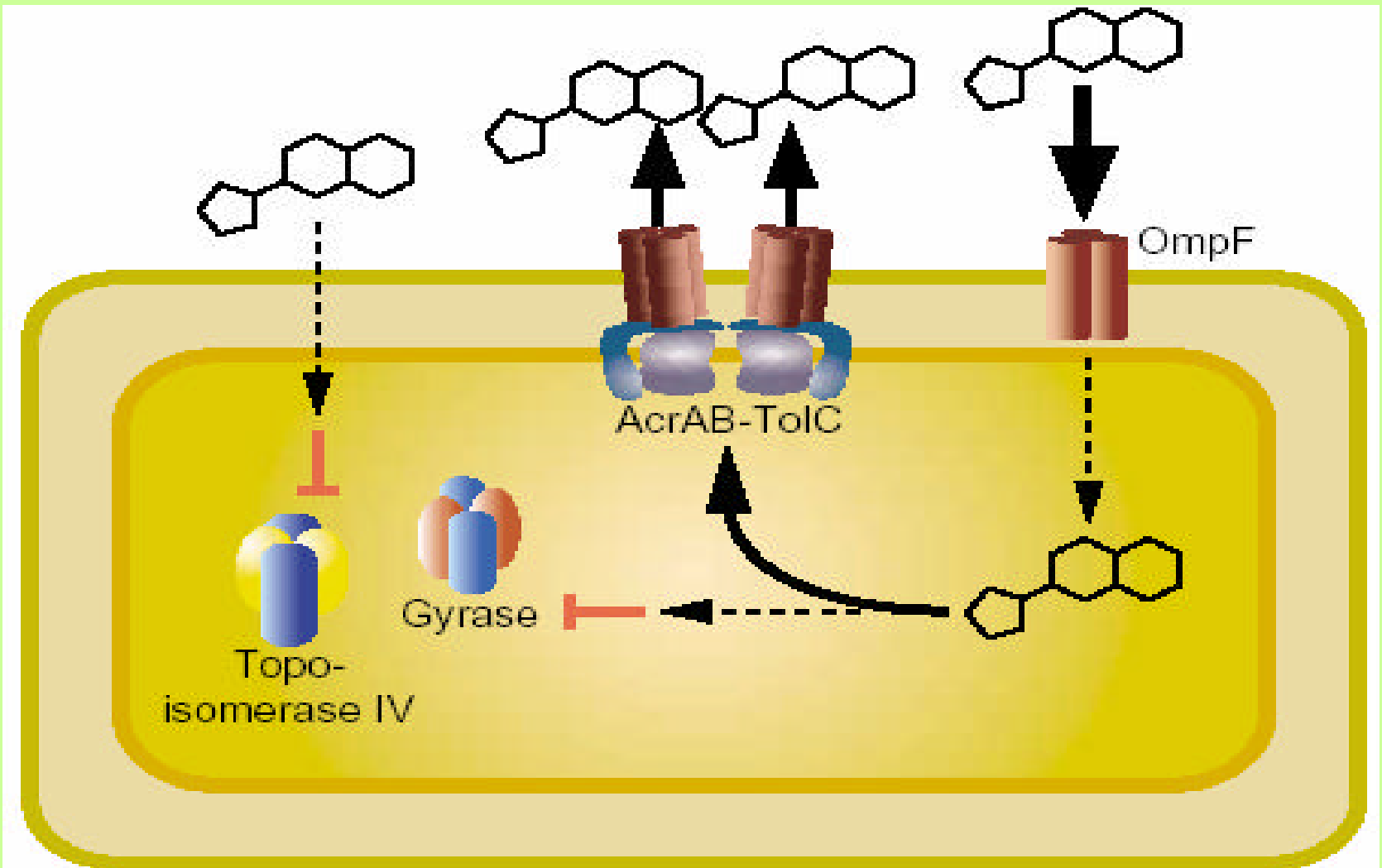
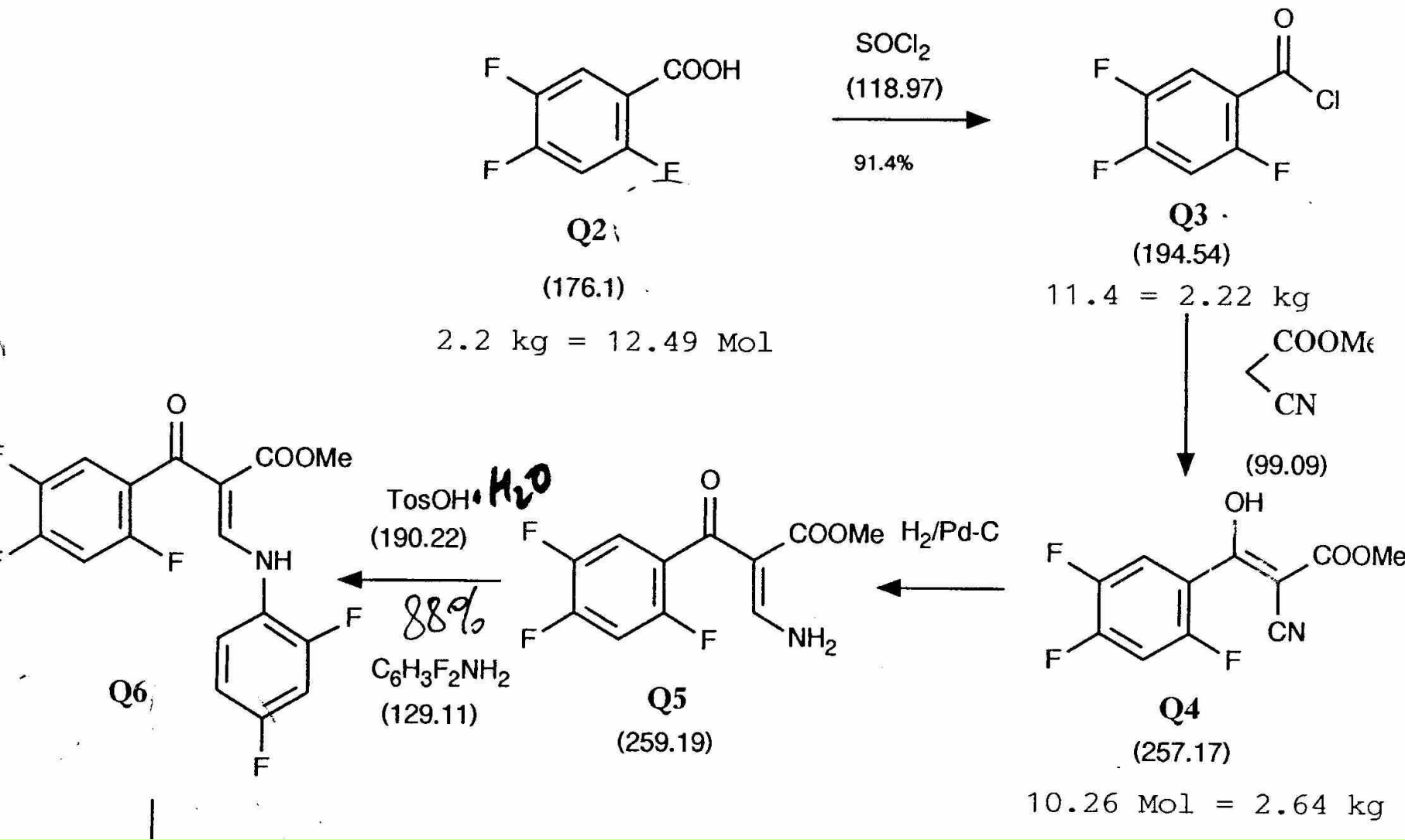


