

ALTERNATIVE METHODS OF MAKING [¹¹C]AMIDES: APPLICATION TO THE PREPARATION OF 5-HT_{1A} RECEPTOR RADIOLIGANDS

V.W. PIKE, S.Y. LU, J. HONG, J.L. MUSACHIO, J.A. McCARRON
Molecular Imaging Branch, National Institute of Mental Health,
National Institutes of Health,
Bethesda, Maryland,
United States of America
pikev@mail.nih.gov

Abstract

Many ligands for brain 5-HT_{1A} receptors contain an amide group that is subject to hydrolysis *in vivo*. In the development of radioligands for use with positron emission tomography (PET), labelling in the carbonyl function of an amide group may be advantageous for avoiding radioactive metabolites that would readily enter the brain to confound PET receptor measurements. Several methods of labelling secondary and tertiary amides in their carbonyl functions with ¹¹C ($T_{1/2} = 20.4$ min) have been developed over the past two decades or so. These methods include reaction of a [carbonyl-¹¹C]acid chloride, [carboxyl-¹¹C]magnesium halide carboxylate or [carboxyl-¹¹C]acid with an amine or reaction of [¹¹C]carbon monoxide with an amine plus an aryl halide, alkyl halide or aryl triflate. Some of these processes are successfully promoted with microwaves, palladium complexes, light or thermally initiated radicals. These methods are surveyed here and especially exemplified from research on the development of 5-HT_{1A} receptor radioligands for brain imaging applications with PET.

1. INTRODUCTION

The amide group is widely found in drug-like ligands for neurotransmitter receptors from which radioligands [1, 2] are sometimes developed for imaging these receptors in the brain using positron emission tomography (PET), either in clinical research [3] or in drug development [4, 5]. An important consideration for radioligand development is the molecular position at which a positron emitting isotope, frequently ¹¹C ($T_{1/2} = 20.4$ min), should be introduced. Careful choice of position may avoid radioactive metabolites that could enter the brain to confound PET measurements of radioligand binding to the target receptor. Amides are often metabolized in phase 1 by simple hydrolysis in the liver and/

or other organs to produce the parent amine and carboxylic acid in the blood. Generally, simple carboxylic acids, because they are ionized at physiological pH 7.4, do not enter the brain to a great extent, whereas the brain penetration of amines, though subject to many factors, can be very appreciable. Hence, for a potential PET radioligand containing an amide linkage, introduction of the ^{11}C label on the carbonyl side of the amide group, and even in the carbonyl entity, may be advantageous. This is strikingly so [6, 7] for PET imaging of human brain 5-HT_{1A} receptors with ^{11}C labelled WAY-100635 (1), where labelling in the carbonyl function has been shown to provide a far more sensitive radioligand [8] than labelling in the methoxy group [9] (Fig. 1). Labelling in the methoxy group gives rise to a radioactive amine, ^{11}C labelled WAY-100634 (2) which readily enters the brain to bind both specifically and non-specifically, whereas labelling in the carbonyl function avoids this radioactive metabolite and instead gives rise to [^{11}C]cyclohexanecarboxylic acid which enters the brain only to a low and transient extent (Fig. 2). Such metabolic considerations create a need for effective methods of labelling amides in their carbonyl functions with cyclotron produced ^{11}C , which is nearly always produced from the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ reaction as either [^{11}C]carbon dioxide or [^{11}C]methane [10].

Various methods of labelling secondary and tertiary amides in the carbonyl function with ^{11}C have been developed over the last two decades or so, and these methods are surveyed here. Although these methods have very wide applicability, they are mainly exemplified in this survey through their previous and ongoing applications in producing antagonist and agonist type

