Chemistry and the Nervous System

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May, 15, 2009

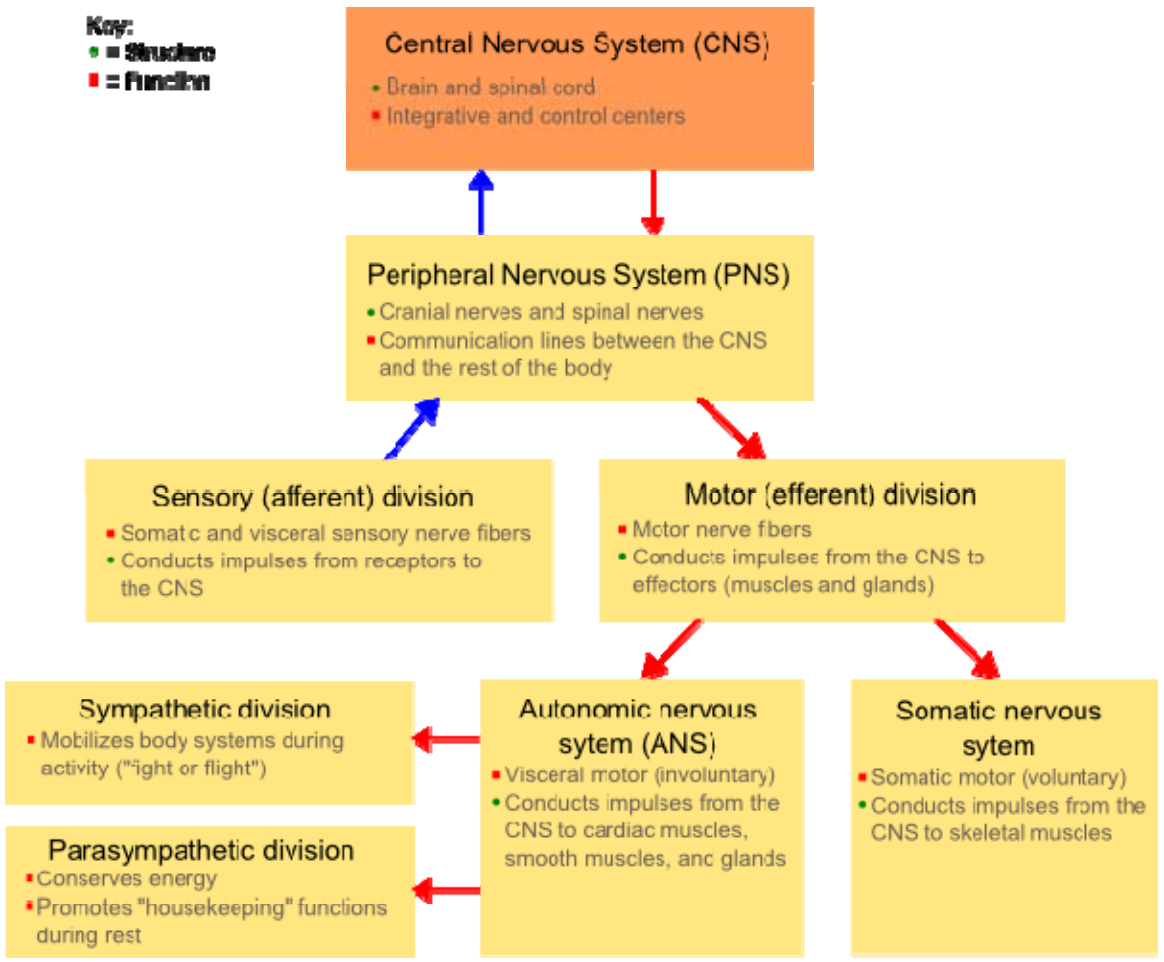
What to expect from this presentation

- Medicinal chemistry
- Biochemistry
- Total synthesis

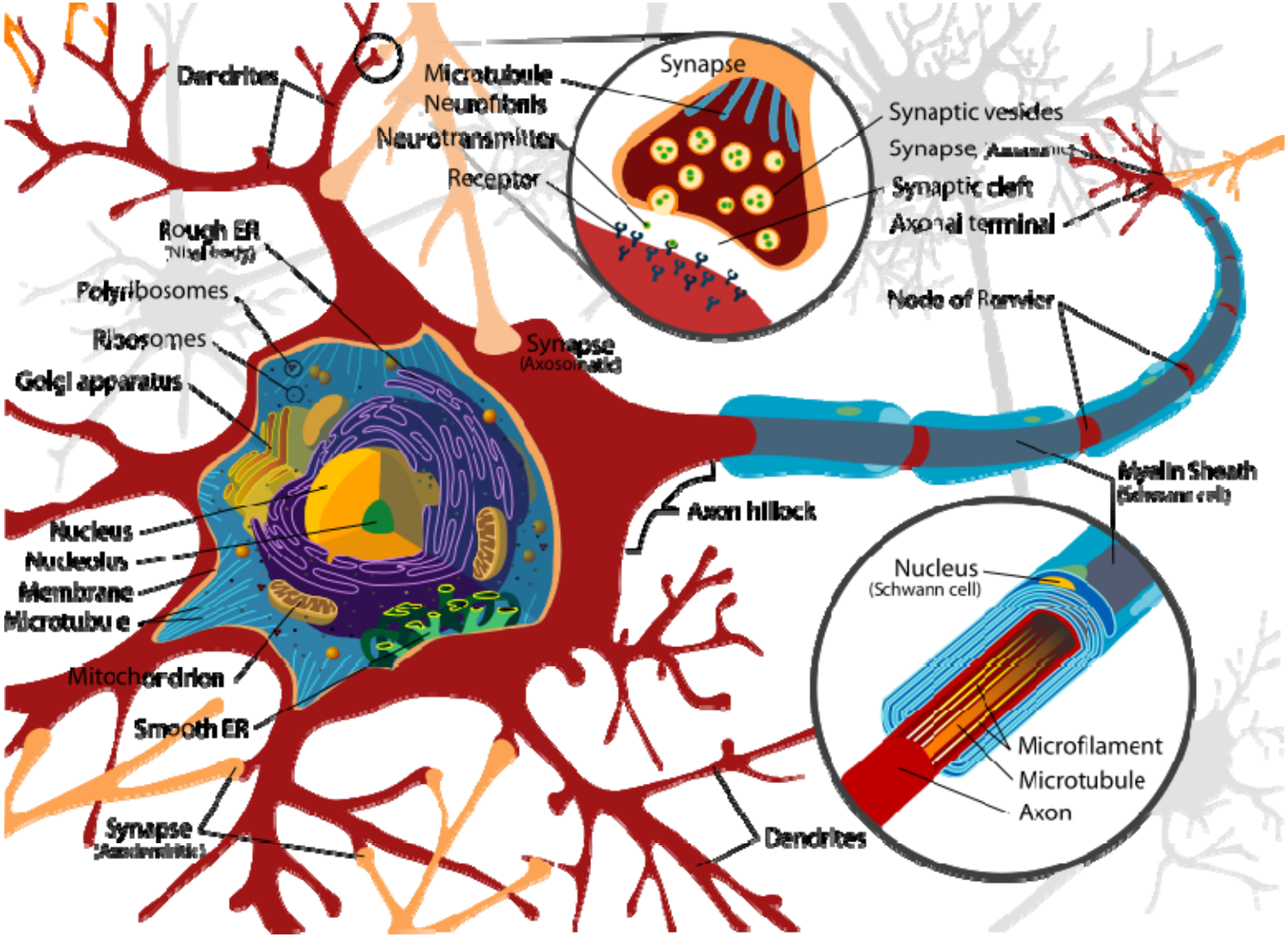
Ouline

- Nervous system
  - Classification
  - Neurons
  - Ionic and metabotropic receptors
- Neurotransmitters
  - Acetylcholin and related chemicals
  - Monoamines and related chemicals
  - Aminoacids and related chemicals
- Conclusion

