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Progress Report.

This progress report cover the period from October 1, 1988 to October 30, 1989.

Our objectives were to 1) synthesize analogues of 4-IQNB which exhibit lower lipophilicity, preferably similar to that of QNB; 2) prepare F-18 analoges of QNB and 3) prepare analogues of 3-quinuclidinyl benzilate containing a lipophilic chelate Tc-99m.

1. Publications

Two manuscripts mentioned in the last report have been published.

a. Cohen, VI; Rzeszotarski, WJ; Gibson, RE; Fan, LH; Reba, RC. Preparation and Properties of (R)-(-)-1-Azabicyclo[2.2.2]oct-3-yl (R)-(+)-α-Hydroxy-α-(4-[^{125}I]iodophenyl)-α-phenylacetate and (R)-(-)-1-Azabicyclo[2.2.2]oct-3-yl (S)-(-)-α-Hydroxy-α-(4-[^{125}I]iodophenyl)-α-phenylacetate as Potential Radiopharmaceuticals. J. Pharm. Sci., 1989, 78, 833.

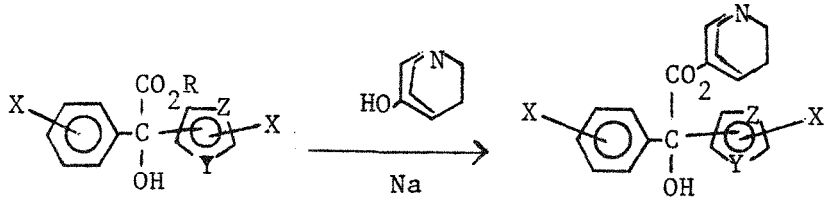
b. Gibson, RE; Schneidau, TA; Cohen, VI; Sood, V; Ruch, J; Melograna, J; Eckelman, WC; Reba, RC. In Vitro and In Vivo Characteristics of [Iodine-125] 3-(R)-Quinuclidinyl (S)-4-Iodobenzilate. J. Nucl. Med., 1989, 30, 1079.

2. Work in Progress.

a) Chemistry.

During the period, we have synthesized 5 heterocyclic analogue (compound I, II, III, IV, and IX; group I) proposed in Table 3. Our initial route for the synthesis of brominated the above compounds, furyl and thienyl analogues of QNB was via scheme 1.

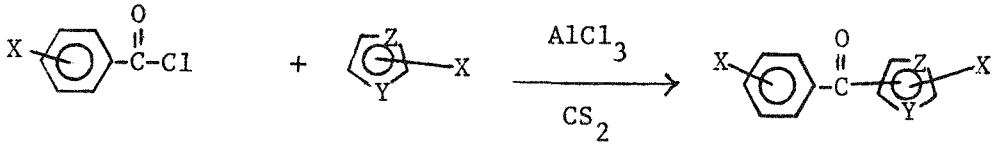
1)



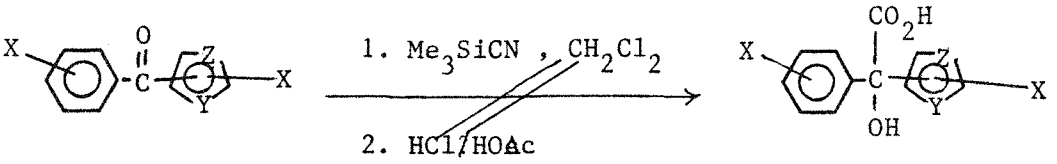
X = H, Br Y = O, S, NH Z = CH, N

The ketone intermediates were obtained in good yields by acylation (scheme 2) of furane or thiophene derivatives with benzoyl or 4-bromobenzoyl chlorides.

2)



Unfortunately, the addition of trimethylsilyl cyanide to these ketones (schemes 3) did not occur.

