

Review

Terpenoids from Marine Soft Coral of the Genus *Xenia* in 1977 to 2019

Shean-Yeaw Ng ¹, Chin-Soon Phan ¹, Takahiro Ishii ², Takashi Kamada ³,
Toshiyuki Hamada ⁴ and Charles Santharaju Vairappan ^{1,*}

¹ Laboratory of Natural Products Chemistry, Institute for Tropical Biology and Conservation, Universiti Malaysia Sabah, Kota Kinabalu 88400, SBH, Malaysia; sheanyeaw@ums.edu.my (S.-Y.N.); yuna123@hotmail.my (C.-S.P.)

² Department of Bioscience and Biotechnology, Faculty of Agriculture, University of the Ryukyus, 1 Senbaru, Nishihara, Okinawa 903-0213, Japan; ishiit@agr.u-ryukyu.ac.jp

³ Department of Materials and Life Science, Faculty of Science and Technology, Shizuoka Institute of Science and Technology, 2200-2 Toyosawa, Fukuroi, Shizuoka 437-8555, Japan; takashi.kamada800@gmail.com

⁴ Graduate School of Science and Engineering, Kagoshima University, 1-21-35 Korimoto, Kagoshima 890-0065, Japan; thamada@sci.kagoshima-u.ac.jp

* Correspondence: csv@ums.edu.my; Tel.: +60-88-320-000 (ext. 2353); Fax: +60-88-320-291

Received: 17 October 2020; Accepted: 12 November 2020; Published: 18 November 2020



Abstract: Members of the marine soft coral genus *Xenia* are rich in a diversity of diterpenes. A total of 199 terpenes consisting of 14 sesquiterpenes, 180 diterpenes, and 5 steroids have been reported to date. Xenicane diterpenes were reported to be the most common chemical skeleton biosynthesized by members of this genus. Most of the literature reported the chemical diversity of *Xenia* collected from the coral reefs in the South China Sea and the coastal waters of Taiwan. Although there was a brief review on the terpenoids of *Xenia* in 2015, the present review is a comprehensive overview of the structural diversity of secondary metabolites isolated from soft coral genus *Xenia* and their potent biological activity as reported between 1977 to 2019.

Keywords: marine soft corals; *Xenia* sp.; natural products; terpenes; bioactivity

1. Introduction

Marine-derived terpenoids have attracted the interest of natural product chemists around the world, leading to the discovery of many novel chemical skeletons and possible lead drug candidates. In recent years, various species of marine soft corals from Taiwan and the South China Sea have been chemically investigated for their chemical diversity and potential as bioactive compounds [1–8]. Among them, marine soft coral of the genus *Xenia* (Alcyonacea, Xenidiidae) has afforded numerous new terpenoids with diverse structures and few biological activities. These terpenoids are mainly dominated by xenicane-type or xenia diterpenoids. Some of these diterpenes have also been found in the alcyonacean soft corals such as *Anthelia glauca* [9], *Asterospicularia laurae* [10], *Capnella thyrsoides* [11], *Eleutherobia aurea* [12], *Heliopora coerules* [13], and *Sinularia gibberosa* [14] and in several gorgonian species [15,16]. In this context, a total of 199 terpenes consisting of 14 sesquiterpenes, 180 diterpenes, and 5 steroids has been reported to date. These terpenes were isolated from species of the soft coral *Xenia*, including *X. blumi*, *X. crassa*, *X. elongata*, *X. faraunensis*, *X. florida*, *X. lilielae*, *X. macrospiculata*, *X. membranacea*, *X. novae-britanniae*, *X. obscuronata*, *X. puerto-galerae*, *X. stellifera*, *X. umbellata*, *X. viridis*, and *Xenia* sp., many of which were collected at Green Island in Taiwan, regions of Kagoshima and Okinawa in Japan, Gulf of Eilat at the Red Sea, Townsville in Australia, and Sarcelle Pass south of New Caledonia. A review about *Xenia* terpenoids was reported in 2015 that listed terpenoids and their

anticancer properties. However, in an effort to better understand the chemistry of marine-derived natural products from the soft coral genus *Xenia* and their bioactive potentials, this review summarizes the collection locations and chemical diversity of specimens and the biological properties of this genus that have been obtained from literature published between 1977 and 2019 (1997 to 2014 were re-reviewed).

2. Diterpenes

Diterpenes are synthesized by four isoprene units, and their basic structure starts with the molecular formula $C_{20}H_{32}$. Many have a variety of modifications such as methylation, acetylation, hydroxylation, epoxidation, and oxygenation, giving them additional carbon and oxygen atoms in their molecular formula. Xenicane diterpenes contain a cyclononane skeleton. Figure 1 shows the three structurally different types of xenicane diterpenes: xenicins (possessing a 2-oxabicyclo[7.4.0]tridecane ring system) [17], xeniolides (the lactone derivatives of xenicins) [18], and xeniaphyllanes (containing a bicyclo[7.2.0]undecane ring system) [19]. Subsequently, more groups were categorized, such as floridicins (tricycyclic diterpenoid) [20], xeniaethers (bearing a oxabicyclo[7.3.0]undecane ring system) [21], and azamilides (having an opened A-ring with the nine-membered carbocyclic skeleton acylated with a series of C16–C20 saturated fatty acids) [22]. Since then, more novel carbon skeletons have been discovered in the 21st century such as blumiolide-A with cyclooctane system of xeniolide [23], umbellactal with γ -lactone fused to a bicyclo[4.3.0]nonane ring system [24], xenibellol A with tetracyclic system [25], and xenibellal with norditerpenoid of cyclononane system [26].

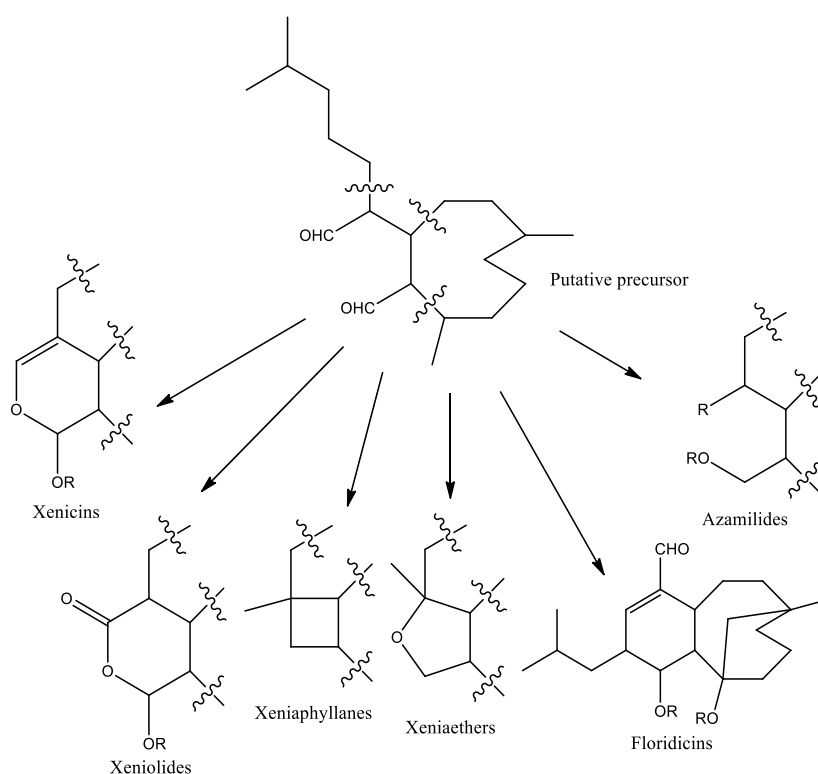


Figure 1. Diversity of chemical skeletons discovered from soft coral genus *Xenia*.

2.1. *Xenia Blumi*

In 2005, eight new diterpenoids, namely blumiolides A–C (1–3), 9-deoxy-isoxeniolide-A (4), 9-deoxy-7,8-epoxy-isoxeniolide-A (5), 9-deacetoxy-7,8-epoxy-13-epi-xenicin (6), 9-deoxy-7,8-epoxy-xeniolide-A (7), and blumicin-A (8) were isolated from *X. blumi* collected from Green Island, Taiwan [23]. Blumiolide-A was reported as a new skeleton of xeniolide with cyclooctane system, and blumiolide-C

(3) showed potent cytotoxicity against HT-29 colorectal cancer and P-388 murine leukemia cell lines at ED₅₀ 0.5 and 0.2 µg/mL, respectively (Figure 2) [23].

