Archerine, a Novel Anti-Histaminic Bromotyrosine-Derived Compound from the Caribbean Marine Sponge *Aplysina archeri*[‡]

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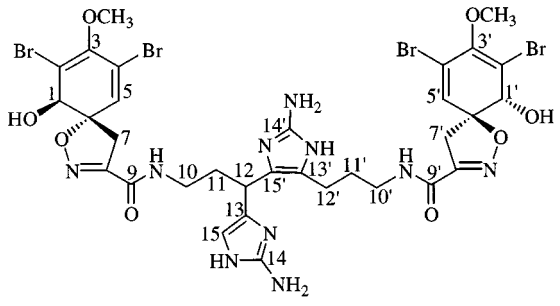
Keywords: *Aplysina archeri* / Bromotyrosine / Bioorganic chemistry / Natural products / NMR spectroscopy

A further chemical investigation of the Caribbean marine sponge *Aplysina archeri* led to the isolation of a novel bromo compound, archerine (**1**). Its structure was established through extensive NMR spectroscopy, including ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC and ^{1}H-^{15}N HMBC experiments, as well as positive FAB MS/MS spectra. The capability of archerine to chelate zinc ions was investigated. Archerine exhibited antihistamine activity on the isolated guinea pig ileum at concentrations as low as 1 μM.

Introduction

Bromo compounds biogenetically related to tyrosine constitute by far the commonest class of secondary metabolites in Verongida sponges.[1] The most widely occurring of these compounds possess as building blocks two 2,4-dibromo-1-hydroxy-3-methoxy-8-carbamoyl spirocyclohexadienyl isoxazole moieties which are connected through two amide linkages to a central chain; in this chain, biogenic diamines[2] or tyrosine-derived groups[3] are incorporated by forming amide or ether bonds.

In this paper we wish to report on a novel bromo compound, archerine (**1**), isolated from the Caribbean sponge *Aplysina archeri*, whose structure innovates the above typical feature of Verongida bromo metabolites in having the central chain formed by two 2-amino-homohistamine residues connected through a carbon-carbon bond.



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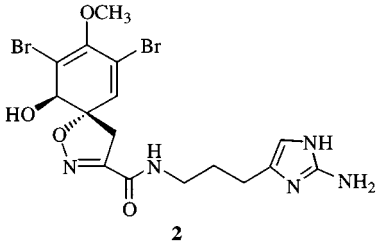

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Results and Discussion

Aplysina archeri (Demospongiae, Aplysinidae Carter, 1875) is a typical West Indian species (found in Yucatan, Florida and Bahamas) which grows in reef habitat at 2−40 m depth. In summer 1990, three specimens of *A. archeri* were collected by hand along the coasts of the Bahamian islands Little San Salvador, San Salvador and Grand Bahama and immediately frozen. After homogenization, they were separately and exhaustively extracted first with a 3:1 mixture of MeOH/toluene and then with $CHCl_3$. The combined MeOH/toluene solutions were partitioned between water and EtOAc, and then water and *n*BuOH. TLC analysis of the extracts indicated that the three analyzed specimens had a very similar metabolic content and therefore the analysis was carried out on the largest specimen SS-1606 (56.6 g dry wt after extraction). The combined EtOAc and $CHCl_3$ extracts of this specimen (17.9 g) were chromatographed on a SiO_2 column with a solvent gradient system from *n*-hexane to EtOAc and then to MeOH. Detailed analysis of the less-polar compounds was previously reported by our group.[4] Fractions eluted with 100% MeOH were further purified to afford 312.4 mg of **1** as a pure compound.

