Three Novel Cytochalasins X, Y, and Z from *Pseudeurotium zonatum*

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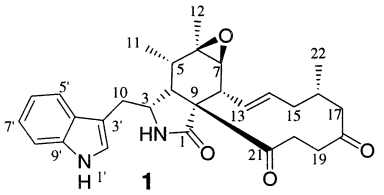
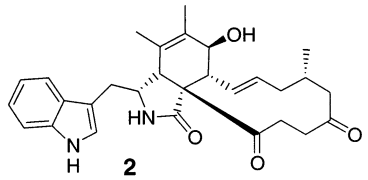
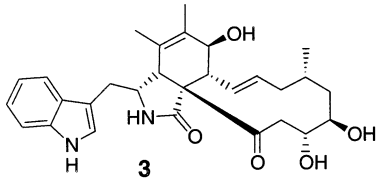
Fermentation of *Pseudeurotium zonatum* led to the isolation of the known cytochalasin G (**1**) and three new cytochalasins, X, Y, and Z (**2**−**4**). These four compounds are the only naturally occurring cytochalasins reported to date that contain an indole-substituted perhydroisoindol-1-one fused with an 11-membered macrocycle.

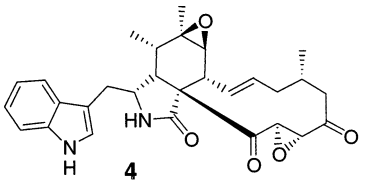
During studies on the production of bioactive metabolites by fungi it was found that an isolate of the soil fungus *Pseudeurotium zonatum* van Beyma produced a number of cytochalasins. The cytochalasins are a group of fungal secondary metabolites that inhibit cytoplasmic cleavage in mammalian cells.[1] Most of the effects initiated by cytochalasins can now be attributed directly or indirectly to the interaction between these drugs and their common target protein, actin.[2,3] Chemically, the cytochalasins are characterized by a highly substituted perhydroisoindol-1-one fused with an 11- or 13-membered macrocyclic ring.[4] The variety of the structures arise from variations in the substituents at C-3 on the perhydroisoindol-1-one ring and the size of the macrocycle.[4]

Of the naturally occurring cytochalasins reported to date, cytochalasin G (**1**) is the only indole-substituted perhydroisoindol-1-one containing an 11-membered macrocycle.[5] In the course of our screening for biologically active metabolites, three new cytochalasins, X, Y, and Z (**2**−**4**), each related to cytochalasin G (**1**), were isolated from *P. zonatum*. We report here on the isolation and structural elucidation of these new cytochalasins.









Results and Discussion

Pseudeurotium zonatum (CANU-H18) was fermented in half-strength malt extract broth under static conditions at 26 °C for 8 weeks. HPLC analysis of the ethyl acetate extract of both the mycelium and culture filtrate suggested they contained a series of compounds with UV maxima at 220, 273, and 290 nm within retention times of 12−16 min. The combined extracts were chromatographed on a flash C_{18} column. Repeated chromatography on diol of two of the C_{18} fractions yielded cytochalasins G (**1**), X (**2**), Y (**3**), and Z (**4**). Cytochalasin G has previously been reported from a *Nigrosabulum* sp. (very closely related to *Pseudeurotium* sp.), but only limited spectral data were reported.[5]

The ES positive-ion mass spectrum of cytochalasin X (**2**) showed strong M + H^+, M + Na^+, and M + K^+ peaks at *m*/*z* 475, 497, and 513, respectively. High-resolution mass measurement on the M + H^+ peak (*m*/*z* 475.2607) in the ESIMS, in combination with ^{1}H and ^{13}C NMR data (Table 1), supported the molecular formula $C_{29}H_{34}N_2O_4$ (14 double bond equivalents). The UV spectrum exhibited strong absorptions at 220, 273, and 290 nm, suggestive of an indole system.

