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QSAR OF NOVEL CHRYSIN BENZIMIDAZOLE DERIVATIVES FOR POTENTIAL ANTI-CANCER AGENTS

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ABSTRACT

The current study focuses on developing a Quantitative Structure-Activity Relationship (QSAR) model for novel chrysin-benzimidazole derivatives as possible anti-cancer drugs for hepatocellular carcinoma (HepG2 cell line). The biological activity of 21 substances was measured using IC_{50} values, which were then converted to pIC_{50} for better statistical analysis. Molecular structures were optimized with the semi-empirical PM3 method, and ChemOffice software was used to calculate several physicochemical characteristics.

Multiple linear regression analysis was used to find relationships between molecular characteristics and biological activity. The created QSAR models revealed a strong link between structural features and anticancer efficacy, emphasizing the significance of descriptors such as molar refractivity, partition coefficient, and related factors. The validated model demonstrated satisfactory prediction ability on both the training and test sets. This study sheds light on the structural prerequisites for anticancer action, which may aid in the rational development of more effective benzimidazole-based medicinal medicines.

***Keywords*:** QSAR, Benzimidazole derivatives, Anti-cancer activity, HepG2 cell line.

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INTRODUCTION

Cancer is the result of aberrant cells growing out of control and significantly altering physiological processes. The normal cells, chemicals, and blood arteries that surround and nourish a tumor are influenced by cancer cells, which have the ability to elude the immune system. The tumors may emit hormones that change bodily functioning and interfere with the digestive, neurological, and circulatory systems. They can also grow and spread to other parts of the body. Creating chemicals that can specifically stop the growth of aberrant cells while having little to no effect on healthy cells is essential for the development of anticancer drugs. Anticancer medication development is therefore crucial on a global scale [1-3]. Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths in developing nations and one of the most prevalent and deadly diseases worldwide, particularly in men [4]. Most HCC patients receive a diagnosis at an advanced or intermediate stage [5]. Systemic chemotherapy with small kinase inhibitors or cytotoxic agents is only marginally beneficial for patients with advanced HCC. For instance, sorafenib, an oral multi-tyrosine kinase inhibitor, is a standard of care for these patients. Still, its median overall survival is only about three months longer than that of patients receiving a placebo [6,7]. Additionally, there is currently no effective treatment for HCC patients with multiple lung metastases, and their prognosis is poor [8]. Thus, the development of new pharmacological drugs is essential for the treatment of HCC [9]. There are several uses for benzimidazole ring systems in the synthesis of new drugs. An essential component of vitamin B12, benzimidazole is a naturally occurring bicyclic molecule [10]. made up of a fused benzene and imidazole ring. Benzimidazoles can readily interact with the biomolecules of living systems due to their structural resemblance to purines. They are therefore a crucial pharmacophore in drug development and have a great deal of potential for use in medicinal chemistry [11-13]. Benzimidazole and its derivatives have a variety of biological activities, including antibacterial [14], anti-tubercular,, antifungal [17], antimicrobial [15,16]. Antiprotozoal [18, 19], anti-proliferative [20], and antiviral activities [21], as well as the potential to act as protein kinase inhibitors [22], synthesized several 2-methylaminobenzimidazole derivatives with potent in-vivo analgesic and anti-inflammatory properties [23]. Based on this information, benzylidene cyanomethyl benzimidazole

demonstrated outstanding anticancer efficacy against human liver carcinoma (HEP-G2) cell lines [24], shown that phenylbenzimidazole analogues have strong anti-cancer action against five human cancer cell lines [25]. Several strong medicines with benzimidazole nuclei are currently available on the market. Albendazole, for example, is used to treat some worm diseases such as pork tapeworm and dog tapeworm [19]. Albendazole also suppresses the development of hepatocellular carcinoma cells in vitro and in vivo [26]. In recent years, there has been a lot of interest in optimizing benzimidazole compounds based on their structural properties [27,28]. This study will use quantitative structure activity relationships (QSAR) to identify parameters influencing the pharmacological characteristics of synthesized analogs and validate their reported activity [29], As a result, it is critical to identify novel anti-cancer drugs with higher pharmacological activity than those now available on the market. QSAR analysis is critical in this scenario since it reduces trial and error when developing innovative drugs.In terms of descriptors, the QSAR technique assists in linking a collection of chemicals' measured or computed molecular properties to their specific biological activities or physical qualities. The use of QSAR techniques accelerates the creation of novel molecular medicines while also saving resources. The major goal of a comprehensive QSAR investigation that has yet to be completed for a number of novel Chrysin-benzimidazole derivative compounds is to find a regression function that accurately predicts the molecule's activity. Finding a regression function that accurately predicts the molecule's activity is the primary goal of a systematic QSAR study that has yet to be conducted for several novel Chrysin-benzimidazole derivative compounds, despite the fact that numerous QSAR studies have been conducted for anti-cancer medication design [30].