Human Nervous System



Neuron



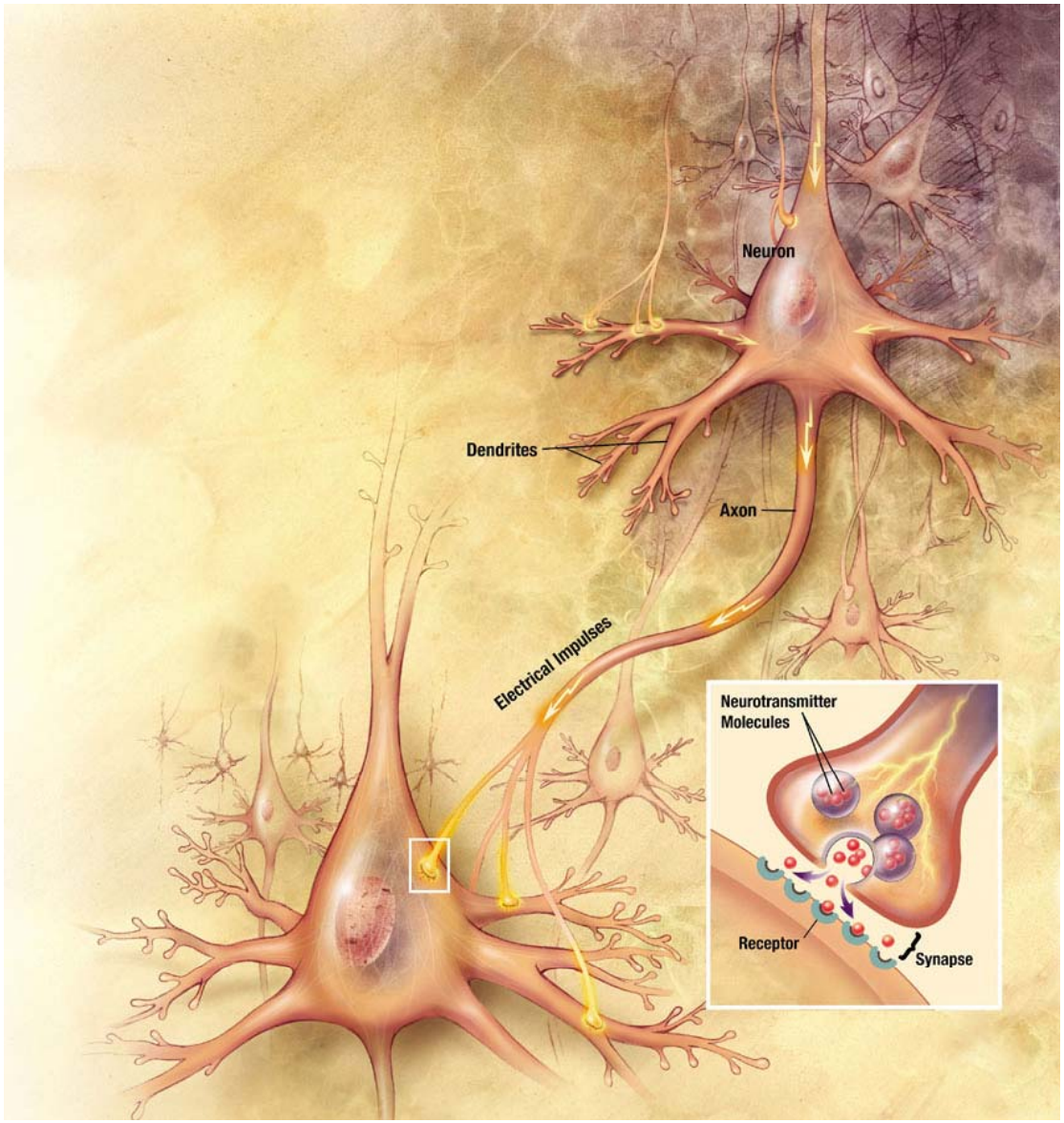
http://en.wikipedia.org/wiki/Neuron

Some facts

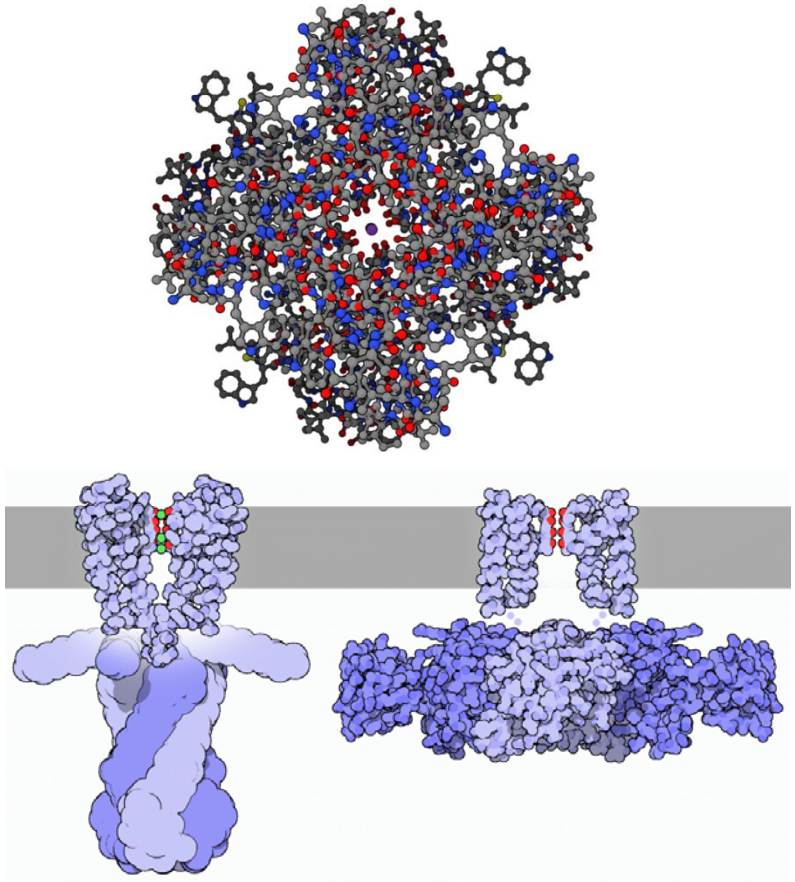
10^{11}- neurons

10^{15}-synapses

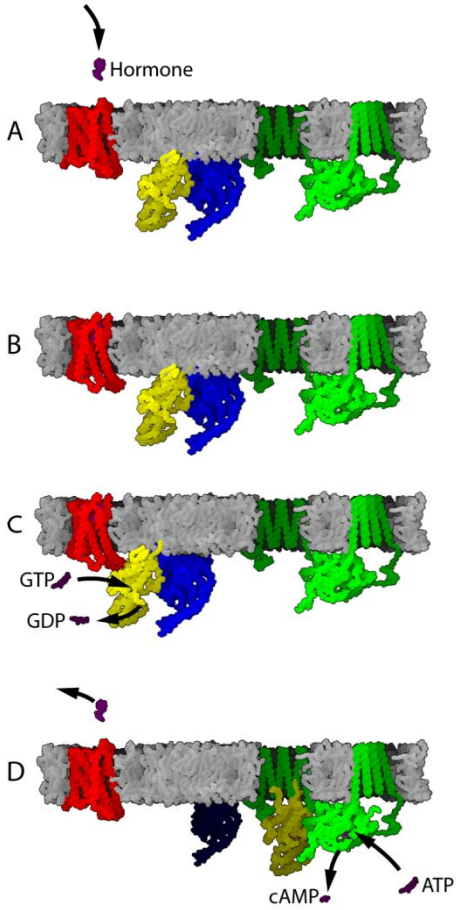
synaptic gap 2×10^{-5} mm



Ions channels and G-proteins

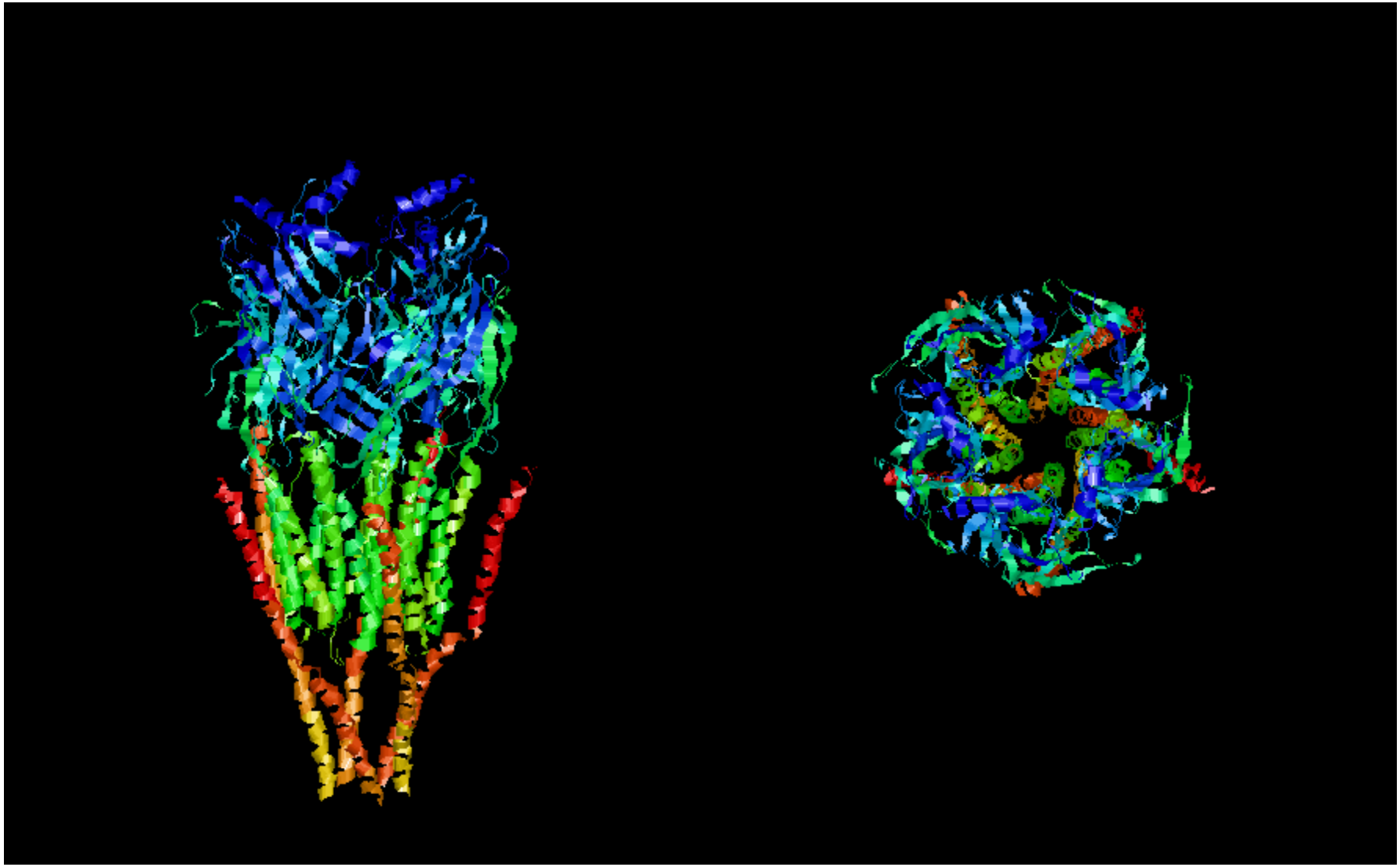


Ionotropic receptor

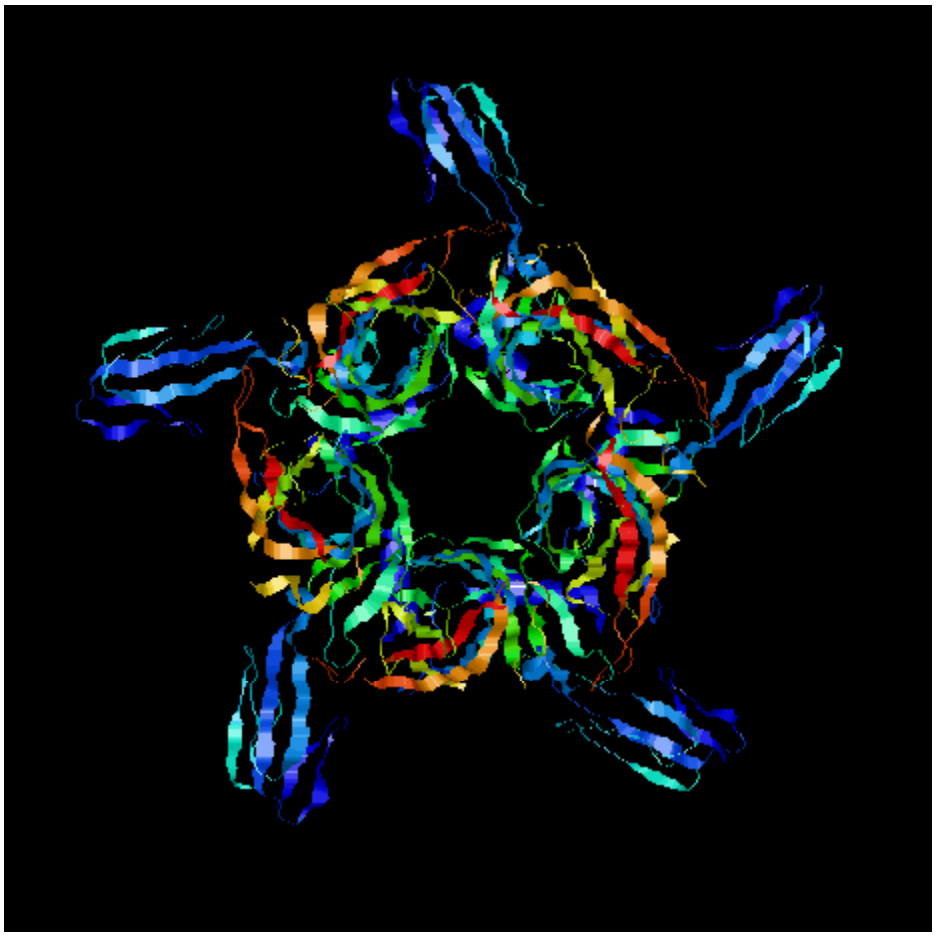


Metabotropic receptor

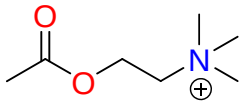
Nicotinic Acetylcholine receptor (nAChr)



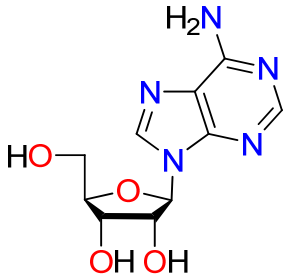
Cobra venom action



Neurotransmitters (NT)



Acetylcholine



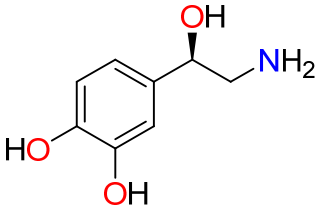
Adenosine ADP, GDP

Purines

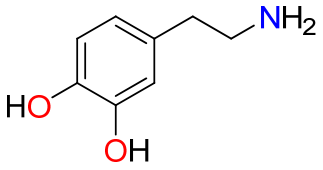
Vasopressin

Oxytocin

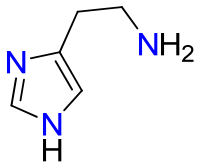
Neuropeptydes



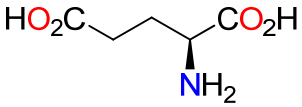
Norepinephrine



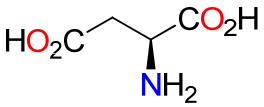
Dopamine



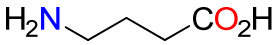
histamine



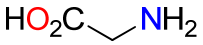
Glu



Asp

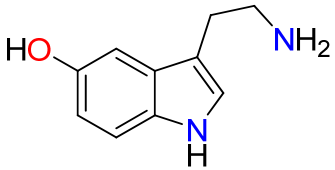


GABA

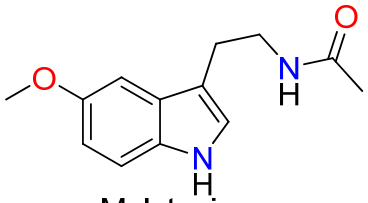


Gly

Aminoacids



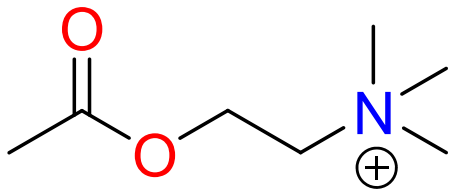
Serotonin



Melatonin

Monoamines

Acetylcholine



Acetylcholine

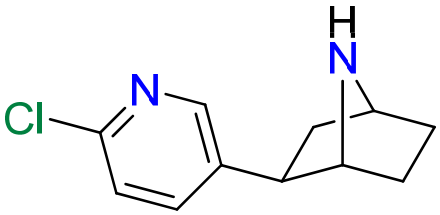
- First isolated in 1914 by Henry Dale, Otto Loewi. Both received 1936 Nobel prize in Medicine
- In the PNS, acetylcholine activates muscles, and is a **major** neurotransmitter in the autonomic nervous system.
- In the CNS, acetylcholine and the associated neurons form a neurotransmitter system, the cholinergic system, which tends to cause excitatory actions.

