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FULL PAPER

Yicathins B and C and analogues: total synthesis, lipophilicity and biological activities

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Abstract: Natural products had always be an important source of new hits and leads in drug discovery. The marine environment has been regarded as a significant souce of novel and exquisite bioactive compounds. Yicathins B and C are two marine derived xanthones that have shown antibacterial and antifungal activities. Herein, the total synthesis of these yicathins is reported for the first time as well as six novel analogues. As marine natural products tend to bear very lipophilic scaffolds, the lipophilicity of yicathins and its analogues was evaluated using the classical octanol:water system and a biomimetic model based system. As the xanthonic nucleus is a "privileged structure", other biological activities were evaluated, namely antitumor and anti-inflammatory activities. An interesting anti-inflammatory activity was identified for yicathins analogues that paves the way for the design of dual activity (anti-infective and anti-inflammatory) marine inspired xanthones derivatives.

Introduction

Marine microorganisms are able to develop different and original pathways to the biosynthesis of secondary metabolites, providing novel scaffolds which are quite different from those found in terrestrial sources.[1] In addition to its chemical uniqueness, these kind of metabolites frequently show important pharmacological activities, making them a valuable source of new hits, leads and drugs.[2]

Xanthones are *O*-heterocyclic compounds with the dibenzo-*γ*-pyrone scaffold (Figure 1, nucleus highlighted in blue). Xanthones are widely distributed in Nature, including the marine environment.[3] Marine xanthones derivatives are mostly isolated from fungi and bacteria, which live in symbiotic relationships with micro- and macroorganisms.[3-4]

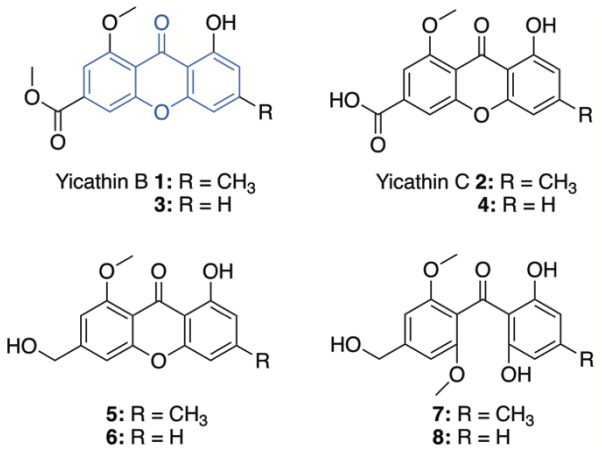


Figure 1. Structure of yicathin B (**1**) and yicathin C (**2**) and its six analogues **3**, **4**, **5**, **6**, **7**, and **8**. Xanthonic scaffold highlighted in blue.

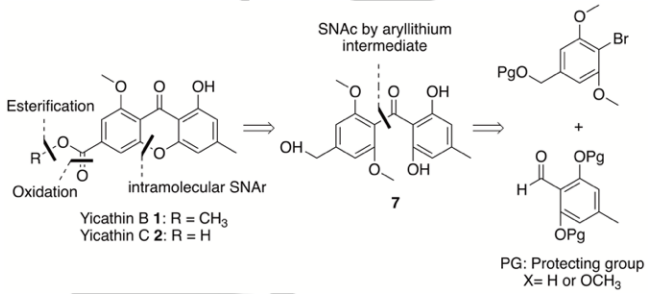
As "privileged structures" in Medicinal Chemistry, xanthone scaffold allows a variety of substitution patterns that lead to diverse pharmacological activities, such as anti-infective, anticancer, and anti-inflammatory activities.[5] Yicathin B (**1**) and yicathin C (**2**) (Figure 1) are two paradigmatic examples of bioactive marine xanthones which have shown a quite interesting antibacterial and antifungal activity.[6] In addition to the reported wide range of biological activities, xanthone derivatives can also have dual activity. For instance, marine xanthones sharing structural similarity to yicathins have been reported showing antimicrobial and antitumor and/or anti-inflammatory activities.[7] Marine natural products (MNPs) are usually difficult to access and the extraction provides relatively small amounts.[8] Laboratory synthesis can surpass the supply issues, and additionally allows the obtention of different substitution patterns besides those furnished by Nature.[9]

