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RESEARCH PAPER

Synthesis of Pyrimido [4, 5-b] Quinolines in the Presence of Fe_3O_4@Nano-Cellulose/Cu (II) as a Natural-Based Catalyst with Their DFT Studies

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ABSTRACT

A simple, efficient, and high yielding one-pot protocol for the synthesis of pyrimido [4,5-b] quinoline derivatives has been developed by three component domino coupling of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, dimedone, and various substituted aldehydes by Fe_3O_4@NCs/Cu(II) as an environmentally catalyst in ethanol at 60 °C. Fe_3O_4@NCs/Cu(II) as a bio-based magnetic nano-catalyst was prepared through in situ co-precipitation of Fe^{3+} and Fe^{2+} ions *via* NH_4OH in an aqueous solution of nano-cellulose. After completion of the reaction, the catalyst was separated by an external magnet. Several advantages of this protocol are good yields, short reaction times, easy work-up, recyclability, and environmentally benign of the catalyst, which are consistent with the computational data. The structures of the products were confirmed by elemental analyses, IR, ^1H NMR and ^{13}C NMR spectra.

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INTRODUCTION

Now a days, green chemistry has attained the status of a major scientific discipline, and it now encompasses wide areas of chemical enterprise and is an alternative way to reduce drastic requirements for reactions [1]. Therefore, considering the green chemistry aspects, biopolymers have attracted much attention as supports for catalytic applications. Among them, cellulose, as one of the most important biopolymers, has received growing attention as a non-toxic, renewable, and biocompatible polymer. Cellulose has many properties, such as a renewable resource, broad chemical modifying capacity, hydrophilicity and large surface area [2,3] Cotton is a natural, cheap, and readily available source of cellulose. Recently, magnetic nanoparticles (MNPs) have appeared as an excellent type of catalyst support because of their good stability, easy synthesis and functionalization, high surface area and facile separation by magnetic forces, as well as low toxicity and price [4]. Other important features of these magnetic catalysts are high catalytic activity, high degree of chemical stability in various organic and inorganic solvents, reusability and benign character in the context of green chemistry [5-7]. Fe_3O_4 nanoparticles are coated with various materials such as surfactants [8], polymers [9], silica [10], biopolymers like cellulose [11] and chitosan [12] to form a core-

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shell structure. Thus, one of the main purposes of the present work was preparation of nano-cellulose by sulfuric acid hydrolysis of cotton and using it for the synthesis of Fe_3O_4@nano-cellulose/Cu (II) that abbreviated to (Fe_3O_4@NCs/Cu (II)).

Multicomponent reactions (MCRs) have emerged as a powerful synthetic tool for the preparation of biologically active compounds [13]. Pyridopyrimidines and pyrimidoquinoline are an important class of heterocycles, which found in a wide variety of biologically active products. Several multi-component reactions methods have been reported for the synthesis of pyridopyrimidines and pyrimidoquinoline [14-17]. A number of these pharmacological activities such as antiviral [18], antitumor [19], antifolate [20], antihistaminic [21], anti-inflammatory [22], antibacterial [23] and antioxidant [24]. This structural moiety is present in ramastine (anti-allergic) [25], anticonvulsive [26], antipyretic [27] and cardiotonic [28]. pyrimido [4,5-*b*] quinoline have been reported in this work by the cyclization of 6-amino-2(methylthio)pyrimidin-4(3*H*)-one, dimedone and various aldehydes.

