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Palladium-Mediated ^{11}C -Carbonylations Using Aryl Halides and Cyanamide

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A robust and high-yielding radiochemical synthesis of ^{11}C -*N*-cyanobenzamides using a palladium-mediated aminocarbonylation with ^{11}C -CO, aryl halides and cyanamide is described. The bidentate ligand 1,1'-bis(diphenylphosphino)ferrocene provided ^{11}C -*N*-cyanobenzamides from aryl-iodides, bromides, triflates and even chlorides in 28-79% radiochemical yield after semi-preparative HPLC. To further highlight the utility of this method, novel ^{11}C -*N*-cyanobenzamide analogs of flufenamic acid, meflamic acid, dazoxiben and tamibarotene were synthesized in 34-71% radiochemical yields.

Introduction

Positron emission tomography (PET) is a powerful noninvasive modality for the visualization of biological functions, in real time, using a positron emitting nuclide incorporated into a bioactive molecule (tracer).^{1,2} PET is an important clinical diagnostic tool and has found extensive use in the monitoring of disease progression and treatment response in cancer patients.²⁻⁴ PET has also emerged as an enabling tool to study the underlying biological processes in many neurological disorders and in the development of drugs targeting the CNS.⁵

One of the most important nuclides used in PET is the cyclotron-produced carbon-11 (^{11}C) with a half-life of 20.4 min.⁶ This is mainly due to the potential introduction of the carbon nuclide into various positions in a molecule of interest without disturbing its biological activity. ^{11}C is typically produced in the form of ^{11}C -carbon dioxide ($^{11}\text{CO}_2$) and can be readily transformed into a number of key building blocks including ^{11}C -carbon monoxide (^{11}CO).^{7,8} The synthetic versatility of ^{11}CO is well-known and it can be utilized in various metal-mediated reactions yielding a host of different carbonyl and carboxylic acid derivatives including amides, acids, esters and ketones.⁹⁻¹³

Despite these advances, there are a multitude of biologically important functional groups and scaffolds that cannot be prepared using existing ^{11}CO technology. This highlights one of the major limitations of PET, namely the lack of generally applicable methods for the incorporation of the radionuclide into a target molecule. This has created a situation where tracer synthesis is dominated by a handful of

synthetic methods (e.g. methylation) and potential tracers are invariably designed to conform within the narrow confines of existing chemistry, rather being naturally guided by target biology. To overcome these issues, there is an increasing demand for the development of new radiochemical methods that are suitable for the labelling of complex biologically active molecules. The use of ^{11}C , however, poses a number of additional challenges as the short half-life of ^{11}C demands the development of fast and efficient reactions.

Bioisosteric replacement has played a vital role in drug discovery and development since the term was first coined in the 1950's by Harris Friedman.^{14,15} The concept is based upon the assumption that atoms or functional groups with comparably shapes and/or physicochemical properties will interact similarly with a biological target and elicit analogous biological effects.¹⁵ Thus, bioisosteres have been employed to improve potency and selectivity, alter physical properties, modulate metabolism, increase permeability and adsorption and reduce the toxicity of a biologically active compound.¹⁶ However, despite the widespread use of bioisosteres to optimize these properties in drug discovery and development, this strategy remains largely unexplored in the field of PET tracer development.

The carboxylic acid is an important functional group capable of interacting with a biological target through both hydrogen bonding and electrostatic interactions. Carboxylic acids can also increase aqueous solubility and influence pharmacokinetics and are found in a wide range of drug and biologically active molecules. This has led to the development of several bioisosteres for this moiety.¹⁵⁻²⁰

N-Cyanobenzamides (Scheme 1) are an interesting, yet relatively unexplored, class of carbonyl derivatives.^{21,22} They have been employed as intermediates in the synthesis of diverse heterocyclic scaffolds and they have also found utility as carboxylic acid bioisosteres in a number of biologically active molecules.^{20,23,24} Recently, we reported the

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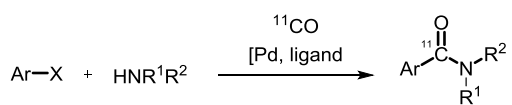
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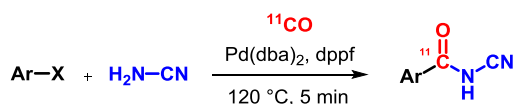
Electronic Supplementary Information (ESI) available: [Radiochromatograms and NMR spectra]. See DOI: 10.1039/x0xx00000x

carbonylative synthesis of this functional group, under palladium(0)catalysis, starting from an aryl halide, cyanamide and carbon monoxide using a bridged two compartment setup.^{25,26} Realizing that this provided an excellent starting point for the development of ¹¹C-carbonylation chemistry we sought to develop the first synthetic procedure for the preparation of ¹¹C-labelled *N*-cyanobenzamides.^{6,27} This would make a valuable addition to the radiochemistry toolbox, opening up a new area of ¹¹C-chemical space, that can be exploited in the design and synthesis of novel PET tracers. Herein, we describe a rapid, robust and high yielding method for the preparation of ¹¹C-*N*-cyanobenzamides via a palladium mediated carbonylation using an aryl halide, cyanamide and ¹¹CO (Scheme 1).

