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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING June 30, 1996

F. F. Knapp, Jr.

K. R. Ambrose
A. L. Beets
S. Guhlke
H. Luo
D. W. McPherson
S. Mirzadeh

MASTER

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SUMMARY

The four stereoisomers of 1-azabicyclo[2.2.2]oct-3-yl α-(1fluoropent-5-yl)-α-hydroxy-α-phenylacetate (FQNPe, **4**) have been resolved and were evaluated as potential candidates for PET imaging agents. Labeling with fluorine-18 involved a two-step synthesis via fluoride displacement of a meslyate intermediate at the ethyl ester stage followed by transesterification with (R)-quinuclidinol. *In vitro* data utilizing cloned human receptor subtypes demonstrated that while the (+,+)-isomer did not have significant receptor binding, the other stereoisomers of FQNPe bound with high affinity to the various mAChR subtypes tested (K_i, nm: **m1**, (-,-), 0.33; (-,+), 1.4; (+,-), 3.8; **m2**, (-,-), 0.1; (-,+), 4.2; (+,-), < 75% binding; **m3**, (-,-), 0.34; (-,+), 3.1; (+,-), 7.6. [^{18}F]-(-,-)- and [^{18}F]-(-,+)-FQNPe (**4**) were prepared in decay corrected radiochemical yields of 14% ([^{18}F]-(-,-)-**4**) and 8% ([^{18}F]-(-,+)-**4**). *In vivo* biodistribution studies were conducted in female rats with [18F]-(-,-)- and (+,-)-FQNPe (**4**). [^{18}F](-,-)-**4** demonstrated high uptake in mAChR regions of the brain up to 3 hours post injection and low accumulation of radioactivity in the bone indicated good *in vivo* stability. Preinjection of (R)QNB (3 mg/kg) 1 hour prior to injection of [^{18}F]-(-,-)-**4** blocked the uptake of activity in various regions of the brain by approximately 90% and the heart by approximately 85%. In contrast, [^{18}F]-(-,+)-**4** demonstrated fairly rapid washout from the various tissues evaluated in addition to low *in vivo* stability as demonstrated by high bone uptake. *In vivo* metabolic studies also demonstrated that [^{18}F]-(-,-)-**4** was the sole radioactive species binding to the receptor site in brain homogenates. These data indicate [^{18}F]-(-,-)-**4** is a potential candidate for continued evaluation as an agent for use in PET studies of mAChR.

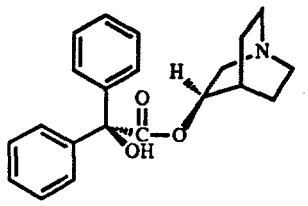
Also during this period several medical radioisotopes and radioisotope generators were provided to collaborators for joint research, including tungsten-188/rhenium-188 generators which were provided to Columbia University, New York, the clinic for Nuclear Medicine in Bonn, Germany, and the Department of Nuclear Medicine in Ulm, Germany. In addition, a sample of rhenium-188 calibrated at ORNL with a NIST standard was provided to Columbia University for calibration of radiation detectors in anticipation of initiation of swine studies.

Medical radioisotopes which were provide on a full cost recovery basis through the ORNL Isotope Distribution Office included rhenium-186, provided to Mallinckrodt Medical, in Petten, The Netherlands. In addition, a solution of processed tungsten-188 was provided to Nordion, Inc.

Synthesis and *In Vitro* and *In Vivo* Evaluation of Fluorine-18 Labeled Isomers of FQNPe

The muscarinic acetylcholinergic receptor (mAChR) complex has been well characterized, and the mAChR subtypes are located in various tissues to different degrees and have been implicated to play important roles in many neurological disorders in the central nervous system (CNS). These observations have stimulated interest in the development of mAChR subtype-specific ligands for use in Positron Emission Tomography (PET). Fluorine-18, with its attractive decay properties, half-life, and availability from medical cyclotrons is an important radioisotope for PET. Although a limited number of fluorine-18 labeled mAChR ligands have been described, these ligands do not demonstrate suitable properties for routine use in PET or are not reported to be mAChR subtype specific.

Analogues of 1-azabicyclo[2.2.2]oct-3-yl α-hydroxy-α-α-phenylacetate (QNB, **1**), a high affinity mAChR antagonist, have been prepared and evaluated as new agents for nuclear medicine studies. Of these analogues, 1-azabicyclo[2.2.2]oct-3-yl α-hydroxy-α-(4-iodophenyl)-α–phenylacetate (4IQNB, **2**) has been labeled with iodine-123 and has been utilized in studies of healthy individuals and patients with dimentias. More recently, a new analogue (IQNP, **3**) has been prepared in which one of the phenyl rings of **1** has been replaced with an iodoallyl group and demonstrates high accumulation in regions of the brain containing mAChR[1-3]. In addition, the resolution of the eight stereoisomers of IQNP has shown that the various stereoisomers demonstrate a modest selectivity for the various mAChR subtypes *in vitro* and *in vivo*.