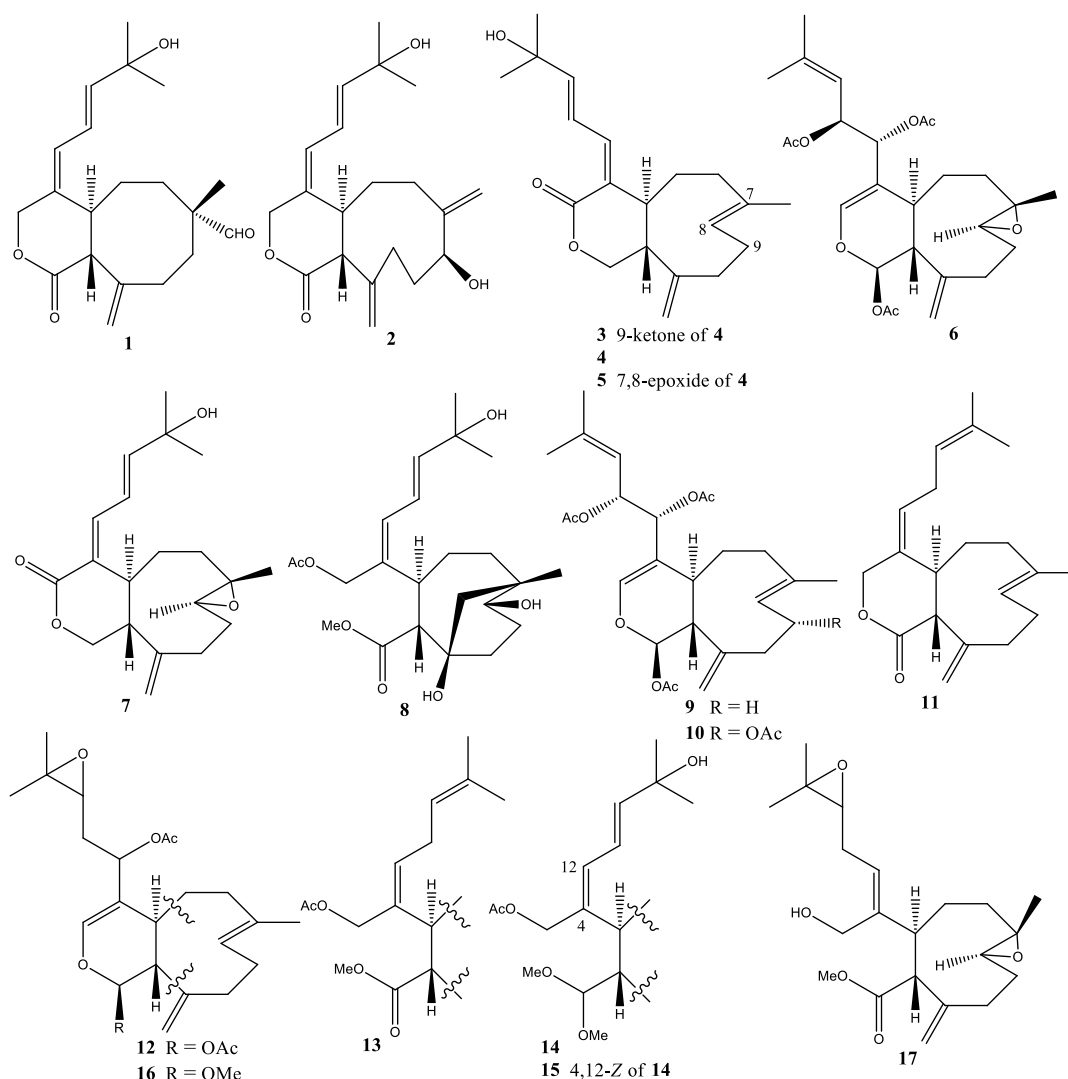


Figure 2. Structures of compounds 1–17.

2.2. *Xenia Crassa*

One new diterpenoid, 9-deacetoxyxenicin (9), was isolated from *X. crassa* collected at John Brewer Reef, Australia [27] (Figure 2).

2.3. *Xenia Elongata*

In 1977, the first representative of the xenicins, xenicin (10), was isolated from *X. elongata* collected at Heron Island, Australia [17]. After 18 years, one new diterpenoid, deoxyxeniolide B (11) was isolated from *X. elongata* collected from Nichinan Coast, Miyazaki Prefecture, Japan [28]. This compound exhibited ichthyotoxicity against mosquito fish (*Orizias latipes*) at LC₁₀₀ 15 ppm within 1 h. In 2007, four new diterpenoids (12–15) without given names were isolated from *X. elongata* cultured at Rutgers University [29]. Furthermore, compound 12 was found to be able to induce apoptosis in MCF 7 (breast carcinoma) cell lines. In 2014, two new diterpenoids (16 and 17) without given names were isolated from *X. elongata*, purchased from Ocean Reef Aquariums and cultured at Rutgers University [30]. In addition, compound 17 showed inhibition of histone deacetylase (HDAC6) with IC₅₀ ~80 µM (Figure 2) [30].

2.4. *Xenia Faraunensis*

In 1994, three new diterpenoids, xeniafaraunols A and B (**18,19**) and faraunatin (**20**), were isolated from *X. faraunensis* collected from the Red Sea [31]. These three compounds **18–20** exhibited cytotoxic activities against P-388 murine leukemia cells ($IC_{50} = 1.2 \mu\text{g/mL}$) (Figure 3) [31].

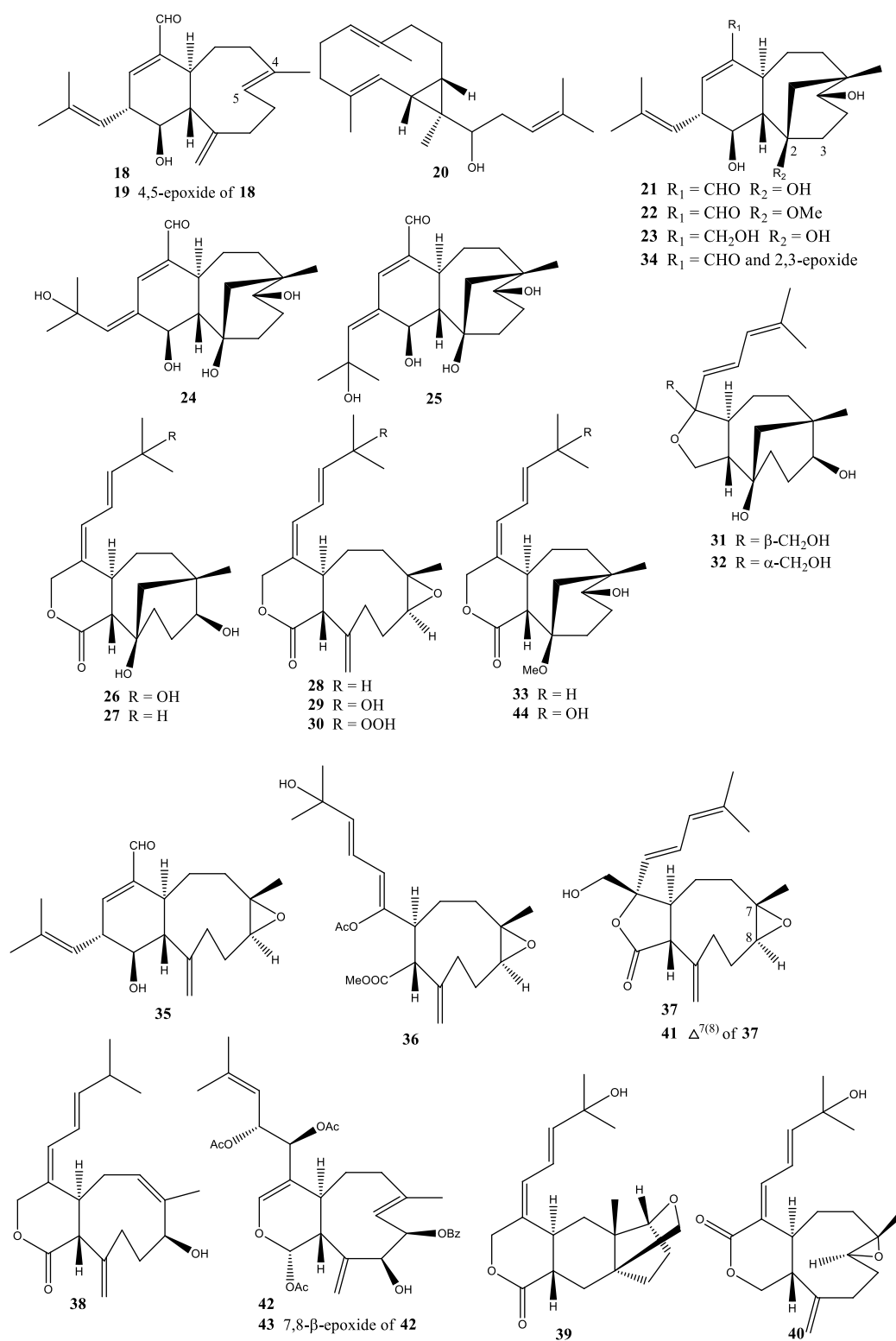


Figure 3. Structures of compounds **18–44**.

2.5. *Xenia Florida*

In 1994, a new class of tricycyclic diterpenoid, floridicin (**21**), was isolated from *X. florida* collected at Bonotsu, Kagoshima Prefecture, Japan [20]. This was the first diterpenoid found possessing an aldehyde group in a soft coral *Xenia* sp. This was followed by the isolation of four new tricycyclic diterpenoids, 2-O-methylfloridicin (**22**) and floridicins A–C (**23–25**), from *X. florida* collected at Bonotsu, Kagoshima Prefecture, Japan [32]. In 1998, seven new diterpenoids, florldes A–E (**26–30**) and florethers A and B (**31** and **32**), were isolated from *X. florida* collected at Bonotsu, Kagoshima Prefecture, Japan [33]. In 2000, six new diterpenoids, namely 11-O-methylflorldide A (**33**), 2 β -epoxyfloridicin (**34**), xeniafaraunol B (**35**), and florldes F–H (**36–38**), were isolated from *X. florida* collected at Bonotsu, Kagoshima Prefecture, Japan [34]. In 2005, three new diterpenoids, xeniolactones A–C (**39–41**), were isolated from *X. florida* collected at Green Island, off Taiwan [35]. In 2006, three new diterpenoids, florxenilides A–C (**42–44**), were isolated from *X. florida* collected at Green Island, off Taiwan [36]. The florxenilide B (**43**) showed strong cytotoxicity against Hepa 1–6 human liver carcinoma cells at ED₅₀ 1.88 μ g/mL (Figure 3) [36].

2.6. *Xenia Lilielae*

In the only report for this species, two new diterpenoids, 4,14-diepoxyxeniaphyllene (**45**) and 4,14-diepoxy-xeniaphyllenol-A (**46**), were isolated from *X. lilielae* collected from the Gulf of Eilat, the Red Sea [37] (Figure 4).