AcetylCholine receptors

- nicotinic acetylcholine receptors nAChR
  - 290 kDa, 5 subunits around central pore. Similarities with GABA, glycine, 5HT receptors
  - Nicotine, choline, epibatidine affinity
- Muscarinic acetylcholine receptors mAChR

Epibatidine and Tebanicline

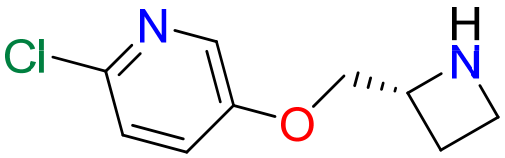
- Isolated from Phantasmal poison frog



Epibatidine

1976 - isolated
1986 -structure elucidated
200 times more potent then morphine

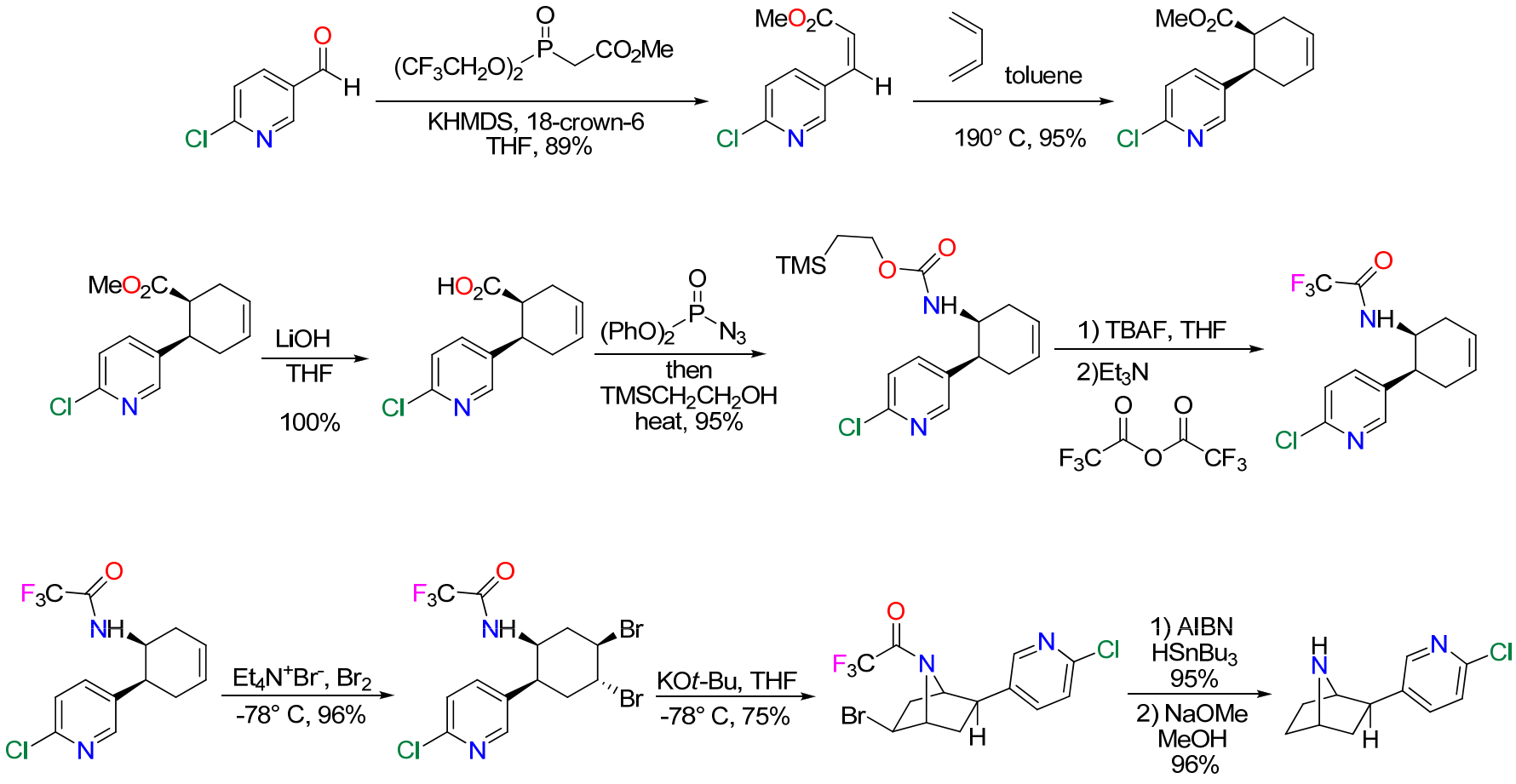
- New lead drug



Tebanicline

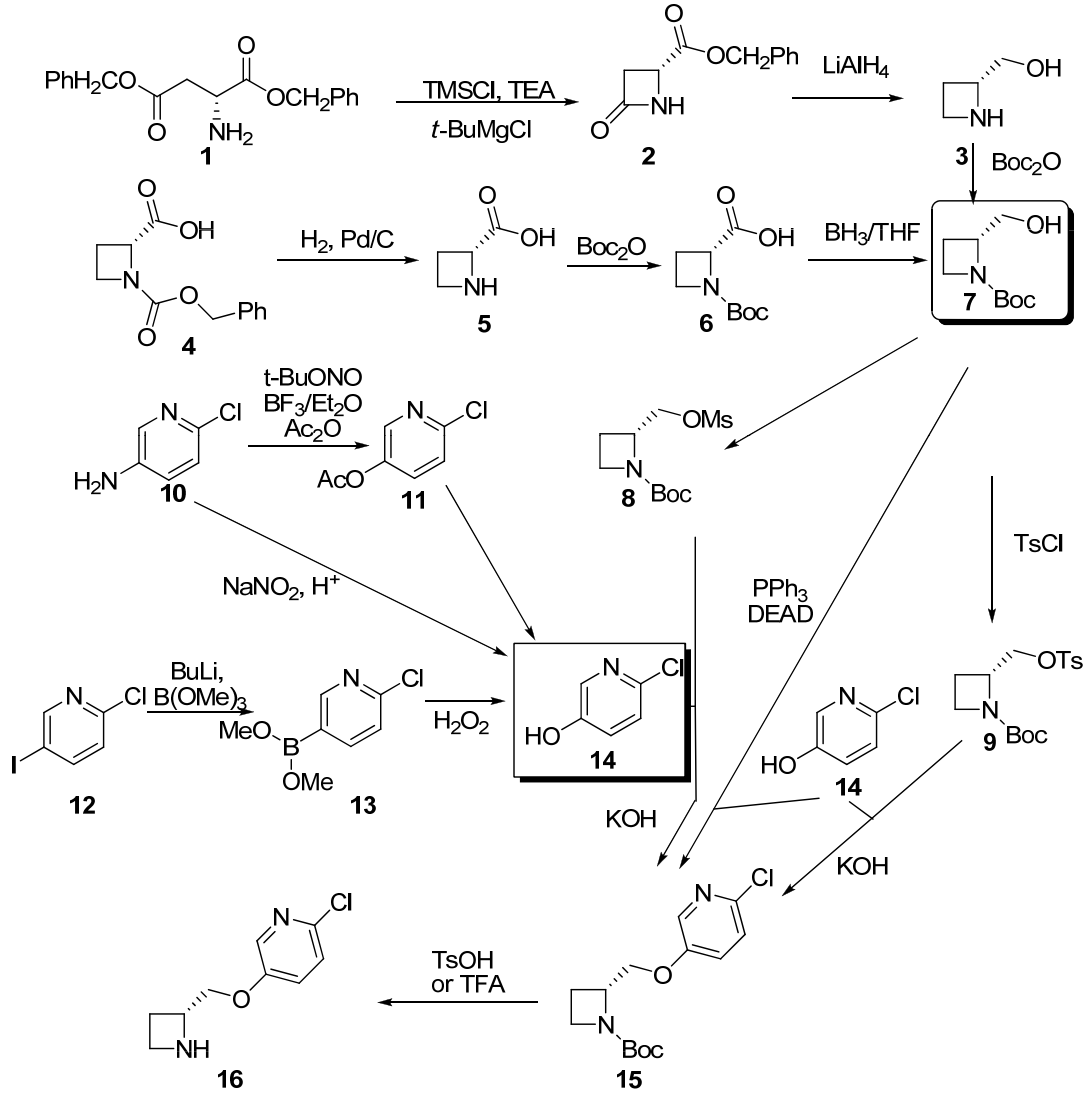
- 50 time more potent than morphine,
- Binds nAchR, not opiod receptors
- Did not gofarther than Phase II trial. Due to gastrointestinal side effects

E.J. Corey Synthesis of Epibatidine



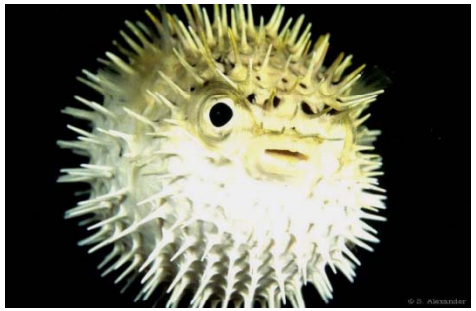
Corey, E. J.; Loh, T. P.; Achyutha, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600

Synthesis of Tebanicline

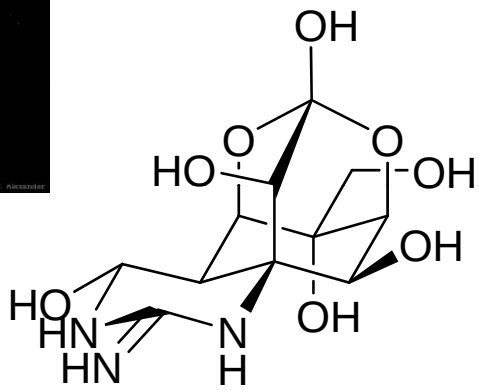


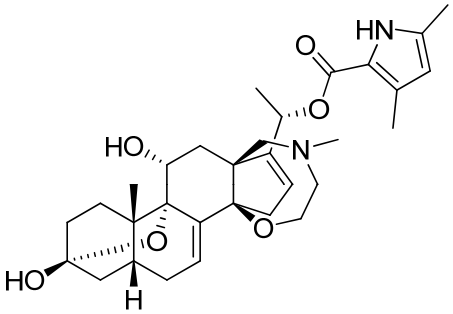
Sorbera, L.A., Revel, L., Leeson, P., Castaner, J. Drugs of the Future 2001, 26(10): 92

Tetrodotoxin and Batrachotoxin



block Na channels in neurons
Inhibitor of nAChr

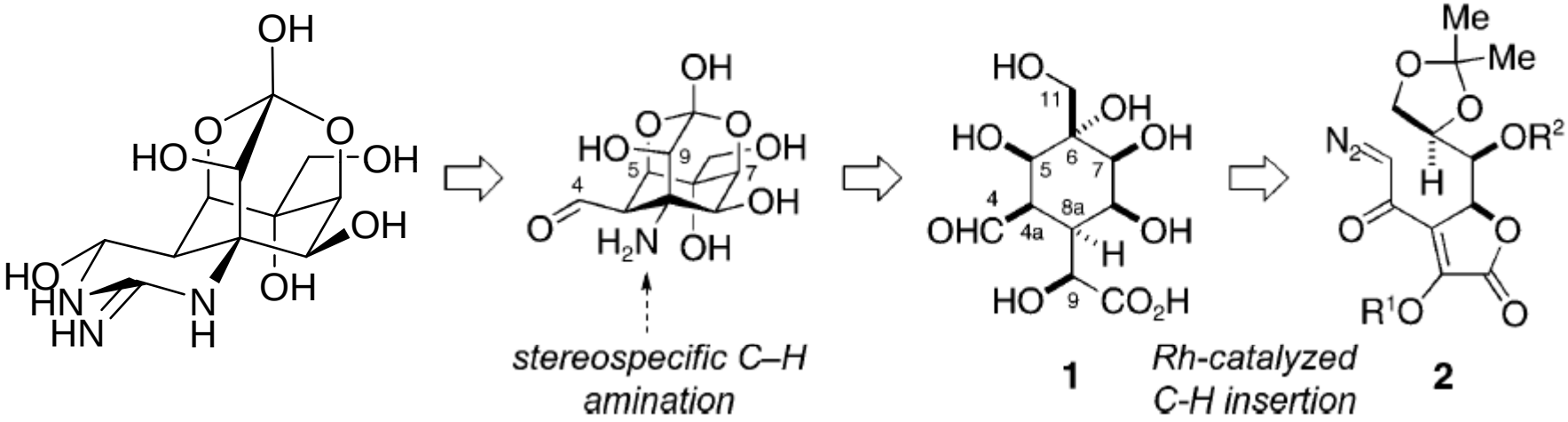




- Y. Kishi 1972 racemic
- *J. Am. Chem. Soc* **94** (26): 9217
- Isobe *J. Am. Chem. Soc* **125** (29): 8798
- Du Bois 2003 asymetric
- *J. Am. Chem. Soc* **125** (38): 11510

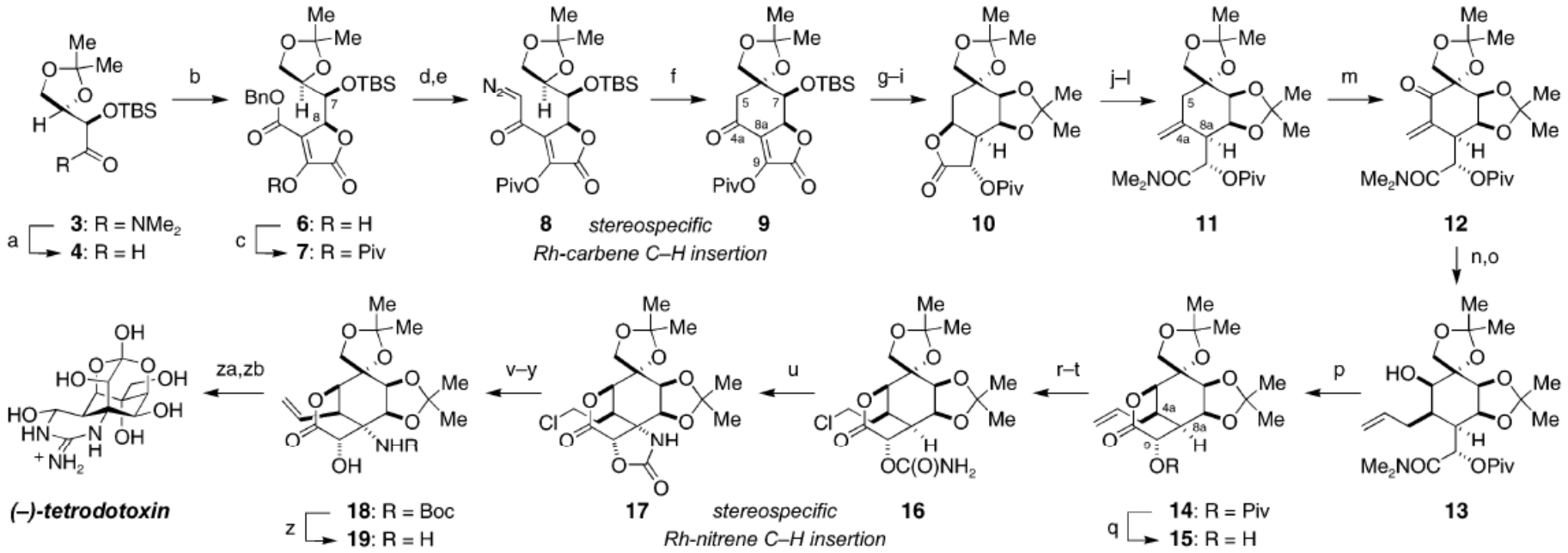
Kurosu, M.; Marcin, L.R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627.

