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The affinity of tigecycline to human serum albumin in the presence of diosmin

Marina Ćendić Serafinović [1,*], Emina Mrkalić [2], Stefan Stojanović [3], Miroslav Sovrlić [3], Ratomir Jelić [3]

[1]University of Kragujevac, Faculty of Sciences, Department of Chemistry, Radoja Domanovića 12, Kragujevac 34000, Serbia

[2] University of Kragujevac, Institute for Information Technologies, Department of Science, Jovana Cvijića bb, Kragujevac 34000, Serbia

[3] University of Kragujevac, Faculty of Science, Department of Chemistry, Svetozara Markovića 69, Kragujevac 34000, Serbia

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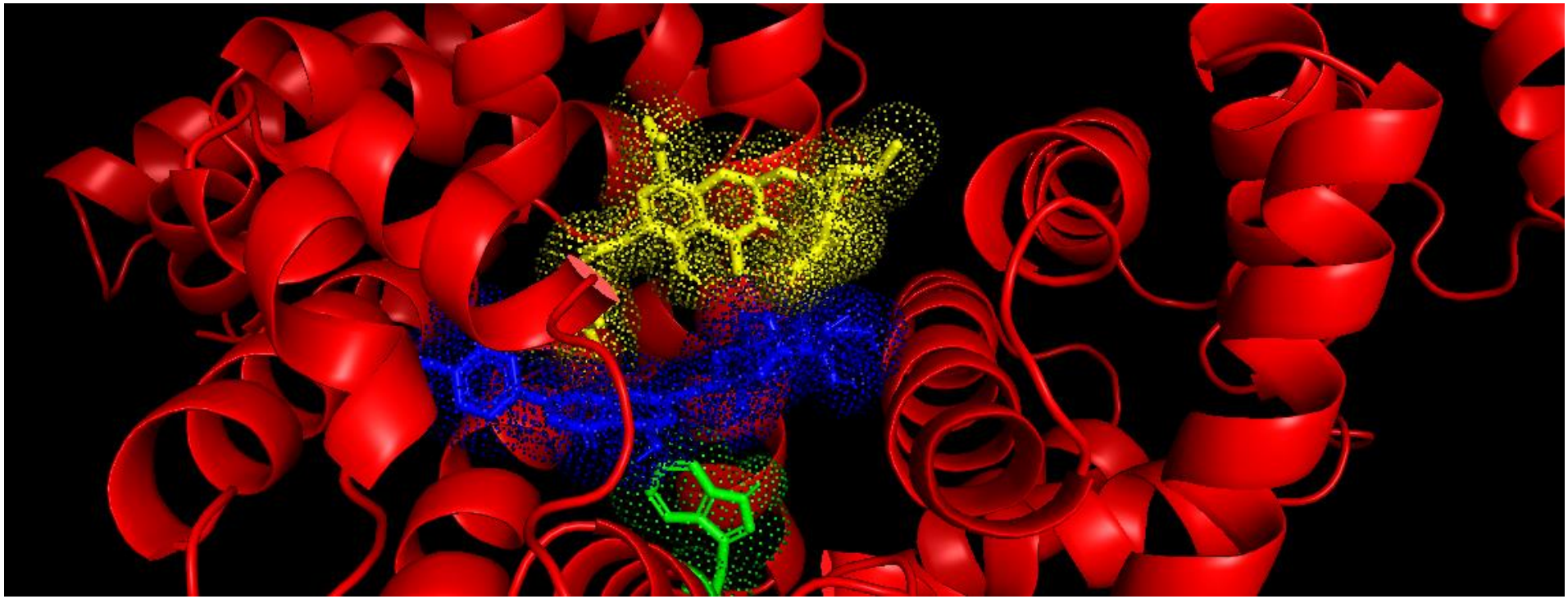

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Abstract:

Tigecycline is a new intravenous broad-spectrum antibiotic with activity against many drug-resistant organisms. Tigecycline is the first member of a new class of antibacterial agents, the glycylcyclines. It is a derivative of minocycline. This group has been specifically developed to overcome the two major mechanisms of tetracycline resistance (ribosomal protection and efflux). Human serum albumin (HSA) is the most widely studied serum albumin. Its primary structure is well known, and its tertiary structure has been determined by X-ray crystallography[1]. The protein has also multiple ligand-binding sites localized in hydrophobic cavities in subdomains IIA and IIIA, called site I and site II, respectively[2]. Here, the we investigated effect of diosmin on the TGC-HSA by fluorescence spectroscopy, synchronous spectroscopy and molecular docking simulations. The aim is to explore the ability of diosmin to bind competitively to HSA with TGC. Experimental and theoretical results showed that diosmin increased the binding affinity of TGC to HSA.

