XXVIII Symposium on Bioinformatics and Computer-Aided Drug Discovery

DEVELOPMENT OF THE "VSAfiR" METHOD AND ITS APPLICATION IN THE DEVELOPMENT OF ANTIEPILEPTICS

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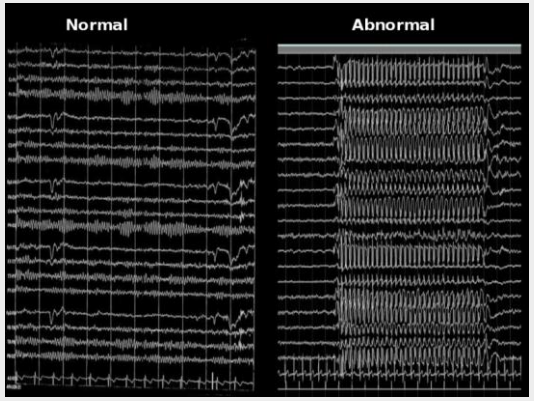
Epilepsy

- Epilepsy is the most common severe non-infectious chronic neurological condition

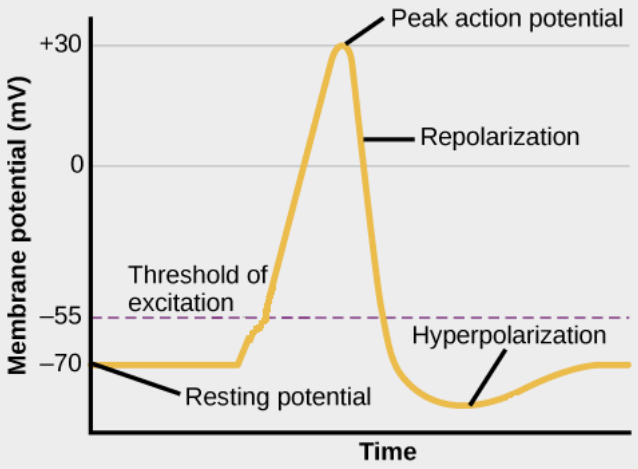


ECG

- Characterized by a set of transient symptoms or signs due to intense and synchronized abnormal neuronal discharge from the brain (seizures)

- This condition affects more than 50 million people around the world, children, youth and adults

Pharmacotherapy



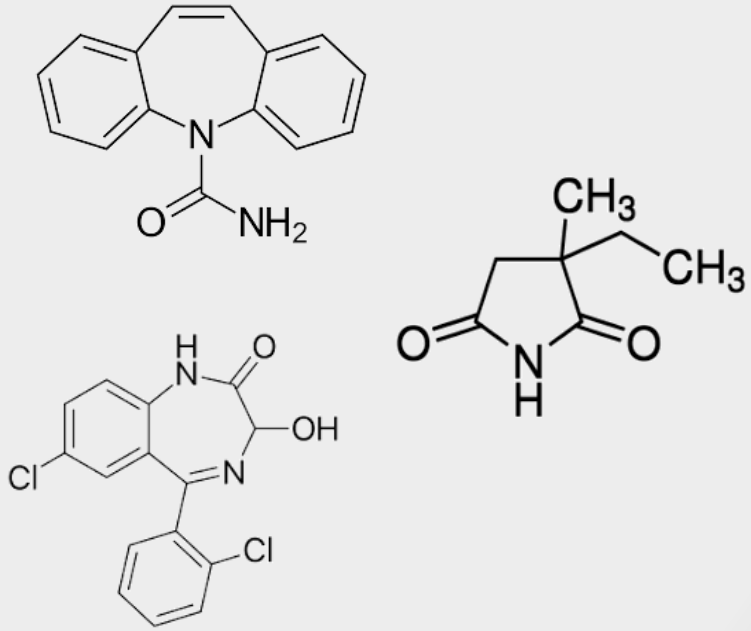
- The treatment of this disease focuses on decreasing the activity of the nervous system

