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Design, Synthesis And In Silico Studies Of Chalcone-Based Tetralone Derivatives For Biological Activity

Mohammad Sarafroz [1], Saman Aqeel [2], Kanchan Sharma [3], Gurcharan singh [4], Ashutosh Jain [5], Vikas Kumar [6], Mamathadevi A.B [7], Sivasubramanian P [8*]

[1]Assistant Professor, Department of Pharmaceutical Chemistry, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, City Dammam, Saudi Arabia

[2]Assistant professor, IIMT College Of Pharmacy Plot No 19 & 20 A Knowledge Park 3 Greater Noida, Pin Code: 201310

[3]Associate Professor, Desh Bhagat University, Mandi Gobindgarh, Punjab, Pin Code: 147301

[4]Associate Professor, Arya college of pharmacy Jaipur, Rajasthan, Pin Code: 302027

[5]Assistant Professor, Rajiv Gandhi Institute of Pharmacy, AKS University, Satna, M.P, Pin Code: 485001

[6]Assistant Professor, Bhagwant Global University Kotdwar Pauri Garhwal Uttarakhand, Pin Code: 246149

[7]Associate professor, Maharani's science college for women (Autonomous) Mysore, Pin Code: 570001

[8*]Associate Professor, SNS College of Pharmacy and Health Sciences, Coimbatore, Tamilnadu Dr. MGR Medical University, Chennai, Pin Code: 60032

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ABSTRACT

The goal of this research is to create hybrid compounds "by" combining chalcone and tetralone into a single structure that might have better antibacterial properties. Five distinct compounds were synthesised in all. Infrared spectroscopy, elemental analysis, and melting point were used to characterise the synthesised substances. The compounds that were synthesised demonstrated anti-bacterial and antifungal characteristics, according to anti-bacterial and antifungal screening. All three compounds fit the target protein's active site with PDB ID: 1M17, according to molecular docking studies. The substances satisfied Lipinski's rule of five, according to in silico pharmacokinetic study, and can be suggested as potential drugs.

KEYWORDS: Chalcone, In-silico, Tetralone, antimicrobial

INTRODUCTION

A worldwide public health issue, antibacterial resistance has made it more difficult to effectively prevent and treat a variety of bacterial illnesses [1, 2]. The overuse or abuse of antibacterial agents in humans and animals exacerbates antibacterial resistance [3]. The two main examples of microorganisms that are resistant to many drugs are Escherichia coli and Staphylococcus aureus [4]. Through longer hospital stays and more intense care, these multidrug-resistant pathogens have raised healthcare costs [2]. According to a World Health Organisation (WHO) research, methicillin-resistant S. aureus infections result in 64% more deaths than non-methicillin-resistant S. aureus infections [2].

Promoting funding for the development of new medications is one of the WHO's tactics for reducing antibiotic resistance [4, 5]. Many research teams are focused on creating new antimicrobial drugs that are more effective and less harmful in order to comply with this advice [2, 5]. Benzothiazole, thiourea, and sulphonamides are the most commonly used derivatives [6]. It has been observed that thiourea derivatives have antibacterial, antioxidant, antiviral, and anticancer

