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As Potential Anti-microbial Agents, Design, Synthesis, Biological, and Docking Studies of Novel Coumarin Analogues

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The objective of the present work is to synthesize coumarin derived aldehydes and study their anti-bacterial in particular. Thus, an attempt has been made in this direction. As expected, coumarin derived aldehydes exhibited anti-bacterial activity in which some of the synthesized compound shown highly significant activity as compared to the standard employed for the study. synthesized are docked for binding affinity using PyRx software. The protein used for the docking are Staphylococcus aureus, Escheria coli. Among the synthesized docked compounds COU5, COU3, and COU6 had shown the more binding affinity against the standard. computational study of all synthesized compounds was performed to determine the surface area and other physicochemical properties in the direction of Lipinski's rules. The most active compounds COU1- COU6 follow all of Lipinski's rules. All the highest active derivatives have a number of hydrogen bonding acceptor groups ranging between 3 to 5, and nonhydrogen

bonding donors. Also, molecular weights range between 300 to 350 and log(P) values range between 0.00 to 2.41, and all these values agree with Lipinski's rules such as HB donor group, HB acceptor groups # 10, M. Wt < 500 and log(P) < 5. The compounds (COU1-COU6) synthesized are screened for antimicrobial activity using disc plate method at concentration 25, 50 and 100 µg/ml using Gram +ve and Gram –ve strains. The strains used for the screening are Staphylococcus aureus, Escheria coli. Among the synthesized screened compounds COU5 and COU6 had shown the potent activity against the standard compounds.

1. Introduction

Since Vogel isolated coumarin from the tonka bean (Dipteryxodorata) in 1820, coumarin has been studied. Coumarin (2H-1-benzopyran-2-one) is a chemical member of the lactone subgroup. These two compounds, which differ in having a carbonyl group at position 1 of the pyrone ring, are benzo-α-pyrone 1, also known as coumarin, and benzo-γ-pyrone 2, also known as chromone (Figure 1).

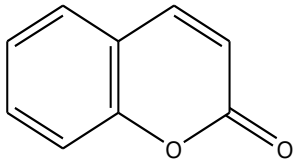


Figure 1: 2H-Chromen-2-one

The creation of novel medications for therapeutic purposes is significantly influenced by their characteristics and biological actions. When coumarin derivatives are extracted from plants, the process steps required to achieve the final product are expensive and time-consuming. However, coumarin derivatives can be obtained from a variety of raw materials using a variety of methods, albeit with significantly varied yields [1]. Coumarin compounds have attracted a lot of attention since the turn of the century, especially when it comes to the synthesis of their derivatives that have antibacterial properties. Single-mutation antibacterial medicines frequently cause bacterial resistance since they only target one enzyme. Medication that acts on numerous sites within an enzyme or on multiple enzymes at once that are crucial for the metabolism of vital microorganisms inhibits the growth of bacteria resistance.

The anti-inflammatory, anticoagulant, anticancer, antibacterial, and anti-neurodegenerative qualities of the coumarin moiety play a significant pharmacological and therapeutic function. Synthesis of heterocyclic compounds and their biological actions: Heterocyclic compounds of pharmacological significance are essential in the fight against diseases that impact plants, animals, and humans. They also uncover novel compounds that may have biological effects.

Although coumarin is widely dispersed in plants, it was initially discovered in tonka beans (Dipteryx odorata Wild) and has since been the subject of substantial research in the biochemical and pharmacological domains [1, 2]. Fruit plants have the largest concentrations

of coumarin, followed by leaves and roots. Rather than Aspergillus forms, certain key coumarin components have been obtained from microbial sources, such as coumermycin and novobiocin from aflatoxins and streptomyces. This lab synthesized a number of coumarin derivative chemicals and used both Gram-positive and Gram-negative bacteria to test their antibacterial properties. In this lab, a number of coumarin derivative compounds were synthesized, and two species of bacteria were used to test the compounds' antibacterial properties. Gram positive and Gram-negative A series of compounds of coumarin derivatives were prepared in this lab, and their antibacterial activity was investigated using two types of bacteria, Gram positive and Gram-negative [3].

The World Health Organization (WHO) has identified antimicrobial resistance as one of the main risks to world health today. Antibiotic resistance has been linked to both the overuse and abuse of these drugs as well as the pharmaceutical industry's inability to produce new drugs as a result of difficult regulatory requirements and diminished financial incentives [4]. Approximately 700 chemical structures of naturally occurring coumarins and their analogues are known from over 100 plant families. Remarkably, the number of core structures of coumarin derivatives keeps growing. The substantial biological significance and range of applications of the center core of coumarins have generated a great deal of research throughout the years.

Fused oxygen heterocycles of this kind have a variety of biological effects, including antiviral, antifungal, antibacterial, antihyperglycemic, anticoagulant, antihypertensive, antiadipogenic, anti-HIV, antibacterial, antimicrobial, and antioxidant properties. They are also linked to antitubercular, anti-inflammatory, anticancer, anticonvulsant, and neuroprotective qualities. The pharmaceutical industry makes extensive use of the coumarin heterocyclic ring system to construct different functional groups that are found in medication compounds. It has been demonstrated through extensive research that it is possible to artificially design and synthesize functionalized coumarin molecules from academia and industry with distinct heterocyclic structures and properties, as well as to isolate and purify biologically active coumarins that are naturally present in a variety of plants, animals, and microbes [5].

