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Investigation on the interaction between lurasidone and human serum albumin

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pharmaceuticals MDPI

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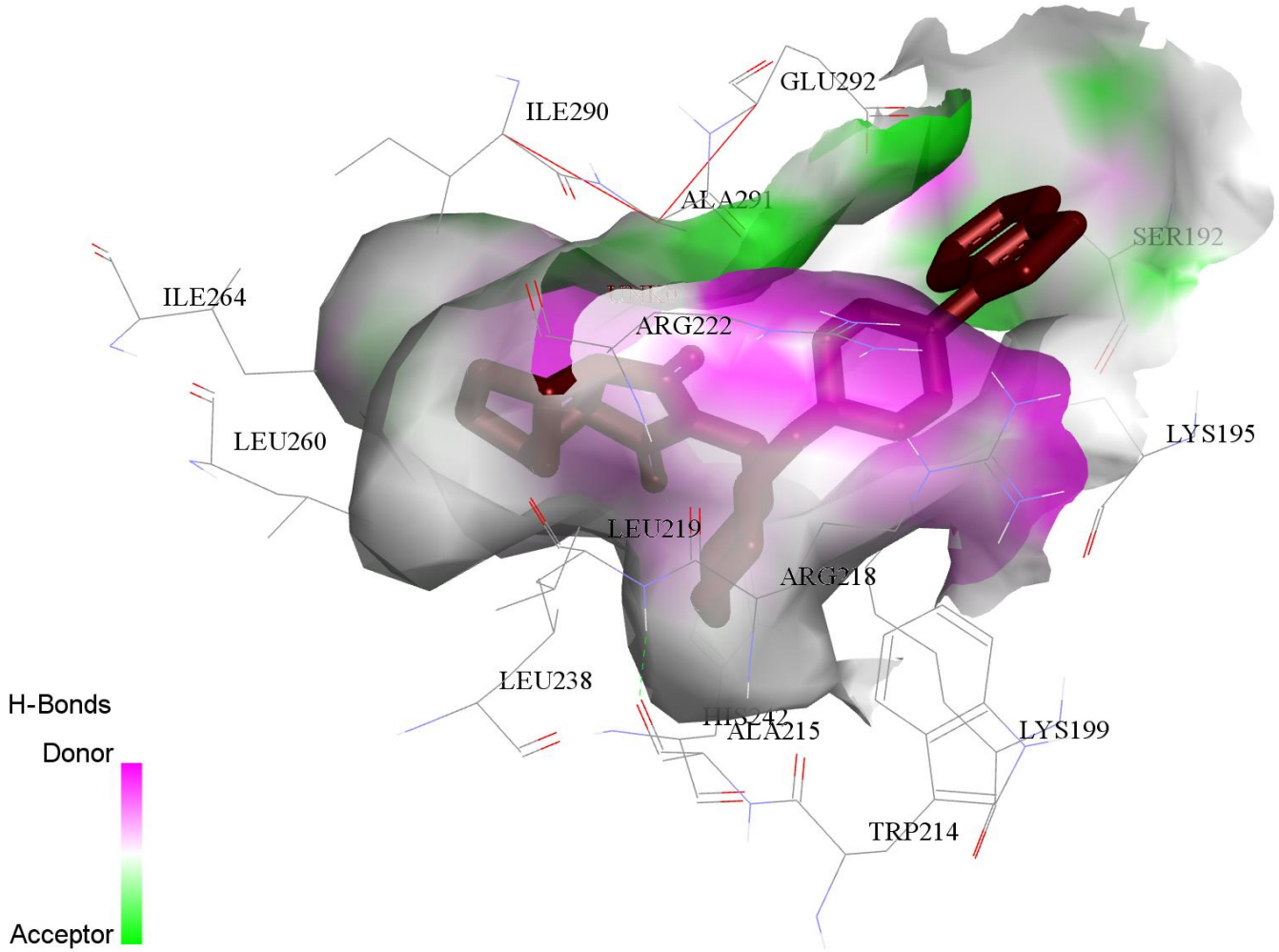


Abstract

Lurasidone hydrochloride is a second-generation (atypical) antipsychotic agent who is used for the treatment of schizophrenia and bipolar depression. The mechanism of action of lurasidone is not completely elucidated, assumed to affect dopamine and serotonin receptors, but is devoid of antihistaminic or anticholinergic activities [1].

Human serum albumin (HSA), the most abundant transport protein in blood plasma, consisting of 585 aminoacids residues and have three binding sites (I, II and III) [2,3]. The most of drugs binds to hydrophobic cavities in subdomains IIA and IIIA, in the site I and II, respetively. Investigation the interactions of drugs to HSA may give useful informations of effectiveness of drugs.