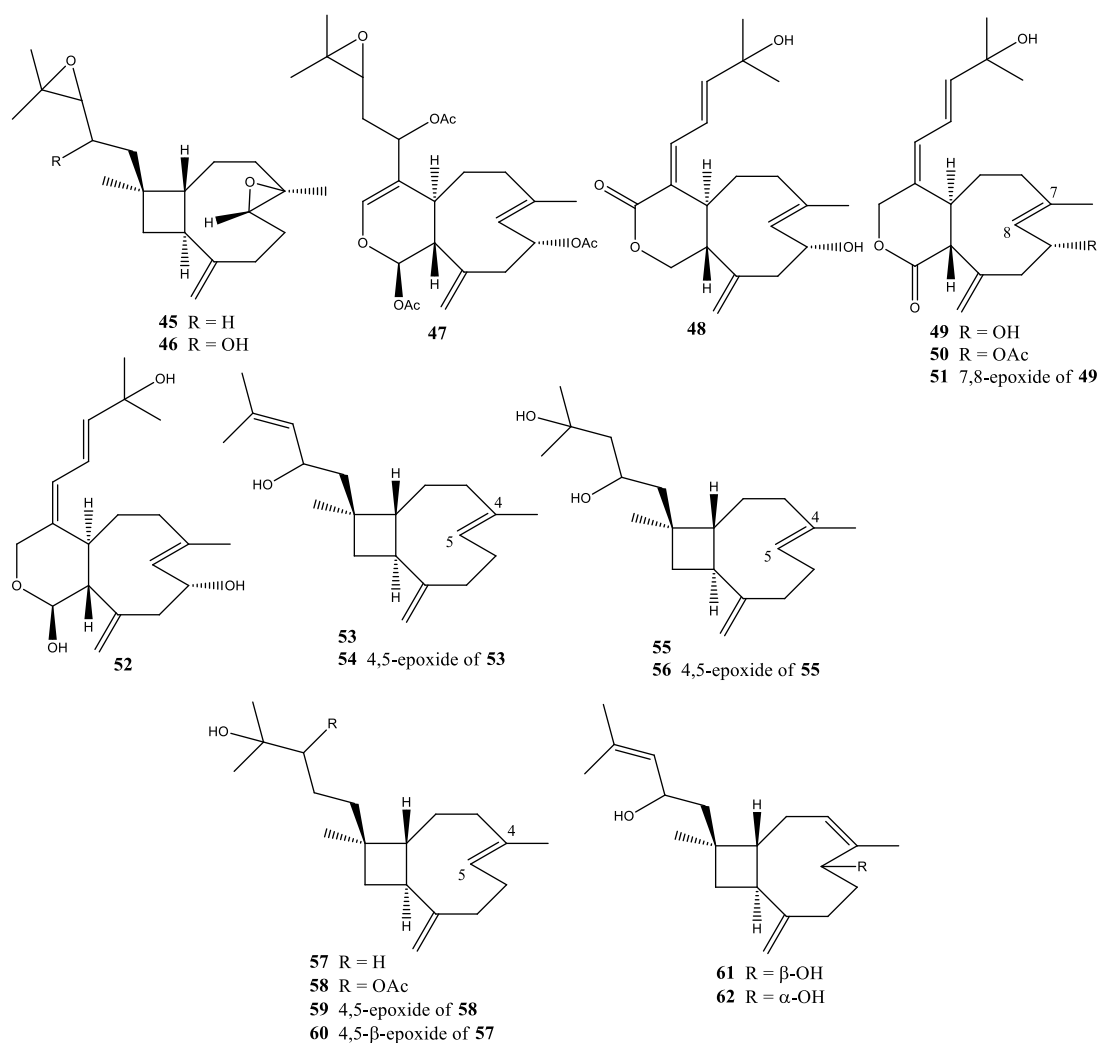


Figure 4. Structures of compounds 45–62.

2.7. *Xenia Macrospiculata*

One year after the discovery of xenicin, a second compound of xenicin, xeniculin (47), was isolated from *X. macrospiculata* collected at the Gulf of Eilat, the Red Sea [38]. In the same year, two new xeniolides, xeniolides A and B (48 and 49), were reported from *X. macrospiculata* collected at the Gulf of Eilat, the Red Sea [18]. In 1980, xeniolide-B 9-acetate (50), 7,8-epoxyxeniolide-B (51), 4,5-epoxyxeniaphyllenol (54), isoxeniaphyllenol (55), xeniaphyllandiol 14-acetate (58), and 4,5-epoxy-14,15-xeniaphyllandiol (59) were first isolated from *X. macrospiculata* collected at the Gulf of Eilat, the Red Sea [19]. In the same year, xenialactol (52), xeniaphyllenol (53), 4,5-epoxyisoxeniaphyllenol (56), and 14,15-xeniaphyllandiol (57), were first discovered in both *X. obscuronata* from the Gulf of Suez (Red Sea) and *X. macrospiculata* from the Gulf of Eilat (Red Sea) [19]. In 1983, 4,5-epoxyxeniaphyllan-14,15-diol (60) was isolated from *X. macrospiculata*, *X. obscuronata*, and *X. lilielae* collected at the Gulf of Eilat, the Red Sea [37]. Xeniaphyllenols B and C (61 and 62) were also isolated from *X. macrospiculata* (Gulf of Eilat, the Red Sea) by the same research group [37] (Figure 4).

2.8. *Xenia Membranacea*

In 1987, two new diterpenoids, havannahine (63) and desoxyhavannahine (64), were isolated from *X. membranacea* collected at Sarcelle Pass, south of New Caledonia [39]. In 1988, four new diterpenoids, namely havannachlorhydrine-11(19) (65), havannachlorhydrine-7(18) (66), havannadichlorhydrine-7(18),11(19) (67), and désacétyl-13 havannachlorhydrine-11(19) (68), were isolated from *X. membranacea* collected at Sarcelle Pass, south of New Caledonia [40]. To date, these compounds 65–68 are the only halogen-based diterpenes found in soft coral *Xenia* sp. In 1989, a pair of new diastereomeric diterpenoids, 11,19-desoxyhavannahine (69) and 7,8,9-epi-11,19-desoxyhavannahine (70), were isolated from *X. membranacea* collected at Sarcelle Pass, south of New Caledonia [41]. In 1990, 17 new diterpenoids, namely acetoxy-19-havannabol-11 (71), chloro-18 acetoxy-19 havannadiol-7,11 (72), havannabol-7 (73), chloro-19 havannadiol-7,11 (74), epi-8,9 deoxy-11,19 havannachlorhydrine-7,18 (75), bis-deoxy-7,18,11,19 havannahine (76), desacetyl-9 epoxy-7,8 epi-13 xenicine (77), desacetyl-9 acetoxy-18 epoxy-7,8 epi-13 xenicine (78), desacetyl-9 hydroxy-6 epi-13 xenicine (79), xenione (80), acetoxy-18 xenione (81), desacetoxy-9 epi-13 xenicine (82), desacetoxy-9 oxo-9 epi-13 xenicine (83), acide branacenoïque (84), branacenoate de metyhle (85), branacenal (86), and diepoxy-7(8),10(11) dichloro-18,19 isoxeniolide A (87), were isolated from *X. membranacea* collected at Sarcelle Pass, south of New Caledonia [42]. However, the stereochemistry of these compounds has remained undetermined to date (Figure 5).

2.9. *Xenia Novae-Britanniae*

In 1979, three new xenicin-related diterpenoids were isolated from *X. novae-britanniae* collected at Laing Island, Papua New Guinea: 13-epi-9-desacetylxicin (88), isoxeniolide-A (89), and 7,8-oxido-isoxeniolide-A (90) [43]. Besides, a total of seven new xenicane-type diterpenoids, novaxenicins A–D (91–94) and xeniolides I–K (95–97), were isolated from *X. novae-britanniae* collected at Kitagamwa, southern Kenya, in 2006 [44]. Furthermore, novaxenicin B (92) induced apoptosis in transformed HEK-293 mammalian cells at a concentration of 1.25 µg/mL, and xeniolide I (95) showed antibacterial activity at a concentration of 1.25 µg/mL against *Escherichia coli* and *Bacillus subtilis* (Figure 6) [44].

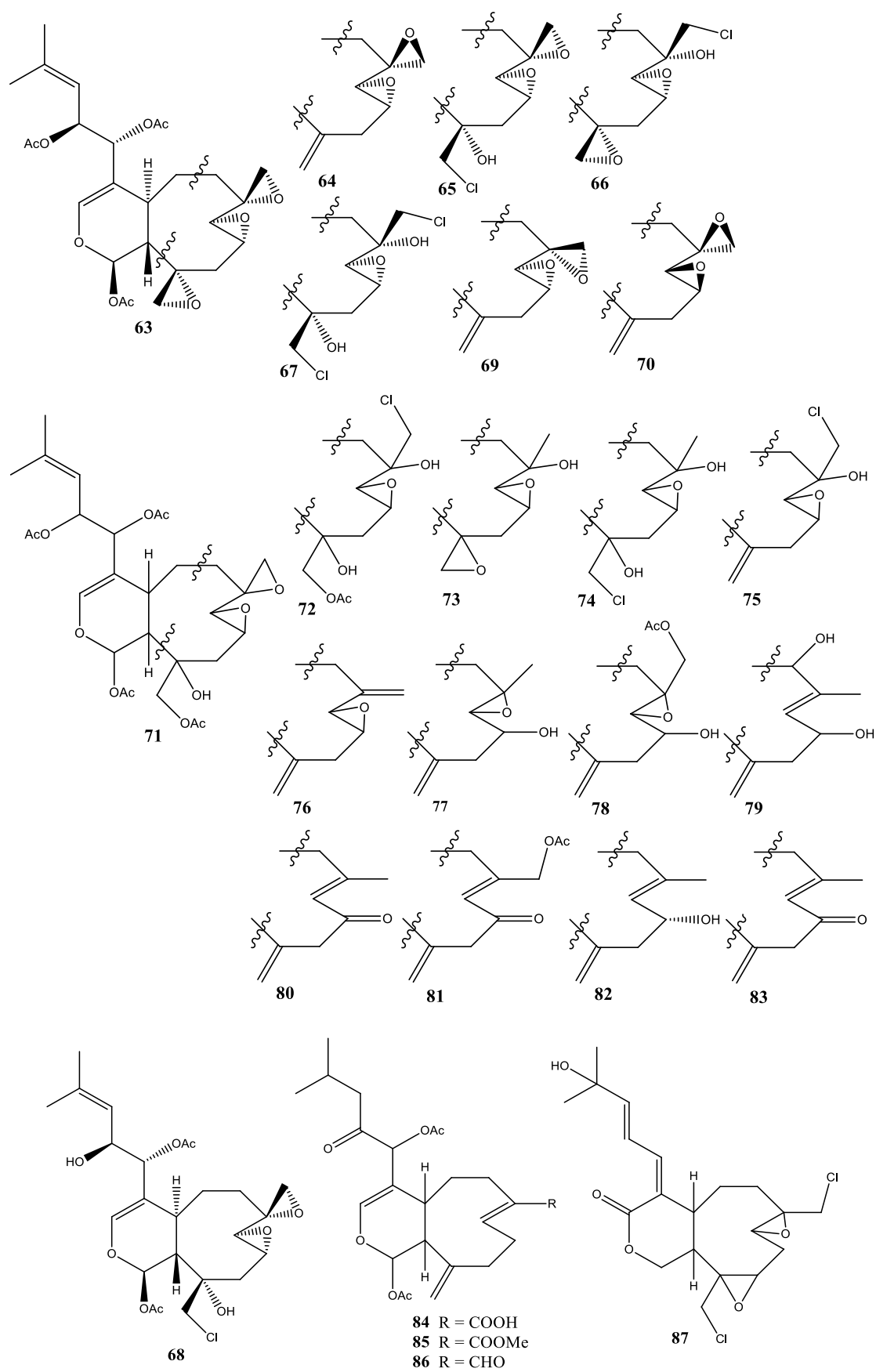


Figure 5. Structures of compounds 63–87.

