JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 1–10.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.871

Research Article

The synthesis of a benzamidine-containing NR2B-selective NMDA receptor ligand labelled with tritium or fluorine-18

Terence G. Hamill[1,*], John A. McCauley[2] and H. Donald Burns[1]
[1] *Merck Research Laboratories, Imaging Research Department, WP44C-2, West Point, PA 19486, USA*
[2] *Merck Research Laboratories, Medicinal Chemistry Department, WP44C-2, West Point, PA 19486, USA*

Summary

A novel tritium or flourine-18-labelled benzamidine-containing NR2B-selective NMDA receptor ligand has been synthesized. This compound was designed to contain the fluoromethoxy group to allow for the synthesis of a high specific activity, fluorine-18-labelled PET tracer for imaging studies of the NR2B receptor. In addition to the fluorine-18-labelled compound, this compound was also tritium labelled. The tritiated ligand (11 Ci/mmol) was synthesized by a gas tritiation reaction of an aryl bromide precursor. The fluorine-18 ligand (2916 Ci/mmol), which was deuterated in the fluoromethoxy group to aid in metabolic stability, was synthesized by alkylating a phenolic precursor with [^{18}F]fluoromethylbromide-d_2.

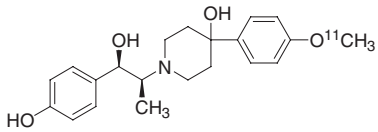
Key Words: fluorine-18; tritium; PET; NR2B; deuterium

Introduction

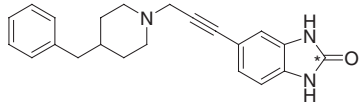
The NMDA receptor is highly expressed in the CNS and is comprised of a minimum of two different subunits, NR1 and NR2. The NR1 subunit has at least eight isoforms (NR1a–h) and the NR2 subunit has four distinct subtypes (NR2A–D).[1] It has been suggested that NR2B selective compounds may have a reduced side-effect profile when compared to NMDA receptor antagonists,[2] and have been shown to be efficacious in preclinical pain models.[3,4] Among the known NR2B-selective compounds are ifenprodil, CP-101,606, Ro-25-6981 and a novel series of benzamidines.[5–8]

*Correspondence to: T. G. Hamill, Merck Research Laboratories, Imaging Research Department, WP44C-2, West Point, PA 19486, USA. E-mail: terence_hamill@merck.com

Received 23 January 2004
Revised 26 April 2004
Accepted 18 May 2004



[^{11}C]Methoxy CP101,606



[^{11}C]5-[3-(4-benzylpiperidin-1-yl)prop--1-ynyl]-1,3-dihydrobenzo-imidazol-2-one (*=^{11}C)

Figure 1.

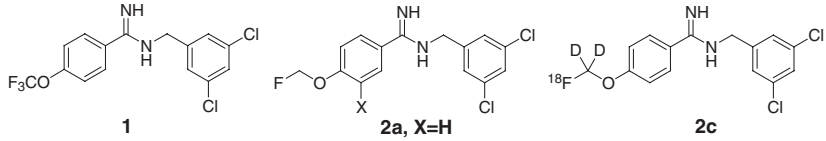


Figure 2.

A suitable NR2B-selective PET tracer would be extremely useful, making receptor imaging studies possible. At present no such ligand exists. The synthesis of a carbon-11-labelled analog of CP-101, 606 (Figure 1) has been reported,[9] although *in vivo* studies showed no apparent specific binding in mouse and monkey brains. More recently, [^{11}C]5-[3-(4-benzylpiperidin-1-yl)prop-1-ynyl]-1,3-dihydrobenzo-imidazol-2-one (Figure 1), which has high affinity and selectivity for the NR2B subtype (IC_{50} 5.3 nM) has also been reported,[10] but this tracer suffered from low and uniform brain uptake in rats and did not exhibit specific binding.

