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CBr_4 Mediated [4 + 1] Dehydrocyclization for the Synthesis of Functionalized Imidazo[1,5-a]heterocycles from Pyridin-2-ylmethanamines and Aldehydes

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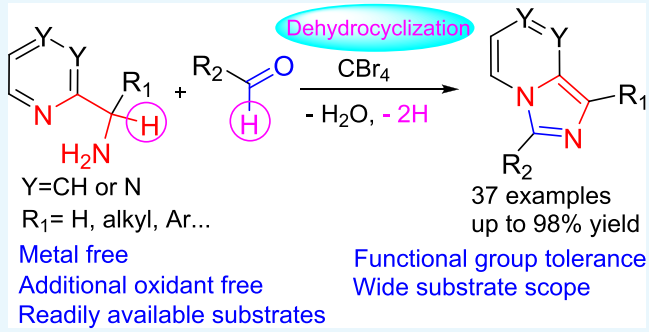
ABSTRACT: A CBr_4 mediated [4 + 1] dehydrocyclization was developed for the synthesis of imidazo[1,5-a]heterocycles from pyridin-2-ylmethanamines and aldehydes. This method was highly practical with the advantages of wide substrate scope, functional group tolerance, and mild reaction conditions.



INTRODUCTION

Imidazo[1,5-a]heterocycles have revealed to be a promising skeleton for their application in the pharmaceutical area in recent years.[1,2] Many efforts were devoted by chemists to the synthetic method development, and several reaction systems were successfully applied in the synthesis of imidazo[1,5-a]heterocycles, in which a typical [3 + 2] strategy was mostly employed. These reports could be roughly summarized as three categories that are different from the classical Vilsmeier-type cyclization,[3] I_2 promoted oxidative cyclizations,[4,5] copper-catalyzed and promoted oxidative cyclization,[6−11] and electrochemistry methods.[12,13] These methods well enriched the synthetic approaches for imidazo[1,5-a]heterocycles; however, relatively violent reaction conditions, such as high temperatures, heavy metals (copper salts), and limited functional group tolerance, hampered their application prospect. Challenge still exists in the development of greener and functional group tolerated approaches.

Aldehydes and pyridin-2-ylmethanamines are simple and readily available materials, making them ideal substrates for imidazo[1,5-a]heterocycles synthesis via a [4 + 1] strategy. However, they were only adopted in limited reports for imidazo[1,5-a]heterocycle construction,[14] and the limitations of modest efficiency, confined substrate scope, and use of heavy metals, even a hypertoxic oxidant, call for a new reaction system. Carbon tetrabromide (CBr_4), an organic substance, was reported to have certain reactivity in the construction of a chemical bond.[15−19] By virtue of the potential reactivity of CBr_4, herein, we report a mild, facile, and practical CBr_4 mediated dehydrocyclization for the synthesis of functionalized imidazo[1,5-a]heterocycles from pyridin-2-ylmethanamines and aldehydes.

RESULTS AND DISCUSSION

Initially, benzaldehyde (**1a**, 0.2 mmol) and pyridin-2-ylmethanamine (**1b**, 0.6 mmol) were employed as model substrates for optimization. With the aim of developing a mild and practical method, a series of potential nonmetal reagents (0.36 mmol) in 1.5 mL of DMF were investigated at room temperature. As shown in Table 1, iodine (I_2) and *N*-iodosuccinimide (NIS) as catalysts only lead to a trace amount of the target molecule (**1c**) (Table 1, entries 1 and 2), and *N*-bromosuccinimide (NBS) and carbon tetrachloride (CCl_4) as catalysts failed in this reaction (Table 1, entries 3 and 4). To our delight, CBr_4 as a catalyst could effectively promote this reaction and gave 69% yield (Table 1, entry 5); replacing the catalyst CBr_4 by CI_4 only gave a 20% yield (Table 1, entry 6). Further increasing the amount of CBr_4 to 0.4 mmol failed to elevate the yield (67%) (Table 1, entry 7). Subsequently, with 0.36 mmol of CBr_4, benzaldehyde (**1a**, 0.2 mmol), and pyridin-2-ylmethanamine (**1b**, 0.6 mmol), various solvents were screened. It was found that the solvents had great influence on this reaction; 1,4-dioxane and toluene as solvents failed in

