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# Radiosynthesis of *N*-[4-(4-fluorobenzyl) piperidin-1-yl]-*N′*-(2-[$^{11}$C]oxo-1,3-dihydrobenzimidazol-5-yl)oxamide, a NR2B-selective NMDA receptor antagonist

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**In order to perform *in vivo* imaging of the NR2B NMDA receptor system by positron emission tomography, a NR2B selective NMDA receptor antagonist has been labelled with carbon-11 (half-life: 20 min). *N*-[4-(4-fluorobenzyl)piperidin-1-yl]-*N′*-(2-oxo-1,3-dihydrobenzimidazol-5-yl)oxamide has been described demonstrating high affinity and selectivity for the NR2B receptors ($IC_{50}$ of 5 nM in [$^3$H]Ro-25,6981 binding assay). The labelling precursor and the reference compound were synthesized by coupling the 4-(4-fluorobenzyl)piperidine with the corresponding oxalamic acid. The reaction of [$^{11}$C]phosgene with phenylenediamine precursor led the formation of the [$^{11}$C]benzimidazolone ring present on the ligand. The labelling occurred in THF or acetonitrile and the decay corrected radiochemical yield was 30–40% from the produced [$^{11}$C]methane. HPLC purification and formulation led to 2.6–3.7 GBq (70–100 mCi) of radioligand within 30–35 min. The specific radioactivity was 72–127 GBq/μmol (2–3.4 Ci/μmol) at the end of synthesis.**

**Keywords:** carbon-11; PET; NR2B; NMDA; radiolabelling

## Introduction

*N*-methyl-D-aspartate (NMDA) receptors play a specific role among the excitatory ionotropic glutamate receptors by its pharmacological and functional properties. Its high permeability to calcium ions confers to the NMDA receptors a specific importance in synaptic plasticity and neuronal death. NMDA receptors are an assembly of four subunits consisting of two NR1 and NR2 subunits.[1] Four different NR2 subunits exist (A, B, C and D) and particularly, the NR2B subtype is involved in synaptic plasticity, schizophrenia, neurodegenerative diseases, pain perception and ischemia.[2] The NR2B subunit containing receptor is still the sole subtype of NMDA receptors having highly selective antagonists such as CP-101,606, Cl-1041 or Ro-25,6981, derived from ifenprodil, the first selective antagonist known (Figure 1).[3,4]

The visualization and quantification of the NR2B receptors by a non-invasive imaging technique like positron emission tomography (PET) could facilitate the understanding of pathologies and offer a diagnostic tool. For a few years, NR2B selective antagonists from the different series were labelled with carbon-11[5–9] or fluorine-18[10] (Figure 2). However, in spite of promising *in vitro* pharmacological data, these compounds demonstrated a lack of specificity or insufficient brain penetration to qualify as good radiotracers.

Recently a new series of NR2B antagonist was described[11] consisting of a benzylpiperidine moiety related to the ifenprodil structure as well as an oxamide function and a condensed heterobicycle. The bicycle containing an NH group offers better metabolic properties than the phenolic groups usually present in NR2B antagonists (Figure 1). These oxamides presented high NR2B affinities and activities and a good selectivity towards NR2A. Compound **1** (*N*-[4-(4-fluorobenzyl)piperidin-1-yl]-*N′*-(2-oxo-1,3-dihydrobenzimidazol-5-yl)oxamide, Figure 3) showed the best affinity in this series with an $IC_{50}$ of 5 nM in [$^3$H]Ro-25,6981 binding assay and 2 nM in functional assays of NMDA-evoked changes of intracellular $Ca^{2+}$ flux measured by fluorescence. These data were of the same order as for Cl-1041 ($IC_{50}$ = 8 nM) but better than Ro-25,6981 ($IC_{50}$ = 57 nM) for the NMDA-evoked $Ca^{2+}$ flux functional assay. Compound **1** also demonstrated a very low NR2A inhibition of 2% at 15 μM measured using the same NMDA-evoked $Ca^{2+}$ assay. This selectivity was better than for compound **E** (50% at 35 μM