Synthesis of (+)-Tetradotoxin



Hinman, A.; Du Bois, J. **2003** *J. Am. Chem. Soc* **125**, 11510

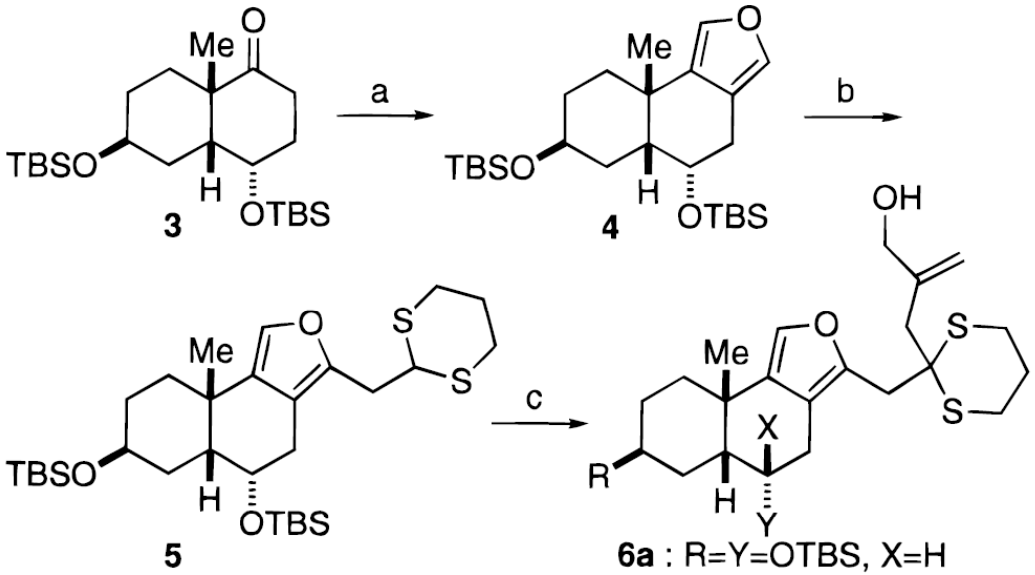
Synthesis of (+)-Tetradotoxine



[a] Conditions: (a) *i*-Bu_2AlH, *n*-BuLi, THF/hexanes; (b) $BnO_2CCH_2C(O)CO_2Bn$ **5**, NaOAc, THF; (c) *t*-BuCOCl, C_5H_5N, THF, 85% (three steps); (d) H_2, Pd−C, THF, 88%; (e) $(COCl)_2$, cat. DMF, THF; then CH_2N_2, CH_2Cl_2, 63−70%; (f) 1.5 mol % $Rh_2(HNCOCPh_3)_4$, CCl_4; (g) $NH_3{\cdot}BH_3$, CH_2Cl_2/MeOH, 75% (two steps); (h) H_2 (1200 psi), 5 mol % Rh−C, 2:1 CF_3CO_2H/MeOH; (i) *p*-TsOH, 2,2-DMP, THF, 77% (two steps); (j) Me_2NH, THF, 83%; (k) cat. (*n*-Pr_4N)RuO_4, NMO, 4 Å MS, CH_2Cl_2, 94%; (l) Zn, $TiCl_4$, CH_2I_2, cat. $PbCl_2$, THF, 72%; (m) Ph_2Se_2, $PhIO_2$, C_5H_5N, C_6H_5Cl, 100 °C, 70%; (n) $H_2C{=}CHMgBr$, CuI, THF; (o) *t*-$BuNH_2{\cdot}BH_3$, DCE, 77% (two steps); (p) *t*-$BuCO_2H$, C_6H_5Cl, 200 °C; (q) NaOMe, THF/MeOH 78% (two steps), (r) $Cl_3CC(O)NCO$, CH_2Cl_2; Zn, MeOH, 93%; (s) O_3; then $NaBH_4$, CH_2Cl_2/MeOH, 83%; (t) $MeSO_2Cl$, C_5H_5N, DCE, 86%; (u) 10 mol % $Rh_2(HNCOCF_3)_4$, $PhI(OAc)_2$, MgO, C_6H_6, 65 °C, 77%; (v) NaSePh, THF/DMF, 77%; (w) *m*-CPBA; C_5H_5N, DCE, 55 °C, 92%; (x) Boc_2O, Et_3N, DMAP, THF; (y) K_2CO_3, THF/MeOH, 84% (two steps); (z) H_2O, 110 °C, 95%; (za) $BocN{=}C(SMe)NHBoc$, $HgCl_2$, Et_3N, $MeCN/CH_2Cl_2$, 80%; (zb) O_3, CH_2Cl_2/MeOH; Me_2S; then aq CF_3CO_2H, 65%.

Hinman, A.; Du Bois, J. **2003** *J. Am. Chem. Soc* **125**, 11510

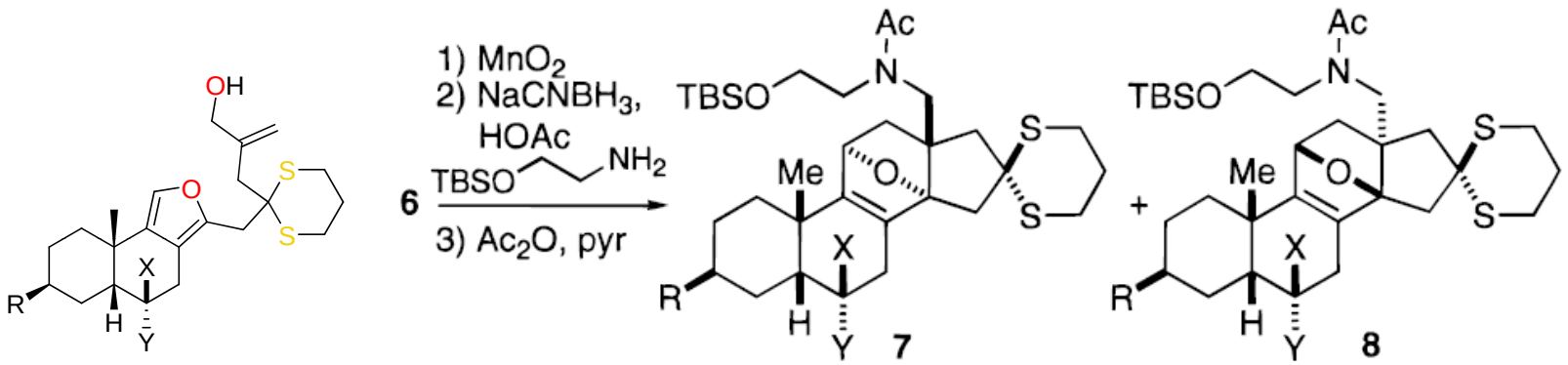
Synthesis of (±)-Batrachotoxine



[a] Reagents and yields: (a) (i) ethyl formate, NaH; (ii) *n*-BuSH, TsOH (88%); (iii) Me_3SI, NaHMDS;[12] (iv) $HgCl_2$ (54%); (b) (i) DMF, $(COCl)_2$ (84%); (ii) KO*t*-Bu, $CH_3OCH_2P(Ph)_3Cl$; (iii) 1,3-propanedithiol, CSA (72%); (c) (i) *t*-BuLi, HMPA, 2-(bromomethyl)-1-(*tert*-butyldimethylsilyloxy)-2-propene; (ii) TBAF (52%).

Kurosu, M.; Marcin, L.R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* 1**998**, *120*, 6627.

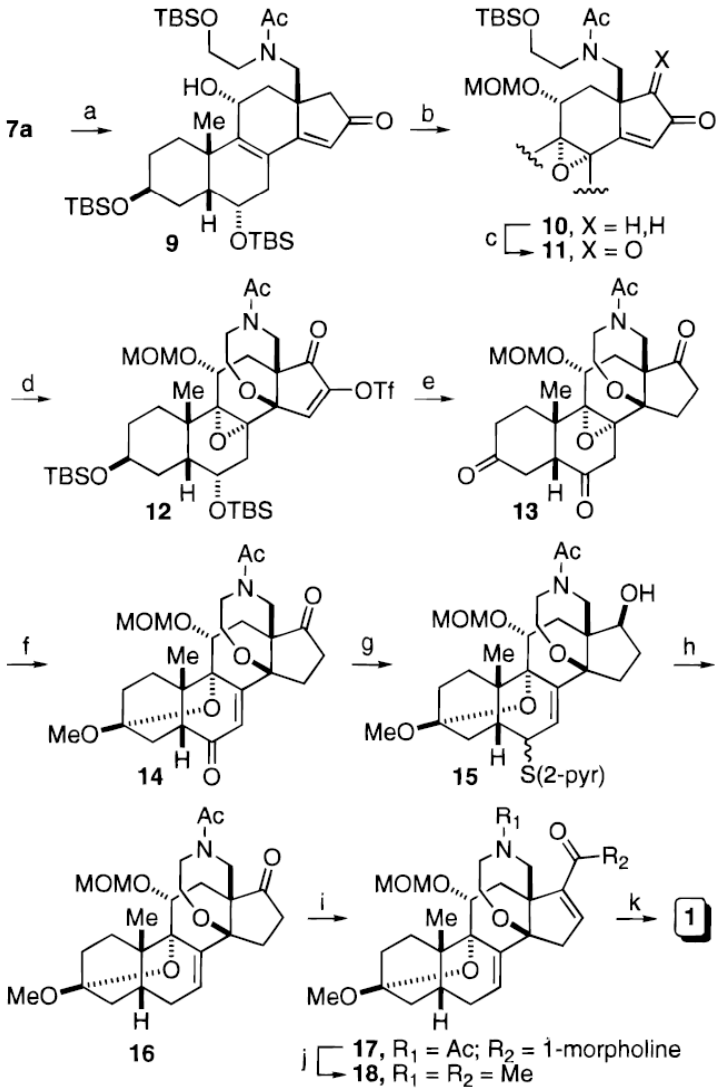
Diels-Alder Cyclization



entry	R	X	Y	yield, %	ratio (**7**:**8**)
a	OTBS	H	OTBS	70-75	>25:1
b	OTBDPS	H	H	75-80	3-4:1
c	OTBDPS	OMPM	H	40-50	1.4:1

Kurosu, M.; Marcin, L.R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* 1**998**, *120*, 6627.

Completion



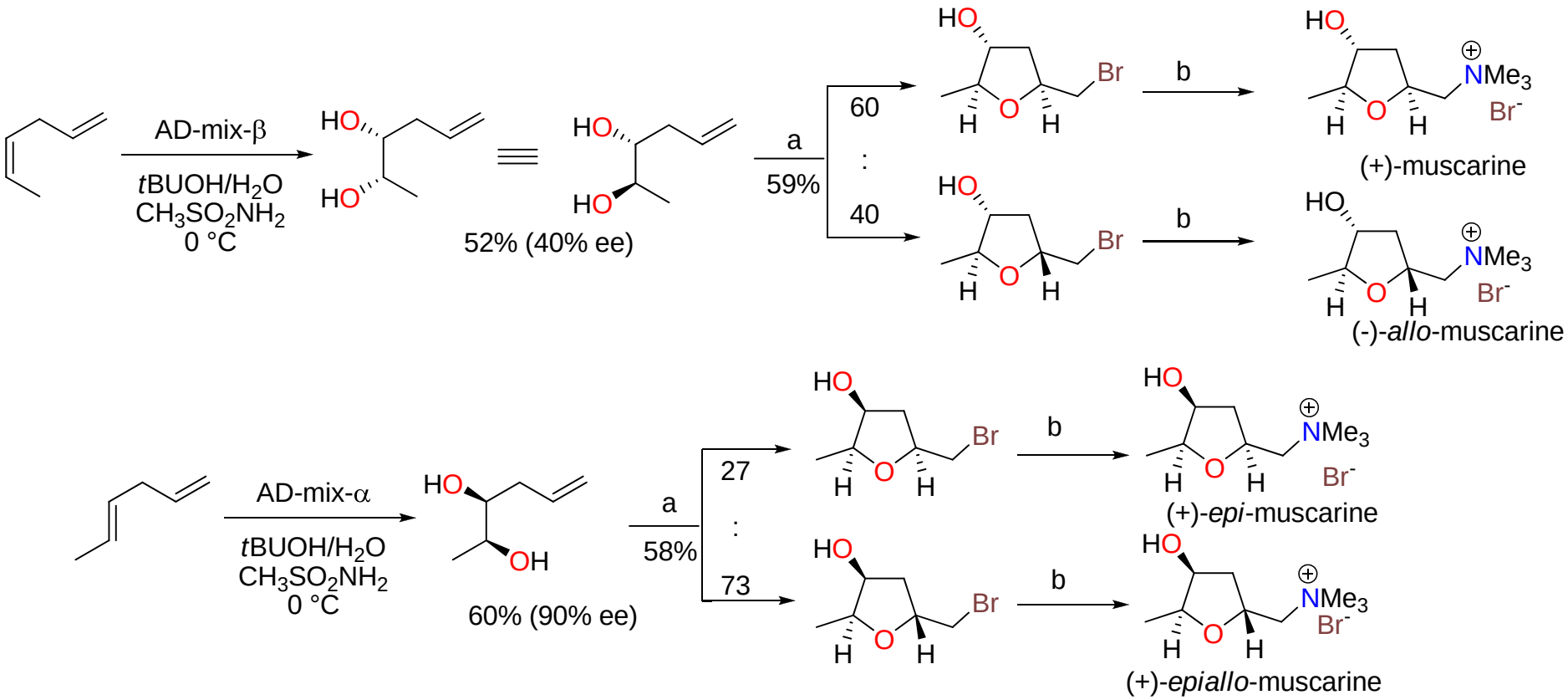
[a] Reagents and yields: (a) (i) $(CF_3CO_2)_2IC_6H_5$,[22] $CaCO_3$, MeOH; (ii) PPTS, acetone; (iii) DBU (68%); (b) (i) *p*-nitroperoxybenzoic acid (90%); (ii) MOMCl, DIEA (93%); (c) (i) KHMDS, Davis' oxaziridine[23] (93%); (ii) TFAA, DMSO, TEA (88%); (d) (i) $(Me_2N)_3S(Me_3SiF_2)$;[17] (ii) $PhNTf_2$, TEA (95%); (e) (i) PtO_2, H_2, 2,6-di-*tert*-butylpyridine (90%);[18] (ii) $NaBH_4$; (iii) TBAF; (iv) Dess−Martin oxidant; (f) (i) DBU; (ii) CSA, MeOH (85%); (g) (i) $NaBH_4$, $CeCl_3$; (ii) 2,2′-dipyridyl disulfide, $(n\text{-}Bu)_3P$; (h) (i) W-2 Raney Ni, H_2; (ii) Dess−Martin oxidant[20] (73%); (i) (i) KHMDS, $PhNTf_2$; (90%); (ii) $Pd(PPh_3)_4$, CO, morpholine (96%);[21] (j) (i) $CeCl_3$, MeLi;[11] (ii) $NaHCO_3$, MeI (80%); (k) (i) $Zn(BH_4)_2$ (80%); (ii) *p*-TsOH, wet acetone (83%).

