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Investigation of the interaction between olanzapine and human transferrin

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pharmaceuticals MDPI

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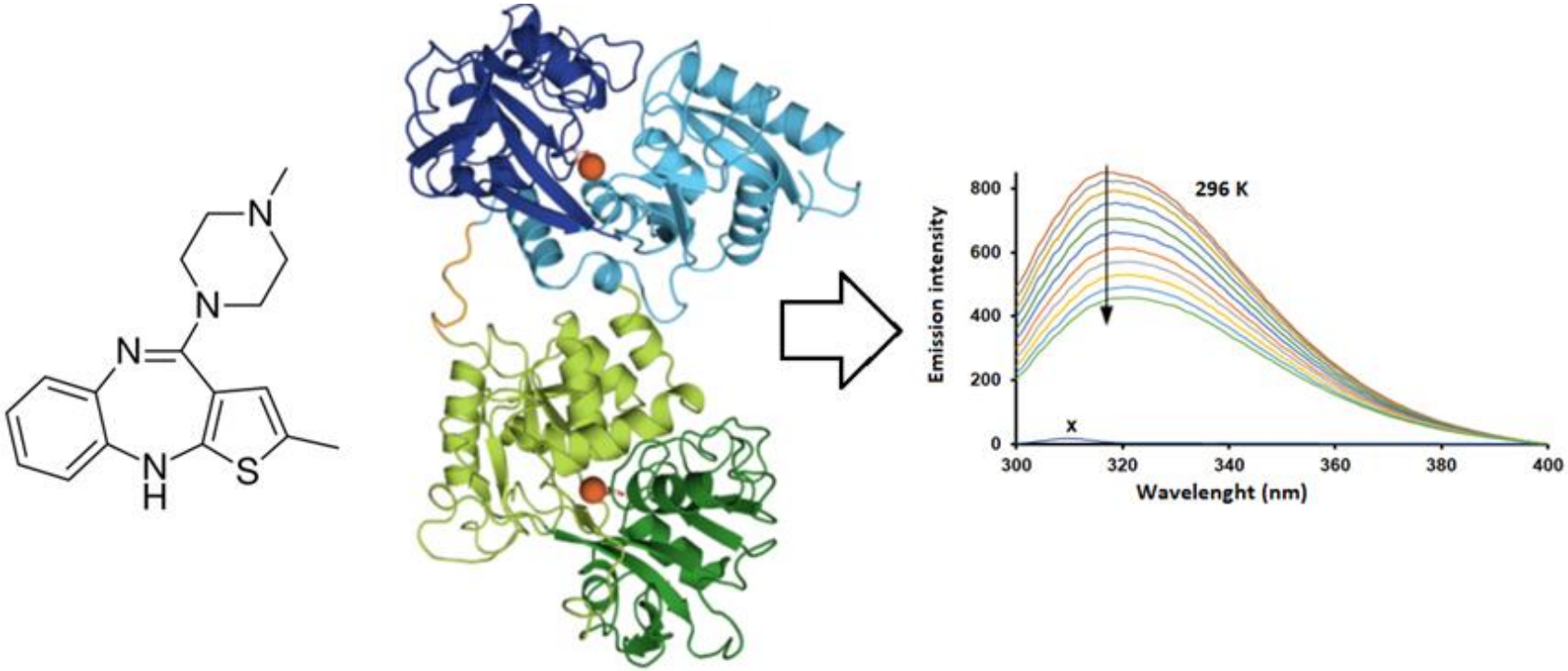

Abstract:

Human Transferrin is a biochemical marker of iron status in the body. Transferrin (TF) is responsible for the transport of iron through the blood to various tissues. It is a blood plasma glycoprotein that plays a central role in iron metabolism. Members of the transferrin family are mostly monomeric glycoproteins, consisting of two lobes capable of binding ferric ions. When the binding sites are empty, transferrin is called apo-transferrin, as opposed to holo-transferrin, when the binding sites are occupied. The aim of this work is to determine the binding constant, number of binding sites and the binding mechanism between Olanzapine (OLZ) and TF by spectroscopic methods (fluorescence and absorption measurements). Results showed that Olanzapine reacts with transferrin and forms a TF-OLZ complex. The binding of olanzapine to transferrin is a spontaneous process. According to the calculated quenching constants, it appears that the quenching mechanism, which involves the formation of a complex, was found to be static. The main interactions between olanzapine and transferrin are hydrogen bonding and weak van der Waals forces.