Bioactive natural products are often potent, but present inadequate ADMET properties. Lipophilicity is one of the most important biophysicochemical properties affecting the ADMET.[10] In the case of MNPs, this property requires even more attention, as these scaffolds tend to be very lipophilic.[1] Traditionally, lipophilicity is evaluated by the partition coefficients between octanol and aqueous systems (Log P and Log D).[11] However, biomimetic models, such as micelles, have proved to be an advantageous alternative to the classical octanol-based systems, as they take into account all the involved interactions, hydrophobic and electrostatic, that occur in the partition of a drug with biological membranes.[12]

Herein, we report the first total synthesis of yicathin B (**1**) and yicathin C (**2**), along with six analogues (**3**, **4**, **5**, **6**, **7**, **8**) (Figure 1). Their lipophilicity was assessed *in silico* using the classical octanol model (Log P and Log $D_{7.4}$ values) and experimentally using the micelles biomimetic model (Log $K_{P\ 7.4}$ values). As the xanthonic nucleus can interact with more than one target,[5b] *in vitro* antitumor and anti-inflammatory activities were evaluated.

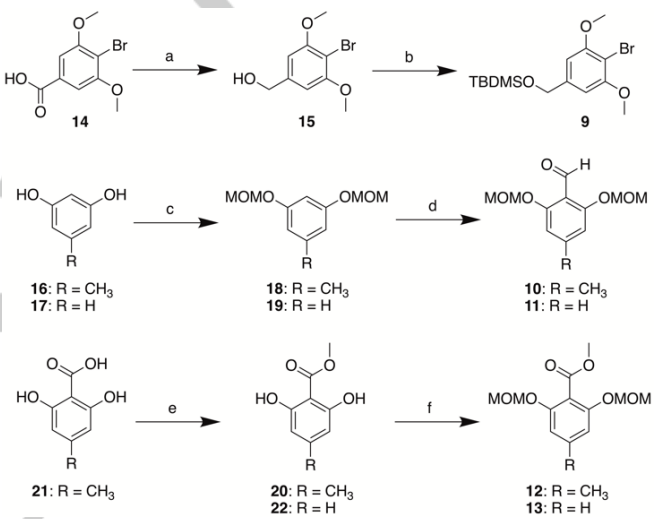
Results and Discussion

Retrosynthetic analysis used to plan the synthesis of yicathins B and C is based on a benzophenone intermediate, which are frequent important precursors of xanthones.[13] The synthetic pathway that requires benzophenone **7**, which was converted to the target yicathins (**1** and **2**) (Scheme 1). This benzophenone was obtained by a convergent synthesis using suitable building blocks (Scheme 1). In addition, six yicathins analogues (**3, 4, 5, 6, 7, 8**) were also prepared using this synthetic route.



Scheme 1. Retrosynthesis of yicathins B (**1**) and C (**2**). S_NAr: aromatic nucleophilic substitution; S_NAc: acyl nucleophilic substitution.

