S-10 [16:40-17:10]

Development of Aricept

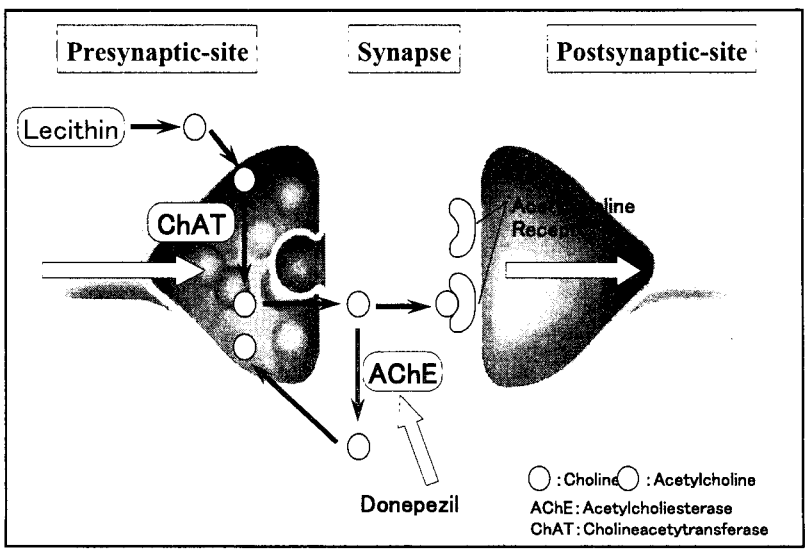
Yang Min Yeul, Excutive Director
(*Eisai Korea Inc.*)

[16:40 – 17:10]

Development of Aricept®

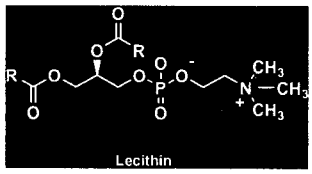
Eisai Korea Inc.
Min-Yeul YANG

Cholinergic Hypothesis

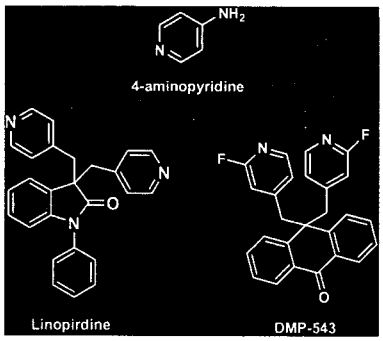


Presynaptic-site

Precursor

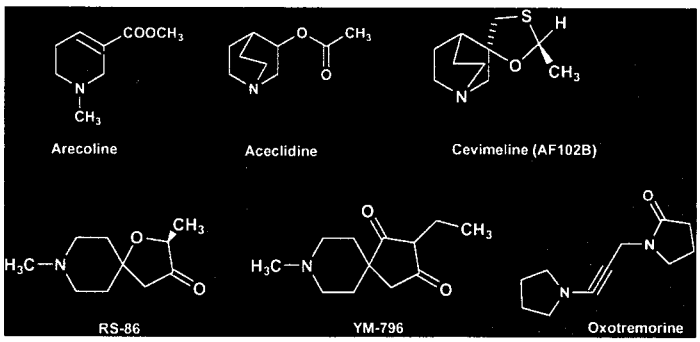


Cholinergic Enhancer



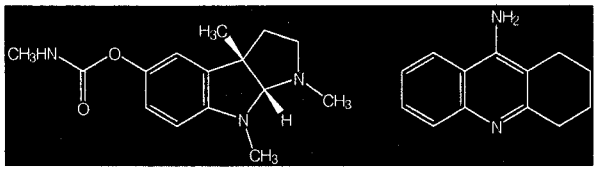
Many compounds were developed based on the presynaptic-site approach.

Postsynaptic-site



Muscarinic Receptor Agonists were developed based on the postsynaptic site approach. There are many muscarinic agonists compounds studied.

