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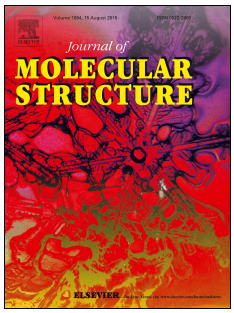

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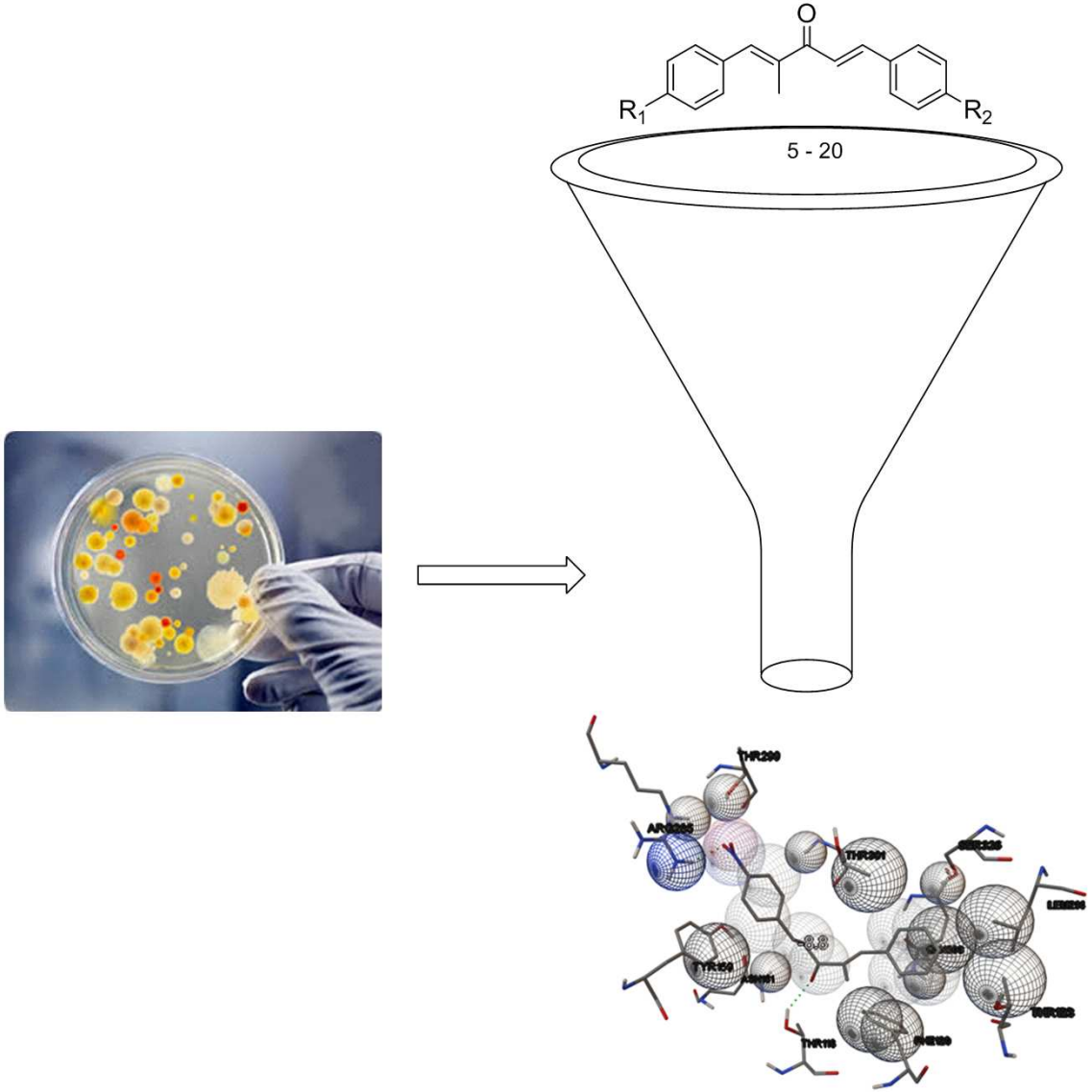
Graphical Abstract



Crystal structures, DFT analysis, *in-silico* study and anti-microbial potential of synthetic monocarbonyl curcuminoids

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Abstract:

