HETEROCYCLES, Vol. 106, No. 12, 2023, pp. -. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 5th October, 2023, Accepted, 25th October, 2023, Published online, 30th October, 2023
DOI: 10.3987/COM-23-14911

BRIASTECHOLIDE N: A NEW CHLORINE-CONTAINING BRIARANE DITERPENOID DERIVING FROM CULTURED *BRIAREUM STECHEI*

You-Ying Chen,[ab] Yueh-Wen Liu,[c] Su-Ying Chien,[d] Yu-Cheng Chen,[e] Fu-Ching Chiu,[b] Po-Wei Huang,[bf] I-Li Su,[bgh] Zhi-Hong Wen,[b] Hung-Tsung Lee,[i]* and Ping-Jyun Sung[abjkl]*

[a] National Museum of Marine Biology and Aquarium, Pingtung 944401, Taiwan. [b] Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 804201, Taiwan. [c] Department of Cosmetics and Fashion Styling, Cheng Shiu University, Kaohsiung 833301, Taiwan. [d] Instrument Center, National Taiwan University, Taipei 106319, Taiwan. [e] Research Center for Chinese Herbal Medicine, Graduate Institute of Healthy Industry Technology, College of Human Ecology, Chang Gung University of Science and Technology, Taoyuan 333324, Taiwan. [f] Division of Urology, Department of Surgery, Zuoying Branch of Kaohsiung Armed Forces General Hospital, Kaohsiung 813204, Taiwan. [g] Division of Cardiovascular Surgery, Department of Surgery, Antai Medical Care Corporation, Antai Tian-Sheng Memorial Hospital, Pingtung 928004, Taiwan. [h] Division of Cardiovascular Surgery, Department of Surgery, Kaohsiung Medical University, Chung-Ho Memorial Hospital, Kaohsiung 807377, Taiwan. [i] Division of Pulmonary Medicine, Antai Tian-Sheng Memorial Hospital, Pingtung 928004, Taiwan. [j] Chinese Medicine Research and Development Center, China Medical University Hospital, Taichung 404394, Taiwan. [k] Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807378, Taiwan. [l] Ph.D. Program in Pharmaceutical Biotechnology, Fu Jen Catholic University, New Taipei City 242062, Taiwan.
E-mail: secobarbitalee@yahoo.com.tw, pjsung@nmmba.gov.tw

Abstract – A new chlorine-containing briarane-type diterpenoid, briastecholide N (**1**) was isolated from cultured octocoral *Briareum stechei via* chemical screening. The structure of **1** was corroborated by 2D NMR experiments and confirmed backed by single-crystal X-ray diffraction analysis. The study found that **1** is capable of increasing the release of alkaline phosphatase (ALP) at 10 μM.

Briarane-type natural products are a group of diterpenoids based on bicyclo[8.4.0]tetradecane ring system, mostly with a γ-lactone moiety. Since the discovery of briarane, briarein A, 46 years ago,[1] over 800 briaranes have been found in various marine invertebrates, with octocorals under genus *Briareum* proven to be the most important sources.[2] Waters in the tropical Indo-Pacific Ocean have been found to be habitats of marine life and organisms with remarkable biodiversity.[3] Given the close correlation between biodiversity and natural product diversity, an encrusting octocoral *Briareum stechei* (Kükenthal 1908) (phylum: Cnidaria, sub-phylum: Anthozoa, class: Octocorallia, order: Scleralcyonacea, family: Briareidae)[4,5] distributed in the waters of Taiwan and Okinawan was collected as a representative specimen,[6,7] due to its rich biota. In order to protect the population and habitats of this endangered species from overexploitation and uphold bioactive materials,[8,9] the study successfully isolated a new highly-oxygenated briarane, briastecholide N (**1**) (Figure 1) from cultured *B. stechei*, in addition to ascertaining the structure and alkaline phosphatase (ALP) activity of **1**. The structure, including the absolute configuration of **1**, was further confirmed *via* a single-crystal X-ray diffraction analysis using a diffractometer equipped with the molybdenum radiation (Mo Kα) source.

