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Zirconium Hydrazinediido Complexes Derived from Cyclic Hydrazines and Their Role in the Catalytic Synthesis of 1,7-Annulated Indoles

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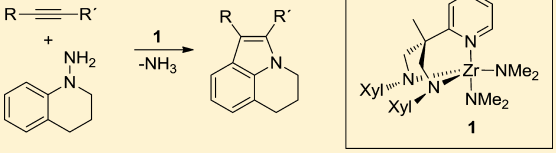
Supporting Information

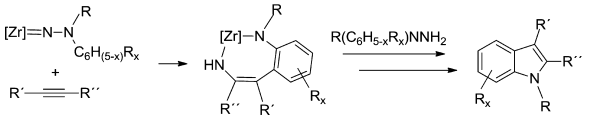
ABSTRACT: Reaction of cyclic 1,1′-disubstituted hydrazines with the bis(dimethylamido)zirconium complex [Zr{$(N^{Xyl})_2N_{py}$} $(NMe_2)_2$] (**1**) in the presence of dmap yielded the hexacoordinate zirconium hydrazinediido complexes [Zr{$(N^{Xyl})_2N_{py}$}(=NNC_9H_{10})$(dmap)_2$] (**2**) and [Zr{$(N^{Xyl})_2N_{py}$}(=$NNC_{12}H_8$)$(dmap)_2$] (**3**). Hydrazinediides are thought to be key intermediates in the zirconium-catalyzed reaction of cyclic 1,1′-disubstituted hydrazines and disubstituted alkynes to yield 1,7-annulated indoles. Their basic structural motif is found in 5-HT_3 receptor antagonists such as Cilansetron.



Recent studies of transformations of the M=N−NR_2 unit in group 4 metal hydrazinediides[1] have established the potential addition of unsaturated molecules at the highly polar M=N bond as well as the facile fragmentation of the N−N bond. Both processes may occur sequentially or almost concomitantly and may lead to the combined formation and scission of several chemical bonds in one process. These include stoichiometric transformations which involve formal insertions into the N−N bond, such as those reported by Mountford et al.[2] as well as the titanium-catalyzed syntheses of N-heterocycles developed by Odom, Beller, and others.[3−5]

Recently we reported a zirconium-catalyzed multistep reaction leading to indoles,[6] which involves hydrazinediido complexes as key species (Chart 1).[7] Closer inspection of the

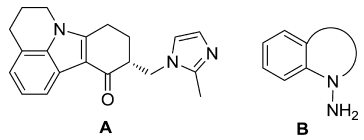
Chart 1



mechanism revealed a non-Fischer-type pathway including combined N−N bond cleavage and N−C coupling, which was first demonstrated by Bergman in 1991 in a stoichiometric transformation of [$Cp_2Zr(N_2Ph_2)$(dmap)] (Cp = C_5H_5, dmap = 4-dimethylaminopyridine).[8]

The indole ring system is one of the most important building blocks in natural bioactive products and in today's pharmaceuticals.[9] In particular, 1,7-annulated indole derivatives such as the prototypical Cilansetron (**A**) display high activity as 5-HT_3 receptor antagonists and are being clinically tested for the treatment of symptoms in the gastrointestinal system such as irritable bowel syndrome (IBS).[10]

To extend our previous synthetic strategy based on the reactivity of zirconium hydrazinediido complexes to annulated



polycyclic indole derivatives, we aimed to prepare such hydrazides derived from cyclic hydrazines (**B**). Moreover, we set out to investigate whether a catalytic transformation involving in situ prepared hydrazides of this type would give access to a target compound related to **A**.

RESULTS AND DISCUSSION

Reaction of the bis(dimethylamido)zirconium complex **1** with 1 molar equiv of the annulated hydrazine in the presence of an excess of DMAP yielded the hexacoordinate zirconium hydrazinediido complexes [Zr{$(N^{Xyl})_2N_{py}$}(=NNC_9H_{10})-$(dmap)_2$] (**2**) and [Zr{$(N^{Xyl})_2N_{py}$}(=$NNC_{12}H_8$)$(dmap)_2$] (**3**) (Scheme 1).

