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QSAR Modeling of a Novel Series of Methoxylated Chalcones as Antioxidant Agents Against Gram-Positive Bacteria *Staphylococcus aureus*

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Abstract

Background: *Chalcones are aromatic ketones belonging to the flavonoid family. They are plant-based compounds and are widely found in nature. For centuries, these bioactive molecules have been utilized in various traditional medicines for the treatment of several ailments. Chalcones have antibacterial, antiviral, antimalarial, antifungal, antioxidant, and antileishmanial properties. They are also used to treat inflammation and cancer. Chalcones act as angiogenesis inhibitors, an important factor in cancer progression and metastasis.* ***Method:*** *QSAR analysis is done on a series of seventeen chalcones derivatives (1–16) using various physicochemical parameters. The study reveals that parameters, such as connectivity indices (χ^5, χ^6), ADME descriptors, molecular weight (MW), molar refractivity (MR), density (D), and LogP showed significant correlations with biological activity. The best results are obtained by performing multiple regression analyses with different models with strong R-squared values indicating robust predictive performance.* ***Result:*** *A combination of various descriptors, such as MR, MW, Pz, D, ADMET (LogS), and connectivity Indices (χ^1–χ^6) have been found to be best for the significant modeling of the anti-bacterial activity. QSAR model pIC_{50} = 3.374+ (–0.4484) χ^5+ (0.5824) χ + (–0.2395) ADMET (LogS) optimized with empirical parameters with good statistical quality (R = 0.66, R^2 = 0.44) was found to be the best model.* ***Conclusion:*** *The ADME solubility level reflects a molecule's aqueous solubility, which can be predicted using molecular descriptors like the number of hydrogen bond donors and acceptors, dipole moment, rotatable bond count, and surface area. These factors are crucial in determining the solubility of the various organic compounds. Increased solubility has been shown to improve the antimicrobacterial activity. The positive sign of the connectivity indices implies that better better-designed drug can be obtained if there is an increase in the branching.*

Keywords: QSAR modeling, methoxylated chalcones, *Staphylococcus aureus*, Gram-positive bacteria, ADME

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INTRODUCTION

With the rise in emerging infectious diseases and the growing prevalence of multidrug-resistant microbial pathogens the treatment of bacterial infections continues to pose a significant therapeutic challenge. Although it is correct that numerous antibiotics and chemotherapeutic agents are available, the revival of both old and new antibiotic-resistant bacterial strains in a few decades is the urgent need for novel classes of antibacterial agents [1]. Chalcones are a vital class of natural compounds. They act as key precursors for synthesizing various types of flavonoids present abundantly in plants. Chalcones are open-chain flavonoids composed of the two rings connected by a three-carbon α, β-unsaturated carbonyl system. They

are also referred to as 1, 3-diphenyl-2-propen1-ones [2]. Chalcone derivatives have significantly attracted attention because of their simple molecular structure and the broad range of pharmacological activities. These compounds have also been reported to exhibit anti-inflammatory [3], anti-tumor [4], anti-ulcer [5], analgesic [6], antiviral [7], anti-malarial [8], and anti-tuberculosis [9] properties. Chalcones are greatly recognized for their antibacterial properties, with dimethylamino chalcones specifically identified as inhibitors of iNOS [10]. These biological activities of chalcone are largely attributed to the presence of an α, β-unsaturated ketone moiety. The antimicrobial and antioxidant properties of methoxylated chalcone derivatives have been extensively researched and are well documented in the literature [11, 12]. The use of small molecules in current treatment protocols has highly motivated us to focus on the chalcone derivatives in the present research [13]. Additionally, licochalcone, a natural product derived from *Glycyrrhiza inflata*, demonstrated low minimum inhibitory concentrations (MICs) ranging from 5 to 20 mg/L against three species: Mycobacterium tuberculosis, *M. avium*, and *M. bovis* [14]. Chalcones and flavonoids have also shown effectiveness against Mycobacterium tuberculosis H37Rv, demonstrating that a 2´-hydroxy substitution enhances antimicrobacterial activity. Chalcones are well-known for their antibacterial properties, and dimethylamino chalcones have been identified as iNOS inhibitors [15]. Literature suggests that NOS2 gene expression plays an important role in the production of nitric oxide (NO), which is basically linked to primary tuberculosis (TB) [16].