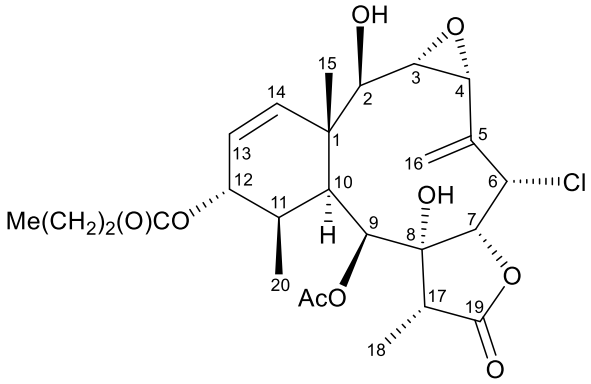

Figure 1. Structure of briastecholide N (**1**)

In the shape of amorphous powder, briastecholide N (**1**) was put into methanol solution for generating colorless crystals, $[\alpha]_D$ +45 (*c* 0.05, $CHCl_3$). The ESIMS spectrum exhibiting a pair of isotopic $[M + Na]^+/[M + 2 + Na]^+$ ion peaked in a ratio of 3:1, underscoring the presence of a chlorine atom in **1**. The following is the molecular formula of **1**: $C_{26}H_{35}ClO_9$ using HRESIMS data (*m/z* 549.18632 $[M + Na]^+$, Calcd for $C_{26}H_{35}ClO_9$ + Na, 549.18618), which needs nine degrees of unsaturation. Its IR bands revealed the presence of hydroxy (ν_{max} 3432 cm^{-1}), γ-lactone (ν_{max} 1774 cm^{-1}), and ester carbonyl (ν_{max} 1734 cm^{-1}) groups. Plus analysis of the ^1H NMR (Table 1), HSQC, and HMBC spectroscopic data, it was suggested that there should be two exchangeable protons in **1**. Because trace amount of **1** was obtained, the ^1H and ^{13}C NMR data were assigned with the assistance of HSQC and HMBC spectra (Table 1). The HSQC and HMBC spectra indicated the presence of disubstituted olefin (δ_C 149.3/CH-13, 142.2/CH-14), while the

presence of exocyclic olefin was confirmed by the typical signal of an sp^2 methylene at δ_C 118.3 (CH_2-16) and exomethylene proton signals at δ_H 5.54 (1H, d, J = 3.0 Hz, H-16a) and 5.98 (1H, d, J = 3.0 Hz, H-16b). In addition, three carbonyls resonating at δ_C 174.0, 172.5, and 169.4 in the ^{13}C NMR spectrum revealed the presence of a γ-lactone and two other ester groups. In the ^1H NMR spectrum, an acetate methyl (δ_H 2.21, 3H, s) and an *n*-butyrate (δ_H 0.94, 3H, t, J = 7.2 Hz; 1.63, 2H, sext, J = 7.2 Hz; 2.22, 2H, t, J = 7.2 Hz) were observed. The aforementioned findings showed that five double bonds accounted for five unsaturated degrees, with the remaining four degrees ascertaining **1** as a tetracyclic molecule. A disubstituted epoxy group was identified by the chemical shifts of two oxymethine carbons at δ_C 62.4 (CH-3) and 58.0 (CH-4), as well as their proton signals at δ_H 3.41 (1H, dd, J = 8.4, 3.6 Hz, H-3) and 3.71 (1H, d, J = 3.6 Hz, H-4), respectively.

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

Position	δ_H[a] (J in Hz)	δ_C[b] (mult.)[c]
1		40.5, C
2	3.14 dd (8.4, 3.0)	76.2, CH
3	3.41 dd (8.4, 3.6)	62.4, CH
4	3.71 d (3.6)	58.0, CH
5		n. o.[d]
6	5.42 ddd (3.0, 3.0, 3.0)	60.8, CH
7	5.08 d (3.0)	76.2, CH
8		85.0, C
9	5.49 d (9.6)	68.6, CH
10	2.28 dd (9.6, 3.0)	35.9, CH
11	2.25 m	35.0, CH
12	4.88 dd (6.0, 2.4)	70.0, CH
13	5.76 ddd (10.2, 6.0, 1.2)	149.3, CH
14	6.24 d (10.2)	142.2, CH
15	1.06 s	15.2, Me
16a/b	5.54 d (3.0); 5.98 d (3.0)	118.3, CH_2
17	2.46 q (7.2)	44.8, CH
18	1.22 d (7.2)	5.9, Me
19		174.0, C
20	1.04 d (7.2)	12.7, Me
OAc-9		169.4, C
	2.21 s	21.7, Me
OC(O)*n*-Pr-12		172.5, C
	2.22 t (7.2)	35.9, CH_2
	1.63 sext (7.2)	18.1, CH_2
	0.94 t (7.2)	13.8, Me
OH-2	2.05 d (3.0)	
OH-8	3.16 s	

[a] 600 MHz in $CDCl_3$. [b] 150 MHz in $CDCl_3$. [c] Multiplicity deduced from HSQC and HMBC spectra. [d] n. o. = not observed.

