DEVELOPMENT OF THERAPEUTIC AGENTS BASED ON HETEROCYCLIC SCAFFOLDS

Thesis

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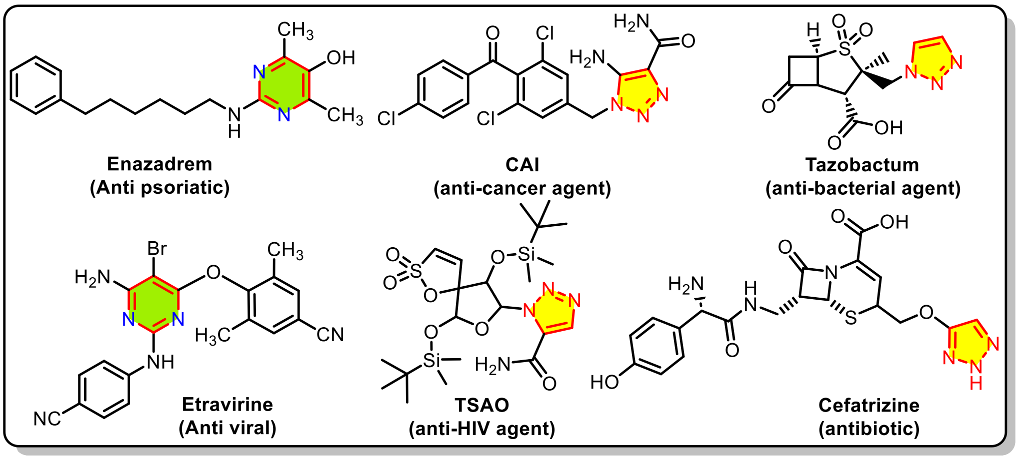
SUMMARY

The thesis entitled **"DEVELOPMENT OF THERAPEUTIC AGENTS BASED ON HETEROCYCLIC SCAFFOLDS"** is divided into six chapters and describes the preparation of (*E,E*)-4,6-bis(styryl)-pyrimidines, 1,4-disubstituted-1,2,3-triazoles and DHPMs *via* biopolymer supported copper catalyst. Heteroatomic molecules containing nitrogen are the most prevalent moiety in nature because they are involved in nearly all of the physiological processes that occur in both plants and animals. In these molecules, the *N*-atom being a part of the complex heterocyclic system, provides basic nature to the molecule. Heteroatomic molecules containing nitrogen are actively involved in a number of biological activities. The formation of *C-N* bonds play an important role in the synthetic organic and medicinal world. Among these, nitrogen-containing heteroatomic molecules, pyrimidines, triazoles, and DHPMs are highly desirable because they are present in natural, semi-synthetic, and synthetic bioactive compounds and are also used as important synthetic intermediates.

There are several methods available in the literature for the synthesis of (*E,E*)-4,6-bis(styryl)-pyrimidines, triazoles, and DHPMs however still some limitations are associated with these methods such as the use of additives, poor yields, narrow substrate scopes, and typical reaction procedures. In this context, we have developed highly efficient, one-pot, atom-economical, mild, and operationally simple methods for the synthesis of (*E,E*)-4,6-bis(styryl)-pyrimidines from acetylacetone, urea, and aromatic aldehyde *via* Aldol condensation. To prepare 1,4-disubstituted-1,2,3-triazoles and DHPMs, we have developed *Cassia fistula* gum-supported copper nanocatalysts. Our catalyst is very useful in Click as well as Biginelli reaction, which are discussed later in different chapters of the thesis.

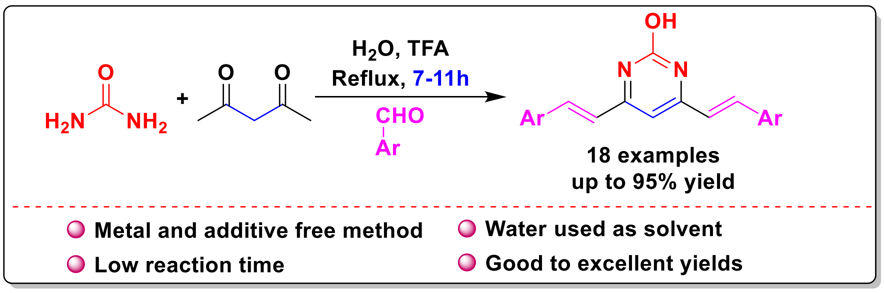
Chapter 1: General Introduction

Chapter 1 includes a brief discussion about the importance of pyrimidines and the various synthetic strategies to develop them. The antibacterial activity of pyrimidine derivatives is also briefly summarized.



