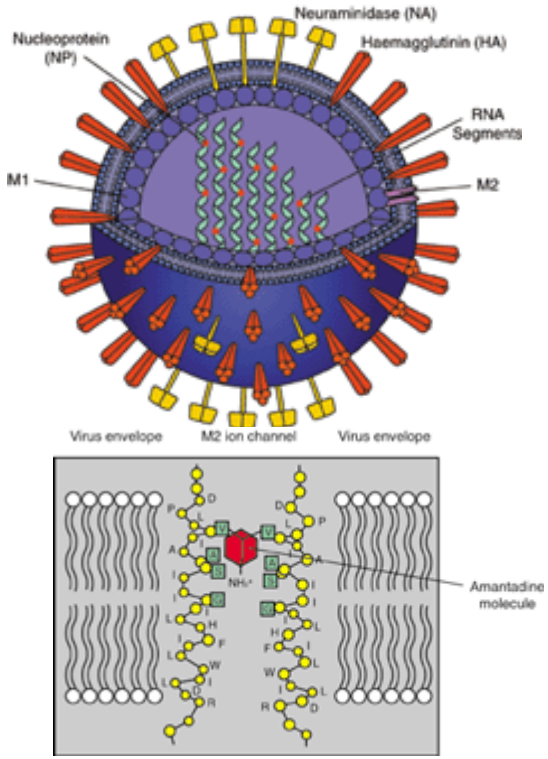
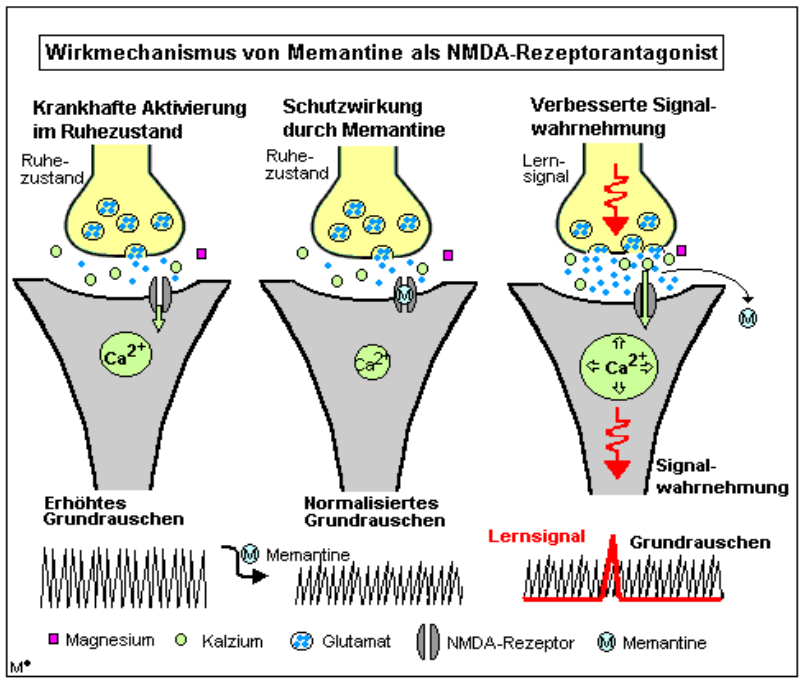
Medicinal Chemistry of Adamantane Derivatives



Antiviral Activity

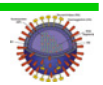


Treatment of Neurological Disorders

PRS Group Seminar Talk

Lukas Wanka

March 03, 2006

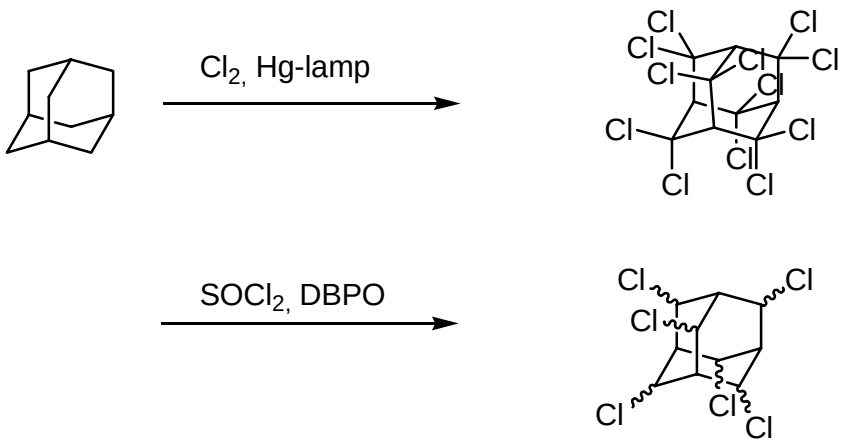


Contents

1. **History**
2. **Influenza A – antiviral Adamantanes**
3. **Parkinson‘s Disease – Amantadine & others**
4. **Alzheimer‘s Disease – Memantine**
5. **Miscellaneous** (still something to be postponed…)

History:

- Point to start from: Schleyer‘s Synthesis of Adamantane
- Before:



…patented as insecticides. Ever used?

Schleyer, P. v. R.; Donaldson, M. M., *J. Am. Chem. Soc.* **1956,** 78, 5702.,

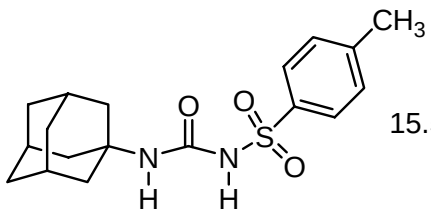
Schleyer, P. v. R.; Donaldson, M. M., *J. Am. Chem. Soc.* **1960,** 82, 4645-4651.

Webber, W. C.; Harthoorn, P. A. Chlorinated and brominated polycyclic hydrocarbons. 819240, 1959.

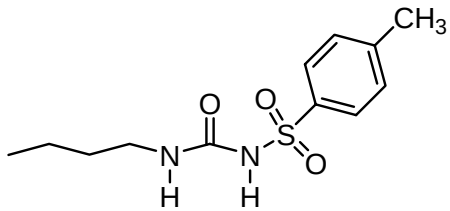
Fort, R. C., Jr.; Schleyer, P. v. R., *Chem. Rev.* **1964,** 64, 277-300.

Scan for possible applications

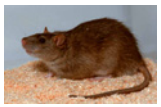
1963: Adamantyl ureas



15.5 times efficacy of



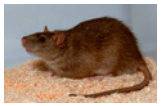
Tolbutamide

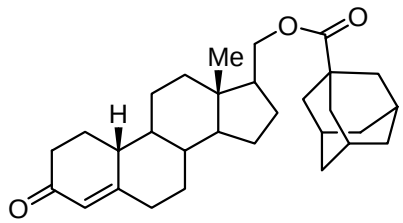


- Hypoglycemic activity (still an up-to-date task)
- Sulfonylureas were known to let pancreas release more insulin – type 2 Diabetes. Screen of 15 Substances – Adamantane as an „add-on“ with increased lipophilicity
- Only „naked“ Adamantane moiety works!
- No Toxicity reported in mice and rats
- Better long-term activity

Gerzon, K.; Krumalns, E. V.; Brindle, R. L.; Marshall, F. J.; Root, M. A., *J. Med. Chem.* **1963,** 6, (6), 760-763.

1965: Anabolic steroids





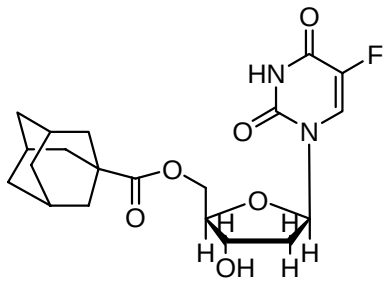
Nortestosterone adamantanoate 17 β

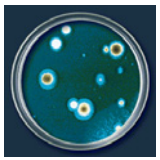
Chemically stable Steroid adamantoates:

- 14 compounds tested
- At least better than Me esters
- Sensitive towards methylation of the Adamantane moiety – “SAR“
- Activity in rats lasts 28 days
- lower androgenicity

Rapala, R. T.; Kraay, R. J.; Gerzon, K., *J. Med. Chem.* **1965,** 8, (5), 580-583.

1966: Modified nucleosides



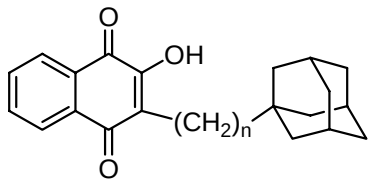


- Antitumor activity, in vitro antiviral studies, Adenosine-deaminase inhibition, cytotoxicity studies
- Adamantane group enhances lipophilicity and metabolic stability
- Adamantanoate as protecting group
- Again: Modifications of Adamantane moiety not tolerated
- SAR: „The possible mode of action of adamantane-containing agents is described in terms of a precise binding of the adamantane moiety to complementary hydrophobic regions in the receptor site protein molecule“

Distribution – metabolic stability – precision of fit

Gerzon, K.; Tobias, D. J.; Holmes, R. E.; Rathbun, R. E.; Kattau, R. W., *J. Med. Chem.* **1967,** 10, (4), 603-606.

1966: Naphthoquinones



n = 1 – 5

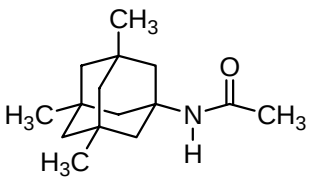
- Only five derivatives tested
- Good experiences with cyclohexyl analogs
- Adamantane derivatives were **less active** than cyclohexyl analogs
- Adamantane derivatives showed some **toxicity**

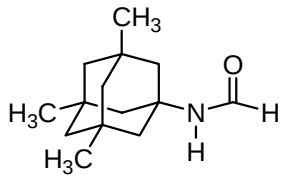
„Three out of five mice died but the other two were cleared from plasmodium berghei“

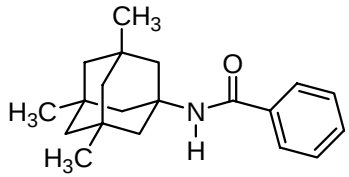
Fieser, L. F.; Nazer, M. Z.; Archer, S.; Berberian, D. A.; Slighter, R. G., *J. Med. Chem.* **1967,** 10, (4), 517-521.

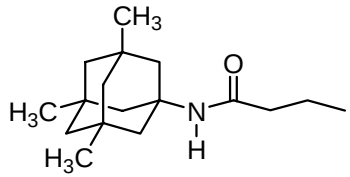
Medicinal Chemistry of Adamantane Derivatives

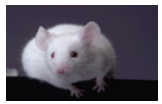
1967: Adamantane carboxamides

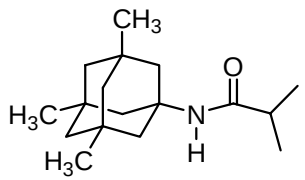


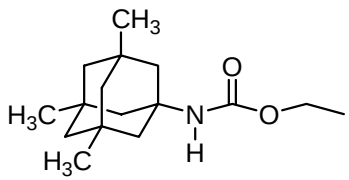


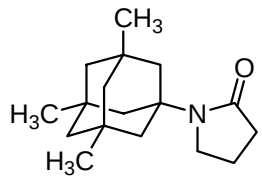


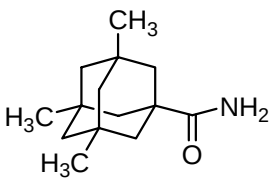


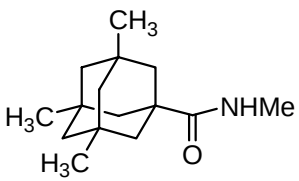


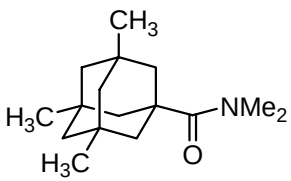


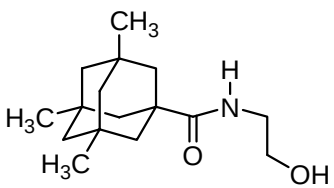


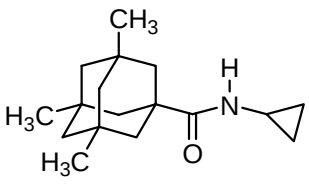












- Amides: „quite“ sedative, formamide is stimulating
- Surprisingly, higher alkylated ones are more efficient
- more lipophilic – better penetration of BBB
- Dead mice – toxicity problems
- Mixed sedative action in dogs – no tests in humans

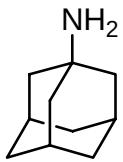
Gerzon, K.; Tobias, D. J.; Holmes, R. E.; Rathbun, R. E.; Kattau, R. W., *J. Med. Chem.* **1967,** 10, (4), 603-606.

