Drugs Acting on CNS: Depressant Drugs

Sedative & Hypnotics

- CNS depressants.
- Used to treat insomnia.
- Sedatives decrease excitability but do not induce sleep.
- Hypnotics induce sleep.

- Insomnia can be classified as:
  - ✓ Primary (pathogenesis unknown).
  - ✓ Secondary (situational stress, lifestyle habits, drugs, and psychiatric or medical disorders).

Sleep Cycle

- Wakefulness.
- Nonrapid eye movement [NREM] sleep.
- Rapid eye movement [REM] sleep.

Sleep Factors

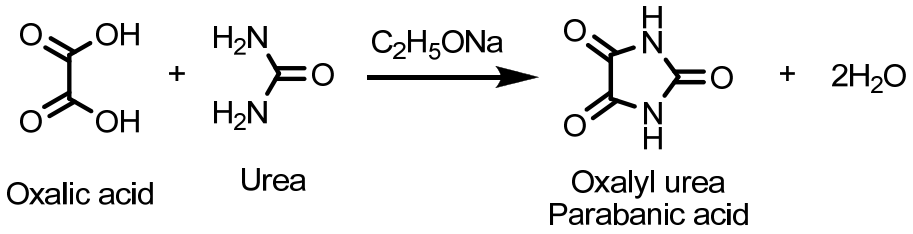
- Autonomic, physiologic, and biochemical changes.
- Neurotransmitters:
  - ✓ Catecholamines, serotonin, histamine, acetylcholine, adenosine, γ-aminobutyric acid.
- Hormones:
  - ✓ Growth hormone, prolactin, and melatonin.

Sedative-Hypnotic Drugs

- Chloral hydrate.
- Barbiturates.
- Benzodiazepines.
- Nonbenzodiazepines
- Melatonin receptor agonists.
- Antihistamines.
- Antidepressants.

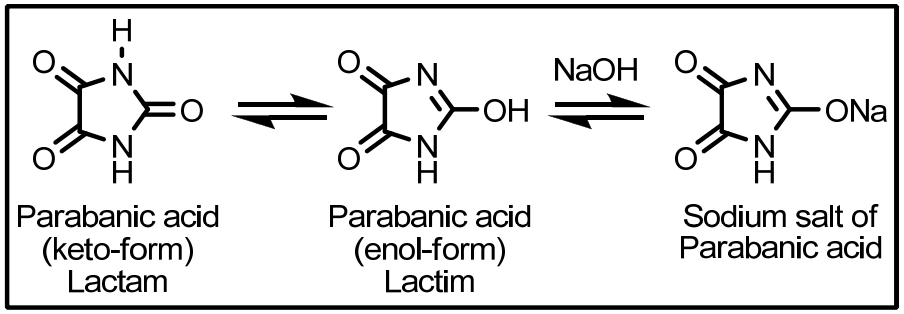
- The ideal sedative-hypnotic should:
  - ✓ Induce and maintain sleep without lingering effects.
  - ✓ Not decrease or arrest respirations (even at relatively high doses).
  - ✓ Produce no abuse, addiction, tolerance or dependence.

Barbiturates

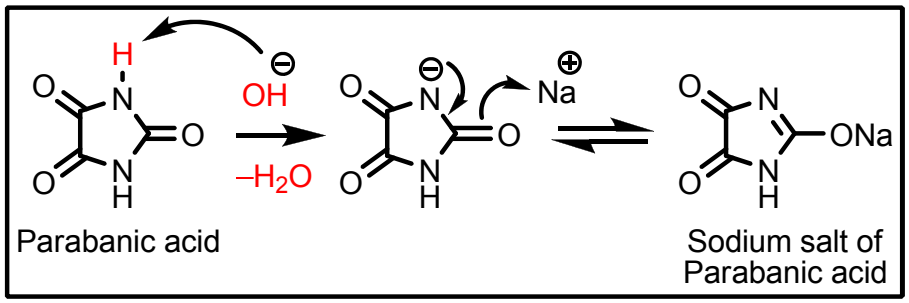


Oxalic acid — Urea — Oxalyl urea Parabanic acid

- Cyclic ureides are formed when a dicarboxylic acid reacts with urea.



