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ORIGINAL PAPER

An improved route to urapidil from 1-(2-methoxyphenyl)piperazine and oxetane

Li-Zhi Zhang[1] · Feng-Liang Liu[1] · Hao-Yue Xiang[1] · Zhen-Yu Zhan[1] · Jie Shen[1]

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Abstract

Urapidil is an important drug for the treatment of essential hypertension and intravenously in hypertensive emergencies. Herein, an improved route to Urapidil was introduced. The new designed synthetic route starts with the addition reaction of 1-(2-methoxyphenyl)piperazine and oxetane catalyzed by $Yb(OTf)_3$ in acetonitrile to form the key intermediate 3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-ol. Additionally, 3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-ol was purified by recrystallization from the optimized solvents, which was beneficial to large scale production. Intermediate 3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl-4-methylbenzenesulfonate was cast directly for the subsequent reaction without further purification. The overall yield of this route is about 45%. The structure of the final product was well confirmed by ^{1}H-NMR, ^{13}C-NMR and HRMS.

Keywords Urapidil · 1-(2-methoxyphenyl)piperazine · Oxetane · $Yb(OTf)_3$ · Catalysis

Introduction

Urapidil (6-[3-[4-(2-methoxyphenyl)piperazin-1-yl] propylamino]-1,3-dimethylpyrimidine-2,4-dione) (**1**), is an α-blocker that lowers peripheral blood pressure without affecting the heart rate or intracranial blood pressure (Siravoka et al. 21). It can also cross the blood–brain barrier and activate the 5HT-1A receptor (Castor et al. 4), resulting in central antihypertensive activity. This unique mechanism makes urapidil can prevent reflex tachycardia in patients (Wu et al. 24), which has been used clinically primarily in the treatment of hypertensive crises and perioperative hypertension (Hirschl 10; Suwelack et al. 22). Due to its rapid onset of action and ease of controllability, urapidil has been developed in a variety of dosage forms including injections, oral capsules (Minushkina 15) and eye drops (Okamoto et al. 19; Morita et al. 17).

