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Cembranoids from the cultured soft coral *Sinularia sandensis*

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This study reports the isolation and characterization of two novel diterpenoids, norcembranoid 10-*epi*-dehydrogyrosanolide E (**1**) and cembranoid 8-*epi*-flexibilisolide G (**2**), from the cultured soft coral *Sinularia sandensis*. In addition to these new compounds, four known natural products were also identified: norcembranoid 10-*epi*-gyrosanolide E (**3**), cembranoid flexibilisolide G (**4**), and sesquiterpenoids sinularioperoxide A (**5**) and sinularioperoxide C (**6**). The chemical structures of the new marine natural products (**1** and **2**) were elucidated through extensive spectroscopic analysis, including 1D and 2D NMR, and by comparison with reported data. Notably, the new metabolites feature rare stereochemical variations within the cembranoid/norcembranoid framework, enriching structure–activity relationship insights for marine diterpenoids. Preliminary biological evaluation revealed that compound **1** exhibited cytotoxic activity against the MCF-7 human breast cancer cell line. Considering the recognized role of *Sinularia*-derived diterpenoids as promising anti-tumor scaffolds, these findings underscore the developmental potential of cultured soft corals as sustainable sources of structurally diverse and bioactive marine natural products.

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1 Introduction

Octocorals (Subclass Octocorallia) have been firmly established as a rich source of structurally diverse secondary metabolites with significant pharmaceutical potential, representing one of the most chemically productive marine invertebrate groups in natural product drug discovery research.[1–5] Marine organisms account for more than half of the world's total biodiversity,[6] and soft corals, in particular, have emerged as exceptional producers of bioactive compounds with unprecedented structural complexity and biological activities.[7,8] The remarkable chemical diversity exhibited by octocorals encompasses an impressive array of compound classes, including cembranes, eunicellin-based diterpenoids, briaranes, steroids, and sesquiterpenoids, which have demonstrated a wide spectrum of pharmacological properties, including cytotoxic, anti-inflammatory, antimicrobial, and antiviral activities.[9–13]

Extensive chemical investigations of both wild and cultured soft corals have led to the isolation of a wide array of bioactive natural products. Among these, the genus *Sinularia* is one of the most intensively studied and is recognized as a rich source of biologically active cembrane-type and norcembranoid diterpenoids.[14,15] Owing to their 14- or 15-membered macrocyclic frameworks, high stereochemical complexity, and diverse functionalization, these compounds have attracted sustained interest in natural products chemistry, synthetic methodology, and pharmacological research.[16–18] Their intricate biosynthetic origins, often involving polycyclic furanobutenolide intermediates, have been linked to ecological defence mechanisms and structure–activity relationships.[16,19] Recent advances in multidimensional NMR spectroscopy coupled with high-resolution mass spectrometry have significantly improved the structural elucidation of these complex metabolites, allowing confident assignment of subtle stereochemical features critical for biological activity.[20–22]

As part of our ongoing efforts to identify bioactive natural products from marine invertebrates, we investigated the cultured soft coral *S. sandensis*, selected for its distinctive terpenoid profile and suitability for aquaculture.[23,24] Chromatographic separation led to the isolation of two new metabolites, norcembranoid 10-*epi*-dehydrogyrosanolide E (**1**) and cembranoid 8-*epi*-flexibilisolide G (**2**), together with four known compounds (**3–6**). Structural elucidation was achieved through

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comprehensive spectroscopic analyses, including 1D and 2D NMR and HR-ESI-MS, supported by comparison with reported analogues.[20–22] The co-occurrence of new and known terpenoids suggests active biosynthetic diversification in *S. sandensis* involving oxidative and cyclization processes.[25,26] All isolated compounds were evaluated for cytotoxicity using the MTT assay against MCF-7, A-375, and B16F10 cancer cell lines.[27–29] Among them, compound **1** exhibited moderate and selective cytotoxicity toward MCF-7 breast cancer cells at micromolar concentrations, indicating potential anticancer relevance and warranting further mechanistic investigation (Fig. 1 and 2).[29–32]

2 Results

2.1. Structure elucidations of the isolated cembranoids

The freeze-dried specimen of the aquaculture soft coral *Sinularia sandensis* (specimen no. 2025CSC-2) was extracted exhaustively with EtOAc, and the obtained crude extract was further fractionated and purified using normal and reversed phase column chromatography. Two previously undescribed compounds were isolated, including 10-*epi*-dehydrogyrosanolide E (**1**) and 8-*epi*-flexibilisolide G (**2**), along with four known ones: 10-*epi*-gyrosanolide E (**3**),[3] flexibilisolide G (**4**),[18] sinularioperoxide A (**5**),[33] and sinularioperoxide C (**6**).[33]

