Advanced Journal of Chemistry-Section A

Journal homepage: www.ajchem-a.com

Original Research Article

Investigation of Amino Chalcone Derivatives as Anti-Proliferative Agents against MCF-7 Breast Cancer Cell Lines-DFT, Molecular Docking and Pharmacokinetics Studies

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ARTICLE INFO

Article history

Submitted: 12 May 2021
Revised: 13 June 2021
Accepted: 16 July 2021
Available online: 17 July 2021
Manuscript ID: AJCA-2105-1261

DOI: **10.22034/AJCA.2021.285869.1261**

KEYWORDS

Amino chalcones
Computer-aided drug design
Molecular modeling
Molecular docking
Breast cancer
Pharmocokinetics

ABSTRACT

Breast cancer is one of the most lethal diseases that has resulted in many deaths in the world. Development of new compounds and repurposing of approved drugs have become very attractive in the field of drug design. Computer-aided drug design has become popular because it is cost effective and time saving. In this work, the molecular descriptors of some amino chalcone derivatives were derived using the density functional theory; some of the optimized molecules were also docked at the active site of a human serine/threonine-protein kinase receptor, 3FC2, to obtain their binding affinities. The potential surface energies for all compounds range from -190.4 kJ/mol to -172.3 kJ/mol for low energy regions and 199.8 kJ/mol to 263.3 kJ/mol for high energy regions indicating that the ligands would bind well with receptors. All compounds have higher binding energy than the standard drug, 5-Fu (-6.19 kcal/mol) when docked into the active site of 3FC2 and their mode of interaction are just like it was in 5-Fu. Our observations are still subject to confirmation via clinical and pre-clinical investigations.

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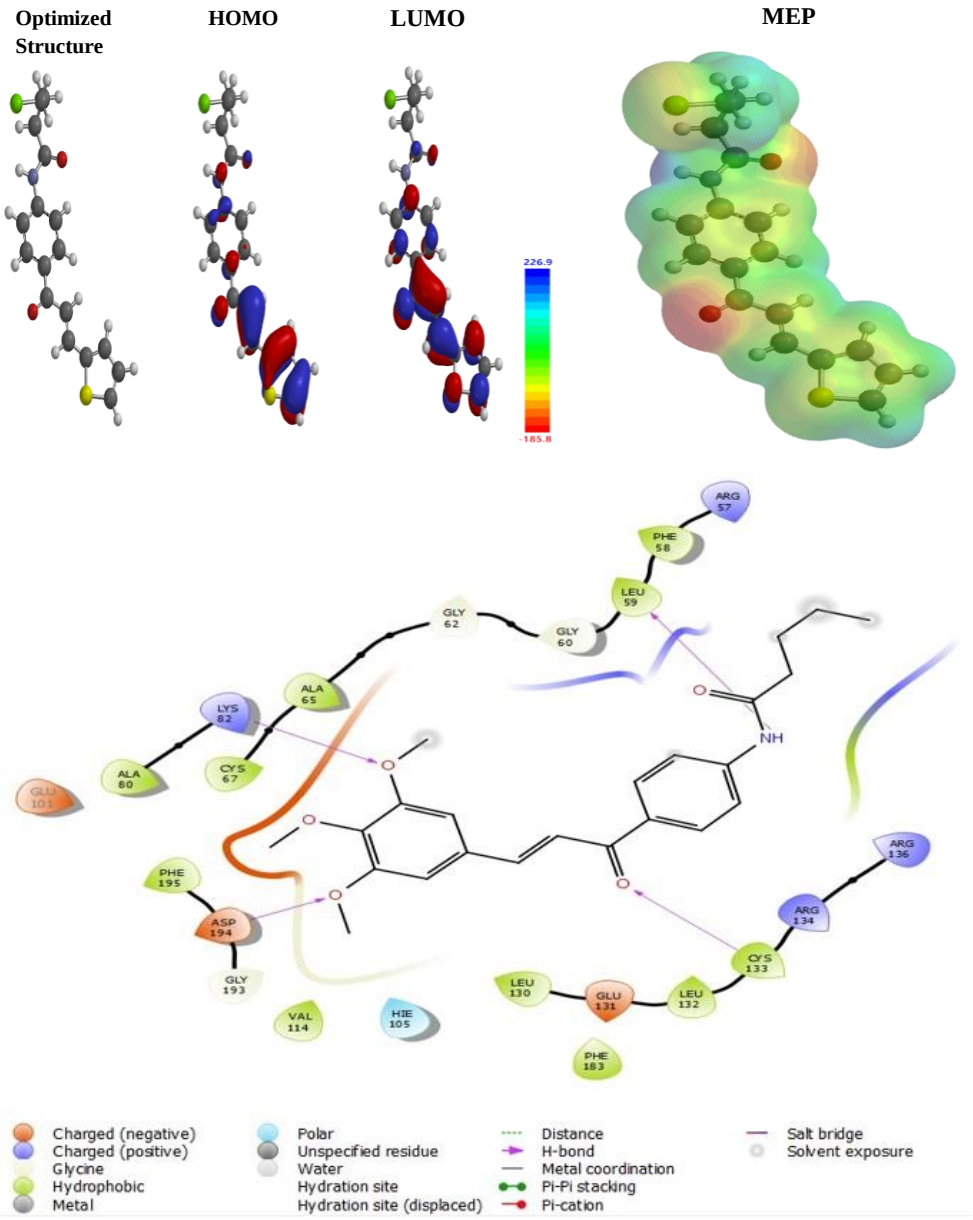
GRAPHICAL ABSTRACT



