New sesquiterpenoids from the South China Sea soft corals *Clavularia viridis* and *Lemnalia flava*

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Abstract

A detailed chemical investigation of the South China Sea soft corals *Clavularia viridis* and *Lemnalia flava* yielded four new halogenated laurane-type sesquiterpenoids, namely, isobromolaurenisol (1), clalaurenol A (2), *ent*-laurenisol (3), clalaurenol B (4), and the new aromadendrane-type sesquiterpenoid claaromadendrene (6), together with three known sesquiterpenoids (5, 7, and 8). Their structures were determined by extensive spectroscopic analysis and by comparison with the previously reported analogues. In a bioassay, compounds 1, 2 and 4 exhibited interesting inhibitory activities in vitro against PTP1B and NF-κB.

Introduction

Marine soft corals are important sources of biologically active compounds, which made them attractive targets for natural product chemists. Soft corals of the genus *Clavularia* (class Octocorallia, order Alcyonacea, family Clavulariidae), are prolific sources of numerous biologically active compounds [1-4]. A variety of structurally unique sesquiterpenes, including aromadendranes [5], maalianes [5], elemanes [6], and trinor-guianes [7-9], have been isolated since the early 1980s from several species of *Clavularia*. Soft corals of the genus *Lemnalia* are also a rich source of sesquiterpenoids and diterpenoids with various intriguing carbon skeletons, such as nardosinanes, neolemnanes, and ylanganes [10]. Many of these secondary metabolites have attracted a lot of attention for further synthetic and pharmacological studies due to their potent bioactivities ranging from neuroprotective, cytotoxic, to anti-inflammatory properties [10].
In the framework of our ongoing research for the bioactive metabolites from South China Sea soft corals [11,12], we made the collection of the title samples Clavularia viridis and Lemnalia flava off the Xisha Islands, Hainan Province, China. The chemical investigation of two title animals led to the isolation of four new halogenated laurane-type sesquiterpenoids 1–4, one new aromadendrane-type sesquiterpenoid 6) together with three related known compounds 5, 7 and 8 (Figure 1). Herein, the isolation, structure elucidation and bioactivity evaluation of these compounds are presented.

Results and Discussion
The frozen bodies of the two soft corals C. viridis and L. flava were cut into pieces and exhaustively extracted with acetone. The Et2O-soluble portion of the acetone extracts were chromatographed repeatedly over silica gel, Sephadex LH-20, and RP-HPLC to yield pure compounds. A total of eight compounds including compounds 1 (1.0 mg), 2 (0.9 mg), 3 (3.4 mg), 4 (1.4 mg), 5 (0.9 mg), 6 (2.8 mg), 7 (7.8 mg), and 8 (6.8 mg) were obtained from the C. viridis sample while two compounds 3 (8.6 mg) and 4 (2.3 mg) were obtained from L. flava. Among them, the known compounds were readily identified as cupalaurenol (5) [13], 1-hydroxyalloaromaden- drone (7) [14], and humulene epoxide II (8) [15] by comparing their NMR spectroscopic data and optical rotation with those reported in the literature.

Isobromolaurenisol (1) was obtained as an optically active colorless oil. Its molecular formula, C15H18OBr2, was deduced by HR-ESIMS with ion peaks at m/z 370.9657, [M – H]− (calcd for C15H17OBr2, 370.9646), indicating six degrees of unsaturation. The 13C NMR and DEPT spectra contained signals attributable to three methyls, two sp3 methylenes, one sp3 methine, one sp3 quaternary carbon, three sp2 methines, and five sp2 quaternary carbons (Table 1). The typical resonances at δC 145.6, δC 113.0, δH/C 7.30/136.8, δC 123.4, δC 153.0, δH/C 6.71/116.8 revealed the presence of a 1,2,4,5-tetrasubstituted benzene ring, and the signals at δH/C 6.08/99.1, δC 154.2 indicated the existence of a trisubstituted double bond. All the above evidence suggested the laurane nature of this molecule, and literature research revealed that 1 should be an isomer of a known laurane-type terpenoid bromolaurenisol (1α) [16,17] due to their extremely similar NMR data and the same molecular weight (Figure 1). In fact, the main difference between 1 and 1α happened only at the tetrasubstituted benzene ring with the substituents exchange between C-7 and C-10 (Figure 1). The assignment of the planar structure of 1 has been further confirmed by 2D NMR experiments, including 1H,1H COSY, HSQC, and HMBC, with the key correlations shown in Figure 2. In particular, the hydroxy group (δH 4.68, s) was confirmed to be attached at C-10 by the clear HMBC correlation from OH to C-10 and C-11.

