Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 13, Issue 6, 2023, 515
https://doi.org/10.33263/BRIAC136.515

Theoretical Evaluation of the Interaction of a Series of Chalcone Derivatives on CK2 Protein Surface

Figueroa-Valverde Lauro [1,*], Rosas-Nexticapa Marcela [2,*], Cervantes-Ortega Catalina [2], López-Ramos Maria [1], Díaz-Cedillo Francisco [3], Alvarez-Ramirez Magdalena [2], Mateu-Armad Maria Virginia [2]

1 Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp., México
2 Nutrition Laboratory, Faculty of Nutrition, Veracruzana University , Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México
3 Laboratory Organic Chemistry, National School of Biological Sciences, National Polytechnic Institute . Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, México, D.F. C.P. 11340
* Correspondence: lfiguero@uacam.mx (F.L.); rosasnm@yahoo.com (R.M.);

Scopus Author ID 55995915500
Received: 6.10.2022; Accepted: 13.11.2022; Published: 4.02.2023

Abstract: Several studies suggest that chalcone derivatives can produce a broad spectrum of biological activities such as antibacterial, antiulcer, antiviral, insecticidal, antiprotozoal, anti-cancer, and antifungal. Besides, other reports suggest that chalcone derivatives exert changes in the cardiovascular system; however, its site of action is not very clear; perhaps this phenomenon could be to differences involved in the chemical structure of chalcone derivatives. This research aimed to carry out a theoretical study on the interaction of a series of chalcone analogs (compounds 1 to 20) on casein kinase 2 (CK2) protein using 3fl5 protein and quinalizarine drug as theoretical tools in a theoretical model (DockingServer). The results showed that chalcone derivatives (compounds 2, 9, 11, and 19) could have a higher affinity for the 3fl5 protein surface translated as greater CK2 inhibition than quinalizarine. These data open the possibility that chalcone derivatives can produce changes in the biological function of CK2, resulting in a decrease in heart failure.

Keywords: chalcone; derivatives; theoretical study; docking.

1. Introduction

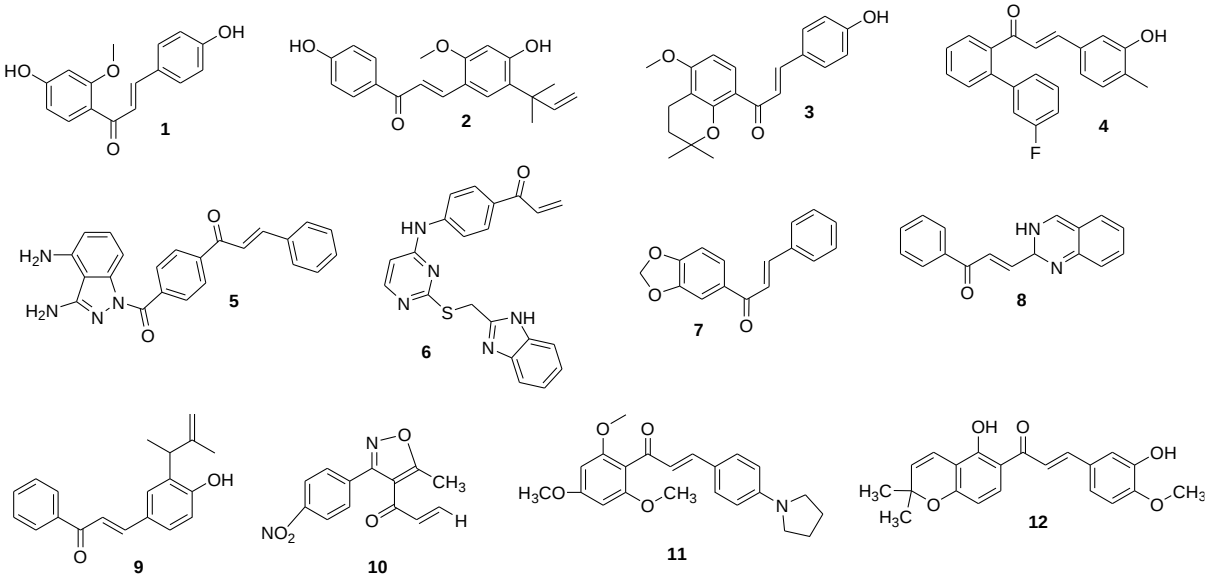
For several years, chalcone derivatives have been used in organic chemistry and pharmaceutical industry fields [1-4]. It is noteworthy that chalcone analogs are α-β-unsaturated ketones [5, 6], which can produce different biological activity against Parkinson's [7] cancer [8], gastric ulcer [9], malaria [10], antiviral [11-14], antibacterial [15], antifungal [16, 17]. Besides, some studies indicate that chalcone derivatives may exert changes in the cardiovascular system [18]; for example, difluoro-chalcone derivative protects cardiomyocytes from hyperglycemia-induced injuries through ROS (reactive oxygen species) and NF-kB (nuclear factor-κB) inhibition [19]. Other reports showed that a chalcone derivative can inhibit inflammation of human aortic smooth muscle cells through increased expression of peroxisome proliferator-activated receptor gamma [20]. Furthermore, a study shows that trans-chalcone inhibits transforming growth factor-β1 in rat heart connective tissue [21]. Recently, a report indicated that hesperidin methyl chalcone produces a cardioprotective through lipid peroxidation inhibition in vitro [22].

On the other hand, different theoretical models have been used to characterize the molecular mechanism involved in the biological activity produced by chalcone derivatives in the cardiovascular system. In this way, a theoretical study showed that some chalcone derivatives could produce a biological effect through interaction with HMG-CoA (β-hidroxi-β-metilglutaril-coenzima A) reductase using CASTp software [23]. Other data indicate that 3,5-disubstituted thiazolidinedione chalcone may interact with PPAR-γ (peroxisome proliferator-activated receptor gamma) using AutoDock-4.2 software [24]. In addition, a report displayed that dihydrospirochalcone-A could have an affinity to the eNOS enzyme (endothelial nitric oxide synthase) using a docking model [25]. All these data suggest that chalcone derivatives could produce changes in the cardiovascular system; however, there is no information on the effect produced by chalcone derivatives on protein kinases, specifically on CK2, which has been involved in heart failure patients [26-28]. Analyzing these data, this study aimed to conduct a theoretical study on the interaction of twenty chalcone analogs with Casein Kinase 2 (CK2) protein using Docking Server software [29].

