Supporting Information
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A Practical One-Pot Synthesis of Positron Emission Tomography (PET) Tracers via Nickel-Mediated Radiofluorination

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Supporting Information

Table of Contents

Materials and Methods S1
Chemistry S4
Radiochemistry S24
HPLC-Chromatogramms S26
Specific activity calculation S29
Biology S30
References S33

Materials and Methods

General: $^1$H-NMR spectra: Bruker Avance II 300 (300 MHz) and Bruker Avance II+ 600 (600 MHz). $^1$H chemical shifts are reported in ppm relative to residual peaks of deuterated solvents. Higher-order NMR spectra were approximately interpreted as first-order spectra, where possible. The observed signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, and br = broad. Coupling constants ($J$) were reported in Hertz (Hz). $^{13}$C-NMR spectra [additional APT (Attached ProtonTest)]: Bruker Avance II 300 (75.5 MHz) and Bruker Avance II+ 600 (125.9 MHz). $^{13}$C chemical shifts are reported relative to residual peaks of deuterated solvents. Low resolution ESI-MS: Finnigan LCQ. High resolution ESI-MS: Bruker APEX IV 7T FTICR MS. TLC: Merck precoated sheets, 0.25 mm Sil G/UV$_{254}$. The chromatograms were viewed under UV light and/or by treatment with phosphomolybdic acid (10%
in ethanol). Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Solvent proportions are indicated in a volume:volume ratio. All reactions were carried out with magnetic stirring unless otherwise stated and, in the case of air- or moisture-sensitive substrates and/or reagents, were handled in flame-dried glassware under argon or nitrogen. Organic extracts were dried with anhydrous MgSO₄. Oxidant 2 was handled and stored in a glove box under nitrogen at < 0.1 ppm RH.

2,[1] 4a,[2] 6-bromo-m-tyrosine,[3] 6-bromodopamine,[4] 4-(chloromethyl)-5-fluoroveratrol,[5] 4-(cyanomethyl)-5-fluoroveratrol,[6] 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide silver(I) salt,[2] 1,1’-(phenyl-λ3-iodandiyl)bis(4-dimethylaminopyridinium) bistri fluoromethansulfonate,[7] iodosobenzene (7a)[8] and iodosomesitylene (7b)[9] were prepared according to literature.

StrataX cartridges were obtained from Phenomenex (Aschaffenburg, Germany) and Sep-Pak Accell Plus QMA carbonate plus light cartridges, 46 mg sorbent per cartridge from Waters GmbH (Eschborn, Germany).

HPLC analyses and purifications were carried out on Dionex Ultimate 3000 System with Ultimate 3000 Diode Array Detector coupled in series with Berthold NaI detector. Unless stated, a Chromolith® SpeedROD RP-18e column (Merck, Darmstadt Germany), 50×4.6 mm, was used for analyses and purifications of radiofluorinated products.

UV and radioactivity detections were connected in series, giving a time delay of 0.5–0.9 min depending on a flow rate. ¹⁸F-labeled compounds were identified by spiking of the reaction mixture with unlabeled standards using HPLC.

Radiolabeled products were analyzed using two sets of conditions. Conditions A (for protected intermediates [¹⁸F]3a-c): column: (Chromolith SpeedROD®), 50×4.6 mm (Merck Milipore); gradient: 0–3 min: 20% MeCN, 3–4 min: 20→99% MeCN, 4–7 min: 99% MeCN, 7–8 min:
99→20% MeCN; flow rate: 1.5 mL/min. Conditions B (for PET-tracers $^{[18\text{F}]}1\text{a-c}$): column: Synergy 4 µm Hydro-RP (150×4.6 mm, Phenomenex); 4% EtOH in 0.02 m sodium phosphate buffer (pH 2.5); flow rate: 1.5 mL/min. $^{[18\text{F}]}1\text{a-c}$ were isolated by semipreparative HPLC using conditions B.

$^{[18\text{F}]}$Fluoride was produced via the $^{18\text{O}}$(p,n)$^{18\text{F}}$ reaction by bombardment of enriched $^{[18\text{O}]}$water with 16.5 MeV protons using a MC16 cyclotron (Scanditronix, Uppsala, Sweden). All isolated radiochemical yields are decay-corrected. Unless otherwise indicated, all radiochemical experiments were carried out at least in triplicates.

