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DESIGN, SYNTHESIS AND CHARACTERIZATION OF N-PHENYLPYRAZOLINE AND 3, 4-DIHYDROPYRIMIDINE FROM CHALCONE DERIVATIVES AND STUDY THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT:-

Chalcone derivatives are considered valuable species because they possess a ketoethylenic moiety, CO-CH=CH-. Due to the presence of a reactive a,ß-unsaturated carbonyl group, chalcones and their derivatives possess a wide spectrum of antiproliferative, antifungal, antibacterial, antiviral, antileishmanial, and antimalarial pharmacological properties. Recent developments in heterocyclic chemistry have led to the synthesis of chalcone derivatives, which had been biologically investigated toward certain disease targets. Pyrazolines are N- heterocyclic compounds that exhibit a wide range of pharmaceutical activities and are synthesized from chalcone with enhanced biological activity.

The present study summarizes the chemistry of various chalcone-based pyrazolines and their derivatives. This study focuses on the synthesis, characterization, and biological evaluation of N-phenylpyrazoline and dihydropyrimidine derivatives, starting from readily available chalcone precursors.The biological activity of this derivatives is determined by membrane stabilization assay. .The anticancer activity of phenylpyrazoline was determined. The characterization of N-phenylpyrazoline and 3,4- Dihydropyrimidine was done by the spectral analysis such as IR , NMR,Mass spectroscopy.

INTRODUCTION

Chalcones and their derivatives have garnered significant interest in the field of medicinal chemistry due to their diverse biological activities and relatively simple chemical structure, which allows for facile modification and synthesis of a broad range of analogs. Structurally, chalcones are open-chain flavonoids

containing a central ketoethylenic moiety (–CO–CH=CH–) that plays a pivotal role in their biological activity. This α,β-unsaturated carbonyl system is not only reactive but also acts as a key pharmacophore in interacting with various biological targets, leading to a wide array of therapeutic properties [1,2].

Over the past few decades, considerable efforts have been directed toward the exploration of chalcone-based compounds for their pharmacological potential. Numerous studies have reported their anticancer, anti-inflammatory, antimicrobial, antiviral, antimalarial, and antileishmanial activities [3,4]. These therapeutic effects stem from the chalcone's ability to modulate various molecular pathways, including inhibition of enzymes, interference with signal transduction, and disruption of cell membrane integrity [5]. Given these promising activities, chalcones serve as crucial intermediates in the design and development of novel therapeutic agents [6].

The versatility of the chalcone scaffold lies in its ease of derivatization. By introducing different substituents on the aromatic rings or modifying the core structure through cyclization reactions, a variety of heterocyclic systems can be synthesized, many of which exhibit improved pharmacokinetic and pharmacodynamic properties [7]. Among these heterocyclic derivatives, pyrazolines have received substantial attention.

Pyrazolines are five-membered N-heterocyclic compounds that are typically synthesized via cyclization of chalcones with hydrazine or its derivatives [8]. These molecules are known for their diverse biological activities, including analgesic, anti-inflammatory, antidepressant, anticonvulsant, antimicrobial, antitumor, and insecticidal properties [9,10]. The presence of a nitrogen-rich ring enhances their ability to form hydrogen bonds and engage in π-π interactions with biological targets, making them potent candidates for drug development. The transformation of chalcones into pyrazolines often leads to enhanced bioactivity, reduced toxicity, and improved solubility, making this conversion an attractive strategy in drug discovery programs [11].

One of the most widely studied derivatives of pyrazoline is N-phenylpyrazoline, which incorporates a phenyl group on the nitrogen atom of the pyrazoline ring. This modification significantly influences the molecule's physicochemical properties and biological activity. Several reports suggest that N-phenylpyrazolines exhibit strong anticancer activity by inducing apoptosis, arresting cell cycle progression, and inhibiting the proliferation of cancerous cells [12]. Their ability to interact with DNA and enzymes such as topoisomerases has been demonstrated, which underscores their potential as anticancer therapeutics [13].

Another important class of compounds synthesized from chalcones are dihydropyrimidines, particularly 3,4-dihydropyrimidine derivatives. These compounds belong to a group known as Biginelli compounds, typically synthesized through a multicomponent reaction involving a β-keto ester, an aldehyde, and urea or thiourea [14]. However, chalcone-derived strategies have also emerged as useful alternatives [15]. Dihydropyrimidines display a wide array of biological activities, including calcium channel blocking, anti-inflammatory, antihypertensive, antiviral, and anticancer properties [16]. Their diverse functionality and pharmacological potential have made them a focal point in heterocyclic drug design.

In the present study, efforts are directed toward the synthesis, structural characterization, and biological evaluation of N-phenylpyrazoline and 3,4-dihydropyrimidine derivatives, utilizing readily available chalcone intermediates. The synthetic route involves the initial formation of chalcones via Claisen-Schmidt

condensation, followed by the reaction with phenylhydrazine to afford N-phenylpyrazoline, and further derivatization to yield dihydropyrimidine analogs [17].

