET scanner bed, isoflurane anesthesia (1.5-2% in pure oxygen) was maintained and important biological parameters (respiration, body temperature) were monitored. To protect the eyes from dehydration, they were covered with eye ointment. A catheter (27G) was inserted into one of the tail veins, flushed with saline (50 µL) and connected to the injection line. The radiotracer [^{18}F]**28** (3.7 - 10.5 MBq) in PBS (+ 10 % EtOH) was injected via tail vein catheter with an injection pump. For the PET imaging (32 modules quadHIDAC, OXFORD POSITRONS SYSTEMS LTD), the scanner bed was positioned automatically in the center of the camera field and the PET data acquisition was started. At the same time, the radiotracer was injected. After 90 min the scanner bed was transferred to a CT scanner (Inveon, SIEMENS MEDICAL SOLUTION) and a CT scan with a resolution of 80 µm was performed for each mouse. Reconstructed image data sets were coregistered based on external markers and recorded and evaluated with the image analysis inhouse developed software MEDgical.

In the CT datasets, three-dimensional "volumes of interest" (VOIs) were defined over the respective organs, transferred to the co-registered PET data and quantitatively analyzed. Regional uptake was calculated as a percentage of the injected dose by dividing the counts per milliliter in the VOI by total mouse decay and then multiplying by 100 (% ID / mL).

After PET imaging, the mice were sacrificed by cervical dislocation, the organs were removed, weighed and analyzed using an automatic Wizard^{2}Gammacounter (PERKIN ELMER). The percentage of accumulation of injected dose per gram of tissue (% ID / g) was calculated.

For the experiments, three 12 week old C57BL/6 mice were used. The experiments were approved by the State Office for Nature, Environment and Consumer Protection North Rhine-Westphalia under license Az. 84-02.04.2015.A410.

All *animal experiments* were conducted in accordance with local institutional guidelines for the care and use of laboratory animals.

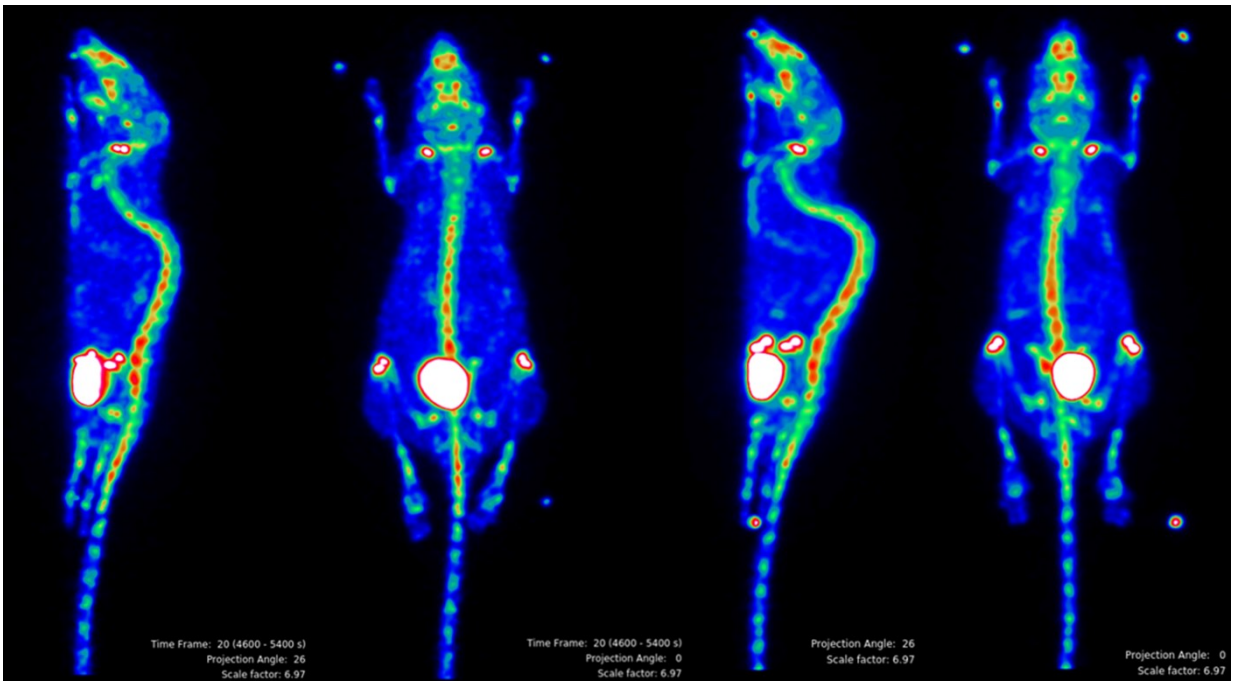


Figure S8: Maximum-intensity-projection of the activity distribution at 4600-5400 sec after injection in two C57BL/6 wild-type mice after injection of [^{18}F]**28**.