Synaptic-site

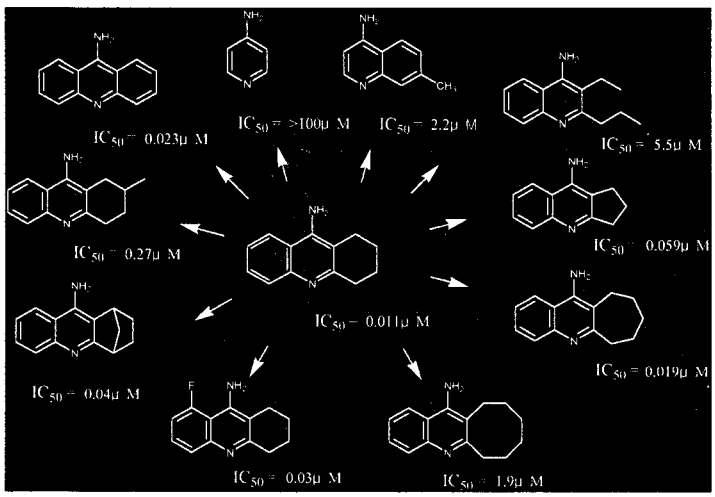


Physostigmine

Tacrine
(Cognex)

These two compounds were the earliest known AChE inhibitors. Tacrine is the first approved drug for AD treatment.

We started to synthesize tacrine derivatives but ....



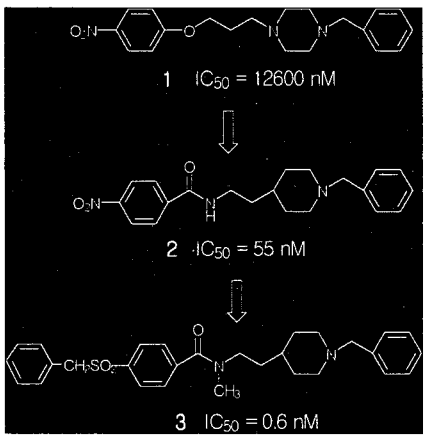
Discovery by coincidence

IC_{50} = 629 nM (enzyme of electric eel)
IC_{50} = 12600 nM (enzyme of rat brain)

Seed Compound

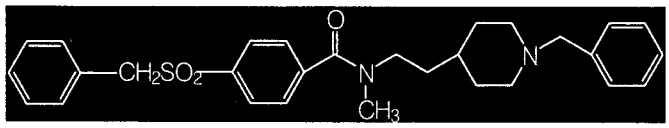
While studying tacrine derivatives, we found this seed compound. This compound was originally being synthesized for an anti-arteriosclerosis drug.

Development from seed compound 1 to the strongest compound 3



From the seed compound 1, we developed about 700 compounds. We found the strongest compound 3 with an IC_{50} of 0.6 nM.

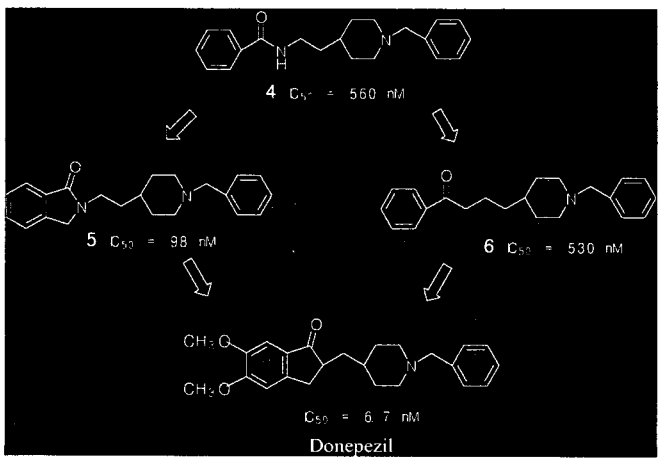
While Compound 3 showed the strongest anti-AChE activity, it has very poor bioavailability 2% (dog)



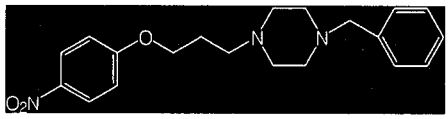
3 IC_{50} = 0.6 nM

We gave up development of this compound.

