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SYNTHESIS OF (R,R)^{123}I-QNB, A SPECT IMAGING AGENT FOR CEREBRAL MUSCARINIC ACETYLCHOLINE RECEPTORS *IN-VIVO*.

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SUMMARY

The high-affinity muscarinic receptor antagonist (R,R) I-QNB[(1)] [(R)-(-)-1-Azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl Acetate(6a)] has been labeled with iodine-123 to give a suitable ligand for SPECT (Single photon emission computed tomography) imaging of the human brain.The radiolabeling is achieved using a copper(I) assisted nucleophilic exchange mechanism[(2)] to give high specific activity (R,R)^{123}I-QNB in reasonable overall yield (36%). The radiolabeling reaction is carried out in the presence of excess reducing agent and the product (R,R)^{123}I-QNB purified on a Sep-Pak cartridge eliminating the need for h.p.l.c. purification The synthesis of the precursor (^{127}I-QNB) for the radiolabeling step is a modification of the procedure reported by Rzeszotarski *et. al.*.[(3)] (R)-α-Hydroxy-α-(4-nitrophenyl)-α-

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phenylacetic acid was produced from 4-nitrobenzophenone and resolved as reported. The methyl ester of the acid was synthesised then the nitro group converted to an amino group to give Methyl, (R)-α-hydroxy-α-(4-aminophenyl)-α-phenyl acetate. The iodo compound Methyl, (R)-α-hydroxy-α-(4-iodophenyl)-α-phenyl acetate was produced from the amino compound via the diazonium salt. Transesterification of the iodo compound with (R)-3-quinuclidinol gave (R,R)-^{127}I-QNB.

The (R,R)^{123}I-QNB produced has been successfully used to image muscarinic receptors in patients suffering from Alzheimers disease.

KEYWORDS (R,R)^{123}I-QNB , Cu(1) nucleophilic exchange SPECT , muscarinic receptors , Alzheimers disease.

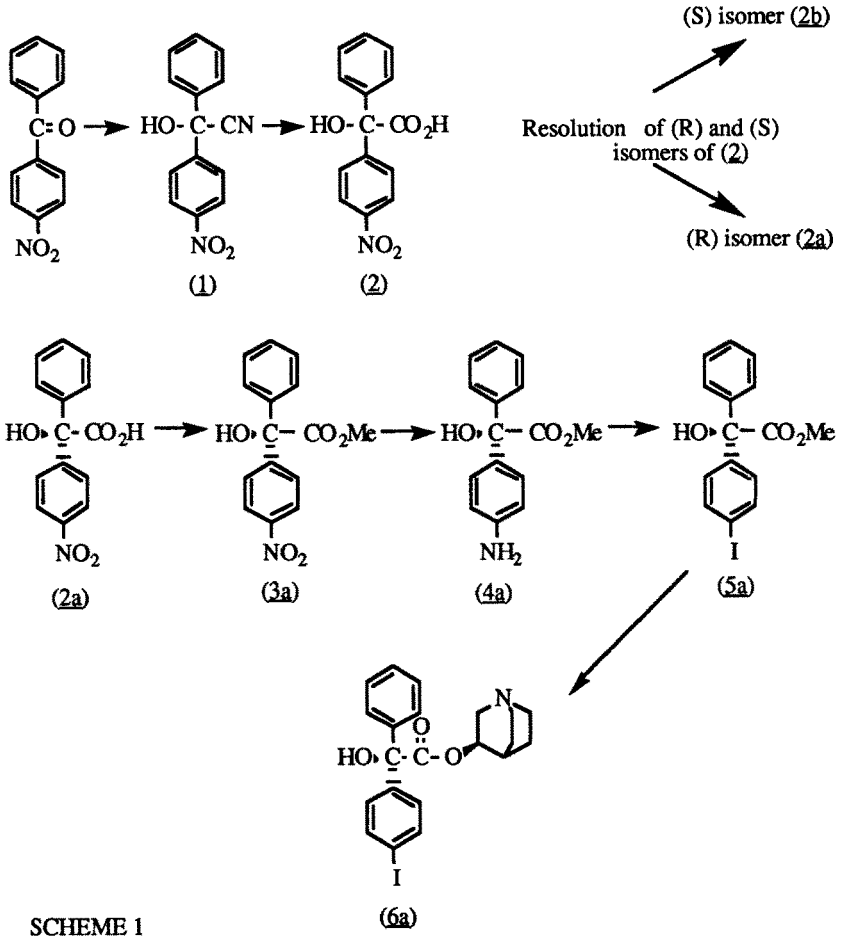
SYNTHESIS/RADIOSYNTHESIS OF (R,R)^{123}I-QNB