In this work the screening of 20 unsymmetrical chalcone and curcuminoids analogues in regard of their antimicrobial properties was conducted. Electron donating groups in the aromatic rings in the chalcone and curcuminoid derivatives produced higher antimicrobial effect. Compounds **1**, **9** and **15** exhibited good activity against *Escherichia coli* and *Staphylococcus aureus*. These compounds were further evaluated against nine micro-organisms of pathological interest. Pharmmaper was used for target fishing of compounds against important bacterial targets. Molecular Docking helped to verify the results of these compounds against the selected bacterial target D-alanyl-D-alanine carboxypeptidase (*PDB ID*: 1PW1). The crystal structure of ligand and docked conformers in the active site of 1PW1 were analyzed. As a result structure-activity relationships are proposed. Structures of compounds **14** and **16** were obtained through single crystals X-ray diffraction studies. Compound **14** crystallizes in monoclinic space group P21/c with unit cell dimensions a = 13.1293(3) Å, b = 17.5364(4) Å, c =15.1433(3) Å, β = 95.6440(10), V = 3469.70(13) Å^3 and Z = 8. Compound **16** crystallizes in triclinic space group Pī with unit cell dimensions a = 6.8226(4) Å, b= 7.2256(4) Å, c = 18.1235(12) Å, β = 87.322(4), V = 850.57(9) Å^3 and Z = 2.

Keywords: Chalcone analogues, curcumin analogues, anti-microbial activity, docking analysis.

1. Introduction:

Antimicrobial resistance within a wide number of bacteria and fungi is a complex public health threat to many countries and multiple sectors. This phenomenon affects ever-widening range of infectious agents, most of which can cause a broad spectrum of diseases in humans and animals. The proportion of *Escherichia coli*, *Klebsiella pneumonia* and *Staphylococcus aureus* resistant to commonly used antibacterial drugs exceeds 50% in many clinical cases [1]. Facing this scenario, there is an urgent need for new efficient antimicrobial agents. Chalcone and their derivatives represent a versatile group of molecules due to its biological properties. Chalcone (Figure 1) is a natural product which consists of two aromatic moieties connected by a three carbon α,β-unsaturated carbonyl group. Chalcones are considered as the precursor of flavonoids and isoflavonoids richly found in plants. The enone linkage presents in the model structure plays a crucial role for the biological activity of chalcone derivatives. Chalcones attracted the attention of scientific community because of their pharmacological activities such as anti-angiogenic effects [2], anti-tumor [3], anti-viral [4], anti-inflammatory [5,6], anti-fungal [7], anti-cancer [8], anti-nematodal [9], anti-plasmodial [10], anti-tuberculosis [11], antiplatele [12], anti-HIV [13] and lipoxygenase inhibitors activities [14]. Several reviews have been published about the chemistry, synthesis and medicinal properties of chalcones [15–17]. Due to the pharmacological potential of chalcone derivatives, which is fully described in the specialized literature and their role in defense mechanisms in plants, we carried investigation to screen the anti-microbial activity of our synthesized chalcone and curcuminoids analogues [18]. It was observed that the presence of an electron-donating moiety in the aromatic rings has a significant effect upon the biological activity. In addition we concluded that the antimicrobial activity of selected chalcone derivatives is reduced when electron-withdrawing groups are substituted in the aromatic rings. Our results are in agreement with that reported in literature [19], which also explain the efficiency of the electron donating group position on aromatic ring. Different researchers have tried to obtain chalcones having electron donating substitution to evaluate their anti-microbial potential [20]. From a literature review it is clear that most efforts have been directed to the synthesis and biological evaluation of chalcone derivatives with electron-donating groups in aromaric rings but the research is far from exhausted [21,22]. Literature survey also suggest that curcumin loses its activity by the replacement of methoxy substitution, that is why most of the analogues were reported in the result of hydroxyl substitution in order to get potent compounds. The underlying mechanisms of action, particularly with respect to the direct cellular targets have not been rigorously characterized, which forces challenges to structure-

guided rational development of therapeutic with acceptable target-selectivity profile [23]. Large number of natural product analogues were found to inhibit D-alanyl-D-alanine carboxypeptidase [24], which is an enzyme involved in bacterial cell wall biosynthesis during the transpeptidation that crosslink the peptide side chains of peptidoglycan. Chalconoids and curcuminoids were found to target the above mentioned protein. Monocarbonyl compounds were reported to have good antimicrobial activities compared to dicarbonyl curcuminoids due to their instability. Molecular docking results showed that synthesized compounds have good activity against target 1PW1, and compounds **1**, **9** and **15** were found most active by exhibiting binding energy of -7.9, -8.0 and -8.5 kcal/mol respectively.