# 8. Block

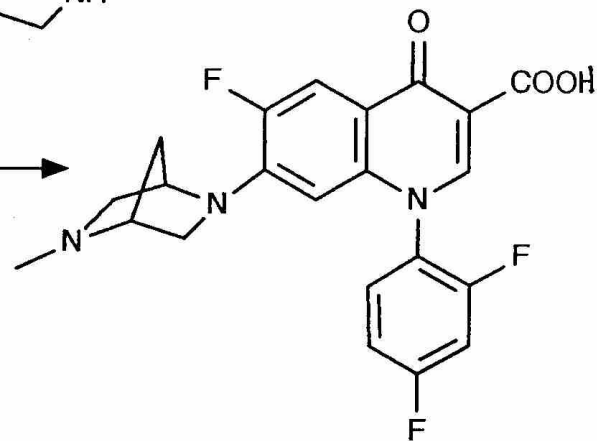
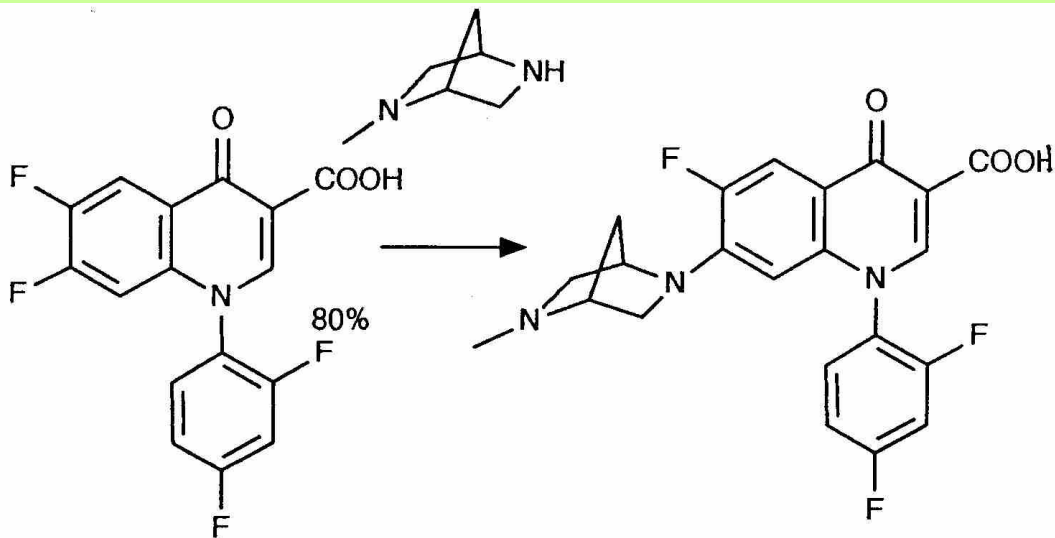
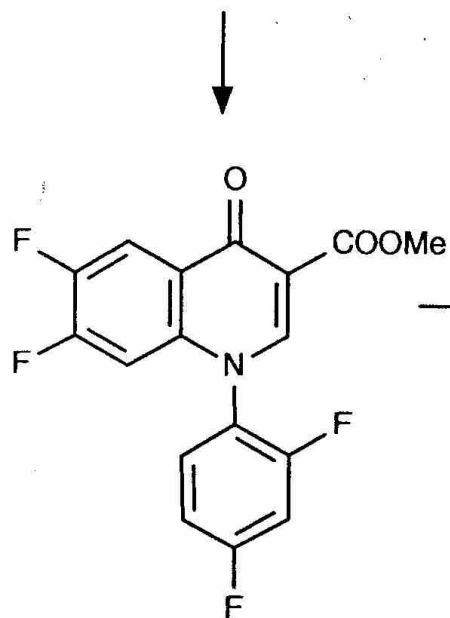
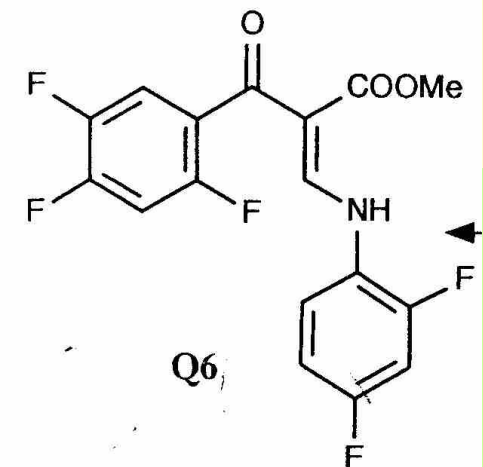
# Chinolonresistenz bei E.coli



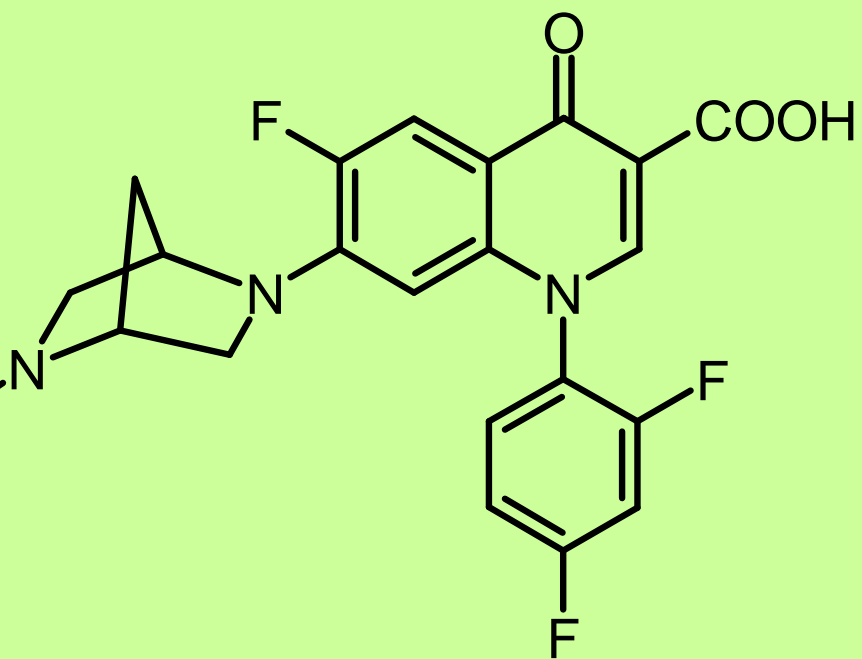
# Synthese v. Arylchinolonen 1



# Synthese v. Arylchinolonen 2



1991 ...



# Die kg Synthese...



# 1991 ...



<http://www.siegfried.ch/e/sfe0/sfe2/sfe24/sfe241.htm>

# Weblinks

<http://www.alzheimers.org/pubs/prog00.htm>

**Alzheimer**



# *Cognitive Function*

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- Memory
- Abstract thought
- Logical reasoning
- Problem solving
- Judgment
- Language

# *Some Conditions Affecting Cognitive Function*

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- Depression
- Anxiety
- Mental retardation
- Dementia
- Taking certain medications



# *Dementia*

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- Nearly 50% of persons age 85+ affected<sup>1</sup>
- Progressive or static
- Reversible or irreversible

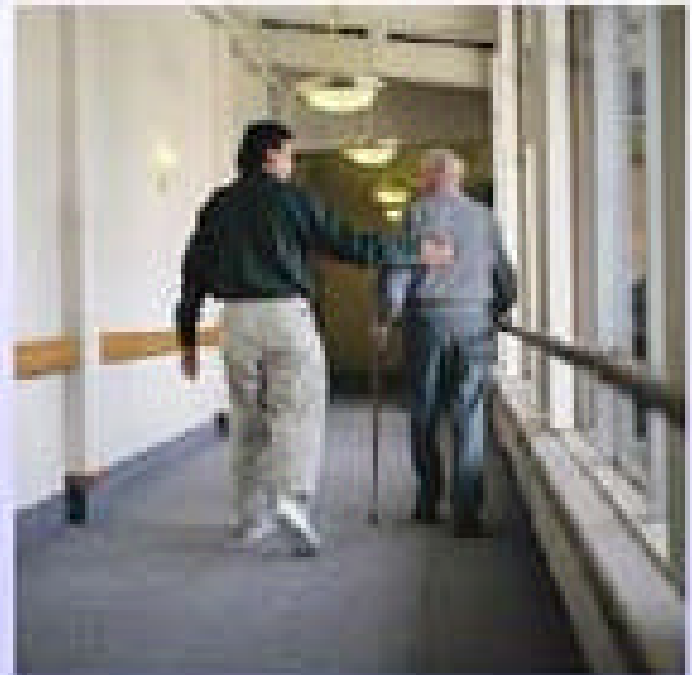
# *Irreversible Dementias*

---

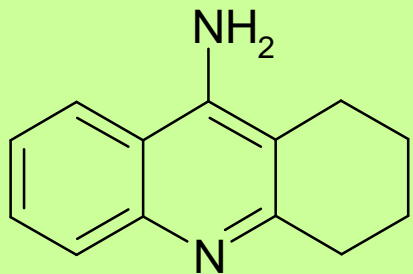
- Degenerative dementias
  - Alzheimer's disease
  - Huntington's disease
  - Parkinson's disease
  - Pick's disease
- Multi-infarct dementia (series of small strokes)

# *Symptoms Associated With Dementia*

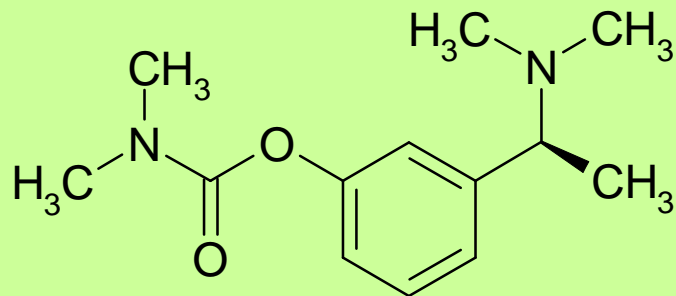
- Delusions
- Hallucinations
- Misidentifications
- Disinhibition
- Wandering
- Agitation
- Aggression



