Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 1192–1199.
Published online 10 September 2007 in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1437

JLCR

Research Article

Synthesis of *N*-(2,5-dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)[*carbonyl*-^{11}C]acetamide ([*carbonyl*-^{11}C]DAA1106) and analogues using [^{11}C]carbon monoxide and palladium(0) complex

OBAIDUR RAHMAN[1] and BENGT LÅNGSTRÖM[1,2,*]

[1]Department of Biochemistry and Organic Chemistry, Box 576, Husargatan 3, BMC, S-751 23 Uppsala, Sweden
[2]Uppsala Imanet AB, Box 967, S-751 09 Uppsala, Sweden

Received 7 May 2007; Revised 14 June 2007; Accepted 5 July 2007

Abstract: *N*-(2,5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106), a potent and selective ligand for peripheral benzodiazepine receptor, and eight structurally related analogues were labelled with ^{11}C at the carbonyl position using a low concentration of [^{11}C]carbon monoxide and the micro-autoclave technique. A combinatorial approach was applied to synthesize the analogues using similar reaction conditions. Palladium-mediated carbonylation using *tetrakis*(triphenylphosphine)palladium, various amines and methyl iodide or iodobenzene was employed in the synthesis. The ^{11}C-labelled products were obtained with 10–55% decay-corrected radiochemical yields and the final product was more than 97% pure in all cases. Specific radioactivity was determined for the compound [*carbonyl*-^{11}C]DAA1106 using a single experiment and a 10-μA h bombardment. The specific radioactivity, measured 36 min after end of bombardment, was 455 GBq/μmol. Synthetic routes to the precursors and reference compounds were also developed. The presented approach is a novel method for the synthesis of [*carbonyl*-^{11}C]DAA1106 and its analogues, and allows the formation of a library of ^{11}C-labelled DAA1106 analogues which can be used to optimize the performance as a potential positron emission tomography tracer. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: [^{11}C]carbon monoxide; [^{11}C]DAA1106; palladium(0); micro-autoclave

Introduction

Positron emission tomography (PET) is a non-invasive imaging technique that may play an important role in the discovery of new drugs. The micro-dosing concept of PET can be a useful strategy for speeding up tracer development as well as being a tool in drug development.[1]

Investigations using PET require compounds labelled with short-lived, positron-emitting radionuclides. ^{11}C is very important from the synthetic point of view because a wide range of compounds can be labelled with this isotope without changing their biological properties. The demand for new methods of synthesizing labelled molecules is increasing in medical and biomedical research, as well as in various clinical applications. Although the most commonly used methods for the synthesis of ^{11}C-labelled compounds are *S*-, *O*- and *N*-methylations using [^{11}C]methyl iodide or [^{11}C]methyl triflate,[2] carbonylation using [^{11}C]carbon monoxide at low concentration has become of interest. Palladium-mediated carbonylation using [^{11}C]carbon monoxide, organohalides or triflates and different nucleophiles has been employed in the synthesis of ^{11}C-labelled carbonyl compounds such as ketones,[3–5] amides,[6–8] imides,[9] hydrazides,[10] etc. Photo-initiated[11–13] and rhodium-mediated[14,15] reactions have also been explored for carbonylation reactions using low concentrations of [^{11}C]carbon monoxide. The synthesis of ^{11}C-labelled amines based on [^{11}C]carbon monoxide, i.e. carbonylation followed by reductive amination, has recently been published.[16]

*Correspondence to: Bengt Långström, Department of Biochemistry and Organic Chemistry, Box 576, Husargatan 3, BMC, S-751 23 Uppsala, Sweden. E-mail: bengt.langstrom@biorg.uu.se, bengt.langstrom@ge.com
Contract/grant sponsor: Uppsala Imanet
Contract/grant sponsor: GE Healthcare

The compound DAA1106 has been shown to be a potent and selective ligand for peripheral benzodiazepine receptor (PBR).[17] PBR is an 18-kDa protein found in the outer mitochondrial membrane of almost all tissues, and is abundant in steroid-producing cells.[18,19] This receptor is also found on glial cells of central and peripheral nervous systems, and its density increases with the inflammatory reaction of the nervous tissue.[20] Although the exact function of PBR is not yet established, a number of functions such as regulation of steroid production, regulation of mitochondrial membrane potential, modulation of voltage-dependent calcium channels, cancer cell proliferation and microglial activation related to brain damage have been suggested.[21] The selective PBR ligands can therefore be potential candidates for diagnosis and treatment of various neurodegenerative and cardiovascular diseases, and a considerable effort has been invested to develop novel ligands for PBR. A number of PBR ligands such as PK11195, Ro5-4864, FGIN-1-27, SSR180575, DAA1106, DAA1097, etc. (Figure 1) have been developed, and three of them (Ro5-4864,[22] PK11195[23] and DAA1106[24]) have been labelled with ^{11}C and applied in PET studies. Methylation using [^{11}C]methyl iodide was employed in the ^{11}C-labelling of those compounds. Moreover, we have developed a carbonylation method for ^{11}C-labelling of PK11195, and that method provided the opportunity to synthesize a number of ^{11}C-labelled analogues of this compound.[25] This paper describes a carbonylation strategy for ^{11}C-labelling of DAA1106, and the preparation of a library of its analogues with the intention of exploring more details in the search for improved PET tracers to study the function of PBR in various diseases.

