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Antimicrobial, Structure-Activity Relationship and Computational Studies of Some Synthesized Chalcone Derivatives

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Several chalcones *viz.* 1,3-diaryl-2-propane-1-one (**1a**), 3-(4-hydroxy phenyl)-1-phenyl-2-propane-1-one (**1b**), 3-(4-amino-phenyl)-1-phenyl-2-propane-1-one (**1c**) and their derivatives 2-ethoxy-4,6-diphenyl-4*H*-pyran-3-carboxylic acid ethyl ester (**2a**), 4-(4-hydroxy-phenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-chromen-5-one (**2b**) and 7-(4-amino-phenyl)-5-phenyl-1,5-dihydropyrano[2,3-*d*]pyrimidine-2,4-dione (**2c**) have been synthesized following both conventional and microwave irradiation methods. The structures of the isolated compounds were elucidated on the basis of UV-visible, FTIR, ^{1}H NMR spectral data. The antimicrobial results showed some remarkable facts about the structure–activity relationship, which states that the electronic atmosphere around the chalcone derivative moieties and substituents considerably affect the antimicrobial potential of the synthesized compounds. Theoretical calculation as well as antimicrobial activity of the compounds were also studied.

Keywords: Chalcone, Antimicrobial activity, Density functional theory, Microwave irradiation.

INTRODUCTION

The chemistry of chalcones has attracted greater attention all over the world for several decades [1-3]. The interest and emphasis has been focused upon the synthesis and biodynamic activities of chalcones and chalcone derivatives. The name "chalcones" was assigned by Kostanecki & Tambor [4], which contain the keto-ethylenic group (–CO–CH=CH-). Chalcones or 1,3-diaryl-2-propen-1-ones belong to the flavonoid family, which consist of open-chain flavonoids where the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system assuming linear or nearly planar structure [5]. Chalcones are used as the precursors in the biosynthesis of anthocyanins and flavones. These types of compounds are generally synthesized by Claisen-Schmidt condensation reaction between acetophenone or substituted acetophenones and aldehydes.

Chalcones serve as a starting material in the formation of different heterocyclic compounds, including flavones, flavanones, flavonols, pyrimidines, aurones, benzoylcoumarones, and pyrazoline like various crucial biological compounds, such as hydantions and deoxybenzoins, which have some therapeutic significance [6-8]. In general, due to the presence of a chromophore (-COCH=CH-), chalcones are coloured and utilized as precursors in the biosynthesis of flavonoid. The presence of α,β-unsaturation and carbonyl systems, which are widely distributed in plants, fruits and vegetables lead to the pharmacological characteristics of chalcones. Chalcones are categorized into the flavonoid group of molecules and some chalcones have many biological activities [9-11]. The enzymatic cyclization of 6-hydroxychalcones results in the synthesis of flavanones and subsequently leads to numerous flavonoid groups, such as flavonols, flavones, aurones, dihydroflavonols and isoflavones [12,13].

