JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2002; **45**: 1011–1017.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.619

Research Article

Radiosynthesis of [^{123}I]*N*-(3-iodoprop-(2*E*)-enyl)-2α-(imino-methyl)-3β-(3′,4′-dichlorophenyl) nortropane as a potential SPET tracer for dopamine transporter

Meixiang Yu[1,*], Anu J. Airaksinen[2], Antony D. Gee[3,†], Simo Lötjönen[2], Jyrki T. Kuikka[1,5], Jouko J. Vepsäläinen[2], Jukka Hiltunen[4] and Kim A. Bergström[1]

[1] *Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, and University of Kuopio, FIN-70210, Kuopio, Finland*
[2] *Department of Chemistry, University of Kuopio, FIN-70210, Kuopio, Finland*
[3] *PET Center, Aarhus University Hospital, Norrebrogade 44, D-8000 Aarhus C., Denmark*
[4] *MAP Medical Technologies Oy, FIN-41160 Tikkakoski, Finland*
[5] *Niuvanniemi Hospital, FIN-70240, Kuopio, Finland*

Summary

The radiosynthesis of a novel tropane derivative [^{123}I]KUC-25019, [[^{123}I] *N*-(3-iodoprop-(2*E*)-enyl)-2α-(imino-methyl)-3β-(3′,4′-dichlorophenyl)nortropane], a potential inhibitor of the dopamine transporter is reported. The synthetic routes include the preparation of standard reference, the stannyl precursor and the ^{123}I-labeling synthesis. The no-carrier-added ^{123}I-labeling has about 20% yield, the specific activity of [^{123}I]KUC-25019 is >107 GBq/μmol and the radiochemical purity of [^{123}I] KUC-25019 is >95%.
Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: KUC-25019; dopamine transporter; tropane analog: SPET: ^{123}I

*Correspondence to: M. Yu, Barlett Hall 500R, Department of Radiology, Massachusetts General Hospital, Boston, MA 02114, USA. E-mail: ymeixiang@partners.org
†Present address: Addenbrooke's Centre for Clinical Investigation, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2GG, U.K.

Contract/grant sponsor: National Technology Agency (TEKES, Helsinki).
Contract/grant sponsor: Kuopio University Hospital; contract/grant numbers: 5031302, 5031301.

Copyright © 2002 John Wiley & Sons, Ltd.

Received 7 January 2002
Revised 30 April 2002
Accepted 31 May 2002

Introduction

Recently, the imaging of the dopamine transporter (DAT) *in vivo* with single-photon emission tomography (SPET) or positron emission tomography (PET) has increased greatly because of a successful development of anumerous of new tropane analogs.[1] Among them, [^{11}C]β-CFT (WIN 35-428)[2] and [^{123}I] β-CIT[3] (compound A, in Figure 1) have been used in clinical brain studies, such as in Parkinson's disease. Recently it is found that a new compound [^{123}I]PE2I[4] (compound B, in Figure 1) is a selective ligand for imaging the DAT with different kinetic properties than [^{123}I]β-CIT. However, cocaine analogs containing 3-carboxylic acid functionalities in the exo-(β-) conformation are known to exhibit powerful stimulant effects.[5] A new cocaine congeners NS 2214 (compound C in Figure 1) having 3-substituted aldoxime prosthetic group in the endo- (α-) configuration has been reported recently to have high DAT affinity and a low toxicity.[5,6]