MATERIAL AND METHOD

Novel chrysin–benzimidazole derivatives synthesized as reported in Zhe Wanget., al. (2017) were used as the primary materials in this study [31]. The inhibitory activity of these compounds was evaluated using the half-maximal inhibitory concentration (IC_{50}) as the key dependent variable, as presented in Table 01.

Instruments

All computational work in this study was performed on an ASUS laptop powered by an Intel® Core™ i5 processor, with 8 GB RAM and a 500 GB SSD. The physicochemical properties of the synthesized compounds (Table: 01) were calculated using ChemOffice software (Version 16.0, Windows). Molecular structures were subjected to complete geometry optimization employing the semi-empirical method in Chem3D. The resulting data were subsequently analyzed using ValStat software (Version 16, Windows) for statistical evaluation.

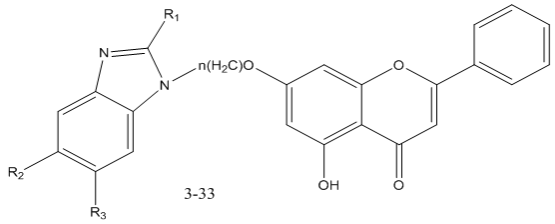

Figure 01 Structure: Novel Chrysin Benzimidazole Compound:

Table 01: Structure, HepG2 IC_{50}, and biological activity of Novel Chrysin Benzimidazole compounds.

S.No.	Compounds	Substitutions				HepG2 IC50	Biological Activity
		n	R1	R2	R3		
1	3	2	H	H	H	100	4
2	4*	2	CH3	H	H	100	4
3	5	2	Cl	H	H	100	4
4	6	2	H	H	NO2	100	4
5	7	2	H	CH3	CH3	100	4
6	8	2	H	CH3	H	91.34	4.039339
7	9	2	H	OCH3	H	100	4
8	10	3	H	H	H	-	-
9	11*	3	CH3	H	H	-	-
10	12	3	Cl	H	H	100	4
11	13	3	H	H	NO2	90.46	4.043543
12	14	3	H	CH3	CH3	97.52	4.010906
13	15	3	H	CH3	H	75.85	4.120044
14	16	3	H	OCH3	H	-	-
15	17	4	H	H	H	-	-
16	18	4	CH3	H	H	53.25	4.27368
17	19*	4	Cl	H	H	100	4
18	20	4	H	H	NO2	85.47	4.068186
19	21	4	H	CH3	CH3	82.37	4.084231
20	22	4	H	CH3	H	-	-
21	23	4	H	OCH3	H	-	-

***test set compounds**

Data Set

Quantitative Structure–Activity Relationship (QSAR) analysis was employed to establish a correlation between the physicochemical properties of the designed chrysin–benzimidazole derivatives and their biological activity. A dataset comprising 21 compounds, adapted from the study by Zhe Wang et al. (2017), was utilized to ensure adequate structural diversity and a reliable activity range for model development. The biological activity of these compounds was expressed in terms of half-maximal inhibitory concentration (IC_{50}) values. For uniformity and improved statistical correlation, the IC_{50} values (initially reported in micromolar units) were converted into molar concentrations and subsequently transformed into their negative logarithmic form ($pIC_{50} = \log (1/IC_{50})$). This transformation enhances data normalization and facilitates the development of robust and predictive QSAR models.

Molecular Structure Generation

The development of the QSAR model in the present study followed a systematic multi-step approach. Initially, a structurally diverse set of chrysin–benzimidazole derivatives along with their experimentally determined IC_{50} values was selected. In the second step, relevant molecular descriptors likely to influence biological activity were identified, ensuring that both structural and electronic features of the compounds were adequately represented. Subsequently, the optimized molecular structures were utilized for the calculation of these descriptors. In the fourth stage, statistical modeling was carried out using VALSTAT software for Windows to derive mathematical relationships correlating the selected descriptors with biological activity. Finally, the robustness and predictive ability of the developed QSAR models were validated using appropriate internal validation techniques.

All molecular structures of the chrysin–benzimidazole derivatives were sketched using ChemDraw (Version 16.0). Each compound was subjected to conformational analysis employing the Molecular Mechanics (MM2) method to identify the lowest energy conformer. The most stable conformations were further refined through semi-empirical optimization using MOPAC. Multiple initial geometries were considered during optimization to minimize the possibility of trapping in local energy minima. The lowest energy conformer obtained for each molecule was then used for descriptor calculation [32]. A comprehensive set of thermodynamic, electronic, steric, and molecular descriptors relevant to QSAR analysis was computed using ChemOffice software, and the results are summarized in Table 02.

