# Four New Polycyclic Meroterpenoids from Ganoderma cochlear 

Xing-Rong Peng, ${ }^{\dagger, \dagger}$ Jie-Qing Liu, ${ }^{\dagger}$ Luo-Sheng Wan, ${ }^{\dagger}$ Xiao-Nian Li, ${ }^{\dagger}$ Yu-Xin Yan, ${ }^{\dagger}$ and Ming-Hua Qiu* ${ }^{*}, \dagger$,<br>${ }^{\dagger}$ Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, People's Republic of China<br>${ }^{\ddagger}$ Graduate University of the Chinese Academy of Sciences, Beijing 100049, People’s Republic of China

## S Supporting Information


#### Abstract

Four pairs of new polycyclic-meroterpenoid enantiomers, ganocins A-C (1-3) possessing a spiro $[4,5]$ decane ring system, along with ganocin $\mathrm{D}(4)$ with an eight-membered ring, were isolated from the fruiting bodies of Ganoderma cochlear. Their structures were determined by spectroscopic data and X-ray diffraction crystallography. Their anti-AChE activities were evaluated, and a possible biogenetic pathway was also proposed.




The genus Ganoderma (Ganodermataceae) is a basidiomycete white rot fungus mainly distributed in tropical and subtropical areas of Asia. The fungus has been used as a folk medicine to treat and prevent various diseases for centuries, particularly in China, Japan, and Korea. ${ }^{1}$ Most of the phytochemical and pharmacological investigations have focused on the ganoderma triterpeniods and polysaccharides. ${ }^{2}$ Our group has been interested in the bioactive constituents of Ganoderma ${ }^{3}$ and was the first to report triterpenoids and the liver-protective activities of G. cochlear. ${ }^{4}$ However, several phenolic meroterpenoids including ganomycins A and $\mathrm{B},{ }^{5}$ fornicins A-C, ${ }^{6}$ ganomycin I, ${ }^{7}$ and ( $\pm$ )-lingzhiol with a rotated door structure ${ }^{8}$ from Ganoderma were reported, which attracts our attention.

Acetylcholinesterase (AChE), mainly present in the central nervous system (CNS), catalyzes the hydrolysis of neurotransmitter acetylcholine to choline. ${ }^{9}$ This enzyme is related to neurological diseases, such as Alzheimer's disease (AD) and epilepsia. ${ }^{10}$ Research has directly demonstrated that Ganoderma can enhance memory and protect the nervous system by inhibiting AChE activity. ${ }^{11}$ Some natural AChE inhibitors (magnolol and ferulic acid) have a phenolic substructure, ${ }^{12}$ suggesting that ganoderma meroterpenoids with the phenolic structure may also show anti-AChE activity.

Thus, we studied the total phenolic parts of G. cochlear, and four unprecedented polycyclic meroterpenoids, ganocins A-C (1-3) possessing a spiro[4,5]decane substructure, and ganocin D (4), with an eight-membered carbon ring, were isolated. Herein, we report the structural elucidation including absolute configuration analysis, a biogenetic pathway, and bioactive evaluation of 1-4.

The molecular formula of ganocin A (1) was assigned as $\mathrm{C}_{21} \mathrm{H}_{24} \mathrm{O}_{4}$ by HREIMS ( $[\mathrm{M}]^{+}, m / z 340.1669$; calcd 340.1679)

with ten degrees of unsaturation. Its IR spectrum showed the presence of an aldehyde group ( 2962 and $1758 \mathrm{~cm}^{-1}$ ). The ${ }^{13} \mathrm{C}$ NMR spectrum (Table 1) exhibited 21 carbon resonances, corresponding to three methyls, four methylenes, five methines (four aromatic/olefinic methines), eight quaternary carbons (one tetrasubstituted carbon, one carbonyl group, one oxygenated quaternary carbon, and four aromatic/olefinic quaternary carbons), and one aldehyde carbon. The ${ }^{1} \mathrm{H}$ NMR spectrum (Table 1) showed three typical aromatic signals at $\delta$ $7.01(\mathrm{~d}, J=2.4 \mathrm{~Hz}), 6.66(\mathrm{dd}, J=2.4$ and 9.0 Hz$)$, and $6.64(\mathrm{~d}$, $J=9.0 \mathrm{~Hz})$, suggesting the presence of a 1,2,4-trisubstituted dihydroxylbenzene substructure (part A in Figure 1), which was similar to that of fornicin C , a meroterpenoid with a 15 carbon side chain. ${ }^{6}$

Similarly, except for the phenol group (part A), the remaining 15 carbons of 1 were representative of four rings based on its 1D-NMR and the degree of unsaturation.