2. Materials and Methods

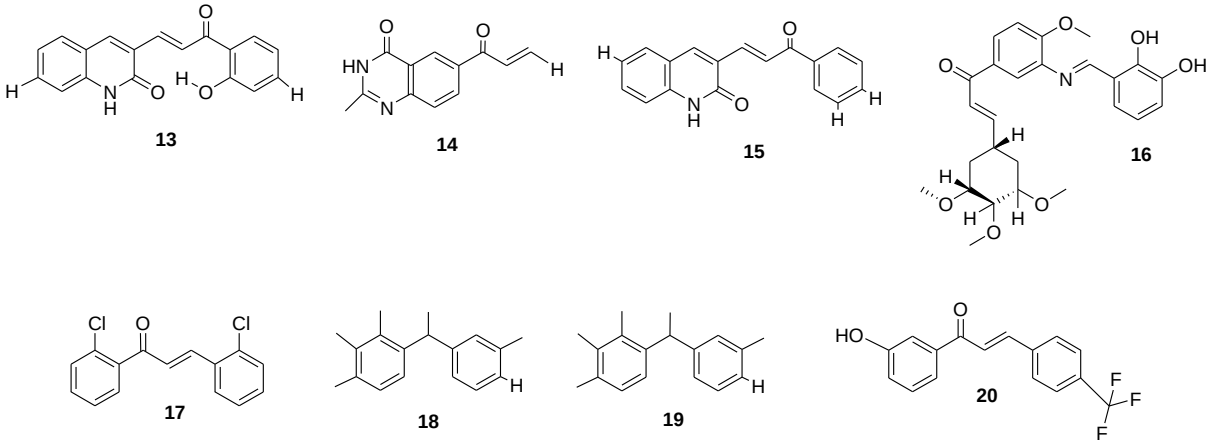
2.1. General methodology.

A series of chalcone derivatives previously reported [30] were used to evaluate their theoretical interaction with CK2 (Figures 1-2) as follows:



1 = 1-(4-Hydroxy-2-methoxy-phenyl)-3-(4-hydroxy-phenyl)-propenone.
2 = 3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1-(4-hydroxy-phenyl)-propenone.
3 = 3-(4-Hydroxy-phenyl)-1-(5-methoxy-2,2-dimethyl-chroman-8-yl)-propenone.
4 = 1-(3'-Fluoro-biphenyl-2-yl)-3-(3-hydroxy-4-methyl-phenyl)-propenone.
5 = 1-[4-(3,4-Diamino-indazole-1-carbonyl)-phenyl]-3-phenyl-propenone.
6 = 1-{4-[2-(1H-Benzoimidazol-2-ylmethylsulfanyl)-pyrimidin-4-ylamino]-phenyl}-propenone.
7 = 1-Benzo[1,3]dioxol-5-yl-3-phenyl-propenone.
8 = 3-(2,3-Dihydro-quinazolin-2-yl)-1-phenyl-propenone.
9 = 3-[3-(1,2-Dimethyl-allyl)-4-hydroxy-phenyl]-1-phenyl-propenone.
10 = 1-[5-Methyl-3-(4-nitro-phenyl)-isoxazol-4-yl]-propenone
11 = 3-(4-Pyrrolidin-1-yl-phenyl)-1-(2,4,6-trimethoxy-phenyl)-propenone.
12 = 1-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-(3-hydroxy-4-methoxy-phenyl)-propenone.

Figure 1. Structure chemical of chalcone derivatives (**1**-**10**).



13 = 3-[3-(2-Hydroxy-phenyl)-3-oxo-propenyl]-1H-quinolin-2-one.
14 = 6-Acryloyl-2-methyl-3H-quinazolin-4-one.
15 = 3-(3-Oxo-3-phenyl-propenyl)-1H-quinolin-2-one.
16 = 1-{3-[(2,3-Dihydroxy-benzylidene)-amino]-4-methoxy-phenyl}-3-(3,4,5-trimethoxy-cyclohexyl)-prope-none
17 = 1,3-Bis-(2-chloro-phenyl)-propenone.
18 = 1,2,3-Trimethyl-4-(1-m-tolyl-ethyl)-benzene.
19 = 3-[3-(1,2-Dimethyl-allyl)-4-hydroxy-phenyl]-1-phenyl-propenone.
20 = 1-(3-Hydroxy-phenyl)-3-(4-trifluoromethyl-phenyl)-propenone.

Figure 2. Structure chemical of chalcone analogs (**6-20**).

2.2. Pharmacophore model.

3D pharmacophore model for chalcone derivatives was evaluated using LigandScout 4.08 software [28, 29].

2.3. Ligand-protein interaction.

The interaction of chalcone derivatives with the CK2 protein surface was evaluated using 3fl5 protein as a theoretical model [30]. In addition, to evaluate the types of binding energy involved in the interaction of chalcone derivatives with the 3fl5 protein surface [33], the DockingServer software was used [29].

2.4 Pharmacokinetics parameter.

Pharmacokinetic parameters were determined using the SwissADME software [34, 35].

3. Results and Discussion

Several studies indicate that chalcone derivatives can affect the cardiovascular system differently [36-39]; however, the interaction with some biological molecules is unclear. Analyzing this data, in this investigation, the theoretical activity of a series of chalcone derivatives on the CK2 protein was evaluated as follows:

3.1. Pharmacophore model.

For several years, various theoretical methods have been developed to design new drugs for treating different diseases. For example, the pharmacophore model provides a new perspective on the design of new compounds useful for developing new drugs. Based on these data, in this study, the LigandScout software [17, 18] was used to design a pharmacophore model to evaluate the possible chemical interactions of chalcone derivatives (compound 1-20) with some biomolecules such as CK2 protein. The results showed differences in functional

groups involved in the chemical structure of the chalcone derivatives, which could interact through hydrophobic or hydrogen bonds with CK2 protein (Figures 3 and 4; Table 1).

