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Interaction between pimethixene and human serum albumin

Chaired by DR. ALFREDO BERZAL-HERRANZ;
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pharmaceuticals MDPI

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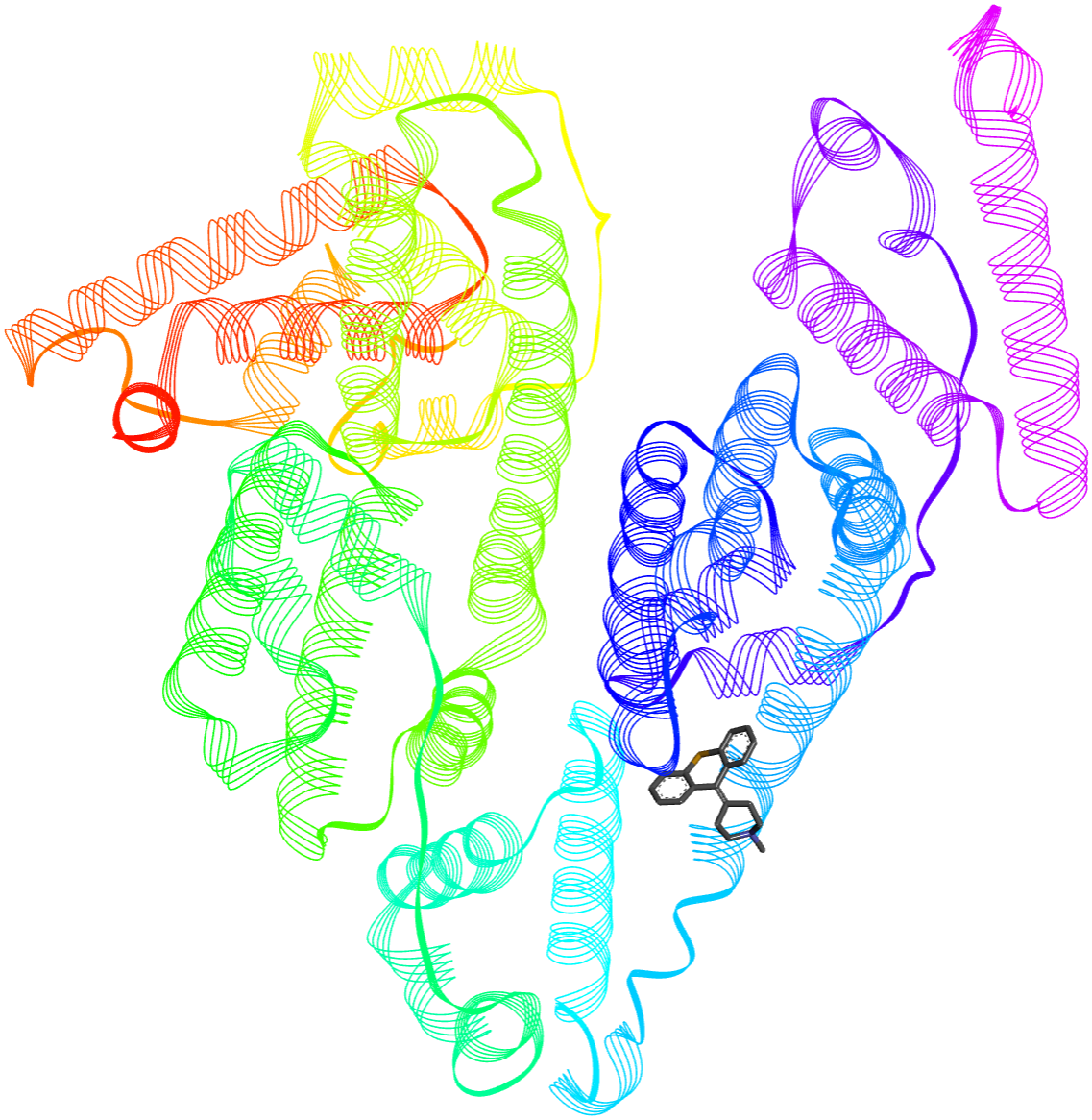

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Abstract

Albumin, is the highly abundant protein in the plasma. The main function of protein is delivery various endogenous (fatty acid, vitamins, hormones) and exogenous compounds such as drugs.[1,2] Further, humen serum albumin has a very important role in distribution, free concentration and effectiveness of these compounds.

