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REVIEW

Chemical and Biological Aspects of Marine Sponges of the Genus *Xestospongia*

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Contents

1. Introduction. – Marine sponges (phylum Porifera) are sessile marine filter feeders that have developed efficient defense mechanisms against foreign attackers such as viruses, bacteria, or eukaryotic organisms, by production of secondary metabolites to repel them [1]. They are among the richest sources of pharmacologically active chemicals isolated from marine organisms. The *Xestospongia* species (class Desmospongia, order Haplosclerida, family Petrosiidae), known as barrel sponges, are large and common members of the coral reef communities at depths greater than 10 m, all over the Indo-Pacific Ocean and the Caribbean Sea. Since the 1970s, with the development of the investigations of marine natural products, the analysis of the chemical constituents of *Xestospongia* sponges has been carried out consecutively all over the world, particularly in the USA, Japan, and Australia. *Xestospongia* sponges have been established as a rich source of diverse secondary metabolites, including

alkaloids, quinones, sterols, and brominated acetylenic acids. Some of these compounds displayed significant bioactivities, such as cytotoxicity, enzyme inhibition, vasodilatation, *etc*. In this review, we summarize the chemical progress and list the compounds isolated from the genus *Xestospongia* until 2009, and also consider their biological activities.

2. Chemical Constituents. – Since the 1970s, 260 additional chemical constituents have been isolated or detected in marine sponges of the genus *Xestospongia*, including alkaloids, quinones, terpenoids, sterols, and fatty acids. Their structures are shown below, and their names and the corresponding sponge sources are compiled in *Table 1*.

2.1. *Alkaloids.* More than 100 alkaloids have been isolated from the sponge genus *Xestospongia* [2–33]. Ten isoquinoline quinones, **1**–**10**, and their dimeric analogues, renieramycins **11**–**17**, were isolated from the hard, blue Fijian sponge *X. caycedoi* and a blue Philippine sponge of the *Xestospongia* sp. [2–7]. Seven 3-alkylpyridine alkaloids including the three xestamines **18**–**20** and the four hachijodines **21**–**24**, four bis[3-alkyldihydropyridine] macrocycles, cyclostellettamines **25**–**28**, and 16 polycyclic alkaloids biogenetically derived from bis[3-alkyldihydropyridine] macrocycles, **29**–**44**, were isolated from *X. wiedenmayeri*, *X. ingens*, and other *Xestospongia* sp. [8–18]. The three β-carboline alkaloids **45**–**47** and ten manzamine-type alkaloids, **48**–**57**, characterized by a complex pentacyclic diamine linked to C(1) of a β-carboline moiety, were found from the Philippine sponge *X. ashmorica* and an Okinawan marine sponge of the *Xestospongia* sp. [19–22]. Twenty-one macrocyclic quinolizidines, **58**–**78**, including xestospongins, araguspongines, and four macrocyclic 2-oxoquinolizidines were isolated from the Australian and Red Sea sponge *X. exigua* and an Okinawan marine sponge of the species *Xestospongia* [19][23–28]. Nine motuporamine alkaloids, **79**–**87**, were obtained from the Papua New Guinean sponge *X. exigua* [29][30]. Eight aaptamine class alkaloids, **88**–**95**, were isolated from an Indonesian marine sponge *Xestospongia* sp. [31]. Three pyridoacridine alkaloids, **96**–**98**, were isolated from two tropical *Xestospongia* sponges, a Philippine *Xestospongia* sp., and *Xestospongia* cf. *carbonaria* from Micronesia [32]. In addition, three indole compounds, **99**–**101**, were obtained from *X. testudinaria* collected in the South China Sea [33].

2.2. *Quinones.* Twenty-five quinone or hydroquinone derivatives have been isolated from the genus *Xestospongia* [34–43]. Most of them were pentacyclic quinones and hydroquinones, such as **102**–**111**, **117**–**122**, **125**, and **126**, derived from halenaquinone (**102**) or xestoquinone (**105**). Two quinone lactones, xestoquinolides A and B (**112** and **113**, resp.) were isolated from the Fijian sponge *Xestospongia* cf. *carbonaria*. Compound **113** and six adociaquinones, **115**–**118**, **123**, and **124**, contained a taurine moiety ($NHCH_2CH_2SO_2$) in their structures [41][42]. The four compounds **115**, **116**, **123**, and **124** are hexacyclic. Moreover, a novel hexacyclic triazine quinine, noelaquinone (**114**), was isolated from an Indonesian *Xestospongia* sp. [40].

2.3. *Terpenoids. Andersen* and co-workers detected four degraded terpenoids, *i.e.*, xestodiol (**127**) [44], xestenone (**128**) [45], xestolide (**129**), and secoxestenone (**130**) [46], and nine squalene-derived triterpenoid glycosides, **131**–**139** [47][48], from the Northeastern Pacific sponge *X. vanilla*. Three sesquiterpene hydroquinones, strongylin A (**140**) and wiedendiols A and B (**141** and **142**, resp.), were isolated from the Bahamas sponge *X. wiedenmayeri* [49].

Table 1. *Chemical Constituents from Sponges of the Genus* Xestospongia

No.	Compound class and name	Source	Reference
	Alkaloids – Isoquinoline Quinones		
1	Renierol	*X. caycedoi*	[2]
2	Mimosamycin	*X. caycedoi*	[2]
3	Renierone	*Xestospongia* sp.	[3]
4	7-Methoxy-1,6-dimethylisoquinoline-5,8-dione	*Xestospongia* sp.	[3]
5	*N*-Ethylene methyl ketone derivative of renierone	*Xestospongia* sp.	[3]
6	Renierol acetate	*Xestospongia* sp.	[4]
7	Renierol propionate	*Xestospongia* sp.	[4]
8	*N*-Formyl-1,2-dihydrorenierol acetate	*Xestospongia* sp.	[4]
9	*N*-Formyl-1,2-dihydrorenierol propanoate	*Xestospongia* sp.	[4]
10	*N*-Formyl-1,2-dihydrorenierone	*X. caycedoi*	[5]
11	Renieramycin G	*X. caycedoi*	[5]
12	Renieramycin M	*Xestospongia* sp.	[6]
13	Renieramycin N	*Xestospongia* sp.	[6]
14	Renieramycin O	*Xestospongia* sp.	[7]
15	Renieramycin Q	*Xestospongia* sp.	[7]
16	Renieramycin R	*Xestospongia* sp.	[7]
17	Renieramycin S	*Xestospongia* sp.	[7]
	Alkaloids – 3-Alkylpyridine Alkaloids		
18	Xestamine A	*X. wiedenmayeri*	[8]
19	Xestamine B	*X. wiedenmayeri*	[8]
20	Xestamine C	*X. wiedenmayeri*	[8]
21	Hachijodine A	*Xestospongia* sp.	[9]
22	Hachijodine B	*Xestospongia* sp.	[9]
23	Hachijodine C	*Xestospongia* sp.	[9]
24	Hachijodine D	*Xestospongia* sp.	[9]
25	Cyclostellettamine A	*Xestospongia* sp.	[10]
26	Cyclostellettamine G	*Xestospongia* sp.	[10]
27	Dehydrocyclostellettamine D	*Xestospongia* sp.	[10]
28	Dehydrocyclostellettamine E	*Xestospongia* sp.	[10]
29	Ingenamine	*X. ingens*	[11]
30	Ingamine A	*X. ingens*	[12]

Table 1 (cont.)

No.	Compound class and name	Source	Reference
31	Ingamine B	*X. ingens*	[12]
32	Ingenamine B	*X. ingens*	[13]
33	Ingenamine C	*X. ingens*	[13]
34	Ingenamine D	*X. ingens*	[13]
35	Ingenamine E	*X. ingens*	[13]
36	Ingenamine F	*X. ingens*	[13]
37	(−)-Halicyclamine B	*Xestospongia* sp.	[14]
38	Xestocyclamine A	*Xestospongia* sp.	[15][16]
39	Xestocyclamine B	*Xestospongia* sp.	[16]
40	Madangamine A	*X. ingens*	[17][18]
41	Madangamine B	*X. ingens*	[18]
42	Madangamine C	*X. ingens*	[18]
43	Madangamine D	*X. ingens*	[18]
44	Madangamine E	*X. ingens*	[18]
	Alkaloids – β-Carboline Alkaloids		
45	Xestoamine	*Xestospongia* sp.	[19]
46	Xestomanzamine A	*Xestospongia* sp.	[20]
47	Xestomanzamine B	*Xestospongia* sp.	[20]
48	Manzamine A	*X. ashmorica*	[21]
49	Manzamine E	*Xestospongia* sp.	[22]
50	Manzamine F	*Xestospongia* sp.	[22]
51	Manzamine J	*X. ashmorica*	[21]
52	Manzamine X	*Xestospongia* sp.	[20]
53	3,4-Dihydromanzamine A	*X. ashmorica*	[21]
54	6-Deoxymanzamine X	*X. ashmorica*	[21]
55	Manzamine A *N*-oxide	*X. ashmorica*	[21]
56	Manzamine J *N*-oxide	*X. ashmorica*	[21]
57	3,4-Dihydromanzamine A *N*-oxide	*X. ashmorica*	[21]
	Alkaloids – Macrocyclic Quinolizidines		
58	(+)-Xestospongin A	*X. exigua*	[23]
59	(+)-Xestospongin B	*X. exigua*	[23]
60	(−)-Xestospongin C	*X. exigua*	[23]

Table 1 (cont.)