Keywords: Olanzapine; Spectroscopic measurements; Transferrin

Introduction

TF is a globular protein structure. It consist of two domains [1]:

- the amino-terminal lobe (N-lobe)
- the carboxylate-terminal lobe (C-lobe)

TF has 19 disulfide bridges, 8 in the protein N-lobe and 11 in the protein C-lobe.
Each lobe divided into two subdomains (N lobe-N1, N2 and C lobe-C1, C2) which connected by a hinge leading to a deep cleft containing the iron binding site. (Figure 1)

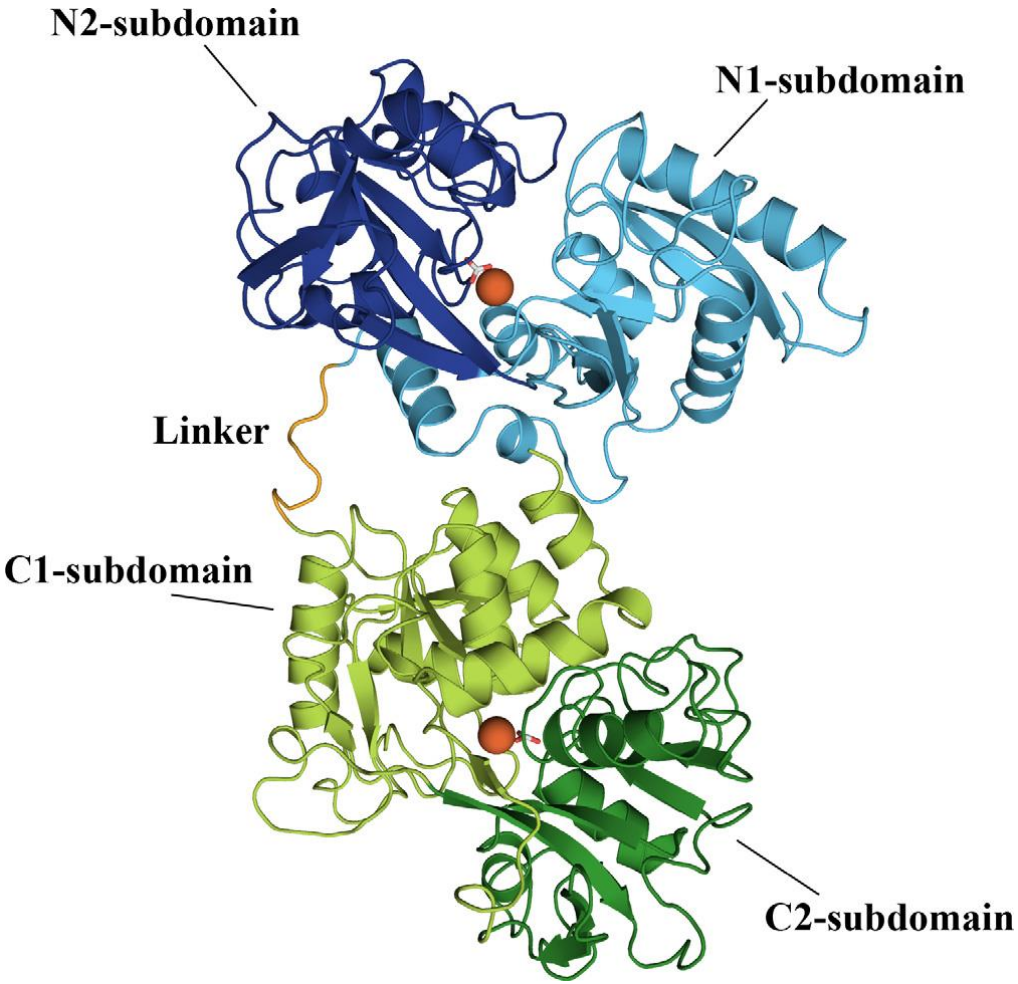

Figure 1. Structure of transferrin (TF), A. M.N. Silva et. al. Coordination Chemistry Reviews 449 (2021) 214186.