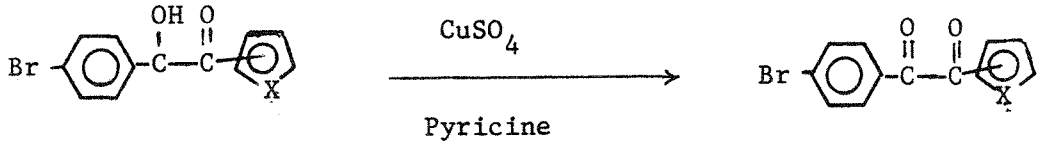
3) 

We have attempted the synthesis of these compound (I, II, III, IV, and IX) via several different routes. The following reaction have been tried:
We obtained the mixed ketone intermediate via scheme 4.

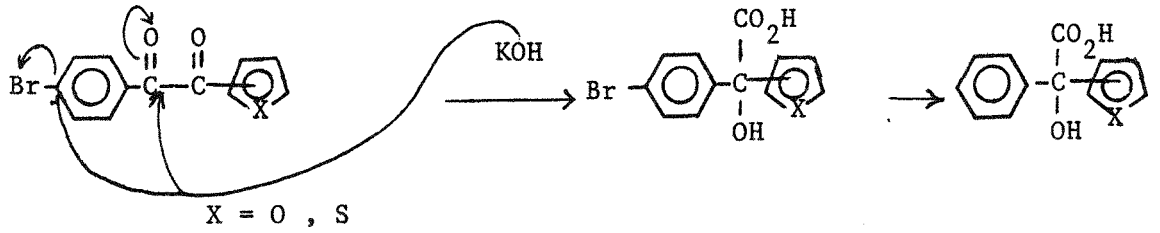
4) 

X = O , S

The mixed benzoin condensation was effected by adding a solution of KCN in water to an ethanolic solution of 4-bromobenzaldehyde and substituted 2- or 3-thiophencarboxaldehyde or furaldehyde. The diketone was obtained by the method of Campaigne & Bourgois.[1] A mixture of copper sulfate, pyridine and water are heated until the copper sulfate has dissolved. To this solution was added the mixed benzoine adduct and the solution heated for 2 hours. The solid product obtained was recrystallized from ethanol-water (scheme 5).

5) 

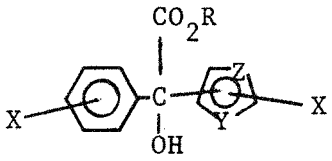
however, benzilic acid rearrangement in aqueous alcoholic potassium hydroxide to form phenyl- or 4-bromophenyl- 2- or 3-furyl-, thienyl- or 5-bromothienylglycolic acid did occur, but presence of the halogen in the reagent led, at the same time, to the elimination of the halogen in the product (scheme 6).

6) 

X = O , S

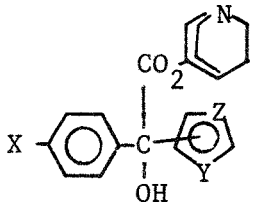
Therefore we turned our attention to the reaction between phenyl-, 4-bromophenyl-, 2-, or 3-furyl-, or 5-bromofuryl-, or 2-, 3-thienyl- or 5-bromothienyl-magnesium bromide with an excess of dimethyl or diethyl oxalate at -70°C,[2] and the reaction between ethyloxalyl chloride with 2-bromothipen.[3] Methyl or ethyl aryl- heteroarylgloxalate and an equivalent amount of Grignard reagent gave then ethyl or methyl aryl- or heteroaryl glycolates (scheme 7).

7)



X = H, Br Y = O, S, NH Z = CH, N R = CH_3, C_2H_5

Transesterification of the ethyl or methyl esters with 3-quinuclidinol in the presence of sodium metal provided the final products.

