JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Labelled Cpd Radiopharm 2002; **45**: 37–47.
DOI: 10.1002/jlcr.532

Research Article

Synthesis of [^{11}C]atipamezole, a potential PET ligand for the α_2-adrenergic receptor in the brain

D. Roeda*[,1], H.T. Sipilä[2], Y. Bramoullé[1], J. D. Enas[†,3], F. Vaufrey[1], F. Dollé[1] and C. Crouzel[1]

[1] *Service Hospitalier Frédéric Joliot, Département de Recherche Médicale, CEA, 4 Place du Général Leclerc, F-91401 Orsay, France*

[2] *Turku PET Centre, Turku University Central Hospital, PO Box 52, 20520 Turku, Finland*

[3] *Center for Functional Imaging, Lawrence Berkeley National Laboratory, Berkeley CA 94703 USA*

Summary

The α_2-adrenergic receptor antagonist atipamezole has been labelled with carbon-11 using [^{11}C]formaldehyde and 2-ethyl-2-oxoacetylindane. Various routes are proposed for the synthesis of the latter: oxidation of 2-acetyl-2-ethylindane, hydrolysis of 2-diethoxy-2-indane and oxidation of 2-diazoacetyl-2-ethylindane. The average radiochemical yield of [^{11}C]atipamezole was 24% based on [^{11}C]formaldehyde, and the synthesis time, including HPLC purification and formulation, was 45 min. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: atipamezole; α_2-adrenergic receptor; carbon-11

Introduction

The α_2-adrenergic receptor in the brain modulates the adrenergic system at the presynaptic level and is thought to be involved in various

*Correspondence to: D. Roeda, Service Hospitalier Frédéric Joliot, Département de Recherche Médicale, CEA, 4 Place du Général Leclerc, F-91401 Orsay, France. E-mail: roeda@dsvidf.cea.fr
[†] Present address: Vical, Inc., 9373 Towne Centre Drive, San Diego, CA, 92121

Received 25 September 2001
Accepted 4 October 2001

neuropsychiatric and neurodegenerative disorders such as depression and Alzheimer's disease.[1,2]

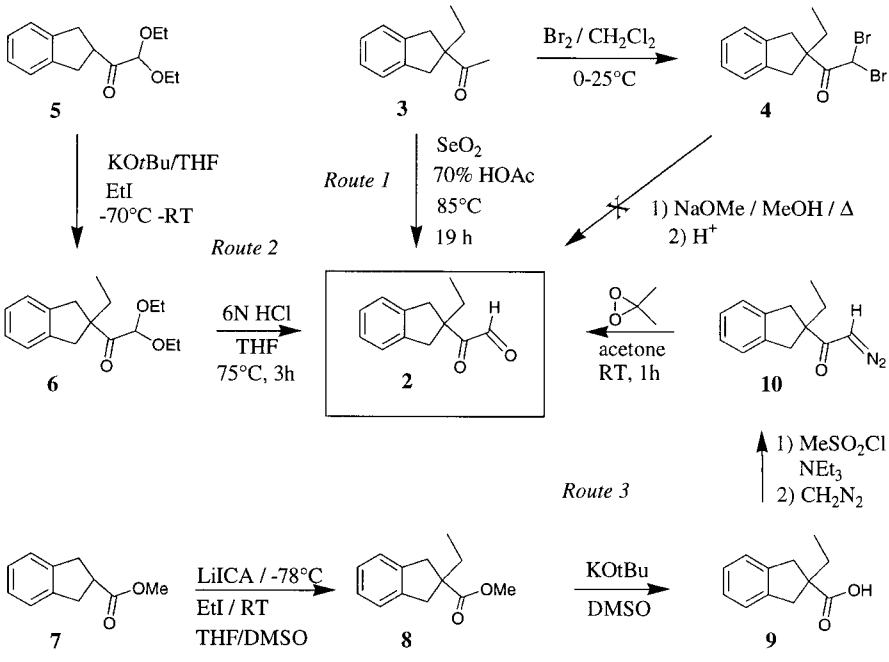
Various α_2-adrenergic receptor ligands have been labelled with positron emitting isotopes for PET studies, e.g. Reference [3–6], but none of these showed a satisfactory *in-vivo* distribution. For example, fluorine-18-labelled 5-fluoroatipamezole, a derivative of the well-known α_2-adrenergic receptor ligand atipamezole, has been synthesized.[4] Introduction of the [^{18}F]fluorine atom resulted in a significant digression of the *in vivo* behaviour of this radioligand compared to what would be expected from atipamezole itself (unpublished results).