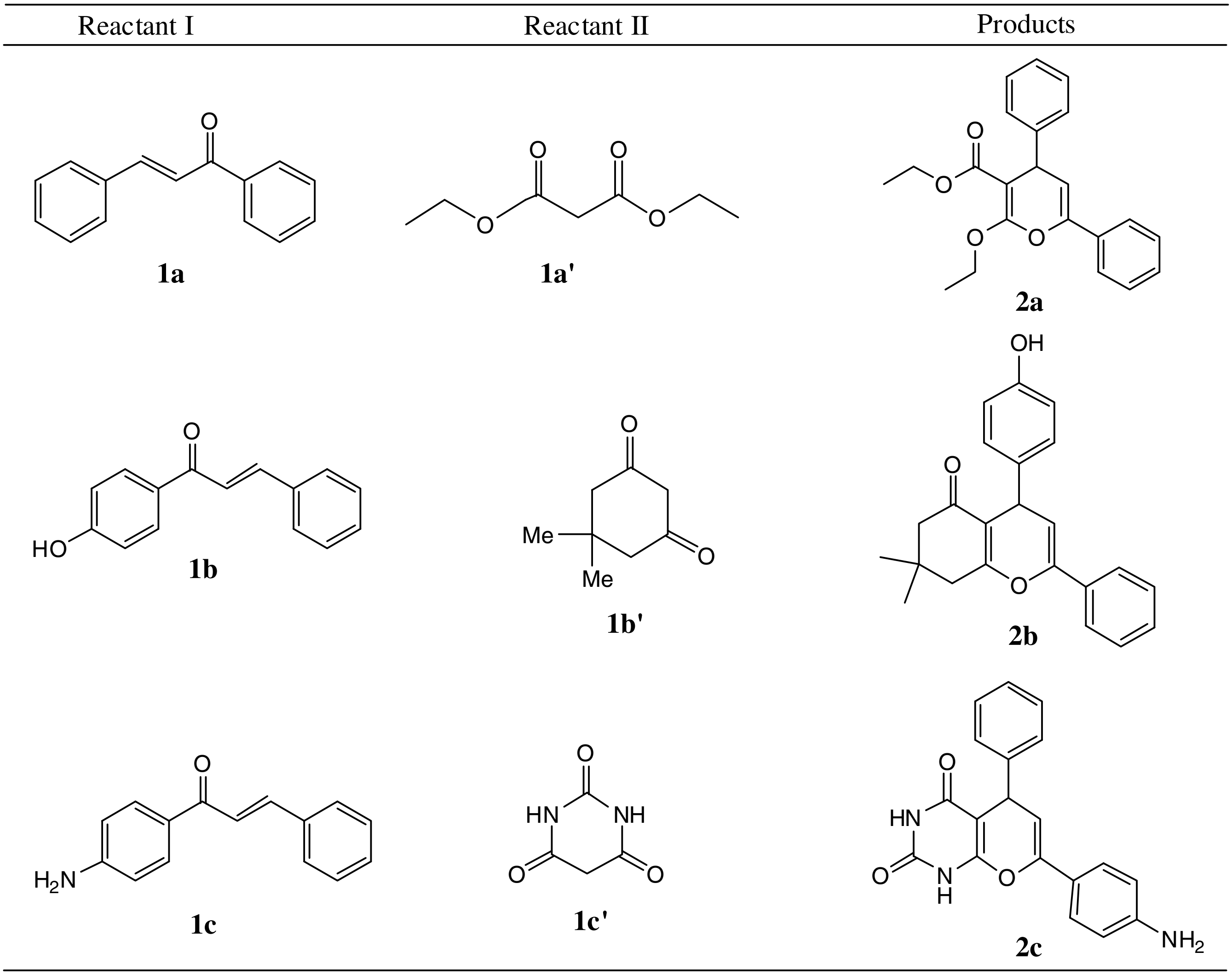
Recently, numerous studies have investigated the formation of chalcones having heterocyclic moieties. In the synthesis of compounds with an effective therapeutic value, chalcones are used as intermediates [14,15]. Chalcone derivatives show various pharmacological activities, including potential cytotoxic, antiviral, antimicrobial, anti-inflammatory and anesthetic. Chalcone derivatives possess antimicrobial, antioxidant, anti-inflammatory, antileishmanial, antibacterial and antitumor activities [1,16,17]. The unsaturated, reactive keto functional group present in chalcones provides them their antimicrobial activity. This activity can be varied depending on the position and type of substituents on rings [18].

Various synthesis approaches have been reported for chalcones fabrication. The most commonly used synthesis route involves the Claisen-Schmidt condensation of equimolar quantities of substituted benzaldehyde with substituted acetophenone in an alcoholic aqueous alkali [19]. In this method, the used concentration of the alkali is 10-60%. This reaction is frequently conducted for 10-72 h at room temperature. Limited studies have investigated the theoretical and experimental aspects of chalcone derivatives [20]. In this work, several chalcones and their derivatives (**Scheme-I**) were synthesized, characterized and studied their electronic properties on the basis computational method and biological activities. The structures were optimized by density functional theory (DFT) method. Furthermore, quantum chemical calculation, molecular orbital energy and frontier orbital constitution were performed to divulge the energy of the synthesized compounds.

EXPERIMENTAL

All materials otherwise noted were purchased and utilized without further purification. UV-visible spectra of the sample were recorded on UV-180 SHIMADZU spectrophotometer with a scanning range of 800-220 nm. FTIR spectrum was recorded on IRTracer-100, SHIMADZU, Japan over the frequency range from 4000-400 cm^{-1} using KBr pellets. Melting point was measured by Stuart's electrothermal melting point apparatus (Model no. SMP 30). ^1H NMR was measured with an AVANCE Bruker NMR spectrometer at 400 MHz using suitable solvent and TMS as an internal standard.