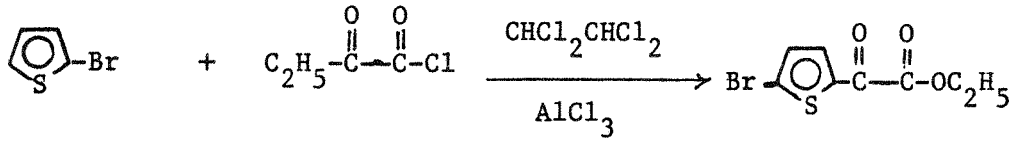


X = H, Br Y = O, S, NH Z = CH, N

Ethyl 2-(5-bromothienyl) glyoxalate.

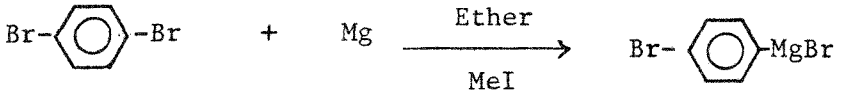
A mixture of 2-bromothiophen, ethyl oxalyl chloride and tetrachloroethane was poured into a flask fitted with a stirrer and a thermometer. Aluminum chloride was added portionwise at -5°C,[3] (scheme 8).

8)

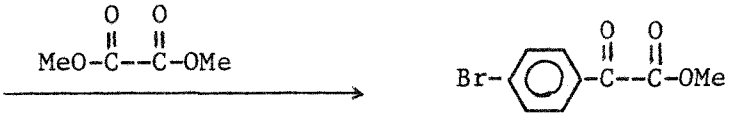


Methyl 4-bromophenylglyoxalate.

4-Bromophenylmagnesium bromide was prepared from 1,4-dibromobenzene in ether and magnesium with a few drops of methyl iodide. It was added dropwise to a solution of dimethyl oxalate in ether cooled to -70°C (scheme 9).



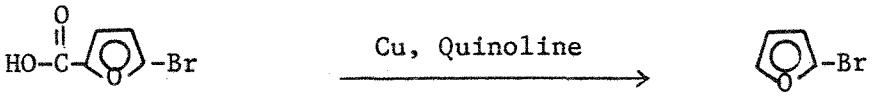
9)



2-Bromofurane.

A mixture of 5-bromofuroic acid, quinoline and copper powder was heated and the product was collected at 87-93°C, according to the method reported by Clennan et al.[4] (scheme 10).

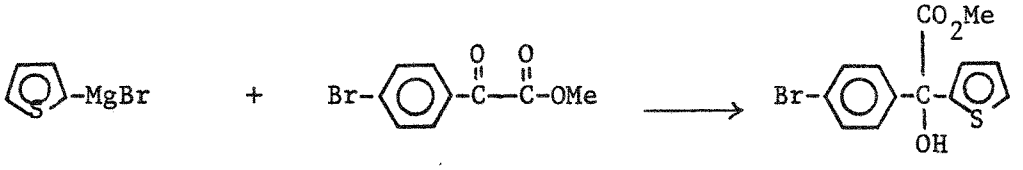
10)



Methyl α-(4-bromophenyl)-α-(2-thienyl)-α-hydroxyacetate.

A solution of 2-thienylmagnesium bromide was cooled to -70°C and was added drop by drop to a solution of methyl 4-bromophenylglyoxalate in ether cooled to 0°C (scheme 11).

11)

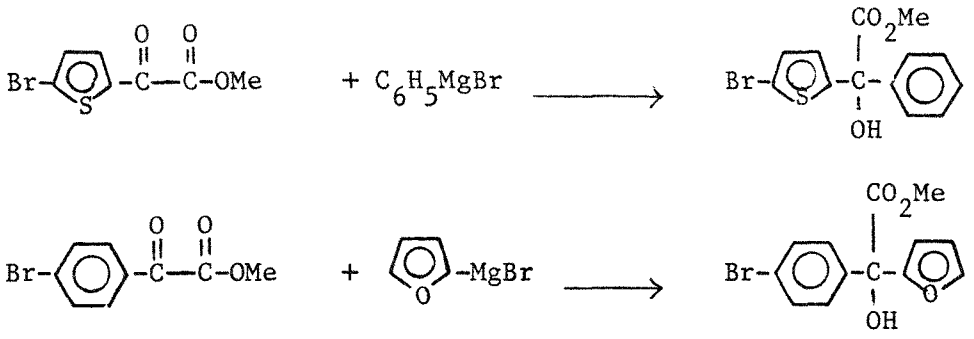


Methyl α-(4-bromophenyl)-α-(2-furyl)-α-hydroxyacetate.

