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One-Pot, Efficient, Microwave Assisted Multi-Component Synthesis of Substituted Pyrano[2,3-*c*]pyrazole derivatives in Aqueous Medium and Evaluation of its Antioxidant Activity

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A green and efficient microwave-assisted protocol was developed for the synthesis of substituted pyrano[2,3-*c*]pyrazole derivatives (**5a-f**) through a one-pot multicomponent condensation reaction involving hydrazine hydrate, ethyl acetoacetate, malononitrile and substituted aromatic aldehydes in the presence of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst/base under aqueous conditions. Microwave irradiation significantly reduced the reaction time (3-6 min) and afforded the desired products in high yields under mild and environmentally benign conditions. TBAB facilitated deprotonation of malononitrile and activation of the aldehyde carbonyl group, thereby accelerating the Knoevenagel condensation and subsequent cyclisation process. The synthesized compounds were characterised by FTIR, ^{1}H NMR and ^{13}C NMR spectral analyses, which confirmed the successful formation of the pyrano[2,3-*c*]pyrazole framework. Spectral studies revealed characteristic absorption bands for –NH and –CN functionalities along with corresponding proton and carbon resonances. Electron-withdrawing substituents on aromatic aldehydes exhibited shorter reaction times and improved yields compared with electron-donating substituents. The antioxidant activity of all synthesized derivatives was evaluated using the DPPH free radical scavenging assay with ascorbic acid as the reference standard. Among the synthesized compounds, derivative **5a** exhibited the highest antioxidant activity, while compounds containing substituted aromatic groups also demonstrated appreciable free radical scavenging potential. The developed methodology provides a rapid, sustainable and high-yielding synthetic approach for biologically important pyrano[2,3-*c*]pyrazole derivatives with promising antioxidant activity.

Keywords: Tetrabutylammonium bromide, Antioxidant activity, Microwave assisted, Aqueous medium.

INTRODUCTION

Multi-component reactions (MCRs) have also led to an organic synthesis revolution, whereas the problem of percent atom economy and that of economy of multiple steps have been considered essential to achieve more complex molecular structures [1-5]. Heterocyclic compounds are widespread in nature and vital to various biological processes. Their unique attributes render them significant in the realm of medicinal chemistry. The synthesis and utilisation of medium-sized ring heterocyclic compounds have seen a rise in interest [6,7]. Recent years have witnessed substantial study on fused heterocyclic compounds having pharmacological relevance [8-10].

The pyranopyrazole class of heterocyclic compounds has attracted considerable attention owing to its diverse biological and pharmacological significance [11,12]. Structurally, pyranopyrazoles consist of a five-membered pyrazole ring fused with a six-membered pyran ring, forming an important fused heterocyclic framework widely employed as a precursor in medicinal chemistry. Depending on the mode of ring fusion, pyranopyrazoles exist as four possible isomeric forms *viz.* pyrano [4,3-*c*]pyrazole, pyrano[2,3-*c*]pyrazole, pyrano[3,4-*c*]-pyrazole and pyrano[3,2-*c*]pyrazole [13]. Among these, pyrano-[2,3-*c*]pyrazole derivatives have been the most extensively investigated due of their prominent pharmacological relevance and broad spectrum of biological activities [14]. These pyrano-[2,3-*c*]pyrazole has considerable importance to medicinal and pharmacological chemistry are attributable to the multiplicity of activities of the embedded heterocyclic structures. Multi-component reactions have gained a greater concern in the field of organic and pharmaceutical industry. Many pyrano-pyrazole derivatives have triggered interest in recent years for their numerous biological activities [15-18]. In addition, chemistry of fused different pyrazole derivatives has attracted tremen-

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dous consideration due to their medicinal significance. The pyrano-pyrazoles are a valuable class of biologically active heterocycles.

