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Synthesis of [^{123}I]N',N'-Dimethyl-6-Methyl-(4'-Iodophenyl)Imidazo[1,2-a]Pyridine-3-acetamide for the Study of Peripheral Benzodiazepine Receptors using SPECT

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SUMMARY

The [^{123}I] labelled imidazo[1,2-a]pyridine [^{123}I]iodozolpidem **4** was found to exhibit preferential activity towards Peripheral rather than Central Benzodiazepine receptors *in vivo* and was synthesised for the potential study of the Peripheral Benzodiazepine Receptors (PBR) using SPECT. [^{123}I]Iodozolpidem was prepared from the corresponding tributyl tin precursor by iododestannylation with Na[^{123}I] in the presence of peracetic acid or chloramine-T. Purification by semipreparative C-18 RP HPLC gave the product in radiochemical yields of 60-85%. The product was obtained in > 97% chemical and radiochemical puritiy with a specific activity > 80 GBq /μmol.

Key Words: Peripheral Benzodiazepine Receptor, Zolpidem, Iodine-123, SPECT.

INTRODUCTION

The peripheral benzodiazepine receptors (PBR), are distinct from the central benzodiazepine receptors in their pharmacology, subcellular location and biological function (1,2,3,4). They are primarily located on the outer mitochondrial membrane of cells in peripheral organs such as kidney, heart, adrenal cortex, testis, and ovaries. In the brain they are mostly found in glial cells and olfactory bulbs (5,6,7). Although

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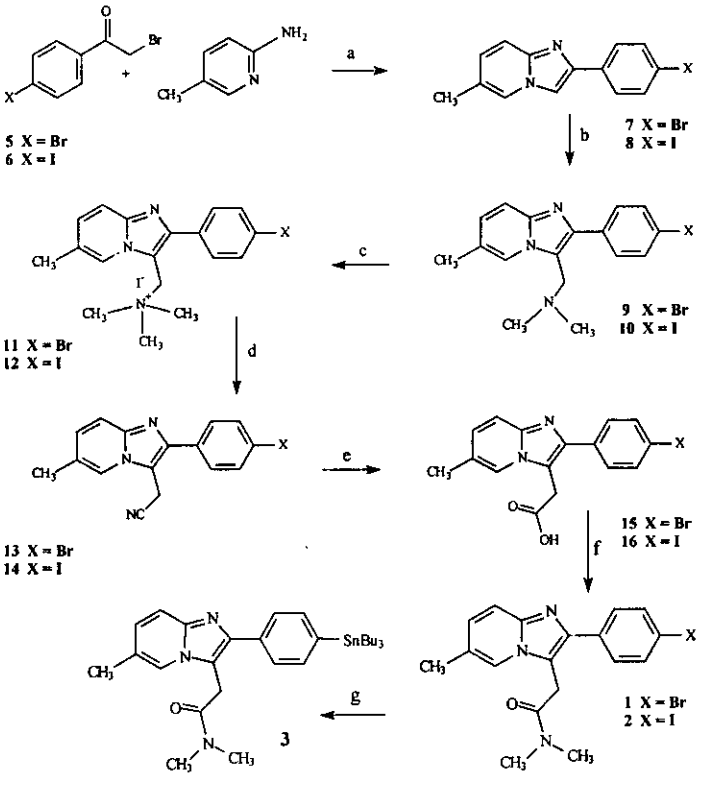
their exact function is unknown they have been implicated in cell differentiation (8), steroidogenesis (9) and calcium homeostasis (10). Several classes of ligands have been shown to exhibit high affinity binding to the PBR, the most widely investigated being the benzodiazepine Ro 5-4864 (1,2) and the isoquinoline PK-11195 (11). Radiolabelled analogues of PK 11195 have been used to map PBR receptors in the human heart, brain and endocrine tissue. Furthermore, radioligands for the PBR have been proposed for development as potential probes for tumours and in the study of neurodegenerative diseases using PET and SPECT (8, 12-14). Several other classes of compounds such as the imidazo[1,2-a]pyridine Alpidem (15) and the structurally related imidazo[1,2-b]-pyridazines (16) also displayed high affinity binding to the PBR in rat kidney mitochondrial membranes. We have recently prepared several halogenated imidazo[1,2-a]pyridines (17, 18, 19) and imidazo[1,2-b]-pyridazines (20) for evaluation as potential probes for the PBR. Here we report the synthesis of the [^{123}I] labelled imidazo[1,2-a]pyridine [^{123}I]N',N'-dimethyl-6-methyl-(4'-iodophenyl)imidazo[1,2-a] pyridine-3-acetamide **4** as a potential SPECT imaging agent for the PBR.

