Int. J. New. Chem., 2024, Vol. 11, Issue 4, pp. 337-349.

International Journal of New Chemistry

Published online in http://www.ijnc.ir/.

Open Access

Print ISSN: 2645-7236

Online ISSN: 2383-188x

Original Research Article

Molecular docking studies on some derivatives of xanthones as potential anticancer agents

***Shabnam Shamei*[1*], *Zahra akbari*[2]**

**Corresponding author email: shabnamshamaie@gmail.com*

[1]**Assistant Professor, Department of Chemistry, Khorramabad Branch, Islamic Azad University, Khorramabad, Iran.*

[2] *Master of Chemistry, Department of Chemistry, Khorramabad Branch, Islamic Azad University,*

Received: 2023-11-24 *Accepted: 2024-02-22* *Published: 2024-02-29*

ABSTRACT

The design of new drug combinations based on molecular docking on Xanthone derivatives as potential anti-cancer agents. In this study interaction of compounds with 1ZXM, 1BNA ,and 1LU51 structures was investigated by molecular docking. In Docking, these compounds with a 1ZXM receptor have a Docking connection energy in the range of -6.87 to -8.69 which is the best binding energy. In Docking, these compounds with the 1BNA receptor, the docking connection energy is in the range of -6.74 to -9.34, which is the best binding energy associated with the 1 ligand, and in docking with 1LU51 receptor, the docking connection energy is in the range of -4.85 to -6.99, which is the best energy for the 1composition. In the binding of these compounds to the 1ZXM protein receptor, they carry key amino acids in the active site of the hydrogen- bonded receptor and are found in binding to 1BNA and 1LU51 receptors, which are mainly bound via the key bands of adenine, thymine, cytosine, and guanine.

Keywords: Molecular docking, Anticancer, Xanthone derivatives

Introduction

The use of computational drug design methods has emerged as a suitable and novel approach for understanding the biochemical processes in drug research and development. The method of drug design based on the structure has been expanded to investigate how to interact, optimize and find application model compounds [1]. Anticancer drugs have various targets, among which DNA is still considered an important target for cancer chemotherapy [2,3]. Therefore, compounds that interact with DNA, such as derivatives of xanthones, have found widespread use in cancer treatment [4]. xanthones are a large group of natural compounds with a three-ring skeleton consisting of two benzene and one pyranoid ring. They are highly regarded as biologically active compounds with diverse biological activities, including anti-inflammatory [5], antimicrobial [6], antiviral [7], antimalarial [8], and anticancer [9] activities. Their ability to bind to different receptors has drawn attention to these compounds, and they are used as a starting point for synthesizing new compounds [10, 11]. Additionally, one of the main goals of drug researchers is to predict the activity of compounds before synthesis and testing, as many experiments require a lot of time and expense. Therefore, the need for theoretical and computational methods that can predict the properties and activities of compounds without conducting experiments is essential [12].

Materials and methods

Preparation of ligands and proteins for docking

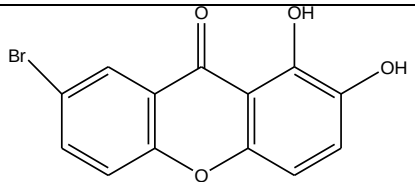
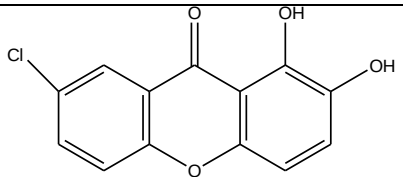
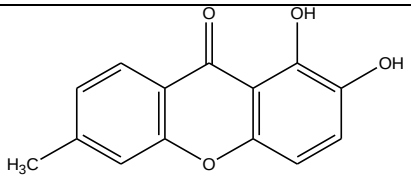
Molecular docking of compounds with DNA was performed to determine the important interactions and effective binding of compounds with target molecules. Molecular docking studies of 34 xanthone molecules were carried out using Autodock version 4.2 software[13]. To perform these studies, crystal structures with codes 1ZXM, 1BNA, and 1LU51 were extracted from the protein database, and all amino acid corrections or DNA ranges were performed using MOE 2014 software[14].Ligands and water molecules were removed, and nonpolar hydrogen atoms were merged into the corresponding carbon atoms. The macroscopic solvent parameters and Coulombic interactions were calculated using Autodock version 4.2 software, and finally, the macroscopic molecule file was saved in pdbqt format.