In the ${ }^{13} \mathrm{C}$ NMR spectrum of $\mathbf{1}$, three low-field carbon signals at $\delta 150.6(\mathrm{~d}), \delta 139.2(\mathrm{~s})$, and $\delta 193.8(\mathrm{~d})$ were attributed to an $\alpha, \beta$-unsaturated aldehyde group ( $\mathrm{C}-2^{\prime} / \mathrm{C}-3^{\prime} / \mathrm{C}-15^{\prime}$ ), based on the HMBC correlations (Figure 1) of $\mathrm{H}-2^{\prime}$ with $\mathrm{C}-2, \mathrm{C}-3^{\prime}$, and C-15'. Meanwhile, the HMBC correlations of $\mathrm{H}-2^{\prime}$ and $\mathrm{H}-$ 3 with an oxyquaternary carbon ( $\delta 78.1$ ) indicated that the oxyquaternary carbon was located at $\mathrm{C}-1^{\prime}$. Moreover, the

[^0]Table 1. ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR Data for Compounds $1-4$ ( $J$ in Hz)

|  | $1^{\text {b }}$ |  | $2^{a}$ |  | $3^{a}$ |  | $4^{a}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\delta_{\mathrm{H}}$ | $\delta_{\text {C }}$ | $\delta_{\text {H }}$ | $\delta_{\text {C }}$ | $\delta_{\text {H }}$ | $\delta_{\text {C }}$ | $\delta_{\text {H }}$ | $\delta_{\text {C }}$ |
| 1 |  | 146.5 (s) |  | 148.4 (s) |  | 149.7 (s) |  | 146.9 (s) |
| 2 |  | 129.9 (s) |  | 120.4 (s) |  | 123.4 (s) |  | 122.3 (s) |
| 3 | 7.01 d (7.4) | 113.4 (d) | 7.65, d (3.0) | 109.9 (d) | 7.66, d (3.0) | 111.4 (d) | 7.14, d (2.4) | 109.0 (d) |
| 4 |  | 151.2 (s) |  | 151.7 (s) |  | 152.6 (s) |  | 152.3 (s) |
| 5 | 6.64, m | 116.1 (d) | 7.20, dd (3.0, 9.0) | 121.9 (d) | 7.16, dd (3.0, 9.0) | 122.1 (d) | 7.03, dd (2.4, 9.0) | 115.8 (d) |
| 6 | 6.64, m | 119.5 (d) | 6.93, d (9.0) | 119.4 (d) | 6.91, d (9.0) | 118.9 (d) | 6.97, d (9.0) | 116.1 (d) |
| $1^{\prime}$ |  | 78.1 (s) |  | 152.6 (s) |  | 154.5 (s) | 3.82, t | 46.0 (d) |
| $2^{\prime}$ | 6.62, m | 150.6 (d) | 6.94, s | 120.9 (d) | 6.99, s | 122.5 (d) | 2.29, m | 27.4 (t) |
| $3^{\prime}$ |  | 139.2 (s) |  | 198.0 (s) |  | 198.8 (s) |  | 212.0 (s) |
| $4^{\prime}$ | 2.37, m; 2.18, m | 19.1 (t) | 2.78, m; 2.55, m | 33.6 (t) | 2.59, m; 2.49, m | 34.6 (t) | 2.25, m | 24.8 (t) |
| $5^{\prime}$ | 2.07, m; 1.66, m | 30.8 (t) | 1.86, m; 1.57, m | 33.9 (t) | 1.84, m; 1.66, m | 30.9 (t) |  | 127.7 (s) |
| $6^{\prime}$ |  | 60.7 (s) |  | 51.3 (s) |  | 52.2 (s) |  | 133.8 (s) |
| $7^{\prime}$ |  | 88.7 (s) |  | 88.5 (s) |  | 90.6 (s) |  | 80.1 (s) |
| $8^{\prime}$ | 2.07, m; 1.57, m | 39.5 (t) | 2.10, m; 1.91, m | 37.7 (t) | 2.62, m; 2.30, m | 28.5 (t) | 2.35, m; 1.78, m | 48.4 (t) |
| $9^{\prime}$ | 1.69, m | 24.0 (t) | 2.23, m; 1.89, m | 28.2 (t) | 2.05, m; 1.85, m | 34.5 (t) | 2.49, m; 2.33, m | 37.5 (t) |
| $10^{\prime}$ | 2.39, m | 62.0 (d) | 3.11, t | 53.0 (d) |  | 134.5 (s) | 5.06, m | 133.8 (d) |
| $11^{\prime}$ |  | 84.7 (s) |  | 145.8 (s) |  | 126.6 (s) |  | 131.2 (s) |
| $12^{\prime}$ | 1.17, s | 25.8 (q) | 1.46, s | 22.5 (q) | 1.53, s | 18.8 (q) | 1.67, s | 27.5 (q) |
| $13^{\prime}$ | 1.30, s | 32.5 (q) | 4.79, s; 4.70, s | 114.3 (t) | 1.34, s | 23.1 (q) | 2.60, br s | 36.7 (t) |
| $14^{\prime}$ | 1.42, s | 23.9 (q) | 1.23, s | 18.9 (q) | 1.21, s | 17.4 (q) | 1.54, s | 24.8 (q) |
| $15^{\prime}$ | 9.40, s | 193.8 (d) |  |  |  |  |  |  |