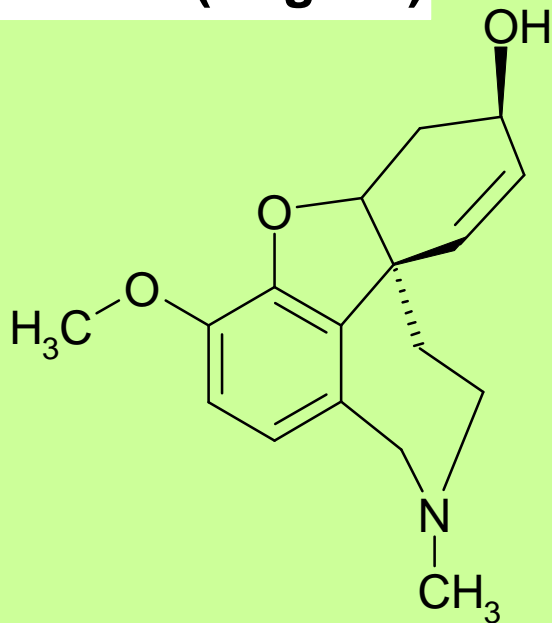
# Anti Alzheimer Drugs



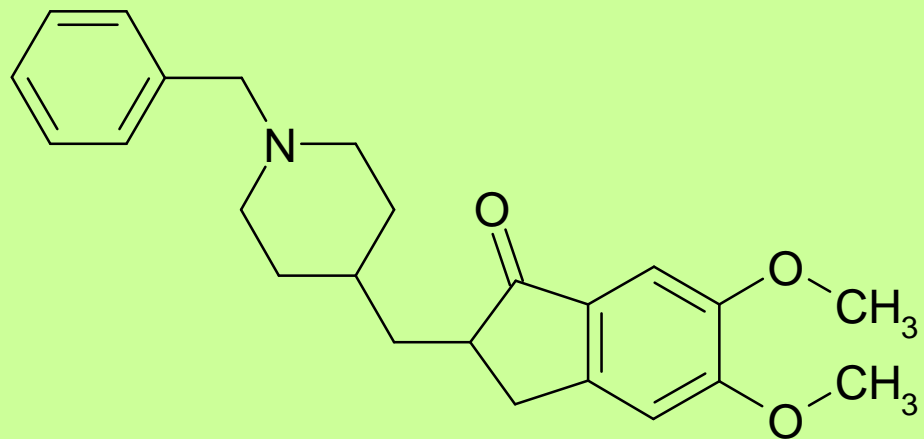
**Tacrine (Cognex)**



**Rivastigmine (Exelon)**



**Galanthamin (Reminyl, Nivalin)**

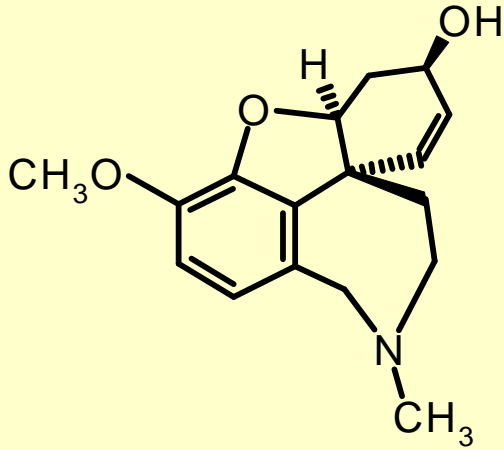


**Arizept, (Donepezil)**

# Leucojum aestrivum L.



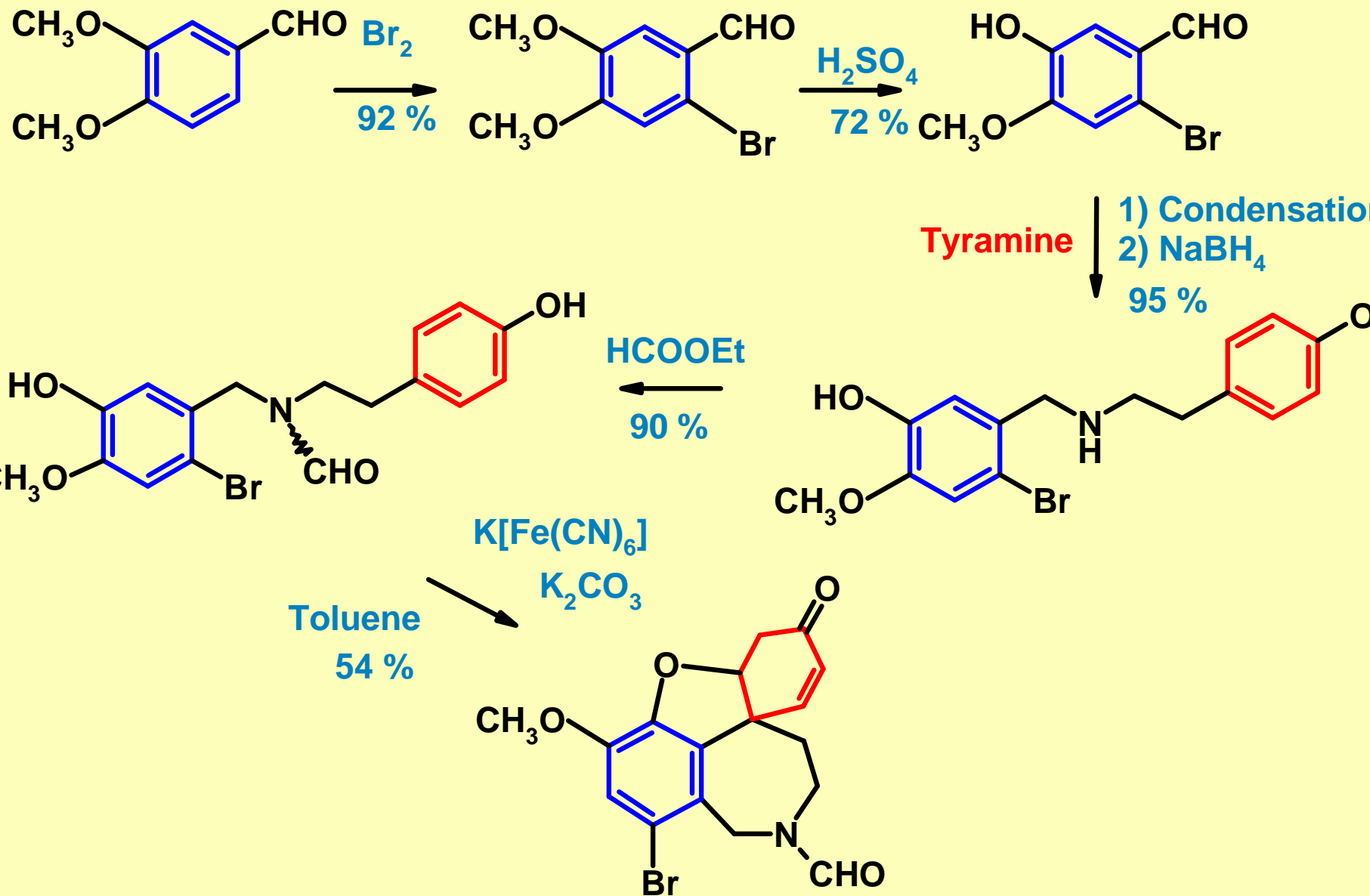
# Galanthamine (REMINYL™)