The therapeutic targets for this condition

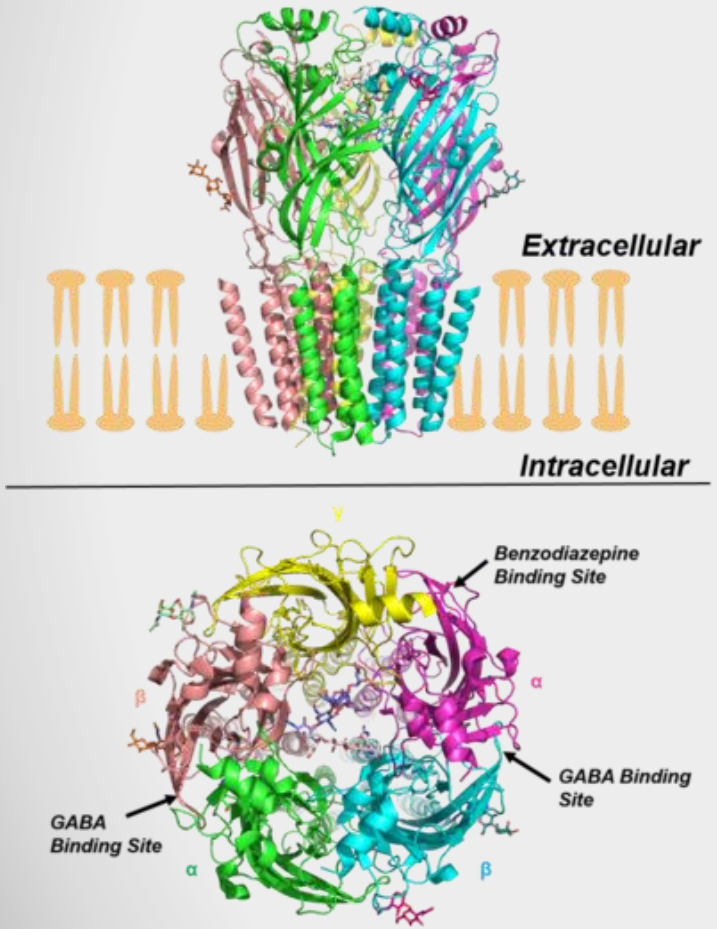
-sodium channels (carbamazepine)

-calcium channels (etosuximide)

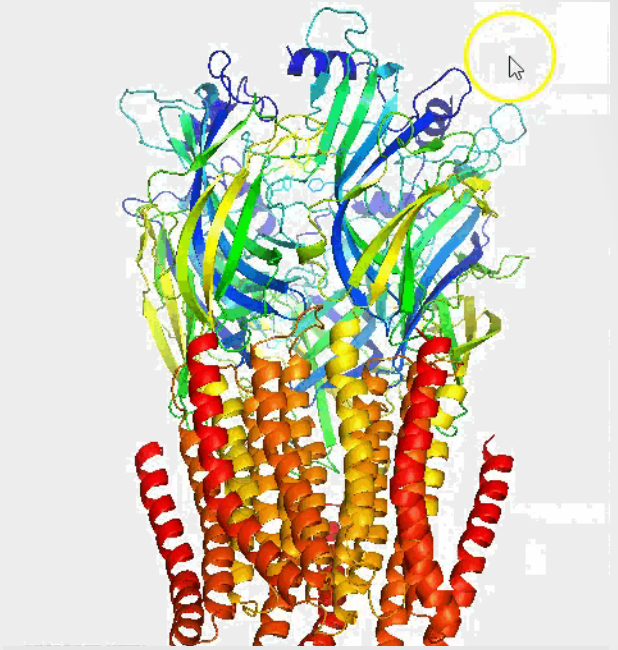
-GABA A receptors (Benzodiacepine)



GABA A Receptor



- It is a pentameric channel to chloride ions
- Its main function is to hyperpolarize the membrane inhibit the action potential



- This channel has several binding sites

GABA, Benzodiazepines and Steroids

Pharmacological tolerance

- It is estimated that between 20-30% of patients do not respond to current treatments
- This tolerance is given by factors such as metabolism, structural changes in the therapeutic target or mutations.
- Therefore, it is necessary to continue looking for therapeutic alternatives for this population.

