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Mini-review

Chemical and bioactive diversities of marine sponge *Neopetrosia*

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Abstract

The marine sponge *Neopetrosia* contains about 27 species that is highly distributed in Indian Ocean, Atlantic Ocean (Caribbean Sea) and Pacific Ocean. It has proven to be valuable to the discovery of medicinal products due to the presence of various types of compounds with variable bio-activities. More than 85 compounds including alkaloids, quinones, sterols and terpenoids were isolated from this genus. Moreover, the crude extracts and the isolated compounds revealed activities such as antimicrobial, anti-fouling, anti-HIV, cytotoxic, anti-tumor, anti-oxidant, anti-protozoal, anti-inflammatory. Because only 9 out of 27 species of the genus Neopetrosia have been chemically studied thus far, there are significant opportunities to find out new chemical constituents from this genus.

Introduction

Marine sponges represent the major rich organisms with promising active pharmaceutical metabolites. The interest for drugs discovery in sponges has started since 1950s due to the discovery of the nucleosides spongo-thymidine and spongouridine from the marine sponge *Cryptotethya crypta* (Laport et al., 2009). Both metabolites were later developed to ara-C, the first marine-derived anti-cancer agent and the antiviral drug ara-A (Proksch et al., 2002). Later, several promising metabolites were discovered from marine sponges with different biological activities including antimicrobial and anti-cancer (Mayer et al., 2013). So far, more than 36% of the metabolites discovered from marine organisms were isolated from the sponges.

Neopetrosia is a genus of marine sponge that belongs to the phylum *Porifera*, the class *Demospongia*, of the order *Haploscleridae*, and family *Petrosiidae*. The genus was established by the Max Walker de Laubenfels in 1932. It contains about 27 species that is highly distributed in Indian Ocean, Atlantic Ocean (Caribbean Sea) and Pacific Ocean. *Neopetrosia* has received great attention in natural product chemistry. Several studies have been conducted lead to report the isolation of more than 85 metabolites. Therefore, the aim of this paper is to review the *Neopetrosia* genus, primarily focusing on their phytochemical characteristics and their biological activities.

Sponge species is identified based on the external morphological characteristics and spicules and skeleton characteristics. However, sponges are among the most difficult organisms to identify. Misidentification of this organism is common (Hooper et al., 2000; Qaralleh et al., 2011). Misidentification of sponges may lead to failure in the prediction of the chemical compo-sitions. Recently, many species belong to the *Xestospongia* or *Petrosia* genera were transferred to *Neopetrosia* genus.

In this study, World Register of Marine Species (www.marinespecies.org) was used to get the species scientific and synonymised names (Table I). Both names were used as a search keys in order to find the relevant literature about each species. The literature was collected by searching the major scientific databases including Marinlit, PubMed, SciFinder, Science direct, Scopus, Medline and Google Scholar. The data were then organised in Table which represented the species name, isolated compounds, place of collection and the bioactivities.

Table I

Scientific names and synonym (s) for neopetrosia species

	Species	Synonym (s)	Distribution
1	*Neopetrosia carbonaria* (Lamarck, 1814)	*Adocia carbonaria* (Lamarck, 1814) *Oceanapia carbonaria* (Lamarck, 1814) *Pachychalina carbonaria* (Lamarck, 1814) *Pellina carbonaria* (Lamarck, 1814) *Spongia carbonaria* Lamarck, 1814 *Thalysias carbonaria* (Lamarck, 1814) *Xestospongia carbonaria* (Lamarck, 1814)	Caribbean Sea
2	*Neopetrosia chaliniformis* (Thiele, 1899)	*Petrosia (Petrosia) chaliniformis* (Thiele, 1899) *Petrosia chaliniformis* (Thiele, 1899)	Indonesia
3	*Neopetrosia compacta* (Ridley and Dendy, 1886)	*Petrosia similis var. compacta* (Ridley and Dendy, 1886)	Philippines
4	*Neopetrosia contignata* (Thiele, 1899)	*Haliclona contignata* (Thiele, 1899) *Petrosia contignata* (Thiele, 1899)	Indonesia East African Coral Coast Gulf of Aden Southern Red Sea
5	*Neopetrosia cylindrica* (Lamarck, 1815)	*Alcyonium cylindricum* (Lamarck, 1815) *Xestospongia cylindrica* (Lamarck, 1815)	Caribbean Sea
6	*Neopetrosia delicatula* (Dendy, 1905)	*Petrosia similis var. delicatula* (Dendy, 1905)	Sri Lanka South India
7	*Neopetrosia densissima* (Wilson, 1904)	*Petrosia similis var. densissima* (Wilson, 1904)	Galapagos
8	*Neopetrosia dominicana* (Pulitzer-Finali, 1986)	*Xestospongia dominicana* (Pulitzer-Finali, 1986)	Dominican Republic Greater Antilles
9	*Neopetrosia exigua* (Kirkpatrick, 1900)	*Haliclona exigua* (Kirkpatrick, 1900) *Neopetrosia pandora* (de Laubenfels, 1954) *Petrosia exigua* (Kirkpatrick, 1900) *Xestospongia exigua* (Kirkpatrick, 1900) *Xestospongia pacifica* (Kelly Borges and Bergquist, 1988)	Indian Ocean Papua New Guinea Singapore Strait East African Coral Coast
10	*Neopetrosia granulosa* (Wilson, 1925)	*Petrosia similis var. granulosa* (Wilson, 1925)	Philippines
11	*Neopetrosia halichondrioides Dendy, 1905*	*Petrosia similis var.halichondrioides* (Dendy, 1905)	Sri Lanka South India
12	*Neopetrosia massa (Ridley & Dendy, 1886)*	*Petrosia similis var. massa* (Ridley and Dendy, 1886)	Falkland Islands Malvinas/Falklands
13	*Neopetrosia perforata (Lévi, 1959)*	*Haliclona perforata* (Lévi, 1959)	Gulf of Guinea Islands Sao Tome and Principe exclusive economic zone
14	*Neopetrosia problematica* (de Laubenfels, 1930)	*Dictyonella problematica* (de Laubenfels, 1930) *Haliclona problematica* (de Laubenfels, 1930) *Prianos problematicus* (de Laubenfels, 1930)	Northern California
15	*Neopetrosia proxima* (Duchassaing and Michelotti, 1864)	*Densa araminta* (de Laubenfels, 1934) *Thalysias proxima* (Duchassaing and Michelotti, 1864) *Xestospongia proxima* (Duchassaing and Michelotti, 1864)	Caribbean Sea North Atlantic Ocean
16	*Neopetrosia rava* (Thiele, 1899)	*Petrosia rava* (Thiele, 1899)	Indonesia
17	*Neopetrosia retiderma* (Dendy, 1922)	*Halichondria retiderma* (Dendy, 1922) *Haliclona retiderma* (Dendy, 1922)	Seychelles Indian Ocean
18	*Neopetrosia rosariensis* (Zea and Rützler, 1983)	*Xestospongia rosariensis* (Zea and Rützler, 1983)	Caribbean Sea North Atlantic Ocean

According to World Register of Marine Species

Table I

Scientific names and synonym (s) for neopetrosia species (Cont.)

	Species	Synonym (s)	Distribution
19	*Neopetrosia sapra* (de Laubenfels, 1954)	*Xestospongia sapra* (de Laubenfels, 1954)	East Caroline Islands Micronesia
20	*Neopetrosia seriata* (Hentschel, 1912)	*Petrosia seriata* (Hentschel, 1912) *Petrosia similis var. seriata* (Hentschel, 1912)	Arafura Sea Indonesian exclusive Economic Zone Southern Vietnam Vietnamese exclusive Economic Zone
21	*Neopetrosia similis* (Ridley and Dendy, 1886)	*Chalina similis* (Ridley and Dendy, 1886) *Petrosia similis* (Ridley and Dendy, 1886)	Agulhas Bank Eastern Philippines Philippines exclusive economic zone South African exclusive economic zone South India, Sri Lanka
22	*Neopetrosia subtriangularis* (Duchassaing, 1850)	*Haliclona doria* (de Laubenfels, 1936) *Haliclona longleyi* (de Laubenfels, 1932) *Haliclona subtriangularis* (Duchassaing and Michelotti, 1864) *Neopetrosia longleyi* (De Laubenfels, 1932) *Pachychalina rugosa* (Duchassaing and Michelotti, 1864) *Pachychalina rugosa var. rubens* (Arndt, 1927) *Schmidtia aulopora* (Schmidt, 1870) *Spongia subtriangularis* (Duchassaing, 1850) *Thalysias rugosa* (Duchassaing and Michelotti, 1864) *Thalysias subtriangularis* (Duchassaing, 1850) *Thalysias subtriangularis var. cylindrica* (Duchassaing and Michelotti, 1864) *Thalysias subtriangularis var. lyriformis* (Duchassaing and Michelotti, 1864) *Xestospongia subtriangularis* (Duchassaing, 1850)	Bahamas Caribbean Sea Caribbean Sea Netherlands Netherlands Antilles United States
23	*Neopetrosia tenera* (Carter, 1887)	*Thalysias tenera* (Carter, 1887)	Andaman and Nicobar Islands Myanmar
24	*Neopetrosia truncata* (Ridley and Dendy, 1886)	*Petrosia truncata* (Ridley and Dendy, 1886)	Philippines
25	*Neopetrosia tuberosa* (Dendy, 1922)	*Haliclona tuberosa* (Dendy, 1922) *Oceanapia tuberosa* (Dendy, 1922) *Reniera tuberosa* (Dendy, 1922)	Indian Ocean Saya de Malha Seychelles Cargados Carajos/Tromelin Island Western Arabian Sea
26	*Neopetrosia vanilla* (de Laubenfels, 1930)	*Haliclona vanilla* (de Laubenfels, 1930) *Xestospongia vanilla* (de Laubenfels, 1930)	California North Pacific Ocean
27	*Neopetrosia zumi* (Ristau, 1978)	*Haliclona (Reniera) zumi* (Ristau, 1978) *Toxadocia zumi* (Ristau, 1978)	California North Pacific Ocean

Chemical Composition

More than 85 compounds have been isolated from *Neopetrosia* species. These compounds were classified into alkaloids, quinones, sterols and terpenoids (Table II).