Kurosu, M.; Marcin, L.R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* 1**998**, *120*, 6627.

Muscarinic acetylcholine receptors mAChr

- Stimulated by muscarine and acetylcholine
- Inhibited by atropine
- Metabotropic in action
- Located in CNS, heart, lungs, sweat glands

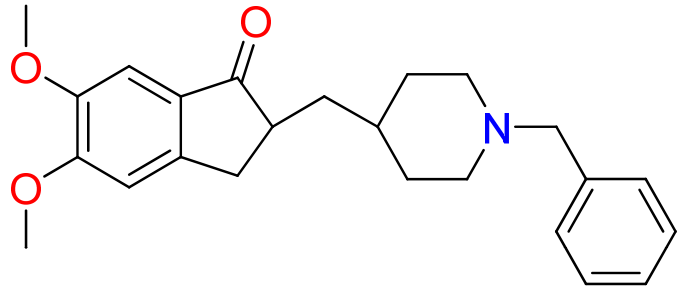
Muscarine



(a) TBHP, pyHBr, $CHCl_3$, 10 mol% of VOL(OEt)(EtOH)
[L = N-(hydroxyphenyl)salicylideneimine dianion], 20 °C, 6 h;
(b) NMe_3, EtOH, 60 °C, 7 d

Hartung, J.; Kuz., P.; Laug. S.; Schmidt, P. *Synlett*, **2003**, *1*, 51

Donepezil



Donepezil

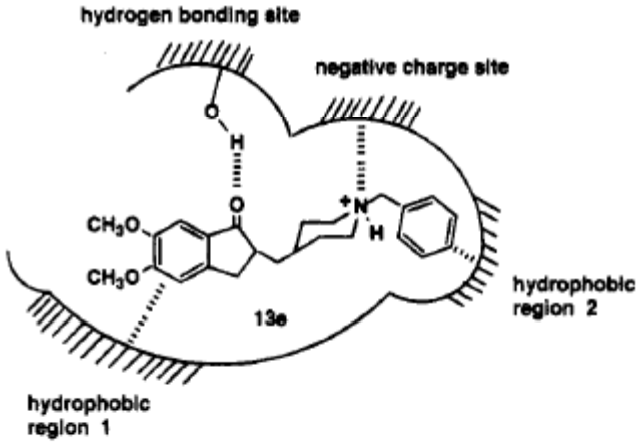
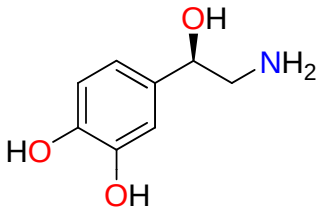


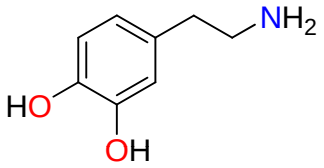
Figure 7. Proposed model of the acetylcholinesterase active site shown with **13e** interacting at the hydrogen-bonding site, negative charge site, and hydrophobic regions 1 and 2 on the binding protein.

- Acetylcholine esterase inhibitor
- Discovered late 1980's
- Introduction 1996 (Eisai)
- Main treatment of Alzheimer's desease

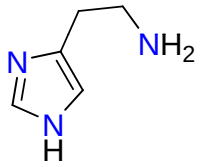
Monoamines



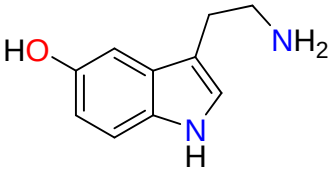
Norepinephrine



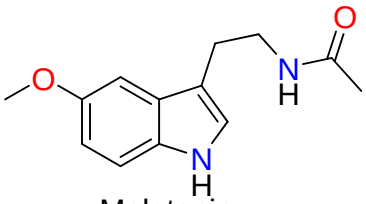
Dopamine



histamine



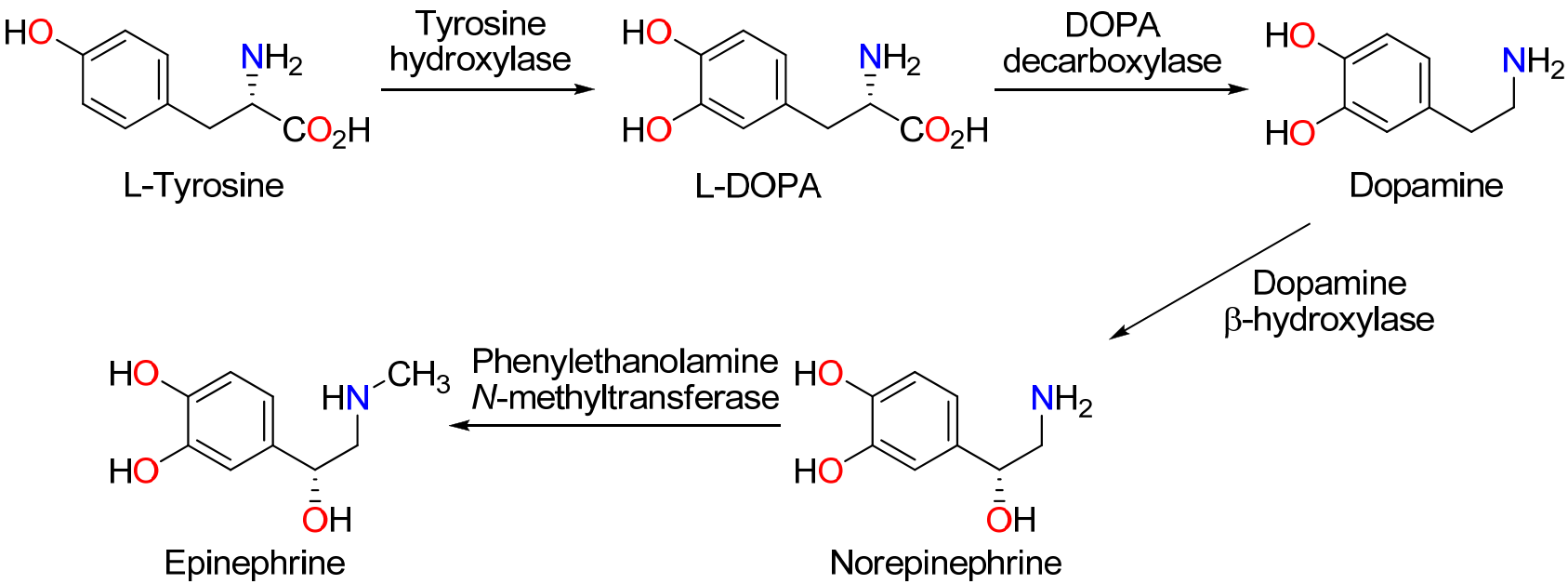
Serotonin



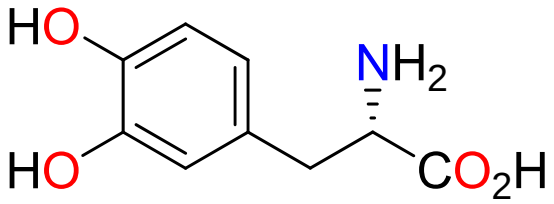
Melatonin

Monoamines

Catecholamines Biosynthetic Relationship

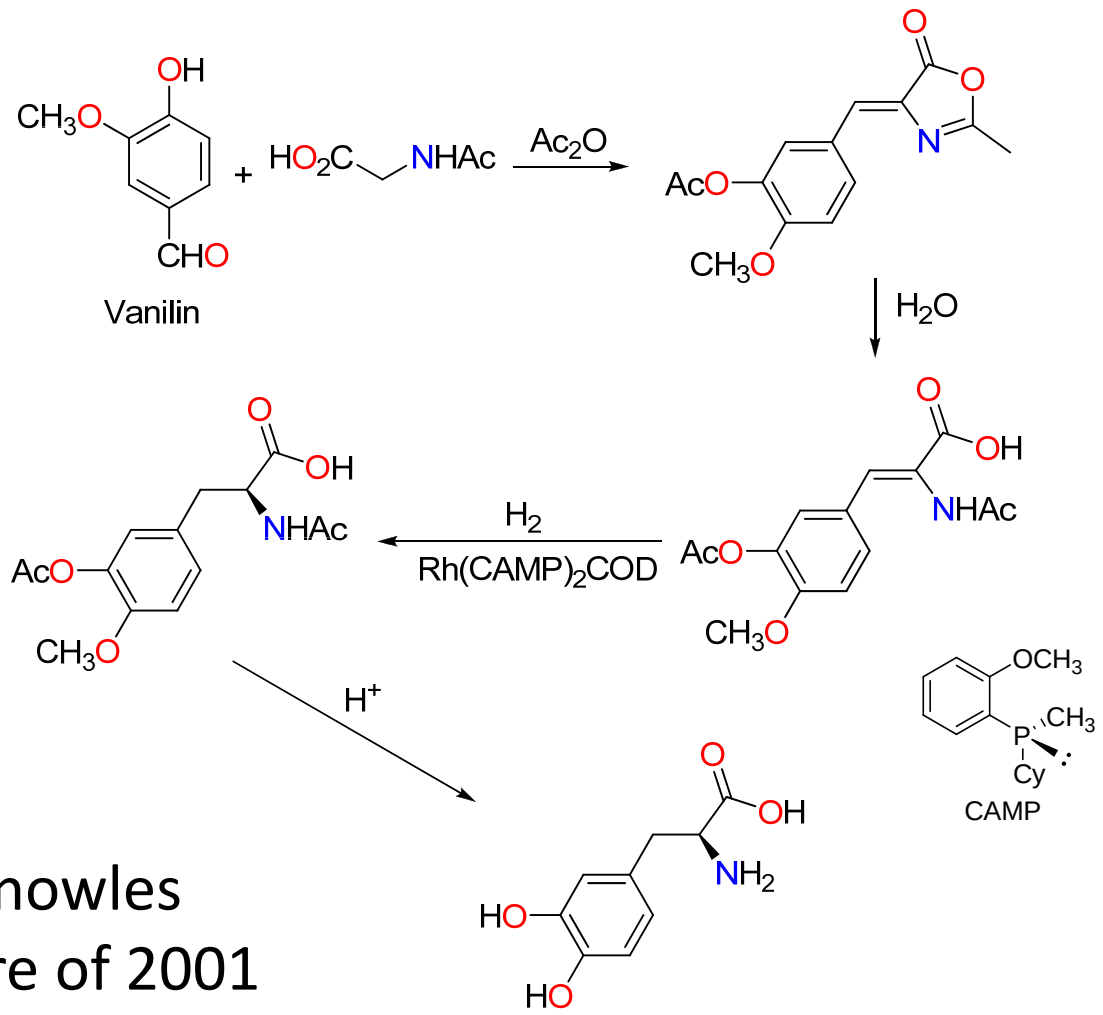


Levodopa (L-DOPA)



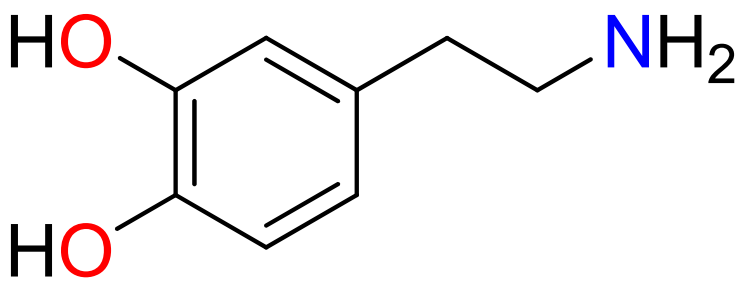
- Discovered 1960's
- Introduction in 1970 (Roche) racemic
- Cross blood-brain barrier while dopamine not
- 2001- William S. Knowles got Nobel prize in Chemistry with R. Noyori, B. Sharpless for the development of asymetric hydrogenation

Monsanto Process of Levodopa



William S. Knowles
Nobel lecture of 2001

Dopamine



1958 discovered by Arvind Calrsson

2000 Nobel prize in Medicine

1910 first synthesis

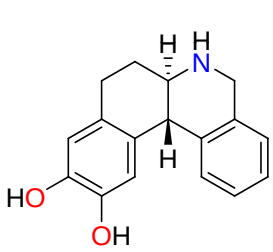
Functions

- Behavior and conditions
- Motor activity
- Motivation and reward
- Mood, learning, attention

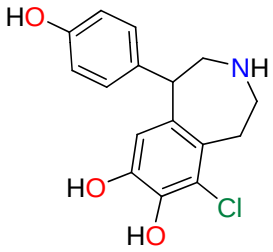
Dopamine Receptors

- Excitory
  - **D_1** most abundant, neuronal growth,

    D_2-mediator.