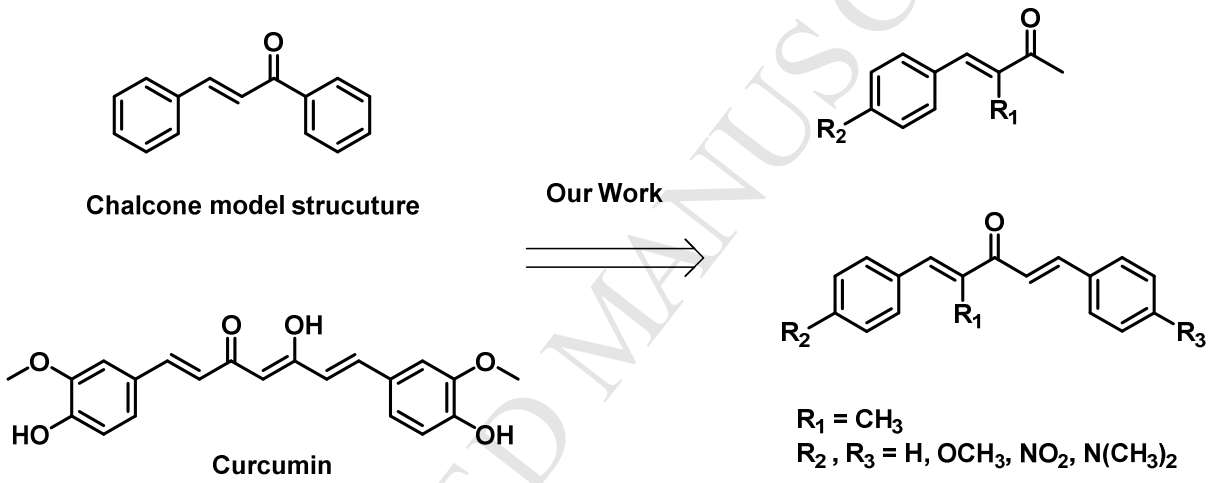

Figure 1: Chalcone and curcumin structure and their analogues

2. Experimental Protocols

2.1. Synthesis of the chalcones

The chalcones were prepared by condensation reactions between four aldehydes with butanone resulting in the four 4-aryl-3-methylbutenones (compounds **1-4**). Each chalcone derivative was used as starting material for the production of sixteen compounds through further condensation reaction with the four aldehydes (compounds **5-20**) [18]. The in vitro anti-microbial activities of compounds **1-20** were evaluated preliminarily against a gram-negative and gram-positive indicator strain. The promising compounds were further studied for their anti-microbial activity against a collection of nine selected clinically relevant pathogens.

2.2. Bioassays

2.2.1. Bacterial strains: species, storage and growth conditions

The indicator strains used in the antimicrobial screening stage were the gram-negative and gram-positive bacteria *Escherichia coli* ATCC 25922 *and Staphylococcus aureus* ATCC 25923, respectively. For the second phase trials, we employed additional gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 14207, *Shigella sonnei* ATCC 29930), gram-positive bacteria (*Bacillus cereus* ATCC 11778, *Enterococcus faecalis* ATCC 29212, *Staphylococcus saprophyticus* ATCC 15305) and fungi (*Candida albicans* ATCC 10231, *Candida krusei* ATCC 90878). All the strains were store at -80 ºC and sub-cultured on Mueller-Hinton broth (MHB) (37°C, 18h). A microbial inoculum was prepared by adjusting the turbidimetry of the medium to 0.5 McFarland standard value [23,24]. Bacteria and fungi were obtained from the Culture Collection of Laboratory of Microbiology and Biomolecules (Federal University of Sao Carlos, Brazil).

2.2.2. Minimum Inhibitory Concentration (MIC)

The broth-micro dilution technique was used for the antimicrobial activity evaluation of the 20 compounds. This biological activity was tested in the indicator strains *E. coli* and *S. aureus* [23,24]. The lyophilized compounds were solubilized in DMSO and then diluted in MHB. The twofold concentrated solutions were transferred to a 24-well microtiter plate and the double-dilutions were sequentially prepared in MHB. The DMSO reached maximal final concentration of 5.0% per well, which did not inhibit microbial strains. The sealed plates were incubated at 37°C for 18 h under gentle agitation of 120 rpm. The MIC value was considered as the lowest concentration in which no microbial growth was observed by naked eye. For confirmation of the MIC value, MTT dye colorimetric method was then applied. In the selected wells, 20 µl (1 mg/mL) of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reagent was added followed by 20 minutes of incubation at 37°C. The solutions remained clear/yellowish for those with no microbial growth, while the emergence of dark blue color indicated growth [27,28]. In the second phase, the compounds that showed inhibitory effect on the indicator strains were further evaluated against the additional gram-negative, gram-positive bacteria and fungi (previously described) through the same broth micro dilution technique. Ciprofloxacin was used as a positive control.