Results and discussion

Palladium-mediated carbonylation using *tetrakis*(triphenylphosphine)palladium(0), various amines, low concentrations of [^{11}C]carbon monoxide and methyl or phenyl iodide was employed to synthesize ^{11}C-labelled DAA1106 and analogues (Scheme 1). By using this method, DAA1106 and eight structurally related analogues (***2a–*2i** in Figure 2) were labelled with ^{11}C. The reaction was performed in a 200-μL micro-autoclave. The conversion of [^{11}C]carbon monoxide to crude products (i.e. the trapping efficiency) was >95% in all cases, and the decay-corrected radiochemical yields of liquid chromatography (LC)-purified products, calculated from [^{11}C]carbon monoxide, were 10–55% (Table 1). The radiochemical purity was over 97% for all compounds. The specific radioactivity of compound ***2a** was 455 GBq/μmol when measured 36 min after the end of a 10 μA h bombardment.

In initial experiments, the reaction was performed with non-activated amines, i.e. amines without any additional base, and the reaction worked poorly. The radiochemical yield was only 5%. Amine activation has

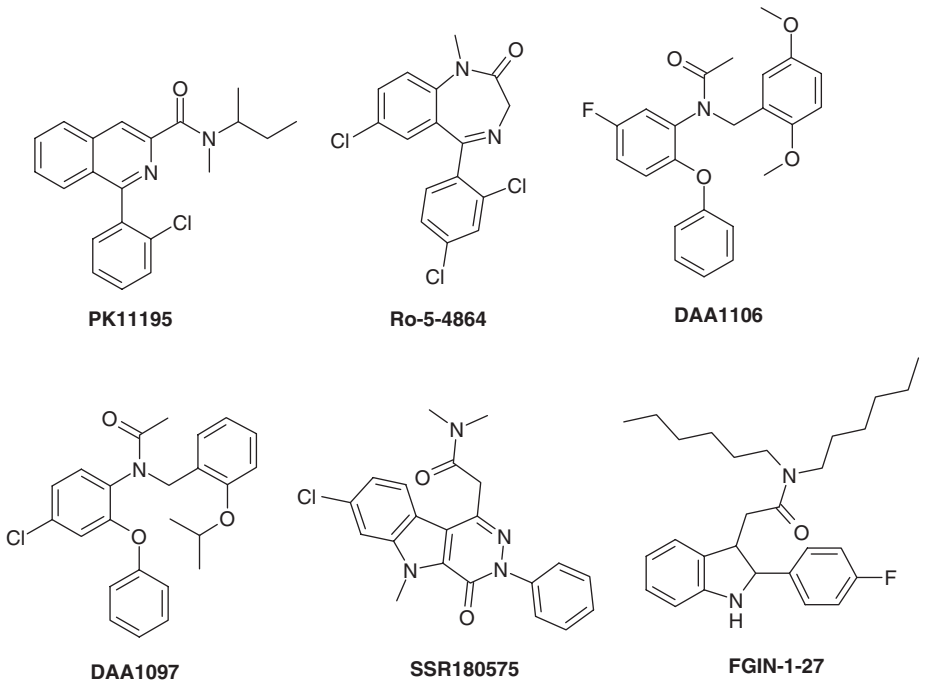
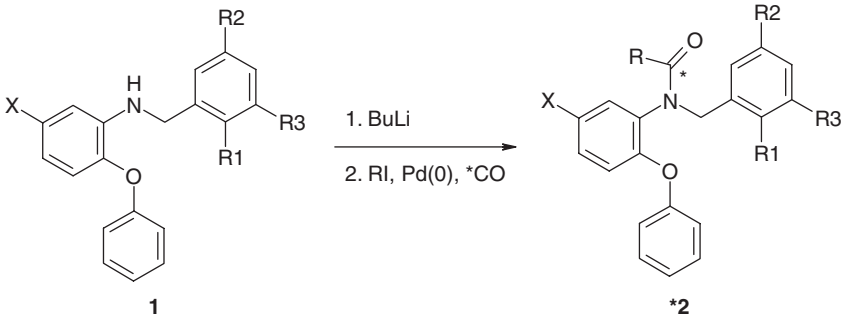


Figure 1 Some selective PBR ligands.

