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Original Research Article

Computational Study and Design of Novel Chemotherapeutic Agents against Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma is the fourth most common cause of cancer related fatality globally and has constituted a serious health care burden owing to dearth of effective systemic chemotherapeutic agents against this disease. In this study, a set of bioactive compounds with proven anticancer activities against HepG2 cell lines were subjected to theoretical investigations via the use of QSAR modelling, molecular docking simulation, ADMET and drug-likeness evaluation. The validated QSAR model (R^2 = 0.94, R^2_{Adj} = 0.93, Q^2_{LOO} = 0.91, R^2_{Pred} = 0.81) revealed the predominant influence of ZMIC2 descriptor on the chemotherapeutic properties of the compounds. Optimization of the anticancer property of the most active compound (template) through its structural modification guided by ZMIC2 descriptor in the model led to the design of more potent analogues; G-1, G-2, and G-3 with predicted IC_{50} value of 9.77 µM, 2.45 µM, and 5.50 µM, respectively. Molecular docking investigation of the designed ligands against the active sites of Aurora B kinase, the protein target found to be strongly involved in hepatocarcinogenesis, reveals that G-1, G-2, and G-3 bind with ΔG value of -8.0 kcal/mol, -7.8 kcal/mol, and -7.7 kcal/mol, respectively. These values are higher and better compared to -7.5 kcal/mol recorded for the template molecule. Also, insilico drug-likeness and ADMET assessment of the novel ligands revealed that they possess good oral bioavailability, excellent pharmacokinetic and toxicity profiles. However, further invivo and invitro studies are required on the designed drug candidates to validate these claims.

Keywords: Hepatocellular carcinoma, HepG2, ADMET, Insilico, QSAR

Introduction

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Cancer has been identified as one of the major cause of mortality and morbidity globally. According to the universal statistic data of the International Agency for Research on Cancer (IARC), the new cases of the disease diagnosed in 2018 was estimated to be 18.1 million with 9.5 million associated mortality rate [1]. In 2020, about 19.3 million new cases and 10 million cancer related deaths were recorded globally. The situation is so critical that it has been projected that by the year 2040, the global incidence and mortality rate associated with this disease would rise to 29.5 million new cases and 16.4 million deaths, respectively [2]. Of particular concern in this research is the rising incidences of hepatocellular carcinoma (HCC), a type of primary liver cancer that arises from hepatocytes and responsible for roughly 80% of primary liver cancer cases [3]. HCC is the fourth foremost cause of cancer death worldwide [4-6] and has constituted a healthcare burden worldwide [7]. The early stage of the disease is managed with curative treatments such as surgery, radiofrequency ablation, and liver transplant [8, 9] but at its advanced stage, cytotoxic chemotherapy becomes ineffective with limited clinical benefits. For instance, the approval of sorafenib by FDA in 2007 paved way for discovery of many molecularly targeted drugs, regrettably, none of these drugs have displayed any survival benefits in HCC patients [10, 11]. This has necessitated the search for novel drug candidates for the treatment of this disease. Benzimidazole nucleus has been confirmed as a significant pharmacophore in the discovery of chemotherapeutic agents [12-18]. Also, chalcones or aromatic α, β-unsaturated ketones have been reported to possess antitumor activities (19-24). Their poor interaction with DNA and low risk of mutagenity (25, 26) makes them more promising in the quest for novel chemotherapeutic agents. Research has shown overexpression of Aurora B kinase during the process of hepatocarcinogenesis and this protein has been reported to play significant role in hepatocellular carcinogenesis (27-30), making it a rational drug target in the search for novel chemotherapeutic agents against HCC. Thus, this study is aimed at the design of potent and non-toxic benzimidazole-chalcone based inhibitors of Aurora B kinase through the application of Computer Aided Drug Design (CADD) techniques. The CADD approach refers to the application of insilico techniques in drug discovery and development. The insilico techniques deployed in this research include Quantitative Structure-Activity Relationship Modelling (QSAR), Molecular Docking, Drug-likeness evaluation, and ADMET prediction. QSAR helps in finding the mathematical link between biological properties of molecules and their descriptors with the view of optimizing the potencies of the molecules. Molecular docking on the hand, helps to ascertain the binding affinities

of therapeutic compounds to the active sites of a protein target. Drug-likeness evaluation assist in ascertaining the oral bioavailability of a therapeutic compound, and ADMET prediction helps in their pharmacokinetic and toxicological profiling [31-37].

Methods

Collection of Data Set of Molecules

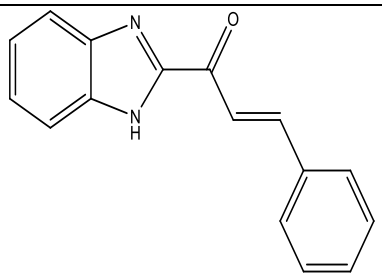
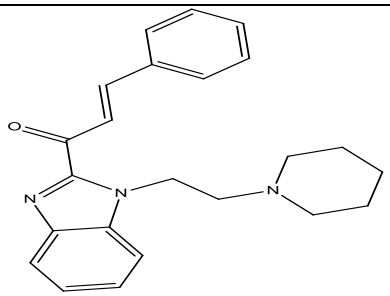
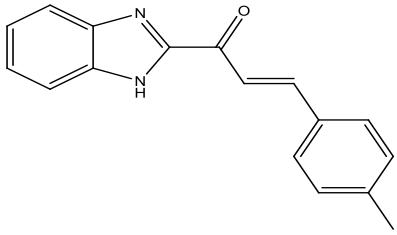
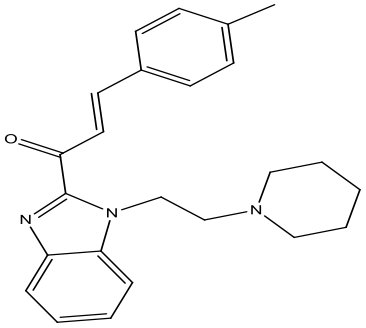
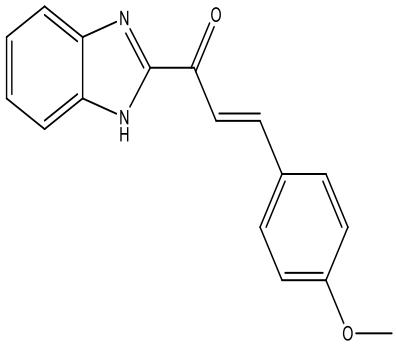
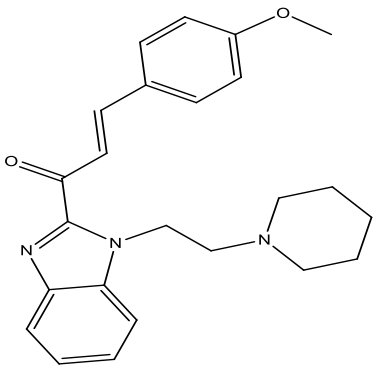
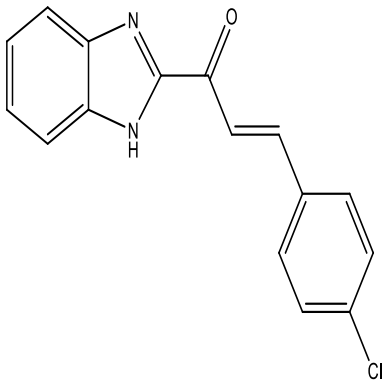
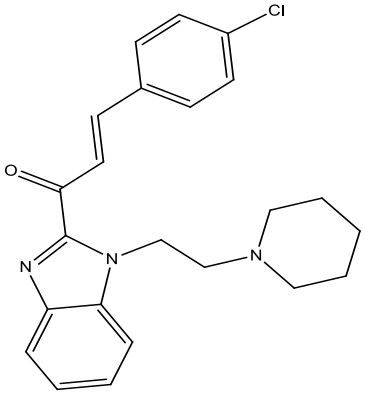
A dataset of twenty four (24) benzimidazole-chalcone derivatives with proven anti-cancer activities against HepG2 cancer cell line were accessed from reported work [38]. The anticancer activities of the compounds expressed as IC_{50} (µM) ab initio were transformed into logarithmic form (pIC_{50} = -log IC_{50}) in order to reduce data dispersion in line with standard QSAR model building procedures [39, 40]. Table 1 presents the 2D chemical structures and pIC_{50} values of the investigated compounds.