The 4*H*-pyrane derivatives show comprehensive range of biological actions such as anticancer [19], anti-HIV [20], anti-inflammatory [21], antimalarial [22], antimicrobial [23], anti-viral [24] and anti-proliferative [25]. These significant biologically active outlines have inspired extensive research into synthesis of pyrazole derivatives. Numerous pyrazole derivatives have beneficial biological properties like analgesic [26], anti-inflammatory [21], insecticidal and molluscicidal activities [27-29] also functioning as biodegradable agrochemicals and potent pharmacological ingredients [30-32].

Pyrano[2,3-*c*]pyrazoles framework appears in many biologically active complexes, therefore nowadays; researchers have remarkable interest in synthesizing this moiety by using different catalysts, solvents and in various media. The various pyrano[2,3-*c*]pyrazoles products are synthesised using diverse catalysts like diaminocyclohexane thiourea [33], urea [34], lipase [35], maltose [36], DBU [37], DABCO [38], acetic acid [39], citric acid [40], pyrrolidine [41], NaOH [42], tetraethylammonium bromide [43], borax [44], cerium ammonium nitrate [45] (CAN), tungstate sulphuric acid [46], piperidine [47], pyridine [47] and nano-ZnO [48]. Numerous of these protocols face challenges including reliance on hazardous solvents, the expense of catalysts demanding reaction conditions, prolonged reaction durations and reduced yields. In the present study, these synthetic challenges were addressed through a green microwave-assisted protocol suitable for pharmaceutical applications. Microwave irradiation provided rapid heating, minimized side reactions and improved product yield and purity with lower energy consumption than conventional methods.

In this study, a series of substituted pyrano[2,3-*c*]pyrazole derivatives were synthesised through a multicomponent condensation reaction involving hydrazine monohydrate, ethyl acetoacetate (EAA), malononitrile and aromatic aldehydes in the presence of tetrabutylammonium bromide (TBAB). TBAB acted as a metal-free phase-transfer catalyst and base, facilitating malononitrile deprotonation and activation of the aldehyde carbonyl group, thereby accelerating the Knoevenagel condensation and improving reaction efficiency. Microwave irradiation further enhanced the reaction by reducing reaction time and increasing product yield compared with reported conventional methods. In addition, the synthesized compounds were evaluated for their antioxidant activity using the DPPH free radical scavenging assay.

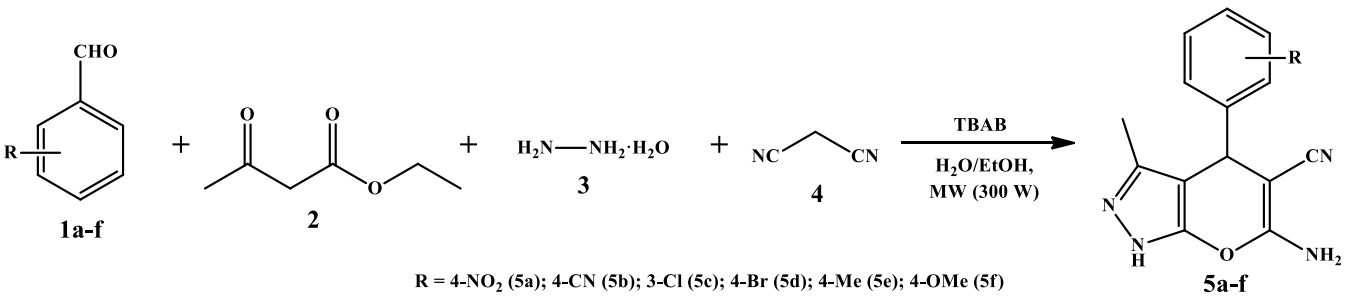
EXPERIMENTAL

All reagents were obtained from commercial suppliers and used without further purification unless otherwise specified. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using tetramethylsilane (TMS) as the internal standard. The ^{1}H NMR spectra were measured at 400 MHz on a Bruker spectrometer. FTIR spectra were recorded using a Bruker FTIR spectrophotometer with KBr pellets. Thin-layer chromatography (TLC) was performed on silica-coated glass plates and visualised under UV light. Melting points were determined using a Systronics EQ730 digital melting point apparatus.