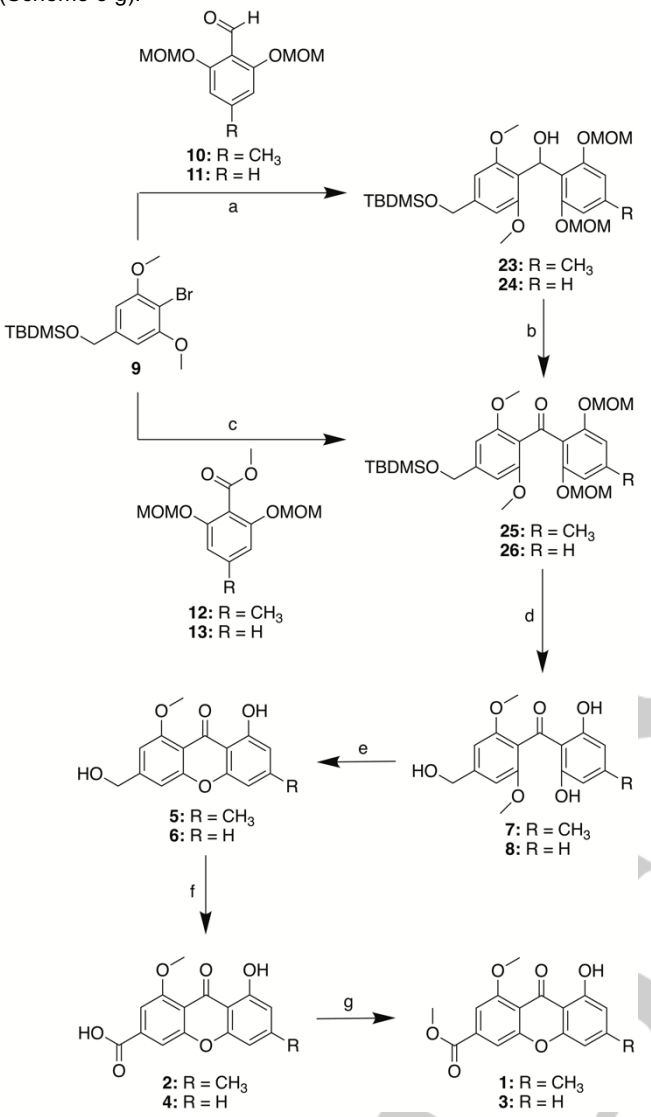
Building blocks **9, 10, 11, 12** and **13** were used for the synthesis of yicathins and its analogues (Scheme 2). Building block **9** was obtained in two steps from 4-bromo-3,5-dimethoxybenzoic acid **14**. This acid was reduced with BH_3:THF to the alcohol **15**,[14] which was subsequently protected with TBDMS-Cl to achieve compound **9** (Scheme 2 a, b).[15] The building blocks **10** and **11**, two benzaldehydes, were obtained in two steps from orcinol **16** and resorcinol **17**, respectively. The phenolic groups were protected with MOM-Cl,[16] followed by an arylformylation (Scheme 2 c, d).[16] Other protecting groups were also explored (MEM and Bn), but lower yields were obtained (data not shown). The building block **12** was obtained by protecting the phenol groups of methyl 2,6-dihydroxy-4-methylbenzoate **20** (Scheme 2 f).[16] The building block **13** was synthetized in two steps from 2,6-dihydroxybenzoic acid **21**, which was esterified to the methyl ester **22,**[17] followed by protection with MOM-Cl to provide **13** (Scheme 2 e, f).[16]



Scheme 2. Synthesis of building blocks **9**, **10**, **11**, **12** and **13**. Reagents and conditions: a) BH_3:THF, THF, 99%; b) TBDMS-Cl, Imidazole, DMF, 88 %; c) MOM-Cl, NaH, DMF, **5**: 91%, **10**: 95%; d) *n*-BuLi, TMEDA, THF, DMF, **10**: 79%, **11**: 85%; e) $(CH_3O)_2SO_2$, K_2CO_3, acetone, 76%; f) MOM-Cl, NaH, DMF, **12**: 72 %, **13**: 71 %.

Using these building blocks, yicathins and its analogues were synthesized accordingly to Scheme 3. The acyl substitution of the benzaldehydes **10** and **11** by an aryllithium intermediate, prepared *in situ* from **9**, yielded the diarylmethanol derivatives **23** and **24** (Scheme 3 a).[18] These diarylmethanol derivatives were then oxidized to the benzophenones **25** and **26** using DMP as oxidant reagent (Scheme 3 b).[18a, 19] This oxidation was also performed with another oxidant, MnO_2, but the main formed products were the result of the cleavage of the precursor diarylmethanol (data not shown). The acyl substitution of the methyl esters **12** and **13** by the aryllithium intermediate, prepared *in situ* from **9**, yielded the benzophenones **25** and **26** (Scheme 3 c).[18] This one-step pathway provided the desired compounds in lower yields, which can be explained by the low carbon electrophilicity of the esters **12** and **13**. Benzophenones **25** and **26** were then deprotected, under acidic conditions, resulting the benzophenones **7** and **8** (Scheme 3 d).[20] Subsequently, compounds **5** and **6** were synthesized by a microwave assisted intramolecular nucleophilic aromatic substitution of **7** and **8**

