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Synthesis of 1-(*trans*-[^{123}I]Iodopropen-2-yl)-4-(4-cyanophenoxymethyl)piperidine: A Selective Sigma Receptor Radioligand for SPECT

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Summary

1-(*trans*-[^{123}I]Iodopropen-2-yl)-4-(4-cyanophenoxymethyl)piperidine has been prepared as a novel sigma receptor ligand for SPECT. This ligand was found to be selective *in vitro* for the sigma receptor site (Ki(σ) = 21.7 nM) when tested in a variety of neuroreceptor binding assays. The lipophilicity of this ligand (log $P_{7.5}$ = 3.36) is appropriate for good brain uptake and relatively low non-specific binding. Radioiodination was accomplished using classical electrophilic iododestannylation methods and specific activity of the purified product was >2100 mCi/μmole. Radiochemical yields were 60-80% EOS and radiochemical purities were >99%. The average time of synthesis and purification was 35 minutes.

Key Words: sigma receptor, SPECT, iodine-123, radiotracers, schizophrenia, tumour imaging

Introduction

Sigma (σ) receptors have been the focus of much research in the past few years due to their implicated role in psychosis. Many widely used antipsychotic drugs interact with sigma receptors and some of these exhibit sigma receptor antagonism as their predominant mode of action (1, 2). There is evidence that sigma receptors modulate several neuroreceptors, including dopaminergic and other catecholaminergic systems (3, 4). It has been reported that the density of sigma receptors in the human brain are higher in the regions associated with mood and emotions than in the regions

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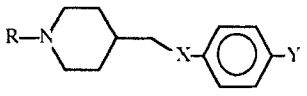
associated with motor function (5). Furthermore, there are indications from post-mortem evaluations of sigma receptors in the human brain that a decrease in the number of these sites occurs selectively in the cortex of schizophrenics (6-8). In light of this evidence, it is thought that radiolabeled sigma ligands might be useful in the *in vivo* investigation of the functional role of sigma receptors using computed tomography (9, 10).

A second possible application of radiolabeled sigma receptor ligands is in nuclear oncology. *In vitro* binding assays using radioligands having affinity for the sigma site have shown that various rodent and human cancer cell lines exhibit significant densities of sigma-1 and sigma-2 receptors. To date, the cell lines studied include mouse B16 melanoma, rat C6 glioma, human malignant melanoma and cancers of the human breast, kidney, colon, lung, and brain (11-15). A few radioiodinated sigma ligands localize in tumours *in vivo* (16) and one compound has been used in clinical trials for imaging malignant melanoma and metastasis (17).

Due to the possible applications of sigma receptor radioligands in nuclear medicine, the search for a suitable PET and SPECT sigma receptor imaging agents is ongoing. To date, several compounds have been reported as potential PET or SPECT sigma receptor radioligands, including [^{18}F]-α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol (18), [^{123}I]-iodobenzamides (19), [^{125}I]-iodobenzovesamicol (20), [^{125}I]-iodophenyl-3-(adamantyl)quanidine (21), [^{18}F]-haloperidol (22), and [^{11}C]-N-benzyl-N-normetazocine (23). Reported herein is the synthesis and preliminary characterisation of 1-(iodopropen-2-yl)-4-(4-cyanophenoxymethyl)piperidine, **2**, as a novel SPECT radioligand for *in vivo* evaluation of sigma receptors.

1-(Iodopropen-2-yl)-4-(4-cyanophenoxymethyl)piperidine was designed based in part on structure/activity information obtained for compounds similar in structure to DuP 734, a sigma ligand that exhibits antipsychotic effects in the rat (24). One of these compounds, 1-cyclopropylmethyl-4-(4-cyanophenoxymethyl)-piperidine **1**, was found to interact with the sigma receptor site and, in contrast to DuP 734, had low affinity for serotonin 5HT$_2$ receptors when examined in *in vitro* receptor binding assays (25) (Table I). It was also reported that replacement of the cyclopropyl group of **1** with a wide variety of alkyl and substituted phenalkyl groups was possible while still maintaining high affinity for sigma receptors *in vitro* (25). It was therefore postulated that the cyclopropylmethyl group of **1** could be replaced by an iodopropenyl group to provide a new compound that could be radiolabeled via classical iododemetalation methods while maintaining high affinity and selectivity for the sigma receptor site. This hypothesis was verified by *in vitro* characterisation of **2** in various neuroreceptor assays which revealed that **2** possessed good

