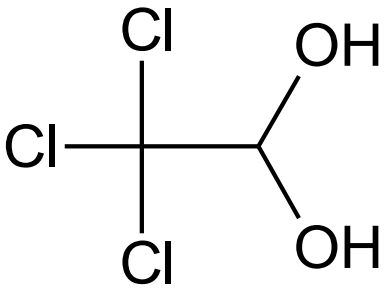
Sedatives & hypnotics

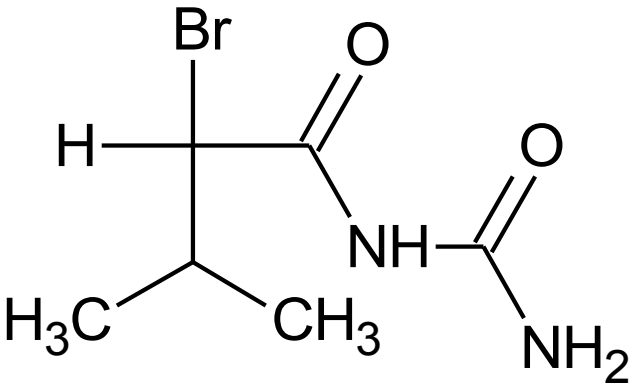
Sedatives = „calmative“ compounds
Hypnotics = compounds causing a condition less or more similar to the physiologic sleep
•often the same; the difference in their action is only in a dose

The sleep in accordance to EEG and other methods:
non-REM (non-rapid eye movement) sleep – 70 - 75%
REM – the rest; deep sleep which is needed to the organism regeneration

(Pre)history
•ethanol
•bromides (KBr, NaBr)



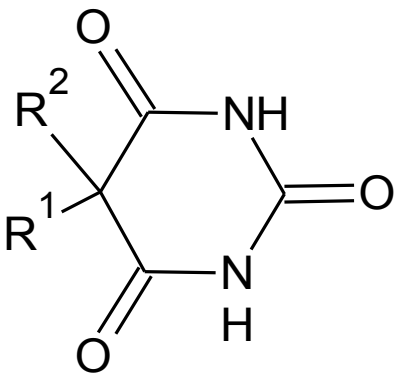
chloral hydrate
•used as a mild sedative and hypnotic in childern up to now (suppositories)



bromisoval

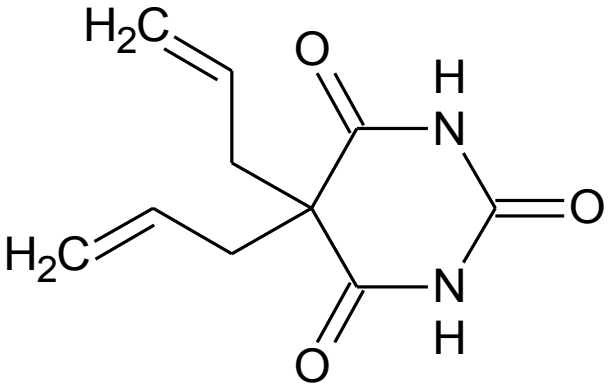
History

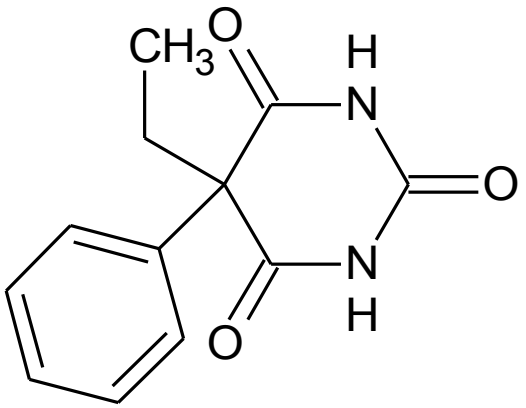
Barbiturates



$R^1 = R^2 = H$ barbituric acid

R^1, R^2= alkyl, alkenyl, aryl barbiturates



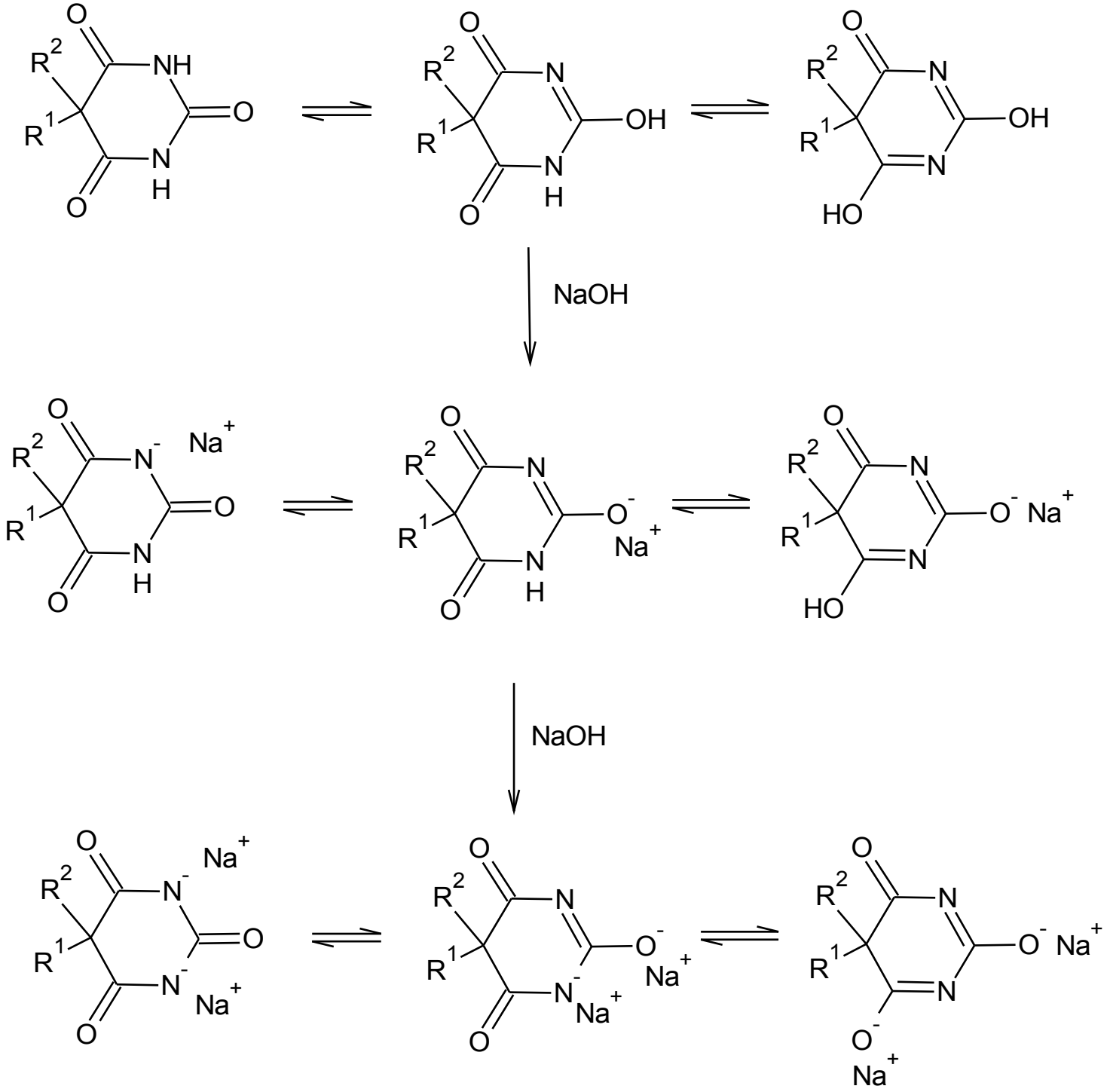


symetric
- slow action onset
- mild activity (sedatives)
- dlouhé odeznívání long decay of action
- usage in analgesic mixtures (irrational, addiction)

asymmetric
- usually more lipophilic
- more efficient, faster onset of action (hypnotics)
- treatment of hyperbilirubinemia and kern icterus in neonates till today (probably irrational)

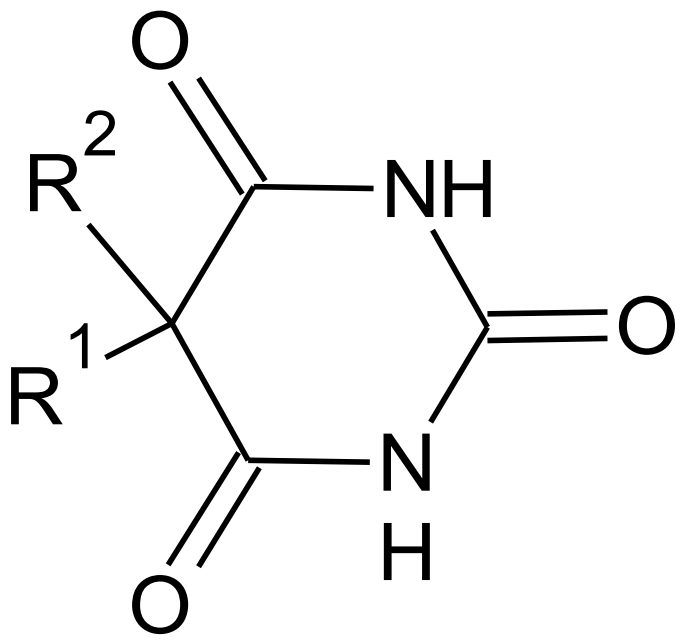
- used on a mass scale approx. 1912 – 1955
- classification according to duration of action
- up to 50 derivatives
- supress REM-sleep ⇒ the patient is not relaxed

Chemical properties of barbiturates: lactam-lactim tautomerism and salts formed by tautomers



- lactam-lactim tautomerism
- dibasic acids
- significant difference of both pK_a values $\Rightarrow$ possilbility of monosodium etc. salts well soluble in water

