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Synthesis and characterization of schiff base-coumarin hybrid

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Abstract:

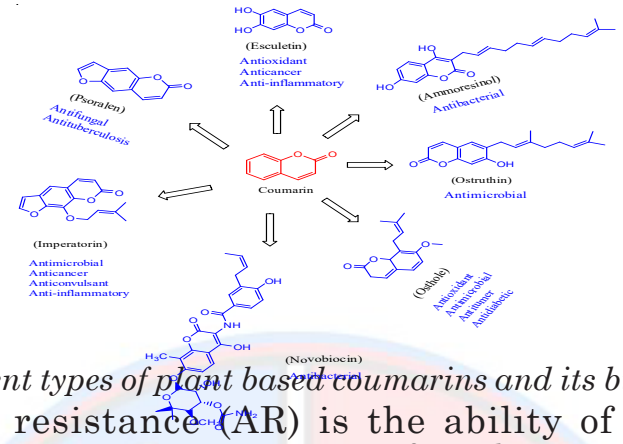
Identifying promising pharmaceutical compounds is challenging, but computational techniques have revolutionized early drug discovery by enabling efficient screening using criteria like Lipinski's Rule of Five. This approach saves time and resources in selecting potential drug candidates. A series of novel Schiff base-coumarin derivatives was designed using *in silico* methods and subsequently synthesized as potential antimicrobial agents. The synthesized compounds were evaluated for their antibacterial and antifungal activities. *In silico* analysis confirmed that all the compounds comply with Lipinski's Rule of Five, indicating favorable drug-like properties.

Keywords: Lipinski's Rule of Five, novel Schiff base-coumarin, silico methods, antimicrobial agents.

Introduction:

Coumarin and its derivatives has been extensively used as scaffold in the synthesis of new heterocyclic derivatives. Coumarin found extensively in nature specially in the tonka bean (*Dipteryx odorata*) also in sweet woodruff (*Galium odoratum*), vanilla grass *(Anthoxanthum odoratum)* and in others. Coumarin and its derivatives shows very crucial role in pharmaceuticals and synthetic dyes. Waffrin derived from sweet clover (*Melilotus officinalis and Melilotus alba*) used as anticoagulants

which overspread in *penicilliun* sp. Novobiocin derived from *Streptomyces* sp, used as an antimicrobial agents. Calanolide derived from *Callophylum lanigerum* tree was used as transcriptase inhibitor against HIV[1-10].



Some diffrent types of plant based coumarins and its biological activity

Antimicrobial resistance (AR) is the ability of bacteria to resist antibiotics they were once sensitive to, often due to overuse and misuse. It poses a major global health threat, driven by environmental antibiotic residues and the spread of resistance genes. The rapid rise of microbial resistance has driven the search for new, effective antimicrobial agents to reduce bacterial mortality. Research efforts focus on developing potent antibacterial scaffolds and addressing emerging pathogenic bacteria[11-18]. Among various biological targets investigated, protein synthesis has emerged as one of the most promising for the development of next-generation antimicrobial drugs [19–23]. Despite significant advances in antibacterial therapy and the development of inhibitors targeting drug-resistant Gram-positive and Gram-negative bacterial strains, there remains a critical need for new drugs or therapeutic regimens that offer high safety profiles to effectively combat antimicrobial resistance [24]. Likewise, life-threatening infections caused by pathogenic fungi continue to pose a serious challenge, particularly among immune compromised individuals. Although fungal infections are common current treatment options are limited, underscoring the urgent need for the development of novel antifungal agents [25,26].

Schiff bases are a class of organic compounds characterized by the presence of an imine group (–C=N–), typically formed by the condensation of a primary amine with an aldehyde or ketone. Their reactivity is largely attributed to the electrophilic nature of the carbon atom in the imine group, making them susceptible to nucleophilic attack. They can undergo hydrolysis in aqueous or acidic environments to regenerate the parent amine and carbonyl compound. Additionally, Schiff bases are known for their strong ability to coordinate with transition metals through the nitrogen atom, forming stable metal complexes that further enhance their chemical and biological versatility. Biologically, Schiff bases exhibit a wide range of activities. They possess antimicrobial, antifungal, and antiviral properties by interfering with microbial cell processes. Many Schiff bases also show significant antioxidant and anti-inflammatory effects, often through scavenging free

radicals or inhibiting enzymes involved in inflammatory pathways. Moreover, their metal complexes, particularly with copper, nickel, and platinum, have demonstrated anticancer properties by interacting with cellular DNA and inhibiting tumor growth. These diverse biological activities make Schiff bases valuable in medicinal and pharmaceutical chemistry[27,28]. Schiff bases related to 2H-chromene (a chromene derivative with a fused benzopyran ring) are highly reactive due to the presence of both the imine group (–C=N–) and the electron-rich chromene ring**,** which enhances conjugation and electron delocalization. This structural feature increases the compound's ability to undergo nucleophilic attack, coordinate with metal ions, and participate in redox reactions. Biologically, Schiff base derivatives of 2H-chromene show strong antimicrobial, anticancer, anti-inflammatory, and antioxidant activities. Their ability to bind to biomolecules and interfere with cellular pathways makes them promising candidates for drug development[29.30,31……36].