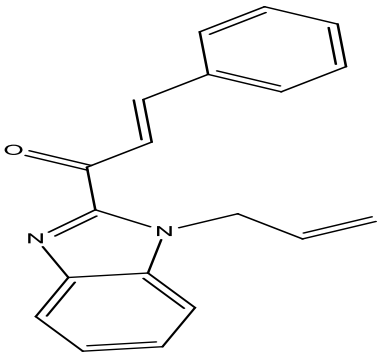
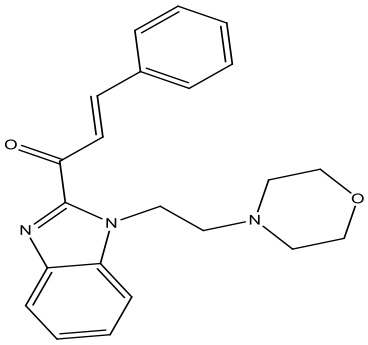
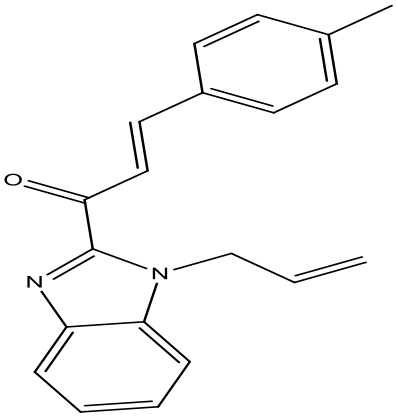
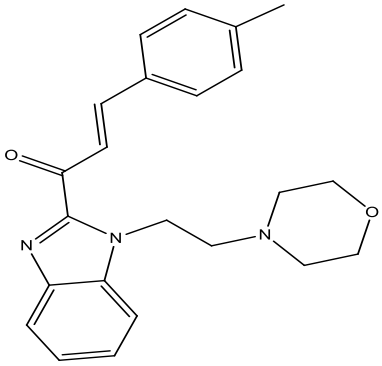
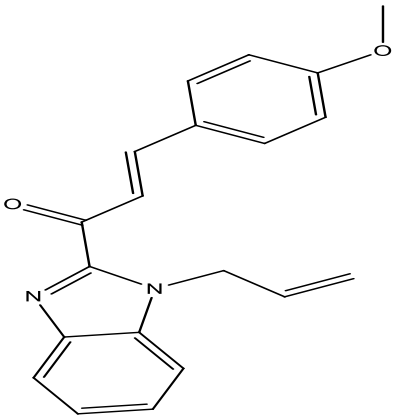
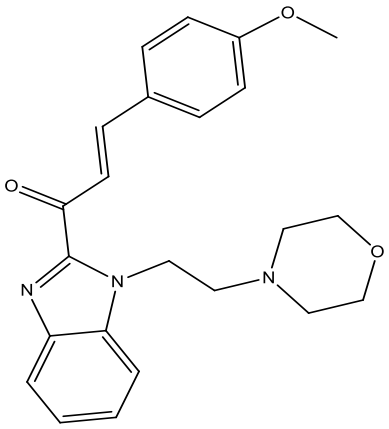
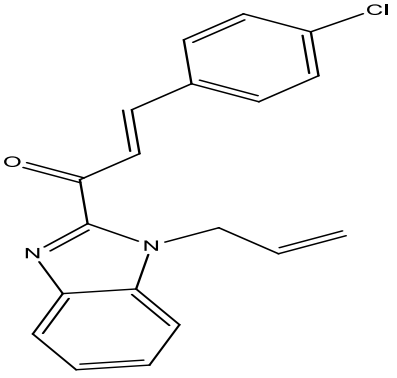
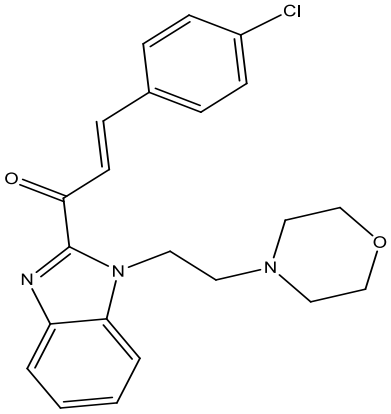
QSAR Model Building