Examples of barbiturates



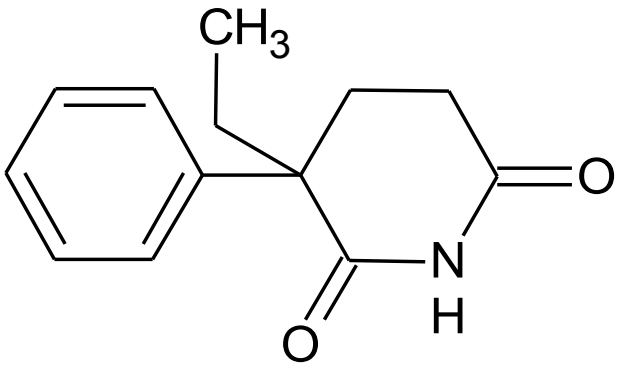
$R^1 = R^2 = C_2H_5$ **barbital**

$R^1 = R^2$ = allyl **allobarbital**

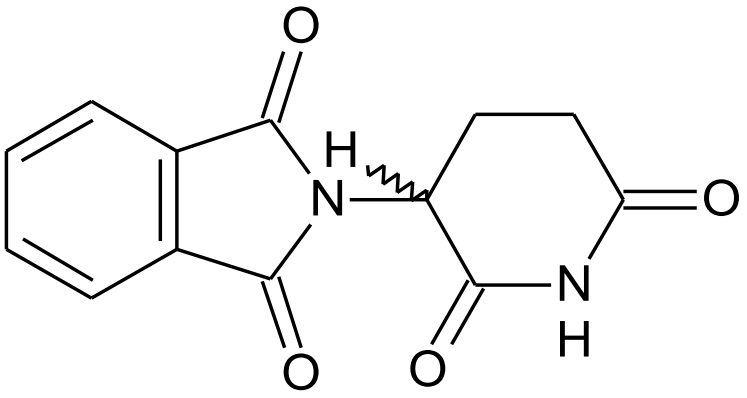
$R^1 = C_6H_5$; $R^2 = C_2H_5$ **phenobarbital**, syn. luminal

- also antiepileptic, treatment of febrile convulsions in babies, till now in neonates yellow-gum (probably irrational; may be connected with enzyme induction)
- $GABA_A$ receptor agonists
- also in mixtures (~~Bellaspon~~®)

Piperidine-2,6-dione (glutarimide) derivatives

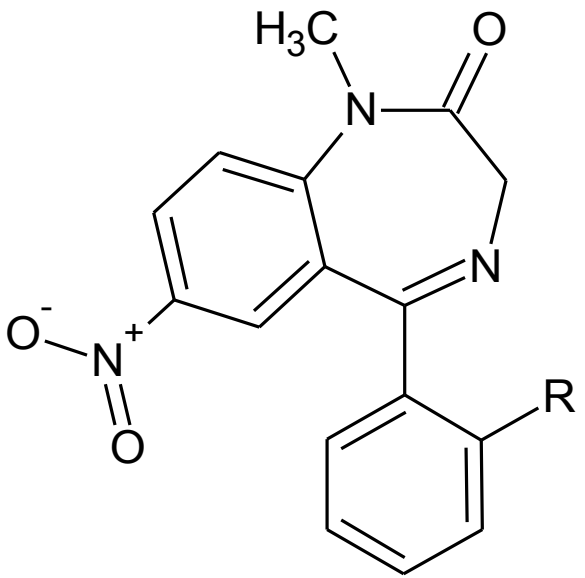


glutethimide
•derived from phenobarbital
•obsolete sedative and hypnotic



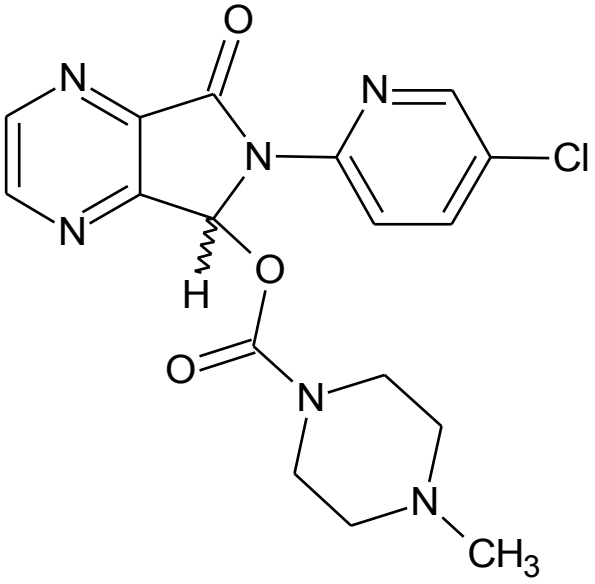
thalidomide
Contergan®
•originally a hypnotic
•withdrawn in 1970th due to tetatogenicity of its S-enantiomer; enantiomers however racemize rapidly; the need of its withdrawal initiated the INN nomenclature introduction
•after 2000 used again: imunosuppresant, antineoplastic, angiogenesis inhibitor; the lead compound of a novel group of anticancer drugs

Benzodiazepins
1,4-benzodiazepins

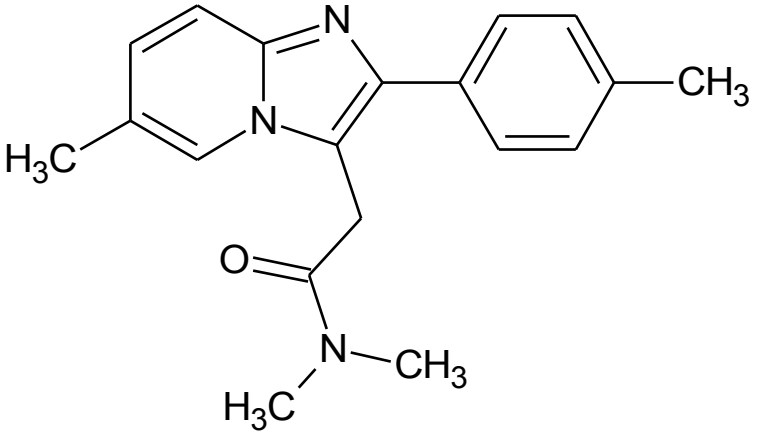


R = H **nitrazepam –** rather sedative
R = F **flunitrazepam** - hypnotic
(~~Rohypnol~~®)
•only minor effect on the REM sleep
AE: amnesia, respiration and circulation attenuation
•tolerance

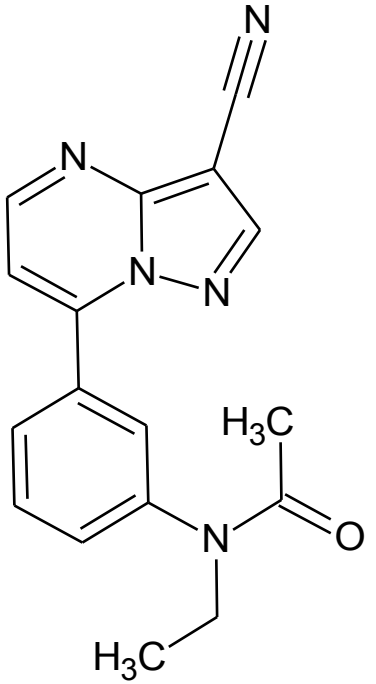
„Z-compounds“



(±)-(5R,S): **zopiclon**
Zopitin®
(+)-(5S): **eszopiclon**



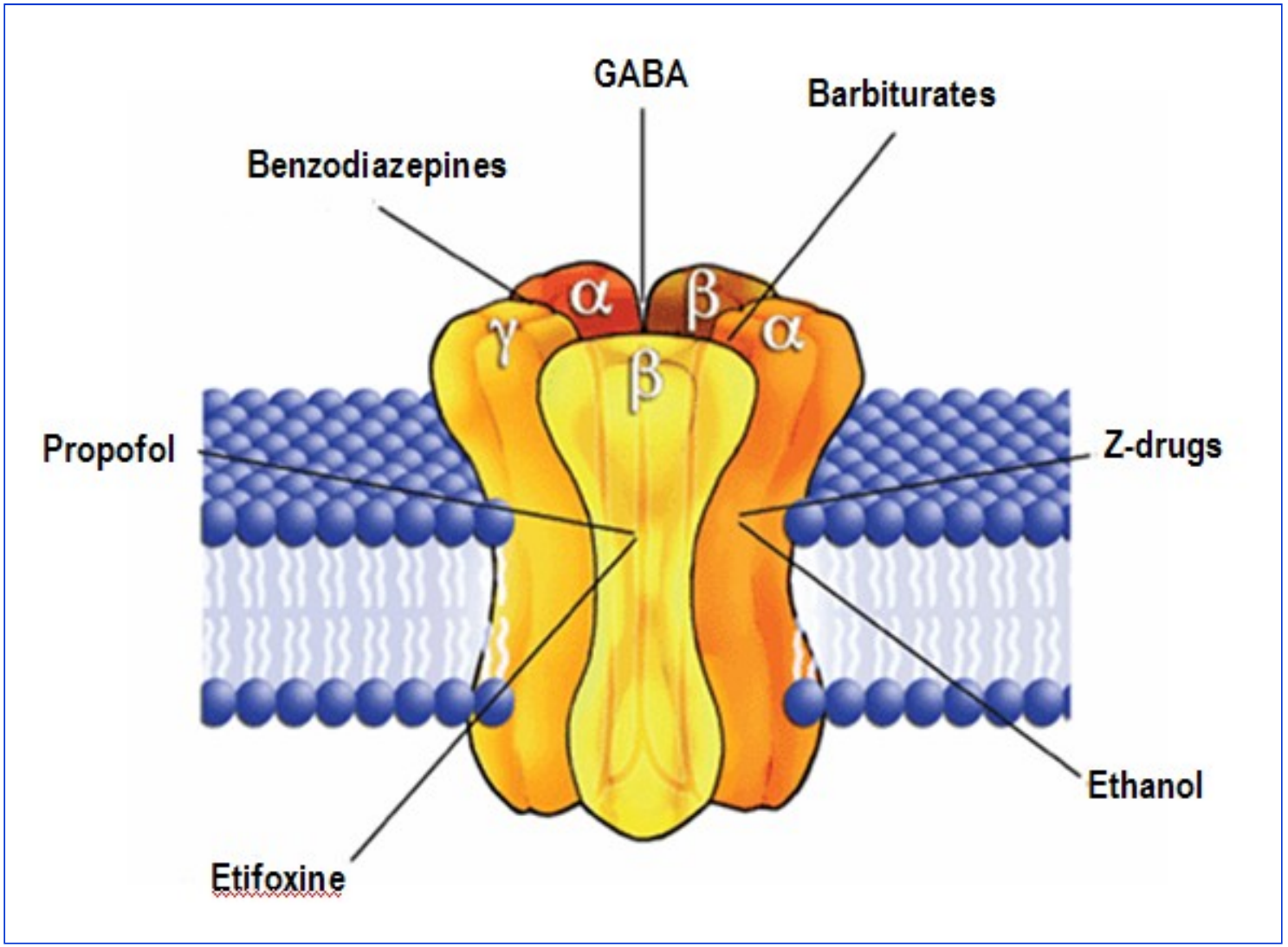
zolpidem
Eanox®, Hypnogen®



zaleplon
•also anticonvulsant activity
Sonata®, Zerene® ...