The H-2/H-3/H-4, H-6/H-7, H-9/H-10/H-11/H-12/H-13/H-14, and H-17/H_3-18 spin systems, measured in a ^1H–^1H COSY experiment (Figure 2), were fit into the regiochemistry of vicinal couplings in **1**. The fused tetracyclic network was established in HMBC experiments, particularly *via* the ^2J- and ^3J-^1H–^{13}C long-

range correlations between protons and non-protonated carbons such as H_3-15/C-1, H_3-18/C-8, and H_3-18/C-19 (Figure 2), thus enabling elucidation of the main carbon skeleton of **1**.

The HMBC correlations between H_3-15/C-1, C-2, C-10, C-14; H_3-18/C-8, C-17, C-19; and H_3-20/C-10, C-11, C-12, indicated that Me-15, Me-18, and Me-20 were located at C-1, C-17 and C-11, respectively. The allylic couplings between H-6/H_2-16 (J = 3.0, 3.0 Hz) revealed the presence of an exocyclic carbon-carbon double bond at C-5 and the hydroxy group situated at C-2 manifested a COSY correlation between H-2 (δ_H 3.14) and a hydroxy proton resonating at δ_H 2.05 (1H, d, J = 3.0 Hz). The remaining acetoxy and *n*-butyroxy groups appeared to be positioned at either C-9 or C-12, two oxymethines, according to analysis of key ^{1}H–^{1}H COSY correlations and characteristic NMR signals (δ_H 5.49, 1H, d, J = 9.6 Hz/δ_C 68.6, CH-9; δ_H 4.88, 1H, dd, J = 6.0, 2.4 Hz/δ_C 70.0, CH-12), but the positions couldn't be confirmed, due to absence of HMBC correlation between H-9/H-12 and the ester carbonyl carbons.

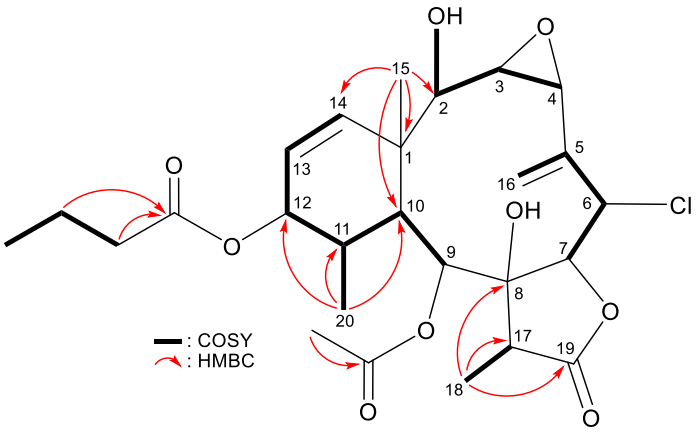

Figure 2. Key COSY and HMBC correlations of compound **1**. Due to absence of HMBC correlation between H-9/H-12 and the ester carbonyl carbons. The structure that shown in Figure 2 was tentative.

Eight of the nine oxygen atoms in the molecular formula accounted for a γ-lactone moiety, an acetoxy, an *n*-butyroxy, an epoxy, and a hydroxy group, with the remaining hydroxy group being positioned at C-8 (δ_C 85.0, C-8), based on the chemical shift of an oxygenated quaternary carbon. The methine unit at δ_C 60.8 was better shielded than expected as an oxygenated C atom and correlated with the methine proton at δ_H 5.42 in the HSQC spectrum. This proton showed a ^3J-correlation with H-7 (J = 3.0 Hz), in the COSY spectrum, underlining the attachment of a chlorine atom at C-6.