Ethyl α-phenyl-α- 2-(5-bromothienyl)-α-hydroxyacetate.

These compounds were prepared from ethyl 2-(5-bromothienyl)glyoxalate & phenylmagnesium bromide, or methyl 4-bromophenylglyoxalate & 2-furylmagnesium bromide in the same manner as above (scheme 12).

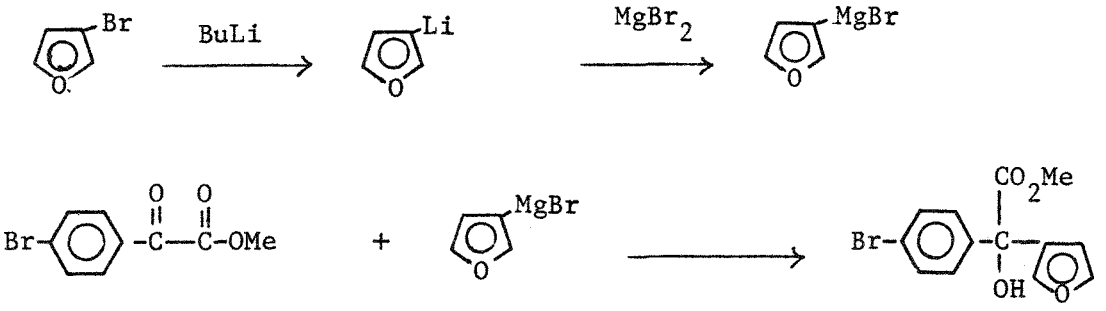
12)



Methyl α-(4-bromophenyl)-α-(3-furyl)-α-hydroxacetate.

A solution of 3-furyllithium in ether was prepared from 3-bromofuran and butyllithium in ether at -70°C. It was added at -70°C under nitrogen to a well-stirred solution of magnesium bromide in ether-benzene. A solution of 3-furylmagnesium bromide was formed which cooled to -70°C, and added dropwise to a stirred solution of methyl 4-bromophenylglyoxalate in ether cooled to 0°C (scheme 13).

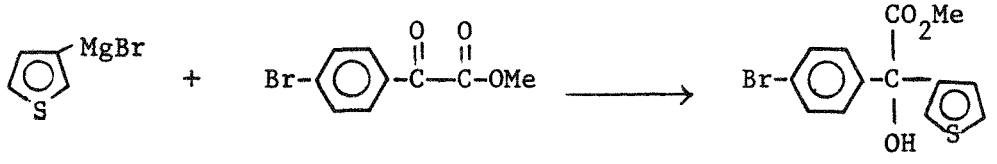
13)



Methyl α-(4-bromophenyl)-α-(3-thienyl) α-hydroxyacetate.

This compound was prepared from a solution of 3-thienylmagnesium bromide and 4-bromophenylgloxalate in the same manner as above (scheme 14).

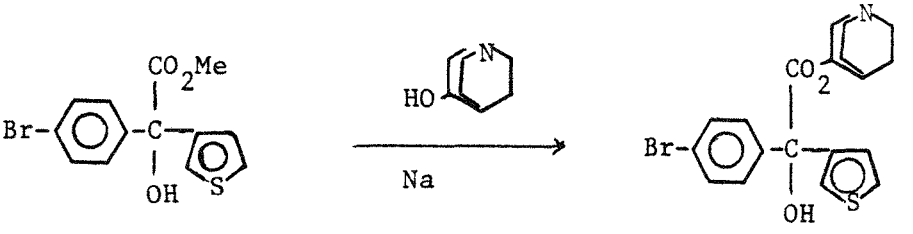
14)



Quinuclidinyl α-(4-bromophenyl)-α-(3-thienyl)α-hydroxyacetate.

