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ORIGINAL RESEARCH ARTICLE

Modelling of the Pyrimidine Derivatives Synthesis by Copper Oxide Nanoparticles as a Catalyst

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ABSTRACT

This research article highlights how Bioactive Pyrimidine Derivatives were synthesized in an environmentally friendly manner via Green Chemistry using Copper Oxide (CuO) NanoParticles (NPs) as recyclable catalysts through the multicombination Biginelli Reaction. The CuO NPs (approximately 18nm) were synthesized efficiently via a cost-effective, simple mechanical mixing/calcination method, with characterization verified with XRD, EDX, FESEM, and FTIR. The one-pot condensation reaction of the three starting reagents (aldehydes, acetylacetone, and urea) was achieved in 30 minutes at 80°C with yields of approximately 90 to 95%, which produced a major compound, (5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one). Box-Behnken design (BBD) design of experiments together with response surface methodology (RSM) using Design-Expert 13 was performed on the condensation reaction to determine the optimal conditions (1mmol of initial aldehyde, 1mmol of urea, 1mmol of acetylacetone, 0.1g of catalyst) and establish a predictive neural network model with R2=0.8684 and Adeq Precision=7.74. CuO NPs outperformed traditional and existing types of catalysts (CdO NPs and copper acetate), exhibited products with tolerance to a wide range of substituents (H, NO2, OH); additionally, they provided consistent three (3) to four (4) cycles of continuous activity, demonstrating a sustainable, scalable method for producing pharmacologically active dihydropyrimidinones.

Keywords: metal nano catalyst; pyrimidine derivatives; copper oxide nanoparticles; biginelli reaction; box-behnken design

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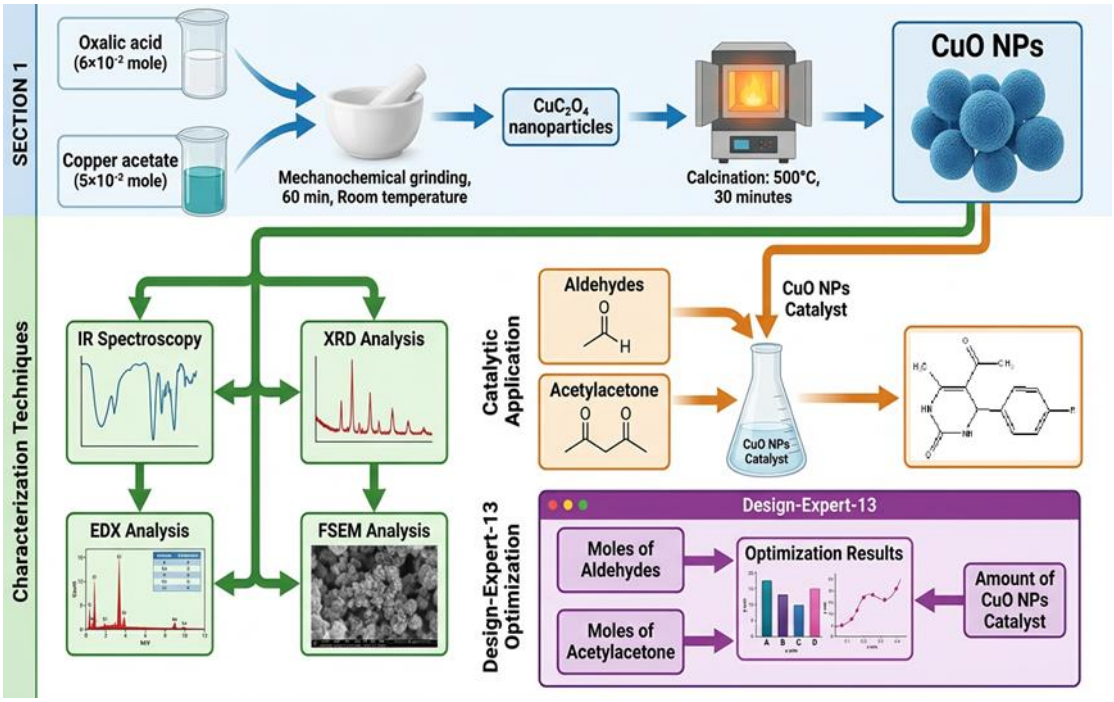
1. Introduction