Alkaloids

More than 44 alkaloids have been isolated. These alkaloids were macrocyclic quinolizidines, 3-alkylpyridine alkaloids, pyridoacridine alkaloids and others.

Macrocyclic quinolizidines

Nineteen macrocyclic quinolizidines alkaloids have been reported from this genus. Several macrocyclic quinolizidines alkaloids (**1**-**13** and **16**-**19**) have been isolated from *N. exigua* and only two have been isolated from *N. similes* (**14** and **15**).

Four macrocyclic quinolizidines were isolated from Australian sponge *N. exigua* (*Xestospongia exigua*) namely xestospongin A (**1**), B (**2**), C (**3**) and D (**4**) (Nakagawa et al., 1984). Several araguspongines alkaloids were obtained from a red sea sponge *N. exigua* (*Haliclona exigua*) including (+)-araguspongine A (**5**), (+)-araguspongine B (**6**), (+)-araguspongine C (**7**), (+)-araguspongine D (**1**), (-)-araguspongine E (**8**), and (+)-xestospongin B (**9**) (Venkateswarlu et al., 1994; Venkateswara et al., 1998). (+)-araguspongine K (**10**) and (+)-araguspongine L (**11**) were isolated from a red sea sponge *N. exigua* (*Xestospongia exigua*) (Orabi et al., 2002). Araguspongin C (**12**) was found from *n*-butanol

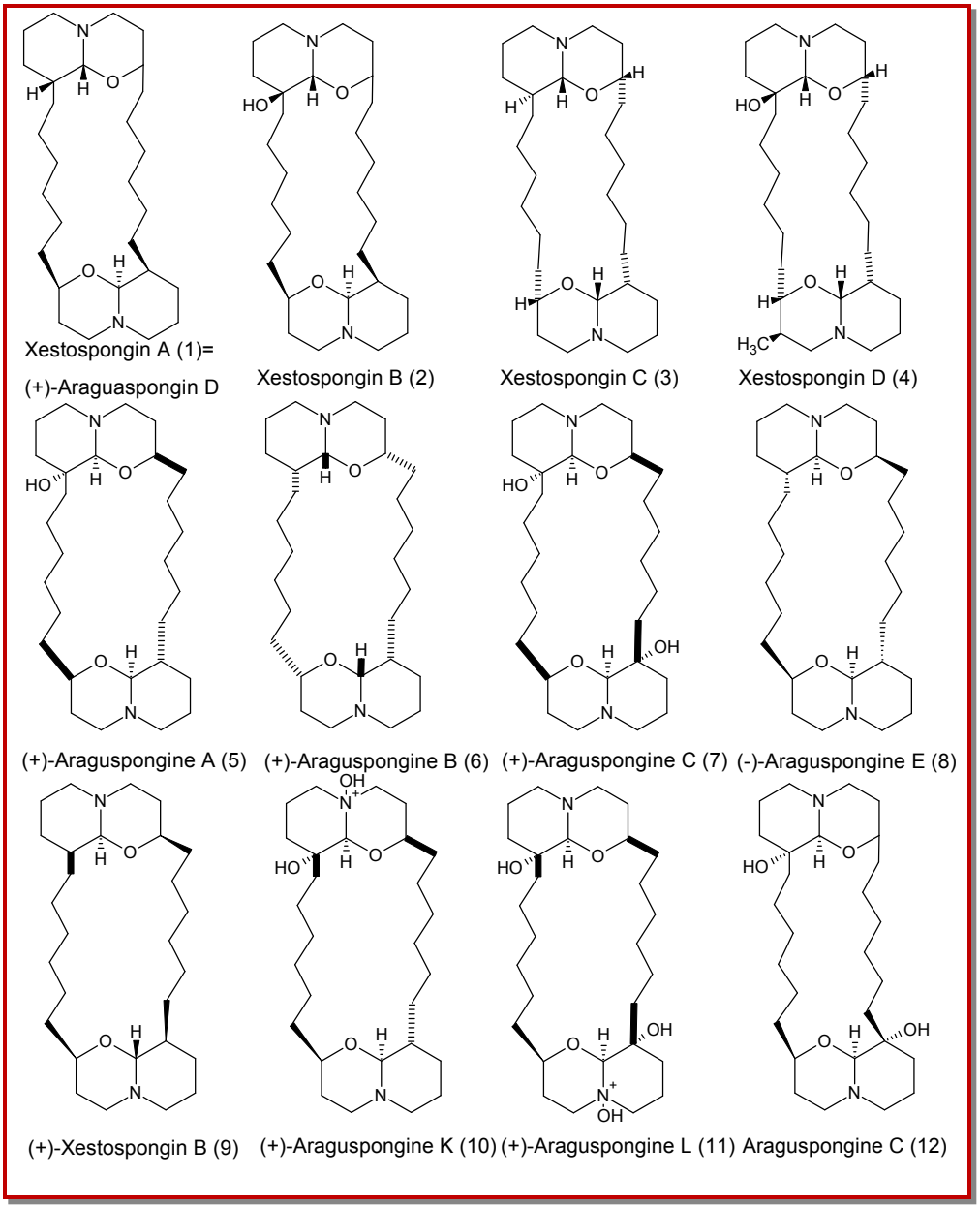


Table II

Chemical constituent of the *Neopetrosia* genus

No.	Compound class and name	Source	Reference
Alkaloids Macrocyclic quinolizidines			
1	Xestospongin A ((+)-araguspongine D)	*N. exigua (Xestospongia exigua)*	Nakagawa et al., 1984; Venkateswarlu et al., 1994, Venkateswara et al., 1998; Liu et al., 2004; Li et al., 2011
2	Xestospongin B	*N. exigua (Xestospongia exigua)*	Nakagawa et al., 1984
3	Xestospongin C	*N. exigua (Xestospongia exigua)*	Nakagawa et al., 1984
4	Xestospongin D	*N. exigua (Xestospongia exigua)*	Nakagawa et al., 1984
5	(+)-Araguspongine A	*N. exigua (Haliclona exigua)*	Venkateswarlu et al., 1994; Venkateswara et al., 1998
6	(+)-Araguspongine B	*N. exigua (Haliclona exigua)* *N. exigua (Xestospongia exigua)*	Venkateswarlu et al., 1994; Venkateswara et al., 1998, Liu et al., 2004
7	(+)-Araguspongine C	*N. exigua (Haliclona exigua)*	Venkateswarlu et al., 1994; Venkateswara et al., 1998
8	(-)-Araguspongine E	*N. exigua (Haliclona exigua)*	Venkateswarlu et al., 1994; Venkateswara et al., 1998
9	(+)-Xestospongin B	*N. exigua (Haliclona exigua)*	Venkateswarlu et al., 1994; Venkateswara et al., 1998
10	(+)-Araguspongine K	*N. exigua (Xestospongia exigua)*	Orabi et al., 2002
11	(+)-Araguspongine L	*N. exigua (Xestospongia exigua)*	Orabi et al., 2002
12	Araguspongin C	*N. exigua (Haliclona exigua)*	Dube et al., 2007
13	Xestosin A	*N. exigua (Xestospongia exigua)*	Iwagawa et al., 2000
14	Petrosin	*N. similis*	Venkateshwar Goud et al., 2003
15	Petrosin-A	*N. similis*	Venkateshwar Goud et al., 2003
16	Araguspongine M	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
17	9'-Epi-3ß,3'ß–dimethylxestospongin C	*N. exigua*	Li et al., 2011
18	3ß,3'ß–Dimethylxestospongin C	*N. exigua*	Li et al., 2011
19	Demethylxestopongin B	*N. exigua*	Li et al., 2011
3-Alkylpyridine alkaloids			
20	Renieramycin J	*Neopetrosia sp.*	Oku et al., 2003
21	Renieramycin A	*Neopetrosia sp.*	Nakao et al., 2004
22	Exiguamine A	*Neopetrosia exigua*	Brastianos et al., 2006
23	Njaoamines G	*Neopetrosia sp.*	Sorek et al., 2007
24	Njaoamines H	*Neopetrosia sp.*	Sorek et al., 2007
25	1,2,3,4-tetrahydroquinolin-4-one	*Neopetrosia sp.*	Sorek et al., 2007
26	Neopetrosiamine A	*Neopetrosia proxima*	Wei et al., 2010
27	Xestoproxamine A	*N. proxima*	Morinaka and Molinski, 2011
28	Xestoproxamine B	*N. proxima*	Morinaka and Molinski, 2011
29	Xestoproxamine C	*N. proxima*	Morinaka and Molinski, 2011
Pyridoacridine alkaloids			
30	1-Hydroxydeoxy-amphimedine	*N. carbonaria*	Wei et al., 2010
31	3-Hydroxydeoxy-amphimedine	*N. carbonaria*	Wei et al., 2010
32	Debromopetrosamine	*N. carbonaria*	Wei et al., 2010

Table II

Chemical constituent of the *Neopetrosia* genus (Cont.)