Atipamezole (**1**) is a highly selective antagonist for the α_2-adrenergic receptor with a K_D of 50 pM.[7] It is an important reference compound in α_2-adrenergic receptor research. *Ex vivo* studies with [^{3}H]atipamezole in the rat[8,9] indicate that [^{11}C]atipamezole could show promise as an excellent PET imaging agent with respect to brain uptake, kinetics, distribution and metabolism. Labelling of atipamezole with carbon-11 would not introduce a foreign atom, thus avoiding the problem encountered with 5-[^{18}F]fluoroatipamezole. We present here the first synthesis of [^{11}C]atipamezole from [^{11}C]formaldehyde and the α-ketoaldehyde **2**.

Results and discussion

Our strategy[10] called for the synthesis of 2-ethyl-2-oxoacetylindane (**2**). We report here our various approaches to this refractory product (Scheme 1).

Route 1 : 2-Acetyl-2-ethylindane (**3**) was synthesized in two steps with an overall yield of 42% from α,α'-dibromo-*o*-xylene, as described in the literature.[11] Initially, we brominated this compound to give dibromoacetyl-2-ethylindane (**4**). However, treatment of **4** with sodium methoxide and subsequent acid hydrolysis, failed to obtain **2** in practical quantities so this route was abandoned. Then, compound **3** was treated with selenium dioxide in acetic acid at 85°C for 19 h. According to ^{1}H-NMR evidence, 70% of the reaction mixture consisted of the desired product **2**. However, all our attempts to purify the product failed. Nevertheless, the mixture as such was successfully applied in the radiosynthesis of [^{11}C]atipamezole (*vide infra*) although the impurities complicated the final HPLC purification. The crude reaction mixture containing **2** could be kept as a solution in THF for at



Scheme 1. Precursor synthesis

least six months at −20°C without affecting its performance in the radiolabelling reaction.

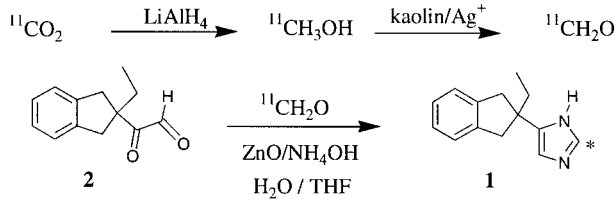
Route 2 : 2-Diethoxyacetylindane (**5**) was prepared in 23% yield from 2-bromoindane[12] and diethoxyacetic acid piperidinyl amide,[13] as described in the literature.[14] Intermediate **5** was then alkylated with iodoethane[11] using potassium *t*-butoxide in THF (−70°C, then raising to room temperature) giving 2-diethoxyacetyl-2-ethylindane (**6**) in 66% yield. Unexpectedly, product **6** resisted a whole range of hydrolysis methods (HCl, TFA, Si/H_2O or Me_3SiI) to afford **2**. Finally, refluxing 6N HCl/THF did convert **6** into **2**; however, we were not able to separate the desired ketoaldehyde **2** from the by-product 1-chloro-4-hydroxybutane, which resulted from ring opening of THF. Although the appropriate experiments have not yet been done, it is conceivable that this mixture as such may serve as a suitable precursor in the radiolabelling reaction, given the good results seen with the crude reaction mixture containing **2** obtained in route 1.

Route 3 : α-Ketoaldehydes can be obtained by the oxidation of the corresponding α-diazoketones with dimethyldioxirane in acetone.[15] This procedure is particularly useful when the product cannot be purified by

chromatography. The by-products acetone and nitrogen are easily removed, and the remaining residue consists only of the desired compound. This procedure became our method of choice for the synthesis of **2**. 2-Methoxycarbonylindane (**7**) was synthesized in three steps from α,α'-dibromo-*o*-xylene (overall yield 28%) as described in the literature.[16] Intermediate **7** was then alkylated with iodoethane using lithium *N*-isopropylcyclohexylamide (LiICA) in THF/DMSO[17] to afford 2-ethyl-2-methoxycarbonylindane (**8**) in 14% yield.

