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Drug repurposing of HNMT inhibitors and their evaluation in a scopolamine-induced amnesia model

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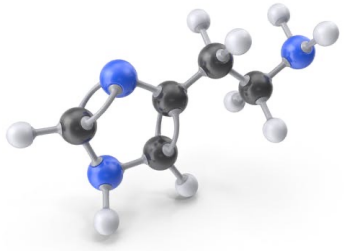
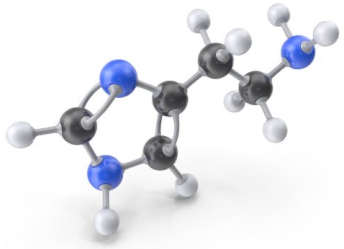


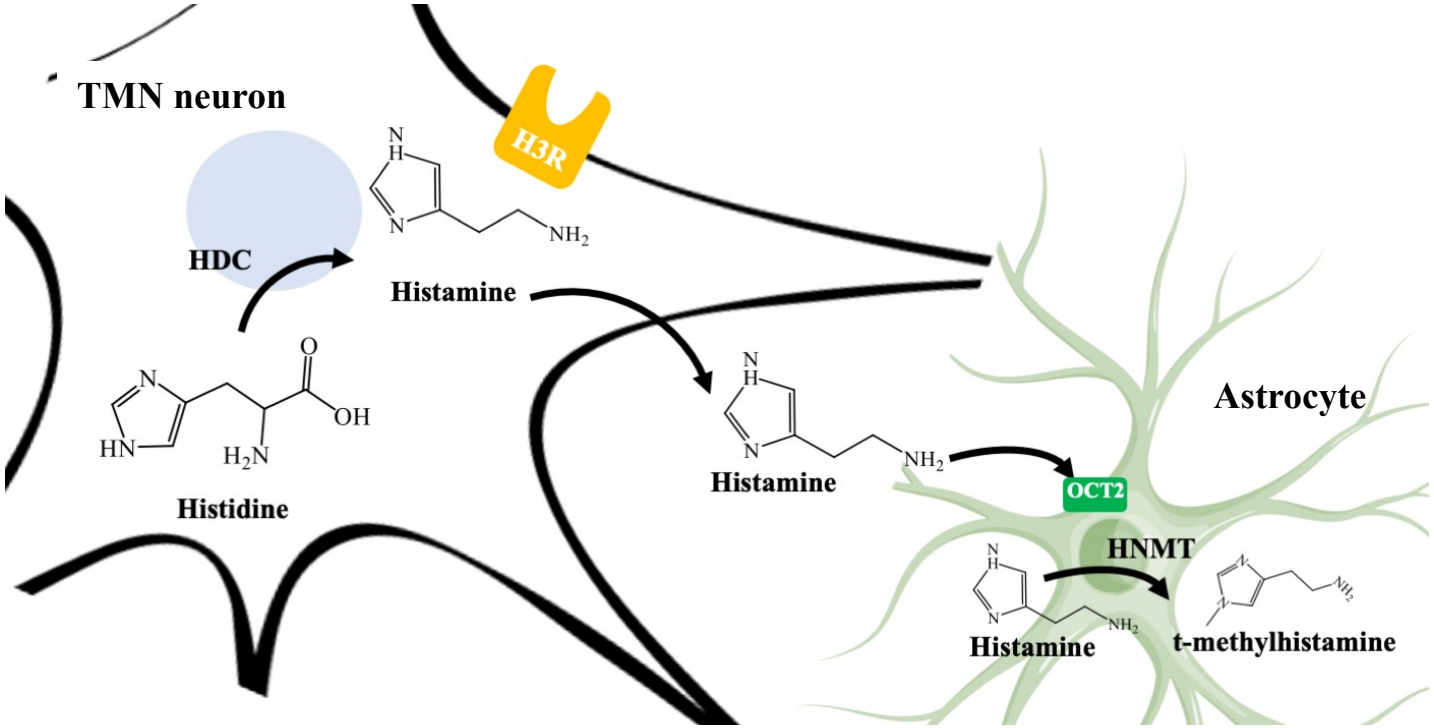
Histamine in the brain

- Histamine is involved in many essential physiological processes such as the regulation of the sleep-wake cycle, learning, memory, stress responses, etc.
- Lower activity of the histaminergic system has been associated with neurological disorders
  - Alzheimer´s disease
  - Narcolepsy
  - Tourette's syndrome
  - Depression

Kárpáti A, et al., 2019.
Panula P, et al., 2013.



