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Manadomanzamines A and B: A Novel Alkaloid Ring System with Potent Activity against Mycobacteria and HIV-1

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Abstract: Two novel alkaloids, named manadomanzamines A (**1**) and B (**2**), were isolated from an Indonesian sponge *Acanthostrongylophora* sp. (Haplosclerida: Petrosiidae). Their structures were elucidated and shown to be a novel organic skeleton related to the manzamine type alkaloids. Their absolute configuration and conformation were determined by CD, NOESY, and molecular modeling analysis. The microbial community analysis for the sponge that produces these unprecedented alkaloids has also been completed. Manadomanzamines A (**1**) and B (**2**) exhibited strong activity against *Mycobacterium tuberculosis* (Mtb) with MIC values of 1.9 and 1.5 μg/mL, respectively. Manadomanzamines A and B also exhibit activities against human immunodeficiency virus (HIV-1) and AIDS opportunistic fungal infections.

Introduction

Tuberculosis has resurged since the mid-1980s, and WHO estimates that one-third of the world's population is currently infected, with 3.1 million deaths annually.[1] Globally, tuberculosis is a leading killer among youth, women, and AIDS patients. The increasing threat of tuberculosis has initiated a renewal of interest in a search for new types of antituberculosis agents. In the interest of identifying marine-derived antiinfective leads, a number of Jamaican and Indonesian sponges have been examined.[2−7] In this paper, we report two novel alkaloids, manadomanzamines[8] A (**1**) and B (**2**), and the microbial community associated with the sponge that produces these novel alkaloids. Manadomanzamines A and B represent an unprecedented rearrangement of the manzamine skeleton and exhibit significant activities against *Mycobacterium tuberculosis* (Mtb) and human immunodeficiency virus (HIV-1) and moderate activity against several AIDS opportunistic infections (OI). The value of a drug lead with activity against both HIV-1 and AIDS-OI would clearly be exceptional.[9]

Results and Discussion

Structure Elucidation. The frozen sponge (4 kg) was collected from Manado Bay, Indonesia by SCUBA. The sample was extracted with acetone and then chromatographed on silica gel and Al_2O_3 to obtain manadomanzamines A (**1**) and B (**2**), as well as the known compounds xestomanzamine A (**3**)[10] and 2-phenyl-acetamide.

(1) NIAID's Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF). Web Site, http://www.taacf.org/about-TB-background.htm (accessed July 4, 2003).

(2) Peng, J.; Walsh, K.; Weedman, V.; Bergthold, J. D.; Lynch, J.; Lieu, K. L.; Braude, I. A.; Kelly, M.; Hamann, M. T. *Tetrahedron* **2002**, *58*, 7809−7819.

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(6) Hu, J.; Schetz, J. A.; Kelly, M.; Peng, J.; Ang, K. K.; Flotow, H.; Leong, C. Y.; Ng, S. B.; Buss, A. D.; Wilkins, S. P.; Hamann, M. T. *J. Nat. Prod.* **2002**, *65*, 476−480.

(7) Rao, K. V.; Santarsiero, B. D.; Mesecar, A. D.; Schinazi, R. F.; Tekwani, B. L.; Hamann, M. T. *J. Nat. Prod.* **2003**, *66*, 823−828.

(8) These novel alkaloids are named after the city of Manado, Indonesia in appreciation of the kind assistance of the people from Manado in this research.

(9) For a complete review of the chemistry, taxonomy, and pharmacology published on the manzamines, please see chapter reference: Hu, J.-F.; Hamann, M. T.; Hill, R.; Kelly, M. The Manzamine Alkaloids. In *The Alkaloids: Biology and Chemistry*; Cordell, G. A., Ed.; Elsevier: U.K., 2003; Vol. 60, pp 207−285.
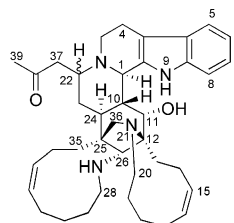
manadomanzamine A (**1**): 22β-H
manadomanzamine B (**2**): 22α-H
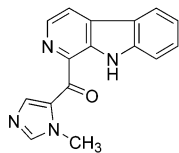
xestomanzamine A (**3**)

