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Biomimetic Synthesis of Thiaplidiaquinones A and B

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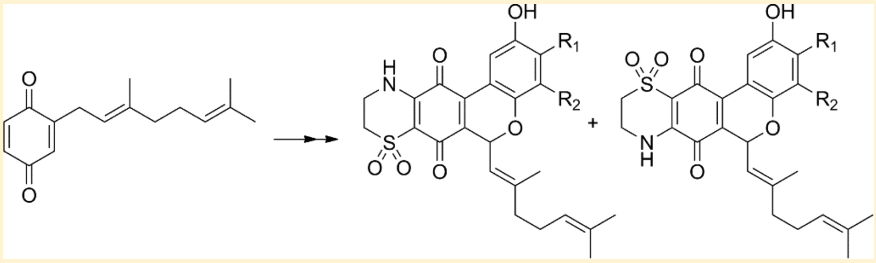
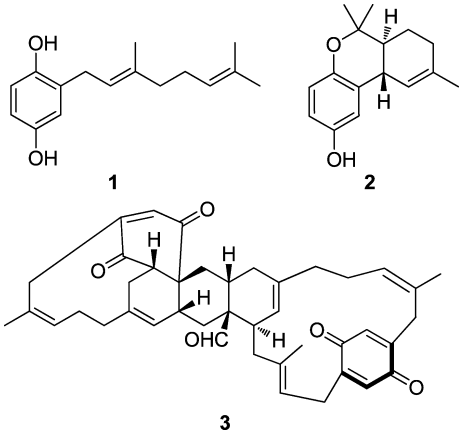
Supporting Information

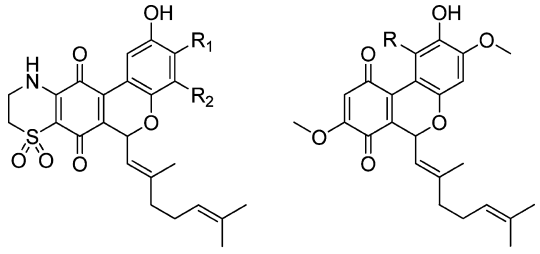


ABSTRACT: A biomimetic synthesis of the biologically active ascidian metabolites thiaplidiaquinones A and B is described. Reaction of geranylbenzoquinone with Et_3N in CH_2Cl_2 yielded two isomeric quinones, comprising the benzo[*c*]chromene-7,10-dione core of the natural products. Subsequent reaction with hypotaurine yielded the title compounds and their dioxothiazino regioisomers.

While the majority of metabolites biosynthesized by ascidians are alkaloids or peptide related,[1] ascidians of the genus *Aplidium* are known as a rich source of prenylated quinone and hydroquinone natural products.[2] Derived from geranylated or farnesylated hydro- or benzoquinone (e.g., **1**),[3] these typically bioactive metabolites can embody intramolecular (e.g., conicol, **2**[4]) or intermolecular ring closures (e.g., longithorone A, **3**[5]), yielding complex architectural scaffolds.



More recently, meroterpenoids bearing a benzo[*c*]chromene-7,10-dione skeleton have been reported from geographically remote species of *Aplidium* ascidians. In 2005, Fattorusso's group isolated thiaplidiaquinones A and B (**4**, **5**) from a Mediterranean ascidian, *Aplidium conicum*, determining that both natural products induced apoptosis in Jurkat cells by a mechanism involving the intracellular production of reactive oxygen species.[6] In contrast, the related metabolite scabellone B (**6**), isolated from a New Zealand collection of *Aplidium scabellum*, was found to be a relatively nontoxic antimalarial lead compound.[7] As part of our interest in exploring the structure−activity relationships of benzo[*c*]chromene-7,10-dione natural products,[8] herein we report a biomimetic synthesis of both thiaplidiaquinones A (**4**) and B (**5**) and their anticipated natural product dioxothiazine regioisomers. While this paper was in preparation, Carbone et al. reported a synthesis of thiaplidiaquinone A.[9]



4 R_1= H, R_2 = geranyl
5 R_1 = geranyl, R_2 = H

6 R = geranyl

We speculated that the biosynthetic origin of the thiaplidiaquinones could stem from hypotaurine addition to one of two tricyclic pyranoquinones (**7**, **8**), in turn derived from oxa-6π electrocyclization[10] of *ortho*-quinone methide tautomers (**9**, **10**) of bis-benzoquinones (**11**, **12**) (Scheme 1).