[1] X.M. He, D.C. Carter, Nature, 358 (1992) 209–215.
[2] G. Sudlow, D. F. Birkett, D. N. Wade, Mol. Pharmacol., 11 (1975) 824–832.

Keywords: diosmin, human serum albumin, binding afinity

Introduction

Flavonoids are a wide class of natural compounds belonging to secondary metabolites. Diosmin is one of the most utilized flavonoid being the active principle of many drug especially for the treatment of various blood vessels disorders, to protect organism against liver toxicity. Also, it investigated for other therapeutic purposes, such as cancer, diabetes, premenstrual syndrome and colitis. It is one of the main flavonoids identify in citrus juices[3]. It was isolated for the first time from Scrophularia nodosa[4].

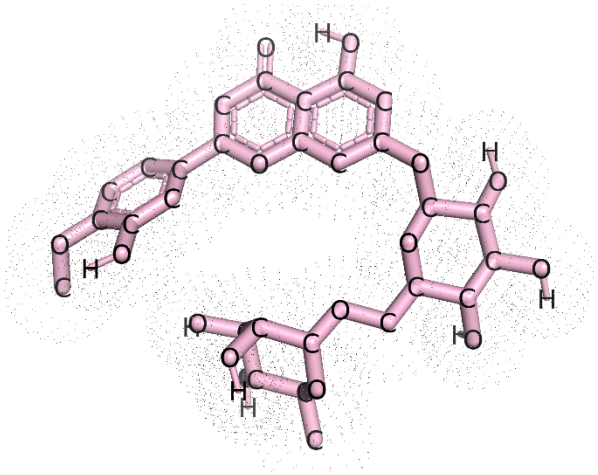

Figure 1. Structure of diosmin

[3] D. Barreca, E. Bellocco, C. Caristi, U. Leuzzi, G. Gattuso, Food Chemistry 129 (2011) 417-422.
[4] Monograph on diosmin, Alternative Medicine Review 9 (2004) 308-311.

Introduction

We investigated effect of diosmin on the TGC-HSA by:

- fluorescence spectroscopy,
- synchronous spectroscopy and
- molecular docking simulations

The aim of this investigations is to explore the ability of diosmin to bind competitively to HSA with tigecycline.