References:
[1]André M.N. Silva, Tânia Moniz, B. de Castro et al. Coordination Chemistry Reviews 449 (2021) 214186.

Introduction

- Transferrin (TF) is an essential glycoprotein responsible for the safe transport of essential micronutrient through circulation and its delivery to requiring cells
- The main function of TF is to bound iron through specific receptors [2,3] and transport ferric ions through the blood plasma, the interstitial fluid, lymph and cerebrospinal fluid [4,5]
- According to many investigations transferrin could be employed as a natural drug carrier [6–8] because of its ability to using transferrin receptor route for targeting drugs to malignant cell
- Analysis of the interactions between drugs and carrier proteins such as transferrin or albumin is important from a clinical and pharmacological point of view

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Results and discussion

The interaction of OLZ with TF was investigate by fluorescence spectroscopy. All measurements were recorded at three temperatures (296, 303 and 310 K). As can be seen in Figure 2. an increasing concentration of OLZ led to decreases in fluorescence intensity of the TF.

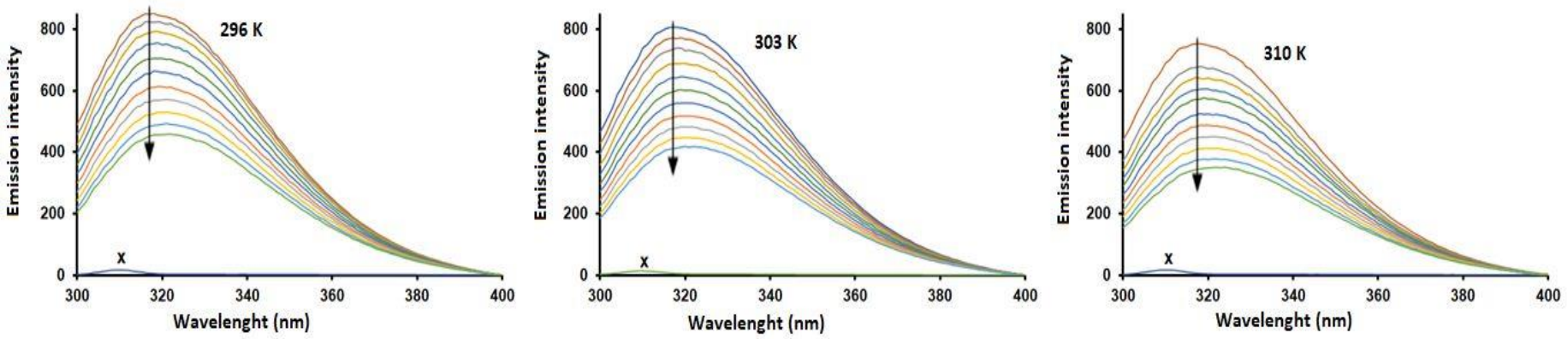

Figure 2. Fluorescence spectra of HF-OLZ systems at three temperatures (pH = 7.40, λ_{ex} = 280 nm)

Results and discussion

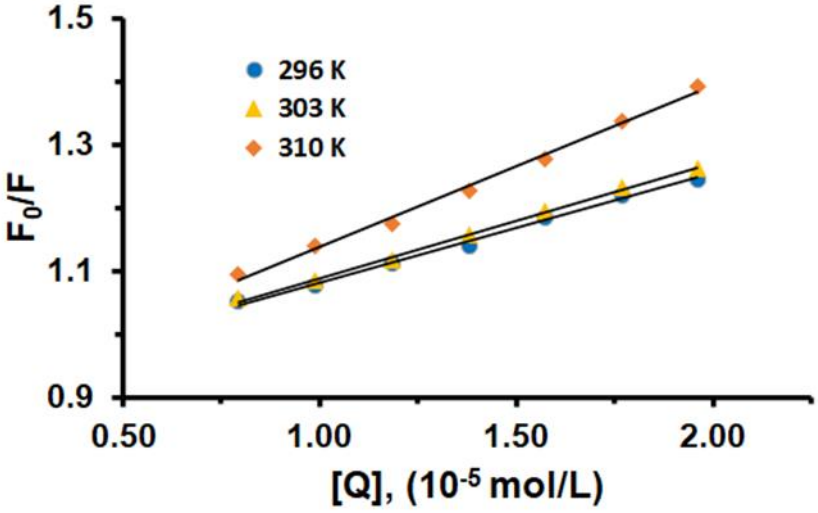

Figure 3. Stern Volmer plot of the OLZ-TF system at three temperatures (296 K, 300 K, 310 K, pH = 7.40, λ_{ex} = 280 nm).