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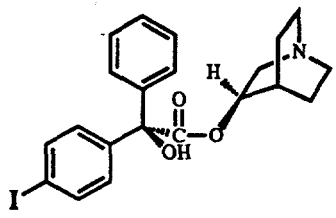

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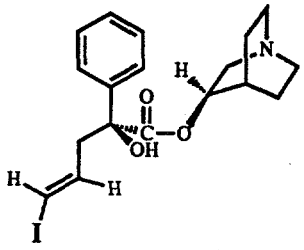

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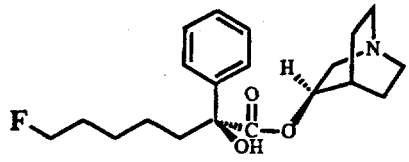

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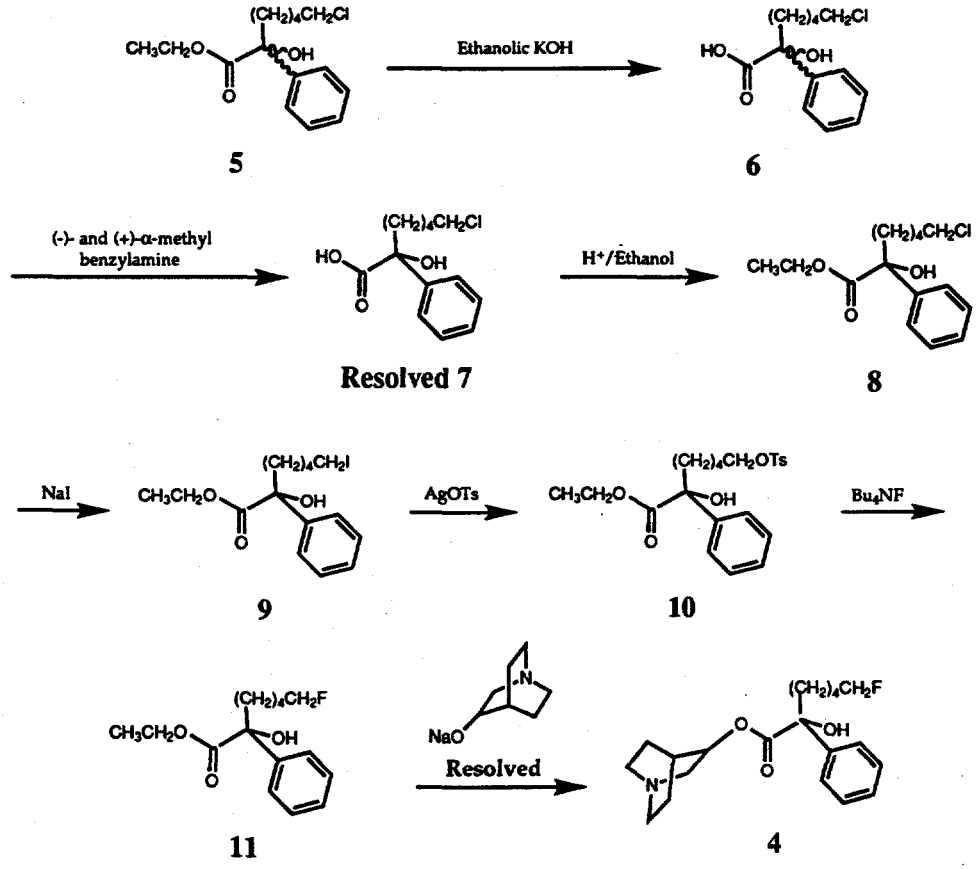
Figure 1. Structures of QNB(**1**), 4IQNB (**2**), (E)-IQNP (**3**), and FQNPe (**4**).

We have previously prepared and evaluated a new analogue of QNB, 1-azabicyclo [2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate (FQNPe, **4**)[4]. The racemic ligand demonstrated high *in vitro* binding affinity for mAChR and pretreatment of rats with racemic **4** significantly blocked receptor localization of subsequently injected iodine-131-Z-(-,-)-IQNP (**1**). We now report the resolution, *in vitro* binding assays, fluorine-18 labeling and initial biodistribution studies in rats of the (-,-)- and (-,+)- stereoisomers of FQNPe.

The resolution of the various stereoisomers of FQNPe (**4**) is shown in Scheme 1. Racemic ethyl α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate (**5**) was prepared and converted to the free acid (**6**) by basic hydrolysis as described previously. Resolution into the corresponding (-)-isomer was accomplished by treatment of racemic α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid with (S)-(-)-α-methylbenzylamine as had been reported for the resolution of the stereoisomers of IQNP[2]. The resultant (-)-diastereomer salt was recrystallized twice from water:ethanol (7.5:2.5 v/v). The acid obtained from the mother liquor by treatment with dilute HCl was subsequently treated with (R)-(+)-α-methylbenzylamine to afford (+)-diastereomeric salt after recrystallization from water:ethanol (7.5:2.5 v/v) twice. The two enantiomeric acetic acids were then released from the corresponding diastereomeric salts by treatment with 3N HCl. The specific rotation values and melting points of these four diastereomeric salts are summarized in Table 1.