A solution of methyl α-(4-bromophenyl)-α-(3-thienyl)-α-hydroxyacetate in anhydrous benzene with sodium metal was refluxed for 1h. Then quinuclidinol was added and the mixture was heated under reflux for 1 day (scheme 15).

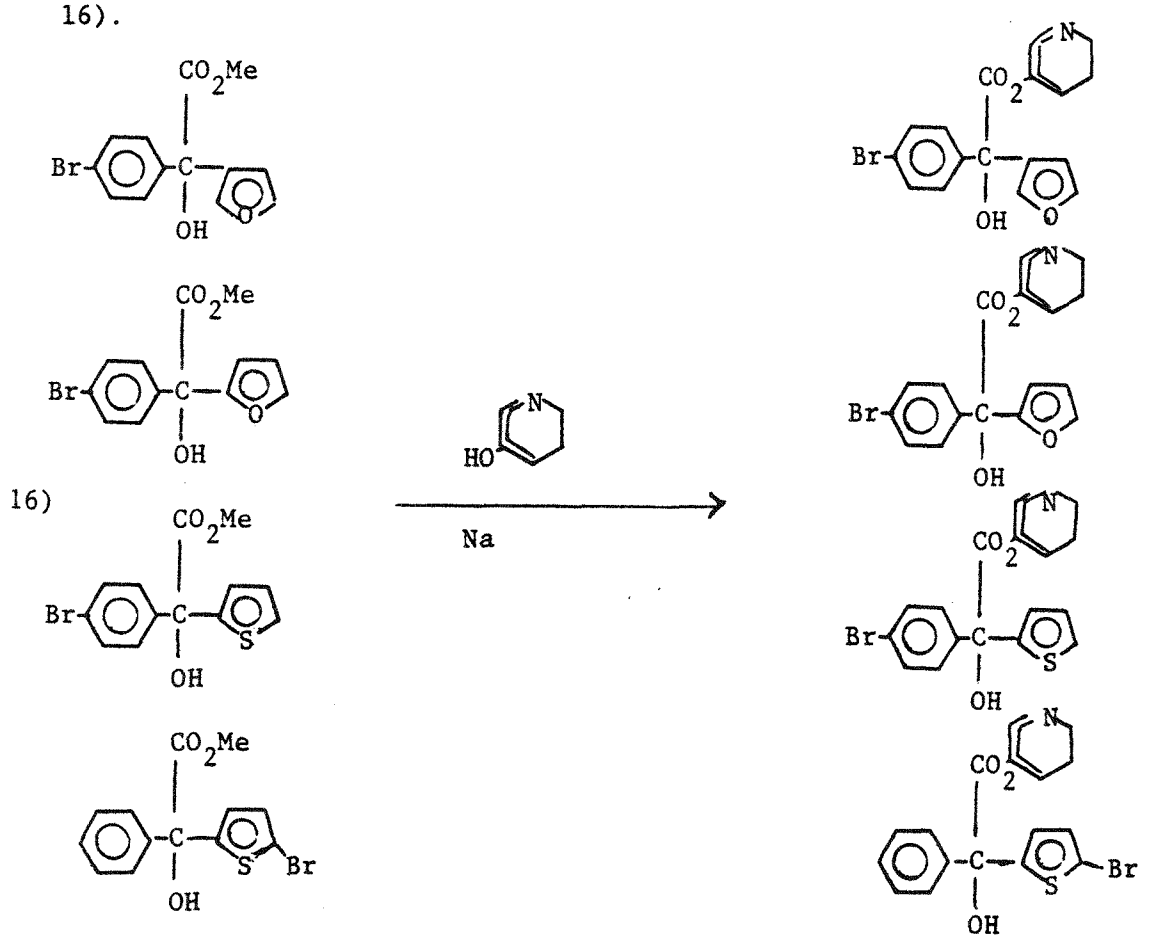
15)