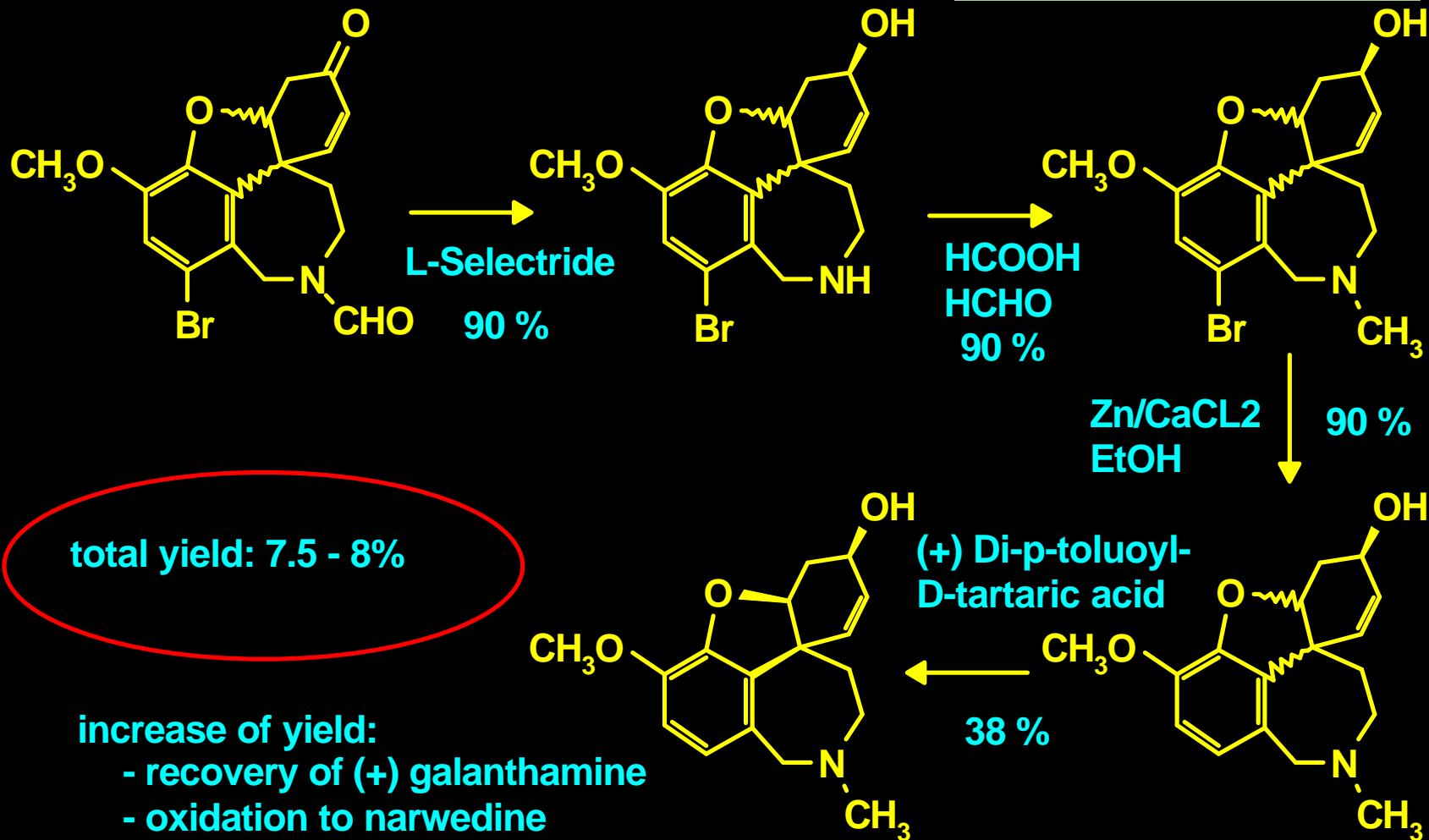
- 2nd generation cholinesterase inhibitor.
- Approved in the EU, USA
- Double blind placebo controlled study in 636 patients, mean age 75, score 4 points higher in Alzheimer's Disease Assessment Scale (ADAS-cog).
- Clinical development has included over 2000 patients in double-blind, placebo-controlled trials.
- Improvement in CIBIC-plus (cognitive ability assessment).
- Registered in Austria as NIVALIN™.
- Dual action: increase of AcCh release by „modulation“ of presynaptic nicotinic receptors.



# Tandem Cyclisation



# Procedure 1

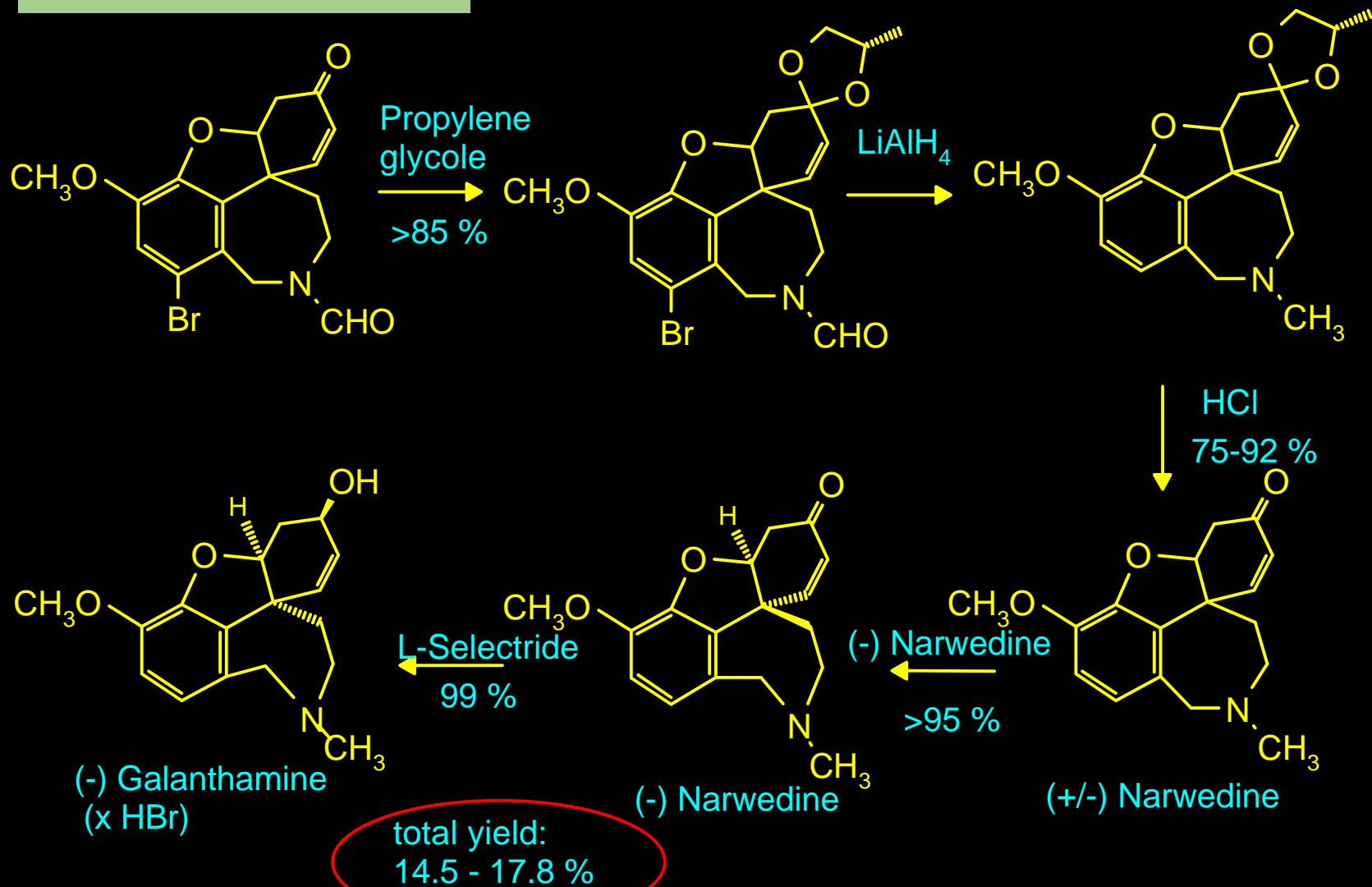


total yield: 7.5 - 8%

increase of yield:

- recovery of (+) galanthamine
- oxidation to narwedine
- reduction with L-selectride

# Procedure 2





Organic Process Research & Development 1999, 3, 425–431

## Development of a Pilot Scale Process for the Anti-Alzheimer Drug (–)-Galanthamine Using Large-Scale Phenolic Oxidative Coupling and Crystallisation-Induced Chiral Conversion

Bernhard Kuenburg,<sup>†</sup> Laszlo Czollner,<sup>1,8</sup> Johannes Fröhlich,<sup>\*,‡,§</sup> and Ulrich Jordis<sup>\*,‡,¶</sup>

*Sanochemia AG, Landeggerstrasse 7, A-2491 Neufeld, Austria, and Institute of Organic Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria*

### Abstract:

(–)-Galanthamine has been synthesised using an efficient nine-step procedure, which in large scale affords 12.4 (6.7–19.1)% overall yield. The process improvements and optimization of each step are described. Notable steps include (i) an oxidative phenol coupling and (ii) crystallisation-induced chiral conversion of (±)-narwedine to (–)-narwedine. This is a practical and cost-effective synthesis of (–)-galanthamine which is amenable to pilot plant scale-up to afford sufficient material for use in clinical trials.

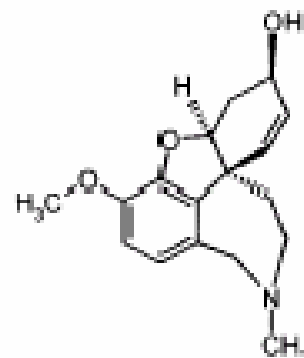


Figure 1. Structure of (–)-galanthamine, nivalin, reminyL.



