Chemistry Project - Eszopiclone

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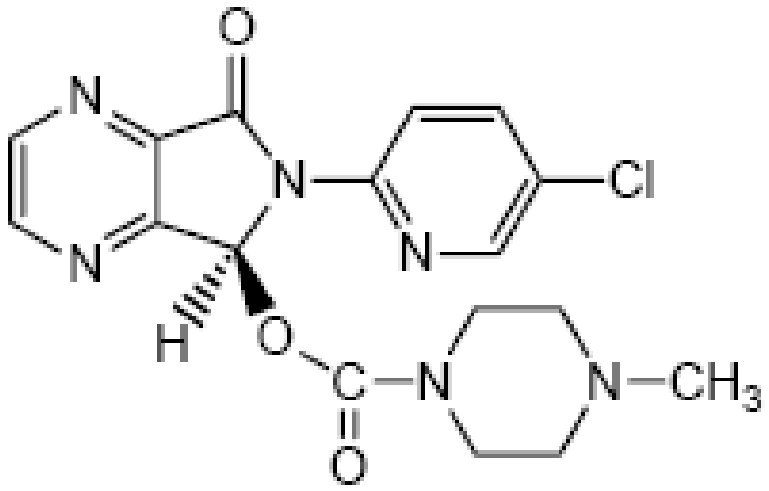
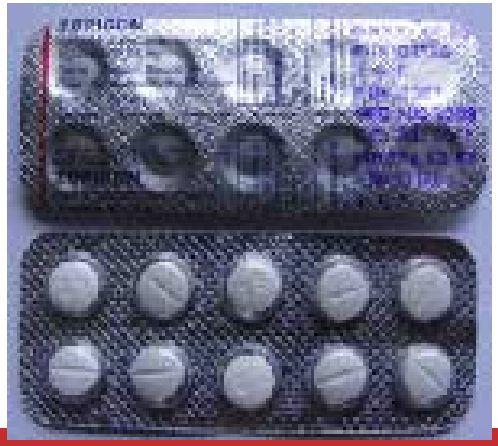
Eszopiclone – sleeping pills





- IUPU name : (+)-(5S)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazin-5-yl 4-methylpiperazine-1- carboxylate.
- empirical formula : C17H17ClN6O3
- molecular weight : 388.81
- half life 6 hours
- white to light-yellow crystalline solid
- slightly soluble in both water and ethanol

Lead Compound discovery

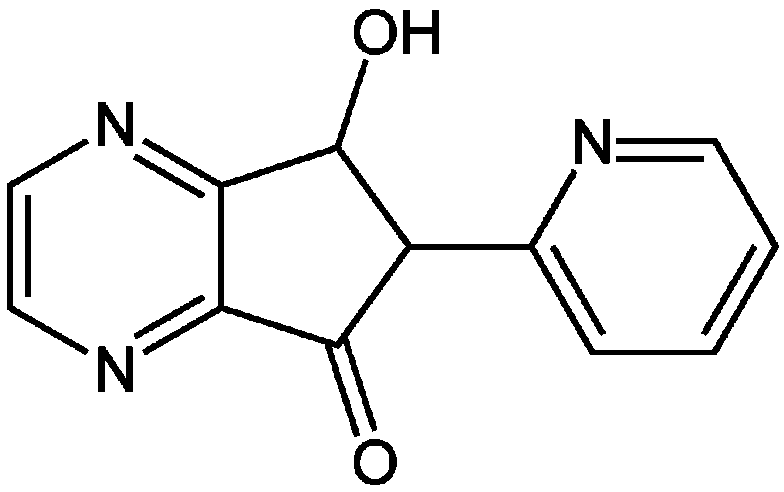
Nonbenzodiazepine

- also called benzodiazepine-like drugs
- a class of psychoactive drugs
- pharmacological actions are similar to those of the benzodiazepines (similar benefits, side effects and risks)
- structurally different to the benzodiazepines

