Computational Analysis of a Series of Chlorinated Chalcone Derivatives

Bradley O. Ashburn

Mathematics, Natural, and Health Sciences Division, University of Hawai'i—West O'ahu, Kapolei, HI, US
Email: bashburn@hawaii.edu

Abstract

A systematic conceptual density functional theory (DFT) analysis was performed on a series of chlorinated chalcones to study the effect of electron distribution on antimicrobial activity. In our previous work, a series of 16 chlorinated chalcones were synthesized to determine the antimicrobial effects of varying the location of the halogen substituent on each aromatic ring of the chalcone. Herein is reported a DFT investigation of those 16 chalcones and a comparison of quantum chemical properties to their antimicrobial activity. DFT global chemical reactivity descriptors (chemical hardness/softness, chemical potential/electronegativity, and electrophilicity) and local reactivity descriptors (Fukui functions and dual descriptor) were calculated for all compounds using Spartan'18 software. All calculations were carried out at the B3LYP/6-31G* level of theory. Reactivity analysis of the Fukui dual descriptor calculations reveals sites of nucleophilic and electrophilic attack. These *in-silico* results provide a foundation for further synthetic optimization of the chalcone skeleton to serve as novel antimicrobial agents.

Keywords

Density Functional Theory, Computational Analysis, *In-Silico*, Chalcone

1. Introduction

Treatment of bacterial infection is a major health issue, with increasing emergence of drug-resistant microbes resulting in two million infections and over twenty thousand deaths each year in the United States alone [1]. Thus, it is crucial to develop new antibiotics to combat these pathogens. Chalcones, of the flavonoid family, are characterized by their dual aromatic rings and α,β-unsaturated ketone moiety which is responsible for their widely known antimicrobial activities [2]-[10]. In addition to antimicrobial activity, chalcones have been shown to

exhibit a multitude of other pharmacological effects including, but not limited to, antioxidant [11] [12], anti-inflammatory [13] [14] [15], and antitumor [16] [17] [18] [19]. Synthesis and biological evaluation of chlorine positioning were previously studied in our laboratory [10]. To further the understanding of halogen placement on biological activity, an *in-silico* analysis can be employed.

Density Functional Theory (DFT) has been shown to elucidate valuable descriptions of chemical reactivity, molecular structure, vibrational frequencies, and the energetics of chemical reactions [20] [21] [22] [23] [24]. DFT has produced powerful tools for the study of organic reactivity via the use of theoretical global and local reactivity indices and is widely utilized by researchers in chemistry, physics and materials science due to the development of accurate density functionals. Novel DFT studies routinely provide insights into chemical reactivity [24] [25] but no such studies have been performed on chlorinated chalcones. The goal of this computational analysis is to investigate the electronic properties of a series of 16 chalcones and compare them to their previously reported antimicrobial activity.

2. Materials and Methods

2.1. Computational Details

Quantum chemical calculations were performed using Spartan'18 computational software on a Macintosh computer. Geometry optimization and single point energy calculations were carried out at the B3LYP/6-31G* level of theory and verified by the absence of any imaginary frequencies.

2.2. Global Quantum Chemical Descriptors

2.2.1. Electronic Chemical Potential (μ) and Mulliken Electronegativity (χ)

The electronic chemical potential (μ) of a molecule is the change in energy with respect to the number of electrons (N) at a fixed external potential $\upsilon(r)$ [27] [28]. This represents the tendency of electrons to escape from an atom or molecule.

$$\mu = \left(\frac{\partial E}{\partial N} \right)_{\upsilon(r)} \tag{1}$$

Application of the finite difference approximation yields the simplified expression:

$$\mu \approx -\frac{(IP + EA)}{2} \tag{2}$$

where IP represents the first ionization potential and EA represents the electron affinity of an atom or molecule. The Koopman theorem [29] and Kohn-Sham formalism [30] show that the ionization potential (IP) can be approximated by the energy of the highest occupied molecular orbital ($-E_{HOMO}$) and the electron affinity (EA) can be approximated by the energy of the lowest unoccupied mo-

lecular orbital ($-E_{LUMO}$).