10-*epi*-Dehydrogyrosanolide E (**1**) was obtained as an oil. The HRESIMS spectrum of **1** exhibited a molecular ion peak at *m*/*z* 353.1357 $[M + Na]^+$, along with ^{13}C NMR data, which suggested a molecular formula of $C_{19}H_{22}O_5$ and implied nine degrees of unsaturation. The IR spectrum revealed the presence of carbonyl (ν_{max} 1747 cm^{-1}) and alkene groups (ν_{max} 1635 cm^{-1}). The ^{13}C NMR (Table 1) spectrum of **1**, showed signals of nineteen carbons, which were further identified by the assistance of DEPT spectrum and the HMQC data as two methyls, five sp^3 methylenes, two sp^3 methines (including one oxymethine), one sp^2 methylene, two sp^2 methines, one sp^3 quaternary carbons and six sp^2 quaternary carbons (including one ester carbonyl and two ketones). The ^1H NMR spectrum of **1** (Table 1) also showed signals of four olefinic protons (δ_H 7.41, s; 5.62, s; 4.63, s; 4.47, s), one oxygen-bearing methine (δ_H 5.32, dd, J = 4.8, 2.4 Hz) and two methyls (δ_H 1.64, s; 1.48, s). The gross structure of **1** was determined by a detailed analysis of 1D and 2D NMR spectra. From the ^1H-^1H COSY spectrum of **1**, it was possible to identify two different structural units, which were assembled with the assistance of an HMBC experiment (Fig. 3). Key HMBC correlations between H-2 to C-3 and C-4; H-4 to C-5 and C-6; H-7 to C-6; H-9 to C-10 and C-11; H-11 to C-19; H-13 to C-19; H_3-17 to C-15 and C-16; H_3-18 to C-7, C-8, and C-9 permitted the connection of the molecular skeleton. Furthermore, comparison of the NMR data of **1** with those of **3** (Table 1) revealed that **1** has the same structural unit extending from C-1 to C-3 and further to C-6 and C-19. However, it was found that **1** possesses one double bond at C-4/C-5 [δ_C 103.0 (CH) and 150.6, (C)] instead of one single bond in **3**. The relative configurations of the three chiral centres at C-1, C-8, and C-11 in **1** were elucidated by detailed analysis of NOE correlations, as shown in Fig. 4. It was found that H_3-18 (δ_H 1.48, s) showed NOE interactions with both H-1 (δ_H 2.76, m) and H-9 (δ_H 2.83, dd, J = 15.6, 4.8 Hz), while H_2-9 was NOE correlated with H-10 (δ_H 5.32, dd, J = 4.8, 2.4 Hz). Therefore, H-1, H-10, and H_3-18 are situated on the β-face. Furthermore, **1** possessed the same configurations at C-1, C-8, and C-10 as those of **3**. Based on the above results, the structure of **1** was unambiguously established.

The HRESIMS of 8-*epi*-flexibilisolide G (**2**) exhibited a $[M + Na]^+$ peak at *m*/*z* 431.2037 (calcd for $C_{22}H_{32}O_7Na$, 431.2040). The

Fig. 1 Aquatic ecological view of the cultured soft coral *S. sandensis*. The photograph shows the morphology and growth characteristics of *S. sandensis* maintained under controlled aquatic ecological conditions. The colony exhibits typical lobed and finger-like projections with a cream to light brown coloration, indicative of healthy polyp expansion. The culture environment provides stable temperature, salinity, and illumination suitable for soft coral maintenance, supporting optimal growth and physiological status.

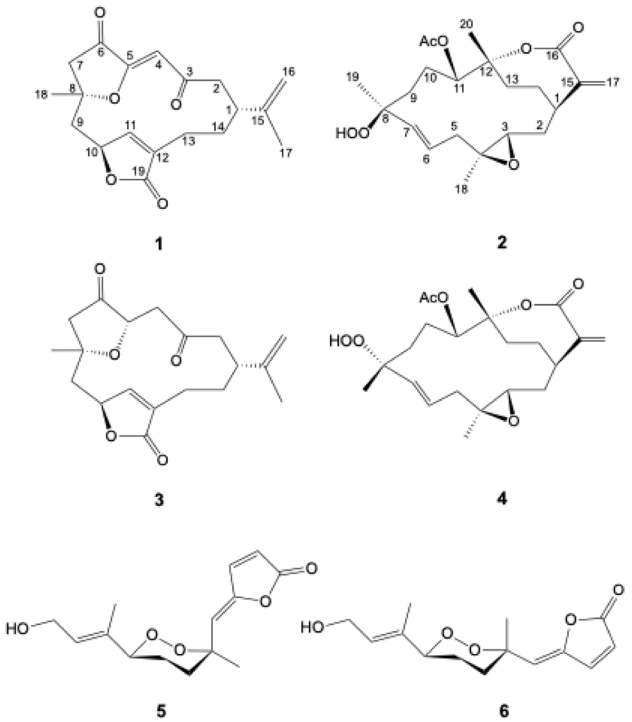

Fig. 2 Structures of the isolated metabolites **1**–**6**.