Currently, multicomponent condensation reactions have emerged as an efficient approach for synthesizing organic compounds. These reactions permit the synthesis of favored products in a single step; at the same time, diversity can be easily achieved by altering each component[1,2]. Green chemistry techniques have proven highly effective in synthesizing numerous organic compounds[3-5]. Key methods include microwave irradiation[6,7], ultrasound-assisted synthesis[8], Green solvents used[6,9,10], and catalytic strategies[11-14]. Among these, catalysis plays a vital role in green chemistry, substantially studied in chemistry and biochemistry[15-18]. Catalysts are extensively hired to provide efficient and selective answers for several industrially applicable natural synthesis demanding situations[19,20]. The Biginelli response, discovered by Pietro Biginelli in 1893, is the most famous one-pot multicomponent reaction. It contains the acid-catalyzed condensation of an aldehyde, a β-ketoester, and urea to provide 3,4-dihydropyrimidin-2(1H)-ones (3,4-DHPs)[21,22]. These heterocyclic compounds show various organic and pharmacological properties, together with antibacterial, antiviral, and antitumor

activities[23-28]. Over the past two decades, the Biginelli reaction has been drastically investigated, mostly due to the diverse applications of its dihydropyrimidinone derivatives. Initially identified for their nifedipine-type calcium channel blocking properties[29,30], those compounds have been established as having significant ability as antitumor[31-34], antibacterial and antiviral[35,36], anti-inflammatory[37,38], analgesic[39], anti-Alzheimer[40], and antioxidant agents[41].

Metal oxide nanoparticles (NPs) exhibit superior catalytic reactivity due to their expansive surface area, which allows less complicated interaction with substrate molecules, leading to improved catalytic performance. Their high floor-location-to-volume ratio offers nanocatalysts particular homes, making them more powerful than bulk substances in catalytic packages[42,43]. To allow quicker organic reactions with improved yields, diverse nanocatalysis methods have been employed[44-46]. The aim of this work is to study the optimal parameters with the Degin-Expert-13 program for the synthesis of pyrimidine derivatives using copper oxide nanoparticles. **Scheme 1** represents the graphical abstract of the fabrication of copper oxide NPs and their use as a catalyst for the synthesis of pyrimidine derivatives.



Scheme 1. Graphical abstract of CuO NPs fabrication and use it as a catalyst for the synthesis of pyrimidine derivatives.

2. Materials and methods

Chemical materials were purchased from BDH, Fluka, and Sigma-Aldrich companies. All the chemical materials were commercial compounds of grade and were utilized without purification. Copper oxide nanoparticles were fabricated using the method reported by *Javad et al.*[47]. The melting points of the synthesized compounds were measured utilizing a Stuart SMP30 melting point equipment (manufactured in Germany). The resulting pyrimidine derivatives were analyzed by FTIR spectroscopy (Bruker Alpha II, Germany) and ^{1}H-NMR spectroscopy (Bruker BioSpin GmbH, 400 MHz, Germany) with deuterated DMSO solvent. The optimum parameters for synthesizing pyrimidine derivatives were studied using the Design-Expert 13 program.

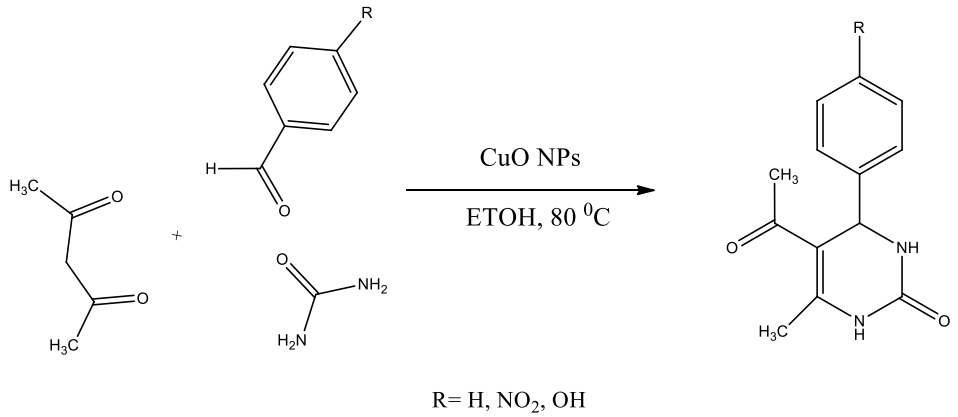
General method for the fabrication of CuO nanoparticles.

In a standard procedure, oxalic acid (6×10^{-2} mole) and copper acetate (5×10^{-2} mole) were combined and ground in a mortar for 60 minutes at room temperature. CuO NPs were then formed by calcining the as-

prepared CuC_2O_4 nanoparticles for 30 minutes at 500 ^{0}C. Using IR, XRD, EDX, and FSEM analysis, CuO NPs have been characterized.

General method for the synthesis of pyrimidine derivatives(A1-A3).