- There are three major chemical classes of nonbenzodiazepines:

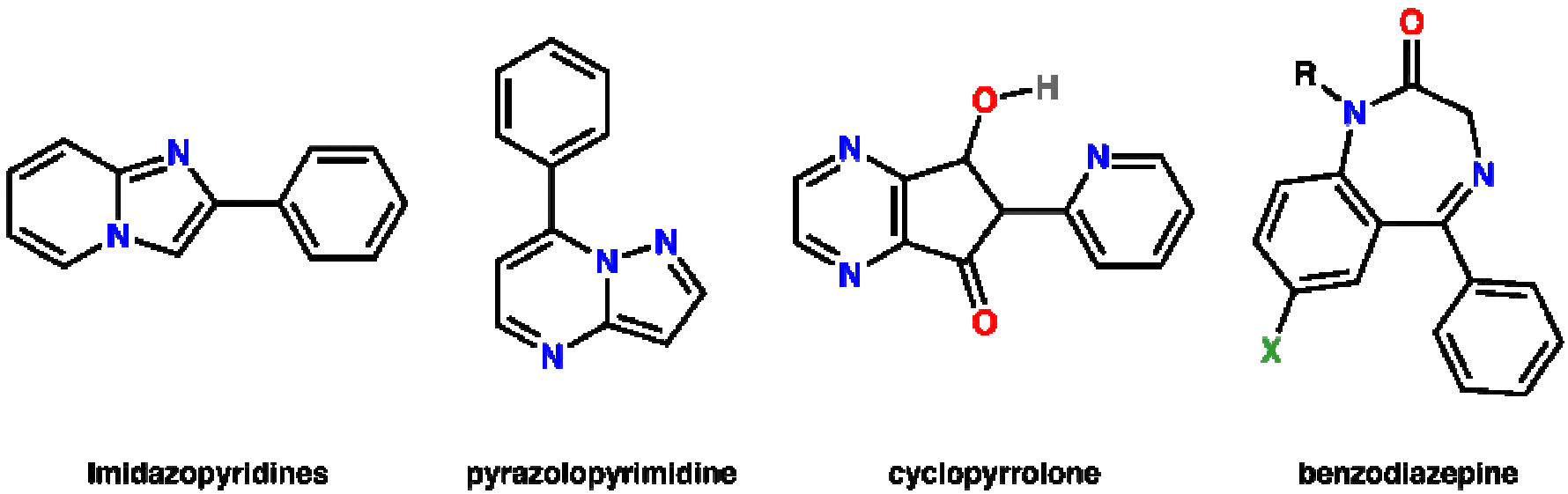
  Imidazopyridines, Pyrazolopyrimidines, Cyclopyrrolones

- Eszopiclone belongs to cyclopyrrolones.



Molecular Modification

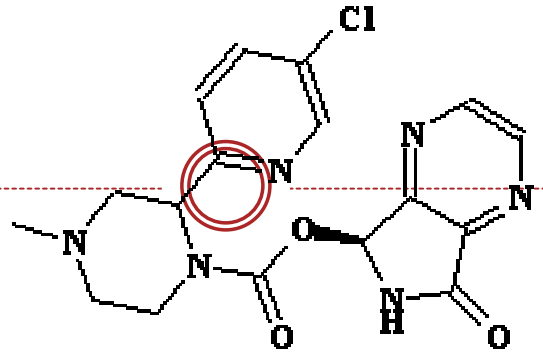
Nonbenzodiazepine



Imidazopyridines | pyrazolopyrimidine | cyclopyrrolone | benzodiazepine

Eszopiclone is under the calss of Cyclopyrrolone.