5 **6** **Resolved 7** **8** **9** **10** **11** **4**

Scheme 1. Resolution of FQNPe (**4**).

Table 1. Specific Rotation Values [a] ($[\alpha]_D$) of the FQNPe Stereoisomers (4) and Intermediates.

Compound	$[\alpha]_D$(°)	c (mg/mL)
(-)-7[b]	(-) 8.2	6.1
(-)-7[c]	(-) 11.1	1.4
(+)-7[b]	(+) 7.8	7.6
(+)-7[c]	(+) 11.3	1.5
(-)-7	(-) 12.1	5.8
(+)-7	(+) 11.6	6.1
(-)-8	(-) 17.4	8.1
(+)-8	(+) 19.3	9.3
(-)-9	(-) 14.1	11.3
(+)-9	(+) 15.5	9.7
(-)-10	(-) 12.0	8.3
(+)-10	(+) 12.2	6.6
(-)-11	(-) 23.8	1.3
(+)-11	(+) 23.7	1.1
(-,-)-4[d]	(-) 11.7	1.3
(-,+)-4	(+) 24.1	1.2
(-,+)-4	(-) 25.8	1.2
(+,+)-4	(+) 12.9	1.2

[a] Rotation measured in chloroform

[b] (S)-(-)-α-methylbenzylamine salt

[c] (R)-(+)-α-methylbenzylamine salt

[d] The first center designates the 3-quinuclidinyl moiety, the second the acetate moiety

Analysis of the proton NMR spectra of the (-)-α-methylbenzylamine-(-)-acid [(-,-)] and (+)-α-methylbenzylamine-(+)-acid [(+,+)] diastereomeric salts provided additional information which could be used to evaluate the optical purity of the acetate moiety of the diastereomeric salts (Figure 2). While the chemical shift of the ortho aromatic proton of the acetate moiety in the ^1H spectrum of the [(+,-)] salt exhibited a resonance at 7.53 ppm, this resonance was observed at 7.41 ppm in the spectrum of the [(+,+)] salt. Similarly, while the chemical shift of the ortho aromatic proton of the acetate moiety in the ^1H spectrum of the [(-,+)] salt exhibited a resonance at 7.51 ppm, these two protons are observed at 7.42 ppm in the spectrum of the [(-,-)] salt. The diastereomeric purity of the acetate moiety can thus be assessed by examination of the chemical shift values of the ortho aromatic protons of the benzene ring of the acetic acid moiety in the proton NMR spectra with a sensitivity of approximately 90%.