Synthesis of substituted pyrano[2,3-*c*]Pyrazoles derivatives (5a-f): Aromatic aldehydes (1.5 mmol), hydrazine monohydrate (1.5 mmol), ethyl acetoacetate (1.0 mmol) and malononitrile (1.0 mmol) were mixed in a microwave vial. Tetrabutylammonium bromide (1.5 mmol) and a small quantity of water were then added to the reaction mixture. The mixture was irradiated under microwave conditions at 300 W for 3-6 min and the reaction progress was monitored by TLC. (**Scheme-I**). After completion, the precipitated product was filtered, washed with hot water and recrystallised from ethanol to obtain the pure compound, which was subsequently dried.

6-Amino-4-(4-nitrophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5a): Yellow colour, yield: 88%, m.p.: 250-252 ºC, time: 3-4 min. FTIR (KBr, ν_{max}, cm^{-1}): 3476 (NH_2), 3222 (-NH), 3094, 2972 (C-H), 2195 (-CN), 1592 (C=C), 1492 (-NH), 1347, 1513 (Ar-NO_2), 881-854 (*p*-NO_2); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.80 (s, 3H, CH_3), 4.83 (s, 1H), 7.06 (s, 2H, NH_2), 7.45-7.48 (d, 2H, Ar-H), 8.20-8.22 (d, 2H, Ar-H), 12.21 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 10.20, 36.39, 56.44, 97.03, 120.95, 124.35, 129.30, 136.38, 146.87, 152.56, 155.14, 161.63.

6-Amino-4-(4-cyanophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5b): White colour, yield: 86%, m.p.: 196-198 ºC, time: 3-4 min. FTIR (KBr, ν_{max}, cm^{-1}): 3480 (NH_2), 3229 (-NH), 3109 (C-H), 2226-2186 (Ar-CN), 1592 (C=C), 1490 (-NH), 876-745 (*p*-CN); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.79 (s, 3H, CH_3), 4.75 (s, 1H), 7.04 (s, 2H, NH_2), 7.38-7.40 (d, 2H, Ar-H), 7.80-7.82 (d, 2H, Ar-H), 12.2 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 10.18, 36.65, 56.58, 97.12, 110.13, 119.25, 120.98, 129.06, 133.06, 136.30, 150.50, 155.19, 161.61.



Scheme-I: Synthetic pathway to produce **5a-f** compounds

6-Amino-4-(3-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5c): White colour, yield: 84%, m.p.: 234-236 ºC, time: 4-5 min. FTIR (KBr, ν_{max}, cm^{-1}): 3404 (NH_2), 3311 (-NH), 3181 (C-H), 2192 (Ar-CN), 1513 (C=C), 1487 (-NH-), 1037 (Ar-Cl), 751 (m-Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.81 (s, 3H, CH_3), 4.66 (s, 1H), 6.97 (s, 2H, NH_2), 7.36-7.21 (m, 3H, Ar-H), 7.16 (s, 1H, Ar-H), 12.16 (s, 1H, NH); ^{13}C NMR (100 MHz, in DMSO-d_6, δ ppm): 10.22, 36.31, 57.05, 97.50, 121.10, 126.74, 127.30, 127.70, 130.89, 133.55, 136.20, 147.51, 155.19, 161.50.

6-Amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5d): White colour, yield: 84%, m.p.: 180-182 ºC, time: 4-5 min. FTIR (KBr, ν_{max}, cm^{-1}): 3476 (-NH_2), 3226 (-NH-), 2969, 3114 (-C-H), 2190 (Ar-CN), 1487 (-NH-), 1592 (C=C), 1051 (Ar-Br), 825-793 (*p*-Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.79 (s, 3H, CH_3), 4.62 (s, 1H), 6.93 (s, 2H, NH_2), 7.12-7.14 (d, 2H, Ar-H), 7.50-7.52 (d, 2H, Ar-H), 12.13 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 10.23, 36.13, 57.20, 97.60, 120.24, 121.11, 130.21, 131.84, 136.17, 144.37, 155.18, 161.39.