Introduction

The World Health Organization (WHO) has labeled cancer as a major threat to human health, it is the second most lethal disease after cardiovascular diseases and has resulted in over 9.6 million deaths in 2018 [1]. Globally, about 70% of cancer death usually occur in developing countries, and around one third of cancer deaths are due to lack of exercise, hereditary variation, intake of alcohol, tobacco use and low intake of vegetables and fruits [1,2]. Among the most common causes of cancer-related death in women, breast cancer is ranked second with approximately 40,610 death and 252,710 diagnosed issues in 2017 [3]. Breast cancer usually develops from breast tissue, mostly from inner lining of the milk ducts or lobules that

supply the ducts with milk. Breast cancer can be divided into invasive and non-invasive types; invasive breast cancer exist when the abnormal cell growth invade nearby breast tissue and can be subdivided into invasive ductal carcinoma, invasive lobular carcinoma, inflammatory breast cancer and triple negative breast cancer while non-invasive breast cancer type does not invade nearby cell tissue and can be subdivided into lobular carcinoma in situ and ductal carcinoma in situ [4,5].

There are various drugs approved by the Food and Drug Administration (FDA) for effective treatment of breast cancer which includes Fluorouracil, Xeloda, Abemacilib and Cisplatin. However, high multidrug resistance of these drugs, which may result in therapeutic failure [6], has challenged researchers to look for more novel drugs with great therapeutic activities. Chalcones are natural compounds that belong to the flavonoid family and are present in many fruits, vegetable and edible plants [7]. They are important molecular compounds that display high pharmacological activities. Their therapeutic and biological activities have attracted the attention of many scientists worldwide. Chalcone derivatives could be used as anti-malaria [8], anti-fungal [9], anti-oxidant [10], anti-HIV [11], anti-inflammatory [12] and anti-cancer [13-15] agents. In recent years, computer aided drug design (CADD) has been a cost-effective, time-saving, and rapid method employed by scientists to design novel drugs with high effectiveness and better potency against disease unlike the traditional method which is time-consuming, costly and labor intensive [16]. Density functional theory (DFT) is a quantum computational method used in predicting the structural and physico-chemical properties of compounds [17-24]. These properties can be used to deduce the correlation between these properties and biological activities of the molecule thus, serving as a guide in arriving at molecules with better biological activities [25]. Also, molecular docking technique is a valuable tool in CADD and it is used to probe into the binding of molecules into biological targets and also provide useful information about the type of interactions between these molecules and the receptors under investigation [18,26-30]. Furthermore, absorption, distribution, metabolism, excretion and toxicity (ADMETox) properties play a vital role in drug development. They provide crucial information on the fate and effectiveness of a molecule after administration in the body.