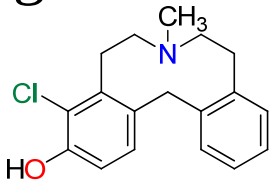
Dihydrexidine



Fenoldopam

  - **D_5**- limbic region of brain (responsible for emotions)

    1 Antagonist

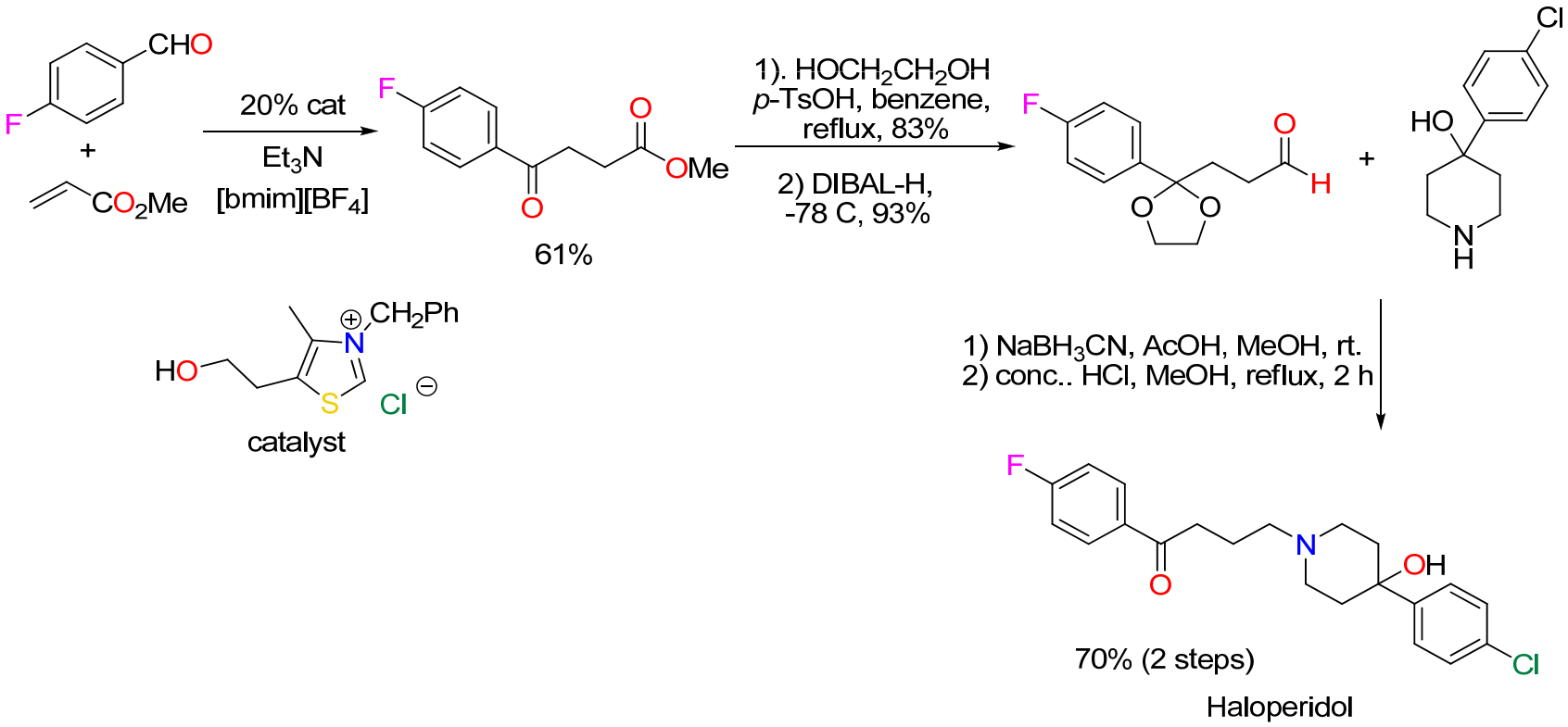


- Inhibitory
  - **D_2** renal system, antipsychotic drugs target

    Antagonist:

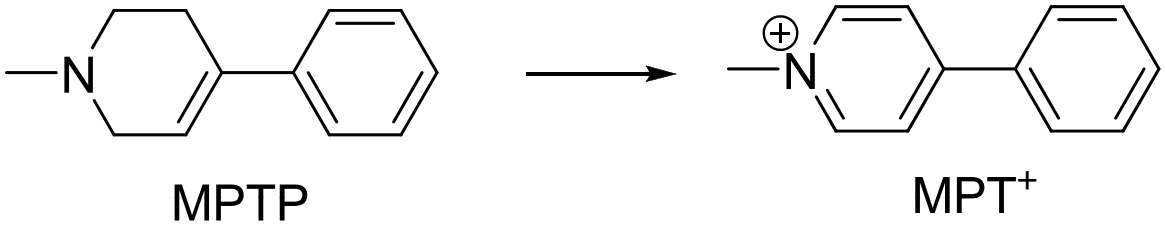
    risperidone, haloperidol
  - **D_3**, limbic system
  - **D_4**, signals cardial output without changing heart rate, ADHD

Haloperidol Synthesis



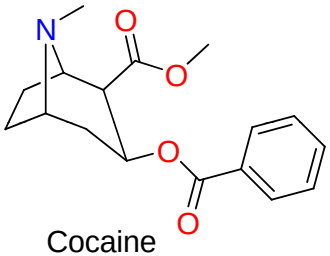
Anjaiah, S.; Chandrasekhar, S.; Gree, R. *Adv. Synth. Catal.* **2004**, *346*, 1329

MPTP (Herbicide Cyperquat)

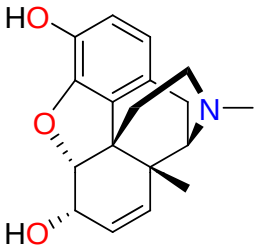


- Bindes to dopamine transporter
- Kills dopamine receptors
- Initiate Parkinson desease in monkeys and rats

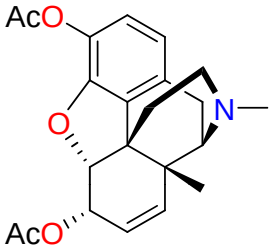
Narcotic drugs among Dopamine and Opioid receptors



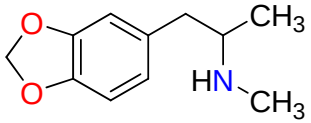
Cocaine



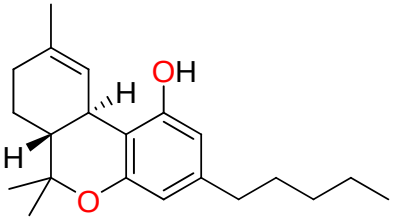
Morphin
First isolated
in 1803



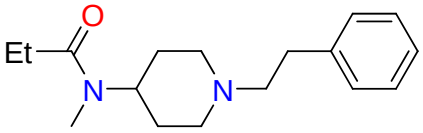
Heroin
sold as cough
suppresant
by Bayer till 1910
was legal
in USA till 1924



MDMA (ecstasy)