No.	Compound class and name	Source	Reference
33	Amphimedine	*N. carbonaria*	Wei et al., 2010
34	Neoamphimedine	*N. carbonaria*	Wei et al., 2010
35	Deoxyamphimedine	*N. carbonaria*	Wei et al., 2010
Others alkaloids			
36	Motuporamines A	*N. exigua (Xestospongia exigua)*	Williams et al., 1998; Williams et al., 2002
37	Motuporamines B	*N. exigua (Xestospongia exigua)*	Williams et al., 1998; Williams et al., 2002
38	Motuporamines C	*N. exigua (Xestospongia exigua)*	Williams et al., 1998; Williams et al., 2002
39	Motuporamines D	*N. exigua (Xestospongia exigua)*	Williams et al., 1998; Williams et al., 2002
40	Motuporamines E	*N. exigua (Xestospongia exigua)*	Williams et al., 1998; Williams et al., 2002
41	Motuporamines F	*N. exigua (Xestospongia exigua)*	Williams et al., 1998; Williams et al., 2002
42	Motuporamines - a mixture of G, H, and I	*N. exigua (Xestospongia exigua)*	Williams et al., 1998; Williams et al., 2002
43	7,8-Dihydrotubastrine	*N. contignata (Petrosia cf. contignata)*	Sperry and Crews, 1998
44	4-Deoxy-7,8-dihydrotubastrine	*N. contignata (Petrosia cf. contignata)*	Sperry and Crews, 1998
Quinones			
45	Tetrahydrohalenaquinone A	*N. carbonaria*	Alviet al., 1993
46	Tetrahydrohalenaquinone B	*N. carbonaria*	Alvi et al., 1993
47	14-Methoxyhalenaquinone	*N. carbonaria*	Alvi et al., 1993
48	Halenquinone	*N. carbonaria* *N. exigua (Xestospongia exigua)*	Alvi et al., 1993
49	Halenquinol	*N. carbonaria* *N. sapra* *N. seriata (Petrosia seriata)*	Alvi et al., 1993
50	Halenquinol sulfate Xestoquinol sulfate	*N. carbonaria* *N. sapra*	Alvi et al., 1993; Kobayashi et al., 1985; Kobayashi et al., 1992
51	Xestoquinone	*N. carbonaria*	Alvi et al., 1993
52	Xestoquinolide A	*N. carbonaria*	Alvi et al., 1993
53	Xestoquinolide B	*N. carbonaria*	Alvi et al., 1993
54	Xestosaprol A	*N. sapra*	Kobayashi et al., 1992
55	Xestosaprol B	*N. sapra*	Kobayashi et al., 1992
56	Xestosaprol C	*N. sapra*	Kubota et al., 2008
57	Neopetrosiquinone A	*N. proxima*	Winder et al., 2011
58	Neopetrosiquinone B	*N. proxima*	Winder et al., 2011
59	1,2-Dihydroisoquinoline	*N. similis (Petrosia similis)*	Ramesh et al., 1999
60	Isoquinolinequinone	*N. similis (Petrosia similis)*	Ramesh et al., 1999
Sterols			
61	Galactosyl diacylglycerols	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
62	Galactosyl diacylglycerols	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
63	Galactosyl diacylglycerols	*N. exigua (Xestospongia exigua)*	Liu et al., 2004

Table II

Chemical constituent of the *Neopetrosia* genus (Cont.)

No.	Compound class and name	Source	Reference
64	24-Methyl cholesterol	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
65	5, 6-Dihydrocholesterol	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
66	β-Sitosterol	*N. exigua (Xestospongia exigua)*	Liu et al., 2004; Cerqueira et al., 2003
67	5α, 8α-Epidioxy sterols	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
68	5α, 8α-Epidioxy sterols	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
69	5α, 8α-Epidioxy sterols	*N. exigua (Xestospongia exigua)*	Liu et al., 2004
70	5α, 8α-Epidioxy-24α-ethylcholest-6-en-3-ol	*N. exigua* (*Xestospongia exigua*)	Cerqueira et al., 2003
71	Clionasterol	*N. exigua (Xestospongia exigua*)	Cerqueira et al., 2003
72	Clionasterol monoacetate	*N. exigua (Xestospongia exigua*)	Cerqueira et al., 2003
73	Xestobergsterol A	*N. contignata (Petrosia cf. contignata)*	Sperry and Crews, 1998
Terpenoids			
74	Xestovanin A	*N. vanilla (X. vanilla)*	Northcote and Andersen, 1989
75	Secoxestovanin A	*N. vanilla (X. vanilla)*	Northcote and Andersen, 1989
76	Isoxestovanin A	*N. vanilla (Xestospongia vanilla)*	Morris et al., 1991
77	Xestovanins B	*N. vanilla (Xestospongia vanilla)*	Morris et al., 1991
78	Xestovanins C	*N. vanilla (Xestospongia vanilla)*	Morris et al., 1991
79	Dehydroxestovanin C	*N. vanilla (Xestospongia vanilla)*	Morris et al., 1991
80	Xestodiol	*N. vanilla*	Northcote and Andersen, 1989; Morris et al., 1991
81	Xestenone	*N. vanilla*	Northcote and Andersen, 1989
82	Xestolide	*N. vanilla*	Morris et al., 1991
83	Secoxestenone	*N. vanilla*	Northcote and Andersen, 1989
84	Secodehydroxestovanine A	*N. vanilla*	Morris et al., 1991
Peptides			
85	Neopetrosiamdes A and B	*Neopetrosia* sp.	Williams et al., 2005; Towle et al., 2013

njaoamines G (23) and H (24) and 1,2,3,4-tetrahydroquinolin-4-one (25) were obtained from the sponge *Neopetrosia* sp. collected from Pemba Island, Tanzania (Sorek et al., 2007). A pentacyclic hydroquinone exiguaquinol was isolated from the methanol extract of the Australian sponge *Neopetrosia exigua* (Leone et al., 2008). Neopetrosiamine A (26) was extracted from the marine sponge *Neopetrosia proxima* collected off the west coast of Puerto Rico (Wei et al., 2010). Three xestoproxamines A (27), B (28) and C (29) were isolated from the Bahamian sponge *N. proxima*(Morinaka and Molinski, 2011).

Pyridoacridine alkaloids

Six pyridoacridine alkaloids have been reported from *N. carbonaria* collected from Palau including 1-hydroxy-deoxyamphimedine (30), 3-hydroxy-deoxyamphimedine (31), debromopetrosamine (32), amphimedine (33), neoamphimedine (34) and deoxyamphimedine (35) (Wei et al., 2010).

Others alkaloids

Eight motuporamines including motuporamine A (36), B (37) and C (38) , D(39), E (40) and F (41) and a mixture of G, H, and I (42) were obtained from *N. exigua* (*Xestospongia exigua*) collected from Papua New Guinea yielded (Williams et al., 1998; Williams et al., 2002). Two phenethyl-guanidine derivatives, 7,8-dihydrotubastrine (43) and 4-deoxy-7,8-dihydrotubastrine (44), were isolated from the from the Indo-Pacific sponge *N. contignata* (*Petrosia cf. contignata*) (Sperry and Crews, 1998).