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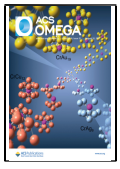

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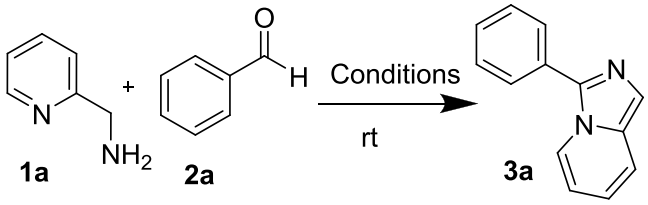
Table 1. Optimization of the Reaction Conditions[a]



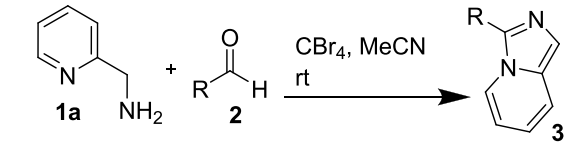
entry	catalysts	solvent	yield (%)[d]
1	I_2	DMF	trace
2	NIS	DMF	trace
3	NIBS	DMF	n.d.[c]
4	CCl_4	DMF	n.d.[c]
5	CBr_4	DMF	69
6	Cl_4	DMF	20
7	CBr_4[b]	DMF	67
8	CBr_4	DMSO	71
9	CBr_4	1,4-dioxane	trace
10	CBr_4	toluene	trace
11	CBr_4	MeCN	86
12	CBr_4	DCM	70
13	CBr_4	EtOH	31
14	CBr_4	MeCN/H_2O	26

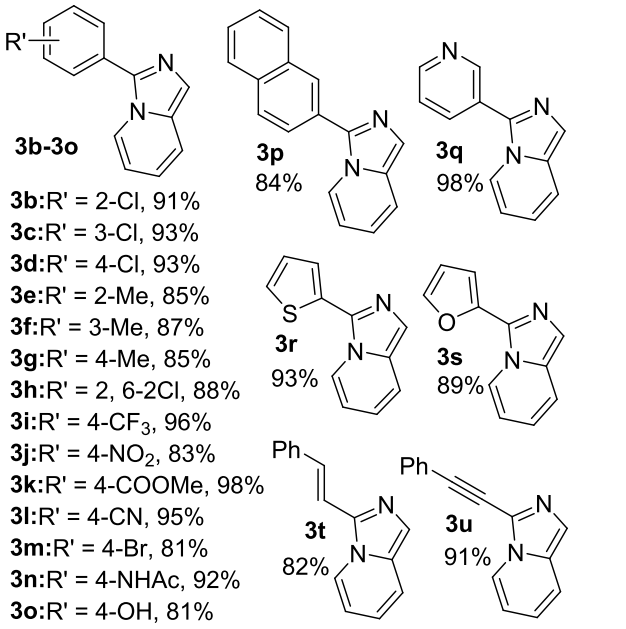
[a]Unless otherwise noted, all the reactions were carried out using pyridin-2-ylmethanamine (**1a**, 0.60 mmol), benzaldehyde (**2a**, 0.20 mmol), and halogen sources (0.36 mmol) in 1.5 mL of solvents and stirred at room temperature for 20 h. [b]0.4 mmol of CBr_4 was used. [c]n.d. = not detected. [d]Isolated yield.

this reaction (Table 1, entries 9 and 10), while DMSO, MeCN, and DCM favored this reaction by providing 71%, 86%, and 70% yield, respectively (Table 1, entries 9, 12, and 13). Other protonic solvents such as EtOH and MeCN/H_2O also provided the product with 31% and 26% yield (Table 1, entries 14 and 15), which indicated that this reaction was proton-tolerant to some degree. With a satisfactory yield obtained (86%) (Table 1, entry 11), the reaction was not further optimized.