${ }^{a}$ Measured in $\mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}$. ${ }^{b}$ Measured in $\mathrm{CDCl}_{3}$. 1D NMR spectra ( $\delta$ ) were measured at 400 (100) MHz for $\mathbf{1}$ and at $600(150) \mathrm{MHz}$ for 2-4. The assignments were based on ${ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ COSY, ROESY, HSQC, and HMBC experiments.


Figure 1. Key $\mathrm{HMBC},{ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ COSY, and ROESY correlations of ( $\pm$ )-1.


Figure 2. X-ray crystallographic structure of 1a.


Figure 3. Key $\mathrm{HMBC},{ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ COSY, and ROESY correlations of ( $\pm$ )-2.


Figure 4. Key $\mathrm{HMBC},{ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ COSY, and ROESY correlations of $( \pm)-4$.
observed HMBC correlations from $\mathrm{H}-2^{\prime}, \mathrm{H}_{2}-4^{\prime}$, and $\mathrm{H}_{2}-5^{\prime}$ to C $3^{\prime}$ and a quaternary carbon ( $\delta 60.7$ ), together with the ${ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ COSY correlations of $\mathrm{H}_{2}-4^{\prime} / \mathrm{H}_{2}-5^{\prime}$, confirmed that $\mathrm{C}-1^{\prime}$ is connected with $\mathrm{C}-6^{\prime}(\delta 60.7)$ to form a cyclohex-1-ene-1carbaldehyde substructure ( B ring) in $\mathbf{1}$.

Subsequently, the presence of $\mathrm{CH}_{2}-8^{\prime} / \mathrm{CH}_{2}-9^{\prime} / \mathrm{CH}-10^{\prime}$ moiety was deduced by the ${ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ COSY correlations. In the HMBC spectrum of $1, \mathrm{H}_{2}-8^{\prime}, \mathrm{H}_{2}-5^{\prime}$, and $\mathrm{H}_{3}-14^{\prime}(\delta 1.42$, s) showed the HMBC correlations with an oxyquaternary carbon ( $\delta$ 88.7), which indicated that $C-7^{\prime}$ was the oxyquaternary carbon. Meanwhile, only H-10' showed the HMBC correlations with another oxyquaternary carbon ( $\delta$ 84.7) and two methyls ( $\delta 25.8, \delta 32.5$ ), suggesting a 2 -oxyisopropyl group was located at C-10'. Importantly, the key HMBC correlations of $\mathrm{H}_{2}-8^{\prime}$ and $\mathrm{H}-10^{\prime}$ with $\mathrm{C}-6^{\prime}$ and $\mathrm{C}-7^{\prime}$ were observed. Thus, we unambiguously deduced that a five-membered ring (part C ) and $B$ ring formed a spiro[ 4,5$]$ decane ring system.