RESULTS AND DISCUSSION

The 4'-bromophenyl and 4'-iodophenyl imidazopyridines **1** and **2** were synthesized by modified literature methods (21) (Scheme 1). Briefly, condensation of α-bromo-4'-bromoacetophenone **5** or α-bromo-4-iodoacetophenone **6** with 2-amino-5-methyl-pyridine gave the corresponding imidazo[1,2-a]pyridine adducts **7** and **8**. Treatment of **7** or **8** with formaldehyde and dimethylamine in acetic acid yielded the N-dimethyl derivatives **9** and **10** which upon treatment with methyl iodide provided the alkylated quaternary ammonium salts **11** and **12**. Nucleophilic displacement of these salts with KCN in a refluxing mixture of ethanol water (1:1) yielded the nitriles **13** and **14** which upon hydrolysis gave the corresponding carboxylic acids **15** and **16**. Activation of the acids with 1,1'-carbonyl diimidazole (CDI) followed by reaction with dry dimethyl amine yielded the 4'-bromophenyl- and 4'-iodophenyl-imidazopyridines **1** and **2** respectively. The corresponding tributyl stannane **3** was prepared by treatment of the 4'-bromophenyl derivative **1** with bistributyltin and palladium tetrakistriphenyl-phosphine in refluxing toluene for 12h.

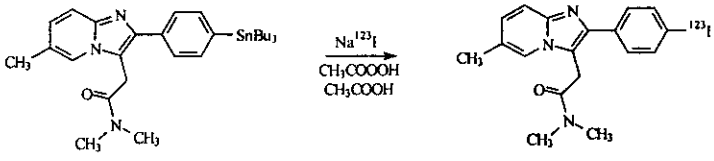


Scheme 1

Reagents. a: $NaHCO_3$, ethanol; b: HCO_2H, $(CH_3)_2NH$, acetic acid; c: CH_3I, benzene; d: KCN, ethanol-water; e: acetic acid-HCl; f: CDI, THF, $(CH_3)_2NH$; g: $Bu_3SnSnBu_3$, $Pd(PPh_3)_4$, toluene, reflux.

SYNTHESIS AND PURIFICATION OF [^{123}I]IODOZOLPIDEM

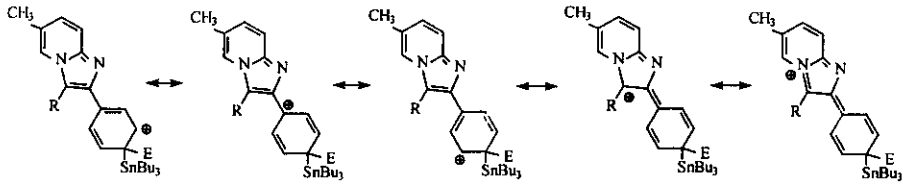
[^{123}I]Iodozolpidem **4** was prepared by iododestannylation reactions with Na[^{123}I] in the presence of peracetic acid or chloramine-T. The optimum reaction conditions were obtained when solutions of the tributyltin precursor in acetic acid were treated with Na^{123}I followed by a 5% solution of peracetic acid at room temperature (Scheme 2).