The positive ion FABMS spectrum of **1** showed a 1:4:6:4:1 quintet for the pseudomolecular ion peak $[M + H]^+$ at m/z = 1005, 1007, 1009, 1011 and 1013, indicating the presence of four bromine atoms in the molecule. The

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complete molecular formula $C_{32}H_{36}Br_4N_{10}O_8$, implying 18 degrees of unsaturation, was established from positive HRFABMS (measured 1008.9488, calculated 1008.9488 for $C_{32}H_{36}{}^{79}Br_2{}^{81}Br_2N_{10}O_8$) and was corroborated by NMR spectroscopy (Table 1). The UV absorption at λ_{max} = 221 nm (ε = 17600) and 279 nm (ε = 9500) indicated the presence of a cyclohexadienyl function, while the IR bands at 3450 and 1665 cm^{-1} showed the presence of an alcohol and an α-iminoamide function, respectively. Inspection of the ^1H and ^{13}C NMR spectra, which showed a series of split signals, suggested that the above groups were included into two 2,4-dibromo-1-hydroxy-3-methoxy-8-carbamoyl spirocyclohexadienyl isoxazole moieties and that they were not symmetrically arranged in the molecule. Decisive information to identify the central part of the molecule was provided by some 2D NMR experiments performed in CD_3OD. In particular, a combination of ^1H-^1H COSY and HSQC spectral data allowed us to identify the following two isolated spin systems: $-CH_2-CH_2-CH-$ (δ_H = 3.28, δ_C = 39.07; δ_H = 2.07 and 2.23, δ_C = 33.92; δ_H = 3.96, δ_C = 33.51) and $-CH_2-CH_2-CH_2-$ (δ_H = 3.29, δ_C = 40.03; δ_H = 1.81, δ_C = 30.10; δ_H = 2.48, δ_C = 23.09). The ^1H-^{13}C HMBC spectrum allowed us to link these fragments separately to the pertinent 2,4-dibromo-1-hydroxy-3-methoxy-8-carbamoyl spirocyclohexadienyl isoxazole moiety, thus determining the substructures **A** and **B** depicted in Figure 1.

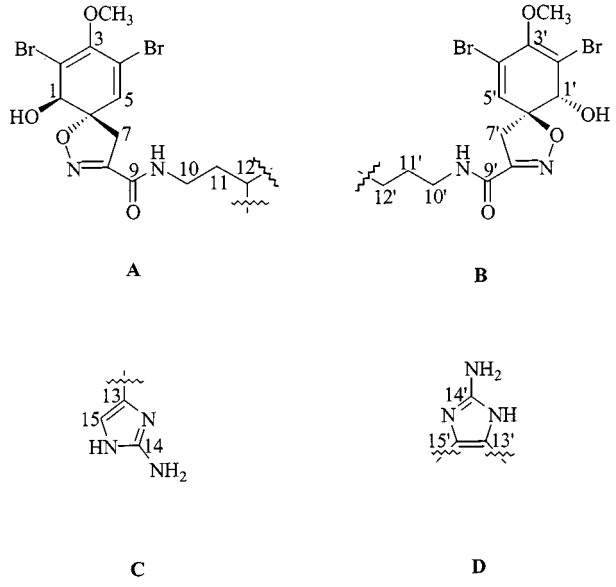

Figure 1. Partial structures leading to the structure of archerine (**1**) generated from a combination of ^1H-^1H COSY, HSQC, ^1H-^{13}C HMBC and ^1H-^{15}N HMBC spectral data

Particularly, ^1H-^{13}C long range couplings were observed between the methylene protons at δ = 3.28 (H_2-10) and C-9 (δ = 161.44) as well as between the methylene protons at δ = 3.29 (H_2-10′) and C-9′ (δ = 161.57). An inspection of

Table 1. ^{13}C and ^1H assignment for archerine **(1)** (CD_3OD)[a] with ^1H-^1H COSY and ^1H-^{13}C HMBC correlations