Treatment of ester **8** with potassium *t*-butoxide in DMSO[18] followed by HPLC purification gave 2-carboxy-2-ethylindane (**9**) in 27%. The standard method of converting an acid into an α-diazoketone via the mixed anhydride using isobutyl chloroformate and diazomethane failed with **9**, giving only its isobutyl ester. However, a recent, mild, one-pot method, developed especially for hindered acids,[19] gave 2-diazoacetyl-2-ethylindane (**10**) in low yield (8%, after HPLC purification) via the corresponding acyl mesylate. The α-diazoketone **10** was then converted quantitatively into the desired α-ketoaldehyde **2** using dimethyldioxirane in acetone at room temperature in an unoptimized time of one hour.[15,20]

The method used to produce radiolabelled atipamezole[10] is outlined in Scheme 2. [^{11}C]Carbon dioxide was reduced to [^{11}C]methanol in lithium aluminium hydride in THF.[21,22] Passage of [^{11}C]methanol vapour over a recently developed silver containing catalyst[23] gave [^{11}C]formaldehyde in an average radiochemical yield of 30% with respect to [^{11}C]carbon dioxide. Reaction of [^{11}C]formaldehyde with compound **2** for 5 minutes in aqueous THF at room temperature in the presence of zinc oxide and ammonium hydroxide gave [^{11}C]atipamezole in radiochemical yields of approximately 24% relative to [^{11}C]formaldehyde, after reversed-phase HPLC purification. We found that zinc precipitation with H_2S, as described in the original method,[10] was not necessary. The synthesis time, including formulation, was 45 min. Thus



Scheme 2. Radiolabelling

starting with 1 Curie of [^{11}C]carbon dioxide 15 mCi of [^{11}C]atipamezole is obtainable at 45 min after end of irradiation. The identity of the product was concluded from its retention time on HPLC and from its Rh value on TLC. Formulation was achieved by a reversed phase SEP-PAK procedure. Alpha-ketoaldehydes such as **2** potentially can generate formaldehyde by water-assisted decomposition. We did not find any indication that the specific radioactivity had been influenced by such a process.

Experimental

Chemicals were purchased from Aldrich, France and were used without further purification. Atipamezole (**1**) was kindly donated by Orion Pharma, Espoo, Finland. TLC was performed on pre-coated plates of 0.2 mm silica gel 60F254 (Merck). The compounds were visualized using both a UV-lamp at 254 nm and iodine staining. Flash chromatography was performed on silica gel (various granulometries, Merck). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AMX (300 MHz) apparatus at room temperature using TMS as an internal standard. The chemical shifts are reported in ppm, downfield from TMS. Abbreviations used: s, d, t, q, m, br for singlet, doublet, triplet, quadruplet, multiplet, and broad, respectively. Mass spectra were obtained with a Nermag R10-10 instrument at 70 eV. Air-or moisture sensitive reactions were conducted in oven-dried glassware and under an argon atmosphere.

*2-Ethyl-2-oxoacetylindane (**2**)*

Route 1. Selenium dioxide (123 mg, 1.11 mmol) was dissolved in 70% aqueous acetic acid (700 µl) by brief heating at 85°C. The hot solution was added into a vessel containing 2-acetyl-2-ethylindane **3** (208 mg, 1,11 mmol). The mixture was heated at 85°C for 19 h (reflux condenser; magnetic stirring) and then filtered on Celite®. The precipitate was rinsed with water and diethyl ether. The combined liquids were extracted with diethyl ether. The organic phase was washed with water, dried on sodium sulphate and evaporated till dryness. The yellow-brown oil (245 mg) consisted mainly of compound **2** (70%) according to ^{1}H-NMR and could not be further purified. It was dissolved in 12.5 ml of THF and used as such in the radiosynthesis of [^{11}C]atipamezole. This solution was stable for at least 6 months when stored at −20°C.