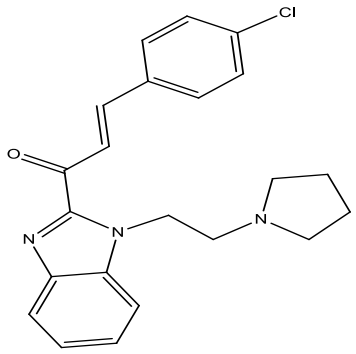
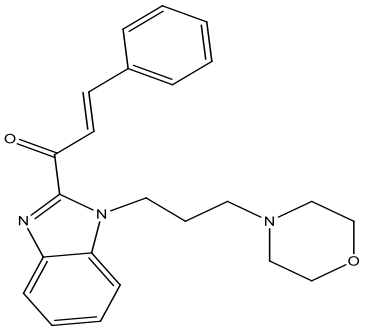
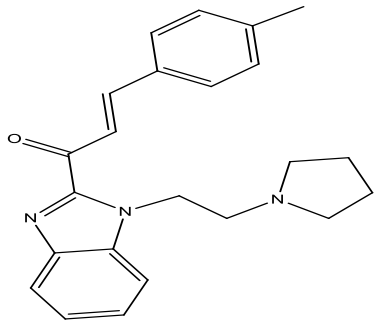
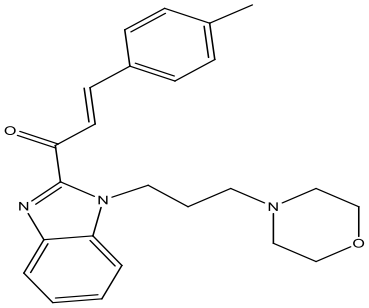
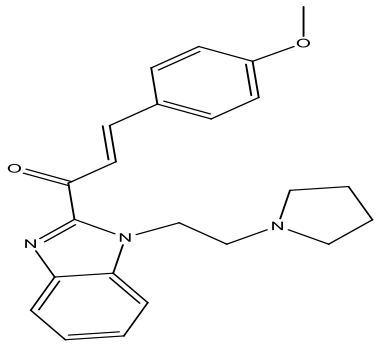
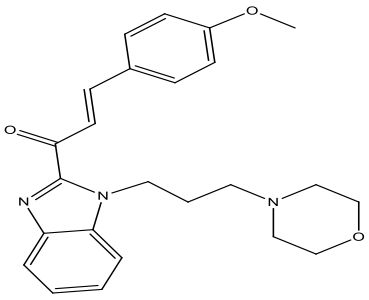
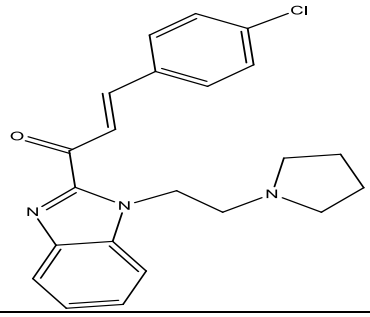
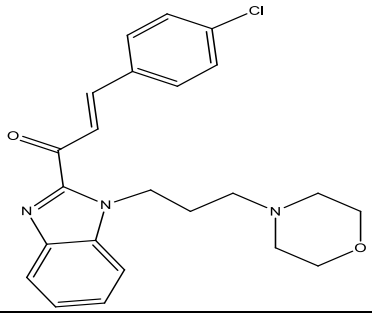
This stage was commenced with geometry optimization of all the molecules in the data set in order to obtain their most stable conformations. This was done using the DFT (B3LYP/631G*) methods enshrined in Spartan 14.11 software. This was followed by the calculation of 0D, 1D, 2D, and 3D descriptors of the optimized molecules using PaDEL Descriptor tool. With the help of V-WSP data pretreatment tool 1.2v, redundant descriptors were expunged from the pool of descriptors. Subsequently, the filtered descriptors were partitioned into 70% training set (for model development) and 30% test set (for model validation) using the Kennard and Stone's algorithm of DTC laboratory. The QSAR model was built using the Genetic Function Approximation (GFA) tool of Material Studio v8.0 by setting mutation probability to 0.3 [41, 42].

Table 1: Structures and Anti-cancer activities of the studied compounds against HepG2 Cell line

S/n	Structure	IC_{50}(µM)	S/n	Structure	IC_{50}(µM)
*1		-1.38	13		-1.01

					
2		-1.77	*A14		-1.51
3		-2.15	*A15		-1.77
4		-1.56	16		-1.75
5		-1.19	*17		-1.56

					
6		-2.07	18		-1.62
7		-2.50	*19		-1.71
8		-1.25	20		-1.33

9		-1.01	*A21		-1.04
10		-1.81	*22		-1.68
A11		-1.56	*A23		-1.52
12		-1.19	A24		-1.98

* Test set molecule; AOutlier

Model Validation

Validation of the built QSAR is necessary to ascertain its stability and robustness. The generated QSAR model was validated using the following internal validation parameters; Friedman Lack of

fit (LOF), square of correlation coefficient (R^2), R^2_{Adj}, and Cross validated R-squared (Q^2cv). External validation is also crucial to obtain a QSAR model with more reliable predictive abilities. The optimum model was externally validated using the test set of eight molecules by using the optimum model to predict the pIC_{50} of the compounds [43].

Model Applicability Domain

Applicability Domain (AD) refers to the physicochemical, structural or biological space in which the training set of the model has been developed. The resulting model can be reliably applicable for only those compounds which are inside this domain. It helps to estimate the uncertainty in the prediction of bioactivities of congeneric set of molecules. The AD of the built QSAR model was defined using the standardization approach in AD executable jar file of DTC laboratory at http://poi.apache.org [44].

Design

In order to obtain analogues of benzimidazole-chalcones with enhanced potencies and excellent ADMET properties, compounds 9 was selected as template for designing new derivatives because it displayed the best anticancer properties in addition to falling within the AD of the model. New ligands were designed via structural modifications of the selected template guided by the predominant descriptor in the model. The IC_{50} of these newly designed bioactive analogues were predicted using the optimum QSAR model.

Molecular Docking Simulation

In order to study the mechanism of interaction of the template and the designed compounds against the active sites of the Aurora B kinase target, they were subjected to molecular docking simulation against the protein target. Their geometries were optimized using the aforementioned procedures for the data set molecules. The optimized structures were then prepared using the AutoDock Vina interface and saved as pdbqt files [45]. The 3-D crystal structure of Aurora B kinase (PDB Code: 2BFY) was retrieved from RCSB protein data bank at www. rcsb.org/pdb. The protein was prepared on the Discovery Studio interface where water molecules, attached ligands and heteroatoms were removed. Using the AutoDock Vina interface, missing atoms were checked and

repaired, partial atomic charges were assigned and all necessary valency tests and H-atom addition were performed on the prepared protein. PyRx virtual screening tool was used to carry out the docking and the grid box revealed the following binding location in the target protease; center_x = 27.2018; center_y = 54.2751; center_z = 56.0685; Dimension-x = 49.4425; Dimension-y = 73.5642; Dimension-z = 91.1188. Discovery Studio Visualizer v16.1.0.15350 was deployed to 2.7 picture the kind of interactions in the stable protein-ligand complexes formed [46, 47].