Before radiosyntheses $^{[18\text{F}]}$fluoride was preprocessed as follows. $^{[18\text{F}]}$Fluoride in $^{[18\text{O}]}$H$_2$O (0.05–40 GBq) was trapped on an anion-exchange resin (QMA cartridge), the resin was washed with MeOH (5 mL) and flushed with a gentle stream of Ar (1 min). $^{[18\text{F}]}$Fluoride was eluted into a conical vial (5 mL), containing 18-crown-6 (24 mg, 90 µmol), with K$_2$CO$_3$ (0.16 mg, 1.16 µmol in 10 µL H$_2$O) in MeOH (200 µL) followed by additional MeOH (700 µL). After evaporation of the solvent under a gentle stream of Ar at 70–80 °C, MeCN (1 mL) was added to the reaction vial and evaporated under a gentle stream of Ar at 100 °C (three times). The residue was taken up in the corresponding solvent and used for further experiments. It should be noted, that the aqueous $^{[18\text{F}]}$fluoride was loaded onto the cartridge from the male side, whereas flushing, washing and $^{18\text{F}^-}$elution were carried out from the female side of the cartridge. If the QMA cartridge had been loaded, flushed and eluted from the female side only, sometimes a significant amount of $^{[18\text{F}]}$fluoride remained on the resin (this is probably because QMA-light (46 mg) cartridges have a single frit on the male side but four on the female side).
**Chemistry**

Methyl N,O-di-tert-butyloxycarbonyl-6-bromo-m-tyrosinate: A solution of Br₂ (0.91 mL, 2.42 g, 16.64 mmol) in AcOH (140 mL) was added dropwise within 45 min to a vigorously stirred suspension of m-tyrosine (3.2 g, 16.64 mmol) in AcOH (140 mL). The reaction mixture (the starting suspension was completely dissolved to give a clear solution; thereafter, a precipitataion of product was begun) was stirred for a further 2 h and filtered. A filter cake was washed with AcOH (3×50 mL) and transferred into a round flask. Toluene (50 mL) was added and evaporated under reduced pressure (three times) to give a crude 6-bromo-m-tyrosine hydrobromide\(^{[3]}\) (2.0 g) as an off-white solid which was used for the next step without any further purification.

SOCl\(_2\) (2.9 mL, 4.76 g, 40 mmol) was added dropwise within 30 min to an ice-cold solution of 6-bromo-m-tyrosine (1.95 g, max. 5.72 mmol) in anhydrous MeOH (30 mL) under Ar. Thereafter, the cooling bath was removed and the reaction mixture was stirred for a further 16 h and concentrated under reduced pressure. The residue was taken up in toluene (50 ml) and volatiles were removed under reduced pressure (two times) to give a crude methyl 6-bromo-m-tyrosinate hydrochloride/hydrobromide (1.7 g) as a rose solid which was directly used for the next step.

Et\(_3\)N (6.7 mL, 4.84 g, 47.87 mmol) was slowly added to a solution of methyl 6-bromo-m-tyrosinate hydrochloride (1.7 g, max. 5.47 mmol) and Boc\(_2\)O (6.7 g, 30.7 mmol) in anhydrous DMF (20 mL) under Ar. The reaction mixture was stirred for a further 16 h and concentrated under reduced
pressure. The residue was taken up in EtOAc (100 mL) and the resulting solution was washed with 
H$_2$O (7×40 mL), brine (2×30 mL), dried and concentrated under reduced pressure. The residue was 
purified by column chromatography (EtOAc:hexane = 1:3) affording the title compound (1.39 g, 
17% on three steps) as a colorless viscous oil. R$_f$ = 0.25, EtOAc:hexane = 1:3. 

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.52 (d, $J$ = 8.7 Hz, 1H), 7.03 (s, 1H), 6.95 (dd, $J$ = 8.7, 2.5 Hz, 1H), 5.07 (d, $J$ = 8.2 Hz, 
1H), 4.63 (dd, $J$ = 14.3, 7.0 Hz, 1H), 3.71 (s, 3H), 3.27 (dd, $J$ = 13.8, 7.0 Hz, 1H), 3.09 (dd, $J$ = 13.8, 
8.2 Hz, 1H), 1.54 (s, 3H), 1.38 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.3, 155.1, 151.5, 150.4, 
137.5, 133.6, 124.2, 121.8, 121.4, 84.0, 80.1, 53.4, 52.6, 38.9, 28.4, 27.8. MS (ESI): positive mode 
m/z = 971.2 ([2M + Na]$^+$), 498.3 ([M + Na]$^+$), 474.1 ([M + H]$^+$); MS (ESI): negative mode m/z = 
472.1 ([M – H]$^-$); ESI HRMS: calcd for C$_{20}$H$_{28}$NO$_7$BrNa$: 496.0937; found: 496.0941; calcd for 
C$_{20}$H$_{29}$NO$_7$Br$: 474.1109; found: 474.1122; calcd for C$_{20}$H$_{27}$NO$_7$Br$: 472.0958; found: 474.0976. 
Correct isotopic pattern.
**N-tert-Butyloxycarbonyl-6-bromodopamine:**