Pimethixene belongs to the group of antihistamines characterized by sedative and antitussive properties. It has shown remarkable ability to bind to receptors such as serotonin 5-HT2A and 2B, histamine H1 and muscarinic acetylcholine M2.[3] Moreover, oral pimethixene is used to calm dry and irritating coughs in children. However, binding constants of pimetixene for human serum albumin, as the most abundant serum transport protein, have not been determined so far.

Accordingly, in the current study explored the interactions between pimethixene and human serum albumin (HSA) by the spectroscopic measurements (fluorescence spectroscopy and circular dichroism) and molecular docking method.

Keywords: Pimethixene; Human serum albumin; Fluorescence; Circular dichroism

References

[1] J.X. He, D.C. Carter, Nature 358 (1992) 209-215.
[2] D. Carter, J.X. Ho, Adv. Protein Chem. 45 (1994) 153-203.
[3] B. Schmitz, C. Ullmer, D. Segelcke, M. Gwarek, X.R. Zhu, H. Lübbert, European Journal of Pharmacology 751 (2015) 73–80.

Introduction

- Human serum albumin (HSA) is the most abundant protein in the extracellular fluid and constitutes approximately 60% of the mass of all proteins present in plasma.[4]
- The most important roles of HSA are maintenance of colloid-osmotic pressure and transport of endogenous (bilirubin, fatty acids, hormones) and exogenous ligands (warfarin, ibuprofen).
- HSA has an antioxidant effect so that it protects the drug from oxidation and also affects the pharmacokinetic and pharmacodynamic properties of the drug.[5]

[4] Rimac H, Bojić M., Farmaceutski glasnik 73 (2017) 793–808.
[5]Ha CE, Bhagavan NV., Biochim Biophys Acta, 1830(12) (2013) 5486-93.

Introduction

- Pimethixene (PMT) is a very potent first-generation antihistaminic. According to its chemical structure, it belongs to the group of organic compounds known as thioxanthenes[6].
- PMT is an antihistamine that is intended for systemic use and is administered orally in the treatment of dry cough in children older than 2 years.
- The mechanism of action is based on binding to histamine H1 receptors, to serotonin 5-HT2A and 5-HT2B receptors, as well as to muscarinic M2 receptors.

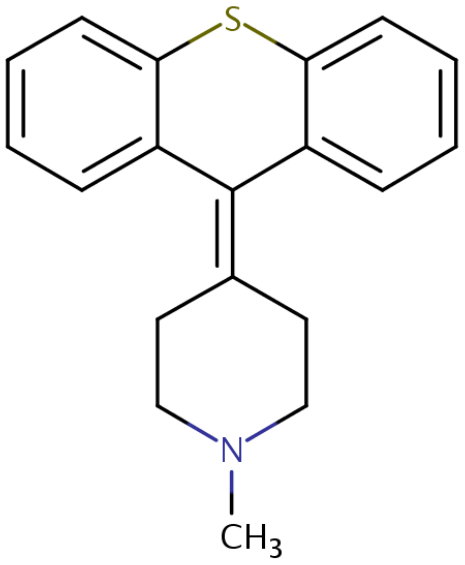


Figure 1. Pimethixene (PMT)[45]

Reference

[6] Pimethixene. https://go.drugbank.com/drugs/DB13292.