Amino chalcone and some of its derivatives have been synthesized and reported for their anti-cancer activities [31], including Michighan Cancer Foundation cell line (MCF-7) [32]. However, the mode of action of these compounds on cancer cell as well as the physico-chemical properties were not ascertained. This study was aimed at predicting the anti-cancer activities of some of these amino chalcone derivatives against breast cancer receptor via computational studies like molecular docking and pharmacokinetics studies. The physico-chemical properties of these compounds, were obtained via DFT calculations while their binding affinities and intermolecular interactions were ascertained molecular docking of these compounds into the active sites of a human serine/threonine-protein kinase receptor, 3FC2.

Methods

Fourteen (14) amino chalcone derivatives were extracted from reports [31]. Figure 2, 3 and 4 show the derivatives while Table 1 shows the attached substituent for each compound.

Quantum Chemical Calculation

DFT calculations were performed on the most stable conformers of the molecules using Spartan 14 computational chemistry software on an Intel Core i5-2520M mobile workstation (8.00GB RAM, 2.50 GHz) using a restricted hybrid Hartree

Fock-DFT self-consistent field calculation (B3LYP) with Pulay's direct inversion of the iterative sub-space and geometric direct minimization [33] and a polar basis set, 6-31G(d) [34]. The energies of the frontier molecular orbitals (FMOs) such as highest occupied molecular orbital (E_{HOMO}), lowest unoccupied molecular orbital (E_{LUMO}), energy band gap, ΔE (eq. 1) and physicochemical parameters like lipophilicity (log P), molecular weight, area, volume, ovality, polar surface area (PSA), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) were obtained from the optimized amino chalcone derivatives. Global reactivity descriptors such as chemical hardness η (eq. 2), chemical softness δ (eq. 3), electronegativity χ (eq. 4), chemical potential C_P (eq. 5) were also calculated using Koopmans' theorem for closed-shell compounds [35].

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (1)$$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (2)$$

$$\delta = \frac{1}{\eta} \quad (3)$$

$$\chi = -\frac{E_{LUMO} - E_{HOMO}}{2} \quad (4)$$

$$C_P = -\chi \quad (5)$$

Molecular Docking Study

The 3D-crystal structure of human serine/threonine-protein kinase receptor, (PDB ID: 3FC2) with a resolution of 2.45 Å was downloaded in PDB format from protein data bank [36] (Figure 1) and prepared for docking using the protein preparation wizard of Schrodinger Suite 2017-1 [37] by removing all hetero atoms, eliminating water molecules, addition of hydrogen to the heavy atoms and by assigning charges and proper bond order. The generation of tautomeric states were achieved at pH of 7.0 ± 2 using Epik [38] and the energy minimization of protein structure was implemented using OPLS3 force filed [39,40]. Also, the ligands were prepared using ligprep module in Schrodinger suite 2017-1 with an OPLS3 force filed [40]. All possible ionization and tautomeric states were generated using Epik at pH 7.0 ± 2. Finally, the molecular docking simulation were done using glide docking [41] in Schrodinger suite 2017-1 with the prepared ligands and a standard drug, fluorouracil (5-Fu) docked into the active site of the receptor (x = 41.76, y = -11.88, z = 13.58).

