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Design and Synthesis of Methoxy-Chalcone Derivatives as Potential Antimicrobial Agent †

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Abstract: In this study, two (2) new methoxy-chalcone derivatives [(E)-1-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**5a**) and (E)-3-(4-methoxyphenyl)-1-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (**5b**)] were designed and synthesized by condensation reaction of 2,4-dimethoxy acetophenone as well as 2,4,5-trimethoxy acetophenone with 4-methoxybenzaldehyde using NaOH as the catalyst. The products were crystallized with ethanol and dried to constant weight. The percentage yield was calculated. The purity of the samples were confirmed using TLC and melting point were determined. The structure of the products were verified on the foundation of FT-IR, proton (^{1}H-NMR). Molecular docking studies were carried out using Auto dock vina of pyrex to predict its antimicrobial potentials, and the docked compound was visualized using discovery studio visualizer. The receptor (Bacteria DNA gyrase) was obtained from protein data bank (PDB) with I.D of (4DUH). Compound **5a** had binding energy of (−7.6 kcal/mol) while compound **5b** had (−7.0 kcal/mol). The two compound exhibited good molecular interaction with receptor, which include the hydrogen bonding and hydrophobic interactions. The result from this work shows that both compounds had good binding affinity to the receptor, and are predicted to inhibit the bacteria DNA gyrase. Compound **5a** had showed to have superior activity when compared to compound **5b**. The compounds have exhibited great potentials to serve as a lead for the development of novel antimicrobial agents.

Keywords: keyword 1; keyword 2; keyword 3

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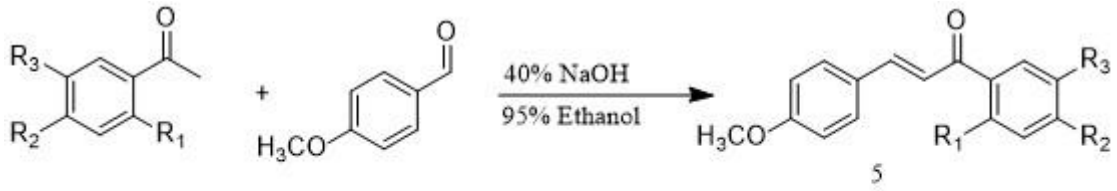
1. Introduction

Antimicrobial resistance (AMR) is a persistent public health issue that, by 2050, is predicted to be the cause of 10 million annual deaths worldwide [1]. and this is linked to the mishandling of antimicrobial drugs, erroneous diagnosis, and changes in the traits of the pathogenic microorganisms [2]. It is predicted that in the upcoming years, drug-resistant bacteria would cause a rise in mortality [3]. In order to always have an adequate supply of drugs, research and development efforts have been driven by the emergence of antibiotic resistance in microorganisms and financial incentives. Discovering novel, secure, and potent antibiotics with a wide range of action is crucial. Chalcones are chemically straightforward molecules that make it simple to synthesize a variety of substituted derivatives. Chalcones, sometimes referred to as "α,β-unsaturated ketones", are important precursors for both synthetic synthesis and natural products [4]. Numerous pharmacological properties, including antibacterial [5–7], antiviral [8], anticancer [9],

antioxidant [10], have been linked to chalcones. One kind of bioinformatic model that incorporates atomic-level protein-ligand interaction is the molecular docking technique. The lock-and-key principle, which has been used to identify target structures for protein active sites and to clarify possible mechanisms of action, is analogous to this relationship. Using molecular docking techniques to design and synthesize novel chalcone derivatives containing the chalcone moiety was thought to be beneficial in order to investigate potential antibacterial characteristics.



5a: R1 = OCH_3, R2 = OCH_3, R3 = H
5b: R1 = OCH_3, R2 = OCH_3, R3 = OCH_3

Scheme 1. Synthetic protocol for methoxy substituted chalcone derivatives, **5a**–**5b**.