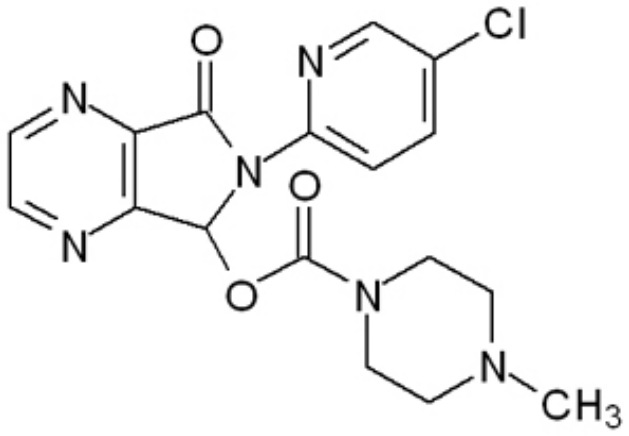
Eszopiclone



$C_{17}H_{17}ClN_6O_3$

systematical name : (S)-6-(5-Chloro-2-pyridinyl)- 7-oxo- 6,7-dihydro- 5H-pyrrolo[3,4-b]pyrazin-5-yl- 4-methyl- 1-piperazinecarboxylate

Molecular formulation of Eszopiclone is modified from Zopiclone,
which is also a member of the class, Cyclopyrrolone.



- Eszopiclone is the S-enantiomer of zopiclone, and is more active and less toxic than the racemic zopiclone.

- The invention relates of eszopiclone to a reproducible process for the preparation of s zopiclone and it's intermediate 6-(5-chloropyridyl-2-yl)-5-hydroxy-7-oxo-5,6 dihydropyrrolo [3,4-b] pyrazine.

- The said invention further relates to effective method for resolution of zopiclone into its enantiomers and furthermore provides a method of recycling of (R)-zopiclone.

Formulation development

Recommended Dosages:

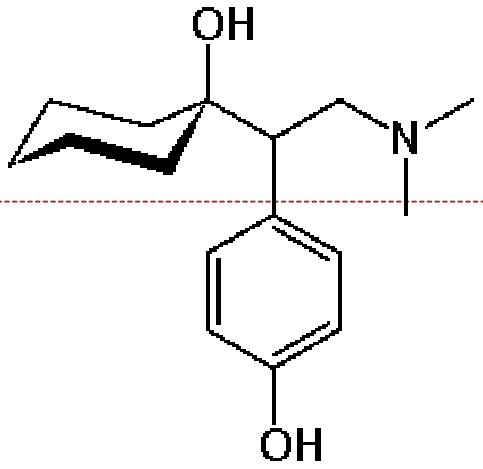
- For treatment to improve sleep onset and/or sleep maintenance :
- 2 mg–3 mg for adult patients (aged 18–64 years)
- 2 mg for older adult patients aged 65 years or older
- 1 mg dose for older adult patients whose problems are related to sleep onset.

- usually in tablet form

pharmaceutically acceptable salt

- refers to salts prepared from non-toxic acids or bases, including inorganic and organic ones.
- Suitable pharmaceutically acceptable acids are used for forming salts with eszopiclone, without limitation.
- E.g. succinate salt, fumarate salt.
- Other optional ingredients combine with active ingredients to insure the stability of the formulation

active metabolite



- O-desmethylvenlafaxine
- 4-[2-dimethylamino-1-(1-hydroxycyclohexyl) ethyl]phenol

- Enantiomers:(-)-O-desmethylvenlafaxine
  (+)-O-desmethylvenlafaxine

- are exist as a racemic mixture, a non-equal mixture of enantiomers of different ratios, or a single enantiomer in different value of e.e.
- e.e. : a number from 0 to 100, zero being racemic and 100 being pure, single enantiomer.