DOI: 10.1002.jlcr



Scheme 1

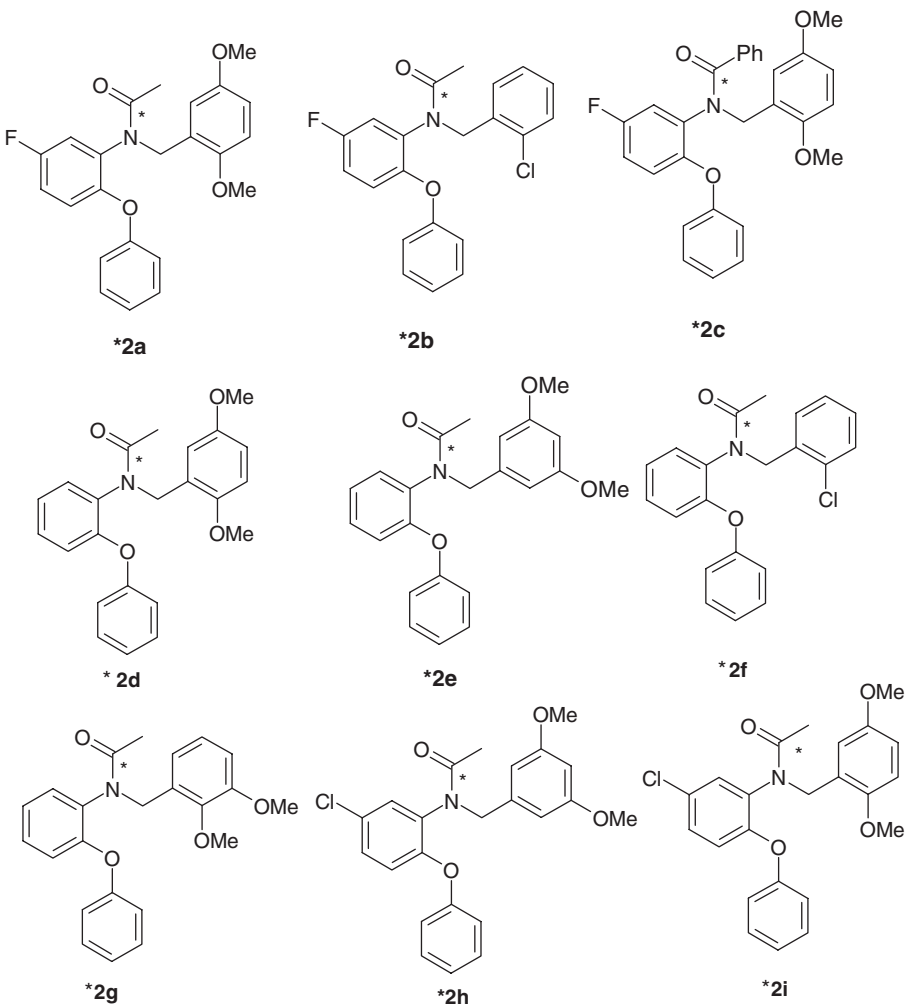


Figure 2 Target ^{11}C-labelled molecules, * = ^{11}C-labelled.

previously been used to improve the radiochemical yields of ^{11}C-labelled amides from carbonylation reactions using [^{11}C]carbon monoxide.[26] Therefore, the effect of bases such as pyridine, triethylamine, potassium *tert*-butoxide and *n*-butyllithium (^{n}BuLi) was explored, and ^{n}BuLi was found to best improve the radiochemical yields.

The precursors for the DAA1106 analogues were prepared by *N*-alkylation of three different 2-phenoxy anilines (**3**) with benzyl halides (**4**). The reaction was performed in the presence of $CsOH \cdot H_2O$ and molecular sieves (MS) in dry *N*,*N*-dimethylformamide (DMF) (Scheme 2).[27] The yields for the precursors varied from 40 to 90% (Table 2). In cases of compounds **1e** and **1h**,

DOI: 10.1002.jlcr

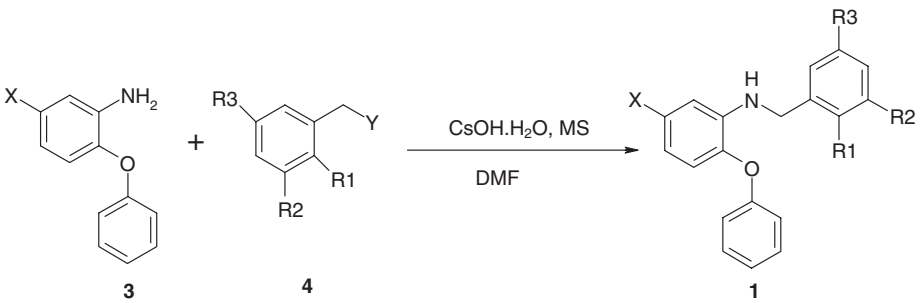
the yields were a little lower at 45 and 40%, respectively. In these cases, benzyl chlorides were used as substrates, rather than benzyl bromides. Only one (**1a**)[28] of the eight prepared amines (**1a–1i**) had been described previously.

The compound 5-fluoro-2-phenoxyaniline (**3**) used in the *N*-alkylation reaction was prepared by the reduction of 4-fluoro-2-nitro-1-phenoxybenzene. The reduction was carried out using hydrazine hydrate in the presence of ferric chloride and activated carbon,[29] giving a yield of 96%. 4-Fluoro-2-nitro-1-phenoxybenzene was prepared as described previously.[28] The two benzyl bromides (**4a** and **4f**) used in the *N*-alkylation reactions were prepared from the corresponding benzyl alcohols by treating with carbon tetrabromide and triphenyl phosphine in dry dichloromethane.[30] The reaction was carried out at ambient temperature for 30 min, and the yield was over 80%. All other benzyl halides used were commercially available. Two reference compounds (**2a** and **2i**) of the labelled target molecules ***2a** and ***2i** were prepared by treating the corresponding amines with acetyl chloride in the presence of pyridine.[31] The yield was over 90% in both cases. The reference compounds for other labelled molecules (***2b–*2h**) were not synthesized, instead those compounds were characterized by liquid chromatography–mass spectrometry (LC–MS). The specific radioactivity was determined only for compound ***2a**.

Table 1 Trapping efficiencies and radiochemical yields for the ^{11}C-labelled DAA1106 and its analogues shown in Figure 2

Product	TE[a] (%)	RCY[b] (% (*n*)[c])	*m*/*z* (*M* + 1)/g/mol[d])
***2a**	95	40 (30)	396.15
***2b**	95	41	370.09
***2c**	96	70 (55)	458.26
***2d**	98	28 (20)	378.16
***2e**	95	40	378.16
***2f**	95	15 (10)	384.09
***2g**	96	41 (30)	378.16
***2h**	95	40 (29)	412.12
***2i**	94	47 (38)	412.12

*on the numbers in column 1 indicates ^{11}C-labelled molecules.
[a]TE =trapping efficiency, decay-corrected; the fraction of radioactivity left in the crude product after a nitrogen purge.
[b]RCY =radiochemical yield; decay-corrected and determined by analytical LC based on radioactivity in the crude product before nitrogen purging and on the purity of crude product. The value is the mean from at least three experiments.
[c]Values in parenthesis are the isolated yields.
[d]Determined by LC–MS[ESI+].