Apart from the above-mentioned two rings, another two rings were finally determined as $1,7^{\prime}$-epoxy and $1^{\prime}, 11^{\prime}$-epoxy rings, based on its formula weight and degrees of unsaturation (Figure 1).

The ROESY correlations of $\mathrm{H}_{3}-14^{\prime} / \mathrm{H}_{2}-5^{\prime} / \mathrm{H}-10^{\prime}$ indicated that $\mathrm{CH}_{3}-14^{\prime}, \mathrm{CH}_{2}-5^{\prime}$, and $\mathrm{H}-10^{\prime}$ were on the same face. Furthermore, the single-crystal X-ray diffraction of acetylated

Scheme 1. A Plausible Biogenetic Pathway for 1-4

derivative of 1 (Figure 2) showed that acetyl ganocin D (1a) was a pair of enantiomers. Thus, the single-crystal X-ray diffraction experiment of 1a performed by using $\mathrm{Cu} \mathrm{K} \alpha$ radiation confirmed $1 a$ as $1^{\prime} R, 6^{\prime} R, 7^{\prime} R, 10^{\prime} R$ and $1^{\prime} S, 6^{\prime} S, 7^{\prime} S, 10^{\prime} S$.

Ganocin B (2) was obtained as a yellow powder with a molecular ion peak at $m / z 310.1564$ [M] ${ }^{+}$in HREIMS, coinciding with the molecular formula $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{O}_{3}$. A comparison of 1D NMR spectroscopic data between 2 and 1 showed that 2 also had a 1,2,4-trisubstituted dihydroxylbenzene substructure and a spiro $[4,5]$ decane ring system, which was further supported by its 2D NMR spectra (Figure 3). However, the ${ }^{13} \mathrm{C}$ NMR spectrum of 2 showed 20 carbons, with one less carbon than 1 . Obviously, in the 1D NMR spectra of 2 , an $\alpha, \beta$ unsaturated ketone ( $\delta 152.6 ; \delta 120.9$, and $\delta$ 198.0) was observed, instead of the aldehyde group signal in $\mathbf{1}$. We speculated that the B ring of 2 was a cyclohexenone moiety and the $\alpha, \beta$-unsaturated ketone was attributable to $\mathrm{C}-1^{\prime}, \mathrm{C}-2^{\prime}$, and C-3'. This was confirmed by the HMBC correlations of the olefinic proton ( $\delta 6.94, \mathrm{~s}$ ) with C-2, the olefinic quaternary carbon ( $\delta 152.6$ ), and the carbonyl group and $\mathrm{C}-6^{\prime}$; of $\mathrm{H}-3$ and $\mathrm{H}_{2}-5^{\prime}$ with the olefinic quaternary carbon; and of $\mathrm{H}_{2}-4^{\prime}$ and $\mathrm{H}_{2}$ $5^{\prime}$ with the carbonyl group and C-6'. Additionally, a terminal double bond ( $\delta 4.79$, s, $\delta 4.70$, s; $\delta 114.3$ and $\delta 145.8$ ) was assigned to $\mathrm{C}-11^{\prime}$ and $\mathrm{C}-13^{\prime}$ by the HMBC correlations of the olefinic protons at $\delta 4.79(\mathrm{~s})$ and $\delta 4.70(\mathrm{~s})$ with $\mathrm{CH}_{3}-12^{\prime}(\delta$ 22.5) and C-10' ( $\delta 53.0$ ). Thus, the planar structure of 2 was established.