However, while Carbone et al. constructed bis-benzoquinones **11** and **12** via a Suzuki−Miyaura reaction, we speculated that such coupling could be achieved simply by allowing geranylbenzoquinone (**13**) to tautomerize in the presence of triethylamine, undergo Michael reaction with another equivalent of quinone, and then follow a cascade of oxidation and

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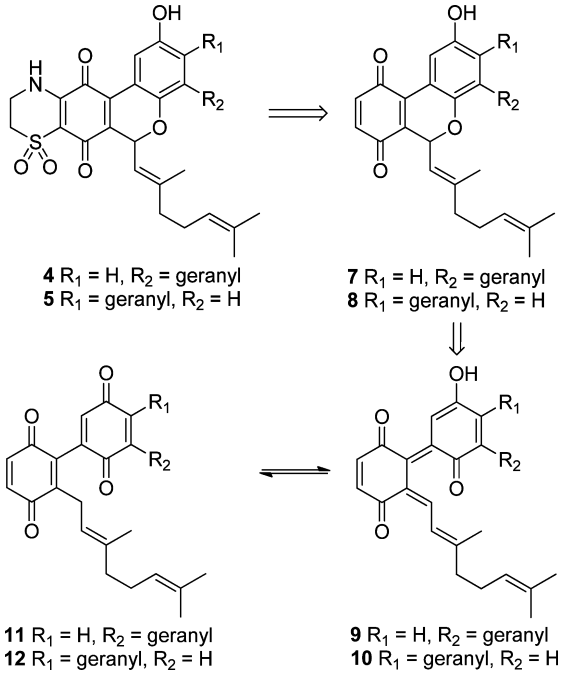
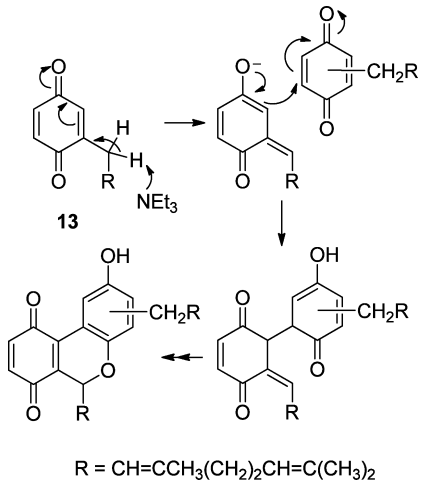
Scheme 1. Retrosynthesis of Thiaplidiaquinones A and B



spontaneous ring closure to form the more advanced thiaplidiaquinone precursors **7** and **8** (Scheme 2).

Scheme 2. Tautomerization and Dimerization of Geranylbenzoquinone

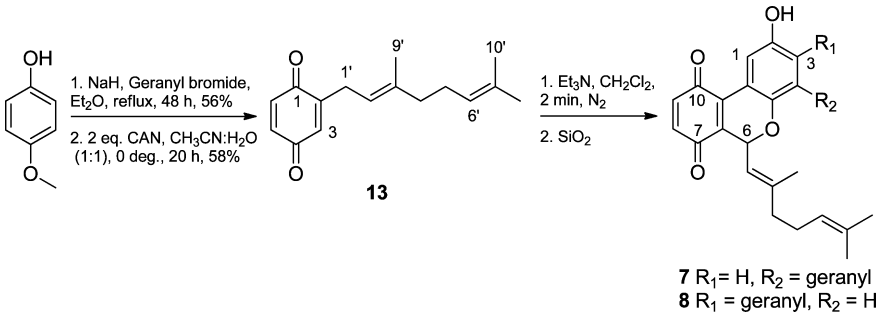


Geranylbenzoquinone (**13**) was prepared in a two-step sequence by reaction of 4-methoxyphenol with geranylbromide to afford 2-geranyl-4-methoxyphenol,[11] oxidation of which with CAN yielded **13**[11] (Scheme 3). Initial assessment of the ability of geranylbenzoquinone to undergo base-induced tautomerization and dimerization was performed in an NMR tube, whereupon addition of Et_3N (1 equiv) to a solution of quinone **13** in $CDCl_3$ caused a rapid change in color of the solution from pale yellow to dark brown, with ^1H NMR spectra of the reaction mixture indicating rapid consumption of starting material and the production of a complex mixture. An HSQC NMR spectrum of the mixture identified the generation of a new oxymethine fragment, with a correlation observed at δ_H 6.18, δ_C 68.4 [cf. scabellone B (**6**) H-5/C-6 (δ_H 6.00 (1H, d, J = 9.3 Hz, H-5); δ_C 67.6)],[7] suggestive of successful formation of a benzo[*c*]chromene ring system. The reaction between quinone **13** and Et_3N (5 equiv) was repeated on a larger scale, with a short reaction time of 2 min, followed by purification using silica gel flash column chromatography. The fraction eluting with 15% MeOH/CH_2Cl_2 was left exposed to silica gel overnight, whereupon a further color change, this time from brown to dark purple, was observed. Further purification of the purple products yielded **7** and **8** in yields of 5.7% and 2.4%, respectively (Scheme 3). Albeit with low yields, the biomimetic transformation of **13** to tricycles **7** and **8** is unprecedented.