(Scheme 3 e).[21] Yicathin C (**2**) and analogue **4** were provided by oxidation of **5** and **6**, respectively, using a modified Jones reagent (Scheme 3 f).[22] Finally, yicathin B (**1**) and analogue **3** were obtained by Fisher esterification of the carboxylic acids **2** and **4** (Scheme 3 g).[23]



Scheme 3. Synthesis of yicathins and analogues. Reagents and conditions: a) 1. *n*-BuLi, THF, -78 ºC, 2. **10** or **11**, -78 ºC to rt, **23**: 53%, **24**: 87%; b) 1. *n*-BuLi, THF, -78 ºC, 2. **12** or **13**, -78 ºC to rt, **25**: 21%, **26**: 19%; c) DMP, DCM, **25**: 90%, **26**: 87%; d) *p*-TsOH, MeOH, **7**: 45%, **8**: 39%; e) MW, NaOH, H_2O/MeOH, 130 ºC, **5**: 93%, **6**: 93%; f) H_5IO_6/CrO_3, wet ACN, **2**: 48%, **4**: 57%; g) H_2SO_4, MeOH, **1**: 45%, **3**: 46%

Log P and Log $D_{7.4}$ values of yicathins and its analogues (**1**-**8**) were predicted using different *in silico* approaches (Supporting Information, Table S1 and S2). The biomimetic partition coefficients of yicathins and its analogues (**1**-**8**), Log $K_{P\ 7.4}$, were experimentally measured using micelles as lipidic phase and phosphate-buffered saline buffer as aqueous phase (PBS: 10 mmol L^{-1}, I = 0.15 mol L^{-1}, pH 7.4).[12a] The determination of Log KP 7.4 was performed by derivative spectrophotometry (Table S3 and Figure S22, Supporting Information).[24] Figure 2 summarizes the *in silico* Log P and Log $D_{7.4}$, and the experimental Log $K_{P\ 7.4}$ in micelles/buffer. The results obtained for each compound using different *in silico* methods provided very different values, which is reflected on the high standard deviation values (up to 1 unit). Log P and Log $D_{7.4}$ values were similar for all compounds, with exception of the compounds **2** and **4**, whose Log $D_{7.4}$ were low. This is due to the deprotonation of the carboxylic acid group of **2** and **4** with consequent reduction of the free acid concentration. Log $K_{P\ 7.4}$ values were higher than Log P and Log $D_{7.4}$ values. Compound **2** (Log $K_{P\ 7.4}$ 3.48 vs. Log $D_{7.4}$ 0.2) illustrates well the difference between biomimetic and classical model. This is ascribed to the fact that micelles system is able to take into account not only the hydrophobic interactions, but also the electrostatic interactions, which are not evaluated by classical octanol system. In accordance, the electrostatic interactions play a minor role on the partition of the more hydrophobic compounds, like **1** and **3**. Log $K_{P\ 7.4}$ values for all evaluated compounds were within the limits preconized for lipophilicity by the most common "drug-like" guidelines.[25]

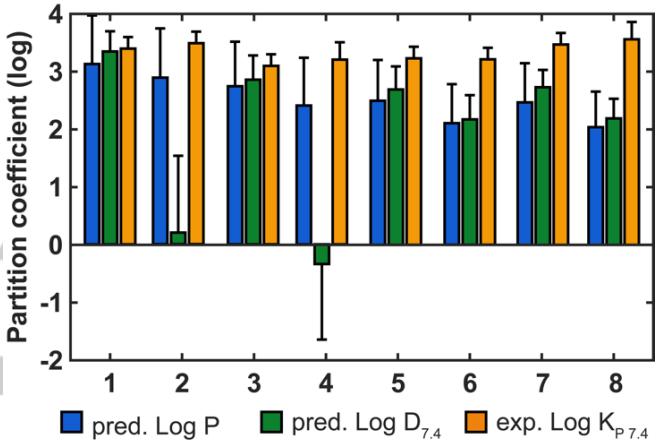


Figure 2. Predicted Log P and Log $D_{7.4}$ and experimentally determined Log $K_{P\ 7.4}$ for yicathins and its analogues (**1**-**8**). Error bars in Log P and Log $D_{7.4}$ indicate mean ± SD of predicted values by fifteen in silico methods. Error bars in Log $K_{P\ 7.4}$ indicate mean ± SD of three replicates.

