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6-(4-PHENYL-BENZYLOXY-METHYL) GUVACINE. SYNTHESIS, GABA UPTAKE INHIBITOR AND MUSCARINIC PROPERTIES.

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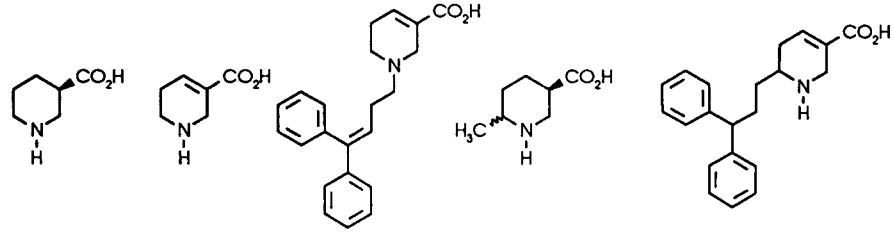
Abstract: 6-(4-Phenyl-benzyloxy-methyl) guvacine was synthesized. Surprisingly the compound was devoid of the γ-aminobutyric acid (GABA) uptake inhibitory activity of its parent compound guvacine, but instead showed affinities for the muscarinic M_1 and M_2 receptors.

Nipecotic acid **1** and guvacine **2** are recognised γ-aminobutyric acid (GABA) uptake inhibitors *in vitro*.[1] However, they show mediocre bioavailabilities when administered *in vivo*.[2] A considerable improvement was the discovery of SKF 100330-A **3**, a *N*-(4,4-diphenyl-3-butenyl) substituted guvacine.[3-5] This compound possesses high affinity (IC_{50} = 0.21 μM) and is orally bioavailable.[3]



1 **2** **3** **4** **5**

Systematic study of substitution on the backbone of nipecotic acid[6,7] showed that compound **4**, which derives from nipecotic acid by a methyl substitution in position 6, retains some uptake inhibitory activity.[12] Moreover, attachment of a 1,1-diphenylpropyl side chain at the position 6 of guvacine yielded compound **5** which possesses an *in vitro* GABA uptake inhibitory activity (IC_{50} = 0.1 μM)[8] equivalent to the N-substituted derivative SKF-100330-A, **3**.

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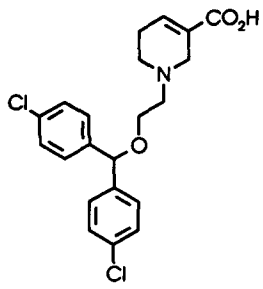
Ether-type analogues of SKF-100330-A, such as **6** and **7** were shown to possess good uptake inhibitory activities.[5,9,10] This finding prompted us to prepare some new 6-substituted analogues bearing an ether function in the side chain.[11]



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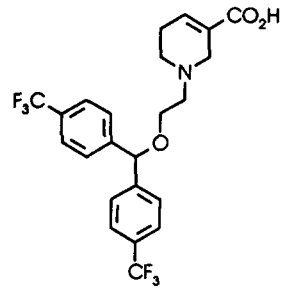

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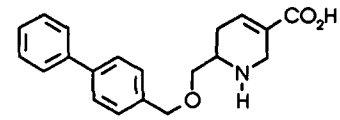


