N-[2-(1-AZABICYCLO[3.3.0]OCTAN-5-YL)ETHYL]-2-NITROANILINE, A POTENT MUSCARINIC AGONIST

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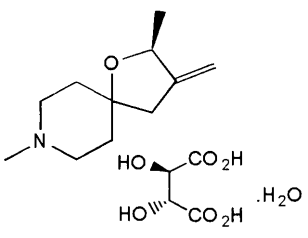
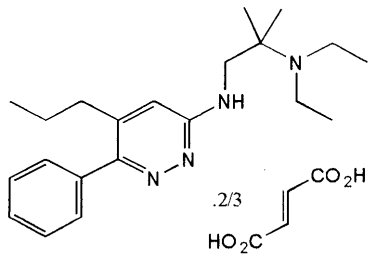
The muscarine receptor agonist SK-946, an aniline derivative with a characteristic bicyclo amine, was found. We describe a new synthetic method for 1-azabicyclo[3.3.0]octane and describe the biological activity of SK-946.

KEY WORDS muscarine receptor agonist; SK-946; 1-azabicyclo[3.3.0]octane

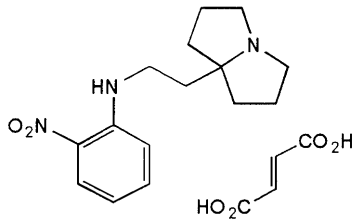
In recent years, medical advances have prolonged the average human life span, and as a result, senile dementias have tended to increase. One of the typical senile dementias is Alzheimer-type dementia. It has become very important to develop drugs effective against dementia symptoms. One of the important biochemical changes observed in brains of Alzheimer-type dementia patients is significant deficits in presynaptic cholinergic markers.[1] The cholinergic hypothesis triggered research efforts aimed at restoring defective cholinergic transmission. The most intensively investigated types of compounds are acetylcholine esterase inhibitors and muscarinic agonists. We aimed at the development of the latter type.



1 (YM796)



2 (SR46559)



3(SK-946)

In the course of our study on muscarinic agonists containing the 1-azabicyclo[3.3.0]octane moiety,[2] we found a potent new muscarinic agonist, SK-946. For detailed biological study of SK-946, large-scale synthesis of 1-azabicyclo[3.3.0]octane was needed, but the conventional synthetic method required high temperature and/or high pressure.[3] Our new synthetic method can be conducted under very mild conditions and is useful for large-scale production. We describe a convenient synthetic method of SK-946 and its agonistic activity for the muscarinic receptors.

1,7-Dichloro-4-heptanone (**5**), the starting material for 1-azabicyclo[3.3.0]octane, was prepared from dicyclopropylketone (**4**) in high yield. The key reaction was the cyclization of **5** with cyanoacetic acid in a 2-

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phase system of ammonia water and n-hexane, providing 5-cyanomethyl-1-azabicyclo[3.3.0]octane (**6**). In this reaction, **5** was converted to bicyclic imine by treatment with ammonia. Then the reaction of this imine with cyanoacetic acid gave the intermediate **6**, which was decarboxylated to give 7 in 61.4% yield (from **5**). Reduction of the cyano compound (7) using Raney-Ni in NaOH-MeOH under hydrogen at atmospheric pressure gave 5-(2-aminoethyl)-1-azabicyclo[3.3.0]octane, which was isolated as the hydrochloride **8** in 76.2% yield (from 7). Condensation with 2-chloronitrobenzene produced *N*-[2-(1-azabicyclo[3,3,0]octan-5-yl)ethyl]-2-nitroaniline (**9**), which led to the fumarate SK-946 (**3**).