The utility of I-QNB (1-azabicyclo[2.2.2]oct-3-yl-α-hydroxy-α-(4-iodophenyl)-α-phenyl acetate) as an agent that binds with high affinity to muscarinic acetylcholine receptors(m-AChR) is well established[1,4-6]. Studies have shown that the isomer with the highest affinity for the m-AChR is (R,R)I-QNB[1] . The radiolabelling of (R,R)I-QNB with ^{125}I and ^{123}I has allowed in-vivo imaging studies to be carried out[7-9] The radiolabelling reported[3,10] has been carried out using modifications of the Wallach triazene approach[11,12]. Reported here is the labelling of (R,R)I-QNB with ^{123}I via a copper(I) assisted nucleophilic exchange mechanism[2]. This method and modifications made to the synthesis of (R,R)I-QNB considerably simplify the procedure and lead to high specific activity (R,R)^{123}I-QNB in reasonable overall yield.

CHEMISTRY

(R)-(-)-1-Azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl acetate(6a) was synthesised by a modification of the procedure reported by Rzeszotarski *et.al.*[3] (see Scheme 1). The reaction of 4-nitrobenzophenone with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide gave after initial hydrolysis the cyanohydrin(1). Further hydrolysis of the cyanohydrin(1) by c.HCl and glacial acetic acid gave the racemic (R,S)-α-hydroxy-α-(4-nitrophenyl)-α-phenylacetic acid(2). The racemic acid(2) was reacted with quinidine and the resulting salt recrystallised to a constant $[\alpha]_D^{22}$. The pure salt was treated with HCl to obtain the (R)-acid(2a).The mother liquors from the preparation of the quinidine salt of the racemic acid(2) were treated with HCl to give mainly (S)-acid which was purified by preparation and recrystallisation of the quinine salt. Methyl, (R)-α-hydroxy-α-(4-nitrophenyl)-α-phenyl acetate(3a) was made by refluxing the (R)-acid(2a) with methanol in the presence of a trace of c.H_2SO_4. The methyl ester (3a) was hydrogenated at room temperature and pressure in ethanol using a 10% Pd on C catalyst to give methyl, (R)-α-hydroxy-α-(4-aminophenyl)-α-phenyl acetate(4a). The diazonium salt of (4a) was made by adding sodium nitrite to a solution of (4a) in 10% H_2SO_4:acetone 5:1 at 0°C. Treatment of the diazonium salt with sodium iodide gave (R)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl acetate(5a). Transesterification of (5a) with (R)-(-)-3-quinuclidinol using potassium *t*-butoxide and molecular sieves gave (R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl acetate(6a). The (R)-(-)-3-quinuclidinol was resolved from (±)-3-

quinuclidinol via the tartrate salt by the method of Ringdahl *et.al.*[13].

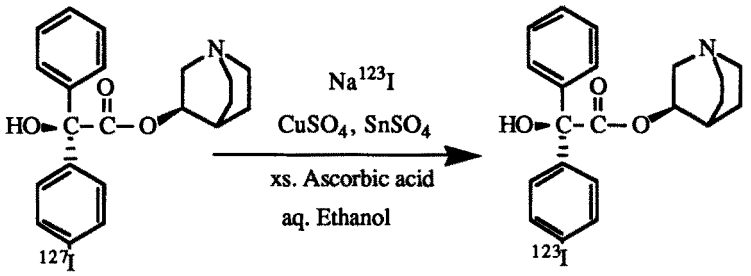


SCHEME 1

RADIOCHEMISTRY

The radiolabelling was achieved using a copper(I) assisted nucleophilic exchange reaction[2] (see Scheme 2). (R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl acetate(6a).was heated with Na^{123}I, copper sulphate, and tin sulphate in the presence of an excess of the reducing agent ascorbic acid to give the ^{123}I labelled compound. Na^{123}I Lab W as supplied by Medgenix was used. Oxygen was excluded from the reaction by

using nitrogen flushed vials and solvents which were nitrogen saturated The solvents used in the preparation of patient doses were sterile water for injection and sterile anhydrous ethanol. The procedure reported was carried out in a laminar airflow cabinet. H.p.l.c. analysis of the radiolabelled product was carried out on a HiChrom 25 cm ODS2 C18 RP column.