- Based on different formulations for different uses

human trial

First two studies

Target: patients who have primary insomnia
Duration: six-month

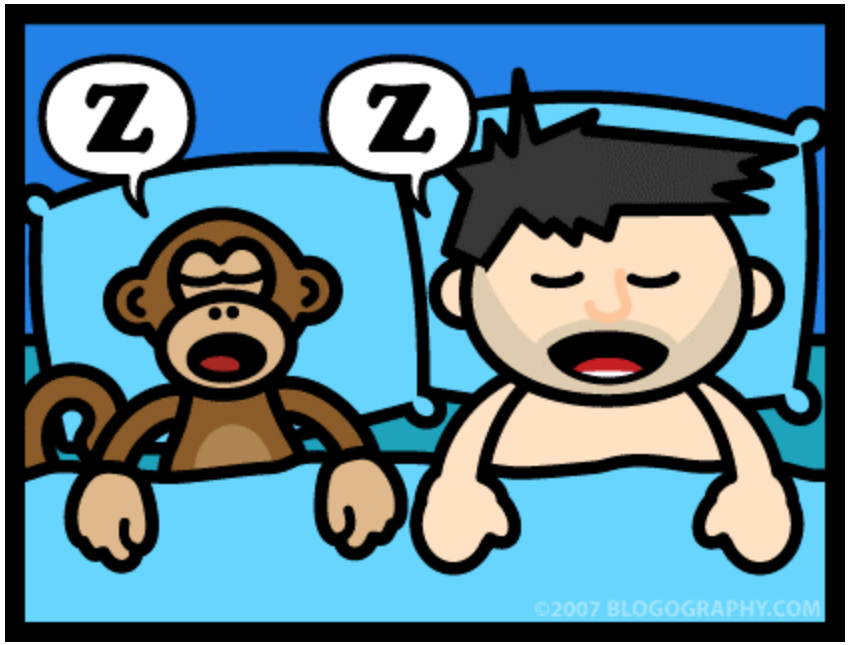
TABLE 1. ESZOPICLONE STUDIES

Study	Intervention	LPS (min)	SE (%)	WASO (min)	TST (min)	NAW
Zammit[10] Mean age: 39.8 yr Caucasian: 66.2% Female: 64.6%	ESZ 2 mg (n=104) ESZ 3 mg (n=105) PL (n=99) 44 nights continuously	15‡ 13.1‡ 29	88.1+ 90.1‡ 85.7	37.1 33.8+ 44.1		6.5 5.7 6
Krystal[9] Mean age: 44 yr Caucasian: 79% Female: 63%	ESZ 3 mg (n=595) PL (n=196) 6 months	30*** 45		21 30 (p=0.0032)	382.5*** 345	1.6*** 2

LPS=latency to persistent sleep; SE=sleep efficiency; WASO=wake time after sleep onset; TST=total sleep time; NAW=number of awakenings/night; ESZ=eszopiclone; PL=Placebo; ***p<0.0001; ‡p≤ 0.001 vs PL; +p<0.01 vs PL; sleep efficiency (ratio of TST: total time in bed of 8 hr x 100)