The Coumarin belongs to the class of significant organic compounds. Additionally, there are other ways to refer to the food additives, colors, and cosmetics. In the medical field, coumarin derivatives have been used to treat HIV, loosen muscles, lower blood pressure, and influence the liver, among many other conditions. The Pechman reaction, which produces a variety of coumarin derivatives by condensation of a phenol or products with a beta keto ester with sulfuric acid, is one industrial technique of synthesizing coumarin [6]. These are the highly dispersed secondary metabolites found in plants, with a bicyclic structure with lactone carbonyl groups and an aromatic character. As the primary phytochemicals, coumarins are a significant class of phenolic compounds that also contribute to the distinct flavor of food. These phenolic compounds have strong antibacterial, antithrombotic, anticoagulant, fungal, antioxidant, growth regulator, and hepatoprotective properties in addition to their strong effect against gram negative bacteria. Chemically, the sesquiterpene fragment consists of a carbonyl group, an alpha pyrone containing a double bond, and a benzene ring [7].

Numerous techniques, such as the Perkin reaction, Knoevenagel condensation, Pechmann condensation, Wittig reaction, Baylis–Hillman reaction, Claisen rearrangement, Vilsmeier–

Haack and Suzuki cross-coupling processes, can be used to manufacture coumarins. Their synthesis has been accomplished using a variety of techniques, each utilizing a unique combination of reactants and starting elements [8]. (Figure 2).

The five-membered furan ring that makes up furanocoumarins is joined to the coumarin nucleus and can be classified as linear or angular depending on whether substituents are inserted at one or both of the remaining benzoid positions [9]. Their conjugated double ring structure makes them intriguing compounds for several kinds of studies. Coumarins are used as food additives, in cosmetics and perfumes, and most notably in the pharmaceutical business, where they are synthesized into a wide range of synthetic medicinal drugs [10].

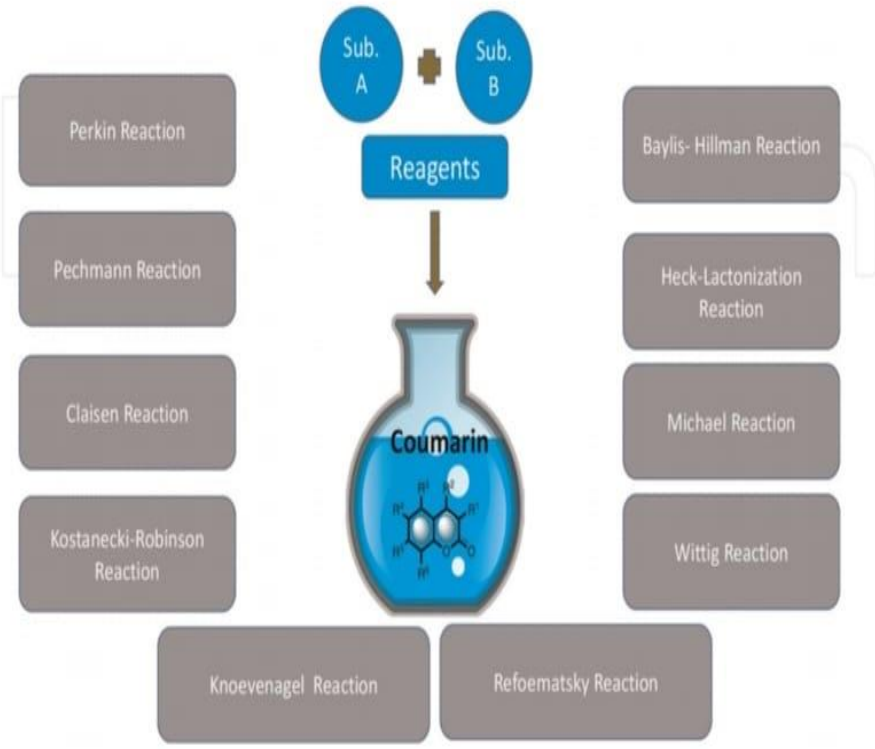


Figure 2: Types of reaction of Coumarin derivatives

2. Materials and Methods

During the synthesis procedure, analytical and laboratory-grade solvents and reagents were employed. Chemicals were cleaned and dried according to protocols. The purity of the products was assessed and the reactions were tracked using TLC analysis. For thin-layer analytical chromatography, we used 60-F 254 (0.5mm) MERCK aluminium back pre-coated silica gel plates. The final synthesis was performed using the Carousel Radleys Parallel Organic Synthesizer. The Schimadzhu UV-visible spectrometer was used to measure the

absorbance of various chemicals [11].

