

## Original Research Article

# A new strategy for the synthesis of dihydropyrano[c]chromene using zinc oxide/copper oxide as a nano and efficient catalyst

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### KEYWORDS

Dihydropyrano[c]chromene

Three-component reaction

Catalyst

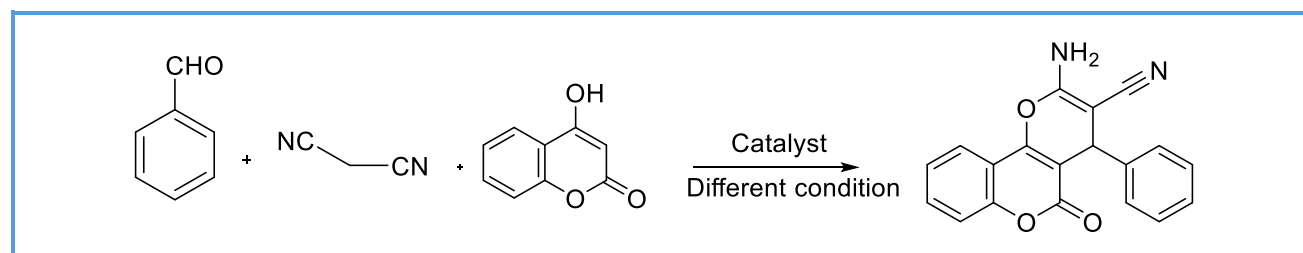
ZnO/CuO

### ABSTRACT

In recent years, dihydropyrano[3.2c]-chromene derivatives have attracted much attention among many researchers, due to their wide range of biological and pharmaceutical properties, including anticoagulant, diuretic, and anti-cancer. Mild conditions, high speed and short reaction time, simplicity of product separation process, high efficiency and purity of synthesized derivatives are the advantages of the proposed method.

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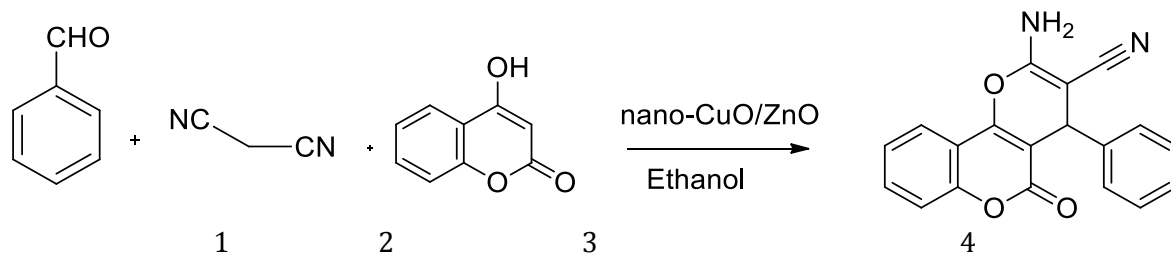
## Graphical Abstract



## Introduction

In recent years, dihydropyrano[3.2c]-chromene derivatives have attracted much attention among many researchers, due to their wide range of biological and pharmaceutical properties. Biological properties such as anticoagulant, diuretic, anti-cancer, anti-anaphylactoid activity, antibacterial, and anti-AIDS virus are highly desirable [2, 3]. These compounds are also like 4H-chromenes utilized in the treatment of diseases such as Huntington, Alzheimer, and Parkinson [4]. Furthermore, these compounds also applied in cosmetics and pigments industries, and biodegradable compounds used in agriculture industry [5–7]. Due to the great importance of these

compounds, various synthesis methods in the presence of different catalysts invented by many researchers using multicomponent reactions [8, 9]. Ultrasonic and microwave processes are examples of these methods [10]. Utilizing the primary compounds of aromatic aldehydes, malononitrile and 4-hydroxycoumarin in the presence of various catalysts and different conditions is one of the most important reactions in the synthesis process of these compounds [11]. A schematic diagram of this reaction is shown in the following picture. Therefore, we wish to report an efficient method for the synthesis of Dihydropyrano[c]chromene catalyzed by nano zinc oxide/copper oxide (Scheme 1).