6-Amino-4-(4-methylphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5e): Yellow colour, yield: 83%, m.p.: 208-210 ºC, time: 5-6 min. FTIR (KBr, ν_{max}, cm^{-1}): 3403, 3314 (-NH_2), 3267 (-NH-), 3186 (-C-H), 2190 (Ar-CN), 1483-1425 (-NH-), 1598-1510 (C=C), 793-772 (*p*-CH_3); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (s, 3H, CH_3), 2.26 (s, 3H, Ar-CH_3), 4.54 (s, 1H), 6.83 (s, 2H, NH_2), 7.05 (d, 2H, Ar-H), 7.10 (d, 2H, Ar-H), 12.07 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 10.23, 21.09, 36.37, 57.94, 98.22, 121.30, 127.84, 129.47, 136.05, 136.21, 141.95, 155.27, 161.27.

6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5f): Yellow colour, yield: 82%, m.p.: 210-212 ºC, time: 5-6 min. FTIR (KBr, ν_{max}, cm^{-1}): 3483, 3367 (-NH_2), 3239 (-NH-), 3124 (-CH), 2937 (-OCH_3), 2222-2190 (Ar-CN), 1491 (-NH-), 1596-1510 (C=C), 803 (*p*-OCH_3); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (s, 3H, CH_3), 2.50-3.3 (s, 3H, Ar-OCH_3), 4.53 (s, 1H), 6.81 (s, 2H, NH_2), 6.85-6.88 (d, 2H, Ar-H), 7.06-7.08 (d, 2H, Ar-H), 12.06 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 10.21, 35.94, 55.45, 58.14, 98.36, 114.23, 121.31, 128.97, 136.06, 136.95, 155.23, 158.44, 161.17.

Antioxidant activity: The antioxidant activity of the synthesized compounds (**5a-f**) was evaluated using the DPPH free radical scavenging assay with ascorbic acid as the reference standard. Different concentrations of the test compounds were prepared in methanol and 10 µL of each solution was added to 0.2 mL of 0.1 mM DPPH solution in a 96-well plate. The assay was performed in quadruplicate including duplicate blanks. Wells containing DPPH solution without sample served as controls, while wells without DPPH were used as blanks. An additional 20 µL of deionised water was included in the control reaction mixture. The reaction mixtures were incubated in the dark for 30 min at room temperature and the decrease in absorbance was measured at 517 nm using a Bio-Rad iMark microplate reader. The percentage radical scavenging activity was calculated relative to the control. The IC_{50} values were determined using GraphPad Prism 6 software by plotting concentration *versus* percentage inhibition.

$$\text{Radical scavenging activity (\%)} = \frac{Abs_{control} - Abs_{sample}}{Abs_{control}} \times 100$$

RESULTS AND DISCUSSION

A modified green protocol was developed for the synthesis of substituted pyrano[2,3-*c*]pyrazole derivatives (**5a-f**) using microwave-assisted multicomponent reactions. The reaction involved ethyl acetoacetate (EAA), aromatic aldehydes, hydrazine hydrate and malononitrile in the presence of TBAB using water as the reaction medium. Microwave irradiation significantly accelerated the reaction process and improved reaction efficiency. TBAB proved to be an effective metal-free catalyst/base, providing better reaction performance than several previously reported catalytic systems for the synthesis of pyrano[2,3-c]pyrazoles (Table-1).