High-resolution ESI mass spectrometry assigned the molecular formula $C_{32}H_{38}O_4$ $[M + Na]^+$ to both **7** and **8**, while detailed analysis of NMR data established the presence of 1-oxygeranyl, geranyl, tetrasubstituted benzene, and 2,3-disubstituted benzoquinone fragments (see Tables S1 and S2). Close similarity of the NMR data to those observed for scabellone B (**6**),[7] also obtained in $CDCl_3$ solvent, gave confidence that **7** and **8** were indeed isomeric benzo[*c*]-chromene-7,10-diones. The most prominent difference between the two reaction products was the coupling, or lack of it, for the two benzenoid ring protons. The observation of 3.0 Hz coupling between H-1 (δ_H 7.67) and H-3 (δ_H 6.75) defined the higher yielding product to be quinone **7**, while the lack of scalar coupling between the two benzenoid protons [δ_H 7.82 (s, H-1); δ_H 6.69 (s, H-4)] of the second reaction product established their relative disposition as being *para*, i.e., quinone **8**.

With precursor quinones **7** and **8** in hand, addition of hypotaurine was undertaken in a manner previously used by us in the synthesis of the anti-inflammatory ascidian metabolite ascidiathiazone A.[12] Thus an aqueous solution of hypotaurine (1 equiv) was slowly added to **7** in CH_3CN/EtOH at 0 °C and stirred for 48 h at room temperature (rt). Chromatographic purification of the reaction product mixture afforded thiaplidiaquinone A (**4**) and dioxothiazine regioisomer **14** in

Scheme 3. Synthesis of Pre-thiaplidiaquinones A and B



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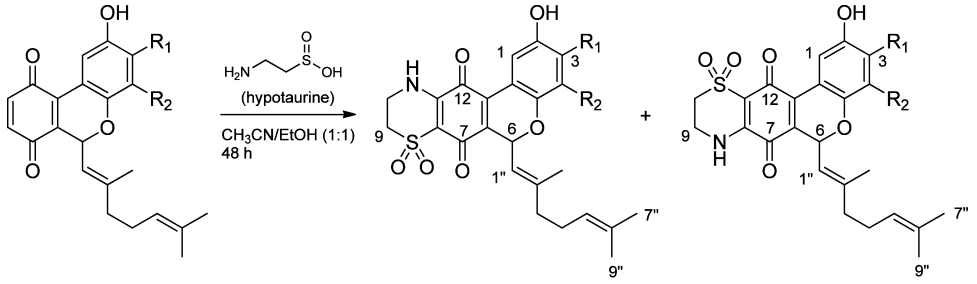
Scheme 4. Synthesis of Thiaplidiaquinones A and B



7 R_1 = H, R_2 = geranyl
8 R_1 = geranyl, R_2 = H

4 R_1 = H, R_2 = geranyl
5 R_1 = geranyl, R_2 = H

14 R_1 = H, R_2 = geranyl
15 R_1 = geranyl, R_2 = H

yields of 21% and 40%, respectively (Scheme 4). ^{1}H and ^{13}C NMR data observed for the minor product were in excellent agreement with those reported for the natural product,[6,9] while data observed for some resonances, in particular H-1 ($\Delta\delta_H$ 0.31) and C-6a/C-9/C-10/C-11a ($\Delta\delta_C$ 7.9−33), of regioisomer **14** were markedly different (see Tables S3 and S4). Reaction of the second precursor, quinone **8**, with hypotaurine in a similar manner afforded two products, identified as thiaplidiaquinone B (**5**) (9.3% yield) and its regioisomer **15** (13%). Once again the spectroscopic data observed for the reaction minor product agreed very well with the data reported for the natural product, while those observed for the isomer were quite different (see Tables S5 and S6).[6] The UV−visible spectra of natural products **4** and **5** were almost superimposable, as were those of the regioisomers **14** and **15**, but the two series were markedly different from each other (see Figure S1), suggesting that this classical spectroscopic technique may be a useful tool in assigning dioxothiazine regiochemistry in this compound class.

In conclusion, we have achieved a biomimetic synthesis of the complex dioxothiazino meroterpenoids thiaplidiaquinones A and B by base-mediated dimerization of geranylbenzoquinone, followed by addition of hypotaurine.

EXPERIMENTAL SECTION

General Experimental Procedures. Ultraviolet−visible spectra were run as MeOH solutions on a UV-2102 PC Shimadzu UV−vis scanning spectrophotometer. Infrared spectra were recorded using a Perkin-Elmer Spectrum One Fourier-transform IR spectrometer as a dry film. ^{1}H and ^{13}C NMR spectra were recorded at 298 K, at 400 and 100 MHz, respectively, or at 600 and 150 MHz, respectively, on Bruker DRX spectrometers. NMR experiments were run in $CDCl_3$ and were referenced to TMS for ^{1}H and to the central peak of the $CDCl_3$ signal at 77.16 ppm[13] for ^{13}C. Standard Bruker pulse sequences were utilized. HRMS data were acquired on a Bruker micrOTOF Q II mass spectrometer. Flash column chromatography was performed using Davisil silica gel (40−63 μm), while analytical thin-layer chromatography was carried out on Merck DC-plastikfolien Kieselgel 60 F254 plates, and products were visualized by UV fluorescence.