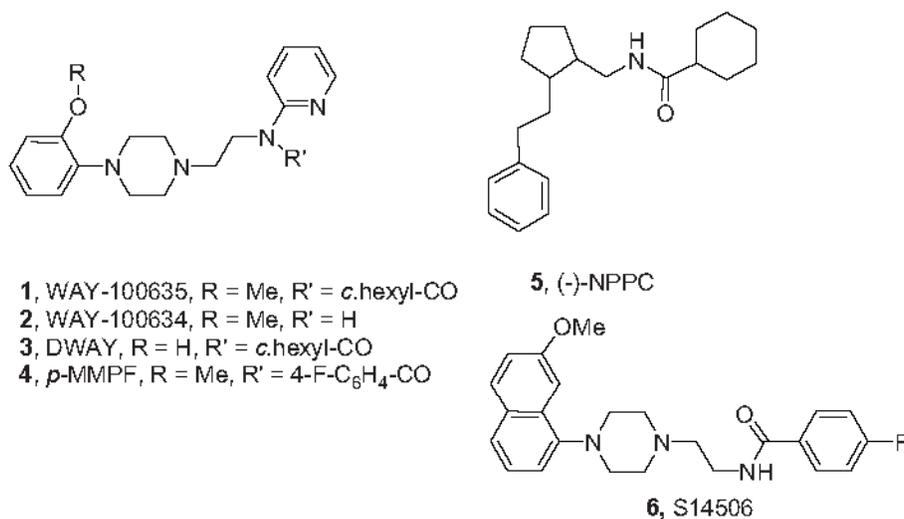


FIG. 1. Labelling with ^{11}C .

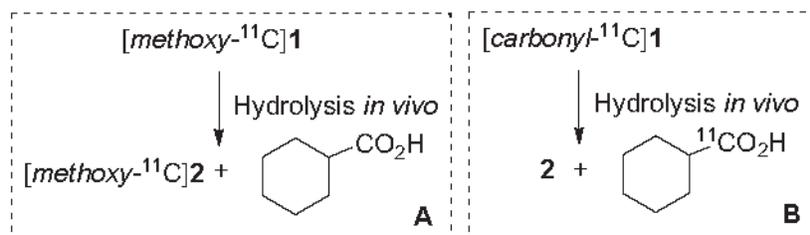


FIG. 2. The metabolic fate of [methoxy- ^{11}C]1 (A) and [carbonyl- ^{11}C]1 in humans (B).

PET radioligands for 5-HT_{1A} receptors. Key considerations with respect to the various methods to be discussed here are their isotope efficiency (i.e. radiochemical yields), speed and ability to deliver high specific radioactivity. If a radioligand is to be obtained in adequately high activity and specific radioactivity for PET investigations, then generally no more than two half-lives of ^{11}C (i.e. a total of 40 min) may be taken for radiosynthesis, purification and formulation. Useful labelling methods typically comply with this time constraint.

2. LABELLING VIA [CARBONYL- ^{11}C]ACID CHLORIDES

A wide range of [carbonyl- ^{11}C]acid chlorides has been prepared by the general method of carboxylation of a Grignard reagent (RMgX , $\text{X} = \text{halogen}$) with cyclotron produced [^{11}C]carbon dioxide followed by chlorination of the adduct (Fig. 3). The ^{11}C -carboxylation reaction has to be controlled in order to avoid further reaction of the adduct or acid with the Grignard reagent, which is necessarily present in excess. Judicious choice of the halogen in the Grignard reagent, reagent concentration, temperature and reaction time often result in efficient carboxylation to give the initial adduct. Chlorination with high boiling

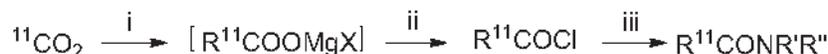


FIG. 3. Synthesis of [carbonyl- ^{11}C]acid chlorides for conversion into [carbonyl- ^{11}C]amides. Typical conditions: (i) RMgX ($\text{X} = \text{Cl}$ or Br) in diethyl ether solution for $\text{R} = \text{lower alkyl or aryl}$, or immobilized in tube for $\text{R} = \text{aryl or c.Hex}$, RT, 2 min; (ii) phthaloyl dichloride and 2,6-di-*t*-butylpyridine for $\text{R} = \text{lower alkyl or aryl}$, or thionyl chloride for $\text{R} = \text{aryl, c.Hex}$, heat, 5–8 min; (iii) primary or secondary amine ($\text{R}'\text{R}''\text{NH}$), solvent (e.g. THF , CH_2Cl_2), 0–37°C, 5–8 min. Reported specific radioactivity (exemplified by [carbonyl- ^{11}C]3 [23, 24]): 74 GBq/ μmol .

point phthaloyl dichloride in the presence of an involatile base allows volatile [^{11}C]acid chlorides (e.g. R^{11}COCl , $\text{R} = \text{Me, Et, Pr, } i\text{-Pr or } i\text{-Bu}$) to be transferred cleanly out of the heated reaction mixture in a nitrogen stream. The [^{11}C]acid chloride may then be trapped within an amine solution to generate the desired [carbonyl- ^{11}C]amide, usually in a moderate decay corrected radiochemical yield (RCY) [11–12].