Position[a]	δ_C, (mult.)	δ_H (mult. *J*/Hz)	^1H-^1H COSY	^1H-^{13}C HMBC[b]
1,1′	75.41 (d)	4.13 (s)	5, 5′, 7a, 7′a, 7b, 7′b	2, 2′, 3, 3′, 5, 5′, 6, 6′,7, 7′
	75.51 (d)	4.14 (s)		
2,2′	114.24 (s)			
3,3′	149.29 (s)			
4,4′	122.75 (s)			
5,5′	132.30 (d)	6.46 (s)	1, 1′, 7a, 7′a	1, 1′, 3, 3′, 4, 4′, 6, 6′, 7, 7′
6,6′	92.39 (s)			
	92.45 (s)			
7a,7′a		3.11 (d, 18.38)	7b, 7′b, 1, 1′, 5, 5′	1, 1′, 5, 5′, 6, 6′, 8, 8′
	40.26 (t)	3.14 (d, 18.38)		
7b,7′b		3.79 (d, 18.38)	7a, 7′a, 1, 1′	1, 1′, 5, 5′, 6, 6′, 8, 8′
		3.83 (d, 18.38)		
8,8′	155.34 (s)			
	155.41 (s)			
9	161.44 (s)			
9′	161.57 (s)			
10	39.07 (t)	3.28[c]	11a, 11b	9, 11, 12
10′	40.03 (t)	3.29[c]	11′	9′, 11′, 12′
11a	33.92 (t)	2.07 (m)	10, 11b, 12	10, 12, 13, 15′
11b		2.23 (m)	10, 11a, 12	
11′	30.10 (t)	1.81 (q, 6.80)	10′, 12′	10′, 12′, 13′
12	33.51 (d)	3.96 (t, 7.35)	11a, 11b, 15	10, 11, 13, 13′, 15, 15′
12′	23.09 (t)	2.48 (t, 6.80)	11′	10′, 11′, 13′, 15′
13	135.87 (s)			
13′	126.09 (s)			
14	150.68 (s)			
14′	149.52 (s)			
15	111.32 (d)	6.36 (s)[d]		13, 14
15′	126.67 (s)			
OCH_3-3,3′	60.44 (q)	3.75 (s)		3, 3′

[a] Assignment based on DEPT, ^1H-^1H COSY, ^1H-^{13}C HSQC, ^1H-^{13}C HMBC and ^1H-^{15}N HMBC experiments. – [b] ^1H correlating with ^{13}C resonance. – [c] Superimposed by other signals. – [d] Chemical shift is within the range ± 0.1 ppm depending on concentration.

the molecular formula showed that the remaining part of the molecule, which had to link the two above determined partial structures, must comprise a $C_6N_6H_7$ fragment, accounting for the remaining six degrees of unsaturation. The ^{13}C NMR experiments indicated that all the six carbon atoms were of the sp^2 type; five of these were fully substituted and one was protonated (δ = 111.32) as indicated by the correlation with the proton at δ = 6.36 in the HSQC spectrum.

The $C_6N_6H_7$ fragment was shown to include two 2-amino imidazole rings whose guanidino carbons resonate at the typical chemical shifts δ = 150.68 and δ = 149.52 (C-14 and C-14′, respectively);[5] of these one was monosubstituted (substructure **C** in Figure 1) and the other one disubstituted (substructure **D** in Figure 1). Strong evidence for the presence of the **C** and **D** units and for their location in the proposed structure was provided by ^1H-^{13}C and ^1H-^{15}N HMBC spectra. In particular, connectivities between H-15/C-13 and H-15/C-14 together with the long range correlations between H-15 and the two nitrogen atoms of the imidazole ring (δ = −237.04 and δ = −200.78) confirmed the proposed substructure **C**. This was substantiated by the observation of the large ^1H-^{13}C coupling constant (198 Hz)[6] of carbon at δ = 111.32 (C-15), which is a typical feature of monosubstituted 2-aminoimidazole rings.[7] A comparison of the ^{13}C NMR chemical shift values with those reported in the literature for aerophobine-2[8] fully agreed with the proposed assignment. The long range couplings H-11a/C-13, H-11b/C-13, H-12/C-13, H-12/C-15 observed in the ^1H-^{13}C HMBC spectrum allowed us to connect substructure **C** to **A**. Similar observations allowed us to define substructure **D** and to link it to the **A**−**C** and **B** units; in particular, the ^1H-^{13}C HMBC spectrum exhibited indicative correlations (H-11a/C-15′, H-11b/C-15′, H-12/C-15′, H_2-12′/C-15′, H_2-11′/C-13′, H_2-12′/C-13′ and H-12/C-13′), while the observed ^{13}C NMR chemical shift values (δ = 126.09, δ = 149.52, δ = 126.67) were found to be quite close to those reported for 4,5-disubstituted 2-aminoimidazoles.[5] The above data were further substantiated by the long range COSY correlation H-12/H-15 and by the interproton contact H-12/H_2-12′, observed in the ROESY spectrum.

