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EFFICIENTLY SYNTHESIZE ISOXAZOL-5(4H)-ONE DERIVATIVES IN AQUEOUS MEDIUM USING CUO NANOPARTICLES CATALYSIS WITH A BIOSYNTHESIZED APPROACH

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ABSTRACT:
In our study, we capitalized on the potential of copper oxide nanoparticles derived from plant extracts as environmentally friendly catalysts for various reactions, particularly in the synthesis of isoxazol-5(4H)-one derivatives. This innovative approach presents a green, efficient, and straightforward method for producing these compounds through a one-pot, three-component reaction involving aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride, all conducted at room temperature. Impressively, this procedure yielded the title compounds in high to excellent yields, all while maintaining short reaction times. Copper oxide nanoparticles are a standout catalyst choice due to their low toxicity, cost-effectiveness, easy availability, and manageable handling. Overall, this method offers several notable benefits, including high yields, swift reaction times, and an environmentally friendly profile, making it a valuable contribution to sustainable chemical synthesis practices.
KEYWORDS: Copper Oxide Nanoparticles, Aldehyde, Biosynthesis, Isoxazol-5(4H)-one.

INTRODUCTION:

One notable approach in organic synthesis is the utilization of multicomponent reactions (MCRs), a strategy involving three or more reactants converging in a single step to form intricate products[i-ii]. MCRs are esteemed for their straightforward procedures, high atom economy, and convergent nature, offering a versatile toolkit in various scientific applications, including material sciences, drug discovery, ligand preparation, and natural product synthesis [iii-iv]. Catalysts play a pivotal role in facilitating MCRs, serving to accelerate complex transformations, provide selectivity, and broaden the scope of applicable substrates[v-vi] Heterocyclic compounds, distinguished by cyclic structures incorporating non-carbon atoms such as nitrogen, oxygen, or sulfur, constitute a significant class of organic molecules, playing pivotal roles in diverse scientific disciplines, including pharmaceuticals, agrochemicals, and materials science [vii-viii]. Within this realm, Isoxazol-5-one derivatives have demonstrated diverse therapeutic and pharmaceutical potentials, encompassing properties such as anticancer, anti-microbial, anti-inflammatory, immunosuppressive, antifungal, and hypoglycemic

activities [ix-xiii]. Numerous synthetic methodologies have been documented to synthesize isoxazol-5-one derivatives, thereby expanding their potential applications (as depicted in fig.1) and facilitating drug discovery and development endeavors. Isoxazoles potent biological activities make them attractive targets for efficient and green synthetic protocols. Diverse synthetic methods for isoxazol-5(4H)-one derivatives have been reported, involving a three-component condensation of aromatic aldehydes, hydroxylamine hydrochloride, and β-oxoesters. These methods employ catalytic quantities of DABCO, potassium hydrogen phthalate, boric acid, pyridine, sodium sulfide, tartaric acid, N-bromosuccinimide, and sodium silicate, among others [xiv–xxi]. Despite their utility, these approaches often entail drawbacks such as the use of toxic or costly reagents and catalysts, stringent acidic or basic conditions, diminished product yields, labor-intensive work-up procedures, and protracted reaction durations. The surge in demand for sustainable chemistry has driven the exploration of eco-friendly catalysis alternatives, notably focusing on nanomaterials or nanoparticles. Transition-metal nanoparticles, particularly CuO nanoparticles, have emerged as significant players in catalysis, replicating metal surface activation and catalytic processes at the nanoscale[xxii-xxiii]. Noteworthy for their cost-effectiveness and environmental friendliness, CuO nanoparticles stand out in heterogeneous catalysis[xxiv] .Their attributes include reduced execution time, minimized waste, and ease of transportation, catalyst recyclability, low corrosion, and disposal, rendering them ideal for diverse catalytic applications [xxv-xxvi]. Recent literature showcases the efficacy of CuO nanoparticles in various organic reactions (as displayed in fig.2), including Aza-Michael [xxvii], Cannizzaro [xxviii], aldol condensation [xxix], Knoevenagel condensation [xxx], Biginelli [xxxi], Ullmann coupling [xxxii], and Mannich reactions [xxxiii]. The catalytic role of CuO nanoparticles extends to the synthesis of diverse compounds such as flavanones, coumarins, β-amino carbonyl compounds, chalcones, quinolines, and dihydropyrimidinones, underscoring their versatility in modern organic synthesis [xxxiv- xxxv]. CuO nanoparticles also find applications in environmental, biomedical, industrial, and agricultural sectors (as exhibited in fig. 3).

Our previous research successfully synthesized CuO nanoparticles through an eco-friendly biological method utilizing plant extracts. Building upon this foundation, we present a novel approach employing these biosynthesized CuO nanoparticles in the synthesis of isoxazole-5(4H)-one derivatives. This innovative process utilizes CuO nanoparticles as efficient and reusable catalysts, with water serving as the solvent (Scheme 1). The significance of this biologically mediated synthesis lies in its mild reaction conditions, operational simplicity, and potential for large-scale production, aligning with the growing emphasis on eco-friendly alternatives in chemical development.