Drug-Likeness, Pharmacokinetics and Toxicity Assessment

Drug-likeness evaluation was performed on the template and the designed compounds in order to ascertain their oral bioavailability. This important parameter was appraised on the compounds using the famous Lipinski's and Veber's rules. The former rule states that for a drug candidate to be orally bioavailable, it must not violate more than one of the following parameters; molecular weight (Mw) < 500, number of hydrogen bond donors (HBD) < 5, octanol/ water partition coefficient (Log P) < 5 and number of hydrogen bond acceptors (HBA) < 10 [48]. The latter rule, on the hand states that for a drug candidate to be orally bioavailable, its topological polar surface area (TPSA) and number of rotatable of bonds (NRB) must be less than 140 $Å^2$ and 10, respectively. The aforementioned physicochemical properties of the molecules were calculated with the aid of SwissADME (www.swissadme.ch/) online tool and DataWarrior chemoinformatic program. Similarly, pharmacokinetics deals with the fate and distribution of pharmacological compounds in the biological system with particular reference to their absorption (A), distribution (D), metabolism (M), and excretion (E). Early ADME/toxicity (T) assays of potential drug candidates is necessary to minimize their failure rates on account of weak pharmacokinetic and toxicological profiles during clinical trials. The newly designed ligands were analyzed for their ADMET properties with the aid of Swiss ADME server (http:// www. swiss adme. ch/ index. Php) and DataWarrior chemoinformatic program.

Results

GFA-QSAR Model and Validation

It is an established paradigm in Chemistry that whatever property a molecule exhibits is a function of the descriptors of its structure. QSAR model links the structure of a molecule to its properties using regression equation. The GFA derived QSAR model that connects the anti-cancer properties of the studied bioactive compounds to their molecular descriptors is shown by equation 1. The

validation parameters for the regression model and the definitions of the descriptors in the model are presented in Tables 2 and 3, respectively while Table 4 presents the correlation matrix for all the descriptors. Furthermore, the plot of experimental pIC_{50} verses predicted pIC_{50} for training and test set molecules are presented by Figures 1 and 2, respectively while Figures 3 and 4 show the residual plot of the model and the significance of the descriptors in the model, respectively.

$$pIC_{50} = -0.1447 * nHBint9 + 0.115 * ZMIC2 - 0.2344 * RDF120m - 5.2588 \ldots\ldots (1)$$

Table 2. Comparison of Standard Validation Metrics and Model's parameters

S/n	Parameter	Threshold	Model value	Statement
1.	Square of Coefficient of determination (R^2)	≥ 0.6	0.94	Excellent
2	Adjusted R-squared ($R^2_{Adj.}$)	≥ 0.6	0.93	Stable
3	Cross validated R-squared (Q^2_{LOO})	≥ 0.5	0.91	Reliable
4	Predictive R-squared (R^2_{pred})	≥ 0.5	0.81	Robust
5	R^2 - Q^2_{LOO}	≤0.3	0.03	Stable
6	Friedman LOF	low	0.04	Stable

Table 3. Symbols, definitions, and classes of the descriptors in equation 1

S/n	Descriptor	Definition	Class
1	nHBint9	Count of E-State descriptors of strength for potential Hydrogen Bonds of path length 9	2D
2	ZMIC2	Z-modified information content index (neighborhood symmetry of 2-order)	2D
3	RDF120m	Radial distribution function - 120 / weighted by relative mass	3D

Table 4. Correlation Matrix of Descriptors

	pIC_{50}	nHBint9	ZMIC2	RDF120m
pIC_{50}	1			
nHBint9	-0.22179	1		
ZMIC2	0.771824	-0.26372	1	
RDF120m	-0.45902	-0.18508	0.147131	1

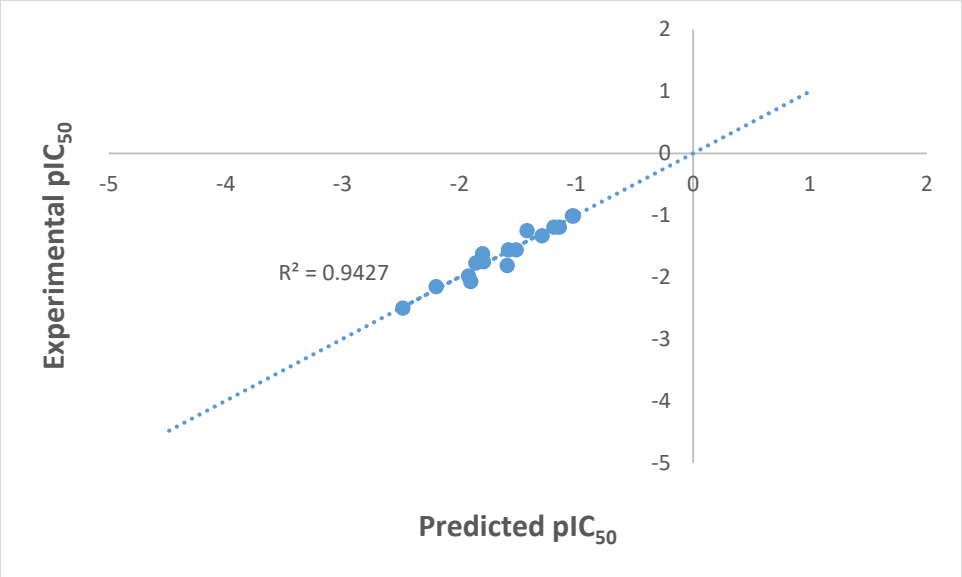


Figure 1. Plot of experimental pIC_{50} against predicted pIC_{50} (training set)

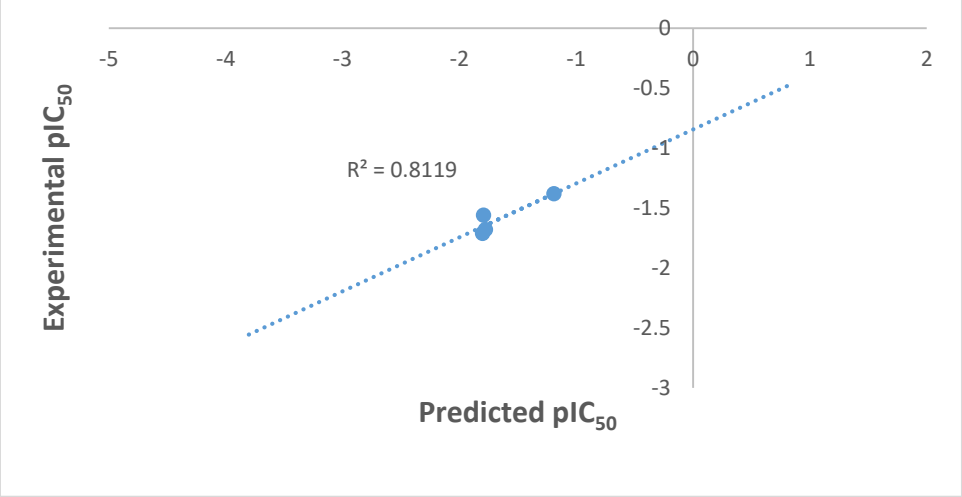


Figure 2. Plot of experimental pIC_{50} against predicted pIC_{50} (test set)