3 **4**

Scheme 2

After quenching with $Na_2S_2O_5$ and neutralisation with $NaHCO_3$ the reaction mixture was purified by reverse phase HPLC using ethanol:water 1:1 at a flow rate of 3 ml/min. Under these conditions **4** was collected at R_t = 25 min in radiochemical yields of 75-85% (n=12) and radiochemical purity exceeding 97%. The specific activity was greater than 80 GBq/μmol based on the detection limits of the HPLC system. Lower radiochemical yields (60-75%) were obtained when the iododestannylation reactions were performed in ethanol and Chloramine-T in 1M HCl as the oxidising agent. These reactions were found to be pH dependent with yields decreasing as the pH increased until no product was formed in the absence of HCl or in buffer solutions at pH>4.5. Furthermore, in reactions with Chloramine-T/HCl no radioactive product corresponding to **4** could be detected either by HPLC or radio-TLC unless the reaction mixtures were first quenched with fresh solutions of $Na_2S_2O_5$ and $NaHCO_3$ and the yellow colour of the reaction mixture discharged suggesting the formation of a stabilised intermediate at low pH.



E= H, ^{123}I

Figure 1

Although this intermediate was not identified the possible formation of a resonance stabilised σ-complex resulting in a quaternary ammonium species (Fig 1) at low pH could not be excluded. No differences were observed in either quenched or unquenched solutions when the reactions were carried out with peracetic acid in acetic acid at higher pH. The use of chloramine-T also resulted in the formation of a UV active product at Rt = 20 min.

MATERIALS AND METHODS

All reagents were purchased from commercial sources and were used without further purification. ^{1}H-NMR spectra were obtained on a Jeol FX400 NMR spectrometer.

Mass spectra were performed on a VG Quattro Triple Quadrupole in Electrospray mode in acetonitrile. Melting points were carried out on a Gallenkamp melting point apparatus and are uncorrected. Elemental analysis were performed on a Carlo Erba 1106 Elemental Analyser by the Australian National University (Canberra, Australia). Chromatographic separations were carried out on an Alltech semipreparative RP C-18 column (10μ, 10mm x 250 mm) using a Waters 510 pump, a Spectrophysics-Linear UV detector set at 254 nm and an on line NaI-Berthold radioactivity detector. No carrier added $Na^{123}I$ was produced by the National Medical Cyclotron in Sydney, Australia using the Xe(p,2n) reaction in 0.1M NaOH.

CHEMICAL SYNTHESIS

6-Methyl-2-(4'-bromophenyl)imidazo[1,2-a]pyridine (7). A mixture of α-bromo-4-bromoacetophenone (5g, 18.0 mmol) and 5-methylpyridine-2-amine (1.95g, 18.0 mmol) in ethanol (100ml) was heated to reflux for 2 h. After cooling the mixture was treated with $NaHCO_3$ (1g, 10 mmol) and heated to reflux for another 5 h. The mixture was cooled and the resultant suspension filtered, washed with ethanol, water and dried. Recrystallisation (hexane) gave 7 as a white solid m.p. 212-214° (2.8g, 55%). ^{1}H-NMR δ ($CDCl_3$) 2.32 (s, 3H, CH_3), 7.05, (dd, $J_{7,8}$= 9.0, $J_{7,5}$= 1.5 Hz, H7), 7.53 (dd, $J_{8,7}$= 9.0, $J_{8,5}$= 3 Hz, H8), 7.54 (d, J= 8.7 Hz, 2H, Ar), 7.76 (s, H3), 7.81 (d, J=8.7 Hz, 2H, Ar), 7.89, (s, H5). MS (ES) m/z: 289 (M^{+2}), 287, 284. Anal. calc'd for $C_{14}H_{11}N_2Br$: C, 58.6; H, 3.9; N, 9.8 %. Found C, 58.8; H, 3.3; N, 9.3 %.