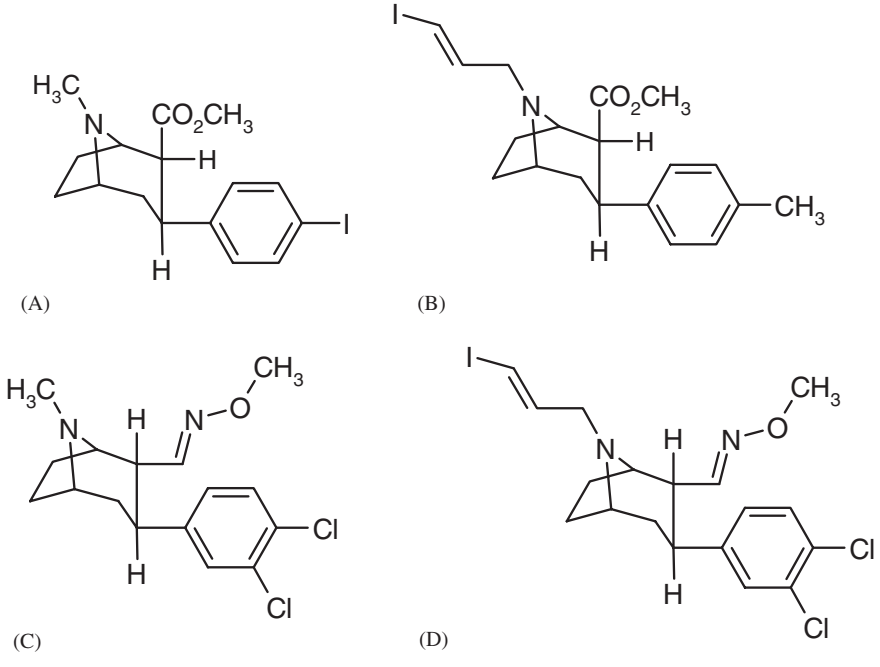


Figure 1. Chemical structures of β-CIT (A), PE2I (B), NS 2214 (C) and KUC-25019 (D)

Copyright © 2002 John Wiley & Sons, Ltd.

We have synthesized a new NS2214 analog, *N*-(3-iodoprop-(2*E*)-enyl)-2α-(imino-methyl)-3β-(3′,4′-dichlorophenyl) nortropane (KUC-25019, compound D in Figure 1). This ligand with a 3-substituted aldoxime prosthetic group in the endo-(α-) configuration may have lower toxicity than those cocaine analogs (such as β-CIT, β-CFT) containing 3-carboxylic acid functionalities in the exo-(β-) conformation. KUC-25019 can be labeled with ^{123}I and may be useful in the imaging of DAT.

Materials and Methods

All chemicals and solvents were of commercial quality and were purified following the standard procedures if necessary. The alkylating agent 3-(tributylstannyl)prop-(2*E*)-enyl chloride (compound A in Figure 2) was prepared by chlorination of pure 3-(tributylstannyl)prop-(2*E*)-en-1-ol with triphenylphosphine and carbon tetrachloride.[7] The pure

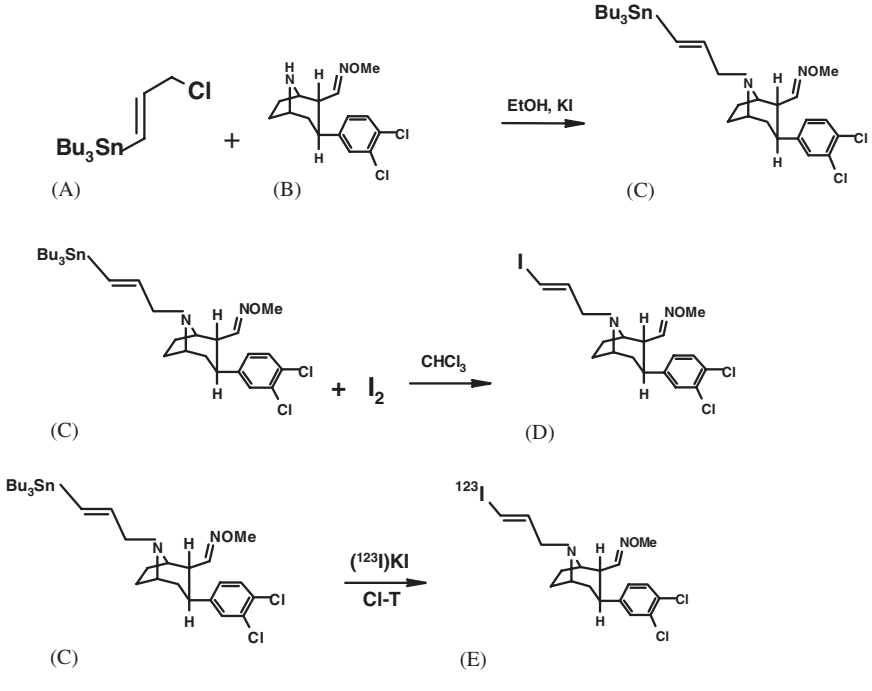


Figure 2. Synthesis of the precursor (C), KUC-25019 (D) and the radiolabelled KUC-25019 (*E*)

Copyright © 2002 John Wiley & Sons, Ltd.

(*E*)-stannyl alcohol was obtained by hydrostannylation of propargyl alcohol[8] followed by flash chromatography purification using petroleum ether/ethyl acetate (9/1).[9] 2α-(Imino-methyl)-3β-(3′,4′-dichlorophenyl) nortropane was kindly offered by Neurosearch A/S (Smedeland, Denmark) and was confirmed by NMR.

^{1}H NMR spectra were obtained on a Bruker 400 MHz spectrometer. $CDCl_3$ was used as a solvent, and the chemical shifts were reported in ppm with a reference to internal TMS. Flash chromatography was used for routine purification of reaction products using silica gel (230–400 mesh).

