Nitrogenous cyclonerane sesquiterpenes from an algicolous strain of *Trichoderma asperellum*†

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Cyclonerins A (1) and B (2) along with seven new congeners, deoxycyclonerins A–D (3–6), cyclonerinal (7), cyclonerizole (8), and cyclonerpyranol (9), were isolated from the culture of a marine algicolous strain (A-YMD-9-2) of *Trichoderma asperellum*. Their structures and absolute configurations were established by spectroscopic techniques, such as 1D/2D NMR, MS, ECD, and X-ray diffraction. Compounds 1–8, highlighted by the presence of an isoxazole ring in sesquiterpene 8, represent the first occurrence of nitrogenous cyclonerane derivatives, with 1 and 2 belonging to an unprecedented family of hydroxamic acids. The new isolates 1–9 exhibited potent inhibition of one or more marine phytoplankton species tested, and it is interesting that the ferric complexes of 1 and 2 feature higher activities than themselves.

Introduction

Cyclonerane-type sesquiterpenes, represented by the first member cyclonerodiol,1 with a monocyclic carbon skeleton have been found in a broad spectrum of fungal species, such as those of the genera *Ascotricha*,2 *Aspergillus*,3 *Botrytis*,4 *Epichloe*,5–7 *Pusarium* (Gibberella),8–11 *Myrothecium*,12 *Paecilomyces*,13 *Trichoderma*,14–19 and *Trichothesium*.1 Several molecules possess antibacterial,5–7 antifungal,5–7 and anti-inflammatory17 activities and have also attracted much attention for chemical synthesis,20 biosynthesis,21 and biotransformation.22 Although they feature high structural diversity, no nitrogenous derivatives have been discovered so far. *Trichoderma* species can not only produce diverse cyclonerane sesquiterpenes but also exhibit outstanding abilities to yield hydroxamic acids, such as coprogen, ferricrocin, and fusigen.23,24 However, most of the hydroxamic acids possess a N5-acyl-N5-hydroxyornithine structural unit,25,26 and none of them are derived from cycloneranes. During our ongoing search for new and bioactive secondary metabolites from marine algicolous *Trichoderma* fungi,14–16 a detailed examination of the endophytic *T. asperellum* A-YMD-9-2 obtained from the marine red alga *Gracilaria verrucosa* led to the isolation of eleven cyclonerane derivatives (1–11) (Fig. 1), especially including two unexpected hydroxamic acids (1 and 2) and other six nitrogenous derivatives (3–8). Herein, the details of isolation, structure elucidation, and algicidal activity of these compounds are described.

Results and discussion

EtOAc extracts of the mycelia and broth were combined, fractionated, and purified by repeated column chromatography (CC) on silica gel, RP-18, and Sephadex LH-20 and preparative thin-layer chromatography (TLC) as well as high performance liquid chromatography (HPLC) to afford compounds 1–11. Among them, 10 and 11 were identified to be the known

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**Fig. 1** Structures of compounds 1–11.

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9-cycloneren-3,7,11-triol and cyclonerodiol, respectively, by comparison of their spectroscopic data with literature values. The structure and absolute configuration of 9, trivially named cyclonerpynanol, were determined by X-ray crystallographic analysis using Cu Kα radiation (Fig. 2), and its 1H and 13C NMR data (Tables S1 and S2†) recorded in CDCl3 and DMSO-d6 were assigned on the basis of HSQC, HMBC, COSY, and NOESY correlations.

Cyclonerin A (1) was obtained as a colorless oil. Its molecular formula was established to be C21H37NO5 on the basis of HRESI+MS analysis giving the molecular formula C21H37NO5, requiring four degrees of unsaturation. The 13C NMR spectrum (Table S2†) showed 21 resonances, classified into five methyls, seven methylenes, four methines, and five nonprotonated carbons by DEPT and HSQC data. A comparison of NMR data with those of palmitoylcoprogen confirmed the presence of an anhydromevalonyl group,24 confirmed by the COSY correlation between H2-4′ and H2-5′ and HMBC correlations from H2-6′ to C-2′, C-3′, and C-4′ (Fig. 3). An E configuration was assigned to the double bond at C-2′ based on the NOE correlation between H2-2′ and H2-3′. The remaining NMR signals resembled those for cyclonerodiol (11),6 except for those for the side chain terminus. HMBC correlations from H2-12 and H2-15 to C-10 and C-11 and COSY correlations of H-9α with H2-8 and H10 indicated a 4-methylpent-4-enyl group that was attached to ring A via C-7 as seen from the HMBC correlations from H-1 to C-6, C-7, and C-8. To satisfy the molecular formula, a hydroxylated nitrogen atom was situated between C-10 and C-1′, which was supported by the chemical shifts of C-10 and C-1′.24 Thus, 1 was assigned to be 10-(N-anhydromevalonyl) hydroxyamino-11-cycloneren-3,7-diol, validated by other COSY and HMBC correlations (Fig. 3).