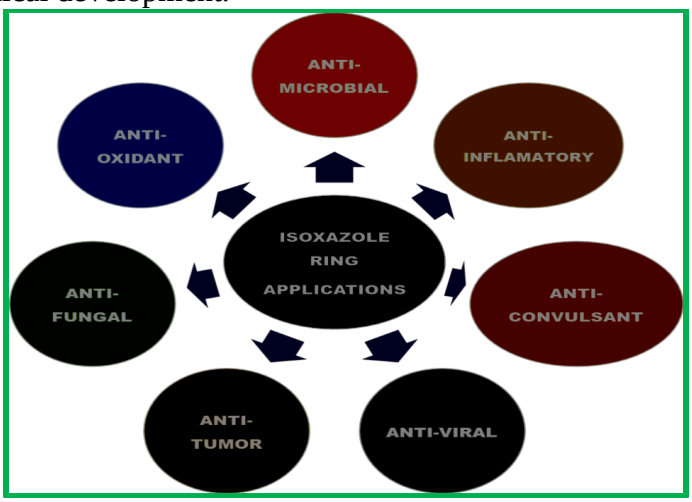


Fig. 1: Isoxazole ring finds applications in diverse fields due to its versatility.

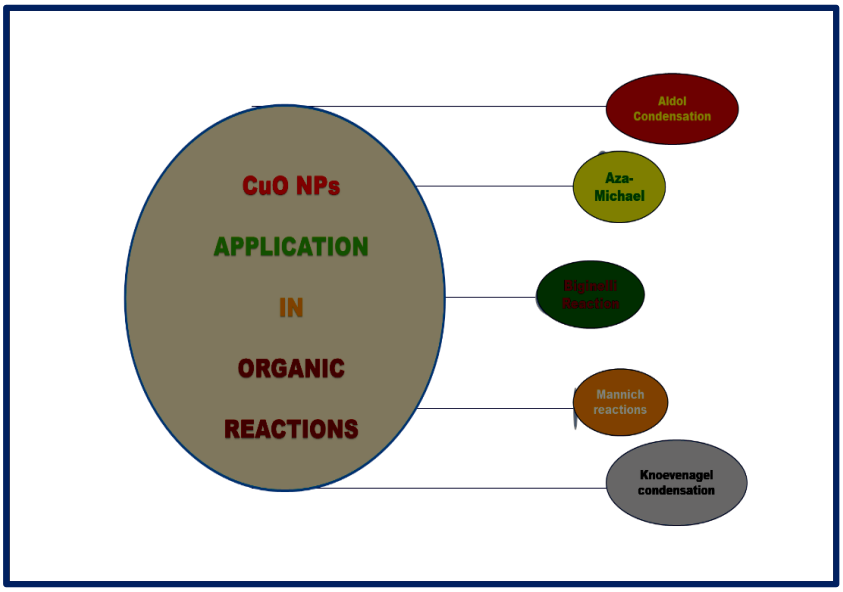


Fig. 2: Application of CuO NPs in organic reaction.

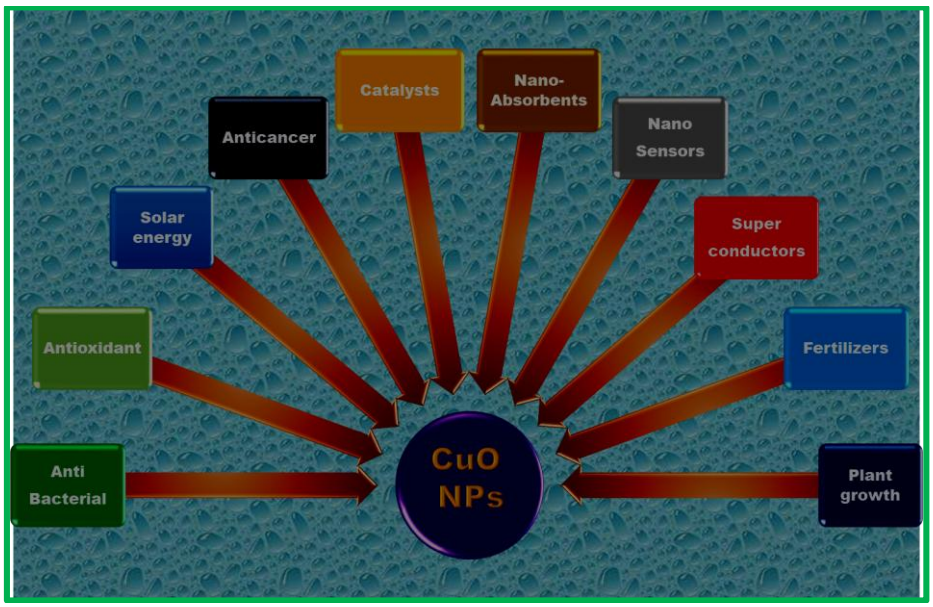
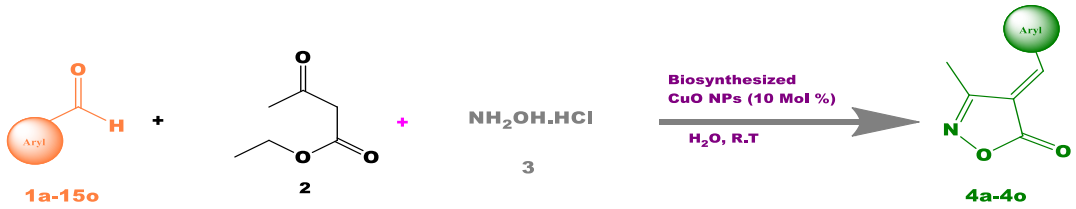