$GABA_A$-receptor – Cl^- channel: the target structure for most sedatives and hypnotics and many antiepileptics

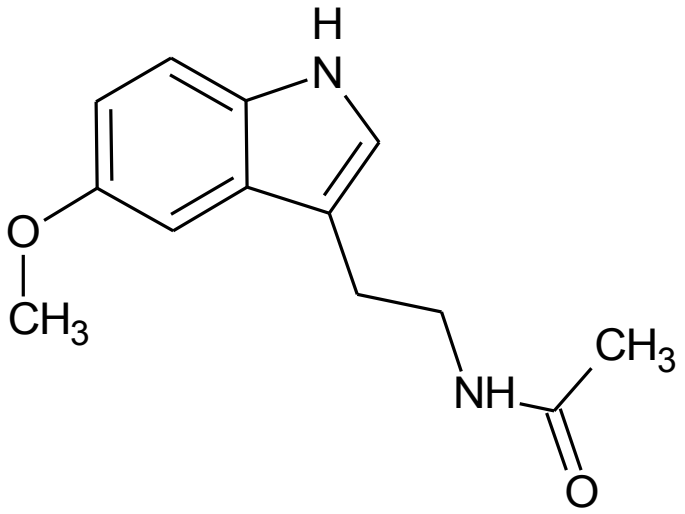
•alosteric receptor agonists



Melatonine receptor agonists („melatonergic“ drugs)

•melatonine is responsible for skin colouring (pigmentation) but also for circadian rhytm

•agonists produce the sleep and „reset circadian pacemaker“ (=“Zeitgeber“) to enable it

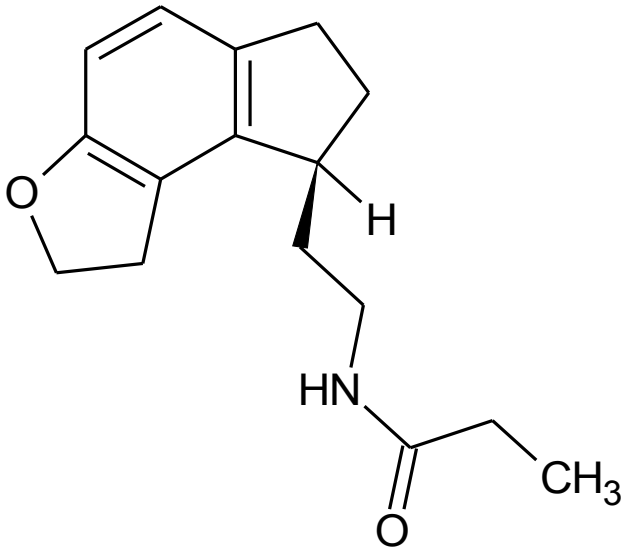


melatonine

•administration in the evening

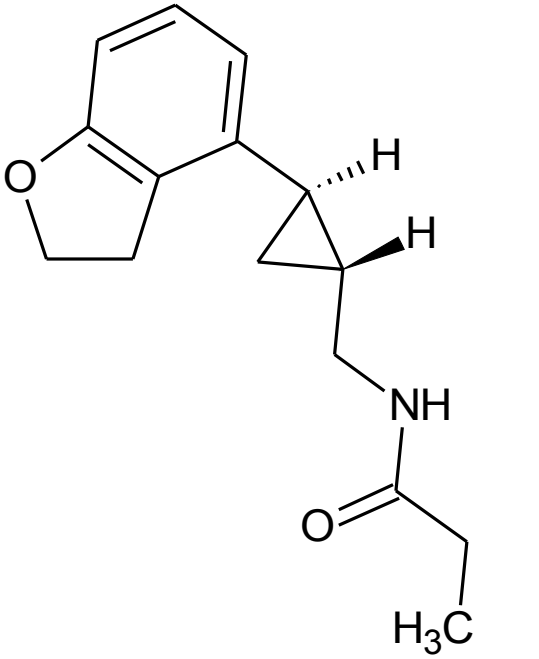
⇒ „re-synchronisation“

• $T_{1/2}$ too short



ramelteon

•melatonine receptors MT_1 and MT_2 agonist



tasimelteon

syn. BMS-214778

Melatonine receptors

- MT_1 and MT_2
- present in various parts of the brain, important namely in supraschiazmatic nucleus („circadian pacemaker = Zeitgeber“-SCN)
- G-protein-coupled receptors
- binding of melatonine to MT_2 $\Rightarrow$ „clock resetting“
- binding to MT_1 $\Rightarrow$ suppressing of neuronal firing
- MT_1 mediated effect of melatonine causes the sleep mainly by means of the „hypothalamic sleep switch“ which under influence of melatonine suppresses neuronal pathes connected with keeping awake and stimulates those connected with the sleep
- thalamus is also of some importance for sleeping effect of melatonine; MT receptors are present here also, spindles which are characterized by non-REM sleep are formed by influence of 5-aminoindole
- there are also other binding structures or sites for melatonine: quinoreductase 2, nuclear receptors which belong into retinoic acid receptors superfamily, Ca^{2+} binding proteins: calmoduline, calreticuline and its analogues in nucleus etc.

Antiepileptics

•compounds selectively suppresing CNS used for treatment of epilepsy

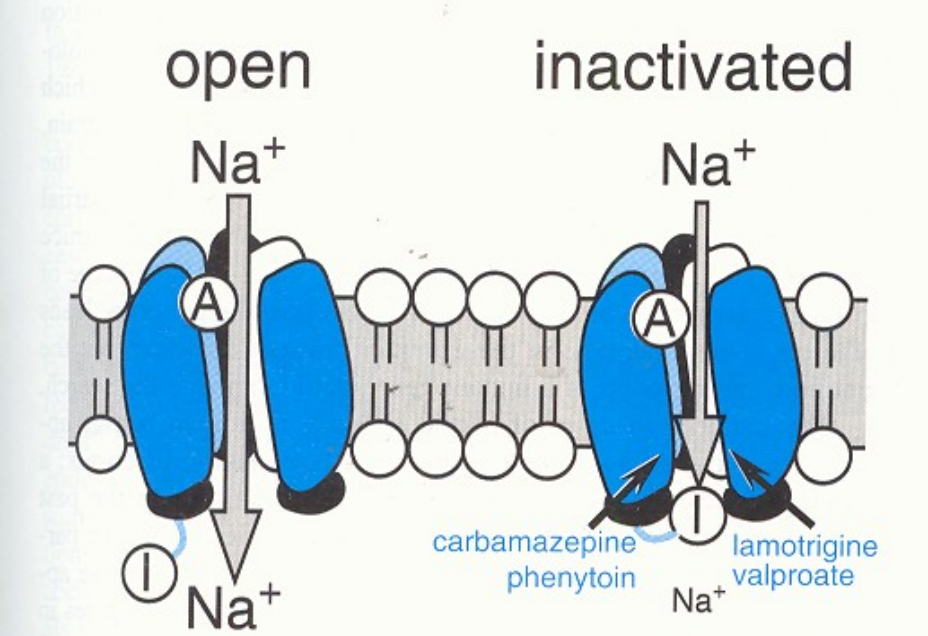
Anticonvulsants

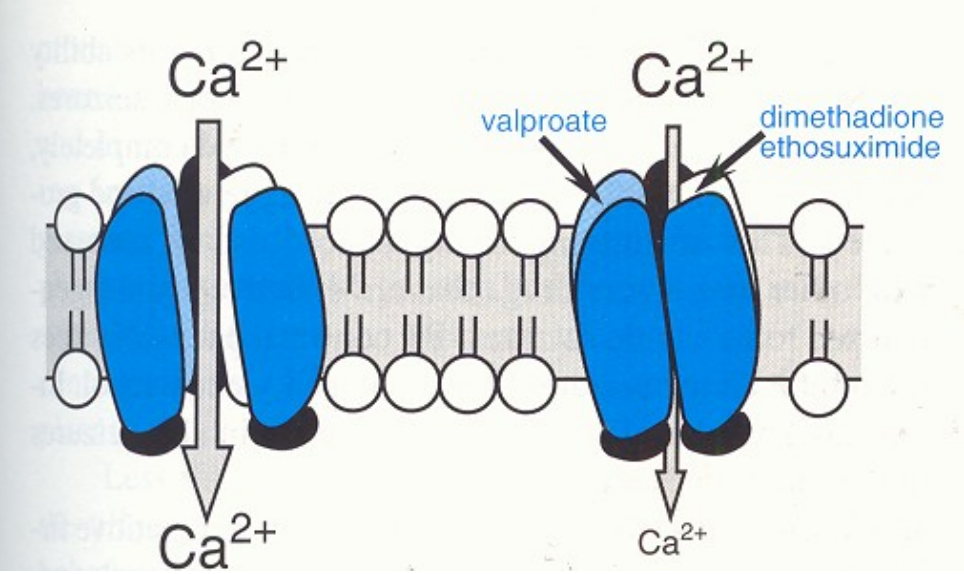
•compounds protecting from convulsions used most frequently (but not only) in epilepsy

•many antiepileptics act as anticonvulsants and vice versa but not all

Modes of action of antiepileptics and some of their target structures

- $GABA_A$-receptor



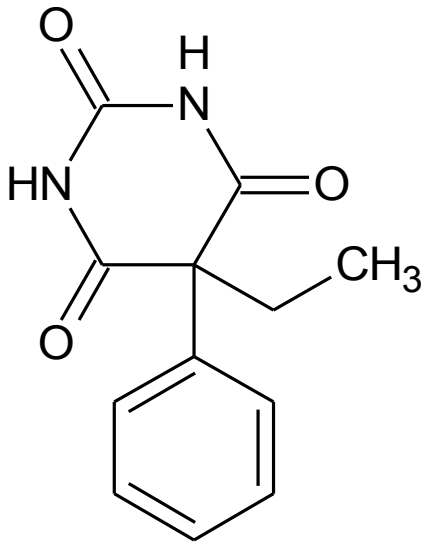


- voltage gated Na^+ channels: extending of inactivation decreases the ability of neurons to spread and impulse on higher frequences
- low threshold Ca^{2+} channels: decrease of the flux of Ca^{2+} throuh T type channels leads to decrease of the current of the pacemaker which conditions the thalamic rhytm in peaks and waves which is seen in generalized seizures