Stern-Volmer quenching constant (K_{sv})was obtained according to equation [9]:

$$\frac{F_0}{F} = 1 + K_q \tau_0 [Q] = 1 + K_{SV}[Q]$$

Where:

F_0 and F are protein fluorescence intensities in the presence and absence of OLZ, respectively. *K*sv is Stern-Volmer quenching constant, [Q] is the quencher concentration *K*q is the bimolecular quenching constant and τ_0 is the mean lifetime of the fluorescent molecule in the absence of a quencher (10^{-8}) s [9].

References:
[9] Lakowicz J.R., Springer, New York, 2006. pp. 52, 277, 530.

Results and discussion

Table 1.
Stern-Volmer constants of TF-OLZ system at different temperatures

T (K)	K_{SV} (M^{-1})	K_q (M^{-1} s^{-1})	R^a
296	$6{,}92 \times 10^4$	$6{,}92 \times 10^{12}$	0,9086
303	$7{,}24 \times 10^4$	$7{,}24 \times 10^{12}$	0,9974
310	$1{,}02 \times 10^5$	$1{,}02 \times 10^{13}$	0,9935

The K_{sv} values are listed in Table 1. Obtained results clearly shows an increase in K_{sv} with increasing temperature which implies that the mode of interaction between TF and OLZ to be dynamic. Meanwhile, the K_q values at three temperatures were much greater than the maximum scatter dynamic quenching constant (2.0×10^{10} $L \cdot mol^{-1} \cdot s^{-1}$). Thus, these data indicated some static quenching mechanism should also be involved in these TF-OLZ systems.

Results and discussion

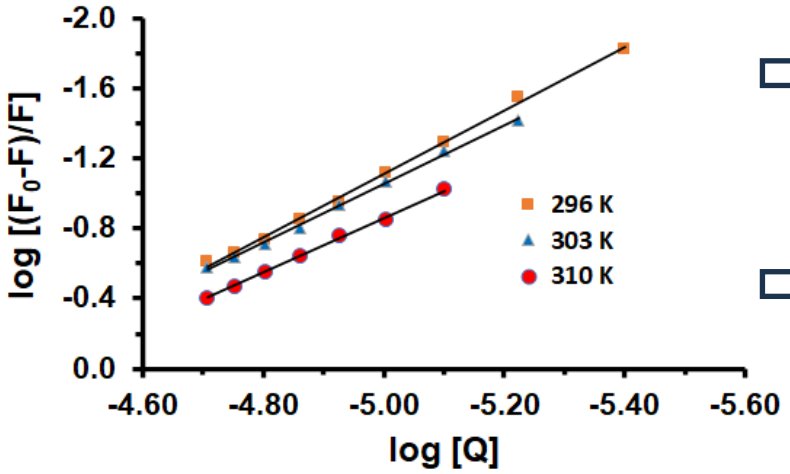

Figure 4. log[(F_0 – F)/F] vs. log[Q]

- The binding constant *K*a and the number of binding sites n derived from the double logarithmic curve.
- Obtained results was used to determination thermodynamic parameters.
- Accordingly, negative values of ΔG, ΔH and ΔS indicate that interctions between TF and OLZ was spontaneous process, driven by van der Waals force and weak hydrogen bonds.

Conclusions

According to results of spectroscopic measurements, we conclude:

- Olanzapine reacts with transferrin and forms a TF-OLZ complex;
- The binding of olanzapine to transferrin is a spontaneous process;
- The calculated quenching constants indicated that the quenching mechanism was static;
- The main interactions between olanzapine and transferrin are hydrogen bonding and weak van der Waals forces.

Acknowledgments

ИНСТИТУТ ЗА ИНФОРМАЦИОНЕ ТЕХНОЛОГИЈЕ КРАГУЈЕВАЦ
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