Fig. 3: CuO NPs have versatile applications across various fields



Scheme 1. CuO NPs-catalyzed synthesis of isoxazole-5(4H)-one derivatives.

EXPERIMENTAL SECTIONS:

CHEMICALS AND MATERIALS

In this study, all the starting materials and solvents were obtained from SD fine Chemicals Ltd. Mumbai, and used as received without undergoing additional purification. All equipment underwent prior cleaning and sterilization before commencing the processes for utmost hygiene and safety. Melting points of the synthesized compounds were determined using an electro thermal melting point apparatus and were reported without any corrections. The progress of reactions was monitored using thin-layer chromatography (TLC) and visualized under UV light. The synthesized compounds were purified via recrystallization from ethanol solvents for enhanced purity and quality. Compound characterization was performed using potassium bromide (KBr) pellets on a Fourier Transform Infrared Spectrophotometer. Additionally, proton nuclear magnetic resonance (^{1}H-NMR) spectra were noted using a 400 MHz Bruker Advance spectrophotometer in $CDCl_3$ solvent and NMR chemical shifts (δ) in ppm. IR stretching values were described in cm^{-1}.

1. PREPARATION OF CATALYST:

In our previously reported research article [xxxvi], we detailed the synthesis of copper oxide (CuO) nanoparticles using extracts from the *Rumex nepalensis (spreng.)* plant. Briefly described here procedure for catalyst preparations. Initially, 20 grams of dried plant material were combined with 200 mL of water in a round-bottom flask, heated to 60-70 °C, and boiled for 30 minutes. After cooling, the extract was filtered and refrigerated. In a separate flask, 100 mL of the plant extract was heated to 70-80 °C with constant stirring. Then, 30 mL of an aqueous solution containing 3 grams of cupric nitrate trihydrate was added, leading to the formation of a greenish glue-like substance. This material was collected, calcined at 400 °C for 3 hours, yielding black CuO nanoparticles and utilized as catalyst. Formation of CuO nanoparticles were confirmed by SEM, TEM, EDAX, XRD etc in our earlier reported articles.

2. GENERAL PROCEDURE FOR PREPARATION OF ISOXAZOL-5(4H)-ONE DERIVATIVES:

The general procedure for the synthesis of isoxazol-5(4H)-one derivatives involved the following steps. Ethyl acetoacetate (1mmole), aryl aldehyde (1mmole), hydroxylamine hydrochloride (1mmole), and 10 mol% of biosynthesized CuO nanoparticles were mixed in distilled water in a Schlenk tube. The reaction mixture was stirred at room temperature. The progress of the reaction was monitored using TLC analysis, and the required time for completion was recorded (Table 2).Upon completion of the reaction, the reaction mixture was filtered, and the residue was dissolved in hot ethanol. Filtration was performed again to separate the product as the filtrate from the catalyst. The same catalyst was reused for the synthesis of further derivatives. The product was obtained by allowing the filtrate to cool, and recrystallization from hot ethanol was conducted to yield pure desired compounds in high yields. The identity of known products was confirmed by comparing their melting points to those documented in the literature and also ^{1}H, IR and ^{13}C spectra of some were noted by using solvent $CDCl_3$ on Brucker 400 MHz and 100 MHz spectrometer, respectively, with TMS as an internal standard.

Spectral data of selected products:

1.1 (E)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one:

Pale Yellow Solid, ^{1}H NMR (400 MHz, $CDC1_3$): δ 2.28 (s, 3H), 3.92 (s, 3H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.34 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDC1_3$): δ11.8, 55.8, 114.8, 125.9, 137.1,149.4, 161.4, 164.7 ppm; IR (KBr) νmax = 3040, 2980, 2795, 1706, 1595, 1220, 1105 cm^{-1}.

1.2 (E)-4-benzylidene-3-methylisoxazol-5(4H)-one:

Light yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.51–7.68 (m, 1H), 7.61 (t, J = 7.7 Hz, 2H), 8.11 (dd, J = 1.3, 6.4 Hz, 2H). 3.31 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (C=N), 174.2 (C=O), 16.0 (-CH3), 114.3, 118.02, 125.9, 137.1, 151.8, 158.2 ppm; IR (KBr): νmax = 3215, 2290, 1730, 1645, 1245, cm^{-1}.