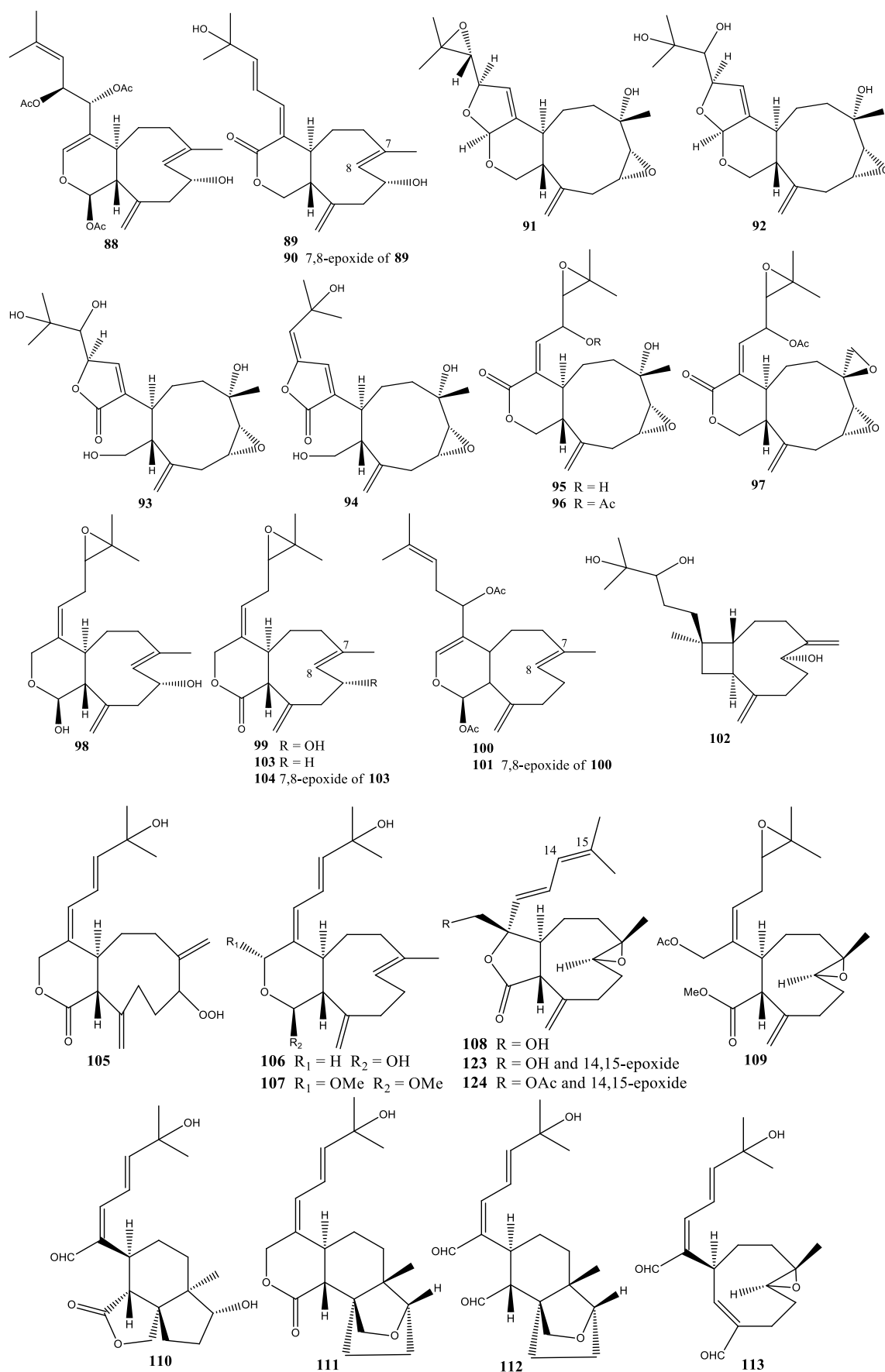


Figure 6. Structures of compounds **88–113** and **123,124**.

2.10. *Xenia Obscuronata*

Two new diterpenoids, xenialactol-D (**98**) and xeniolide-E (**99**), were first recorded in both *X. obscuronata* from the Gulf of Suez, the Red Sea, and *X. macrospiculata* from Gulf of Eilat, the Red Sea [19]. In the same year, two new diterpenoids, 9-deacetoxy-14,15-deepoxyxeniculin (**100**) and 9-deacetoxy-14,15-deepoxyxeniculin 7,8-epoxide (**101**), were isolated from *X. obscuronata* collected at the Gulf of Suez, the Red Sea [19]. In 1983, one new diterpenoid, xeniaphyllantriol (**102**), was isolated from *X. obscuronata* collected at the Gulf of Eilat, the Red Sea [37] (Figure 6).

2.11. *Xenia Umbellata*

In 2002, the *X. umbellata*, which was collected from Green Island, Taiwan, exhibited seven new diterpenoids: 9-deoxyxeniloide-E (**103**), 9-deoxy-7,8-epoxyxeniloide-E (**104**), xeniolide-G (**105**), 9-deoxyxenialactol-C (**106**), xenibecin (**107**), xeniolide-H (**108**), and xenitacin (**109**) [45]. In addition, xeniolide-G (**105**) showed potent cytotoxicity against P-388 (obtained from Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago) cell line at ED₅₀ 0.04 µg/mL, while xenitacin (**109**) showed potent cytotoxicity against A-549 (purchased from American Type Culture Collection), HT-29 (purchased from American Type Culture Collection), and P-388 (obtained from Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago) cell lines at ED₅₀ 3.26, 1.12, and 1.09 µg/mL, respectively. In 2005, four new diterpenoids with novel skeleton, namely umbellactal (**110**), xenibellols A and B (**111** and **112**), and xenibellal (**113**), were isolated from *X. umbellata* (Green Island, off Taiwan) and showed cytotoxicity against P-388 cells with ED₅₀ 3.6, 3.6, 2.8, and 3.2 µg/mL, respectively [24–26], as shown in Figure 6. In 2006, 11 new diterpenoids, namely umbellacins A–I (**114–122**), 14,15-epoxy-xeniolide H (**123**), and 3-acetyl-14,15-epoxy-xeniolide H (**124**), were isolated from *X. umbellata* collected at Green Island, off Taiwan [46]. Cytotoxicity of umbellacins B (**115**), D–F (**117–119**), and H–I (**121,122**) against P-388 cells showed ED₅₀ of 1.6, 4.2, 3.8, 3.7, 3.4, and 3.6 µg/mL, respectively. In the following year, two new xeniolides, xenibelatols A and B (**125** and **126**), were isolated from *X. umbellata* collected at Green Island, off Taiwan [47]. In 2016, one new diterpenoid, xeniumbellal (**127**), was isolated from *X. umbellata* collected at Red Sea Coast, Jeddah, Saudi Arabia [48]. Moreover, xeniumbellal (**127**) and pentahydroxygorgosterol (**201**) displayed antibacterial activity against *Acinetobacter baumannii* with MIC values of 0.22 and 0.28 mM, respectively [48] (Figure 7).

2.12. *Xenia Viridis*

In 1979, the first modified tricyclic xenicin (**128**) was isolated from *X. viridis* collected at Old Reef, off Townsville, Australia [27]. In 2007, two new xenicins, 16,17-diacetoxy-9,13-deacetoxyxenicin (**129**) and 16,17-diacetoxy-7,8-oxirene-9,13-deacetoxyxenicin (**130**), were isolated from *X. viridis* collected at New Caledonia [49] (Figure 7).

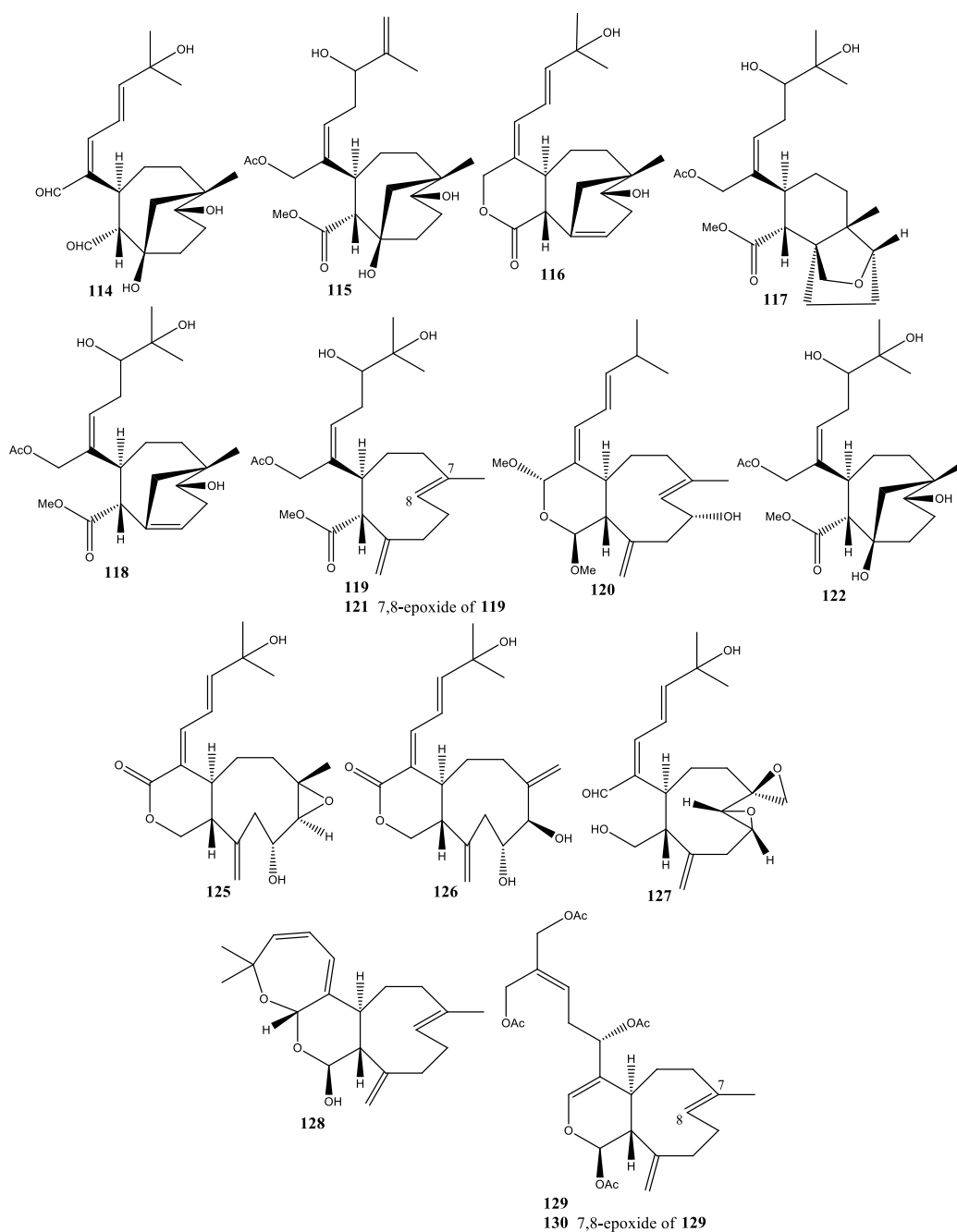


Figure 7. Structures of compounds 114–122 and 125–130.