No.	Compound class and name	Source	Reference
61	(+)-Xestospongin D (=(+)-Araguspongine A)	*X. exigua*	[23]
62	(+)-Demethylxestospongin B	*Xestospongia* sp.	[19]
63	(+)-3β,3′β-Dimethylxestospongin C	*Xestospongia* sp.	[24]
64	(+)-(7*S*)-Hydroxyxestospongin A	*Xestospongia* sp.	[24]
65	(+)-Araguspongine B	*Xestospongia* sp.	[25]
66	(+)-Araguspongine C	*Xestospongia* sp.	[25]
67	(−)-Araguspongine D	*Xestospongia* sp.	[25]
68	(+)-Araguspongine E	*Xestospongia* sp.	[25]
69	(+)-Araguspongine F	*Xestospongia* sp.	[25]
70	(−)-Araguspongine G	*Xestospongia* sp.	[25]
71	(+)-Araguspongine H	*Xestospongia* sp.	[25]
72	(−)-Araguspongine J	*Xestospongia* sp.	[25]
73	(+)-Araguspongine K	*X. exigua*	[26]
74	(+)-Araguspongine L	*X. exigua*	[26]
75	Aragupetrosine A	*Xestospongia* sp.	[27]
76	Petrosin	*Xestospongia* sp.	[27]
77	Petrosin A	*Xestospongia* sp.	[27]
78	Xestosin A	*X. exigua*	[28]
	Alkaloids – Other Alkaloids		
79	Motuporamine A	*X. exigua*	[29][30]
80	Motuporamine B	*X. exigua*	[29][30]
81	Motuporamine C	*X. exigua*	[29][30]
82	Motuporamine D	*X. exigua*	[30]
83	Motuporamine E	*X. exigua*	[30]
84	Motuporamine F	*X. exigua*	[30]
85	Motuporamine G	*X. exigua*	[30]
86	Motuporamine H	*X. exigua*	[30]
87	Motuporamine I	*X. exigua*	[30]
88	Aaptamine	*Xestospongia* sp.	[31]
89	Isoaaptamine	*Xestospongia* sp.	[31]
90	Demethyl(oxy)aaptamine	*Xestospongia* sp.	[31]
91	Dimethylketal aaptamine	*Xestospongia* sp.	[31]

Table 1 (cont.)

No.	Compound class and name	Source	Reference
92	Benzo[*de*][1,6]naphthyridine derivative A	*Xestospongia* sp.	[31]
93	Benzo[*de*][1,6]naphthyridine derivative B	*Xestospongia* sp.	[31]
94	Benzo[*de*][1,6]naphthyridine derivative C	*Xestospongia* sp.	[31]
95	Benzo[*de*][1,6]naphthyridine derivative D	*Xestospongia* sp.	[31]
96	Amphimedine	*X.* cf. *carbonaria*	[32]
97	Neoamphimedine	*X.* cf. *carbonaria*	[32]
98	Deoxyamphimedine	*X.* cf. *carbonaria*	[32]
99	1*H*-Indole-3-carboxaldehyde	*X. testudinaria*	[33]
100	1*H*-Indole-3-carboxylic acid	*X. testudinaria*	[33]
101	Ethyl 1*H*-indole-3-carboxylate	*X. testudinaria*	[33]
	Quinones		
102	Halenaquinone	*X. exigua*	[34]
103	Halenaquinol	*X. sapra*	[35]
104	Halenaquinol sulfate	*X. sapra*	[35]
105	Xestoquinone	*X. sapra*	[36]
106	Xestoquinol sulfate	*X. sapra*	[37]
107	Xestosaprol A	*X. sapra*	[37]
108	Xestosaprol B	*X. sapra*	[37]
109	Tetrahydrohalenaquinone A	*X. sapra*	[37]
110	Tetrahydrohalenaquinone B	*X.* cf. *carbonaria*	[38][39]
111	14-Methoxyhalenaquinone	*X.* cf. *carbonaria*	[38]
112	Xestoquinolide A	*X.* cf. *carbonaria*	[38]
113	Xestoquinolide B	*X.* cf. *carbonaria*	[38]
114	Noelaquinone	*Xestospongia* sp.	[40]
115	Adociaquinone A	*Xestospongia* sp.	[41]
116	Adociaquinone B	*Xestospongia* sp.	[41]
117	Secoadociaquinone A	*Xestospongia* sp.	[41]
118	Secoadociaquinone B	*Xestospongia* sp.	[41]
119	14-Methoxyxestoquinone	*Xestospongia* sp.	[41]
120	15-Methoxyxestoquinone	*Xestospongia* sp.	[41]
121	15-Chloro-14-hydroxyxestoquinone	*Xestospongia* sp.	[41]
122	14-Chloro-15-hydroxyxestoquinone	*Xestospongia* sp.	[41]

Table 1 (cont.)

No.	Compound class and name	Source	Reference
123	3-Ketoadociaquinone A	*Xestospongia* sp.	[42]
124	3-Ketoadociaquinone B	*Xestospongia* sp.	[42]
125	13-*O*-Methylxestoquinol sulfate	*Xestospongia* sp.	[42]
126	Xestosaprol C	*X. sapra*	[43]
	Terpenoids		
127	Xestodiol	*X. vanilla*	[44]
128	Xestenone	*X. vanilla*	[45]
129	Xestolide	*X. vanilla*	[46]
130	Secoxestenone	*X. vanilla*	[46]
131	Xestovanin A	*X. vanilla*	[47]
132	Secoxestovanin A	*X. vanilla*	[47]
133	Xestovanin B	*X. vanilla*	[48]
134	Xestovanin C	*X. vanilla*	[48]
135	Dehydroxestovanin A	*X. vanilla*	[48]
136	Epidehydroxestovanin A	*X. vanilla*	[48]
137	Dehydroxestovanin C	*X. vanilla*	[48]
138	Secodehydroxestovanin A	*X. vanilla*	[48]
139	Isoxestovanin A	*X. vanilla*	[48]
140	Strongylin A	*X. wiedenmayeri*	[49]
141	Wiedendiol A	*X. wiedenmayeri*	[49]
142	Wiedendiol B	*X. wiedenmayeri*	[49]
	Sterols – Conventional Sterols		
143	Cholesterol	*X. testudinaria*; *X. muta*	[50]
144	Cholestanol	*X. testudinaria*; *X. muta*	[50]
145	Cholesta-5,22-dien-3β-ol	*X. muta*	[50]
146	Desmosterol	*X. testudinaria*	[50]
147	Epioccelasterol (24*R*) and/or occelasterol (24*S*)	*X. testudinaria*; *X. muta*	[50]
148	Brassicasterol (24*R*) and/or crinosterol (24*S*)	*X. testudinaria*; *X. muta*	[50]
149	24-Methylenecholesterol	*X. testudinaria*	[50]
150	Campesterol (24*R*) and/or 22,23-dihydrobrassicasterol (24*S*)	*X. testudinaria; X. muta*	[50]
151	24-Methylcholestanol	*X. muta*	[50]
152	Isofucostanol	*X. testudinaria*; *X. muta*	[50]

Table 1 (cont.)

No.	Compound class and name	Source	Reference
153	Fucosterol	*X. testudinaria*; *X. muta*	[50]
154	24-Ethylcholesta-5,25-dien-3β-ol	*X. testudinaria*; *X. muta*	[50]
155	26-Methyl-24-methylidenecholesterol	*X. muta*	[50]
156	Sitosterol	*X. testudinaria*; *X. muta*	[50]
157	24,26-Dimethylcholesterol	*X. muta*	[50]
158	Poriferasterol (24*R*) and/or stigmasterol (24*S*)	*X. testudinaria*; *X. muta*	[50]
159	Clionasterol	*X. exigua*	[51]
	Sterols – Sterols with High Degrees of Alkylation		
160	Xestosterol	*X. muta*	[52]
161	Xestostanol	*X. muta*	[52]
162	Mutasterol	*X. muta*	[53]
163	24-Isopropylcholesta-5,25-dien-3β-ol	*Xestospongia* sp.	[50]
164	Pulchrasterol	*Xestospongia* sp.	[54]
165	Stelliferasterol	*Xestospongia* sp.	[54]
166	Δ^7 Isomer of stelliferasterol	*Xestospongia* sp.	[54]
167	Xestospongesterol	*Xestospongia* sp.	[55]
168	Isoxestospongesterol	*Xestospongia* sp.	[55]
169	25-Methylxestosterol	*Xestospongia* sp.	[53]
170	Sutinasterol	*Xestospongia* sp.	[54]
171	24-Ethyl-3β-hydroxy-26,26-dimethylcholest-25-ene	*Xestospongia* sp.	[54]
172	24-Ethyl-3β-hydroxy-26,26,27-trimethylcholesta-7,26(30)-diene	*Xestospongia* sp.	[54]
	Sterols – Sterols with a Cyclopropane Ring		
173	Xestokerol A	*Xestospongia* sp.	[56]
174	Xestokerol B	*Xestospongia* sp.	[56]
175	Aragusterol A	*Xestospongia* sp.	[57]
176	Aragusterol B	*Xestospongia* sp.	[58]
177	Aragusterol C	*Xestospongia* sp.	[59]
178	Aragusterol D (Xestokerol C)	*Xestospongia* sp.	[58]
179	Aragusterol E	*Xestospongia* sp.	[60]
180	Aragusterol F	*Xestospongia* sp.	[60]
181	Aragusterol G	*Xestospongia* sp.	[60]
182	Aragusterol H	*Xestospongia* sp.	[60]

Table 1 (cont.)