Table 1 ^{1}H and ^{13}C NMR data for **1**

C/H	δ_H[a] (J in Hz)	δ_C,[b] mult.[c]	C/H	δ_H[a] (J in Hz)	δ_C,[b] mult.[c]
1	2.76 m	40.4, CH	11	7.41 s	151.7, CH
2	2.37 m; 3.07 dd (12.0, 4.8)	45.4, CH_2	12		131.1, C
3		199.0, C	13	2.49 m; 2.52 m	22.7, CH_2
4	5.62 s	103.0, CH	14	1.64 m; 2.17 m	29.9, CH_2
5		150.6, C	15		146.3, C
6		198.3, C	16	4.47 s; 4.63 s	112.7, CH_2
7	2.50 m; 2.67 m	49.4, CH_2	17	1.64 s	18.4, CH_3
8		85.5, C	18	1.48 s	27.3, CH_3
9	2.37 m; 2.83 dd (15.6, 4.8)	41.2, CH_2	19		173.1, C
10	5.32 dd (4.8, 2.4)	78.0, CH			

[a] Spectra obtained in $CDCl_3$ at 600 MHz and. [b] At 150 MHz. [c] Attached protons were determined by DEPT experiments.

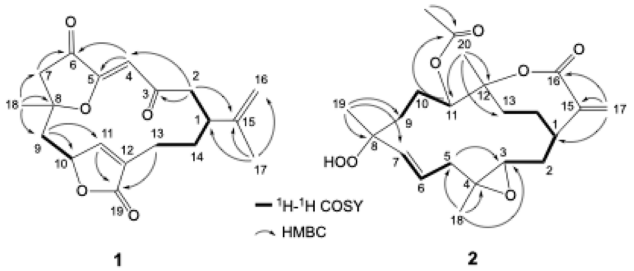

Fig. 3 ^{1}H-^{1}H COSY and HMBC correlations for **1** and **2**.

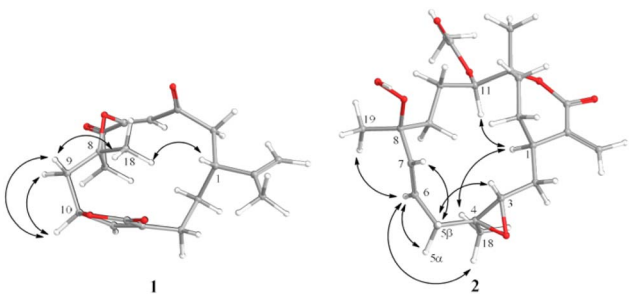

Fig. 4 Selective NOESY correlations for **1** and **2**.

HRESIMS and ^{13}C NMR data suggested a molecular formula of $C_{22}H_{32}O_7$, implying seven degrees of unsaturation. The IR spectrum also revealed the presence of carbonyl (ν_{max} 1733 cm^{-1}) and hydroxy (ν_{max} 3391 cm^{-1}) moieties. The ^{13}C NMR spectrum of **2** (Table 2) showed the presence of 22 carbon signals. It was found that an acetoxyl group (δ_H 2.15, 3H, s; δ_C 20.9, CH_3, 171.1, C). From the ^{1}H NMR (Table 2) spectrum of **2**, the presence of one hydroperoxyl proton resonating as a broad singlet at δ_H 7.61 was observed. Moreover, the ^{1}H NMR spectrum revealed the presence of two olefinic methylene protons as two singlets at δ_H 6.30 and 5.49. A proton signal appearing at δ_H 2.95 (1H, dd, J = 10.8, 3.6 Hz) correlated with a carbon signal at δ_H 61.3 in the HMQC spectrum was attributed to the proton of the trisubstituted epoxide. A detailed comparison of the NMR spectroscopic data of **2** (Table 2) with those of flexibilisolide G (**4**) showed that both compounds have similar structures.

Using 2D NMR spectra (^{1}H-^{1}H COSY, HMQC, and HMBC) (Fig. 3), compound **2** was shown to possess the same molecular framework as that of **4**, while its stereochemistry, particularly at C-8, was resolved by the NOESY experiments (Fig. 4). It was found that H_3-18 (δ_H 1.27, s) showed NOE interactions with both H-1 (δ_H 2.55, m) and H-6 (δ_H 5.73, ddd, J = 16.2, 12.6, 4.8 Hz) and H-6 was NOE correlated with H_3-19 (δ_H 1.39, s) and one of the methylene protons at C-5 (δ_H 2.76, dd, J = 12.6, 4.8 Hz), while one of the methylene protons at C-5 (δ_H 1.75, m) was NOE correlated with H-7 (δ_H 5.63 d, J = 16.2 Hz) and H-3 (δ_H 2.95, dd, J = 10.8, 3.6 Hz). Therefore, H-1, H_3-18, and H_3-19 are situated on the same α-face, and, in contrast, H-3 should be positioned on the β-face of the molecule. The above finding, together with the J value of both H-6 and H-7 (16.2 Hz), also confirmed the *E*-configuration of the 6,7-double bond. Further analysis of other NOE interactions revealed that **2** possessed the same configurations at C-1, C-3, C-4, C-11, and C-12 as those of **4** (Fig. 4). Based on the above results, the structure of **2** was unambiguously established.