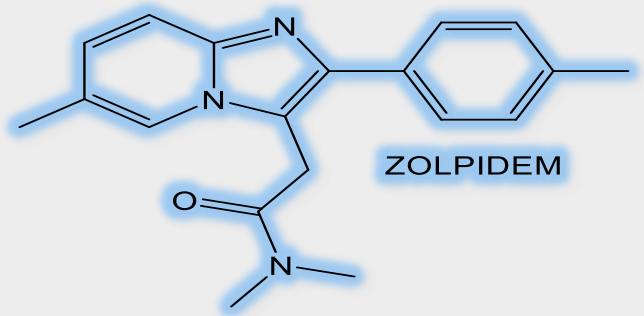
zolpidem as an alternative

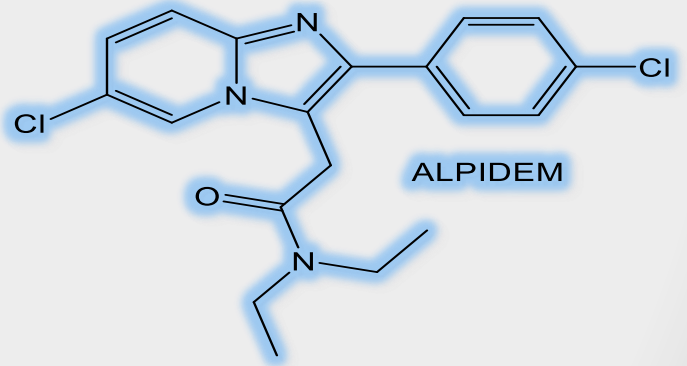
- It is part of the so-called Z drug

- Zolpidem is a heterocyclic drug with GABA A receptor affinity at the benzodiazepine binding site, is used to treat anxiety

- There is evidence, it can be used to treat epilepsy

- The sedative and locomotor effects at the antiepileptic dose do not allow it to be a good option for the treatment of epilepsy.





Objective

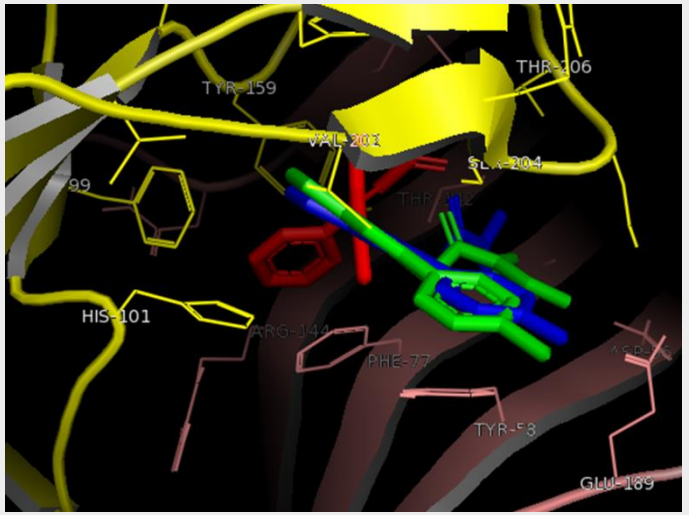
- Obtain antiepileptic compounds analogous to zolpidem.
- Develop a virtual screening methodology to suggest structural changes that allow the rapid generation of molecular alternatives for the treatment and study of epilepsy.