The whole of these data allowed us to assign structure **1**, apart from the stereochemistry, to the compound under investigation. The positive FAB MS/MS spectrum provided additional evidence (Figure 2). The spectrum was obtained by using the molecular-related ion at $[M + H]^+$ m/z = 1005 (corresponding to $C_{32}H_{36}{}^{79}Br_4N_{10}O_8$ molecular formula) as

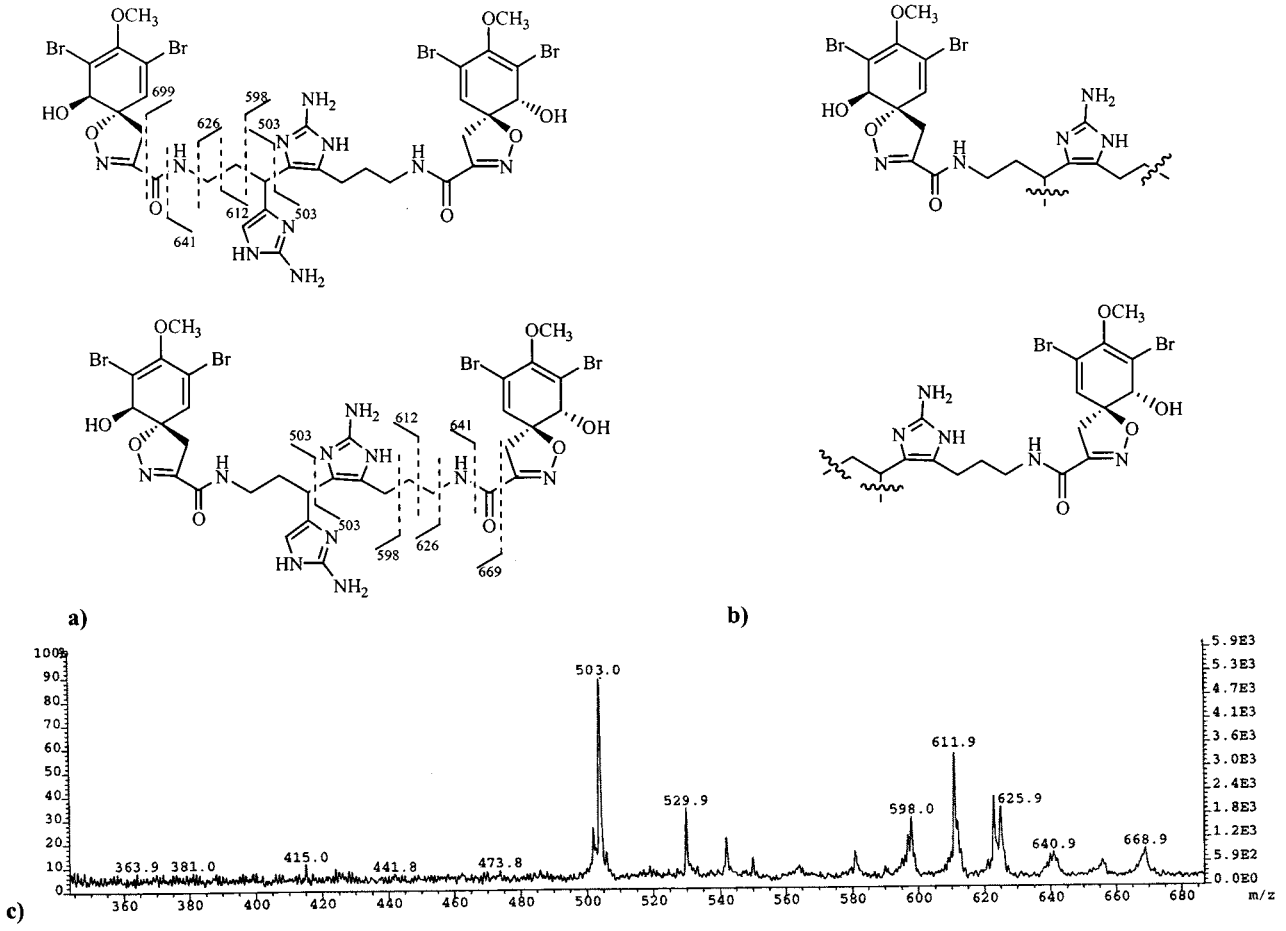

Figure 2. (a) Characteristic fragment ions observed in the tandem mass spectra of archerine (**1**); the fragmentation can occur from both left and right side of the molecule; (b) fragment ions which generate the peak at m/z = 529.9; (c) positive ion FAB MS/MS spectrum of archerine (**1**) with the molecular peak at m/z = 1005 as a precursor