A solution of Br₂ (1.13 mL, 3.51 g, 21.99 mmol) in AcOH (25 mL) was added dropwise within 2 h to a vigorously stirred suspension of dopamine hydrochloride (4.17 g, 21.99 mmol) in AcOH (100 mL) and the reaction mixture was concentrated under reduced pressure. The dark-brown residue was taken up in toluene (50 mL) and volatiles were evaporated under reduced pressure (three times) to
give a crude 6-bromodopamine hydrobromide\(^4\) which was directly used for the next step without any further purification.

Boc\(_2\)O (5.50 g, 25.2 mmol) in acetone (40 mL) was added to a solution of 6-bromodopamine hydrobromide (6.9 g, max. 21.99 mmol) and NaHCO\(_3\) (5.54 g, 66.0 mmol) in H\(_2\)O (70 mL; degassed by passing of a gentle stream of argon for 1 h) under Ar and the reaction mixture was stirred for 2 h (if necessary additional acetone and/or H\(_2\)O was added to homogenize the mixture). Thereafter, the mixture was concentrated under reduced pressure. To remove the residual water the residue was taken up in toluene (50 ml) and volatiles were removed under reduced pressure (three times). The residue was purified by column chromatography (acetone:hexane = 1:2) to give after recrystallization from CH\(_2\)Cl\(_2\)/hexane the title compound (3.33 g, 46% on two steps) as a colorless solid.

\(R_f = 0.38\), acetone:hexane = 1:2. \(^1\)H NMR [300 MHz, (CD\(_3\))\(_2\)SO] \(\delta\) 9.19 (s, 1H), 9.07 (s, 1H), 6.87 (s, 2H), 6.65 (s, 1H), 3.04 (dd, \(J = 14.3, 6.8\) Hz, 2H), 2.60 (t, \(J = 6.8\) Hz, 2H), 1.36 (s, 9H).\(^{13}\)C NMR [75 MHz, (CD\(_3\))\(_2\)SO] \(\delta\) 155.5, 145.0, 144.9, 128.7, 118.8, 117.6, 111.3, 77.5, 40.4, 35.0, 28.3. MS (ESI): positive mode \(m/z = 687.1\) ([2M + Na]\(^+\)), 354.0 ([M + Na]\(^+\)); MS (ESI): negative mode \(m/z = 663.1\) ([2M – H]\(^–\)), 330.0 ([M – H]\(^–\)); ESI HRMS: calcd for C\(_{13}\)H\(_{18}\)NO\(_4\)BrNa\(^+\): 354.03111; found: 354.0309; calcd for C\(_{13}\)H\(_{17}\)NO\(_4\)Br\(^–\): 330.0346; found: 330.0345. Correct isotopic pattern.