Table 02: Descriptors for training and test set compounds of series.

S.No.	HENRY'S LAW CONSTANT	LOG P	MOLAR REFRACTIVITY	NO. OF H BOND ACCEPTORS	NO. OF H BOND DONOR	PKa	POLAR SURFACE AREA	NO. of ROTABLE BONDS
1	3.32	3.35	112.8	6	1	6.84	71.36	5
2	3.32	4.03	117.71	6	1	6.93	71.35	5
3	3.32	4.52	117.829	6	1	6.82	71.82	5
4	0.48	0	0	7	1	6.84	71.81	6
5	3.64	3.86	117.84	6	1	6.84	71.36	5
6	3.82	3.23	119.26	7	1	6.84	80.59	6
7	3.32	3.46	117.66	6	1	6.91	71.36	6
8	3.32	4.13	122.58	6	1	6.91	71.36	6
9	3.32	4.63	122.69	6	1	6.91	71.36	6
10	0.48	0	0	7	1	6.91	123.17	7
11	3.59	4.43	127.75	6	1	6.91	71.36	6
12	3.64	3.95	122.71	6	1	6.91	71.36	6
13	3.82	3.33	124.13	7	1	6.91	80.59	7
14	13.64	3.91	122.31	6	1	6.96	71.36	7
15	13.64	4.58	127.22	6	1	6.96	71.36	7
16	0	0	0	6	1	6.96	71.36	6
17	0.48	0	0	7	1	6.96	123.17	8
18	13.91	4.89	132.39	6	1	6.96	71.36	7
19	0	0	0	6	1	6.96	71.36	6
20	3.82	3.79	128.77	7	1	6.96	80.59	8
21	3.79	3.6	122.77	6	1	6.96	71.36	7

Statistical Analysis

A descriptor data matrix (D) of dimension (n × m) was constructed to compile the calculated molecular descriptors corresponding to the enzyme/cell-line inhibitory activity of the studied compounds, where *n* denotes the number of molecules and *m* represents the number of descriptors assigned to each molecule. Initially, descriptors exhibiting constant or near-constant values across the dataset were identified and removed to avoid redundancy and improve model reliability. Subsequently, correlation analysis was performed to evaluate the relationship between the remaining descriptors and the biological activity data. This analysis was carried out using VALSTAT software, which facilitated the selection of the most significant descriptors contributing to the inhibitory activity and supported the development of an optimized QSAR model.

Model Development and Validation

Multiple Linear Regression (MLR) was employed to construct QSAR models describing the relationship between selected molecular descriptors and the biological activity of the compounds. A stepwise variable selection approach, integrating both forward inclusion and backward elimination techniques, was utilized to identify the most relevant subset of descriptors contributing significantly to the model. All regression analyses were performed using the VALSTAT software package for Windows. The predictive performance and reliability of the developed QSAR models were assessed through external validation. In this approach, the biological activity (pIC_{50}) of compounds in the test set was predicted using the derived model and compared with their experimentally observed values. The cross-validation coefficient (q^2) was calculated to evaluate the model's predictive accuracy and robustness. A q^2 value greater than 0.5 is generally considered indicative of a statistically significant and reliable QSAR model with acceptable predictive capability.

RESULT AND DISCUSSION

The molecular descriptors considered in the present study were Henry's Law Constant, Log P, Molar Refractivity, Number of Hydrogen Bond Acceptors, Number of Hydrogen Bond Donors, pKa, Polar Surface Area (PSA), and Number of Rotatable Bonds. These descriptors were selected to comprehensively represent the physicochemical, electronic, and steric characteristics influencing the biological activity of the chrysin–benzimidazole derivatives. Following complete geometry optimization, all descriptors were calculated from the optimized molecular structures using the semi-empirical PM3 method, which is well-suited for organic compounds composed primarily of carbon, hydrogen, nitrogen, and oxygen atoms.

For QSAR model development, the calculated descriptors were subjected to statistical analysis using a regression-based approach. The dataset was divided into training and test sets, and multiple linear regression (MLR) analysis was applied to the training set compounds. Descriptor selection was performed based on their correlation with biological activity, ensuring minimal inter-correlation among descriptors (typically $r < 0.6$) to avoid multicollinearity. Several regression models were generated, and their performance was evaluated using statistical parameters such as the correlation coefficient (r), coefficient of determination (r^2), Fisher's test value (F), and standard error of estimation. All statistical calculations were carried out using VALSTAT software.