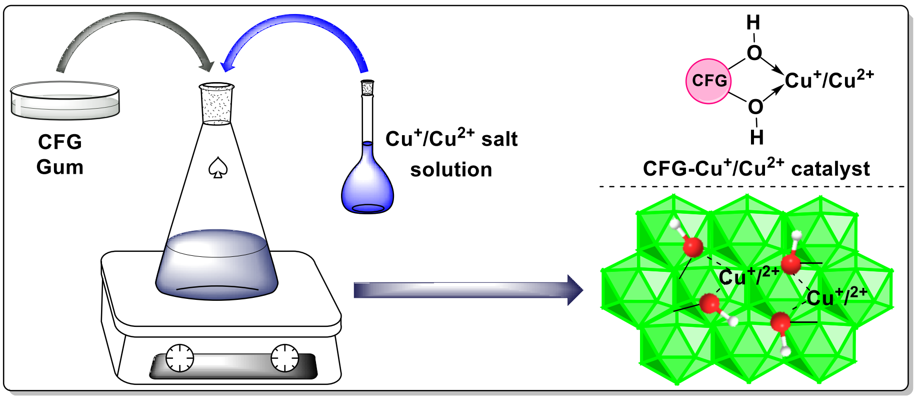
Chapter 2: Lewis acid catalyzed one pot synthesis of (E,E)-4,6-Bis(styryl)-Pyrimidines in aqueous medium.

Chapter 2 presents an efficient and straightforward method for the synthesis of (*E*,*E*)-4,6-bis(styryl)-pyrimidines. The synthesis involved a one-pot, two-step process carried out in water, which serves as an environment-friendly solvent. In the first step, the synthesis proceeds through a [3+3] annulation reaction between acetylacetone and urea, leading to the formation of the pyrimidine ring. Subsequently, in the second step, an aldol condensation reaction occurred between the resulting pyrimidine and variously substituted aromatic aldehydes. This aldol condensation resulted in the desired (*E*,*E*)-4,6-bis(styryl)-pyrimidines in moderate to good yields.



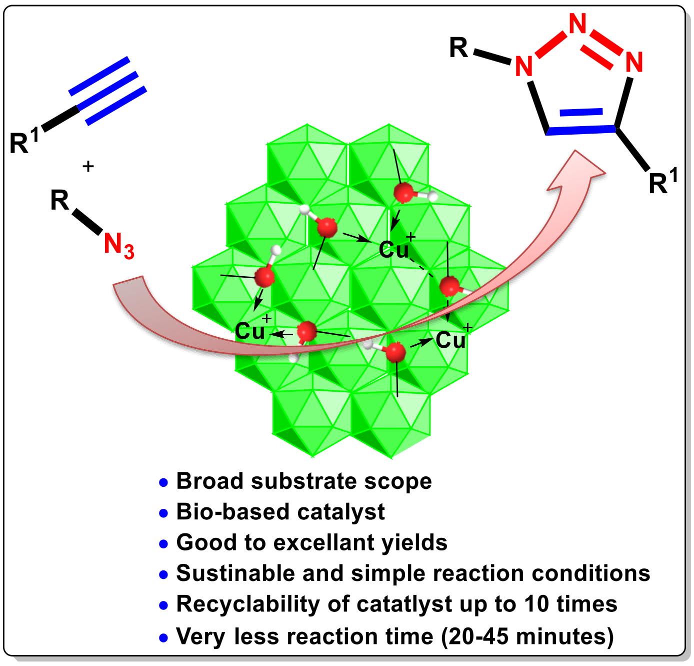
Chapter 3: Development and characterization of biopolymer supported copper catalysts.

