Chapter- 7

MCM 41 supported perchloric acid catalytic system: A Versatile and Recyclable Heterogeneous Catalyst for Solvent-Free Green Synthesis of Novel 1,4-Dihydropyrano[2,3-c]pyrazole Heterocycle and Its Molecular Docking Studies

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Abstract

Herein, we synthesized novel 1,4-Dihydropyrano[2,3-c]pyrazole heterocycle using a solvent-free approach with recyclable MCM 41 supported perchloric acid catalytic system. The reaction was carried out via multi-component one pot synthesis involving 1,3- Dimethyl barbituric acid, 4-Dimethyl amino benzaldehyde, acetoacetic ester and hydrazine hydrate at room temperature. MCM 41 supported perchloric acid catalytic system was known for its high catalytic activity compared to conventional heterogeneous catalysts, potentially reducing energy consumption and raw material usage in various chemical processes. The synthesized novel compound was characterized using ^{1}HNMR and FT- IR spectroscopic techniques. The biological significance of the newly synthesized compound was further validated through in silico docking studies. Computational analyses were conducted using software such as Auto Dock Vina, Discovery Studio, and Open Babel etc. This research highlights the synthesis of a pyrazole derivative via an environmentally sustainable approach, employing a recyclable catalyst. This work not only contributes to the field of medicinal chemistry but also adheres to the principles of green chemistry. Additionally, the docking studies demonstrated that the novel heterocyclic framework exhibits potential as an antimicrobial agent.

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Keywords: Solvent free reaction, MCM 41 supported perchloric acid, Molecular docking, Pyrazole derivatives, Conventional synthesis.

Introduction

Green chemistry and methodologies possess several advantages in organic synthesis over conventional methods of synthesis [1, 2]. Adopting the principles of green chemistry help the chemists in designing environment safer products thereby simplifying the conventional operational procedures [3]. Nowadays solvent less reactions are getting much attention in the sense of green chemistry as they are efficient and economical way for organic synthesis [4]. Acidic composites frequently have superior mechanical qualities, such as greater strength, hardness, and toughness and hence they are widely used as catalysts in organic synthesis [5]. Pyranopyrazoles are referred to as a fused five membered pyrazole ring with a six member pyrano ring. They are even more relevant at the study level because of their high pharmacological prominence and due to several activities of the heterocyclic core [6]. In the past decade, there has been a notable spike in interest surrounding pyrazole chemistry due to the invention of various exciting properties exhibited by numerous derivatives of pyrazole. Pyrazoles, hold significant importance in organic synthesis and are extensively studied within the azole family. Pyranopyrazoles are gaining much attention among chemists due to widespread synthetic utilities and potential biological activities such as anti-cancer, anti-bacterial, analgesic properties and also have acted as insecticidal [7]. A wide range of synthesis methods and synthetic analogs have been documented over the years, emphasizing their relevance in both research and practical applications [8]. Significant advancements have been made in the synthesis of diverse and biologically significant pyrano [2, 3-c] pyrazole derivatives using environmentally friendly methods. These advancements include the use of energy-efficient techniques like microwave and ultrasound-assisted synthesis, as well as the employment of benign catalysts and biodegradable composites [9].

To the best of our knowledge, we are the first to report the synthesis of a novel 1,4-Dihydropyran[2,3-c]pyrazole heterocycle using a recyclable and reusable MCM-41-supported perchloric acid catalytic system under

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solvent-free conditions. This work details the green synthesis, characterization, and molecular docking studies of the newly synthesized compound.

Experimental

General:

The reagents such as 4-Dimethylamino benzaldehyde, 1, 3-Dimethyl barbituric acid, methanol, hydrazine hydrate, ethanol and acetoacetic ester were purchased from commercial sources. The reaction was monitored using thin layer chromatography (TLC) on glass plates coated with silica gel-G using chloroform and methanol as mobile phases and visualized by iodine vapors. ^{1}H NMR spectra of compounds were found with the help of VARIAN 400 MHZ NMR spectrometer. IR spectrum of the compound was recorded using Shimadzu Spirit FT- IR spectrometer. The values of chemical shifts are quoted in delta scale in ppm relative to tetramethylsilane (TMS) as an internal standard and DMSO D_6 as solvent system.

General Procedure for Synthesis of Pyrazole Heterocycles under Conventional method:

Hydrazine hydrate (3.35 mmol) and acetoacetic ester (3.35 mmol) were added to the mixture of 4-Dimethylamino benzaldehyde (3.35 mmol) and 1,3-Dimethylbarbituric acid (3.35 mmol) taken in a RB flask and stirred at room temperature using a magnetic stirrer after 10 ml of methanol (solvent) was added. To this PTS catalyst was added. A suction pump was used to filter the precipitate that had developed once the reaction was finished, as determined by TLC. After being collected, the product was cleaned. This is followed by recrystallization using chloroform -methanol mixture.