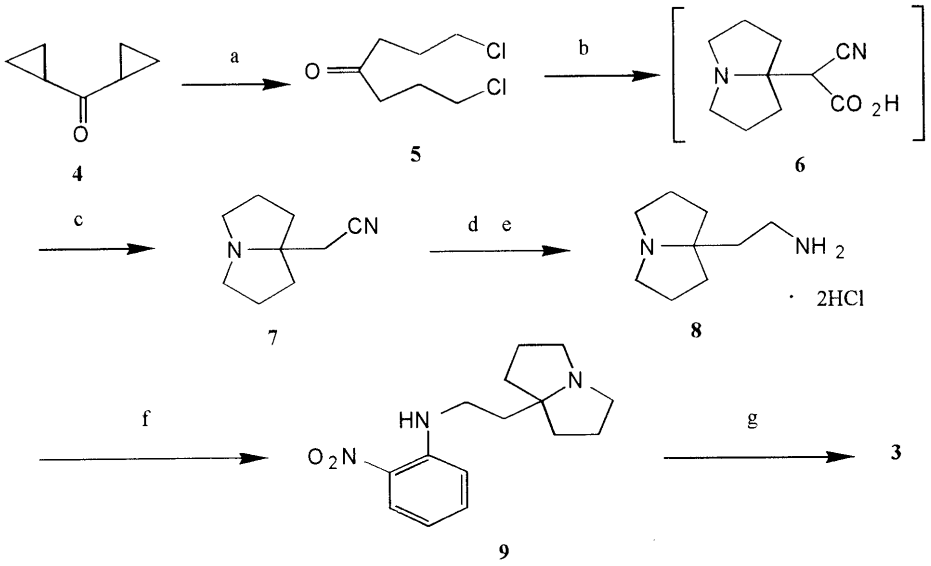

Chart a) HCl gas, 15-20°C, 98.6%. b) $NCCH_2CO_2H/NH_4OH$-n-hexane, 15-20°C. c) Concentration, 70°C, 61.4%. d) H_2, Ra-Ni/NaOH-MeOH, 1 atm. 15-20°C. e) HCl-MeOH, 76.2%. f) o-Chloronitrobenzene, $NaHCO_3$/Py, reflux, 97.9%. g) Fumaric acid/EtOH, 85.2%.

The affinities of compounds for the M1 and M2 receptors were evaluated in terms of the abilities of the compounds to displace [^{3}H]pirenzepine, an M1-selective ligand, from the rat cerebral cortex homogenate and [^{3}H]quinuclidinyl benzilate from the rat cerebellum homogenate, respectively (Table 1).[4]

SK-946 was attached to the M1 muscarine receptor with an IC_{50} value of 0.10 μM, and M2 with an IC_{50} value of 8.3 μM. As the M2/M1 ratio was 83, it showed a much higher affinity in the M1 than that in the M2 receptor. Although YM796[5] and SR46559[6] have already been developed in this field, SK-946 is superior with regard to affinity and selectivity to the M1 receptor.

Table 1 Inhibition of cerebral cortical [^{3}H]pirenzepine binding and cerebellum [^{3}H]quinuclidinyl benzilate binding by 3 compounds

Compounds	[^{3}H]pirenzepine (M1 receptor) (IC_{50} μM)	[^{3}H]quinuclidinyl benzilate (M2 receptor) (IC_{50} μM)	M2/M1
SK-946	0.10	8.3	83
SR46559A	0.10	3.8	38
(±) YM796	23.6	930	39

The agonistic property of SK-946 was supported by receptor-stimulated phosphoinositide hydrolysis in primary cultured rat fetal hippocampal neuronal cells preloaded with [^{3}H]-myo-inositol (Table 2).[7] Inositol phosphate (IP) production was expressed as [^{3}H] IP / ([^{3}H] IP + incorporated [^{3}H]-myo-inositol)%. SK-946 increased IP production at a concentration of more than 10^{-7} M.

The ability of SK-946 to improve cognitive function was assessed using passive avoidance tests in pirenzepine-, scopolamine-, cycloheximide- and electric shock-induced mice and rats. These tests suggested that SK-946 was effective for Alzheimer-type dementia.

Table 2 Concentration-effect relationship of SK-946 on IP production in primary cultured rat fetal hippocampal cells preloaded with [^{3}H]-myo-inositol.

SK-946 concentration (M)	IP production (%)
control	9.67±0.16
10^{-7}	11.61±0.45 **
10^{-6}	12.45±0.49 **
10^{-5}	13.60±0.50 ***

Each value represents the mean ± SE of 4 wells. *P<0.05, **P<0.01,***P<0.001: Significant difference from control (Fisher's protected least significant difference test).

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