An initial regression analysis was conducted on the training set to obtain preliminary models, which were further refined to identify the most statistically significant equation. The optimal QSAR model was characterized by a high r^2 and q^2 value (close to 1), a high F-value, low standard error, and a statistically significant p-value ($P < 0.001$), indicating strong predictive ability and robustness. The final QSAR equation was derived using the MLR method, representing the quantitative relationship between the selected descriptors and the inhibitory activity (pIC_{50}) of the studied compounds.

Four QSAR models were developed using different combinations of descriptors including Henry's Law Constant (LAW), Log P, Molar Refractivity (MOLAR), and structural parameters.

Model no. 1 results are..... BA = [-1.35804(± 2.43243)] +MOLAR [0.798619(± 0.355138)] +REFRACTIVITY [-0.00137982(± 0.00100934)] Fraction contribution of MOLAR is = 0.621923 Fraction contribution of REFRACTIVITY is = -0.378077

n=15, r=0.570174, r^2=0.325098, r^2adj=0.212615, variance=0.00434843, std=0.0659426, QF=8.64652, PE=0.116173, F=2.89018, FIT=0.30423, LOF=0.117408, AIC=0.00652264 standard Fmax value at 95% confidence=9.65154 Model 1 (MOLAR + REFRACTIVITY) showed the best performance among all models with $r^2 = 0.325$ and lowest standard deviation (0.0659), indicating relatively better stability. MOLAR contributed positively (62.19%), while REFRACTIVITY showed a negative influence.

Model no. 2 results are..... BA = [4.25181(± 0.115973)] +LAW [-0.0200474(± 0.0111575)] +REFRACTIVITY [-0.00197284(± 0.0012154)] Fraction contribution of LAW is = -0.525375 Fraction contribution of REFRACTIVITY is = -0.474625

n=15, r=0.494024, r^2=0.24406, r^2adj=0.11807, variance=0.00487056, std=0.0697894, QF=7.07879, PE=0.130122, F=1.93714, FIT=0.203909, LOF=0.131505, AIC=0.00730584 standard Fmax value at 95% confidence=9.65154

Model 2 (LAW + REFRACTIVITY) showed weaker correlation ($r^2 = 0.244$, std = 0.0698), with both descriptors contributing negatively, indicating an inverse relationship with activity.

Model no. 3 results are..... BA = [-0.187242(± 2.65264)] +LAW [-0.0057677(± 0.01)] +MOLAR [0.615206(± 0.383279)] Fraction contribution of LAW is = -0.264345 Fraction contribution of MOLAR is = 0.735655

n=15, r=0.490949, r^2=0.241031, r^2adj=0.114536, variance=0.00489008, std=0.0699291, QF=7.02067, PE=0.130643, F=1.90546, FIT=0.200575, LOF=0.132032, AIC=0.00733512 standard Fmax value at 95% confidence=9.65154

Model 3 (LAW + MOLAR) yielded similar performance to Model 2 ($r^2 = 0.241$), where MOLAR had a strong positive contribution (73.56%), but LAW contributed negatively.

Model no. 4 results are..... BA = [-1.80005(± 3.2527)] +MOLAR [0.862777(± 0.490084)] +NO. [-0.0184087(± 0.0331487)] Fraction contribution of MOLAR is = 0.760197 Fraction contribution of NO. is = -0.239803 n=15, r=0.489422, r^2=0.239534, r^2adj=0.112789, variance=0.00489972, std=0.069998, QF=6.99194, PE=0.130901, F=1.8899, FIT=0.198936, LOF=0.132293, AIC=0.00734958 standard Fmax value at 95% confidence=9.65154

Model 4 (MOLAR + H-bond acceptors) also showed weak correlation ($r^2 = 0.239$), with MOLAR dominating (76.02%) and the number of H-bond acceptors contributing negatively. Table 3 presents the predicted pIC_{50}, biological activity, and residual values for both the training and test sets of the series using Model-1, Figure 02 shows the graph between pIC_{50} and actual IC_{50} values, and Figure 03 shows the residual values of the compounds.