2.2. Evaluation of the cytotoxic potential of the isolated cembranoids

The cytotoxicity of **1–6** against three cancer cell lines, including human breast carcinoma cell (MCF-7), human melanoma cell (A-375), and murine melanoma cell (B16F10) lines, was assayed. The MCF-7 cell line represents one of the most widely studied models for hormone-responsive breast cancer, while the A-375 and B16F10 melanoma cell lines provide complementary insights into the potential anti-melanoma activity across human and murine systems.[29,30] These cell lines were selected based on their established relevance in cancer research and the significant clinical need for novel therapeutic agents targeting these malignancies.[31,32] The cytotoxicity assessment protocol followed standardized procedures with appropriate positive controls and multiple concentration points to establish reliable IC_{50} values.[27–29] The results showed that only compound **1** exhibited cytotoxicity against the proliferation of MCF-7 cells (IC_{50} 7.26 μM), and other metabolites were inactive (IC_{50} > 20 μM). This observed activity, although weak compared to established chemotherapeutic agents, represents a valuable starting point for structure–activity relationship (SAR) studies and

Table 2 ^{1}H and ^{13}C NMR data for **2**

C/H	δ_H[a] (J in Hz)	δ_C,[b] mult.[c]	C/H	δ_H[a] (J in Hz)	δ_C,[b] mult.[c]
1	2.55 m	36.0, CH	11	5.10 dd (9.6, 3.0)	76.7, CH
2	1.41 m; 2.04 m	32.9, CH_2	12		86.7, C
3	2.95 dd (10.8, 3.6)	61.3, CH	13	1.94 m	34.3, CH_2
4		61.1, C	14	2.33 m	31.3, CH_2
5	2.76 dd (12.6, 4.8); 1.75 m	42.9, CH_2	15		144.0, C
6	5.73 ddd (16.2, 12.6, 4.8)	129.3, C	16		168.9, C
7	5.63 d (16.2)	135.0, CH	17	6.30 s; 5.49 s	125.0, CH_2
8		85.1, C	18	1.27 s	16.4, CH_3
9	1.63 m; 2.01 m	33.2, CH_2	19	1.39 s	20.6, CH_3
10	1.82 m; 1.80 m	26.3, CH_2	20	1.31 s	26.7, CH_3
			8-OOH	7.61 s	
			11-OAc	2.15 s	20.9, CH_3
					171.1, C

[a] Spectra obtained in $CDCl_3$ at 600 MHz and. [b] At 150 MHz. [c] Attached protons were determined by DEPT experiments.

potential structural optimization.[34,35] The selective activity against MCF-7 cells, as opposed to the melanoma cell lines, suggests that the mechanism of action may involve hormone receptor pathways or other breast cancer-specific molecular targets, providing an intriguing avenue for future pharmacological investigation.[30,36]

3 Materials and methods

3.1. General experimental procedures

Infrared (IR) spectra were obtained on a Fourier-transform IR spectrophotometer (model: JASCO P-2000). ^{1}H and ^{13}C NMR spectra were recorded on a 600 R NMR spectrometer (JEOL, Tokyo, Japan) with $CDCl_3$ (Sigma-Aldrich, St. Louis, MO, USA) as the deuterated solvent. The detected signals in ^{1}H and ^{13}C NMR spectra were corrected at 7.26 ppm (singlet) and 77.0 ppm (triplet), respectively. The coupling constants (J) were converted to Hz. MS data, including ESIMS and HRESIMS, were obtained using a Bruker 7 tesla Solera FTMS system (Bruker, Bremen, Germany). Optical rotations were determined by a digital polarimeter (Jasco P-1010). Single-crystal X-ray analyses were performed on a Bruker D8 Venture diffractometer. Thin-layer chromatography was performed on plates precoated with silica gel 60 F_{254} (0.25 mm-thick, MERCK); the plates were then sprayed with 10% (v/v) H_2SO_4 in methanol, followed by heating to visualize the spots. A normal-phase (NP) HPLC was performed using a system comprised of a HITACHI 5110 pump, a RHEODYNE 7725i injection port, and a NP column (YMC pack SIL, 5 μm, 12 nm, 250 × 20 mm, YMC group).

3.2. Animal material

Specimens of the cultured soft coral *Sinularia sandensis* (specimen no. 2025CSC-2) were collected by hand in a 4-ton cultivating tank located in the National Museum of Marine Biology and Aquarium, Taiwan, in July 2020. A voucher sample was deposited at the National Museum of Marine Biology and Aquarium (voucher no. 2025CSC-2).