Pyrimidine derivatives(A1-A3) were synthesized through a one-pot reaction catalyzed with the aid of nano copper oxide (CuO NPs). A mixture of various aldehydes (1×10^{-3} mol), acetylacetone (1×10^{-3} mol), urea (1×10^{-3} mol), and CuO NPs (0.1 g) was heated at 80 °C for 30 min in ethanol as a solvent (**Scheme 2**). After the final touch, the response combination was cooled to twenty-five °C, centrifuged at 5000 rpm for 20 min, and the solvent was decanted. The remaining ethanol was evaporated, and the crude product was purified by recrystallization in 30% aqueous EtOH. The final compounds were characterized by 1H NMR, FTIR spectroscopy, and comparison of their physical properties with known pyrimidine derivatives.



R= H, NO_2, OH

Scheme 2. General procedure for the synthesis of pyrimidine derivatives.

5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(A1).

Yellow powder: m.p 194-199 ^{0}C ;FTIR (cm^{-1}): 3335, 3258 (N-H), 3029(C-H) $_{Or.}$, 2929(C-H) $_{Al.}$, 1702(C=O of acetyl), 1674(C=O of lactam), 1597 (C=C $_{Or.}$); H-NMR (DMSO-d_6, 400 MHz): δ 9.21(s,2H,NH), 7.84-7.99(m,5H, aromatic proton), 2.51(s,3H,$COCH_3$ group), 2.30(s, 3H, C-CH_3 group), 5.86(m, 1H,Methine proton) .

5-acetyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one(A2).

Brown powder: m.p 205- 209 ^{0}C; FTIR (cm^{-1}): 3463, 3363 (N-H), 3078(C-H) $_{Or.}$, 2972(C-H) $_{Al.}$, 1699(C=O of acetyl), 1665(C=O of lactam), 1567 (C=C $_{Or.}$), 1514,1342(sym. & Asym. Of NO_2); H-NMR (DMSO-d_6, 400 MHz): δ 10.18(s, 1H, NH), 9.35(s,1H, NH), 7.60-8.30(d,4H, aromatic protons), 2.40(s,3H, $COCH_3$ group), 2.29(s, 3H, C-CH_3 group), 5.42(m, 1H, methine proton).

5-acetyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one(A3).

Brown powder: m.p 211- 214 ^{0}C; FTIR (cm^{-1}): 3434 (O-H), 3332, 3215 (N-H), 2972(C-H) $_{Al.}$, 1657(C=O of lactam), 1579 (C=C $_{Or..}$), 1234(C-O phenolic); H-NMR (DMSO-d_6, 400 MHz): δ 9.76(s, 1H, NH), 9.13(s,1H, NH), 9.71(s,1H, OH), 6.72-7.75(d,4H, aromatic protons), 2.59(s,3H, $COCH_3$ group), 2.28(s, 3H, C-CH_3 group), 5.59(m, 1H, methine proton).

3. Results and Discussion

In the preliminary experiments, nanoparticles were characterized with FTIR, FSEM, XRD, and EDX analysis. X-ray diffraction (XRD) analysis was used to determine the crystallinity and crystal phases of the as-grown structures, and the results are displayed in **Figure 1**. Pure CuO's XRD pattern, which uses Cu-Kα radiation with λ = 1.5406 Å, exhibits distinctive peaks at particular 2θ angles. The presence of peaks at 35.5°,

38.7°, and 61.9°, etc., confirms the formation of pure monoclinic CuO (tenorite phase). The average crystallite size of the CuO nanoparticles was determined to be 18 nm using Scherrer's equation.

$$D=0.89\lambda/\beta\cos\theta$$

where D represents the mean particle size, λ is the X-ray wavelength, β denotes the full width at half maximum (FWHM) of the diffraction peak, and θ is the Bragg angle.