Quinuclidinyl α-(4-bromophenyl)-α-(3-furyl)-α-hydroxyacetate,
Quinuclidinyl α-(4-bromophenyl)-α-(2-furyl)-α-hydroxyacetate,
Quinuclidinyl α-(4-bromophenyl)-α-(2-thienyl)-α-hydroxyacetate, and
Quinuclidinyl α-phenyl-α-2-(5-bromothienyl)-α-hydroxyacetate.

These compounds were prepared from respective methyl or ethyl esters by transesterification with quinuclidinol in the same manner as above (scheme 16).

16)



Fluorinated Analogues of QNB (Group II).

We have attempted the synthesis of quinuclidinyl α-phenyl α-(4-fluorobutyl) α-hydroxyacetate (compound XIII, Table 3, page 54 of the 1988 submission, and quinuclidinyl α-phenyl α-fluromethyl α-hydroxyacetate (page 56 of the 1988 submission) via several different route. The following reaction sequences have been tried:

Synthesis of 4-Chlorobutyrophenone.

It was prepared by reaction of 5-chlorovaleric acid with phenyllithium in ether at -65°C (scheme 17).

17) $$Cl\{CH_2\}_4CO_2H + C_6H_5Li \xrightarrow{-65\,^{\circ}C} Cl\{CH_2\}_4\overset{O}{\overset{\|}{C}}-C_6H_5$$

General Method for synthesis of Ethyl α-Chloromethyl or α-(4-Chlorobutyl) α-Phenyl α-Hydroxyacetate.

Reaction of chloroacetophenone and 4-chlorobutyrophenone with trimethylsilyl cyanide followed by acid hydorlysis at room temperature and esterification with ahydrous ethanol and trifluoromethansulfonic anhydride provided respective ethyl ester (scheme 18).

18) $$Cl\{CH_2\}_n\overset{O}{\overset{\|}{C}}-C_6H_5 \xrightarrow[2.\ HCl/HOAc]{1.\ Me_3SiCN} Cl\{CH_2\}_n\overset{CO_2H}{\overset{|}{C}}(OH)-C_6H_5$$

$$\xrightarrow[(CF_3SO_2)_2O]{EtOH} Cl\{CH_2\}_n\overset{CO_2Et}{\overset{|}{C}}(OH)-C_6H_5$$

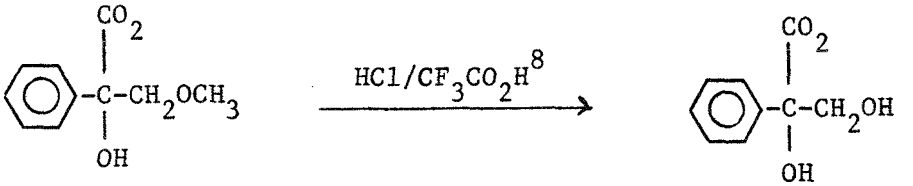
n = 1 and 4

Cleavage of α-Methoxymethyl α-Phenyl α-Hydroxyacetate.

We have attempted several different selective cleavage. Usually, a methyl ether is selectively cleaved in the presence of an ester. The following cleavage methods have been tried but without success (scheme 19):

$BF_3.Et_2O$, RSH [6]

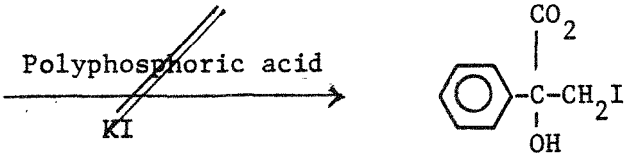
$AlCl_3$, EtSH [7]

19) 