Manadomanzamine A (**1**) was isolated as a white powder and its molecular formula $C_{39}H_{54}N_4O_2$ was determined by HRESIMS 611.4348 [M + H] (calcd 611.4319). The absence of the H-3 and H-4 aromatic signals in the ^1H NMR spectrum combined with the UV absorption at 282 nm suggested a tetrahydro-β-carboline. The ^1H and ^{13}C NMR spectra data displayed some similarity with those of manzamine B (**4**).[11] Two sets of $(CH_2)_2CH=CH(CH_2)_4N$ units [δ_C 31.0, δ_H 1.37, 2.47 (C-13, H-13) to δ_C 46.6, δ_H 2.12, 2.55 (C-20, H-20) and δ_C 48.0, δ_H 2.72, 3.09 (C-28, H-28) to δ_C 33.3, δ_H 1.50, 1.60 (C-35, H-35)] were deduced from the COSY, HMQC, and HMBC spectra. The C-10−12,24−26 six-membered ring was elucidated using the HMBC experiments: H-26 (δ 2.93) correlated to C-11 (δ 74.5), C-12 (δ 64.7), C-24 (δ 33.6), and C-25 (δ 45.2); H-11 (δ 3.51) correlated to C-24, C-12, and C-26 (δ 66.9); and finally H-1 (δ 4.16) correlated to C-10 (δ 43.0) and C-24. The unprecedented six-membered ring (C-1,10,22−24,N-2) was established on the basis of the long-range heteronuclear correlations in the HMBC spectrum in which H-1 (δ 4.16) correlated to C-10 (δ 43.0) and C-24 (δ 33.6) and H-22 (δ 3.75) correlated to C-1 (δ 53.5), C-3 (δ 49.3), C-23 (δ 26.8), and C-24 (δ 33.6). This indicated the cleavage of the bond between C-22 and N-21 in the typical manzamine type skeleton. The connection of N-21 to C-12 was deduced by the ^3J heteronuclear correlations of H-20 (δ 2.55) and H-36 (δ 2.88) to C-12 (δ 64.7) in the HMBC spectrum. The chemical shift of C-11 (δ 74.5) suggested a hydroxyl group at C-11 rather than the epoxy group found in manzamine B. A 2-ketopropyl group was readily deduced from the ^1H, ^{13}C NMR data [δ_H 2.17 (H$_3$-39), 3.06, 2.63 (H$_2$-37); δ_C 30.9 (C-39), 208.6 (C-38), and 45.2 (C-37)] and the HMBC correlations (H-39 to C-38 and C-37; H-37 to C-38 and C-39). The ^3J coupling of H-37 and H-22 (δ 3.75) in the COSY spectrum indicated that the 2-ketopropyl group was connected to C-22. Additional significant evidence for the structure was provided by the natural abundance $^1H−^{15}N$ HMBC experiment: H-13 (δ 1.37, 2.47) to N-21 (δ 36.9) supports the connection of C-12 to N-21; H-37 (2.63, 3.06) and H-23 (δ 1.44) to N-2 (δ 46.3) support the connection of C-22 to N-2 to form the new six-membered ring. The relative stereochemistry of **1** was determined through a combination of NOE, coupling constant data and molecular modeling experiments. The correlations of H-1 to H-24 and H-37 in the NOESY spectrum indicated the α configuration for H-1, H-24, and the 2-keto-propyl group. The large coupling constant ($^3J_{H−1,10}$ = 9.6 Hz) suggested the axial−axial relationship of H-1 and H-10, indicating H-10 is β in configuration. The small coupling constant ($^3J_{H−10,11}$ = 2.7 Hz) indicated the β-configuration for