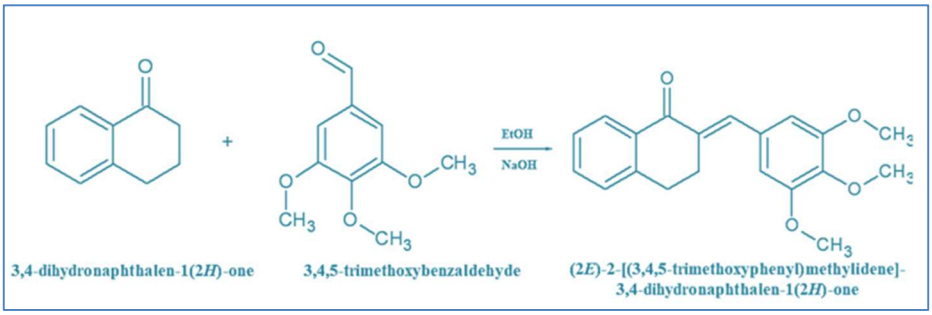
activities [3, 6]. There is evidence of tetralone derivatives having antibacterial, analgesic, anti-inflammatory, anticancer, and antimalarial properties [6–9]. Heterocyclic chalcone compounds have a variety of biological properties, including analgesic, antidiabetic, anti-inflammatory, anti-cancer, and antibacterial properties [10]. Antimicrobial resistance is still an issue, even with the large number of antimicrobial agents available to treat microbial infections. The goal of this research is to create hybrid compounds with potential enhanced antibacterial and antifungal properties by combining chalcone and tetralone into a single structure.

MATERIALS AND METHODS

Chemicals and Regents: Analytical-grade compounds were utilised without additional purification. Melting points are uncorrected and were measured using an open capillary melting point device. Silica gel-G (Marck 60) was used in thin layer chromatography (TLC) to track reaction completion. Sigma Aldrich provided the high-purity solvents and chemicals used in this study, which were used straight away without any additional purification.

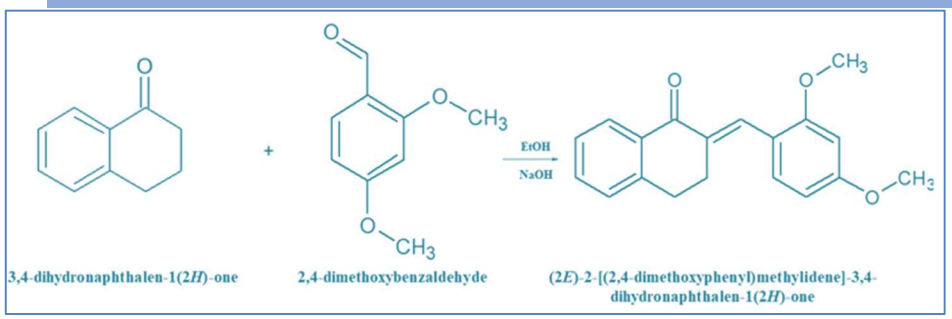
Experimental Work:

(2E)-2-[(3, 4, 5-trimethoxyphenyl)methylidene]-3, 4-dihydronaphthalen-1(2H)- one (Comp-1): A transparent solution was prepared by adding 100 mL of pure alcohol to a 250 mL conical flask containing an equimolar ratio of 3,4-Dihydro-1(2H)-naphthelenone (2 mL, 0.015mol) and 3,4,5-dimethoxy benzaldehyde (3g, 0.015mol). The resulting solution was mixed for two hours with a freshly made 10% NaOH solution. For twenty-four hours, this solution was let to rest at room temperature. To get rid of any remaining traces of NaOH, the yellow precipitate that developed after adding ice-cold water was repeatedly rinsed with water. Following a week of recrystallisation of the filtered and dried product in a 1:1 combination of acetone and ethylmethyl ketone, a yellowish-black product with an 89% yield was harvested (MP:121°C). [11]



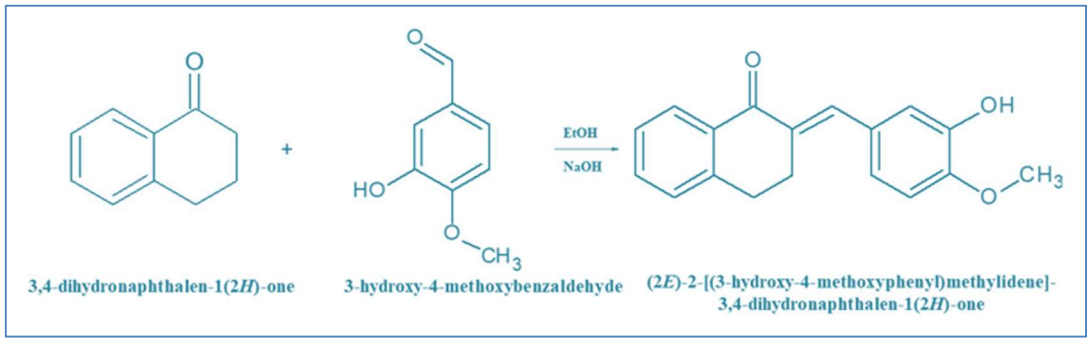
Scheme 1:

(2E)-2-[(2, 4-dimethoxyphenyl) methylidene]-3, 4-dihydronaphthalen-1(2H)-one (Comp-2): An equimolar ratio of 2,4-dimethoxy benzaldehyde (2.5g, 0.015mol) and 3,4-Dihydro-1(2H)-naphthelenone (2mL, 0.015mol) was prepared in a 250 mL conical flask. 100 mL of pure alcohol was then added, and the mixture was swirled until a clear solution was achieved. The resulting solution was mixed for two hours with a freshly made 10% NaOH solution. For twenty-four hours, this solution was let to rest at room temperature. After filtration, a bright yellow precipitate was formed, which was then repeatedly cleaned with distilled water to get rid of any remaining NaOH. A week later, yellow-black crystals with a 91% yield were extracted from the filtered and dried product after it had been recrystallised twice in acetone. (M.P. 123 °C) [12]



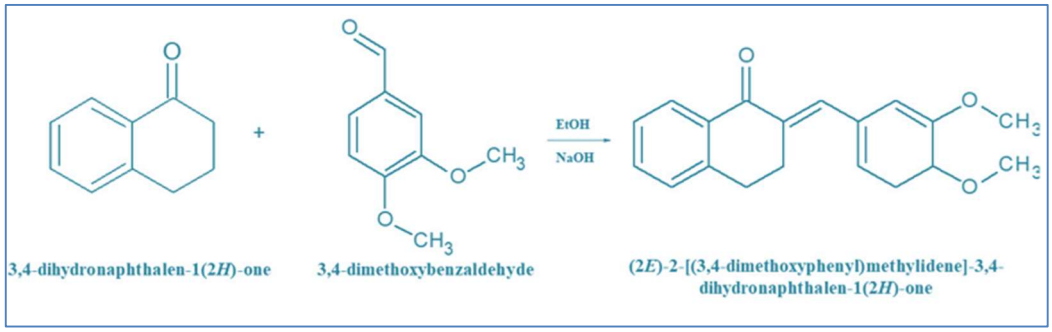
Scheme 2:

(2E)-2-[(3-hydroxy-4-methoxyphenyl) methylidene]-3, 4-dihydronaphthalen-1(2H)- one (Comp-3): A 250 mL conical flask was filled with an equimolar ratio of 3,4-Dihydro-1(2H)-naphthelenone (2 mL, 0.015mol) and 3-hydroxy-4-methoxy benzaldehyde (3g, 0.015mol). Absolute alcohol (100 mL) was then added, and the mixture was swirled until a clear solution was achieved. The resulting solution was mixed with a freshly made 10% NaOH solution and left for three hours. After leaving this solution at rest for the entire night, 50 millilitres of 36% hydrochloric acid was added, and it was once more left at rest for a day at 7°C. The resulting precipitate was dried and filtered. In acetone, the resultant compound underwent three recrystallisations. Black crystals with an 83% yield were achieved after 5 days (MP: 117°C). [13]



Scheme 3:

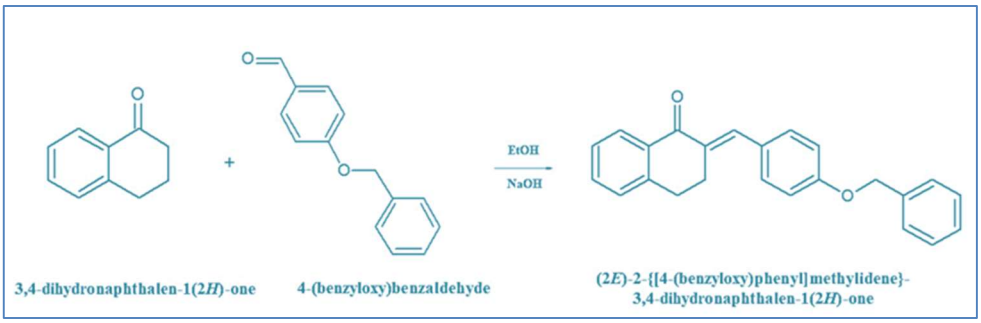
(2E)-2-[(3, 4-dimethoxyphenyl) methylidene]-3, 4-dihydronaphthalen-1 (2H)-one (Comp=4): In a 250mL conical flask, a corresponding amount of α-tetralone (2mL, 0.015mol) and 3,4 dimethoxy benzaldehyde (2.51g, 0.015mol) were dissolved in pure alcohol and swirled for 15 minutes. After adding a freshly made 10% NaOH solution, the mixture was agitated once more for an hour. After a day at room temperature, this mixture was transferred to ice-cold water. To get rid of any remaining residues of NaOH, distilled water was used to wash the yellow precipitate. In acetone, the dried and filtered crude product underwent three recrystallisations. Yellow crystals (Yield: 84%; mp: 119 °C) were harvested after 4 days. [14]



Scheme 4:

(2E)-2-{[4-(benzyloxy) phenyl] methylidene}-3, 4-dihydronaphthalen-1(2H)-one (Comp-5): 50mL of pure alcohol

and 4.78g (0.0225mol) of 4-benzyloxy benzaldehyde were combined in a 250mL conical flask, and the mixture was stirred for 10 minutes. 30mL of ethanol and 3mL (0.0225mol) of alpha tetralone were added to this solution, which was once more agitated for an hour. When this combination was mixed with newly made 10% NaOH (0.3g in 10mL), a vivid yellow solution was produced. After another hour of stirring, the solution was left overnight at room temperature. To get rid of any remaining traces of NaOH, the yellow precipitate that developed when ice-cold water was added was repeatedly rinsed with water. To purify the dried, filtered crude product, it underwent three recrystallisations in acetone. Yellow crystals were extracted four days later (yield: 79%, MP: 145°C). [15, 16]



Scheme 5:

Antibacterial Activity: The substances underwent antibacterial screening against Salmonella typhi and Escherichia coli, two Gram-negative bacteria, and two Gram-positive bacteria, Staphylococcus aureus and Streptococcus sp. Ampicillin served as the standard reference antibiotic. The primary stock cultures were maintained at 4°C on a nutrient agar slant. In order to create active cultures, a loop full of culture was transferred from the preserved stock cultures into the test tubes containing the protein broth that was high in nutrients. The test tubes were then incubated for a day at the ideal temperature of 37ºC. [17]

The agar disc diffusion method was used to conduct the antibiotic assay on Muller Hinton Agar medium. Following sterilisation, the petri plate was effused with Muller Hinton Agar (MHA) medium. Using a sterile spreader saturated in the bacterial suspension, the solidified inoculums were equally disseminated throughout the solid plates. 20 µL of samples with different concentrations (1000, 750, and 500 µg/mL) were added to a disc that had a 6 mm diameter and was housed in MHA plates. They were kept in an incubator set at 37ºC for a day. The chemicals' antibacterial activity is directly correlated with the zone of inhibition. [18]

Antifungal Activity: The substances underwent antifungal screening against three strains of Aspergillus niger, Candida albicans, and other fungi. The primary stock cultures were maintained at 4°C on Sabouraud Dextrose agar (SDA) slant media. A loop full of culture from the preserved stock cultures was transferred into the test tubes containing the nutrient-rich protein broth in order to prepare the active cultures. The tubes were then allowed to sit at room temperature for two days. [19]