Previously, uracil derivatives with cyclic ketones or cyclic 1, 3-diketones and the aromatic aldehydes has been catalyzed by several techniques like reflux in ethanol [29], 1,3-disulfonic acid imidazolium hydrogen sulfate ([dsim]HSO_4) [30], Fe_3O_4NPs-cell [16], $RuCl_3.xH_2O$ [31], DMF/MW [32], piperidine/reflux [33] and sulfonic acid supported on hydroxyapatite-encapsulated-γ-Fe_2O_3 ([γ-Fe_2O_3@HAp-SO_3H])[17],Fe_3O_4@nano-cellulose/Sb(V) [34], Fe_3O_4@SiO_2-$SnCl_4$ [35], SBA-15/PrN $(CH_2PO_3H_2)_2$ [36]. Some of these methods have limitations such as require drastic conditions, longer reaction times, expensive reagents, strongly acidic conditions, high temperatures, and using organic solvents which has environmental limitations. Thus, new routes for the synthesis of these molecules has prompted an extensive search for a rapid entry to these heterocycles. Fe_3O_4@nano-cellulose/Cu (II) (Fe_3O_4@NCs/Cu (II)) as an efficient, bio-based, inexpensive, eco-friendly and reusable magnetic nanocatalyst (Fig. 1) [37]. And so, the obtained catalyst was used for one-pot synthesis of pyrimido [4,5-b] quinolone via three-component reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, dimedone and various arylaldehydes in ethanol as solvent at 60 °C.

MATERIALS AND METHODS

All compounds were purchased from Merck chemical companies. Nano-cellulose and Fe_3O_4@NCs were synthesized *via* our previously reported methods [11]. 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one was synthesized in our laboratory. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ^{13}C NMR and ^{1}H NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus.

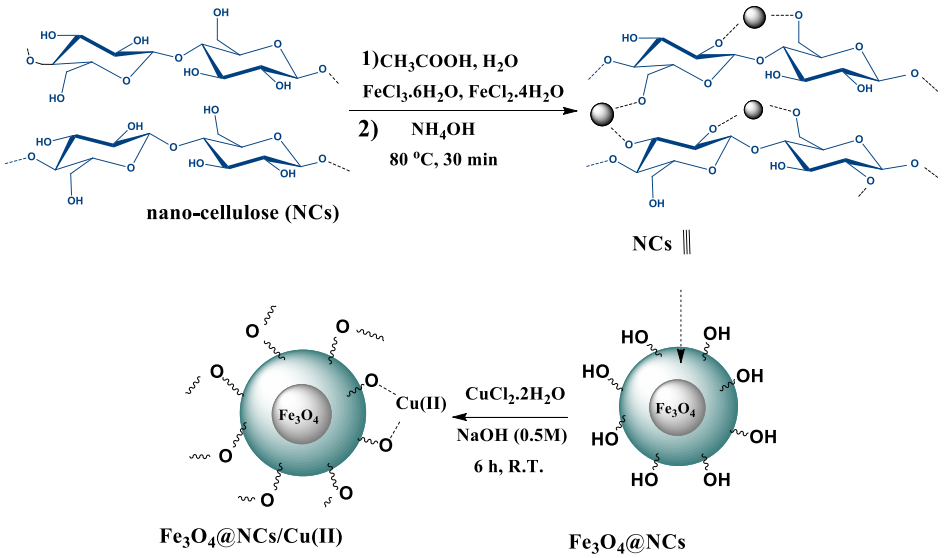


Fig. 1. Synthesis protocol for Fe_3O_4@NCs/Cu (II).

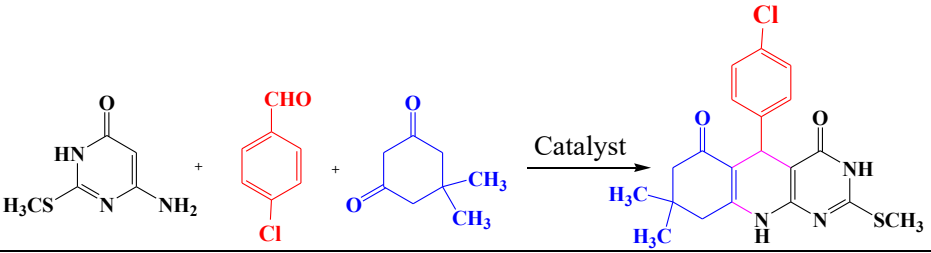
Preparation of Fe_3O_4@NCs/Cu (II)

In a vessel containing 50 ml of 0.5 M NaOH, Fe_3O_4@NCs (0.5 g) was added with stirring. Then, 75 ml of 0.04 M $CuCl_2$ (0.34 g) solution was added. A dark blue solution was obtained immediately that was stirred at room temperature. After 6 h, the magnetically heterogeneous catalyst, Fe_3O_4@ NCs/Cu (II), removed from solution by an external magnet. The catalyst washed with ethanol and water two times and dried at an oven at 80 °C.