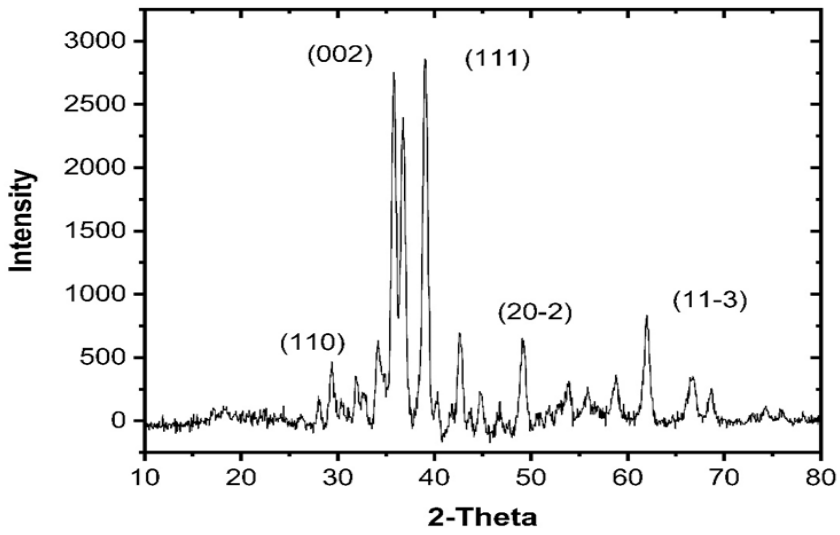


Figure 1. XRD spectra of CuO NPs.

EDX analysis of the CuO nanoparticles was performed at 10 keV, confirming the presence of only copper (Cu) and oxygen (O) without any impurities, as shown in **Figure 2**. The measured weight percentages were 91.27% Cu (0.804 keV) and 8.73% O (0.525 keV), while the atomic ratio of Cu:O was approximately 1:1, indicating near-stoichiometric CuO formation. The absence of extraneous peaks in the EDX spectrum confirmed the high purity of the nanoparticles. No signals from chlorine or other potential contaminants were detected, suggesting an effective synthesis and purification process. These results align with XRD data, which previously identified the sample as pure monoclinic CuO.

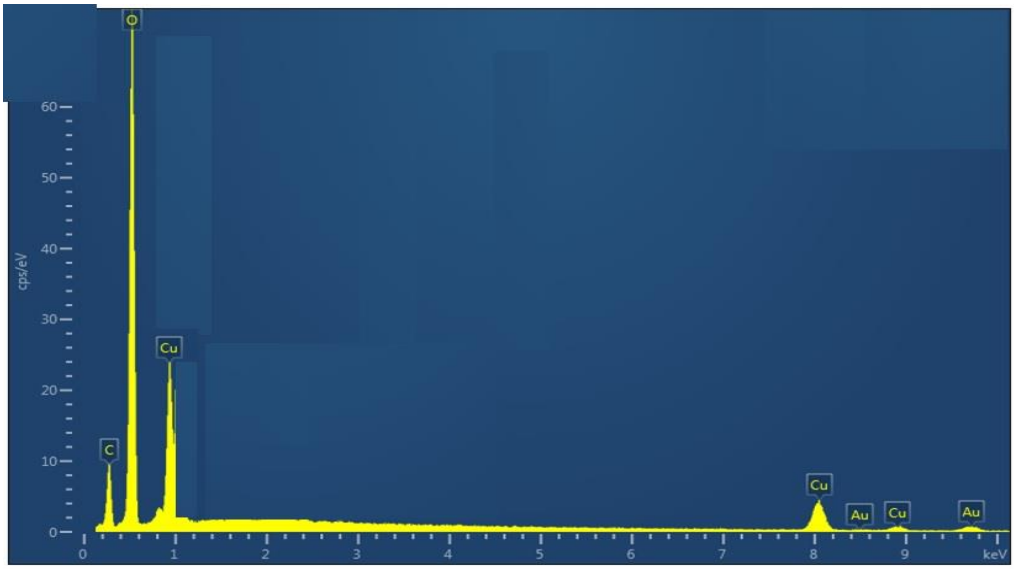


Figure 2. shows the EDX analysis of CuO nanoparticles.

The morphology of the CuO nanoparticles prepared by the precipitation method was analyzed using FSEM, as shown in **Figure 3**. At low magnification (**Figure 3a**), the sample exhibits a heterogeneous morphology, consisting of both irregularly shaped particles and distinct nanorods. However, upon closer examination at high magnification (**Figure 3b**), it becomes apparent that these structures are not monolithic. Instead, they are aggregates of much smaller, primary particles that are predominantly spherical in shape, with the J image software the average particle size was approximately 20.45±1.02 nm as shown in (**Figure 3b**). This clustering is a common phenomenon in nanoparticle synthesis, often driven by the high surface energy of the primary particles, which leads to agglomeration to achieve a more thermodynamically stable state.