(10) Kobayashi, M.; Chen, Y.; Aoki, S.; In, Y.; Ishida, T.; Kitagawa, I. *Tetrahedron* **1995**, *51*, 3727−3736.
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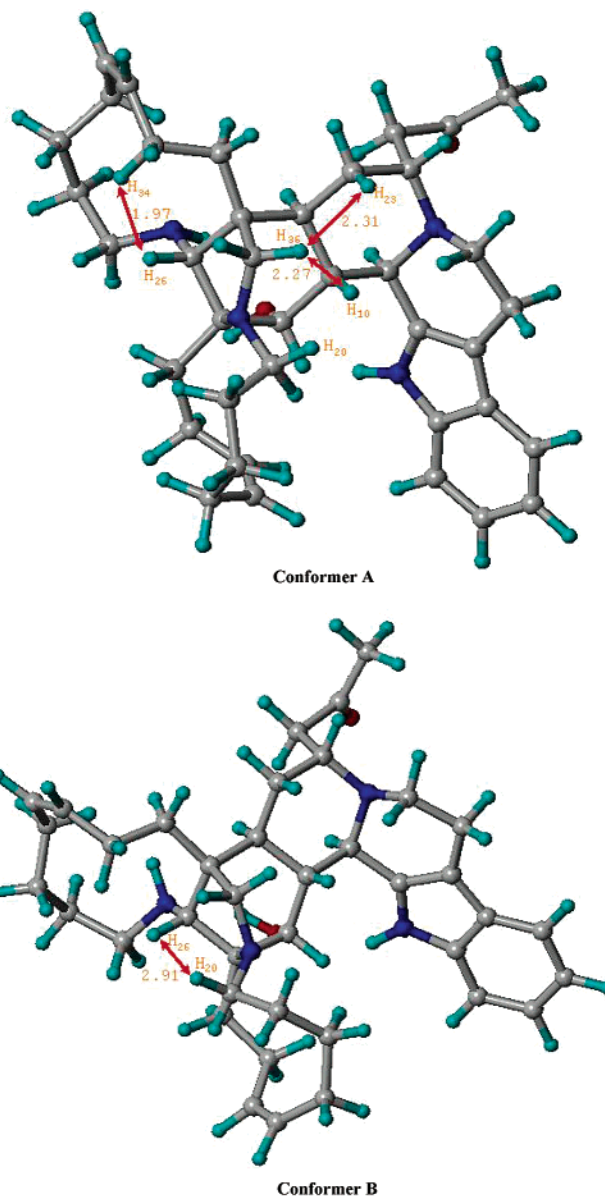
Conformer A

Conformer B

Figure 1. Modeled conformation of manadomanzamine A. In this figure, carbon atoms are represented by gray; nitrogen atoms, by blue; oxygen atoms, by red; and hydrogen atoms, by cyan.