The detailed structures of both complexes **2** and **3** were established by X-ray diffraction and are depicted in Figure 1. The coordination geometry is distorted octahedral with the amido groups of the facial-coordinating tripodal ligand and the DMAP nitrogens lying in a common plane. The hydrazinediido ligand adopts an essentially linear coordination geometry. The Zr−N(4) and the N(4)−N(5) bond lengths are in good agreement with those found for other zirconium hydrazinediido complexes reported by Bergman and ourselves.[6−8]

The amidozirconium complex [$Zr(N^{Xyl})_2N_{py}(NMe_2)_2$] (**1**) was tested as a catalyst for the formation of 1,7-annulated indoles, starting from the corresponding hydrazines and disubstituted alkynes (Table 1).[11] The reactions were carried out at 80 °C in toluene using a catalyst loading of 10 mol %. As

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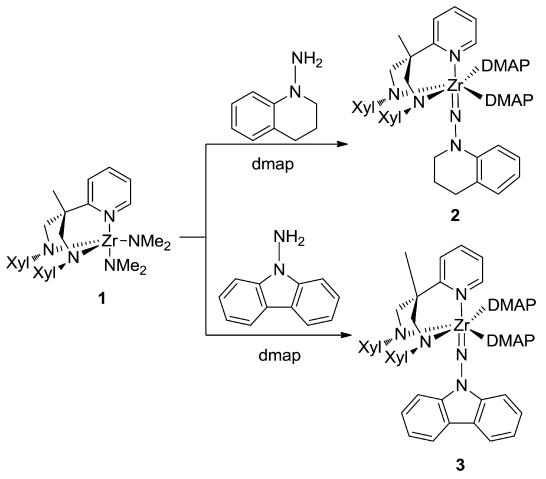
Scheme 1. Synthesis of the Cyclic Zirconium Hydrazinediido Complexes 2 and 3 from the Bis(dimethylamido)zirconium Precursor 1



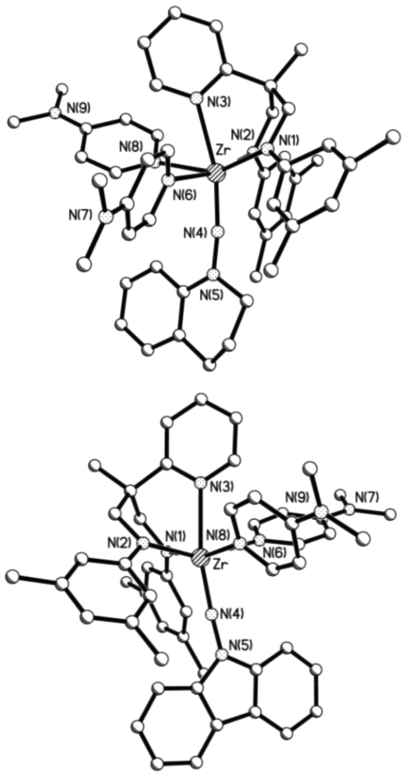
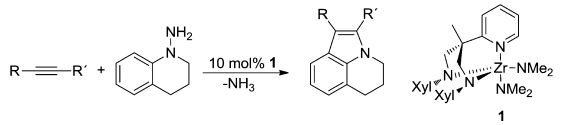


Figure 1. Molecular structures of **2** (top) and **3** (bottom). Selected bond lengths (Å) and angles (deg) are as follows. **2**: Zr–N(1)/N(2) = 2.201(2)/2.193(2), Zr–N(3) = 2.449(2), Zr–N(4) = 1.875(2), Zr–N(6) = 2.405(2), N(4)–N(5) = 1.377(2); N(3)–Zr-N(4) = 166.83(7), N(4)–Zr–N(6) = 88.40(7), Zr–N(4)–N(5) = 172.1(2). **3**: Zr–N(1)/N(2) = 2.197(2)/2.182(2), Zr–N(3) = 2.447(3), Zr–N(4) = 1.883(3), Zr–N(6) = 2.400(2), N(4)–N(5) = 1.362(4); N(3)–Zr–N(4) = 166.9(1), N(4)–Zr–N(6) = 96.2(1), Zr–N(4)–N(5) = 174.7(2).