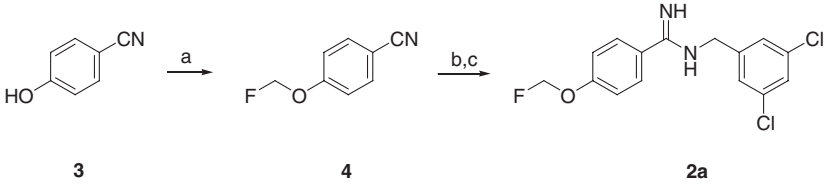
We were interested in developing NR2B-selective PET tracers for receptor occupancy studies of unlabelled NR2B-selective antagonists, and a fluorine-18-labelled tracer was attractive to us. Because of the longer half-life of flourine-18, as compared to carbon-11 (110 vs 20 min), longer imaging times with a fluorine-18-labelled tracer would be possible if the *in vivo* kinetics required longer times for a specific signal to develop. Based on the benzamidine class of compounds,[8] we have synthesized the fluorine-18-labelled tracer **2c** (Figure 2) for PET imaging studies and the tritium-labelled tracer **2b** for *in vitro* studies.

Results and discussion

The known trifluoromethoxy-containing compound **1**[8] is a high affinity (Ki 0.6 nM), NR2B-selective compound with a log *P* value of 2.9. Due to the lack of methods for producing high specific activity [^{18}F]trifluoromethoxy groups, and with the possibility of synthesizing high specific activity [^{18}F]fluoromethoxy containing compounds,[11,12] we thought compound **2a**, if

it maintained affinity and selectivity, could be labelled with fluorine-18 and would make an attractive NR2B-selective PET tracer. The lipophilicity of **2a** would also be expected to be less than that of **1**.

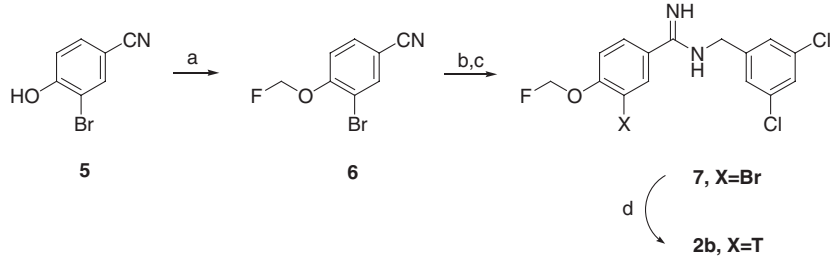
Compound **2a** was synthesized as shown in Scheme 1. Commercially available cyanophenol **3** was alkylated using chlorofluoromethane in DMF with cesium carbonate as the base. The resulting nitrile **4** was converted to **2a** via the Pinner synthesis.[13] Compound **2a** was found to have an NR2B Ki value of 1.5 nM[14] and a log *P* value of 0.9. This compound also maintained its selectivity for the NR2B subtype (NR2B Ca^{2+} influx IC_{50} (nM) 3.4. NR2A Ca^{2+} influx IC_{50} (nM) >10,000. See Reference[7] for details.). Encouraged by these properties, we proceeded to synthesize **2b** and **2c** for use in *in vitro*/*in vivo* assays and imaging studies.



3 **4** **2a**

Scheme 1. (a) FCH_2Cl, DMF, Cs_2CO_3, RT, (b) EtOH, HCl (g), 0°C–RT, (c) 3,5-dichlorobenzylamine, Et_3N, EtOH, RT

Scheme 2 shows the route followed for synthesizing **2b**, the tritium-labelled ligand. As in Scheme 1, commercially available **5** was alkylated using chlorofluoromethane. Conversion of **6** to the imidate and coupling with 3,5-dichlorobenzylamine gave **7**, the bromo-containing benzamidine precursor for the tritiated ligand. Model tritiation reactions using hydrogen gas in the presence of triethylamine led to loss of the aryl chlorides as shown by ^1H NMR and mass spectral analysis. Eliminating triethylamine from the reaction