- The cyclic ureides are acidic owing to enolization.



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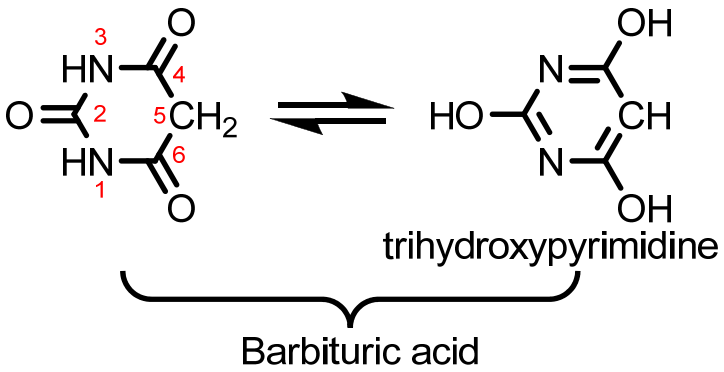
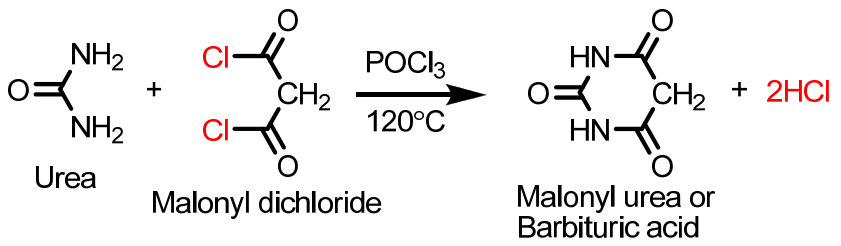
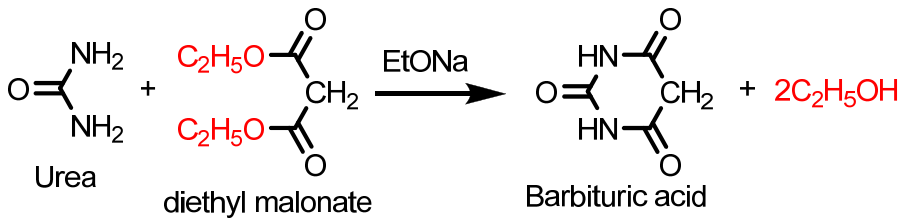
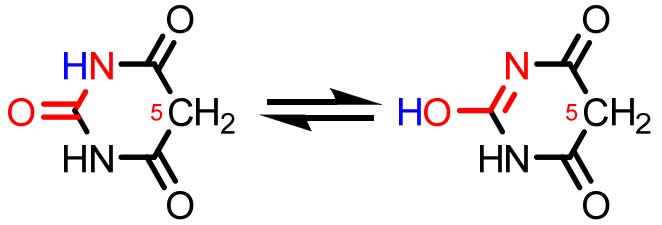


- Cyclic ureides derived from malonic acid or malonic esters are known as barbiturates because of their relationship with barbituric acid (malonyl urea).