H-11. H-36 (δ 2.39) showed NOE correlations to H-10 (δ 1.58) and H-23 (δ 1.78), indicating that C-36 and N-21 are in β-positions. The NOE correlation between H-26 (δ 2.93) and H-20 (δ 2.55) required that H-26 is in a β-position and C-20 has the same orientation as H-26 leaving the lone pair of the N-21 electrons in the opposite orientation. The stereochemistry of **1** is also consistent with the corresponding stereochemistry of manzamine B (**4**); the proposed biogenetic precursor to the manadomanzamines is shown in Scheme 1. A positive CD Cotton effect at 226 nm was observed, indicating an *R*-configuration at C-1 of the tetrahydro-β-carboline ring.[12] The absolute stereochemistry of the rest of the structure could readily be assigned relative to C-1.
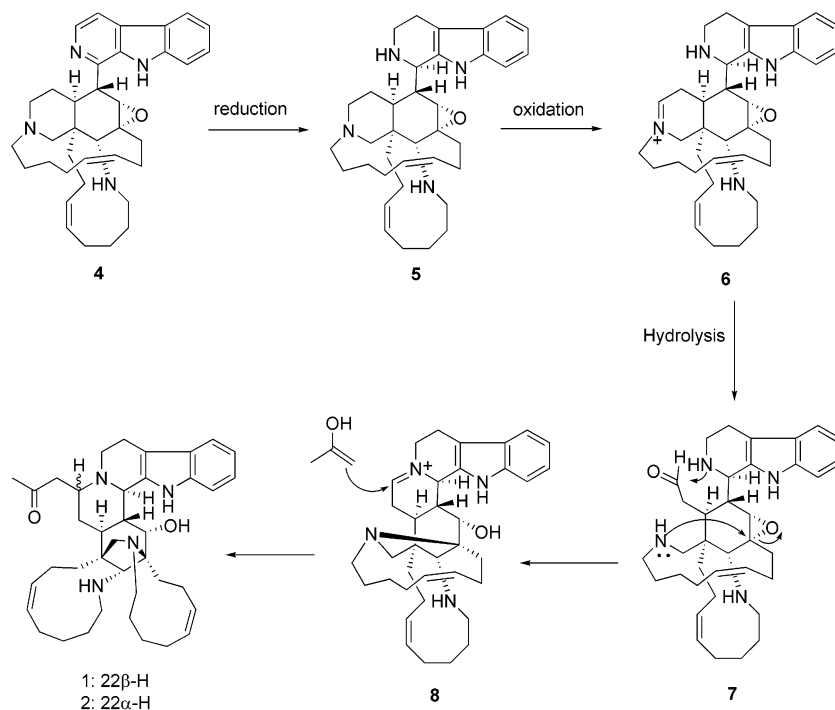
Molecular modeling of manadomanzamine A was performed using a Sybyl 6.8 software package. The minimized energy conformer A (140.4 kcal/mol) shown in Figure 1, with the

(12) Stöckigt, J.; Zenk, M. H. *J. Chem. Soc., Chem. Commun.* **1977**, 646−648.

Scheme 1. Plausible Biogenetic Path of Manadomanzamine A (**1**) and B (**2**)

distances between H-26 and H-34 (1.97 Å), H-36 and H-10 (2.28 Å), and H-36 and H-23 (2.32 Å), supports the NOESY data extremely well with the exception of the inverted configuration of N-21. With the restraint of the configuration at N-21, a minimized energy conformer B (143.2 kcal/mol) was obtained (Figure 1), with a distance of 2.91 Å between H-26 and H-20 which fits the NOE correlation between H-26 and H-20. The rest of the conformation is consistent with conformer A. This indicated that the conformation, as conformer B, would be predominant in CDCl$_3$, although it may not be the preferred conformation in energy level. This will no doubt be helpful in future SAR studies, since the ligand-based drug design takes solvent effects into consideration.

Manadomanzamine B (**2**) gives the same molecular formula as manadomanzamine A (**1**), and its ^{1}H and ^{13}C NMR data were comparable to that of **1**, suggesting **2** is diastereomeric **1**. The chemical shifts of C-1 (δ 60.1) and C-24 (δ 39.4) for **2** are 6.6 and 5.8 ppm downfield in comparison with **1**, while C-3 (δ 40.4) for **2** is 8.9 ppm upfield relative to **1** (Table 1. The NOESY spectral data [H-1 (δ 4.13) to H-22 (δ 3.54) and H-24 (δ 1.98)] revealed an α-configuration of H-22 for **2**, unlike H-22β for **1**. Manadomanzamine B (**2**) has the same positive Cotton effect in the CD spectrum at 224 nm as **1**, suggesting the same *R*-configuration at C-1.

Manadomanzamines A (**1**) and B (**2**) represent a novel class of manzamine-related alkaloids with significant activity against both HIV-1 and Mtb. A plausible biogenetic path of manadomanzamines A (**1**) and B (**2**) beginning with manzamine B (**4**) is shown in Scheme 1, in which manzamine B is first reduced to tetrahydromanzamine B (**5**) and then oxidation of C-22 to form the imine (**6**) is followed by hydrolysis of the C-22−N-21 bond to form an aldehyde (**7**). The aldehyde (**7**) is condensed with N-2 to form the new ring (**8**), and N-21 is attacked at C-12 leading to the epoxide ring opening. The addition of the 2-ketopropyl may occur before the cleavage of the C-22−N-21 bond or after forming the C-22−N-2 bond. The nonstereo-