The relative configuration of 1 was established by a NOESY experiment (Figure 3), in which the correlations of H-15 with H-13 (δH 1.29, s) and H-14 (δH 3.56, q, J = 7.2 Hz) and H-5β (δH 2.34, m) indicated that these protons were on the same side of the molecule and were tentatively assigned to be β-oriented, while the correlation of H-5α (δH 1.88, m) and H-14 (δH 0.74, d, J = 7.3) at C-2 indicated CH3-14 was α-oriented. Besides, the trisubstituted olefin (Δ5/15) was determined to be in E configuration due to the clear NOE correlations of H-15 with H-13 and H-14. In view of the above evidences, the relative configuration of compound 1 was determined as 1R*,2R*, the same as 1α [16,17].

Compound 2 was isolated as an optically active colorless oil. The molecular formula, C13H18OBr, was established by the mo-

![Figure 1: Structures of compounds 1–8.](image-url)
Table 1: $^1$H and $^{13}$C NMR data of 1–3 recorded in CDCl$_3$.

| No. | $^1$H δ (J in Hz) | $^{13}$C δ | $^1$H δ (J in Hz) | $^{13}$C δ | $^1$H δ (J in Hz) | $^{13}$C δ |
|-----|-----------------|------------|-----------------|------------|-----------------|------------|
| 1   | 52.0, qC        | -          | 51.1, qC        | -          | 48.4, qC        | -          |
| 2   | 3.56, q (7.2)   | 47.5, CH   | 4.31, q (7.2)   | 47.1, CH   | 3.37, q (7.1)   | 48.1, CH   |
| 3   | -               | -          | 157.6, qC       | -          | -               | -          |
| 4   | 2.40, m; 2.51, m| 29.0, CH$_2$| 2.48, m         | 28.2, CH$_2$| 2.49, m         | 28.0, CH$_2$|
| 5   | 1.88, m; 2.34, m| 35.1, CH$_2$| 1.79, m; 2.27, m| 36.1, CH$_2$| 1.93, m; 2.34, m| 34.9, CH$_2$|
| 6   | -               | -          | 145.6, qC       | -          | -               | -          |
| 7   | -               | -          | 113.3, qC       | -          | -               | -          |
| 8   | 7.30, s         | 136.8, CH  | 7.31, s         | 136.7, CH  | 6.52, s         | 116.6, CH  |
| 9   | -               | 123.4, qC  | -               | 123.1, qC  | -               | 137.2, qC  |
| 10  | -               | 153.0, qC  | -               | 152.9, qC  | 6.71, d (7.7)   | 121.5, CH  |
| 11  | 6.71, s         | 116.8, CH  | 6.73, s         | 116.8, CH  | 7.01, d (7.8)   | 128.2, CH  |
| 12  | 2.18, s         | 15.0, CH$_3$| 2.18, s         | 15.0, CH$_3$| 2.28, s         | 20.7, CH$_3$|
| 13  | 1.29, s         | 25.0, CH$_3$| 1.30, s         | 25.1, CH$_3$| 1.23, s         | 25.7, CH$_3$|
| 14  | 0.74, d (7.3)   | 19.2, CH$_3$| 0.73, d (7.2)   | 19.9, CH$_3$| 0.76, d (7.2)   | 15.0, CH$_3$|
| 15  | 6.08, s         | 99.1, CH   | 4.89, s; 4.99, s| 106.9, CH$_2$| 5.93, s         | 97.5, CH   |
| OH  | 4.68, s         | -          | 4.67, s         | -          | 4.66, s         | -          |

$^a$Bruker DRX-500 spectrometer (125 MHz for $^{13}$C NMR and 500 MHz for $^1$H NMR) in CDCl$_3$, chemical shifts (ppm) referred to CHCl$_3$ ($^1$C 77.16; $^1$H 7.26); assignments were deduced by analysis of 1D and 2D NMR spectra.