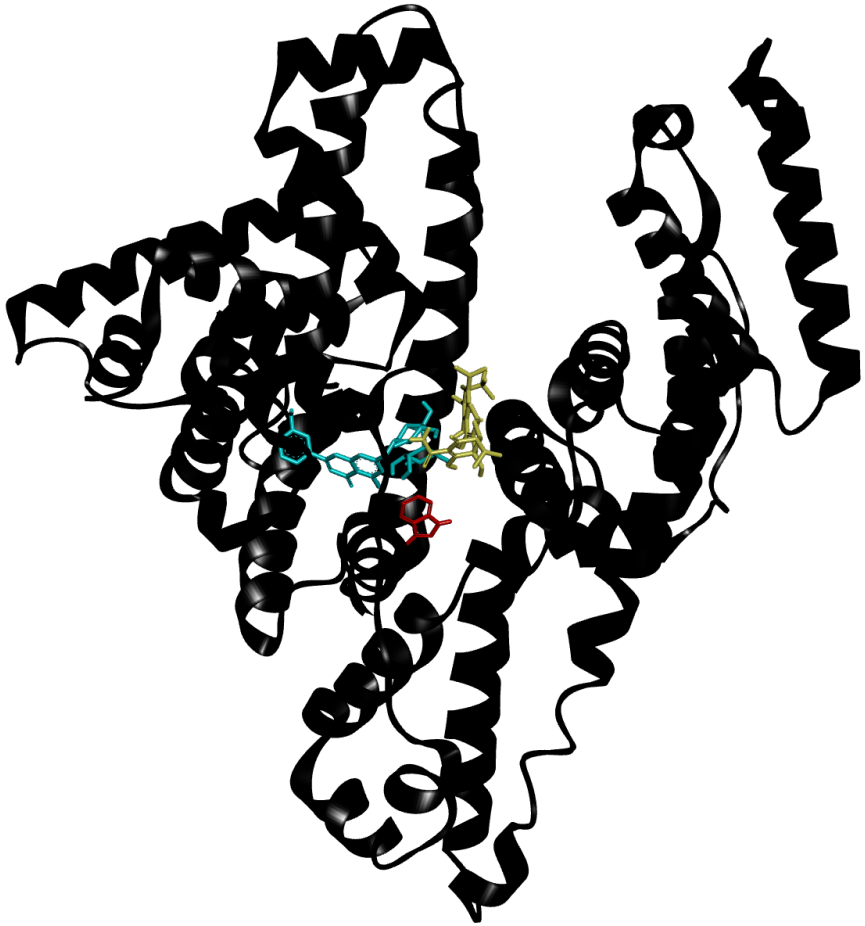

Figure 2. Structure of human serum albumin, tigecycline, diosmin and tryptophan

Results and discussion

Fluorescence measurements

- The fluorescence intensity was corrected for absorption/re-absorption of exciting/emitted light[5]
- Stern Volmer Equation[5] was used to analyze the quenching mechanism of HSA in the presence of diosmin in ternary HSA-TGC-DIO system

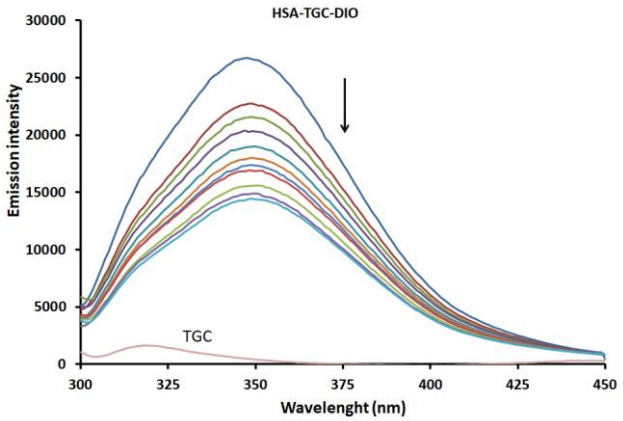

Figure 3. Fluorescence emission spectra of HSA-TGC in the presence of DIO (T = 298 K, pH = 7.4). [HSA] = 2 µM and [DIO] = 2 µM and [TGC] = 0 to 1 x 10^{-5} M.

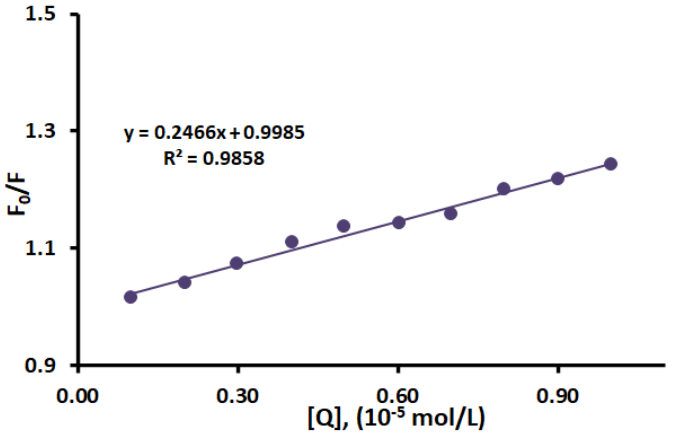

Figure 4. Stern-Volmer plots of the fluorescence quenching of HSA-TGC system by DIO at 298 K

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

Results and discussion

- The binding constants (K_a) and the number of binding sites (n) can be calculated by the double logarithm equation:

$$\log\frac{F_0 - F}{F} = \log K_a + n\log[Q]$$

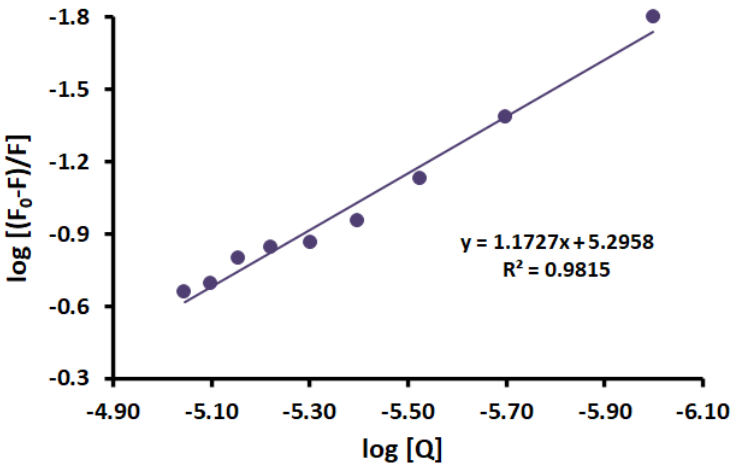

Figure 5. Logarithmic plots of the fluorescence quenching of HSA by TGC in the presence of DIO at 298 K