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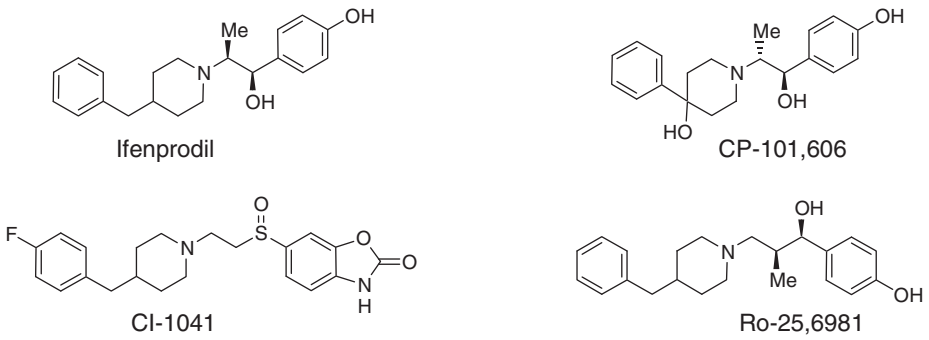



**Figure 1.** NR2B NMDA receptor antagonists.

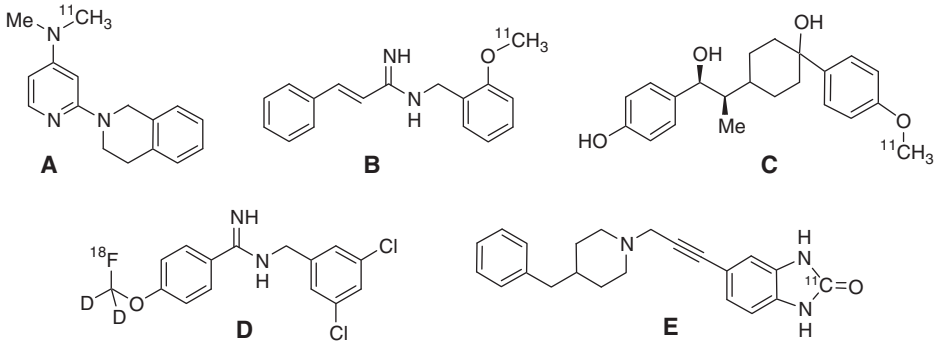



**Figure 2.** Radiolabelled selective NR2B antagonists : [$^{11}$C]Ro-647312 (**A**), *N*-(2-[$^{11}$C]methoxyphenyl)cinnamidine (**B**), [$^{11}$C]methoxy-CP-101,606 (**C**), *N*-(3,5-dichlorobenzyl)-4-([$^{18}$F]fluoromethoxy)phenylcarboximidamine-$d_2$ (**D**), 5-[3-(4-benzylpiperidin-1-yl)prop-1-ynyl]-1,3-dihydrobenzimidazol-2-[$^{11}$C]one (**E**).

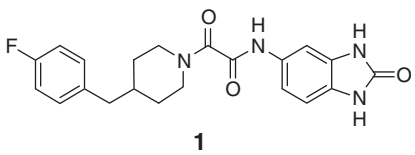



**Figure 3.** Compound **1**.

towards NR2A subunit) and **1** presented no adrenergic activity[3] when **E** showed an $IC_{50}$ of 500 nM for $\alpha$1 adrenergic receptors.[12] Due to its planarity, the series of alkynyl compounds demonstrated a poor solubility[13] that would be better with the oxamides. Moreover, the fluorinated compound **1** offers the possibility of a labelling with fluorine-18 in case of promising *in vivo* properties.

The intention of this study was to develop the labelling of compound **1** with carbon-11 to evaluate *in vivo* its potency as a PET radiotracer for imaging NR2B containing NMDA receptors.