N-[3-(Tri-N-butylstannyl)prop-(2E)-enyl]-2α-(imino-methyl)-3β-(3′,4′-dichlorophenyl) nortropane

2α-(Imino-methyl)-3β-(3′,4′-dichlorophenyl) nortropane (compound B in Figure 2) 32 mg (0.10 mM) and 3-(tributylstannyl)prop-(2E)-enyl chloride (compound A in Figure 2, 55 mg, 0.15 mM) were dissolved into 10 ml absolute EtOH containing 1.0 ml dry triethyl amine and a catalytic amount of KI. The mixture was refluxed under nitrogen atmosphere for 14 h. The solvent was evaporated and the residue was purified by flash chromatography (petroleum ether 40–65°C:AcOEt, 8:2) to give a colorless oil product (22.5 mg, 35%).

N-[3-Iodoprop-(2E)-enyl]-2α-(imino-methyl)-3β-(3′,4′-dichloro-phenyl) nortropane

Stannyl derivative (21 mg) (compound C in Figure 2, 0.033 mM) was dissolved in 5 ml dry $CHCl_3$, and the resulting mixture was cooled in ice-water bath. A solution of iodine in $CHCl_3$ (0.5 M) was then added dropwise to the stirred mixture until a color solution resulted. The reaction solution was washed with saturated NaCl solution, dried (anhydrous Na_2SO_4) and evaporated. The residue was purified by flash chromatography (Et_2O) to give an oil product (7.5 mg, 47%).

No-carrier-added (NCA) [^{123}I] N-(3-iodoprop-(2E)-enyl)-2α-(imino-methyl)-3β-(3′,4′-dichlorophenyl) nortropane

NCA ^{123}I solution (130 µl) (15.2 mCi, specific activity 35–280 Ci/mg, PSI, Switzerland) was added to the stannyl precursor solution (100 µg in 100 µl EtOH) in a reaction vial. After addition of 100 µl 0.2 M HCl,

Copyright © 2002 John Wiley & Sons, Ltd.

100 µl chloramine-T (1 mg/ml) was added. The reaction mixture was kept at room temperature. After 5 min, 300 µl of HPLC solvent (acetonitrile/10 mM phosphoric acid, 1/1 v/v) was added and the reaction mixture was injected into the semipreparative HPLC RP18 (HPLC Technology, Macclesfield, UK) column (25 cm × 4.6 cm) using above HPLC solvent system at 4 ml/min. The radioactive peak with a retention time similar to a reference standard was collected. After evaporation, the residue was dissolved in ethanol and phosphate buffer in order to formulate an injection solution. The product was sterilized by filtration through a 0.2-µm filter. The final product contained < 15 % (w/w) ethanol.

Radiochemical Purity Determination

The radiochemical purity of the tracer was assayed with a HPLC system consisting of a Packard (Packard Instrument Co., Meriden, CT, USA) radioisotope detector with computer data acquisition.[10] The HPLC system is the same as above.

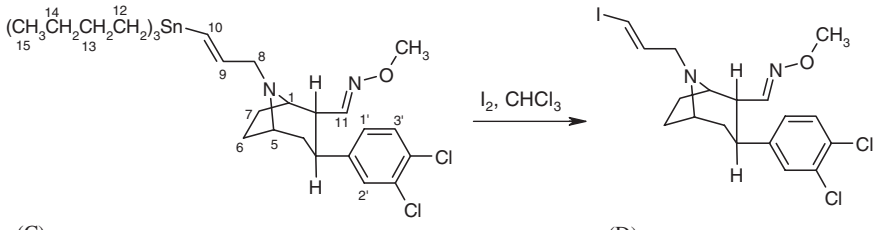
Results and Discussion

Organic synthesis and radiolabeling

The tributyltin precursor (compound C in Figure 2) was prepared by reacting 3-(tri-*n*-butylstannyl)prop-(2*E*)-enyl chloride (compound A in Figure 2 with nortropane (compound B in Figure 2) by the same method as reported.[11] The alkylating agent A was prepared by chlorination of pure 3-(tri-*n*-butylstannyl)prop-(2*E*)-en-1-ol with triphenylphosphine and carbon tetrachloride.[7,9] The pure (*E*)-stannyl alcohol was obtained by hydrostannylation of propargyl alcohol[8] followed by flash chromatography separation using petroleum ether/ethyl acetate (9/1).[9] The reference compound *N*-(3-iodoprop-(2*E*)-enyl)-2α-(iminomethyl)-3β-(3′,4′-dichlorophenyl) nortropane was obtained by iododestannylation of its stannyl precursor (compound C in Figure 2) by treatment with iodine in dry chloroform. All these organic synthesis reactions were well done, and Figure 3 showed the NMR data of the tributyl precursor and the standard KUC-25019.