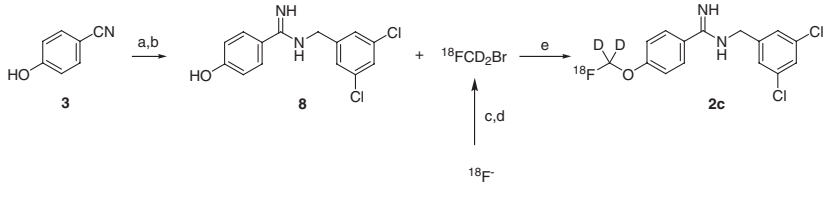


5 **6** **7, X=Br** **2b, X=T**

Scheme 2. (a) FCH_2Cl, DMF, Cs_2CO_3, RT, (b) EtOH, HCl (g), 0°C–RT, (c) 3,5-dichlorobenzylamine, EtOH, RT, (d) T_2, 10% Pd/C, DMF

mixture eliminated this side reaction. The gas tritiation reaction was carried out to give crude **2b**, which had a radiochemical purity of ~95%. Purification of the tracer gave **2b** with a specific activity of 11 Ci/mmol and > 98% radiochemical purity.

The route used for the synthesis of the fluorine-18-labelled ligand **2c** is shown in Scheme 3. As in Scheme 1, nitrile **3** was converted to the imidate and then coupled with 3,5-dichlorobenzylamine to give the phenolic precursor **8**. Because the fluoromethyl group can be metabolically labile (for benzyl fluoride see Reference[15]; for S-fluoromethyl see Reference[16]; for stable O-fluoromethyl see Reference[17])[15–17] we routinely synthesize [^{18}F]fluoromethoxy-containing tracers[12] with deuterium incorporated into the methylene group to slow defluorination.[18,19] By substituting commercially available dibromomethane-d_2 for dibromomethane, [^{18}F]FCD_2Br was synthesized and used in the alkylation reaction. In this manner, high specific activity **2c** was synthesized by alkylating **8** with [^{18}F]FCD_2Br at 100°C in DMF for 5 min with cesium carbonate as the base. After HPLC purification, **2c** was isolated with a radiochemical purity of >98% and a specific activity of 2916 Ci/mmol as measured by HPLC. The uncorrected radiochemical yield from starting fluoride was ~5% (24 syntheses). When carrying out this reaction, rather than distilling the [^{18}F]FCD_2Br until the amount of radioactivity in the precursor vessel peaked, and thus optimizing the radiochemical yield, the distillation was generally carried out until there was sufficient [^{18}F]FCD_2Br trapped to synthesize the amount of **2c** needed for the planned study. The overall radiochemical yields, starting from [^{18}F]F^-, ranged from ~2 to 10%, with the lower yields resulting from a partial distillation. In cases where the amount of trapped [^{18}F]FCD_2Br was counted ($n = 22$), the radiochemical yield of **2c** based on [^{18}F]FCD_2Br trapped was 27% (range 7–48%).



Scheme 3. (a) EtOH, HCl (g), 0°C–RT, (b) 3,5-dichlorobenzylamine, EtOH, RT, (c) K_2CO_3, Kryptofix222, MeCN, (d) CD_2Br_2, MeCN, 95°C, (e) Cs_2CO_3, DMF, 100°C, 5 min

Conclusion

We have synthesized the NR2B-selective NMDA ligands **2b** and **2c** for use in *in vitro*/*in vivo* studies of the NR2B receptor system. The tritiated ligand was

synthesized from the corresponding aryl bromide by catalytic gas tritiation to give **2b** with a specific activity of 11 Ci/mmol. The deuterium containing fluorine-18-labelled compound was synthesized by alkylating the corresponding phenol with [^{18}F]FCD_2Br to give **2c** with a specific activity of 2916 Ci/mmol. The *in vitro* and *in vivo* characterization of these ligands will be reported elsewhere.