Where the required [^{11}C]acid chloride is not very volatile (e.g. R^{11}COCl , $\text{R} = i\text{-Hex, Ar}$), reaction with the amine partner may be performed in situ [13, 14]. However, this method may pose a severe separation challenge. Hence, an alternative technique has been devised to limit the amount of material that needs to be separated [15]. A narrow plastic (e.g. polypropylene) tube is coated with an almost dry film of the Grignard reagent. ^{11}C -carboxylation is achieved by controlled passage of the cyclotron produced [^{11}C]carbon dioxide into the tube and the generated adduct washed out with a solution of thionyl chloride into a solution of the amine partner. This method has been automated and applied routinely to the production of [carbonyl- ^{11}C](1) ([^{11}C]WAY) from [carbonyl- ^{11}C]cyclohexanecarbonyl chloride [16]. Some laboratories prefer to use the one pot process and this method has also been automated for the production of [^{11}C]WAY [17, 18]. Practical aspects with regard to the regular production of [^{11}C]WAY, by either the one pot or ‘immobilized’ Grignard reagent procedure, have been discussed in an EC sponsored workshop and the key conclusions published [19].

Desmethyl-WAY (DWAY, 3), may also be labelled in a similar manner to WAY without need for protection of the phenolic hydroxyl group [20]. In fact, [^{11}C]DWAY is superior to [^{11}C]WAY as a PET radioligand for 5-HT_{1A} receptors in monkey and human subjects [21]. Several analogues of WAY have also been labelled similarly, either from [carbonyl- ^{11}C]cyclohexanecarbonyl chloride [22–23] or one of the various [carbonyl- ^{11}C]benzoyl chlorides [24]. These analogues include *p*-MPPF (4), which it may be noted has been exploited extensively as a 5-HT_{1A} receptor radioligand in humans with a longer lived ^{18}F ($T_{1/2} = 109.7$ min) radiolabel [25].

This method can deliver acceptably high specific radioactivities if care is taken to exclude atmospheric carbon dioxide during the preparation and use of the Grignard reagent.

3. LABELLING VIA [CARBONYL- ^{11}C]MAGNESIUM HALIDE CARBOXYLATES

Aubert et al. [26] have reported the rapid one pot synthesis of aliphatic [carbonyl- ^{11}C]amides in moderate RCYs (15–60%) by direct treatment of

SESSION 10

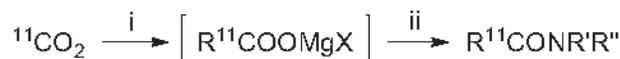


FIG. 4. Preparation of aliphatic [carbonyl- ^{11}C]amides by reaction of [carboxyl- ^{11}C]magnesium halide carboxylates with amines. Typical conditions: (i) RMgX (R = lower alkyl; X = Cl or Br), THF or diethyl ether, 0°C , 3–8 min; (ii) $\text{R}'\text{R}''\text{NH}$ (primary or secondary amine with R' and R'' aliphatic or alicyclic, THF, 70°C , 1–10 min and then aq. HCl or aq. NH_4Cl at 0°C). Specific activity: no carrier added.

[^{11}C]magnesium halide carboxylates with amines in THF in the presence of 2.5 equivalents of alkylmagnesium halide (Fig. 4). The 5-HT $_{1A}$ agonist (-)-NPCC (5) has been labelled successfully with this type of procedure [Lu et al., unpublished results]. Aniline, however, failed to give a labelled amide by this route under thermal conditions [31].

With the application of microwaves, this approach has been extended to encompass the preparation of a [carbonyl- ^{11}C]amide having a benzoyl moiety (4-F-C $_6$ H $_4$ ^{11}CO) in up to 45% RCY in 10 min (Fig. 5) [27]. This method has been applied to label the 5-HT $_{1A}$ receptor agonist, S14506 (6) in the carbonyl function with ^{11}C in 10–18% overall RCY [28].

4. LABELLING VIA [CARBOXYL- ^{11}C]ACIDS

The controlled carboxylation of organometallic reagents, such as Grignard reagents or organolithiums, with [^{11}C]carbon dioxide followed by hydrolysis has been exploited for generally efficient radiosynthesis of a very wide range of aliphatic and aryl [carboxyl- ^{11}C]acids [29]. In non-radioactive chemistry, many methods, aside from conversion into acid chlorides, are known for activating acids for amide formation. However, such methods have been adapted only sparsely for preparing [carbonyl- ^{11}C]amides. Rogers et al. [30]



FIG. 5. Preparation of aryl [carbonyl- ^{11}C]amides by reaction of [carboxyl- ^{11}C]magnesium halide carboxylate with amine. Typical conditions: (i) 4-F-C $_6$ H $_4$ MgX, THF, RT, 6 min; (ii) $\text{R}'\text{R}''\text{NH}$ (primary arylamine or primary or secondary aliphatic amine), THF, microwaves, 70 – 130°C , 2–10 min, and then aq. H_2SO_4 . Specific radioactivity: no carrier added.