X = F, R1 = R3 = OMe, R2 = H (**1a**); X = F, R1 = Cl, R2 = R3 = H (**1b**); X = H, R1 = R3 = OMe, R2 = H (**1d**); X = H, R1 = H, R2 = R3 = OMe (**1e**); X = H, R1 = Cl, R2 = R3 = H (**1f**); X = H, R1 = R2 = OMe, R3 = H (**1g**); X = Cl, R1 = H, R2 = R3 = OMe (**1h**); X = Cl, R1 = R3 = OMe, R2 = H (**1i**); Y = Br, Cl.

Scheme 2

Table 2 Yields of the precursor amines (**1a–1h**)

Benzyl halides	Phenoxy anilines	Target amine	Yield (%)	M.p. (°C)
2-(Bromomethyl)-1,4-dimethoxybenzene	5-Fluoro-2-phenoxyaniline	**1a**	71	71
1-(Bromomethyl)-2-chlorobenzene	5-Fluoro-2-phenoxyaniline	**1b**	75	Brown oil
2-(Bromomethyl)-1,4-dimethoxybenzene	2-Phenoxyaniline	**1d**	70	55
1-(Chloromethyl)-3,5-dimethoxybenzene	2-Phenoxyaniline	**1e**	45	59
1-(Bromomethyl)-2-chlorobenzene	2-Phenoxyaniline	**1f**	93	Brown oil
1-(Bromomethyl)-2,3-dimethoxybenzene	2-Phenoxyaniline	**1g**	65	78
1-(Chloromethyl)-3,5-dimethoxybenzene	5-Chloro-2-phenoxyaniline	**1h**	40	76
2-(Bromomethyl)-1,4-dimethoxybenzene	5-Chloro-2-phenoxyaniline	**1i**	73	55

DOI: 10.1002.jlcr

Experimental

General

All chemicals and reagents were purchased from Aldrich or Lancaster. Freshly distilled THF (distilled from sodium/benzophenone under nitrogen) was used in the labelling reactions.

[^{11}C]Carbon dioxide was produced by the Scanditronix MC-17 cyclotron at Uppsala Imanet AB using the $^{14}N(p,\alpha)^{11}C$ reaction with 17-MeV protons in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.05% oxygen (AGA, Oxygen 4.8). [^{11}C]Carbon monoxide was produced by the reduction of [^{11}C]carbon dioxide in a zinc furnace at 400°C using a remote-controlled work station.[32]

Liquid chromatographic (LC) analysis was performed with a Beckman 126 gradient pump and a Beckman 166 variable-wavelength UV detector in series with a Bioscan β^+-flow detector. The following mobile phases were used: 0.05 M ammonium formate, pH 3.5 (A1); acetonitrile/H_2O: 50/7 (B) and 0.01 M formic acid in H_2O (A2). For analytical LC, a Jones Chromatography Genesis C_{18}, 4-μm, 250 × 4.6 mm (i.d.) column was used with a flow of 1.5 mL/min. For semi-preparative LC, a Jones Chromatography Genesis C_{18}, 4-μm, 250 × 10 mm (i.d.), column was used with a flow of 5 mL/min. Synthia,[33] an automated synthesis system, was used for LC injection and fraction collection. Data collection and LC control were performed using a Beckman System Gold chromatography software package. Radioactivity of products was measured in an ion chamber, Veenstra Instrumenten bv, VDC-202. For coarse estimations of radioactivity during the production, a portable dose-rate meter Långenäs Eltekniska AB, was used.

Non-radioactive compounds were characterized by ^{1}H and ^{13}C NMR spectroscopies and by gas chromatography–mass spectrometry (GC–MS). NMR spectra were recorded on a Varian Unity-400 NMR spectrometer. Chloroform-*d* was used as the internal standard. GC–MS was performed with a Finnigan GCQ mass spectrometer coupled to a Finnigan Q-GC. LC–MS was used for the final characterization of labelled compounds and for determining the concentration of non-radioactive products present in the labelled products. Waters Quattra Premier micromass coupled with Waters Alians LC instrument was used for LC–MS analysis. The ionization mode used was electrospray positive ionization (ESI+). Mobile phases used were B and A2. Melting points were determined by Bibby Sterilin's melting point apparatus Stuart SMP3.

General method for ^{11}C-labelling synthesis

tetrakis(Triphenylphosphine)palladium (3.0 mg, 2.7 μmol) was placed in a vial (1 mL), flushed with nitrogen and anhydrous THF (200 μL) was added. The mixture was shaken until the solution became homogeneous, and methyl iodide (6 μL, 13.6 mg, 96.4 μmol) was added. The mixture was heated for 5 min at 60°C and the solvent was removed by flushing with nitrogen. The residue was dissolved in fresh anhydrous THF (250 μL). Amine **1** (14.1 μmol) was taken in another vial (1 mL), flushed with nitrogen and dissolved in anhydrous THF (200 μL). The solution was treated with BuLi (10 μL of 1.6 M solution, 16.0 μmol), heated for 5 min at 60°C (no heating was needed for compound ***2a**) and when the heating was finished the solvent was removed by flushing with nitrogen. The residue was dissolved in fresh anhydrous THF (250 μL). The two reagent solutions were mixed together, filtered and loaded into the injection loop of the equipment. From the loop, the mixture was transferred with pressure (35 MPa) into the micro-autoclave (200 μL), which had been precharged with [^{11}C]carbon monoxide in helium. The micro-autoclave was immersed in an oil bath at 150°C for 5 min. The crude product was transferred to a vial (1 mL), THF was removed by flushing with nitrogen and acetonitrile (1 mL) was added. The resulting solution was injected on the semi-preparative HPLC for purification. Solvent: A1(40)–B(60) linear gradient to 0:90 within 5 min and isocratic for another 10 min, flow 5 mL/min.