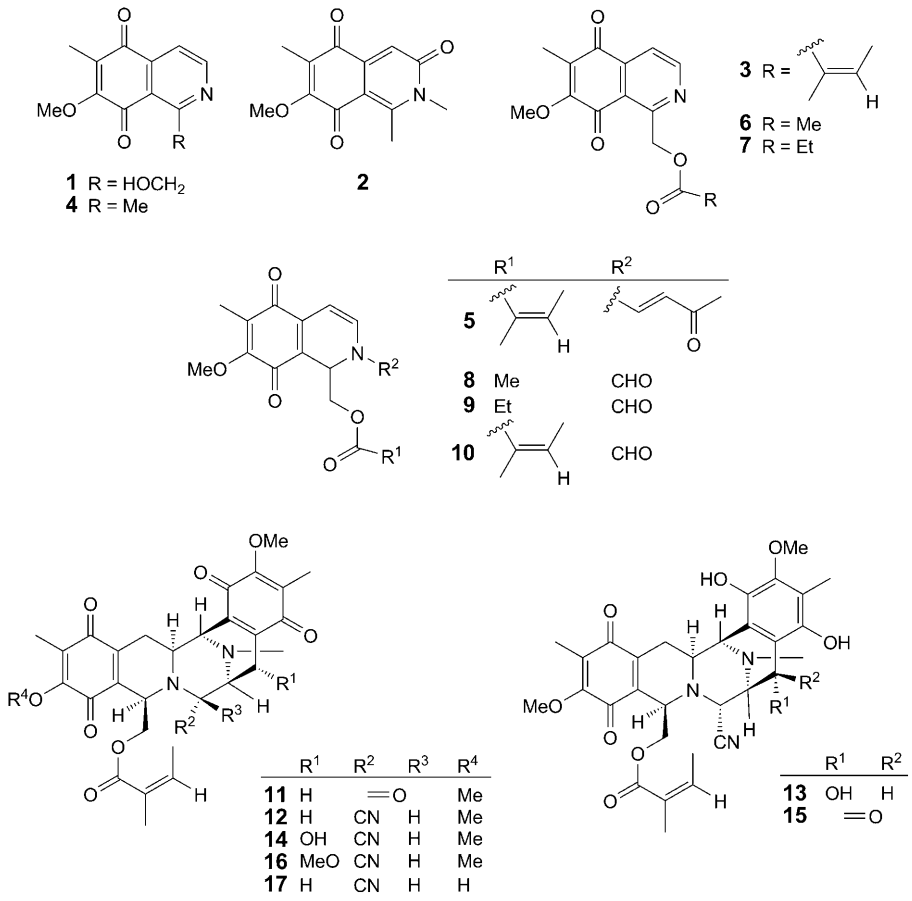
No.	Compound class and name	Source	Reference
183	Aragusteroketal A	*Xestospongia* sp.	[61]
184	Aragusteroketal C	*Xestospongia* sp.	[61]
185	(22*E*)-24,26-Cyclo-5α-cholest-22-en-3β-ol 4′,8′,12′-trimethyltridecanoate	*Xestospongia* sp.	[62]
	Sterols – Polyhydroxy Sterols		
186	Haplosamate A	*Xestospongia* sp.	[63]
187	Haplosamate B	*Xestospongia* sp.	[63]
188	Xestobergsterol A	*X. bergquistia*	[64]
189	Xestobergsterol B	*X. bergquistia*	[64]
190	Ibisterol sulfate B	*Xestospongia* sp.	[65]
191	Ibisterol sulfate C	*Xestospongia* sp.	[65]
192	(22*S*)-4β,5β-Epoxy-2β,3α,12β,22-tetrahydroxy-14α-methylcholesta-7,9(11)-diene-6,24-dione	*Xestospongia* sp.	[65]
	Sterols – Other Sterols		
193	5α,8α-Epidioxy-24α-ethylcholest-6-en-3β-ol	*X. exigua*	[51]
194	Xestosterol (9*E*,17*E*)-18-bromooctadeca-9,17-diene-7,15-diynoate	*X. testudinaria*	[66]
195	Xestosterol (9*E*,17*E*)-18-bromooctadeca-9,17-diene-5,7,15-triynoate	*X. testudinaria*	[66]
	Fatty Acids – Brominated Polyunsaturated Fatty Acids		
196	(7*E*,13*E*,15*Z*)-14,16-Dibromohexadeca-7,13,15-trien-5-ynoic acid	*X. muta*	[67]
197	(9*E*,17*E*)-18-Bromooctadeca-9,17-diene-7,15-diynoic acid	*X. testudinaria*	[68]
198	Methyl (9*E*,17*E*)-18-bromooctadeca-9,17-diene-7,15-diynoate	*X. testudinaria*	[69]
199	Methyl (9*Z*,17*E*)-18-bromooctadeca-9,17-diene-7,15-diynoate	*X. testudinaria*	[69]
200	Methyl (9*E*,17*E*)-18-bromooctadeca-9,17-diene-5,7,15-triynoate	*X. testudinaria*	[69]
201	(9*E*,17*E*)-18,18-Dibromooctadeca-9,17-diene-5,7-diynoic acid	*Xestospongia* sp.	[70]
202	(7*E*,11*E*,15*E*)-16-Bromohexadeca-7,11,15-triene-5,13-diynoic acid	*Xestospongia* sp.	[70]
203	(7*E*,11*E*,15*Z*)-16-Bromohexadeca-7,11,15-triene-5,13-diynoic acid	*Xestospongia* sp.	[70]
204	(7*E*,15*E*)-16-Bromohexadeca-7,15-diene-5,13-diynoic acid	*Xestospongia* sp.	[70]
205	9,9-Dibromonon-8-enoic acid	*Xestospongia* sp.	[70]
206	Xestospongic acid	*X. testudinaria*	[71]
207	Xestospongic acid ethyl ester	*X. testudinaria*	[71]
208	(9*E*,13*E*,17*E*)-18-Bromooctadeca-9,13,17-triene-5,7,15-triynoic acid	*X. muta*	[72]
209	Methyl (9*E*,13*E*,17*E*)-18-bromooctadeca-9,13,17-triene-5,7,15-triynoate	*X. muta*	[72]
210	(7*E*,13*E*,17*E*)-18-Bromooctadeca-7,13,17-triene-5,15-diynoic acid	*X. muta*	[72]

Table 1 (cont.)

No.	Compound class and name	Source	Reference
211	Methyl (7*E*,13*E*,17*E*)-18-bromooctadeca-7,13,17-triene-5,15-diynoate	*X. muta*	[72]
212	(9*E*,17*E*)-18-Bromooctadeca-9,17-diene-5,7,15-triynoic acid	*X. muta*	[72]
213	(9*E*,15*E*)-16-Bromohexadeca-9,15-diene-5,7-diynoic acid	*X. muta*	[72]
214	Methyl (9*E*,15*E*)-16-bromohexadeca-9,15-diene-5,7-diynoate	*X. muta*	[72]
215	(9*E*,17*E*)-18-Bromooctadeca-9,17-diene-5,7-diynoic acid	*X. muta*	[72]
216	Methyl (9*E*,17*E*)-18-bromooctadeca-9,17-diene-5,7-diynoate	*X. muta*	[72]
217	(9*E*,15*E*)-18-Bromooctadeca-9,15-diene-5,7,17-triynoic acid	*X. muta*	[72]
218	(5*E*,11*E*,15*E*,19*E*)-20-Bromoeicosa-5,11,15,19-tetraene-9,17-diynoic acid	*Xestospongia* sp.	[73]
219	(5*Z*,11*E*,15*E*,19*E*)-6,20-Dibromoeicosa-5,11,15,19-tetraene-9,17-diynoic acid	*Xestospongia* sp.	[73]
220	Methyl (4*Z*,6*E*)-14,14-dibromotetradeca-4,6,13-trienoate	*Xestospongia* sp.	[73]
221	(5*Z*,17*E*)-18-Bromooctadeca-5,17-dien-7-ynoic acid	*Xestospongia* sp.	[74]
222	(5*Z*)-18,18-Dibromooctadeca-5,17-dien-7-ynoic acid	*Xestospongia* sp.	[74]
223	Methyl (5*Z*,17*E*)-18-bromooctadeca-5,17-dien-7-ynoate	*Xestospongia* sp.	[74]
224	Methyl (5*Z*)-18,18-dibromooctadeca-5,17-dien-7-ynoate	*Xestospongia* sp.	[74]
225	(17*E*)-18-Bromooctadec-17-en-7-ynoic acid	*Xestospongia* sp.	[74]
226	18,18-Dibromooctadec-17-en-7-ynoic acid	*Xestospongia* sp.	[74]
227	(15*E*)-16-Bromohexadec-15-en-5-ynoic acid	*Xestospongia* sp.	[74]
228	16,16-Dibromohexadec-15-en-5-ynoic acid	*Xestospongia* sp.	[74]
229	(5*E*)-6,16,16-Tribromohexadeca-5,15-dienoic acid	*Xestospongia* sp.	[74]
230	(5*E*,9*Z*)-6-Bromohexadeca-5,9-dienoic acid	*Xestospongia* sp.	[74]
231	(5*E*,9*Z*,24*Z*)-6-Bromooctacosa-5,9,24-trienoic acid	*Xestospongia* sp.	[74]
232	(5*E*,9*Z*,24*Z*)-6-Bromoheptacosa-5,9,24-trienoic acid	*Xestospongia* sp.	[74]
233	(5*E*,9*Z*)-6-Bromo-26-methyloheptacosa-5,9-dienoic acid	*Xestospongia* sp.	[74]
234	(5*E*,9*Z*)-6-Bromo-27-methyloctacosa-5,9-dienoic acid	*Xestospongia* sp.	[74]
235	Mutafuran A	*X. muta*	[75]
236	Mutafuran B	*X. muta*	[75]
237	Mutafuran C	*X. muta*	[75]
238	Mutafuran D	*X. muta*	[75]
239	Mutafuran E	*X. muta*	[75]
240	Mutafuran F	*X. muta*	[75]
241	Mutafuran G	*X. muta*	[75]