The cell growth inhibitory activities of yicathins and derivatives (**1** to **8**) were evaluated for their *in vitro* growth inhibitory effect on three human tumor cell lines: A375 (melanoma), MCF-7 (breast adenocarcinoma), and NCI-H460 (non-small-cell lung cancer) (Table 1). All the compounds required higher than 150 μM to reduce growth rates to 50% (GI_{50}) in human cell lines tested, namely, compounds **7** and **6**. Overall, melanoma A376 cell line was more sensitive to the test compounds than MCF-7 and NCI-H460 cell lines. Compound **2** displayed the greatest growth inhibitory activity in the three human cells lines studied (range between 48.70 to 86.21 μM). Comparison of the GI_{50} values of the compounds **7** and **8** (benzophenone analogues), seems to indicate that the absence of a methyl group (R = H) of compound **8** is associated with an increase in the growth inhibitory activity.

Table 1. GI_{50} concentrations (μM) of the synthesized compounds in A375, MCF-7 and NCI-H460 cell lines.

Compd	GI_{50} ± SD (μM)[a]		
	A375	MCF7	NCI-H460
1	47.70 ± 2.62	79.83 ± 18.45	98.93 ± 9.83
2	48.70 ± 4.24	86.21 ± 2.30	73.92 ± 2.28

3	61.59 ± 7.25	110.95 ± 34.47	100.78 ± 1.64
4	74.40 ± 1.23	115.94 ± 16.95	134.36 ± 13.65
5	55.71 ± 4.16	87.57 ± 9.23	101.54 ± 7.53
6	102.76 ± 3.90	>150	>150
7	137.12 ± 1.07	>150	138.65 ± 0.92
8	63.61 ± 1.70	105.32 ± 0.45	74.74 ± 2.74
Doxorubicin	0.010 ± 0.002	0.012 ± 0.001	0.018 ± 0.005

[a] Results are expressed as mean ± SD. Doxorubicin was used as positive control

The anti-inflammatory activity of yicathins and its analogues was evaluated based on their capacity to decrease the concentration of the pro-inflammatory cytokine IL-6 on LPS-stimulated macrophages. Figure 3 presents the metabolic activity, DNA concentration and IL-6 amount obtained for LPS-stimulated macrophages in the absence or in the presence of the different compounds.