affinity for sigma receptors (Ki = 21.7 nM) and negligible affinity (Ki > 10,000 nM) for all other receptors examined in the screening process, including serotonin ($5HT_{1C}$, $5HT_2$, $5HT_3$), dopamine (D_1, D_2), PCP, muscarinic (M_1, M_2, M_3), and NMDA receptors (32-41). In view of these results, the corresponding ^{123}I-labeled analog of **2** has been prepared for *in vivo* evaluation.



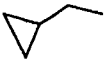
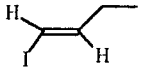
Compound	R	X	Y	Ki (σ) (nM)	Ki (5HT2) (nM)
DuP 734*		CO	F	10	15
1*		O	CN	10	2818
2**		O	CN	22	>10,000

Table I: *In Vitro* Characterisation of **2** and Related Compounds.

* Data taken from reference (25)
** Sigma receptor binding assays were performed using guinea pig bain membranes and [5-^{3}H](1,3-di-O-2-tolylguanidine (32). Serotonin $5HT_2$ assays were performed using rat cortical membranes with [^{3}H]Ketanserin as the competing ligand (33). These assays were performed by NovaScreen (Hanover, MD).

Materials and Methods:

Proton NMR spectra were recorded on a JEOL 400 MHz FT-NMR spectrometer. Chemical shifts were recorded in ppm (δ) from an internal tetramethylsilane standard in deuterochloroform and coupling constants (J) are reported in Hz. High resolution fast atom bombardment mass spectroscopy (HRMS) was performed using a ZAB-EQ mass spectrometer at the Department of Chemistry, The University of Tennessee (Knoxville, TN). Melting points were recorded on a GallenKramp melting point apparatus and are uncorrected. Elemental analysis was performed by Atlantic Microlabs Inc. (Norcross Georgia). Gravity chromatography was performed using silica gel (Fluka, 70-230 mesh, ASTM) using the solvent systems indicated in the text. For mixed solvent systems, the ratios are given with respect to volumes.

All reagents were purchased from commercial sources and were used without further purification. Sodium ^{123}I-iodide was obtained from the National Medical Cyclotron in Sydney,

Australia as a solution in 0.1 N sodium hydroxide. HPLC analysis of the radioligand was performed using a Waters 510 HPLC pump, a Waters 440 UV detector, and a Berthold LB506 radiation detector. The column used was a reverse-phase base-deactivated column (Activon, Goldpak Exsil, ODS B, 1 x 25 cm) and the mobile phases used are indicated in the text below.

1-(*tert*-Butoxycarbonyl)-4-hydroxymethylpiperidine **4**: 4-Hydroxymethylpiperidine (6.50 g, 56.4 mmol) was dissolved in ethanol-free dichloromethane (80 ml) and to this was added in several portions di-*tert*-butyl dicarbonate (13.97 g, 62.1 mmol). The resulting cloudy, colorless mixture was stirred at room temperature for 30 minutes and then the solvent was removed *in vacuo* to provide a clear, light yellow oil. The product was purified by column chromatography (ethyl actetate/ethanol, 17:3) to provide 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine (11.8 grams, 54.4 mmol, 96%) as a white, crystalline solid, mp 73°C; ^{1}H NMR: δ 1.03-1.17 (m, 2H), 1.42 (s, 9H), 1.55-1.73 (m, 3H), 2.56-2.73 (m, 2H), 3.34 (t, 1H, J = 5.40), 3.41 (t, 2H, J = 5.40), 4.00-4.14 (m, 2H); MS m/z 216; Anal. calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.46; H, 9.82; N, 6.56.