Figure 2: $^1$H, $^1$H COSY and key HMBC correlations of compounds 1–4 and 6.
differing only in the stereochemistry. The relative configuration of 6a had the same planar structure as 6 and co-occurring 7 pound was isolated as an optically active colorless oil. The molecular formula, C18H28O4, the same as 6, was established by HR-ESIMS ion peaks at m/z 370.9654, [M – H]− (calcd for C18H28O4Br2, 370.9646). The 1H and 13C NMR data of 6 were identical to those of 4a, a C-10 bromonated analogue of 3a. In addition, the NOE correlations between H3-13 (δH 1.21, s) with H-2 (δH 3.34, q, J = 7.3 Hz) and H-5a (δH 1.91, m); H3-14 (δH 0.76, d, J = 7.2 Hz) with H-5b (δH 2.32, m); a proton at C-15 (H-15, δH 5.94, s) and two protons at C-4 (δH 2.48, m) suggested the relative configuration (C-1, C-2 and Δ1,15) of 6 is the same as 3. Moreover, the sign of their [α]D20 values [α]D20 = 52.1 (c 0.08, CHCl3); [α]D20 = 22.5 (c 0.10, MeOH) for 6 and [α]D20 +74 (c 0.58, CHCl3) for 4a, indicating that compound 6 should be the enantiomer of 4a [18].

Compound 6 was isolated as an optically active colorless oil. The molecular formula C15H24O4, the same as 7 [14] and 6a [19,20], was established by HR-ESIMS ion peak at m/z 220.1824 [M]+ (calcd for C15H24O4, 220.1825). A detailed analysis of 2D NMR experiments (Figure 2), revealed that compound 6 had the same planar structure as 6a and co-occurring 7 differing only in the stereochemistry. The relative configuration of 6 was established by NOESY correlations (Figure 3) in which the correlations of H-6 (δH 0.62, dd, J = 11.4, 9.1 Hz) with H-7 (δH 0.81, m) and H5-15 (δH 1.01, d, J = 7.2 Hz); H3-12 (δH 1.08, s) with H-6 and H-7, indicating that these protons were on the same side of the molecule and were tentatively assigned to be α-oriented, while correlations of H-5 (δH 1.60, m) with H-4 (δH 2.20, m) and H3-13 (δH 0.99, s) suggesting these protons were on the opposite orientation. In view of the above evidences, the relative configuration of compound 6 was determined as 4R*,5S*,6R*,7R*. In fact, the only difference between compounds 6 and 6a was the configuration of the hydroxy group at C-1 with α-orientation for 6 while β-orientation for 6a [19,20]. Further, due to the influence of the configuration inversions of C-1, the 13C NMR chemical shift of the carbon at C-1 (δc 85.5, qC), was apparently upfield shifted (Δδ = −3.0) comparing to compound 6a (Table 2), giving the further support of the assigned structure for 6 (Figure 1). Thus, compound 6 was determined as a C-1 isomer of ent-1-hydroxyalloaromadendrene (6a), namely, claraomadendrene.

In bioassays, all the isolated compounds were tested for protein tyrosine phosphate-1B (PTP1B) and NF-κB inhibitory activity. In the PTP1B inhibitory assay, the inhibitory effects of compounds 1–8 were evaluated against PTP1B, and the result showed that compounds 1, 2 and 4 had a moderate PTP1B inhibitory activity with IC50 values of 18.8, 21.8 and 15.6 μM, respectively. The known PTP1B inhibitor oleanolic acid (IC50 = 3.0 μM) were used as positive control in this assay. In the NF-κB inhibitory assay, compounds 2 and 4 showed the most potent NF-κB signaling pathway inhibition with IC50 values of
F. viridis and L. flava. In fact, to our knowledge, naturally occurring laurane- (1–4) and cuparane-derived (5) sesquiterpenoids, are extremely rare in soft corals. Previously, such sesquiterpenoids have only been isolated from the red algae of the genus Laurencia [14,16,17,21] and some sea haresthat prey on it [13,22]. In this paper, the chemical investigation of two different soft corals collected off the South China Sea, which belong to two different genera, have resulted in the discovery of two common new halogenated laurane-type sesquiterpenoids (3 and 4). Based on these findings, other than prey–predator relationship, the common symbiotic organisms in the algae and the soft corals might be the source of these metabolites. In fact, many investigations have proved that [23] numerous natural products are actually produced by microbes and/or microbial interactions with the “host from whence it was isolated”. Further chemical investigation of these soft corals in the South China Sea as well as their associated microorganisms should be conducted to verify the true origin of these metabolites and to further understand the real biological/ecological roles they played in the life cycle of the title animals in the South China Sea.