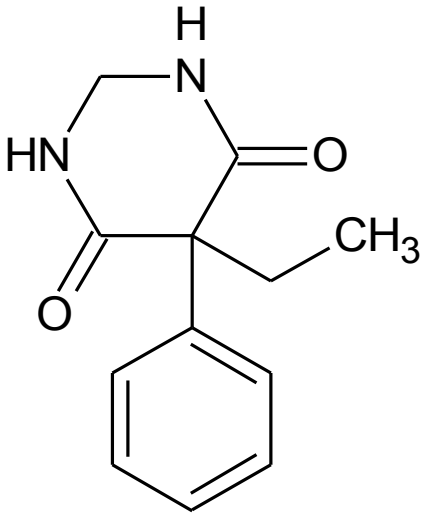
Synaptic vesicular protein 2A (SV2A)

- widely spread in whole CNS; its participation in exocytosis of synaptic vesicles and release of neurotransmitters is assumed
- afinity of levetiracetam and its analogues to SV2A closely correlates with their ability to protect against convulsions induced experimentally in animal models

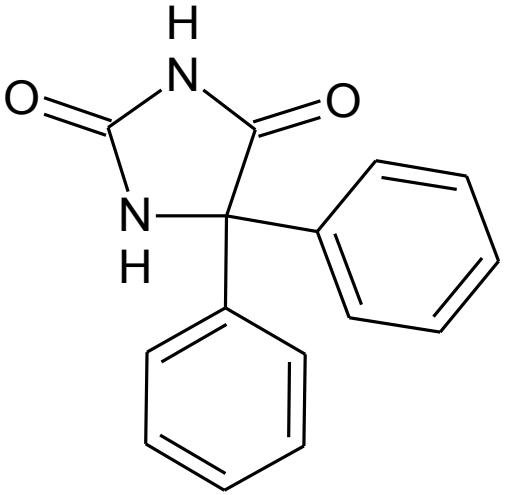
Phenobarbital and its analogues



phenobarbital
Luminal® inj.,
Pheneamal 0.1®,
Phenaemaletten®
•drug of the 2nd choice: teratogenic, induction of hepatic enzymes, sedation, depression, irritation in childern and the elderly

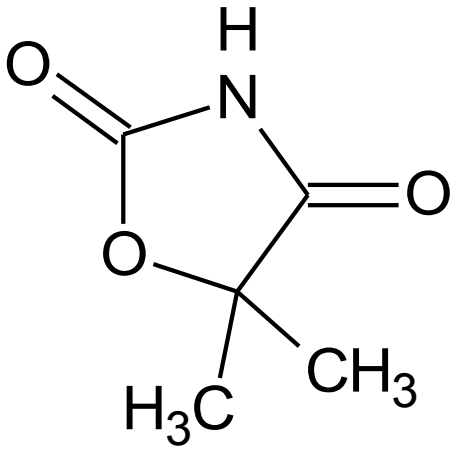


primidone
Liskantin® tbl.
•metabolized to phenobarbital
•drug of the 2nd choice: sedation, ataxia, attenuated libido

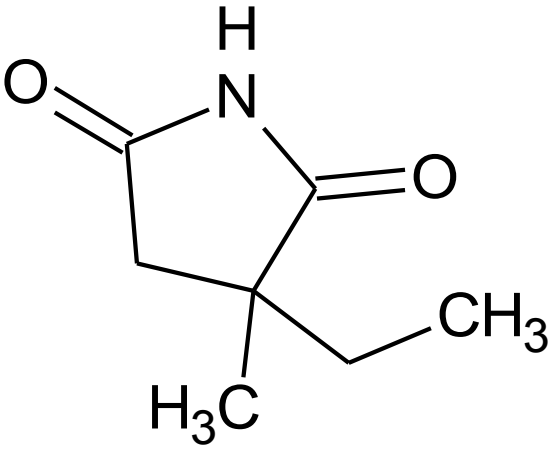


phenytoin
5,5-diphenylhydantoin
•since 1938
•compared with phenobarbital nearly „non-sedative“
•acts on Na^+ channel; prolongs its opened period
Epilan D Gerot® tbl.,
Epanutin® inj.
•in fact monobasic acid; Na^+ salt also used

Isosteric analogues of hydantoins – oxazolidine-2,4-diones a succinimides



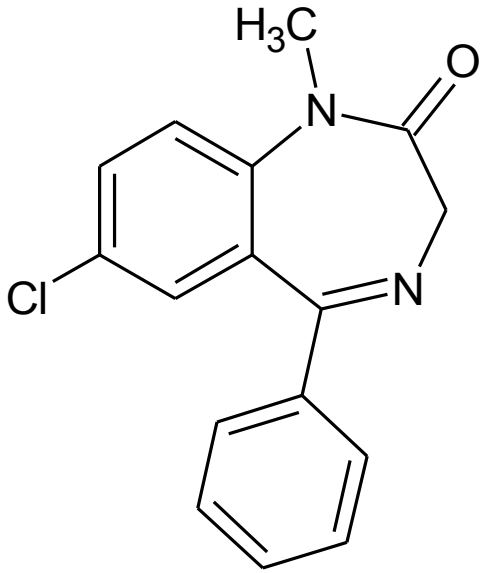
dimethadione



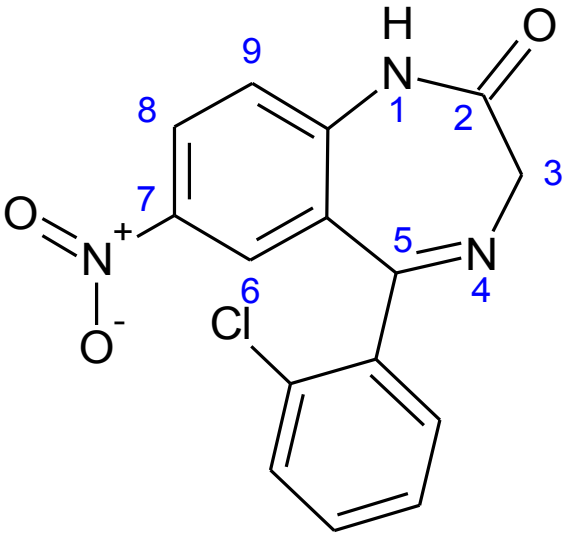
ethosuximide
Pethinimid® cps.
•effective in patients with absences but not in generalized and tonic-clonic seizures
•does not intertact with other drugs
•AE: nausea, vomitting , abdominal pain, headache, alergic rash ...

•block Ca^{2+} type T channels in thalamic neurons

Benzodiazepins
1,4-benzodiazepins



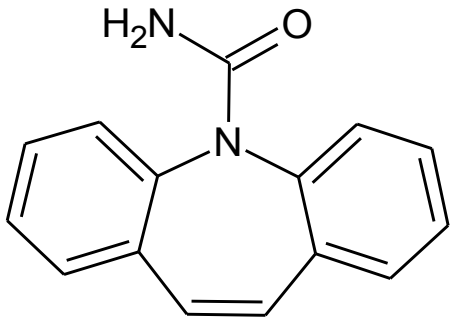
diazepam
•also prevention of febrile convulsions in babies
Diazepam Desitin®Rectal Tube



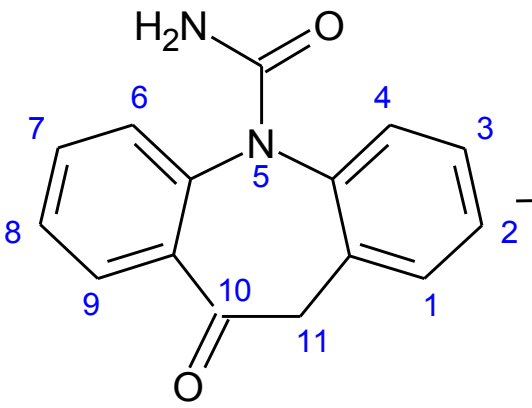
clonazepam
Rivotril®tbl., gtt.

•$GABA_A$-receptor

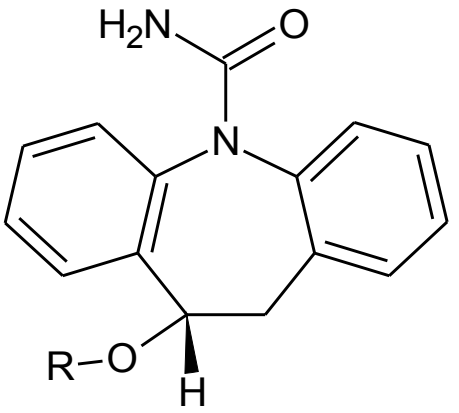
Dibenzo[*b,f*]azepins



5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

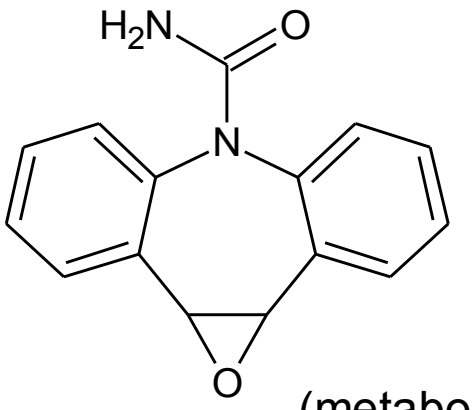


(prodrug)



carbamazepine
Carbamazepinum PhEur
Biston®, Neurotop®, Tegretol® CR …
•blocks voltage gated Na^+ channels and thus hinders uncontroled impulses spreading