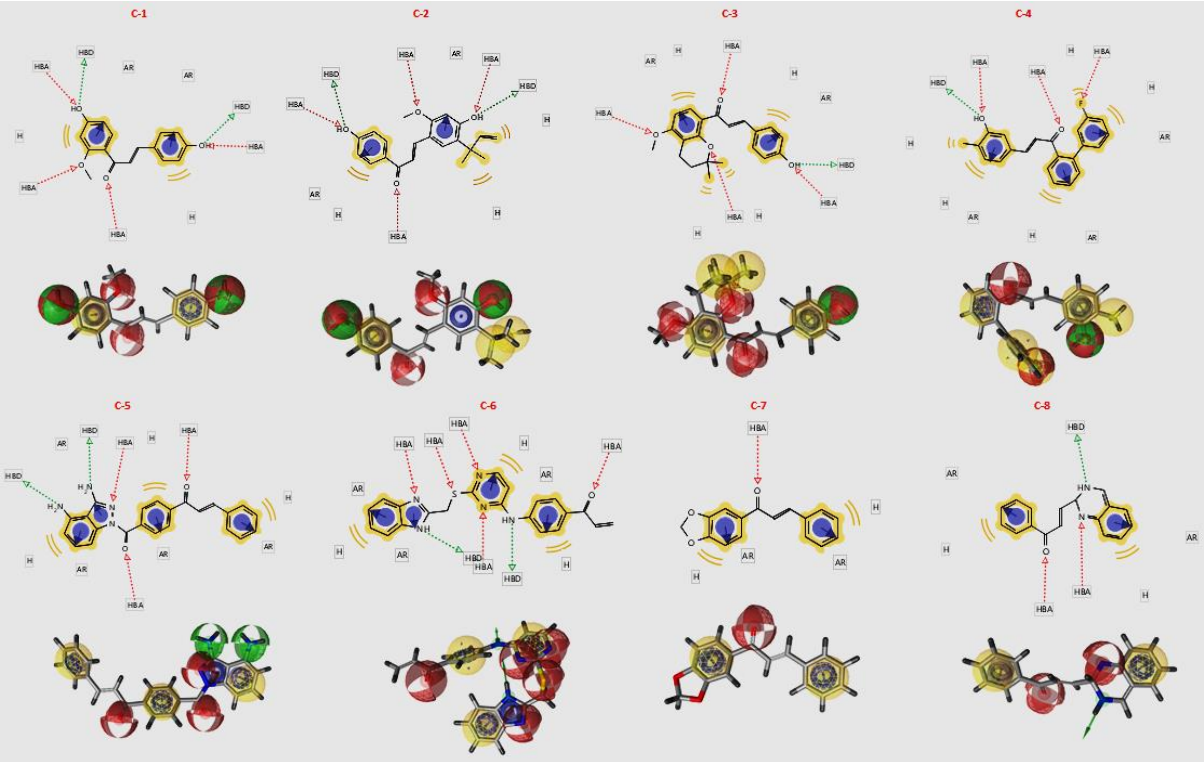


Figure 3. Pharmacophore was developed for chalcone derivatives (compounds **1** to **8**) using the LigandScout software. Hydrogen bond acceptors (HBA, red) and hydrogen bond donors (HBD, green).

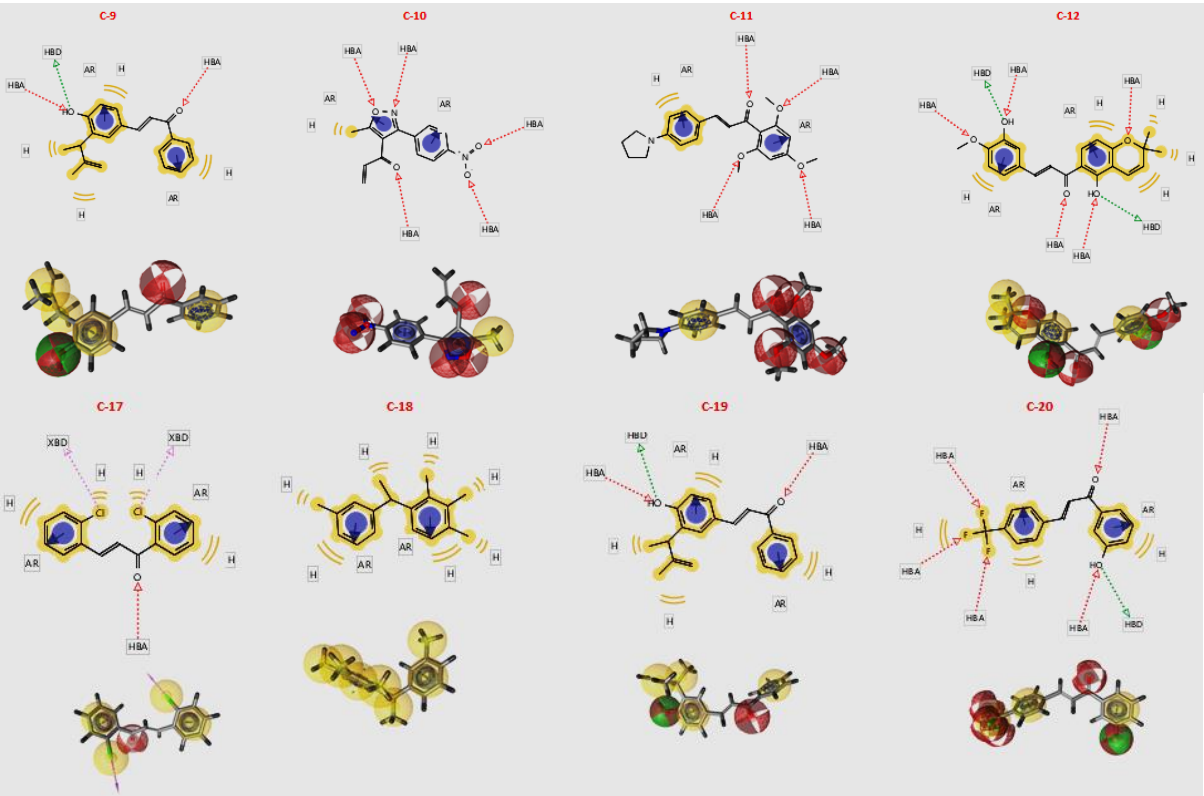


Figure 4. Pharmacophore was prepared to chalcone derivatives (compounds 9 to 20) using the LigandScout software. Hydrogen bond acceptors (HBA, red) and hydrogen bond donors (HBD, green).

Table 1. Physicochemical parameters of chalcone derivatives (Compounds **1** to **20**).