Synthesis of precursor amines 1a–1h

General procedure. A suspension of activated, powdered, 4-Å Ms (5.00 g) and cesium hydroxide monohydrate (3.12 g, 18.93 mmol) in anhydrous DMF (100 mL) was stirred vigorously for 10 min at ambient temperature. A solution of amine **3** (16.25 mmol) in anhydrous DMF (10 mL) was added slowly and the mixture was stirred for an additional 30 min at the same temperature. Finally, a solution of benzyl halide **4** (16.25 mmol) in dry DMF (10 mL) was added to the white suspension, and the reaction was allowed to proceed at 70°C for 4 h. The reaction mixture was filtered to remove the undissolved materials and the precipitate was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the residue was taken up in 1 N NaOH (100 mL) and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to give the crude product. All of the products

DOI: 10.1002.jlcr

were purified by flash column chromatography (twice, first using pentane/dichloromethane/diethyl ether (8:1:1 v/v), then pentane/diethyl ether (8:2 v/v), as the eluents).

N-(2,5-Dimethoxybenzyl)-N-(5-fluoro-2-phenoxyphenyl)amine ***1a***. δ_H (400 MHz, $CDCl_3$): 7.32–7.36 (2H, m), 7.10–7.12 (1H, m), 6.98–7.01 (2H, m), 6.84–6.88 (2H, m), 6.80–6.81 (2H, m), 6.51–6.55 (1H, m), 6.36–6.38 (1H, m), 4.91 (1H, bs), 3.36 (2H, s), 3.75 (3H, s), 3.76 (3H, s).

δ_C (100 MHz, $CDCl_3$): 161.8, 159.5, 158.0, 153.5, 151.4, 141.9, 138.4, 129,7, 127.6, 122.5, 120.8, 116.5, 114.8, 112.3, 111.1, 102.4, 102.2, 99.4, 99.1, 55.6, 55.6, 42.8.

GC–MS (EI): $m/z = 353.1$ ($M^{+\cdot}$, 86.6%), 322.2 (7.9%), 227.1 (14.6%), 214.2 (8.2%), 151.1 (100.0%), 121.2 (19.7%), 91.1 (23.2%), 77.1 (11.5%).

N-(2-Chlorobenzyl)-N-(5-fluoro-2-phenoxyphenyl)amine ***1b***. δ_H (400 MHz, $CDCl_3$): 7.35–7.43 (4H, m), 7.25–7.27 (3H, m), 7.13–7.15 (1H, m), 7.03–7.05 (1H, m), 6.88–6.90 (1H, m), 6.40–6.42 (2H, m), 4.90 (1H, bs), 4.49 (3H, s), 4.48 (3H, s).

δ_C (100 MHz, $CDCl_3$): 161.0, 160.0, 159.1, 142.0, 138.1, 135.8, 133.2, 129.8, 129.7, 128.6, 128.5, 127.0, 122.8, 120.6, 116.9, 102.8, 102.6, 99.2, 99.0, 45.2.

GC–MS (EI): $m/z = 327.1$ ($M^{+\cdot}$, 100.0%), 292.2 (11.3%), 214.2 (17.0%), 201.1 (90.0%), 166.3 (24.9%), 125.2 (31.7%).

N-(2,5-Dimethoxybenzyl)-N-(2-phenoxyphenyl)amine ***1d***. δ_H (400 MHz, $CDCl_3$): 7.33–7.37 (2H, m), 7.01–7.10 (4H, m), 6.92–6.93 (2H, m), 6.79–6.91 (3H, m), 6.60 (1H, m), 4.80 (1H, bs), 4.42 (2H, s), 3.76 (3H, s), 3.75 (3H, s).

δ_C (100 MHz, $CDCl_3$): 157.8, 153.6, 151.5, 142.9, 140.6, 129.6, 128.4, 125.1, 122.5, 119.6, 117.1, 116.9, 114.9, 112.2, 111.1, 55.7, 43.1.

GC–MS (EI): $m/z = 335.1$ ($M^{+\cdot}$, 100.0%), 304.3 (15.0%), 227.2 (20.6%), 196.2 (10.0%), 151.1 (76.2%), 121.2 (17.3%), 91.1 (18.8%), 77.1 (10.4%).

N-(3,5-Dimethoxybenzyl)-N-(2-phenoxyphenyl)amine ***1e***. δ_H (400 MHz, $CDCl_3$): 7.34–7.38 (2H, m), 7.05–7.12 (4H, m), 6.93–6.95 (1H, m), 6.72–6.77 (2H, m), 6.55–6.56 (2H, m), 6.42–6.43 (1H, m), 4.70 (1H, bs), 4.37 (2H, s), 3.79 (6H, s).