a precursor ion and showed several intense fragment peaks. The fragmentation in this experiment is known to occur by losing neutral species and all the fragment ions in **1** could derive from both the left- and the right side of the molecule. The relatively intense fragment ion at *m/z* = 530 (Figure 2b) derives from the fragment ion at *m/z* = 612 by cleavage of the C-12−C-13 bond and consequent loss of the monosubstituted aminoimidazole ring.

At this point, the determination of the complete structure of compound **1** required the assignment of its stereochemistry. The *trans* geometry of the two vicinal oxygen atoms at C-1 (C-1′) and C-6 (C-6′), which is a common feature of all spirocyclohexadienyl isoxazole bromo compounds, was indicated by the ^{1}H and ^{13}C NMR chemical shift values of the spiro system atoms,[9] thus defining the relative stereochemistry of the chiral centers C-1 (C-1′) and C-6 (C-6′). Their absolute configuration was suggested by the CD spectrum [(MeOH) $[\theta]_{245} = +60000$, $[\theta]_{285} = +53000$] which is analogous to that reported for aerothionin, whose stereochemistry was established by X-ray studies as 1*R*, 1′*R*, 6*S*,

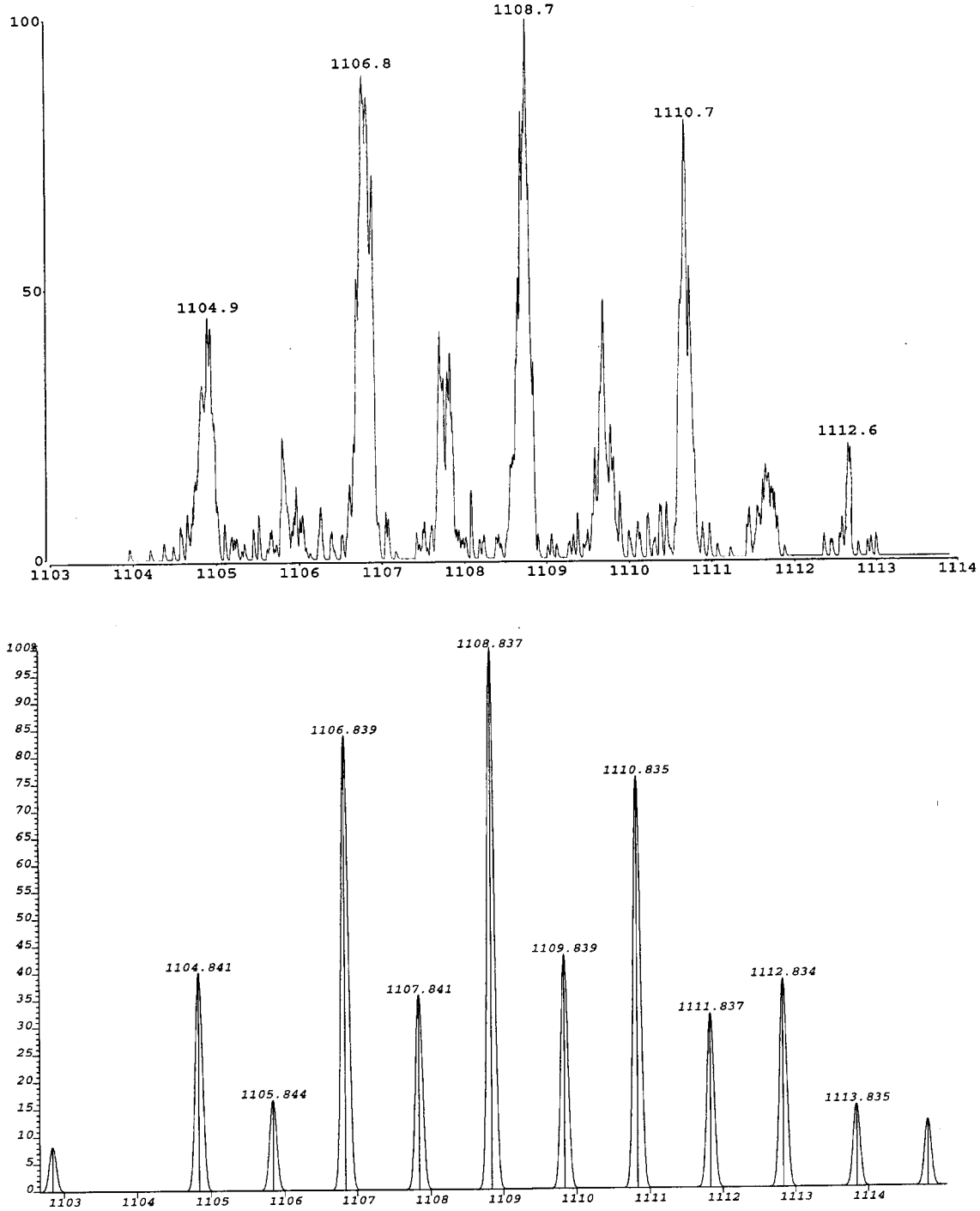

Figure 3. Observed (top) and simulated (below) positive ESIMS spectra of archerine zinc complex

and 6′*S*.[10] The configuration of C-12 still remains to be assigned.

The structure of archerine is suggestive of its biogenetic origin from a [1+1] intermolecular oxidative coupling of two molecules of aerophobin-2 (**2**). Aerophobin-2, which was initially isolated by Cimino et al.[8] from the butanolic extract of *Verongia aerophoba*, was actually contained in the butanolic extracts of each analyzed specimen.