## Results and discussion

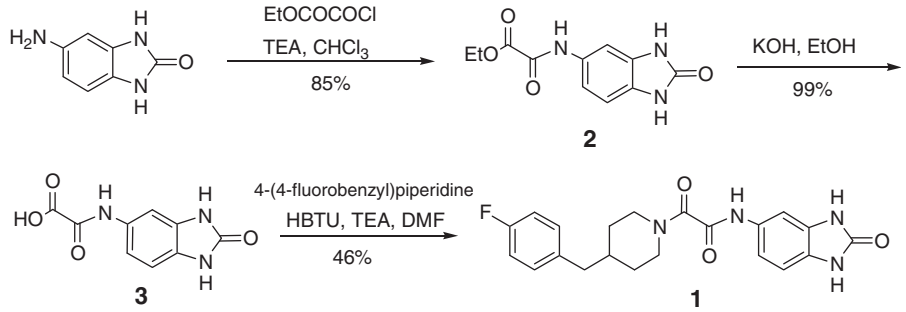
The presence of a benzimidazolinone moiety on **1** (Figure 3) permits the labelling by cyclization reaction with [$^{11}$C]phosgene of the corresponding ring-open precursor phenylenediamine. The reference compound **1** and the labelling precursor **7** were prepared following the same strategy (Schemes 1 and 2). The synthesis of compound **1** was slightly different than the previously described pathway using a coupling reaction between the 5-amino-2-benzimidazolinone and *N*-[4-(4-fluorobenzyl)piperidin-1-yl]oxalamic acid.[11] The ethyl chlorooxoacetate was added to the 5-amino-2-benzimidazolinone affording the ethyl ester **2**. After hydrolysis, the coupling reaction of the corresponding oxalamic acid **3** with 4-(4-fluorobenzyl)piperidine[14] in presence of HBTU led to the compound **1** with an overall yield of 39%.

The labelling precursor **7** was obtained analogously (Scheme 2) from 2-nitro-1,4-phenylenediamine. After the addition of the ethyl chlorooxoacetate and hydrolysis, the resulting acid **5** has reacted with 4-(4-fluorobenzyl)piperidine in the presence of HBTU. The reduction of the nitro group was not optimized since the amount of product obtained was sufficient for this study. The precursor **7** was obtained in 15% overall yield in 5 steps.

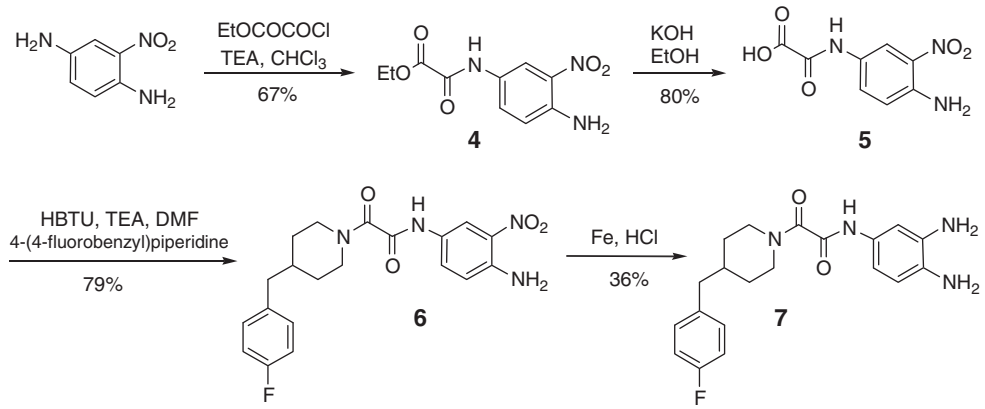
The ligand **1** was labelled (Scheme 3) by reaction of precursor **7** with [$^{11}$C]phosgene obtained as described previously.[15] The cyclization reaction occurred instantaneously during the bubbling of [$^{11}$C]phosgene in a reactor containing precursor **7** (3 μmol) in solution either in acetonitrile or in THF containing TEA. The decay-corrected radiochemical yield was 30–40% from the [$^{11}$C]methane in both conditions. After HPLC purification using a C18 column, the collected fraction was diluted and passed through a C18 SPE cartridge to retain **[$^{11}$C]-1** that was then eluted with ethanol. A dilution with saline followed by sterilization by filtration (0.22 μm) resulted in a 10% ethanol physiological solution with a pH of 5–7. Typically, 2.6–3.7 GBq (70–100 mCi) of **[$^{11}$C]-1** was produced within 30–35 min including the purification and formulation with chemical and radiochemical purities measured by HPLC greater than 98%. The specific radioactivities were 72–127 GBq/μmol (2–3.4 Ci/μmol) at the end of the synthesis.