2.13. *Xenia* sp.

Two pairs of new diastereomeric diterpenes, the first pair being xeniolone (**131**) and isoxeniolone (**132**) and the second pair being hydratoxeniolone (**133**) and hydratoisoxeniolone (**134**), and a new germacranolide-type diterpenoid, germacrexeniolone (**135**), were isolated from *Xenia* sp. collected at Zamami-jima, Okinawa Prefecture, Japan [50,51]. This was the first isolation of perhydroazulene skeleton diterpenoids from the soft coral of *Xenia* sp. In 1995, two new diterpenoids, 9-deoxyxeniolide-A (**136**) and 9-deoxyxeniolide-B (**137**), were isolated from *Xenia* sp., and the 9-deoxyxeniolide-A (**136**) showed the greatest potency of antibacterial activity [52]. In the same year, six new diterpenoids, namely xeniatine A (**138**), xeniatine A epoxide (**139**), isoxeniatines A and B (**140** and **141**), and xeniaethers A and B (**142** and **143**), were isolated from *Xenia* sp. collected at Bonotsu, Kagoshima Prefecture, Japan [21]. These compounds, xeniaethers A and B (**142** and **143**), represented the first isolation of

diterpenoids containing a tetrahydrofuran fused to a nine-membered ring from soft coral *Xenia* sp. In 1996, seven new diterpenoids, namely xeniaethers F–H (**144–146**), isoxeniatine C (**147**), azamials A and B (**148** and **149**), and xenicindial (**150**), were isolated from soft coral *Xenia* sp. collected at Sata Cape, Kagoshima Prefecture, Japan [53]. In the same year, the same research group reported 13 new diterpenoids, azamilides A–J (**151–160**) and xeniaethers C–E (**161–163**), from *Xenia* sp. collected at Bonotsu, Kagoshima Prefecture, Japan [22,54]. In addition, azamilides A–J (**151–160**) were the first example of xenicane-type diterpenoids from the genus *Xenia* with an open A-ring. In 1999, three new diterpenoids, namely xeniaol (**164**), xeniadiol (**165**), and xeniatriol (**166**), were isolated from *Xenia* sp. collected at Ishigaki Island, Okinawa, Japan [55]. In 2000, one new diterpenoid, xeniaoxolane (**167**), was isolated from *Xenia* sp. collected at Ishigaki Island, Okinawa, Japan [56]. In 2002, two new xeniolides, xeniolide-F (**168**) and 9-hydroxyxeniolide-F (**169**), were isolated from *Xenia* sp. collected at Togian Islands near Sulawesi Island, Indonesia [57]. In 2003, two new diterpenoids, dihydroxeniolide-A (**170**) and isoxeniatricetate (**171**), were isolated from *Xenia* sp. collected at Ishigaki Island, Okinawa, Japan [58]. In 2008, four new diterpenoids, xenimanadins A–D (**172–175**), were isolated from *Xenia* sp. collected at Bunaken Marine Park off Manado, North Sulawesi, Indonesia [59]. In 2015, three new diterpenoids (**176–178**) without given names were isolated from *Xenia* sp. collected at Miyako Island, Okinawa, Japan [60]. From 2017 to 2018, two new diterpenoids, 12-epi-9-deacetoxyxenicin (**179**) and 15-deoxy-isoxeniolide-A (**180**), were isolated from *Xenia* sp. collected at Mengalum and Mantanani Islands, Sabah, Malaysia [5,61]. In addition, compound **179** showed cytotoxicity against adult T-cell leukemia S1T cells at IC₅₀ 5.89 µg/mL (Figure 8) [61].

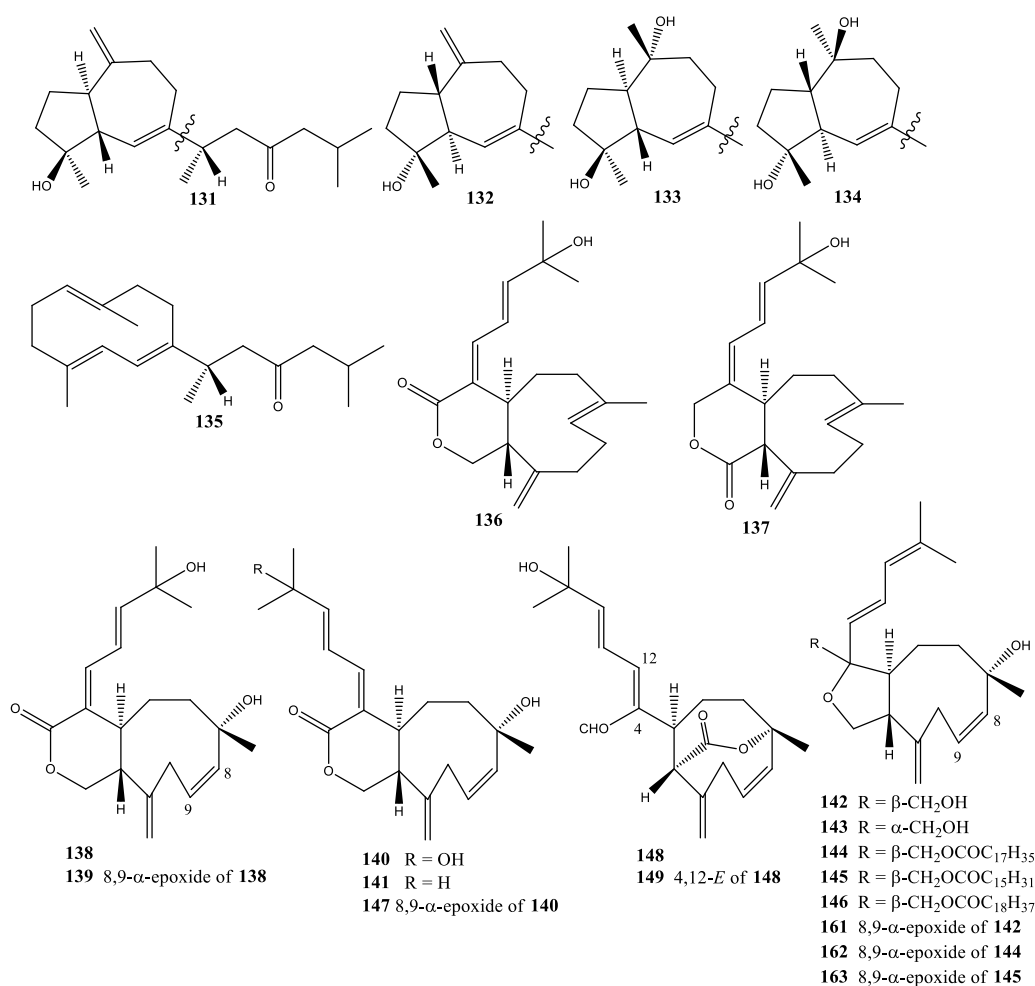


Figure 8. Cont.

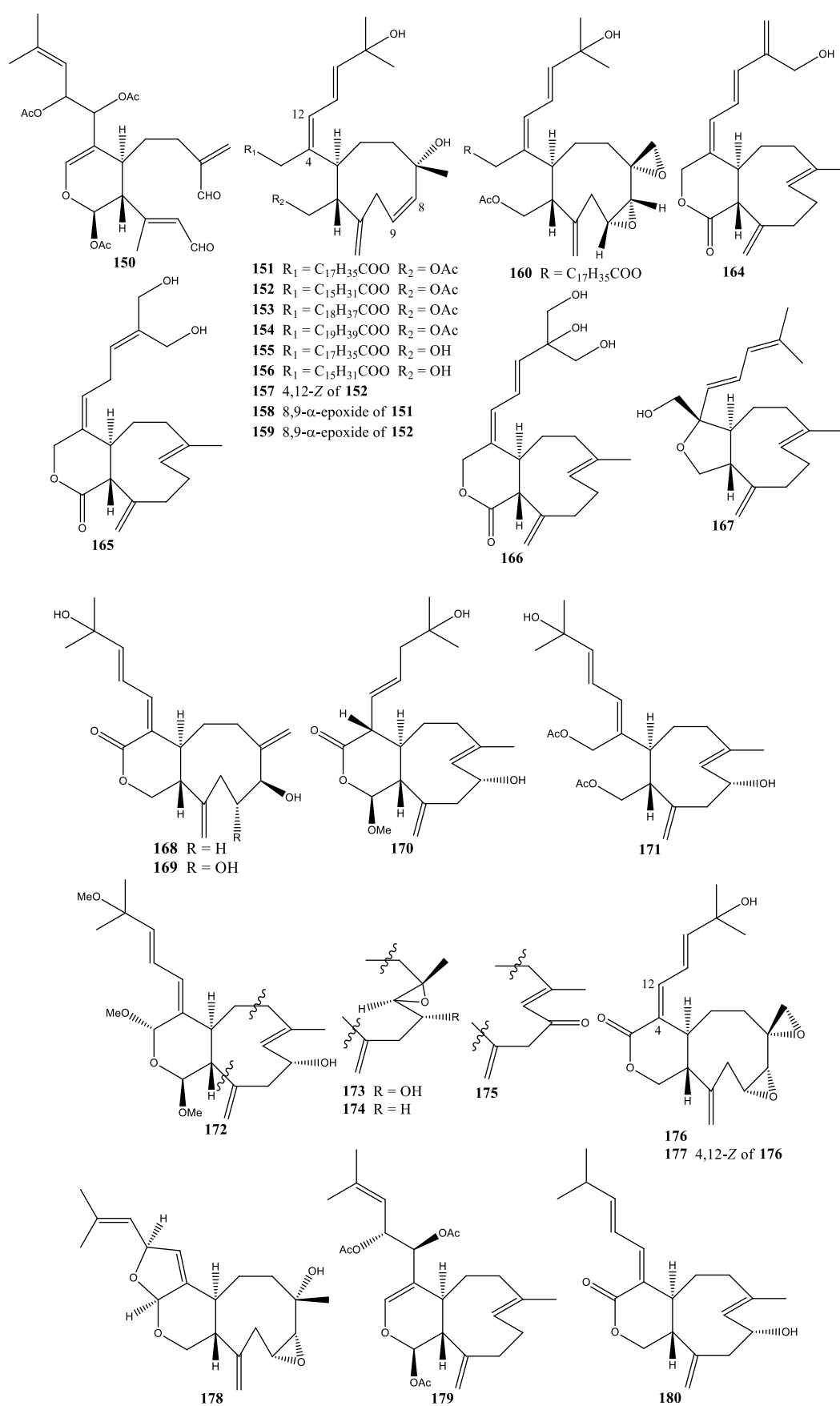


Figure 8. Structures of compounds 131–180.