**Scheme 1.** Preparation of dihydropyrano[c]chromene derivatives

Nanocatalyst have been suitable for many synthetic and functional reactions due to their properties [12]. Nanocatalyst are widely used for the synthesis of organic compounds [13–19]. Nanocatalysts have the ability to advance the reaction in a specific direction by selecting raw materials. This means that in the presence of nanocatalysts, unwanted compounds cause fewer by-reactions and prevent the production of by-products during the process. In addition, the nanocatalyst with its very high active surface increases the reaction efficiency in its main path. In other words, it can be said that a larger volume of raw materials is converted into the final product. Due to the high importance of nanocatalysts, in this study, zinc oxide/copper

oxide catalyst was used for the synthesis of dihydropyrano[c]chromene derivatives.

## Experimental

### Materials and methods

Chemicals were purchased from the Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. All products were characterized using spectra and physical data. Characterizations were carried out using the Melting points (Electrothermal 9100),  $^1\text{H}$ -NMR (Bruker 500 MHz), TEM (HRTEM, TF 20 Tecnai G2 200 kV FEI), Fourier transform infrared (model Nexus-870, Nicolet Instrument), thin layer chromatography (TLC)

on commercial aluminum-backed plates of silica gel.

#### *Preparation of nano ZnO/CuO catalyst*

zinc oxide (1 g) after calcination at 400 °C was stirred in an aqueous solution of copper(II) sulfate:5 H<sub>2</sub>O (8%) for 48 hours till copper ions penetrate into zinc oxide crystals (ZnO). Then, the mixture was heated at 100 °C for 24 h. Finally, the obtained product was calcined at 550 °C for 5 h [20].

#### *General procedure for the synthesis of dihydropyrano[c]chromene in the presence of zinc oxide/copper oxide nanoparticle catalysts*

In this method, 1 mmol of malononitrile (0.06 g), 1 mmol of 4-hydroxycoumarin (0.162 g), 1 mmol of aldehyde in water (5 mL), nano-zinc oxide/copper oxide (0.05 g) were added as the catalyst, and the mixture was stirred for an appropriate time at reflux condition. After the reaction was completed, the solid compound obtained was filtered off and the crude products were purified by recrystallization from ethanol.

**4c:** IR (KBr) ( $\nu_{\max}$ / cm<sup>-1</sup>): 3376, 3261, 3156, 2188, 1716, 1679, 1612, 1385, 1068, and 762. <sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  4.66 (s, 1H), 7.34 (d, 2H,  $J$  = 8.3 Hz, HAr), 7.39 (br s, 2H, NH<sub>2</sub>), 7.41 (br s, 2H, Ar-H), 7.55 (d, 1H,  $J$  = 7.78 Hz, Ar-H),

7.48 (t, 1H,  $J$  = 7.78 Hz, Ar-H), 7.75 (dt, 1H,  $J$  = 7.26, Hz, Ar-H), 7.91 (dd, 1H,  $J$  = 7.78, 1.28 Hz, Ar-H).

**4e:** IR (KBr) ( $\nu_{\max}$ / cm<sup>-1</sup>): 3389, 3314, 3193, 2196, 1715, 1677, 1609, 1378, 1060, and 759. <sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  2.69 (s, 3H, CH<sub>3</sub>), 4.51 (s, 1H), 7.06 (s, 2H,  $J$  = 7.48 Hz, Ar-H), 7.17 (s, 2H,  $J$  = 7.48 Hz, Ar-H), 7.43 (br s, 2H, NH<sub>2</sub>), 7.52 (dd, 2H,  $J$  = 7.48 Hz, Ar-H), 7.69 (t, 1H,  $J$  = 7.48 Hz, Ar-H), 7.95 (dd, 1H,  $J$  = 7.48 Hz, Ar-H).