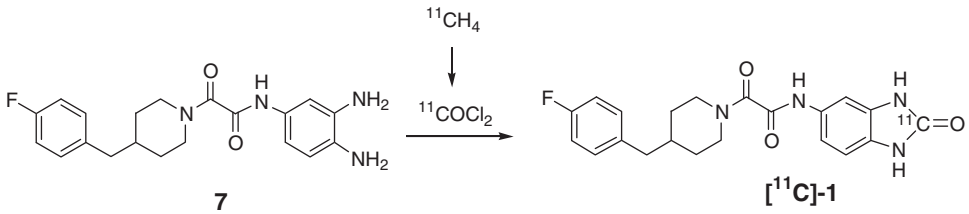
  




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

## Conclusion

We have labelled compound **1,** a NR2B-selective NMDA antagonist, by a cyclization reaction from the phenylenediamine precursor **7** with [$^{11}$C]phosgene. The radiochemical yield was 30–40%. The μPET scans on rodents are under progress to evaluate the potential of **[$^{11}$C]-1** as a PET radiotracer for imaging the cerebral NR2B NMDA receptors.

## Experimental

All reagents were purchased from Fluka or Sigma-Aldrich (Saint-Quentin Fallavier, France) and were used without further purification. Anhydrous THF, DMF and acetonitrile were obtained from a Mbraun SPS-800 solvents delivery system. HPLC quality solvent was purchased from Merck (France) or SDS (Peypin, France). No-carrier-added [$^{11}$C]methane was produced using a Cyclone 18/9 (IBA) cyclotron using the $^{14}$N($p$,$\alpha$)$^{11}$C nuclear reaction with a 20 MeV proton beam. Irradiation occurred on a target filled with nitrogen containing 5% hydrogen (Air Liquide, N60 quality).

All melting points were determined on a Barnstead Electrothermal IA 9100 melting point apparatus and are uncorrected. $^{1}$H, $^{13}$C and $^{19}$F NMR spectra were measured on a Brucker DRX 400, at 400 MHz ($^{1}$H), 100.6 MHz ($^{13}$C) and 376.4 MHz ($^{19}$F) or on a Brucker DPX 250, at 250 MHz ($^{1}$H), 62.5 MHz ($^{13}$C) and 235 MHz ($^{19}$F). Chemical shifts are reported as parts per million (δ) by reference to the proton resonance resulting from the incomplete deuteration of the NMR solvent. Coupling constants are given in Hz and coupling patterns are abbreviated as: s (singlet), d (doublet), t (triplet), q (quadruplet), m (mutiplet), bs (broad singlet) and dd (doublet of doublet). High-resolution mass spectra (HRMS) were obtained on a Waters Q-TOF micro spectrometer by electrospray ionisation (ESI). Elemental analyses were performed on a ThermoQuest analyser CHNS and were within ±0.4% of the calculated values.