5.7 Determination of metabolic stability

Determination of metabolic stability in vitro was conducted with the [^{19}F]reference compound **28** by adding liver microsomes to an Eppendorf cap filled with sodium phosphate buffer pH 7.4 (PBS, 0.1 M), $MgCl_2$ solution (0.05 M), NADPH (2 mg/mL in PBS) and DMSO stock solution, giving a total volume of 200 µL. Final concentrations for the incubations were 75 mM PBS, 0.6 mM NADPH, 1 mg/mL microsomal protein, 50 µM of the respective compound, 12.5 mM $MgCl_2$, and 0.5% DMSO. The suspension was mixed vigorously and incubated (37 °C, 90 min, 900 rpm). Subsequently, the incubation was stopped by addition of CH_3CN/CH_3OH (1:1, 400 µL), the caps were cooled down (0 °C, 10 min) and the precipitated proteins were separated by centrifugation (4 °C, 15 min, 16000 rpm). Afterward, the supernatant was analyzed by LC-MS.

For the determination of exact masses and for conducting MS/MS experiments, a LC system was coupled with a quadrupole time-of-flight (qToF) mass spectrometer.

HPLC-DAD (Thermo Fisher Scientific, Dreieich, Germany): Solvent rack (SRD 3600); pump (DGP-3600RS); autosampler (WPS-3000RS); column oven (TCC-3000RS); precolumn: SecurityGuard™ Cartridge AQ C18 (4.0 x 2.0 mm, 4.0 µm particle size); column: Synergi™ Hydro-RP (50 x 2.1 mm, 2.5 µm particle size, Phenomenex®, Aschaffenburg, Germany); temperature: 30 °C and DAD-detector (DAD-3000RS). The LC system was coupled with a micrOToF-Q II (Bruker Daltonics, Bremen, Germany).

The ESI-qToF was operated in positive ion polarity in the full scan mode (*m/z* 70 – 700 , 200 – 1000 or 500 – 1600) with the following settings: capillary voltage 4500 V; end plate offset -500 V; collision cell RF 300.0 Vpp; nebulizer 2.0 bar; dry heater 200 °C; dry gas 9.0 L/min. To protect the MS from salts or other components of the

matrices, a six-port valve was used to elute the first 2.0 min of each run into the waste (cut-off). For data handling and control of the system the software Data Analysis and Hystar from Bruker Daltonics (Bremen, Germany) was used. The calibration of the ToF spectra was achieved by injection of $LiHCO_2$ (*m/z* < 700, *i*-propanol/H_2O 1:1, 10 mM) via a 20 µL sample loop within each LC run at 2.0 – 2.2 min.

LC parameters: mobile phase A: H_2O/ CH_3CN 90:10 + 0.1% FA; mobile phase B: CH_3CN/H_2O 90:10 + 0.1% FA; mobile phase C: H_2O + 0.1% FA; pump 1: flow rate: 0 – 3 min: 0.1 mL/min, 3 – 3.1 min: from 0.1 mL/min to 0.4 mL/min, 3.1 – 17.9 min: 0.4 mL/min, 17.9 – 18 min: from 0.4 mL/min to 0.1 mL/min; gradient elution: (A%): 0 – 3.1 min: 100%, 3.1 – 12 min: gradient from 100% to 0%, 12 – 14.5 min: 0%, 14.5 – 15 min: gradient from 0% to 100%, 15 – 18 min: 100%; pump 2: flow rate: 0 – 3 min: 0.3 mL/min, 3 – 3.1 min: from 0.3 mL/min to 0.0 mL/min, 3.1 – 17.9 min: 0.0 mL/min, 17.9 – 18 min: from 0.0 mL/min to 0.3 mL/min; isocratic: (C%): 0 – 18 min: 100%.

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