Histaminergyc system in the brain



H1R

- Neuronal Excitability
- Cell Survival
- Modulation of Inflammatory Response

H2R

- Neuronal Plasticity
- Neuronal Excitability

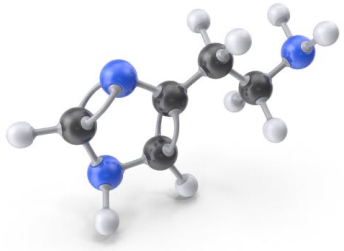
H3R

- Neuronal Excitability
- Neurotransmitter Release
- Cognition

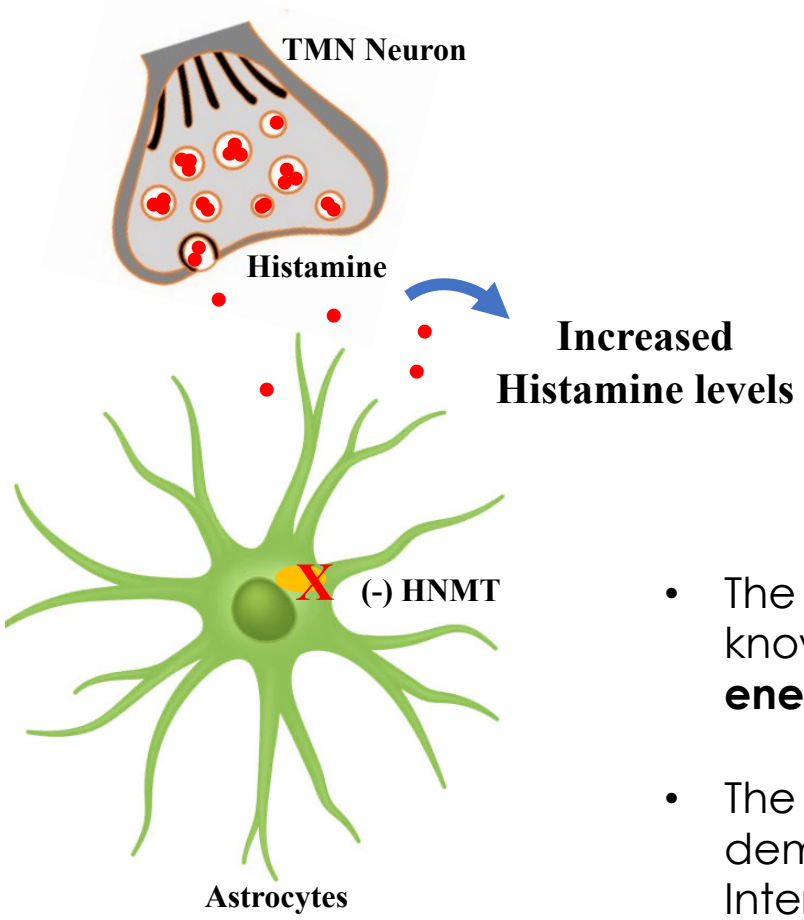
H4R

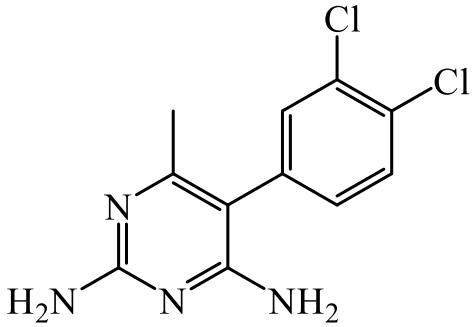
- Inflammatory Response

Flores-Clemente C et al, 2021.



Increasing histamine levels by HNMT inhibition



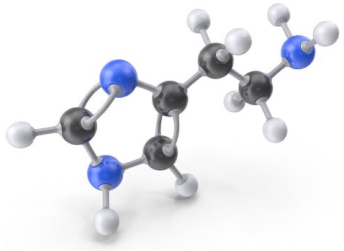


Metoprine
IC_{50} = 100 nM

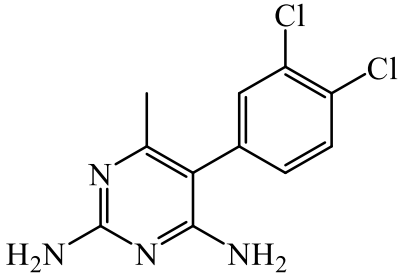
Metoprine administered at 10 mg/kg to Wistar rats can increase histamine brain levels, being the highest 5 hr after administration.