Table 1. Zirconium-Catalyzed Synthesis of Annulated Heterocycles[a]



Entry	Hydrazine	Indole	Ratio of regio-isomers[b,d]	Yield [%][c]
Ind1			-	37
Ind2			3:2	20
Ind3			-	15
Ind 4			4:1	22
Ind5			-	58
Ind6			5:3	42
Ind7			-	35
Ind8			-	15
Ind9			10:1	50
Ind10			-	37
Ind11			3:2	30
Ind12			-	20
Ind13			5:1	20
Ind14			-	20
Ind15			-	10

[a]Reaction conditions: 1.2 mmol of alkyne, 1.44 mmol of hydrazine, 10 mol % of $[Zr(N^{Xyl})_2N_{py}(NMe_2)_2]$, 24 h in 2 mL of toluene at 80 °C. [b]Determined by ^{1}H NMR spectroscopy. [c]Yields of isolated products determined after chromatographic workup. [d]Major isomer is shown.

shown in Table 1, a variety of 1,7-annulated indoles could be isolated in moderate yields, probably due to the ring strain in these tricyclic N-heterocycles.

Notably, the best yields for each hydrazine derivative were obtained in combination with 2-butyne. For unsymmetrically disubstituted alkynes the indole with a bulkier substituent at the 3-position was the major product (Table 1, **Ind2**, **Ind4**, **Ind6**, **Ind9**, **Ind11**, and **Ind13**). This was established unambiguously by X-ray diffraction of **Ind4** (Figure 2).[12] In general, sterically bulky substituents at the C≡C triple bond, such as an aryl ring, lead to better regioselectivities. This is further enhanced by the

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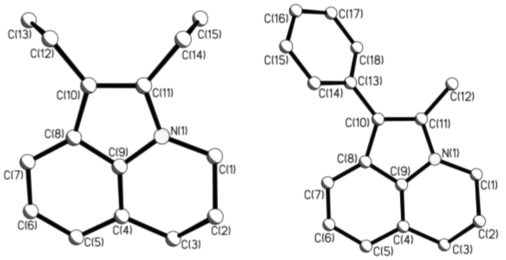
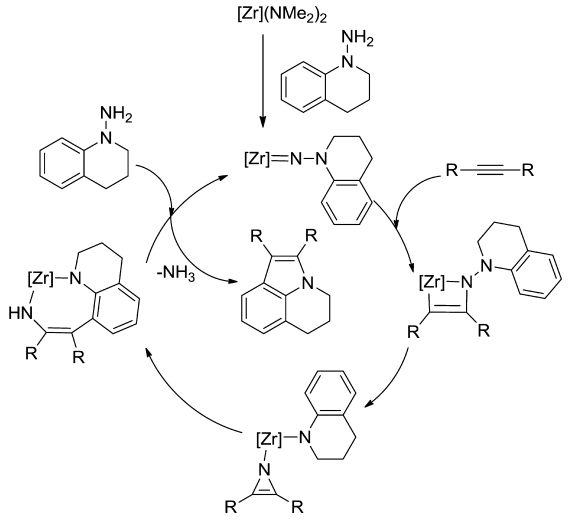


Figure 2. Molecular structures of annulated indoles **Ind3** (left) and **Ind4** (right) (only one of the two independent molecules is shown). Selected bond lengths (Å) and angles (deg) are as follows; data for the second independent molecule for **Ind4** are given in brackets. **Ind3**: N(1)−C(11) = 1.392(2), C(11)−C(10) = 1.378(2), C(10)−C(8) = 1.440(2); C(9)−N(1)−C(11) = 108.3(1), C(8)−C(9)−N(1) = 109.0(1); C(9)−C(8)−C(10) = 106.9(1). **Ind4**: N(1)−C(11) = 1.382(2) [1.379(2)], C(11)−C(10) = 1.394(2) [1.396(2)], C(10)−C(8) = 1.445(2) [1.444(2)]; C(9)−N(1)−C(11) = 108.9(1) [109.3(1)], C(8)−C(9)−N(1) = 109.1(1) [108.9(1)], C(9)−C(8)−C(10) = 106.1(1) [106.2(1)].

presence of a secondary alkyl substituent at the hydrazine N atom (Table 1, **Ind6** and **Ind9**). We note that a ring expansion of the annulated hydrazine from six to eight resulted in lower yields (Table 1, **Ind14** and **Ind15**).[13] Unfortunately, all attempts to obtain tetracyclic indole derivatives starting from the hydrazine employed in the synthesis of complex **3** gave no detectable quantities of the target species and only led to nonspecific degradation. This is propably due to the increased ring strain in such tetracycles.