The ROESY correlations of $\mathrm{H}_{3}-14 / \mathrm{H}_{2}-5 / \mathrm{H}-10^{\prime}$ suggested that $\mathrm{CH}_{3}-14^{\prime}, \mathrm{C}-6^{\prime}$, and $\mathrm{C}-10^{\prime}$ had the same relative configuration (Figure 3). Its optical rotation value $\left([\alpha]^{20}{ }_{D}\right.$ +1.8 ) indicated a racemic nature, and the subsequent chiral
resolution of 2 by HPLC afforded the anticipated enantiomers, $\mathbf{2 a}$ and $\mathbf{2 b}$, which were opposite in terms of their CD curve and $[\alpha]_{\mathrm{D}}$ spectra $\left([\alpha]_{\mathrm{D}}^{20}+117.9\right.$ and $[\alpha]_{\mathrm{D}}^{20}-104.6$ ) (see Supporting Information (SI)). Therefore, 2 was deduced to be $6^{\prime} R, 7^{\prime} R, 10^{\prime} R$ and $6^{\prime} S, 7^{\prime} S, 10^{\prime} S$.

Ganocin C (3) has the same molecular formula $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{O}_{3}$ established by the $[\mathrm{M}]^{+}$ion peak at $m / z 310.1566$ in the HREIMS as compound 2. The 1D NMR spectroscopic data of 3 were similar to those of $\mathbf{2}$, except that a methyl ( $\delta 23.1$, C$13^{\prime}$ ) and two olefinic quaternary carbons ( $\delta 134.5, \mathrm{C}-10^{\prime}$ and $\delta$ 126.6, C-11') in 3 replaced the terminal double bond and a methine in 2 , which was confirmed by the HMBC correlations of $\mathrm{H}_{3}-12^{\prime}(\delta 1.54, \mathrm{~s})$ and $\mathrm{H}_{3}-13^{\prime}(\delta 1.34, \mathrm{~s})$ with two olefinic quaternary carbons and of $\mathrm{H}_{2}-5^{\prime}, \mathrm{H}_{2}-8^{\prime}$ and $\mathrm{H}_{2}-9^{\prime}$ with the olefinic quaternary carbon ( $\delta$ 134.5). Its ROESY spectrum showed an interaction between $\mathrm{H}_{2}-5^{\prime}$ and $\mathrm{H}_{3}-14^{\prime}$, suggesting that $\mathrm{CH}_{3}-14^{\prime}$ and $\mathrm{C}-5^{\prime}$ were ipsilateral. Its optical rotation value $\left([\alpha]^{20}{ }_{\mathrm{D}}-0.7\right)$ indicated that 3 could be a pair of enantiomers, which was supported by HPLC analysis on an analytical chiral column, showing two peaks (see SI). Due to only two chiral centers in $3, \mathrm{C}-6^{\prime}$ and $\mathrm{C}-7^{\prime}$ were assigned as $R, R$ and $S, S$.

The molecular formula of ganocin D (4) assigned as $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{O}_{3}$ by its ion peak at $\mathrm{m} / \mathrm{z} 310.1573$ [M] ${ }^{+}$(calcd 310.1569 ) in the HREIMS spectrum was also the same as that for compound 3. However, the chemical shift of the carbonyl carbon was shifted low-field to 212.0 ppm , suggesting the absence of the double bond $\left(\Delta^{1,2}\right)$ in 4 . This was confirmed by the HMBC correlations (Figure 4) of $\mathrm{H}-1^{\prime}(\delta 3.82, \mathrm{t}), \mathrm{H}_{2}-2^{\prime}(\delta$ $2.29, \mathrm{~m}$ ) with $\mathrm{C}-1$ and $\mathrm{C}-3^{\prime}$ and of $\mathrm{H}-3$ with $\mathrm{C}-1^{\prime}$ (Figure 4). Additionally, the observed HMBC correlations of $\mathrm{H}-1^{\prime}$ and $\mathrm{H}_{2}$ $4^{\prime}$, with two olefinic quaternary carbons ( $\delta 127.7$ and $\delta 133.8$ ), suggested the existence of $\mathrm{C}-5^{\prime}=\mathrm{C}-6^{\prime}$, which indicated that the quaternary carbon ( $\mathrm{C}-6^{\prime}$ ) in 3 was replaced by an olefinic quaternary carbon in 4 . From this, we speculated that its C ring was different from that of 3 .