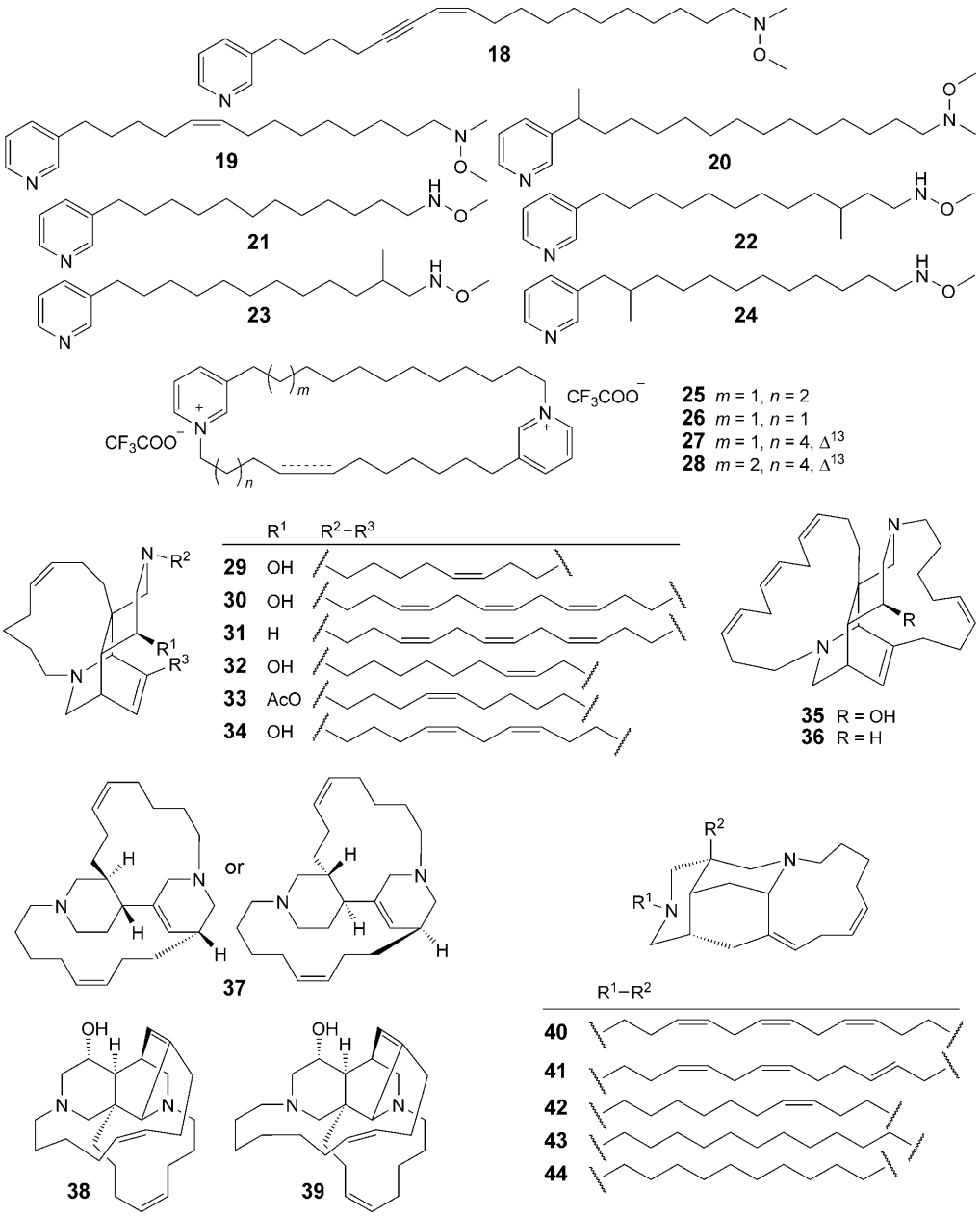
Table 1 (cont.)

No.	Compound class and name	Source	Reference
	Fatty Acids – Conventional Fatty Acids		
242	3,7,11-Trimethyldodecanoic acid	*X. muta*	[76]
243	Tetradecanoic (myristic) acid	*X. muta*	[76]
244	12-Methyltetradecanoic acid	*X. muta*	[76]
245	Pentadecanoic acid	*X. muta*	[76]
246	14-Methylpentadecanoic acid	*X. muta*	[76]
247	Hexadeca-5,9-dienoic acid	*X. muta*	[76]
248	Hexadec-9-enoic (palmitoleic) acid	*X. muta*	[76]
249	Hexadecanoic (palmitic) acid	*X. muta*	[76]
250	12-Methylhexadecanoic acid	*X. muta*	[76]
251	15-Methylhexadecanoic acid	*X. muta*	[76]
252	14-Methylhexadecanoic acid	*X. muta*	[76]
253	Heptadecanoic acid	*X. muta*	[76]
254	Octadecanoic (stearic) acid	*X. muta*	[76]
255	16-Methyloctadecanoic acid	*X. muta*	[76]
256	Nonadecanoic acid	*X. muta*	[76]
257	Eicosanoic (arachidic) acid	*X. muta*	[76]
258	Docosanoic (behenic) acid	*X. muta*	[76]
259	Octacosa-5,9,19-trienoic acid	*X. muta*	[76]
	Fatty Acids – Others		
260	Nepheliosyne A	*Xestospongia* sp.	[77]
261	2-Oxo-2,5-dihydrofuran-5-acetic acid methyl ester	*Xestospongia* sp.	[78]
262	Xestin A	*Xestospongia* sp.	[78]
263	Xestin B	*Xestospongia* sp.	[78]
264	(2*S*,3*S*)-2-Aminotetradeca-5,7-dien-3-ol	*Xestospongia* sp.	[79]
265	(2*S*,3*R*)-2-Aminotetradeca-5,7-dien-3-ol	*Xestospongia* sp.	[79]
266	Xestoaminol A	*Xestospongia* sp.	[80]
267	Xestoaminol B	*Xestospongia* sp.	[80]
268	Xestoaminol C	*Xestospongia* sp.	[80]

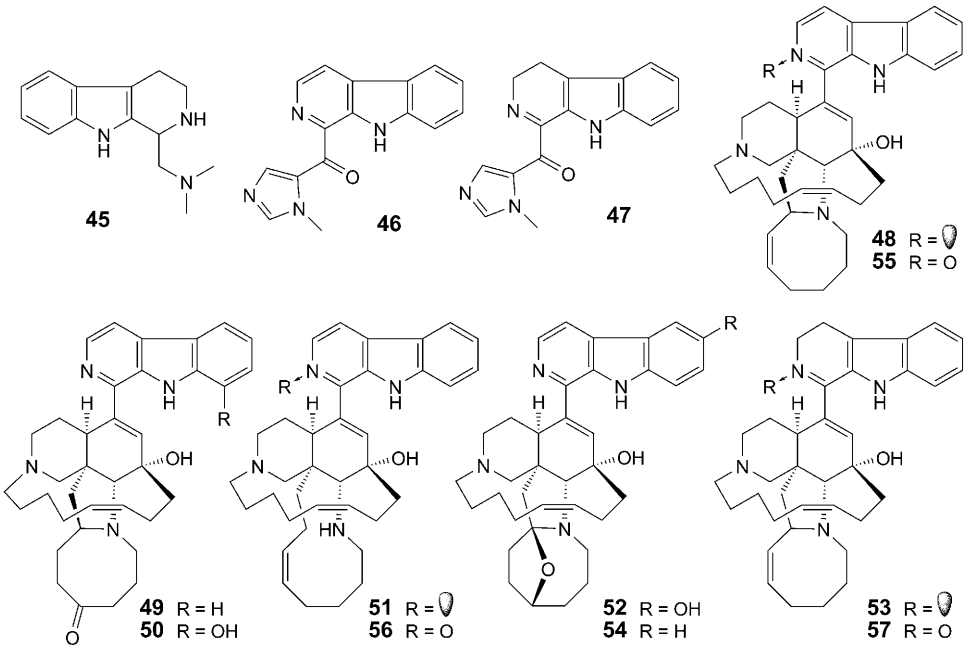


2.4. *Sterols.* Sterols are widely distributed in marine sponges. Analysis by GC and GC/MS allowed determination of the sterol composition of the *Xestospongia* sp., and the C_{27}, C_{28}, and C_{29} conventional sterols **143**–**159** were shown to be widely distributed [50][51]. Some sterols with higher degrees of alkylation (C_{30}, C_{31}, and C_{32}), **160**–**172**, have also been found in some *Xestospongia* sp. [50][52–55], and most of them were minor or trace components. However, xestosterol (**160**; C_{30}) was shown to be the major sterol component (46%) of the Caribbean sponge *X. muta* [52], and sutinasterol (**170**; C_{31}) constituted the bulk (94%) of the sterol fraction of a *Xestospongia* sp. from Puerto Rico [54].

The twelve 26,27-cyclosterols **173**–**184** [56–61] were isolated by Japanese researchers from an Okinawan *Xestospongia* sp. Seven compounds, *i.e.*, xestokerols A and B (**173** and **174**, resp.) [56], aragusterols A–C (**175**–**177**) [57–59], and aragusteroketals A (**183**) and C (**184**) [61], are very rare C(20)-oxidized steroids from marine origin. A fatty acid ester of 24,26-cyclosterol, **185**, was isolated from a deep water marine sponge of the *Xestospongia* sp. collected in the Bahamas at a depth of 170 feet [62]. The seven polyhydroxysterols **186**–**192** were isolated from the Okinawan