New environment-friendly nanocatalysts based on *Cassia fistula* gum-copper complex called CFG-Cu nanocatalysts were developed by utilizing sustainable *Cassia fistula* gum (CFG) as a stabilizing agent for copper (I & II). The CFG, a galactomannan gum extracted from *Cassia fistula*, was used to react with copper (I or II) salts to form the CFG-Cu(I) and CFG-Cu(II) nanocatalysts. To characterize the morphology and structural properties of these nanocatalysts, various analytical techniques were employed. These techniques included Fourier-transform infrared spectroscopy (FTIR) to study the chemical bonds, scanning electron microscopy (SEM) to examine the surface morphology, energy-dispersive X-ray spectroscopy (EDX) to analyze the elemental composition, X-ray diffraction (XRD) to investigate the crystal structure, inductively coupled plasma mass spectrometry (ICP-MS) to determine the elemental concentrations, thermogravimetric analysis (TGA) to study the thermal stability and XPS analysis to check oxidation state of copper present in nanocatalyst. These characterization techniques collectively provided insights into the morphology and structural characteristics of the CFG-CuI and CFG-$CuSO_4$ nanocatalysts, allowing for a comprehensive understanding of their properties.



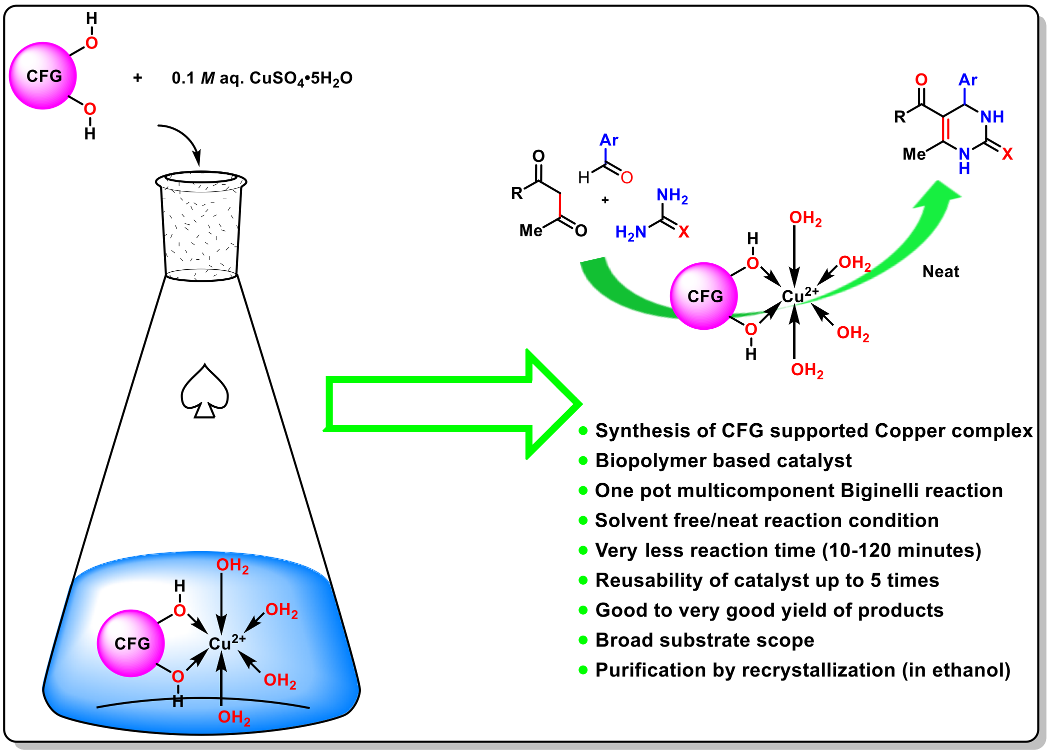
Chapter 4: Application of Bio-polymer Supported Cu(I) Catalyst (CFG-CuI) in Click Reaction.

The CFG-CuI nanocatalyst was successfully utilized in the [3 + 2] cycloaddition reactions using click chemistry principles. These cycloadditions involved the combination of phenyl azides, aryl azides, alkyl azides, and terminal aryl alkynes. Notably, these reactions were successfully achieved with low catalyst loading and water as the solvent. The simplicity of the reaction work-ups was another advantage of using this nanocatalyst. The catalyst could be easily recovered and recycled for at least ten consecutive cycles without any significant loss in efficiency or selectivity. The prepared nanocatalyst exhibited high efficiency, resulting in high yields (82% to 99%) for a wide range of substrates. Additionally, the nanocatalyst demonstrated regioselectivity, by exclusively yielding 1,4-disubstituted-1,2,3-triazoles as the desired products.



Chapter 5: Application of Bio-polymer Supported Cu(II) Catalyst (CFG-CuSO$_4$) in Biginelli Reaction.