Thin-layer chromatographies (TLC) were run on pre-coated aluminium plates of silica gel 60$F_{254}$ (Merck) and Rf were

established using an UV-lamp at 254 nm or by ninhydrin or phosphomolybdic acid hydrate spray reagents. Liquid chromatographies were performed on 40–63 mesh silica gel 60 (Merck) columns. Radioactive TLC was measured using an Instant Imager® Packard apparatus. Radioactivity quantities were determined with a dose calibrator (Capintec R15C). Semi-preparative HPLC was performed using a Waters 501 pump, a spectrophotometer ($\lambda = 254$ nm) coupled with a Geiger-Müller probe (SDS, Paris, France) using a Symmetry C18 column (300 × 7.8 mm, 7 μm, Waters) with an eluent made of water/acetonitrile/trifluoroacetic acid (63/37/0.1) at 7 mL/min ($t_R$ (**1**) = 5.5–6.0 min). Radiochemical purity analysis were performed on a Merck HPLC system coupled with a NaI radioactive detector (Novelec, France) using a Macherey Nagel Nucleosil 100–5 Protect 1 column (4.6 × 250 mm, 5 μm) at a flow rate of 1 mL/min with methanol/0.01 M phosphoric acid solution (64/36) as eluent.

### Ethyl 2-acetamido-*N*-(2-oxo-2,3-dihydrobenzimidazol-5-yl) acetate 2

Ethyl chlorooxoacetate (900 μL, 8.05 mmol) was added dropwise to a solution of 5-amino-1,3-dihydrobenzoimidazol-2-one (1.0 g, 6.70 mmol) and sodium acetate (660 mg, 8.05 mmol) in acetic acid (35 mL). The reaction mixture was stirred at 35°C for 1 h and further 45 min at 90 C. Then, water was added (70 mL) and the resulting precipitate was filtered, washed with water (2 × 30 mL) and dried overnight under vacuum affording **2** (1.41 g, 85%) as a white solid. M.p.: dec. 330°C. $^1$H NMR (DMSO-$d_6$): 10.66 (s, 1H), 10.65 (s, 1H), 10.61 (s, 1H), 7.52 (d, $J$ = 1.5 Hz, 1H), 7.26 (dd, $J$ = 8.4 Hz, $J$ = 1.5 Hz, 1H), 6.88 (d, $J$ = 8.4 Hz, 1H), 4.30 (q, $J$ = 7.1 Hz, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (DMSO-$d_6$): 160.9, 155.5, 155.1, 131.0, 129.6, 126.8, 113.2, 108.2, 101.6, 62.3, 13.9. HRMS: *m/z* found for $[M+H]^+$ $C_{11}H_{12}N_3O_4$: 250.0840 (calcd.: 250.0828). Anal. found for $C_{11}H_{11}N_3O_4$: C = 53.11%, H = 4.83%, N = 16.50% (calcd.: C = 53.01%, H = 4.45%, N = 16.86%).

### 2-Acetamido-*N*-(2-oxo-2,3-dihydrobenzimidazol-5-yl)acetic acid 3

A solution of potassium hydroxide (810 mg, 14.4 mmol) in water (3 mL) was added to a suspension of compound **2** (1.2 g, 4.8 mmol) in ethanol (25 mL). Once the reaction mixture was stirred at room temperature for 2 h, water (15 mL) was added and the solution was acidified using concentrated hydrochloric acid. The resulting precipitate was filtered off and dried overnight under vacuum to afford the hydrochloride salt (1.22 g, 99%) as a white solid. M.p.: dec. 360°C. $^1$H NMR (DMSO-$d_6$): 10.64 (s, 1H), 10.60 (s, 1H), 10.58 (s, 1H), 7.54 (d, $J$ = 2.0 Hz, 1H), 7.28 (dd, $J$ = 2.0 Hz, $J$ = 8.4 Hz, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): 163.2, 157.3, 156.3, 132.1, 130.4, 127.5, 114.0, 109.1, 102.3. HRMS: *m/z* found for $[M-H]^-$ $C_9H_6N_3O_4$: 220.0357 (calcd.: 220.0358 ). Anal. found for $C_9H_7N_3O_4 \cdot HCl \cdot 0.2\ H_2O$ : C = 41.48%, H = 3.53%, N = 16.05% (calcd.: C = 41.38%, H = 3.24%, N = 16.09%).