Me_3SiI [9]

MeSiCl, NaI [10]

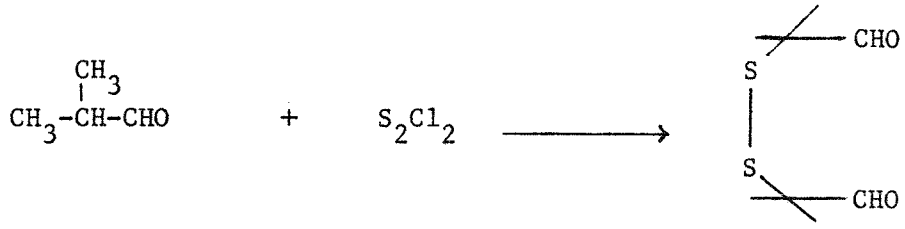
And cleavage to the branched iodide (scheme 20):

20) 

Additional progress concerns the synthesis of some intermediate in Group III.

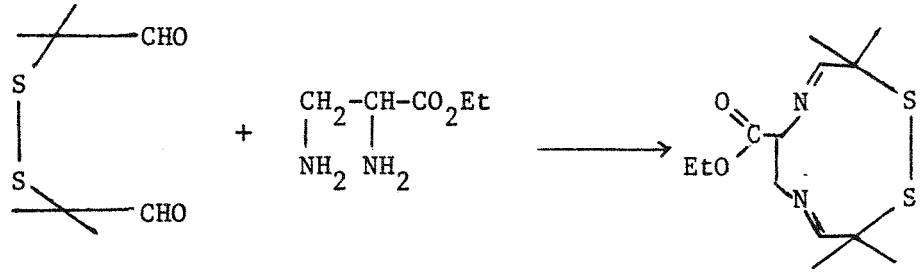
2,2-Dithio-bis(2-methylpropanal).

This compound was prepared according to a reported method from isobutyraldehyde and S_2Cl_2,[5] (scheme 21).

21) 

Ethyl(5,6-dithia-4,4,7,7-tetramethyl-2,9-diaza-2,8-dienecyclodecyl) formate.

It was prepared from 2,2-dithio-bis(2-methylpropanal) and ethyl 3,4-diaminopropionate dihydrochloride (scheme 22).

22) 

b)BIOCHEMISTRY.

We have determined the afinity constants of compound II (quinuclidinyl α-(4-bromophenyl)-α-(3-furyl)-α-hydroxyacetate), compound III(quinuclidinyl α-(4-bromophenyl)-α-(2-thienyl)-α-hydroxyacetate, compound IV (quinuclidinyl α-(4-bromophenyl-α-(3-thienyl)-α-hydroxyacetate, and compound IX (quinuclidinyl-α-phenyl-α-2-(5-bromothienyl)-α-hydroxyacetate analogues of QNB for the muscarinic receptor. The affinity constants are provided in Table 1.

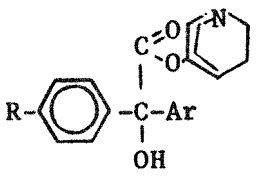
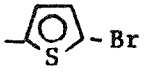


Table 1 - Results of affinity constants for heterocyclic analogues .

COMPOUND R	Ar	K_A	C.V.[a]	QNB K_A	C.V.	RBI[b]
Br		1.67 X 10^9 M^{-1}	(4.97%)	4.94 X 10^9 M^{-1}	(4.05%)	33.80%
Br		5.54 X 10^9 M^{-1}	(4.14%)	4.62 X 10^9 M^{-1}	(4.76%)	120.00%
Br		2.34 X 10^7 M^{-1}	(6.06%)	4.54 X 10^9 M^{-1}	(3.72%)	0.50%
H		5.07 X 10^9 M^{-1}	(3.71%)	4.51 X 10^9 M^{-1}	(3.22%)	112.00%

a - Coefficient of variation b - Relative binding index

R. C. Reba

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