With the optimal conditions in hand, we investigated the substrate scope of reaction. Firstly, various aldehydes (**2**) were investigated. As shown in Table 2, the electronic effect and steric effect on the benzene ring were all investigated. For the electronic effect, electron-withdrawing group chloride at the ortho-, meta-, and para-position on benzaldehyde and electron-donating group methyl at the ortho-, meta-, and para-position on benzaldehyde were all investigated and effectively provided the target product with 85−93% yield (Table 2, **3b**−**3g**). Electron-withdrawing group chloride on the benzene ring provided a higher yield than electron-donating group methyl (Table 2, **3b**−**3d**: 91−93% vs **3e**−**3g**: 85−87%), indicating that electron-withdrawing groups on the benzene ring were in favor of the reaction. 2,6-Dichlorobenzaldehyde was employed as a steric aromatic aldehyde for the steric effect evaluation; an 88% yield (**3h**) indicated that this reaction was fairly applicative for steric aldehyde. To evaluate the function group tolerance, a series of substituted benzaldehydes were investigated. The $-CF_3$, $-NO_2$, −COOMe, −CN, −Br, −NHAc, and −OH groups at the para-position of benzaldehyde successfully provided the corresponding products (**3i**−**3o**: 81−98%), indicating that this reaction had good functional-group tolerance even for the protonic group −OH (**3o**, 81%). Other fused aromatic aldehyde (2-naphthaldehyde)

Table 2. Investigation on Various aldehydes[a]





[a]Unless otherwise noted, all the reactions were carried out using aldehydes (0.20 mmol), pyridin-2-ylmethanamine (0.60 mmol), and halogen sources (0.36 mmol) in 1.5 mL of MeCN and stirred at room temperature for 20 h. Yields were isolated yields.

and hetero-aromatic aldehydes (nicotinaldehyde, thiophene-2-carbaldehyde, and furan-2-carbaldehyde) were applicable in this reaction as well and provided the corresponding products (**3p**−**3s**: 84−98%). Allylaldehyde and alkyne aldehyde, which had two potential reactive sites (aldehyde group and beta-C of the aldehyde), presented good chemoselectivity and provided the product **3t** (82%) and **3u** (91%) with good yield.

Subsequently, to focus on the amine scope investigation, a cross-evaluation was performed under the optimized conditions (Table 3). As for the R_1 investigation, (6-methylpyridin-2-yl)methanamine (**1b**), which possessed a steric methyl at the 6-position on the pyridine ring, could react smoothly with benzaldehyde, 4-nitrobenzaldehyde, 4-methylbenzaldehyde, and nicotinaldehyde and provided the corresponding products **3v** (71%), **3w** (82%), **3x** (71%), and **3y** (88%). This indicated that the steric methyl had little influence on this reaction. Nicotinaldehyde, possessing important pyridine moieties in various drugs, was preferentially fixed for further investigation. (5-Methylpyridin-2-yl)methanamine, with an electron-donating group methyl at the 5-position of **1a**, and nicotinaldehyde smoothly reacted and gave the product **3z** (86%). (5-(Trifluoromethyl)pyridin-2-yl)methanamine, with a strong electron-withdrawing group $-CF_3$ at the 5-position of **1a**, failed to give the product under CBr_4/MeCN/rt conditions (general procedure I), but this could be redeemed by employing CBr_4/DMSO/80 °C conditions (general procedure II in the Supporting Information) for 5 h, which gave the product **3aa** with 86% yield. This implied that electron-deficient pyridin-2-ylmethanamines were not favorable in this