# „Galanthamine-Plus“

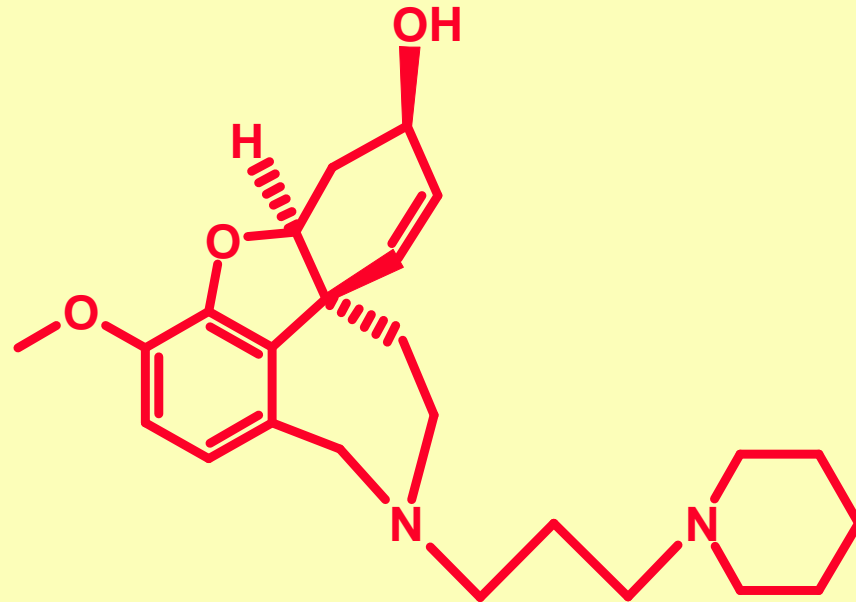
Journal of Cerebral Blood Flow and Metabolism Vol. 19(Suppl. 1), p. S19 (1999)

**SPH-1286, A NOVEL POTENT INHIBITOR OF BRAIN**

**ACETYLCHOLINESTERASE, CAN**

**PREVENT AMNESIA AFTER ACUTE MODERATE HYPOXIA-HYPERCARBIA**

H. A. M. Mucke and K. Czollner

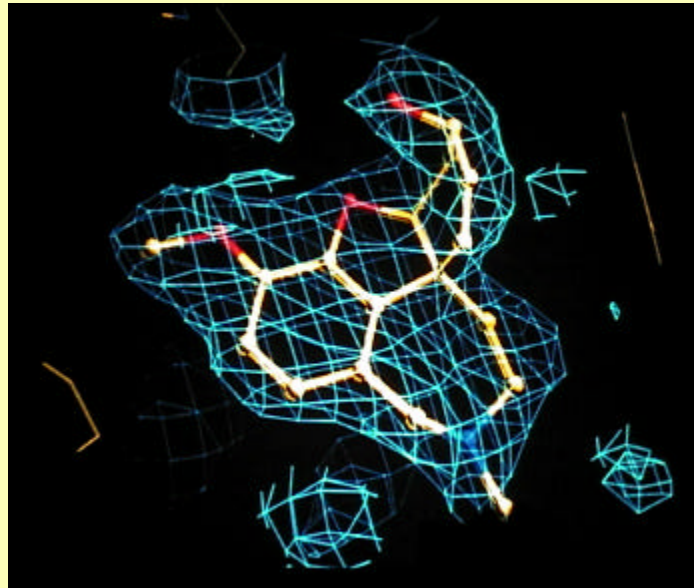
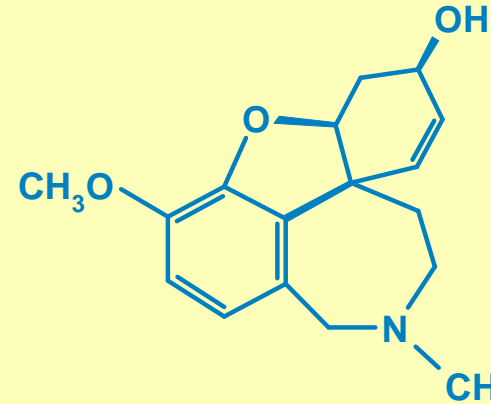
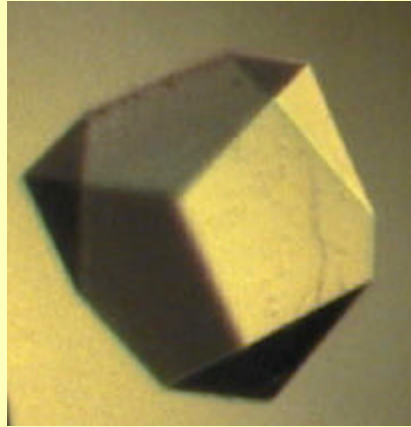


IC<sub>50</sub> values, 0.3  $\mu$ M for SPH-1286 vs. 2.3  $\mu$ M for galanthamine).

# Structure-based Drug Design



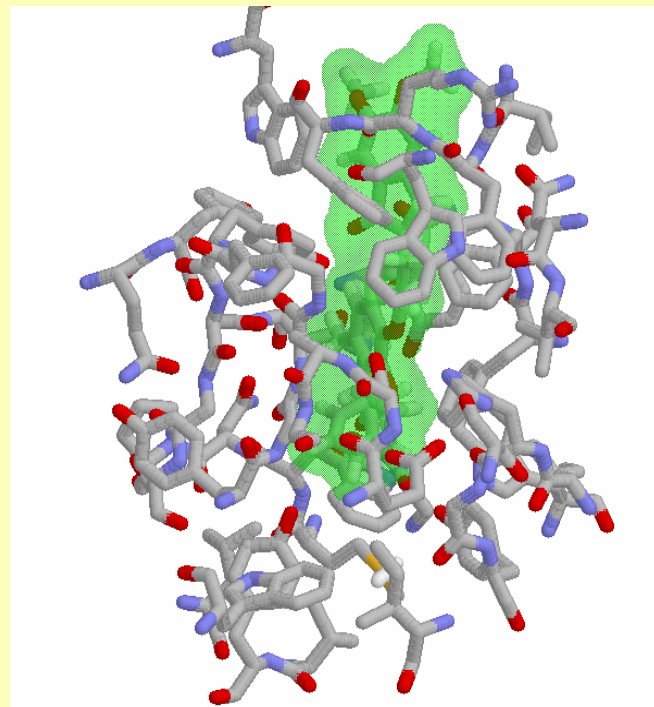
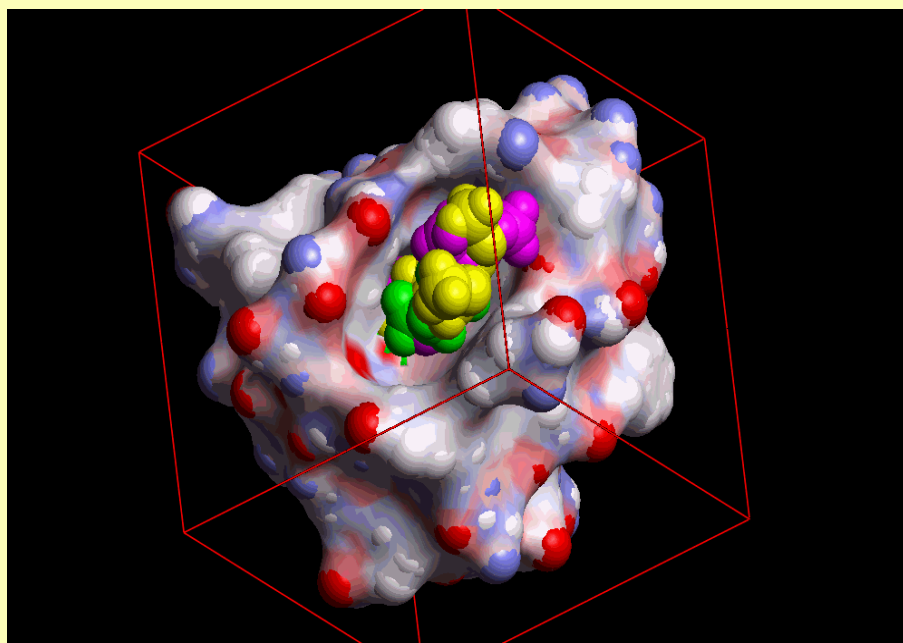
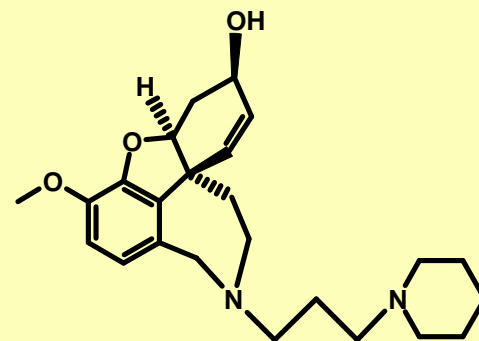
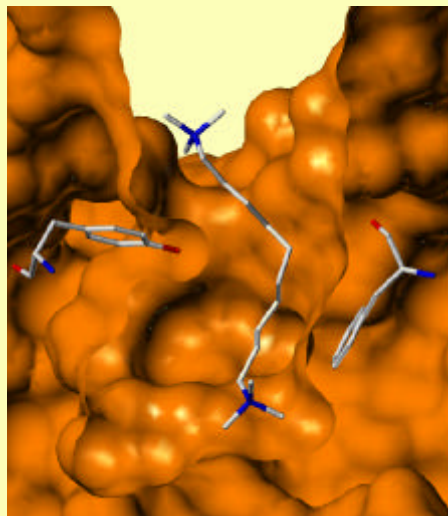
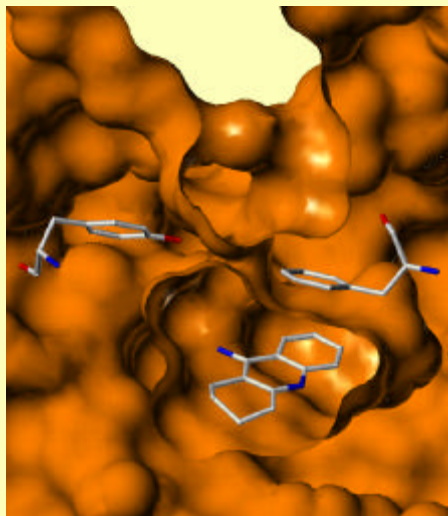
Torpedo californica