In this study, we investigate interactions between lurasidone and human serum albumin (HSA) by the fluorescence quenching technique, synchronous fluorescence spectroscopy and molecular docking.

References

[1] W. M. Greenberg, L. Citrome, Clin Pharmacokinet 56(5) (2017) 493.
[2] S. Curry, P. Brick, N.P. Franks, Biochim. Biophys. Acta 1441 (1999) 131.
[3] X.M. He, D.C. Carter, Nature 358 (1992) 209.

Keywords: Lurasidone; human serum albumin; fluorescence spectroscopy; molecular docking

Introduction

- Human serum albumin is the most important plasma protein which can bind many drugs

- The degree of drug binding to plasma proteins depends on:

  - affinity for the binding site on the protein,
  - concentration of free drug,
  - target protein concentrations

- And directly affect on the pharmacokinetics and pharmacodynamics of those drugs

Introduction

- Lurasidone (LZD) is an atypical antipsychotic, a benzothiazole derivative, which has a high affinity for D2 dopamine, and 5HT2A and 5HT7 serotonin receptors. It is used to treat schizophrenia and bipolar disorders [4].

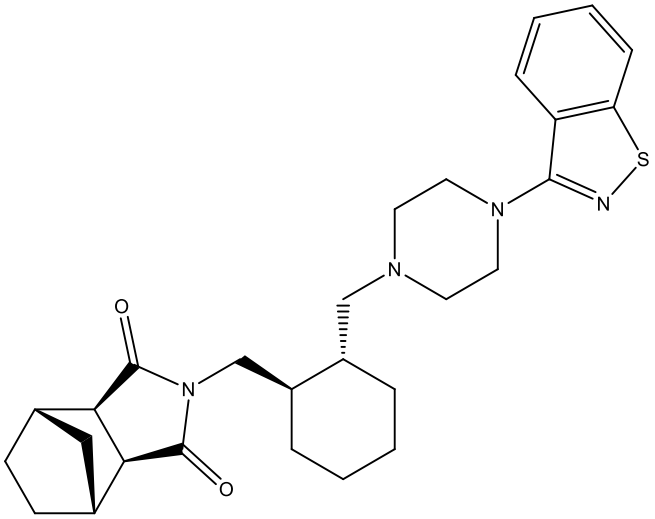


Figure 1. Lurasidone (LZD)

4.Chiu Y., Ereshefsky L., Sheldon H. et al. "Lurasidone drug-drug interaction studies: a comprehensive review" Drug Metabolism and Drug Interactions, 2014; 29(3): 191-202.

Results and discussion

Fluorescence quenching measurements

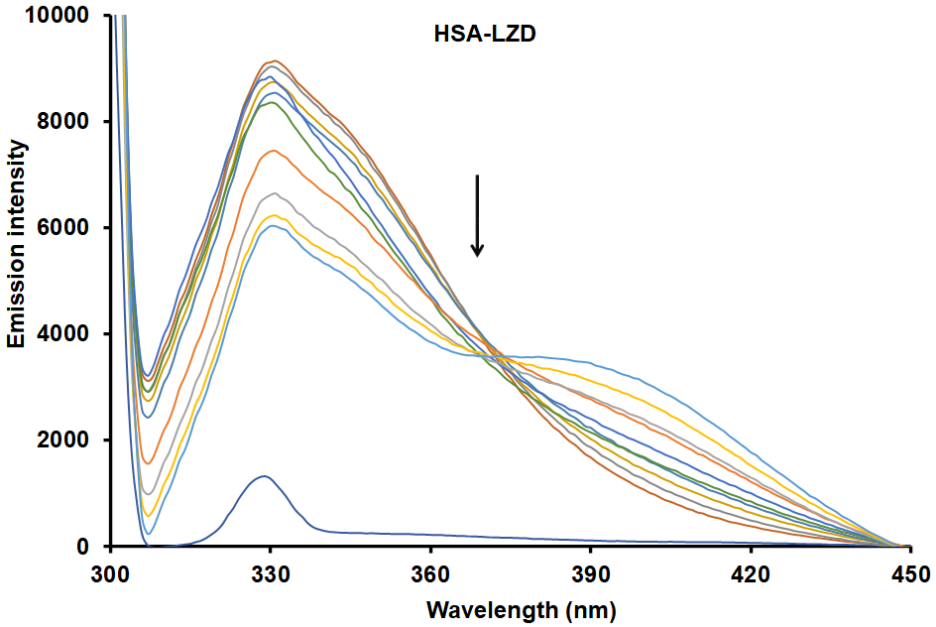


Figure 2. Fluorescence emission spectra of HSA in the presence of LZD(T = 298 K, pH = 7.4). [HSA] = 1.6 µM and [LZD] = 0-3.2 µM

Results and discussion

Based on the performed spectroscopic measurements, the Stern-Volmer and binding constants were determined[5].