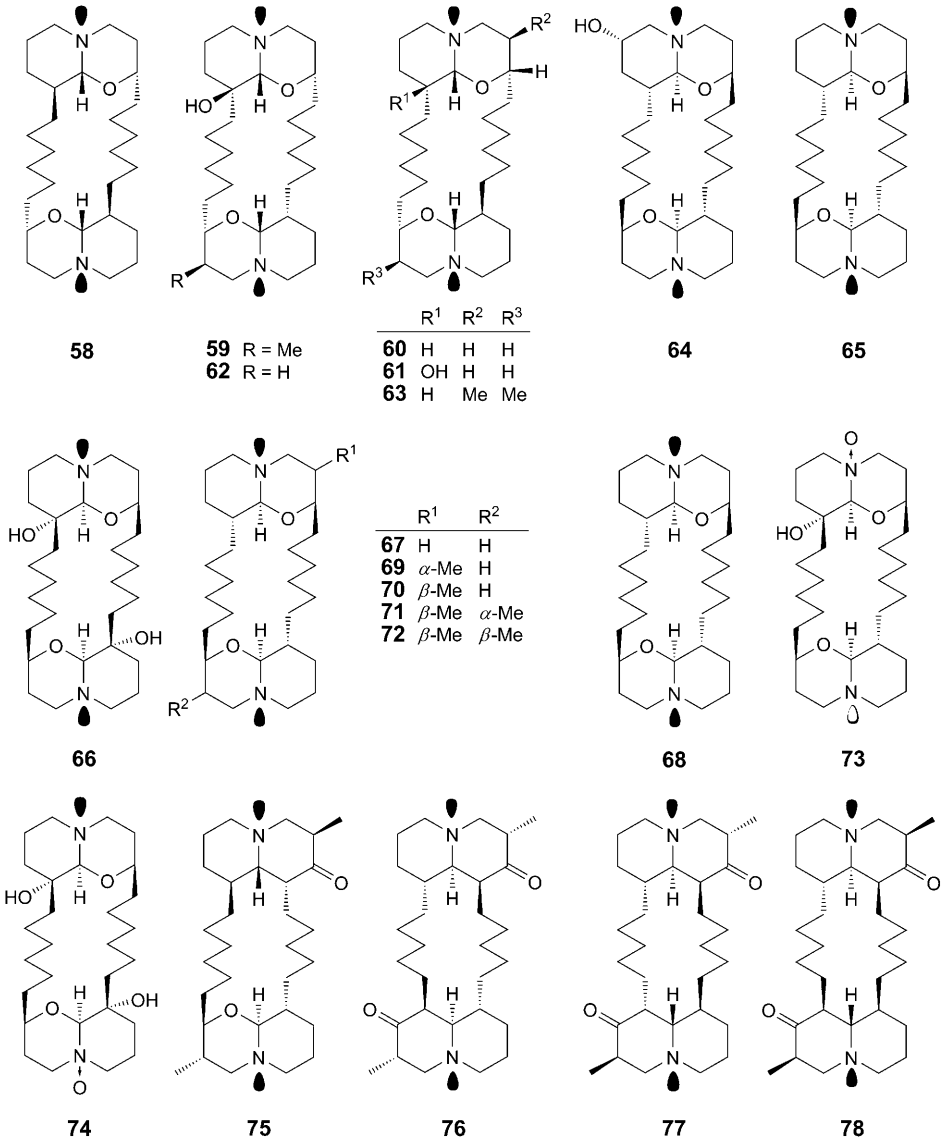
sponge *X. bergquistia* and *Xestospongia* sp. collected in the Philippines [63–65], and four of them, haplosamates A and B (**186** and **187**, resp.) [63] and ibisterol sulfates B and C (**190** and **191**, resp.) [65], were sulfamates. In addition, an 5α,8α-epidioxysterol, **193**, was obtained from the Thai sponge *X. exigua* [51], and two xestosterol esters of



brominated acetylenic fatty acids, **194** and **195**, were isolated from the sponge *X. testudinaria* collected in Coral Sea, Australia [66].

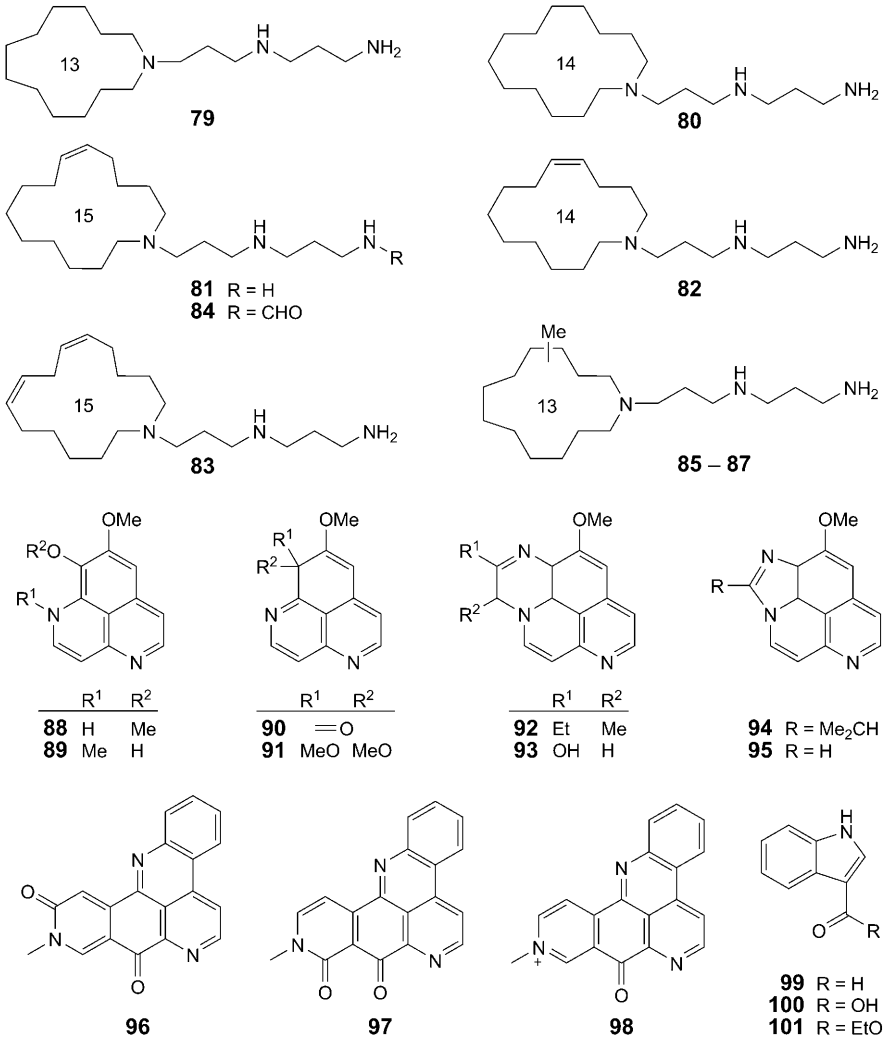
2.5. *Fatty Acids.* Since 1978, 46 brominated polyunsaturated fatty acids (BPUFAs), *i.e.*, **196**–**241**, were isolated from *X. muta*, *X. testudinaria*, and other *Xestospongia* sp. [67–75]. For convenience, BPUFAs were often characterized as their methyl esters, and most of them were brominated acetylenic acids, except eight brominated olefinic acids or esters, **205**, **220**, and **229**–**234** [70][73][74]. Seven brominated ene-yne tetrahydrofurans, mutafurans A–G (**235**–**241**, resp.), the first tetrahydrofuranyl BPUFAs from marine sponges, were isolated from the Bahamian sponge *X. muta* [75]. Besides those BPUFAs, 18 conventional fatty acids, **242**–**259**, were identified from the Caribbean sponge *X. muta* [76]. Furthermore, a new C_{47} acetylenic acid, nepheliosyne A (**260**), was isolated from an Okinawan *Xestospongia* sp. [77]. A heterocyclic fatty acid methyl ester (**261**) and its derivates, xestins A and B (**262** and **263**, resp.), were isolated from a *Xestospongia* sp. from Fiji [78]. In addition, five amino alcohols, **264**–**268**, were isolated from marine sponges of the genus *Xestospongia* [79][80].

3. Biological Activities. – 3.1. *Cardiovascular Activity.* In 1985, *Nakamura et al.* examined pharmacological activities of extracts of *ca.* 500 species of marine organisms by using isolated muscle preparations, and the extract of the Okinawan sponge *X. sapra* showed a powerful cardiotonic activity [36]. Xestoquinone (**105**) was then isolated and identified as a bioactive component from *X. sapra*. Compound **105** was the first example of marine natural products having parallelism between the inotropic action

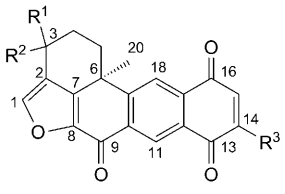


and Na^+/K^+-ATPase inhibition as cardiotonic glycosides [81][82]. It might provide a novel lead compound for valuable cardiotonic agents.

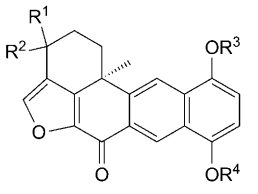
In 1987, xestospongins A–D (**58**–**61**, resp.), four vasodilative compounds that can induce relaxation of blood vessels *in vivo*, represented a new class of macrocyclic quinolizidines isolated from *Xestospongia* [23]. Other macrocyclic quinolizidines, such as araguspongines C–E (**66**–**68**, resp.) and J (**72**) [25], aragupetrosine A (**75**), petrosin (**77**), and petrosin A (**78**), also showed vasodilative activities in a perfusion model experiment using an isolated mesenteric artery of SD rats [27]. Compounds **58**–**61**



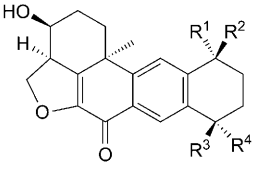
were shown to be potent blockers of the inositol 1,4,5-trisphosphate (IP_3)-induced Ca^{2+} release in bi-directional Ca^{2+}-flux conditions [83][84]. Inhibitory mechanisms of xestospongin C (**60**) on contraction and ion channels in the intestinal smooth muscle were discussed, and it was shown that **60** was a selective blocker of the IP_3 receptor in permeabilized cells, but not in cells with intact plasma membranes [85]. Another report showed that hydroxylated bis-oxaquinolizadine derivatives **60**, **61**, **64**, and **66** were novel bifunctional reagents that may be useful in elucidating how IP_3 receptors and ryanodine receptors contribute to cell signaling [86]. Macrocyclic quinolizidines also showed inhibitory activities against collagen- or epinephrine-induced platelet aggregation [87]. Strongylin A (**140**) and wiedendiols A and B (**141** and **142**, resp.) showed inhibitory activities of the cholesteryl ester transfer protein (CETP) [49].