(6a) (7a)

SCHEME 2

GENERAL METHODS

Spectral analyses were performed for unlabelled compounds only. 90 MHz ^{1}H n.m.r. spectra were recorded on a Perkin Elmer R32 spectrometer. 200 MHz ^{1}H and ^{13}C n.m.r. spectra were recorded on a Bruker W.P. 200SY instrument. All n.m.r. spectra were carried out in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard unless otherwise noted. I.r. spectra recorded as liquid film or KCl disc on Perkin Elmer 580 or 257 spectrometers. Mass spectra were obtained at 70 e.V. on an A.E.I.M.S. 12 instrument. H.p.l.c. analyses were performed on a Perkin Elmer series 400 machine(unlabelled compounds) and a Pye Unicam series 4000 instrument(labelled compounds). Melting points were obtained on a Kofler hot stage apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity AA100 polarimeter.

EXPERIMENTAL

(R,S)-α-Hydroxy-α-(4-nitrophenyl)-α-phenylacetonitrile(1)

Trimethylsilyl cyanide (25.0 g, 0.25 mol) was added dropwise to a stirred solution of 4-nitrobenzophenone (47.0 g, 0.21 mol) and zinc iodide (0.5 g) in dry dichloromethane (600 ml). The mixture was stirred under dry N_2.for 72h then evaporated *in-vacuo* to give an oil. The oil was suspended in 3N HCl (400 ml) and stirred for 24h. The white solid which formed was filtered of and dried *in-vacuo* over silica gel to give the cyanohydrin (R,S)-α-hydroxy-α-(4-nitrophenyl)-α-phenylacetonitrile(1) 49.0g (92%); m.p. 94-95°C. T.l.c.[silica, 10% ethyl acetate:40-60°C petroleum ether]R_f 0.29. δ_H (90 MHz,$CDCl_3$,TMS): 4.1(1H,s,OH,exch.), 7.4(5H,s,Ar), 7.7(2H,d,Ar), 8.2(2H,d,Ar). υ_{max}(KCl): 3340(OH), 1605(C=C), 1520(C=C), 855(Ar), 770(Ar), 705 cm^{-1}(Ar). M^+= 254 as expected.

(R,S)-α-Hydroxy-α-(4-nitrophenyl)-α-phenylacetic Acid(2)

The cyanohydrin (1) (20.0 g, 0.076 mol) was added to a mixture of glacial acetic acid (50.0 ml) and 10N HCl (50.0ml) , and stirred at 110°C for 24h then cooled to room temperature. A saturated aqueous solution of $NaHCO_3$ was added cautiously until the reaction mixture was pH9. This basic mixture was extracted with dichloromethane (3 X 200 ml) and the combined extracts concentrated *in-vacuo* to give unreacted 4-nitrobenzophenone. The basic solution was then carefully acidified to pH2 with 5N HCl and extracted with dichloromethane (3 X 200 ml). The combined extracts were washed with 3N HCl (3 X 200 ml) , dried over anhydrous

Na_2SO_4 and then concentrated *in-vacuo* to give a clear oil. The oil solidified on standing yielding (R,S)-α-hydroxy-α-(4-nitrophenyl)-α-phenylacetic acid(2) as an off-white solid , 13.8g (66%); m.p. 112-113°C. T.l.c.[silica, chloroform]R_f 0.05. δ_H (90 MHz,$CDCl_3$,TMS): 6.20(1H,br s,OH), 7.41(5H,s,Ar), 7.73(2H,d,Ar), 8.20(2H,d,Ar). υ_{max} (KCl): 3480(OH), 1725(C=O), 1520 cm^{-1}(C=C). M^+= 227 due to loss of CH_2O_2 from $C_{14}H_{11}NO_5$.