The radiochemical labeling yield of [^{123}I]KUC-25019 was about 20% calculated by dividing the radioactivity in the final product by the radioactivity in the NCA ^{123}I vial, corrected for decay ($T_{1/2}$ 13.2 h). The specific radioactivity of the product was > 107 GBq/µmol. The

Copyright © 2002 John Wiley & Sons, Ltd.



(C) (D)

C: ^{1}H NMR ($CDCl_3$): δ (ppm) 0.90 (t, 9H^{15}, J = 7.3 Hz), 1.26 - 2.10 (m, 24 H$^{12\text{-}14,4,6,7}$), 2.81 - 2.85 (m, 2H^{2,3}), 3.16 (d, 2H^{8}, J = 4.7 Hz), 3.32 (m, 1H^{5}), 3.35 (dm 1H^{1}, J = 6.0 Hz), 3.70 (s, 3H), 5.95 – 6.35 (m, 2H^{9,10}), 7.02 (d, 1H^{11}, J = 5.3 Hz), 7.07 (dd, 1H$^{1'}$, J = 8.3 Hz, J = 2.1 Hz), 7.30 – 7.35 (m, 2H$^{2',3'}$).

D: ^{1}H NMR ($CDCl_3$): δ (ppm) 1.40 – 2.05 (m, 6 H^{4,6,7}), 2.78 – 2.84 (m, 2H^{2,3}), 3.03 (d, 2H^{8}, J = 6.2 Hz), 3.29 (m, 1H^{5}), 3.32 (dm, 1H^{1}, J = 6.1 Hz), 3.72 (s, 3H), 6.28 (dt, 1H^{10}, J = 14.6 Hz, J = 1.5 Hz), 6.61 (ddd, 1H^{9}, J = 14.6 Hz, J = 6.5 Hz, J = 6.2 Hz), 7.02 (d, 1H^{11}, J = 5.5), 7.06 (dd, 1H$^{1'}$, J = 8.4 Hz, J = 2.0 Hz), 7.31 – 7.36 (m, 2H$^{2',3'}$).

Figure 3. NMR data for KUC-25019 and its stannyl precursor

radiochemical purity of [^{123}I] KUC-25019 was >95% based on the radio-HPLC analysis of the purified product. Free ^{123}I with a retention time of 1.6–1.9 min was identified as impurity. The product was eluted out with retention time of 10 min as determined by reference compound. The labeling yield (20%) was low probably due to the decomposition of the precursor (impurity was determined afterwards by NMR). The demonstrated radiosynthesis method was good enough to obtain sufficient amount of [^{123}I]KUC-25019 for the animal study which will be done in the future.

Acknowledgements

The study was supported by National technology Agency (TEKES, Helsinki) and Kuopio University Hospital (5031302, 5031301)

References

1. Singh S. *Chem Rev* 2000; **100**: 925–1024.
2. Rinne JO, Laihinen A, Någren K, Ruottinen H, Ruotsalainen U, Rinne UK. *Synapse* 1995; **21**: 97–103 [2.838].

Copyright © 2002 John Wiley & Sons, Ltd.

3 Rinne JO, Kuikka JT, Bergström KA, Rinne UK. *Parkinsonism Relat Disorders* 1995; **1**: 47–51.
4. Kuikka JT, Baulieu JL, Hiltunen J, *et al*. *Eur J Nucl Med* 1998; **25**(5): 531–534.
5. Gee AD, Moldt P, Gjedde A. *J Label Compd Radiopharm* 1997; **39**: 959–972.
6. Neumeyer JL, Tamagnan G, Wang S, *et al*. *J Med Chem* 1996; **39**: 543–548.
7. Goodman MM, Kung M-P, Kabalka GW, Kung HF, Switzer R. *J Med Chem* 1994; **37**: 1535–1542.
8. Jung ME, Light LA. *Tetrahedron Lett* 1982; **23**: 3851–3854.
9. Emond P, Garreau L, Chalon S, *et al*. *J Med Chem* 1997; **40**: 1366–1372.
10. Bergström KA, Halldin C, Lundkvist C, *et al*. *Hum Psychopharmacol* 1996; **11**: 483–490.
11. Swahn C-G, Halldin C, Gunther I, Patt J, Ametamey S. *J Label Compd Radiopharm* 1996; **38**: 675–685.

Copyright © 2002 John Wiley & Sons, Ltd.