$$\mu \approx \frac{\left(E_{HOMO} + E_{LUMO}\right)}{2} \tag{3}$$

Given that electronegativity (χ) is characterized as the tendency of an atom to attract electrons, it can be written as the negative of the chemical potential (μ):

$$\chi = -\mu \tag{4}$$

2.2.2. Chemical Hardness (η) and Softness (S)

The hard and soft acids and bases (HSAB) principle presented by Pearson [30] [31] [32] states that Lewis acids can be classified as either hard or soft [33] and that the most favorable interactions in an acid/base reaction occur between hard/hard or soft/soft pairs. It would thus be beneficial to have a metric that measures the hardness/softness of molecules. Parr defined a quantitative expression for chemical hardness (η) as the change in chemical potential (μ) of a molecule with respect to the number of electrons (N) at a fixed external potential $\upsilon(r)$. This represents the resistance of a molecule to exchange electron density with the environment.

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{\upsilon(r)} \tag{5}$$

Using the finite difference approximation and substituting the ionization potential (IP) for $-E_{HOMO}$ and electron affinity (EA) for $-E_{LUMO}$, the chemical hardness can be expressed as:

$$\eta \approx \frac{\left(IP - EA\right)}{2} \approx \frac{\left(E_{LUMO} - E_{HOMO}\right)}{2} \tag{6}$$

Chemical softness (S) is the reciprocal of chemical hardness (η):

$$S = \frac{1}{\eta} \tag{7}$$

2.2.3. Electrophilicity Index (ω)

Maynard [34] and Parr [35] defined the electrophilicity index (ω) as the tendency of an electrophile to acquire more electron density (chemical potential) divided by the resistance to exchange electron density with the environment (chemical hardness). It is a quantitative value intrinsic to a molecule and has become a powerful tool to predict reactivity.

$$\omega = \frac{\mu^2}{2\eta} \tag{8}$$

2.3. Local Quantum Chemical Descriptors

Fukui Functions and Dual Descriptor

The Fukui function $f(r)$ represents the change in electron density at point r with respect to the change in the number of electrons N at a fixed external potential $\upsilon(r)$ [36]:

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N} \right)_{\upsilon(r)} \qquad (9)$$

Parr expanded the use of the Fukui function to show localized areas of nucleophilicity (f^+) and electrophilicity (f^-) called the condensed Fukui functions [37] [38].

$$f^+(r) \approx \rho_{N+1}(r) - \rho_N(r) \qquad (10)$$

and

$$f^-(r) \approx \rho_N(r) - \rho_{N-1}(r) \qquad (11)$$

where ρ_N, ρ_{N-1}, and ρ_{N+1} are the atomic charges in the neutral, anionic and cationic species, respectively.

Combining the two functions provides the most useful description in what is known as the dual descriptor [39] [40] [41]. Where $\Delta f_k(r) < 0$ represents an atom k of a molecule that is electrophilic and $\Delta f_k(r) > 0$ an atom k that is nucleophilic.

$$\Delta f(r) = \left(\frac{\partial f(r)}{\partial N} \right)_{\upsilon(r)} \qquad (12)$$

A condensed form is represented by:

$$\Delta f(r) = f_k^+ - f_k^- \qquad (13)$$

3. Results and Discussion

Chalcones **1a-d**, **2a-d**, **3a-d**, and **4a-d** were previously synthesized and tested for antimicrobial activity in our laboratory [10] using agar well diffusion assay by measuring the zones of inhibition against pathogenic bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*). The results show that nearly all the chlorinated chalcones synthesized display antibacterial activity comparable to the known antibiotic sulfanilamide. The 16 chalcones, shown in Figure 1 below, vary the positioning of chlorine substituents on each ring of the chalcone skeleton. In order to probe the chemical rationale for the differences in biological activity, each chalcone was analyzed computationally.