General procedure for synthesis of pyrimido [4, 5-b] quinoline derivatives

A mixture of 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one (1 mmol), aldehyde (1 mmol), dimedone (1 mmol), was heated at 60 °C in the presence of Fe_3O_4@NCs/Cu (II) (0.03 g) in ethanol as solvent. After completion of the reaction (monitored by TLC, EtOAc:petroleum ether 8:4) the catalyst was separated by an external magnet and reused for the next experiment. Then the reaction mixture

Table 1. The reaction of 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one, dimedone and 4-chlorobenzaldehyde in the presence of Fe_3O_4@NCs/Cu (II) under various conditions [a]



Entry	Solvent	Catalyst (g)	Condition	Time (min)	Yield (%)[b]
1	-	-	60 ˚C	40	35
2	-	Fe_3O_4@NCs	60 ˚C	30	49
3	C_2H_5OH	-	R. T.	30	25
4	C_2H_5OH	Catalyst (0.03)[c]	R. T.	12	83
5	C_2H_5OH	Catalyst (0.03)[c]	60 ˚C	4	98
6	H_2O	Catalyst (0.03)[c]	60 ˚C	7	90
7	H_2O	Catalyst (0.03)[c]	R. T.	25	75
8	-	Catalyst (0.03)[c]	R. T.	15	84
9	-	Catalyst (0.03)[c]	70 ˚C	8	93
10	-	Catalyst (0.05)[c]	60 ˚C	8	88
11	-	Catalyst (0.04)[c]	60 ˚C	8	90
12	-	Catalyst (0.03)[c]	60 ˚C	8	93
13	-	Catalyst (0.02)[c]	60 ˚C	8	83
14	-	Catalyst (0.03), 2th run[c]	60 ˚C	6	94
15	-	Catalyst (0.03), 3rd run[c]	60 ˚C	6	89
16	-	Catalyst (0.03), 4th run[c]	60 ˚C	6	81

[a] The amount ratio of 6-amino-2-(methylthio) pyrimidin-4(3H)-one (mmol), dimedone (mmol) and 4-chlorobenzaldehyde (mmol) are equal to 1 : 1 : 1. [b] Isolated yield. [c] Fe_3O_4@ NCs/Cu (II).

Table 2. Comparative study of the present method and some other reported methods for synthesis of pyrimido [4, 5-b] quinoline derivatives.

Entry	Solvent	Catalyst	Temperature (˚C)	Time (min)	Yield (%)[a]
1	C_2H_5OH	-	Reflux	30	78 [29]
2	C_2H_5OH	[dsim]HSO_4[b]	70	15	91 [30]
3	H_2O	Fe_3O_4NPs-cell	Reflux	2 h	86 [16]
4	H_2O	$RuCl_3.xH_2O$	85	30	95 [31]
5	C_2H_5OH	[γ -Fe_2O_3@HAp-SO_3H][c]	60	4	94 [17]
6	C_2H_5OH	piperidine	Reflux	30	80 [33]
7	C_2H_5OH	Fe_3O_4@NCs/Cu(II) (0.03 g)	60	4	98 (This work)

[a] Isolated yield
[b] 1,3-disulfonic acid imidazolium hydrogen sulfate
[c] sulfonic acid supported on hydroxyapatite-encapsulated-γ -Fe_2O_3

was concentrated and cooled. The solid obtained was filtered off and recrystallized from EtOH: H_2O (1:1) to furnish the desired pure product. The recovered catalyst was washed 3 times with ethanol, dried and reused for subsequent runs under the same reaction conditions.