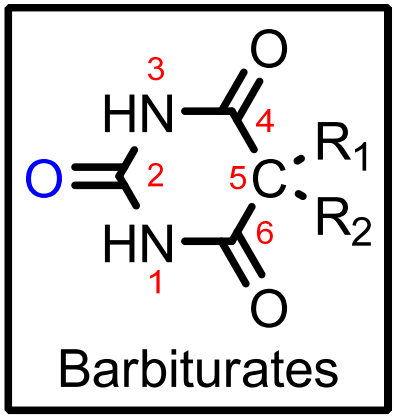


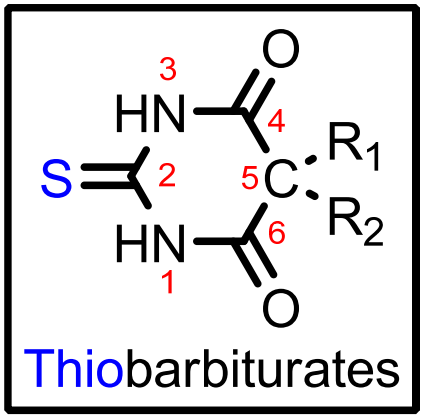


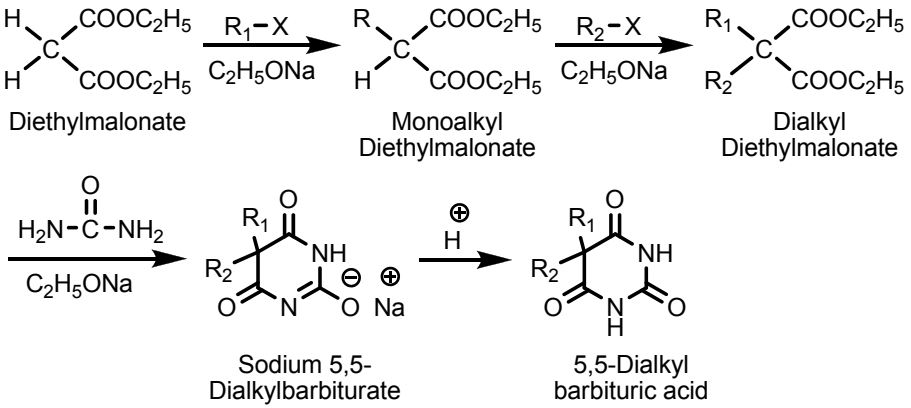
Barbituric acid (keto-form) Lactam

Barbituric acid (enol-form) Lactim

- Barbituric acid does not possess any hypnotic properties.
- To be active the hydrogen atoms at C-5 should be replaced by organic groups (alkyl or aryl).

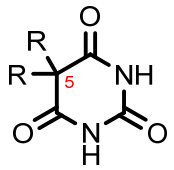






Diethylmalonate → Monoalkyl Diethylmalonate → Dialkyl Diethylmalonate

Sodium 5,5-Dialkylbarbiturate → 5,5-Dialkyl barbituric acid

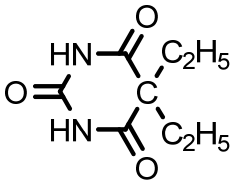


Barbiturate	R_5	R_5	Hypnotic Dose (mg)	Onset (min)	Duration (hours)
Amobarbital	C_2H_5–	$(CH_3)_2CHCH_2CH_2$–	100–200	45–60	6–8
Aprobarbital	CH_2=$CHCH_2$–	$(CH_3)_2CH$–	40–160	45–60	6–8
Butabarbital	C_2H_5–	$CH_3CH_2CH(CH_3)$–	50–100	45–60	6–8
Pentobarbital	C_2H_5–	$CH_3(CH_2)_2CH(CH_3)$–	100	10–15	3–4
Phenobarbital	C_2H_5–	C_6H_5–	100–320	30–60	10–16
Secobarbital	CH_2=$CHCH_2$–	$CH_3(CH_2)_2CH(CH_3)$–	100	10–15	3–4

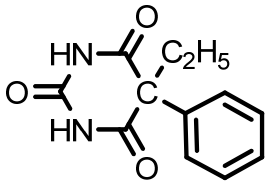
Classification of Barbiturates

- Long acting (6-8 hours).
- Intermediate acting (2-6 hours).
- Short acting (1-2 hours).
- Ultra-Short acting (minutes).