2-Geranyl-4-methoxyphenol. Sodium metal (0.71 g, 0.031 mol) was added portionwise to a solution of 4-methoxyphenol (1.91 g, 0.015 mol) in dry Et_2O (65 mL) under a nitrogen atmosphere and then stirred for 3 h at rt. Geranyl bromide (3.34 g, 3.04 mL, 0.015 mol) was then added dropwise, and the solution heated at reflux for 48 h under nitrogen. After the solution cooled to rt, 10% HCl(aq) (5 mL) was added, the aqueous layer was extracted with Et_2O (2 × 10 mL), the combined organic layers were washed with water (2 × 50 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (EtOAc/*n*-hexane, 1:4) gave 2-geranyl-4-methoxyphenol as a pale yellow oil (2.24 g, 56%): R_f (CH_2Cl_2) 0.56; IR (ATR) ν_{max} 3352, 2935, 2834, 1506, 1440, 1220, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.73 (1H, d, J = 8.7 Hz, H-6), 6.68 (1H, d, J = 2.8 Hz, H-3), 6.65 (1H, dd, J = 8.7, 2.8 Hz, H-5), 5.34−5.28 (1H, m, H-2′), 5.10−5.04 (1H, m, H-6′), 4.80 (1H, s, OH), 3.75 (3H, s, H_3-7), 3.33 (2H, d, J = 7.2 Hz, H_2-1′), 2.16−2.10 (2H, m, H_2-4′), 2.10−2.05 (2H, m, H_2-5′), 1.76 (3H, s, H_3-9′), 1.68 (3H, s, H_3-8′), 1.60 (3H, s, H_3-10′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.8 (C-4), 148.5 (C-1), 138.7 (C-3′), 132.1 (C-7′), 128.3 (C-2), 124.0 (C-6′), 121.6 (C-2′), 116.5 (C-6), 115.8 (C-3), 112.2 (C-5), 55.8 (C-7), 39.8 (C-4′), 30.1 (C-1′), 26.6 (C-5′), 25.8 (C-8′), 17.8 (C-10′), 16.3 (C-9′); (+)-HRESIMS m/z 283.1669 [M + Na]$^+$ (calcd for $C_{17}H_{24}NaO_2$, 283.1669).

*Geranylbenzoquinone (**13**).* A solution of cerium ammonium nitrate (9.15 g, 0.019 mol) in CH_3CN/H_2O (1:2, 75 mL) was added dropwise to a stirred solution of 2-geranyl-4-methoxyphenol (2.18 g, 9.4 mmol) in CH_3CN (25 mL) at 0 °C. The mixture was stirred overnight at 0 °C, then poured into 10% NaCl(aq) (100 mL) and extracted with Et_2O (2 × 50 mL). The organic extract was then dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by silica gel column chromatography (EtOAc/*n*-hexane, 1:4) gave quinone **13** as a bright yellow oil (1.19 g, 58%): R_f (30% EtOAc/*n*-hexane) 0.83; IR (ATR) ν_{max} 2966, 2919, 2859, 1656, 1599, 1297 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.76 (1H, d, J = 10.1 Hz, H-6), 6.71 (1H, dd, J = 10.1, 2.4 Hz, H-5), 6.55−6.51 (1H, m, H-3), 5.19−5.12 (1H, m, H-2′), 5.11−5.05 (1H, m, H-6′), 3.13 (2H, d, J = 7.2 Hz, H_2-1′), 2.14−2.09 (2H, m, H_2-4′), 2.09−2.05 (2H, m, H_2-5′), 1.70 (3H, s, H_3-8′), 1.63 (3H, s, H_3-9′), 1.60 (3H, s, H_3-10′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.1 (C-4), 187.7 (C-1), 148.7 (C-2), 140.3 (C-3′), 136.9 (C-6), 136.5 (C-5), 132.5 (C-3), 132.0 (C-7′), 124.0 (C-6′), 117.8 (C-2′), 39.8 (C-4′), 27.5 (C-1′), 26.6 (C-5′), 25.8 (C-8′), 17.8 (C-10′), 16.2 (C-9′); (+)-HRESIMS m/z 267.1359 [M + Na]$^+$ (calcd for $C_{16}H_{20}NaO_2$, 267.1356).