**C. Bartolucci, Rom  
Inst. de Strutt. Chim.**

**D. Lamba, Triest  
Internat. Centre Gen.  
Eng. Biotech.**

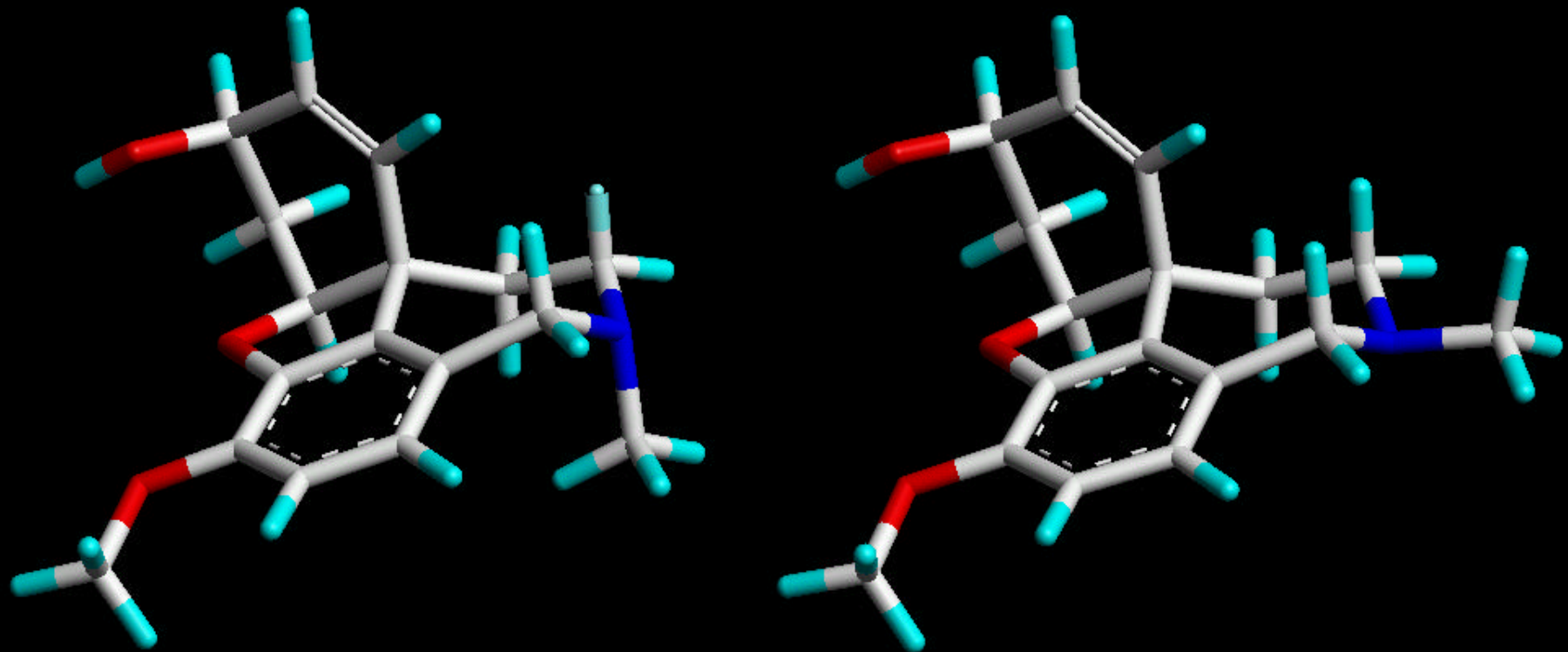
# Enzyme / Substrate Modeling



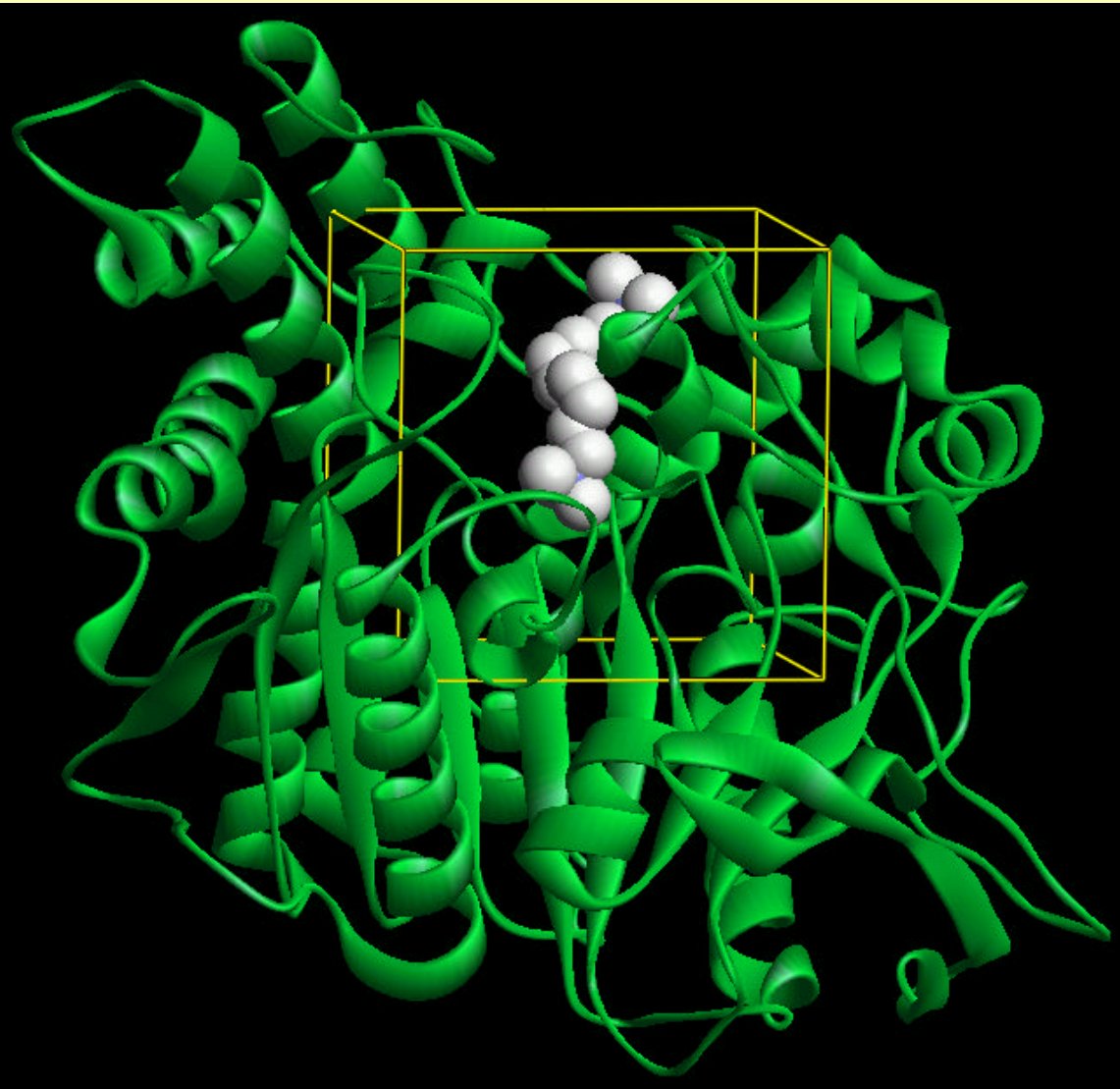
G. Fels, Univ. Paderborn, A. Tropsha,  
Univ. North Carolina