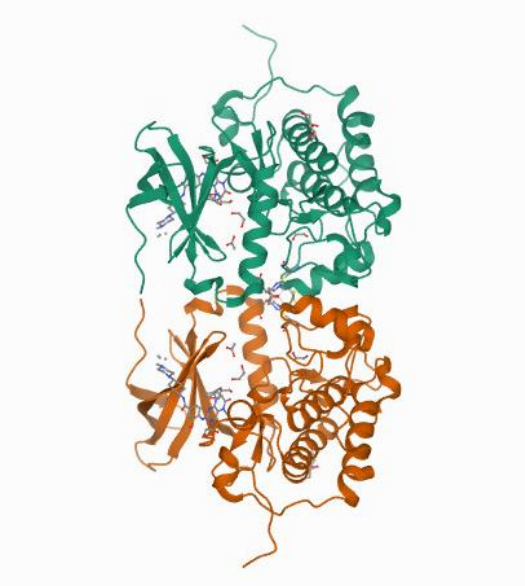


Figure 1. Structure of 3FC2

Pharmacokinetics and Drug Likeness Analysis

Poor pharmacokinetics properties of compounds are one of the major challenges at early stage of drug development. Therefore, the physicochemical and pharmacokinetics properties can be monitored in order to minimize poor pharmacokinetics related issues. Admetsar, a web user-friendly interface to search for absorption, distribution, metabolism, excretion and toxicity (ADME/Tox) was used to predict the physicochemical and pharmacokinetic properties of the compounds [42] after inputting the chemical structures of each compound in SMILES (simplified molecular-input line-entry system) format.

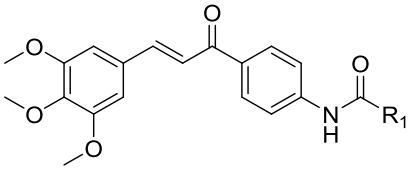


Figure 2. Compounds 1-7

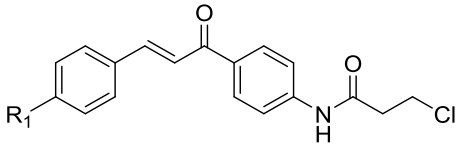


Figure 3. Compounds 8-12

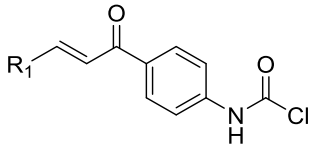
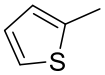


Figure 4. Compounds 13, 14

Table 1. Aminochalcone compounds

Compound	R_1
1	CH_3
2	$CH_2CH_2CH_2CH_3$
3	CH_2Cl
4	CH_2CH_2Cl
5	$CH_2CH_2CH_2Cl$
6	$CH_2CH_2CH_2CH_2Cl$
7	CH_2CH_2
8	H
9	CH_3
10	F
11	Br
12	3,4-OCH_3
13	
14	

Results

Frontier Molecular Orbitals

The frontier molecular orbitals energies, energy band gap, chemical hardness, softness, electronegativity and chemical potential were obtained with DFT/B3LYP with a polar basis set, 6-31G(d) and are presented in Table 2. The molecular electrostatic potentials which probe into the nucleophilic and electrophilic sites of the molecules are displayed in Figures 5 and S1-13. The physicochemical properties like the molecular weight, log P, polar surface area, polarizability, hydrogen bond acceptor and hydrogen bond donor counts are presented in Table 3.

Table 2. Chemical parameters obtained from amino chalcone derivatives via DFT at the B3LYP/6-31G(d) level of theory

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	η (eV)	δ (eV^{-1})	χ (eV)
1	-5.98	-1.98	4.00	2.00	0.50	3.98
2	-5.96	-1.96	4.00	2.00	0.50	3.96
3	-6.06	-2.09	3.97	1.99	0.50	4.08
4	-6.06	-2.08	3.98	1.99	0.50	4.07
5	-6.01	-2.02	3.99	1.99	0.50	4.02
6	-6.02	-2.03	3.99	1.99	0.50	4.03
7	-5.97	-1.96	4.01	2.01	0.49	3.97
8	-6.20	-2.07	4.13	2.07	0.48	4.14
9	-6.07	-2.07	4.07	2.04	0.49	4.04
10	-6.22	-2.11	4.11	2.06	0.49	4.17
11	-6.29	-2.26	4.03	2.02	0.49	4.28
12	-6.06	-2.06	4.00	2.00	0.50	4.06
13	-6.35	-2.28	4.07	2.04	0.49	4.32
14	-5.99	-2.14	3.85	1.93	0.52	4.07