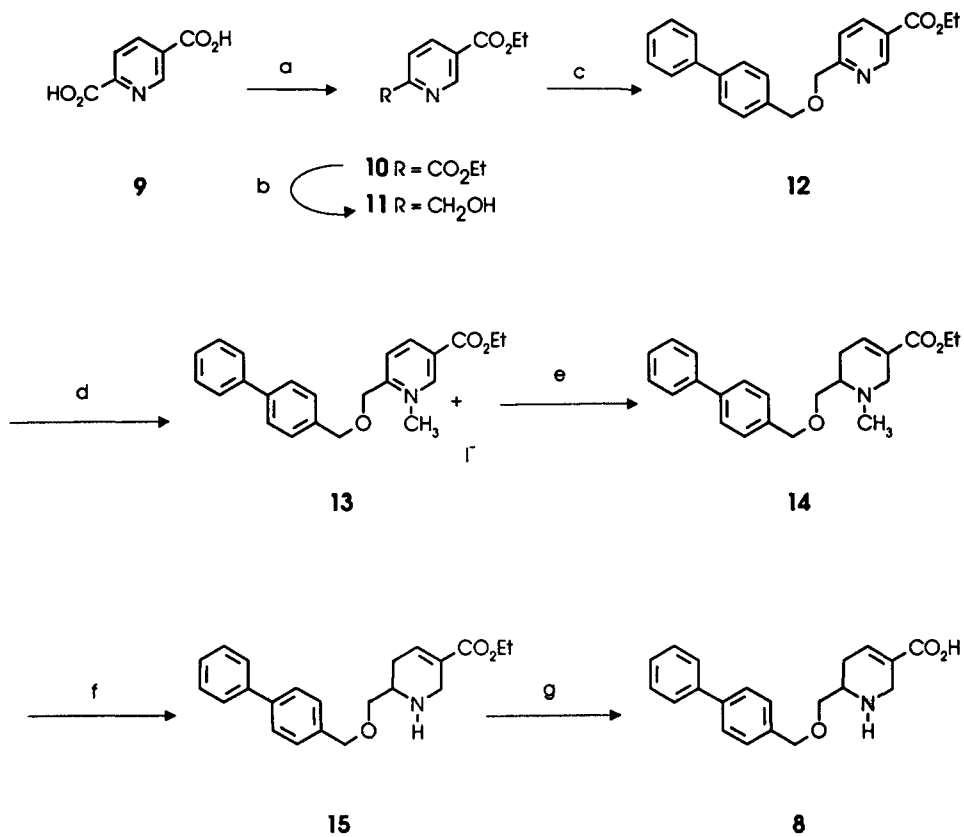
8

We report, here, the synthesis of 6-(4-phenyl-benzyloxy-methyl) guvacine **8**. The compound was tested as a GABA uptake inhibitor and for M_1 and M_2 muscarinic receptor binding affinities.

Compound **8** was obtained in a multi-step synthesis starting from 2,5 pyridine dicarboxylic acid **9** as outlined in Scheme 1. Esterification with ethanol and sulfuric acid followed by the selective reduction of the ester in position 2[12] afforded the alcohol **11**. The alcoholate of **11**, generated with sodium hydride in DMF, was reacted with 4-(bromomethyl) biphenyl to yield the corresponding ether **12**. The pyridine nitrogen was quaternarized with a large excess of methyl iodide in a mixture of acetone and acetonitrile to yield the pyridinium salt **13**. Reduction of **13** with sodium borohydride in methanol[13] gave the tetrahydropyridine **14** on which N-dealkylation was performed by treatment with 1-chloroethylchloroformate in refluxing 1,2 dichloroethane.[14] Acidic hydrolysis of the ester function of **15** gave compound **8**.

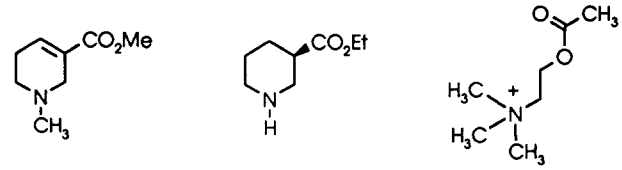
Compound **8** had no *in vitro* GABA uptake inhibition at the concentrations tested (10^{-7} 10^{-6} and 10^{-5}M, with less than 10% displacement at 10^{-5} M) following the method described in the literature.[15] This lack of affinity can be attributed to a mislocation of the second aromatic ring or to a poor orientation of the oxygen atom on the lateral chain. Surprisingly, compound **8** displayed affinity of muscarinic M_1 and M_2 receptors as measured by displacement of[^{3}H]-pirenzepine and [N-methyl-^{3}H] scopolamine methyl chloride ([^{3}H]-NMS) respectively.[16,17] Compound **8** inhibited, at 100 nM, the binding of these ligands by 57% and 59% respectively.

The ethyl ester **15** showed clearly less affinity for the M_1 and M_2 receptors with 12 % and 14 % inhibition of binding respectively at 100 nM.



Scheme 1: *Synthesis of compound 8. a: H_2SO_4, EtOH, 100%; b: $NaBH_4$, $CaCl_2$, MeOH, 76%; c: NaH, DMF, 4-diphenyl bromomethane, 79%; d: CH_3I, acetonitrile, acetone, 77%; e: $NaBH_4$, MeOH, 43%; f: α-chloroethylchloroformate, CH_2Cl_2, 42%; g: Acetic acid, HClgas, 51%*

Arecoline **16**, the methyl ester of N-methyl-guvacine[18] as well as the ethyl ester **17** of the nipecotic acid[19] are muscarinic agonists. However, the corresponding free acids do not show any muscarinic activity.



16 **17** **18**

The cholinomimetic properties of arecoline are easily understandable if arecoline is compared to the endogenous transmitter acetylcholine **18**; the acetoxy group of acetylcholine corresponds to the

carboxymethyl group of arecoline (inverted ester bioisostery) and the trimethyl ammonium group of acetylcholine to the N-methylated nitrogen of arecoline. For both compounds similar distances between the cationic nitrogen and the negative end of the carbonyl dipole can be observed. Hydrolysis of arecoline yields an inactive free carboxylic acid, the same inactivation is observed with methyl or ethyl nipecotate. It is therefore highly surprising to observe an opposite profile for compound **8** and its ethyl ester. To our knowledge compound **8** represents the first example of a free amino acid functioning as ligand for muscarinic receptors.

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