\textit{NMR-Spectra}
**N,O,O-tri-tert-Butyloxy carbonyl-6-bromodopamine**: Et$_3$N (3.4 mL, 2.46 g, 24.31 mmol) was slowly added to a solution of N-tert-butyloxy carbonyl-6-bromodopamine (3.23 g, 9.72 mmol) and Boc$_2$O (5.31 g, 24.31 mmol) in anhydrous DMF (30 mL) under Ar. The reaction mixture was stirred for a further 16 h and concentrated under reduced pressure. The residue was taken up in Et$_2$O (100 mL) and the resulting solution was washed with H$_2$O (8×40 mL), 1 M NaHSO$_4$ (3×30 mL), 5% NaHCO$_3$ (3×30 mL), brine (2×30 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexane = 1:3) affording after recrystallization from Et$_2$O/hexane the title compound (3.83 g, 74%) as a colorless solid. $R_f = 0.29$, EtOAc:hexane = 1:3. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.47 (s, 1H), 7.13 (s, 1H), 4.62 (br, 1H), 3.36 (dd, $J = 12.4$, 6.5 Hz, 2H), 2.92 (t, $J = 6.5$ Hz, 2H), 1.54 (2s, 2×9H), 1.43 (s, 9H). $^{13}$C
NMR (75 MHz, CDCl₃) δ 156.0, 150.6, 150.5, 141.9, 141.5, 137.1, 127.4, 125.0, 120.4, 84.4, 84.2, 79.4, 40.2, 36.1, 28.5, 27.7 (×2). MS (ESI): positive mode m/z = 1087.3 ([2M + Na]⁺), 570.1 ([M + K]⁺), 554.1 ([M + Na]⁺), 549.2 ([M + NH₄]⁺), 532.2 ([M + H]⁺); MS (ESI): negative mode m/z = 530.2 ([M – H]⁻); ESI HRMS: calcd for C₂₃H₃₄NO₈BrK⁺: 570.1099; found: 570.1096; calcd for C₂₃H₃₄NO₈BrNa⁺: 556.1341; found: 556.1343; calcd for C₂₃H₃₃NO₈Br⁻: 530.1395; found: 530.1383. Correct isotopic pattern.
2-Fluoro-4,5-dimethoxyphenethylamine hydrochloride\cite{[10]}: TFA (2.51 mL, 3.74 g, 32.79 mmol) was added dropwise to a stirred suspension of NaBH₄ (1.24 g, 32.79 mmol) in THF (30 mL) under Ar over 10 min. Afterwards, a solution of 2-fluoro-4,5-dimethoxybenzonitrile\cite{[6]} (0.63 g, 3.22 mmol) in THF (10 mL) was added via a cannula and the reaction mixture was stirred for further 16 h. Thereafter, the mixture was ice-cooled and quenched by the careful addition of water. The resulting mixture was concentrated under reduced pressure to give the residue which was extracted with CH₂Cl₂ (5×30 mL). The extract was washed with H₂O (10 mL) and brine (2×20 mL), dried, filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and the resulting solution was treated with 2 m HCl in EtOAc (5 mL). The solution was evaporated to dryness under reduced pressure and the residual oil was taken in EtOAc (30 mL) and heated to reflux for a short time using a heat gun. After cooling to ambient temperature, the precipitate was
collected by filtration. The filter cake was washed with EtOAc (10 mL) and dried to give the title compound (0.45 g, 59%) as a rose solid. $^1$H NMR (300 MHz, CDCl$_3$) 8.36 (br, 3H), 6.78 (d, $J$ = 7.1 Hz, 1H), 6.58 (d, $J$ = 11.1 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.32–3.15 (m, 2H), 3.12–2.99 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.4 (d, $J$ = 237 Hz), 149.3 (d, $J$ = 9.8 Hz), 145.5 (d, $J$ = 3.0 Hz), 113.7, 113.4, 100.5 (d, $J$ = 27.8 Hz), 56.8, 56.3, 40.0 (d, $J$ = 1.5 Hz), 27.5.
6-Fluorodopamine hydrobromide ([c·HBr]): A solution of 2-fluoro-4,5-dimethoxyphenethylamine hydrochloride (0.42 g, 1.78 mmol) in 48% HBr (4 mL) was heated under Ar at 140 °C for 90 min. Thereafter, the reaction mixture was cooled to ambient temperature and placed in a refrigerator. After 3 h the precipitated solid was collected by filtration and washed with cold water (5 mL) to give the first crop of 3c·HBr (110 mg, 25%) as an off-white solid. The mother liquor was concentrated under reduced pressure and the residue was triturated with Et₂O to give the second drop of 3c·HBr (0.29 g, overall yield: 89%). ¹H NMR (CD₃OD, 300 MHz): δ 6.69 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 11.0 Hz, 1H), 3.11 (t, J = 7.6 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H); ¹³C NMR (CD₃OD, 75 MHz): δ 155.8 (d, J = 233.3 Hz), 146.7 (d, J = 12 Hz), 143.0 (d, J = 2.3 Hz),
117.5 (d, J = 5.3 Hz), 114.0 (d, J = 17.3 Hz), 104.1 (d, J = 26.3 Hz), 41.1 (d, J = 1.5 Hz), 27.7 (d, J = 2.3 Hz).
**N,O,O-tri-tert-Butyloxycarbonyl-6-fluorodopamine (3c):** Et$_3$N (0.95 mL, 0.69 g, 6.82 mmol) was slowly added to a solution of 1c·HBr (0.29 g, 1.15 mmol) and Boc$_2$O (1.6 g, 7.33 mmol) in anhydrous DMF (10 mL) under Ar. Thereafter, the reaction mixture was stirred for a further 16 h and concentrated under reduced pressure. The residue was taken up in Et$_2$O (100 mL) and the resulting solution was washed with H$_2$O (8×40 mL), 1 M NaHSO$_4$ (3×30 mL), 5% NaHCO$_3$ (3×30 mL), brine (2×30 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexane = 1:3). The product fractions were concentrated under reduced pressure. The residual colorless oil was triturated with pentane to give 3c (0.44 g, 62%) as a colorless solid. $R_f = 0.24$, EtOAc:hexane = 1:3. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.08 (d, $J = 7.1$ Hz, 1H), 7.01 (d, $J = 9.6$ Hz, 1H), 4.62 (br, 1H), 3.34 (q, $J = 6.4$ Hz, 2H), 2.81 (t, $J =$$\ldots$
6.7 Hz, 2H), 1.54 (s, 18H), 1.43 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.1 (d, $J = 244.5$ Hz), 156.0, 150.9, 150.5, 141.6 (d, $J = 12$ Hz), 138.7 (d, $J = 3.8$ Hz), 124.8 (d, $J = 6.0$ Hz), 124.3 (d, $J = 18$ Hz), 111.1 (d, $J = 27$ Hz), 84.4, 84.1, 79.5, 40.5, 29.4, 28.5, 27.75, 27.73. MS (ESI): positive mode $m/z = 494.2$ ([M + Na]$^+$), 489.3 ([M + NH$_4$]$^+$); MS (ESI): negative mode $m/z = 470.2$ ([M – H]$^-$); ESI HRMS: calcd for C$_{23}$H$_{34}$NO$_8$BrNa+: 556.1341; found: 556.1343; calcd for C$_{23}$H$_{34}$NO$_8$Na$: 494.2161; found: 494.2158; calcd for C$_{23}$H$_{33}$NO$_8$F$: 470.2196; found: 470.2177.
Ni-aryl complex 4b:

To a solution of TMEDA (0.386 mL, 0.297 g, 2.56 mmol) and methyl N,O-di-tert-butyloxycarbonyl-6-bromo-m-tyrosinate (1.3 g, 2.72 mmol) in toluene (8 mL) was added Ni(COD)$_2$ (0.72 g, 2.62 mmol) and the mixture was stirred at room temperature for a further 2 h. The solution was concentrated under reduced pressure. Pentane (16 mL) was added to the residue and the formed
precipitate was filtered off, washed with pentane (3×5 mL) and dried in vacuo affording [Boc-6-m-Tyr(Boc)OMe]Ni(TMEDA)Br (1.04 g, 71%) as a yellow solid, which was directly used for the next step without any further purification.

To 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide silver(I) (571 mg, 1.24 mmol) and nickel aryl bromide complex [Boc-6-m-Tyr(Boc)OMe]Ni(TMEDA)Br (715 mg, 1.28 mmol) was added a solution of pyridine (105 µL, 104 mg, 1.31 mmol) in toluene (8 mL) followed by acetonitrile (2.0 mL). After stirring for 15 min the mixture was filtered through a glass frit, and the filter cake was extracted with dichloromethane (3×5 mL). Combined filtrates were concentrated under reduced pressure. The residue was purified by column chromatography [hexane/EtOAc 1:6 (0.5% Et₃N)] and recrystallization from CH₂Cl₂/pentane to afford 4b (0.43 g, 38%) as a yellow solid which contained about 30 mol. % (2.6 weight %) ethyl acetate. Broadness of signals in ¹H- and ¹³C-NMR spectra was already observed previously for the similar nickel complex 4a.[¹²] Conformational isomers were observed in the ¹H-spectra, which are possibly due to slow rotation about bonds as seen before for such complexes.[¹²]