2. Result and Analysis

2.1. Overall Chemistry

Compounds **5a** and **5b** have percentage yields of 65.87% and 68.08%, respectively. Yellow crystals for compound **5b** and pale yellow crystals for compound 5a were visible. The two compounds' observed sharp melting points implying a high degree of purity for the compounds. The FT-IR data shows that both **5a** and **5b** include functional groups (C=O, =C-H, and C-O-C). A notable carbonyl peak C=O can be seen at 1572.9 cm^{-1} and 1647 cm^{-1}, and an olefinic =C-H vibration can be seen at 3004 cm^{-1} and 3008 cm^{-1}. Additionally, there was a noticeable, significant coupled absorption of C-O-C stretching at (1285 and 1025 cm^{-1}) and (1207 and 1028 cm^{-1}). The formation of the chalcones is indicated by the olefinic peak seen in the area above. Furthermore, the pronounced bands in the region above for both chalcones corroborated the characteristic α, β-unsaturated carbonyl group of the chalcones. Furthermore, associated strong vibration at for C-O-C stretching vibrations provides proof of the methoxy function. The ^{1}H NMR spectra verified the **5a** and **5b** structures. The remaining protons appear in their expected regions with their usual coupling constants, with the exception of the α,β-unsaturated ketone linker protons as doublets, which were observed in the regions of 7.36–6.93 ppm (H–α) and 7.65–7.39 ppm (H–β) with coupling constants of 15.7–15.6 Hz (trans–isomers) and the methoxy protons as a singlet in the region of 3.98–3.77 ppm.

2.2. Molecular Docking Studies

In order to reveal the bio-efficacy of the synthesized chalcones, the in silico docking studies was performed in the active site of DNA gyrase of *E. coli* (PDB ID: 4DUH). Compound **5a** exhibited conventional hydrogen bond with LYS103 (2.36A^0), and carbon hydrogen bonding with LYS103 (3.34A^0), and Pi-alkyl bond with LYS103 (4.31A^0). The hydrophobic bond formed is due to the alkyl interaction of the methoxy group with VAL120 (5.20A^0), VAL167 (4.89A^0), VAL43 (5.31A^0), ILE78 (5.49A^0, 5.10A^0), amino residue and Pi alkyl interaction of the delocalized pi electron of the benzene ring with VAL120 (5.20A^0), PHE104 (5.42A^0), LYS103 (4.31A^0), ILE78 (4.45A^0). Compound **5b** formed conventional hydrogen bond with ASN32 (3.66A^0), carbon hydrogen bonding with ILE64 (2.31A^0), PRO65 (2.40A^0), LYS89 (3.56A^0), amino residue. The pi orbital containing delocalized electron in the benzene ring interact with the alkyl groups of ILE64 (4.47A^0), ILE80 (4.49A^0), LYS89 (4.60A^0), amino residue to form hydrophobic bond. The methoxy

group formed an alkyl interaction with ILE64 (4.42A^0), PRO65 (2.40A^0, 4.99A^0), and LYS89 (4.33A^0). Both alky and pi alkyl group formed hydrophobic bonding.

3. Materials and Methods

3.1. Measurements

All of the reagents and solvents utilized were of laboratory grade (LR grade) and didn't require any additional purification. The melting point was measured using a Stuart automated melting point appliance, and it was discovered to be incorrect. Fourier Transformed Infrared Spectroscopy was recorded using an Agilent Technologies spectrophotometer model 543. Nuclear magnetic resonance (NMR) measurements were carried out using a Brucker AMX 400 MHz equipment. Proton (1H) NMR measurements were among the NMR tests.

*3.2. General Protocol for the Synthesis of Chalcone Derivatives with Methoxy Substitution (***5a** *and* **5b***)*

20 mL of ethanol was combined with equimolar quantities of 2,4-dimethoxyacetophenone (0.01 moles) and 4-methoxybenzaldehyde (0.01 moles) in a round-bottom flask. Dropwise addition of 10 mL of 40% sodium hydroxide solution was made to this, stirring constantly for 30 min while the liquid remained cold. A magnetic stirrer was then used to continue the mixing for an additional two hours at room temperature. Until the mixture solidified into an orange mass, it was refrigerated for the entire night. 10% HCl drops were applied to stop the reaction. After diluting the combination with 40 milliliters of ice-cold distilled water and filtering it, the residue was thoroughly cleaned with more ice-cold distilled water and allowed to dry in the open.

The product was crystallized with ethanol and dried to constant weight. The percentage yield was calculated. The purity of the samples were confirmed using TLC and melting point determined.