Synthesis of substituted chalcones: Equimolar amount (0.05 mol) of acetophenone and benzaldehyde were dissolved in ethanol (50 mL) in a round-bottomed flask, equipped with a magnetic stirrer. Then the reaction vessel was immersed in a cold water bath and aqueous NaOH solution (40%, 10 mL) was added dropwise to the mixture over 30 min. The reaction temperature was adjusted to 20-25 ºC. The progress of the reaction was monitored by TLC (silica gel plates, eluting solvent; *n*-hexane and ethanol). Then the stirring of the reaction mixture



Scheme-I: Chalcone derivatives synthesized followed by Claisen-Schmidt condensation reaction and microwave irradiation method was continued for 6 h at the same temperature. The reaction mixture was neutralized by 0.1 M HCl when both reactants disappeared and precipitation occurred instantly. The precipitate was filtered and washed with cold water until the washings were neutral to litmus and solids were collected [21]. The crude product was recrystallized from hot rectified spirit to get the crystalline product.

1,3-Diphenyl-2-propen-1-one (1a): White crystalline powder, yield 94%, m.p. 42-43 ºC. IR (KBr, cm^{-1}): 3050, 2926, 1661, 1603, 1447, 1217, 746. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.054 (d, *J* = 7.2 Hz, 2H, Ar), 7.856 (d, *J* = 16 Hz, 1H), 7.565 (d, *J* = 16, 1H), 7.440-7.688 (*m*, 8H, Ar).

3-(4-Hydroxy phenyl)-1-phenyl-2-propen-1-one (1b): Yellow powder, yield 93%, m.p. 184-185 ºC. IR (KBr, cm^{-1}): 3268, 3050, 1650, 1602, 936 and 836. ^1H NMR (400 MHz, $CDCl_3$): δ 8.036 (d, *J* = 8.8 Hz, 2H, Ar), 7.807 (d, *J* = 15.6 Hz, 1H), 7.509-7.609 (m, 5H, Ar), 7.435 (d, *J* = 16 Hz, 1H), 6.926 (d, *J* = 8.8 Hz, 2H), 5.820 (s, OH).

3-(4-Aminophenyl)-1-phenyl-2-propen-1-one (1c): Yellow powder, yield 89%, m.p. 142-143 ºC. IR (KBr, cm^{-1}): 3362, 3000, 1662 and 1229. ^1H NMR (400 MHz, $CDCl_3$): δ 5.067 (NH_2), 6.595-6.742 (m, 2H, Ar), 7.332-7.587 (m, 5H, Ar), 7.608-7.789 (m, 3H), 7.962 (d, *J* = 8.8 Hz, 1H).

Synthesis of chalcone derivatives [22]

Conventional method: A mixture of substituted chalcones (**1a-c**) (2.5 mmol), electron donating substances (**1a′-c′**) (2.5 mmol) and anhydrous zinc chloride (0.05 g) were taken in a 250 mL round bottomed flask followed by addition of 50 mL benzene to this mixture. The mixture was then refluxed for 48-70 h with constant stirring. The progress of the reaction was monitored by TLC on silica plates (eluting solvent ethyl acetate:*n*-hexane). When both reactants disappeared, the reaction mixture was neutralized by 0.1 M HCl and precipitation occurred instantly. The precipitate was filtered and washed with cold water until the washings were neutral to litmus and finally solids were collected. The product was recrystallized with suitable solvent or separated by column chromatography.

Microwave irradiation method: In a 250 mL conical flask, an equimolar amount (0.05 mol) of compound (**1a-c**) and compound (**1a′-c′**) were dissolved in 50 mL rectified spirit. The reaction mixture was irradiated under 160-320 watt microwave irradiation for 60-120 s. The progress of the reaction was monitored by TLC after every 30 s. After completion of the reaction, the conical flask was removed from the oven and cooled in ice-cold water resulting in the formation of crude product. It was then recrystallized from suitable solvent system or separated by column chromatography.