Development

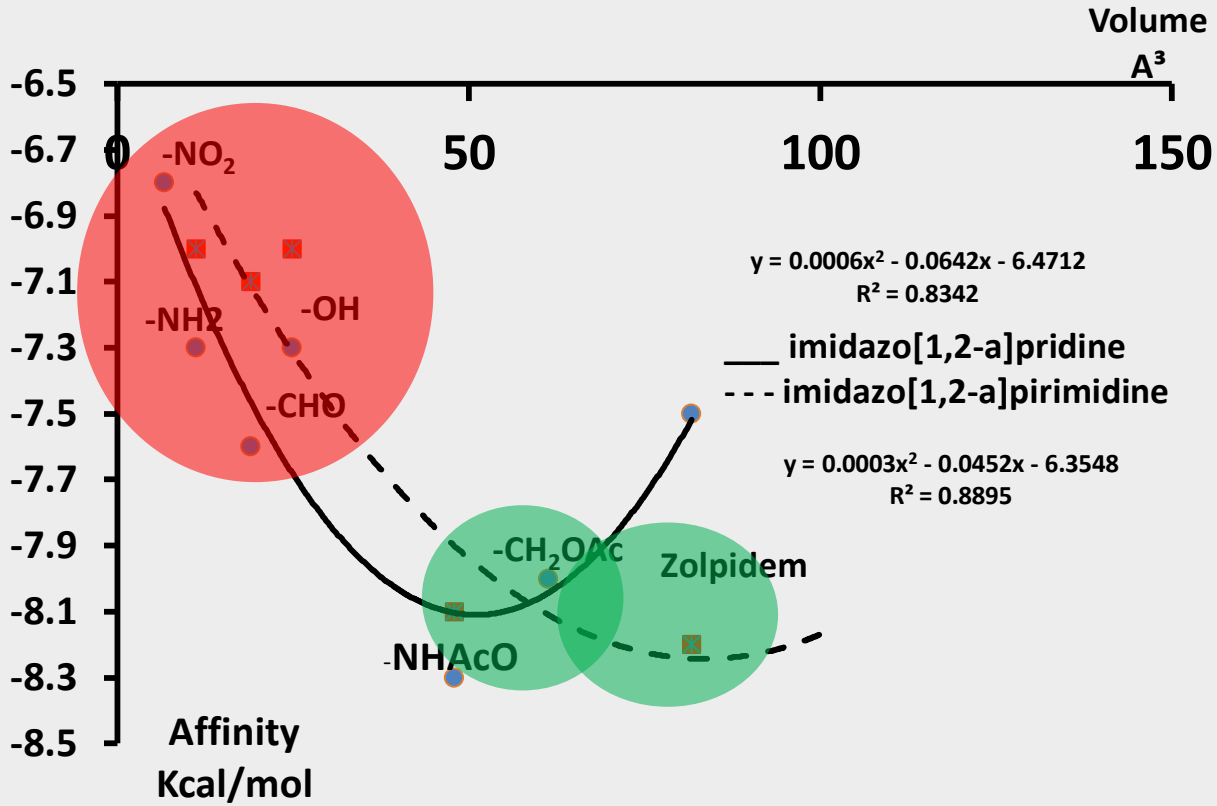
- First take zolpidem and alpidem as hit
- The second step was to suggest structural changes

obtaining 96 candidate molecules

- Third step was perform docking experiments on the reported binding site of the GABA A receptor
- Fourth step tabulate the results and correlate them with some descriptors
- Fifth step plot the average results of each substitution on a graph