¹H NMR (300 MHz, CD₂Cl₂) δ 9.10 (d, J = 6.0 Hz, 2H), 8.31 – 8.21 (m, 1H), 7.76 – 7.59 (m, 3H), 7.57 – 7.35 (m, 3H), 7.29 – 7.25 (m, 1H), 6.76 – 6.65 (m, 1H), 6.34 (dd, J = 24.4, 2.4 Hz, 1H), 4.12 (m, 1H), 3.91 (t, J = 6.6 Hz, 2H), 3.55, 3.51 (2×s, 3H), 1.48 (s, 9H); 1.34, 1.59 (2×s, 9H). ¹³C NMR (75 MHz, CD₂Cl₂) δ 172.9, 167.2, 163.6, 162.6, 155.9, 154.2, 151.0, 148.6, 148.6, 148.1, 141.9, 140.5, 137.8, 137.5, 137.0, 136.2, 135.4, 134.3, 131.6, 130.1, 130.0, 129.7, 128.7, 128.4, 128.2, 125.2, 124.3, 124.2, 124.1, 123.2, 122.6, 118.4, 117.8, 116.0, 82.6, 80.0, 51.9, 39.6, 27.9, 27.4. MS (ESI): positive mode m/z = 829.2 ([M – Py + Na⁺), 807.2 ([M – Py + H⁺); ESI HRMS: calcd for C₃₇H₄₀N₄O₁₁SNiNa⁺: 829.1660; found: 829.1650. Correct isotopic pattern.
To a solution of TMEDA (0.291 mL, 0.224 g, 1.91 mmol) and N,O,O-tri-tert-butyloxycarbonyl-6-bromodopamine (1.01 g, 1.90 mmol) in toluene (10 mL) was added Ni(COD)\(_2\) (0.53 g, 1.93 mmol) and the mixture was stirred at room temperature for a further 2 h. The solution was concentrated under reduced pressure. Pentane (16 mL) was added to the residue and the formed precipitate was
filtered off, washed with pentane (3×5 mL) and dried in vacuo affording [Boc-6-DA(Boc)₂]Ni(TMEDA)Br (1.1 g, 82%) as a peach solid, which was directly used for the next step without any further purification.

To 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide silver(I) (0.53 g, 1.15 mmol) and nickel aryl bromide complex Boc-6-DA(Boc)₂Ni(TMEDA)Br (0.8 mg, 1.13 mmol) was added a solution of pyridine (185 μL, 181 mg, 2.288 mmol) in toluene (12 mL) followed by addition of acetonitrile (3 mL). After stirring for 15 min the mixture was filtered through a glass frit, and the filter cake was extracted with dichloromethane (3×5 mL). Combined filtrates were concentrated under reduced pressure. The residue was purified by column chromatography [hexane/EtOAc 1:3 (0.5% Et₃N)] and recrystallization from CH₂Cl₂/pentane (two times) to afford 4c (0.81 g, 70%) as a brown solid which contained 46 mol % (3.5 weight %) pentane and 35 mol % (3 weight %) ethyl acetate. Broadness of signals in ¹H- and ¹³C-NMR spectra was already observed previously for the similar nickel complex 4a.¹²

¹H NMR (600 MHz, CD₂Cl₂) δ 9.10 (d, J = 5.1 Hz, 2H), 8.42 – 8.35 (m, 1H), 7.96 (s, 1H), 7.73–7.65 (m, 2H), 7.59–7.53 (m, 1H), 7.52–7.44 (m, 1H), 7.44–7.36 (m, 1H), 7.32–7.25 (m, 2H), 7.24–7.16 (m, 2H), 6.78–6.74 (m, 1H), 4.00–3.89 (m, 1H), 3.50–3.32 (m, 1H), 3.16–3.00 (m, 1H), 2.88–2.67 (m, 1H), 1.62 (s, 9H), 1.49 (s, 9H), 1.46 (s, 9H). ¹³C NMR (126 MHz, CD₂Cl₂) δ 155.7, 155.3, 153.4, 151.4, 151.2, 151.03, 151.00, 146.8, 141.8, 140.6, 138.8, 138.7, 137.8, 137.1, 136.1, 135.8, 131.7, 130.5, 130.0, 128.3, 128.2, 127.2, 124.5, 124.2, 123.0, 122.6, 122.3, 118.7, 83.1, 83.0, 78.6, 41.4, 39.1, 28.2, 27.5, 27.3. MS (ESI): positive mode m/z = 887.2 ([M – Py + Na]⁺), 865.2 ([M – Py + H]⁺); MS (ESI): negative mode m/z = 882.3 ([M – H + NH₃⁻]), 863.2 ([M – H]⁻); ESI HRMS: calcd for C₄₀H₄₆N₄O₁₂NiSNa⁺: 887.2079; found: 887.2080; calcd for C₄₀H₅₀N₅O₁₂NiS⁺: 882.2525; found: 882.2515; calcd for C₄₀H₄₇N₄O₁₂NiS⁺: 865.2259; found: 865.2251; calcd for C₄₀H₄₅N₄O₁₂NiS⁻: 863.2103; found: 863.2091. Correct isotopic pattern.
Radiochemistry

Synthesis of $[^{18}\text{F}]3c$ – Optimization study – General procedure 1 (GP1): A solution of $[^{18}\text{F}]\text{KF}/18$-crown-6 (50–500 MBq; vide supra) in the corresponding solvent (900 µL) was added to a mixture of Ni-complex precursor 4c and oxidant 2, weighted in a glove box and the mixture was stirred for a given time at ambient temperature. Thereafter, water (5 mL) was added, the mixture was vigorously stirred for 1 min and analyzed by radio-HPLC (Conditions A: $[^{18}\text{F}]3c$: $t_\text{R}=5.3$ min).