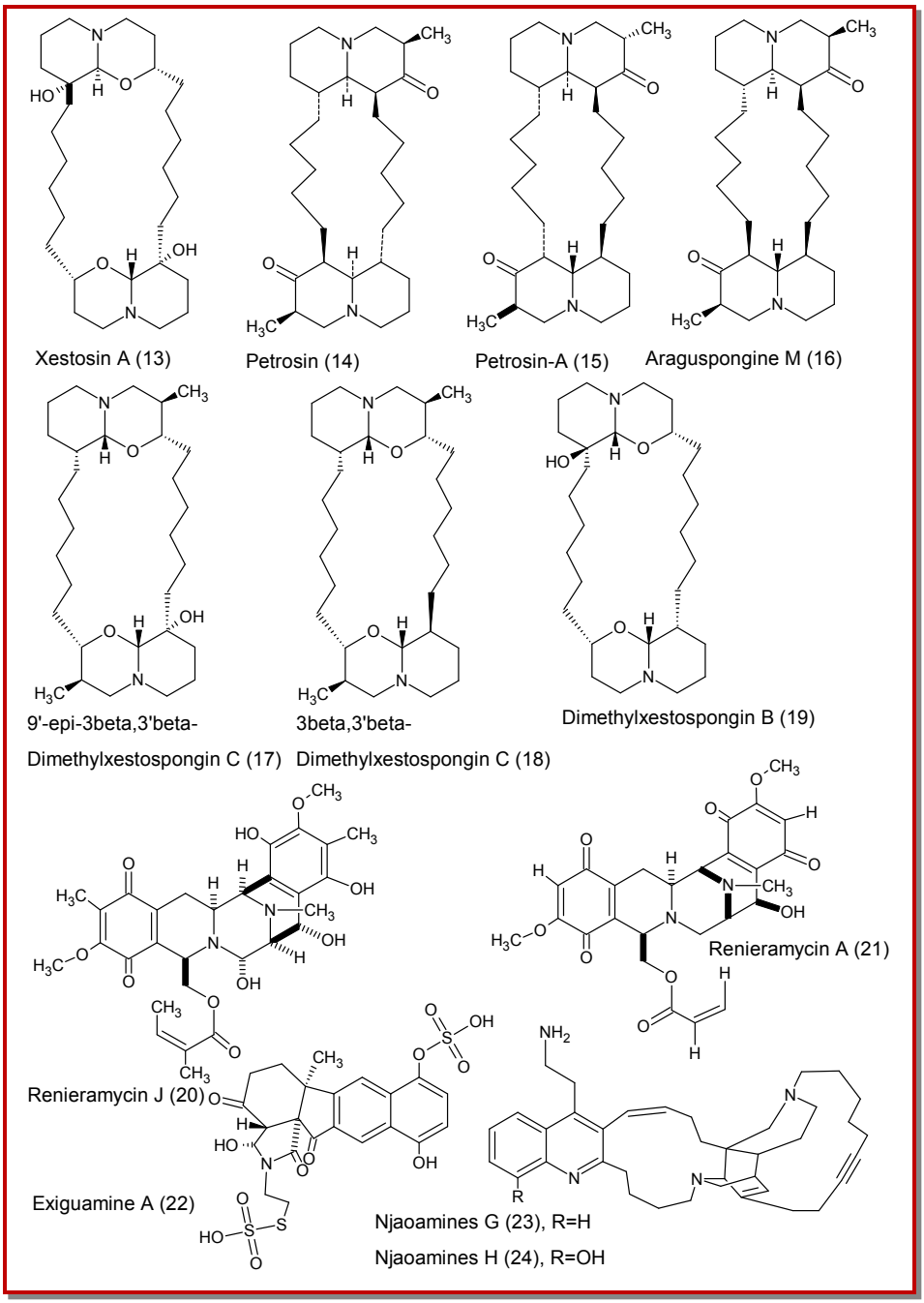
Quinones

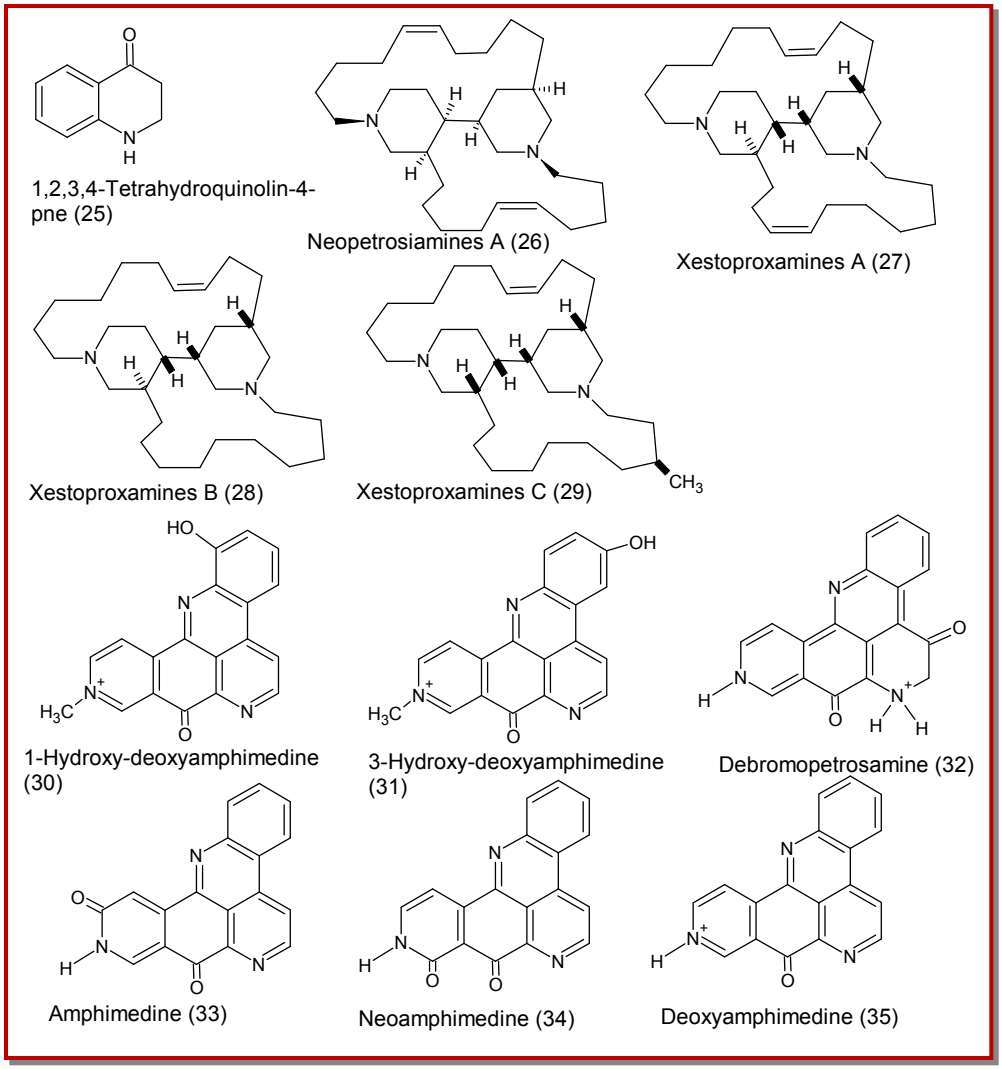
More than 21 quinone and hydroquinone derivatives have been isolated from *Neopetrosia* genus. Several

soluble fraction of *N. exigua* (*Haliclona exigua*) (Dube et al., 2007). A bis-quinolizidine alkaloid, xestosin A (**13**), was isolated from the Papua New Guinean sponge *N. exigua* (*Xestospongia exigua*) (Iwagawa et al., 2000). Two bis-quinolizidine alkaloids namely, petrosin (**14**) and petrosin-A (**15**) were isolated from *N. similis* (Venkateshwar Goud et al., 2003). Three macrocyclic quinolizidines alkaloids were obtained from the n-butanol extract of *N. exigua* (*Xestospongia exigua*) collected in Palau including araguspongine M (**16**), araguspongines B (**6**) and D (**1**) (In 2004, Liu et al., 2004). 9'-Epi-3ß,3'ß–dimethylxestospongin C (**17**), xestospongin A (**1**), 3ß,3'ß–dimethylxestospongin C (**18**) and demethylxestopongin B (**19**) were isolated from the Hainan sponge *N. exigua* (Li et al., 2011).

3-Alkylpyridine alkaloids

Ten 3-alkylpyridine alkaloids were reported from *Neopetrosia* genus. Renieramycin J (**20**), a tetrahydro-isoquinoline alkaloid, was reported from *Neopetrosia* sp. collected from Iwo-Jima Island, Japan (Oku et al., 2003). Renieramycin A (**21**) was reported from the Japanese sponge *Neopetrosia* sp. (Nakao et al., 2004). A hexacyclic alkaloid, exiguamine A (**22**), was isolated from *Neopetrosia exigua* collected in Papua New Guinea (Brastianos et al., 2006). Two polycyclic alkaloids,





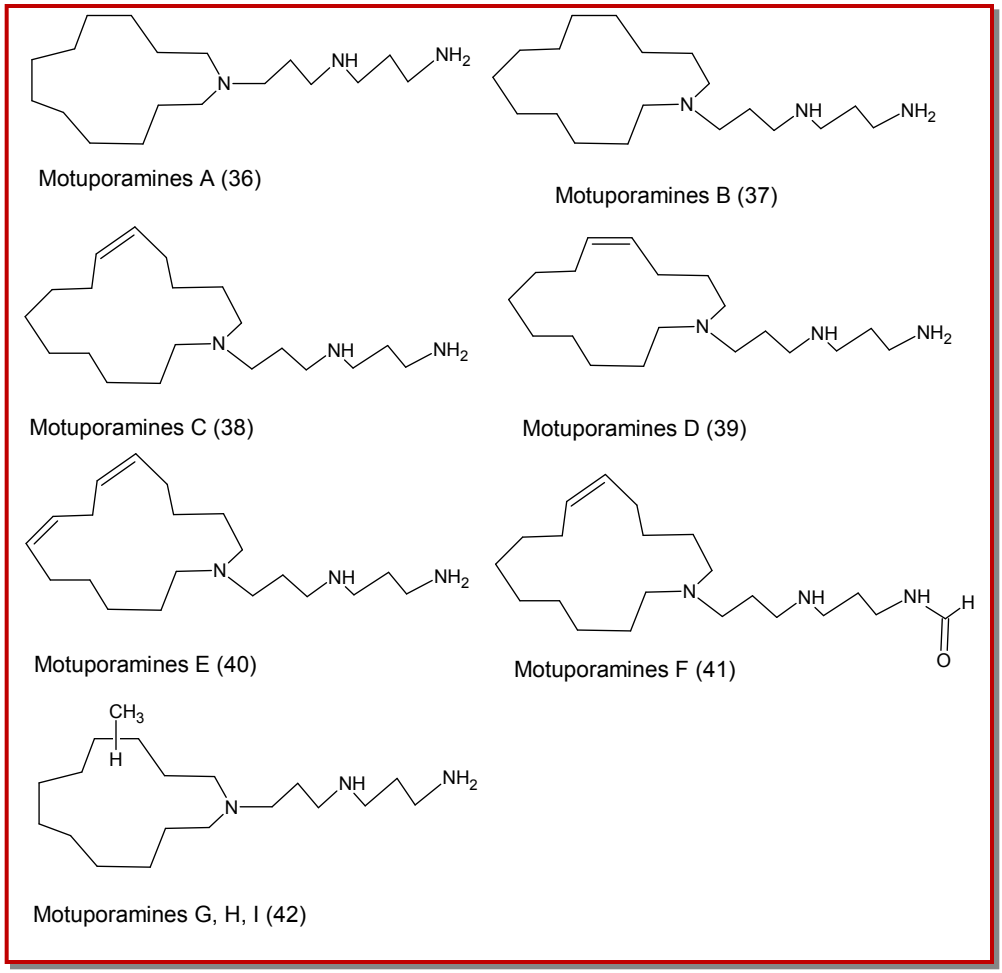
polycyclic quinones and hydroquinones compounds were isolated from *N. Carbonaria* including tetrahydrohalenaquinone A (**45**), tetrahydrohalenaquinone B (**46**), 14-methoxyhalenaquinone (**47**), halenquinone (**48**), halenquinol (**49**), halenquinol sulfate (**50**), xestoquinone (**51**), xestoquinolide A (**52**) and xestoquinolide B (**53**) (Alvi et al., 1993). Halenaquinone (**48**) was obtained from *N. exigua* (*Xestospongia exigua)* benzene extract (Roll et al., 1983). Halenaquinol (**49**) was reported from *N. Sapra* (Kobayashi et al., 1985) and *N. seriata* (*Petrosia seriata*) (Gorshkova et al., 1999). Halenaquinol sulfate (also called xestoquinol sulfate) (**50**) was isolated from Okinawan sponge *N. Sapra* (Kobayashi et al., 1985; Kobayashi et al., 1992). Two other hydroquinones were isolated from Okinawan marine sponge *N. sapra* namely xestosaprols A (**54**) and B (**55**) (Kubota et al., 2008). Xestosaprol C (**56**), a pentacyclic hydroquinone sulfate, was obtained from an Okinawan marine sponge *N. sapra* (Kubota et al, 2008). Two sesquiterpene benzoquinones neopetrosiquinones A (**57**) and B (**58**), were reported from the ethanol extract of *N. Proxima* (Winder et al., 2011). 1, 2-dihydroisoquinoline (**59**) and isoquinoline-quinone (**60**) were obtained from the sponge *N. similis* (*Petrosia similis*) (Ramesh et al., 1999).