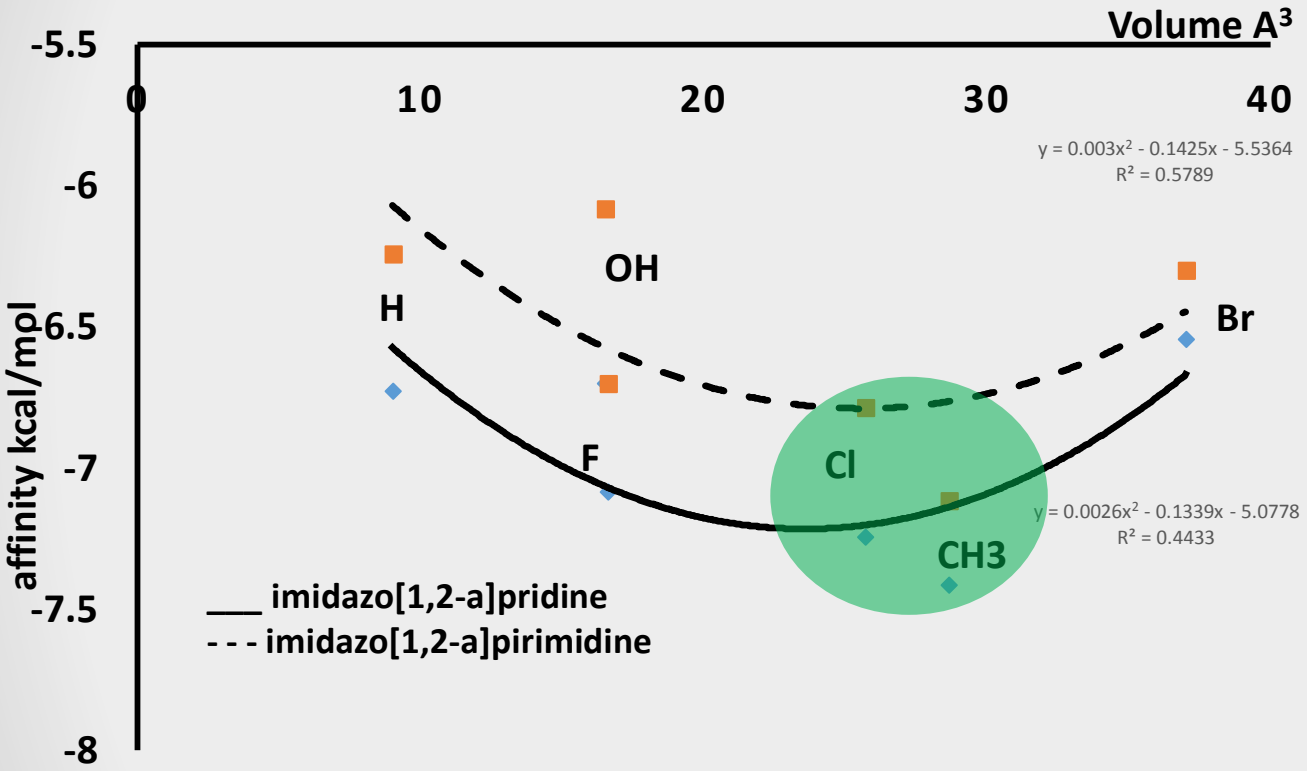
Results substitution in position 3



correlation between volume and affinity of the substituent in position 3

the plot shows that the best substituents are the ester and amide group in position 3

Results substitution in position 7 and para



correlation between volume and affinity of the substituent in 7 and para positions

suggesting that the methyl group and chloride are a good option to carry out the substitution in position 7 and to

Results VSAfiR

- The structural changes suggested by the VSAfiR method to have the best affinity for the GABA A receptor were:

--Amide or ester group in position 3

-Methyl group at 7 and para at the phenyl

- The model suggests that the alcohol and amine groups will have low affinity for the receptor, which could translate into low or no activity.

Synthesis

- To validate the VSAfiR methodology, we carry out synthesis of the target compound.
- Synthesis steps

-Condensation

-Nitrosation or formylation

-Reduction to obtain amine and alcohol groups

-Finally acetylation

Pharmacological and toxicological evaluation

- Anticonvulsant effect (PTZ model, ED_{50})
- Evaluated hypnotic/sedative effect (spontaneous locomotor activity)
- The lethal dose 50 (LD_{50}) was determined