Full unconstrained molecular geometry optimizations of 16 chalcones were carried out using Wavefunction Spartan'18 software [42] using the exchange correlation functional by Becke [43] with gradient-corrected correlation provided by Lee, Yang and Parr [44] with the 6-31G* basis set. This DFT method was chosen since it is fast, less computationally intensive, takes electron correlation into account, and provides accuracy in reproducing experimental data [45]. Optimized geometries depicting the molecular structures of the most stable forms of each chalcone were confirmed by vibrational analysis calculations and characterized as minima in their potential energy surface via the absence of an imaginary frequency.
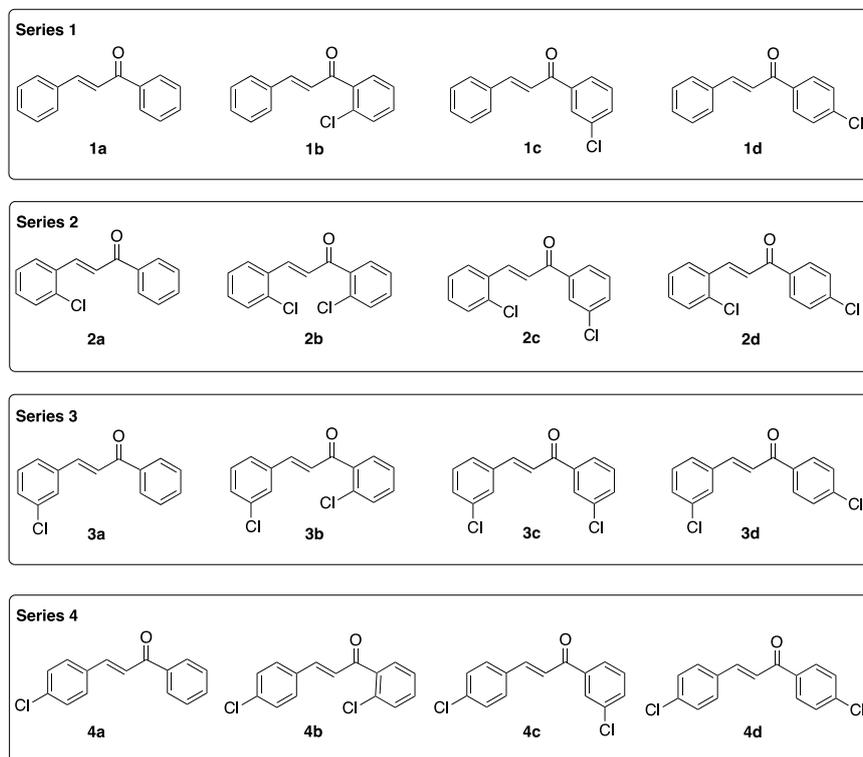
Figure 1. Structures of 16 chalcones with varying chlorine substitution patterns.

Visualization of the contour plots of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) are shown in Figures 2-5. Analysis of the frontier molecular orbitals provides valuable information regarding nodal patterns and individual atom contributions.

The largest HOMO-LUMO energy gaps are occurring in chalcones **1b**, **2b**, **3b**, **4a**, and **4b**, four of which have a chlorine substituent in the 2'-position. The largest energy gap average was in Series 3, where a chlorine is in the 3-position. Chalcone **3b** has the highest HOMO-LUMO energy gap of all 16 chalcones.