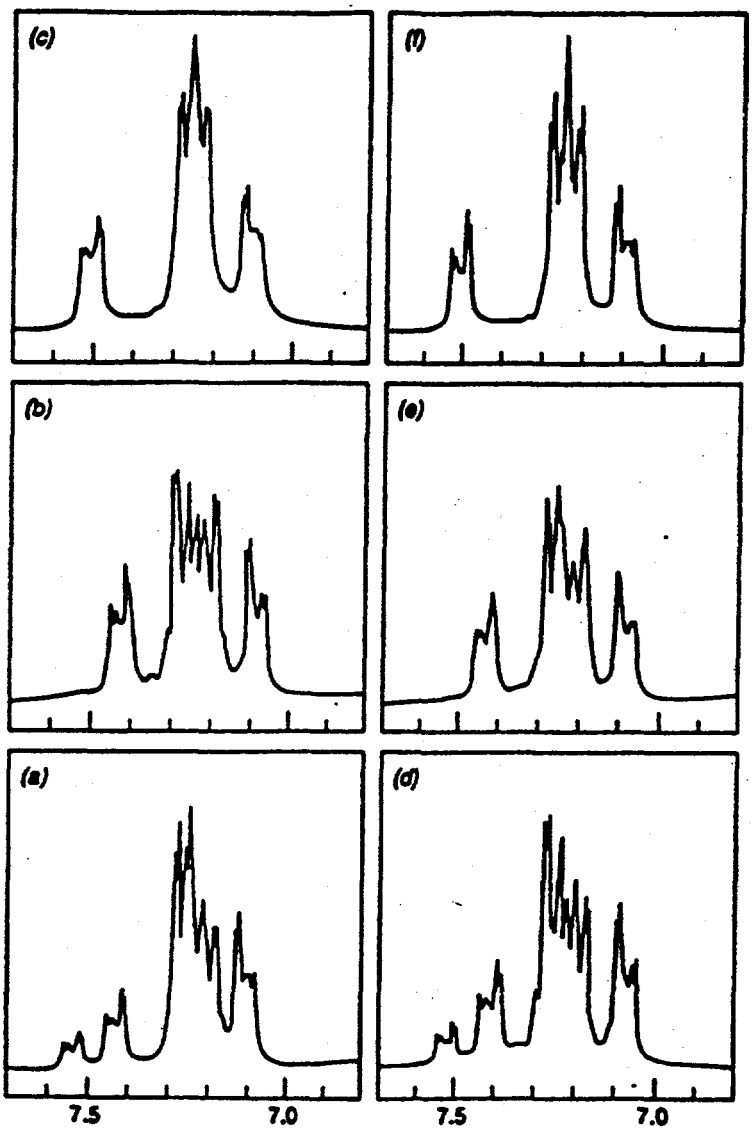


Figure 2. Selected aromatic regions from the ^{1}H NMR spectra of crude (-)-7 salt (a), purified (-)-7 salt (b), (+)-7 salt (c), crude (+)-7 salt (d), purified (+)-7 salt (e) and (-)-7 salt (f).

The stepwise treatment of (-)- and (+)-7 with acidic ethanol, sodium iodide, silver p-toluenesulfonate and tetrabutylammonium fluoride afforded (-)- and (+)-ethyl α-(1-fluoropent-5yl)-α-hydroxy-α-phenylacetates (**11**) which were then transesterified with resolved 3-quinuclidinol to afford the four stereoisomers of FQNPe (**4**). Specific rotation values for each intermediate and the diastereomers of **4** are summarized in Table 1. It was observed in previous studies with racemic FQNPe that stereoisomers of the acetate center were effectively separated by HPLC under normal phase conditions. The refore, the enantiomeric purity achieved from the resolution of the acetate center was determined by HPLC to be 90.0 % and 88.3 % for (-)- and (+)-**7**, respectively.

Table 2. *In Vitro* Binding Assay Data for FQNPe Stereoisomers (K_i, nM).

FQNPe Stereoisomer	m1 Subtype	m2 Subtype	m3 Subtype
(-,-)	0.33	0.1	0.34
(-,+)	1.4	4.2	3.1
(+,-)	3.8	< 75%	7.6
(+,+)	< 75%	<75%	< 75%

The *in vitro* binding affinity to human m1, m2, and m3 mAChR subtypes was determined by Novascreen® in at least a five point binding curve and are summarized in Table 2. The (-,-)-, (-,+)- and (+,-)-FQNPe[5] isomers exhibited nanomolar binding affinity for the m1 (Figure 3) and m2 (Figure 4) subtypes. Although (-,-)-FQNPe showed the highest binding affinity for the mAChR subtypes, it demonstrated no subtype selectivity. (+,-)-FQNPe demonstrated a good binding affinity for m1 and m3 receptor subtypes and a low binding affinity for the m2 subtype making this isomer an attractive *in vitro* tool in the development of m2 selective mAChR ligands.

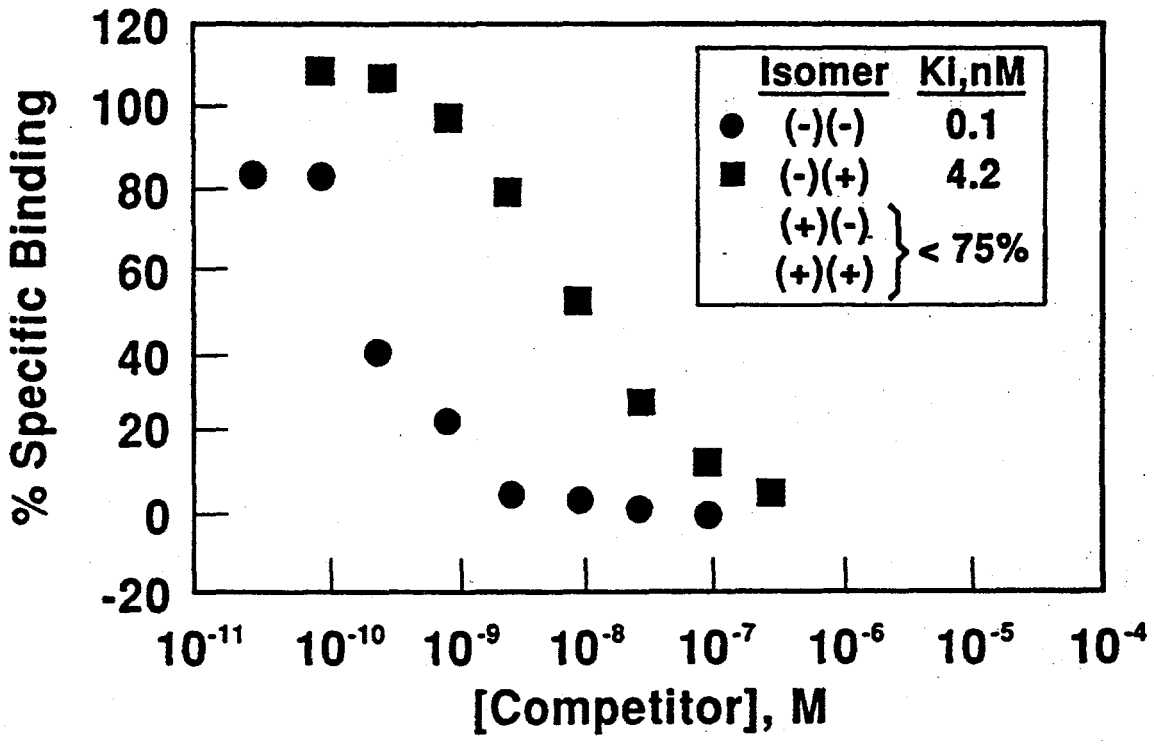


Figure 3. *In vitro* binding data for the four FQNPe isomers using human cloned m1 receptors.