In the aromatic region of the ^{1}H NMR spectrum of **2** there were two doublets, two triplets, and one sharp doublet. The chemical shifts and coupling constants in combination with the UV data confirmed a C-3-substituted indole moiety in the structure. Three methyl groups (two broad singlets and one doublet) were also readily assigned. All 29 carbons of **2** were observed in the APT sequence experiment. In addition to the eight characteristic carbon signals for an indole system, four more sp^2 carbon signals (126.3, 127.4, 132.1, and 137.7 ppm) accounted for a further two double bonds. Three quaternary carbon signals at 174.6, 206.1, and 208.3 ppm indicated the presence of three carbonyl groups. The remaining signals were accounted for by three methyl, five methylene, five methine, and one quaternary carbon.

COSY and HSQC NMR correlation experiments established a number of partial connectivities and defined subunits **a**, **b**, and **c** (Figure 1 in bold). A long-range ^{1}H−^{13}C correlation experiment (CIGAR)[6] (Table 2) permitted all the nonprotonated carbons to be assigned and allowed the partial structures to be assembled (Figure 1). The

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Table 1. ^{1}H and ^{13}C NMR Data for Compounds **1**−**4**[a]

	1		**2**		**3**		**4**	
postion	δ_H (mult., *J* Hz)	δ_C	δ_H (mult., *J* Hz)	δ_C	δ_H (mult., *J* Hz)	δ_C	δ_H (mult., *J* Hz)	δ_C
1	−	174.9	−	174.6	−	174.5	−	172.8
2	5.98 (br s)	−	5.87 (br s)	−	5.91 (br s)	−	6.65 (br s)	−
3	3.80 (t, 5.5)	52.1	3.56 (t, 8.5)	57.5	3.56 (t, 7.5)	57.6	3.84 (m)	52.8
4	2.87 (br d, 5.0)	48.3	3.31 (br s)	49.2	3.41 (br s)	48.2	3.21 (dd, 5.5, 2.0)	45.7
5	1.89 (br s)	36.3	−	126.3	−	126.4	1.77 (t, 6.5)	35.8
6	−	57.3	−	132.1	−	131.7	−	58.1
7	2.82 (d, 5.5)	61.2	3.96 (d, 10.0)	68.8	4.04 (d, 9.5)	69.3	2.81 (d, 5.5)	61.3
8	2.10 (dd, 10.5, 6.5)	49.3	2.10 (t, 9.5)	52.5	2.14 (t, 9.5)	53.4	2.12 (dd, 10, 5.5)	48.6
9	−	64.5	−	62.0	−	63.7	−	67.4
10a	2.89 (dd, 14.0, 4.5)	39.8	2.72 (d, 7.5)	32.7	2.80 (dd, 14.0, 6.5)	32.9	2.95 (dd, 14.0, 4.0)	34.0
10b	2.64 (dd, 14.5, 6.5)	39.8	2.72 (d, 7.5)	32.7	2.68 (dd, 14.0, 8.3)	32.9	2.72 (dd, 14.0, 8.5)	34.0
11	1.09 (d, 7.0)	12.6	1.41 (br s)	17.2	1.52 (br s)	17.4	1.22 (d, 7.5)	12.8
12	1.20 (s)	19.3	1.65 (br s)	14.1	1.68 (br s)	14.0	1.24 (s)	19.4
13	6.14 (dd, 15.5, 10.0)	127.4	6.20 (dd, 15.0, 11.5)	127.4	6.17 (dd, 16.5, 11.5)	128.4	6.36 (dd, 15.5, 10.0)	129.7
14	5.05 (dtd, 11.5, 3.5)	134.9	5.23 (dtd, 11.5, 3.5)	137.7	5.38 (dtd, 10.5, 3.5)	137.2	5.40 (dtd, 11.5, 3.5)	133.7
15a	2.25 (m)	42.7	2.30 (m)	42.8	2.10 (m)	42.5	2.33 (m)	39.7
15b	1.6−1.7 (m)	42.7	1.6−1.7 (m)	42.8	1.6−1.8 (m)	42.5	1.9−2.0 (m)	39.7
16	2.3−2.4 (m)	27.8	2.4−2.5 (m)	27.7	1.6−1.8 (m)	27.3	2.25−2.30 (m)	30.7
17a	2.4−2.5 (m)	47.4	2.5−2.6 (m)	47.8	1.7−1.8 (m)	37.1	2.60 (dd, 15.5, 4.0)	46.2
17b	1.86 (t, 3.5)	47.4	1.98 (d, 17.5)	47.8	1.6−1.7 (m)	37.1	2.36−2.42 (m)	46.2
18	−	208.4	−	208.3	3.62 (m)	72.1	−	204.6
19a	2.6−2.7 (m)	37.3	2.84 (t, 12.5)	37.4	3.76 (t, 7.5)	69.6	4.57 (d, 2.0)	58.0
19b	2.3−2.4 (m)	37.3	2.5−2.6 (m)	37.4	−	−	−	−
20a	3.42 (dd, 17.0, 12.5)	36.4	3.68 (dd, 17.0, 13.0)	36.8	3.89 (d, 18.0)	43.8	3.42 (d, 2.0)	60.2
20b	1.6−1.7 (m)	36.4	2.4−2.5 (m)	36.8	1.98 (dd, 18.5, 7.0)	43.8	−	−
21	−	205.9	−	206.1	−	205.3	−	199.1
22	0.95 (d, 6.5)	22.5	0.98 (d, 7.0)	22.5	1.05 (d, 6.0)	25.7	1.17 (d, 6.5)	23.4
1′	8.31 (br s)	−	8.27 (br s)	−	8.30 (br s)	−	8.59 (br s)	−
2′	6.97 (d, 2.5)	123.9	7.04 (d, 2.0)	123.3	7.01 (d, 2.0)	123.1	7.04 (d, 2.5)	122.9
3′	−	109.9	−	110.8	−	110.9	−	110.5
4′	−	127.2	−	126.9	−	126.9	−	127.0
5′	7.49 (d, 8.0)	118.5	7.50 (d, 7.5)	118.2	7.50 (d, 8.5)	118.3	7.53 (d, 8.0)	117.9
6′	7.15 (t, 8.0)	119.9	7.13 (t, 8.0)	119.8	7.14 (t, 7.5)	119.8	7.16 (t, 6.5)	119.6
7′	7.20 (t, 8.0)	122.2	7.24 (t, 7.5)	122.3	7.21 (t, 7.5)	122.4	7.24 (t, 7.0)	122.2
8′	7.35 (d, 8.5)	111.5	7.38 (d, 8.0)	111.5	7.38 (d, 8.5)	111.5	7.46 (d, 8.5)	111.6
9′	−	136.3	−	136.3	−	136.3	−	136.4