Tables 1-4 show the global chemical reactivity descriptors and the $\log P$ for each series of chalcones. The partition coefficient of a compound is a widely used metric for determining lipophilicity, which is useful for identifying compounds which may have similar likeness to drugs and possible interaction with biological macromolecules such as receptors and enzymes [46]. Lipophilicity is an important physicochemical property of a potential drug as it describes solubility, absorption, membrane penetration, distribution, and excretion. The partition coefficient is the quotient of the concentration of the compound in a lipophilic solvent (typically 1-octanol) and the concentration of the compound in water. The logarithm of the partition coefficient is referred to as $\log P$. A positive value for $\log P$ means the compound is more lipophilic, whereas a negative value means the compound is more hydrophilic.

The electrophilicity value (ω) holds significant interest due to the enone moiety's susceptibility to nucleophilic attack. Series 4 contained the most electrophilic
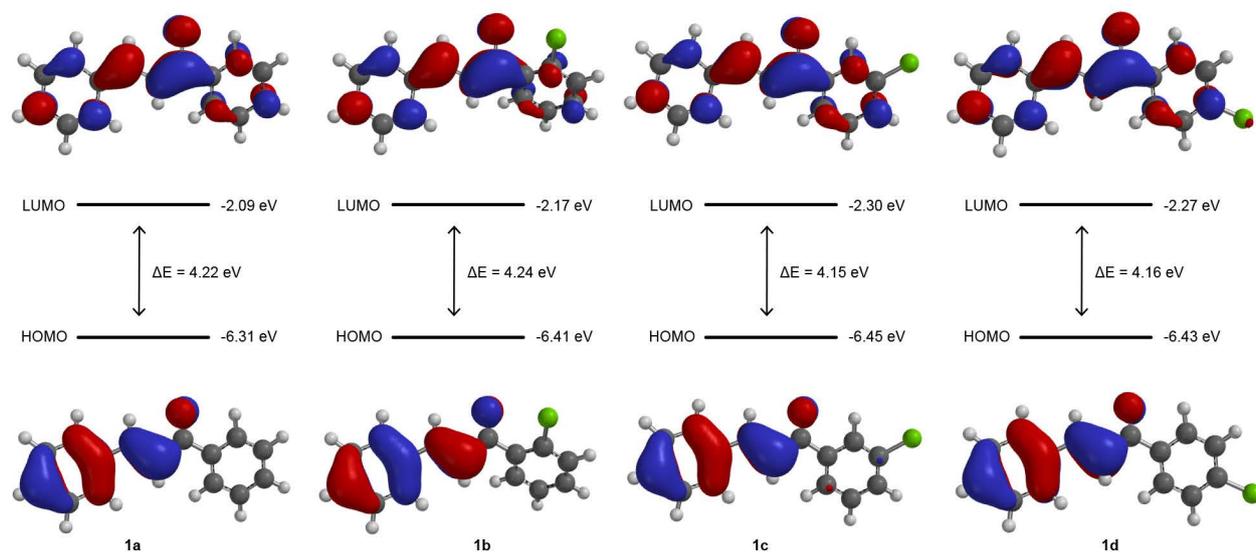
**Figure 2.** Frontier molecular orbitals of chalcone series 1.
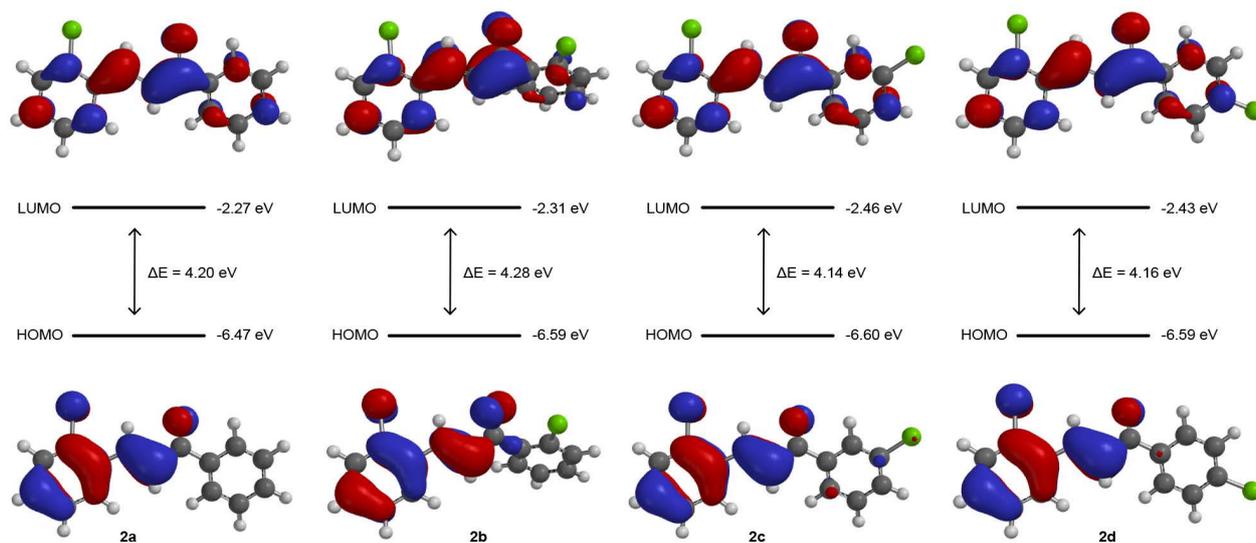
Figure 3. Frontier molecular orbitals of chalcone series 2.