Results and discussion

Fluorescence quenching measurements

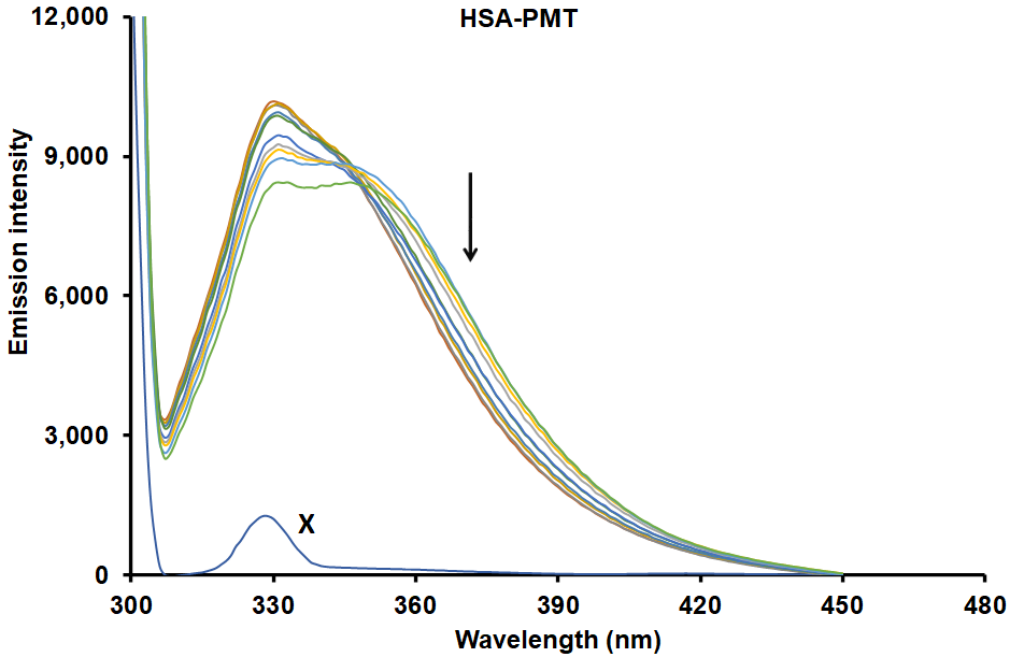


Figure 2. Fluorescence emission spectra of HSA in the presence of PMT(T = 298 K, pH = 7.4). [HSA] = 1.6 µM and [LZD] = 0-32 µM. X represents 1.6 µM buffer only.

Results and discussion

According to the Stern-Volmer equation and by the double logarithm equation, K_{SV} and K_a were determined[5].

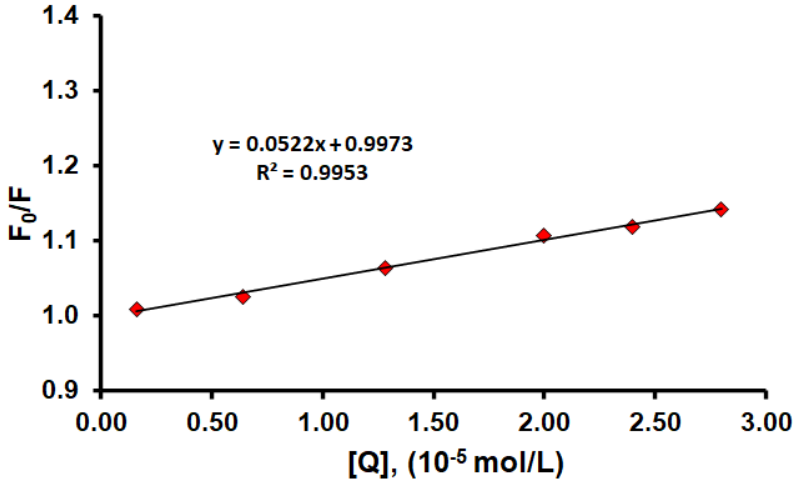


Figure 2. Stern-Volmer plots of the fluorescence quenching of HSA by PMT at 298 K