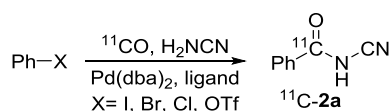
Previous work: ¹¹C-Benzamides



This work: ¹¹C-*N*-Cyanobenzamides



- ✓ Up to 79% isolated yield
- ✓ CO₂H Bioisostere
- ✓ 22 Diverse examples
- ✓ New ¹¹C-chemical space



Scheme 1. Pd-mediated synthesis of ¹¹C-*N*-cyanobenzamides and ¹¹C-benzamides

Results and discussion

Method development

We initiated our search for suitable reaction conditions using iodobenzene and cyanamide as model substrates, with bis(dibenzylidene-acetone)palladium(0) as the palladium source. THF has previously been successfully used as a solvent for ¹¹C-carbonylations,²⁸ however, the more polar DMF readily dissolved all components and was therefore chosen for further evaluation. The radiotrapping efficiency (RTE, defined here as the fraction of immobilized ¹¹CO at the end of synthesis [EOS]) was determined by removal of non-reacted ¹¹CO by flushing the crude reaction mixture with helium for 1 min.

The ligand-free carbonylation resulted in a RTE of 85% and gave conversion of trapped ¹¹CO to product (RCP) of 88% (Table 1, entry 1) as measured by radio-HPLC. We continued by evaluating the monodentate ligand triphenylphosphine, which gave the desired product in the same quantity (RTE 95%, RCP 75%, entry 2). Analysis of the crude reaction mixture suggested the presence of a side-product, which was identified as ¹¹C-benzoic acid by co-elution using analytical radio-HPLC. The bidentate ligand 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) has previously been successfully used in both ¹¹CO and CO carbonylations.^{9,29-31} In our setup complete consumption of ¹¹CO (RTE >99%) was achieved with this ligand at 120 °C and 150 °C but with lower RCP (61% and 72%, entry 3-4). Interestingly, no formation of acid was

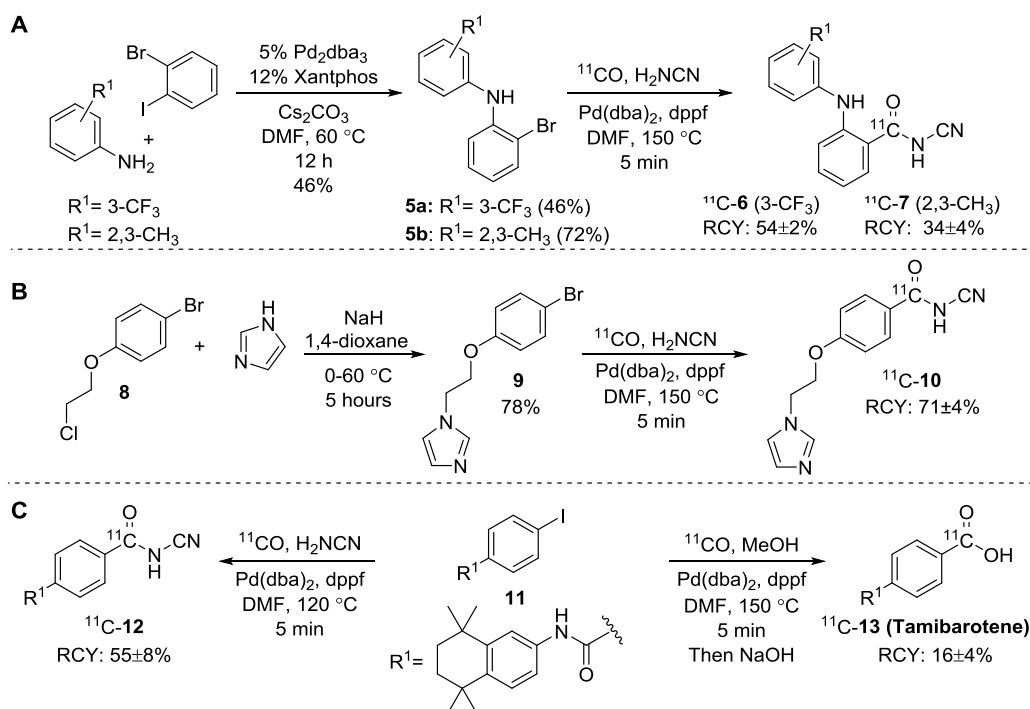
detected using this ligand. The lower RCP was due to the formation of a highly lipophilic impurity, possibly the ¹¹CO-Pd-Xantphos intermediate prior to nucleophilic attack by cyanamide.²⁹ We continued our ligand screening by using the less strained oxydi-2,1-phenylenebis(diphenylphosphine) (DPEPhos), however full trapping of ¹¹CO was not achieved in the range 90-150 °C and no improvement in RCP was observed (entry 5-7). To our delight, the bidentate ligand 1,1'-bis(diphenylphosphino)ferrocene (dppf) gave complete trapping of ¹¹CO (RTE >99%) and the desired product in high RCP (94±2%, entry 8). This may be attributed to the flexible ligand backbone, allowing it to stabilize the electronically and structurally disparate intermediates (i.e. Pd(0) and Pd(II)) formed during the reaction.³²⁻³⁴ When the temperature was increased to 150 °C, small amounts of unknown side-products were detected in the reaction mixture (entry 9). Using lower temperature gave lower RTE (84%) indicating that higher temperatures were essential for the effective conversion of iodobenzene to the corresponding ¹¹C-*N*-cyanobenzamide **11C-2a**.