# Global minimum structures of galanthamine (ax)-conformer (left) and (eq)-conformer (right).

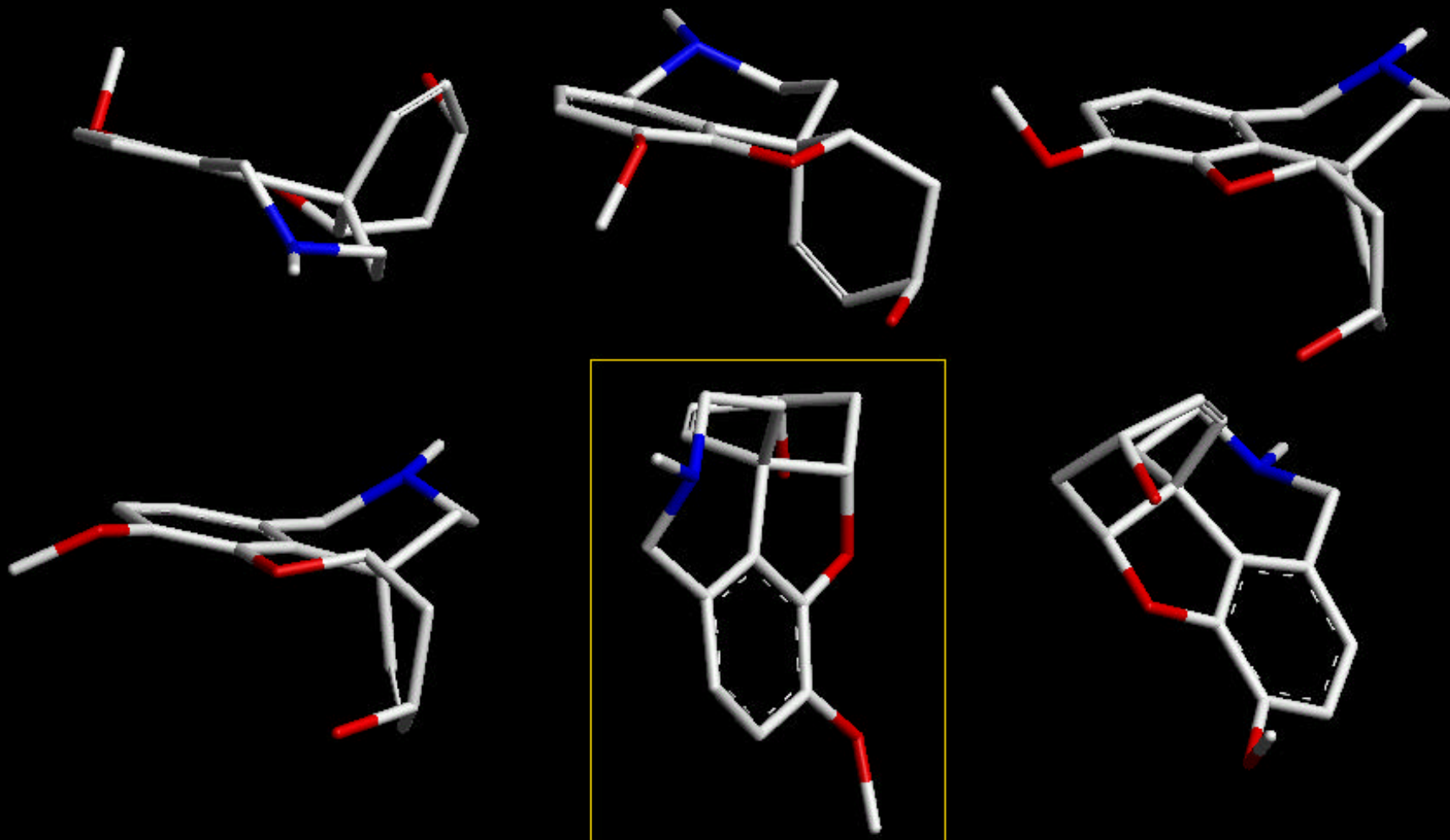


**Location of the active site box (yellow) used in the AUTODOCK procedure to predict galanthamine binding in the active site.**

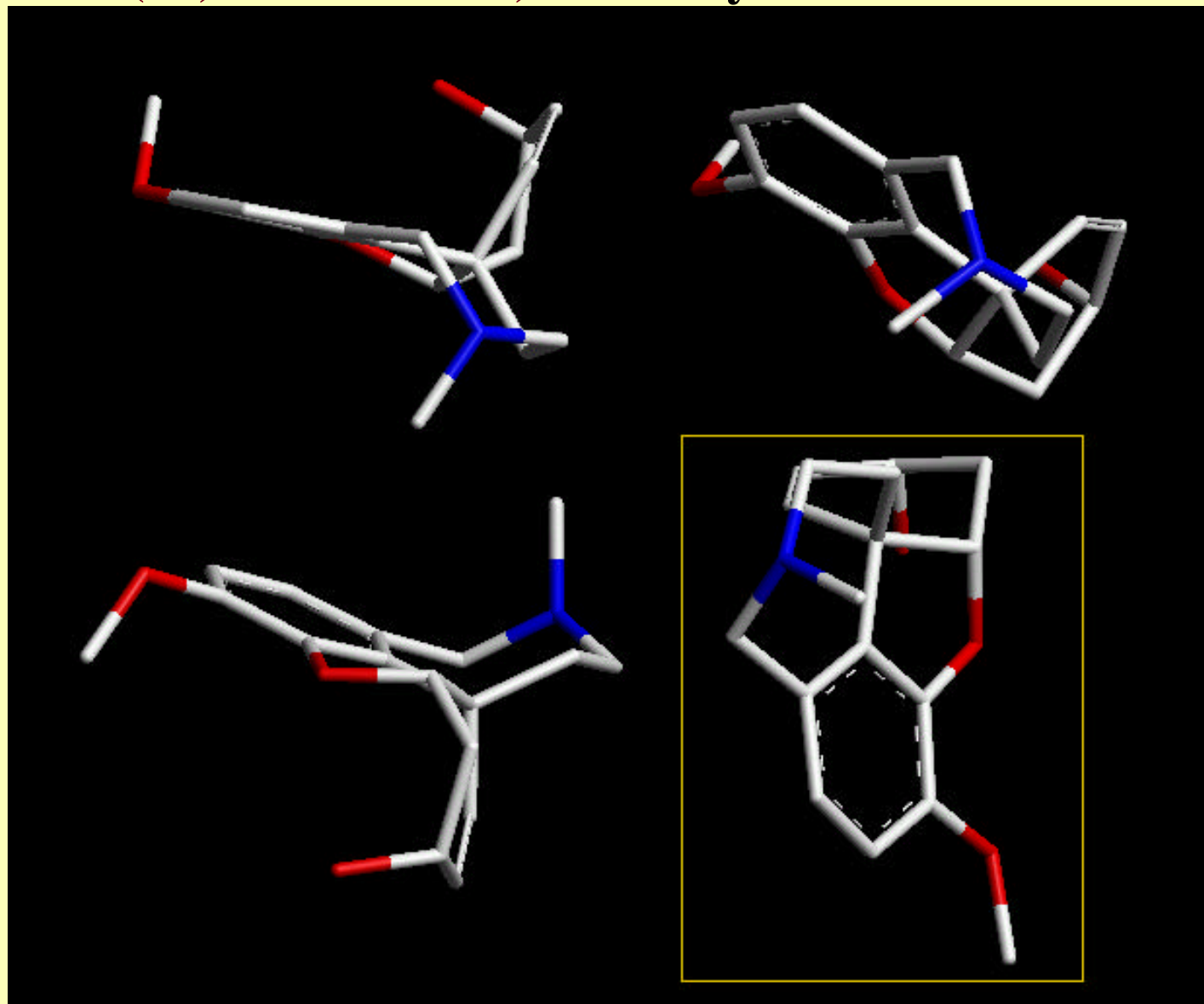


For comparison the structure of decamethonium (white) is placed in the enzyme according to the known crystal structure

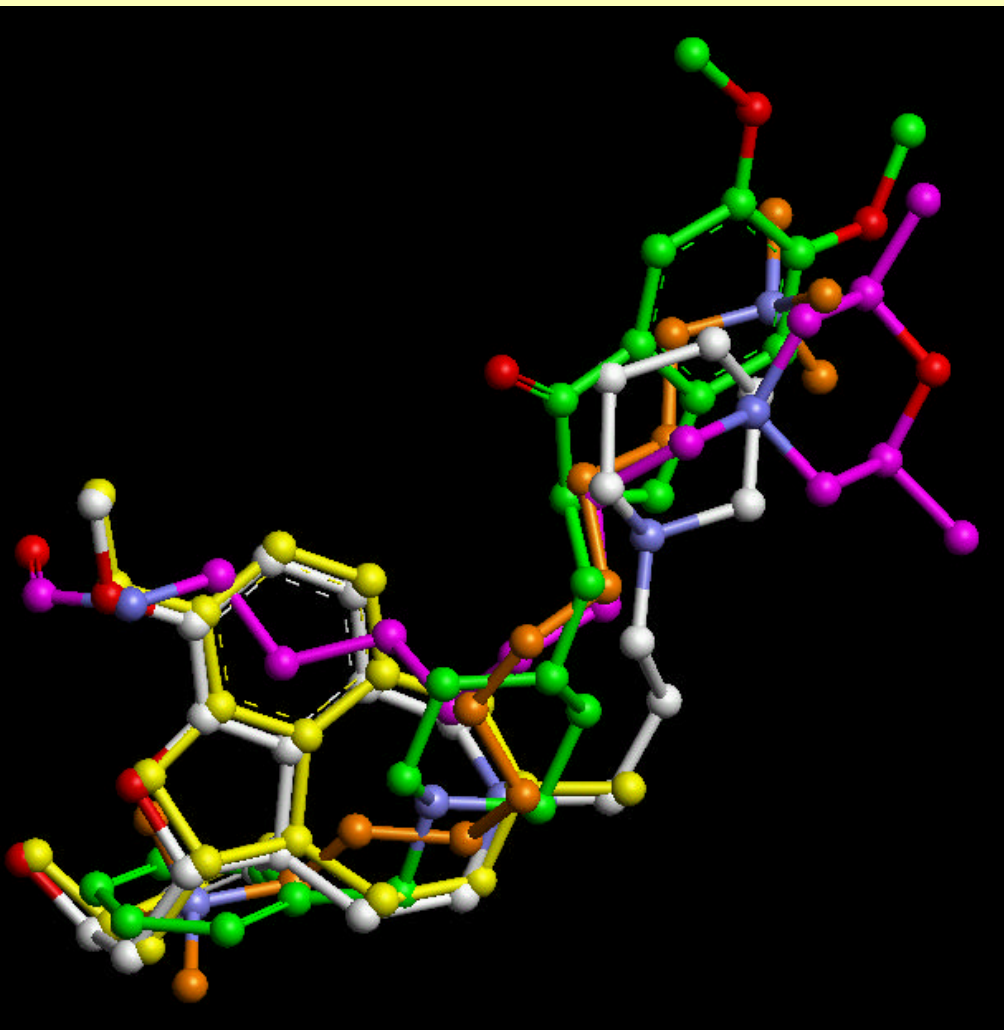
# Typical orientations of galanthamine in the active site of AChE: (eq)- conformers