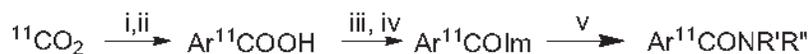


FIG. 6. Preparation of aryl [carbonyl- ^{11}C]amides from a [carboxyl- ^{11}C]benzoic acid by activation with carbonyldiimidazole. Typical conditions: (i) ArMgBr , 5 min; (ii) imidazole-HCl (Im HCl), 1 min; (iii) bromine, 2 min; (iv) carbonyldiimidazole, 5 min; (v) $\text{R}'\text{R}''\text{NH}$ (e.g. piperidine), 5 min. Specific radioactivity: no carrier added.

demonstrated activation of [carboxyl- ^{11}C]benzoic acids with carbonyldiimidazole for one pot amide synthesis (Fig. 6). As for many one pot radiosyntheses with ^{11}C , separation of the radioactive product from unused reagents and by-products was challenging. In this work, an aryl by-product was produced that was incompletely resolved from labelled amide during HPLC. This separation problem was circumvented by brominating the aryl byproduct with bromine, before activation of the labelled acid. The desired [carbonyl- ^{11}C]amide was then obtained pure in >80% RCY in a preparation time of 22 min.

5. LABELLING VIA [^{11}C]CARBON MONOXIDE

5.1. Palladium mediated

Carbon monoxide has a versatile transition metal mediated chemistry for the introduction of the carbonyl function into organic compounds, including amides. [^{11}C]carbon monoxide of high specific activity may be produced efficiently from [^{11}C]carbon dioxide by on-line reduction over heated zinc [31] or molybdenum [32]. The low solubility of [^{11}C]carbon monoxide in organic solvents had impeded its application in radiosynthesis until techniques were developed quite recently to overcome this obstacle, including recirculation [33], the use of high pressure miniature autoclaves [34, 35] and reversible entrapment as a borane complex [36, 37]. Synthia Lab Systems AB (Uppsala, Sweden) has shown that its miniature high pressure apparatus may be automated for radiation safe radiosynthesis with [^{11}C]carbon monoxide.

5.1.1. From aryl halides

Kihlberg and Långström first demonstrated the potential of palladium mediated reactions of [^{11}C]carbon monoxide with aryl and benzyl halides and primary and secondary amines for the preparation of biologically active [carbonyl- ^{11}C]amides in almost quantitative RCYs (Fig. 7) [38].

SESSION 10

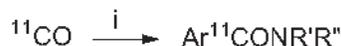


FIG. 7. Preparation of [carbonyl- ^{11}C]amides from [^{11}C]carbon monoxide, aryl or benzyl halides and primary or secondary amines. Typical conditions: (i) aryl or benzyl halide, $\text{Pd}(\text{PPh}_3)_4$, 1,4-dioxane, primary or secondary alkyl amine, 130–150°C, 5 min. Reported specific activities: = 1000 GBq/ μmol [43]; = 1250 GBq/ μmol [45].

In an extension of this work, less reactive amines were activated with lithium *bis*(trimethylsilyl)amide, resulting in greatly improved RCYs over reactions conducted without activation [39]. Several analogues of (1) have been labelled in this manner [B. Långström, personal communication]. Alternatively, addition of 1,2,2,6,6-pentamethylpiperidine to the reactions also increased RCYs for less reactive amines, such as methylamine [40].

5.1.2. From aryl triflates

Rahman et al. [41] have shown that aryl triflates may serve well in place of aryl halides in the palladium mediated radiosynthesis of [carbonyl- ^{11}C]amides from [^{11}C]carbon monoxide. Lithium bromide facilitates the reactions which may be performed in the miniaturized autoclave described by Synthia AB. A variety of [carbonyl- ^{11}C]amides was prepared from aryl triflates and primary or secondary aliphatic amines or aniline in RCYs of 2–63% from 5 min reaction times (Fig. 8).

This method has been applied successfully to the preparation of several candidate radioligands for the peripheral benzodiazepine receptor (PBR) in RCYs ranging from 10 to 55% and with high specific radioactivities (200–900 GBq/ μmol) [42].