The relative configuration of **1** was deduced mainly from the interactions observed in a NOESY experiment and backed by MM2 force field analysis,[10] demonstrating a stable conformer, as shown in Figure 3. As per convention, when analyzing the stereochemistry of naturally-occurring briaranes, H-10 and the ring junction C-15 methyl group were assigned to the α- and β-faces, respectively, backed by stereochemical analysis, due to absence of correlation between H-10 and H_3-15. In the NOESY spectrum, H-10 correlated

with H-2/H-11/OH-8, suggesting location of H-2, H-11, and the hydroxy group at C-8 on the same face, capable to be assigned as α protons, as C-15 methyl is β-oriented at C-1 and H-10 was not correlated with H_3-15. H-9 was correlated with H-11, H-17, H_3-18, and H_3-20. Molecular model showed that reasonably close to H-11, H-17, H_3-18, and H_3-20, H-9 could be placed on the α-face in the 10-membered ring of **1**. H-17 was found to be correlated with H-9 and H-7 but uncorrelated with OH-8, suggesting that H-17 and H-7 should be placed on β-face in the γ-lactone moiety. There existed a small coupling constant between H-6 and H-7 (J = 3.0 Hz), plus correlation between these two protons, indicating that the dihedral angle between H-6 and H-7 was approximately 70°,[11] and H-6 was β-oriented, according to modeling study. The *cis* geometry of C-13/14 double bond was indicated by a 10.2 Hz coupling constant between H-13 (δ_H 5.76) and H-14 (δ_H 6.24) and backed by a response between these two olefin protons. Furthermore, H-3 was correlated with H-4 and H_3-15; and H-4 showed correlations with H-6 and H-7, suggesting the 3,4-epoxy group was α-oriented.

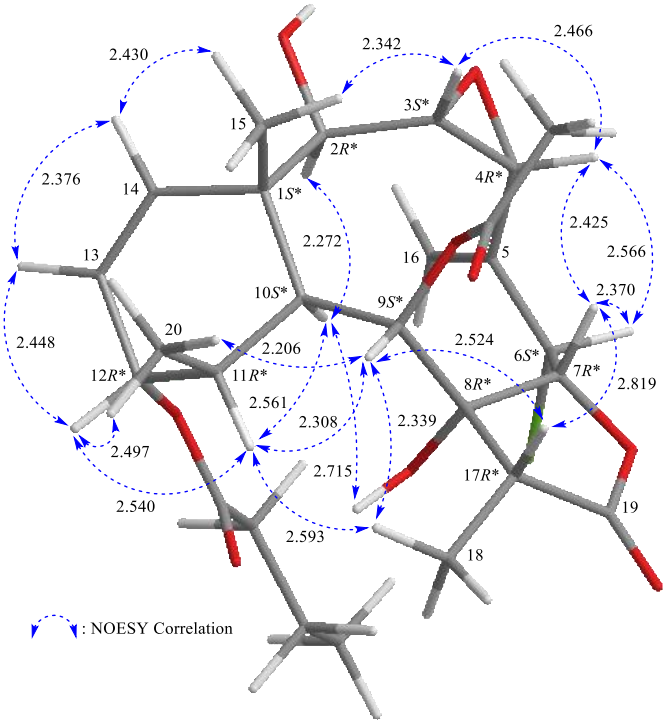

Figure 3. Stereoview of **1** and calculated distances (Å) between particular pairs protons that have crucial NOESY correlations. Due to absence of HMBC correlation between H-9/H-12 and the ester carbonyl carbons. The structure that shown in Figure 3 was tentative. 3D Structure was created with ChemDraw software in MM2 force field.

A single-crystal X-ray diffraction analysis was conducted to validate the structure of **1**, which was established with X-ray crystallography and observed with Mo Kα radiation (λ = 0.71073 Å). The X-ray structure (Figure 4) shows the locations of acetoxy and *n*-butyroxy groups on the β- and α-orientations of C-9 and C-12, respectively, while exhibiting a heavy atom (chlorine) in the structure of **1**. The stereogenic

centers in **1** were assigned as C-1(*S*), C-2(*R*), C-3(*S*), C-4(*R*), C-6(*S*), C-7(*R*), C-8(*R*), C-9(*S*), C-10(*S*), C-11(*R*), C-12(*R*) and C-17(*R*).[12] The structure, including the absolute configuration, was thus elucidated.