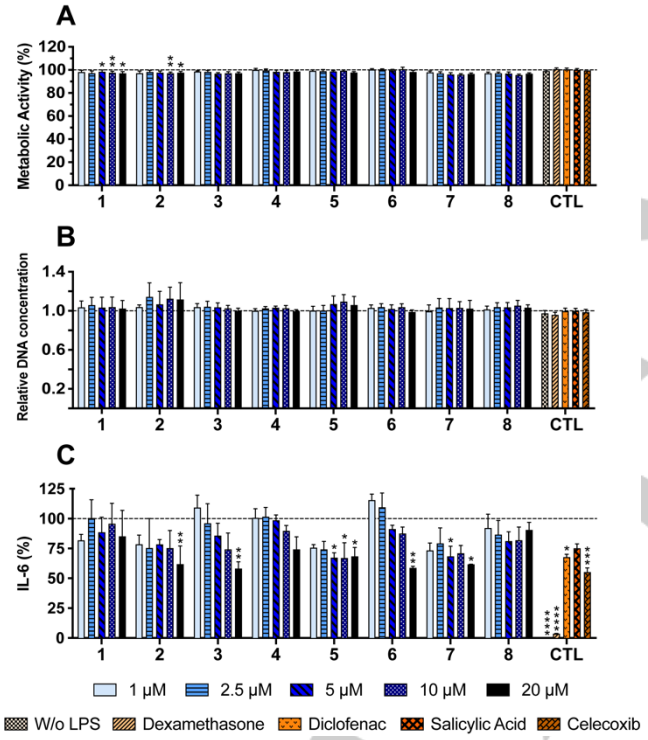


Figure 3. Metabolic activity (A), relative DNA concentration (B) and IL-6 cytokine percentages (C) of LPS-activated macrophages cultured in the presence of different concentrations of the tested compounds and clinically used anti-inflammatory drugs (dexamethasone, diclofenac, salicylic acid and celecoxib) for 24 h of culture at 37 °C. Results are expressed as mean ± SD and statistically significant differences are * ($p < 0.0471$), ** ($p < 0.0077$), *** ($p < 0.0007$), **** ($p < 0.0001$) in comparison to the LPS-stimulated control (0 µM) for each different tested compound.

The compounds were not cytotoxic for all tested concentrations as the cell metabolic activity was not affected (Figure 3A) and the DNA was preserved in the presence of the different compounds in an inflammatory scenario (Figure 3B). Additionally, all the compounds, with exception of some tested conditions, allowed cells to reach the metabolic activity state of the non-stimulated cells (without LPS), which can be related with their anti-inflammatory activity. These results were corroborated by DNA quantification analyses, as a similar amount of this nucleic acid was obtained for non-stimulated or LPS-stimulated macrophages in the presence of the different compounds.The stimulation of macrophages with LPS (100 ng/mL) led to a significant IL-6 production (non-stimulated macrophages did not produce this pro-inflammatory cytokine; Figure 3C). However, the amount of this cytokine in the medium was significantly reduced in the presence of some of the tested compounds. Compound **7** presented the strongest anti-inflammatory activity (higher IL-6 reduction), followed by **5**, booth showing a significant reduction with a minimum concentration of 5 µM. In spite of lower concentrations of **6** and **3** did not present anti-inflammatory activity in this *in vitro* scenario, its higher concentration (20 µM) presented the highest IL-6 reduction, followed by **2**, **5** and **7** (Figure 3C). The compounds **1**, **4** and **8** were not effective in the reduction of IL-6, even for the highest tested concentration (20 µM). Dexamethasone (10 µM) was the most efficient control in reducing the IL-6 production. Celecoxib (10 µM) and diclofenac (10 µM) also led to a significant reduction of the IL-6 amount, while salicylic acid (10 µM) did not show ability to significantly reduce the IL-6 concentration in this *in vitro* inflammatory model. None of the tested compounds showed a similar anti-inflammatory activity of dexamethasone (corticosteroid). However, the compounds in some concentrations led to a higher decrease of the pro-inflammatory cytokine amount than well-known nonsteroidal anti-inflammatory drugs (NSAIDs), namely diclofenac, salicylic acid and celecoxib.

Conclusions

Total synthesis of yicathin B (**1**), yicathin C (**2**), and six new yicathins analogues was described for the first time. The desired compounds were obtained with a suitable overall yield. Lipophilicity of yicathins and its analogues was evaluated using *in silico* and experimental biomimetic methodologies. The obtained partition coefficients were quite different, namely for ionized compounds at physiological pH. Nevertheless, the lipophilicity of the synthetized compounds were within the limits preconized by the most common “drug-like” guidelines. Additional biological activities were explored for the yicathins and its analogues. Antitumor activity was screened in three human tumor cell lines, but the compounds did not revealed a significant ability to inhibit cell growth, being 48.70 µM the lowest found value of GI_{50}. Nevertheless, compounds **2**, **5**, and **7** shown a significant *in vitro* anti-inflammatory activity, which was comparable with well-known NSAIDs, like diclofenac and celecoxib. Unfortunately, a detailed and ascertain SAR cannot be established due to the limited number of compounds. However, one hit compound was identified which are being currently explored by us in the design of dual activity (anti-infective and anti-inflammatory) marine inspired xanthones derivatives.