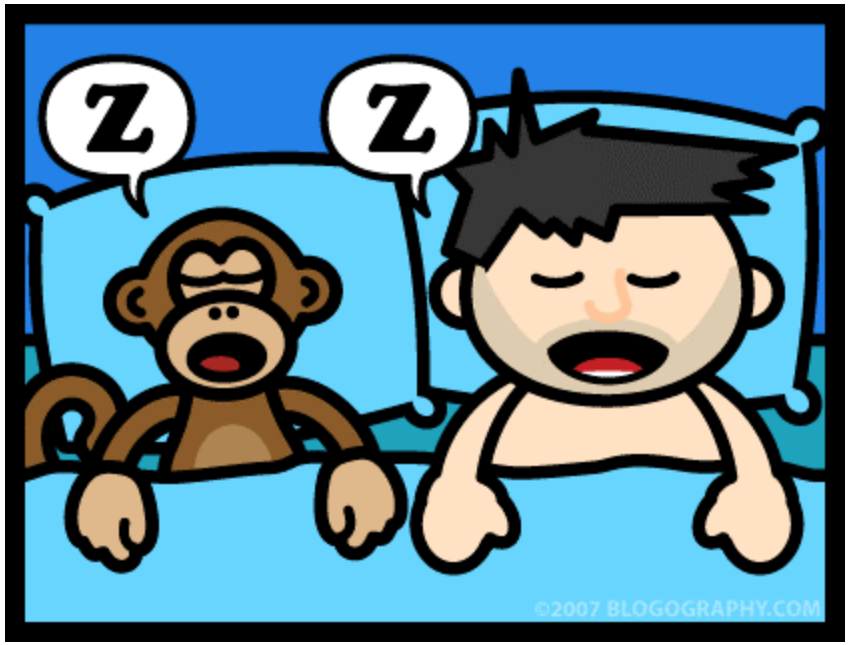
Assessments

- latency to persistent sleep (LPS)
- wake time after persistent sleep (WASO)
- total sleep time (TST)
- number of awakenings (NAW).



Result

- eszopiclone increased slightly but significantly the time in stage two of sleep but the amount of time in the other stages of sleep was not significantly affected.



The third studies

- evaluate the safety and effectiveness of eszopiclone

Target: normal, healthy adults

medication : doses of 1, 2, 3 and 3.5 mg

Result(compare with placebo)

1. sleep was significantly shorter with eszopiclone compared to placebo for all doses.

2. Wake time after sleep onset was also significantly less with eszopiclone compared with placebo.

3. The reduction in number of awakenings was significant with eszopiclone 3 mg and 3.5 mg but not with 1 and 2 mg.

4. Sleep efficiency was improved with eszopiclone

Safety tests -

ADVERSE EVENTS compare with placebo

- evaluate include residual daytime sedation, tolerance and withdrawal syndrome.

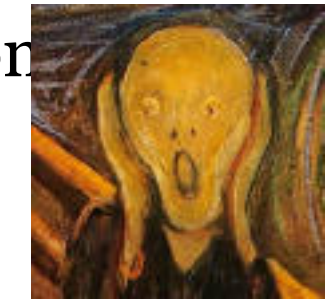
Residual daytime sedation

- daytime ability to function improved

Withdrawal syndrome

mental disorder that follows the use or reduction in intake of a psychoactive substance that had been regularly used

- no reports of withdrawal symptom
- one report of anxiety

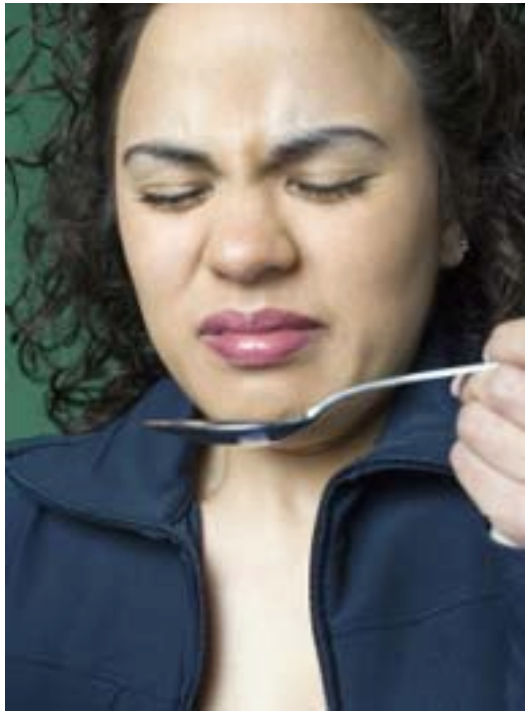


Tolerance

decrease in susceptibility to the effects of a drug due to its continued administration.

- no evidence of tolerance

Other adverse events



unpleasant taste (placebo 3%, eszopiclone 2 mg 16.3%, eszopiclone 3 mg 33.3%). abnormal dreams, nervousness, back pain, dizziness, dry mouth, headache, and somnolence.

Approval for marketing

marketed by Separator under the brand-name Lunesta

- under patent control in the United States.
- available off-patent in a number of European countries as well as Brazil.

Lunesta™
(eszopiclone)c
1, 2 AND 3 MG TABLETS