Table 3. Physicochemical Parameters obtained from Amino chalcone derivatives *via* DFT at the B3LYP/6-31G* level of theory

Compounds	MW	Log P	PSA (A^2)	Polarizability	HBD	HBA
1	355.39	2.29	56.56	70.48	1	6
2	397.47	3.78	55.95	74.96	1	6
3	389.84	2.81	55.37	71.61	1	6
4	403.86	3.11	55.81	73.11	1	6
5	417.89	3.39	55.75	74.60	1	6
6	431.92	3.80	55.94	76.10	1	6
7	369.42	2.94	56.01	71.97	1	6
8	327.81	3.77	36.26	67.87	1	3
9	341.84	4.25	36.23	69.37	1	3
10	345.80	3.92	36.14	68.25	1	3
11	406.71	4.59	36.10	69.37	1	3
12	387.86	3.51	49.07	72.36	1	5
13	328.80	2.15	43.02	67.37	1	4
14	333.84	2.46	36.75	66.94	1	4
5-Fu	130.078	-1.31	51.77	46.68	2	4

PSA = Polar surface area; HBD = Hydrogen bond donor, HBA = Hydrogen bond acceptor

Molecular Docking and Pharmacokinetic Studies

Some of the molecules (2, 3, 4, 5 and 7), together with the standard drug, 5-Fu were docked at the active site of human serine/ threonine-protein kinase receptor, 3FC2. Their binding affinities, interaction types and the amino acid they interact with are on Table 4. The pharmacokinetics properties obtained from Admetsar are presented on Table 5. The ligand-receptor interaction diagrams are displayed (Figures 6 and S14-18).

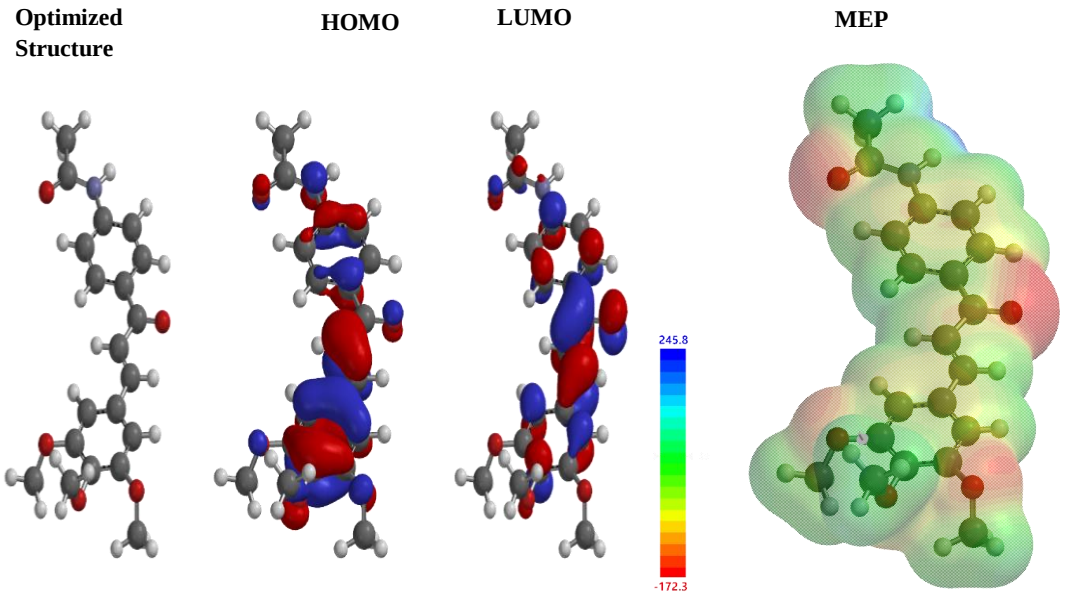


Figure 5. Compound 1

Table 4. Binding affinities and the bond types between some of the compounds and the receptor