### *N*-[4-(4-Fluorobenzyl)piperidin-1-yl]-*N*′-(2-oxo-1,3-dihydro-benzimidazol-5-yl)oxamide 1

Under a nitrogen atmosphere, triethylamine (242 μL, 1.72 mmol), 4-(4-fluorobenzyl)piperidine (221 mg, 0.86 mmol) and HBTU (391 mg, 1.03 mmol) were added to a solution of **3** (266 mg, 1.03 mmol) in DMF (20 mL). The solution was stirred for 24 h at room temperature then 10% aqueous $NaHCO_3$ (80 mL) and dichloromethane (50 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by chromatography on silica gel (96/4/0.1 to 94/6/0.1, dichloromethane/methanol/$NH_4OH$) to afford **1** as a white solid (156 mg, 46%). M.p.: 295–300°C. $^1$H NMR (DMSO-$d_6$): 10.64–10.53 (m, 3H), 7.45 (d, $J$ = 1.6 Hz, 1H), 7.25–7.17 (m, 2H), 7.14–7.04 (m, 3H), 6.85 (d, $J$ = 8.4 Hz, 1H), 4.33–4.23 (m, 1H), 3.77–3.67 (m, 1H), 3.09–2.98 (m, 1H), 2.72–2.61 (m, 1H), 2.53 (m, 2H), 1.85–1.73 (m, 1H), 1.66–1.55 (m, 2H), 1.21–1.04 (m, 2H). $^{13}$C NMR (DMSO-$d_6$): 162.7, 162.0, 160.7 (d, $J$ = 240.9 Hz), 155.5, 136.0 (d, $J$ = 3.1 Hz), 131.4, 130.7 (d, $J$ = 7.6 Hz), 129.7, 126.3, 114.8 (d, $J$ = 20.8 Hz), 112.4, 108.3, 101.0, 45.8, 41.0, 40.7, 37.2, 31.8, 30.8. $^{19}$F NMR (DMSO-$d_6$): −117.42. HRMS: *m/z* found for $[M+H]^+$ $C_{21}H_{22}FN_3O_4$: 397.1662 (calcd.: 397.1676). Anal. found for $C_{21}H_{21}FN_4O_3 \cdot 0.3\ H_2O$: C = 62.59%, H = 5.77%, N = 13.79% (calcd.: C = 62.41%, H = 5.45%, N = 13.86%).

### Ethyl 2-acetamido-*N*-(4-amino-3-nitrophenyl)acetate 4

A solution of ethyl chlorooxoacetate (2.92 mL, 26 mmol) in DMF (20 mL) was added dropwise at 0°C to a solution of 2-nitro-1,4-phenylenediamine (2.0 g, 13 mmol) and triethylamine (3.66 mL, 26 mmol) in chloroform (100 mL). The reaction was stirred at room temperature for 1 h and decomposed with a 10% $NaHCO_3$ solution (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by column chromatography (70/30 to 50/50, heptane/ethyl acetate) to give **4** as an orange solid (2.21 g, 67%). M.p.: 176°C. $^1$H NMR ($CDCl_3$): 8.19 (d, $J$ = 2.4 Hz, 1H), 7.46 (dd, $J$ = 9.2 Hz, $J$ = 2.4 Hz, 1H), 6.68 (d, $J$ = 9.2 Hz, 1H), 4.28 (bs, 3H), 4.14 (q, $J$ = 7.2 Hz, 2H), 1.16 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$): 160.9, 155.7, 144.2, 130.9, 129.9, 126.3, 119.8, 117.8, 63.8, 14.1. HRMS: *m/z* found for $[M+H]^+$ $C_{10}H_{12}N_3O_5$ : 254.0767 (calcd.: 254.0777). Anal. found for $C_{10}H_{11}N_3O_5$: C = 47.42%, H = 4.53%, N = 16.61% (calcd.: C = 47.43%, H = 4.38%, N = 16.59%).