1.3 (E)-4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one:

Red Solid, ^{1}H NMR (400 MHz, CDCl3): δ 10.8 (s, 1H), 7.12 (d, J = 8.2 Hz, 2H), 8.10(d, J = 8.9 Hz, 2H), 7.91 (s, 1H), 3.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0 (C=N), 174.0 (C=O), 16.1($-CH_3$), 115.0, 125.3, 125.9, 134.9, 151.6, 160.2 ppm; IR (KBr): νmax = 3520, 3000, 2920, 1750, 1610, 1240, cm^{-1}.

1.4 (E)-4-(2-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one:

Yellowish Solid, ^{1}H NMR (400 MHz, $CDC1_3$): δ 6.89 (t, J = 9.86 Hz, 1H), 7.14 (d, J = 8.91 Hz, 1H), 7.35–7.47 (m, 1H), 8.11(s, 1H), 8.55 (dd, J = 1.90 Hz, 1H), 11.21 (s, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1 (C=N), 173.9 (C=O), 16.0 (-CH3), 116.8, 117.0, 119.9, 120.1, 131.9, 139.1, 148.2, 159.9 ppm; IR (KBr): νmax = 3500, 3250, 2320, 1750; 1680; 1156 cm^{-1} .

1.5 (E)-4-(3-hydroxy-4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one:

Yellowish solid, ^{1}H NMR (400 MHz, CDC13): δ 2.40 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.10 (d,
J = 7.94 Hz, 1H), 7.67 (s, 1H), 8.10 (d, J = 9.56 Hz, 1H), 7.93(s, 1H), 9.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 164.22(C=N), 173.90(C=O), 16.14, ($-CH_3$), 55.9 (-OCH3), 112.81, 115.26, 119.02, 127.11, 130.13, 148.54, 154.51, 155.8 ppm; IR (KBr): νmax =3510, 2330, 1705, 1539, 1122, 1139 cm^{-1}.

1.6 (E)-4-(3-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one:

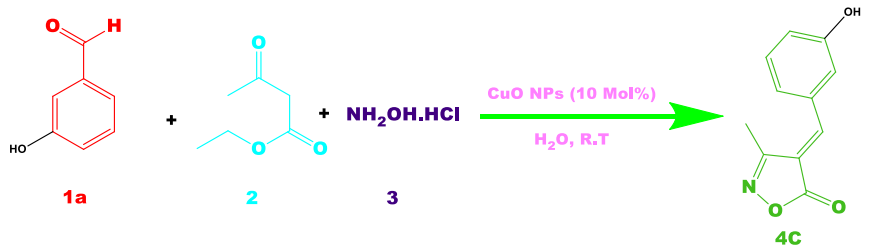
Orange solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.1 Hz, 1H), 7.69 (s, 1H), 7.54 (t, J = 7.92 Hz, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.82 (s, 1H), 9.78 (s, 1H), 3.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1 (C=N), 174.1(C=O), 16.1(-CH3), 117.8, 119.0, 120.9, 125.3, 131.9, 133.9, 153.1, 158.8 ppm; IR (KBr): νmax = 3434, 3222, 2350,1740,1622,1296 cm^{-1}.

RESULTS AND DISCUSSIONS

In our preceding investigation, copper oxide nanoparticles (CuO NPs) were synthesized following a documented procedure. The synthesized CuO NPs underwent thorough characterization using advanced analytical techniques, encompassing X-ray diffraction (XRD), transmission electron microscopy (TEM), Energy Dispersive X-ray Analysis (EDAX), and scanning electron microscopy (SEM).The nanostructure and crystallite size of the particles were meticulously confirmed through a comprehensive analysis that incorporated XRD, SEM, and TEM. The application of these techniques allowed for a detailed examination of the structural features and dimensions of the nanoparticles. Additionally, EDAX provided valuable insights into the elemental composition of the synthesized CuO NPs. To ensure the credibility of our findings, the results obtained were further validated through a comparative analysis with pertinent literature. This rigorous comparison served to enhance the robustness and reliability of the reported properties of the synthesized copper oxide nanoparticles.

In the model reaction, a multi-component condensation reaction was conducted using benzaldehyde (C_6H_5CHO), hydroxylamine hydrochloride ($NH_2OH.HCl$), and ethyl acetoacetate in water (H_2O) as the solvent. Synthesized copper oxide nanoparticles (10%), as illustrated in Scheme 2, were employed as a catalyst to optimize the reaction conditions and facilitate the production of isoxazole-5(4H)-one derivatives (Scheme 2.). The study's findings reveal a clean reaction profile, obviating the need for chromatographic separation due to the absence of observed impurities. Following the completion of the reaction, the solid product

was easily collected through simple filtration. When necessary, the product underwent recrystallization in ethanol, ensuring the obtainment of pure products. This straightforward purification method further underscores the efficiency and selectivity of the synthesized copper oxide nanoparticles as a catalyst in the described multi-component condensation reaction.