Table 1. Optimization of Reaction Conditions^a

n	Ligand	Temp (°C)	RTE (%) ^b	RCP (%) ^c
1	-	120	85	88
2	PPh ₃	120	95	75
3	Xantphos	120	>99	61
4	Xantphos	150	>99	72
5	DPEPhos	90	85	88
6	DPEPhos	120	76	79
7	DPEPhos	150	82	86
8	dppf	120	>99	94±2 ^d
9	dppf	150	>99	87
10	dppf	90	84	86
11 ^e	dppf	120	84	87
12 ^e	dppf	140	96±2	93±3 ^d
13 ^e	dppf	150	93	90
14 ^f	dppf	170	63	74
15 ^g	dppf	120	89	88

^aReaction conditions: Ph-I (20 μmol), H₂NCN (400 μmol), Pd(dba)₂ (8 μmol), Ligand (monodentate 20 μmol, bidentate 10 μmol), DMF (400 μL), temp, 5 min. ^bThe fraction of immobilized ¹¹CO after purging with N₂. ^cDetermined by analytical radio-HPLC. ^dAverage of three experiments. ^ePh-Br was used. ^fPh-Cl was used. ^gPh-OTf was used.

Encouraged by the promising result obtained with iodobenzene, the best conditions (entry 8) were used for the reaction of cyanamide with bromobenzene. This gave a RTE of 84% and RCP of 87%. When the temperature was increased to 140 °C, the product was formed in a high RCP of 89±3% with almost quantitative RTE (96±2%, Table 1, entry 12). Increasing the temperature to 150 °C again resulted in an erosion of the yield due to the formation of unknown side-products (entry



Scheme 2A. Precursor synthesis and radiolabeling of $^{11}\text{C-6}$ and $^{11}\text{C-7}$, analogs of flufenamic acid and mefenamic acid, respectively; **2B.** Synthesis of $^{11}\text{C-N}$ -cyanobenzamide analog of dazoxiben $^{11}\text{C-10}$. **2C.** Radiosynthesis of $^{11}\text{C-N}$ -cyanobenzamide $^{11}\text{C-12}$ and ^{11}C -tamibarotene ($^{11}\text{C-13}$)

Finally, we synthesized compound **11** a precursor for the labelling of tamibarotene, a synthetic retinoic acid receptor agonist.^{39,40} Tamibarotene is approved in Japan for use against all-*trans*-retinoic acid refractive acute promyelocytic leukemia⁴¹ and is currently being investigated for the treatment of insulin resistance,⁴² vasculitis⁴³ intracerebral hemorrhage⁴⁴ and Alzheimer's disease.^{45,46} ^{11}C -Tamibarotene ($^{11}\text{C-13}$) was prepared from the iodo-precursor **11** via an alkoxyacylation using the conditions from Table 3 at 150 °C using methanol as the nucleophile (Scheme 2C). Subsequent hydrolysis of the methyl ester intermediate using sodium hydroxide the afforded $^{11}\text{C-13}$ in 16% RCY and a specific activity of 205 GBq/ μmol . Notably, our method gave a similar yield with a 5-fold improvement in specific activity compared to the oxidative alkoxylation procedure reported by Suzuki and co-workers (44 GBq/ μmol and RCY 26±13%).⁴⁷ Importantly, the corresponding $^{11}\text{C-N}$ -cyanobenzamide analogue was synthesized using the optimized conditions for aryl iodides yielding $^{11}\text{C-12}$ in 55±8% RCY and a specific activity of 291 GBq/ μmol after semi-preparative-HPLC. The radiochemical purity in both syntheses was in excess of 99%. Thus, both the ^{11}C -labelled parent molecule and its corresponding ^{11}C -cyanobenzamide bioisostere were efficiently prepared from a common precursor, using similar reaction conditions, further highlighting the utility of the method developed herein.

Conclusions

In conclusion, a palladium mediated ^{11}C -carbonylative methodology yielding $^{11}\text{C-N}$ -cyanobenzamides from aryl halides has been described. The substrate scope was found to be excellent and electron rich as well as electron deficient aryl iodides and bromides all performed well. The method was also extended to include the carbonylation of challenging heteroaryl bromides, phenyl triflate and even chlorobenzene. Notably, good to high isolated radiochemical yields were obtained ranging from 28-79% after semi-preparative HPLC. Moreover, the developed method was exemplified by synthesizing novel $^{11}\text{C-N}$ -cyanobenzamide analogs of the NSAID's flufenamic acid and mefenamic acid as well as dazoxiben and tamibarotene in 34-71% decay corrected RCY. This method allows rapid and robust access to new ^{11}C -chemical space and exploration of cyanobenzamide bioisosteres of the ubiquitous carboxylic acid group.