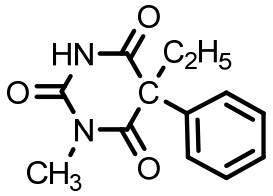
Long Acting Barbiturates



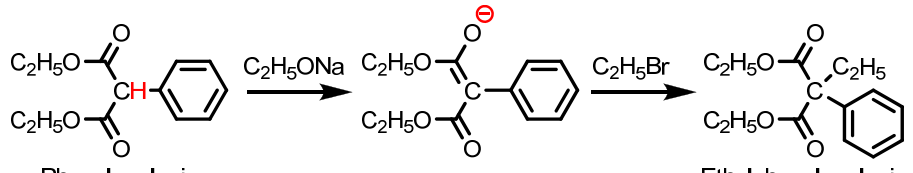
Barbitone

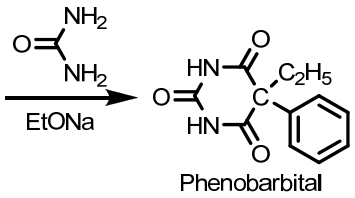


Phenobarbital

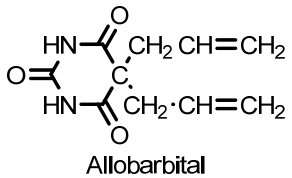


Methylphenobarbital

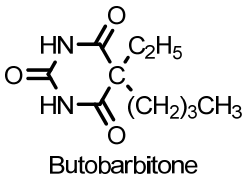




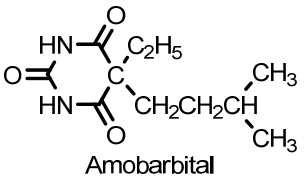
Intermediate Acting Barbiturates



Allobarbital

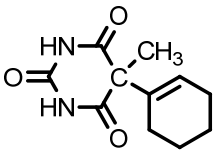


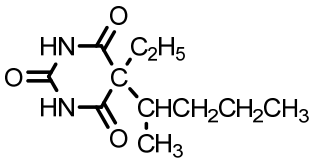
Butobarbitone

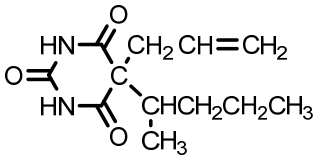


Amobarbital

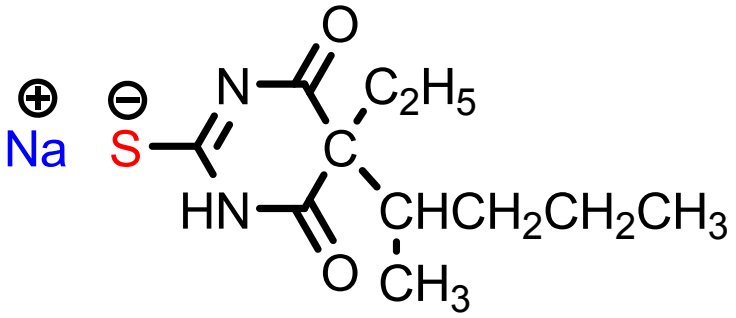
Short Acting Barbiturates


Hexobarbital


Pentobarbital


Secobarbital

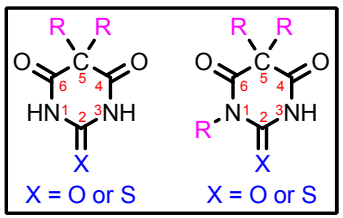
Ultra-Short Acting Barbiturates


Thiopental sodium

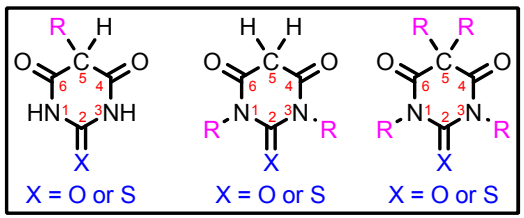
Mechanism of Action of Barbiturates

- GABA is the principal inhibitory neurotransmitter in CNS.
- Barbiturates bind to GABA-A receptors.
- Ligand-gated ion channels (Cl^- influx).
- Decrease excitability (hyperpolarization).
- Barbiturates potentiate the effect of GABA at these receptors (distinct binding site).
- ……

Structure Activity Relationships

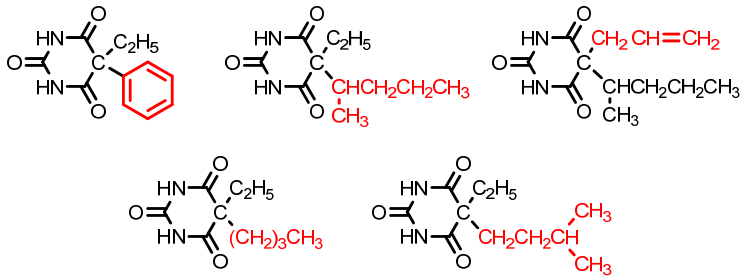


hypnotic, anticonvulsant, or anesthetic activity



not active

Structure Activity Relationships: 5,5-Disubstitution



- Lipophilic groups increase the activity of barbiturates (to certain limit).
- Polar groups decrease the activity of barbiturates.