selective addition of the 2-ketopropyl and the use of acetone as an extraction solvent raised the question that the addition of 2-ketopropyl may have occurred during the isolation procedure. To answer this question, the ethanol extract of a voucher specimen was evaporated and purified using silica gel thin-layer chromatography. The band corresponding to manadomanzamine A was eluted and examined by high-resolution mass spectrometry measurements. A peak at 611.4381, which corresponds to the exact mass of manadomanzamine A 611.4319 [M + H], indicated the existence of manadomanzamine A in the sample without any contact with acetone.

To better understand the role that sponge-associated microbes may have in the formation of these metabolites, a detailed microbial community analysis was completed. The cultivable microbial community associated with the sponge was investigated. Cultivable isolates of heterotrophic bacteria were obtained and unequivocally identified by 16S ribosomal RNA gene sequence analysis as described previously.[13] Eight isolates were obtained and the nearest relative of each isolate was found by BLAST analysis. Phylogenetic trees were inferred for these isolates as described previously (Figure 2).[5] Isolates included α-proteobacteria, γ-proteobacteria, and actinomycetes. The isolation of actinomycetes, generally regarded as soil microbes, is significant considering the excellent track record of these microbes in the production of antibiotics. This finding supports the contention that sponges may provide a good source of novel actinomycetes for drug discovery and development.[14] The eight isolates are currently being screened for manzamine production and for their potential to bioconvert previously described manzamines to manadomanzamines A and B.

Bioactivity. Both manadomanzamines A and B exhibited strong activity against *Mycobacterium tuberculosis* (Mtb) with MIC values of 1.9 and 1.5 μg/mL (the MIC of the positive

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(14) Webster, N. S.; Wilson, K. J.; Blackall, L. L.; Hill, R. T. *Appl. Environ. Microbiol.* **2001**, *67*, 434−444.

Table 1. NMR Data of Compounds **1** and **2**

	1			2	
	^{1}H NMR	^{13}C NMR	^{15}N NMR	^{1}H NMR	^{13}C NMR
1	4.16 (d, 9.6)	53.5		4.13 (d, 9.3)	60.1
N-2[a]			46.3		
3	3.25 (dt, 11.5, 6.0)	49.3		2.96 (m)	40.4
	2.84 (m)			2.90 (m)	
4	2.80 (2H, m)	23.0		2.77 (2H, m)	23.0
4a		108.7			108.3
5a		127.4			127.4
5	7.46 (d, 7.6)	118.2		7.45 (d, 7.6)	118.2
6	7.04 (t, 7.6)	119.0		7.03 (t, 7.6)	118.9
7	7.11 (t, 7.6)	121.3		7.10 (t, 7.6)	121.3
8	7.31 (d, 8.0)	111.3		7.30 (d, 7.6)	111.3
8a		136.1			136.1
9	9.17 (s)			9.04 (s)	
N-9			123.8		
9a		134.7			134.9
10	1.58 (m)	43.0		1.63 (m)	40.4
11	3.51 (d, 2.7)	74.5		3.39 (d, 2.7)	74.7
12		64.7			64.6
13	2.47 (ddd, 15.1, 10.5, 4.0)	31.0		2.45 (m)	31.4
	1.37 (m)			1.20 (m)	
14	2.63 (m)	18.6		2.54 (m)	18.7
	1.80 (m)			1.73 (m)	
15	5.48 (m)	130.0		5.46 (m)	130.1
16	5.29 (m)	131.1		5.30 (m)	131.0
17	2.70 (m)	25.0		2.68 (m)	25.0
	1.81 (m)			1.82 (m)	
18	1.15 (m)	27.6		1.16 (m)	27.6
	1.77 (m)			1.76 (m)	
19	1.73 (m)	27.0		1.37 (m)	27.0
	1.41 (m)			1.74 (m)	
20	2.55 (m)	46.6		2.52 (m)	46.7
	2.12 (m)			2.08 (m)	
N-21			36.9		
22	3.75 (q, 5.6)	57.9		3.54 (m)	58.6
23	1.44 (m)	26.8		1.49 (m)	27.9
	1.78 (m)			1.74 m)	
24	2.11 (m)	33.6		1.98 (m)	39.4
25		45.2			45.3
26	2.93 (s)	66.9		2.95 (s)	66.7
N-27			32.6		
28	3.09 (m)	48.0		3.10 (m)	48.1
	2.72 (m)			2.69 (m)	
29	1.74 (2H, m)	27.3		1.65 (2H, m)	27.4
30	1.47 (m)	26.2		1.46 (m)	26.2
	1.86 (m)			1.72 (m)	
31	2.22 (m)	24.3		2.25 (m)	24.3
	2.03 (m)			1.98 (m)	
32	5.53 (m)	131.1		5.55 (m)	130.8
33	5.53 (m)	130.8		5.55 (m)	130.6
34	2.05 (m)	21.4		2.26 (m)	21.2
	2.24 (m)			2.00 (m)	
35	1.50 (m)	33.3		1.63 (m)	33.1
	1.60 (m)			1.44 (m)	
36	2.88 (d, 10.0)	57.5		2.93 (d, 9.6)	57.2
	2.39 (d, 10.0)			2.28 (d, 9.6)	
37	3.06 (dd, 16.6, 5.8)	45.2		2.89 (m)	49.6
	2.63 (dd, 16.6, 8.6)			2.54 (dd, 15.8, 7.6)	
38		208.6			207.4
39	2.17 (3H, s)	30.9		2.27 (s)	30.6