Compounds	Binding affinity (kcal/mol)	Amino acid	Bond types
2	-8.19	LEU59, CYS133, ASP194, LYS82	Conventional hydrogen bond
3	-8.12	LEU59, CYS133, ASP194, LYS82	Conventional hydrogen bond
4	-7.54	LEU59, CYS133, LYS82	Conventional hydrogen bond
5	-8.25	LEU59, CYS133, ASP194, LYS82	Conventional hydrogen bond
7	-8.06	LEU59, CYS133	Conventional hydrogen bond
5-Fu	-6.19	LYS82, ASP194	Conventional hydrogen bond and Salt bridge

Table 5. Some selected pharmacokinetics properties of some of the compounds

Compound	GI absorption	BBB permeant	P-gp substrate	hERG	Rat acute toxicity LD50 (mol/kg)	Acute oral toxicity	Carcinogen
2	+(0.987)	+(0.937)	S(0.538)	WI(0.978)	2.19	III(0.728)	No(0.866)
3	+(0.983)	+(0.958)	NS(0.676)	WI(0.954)	2.28	III(0.749)	No(0.760)
4	+(0.995)	+(0.954)	NS(0.664)	WI(0.961)	2.23	III(0.742)	No(0.819)
5	+(0.987)	+(0.959)	NS(0.639)	WI(0.964)	2.24	III(0.734)	No(0.833)
7	+(0.978)	+(0.921)	NS(0.601)	WI(0.961)	2.15	III(0.765)	No(0.808)
5-Fu	+(0.939)	+(0.943)	NS(0.721)	WI(0.939)	2.28	III(0.556)	No(0.906)