Experimental

General Chemical Information

Chemicals were purchased from commercial suppliers and were used without further purification. NMR spectra were recorded on a Varian Mercury plus spectrometer (^1H at 400 MHz and ^{13}C at 101 MHz) at ambient temperature. Chemical shifts (δ) are reported in ppm referenced to methanol, chloroform or DMSO. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with silica gel 60

F254 (0.2 mm, Merck) and visualized by UV-light (254 nm). Flash column chromatography (FCC) was performed using silica gel 60 (40–63 μm , Merck). Analytical UHPLC-MS was performed with an ion-trap mass spectrometer and UV-DAD detection using a C18 (50 \times 3 mm) column using a gradient of 10–90 (1.5 mL/min, 2 min) and MeCN (0.05% HCOOH) in H₂O (0.05% HCOOH) as the eluent.

¹¹CO₂ was created through the ¹⁴N(p,n)¹¹C nuclear reaction at the Uppsala University Hospital by a Scandtronix MX17 cyclotron and transferred to the hotlab where it was reduced over a bead of zinc (400 °C) and then used in the carbonylation reaction which was remotely controlled.⁴⁸ Semi-preparative radio-HPLC was performed using a VWR LaPrep HPLC system (P110, P311) with a Beckman Coulter™ Ultrapshere™ ODS column (10 \times 250mm) with a gradient of 10–90 % (6 mL/min, 10 min) of MeCN in H₂O. Analytical radio-HPLC was performed using a VWR LaChrom ELITE system (L-2130, L-2200, L-2400) with a Merck Chromolith Performance RP-18e column (4.6 \times 100mm) and a gradient of 10–90 (*method 1*: 4 mL/min, 10 min. *Method 2*: 4 mL/min, 5 min. *Method 3*: 4 mL/min, 7 min) MeCN in H₂O. Both HPLC-systems were buffered with 0.09% TFA (for purification of ¹¹C-6, 0.1% HCOOH was used), used 254 nm UV-detection and were equipped with a Bioscan Flow-Count PMT radioactivity detector. See supporting information for further information.

Synthesis and characterization of precursors and references

Compounds **2a–e**, **4a** and **4e** are known and were synthesized according to reference 24. Compounds **2f**, **2g**, **4b**, **4d**, **6**, **7**, **10**, **12** were synthesized in a peptide coupling reaction from the corresponding carboxylic acid. The carboxylic acid (0.5 mmol), PyBOP (260 mg, 0.5 mmol), Et₃N (436 μL , 2.5 mmol), cyanamide (32 mg, 0.75 mmol) were dissolved in 1,4-dioxane (2 mL) and the reaction was stirred for 12 hours at ambient temperature. The crude mixture was concentrated and purified by FCC (Acetone/MeOH [99:1] containing 2% Et₃N). Compounds **2h** and **4c** were synthesized from the corresponding acid chloride. The acid chloride (0.5 mmol), cyanamide (32 mg, 0.75 mmol), Et₃N (174 μL , 1 mmol) were dissolved in 1,4-dioxane (2 mL) and stirred at 50 °C for 12 hours. The mixture was concentrated and purified by FCC (Acetone/MeOH [99:1] containing 2% Et₃N). This yielded 40–70% of the corresponding *N*-acyl cyanamides as the Et₃N-salt.

***N*-Cyano-4-formylbenzamide (2f)**. ¹H NMR (400 MHz, MeOD) δ 10.04 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 8.3 Hz, 2H), 3.22 (q, *J* = 7.3 Hz, 6H), 1.31 (t, *J* = 7.3 Hz, 9H). ¹³C NMR (100 MHz, MeOD) δ 193.8, 178.2, 143.6, 139.6, 130.2, 130.1, 122.6, 47.9, 9.2. HRMS calcd for C₉H₆N₂O₂ [M+H]⁺ *m/z* 175.0508, found *m/z* 175.0509.

***N*-Cyano-3-methoxybenzamide (2g)**. ¹H NMR (400 MHz, MeOD) δ 7.55–7.52 (m, 2H), 7.30–7.26 (m, 1H), 7.04–7.01 (m, 1H), 3.81 (s, 3H), 3.20 (q, *J* = 7.3 Hz, 6H), 1.30 (t, *J* = 7.3, 9H). ¹³C NMR (100 MHz, MeOD) δ 178.8, 160.9, 139.0, 130.0, 121.9, 118.4, 114.4, 55.7, 47.9, 9.2. HRMS calcd for C₁₀H₆N₂O₂ [M+H]⁺ *m/z* 177.0664, found *m/z* 177.0660.

***N*-Cyano-2-(trifluoromethyl)benzamide (2h)**. ¹H NMR (400 MHz, MeOD) δ 7.71–7.68 (m, 1H), 7.64–7.52 (m, 3H), 3.21 (q, *J*

= 7.3 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 9H). ¹³C NMR (100 MHz, MeOD) δ 179.1, 138.6 (d, *J* = 2.3 Hz), 131.6 (q, *J*_{C-F} = 1.1 Hz), 128.8, 128.2, 126.5 (q, *J*_{C-F} = 31.8 Hz), 125.8 (q, *J* = 5.1 Hz), 124.0 (q, *J* = 272.9 Hz), 119.4, 46.5, 7.8. HRMS calcd for C₉H₅F₃N₂O [M+H]⁺ *m/z* 215.0432, found *m/z* 215.0429.