Route 2. Compound **6** (36 mg, 130 μmol) was heated in a mixture of 6N HCl (1 ml) and THF (1 ml) at 75°C (reflux) for 3 h. After cooling to room temperature the mixture was extracted with dichloromethane. The organic layer was dried over sodium sulphate and evaporated to give a colourless oil (100 mg). Based on ^{1}H-NMR evidence, the oil contained the desired ketoaldehyde **2** along with a substantial amount of 1-chloro-4-hydroxybutane which was inseparable.

Route 3. To 2-diazoacetyl-2-ethylindane (**10**) (3 mg, 14 μmol) in acetone (100 μl) was added dimethyldioxirane in acetone (28 μmol/ml, 700 μl), a solution that had been prepared according to Adam.[20] Immediate nitrogen development was discernible. The mixture was left at room temperature for one hour and was then evaporated till dryness leaving a yellow oil (**2**, quantitative).

^{1}H-NMR (CD_2Cl_2) : δ : 0.81 (3H, *t*, $J = 7$ Hz), 1.88 (2H, *q*, $J = 7$ Hz), 3.01 (2 H, *d*, $J = 15$ Hz), 3.48 (2H, *d*, $J = 15$ Hz), 7.12–7.20 (4 H, *m*), 9.31 (1H, *s*). GC/MS : [M] = 202.

*2-Acetyl-2-ethylindane (**3**)*

Compound **3** was synthesized from α,α′-dibromo-*o*-xylene in two steps with an overall yield of 42%, as described in the literature.[11] ^{1}H-NMR (CD_2Cl_2) : δ : 0.81 (3H, *t*, $J = 7.3$ Hz), 1.79 (2H, *q*, 7.3 Hz), 2.15 (3H, *s*), 2.83 (2H, *d*, $J = 15$ Hz), 3.35 (2H, *d*, $J = 15$ Hz), 7.09–7.18 (4 H, *m*). DCI(NH_4^+)MS : [M + H$^+$] = 189, [M + NH_4^+] = 206.

*2-Diethoxyacetylindane (**5**)*

Compound **5** was prepared from 2-bromoindane[12] and diethoxyacetic acid piperidinyl amide[13] in 23% yield as described in the literature[14]. ^{1}H-NMR (CD_2Cl_2) : δ : 1.24 (6H, *t*, $J = 6$ Hz), 3.14 (2H, *s*), 3.17 (2H, *s*), 3.60 (2H, *q*, $J = 6$ Hz), 3.70 (2H, *q*, $J = 6$ Hz), 3.80 (1H, *t* of *t*), 4.71 (1H, *s*), 7.08–7.22 (4 H, *m*). ^{13}C-NMR (CD_2Cl_2) : δ : 15.4 (CH_3), 35.9 (CH_2 benzyl), 46.4 (CH_2), 63.7 (CH), 102.8 (CH(OEt)$_2$) 124.6 (C_{Ar}), 126.8 (C_{Ar}), 142.2 (C_q), 207.1 (CO). DCI(NH_4^+)MS : [M + NH_4^+] = 266.

*2-Diethoxyacetyl-2-ethylindane (**6**)*

Compound **5** (1.575 g, 6.35 mmol) was dissolved in THF (3 ml) and cooled in a dry ice/acetone bath under an argon atmosphere. Potassium

t-butoxide (6.6 mmol) in THF (6.6 ml) was added dropwise in 30 min while stirring. Stirring was continued for 30 min at low temperature. Iodoethane (490 µl, 6.1 mmol) was then added dropwise over 10 min. The temperature was then allowed to rise to ambient over 5 h, and the mixture was stirred an additional hour at room temperature. Cold water (4 ml) was added followed by extraction with ethyl acetate. After drying the organic layer over sodium sulphate and solvent evaporation, the residue (1.75 g) was purified by flash chromatography (SiO_2, 63/200 mesh, heptane) to afford 1.162 g of a yellow oil (66% yield). ^{1}H-NMR (CD_2Cl_2) : δ : 0.80 (3H, *t*, $J = 7.5$ Hz), 1.18 (6H, *t*, $J = 7.5$ Hz), 1.83 (2H, *q*, $J = 7.5$ Hz), 2.87 (2H, *d*, $J = 16$ Hz), 3.47 (2H, *d*, $J = 16$ Hz), 3.55 (2H, *q*, $J = 7.5$), 3.62 (2H, *q*, $J = 7.5$ Hz), 4.91 (1H, *s*), 7.08–7.20 (4H, *m*). DCI(NH_4^+)MS : $[M + H^+] = 277$, $[M + NH_4^+] = 294$.