Experimental

Materials and methods

^{1}H NMR spectra were recorded using a Varian Unity Inova 400 spectrometer or a Varian Infinity-300 spectrometer. Samples provided for accurate mass measurement were taken up in acetonitrile:water:glacial acetic acid (50:50:0.1%v/v). The solutions were analyzed by use of electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on either a Bruker Daltonics 3T or 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. External calibration was accomplished with polypropylene glycol (425 or 750). Melting points were taken using a Thomas Hoover capillary melting point apparatus or a Fisher Scientific hot stage melting point apparatus and are uncorrected. Analytical and preparative HPLC was carried out using a Waters 600E Powerline Multi Solvent Delivery System with 100 µl heads, a Rheodyne 7125 injector, a Waters 990 Photodiode Array Detector and a Gilson FC203 Microfraction collector. The aceto nitrile used for the HPLC purification and analyses was Fisher Optima grade. The [^{18}F]F^- was purchased from PETNet Pharmaceuticals Inc., North Wales, PA and was delivered on an anion-exchange resin. The HPLC radiodetector used was either a Beckman 171 Radioisotope detector with a Beckman 110B solvent delivery system and Beckman Ready Flow III scintillation cocktail (tritium) or a photodiode radiodetector (Pharmacia-Biotech, fluorine-18). For HPLC purification of the tritiated ligand, a Vydac C18 Protein and Peptide column (4.6 × 250 mm, 5 µm, The Nest Group) was used, and for HPLC purification of the fluorine-18 ligand, a C18 µBondapak column, (7.8 × 300 mm, 10 µm, Waters) was used. Solutions of tritium radioactivity were concentrated using a Jouan vacuum centrifuge. Calibration curves and chemical concentrations used to determine the specific activity of the tritium-labelled compound was determined using a Hewlett Packard Model 8452A UV/Vis Diode Array Spectrophotometer. Sample radioactivities were determined in an LKB Wallac 1410 liquid scintillation counter. The identity of labelled compounds was determined by HPLC coelution with authentic compounds. The chlorofluoromethane was purchased from Synquest and all other reagents were purchased from Aldrich Chemical Co.

Nonradioactive syntheses

*4-(Fluoromethoxy)benzonitrile (**4**).* To a solution of 4-cyanophenol **3** (4.0 g, 33.6 mmol) in DMF (50 ml) was added cesium carbonate (21.9 g, 67.2 mmol). In a separate flask, chlorofluoromethane (6.9 g, 100 mmol) was condensed at −78°C. The condensed chlorofluoromethane was transferred via canula to the 4-cyanophenol solution. The reaction mixture was stirred at room temperature for 22 h at which time HPLC analysis showed complete conversion. The reaction mixture was partitioned between Et_2O and water and the layers separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give 4-fluoromethoxy-benzonitrile (**4**) as a clear oil (4.6 g, 91% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, $J = 9.0$ Hz, 2 H), 7.15 (d, $J = 9.0$ Hz, 2 H), 5.76 (d, $J = 53.6$ Hz, 2 H) ppm; HRMS (APCI) m/z 152.0505 $[(M+H)^+$; calcd. for C_8H_7FNO: 152.0506].

*N-(3,5-Dichlorobenzyl)-4-(fluoromethoxy)benzenecarboximidamide (**2a**).* A solution of 4-fluoromethoxy-benzonitrile **4** (3.0 g, 19.9 mmol) in EtOH (40 ml) under N_2 was cooled to 0°C. HCl (g) was bubbled through the solution for 10 min and the solution was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated, diluted with Et_2O, sonicated for 5 min and filtered to give the corresponding imidate salt as a white solid.

To a solution of the imidate salt in EtOH (20 ml) at ambient temperature was added 3,5-dichlorobenzyl amine (3.49 g, 19.9 mmol) and triethylamine (3 ml). After 4 h, the reaction mixture was concentrated and purified by reverse-phase HPLC. The TFA salt of **2a** was partitioned between EtOAc/$NaHCO_3$, dried and evaporated to give the free base. A solution of HCl/Et_2O (7.0 ml, 7.0 mmol) was then added to a CH_2Cl_2 (10 ml) solution of the free base (2.3 g, 7.0 mmol). The mixture was sonicated and filtered to give the HCl salt of **2a** as a white solid (2.2 g, 30% yield, 2 steps): mp = 212−213°C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.81 (d, $J = 8.8$ Hz, 2 H), 7.50 (s, 1 H), 7.43 (s, 2 H), 7.33 (d, $J = 8.8$ Hz, 2 H), 5.88 (d, $J = 53.4$ Hz, 2 H), 4.68 (s, 2 H) ppm; HRMS (APCI) m/z 327.0439 $[(M+H)^+$; calcd. for $C_{15}H_{14}Cl_2FN_2O$: 327.0462].