3. Sesquiterpenes

The first sesquiterpenes isolated from soft coral *Xenia* were palustrol (**181**) and 7-acetoxymurolene (**182**) from *X. obscuronata* collected at the Gulf of Eilat, the Red Sea [37]. In 1986, three new sesquiterpenoids, namely 1,2-epoxy-4-isopropyl-1,6-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (**183**), 4-isopropyl-6-methyl-3,4,4a,7,8,8a-hexahydronaphthalene-1-methanol (**184**), and 5,6-epoxy-4-isopropyl-6-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-methanol acetate (**185**), were isolated from two species of *Xenia* collected at Rib Reef, in the Central Region of the Great Barrier Reef north of Townsville and Hook Reef near the Whitsunday Islands south of Townsville [62]. In 1987, one new sesquiterpenoid, 3,3,7,11-tetramethyltricyclo[6.3.0.0]undec-1(8)-en-4-ol (**186**), isolated from *X. novae-britanniae*, was collected at Rib Reef, Townsville, Australia [63]. In 2002, six new cadinenes, xenitorins A–F (**187–192**), were isolated from *X. puerto-galerae* collected at Green Island, off Taiwan [64]. In 2007, three new cadinenes, namely 8-*epi*-xenitorin A (**193**), 10-*epi*-xenitorin C (**194**), and 7-isopropenyl-4,10-dimethyl-2,3,4,5-tetrahydronaphthalene (**195**), were isolated from *X. puerto-galerae* collected at Green Island, off Taiwan [65]. In 2018, one new sesquiterpenoid, 10 β -O-methyl-1 α H,5 α H-guaia-6-en-4 β -ol (**196**), was isolated from *X. stellifera* collected at Mengalum Island, Sabah, Malaysia [6] (Figure 9).

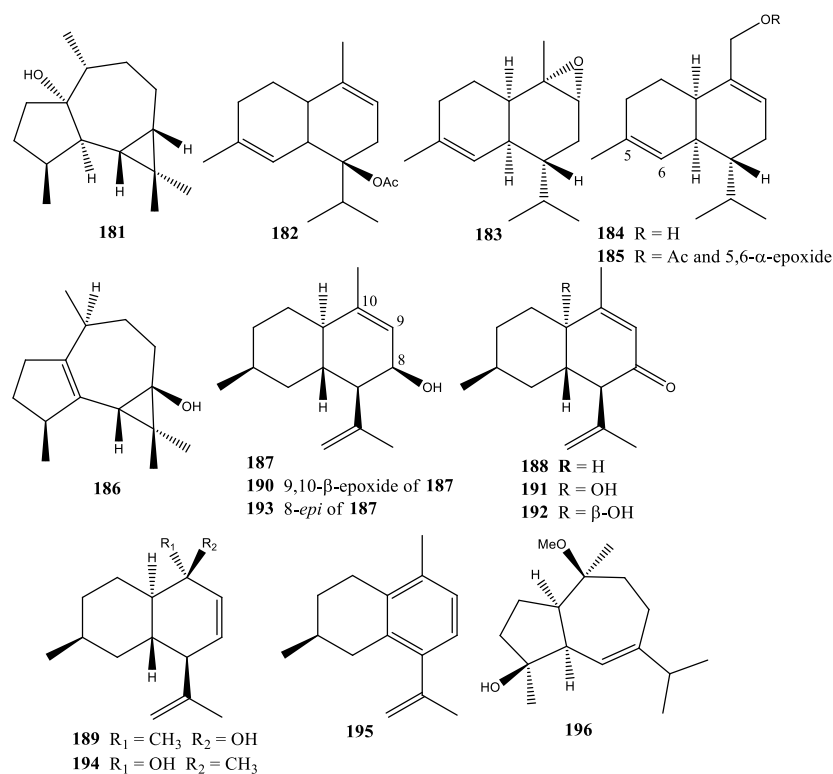


Figure 9. Structures of compounds 181–196.

4. Steroids

In 1986, four new steroids, xeniasterols a–d (**197–200**), were isolated from *Xenia* sp. collected at Zamami-jima, Okinawa Prefecture, Japan [66]. Moreover, steroids **197–200** showed growth inhibitory activity against B-16 melanoma cells at IC₅₀ 5 μ g/mL. In 2016, one new steroid, pentahydrogorgosterol (**201**), was isolated from *X. umbellata* collected at Red Sea Coast, Jeddah, Saudi Arabia [48] (Figure 10).

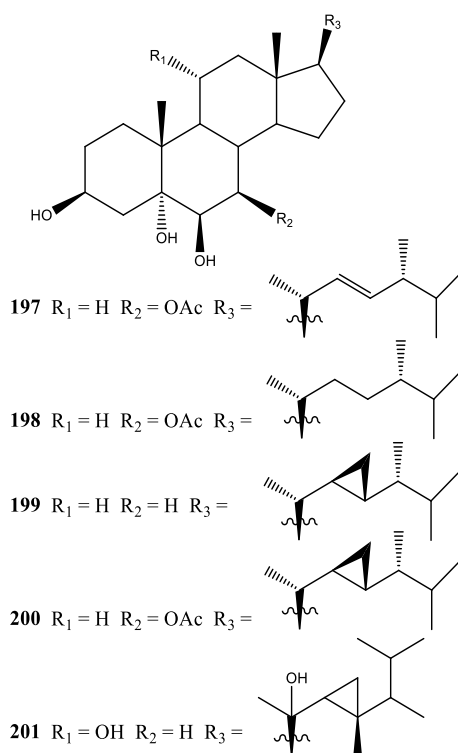


Figure 10. Structures of compounds 197–201.

5. Synthesis of *Xenia* Diterpenoids

As reviewed in the earlier part of this paper, *Xenia* is well known as a rich source of bioactive compounds, especially possessing anticancer activity. The promising anticancer and antimicrobial activities of the isolated compounds from *Xenia* as lead pharmaceuticals have attracted the interest of synthetic chemists. However, synthesis of the diterpenoids is challenging, especially when they consist of an *E*-configuration on the nine-membered rings. Various synthetic approaches have been proposed for a few total syntheses of xeniolides. Ring expansion, ring-closing, and ring-contracting reactions are among the approaches depending on the individual substitution pattern of the target compound [67]. As for reports on the synthesis of such diterpenoids, there is an apparent lack of data due to the challenge of synthesizing nine-membered rings. To date, there is no reported total synthesis of xenicins, and only a few total syntheses of xeniolides have been accomplished [67].

6. Conclusions

This paper presents a review of the terpenes discovered in the soft coral *Xenia* and their biological activities. From 1977 to 2018, a total of 199 terpenes, including 14 sesquiterpenes, 180 diterpenes and 5 steroids, were found in soft coral *Xenia* for the first time. These species of soft coral *Xenia*, including *X. blumi*, *X. crassa*, *X. elongata*, *X. faraunensis*, *X. florida*, *X. lilielae*, *X. macrospiculata*, *X. membranacea*, *X. novae-britanniae*, *X. obscuronata*, *X. puerto-galerae*, *X. stellifera*, *X. umbellata*, *X. viridis*, and *Xenia* sp., were primarily collected at Green Island in Taiwan, regions of Kagoshima and Okinawa in Japan, Gulf of Eilat at the Red Sea, Townsville in Australia, and Sarcelle Pass south of New Caledonia. The assessment of cytotoxicity against cancer cell lines is the most frequent biological evaluation reported for these terpenes, and most of them were not widely tested for their biological potential. An investigation of the diversity in soft coral family XenIIDae revealed that *Xenia* was polyphyletic [68]. This suggested that it might not be suitable to place soft coral belonging to the genus *Xenia* in a single taxon as their morphological characteristics used for traditional taxonomy are not well reflected in the phylogeny in this genus [68]. A recent study from Maloney and McFadden's group suggested that chemical studies in the last 50 years on soft coral *Sarcophyton* may have unknowingly comprised different cryptic

species of *Sarcophyton glaucum*, leading to apparently distinctive chemical variation [69]. In the future, such studies should be carried out for soft coral *Xenia* to gain more understanding of their idiosyncratic chemical variation. In the course of this review, we realized that most of the early reports of natural products chemistry of this genus did not place much importance on the proper authentication of the collected specimens. Most did not report voucher specimen numbers or deposits at biodiversity collection centers. This is quite understandable, but with the Nagoya Protocol coming into force in 2014, these are important matters that a natural products chemist can no longer avoid. Therefore, because the collected marine invertebrate specimens always exhibit a high degree of morphological plasticity and differences due to geographical locations, their proper identification and voucher specimen deposition is warranted for future reference. In addition, recent advancement of technology, particularly in DNA sequencing, has provided sufficient molecular information to facilitate soft coral identification in a more precise and swift manner. The authors recommend the inclusion of morphological and molecular information in articles in future studies. It is also important to realize that compounds isolated from these invertebrates are important not only for their biological potential, but also as a vital tool for chemo-taxonomical studies.