2-Methoxycarbonylindane (7)

Compound **7** was synthesized from α, α'-dibromo-*o*-xylene in three steps (overall yield 28%) as described in the literature.[16] ^{1}H-NMR (CD_3OD) : δ : 3.15 (2H, *s*), 3.18 (2H, *s*), 3.26–3.34 (1H, *t* of *t*), 3.69 (3H, *s*), 7.07–7.18 (4H, *m*). ^{13}C-NMR (CD_3OD) : δ : 37.1 (CH_2), 44.6 (CH_3) 52.4 (CH), 125.2 (C_{Ar}), 127.7(C_{Ar}), 142.7 (C_q), 177.5 (CO).

*2-Ethyl-2-methoxycarbonylindane (**8**)*

N-Isopropylcyclohexylamine (2.538 g, 18 mmol) was dissolved in dry THF (8 ml) and cooled in a dry-ice/acetone bath. *n*-Butyllithium (2.5 M in hexanes, 7.2 ml, 18 mmol) was added dropwise over 5 min with stirring. The mixture was stirred for an additional hour while cooling. Ester **7** (3.17 g, 18 mmol) was then added over 5 min, and the mixture was allowed to reach room temperature. The solution of the resulting enolate of ester **7** was then added dropwise over 10 min to a stirred solution of iodoethane (2.16 ml, 27 mmol) in a mixture of dry THF (4.5 ml) and dry DMSO (4.5 ml) maintained at room temperature by occasional cooling. Stirring was continued for one hour. The mixture was poured into ice/water, acidified with HCl and extracted with diethyl ether. The organic phase was washed with much water, to remove DMSO, and dried over sodium sulphate. After evaporation of solvent the residue (3.92 g) was subjected to flash chromatography twice (SiO_2, 63–200 mesh, heptane/EtOAc 97/3 and 40–63 mesh, heptane/EtOAc 99/1) but could not be obtained better than 35% pure. This preparation

was used as such in the subsequent hydrolysis reaction (*vide infra*). ^{1}H-NMR (CD_2Cl_2) : δ : 0.72 (3H, *t*, $J = 7.4$ Hz), 1.76 (2H, *q*, $J = 7.4$ Hz), 2.97 (2H, *d*, $J = 16.5$ Hz), 3.38 (2H, *d*, 16.5 Hz), 3.49 (3H, *s*), 7.02–7.30 (4H, *m*).

*2-Carboxy-2-ethylindane (**9**)*

To compound **8** (0.69 mmol, purity : 35%, *vide supra*) was added DMSO (10 ml) containing potassium *t*-butoxide (8 mmol). The mixture was stirred under argon at room temperature for 40 min. It was then poured into ice/water and acidified with HCl (a precipitate forms). The mixture was extracted with diethyl ether and the organic phase was washed with much water to remove DMSO. The solvent was evaporated, and the residue was taken up in 1N sodium hydroxide followed by extraction with dichloromethane. The aqueous phase was acidified with HCl and extracted with dichloromethane. After solvent evaporation the above extraction procedure was repeated once more. The residue (88 mg) was further purified with semi-preparative HPLC (Column : Symmetry C18, 7 µm; mobile phase : 10 mM sodium phosphate buffer pH 2.3/acetonitrile 55/45; 5 ml/min; UV 254 nm; retention time of **9** : 7.7 min). White solid, pure **9**; 36 mg (27%). ^{1}H-NMR (CD_2Cl_2) : δ : 0.92 (3H, *t*, $J = 7.5$ Hz), 1.81 (2H, *q*, $J = 7.5$), 2.91 (2H, *d*, $J = 16.2$ Hz), 3.45 (2, *d*, $J = 16.2$ Hz), 7.10–7.25 (4 H, *m*), 9.7–13.0 (1H, br). ^{13}C-NMR (CD_2Cl_2) : δ : 10.0 (CH_3), 31.7 (CH_2), 42.0 (CH_2 benzyl), 55,2 (C_q), 124.7 (C_{Ar}), 126.9 (C_{Ar}), 141.8 ($C_{Ar,q}$), 183.9 (COOH). DCI(NH_4^+) MS : $[M + NH_4^+] = 208$.