On the basis of our previous detailed mechanistic work on the formation of simple indoles we propose an analogous mechanistic non-Fischer type pathway, as presented in Scheme 2.[6]

Scheme 2. Proposed Simplified Mechanistic Cycle for the Catalytic Transformation of Tricylic Heterocycles



In conclusion, we succeeded in extending the scope of the zirconium-catalyzed indole synthesis to annulated tricyclic target compounds in moderate yields. Attempts to extend the synthetic concept to more highly condensed systems were unsuccessful. This represents a limitation of the chosen approach.

EXPERIMENTAL SECTION

Preparation of $[Zr(N^{Xyl})_2N_{py}(NNC_9H_{10})(DMAP)_2]$. $Zr(N^{Xyl})_2N_{py}(NMe_2)_2]$ (200.00 mg, 0.36 mmol), DMAP (134.00 mg, 1.08 mmol), and 3,4-dihydroquinolin-1(2*H*)-amine (54.00 mg, 0.36 mmol) were dissolved in toluene (4 mL). After the mixture stood in a refrigerator at −30 °C for 2 days, a brown solid precipitated as thin needles. The solvent was removed by filtration, and the crude product was washed with pentane (3 mL) to give $[Zr(N^{Xyl})_2N_{py}(NNC_9H_{10})(DMAP)_2]$ as brown needles. Yield: 243.0 mg (0.28 mmol, 79%). Single crystals for X-ray diffraction were obtained from these needles. ^{1}H NMR (399.89 MHz, C_6D_6, 296 K): δ 1.55 (s, 3H, C-CH_3), 1.82 (quint, 2H, $^3J_{HH}$ = 5.7 Hz, NCH_2CH_2), 2.31 (s, 12H, CH_3 (Xylyl)), 2.32 (s, 12H, $N(CH_3)_2$ DMAP), 2.65 (t, $^3J_{HH}$ = 6.2 Hz, 2H, $N(CH_2)_2CH_2$), 3.46−3.51 (m, 2H, CH*H*), 3.85 (d, $^2J_{HH}$ = 14.7 Hz, 2H, CH*H*), 4.07 (t, $^3J_{HH}$ = 5.7 Hz, 2H, NCH_2), 5.71 (d, $^3J_{HH}$ = 6.7 Hz, 4H, CH_{ar} DMAP), 6.23−6.34 (m, 2H, $CH_{arHydrazine}$, HS_{py}), 6.39 (s, 2H, CH_{xyl}), 6.73−6.79 (m, 1H, $H3_{py}$), 6.91−7.00 (m, 2H, $CH_{arHydrazine}$, $H4_{py}$), 7.32 (s, 4H, CH_{xyl}), 7.68 (d, $^3J_{HH}$ = 5.4 Hz, 1H, $CH_{arHydrazine}$), 7.78 (d, $^3J_{HH}$ = 8.1 Hz, 1H, $CH_{arHydrazine}$), 8.32 (d, $^3J_{HH}$ = 5.4 Hz, 1H, $H6_{py}$), 8.53 (d, $^3J_{HH}$ = 6.4 Hz, 4H, CH_{ar} DMAP). $^{13}C\{^1H\}$ NMR (100.56 MHz, C_6D_6, 296 K): δ 22.4 (NCH_2CH_2), 22.5 (CH_3 (Xylyl)), 27.8 (C-CH_3), 28.9 ($N(CH_2)_2CH_2$), 38.9 ($N(CH_3)_2$), 43.5 (C-CH_3), 54.4 (NCH_2), 62.7, 63.8 (CH_2), 106.6 (CH_{ar} DMAP), 112.7 ($CH_{arHydrazine}$), 114.0, 114.2 (CH_{ar} Xylyl), 116.3 (*C*-NMe_2), 120.1 (CS_{py}), 120.5 ($CH_{arHydrazine}$), 127.0, 127.1 ($C4_{py}$, $CH_{arHydrazine}$), 136.3 (*C*-CH_3 Xylyl), 147.4 ($CH_{arHydrazine}$), 150.5 ($C6_{py}$), 152.4 ($CH_{arHydrazine}$), 154.1 (C_q Hydrazine), second C_q n.o., 165.9 ($C2_{py}$), $C3_{py}$ and C_{ar}-N n.o; IR (Nujol, NaCl, cm^{-1}): $\tilde{\nu}$ 2924 s, 2854 s, 2725 w, 1597 m, 1539 m, 1299 m, 1225 m, 1198 w, 1170 m, 1002 m, 939 m, 813 m, 803 w, 690 m. Anal. Calcd for $C_{48}H_{59}N_9Zr$·1.5(toluene): C, 70.69; H, 7.26; N, 12.79. Found: C, 70.40; H, 7.24; N, 12.89.