1-(*tert*-Butoxycarbonyl)-4-(methansulfonyloxymethyl)piperidine **5**: 1-(*tert*-Butoxycarbonyl)-4-hydroxymethylpiperidine (3.60 g, 16.6 mmol) was dissolved in ethanol-free dichloromethane (50 ml) and to this was added anhydrous triethylamine (8.10 ml, 58.0 mmol) followed by methanesulfonyl chloride (1.54 ml, 19.6 mmol). This mixture was stirred at 0°C for 60 minutes, turning dark brown in color and containing a yellow precipitate that formed as the reaction progressed. The reaction mixture was made basic with aqueous potassium carbonate (0.1M, 100 ml) and the product extracted into dichloromethane (2 x 100 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a pale yellow oil. The product was purified by column chromatography (hexanes/ethyl acetate 2.5:1.0) to provide a clear, colorless oil (4.51g, 15.3 mmol, 92.9%) which solidified upon standing to a white, crystalline solid, mp 76-77°C; ^{1}H-NMR: δ 1.15-1.28 (m, 2H), 1.46 (s, 9H), 1.82 (d, 2H, J = 11.40), 1.90-1.97 (m, 1H), 2.67-2.77 (m, 2H), 3.02 (s, 3H), 4.07 (d, 2H, J = 6.55), 4.12-4.25 (m, 2H); MS m/z 294.

1-(*tert*-Butoxycarbonyl)-4-(4-cyanophenoxymethyl)piperidine **6**: 4-Cyanophenol (3.55 g, 29.8 mmol) was dissolved in 30 ml anhydrous N,N-dimethyl formamide and to this solution was

added sodium hydride (894 mg, 22.4 mmol) in several portions over a 10 minute period. The resulting light-brown mixture was stirred at room temperature for an additional 10 minutes and then 1-(*tert*-butoxycarbonyl)-4-(methanesulfonyloxymethyl)piperidine (2.20g, 7.45 mmol) was added in one portion. The reaction mixture was heated at 60°C for 16 hours and then cooled to room temperature. The resulting dark-brown solution was made basic with aqueous sodium hydroxide solution (1 N, 200 ml) and the product was extracted into dichloromethane (3 x 100 ml). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo* to give a dark-brown oil. The product was purified by column chromatography (hexanes/ethyl acetate 2.5:1) to provide a white solid (1.85 g, 5.81 mmol, 78%), mp 109-110°C; δ ^{1}H NMR: δ 2.10-3.12 (m, 2H), 1.47 (s, 9H), 1.80-1.90 (m, 2H), 1.94-2.00 (m, 1H), 2.68-2.80 (m, 2H), 3.80 (d, 2H, J = 6.61), 3.85 (d, 2H, J = 5.71), 6.93 (d, 2H, J = 9.00), 7.58 (d, 2H, J = 9.0); MS m/z 317; Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.21; H, 7.61; N, 8.77.

4-(4-Cyanophenoxymethyl)piperidine **7**: 1-(*tert*-Butoxycarbonyl)-4-(4-cyanophenoxymethyl)-piperidine (950 mg, 2.98 mmol) was stirred together with 15 ml of a mixture of dichloromethane and trifluoroacetic acid (3:2 v/v) for 30 minutes at room temperature. The reaction mixture was then basified by the addition of aqueous potassium carbonate (1M, 200 ml) followed by aqueous potassium hydroxide solution (0.1N, 50 ml). The desired product was extracted into dichloromethane (2 x 75 ml) and the organic extracts were combined, dried over magnesium sulfate, and the solvent removed *in vacuo* to provide the product (612 mg, 2.83 mmol, 95%) as an off-white solid having identical spectroscopic characteristics as described when obtained from a similar synthetic route (25): ^{1}H NMR: δ 1.23-1.38 (m, 2H), 1.79-1.86 (m, 2H), 1.90-2.01 (m, 1H), 2.20-2.30 (s, 1H), 2.61-2.78 (m, 2H), 3.14 (d, 2H, J = 12.05), 3.86 (d, 2H, J = 5.70), 6.93 (d, 2H, J = 9.00), 7.58 (d, 2H, J = 9.00).