The well-known capacity of imidazole to chelate transition metals, and particularly zinc ion,[11] to give ionic or neutral complexes prompted us to investigate the ability of archerine to form Zn^{II} complexes. Treatment of a methanolic solution of **1** with an excess of a methanolic solution of $ZnCl_2$ at room temp. yielded a zinc-coordinated derivative whose presence was detected by performing the ESIMS positive ion mode experiment. The ESIMS mass spectrum contained a very intense molecular ion cluster at *m/z* = 1104.9, 1106.8, 1108.7, 1110.7 and 1112.6 while the quintet centered at *m/z* = 1009 was completely lacking. The characteristic isotopic pattern suggested the presence of a complex between archerine and ZnCl. This was confirmed by a comparison of the above cluster of peaks with a simulated mass spectrum of $C_{32}H_{36}Br_4ClN_{10}O_8Zn$; the two spectra were fully superimposable (Figure 3). The stereostructure of the archerine zinc complex could not be determined since it rapidly decomposes giving rise to a quite complex mixture.

The biological effect of archerine was assessed for antihistaminic activity on histamine-induced contractions of guinea pig isolated ileum. The histamine agonist (10^{-8}–10^{-4} M) caused a concentration-dependent contraction of the isolated organ. Archerine at the concentration 1.2×10^{-4} M completely abolished the 1 μM response of histamine while a milder effect was observed at the concentrations 1.2×10^{-5} M and 1.2×10^{-6} M (Figure 4). This inhibition was removed by washing the tissue with fresh medium, indicating that the antagonism produced by archerine is reversible. This result is particularly interesting if we consider that archerine appears not to possess all the structural features which are currently used as guidelines for the synthesis of antihistamine drugs.[12]