6-Methyl-2-(4'-iodophenyl)imidazo[1,2-a]pyridine (8). Reaction of α-bromo-4-iodoacetophenone (5g, 15.4 mmol) and 5-methylpyridine-2-amine (1.66g, 15.4 mmol) as above gave **8** as a white solid (hexane) m.p. 212-214° (3.1g, 60%). ^{1}H-NMR δ ($CDCl_3$) 2.34 (s, 3H, CH_3), 7.06 (dd, $J_{7,8}$=9.0, $J_{7,5}$= 1.5 Hz, H7), 7.59 (d, $J_{8,7}$= 9.0 Hz, H8), 7.69 (d, J= 8.7Hz, 2H, Ar), 7.75 (d, J=8.5Hz, 2H,Ar), 7.78 (s, H3), 7.91 (s, H5). MS (ES) m/z: 335 (M^+). Anal. calc'd for $C_{14}H_{11}N_2I$: C, 50.3; H, 3.3; N, 8.4 %. Found C, 50.6; H, 3.0; N, 8.4 %.

6-Methyl-2-(4'-bromophenyl)-3-dimethylaminomethylimidazo[1,2-a] pyridine (9). A mixture of 7 (5g, 17.4 mmol), aqueous formaldehyde (37%, 0.10mol, 9ml), and aqueous dimethylamine (40%, 22ml) in acetic acid (60ml) was stirred at 55° for 24 h.

The mixture was evaporated to dryness and the residue taken up in chloroform (80ml). The chloroform layer was washed with 2N HCl (3 x 75 ml) and the combined aqueous layers basified to pH 12. The resultant precipitate was recrystallised to give **9** as a white solid (ethyl acetate) m.p. 160-162° (4.2g, 70%). ^{1}H-NMR δ ($CDCl_3$) 2.25 (s, 6H, $N(CH_3)_2$), 2.37 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 7.07, (dd, $J_{7,8}$= 9.0, $J_{7,5}$= 1.5 Hz, H7) 7.52 (d, $J_{8,7}$= 9.0 Hz, H8), 7.58-7.61 (m, 2H, Ar), 7.65-7.70 (m, 2H, Ar), 8.1 (s, H5). MS (ES) m/z: 346 (M^{+2}), 344, 317, 302, 299. Anal. calc'd for $C_{17}H_{18}N_3Br$: C, 59.3; H, 5.2; N, 12.2 %. Found C, 59.4; H, 5.2; N, 11.8 %.

6-Methyl-2-(4'-iodophenyl)-3-dimethylaminomethylimidazo[1,2-a]pyridine (10) was prepared as above as a pale yellow solid m.p. 148-150° (3.8g, 80%). ^{1}H-NMR δ (DMSO-d_6) 2.16 (s, 6H, $N(CH_3)_2$), 2.32 (s, 3H, CH_3), 3.83 (s, 2H, CH_2), 7.13 (dd, $J_{7,8}$=9.3, $J_{7,5}$= 1.7 Hz, H7) 7.49 (d, $J_{8,7}$= 9.2 Hz, H8), 7.67 (d, J=8.4 Hz, 2H, Ar), 7.81 (d, J=8.4 Hz, 2H, Ar), 8.30 (s, H5). MS (ES) m/z: 393 (M^{+2}), 347, 97, 90. Anal. calc'd for $C_{17}H_{18}N_3I$: C, 52.2; H, 4.6; N, 10.7 %. Found C, 52.0; H, 4.6; N, 10.4 %.

6-Methyl-2-(4'-bromophenyl)-3-dimethylaminomethylimidazo[1,2-a]pyridinyl methiodide (11). A mixture of **9** (5g, 14.5 mmol) and methyl iodide (2.5ml) in benzene (60ml) was stirred for 72 h at room temperature in the dark. The resultant white suspension was filtered, washed with ether and dried to give the methiodide salt m.p. 186-188° (6.7 g, 95%). ^{1}H-NMR δ (DMSO-d_6) 2.88 (s, 9H, $N(CH_3)_3$), 2.38 (s, 3H, CH_3), 5.19 (s, 2H, CH_2), 7.35 (dd, $J_{7,8}$=9.1, $J_{7,5}$ =1.4 Hz, H7) 7.66 (d, J=8.6 Hz, 2H, Ar), 7.69 (d, $J_{8,7}$ =9.2, H8), 7.79 (d, J=8.4 Hz, 2H, Ar), 8.8 (s, H5). MS (ES) m/z: 300 [M-186 ($N(CH_3)_3I$)]. Anal. calc'd for $C_{18}H_{21}N_3IBr$: C, 44.4; H, 4.3; N, 8.6 %. Found C, 44.1; H, 4.1; N, 8.2 %.