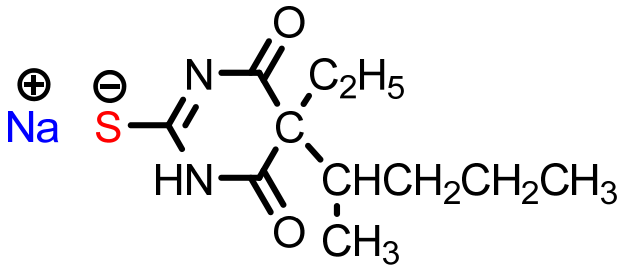
Structure Activity Relationships: Substitution on Nitrogen

R = CH_3, C_2H_5, C_3H_7

not acid

- Monosubstitution increases lipophilicity.
- Disubstitution renders barbiturates inactive.

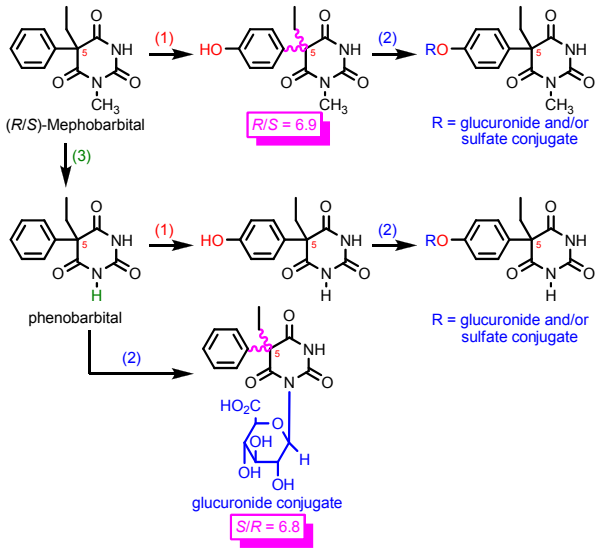
Structure Activity Relationships: Modification of Oxygen



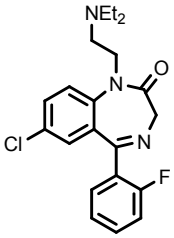
Thiopental sodium

- Replacement of C_2 oxygen by sulfur increases lipid solubility.

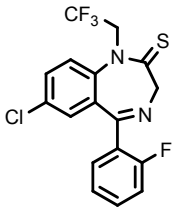
Metabolism of Barbiturates



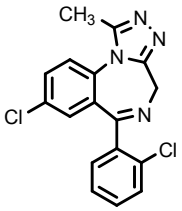
Benzodiazepines



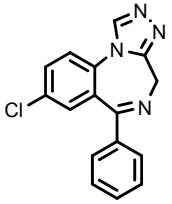
Flurazepam



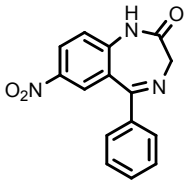
Quazepam



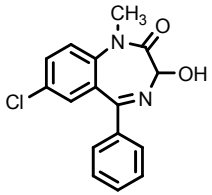
Triazolam



Estazolam

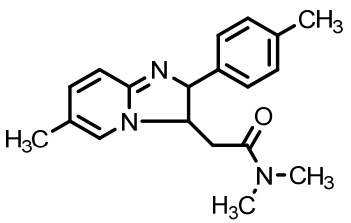


Nitrazepam

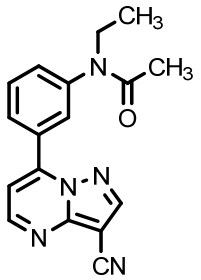


Temazepam

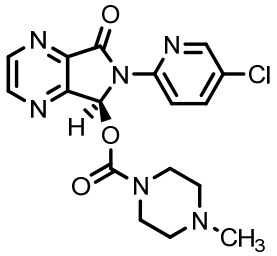
Nonbenzodiazepines (Z compounds)