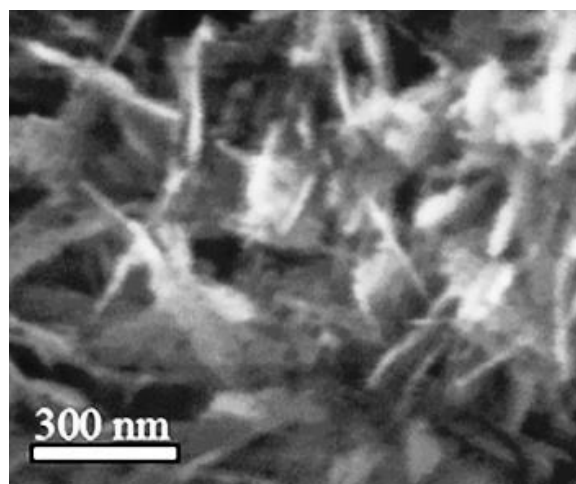
## Results and Discussion

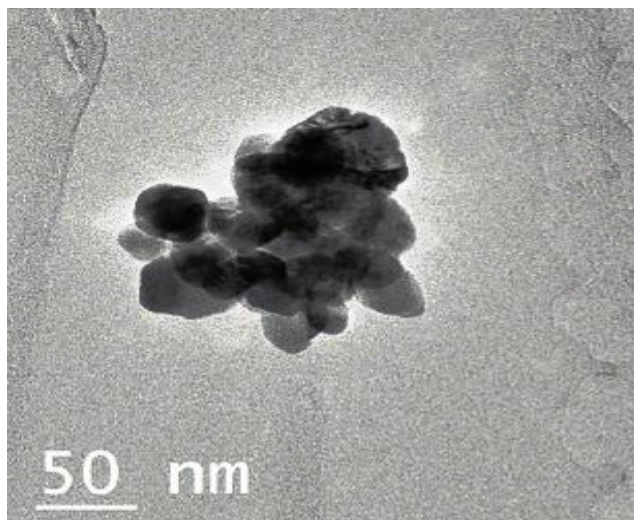
The TEM and SEM images of the catalyst are demonstrated in Figures 1 and 2. The size of nano ZnO/CuO was found in the range of 20-50 nm.

The XRD pattern of ZnO, CuO and ZnO/CuO nanoparticle catalyst was showed in Figure 3. As you can see, there are no peaks other than CuO and ZnO. In the spectrum, CuO/ZnO nanoparticles showed sharp and also high peaks at 33° and 36°, which is due to the formation of CuO/ZnO nanoparticles.

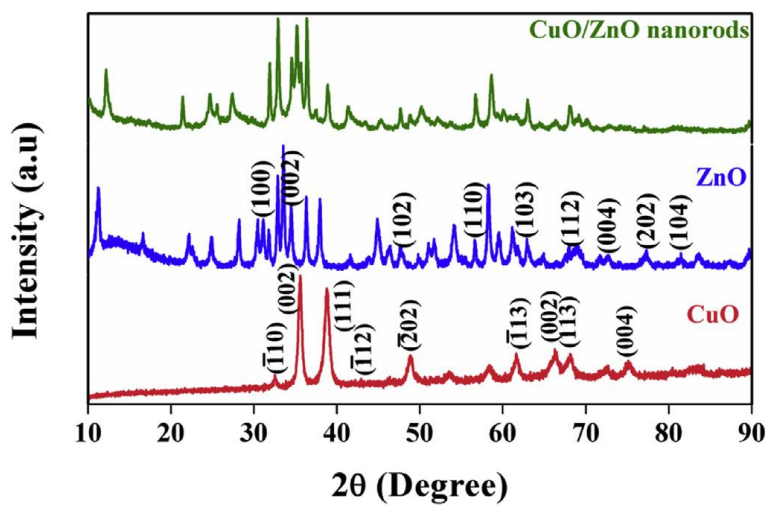
The elemental analysis is characterized by the EDS spectra and as shown in the Figure 4, the three elements (copper, zinc and oxygen) are observed in the spectrum. EDX spectra were analyzed (as shown in Figure 5), It is shown that ZnO/CuO actually consists of Cu, Zn, and O atoms.