2.3. Molecular Docking

2.3.1. Selection of protein structure and considerations

The crystal structure of D-alanyl-D-alanine carboxylpeptidas was selected from the Protein Data Bank (PDB ID: 1PW1, resolution 1.20 Å) [29]. DD-Peptidase structure was prepared for docking by removal of native ligand (2-amino-2-deoxy-D-glucitol-6-phosphate) and water molecules. Swiss PDB Viewer was used to check structure for missing segments and minimization energy [30]. Pdbsum [31] was used to find residues involved in active site are Gly61, Ser62, Phe120, Thr-123, Tyr159, Asn161, Leu214, Trp233 Arg285, His298, Thr299, Gly300, Thr301, Gln303, Ser326 and Asn327.

2.3.2. Preparation of chalcone structures for docking

The ligands were drawn in ChemSketch v15.0.9 (Chemaxon) assigned with proper 2D orientation and the structure of each compound was analyzed for connection error in bond order. Energy of the molecules was minimized using Avogadro [32] with MMFF94 force field.

2.3.3. Protein-Ligand Docking Studies

PharmMapper Server was used to obtain information regarding possible mechanisms behind the activity of studied compounds [33]. PharmMapper Server is a freely accessed web-server designed to identify potential target candidates for the given probe small molecules (drugs, natural products, or other newly discovered compounds with binding targets unidentified). PharmMapper utilizes an integrated pharmacophore matching platform with statistical method for potential target identification [34]. Compounds are scored according to their fitness on the pharmacophore models. Moreover, the program encompasses z^0 score which is a score generated from the molecule's fit score and a library score matrix calculated beforehand. It combines the fit score and its corresponding vector in the score matrix together and normalizes it to a vector with a mean of zero and a standard deviation of one. Compared to the fit score z^0-score not only applies the pharmacophore matching method but also considers statistic factors lying behind. Generally, large positive z^0-score indicates high significance of the target to a query compound; as well large negative z^0-score indicates that the target may not be significant enough.

Docking studies calculations were performed by Auto dock Vina v1.1.2 [35]. Protein and chalcone derivatives structures were converted to pdbqt files by MGL Tools 1.5.6 RC1. The grid size box was set at 22 x 26 x 22, and the grid center was set to 20.089, -11.808 and 38.599 for *x*, *y* and *z* respectively, which covered all amino acid residues in the considered active pocket. The spacing between grid points was 1.000 Å. Kollman charges and polar hydrogen atoms were added to protein structure. Gastiger charges were added and non-polar hydrogen atoms were merged for ligands structure. After calculation docking results provide different conformation of ligands in active site. Each of them is studied and best conformation was chosen with the lowest binding energy (kcal/mol) between protein and ligand (chalcone derivative). The interactions of complex protein-ligand conformations, were analyzed using Auto dock Tools 4.2 [35], Discovery studio 4.1 [36].

2.4. X-ray crystallography

Compounds **14** and **16** were recrystallized from ethanol. The X-ray diffraction data were collected using a BRUKER APEX II duo diffractometer with Mo-Kα radiation (λ = 71.073 pm). Structure solution and refinement were performed with SHELXS-97 [37]. All non-hydrogen atoms were refined with anisotropic displacement parameters with SHELXL-2013. The hydrogen atoms' positions were found in Fourier maps or calculated in their idealized positions. More details on data collections and structure calculations are summarized in Table 1.

Table 1.Crystal data and structure refinement details of compounds **14** and **16.**

Identification code	**Compound (14)**	**Compound (16)**
Empirical formula	$C_{21}H_{23}NO_2$	$C_{20}H_{22}N_2O_3$
Formula weight	321.40	336.38
Temperature (K)	296(2)	296(2)
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	$P\bar{1}$
Unit cell dimensions		
a	13.1293(3) Å	6.8226(4) Å
b	17.5364(4) Å	7.2256(4) Å
c	15.1433(3) Å	18.1235(12) Å

α (deg)	90	88.371(4)
β (deg)	95.6440(10)	87.322(4)
γ (deg)	90	72.394(3)
Volume ($Å^3$)	3469.70(13)	850.57(9)
Z	8	2
Density (calculated)	1.231 Mg/m^3	1.313 Mg/m^3
Absorption coefficient	0.078 mm^{-1}	0.089 mm^{-1}
F(000)	1376	356
Theta range for data collection	1.78 to 25.04°	2.25 to 25.05
Index ranges	-15<=h<=15, -16<=k<=20, -17<=l<=18	-8<=h<=8, -8<=k<=8, -21<=l<=21
Reflections collected	20977	9772
Independent reflections	6116 [R(int) = 0.0155]	2965 [R(int) = 0.0260]
Absorption correction	Multi-scan	Multi-scan
max/min transmission	0.9529 and 0.9228	0.9911 and 0.9746
Data / restraints / parameters	6116 / 0 / 441	2965 / 0 / 229
Goodness-of-fit on F^2	1.031	1.057
Final *R* indices [I>2sigma(I)]	R_1 = 0.0389, wR_2 = 0.1004	R_1 = 0.0480, wR_2 = 0.1315
R indices (all data)	R_1 = 0.0447, wR_2 = 0.1046	R_1=0.0685, wR_2 = 0.1469
Largest diff. peak and hole	0.176 and -0.162 $e.Å^{-3}$	0.161d -0.203 $e.Å^{-3}$

3. Results and discussion

3.1. Chemistry

Compounds **1-20** were prepared by standard procedures [18]. Structure representations of compounds **1-20** are presented in Figure 2a and 2b. Compounds **1-4** were produced by acid catalyzed reaction (HCl gas) and act as intermediate for the synthesis of compounds **5-20**.