- The biological effects of increasing histamine levels in the brain have been known by employing metoprine, such as **antinociception**, **suppression of energy intake**, **improvement of cognitive function**, etc.
- The beneficial effects in cognitive performance by metoprine have been demonstrated in a mouse model of amnesia induced by scopolamine. Interestingly this beneficial effect was reverted by a blockade of H1R.

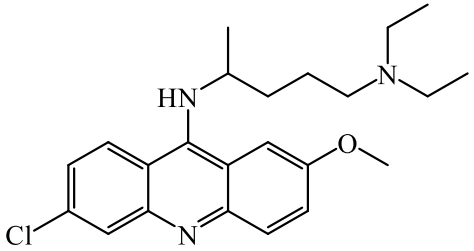
Malmberg-Aiello P, et al., 2000



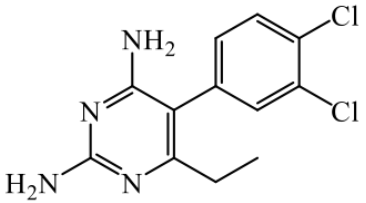
HNMT inhibitors



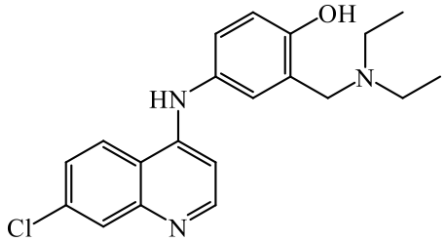
Metoprine
IC_{50}=100 nM



Quinacrine
IC_{50}=400 nM



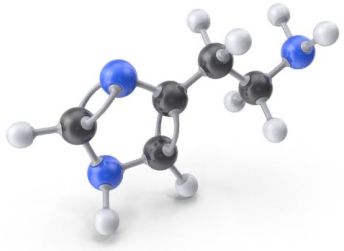
Etoprine
IC_{50}=760 nM



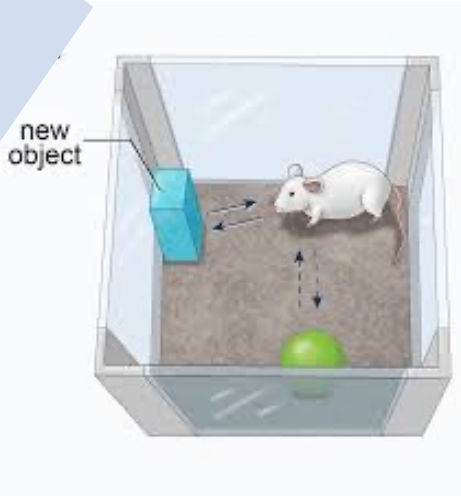
Amodiaquine
IC_{50}= 400 nM

A small number of molecules have been identified as HNMT inhibitors. Furthermore, only a few of them have been studied due to their poor penetration into the blood-brain barrier or due to their toxic effects.

Flores-Clemente C et al, 2021.



Repurposing HNMT inhibitors



DISCOVERY studio

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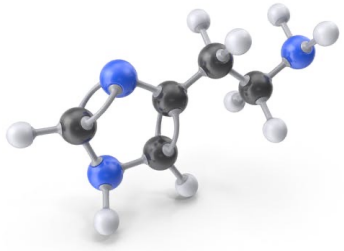
Docking studies and Molecular Dinamics simulations