**Figure 1.** The SEM image of ZnO/CuO nanoparticle catalys

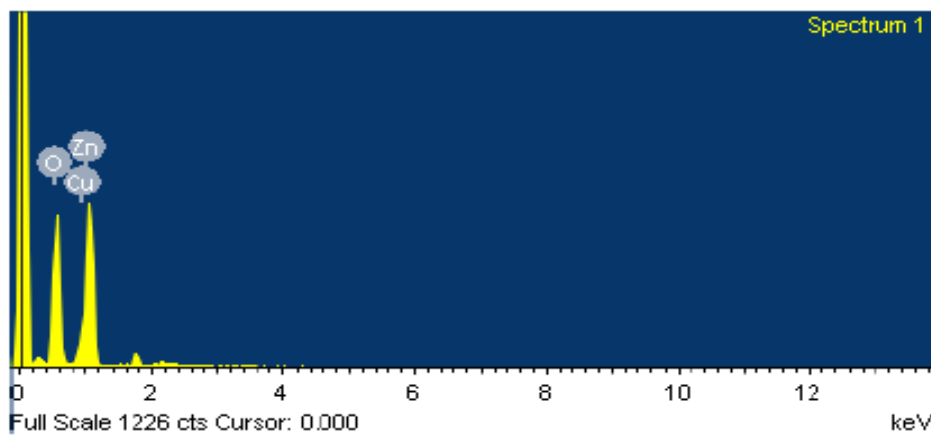




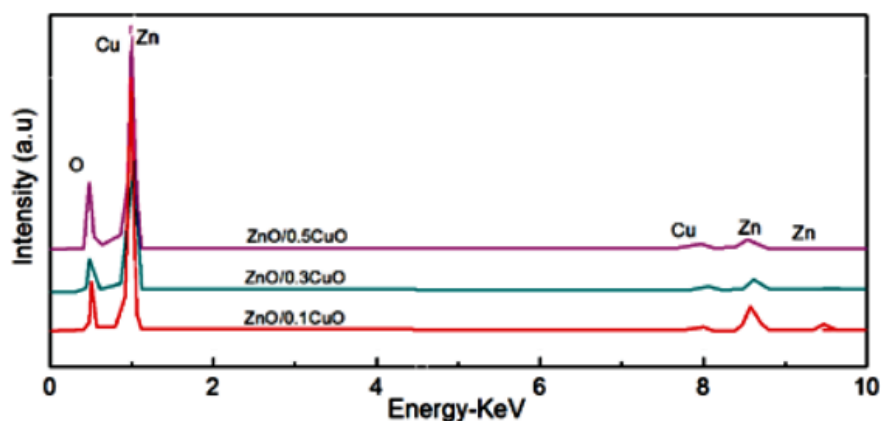
**Figure 2.** The TEM image of ZnO/CuO nanoparticle catalyst



**Figure 3.** The XRD pattern of ZnO, CuO and ZnO/CuO nanoparticle catalyst



**Figure 4.** The EDS Spectra of ZnO/CuO nanoparticle catalyst



**Figure 5.** The EDX Spectra of ZnO/CuO nanoparticle catalyst

#### *Optimization of the catalyst amount*

To obtain the optimal amount of catalyst, different concentrations of catalyst (0.02, 0.03, 0.05 and 0.1 g) were evaluated in the reaction, and the optimal amount with the highest efficiency was calculated. Therefore, the optimum amount of zinc oxide/copper oxide was determined 0.05 g. The results are shown in [Table 1](#).

#### *Optimization of the reaction time*

In order to determine the optimal reaction time, the reaction modeled in the different time. The results are shown in [Table 2](#). The results

showed that with increasing reaction time, the efficiency increased and after 10 min reached 94%. After this time, no increase in efficiency was observed, so it can be concluded that the optimal reaction time was 10 min ([Table 2](#)).

#### *Selecting the suitable solvent*

To select appropriate solvent, the reaction was modeled using the optimal amount of 0.05 g of nano catalyst at the presence of different solvents. The results are presented in [Table 3](#) and showed that via using water as solvent, a high-efficiency product is synthesized. Therefore, water was considered as a suitable solvent for this reaction.

**Table 1.** Optimization of the amount of ZnO/CuO catalyst (g)

Row	Zinc Oxide/Copper Oxide (g)	Time (min)	Efficiency (%)
1	0	10	15
2	0.02	10	75
3	0.03	10	80
4	0.05	10	94
5	0.1	10	94