Zolpidem

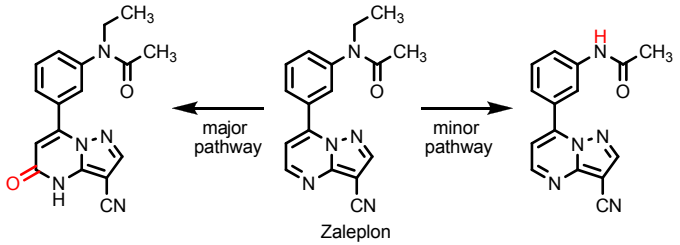


Zaleplon

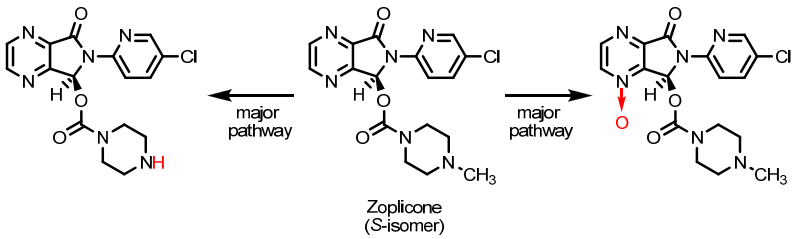


Zoplicone
(*S*-isomer)

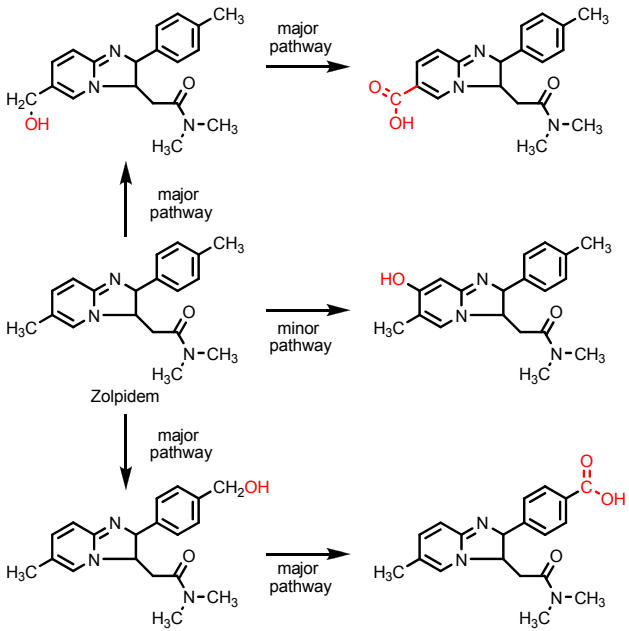
Metabolism of the Z Compounds



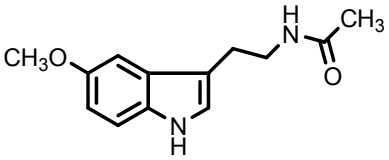
Zaleplon



Zoplicone
(*S*-isomer)



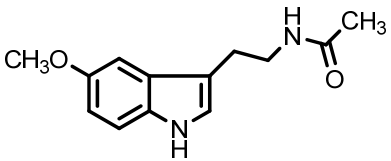
Melatonin Receptor Agonists



Melatonin
N-acetyl-5-methoxytryptamine

- Hormone of darkness.
- Synthesized in the pineal gland.
- Secreted during the night.
- Used to alleviate jet lag.

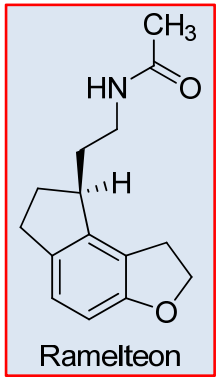
Melatonin Receptor Agonists



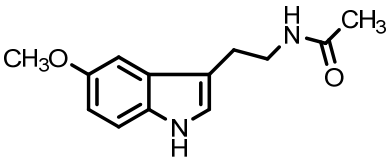
Melatonin
As a lead compound

- Poor absorption.
- Low oral bioavailability.
- Rapid first-pass metabolism to 6-hydroxymelatonin (its primary metabolite).