3.2.1. (E)-1-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**5a**)

Pale yellow crystals, R_f (0.57), Yield (56.87%), M.p (117–118.9 °C). FT-IR [(KBr), cm^{-1}]: (C=O: 1572.9), (=C-H: 3004), (C-O-C: 1285.9 & 1025). ^{1}H NMR (400 MHz; DMSO-d6) δ: (7.36: d, J = 15.7 Hz, 1H, C2-CH), (7.65: d, J = 15.57 Hz, 1H C3-CH), (6.48: d, J = 1.8 Hz, 1H C3′-CH), (6.54: dd, J = 8.2 Hz; 1.4 Hz, 1H, C5′-CH), (7.74: d, J = 8.4 Hz, 1H, C6′-CH), (7.54: d, J = 8.5 Hz, 1H, C2″-CH) (6.90: d, J = 8.4 Hz, 1H, C3″-CH), (6.90: d, J = 8.4 Hz, 1H, C5″-CH), (7.54: d, J = 8.5 Hz, 1H, C6″-CH), (3.88: s, 3H, C2′-OCH$_3$), (3.86: s, 3H, C4′-OCH$_3$), (3.88: s, 3H, C4″-OCH$_3$).

3.2.2. (E)-3-(4-Methoxyphenyl)-1-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (**5b**)

Yellow crystals, R_f (0.47), Yield (68.08%), M.p (126.2–127.9 °C). FT-IR [(KBr), cm^{-1}]: (C=O: 1647), (=C-H: 3008), (C-O-C: 1207 & 1028). ^{1}H NMR (400 MHz; DMSO-d6) δ: (6.93: d, J = 15.6 Hz, 1H, C2-CH), (7.39: d, J = 15.0 Hz, 1H C3-CH), (6.55: d, J = 0.5 Hz, 1H C3′-CH), (7.72: d, J = 8.0 Hz, 1H, C6′-CH), (7.55: d, J = 8.0 Hz, 1H, C2″-CH) (7.26: d, J = 8.0 Hz, 1H, C3″-CH), (7.26: d, J = 8.0 Hz, 1H, C5″-CH), (7.55: d, J = 8.0 Hz, 1H, C6″-CH), (3.90: s, 3H, C2′-OCH$_3$), (3.98: s, 3H, C4′-OCH$_3$), (3.83: s, 3H, C5′-OCH$_3$), (3.77: s, 3H, C4″-OCH$_3$).