Table 1. The interaction parameters of the binary (HSA-TGC) and ternary (HSA-TGC-DIO, HSA : DIO = 1 : 1) systems

System [a]	K_{SV} x 10^{-4} [b]	k_q x 10^{-12} [c]	R^2 [d]	K_a x 10^{-5} [b]	n	R^2
HSA-TGC	5.00	5.00	0.996	0.18	0.9	0.991
HSA-TGC-DIO	2.47	2.47	0.9858	1.98	1.17	0.9815

[a] 298 K; [b] M^{-1}; [c] $M^{-1}s^{-1}$; [d] R is the correlation coefficient

Results and discussion

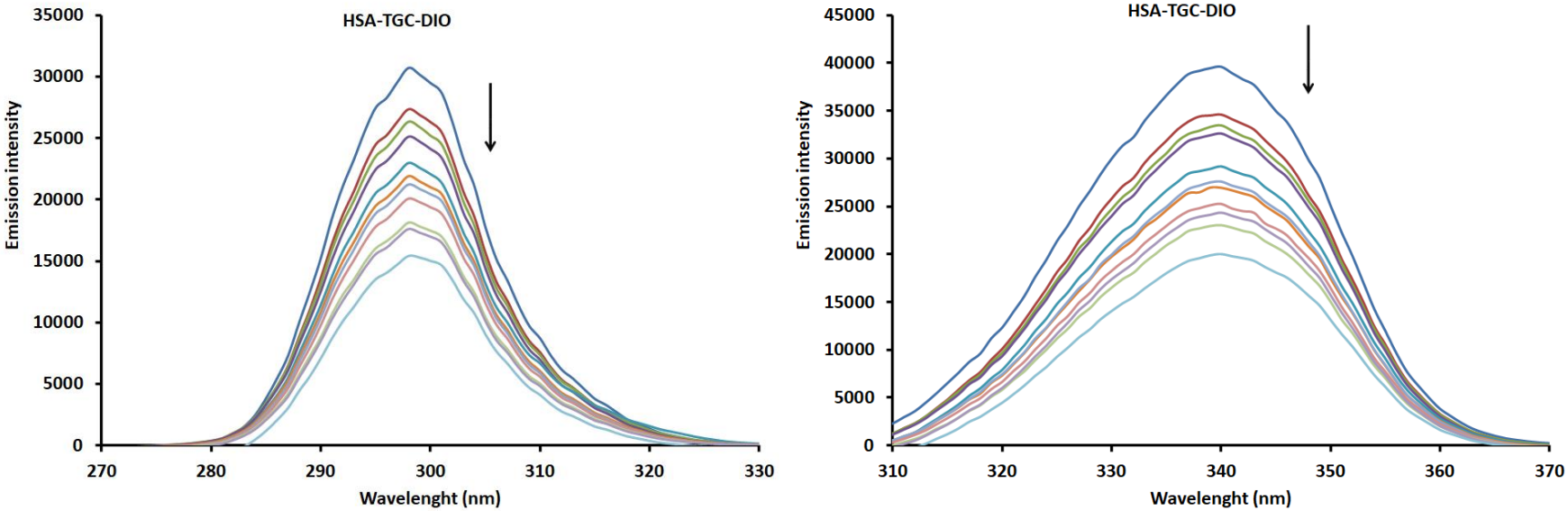

Figure 6. The effect of DIO on the synchronous fluorescence emission spectra of HSA-TGC system (Left: $\Delta\lambda$=15 nm and Right: $\Delta\lambda$=60 nm) (T = 298 K, pH = 7.4). [HSA] = 2 µM, [DIO] = 2 µM and [TGC] = 0 to 1 x 10^{-5} M.

Results and discussion

Table 2. ΔG[a] values of site I (subdomain IIA) versus site II (subdomain IIIA)			
System[b]	Autodock		Ref.
	Site I	Site II	
HSA-TGC	-24.36	-14.60	6
HSA-TGC-DIO	-26.40	-17.36	This work
[a] kJ·mol^{-1}; [b] 298 K.			