δ_C (100 MHz, $CDCl_3$): 161.1, 157.6, 142.9, 142.0, 140.3, 129.7, 125.0, 122.7, 119.4, 117.3, 117.0, 111.8, 105.0, 99.2, 55.3, 47.9.

GC–MS (EI): $m/z = 335.2$ ($M^{+\cdot}$, 100.0%), 320.3 (9.6%), 242.2 (9.1%), 227.2 (71.3%), 212.2 (15.7%), 196.2 (22.4%), 184.2 (12.2%), 151.2 (38.4%), 121.2 (4.7%), 91.1 (9.2%), 77.1 (5.2%).

N-(2-Chlorobenzyl)-N-(2-phenoxyphenyl)amine ***1f***. δ_H (400 MHz, $CDCl_3$): 7.40–7.45 (4H, m), 7.26–7.28 (2H, m), 7.17 (1H, m), 7.09–7.13 (3H, m), 6.93 (1H, m), 6.73–6.76 (2H, m), 4.90 (1H, bs), 4.56 (2H, s).

δ_C (100 MHz, $CDCl_3$): 157.6, 143.1, 140.0, 136.6, 133.2, 129.8, 129.5, 128.6, 128.3, 126.9, 125.0, 122.8, 119.4, 117.4, 117.2, 111.8, 45.3.

GC–MS (EI): $m/z = 309.2$ ($M^{+\cdot}$, 100.0%), 274.3 (10.3%), 201.1 (79.6%), 184.2 (47.8%), 166.3 (22.5%), 156.2 (14.8%), 129.2 (21.7%).

N-(2,3-Dimethoxybenzyl)-N-(2-phenoxyphenyl)amine ***1g***. δ_H (400 MHz, $CDCl_3$): 7.28–7.31 (2H, m), 6.97–7.05 (5H, m), 6.84–6.90 (3H, m), 6.77–6.79 (1H, m), 6.64 (1, m), 4.41 (2H, s), 3.86 (4H, bs), 3.83 (3H, s).

δ_C (100 MHz, $CDCl_3$): 157.7, 152.7, 147.1, 143.1, 133.0, 129.7, 127.1, 125.0, 124.1, 122.7, 120.6, 119.3, 117.5, 116.9, 111.9, 111.6, 60.8, 55.8, 42.7.

GC–MS (EI): $m/z = 335.2$ ($M^{+\cdot}$, 100.0%), 320.3 (7.7%), 304.2 (11.3%), 227.2 (11.4%), 196.2 (17.6%), 186.2 (6.7%), 167.2 (9.5%), 151.1 (46.6%), 136.1 (60.0%), 121.2 (5.4%), 91.1 (12.6%), 77.1 (5.7%).

N-(5-Chloro-2-phenoxyphenyl)-N-(3,5-dimethoxybenzyl)amine ***1h***. δ_H (400 MHz, $CDCl_3$): 6.37–7.33 (11H, m), 4.79 (1H, bs), 4.28 (2H, s), 3.75 (6H, s).

δ_C (100 MHz, $CDCl_3$): 161.4, 157.4, 141.4, 141.3, 130.3, 129.9, 123.2, 120.1, 117.5, 116.7, 111.7, 105.3, 99.6, 55.5, 47.9.

GC–MS (EI): $m/z = 369.1$ ($M^{+\cdot}$, 100.0%), 338.2 (6.7%), 276.1 (12.8%), 241.2 (22.4%), 227.2 (86.8%), 212.2 (19.8%), 151.2 (72.8%), 91.1 (16.8%), 77 (9.2%).

N-(5-Chloro-2-phenoxyphenyl)-N-(2,5-dimethoxybenzyl)amine ***1i***. δ_H (400 MHz, $CDCl_3$): 6.58–7.33 (11H, m), 4.82 (1H, bs), 4.34 (2H, s), 3.75 (3H, s), 3.74 (3H, s).

δ_C (100 MHz, $CDCl_3$): 157.8, 154.0, 151.9, 142.0, 141.8, 130.5, 130.0, 128.1, 123.2, 120.5, 117.5, 116.6, 115.3, 113.0, 112.2, 111.7, 56.0, 43.2.

GC–MS (EI): $m/z = 369.1$ ($M^{+\cdot}$, 55.9%), 338.1 (5.9%), 227.1 (17.4%), 151.1 (100.0%), 121.2 (16.1%), 91.1 (18.1%), 77.1 (9.6%).

Synthesis of 5-fluoro-2-phenoxyaniline 3

4-Fluoro-2-nitro-1-phenoxybenzene (1.51 g, 6.48 mmol), $FeCl_3 \cdot 6H_2O$ (0.17 g, 0.61 mmol) and activated carbon (0.17 g) were suspended in absolute ethanol (50 mL). Hydrazine hydrate (0.7 mL, 0.72 g, 14.40 mmol) was added, and the resulting mixture was refluxed for 4 h. The cooled reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between chloroform (100 mL) and water (100 mL). The separated chloroform extract was washed with water (3×100 mL), dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give the 1.27 g of the target compound as white solid. Yield = 96%, m.p. 45°C. The product was used in the next step without further purification.

DOI: 10.1002.jlcr

δ_H (400 MHz, $CDCl_3$): 7.36–7.40 (2H, m), 7.14 (1H, m), 7.03–7.05 (2H, m), 6.89–6.91 (1H, m), 6.54–6.57 (1H, m), 6.48 (1H, m), 3.99 (2H, bs).

δ_C (100 MHz, $CDCl_3$): 161.0, 158.6, 157.4, 140.1, 140.0, 138.3, 129.5, 122.4, 121.3, 121.2, 116.3, 104.4, 104.2, 102.8, 102.6.