Sterols

14 sterols compounds were isolated from Neopetrosia genus. Seven sterols derivatives were obtained from the n-butanol extract of *N. exigua* (*Xestospongia exigua*) collected in Palau including three galactosyl diacylglycerols (**61**, **62**, **63**), 24-methyl cholesterol (**64**), 5, 6-dihydrocholesterol (**65**), β-sitosterol (**66**), and three 5α, 8α-epidioxy sterols (**67**, **68**, 69). 5α, 8α-epidioxy sterol, 5α, 8α-epidioxy-24α-ethylcholest-6-en-3-ol (**70**), and clionasterol (**71**), clionasterol monoacetate (**72**) and β-sitosterol (**66**) were reported from *N. exigua* (*Xestospongia exigua*) (Cerqueira et al., 2003). The sterol xestobergsterol A (**73**), was isolated from *N. contignata* (*Petrosia cf. contignata*) (Sperry and Crews, 1998).

Terpenoids

Twelve terpenoids were found in *Neopetrosia* genus.



Two triterpene glycosides, xestovanin A (74) and secoxestovanin A (75) were reported from the Northeastern Pacific sponge *N. vanilla* (*X. vanilla*) (Northcote and Andersen, 1989; Andersen et al., 1988). Isoxestovanin A (76), Xestovanins B (77), C (78) and dehydroxestovanin C (79) were obtained from the Northeastern Pacific species of *N. vanilla* (*Xestospongia vanilla*) (Morriset al., 1991). Xestodiol (80), Xestenone (81), Xestolide (82), secoxestenone (83), and secodehydroxestovanine A (84) were isolated from *N. Vanilla* (Northcote and Andersen, 1987; Northcote and Andersen, 1989; Morriset al., 1991).

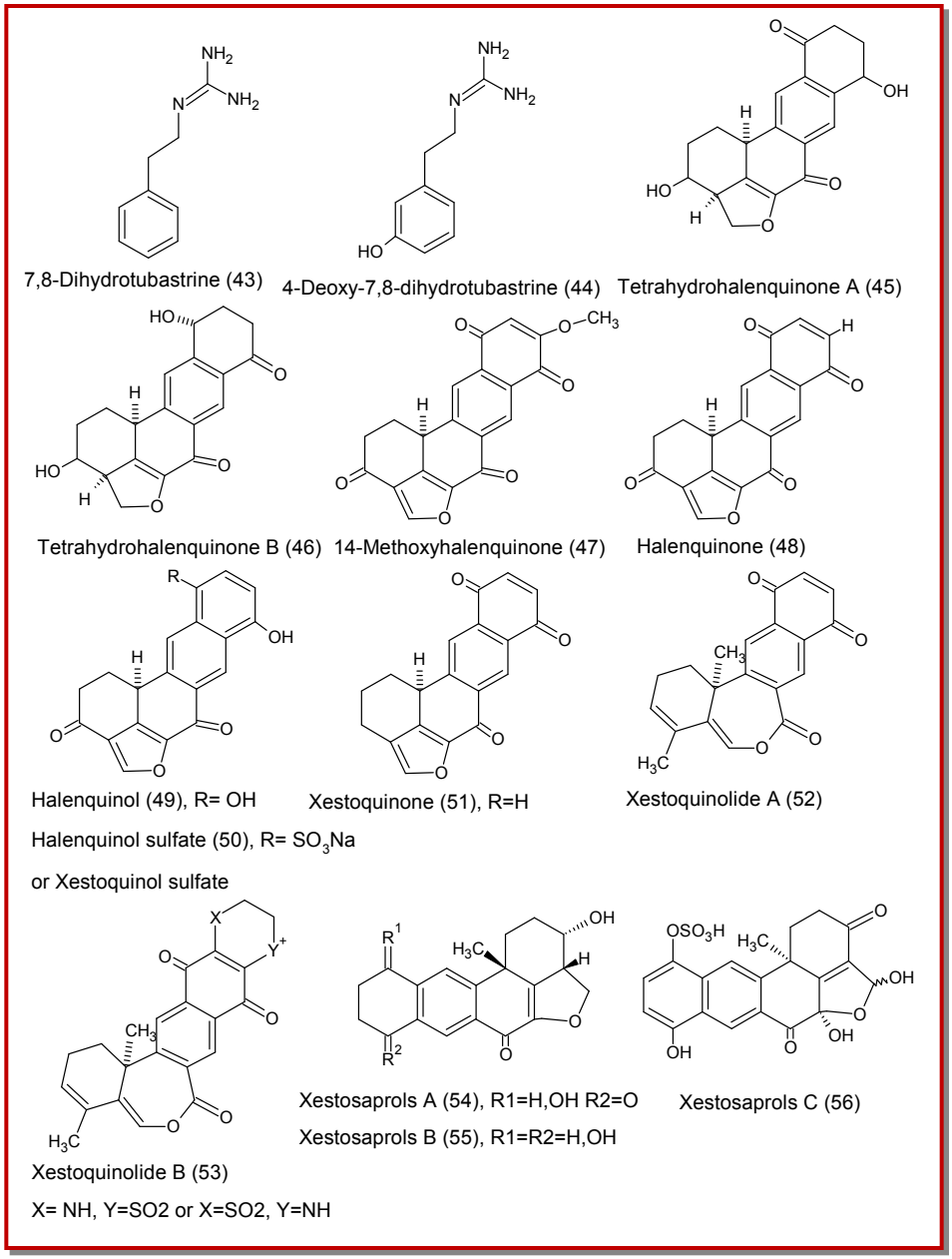
Peptides

Only two diastereomeric tricyclic peptides, neopetrosiamdes A and B (85), which differ only by the stereochemistry of the sulfoxide group, were isolated from *Neopetrosia* sp. collected in Papua New Guinea (Williams et al., 2005; Towle et al., 2013).

Biological activities

Antimicrobial, antifouling and anti-HIV activities

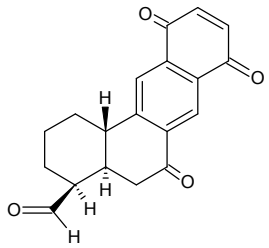
The *in vitro* antimicrobial and antifouling activities of Neopetrosia extracts have been confirmed. In screening of invertebrate materials for antifouling activity, Mora-Cristancho and co-authors (2011) identified the CH2Cl2/MeOH extract of *N.carbonaria* as a potent antimicrobial extract against the fouling bacterial strains *Oceanobacillus iheyensis, Kocuria* sp., *Vibrio harveyi and Bacillus megaterium* with more than 12 mm inhibition zone (300 µg extract concentration) (Mora-Cristancho et al., 2011). Aqueous and organic extracts from *N. exigua* exhibited stronger antibacterial and antifungal activities. The highest activity was obtained for the aqueous extract against the Gram-positive bacteria *B. cereus* (inhibition zone 25 mm and MIC 0.07 mg/mL) and *S. aureus* (17.5 mm and 0.12 mg/mL) and against *C. albicans* (21 mm and 0.32 mg/mL) (Qaralleh et al., 2010; Majali et al., 2015). The methanol extract of the marine sponge *N. exigua* (*Haliclona exigua*) was tested in micro-dilution method and indicated significant antifungal activity *in vitro* against *Candida albicans* (MIC = 7.8 µg/mL), *Cryptococcus neoformans* (MIC = 31.2 µg/mL), *Sporothrix schenckii* (MIC = 31.2 µg/mL), *Trichophyton mentagrophytes* (MIC = 31.2 µg/mL), *Aspergillus fumigatus* (MIC = 31.2 µg/mL) and *Candida parapsilosis* (MIC = 7.8 µg/mL) (Lakshmi et al., 2010). The extract provided one active compound



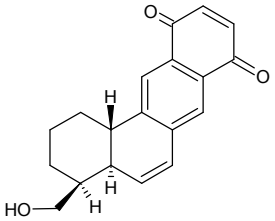
namely araguspongin C (7), that showed promising activity against *Cryptococcus neoformans*, *Sporothrix schenckii*, *Trichophyton mentagrophytes* and *Aspergillus fumigatus* with identical MIC of 50 µg/mL. In another study, araguspongin C (7) isolated from *N. exigua* exhibited potent antifouling activity with EC50 = 6.6 µg/mL and low toxicity with LC50 = 18 µg/mL (Limna Mol et al., 2009; Limna Mol et al., 2010).

In a screening of crude extracts of 6 species of sponges for their antifouling activity, Limna Mol and co-authors (2010)reported the methanol/acetone extract of the *N. exigua* as a moderate antifouling extract. *N. exigua* extract exhibited moderate antibacterial activity against the fouling bacterial strains; *Bacillus cereus*; *B. pumilus*; *B. megaterium*; *Pseudoalteromonas haloplanktis*; *Pseudomonas chlororaphis*; *P. putida*; *P. aeruginosa*. In a preliminary screening study, the chloroform and methanol extracts of *N. proxima* collected from the Uraba Gulf in the Colombian Caribbean region, showed no antibacterial activity against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 and antifungal activity against *Candida albicans* ATCC 10231 (Galeano and Martínez, 2007). In contrast, the organic extract obtained from *N. proxima* showed *in vitro* antibacterial activity against the Gram-positive *Staphylococcus aureus* and *Streptococcus faecalis* and antifungal activity against *Candida albicans* (Mora et al., 2008).