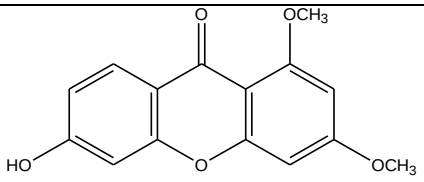
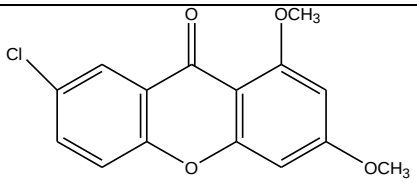
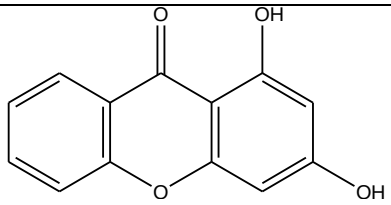
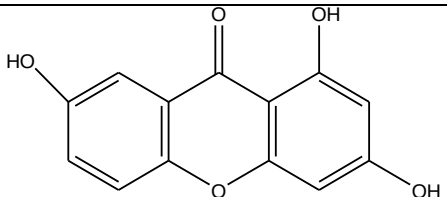
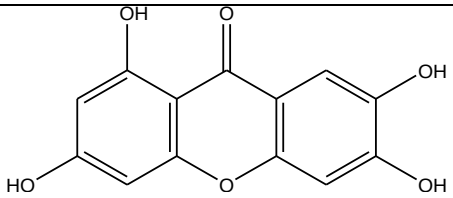
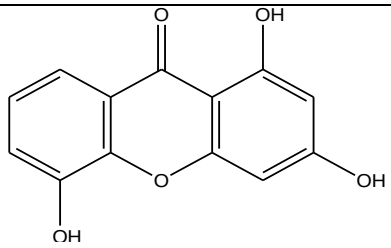
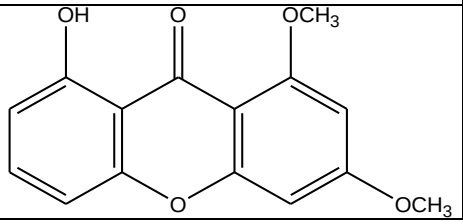
First, the 2D and 3D structures of ligands were drawn using Chem Bio Draw ultra 13.0 (3D) and ChemBioDraw2D software and then transferred to the software environment. Ligand conformation optimization was performed for energy using the molecular mechanics (MM+) and semi-empirical PM3 methods. After preparing the required input files for docking studies (macromolecule, ligand, and connection map), docking studies were performed using an algorithm called Lamarckian genetic algorithm to model the interactions between ligands and DNA [15].

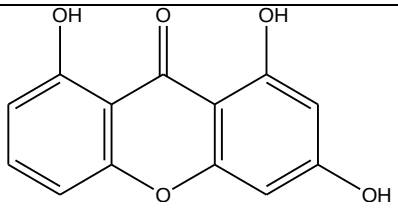
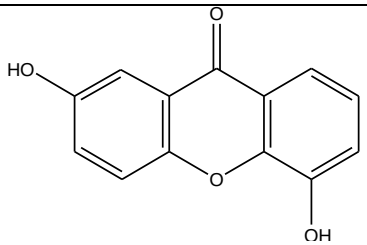
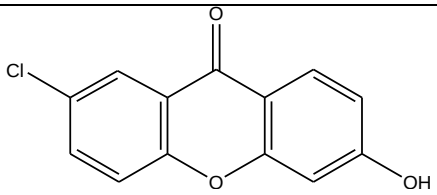
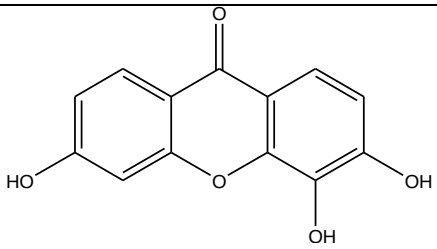
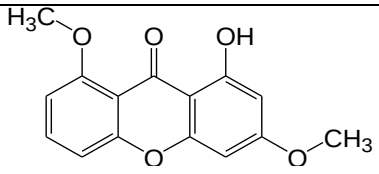
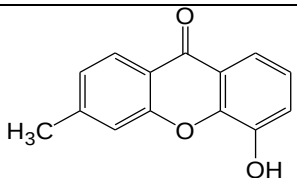
Observation and analysis of docking results