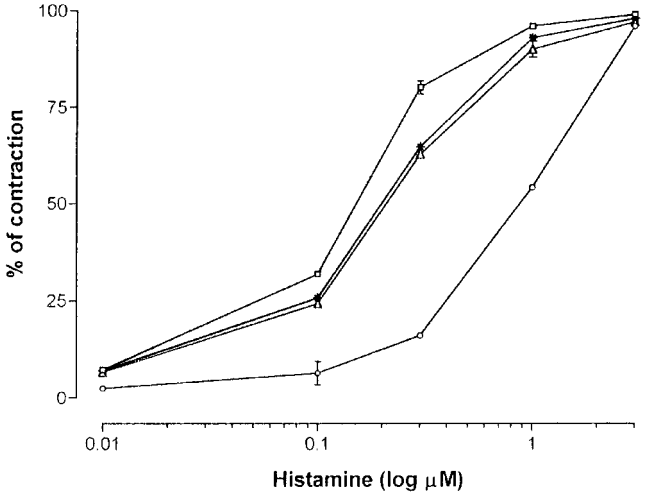

Figure 4. Concentration-response curves depicting histamine-evoked contractions of guinea pig ileum in the absence (□) and presence of 1.2×10^{-4} M (○), 1.2×10^{-5} M (Δ) and 1.2×10^{-6} M (*) archerine; values are percentage of histamine curve maximum response expressed as means ± s.e.m. ($n = 3$–4); differences statistically significant ($P < 0.001$) vs. histamine control

Experimental Section

General: ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a Bruker AMX-500 spectrometer; chemical shifts are referenced to the residual solvent signal (CD_3OD: $\delta_H = 3.34$; $\delta_C = 49.0$). Methyl, methylene and methine carbons were distinguished by a DEPT experiment. Homonuclear ^1H connectivities were determined by using COSY experiments. One bond heteronuclear ^1H-^{13}C connectivities were determined with the Willker, Leibfritz, Kerssebaum, and Bermel HSQC pulse sequence[13] on a Bruker DRX-600 spectrometer. Two- and three bond ^1H-^{13}C connectivities were determined by HMBC experiments optimized for a $^{2,3}J$ of 10 Hz on a Bruker DRX-600 spectrometer. Two- and three bond ^1H-^{15}N connectivities were determined by HMBC experiments optimized for a $^{2,3}J$ of 10 Hz on a Bruker AMX-500 spectrometer; chemical shifts are referenced to the nitromethane signal (CH_3NO_2: $\delta_N = 0$). – Low- and high resolution FABMS (positive ion mode) were performed by M-Scan S. A. (12, chemin des Aulx, 1228 Planles-Ouates, Switzerland) on a VG Analytical ZAB 2SE high field mass spectrometer. Positive FAB MS/MS was carried out with an AutoSpecTOF mass spectrometer (glycerol matrix). Positive ESI MS was carried out with an LCQ Finnigan (ion trap) mass spectrometer. – FT-IR spectra were recorded on a Bruker IFS-48 spectrophotometer with a KBr matrix. – UV spectra were performed on a Beckman DU70 spectrophotometer in MeOH solution. CD spectra were measured on a JASCO 500 A polarimeter in MeOH solution. – Medium pressure liquid chromatography (MPLC) was performed on a Büchi 861 apparatus using SiO_2 (230–400 mesh) and RP-18 (40–63 μm) stationary phases.

Collection, Extraction and Isolation: Specimens of the sponge *A. archeri* were collected in summer 1990 along the coasts of Little San Salvador Island (PSS-2105) at 15 m depth, San Salvador Island (SS-1606) at 18 m depth and Grand Bahama Island (GB-2505) at 20 m depth. The organisms were kept frozen at −20 °C until used and identified by Prof. M. Pansini (Dip.Te.Ris., Universita di Genova, Italy). Reference specimens are deposited as sub-samples in the collection of the Dip.Te.Ris. under the same voucher numbers.

All the specimens were separately homogenized and extracted with MeOH/toluene 3:1 (3 × 1 L) and subsequently with $CHCl_3$ (3 × 1 L) at room temperature. The combined MeOH/toluene solutions, after filtration, were concentrated in vacuo to give an aqueous suspension which was subsequently extracted initially with EtOAc and then with *n*BuOH. TLC analysis of the combined EtOAc and $CHCl_3$ extracts and of the BuOH extracts indicated that the three analyzed specimens had a very similar metabolic content and therefore the isolation and quantitation of the metabolites were carried out on the largest specimen SS-1606 (56.6 g dry wt after extraction). The combined EtOAc and $CHCl_3$ extracts of this specimen (17.9 g of a dark brown viscous oil) were chromatographed by MPLC on a Si gel column using a solvent gradient system from *n*-hexane to EtOAc and then to MeOH. Fractions eluted with 100% MeOH were rechromatographed by MPLC using an RP-18 column (40–63 μm) eluted with a linear gradient solvent system from 100% H_2O to 100% MeOH. Compound **1** (312.4 mg) emerged from the column as a pure compound with H_2O/MeOH = 4:6.