The agar disc diffusion method was used to conduct the antimicrobial experiment on an SDA medium. After sterilisation, SDA medium was put into the Petri plate. A sterile spreader drenched in the fungal suspension was used to evenly distribute the solidified inoculums on the solid plates. Amphotericin-B served as the standard reference or positive control. 20 µL of samples with different concentrations (1000, 750, and 500 µg/mL) were put to a disc with a 6 mm diameter that was kept in SDA plates. They were kept in an incubator set at 28ºC for a day. The chemicals' antifungal activity is directly correlated with the zone of inhibition.

Molecular Docking [In-Silico] Analysis: To determine the compound's chemical interaction and binding conformation in the binding sites of biological therapeutic targets against breast cancer, molecular docking was used. The AutoDock 4.2.6 software package was used to study the ligand-target interactions, and PyMOL graphic software was made available for both preparing the protein target and viewing the ligand-target interaction. The search algorithm for the ligand that fits the target protein cavity the best is provided by the molecular docking program, which may be a viable option for

drug design. The three-dimensional binding interactions between a ligand and a receptor were examined using AutoDock 4.2.6 software. RCSB Protein Data Bank provided the target protein's crystal structure, which has PDB ID 1M17. [20] The target protein was free of the co-crystal inhibitor, water, solvents, and non-interacting ions. The Kollman method was used to estimate the atomic charges once the polar hydrogen was adjacent. Open Bable software was used to convert the ligand from CIF to PDB format [21]. To ascertain Lipinski's parameters, in-silico computational investigations were conducted utilising the Molinspiration online property calculation tools [22] [23, 24]. Lipinski's rule of five is a general guideline for assessing drug-likeness, or if a chemical molecule with a certain pharmacological or biological action possesses physical and chemical characteristics that would likely make it an oral drug in humans. Based on Lipinski's rule of five and Veber's rule, the title compound's molecular weight, number of rotatable bonds, logP value, hydrogen-bond donors (HBD), hydrogen-bond acceptors (HBA), molecular refractivity, and total polar surface area (TPSA) were estimated [25, 26, 27]. Compounds that break more than one of these guidelines may have issues with their bioavailability. An ADME web server from Switzerland can be used to forecast the pharmacokinetics of the orally active title chemical. [28, 29, 30].