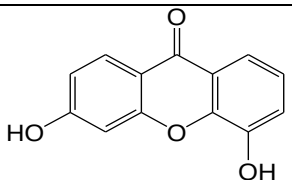
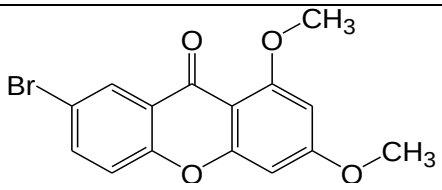
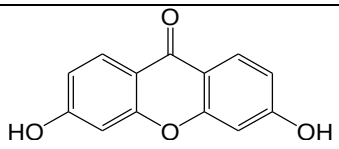
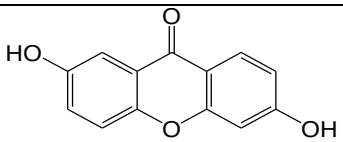
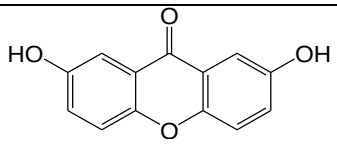
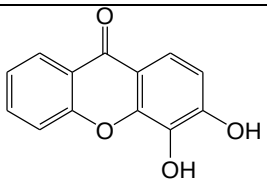
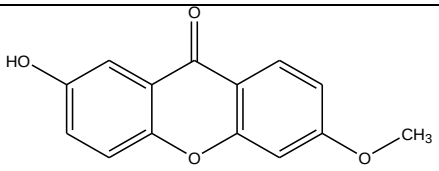
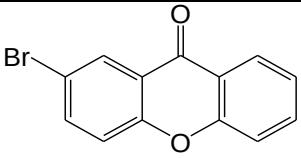
The interactions of xanthone compounds with 1ZXM, 1BNA, and 1LU51 receptors were investigated by molecular docking, and the results of their docking energy were presented in Table 1.

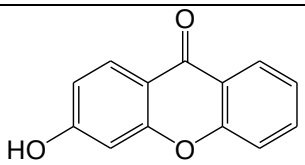
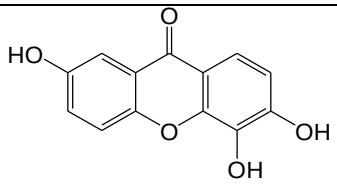
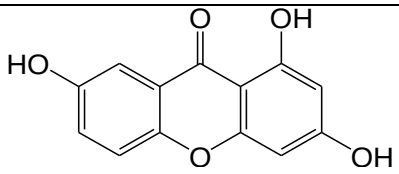
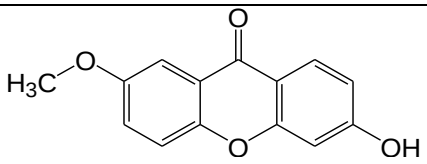
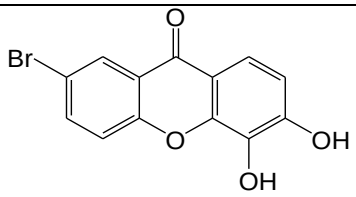
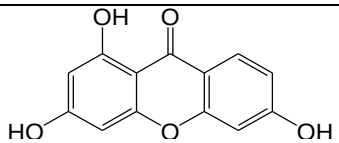
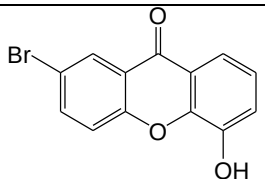
Table 1. Docking energy of xanthone compounds on 1ZXM, 1BNA, and 1LU51 receptors.