Antiviral Activity

In 1918/19, the „Spanish Flu“ killed about 20-40 mio people. Especially young and very old people died from influenza. The heavy death toll of this pandemic disease has to be compared to the number of 11 mio victims of World War I.

Egon Schiele prepared this drawing of his wife, one day before her death and four days before he died himself, only 28 years old. Both were victims of the spanish Flu pandemic

1964: Antiviral Activity of 1-Adamantanamine



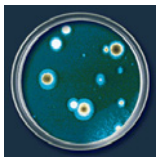
„1- Adamantanamine (amantadine) causes a selective, reproducible, dose-related inhibition of influenza infection in tissue culture, chick embryos and mice. The compound is not virucidal and appears to act by interfering with the penetration of the host cell by the virus. In influenza infections of mice, greatest efficacy occurs with treatment at the time of the infection; however, there is significant antiviral activity with treatment delayed up to 72 hours after infection. Virus inhibition is not complete and survivors are immune to a challenge infection with the original infecting virus“

LD_{50}: Orally 1080 mg/kg (!)

Table 2. Effects of graded doses of amantadine hydrochloride on experimental influenza infections in mice. The mice were observed for 14 days after infection. The virus (0.05 ml) was administered intranasally in white mice lightly anesthetized with ether. There were 50 to 100 mice in each group for strains S-15 and A^2/AA, and 20 to 60 mice in each group for strain WS.

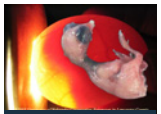
Amantadine HCl * (mg/kg)	Survivors (%)	MSD †
Influenza A, S-15 (Swine)		
40	70	12.5
10	62	12.4
2.5	43	10.7
0.62	25	9.1
0	13	8.1
Influenza A WS		
40	74	12.8
10	56	11.4
2.5	21	9.7
0.62	21	8.3
0	15	7.8
Influenza A-2 A^2/AA (Asian)		
40	58	11.9
10	38	10.7
2.5	33	10.3
0.62	26	9.4
0	14	8.7

* The amantadine hydrochloride was given intraperitoneally 30 minutes before virus at 4-hour intervals for 48 hours. † Mean survival day $= \frac{[\Sigma(\text{No. of mice alive each day to day 14})]}{(\text{Total No. of mice in the group})}$

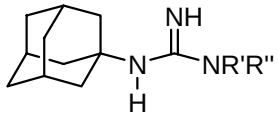


Davies, W. L.; Grunert, R. R.; Haff, R. F.; McGahen, J. W.; Neumayer, E. M.; Paulshock, M.; Watts, J. C.; Wood, T. R.; Hermann, E. C.; Hoffmann, C. E., *Science* **1964,** 144, 862-863.

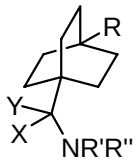
Medicinal Chemistry of Adamantane Derivatives



Optimization efforts



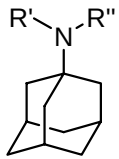
8 Substances – no improvement



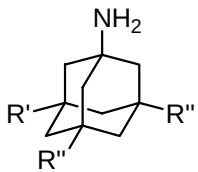
No improvement

(50 derivatives)

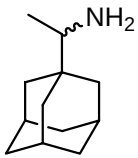
Optimizing Adamantane pharmacophor (91 substances)



No improvements – the bigger, the worse

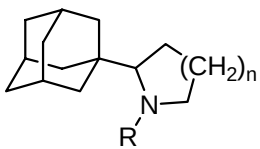


Substitution in tertiary positions is highly detrimental for activity



Significant improvement in activity. Enantiomers: Equipotent. Rimantadine has lowest AVI_{50} in mice

Optimizing aminoalkyl moiety



Some improvements against influenza A;

Some also suited against HIV-1 and HIV-2

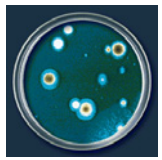
Geluk, H. W.; Schut, J.; Schlatmann, J. L. M. A., *J. Med. Chem.* **1969,** 12, 712-715.

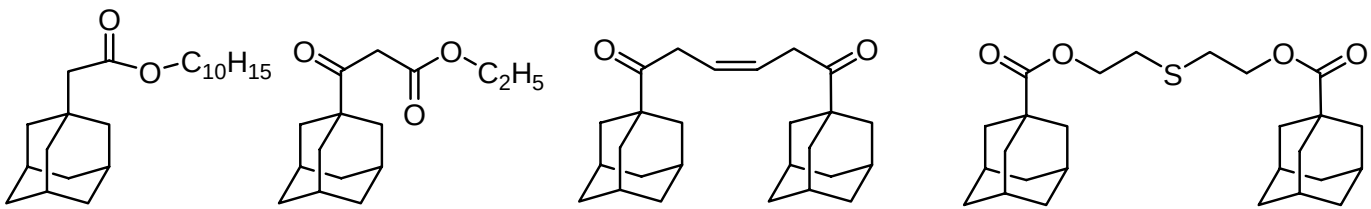
Whitney, J. G.; Gregory, W. A.; Kauer, J. C.; Roland, J. R.; Snyder, J. A.; Benson, R. E.; Hermann, E. C., *J. Med. Chem.* **1970,** 13, (2), 254-260.

Aldrich, P. E.; Hermann, E. C.; Meier, W. E.; Paulshock, M.; Prichard, W. W.; Synder, J. A.; Watts, J. C., *J. Med. Chem.* **1971,** 14, (6), 535-543.

Another 58 Adaman-

tane derivatives, e. g.



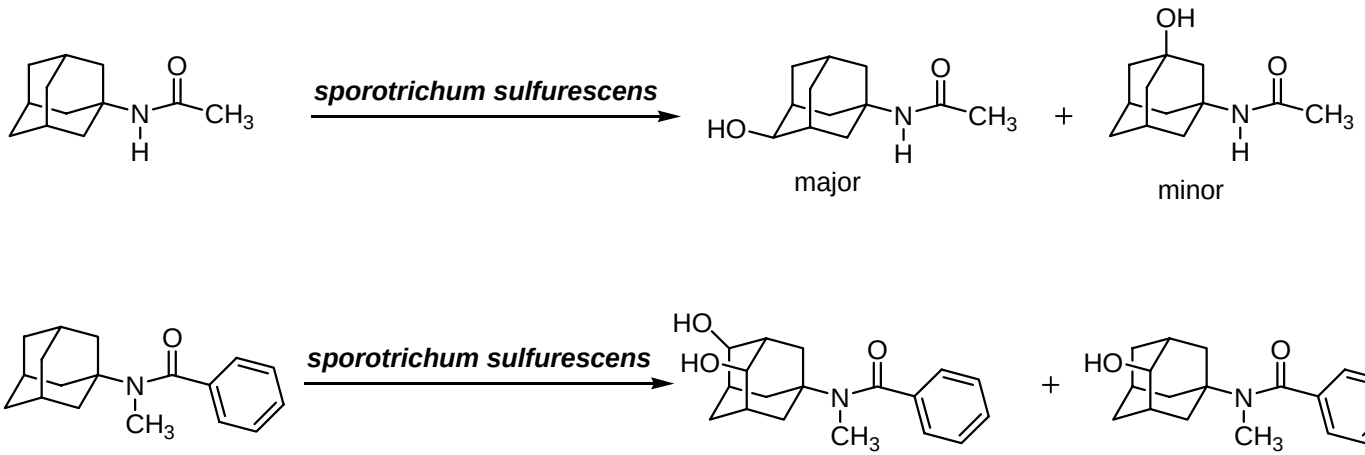


MCC vs. MIC

„Cytotoxicities of the compounds usually paralleled the antiviral activities, the activity and cytotoxicity appearing at similar concentrations“

Aigami, K.; Inamoto, Y.; Takaishi, N.; Hattori, K.; Takatsuki, A.; Tamura, G., *J. Med. Chem.* **1975,** 18, (7), 713-721.

Degradation

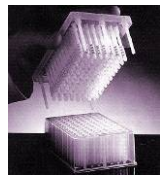


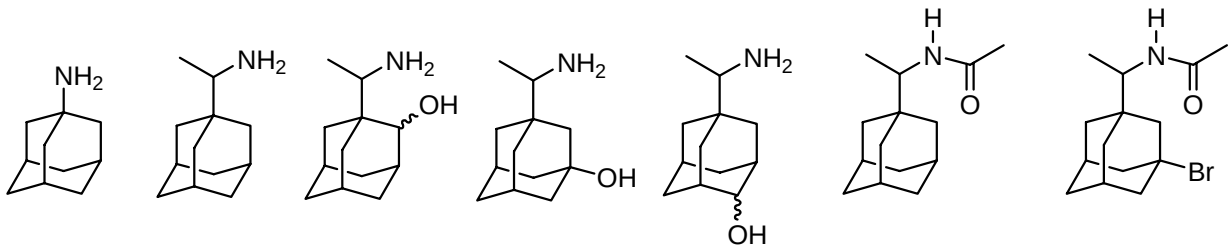
- Oxygenation preferentially at an optimal distance of 5.5 Angstroms from an electron-rich center
- Amantadine, Rimantadine: Storage for decades without loss of efficacy
- Therefore, they are proposed for storage for the next pandemia

Herr, M. E.; Johnson, R. A.; Murray, H. C.; Reineke, L. M.; Fonken, G. S., *J. Org. Chem.* **1968,** 33, (8), 3201-3207.

Scholtissek, C.; Webster, R. G., *Antivir. Res.* **1998,** 38, (3), 213-215.