RESULTS AND DISCUSSION

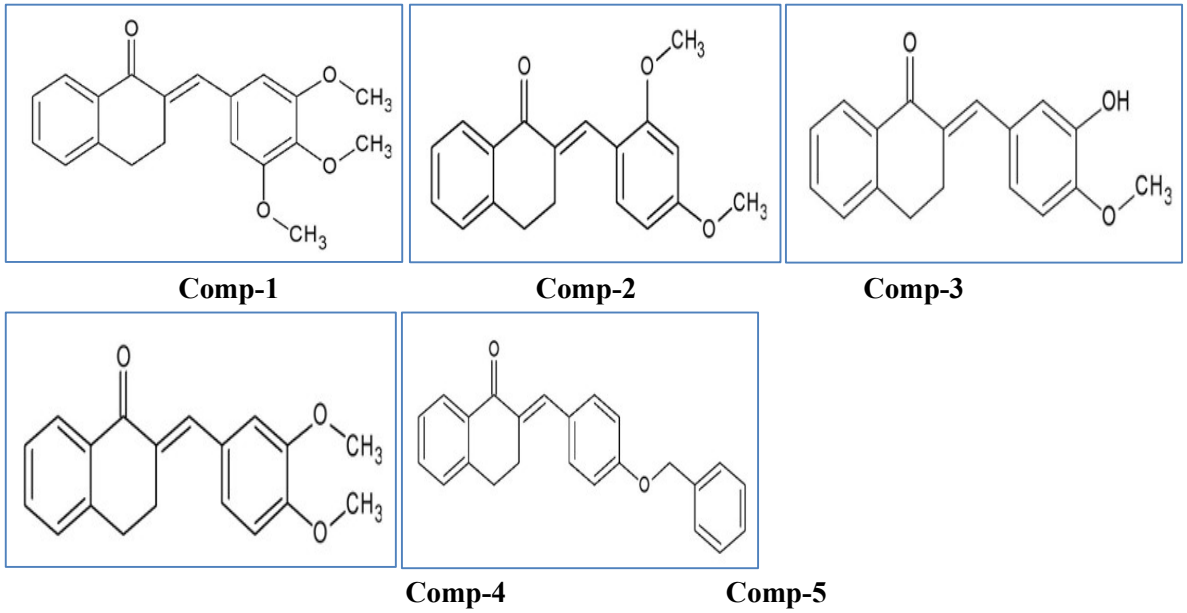


Fig. 1: Synthesized compound tetralone and chalcone

Antibacterial Activity: The antibacterial activity of the five as-synthesised compounds was assessed using the agar diffusion method on the MHA medium. The measurement of the compound's antibacterial activity was equal to the measurement of the zone of inhibition's diameter. The results from the title compounds Comp-1, Comp-2, Comp-3, Comp-4, and Comp-5 were compared using ampicillin as the reference standard. Against the bacterial strains, compounds 1 and 5 exhibited intermediate activity, whilst compounds 2 and 3 had moderate activity. Compounds Comp-2, Comp-5, and 1 show moderate effectiveness against the Salmonella typhi bacterial strain, whilst Comp-5 and Comp-3 show intermediate action. The activity of all five drugs against Escherichia coli was moderate. When it comes to Streptococcus sp., all five of the title compounds exhibit intermediate activity.

Table 1 Antibacterial activity of the compounds

Compounds	Organisms	Zone of Inhibition (mm)			Ampicillin (1000 µg/mL)
		Sample Concentration (µg/mL)			
		1000	750	500	

Comp-1	*Salmonella typhi*	8	7	-	22
	Escherichia coli	7	7	7	21
	Staphylococcus aureus	8	8	7	25
	Streptococcus sp.	9	10	8	19
Comp-2	*Salmonella typhi*	9	8	7	15
	Escherichia coli	7	7	-	25
	Staphylococcus aureus	9	-	-	15
	Streptococcus sp.	8	7	7	20
Comp-3	*Salmonella typhi*	8	7	8	25
	Escherichia coli	9	7	8	27
	Staphylococcus aureus	10	8	7	15
	Streptococcus sp.	8	7	-	16
Comp-4	*Salmonella typhi*	9	7	-	15
	Escherichia coli	9	8	7	24
	Staphylococcus aureus	9	9	8	25
	Streptococcus sp.	8	7	-	15
Comp-5	*Salmonella typhi*	8	8	6	24
	Escherichia coli	9	7	-	23
	Staphylococcus aureus	9	7	9	25
	Streptococcus sp.	10	8	8	18

Antifungal Activity: Title compounds Comp-1, Comp-2, Comp-3, Comp-4, and Comp-5 were tested for antibacterial activity using the agar diffusion method on the SDA medium. The activity of the as-synthesised compounds was examined using amphotericin-B as the standard medication reference. While compound comp-1 had considerable effectiveness against the fungus strain Candida albicans, compounds comp-2, comp-3, comp-4, and comp-5 shown intermediate activity. Each of the five substances shown susceptibility to the Aspergillus niger bacterium.