Scheme 2. Model reaction using catalyst green synthesized CuO NPs for Optimization of the reaction conditions

In the initial phase of this research, an extensive examination of various solvents (including n-hexane, acetone, ethanol, methanol, water, etc.) was conducted to evaluate their influence on the model reaction, as detailed in Table 1. The results revealed that solvents such as ethanol, methanol, n-hexane, and acetone, when employed with 5 mole % CuO NPs as a catalyst, yielded products in amounts of 30%, 37%, 68%, and 70%, respectively. However, a noteworthy improvement in product yield was observed when these solvents were replaced with water. The use of water as a solvent led to a substantial increase in the yield of products. This unequivocal observation indicates that employing water as the solvent significantly enhanced the reaction rate, resulting in elevated product yields for all target compounds. This underscores the pivotal role of water as a solvent, facilitating effective interactions between reactants and the catalyst. Consequently, it improved reaction kinetics, ultimately contributing to superior product formation. These findings highlight the critical importance of solvent selection, particularly emphasizing the advantageous impact of water, in optimizing reaction outcomes. The judicious choice of solvent, as evidenced by the increased yields in the presence of water, is integral to the overall success of the model reaction.

Table 1: Model reaction using different solvents.

Sr. no.	**Solvent**	**Catalyst (Mol %)**	**Time (Min)**	**% Yields**
1	Ethanol	5	80	30
2	Methanol	5	80	37
3	n-hexane	5	80	68
4	Acetone	5	80	70
5	Water	5	80	73
6	Water **(Present Work)**	10	80	93
7	Water	15	80	93
8	Water	20	80	93
9	Water	25	80	93

Our research also focused on optimizing the quantity of copper oxide nanoparticles (CuO NPs) in the model study (Scheme 2.), with an investigation into various concentrations of CuO NPs to discern their impact on the reaction. Initially, we chose to employ 5 mole % of CuO NPs as a catalyst in the model reaction. The outcome of this reaction yielded the corresponding product

(4c) with an isolated reaction yield of 73% within 80 minutes (Table 1, entry no. 5). This result was promising and prompted further exploration of other catalyst amounts. Upon utilizing 10 mol% of CuO NPs as a catalyst, the desired heterocyclic product (4c) was obtained with a 93% isolated reaction yield after 80 minutes (Table 1, entry no.6). Subsequently, employing 15 mol% of the catalyst, the model reaction progressed to afford the product (4c) with a 93% isolated reaction yield (Table 1, entry no.7). Similarly, applying 20 mol% and 25 mol% of the catalyst, the model reaction proceeded to yield the desired product (4c) with 93% isolated reaction yield, respectively (Table 1, entry no. 8 and 9). Due to the consistent increase in the catalyst amount correlating with an increase in the reaction yield while maintaining the same reaction time (in Fig. 4). In this instance, the reaction yielded the highest isolated reaction yield at 93% (10 mol% of the catalyst) at after 80 minutes. Notably, employing higher amounts of the catalyst (15 mol% and 25 mol%) did not result in an improvement in the reaction yield (Table 1, entries no.10 and 11). Therefore, the optimal catalyst amount was determined to be 10 mol % based on the achieved high yield and efficiency.

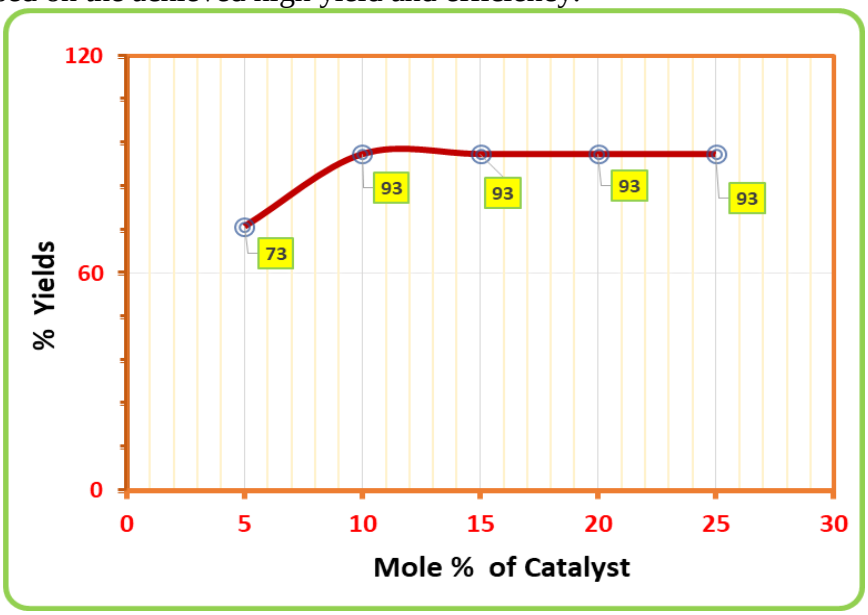


Fig.4: Catalyst quantity's impact on the model reaction's outcome was studied.