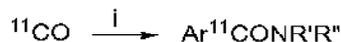


FIG. 8. Preparation of [carbonyl- ^{11}C]amides from [^{11}C]carbon monoxide, aryl triflates and amines. Typical conditions: (i) $\text{Pd}(\text{PPh}_3)_4$, LiBr, THE, aryl triflate, primary or secondary alkyl amine or aniline, 150°C, 5 min. Reported specific radioactivity: 200–900 GBq/ μmol [47].



FIG. 9. Preparation of [carbonyl- ^{11}C]amides via photoinitiated carbonylation with [^{11}C]carbon monoxide using amines and alkyl iodides. Typical conditions: (i) *N*-methyl pyrrolidinone, primary or secondary aliphatic amine or primary aromatic amine, alkyl bromide or iodide or aryl iodide, $h\nu$, 400 s. Reported specific activity: 192 GBq/ μmol [48].

5.2. Radical carbonylation

5.2.1. Photoinitiation

The use of palladium to mediate the insertion of [^{11}C]carbon monoxide into amides and other carbonyl compounds is restricted when competing β -hydride elimination is possible in the electrophile. For this reason, this approach is inapplicable to the radiosynthesis of [^{11}C]WAY since an appropriate electrophile (cyclohexyl halide) would have a β -hydrogen. Recently, photoinitiated radical carbonylation was shown to be successful for the preparation of [carbonyl- ^{11}C]amides and alkyl halides bearing β -hydrogens, such as ethyl iodide and cyclohexyl bromide, from [^{11}C]carbon monoxide, amines and alkyl halides [43] (Fig. 9). In particular examples, conversions of [^{11}C]carbon monoxide in fast reactions (e.g. 400 s) may reach up to 95%, with RCYs of labelled amides reaching 74%.

This method has been adapted to the one step synthesis of [^{11}C]WAY in 40–50% RCY in 30 min synthesis time (Fig. 10) [44].

5.2.2. Thermal initiation

Recently, it was briefly reported that the preparation of a [carbonyl- ^{11}C]amide from [^{11}C]carbon monoxide, alkyl halide and amine may be achieved through thermal generation of free radicals [45]. In a preliminary finding, a 30% conversion of [^{11}C]carbon monoxide and a 19% RCY of [carbonyl- ^{11}C]amide was achieved. Further development of this approach may provide practical advantages over the corresponding photoinitiated process, since these reactions may be conducted simply in a ‘windowless’ miniature autoclave.



FIG. 10. One step preparation of [^{11}C]WAY from [^{11}C]carbon monoxide. Conditions: (i) WAY-100634 (2), base, *n*-hexyl iodide, $h\nu$, 5 min. Specific radioactivity: no carrier added.

SESSION 10

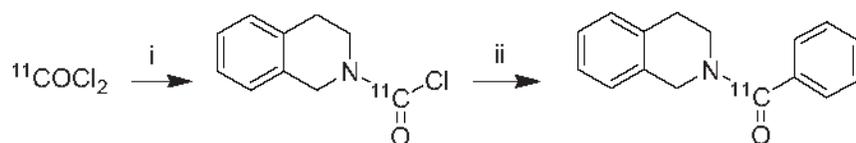


FIG. 11. Synthesis of a [carbonyl-¹¹C]amide via [¹¹C]phosgene and a [carbonyl-¹¹C]carbamoyl chloride. Sample conditions: (i) 2,4-dimethoxybenzyl-tetrahydroisoquinoline, dichloromethane, 20°C; (ii) Ph₂CuMgBr.BrMgCN, THF, -30°C, 5 min then sat. aq. NH₄Cl. Specific radioactivity: no carrier added.

6. LABELLING VIA [CARBOXYL-¹¹C]CARBAMOYL CHLORIDES

[¹¹C]phosgene may be obtained by different methods from cyclotron produced ¹¹C. The most effective, especially with regard to achieving high specific radioactivity, is the conversion of cyclotron produced [¹¹C]methane into [¹¹C]carbon tetrachloride with subsequent oxidation [46]. Lemoucheux et al. [47] have shown that [¹¹C]carbamoyl chlorides can be formed efficiently (RCY = 76%) by reactions of tertiary amines with [¹¹C]phosgene and in one example (Fig. 11) that such a [¹¹C]carbamoyl chloride may be converted with high RCY (54%) into a [carbonyl-¹¹C]amide by treatment with an organometallic reagent (cyanocuprate, or a Grignard reagent in the presence of a nickel catalyst).