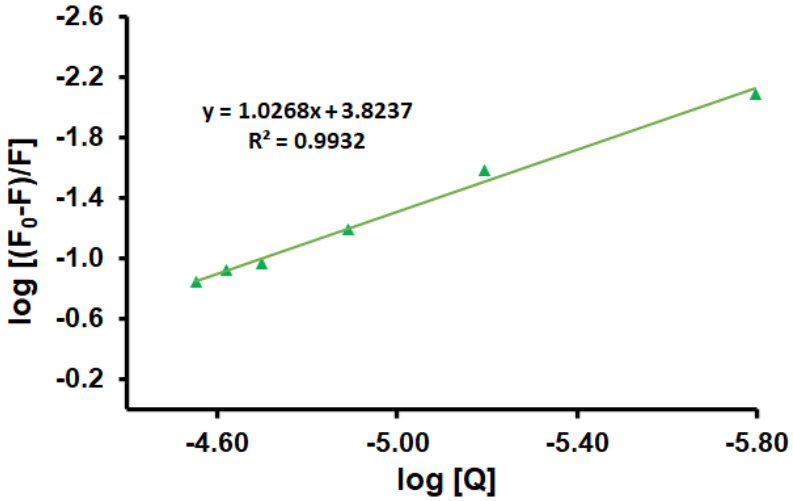


Figure 3. Logarithmic plots of the fluorescence quenching of HSA by PMT at 298 K

5 J.R. Lakowicz, Principles of fluorescence spectroscopy, 3rd ed. Springer, New York, (2006)

Results and discussion

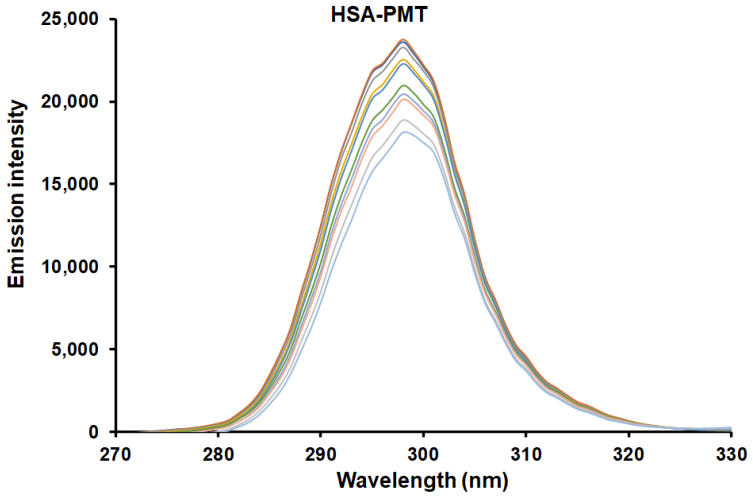


Figure 4. The effect of PMT on the synchronous fluorescence emission spectra of HSA ($\Delta\lambda$=15 nm) (T = 298 K, pH = 7.4). [HSA] = 1.6 µM and [PMT] = 0 to 32 µM.

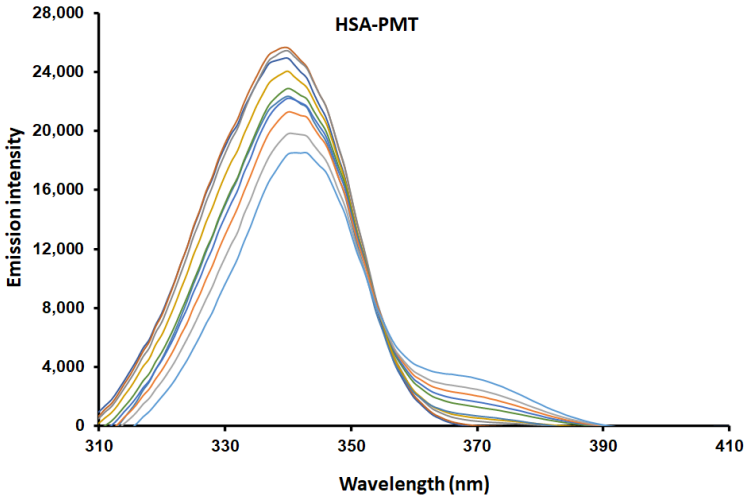
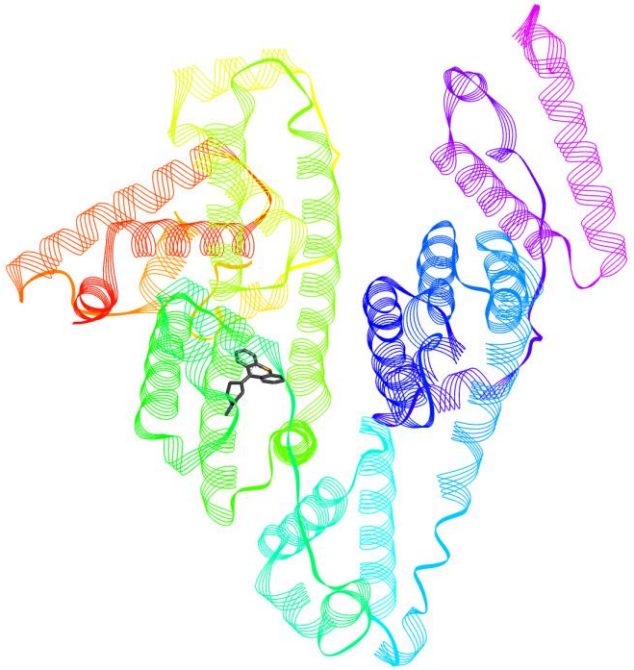


Figure 5. The effect of PMT on the synchronous fluorescence emission spectra of HSA ($\Delta\lambda$=60 nm) (T = 298 K, pH = 7.4). [HSA] = 1.6 µM and [PMT] = 0 to 32 µM.

Results and discussion- Molecular docking



Conclusions

- Pimethixene binds to human serum albumin, forming an HSA-PMT complex.
- There is a strong binding between pimethixene and human serum albumin ($6{,}6 \cdot 10^3$ M^{-1}).
- Synchronous spectra showed that there is no significant change in the microenvironment on the Trp residues in the IIA subdomain.
- Theoretical and experimental results are in good agreement.

Acknowledgments

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