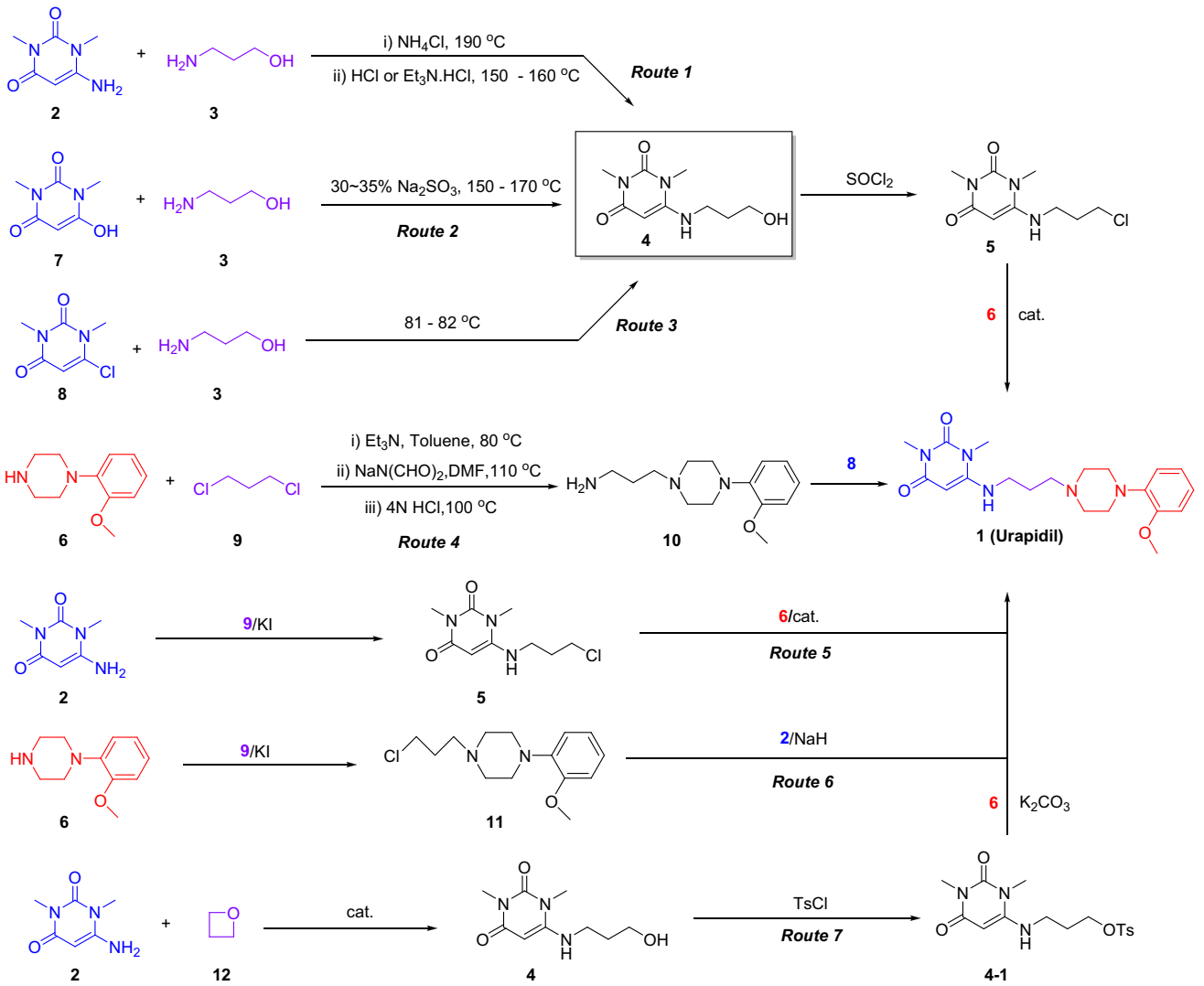
Urapidil was first developed and synthesized as an antihypertensive drug by Klemm's group (11), wherein two key raw materials, 6-amino-1,3-dimethyluracil (**2**) and 1-(2-methoxyphenyl)piperazine (**6**), was involved for its synthesis (Scheme 1, route 1). At the first step, a solvent-free reaction was employed. However, it is quite challenging to stir the reaction mixture adequately, due to the high viscosity of the compounds. Moreover, this problem can further cause localized overheating, leading to the generation of by-products, post-processing difficulties, and low yield. The issues still persisted while using HCl or triethylamine hydrochloride (Cichy et al. 6) as catalysts, or changing the substrate to 1,3-dimethyl-6-hydroxyuracil (**7**) (Route 2) (Peng 20). These improvements had little effect on the improvement of the post-treatment process and yield. Alternatively, prepared the intermediate **4** from chlorinated substrate 1,3-dimethyl-6-chlorouracil (**8**), as shown in Route 3, the reaction condition became milder with improved yield. However, the use of $POCl_3$ in the chlorination process for synthesis of **8** hindered the further application of this strategy, which was highly corrosive to the equipment.

In addition, urapidil could be obtained from substrate **6** as shown in Route 4 (Zhang et al. 26). However, the synthesis of intermediate **10** is complicated, which is difficult to be purified. The utilization of $NaN(CHO)_2$ and **8** makes the entire route costly and inappropriate for industrial production.

The synthetic Routes 5 and 6 were shortened by replacing substrate connecting **2** and **6** with 1,3-dichloropropane (**9**) (Gharpure et al. 8). But the reaction speed for the first step