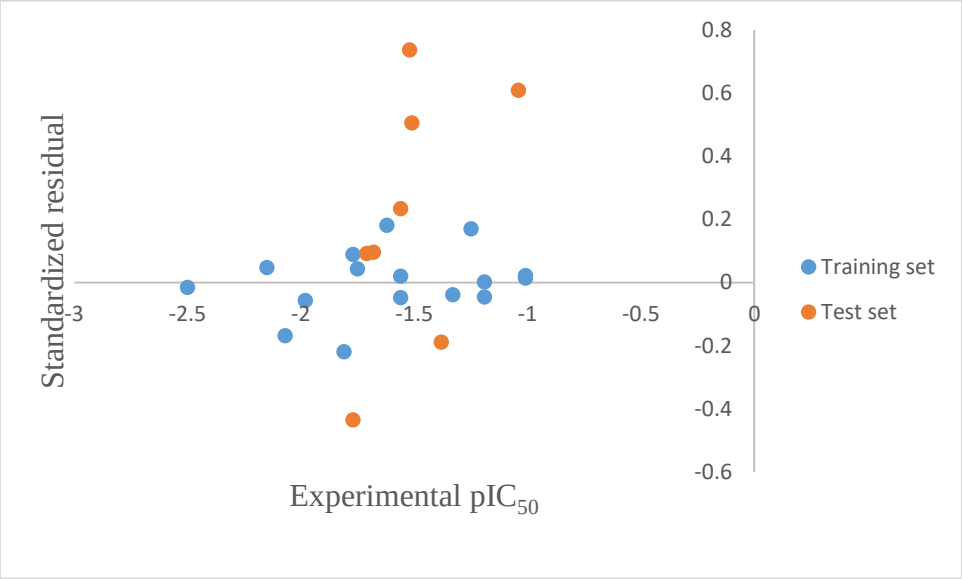


Figure 3. Residual Plot of the Model

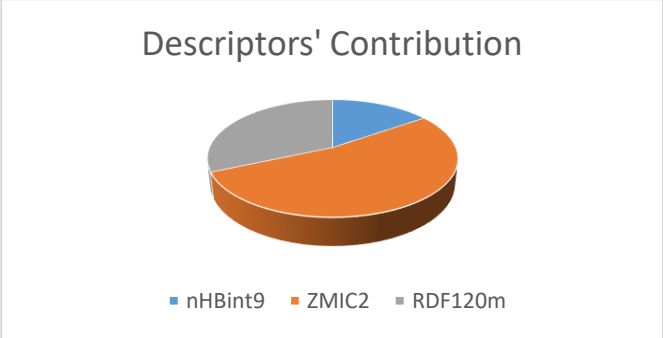
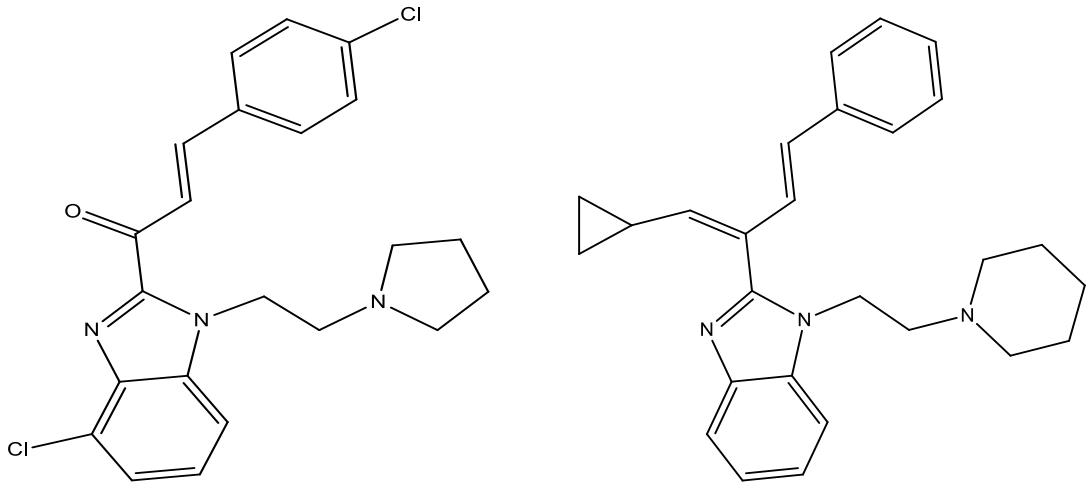


Figure 4. Influence of the descriptors on anticancer properties of the compounds

Novel ligands and their predicted IC_{50} values

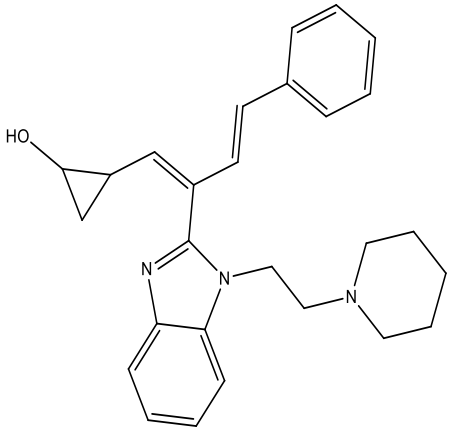
The built QSAR model in equation 1 reveals the dominant influence of *ZMIC2* descriptor on the anticancer activities of the studied bioactive molecules as it accounts for 77.18% of the observed chemotherapeutic activities of the compounds against HepG2 cancer cell line. It was also revealed by the model that the anticancer activities of the molecules could be enhanced by increasing the value of this descriptor owing to its positive coefficient in the regression equation. Guided by this revelation, different benzimidazole-chalcone analogues were designed from the template and their descriptors computed. The derivatives with higher values of *ZMIC2* than the template were filtered out from the pool of the designed molecules and their pIC_{50} computed using the model. The 2D chemical structures of the designed ligands codenamed G-1, G-2, and G-3 as well as that of the

template are presented in Figure 5. Also, the computed descriptors of G-1, G-2, and G-3 and their predicted anticancer activities are presented in Table 5.