Preparation of $[Zr(N^{Xyl})_2N_{py}(NNC_{12}H_{10})(DMAP)_2]$. 9*H*-Carbazol-9-amine (16.70 mg, 91.74 mmol), DMAP (33.58 mg, 275.23 mmol), and $[Zr(N^{Xyl})_2N_{py}(NMe_2)_2]$ (50 mg, 91.74 mmol) were dissolved in toluene. After standing at room temperature for 24 h, decoloration of the formerly red solution was noticed as well as the formation of red needles. Yield: 70.0 mg (79.06 mmol, 86%). ^{1}H NMR (C_6D_6, 600.13 MHz, 296 K): δ 1.46 (s, 3 H, C−CH_3), 1.91 (s, 3 H, $N(CH_3)_2$(DMAP)), 2.02 (s, 3 H, CH_3 (Xylyl)), 2.37 (s, 3 H, CH_3 (Xylyl)), 2.19 (bs, 9 H, $N(CH_3)_2$(DMAP)), 3.51 (d, $^3J_{HH}$ = 12.3 Hz, 1 H, CH*H*), 3.55 (s, 6 H, CH_3 (Xylyl)), 3.78 (d, $^3J_{HH}$ = 12.2 Hz, 1 H, CH*H*), 3.82 (d, $^3J_{HH}$ = 12.2 Hz, 1 H, CH*H*), 3.92 (d, $^3J_{HH}$ = 12.8 Hz, 1 H, CH*H*), 5.44 (t, $^3J_{HH}$ = 6.5 Hz, 1 H, HS_{py}), 5.58 (d, $^3J_{HH}$ = 7.8 Hz, 4 H, CH_{ar} DMAP), 6.41 (s, 1 H, CH_{Xyl}), 6.25 (s, 1 H, CH_{Xyl}), 6.54 (m, 3 H, CH_{Xyl}), 6.58 (t, $^3J_{HH}$ = 7.8 Hz, 1 H, $H4_{py}$), 6.80 (s, 1 H, CH_{Xyl}), 6.84 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, $H3_{py}$), 7.01 (t, $^3J_{HH}$ = 7.4 Hz, 2 H, H_{Carb}), 7.20−7.11 (m, 3 H, H_{Carb}, $H6_{py}$), 7.49 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, H_{Carb}), 7.93 (d, $^3J_{HH}$ = 7.6 Hz, 2 H, H_{Carb}), 8.46−8.38 (m, 4 H, CH_{ar} DMAP). $^{13}C\{^1H\}$ NMR (C_6D_6, 150.92 MHz, 296 K): δ 22.0 (CH_3 (Xylyl)), 27.1 (C-CH_3), 38.8 ($N(CH_3)_2$), 45.9 (*C*-CH_3), 63.0 (CH_2), 106.6 (CH_{ar} DMAP), 110.1 (C_{Carb}), 113.9 (C_o/C_p (Xylyl)), 117.5 (C_o/C_p (Xylyl)), 119.2 (C_{Carb}), 119.8 (CS_{py}), 120.0 (C_{Carb}), 120.2 (C_{Carb}), 124.9 (C_{Carb}), 136.3 (C_m (Xylyl)), 142.2 (C_{Carb}), 150.1 (CH_{ar} DMAP), 153.2 (CH_{ar} DMAP), 164.7 ($C2_{py}$), n. o. C_i(*Xyl*). DMAP, IR (Nujol, NaCl, cm^{-1}): $\tilde{\nu}$ 3356 w, 2920 s, 2852 s, 2724 w, 1617 m, 1261 m, 1226 w, 1094 m, 1016 m, 863 w, 802 m. Anal. Calcd for $C_{48}H_{59}N_9Zr$·(toluene): C, 71.13; H, 6.69; N, 12.87. Found: C, 70.64; H, 6.83; N, 12.97.