The promising PTP1B inhibitory activity of laurane-type sesquiterpenoids [24] in a previously report from our group, inspired us to test the PTP1B inhibitory activity of compounds 1–4. Among them, compound 3 was inactive against PTP1B enzyme, whereas compounds 1, 2 and 4 exhibited considerable PTP1B inhibitory activity with IC₅₀ values of 18.8, 21.8, and 6.8 and 7.3 μM, respectively, while compound 1 showed moderate activity with an IC₅₀ value of 19.9 μM (Table 3).

Table 2: ¹H and ¹³C NMR data of 4a and 6a and ¹³C NMR data of 6a and 7 recorded in CDCl₃.

| No. | δ_1H mult (J in Hz) | δ_C | δ_1H mult (J in Hz) | δ_C | δ_1H mult (J in Hz) | δ_C |
|-----|---------------------|-----|---------------------|-----|---------------------|-----|
| 1   | –                   | 48.4, qC | –                   | 85.5, qC | 88.5, qC | 88.7, qC |
| 2   | 3.34, q (7.3)       | 47.9, CH | 1.76, m; 1.96, m    | 37.1, CH₂ | 36.5, CH₂ | 36.6, CH₂ |
| 3   | –                   | 153.1, qC | 1.55, m; 1.90, m    | 33.3, CH₂ | 30.6, CH₂ | 30.7, CH₂ |
| 4   | 2.48, m             | 27.9, CH₂ | 2.20, m             | 34.9, CH | 34.3, CH | 34.4, CH |
| 5   | 1.91, m; 2.32, m    | 34.9, CH₂ | 1.60, m             | 46.8, CH | 49.0, CH | 49.1, CH |
| 6   | –                   | 133.2, qC | 0.62, dd (11.4, 9.1)| 21.8, CH | 23.3, CH | 23.4, CH |
| 7   | –                   | 152.3, qC | 0.81, m             | 27.5, CH | 25.4, CH | 25.5, CH |
| 8   | 6.59, s             | 118.1, CH | 0.98, m; 2.02, m    | 25.2, CH₂ | 21.2, CH₂ | 21.4, CH₂ |
| 9   | –                   | 136.5, qC | 2.27, m; 2.47, dd (13.9, 12.6)| 34.1, CH₂ | 32.0, CH₂ | 32.2, CH₂ |
| 10  | –                   | 115.5, qC | –                   | 155.1, qC | 152.9, qC | 153.0, qC |
| 11  | 7.23, s             | 131.9, CH | –                   | 19.8, qC | not detected | 18.1, qC |
| 12  | 2.30, s             | 22.3, CH₃ | 1.08, s             | 29.0, CH₃ | 28.6, CH₃ | 28.7, CH₃ |
| 13  | 1.21, s             | 25.4, CH₃ | 0.99, s             | 15.7, CH₃ | 15.9, CH₃ | 16.0, CH₃ |
| 14  | 0.76, d (7.2)       | 15.0, CH₃ | 4.66, t (1.6); 4.80, d (1.7)| 108.3, CH₂ | 111.7, CH₂ | 111.8, CH₂ |
| 15  | 5.94, s             | 97.8, CH | 1.01 d (7.2)        | 18.8, CH₃ | 16.6, CH₃ | 16.7, CH₃ |
| OH  | 4.75, s             | –       | –                   | –       | –       | –       |
| a    | –                   | –       | –                   | –       | –       | –       |
| b    | –                   | –       | –                   | –       | –       | –       |

Table 3: PTP1B and NF-κB inhibitory effect of compounds 1–8.

| Compounds | IC₅₀ (μM) | PTP1B | IC₅₀ (μM) | NF-κB |
|-----------|-----------|-------|-----------|-------|
| 1         | 18.8      | 19.9  |           |       |
| 2         | 21.8      | 6.8   |           |       |
| 3         | –         | –     |           | –     |
| 4         | 15.6      | 7.3   |           | –     |
| 5         | –         | –     |           | –     |
| 6         | –         | –     |           | –     |
| 7         | –         | –     |           | –     |
| 8         | –         | –     |           | –     |
| A³        | 3.0       | –     |           | –     |
| B³        | –         | 14.0  |           | –     |

⁴Bruker DRX-500 spectrometer (125 MHz for ¹H NMR and 500 MHz for ¹³C NMR in CDCl₃); chemical shifts (ppm) referred to CHCl₃ (δ_C 77.16; δ_1H 7.26); assignments were deduced by analysis of 1D and 2D NMR spectra. ⁵Data reported in ref. [19] (in CDCl₃).

