Synthesis of Heterocyclic Substituted Pyridine Analogs as Potential Therapeutics for Neurodegenerative Diseases

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Abstract :

The potential therapeutic benefit of nicotinic ligands in a variety of neurodegenerative pathologies involving the CNS has energized research efforts to develop nicotinic acetylcholine receptor (nAChR) subtype-selective ligands. In particular, there has been a concerted effort to develop nicotinic compounds with selectivity for CNS nAChRs as potential pharmacological tools in the management of these disorders. The characterization of other novel nicotinic ligands such as epibatidine, showing a marked increase in potency at nAChRs, has provided additional support for the development of potent, selective ligands at individual nAChR subtypes.

We have developed and studied a number of nicotinic compounds to identify potential candidates exhibiting such selectivity. In the present study, we report the synthesis and biological evaluations of some azabicyclic and azatricyclic nicotine analogs to decipher the relationship among steric requirements of the nicotine's pyrrolidine ring system, binding affinity and subtype-selectivity.

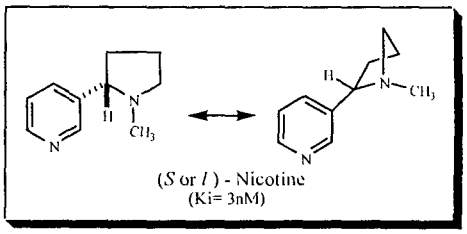
Alzheimer's Disease

- ▶ The Most Common Form of Dementia: 50%
- ▶ Progressive Deterioration in Cognitive Performance
- ▶ The Early Signs: Confusion and Forgetfulness

Pathophysiology of Alzheimer's Disease

- ▶ Cortical Atrophy: 대뇌피질의 위축
- ▶ Neurofibrillary Tangles 존재
- ▶ Neuritic Plaques 축적
- ▶ Loss of Cholinergic Neurons

INTRODUCTION



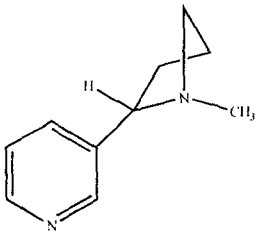
Drugs for Cognition Improvement

- ▶ Acetylcholinesterase Inhibitor:
  Tacrine (Cognex®, Parke-Davis, 1993)
  Donepezil (Aricept®, Eisai, 1996)
- ▶ Cholinergic Agonists:
  Muscarinic Receptor Agonists: Mirameline (Parke-Davis)
  Nicotinic Receptor Agonists: ABT-418 (Abbott)
  RJR-2403 (Tagacept)
- ▶ Nootropics
- ▶ Ganglioside: 신경재생
- ▶ Radical Scavengers:
  Anti-Oxidants: Vitamine E
  MAO-B Inhibitors: Selegiline (L-deprenyl)

Nicotinic Rationale for Drug Discovery:
Alzheimer's Disease

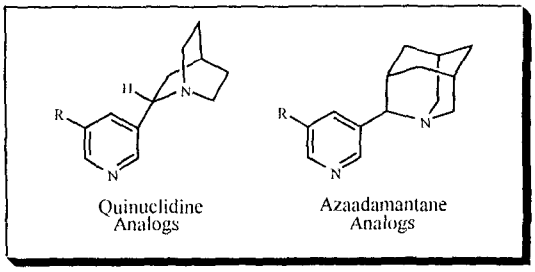
Alzheimer's Disease	Nicotinic Agonist Effects
▶Loss of cholinergic neurons	*In vitro/In vivo* neuroprotection
▶Fewer $\alpha_4\beta_2$ nicotinic receptors	Up-regulation of $\alpha_4\beta_2$ receptors
▶Depletion of acetylcholine	Modulation of acetylcholine release
▶β-Amyloid plaques	Reduced β-Amyloid aggregation
▶Progressive symptoms	Delays onset in smokers (4 yrs)
▶Multi-infarct complications	Increased cerebral blood flow
▶Inflammation	Anti-inflammatory effects
▶Memory loss	Improved attention and learning in AD patients(nicotine patch: ABT-418)

Requirements for Biological Activity



* Cationic Center
* *H-bond Acceptor Site*
* N-N Distance: 4.8-5.5A^{o}

TARGET MOLECULES



Quinuclidine Analogs

Azaadamantane Analogs

Criteria for Selecting Lead Compounds

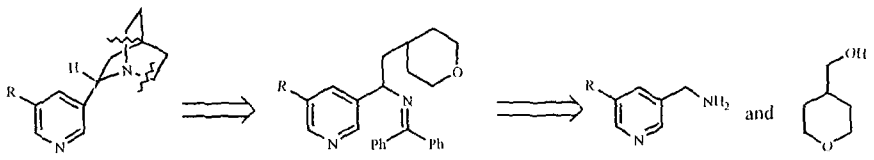
* Ki : Equi- to More Potent than Nicotine ($\leq$ 3nM)

* CNS nAchR Subtype-Selective

  { Brain (CNS)
  Muscle (PNS)
  Ganglionic (PNS) }

* Dopamine Release (Agonists or Antagonists)

Retrosynthetic Analysis of Quinuclidine Analogs



Retrosynthetic Analysis of Azaadamantane Analogs