6-Methyl-2-(4'-iodophenyl)-3-dimethylaminomethylimidazo[1,2-a]pyridinylmethiodide (12) was prepared from **10** as above in 95% (5.2g) yield, m.p. 178-180°. ^{1}H-NMR δ (DMSO-d_6) 2.38 (s, 3H, CH_3), 2.88 (s, 9H, $N(CH_3)_3$), 5.19 (s, 2H, CH_2), 7.32-7.36, (m, H7) 7.64 (d, J= 8.5Hz, 2H, Ar), 7.66 (d, $J_{8,7}$=9.0, Hz, H8), 7.86 (d, J=8.4Hz, 2H, Ar), 8.8 (s, H5). MS (ES) m/z: 347 [M-186 ($N(CH_3)_3I$)].

6-Methyl-2-(4'-bromophenyl)imidazo[1,2-a]pyridine-3-acetonitrile (13). The methiodide salt (**11**) (5g, 10.3mol) and KCN (2.9g, 41.2 mmol,) were heated to

reflux in a 1:1 mixture of ethanol and water (110ml) for 24 h. The solvent was concentrated and the resultant solid filtered and recrystallised (ethanol) to give the nitrile **13** as a white solid m.p. 190-193° (2.4g, 70 %). ^{1}H-NMR δ (DMSO-d_6) 2.43 (s 3H, CH_3), 4.11 (s, 2H, CH2), 7.19 (dd, $J_{7,8}$=9.2 Hz, $J_{7,5}$= 1.5 Hz, H7) 7.57 (d, J=8.0 Hz, 2H, Ar), 7.60 (m, 1H, H8), 7.63 (d, J=7.8Hz, 2H, Ar), 7.82 (s, H5). MS (ES) m/z: 344 (M+H_2O). Anal. calc'd for $C_{16}H_{22}N_3Br$: C, 58.9; H, 6.8; N, 12.9 %. Found C, 58.9; H, 6.5; N, 12.9 %.

6-Methyl-2-(4'-iodophenyl)imidazo[1,2-a]pyridine-3-acetonitrile (14). Reaction of the methiodide salt (**12**) (3g, 5.6 mmol) with KCN (1.6g, 22.5mmol) as above gave **14** as a white solid m.p. 242-244° (1.3g, 70%). ^{1}H-NMR δ (DMSO-d_6) 2.31 (s 3H, CH_3), 3.92 (s, 2H, CH2), 7.14 (d, $J_{7,8}$=9.3 Hz, H7) 7.49 (d, $J_{8,7}$=9.2 Hz H8), 7.60 (d, J=8.2Hz, 2H, Ar), 7.82 (d, J=8.2Hz, 2H, Ar), 8.16 (s, H5). MS (ES) m/z: 392 (M^++ H_2O). Anal. calc'd for $C_{16}H_{22}N_3I$: C, 51.5; H, 5.9; N, 11.3 %. Found C, 51.3; H, 5.7; N, 11.4 %.