2.1. Molecular docking:

PyRx 0.8 was used to perform the docking research. PyRx is a Python-based programming language that runs on almost any contemporary machine, from personal computers to supercomputers. PyRx has been used to determine the binding affinity of a ligand to a protein in order to facilitate molecular docking. PyRx, a structure-based docking program, was used to screen all 152 secondary metabolites for IL-6 (PDB: 2AS9 and 2EA9) at a resolution of 1.90. Additionally, ligands for energy reduction interact in good ways. The MMFF94 force field performed the minimization in 200 steps with an RMS gradient of 0.1. Following the devaluation, the ligands were transferred to PDBQT format. First, we had chosen the macromolecule that will define the produced protein's binding site. Next, the active docking site was constructed utilizing bound ligand binding locations. Then, virtual screening was performed on a molecular window, with all produced ligands interacting with the specified active site. All ligands were categorized according to their binding affinity as determined by the PyRx score [12, 13]. Following that, the ligands were classified according to their binding energy levels. The top scorer quercetin was converted into imines, oximes, and hydrazides. The docking analysis for these analogues was then re-evaluated and re-constructed by the binding energy estimations [14].

2.2. ADME and Toxicity prediction:

Using the SwissADME tool, ADME properties were estimated, and toxicity properties were calculated using the online bioinformatics tool PreADMET. ADMET studies were conducted for designed metal complexes, such as their aqueous solubility, blood-brain barrier (BBB), plasma protein binding (PPB), hepatotoxicity, and polar surface area, cytochrome P450, CYP2D6 inhibition, human gut absorbance, rodent carcinogenicity, Ames mutagenicity and toxicology potential development. A logP value that indicates lipophilicity in a molecule is the partition coefficient value in an octanol/water system. LogP is an important metric that reflects the impact on bioavailability, distribution, volume clearance, the permeability of the membrane. Diverse tissues have been investigated in this study with the expectations and significant characteristics of the compounds as mutagenicity and toxicity. The PreADMET serve has predicted pharmacologically relevant properties [15].

2.3. Molinsipiration:

This drug-likeness study of the selected ligand (CID: 155903259) and the reference ligand (CID: 6483648) were carried out using the online software “Molinsipiration Cheminformatics” (https://www.molinspiration.com/). In this software, only SMILES of ligands were required for the preparation; no knowledge of the active site or binding mechanism was necessary [16].

Synthesis 2-phenyl-1H-benzimidazol-5-ol

0.01 moles of phenylene diamine and 0.01 mole Benzaldehyde are taken in round bottom flask; to this added phosphoric acid is used as catalyst and refluxed for one hour at 80°C. After completion of reflux, mixture was added in to ice container. The solid mass that separated out was filtered, and recrystallized from ethanol (Figure 3).

2.4. Synthetic Scheme:

Synthesis of 8-methyl-phenylechromeno [6,7-d] imidazole-6(1H)-one

To a mixture of 2-phenyl-1H-benzimidazole -5-ol [0.01 mole, and to this added ethyl aceto acetate [0.01 mole] in the concentration sulphuric acid entire mixture was refluxed for one hour at 80c. after completion of reflux poured in to ice container. The solid mass that separated out was filtered, washed with water and recrystallized from ethanol. The list of synthesized compounds was shown in Table 1.

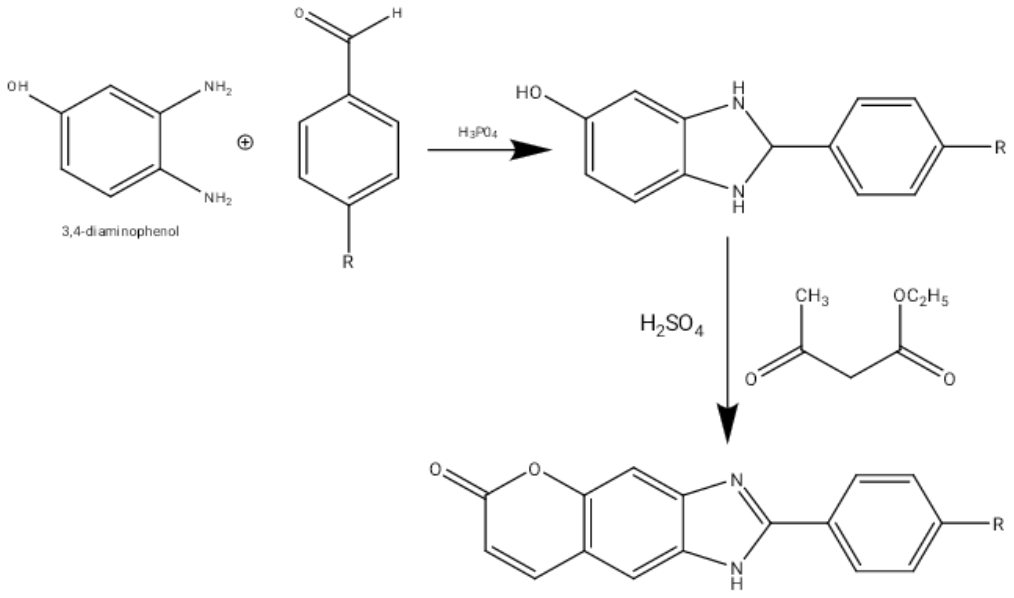
3. Antimicrobial Evaluation

Requirement:

Mueller Hinton broth, Agar, Conical flask, Petri dish, Distilled water

Procedure:

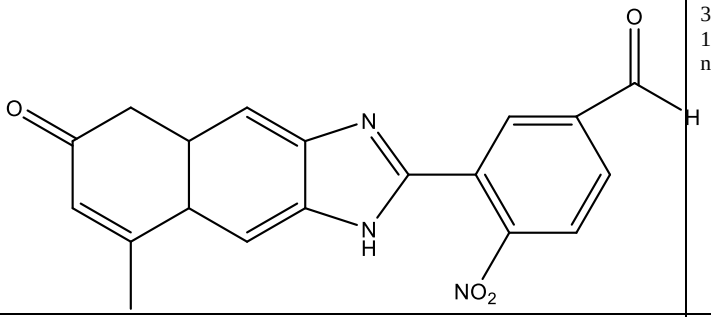
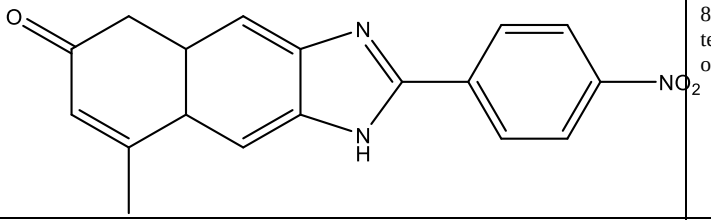
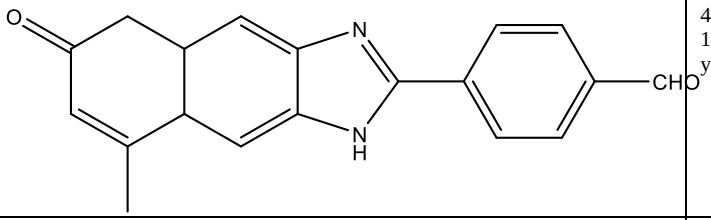
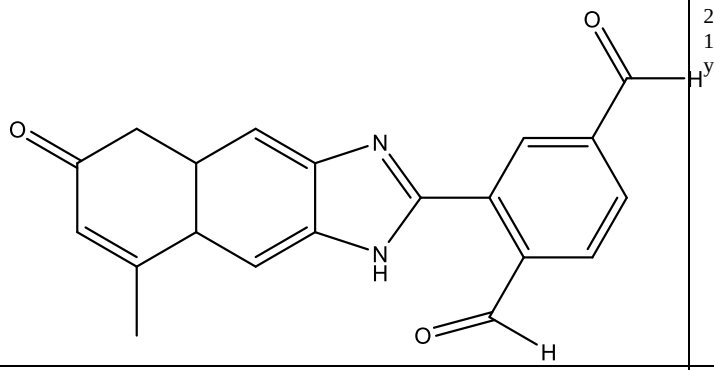
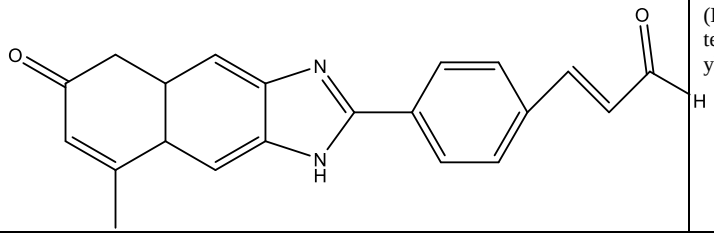
The antibacterial activity of newly synthesized Coumarins was conducted against Gram positive bacteria i.e. Staphylococcus aureus and Gram-negative bacteria i.e. Escherichia coli by using cup plate method. Tetracycline was employed as reference standard to compare the results. Mueller Hinton broth was used for the preparation of inoculation of the bacteria and agar was used for the screening methods. All the compounds were tested at a concentration of 25 µg, 50 µg and 100 µg level. After the inoculation the Petri dish were subsequently incubated at 37±10C for 24 hours. After incubation, the diameter of zone of inhibition surrounding each of the cups was measured [17, 18].

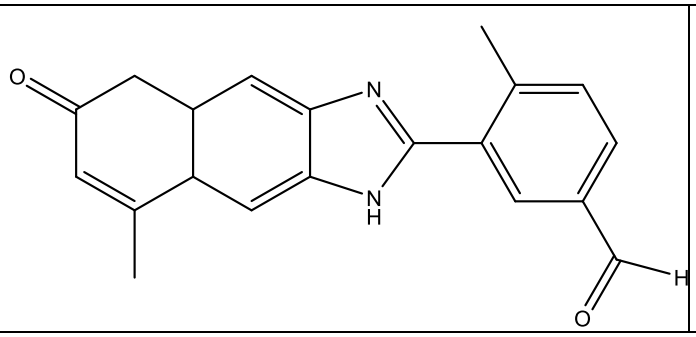


Reaction conditions: o-phenylediame, Aldehydes, Phosphoric acid, Sulphuric acid, Ethyl aceto acetate, Reflux for 2 hr at 80