chalcones. It is also notable that Series 4 chalcones were the softest as well. The most electrophilic chalcone overall was **3c** however.

All dichlorinated chalcones had the same log$P$ values, as did the three mono-substituted chlorinated chalcones. Adding chlorine atoms (from zero to two) increases log$P$ regardless of the positioning on the aromatic rings. Higher log$P$ values represent greater lipophilicity. This was evidenced experimentally by decreased water solubility during biological evaluation. All 16 chalcones did maintain log$P$ values less than 5 which, according to Lipinski's Rule of 5, is desirable for molecules to be considered drug-like [47] [48].

Tables 5-8 show the natural bond orbital charge, f^+ value, f^- value, and the dual descriptor (Δf) value calculated for the three carbons comprising the
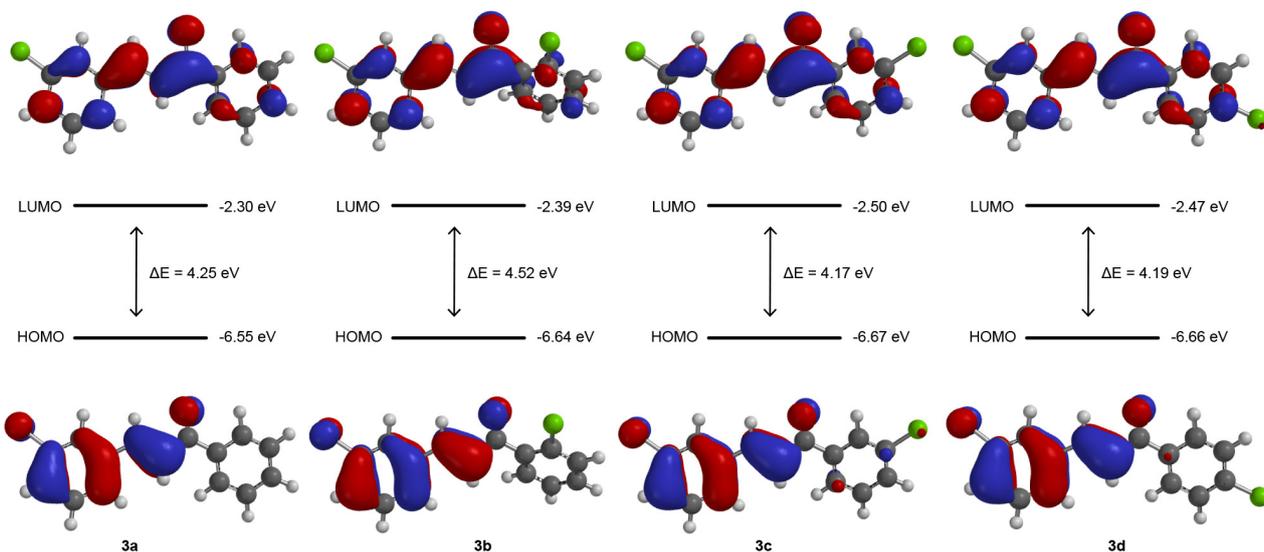
Figure 4. Frontier molecular orbitals of chalcone series 3.
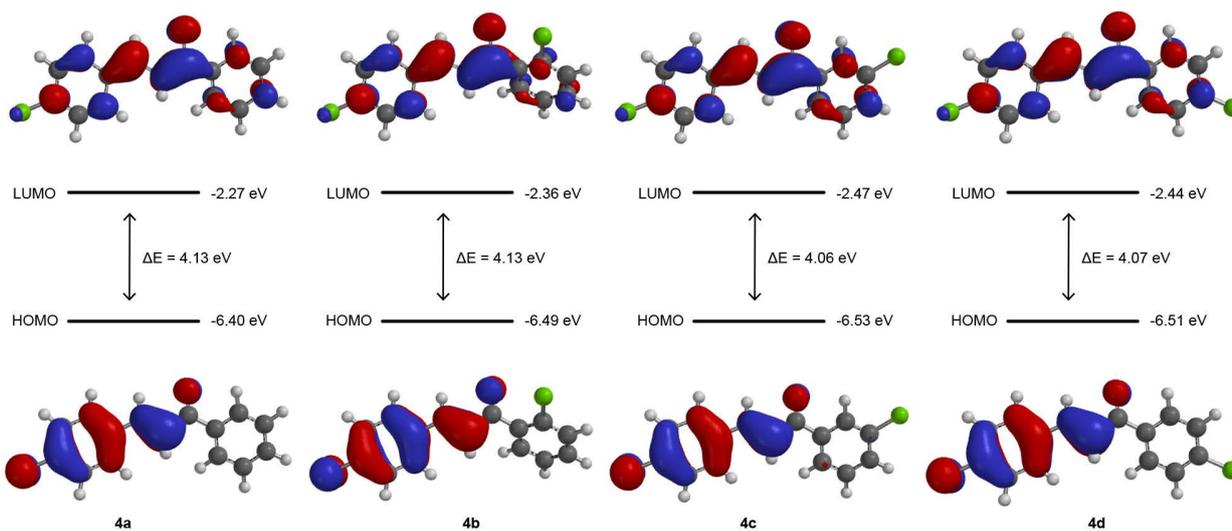
Figure 5. Frontier molecular orbitals of chalcone series 4.

Table 1. Global reactivity indicators for chalcone series 1.

Reactivity Index	B3LYP/6-31G*			
	1a	**1b**	**1c**	**1d**
E_{HOMO} (eV)	−6.31	−6.41	−6.45	−6.43
E_{LUMO} (eV)	−2.09	−2.17	−2.30	−2.27
E_{Gap} (eV)	4.22	4.24	4.15	4.16
μ (eV)	−4.20	−4.29	−4.38	−4.35
χ (eV)	4.20	4.29	4.38	4.35
η (eV)	2.11	2.12	2.08	2.08
S (eV^{-1})	0.474	0.472	0.481	0.481
ω (eV)	4.18	4.34	4.61	4.55
$\log P$	3.76	4.32	4.32	4.32

Table 2. Global reactivity indicators for chalcone series 2.