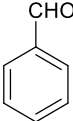
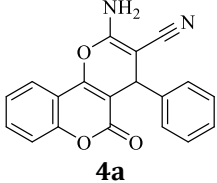
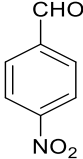
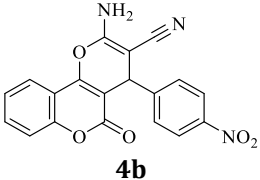
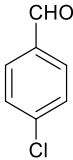
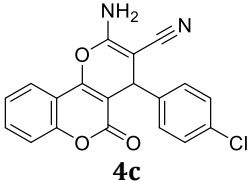
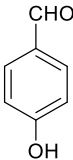
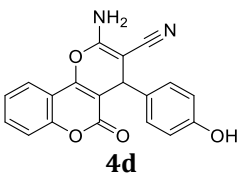
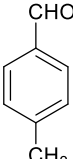
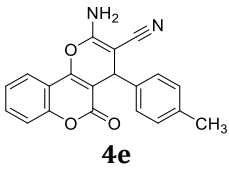
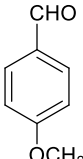
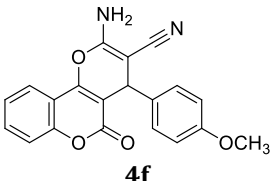
**Table 2.** Comparison of various time for the synthesis of **4a**

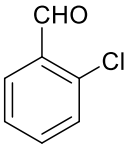
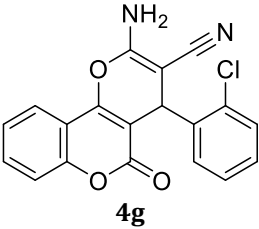
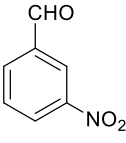
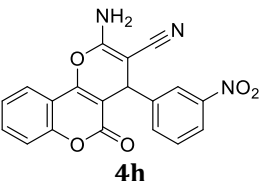
Entry	Time (min)	Yield (%)
1	1	40
2	5	75
3	10	94
4	15	94

**Table 3.** Selecting the suitable solvent

Row	Solvent	Time (min)	Efficiency (%)
1	CH <sub>3</sub> CN	10	88
2	H <sub>2</sub> O	10	94
3	CH <sub>2</sub> Cl <sub>2</sub>	10	70
4	CH <sub>3</sub> OH	10	90
5	Solvent-free	10	92
6	C <sub>2</sub> H <sub>5</sub> OH	10	91

**Table 4.** Synthesis of dihydropyrano[c]chromene derivatives

Entry	Aldehyde	Product	Time (min)	Yield (%)	Experimental Melting Point	Theory Melting Point [21]
1		 <b>4a</b>	10	94	259-257	257-256
2		 <b>4b</b>	10	95	261-260	260-257
3		 <b>4c</b>	10	95	265-263	267-266
4		 <b>4d</b>	10	92	268-266	266-262
5		 <b>4e</b>	10	92	266-264	267-265
5		 <b>4f</b>	10	92	242-243	240-242

6			10	94	265-264	266-264
7			10	95	262-260	263-260

### Comparing reaction results with other methods

By comparing the reaction results with other methods, we find that the nano-CeO<sub>2</sub> catalyst performs the reaction in shorter time (10 min) and with higher efficiency (94%) (Table 5).

### Optimization of reaction temperature

To reach the appropriate temperature conditions, the model reaction was performed at different temperatures and reflux. As indicated, the highest efficiency was observed in reflux conditions (Table 6).

### Reusability of catalyst

After the reaction, 10 mL of ethyl acetate was added to the compounds on filter paper containing catalyst. The mixture was stirred at room temperature for 5 min using a magnetic stirrer. The reaction mixture was filtered, and the catalyst remained on filter paper due to its insolubility in ethyl acetate solvent. Then, to reuse the catalyst, the filter material was washed several times with acetone. After drying, the reaction was repeated to check the potency of the catalyst (Table 4). As seen in the Table 4, the reaction can be performed up to six times with good efficiency by the recycled catalyst (Figure 6).