However, it is recognized that the two step catalyzed production of [¹¹C]phosgene requires a high level of skilled maintenance for reliability and hence this method is unlikely to supplant the simpler alternatives.

7. CONCLUSIONS

Several useful and alternative methods are now known for the versatile and efficient labelling of secondary and tertiary amides in their carbonyl functions with cyclotron produced ¹¹C and these are finding extensive application in the preparation of PET radioligands for 5-HT_{1A} receptors and other targets (e.g. opiate receptors [11, 17, 42], α₁-adrenoceptors [15], σ₁ receptors [42], CK receptors [42], PBR [47] and MAO [42]).

ACKNOWLEDGEMENTS

This work was supported by the Intramural Research Program of the National Institutes of Health (National Institute of Mental Health).

REFERENCES

- [1] PIKE, V.W., Positron-emitting radioligands for studies in vivo — probes for human psychopharmacology, *J. Psychopharmacology* **7** (1993) 139–158.
- [2] HALLDIN, C., GULYAS, B., LANGER, O., FARDE, L., Brain radioligands - state of the art and new trends, *Q. J. Nucl. Med.* **45** (2001) 139-152.
- [3] SEDVALL, G., PET scanning as a tool in clinical psychopharmacology, *Triangle* **30** (1991) 11-20.
- [4] FARDE, L., The advantage of using positron emission tomography in drug research, *Trends Neurosci.* **19** (1996) 211-214.
- [5] BURNS, H.D., et al., Positron emission tomography neuroreceptor imaging as a tool in drug discovery, research and development, *Curr. Opin. Chem. Biol.* **3** (1999) 388-394.
- [6] OSMAN, S., et al., Characterization of the radioactive metabolites of the 5-HT_{1A} receptor radioligand, [*O-methyl*-¹¹C]WAY-100635, in monkey and human plasma by HPLC — comparison of the behaviour of an identified radioactive metabolite with parent radioligand in monkey using PET, *Nucl. Med. Biol.* **23** (1996) 627–634.
- [7] OSMAN, S., et al., Characterisation of the appearance of radioactive metabolites in monkey and human plasma from the 5-HT_{1A} receptor radioligand, [*carbonyl*-¹¹C]WAY-100635 — explanation of high signal in PET and an aid to biomathematical modelling, *Nucl. Med. Biol.* **25** (1998) 215–223.
- [8] PIKE, V.W., et al., Exquisite delineation of 5-HT_{1A} receptors in human brain with PET and [*carbonyl*-¹¹C]WAY-100635, *Eur. J. Pharmacol.* **301** (1996) R5–R7.
- [9] PIKE, V.W., et al., First delineation of 5-HT_{1A} receptors in human brain with PET and [¹¹C]WAY-100635, *Eur. J. Pharmacol.* **283** (1995) R1–R3.
- [10] QAIM, S.M., et al., PET radionuclide production, in *Radiopharmaceuticals for Positron Emission Tomography*, Stöcklin G., Pike V.W. (Eds), Kluwer Academic Publishers, the Netherlands (1993) pp. 1-43.
- [11] LUTHRA, S.K., PIKE, V.W., BRADY, F., The preparation of carbon-11 labelled diprenorphine: a new radioligand for the study of the opiate receptor system *in vivo*, *J. Chem. Soc., Chem. Commun.* (1985) 1423–1425.
- [12] EHRIN, E., LUTHRA, S.K., CROUZEL, C., PIKE, V.W., Preparation of carbon-11 labeled prazosin, a potent and selective α 1-adrenoceptor antagonist, *J. Label. Compd. Radiopharm.* **25** (1987) 177-183.
- [13] PIKE, V.W., et al., Pre-clinical development of a radioligand for studies of central 5-HT_{1A} receptors *in vivo* — [¹¹C]WAY-100635, *Med. Chem. Res.* **5** (1995) 208–227.
- [14] SCRIPKO, J.G., HUANG, C.C., KILBOURN, M.R., Synthesis of [*carbonyl*-¹¹C]CI-99, a potent κ -opioid receptor agonist, *J. Label. Compd. Radiopharm.* **38** (1996) 141 (Abstract).