*4-Geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6H-benzo[c]chromene-7,10-dione (**7**) and 3-Geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6H-benzo[c]chromene-7,10-dione (**8**).* Triethylamine (0.26 mL, 0.19 g, 1.84 mmol) was added dropwise to a rapidly stirring solution of geranylbenzoquinone (0.09 g, 0.37 mmol) in CH_2Cl_2 (10 mL) under an atmosphere of nitrogen. When the reaction mixture became a dark brown color (approximately 2 min), it was loaded onto a silica gel chromatography column (CH_2Cl_2). The fraction that eluted with 10−15% MeOH/CH_2Cl_2 was then loaded onto another silica gel chromatography column (CH_2Cl_2) and left exposed to silica overnight. The purple compounds formed were eluted with CH_2Cl_2 to yield 4-geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione (**7**) as a purple oil (5.13 mg, 5.7%) and 3-geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione (**8**) as a purple oil (2.13 mg, 2.4%):

*Compound **7**:* R_f (CH_2Cl_2) 0.29; IR (ATR) ν_{max} 3266, 2977, 1643, 1390 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (1H, d, J = 3.0 Hz, H-1), 6.75 (1H, d, J = 3.0 Hz, H-3), 6.73 (2H, s, H-8, 9), 6.04 (1H, d, J = 9.5 Hz, H-6), 5.32 (1H, d, J = 9.5 Hz, H-1″), 5.25 (1H, t, J = 7.3 Hz, H-2′), 5.09 (1H, t, J = 6.5 Hz, H-6′), 4.92 (1H, t, J = 6.6 Hz, H-5″), 4.70 (1H, br s, OH), 3.24 (2H, dd, J = 7.3, 3.0 Hz, H_2-1′), 2.11−2.05 (2H, m, H_2-5′), 2.04−2.00 (2H, m, H_2-4′), 2.00−1.97 (2H, m, H_2-4″),

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1.97−1.90 (2H, m, H_2-3″), 1.94 (3H, s, H_3-8″), 1.68 (3H, s, H_3-8′), 1.67 (3H, s, H_3-9′), 1.59 (3H, s, H_3-10′), 1.58 (3H, s, H_3-7″), 1.50 (3H, s, H_3-9″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.1 (C-10), 185.2 (C-7), 149.9 (C-2), 147.0 (C-4a), 144.3 (C-2″), 137.2 (C-8/9), 137.0 (C-3′), 135.8 (C-8/9), 134.9 (C-6a), 132.3 (C-4), 131.9 (C-6″), 131.6 (C-7′), 130.5 (C-10a), 124.4 (C-6′), 123.6 (C-5″), 121.6 (C-2′), 120.2 (C-3), 118.4 (C-1″), 117.6 (10b), 112.5 (C-1), 67.3 (C-6), 39.9 (C-3″), 39.8 (C-4′), 28.2 (C-1′), 26.8 (C-5′), 26.3 (C-4″), 25.8 (C-8′), 25.7 (C-7″), 17.8 (C-10′), 17.8 (C-9″), 17.4 (C-8″), 16.6 (C-9′); (+)-HRESIMS *m/z* 509.2645 $[M + Na]^+$ (calcd for $C_{32}H_{38}O_4Na$, 509.2662).

Compound ***8****:* R_f (CH_2Cl_2) 0.43; IR (ATR) ν_{max} 3393, 2922, 1647, 1423 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (1H, s, H-1), 6.72 (2H, s, H-8, 9), 6.69 (1H, s, H-4), 5.99 (1H, d, *J* = 9.5 Hz, H-6), 5.35 (1H, d, *J* = 9.5 Hz, H-1″), 5.30 (1H, t, *J* = 7.1 Hz, H-2′), 5.11−5.05 (1H, m, H-6′), 4.98 (1H, br s, OH), 4.94−4.90 (1H, m, H-5″), 3.33 (2H, dd, *J* = 7.1, 4.0 Hz, H_2-1′), 2.16−2.11 (2H, m, H_2-5′), 2.11−2.07 (2H, m, H_2-4′), 2.03−1.95 (2H, m, H_2-4″), 1.97−1.92 (2H, m, H_2-3″), 1.92 (3H, s, H_3-8″), 1.73 (3H, s, H_3-9′), 1.69 (3H, s, H_3-8′), 1.59 (3H, s, H_3-7″), 1.59 (3H, s, H_3-10′), 1.50 (3H, s, H_3-9″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.2 (C-10), 185.1 (C-7), 149.2 (C-4a), 149.1 (C-2), 144.0 (C-2″), 139.0 (C-3′), 137.0 (C-8/9), 135.9 (C-8/9), 133.8 (C-6a), 133.4 (C-3), 132.1 (C-7′), 131.9 (C-6″), 130.2 (C-10a), 124.0 (C-6′), 123.7 (C-5″), 120.7 (C-2′), 118.6 (C-4), 118.2 (C-1″), 115.8 (C-10b), 115.1 (C-1), 67.6 (C-6), 39.8 (C-3″), 39.8 (C-4′), 29.7 (C-1′), 26.6 (C-5′), 26.2 (C-4″), 25.8 (C-8′), 25.7 (C-7″), 17.9 (C-9″), 17.8 (C-10′), 17.4 (C-8″), 16.4 (C-9′); (+)-HRESIMS *m/z* 509.2649 $[M + Na]^+$ (calcd for $C_{32}H_{38}O_4Na$, 509.2662).