HNMT inhibition assay

Brain histamine levels

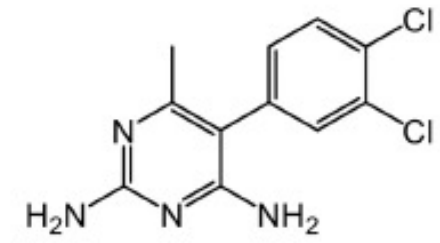
Effects in memory



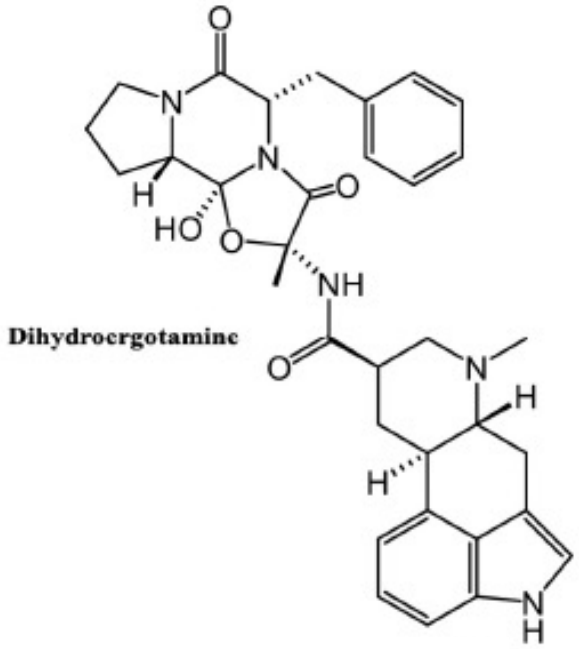
Virtual Screening of Compound against HNMT

Table 1. FDA-approved drugs with the lowest Gibbs free energy (ΔG)

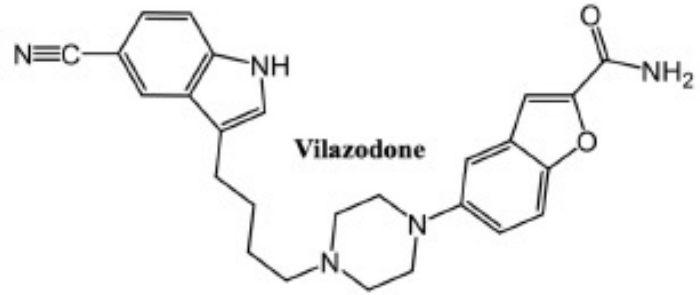
ΔG (kcal/mol)	Drug
−13.41	Dihydroergotamine
−12.86	Vilazodone
−9.08	Metoprine



Metoprine

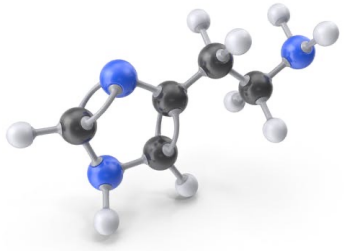


Dihydroergotamine



Vilazodone

Figure 1. Structure of selected compounds

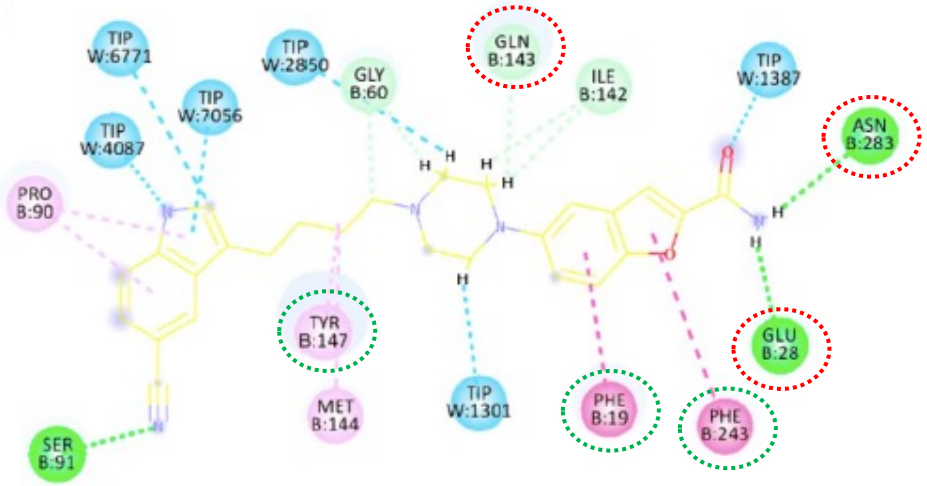


Evaluation of Interactions with the Histamine-Binding Site of HNMT by MD Simulations

Table 2. Theoretical free energy of binding to the HNMT enzyme of dihydroergotamine, vilazodone, and metoprine obtained by MD simulations.