**Table 5.** Comparison of various catalysts for the synthesis of dihydropyrano[c]chromene derivatives

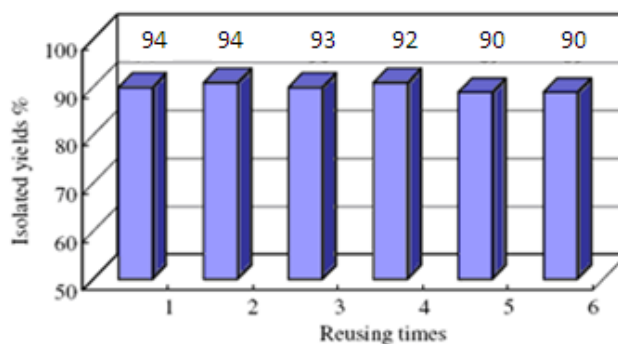
Entry	Catalyst	Yield (%)	Time(min)	Ref
1	thiourea dioxide	91	10	[21]
2	DABCO	96	30	[21]
3	pTSA	90	40	[21]
4	TEA	52	120	[21]
5	SiO <sub>2</sub> -NaHSO <sub>3</sub>	48	120	[21]
6	(S)-proline	82	240	[21]
7	Nano-ZnO	81	120	[14]
8	Nano-CuO	90	120	[15]
9	Nano-ZnO/CuO	94	10	Present study

Yields refer to isolated products



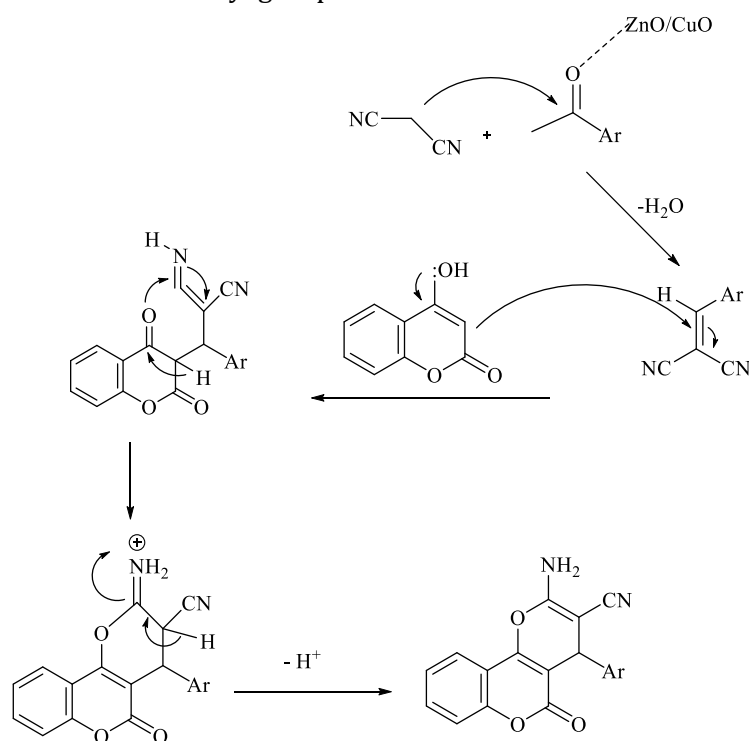
**Table 6.** Comparison of various temperature for the synthesis of **3a**

Entry	Time (min)	Temperature (°C)	Yield (%)
1	10	25	66
2	10	50	75
3	10	reflux	94

**Figure 6.** Reusing of ZnO/CuO for the synthesis of **4a***The proposed mechanism*

First, the catalyst acts like Lewis acid, absorbing the electrons of the carbonyl group and activating the carbon of the carbonyl group

in the aldehyde, and malononitrile easily attacks it. Then, hydroxycoumarin attacked them and after tautomerization, the desired product is obtained.

**Scheme 2.** The proposed mechanism for the dihydropyrano[c]chromene compounds



## Conclusions

In this study, we introduced a suitable and green method for to prepare dihydropyrano[c]chromene derivatives through the malononitrile, 4-hydroxycoumarin and aldehyde using nano-zinc oxide/copper oxide as a catalyst in water. This reaction has several advantages that can be explained using green water solvent, the use of a small amount of nano catalyst, catalyst recyclability, high efficiency and short reaction time. In this research study, nano-zinc oxide/copper oxide as an efficient catalyst was synthesized and characterized by SEM, TEM, XRD, EDX and EDX analysis. According to Table 5, you can see that the highest efficiency (94%) was obtained in a short time (10 minutes) in this study, which is much better and more useful compared to other previous methods. The results also demonstrated that, the best efficiency (94%) was obtained in the water as a solvent.

## Acknowledgements

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## Disclosure Statement

No potential conflict of interest was reported by the authors.

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