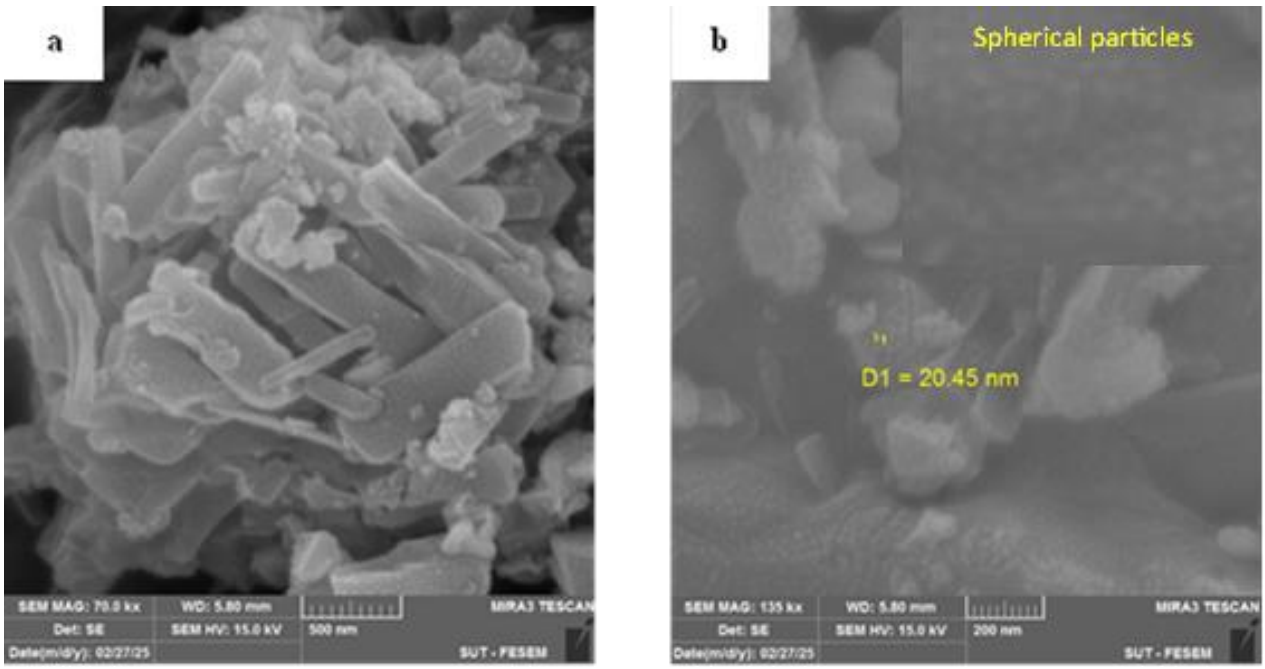
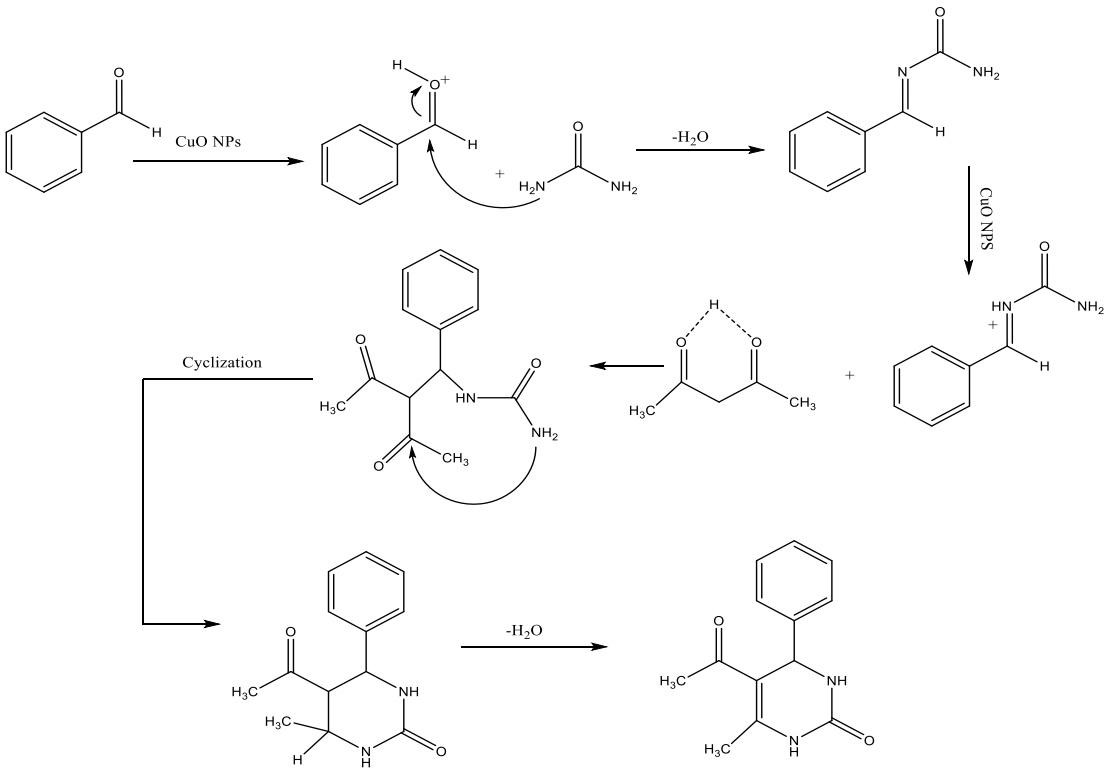


Figure 3. Shows the FSEM image of CuO nanoparticles.