RESULTS AND DISCUSSION

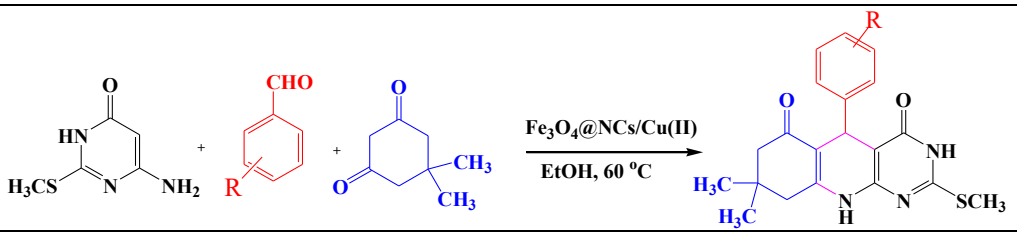
Catalyst efficiency for synthesis of pyrimido [4, 5-b] quinoline derivatives

After characterization of Fe_3O_4@NCs/Cu (II), the activity of catalyst was evaluated for the synthesis of pyrimido [4, 5-*b*] quinoline derivatives. For optimization of the reaction conditions, the reaction of 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one, dimedone and 4-chlorobenzaldehyde as a model reaction was investigated (Table 1). As shown in Table 1, entry 5, it was found that 0.03 g of Fe_3O_4@NCs/Cu (II) in ethanol as solvent at 60 °C is the best reaction condition. In order to compare the efficiency of present nano-catalyst with other catalysts, the model reaction was also performed using the reported catalysts for the synthesis of pyrimido [4, 5-b] quinoline derivatives. As Table 2 indicates, in comparison with other catalysts, we have observed good and high yields of products in green conditions using Fe_3O_4@NCs/Cu (II). Finally, the above optimized reaction conditions were explored for the synthesis of pyrimido [4, 5-*b*] quinoline derivatives and the results are summarized in Table 3. The reusability of the catalyst was also investigated on the model reaction. The magnetic nature of the catalyst allowed its facile recovery by simple separation by an external magnet, washing with ethanol and drying at room temperature to provide an opportunity for recycling experiments. The separated nano-catalyst was reused in the above-mentioned reaction for the synthesis of 4k for four times without considerable loss of its catalytic activity (Table 1). Partial loss of activity may be due to active sites blockage of the catalyst and/or partial leaching of Cu from the catalyst.

Proposed mechanism for the synthesis of pyrimido [4, 5-b] quinolines

Aromatic aldehydes containing electron-donating groups or electron-withdrawing groups were employed and reacted to give the corresponding products 4a-o in high yield under the present reaction conditions. Suggested mechanism for the synthesis of pyrimido [4, 5-*b*] quinoline (VII) was shown in Fig. 2. The carbonyl oxygen of aldehyde coordinates with the Lewis acid moiety increasing the electrophilicity of the carbonyl carbon and thereby making it possible to

Table 3. Synthesis of pyrimido [4,5-*b*] quinoline derivatives (4a-o) in the presence of Fe_3O_4@NCs/Cu(II) in ethanol as solvent at 60 °C[a].



Entry	R	Product	Time (min)	Yield (%)[b]	M.P. ˚C
1	4-MeO-	4a	5	97	>300
2	2,4-$(MeO)_2$-	4b	5	97	>300
3	2,4-$(Cl)_2$-	4c	4	95	>300
4	4-NO_2-	4d	4	96	>300
5	H-	4e	5	94	>300
6	4-OH-3-MeO-	4f	5	93	>300
7	4-CO_2Me-	4g	4	91	>300
8	3,4,5-F-	4h	4	92	>300
9	3-Br-	4i	3	93	>300
10	4-Me-	4j	5	79	>300
11	4-Cl-	4k	4	98	>300
12	3-NO_2-	4l	4	93	>300
13	3,4-OH-	4m	5	96	>300
14	4-Br-	4n	4	97	>300
15	4-CO_2H-	4o	4	92	>300

[a] I (mmol) : II (mmol) : III (mmol) : Fe_3O_4@NCs/Cu(II) is equal to 1 : 1 : 1 : 0.03. [b]Isolated yield.

carry out the reaction in short time. In a plausible mechanism, it is assumed that the reaction may proceed initially through the Knoevenagel condensation between aldehydes and dimedone to form intermediate III. Next, Michael addition of 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one to