[a] Spectra were recorded at 500 MHz for ^{1}H and at 125 MHz for ^{13}C using $CDCl_3$ as solvent and TMS as internal standard.

Table 2. Long-Range ^{1}H−^{13}C NMR Correlations (CIGAR) for **1**−**4**

	correlated carbons			
position	**1**	**2**	**3**	**4**
2	C-3, C-4, C-9	−	C-9	−
3	C-1, C-4, C-5, C-3′	C-1, C-4, C-5, C-9, C-3′	C-1, C-4, C-5, C-9, C-3′	−
4	C-1, C-5, C-6, C-9, C-10, C-21	C-1, C-5, C-6	−	C-1, C-3, C-5, C-6, C-9, C-10, C-21
5	−	−	−	C-3, C-4, C-6, C-11
7	C-8, C-12, C-13	−	−	C-8, C-13
8	C-1, C-7, C-9, C-13, C-14	C-1, C-7, C-9, C-13, C-14	C-1, C-7, C-13	C-1, C-7, C-9, C-13, C-14
10	C-3, C-4, C-2′, C-3′, C-4′	C-3, C-4, C-2′, C-3′, C-4′	C-3, C-4, C-2′, C-3′, C-4′	C-3, C-2′, C-3′, C-4′
11	C-4, C-5, C-6	C-4, C-5, C-6	C-3, C-5, C-6	C-4, C-5
12	C-5, C-6, C-7	C-5, C-6, C-7	C-5, C-6, C-7	C-6, C-7
13	C-7, C-15	C-15	C-8, C-15	−
15	C-13, C-14, C-16	−	C-13, C-17	−
16	−	C-18	−	C-15, C-18
17	C-15, C-16, C-18, C-22	C-15, C-16, C-18, C-22	−	C-15, C-16, C-18
19	C-18, C-20, C-21	C-18, C-20, C-21	−	C-20, C-21
20	C-21	C-19, C-21	−	C-21
22	C-15, C-16, C-17	C-15, C-16, C-17	C-15, C-16, C-17	C-15, C-16, C-17
2′	C-3′, C-4′, C-9′	C-3′, C-4′, C-9′	C-3′, C-4′, C-9′	C-3′, C-4′, C-9′
5′	C-7′, C-9′	C-7′, C-9′	C-7′, C-9′	C-7′, C-9′
6′	C-4′, C-8′	C-4′, C-8′	C-4′, C-8′	C-4′, C-8′
7′	C-5′, C-9′	C-5′, C-9′	C-5′, C-8′, C-9′	C-5′, C-9′
8′	C-4′, C-6′	C-4′, C-6′	C-4′, C-6′	C-4′, C-6′