Metabolism – in humans





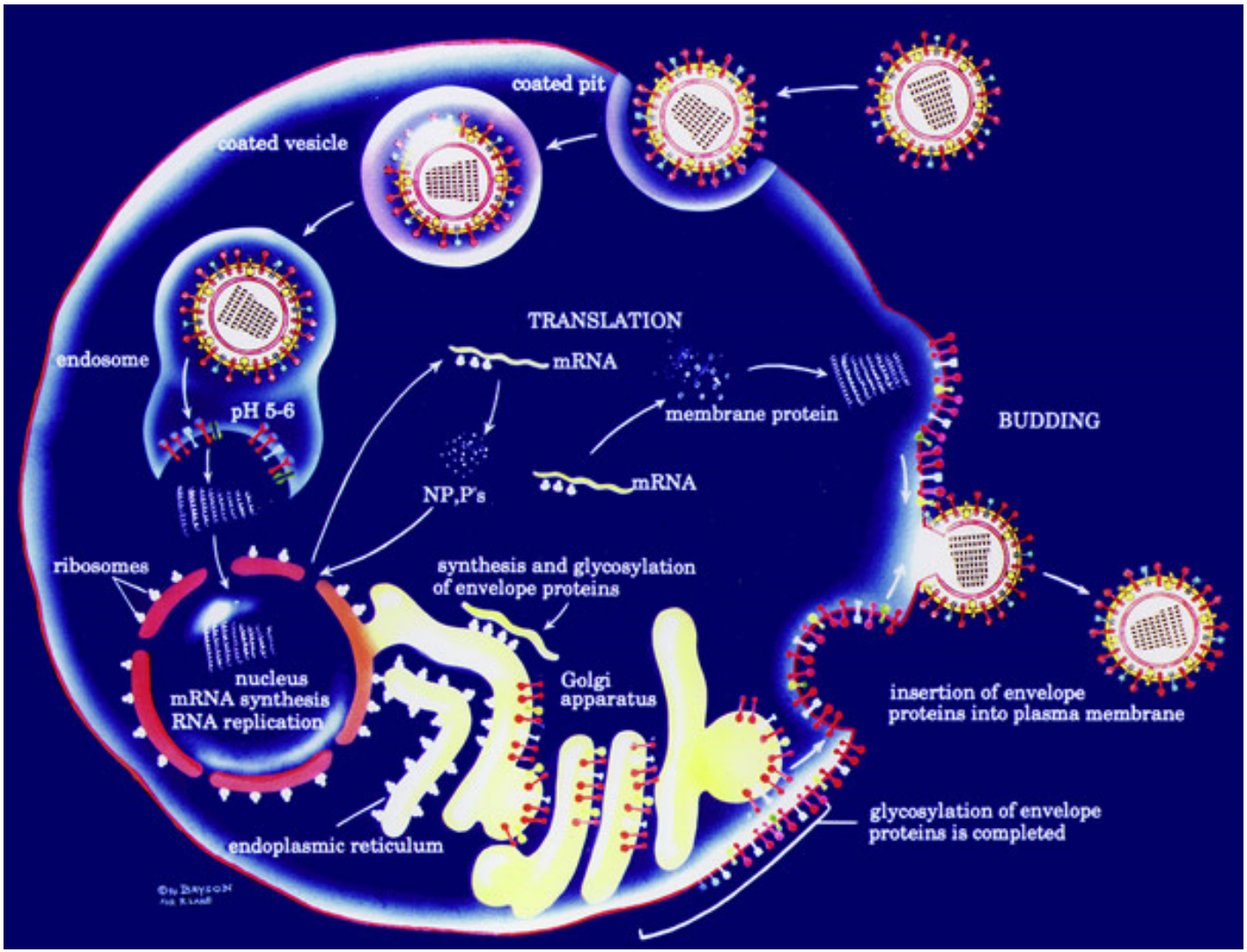
1 **2** **3** **4** **5** **6** **7**

- Amantadine: Excreted with no metabolism
- Rimantadine: Extensively metabolized by hydroxylation
- All the metabolites are less active
- In man: Excreted after 72 h: 32% unchanged rimantadine
  18% of **4**
  24 % of **5**

Rimantadine‘s high efficacy is not yet finally understood

Manchand, P. S.; Cerruti, R. L.; Martin, J. A.; Hill, C. H.; Merrett, J. H.; Keech, E.; Belshe, R. B.; Connell, E. V.; Sim, I. S., *J. Med. Chem.* **1990,** 33, (7), 1992-1995.

Mechanism of action



Mechanism of action – blocking M2

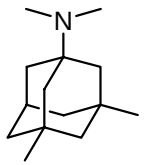
```
                                                  10                                                  20                                                  30
AUG AGC CUU CUA ACC GAG GUC GAA ACG CCU AUC AGA AAC GAA UGG GGG UGC AGA UGC AAC GAU UCA AGU GAC CCU CUU GUU GUU GCU GCG AGU AUC AUU GGG
                                                                                                                                          U     A
 M   S   L   L   T   E   V   E   T   P   I   R   N   E   W   G   C   R   C   N   D   S   S   D   P   L   V   V   A   A   S   I   I   G
                                                                                                                                          *     *
                                                                                                                                          V     N

                                  40                                                  50                                                  60
AUC UUG CAC UUG AUA UUG UGG AUU CUU GAU CGU CUU UUU UUC AAA UGC AUC UAU CGA CUC UUC AAA CAC GGC CUG AAA AGA GGG CCU UCU ACG GAA GGA GUA
                                                                                                                  U
 I   L   H   L   I   L   W   I   L   D   R   L   F   F   K   C   I   Y   R   L   F   K   H   G   L   K   R   G   P   S   T   E   G   V
                                                                                                                  #
                                                                                                                  F

     70                                                  80                                                  90
CCU GAG UCU AUG AGG GAA GAA UAU CGA AAG GAA CAG CAG AAU CGU GUG AAU GCU GAC GAC AGU CAU UUU GUC AGC AUA GAG CUG GAG
 P   E   S   M   R   E   E   Y   R   K   E   Q   Q   N   R   V   N   A   D   D   S   H   F   V   S   I   E   L   E
```

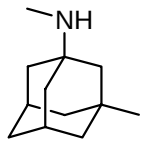
Coding and amino acid sequence of M2 – Rimantadine sensitive and resistant

How to overcome resistance?

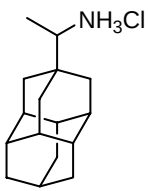
- By combining two different compounds with comparable pharmacokinetics, but different targets
- By developing a new drug that acts at two targets – M2 and HG

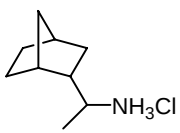
Candidates:

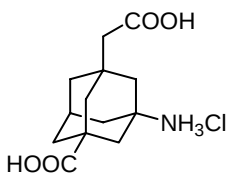


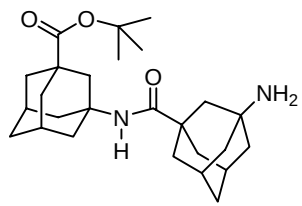


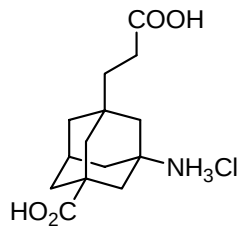
- By applying new substances

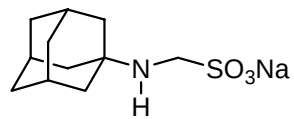




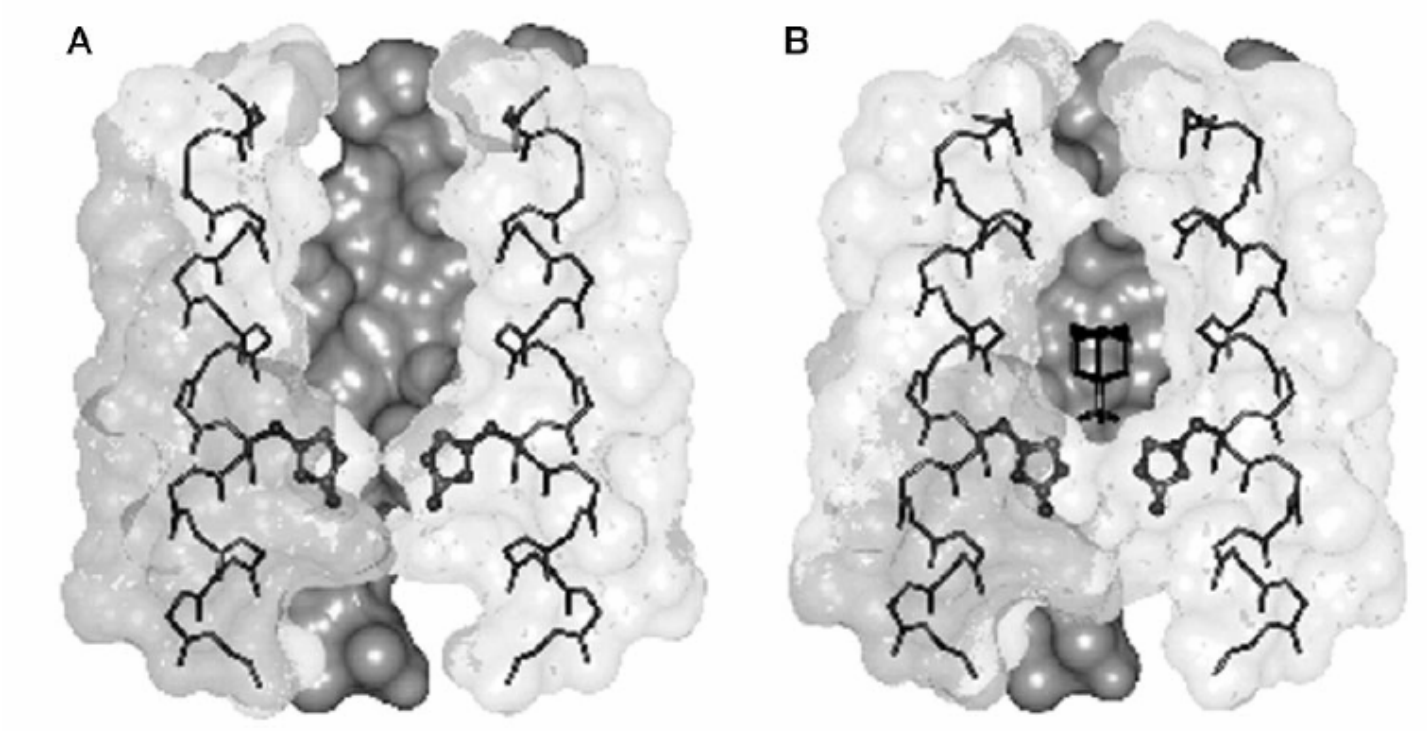








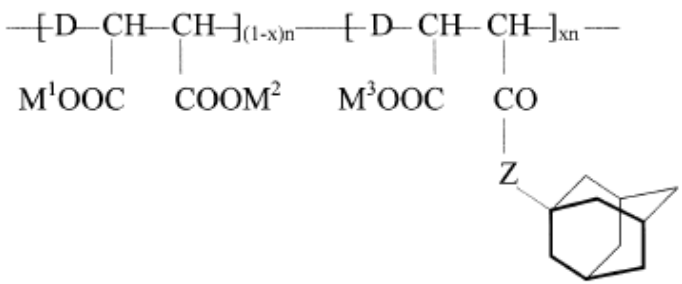
Scholtissek, C.; Quack, G.; Klenk, H. D.; Webster, R. G., *Antivir. Res.* **1998,** 37, (2), 83-95.



Gandhi, C. S.; Shuck, K.; Lear, J. D.; Dieckmann, G. R.; DeGrado, W. F.; Lamb, R. A.; Pinto, L. H., *J. Biol. Chem.* **1999,** 274, (9), 5474-5482.

Other Viruses fought with Adamantane derivatives:

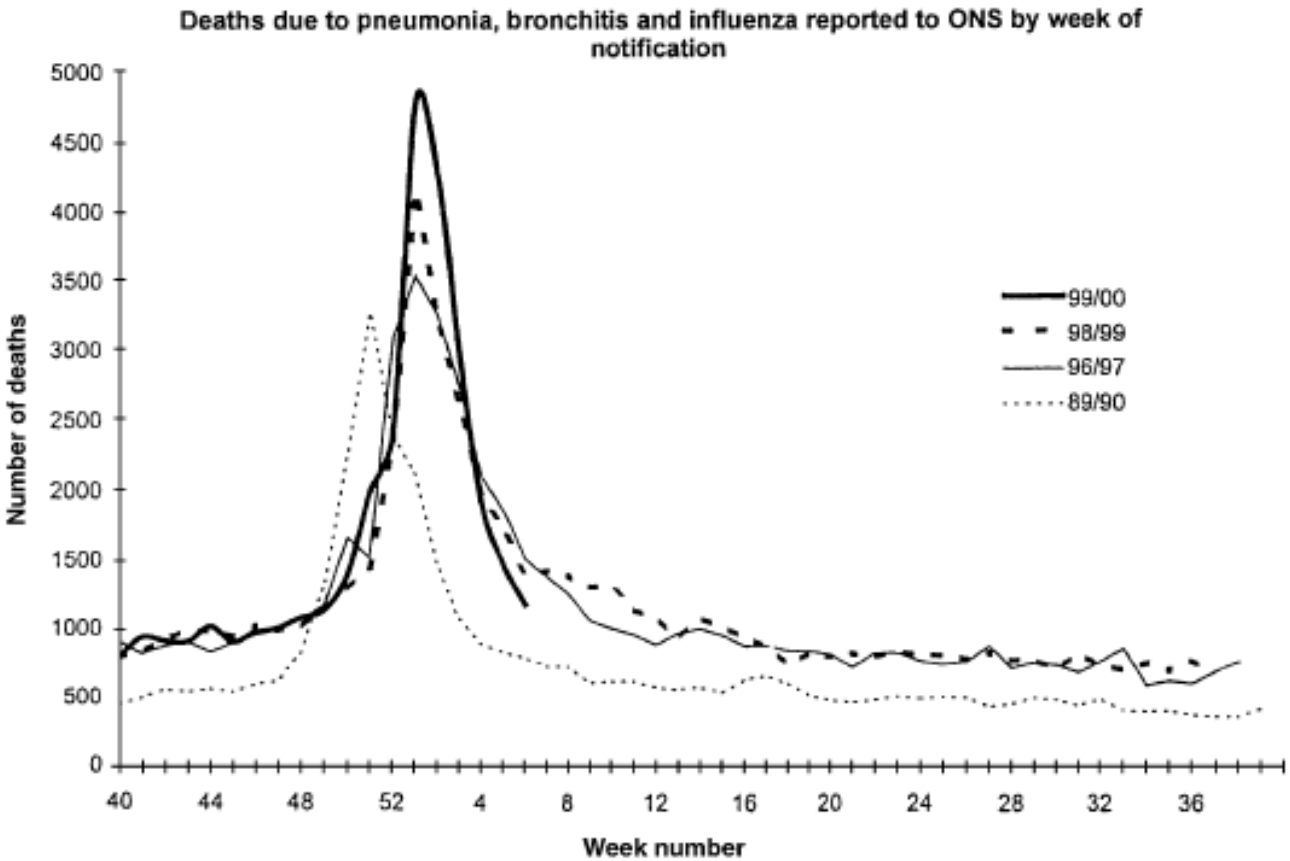
- Posttransplantation Hepatitis C – Amantadine is being tested in a combination approach
- Rubella
- Rous sarcoma
- Esh sarcoma
- SARS: No M2 channel – no inhibition by Aminoadamantanes
- HIV-1 replication with exotic „Amant“