Experimental Section

General. All reagents and solvents were purchased from TCI (Tokyo Chemical Industry Co. Ltd., Chuo-ku, Tokyo, Japan), Acros Organics (Geel, Belgium), Sigma-Aldrich (Sigma-Aldrich Co. Ltd., UK), or Alfa Aesar

(Thermo Fisher GmbH, Kandel, Germany) and were used directly without any further purification. Anhydrous solvents were dried according to the published procedures.[26] All reactions were monitored by TLC, carried out on Merck silica gel 60 (GF254) precoated plates using with appropriate mobile phases, and/or by GC-MS. Purification of the synthesized compounds was usually performed by flash column chromatography using Merck silica gel 60 (0.040–0.063 mm). MW reactions were performed in a CEM Discovery SP® from CEM Corporation (Matthews, NC, US). All MW reactions were performed in a closed vessel at fixed temperature, which was monitored by an integrated infrared sensor. Melting points (mp) were measured in a Köfler microscope (Wagner and Munz, Munich, Germany) equipped with a Crison TM 65 (Crison Instruments, Barcelona, Spain) and were uncorrected. IR spectra were measured on an ATI Mattson Genesis series FTIR (software: WinFirst v. 2.10) spectrophotometer in KBr microplates (cm^{-1}). EIMS spectra were recorded on a ThermoQuest Finnigan GC 2000 series/GCQ plus. Injections were performed using compounds directly dissolved in ethyl acetate or previously derivatized with MSTFA at 80 °C for 30 minutes. HRMS spectra were recorded as ESI (electrospray ionization) mode either on VG Autoespec MicroTOF FOCUS spectrometer (Bruker Daltonics, Bremen, Germany) or on LTQ OrbitrapTM XL hybrid mass spectrometer (Thermo Fischer Scientific, Bremen, Germany). ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ or DMSO-d_6 (Deutero GmbH, Kastellaun, Germany) at room temperature on Bruker Avance 300 instrument (300.13 or 500.16 MHz for ^1H and 75.47 or 125.77 MHz for ^{13}C, Bruker Biosciences Corporation, Billerica, MA, USA) or Bruker AVANCE III (400.14 MHz for ^1H and 100.62 MHz for ^{13}C). Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference. Coupling constants are reported in hertz (Hz).^{13}C NMR assignments were made by 2D HSQC and HMBC experiments.

Synthesis of Yicathin B (1) and methyl 8-hydroxy-1-methoxy-6-methyl-9-oxo-9*H*-xanthene-3-carboxylate (3): In a round-bottom flask, compound **2** (140 mg, 466 µmol) was dissolved in 10 mL of methanol and H_2SO_4 (78 µL, 1.40 mmol) was added. The reaction mixture was heated under reflux overnight. Water and $NaHCO_3$ were added to the flask and the solution extracted with ethyl acetate (3 x 5 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by crystallization with DCM and MeOH. Compound **1** was obtained as a yellow solid (66 mg, 45 %).

Yicathin B (1): yellow solid; mp: 155–156 °C; IR (KBr): $\tilde{\nu}$ = 3004, 2955, 2920, 2850, 1735, 1659, 1564, 1508, 1474, 1428, 1360, 1333, 1305, 1272, 1242, 1209, 1189, 1155, 1139, 1114, 1090, 989, 880, 835, 823, 807 cm^{-1}; ^1H NMR (400.14 MHz, DMSO-d_6): δ = 12.73 (s, OH), 7.56 (s, 1H), 7.37 (s, 1H), 6.79 (s, 1H), 6.60 (s, 1H), 4.00 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 2.40 (s, 3H); ^{13}C-NMR (100.63 MHz, DMSO-d_6): δ = 180.8, 164.8, 160.8, 160.4, 157.0, 154.7, 148.9, 135.8, 112.9, 111.4, 110.2, 107.0, 106.9, 105.7, 54.9, 53.0, 21.9; EIMS: m/z 387 (1, $[M+TMS]^{+\cdot}$), 371 (18), 356 (14), 312 (10), 299 (16), 298 (83), 297 (10), 271 (22), 270 (100), 269 (18), 242 (17), 241 (51), 227 (10), 143 (18), 134 (11); HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_6$ $[M+H]^+$: 315.08631; found: 315.08600.