SESSION 10

- [15] MCCARRON, J.A., TURTON, D.R., PIKE, V.W., POOLE, K.G., Remotely-controlled production of the 5-HT_{1A} receptor radioligand, [*carbonyl*-¹¹C]WAY-100635, via ¹¹C-carboxylation of an immobilized Grignard reagent, *J. Label Compd. Radiopharm.* **38** (1996) 941–953.
- [16] TRUONG, P., KRASIKOVA, R.N., HALLDIN, C., A fully automated production of [carbonyl-¹¹C]WAY-100635 for clinical studies, *J. Label Compd. Radiopharm.* **46** (2003) S244 (Abstract).
- [17] HWANG, D.R., SIMPSON, N.R., MONTOYA, J., MANN, J.J., LARUELLE, M., An improved one-pot procedure for the preparation of [¹¹C-*carbonyl*]-WAY100635. *Nucl. Med. Biol.* **26** (1999) 815–819.
- [18] SHCHUKIN, E.V., KRASIKOVA, R.N., ANDERSSON, J., TRUONG, P., HALLDIN, C., A fully automated one-pot synthesis of [carbonyl-¹¹C]WAY-100635: validation in routine PET studies, *J. Label. Compd. Radiopharm.* **48** (2005) S208 (Abstract).
- [19] PIKE, V.W., European concerted action on “New radiotracers for quality assurance for nuclear medicine applications” *Eur. J. Nucl. Med.* **24** (1997) BP15–BP19.
- [20] PIKE, V.W., et al., [*carbonyl*-¹¹C]Desmethyl-WAY-100635 (DWAY) is a potent and selective radioligand for central 5-HT_{1A} receptors *in vitro* and *in vivo*, *Eur. J. Nucl. Med.* **25** (1998) 338–346.
- [21] ANDRÉE, B., et al., The PET radioligand [*carbonyl*-¹¹C]desmethyl-WAY-100635 binds to 5-HT_{1A} receptors and provides a higher radioactive signal than [*carbonyl*-¹¹C]WAY-100635 in the human brain, *J. Nucl. Med.* **43** (2002) 292–303.
- [22] PIKE, V.W., et al., Radioligands for the study of brain 5-HT_{1A} receptors *in vivo* – development of some new analogues of WAY, *Nucl. Med. Biol.* (2000) **27**, 429–527.
- [23] MCCARRON, J.A., et al., Two *C*-methyl derivatives of [¹¹C]WAY-100635 – effects of an amido α -methyl group on metabolism and brain 5-HT_{1A} receptor radioligand behavior in monkey, *Mol. Imaging & Biol.* **7** (2005) 209–219.
- [24] MCCARRON, J.A., Development of radioligands for the study of brain 5-HT_{1A} and α_2 adrenoceptors with PET. PhD Thesis, University of London, U.K. (1998).
- [25] SHIUE, C.Y., et al., *p*-[¹⁸F]-MPPF: a potential radioligand for PET studies of 5-HT_{1A} receptors in humans, *Synapse* **25** (1997) 147–154.
- [26] AUBERT, C., HUARD-PERRIO, C., LASNE, M.-C., Rapid synthesis of aliphatic amides by reaction of carboxylic acids, Grignard reagent and amines: application to the preparation of [¹¹C]amides, *J. Chem. Soc., Perkin Trans. 1* (1997) 2837–2842.
- [27] LU, S.Y., HONG, J.S., PIKE, V.W., Synthesis of NCA [*carbonyl*-¹¹C]amides by direct reaction of in situ generated [¹¹C]carboxymagnesium halides with amines under microwave-enhanced conditions, *J. Label. Compd. Radiopharm.* **46** (2003) 1249–1259.
- [28] LU, S.Y., et al., Alternative methods for labeling the 5-HT_{1A} receptor agonist, 1-[2-(4-fluorobenzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine (S14506), with carbon-11 or fluorine-18, *J. Label. Compd. Radiopharm.* **48** (2005), 971.