3.3. Extraction and isolation

The sliced bodies of the cultured soft coral (11 kg, wet wt) were minced and extracted with EtOAc (5 L × 5). The EtOAc extract was filtered and concentrated under reduced pressure. This procedure resulted in a crude extract weighing 150 g. The solvent-free extract EtOAc was subjected to column chromatography on silica gel (230–400 mesh) and eluted with EtOAc in *n*-hexane (0–100%, gradient) to yield 26 fractions. Fraction 7, eluted with EtOAc–*n*-hexane (1 : 5), was further purified over silica gel using EtOAc–*n*-hexane (1 : 3) to afford five subfractions (7A–7E). Subfraction 7D was separated by normal phase HPLC using EtOAc–*n*-hexane (2 : 5) to yield **2** (1.2 mg) and **4** (1.3 mg). Fraction 14, eluted with EtOAc–*n*-hexane (1 : 2), was purified by normal phase HPLC, using EtOAc–*n*-hexane (3 : 4) to afford six subfractions (14A–14F). Subfraction 14D was separated by normal-phase HPLC using CH_2Cl_2–MeOH (120 : 1) to give **5** (1.1 mg) and **6** (1.4 mg). Fraction 21 eluted with pure EtOAc was further separated by silica gel column chromatography with gradient elution (EtOAc–*n*-hexane, 2 : 1) to afford eight subfractions (21A–21H). Subfraction 21G was separated by normal-phase HPLC using EtOAc–*n*-hexane (3 : 1) to afford **1** (2.8 mg) and **3** (3.2 mg).

10-*epi*-Dehydrogyrosanolide E (**1**): colourless oil; $[\alpha]^{24}_D$ +36.6 (*c* 0.09, $CHCl_3$); IR (neat) ν_{max} 2927, 1747, 1635, 1377 and 1251 cm^{-1}; ^{13}C and ^{1}H NMR data, see Table 1; ESIMS *m*/*z* 353 $[M + Na]^+$; HRESIMS *m*/*z* 353.1357 $[M + Na]^+$ (calcd for $C_{19}H_{22}O_5Na$, 353.1359).

8-*epi*-Flexibilisolide G (**2**): colourless oil; $[\alpha]^{25}_D$ +31.1 (*c* 0.12, $CHCl_3$); IR (neat) ν_{max} 3391, 2921, 2850, 1733, 1705, 1437 and 1248 cm^{-1}; ^{13}C and ^{1}H NMR data, see Table 2; ESIMS *m*/*z* 431 $[M + Na]^+$; HRESIMS *m*/*z* 431.2037 $[M + Na]^+$ (calcd for $C_{22}H_{32}O_7Na$, 431.2040).

3.4. Bioassay materials

All cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were maintained at 37 °C in a humidified incubator with 5% CO_2 and cultured in either RPMI-1640 or DMEM medium supplemented with 10%

fetal calf serum (FCS), 2 mM L-glutamine, 100 U mL^{-1} penicillin, and 100 μg mL^{-1} streptomycin. RPMI-1640 medium, DMEM, FCS, penicillin G, streptomycin, and trypan blue were purchased from GibcoBRL (Gaithersburg, MD, USA). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), dimethyl sulfoxide (DMSO), and all other reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA).

3.5. Cytotoxicity evaluation

Cytotoxicity assays of compounds **1–6** were performed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[37]

4 Conclusions

The present study demonstrates that sustainably cultured *Sinularia sandensis* remains a productive source of structurally novel diterpenoids, including rare epimeric variants within the cembranoid and norcembranoid classes. Given the established significance of *Sinularia*-derived diterpenoids in marine anticancer research, the discovery of new stereochemical frameworks with measurable cytotoxic activity reinforces their value as lead structures for drug development. Furthermore, the identification of unique metabolites from cultured specimens suggests that *ex situ* aquaculture can maintain or modulate biosynthetic capacity while providing ecological sustainability and supply stability. Together, these findings strengthen the foundation for sustainable marine bioprospecting and highlight cultured octocorals as strategically important platforms for future marine-derived anticancer agent discovery.

Author contributions

Kuei-Hung Lai and Jui-Hsin Su conceived and designed the experiments; Chih-Yuan Liang performed the sample collections, extraction, isolation, structure determination, and qualitative HPLC analysis; the pharmacological experiments were carried out by You-Ying Chen; Jui-Hsin Su contributed reagents and analysis tools; Ting-Wei Liao, Lo-Yun Chen, Bo-Rong Peng, Mohamed El-Shazly, and Jui-Hsin Su participated in data interpretation, wrote the manuscript, and revised the paper.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6ra00391e.

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Notes and references

1 Y.-F. Lin, C.-Y. Kuo, Z.-H. Wen, Y.-Y. Lin, W.-H. Wang, J.-H. Su, J.-H. Sheu and P.-J. Sung, Flexibilisquinone, a New Anti-Inflammatory Quinone from the Cultured Soft Coral *Sinularia flexibilis*, *Molecules*, 2013, **18**, 8160–8167, DOI: 10.3390/molecules18078160.

2 J.-H. Su, Y.-F. Lin, Y. Lu, H.-C. Yeh, W.-H. Wang, T.-Y. Fan and J.-H. Sheu, Oxygenated Cembranoids from the Cultured and Wild-Type Soft Corals *Sinularia flexibilis*, *Chem. Pharm. Bull.*, 2009, **57**, 1189–1192, DOI: 10.1248/cpb.57.1189.