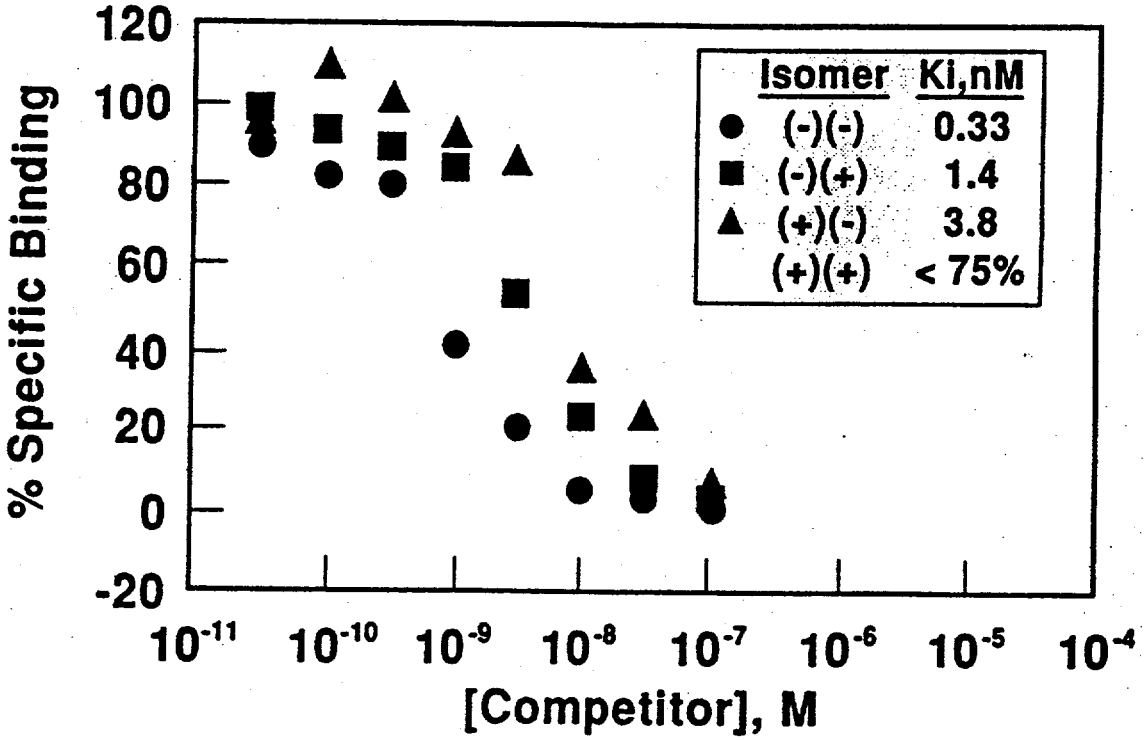
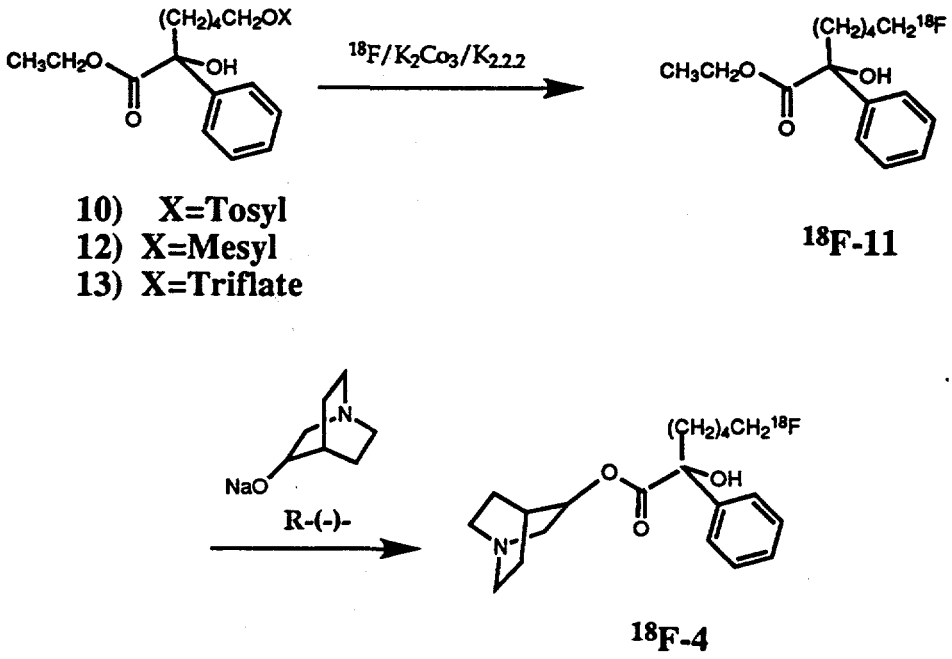


Figure 4. *In vitro* binding data for the four FQNPe isomers using human cloned m2 receptors.