*2-Diazoacetyl-2-ethylindane (**10**)*

A dry solution of diazomethane in diethyl ether was prepared from Diazald® (2.5 g) according to Aldrich[24] using the ethanol-free procedure. The diazomethane concentration was estimated by addition of an aliquot to 3-nitrobenzoic acid in ethylene glycol dimethyl ether, followed by evaporation to dryness, dissolution in THF, and estimation of 3-nitrobenzoic acid methyl ester by HPLC (C18 µBondapak, Waters, 7.8 × 300 mm, MeCN/H_2O 6/4, 5 ml/min UV : 254 nm). Product **9** (32 mg, 0.17 mmol) was dissolved in dry acetonitrile (4 ml). The solution was cooled at −10°C (ethanol/dry-ice bath) under an argon atmosphere. Methanesulfonyl chloride (66 µl, 0.85 mmol) was added by syringe through a septum while stirring, followed by triethylamine (237 µl,

1.7 mmol). The mixture was stirred for another 5 minutes after which the temperature was raised to 0°C. The diazomethane solution (3.8 ml, 1.7 mmol) was added via the septum over 3 min. The temperature was then allowed to rise to room temperature over one hour. Diethyl ether (20 ml) was added and the volume of the mixture was reduced to about one third by evaporation (removal of excess diazomethane). Water (20 ml) was added, dissolving all solids, and the mixture was extracted with diethyl ether. The organic phase was washed with water, saturated sodium bicarbonate, and brine and then dried on magnesium sulphate. The residue (80 mg), obtained after evaporation of solvent, was subjected to two consecutive preparative HPLC purifications: (1) Zorbax Rx SIL, Hewlett Packard, 9.4 × 250 mm; heptane/dioxane 8/2; 5 ml/min; UV : 254 nm; collected : multiple peaks between retention times 3.0 and 4.8 min. (first, low-retention group), (2) Same column; heptane/dioxane 95/5; injected : mixture from HPLC 1; collected : pure **10** (largest peak, retention time : 6.8 min; 3 mg, 8%).). ^{1}H-NMR (CD_2Cl_2) : δ : 0.87 (3H, *t*, $J = 7.5$ Hz), 1.73 (2H, *q*, $J = 7.5$ Hz), 2.86 (2H, *d*, $J = 16.5$ Hz), 3.33 (2H, *d*, $J = 16.5$ Hz), 5.39 (1H, *s*), 7.09–7.19 (4 H, *m*). DCI(NH_4^+)MS : $[M + H^+] = 215$, $[M + NH_4^+] = 232$.

*[^{11}C]Atipamezole ([^{11}C]**1**)*

Cyclotron-produced [^{11}C]carbon dioxide[21,22] was converted into [^{11}C]methanol by passing it through a THF solution (50 µl) containing lithium aluminium hydride (5–10 µmol) cooled in an ethanol/dry ice bath.[22] After evaporation of the THF and hydrolysis with water (100 µL), the [^{11}C]methanol was distilled and passed with a nitrogen stream (20 ml/min.) through a glass tube (5 mm diameter) heated at 350°C containing a 10 mm long bed of silver-doped (10%) ceramic catalyst.[23] The resulting [^{11}C]formaldehyde was trapped in either a mixture of water (300 µl) and THF (300 µl) containing precursor **2** (14 µmol) at 0°C or in just water (300 µl) at 0°C. In the latter case a small aliquot was taken for [^{11}C]formaldehyde estimation using the dimedone method[21] after which the THF/precursor **2** solution (300 µl/14 µmol) was added. In this way the [^{11}C]atipamezole yield based on [^{11}C]formaldehyde could be calculated. The reaction mixture was taken out of the cooling bath, and zinc oxide (4 mg), suspended in concentrated ammonia (100 µl), was added. After standing for 5 min, glacial acetic acid (150 µl) was added resulting in a clear, colorless solution. The whole solution was then purified by HPLC (Xterra MS C18 column,

7 μm, 7.8 × 300 mm; 50 mM phosphate buffer pH 3.2/acetonitrile 8/2; 5 ml/min.; UV: 254 nm). The [^{11}C]atipamezole peak was collected (retention time varying between 15 and 20 min). Isolation can be achieved by basifying with 1M NaOH (15 ml) and subsequent trapping of [^{11}C]atipamezole on a SEP-PAK cartridge. After washing the cartridge with water the product can be eluted with a small amount of ethanol preferably mixed with an injectable acid buffer. The chemical identity of the product was confirmed by radio-TLC (chloroform/methanol 8/2; $R_f = 0.44$) and analytical HPLC (same system as above).