*3-Bromo-4-(fluoromethoxy)benzonitrile (**6**).* To a solution of 2-bromo-4-cyanophenol **5** (4.0 g, 20.2 mmol) in DMF (50 ml) was added cesium carbonate (13.1 g, 40.4 mmol). In a separate flask, chlorofluoromethane (6.9 g, 100 mmol) was condensed at −78°C. The condensed chlorofluoromethane was transferred via canula to the 2-bromo-4-cyanophenol solution. The reaction mixture was stirred at room temperature for 48 h and was partitioned between Et_2O and water and the layers separated. The organic layer was washed with 1 M aqueous NaOH, water, brine, dried over $MgSO_4$, filtered and concentrated to give 3-bromo-4-(fluoromethoxy)benzonitrile (**6**) as a white solid (3.0 g, 64%

yield): mp = 104–105°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 2.0 Hz, 1 H). 7.63 (dd, J = 8.6, 2.0 Hz, 1 H), 7.24 (d, J = 8.6 Hz, 1 H), 5.81 (d, J = 53.0 Hz, 2 H) ppm.

*3-Bromo-N-(3,5-dichlorobenzyl)-4-(fluoromethoxy)benzenecarboximidamide (**7**)*. A solution of 3-bromo-4-(fluoromethoxy)benzonitrile **6** (600 mg, 2.61 mmol) in EtOH (10 ml) under N_2 was cooled to 0°C. HCl (g) was bubbled through the solution for 10 min and the solution was warmed to room temperature and stirred for 15 h. The reaction mixture was concentrated, diluted with Et_2O, sonicated for 5 min and filtered to give the corresponding imidate salt as a white solid.

To a solution of the imidate salt in EtOH (5 ml) at room temperature was added 3,5-dichlorobenzyl amine (460 mg, 2.61 mmol) and triethylamine (0.5 ml). After 3 h, the reaction mixture was concentrated and purified by reverse-phase HPLC. The TFA salt of **7** was partitioned between EtOAc/$NaHCO_3$, dried and evaporated to give the free base. A solution of HCl/Et_2O (1.06 ml, 1.06 mmol) was then added to a CH_2Cl_2 (2 ml) solution of the free base (430 mg, 1.06 mmol). The mixture was sonicated and filtered to give the HCl salt of **7** as a white solid (400 mg, 35% yield, 2 steps): mp = 206–207°C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.11 (d, J = 2.4 Hz, 1 H), 7.82 (dd, J = 8.7, 2.4 Hz, 1 H), 7.49–7.44 (m, 4 H), 5.94 (d, J = 52.8 Hz, 2 H), 4.67 (s, 2 H); HRMS (APCI) m/z 404.9529 [$(M+H)^+$; calcd. for $C_{15}H_{13}BrCl_2FN_2O$: 404.9567].

*N-(3,5-Dichlorobenzyl)-4-hydroxybenzenecarboximidamide (**8**)*. A solution of 4-cyanophenol **3** (500 mg, 4.2 mmol) in ethanol (10 ml) was cooled to 0°C and HCl (g) was bubbled through the reaction mixture. The solution was stirred at 0°C for 1 h and at room temperature for 1 h, giving a white opaque mixture. The mixture was filtered, rinsed with diethyl ether and dried to give the corresponding imidate salt (470 mg, 56% yield) as a white solid.