Compound	Concensus Log $P_{o/w}$	HBA	HBD	Molar refracty	TPSA Å
Quinalizarin	1.38	6	4	67.94	115.06
1	2.55	4	2	76.79	66.76
2	3.93	4	2	100.39	66.76
3	3.85	4	1	98.57	55.76
4	3.85	3	1	98.63	37.30
5	3.39	3	2	114.52	104.00
6	3.60	4	2	111.96	108.86
7	3.17	3	0	72.31	35.53
8	2.46	2	1	95.39	41.46
9	4.95	2	1	91.99	37.30
10	1.87	5	0	70.25	88.92
11	3.69	4	0	110.37	48.00
12	3.60	5	2	100.91	75.99
13	3.03	3	2	86.40	70.16
14	1.76	3	1	61.86	62.82
15	3.23	2	1	84.38	49.93
16	3.01	8	2	129.61	106.81
17	4.50	1	0	76.27	17.07
18	5.30	0	0	80.57	0.00
19	4.48	2	1	91.99	37.30
20	3.96	5	1	73.27	37.30

3.2. Interaction theoretical evaluation.

Several theoretical methods have been used to predict some ligands' interaction with proteins and enzymes [40, 41].

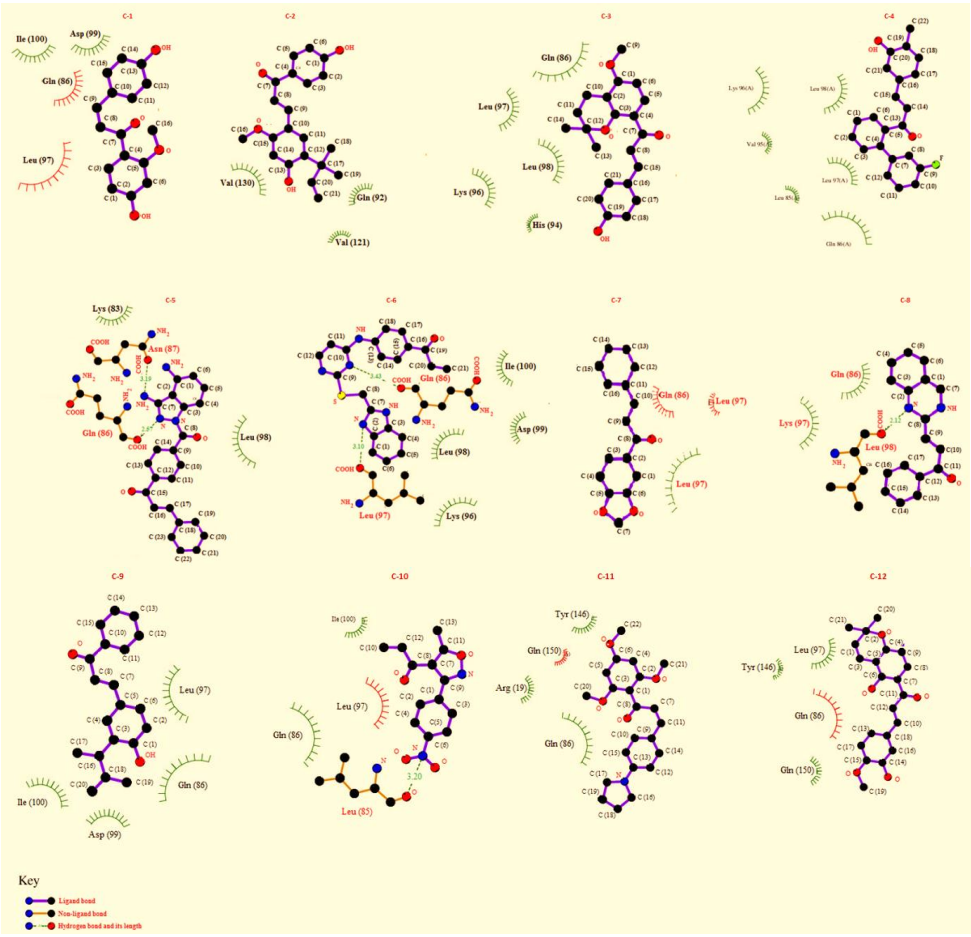


Figure 5. The scheme shows the binding sites of chalcone derivatives (C-1 to C-12) with some amino acid residues involved on the protein kinase surface (3FL5). The visualization was carried out using DockingServer software.

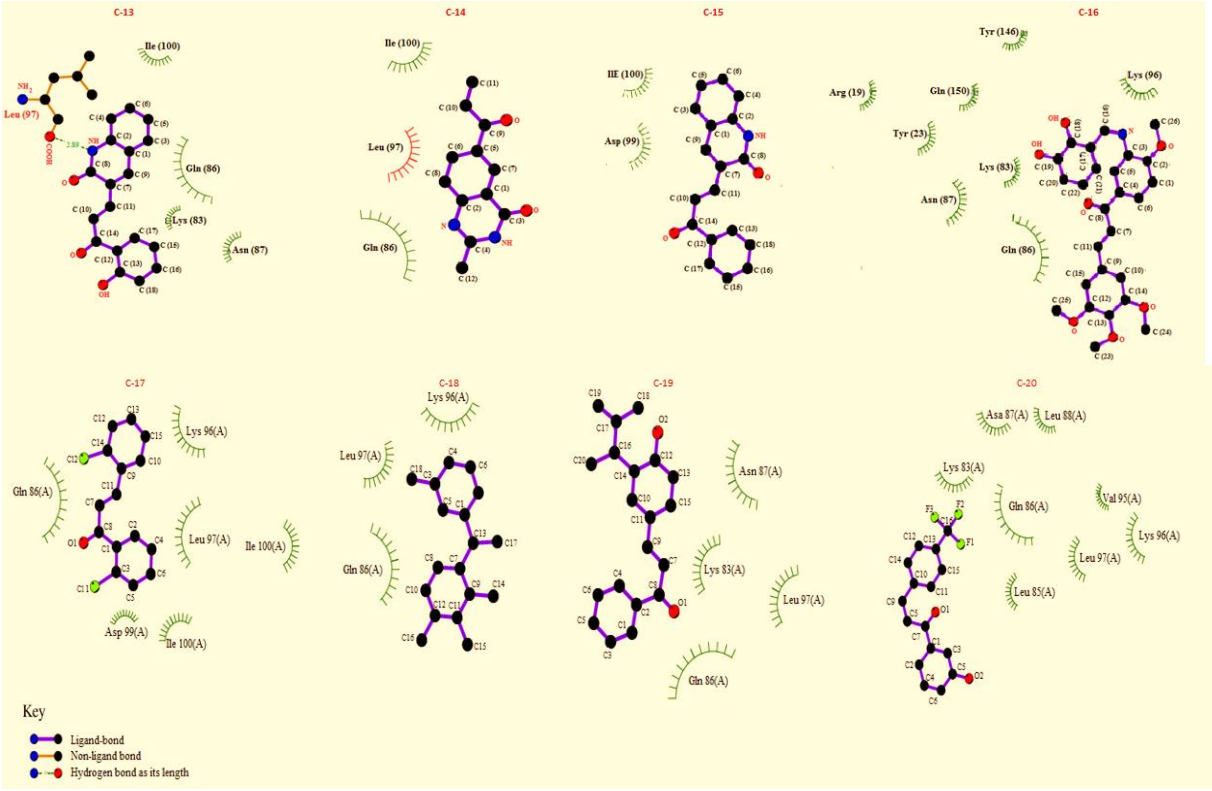


Figure 6. The Figure display some binding sites of chalcone derivatives (C-13 to C-20) with some amino acid residues involved on *the* protein kinase surface (3FL5). The visualization was carried out using DockingServer software.