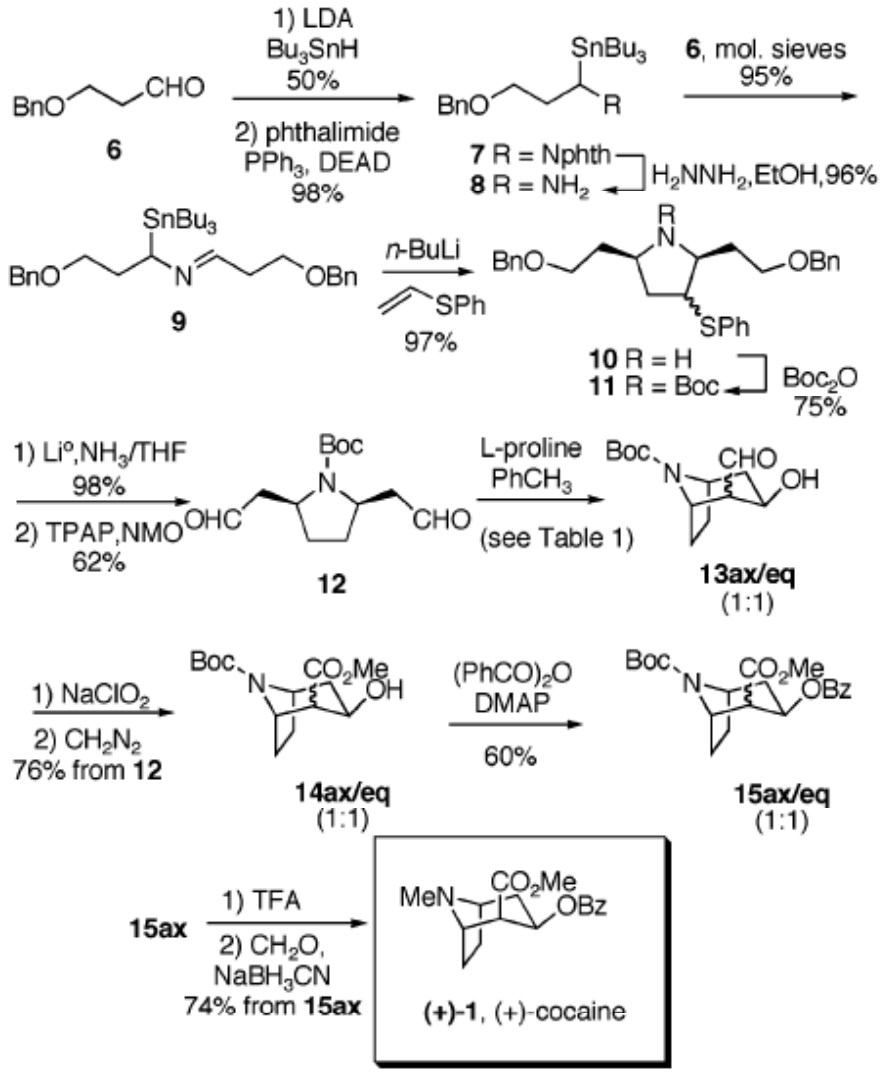


Tetrahydrocannabinol
cannabinoid receptor



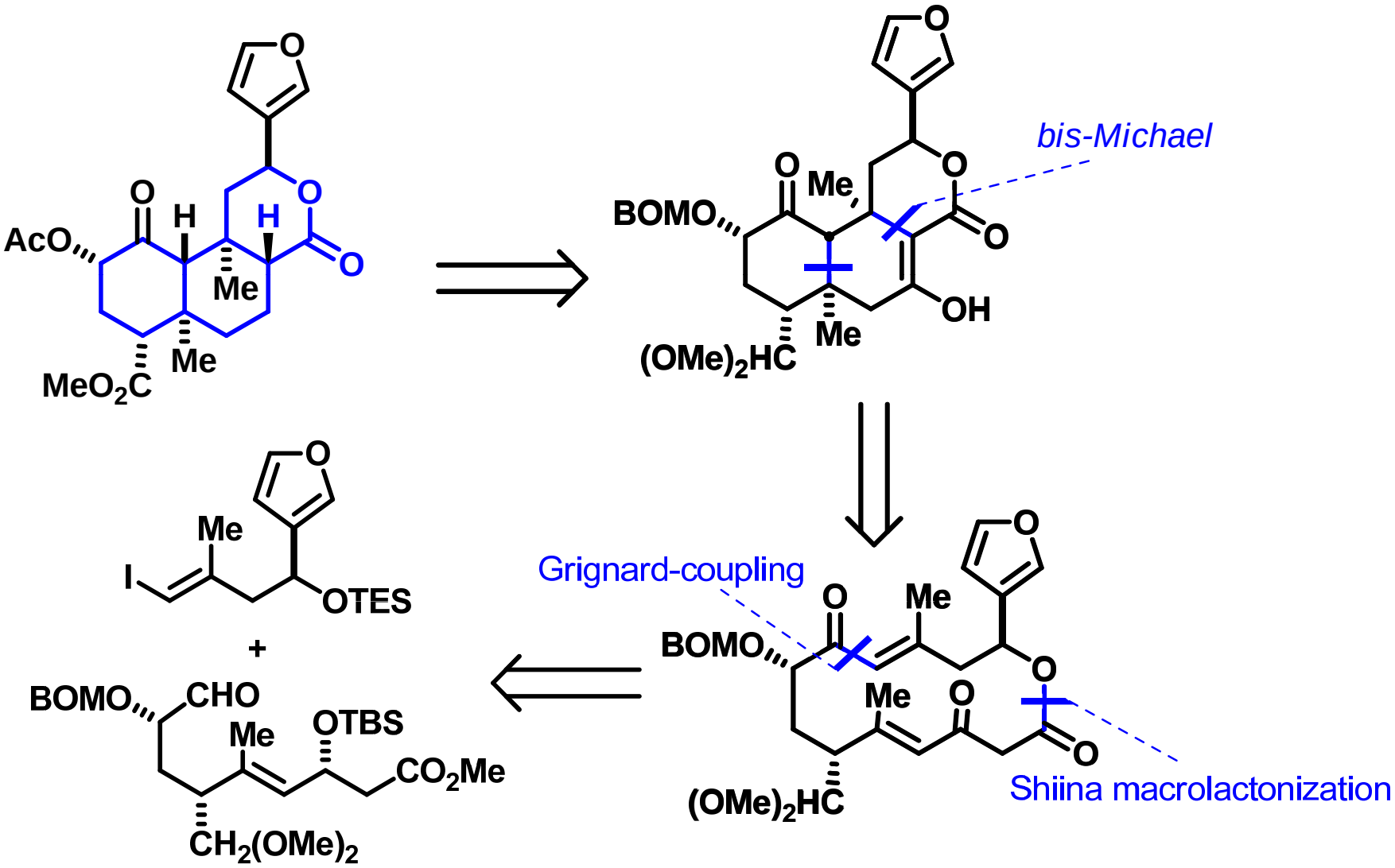
Fentanyl

The last synthesis of Cocaine



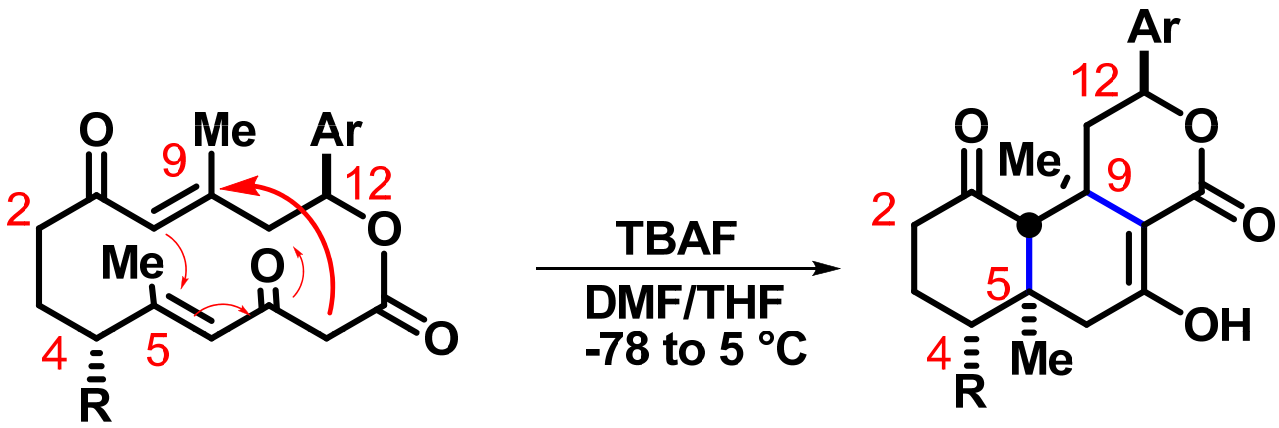
Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305

Salvinorin A
(μ-opioid receptor agonist)



Scheerer, J. R.; Lawrence, J. F.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968

Bis-Michael Addition Cascade

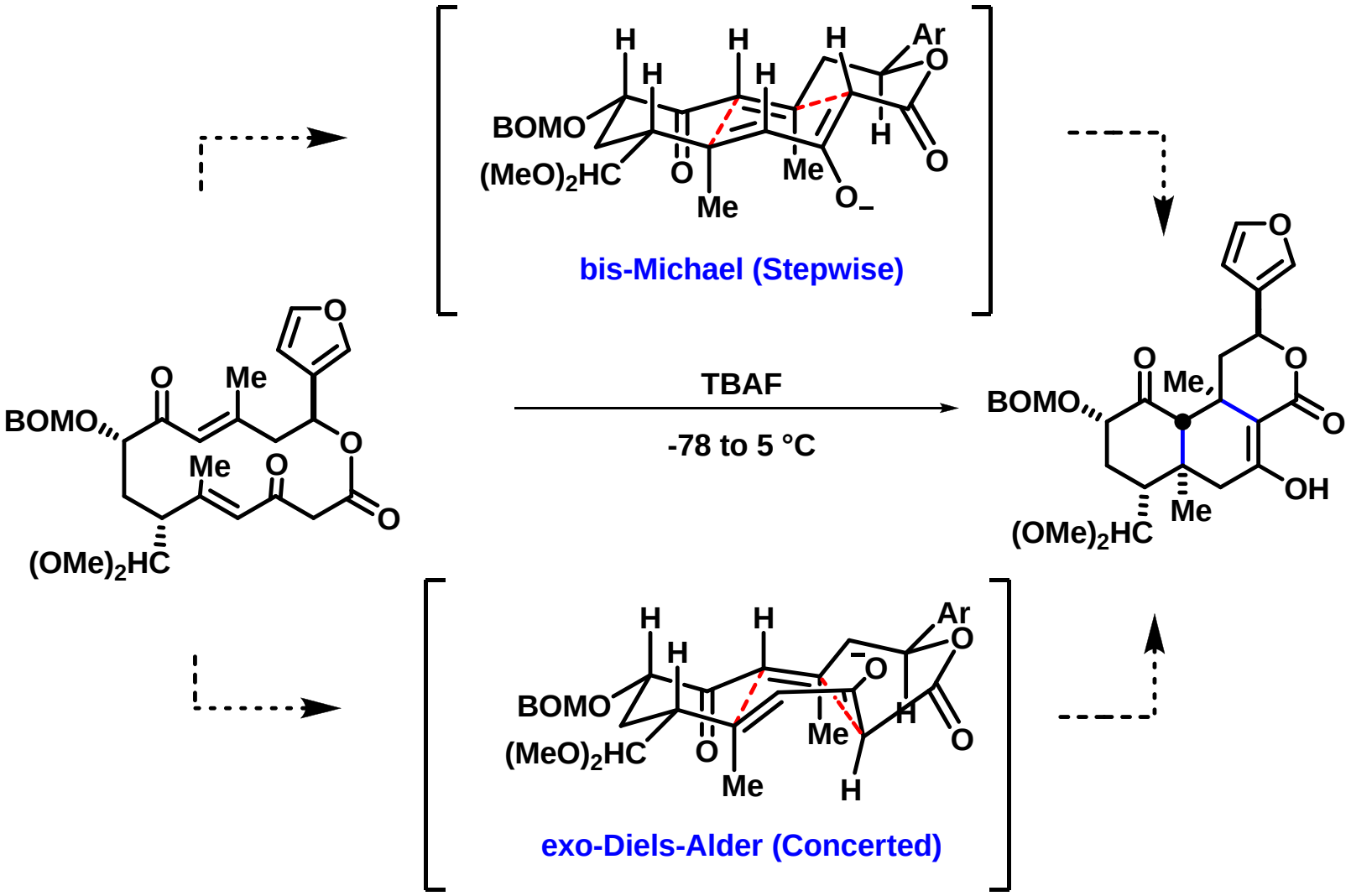


Ar= 2-furyl

entry	R	yield(%)	dr
1	H	95	95:5
2	$CH(OMe)_2$	95	>95:5

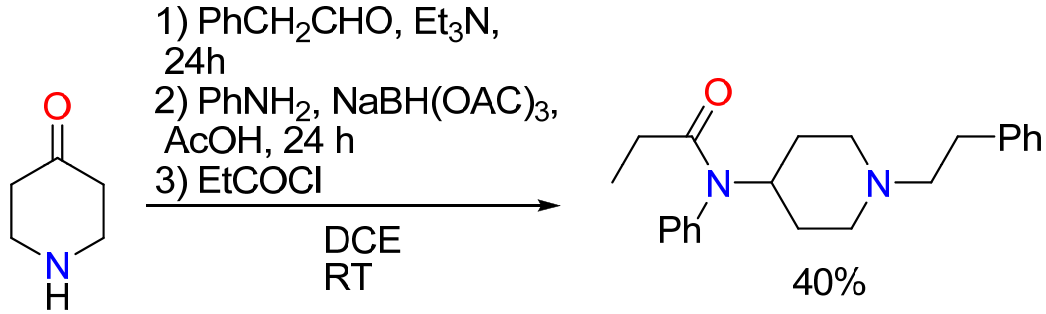
Scheerer, J.R.; Lawrence, J.F.; Evans, D.A. *J. Am. Chem. Soc.* **2007**, *129*, 8968

Transannular Cyclization Analysis



Scheerer, J. R.; Lawrence, J. F.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968

One pot synthesis of Fentanyl



μ-Opioud receptor agonist
Analgesic
Derivatives used in heart surgery,
Sedation of big animals

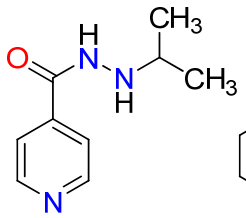
- Gupta, P.K.; Ganesan, K.; Pande, A.; Malhorta, R. *J. Chem. Res.* **2005**, 452

Antidepresants

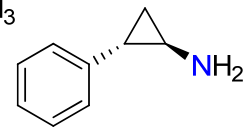
- Monoamine Oxidize Inhibitores (MAOIs) (historically first)
- Tricyclic Antidepressants (TCA) (very common antidepressants)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Common Antidepressants

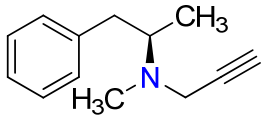
Monoamine Oxidase Inhibitors (MAOI)



Iproniazid
First
antidepressant

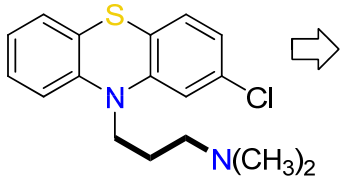


Parnate™
Posttraumatic
stress disorder

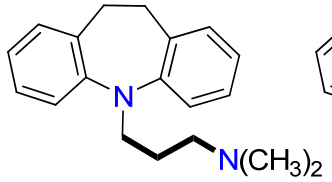


Selegline (Emsam™)

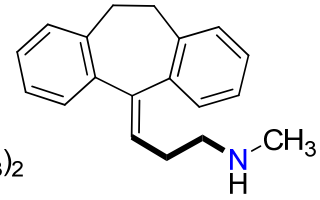
Tricyclic Antidepressants (TCA)



Chlorpromazine
First TCA



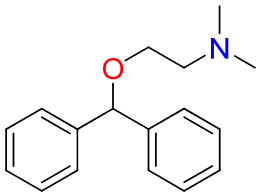
Tofranil™



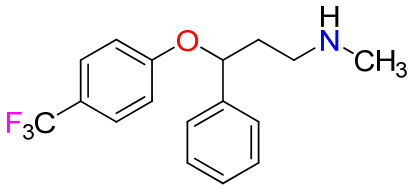
Pamelor™
Selective to
norepinephrine

Inhibit reuptake of serotonin and norepinephrine
inhibit ion channels
narrow therapeutic window

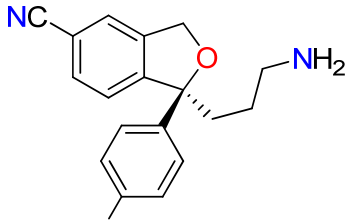
Selective Serotonin Reuptake Inhibitors (SSRIs)



Benadryl
Diphenhydramine

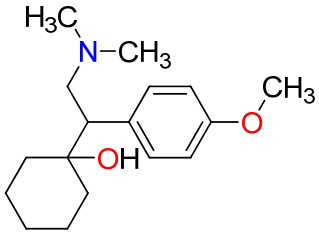


Fluoxetine (Prozac™)
sales 3 billion$

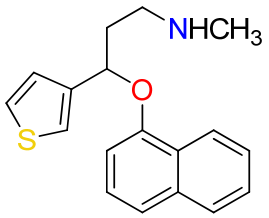


Lexapro™

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

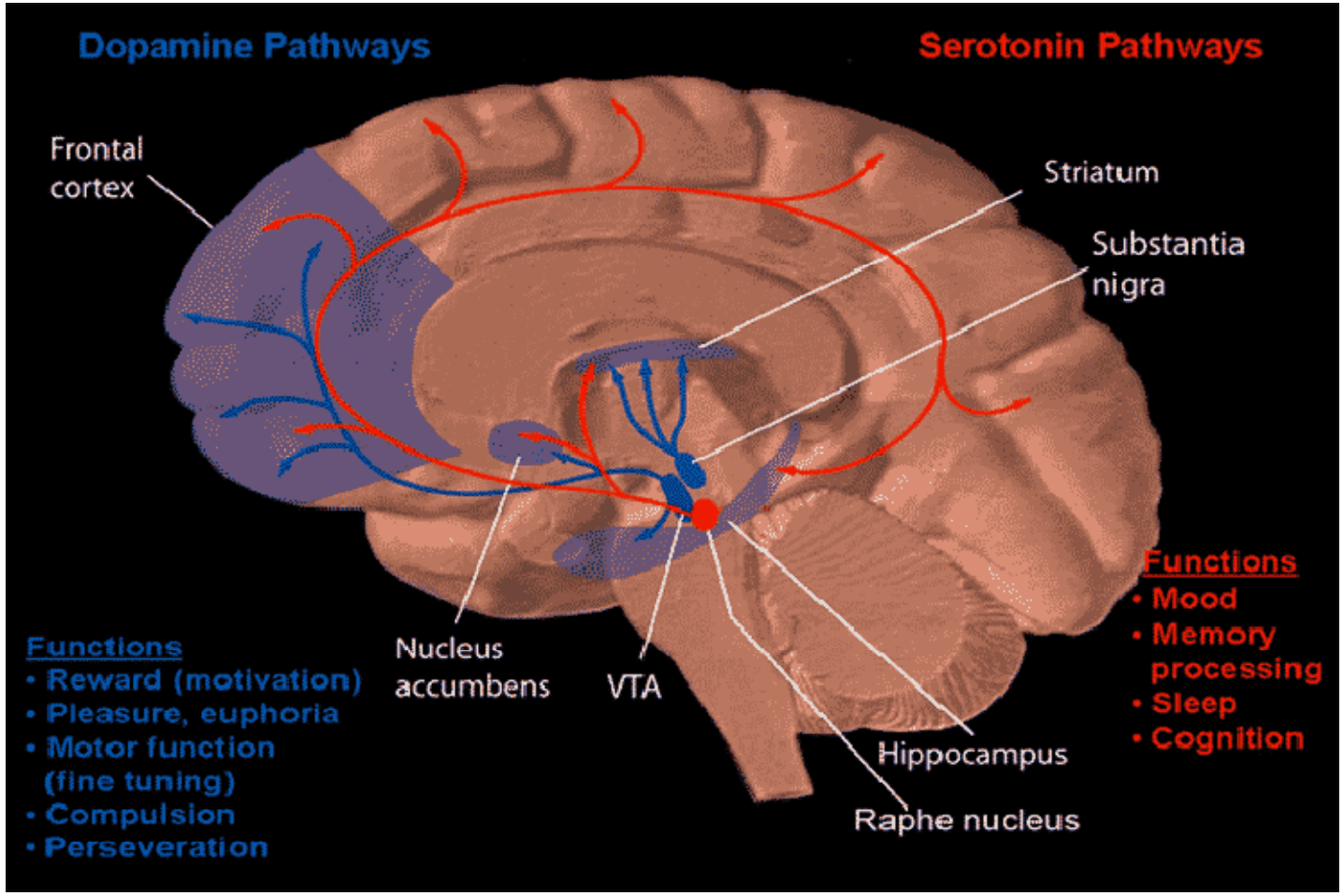


Venlafaxine (Effexor™)