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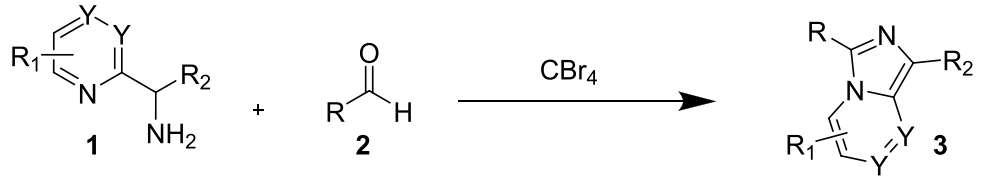
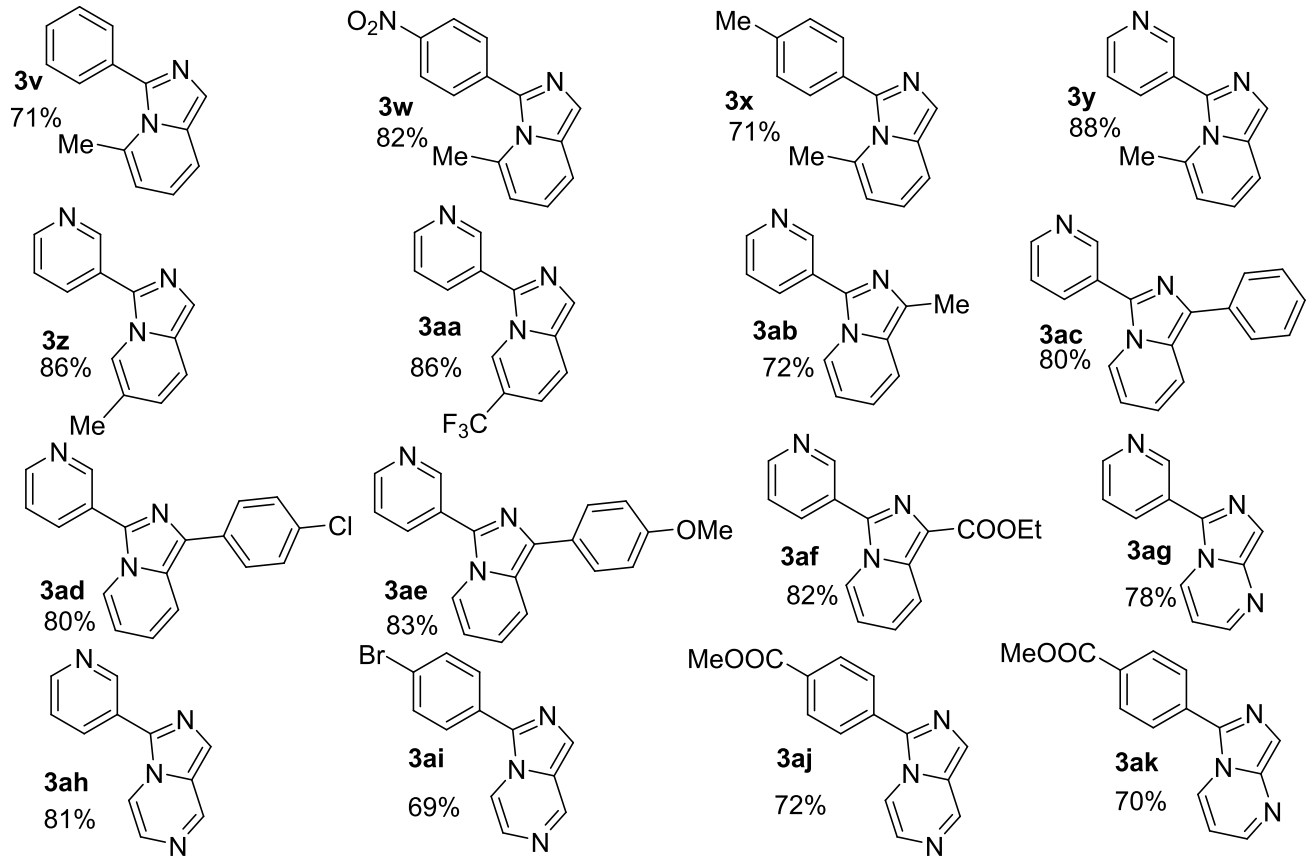
Table 3. Investigation on Pyridin-2-ylmethanamine Analogues[a]





[a]Conditions for compounds **3v**−**3z**: aldehydes (0.20 mmol), amines (0.60 mmol), and CBr_4 (0.36 mmol) in 1.5 mL of MeCN and stirred at room temperature for 20 h. Conditions for compounds **3aa**−**3kk**: the reactions were carried out using aldehydes (0.20 mmol), amines (0.60 mmol), and CBr_4 (0.36 mmol) in 1.5 mL of DMSO and stirred at 80 °C for 4 h. Yields were isolated yields.