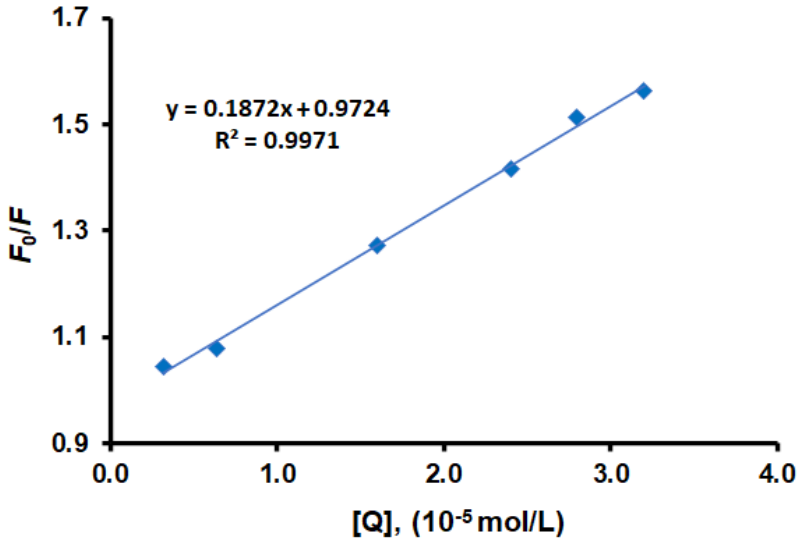


Figure 2. Stern-Volmer plots of the fluorescence quenching of HSA by LZD at 298 K

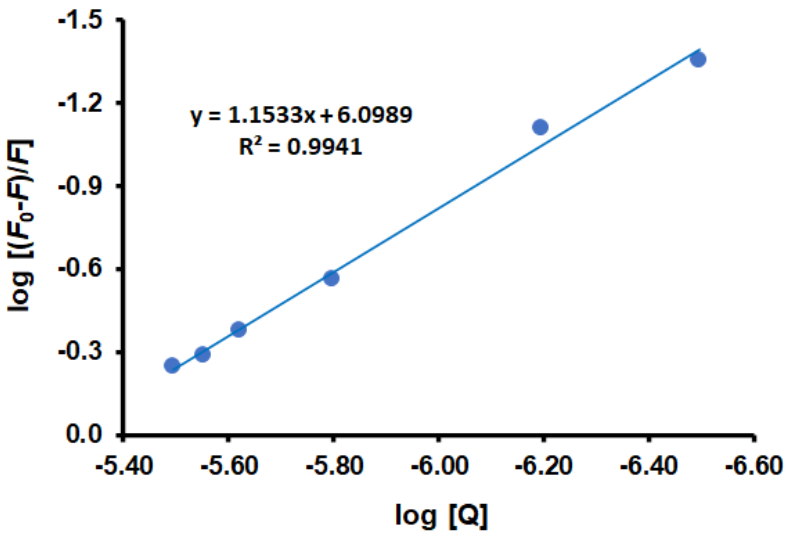


Figure 3. Logarithmic plots of the fluorescence quenching of HSA by LZD at 298 K

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

Results and discussion

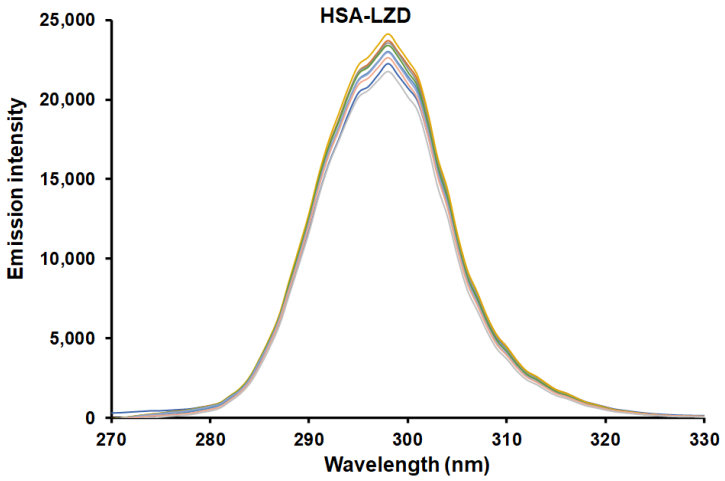


Figure 4. The effect of LZD on the synchronous fluorescence emission spectra of HSA ($\Delta\lambda$=15 nm) (T = 298 K, pH = 7.4). [HSA] = 1.6 µM and [LZD] = 0 to 3.2 µM.