3 T.-C. Tsai, H.-Y. Chen, J.-H. Sheu, M. Y. Chiang, Z.-H. Wen, C.-F. Dai and J.-H. Su, Structural Elucidation and Structure–Anti-inflammatory Activity Relationships of Cembranoids from Cultured Soft Corals *Sinularia sandensis* and *Sinularia flexibilis*, *J. Agric. Food Chem.*, 2015, **63**, 7211–7218, DOI: 10.1021/acs.jafc.5b01931.

4 L.-W. Chen, H.-L. Chung, C.-C. Wang, J.-H. Su, Y.-J. Chen and C.-J. Lee, Anti-Acne Effects of Cembrene Diterpenoids from the Cultured Soft Coral *Sinularia flexibilis*, *Mar. Drugs*, 2020, **18**, 487, DOI: 10.3390/md18100487.

5 L.-G. Zheng, K.-H. Lai, P.-J. Sung, Y.-Y. Chen, J. Kuo, J.-H. Su and M. El-Shazly, Microbial dynamics of wild and cultured *Sinularia flexibilis*: Implications for coral aquaculture, *Aquaculture*, 2026, **611**, 742959, DOI: 10.1016/j.aquaculture.2025.742959.

6 W. Appeltans, S. T. Ahyong, G. Anderson, M. V. Angel, T. Artois, N. Bailly, R. Bamber, A. Barber, I. Bartsch, A. Berta, M. Błażewicz-Paszkowycz, P. Bock, G. Boxshall, C. B. Boyko, S. N. Brandão, R. A. Bray, N. L. Bruce, S. D. Cairns, T.-Y. Chan, L. Cheng, A. G. Collins, T. Cribb, M. Curini-Galletti, F. Dahdouh-Guebas, P. J. F. Davie, M. N. Dawson, O. De Clerck, W. Decock, S. De Grave, N. J. de Voogd, D. P. Domning, C. C. Emig, C. Erséus, W. Eschmeyer, K. Fauchald, D. G. Fautin, S. W. Feist, C. H. J. M. Fransen, H. Furuya, O. Garcia-Alvarez, S. Gerken, D. Gibson, A. Gittenberger, S. Gofas, L. Gómez-Daglio, D. P. Gordon, M. D. Guiry, F. Hernandez, B. W. Hoeksema, R. R. Hopcroft, D. Jaume, P. Kirk, N. Koedam, S. Koenemann, J. B. Kolb, R. M. Kristensen, A. Kroh, G. Lambert, D. B. Lazarus, R. Lemaitre,

M. Longshaw, J. Lowry, E. Macpherson, L. P. Madin, C. Mah, G. Mapstone, P. A. McLaughlin, J. Mees, K. Meland, C. G. Messing, C. E. Mills, T. N. Molodtsova, R. Mooi, B. Neuhaus, P. K. L. Ng, C. Nielsen, J. Norenburg, D. M. Opresko, M. Osawa, G. Paulay, W. Perrin, J. F. Pilger, G. C. B. Poore, P. Pugh, G. B. Read, J. D. Reimer, M. Rius, R. M. Rocha, J. I. Saiz-Salinas, V. Scarabino, B. Schierwater, A. Schmidt-Rhaesa, K. E. Schnabel, M. Schotte, P. Schuchert, E. Schwabe, H. Segers, C. Self-Sullivan, N. Shenkar, V. Siegel, W. Sterrer, S. Stöhr, B. Swalla, M. L. Tasker, E. V. Thuesen, T. Timm, M. A. Todaro, X. Turon, S. Tyler, P. Uetz, J. van der Land, B. Vanhoorne, L. P. van Ofwegen, R. W. M. van Soest, J. Vanaverbeke, G. Walker-Smith, T. C. Walter, A. Warren, G. C. Williams, S. P. Wilson and M. J. Costello, The Magnitude of Global Marine Species Diversity, *Curr. Biol.*, 2012, **22**, 2189–2202, DOI: 10.1016/j.cub.2012.09.036.

7 G. H. Phan, Y.-C. Tsai, Y.-H. Liu, L.-S. Fang, Z.-H. Wen, T.-L. Hwang, Y.-C. Chang and P.-J. Sung, Sterol constituents from a cultured octocoral *Sinularia sandensis* (Verseveldt 1977), *J. Mol. Struct.*, 2021, **1246**, 131175, DOI: 10.1016/j.molstruc.2021.131175.

8 C.-Y. Huang, C.-C. Liaw, B.-W. Chen, P.-C. Chen, J.-H. Su, P.-J. Sung, C.-F. Dai, M. Y. Chiang and J.-H. Sheu, Withanolide-Based Steroids from the Cultured Soft Coral *Sinularia brassica*, *J. Nat. Prod.*, 2013, **76**, 1902–1908, DOI: 10.1021/np400454q.

9 C.-Y. Huang, A. F. Ahmed, J.-H. Su, P.-J. Sung, T.-L. Hwang, P.-L. Chiang, C.-F. Dai, C.-C. Liaw and J.-H. Sheu, Bioactive new withanolides from the cultured soft coral *Sinularia brassica*, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 3267–3271, DOI: 10.1016/j.bmcl.2017.06.029.