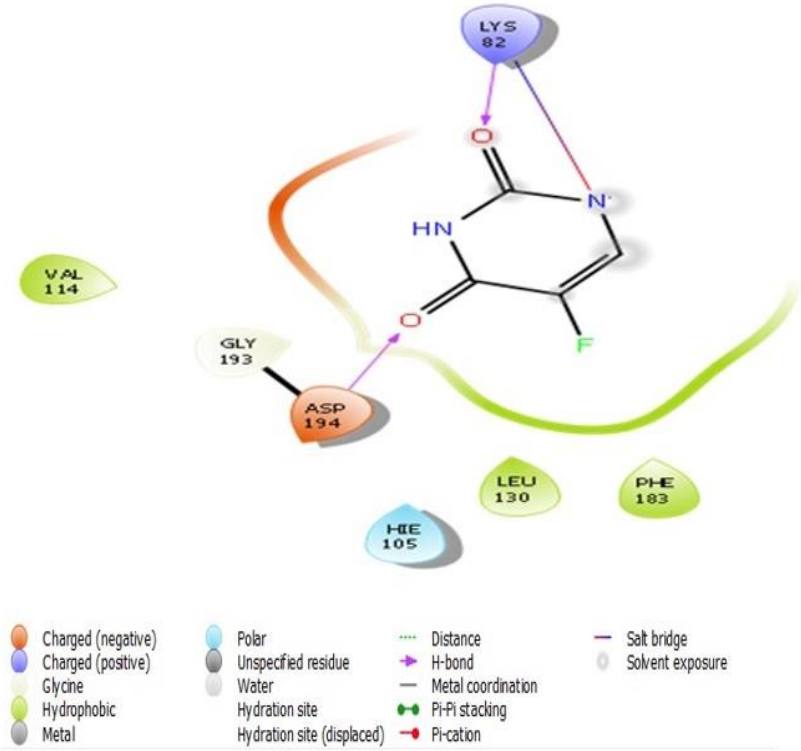


Figure 6. 5-Fu with 3FC2

Discussion

Frontier Molecular Orbitals

The energies of the FMOs as well as other reactivity descriptors generated from the DFT calculations were used to predict the reactivity of the compounds. The principle is based on the formation of two molecular orbitals through the interaction and overlapping of two different reactants [43-45]. The energy of the HOMO indicates the ability of a molecule to donate electron to the other molecule, the higher the HOMO value is, the stronger it will donate electron while the energy of the LUMO indicates the tendency of a molecule to accept electron, the lower the LUMO energy is, the stronger it will accept electron. Hence, high energy of HOMO and low energy of LUMO enhance reactivity of molecules [46,47]. The chemical parameters (Table 2) shows that the HOMO energy values of amino chalcone derivatives range from -5.9 eV to -6.35 eV, showing that the compounds will readily donate electron. The LUMO energy values for all compounds vary between -2.28 eV and -1.96 eV. The energy band gap, ΔE, is an indicator of the chemical reactivity and stability of a molecule. Higher ΔE value denotes greater stability, lower reactivity and less bioavailability [46].

Global Reactivity Descriptors

Global reactivity descriptor (Table 2) were calculated to gain deep insight into the stable and reactive nature of the selected aminochalcone derivatives. According to the principle of Maximum Hardness [48], higher chemical hardness (η) and lower chemical softness (δ) values for a molecule translate to higher stability and lower reactivity. The chemical hardness and softness values for the studied compounds range from 1.99 eV to 2.06 eV and 0.48 eV to 0.52 eV respectively with compound 14 having the lowest hardness and highest softness values among them. The electronegativity (χ) values for

all derivative compounds range between 3.96 eV and 4.32 eV, with compound 13 having the highest value and thus the highest propensity for attracting electrons.

Molecular Electrostatic Potential (MEP)

MEP surface maps (Figures 5 and S1-13) show the reactive sites on the compounds of interest where electrophilic by acids and nucleophilic attacks by bases are possible [49]. Regions of negative, zero and positive electrostatic potentials in that increasing order are depicted in red, green and blue respectively. The negative potential (red) regions are low energy sites for electrophilic attacks and are located around oxygen atoms in the molecules, the most negative potentials around the carbonyl oxygen atoms. Positive potential (blue) regions, on the other hand, are high energy sites for nucleophilic attacks, the most positive being located on the hydrogen atom attached to the nitrogen atoms and as a result these hydrogen atoms repel the approach of a proton due to extremely low electron density around it, hence the very high positive MEP value. The potential surface energies for all compounds range from -190.4 kJ/mol to -172.3 kJ/mol for low energy regions and 199.8 kJ/mol to 263.3 kJ/mol for high energy regions. This is an indication that the compounds could act as good ligands.

Other important molecular parameters obtained are molecular weight (MW), partition coefficient (log P), polar surface area (PSA), polarizability, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA)**.** According to the eminent rule of five (RO5) by Lipinski, an orally active drug should have the following properties: molecular mass < 500, log P $\leq$ 5, HBD $\leq$5 and HBA $\leq$ 10 [50,51]. The violation of 2 or more of these properties implies that a biological active compound is not orally active. Table 3 shows the result of the Lipinski's RO5, all the studied compounds fall within the acceptable range and are in good agreement with this rule. This shows that all the compounds are orally bioavailable. Furthermore, PSA is mostly used for the ability of biological active compound to permeate cells. For a compound to permeate cell membrane, the PSA should not be greater than 140 A^2 and also, PSA less than 90 A^2 is needed for a compound to enter the blood-brain barrier [52]. The PSA values of the studied compound range from 36.10 - 56.56 A^2. This shows that all the studied compounds can permeate cell membrane and can also, penetrate blood-brain barrier.