***N*-Cyanobenzofuran-2-carboxamide (4b)**. ¹H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.43–7.36 (m, 2H), 7.29–7.24 (m, 1H), 3.20 (q, *J* = 7.3 Hz, 6H), 1.29 (t, *J* = 7.3 Hz, 9H). ¹³C NMR δ 170.8, 156.6, 153.1, 129.1, 127.6, 124.5, 123.4, 121.3, 112.7, 111.2, 47.9, 9.2. HRMS calcd for C₁₀H₆N₂O₂ [M+H]⁺ *m/z* 187.0508, found *m/z* 187.0509.

***N*-Cyanothiophene-2-carboxamide (4c)**. ¹H NMR (400 MHz, MeOD) δ 7.64–7.61 (m, 1H), 7.53–7.50 (m, 1H), 7.15–6.91 (m, 1H), 3.20 (q, *J* = 7.3 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 9H). ¹³C NMR (100 MHz, MeOD) δ 173.9, 142.9, 131.4, 131.3, 128.5, 121.8, 47.9, 9.2. HRMS calcd for C₆H₄N₂OS [M+H]⁺ *m/z* 153.0123, found *m/z* 153.0129.

***N*-Cyanonicotinamide (4e)**. ¹H NMR (400 MHz, MeOD) δ 9.14–9.07 (m, 1H), 8.62 (dd, *J* = 5.1, 1.7 Hz, 1H), 8.41 (ddd, *J* = 8.0, 2.2, 1.7 Hz, 1H), 7.51 (ddd, *J* = 8.0, 5.1, 0.9 Hz, 1H), 3.22 (q, *J* = 7.3 Hz, 6H), 1.32 (t, *J* = 7.3 Hz, 9H). ¹³C NMR (100 MHz, MeOD) δ 176.5, 151.4, 149.9, 138.6, 134.5, 124.9, 122.1, 47.9, 9.2. HRMS calcd for C₇H₅N₃O [M+H]⁺ *m/z* 148.0511, found *m/z* 148.0514.

2-Bromo-*N*-(3-(trifluoromethyl)phenyl)aniline (5a). 3-(trifluoromethyl)aniline (80 mg, 0.5 mmol), 1-bromo-2-iodobenzene (141 mg, 0.5 mmol), tris(dibenzylideneacetone)dipalladium(0) (23 mg, 5 mol%), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (35 mg, 12 mol%), cesium carbonate (488 mg, 1.5 mmol) was added to DMF (5 mL), capped and stirred at 60 °C for 12 hours. After cooling, the mixture was filtered, concentrated and purified by FCC (pentane:EtOAc [7:1] yielding 73 mg (46%) of **5**. ¹H NMR δ 7.61 (ddd, *J* = 8.0, 1.3, 0.5 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.32–7.24 (m, 2H), 7.24–7.18 (m, 2H), 7.14–7.10 (m, 1H), 6.93 (ddd, *J* = 8.0, 6.4, 2.5 Hz, 1H). ¹³C NMR δ 146.0, 142.0, 134.6, 132.6 (q, *J*_{C-F} = 31.8 Hz), 131.0, 129.4, 125.7 (d, *J*_{C-F} = 271.4 Hz), 124.9, 122.1, 121.4, 117.6 (q, *J*_{C-F} = 4.0 Hz), 117.1, 114.5 (q, *J*_{C-F} = 4.0 Hz). HRMS calcd for C₁₃H₉NBrF₃ [M+H]⁺ *m/z* 315.9949, found *m/z* 315.9944.

***N*-(2-bromophenyl)-2,3-dimethylaniline (5b)**. Synthesized as per **5a** from 2,3-dimethylaniline. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.41 (s, 1H), 7.28–7.21 (m, 3H), 7.17–7.15 (m, 1H), 6.87 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.81 (ddd, *J* = 8.0, 7.2, 1.5 Hz, 1H), 2.49 (s, 3H), 2.32 (s, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 143.04, 139.38, 138.24, 132.68, 131.25, 128.15, 126.39, 126.12, 121.72, 119.56, 110.82, 20.67, 13.89. HRMS: *m/z* = 276.0395 [M + H]⁺, calculated for C₁₄H₁₅NBr: 276.0388

***N*-Cyano-2-((3-(trifluoromethyl)phenyl)amino)benzamide (6)**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.01 (d, *J* = 7.9 Hz, 1H), 7.48–7.37 (m, 3H), 7.29 (d, *J* = 3.1 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.86–6.77 (m, 1H), 3.18 (q, *J* = 7.3 Hz, 6H), 1.28 (t, *J* = 7.3 Hz, 9H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 180.6, 145.6, 144.6, 132.9, 132.7, 132.6 (q, ²*J*_{CF} = 32.0 Hz), 131.2, 125.6 (q, ¹*J*_{CF} = 271.4 Hz), 123.5 (q, ⁴*J*_{CF} = 1.5 Hz), 123.0, 122.4, 119.8, 118.6 (q,

$^3J_{CF} = 4.0$ Hz), 116.24 (d, $^3J_{CF} = 4.0$ Hz), 116.18, 47.9, 9.2. HRMS calcd for $C_{15}H_{10}F_3N_3O$ $[M+H]^+$ m/z 306.0854, found m/z 306.0859.