Utilizing the *in vitro* binding data and previous examples in which the R enantiomer of the quinuclidinyl moiety demonstrate high *in vivo* binding to mAChR[6-8], both (-,-)- and (-,+)-FQNPe were radiolabeled with fluorine-18 via a 2 step reaction sequence as shown in Scheme 2. The radiolabeling of (-)-**11** was investigated with different leaving groups [X = tosyl (**10**), mesylate (**12**), and triflate (**13**)] under identical conditions with decay-corrected radiolabeling yields of 15%, 70% and 33%, respectively. [^{18}F]-(-)-**11** and [^{18}F]-(+)-**11** were then transesterified with the sodium salt of R-(-)-3-quinuclidinol in anhydrous benzene at 90 °C. [^{18}F]-(-,-)-**4** and [^{18}F]-(-,+)**4** were purified by HPLC after passage through a C_{18} Sep Pak and obtained in 8% and 14% radiochemical yield, respectively. Specific activity values were determined to be 1.35 mCi/μmol for (-,-)-**4** and 8.45 mCi/μmol for (-,+)-**4** by comparison of the UV trace from the HPLC purification to that of a standard curve from known concentrations of **4**.

The results of initial biodistribution studies in female rats (n=5) with (-,-)- and (-,+)FQNPe over a three hour time period are shown in Tables 3 and 4, respectively. Although each isomer displayed similar initial uptake, (-,-)-FQNPe ((**-,-**)-**4**) was significantly retained in tissues at a higher level compared to (-,+)-**4**. Radioactivity following administration of (**-,-**)-**4** distributed relatively uniformly in the various regions of the brain except for the cerebellum, a tissue which contains a low concentration of the M_2 (m2) mAChR subtype. In other tissues, the levels of activity in the blood and bone were lower for (-,-)-**4** as compared to (-,+)-**4**, indicating a greater *in vivo* stability of (-,-)-**4**.



Scheme 2. Fluorine-18 labeling of the stereoisomers of FQNPe (**4**).

Table 3. Biodistribution Data for F-18-(-,-)-FQNPe [(-,-)-4] in Female Rats (n=5).

	Percent Injected Dose/Gram (±S.D.) Time After Injection		
Organ	**15 minutes**	**60 minutes**	**180 minutes**
Blood	0.18±0.05	0.08±0.01	0.03±0.01
Liver	2.51±0.19	1.52±0.07	1.12±0.07
Kidney	1.85±0.20	0.64±0.06	0.19±0.13
Heart	1.10±0.12	0.88±0.43	0.24±0.01
Lung	6.25±0.80	1.50±0.31	0.28±0.05
Medulla	1.27±0.20	0.46±0.18	0.38±0.29
Pons	0.66±0.35	0.72±0.23	0.54±0.17
Cerebellu	0.24±0.05	0.12±0.02	0.07±0.01
Cortex	0.62±0.14	0.68±0.06	0.76±0.06
Striatum	0.64±0.23	0.66±0.10	0.70±0.31
Hippocampus	0.43±0.14	0.51±0.07	0.50±0.09
Thalamus	0.56±0.18	0.59±0.20	0.45±0.19
Superior Colliculi	0.61±0.27	0.61±0.11	0.40±0.24
Inferior Colliculi	0.49±0.15	0.63±0.28	0.55±0.29
Bone	0.33±0.13	0.22±0.07	0.25±0.11

Table 4. Biodistribution Data for F-18-(-,+)-FQNPe [(-,+)-4] in Female Rats (n=5).

	Percent Injected Dose/Gram (±S.D.) Time After Injection		
Organ	**15 minutes**	**60 minutes**	**180 minutes**
Blood	0.43±0.02	0.21±0.02	0.04±0.00
Liver	2.35±0.12	0.72±0.07	0.24±0.12
Kidney	3.77±0.37	1.18±0.15	0.16±0.06
Heart	0.94±0.05	0.41±0.03	0.11±0.05
Lung	6.05±0.38	1.46±0.24	0.20±0.03
Medulla	0.23±0.17	0.36±0.33	0.10±0.16
Pons	0.31±0.19	0.20±0.12	0.11±0.13
Cerebellum	0.23±0.04	0.07±0.02	0.03±0.01
Cortex	0.75±0.04	0.67±0.07	0.22±0.04
Striatum	0.62±0.12	0.63±0.25	0.23±0.04
Hippocampus	0.49±0.16	0.56±0.22	0.26±0.06
Thalamus	0.42±0.09	0.33±0.10	0.10±0.12
Superior Colliculi	0.40±0.15	0.16±0.04	0.05±0.05
Inferior Colliculi	0.37±0.17	0.23±0.18	0.03±0.03
Bone	0.65±0.17	1.39±0.38	2.14±1.02