Bizollon, T.; Adham, M.; Pradat, P.; Chevallier, M.; Ducerf, C.; Baulieux, J.; Zoulim, F.; Trepo, C., *Transplantation* **2005,** 79, (3), 325-329.

Aldrich, P. E.; Hermann, E. C.; Meier, W. E.; Paulshock, M.; Prichard, W. W.; Synder, J. A.; Watts, J. C., *J. Med. Chem.* **1971,** 14, (6), 535-543.

We could need a supply…



Oxford, J. S.; Bossuyt, S.; Balasingam, S.; Mann, A.; Novelli, P.; Lambkin, R., *Clinical Microbiology and Infection* **2003,** 9, (1), 1-14.

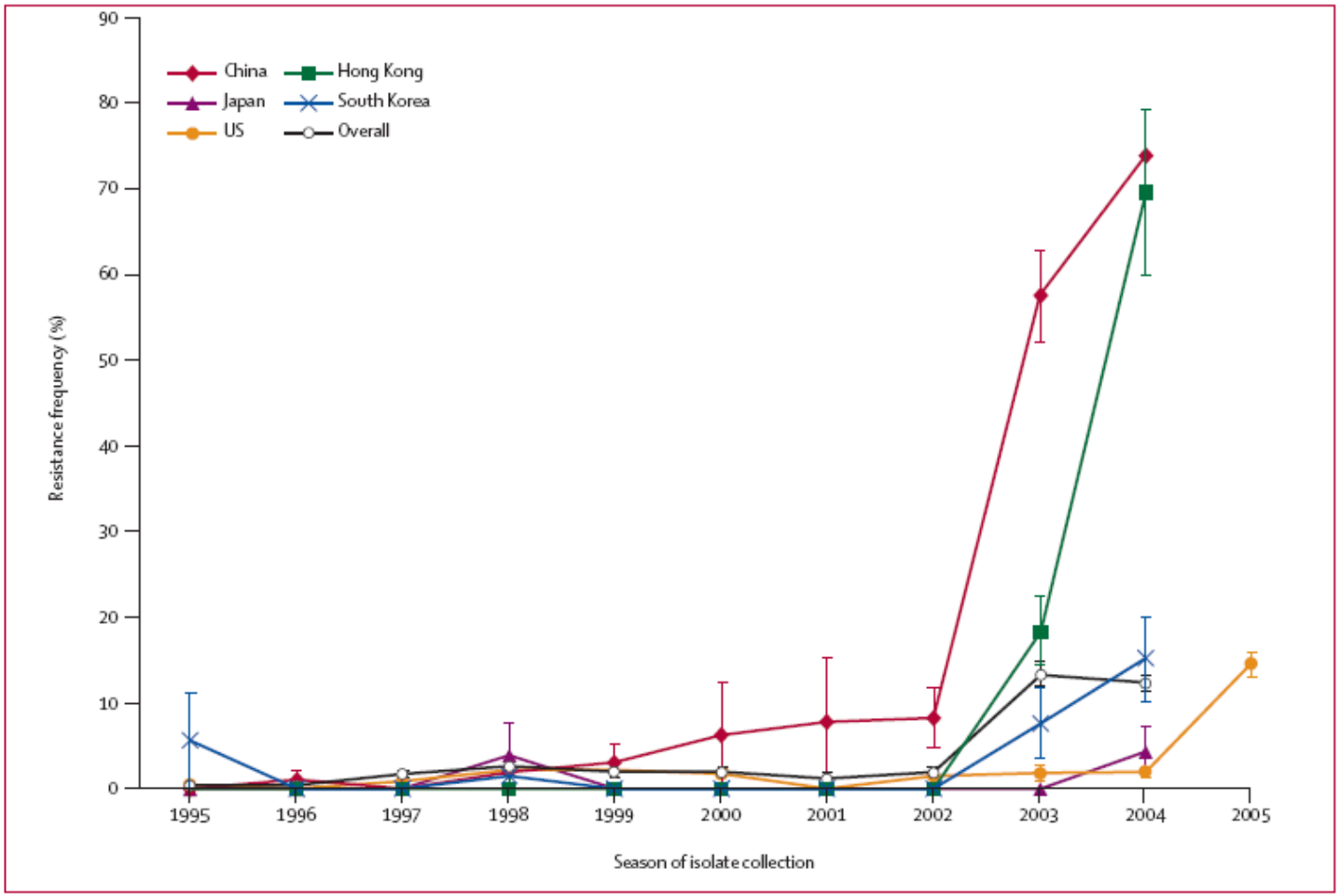


Figure: Trend of adamantane-resistant H3N2 viruses, 1994–2005
Each point represents the percentage of resistant viruses of the total tested. Error bars represent the 95% CI for the proportion of resistant viruses out of the total tested.

Aminoadamantanes alone won‘t do it!

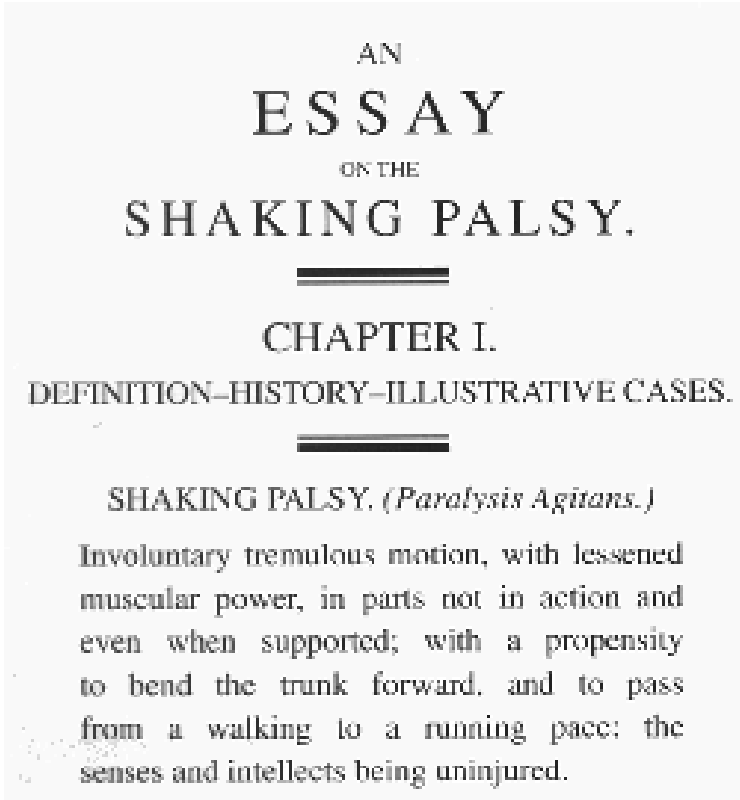
Bright, R. A.; Medina, M.-j.; Xu, X.; Perez-Oronoz, G.; Wallis, T. R.; Davis, X. M.; Povinelli, L.; Cox, N. J.; Klimov, A. I., *Lancet* **2005,** 366, (9492), 1175-1181.

Treatment of Parkinson‘s Disease

What is Parkinson‘s disease?

- Known since antiquity
- First reported by engish physician James Parkinson in 1817
- Slowly proceeding neurological disorder
- 0.1 – 0.2 % of population suffer from PD
- Over the age of 60: **~ 1%**

AGE	MALE	FEMALE
All ages	**58%**	**42%**
31-60	14%	22%
61-70	27%	12%
71-75	11%	14%
76+	48%	52%



AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

1969: Schwab (1964): Clinical trials with amantadine (anti-influenza) – benefits in Parkinson‘s sympthoms

Schwab, R.; England, A. C.; Postkanzer, D.; Young, R. *J. Am. Med. Assoc.* **1969**, *208,* 1168.

Molecular Basics:

• Dopamine, an excitatory neurotransmitter, is manufactured in substantia nigra neurons in basal gangliae

• Neurons in substantia nigra die – reason not known. Theories:

• Pesticides, oxidative stress, (genetic disposition)

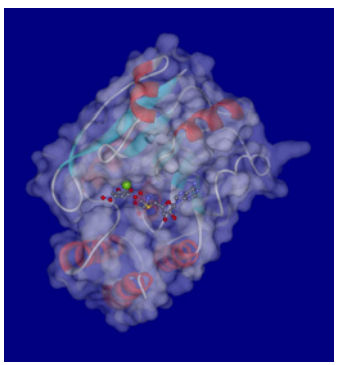
• released through action potential (Ca^{2+} dependent mechansim)

• exocytose, docking on receptors follow the classic scheme

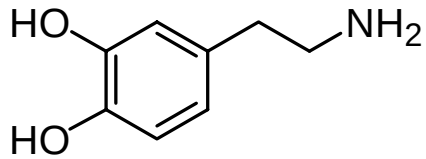
• activation **or** inactivation of postynaptic neuron

• presynaptic membrane contains **autoreceptors** for dopamine to monitor its concentration within the synaptic cleft

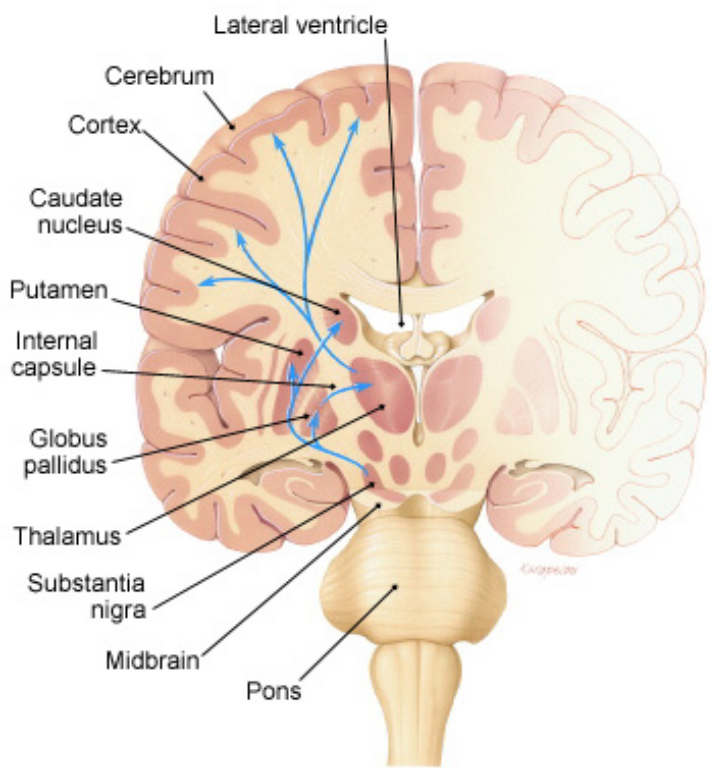
• Degradation: Through Catechol-O-methyltransferase