Methods of Preparation of Chalcones Derivatives

2, 4, 5-trimethoxychalcone derivatives (1–16) were synthesized through Claisen-Schmidt condensation (Figure 1). A mixture of substituted 2-hydroxyacetophenone (1 equivalent) and 2, 4, 5-trimethoxybenzaldehyde (1 equivalent) in 15 mL of ethanol (EtOH) was prepared. To this, a 60% potassium hydroxide (KOH) solution (5 mL) was added dropwise at 0°C. The reaction was carried out by adding ethanol/KOH at a temperature of 0–5°C, followed by stirring at room temperature for 6–8 hours. After completion, the reaction mixture was cooled, poured into ice water, and neutralized using 1N HCl. The resulting light-yellow solid was collected by filtration and subsequently purified either through silica gel column chromatography (using a 1:9 ethyl acetate to hexane ratio) or by recrystallization from ethanol. This process resulted in the formation of the desired 2, 4, 5-trimethoxychalcone analogs (2–23) with an average yield of 60–70% [17].

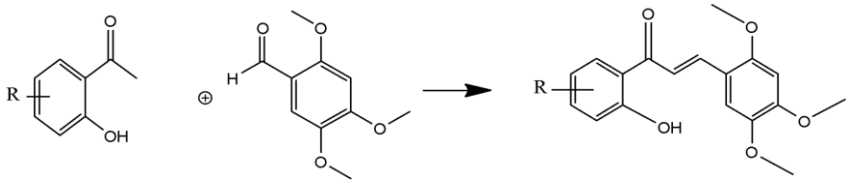

Figure 1. Reagents and condition: (a) EtOH, 60% KOH, 0-rt 6–8 hr.

MATERIALS AND METHODS

2-D structures of 16 chalcone derivatives were drawn using ACD Lab Chem Sketch software [17] version 10. Physicochemical descriptors [18], such as molecular weight (MW), molar refractivity (MR), density (D), polarizability (Pz), partition coefficient (LogP), connectivity indices [19, 20] (χ^1–χ^6) were calculated by the PaDEL software [21], E-Dragon software [22, 23] and ADME (LogS) values were calculated by the Swiss ADME software [24]. E-Dragon software primarily accepts molecular structures in SMILES notation, which can be generated using Babel software [25]. Similarly, PaDEL software processes input files in the form of SMILES directories for its analyses. Hansch analysis was carried out to perform multiparametric regression analysis using structural parameters and inhibitory activity, utilizing SPSS (v7.5) software [26] for data processing. In this QSAR analysis, Table 1 showcases various analogs of the parent structure along with their corresponding inhibitory activities. All calculated parameters for QSAR analysis are detailed in Table 2. In multiparametric modeling, it is essential to first assess the presence of collinearity between the parameters to ensure the development of a statistically significant model. The correlation matrix displaying the relationships between the various parameters is provided in Table 3.

Table 1. Structural details and biological activity for a series of chalcone derivatives against Gram-positive bacteria *Staphylococcus aureus*.

S.N.	R	pIC_{50}
1	3′-Cl	4.56
2	3′-Cl, 5′-CH_3	4.42
3	6′-Cl	5.12
4	4′-Cl, 6′-Cl	5.12
5	3′-CN, 5′-Cl	4.48
6	3′-Br	4.42
7	4′-Br, 6′-NO_2	4.48
8	3′-F	4.52
9	5′-F	4.39
10	4′-F	4.69
11	4′-F, 6′-F	4.90
12	3′-F, 5′-F	4.82
13	4′-CN, 6′-F	4.37
14	4′-CF_3	4.69
15	4′-SO_2Me	4.75
16	3′-CN	4.34

Table 2. Physicochemical and topological descriptors with the predicted activity of the training test (16 compounds).