On the basis of the HMBC correlations of methylene protons ( $\delta 2.35, \mathrm{~m} ; \delta 1.78, \mathrm{~m}$ ), $\mathrm{H}-1^{\prime}$ and $\mathrm{H}_{3}-14^{\prime}$ with $\mathrm{C}-7^{\prime}(\delta$ 80.1), the methylene was assigned to $\mathrm{C}-8^{\prime}$. The ${ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ COSY spectrum deduced the presence of the $-\mathrm{CH}_{2}-\mathrm{CH}_{2}-\mathrm{CH}=$ moiety ( $\mathrm{C}-8^{\prime} / \mathrm{C}-9^{\prime} / \mathrm{C}-10^{\prime}$ ), of which $\mathrm{H}-10^{\prime}$ showed an HMBC correlation with $\mathrm{C}-11^{\prime}, \mathrm{CH}_{3}-12^{\prime}$, and a methylene ( $\delta$ 36.7). This indicated that the methylene in 4 replaced $\mathrm{CH}_{3}-13^{\prime}$ in 3. Meanwhile, $\mathrm{H}_{2}-13^{\prime}$ showed the HMBC correlations with $\mathrm{C}-4^{\prime}$, $\mathrm{C}-5^{\prime}$, and $\mathrm{C}-6^{\prime}$, which confirmed that the C ring of 4 was an eight-membered ring. Thus, the planar structure of 4 was determined as shown in Figure 4.

The ROESY correlations of $\mathrm{H}_{2}-2^{\prime} / \mathrm{H}_{3}-14^{\prime}$ indicated that the relative configurations of $\mathrm{H}-1^{\prime}$ and $\mathrm{CH}_{3}-14^{\prime}$ were reverse (Figure 4). On the basis of its optical rotation value and the chiral HPLC analysis result (see SI), 4 was finally established to be $1^{\prime} R, 6^{\prime} R$ and $1^{\prime} S, 6^{\prime} S$.

Ganocins A-C (1-3) possessing a spiro[4,5]decane substructure and ganocin $D(4)$ with an eight-membered ring were established to be polycyclic enantiomers. Compared to fornicins A-C, all of them have a 1,2,4-trisubstituted dihydroxylbenzene moiety. We deduced that the $B$ and $D$ rings of 1-4 were formed by the hetero-Diels-Alder reaction of fornicin C. Meanwhile, the prenylated side chain of fornicins A-C could provide appropriate conditions for a free radical reaction. The dienophile may be directed away from diene (exo approach) or toward the diene (endo approach) to produce a pair of enantiomers, ${ }^{13}$ which also would biosynthetically explain the racemic nature of compounds $\mathbf{1 - 4}$. The C ring was
subsequently derived from the further free radical reactions. Thus, a plausible biogenetic pathway for $1 \mathbf{1}$ was proposed (Scheme 1).

Research showed that the extracts of Ganoderma can decrease AChE to protect the CNS and improve memory. ${ }^{11}$ In the present study, the evaluation of anti-AChE effects showed that compound 4 had weak anti-AChE activity with an inhibition of $32 \%(50 \mu \mathrm{M})$. Nevertheless, other compounds are inactive. Compared to natural phenolic AChE inhibitors with a big conjugated system (flavonoids and anthraquinones), ${ }^{12}$ compounds 1-4 only had a benzene ring. We deduced that their low conjugation system and coplanarity affected their antiAChE activity.

## ASSOCIATED CONTENT

## (s) Supporting Information

1D and 2D NMR spectra of $\mathbf{1 - 4}$, the data for single-crystal Xray diffraction of 1a (CIF), $[\alpha]_{\mathrm{D}}$ spectra and CD spectra for 2a and $\mathbf{2 b}$, and in vitro anti-AChE activity of $\mathbf{1 - 4}$, together with experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

## Corresponding Author

*E-mail: mhchiu@mail.kib.ac.cn.
Notes
The authors declare no competing financial interest.

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