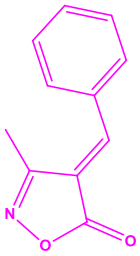
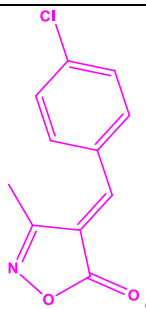
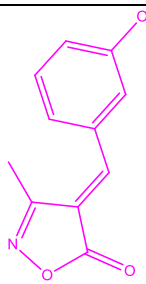
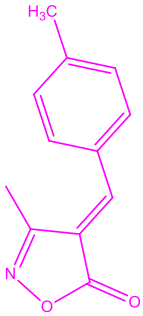
Following the determination of the optimized reaction conditions, the generality of the reaction was assessed using substituted aromatic aldehyde precursors. Aromatic rings featuring electron-donating groups, such as hydroxyl (-OH), methyl (-CH3), and methoxy (-OCH3), underwent heterocyclization within 60-90 minutes, resulting in the corresponding heterocyclic compounds (entries no. 3c, 4d, 5e, and 6f) with impressive isolated yields of 91-93% (Table 2, entries no. 3c, 4d, 5e, and 6f). The presence of these electron-donating groups led to shorter reaction times and higher yields, likely attributed to their ability to donate electron density to the ring, enhancing its nucleophilic character. Consequently, phenyl rings carrying such electron-donating groups consistently exhibited exceptional efficiency and yielded products in shorter timeframes. A substantial body of research, conducted by various scientists, has consistently demonstrated that substituted benzaldehydes with electron-donating groups consistently yield heterocyclic products with remarkable efficiency and significant isolated yields [xxxvii- xxxix].

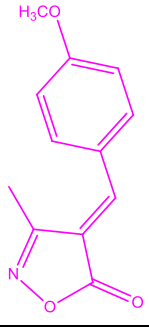
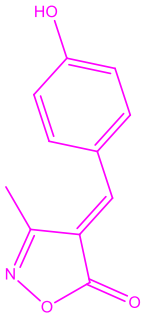
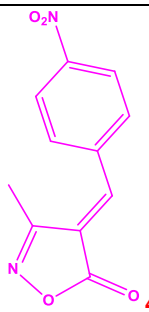
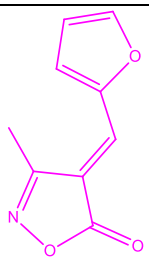
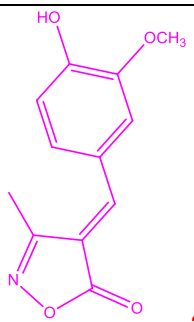
Conversely, electron-withdrawing substituents, as evidenced by entries no. 2b and 7g in Table 2 (containing -Cl, NO_2, etc.), were associated with reduced reaction rates and yielded no products [xl-xli]. This observation is likely due to the destabilizing effect of these substituents,

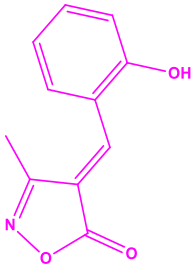
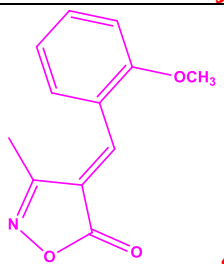
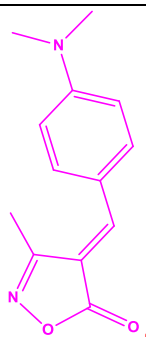
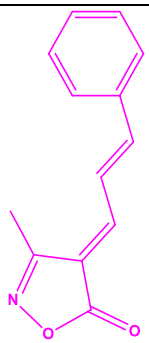
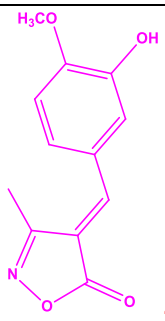
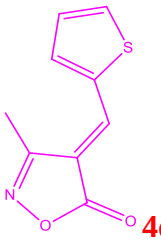
highlighting the importance of the substrate's structure in shaping the reaction outcomes. The broad applicability of the procedure is underscored, emphasizing how the nature of the substituents plays a pivotal role in determining the reaction's success.

Examining aromatic aldehydes with hydroxyl groups, particularly o-hydroxybenzaldehyde (Table 2, entry no. 10j), it becomes evident that the reaction requires more time and produces less of the desired product compared to p-hydroxybenzaldehyde (Table 2, entry no. 6f) and m-hydroxybenzaldehyde (Table 2, entry no. 3c). This discrepancy can be elucidated by the crowded spatial arrangement around the hydroxyl group in the ortho position, making it more challenging for the reactants to access each other and thereby slowing down the overall reaction efficiency, as indicated in Table 2.

Table 2: CuO NPs -catalyzed synthesis of various synthesis of isoxazole-5(4H)-one derivatives.