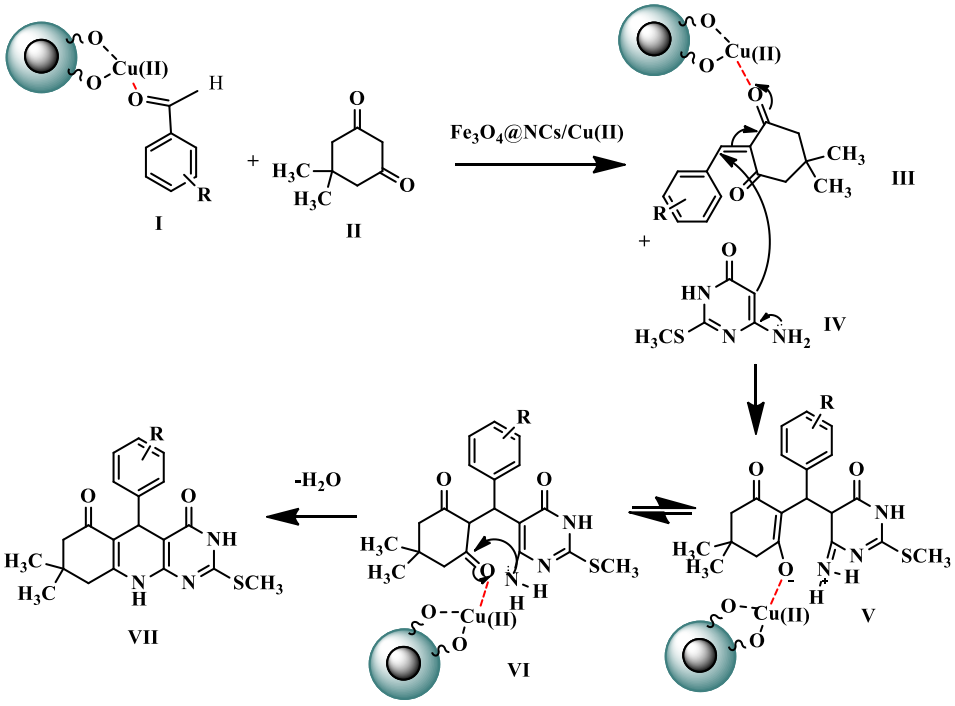


Fig. 2. Proposed mechanism for the synthesis of pyrimido [4, 5-b] quinoline derivatives 4a-o.

Table 4. The total energy and band gap (E_g=E_{HOMO}-E_{LUMO}) calculations for all pyrimido [4, 5-*b*] quinoline derivatives (4a-o).

Entry	R	Product	E_{tot} (a.u)	E_g=E_{HOMO}-E_{LUMO}
1	4-MeO-	4a	-3698.7389	0.0835
2	2,4-$(MeO)_2$-	4b	-3688.7074	0.0832
3	2,4-$(Cl)_2$-	4c	-3604.0356	0.0831
4	4-NO_2-	4d	-3689.3221	0.0795
5	H-	4e	-1484.8995	0.0805
6	4-OH-3-MeO-	4f	-1674.5760	0.0764
7	4-CO_2Me-	4g	-1673.8076	0.0548
8	3,4,5-F-	4h	-1782.5159	0.0837
9	3-Br-	4i	-3036.3726	0.0823
10	4-Me-	4j	-1524.2082	0.0798
11	4-Cl-	4k	-4044.4758	0.0840
12	3-NO_2-	4l	-1689.3243	0.0825
13	3,4-OH-	4m	-3690.2791	0.0804
14	4-Br-	4n	-3685.8725	0.0817
15	4-CO_2H-	4o	-1673.4073	0.0826