(R)-α-Hydroxy-α-(4-nitrophenyl)-α-phenylacetic Acid(2a)

The racemic acid (2) (10.0 g, 0.037 mol) was added to quinidine (12.0 g, 0.037 mol) dissolved in boiling ethyl acetate and the mixture left at 20°C for 20h. The salt which crystallised was filtered off and recrystallised (6 times) from ethyl acetate.until it had a constant m.p. 111-112°C and $[\alpha]_D^{22}$ +124.7° (c 0.34, pyridine). The quinidine salt (7.6 g)was stirred with 6N HCl (75 ml) for 2h and the mixture extracted with dichloromethane (5 X 30 ml). The combined extracts were dried over anhydrous Na_2SO_4 then concentrated *in-vacuo* to give (R)-α-hydroxy-α-(4-nitrophenyl)-α-phenylacetic acid(2a) (4.2 g,0.015 mol) as a yellow oil. T.l.c.[silica, chloroform]R_f 0.05. δ_H (90 MHz,$CDCl_3$,TMS): 6.20(1H,br s,OH), 7.41(5H,s,Ar), 7.73(2H,d,Ar), 8.20(2H,d,Ar). υ_{max} (KCl): 3480(OH), 1725(C=O), 1520 cm^{-1}(C=C). M^+= 227 due to loss of CH_2O_2 from $C_{14}H_{11}NO_5$.

Methyl, (R)-α-hydroxy-α-(4-nitrophenyl)-α-phenyl Acetate(3a)

The (R)-acid (2a) (7.43 g,0.027 mol) , methanol (50 ml) and c.H_2SO_4 (1 ml) were refluxed for 20h.then cooled to

room temperature. The methanol was removed *in-vacuo* and water (100 ml) was added to the residue. This mixture was extracted with dichloromethane (3 X 75 ml) and the combined extracts washed with sat. aqueous $NaHCO_3$ solution (2 X 50 ml) then dried over anhydrous Na_2SO_4. The dichloromethane was removed *in-vacuo* to give methyl, (R)-α-hydroxy-α-(4-nitrophenyl)-α-phenyl acetate(3a) 6.6 g (84%) as a golden oil which solidified slowly on standing m.p. 60-61°C. T.l.c.[silica, chloroform]R_f 0.35. δ_H (90 MHz,$CDCl_3$,TMS): 3.9(3H,s,CH_3), 4.3(1H,br s,OH), 7.3(5H,s,Ar), 7.65(2H,d,Ar), 8.15(2H,d,Ar). υ_{max}(KCl): 3490(OH), 1730(C=O), 1255(C-O), 850,755 and 700 cm^{-1}(Ar). M^+= 228 due to loss of $C_2H_3O_2$ from $C_{15}H_{13}NO_5$.

Methyl, (R)-a-hydroxy-a-(4-aminophenyl)-a-phenyl Acetate(4a)

The nitro compound (3a) (5 g, 0.9175 mol) was dissolved in absolute ethanol (100 ml) and 10% Pd on charcoal (0.5 g) added This mixture was hydrogenated at ambient temperature and pressure until uptake of hydrogen ceased. The mixture was filtered through celite and the filtrate concentrated *in-vacuo* to give methyl, (R)-α-hydroxy-α-(4-aminophenyl)-α-phenyl acetate(4a) as an off-white solid 4.18g (93%); m.p. 120-121°C. T.l.c.[silica, chloroform]R_f 0.09. δ_H (90 MHz,$CDCl_3$,TMS): 3.55(3H,br s,OH + NH_2), 3.83(3H,s,CH_3), 6.6(2H,d,Ar), 7.15(2H,d,Ar), 7.35(5H,s,Ar). υ_{max}(KCl): 3420 and 3330(NH_2), 3230(OH), 1720(C=O), 1250(C-O), 840,760 and 705 cm^{-1}(Ar). M^+= 257 as expected.

Methyl, (R)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl Acetate(5a)

The amino compound (4a) (1.0 g, 0.0039 mol) was dissolved in 10% H_2SO_4:acetone 5:1 (15 ml) and cooled to 0-5°C. A solution of sodium nitrite (0.55 g, 0.0078 mol) in water (3 ml) was added dropwise and the mixture stirred for 15 min at 0-5°C. Maintaining this temperature , urea (0.47 g, 0.0078 mol) was added to the mixture and stirred for 10 min before adding dropwise a solution of sodium iodide (1.17 g, 0.0078 mol) in water (3 ml). The reaction vessel was warmed to ambient temperature and stirred for 90 min. The reaction mixture was treated cautiously with 5N NaOH until pH11. This basic solution was extracted with dichloromethane , the combined extracts dried over anhydrous Na_2SO_4 and then concentrated *in-vacuo* to give a golden oil. This oil was purified by flash column chromatography [HF_{254} silica, dichloromethane] to give methyl, (R)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl acetate(5a) as a white solid 0.68g (45%); m.p. 78-79°C (from hexane). T.l.c.[silica, dichloromethane]R_f 0.43. δ_H (200 MHz,$CDCl_3$,$CHCl_3$): 3.85(3H,s,CH3), 4.20(1H,s,OH), 7.18(2H,d,Ar), 7.35(5H,s,Ar), 7.66(2H,d,Ar). υ_{max}(KCl): 3470(OH), 1720(C=O), 1275 cm^{-1}(C-O). M^+= 368 as expected.