✉ Feng-Liang Liu
lflcsu@csu.edu.cn; 2108017629@qq.com

[1] College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, China



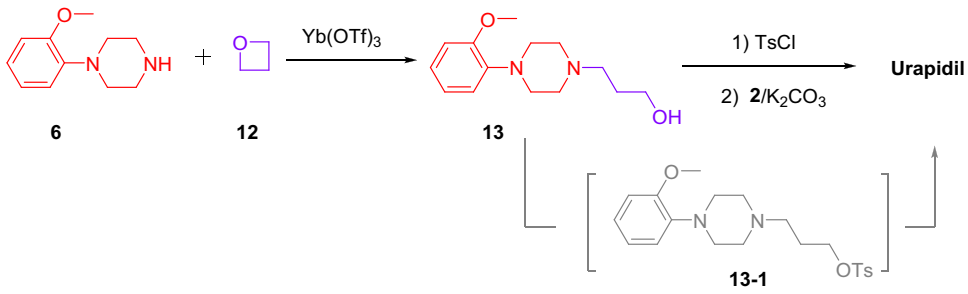
Scheme 1 Existing routes for the synthesis of Urapidil

is very slow. To this end, KI was needed to accelerate this transformation, which is a more expensive option that produces a less selective reaction with impurities and low yields as side effects. Meanwhile, the second step of the reaction of Route 5 requires the use of phase transfer catalyst (Li et al. 12), which is cumbersome and environmentally unfriendly for post-processing. Similarly, the second step of Route 6 requires the use of NaH, which is more hazardous. As a result, neither of these methods are suitable for industrial production.

Oxetane is a significant intermediate in organic synthesis due to its unique four-membered ring structure, which confers high reactivity. It is commonly utilized to introduce hydroxypropyl groups into compounds because it can undergo ring-opening reactions when exposed to nucleophilic reagents and metal catalysts. As early as 1994, Crotti et al. found that aliphatic amines or aromatic amines were able to act as nucleophilic reagents in the ring-opening reaction of oxetanes catalyzed by $LiBF_4$ (Chini et al. 5) or lanthanide(III) trifluoromethansulfonates (Crotti et al. 7). Mohammad et al. reported a high yield of oxetane ring opening catalyzed by 10% mol of $MgBr_2{\cdot}OEt_2$ with $PhNH_2$ and pyrrolidine under solvent-free condition (Mohammad et al. 16). Various catalysts and synthetic methods are being developed to enable the ring-opening reaction of amines with oxetanes. (Wang et al. 23; Bagal et al. 2; Nigríni et al. 18).

Our group proposed an alternative route by starting from nucleophilic ring-opening reaction of **2** with oxetane (**12**) to obtain **4**. Further activation of the hydroxyl group of **4** by TsCl and treatment with **6** could give the target urapidil (Route 7) (Liu et al. 13). However, due to the conjugation effect between the amino group and double bond in **2**, its nucleophilic activity was low and ring-opening proved low

Scheme 2 Our designed route for the synthesis of Urapidil



efficiency. Therefore, the search or development of a more efficient catalyst is appealing.

In this study, $Yb(OTf)_3$ was used as a catalyst for the nucleophilic addition ring-opening reaction of **6** and **12** to synthesize the intermediate 3-[4-(1-(2-methoxyphenyl) piperazinyl]-1-propanol (**13**) (Scheme 2). The impact of the catalyst, solvent, and reaction temperature on the reaction were comprehensively investigated. The urapidil was synthesized using a one-pot method with **2** after activating the hydroxyl group with TsCl. This method offered a novel route for the industrial production of urapidil.

Experimental

Materials and methods

All the solvents and reagents were purchased from commercial reagent suppliers and used without further purification. All the reagents were weighted in air at room temperature. The reactions were monitored by thin layer chromatography (TLC) on 25 × 80 mm silica gel plates (GF-254). The ^1H and ^{13}C NMR spectra were recorded on Bruker ADVANCE III 400 NMR spectrometer using TMS as internal standard. Melting points (m.p.) were measured by WRS-1A digital melting point apparatus and were uncorrected. IR were measured by Thermo Nicolet Avatar 360 FTIR System. Mass spectroscopy were recorded on Bruker Compact high-resolution mass spectrometer.