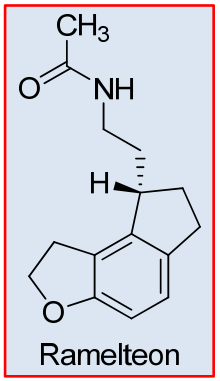
Design of Ramelteon



Ramelteon



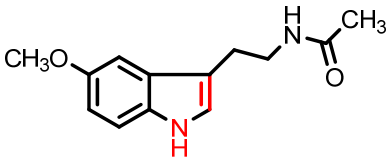
Melatonin
A lead compound for Ramelteon



Ramelteon

- Ramelteon (Rozerem®, FDA approved in 2005) as a very potent and very selective ligand for MT_1 receptor, with superior in vivo activity and safety profile for use in the treatment of insomnia.

Design of Ramelteon (Rozerem®)



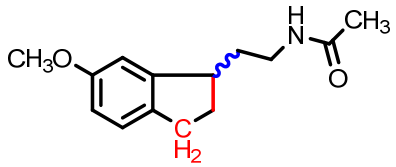
Melatonin
A lead compound for Ramelteon

- Rational Drug Design:

✓ Ligand-Based Drug Design.

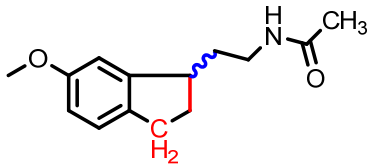
✓ Structure-Based Drug Design.

Design of Ramelteon (Rozerem®)



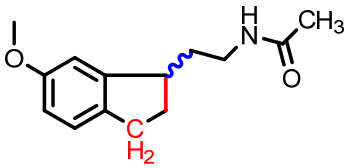
- The indole ring was converted into an indane ring bio-isostere of melatonin.
- 5-Methoxy conformation!!
- Stereochemistry!!

Design of Ramelteon (Rozerem®)



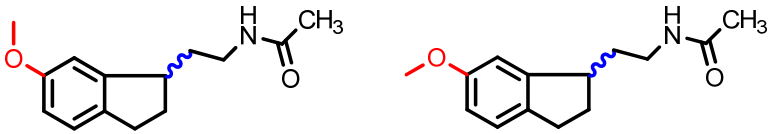
- Conformational flexibility of the 5-methoxy group!!

Design of Ramelteon (Rozerem®)



- Conformational flexibility of the 5-methoxy group!!

Design of Ramelteon (Rozerem®)



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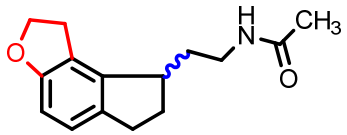
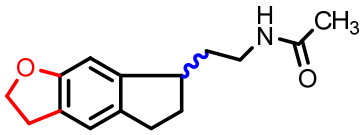
Design of Ramelteon (Rozerem®)