Complex	ΔG_{bind} [kcal/mol]
Dihydroergotamine	−55.45
Vilazodone	−89.42
Metoprine	−98.61

HNMT-vilazodone complex



HNMT-dihydroergotamine complex

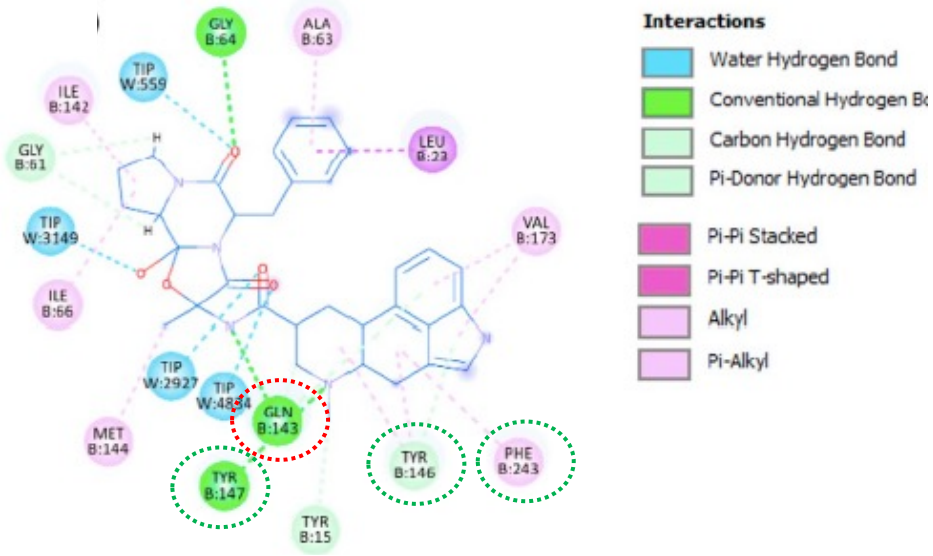
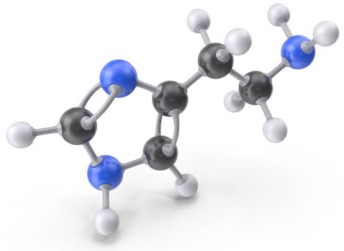


Figure 2. Interactions of the selected compounds with HNMT were obtained by 50 ns of MD simulations. A)Vilazodone–HNMT complex; non-bonding interactions B) Dihydroergotamine–HNMT complex; and non-bonding interactions.



HNMT inhibition assay and brain histamine levels

Table 3. Inhibition of HNMT

Compound	IC_{50}
Metoprine	66 nM
Vilazodone	45.01 µM
Dihydroergotamine	72.89 µM

Mera Jimenéz E, et al, 2023.