Table 03: The Actual BA and predicted pIC50 values of the training set of series by using model-1

S.No.	Compound No.	Predicted pIC50	Actual Biological Activity	Residual Value
1	3	4.00727	4	0.00727
2	4*	4.08841	4	0.08841
3	5	3.98609	4	-0.01391
4	6	4.00652	4	0.00652
5	7	4.00727	4	0.00727
6	8	3.98364	4.039339	-0.055699
7	9	4.06798	4	0.06798
8	10	-	-	-
9	11*	-	-	-
10	12	3.98103	4	-0.01897
11	13	4.06375	4.043543	0.020207
12	14	4.06692	4.010906	0.056014
13	15	4.04394	4.120044	-0.076104
14	16	-	-	-
15	17	-	-	-
16	18	4.05722	4.27368	-0.21646
17	19*	4.0624	4	0.0624
18	20	4.11065	4.068186	0.042464
19	21	4.10648	4.084231	0.022249
20	22	-	-	-
21	23	-	-	-

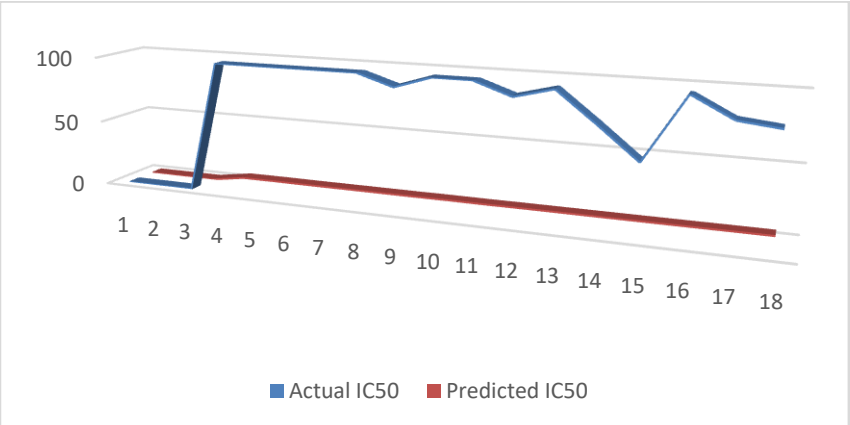

Figure 02: shows the graph between pIC_{50} and actual IC_{50} values

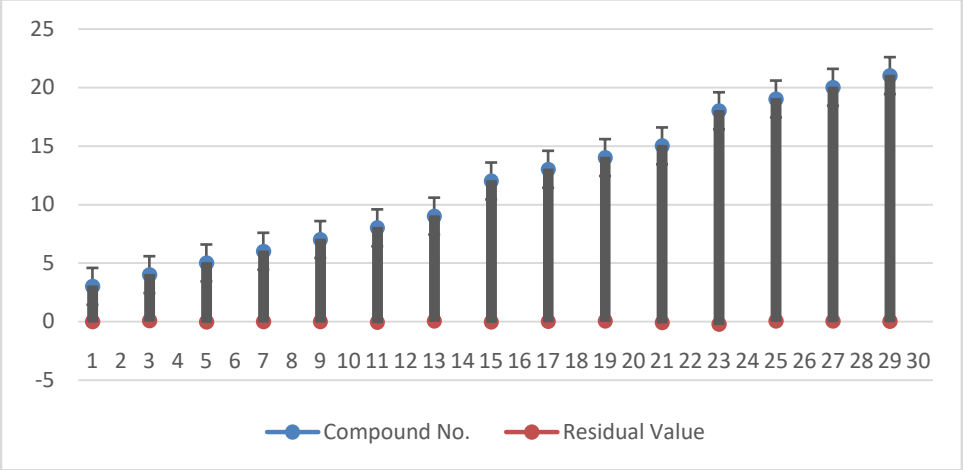

Figure 03: shows the residual values of the compounds.

CONCLUSION

We investigated the development of multiple QSAR models for the HepG2 cell line using various molecular descriptors, including Molar Refractivity, Henry's Law Constant, Partition Coefficient (Log P), Mass, Exact Mass, and hydrogen bonding parameters. Among the developed models, Models 1, 2, 3, and 4 incorporated different combinations of these descriptors. Comparative statistical analysis revealed that Model 1 demonstrated relatively better performance than the other models, with an r^2 value of 0.325098 and a lower standard deviation of 0.0659426, although the overall predictive power of all models remained modest and statistically insignificant. The results indicate that HepG2 inhibitory activity shows a positive correlation with Molar Refractivity, suggesting that compounds with higher molecular volume or bulkiness play a significant role in enhancing biological activity. Conversely, descriptors such as Henry's Law Constant, refractivity, and hydrogen bonding parameters exhibited negative contributions, implying that increased polarity and hydrogen bonding capacity may reduce activity. The influence of the Partition Coefficient (Log P) suggests that moderate hydrophobicity favors activity, indicating that less polar compounds tend to be more effective against the HepG2 cell line.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

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ETHICAL APPROVAL

Ethical approval was not required for this study.

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