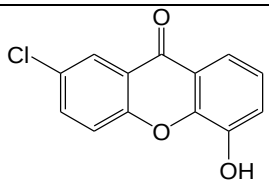
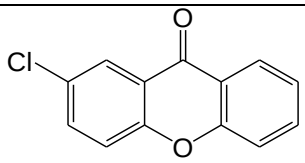
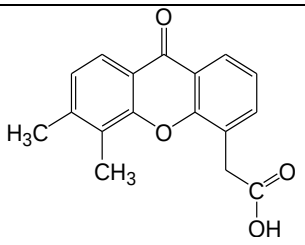
Compounds	Structure	ΔE (1ZXM)	ΔE (1BNA)	ΔE (1LU51)
1		-7.92	-9.34	-6.99
2		-7.68	-9.08	-6.81
3		-7.16	-9.27	-6.53

4		-7.57	-8.81	-6.18
5		-8.13	-9.01	-6.21
Compounds	Structure	ΔE (1ZXM)	ΔE (1BNA)	ΔE (1LU51)
6		-7.01	-8.61	-6.31
7		-7.43	-8.03	-6.13
8		-7.00	-8.27	-6.20
9		-7.04	-8.34	-6.53
10		-7.14	-8.60	6.17

11		-6.87	-8.07	-6.23
Compounds	Structure	ΔE (1ZXM)	ΔE (1BNA)	ΔE (1LU51)
12		-7.11	-7.60	-6.45
13		-7.94	-8.80	-6.30
14		-7.58	-8.47	-6.87
15		-7.31	-8.44	-6.12
16		-7.37	-8.48	-6.18

17		-7.21	-8.23	-6.24
18		-8.36	-9.16	-6.44
Compounds	Structure	ΔE (1ZXM)	ΔE (1BNA)	ΔE (1LU51)
19		-7.33	-8.59	-6.74
20		-7.44	-8.38	-6.47
21		-7.43	-7.74	-6.32
22		-7.43	-8.09	-6.60
23		-7.54	-8.64	-6.24
24		-8.01	-8.71	-6.76

25		-7.25	-8.34	-6.47
26		-7.24	-8.29	-6.45
Compounds	Structure	ΔE (1ZXM)	ΔE (1BNA)	ΔE (1LU51)
27		-6.95	-8.47	-6.23
28		-7.68	-8.43	-6.59
29		-7.35	-9.22	-6.27
30		-7.02	-8.57	-6.55
31		-7.72	-8.65	-6.05

32		-7.66	-8.74	-6.85
33		-7.74	-8.45	-6.57
Compounds	Structure	ΔE (1ZXM)	ΔE (1BNA)	ΔE (1LU51)
DMXAA		-8.69	-6.74	-4.85