definition of a dimethylalkenyl unit by observation of strong correlations from two methyl singlets (1.41 and 1.65 ppm) to two sp^2 carbon signals (126.3 and 132.1 ppm) served to link subunits **a** and **b** (correlations from H-3 at 3.56 ppm to C-5 at 126.3 ppm and H-12 at 1.65 ppm to C-7 at 68.8 ppm). Correlations from the methylene doublet (2.72 ppm) to the indole carbon signals (126.9, 123.3, and 110.8 ppm) established the connectivity of subunit **a** to the indole ring (Figure 1). Further correlations from the same CH_2 protons to the carbon signal at 49.2 ppm, when considered with additional correlations from the two triplets at 2.10 and 3.56 ppm to the carbonyl signal (174.6 ppm), quaternary carbon (62.0 ppm), and two sp^2 carbons (126.3 and 132.1 ppm), defined the indole-substituted perhydroisoindol-1-one structure. The connectivity of subunit **b** to **c** through a common carbonyl group was con-

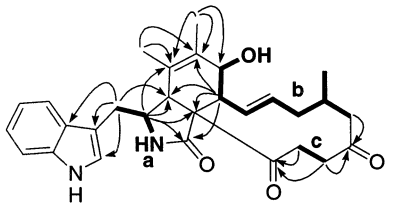

Figure 1. Subunits **a**, **b**, and **c** and CIGAR correlations for cytochalasin X (**1**).

firmed by correlations from the H-17b and H-19a protons (1.98 and 2.84 ppm, respectively) to the C-18 carbonyl (208.3 ppm). The H-19a proton and the H-20a proton (3.68 ppm) were in turn correlated with C-21 (206.1 ppm). However, no other correlations were observed to C-21 under a wide range of experimental conditions. The final definition of the structure as **2** was therefore based on consideration of the molecular formula, double-bond equivalents, valency requirements, and the observation of the critical H-4/C-21 correlation in **1** and **4**.

Cytochalasin Y (**3**), $C_{29}H_{36}N_2O_5$ from HRESIMS, possessed spectral properties very similar to **2**. The structure of **3** differed from **2** only in the region of C-18 to C-19, where a vicinal diol (72.1 ppm, C-18 and 69.6 ppm, C-19) replaced the $-CO-CH_2-$ moiety (208.3 ppm, C-18 and 37.4 ppm, C-19) in keeping with the molecular formula. The ^{1}H NMR spectrum was also consistent with this change. Analysis of the 2D spectral data (COSY, HSQC, and CIGAR) confirmed that cytochalasin Y has the structure **3**.

Cytochalasin Z (**4**) was the least polar of the cytochalasins. HRESIMS indicated a molecular formula of $C_{29}H_{32}N_2O_5$ (15 double-bond equivalents). In contrast to **2**, the C-5/C-7 hydroxydimethylalkeneyl unit was replaced by the saturated dimethyloxirane system found in **1**. This was suggested by the replacement of the two broad methyl singlets by a sharp methyl singlet and a methyl doublet with a concomitant upfield shift of H-7 (2.81 ppm). Another point of difference of **4** from compound **2** was in the C-19/C-20 region. The H-19 and H-20 signals now appeared as two mutually coupled CH doublets (4.57 and 3.42 ppm, respectively; $J = 2$ Hz) and were assigned as part of an additional oxirane ring system. Further analysis of the 2D NMR (COSY, HSQC, and CIGAR) experiments confirmed the structure as **4**.