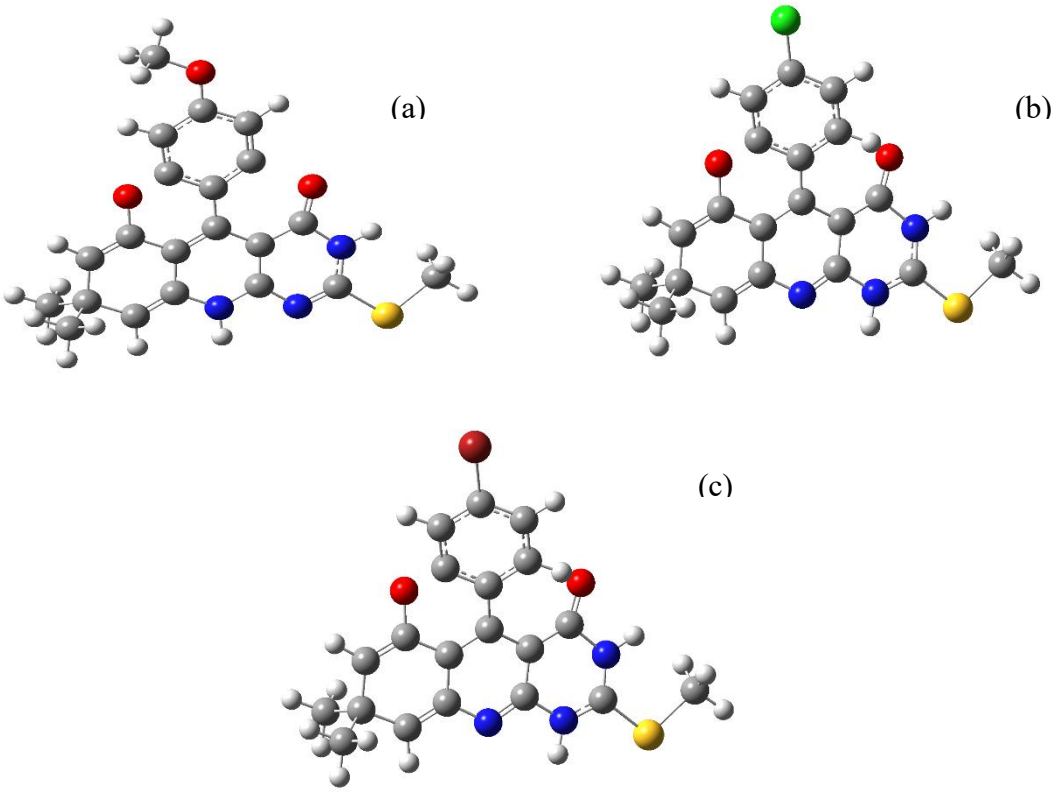


Fig. 3. The optimized structures for (a) 4k, (b) 4a, and (c) 4n compounds.

intermediate III affords V. Intermediate V converts to VI after tautomerization. Then, intermediate VI converts *via* cyclization to product VII. The structures of the products 4a-o were studied by their melting point, IR and ^{1}H, and ^{13}C NMR spectra.

COMPUTATIONAL DETAILS

In this paper, we also used density functional theory (DFT) simulations to determine the most stable combination of pyrimido [4, 5-b] quinoline derivatives (4a-o) in the presence of Fe_3O_4@NCs/Cu (II) in ethanol. The 6-311G (d, p) basis set and the B3LYP exchange-correlation functional (Beck, 3-parameter, Lee-Yang-Parr) utilized in all optimized computations [38-42]. The band gap (E_g=E_{HOMO}-E_{LUMO}) [43-45] and total energy calculations for all pyrimido [4, 5-*b*] quinoline derivatives are displayed in Table 4. The 4k compound is more stable than the other compounds [41], according to total energy and stability statistics.

The relaxed structures of 4k, 4a, and 4n compounds with the highest total energies are illustrated in Fig. 3. This figure indicates that the 4k structure is at its most stable configuration.

Based on these results, it can be deduced that the overall energy of the 4k compound is negative than those of the other compounds, which is in excellent agreement with the experimental data.

CONCLUSION

We have developed a facile and green one-pot three-component reaction for the synthesis of pyrimido [4,5-*b*] quinoline derivatives using Fe_3O_4@NCs/Cu(II) as a highly efficient, magnetite recoverable, eco-friendly, inexpensive and novel natural based heterogeneous catalyst. This protocol includes some important advantages such as mild reaction conditions, short reaction time, excellent yields, easy work-up procedure, product purity and magnetic separation and reusability of nanocatalyst. The computational outcomes demonstrated that the DFT results validated the experimental data.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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