S.N.	Pic50	Mr	LogP	Mw	ADMET (LogS)	Density	Pz	X1	X2	X3	X4	X5	X6
1	4.56	95.59	3.968	348.8	-5.34	1.281	37.23	11.511	9.722	8.611	6.158	4.942	3.223
2	4.42	101.48	4.276	362.8	-5.72	1.257	39.14	11.905	10.368	8.863	6.889	5.371	3.383
3	5.12	95.59	3.968	348.8	-5.34	1.281	37.23	11.511	9.754	8.4	6.9	4.817	3.274
4	5.12	100.19	3.93	383.2	-5.93	1.348	39.17	11.905	10.4	8.63	7.433	4.893	3.657
5	4.48	101.69	3.839	373.8	-5.41	1.36	37.81	12.443	10.559	9.164	7.238	5.724	3.553
6	4.42	98.67	4.077	393.2	-5.54	1.422	38.34	11.511	9.722	8.611	6.518	4.942	3.223
7	4.48	103.26	3.985	438.2	-4.88	1.52	40.93	12.815	11.33	9.224	7.702	6.001	3.826
8	4.52	91.39	3.453	332.3	-5.01	1.256	35.29	11.511	9.722	8.611	6.518	4.942	3.223
9	4.39	91.39	3.456	332.3	-5.01	1.256	35.29	11.494	9.85	8.361	6.462	5.234	3.219
10	4.69	91.39	3.453	332.3	-5.01	1.256	35.29	11.494	9.85	8.339	6.626	4.859	3.49
11	4.9	91.79	3.592	350.3	-5.28	1.303	35.28	11.905	10.4	8.63	7.433	4.893	3.657
12	4.82	91.79	3.592	350.3	-5.28	1.303	35.28	11.905	10.368	8.863	6.889	5.371	3.383
13	4.37	97.49	3.325	357.3	-5.08	1.33	35.94	12.443	10.569	9.069	7.548	5.326	3.722
14	4.69	97.49	4.333	382.3	-5.58	1.301	37.26	12.705	11.808	9.302	7.144	5.483	3.776
15	4.75	105.76	2.718	392.4	-5	1.299	39.42	12.705	11.808	9.302	7.144	5.483	3.776
16	4.34	97.08	3.186	339.3	-4.82	1.29	35.9	12.049	9.913	8.897	6.962	5.143	3.432

RESULTS AND DISCUSSION

Any pair of parameters with an R-value greater than 0.5 should not be used together due to collinearity in the correlation matrix [27, 28]. Parameters that do not show autocorrelation are suitable for performing the multiparametric regression analysis [29, 30]. While many parameters do not exhibit collinearity, only statistically significant multiparametric equations are reported in this study. Multi-parametric regression analysis of the data gave several models, but we have reported the best model-the following equation has been presented and was found to be extremely significant.

The ADME solubility level mainly reflects a molecule's aqueous solubility, which can be predicted using molecular descriptors like the number of hydrogen bond donors and acceptors, dipole moment,

rotatable bond count, and surface area. The solubility of the organic compounds is significantly influenced by these factors [31]. The increased value of solubility has been shown to improve antimicrobacterial activity. The positive sign of the connectivity indices implies that an increase in branching will give a better design in the future.

Table 3. Correlation matrix between different parameters.

	Pic50	***Mr***	***LogP***	***Mw***	***ADMET (LogS)***	***Density***	***Pz (polarizability)***	***X1***	***X2***	***X3***	***X4***	***X5***	***X6***
Pic50	1												
Mr	-0.101656	1											
LogP	0.0919678	0.0800794	1										
Mw	0.0076546	0.7892353	0.294063	1									
ADMET (LogS)	-0.401789	-0.204794	-0.69537	-0.18359	1								
Density	-0.125563	0.5280333	0.268865	0.863189	-0.001345238	1							
Pz(polarizability)	0.0468	0.8970834	0.341453	0.87528	-0.324855906	0.6381029	1						
X1	-0.118136	0.6824125	-0.08827	0.67695	0.109234887	0.4781306	0.493577334	1					
X2	0.0869004	0.6151139	-0.04497	0.667067	-0.021804055	0.3348757	0.50525418	0.915664	1				
X3	-0.238847	0.6977177	-0.04983	0.632836	0.052740921	0.4183503	0.479395891	0.948723	0.855081	1			
X4	0.2120811	0.4786941	-0.03315	0.561765	-0.038961539	0.5170189	0.378767464	0.763449	0.642736	0.599117	1		
X5	-0.390341	0.590857	0.044125	0.629014	0.194043526	0.5230273	0.488582478	0.82407	0.708218	0.820676	0.50589	1	
X6	0.1646791	0.5224758	-0.12502	0.598457	0.030364229	0.4181007	0.399591646	0.874136	0.856094	0.71846	0.86872	0.548467	1