The butyl alcohol soluble material (14 g) was subjected to a medium pressure liquid chromatography on an RP-18 column using solvents of decreasing polarity from H_2O to MeOH and then to $CHCl_3$. The fractions eluted with H_2O/MeOH = 2:8 contained 50 mg of aerophobine-2 **(2)** identified by comparison of its spectroscopic properties with literature values.[8]

Archerine (1): Brown amorphous solid; $[\alpha]_D^{25} = +111.4$ ($c = 0.07$, MeOH). − UV (MeOH): $\lambda_{max} = 221$ nm ($\varepsilon = 17600$), 279 nm ($\varepsilon = 9500$). − CD (MeOH): $[\theta]_{245} = +60000$, $[\theta]_{285} = +53000$. − IR (KBr matrix): $\nu_{max} = 3450$ and 1665 cm^{-1}. − LR-FABMS $[M + H]^+$: *m/z* = 1005, 1007, 1009, 1011, 1013. − HR-FABMS: observed $[M + H]^+$ peak *m/z* = 1008.9488; calcd. for $C_{32}H_{36}{}^{79}Br_2{}^{81}Br_2N_{10}O_8$, 1008.9488. − ^1H and ^{13}C NMR spectroscopic data in CD_3OD, see Table 1. Observed ^1H-^{15}N correlations from a ^1H-^{15}N HMBC spectrum in CD_3OD: $\delta_H = 6.36$ (H-15)/$\delta_N = -200.78$; $\delta_H = 6.36$ (H-15)/$\delta_N = -237.04$; $\delta_H = 3.11$, 3.79 (H_2-7)/$\delta_N = -0.236$; $\delta_H = 3.14$, 3.83 (H_2-7′)/$\delta_N = -0.236$; $\delta_H = 1.81$ (H_2-11′)/$\delta_N = 262.83$.

Zinc Complex of Archerine: A 0.1 M methanolic solution of $ZnCl_2$ and archerine **(1)** (20 mg in 10 mL) were kept under stirring at room temperature for 30 min. The solution, after evaporation of the solvent, afforded 23.7 mg of a complex whose presence was detected by performing the ESIMS positive ion mode experiment: LR-ESIMS $[M + H]^+$: *m/z* = 1104.9, 1106.8, 1108.7, 1110.7, 1112.6

Biological Assay: Experiments were carried out on male Dunkin Hartley guinea pigs weighing 250−300 g. The animals were killed by being stunned and bled via the carotid arteries. The ileum (3−4 cm long) was removed and mounted vertically in a 10 mL organ bath containing an oxygenated (O_2 95%−CO_2 5%) Tyrode solution (composition in mM: NaCl 136.9; KCl 2.7; $CaCl_2$ 1.8; NaH_2PO_4 0.4; $MgCl_2$ 2.1; $NaHCO_3$ 11.9 and glucose 11.1) at 37 °C and was submitted to a constant tension of 0.5 g. Isotonic contractions were recorded using a transducer (type 7006 Ugo Basile). After a 60−90 min. equilibration period, during which the physiological medium was washed out every 15 min., the ileum was contracted with histamine at different concentrations (10^{-8}−10^{-4} M) every 5 min. and three different concentration response curves were produced. In these specific experiments the following antagonists were also added to the Tyrode solution: propanol 10 μM, atropine 1 μM, phentolamine 1 μM. The tissue was exposed to a single concentration of archerine (**1**) (dissolved in DMSO) and each experiment was repeated 3 or 4 times. Archerine was tested at concentrations 1.2×10^{-4} M, 1.2×10^{-5} M and 1.2×10^{-6} M and was added 15 min. before the agonist addition.

Acknowledgments

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