Author Contributions: Conceptualization, T.I. and T.H.; resources, T.K.; writing—original draft preparation, C.-S.P.; writing—review and editing, S.-Y.N.; editing of draft and supervision, C.S.V.; funding acquisition, T.K. and C.S.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors acknowledge the University of the Ryukyus and Shizuoka Institute of Science and Technology for the SciFinder facility.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ahmed, A.F.; Chen, Y.W.; Huang, C.Y.; Tseng, Y.J.; Lin, C.C.; Dai, C.F.; Wu, Y.C.; Shen, J.H. Isolation and structure elucidation of cembranoids from a Dongsha Atoll soft coral *Sarcophyton stellatum*. *Mar. Drugs* **2018**, *16*, 210. [[CrossRef](#)]
2. Huang, C.Y.; Tseng, W.R.; Ahmed, A.F.; Chiang, P.L.; Tai, C.L.; Hwang, T.L.; Dai, C.F.; Sheu, J.H. Anti-inflammatory polyoxygenated steroids from the soft coral *Lobophytum michaelae*. *Mar. Drugs* **2018**, *16*, 93. [[CrossRef](#)] [[PubMed](#)]
3. Li, S.W.; Chen, W.T.; Yao, L.G.; Guo, Y.W. Two new cytotoxic steroids from the Chinese soft coral *Sinularia* sp. *Steroids* **2018**, *136*, 17–21. [[CrossRef](#)] [[PubMed](#)]
4. Liang, L.F.; Kurtán, T.; Mándi, A.; Yao, L.G.; Li, J.; Lan, L.F.; Guo, Y.W. Structural, stereochemical, and bioactive studies of cembranoids from Chinese soft coral *Sarcophyton trocheliophorum*. *Tetrahedron* **2018**, *74*, 1933–1941. [[CrossRef](#)]
5. Phan, C.S.; Kamada, T.; Kobayashi, K.; Hamada, T.; Vairappan, C.S. 15-Deoxy-isoxeniolide-A, new diterpenoid from a Bornean soft coral, *Xenia* sp. *Nat. Prod. Res.* **2018**, *32*, 202–207. [[CrossRef](#)] [[PubMed](#)]
6. Phan, C.S.; Kamada, T.; Ishii, T.; Hamada, T.; Vairappan, C.S. A new guaiane-type sesquiterpenoid from a Bornean soft coral, *Xenia stellifera*. *Nat. Prod. Commun.* **2018**, *13*, 15–16. [[CrossRef](#)]
7. Wu, C.H.; Chai, C.H.; Huang, T.Z.; Huang, C.Y.; Hang, T.L.; Dai, C.F.; Sheu, J.H. Cembranoid-related metabolites and biological activities from the soft coral *Sinularia flexibilis*. *Mar. Drugs* **2018**, *16*, 278. [[CrossRef](#)]
8. Ye, F.; Li, J.; Wu, Y.; Zhu, Z.D.; Mollo, E.; Gavagnin, M.; Gu, Y.C.; Zhu, W.L.; Li, X.W.; Guo, Y.W. Sarinacetamides A and B, nitrogenous diterpenoids with tricycle[6.3.1.0^{1,5}]dodecane scaffold from the South China Sea soft coral *Sarcophyton infundibuliforme*. *Org. Lett.* **2018**, *20*, 2637–2640. [[CrossRef](#)]
9. Green, D.; Carmely, S.; Benayahu, Y.; Kashman, Y. Antheliolide A & B: Two new C₂₄-acetoacetylated diterpenoids of the soft coral *Anthelia glauca*. *Tetrahedron* **1988**, *29*, 1605–1608.
10. Lin, Y.S.; Fazary, A.E.; Chen, C.H.; Kuo, Y.H.; Shen, Y.C. Bioactive xenicane diterpenoids from the Taiwanese soft coral *Asterospicularia laurae*. *Chem. Biodivers.* **2011**, *8*, 1310–1317. [[CrossRef](#)]
11. Hooper, G.J.; Davies-Coleman, M.T. New metabolites from the south African soft coral *Capnella thyrsoidea*. *Tetrahedron* **1995**, *51*, 9973–9984. [[CrossRef](#)]

12. Hooper, G.J.; Davies-Coleman, M.T.; Schleyer, M. New diterpenes from the South African soft coral *Eleutherobia aurea*. *J. Nat. Prod.* **1997**, *60*, 889–893. [[CrossRef](#)] [[PubMed](#)]
13. Tanaka, J.; Ogawa, N.; Liang, J.; Higa, T. Helioxenicins A-C: Diterpenes from the blue coral *Heliopora coerulea*. *Tetrahedron* **1994**, *50*, 9989–9996. [[CrossRef](#)]
14. Chen, S.P.; Su, J.H.; Ahmed, A.F.; Dai, C.F.; Wu, Y.C.; Sheu, J.H. Xeniaphyllane-derived terpenoids from the Formosan soft coral *Sinularia gibberosa*. *Chem. Pharm. Bull.* **2007**, *55*, 1471–1475. [[CrossRef](#)]
15. Schwartz, R.E.; Scheuer, P.J.; Zabel, V.; Watson, W.H. The coraxeniolides, constituents of pink coral, *corallium* sp. *Tetrahedron* **1981**, *37*, 2725–2733. [[CrossRef](#)]
16. Fusetani, N.; Asano, M.; Matsunaga, S.; Hashimoto, K. Acalycixeniolides, novel norditerpenes with allene functionality from two gorgonians of the genus *Acalycigorgia*. *Tetrahedron* **1989**, *45*, 1647–1652. [[CrossRef](#)]
17. Vanderah, D.J.; Steudler, P.A.; Ciereszko, L.S.; Schmitz, F.J.; Ekstrand, J.D.; van der Helm, D. Marine natural products. Xenicin: A diterpenoid possessing a nine-membered ring from the soft coral, *Xenia elongata*. *J. Am. Chem. Soc.* **1977**, *99*, 5780–5784. [[CrossRef](#)]
18. Kashman, Y.; Groweiss, A. Xeniolide-A and xeniolide-B, two new diterpenoids from the soft-coral *Xenia macrospiculata*. *Tetrahedron Lett.* **1978**, *19*, 4833–4836. [[CrossRef](#)]
19. Kashman, Y.; Groweiss, A. New diterpenoids from the soft corals *Xenia macrospiculata* and *Xenia obscuronata*. *J. Org. Chem.* **1980**, *45*, 3824–3827. [[CrossRef](#)]
20. Iwagawa, T.; Kawasaki, J.; Hase, T.; Yu, C.M.; Walter, J.A.; Wright, J.L.C. A new tricyclic diterpene structure from the soft coral *Xenia florida*. *J. Chem. Soc. Chem. Commun.* **1994**, *18*, 2073–2074. [[CrossRef](#)]
21. Iwagawa, T.; Amano, Y.; Hase, T.; Shiro, M. New xenia diterpenoids from a soft coral, *xenia* species 1. *Tetrahedron* **1995**, *51*, 11111–11118. [[CrossRef](#)]
22. Iwagawa, T.; Amano, Y.; Nakatani, M.; Hase, T. New xenia diterpenoids from a soft coral, *Xenia* species containing fatty acyl side chains. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1309–1312. [[CrossRef](#)]
23. El-Gamal, A.A.H.; Chiang, C.Y.; Huang, S.H.; Wang, S.K.; Duh, C.Y. Xenia diterpenoids from the Formosan soft coral *Xenia blumi*. *J. Nat. Prod.* **2005**, *68*, 1336–1340. [[CrossRef](#)] [[PubMed](#)]
24. El-Gamal, A.A.H.; Wang, S.K.; Duh, C.Y. Umbellactal, a novel diterpenoid from the Formosan soft coral *Xenia umbellata*. *Tetrahedron Lett.* **2005**, *46*, 6095–6096. [[CrossRef](#)]
25. El-Gamal, A.A.H.; Wang, S.K.; Duh, C.Y. Xenibellols A and B, new diterpenoids from the Formosan soft coral *Xenia umbellata*. *Org. Lett.* **2005**, *7*, 2023–2025. [[CrossRef](#)]
26. El-Gamal, A.A.H.; Wang, S.K.; Duh, C.Y. Xenibellal, a novel norditerpenoid from the Formosan soft coral *Xenia umbellata*. *Tetrahedron Lett.* **2005**, *46*, 4499–4500. [[CrossRef](#)]
27. Bowden, B.F.; Coll, J.C.; Ditzel, E.; Mitchell, S.J.; Robinson, W.T. Studies of Australian soft corals. XXVIII. The structure determination of two new diterpenes from the genus *Xenia* (Alcyonacea). *Aust. J. Chem.* **1982**, *35*, 997–1002. [[CrossRef](#)]
28. Miyamoto, T.; Takenaka, Y.; Yamada, K.; Higuchi, R. Bioactive diterpenoids from Octocorallia, deoxyxeniolide B, a novel ichthyotoxic diterpenoid from the soft coral *Xenia elongata*. *J. Nat. Prod.* **1995**, *58*, 924–928. [[CrossRef](#)]
29. Andrianasolo, E.H.; Haramaty, L.; Degenhardt, K.; Mathew, R.; White, E.; Lutz, R.; Falkowski, P. Induction of apoptosis by diterpenes from the soft coral *Xenia elongata*. *J. Nat. Prod.* **2007**, *70*, 1551–1557. [[CrossRef](#)]
30. Andrianasolo, E.H.; Haramaty, L.; White, E.; Lutz, R.; Falkowski, P. Mode of action of diterpene and characterization of related metabolites from the soft coral, *Xenia elongata*. *Mar. Drugs* **2014**, *12*, 1102–1115. [[CrossRef](#)]
31. Kashman, Y.; Saltoun, M.; Rudi, A.; Benayahu, Y. Xeniafaraunol A and B, and faraunatin; three new cytotoxic diterpenes from the soft coral *Xenia faraunensis*. *Tetrahedron Lett.* **1994**, *35*, 8855–8858. [[CrossRef](#)]
32. Iwagawa, T.; Kawasaki, J.; Hase, T.; Wright, J.L.C. New di- and tricyclic diterpenes possessing a bicyclic [4.3.1] ring system isolated from the soft coral, *Xenia florida*. *Tetrahedron* **1997**, *53*, 6809–6816. [[CrossRef](#)]
33. Iwagawa, T.; Kawasaki, J.; Hase, T. New xenia diterpenoids isolated from the soft coral, *Xenia florida*. *J. Nat. Prod.* **1998**, *61*, 1513–1515. [[CrossRef](#)] [[PubMed](#)]
34. Iwagawa, T.; Nakamura, K.; Hirose, T.; Okamura, H.; Nakatani, M. New xenicane diterpenes isolated from the acetone extract of the soft coral *Xenia florida*. *J. Nat. Prod.* **2000**, *63*, 468–472. [[CrossRef](#)] [[PubMed](#)]
35. Shen, Y.C.; Lin, Y.C.; Ahmed, A.F.; Kuo, Y.H. New xenicane diterpenoids from *Xenia florida*. *Tetrahedron Lett.* **2005**, *46*, 4793–4796. [[CrossRef](#)]
36. Cheng, Y.B.; Jang, J.Y.; Khalil, A.T.; Kuo, Y.H.; Shen, Y.C. Xenicane-type diterpenes with cytotoxicity from *Xenia florida*. *J. Nat. Prod.* **2006**, *69*, 675–678. [[CrossRef](#)] [[PubMed](#)]