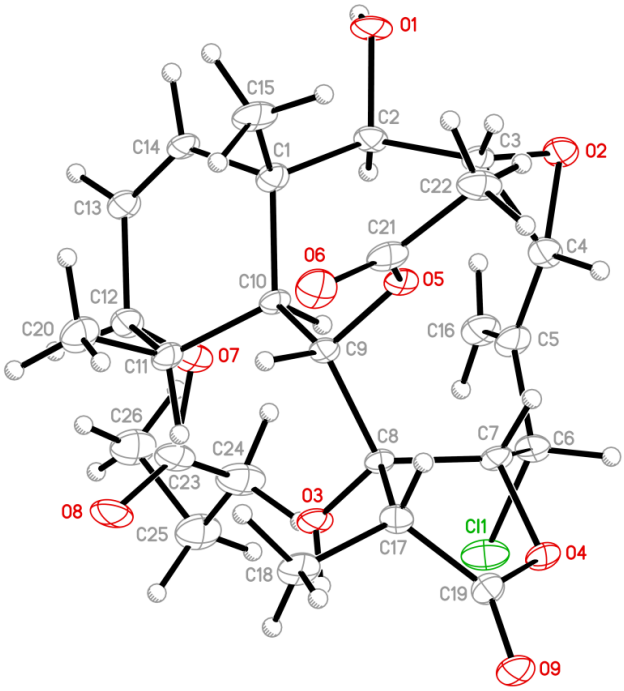

Figure 4. ORTEP structure of briastecholide N (**1**)

In previous studies, briarane-type natural products were found to be as a new natural scaffold to remedy osteoclastogenic disease.[13,14] To investigate the effect of briarane **1** on alkaline phosphatase (ALP) activity, the study carried out an ALP ELISA assay with MG63 human mesenchymal stem cells (Table 2), finding that **1** enhanced ALP activity, resulting in a level of 16.72 king unit/mgprot without cytotoxic effect. Moreover, an MTT assays indicated that **1** increased the proliferation rate of MG63 cells to 130.23%, suggesting that briarane **1** may be conducive to osteoblast proliferation.

Table 2. The ALP activity was assessed after treating MG63 cells with briastecholide N (**1**) and alendronate sodium (positive control) at a concentration of 10 μM for 72 h.

Compounds	ALP activity (king unit/mgprot)	MTT (% control)
1	16.72 ± 0.38 ***	130.23 ± 3.57***
Alendronate sodium	21.45 ± 5.21 **	95.14 ± 12.24
Control	2.53 ± 0.63	100.03 ± 2.28

Data are expressed with the mean standard error of the mean (SEM) (n = 3). The significance was determined by Student's t-test. ** $p < 0.01$, *** $p < 0.001$ and compared with untreated cells.

EXPERIMENTAL

General Experimental Procedures. Optical rotation values were ascertained with JASCO P-2000 digital polarimeter, IR spectra were learned with Thermo Scientific Nicolet iS5 FT-IR spectrophotometer, and ^{1}H and ^{13}C NMR spectra were depicted with Jeol ECZ NMR spectrometer at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR, respectively. Chemical shifts were reported in parts per million (δ) and coupling constants (J) expressed in Hertz (Hz). The residual peaks of the deuterated solvent, $CDCl_3$, taken as reference points, stood at δ_H 7.26 and δ_C 77.0 ppm, respectively. ESIMS and HRESIMS were recorded with Bruker 7 Tesla solariX FTMS system, equipped with an ESI ion source in positive ionization mode. The extracted samples were separated with column chromatography (C. C.) using silica gel (particle size, 230–400 mesh; Merck, Germany). TLC was performed on plates precoated with silica gel 60 (DC-Fertigfolien Alugram Xtra SIL G/UV_{254}, layer thickness 0.20 mm, Macherey-Nagel, Germany) and RP-18 F_{254}s (layer thickness 0.16–0.20 mm, Merck), and for the visualization of the TLC plates, an aqueous solution of 10% H_2SO_4 was heated to show the spots of signals. Normal-phase HPLC (NP-HPLC) separation was conducted with a system consisting of a pump (Hitachi, model L-7110, Japan), in conjunction with an injection port (Rheodyne, model: 7725, U.S.A.); the system was equipped with a semi-preparative normal-phase column (Supelco Ascentis Si, Cat#: 581514-U, 250 × 10 mm, 5 μm, Sigma-Aldrich, U.S.A.). Reverse-phase HPLC (RP-HPLC) separation was carried out with a system containing a pump (Hitachi, model L-7110) with a photo-diode array detector (Hitachi, model L-2455), equipped with a reverse-phase column (Luna, 5 μm, C18(2) 100 Å, 250 × 21.2 mm, Phenomenex, U.S.A.).