Table 3. Energies and inhibition constants of site I (subdomain IIA)			
	Autodock		Ref.
System[a]	ΔG[b]	Ki[c]	
HSA-TGC	-24.36	5.44 x 10^{-5}	6
HSA-TGC-DIO	-26.40	2.37 x 10^{-5}	This work
[a] 298 K; [b] kJ·mol^{-1}; [c] mol·dm^{-3}.			

[6] S.D. Stojanovic, S.M. Jankovic, Z.D. Matovic, I.Z. Jakovljevic, R.M. Jelic, Monatsh Chem 146 (2015) 399-409

Results and discussion

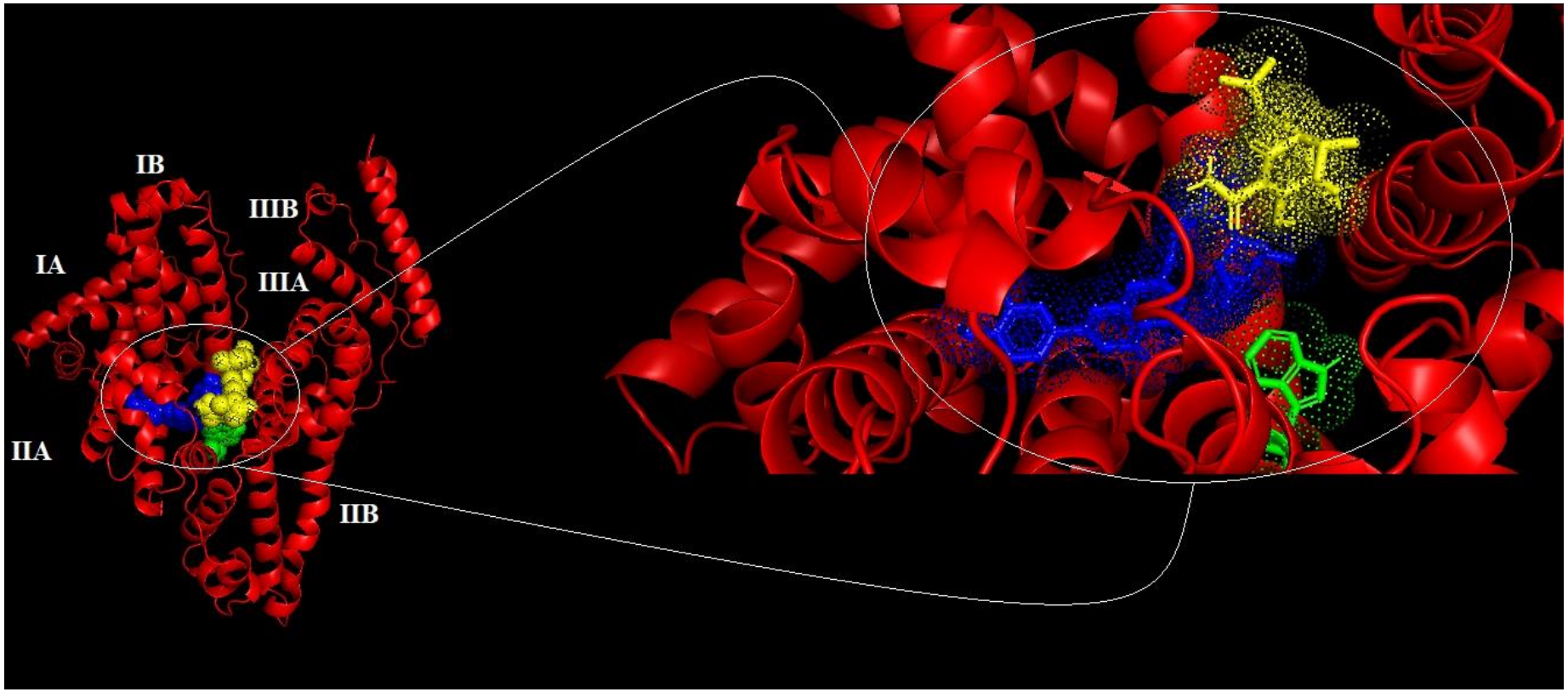

Figure 7. HSA-TGC-DIO system (DIO colored blue, TGC colored yellow and TRP214 colored green).