Although cytochalasin G (**1**), $C_{29}H_{34}N_2O_4$ from HRESIMS measurement, had previously been isolated, only limited ^{1}H NMR spectral data had been reported.[5] Full ^{1}H and ^{13}C NMR assignments for **1** were made (Table 1) by comparison with spectral data for cytochalasins X−Z (**2**−**4**) and further analysis of the 2D NMR spectral data (COSY, HSQC, and CIGAR) of cytochalasin G.

Previous studies have suggested that the essential elements of the cytochalasin skeleton have the same stereochemistry, viz., the *cis*-stereochemistry across the 5/6 ring junction and the *trans*-stereochemistry of the macrocyclic ring.[3,7] The X-ray analysis of cytochalasin G suggested that the six-membered ring adopts a slightly twisted boat conformation, and the macrocyclic ring, which contains an *E*-alkene, is arranged in a chairlike conformation.[5] A series of 2D NOE experiments on these new cytochalasins suggested the same stereochemistry, as correlations were observed between protons H-3/H-11, H-4/H-8, H-7/H-12, and H-11/H-13. Correlations between H-5/H-8 were also observed in compounds **1** and **4**. The stereochemistry at C-16 in **1**−**4** was determined by the correlations between H-13/H-15b and H-15b/H-22. In compound **3**, the stereochemistry at C-18 was determined by further correlations between H-22/H-17b and H-17b/H-18. Lack of enhancement of H-19 on irradiation of H-18 suggested that H-19 was *trans* to H-18. In compound **4**, the stereochemistry of the C-19/C-20 oxirane group was determined by the observed correlations between H-16/H-17b, H-17b/H-19, and H-19/H-20 in the 2D NOE experiment.

To date, more than 50 cytochalasins have been isolated from a range of fungi.[3,7] Their diverse biological activities, especially their ability to inhibit cytoplasmic cleavage in mammalian cells, are unprecedented in any other class of chemical compounds.[3] The cytochalasins isolated in this study showed weak cytotoxicity against murine P388 leukemia cells.[8] However, their potential as cytoplasmic cleavage inhibitors remains an exciting area to be explored.

Experimental Section

General Experimental Procedures. The $[\alpha]_D$ values were measured with a Perkin-Elmer 341 polarimeter. UV and IR spectra were measured with a GBC UV/vis 920 spectrometer and a Shimadzu FTIR-8201 PC spectrometer, respectively. ^{1}H, ^{13}C-APT and 2D NMR (^{1}H−^{1}H COSY, ^{1}H−^{13}C HSQC, ^{1}H−^{13}C CIGAR) spectra were recorded on a Varian INOVA 500 MHz spectrometer. Mass spectra were acquired using a Micromass TOF LCT mass spectrometer. Column chromatography used J.T. Baker 40 μM Prep LC Bakerbond octadecyl (C_{18}) and 40 μM Prep LC Bakerbond diol (COHCOH), and TLC was performed with Merck diol TLC plates. Solvents for extraction and chromatography were distilled prior to use. Culture media included Oxoid malt extract broth, Gibco peptone 100, and BDH glucose.

Fungal Material. The ascomyceteous fungus *Pseudeurotium zonatum* was isolated from a soil sample taken at 3900 m from Tserum, Nepal. Colony and reproductive structures were identical to the description of *P. zonatum* by Domsch et al.[9] A voucher of the fungus has been deposited in the University of Canterbury fungal herbarium and assigned as CANU-H18.

HPLC Analysis of Crude Extracts. Crude extracts were analyzed by a Shimadzu HPLC system including a Phenomenex 5 μm C_{18} column (250 × 4.60 mm), diode array detection, and Class VP data processing program; flow rate at 1.0 mL/min; linear gradient elution, H_2O/acetonitrile, 90:10−25:75 in 14 min, held at 25:75 for 10 min, 25:75−0:100 in 2 min, held at 0:100 for 4 min, then 0:100−90:10 in 2 min, and held at 90:10 for 8 min. The retention times for cytochalasins G (**1**), X (**2**), Y (**3**), and Z (**4**) were 14.51, 13.87, 12.38, and 15.19 min, respectively.