6-Methyl-2-(4'-bromophenyl)imidazo[1,2-a]pyridine-3-acetic acid (15). The nitrile **13** (2.6g, 8.0 mmol) was heated to reflux in a mixture of concentrated hydrochloric acid and acetic acid (1:1) 70 ml for 16 h. The mixture was evaporated to dryness and the residue basified with aqueous NaOH. The precipitated solid was filtered and the filtrate acidified with acetic acid. The resultant solid was filtered, washed with water and dried to give the carboxylic acid **15** as a white solid 2.7g, 85% m.p. 228-230°. ^{1}H-NMR δ (DMSO-d_6). 2.46 (s, 3H, CH_3), 4.25 (s, 2H, CH2), 7.67-7.70 (m, 2H, Ar), 7.85 (d, $J_{7,8}$=9.1 Hz, H7), 7.84-7.86 (m, 2H, Ar), 7.91 (d, $J_{8,7}$ =9.7 Hz, H8), 8.78 (s, H5). MS (ES) m/z: 348 (M^{+3}), 347 (M^{+1}), 345. Anal. calc'd for $C_{16}H_{13}N_2O_2Br$ C, 55.7; H, 3.8; N, 8.1 %. Found C, 55.7; H, 3.6; N, 8.0 %.

6-Methyl-2-(4'-iodophenyl)imidazo[1,2-a]pyridine-3-acetic acid (16). Hydrolysis of the nitrile **14** (2g, 5.3mmol) as above gave the acid **16** as a white solid m.p. 208-210° (1.5g, 70%). ^{1}H-NMR δ (DMSO-d_6) 2.29 (s, 3H, CH_3), 3.89 (s, 2H, CH2), 7.10 (dd, $J_{7,8}$= 9.2, $J_{7,5}$=1.6 Hz, H7) 7.47 (d, $J_{8,7}$= 9.2 Hz, H8), 7.65 (d, J=8.4Hz, 2H, Ar), 7.79 (d, J=8.4Hz, 2H, Ar), 8.19 (s, H5). MS (ES) m/z: 394 (M^{+2}), 393 (M^{+1}), 391, 348, 347, 127, 97, 89, 62, 59. Anal. calc'd for $C_{16}H_{13}N_2O_2I$.HCl C, 44.8; H, 3.3; N, 6.5 %. Found C, 45.0; H, 2.9; N, 6.3 %.

6-Methyl-2-(4'-bromophenyl)-3-(N,N-dimethyl)imidazo[1,2-a]yridine-3-acetamide (1). A suspension of the acid **15** (2g, 5.8 mmol) in dry THF (100ml) was treated with CDI (1.3g, 7.0 mmol) and the resultant mixture stirred for 1 h at room temperature and for 1 h at 55°. After cooling the solution was treated with a (1M) solution of dimethyl amine (0.65g, 6.4 mmol) in THF. The mixture was stirred for one hour and the solvent evaporated. The residue was taken up in CH_2Cl_2 washed with 10% $NaHCO_3$ and the aqueous layer extracted 3 x with CH_2Cl_2 (dichloromethane). The organic layers were dried and evaporated to give the crude product which was recrystallised from CH_2Cl_2 to give **1** as a white solid m.p. 204-205° 1.6g, 72%. ^{1}H-NMR δ ($CDCl_3$) 2.35 (s, 3H, CH_3), 3.96 (6H, $(CH_3)_2$), 4.06 (s, 2H, CH2), 7.06 (d, $J_{7,8}$=9.2 Hz, H7) 7.53 (d, $J_{8,7}$=9.2 Hz, H8), 7.53-7.55 (m, 2H, Ar), 7.58-7.60 (m, 2H, Ar), 7.95, (s, H5). MS (ES) m/z: 374 (M^{+2}), 372. Anal. calc'd for $C_{18}H_{18}N_3OBr$: C, 58.1; H, 4.8; N, 11.3 %. Found C, 57.9; H, 4.9; N, 11.3 %.

6-Methyl-2-(4'-iodophenyl)-3-(N,N-dimethyl)imidazo[1,2-a]pyridine-3-acetamide (2). Treatment of the acid **16** (1g, 2.3 mmol) as above gave the amide **2** as a white crystalline solid m.p. 194-196° (0.7g, 75%). ^{1}H-NMR δ ($CDCl_3$) 2.34, (s, 3H, CH_3), 2.96 (6H, $(CH_3)_2$), 4.04 (s, 2H, CH2), 7.06 (dd, $J_{7,8}$=9.0, $J_{7,5}$ = 1.6 Hz, H7) 7.39-7.42 (m, 2H, Ar), 7.52 (d, $J_{8,7}$=9.8, Hz, H8), 7.76-7.80 (m, 2H, Ar), 7.93 (s, H5). MS (ES) m/z: 422 (M^{+3}), 421 (M^{+2}), 420 (M^{+1}). Anal. calc'd for $C_{18}H_{18}N_3OI$: C, 51.6; H, 4.3; N, 10.0 %. Found C, 51.6; H, 4.0; N, 9.7 %.