This enzyme is one target to increase dopamine concentrations, **BUT**

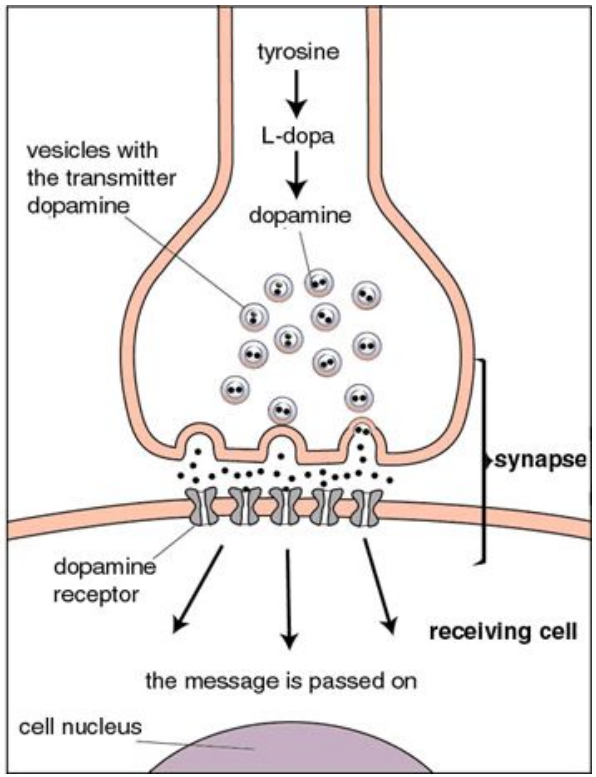


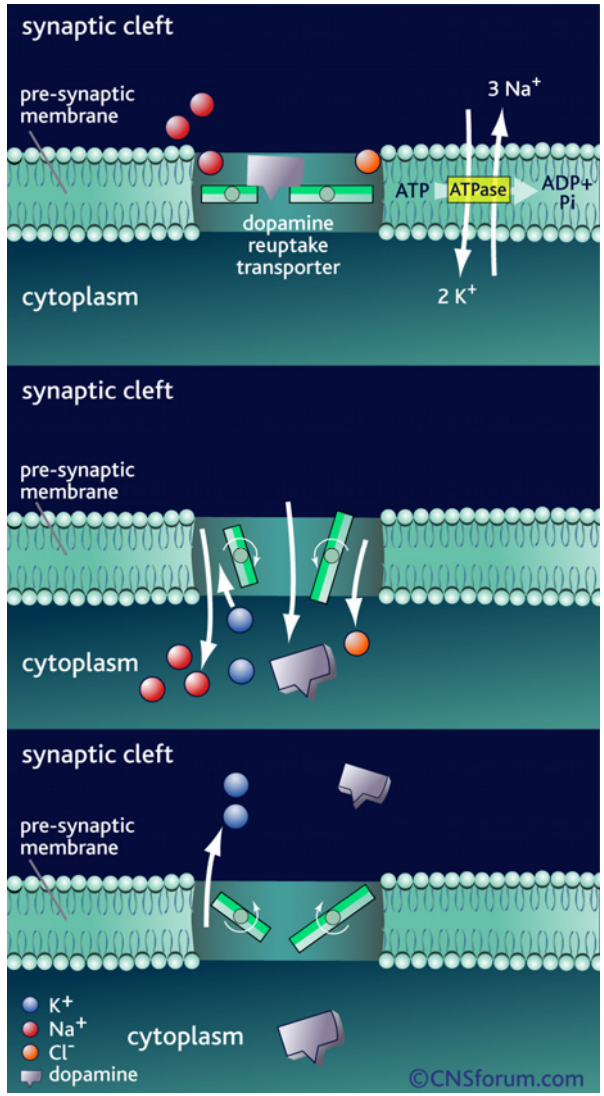
Dopamine



Lerner, C., Ruf, A., Gramlich, V., Masjost, B., Zürcher, G., Jakob-Roetne, R., Borroni, E., Diederich, F. *Angew. Chem.* **2001**, *113*, 4164-4166; *Angew. Chem.-Int. Edit.* **2001**, *40*, 4040-4042.

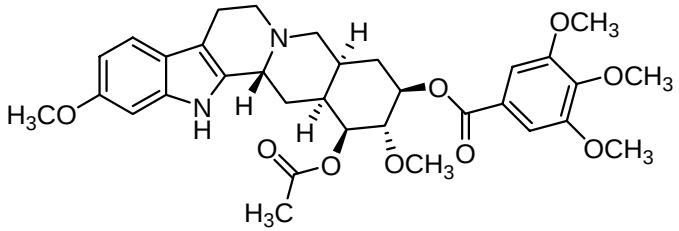
Specific dopamine transporters support the reuptake - 80% of dopamine is taken back from neurons



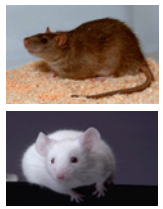


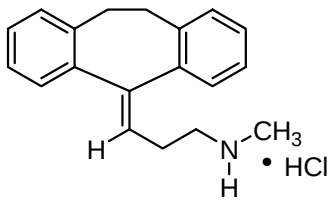
Trying to improve Amantadine…

1973: Lilly did a screening of 69 Adamantane Derivatives (reserpine induced hypothermia, anti-depressant action)



Reserpine

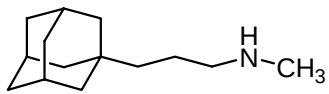




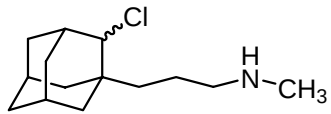
Nortriptyline (antidepressant)

LD50 = 85 / 325 mg/kg

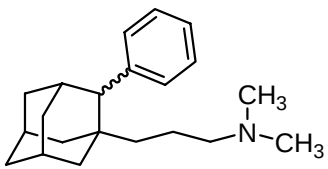
Highly active at 20 mg/kg



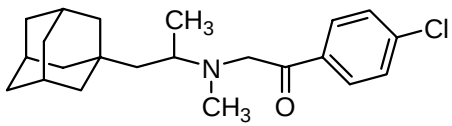
LD_{50} = 200 / 600 mg/kg
Activity: "very high" at 10 / 20 mg/kg



No Toxicity tested
identical activity



LD_{50} = 300 / 800 mg/kg
identical activity

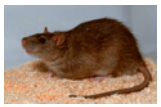


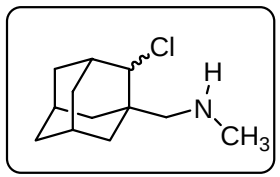
LD_{50} = 600 / >1600 mg/kg
almost identical activity

Bioavailability: respective hydrochlorides were used

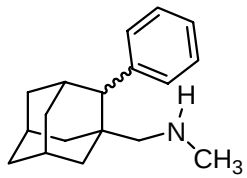
Chakrabarti, J. K.; Foulis, M. J.; Hotten, T. M.; Szinai, S. S.; Todd, A., *J. Med. Chem.* **1974,** 17, (6), 602-609.

Reversal of reserpine induced catalepsy (measures antiparkinson activity)

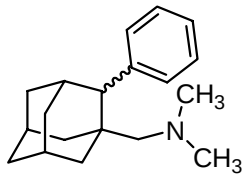

(female only)



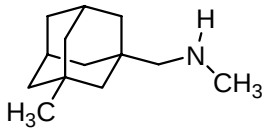
20 mg/kg: marginal
40 mg/kg: complete



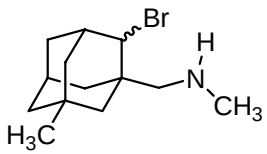
20 mg/kg: no effect
40 mg/kg: marked effect



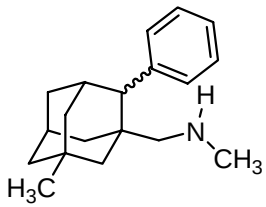
20 mg/kg: no effect
40 mg/kg: marked efect



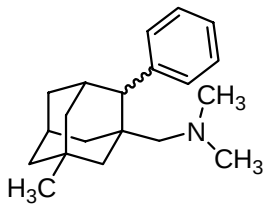
20 mg/kg: not tested
40 mg/kg: no effect



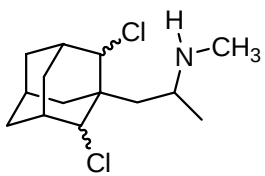
20 mg/kg: significantl
40 mg/kg: marked effect



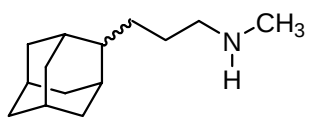
20 mg/kg: marginal
40 mg/kg: marked effect



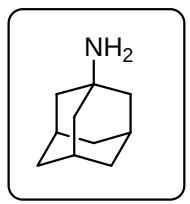
20 mg/kg: not tested
40 mg/kg: no effect



20 mg/kg: significant
40 mg/kg: marked effect



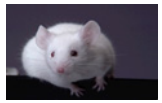
20 mg/kg: no effect
40 mg/kg: marked effect

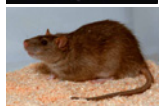


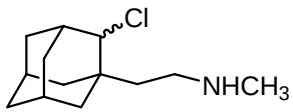
20 mg/kg: no effect
40 mg/kg: significant

Chakrabarti, J. K.; Foulis, M. J.; Hotten, T. M.; Szinai, S. S.; Todd, A., *J. Med. Chem.* **1974,** 17, (6), 602-609.

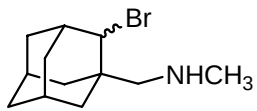
1976 (Lilly): Reserpine induced catalepsy in mice and rats – same test, new substances – new publication



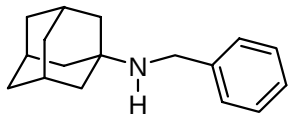




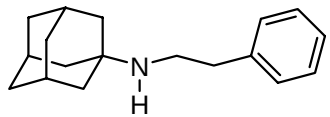
Marked - 0.15 mmole/kg



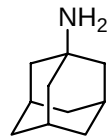
Marked - 0.17 mmole/kg



Marked - 0.09 mmole/kg



Marked - 0.09
significant - 0.07

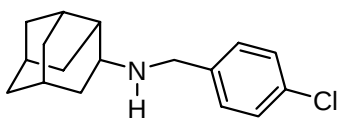


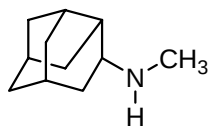
...only active in rats, not mice!

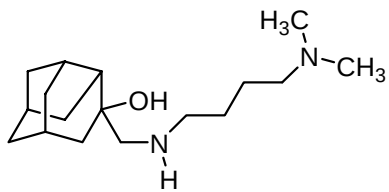
Toxicities were all lower than that of Amantadine

Protoadamantane derivatives were NOT active in reversing catalepsy

(they did to some extent reverse hypothermia)

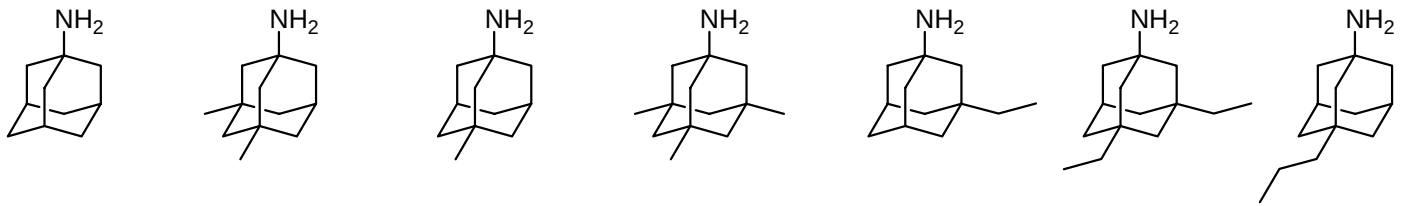






Chakrabarti, J. K.; Hotten, T. M.; Sutton, S.; Tupper, D. E., *J. Med. Chem.* **1976,** 19, (7), 967-969.