Fermentation and Isolation. *P. zonatum* (CANU-H18) was fermented in half-strength malt extract broth (4.25 g of malt extract, 0.75 g of peptone 100, and 2 g of glucose in 500 mL of distilled water) under static conditions at 26 °C for 8 weeks (the culture broth was a dark red color). The culture broth (600 mL) was homogenized and filtered through Celite. The mycelium was extracted by stirring with ethyl acetate overnight (3 × 200 mL), as was the culture broth (3 × 500 mL). The combined ethyl acetate extracts were concentrated under vacuum, yielding a dark red residue (284 mg). The residue was chromatographed on C_{18} using a steep, stepped solvent gradient from 10% MeOH/H_2O to MeOH to CH_2Cl_2. The fraction eluted with 60% MeOH/H_2O (11.6 mg) was further chromatographed on diol with petroleum ether/EtOAc (3:2) to yield cytochalasin Y (**3**, 2.5 mg). The fraction that eluted with 70% MeOH/H_2O (15.5 mg) was repeatedly chromatographed on diol using petroleum ether/EtOAc gradients to give cytochalasin X (**2**, 2.2 mg), cytochalasin G (**1**, 1.5 mg), and cytochalasin Z (**4**, 1.8 mg).

Cytochalasin G (1): white solid; $[\alpha]_D^{20}$ −40.6° (*c* 0.016, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.98), 273 (4.32), 290 (4.27); IR (chloroform) ν_{max} 3490, 3423, 2929, 2360, 2331, 1699, 1454, 1425, 1296, 1093, 1020, 983 cm^{-1}; full ^{1}H and ^{13}C assignments were made from ^{1}H, COSY, HSQC, and CIGAR

NMR experiments, and the data are summarized in Tables 1 and 2; HRESIMS 475.2610 ($M + H^+$) (calcd for $C_{29}H_{35}N_2O_4$, 475.2597).

Cytochalasin X (2): white solid; $[\alpha]_D^{20}$ +13.2° (*c* 0.025, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.94), 273 (4.22), 290 (4.18); IR (chloroform) ν_{max} 3587, 3477, 3421, 2927, 2378, 2335, 1699, 1456, 1423, 1298, 1126, 1093 cm^{-1}; full ^1H and ^{13}C assignments were made from ^1H, ^{13}C-APT, COSY, HSQC, and CIGAR NMR experiments, and the data are summarized in Tables 1 and 2; HRESIMS 475.2607 ($M + H^+$) (calcd for $C_{29}H_{35}N_2O_4$, 475.2597).

Cytochalasin Y (3): white solid; $[\alpha]_D^{20}$ +47.3° (*c* 0.022, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.95), 273 (4.11), 290 (4.09); IR (chloroform) ν_{max} 3587, 3477, 3427, 2927, 2366, 2341, 1697, 1456, 1419, 1383, 1091, 1056, 1018 cm^{-1}; full ^1H and ^{13}C assignments were made from ^1H, ^{13}C-APT, COSY, HSQC, and CIGAR NMR experiments, and the data are summarized in Tables 1 and 2; HRESIMS 493.2707 ($M + H^+$) (calcd for $C_{29}H_{37}N_2O_5$, 493.2702).

Cytochalasin Z (4): white solid; $[\alpha]_D^{20}$ −20° (*c* 0.019, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.88), 273 (4.24), 290 (4.20); IR (chloroform) ν_{max} 3475, 3409, 2929, 2372, 1699, 1456, 1425, 1018, 983 cm^{-1}; full ^1H and ^{13}C assignments were made from ^1H, ^{13}C-APT, COSY, HSQC, and CIGAR NMR experiments, and the data are summarized in Tables 1 and 2; HRESIMS 489.2399 ($M + H^+$) (calcd for $C_{29}H_{33}N_2O_5$, 489.2389).

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