10 C.-Y. Huang, J.-H. Su, C.-C. Liaw, P.-J. Sung, P.-L. Chiang, T.-L. Hwang, C.-F. Dai and J.-H. Sheu, Bioactive Steroids with Methyl Ester Group in the Side Chain from a Reef Soft Coral *Sinularia brassica* Cultured in a Tank, *Mar. Drugs*, 2017, **15**, 280, DOI: 10.3390/md15090280.

11 T.-C. Tsai, Y.-J. Wu, J.-H. Su, W.-T. Lin and Y.-S. Lin, A New Spatane Diterpenoid from the Cultured Soft Coral *Sinularia leptoclados*, *Mar. Drugs*, 2013, **11**, 114–123, DOI: 10.3390/md11010114.

12 H. F. Lin, H. J. Su, N. L. Lee and N. L. Lee, Cembranoids from the cultured soft coral *Sinularia gibberosa*, *Nat. Prod. Commun.*, 2013, **8**, 1363–1364, DOI: 10.1177/1934578X1300801004.

13 J.-H. Su, Y. Lu, W.-Y. Lin, W.-H. Wang, P.-J. Sung, J.-H. Sheu and A. Cembranoid, Trocheliophorol, from the Cultured Soft Coral Sarcophyton trocheliophorum, *Chem. Lett.*, 2012, **41**, 340, DOI: 10.1246/cl.2012.340.

14 C.-Y. Huang, P.-J. Sung, C. Uvarani, J.-H. Su, M.-C. Lu, T.-L. Hwang, C.-F. Dai, S.-L. Wu and J.-H. Sheu, Glaucumolides A and B, Biscembranoids with New Structural Type from a Cultured Soft Coral *Sarcophyton glaucum*, *Sci. Rep.*, 2015, **5**, 15624, DOI: 10.1038/srep15624.

15 T.-H. Hsiao, C.-S. Sung, Y.-H. Lan, Y.-C. Wang, M.-C. Lu, Z.-H. Wen, Y.-C. Wu and P.-J. Sung, New Anti-Inflammatory Cembranes from the Cultured Soft Coral *Nephthea columnaris*, *Mar. Drugs*, 2015, **13**, 3443–3453, DOI: 10.3390/md13063443.

16 R. A. Craig and B. M. Stoltz, Polycyclic Furanobutenolide-Derived Cembranoid and Norcembranoid Natural Products: Biosynthetic Connections and Synthetic Efforts, *Chem. Rev.*, 2017, **117**, 7878–7909, DOI: 10.1021/acs.chemrev.7b00083.

17 M. Y. Nurrachma, D. Sakaraga, A. Y. Nugraha, S. I. Rahmawati, A. Bayu, L. Sukmarini, A. Atikana, A. Prasetyoputri, F. Izzati, M. F. Warsito and M. Y. Putra, Cembranoids of Soft Corals: Recent Updates and Their Biological Activities, *Nat. Prod. Bioprospect.*, 2021, **11**, 243–306, DOI: 10.1007/s13659-021-00303-2.

18 H.-J. Shih, Y.-J. Tseng, C.-Y. Huang, Z.-H. Wen, C.-F. Dai and J.-H. Sheu, Cytotoxic and anti-inflammatory diterpenoids from the Dongsha Atoll soft coral *Sinularia flexibilis*, *Tetrahedron*, 2012, **68**, 244–249, DOI: 10.1016/j.tet.2011.10.054.

19 P. D. Scesa, Z. Lin and E. W. Schmidt, Ancient defensive terpene biosynthetic gene clusters in the soft corals, *Nat. Chem. Biol.*, 2022, **18**, 659–663, DOI: 10.1038/s41589-022-01027-1.

20 S. S. Ebada, R. A. Edrada, W. Lin and P. Proksch, Methods for isolation, purification and structural elucidation of bioactive secondary metabolites from marine invertebrates, *Nat. Protoc.*, 2008, **3**, 1820–1831, DOI: 10.1038/nprot.2008.182.

21 T. L. Suyama, W. H. Gerwick and K. L. McPhail, Survey of marine natural product structure revisions: A synergy of spectroscopy and chemical synthesis, *Bioorg. Med. Chem.*, 2011, **19**, 6675–6701, DOI: 10.1016/j.bmc.2011.06.011.

22 I. Pérez-Victoria, J. Martín and F. Reyes, Combined LC/UV/MS and NMR Strategies for the Dereplication of Marine Natural Products, *Planta Med.*, 2016, **82**, 857–871, DOI: 10.1055/s-0042-101763.

23 B.-W. Chen, Y.-C. Wu, M. Y. Chiang, J.-H. Su, W.-H. Wang, T.-Y. Fan and J.-H. Sheu, Eunicellin-based diterpenoids from the cultured soft coral *Klyxum simplex*, *Tetrahedron*, 2009, **65**, 7016–7022, DOI: 10.1016/j.tet.2009.06.047.