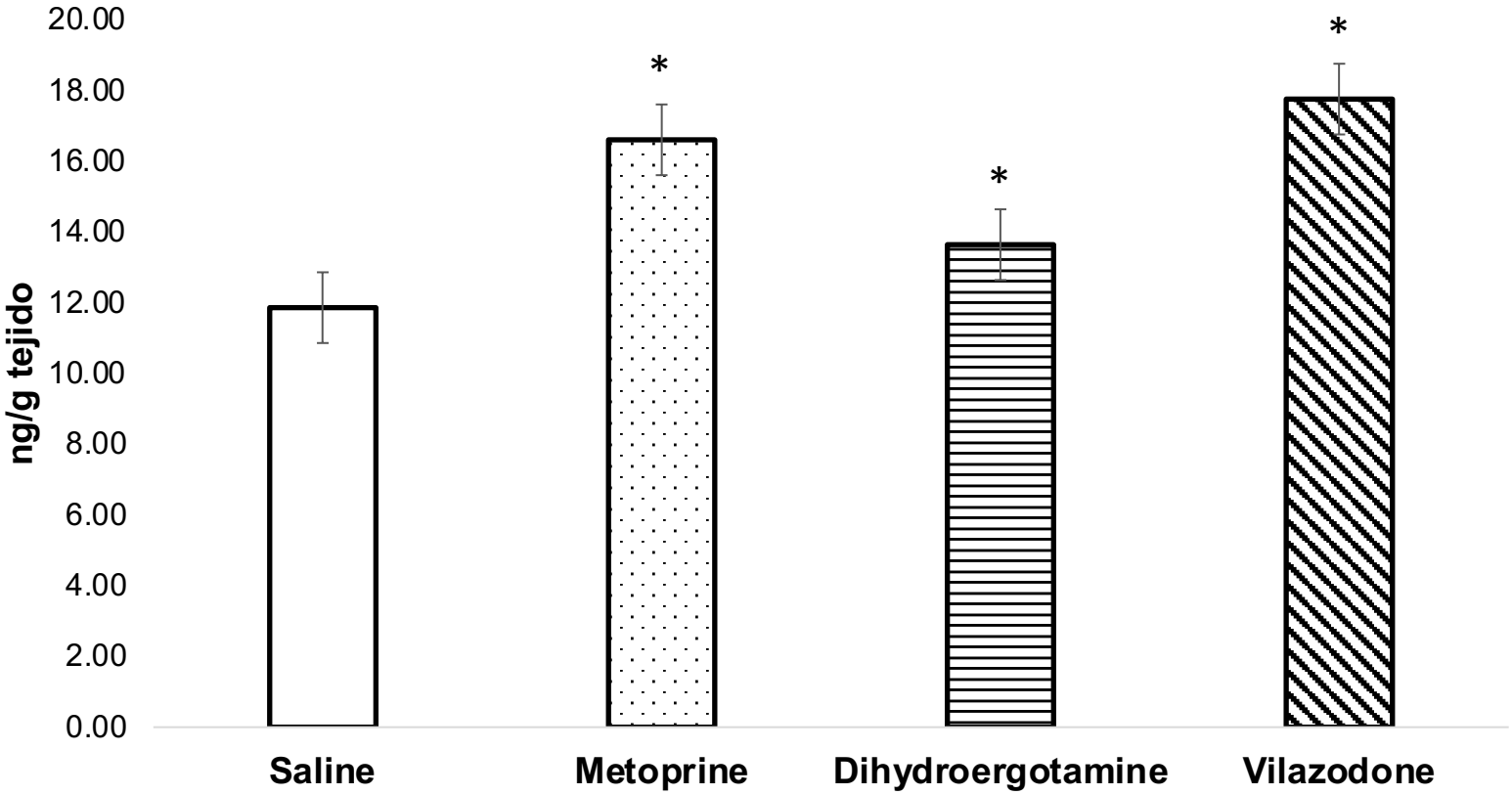


Figure 3. Histamine levels in the hippocampus of Wistar rats treated with, dihydroergotamine and vilazodone. Rats were administered intraperitoneally with saline solution (2 ml/Kg), metoprine (10 mg/Kg), dihydroergotamine (1 mg/Kg) and vilazodone (4 mg/Kg). After 3 hours, rats were sacrificed, and the histamine brain levels were determined employing a colorimetric competitive-ELISA kit. The concentration of histamine in the samples is then determined by comparing the O.D. at 450 nm with the standard curve. Data are expressed as Mean ± SEM, n = 3 and statistical analysis by one-way ANOVA *P < 0.05.