General procedure for the synthesis of pyrazole heterocycles under solvent- free conditions using recyclable and reusable MCM 41 supported perchloric acid catalytic system:

MCM 41 supported perchloric acid catalytic system (150 mg) was added to a combination of Hydrazine hydrate (3.35 mmol), Acetoacetic ester (3.35 mmol), 4-Dimethylamino benzaldehyde (3.35 mmol) and 1,3 Dimethyl barbituricacid (3.35 mmol).

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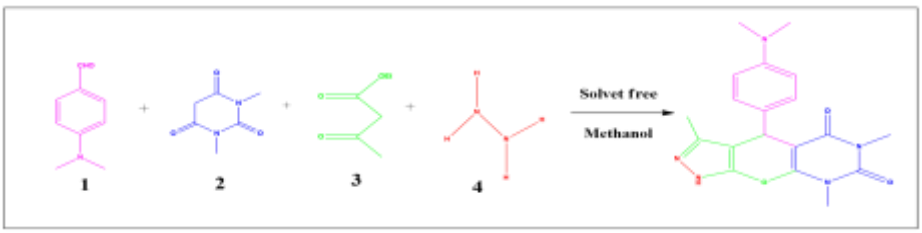
The reaction mixture was placed in a mortar and continuously ground with a pestle at room temperature. Following the reaction's completion (as shown by TLC), the product was separated by dissolving it in a mixture of chloroform and methanol, and the residue contains a catalyst. The filtrate is recrystallized after the undissolved catalyst was removed through filtering.

General procedure for the recycling and reusing of MCM 41 supported perchloric acid catalytic system for the synthesis of pyrazoles under solventless conditions:

Hydrazine hydrate (3.35 mmoles), Acetoacetic ester (3.35 mmoles), 4-Dimethylaminobenzaldehyde (3.35 mmol) and 1, 3 Dimethyl barbituricacid (3.35 mmol) were allowed to react together. At room temperature, the reaction mixture was placed in a mortar and continuously ground with a pestle. Following the reaction's completion, which was observed by TLC, a recycling analysis was carried out by adding ethyl acetate to the reaction mixture. The resulting catalyst, which is insoluble in ethyl acetate, was dried and cleaned using methanol before being utilized in the subsequent catalytic cycle. The yield of the product was used to calculate the reusability and recyclable nature of catalyst.

Results and discussion



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Scheme 1: Scheme for the synthesis of pyranopyrazole derivatives.

Optimization of reaction conditions:

Comparative study of conventional and solvent-free methodologies

In the current study, when the reaction was carried out in conventional method using PTS as catalyst , it took 40-45 hrs for its completion while in solvent free method the reaction completed within 1-3 minutes using MCM 41 supported perchloric acid catalytic system in very high yields (82%) (Table 1).

Table 1: Comparative study of conventional and solvent-free methodologies.

Sl. No.	Products	Conventional Methods		Solvent-free Methods	
		Time (hrs)	Yield (%)	Time (min)	Yield (%)
1	Pyrazole derivative	48	62	3 min	82

Recyclability and reusability study of MCM 41 supported perchloric acid catalytic system

The MCM 41 supported perchloric acid catalytic system demonstrated recyclability for up to four cycles with minimal loss in catalytic activity. The reaction completed within 3 minutes in the initial cycle, with complete catalyst recovery upon filtration and methanol/ethyl acetate washing. Subsequent cycles yielded similar outcomes. However, by the fifth cycle, reduced yield and increased reaction time were observed, suggesting a decline in catalytic activity, possibly due to catalyst activity reduction.

Table 2: Recyclability Data.

Entry	Reaction cycle	Time	Yield (%)
1	1st cycle	3 min	82
2	2nd cycle	3 min	82
3	3rd cycle	3 min	82
4	4th cycle	5 min	73

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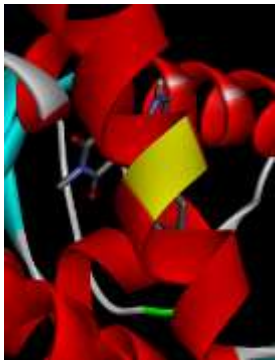
Insilico Docking results