Animal Materials. The study employed as specimens *Briareum stechei*, collected from the coast of Pingtung County, Taiwan, in April 2016 and kept in an 80-ton culture reservoir containing a flowing seawater filtration system at the National Museum of Marine Biology and Aquarium (NMMBA), Taiwan. The species were identified via comparison of its morphology and micrographs of the coral sclerites with descriptions in previous studies.[4,5] Samples organisms used as reference were kept in our coral culture reservoirs, and specimens in use as sample vouchers were also stored at the NMMBA (voucher number: NMMBA-TW-GC-2016-031).

Extraction and Isolation. The freeze-dried coral specimen (wet/dry weight = 3980/1860 g) was sliced and then subjected to a 1:1 mixture solvent of MeOH and CH_2Cl_2 at room temperature to generate crude extract, which was subsequently applied on a silica gel C. C. and eluted with a gradient solvent system of *n*-hexane/EtOAc mixtures (from 50:1−1:2, stepwise) to obtain 12 fractions A−L. Fractions H and I were combined and then separated with Si C. C. using *n*-hexane/EtOAc mixtures (stepwise from 50:1−pure EtOAc) to obtain 8 fractions H1−H8. Fraction H6 was further chromatographed with Si C. C. with a mixture solvent system of *n*-hexane/EtOAc/acetone (*n*-hexane/EtOAc 2:1, 1:1 (*v*/*v*), pure EtOAc, and pure acetone) to obtain 11 fractions H6A−H6K. Fraction H6E4 was purified again with NP-HPLC containing an isocratic

solvent system of CH_2Cl_2/acetone (2:1), thereby yielding 11 fractions H6E1A−H6E1K. Fraction H6E1G was further purified with RP-HPLC using an isocratic solvent system of MeCN/H_2O mixture (60:40; flow rate = 3 mL/min) to form **1** (0.5 mg).

Briastecholide N (1): colorless prisms (MeOH); $[\alpha]_D$ +45 (*c* 0.05, $CHCl_3$); IR (KBr) ν_{max} 3432, 1774, 1734 cm^{-1}; ^1H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz, $CDCl_3$) NMR data, see Table 1; ESIMS *m/z* 549 $(M + Na)^+$, 551 $(M + 2 + Na)^+$; HRESIMS *m/z* 549.18632 (Calcd for $C_{26}H_{35}ClO_9$ + Na, 549.18618).

Single-Crystal X-Ray Crystallography of Briastecholide N (1). Suitable colorless prisms of **1** were obtained from MeOH solution. Crystal (0.378 × 0.068 × 0.033 mm^3) was identified as an orthorhombic system, space group $P2_12_12$ (#18), with a = 11.3978(9) Å, b = 26.717(2) Å, c = 8.7890(7) Å, V = 2676.4(4) $Å^3$, Z = 4, D_{calcd} = 1.308 Mg/m^3 and λ (Mo Kα) = 0.71073 Å. Intensity data were generated with a crystal diffractometer (Bruker, model: D8 Venture), up to θ_{max} of 25.000°. All the measurement data of 18772 reflections were collected, of which 4713 was independent. The structure was solved with direct methods and refined with full-matrix least-squares on F^2 procedure.[15,16] The refined structural model converged to final R^1 = 0.1085, with wR^2 = 0.2538 for 2353 observed reflections [$I > 2\sigma(I)$] and 334 variable parameters.[17]

Molecular Mechanics Calculations. A 3D model was created via implementation of the MM2 hydrocarbon force field[10] in 3D Ultra software from CambridgeSoft Corporation (version 15.00).