Notably, the molecular recognition of protein-ligand interactions is essential to understand some biological activities, which can be of great importance for designing and developing new compounds with pharmacological activity [42]. Besides, it is important to mention that the drug quinalizarine was used as a control because some reports indicate that this drug can produce changes in the biological activity of CK2 [28, 43]. The results showed different amino acid residues involved in the interaction of chalcone derivatives with 3fl5 protein surface compared with quinalizarin (Figures 5 and 6; Table 2); this phenomenon could be due to differences in their chemical structure (Figures 1 and 2).

Table 2. Aminoacid residues involved in the interaction of chalcone derivatives (1 to 20) and quinalizarin with 3fl5-protein surface.

Compound	Aminoacid Residues
Quinalizarin	Gly_{86}, Leu_{97}, Ile_{100}
C-1	Gln_{86}, Leu_{97}, Asp_{99}, Ile_{100}
C-2	Arg_{13}, Tyr_{23}, $Asn_{87}Tyr_{146}$, Gln_{158}
C-3	Gl_{86}, Lys_{96}, Leu_{97}, Leu_{98}
C-4	Leu_{85}, Gln_{86}, Val_{96}, Lys_{96}, Leu_{97}, Leu_{98}
C-5	Lys_{83}, Gln_{86}, Asn_{87}, Leu_{98}
C-6	Gly_{86}, Lys_{96}, Leu_{97}, Leu_{98}, Asp_{99}, Ile_{100}
C-7	Gln_{86}, Lys_{96}, Leu_{97}
C-8	Gln_{86}, Leu_{97}, Asp_{99}
C-9	Gln_{86}, Leu_{97}, Asp_{99}, Ile_{100}
C-10	Gln_{86}, Gln_{86}, Leu_{97}, Ile_{100}
C-11	Arg_{19}, Gln_{86}, Tyr_{146}, Gln_{150}
C-12	Gln_{86}, Leu_{97}, Tyr_{146}, Gln_{150}
C-13	Lys_{83}, Gln_{86}, $Asn_{87}Leu_{97}$, Ile_{100}
C-14	Glu_{86}, Leu_{97} Ile_{100}
C-15	Asp_{99}, Ile_{100}

Compound	Aminoacid Residues
C-16	Arg_{19}, Tyr_{23}, Lys_{83}, Gln_{86}, Asn_{87}, Lys_{96}, Tyr_{146}, Gln_{150}
C-17	Gln_{86}, Lys_{96}, Leu_{97}, Asp_{99}, Ile_{100}
C-18	Gln_{86}, Lys_{96}, Leu_{97}, Ile_{100}
C-19	Lys_{83}, Gln_{86}, Asn_{87}, Leu_{97}
C-20	Lys_{83}, Leu_{85}, Gln_{86}, Asn_{87}, Leu_{88}, Val_{95}, Lys_{96}, Leu_{97}

3.3 Bond energies.

Some studies suggest that different thermodynamic factors could be involved in the drug-protein interaction, such as i) binding free energy, which involves the energy level produced by ligand-protein interaction; *ii*) ii) electrostatic energy that involves an electrical charge and electrostatic potential; *iii*) total intermolecular energy; and *iv*) Van der Waals (vdW) interactions, hydrogen bond (H bond), desolvation energy [44, 45]. Based on these data, in this research, some thermodynamic parameters involved in the interaction of chalcone derivatives with CK2 surface (3fl 5 protein) were evaluated using quinalizarin as a control. Table 3 shows the energy requirements involved in the interaction of compounds 2, 9, 11, and 19 with the 3fl5 protein surface were lower compared to compounds 1, 3-8, 10-18, 20, and quinalizarin. The results indicate that these compounds could interact with the surface of the 3RUK protein, implying differences in energy levels and constant inhibition. This phenomenon may result in changes in the biological activity of the CK2 enzyme, which translates into a decrease in heart failure.

Table 3. Thermodynamic parameters involved the interaction of Bay-K-8644 drug and compounds **4** with 1t0j-protein surface.

Compound	Est: Free Energy of Binding (kcal/mol)	Est. Inhibition Constant, Ki (mM)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy	Total Intermolec. Energy (kcal/mol)	Interact. Surface
Quinalizarin	-5.09	185.45	-3.57	-0.32	-3.89	437.26
C-1	-3.60	2.31	-5.01	-0.11	-5.11	514.86
C-2	-2.98	6.57	-5.25	0.03	-5.28	611.65
C-3	-4.10	993.60	-5.33	0.11	-5.22	535.19
C-4	-5.65	72.29	-6.72	-0.02	-6.74	554.13
C-5	-5.13	173.28	-6.13	-0.28	-6.40	631.31
C-6	-6.34	22.59	-6.54	-0.10	-6.64	626.60
C-7	-4.17	882.31	-5.06	1.05	-5.00	505.48
C-8	-4.24	779.52	-4.61	-0.38	-4.99	545.77
C-9	-3.84	1.52	-5.41	-0.15	-5.96	577.09
C-10	-5.06	195.53	-6.12	-0.14	-6.26	474.70
C-11	-3.26	4.05	-5.13	-0.10	-5.23	674.48
C-12	-4.49	513.08	-5.44	-0.21	-5.66	662.33
C-13	-4.80	301.75	-5.30	-0.03	-5.33	515.46
C-14	-4.77	321.26	-5.19	-0.16	-5.35	479.32
C-15	-4.49	510.79	-5.32	-0.06	-5.38	572.74
C-16	-5.07	190.89	-7.09	-0.11	-7.20	711.60
C-17	-5.54	87.32	-6.39	-0.01	-6.40	552.05
C-18	-5.61	77.57	-5.98	-0.01	-5.99	529.89
C-19	-3.69	1.98	-5.36	-0.08	-5.44	540.00
C-20	-4.41	590.31	-5.78	-0.11	-5.89	482.66

3.7. Pharmacokinetic evaluation.

For several years, different protocols have been used to predict some pharmacokinetic parameters, such as PKQuest [46], PharmPK [47], and SwissADME [48]. In this investigation, some pharmacokinetic factors involved in chalcone derivatives were analyzed using

SwissADME software (Table 3). The results showed differences in gastrointestinal absorption and metabolism (involving different types of cytochrome P450 systems). This phenomenon could depend on each chalcone derivative's chemical structure and the lipophilicity degree (Tables 1, 4, and 5).