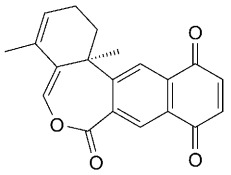
	R^1	R^2	R^3
102	=O		H
105	H	H	H
111	=O		MeO



	R^1	R^2	R^3	R^4
103	=O		H	H
104	=O		$NaSO_3$	H
106	H	H	$NaSO_3$	H
125	H	H	$NaSO_3$	MeO



	R^1	R^2	R^3	R^4
107	H,OH			=O
108	H,OH		H,OH	
109	=O		H	OH
110	OH	H		=O



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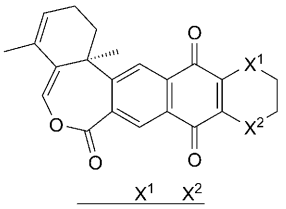
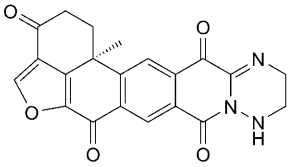


	X^1	X^2
113	NH,SO_2	



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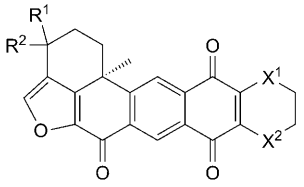
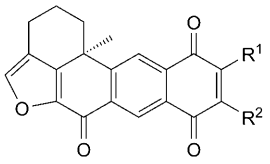
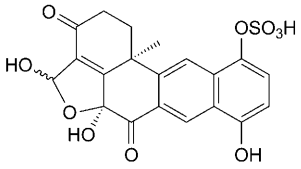


	R^1	R^2	X^1	X^2
115	H	H	NH	SO_2
116	H	H	SO_2	NH
123	=O		NH	SO_2
124	=O		SO_2	NH



	R^1	R^2
117	$HSO_3(CH_2)_2NH$	H
118	H	$HSO_3(CH_2)_2NH$
119	H	MeO
120	MeO	H
121	Cl	OH
122	OH	Cl



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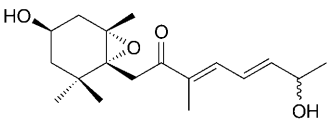
3.2. *Cytotoxic and Antitumor Activities.* Many compounds from the sponges of the genus *Xestospongia* were reported for cytotoxic activities, including **1**, **11**–**17**, **20**–**31**, **48**–**50**, **56**, **57**, **59**, **61**, **62**, **79**–**81**, **88**–**91**, **102**, **105**, **115**–**122**, **173**–**184**, and **262** [2][5–12][19][21–23][29–31][41][56–61][88]. A cytotoxic structure–activity relationship (SAR) study of xestoquinone (**105**) and its analogues indicated that the terminal quinine structure of the polycyclic molecules is important for the activity (**105**, *etc.*) and that the presence of a ketone group at C(3) of the opposite terminus dramatically diminishes the activity (**102**, *etc.*) [88]. However, gel electrophoretic DNA and flow cytometric analysis of PC12 cells treated with halenaquinone (**102**) showed a typical apoptotic DNA ladder in a concentration- and time-dependent manner, while **105** with a CH_2 group at C(3) failed to induce apoptosis. Compound **102** causes the death of PC12 cells through an apoptotic process, and the mechanism of apoptosis induced by **102** may be partially explained by the inhibition of phosphatidylinositol 3-kinase activity [89]. Aragusterol A (**175**) strongly inhibited the cell proliferation of KB,



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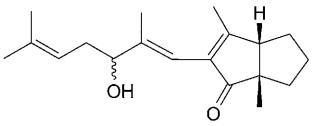

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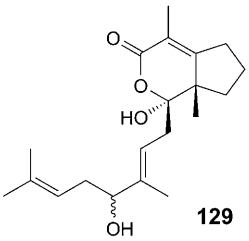

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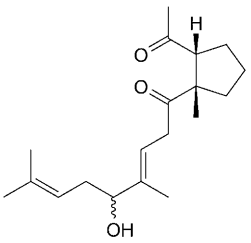

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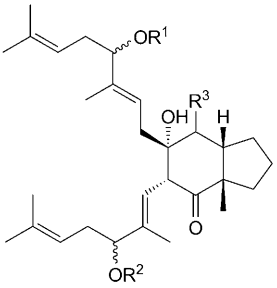
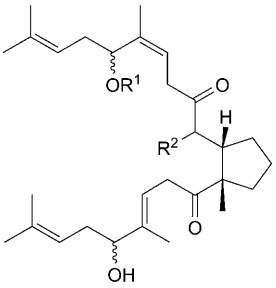
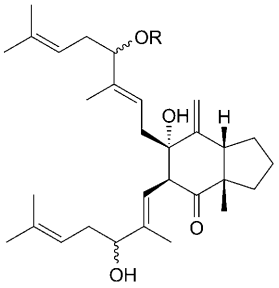


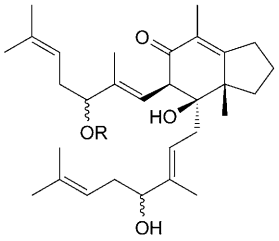
	R^1	R^2	R^3
131	DSac	H	Me
133	DSac	MSac	Me
134	TSac	H	Me
135	DSac	H	$=CH_2$
137	TSac	H	$=CH_2$



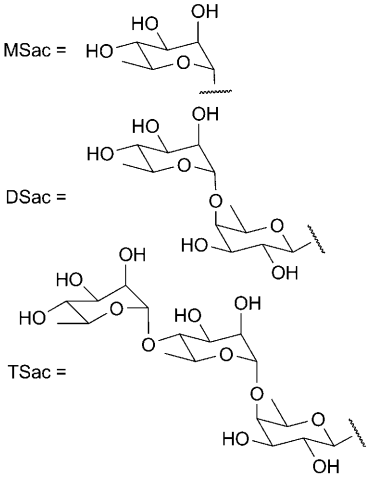
	R^1	R^2
132	DSac	Me
138	DSac	$=CH_2$

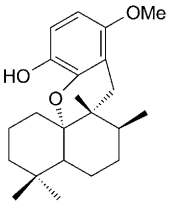


136 R = DSac



139 R = DSac





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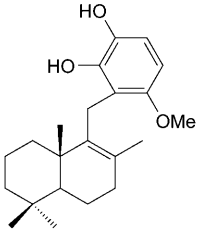

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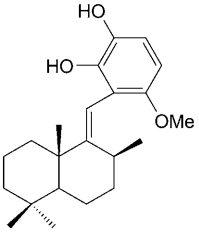

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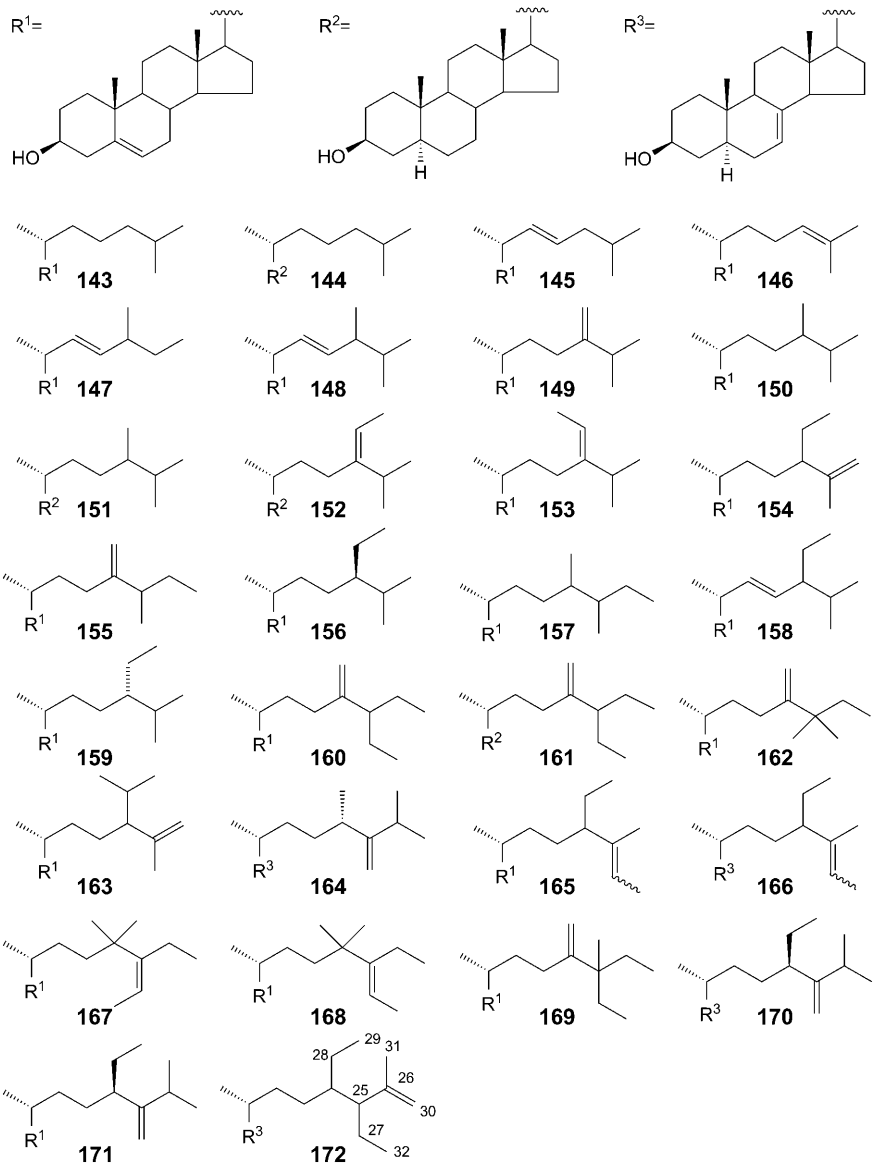
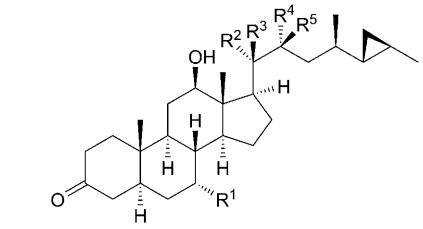
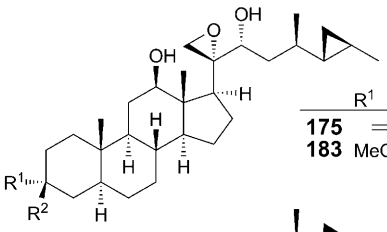


HeLaS3, P388, and LoVo cells *in vitro*, and also showed potent *in vivo* antitumor activity toward P388 and L1210 in mice [57]. Aragusterol C (**177**) also showed potent antitumor activity *in vivo* against L1210 cells in mice [59].