[a] ^{15}N NMR chemical shifts were measured using ^{1}H$-^{15}$N HMBC spectra.

control, rifampin, is 0.16 μg/mL), suggesting manadomanzamines are a new class of anti-Mtb leads. Manadomanzamines A, B and xestomanzamine A are active against human immunodeficiency virus (HIV-1) with EC$_{50}$ values of 7.0, 16.5, and 11.2 μg/mL, respectively. Manadomanzamine A is active against human lung carcinoma A-549 and human colon carcinoma
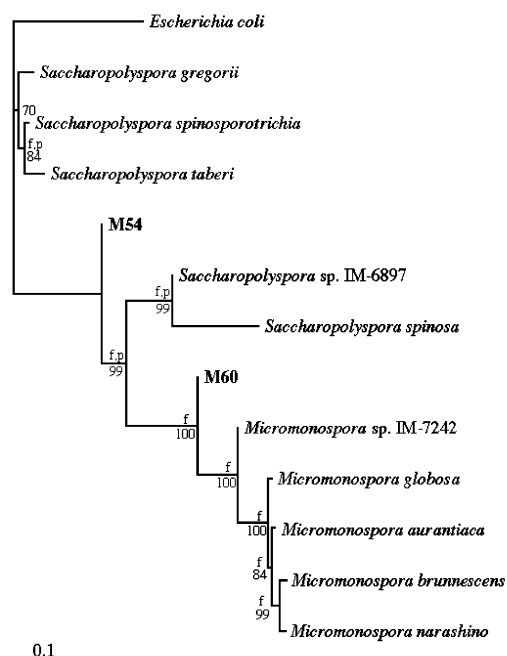

Figure 2. Neighbor-joining phylogenetic tree from analysis of ca. 500 bp of 16S rRNA gene sequence of actinomycetes isolated from sponge. "f" and "p" indicate branches that were also found using the Fitch−Margoliash and maximum parsimony methods, respectively. The numbers at the nodes are percentages indicating the levels of bootstrap support.