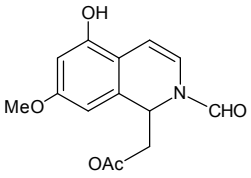
A pentacyclic polyketide, halenaquinone (48) isolated from the benzene extract of *N. exigua* (*Xestospongia*



Neopetrosiquinones A (57)

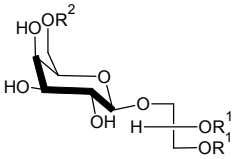


Neopetrosiquinones B (58)



1,2-Dihydroisoquinoline (59)

Isoquinolinequinone (60)

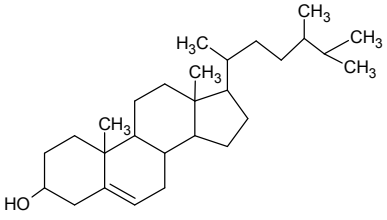


Galactosyl diacylglycerol

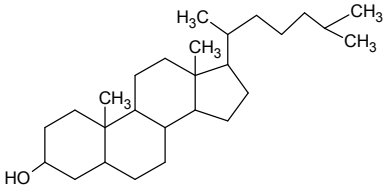
R1=16:0\16:1 R2=H (61)

R1=16:0\18:2 R2=H (62)

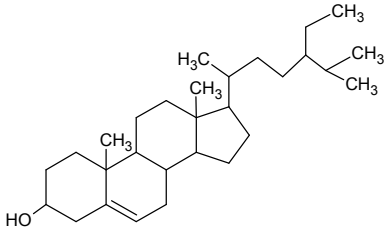
R1=16:0\16:1 R2= alpha-D-galactopyranosyl (63)



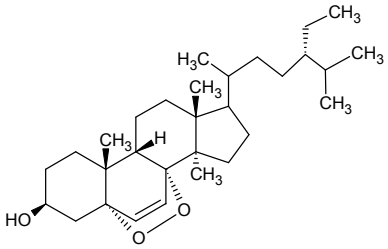
24-Methylcholestrol (64)



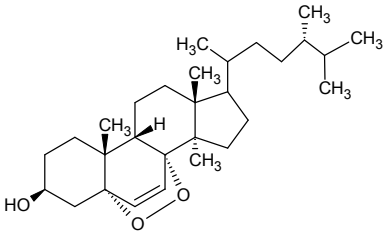
5,6-Dihydroxycholestrol (65)



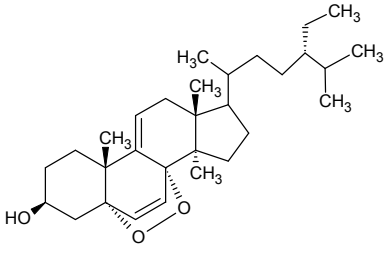
Beta-sitosterol (66)



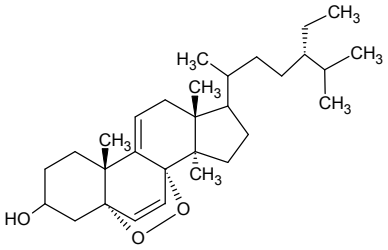
5Alpha,8alpha-epidioxy sterol (67)



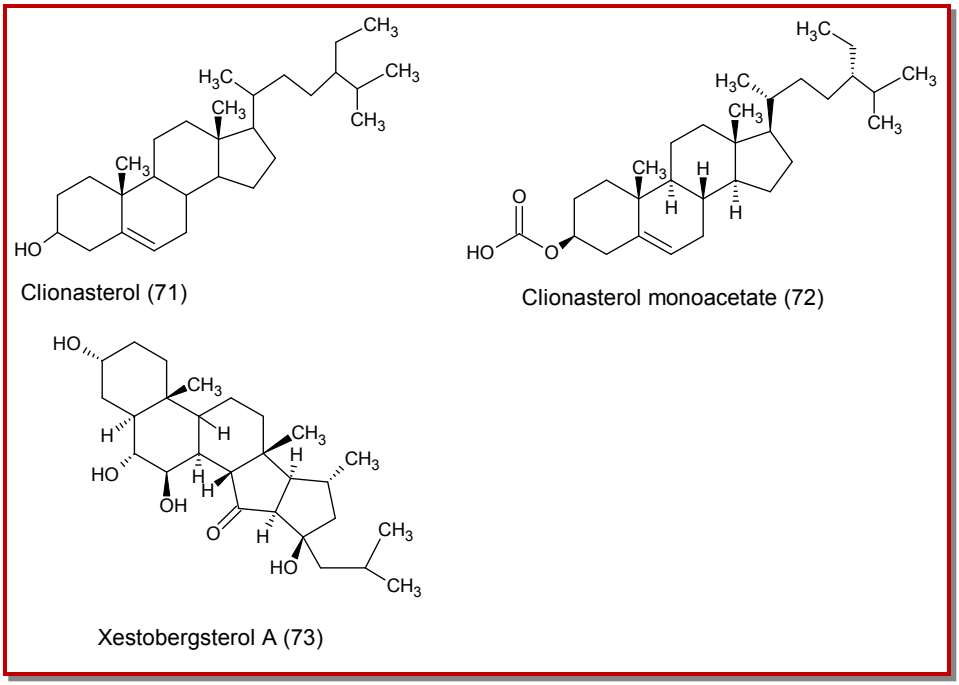
5Alpha,8alpha-epidioxy sterol (68)



5Alpha,8alpha-epidioxy sterol (69)



5Alpha,8alpha-epidioxy-24alpha -ethylcholestrol-6-en-3-ol (70)



exigua) was reported with antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* (Roll et al., 1983). (+)-Araguspongine C (**7**) was reported with anti-tuberculosis activity with MIC 3.9 µM (Orabi et al., 2002). The anti-tuberculosis activity was confirmed for neopetrosiamine A (**26**) *in vitro* against a pathogenic strain of *Mycobacterium tuberculosis* (H37Rv) with MIC value of 7.5 µg/mL (Weiet al., 2010). A pentacyclic hydroquinone exiguaquinol inhibited *Helicobacter pylori* glutamate racemase (MurI) with an IC_{50} of 4.4 µM. The triterpene glycosides, xestovanin A was reported from *N. vanilla* with antifungal activity against *Phytium ultimum* (Northcote and Andersen, 1989).

Two bis-quinolizidine alkaloids namely, petrosin (**14**) and petrosin-A (**15**) were reported as anti-HIV inhibitors with IC_{50} values of 41.3 and 52.9 µm, respectively (Venkateshwar et al., 2003).

Cytotoxic, antitumor, anti-proliferation, anti-angiogenic and anti-invasion activities

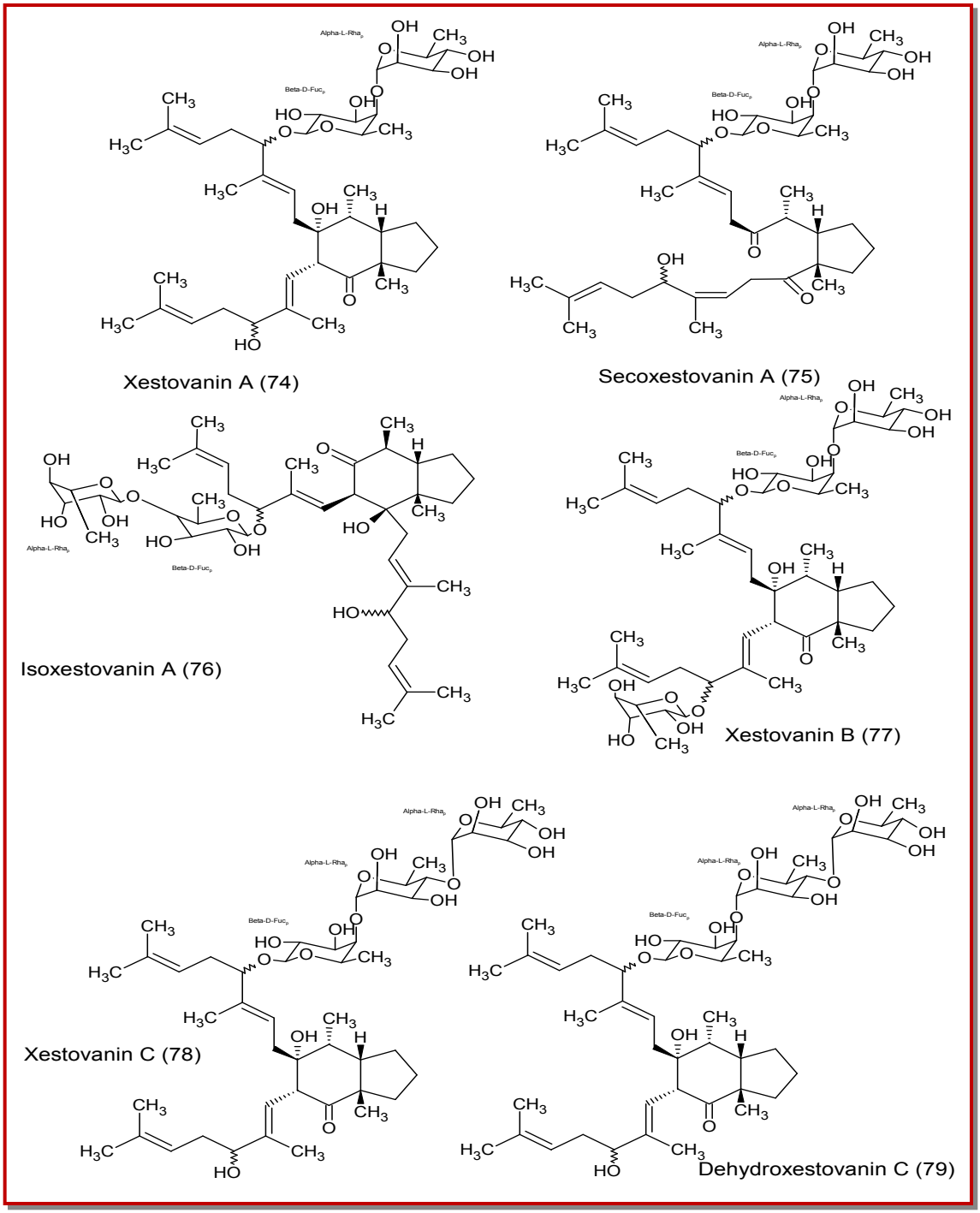
Selective cytotoxic activity was indicated for *N. contignata* extract against tumor cell lines HT-29, T47D and Casky with IC_{50} of 78.9, 35.6 and 36.2 µg/mL, respectively (Abdillah et al., 2013a). Using BST test, the hydro-ethanolic extract of *N. contignata* and *N. exigua* (*X. exigua*) exhibited strong toxicity with LC_{50} equal to 155 and 547 ppm, respectively.