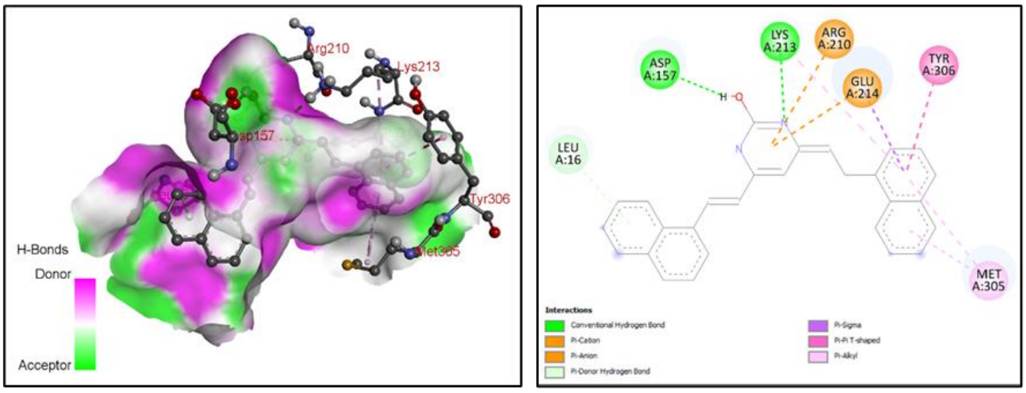
After following the characterization process, the catalyst was employed in a single-pot multicomponent reaction known as the Biginelli reaction.



This reaction involved the use of benzaldehyde or its derivatives, urea/thiourea, and ethyl acetoacetate/acetylacetone as starting materials. The goal of the reaction was to synthesize 3,4-dihydropyrimidin-2-(1H)-one (DHPM) compounds. The reaction was carried out under solvent-free and additive-free conditions. Additionally, the catalyst was easily recovered and reused in subsequent reactions, which further enhanced the sustainability and practicality of the process.

Chapter 6: Docking studies & Biological evaluation of **(*E*,*E*)-4,6-bis(styryl)-pyrimidines.**

The (*E,E*)-4,6-bis(styryl)-pyrimidines (of chapter 2) were selected for computational (*in silico*) as well as for *in vitro* studies. The human proximal tubule cell line (HK-2 cell) was chosen for cytotoxicity analysis. Molecular Docking studies were performed for the mechanistic establishment using the molecular target *aldolase A*, *enolase 1*, *β-actin*, and *tropomyosin 3* receptors with PDB IDs: 4ALD (aldolase A), 2PSN (enolase 1), 6NBW (β-actin), and 7KO5 (tropomyosin 3).



LIST OF PUBLICATIONS

1. **Singh, B. D.**; Pandey, J.; Khanam, H.; Singh, S. Lewis Acid Catalyzed [3+3] Annulation/Aldol Condensation in Water: One Pot Synthesis of (*E,E*)-4,6-Bis (styryl)-Pyrimidines. *Asian J. Org. Chem.* **2022**, *11*, e202200479.

2. Pandey, J.; **Singh, B. D**.; Khanam, H.; Tiwari, B.; Azaz, T.; Singh, R. *Cassia fistula* galactomannan stabilized copper nanocatalyst as an efficient, recyclable heterogeneous catalyst for the fast clickable [3+ 2] Huisgen cycloadditions in water. *Int. J. Biol. Macromol.* **2024**, *255*, 128098.

3. **Singh, B. D.**; Pandey, J.; Khanam, H.; Tiwari, B.; Azaz, T.; Singh, R.; Mishra, A.; Kanchan, P, Green synthesis of Copper (II) nanodots anchored on *Cassia fistula* galactomannan: roboust and recyclable catalyst for clean Biginelli reaction. (Communicated, Manuscript number: chem.202400954).

4. Pandey, J.; Khanam, H.; Shaheen, F.; **Singh, B. D**.; Pathak, A.; Sharma, A,; Tiwari, S,; Pandey, D,; Bishnoi, A, Synthesis and photophysical properties of D-π-A-π-D 2-hydroxy-4,6-bis-(arylvinyl)-pyrimidines based push-pull fluorophores: DFT studies and antibacterial activity. (Communicated: SAA-D-24-00224).

5. Synthesis and biological activity of pyrimidines: An overview (Manuscript under preparation).

6. Synthesis and application of biopolymer-supported transition metal catalysts: An overview (Manuscript under preparation).

7. Synthesis, docking, and anticancer activity of (*E,E*)-4,6-bis (styryl)-pyrimidines on human kidney (HK-2) cell lines (Manuscript under preparation).