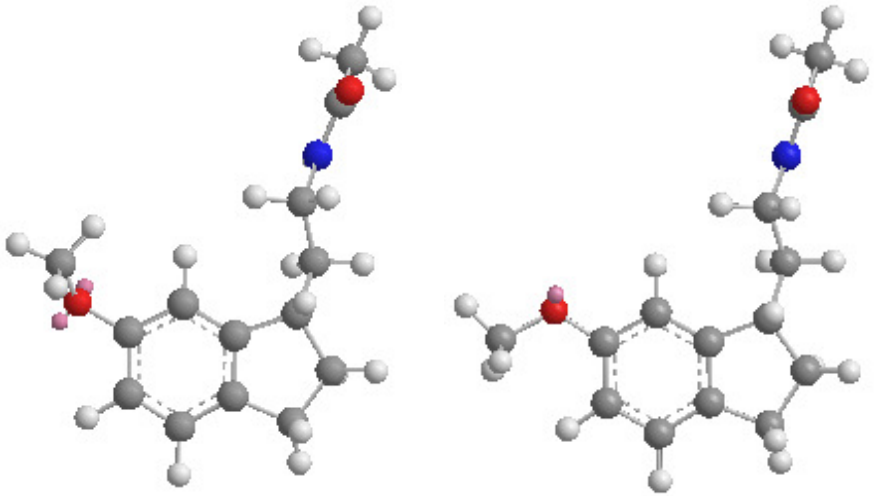


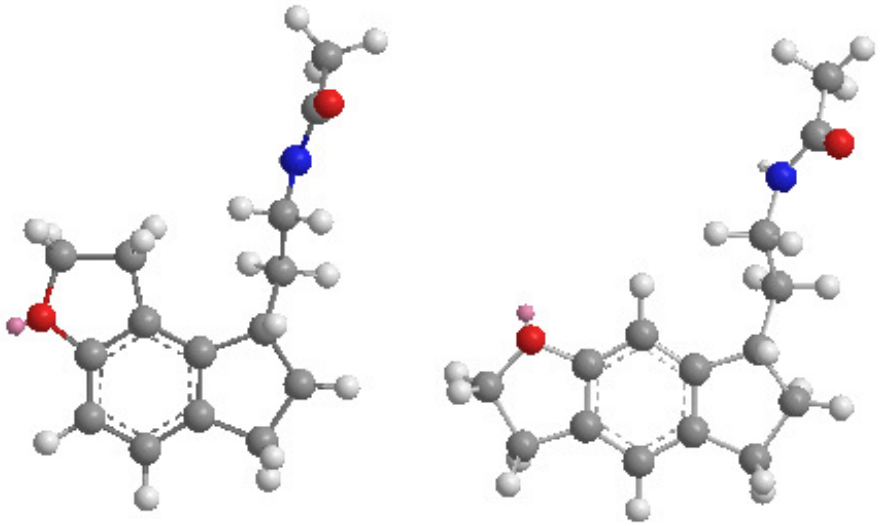
Angular
indeno[5,4-b]furan



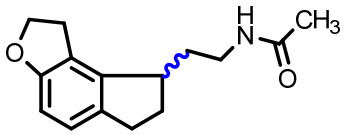
Linear
indeno[5,6-b]furan

- The linear isomer has approximately 15000 fold weaker affinity for the MT_1 receptor than the angular one.
- Binding of nonbonding oxygen pairs to a histidine residue in the receptor (Mol. Mod.).



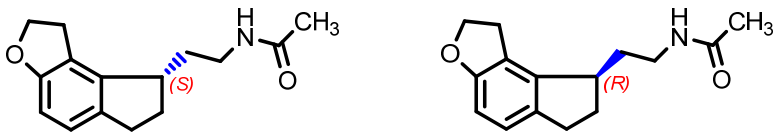


Design of Ramelteon (Rozerem®)



- Stereochemistry!!

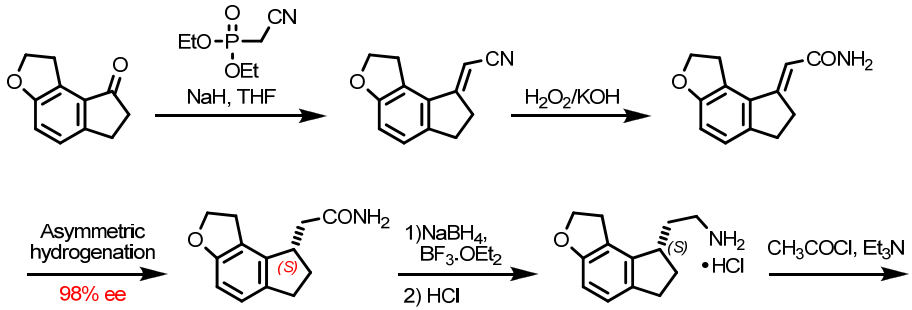
Design of Ramelteon (Rozerem®)

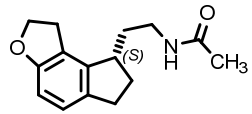


Ramelteon

- The S-enantiomer of indeno[5,4-b]furan showed approximately 500 fold greater affinity than the R-isomer for MT_1 receptor.

Synthesis of (S)-Ramelteon





S-Ramelteon

Yamano, T.; Yamashita, M.; Adachi, M.; Tanaka, M.; Matsumoto, K.; Kawada, M.; Uchikawa, O.; Fukatsu, K.; Ohkawa, S. *Tetrahedron: Asymmetry* **2005**, *17*, 184–190.