**Typical orientations of galanthamine in the active site of AChE:  
(ax)- conformers) found by AUTODOCK.**

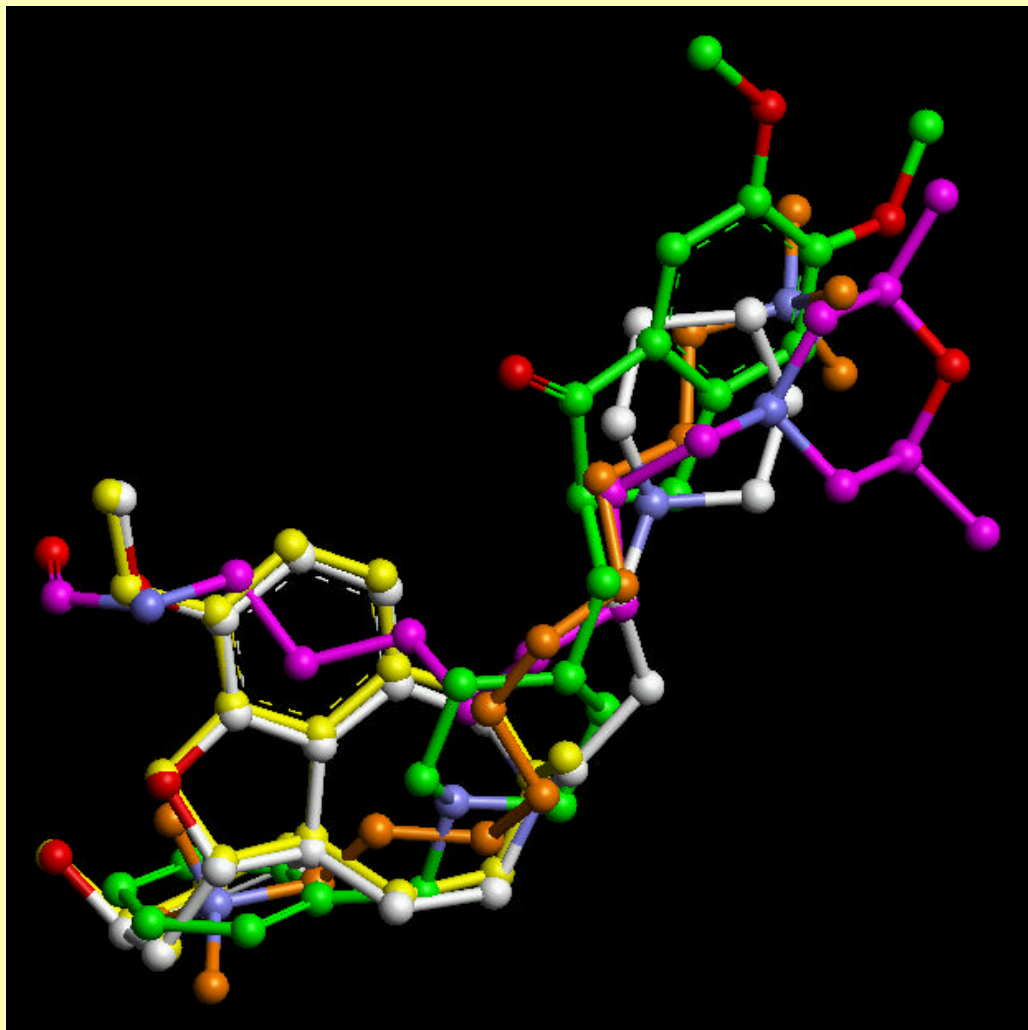


Structural overlay of the highest scoring **(ax)-conformer** of SPH1107 (white) with the respective galanthamine (ax)-conformer as revealed by the modeling study (yellow).



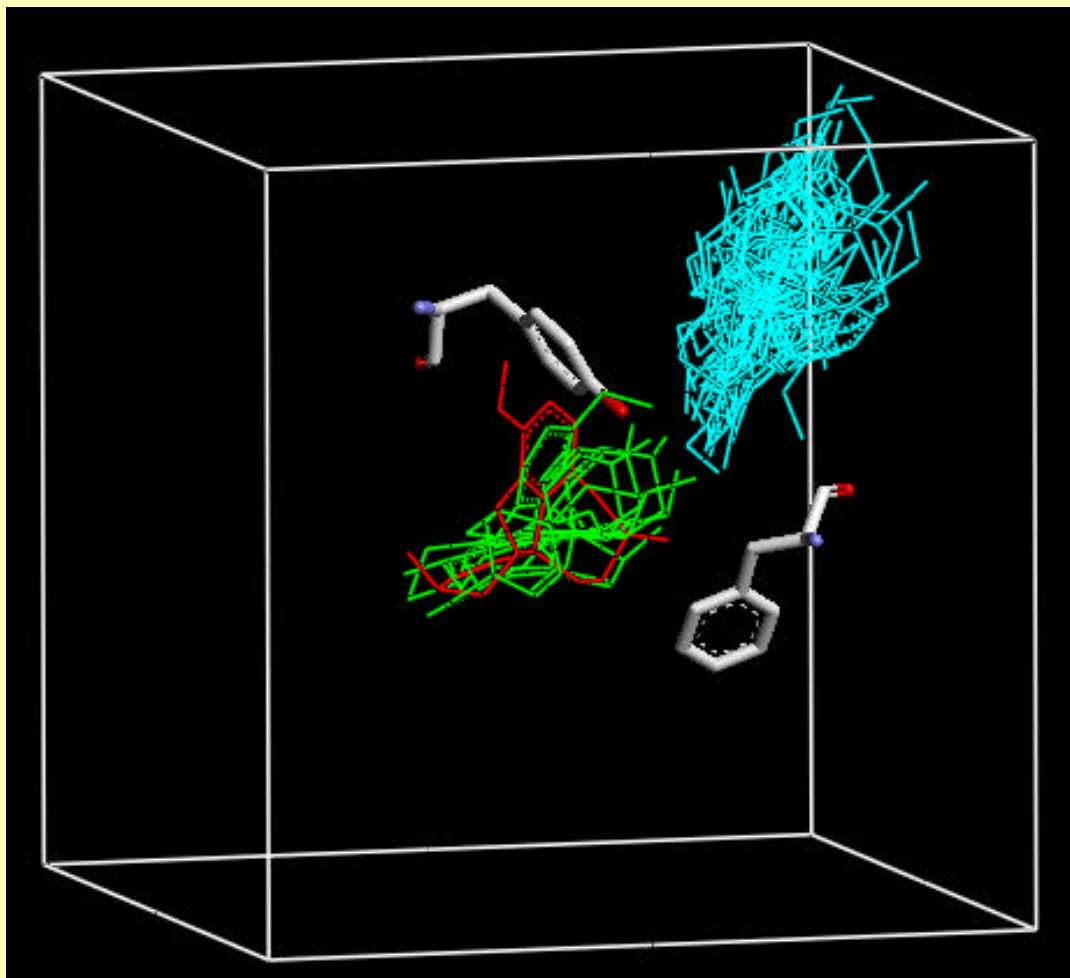
decamethonium  
(brown),  
donepezil (green)

Structural overlay of the highest scoring **(eq)-conformer** of SPH1107 (white) with the respective galanthamine (eq)-conformer as revealed by the modeling study (yellow).



decamethonium  
(brown),  
donepezil (green)

**Binding location of all AUTODOCK clusters found with the (eq)-conformer of galanthamine.**



**Structural overlay of galanthamine models Teq26 (left), and Tax24 (right) as revealed by the docking study with that of galanthamine present in the crystal structure of the TcAChE-galanthamine complex (green).**