reaction. As for R_2, the alkyl, aromatic, and ester groups all successfully reacted with nicotinaldehyde under the CBr_4/DMSO/80 °C conditions and gave the corresponding product **3ab** (72%), **3ac** (80%), **3ad** (80%), **3ae** (83%), and **3af** (82%). It was found that the aromatic and ester groups provided a better yield than alkyl (**3ac**−**3ae** and **3af** vs **3ab**), indicating that the aromatic ring and electron-withdrawing ester groups were more favorable than the electron-donating alkyl group at the R_2 position. Besides pyridin-2-ylmethanamines, pyrimidin-2-ylmethanamine and pyrazin-2-ylmethanamine were also applicative in this reaction and gave the corresponding products **3ag** (78%) and **3ah** (81%).

To investigate the mechanism of the reaction, two control experiments were performed (Scheme 1a,b). First, a radical trap experiment was performed, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) (0.4 mmol) was added to the reaction system in the **3a** synthesis, and the result (Scheme 1a) showed that the addition of TEMPO had little effect on the yield of **3a** (78%), indicating that this reaction did not proceed by a radical process. Besides, an oxygen-free experiment under the N_2 protection was also performed in the synthesis of **3a**, and an 86% yield of **3a** also indicated that the oxidative de-hydrogen process was not promoted by oxygen. Based on previous reports[16,17] and the critical information obtained, a possible mechanism was proposed in Scheme 1c. Pyridin-2-ylmethanamine condenses with benzaldehyde and forms intermediate **I** phenyl-*N*-(pyridin-2-ylmethyl)methanimine. Imine I reacts with CBr_4 and gives intermediate **II** that experiences an elimination reaction to form intermediate **III** and HBr. Finally, intermediate **III** experiences synergetic intramolecular nucleophilic attack, de-hydrogen reaction, and rearrangement and forms the product **3a**. The de-hydrogen process is possibly mediated by the bromoform anion formed in the second step and synergetically promoted the cyclization.

We are seeking for a new ligand that can be adopted in kinase inhibitor discovery,[20−22] and the moieties of **3ag** and **3ah** were presented to be good hinge binding ligands for c-Kit kinase in the virtual screening. As shown in Figure 1, **3ag** and **3ah** both fitted well into the hydrophobic pocket of c-Kit kinase, and the bindings were mediated by a hydrogen bond and the $\pi-\pi$ stacking interaction; these interactions make them potential fragments. Considering their potential

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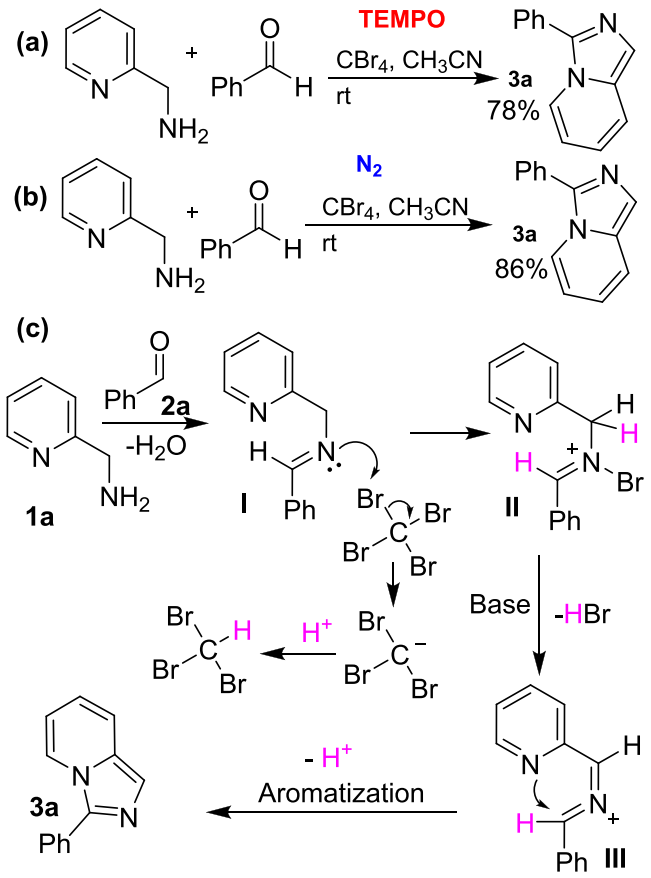
Scheme 1. Control Experiments and Possible Mechanism of the Reaction[a]



[a](a) Radical trapping experiment. (b) Oxygen free experiment. (c) Possible mechanism.