GC–MS (EI): $m/z = 303.1$ (M^+, 100.0%), 186.2 (22.1%), 174.2 (10.6%), 126.1 (16.3%), 98.1 (16.5%), 78.1 (4.3%).

Synthesis of 2-(bromomethyl)-1,4-dimethoxybenzene and 1-(bromomethyl)-2,3-dimethoxybenzene 4a and 4f

General procedure. Carbon tetrabromide (2.11 g, 6.50 mmol) was dissolved in dry dichloromethane and cooled to 0°C in an ice bath. 2,5- or 2,3-Dimethoxybenzyl alcohol was added. A solution of triphenylphosphine (1.70 g, 6.48 mmol) in dry dichloromethane was added. The reaction mixture was allowed to warm to ambient temperature and stirred at that temperature for 30 min. The solvent was removed under reduced pressure. Diethyl ether (150 mL) was added and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography using pentane/ether (9:2) as the eluent.

2-(Bromomethyl)-1,4-dimethoxybenzene ***4a***. Yield 85%, white crystals, m.p. 76°C (lit.[34] 73°C). δ_H (400 MHz, $CDCl_3$): 6.90 (1H, m), 6.82 (2H, m), 4.53 (2H, s), 3.85 (3H,s), 3.77 (3H, s).

δ_C (100 MHz, $CDCl_3$): 153.5, 151.7, 127.0, 116.4, 115.1, 112.3, 56.3, 55.8, 29.0.

GC–MS (EI): $m/z = 232.0$ and 229.9 (M^+, 12.2 and 13.7%), 151.1 (100.0%), 121.1 (18.8%), 91.1 (30.1%), 77.1 (16.5%).

1-(Bromomethyl)-2,3-dimethoxybenzene ***4f***. Yield 87%, colorless oil.

δ_H (400 MHz, $CDCl_3$): 7.01 (1H, m), 6.96 (1H, m), 6.88 (1H, m), 4.56 (2H, s), 3.96 (3H,s), 3.84 (3H, s).

δ_C (100 MHz, $CDCl_3$): 152.6, 147.3, 131.6, 123.9, 122.3, 112.9, 60.6, 55.6, 28.1.

GC–MS (EI): $m/z = 231.9$ and 229.9 (M^+, 16.1 and 16.4%), 151.1 (100.0%), 136.1 (88.5%), 121.1 (3.1%), 91.1 (16.5%), 77.1 (8.6%).

Synthesis of *N*-(2,5-dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide and *N*-(2,5-dimethoxybenzyl)-*N*-(5-chloro-2-phenoxyphenyl)acetamide 2a and 2i

General procedure. A solution of **1a** or **1i** (1.70 mmol) and anhydrous pyridine (3.70 mmol) in dry THF (30 mL) was cooled to 0°C in an ice bath. Acetyl chloride (0.2 mL, 0.22 g, 2.80 mmol) was added slowly. The resulting reaction mixture was allowed to warm to ambient temperature and stirred at that temperature for 1 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (75 mL) and water (100 mL). The separated organic layer was washed with 10% $CuSO_4$ (2×50 mL) solution and water (2×50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the target compound.

N-(2,5-Dimethoxybenzyl)-N-(5-fluoro-2-phenoxyphenyl)acetamide **2a**. Yield 95%, white solid, m.p. 90°C.

δ_H (400 MHz, $CDCl_3$): 7.28–7.32 (2H, m), 7.10 (1H, m), 6.67–6.93 (8H, m), 5.09–5.12 (1H, d), 4.63–4.66 (1H, d), 3.65 (3H, 3), 3.54 (3H, s), 1.96 (3H, s).

δ_C (100 MHz, $CDCl_3$): 170.5, 159.0, 156.0, 153.5, 151.7, 148.0, 138.0, 129.8, 126.1, 123.9, 119.7, 119.6, 118.6, 117.2, 117.0, 116.4, 115.7, 115.5, 113.4, 111.3, 55.7, 55.6, 45.9, 22.1.

GC–MS (EI): $m/z = 395.1$ (M^+, 15.3%), 352.2 (6.9%), 302.0 (28.2%), 214.2 (8.9%), 151.1 (100.0%), 123.2 (10.2%), 91.1 (10.9%), 77.1 (6.3%).

N-(2,5-Dimethoxybenzyl)-N-(5-chloro-2-phenoxyphenyl)acetamide ***2i***. Yield 96%, yellow solid, m.p. 110°C.

δ_H (400 MHz, $CDCl_3$): 6.67–7.33 (11H, m), 4.67 (1H, d), 5.07 (1H, d), 3.65 (3H, m), 3.54 (3H, m), 1.59 (2H, bs).

δ_C (100 MHz, $CDCl_3$): 170.6, 155.9, 153.8, 152.7, 152.1, 134.4, 130.6, 130.1, 129.0, 127.7, 126.4, 124.5, 119.4, 119.2, 116.9, 114.0, 111.6, 55.9, 55.8, 46.2, 22.3.

GC–MS (EI): $m/z = 411.0$ (M^+, 10.1%), 368.1 (5.2%), 318.1 (24.2%), 230.1 (6.5%), 151.1 (100.0%), 123.2 (11.2%), 91.2 (12.7%), 77.1 (6.9%).