Synthesis of $[^{18}\text{F}]1a-c$ with SPE purification of intermediates $[^{18}\text{F}]3a-c$ – General Procedure 2 (GP2): A solution of $[^{18}\text{F}]\text{KF}/18$-crown-6 (50–500 MBq; vide supra) in MeCN (900 µL) was added to a mixture of the corresponding Ni-complex precursor 4a-c (5 µmol) and oxidant 2 (4.7 mg, 6.5 µmol), weighted in a glove box and the mixture was stirred for 5 min at ambient temperature.
Thereafter, water (5 mL) was added; the mixture was vigorously stirred for 1 min and passed through a polymer-RP cartridge (StrataX, Phenomenex). The cartridge was washed with 40% MeCN (2 mL) and the partially purified radiolabeled intermediates $[^{18}\text{F}]3\text{a-c}$ were eluted with MeCN (0.5 mL). MeCN was evaporated under a gentle stream of argon. The residue was taken up in 37% HCl (200 µL) and the reaction mixture was stirred at 130° C for 10 min. All volatiles were removed under a gentle stream of argon and the residue was dissolved in 0.02 M sodium phosphate buffer (500 µL, pH 2.5). PET-tracers $[^{18}\text{F}]1\text{a-c}$ were isolated by semi-preparative HPLC (system B: $[^{18}\text{F}]1\text{a}: t_R=3.2$ min; $[^{18}\text{F}]1\text{b}: t_R=5.4$ min; $[^{18}\text{F}]1\text{c}: t_R=3.6$ min) and obtained as ready to use solutions.

**One-pot synthesis of $[^{18}\text{F}]1\text{a-c}$ – General Procedure 3 (GP3):** A solution of $[^{18}\text{F}]\text{KF}/18$-crown-6 (0.05–40 GBq; vide supra) in MeCN (900 µL) was added to a mixture of the corresponding Ni-complex precursor 4a-c (5 µmol) and oxidant 2 (4.7 mg, 6.5 µmol), weighted in a glove box and the mixture was stirred for 5 min at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was taken up in 37% HCl (200 µL) and the reaction mixture was stirred at 130° C for 10 min. Acetone (1 mL) was added and all volatiles were removed under a gentle stream of argon (two times). The residue was dissolved in 0.02 M sodium phosphate buffer (500 µL, pH 2.5). PET-tracers $[^{18}\text{F}]1\text{a-c}$ were isolated by semi-preparative HPLC (system B) and obtained as ready to use solutions.
HPLC-chromatograms

Radio HPLC trace

Radio HPLC trace isolated product
Radio HPLC trace crude product
UV trace of $^{19}\text{F}$-reference substance ($\lambda=210\ \text{nm}$)
Chromatograms of the isolated and the crude product are identically.
Specific activity calculation

The specific activities (GBq/µmol) were calculated by dividing the radioactivity of the $^{18}$F-labeled product by the amount of the unlabeled tracer determined from the peak area in the UV-HPLC chromatograms ($\lambda=210$ nm). The amounts of unlabeled compounds were determined from the UV-absorbance/concentration calibration curve. The solutions of 6-$[^{18}$F]$^1$FDOPA and 6-$[^{18}$F]$^1$FDA (all synthesis started from 7 GBq of $^{18}$F$^-$) obtained after HPLC purification were concentrated under reduced pressure, the residues were redissolved in 4% EtOH in 0.02 M sodium phosphate buffer (300 µL, pH 2.5) and the resulting solutions were completely injected. The specific activity of 6-$[^{18}$F]$^1$FDOPA was 175 GBq/µmol. The specific activity of 6-$[^{18}$F]$^1$FDA was 60 GBq/µmol.

![Graph showing specific activity of 6-$[^{18}$F]$^1$FDOPA](image)
**In vivo evaluation**

All experiments were carried out in accordance with the EU directive 2010/63/EU for animal experiments and the German Animal Welfare Act (TierSchG, 2006) and approved by regional authorities (LANUV NRW).