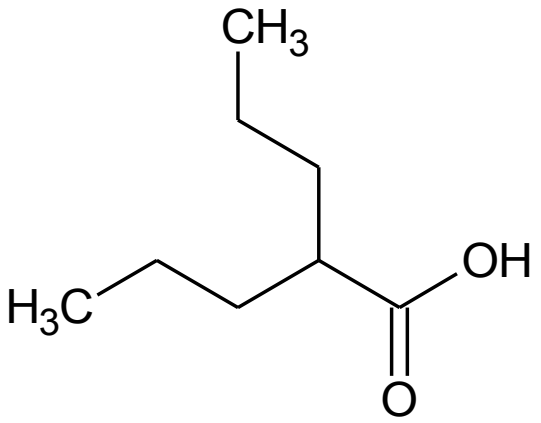
oxcarbazepine
Oxkarbazepin Merck®, … Mylan®; Trileptal®



(metabolite)

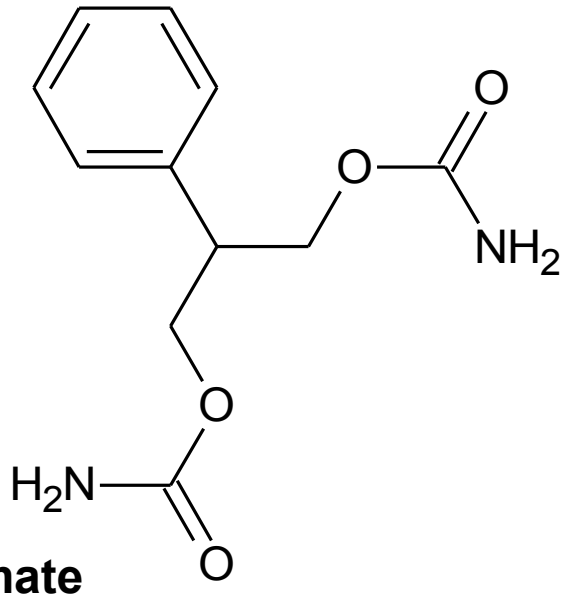
carbamazepine-epoxide

R = H-
eslicarbazepine
R = CH_3CO-
eslicarbazepine acetate
Exalief ® tbl., Zebinix ® tbl.
•also modulate currents mediated by Ca^{2+} a K^+



valproic acid
Acidum valproicum PhEur
•**sodium valproate** more fraquently used
Natrii valproas PhEur
•blocks voltage gated Na^+ channels
•amplifies inhibition effect of GABA
•lowers currents through voltage gated low threshold Ca^{2+}-T-channels
•all types of seizures
•teratogenic
Absenor ® , Convulex ® (valproic acid), Depakine ® , Orfiril ® … (sodium vaproate)

Carbamates



felbamate

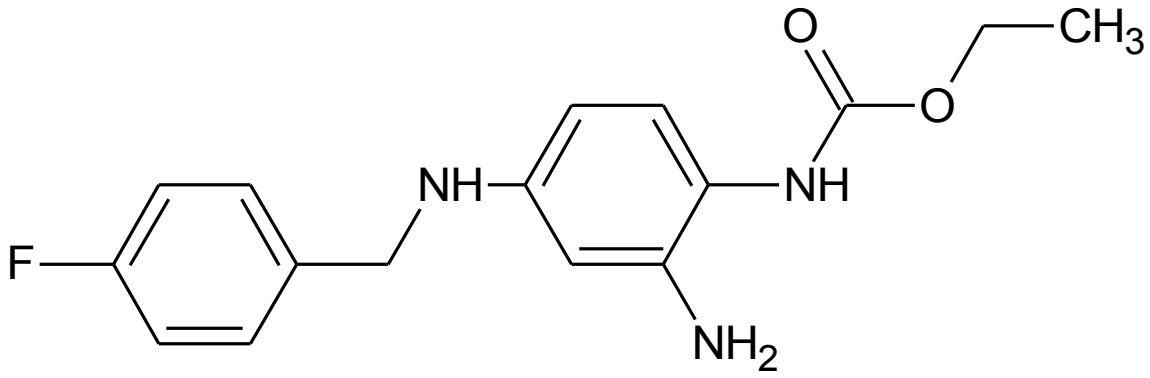
•an analogue of meprobamate and carisoprodole

Modes of action:

- potentiates GABA mediated inhibition
- blocks voltage gated Na^+ channels
- blocks ion channels of N-methyl-D-aspartate (NMDA) receptors

•treatment of generalized seizures including Lennox–Gastaut syndrome (= a difficult-to-treat form of childhood-onset epilepsy characterized by frequent seizures of various types and often accompanied by mental retardation)

•high risk of fatal hepatitis and aplastic anaemia



retigabin

syn. D 23129

•developed from the analgesic flupirtine

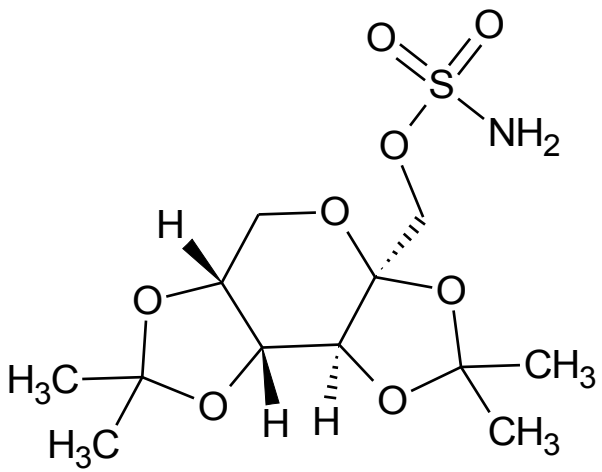
Modes of action: activates K^+ channels of Kv7 type + potentiates GABA-induced currents in cortical neurones

•adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above

•risk of QT-interval prolongation and psychiatric problems

Trobalt ® authorized by EMA 28th March 2011

Compounds with a sulphonamide eventually a sulphamic acid fragment



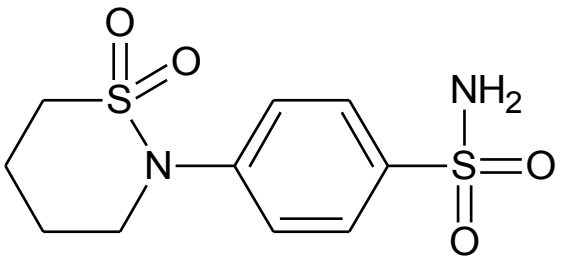
topiramate

2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate

Topilept® tbl., Topilex® tbl., Topiragis® tbl....

•many structural changes proceeded but analogues inactive

•blocks Na^+ channels and high voltage gated Ca^{2+} channels, attenuates effects of excitation transmitters and amplifies GABA effect; impact of carboanhydrase inhibition on its action is not clear



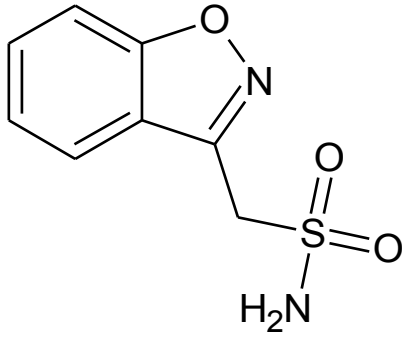
sulthiame

•a sulphanilamide derivative

•introduced 1961

•carboanhydrase inhibitor

Ospolot®tbl.

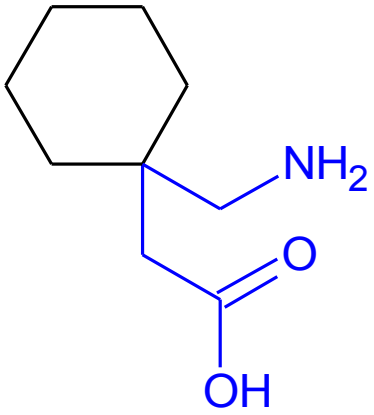


zonisamide

- blocks voltage gated Na^+ channels & Ca^{2+} channels of T type
- inhibits carboanhydrase

Zonegran®tbl.

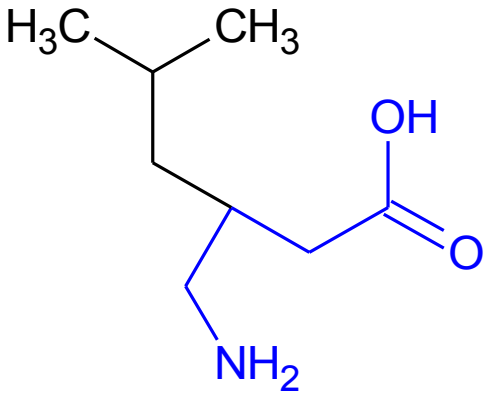
Substitution derivatives of γ-amino butyric acid (GABA)



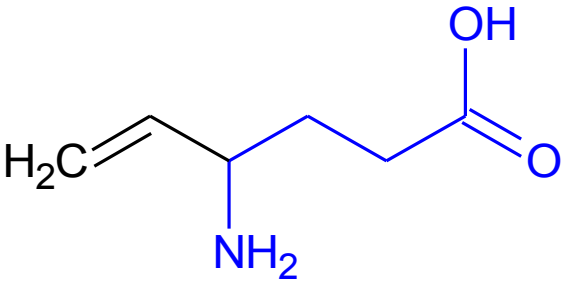
[1-(aminomethyl)cyclohexyl]acetic acid

gabapentin
Gabagamma®tbl., Gabanox®tbl.
…

•AE: weight increase



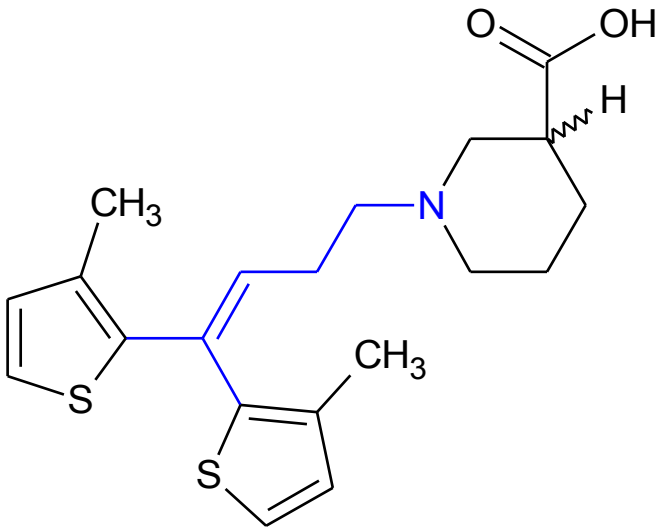
pregabalin
Lyrica®
•6 – 8x more effective than gabapentin
•also for neuropathic pain and generalized anxious disorder