***N*-Cyano-2-((2,3-dimethylphenyl)amino)benzamide (7).** 1H NMR (400 MHz, DMSO- d_6) δ 8.01 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.49 – 7.35 (m, 3H), 7.28 – 7.18 (m, 2H), 6.26 (dd, $J = 8.4, 0.9$ Hz, 1H), 2.36 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 167.2, 155.2, 141.4, 139.6, 135.3, 133.8, 133.0, 131.6, 127.9, 126.9, 126.6, 123.3, 117.9, 114.6, 20.0, 13.3. HRMS calcd for $C_{16}H_{16}N_3O$ $[M+H]^+$, 266.1293, found 266.1301.

1-(2-(4-Bromophenoxy)ethyl)-1*H*-imidazole (9). 1H NMR (400 MHz, MeOD) δ 7.71 (t, $J = 1.1$ Hz, 1H), 7.41–7.33 (m, 2H), 7.21 (t, $J = 1.3$ Hz, 1H), 6.97 (t, $J = 1.2$ Hz, 1H), 6.86–6.81 (m, 2H), 4.40 (dd, $J = 5.5, 4.5$ Hz, 2H), 4.23 (dd, $J = 5.5, 4.5$ Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 159.0, 138.9, 133.4, 129.0, 121.0, 117.6, 114.3, 68.8, 47.5. ESI-HRMS calcd for $C_{11}H_{12}BrN_2O$ $[M+H]^+$ m/z 267.0133, found m/z 267.0133.

4-(2-(1*H*-Imidazol-1-yl)ethoxy)-*N*-cyanobenzamide (10). 1H NMR (400 MHz, MeOD) δ 7.91 (d, $J = 9.0$ Hz, 2H), 7.77 (s, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 6.89 (d, $J = 9.0$ Hz, 1H), 4.47 – 4.39 (m, 2H), 4.34 – 4.27 (m, 2H), 3.20 (q, $J = 7.3$ Hz, 6H), 1.30 (t, $J = 7.3$ Hz, 12H). ^{13}C NMR (101 MHz, MeOD) δ 179.4, 162.3, 138.8, 131.6, 131.1, 128.7, 123.3, 121.2, 114.7, 68.5, 47.9, 29.9, 9.3. ESI-HRMS calcd for $C_{13}H_{13}N_4O_2$ $[M+H]^+$ m/z 257.1039, found m/z 257.1037.

4-Iodo-*N*-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide (11). The compound was synthesized according to reference 49 using 4-iodobenzoic acid. 1H NMR (400 MHz, DMSO) δ 10.12 (s, 1H), 7.91 (d, $J = 8.2$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz, 2H), 7.65 (d, $J = 1.8$ Hz, 2H), 7.55 (d, $J = 8.7$ Hz, 1H), 7.27 (d, $J = 8.6$ Hz, 1H), 1.64 (s, 4H), 1.23 (d, $J = 4.7$ Hz, 12H). ^{13}C NMR (101 MHz, DMSO) δ 164.5, 144.5, 140.0, 137.2, 136.4, 134.4, 129.5, 126.4, 118.3, 118.1, 99.1, 34.6, 34.6, 34.0, 33.6, 31.6, 31.6. ESI-HRMS calcd for $C_{21}H_{25}INO$ $[M+H]^+$ m/z 434.0981, found m/z 434.0982.

***N*1-Cyano-*N*4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)terephthalamide (12).** 1H NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 8.09 (d, $J = 8.6$ Hz, 2H), 8.03 (d, $J = 8.6$ Hz, 2H), 7.73 – 7.64 (m, 1H), 7.64 – 7.53 (m, 1H), 7.29 (d, $J = 8.6$ Hz, 1H), 1.65 (s, 6H), 1.24 (d, $J = 5.2$ Hz, 12H). ^{13}C NMR (101 MHz, DMSO) δ 167.0, 164.2, 144.6, 140.2, 139.2, 136.3, 134.1, 128.3, 128.0, 126.5, 118.3, 118.1, 109.6, 34.6, 34.6, 34.0, 33.6, 31.7, 31.6. ESI-HRMS calcd for $C_{23}H_{26}N_3O_2$ $[M+H]^+$ m/z 376.2025, found m/z 376.2037.

4-((5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl)benzoic acid (13). 1H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.13 – 7.93 (m, 4H), 7.67 (s, 1H), 7.58 (d, $J = 10.9$ Hz, 1H), 7.29 (d, $J = 8.6$ Hz, 1H), 1.64 (s, 4H), 1.24 (d, $J = 5.0$ Hz, 12H). ^{13}C NMR (101 MHz, DMSO) δ 167.2, 165.0, 145.0, 140.5, 139.2, 136.8, 133.8, 129.7, 128.2, 126.9, 118.8, 118.6, 35.0, 34.4, 34.0, 32.1, 32.1. ESI-HRMS calcd for $C_{22}H_{26}NO_3$ $[M+H]^+$ m/z 352.1913, found m/z 352.1913.

