NOTE

Novel preparation of (R,R)Bromo-3-Quinuclidinylbenzilate (Br-QNB), a precursor for the synthesis of (R,R)[^{123}I]Iodo-QNB

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Summary

Radioiodinated QNB (3-quinuclidinylbenzilate) (IV) is a potential SPET-ligand with high affinity muscarinic receptor binding. The synthesis of the precursor BrQNB (III) ((R)-(-)-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-bromophenyl)-α-phenylacetate) described previously was modified. Radiolabelling with iodine-123 was achieved using a copper(I) assisted nucleophilic exchange reaction resulting in high specific activity (80 GBq/μmol) and an overall yield of 56 %.

Keywords (R,R)[^{123}I]Iodo-QNB, n.c.a. Cu(I)-assisted iodine exchange, muscarinic receptors, SPET radioligands

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Introduction

The muscarinic acetylcholine receptor (m-AChR) plays an essential role in physiological and pathophysiological processes (1, 2). A decrease in m-AChR density has been observed in patients with Alzheimer's disease (3, 4, 5, 6, 7, 8). Most of these observations have been made by autopsy studies in humans or by animal studies (9). Some previous results (4, 5) indicated that (R,R)[^{123}I]IQNB may be a suitable radiopharmaceutical for cerebral imaging studies with SPET. There is, however, no standard, established production method for (R,R)[^{123}I]Iodo-QNB (IQNB) available, hence the current note.

Selection of adequate precursor and results

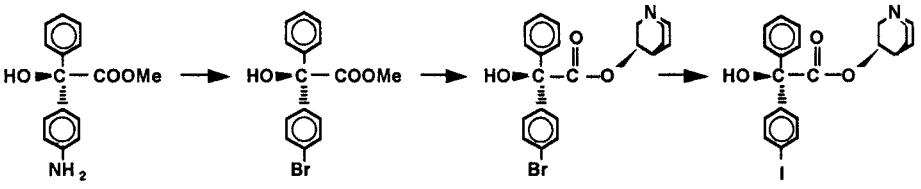
Earlier methods describing the preparation of (R,R)[^{123}I]Iodo-QNB are based on different procedures (Table 1).

Precursor	**Method**	**Specific activity**	**Radiochemical Yield [%]**	**Reference**
[^{127}I]IQNB	Cu(I) assisted isotopic exchange	no details	36	(11)
Tributylstannyl-QNB	Destannylation	40 GBq/µmol	65,6	(12)
Boron-QNB	Deboronation	no details	60,4	(13)
Triazene-QNB	Wallach-Triazene	40 MBq/µmol	17	(10)

Table 1: Reported methods for the synthesis of (R,R)[^{123}I]Iodo-QNB

Another approach for IQNB synthesis could use BrQNB, since this precursor is particularly easy to synthesize and promises to result in a product of high specific activity and radio-chemical yield (14, 15, 16). The non-isotopic exchange of bromine with n.c.a. [^{123}I]NaI

using 10 μg of the precursor in the presence of Cu(I) in acetic acid, and reducing agents in excess, resulted in a specific activity of > 80 GBq/μmol and a radiochemical yield of 56 %. This compares favorably with the results in Table 1.



(I) (II) (III) (IV)

Experimental

Analytical data (elemental analysis, MS, ^{1}H-NMR) obtained for compound II and III were found in good agreement with theory. The chemicals were purchased from Merck (Darmstadt, Germany), [^{123}I]NaI solution in 0.05 M NaOH was obtained from Amersham (Braunschweig, Germany) (~ 8200 MBq/ml; pH 7-12).

(R)-α-hydroxy-α-(4-aminophenyl)-α-phenylacetate (I) was synthesized by modifying the procedure reported by Rzeszotarski et. al. and Owens et. al. (1, 2). For radiohalogenation of aromatic rings Rzeszotarski et. al. have selected the Wallach triazene approach and Owens et. al. produced (R)-α-hydroxy-α-(4-iodophenyl)-α-phenylacetate from the amino compound via the diazonium salt.

(R)-α-Hydroxy-α-(4-bromophenyl)-α-phenyl acetate (II) was synthesized instead of the iodo-compound. The transesterificaticion of the bromo-compound with (R)-(-)-3-quinuclidinol gave (R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(4-bromophenyl)-α-phenylace-tate (III) [(R,R)BrQNB]. Radioiodination was achieved using a copper(I)-assisted

nucleophilic exchange reaction in the presence of excess of reducing agents. The reaction was optimized with respect to adduct concentration, reaction time and temperature.