1-Propargyl-4-(4-cyanophenoxymethyl)piperidine **8**: To ethanol-free dichloromethane (20 ml) was added 4-(4-cyanophenoxymethyl)piperidine (500 mg, 2.31 mmol), potassium carbonate (1.29 g, 9.24 mmol) and propargyl bromide (0.22 ml, 2.8 mmol). The resulting solution was stirred at room temperature for 2 hours and a white precipitate formed over time. The reaction mixture was then diluted with 100 ml of water and the product was extracted into dichloromethane (2 x 20 ml). The organic extracts were combined, dried over magnesium sulfate, and the solvent removed *in vacuo* at room temperature to provide the crude product as a dark-yellow oil. The product was purified by

column chromatography (silica; ethyl acetate) to give a clear, colorless oil (290 mg, 1.14 mmol, 49%) that solidified upon standing, mp 93°C; ^{1}H NMR: δ 1.21-1.35 (m, 2H), 1.55-1.66 (m, 1H), 1.85-1.91 (m, 2H), 2.22-2.34 (m, 3H), 2.97 (d, 2H, J = 11.54), 3.33 (d, 2H, 0.01), 3.85 (d, 2H, J = 5.97), 6.93 (d, 2H, J = 9.00), 7.58 (d, 2H, J = 9.00); MS m/z 254; Anal. calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.14; N, 11.01. Found: C, 75.46; H, 7.15; N, 10.99.

1-[*trans*-(*tri*-n-Butyltin)propen-2-yl]-4-(4-cyanophenoxymethyl)piperidine **2**: 1-Propargyl-4-(4-cyanophenoxymethyl)piperidine (130 mg, 0.51 mmol) was dissolved in 10 ml anhydrous toluene and to this solution was added tri-n-butyltin hydride (0.18 ml, 0.66 mmol) and a catalytic amount of azo*bis*isobutyronitrile (20 mg). This solution was heated at reflux for 16 hours and then cooled to room temperature. The solvent was removed *in vacuo* and the product was purified by column chromatography (silica; toluene/ethyl acetate 17:3) to provide a clear colorless oil (219 mg, 0.40 mmol, 82%), ^{1}H-NMR: δ 0.85-0.98 (m, 9H), 1.25-1.39 (m, 14H), 1.51-1.76 (m, 6H), 1.81-1.90 (m, 2H), 2.02-2.12 (m, 1H), 3.03-3.20 (m, 4H), 3.83 (d, 2H, J = 6.01), 5.95-6.20 (m, 2H, J_{ab} = 19.5), 6.92 (d, 2H, J = 8.90), 7.57 (d, 2H, J = 8.90); MS m/z 545; Anal. calcd for $C_{28}H_{46}N_2OSn$: C, 61.66; H, 8.50; N, 5.14. Found: C, 61.89; H, 8.56; N, 5.07.

1-(*trans*-Iodopropen-2-yl)-4-(4-cyanophenoxymethyl)piperidine **2**: To 10 ml of dichloromethane was added 1-(*trans*-(*tri*-n-butyltin)propen-2-yl)-4-(4-cyanophenoxymethyl)piperidine (200 mg, 0.37 mmol) followed by a solution of iodine (140 mg, 0.55 mmol) in dichloromethane (5 ml) in the absence of light over a period of 10 minutes. This solution was stirred at room temperature for another 15 minutes and then the excess iodine was reduced by the addition of 0.1 M aqueous sodium hydrogen sulfite solution (5 ml). The reaction mixture was then diluted with distilled water (50 ml) and the product was extracted into dichloromethane (2 x 20 ml). The organic extracts were combined, dried over magnesium sulfate, and the solvent removed *in vacuo* to provide a crude yellow oil. The product was purified by column chromatography (silica; ethyl acetate/ethanol 9:1) to give a clear, colorless oil (120 mg, 0.31 mmol, 86%), ^{1}H-NMR: δ 1.32-1.47 (m, 2H), 1.80-1.89 (m, 3H), 1.96-2.07 (m, 2H), 2.92-3.04 (m, 4H), 3.84 (d, 2H, J = 6.0), 6.24-6.44 (m, 1H, Jab = 14.2), 6.57-6.65 (m, 1H, J_{ab} = 14.2), 6.93 (d, 2H, J = 9.0), 7.56 (d, 2H, J = 9.0); FAB HRMS 383.0620 $(M+H)^+$; calcd for $C_{16}H_{19}N_2OI$: 383.0622.