Cyclonerin B (2) was isolated as a colorless oil, and HRESI+MS analysis gave the molecular formula C21H37NO5, the same as for 1, but some differences around H-10 appeared in the 1H NMR spectrum (Table S1†). Thus, 2 was proposed to be a C-10 epimer of 1, supported by the COSY correlations of H2-1/H-2/H-6/H2-5/H2-4, H3-8/H3-9/H-10, and H3-4′/H3-5′ and HMBC correlations from H2-1 to C-2, C-3, and C-6, from H-13 to C-2, C-3, and C-4, from H2-14 to C-6, C-7, and C-8, from H2-12 and H2-15 to C-10 and C-11, and from H3-6′ to C-2′, C-3′, and C-4′ (Fig. 3).

Deoxycyclonerin A (3) was purified as a colorless oil. A molecular formula of C21H37NO4, one less oxygen atom than for 1 and 2, was assigned by interpretation of HREIMS data. Its 13C NMR data (Table S2†) resembled those of 1 and 2, except for the signals around C-10. A doublet at δH 6.12 for an exchangeable proton appeared in the 1H NMR spectrum (Table S1†), and it showed a COSY correlation with H-10 and an HMBC correlation with C-1′. The above information along with the other COSY and HMBC correlations (Fig. 3) evidenced 3 to be an N-deoxy derivative of 1 or 2.

Deoxycyclonerin B (4) was separated as a colorless oil, and HREIMS analysis afforded the molecular formula C21H37NO4, the same as for 3. Compared to 3, this compound exhibited a shielded signal for NH (δH 5.63) and a deshielded signal for H-10 (δH 4.42) in the 1H NMR spectrum, despite the identical splitting patterns. However, their 13C and other 1H NMR resonances (Tables S1 and S2†) appeared very similar to each other. The above information suggested 4 to be a C-10 epimer of 3, corroborated by COSY and HMBC correlations (Fig. 3).

Deoxycyclonerin C (5) was isolated as a colorless oil. Its molecular formula was established as C21H37NO4 by interpretation of HREIMS data, implying four degrees of unsaturation. A detailed comparison of its 1H and 13C NMR data (Tables S1 and S2†) with those of 9 revealed the presence of a cyclonerpynanol residue, which were supported by the COSY correlations of H-1′/H-2'/H-6/H2-5/H2-4 and of H3-8/H3-9/H-10 and HMBC correlations from H2-1′ to C-2, C-3, and C-6, from H-13 to C-2, C-3, and C-4, from H2-14 to C-6, C-7, and C-8, and from H2-12 and H2-15 to C-10 and C-11 (Fig. 3). The other NMR data corresponded to a trans-anhydromevalonyl group as seen from the HMBC correlations from H2-2′ to C-1′ and from H2-6′ to C-2′, C-3′, and C-4′ and COSY correlation between H2-4′ and H2-5′ as well as NOE correlation between H-2′ and H2-4′. The linkage of

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**Fig. 2** X-ray crystallographic structure of 9.

**Fig. 3** Key COSY (bold lines) and HMBC (arrows) correlations of 1–9.
these two moieties was confirmed by the COSY correlation between NH and H-10 and HMBC correlations from H-10 and NH to C-1'. Additionally, H-10 and CH3-12 were located on the same face of ring B by their NOE correlation.