(R)-(-)-1-Azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl Acetate(6a)

The compound (5a) (1.93 g, 5.2 X 10^{-3} mol) , (R)-3-quinuclidinol (1.0 g, 7.9 X 10^{-3} mol) , potassium tert-butoxide (200 mg) , activated 4Å molecular sieves (8 g) and dry benzene (100 ml) were placed in a flask and refluxed

for 3h. The mixture was filtered and the sieves washed well with benzene (3 X 25 ml). The combined benzene fractions were evaporated *in-vacuo* to dryness and the residue suspended in water (100 ml). The aqueous phase was extracted with dichloromethane (3 X 75 ml) and the combined extracts washed with water (3 X 100 ml) then dried over anhydrous Na_2SO_4. Concentration *in-vacuo* gave a cloudy oil which was purified by flash column chromatography [HF_{254} silica, dichloromethane:ethanol:ammonia 100:8:1] to give (R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl acetate(6a) as a white solid 0.63g (26%); m.p. 133-134°C. T.l.c.[silica, dichloromethane:ethanol:ammonia 100:8:1]R_f 0.32. H.p.l.c.[ODS2 C18 RP; methanol:water 60:40, 5mM octanesulphonic acid (pH4 formic acid)]. δ_H (200 MHz,$CDCl_3$,$CHCl_3$): 1.31-1.44(2H,m,CH_2), 1.48-1.78(2H,m,CH_2), 2.00(1H,m,CH), 2.49-2.83(5H,m,2 X CH_2 + O-CHC<u>H</u>HN), 3.21(1H,m,O-CHC<u>H</u>HN), 4.95(1H,m,O-CH), 7.18(2H,d,Ar), 7.35(5H,s,Ar), 7.65(2H,d,Ar). υ_{max}(KCl):cm^{-1}. M^+= 463 as expected.

(±)-3-Acetoxyquinuclidine

(±)-3-Quinuclidinol (9.0 g, 0.07 mol) was dissolved in acetic anhydride (60 ml) and refluxed for 3h. The remaining acetic anhydride was removed *in-vacuo* and the residue added to sat. aqueous K_2CO_3 solution. The aqueous phase was extracted with chloroform (3 X 30 ml). The combined extracts were dried over anhydrous K_2CO_3 then concentrated *in-vacuo* to leave a brown oil. This oil was distilled to give (±)-3-acetoxyquinuclidine as a clear colourless oil 10.1g (85%); b.p. 70-72°C @ 0.8mmHg.(Lit[13] . b.p. 113-115°C @ 11mmHg). δ_H (90 MHz,$CDCl_3$,TMS): 1.3-1.9(4H,m,CH_2),

2.1(3H,s,CH_3), 2.5-3.5(7H,m,CH_2+CH), 4.7-4.9(1H,m,CH). υ_{max}(liq. film): 2950 and 2870(CH), 1735(C=O), 1250(C-O), 1030 cm^{-1}(-O-R). M^+= 169 as expected.