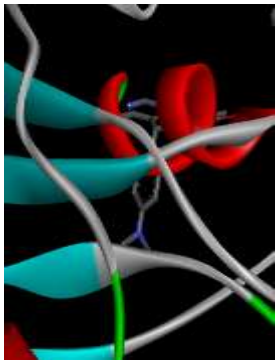
Table 3: Docking scores

Protein	Binding affinity
6uex	-8.6
6sbn	-7.7
1ex9	-5.4
5wze	-9.4
3jzz	-6.5
3h78	-7.5
2zco	-8.7
1t2p	-3.1
2w38	-3.0

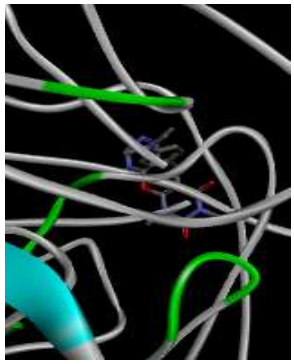
Docking scores:



6uex

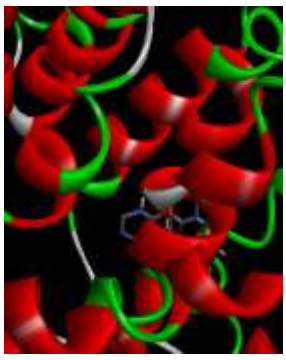


6sbn

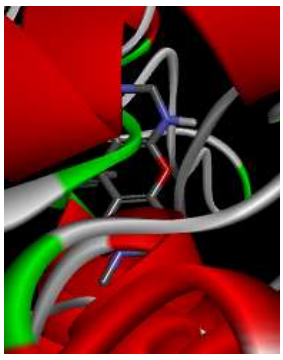


1t2p

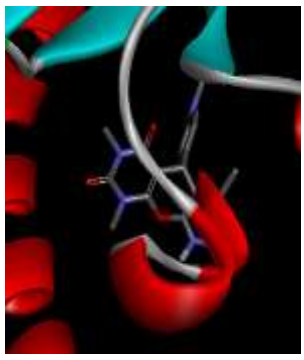
3D Diagrams



2w38



5wze



3jzz

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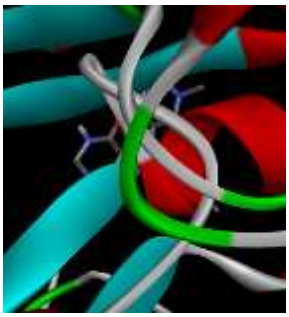
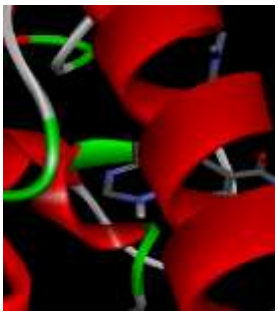
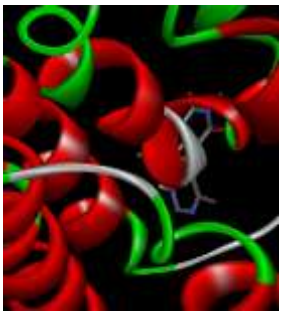
2D Diagrams



3h78



1ex9



2zco

6uex

6sbn

1t2p

3h78

1ex9

2zco

2w38

5wze

3jzz

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Based on the docking scores, we conclude that the protein 5WZE shows the strongest binding affinity for our synthesized pyrazoles, suggesting that these compounds possess enhanced antibacterial and anti-pathogenic properties. Following 5WZE, the next highest binding affinities were observed with the proteins 2ZCO, 6UEX, 6SBN, 3H78, 3JZZ, 1EX9, 1T2P, and 2W38, respectively.

Conclusion

In summary, we have developed an efficient and environmentally friendly method for synthesizing pyrazoles from 1,3-Dimethylbarbituric acid, 4-Dimethylaminobenzaldehyde, acetoacetic ester, and hydrazine hydrate. This reaction was conducted using a recyclable and reusable MCM-41-supported perchloric acid catalytic system in a one-pot, three-component reaction under solvent-free conditions. The protocol is distinguished by its minimal environmental impact, mild reaction parameters, and straightforward experimental procedures. This green synthesis method outperforms conventional approaches in terms of reaction efficiency, yield, and simplicity. Key features include solvent-free conditions, the use of non-contaminating renewable catalysts, rapid reaction times, and ease of execution, enhancing its applicability for preparing various pyrazole derivatives. We have also conducted molecular docking studies on newly synthesized compounds, a modern strategy for identifying both the structural and biological properties of these compounds through virtual screening. Our molecular docking studies demonstrated that the novel heterocyclic framework exhibits promising potential as an antimicrobial agent. This research represents a significant contribution to the fields of medicinal chemistry and green chemistry.

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