- [29] WINSTEAD, M.B., LAMB, J.F., WINCHELL, H.S., Relationship of chemical structures to in vivo scintigraphic distribution patterns of ^{14}C -compounds. 1. ^{14}C -carboxylates, *J. Nucl. Med.* **14** (1973) 747-754.
- [30] ROGERS, G.A., STONE-ELANDER, S., INGVAR, M., Rapid one-pot method for synthesizing substituted [^{14}C]amides, *J. Label. Compd. Radiopharm.* **25** (1994) 327 (Abstract).
- [31] WELCH, M.J., TER-POGOSSIAN, M.M., The preparation of short-lived gases for medical studies, *Radiat. Res.* **36** (1968) 580-589.
- [32] ZEISLER, S.K., NADER, M., THEOBALD, A., OBERDORFER, F., Conversion of no-carrier-added [^{14}C]carbon dioxide to [^{14}C]carbon monoxide on molybdenum for the synthesis of ^{14}C -labelled aromatic ketones, *Appl. Radiat. Isot.* **48** (1997) 1091-1095.
- [33] LIDSTRÖM, P., KIHLEBERG, T., LÅNGSTRÖM, B., [^{14}C]Carbon monoxide in the palladium-mediated synthesis of ^{14}C -labelled ketones, *J. Chem. Soc. Perkin Trans. 1* (1997) 2701-2706.
- [34] KIHLEBERG, T., LÅNGSTRÖM, B., Method and apparatus for production and use of [^{14}C]carbon monoxide in labeling synthesis, *PCT Int Appl. PCT/SE02/01222*.
- [35] HOSTETLER, E.D., BURNS, H.D., A remote-controlled high pressure reactor for radiotracer synthesis with [^{14}C]carbon monoxide, *Nucl. Med. Biol.* **29** (2002) 845-848.
- [36] AUDRAIN, H., MARTARELLO, L., GEE, A., BENDER, D., A new method for trapping [^{14}C]carbon monoxide and its application for the synthesis of PET radiopharmaceuticals, *J. Label. Compd. Radiopharm.* **46** (2003) S77 (Abstract).
- [37] AUDRAIN, H., MARTARELLO, L., GEE, A., BENDER, D., Utilisation of [^{14}C]labelled boron carbonyl complexes in palladium carbonylation reaction, *Chem. Commun.* (2004) 558-559.
- [38] KIHLEBERG, T., LÅNGSTRÖM, B., Biologically active ^{14}C -labeled amides using palladium-mediated reactions with aryl halides and [^{14}C]carbon monoxide, *J. Org. Chem.* **64** (1999) 9201-9205.
- [39] KARIMI, F., LÅNGSTRÖM, B., Synthesis of ^{14}C -amides using [^{14}C]carbon monoxide and in situ activated amines by palladium-mediated carboxaminations, *Org. & Biomol. Chem.* **1** (2003) 541-546.
- [40] KARIMI, F., LÅNGSTRÖM, B., Synthesis of ^{14}C -labelled amides by palladium-mediated carboxamination using [^{14}C]carbon monoxide, in situ activated amines and 1,2,2,6,6-pentamethylpiperidine, *Eur. J. Org. Chem.* (2003) 2132-2137.
- [41] RAHMAN, O., KIHLEBERG, T., LÅNGSTRÖM, B., Aryl triflates and [^{14}C]/(^{13}C)carbon monoxide in the synthesis of ^{14}C -/ ^{13}C -amides, *J. Org. Chem.* **68** (2003) 3558-3562.
- [42] RAHMAN, O., KIHLEBERG, T., LÅNGSTRÖM, B., Synthesis of *N*-methyl-*N*-(1-methylpropyl)-1-(2-chlorophenyl)isoquinoline-3- ^{14}C carboxamide ([^{14}C -carbonyl]PK11195) and some analogues using [^{14}C]carbon monoxide and 1-(2-chlorophenyl)isoquinolin-3-yl triflate, *J. Chem. Soc., Perkin Trans. 1* (2002) 2699-2703.

SESSION 10

- [43] ITSENKO, O., KIHLEBERG, T., LÅNGSTRÖM, B., Photoinitiated carbonylation with [^{11}C]carbon monoxide using amines and alkyl iodides, *J. Org. Chem.* **69** (2004) 4356-4360.
- [44] ITSENKO, O., KIHLEBERG, T., BLOM, E., LÅNGSTRÖM, B., One step synthesis of [*carboxyl*- ^{11}C]WAY-100635, *J. Label. Compd. Radiopharm.* **48** (2005) S135 (Abstract).
- [45] ITSENKO, O., LÅNGSTRÖM, B., Labeling via free radical carbonylation using ^{11}CO . *J. Label. Compd. Radiopharm.* **48** (2005) S25 (Abstract).
- [46] LANDAIS, P., CROUZEL, C., A new synthesis of of carbon-11 labeled phosgene, *Appl. Radiat. Isot.* **38** (1987) 297-300.
- [47] LEMOUCHEUX, L., ROUDEN, J., IBAZIZENE, M., SOBRIQ, F., LASNE, M.-C., Debzylation of tertiary amines using phosgene or triphosgene: An efficient and rapid procedure for the preparation of carbamoyl chlorides and unsymmetrical ureas Application in carbon-11 chemistry, *J. Org. Chem.* **68** (2003) 7289-7297.