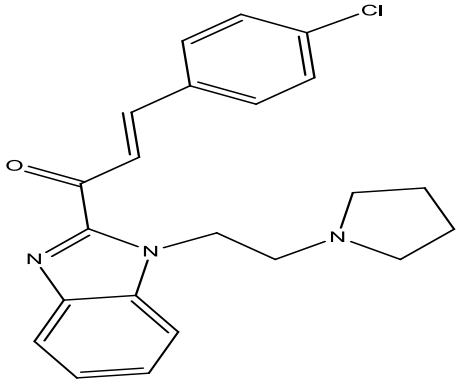


G-1

G-2



G-3



template (9)

Figure 5. 2D chemical structures of the designed ligands and the template molecule

Table 5: Predicted IC_{50} of the designed ligands

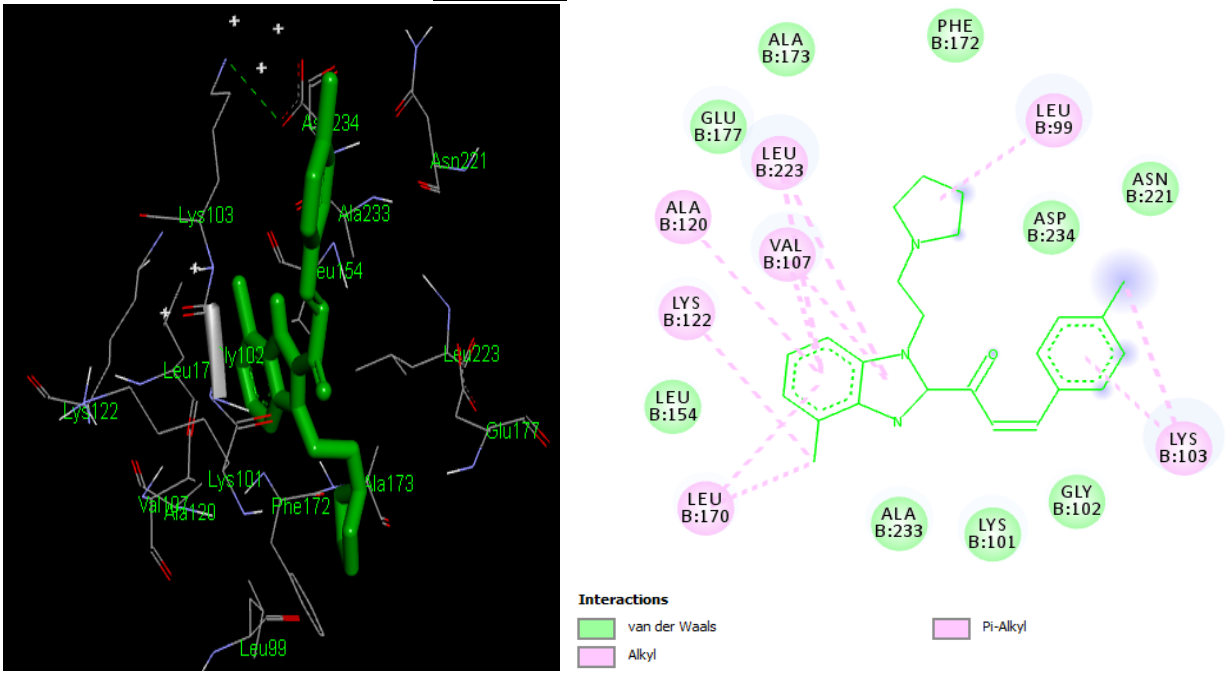
S.No	nHBint9	ZMIC2	RDF120m	pIC_{50}	IC_{50}(µM)
G-1	0	40.90175	1.861729	-0.99	9.77
G-2	0	42.37019	0.009648	-0.39	2.45
G-3	1	40.94982	0.178367	-0.74	5.50
9	0	39.15723	1.146116	-1.01	10.23

3.3 Molecular Docking Simulations of the Designed Compounds

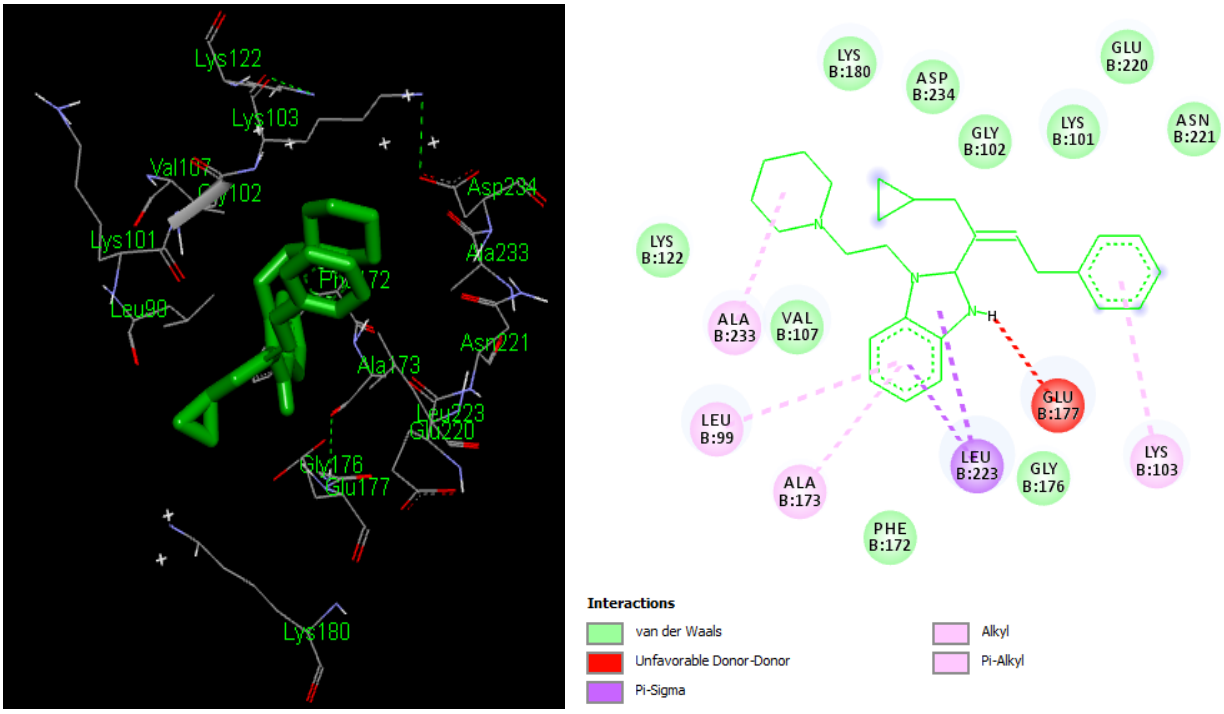
Chemotherapeutic agents, like many other drugs function by binding to the active sites of targeted enzymes thereby inhibiting their biological roles in certain cells of an organism. Aurora B kinase, which is the target enzyme in this study plays significant roles in hepatocellular carcinogenesis. Inhibition of this enzyme by bioactive molecules will certainly affects their physiological functions and subsequently disrupt the growth of cancerous cells. The binding affinities (ΔG) of the novel ligands and template molecule against the active sites of the Aurora B kinase are presented in Table 6 and their 2D diagrams of interactions with the protein target in Figure 6.