Table 4. Pharmacokinetic parameters involved in the chemical structure of compounds 1 to 10.

Parameter	1	2	3	4	5	6	7	8	9	10
GI absorption	High	High	High	High	High	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
P-gp substrate	No	No	No	No	No	No	No	No	Yes	No
CyP1A2 Inhibitor	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
CyP2C19 Inhibitor	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
CyP2C9 Inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
CyP2D6 Inhibitor	No	No	Yes	Yes	No	Yes	No	No	Yes	No
CyP3A4 Inhibitor	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No

Table 5. Pharmacokinetic parameters involved in the chemical structure of compounds 11 to 20.

Parameter	11	12	13	14	15	16	17	18	19	20
GI absorption	High	High	High	High	High	High	High	Low	High	High
BBB permeant	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
P-gp substrate	No	No	No	No	No	Yes	No	No	Yes	No
CyP1A2 Inhibitor	No	Yes	No	Yes	No	No	Yes	No	Yes	Yes
CyP2C19 Inhibitor	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes
CyP2C9 Inhibitor	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No
CyP2D6 Inhibitor	No	No	No	No	No	Yes	No	Yes	Yes	Yes
CyP3A4 Inhibitor	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes

4. Conclusions

Theoretical analyzes on the interaction of chalcone derivatives (compounds 2, 9, 11, and 19) with the 3fl5 protein surface suggest that these chalcone derivatives might have a higher affinity for 3fl5 translated as greater CK2 inhibition compared to quinalizarine drug. These data open the possibility that chalcone derivatives can produce changes in the biological function of CK2, resulting in a decrease in heart failure.

Funding

This research received no external funding.

Acknowledgments

None.

Conflicts of Interest

We declare that this manuscript has no conflict of financial interests (political, personal, religious, ideological, academic, intellectual, commercial, or otherwise) for publication.

References

1. Liu, S.; Zhang, Y.; Sun, K.; Graff, B.; Xiao, P.; Dumur, F.: Lalevée, J. Design of photoinitiating systems based on the chalcone-anthracene scaffold for LED cationic photopolymerization and application in 3D printing. *European Polymer Journal* **2021**, *147*, 110300, https://doi.org/10.1016/j.eurpolymj.2021.110300.
2. Chen, H.; Noirbent, G.: Liu, S.: Brunel, D.: Graff, B.; Gigmes, D.; Lalevée, J. Bis-chalcone derivatives derived from natural products as near-UV/visible light sensitive photoinitiators for 3D/4D printing. *Materials Chemistry Frontiers* **2021**, *5*, 901-916, https://doi.org/10.1039/D0QM00755B.
3. Ibrahim-Ouali, M.; Dumur, F. Recent advances on chalcone-based photoinitiators of polymerization. *European Polymer Journal* **2021**, *158*, 110688, https://doi.org/10.1016/j.eurpolymj.2021.110688.
4. Fayed, E.; Eldin, R.; Mehany, A.; Bayoumi, A.;Ammar, Y. Isatin-Schiff's base and chalcone hybrids as chemically apoptotic inducers and EGFR inhibitors; design, synthesis, anti-proliferative activities and in silico evaluation. *Journal of Molecular Structure* **2021**, *1234*, 130159, https://doi.org/10.1016/j.molstruc.2021.130159.
5. Goyal, K.; Kaur, R.; Goyal, A.; Awasthi, R. Chalcones: A review on synthesis and pharmacological activities. *Journal of Applied Pharmaceutical Science* **2021**, *11*, 001-014. https://doi.org/10.7324/JAPS.2021.11s101
6. Narwal, S.; Kumar, S.; Verma, P. Synthesis and biological activity of new chalcone scaffolds as prospective antimicrobial agents. *Research on Chemical Intermediates* **2021**, *47*, 1625-1641, https://link.springer.com/article/10.1007/s11164-020-04359-6.
7. Thapa, P.; Upadhyay, S.; Suo, W.; Singh, V.; Gurung, P.; Lee, E.; Sharma, M. Chalcone and its analogs: Therapeutic and diagnostic applications in Alzheimer's disease. *Bioorganic Chemistry* **2021**, *108*, 104681, https://doi.org/10.1016/j.bioorg.2021.104681.
8. Ouyang, Y.; Li, J.; Chen, X.; Fu, X.; Sun, S.; Wu, Q. Chalcone derivatives: Role in anti-cancer therapy. *Biomolecules* **2021**, *11*, 894, https://doi.org/10.3390/biom11060894.
9. Liu, C.; Song, J.; Cui, X.; Liu, W.; Li, Y.; Yu, G.; Zhang, S. Discovery of novel 1, 2, 4-triazine-chalcone hybrids as anti-gastric cancer agents via an axis of ROS-ERK-DR5 in vitro and in vivo. *Arabian Journal of Chemistry* **2022**, *15*, 103644, https://doi.org/10.1016/j.arabjc.2021.103644.
10. Vinindwa, B.; Dziwornu, G.; Masamba, W. Synthesis and evaluation of Chalcone-Quinoline based molecular hybrids as potential anti-malarial agents. *Molecules* **2021**, *26*, 4093, https://doi.org/10.3390/molecules26134093.
11. Duran, N.; Polat, M.; Aktas, D.; Alagoz, M.; Ay, E.; Cimen, F.; Algul, O. New chalcone derivatives as effective against SARS-CoV-2 agent. *International Journal of Clinical Practice* **2021**, *75*, e14846, https://doi.org/10.1111/ijcp.14846.
12. Elkanzi, N.; Hrichi, H.; Alolayan, R.; Derafa, W.; Zahou, F.; Bakr, R. Synthesis of Chalcones Derivatives and Their Biological Activities: A Review. *ACS Omega* **2022**, *7*, 27769-27786, https://doi.org/10.1021/acsomega.2c01779.
13. Zhou, X.; Ye, Y.; Liu, S.; Shao, W.; Liu, L.; Yang, S.; Wu, Z. Design, synthesis and anti-TMV activity of novel α-aminophosphonate derivatives containing a chalcone moiety that induce resistance against plant disease and target the TMV coat protein. *Pesticide Biochemistry and Physiology* **2021**, *172*, 104749, https://doi.org/10.1016/j.pestbp.2020.104749.
14. Elkhalifa, D.; Al-Hashimi, I.; Al Moustafa, A.; Khalil, A. A comprehensive review on the antiviral activities of chalcones. *Journal of Drug Targeting* **2021**, *29*, 403-419, https://doi.org/10.1080/1061186X.2020.1853759.
15. Da Silva, P.; Xavier, J.; Freitas, T.; Oliveira, M.; Coutinho, H.; Leal, A.; Teixeira, A. Synthesis, spectroscopic characterization and antibacterial evaluation by chalcones derived of acetophenone isolated from Croton anisodontus Müll. Arg. *Journal of Molecular Structure* **2021**, *1226*, 129403, https://doi.org/10.1016/j.molstruc.2020.129403.