### 2-Acetamido-*N*-(4-amino-3-nitrophenyl)acetic acid 5

Potassium hydroxide (10 N, 2.1 mL, 21.3 mmol) was added under vigorous stirring to a suspension of **4** (1.8 g, 7.1 mmol) in ethanol (60 mL). The reaction mixture was stirred for 1 h at room temperature and was acidified with concentrated hydrochloric acid. The precipitate was filtered off and dried overnight under vacuum affording **5** as a red solid (1.27 g, 80%). M.p.: 231°C. $^1$H NMR (DMSO-$d_6$): 10.74 (s, 1H), 8.56 (d, $J$ = 2.4 Hz, 1H), 7.72 (dd, $J$ = 9.2 Hz, $J$ = 2.4 Hz, 1H), 7.43 (bs, 2H), 7.00 (d, $J$ = 9.2 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): 162.0, 156.5, 143.7, 129.7, 129.1, 126.3, 119.4, 115.8. HRMS: *m/z* found for $[M-H]^-$ $C_8H_6N_3O_5$: 224.0310 (calcd.: 224.0307). Anal. found for $C_8H_7N_3O_5$: C = 42.52%, H = 3.30%, N = 18.26% (calcd.: C = 42.67%, H = 3.13%, N = 18.66%).

### *N*-[4-(4-Fluorobenzyl)piperidin-1-yl]-*N*′-(4-amino-3-nitrophenyl) oxamide 6

Triethylamine (548 μL, 3.90 mmol), 4-(4-fluoro-benzyl)piperidine (276 mg, 1.43 mmol) and HBTU (542 mg, 1.43 mmol) were added to **5** (340 mg, 1.52 mmol) in solution in DMF (20 mL). The solution was stirred for 24 h at room temperature then sodium bicarbonate aqueous solution (10%, 40 mL) was added. The aqueous phase was extracted with dichloromethane (4 × 50 mL).

The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by chromatography on silica gel (99/1/0.1, dichloromethane/methanol/$NH_4OH$) to afford **6** as an orange solid (452 mg, 79%). M.p.: 191°C. $^1$H NMR (DMSO-$d_6$): 10.68 (s, 1H), 8.45 (d, $J$ = 2.4 Hz, 1H), 7.55 (dd, $J$ = 9.2 Hz, $J$ = 2.4 Hz, 1H), 7.38 (s, 2H), 7.23–7.16 (m, 2H), 7.11–7.03 (m, 2H), 7.01 (d, $J$ = 9.2 Hz, 1H), 4.34–4.25 (m, 1H), 3.84–3.75 (m, 1H), 3.09–2.98 (m, 1H), 2.72–2.62 (m, 1H), 2.53 (m, 2H), 1.86–1.71 (m, 1H), 1.70–1.55 (m, 2H), 1.25–1.05 (m, 2H). $^{13}$C NMR (DMSO-$d_6$): 162.3, 162.0, 160.7 (d, $J$ = 241.5 Hz), 143.5, 138.4, 136.1, 136.0, 130.7 (d, $J$ = 7.5 Hz), 129.1 (d, $J$ = 11.3 Hz), 126.4, 119.6, 114.8 (d, $J$ = 27.0 Hz), 45.8, 41.0, 40.8, 37.3, 31.8, 30.9. $^{19}$F NMR (DMSO-$d_6$): −117.42. HRMS: *m/z* found for $[M+H]^+$ $C_{20}H_{22}FN_4O_4$: 401.1613 (calcd.: 401.1625). Anal. for $C_{20}H_{21}FN_4O_4.0.2H_2O$: C = 59.34%, H = 5.72%, N = 13.92% (calcd.: C = 59.33%, H = 5.35%, N = 13.84%).