In the FTIR spectrum of CuO NPs, the band at 513 cm^{-1} is assigned to the stretching of water molecules, confirming hydration. The band at 1425 cm^{-1} is due to carbonate species from atmospheric CO_2 adsorption. After the fabrication of copper oxide NPs, it is used as a catalyst for the synthesis of pyrimidine derivatives, as shown in **Scheme 3**. To optimize conditions, the model reaction was achieved using a variety of aldehydes, acetylacetone, and urea in the presence of ethanol as solvent. Firstly, the effect of the catalyst type (CuO NPs) and its comparison with different catalysts was investigated in the model study (**Table 1**). It was detected that CuO NPs exhibited higher activity than other catalysts due to the greater surface area of CuO NPs (20 nm). With in-hand results, we are encouraged to utilize CuO NPs instead of other catalysts.



Scheme 3. A plausible mechanism for the Biginelli reaction in the presence of CuO NPs.

Table 1. The effect of different catalysts on the yield of a reaction.

Catalyst type	Time(min)	Yield (%)
CdO NPs		77
$NiCdO_2$ NPs		82
CuO NPs	30	93
Cd $(NO_3)_2$		25
$(CH_3COO)_2Cu$		31

We conducted the reaction with several solvents in order to examine the impact of the solvent on the yield of the desired product; the outcomes are displayed in **Table 2**. The findings demonstrated that the ethanol increased the rate of reaction and produced excellent product yields.

Table 2. Effect of different solvents on the yield of the product in the presence of CuO NPs.

Solvent type	Time(min)	Yield (%)
EtOH		93
MeOH		88
CH_3CN	30	89
CH_2Cl_2		77
n-Hexane		72

On the other hand, the rest of the parameters, such as the amount of acetylacetone, the aldehyde amount, and the amount of urea, were achieved by the Design-Expert 13 program. Statistical tests such as analysis of variance (ANOVA), coefficient of determination (R^2), and analysis of residuals were used to assess the applicability of the BBD technique[48]. **Table 3** shows the outcomes of statistical testing regarding the method's effectiveness in synthesizing pyrimidine derivatives. The F value for the synthesis of pyrimidine derivatives

was obtained as 4.71. The P-value was 0.0092 for the model, indicating that the model is significant. The P value of 0.0092 specifies that the factor and its interaction with the other parameters are effective.

Table 3. Analysis of variance (ANOVA) for pyrimidine derivatives synthesis.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2951.86	14	210.85	4.71	0.0092	significant
A-mmol of acetylacetone	108.00	1	108.00	2.41	0.1514	
B-mmol of urea	588.00	1	588.00	13.14	0.0047	
C-mmol of aldehyde	1633.33	1	1633.33	36.50	0.0001	
D-Catalyst amount	108.00	1	108.00	2.41	0.1514	
AB	20.25	1	20.25	0.4525	0.5164	
AC	42.25	1	42.25	0.9441	0.3541	
AD	9.00	1	9.00	0.2011	0.6634	
BC	12.25	1	12.25	0.2737	0.6122	
BD	9.00	1	9.00	0.2011	0.6634	
CD	16.00	1	16.00	0.3575	0.5632	
A^2	1.77	1	1.77	0.0395	0.8464	
B^2	103.06	1	103.06	2.30	0.1601	
C^2	230.83	1	230.83	5.16	0.0465	
D^2	18.24	1	18.24	0.4076	0.5375	
Residual	447.50	10	44.75			
Cor Total	3399.36	24				

Based on the data provided above, it can be concluded that the amount of urea, aldehyde, and acetylacetone is a critical component in the synthesis of pyrimidine derivatives. The coefficient of determination (R^2) was used to assess how well the model matched the experimental findings. The values of R^2 for the synthesis of pyrimidine derivatives were 0.8684. Adeq Precision evaluates the signal-to-noise ratio, with a value above 4 being ideal. The ratio of 7.736 shows a sufficient signal, meaning this model is suitable for exploring the design space (**Table 4**).

Table 4. Shows the determination coefficient and adequate precision.