Reactivity Index	B3LYP/6-31G*			
	2a	2b	2c	2d
E_{HOMO} (eV)	−6.47	−6.59	−6.60	−6.59
E_{LUMO} (eV)	−2.27	−2.31	−2.46	−2.43
E_{Gap} (eV)	4.20	4.28	4.14	4.16
μ (eV)	−4.37	−4.45	−4.53	−4.51
χ (eV)	4.37	4.45	4.53	4.51
η (eV)	2.10	2.14	2.07	2.08
S (eV^{-1})	0.476	0.467	0.483	0.481
ω (eV)	4.55	4.63	4.96	4.89
$\log P$	4.32	4.88	4.88	4.88

Table 3. Global reactivity indicators for chalcone series 3.

Reactivity Index	B3LYP/6-31G*			
	3a	3b	3c	3d
E_{HOMO} (eV)	−6.55	−6.64	−6.67	−6.66
E_{LUMO} (eV)	−2.30	−2.39	−2.50	−2.47
E_{Gap} (eV)	4.25	4.52	4.17	4.19
μ (eV)	−4.43	−4.52	−4.59	−4.57
χ (eV)	4.43	4.52	4.59	4.57
η (eV)	2.13	2.26	2.09	2.10
S (eV^{-1})	0.469	0.442	0.478	0.476
ω (eV)	4.61	4.52	5.04	4.97
$\log P$	4.32	4.88	4.88	4.88

Table 4. Global reactivity indicators for chalcone series 4.

Reactivity Index	B3LYP/6-31G*			
	4a	4b	4c	4d
E_{HOMO} (eV)	−6.40	−6.49	−6.53	−6.51
E_{LUMO} (eV)	−2.27	−2.36	−2.47	−2.44
E_{Gap} (eV)	4.13	4.13	4.06	4.07
μ (eV)	−4.34	-4.43	−4.50	−4.48
χ (eV)	4.34	4.43	4.50	4.48
η (eV)	2.07	2.07	2.03	2.04
S (eV^{-1})	0.483	0.483	0.493	0.490
ω (eV)	4.55	4.74	4.99	4.92
$\log P$	4.32	4.88	4.88	4.88

Table 5. Fukui indices for chalcone series 1.

Atom	Charge	f_k^+	f_k^-	Δf
		Chalcone **1a**		
C1	+0.522	−0.116	+0.017	−0.133
C2	−0.312	−0.027	−0.156	+0.129
C3	−0.134	−0.133	−0.029	−0.104
		Chalcone **1b**		
C1	+0.526	−0.118	+0.021	−0.139
C2	−0.325	−0.034	−0.139	+0.105
C3	−0.129	−0.138	−0.021	−0.117
		Chalcone **1c**		
C1	+0.523	−0.118	+0.019	−0.137
C2	−0.316	−0.017	−0.138	+0.121
C3	−0.128	−0.135	−0.025	−0.110
		Chalcone **1d**		
C1	+0.521	−0.117	+0.032	−0.149
C2	−0.315	−0.018	−0.149	+0.131
C3	−0.129	−0.134	−−0.023	−0.111

Table 6. Fukui indices for chalcone series 2.

Atom	Charge	f_k^+	f_k^-	Δf
		Chalcone **2a**		
C1	+0.522	−0.107	+0.013	−0.120
C2	−0.299	−0.040	−0.137	+0.097
C3	−0.144	−0.128	−0.033	−0.095
		Chalcone **2b**		
C1	+0.528	−0.115	+0.014	−0.129
C2	−0.317	−0.041	−0.107	+0.066
C3	−0.137	−0.136	−0.024	−0.112
		Chalcone **2c**		
C1	+0.523	−0.111	+0.016	−0.127
C2	−0.304	−0.028	−0.123	+0.095
C3	−0.138	−0.130	−0.028	−0.102
		Chalcone **2d**		
C1	+0.521	−0.109	+0.030	−0.139
C2	−0.303	−0.029	−0.133	+0.104
C3	−0.139	−0.130	−0.026	−0.104

Table 7. Fukui indices for chalcone series 3.