Deoxycyclonerin D (6) was obtained as a colorless oil, and the molecular formula C21H37NO6 was determined by HREIMS. An analysis of its 1H and 13C NMR data (Tables S1 and S2) revealed the presence of a trans-anhydridevalonyl group and a 9-cyclonerin-3,7,11-triol (10) residue,28,24 which were verified by the COSY and HMBC correlations as shown in Fig. 3. The connectivity of these two moieties was confirmed by the HMBC correlations from NH to C-11, C-12, C-15, and C-1', and the E configurations of double bonds at C-9 and C-2' were further verified by the large coupling constant (J = 15.7 Hz) between H-9 and H-10 and by the NOE correlation between H-2' and H3-15.

Cyclonerinal (7) was separated as a colorless oil, and HREIMS analysis gave the molecular formula C15H25NO3 with four degrees of unsaturation. Four exchangeable protons appeared in the 1H NMR spectrum (Table S1†) recorded in DMSO-d6, and the most deshielded one resonating at δH 6.79 was assigned to the hydroxy group that was attached to a methine group (CH-12) as seen from their COSY correlation. This methine group was bonded to an additional oxygen atom to form a hemiacetal group based on its deshielded 1H and 13C NMR signals,27 and it was further extended to C-15 and C-7 according to the COSY correlations of H-11 with H-10, H-12, and H2-15 and HMBC correlations from H2-15 to C-10, C-11, and C-12 and from H-11 to C-9 and C-10. The remaining NMR data appeared similar to those of 3 and 4, suggesting the preliminary connectivity of the molecule. Other three exchangeable protons were assigned to the hydroxy groups at C-3, C-7, and C-5' by the COSY correlation between OH-5' and H2-5' and HMBC correlations from OH-3 to C-3 and from OH-7 to C-7. The nitrogen atom indicated by the molecular formula was situated between C-10 and C-1' according to their NMR data and the HMBC correlation from H-10 to C-1', and it was also connected to the hemiacetal group to form ring B in view of the unsaturation requirement. The presence of ring B was supported by the identical NMR data with those of an analogous unit,28 and the whole structure was confirmed by other COSY and HMBC correlations (Fig. 3). NOE correlations of CH3-15 with H10-15 and H12-12 located them on the same face of ring B.

Cyclonerizole (8) was purified as a colorless oil. The molecular formula C15H25NO3 was determined by HREIMS, corresponding to four degrees of unsaturation. A detailed comparison of NMR data (Tables S1 and S2) with those of 11 revealed that this compound possesses a different side chain terminus, of which the connectivity was established by the HMBC correlations from H2-8 and H2-9 to C-10, from H2-15 to C-10, C-11, and C-12, and from H-12 to C-10 and C-11. The deshielded signals for C-10, C-11, C-12, and H-12 indicated the presence of an isoxazole ring,29 and the whole structure was further confirmed by other COSY and HMBC correlations (Fig. 3).

Based on biogenetic considerations, the absolute configurations at C-2, C-3, C-6, and C-7 of 1-8 were deduced to be the same as those of 9-11.3 In addition, C-10 of 1-5 and C-10, C-11, and C-12 of 7 are also asymmetric carbon atoms, of which the absolute configurations need to be assigned. The oily property of these compounds precludes the application of X-ray crystallography, but their electronic circular dichroism (ECD) spectra (Fig. 4) are informative due to the presence of a conjugated acyl group, especially for the epimeric pairs 1/2 and 3/4 that feature reverse Cotton effects, respectively. The ECD curves of 1-5, and 7 were computed at the B3LYP/6-31G (d) level after conformational optimization at the same level via Gaussian 09 software and then weighted according to the Boltzmann populations after spectral depiction through SpecDis software.31,32 Based on the agreements of experimental and calculated ECD spectra (Fig. 4), the absolute configurations at C-10 of 1, 3, and 5 and at C-10, C-11, and C-12 of 7 were assigned to be S, and the absolute configurations at C-10 of 2 and 4 were proposed to be R. To confirm the absolute configuration of 1, its specific optical rotation was computed.
at the B3LYP/6-31+G(d,p) level in MeOH. The calculated value −77 is close to the experimental result (−81), which validated the absolute configuration of 1. Additionally, the ECD curve of 3 was further simulated at the B3LYP/6-31+G(d,p) level after conformational optimization at the same level, and the calculated data (Fig. S1†) also supported the absolute configuration of 3. During quantum chemical calculations, the ECD curve of each conformer was found to be correlated with twists of the conjugated system in the anhydromevalonyl group. If this group is linked to an achiral center via a nitrogen atom, its twists can keep balance and result in no Cotton effects. The lack of any peak at >200 nm in the ECD spectrum of 6 supported this deduction. Reciprocally, a chiral amine attached to this group is able to disrupt the twist balance, which leads to one or more ECD peaks, such as those in the ECD spectra of 1–5 and 7. As for the conformers of 1–4, the values and signs of their Cotton effects are also influenced by the rotation of the isopropenyl group. However, it is difficult to conclude the relationship between Cotton effects and conformational characteristics.