Std. Dev.	6.69	R^2	0.8684
Mean	76.16	Adjusted R^2	0.8841
C.V. %	8.78	Predicted R^2	0.9011
		Adeq Precision	7.7356

The normal plot diagrams, **Figure 4**, indicate that there is the best linear correlation between the predicted and the experimental data. Based on the findings, it can be said that the predicted models are appropriate for pyrimidine derivative synthesis optimization parameters. Two variables are used to represent a three-dimensional response surface, while the other parameters are held constant at a set level (central level). The three-dimensional response levels' nonlinearity suggests that each of the independent variables significantly interacts with the others. This experiment took into account four factors: the amount of acetylacetone, the amount of aldehyde, the amount of urea, and the amount of catalyst. The connections between the independent

variables and response values are represented by a three-dimensional response surface. 3-D response surface graphs for the production of pyrimidine derivatives are shown in **Figure 5**.

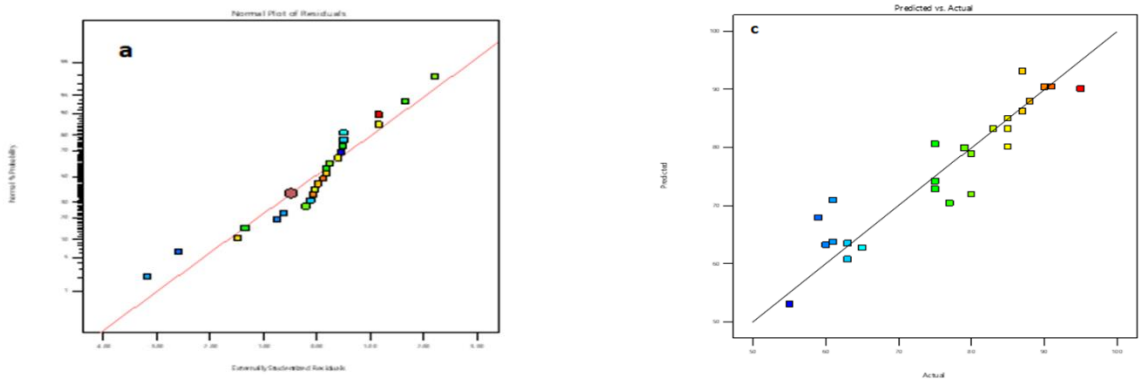
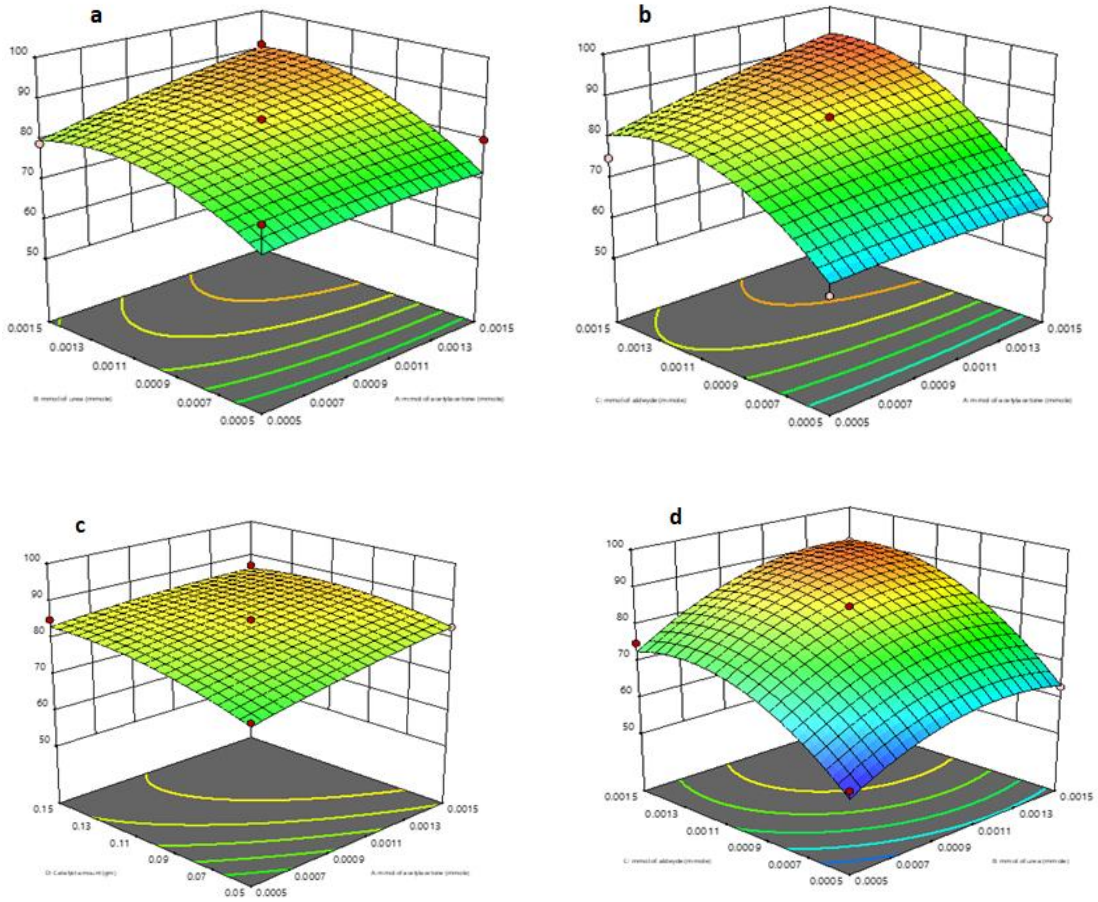