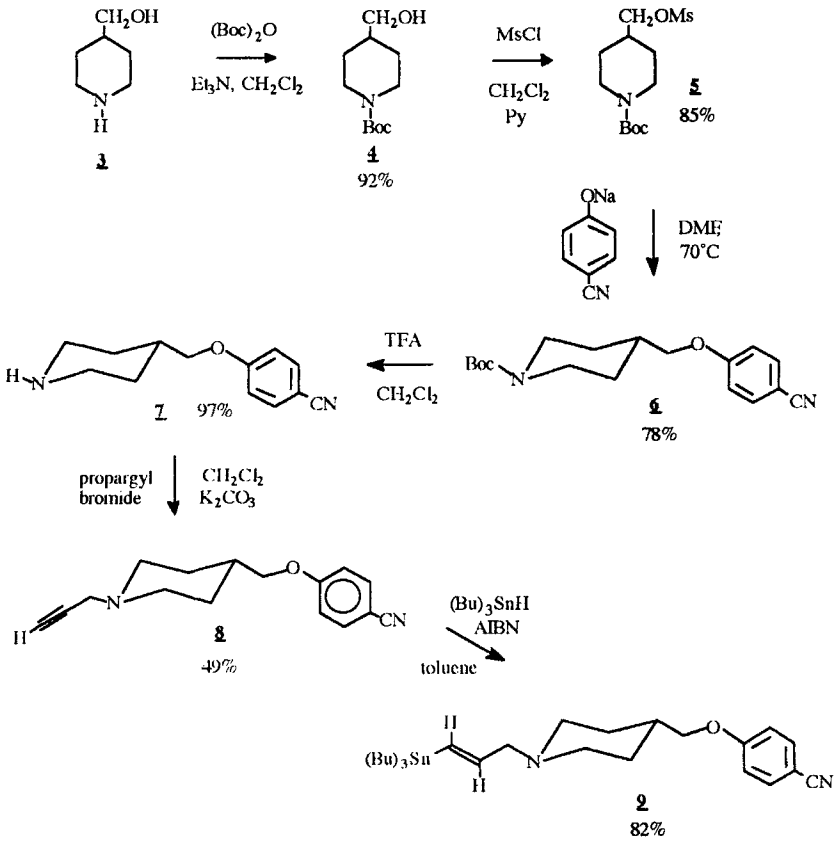
Synthesis and Purification of 1-(*trans*-[^{123}I]Iodopropen-2-yl)-4-(4-cyanophenoxymethoxy)-piperidine ^{123}I-**2**: To a solution of sodium [^{123}I]iodide (1.52 mCi) in aqueous sodium hydroxide

solution (0.1 N, 45 μl) in a 10 ml Wheaton vial was added N-chloramine-T (0.5 mg) dissolved in a solution of methanol (30 μl) and phosphate buffer (0.017 M, pH = 6.5, 170 μl), followed immediately by a solution of 1-[(tributyltin)propen-2-yl]-4-(4-cyanophenoxymethyl)piperidine, **2**, in ethanol (1 mg, 200 μl). The reaction mixture was allowed to stand at room temperature for 2 minutes and then quenched with aqueous sodium metabisulfite (20 μl, 1N). The reaction mixture was diluted with water (1 ml) and the product extracted into dichloromethane (1 ml). The organic layer was dried over sodium carbonate (75 mg) and the solvent filtered and evaporated under a stream of nitrogen gas. The residue was taken up in ethanol (500 μl) and the product purified by HPLC (mobile phase: methanol/water 85:15) to provide 1.24 mCi (80% EOS) of the desired radiotracer. The radiochemical purity of the product was >99% as determined by HPLC analysis and the radioligand co-eluted with the standard when a spiked aliquot of the purified product was analyzed using identical chromatographic conditions.