Figure 3: Synthetic scheme

Table 1: List of synthesized compounds

Compounds	Chemical Structures	IUPAC
COU1		3-(8-methyl-oxo-4a,5,6,8a-tetrahydro-1H-naptho[2,3-d]imidazol-2-yl)-4-nitrobenzaldehyde
COU2		8-methyl-2-(4-nitrophenyl)-1,4a,5,8a-tetrahydro-6H-naptho[2,3-d]imidazol-6-one
COU3		4-(8-methyl-6-oxo-4a,5,6,8a-tetrahydro-1H-naptho[2,3-d]imidazol-2-yl)benzaldehyde
COU4		2-(8-methyl-6-oxo-4a,5,6,8a-tetrahydro-1H-naptho[2,3-d]imidazol-2-yl)terephthaldehyde
COU5		(E)-3-(4-(8-methyl-6-oxo-4a,5,6,8a-tetrahydro-1H-naptho[2,3-d]imidazol-2-yl)phenyl)acrylaldehyde

COU6		4-methyl-3-(8-methyl-6-oxo-4a,5,6,8a-tetrahydro-1H-naptho[2,3-d]imidazol-2-yl)benzaldehyde

4. Results and Discussion:

Compounds (COU1-COU6) synthesized are docked for binding affinity using PyRx software.

The protein used for the docking are Staphylococcus aureus, Escheria coli. Among the synthesized docked compounds COU5, COU3, and COU6 had shown the more binding affinity against the standard. which shown in Table 2. The three-dimensional structure of COU1 to COU6 (PDB: 2AS9E.coli and 2EA9 S. aureus) was used in the study. Prior to docking active site amino acid residues were identified. The following amino acids viz., LEU A:34 , ILE A:62 , TYR A:36 , HOH A:153 , PHE A:59 , HIS A:35 , ASP A:56 , PRO A:60 , SER A:64 , GLU A:67 , CYS A:52 , LYS A:46 , HOH A:118 , HOH A:153 , GLY A:186 , SER A:158 , ASN A:157 , MET A:1 , are present in the catalytic pocket of the protein molecule, as shown in (Figure 4).

Table 2: Docking results of synthesized compounds

S. No	Compound	Binding Affinity (2as9) E. Coli	Binding Affinity (2ea9) S. Aureus
1	COU1	7.9	7.4
2	COU2	7.8	7.1
3	COU3	8.0	7.8
4	COU4	7.8	6.8
5	COU5	8.3	7.2
6	COU6	7.9	7.1
7	Ciprofloxacin	6.9	6.1
8	Tetracycline	7.4	6.5