Base catalysis was carried for the preparation of compounds **5-20** by NaOH in ethanol.

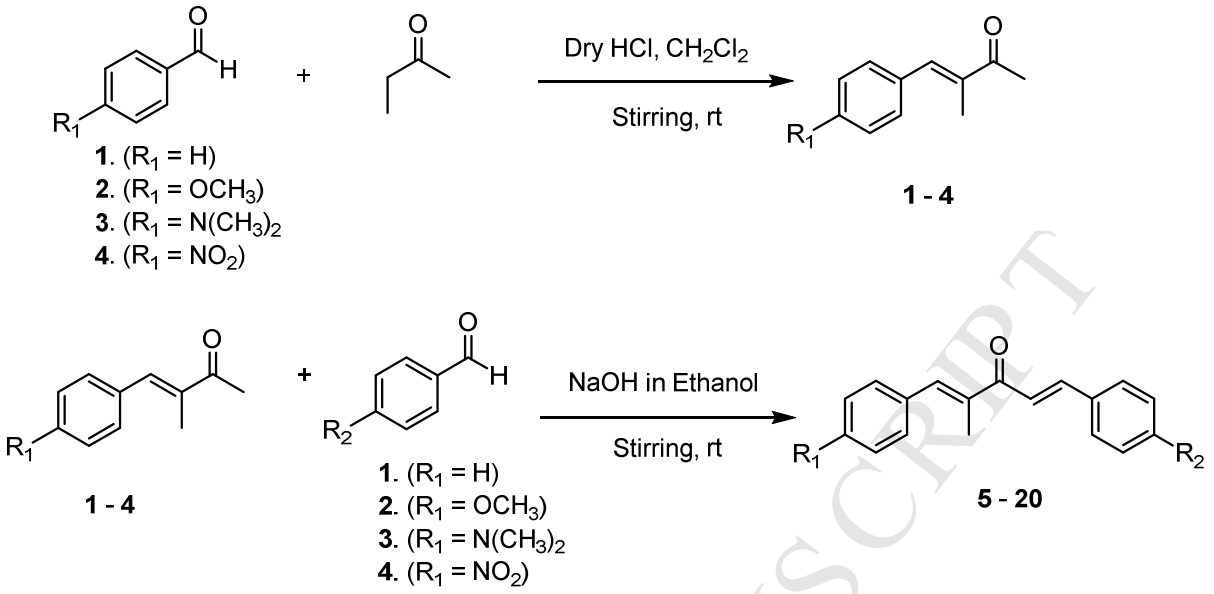

Figure 2a: Synthesis of the intermediate compounds **1-4** and chalconoids **5-20.**