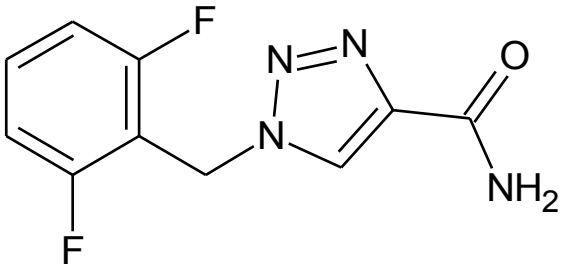
vigabatrin
Sabril®tbl.
• GABA-aminotransferase inhibitor

•bind to α2δ subunit of neuronal voltage gated Ca^{2+} channel and inhibit stream of Ca^{2+}
•excreted by urine, do not interfere with metabolism of other drugs

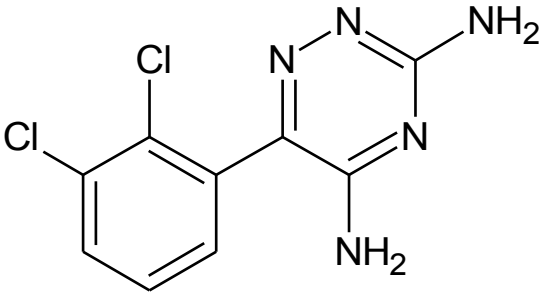
Some „newer“ antiepileptics with heterocyclic fragments



tiagabin
Gabitril®tbl.
•inhibits GABA reuptake in neurones and glias ⇒ ↑ availability of GABA for inbibition of postsynaptic neurones

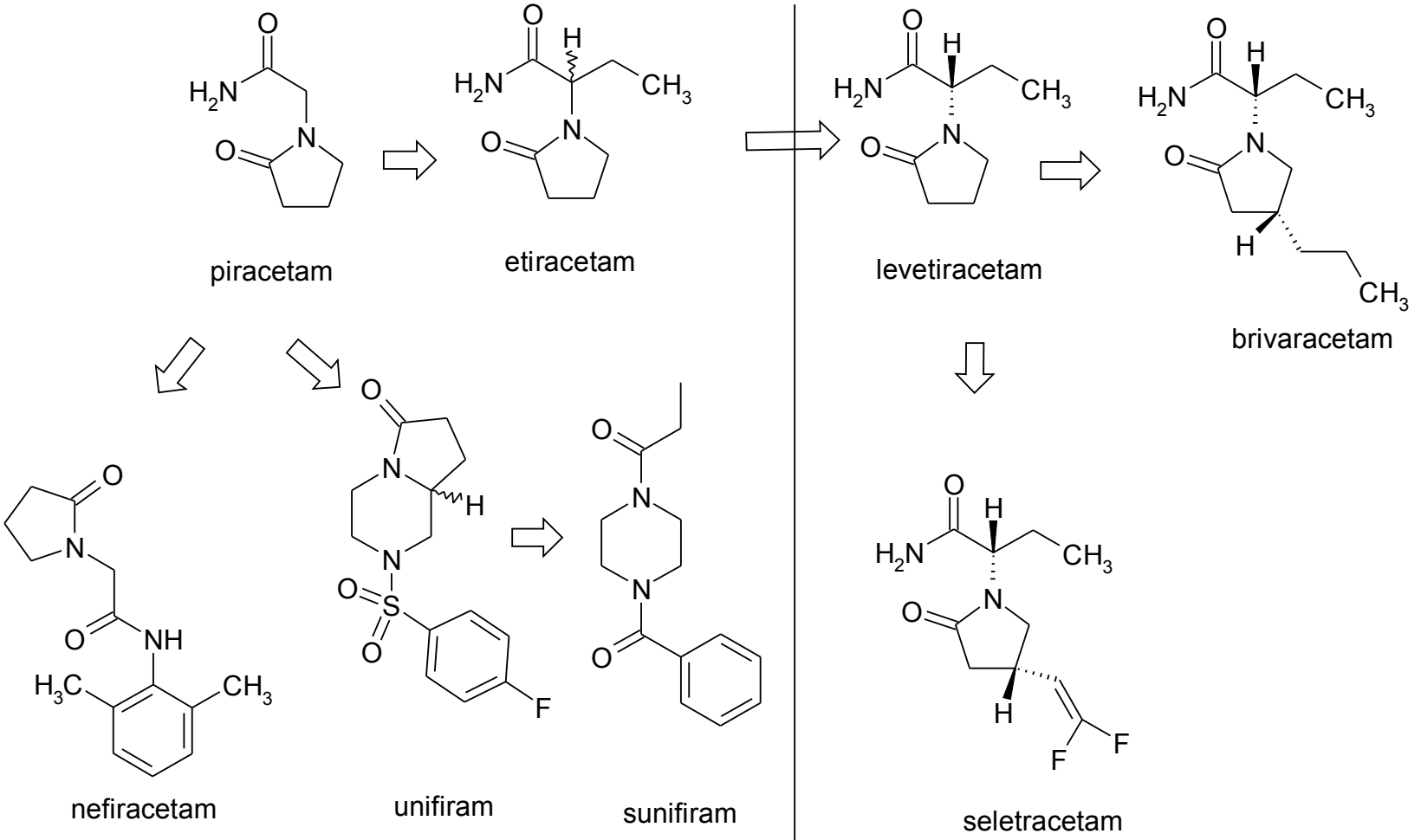


rufinamide
•modulation of Na^+ channels – keeps their inactive state
•AE heart: shortening of QT interval
Inovelon®tbl.



lamotrigin
Epimil®tbl., Lamictal®tbl. …
•Na^+ channels blocker
•can also trigger myoclonic seizures
•embryotoxicity: ↑ risk of cleft of lip and palate

„Geneaology“ of racetams



klasická nootropika, posilovače kognitivních funkcí

"neklasická" antiepileptika, agonisté synaptického vezikulového proteinu 2A (SV2A)

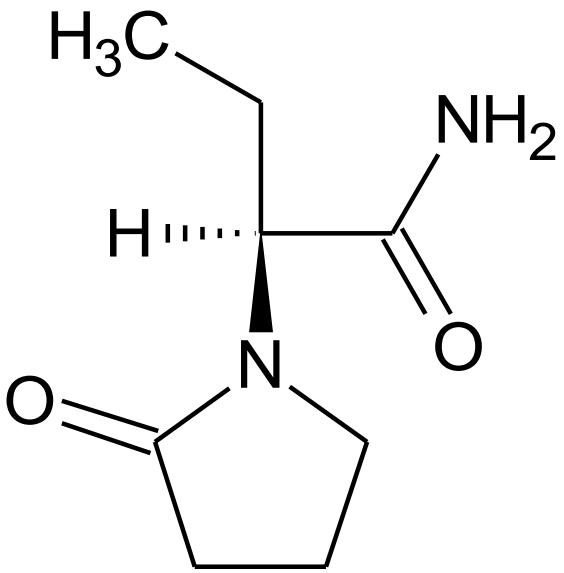
classical nootropics, cognitive functions enhancers

„non-classical antiepileptics, synaptic vesicular protein 2A (SV2A) antagonists

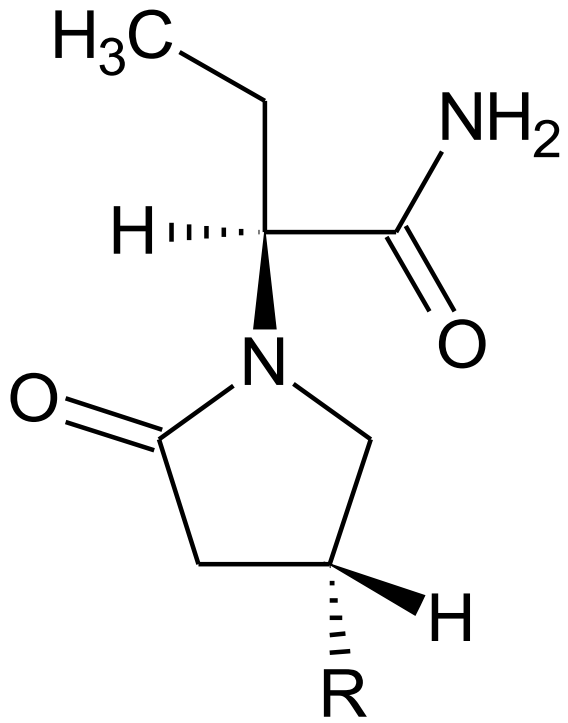
Antiepileptic **racetams**

•interact with SV2A

•probably also inhibit high voltage activated (HVA) Ca^{2+} channels (like topiramate)



levetiracetam
Keppra®



(2S), (4R)

•10x higher afinity to SV2A than levetiracetam

R = C_3H_7 **brivaracetam**

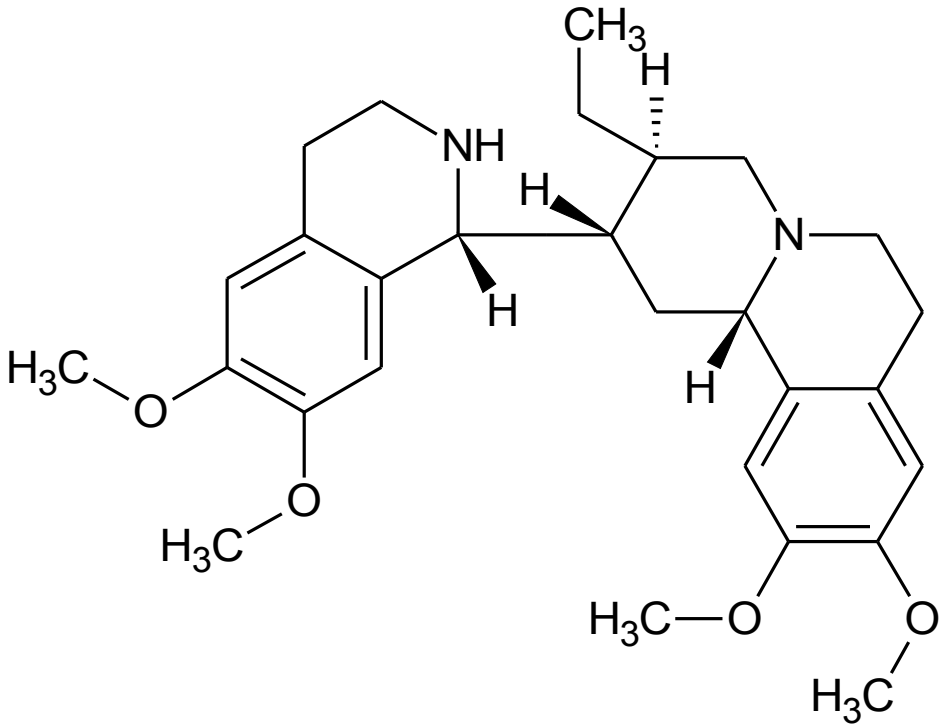
•EMA has authorized clinical studies for treatment of epilepsy in childern and febrile convulsions in neonates