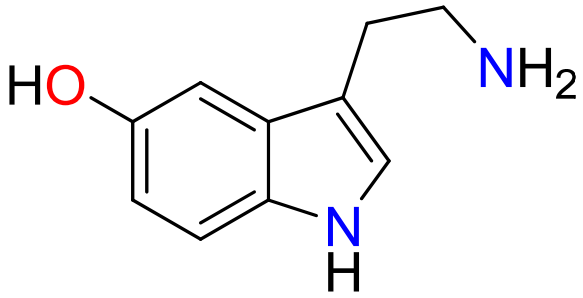
Duloxetine (Cymbalta™)

Dopamine and Serotonin pathways



http://wpcontent.answers.com/wikipedia/en/1/1c/Dopamineseratonin.gif

Serotonin or 5-hydroxytryptamine, 5-HT



Modulate

- Anger
- Body temperature
- Mood
- Sleep
- Apetite
- Metabolism
- Vomiting

Release

raphe nuclei

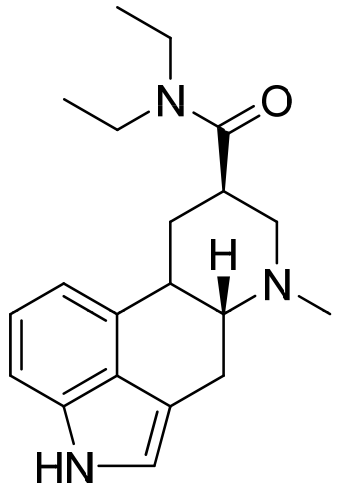
Receptors

7 receptors

Only one 5-HT_3 is ionotropic

Others metabotropic

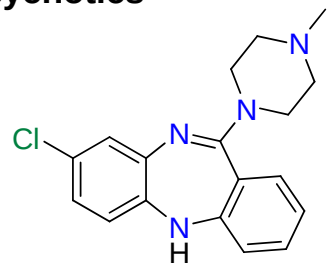
Lysergic acid diethylamide (LSD)



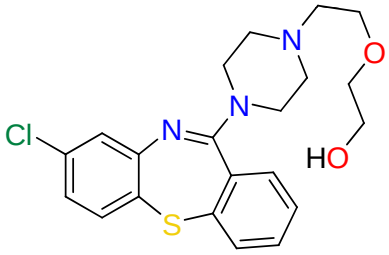
- 5-HT_{2A} serotonin receptor
- first synthesized in November 16, 1938 by Dr. Albert Hoffmann, published in 1943

Antipsychotics and Antianxiety agents

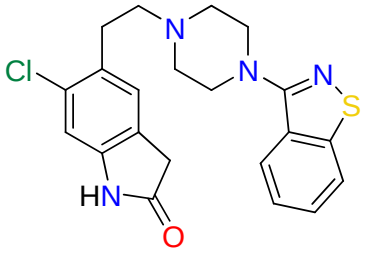
Antipsychotics



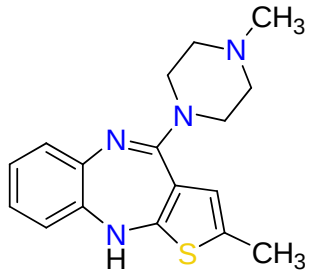
Clozapine (Clozaril™)



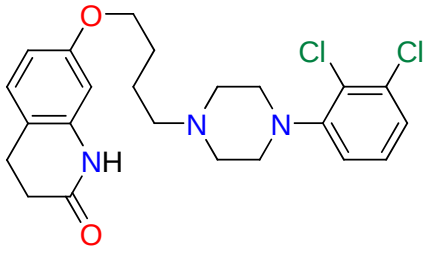
Seroquel™



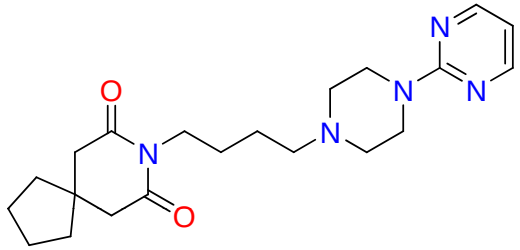
Ziprasidone (Geodon™)



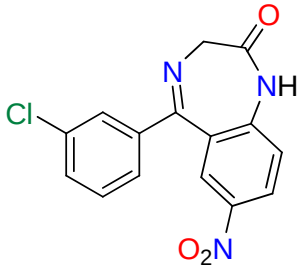
Olanzapine (Zyprexa™)



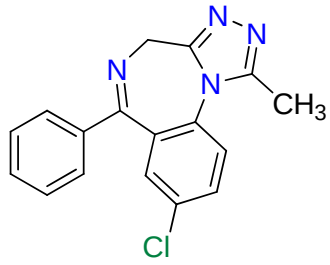
Apiprazole (Abilify™)



Buspirone (BuSpar™)



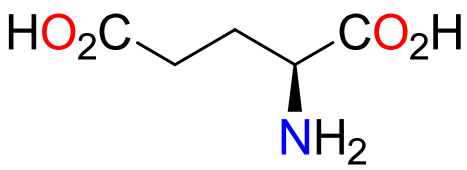
Clonazepam (Klonopin™)



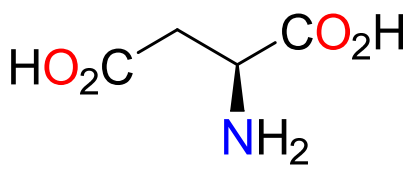
Alprazolam (Xanax™)

Antianxiety Agents

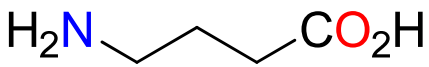
Aminoacids as Neurotransmitters



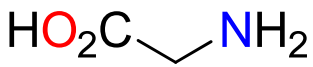
Glu



Asp



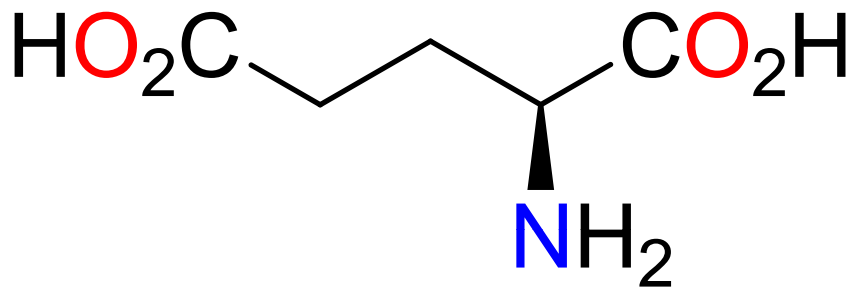
GABA

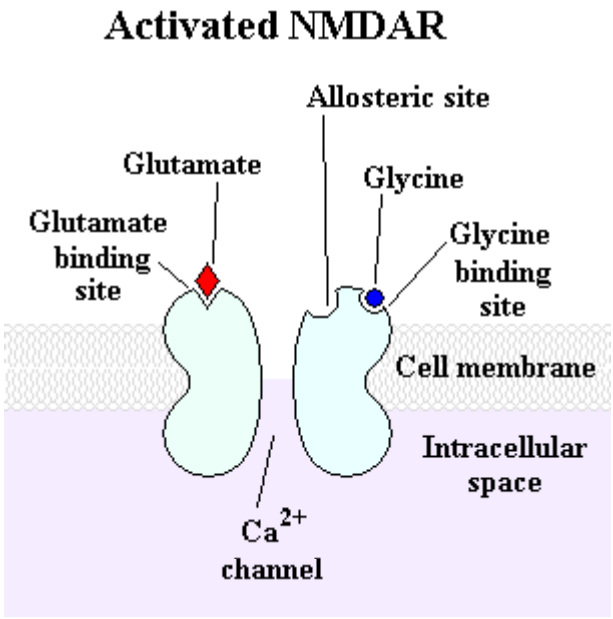


Gly

Aminoacids

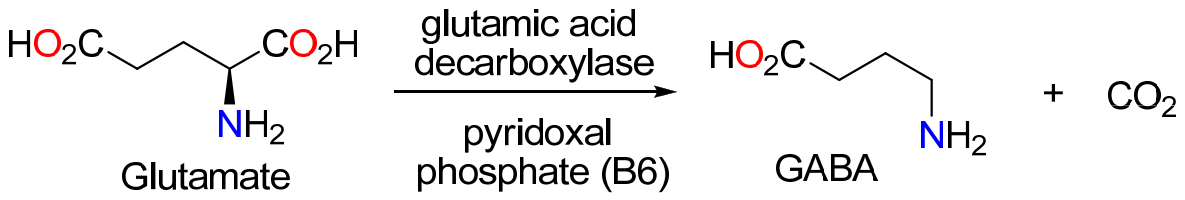
Glutamate

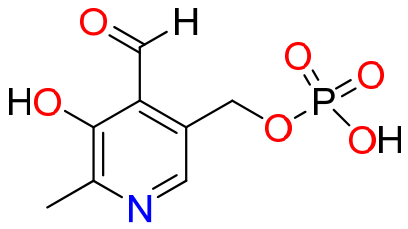




- Most abundant neurotransmitter (90%)
- Binds to NMDA receptors
- Responsible for synaptic plasticity
- Learning and memory
- Implicated in epileptic seizures

GABA





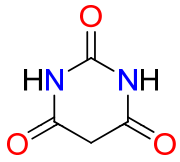
Vitamin B6

- Second most abundant neurotransmitter (9%)
- GAD is in cerebellum and pancreas
- Chief inhibitory neurotransmitter
- $GABA_A$-Chlorine transmiters
- $GABA_B$- metabotropic receptor

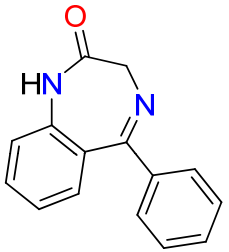
Drugs related to GABA receptors

- Ethanol
- Barbiturates
- Benzodiazepine
- Valleriana
- Theanine (grean tea)

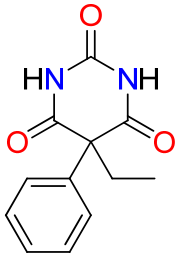
Barbiturates and Benzodiazepines



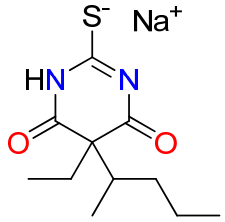
Barbiturate



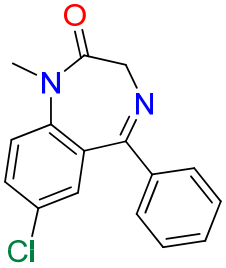
Benzodiazepine



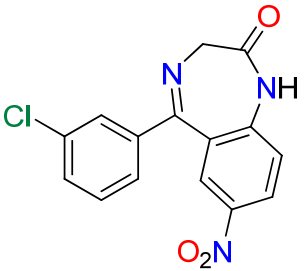
Luminal,
Phenobarbital
Anticolvusant



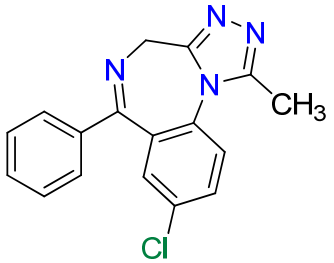
Sodium
thiopental
Truth serum
lethal injection



Diazepam
Anticonvulsants



Clonazepam (Klonopin™)



Alprazolam (Xanax™)

Conclusion

- Correlation between neurotransmitters and drug candidates (Epibatidine and Tebanicline)
- Recognizable part of certain types of specifically acting drugs (benzodiazepines, barbiturates etc)
- 11 Industrial and total synthesis of drugs discussed
- Important neurotransmitters were covered