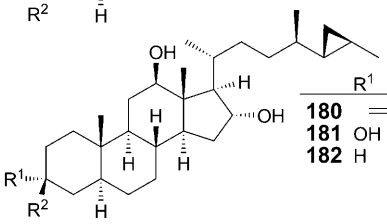
Eight quinone compounds, adociaquinones **115**–**118** and xestoquinones **119**–**122**, showed inhibition of topoisomerase II in catalytic DNA unwinding and/or decatenation assays [41]. Compounds **105** and **102** also showed inhibitory activities of topoisomerase I [90]. Motuporamines A–C (**79**–**81**, resp.) and a mixture of motuporamines G–I (**85**–



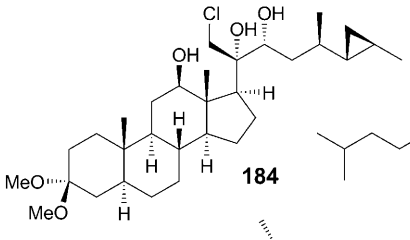
	R^1	R^2	R^3	R^4	R^5
173	H	OH,$HOCH_2$		H,OH	
174	OH	OH,Me		H	H
176	H	Me	OH	H	H
177	H	OH	$ClCH_2$	OH	H
178	H	$=CH_2$		$=O$	
179	H	$=CH_2$		OH	H



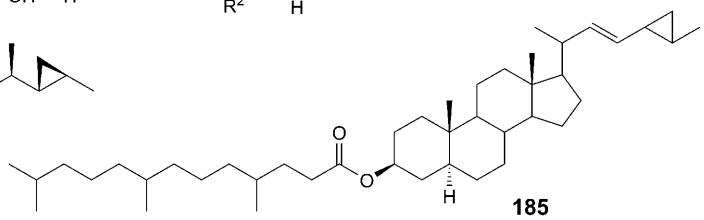
	R^1	R^2
175	$=O$	
183	MeO	MeO



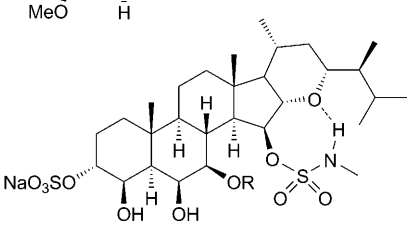
	R^1	R^2
180	$=O$	
181	OH	H
182	H	OH



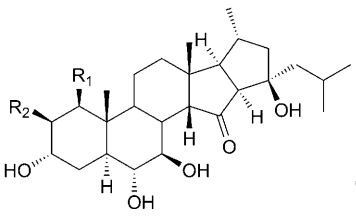
184



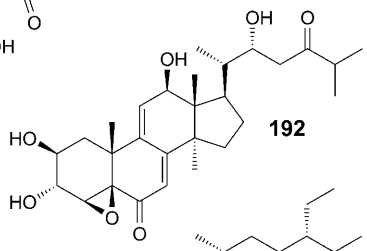
185



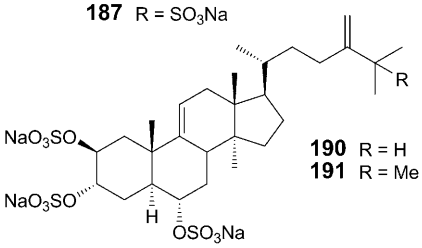
186 R = H
187 R = SO_3Na



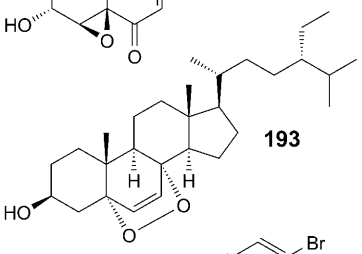
188 $R^1 = R^2 = H$
189 $R^1 = R^2 = OH$