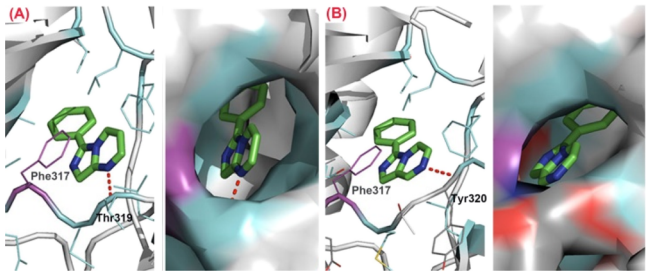


Figure 1. Structural basis of the binding mechanism of **3ag** and **3ah** against c-KIT kinase (PDB ID: 4U0I). (A) **3ag** docked into c-KIT kinase (PDB ID: 4U0I). (B) **3ah** docked into c-KIT kinase.

application in drug discovery, functionalized **3ai** (69%), **3aj** (72%), and **3ak** (70%) were successfully synthesized, and they could act as potential moities for the type II C-KIT inhibitor; this part of work is being undertaken in our laboratory. Results above demonstrated that this method had a wide substrate scope and could be used for the preparation of various functionalized N-hetero-fused aromatic rings.

CONCLUSIONS

In conclusion, we have developed a CBr_4 mediated [4 + 1] dehydrocyclization for the efficient synthesis of functionalized imidazo[1,5-a]heterocycles with a wide substrate scope and functional group tolerance advantages. Besides, this reaction employed mild conditions such as room temperature, metal-free, additional oxidant free, etc. More importantly, some of these compounds were potential moieties for the type II c-KIT inhibitors. This method may provide great help in conveniently obtaining various potential active fragments for c-KIT kinase and other structure-similar kinases, and this work is ongoing in our laboratory.

EXPERIMENTAL SECTION

Experimental Reagents and Instruments. Unless otherwise noted, all reactions were carried out under air atmosphere, and commercial materials and solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were measured on a 600 MHz spectrometer (^{1}H NMR: 600 MHz, ^{13}C NMR: 150 MHz) using $CDCl_3$ or DMSO-*d6* as the solvent at room temperature. High-resolution mass spectra (HRMS) were recorded on a BRUKER VPEXII spectrometer with ESI mode. Flash column chromatography was performed on a silica gel, 200−300 mesh.

Experimental Procedures. *General Procedure I (**3a**−**3z**).* To a solution of aldehydes (0.2 mmol) and amines (0.6 mmol) in 1.5 mL of MeCN was added carbon tetrabromide (0.36 mmol, 119.4 mg). The system was stirred at room temperature for 20 h. Ten milliliters of water was added, and the system was extracted by ethyl acetate (3 × 15 mL). The organic phase was combined and dried by anhydrous sodium sulfate. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography by using CH_2Cl_2/MeOH as the eluent to afford the products **3a**−**3z**.

*General Procedure II (**3aa**−**3ak**).* To a solution of aldehydes (0.2 mmol) and amines (0.6 mmol) in 1.5 mL of DMSO was added carbon tetrabromide (0.36 mmol, 119.4 mg), and then the system was stirred at 80 °C for 4 h. The system was cooled to room temperature, 10 mL of water was added, and the system was extracted by ethyl acetate (3 × 15 mL). The organic phase was combined and dried by anhydrous sodium sulfate. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography by using CH_2Cl_2/MeOH as the eluent to afford the products **3aa**−**3ak**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02181.

Details of characterization data and NMR spectra (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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