The synthesized compounds are characterized by various spectroscopic techniques such as Infrared Spectroscopy (IR), Nuclear Magnetic Resonance (NMR), and Mass Spectrometry (MS). IR spectroscopy is employed to identify functional groups and confirm the presence of key bonds, such as C=O, C=N, and N-H. NMR, particularly ^1H and ^13C NMR, provides detailed information on the hydrogen and carbon framework of the molecules, confirming ring formation and substitution patterns [18]. Mass spectrometry further aids in confirming the molecular weight and the structural integrity of the synthesized compounds [19].

To assess the therapeutic potential of these synthesized derivatives, biological evaluations were conducted. The membrane stabilization assay was used to determine the anti-inflammatory activity of the compounds. This assay is based on the principle that compounds which prevent or reduce hemolysis of red blood cells under stress conditions may possess potential anti-inflammatory effects, as the erythrocyte membrane is analogous to the lysosomal membrane [20]. Stabilization of these membranes is indicative of potential to prevent the release of lysosomal constituents of activated neutrophils, which contribute to inflammatory responses [21].

In addition, the anticancer potential of N-phenylpyrazoline was evaluated, possibly using standard in vitro assays such as MTT, SRB, or flow cytometry-based apoptosis detection [22]. Preliminary results suggest that N-phenylpyrazoline exhibits significant cytotoxicity against selected cancer cell lines, warranting further investigation into its mechanism of action and therapeutic potential [23].

The integration of chalcone chemistry with heterocyclic synthesis strategies offers a powerful platform for the generation of bioactive molecules. This study not only highlights the synthetic utility of chalcones but also explores the potential of their derivatives as promising pharmacophores in drug discovery. The dual focus on both N-phenylpyrazoline and dihydropyrimidine analogs expands the scope of chalcone-based molecules and emphasizes the relevance of molecular hybridization in the search for new therapeutic agents [24].

Based on your provided conclusion, here's a suggested structure for the **research paper sections** (excluding Abstract, Introduction, and Citations), designed to logically present your synthesis, characterization, and biological evaluation results:

Materials and Methods

1 Design and Synthesis of Compounds

- Description of the software tools used for molecular design.
- Synthetic procedure:
    - **Claisen-Schmidt Reaction** for chalcone synthesis.
    - **Phenyl hydrazine treatment** to obtain N-phenylpyrazoline.
    - **Urea treatment** to synthesize 3,4-dihydropyrimidine derivatives.
- Thin Layer Chromatography (TLC) procedure used for monitoring reaction progress.

2 Characterization of Synthesized Compounds

- **Fourier Transform Infrared Spectroscopy (FT-IR):** Detection of C=C, C=N, and C=O functional groups.

- **Proton Nuclear Magnetic Resonance (^{1}H-NMR):** Identification of relevant proton environments.
- **Mass Spectrometry (MS):** Confirmation of molecular ion peaks and molecular weights.

3 In-vitro Biological Assays

- **Anti-oxidant Activity:** Description of assay and standard used.
- **Anti-diabetic Activity:** Description of assay and comparison method with standard.
- **Anti-inflammatory Activity:** Description of assay and standard comparison.
- **Anti-tuberculosis Activity:** Testing against *Mycobacterium tuberculosis*, only for selected compounds based on anti-oxidant screening.

Results and Discussion

1. Chemical Synthesis and Characterization

- Summary of the successful synthesis of chalcone derivatives and their subsequent transformation into N-phenylpyrazoline and 3,4-dihydropyrimidine scaffolds.
- Discussion of TLC results confirming product formation.
- Spectral data interpretation:
    - Key FT-IR peaks corresponding to functional groups.
    - ^{1}H-NMR spectral data confirming structural assignments.
    - Mass spectrometric data supporting molecular structures.

2. Biological Evaluation

2.1 In-vitro Anti-oxidant Activity

- All compounds exhibited positive activity.
- Compounds **K1, K3, K6, and K8** showed potent antioxidant effects.
- These results guided further testing for anti-tuberculosis potential.

2.2 In-vitro Anti-diabetic Activity

- Comparative analysis with standard drug.
- Compounds **K1, K2, K6, and K7** showed enhanced activity.
- Structural features contributing to potency (e.g., P-chloro and trimethoxy substitutions).

2.3 In-vitro Anti-inflammatory Activity

- All compounds demonstrated significant anti-inflammatory properties.
- Notably potent compounds: **K1, K3, K6, and K8**.

2.4 In-vitro Anti-tuberculosis Activity

- Based on antioxidant screening, K1, K3, K6, and K8 were selected.
- Compound **K3** displayed the most potent activity against *Mycobacterium tuberculosis*.
- Discussion of structure-activity relationship (SAR), emphasizing the N-phenylpyrazoline moiety and P-dimethylamino benzaldehyde substitution.

Conclusion

- Restate the promising bioactivities of synthesized compounds.
- Emphasize the most active compounds across assays.
- Suggest future in-vivo studies for compounds K1, K2, K6, and K7 based on their significant in-vitro

anti-diabetic activity.

converting this into a manuscript format (e.g., for journal submission).

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