Development of Donepezil from Amide compound

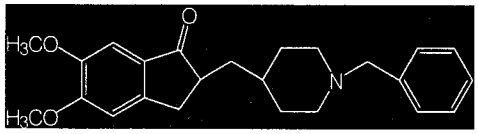


Donepezil was chosen from among 1000 compounds



1983

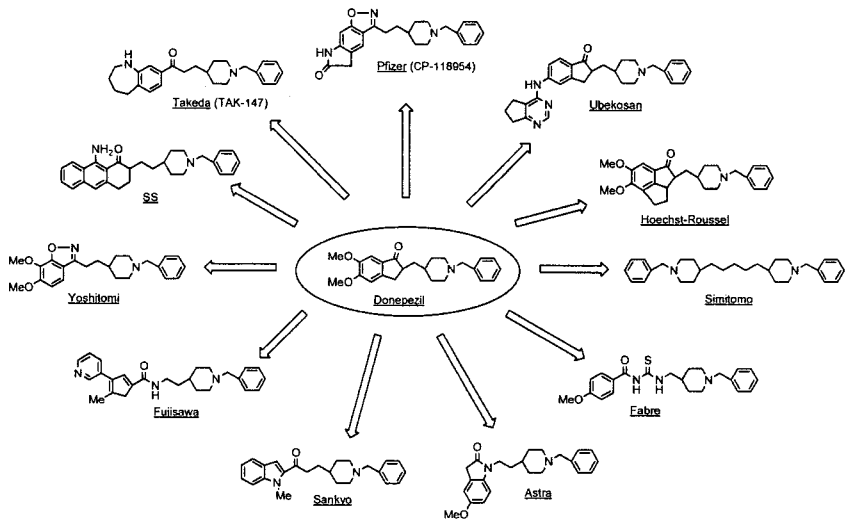
Seed Compound IC_{50} = 12600 nM



1986

Donepezil IC_{50} = 6.7 nM

Benzylpiperidine derivatives for Alzheimer's Disease

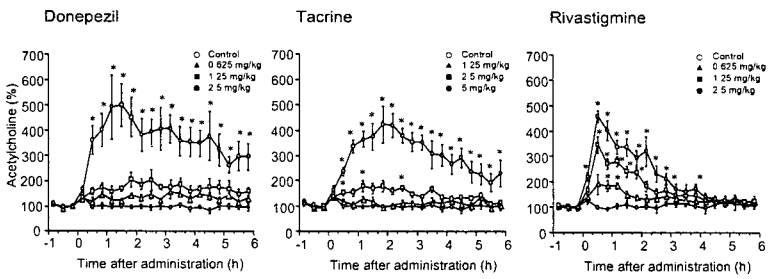


Inhibitory effects of ChE inhibitors on rat brain AChE and rat plasma BuChE

Compound	IC_{50} (nM)		Ratio
	AChE	BuChE	(BuChE/AChE)
Donepezil	6.7 ±0.35	7400 ±130	1100
Tacrine	77 ±1.4	69 ±1.4	0.90
Physostigmine	0.67 ±0.015	16 ±0.65	24
Rivastigmine	4.3 ±0.087	31 ±2.0	7.2
Galantamine	1200 ±33	18000 ±333	15
TAK-147	12 ±0.29	22000 ±410	1800
NIK-247	270 ±7.5	220 ±4.8	0.81

Values represent the mean ± S.E. from 4 dose-response curves for each test compound.

Effects of drugs on the basal concentration of extracellular ACh in the hippocampus of rats



Data are expressed as a percentage of the pre-levels (average of three samples prior to administration = 100%). Values are mean ± S.E. n=6.