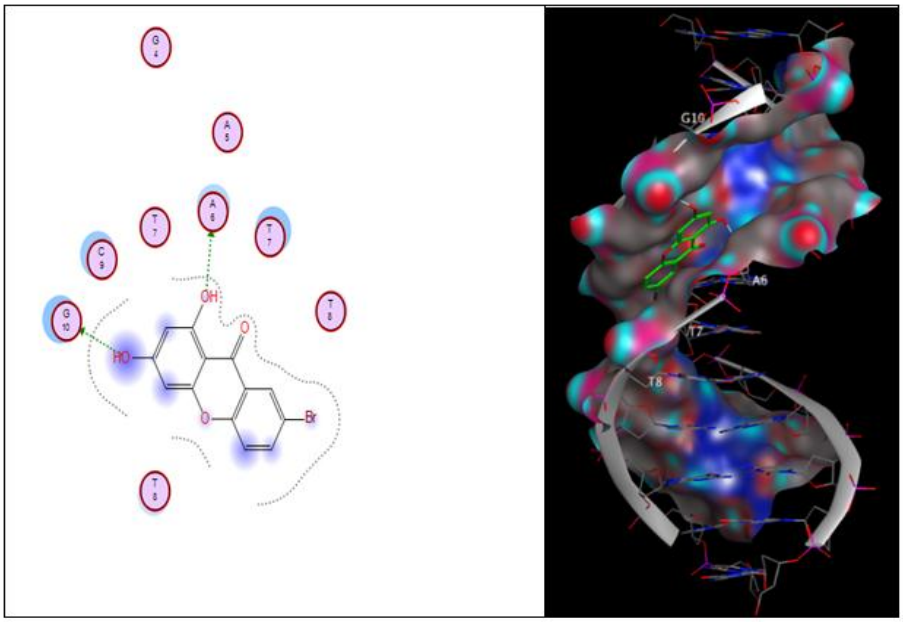


Figure 1: 2D and 3D representation of the interaction mode of compound 1 with key organic residues at the active site of receptor 1BNA.

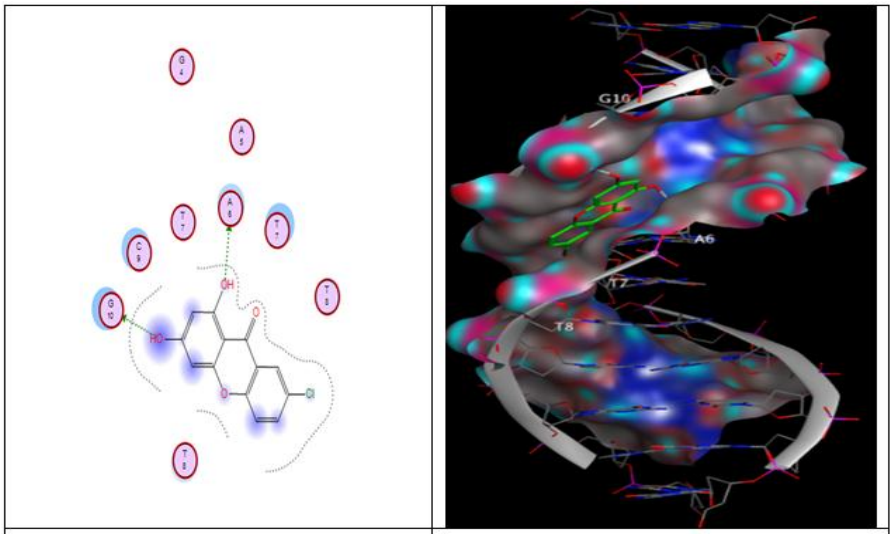


Figure 2 . 2D and 3D representation of the interaction mode of compound 2 with key organic residues at the active site of receptor 1BNA.

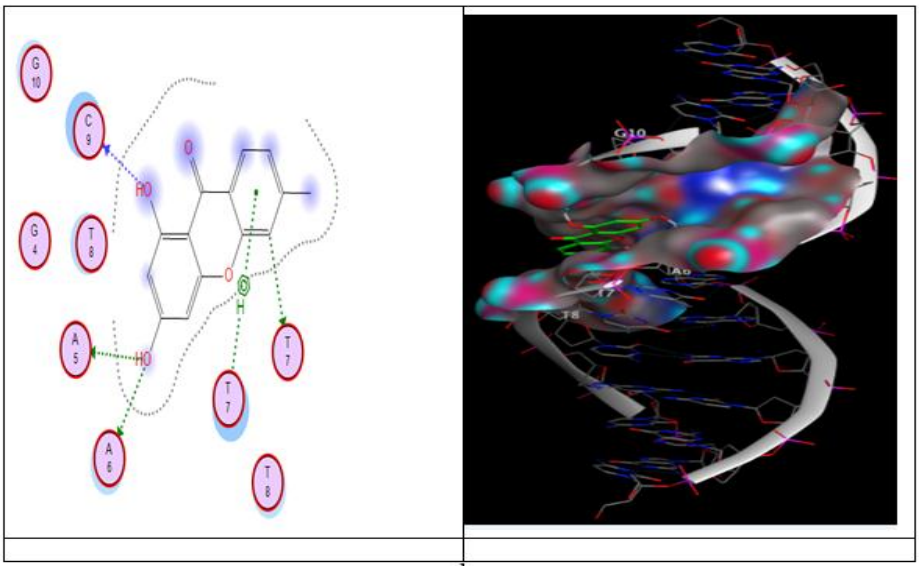


Figure 3. 2D and 3D representation of the interaction mode of compound 3 with key organic residues at the active site of receptor 1BNA.