(R)-α-Hydroxy-α-(4-bromophenyl)-α-phenylacetate (II)

9.92 g of the amino compound (I) (0.0386 mol) was dissolved in 10% H_2SO_4 / acetone (5 / 1) and cooled to 0°C. A solution of 5.5 g sodium nitrite (0.078 mol) in 30 ml water was added dropwise at 0-5°C and the mixture stirred for 15 min. 4.7 g urea (0.078 mol) was added and stirred for 15 min at 0°C before adding a solution of 7 g CuBr in 100ml HBr / water = 1 / 1. The reaction vessel was allowed to warm to ambient temperature, stirred for 2 hours and then at 80°C for 1 hour. The separated oil was dissolved ($NaHCO_3/H_2O$ solution), extracted in dichloromethane, dried over anhydrous Na_2SO_4 and then concentrated in vacuum. The purification was carried out by flash column chromatography (silica gel 60, dichloromethane) and resulted in a white solid 8.67 g (69.9 % theory); m.p. 62-63°C (from CCl_4/n heptane).

$[\alpha]_D^{22} = +24$ (c = 1, $CHCl_3$).

(R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-(bromophenyl)-α-phenylacetate [(R,R)BrQNB] (III)

2.9 g of compound (II) (0.00934 mol) and 1.7 g (R)-3-quinuclidinol (0.0136 mol) were dissolved in 100 ml dry benzene. Activated 4 Å molecular sieves and 1.038 g potassium tert-butoxide were added and the solution refluxed for 3 h. The mixture was filtered, and the sieves were washed with 3 x 25 ml benzene. The fractions were evaporated to dryness and the residue suspended in 100 ml water. The aqueous phase was extracted with dichloromethane and dried over anhydrous Na_2SO_4. After evaporation the oil was purified by flash chromatography to give a white solid. 1.05 g (27 % theory), m.p. 134-136°C (dichloromethane/hexane).

$[\alpha]_D^{22} = -16,8$ (c = 0.475, 1 M HCl).

(R)-(-)-1-azabicyclo[2.2.2]oct-3-yl-(R)-(+)-α-hydroxy-α-[^{123}I]iodophenyl-α-phenylacetate (R,R)[^{123}I]IQNB (IV)

(R,R)BrQNB (III) (4.6 x 10^{-7}mol) was dissolved in 20 µl water and 20 µl ethanol , and together with copper(I)chloride (50 µl of a 0.01 M solution in water), stannous(II)sulphate (50 µl of a 0.009 M solution in water), and ascorbic acid (50 µl of a 0.6 M solution in water) were added to 100µl of a solution of radioactive NaI (150 MBq). The closed vial was kept in an autoclave at 132°C for 60 min. The resulting mixture was neutralized with 1M NaOH.

Purification was carried out on a C18 reverse phase cartridge (Waters). The mixture was loaded onto the Sep-Pak cartridge which was then eluted with 20 ml water in order to remove unreacted radioiodide. The product was eluted with 10 ml ethanol. The first 4 ml ethanol fractions contained the [^{123}I]IQNB tracer. The IQNB fraction was collected and evaporated to remove the solvent. The residue was then dissolved in phosphate buffered saline (pH 7.4), and filtered through a 0.22 µm filter. Quality control of the product was performed with HPLC on a RP-18 column (ODS2), 250 x 4mm, using the eluent methanol/water 60/40 containing 5mM octanesulfonic acid (pH 4). At a flow rate of 1 ml/min the retention time for the radioiodide, precursor and [^{123}I]IQNB were 2.9 min, 5.4 min and 6.37 min, respectively.

UV detection was performed at 220 nm; radioactivity was measured continously. The radiochemical purity of the product was > 97 % and the specific activity 80 GBq/µmol; the radiochemical yield was in the range 56.8 ± 5 %.

Conclusion

Although the labelling method reported compares unfavorably with some other methods in that it is more time consuming it does have significant advantages as it generates the product in high radiochemical yield and high specific activity. Furthermore. (R,R)BrQNB is easily prepared and is a suitable precursor for the synthesis of (R,R)[^{123}I]IQNB.

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