The ability of 1 and 2 to chelate ferric ion was detected by addition of FeCl₃ solution (MeOH), and each formed a 3 : 1 ferric complex accompanied by deprotonation as seen from the sodium adduct ion peak at m/z 1226 [M + Na]⁺ in the ESI⁺MS spectrum. Additionally, HRESI⁺MS analyses gave the molecular formula C₆₃H₁₀₈FeN₃O₁⁵ for these two complexes, and their UV spectra exhibited an absorption band at 442 nm (Fig. 5). The above data further evidenced the formation of hydroxamate-iron(III) complexes with 1 and 2 being bidentate ligands, respectively.²⁴,³³ Both the octahedral ferric complexes were deduced to exist predominantly as Δ optical isomers in MeOH based on their similar ECD curves (Fig. 5) at 350–550 nm to that of ferric N,N',N″-triacetylfusarinine,³³ but their tendencies toward cis or trans geometric isomers remain amphibolous.

To develop new inhibitors against harmful microalgae that greatly threaten marine aquaculture, compounds 1–9, Fe(1)₃, and Fe(2)₃ were evaluated for growth inhibition of four phytoplankton species (Chattonella marina, Heterosigma akashiwo, Karlodinium veneficum, and Prorocentrum donghaiense).³⁴ The results (Table 1) show that Fe(1)₃ is more active against C. marina, K. veneficum, and P. donghaiense than the others, whereas 5 can highly inhibit H. akashiwo. Compared to 1 and 2, their ferric complexes exhibit potent inhibition of the four phytoplankton species tested, and the antagonistic ability of Fe(1)₃ exceeds that of Fe(2)₃ with the different configuration at C-10. On the other hand, the toxicity of these isolates against the marine zooplankton Artemia salina was also assayed,³⁵ but none of them feature any lethality. In view of the high activity and low toxicity of the ferric complexes of 1 and 2, they might be developed as promising agents to control harmful algal blooms in the future.

### Table 1  Inhibition of four marine phytoplankton species by 1–9, Fe(1)₃, and Fe(2)₃

|                | Chattonella marina | Heterosigma akashiwo | Karlodinium veneficum | Prorocentrum donghaiense |
|----------------|--------------------|----------------------|-----------------------|--------------------------|
| 1              | 2.1                | 46                   | 15                    | 54                       |
| 2              | 5.1                | 55                   | 19                    | 40                       |
| 3              | 2.6                | 39                   | 51                    | 9.6                      |
| 4              | 10                 | 6.9                  | 31                    | 7.0                      |
| 5              | 2.1                | 0.63                 | 49                    | 34                       |
| 6              | 1.1                | 10                   | 23                    | 49                       |
| 7              | 30                 | 3.5                  | 87                    | 74                       |
| 8              | 7.5                | 11                   | 8.1                   | 11                       |
| 9              | 12                 | 13                   | 3.8                   | 20                       |
| Fe(1)₃        | 0.12               | 2.7                  | 0.21                  | 0.99                     |
| Fe(2)₃        | 0.68               | 10                   | 2.1                   | 2.1                      |
| K₂Cr₂O₇       | 0.46               | 0.98                 | 0.89                  | 1.9                      |
Conclusions

Chemical investigation toward the marine-alga-endophytic fungus Trichoderma asperellum A-YMD-9-2 resulted in the isolation and identification of nine new cyclonerane derivatives (1-9) and two possible precursors (10 and 11). Compounds 1-8, highlighted by the occurrence of an isoxazole ring in 8, are nitrogenous cyclonerane derivatives that have never been reported in nature. Among those, 1 and 2 possess an excellent ability to inhibit some marine phytoplankton species, which greatly profits from the coordination behavior.