2-Ethoxy-4,6-diphenyl-4*H*-pyran-3-carboxylic acid ethyl ester (2a): White crystalline powder, yield 83%, m.p. 130-131 ºC. IR (KBr, cm^{-1}): 3459, 3059, 2926, 1661, 1604, 1574, 1447, 1340, 746, 688. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.118-1.605 (m, 6H, CH_3), 3.276 (d, *J* = 8.0 Hz, 1H), 4.212-4.248 (m, 4H, CH_2), 5.423-5.493 (m, 1H), 7.442-8.061 (m, 10H, Ar).

4-(4-Hydroxy-phenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydrochromen-5-one (2b): Yellow powder, yield 79%, m.p. 162-163 ºC. IR (KBr, cm^{-1}): 3326, 2980, 1666, 1620. ^1H NMR (400 MHz, $CDCl_3$): δ 11.910 (s, 1H, OH), 6.636-7.286 (m, 9H, Ar), 5.490 (s, 2H), 2.314 (s, 2H, CH_2), 2.256 (s, 2H CH_2), 1.093 (s, 6H, CH_3).

7-(4-Aminophenyl)-5-phenyl-1,5-dihydropyrano[2,3-*d*]-pyrimidine-2,4-dione (2c): Flash column chromatography on silica gel using eluent (hexane/EtOAc = 9/1; v/v). Yellow powder, yield 81%, m.p. 133-134 ºC. IR (KBr, cm^{-1}): 3482, 3430, 3000, 1698, 1602, 1367. ^1H NMR (400 MHz, $CDCl_3$): δ 3.70-3.90 (s, 1H, NH_2), 6.00-6.20 (m, 1 H, NH), 6.50-6.60 (m, 2H, Ar), 7.10-7.80 (m, 7H, Ar), 10.90-11.20 (m, 1H, NH).

Antimicrobial Studies

Organisms: Antimicrobial activity was carried out against three Gram-positive bacteria (*Bacillus cereus*, *Staphylococcus aureus* and *Listeria monocytogenes* and three Gram-negative bacteria *Citobacter freundi*, *Escherichia coli* and *Salmonella typhimurium*. Besides, antifungal screening was carried out against one fungi *Trichoderma harzianum*. The organisms were collected from Centre for Advanced Research in Sciences (CARS), University of Dhaka, Dhaka, Bangladesh.

Media: Nutrient agar media (Difco Laboratories) having pH 7.2-7.4 was used for the antibacterial screening and potato dextrose agar (Scharlau Chemi) was used for the antifungal screening.

Antimicrobial assay: Kirby-Bauer disc diffusion method [23-25] was used to investigate the antimicrobial activity of the synthesized Schiff base derivatives at the concentration of 300 µg/disc. Briefly, for the antibacterial screening, the nutrient agar media was streaking with a sterilized cotton swab of the 24 h liquid cultures containing microorganisms. Oxoid™ Antimicrobial susceptibility discs having different derivatives concentration of 300 µg/disc were placed gently onto the pre-inoculated agar plates. The synthesized derivatives were dissolved with acetone and evaporated completely. Blank disc impregnated with acetone followed by evaporation and ciprofloxacin hydrochloride at 25 µg/disc was used as negative and positive control respectively. After 24 h of incubation at 37 ºC aerobically, inhibitory activity was measured (mm) as the diameter of the observed inhibition zone.

For antifungal screening, Oxoid™ Antimicrobial susceptibility discs having 300 µg/disc synthesized derivatives were placed gently onto the inoculated potato dextrose agar plates. Blank disc impregnated with acetone followed by evaporation and miconazole at 50 µg/disc was used as negative and positive control, respectively. After 72 h of incubation at 30 ºC, inhibitory activity was measured (in mm) as the diameter of the observed inhibition zone.

Computational method: Theoretical calculations were carried out using Gaussain 16 program suite [26]. The geometries were completely optimized by DFT-B3LYP/6-311+G (d,p) level of theory. The vibrational normal-mode analyses were performed at the same level to ensure that each optimized structure was a true minimum on the potential energy surface. Moreover, unscaled B3LYP/6-311+G(2d,p) frequencies were used to procure thermochemical quantities, thermal enthalpy and free energy corrections. After optimizations of the properties of frontier molecular orbitals (FMO) involving the studied compounds were investigated using the results calculated at B3LYP/6- 311G(d,p) level.