Sr. No.	**Aldehyde**	**Products**	**Time (Min)**	**Isolated % Yield**	**M.P (^{0}C)**	
					Found	**Reported (Ref)**
1	C_6H_5CHO **1a**	 **4a**	90	93	143–145	142–144[xlii]
2	p-ClC_6H_5CHO **2b**	 **4b**	180	-	-	-
3	m-OHC_6H_4CHO **3c**	 **4c**	90	93	201-203	202 – 203[xliii]
4	p-MeC_6H_4CHO **4d**	 **4d**	65	93	128 -131	129 -131[xliv]

5	p-$OMeC_6H_4CHO$ **5e**	 **4e**	70	92	173 - 174	173 -175[xlv]
6	p-OHC_6H_4CHO **6f**	 **4f**	70	92	211 – 214	212 – 215 [xlvi]
7	C_6H_5CHO2N **7g**	 **4g**	150	-	-	-
8	C_4H_3OCHO **8h**	 **4h**	80	89	235–240	238–241 [xlvii]
9	p-$OHC_8H_7O_2CHO$ **9i**	 **4i**	80	94	213–216	211–214 [xlviii]

10	o-OHC_6H_4CHO **10j**	 **4j**	95	89	195 - 199	195 – 197 [xlix]
11	o-OMe-C6H4CHO **11k**	 **4k**	60	93	160 -162	162 -164 [l]
12	4-$N(CH_3)_2$ - C6H4CHO **12l**	 **4l**	65	93	207-210	206-209[li]
13	C6H5CH=CHCHO **13m**	 **4m**	75	91	170–173	173–178[lii]
14	3-OH-4-OCH3C6H3CHO **14n**	 **4n**	70	92	184–186	185–187 [liii]
15	C_4H_3SCHO **15o**	 **4o**	75	90	141–143	144–146[liv]

The assessment of recyclability and the catalyst's reusability holds significance in the context of green chemistry [lv]. In consideration of this aspect, the cyclability and reuse of the catalyst were thoroughly investigated. Upon completion of the reaction, the crude product, along with the catalyst, was collected through simple filtration from the reaction mixture and subsequently purified with a minimal amount of chloroform. The catalyst was then separated from the products and dried.

The recovered CuO NPs catalyst was reintroduced into the model reaction under the optimized conditions. Experimental results indicated that the catalyst demonstrated recyclability for up to four cycles (Table 3.). Across these four runs, the product was consistently obtained with yields of 93%, 92%, 92%, and 88%, while maintaining the same reaction time of 80 minutes. This observation underscores the catalyst's stability and effectiveness over multiple cycles, affirming its potential for sustainable and environmentally friendly catalysis in the synthesis of the desired products (as shown in Table 3.).

Table 3: Recycling the catalyst in the experiment involving the reaction was performed.

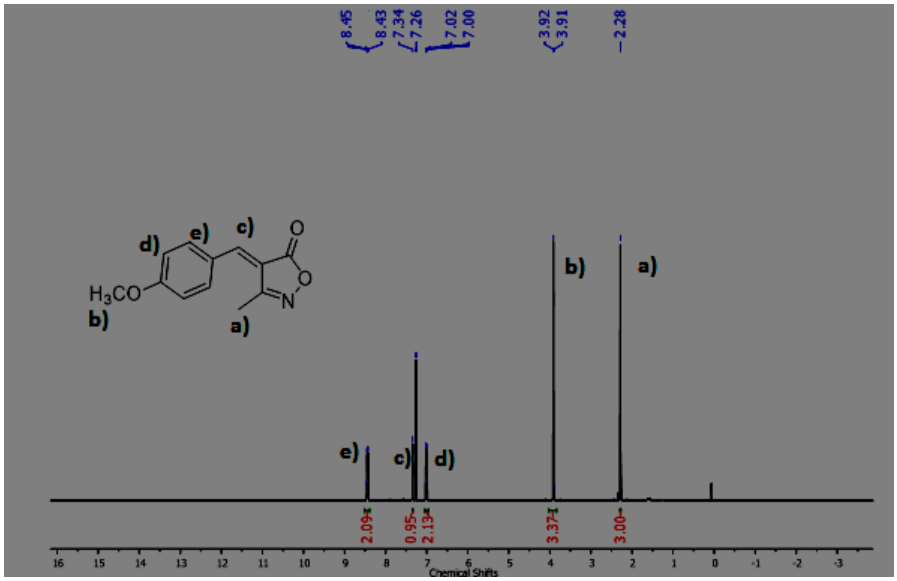
Entry	No. of repetition	%Yield	Time (Min)
1	1(Fresh)	93	80
2	2	92	80
3	3	92	80
4	4	88	80

Further, we conducted a comparative analysis to evaluate the catalytic efficiency of synthesized copper oxide nanoparticles, as outlined in Table 4.The findings of these investigations reveal several advantages of this work over some of the previous catalysts. Notably, our approach demonstrated the use of a lower amount of catalyst compared to entries no. 1–5 in Table 4. Additionally, the reaction times in our study were comparatively shorter than those reported in entries no. 1, 2, and 4 in Table 4. Furthermore, our methodology yielded relatively higher product yields when compared to entries no. 1–5 in Table 4. Moreover, executing the reaction in water as the solvent, as employed in our study, represents an advantage over entries no. 1, 3, 4, and 5 in Table 4, where alternative solvents were used. These observed advantages underscore the efficiency and efficacy of the proposed methodology, positioning it favorably in comparison to prior reported works. The utilization of a reduced catalyst amount, shorter reaction times, higher yields, and the environmentally friendly choice of water as the solvent collectively contribute to the overall advancement and applicability of this synthetic approach.

Table 4: Various catalysts were used to synthesize isoxazol-5(4H)-one derivatives for evaluation.