Figure 4. The normal plot for the pyrimidine synthesis method.



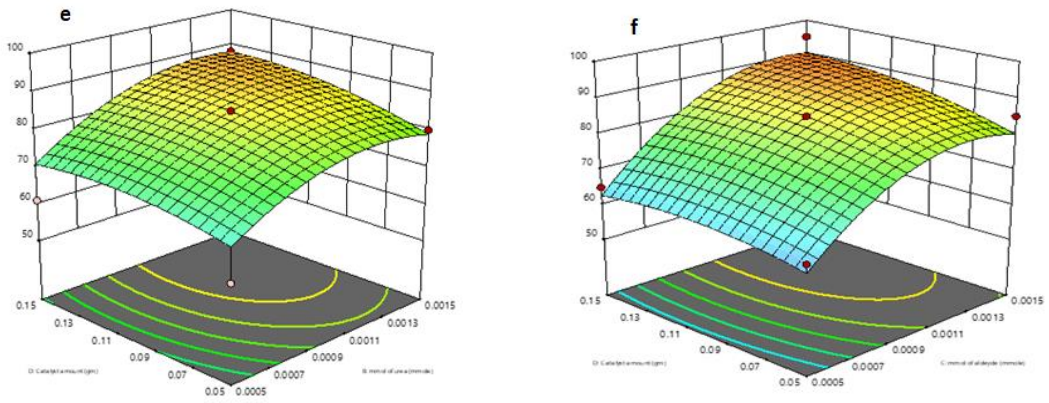


Figure 5. 3-D response surface plots of the effect of (a) amount of urea and acetylacetone, (b) amount of aldehyde and acetylacetone, (c) amount of catalyst and acetylacetone, (d) amount of aldehyde and urea, (e) amount of catalyst and urea, (f) amount of catalyst and aldehyde.

Table 5 provides the most reliable conditions for synthesizing pyrimidine derivatives and examines the effect of substituents on the benzene ring. The outcomes suggest that introducing a catalyst neutralized the impact of the substituent groups on the product yield.

Table 5. Optimum conditions and the effect of the substituted group.

Substituted group(R)	Type of catalyst	Solvent type	Amount of catalyst(gm)	Time (hrs)	Yield (%)
H	CuO NPs	EtOH	0.1	30	95
NO_2					94
OH					90

4. Conclusion

We correctly synthesized pyrimidine derivatives using copper oxide nanoparticles (CuO NPs) as a green catalyst in ethanol. CuO NPs proved fairly effective in facilitating the synthesis of biologically active compounds. Remarkably, a few reactions proceeded fairly quickly, a fast and efficient protocol, whilst conducted with CuO NPs in ethanol. Additionally, the catalyst validated extraordinary reusability, maintaining high activity over 4 consecutive cycles with minimum loss in performance. The present work was compared with several studies, as shown in the **Table 6**.

Table 6. Comparison of the present work with several studies.

Entry	Catalyst	Time(min)	Yeild(%)	Ref.
1	Fe3O4@SiO2–SnCl4 NPs	2-4	90-98	[49]
2	CaO@SiO2@BAIL ionic liquid-coated NPs	---	82-92	[50]
3	CaO@ SiO2@ BAIL	---	---	[51]
4	CuO/ZnO@N-GQDs@NH2 nanocomposite	50-400	32-94	[52]
5	Fe3O4@iron-based MOF nanocomposite	2.0-55	25-98	[53]
6	CuFe2O4/KCC-1/PMA magnetic nanocatalyst	---	---	[54]
7	CuO NPs	30	90-95	Present Work

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Conflict of interest

The authors declare no conflicts of interest.

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