Molecular Docking Analysis

The lead compounds as reported [25] (2, 3, 4, 5 and 7) were docked at the receptor's active site; their binding affinities (Table 4) revealed that all of them have better binding energies than that of 5-Fu. Compounds 2, 3 and 5 (Figures S14, S15 and S17) showed convectional hydrogen bonds with LEU59 (via –NH group), CYS133 (via the carbonyl oxygen group), ASP194 and LYS82 via the terminal methoxy oxygen groups. Compound 4 (Figure S16) showed conventional hydrogen bond with LEU59 (via the –NH group), CYS133 (via the carbonyl oxygen group) and LYS82 (via a methoxy oxygen group). Compound 7 (Figure S18) showed conventional hydrogen bond with LEU59 (via the –NH group) and CYS133 (via the carbonyl oxygen group). All these compounds have higher binding energy than the standard drug, 5-Fu (-6.19 kcal/mol).

Pharmacokinetics Studies

Pharmacokinetics properties such as GI absorption, BBB permeant, P-gp substrate, cytochrome P (CYP) 450 isoforms inhibitor, hERG, rat acute toxicity, acute oral toxicity and carcinogenicity are shown in Table 5. The pharmacokinetics properties predicted show that all the docked compounds could be absorbed by the human intestine. Blood-brain barrier (BBB) and cerebrospinal fluid barrier are the primary

interface bridging the central nervous system (CNS) and the circulation of blood. BBB permeation is a vital property in drug development, which helps to predict if a molecule will pass over the BBB and effects its therapeutic properties on the brain [53]. The BBB permeation predicted showed that all the lead compounds possess the ability to cross the BBB without affecting the normal central nervous system function. P-gp is a transmembrane efflux pump that carries drugs away from cell membrane and cytoplasm which lead to further metabolism and clearance of the drug thereby enhancing the therapeutic failure due to decrease in drug concentration [54]. The results showed that none of the compounds is a substrate for P-gp. Weak inhibition of the molecules against human ether-a-go-go-related gene (hERG) were observed; this may consequently result in long QT syndrome [55,56]. All the molecules are non-carcinogenic and exhibit III category acute oral toxicity, just like the standard drug, 5-Fu. This is indicative that they are harmless.

Conclusion

Fourteen aminochalcone derivatives were modeled and optimized using DFT calculations, the energy band gap and some global reactivity descriptors were obtained to understand how the structure of the different derivatives affect their properties. To probe further into their mechanism of action with biological cells, the lead molecules were docked with a human serine/threonine-protein kinase receptor, 3FC2. From the results, the potential surface energies for all compounds range from -190.4 kJ/mol to -172.3 kJ/mol for low energy regions and 199.8 kJ/mol to 263.3 kJ/mol for high energy regions, an indication that the compounds could act as good ligands. The polar surface area values of the studied compound range from 36.10 - 56.56 A^2. This shows that all the studied compounds can permeate cell membrane and can also, penetrate blood-brain barrier. The lead compounds have higher binding energy than the standard drug, 5-Fu (-6.19 kcal/mol). All the molecules are non-carcinogenic and exhibit III category acute oral toxicity, just like the standard drug, 5-Fu. This is indicative that they are harmless. This is in line with what was observed earlier [27,30].

Acknowledgements

Appreciation goes to the Adekunle Ajasin University for creating an enabling environment to carry out this research work.

Disclosure Statement

Authors declare that there is no conflict of interest.

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HOW TO CITE THIS ARTICLE

Oluwatoba Emmanuel Oyeneyin*, Toluwalope Gbemileke Abayomi, Nureni Ipinloju, Eric Bamidele Agbaffa, Daniel Dada Akerele, Oluwatobiloba Amusa Arobadade. Investigation of Amino Chalcone Derivatives as Anti-Proliferative Agents against MCF-7 Breast Cancer Cell Lines-DFT, Molecular Docking and Pharmacokinetics Studies. *Adv. J. Chem. A.*, **2021**, 4(4), 288-299.

DOI: 10.22034/AJCA.2021.285869.1261
URL: http://www.ajchem-a.com/article_133740.html