Validation of molecular docking can be done using various methods to assess the accuracy of the docking process and the scoring function. One common method is to calculate the root mean square deviation (RMSD) of the atomic coordinates of the main ligand conformation extracted from the crystallographic structure and the top-ranked conformer predicted by the docking calculations as a measure of the accuracy of the predicted conformation. Another method to measure the performance of the molecular docking algorithm is to evaluate the software's ability

to predict the crystallographic binding mode of the ligand to the same receptor, which is measured by defining the root mean square deviation from the crystallographic state. The predicted conformer by docking should have an RMSD of less than Å2 compared to the crystallographic structure (usually between 1.5 to 5 Å2 depending on the size of the ligand). This process was performed for the receptors under investigation, and the RMSD result was less than Å2.

The Molecular docking of 34 compounds with structures of 1ZXM, 1BNA, and 1LU51 has been investigated. The binding energies of the compounds to these three targets are listed in Table (1). As observed in this table, in the docking of these compounds with the 1ZXM receptor, the docking binding energy is in the range of -6.87 to -8.69 kcal/mol, and the best binding energy is related to the LigDMXAA ligand. In the docking of these compounds with the 1BNA receptor, the docking binding energy is in the range of -6.47 to -9.36 kcal/mol, and the best binding energy is related to compound 1. Finally, in the docking of these compounds with the 1LU51 receptor, the docking binding energy is in the range of -4.85 to -6.99 kcal/mol, and the best energy is related to compound 1. After determining the position of each compound in the docking ranking, an important factor that was investigated is the interaction patterns of the compounds with key amino acids at the active site of the 1ZXM, 1BNA, and 1LU51 receptors. To evaluate the interaction mode of the predicted models by docking with the active site of 1ZXM, 1BNA, and 1LU51, the 2D and 3D maps of the compounds' binding to these three targets were used, and three examples of interactions are provided below. For example, in the case of compound 1 interacting with the 1ZXM receptor, it forms hydrogen bonds with the amino acid residues Lys27, Thr28, and Glu31. In the case of compound 2 interacting with the 1BNA receptor, it forms hydrogen bonds with the amino acid residues Glu129, Asp151, and Lys153. Finally, in the case of compound 3 interacting with the 1LU51 receptor, it forms hydrogen bonds with the amino acid residues Asn22, Asp25, Asp26, and Lys27.

These interactions show the importance of considering the interaction patterns of the compounds with key amino acids at the active site of the receptors in the molecular docking process, which can provide valuable insights into the binding mechanisms of the compounds and aid in the design of more potent and selective ligands.

In Figure (1), the interaction between compound 1 and the 1BNA receptor is shown. This compound forms hydrogen bonds with the NH group of the guanine G10 residue through its own OH group attached to carbon 6, and with the NH group of the adenine A6 residue through its own OH group attached to carbon 8. In Figure (2), the interaction between compound 2 and the 1BNA receptor is shown. This compound forms hydrogen bonds with the NH group of the guanine G10 residue through its own OH group attached to carbon 6, and with the NH group of the adenine A6 residue through its own OH group attached to carbon 8. In Figure (3), the interaction between compound 3 and the 1BNA receptor is shown. This compound forms hydrogen bonds with the NH group of the thymine T7 residue through its OH group attached to carbon 1, with the NH groups of the adenine A6 and A5 residues through its own OH group attached to carbon 6, and with the NH group of the cytosine C9 residue through its own OH group attached to carbon 8. Additionally, it creates a pi-pi stacking interaction with the open ring of the thymine T7 residue through its own ring A structure.