1982: Influence of bridgehead substitution:



Druggable anti-Parkinson agents:

(a) Postsynaptic dopaminergic agonist action

(b) Lipophilic – able to cross BBB and enter CNS

(c) Metabolic stability

(d) Low Toxicity

Biological tests:

⇨ Stimulation of spontaneous locomotor activity

⇨ modification of circling behaviour in dopamine treated mice with unilateral lesions from 6-Hydroxydopamine injections

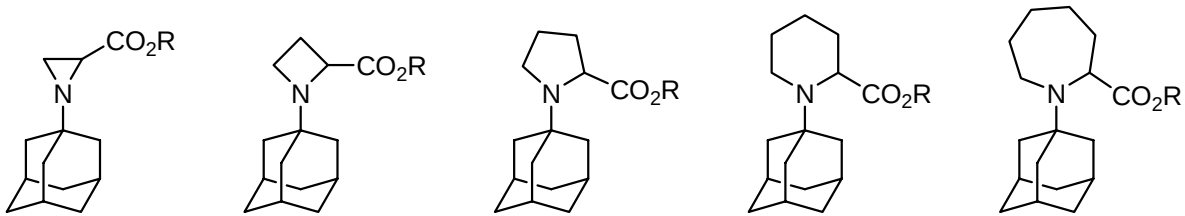
⇨ reversal of reserpine-induced akinesia in mice

All of the alkylated compounds were more active than Amantadine at toxicities from 0.4 – 0.8 mmol /kg (ca. 90 – 180 mg/kg)

Henkel, J. G., Hane, J. T., *J. Med. Chem.* **1982,** 25, 51-56.

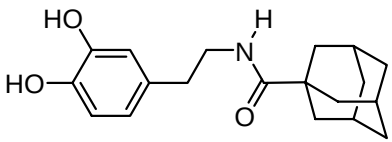
Schering (Several Patents 1975 – 1976):

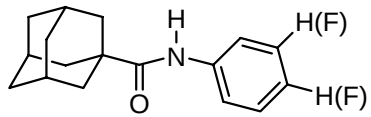
…“useful in treatment of parkinsonism“



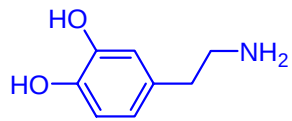
R = H, CH_3

…“particularly suitable for treatment of parkinsonism“

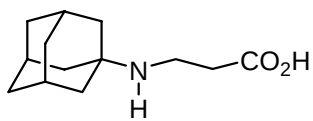


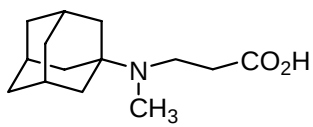


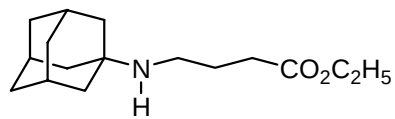
You know why!



…“useful in treating parkinson patients with less debiliating side effects than L-Dopa and Amantadine“





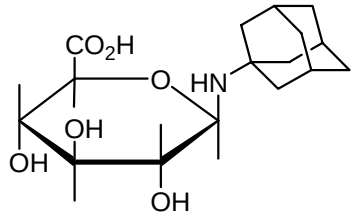


E. H. Gold, US Patent 3917840 19751104

S. Symchowicz, H. P. Faro, US Patent 3944675 19760316

E. H. Gold, US Patent 3941885 19760302

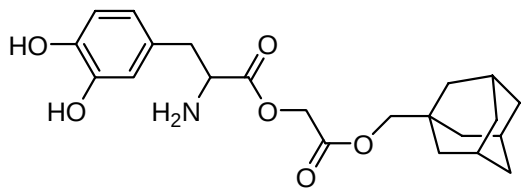
Remember Maksims
Vanejews / Riga, Latvia?



Adamantylamino-1-N-Glucuronide

…“was an effective inhibitor of parkinsonism. Also effective in atheriosclerotic parkinsonism and, to a lesser extend, in postencephalitic parkinsonism“

Synthelabo‘s Patent



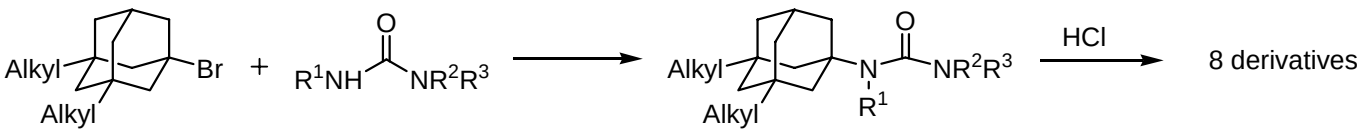
-Tridecyl
-Pentadecyl
-Bornyl
-Isobornyl

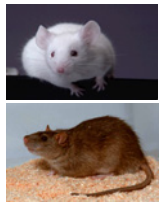
…“were prepared as antihypertensive agents and for the treatment of parkinsonism“

e.g., S. Hillers, J. Polis, I. M. Kamyanov, FR 2268530 19751121

FR 77-28872 19770926

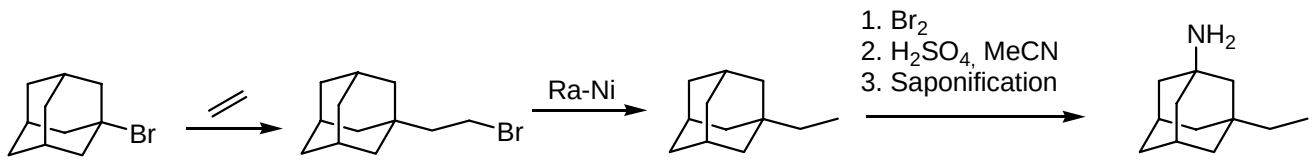
Medicinal Chemistry of Adamantane Derivatives





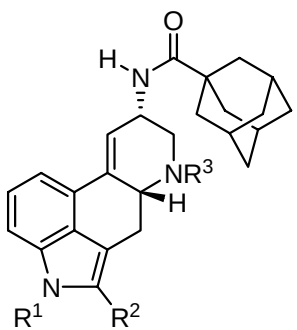
Our Friends

from Merz



...reference is described wrong – at least in SciFinder!

Sandoz



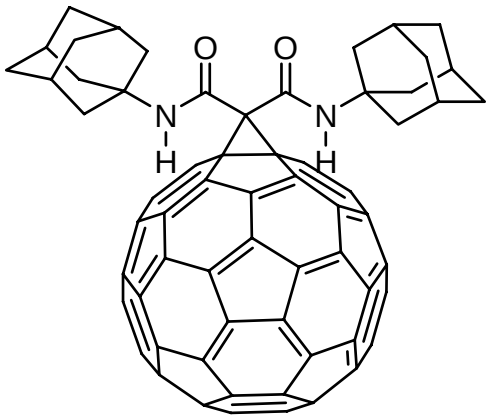
…“ useful as neuroleptics, prolactin secretion inhibitors and in treating schizophrenia and parkinsonism“

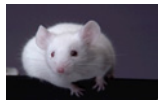
A. Scherm, D. Peteri, DE 73-2318461 19730412

A. Scherm, D. Peteri, B. Janiak, DE 2232735 19740124

W. Haeflinger, DE 85-3544365 19851214

A nice concept from Japan





(male only)

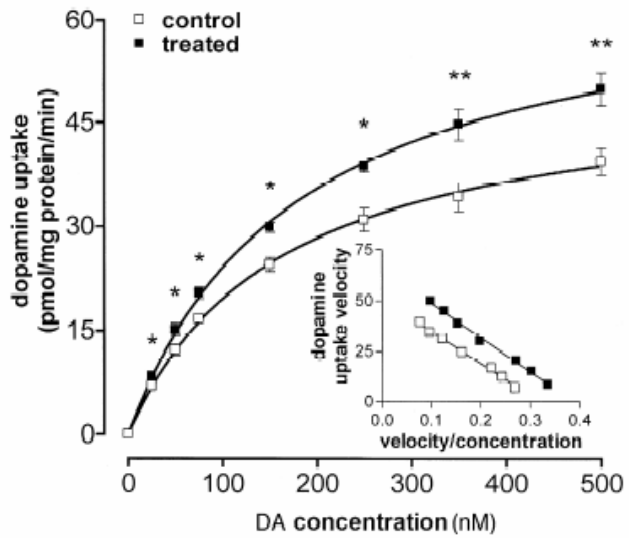
This compound fuses (at least in theory):

- Passes blood-brain-barrier due to lipophilic Adamantanes and C_{60} moiety)
- Leads to an increase in dopamine release (action of Amantadine, as proven in rat striatum tissue)
- Antioxidant activity of fullerene moiety – releases oxidative stress
- Neuroprotective effect

BUT

•Administration of 10 mg/kg caused antagonistic effect on haloperidol-induced catalepsy

• Administration of 32 or 100 mg/kg had no effect – possibly due to inhibition of faty acid amide hydrolase

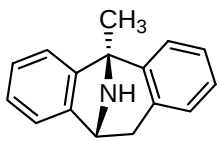


Nakazono, M.; Hasegawa, S.; Yamamoto, T.; Zaitsu, K., *Bioorgan. Med. Chem.* **2004,** 14, (22), 5619-5621.

Page, G.; Peeters, M.; Maloteaux, J. M.; Hermans, E., *Eur. J. Pharmacol.* **2000,** 403, (1/2), 75-80.

Research on the mechanisms of action of amino adamantanes in PD:

- Neuroprotection from Glutamate toxicity,
- Profile of Neuroprotection of Amantadine and Memantine parallels that of MK-801
- Those drugs act through NMDA receptor antagonism



MK-801

…"recent in vivo studies have described neurotoxicity induced by MK-801 and others"

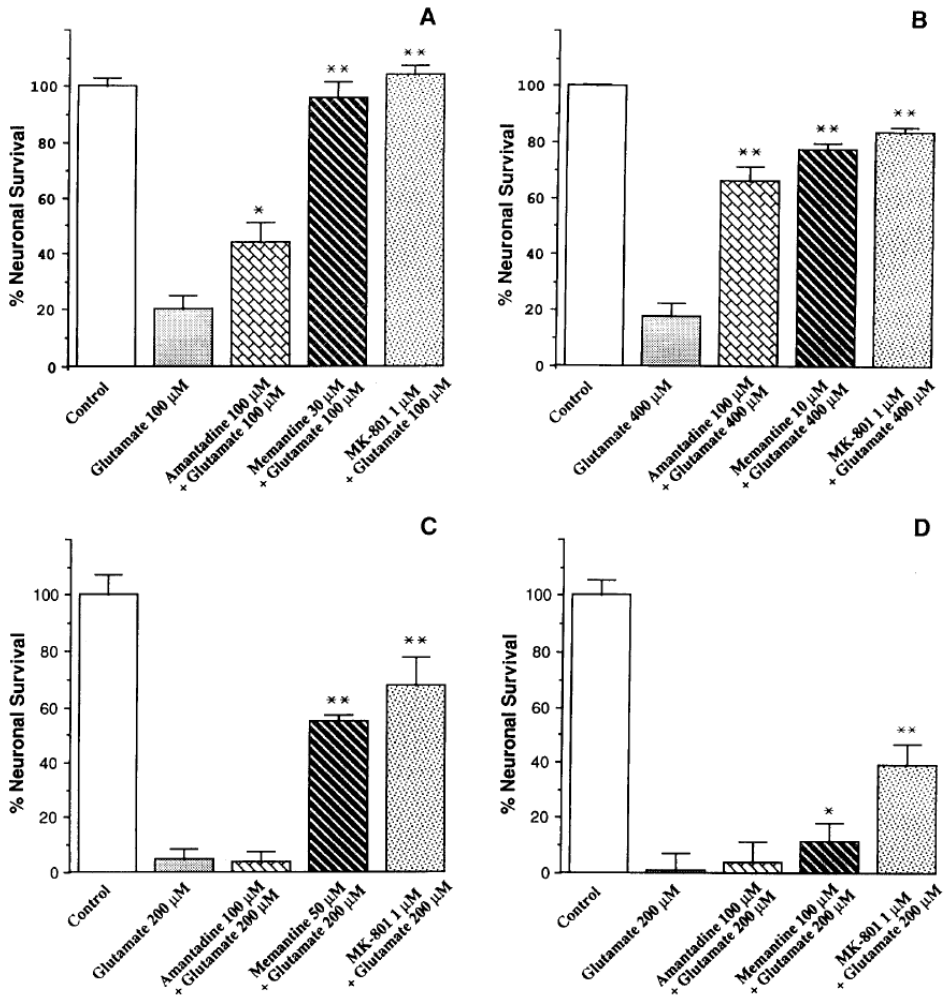


Fig. 3. A–D: neuronal survival (%) assessed as detailed in the text after exposure to glutamate alone or to glutamate after pre-exposure to amantadine, memantine, or MK-801. A, cerebellar granule neurons. B: cortical neurons. C: mesencephalic neurons; D: mesencephalic (dopaminergic) neurons. Data are representative of triplicate experiments and show neuroprotective effects of amantadine and memantine at concentrations which when applied alone did not affect neuronal viability. Asterisks indicate significant difference as compared to glutamate treatment alone by Student's *t*-test (* $P < 0.01$, ** $P < 0.001$).