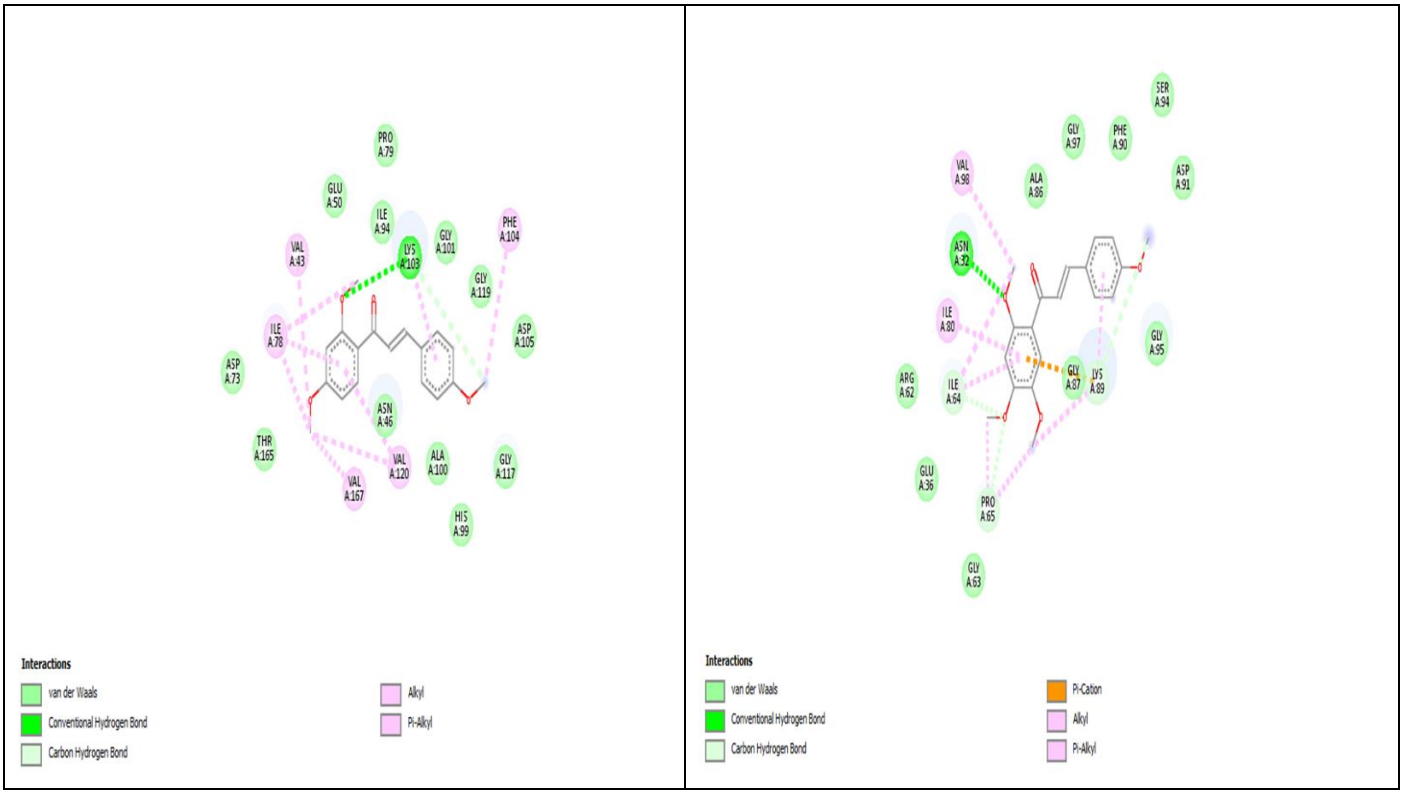


Figure 1. 2D Configuration of complex **5a** and **5b**.

Table 1. Binding affinities, Bonding interaction, types, distances between the ligands and the receptor.

Complex	Binding Energy (kcal/mol)	A.A	B.T	Interaction	B.D (A^0)
5a	−7.6	LYS103	Hydrogen bond	Conventional hydrogen bond	2.63
		LYS103	Hydrogen bond	Carbon hydrogen bond	3.34
		LYS103	Hydrophobic	Pi Alkyl	4.31
		PHE104	Hydrophobic	Pi Alkyl	5.42
		VAL120	Hydrophobic	Pi Alkyl	5.20
		VAL120	Hydrophobic	Alkyl	4.94
		VAL167	Hydrophobic	Alkyl	4.89
		ILE78	Hydrophobic	Alkyl	5.49
		ILE78	Hydrophobic	Alkyl	5.10
		ILE78	Hydrophobic	Pi Alkyl	4.45
		VAL43	Hydrophobic	Alkyl	5.31
5b	−7.0	ASN32	Hydrogen bond	Conventional hydrogen bond	2.41
		ILE64	Hydrogen bond	Carbon hydrogen bond	2.31
		ILE64	Hydrophobic	Pi Alkyl	4.74
		ILE64	Hydrophobic	Alkyl	4.42
		PRO65	Hydrogen bond	Carbon hydrogen bond	2.40
		PRO65	Hydrophobic	Alkyl	5.39
		PRO65	Hydrophobic	Alkyl	4.99
		ILE80	Hydrophobic	Pi Alkyl	4.49
		LYS89	Hydrogen bond	Carbon hydrogen bond	3.34
		LYS89	Hydrophobic	Pi Alkyl	4.60
		LYS89	Electrostatic	Pi Cation	4.77
		LYS89	Hydrophobic	Alkyl	4.33

NB: A.A (Amino acid); B.T (Bond type); B.T (Bond interaction); B.D (Bond distance).

3.3. Molecular Docking Studies

The DNA gyrase from *E. coli* was used in molecular docking investigations using the methoxy benzaldehyde Chalcones derivative (PDB ID: 4DUH). We acquired the crystal structure from the RCSB PDB (https://www.rcsb.org). Using Pyrx's Autodock Vina, the docking scores of the ligand-receptor complex were determined [11]. The Discovery Studio visualizer was utilized to comprehend the connections between the ligand and protein target.

4. Conclusions

In this studies, two (2) new chalcone compounds were designed, synthesized, characterized using FTIR and proton NMR analysis and evaluated as potential antimicrobial agents using molecular docking. The Docking studies was used to estimate the antimicrobial activities of the new compounds, whereby compound **5a** have shown to exhibit a high affinity for DNA gyrase (4DUH) than **5b**. In summary, the newly developed chalcones derivatives could serve as potent leads toward the development of novel antimicrobial agents.

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Data Availability Statement:

Conflicts of Interest:

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