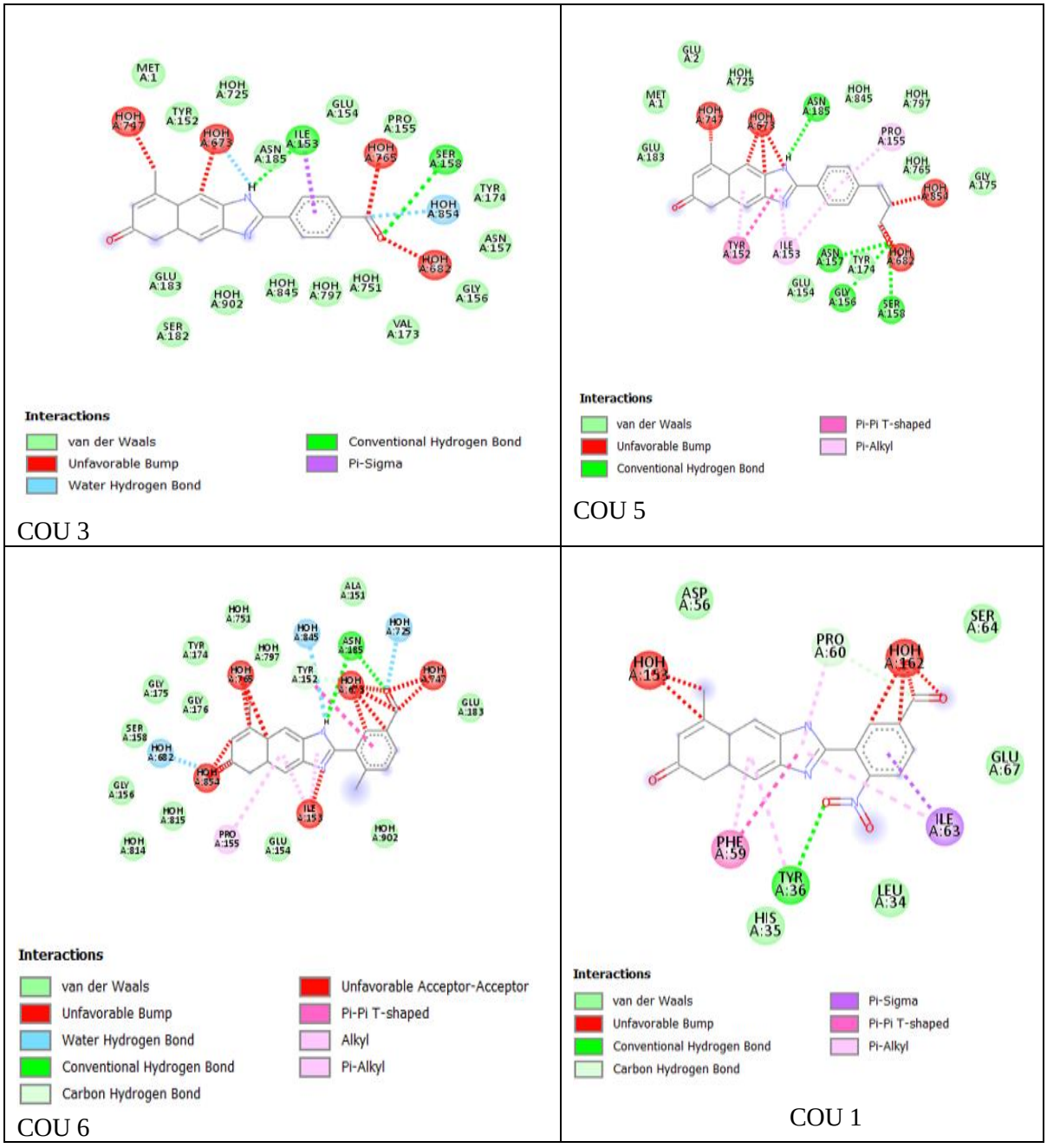


Figure 4: 2D interactions of synthesized compounds

Swiss ADME:

In this study, a computational study of all synthesized compounds was performed to determine the surface area and other physicochemical properties in the direction of Lipinski's rules (Tables 3, 4 and 5). The most active compounds COU1- COU6 follow all of Lipinski's rules.

All the highest active derivatives have a number of hydrogen bonding acceptor groups ranging between 3 to 5, and nonhydrogen bonding donors. Also, molecular weights range between 300 to 350 and log(P) values range between 0.00 to 2.41, and all these values agree with Lipinski's rules such as HB donor group, HB acceptor groups # 10, M. Wt < 500 and log(P) < 5.

Table 3: Physical Properties of synthesized compounds

Formula	Molecular weight (g/mol)	No. of Heavy atoms	No. of Aromatic Heavy atoms	Fraction CSp3	No. of rotatable bonds	No. of H-bond acceptors	No. of H-bond Donors	Molecular refractivity	TPSA
C19H15N304	349.34	26	11	0.21	3	5	1	97.67	105.04Å²
C18H15N3O3	321.33	24	11	0.22	2	4	1	92.29	91.57Å²
C19H16N202	304.34	23	11	0.21	2	3	1	88.85	62.82Å²
C20H16N203	332.35	25	11	0.20	3	4	1	94.24	79.89Å²
C21H18N202	330.38	25	11	0.19	3	3	1	98.56	62.82Å²
C20H18N202	318.37	24	11	0.25	2	3	1	93.82	0282Å²

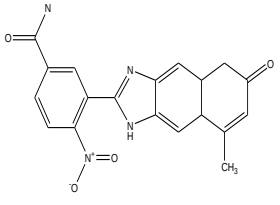
Table 4: Drug likeness properties of synthesized compounds

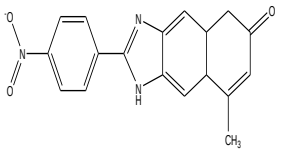
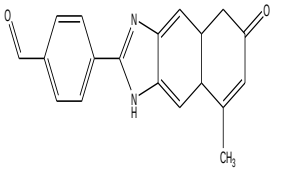
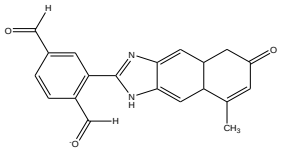
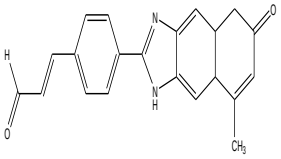
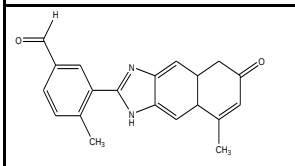
Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
Yes	yes	yes	yes	Yes	0.55
Yes	yes	yes	yes	Yes	0.55
Yes	yes	yes	yes	Yes	0.55
Yes	yes	yes	yes	Yes	0.55
Yes	yes	yes	yes	Yes	0.55
Yes	yes	yes	yes	Yes	0.55
Yes	yes	yes	yes	Yes	0.55
Yes	yes	yes	yes	Yes	0.55

Table 5: Lipophilicity properties of synthesized compounds

Log Po/w (ILogP)	Log Po/w (X LogP3)	Log Po/w (W LogP)	Log Po/w (M LogP)	Log Po/w (silicos-IT)
1.35	0.96	1.52	0.88	1.74
1.91	1.50	1.71	1.52	1.53
2.12	1.13	1.62	1.84	3.92
1.77	0.60	1.43	1.17	4.12
2.40	1.56	1.91	2.22	4.51
2.41	1.50	1.92	2.07	4.43

Table 6: Molinsipiration results of synthesized compounds

STRUCTURE	**miLogP**	**TPA**	**NATOMS**	**MW**	**nON**	**nOHNH**	**n-viol**	**nrotb**	**Volume**
	2.97	108.65	26	349.35	7	1	0	3	297.75