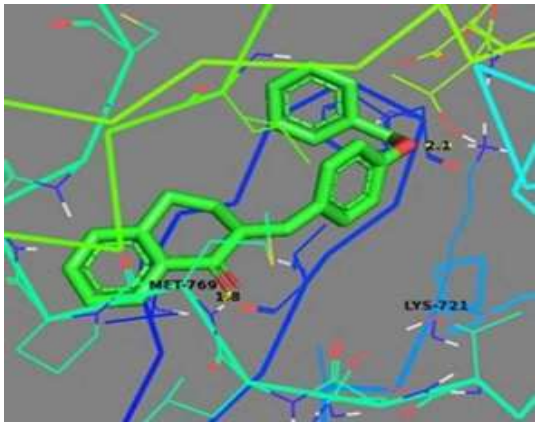
Table 2 Antifungal activity of the compounds

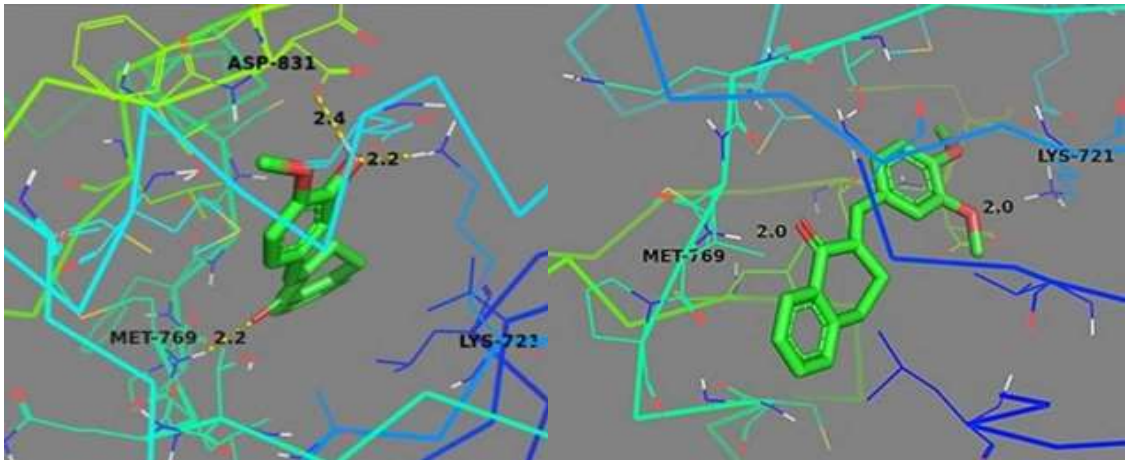
Compounds	**Organisms**	**Zone of Inhibition (mm)**			**Amphotericin-B (1000 µg/mL)**
		Sample Concentration (µg/mL)			
		1000	**750**	**500**	
Comp-1	*Candida albicans*	7	-	-	17
	Aspergillus niger	10	7	7	11
Comp-2	*Candida albicans*	10	9	8	15
	Aspergillus niger	9	8	8	13
Comp-3	*Candida albicans*	8	8	-	16
	Aspergillus niger	9	6	6	10
Comp-4	*Candida albicans*	11	7	6	14
	Aspergillus niger	9	8	6	13
Comp-5	*Candida albicans*	8	9	6	15
	Aspergillus niger	9	9	6	10

Molecular Docking Studies: Figure 2 displays the binding site interactions between the target protein with PDB ID: 1M17 and the ligands (small molecules). After ten attempts, the best fit interaction with the lowest binding energy was

discovered using AutoDock Tools 1. 5. 6. Table 3 provides the binding energy, D-H…A (donor-acceptor) distance, and binding site interactions values.

In-Silico Molecular Properties Prediction: Analysing whether the molecule complies with Lipinski's and Veber's guidelines allowed for the prediction of the compounds' drug-likeness and bioavailability. Good permeability across the cell membrane was suggested by the synthesised compounds' logP values, which were fewer than five. Since their molecular weights were less than 500, it was predicted that they would be easily transported, absorbed, and diffused. The range was well within the range of hydrogen bond donors (should be fewer than 10) and acceptors (should be less than 5). In the sphere of medicinal science, the five title compounds' biological activity and bioavailability guarantee drug-likeness and clarify their pharmacological nature.