Alkaline Phosphatase (ALP) Activity Assay. The release of ALP assay was employed to assess the activity of compound **1** from MG63 human mesenchymal stem cells, in line with suggestion of literature.[17]

Cell Viability Assay. Cells were seeded at a density of 1×10^3 cells/well in a 96-well plate. After 24 h, 0.01 μM alendronate sodium hydrate or 10 μM of a specific drug mixed with culture medium was added to the cells. Following incubation at 37 °C for 72 h, the cells were washed, and then treated with 10 μL of MTT solution (5 mg/mL) mixed with 90 μL of culture medium per well, followed by an incubation at 37 °C for 4 h. The formazan crystals in each well were dissolved in 100 μL of DMSO, and once fully dissolved, the optical density was measured using an ELISA reader (Thermo Fischer, Waltham, MA, USA) at a wavelength of 570 nm.[18]

ACKNOWLEDGEMENTS

The authors are grateful to Hsiao-Ching Yu and Chao-Lien Ho, of the High Valued Instrument Center, National Sun Yat-sen University, for their assistance in obtaining the mass (MS 006500) and NMR (NMR 001100) spectra (NSTC 112-2740-M-110-002), and to the Instrumentation Center, National Taiwan University, for the use of X-ray facilities (NSTC 112-2740-M-002-006, XRD 000200). This study was mainly funded by grants from the National Museum of Marine Biology & Aquarium, the National Science and Technology Council (MOST 111-2320-B-291-001 and NSTC 112-2320-B-291-002-MY3, 112-2320-B-291-001 and 112-2811-B-291-002), Taiwan, awarded to P.-J.S. All funding is gratefully acknowledged.

REFERENCES AND NOTES

1. J. E. Burks, D. van der Helm, C. Y. Chang, and L. S. Ciereszko, *Acta Crystallogr.*, 1977, **B33**, 704.
2. Y.-H. Chen, H.-K. Chien, B.-R. Peng, Y.-Y. Chen, C.-C. Hu, L.-G. Zheng, T. H. Huynh, T.-P. Su, Y.-L. Zhang, Z.-H. Wen, T.-L. Hwang, Y.-C. Wu, and P.-J. Sung, *Heterocycles*, 2020, **100**, 857.
3. W. Zhang, Y.-W. Guo, and Y. Gu, *Curr. Med. Chem.*, 2006, **13**, 2041.
4. C. S. McFadden, L. P. van Ofwegen, and A. M. Quattrini, *Bull. Soc. Syst. Biol.*, 2022, **1**, 8735.
5. K. Samimi-Namin and L. P. van Ofwegen, *ZooKeys*, 2016, **557**, 1.
6. T. H. Hao, Z.-H. Wen, J.-H. Su, Z.-K. Yao, L.-G. Zheng, Y.-C. Tsai, J. Tanaka, C.-C. Liaw, and P.-J. Sung, *Chem. Pharm. Bull.*, 2023, **71**, 183.
7. T. H. Hao, S.-Y. Chien, Z.-H. Wen, C.-C. Liaw, Y.-C. Tsai, and P.-J. Sung, *Tetrahedron*, 2022, **120**, 132909.
8. H.-Y. Yan, *Changhua J. Med.*, 2004, **19**, 1.
9. M. C. Leal, R. Calado, C. Sheridan, A. Alimonti, and R. Osinga, *Trends Biotechnol.*, 2013, **31**, 555.
10. N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127.
11. M. Karplus, *J. Am. Chem. Soc.*, 1963, **85**, 2870.
12. S. Parsons, *Tetrahedron: Asymmetry*, 2017, **28**, 1304.
13. X. Qi, X. Zhang, J. Meng, J. Wu, W. Cheng, J. Huang, and W. Lin, *Eur. J. Med. Chem.*, 2023, **246**, 114948.
14. Y.-Y. Lin, Y.-H. Jean, H.-P. Lee, S.-C. Lin, C.-Y. Pan, W.-F. Chen, S.-F. Wu, J.-H. Su, K.-T. Tsui, J.-H. Sheu, P.-J. Sung, and Z.-H. Wen, *Mar. Drugs*, 2017, **15**, 9.
15. G. M. Sheldrick, *Acta Crystallogr.*, 2015, **A71**, 3.
16. G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3.
17. Crystallographic data for the structure of **1** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 2264781. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
18. Y. Wang, B. Kong, X. Chen, R. Liu, Y. Zhao, Z. Gu, and Q. Jiang, *J. Nanobiotechnol.*, 2022, **20**, 444.
19. H.-M. Kuo, C.-C. Tseng, N.-F. Chen, M.-H. Tai, H.-C. Hung, C.-W. Feng, S.-Y. Cheng, S.-Y. Huang, Y.-H. Jean, and Z.-H. Wen, *Mar. Drugs*, 2018, **16**, 8.