Effects in memory

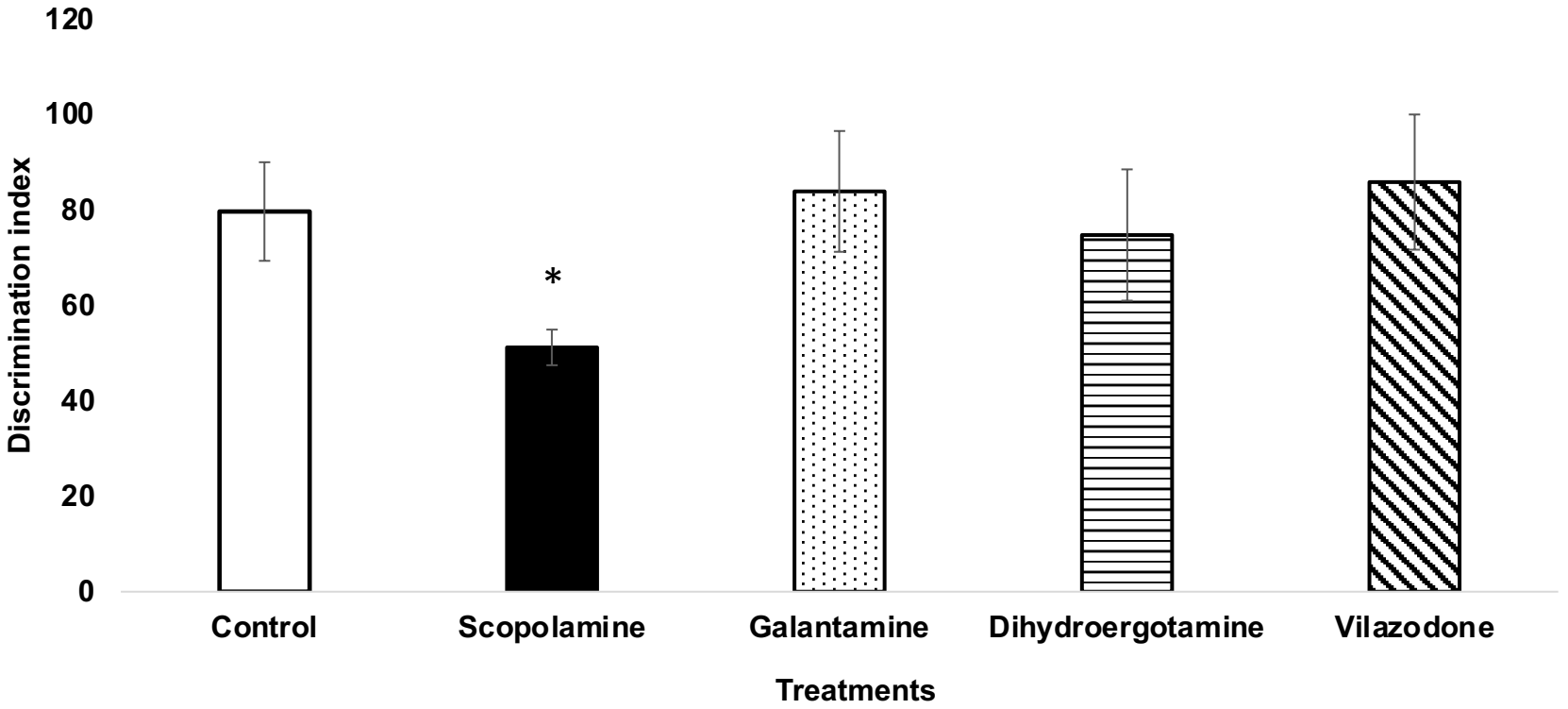
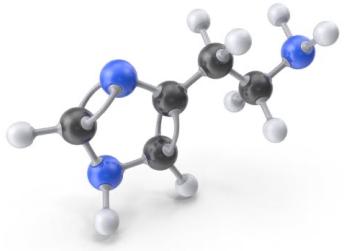
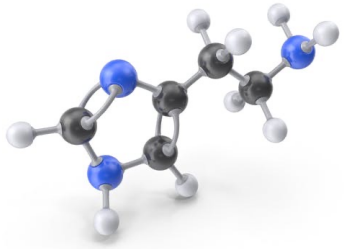


Figure 4. Effects of dihydroergotamine and vilazodone on behavioral analysis for NOR in a scopolamine-induced amnesia model. In trials separated by 180 min, the discrimination index is similar for all the groups, except for scopolamine, which showed a decrease in the percentage of recognition index. Data are expressed as Mean ± SEM, n = 5 and statistical analysis by one-way ANOVA *P < 0.05.



Conclusion

- Drug repurposing of HNMT was achieved by employing computational studies.
- HNMT inhibitory effect of vilazodone and dihydroergotamine by in vitro assay was demonstrated.
- Vilazodone and dihydroergotamine increases histamine brain levels and improve memory in the NOR paradigm in the scopolamine-induced amnesia model.



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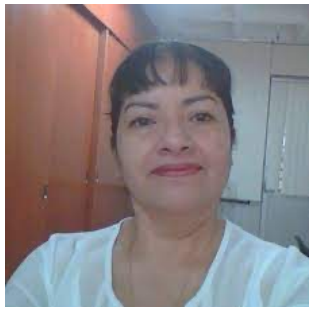

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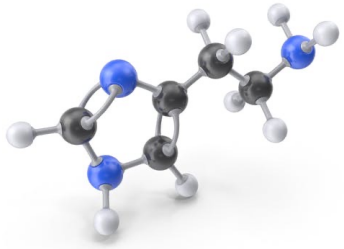

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