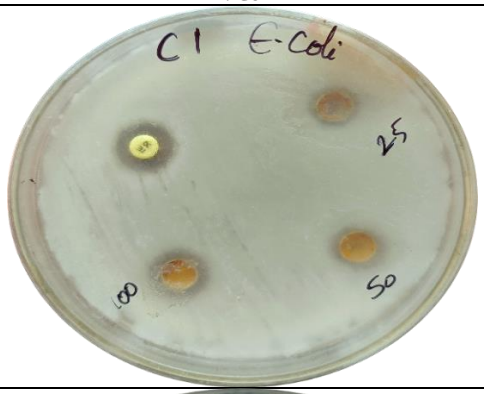
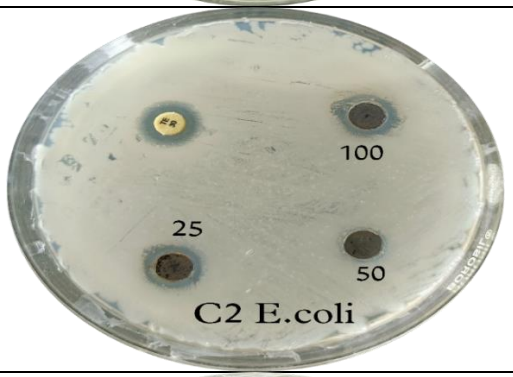
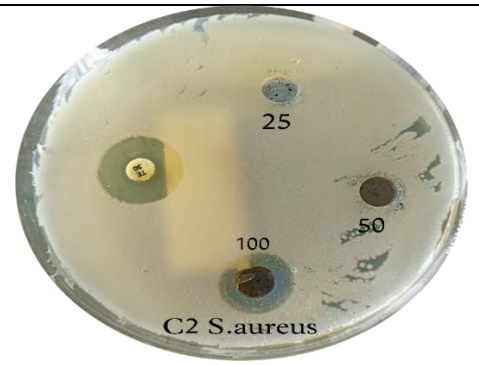
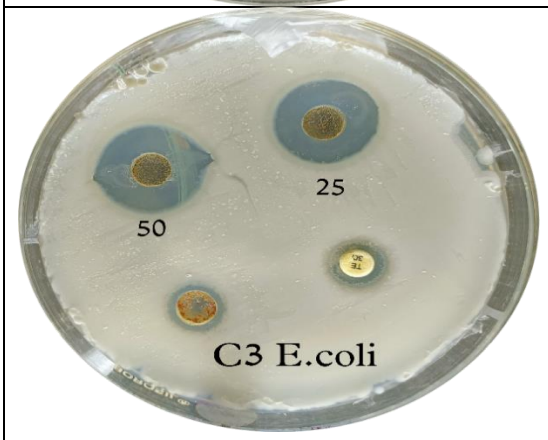
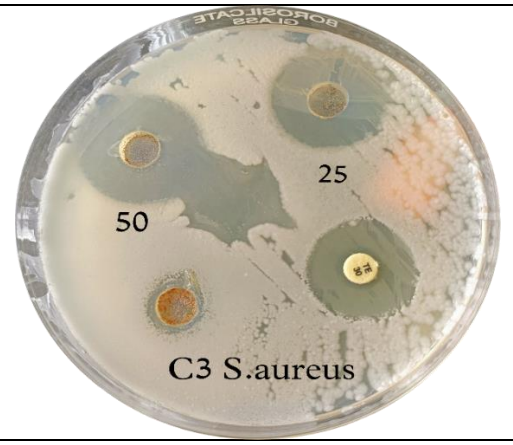
	3.25	91.58	24	321.34	6	1	0	2	278.77
	3.08	62.83	23	304.35	4	1	0	2	274.42
	2.80	79.90	25	332.36	5	1	0	3	293.40
	3.84	62.83	25	330.39	4	1	0	3	301.83
	3.46	62.83	24	318.38	4	1	0	2	290.98

computational study of all synthesized compounds was performed to determine the surface area , logP value , number of atoms . All the highest active derivatives have a number of non-hydrogen bonding acceptor groups 1. molecular weights range between 300 to 350 and log(P) values range between 2.80 to 3.84 ,M. Wt < 500 and log(P) < 5 (Table 6).

5. Antimicrobial Evaluation:

Compounds (COU1-COU6) synthesized are screened for antimicrobial activity using cup plate method at concentration 25, 50 and 100 µg/ml using Gram +ve and Gram –ve strains. The strains used for the screening are Staphylococcus aureus, Escheria coli. Among the synthesized screened compounds COU5 and COU6 had shown the potent activity against the standard. Compounds COU1, COU2, COU3 had shown the moderate activity while compound. COU4 had shown the no activity (Table 7, 8).

Table 7: Minimum Inhibitory concentrations of the synthesized compounds

E. Coli	S. aureus
	
	
	