Experimental section

General experimental procedures

Optical rotations, UV, and ECD spectra were measured on a Chirascan CD spectrometer. IR spectra were acquired on a Nicolet iS10 FT-IR spectrometer. 1D and 2D NMR spectra were recorded on a Bruker Avance III 500 NMR spectrometer. Low and high resolution EI mass spectra were obtained on an Autospec Premier P776 mass spectrometer. Low and high resolution ES+ mass spectra were determined on an Agilent 1260 HPLC system using an Eclipse SB-C18 (5 μm, 9.4 × 250 mm) column. CC was carried out with precoated silica gel (200–300 mesh, Qingdao Haiyang Chemical Co.), RP-18 (50 g rice, 0.6 g peptone, 50 mL pure water, and 1649, 1604, 1444, 1376, 1294, 1267, 1160, 1053, 919, 886, 737 cm⁻¹; 1H and 13C NMR data, Tables S1 and S2;† ESI+MS m/z 406 [M + Na]+; HRESI+MS m/z 406.2565 [M + Na]+ (calcd for C21H37NO5Na, 406.2569).

Cyclonerin A (1). Colorless oil; [α]D 20 −81 (c 0.70, MeOH); UV (MeOH) λmax (log ε) 221 (4.2) nm; IR (KBr) νmax 3387, 2965, 1649, 1604, 1444, 1376, 1294, 1267, 1160, 1053, 919, 886, 737 cm⁻¹; 1H and 13C NMR data, Tables S1 and S2;† ESI+MS m/z 406 [M + Na]+; HRESI+MS m/z 406.2565 [M + Na]+ (calcd for C21H37NO5Na, 406.2569).

Cyclonerin B (2). Colorless oil; [α]D 20 36 (c 1.2, MeOH); UV (MeOH) λmax (log ε) 221 (4.2) nm; IR (KBr) νmax 3385, 2965, 1649, 1604, 1444, 1376, 1294, 1267, 1160, 1053, 919, 886, 737 cm⁻¹; 1H and 13C NMR data, Tables S1 and S2;† ESI+MS m/z 406 [M + Na]+, 790 [2M + Na]+; HRESI+MS m/z 406.2562 [M + Na]+ (calcd for C21H37NO5Na, 406.2569).

Deoxycyclonerin A (3). Colorless oil; [α]D 20 −19 (c 0.63, MeOH); UV (MeOH) λmax (log ε) 221 (4.2) nm; IR (KBr) νmax 3386, 2962, 1662, 1629, 1532, 1449, 1376, 1263, 1171, 1041, 919, 886, 736 cm⁻¹; 1H and 13C NMR data, Tables S1 and S2;† EIMS m/z (% 367 [M]+ (100), 332 (20), 254 (59), 182 (66), 113 (80), 85 (60), 83 (100), 44 (40); HREIMS m/z 367.2731 [M]+ (calcd for C21H37NO5Na, 367.2723).

Deoxycyclonerin B (4). Colorless oil; [α]D 20 44 (c 0.28, MeOH); UV (MeOH) λmax (log ε) 221 (4.1) nm; IR (KBr) νmax 3387, 2961, 1654, 1629, 1530, 1449, 1376, 1258, 1171, 1041, 919, 885, 734 cm⁻¹; 1H and 13C NMR data, Tables S1 and S2;† EIMS m/z (% 367 [M]+ 0.70, MeOH); UV (MeOH) λmax (log ε) 220 (4.0) nm; IR (KBr) νmax 3417, 2959, 1662, 1634, 1533, 1452, 1373, 1255, 1171, 1127, 1048, 991, 920, 891, 736 cm⁻¹; 1H and 13C NMR data, Tables S1 and S2;† EIMS m/z (% 367 [M]+ (100), 291 (15), 254 (61), 155 (74), 113 (100), 68 (21), 44 (34); HREIMS m/z 367.2725 [M]+ (calcd for C21H37NO5Na, 367.2723).