24 T.-C. Chang, A. B. Mayfield and T.-Y. Fan, Culture systems influence the physiological performance of the soft coral *Sarcophyton glaucum*, *Sci. Rep.*, 2020, **10**, 20200, DOI: 10.1038/s41598-020-77071-5.

25 P.-J. Sung, M.-R. Lin, Y.-D. Su, M. Y. Chiang, W.-P. Hu, J.-H. Su, M.-C. Cheng, T.-L. Hwang and J.-H. Sheu, New briaranes from the octocorals *Briareum excavatum* (Briareidae) and *Junceella fragilis* (Ellisellidae), *Tetrahedron*, 2008, **64**, 2596–2604, DOI: 10.1016/j.tet.2008.01.023.

26 P.-J. Sung, M.-R. Lin and M. Y. Chiang, The Structure and Absolute Stereochemistry of Briaexcavatin U, a New Chlorinated Briarane from a Cultured Octocoral *Briareum excavatum*, *Chem. Lett.*, 2009, **38**, 154–155, DOI: 10.1246/cl.2009.154.

27 P. Senthilraja and K. Kathiresan, In vitro cytotoxicity MTT assay in Vero, HepG2 and MCF -7 cell lines study of Marine Yeast, *J. Appl. Pharm. Sci*, 2015, 80–84, DOI: 10.7324/japs.2015.50313.

28 O. O. Ogbole, P. A. Segun and A. J. Adeniji, In vitro cytotoxic activity of medicinal plants from Nigeria ethnomedicine on Rhabdomyosarcoma cancer cell line and HPLC analysis of active extracts, *BMC Complement. Altern. Med.*, 2017, **17**, 494, DOI: 10.1186/s12906-017-2005-8.

29 M. L. de Mesquita, J. E. de Paula, C. Pessoa, M. O. de Moraes, L. V. Costa-Lotufo, R. Grougnet, S. Michel, F. Tillequin and L. S. Espindola, Cytotoxic activity of Brazilian Cerrado plants used in traditional medicine against cancer cell lines, *J. Ethnopharmacol.*, 2009, **123**, 439–445, DOI: 10.1016/j.jep.2009.03.018.

30 A. A. Al-Karmalawy, M. Sun, M. F. Abdelwahab, J. Zhang, M. N. Samy, N. M. Mohamed, I. M. Abdel-Rahman, F. Alsenani, U. R. Abdelmohsen and B. K. Mahmoud, Cytotoxic metabolites from Sinularia levi supported by network pharmacology, *PLOS One*, 2024, **19**, e0294311, DOI: 10.1371/journal.pone.0294311.

31 R. A. Rafiudeen, N. H. Anwardeen, V. Lavanya, S. Jamal and N. Ahmed, Coral Reef Metabolites for Cancer Treatment, *Curr. Pharmacol. Rep.*, 2024, **11**, 386–388, DOI: 10.1007/s40495-024-00386-8.

32 E. V. Ermolenko, A. B. Imbs, T. A. Gloriozova, V. V. Poroikov, T. V. Sikorskaya and V. M. Dembitsky, Chemical Diversity of Soft Coral Steroids and Their Pharmacological Activities, *Mar. Drugs*, 2020, **18**, 613, DOI: 10.3390/md18120613.

33 C.-H. Chao, C.-H. Hsieh, S.-P. Chen, C.-K. Lu, C.-F. Dai, Y.-C. Wu and J.-H. Sheu, Novel cyclic sesquiterpene peroxides from the Formosan soft coral Sinularia sp, *Tetrahedron Lett.*, 2006, **47**, 2175–2178, DOI: 10.1016/j.tetlet.2006.01.107.

34 N. K. Fuloria, R. K. Raheja, K. H. Shah, M. J. Oza, Y. A. Kulkarni, V. Subramaniyan, M. Sekar and S. Fuloria, Biological activities of meroterpenoids isolated from different sources, *Front. Pharmacol.*, 2022, **13**, 830103, DOI: 10.3389/fphar.2022.830103.

35 F. Berrue and R. G. Kerr, Diterpenes from gorgonian corals, *Nat. Prod. Rep.*, 2009, **26**, 681–710, DOI: 10.1039/B821918B.

36 G. Said, X.-M. Hou, X. Liu, R. Chao, Y.-Y. Jiang, J.-Y. Zheng and C.-L. Shao, Antimicrobial and Cytotoxic Activities of Secondary Metabolites from the Soft Coral Derived Fungus Aspergillus sp, *Chem. Nat. Compd.*, 2019, **55**, 531–533, DOI: 10.1007/s10600-019-02732-5.

37 B.-R. Peng, M.-C. Lu, M. El-Shazly, S.-L. Wu, K.-H. Lai and J.-H. Su, Aquaculture Soft Coral Lobophytum crassum as a Producer of Anti-Proliferative Cembranoids, *Mar. Drugs*, 2018, **16**, 15, DOI: 10.3390/md16010015.