Sr. no.	**Catalyst**	**Condition**	**Minutes**	**Mol%**	**% Yield**
1	Antimony trichloride	Water, rt	120	22	**85** [lvi]
2	Pyridine	EtOH, reflux	120	100	**52.5** [lvii]
3	Pyridine	Water, Ultrasound	90	100	**67** [lviii]
4	Cetyltrimethylammonium chloride	Water, 90 ^{0}C	240	30	**89** [lix]
5	γ-Alumina	Water, reflux		30	**80** [lx]
6	**Synthesized CuO NPs**	Water, rt	**80**	**10**	**93 Present work**

The structures of the title products were deduced from their spectra analysis. For instance, the 1H NMR spectrum of (E)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one revealed the structural characteristics of both isoxazol-5(4H)-one and 4-methoxybenzene (fig.1). The 1H NMR spectrum revealed distinctive singlet signals at δ = 2.28 and 7.34 ppm for 3-methyl- and olfinic (C=CH-Ar) protons of 3-methyl-isoxazol-5(4H)-one, respectively. Also, protons of the 4-methoxy phenyl heterocyclic unit appear at δ = 7.01and 8.44 ppm as doublet with *J* coupling 8.00 Hz and methoxy proton appeared at δ = 3.92 ppm as singlet.



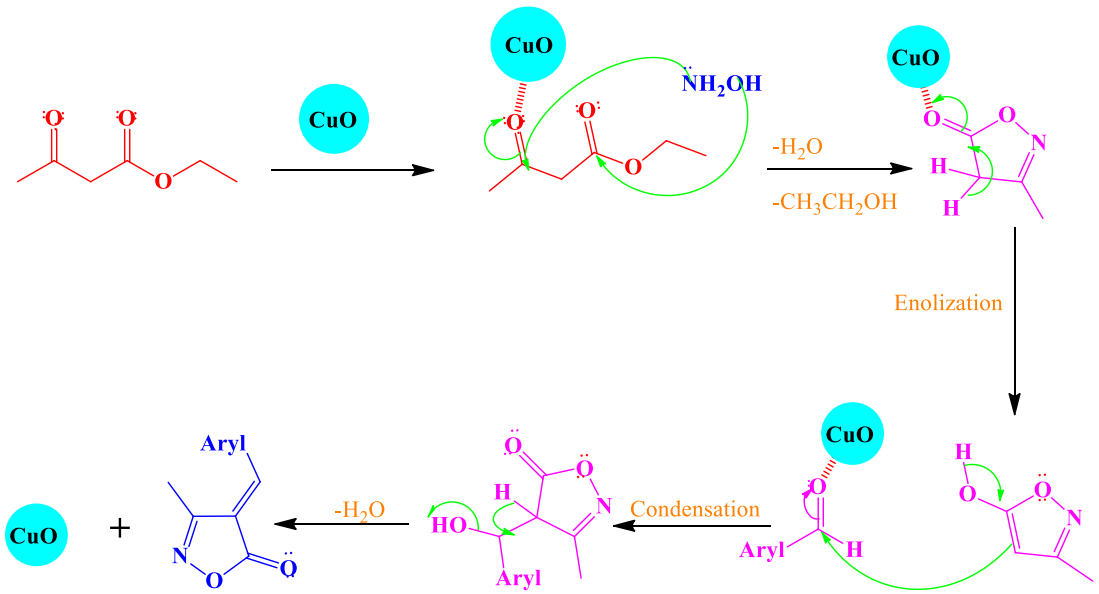


Fig. 6: Possible mechanism for all the synthesized compounds (4a-4o).

In accordance with literature [lxi], the proposed reaction mechanism is depicted in Fig. 6. Initially, copper oxide nanoparticles activate the carbonyl carbon in ethyl acetoacetate. Subsequently, hydroxyl (-OH) and amino (-NH2) groups in hydroxylamine hydrochloride act as nucleophiles, facilitated by copper oxide nanoparticles, attacking both carbonyl carbons in ethyl acetoacetate, leading to the formation of a cyclic adduct. This adduct undergoes a condensation reaction with

an aldehyde, resulting in the desired product. This process eliminates a water molecule and removes copper oxide nanoparticles, ensuring the purity of the final product.

CONCLUSIONS:

To recap, we have presented an efficient methodology for the one-pot synthesis of isoxazol-5(4H)-one derivatives utilizing CuO nanoparticles as a solid catalyst. These nanoparticles exhibit reusability and are non-toxic. The primary merits of this approach encompass high product yields, straightforward experimental protocols, brief reaction durations, compatibility with various substrates, facile work-up procedures, avoidance of hazardous organic solvents, and the convenience of catalyst recovery and recycling. These attributes render it a valuable, appealing, and environmentally benign strategy for the preparation of isoxazol-5(4H)-one derivatives. This has promising prospects in materials science, agrochemicals, medicinal chemistry, pharmaceutical intermediates, photo stabilizers, photodynamic therapy, and biochemical research. Consequently, these derivatives maintain considerable appeal across various scientific and industrial domains, offering substantial potential for future progress and creativity.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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