A portion of this material (100 mg, 0.50 mmol) was added to ethanol (2 ml), giving a slurry, and treated with 3,5-dichlorobenzylamine (88 mg, 0.50 mmol) and triethylamine (0.25 ml). After 3 h, the reaction mixture was concentrated and purified by reverse-phase HPLC. The TFA salt of **8** was partitioned between EtOAc/$NaHCO_3$, dried and evaporated to give the free base. A solution of HCl/Et_2O (0.31 ml, 0.31 mmol) was then added to a CH_2Cl_2 (1 ml) solution of the free base (93 mg, 0.31 mmol). The mixture was sonicated and filtered to give the HCl salt of **8** as a white solid (90 mg, 54% yield): mp = 108–111°C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.67 (d, J = 8.7 Hz, 2 H), 7.47 (s, 1 H), 7.40 (s, 2 H), 6.97 (d, J = 8.7 Hz, 2 H), 4.66 (s, 2 H) ppm; HRMS (APCI) m/z 295.0405 [$(M+H)^+$; calcd. for $C_{14}H_{13}Cl_2N_2O$: 295.0399].

Radioactive syntheses

*[^{3}H]N-(3,5-Dichlorobenzyl)-4-(fluoromethoxy)benzenecarboximidamide (***2b***).* A room temperature solution of **7** (5.9 mg, 0.011 mmol) in DMF (1.6 ml) was treated with 10% Pd/C (3.7 mg). The reaction vessel and its contents were degassed by cooling with dry ice/acetone and evacuating quickly and was then exposed to tritium gas (5 Ci). After 110 min at room temperature and atmospheric pressure, the reaction was passed through a short column of celite and rinsed with DMF (3×1 ml) and methanol (3×1 ml). The solvents were removed *in vacuo* and labile tritium was washed out by evaporation with methanol (3×2 ml). The residue was dissolved in ethanol (20 ml) to give 208 mCi of activity. An aliquot (7 mCi) was concentrated *in vacuo*, dissolved in ethanol (75 µl) for purification by HPLC (Vydac C18 Protein and Peptide column, 4.6×250 mm, 5 µm, 1 ml/min, 20 min linear gradient of 10% MeCN:H_2O(0.1% TFA) to 90% MeCN, 254 nm). Fractions (0.2 ml) were collected and the product eluted at ~17 min. Fractions containing the most radioactivity were analyzed by HPLC and the center cut was combined, concentrated *in vacuo* and diluted with ethanol (4 ml) to give 3.2 mCi of **2b** with a specific activity of 11 Ci/mmol and a radiochemical purity > 98%.

*N-(3,5-Dichlorobenzyl)-4[^{18}F]-(fluoromethoxy)benzenecarboximidamide-d_2 (***2c***).* The resin containing the $[^{18}F]F^-$ was eluted with 1.5 ml of a solution of 80:20 MeCN:Oxalate solution [0.05 ml of (200 mg $K_2C_2O_4$/3 mg K_2CO_3/5 ml H_2O) + 0.25 ml H_2O + 1.2 ml MeCN] and transferred to the reaction vessel giving 475 mCi of activity. A solution (0.2 ml) of Kryptofix222 (36 mg/ml MeCN) was added and the mixture was heated to 95°C under vacuum and argon flow to dryness. Additional aliquots of MeCN (3×0.7 ml) were used to further dry the $[^{18}F]F^-$. A solution of CD_2Br_2 (0.05 ml) in MeCN (1 ml) was added and the mixture was heated at 95°C. Argon flow was used to distill the $[^{18}F]FCD_2Br$ into a 0°C mixture of **8** (0.3 mg) in DMF (0.2 ml) containing Cs_2CO_3 (~1–2 mg). When the amount of trapped activity was sufficient, the mixture was heated at 100°C for 5 min. The reaction was diluted with H_2O (0.7 ml) and purified by HPLC (Waters C18 µBondapak, 7.8×300 mm, 10 µm, 3 ml/min, 254 nm, 30 min linear gradient, 10% MeCN:95:5:0.1 H_2O:MeCN:TFA to 80% MeCN, product elutes at ~20.5 min). The product fraction was collected in a heated round bottom flask attached to a rotary evaporator, the solvent was removed and the product was transferred to a vial using physiologic saline to give 42 mCi of **2c** in a synthesis time of 1 h. An aliquot (0.5 ml) was removed, counted and allowed to decay. The mass contained in the aliquot was determined by HPLC (254 nm) against a calibration curve of the standard to give a specific activity of 2916 Ci/mmol.