Model	**n**	**R^2**	**Adjusted R^2**	**F-Valve**	**Standard Error**
3.374 + (–0.4484) χ^5 + (0.5824) χ^6 + (–0.2395) ADMET (LogS)	16	0.44	0.3027	3.17	0.2125

To assess the predictive potential of the models, the predictive correlation coefficient R^2 (Pred) was determined by plotting graphs between the observed and calculated pIC_{50} values. Such correlations are shown in Figure 2. From Figure 2, R^2 (Pred) values obtained came out to be 0.44 and this is high indicating the quality of the models.

CONCLUSIONS

The primary goal of this research is to develop novel derivatives of Indomethacin that hold the potential to serve as superior therapeutics for combating specific diseases. The ADME solubility profile predominantly reflects a molecule's aqueous solubility, which can be quantitatively predicted using molecular descriptors, such as the count of hydrogen bond donors and acceptors, dipole moment, number of rotatable bonds, and molecular surface area. These physicochemical parameters critically influence the solubility characteristics of organic compounds. Importantly, increased solubility has been

correlated with enhanced antimycobacterial activity, highlighting its significance in drug design and optimization. A positive value for the connectivity indices indicates that an increase in molecular branching is likely to lead to improved designs in the future. This relationship underscores the potential of branching as a key structural feature in optimizing molecular properties for advanced applications.

Table 4. Comparison between observed values and predicted activities and their residual values.

S.N.	Observed Activity	Equation Formed	
		Predicted Value	Residual Value
1	4.56	4.31	0.25
2	4.42	4.31	0.11
3	5.12	4.40	0.72
4	5.12	4.73	0.39
5	4.48	4.17	0.31
6	4.42	4.36	0.06
7	4.48	4.08	0.40
8	4.52	4.23	0.29
9	4.39	4.10	0.29
10	4.69	4.42	0.27
11	4.90	4.57	0.33
12	4.82	4.20	0.62
13	4.37	4.37	0.00
14	4.69	4.45	0.24
15	4.75	4.31	0.44
16	4.34	4.22	0.12

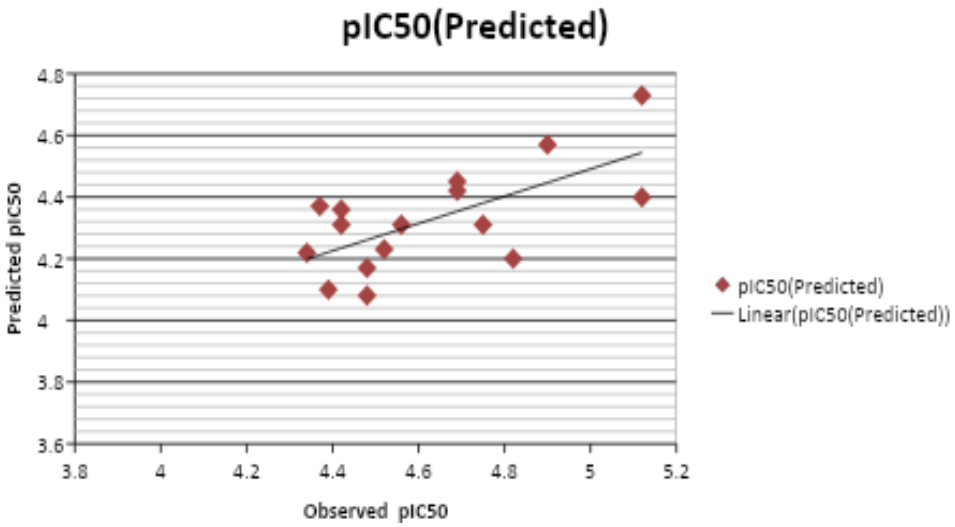

Figure 2. A plot showing a comparison between observed and predicted pIC_{50} values based on the model presented above.

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