*Thiaplidiaquinone A (****4****) and Regioisomer* ***14****.* A solution of hypotaurine (1.2 mg, 0.01 mmol) in H_2O (0.10 mL) was added dropwise to a solution of 4-geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione (**7**) (4.02 mg, 0.01 mmol) in CH_3CN/EtOH (1:1, 0.8 mL) at 0 °C. The resulting mixture was stirred for 2 days, after which H_2O (3 mL) was added. The aqueous solution was then extracted with CH_2Cl_2 (2 mL × 2) and dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude reaction product was purified using silica gel chromatography (EtOAc/*n*-hexane, 1:1) to yield thiaplidiaquinone A (**4**) as a red oil (1.02 mg, 21%) and regioisomer **14** as a dark blue oil (1.93 mg, 40%).

*Thiaplidiaquinone A (****4****):* R_f (EtOAc) 0.63; UV (MeOH) λ_{max} (log ε) 331 (3.04) nm; IR (ATR) ν_{max} 3304, 2926, 1683, 1622, 1587, 1445, 1348, 1282, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.54 (1H, br s, H-1), 6.90 (1H, br s, NH-11), 6.71 (1H, br s, H-3), 6.08 (1H, d, *J* = 9.5 Hz, H-6), 5.28−5.23 (1H, m, H-1″), 5.23−5.19 (1H, m, H-2′), 5.08 (1H, tt, *J* = 7.0, 1.4 Hz, H-6′), 4.98−4.87 (1H, m, H-5″), 4.19−4.04 (2H, m, H_2-10), 3.43−3.31 (2H, m, H_2-9), 3.28 (1H, dd, *J* = 15.5, 7.1 Hz, H-1′a), 3.17 (1H, dd, *J* = 15.5, 7.4 Hz, H-1′b), 2.10−2.04 (2H, m H_2-5′), 2.04−1.99 (2H, m, H_2-4′), 1.99−1.96 (2H, m, H_2-4″), 1.96−1.92 (2H, m, H_2-3″), 1.92 (3H, s, H_3-8″), 1.68 (3H, s, H_3-8′), 1.66 (3H, s, H_3-9′), 1.59 (3H, s, H_3-10′), 1.59 (3H, s, H_3-7″), 1.50 (3H, s, H_3-9″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.3 (C-12), 175.3 (C-7), 149.7 (C-2), 146.2 (C-4a), 145.6 (C-2″), 143.9 (C-11a), 138.8 (C-6a), 137.1 (C-3′), 132.5 (C-4), 131.9 (C-6″), 131.6 (C-7′), 128.2 (C-12a), 124.4 (C-6′), 123.7 (C-5″), 121.4 (C-2′), 120.1 (C-3), 117.0 (C-1″), 116.8 (C-12b), 111.6 (C-1), 110.6 (C-7a), 67.5 (C-6), 48.8 (C-9), 40.1 (C-10), 39.9 (C-4′), 39.9 (C-3″), 28.2 (C-1′), 26.8 (C-5′), 26.3 (C-4″), 25.8 (C-8′), 25.7 (C-7″), 17.8 (C-9″), 17.8 (C-10′), 17.6 (C-8″), 16.3 (C-9′); (+)-HRESIMS $[M + Na]^+$ 614.2536 (calcd for $C_{34}H_{41}NNaO_6S$, 614.2547).

Regioisomer ***14****:* R_f (50% EtOAc/*n*-hexane) 0.14; UV (MeOH) λ_{max} (log ε) 304 (3.03), 368 (3.36), 442 (2.54), 575 (2.46) nm; IR (ATR) ν_{max} 3304, 2970, 1661, 1594, 1571, 1441, 1350, 1282, 1124, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (1H, d, *J* = 2.7 Hz, H-1), 6.78 (1H, d, *J* = 2.7 Hz, H-3), 6.73 (1H, br s, NH-8), 5.98 (1H, d, *J* = 9.4 Hz, H-6), 5.28 (1H, d, *J* = 9.4 Hz, H-1″), 5.20 (1H, t, *J* = 7.4 Hz, H-2′), 5.08 (1H, t, *J* = 6.4 Hz, H-6′), 4.92 (1H, t, *J* = 6.1 Hz, H-5″), 4.19−4.05 (2H, m, H_2-9), 3.42−3.34 (2H, m, H_2-10), 3.23 (1H, dd, *J* = 15.8, 7.0 Hz, H-1′a), 3.15 (1H, dd, *J* = 15.8, 7.3 Hz, H-1′b), 2.11−2.04 (2H, m, H_2-5′), 2.03−1.95 (2H, m, H_2-4′), 2.03−1.95 (2H, m, H_2-4″), 1.94−1.91 (2H, m, H_2-3″), 1.90 (3H, s, H_3-8″), 1.67 (3H, s, H_3-8′), 1.64 (3H, s, H_3-9′), 1.59 (3H, s, H_3-10′), 1.59 (3H, s, H_3-7″), 1.51 (3H, s, H_3-9″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7 (C-12), 177.5 (C-7), 150.4 (C-2), 148.4 (C-4a), 144.8 (C-2″), 143.8 (C-7a), 137.1 (C-3′), 133.6 (C-12a), 132.3 (C-4), 132.0 (C-6″), 131.7 (C-7′), 130.9 (C-6a), 124.3 (C-6′), 123.5 (C-5″), 122.1 (C-3), 121.4 (C-2′), 118.2 (C-1″), 117.5 (C-12b), 113.7 (C-1), 111.4 (C-11a), 67.1 (C-6), 49.2 (C-10), 40.2 (C-9), 39.9 (C-4′), 39.7 (C-3″), 28.2 (C-1′), 26.8 (C-5′), 26.3 (C-4″), 25.8 (C-8′), 25.7 (C-7″), 17.8 (C-9″), 17.8 (C-10′), 17.4 (C-8″), 16.2 (C-9′); (+)-HRESIMS $[M + Na]^+$ 614.2531 (calcd for $C_{34}H_{41}NNaO_6S$, 614.2547).