**Rat model of hemi-Parkinson's disease:** Adult male Long Evans rats (Janvier, France) were used. Rats were anesthetized (initial dosage: 5% isoflurane in O₂/N₂O (3:7), then reduction to 2.5%) and fixed in a stereotaxic frame. Body temperature was monitored rectally and was held constant at 37 °C using a heating pad. After removing skin and periosteum, a small hole (approx. 1 mm in diameter) was drilled in the skull 1.2 mm lateral and 4.4 mm posterior from bregma, and the cannula of a Hamilton syringe was inserted 8 mm deep, measured from the level of the dura mater. 6-Hydroxydopamine hydrobromide (6-OHDA, Sigma Aldrich, contains ascorbic acid as stabilizer) (21 µg) in isotonic saline (3 µL) was slowly injected, and the cannula was left in place for 10 min. After
retraction of the cannula, the burr hole was closed with bone wax and the skin wound was sutured. Finally, carprofen for analgesia (Rimadyl®) (3 mg) was subcutaneously injected.

**µPET-Imaging**: PET measurements were carried out 6–8 weeks after 6-OHDA injection. Prior to the PET measurement animals were anesthetized (initial dosage: 5% isoflurane in O₂/N₂O (3:7), then reduction to 2%), and a catheter for tracer-injection was inserted into the lateral tail vein. Rats were placed on an animal holder (medres GmbH, Cologne, Germany), and fixed with a tooth bar in a respiratory mask. Dynamic PET scans in list mode were performed using a Focus 220 micro PET scanner (CTI-Siemens, Erlangen, Germany) with a resolution at the center of field of view of 1.4 mm. Data acquisition started immediately after intravenous injection of 6-[¹⁸F]FDOPA [56–93 MBq in 0.5 mL of 4% EtOH 0.02 M sodium phosphate buffer (pH 2.5–4)] and was carried out for 60 min. Thereafter a 10 min transmission scan was acquired using a $^{57}$Co point source. Breathing rate was monitored with a Dasy Lab system 9.0 (DasyLab, Mönchengladbach, Germany) and kept around 60/min by adjusting the isoflurane concentration (1.5–2.5%). Body temperature was maintained at 37 °C by a feedback-controlled system (medres GmbH, Cologne, Germany). Following Fourier rebinning, data were reconstructed using an iterative OSEM3D/MAP procedure$^{[13]}$ including attenuation correction in two different ways: 1) 24 frames (6×30 s, 3×1 min, 3×2 min, 12×4 min) for compilation of striatal time activity curves. 2) 2 frames (2×30 min) for other VOI analyses.

Resulting voxel sizes were always $0.38\times0.38\times0.82$ mm.

**MR-Imaging**: To rule out gross structural brain anomalies and to provide individual templates for co-registration of the PET images, T2-weighted structural MR images were acquired. MRI scans were performed in an 11.7-T BioSpec animal scanner (Bruker BioSpin®) using a quadrature receive-only rat brain surface coil (Bruker BioSpin®) in combination with an actively decoupled, transmit-only quadrature resonator with 72 mm inner diameter (Bruker Biospin), fitting into the
BFG-150/90-S14 combined gradient and shim set of 90 mm inner diameter (Resonance Research Inc., Billerica, MA, USA) with a maximum gradient strength of 745 mT/m. A T2-weighted sequence, rapid acquisition with relaxation enhancement (RARE) was used: RARE factor = 8, repetition time/effective echo time = 6500/32.5 ms, averages = 2, matrix size = 256×256, FOV = 3.2×3.2 cm², 58 slices, slice thickness = 0.5 mm, interslice spacing = 0.5 mm. The inhalation anesthesia procedure was the same as that used for the μPET scan. During scanning, body temperature was recorded and maintained at 37° using feedback water control (medres GmbH, Cologne, Germany); physiological parameters, in particular respiration rate, were monitored using DASYLab 9.0 (DasyLab, Moenchengladbach, Germany).

**Imaging Data Analysis:** MR- [Gauss filtered (2 mm FWHM)] and μPET-Images were manually co-registered using VINCI 4.04 software.\[14\] SUVs (%ID/g) were calculated by dividing the concentration of \[^{18}\text{F}\]FDOPA in the region of interest by the total injected dose (ID) and multiplying by 100.

To obtain time activity curves, an elliptical 10 mm³ volume of interest (VOI) was placed over the intact striatum. Mean SUV values were extracted from each of the 24 frames, decay corrected, and plotted over time.

For other VOI analyses, the frame covering 30–60 min post injection was used. Two elliptical VOIs (17 mm³ each) were placed in the left and right striatum, respectively, and a 90 mm³ VOI was used for the cerebellum. Mean SUV values were used to calculate striatum-to-cerebellum and ipsi-to-contralateral striatal ratios.
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