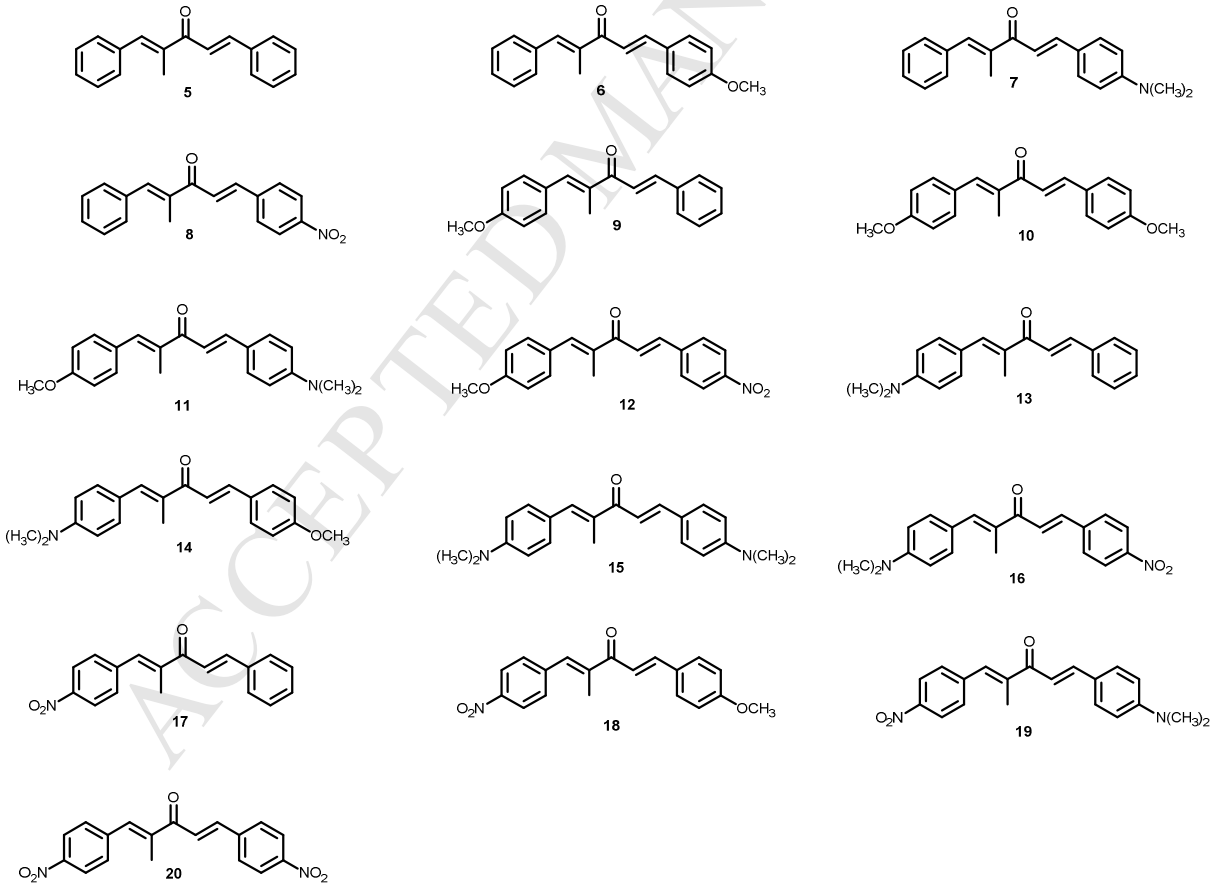

Figure 2b: Chemical structure of compounds **5-20.**

3.2.Crystallographic Characterization

Ellipsoid representations of the molecular structures of the compounds **14** and **16** with numbering scheme are presented in Figure 3, while crystal packing and selected bond distances are reported in Fig. S1 and Table S3 in Electronic Supporting Information. Selected bond distances are reported in Table 2. As can be observed, the bond lengths along the carbon chain between the two aromatic rings are within values for alternate single and double bonds. For example, the C(12)-C(13) bond presents a single bond character while the C(11)-C(12) is a typical double bond. This alternation of single and double bonds make the structure more flexible and less planar. As expected, only weak interactions are observed in the crystal packing of the compounds. Detailed information about the structure determination is given in Table 1. The complete information of both crystal structures is reported in Electronic Supporting Information (see table S1 and S2).

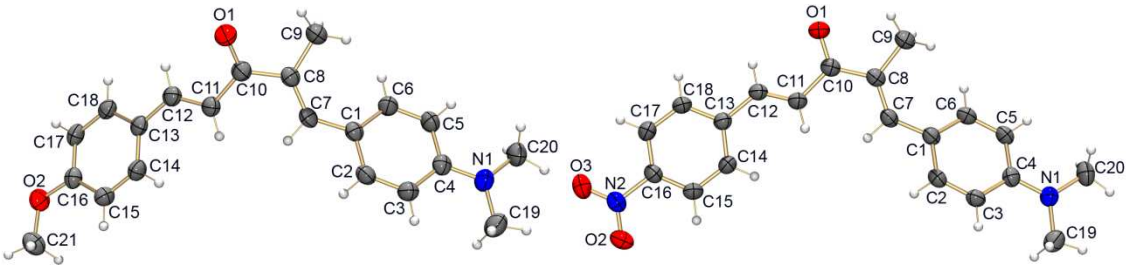

Figure 3. Ortep view with thermal ellipsoids at the 50% probability level and atomic numbering scheme compound **14** (left) and compound **16** (right).

3.3. Biological activity

The compounds (**1-20**) were preliminarily screened for their *in vitro* anti-microbial activity against *Escherichia coli* and *Staphylococcus aureus* (Table 2). The active compounds (**1**, **9** and **15**) were further screened against 7 different bacteria's and 2 fungi to evaluate their anti-biotic potential (see Table S4 in Electronic Supporting Information).