TABLE-1
OVERALL COMPARISON OF CATALYTIC ACTIVITY OF DIFFERENT CATALYSTS FOR SYNTHESIS OF **5a-f** PRODUCTS

Catalyst	Time (min)	Yield (%)	Ref.
Sodium benzoate	50	87	[26]
K-*t*-BuO	10	62	[49]
Thiourea dioxide	30-60	70-90	[50]
$ZnCl_2$	40	72	[50]
CAN	40	68	[50]
Ionic liquid [Et_3NH][HSO_4]	15	70	[51]
TBAB	3-6	80-88	Present work

All the synthesized compounds (**5a-f**) were characterised by FTIR, ^{1}H NMR and ^{13}C NMR spectroscopy. FTIR spectra exhibited characteristic absorption bands in the ranges of 3483-3222 and 2226-2186 cm^{-1}, corresponding to pyrazole-NH and nitrile (–CN) groups, respectively. Similarly, ^{1}H NMR spectra showed aromatic proton signals in the range of δ 6.80-8.22 ppm and pyrazole –NH signals at δ 12.06-12.21 ppm. These spectral observations, together with melting point and TLC analyses, confirmed the successful formation of the desired pyrano[2,3-*c*]pyrazole derivatives. Aromatic aldehydes containing electron-withdrawing substituents such as -NO_2 (**5a**) and -CN (**5b**) exhibited shorter reaction times (3-4 min) and higher yields compared with derivatives containing electron-donating substituents.

The antioxidant activity of all synthesized compounds (**5a-f**) was evaluated using the DPPH free radical scavenging assay. Ascorbic acid was used as the reference standard at concentrations ranging from 0-50 µg/mL, whereas the synthesised compounds were evaluated over a wider concentration range of 0-1000 µg/mL. The IC_{50} values obtained from the assay are summarised in Table-2. Among the synthesized compounds, derivative **5a** exhibited the highest antioxidant activity. Compounds **5b**, **5d** and **5f** also demonstrated appreciable free radical scavenging activity with IC_{50} values of 902.1, 947 and 833.5 µg/mL, respectively, compared with 9.52 µg/mL for ascorbic acid. The antioxidant results indicated that substituent variation on the pyrano[2,3-*c*]pyrazole framework significantly influenced radical scavenging efficiency, with

TABLE-2
EVALUATION OF ANTIOXIDANT ACTIVITY OF PRODUCTS

Product	IC_{50} value in (µg/mL), (Mean ± SEM*)
Ascorbic acid	9.52 ± 0.026
5a	529.2 ± 0.03
5b	902.1 ± 0.03
5c	Above maximum dose limit
5d	947 ± 0.072
5e	Above maximum dose limit
5f	833.5 ± 0.052

*SEM: Standard error of mean

substituted aromatic groups contributing to enhanced antioxidant behaviour.

Mechanism: A plausible reaction mechanism for the formation of compounds (**5a-f**) involves four major steps. Initially, EAA reacts with hydrazine hydrate to form 3-methylpyrazol-5-one intermediate through cyclocondensation. Simultaneously, aromatic aldehydes undergo Knoevenagel condensation with malononitrile in the presence of TBAB, generating arylidene malononitrile intermediates. Subsequently, the pyrazolone intermediate undergoes Michael addition with the activated dicyano alkene to form a key acyclic intermediate. Finally, intramolecular cyclisation followed by tautomerisation produces the stable 6-amino-5-carbonitrile substituted pyrano-[2,3-*c*]pyrazole derivatives (**Scheme-II**).

Conclusion

A green and efficient microwave-assisted protocol was successfully developed for the synthesis of substituted pyrano-[2,3-*c*]pyrazole derivatives (**5a-f**) using TBAB as a metal-free catalyst/base in aqueous medium. The method provided shorter reaction times, simple work-up, improved yields and lower energy consumption compared with conventional methods. Spectroscopic analyses confirmed the successful synthesis of all derivatives (**5a-f**). The results demonstrated that substituent variation on the aromatic aldehyde influenced both reaction efficiency and antioxidant activity. Electron-withdrawing substituents promoted faster reactions and higher yields, while DPPH assay results revealed appreciable antioxidant potential among the synthesized compounds, particularly compound **5a**. The proposed reaction mechanism involving pyrazolone formation, Knoevenagel condensation, Michael addition and cyclisation supported the formation of the target heterocyclic framework. This study highlights the potential of microwave-assisted green synthesis for developing biologically relevant pyrano[2,3-*c*]pyrazole derivatives with promising antioxidant properties.