•inhibits also Na^+ channels

R = $CH{=}CF_2$ **seletracetam**

Vomitics

- induce vomiting e.g. in intoxications
- an obsolete group



emetine

•alcaloid from the roots of *Cephaëlis ipecacuanha, Rubiaceae*

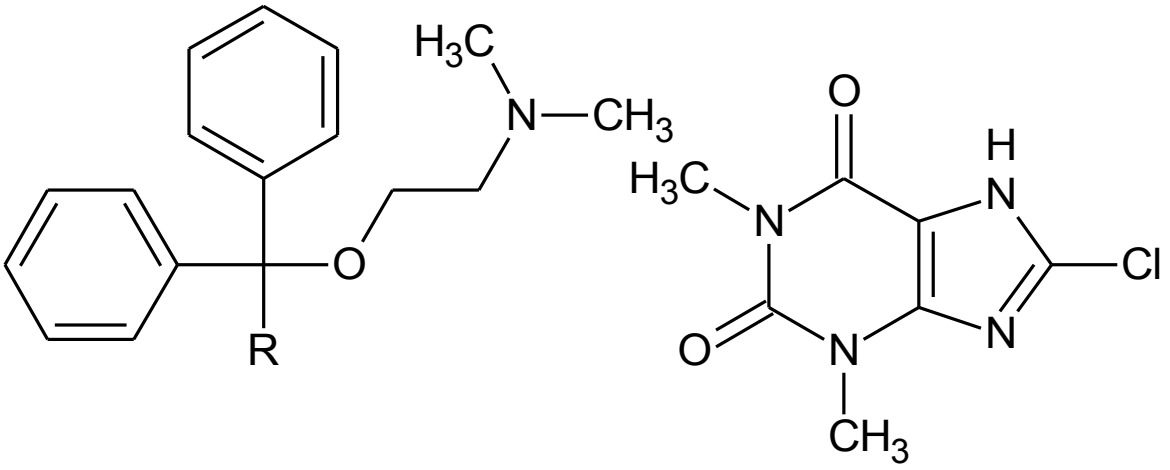
•emetic (central: *medulla oblongata*), antiprotozoal, anthelmintic effects

•formerly also used as „caugh modulator“ - combined with codein – Kodynal® (50 mg codeine + 5 mg emetine)

Antivomitics (= antiemetics), antikinetics

- parasympatolytics: tropane alkaloids
- H_1-antihistamines
- antipsychotics: phenothiazine derivatives
- compounds enhancing intestinal perislalsis
- setrons
- NK-1 antagonists

H_1-antihistamines used as antiemetics and antikinetics



R = H **moxastine theoclate**

syn. mephenhydrinate

Kinedryl®

R = CH_3 **dimenhydrinát**

= diphenhydramine + 8-chlorotheophylline

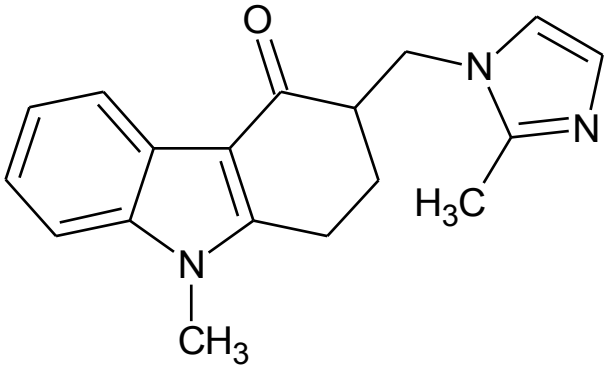
•molecular complexes

•motion sickenesses, gravidity nausea

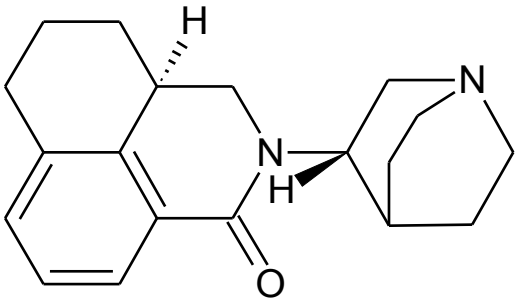
•AE: sedation

Setrons

- suppress nausea and vomitting by inhibition of serotonine 5-HT_3 receptors on periphery
- treatment of serious nausea accompanying cancer chemotherapy
- also in general anaesthesia

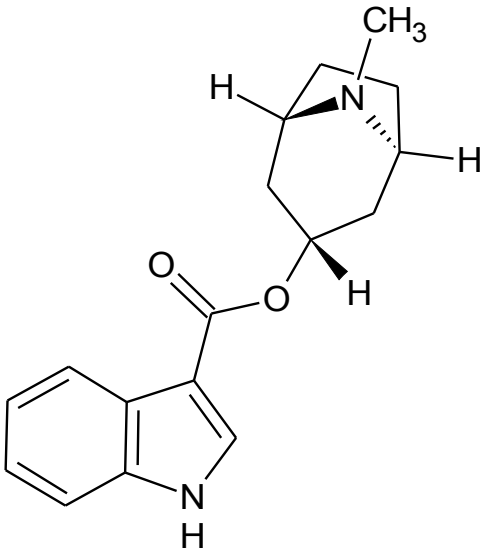


ondansetrone
Emeset®, Zofran® ...

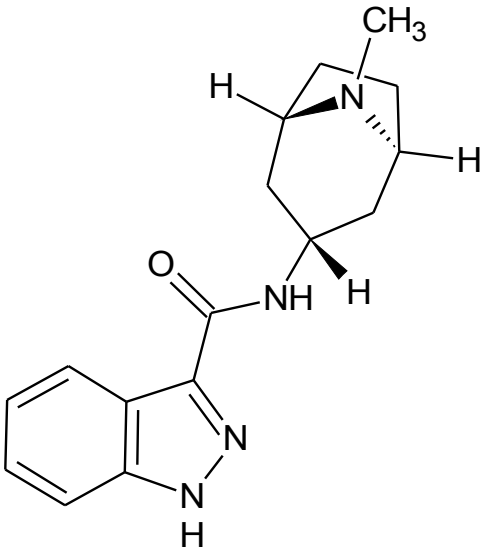


palonosetrone
- the most modern
Aloxi® inj.

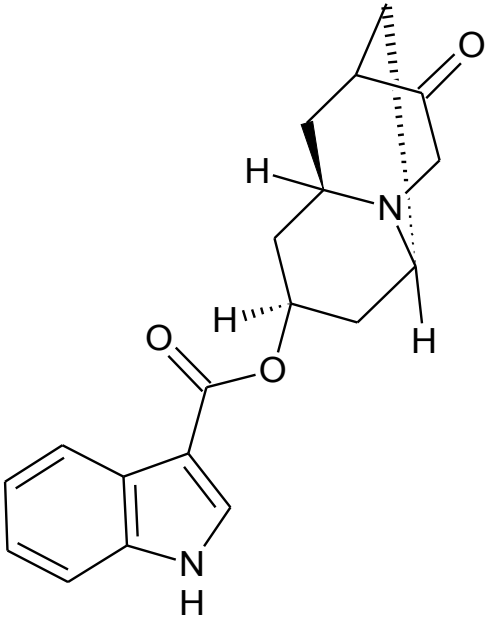
Setrons – derivatives of indole and isosteric heterocycles



tropisetron
•effective for 24 hours
•fully metabilized in liver



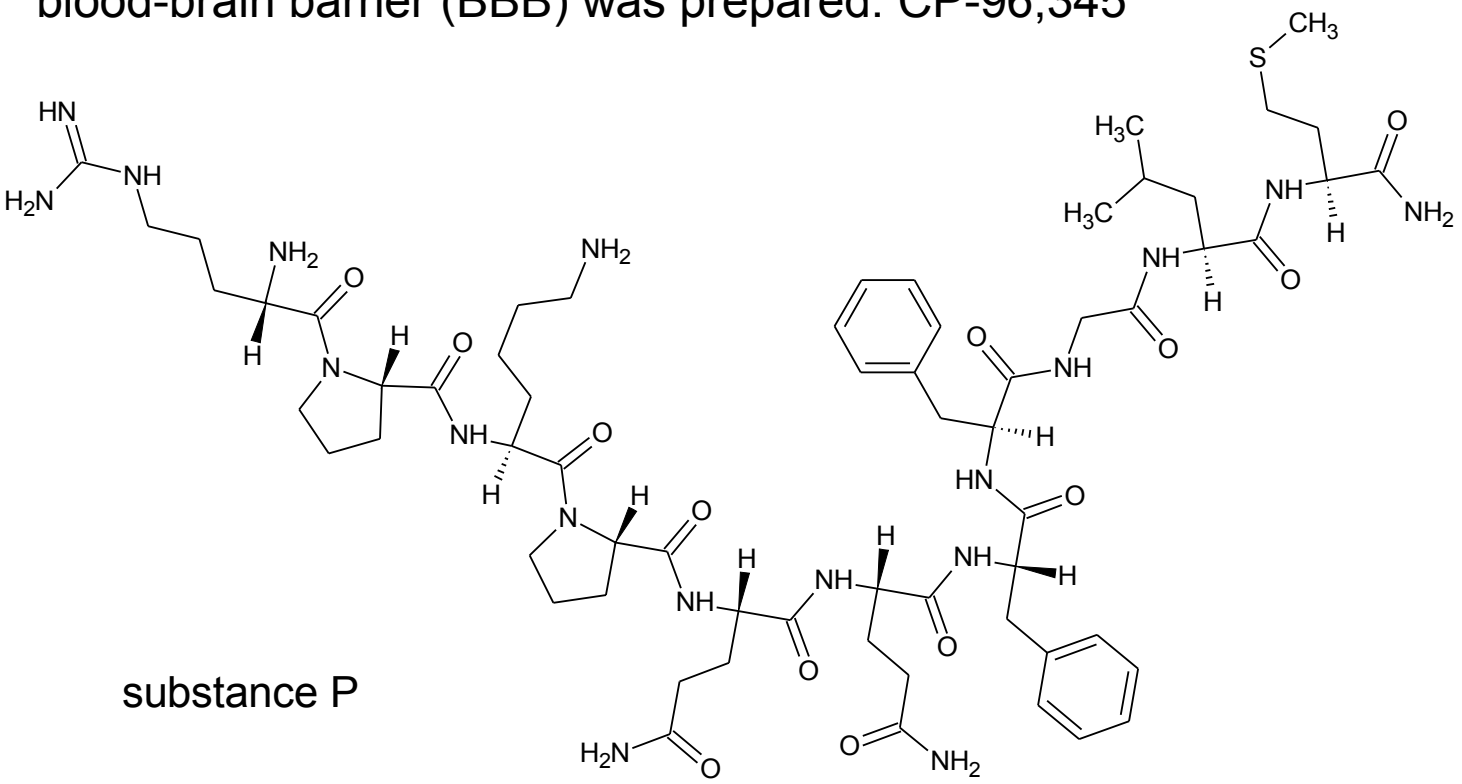
granisetron
•isosteric
Emegar, Granegis ...