In preliminarily screening compound **15** was the only one able to inhibit the growth of both microbial indicator strains: *E. coli* and *S. aureus* (MIC of 500 µg/mL and 250 µg/mL respectively). Compound **1** (MIC 250 µg/mL) and **9** (MIC 62.5 µg/mL) were selectively good inhibitors for gram-negative and gram-positive strains respectively. Compounds **9** (MIC 62.5 µg/mL) and **15** (MIC 250 µg/mL) (for *S. aureus*) showed lower MIC values when compared with the positive control: ciprofloxacin. Taking into account the structure, compound **1** has no substituents in the aromatic rings, compounds **9** has one *p*-methoxy substitution in aromatic

ring A and **15** has two *p-N,N*-dimethyl substitution in both ring A and B. It is concluded that among three active compounds two afforded electron-donating substituent's showed good inhibitory activity, even better than the positive control.

Table 2. Inhibitory activity (MIC, µg/mL) of compounds **1-20**

S. Number	*Escherichia coli* ATCC 25922	*Staphylococcus aureus* ATCC 25923
1	250	> 1000
2	> 1000	1000
3	> 1000	> 1000
4	> 1000	> 1000
5	> 1000	> 1000
6	> 1000	> 1000
7	> 1000	> 1000
8	> 1000	> 1000
9	> 1000	62.5
10	> 1000	> 1000
11	> 1000	> 1000
12	> 1000	> 1000
13	> 1000	> 1000
14	> 1000	> 1000
15	500	250
16	> 1000	> 1000
17	> 1000	> 1000
18	> 1000	> 1000
19	> 1000	> 1000
20	> 1000	> 1000
PC	500	500

PC (positive control): Ciprofloxacin

The biological activity of compounds against *E. coli* showed that electron donating substitution *(p-N,N*-dimethyl) on both aromatic ring A and B in case of compounds **15** exhibited increase in antimicrobial activity. Compound **1** is monoaryl having no substitution on aromatic ring A also shows good activity. The rest of compounds tested showed a decrease in potency. Concerning the biological activity of compounds against *S. aureus*, it is remarkable that electron donating substitution of aromatic ring A and B reflected an improvement in antimicrobial action. Compound **9** having *p*-methoxy substitution on aromatic ring A, and compound **15** having two *p-N,N*-dimethyl substitution on aromatic ring A and B, show potency in activity.

Biological activity results indicated that electron donating groups (*p*-methoxy on compounds **5** while *p-N,N*-dimethyl on compound **15**) significantly enhances the activity. Some other factors which also influence the activity include length and size of side chains and polar or non-polar hydrophilic groups are more favorable to improve the biological activity of the chalcone compounds. The modifications discussed may facilitate the interaction of the compounds with microbial cellular membrane. It is noteworthy that the weak antimicrobial activity is linked with the polar nature of some compounds that did not allow the membrane penetration.

According to the data presented (see Table S4 in Electronic Supporting Information), compound **1** displayed its activity preferentially against gram-negative bacteria (and weak antimicrobial action against fungi) if compared to the gram-positive ones. Compound **2** exhibited potent activity against gram negative bacteria *Shigella sonnei,* gram positive bacteria *Staphylococcus saprophyticus,* and against two fungi *Candida albicans* and Candida *krusei.* Compound **9** was found the most potent one against gram positive, negative bacteria and fungi. Additionally, the compound **9** showed good bioactivity for *Shigella sonnei, Staphylococcus aureus, Staphylococcus saprophyticus, Candida albicans* and *Candida krusei*. The same antimicrobial behavior of compound **9** was demonstrated by compound **15**.

3.5. Molecular Docking

The pharmmapper produced the top 300 ligand ranked based on the fit score. Working on the highest antimicrobial targets, the key bacterial enzymes found were D-alanyl-D-alanine carboxypeptidase (1PW1), glucousamine 6-Photsphate Synthase (1MOQ) and beta-lactamase (1I2W). By reverse-docking of potent compounds (**1**, **9**, and **15)** for selected target, the enzyme D-alanyl-D-alanine carboxylpeptidase (1PW1) was found the suitable target for our ligands (Table 3).

Table 3. Pharmmaper and Autodock vina results for selected targets

Ligands	PDB ID,S					
	1MOQ		1PW1		1I2W	
	z-score	kcal/mol	z-score	kcal/mol	z-score	kcal/mol
1	-0.21	-7.3	1.123	-7.9	0.195	-6.5
9	-0.429	-7.5	0.842	-8.0	0.312	-6.8
15	-0.214	-7.4	1.32	-8.5	1.438	-6.5