Ligand Binding Assays: Compound **2** was tested through the NIMH/NovaScreen Drug Discovery & Development Program (Contract No. NIMH-2003). Briefly, competitive binding assays were performed in either 250 or 500 μl volumes containing, by volume, 80% receptor preparations, 10% radioligand and 10% of **2** (non-specific binding determinant /4% DMSO (total binding determinant)). All compounds were solubilised in neat DMSO and diluted with water to a final concentration of 0.4% DMSO for use in the assay. Assays were terminated by rapid vacuum filtration over glass fiber filters (Whatman) followed by rapid washing with cold buffer. Radioactivity was determined by either liquid scintillation or gamma spectrometry. Data was reduced by a software program proprietary to NOVASCREEN.

Results and Discussion

The *trans*-vinyl stannane precursor, **2**, was prepared as is outlined in Scheme I. Briefly, 4-hydroxymethylpiperidine was reacted with di-*tert*-butyl dicarbonate in dichloromethane to provide 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine, **4**. The alcohol, **4**, was dissolved in ethanol-free dichloromethane and stirred with methanesulfonyl chloride and anhydrous triethylamine to provide the mesylate **5**. The sodium salt of 4-cyanophenol was prepared and then reacted with **5** at 75°C to provide 1-(*tert*-butoxycarbonyl)-4-[(4-cyano-phenoxy)-methyl]piperidine, **6**. Removal

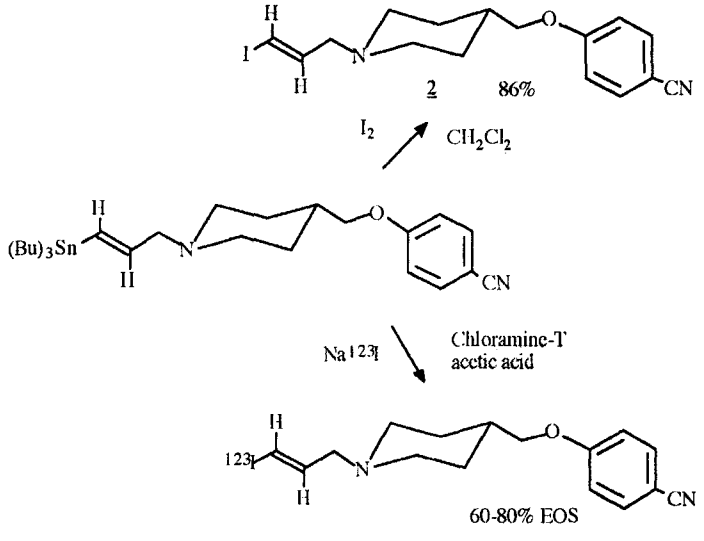


Scheme I: Synthesis of **9**

of the *tert*-butoxycarbonyl protecting group accomplished by stirring **6** in a mixture of dichloromethane and trifluoroacetic acid (3:2) for 30 minutes at room temperature, providing 4-(4-cyanophenoxymethyl)piperidine, **7**. The amine was stirred with propargyl bromide for 24 hours in in the presence of potassium carbonate to provide the alkyne **8**. In the final step, the vinyl stannane **9** was obtained by refluxing **8** in toluene with an excess tri-n-butyltin hydride in the presence of a catalytic amount of azo*bis*isobutyronitrile. Purification of **9** was easily accomplished by column chromatography [silica, hexanes/ethyl acetate (1:1)] to yield a clear, colorless oil.

The stereochemistry of **9** was determined by analysis of the coupling constants of the vinylic protons (J = 19.5 Hz) in the ^{1}H NMR spectrum and only the *trans* isomer was detected. For vinyl stannanes, coupling constants for vinylic protons in the *cis* configuration are smaller (J = 12-13 Hz) than for protons in the *trans* configuration (J = 18-20 Hz) (26, 27). Compound **9** was stored at -4°C for up to five months and used directly in radiolabeling experiments.