RESULTS AND DISCUSSION

A one-pot synthesis of chalcones was acheived by reacting different acetophenones and aromatic aldehydes in presence of a strong base *via* Claisen-Schmidt condensation reaction. The structures of the synthesized compounds were elucidated on the basis of UV-visible, FTIR and ^{1}H NMR data. All the compounds **1a-c** agreed well to the FTIR data in the range 1662-1602 cm^{-1} indicating the presence of >C=O in conjugation with C=C and >C=C<, respectively. The band at 3268-3050 cm^{-1} is due to the presence of O-H stretching in compound **1b** and that of 3362-3000 cm^{-1} is assigned for the presence of N-H stretching in compound **1c.** The peaks at 836, 746 cm^{-1} are assigned for C=C bonds in aromatic rings in the synthesized chalcones. Similar observations were also observed in the synthesized chalcone derivatives (**2a-c**).

In ^{1}H NMR spectra for the synthesized chalcones, the aromatic hydrogens showed peaks, which agreed well to the literature value [27]. The singlet hydrogen peaks at δ 6.037 and 5.820 ppm are due to presence of aromatic N-H and O-H groups in compound **1b** and **1c**, respectively. The peak at δ 1.118-1.605 ppm as multiplet is due to the presence of CH_3 in compound **2a**. The peak at δ 4.212-4.248 ppm for four $–CH_2$-protons is deshielded due to the presence of neighboring oxygen atom in the ester group. The methyl peaks in compound **2b** was observed as a singlet at δ 1.093 ppm and the singlet peak at δ 11.910 ppm was assigned for aromatic –OH proton. The peaks for olefinic and aromatic protons agreed well to the literature values [28]. In compound **2c**, the singlet peak at δ 3.70-3.90 ppm corresponds to $–NH_2$ protons and that of at δ 6.00-6.20 ppm is for –NH proton in the barbituric acid moiety. Moreover, the peak at δ 10.90-11.20 ppm is responsible for –NH proton attached to neighboring carbonyl group and relatively deshielded due to anisotropy and presence of electronegative oxygen atom attached to this group. All the aromatic peaks showed signals at appropriate positions. The sharp melting point range and TLC spot confirms the purity of the synthesized compounds.

Computational study

Geometry optimization: Optimized structures is the key materials to define its structural parameters. The examined compounds were optimized with DFT/6-311G+(d,p) basis set. All the optimized structures are shown in Fig. 1. The structural parameters such as bond lengths, bond angles and dihedral angles of the examined compounds were obtained by using DFT/6-311G+(d,p) basis set are given on Table-1.

TABLE-1
SELECTED BOND LENGTHS, BOND ANGLES AND DIHEDRAL ANGLES OF COMPOUNDS **2a-c**

	Compounds		
	2a	**2b**	**2c**
Bond distance (Å)			
C3-C5	1.5243	1.5176	1.5119
C5-C6	1.5040	1.5071	1.5099
C2-C3	1.3572	1.3498	1.3537
C6-C7	1.3311	1.3367	1.3365
C2-O30	1.3600	1.3605	1.3453
C7-O30	1.3973	1.3959	1.4092
C3-C4	1.4704	1.4605	1.4528
C5-C19	1.5351	1.4699	1.5348
Bond angle (°)			
C3-C5-C6	110.23	108.85	108.74
C2-O30-C7	119.58	118.78	117.55
Dihedral angle (°)			
C2-C3-C5-C19	-106.58	-107.56	-111.48
C7-C6-C5-C19	108.57	107.90	110.88
C3-C5-C19-C20	67.64	75.43	68.96

The bond distance of C3-C4, C3-C5 and C5-C19 for compound **2a** is significantly larger than the other examined compounds. This result could be explained that in the acetyl group containing two electronegative oxygen atoms withdrawing electron density towards oxygen atom resulting larger the bond length. The bond angles of C3-C5-C6 and C2-O30-C7 for compound **2a** are somewhat larger than the other compounds. This result is meaningful as the bond length is larger for compound **2a**, it would have tendency to become more relax of the bond angle.