Conclusion

[^{11}C]Atipamezole can be synthesized in reasonable quantities from [^{11}C]formaldehyde and 2-ethyl-2-oxoacetylindane. In the light of the wealth of information already available on this antagonist, this may open the way to the study of the α2-adrenergic receptor system in the brain with positron emission tomography, hitherto hampered by the lack of suitable radioligands.

Acknowledgements

We wish to thank Dr. Arja Karjalainen and Dr. Antti Haapalinna of Orion Pharma, PO Box 65, FIN-02101 Espoo, Finland, for providing helpful information and an atipamezole sample, respectively, and the cyclotron operators Daniel Gouel, Christophe Lechêne and Christophe Peronne for carrying out the irradiations.

References

1. Russo-Neustadt A, Cotman CW. *J Neurosci* 1997; **17**: 5573–5580.
2. De Paermentier A. *Brain Res* 1997; **757**: 60–68.
3. Shiue C, Pleus RC, Shiue GG, *et al. Nucl Med Biol* 1998; **25**: 127–133.
4. Solin O, Enas JD, Bergman J, Haaparanta M, VanBrocklin HF, Budinger TF. *J Nucl Med* 1996; **37**: 51P.
5. Enas JD, Clark RD, VanBrocklin HF. *J Labelled Cpd Radiopharm* 1997; **40**: 628–630.
6. Hume SP, Hirani E, Opacka-Juffry J, *et al.*, *Eur J Nucl Med* 2000; **27**: 475–484.

7. Virtanen R, Savola J-M, Saano V. *Arch Int Pharmacodyn* 1989; **297**: 190–204.
8. Biegon A, Mathis CA, Budinger TF. *Eur J Pharmacol* 1992; **224**: 27–38.
9. Sjöholm B, Voutilainen R, Luomala K, Savola J-M, Scheinin M. *Eur J Pharmacol* 1992; **215**: 109–117.
10. Roeda D, Dollé F, Crouzel C. *J Labelled Cpd Radiopharm* 1997; **40**: 725–726.
11. Wong WC, Gluchowski C. *Synthesis* 1995; 139–140.
12. Porter TH, Shive W. *J Med Chem* 1968; **11**: 402–403.
13. Wohl A, Lange M. *Chem Ber* 1908; **41**: 3612–3620.
14. Karjalainen AJ, Virtanen RE, Karjalainen AL, Kurkela KOA. US Patent 1987; 4,689,339.
15. Ihmels H, Maggini M, Prato M, Scorrano G. *Tetr Lett* 1991; **32**: 6215–6218.
16. Tomiyama T, Wakabayashi S, Yokota M. *J Med Chem* 1989; **32**: 1988–1996.
17. Rathke MW, Lindert A. *J Amer Chem Soc* 1971; **93**: 2318–2320.
18. Chang FC, Wood NF. *Tetr Lett* 1964; **40**: 2969–2973.
19. Nicolaou KC, Baran PS, Zhong Y-L, *et al*., *Org Lett* 1999; **1**: 883–886.
20. Adam W, Bialas J, Hadjiarapoglou L. *Chem Ber* 1991; **124**: 2377.
21. Roeda D, Crouzel C. *Appl Radiat Isot* 2001; **54**: 935–939.
22. Crouzel C, Langström B, Pike VW, Coenen HH. *Appl Radiat Isot* 1987; **38**: 601–603.
23. Roeda D, Dollé F, Crouzel C. *J Labelled Cpd Radiopharm* 2001; **44** (Suppl. 1): 1050–1052.
24. Aldrich, Technical Information Bulletin Number AL-180.