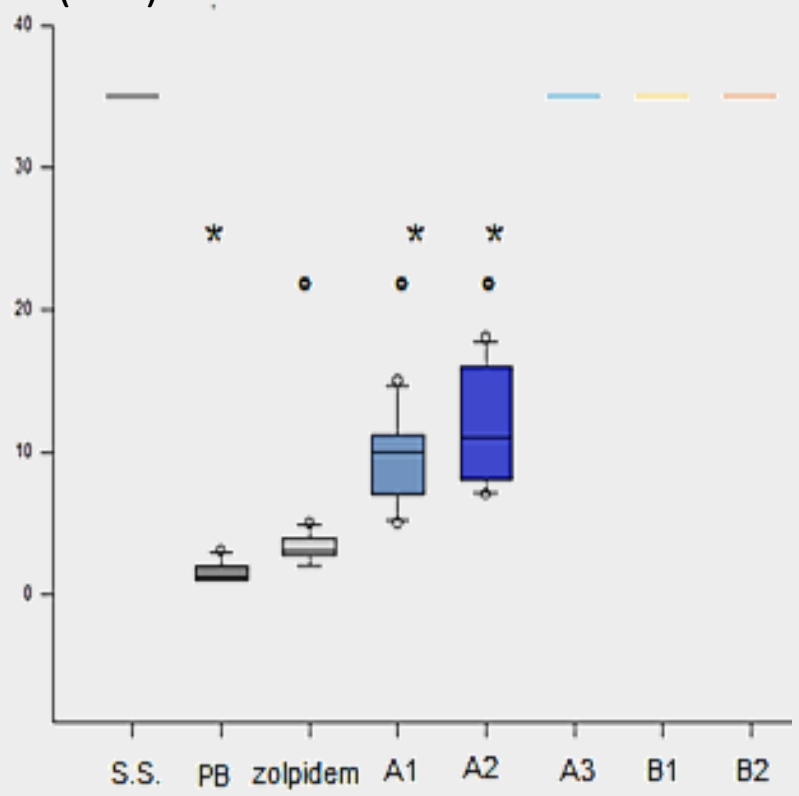
Antiepileptic effect

compound	ED_{50} mg/kg mice	observation
Valproic acid	**159.7**	Fine
Phenobarbital	**12.7**	Muscle relaxant
Zolpidem	**42.81**	Strong sedative
A1	**18.44**	Strong sedative
A2	**18.7**	Strong sedative
A3	**38.32**	hyperactive
B1	**93.91**	Fine
B2	**75.11**	Fine
I1	**NA**	Fine
I2	**NA**	Fine

ED_{50} effective dose, NA inactive

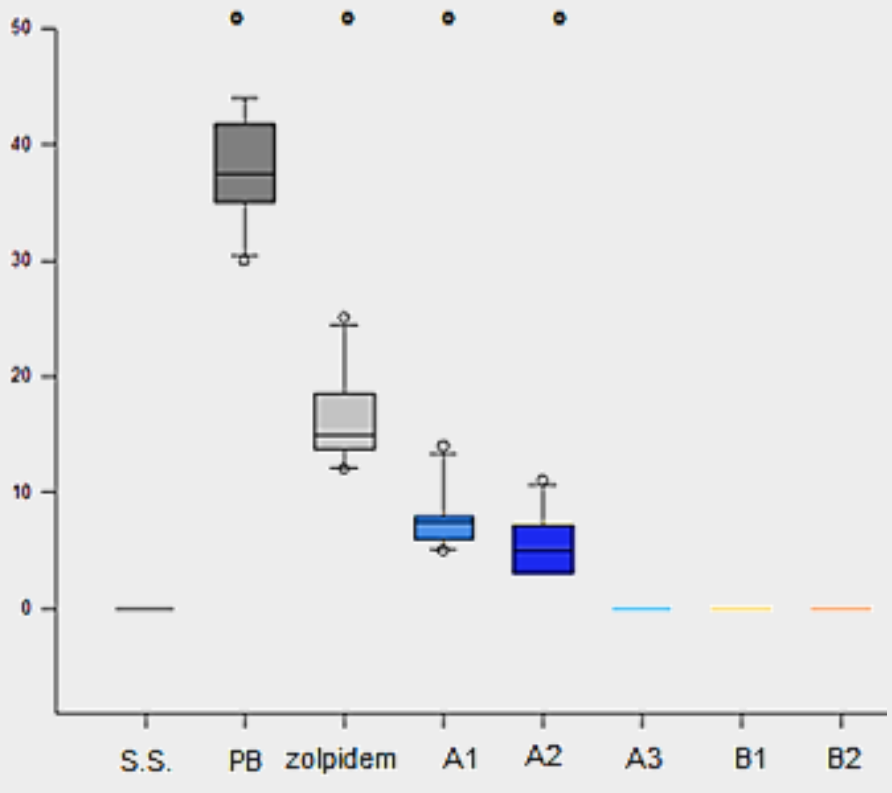
Results hypnotic/sedative effect (ED_{50})

Time (min)



Latency time in appearing alterations in spontaneous locomotor activity.

Time (min)



Duration of the alteration in spontaneous locomotor activity.

Results (toxicity lethal dose)

compound	ED_{50} mg/kg mice	LD_{50} mg/kg mice	IT
A1	18.44	122.4	6.63
A2	18.7	48.9	2.61
A3	38.32	223.6	5.83
B1	93.91	>500	5.32
B2	75.11	424	5.64
zolpidem	42.81	695	16.23

ED effective dose, LD lethal dose, IT therapeutic index

Outlook

- Perform optimization of antiepileptic activity
- Optimize therapeutic index
- Evaluate molecules in models of epileptic tolerance

conclusions

- The implemented VSAfiR methodology is simple, fast and economical
- The VSAfiR methodology was able to suggest the structural changes that would have better and worse results when evaluated in in vivo models.
- Antiepileptic compounds without sedative effects were obtained
- Imidazo[1,2-a]azines are an alternative for the development of new antiepileptic entities

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