Preclinical studies

- Preclinical pharmacology
  - Effects related to the therapeutic indication
  - Effects related to possible adverse reactions
  - Interaction with other drugs
- Toxicology
  - Acute toxicity
  - Subchronic toxicity
  - Chronic toxicity
  - Special toxicity
  - Reproductive toxicity
  - Mutagenicity
- ADME studies

Clinical studies (I)

- Phase I
  - A single-ascending oral study to evaluate the safety, tolerance and pharmacokinetic profile of E2020 in healthy male subjects
  - A single oral-dose crossover study of the effect of food on the pharmacokinetics of E2020 in healthy male subjects
  - A placebo-controlled multiple-dose study to evaluate the safety and tolerance and to establish the pharmacokinetic profile of E2020 in healthy male subjects
  - A single-dose study to evaluate the safety, tolerance and pharmacokinetic profile of E2020 in elderly subjects

Clinical studies (II)

- Phase II
  - A preliminary, multicenter, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of E2020 in patients with AD
  - An open-label, multicenter, extended evaluation of safety and efficacy of E2020 in patients with AD
- Phase III
  - A 15 week, multicenter, randomized, double-blind, placebo-controlled evaluation of safety and efficacy of E2020 in patients with AD
  - A 30 week, multicenter, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of E2020 in patients with AD

Phase III Clinical Studies

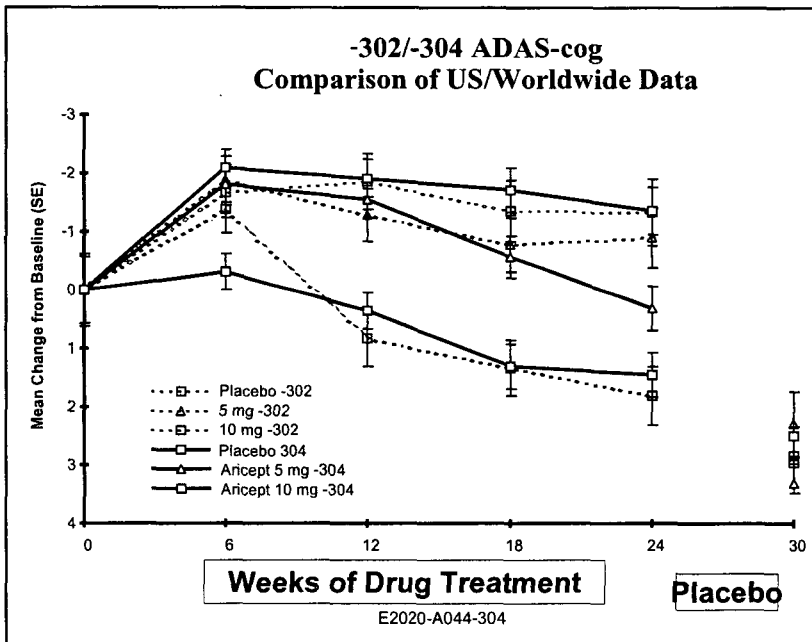
- Primary Efficacy Measures
  - ADAS-cog (Alzheimer's Disease Assessment Scale-Cognitive subscale)
  - CIBIC (Clinician's Interview-based Impression of Change Plus version)
- Secondary Efficacy Measures
  - MMSE (Mini-Mental State Examination)
  - QoL (Quality of Life scale)
  - CDR-SB (Clinical Dementia Rating Scale-Sum of Boxes)

ADAS-cog

Assessment of Cognitive Function

- Score range: 0-70
- Higher score = Greater impairment
- ADAS-cog ↑ 6-12 units/year in untreated mild to moderate AD patients*
- Domains:
  - memory
  - language
  - orientation
  - attention
  - praxis
  - reasoning

Stern et al. 1994



CGIC Plus

Assessment of Global Function

- Clinician interviews: patient and caregiver
- Four domains evaluated:
  - general
  - cognitive
  - behavioral
  - activities of daily living
- Score range: 1-7
- Higher score = Greater impairment

1	4	7
Markedly Improved	No Change	Markedly Worse