16. Shinde, R.; Adole, V.; Jagdale, B. Synthesis, Computational, Antibacterial and Antifungal Investigation of Two Tri-Fluorinated Chalcones of 1-(2, 3-Dihydrobenzo [b][1, 4] dioxin-6-yl) ethan-1-one. *Polycyclic Aromatic Compounds* **2021**, *42*, 1-18, https://doi.org/10.1080/10406638.2021.1977346.
17. Salehi, B.; Quispe, C.; Chamkhi, I.; El Omari, N.; Balahbib, A; Sharifi-Rad, J.; Les, F. Pharmacological properties of chalcones: a review of preclinical including molecular mechanisms and clinical evidence. *Frontiers in Pharmacology* **2021**, *11*, 592654, https://doi.org/10.3389/fphar.2020.59265.
18. Mahapatra, D.; Bharti, S. Therapeutic potential of chalcones as cardiovascular agents. *Life Sciences* **2016**, *148*, 154-172, https://doi.org/10.1016/j.lfs.2016.02.048.
19. Zhong, P.; Wu, L.; Qian, Y.; Fang, Q.; Liang, D.; Wang, J.; & Liang, G. Blockage of ROS and NF-κB-mediated inflammation by a new chalcone L6H9 protects cardiomyocytes from hyperglycemia-induced injuries. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* **2015**, *1852*, 1230-1241. https://doi.org/10.1016/j.bbadis.2015.02.011.
20. Liu, C.; Chang, C.; Du, Y.; Chang, F.; Wu, Y.; Chang, W.; & Hsieh, T. 2-Hydroxy-4'-Methoxychalcone Inhibits Proliferation and Inflammation of Human Aortic Smooth Muscle Cells by Increasing the Expression of Peroxisome Proliferator–Activated Receptor Gamma. *Journal of Cardiovascular Pharmacology* **2012**, *59*, 339-351, https://doi.org/10.1097/FJC.0b013e3182440486.
21. Karimi S.; Jeddi, S.; Alipour, M. *trans*-Chalcone inhibits transforming growth factor-β1 and connective tissue growth factor-dependent collagen expression in the heart of high-fat diet-fed rats. *Archives of Physiology and Biochemistry* **2020**, *128*, 1221-1224, https://doi.org/10.1080/13813455.2020.1764045.
22. Aswini, G.; Manjunatha, P.; Mudagal, R. Ameliorative effect of Hisperidin methyl chalcone om isoproterenol-induced oxidative damage in rat myocardium. *World Journal of pharmaceutical Research* **2020**, *9*, 748-764, https://wjpr.s3.ap-south-1.amazonaws.com/article_issue/1601448493.pdf.
23. Chandran, M.; Synthesis and molecular docking studies of certain chalcones of benzimidzole. *Journal of Pharmacy Research*, **2012**, *5*, 324-326, https://www.academia.edu/20860061/Synthesis_and_molecular_docking_studies_of_certain_chalcones_of_benzimidzole.
24. Fathima, F.; Haridas, A.; Lakshmanan, B. Docking studies of 3, 5-disubstituted thiazolidinedione chalcones as PPAR-γ agonist. *Journal of Pharmaceutical Chemistry* **2016**, *3*, 19-23, https://pubs.vensel.org/index.php/jphchem/article/view/64.
25. Avila, Villarreal.; Hernández, A.; Hidalgo, F.; Navarrete, V.; Escalante, E.; Peña, R.; Estrada, Soto. Antihypertensive and vasorelaxant effects of Dihydrospinochalcone-A isolated from Lonchocarpus xuul Lundell by NO production: Computational and ex vivo approaches. *Phytomedicine* **2013**, *20*,1241-1246, https://doi.org/10.1016/j.phymed.2013.06.011.
26. Yang, D.; Wang, T.; Ni, Y.; Song, B.; Ning, F.; Hu, P.; Ma, A. Apamin-sensitive K+ current upregulation in volume-overload heart failure is associated with the decreased interaction of CK2 with SK2. *The journal of Membrane Biology* **2015**, *248*, 1181-1189, https://doi.org/10.1007/s00232-015-9839-0.
27. Schechter, M.; Hsieh, M.; Njoroge, L.; Thompson, J.; Soderblom, E.; Feger, B.; Bowles, D. Phosphoproteomic profiling of human myocardial tissues distinguishes ischemic from non-ischemic end stage heart failure. *PLoS One* **2014**, *9*, e104157, https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0104157.
28. Lauro, F.; Francisco, D.; Marcela, R. N.; Virginia, M.; Eduardo, P.; Maria, L.; Jhair, C. Preparation of a steroid-oxazole-1, 2′-[1, 3] oxazete] derivative: biological and theoretical evaluation of its interaction with a kinase protein (CK2). *SN Applied Sciences* **2019**, *1*, 1-12.
29. Kong, R.; Yang, G.; Xue, R.; Liu, M.; Wang, F.; Hu, J.; Chang, S. COVID-19 Docking Server: A meta server for docking small molecules, peptides and antibodies against potential targets of COVID-19. *Bioinformatics* **2020**, *36*, 5109-5111, https://doi.org/10.1093/bioinformatics/btaa645.
30. Kar, M.; Asati, V.; Bharti, S. An updated patent review of therapeutic applications of chalcone derivatives (2014-present). *Expert Opinion on Therapeutic Patents* **2019**, *29*, 385-406, https://doi.org/10.1080/13543776.2019.1613374.
31. Abe, H.; Okazawa, M.; Oyama, T.; Yamazaki, H.; Yoshimori, A.; Kamiya, T.; Tanuma, S. A Unique Anti-Cancer 3-Styrylchromone Suppresses Inflammatory Response via HMGB1-RAGE Signaling. *Medicines* **2021**, *8*, 17, https://doi.org/10.3390/medicines8040017.
32. Alamri, M.; ul Qamar, M.; Afzal, O.; Alabbas, A.; Riadi, Y.; Alqahtani, S. Discovery of anti-MERS-CoV small covalent inhibitors through pharmacophore modeling, covalent docking and molecular dynamics simulation. *Journal of Molecular Liquids* **2021**, *330*, 115699, https://doi.org/10.1016/j.molliq.2021.115699.