H-116 with IC$_{50}$ values of 2.5 and 5.0 μg/mL, while manadomanzamine B is only active against H-116 with an IC$_{50}$ of 5.0 μg/mL (Table 2). Manadomanzamines A, B and xestomanzamine A did not show cytotoxicity against the normal Vero cell line (African Green Monkey kidney cells) at the tested concentration (4.8 μg/mL). Manadomanzamine B and xestomanzamine A are active against the fungus *Cryptococcus neoformans* with IC$_{50}$ values of 3.5 and 6.0 μg/mL. Manadomanzamine A was active against the fungus *Candida albicans* with an IC$_{50}$ of 20 μg/mL. It is worthy to note that manadomanzamines A, B and xestomanzamine A, unlike manzamine A, 8-hydroxymanzamine A, and neo-kualuamine which are very active antimalarial agents,[4,15] only exhibit marginal activity against the malaria parasite indicating that the polycyclic ring system of the typical manzamine structure is important for the antimalarial activity.

Experimental Section

General Experiment Procedures. IR and UV spectra were obtained using an AATI Mattson Genesis Series FTIR and a Hewlett-Packard 8452A Diode Array spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. CD spectra were recorded using a JASCO J-715 spectropolarimeter. NMR spectra were measured on Bruker Avance DRX-400 and -500 spectrometers. ^{1}H and ^{13}C NMR spectra were measured and reported in ppm by using the residual solvent peak as an internal standard. ESI-FTMS analyses were measured on a Bruker-Magnex BioAPEX 30es ion cyclotron HR HPLC-FT spectrometer by direct injection into an electrospray interface.

^{15}N NMR. Inverse detected ^{15}N NMR spectra were recorded using a 500 Hz NMR spectrometer equipped with a 3 mm inverse-detection gradient probe. A gradient HMBC pulse sequence with 1 ms Gaussian Z-axis gradient pulses (70:30:50) was used. Referencing of the indirectly detected ^{15}N dimension was accomplished using nitromethane as an

(15) Ang, K. K. H.; Holmes, M. J.; Higa, T.; Hamann, M. T.; Kara, U. A. *Antimicrob. Agents Chemother.* **2000**, *44*, 1645−1649.

Table 2. Bioactivity of Manadomanzamines A, B and Xestomanzamine A[a]

| compd | anti-TB MIC (μg/mL) | anti-HIV-1 EC$_{50}$ (μg/mL) | antifungal IC$_{50}$ (μg/mL) | | cytotoxicity IC$_{50}$ (μg/mL) | |
			Candida albicans	*Cryptococcus neoformans*	A-594	H-116
manadomanzamine A	1.9	7.0	20	NA	2.5	5.0
manadomanzamine B	1.5	16.5	NA	3.5	>5	5.0
xestomanzamine A	14.1	11.2	NA	6.0	>5	>5

[a] A-594 = human lung carcinoma; H-116 = human colon carcinoma; NA = not active.

external standard. A GHMBC experiment was performed with nitromethane, and the ^{15}N correlation was calibrated to 380.2 ppm. This same calibration value was then used for the samples.

Molecular Modeling. The molecular modeling study was performed on a Silicon Graphics Octane2 workstation. The molecular structure was constructed using standard geometries and standard bond lengths in a Sybyl 6.8 software package and was manipulated using standard Tripos force. The initial conformations of the molecule were obtained from 10 rounds of simulated annealing experiments. In each round of simulation, the molecule was heated to 500 K within 500 fs and then allowed to cool to 200 K within 5000 fs. All collected conformations constructed an energy project curve, of which eight energy optimal conformations were selected from the temperature−time frame. These conformations were refined by minimization using Powell's method, MMFF94 force field, and partial charges, until a root-mean-square deviation of 0.001 kcal/mol Å was achieved. A distance-dependent dielectric of 4.00 was used throughout the calculation. A strategy of simplex algorithm followed by conjugate gradient algorithm was used in the minimization. Finally, from these refined conformations, the conformer with the lowest energy was selected as the final molecular conformation.