Atom	Charge	f_k^+	f_k^-	Δf
Chalcone **3a**				
C1	+0.523	−0.111	+0.012	−0.123
C2	−0.303	−0.037	−0.127	+0.090
C3	−0.139	−0.127	−0.031	−0.096
Chalcone **3b**				
C1	+0.527	−0.113	+0.019	−0.132
C2	−0.316	−0.042	−0.110	0.068
C3	−0.134	−0.131	−0.021	−0.110
Chalcone **3c**				
C1	+0.524	−0.114	+0.016	−0.130
C2	−0.307	−0.027	−0.112	+0.085
C3	−0.133	−0.130	−0.026	−0.104
Chalcone **3d**				
C1	+0.522	−0.113	+0.029	−0.142
C2	−0.306	−0.028	−0.121	+0.093
C3	−0.135	−0.128	−0.025	−0.103

Table 8. Fukui indices for chalcone series 4.

Atom	Charge	f_k^+	f_k^-	Δf
Chalcone **4a**				
C1	+0.522	−0.110	+0.017	−0.127
C2	−0.306	−0.035	−0.150	+0.115
C3	−0.139	−0.126	−0.020	−0.106
Chalcone **4b**				
C1	+0.527	−0.113	+0.020	−0.133
C2	−0.320	−0.041	−0.128	+0.087
C3	−0.134	−0.131	−0.013	−0.118
Chalcone **4c**				
C1	+0.523	−0.113	+0.017	−0.130
C2	−0.311	−0.025	−0.128	+0.103
C3	−0.133	−0.129	−0.017	−0.112
Chalcone **4d**				
C1	+0.521	−0.112	+0.029	−0.141
C2	−0.310	−0.026	−0.138	+0.112
C3	−0.134	−0.128	−0.015	−0.113

enone moiety. C1 is the carbonyl carbon, C2 is the alpha carbon, and C3 is the terminal alkene carbon. The natural bond orbital charges were used in Equations (10) and (11) to determine the f^+ and f^- Fukui indices respectively. The combined values according to equation 13 yields the dual descriptor, where Δf is a function that represents the reactivity of the atoms in each molecule.

All 16 chalcones have negative values on C1 (carbonyl carbon) and C3 (terminal alkene carbon) which follows the logic predicted by modern resonance theory. C1 had a larger negative value than C3, representing a higher likelihood for nucleophilic attack to occur there. Chalcone 1d had the highest value on C1 while chalcone **1b** has the highest value on C3. Chalcone **4d** had the overall highest values for both atoms.

The four chalcones of Series 4 showed the highest antibacterial activity from our previous testing, with **4c** showing the largest zone of inhibition of all 16 chalcones [10]. From our computational analysis, the chalcones of Series 4 were also the most electrophilic and softest. In addition, chalcone **4c** had the highest averagezone of inhibition when taking into account all three bacterial strains evaluated and was the softest of all 16 chalcones. From these results, it can be determined that increasing electrophilicity and softness are vital for enhancing antimicrobial effectiveness.

Future studies will build on this discovery by synthesizing chalcones substituted in the 4-position and containing substituents that result in greater electrophilic nature. The high values of $\log P$ were also confirmed experimentally with less than ideal solubility in aqueous media. Choosing substituents that will reduce the lipophilicity should result in an enhanced bioavailability.

4. Conclusion

Using conceptual DFT, it was determined that chalcones with a chlorine in the 4-position (Series 4) generally contained the most electrophilic and softest chalcones. These were the most active chalcones in previous antimicrobial evaluation. Adding chlorine moieties increases lipophilicity regardless of the positioning, but none of the 16 chalcones exceeded a $\log P$ of 5. Having a chlorine atom in position 4 of the chalcone skeleton proves to be the most effective location. The results of this study enable further optimization of the chalcone skeleton by retaining the chlorine in position 4 while probing the effects of adding more electrophilic substituents.

Acknowledgements

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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