33. Graciotti M, Alam M, Solyakov L, Schmid R, Burley G, Bottrill A, Tobin A. Malaria protein kinase CK2 (PfCK2) shows novel mechanisms of regulation. *PLoS ONE* **2014**, *9*, 1-8, https://doi.org/10.1371/journal.pone.0085391.
34. Mahanthesh, M.; Ranjith, D.; Yaligar, R.; Jyothi, R.; Narappa, G.; Ravi, M. Swiss ADME prediction of phytochemicals present in Butea monosperma (Lam.) Taub. *Journal of Pharmacognosy and Phytochemistry* **2020**, *9*, 1799-1809, https://www.phytojournal.com/archives/2020.v9.i3.11579/swiss-adme-prediction-of-phytochemicals-present-in-butea-monosperma-lam-taub.
35. Kadri, A.; Aouadi, K. In vitro antimicrobial and α-glucosidase inhibitory potential of enantiopure cycloalkylglycine derivatives: Insights into their in silico pharmacokinetic, druglikeness, and medicinal chemistry properties. *Journal of Applied Pharmaceutical Science* **2020**, *10*, 107-115, https://doi.org/10.7324/JAPS.2020.10614.
36. Opletalova, V.; Jahodar, L.; Jun, D.; Opletal, L. Chalcones (1, 3-diarylpropen-1-ones) and their analogs as potential therapeutic agents in cardiovascular system diseases. *Ceska a Slovenska farmacie:Casopis Ceske Farmaceuticke Spolecnosti a Slovenske Farmaceuticke Spolecnosti* **2003**, *52*, 12-19, https://pubmed.ncbi.nlm.nih.gov/12685329/.
37. Mahapatra, D.; Bharti, S. Therapeutic potential of chalcones as cardiovascular agents. *Life Sciences* **2016**, *148*, 154-172, https://doi.org/10.1016/j.lfs.2016.02.048.
38. Karkhaneh, L.; Yaghmaei, P.; Parivar, K.; Sadeghizadeh, M.; Ebrahim-Habibi, A. Effect of trans-chalcone on atheroma plaque formation, liver fibrosis and adiponectin gene expression in cholesterol-fed NMRI mice. *Pharmacological Reports* **2016**. *68*, 720-727, https://doi.org/10.1016/j.pharep.2016.03.004.
39. Zhong, P.; Wu, L.; Qian, Y.; Fang, Q.; Liang, D.; Wang, J.; Liang, G. Blockage of ROS and NF-κB-mediated inflammation by a new chalcone L6H9 protects cardiomyocytes from hyperglycemia-induced injuries. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* **2015**, *1852*, 1230-1241, https://doi.org/10.1016/j.bbadis.2015.02.011.
40. Gapsys, V.; Yildirim, A.; Aldeghi, M.; Khalak, Y.; VanDer-Spoel, D.; DeGroot, B. Accurate absolute free energies for ligand–protein binding based on non-equilibrium approaches. *Communications Chemistry* **2021**, *4*, 1-13, https://www.nature.com/articles/s42004-021-00498-y.
41. Adasme, M.; Linnemann, K.; Bolz, S.; Kaiser, F.; Salentin, S.; Haupt, V.; Schroeder, M. PLIP 2021: expanding the scope of the protein–ligand interaction profiler to DNA and RNA. *Nucleic Acids Research* **2021**, *49*, W530-W534, https://doi.org/10.1093/nar/gkab294.
42. 42, Yang, J.; Shen, C.; Huang, N. Predicting or pretending: artificial intelligence for protein-ligand interactions lack of sufficiently large and unbiased datasets. *Frontiers in Pharmacology* **2020**, *11*, 69, 1-9, https://doi.org/10.3389/fphar.2020.00069.
43. Erdagi, S.; Ngwabebhoh, F.; Yildiz, U. Pickering stabilized nanocellulose-alginate: A diosgenin-mediated delivery of quinalizarin as a potent cyto-inhibitor in human lung/breast cancer cell lines. *Materials Science and Engineering* **2020**, *109*, 110621, https://doi.org/10.1016/j.msec.2019.110621.
44. Yang, J.; Shen, C.; Huang, N. Predicting or pretending: artificial intelligence for protein-ligand interactions lack of sufficiently large and unbiased datasets. *Frontiers in Pharmacology* **2020**, *11*, 69, 1-9, https://doi.org/10.3389/fphar.2020.00069.
45. Cho, H.; Lee, E.; Choi, I. Layer-wise relevance propagation of Interaction Net explains protein-ligand interactions at the atom level. *Scientific Reports* **2020**, *10*, 1-11, https://www.nature.com/articles/s41598-020-78169-6.
46. Levitt, D. PKQuest: measurement of intestinal absorption and first pass metabolism–application to human ethanol pharmacokinetics. *BMC Clinical Pharmacology* **2002**, *2*, 1-12, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC122094/.
47. Ishaku, S.; Bakare-Odunola, M.; Musa, A.; Yakasai, I.; Garba, M.; Adzu, B. Effect of dihydro-artemisinin on the pharmacokinetics of gliclazide in diabetic subjects. *International Journal of Biological and Chemical Sciences* **2020**, *14*, 2267-2276, https://doi.org/10.4314/ijbcs.v14i6.27.
48. Figueroa-Valverde, L.; Francisco, D.; Marcela, R.; Virginia, M.; Elizabeth, M.; Maria, L.; Jhair, C. Design and Synthesis of a Diaza-bicyclo-naphthalen-oxiranyl-methanone Derivative. Theoretical Analysis of Their Interaction with Cytochrome P450-17A1. *Chemical Methodologies* **2019**, *3*, 194-210, http://www.chemmethod.com/article_75430.html.