Resolution of (±)-3-Acetoxyquinuclidine

L-(+)-Tartaric acid (21.3 g, 0.14 mol) was dissolved in 80% aqueous ethanol (100 ml) and (±)-3-acetoxyquinuclidine (24.0 g, 0.14 mol) was added. The solution was left overnight at room temperature The salt which formed was recrystallised twice from 80% aqueous ethanol (170 ml) to give resolved (+)-hydrogen tartrate 16.0 g (65%) m.p. 94-95°C , $[\alpha]_D^{22}$ +3.6° (c 2.2, water). (Lit[13] . m.p. 94-95°C , $[\alpha]_D^{22}$ +3.6° (c 2.2, water)). The m.p. and $[\alpha]_D^{22}$ did not change on further recrystallisation. The mother liquor obtained after the separation of the (+)-hydrogen tartrate was concentrated *in-vacuo* and the residue made slightly alkaline with K_2CO_3 solution. The ester was extracted with chloroform (3 X 50 ml) and the combined extracts dried over anhydrous K_2CO_3 then concentrated *in-vacuo*. The residue was distilled to give 3-acetoxyquinuclidine 9.0 g; b.p. 105°C @ 10mmHg. This ester was added to a solution of (-)-tartaric acid (8.0 g, 0.053 mol) in 80% aqueous ethanol (45 ml) and the salt formed was purified as for the enantiomeric salt.This gave 13.0 g (69% based on recovered 3-acetoxyquinuclidine) of the resolved (-)-hydrogen tartrate m.p. 94-96°C , $[\alpha]_D^{22}$ -3.7° (c 2.2, water) in agreement with the reported values[13] .

(R)-(-)-3-Quinuclidinol

Resolved (+)-hydrogen tartrate of 3-acetoxyquinuclidine (12.05 g, 0.034 mol) was dissolved in

2M NaOH (100 ml) and the resulting solution saturated with K_2CO_3 The mixture was heated at 60°C for 40 min. then extracted with hot benzene (5 X 50 ml). The combined extracts were concentrated *in-vacuo*.to give an off-white solid. This solid was recrystallised from acetone-ether to give (R)-3-quinuclidinol as white needles 3.05g (71%); m.p. 220-223°C , $[\alpha]_D^{22}$ -42.9° (c 3.0, 1M HCl) (Lit[13] . m.p. 223.5-224.5°C , $[\alpha]_D^{22}$ -45.7° (c 2.9, 1M HCl)). δ_H (200 MHz,$CDCl_3$,$CHCl_3$): 1.23-1.53(2H,m,CH_2), 1.55-2.01(3H,m,CH_2 + CH), 2.47-2.97(5H,m,2 X CH_2 + O-CHC<u>H</u>HN), 3.04(1H,m,O-CHC<u>H</u>HN), 3.34(1H,br s,OH), 3.79(1H,m,O-CH). υ_{max}(KCl): 3100(OH), 2940 and 2870(C-H), 1045 cm^{-1}(C-O). M^+=127 as expected.

(R)-(-)-1-Azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{123}I]iodophenyl)-α-phenyl Acetate(<u>7a</u>)

To a septum sealed V vial containing 28 mCi $Na^{123}I$ in aqueous solution(≈ 100µl) at pH7 was added (R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{127}I]iodophenyl)-α-phenyl acetate(<u>6a</u>) (4 X 10^{-5}g , 8.6 X 10^{-8}mol in 40µl 50:50 ethanol:water), copper(I) sulphate pentahydrate (1.3 X 10^{-4}g , 5.2 X 10^{-7}mol in 130µl water), tin(II) sulphate (5 X 10^{-4}g , 2.3 X 10^{-6}mol in 100µl water) and ascorbic acid (0.1g , 5.7 X 10^{-4}mol in 390µl water). The vial was then subject to an autoclave cycle (121°C for 45 min) then cooled to ambient temperature. The contents of the vial were removed and loaded on a C18 Reverse phase Sep-Pak™ cartridge the cartridge was washed with water (12 X 2ml fractions). The direction of elution was then reversed and the cartridge eluted with ethanol (5 X 2ml fractions). The first 2ml fraction collected after reversal of the direction of elution contained 10mCi of the product

(R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-[^{123}I]iodophenyl)-α-phenyl acetate(7a).The 2ml fraction containing the product was sterillised by 0.22μm millipore™ filtration. The filter was pre-treated with a 0.01% aqueous solution of Na^{127}I (3ml) and water (3ml) before the filtration of the product. The 2ml fraction containing the product was washed through the filter with water (2ml) into a septum sealed sterile vial. H.p.l.c. analysis [ODS2 RP C18; methanol:water 60:40, 5mM octanesulphonic acid (pH4 formic acid)] showed the product to be predominantly(96%) ^{123}I-QNB.