Weller, M.; Finiels-Marlier, F.; Paul, S. M., *Brain Research* **1993,** 613, (1), 143-148.

Today‘s consensus:

• Amantadine and Memantine are mild, non-competitive NMDA-receptor antagonists with rapid blocking / unblocking channel kinetics

• Estimations of Amantadine concentrations in CNS under therapeutic conditions: Mean amantadine concentration in post-mortem brain tissue from 48.2 – 386 µM

• Neurotoxic effects of excitatory amino acids are involved in pathogenesis of PD

• From Pharmacokinetic microdialysis: Memantine (& Amantadine) exerts its main actions on NMDA-receptor; increase in dopamine release is an indirect effect

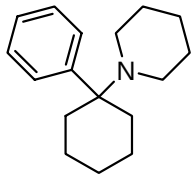
• No support for suggested use of Memantine and Amantadine in use against epilepsy

• Amantadine and Memantine can be applied for years without serious side effects

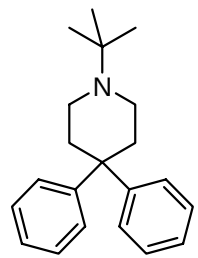
• NMDA antagonists block the channel, thereby preventing Ca^{2+} influx that is finally responsible for cell death

• Adamantanes are indeed „open channel blockers“ like PCP (Phencyclidine, „Angel Dust“)

• Budipine: Recently introduced open channel blocker

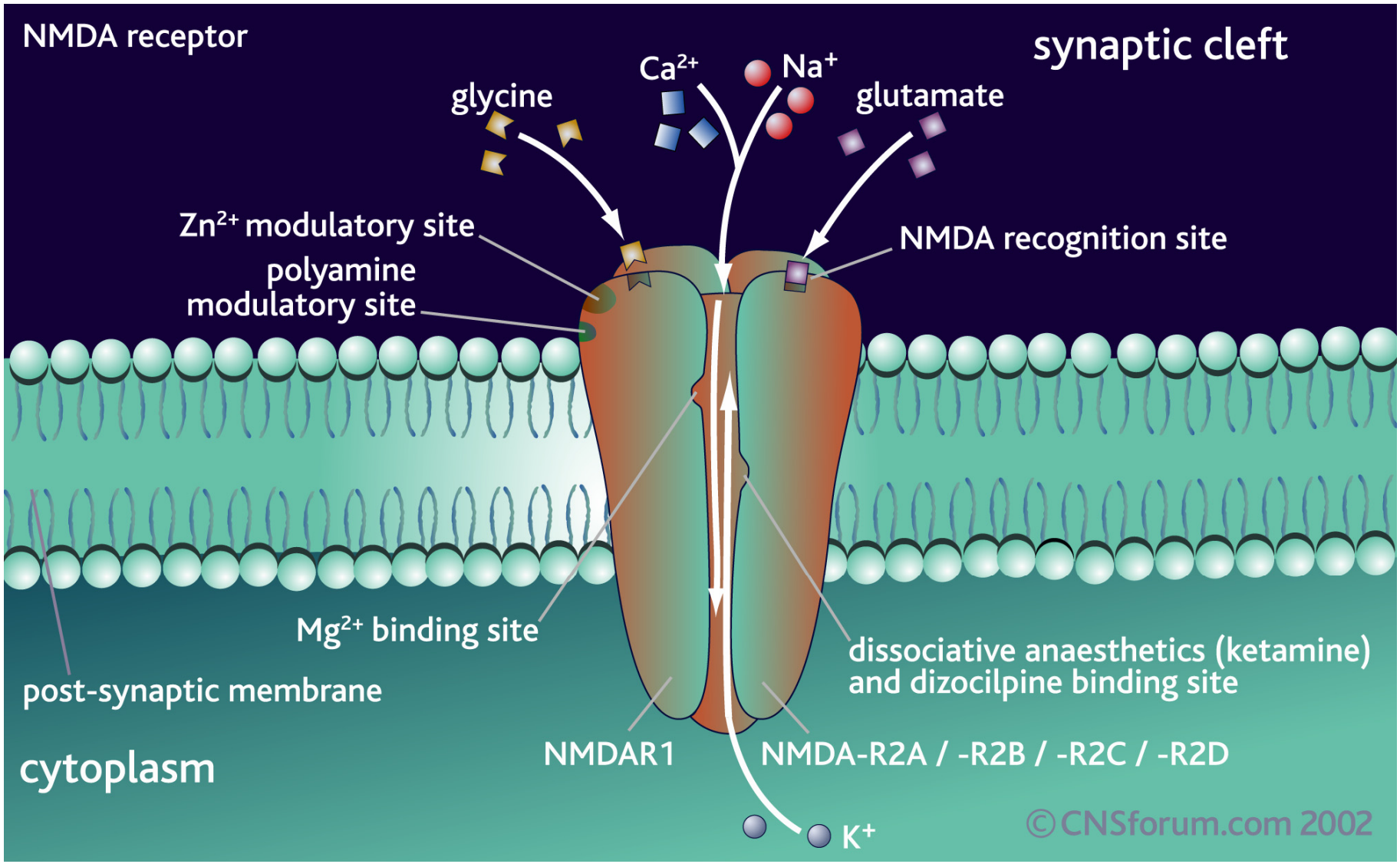


Phencyclidine



Budipine

Kornhuber, J.; Quack, G.; Danysz, W.; Jellinger, K.; Danielczyk, W.; Gsell, W.; Riederer, P., *Neuropharmacology* **1995,** 34, (7), 713-721.
Lange, K. W.; Riederer, P., *Life Sciences* **1994,** 55, (25/26), 2067-2075.
Spanagel, R.; Eilbacher, B.; Wilke, R., *Eur. J. Pharmacol.* **1994,** 262, (1-2), 21-26.
Stark, H.; Reichert, U.; Grassmann, S., *Pharmazie in Unserer Zeit* **2000,** 29, (4), 228-236.


NMDA receptor
synaptic cleft
glycine
Ca^{2+}
Na^{+}
glutamate
Zn^{2+} modulatory site
polyamine modulatory site
NMDA recognition site
Mg^{2+} binding site
post-synaptic membrane
dissociative anaesthetics (ketamine) and dizocilpine binding site
cytoplasm
NMDAR1
NMDA-R2A / -R2B / -R2C / -R2D
K^{+}
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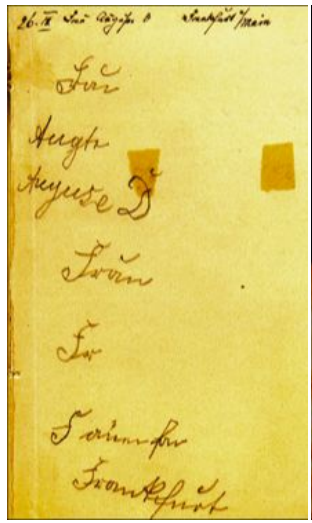
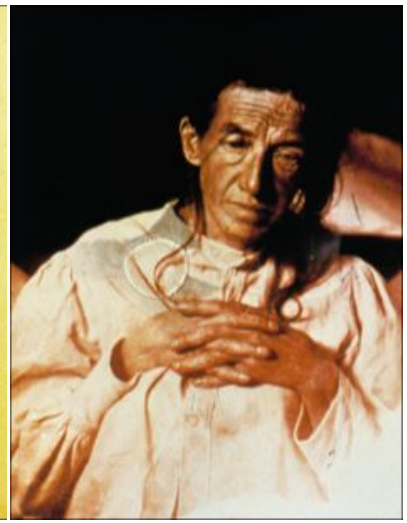
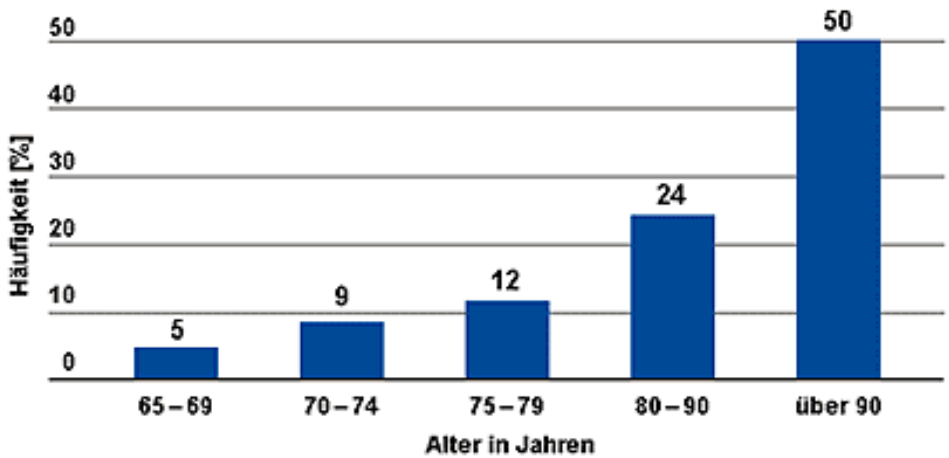
Treatment of Morbus Alzheimer

What is Alzheimer‘s disease?

- First described in 1906 by Alois Alzheimer in Würzburg
- Auguste D.: "Eine Frau von 51 Jahren zeigte als erste auffällige Krankheitserscheinung Eifersuchtsideen gegen den Mann. Bald machte sich eine rasch zunehmende Gedächtnisschwäche bemerkbar, sie fand sich in ihrer Wohnung nicht mehr zurecht, schleppte Gegenstände hin und her, versteckte sie, zuweilen glaubte sie, man wolle sie umbringen und begann, laut zu schreien.“
- When she died 5 years later, Alzheimer found characteristic plaques in her brain
- 60% of the total dementia cases are caused by Alzheimer‘s disease



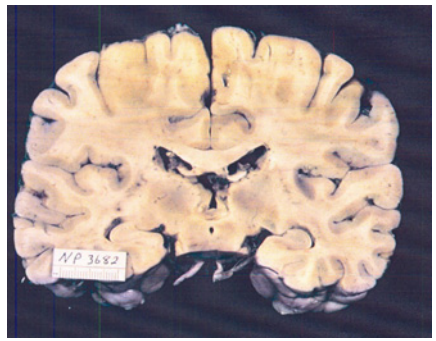


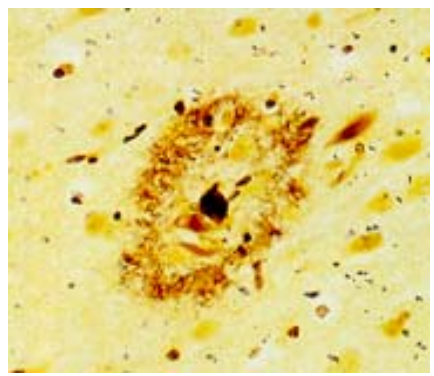


Molecular Basics of AD?