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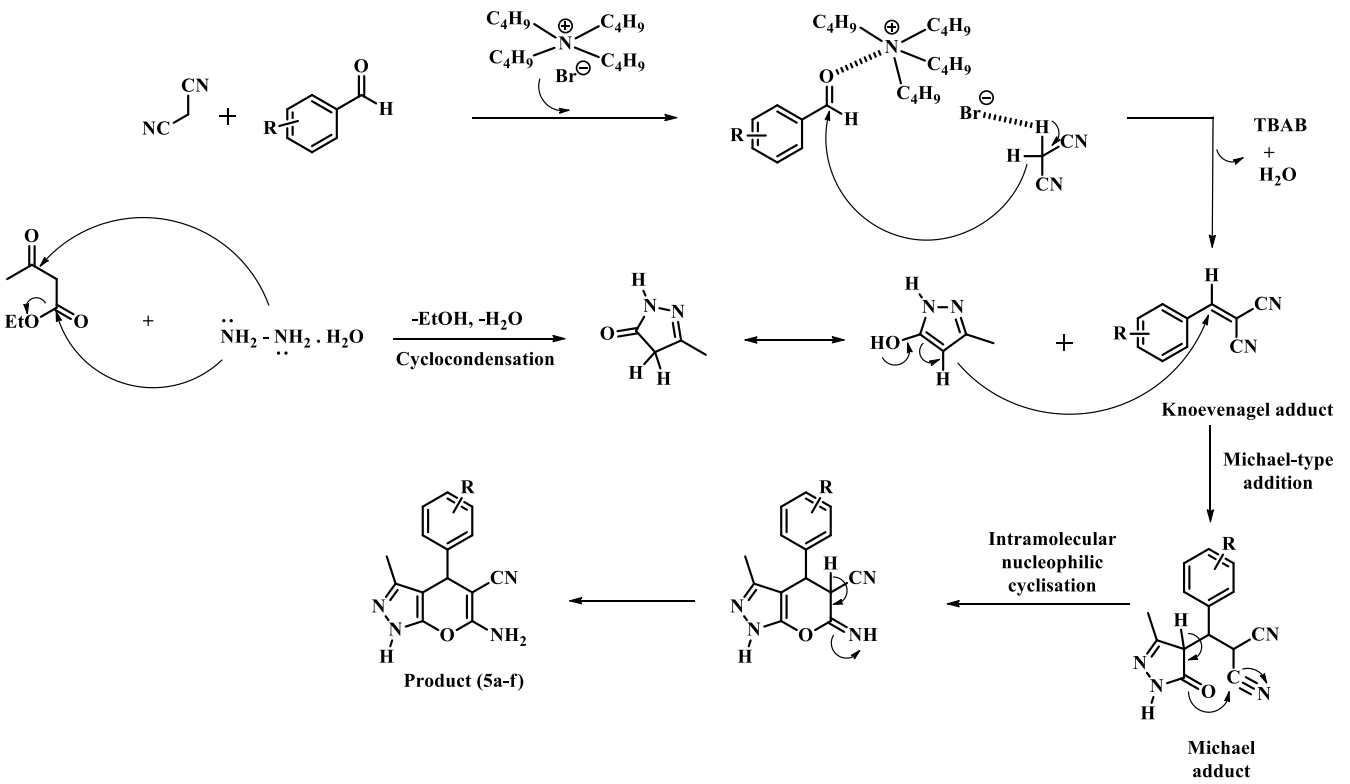
CONFLICT OF INTEREST

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



Scheme-II: Plausible mechanism

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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