Molecular docking results confirmed that the most suitable target for our compounds is D-alanyl-D-alanine carboxylpeptidase (*PDB ID*: 1PW1). Auto dock *vina* allows the flexible docking of ligands into its site of action. It has ability to use all the rotatable bonds of the ligands to give a number of conformations from which the best mode could be achieved. Our ligands occupy the same space in the active site as that of native ligand in the crystal of enzyme (see Figure S2 in Electronic Supporting Information). Ligands **1**, **9** and **15** were most active ligands with lowest binding energy -7.9, -8.0 and -8.5 kcal/mole (see Table S5 in Electronic Supporting Information). Our ligands formed hydrogen bond contact with Thr-116, Tyr-159,Asn-161 and Thr-299. While hydrophobic contacts were with Phe-120, Thr-123, Tyr-159, Gln-278 and Arg-285. Based on interactions of ligands with protein`s residues, it is clear that mechanism of action of ligands are based on both types of interactions; hydrogen bonds and hydrophobic contacts (including π-π stacked, π-alkyl and π-σ). The inhibition constant (Ki) was also calculated and show best value for compounds **1**, **9** and **15** to be 3.80, 2.65 and 2.14 µM. The smaller the Ki, the greater the binding affinity and the smaller amount of drug may be needed in order to inhibit the activity of enzyme. If Ki is much larger, then that drug is not likely to inhibit the activity of that enzyme. The potent compound **9** is shown in the active site of enzyme in Figure 4. Figure S3 in Electronic Supporting Information shows protocol validation of docking through re-docked native ligand in same conditions. Some of our compounds have shown docking scores much better than the docking score of co-crystallized ligand which is docked in same condition as studied ligands (-7.5 kcal/mol) and Ciprofloxacin used as comparing standard. In general a good correlation was observed between *in vitro* and *in silico* results of analysis.

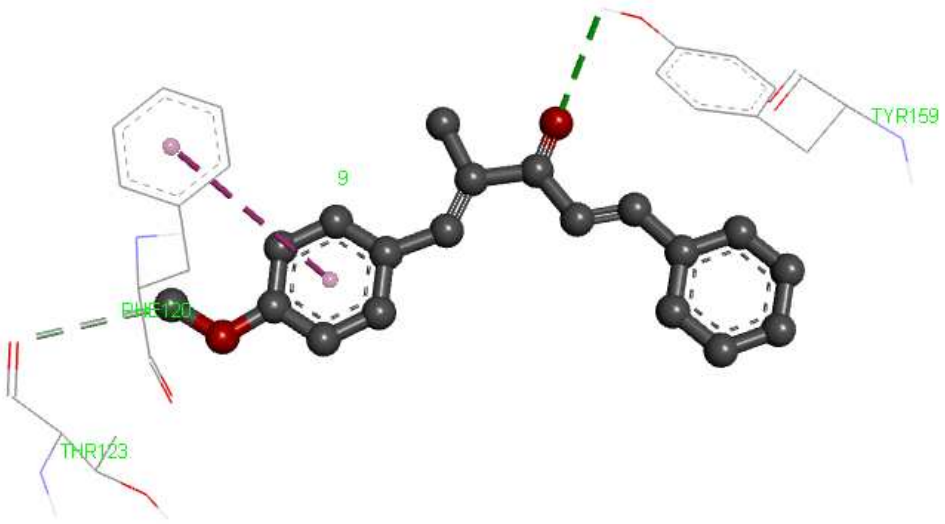

Figure 4. Best poses of ligands compound **9** interacting with active site residues of 1PW1. The hydrogen bonds are represented as dashed-green and white lines.

4. Conclusion:

This work has proved that synthetic curcumin and chalcone analogues can be used as anti-microbial compounds. The bioassays and the computational calculations showed that electron donating group on both rings A and B in this class of compounds is crucial for obtaining anti-microbial activity. Among 20 studied compounds, compound **1** with no substitution, compound **9** with one *p*-methoxy while compound **15** with two *p*-*N*,*N*-dimethyl moiety on aromatic ring were found more active. Compound **1** was found active against *Escherichia coli*, compound **9** against *Staphylococus aureus* while compound **15** were active against both types of bacteria. In addition, electron-withdrawing substituents have no antimicrobial activity. The present study provides a template to design new combinations of antibiotics and non-antibiotics for the treatment of *Staphylococus aureus* and *Escherichia coli* infections. Pharmmaper and molecular docking results provided significant interactive detail. Therefore optimization must be performed in order to obtain more potent compounds.

Acknowledgments

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Supplementary data

Some other necessary detail regarding biological activity and crystal structure are given in Electronic Supporting Information.

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Research highlight

- We synthesized a series of close related monocarbonyl curcuminoids.
- Crystal, DFT, *in-silico* study and anti-microbial potential were also studied.
- The compounds were tested against gram-negative and gram-positive bacteria.
- Compounds **1**, **9** and **15** exhibited good activity against *Escherichia coli* and *Staphylococcus aureus*.
- Docking studies helped understanding these results.