Deoxycyclonerin C (5). Colorless oil; [α]D 20 −30 (c 0.32, MeOH); UV (MeOH) λmax (log ε) 220 (4.0) nm; IR (KBr) νmax 3417, 2959, 1662, 1634, 1533, 1452, 1373, 1255, 1171, 1127, 1048, 991, 920, 891, 736 cm⁻¹; 1H and 13C NMR data, Tables S1 and S2;† EIMS m/z (% 367 [M]+ (100), 291 (15), 254 (61), 155 (74), 113 (100), 68 (21), 44 (34); HREIMS m/z 367.2725 [M]+ (calcd for C21H37NO5Na, 367.2723).

Deoxycyclonerin D (6). Colorless oil; [α]D 20 −22 (c 0.30, MeOH); UV (MeOH) λmax (log ε) 219 (4.2) nm; IR (KBr) νmax 3416, 2966, 1654, 1534, 1449, 1383, 1264, 1170, 1046,
Cyclonerizole [8]. Colorless oil: [α]D^20^0~−13 (c 0.30, MeOH); UV (MeOH) λ_max (log ε) 225 (3.7) nm; IR (KBr) ν_max 2963, 2874, 1460, 1372, 1126, 1071, 1018, 919, 890 cm^−1; 1H and 13C NMR data, Tables S1 and S2; EIMS m/z (%) 267 [M]^+ (<1), 253 (11), 234 (12), 154 (45), 81 (25), 56 (22), 44 (60); HREIMS m/z 267.1836 [M]^+ (calcd for C_{15}H_{28}O_{3}, 267.1834).

Cycloneripynanol [9]. Colorless crystals; mp 99–101 °C; [α]D^20^0~−22 (c 0.75, MeOH); UV (MeOH) λ_max (log ε) 225 (3.7) nm; IR (KBr) ν_max 3426, 2961, 2934, 1460, 1372, 1126, 1071, 1018, 919, 890 cm^−1; 1H and 13C NMR data, Tables S1 and S2; EIMS m/z (%) 256 [M]^+ (1), 252 (24), 180 (25), 143 (100), 137 (31), 125 (45), 71 (49), 44 (86); HREIMS m/z 256.2045 [M]^+ (calcd for C_{15}H_{28}O_{3}, 256.2038).

X-ray crystallographic analysis of 9
All crystallographic data were collected on a Bruker Smart-1000 CCD diffractometer equipped with a graphite-monochromatic Cu Kα radiation (λ = 1.54178 Å) at 293(2) K. The data were corrected for absorption by using the program SADABS. The structure was solved by direct methods with the SHELXTL software package. All non-hydrogen atoms were refined anisotropically. The H atoms were located by geometrical calculations, and their positions and thermal parameters were fixed during the structure refinement. The structure was refined by full-matrix least-squares techniques.

The data have been deposited at the Cambridge Crystallographic Data Centre, with deposition no. CCDC 1865404.

Bioassay
The inhibition of the marine phytoplankton Chattonella marina, Heterosigma akashiwo, Karlodinium veneficum, and Prorocentrum donghaiense and the marine zooplankton Artemia salina were assayed as described previously, with K_{2}Cr_{2}O_{7} as the positive controls.

Computational details
Conformational searches for 1–5 and 7 were performed via the Dreiding force field in MarvinSketch (optimization limit = normal, diversity limit = 0.1) regardless of the methyl group rotations, and the energy-minimized conformers (Fig. S2-S7) without vibrational imaginary frequencies were obtained after conformational optimization at the B3LYP/6-31G(d) level in MeOH via Gaussian 09 software. Subsequently, the ECD spectrum of each conformer within a 3 kcal mol^−1 energy threshold from the global minimum was simulated at the same level in MeOH through the time-dependent density functional theory (TD-DFT) method and then drawn by SpecDis software with sigma = 0.6 for 1 and 5, 0.5 for 2, 0.3 for 3 and 7, and 0.4 for 4 and with UV-shift = 0 nm for 3–5 and –10 nm for 1, 2, and 7. The overall calculated ECD curve of each compound was generated by Boltzmann weighting and magnified according to the experimental data. Additionally, the specific optical rotation of 1 was calculated at the B3LYP/6-31+G(d,p) level in MeOH. The conformers (Fig. S8) of 3 were reoptimized and their ECD curves were further calculated at the B3LYP/6-31+G(d,p) level in MeOH. All of the above calculations were performed with the integral equation formalism variant (IEF) of the polarizable continuum model (PCM) as implemented in Gaussian 09.

Conflicts of interest
There are no conflicts to declare.

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