Our study employed a range of in silico techniques to evaluate the physicochemical and pharmaceutical properties of the designed molecules, with the collected data compiled for detailed analysis. Antibacterial activity was assessed by determining the *Minimum Inhibitory Concentration (MIC)* of the synthesized compounds, and a combination method was used to calculate the *Fractional Inhibitory Concentration (FIC)*, allowing investigation of potential synergistic effects between the compounds and standard drugs, which could inform future therapeutic strategies against pathogenic bacteria. Antifungal activity was similarly evaluated using both the *zone of inhibition* assay and the *serial broth micro-dilution* method [37…..41].

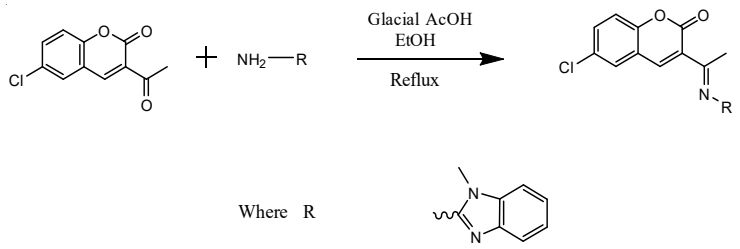
Experimental:

Using Molinspiration and Chem Draw software, some physically significant descriptors and pharmaceutically relevant properties of compounds, like molecular weight, H-bond donors, H-bond acceptors, log P, rotatable bonds and TPSA have been analyze and on the basis of Lipinski's rule of five .ADME properties like aqueous solubility(LogS), skin permeability (Log Kp), synthetic accessibility scores and Absorption (%ABS) were calculate dusing DS2.5 software.

Chemistry:

All the reagents and chemicals were purchased from Sigma Aldrick chemical company USA and E. Merck India Ltd. India. For the synthesis of coumarin derivatives 3-acetyl-6-chloro-2H-chromen-2-one and different types of artomatic amines have been used in the ratio of (1:1) in ethanol (30 ml) containing few drops of glacial acitic acid and then mixture was heat at 40°-50° C..Reaction process was checked by TLC. After the completion of the reaction, the reaction mixture was cooled at room temperature, concentrated, poured into ice-cold water, and basified with 2M NaOH (pH 10) resulting in the formation of a precipitate. The precipitate was filtered, washed with water, and dried over CaCl2 in the vacuum chamber to obtain the crude product. The product was then purified by column chromatography and finally crystallized using ethanol. The characterization was done by ^{1}H NMR, mass spectra and

elemental analysis techniques.



(E)-6-chloro-3-(1-((1,6-dimethyl-1H-imidazo[4,5-b]pyridin-2-yl)imino)ethyl)-2H chromen-2-one

(E)-6-chloro-3-(1-((1,6-dimethyl-1H-imidazo[4,5-b]pyridin-2-yl)imino)ethyl)-2H chromen-2-one

White color solid, M.P. 176-180 °C. ^{1}H NMR: δ 2.17 (3H, s), 2.34 (3H, s), 4.02 (3H, s), 7.41-7.67 (3H, 7.47 (dd, J = 8.2, 0.4 Hz), 7.56 (dd, J = 1.6, 0.4 Hz), 7.61 (dd, J = 8.2, 1.6 Hz)), 8.11 (1H, d, J = 1.7 Hz), 8.50-8.67 (2H, 8.55 (s), 8.62 (d, J = 1.7 Hz)). ^{13}C NMR: δ 18.4 (1C, s), 24.6 (1C, s), 32.9 (1C, s), 114.8 (1C, s), 116.0 (1C, s), 117.5 (1C, s), 119.5 (1C, s), 120.4 (1C, s), 130.4 (1C, s), 133.1 (1C, s), 133.5 (1C, s), 139.9 (1C, s), 144.6 (1C, s), 147.3 (1C, s), 151.1 (1C, s), 154.4 (1C, s), 159.1 (1C, s), 160.8 (1C, s), 164.4 (1C, s).

Result and discussion

A Schiff base derivative of 3-acetyl coumarin was evaluated as a potential antimicrobial agent using an in silico structure-based approach. The physicochemical properties of this compound were calculated using Molinspiration and ChemDraw software tools, and were compared to standard antimicrobial agents such as chloramphenicol, cycloheximide, nevirapine, and fluconazole.

Conclusion:

The Schiff base derivative of 3-acetyl coumarin demonstrated a promising drug-likeness profile, satisfying the criteria for oral bioavailability, cell permeability, and pharmacokinetic compatibility, making it a strong candidate for further antimicrobial studies.

Author's Declaration:

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