Preparation of 3-(4-(2-methoxyphenyl) piperazin-1-yl)propan-1-ol (13)

To a 50 mL dry round-bottomed flask were added 305.0 mg (1.6 mmol) **6**, 139.4 mg (2.4 mmol) **12**, 49.3 mg (0.08 mmol) $Yb(OTf)_3$ and acetonitrile (5 mL). The obtained mixture was refluxed for 48 h. At the end of the reaction, the mixture was cooled to room temperature, diluted with water and then extracted with dichloromethane. The aqueous phase after partitioning was retained for catalyst recovery. The organic phase was washed with water, dried with anhydrous Na_2SO_4. Thereafter, the solvent was removed under reduced pressure to yield a brown solid consisting of the desired product and unreacted raw material **12**. The brown solid was dissolved in 1 mL of methanol, and then 15 mL of petroleum ether was added. The above solution was heated to reflux for 15 min, then cooled to room temperature and placed in a refrigerator overnight. The crystals were precipitated, filtered, and the filter cake was washed with 2 mL of cold mixed solvents (methanol/ petroleum ether 1/15, V/V), collected and dried in a vacuum oven at 45 °C for 4 h to give compound **13**.

Separation and recycle of catalyst $Yb(OTf)_3$

The retained aqueous phase was distilled under reduced pressure to obtain the white solids, and then dried in a vacuum oven at 180 °C for 4 h to obtain the recycled $Yb(OTf)_3$ crystals.

3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-ol (13)

Yield: 200.3 mg, 50%, white solid. ^1H-NMR (400 MHz, $CDCl_3$): δ 7.07–6.78 (m, 4H), 3.86 (s, 3H), 3.84 (t, 2H), 3.08 (broad s, 4H), 2.74 (broad s, 4H), 2.70 (t, 2H), 1.80–1.73 (m,2H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ 152.25, 140.27, 123.62, 121.14, 118.54, 111.31, 63.14, 58.30, 55.41, 53.47, 49.69, 26.58. IR (cm^{-1}): 3358.33, 2929.79, 2815.66, 1595.65, 1499.31, 1451.09, 1238.04, 1022.46, 735.87. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{23}N_2O_2^+$, 251.1754, found 251.1754.

Preparation of compound 13-1 and urapidil (1)

At 0–5 °C, 108.8 mg (0.43 mmol) **13**, 90 μL (0.645 mmol) Et_3N and 5 mL CH_2Cl_2 were added to a 50 mL dry round-bottomed flask. Then 98.8 mg (0.516 mmol) TsCl dissolved in 1 mL CH_2Cl_2 was added to the flask in two portions within 10 min. After the addition, the reaction was stirred until completed, the mixture was diluted with water and separated. The organic phase was washed with dilute hydrochloric acid solution, saturated Na_2CO_3 and NaCl solution, and dried with anhydrous Na_2SO_4. Low-boiling

point substances were removed by distillation under reduced pressure to obtain **13-1**, which was then used directly in the next step.

66.7 mg (0.43 mmol) **2** and 89.8 mg (0.65 mmol) K_2CO_3, was add to a solution of the obtained **13-1** in 5 mL of acetonitrile. And the reaction mixture was refluxed for 6 h with stirring. At the end of the reaction, the mixture was cooled to room temperature, extracted and filtered, and the filter cake was washed with acetonitrile (2 mL × 3). The filtrate was collected and concentrated under reduced pressure, the resulting residue was dissolved with CH_2Cl_2 and extracted with water. The organic layer was washed with water and dried with anhydrous Na_2SO_4, then evaporated under reduced pressure to remove the solvent. Toluene was added to the residue and heated to 65–70 °C to dissolve. The mixture was then allowed to cool down to room temperature, resulting in crystal precipitation. The crystals were filtered, and the filter cake was washed with toluene, dried at 45 °C under vacuum, to yield urapidil.