General Procedure for Zirconium-Catalyzed Synthesis of Tricyclic Heterocycles. If not stated otherwise, a sample of the alkyne (1.20 mmol), the particular hydrazine (1.44 mmol), and the precatalyst $[Zr(N^{Xyl})_2N_{py}(NMe_2)_2]$ (0.12 mmol, 10 mol %) were dissolved in toluene and stirred at 80 °C for 24 h. At this stage complete conversion of the starting materials was confirmed by GC-MS analysis. The reaction mixture was subsequently filtered through a silica column and washed with dichloromethane. After all volatiles were removed, the crude product was subjected to column chromatography. In the case of regioisomers the ratio was determined by ^{1}H NMR spectroscopy of the isolated product.

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X-ray Diffraction Studies: Crystal Data. ***2*·1.5(toluene):** $C_{58.50}H_{71}N_9Zr$, M = 991.46, monoclinic, a = 18.8426(2) Å, b = 15.3591(2) Å, c = 18.8516(2) Å, β = 105.363(1)°, V = 5260.8(1) Å^3, T = 115(1) K, space group $P2_1/n$, Z = 4, Cu Kα λ radiation, λ = 1.5418 Å, 59622 reflections measured, 9353 unique (R_{int} = 0.0507), final R values ($F_o > 4\sigma(F_o)$) $R(F)$ = 0.0331, $R_w(F^2)$ = 0.0740.

***3*·2(toluene):** $C_{65}H_{73}N_9Zr$, M = 1071.54, monoclinic, a = 11.0816(1) Å, b = 15.8271(2) Å, c = 17.4213(2) Å, β = 106.928(1)°, V = 2923.12(7) Å^3, T = 110(1) K, space group $P2_1$, Z = 2, Cu Kα λ radiation, λ = 1.5418 Å, 47425 reflections measured, 11106 unique (R_{int} = 0.0631), final R values ($F_o > 4\sigma(F_o)$) $R(F)$ = 0.0394, $R_w(F^2)$ = 0.1027; absolute structure parameter −0.004(8). Electron density attributed to disordered toluene was removed from the structure with the BYPASS procedure.[14]

***Ind3*:** $C_{15}H_{19}N$, M = 213.31, orthorhombic, a = 7.8641(1) Å, b = 9.0823(1) Å, c = 16.9708(2) Å, V = 1212.12(3) Å^3, T = 115(1) K, space group $P2_12_12_1$, Z = 4, Cu Kα λ radiation, λ = 1.5418 Å, 22409 reflections measured, 2368 unique (R_{int} = 0.0565), final R values ($F_o > 4\sigma(F_o)$) $R(F)$ = 0.0280, $R_w(F^2)$ = 0.0691; absolute structure parameter 0.1(2).

***Ind4*:** $C_{18}H_{17}N$, M = 247.32, orthorhombic, a = 8.455(4) Å, b = 14.579(6) Å, c = 21.010(9) Å, V = 2589.7(18) Å^3, T = 100(2) K, space group $P2_12_12_1$, Z = 8, Mo Kα λ radiation, λ = 0.71073 Å, 68299 reflections measured, 8955 unique (R_{int} = 0.0297), final R values ($F_o > 4\sigma(F_o)$) $R(F)$ = 0.0387, $R_w(F^2)$ = 0.1009; absolute structure parameter −0.2(4).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text giving general experimental procedures and CIF files giving crystallographic data for **2**, **3**, **Ind3**, and **Ind4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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