37. Groweiss, A.; Kashman, Y. Eight new xenia diterpenoids from three soft corals of the Red Sea. *Tetrahedron* **1983**, *39*, 3385–3396. [[CrossRef](#)]
38. Groweiss, A.; Kashman, Y. Xeniculin, xeniaphyllenol and xeniaphyllenol oxide, new diterpenoids from the soft-coral *Xenia macrospiculata*. *Tetrahedron Lett.* **1978**, *19*, 2205–2208. [[CrossRef](#)]
39. Lelong, H.; Ahond, A.; Chiaroni, A.; Poupat, C.; Riche, C.; Potier, P.; Pusset, J.; Pusset, M.; Laboute, P.; Menou, J.L. Invertébrés marins du lagon Néo-Calédonien, VIII. Métabolites terpéniques de *Xenia membranacea*. *J. Nat. Prod.* **1987**, *50*, 203–210. [[CrossRef](#)]
40. Almourabit, A.; Ahond, A.; Chiaroni, A.; Poupat, C.; Riche, C.; Potier, P.; Laboute, P.; Menou, J.L. Invertébrés marins du lagon Néo-Calédonien, IX. Havannachlorhydrines, nouveaux métabolites de *Xenia membranacea*: Étude structural et configuration absolue. *J. Nat. Prod.* **1988**, *51*, 282–292. [[CrossRef](#)]
41. Almourabit, A.; Gillet, B.; Ahond, A.; Beloeil, J.C.; Poupat, C.; Potier, P. Invertébrés marins du lagon Néo-Calédonien, XI. Les desoxyhavannahines, nouveaux métabolites de *Xenia membranacea*. *J. Nat. Prod.* **1989**, *52*, 1080–1087. [[CrossRef](#)]
42. Almourabit, A.; Ahond, A.; Poupat, C.; Potier, P. Invertébrés marins du lagon Néo-Calédonien, XII. Isolement et étude structural de nouveaux diterpènes extraits de l'alcyonaire *Xenia membranacea*. *J. Nat. Prod.* **1990**, *53*, 894–908. [[CrossRef](#)]
43. Braekman, J.C.; Daloz, D.; Tursch, B.; Declercq, J.P.; Germain, G.; van Meerssche, M. Chemical studies of marine invertebrates. XXXIX. Three novel diterpenoids from the soft coral *Xenia novae-britanniae*. *Bull. Soc. Chem. Belg.* **1979**, *88*, 71–77. [[CrossRef](#)]
44. Bishara, A.; Rudi, A.; Goldberg, I.; Benayahu, Y.; Kashman, Y. Novaxenicins A-D and xeniolides I-K, seven new diterpenes from the soft coral *Xenia novaebritanniae*. *Tetrahedron* **2006**, *62*, 12092–12097. [[CrossRef](#)]
45. Duh, C.Y.; El-Gamal, A.A.H.; Chiang, C.Y.; Chu, C.J.; Wang, S.K.; Dai, C.F. New cytotoxic xenia diterpenoids from the Formosan soft coral *Xenia umbellata*. *J. Nat. Prod.* **2002**, *65*, 1882–1885. [[CrossRef](#)]
46. El-Gamal, A.A.H.; Wang, S.K.; Duh, C.Y. Cytotoxic xenia diterpenoids from the soft coral *Xenia umbellata*. *J. Nat. Prod.* **2006**, *69*, 338–341. [[CrossRef](#)] [[PubMed](#)]
47. Shen, Y.C.; Chen, Y.H.; Cheng, Y.B.; Kuo, Y.H.; Khalil, A.T. Two new xeniolides from a Taiwanese *Xenia* soft coral. *Nat. Prod. Res.* **2007**, *21*, 1171–1177. [[CrossRef](#)]
48. Ayyad, S.E.N.; Alarif, W.M.; Al-Footy, K.O.; Selim, E.A.; Ghandourah, M.A.; Aly, M.M.; Alorfi, H.S. Isolation, antimicrobial and antitumor activities of a new polyhydroxysteroid and a new diterpenoid from the soft coral *Xenia umbellata*. *Z. Nat.* **2016**, *72*, 27–34. [[CrossRef](#)]
49. Janairo, J.R.; Janairo, G.C.; Ragasa, C.Y.; Bowden, B.F. New xenicanes from *Xenia viridis*. *Nat. Prod. Res.* **2007**, *21*, 1067–1072. [[CrossRef](#)]
50. Kobayashi, M.; Zheng, C.; Yang, C.; Kyogoku, Y.; Kitagawa, I. Xeniolone and isoxeniolone two new diterpenes having a perhydroazulene skeleton from an Okinawan soft coral of *Xenia* sp. *Chem. Pharm. Bull.* **1985**, *34*, 4641–4652. [[CrossRef](#)]
51. Kitagawa, I.; Zheng, C.; Yang, C.; Kobayashi, M.; Kyogoku, Y. Marine natural products. XVI. Structures of five new diterpenes from an Okinawan soft coral of *Xenia* sp. (Xeniidae). *Chem. Pharm. Bull.* **1986**, *34*, 4641–4652. [[CrossRef](#)]
52. Vervoort, H.C.; Fenical, W. Antibacterial diterpenoids from an undescribed soft-coral of the genus *Xenia*. *Nat. Prod. Lett.* **1995**, *6*, 49–55. [[CrossRef](#)]
53. Iwagawa, T.; Masuda, T.; Okamura, H.; Nakatani, M. New xenia diterpenoids from a *Xenia* species of a soft coral. *Tetrahedron* **1996**, *52*, 13121–13128. [[CrossRef](#)]
54. Iwagawa, T.; Amano, Y.; Okamura, H.; Nakatani, M.; Hase, T. New xenia diterpenoids from a soft coral *Xenia* species. *Heterocycles* **1996**, *43*, 1271–1277. [[CrossRef](#)]
55. Miyaoka, H.; Nakano, M.; Iguchi, K.; Yamada, Y. Three new xenicane diterpenoids from Okinawan soft coral of the genus *Xenia*. *Tetrahedron* **1999**, *55*, 12977–12982. [[CrossRef](#)]
56. Miyaoka, H.; Mitome, H.; Nakano, M.; Yamada, Y. Xeniaoxolane: A new xenicane-type diterpenoid from the Okinawan soft coral, *Xenia* sp.; absolute configurations of xeniaoxolane, xeniolide-A and xenialactol. *Tetrahedron* **2000**, *25*, 7737–7740. [[CrossRef](#)]
57. Anta, C.; González, N.; Santafé, G.; Rodríguez, J.; Jiménez, C. New xenia diterpenoids from the Indonesian soft coral *Xenia* sp. *J. Nat. Prod.* **2002**, *65*, 766–768. [[CrossRef](#)]
58. Miyaoka, H.; Nakano, M.; Iguchi, K.; Yamada, Y. Two new xenicane diterpenoids from Okinawan soft coral of the genus *Xenia*. *Heterocycles* **2003**, *61*, 189–196. [[CrossRef](#)]

59. Fattorusso, E.; Romano, A.; Tagliatela-Scafati, O.; Achmad, M.J.; Bavestrello, G.; Cerrano, C. Xenimanadins A-D, a family of xenicane diterpenoids from the Indonesian soft coral *Xenia* sp. *Tetrahedron* **2008**, *64*, 3141–3146. [[CrossRef](#)]
60. Maarisit, W.; Yano, K.; Miyazato, T.; Roy, P.K.; Taira, J.; Ueda, K. Structures and bioactivities of xenicanes from an Okinawan soft coral *Xenia* sp. *Heterocycles* **2015**, *91*, 505–514.
61. Phan, C.S.; Kamada, T.; Ishii, T.; Hamada, T.; Vairappan, C.S. 12-Epi-9-deacetoxyxeninin, new cytotoxic diterpenoid from Bornean soft coral, *Xenia* sp. *Nat. Prod. Res.* **2017**, *33*, 808–813. [[CrossRef](#)] [[PubMed](#)]
62. Bowden, B.F.; Coll, J.C.; Willis, R.H. Studies of Australian soft corals. XXXIX. New sesquiterpene metabolites from several *Xenia* species (Xeniidae, Octocorallia, Anthozoa). *Aust. J. Chem.* **1986**, *39*, 1717–1722. [[CrossRef](#)]
63. Bowden, B.F.; Coll, J.C.; Engelhardt, L.M.; Heaton, A.; White, A.H. Studies of Australian soft corals. XLI structure determination of a new sesquiterpene from *Xenia novae-britanniae* and an investigation of a *Xenia* species. *Aust. J. Chem.* **1987**, *40*, 1483–1489. [[CrossRef](#)]
64. Duh, C.Y.; Chien, S.C.; Song, P.Y.; Wang, S.K.; El-Gamal, A.A.H.; Dai, C.F. New cadinene sesquiterpenoids from the Formosan soft coral *Xenia puerto-galerae*. *J. Nat. Prod.* **2002**, *65*, 1853–1856. [[CrossRef](#)] [[PubMed](#)]
65. Shen, Y.C.; Tzeng, G.L.; Chen, M.H.; Khalil, A.T. Three new cadinene derivatives from *Xenia puerto-galerae*. *J. Chin. Chem. Soc.* **2007**, *54*, 1347–1352. [[CrossRef](#)]
66. Kitagawa, I.; Kobayashi, M.; Cui, Z.; Kiyota, Y.; Ohnishi, M. Marine natural products. XV. Chemical constituents of an Okinawan soft coral of *Xenia* sp. (Xeniidae). *Chem. Pharm. Bull.* **1986**, *34*, 4590–4596. [[CrossRef](#)]
67. Huber, T.; Weisheit, L.; Magauer, T. Synthesis of *Xenia* diterpenoids and related metabolites from marine organisms. *Beilstein J. Org. Chem.* **2015**, *11*, 2521–2539. [[CrossRef](#)]
68. Koido, T.; Imahara, Y.; Fukami, H. High species diversity of the soft coral family Xeniidae (Octocorallia, Alcyonacea) in the temperate region of Japan revealed by morphological and molecular analyses. *ZooKeys* **2019**, *862*, 1–22. [[CrossRef](#)]
69. Maloney, K.N.; Botts, R.T.; Davis, T.S.; Okada, B.K.; Maloney, E.M.; Leber, C.A.; Alvarado, O.; Brayton, C.; Caraballo-Rodríguez, M.A.; Chari, J.V.; et al. Cryptic species account for the seemingly idiosyncratic secondary metabolism of *Sarcophyton glaucum* specimens collected in Palau. *J. Nat. Prod.* **2020**, *83*, 693–705. [[CrossRef](#)]

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).