*Thiaplidiaquinone B (****5****) and Regioisomer* ***15****.* A solution of hypotaurine (2.55 mg, 0.02 mmol) in H_2O (0.15 mL) was added dropwise to a solution of 3-geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione (**8**) (11.39 mg, 0.02 mmol) in CH_3CN/EtOH (1:1, 1 mL) at 0 °C. The resulting mixture was stirred for 2 days, after which H_2O (3 mL) was added. The aqueous solution was then extracted with CH_2Cl_2 (3 mL × 2) and dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude reaction product was purified using silica gel chromatography (EtOAc/*n*-hexane, 1:1) to yield thiaplidiaquinone B (**5**) as a light purple oil (1.29 mg, 9.3%) and regioisomer **15** as a dark blue oil (1.84 mg, 13%).

*Thiaplidiaquinone B (****5****):*. R_f (EtOAc) 0.59; UV (MeOH) λ_{max} (log ε) 324 (3.00), 362 (sh, 2.84), 558 (2.17) nm; IR (ATR) ν_{max} 3447, 3301, 2928, 1618, 1586, 1424, 1282, 1164, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.69 (1H, br s, H-1), 6.85 (1H, br s, NH-11), 6.69 (1H, br s, H-4), 6.06 (1H, d, *J* = 9.6 Hz, H-6), 5.31−5.25 (1H, m, H-1″), 5.31−5.25 (1H, m, H-2′), 5.07 (1H, t, *J* = 6.7 Hz, H-6′), 4.94 (1H, t, *J* = 6.5 Hz, H-5″), 4.14−4.07 (2H, m, H_2-10), 3.37−3.29 (2H, m, H_2-9), 3.37−3.29 (2H, m, H_2-1′), 2.14−2.10 (2H, m H_2-5′), 2.10−2.06 (2H, m, H_2-4′), 2.01−1.97 (2H, m, H_2-4″), 1.97−1.92 (2H, m, H_2-3″), 1.91 (3H, s, H_3-8″), 1.73 (3H, s, H_3-9′), 1.69 (3H, s, H_3-8′), 1.60 (3H, s, H_3-10′), 1.60 (3H, s, H_3-7″), 1.51 (3H, s, H_3-9″); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 179.2 (C-12), 175.3 (C-7), 149.0 (C-2), 148.1 (C-4a), 145.4 (C-2″), 143.9 (C-11a), 139.3 (C-3′), 137.5 (C-6a), 133.1 (C-3), 132.2 (C-7′), 132.0 (C-6″), 127.9 (C-12a), 123.9 (C-6′), 123.7 (C-5″), 120.4 (C-2′), 118.8 (C-4), 116.6 (C-1″), 114.8 (C-12b), 114.3 (C-1), 110.2 (C-7a), 67.7 (C-6), 48.7 (C-9), 40.0 (C-10), 39.9 (C-3″), 39.8 (C-4′), 29.8 (C-1′), 26.5 (C-5′), 26.1 (C-4″), 25.9 (C-8′), 25.8 (C-7″), 17.9 (C-10′), 17.8 (C-9″), 17.6 (C-8″), 16.4 (C-9′); (+)-HRESIMS *m/z* 614.2538 $[M + Na]^+$ (calcd for $C_{34}H_{41}NNaO_6S$, 614.2547).