CLINICAL USE

The (R,R)^{123}I-QNB(7a) produced has been used to image cerebral muscarinic receptors in patients with Alzheimer's disease. 5mCi of (R,R)^{123}I-QNB(7a) in 5ml aqueous solution (1ml absolute ethanol + 4ml water for injection) was administered intravenously to each patient. SPECT imaging was performed using a SME 810 multi detector section scanner. (R,R)^{123}I-QNB(7a) images of transverse slices of the brain parallel to the orbital-meatal(OM) line were obtained 21 hours post injection. At this time there is sufficient activity in the brain to scan a single slice in 3 minutes. These images were compared with cerebral blood flow(rCBF) images generated using the flow agent ^{99m}Tc-HMPAO[14](see figure 1). The ^{99m}Tc-HMPAO images in figure 1 show a large signal from cerebellum whereas the (R,R)^{123}I-QNB(7a) images show no signal from this region. This observation suggests that (R,R)^{123}I-QNB(7a) uptake is receptor mediated as the concentration of muscarinic receptors in the cerebellum is low. It also appears that (R,R)^{123}I-QNB(7a) maps only the M_1 subtype of the

muscarinic receptor population. The thalamus is clearly visible on the ^{99m}Tc-HMPAO images but not evident with (R,R)^{123}I-QNB(7a); it is known that in the thalamus

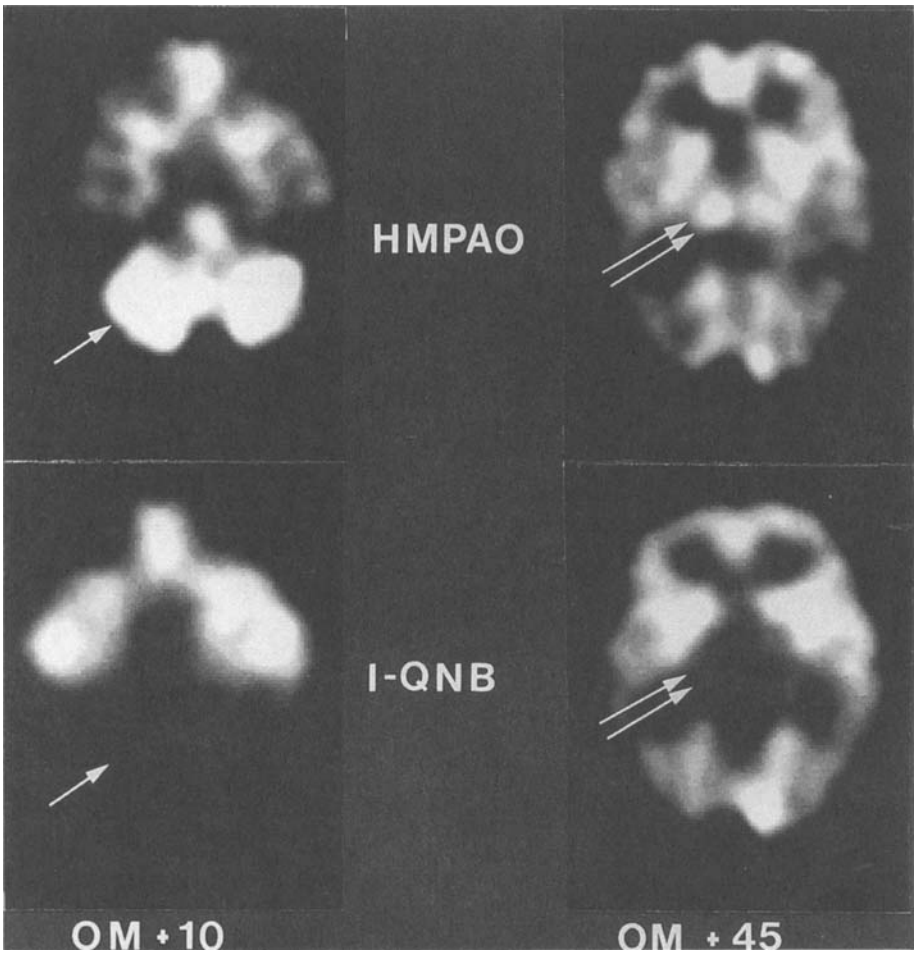


Figure 1: (R,R)^{123}I-QNB(7a) and rCBF images from the same patient. The top images were generated using ^{99m}Tc-HMPAO and the lower images with (R,R)^{123}I-QNB(7a). The two right-hand images are of the OM +10 slice, the left-hand images of the OM +45 slice. The position of the cerebellum is marked (→) and the thalamus (⇉).

muscarinic receptors of the M_2 subtype predominate.

A more detailed analysis of the (R,R)^{123}I-QNB(7a) images obtained will be presented elsewhere[15].

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