The pyridoacridine alkaloids, amphimedine (**33**) isolated from *N. carbonaria* exhibited potent cytotoxic activity that caused a phenotype in zebra fish embryos at 30 µM (Wei et al., 2010).

In 2004, Liu and colleagues (2004) reported the cytotoxic activities of araguspongine M (**16**), araguspongines B (**6**) and D (**1**) and three 5α, 8α-epidioxy sterols (**67**–**69**) against the human leukemia cell line HL-60 with IC_{50} values of 5.5, 5.5, 5.9, 22.4, 9.5, and 9.6 µM, respectively. Renieramycin A (**21**) obtained from *Neopetrosia* sp. exhibited cytotoxicity with IC_{50}= 2.2 µg/mL. Renieramycin J (**20**) was reported with cytotoxic activity against 3Y1, HeLa, and P388 cells with IC_{50} of 5.3, 12.3, and 0.53 nM, respectively (Oku et al., 2003). High concentration of renieramycin J induced morphological changes in 3Y1 cells in which these changes might be refer to RNA and/or protein synthesis inhibition. Sorek and co-authors (2007) reported that njaoamines G (**23**) and H (**24**) possess potent brine shrimp toxicity with LD_{50} values of 0.17 and 0.08 µg/mL, respectively. Demethylxestopongin B (**19**) was isolated from the Hainan sponge *N. exigua* as a potent cytotoxic compound against human tumor cell line A-549 with inhibition ratio of 94.3% at 10 µM (Liet al., 2011).

Halenaquinone (**48**) was found to exhibit anticancer activity through apoptosis. Fujiwara and co-authors (2001) reported that the mechanism of halenaquinone-induced apoptosis may be explained by the inhibition of phosphatidylinositol 3-kinase activity.

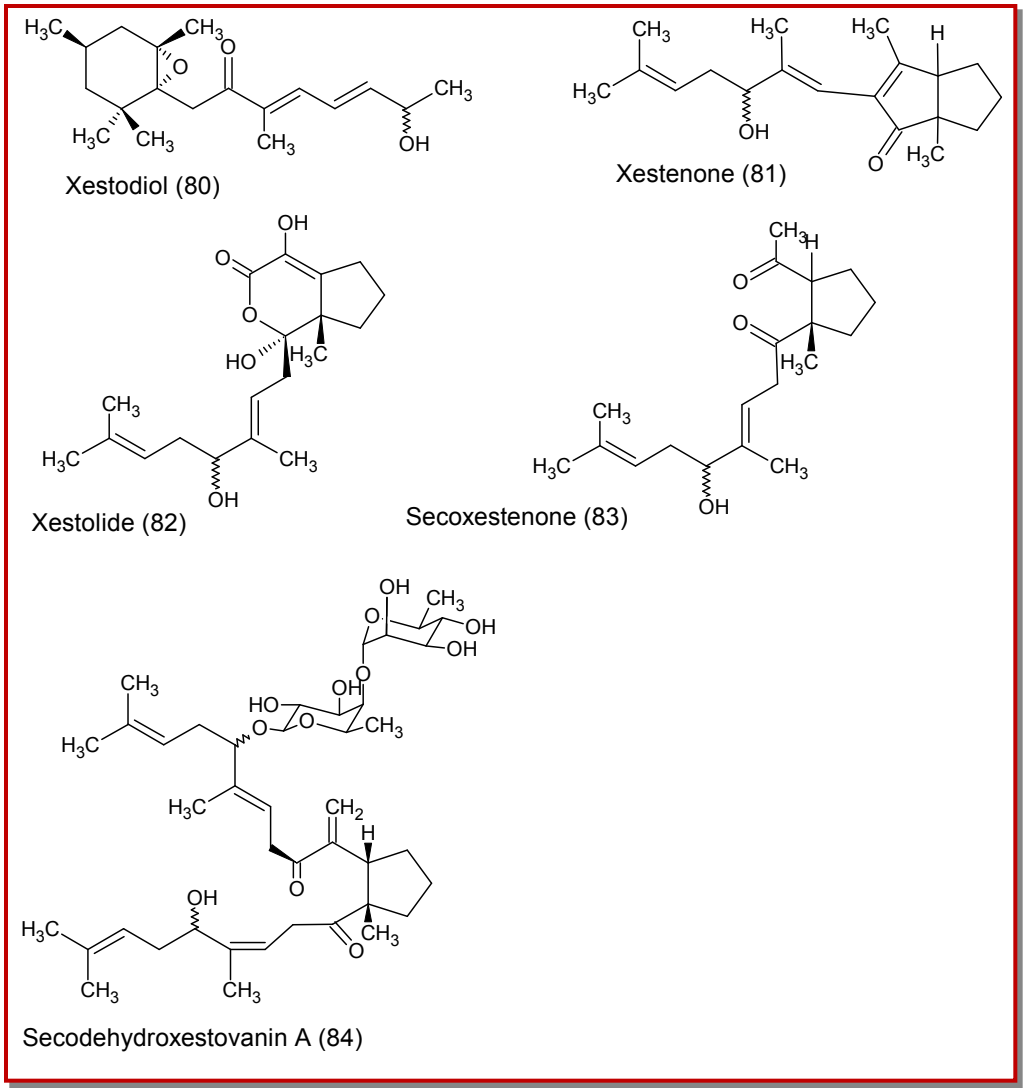
Winder and colleagues (2011) reported the anti-proliferation activity of neopetrosiquinones A (**57**) and B (58) against the DLD-1 human colorectal adenocarcinoma cell line with IC50 values of 3.7 and 9.8 µM, respectively and the PANC-1 human pancreatic carcinoma cell line with IC_{50} values of 6.1 and 13.8 µM, respectively. Neopetrosiquinone A (**57**) also inhibited the *in vitro* proliferation of the AsPC-1 human pancreatic carcinoma cell line with an IC_{50} value of 6.1 µM.



In vitro anti-tumor screening showed that neopetrosiamine A (**26**) exhibited strong inhibitory activity against MALME-3M melanoma cancer, CCRFCEM leukemia and MCF7 breast cancer with IC values of 1.5, 2.0, and 3.5 µM, respectively. Notably, neopetrosiamine A did not exhibit cytotoxicity against VERO cells (IC_{50} = 42.4 µg/mL).

Motuporamines A (**36**), B (**37**) and C (**38**) and the mixture of G, H and I (**42**) exhibited anti-invasion activity. In 2001, Roskelley and colleagues (2001) showed that the compound motuporamine C (**38**) interferes with the migration of human breast carcinoma, prostate carcinoma and glioma cells in culture and inhibited angiogenesis in both an *in vitro* sprouting assay and an *in vivo* chick chorioallantoic membrane assay (Williams et al., 1998; Roskelley et al., 2001; Williams et al., 2002).

Neopetrosiamdes A and B (**85**) were reported as potential anti-metastatic agents that inhibit tumour cell invasion by both amoeboid and mesenchymal



migration pathways (Williams et al., 2005; Towle et al., 2013).

Anti-oxidant activity

Anti-oxidant activities of *N. contignata* and *N. exigua* (*Xestospongia exigua*) extract were reported. The hydro-ethanolic extract of *N. contignata* and *N. exigua* exhibited moderate antioxidant activity with IC_{50} <100 µg/mL using DPPH method (Abdillah et al., 2013a).