Urapidil (1)

Yield: 149.9 mg, 90%, white solid. m.p. 157–159 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.06–6.85 (m, 4H), 4.78 (s, 1H), 3.87 (s, 3H), 3.40 (s, 3H), 3.31 (s, 3H), 3.18 (dd, J = 9.6, 5.6 Hz, 2H), 3.09 (s, 4H), 2.75 (s, 4H), 2.66 (t, J = 0.4 Hz, 2H), 1.94–1.86 (m, 2H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 163.16, 153.44, 152.29, 152.02, 140.56, 123.51, 121.14, 118.14, 111.39, 74.93, 58.86, 55.43, 53.86, 50.37, 44.68, 30.15, 27.69, 22.50. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{20}H_{30}N_5O_3^+$, 388.2343, found 388.2323.

Results and discussion

Optimization of the reaction conditions for the first step

Screening of catalyst

As shown in Table 1, the reaction could not be carried out by using conventional Lewis acids (Table 1, entries 1–3) as catalysts, probably because these Lewis acids do not have enough affinity to oxygen atom. After switching the catalyst to $Sc(OTf)_3$, $Y(OTf)_3$ and $Yb(OTf)_3$, the reaction underwent successfully. When using the same amount of catalyst (10%), the yields of the addition reaction catalyzed by $Sc(OTf)_3$, $Y(OTf)_3$ and $Yb(OTf)_3$ were 27%, 14% and 40% respectively (Table 1, entries 4–5, 10). The amount of catalyst $Yb(OTf)_3$ was from 1, 3 to 5%, and the yields were 25%, 30% and 50% respectively (Table 1, entries 6–8). However, when the amount of $Yb(OTf)_3$ was further increased, the yield decreased, or even no reaction occurred (Table 1, entries 9–10). The catalyst $Yb(OTf)_3$ was recycled twice, with a 46% reaction yield in the first recycling and a significantly lower 21% yield in the second (Table 1, entries 11–12).

Table 1 Effect of different catalysts on the reaction

Entry	Catalyst	Mol (%)	Yield (%)
1	$LiBF_4$	10	No reaction
2	$LiClO_4$	10	No reaction
3	$Zn(OTf)_2$	10	No reaction
4	$Sc(OTf)_3$	10	27
5	$Y(OTf)_3$	10	14
6	$Yb(OTf)_3$	1	25
7		3	30
8		5	50
9		10	40
10		100	No reaction
11	$Yb(OTf)_3$[c]	5	46
12	$Yb(OTf)_3$[d]	5	21

Reaction condtions: **6** (1.6 mmol), **12** (2.4 mmol) in MeCN, catalyst, 82 °C, 48 h, isolated yield

[c]Catalyst recycled once

[d]Catalyst recycled twice

Table 2 Effect of different solvents on the reaction

Entry	Solvent	V (ml)	Temperature (°C)	Yield (%)
1	THF	5	reflux	No reaction
2	DMF	5	82	No reaction
3	toluene	5	82	No reaction
4	dichloromethane	5	reflux	No reaction
5	1,4-Dioxane	5	82	No reaction
6	water	5	82	No reaction
7	acetonitrile	5	82	50

Reaction condtions: **6** (1.6 mmol), **12** (2.4 mmol) in solvent, $Yb(OTf)_3$ (5 mol%), 48 h, isolated yield

Screening of solvents

With the optimal catalyst in hand, various solvents were also evaluated. As detailed in Table 2, only acetonitrile (Table 2, entry 6) yielded the product, whereas the other solvents failed (entries 1–5). The possible reasons for such a result are as follows. The O atoms in THF, DMF, 1,4-Dioxane and H_2O form hydrogen bonds with the nucleophile **6**, thus reducing its nucleophilicity. In contrast, the weak electron donating ability of the N atoms in acetonitrile results in a weak ability to form hydrogen bonds with **6,** and therefore has little effect on the nucleophilicity of **6**. At the same time,

Table 3 Effect of different temperature on the reaction

Entry	Temperature (°C)	Yield (%)
1	25	No reaction
2	40	No reaction
3	60	No reaction
4	82	50

Reaction condtions: **6** (1.6 mmol), **12** (2.4 mmol) in MeCN, $Yb(OTf)_3$ (5 mol%), 48 h, isolated yield