conclusion

The results of molecular docking studies are one of the most common computational methods in the field of medicinal chemistry [16]. Molecular docking provides information such as the binding site of the ligand to the protein, the role of each amino acid of the protein or ligand atoms in the interaction, and their binding energies [17]. Pharmacophore maps containing the ligand-receptor binding pattern for the molecule set were obtained. After identifying the pharmacophore features and key interaction sites between the ligand and enzyme from the bond map, the appropriate orientation was determined at the active site of the receptor. The interaction mode of some compounds is shown in Figures 1 to 3.

Acknowledgments

The authors are grateful to Islamic Azad University, Khorramabad Branch, Iran for providing the financial support.

References

[1] NM . Reddy, SR . Kleeberger, TW. Kensler, M. Yamamoto, PM. Hassoun, SP. Reddy, JImmunol. 182,7264-71(2009).

[2] N . Shankaraiah, NP . Kumar, R. Tokala, BS. Gayatri, V. Talla, LS. Santos. J Braz Chem Soc. 30,454-61(2019).

[3] B. Ohadi, E. Azarnoosh, M. Vazirian, Z. Yasrebinezhad. Pharmacogn Res, 4,84 (2017).

[4] RL .Siegel, KD. Miller, A. Jemal. CA Cancer J Clin. 69(1):7-34(2019).

[5] C. T. Yen, K. N. Goto, T. L. Hwang, S. L. M . Natschke., K. F. Bastow, Y. C. Wu, K. H. Lee, Bioorg. Med. Chem. Lett. 22,4018(2012).

[6] J. J. Koh, S. Lin, T. T. Aung, F. Lim., H. Y. Zou, J. Med. Chem. 58,739(2015).

[7] A. M. Waszkielewicz, A. Gunia, N. Szkaradek, K. Pytka, A. Siwek, G. Satala, A. J. Bojarski, E. Szneler, H. Marona, Bioorg. Med. Chem. Lett .23,4419(2013).

[8] C. Portela, C. M. M. Afonso, M. M. M. Pinto, D. Lopes, F. Nogueira, V.Rosario, Chem. Biodiversity. 4,1508(2007).

[9] C. Fernandes, K. Masawang, M. E. Tiritan, E. Sausa, V. Lima, C. Afonso, H. Bousbaa, W. Sudprasert, M. Pedro, M. M. M. Pinto ,Bioorg. Med. Chem. 22,1049(2014).

[10] S. Alam, F. Khan. Scientific Reports. 8,55(2018).

[11] Q. Su, Y. Liu, Y. Cai, Y. Sun, B . Wang, LJ . Xian, Invest New Drugs. 29,1230(2011).

[12] NM . Reddy, SR. Kleeberger, TW. Kensler, M . Yamamoto, PM . Hassoun, SP. Reddy. JImmunol , 183,4601(2009).

[13] GM . Morris, R . Huey, W . Lindstrom, MF . Sanner, RK . Belew, DS . Goodsell,A . Olson, J Comput Chem. 30,2785(2009).

[14] GM. Morris, D.S. Goodsell, RS. Halliday, R. Huey, W.E. Hart, R.K Belew, A.J.J. Olson. Comput. Chem. 19, 1639(1998).

[15] M . Khaledi, H . Ziyaee Qychan Atiq, N . Chamkouri, A . Mojaddami. Eurasian Chem Commun, 1,419(2019).

[16] FN. Novikov, GG. Chilov, Mendeleev Communications 5, 237(2009).

[17] B . Taheri, M . Taghavi, M . Zarei, N. Chamkouri, A . Mojaddami. Bull Chem Soc Ethiop. 34,377(2020).

HOW TO CITE THIS ARTICLE

Shabnam Shamei[1*], Zahra akbari[2], Molecular docking studies on some derivatives of xanthones as potential anticancer agents" International Journal of New Chemistry., 2024; 11(4), 337-349. DOI: 10.22034/ijnc.2023.2003521.1340