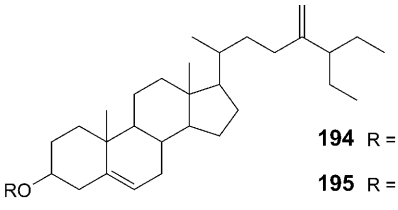
192



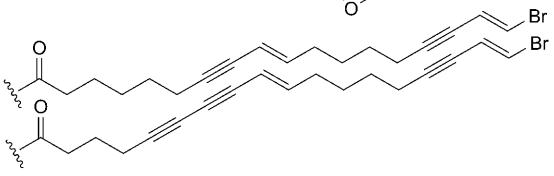
190 R = H
191 R = Me

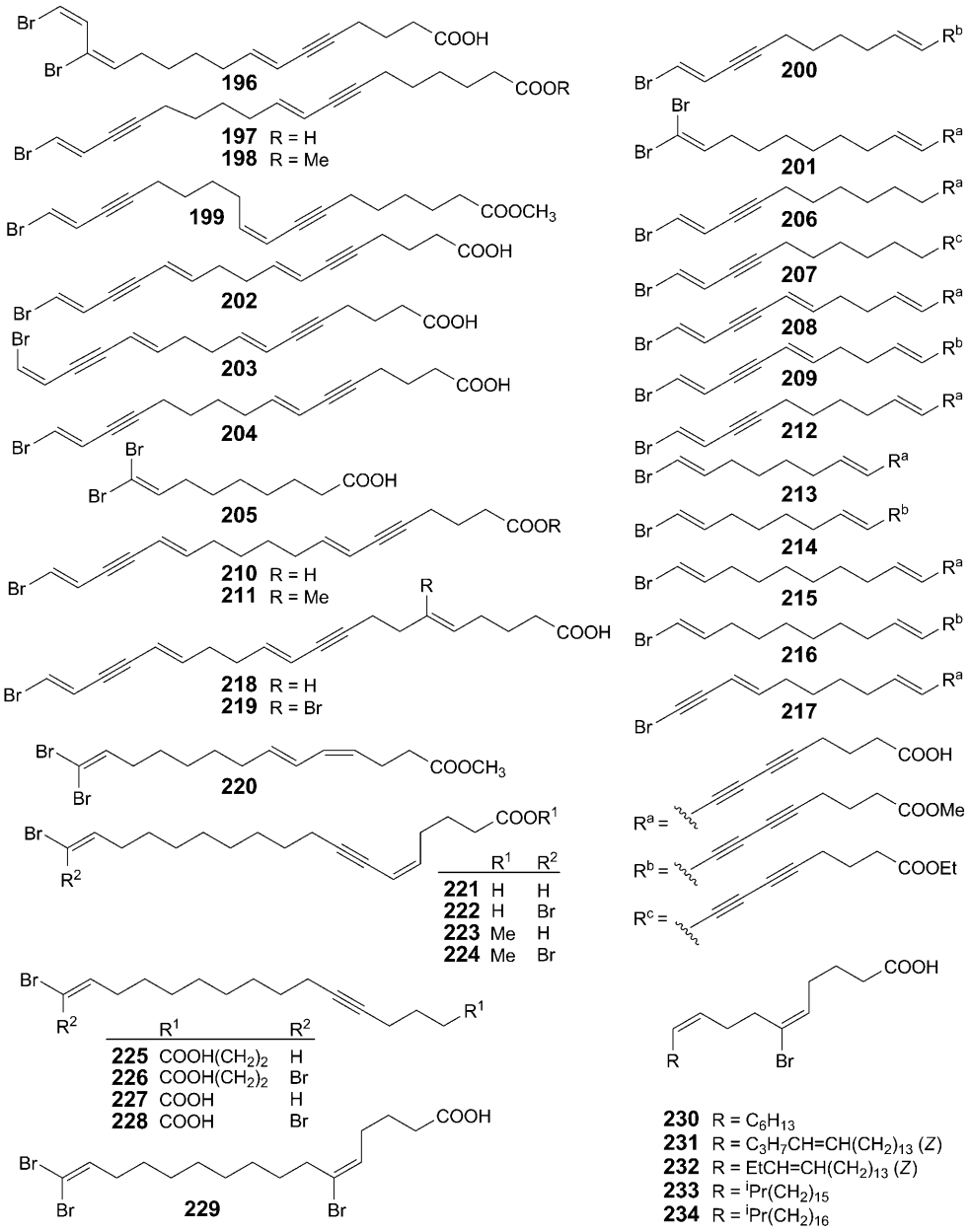


193

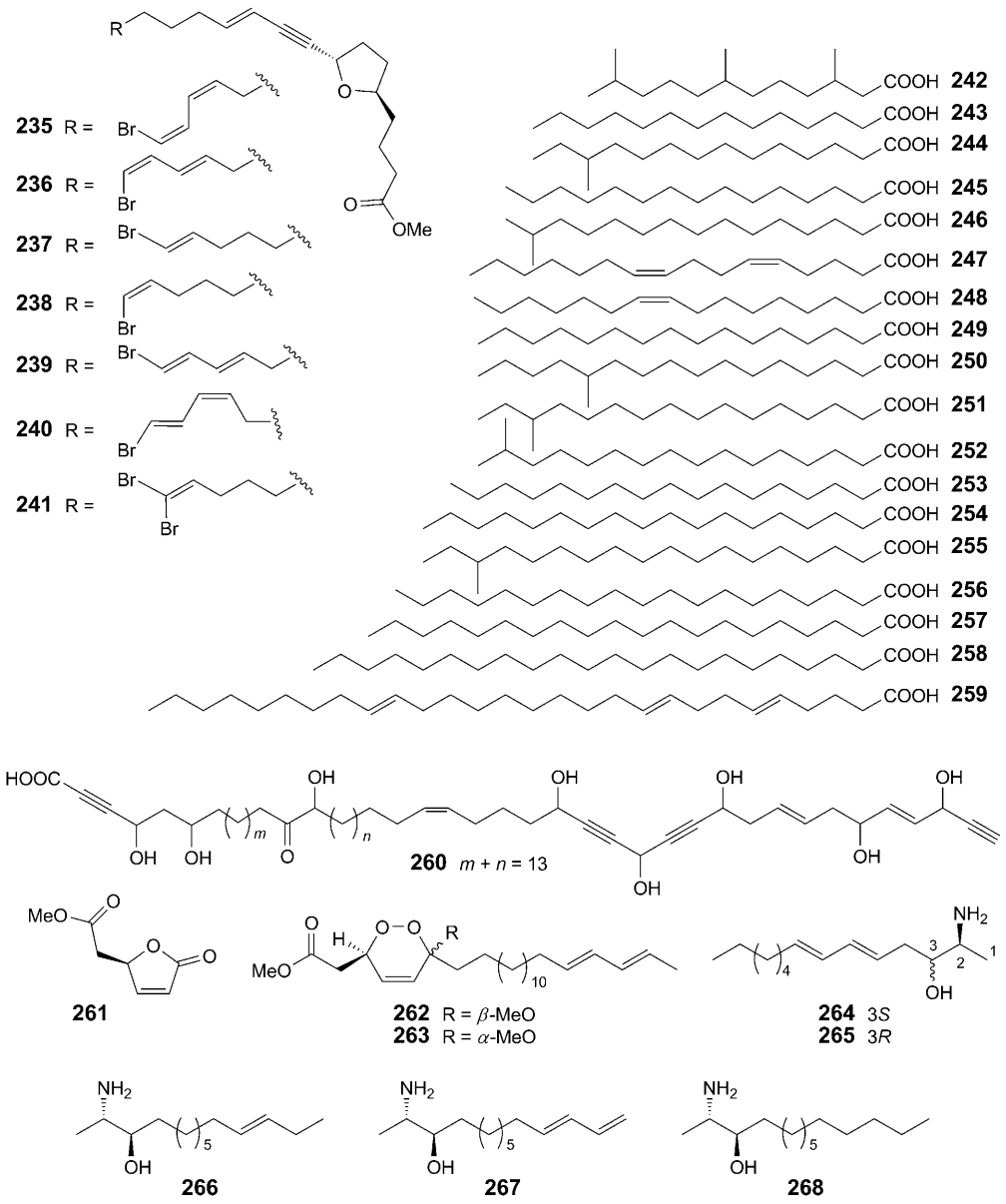


194 R =
195 R =





87, resp.) showed significant anti-invasive activity (IC_{50} values < 15 μM), and motuporamine C (**81**) also revealed to be an anti-angiogenesis agent [30]. It was suggested that they could block metastasis and angiogenesis by inhibiting invasion and be useful in treating cancers of various genetic origins. A series of analogues of the motuporamines had been synthesized and evaluated for anti-invasive activity. The SAR results revealed



that a saturated 15-membered cyclic amine fused to the natural motuporamine diamine side chain (*i.e.*, saturated **81**) represented the optimal structure for anti-invasive activity in this family.

3.3. *HIV Protease Inhibitory Activity.* Four steroidal sulfamate esters, haplosamates A and B (**186** and **187**, resp.) and ibisterol sulfates B and C (**190** and **191**, resp.), and the

epoxy-polyhydroxysterol **192** showed HIV-1 integrase inhibitory activities with IC_{50} values of 50.0, 15.0, 2.3, 1.8, and 26.0 μg/ml, respectively [63][65]. Many brominated acetylenic acids isolated from *Xestospongia* sp., such as **202**, **208**, **212**, and **215**–**217**, also showed HIV-1 protease inhibitory activities with IC_{50} values of 6–12 μM [72].

3.4. *Other Enzyme-Inhibitory Activities.* Derivatives of **102** and **105** showed various enzyme inhibitory activities besides the phosphatidylinositol 3-kinase and topoisomerase I and II inhibitory activities mentioned above. Compound **105** inhibited both Ca^{2+} and K^+-ATPase of skeletal muscle myosin [91]. SAR Investigations showed that **102** and three synthetic analogues with a quinone structure significantly inhibited Ca^{2+} ATPase activity. In contrast, four xestoquinone analogues in which the quinone structure was converted to quinol dimethyl ether did not inhibit the Ca^{2+} ATPase activity [92]. The protein tyrosine kinase (PTK) inhibitory activities of halenaquinone (**102**), halenaquinol (**103**), and 14-methoxyhalenaquinone (**111**) were the most remarkable with IC_{50} values < 10 μM. The other analogues were either less potent or inactive, and a rationalization for this SAR pattern was also reported [38]. Compound **105** also showed significant protein kinase inhibitory activity toward Pfnek-1, a serine/threonine malarial kinase, with an IC_{50} value of *ca.* 1 μM, and moderate activity toward PfPK5, a member of the cyclin-dependent kinase (CDK) family [93].

Adociaquinone B (**116**) and 3-ketoadociaquinone B (**124**) were the most potent inhibitors of the Cdc25B phosphatase inhibitory activities, and the dihydro-benzothiazine dioxide in compounds **115**, **116**, **123**, and **124** appeared to be an important structural feature for this enhanced activity. Four cyclostellettamines, **25**–**28**, inhibited histone deacetylase derived from K562 human leukemia cells with IC_{50} values ranging from 17 to 80 μM [10]. Xestospongic acid ethyl ester (**207**) was found to inhibit the Na^+/K^+ ATPase [71].

3.5. *Antimicrobial and Insecticidal Activities.* Compounds **1**, **2**, **48**, **95**, **102**, **131**, **135**–**137**, **173**, **178**, **206**, **207**, and **235**–**241** showed antimicrobial (antibacterial and/or antifungal) activities [2][21][31][47][48][71][75][88]. Compounds **3**–**5** and **48** showed insecticidal activities [3][21].

3.6. *Other Activities.* Xestoquinone (**105**) showed moderate *in vitro* antiplasmodial activity against the FCB1 *Plasmodium falciparum* strain with an IC_{50} value of 3 μM and weak *in vivo* activity at 5 mg/kg in *Plasmodium berghei* NK65 infected mice [93]. Xestobergsterols A and B (**188** and **189**, resp.) were reported to be potent inhibitors of histamine release from rat mast cells induced by anti-IgE [64][94]. Clionasterol (**159**) was found to be a potent inhibitor of the classical pathway of activation of the human complement system *in vitro*, and the anti-complementary effect might be due to a direct interference with the complement component C1 [51].

4. Concluding Remarks. – Besides the sponges of the genus *Xestospongia* with unidentified species, eleven species of sponges have been studied for their chemical constituents including *X. muta*, *X. ingens*, *X. exigua*, *X. sapra*, *X. vanilla*, *X. testudinaria*, *X. wiedenmayeri*, *X. caycedoi*, *X. ashmorica*, *X.* cf. *carbonaria*, and *X. bergquistia*. The classes of chemical constituents from different species of *Xestospongia* are extremely diverse (*Table 2*). Isoquinoline quinone alkaloids seem to be characteristic metabolites of *X. caycedoi* and macrocyclic quinolizidine alkaloids of *X. exigua*. Polyhydroxysterols showed to be hallmark constituents of *X. bergquistia*. BPUFAs

Table 2. *Classes of Chemical Constituents in Different Species of* Xestospongia

Species	Classes of chemical constituents
X. muta	Conventional sterols
	Sterols with high degrees of alkylation
	Brominated polyunsaturated fatty acids
	Conventional fatty acids
X. ingens	3-Alkylpyridine alkaloids
X. exigua	Macrocyclic quinolizidines (alkaloids)
	Other alkaloids
	Quinones
	Other sterols
X. sapra	Quinones
X. vanilla	Terpenoids
X. testudinaria	Other alkaloids
	Conventional sterols
	Other sterols
	Brominated polyunsaturated fatty acids
X. wiedenmayeri	3-Alkylpyridine alkaloids
	Terpenoids
X. caycedoi	Isoquinoline quinones (alkaloids)
X. ashmorica	β-Carboline alkaloids
X. cf. *carbonaria*	Other alkaloids
	Quinones
X. bergquistia	Polyhydroxysterols

were only found in *X. muta* and *X. testudinaria*, from which only sterols, fatty acids, and indole compounds were isolated.

The genus *Xestospongia* belongs to sponges with high symbiotic bacterial populations. The various colors of the *Xestospongia* sponges are due to the presence of cyanobacterial symbionts in the ectosome [95]. It has been shown that eubacterial rRNA accounted for an average of 46% of the total sponge rRNA in three *Xestospongia* specimens examined [73]. The bacterial flora may contribute to the secondary metabolism of the sponges and develop efficient chemical defense mechanisms. The renieramycin-type alkaloids from *Xestospongia* sponges, which showed striking similarity to the *Streptomyces* bacterial metabolites saframycins and safrins, were speculated to be produced by an epiphytic or symbiotic bacterium [5]. The metabolic products of the isolated *Xestospongia*-associated microorganisms such as bacteria and fungi, which were not included in this review, have also shown to be attractive [96][97].

Sponges of the genus *Xestospongia* are among the richest resources of pharmacologically active chemicals isolated from marine organisms. Some of their components even exhibit strong bioactivities. However, the chemical and biological characterization of those sponges in some sea areas, such as the South China Sea, is still lacking. So, chemical and biological studies should still be carried out on this genus in order to discover more pharmacologically active chemicals and develop drug candidates.

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