Table 6: Binding affinities (ΔG) of the designed compounds and Doxorubicin against EFGR target

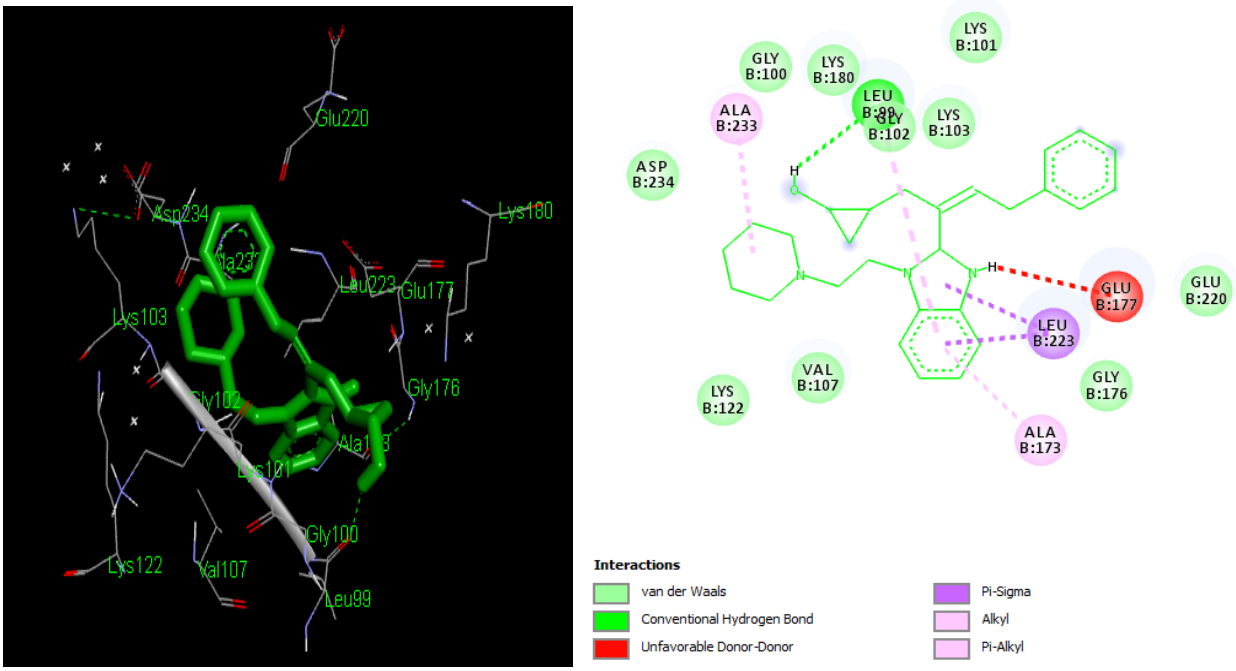
Compound	ΔG (kcal/mol)
G-1	-8.0
G-2	-7.8
G-3	-7.7
9	-7.5



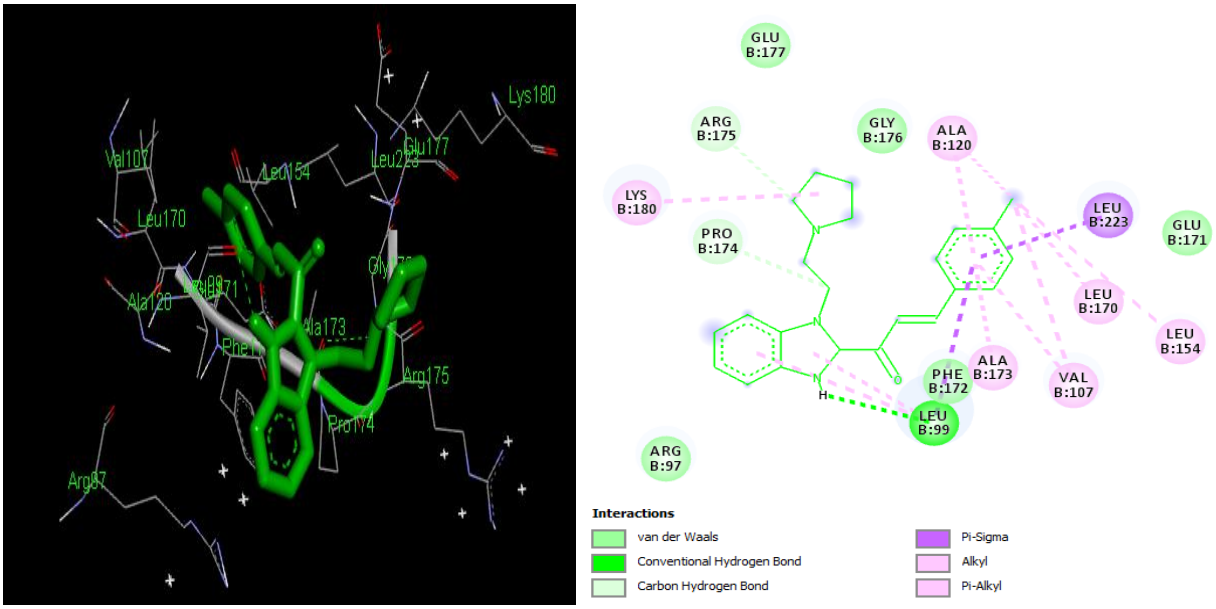
Complex of G-1 with active sites of the target



Complex of G-2 with active sites of the target



Complex of G-3 with active sites of the target



Complex of template with active sites of the target

Figure 6. 3D and 2D diagram of interactions of the designed ligands and the template with active sites of Aurora B kinase.

Insilico Drug-likeness and ADMET Assay

The key physicochemical descriptors of the novel ligands used for the assessment of their drug likeness and ADMET profiles are presented in Tables 7 and 8, respectively.

Table 7: Physicochemical Properties of the Compounds

Compound Rule	G-1	G-2	G-3
Lipinski's	yes	yes	yes
HBA	2	2	3
HBD	0	0	1
Mw ($gmol^{-1}$)	414.33	397.56	413.55
$MLogP_{(o/w)}$	3.92	4.7	3.85
Veber's	yes	yes	yes
NRB	6	7	7
TPSA ($Å^2$)	38.13	21.06	41.29

HBA: number of hydrogen bond acceptor, HBD: number of hydrogen bond donor, Mw: molecular weight, NRB: number of rotatable bond, TPSA: topological polar surface area

Table 8: Pharmacokinetics and Toxicity profiles of the Compounds

Cpd	T	M	R	CYP45 substrate	GIA	BBB	Pg-P substrate
G-1	No	No	No	No	High	Yes	No
G-2	No	No	No	Yes	High	Yes	Yes
G-3	No	No	No	Yes	High	Yes	Yes

T; Tumorigenic, M; Mutagenic, R; Reproductive effect, GIA: gastrointestinal absorption, BBB: blood brain barrier penetration, Pg-P: P-glycoprotein

Discussions

QSAR Model

The GFA-derived QSAR model linking the dominant descriptors of the studied benzimidazole-chalcones to their observed anti-cancer activities is presented by equation 1. The statistical parameters of the QSAR model is in agreement with the standard validation metrics shown in Table 2, confirming the stability, robustness, and reliability of the model [49, 50]. Likewise, the high linearity of the plot of experimental pIC_{50} against predicted pIC_{50} for the training set of molecules shown in Figure 1 further lay credence to the high extrapolative power of the model.