Quantum chemical study: The molecular electrostatic potential (MEP) and frontier molecular orbital (FMO) of

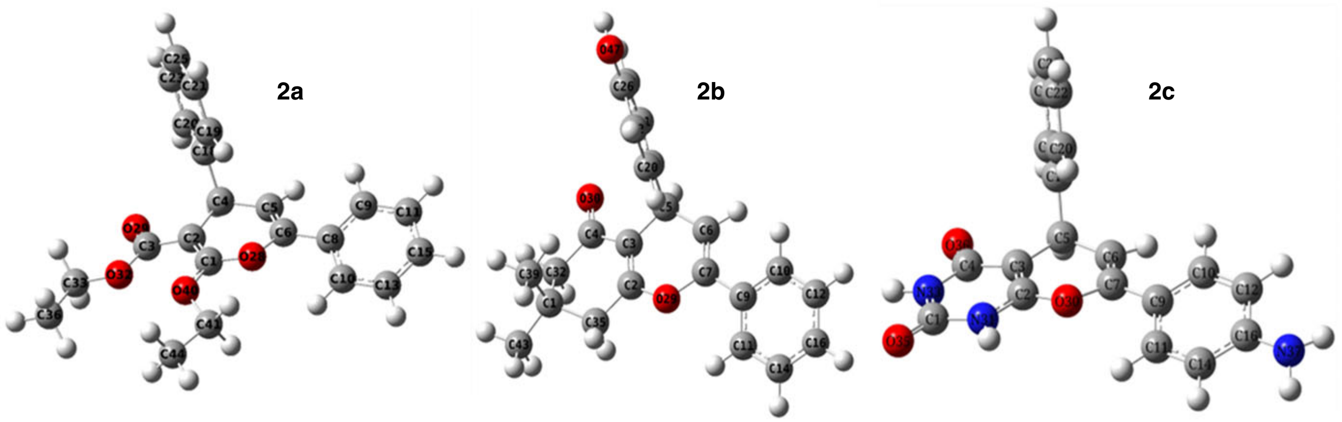


Fig. 1. Optimized structure of compounds **2a-c**

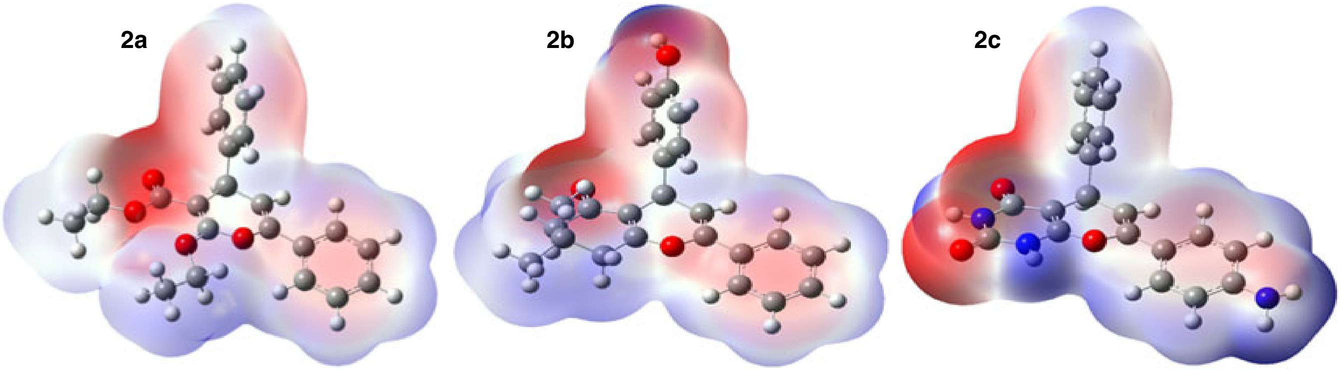


Fig. 2. Molecular electrostatic potential (MEP) of compounds **2a-c**

compounds were calculated using the DFT/B3LYP/6-311G+(d,p) method [22]. On the MEP map (Fig. 2), the red, blue, and green regions represent negative, positive, and zero potential areas, respectively. These regions were focused to estimate the intermolecular charge transfer (ICT) and possible intramolecular and intermolecular hydrogen bonds. The MEP map (Fig. 3) indicates that according to the positions of N and O atoms, the lowest and highest negative regions, respectively, line up.

LUMO and HOMO are the outermost orbitals and present the electron accepting and donating abilities, respectively, of a molecule [29,30]. E_{LUMO} and E_{HOMO} energies correspond to the electron affinity (A) and ionization energy (I), respectively. LUMO is located in the whole region, and HOMO is situated in the entire region except in a phenyl ring (Fig. 3). Therefore, intermolecular charge transfer interaction predominantly occurs during molecule excitation.