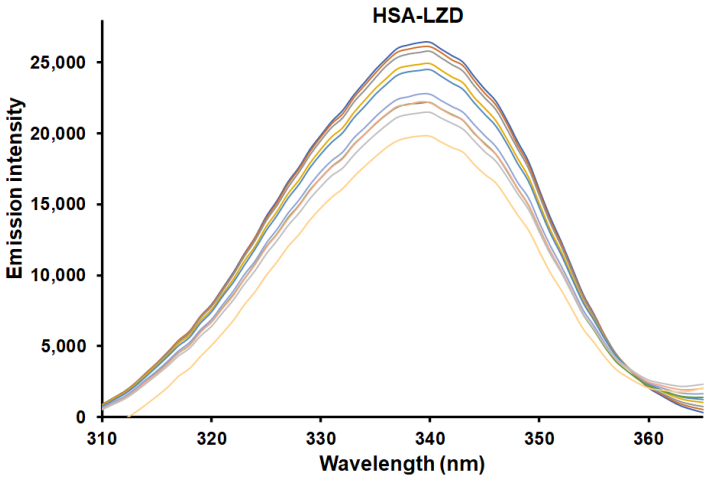
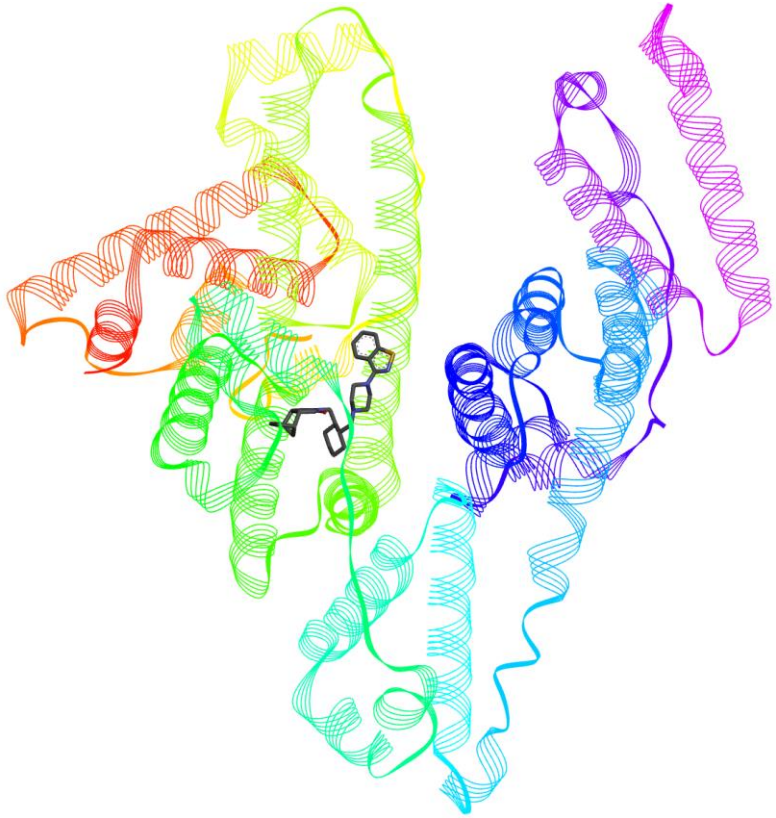


Figure 5. The effect of LZD on the synchronous fluorescence emission spectra of HSA ($\Delta\lambda$=60 nm) (T = 298 K, pH = 7.4). [HSA] = 1.6 µM and [LZD] = 0 to 3.2 µM.

Results and discussion – Molecular docking



Conclusions

- *The fluorescence spectra was shown that there is a quenching of the fluorescence of HSA with increasing concentration of lurasidone. Accordingly, we can conclude that LZD interacts with HSA, whereby the LZD-HSA complex is formed.*

- *By analyzing the Stern-Volmer graph and* logarithmic plot of the fluorescence quenching of HSA by LZD*, Ksv ($1.87 \cdot 10^5$ M^{-1}) and Ka ($1.26 \cdot 10^6$ M^{-1})were obtained.*

- *The values of n at room temperature was approximately 1 (1.15), so it was concluded that LZD binds to only one site on HSA.*

- There is no significant change in the microenvironment on the Trp residues in the IIA subdomain.

- Docking experiments toward HSA protein have been done indicating a good correlation with experimental results.

Acknowledgments

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