- Amyloid plaques or fibres – reason or consequence of neuronal death?
- Amyloid precursor protein (APP): If genetic code is disturbed – AD at an much younger age
- APOE: Participates in Cholesterine transport in the circulation
- APOE4 genotype is an established risk factor for Alzheimer's disease – increases risk of AD affection by factor 4
- A blood test is available
- Reason is not known
- Medication: improves symptoms only
- New medications protract loss in „quality-of-life"about 1 – 2 years
- Strategies: Acetylcholine Esterase inhibition
- Neuroprotection – cf. Parkinson section

No Details!





Medicinal Chemistry of Adamantane Derivatives

Memantine is the only medication for intermediate and severe forms of AD

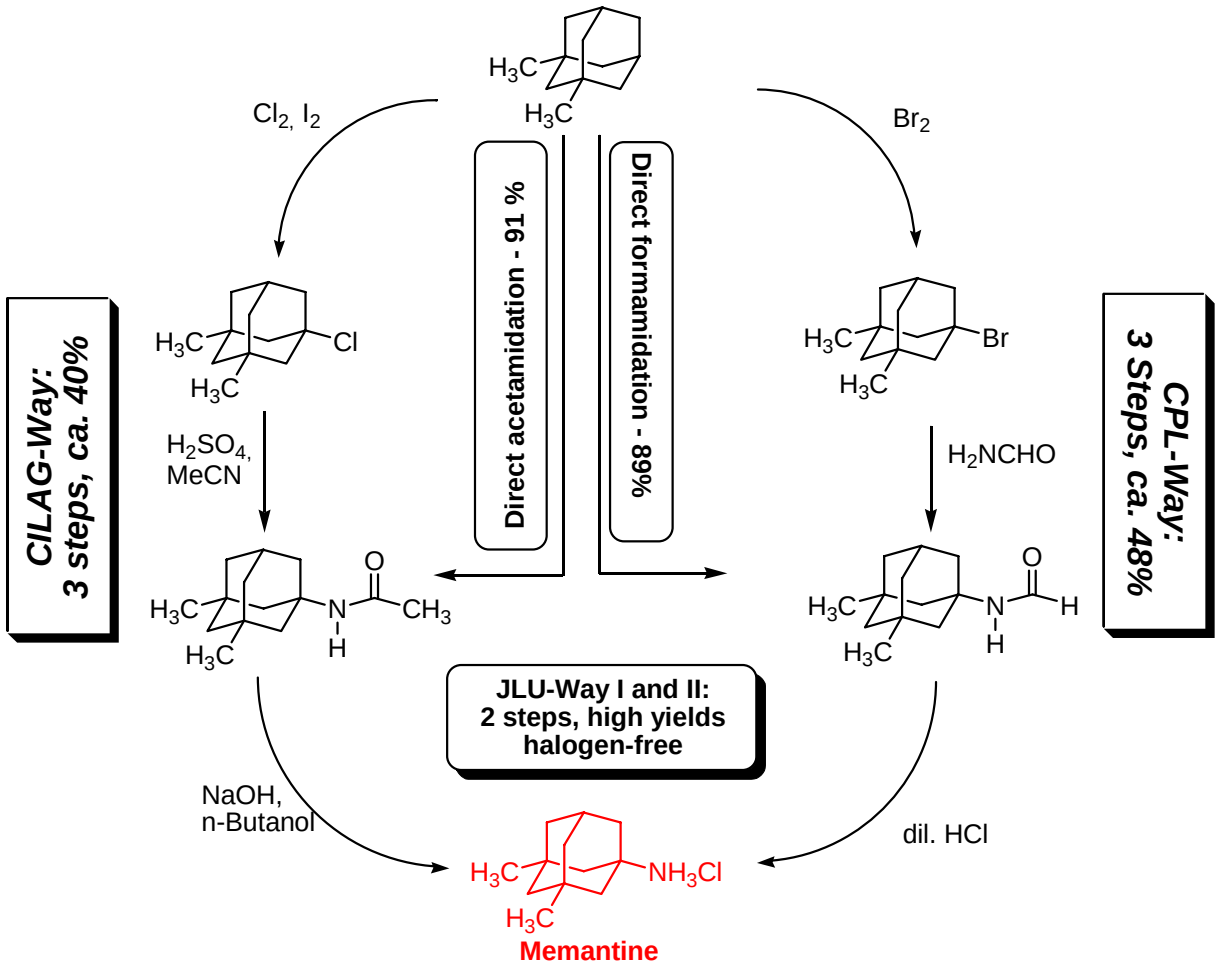
- Approval in Europe: February, 2002
- FDA approval (US): October, 2003
- …"After US-FDA approval, memantine looks all set to cross US$ 1,000,000,000 mark in annual sales by the year 2005."

NMDA antagonists at different stages of development

Name of drug	Licensee	Developmental Stage	K_i or IC_{50}	Reference
Agmatine	Harvard University	Preclinical	219 μM in rat cerebral cortex[a]	[142]
Eliprodil	Pharmacia, Sanofi-Synth	Phase III	0.277 ± 0.103 in hippocampus[b]	[143]
Amantadine	DuPont Pharmaceuticals	Launched	219 μM in cortex[a]	[142]
Amisulpiride	Sanofi-Synth,Labo	Launched	>10 μM in cortex[b]	[144]
Aptiganel	Cambridge NeuroScience	Phase II	0.029 ± 0.005 μM in cortex[a]	[145]
Dizocilpine (MK-801)	Merck Sharp and Dohme	Phase II	0.0086 μM in cortex[a]	[146]
Fanapanel	Novo Nordisk, Schering AG	Phase I	11 ± 2.1 μM in cortex[b]	[147]
Ifenprodil	Sanofi-Synth, Labo	Launched in 1973	10 μM in cortex[b]	[148]
Ketamine HCl	Pfizer, Bristol-Myer's Squibb	Launched in 1966	3.9 ± 0.5 μM in entorhinal cortex[b]	[124]
Methoxy idazoxan	Pierre Fabre, Reckitt & Colman	Phase I	190 μM cortex[a]	[142]
Neramexane HCl	Forest, Merz	Phase II	1.47 ± 0.13 μM in cortex [a]	[60]
Phencyclidine HCl	Pfizer	Unspecified phase	1.06 ± 0.07 μM in hippocampus[b]	[124]
Remacemide HCl	Astra Zeneca	Phase III	968 ± 45 μM in hippocampus[b]	[124]
Safinamide mesilate	Newron	Phase II	>100 μM in hippocampus[b]	[149]
Selfotel	Novartis	Phase III	22.4 μM in rat brain[b]	[150]

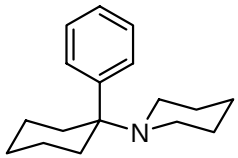
Sonkusare, S. K.; Kaul, C. L.; Ramarao, P., *Pharmacol. Res.* **2005,** 51, (1), 1-17.

Chemistry!

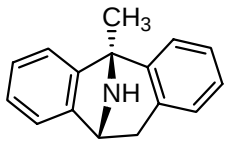


Bormann, J.; Gold, M. R.; Schatton, W. Use of adamantane derivatives in the prevention and treatment of cerebral ischemia. 89-106657 392059, 19890414., 1990.
But: Henkel, J. G., Hane, J. T., *J. Med. Chem.* **1982,** 25, 51-56.

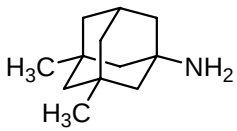
There is already a follow-up in clinical phase II: **Neramexane**.



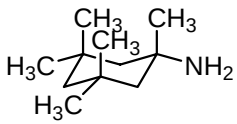
Phenylcyclidine



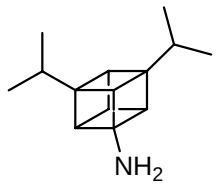
(+)MK-801

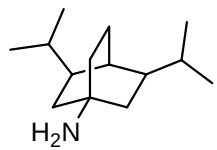


Memantine

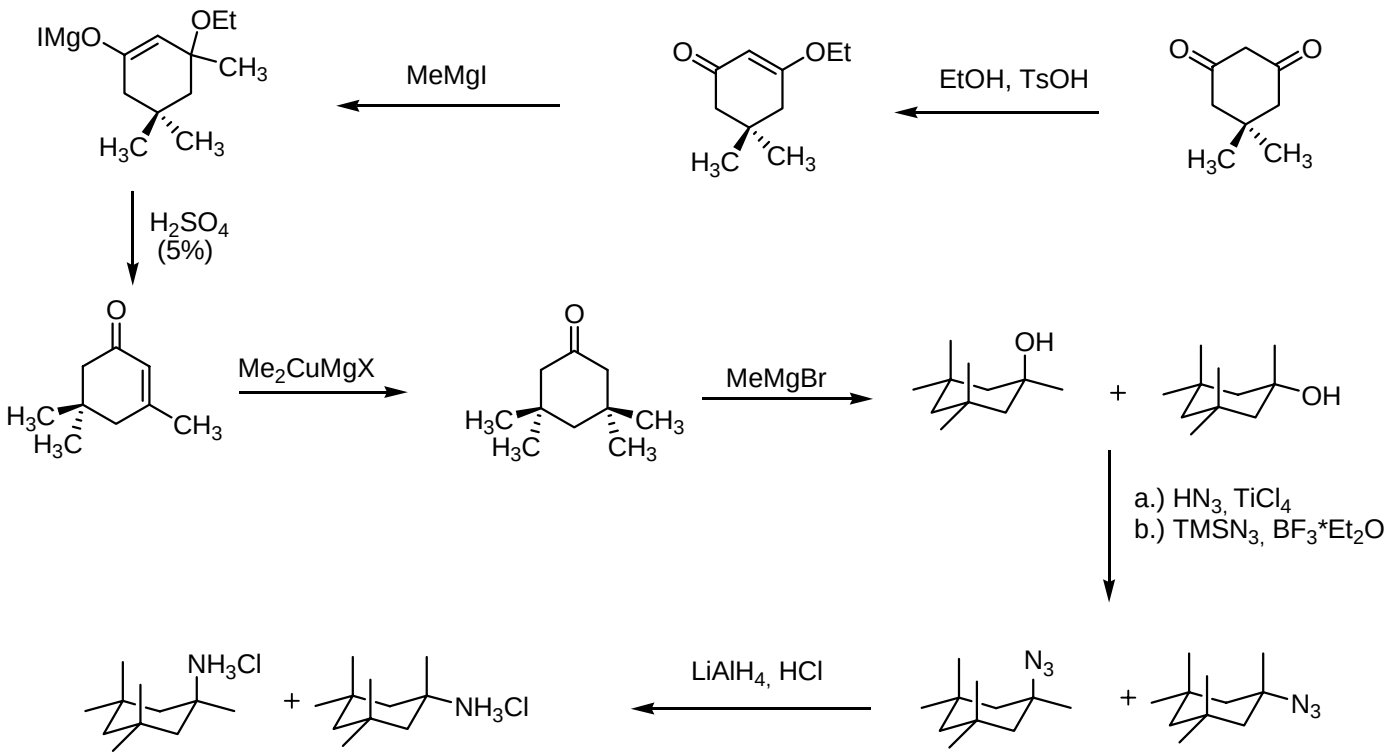


Neramexane





Synthesis:



7 steps; a/e stereoisomers!

Jirgensons, A.; Kauss, V.; Kalvinsh, I.; Gold, M. R.; Danysz, W.; Parsons, C. G.; Quack, G., *European journal of medicinal chemistry* **2000,** 35, (6), 555-565.

Thank you once more for your attendance…