A blocking study was performed in which (R)-QNB (3 mg/kg), an established muscarinic antagonist, was injected into a series of rats (n=5) one hour prior to the injection of [^{18}F]-(-,-)FQNPe. The animals were killed one hour post-injection of FQNPe and the uptake of activity in the various tissues evaluated (Figure 5). The results show the levels of activity in the various regions of the brain were decreased by approximately 90 % indicating that radioactivity in the brain is associated with the mAChR complex. These results also suggest that [^{18}F]-(-,-)-FQNPe does not demonstrate selectivity for the various subtypes of mAChR as indicated by the *in vitro* assays since the preinjection of (R)-QNB effectively blocks the uptake of activity in M_2 rich tissues of the brain (cerebellum, pons) and the heart as well as M_1 rich areas of the brain (cortex, striatum).

The radioactive species which is binding to the mAChR complex in the brain and heart in addition to radioactive species in selected tissue was also evaluated (Table 5). The organic extracts of the brain, heart, liver, lungs and blood components were analyzed 60 minutes post-injection of [^{18}F]-(-,-)-**4**. In these initial studies global analysis of the brain contents indicated that approximately 90% of the activity associated with the brain was unmetabolized FQNPe as analyzed by TLC.

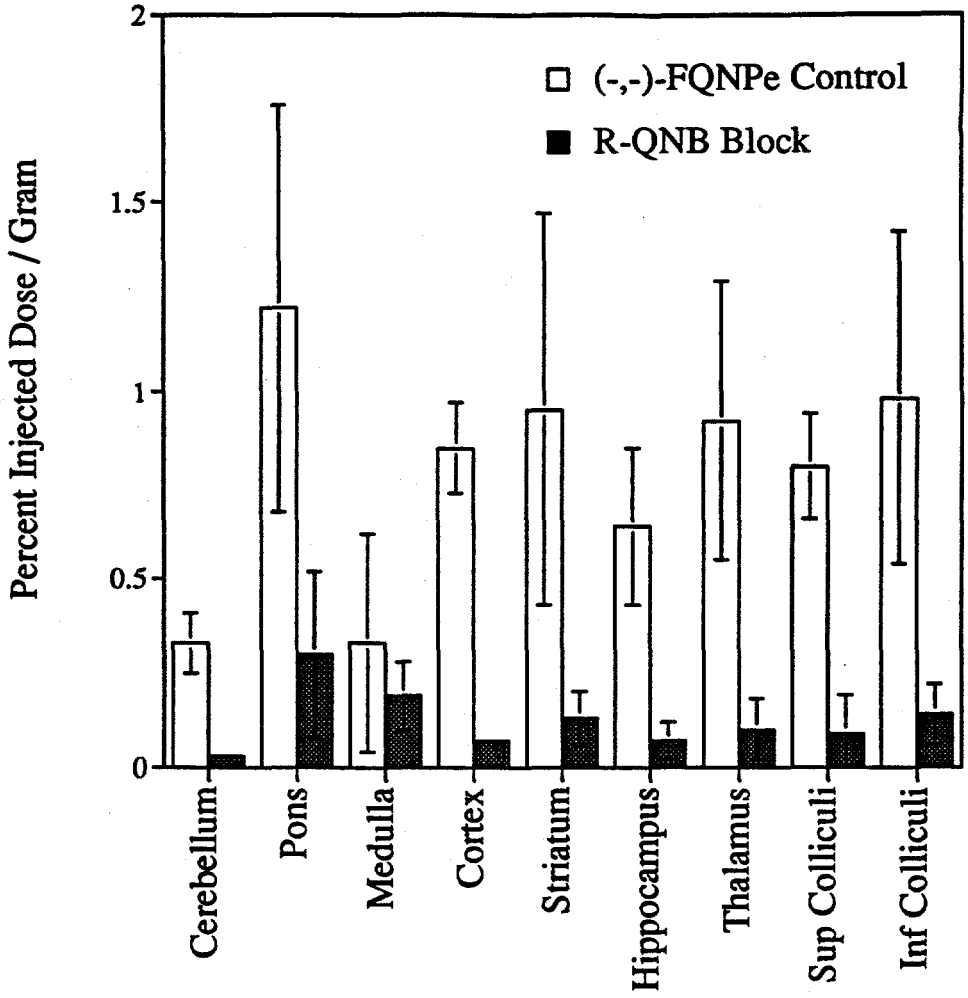


Figure 5. Preblocking of (R)-QNB on the regional brain distribution of [^{18}F]-(-,-)-FQNPe.