Results and discussion

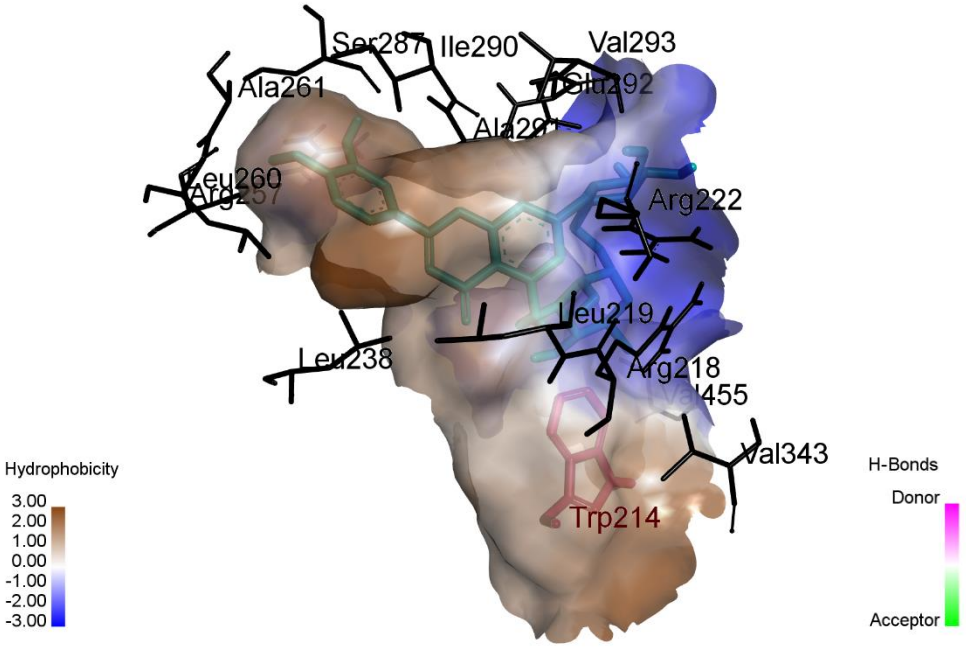

Figure 8. Hydrophobic contributions in HSA-TGC-DIO

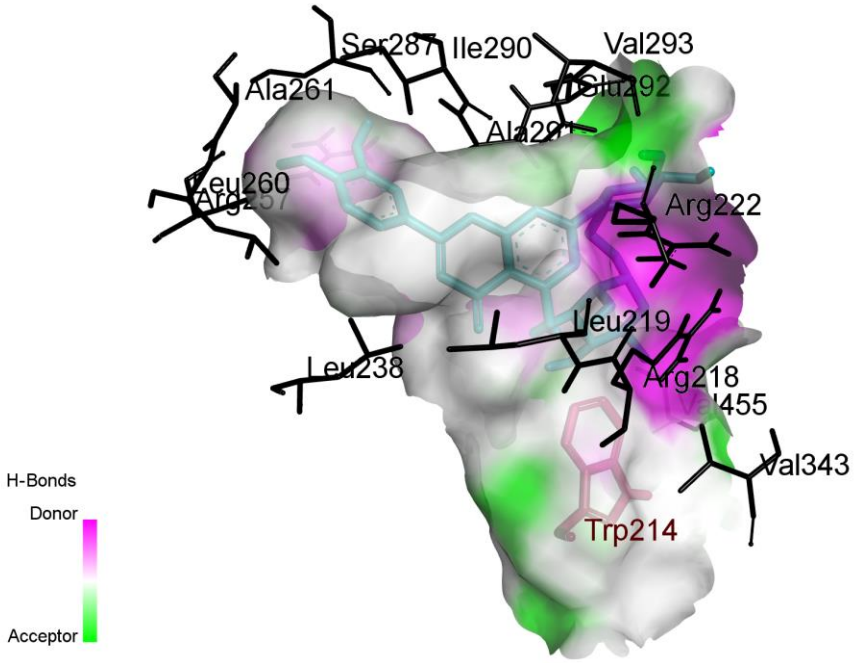

Figure 9. Contribution of H-bonds in HSA-TGC-DIO

Conclusions

- ✓ Diosmin share IIA subdomain in HSA with tigecycline drug
- ✓ The binding affinity of tigecycline to HSA increased in the presence of diosmin
- ✓ The interaction of HSA-TGC with diosmin does not show an obvious effect of conformation of the micro-region of Tyr and Trp [7]
- ✓ Results of docking experiments toward HSA protein are in good agreement with experimental results

[7] J.-H. Shi, K.-L. Zhou, Y.-Y. Lou, D.-Q. Pan, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 188 (2018) 362-371.

- **Acknowledgments**