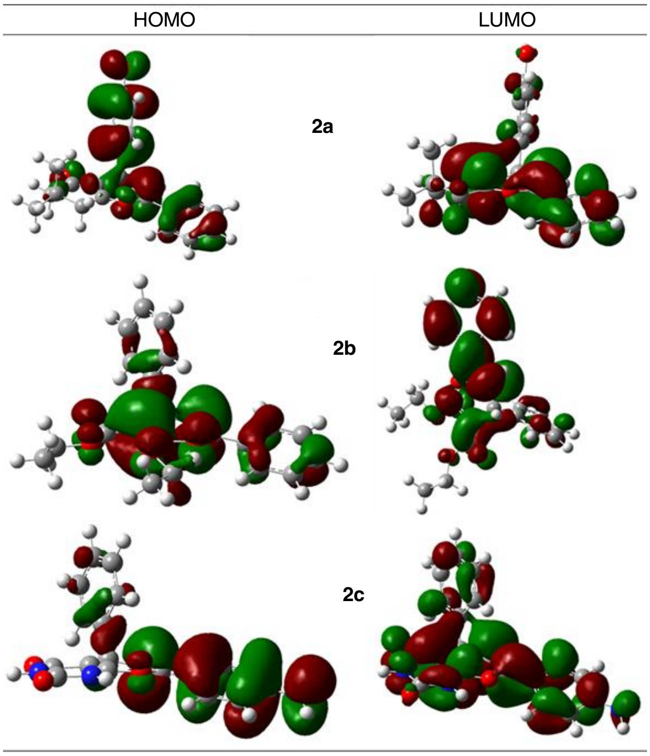


Fig. 3. HOMO and LUMO molecular orbitals of compounds **2a-c**

The calculated HOMO and LUMO energies are –5.92797 eV and –1.50798 eV, respectively, compound for **2a**, –6.08688 and –1.46036 eV, respectively, for **2b**, –6.05286 and –1.63913 eV, respectively, for **2c**. The energy absorbed when one electron is released from HOMO is the ionization potential. The ionization potential trend follows a decreasing order: **2b** > **2c** > **2a**. Electron affinity is the energy released when one electron is added to LUMO. Electron affinity decreases in the following order: **2c** > **2a** > **2b**. These results indicated that the compound **2b** absorbs and releases highest and lowest energy, respectively, to become a cation and an anion, respectively, among all the compounds present in the group. Quantum theory suggests that the mixing of ground and appropriately excited state wave functions leads to changes in the electron density of a chemical entity. Moreover, the excitation energy between the excited and ground states is inversely proportional to the mixing coefficient. Thus, rigid and soft molecules exhibit large and small HOMO-LUMO gaps, respectively. Considering chemical reactivity, soft molecules having small gaps in the electron density are altered more easily than hard molecules and hence are more reactive than hard molecules. Compound **2b** with a small HOMO-LUMO gap is a soft molecule; however, its energy difference is high (4.41 eV).

Quantum chemical parameters, such as chemical hardness (η) and softness (σ); chemical potential (μ) and electronegativity (χ); nucleophilicity (ε) and electrophilicity (ω) can be calculated using the following equations [25] and the results are summarized in Table-2.

$$\chi = -\mu = (I+A)/2;\ \eta = (I-A)/2;\ \sigma = 1/h;$$

TABLE-2
QUANTUM CHEMICAL PARAMETERS

Compd. No.	Quantum chemical parameters (eV)					
	χ	μ	η	σ	ω	ε
2a	-3.71797	3.71797	-2.2100	-0.45249	-3.12746	-0.31975
2b	-3.77362	3.77362	-2.31326	-0.43229	-3.07795	-0.32489
2c	-3.8460	3.8460	-2.20687	-0.45313	-3.35129	-0.29839