Radiochemistry

The aryl halide (20 μ mol) and cyanamide (16.8 mg, 400 μ mol) were added to an oven dried 2 mL vial, capped and flushed for 2 min with argon. To a second oven dried 2 mL vial was added

bis(dibenzylideneacetone)-palladium(0) (2.3 mg, 8 μ mol) and 1,1'-bis(diphenyl-phosphino)ferrocene (4.8 mg, 10 μ mol) which was then capped and flushed with argon for 2 min before dry DMF (400 μ L) was added. After a second flush with argon (2 min) the DMF/Pd(dba) $_2$ /dppf solution was heated at 90 °C for 1 min, creating a homogenous solution. The mixture was added to the first vial and subsequently added to the injection loop (200 μ L capacity) of the ^{11}C -carbon monoxide system.⁴⁷ After the reaction was finished, the radioactivity was measured. After flushing with nitrogen for 1 min, the activity was measured again yielding the RTE. An aliquot was taken for the determination of RCP. The crude mixture was diluted with 50% aqueous MeCN (total volume 500 μ L) and purified by semi-preparative radio-HPLC. After collecting the product, RCP was determined for the pure product. The identity was determined by co-elution of the corresponding non-isotopically labeled *N*-cyanobenzamide. For the molar activity of ^{11}C -**12** and ^{11}C -**13**, a calibration curve with five points using the corresponding reference. The total mass and the concentration of the purified product was then determined. The amount of activity was calculated back to the end of synthesis to get comparable data, expressed in GBq/ μ mol. The molar activity was determined to be 291 GBq/ μ mol for ^{11}C -**12** and 205 GBq/ μ mol for ^{11}C -**13**.

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Notes and references

- S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501-1516.
- M. Bergström, A. Grahnen, B. Långström, *Eur. J. Clin. Pharmacol.* **2003**, *59*, 357-366.
- J. M. Miller, D. Kumar, J. J. Mann, R. V. Parsey, *Curr. Radiopharm.* **2008**, *1*, 12-16.
- P. M. Matthews, E. A. Rabiner, J. Passchier, R. N. Gunn, *Brit. J. Clin. Pharmacol.* **2012**, *73*, 175-186.
- C. M. Lee, L. Farde, *Trends Pharmacol. Sci.* **2006**, *27*, 310-316.
- B. Långström, O. Itsenko, O. Rahman, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 794-810.
- P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem., Int. Ed.* **2008**, *47*, 8998-9033.
- B. H. Rotstein, S. H. Liang, M. S. Placzek, J. M. Hooker, A. D. Gee, F. Dollé, A. A. Wilson, N. Vasdev, *Chem. Soc. Rev.*, **2016**, *45*, 4708-4726.
- F. Karimi, B. Långström, *Eur. J. Org. Chem.* **2003**, *11*, 2132-2137.
- K. Dahl, M. Schou, N. Amini, C. Halldin, *Eur. J. Org. Chem.* **2013**, *7*, 1228-1231.
- O. Rahman, *J. Labelled Compd. Radiopharm.* **2015**, *58*, 86-98.
- T. L. Andersen, S. D. Friis, H. Audrain, P. Nordeman, G. Antoni, T. Skrydstруп, *J. Am. Chem. Soc.* **2015**, *137*, 1548-1555.
- S. Kealey, A. D. Gee, P. W. Miller, *J. Labelled Compd. Radiopharm.* **2014**, *57*, 195-201.
- H. L. Friedman, *NASNRS* **1951**, *206*, 295-358.
- N. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529-2591.