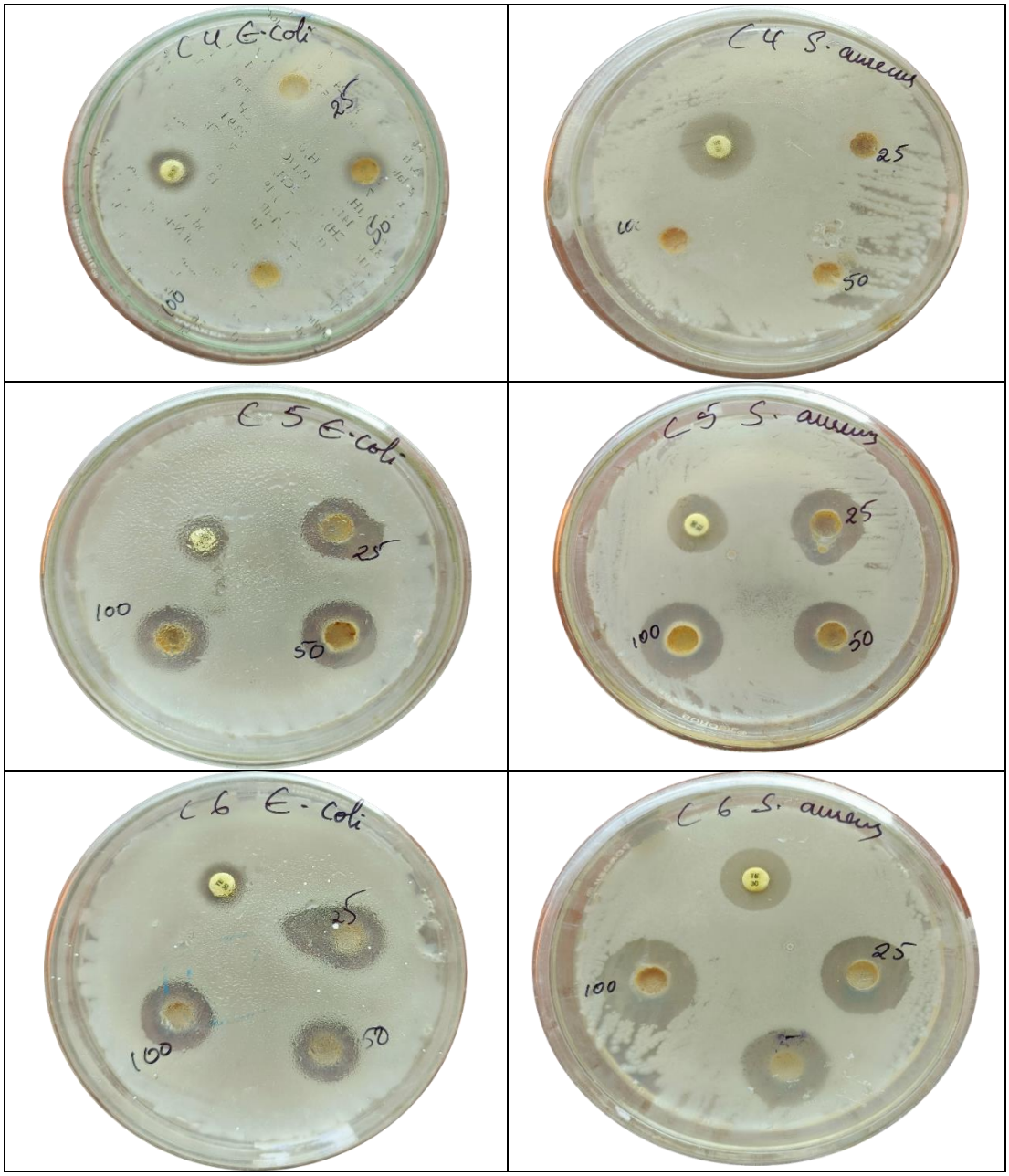


Table 8: Zone of Inhibition of Synthesized Compounds

Compound	Std. (Tetracycline)	(+) Zone of inhibition (S. Aureus)			(-) Zone of inhibition (E. coli)		
		25mg	50mg	100mg	25mg	50mg	100mg
COU1	1(-)	-	-	-	0.5cm	0.5cm	1cm
COU2	1(-)/1.5(+)	-	-	1cm	0.5cm	0.5cm	0.5cm

COU3	1(-)/1.5(+)	2cm	2cm		1.5cm	1.7cm	
COU4							
COU5	0.5(-)/1(+)	1.5cm	1.6cm	1.7cm	1cm	1.5cm	1.5cm
COU6	0.5(-)/1(+)	1.8cm	1.9cm	2cm	1.1cm	1cm	1.5cm

6. Conclusion:

The current work aims to manufacture aldehydes derived from coumarins and investigate their antibacterial properties specifically. Consequently, an effort has been made in this regard. Aldehydes produced from coumarins had antibacterial action as predicted; among the synthesized compounds, some demonstrated significantly more activity than the standard used in the investigation. Out of all the compounds, COU5 and COU6 exhibited noteworthy activity.

Using Pyrx software, compounds (COU1–COU6) are synthesized and docked for binding affinity. Escheria coli and Staphylococcus aureus proteins were utilized for the docking. COU5, COU3, and COU6 were the generated docked compounds that exhibited the highest binding affinity against the standard. The work made use of the three-dimensional structures of COU1 through COU6 (PDB: 2AS9E. coli and 2EA9 S. aureus). Amino acid residues were found prior to active site docking. The following amino acids are as follows: ASP A:56, PRO A:60, CYS A:52, LYS A:46, GLU A:67, ASP A:34, ILE A:62, TYR A:36, HOH A:153, PHE A:59, HIS A:35, MET A:158, SER A:64, and GLU A:67 is present in the catalytic pocket of the protein molecule.

Conflict of Interest: Authors are declared there is no conflict of interest.

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