### *N*-(3,4-Diaminophenyl)-*N*′-[4-(4-fluorobenzyl)piperidin-1-yl] oxamide 7

A suspension of **6** (400 mg, 0.99 mmol) and powdered iron (392 mg, 6.99 mmol) in water (2 mL) was refluxed during 30 min under vigorous stirring. Then concentrated hydrochloric acid (83 μL, 0.49 mmol) was carefully added and the reaction mixture was heated for further 3 h. After cooling to room temperature, the iron was filtered off and washed with methanol (5 × 10 mL). The combined filtrates were concentrated under vacuum and purified on silica gel column (98/2/0.1 to 95/5/0.1 dichloromethane/methanol/$NH_4OH$) to give **7** as a white solid (131 mg, 36%). M.p.: 185°C. $^1$H NMR (DMSO-$d_6$): 10.09 (s, 1H), 7.25–7.05 (m, 4H), 6.87 (d, $J$ = 2.2 Hz, 1H), 6.59 (dd, $J$ = 8.2 Hz, $J$ = 2.2 Hz, 1H), 6.42 (d, $J$ = 8.2 Hz, 1H), 4.54 (bs, 2H), 4.37–4.22 (m, 3H), 3.75–3.65 (m, 1H), 3.10–2.90 (m, 1H), 2.75–2.60 (m, 1H), 2.53 (m, 2H), 1.88–1.48 (m, 3H), 1.25–0.98 (m, 2H). $^{13}$C NMR (DMSO-$d_6$): 163.1, 161.5, 160.7 (d, $J$ = 240.8 Hz), 136.3 (d, $J$ = 3.1 Hz), 135.1, 131.8, 130.7 (d, $J$ = 7.5 Hz), 128.3, 114.8 (d, $J$ = 20.7 Hz), 114.1, 109.3, 106.9, 45.7, 40.6, 41.0, 37.3, 31.7, 30.8. $^{19}$F NMR (DMSO-$d_6$): −117.44. HRMS: *m/z* found for $[M+H]^+$ $C_{20}H_{24}FN_4O_2$: 371.1883 (calcd.: 371.1883). Anal. for $C_{20}H_{23}FN_4O_2 \cdot 0.5\ H_2O$: C = 63.48%, H = 6.54%, N = 14.77% (calcd.: C = 63.31%, H = 6.38%, N = 14.77%).

### *N*-[4-(4-Fluorobenzyl)piperidin-1-yl]-*N*′-(2-[$^{11}$C]oxo-1,3-dihydrobenzimidazol-5-yl)oxamide [$^{11}$C]-1

#### *Preparation of [$^{11}$C]$COCl_2$*

Briefly, the [$^{11}$C]$CH_4$ produced by the cyclotron was passed through two guards containing soda lime or $P_2O_5$. The [$^{11}$C]$CH_4$ was separated from the target gas and concentrated by trapping in two successive U-tube filled with Porapak-Q (80–100 mesh, Waters) dipped in liquid argon. [$^{11}$C]$CH_4$ was then released and gently swept in a minimum volume of helium into a 20 mL mixing chamber containing chlorine (99.99%, Air Liquide). Using $N_2/O_2$ (98/2) gas, the [$^{11}$C]$CH_4$/chlorine mixture was passed successively through an empty horizontal quartz tube (300 mm length, 4 mm internal diameter) heated at 560°C and then through a Pyrex tube (300 mm length, 4 mm internal diameter) containing 2 g of iron chips (Aldrich 99.98%) heated at 320°C. Finally, the gaseous reaction mixture containing the [$^{11}$C]$COCl_2$ was passed on-line through an antimony-guard in order to remove the excess of chlorine.

#### *Radiosynthesis and purification of [$^{11}$C]-1*

The synthesized [$^{11}$C]$COCl_2$ was bubbled at room temperature in a conic reaction vial containing the labelling precursor **7** (1–1.6 mg) dissolved in 300 μL of THF or 500 μL of acetonitrile. When the transfer of [$^{11}$C]$COCl_2$ was completed, the reaction solution was diluted with 0.5 mL of the HPLC mobile phase and injected onto the column. The pure fraction of **[$^{11}$C]-1** was collected and diluted with water (30 mL). The solution was passed through a Chromabond C18ec Shorty cartridge (20 mg, Macherey Nagel). The cartridge was washed twice with water (5 mL) and the radiotracer was eluted with ethanol (500 μL). Physiological saline (5 mL) was added and the resulting solution was filtered on a sterile 0.22 μm GV-Millipore filter.

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