Table 5. Analysis of the Organic, Aqueous and Pellet Fractions of Tissues 60 Minutes PostInjection of [^{18}F]-(-,-)-FQNPe[a] (±S.D.)

Tissue	Organic Extract	Aqueous Extract	Filter/ Pellet	TLC Analysis[b]
Brain	74.9±3.1	3.5±1.5	21.7±2.6	89.0±3.1
Heart	70.8±4.0	9.8±2.0	19.4±3.2	81.9±3.1
Liver	20.5±0.9	20.4±2.3	59.0±2.8	ND
Lung	77.3±3.3	3.4±0.8	19.3±3.2	69.4-86.3
Blood	26.9±3.6	24.2±6.4	48.9±6.2	87.7-93.1

[a] Five female Fischer rats for each time point.

[b] TLC analysis of organic solution (silica, chloroform:methanol [85:15])

In conclusion, the stereoisomers of the acetate moiety of FQNPe (**4**) were resolved via the diastereomeric salts of α-methylbenzylamine and the four stereoisomers of FQNPe were subsequently prepared utilizing resolved 3-quinuclidinol. The (-,-)-, (-,+)- and (+,-)- stereoisomers of 4 demonstrate nanomolar binding affinity for m1, m2 and m3 mAChR subtypes in vitro. (-,-)-4 and (-,+)-4 were radiolabeled with fluorine-18 via a two step labeling reaction in radiolabeling yields of 8% and 14%, respectively. The results from our initial *in vivo* biodistribution studies demonstrated that the levels of radioactivity following administration of [^{18}F]-(-,-)-**4** were higher in the various brain regions examined and lower in the blood and bone compared to levels of radioactivity observed for (-,+)-**4**. The preinjection of (R)-QNB was observed to block the uptake of [^{18}F]-(-,-)-**4** in the various regions of the brain. *In vivo* metabolic studies indicate approximately 90% of [^{18}F]-(-,-)-**4** observed in the brain represented unmetabolized FQNPe. These combined results suggest (-,-)-FQNPe (**4**) is an attractive candidate for further evaluation for the imaging of mAChR by PET.

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4. Luo H, Hasan A, Sood V, McRee RC, Zeeberg B, Reba RC, McPherson DW, Knapp FF Jr. Synthesis and evaluation of new 1-azabicyclo[2.2.2]oct-3-yl α-fluoroalkyl-α-hydroxy-α-phenylacetates as ligands for the study of muscarinic receptor density by positron emission tomography. *Nucl Med Biol* 1995; 23: 267-276.

5. The notation, for example, (-,-)-FQNPe refers to the first center as the quinuclidinyl moiety and the second center as the acetate moiety.

6. Rzeszotarski WJ, McPherson DW, Ferkany JW, Kinnier WJ, Noroha-Blob L, Kirken-Rzeszotarski A. Affinity and selectivity of the optical isomers of 3-quinuclidinyl benzilate and related muscarinic antagonists. *J Med Chem* 1988; 31: 1463-1466.

7. Inch TD, Green DM, Thompson PBJ. The central and peripheral activities of antiacetylcholine drugs. Some concepts of practical relevance. *J Pharm Pharmacol* 1973; 25: 359-370.

8. Meyerhoffer A. Absolute configuration of 3-quinuclidinyl benzilate and the behavior effect in the dog of the optical isomers. *J Med Chem* 1972; 15: 994-995.

Other Nuclear Medicine Group Activities

Medical Cooperative Programs

During this period several radioisotope generators and other medical radioisotopes were provided to collaborators for joint research and included tungsten-188/rhenium-188 generators which were provided to Columbia University, New York; Montevideo, Uruguay; Bonn, Germany; and Ulm, Germany. Tungsten-188 sodium tungstate solution and rhenium-188 were provided to the Columbia University, New York, for a research project involving the use of rhenium-188 for inhibition of restenosis after coronary angioplasty.

Distribution of Radioisotopes By Cost Recovery Through the ORNL Isotopes Distribution Office (IDO)

Medical radioisotopes which were provided for full cost recovery through the ORNL Isotope Production and Distribution Program included high specific activity rhenium-186 which was provided to Mallinckrodt Medical, Petten, Holland. In addition, tungsten-188 sodium tungstate solution was provided to Nordion, Inc., Canada.

Recent Publications

E. Dadachova, S. V. Smith and S. Mirzadeh, "Electrolytic Reduction of Carrier-free Rhenium-188," *Appl. Radiat. Isot.*, 47, 293-296 (1996).

S.-J. Wang, W.-Y. Lin, M.-N. Chen, B.-T. Hseih, Z.-T. Tsai, G. Ting, and F. F. Knapp, Jr., "Radiolabeling of Lipiodol with Generator-Produced Rhenium-188 for Hepatic Tumor Therapy," *Appl. Radiat. Isot.*, 47, 267-272 (1996).

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