- 16 C. Ballatore, D. M. Huryn, A. B. Smith III, *ChemMedChem* **2013**, *8*, 385-95.
- 17 T. S. Elliott, A. Slowey, Y. Ye, S. J. Conway, *MedChemComm* **2012**, *3*, 735-751.
- 18 P. Lassalas, B. Gay, C. Lasfargeas, M. J. James, V. Tran, K. G. Vijayendran, K. G. Brunden, M. C. Kozlowski, C. J. Thomas, A. B. Smith III, D. M. Huryn, C. Ballatore, *J. Med. Chem.* **2016**, *59*, 3183-3203.
- 19 F. Allen, C. Groom, J. Liebeschuetz, D. Bardwell, T. Olsson, P. Wood, *J. Chem. Inf. Model.* **2012**, *52*, 857-866.
- 20 R. Rönn, T. Gossas, Y. A. Sabnis, H. Daoud, E. Åkerblom, U. H. Danielson, A. Sandström, *Bioorg. Med. Chem.* **2007**, *15*, 4057-4068.
- 21 J. C. J. Howard, *Org. Chem.* **1964**, *29*, 761-762.
- 22 W. Mock, X. Xu, *Bioorg. Chem.* **1994**, *22*, 373-386.
- 23 S. Kleeb, L. Pang, K. Mayer, D. Eris, A. Sigl, R. C. Preston, P. Zihlmann, T. Sharpe, R. P. Jakob, D. Abgottspon, A. S. Hutter, M. Scharenberg, X. Jiang, G. Navarra, S. Rabbani, M. Smiesko, N. Lüdin, J. Bezençon, O. Schwardt, T. Maier, B. Ernst, *J. Med. Chem.* **2015**, *8*, 2221-2239.
- 24 T. Tomoo, T. Nakatsuka, T. Katayama, Y. Hayashi, Y. Fujieda, M. Terakawa, K. Nagahira, *J. Med. Chem.* **2014**, *57*, 7244-7262.
- 25 R. S. Mane, P. Nordeman, L. R. Odell, M. Larhed, *Tetrahedron Lett.* **2013**, *54*, 6912-6915.
- 26 P. Nordeman, L. R. Odell, M. Larhed, *J. Org. Chem.* **2012**, *77*, 11393-11398.
- 27 K. Serdons, A. Verbruggen, G. M. Bormans, *Methods* **2009**, *48*, 104-111.
- 28 O. Åberg, M. Stevens, J. Lindh, C. Wallinder, H. Hall, A. Monazzam, M. Larhed, B. Långström, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 616-624.
- 29 J. Martinelli, D. Watson, D. Freckmann, T. Barder, S. Buchwald, *J. Org. Chem.* **2008**, *73*, 7102-7107.
- 30 A. Więckowska, R. Fransson, L. R. Odell, M. Larhed, *J. Org. Chem.* **2011**, *76*, 978-981.
- 31 P. W. Miller, L. E. Jennings, A. J. deMello, A. D. Gee, N. J. Long, R. Vilar, *Adv. Synth. Catal.* **2009**, *351*, 3260-3268.
- 32 Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6232-6235.
- 33 B. Roberts, D. Liptrot, L. Alcaraz, *Org. Lett.* **2010**, *12*, 1264-1267.
- 34 D. Young, S. Chien, T. Hor, *Dalton Trans.* **2012**, *41*, 12655-12665.
- 35 R. Guinamard, C. Simard, C. Del Negro, *Pharmacol. Ther.* **2013**, *138*, 272-284.
- 36 J. J. Prusakiewicz, K. C. Duggan, C. A. Rouzer, L. J. Marnett, *Biochemistry* **2009**, *48*, 7353-7355.
- 37 Y. Chi, K. Li, Q. Yan, S. Koizumi, L. Shi, S. Takahashi, Y. Zhu, H. Matsue, M. Takeda, M. Mitamura, *Pharmacol. Exp. Ther.* **2011**, *339*, 257-266.
- 38 Y. Guari, D. S. van Es, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron Lett.* **1999**, *40*, 3789-3790.
- 39 H. Kagechika, E. Kawachi, Y. Hashimoto, K. Shudo, T. Himi, *J. Med. Chem.* **1988**, *31*, 2182-2192.
- 40 C. Yuan, Y. S. Zhang, Y. N. Cheng, X. Xue, W. F. Xu, X. J. Qu, *Leuk. Lymphoma* **2012**, *53*, 295-304.
- 41 T. Tobita, A. Takeshita, K. Kitamura, K. Ohnishi, M. Yanagi, A. Hiraoka, T. Karasuno, M. Takeuchi, S. Miyawaki, R. Reda, *Blood* **1997**, *90*, 967-973.
- 42 O. Yoshikawa, Y. Ebata, H. Tsuchiya, A. Kawahara, C. Kojima, Y. Ikeda, S. Hama, K. Kogure, K. Shudo, G. Shiota, *Obesity* **2013**, *21*, E22-E25.
- 43 C. Miyabe, Y. Miyabe, N. N. Miura, K. Takahashi, Y. Terashima, E. Toda, F. Honda, T. Morio, N. Yamagata, N. Ohno, *Arthritis Rheum.* **2013**, *65*, 503-512.
- 44 H. Matsushita, M. Hijioka, A. Hisatsune, Y. Isohama, K. Shudo, H. Katsuki, *Blood F. Metab.* **2011**, *31*, 222-234.
- 45 D. Holthoewer, K. Endres, F. Schuck, C. Hiemke, U. Schmitt, F. Fahrenholz, *Neurodegener. Dis.* **2011**, *10*, 224-228.
- 46 H. Fukasawa, M. Nakagomi, N. Yamagata, H. Katsuki, K. Kawahara, K. Kitaoka, T. Miki, K. Shudo, *Biol. Pharm. Bull.* **2012**, *35*, 206-1212.
- 47 M. Takashima-Hirano, H. Ishii, M. Suzuki, *ACS Med. Chem. Lett.* **2012**, *3*, 804-807.
- 48 T. Kihlberg, B. Långström, Method and Apparatus for Production and use of [¹³C]carbon monoxide in Labelling Synthesis., PCT/SE02/01222, **2002**.
- 49 S. D. Friis, T. L. Andersen, T. Skrydstrup, *Org. Lett.*, **2013**, *15*, 1378-1381.