TABLE-3
ANTIMICROBIAL AND ANTIFUNGAL ACTIVITIES OF THE SYNTHESIZED COMPOUNDS

Compd.	Diameter of inhibition zone (mm)						
	Bacillus cereus	*Staphylococcus aureus*	*Listeria monocytogenes*	*Escherichia coli*	*Salmonella typhimurium*	*Citrobacter freundii*	*Trichoderma harzianum*
1a	8.0 ± 0.5	14.0 ± 1.0	15.0 ± 1.0	–	–	14.0 ± 1.0	24.0 ± 1.0
1b	–	8.0 ± 0.5	–	–	–	–	10.0 ± 0.5
1c	–	–	–	–	–	–	11.0 ± 1.0
2a	13.0 ± 1.0	16.0 ± 1.0	–	12.0 ± 1.0	10.0 ± 0.5	12.0 ± 1.0	20.0 ± 1.0
2b	6.0 ± 0.5	8.0 ± 0.5	–	–	–	13.0 ± 1.0	8.0 ± 1.0
2c	11.0 ± 0.5	16.0 ± 1.0	–	16.0 ± 1.0	11.0 ± 0.5	14.0 ± 1.0	–
Std.	30.0 ± 1.0	32.0 ± 1.0	40 ± 1.0	35.0 ± 1.0	30.0 ± 1.0	35.0 ± 1.0	30.0 ± 1.0

$$\omega = m^2/2\eta = \chi^2/2\eta; \text{ and } \varepsilon = 1/\omega$$

According to these parameters, it was summarized that the chemical reactivity varies with the variation of substituents.

Antimicrobial studies: The antibacterial and antifungal activity of the synthesized compounds are presented in Table-3. From the antimicrobial screening, it has been observed that the synthesized compounds **1a, 2a** and **2c** exhibited good activity against two Gram-positive bacterial strains *Bacillus cereus* and *Staphylococcus aureus* and three Gram-negative strains *Escherichia coli*, *Salmonella typhimurium* and *Citobacter freundi*. Compound **1a** showed activity against the tested bacterial strains for *Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Citobacter freundi* and *Trichoderma harzianum* having 8,14,15,14 and 24 mm zone of inhibition did not show any antibacterial activity against *Escherichia coli* and *Salmonella typhimurium*. Compound **1c** possessed no activity against the tested bacterial strains and compound **1b** showed the activity against only one *Staphylococcus aureus* having 8 mm zone of inhibition. Synthesized compounds **2a** and **2c** exhibited moderate activity against two Gram-positive bacterial strains *B. cereus* and *S. aureus* and three Gram-negative strain *E. coli*, *S. typhimurium* and *C. freundi* having inhibition zone 13, 16, 12, 10 and 12 mm as well as 11, 16, 16, 11 and 14 nm, respectively. Compound **2b** exhibited moderate to lower activity against two Gram-positive bacterial strains *B. cereus* and *S. aureus* and one Gram-negative strain *C. freundi* having inhibition zone 6, 8 and 13 mm, respectively. All of the synthesized compounds except compound **2c** produce moderate activity against the fungi strain *T. harzianum* compared to the standard used miconazole. The antimicrobial data exposed some remarkable facts about the structure-activity relationship, which states that the electronic atmosphere around the chalcone derivative moieties and substituent considerably affect the antimicrobial potential of the synthesized compounds. The presence of unsaturated keto functional group and the substituents of the synthesized compound are attributed to their antibacterial and antifungal activity in the synthesized compounds. Thus, the presence of reactive amino and unsaturated keto group, compound **2c** enhances their antimicrobial activity.

Conclusion

In summary, some chalcone derivatives *via* Claisen-Schmidt condensation reaction were synthesized, characterized and screened for the antimicrobial activities. The structure of the synthesized compounds were confirmed on the basis of UV-visible, FTIR and NMR spectra analysis. Computational study revealed that ionization potential follows the order of **2b > 2c > 2a** whereas electron affinity follows the order of **2c > 2a > 2b**. The value of HOMO-LUMO gap for compound **2b** was found small indicating a soft molecule although the energy difference is high and its value was 4.41 eV. It was observed from the anti-microbial analysis that the synthesized compound **1a, 2a** and **2c** exhibited good activity against two Gram-positive bacterial strains *Bacillus cereus* and *Staphylococcus aureus* and three Gram-negative strains such us *Escherichia coli*, *Salmonella typhimurium* and *Citobacter freundi*. All the synthesized compounds except compound **2c** found moderate activity against the fungi strain *Trichoderma harzianum*. The presence of unsaturated keto functional group and the substituents of the synthesized compounds are responsible for their antibacterial and antifungal activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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