dolasetron

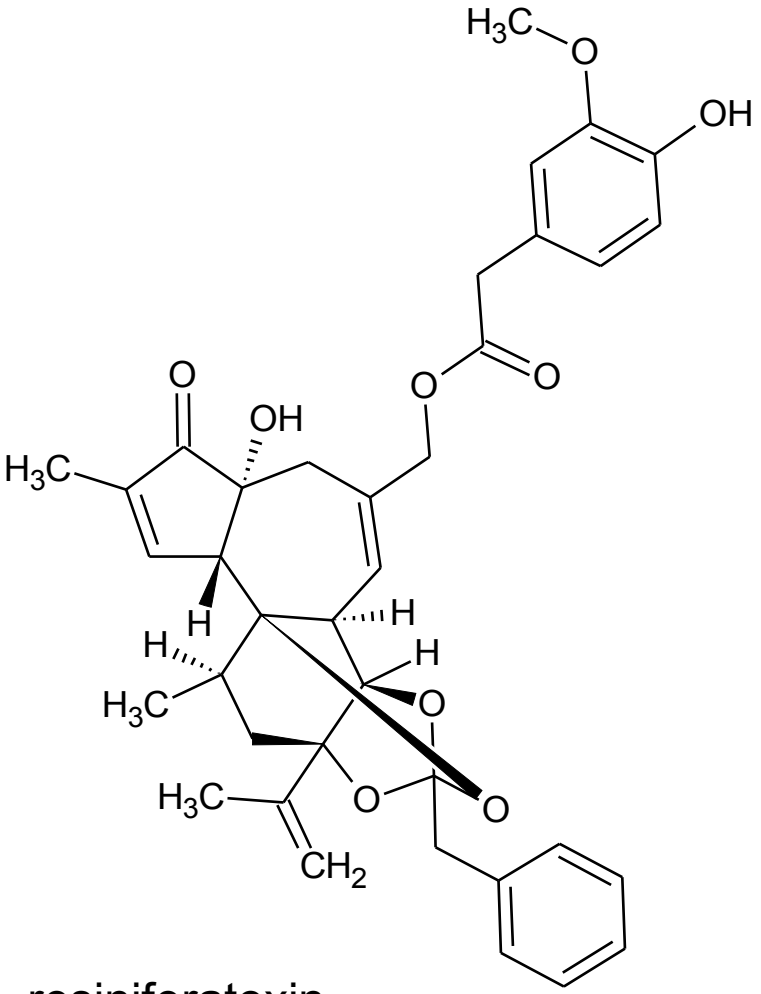
Neurokinine receptor 1 (NK_1) antagonists

- substance P (SP) was isolated in 1931, it was purified and its sequence was determined in 1970th : Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2
- belongs to family of small peptides – mammal tachykinins (TK)
- 3 types of receptors for TK have been cloned: neurokinines NK_1, NK_2, NK_3
- SP is predominantly an agonist of NK_1 receptor
- 1984: administration of SP induced vomitting in dogs
- 1993: resiniferatoxin acts antiemetic in ferrets by competiton with SP
- 1993: the first non-peptide „pure“ NK_1 antagonist permeating through blood-brain barrier (BBB) was prepared: CP-96,345

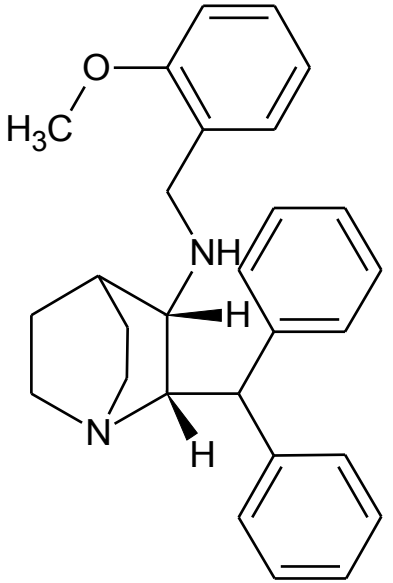


substance P

Neurokinine receptor 1 (NK_1) antagonists

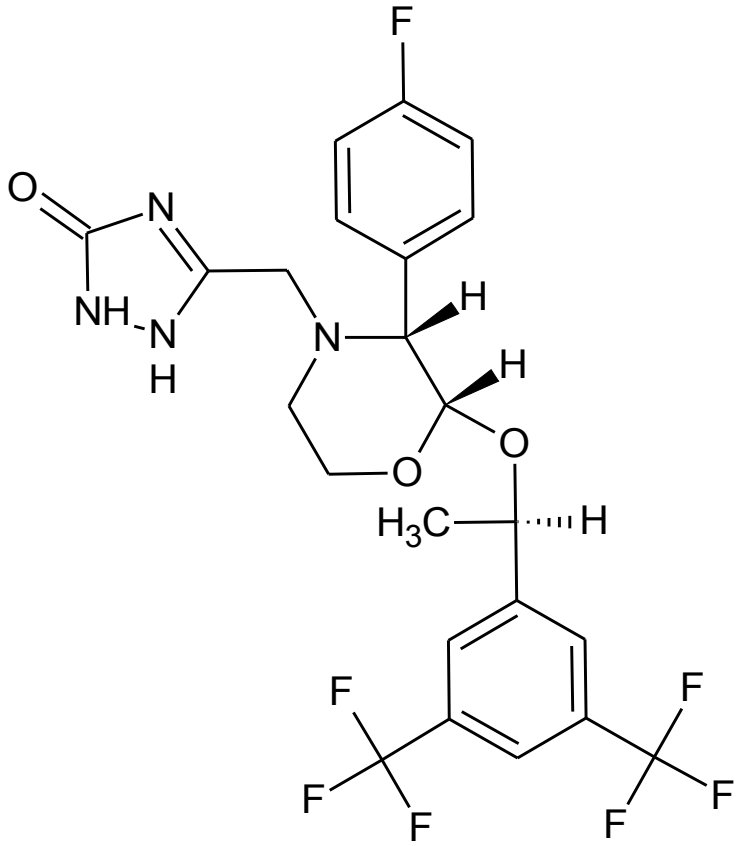


resiniferatoxin
•a terpene from latex of *Euphorbia* genus (*E. poisonii, E. resinifera*)
•also vaniloid (capsaicine) receptors agonist
•emetic/antiemetic in dependence on the mode of application



CP-96,345

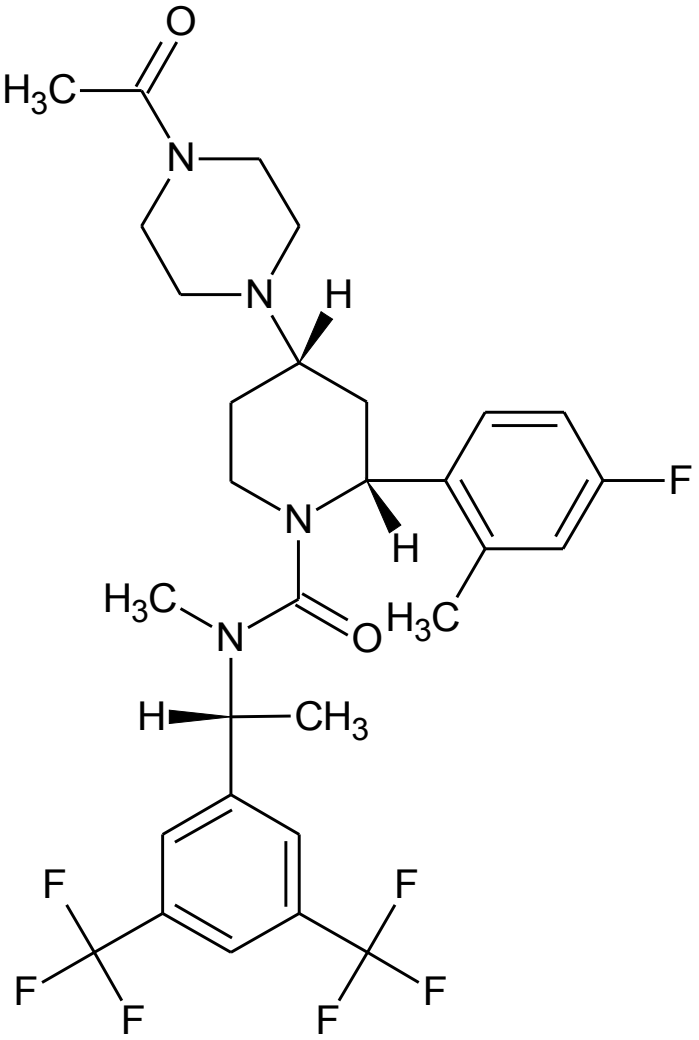
Neurokinine receptor 1 (NK_1) antagonists



aprepitant

- 1st NK_1 antagonist available in clinic

Emend® cps., Ivemend® plv. inf.



casopitant

syn. GW679769

- phase 3 of clinical evaluation has been finished