Conclusion

In summary, eight sesquiterpenoids (1–8), belonging to four different structural types, were isolated from two South China Sea soft corals (C. viridis and L. flava) for the first time. The discovery of these metabolites extended the structural diversity and complexity of sesquiterpenoids derived from soft corals C. viridis and L. flava. In fact, to our knowledge, naturally
15.6 μM, respectively. Compounds 1, 2 and 4 also showed strong NF-kB inhibitory activity with IC50 values of 19.9, 6.8 and 7.3 μM, respectively. With regard to their structure-activity relationship, the bromine atom on the benzene ring may play the key functional role in the inhibitory activity. This study could thus provide a clue for the further biological study and structure modification of marine brominated laurane sesquiterpenoid derivatives towards new effective PTP1B and/or NF-kB inhibitors.

**Experimental**

**General experimental procedures**

Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. IR spectra were recorded on a Nicolet-Magna FT-IR 750 spectrometer. EIMS and HR-EIMS spectra were recorded on a Finnigan MAT-95 mass spectrometer. HR-ESIMS spectra were recorded on a Q-TOF Micro LC–MS–MS mass spectrometer. The NMR spectra were measured on a Bruker DRX-500 spectrometer with the residual CHCl3 (δH 7.26 ppm, δC 77.2 ppm) as internal standard. Chemical shifts are expressed in δ (ppm) and coupling constants (J) in Hz. 1H and 13C NMR assignments were supported by 1H,1H COSY, HSQC, HMBC and NOESY experiments. Commercial silica gel (Qing Dao Hai Yang Chemical Group Co., 300–400 and 500–600 mesh) and Sephadex LH-20 (Amersham Biosciences) were used for column chromatography. Precoated silica gel GF254 plates (Sinopharm Chemical Reagent Co., Shanghai, China) were used for TLC. Reversed-phase (RP) HPLC purification was carried out on an Agilent 1260 series liquid chromatography system equipped with a DAD G1315D detector at 210 and 254 nm and with a semi-preparative ODS-HG-5 column [5 μm, 250 × 9.4 mm]. All solvents used for CC were of analytical grade, and solvents used for HPLC were of HPLC grade.

**Collection of biological materials**

The soft corals *C. viridis* and *L. flava* were collected by scuba from Xisha Island, Hainan Province, China, on March 23, 2013, at a depth of 15 to 20 m, and identified by Professor Xiu-Bao Li from Hainan University. The voucher samples, both *C. viridis* and *L. flava* are deposited at the Shanghai Institute of Materia Medica, CAS, under registration Nos. 13XS-49 and 13XS-52, respectively.

**Extraction and isolation**

The lyophilized bodies of *C. viridis* (80 g, dry weight) were minced into pieces and exhaustively extracted with acetone at room temperature (4 × 1 L). The solvent-free acetone extract was partitioned between Et2O and H2O. The organic phase was evaporated under reduced pressure to give a dark-red residue (1.1 g), which was subjected to a gradient silica gel column chromatography (CC) [Et2O/petroleum ether (PE), 0–100%] to yield 6 fractions (A–F). Fraction C was subjected to Sephadex LH-20 CC (PE/CH2Cl2/MeOH, 2:1:1) to give 4 sub-fractions (C1–C4). Fraction C4 was purified by silica gel CC (500–600 mesh, Et2O/PE, 4:96) to afford pure 3 (3.4 mg), 4 (1.4 mg) and 8 (6.8 mg). Fraction D eluted with Sephadex LH-20 CC (PE/CH2Cl2/MeOH, 2:1:1), followed by CC on silica gel (500–600 mesh, Et2O/PE, 5:95) to afford pure 1 (1.0 mg), 2 (0.9 mg) and 5 (0.9 mg). Fraction E gave compounds 6 (2.8 mg) and 7 (7.8 mg) after CC on Sephadex LH-20 (PE/CH2Cl2/MeOH, 2:1:1) and silica gel (500–600 mesh, Et2O/PE, 8:92).