Acknowledgements

The authors thank Dr. Charles W. Ross, III and Ms. Joan S. Murphy for determination of high resolution mass spectra, Mr. Matthew Zrada for determining the log *P* value of **2a**, and Chemsyn Science Laboratories for carrying out the gas tritiation reactions.

References

1. Mori H, Mishina M. *Neuropharm* 1995; **34**: 1219–1237.
2. Taniguchi K, Shinjo K, Mizutani M, Shimada K, Ishikawa O, Menniti FS, Nagahisa A. *Br J Pharmacol* 1997; **122**: 809–812.
3. Boyce S, Wyatt A, Webb JK, O'Donnell R, Mason G, Rigby M, Sirinathsinghji D, Hill RG, Rupniak NM. *Neuropharm* 1999; **38**: 611–623.
4. Chizh BA, Headley PM, Tzchentke TM. *Trends Pharmacol Sci* 2001; **22**: 636–642.
5. Williams K. *Mol Pharmacol* 1993; **44**: 851–859.
6. Chenard BL, Bordner J, Butler TW, Chambers LK, Collins MA, De Costa DL, Ducat MF, Dumont ML, Fox CB, Mena EE, Meniti FS, Nielsen J, Pagnozzi MJ, Richter KEG, Ronau RT, Shalaby IA, Stemple JZ, White WF. *J Med Chem* 1995; **38**: 3138–3145.
7. Fischer G, Mutel V, Trube G, Malherbe P, Kew JNC, Mohacsi E, Heitz MP, Kemp JA. *J Pharmacol Exp Ther* 1997; **283**: 1285–1292.
8. Claiborne CF, McCauley JA, Libby BE, Curtis NR, Diggle HJ, Kulagowski JJ, Michelson SR, Anderson KD, Claremon DA, Freidinger RM, Bednar RA, Mosser SD, Gaul SL, Connolly TM, Condra CL, Bednar B, Stump GL, Lynch JJ, Macaulay A, Wafford KA, Koblan KS, Liverton NJ. *Bioorg Med Chem Lett* 2003; **13**: 697–700.
9. Haradahira T, Maeda J, Okauchi T, Zhang M-R, Hojo J, Kida T, Arai T, Fumihiko Y, Sasaki S, Maeda M, Suzuki K, Suhara T. *Nucl Med Biol* 2002; **29**: 517–525.
10. Roger G, Lagnel B, Besret L, Bramoulle Y, Coulon C, Ottaviani, Kassiou M, Bottlaender M, Valette H, Dolle F. *Bioorg Med Chem* 2003; **11**: 5401–5408.
11. Zheng L, Berridge MS. *Appl Radiat Isot* 2000; **52**: 55–61.
12. Bergman J, Eskola O, Lehikoinen P, Solin O. *Appl Radiat Isot* 2001; **54**: 927–933.
13. Dox AW. *Org Synth* (Col) 1932; **1**: 5–7.
14. McCauley JA, Theberge CR, Liverton NJ, Claremon DA, Claiborne CF. US Patent 6,316,474 B1, 2001. *Chem Abstr* 2001; **134**: 340508.
15. Petric A, Barrio JR, Namavari M, Huang S-C, Satyamurthy N. *Nucl Med Biol* 1999; **26**: 529–535.
16. Zessin J, Eskola O, Brust P, Bergman J, Steinbach J, Lehikoinen P, Solin O, Johannsen B. *Nucl Med Biol* 2001; **28**: 857–863.
17. Iwata R, Pascali C, Bogni A, Furumoto S, Terasaki K, Yanai K. *Appl Radiat Isot* 2002; **57**: 347–352.

18. Hamill TG, Burns HD, Eng W, Ryan C, Krause S, Gibson RE, Hargreaves RJ. *Mol Imag Biol* 2002; **4**(4)(Suppl 1): S34.
19. Schou M, Halldin C, Pike VW, Sovago J, Gulyas B, Shchukin E, Mozley D, Dobson D, Johnson DP, Innis RB, Farde L. *J Label Compd Radiopharm* 2003; **46**: S59.