6-Methyl-2-(4'-tributylstannylphenyl)-3-(N,N-dimethyl)imidazo[1,2-a]pyridine-3-acetamide (3). A mixture of **1** (1g, 2.0 mmol), hexabutylditin (2.25g, 4 mmol) and $Pd(PPh_3)_4$ (200mg) in dry toluene (30ml) under nitrogen was heated to reflux for 6h. The black mixture was diluted with CH_2Cl_2 filtered and the solvent evaporated. The residue was purified by flash chromatography (ethylacetate:hexanes 60:40) to yield the tri-n-butylstannane **3** as a white solid m.p. 158-160^0 (0.8g, 70%). ^{1}H-NMR δ ($CDCl_3$) 0.84-0.88, (m, 9H), 1.04-1.08, (m, 6H), 1.27-1.35 (m, 6H), 1.49-1.55 (m, 6H), 2.31 (s, 3H, CH_3), 2.90 (s, 3H, $N(CH_3)$), 3.15 (s, 3H, $N(CH_3)$), 4.19 (s, 2H, CH_2), 7.12 (dd, $J_{7,8}$=9.3, $J_{7,5}$= 1.4 Hz, H7) 7.48 (d, $J_{8,7}$=9.3 Hz, H8), 7.51 (d, J=8.1Hz, 2H, Ar), 7.60, (d, J=7.9Hz, 2H, Ar), 8.04 (s, H5). MS (ES) m/z: 585 (M^{+3}), 581, 142.

Anal. calc'd for $C_{30}H_{45}N_3OSn$: C, 61.9; H, 7.8; N, 7.2 %. Found C, 62.0; H, 8.1; N, 7.4 %.

Synthesis and purification of [^{123}I]Zolpidem

A. Peracetic acid. The tributyltin precursor **3** (0.2-0.5 mg) in acetic acid (200-500 μl) was treated with a solution of $Na^{123}I$ followed by peracetic acid (5 %, 100μl). After 5 min the solution was quenched ($Na_2S_2O_5$) (200μl, 50mg/ml), neutralised ($NaHCO_3$) (200μl, 50mg/ml) and injected onto a semipreparative C-18 RP HPLC column. With a mobile phase consisting of ethanol water 1:1 and a flow rate of 3 ml/min the product was eluted at 25 minutes. The solvent was evaporated under reduced pressure and the product reconstituted in saline. The product **4** was obtained in a radiochemical yield of 75-85% (n = 12) with chemical and radiochemical purity exceeding 97%. The specific activity exceeded 80 GBq/μmol.

B. Chloramine-T. The tributyltin precursor **3** (0.2-0.5 mg) in ethanol (200-500 μl) was treated with a solution of $Na^{123}I$ followed by Chloramine-T (150-200 μg) in water (100μl). The reaction was initiated by the addition of 1M HCl (50-100 μl) forming a yellow coloured solution. After 5 min the solution was quenched ($Na_2S_2O_5$) (200μl, 50mg/ml), neutralised ($NaHCO_3$) (200μl, 50mg/ml) and processed as above to give **4** in 60-75% radiochemical yield (n=28).

CONCLUSION

The [^{123}I]iodinated analogue of the imidazo[1,2-a]pyridine Zolpidem was prepared in 75-85% radiochemical yields using peracetic acid as the oxidising agent in acetic acid. The use of chloramine-T not only gave lower radiochemical yields 60-75% but required quenching ($Na_2S_2O_5$) and neutralisation ($NaHCO_3$) before the required product could be isolated.

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