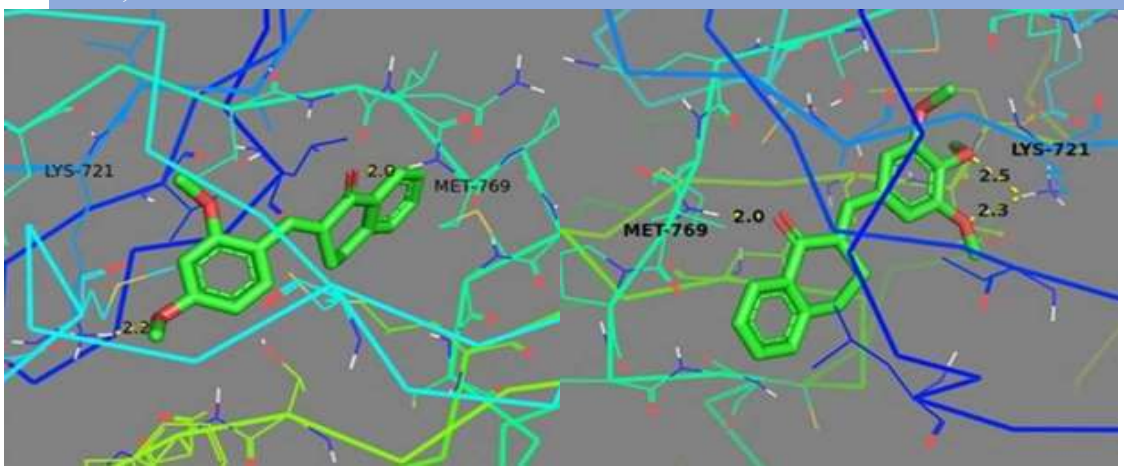


Fig. 2: Molecular docking of synthesized compounds

Table 3: Binding site interactions and binding energies

Ligand	Run number	Binding siteinteraction	D-H…A (Interaction Distance) Å	Bindingenergy kcal/mol
Comp-1	4	[Met-769]N-H...O [Lys-721]N-H…O	1.8 2.1	-9.00
Comp-2	4	[Met-769]N-H…O[Lys-721]N-H…O [Asp-831]O-H…O	2.2 2.2 2.4	-10.11
Comp-3	5	[Met-769] N-H…O [Lys-721]N-H…O	2.0 2.3	-10.96
Comp-4	3	[Met-769]N-H...O [Lys-721]N-H…O	2.0 2.2	-10.27
Comp-5	3	[Met-769] N-H…O [Lys-721]N-H…O	2.0 2.0	-10.57

Table 4: Drug likeness score

Compounds	miLogP	TPS	nAtoms	nON	nOH-NH	n-violation	rotb	volume
Comp-1	5.23	26.30	25	2	0	1	3	298.11
Comp-2	3.78	46.53	24	2	1	0	2	245.87
Comp-3	3.67	44.77	21	3	1	1	3	288.56
Comp-4	4.17	35.54	25	3	0	1	2	264.43
Comp-5	3.85	35.54	25	2	1	0	4	243.71

CONCLUSION

Molecular docking analysis, pharmacological, and biological activity results were compared and interpreted. When tested against Salmonella typhi, Escherichia coli, Staphylococcus aureus, and Streptococcus sp., the synthesised chalcone derivatives exhibited intermediate to moderate efficacy. The compounds demonstrated susceptible activity against Aspergillus niger, but only intermediate to moderate activity against Candida albicans, according to the antifungal activity study. The three synthesised drugs' in-silico pharmacokinetic examination revealed no infractions of Veber's and Lipinski's criteria. After more preclinical testing, the compounds under study—comp-2, comp-3, and comp-5 in

particular—may be viable lead molecules for the creation of safer and more effective antibacterial medications because they all exhibit a decent pharmacokinetic profile.

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