Conclusion

A novel method for the synthesis of [*carbonyl*-^{11}C]-DAA1106 and its analogues was described. The carbonylation reaction using [^{11}C]carbon monoxide, palladium(0) complex, methyl iodide or iodobenzene and several amines was employed in the synthesis. The activation of amine using strong base such as *n*-butyllithium (^{n}BuLi) was used to improve the radiochemical yields. The presented approach has opened a way to make a library of a series of ^{11}C-labelled analogues of the interesting PBR ligand DAA1106 with moderate radiochemical yields and high specific radioactivity.

Acknowledgements

Uppsala Imanet and GE Healthcare are acknowledged for financial support of this work.

REFERENCES

1. Bergström M, Grahnén A, Långström B. *Eur J Clin Pharmacol* 2003; **59**: 357–366.
2. Långström B, Kihlberg T, Bergström M, Antoni G, Björkman M, Forngren BH, Forngren T, Hartvig P, Markides K, Yngve U, Ögren M. *Acta Chem Scand* 1999; **53:** 651–669.
3. Rahman O, Kihlberg T, Långström B. *Eur J Org Chem* 2004; 474–478.
4. Rahman O, Llop J, Långström B. *Eur J Org Chem* 2004; 2674–2678.
5. Karimi F, Barletta J, Långström B. *Eur J Org Chem* 2005; 2374–2378.
6. Kihlberg T, Långström B. *J Org Chem* 1999; **64**: 9201–9205.
7. Rahman O, Kihlberg T, Långström B. *J Org Chem* 2003; **68**: 3558–3562.
8. Karimi F, Långström B. *Org Biomol Chem* 2003; **1:** 541–546.
9. Karimi F, Kihlberg T, Långström B. *J Chem Soc, Perkin Trans 1* 2001; 1528–1531.
10. Karimi F, Långström B. *J Chem Soc, Perkin Trans 1* 2002; 2111–2115.
11. Itsenko O, Kihlberg T, Långström B. *J Org Chem* 2004; **69:** 4356–4360.
12. Itsenko O, Långström B. *J Org Chem* 2005; **70**: 2244–2249.
13. Itsenko O, Kihlberg T, Långström B. *Eur J Org Chem* 2005; 3830–3834.
14. Doi H, Barletta J, Suzuki M, Noyori R, Watanabe Y, Långström B. *Org Biomol Chem* 2004; **2:** 3063–3066.
15. Barletta J, Karimi F, Långström B. *J Label Compd Radiopharm* 2006; **49**: 429–436.
16. Rahman O, Kihlberg T, Långström B. *Org Biomol Chem* 2004; **2**: 1612–1616.
17. Okuyama S, Chaki S, Yoshikawa R, Ogawa S-I, Suzuki Y, Okubo T, Nakazato A, Nagamine M, Tomisawa K. *Life Sci* 1999; **64:** 1455–1464.
18. Farges RC. *Curr Med Chem – Anti-Inflamatory and Anti-Allergy Agents* 2003; **2**: 409–416.
19. Kruegel KE, Papadopoulos V. *Annu Rev Pharmacol Toxicol* 1992; **32**: 211–237.
20. Ferzaz B, Brault E, Bourliaud G, Robert J-P, Poughon G, Claustre Y, Marguet F, Liere P, Schumacher M, Nowicki J-P, Fournier J, Marabout B, Sevrin M, George P, Soubrie P, Benavides J, Scatton B. *J Pharmacol Exp Ther* 2002; **301**: 1067–1078.
21. Veenman L, Gavish M. *Pharmacol Ther* 2006; **110**: 503–524.
22. Watkins GL, Jewett DM, Mulholland GK, Kilbourn MR, Toorongian SA. *Appl Radiat Isot* 1988; **39:** 441–444.
23. Shah F, Hume SP, Pike VW, Ashworth S, McDermott J. *Nucl Med Biol* 1994; **21**: 573–581.
24. Zhang M-R, Kida T, Noguchi J, Furutsuka K, Maeda J, Suhara T, Suzuki K, *Nucl Med Biol* 2003; **30:** 513–519.
25. Rahman O, Kihlberg T, Långström B. *J Chem Soc, Perkin Trans 1* 2002; 2699–2703.
26. Karimi F, Långström B. *Eur J Org Chem* 2003; 2132–2137.
27. Salvatore RN, Nagle AS, Jung KW. *J Org Chem* 2002; **67**: 674–683.
28. Okubo T, Yoshikawa R, Chaki S, Okuyama S, Nakazato A. *Bioorg Med Chem* 2004; **12**: 423–438.
29. Protiva M, Jilek J, Cervena I, Pomykacek J, Bartl V, Dlabak A, Valchar M, Metysova J, Holubak J, Svatek E. *Collect Czech Chem Commun* 1986; **51**: 2598–2616.
30. Fumiko Y, Tomoko N, Shuichi H, Yumiko S, Takashi H, Masayoshi A, Hisahiro H. *Helv Chim Acta* 2001; **84**: 2051–2063.
31. White E. *Org Synth, Collect Vol. V*, 1973; 336–337.
32. Kihlberg T, Långström B. Method and apparatus for production and use of [^{11}C]carbon monoxide in labelling synthesis. PCT International Application No. PCT/SE02/01222.
33. Bjurling P, Reineck R, Westerberg G, Gee AD, Sutcliffe J, Långström B. *Proceedings of the VIth Workshop on Targetry and Target Chemistry*; TRIUMF, Vancouver, Canada, 1995; 282.
34. Brehm I, Hinneschiedt S, Meier H. *Eur J Org Chem* 2002; **67**: 3162–3170.

DOI: 10.1002.jlcr