1-(*trans*-Iodopropen-2-yl)-4-(4-cyanophenoxymethyl)piperidine, **2**, was synthesized as shown in Scheme II. 1-[*trans*-(*Tri*-n-butyltin)propen-2-yl]-4-(4-cyanophenoxymethyl)piperidine was dissolved in dichloromethane and to this was added in the absence of light and over a period of 10 minutes a solution of iodine in dichloromethane. The excess iodine was destroyed by the addition of aqueous sodium metabisulfite. The product was extracted into dichloromethane and the combined organic layers were dried and the solvent removed *in vacuo* to provide the crude product. Purification was accomplished via column chromatography [ethyl acetate/ethanol (9:1), silica] to provide **2** as a clear, colorless oil. The stereochemistry of **2** was confirmed by determination of the



Scheme II: Synthesis of **2** and ^{123}I-**2** from stannane precursor, **9**

coupling constants (J = 14.2 Hz) of the vinylic protons in the ^{1}H-NMR spectrum which are smaller for *cis* vinyl iodides (J = 7-8 Hz) than for *trans* vinyl iodides (J = 13-15 Hz) (26,27).

The corresponding ^{123}I-labeled analog of **2** was prepared by reacting **9** with $Na^{123}I$ in the presence of chloramine-T at a pH = 6.5 (Scheme II). The radioligand was purified by high performance liquid chromatography (HPLC) using a reverse-phase base-deactivated column (Activon, Goldpak Exsil, ODS B, 1 x 25 cm) and a mobile phase consisting of methanol and water (85:15, flow rate = 2 ml/min). Typical radiochemical yields were 60-80% EOS. In order to prepare suitable preparations of ^{123}I-**2** for use *in vivo*, the eluted radioactive peak (ret. time = 11.8 min.) corresponding to ^{123}I-**2** was collected, the mobile phase removed *in vacuo* and the product was

taken up in saline. The resulting solution was passed through a sterile filter (Millipore, 0.22 μM) into an evacuated sterile vial and diluted with sterile saline to provide a solution that contained approximately 10 μCi of ^{123}I-**2** per 100 μl solution. Preparations of this type are suitable for use *in vivo* in rodents. Up to 11.5 mCi of the radiotracer was prepared in this manner and the average time of synthesis, purification and formulation was 35 minutes.

The specific activity of the product was determined by HPLC analysis using the reverse-phase base-deactivated column and a mobile phase consisting of methanol and water (85:15), with a flow rate of 2.0 ml/min. The limit of detection of **2** was determined by plotting the mass of **2** injected versus UV detector response at 254 nM. The detection limit was determined to be the response of the detector providing a peak height 2.5 times the noise level. From extrapolation, this response corresponded to 7.8 X 10^{-10} mol of **2** injected. As no response was detected in the UV trace upon analysis of 1.71 mCi of ^{123}I-**2** (in ethanol, 200 μl), the specific activity of **2** was calculated to be >2,100 mCi/μmol.

The lipophilicity of **2** was examined by determination of the log $P_{7.5}$ value using a HPLC method previously described (28). Briefly, samples were analysed using a C18 column (Goldpak Exsil 10μm, 4.6 x 250mm) and a mobile phase of MeOH and phosphate buffer (85:15 v/v, pH = 7.5) at 1.0 ml/min. The lipophilicity of **2** was determined by comparison of the retention time of the compound to that of standards having known log P values. The standards used in our study were catechol, aniline, benzene, bromobenzene, ethyl benzene, trimethylbenzene and hexachlorobenzene dissolved in an appropriate solvent. Relative retention times, RRT (to catechol), were calculated, and a calibration curve of log P vs. log RRT was generated. The calibration equations were polynomial with r^2 of 0.994 or greater. All sample injections were done in triplicate and the results averaged to provide the final values. Using this method, the log $P_{7.5}$ value for **2** was 3.36, indicating that this ligand should readily cross the blood brain barrier but should not exhibit a large degree of non-specific binding as normally results with compounds having high lipophilicities (29-31).

Conclusions

1-(*trans*-Iodopropen-2-yl)-4-[(4-cyanophenoxy)methyl]piperidine is a selective sigma receptor ligand having appropriate lipophilicity for use as a neuroreceptor imaging agent. The

corresponding SPECT radioligand, 1-(*trans*-[^{123}I]iodopropen-2-yl)-4-[(4-cyanophenoxy)methyl]-piperidine, has been prepared in high specific activity and good radiochemical purity in sufficient quantities to permit *in vivo* evaluations in rodents and in primates.

Acknowledgments

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