External validation of the model was performed by using the regression equation to predict the pIC_{50} of test set of molecules. The high linearity of the plot of their experimental pIC_{50} values against predicted pIC_{50} values ($R^2_{pred} = 0.81$) for the test set as displayed in Figure 2 implies that the model can predict accurately, new set of chemicals within its applicability domain. Also, the presence of possible biases in the process of model building was checked via the plot of standardized residuals against the experimental pIC_{50} values (Figure 3). The dispersal of residuals on both sides of the zero line implies there is no systematic error in the process of building the model [51, 52].Strong inter-correlation among the descriptors in the model (i.e., multicollinearity) weakens its statistical power and stability. The presence of possible significant multi-collinearity among the descriptors in the regression equation (model) was checked via the correlation matrix in Table 4. The low inter-correlation ($R^2 < 0.5$) among the three descriptors confirms the high statistical power of the model.

Influence of the descriptors in the Model

One of the fundamental functions of QSAR modelling is to harness the dominant descriptors of a set of molecules responsible for their observed bioactivities. The optimum model in equation 1 reveals the dominant influences of *ZMIC2, RDF120m,* and nHBint9 descriptors on the observed chemotherapeutic properties of benzimidazole chalcones against HepG2 cancer cell line. Among the three descriptors, *ZMIC2* exerts the foremost influence as shown in Figure 4. Its positive coefficient as shown in equation 1 shows that the anti-cancer properties of the studied compounds varies directly with the value of the descriptor in the molecules. Thus, for an enhanced potency, the structures of the bioactive compounds could be optimized to have higher value of this descriptor. Also crucial to the observed anti-tumor properties of the studied compounds are *RDF120m* and nHBint9 descriptors. Their negative coefficients in the model reveal the inverse relationship between these descriptors and the anti-cancer properties of the studied benzimidazole-chalcone compounds. Consequently, for an enhanced bioactivities of the compounds, the values of these descriptors should be kept as low as possible.

Molecular Docking Studies

Aurora B kinase, which is the target enzyme in this study, plays significant roles in hepatocellular carcinogenesis. The inhibition of the physiological roles of this enzyme target by the binding of bioactive compounds to its active sites is a rational drug discovery strategy. In this work, molecular docking analysis of the designed ligands was performed to examine their binding patterns with the active sites of Aurora B kinase protease and compare them with the template molecule. The result of the docking simulation displayed in Table 6 reveals that the newly designed compounds (Figure 5) have minimum binding energy ranging from –7.7 to – 8.0 kcal/mol, with the best result achieved with G-1 (ΔG = -8.0 kcal/mol). All the compounds displayed better binding efficacies when compared with the template molecule (ΔG = -7.5 kcal/mol). The 3D and 2D diagrams of interaction of the designed ligands and the template within the binding pocket of the target protein shown in Figure 6 reveals that G-1 binds to the active sites of the protease through pi-alkyl interactions with VAL107, LEU223, LEU170, ALA120, and LYS103 amino acid residues of the target protein. Likewise, alkyl interactions with VAL107, LEU223, LEU170, LEU99, LYS122, and LYS103 were also observed. The following interactions were found in the complex of G-2 with the active sites of the target; pi-alkyl with LEU99, ALA173, and LYS103; an alky interaction

with ALA233; two pi-sigma interactions with LEU223; and an unfavorable donor-donor interaction with GLU177. Furthermore, G-3 forms pi-alkyl interactions with the active sites of the target via ALA173, and GLY102; an alkyl interaction with ALA233; two pi-sigma interactions with LEU223; an unfavorable donor-donor interaction with GLU177; and a conventional hydrogen bond with LEU99. In addition, the template molecule binds to the target protein via pi-alkyl interactions with ALA120, ALA173, VAL107, and LEU99; alkyl interactions with LYS180, LEU99, LEU170, LEU154, VAL107, and ALA120; pi-sigma interactions with LEU99 and LEU223; and a conventional hydrogen bond interaction with LEU99.

ADMET and Drug-likeness Assessment

Poor drug-likeness (oral bioavailability), unfavorable pharmacokinetic and toxicity profiles constitute significant hurdles in the development of drug candidates at clinical trials. Thus, the need to evaluate the oral bioavailability as well as the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of drug candidates is necessary in the initial phase of drug discovery [53]. The Lipinski's and Verber's rules were used to assess the drug-likeness of the designed ligands. The results (Table 7) reveal that the compounds violate none of the rules and as such could be said to have positive drug-likeness. Furthermore, the pharmacokinetic data in Table 8 shows that they possess good gastrointestinal absorption and could penetrate the BBB, a unique feature of the blood vessels that vascularized the central nervous system that regulates movement of ions, molecules, and cells between the blood and the brain [54]. Also, the designed ligands with the exception of G-1 were found to be substrate of P-glycoprotein (P-gp), a protein expressed naturally in many tissues of the human body that functions as biological barrier by extruding toxins and xenobiotic from the system as well as maintaining the integrity of BBB [55]. Another aspect of pharmacokinetic worthy of note is the biotransformation of drugs into inactive metabolites and its subsequent excretion through the kidney and bile. This function is performed mostly by Cytochrome P450 (CYP450) enzymes found largely in the liver and in lesser amount in the small intestine, lungs, placenta, and kidneys [56]. All the designed anticancer agents with the exception of G-1 (Table 8) were found to be substrate of one or more CYP450 enzymes and as such could be metabolized and excreted from the biological system. Likewise, the insilico toxicity assays of the designed compounds (Table 8) reveals that they exhibit no tendencies of causing cancer, genetic deformity, and reproductive ill-health.

Conclusion

The present study entails theoretical investigation of the anticancer properties of some benzimidazole-chacone analogues using computer aided techniques. The QSAR modelling revealed the dominant influences of ZMIC2, RDF120m, and nHBint9 descriptors on the chemotherapeutic activities of compounds. Through structural modification and potency optimization of the most active derivative (template) using information gotten from the model, three drug candidates more potent than the template were designed. Molecular docking simulation of the designed compounds against the active sites of Aurora B kinase, the protein target found to be strongly involved in hepatocarcinogenesis, reveals that the compounds binds better compared to the template molecule. Also, insilico drug-likeness and ADMET assessment of the novel ligands revealed that they possess good oral bioavailability, excellent pharmacokinetic and toxicity profiles. However, further invivo and invitro studies are required to validate these claims.

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