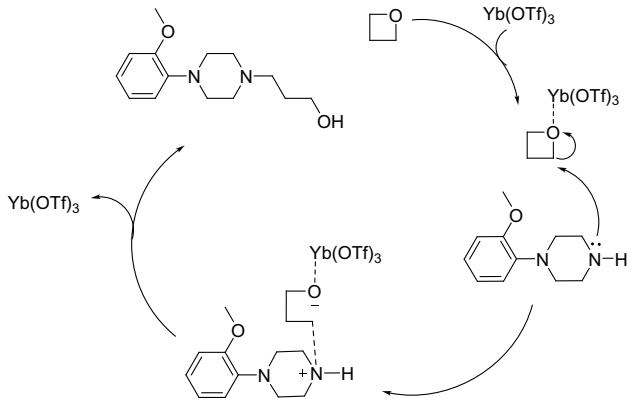


Fig. 1 Proposed mechanism for oxetane ring-opening reaction catalyzed by $Yb(OTf)_3$

the larger polarity of acetonitrile has the ability to stabilize the reaction intermediate.

Screening of reaction temperature

The reaction temperature was investigated by performing the reaction in the solvent acetonitrile using $Yb(OTf)_3$ as a catalyst (Table 3). And the results showed that the reaction could take place only under refluxed condition. The oxetane ring structure has a low ring strain energy, and ring opening of oxetane requires a higher activation energy (Ahmad et al. 1), resulting in a need for high temperature during its reaction with **12**.

Possible mechanism of the first step

According to Meguro's report (14), this reaction maybe a nucleophilic addition ring-opening reaction (Fig. 1). The strained C–O–C bond angle exposes the oxygen lone pair of electrons, allowing oxetane to act as an excellent Lewis base (Bull et al. 3). The Yb atom in $Yb(OTf)_3$ has a strong affinity for oxygen atom (Hannachi et al. 9), thereby forming complex with the oxygen atom in oxetane. This strengthens the ability of it to attract electrons, and increasing the electropositivity of the carbon atom adjacent to the oxygen atom. As a result, the lone pair of electrons of the nitrogen atom in **6** can attack the positively charged carbon atom easily, leading to ring-opening addition of oxetane. Finally, the ring-opening intermediate produced undergoes rapid proton transfer, yielding the desired γ-amino alcohol with regeneration of the catalyst.

Optimization of the second and third step reaction conditions

Conventional activation of alcohol hydroxyl groups by TsCl uses pyridine as the reaction solvent and acid-binding agent, but pyridine has a high toxicity. Referring to Yoshida's report (25), the hydroxyl group can effectively be activated by Et_3N as the acid-binding agent and CH_2Cl_2 as the solvent. After the reaction ended, excess Et_3N and TsCl were removed through acid washing and hydrolysis. The organic phase was then dried and evaporated to remove CH_2Cl_2, allowing the product to be directly utilized in the subsequent reaction.

The activation of the hydroxyl group of **13** by TsCl makes the reaction of **13-1** with **6** easy to occur. By 1:1 feeding of the starting materials and using 1.5 eq of K_2CO_3 as an acid-binding agent, urapidil could be obtained in high yield after refluxed in acetonitrile for 6 h. No phase-transfer or reverse-phase-transfer catalyst addition was required for this step.

Conclusion

In this paper, a new synthetic route for the antihypertensive drug urapidil was designed and successfully established. 1-(2-Methoxyphenyl)piperazine reacted with oxetane (1:1.5) under the catalyst of 5 mol% of $Yb(OTf)_3$ under reflux in acetonitrile for 48 h to obtain the key intermediate γ-amino alcohol. After activated by TsCl, γ-amino alcohol was directly reacted with 1,3-dimethyl-6-aminouracil, to deliver the final product urapidil with 45% overall yield, while using K_2CO_3 as an acid-binding agent. This improved route is characterized by easy availability of raw materials, recyclable catalyst, simple operation and good yield.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11696-024-03398-2.

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Declarations

Competing interest The authors declare no competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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