Enzymes inhibitors

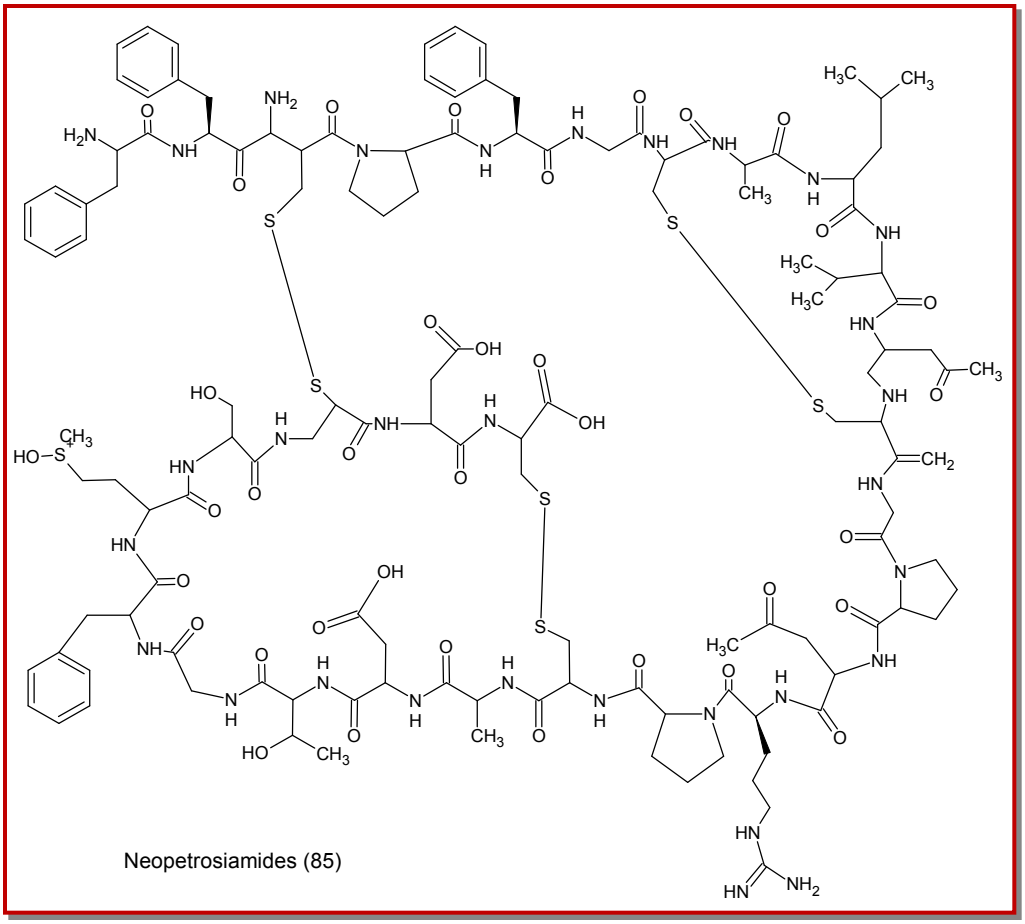
Exiguamine A (**22**), has been found to be one of the most potent inhibitor of indoleamine-2, 3-dioxygenase (IDO) *in vitro*. IDO inhibition can delay tumor growth (Brastianos et al., 2006).

Halenaquinone (**48**) and 14-methoxyhalenaquinone (**47**) were reported as a potent protein tyrosine kinase (PTK) inhibitors with IC_{50} values <10 muM (Alvi et al., 1993). This enzyme is associated with proliferative disease such as cancer.

Halenaquinol (**49**), isolated from *N. seriata*, was reported as inhibitor for rat brain cortex Na^+, K^+-ATPase with an I_{50} value of 1.3 x 10 - 6 M or 325 nmol per mg of protein (Gorshkova et al., 1999). Further investigation suggested that halenaquinol interacts with the essential sulfhydryls in or near the ATP-binding site of Na+, K+-ATPase. This interaction resulted in a change of protein conformation and subsequent alteration of overall and partial enzymatic reactions (Gorshkova et al., 2001).

Araguspongines A (**5**) and C (**7**) showed an ability to inhibit rat brain nitric oxide synthase activity *in vitro* with an estimated IC_{50} of 31.5 and 46.5 mM respectively (Venkateswara et al., 1998).

Araguspongines A (**5**) and C (**7**) and xestospongin B (**2**) were reported as a potent inhibitors for inositol 1, 4, 5-triphosphate receptor mediated Ca^{2+} release and endoplasmic reticulum-calcium pump (Gafni et al., 1997; De Smet et al., 1999).



Antiprotozoal activity

Recently, the anti-malarial activity of *N. exigua* has been reported. Ethanol soluble extracts of *N. exigua* with doses of 400 and 200 mg/kg showed suppression of growth activity against *Plasmodium berghei* by 80.7% and 60.6%, respectively (Abdillah et al., 2013a).

Neopetrosamine A (**26**) was reported with anti-plasmodial activity against *Plasmodium falciparum* with an IC_{50} value of 2.3 µM (Wei et al., 2010). Renieramycin A (21) exhibited anti-protozoal activity against *Leishmania amazonensis* with IC_{50} = 0.2 µg/mL and cytotoxicity with IC_{50} = 2.2 µg/mL (Nakao et al., 2004). Araguspongine C (**7**) exhibited *in vitro* anti-malarial activity against *Plasmodium falciparum* with IC_{50} ranged from 280 to 670 ng/mL (Orabi et al., 2002).

Anti-inflammatory activity and anti-complementary inhibitor

The anti-inflammatory activity of *N. proxima* and *N. rosariensis* collected from the Colombian Caribbean has been confirmed. The methanolic extract and the different polarity fractions of *N. Proxima* exhibited *in vitro* and *in vivo* anti-inflammatory activities. Total extracts of *N. proxima* (100 mg/Kg) significantly inhibited the paw edema of rats (60%). Dichloro-methane and methanol fractions reduced myeloperoxidase activity (MPO) while there was no significant reduction for the nitric oxide (NO), prostaglandin E2 (PGE2) and tumor necrosis factor alpha (TNF- alpha) (Franco et al., 2012). Total extracts of *N. rosariensis* (100 mg/Kg) significantly inhibited the paw edema of rats (72%). Dichloromethane and methanol fractions reduced myeloperoxidase activity (MPO). Only, dichloromethane fraction of *N. rosariensis* significantly inhibited nitric oxide (NO) (66%), prostaglandin E2 (PGE2) (30.5%) and tumor necrosis factor alpha (TNF-alpha) production (72%) (Franco et al., 2012). Clionasterol (71), isolated from *N. exigua* (*Xestospongia exigua*), exhibited potent anti-complementary inhibitor with IC_{50} = 4.1 µM (Cerqueira et al., 2003).

Other

Xestospongin A (**1**), B (**2**), C (**3**) and D (**4**) were found to be active as a vasodilator compounds since they induce relaxation of blood vessel *in vivo* (Zhou et al., 2010). Halenaquinol (49) was reported from *N. seriata* with a cardioactivity (Gorshkova et al., 1999). Xestosaprol C (**56**) was reported with cardiotonic activity (Nakamura et al., 1985). Halenaquinone (**48**), was found to be as an inhibitor of osteoclastogenic differentiation of murine

RAW264 cells (Tsukamoto et al., 2014).

Chemotaxonomic significance

A literature search showed that only 9 species out of 27 of *Neopetrosia* that have been chemically investigated. In general, these species produced alkaloids, quinones, sterols and terpenoids. Macrocyclic quinolizidines are a major kind of metabolite that existed in this genus and more specifically in *N. exigua* and *N. similis*. Most other similar macrocyclic quinolizidines [(+)-araguspongine A-J] were reported from *Xestospongia* sp. that has been identified to the genus level(Kobayashi et al., 1989). In this study, 3-alkylpyridine alkaloids were found in *N. exigua, N. proxima* and *Neopetrosia* sp. The occurrence of 3-alkylpyridine alkaloids has been reported from other sponge genera including xestospongia, amphimedon and *Topsentia* suggested that these genera share similar biosynthetic pathways. Previous studies reported that *Xestospongia wiedenmayeri* and *X. ingens* contain 3-alkylpyridine alkaloids such as xestamine and ingamine, respectively (Quirion et al., 1992; Kong and Andersen, 1995; Takekawa et al., 2006).

In this review, six pyridoacridine alkaloids were reported from *N. carbonaria*. Previous reports showed that pyridoacridine alkaloids are produced by other marine sponge including *Oceanapia* sp. (Eder et al., 1998), *Petrosia* sp (Nukoolkarn et al., 2008) and from ascidian species such as *Cystodytes dellechiajei* (Torres et al., 2002) and *Lissoclinum cf. Badium* (Clement et al., 2008). About eight motuporamines (36-42) were found in *N. exigua* (Williams et al., 1998; Williams et al., 2002). The occurrence of motuporamines in *N. exigua* only could be considered as important marker for this species. Only two phenethylguanidine derivatives were found in *Neopetrosia* genus. These two compounds, 7, 8-dihydrotubastrine (**43**) and 4-deoxy-7,8-dihydrotubastrine (**44**), were found in *N. contignata* (*Petrosia cf. contignata*) (Sperry and Crews, 1998). According to literatures, there are no phenethylguanidine derivatives with similar skeleton have been reported from marine origin.

More than 21 quinone and hydroquinone derivatives have been isolated from *Neopetrosia* genus. These derivatives were found in *N. carbonaria*, *N. exigua*, *N. sapra*, *N. proxima*, *N. seriata* and *N. similis*. Many quinone and hydroquinone derivatives have been obtained from Xestospongia specimen that identified to the genus level (Zhu et al., 1998; Concepción et al., 1995). Xestoquinone and halenaquinone have been found in marine sponge *Adocia* sp *(*Schmitz and Bloor, 1988*)*.

In this study, 13 sterols compounds were found in *N. exigua* while one was obtained from *N. contignata*. Many of these sterols or others with similar skeleton have been reported from *Xestospongia* genus. Some of these sterols appear to be widely distributed in other organisms such as marine sponge *Spirastrella inconstans* (Das et al., 1993) and green alga *Halimeda macroloba* (Dzeha et al., 2004). The only *Neopetrosia* sp that has been reported to produce terpenoids is *N. vanilla*. These terpenoids (**74**-**79**) might be used as a specific marker for this species.

Conclusion

Out of 27 species of the genus Neopetrosia only *Neopetrosia carbonaria, Neopetrosia contignata, Neopetrosia exigua, Neopetrosia proxima, Neopetrosia rosariensis, Neopetrosia sapra, Neopetrosia seriata, Neopetrosia similis* and *Neopetrosia vanilla* have been studied so far. Most species of *Neopetrosia* haven't been investigated yet for their secondary metabolite profiles and potential bioactivities, some of taxa mentioned in the literature have been assigned to a genus level. Accordingly, it is difficult to determine such compounds as chemosystematic markers for particular species in this genus. Beside, sponge metabolites could be synthesised by the sponge itself or it is obtained from other sources such as the symbiotic microbes or the free living microbes in the marine environment (Garson et al., 1992; Lindquist et al., 2005).

Because only 9 out of 27 species of the genus *Neopetrosia* have been chemically studied thus far, there is significant opportunity to find out new chemical constituents from this genus.

Acknowledgement

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