Regioisomer ***15****:* R_f (50% EtOAc/*n*-hexane) 0.17; UV (MeOH) λ_{max} (log ε) 303 (3.17), 370 (3.39), 450 (2.69), 587 (2.68) nm; IR (ATR) ν_{max} 3457, 3335, 2930, 1659, 1613, 1584, 1552, 1425, 1277, 1214, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.98 (1H, s, H-1), 6.67 (1H, br s, NH-8), 6.64 (1H, s, H-4), 5.94 (1H, d, *J* = 9.4 Hz, H-6), 5.33 (1H, d, *J* = 9.4 Hz, H-1″), 5.27 (1H, t, *J* = 7.0 Hz, H-2′), 5.08 (1H, t, *J* = 6.8 Hz, H-6′), 4.96−4.91 (1H, br m, H-5″), 4.15−4.05 (2H, m, H_2-9), 3.38−3.33 (2H, m, H_2-10), 3.31 (2H, d, *J* = 7.0 Hz, H_2-1′), 2.14−2.09 (2H, m, H_2-5′), 2.09−2.04 (2H, m, H_2-4′), 2.02−1.96 (2H, m, H_2-4″), 1.96−1.91 (2H, m, H_2-3″), 1.88 (3H, s, H_3-8″), 1.69 (3H, s, H_3-9′), 1.68 (3H, s, H_3-8′), 1.60 (3H, s, H_3-7″), 1.60 (3H, s, H_3-10′), 1.51 (3H, s, H_3-9″); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 177.9 (C-12), 177.2 (C-7), 150.7 (C-4a), 149.5 (C-2), 144.4 (C-2″), 143.7 (C-7a), 138.7 (C-3′), 136.2 (C-3), 133.3 (C-12a), 132.0 (C-7′), 132.0 (C-6″), 129.5 (C-6a), 124.1 (C-6′), 123.6 (C-5″), 120.4 (C-2′), 118.4 (C-4), 118.0 (C-1″), 116.0 (C-1), 115.6 (C-12b), 111.3 (C-11a), 67.3 (C-6), 49.2 (C-10), 40.1 (C-9), 39.9 (C-4′), 39.8 (C-3″), 29.4 (C-1′), 26.6 (C-5′), 26.3 (C-4″), 25.8 (C-8′), 25.8 (C-7″), 17.9 (C-9″), 17.8 (C-10′), 17.4 (C-8″), 16.3 (C-9′); (+)-HRESIMS *m/z* 614.2529 $[M + Na]^+$ (calcd for $C_{34}H_{41}NNaO_6S$, 614.2547).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables of NMR data for **4**, **5**, **7**, **8**, **14**, and **15**, figure of UV spectra of **4**, **5**, **14**, and **15**, and copies of ^{1}H and ^{13}C NMR spectra for 2-geranyl-4-methoxyphenol, geranylbenzoquinone,

and compounds **4**, **5**, **7**, **8**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to the memory of Prof. Ernesto Fattorusso (1937−2012).

REFERENCES

(1) Menna, M.; Fattorusso, E.; Imperatore, C. *Molecules* **2011**, *16*, 8694−8732.
(2) Zubía, E.; Ortega, M. J.; Salvá, J. *Mini-Rev. Org. Chem.* **2005**, *2*, 389−399.
(3) Sunassee, S. N.; Davies-Coleman, M. T. *Nat. Prod. Rep.* **2012**, *29*, 513−535.
(4) Garrido, L.; Zubía, E.; Ortega, M. J.; Salvá. *J. Nat. Prod.* **2002**, *65*, 1328−1331.
(5) Fu, X.; Hossain, M. B.; Schmitz, F. J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810−3819.
(6) Aiello, A.; Fattorusso, E.; Luciano, P.; Macho, A.; Menna, M.; Munoz, E. *J. Med. Chem.* **2005**, *48*, 3410−3416.
(7) Chan, S. T. S.; Pearce, A. N.; Januario, A. H.; Page, M. J.; Kaiser, M.; McLaughlin, R. J.; Harper, J. L.; Webb, V. L.; Barker, D.; Copp, B. R. *J. Org. Chem.* **2011**, *76*, 9151−9156.
(8) Cadelis, M. M.; Barker, D.; Copp, B. R. *Synlett* **2012**, *23*, 2939−2942.
(9) Carbone, A.; Lucas, C. L.; Moody, C. J. *J. Org. Chem.* **2012**, *77*, 9179−9189.
(10) Lumb, J.-P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865−5868.
(11) Baeza, E.; Catalán, K.; Peña-Cortés, H.; Espinoza, L.; Villena, J.; Carrasco, H. *Quim. Nova* **2012**, *35*, 523−526.
(12) Pearce, A. N.; Chia, E. W.; Berridge, M. V.; Clark, G. R.; Harper, J. L.; Larsen, L.; Maas, E. W.; Page, M. J.; Perry, N. B.; Webb, V. L.; Copp, B. R. *J. Nat. Prod.* **2007**, *70*, 936−940.
(13) Gottlieb, H. E.; Kotlyar, V.; Nudelamn, A. *J. Org. Chem.* **1997**, *62*, 7512−7515.