The frozen animals of *L. flava* (350 g, dry weight) were cut into pieces and extracted exhaustively with acetone at room temperature (6 × 2.0 L). The organic extract was evaporated under reduced pressure to give a brown residue, which was then partitioned between H2O and Et2O. The upper layer was concentrated under reduced pressure to give a brown residue 8.0 g. The resulted residue was separated into seven fractions (A–G) by gradient silica-gel CC. The resulting fractions were then fractionated into sub-fractions by Sephadex LH-20. The sub-fraction C5 was purified by Semi-preparative HPLC (87% MeOH), yielding compounds 3 (8.6 mg) and 4 (2.3 mg).

Isobromolaurenisol (1): Colorless oil; [α]D20 +33.1 (c 0.07, CHC13); 1H and 13C NMR data, see Table 1; HR-ESIMS m/z: [M – H]– 370.9657, 372.9635, 374.9619 (calcd for C15H17OBr2, 370.9646).

Clalaurenol A (2): Colorless oil; [α]D20 +69.7 (c 0.05, CHCl3); 1H and 13C NMR data, see Table 1; HR-ESIMS m/z: [M + H]+ 293.0548, 295.0536 (calcd for C13H18OBr, 293.0541).

*ent*-Laurenisol (3): Colorless oil; [α]D20 –24.2 (c 0.06, CHCl3); [α]D20 –16.0 (c 0.10, MeOH); 1H and 13C NMR data, see Table 1; HR-ESIMS m/z: [M + H]+ 294.0617, 296.0594 (calcd for C15H19OBr, 294.0619).

Clalaurenol B (4): Colorless oil; [α]D20 –52.1 (c 0.08, CHCl3); [α]D20 –22.5 (c 0.10, MeOH); 1H and 13C NMR data, see Table 1; HR-ESIMS m/z: [M – H]+ 370.9654, 372.9637, 374.9618 (calcd for C15H17OBr2, 370.9646).

Claaromadendrene 6: Colorless oil; [α]D20 –83.0 (c 0.20, CHCl3); 1H and 13C NMR data, see Table 1; HR-ESIMS m/z: [M]+ 220.1824 (calcd for C13H23O, 220.1825).

**PTP1B inhibitory activity assay**

The recombinant PTP1B catalytic domain was expressed and purified according to a previous report [24]. The enzymatic ac-
activities of the PTP1B catalytic domain were determined at 30 °C by monitoring the hydrolysis of pNPP. Dephosphorylation of pNPP generated the product pNP, which was monitored at an absorbance of 405 nm with an EnVision multilabel plate reader (Perkin–Elmer Life Sciences, Boston, MA). In a typical 100 L assay mixture containing 50 mmol/L 3-morpholinopropanesulfonic acid, pH 6.5, 2 mmol/L pNPP, and 30 mmol/L recombina- nt PTP1B, activities were continuously monitored and the initial rate of hydrolysis was determined by using the early linear region of the enzymatic reaction kinetic curve. The IC$_{50}$ was calculated with Prism 4 software (Graphpad, San Diego, CA) from the nonlinear curve fitting of the percentage of inhibition (% inhibition) vs the inhibitor concentration [I] by using the following equation: % inhibition = 1/(1 + [IC$_{50}$/I]$_{h}$)$^k$, where k is the Hill coefficient; IC$_{50}$ ≥ 50 μM was considered inactive.

NF-κB signaling pathway inhibitory activity assays

NF-κB signaling pathway inhibitory activity was evaluated according to the previously reported protocol [25]. Stable HEK293/NF-κB cells were plated into 384-well plates at a concentration of approximate 2500 cells per well. After culturing overnight, compounds were added to the medium at a final concentration of 0.1 μg/mL. HEK293/NF-κB cells were seeded into 96-well cell culture plates (Corning, NY, USA) and allowed to grow for 24 h. The cells were then treated with compounds, followed by stimulation with TNF-α. 6 h later, the luciferase sub- strate was added to each well, and the released luciferin signal was detected using an EnVision microplate reader. The IC$_{50}$ was calculated with Prism 4 software (Graphpad, San Diego, CA) from the nonlinear curve fitting of the percentage of inhibition (% inhibition) versus the inhibitor concentra- tion [I] by using the following equation: % inhibition = 100/(1 + [IC$_{50}$/I]$_{h}$)$^k$, where k is the Hill coefficient. Bortezomib was used as a positive control with an IC$_{50}$ value of 14.0 μM.

Supporting Information

Supporting Information File 1
Spectral data of compounds 1–4 and 7. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-64-S1.pdf]

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