Sponge Collection and Taxonomy. The sponge was collected on 30 March 2001 from a silty sand bottom south of Black Reef Point, Manado Bay, Suluwasi, Indonesia, where it was particularly abundant between 6 and 23 m depth. The sponge forms a thickly encrusting mass with digitate projections, the external color is brown, and the internal color is tan. The texture is fragile and crumbly, and the sponge has an extremely foul smell when removed from water. The skeleton is composed of delicate irregular tracts of strongyles, 100−150 μm long, forming an irregular elongate mesh. The sponge is an undescribed species of *Acanthostrongylophora* (Haplosclerida: Petrosiidae). This species differs morphologically from previously described species[5] in the interior coloration (tan instead of yellow) and in their preferred environment (silty reef slopes vs clear vertical reef faces). A voucher specimen has been deposited at The Natural History Museum, London, United Kingdom (BMNH 2003.2.17.1).

Extraction and Isolation. The sponge (4 kg, wet weight) was extracted with acetone using a blender to furnish 750 g (semidry) of a crude extract. The crude material was passed through a vacuum liquid chromatograph column eluted with CHCl$_3$−MeOH (95:5−80:20) to yield six fractions. Fraction 1 (11.2 g) was subjected to silica gel column chromatography with a step gradient elution of CHCl$_3$−acetone 8:2, 7:3, and 1:1 to give 120 fractions. Fraction 37 was purified by crystallization from acetone to give 2-phenyl-acetamide (32 mg). Fractions 12−16 (1.03 g) were chromatographed on Al$_2$O$_3$ column eluted with hexane−acetone 8:2 then 7:3 to give **1** (95 mg) and **2** (191 mg), respectively. Fraction 73 (1.17 g) was dissolved in MeOH and passed through a Sephadex LH-20 column (MeOH) to afford xestomanzamine A (**3**, 140 mg).

Antituberculosis Assay. Primary assay is conducted at 6.25 μg/mL against *Mycobacterium tuberculosis* H$_{37}$Rv (ATCC 27294) in-BACTEC 12B MEDIUM using a broth microdilution assay (the Microplate Alamar Blue Assay).[16]

Anti-HIV Assay. Anti-HIV-1 activity was determined in PBM cells as described previously.[17] Stock solutions (20 or 40 mM) of the compounds were prepared in sterile DMSO and then diluted to the desired concentration in growth medium. Cells were infected with the prototype HIV-1$_{LAV}$ at a multiplicity of infection of 0.1. Details on the infection of cells and assessment of antiviral effects were described previously.[18]

Manadomanzamine A (1). White powder. HRESIMS 611.4348 [M + H] (calcd for C$_{39}$H$_{55}$N$_4$O$_2$ 611.4319); [α]$_D$ −19° (*c* 0.11, MeOH); UV λ_{max} (nm) 282 (ϵ = 7700); IR (film) ν 3372, 3002, 2919, 1707, 1468, 1354, 1164, 736 cm^{-1}; CD [θ]$_{201}$ −74 800, [θ]$_{208}$ +40 713, [θ]$_{226}$ +44 203, [θ]$_{271}$ −11 933 (*c* 4.50 × 10^{-5}, MeOH); for ^{1}H and ^{13}C NMR data, see Table 1.

Manadomanzamine B (2). White powder. HRESIMS 611.4310 [M + H] (calcd for C$_{39}$H$_{55}$N$_4$O$_2$ 611.4319); [α]$_D$ −18° (*c* 0.11, MeOH); UV λ_{max} (nm) 282 (ϵ = 7.2 × 10^3); IR (film) ν 3387, 3001, 2917, 1711, 1460, 1355, 1162, 736 cm^{-1}; CD [θ]$_{200}$ +66 840, [θ]$_{205}$ −45 260, [θ]$_{224}$ +52 520, [θ]$_{269}$ −12 150 (*c* 4.50 × 10^{-5}, MeOH); for ^{1}H and ^{13}C NMR data, see Table 1.

Supporting Information Available: ^{1}H, ^{13}C, DEPT135, COSY, HMQC, HMBC, NOESY, and ^{1}H−^{15}N HMBC spectra of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP: The structure of xestomanzamine A (**3**) was incorrect in the version published on the Web 10/11/2003. The final Web version published 10/20/2003 and the print version are correct.

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