Compound 3: yellow solid (8.7 mg, 46 %); mp. 178–181 °C; IR (KBr): $\tilde{\nu}$ = 3446, 2921, 2851, 1728, 1647, 1636, 1617, 1592, 1559, 1472, 1458, 1435, 1419, 1325, 1307, 1231, 1209, 1114, 1098, 762 cm^{-1}; ^1H NMR (500.16 MHz, DMSO-d_6): δ = 12.82 (s, H), 7.71 (t, *J* = 8.3 Hz, H), 7.62 (s, H), 7.42 (s, H), 7.03 (d, *J* = 8.3 Hz, H), 6.81 (d, *J* = 8.3 Hz, H), 4.02 (s, H), 3.95 (s, 3H).^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 181.5, 164.8, 161.1, 160.5, 157.1, 154.9, 137.2, 136.1, 113.0, 110.7, 110.2, 109.4, 106.0, 102.8, 56.7, 53.1; EIMS: m/z 372 (2, $[M+TMS]^{+\bullet}$), 358 (12), 357 (48), 322 (21), 285 (24), 284 (100), 283 (12), 257 (22), 256 (99), 255 (18), 202 (12), 198 (11), 185 (13), 165 (11), 73 (10). HRMS (ESI): *m/z* calcd for $C_{16}H_{11}O_6$ $[M-H]^-$: 299.05501; found: 299.05582.

Synthesis of Yicathin C (2) and 8-hydroxy-1-methoxy-6-methyl-9-oxo-9*H*-xanthene-3-carboxylic acid (4): In a typical experiment, H_5IO_6 (1.0 g, 4.6 mmol) and chromium (VI) oxide (4.6 mg, 46 µmol) was placed in a 50 mL Erlenmeyer, and then dissolved with 10 mL of wet ACN (75 %). In a round-bottom flask, compound **5** (50 mg, 0.18 mmol) was dissolved in 35 mL of wet ACN (75 %) and 10 mL of the H_5IO_6/CrO_3 solution was added. The reaction mixture stirred for 26 hours at room temperature. $NaHSO_3$ was added and the solution was extracted with chloroform (3 x 15 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by silica gel flash chromatography (hexane/EtOAc/formic acid 6:4:0.1). Compound **2** was obtained as a yellow solid (50 mg, 48 %).

Yicathin C (2): yellow solid; mp. 204–205 °C; IR (KBr): $\tilde{\nu}$ = 3446, 2924, 2853, 1718, 1652, 1615, 1559, 1478, 1419, 1386, 1329, 1301, 1250, 1203, 1141, 1115, 1087, 1006, 895, 824, 770 cm^{-1}; ^1H NMR (500.16 MHz, DMSO-d_6): δ = 13.85 (s, OH), 12.74 (s, OH), 7.54 (d, *J* = 1.4 Hz, H), 7.36 (d, *J* = 1.4 Hz, H), 6.83 (q, *J* = 1.3 Hz, H), 6.63 (q, *J* = 1.3 Hz, H), 3.93 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 180.8, 164.8, 160.9, 160.4, 157.0, 154.7, 148.9, 135.9, 112.9, 111.4, 110.2, 107.1, 107.0, 105.8, 53.0, 21.9; EIMS: m/z 445 (0.5, $[M+TMS]^{+\cdot}$), 429 (10), 369 (10),313 (22), 312 (100), 297 (21), 283 (33), 241 (15), 217 (15); HRMS (ESI): *m/z* calcd for $C_{16}H_{11}O_6$ $[M-H]^-$: 299.05611; found: 299.05606.

Compound 4: yellow solid (30 mg, 57 %); mp: 238–240 °C; IR (KBr): $\tilde{\nu}$ = 3447, 2922, 1708, 1654, 1594, 1473, 1384, 1352, 1261, 1100 cm^{-1}; ^1H NMR (300.16 MHz, $CDCl_3$): δ = 12.99 (s, OH), 12.96 (s, COOH), 7.38 (t, *J* = 8.3 Hz, H), 7.34 (s, H), 7.12 (s, H), 6.64 (d, *J* = 8.4 Hz, H), 6.28 (d, *J* = 8.2 Hz, H), 3.80 (s, 3H) ;^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 181.8, 165.8, 161.3, 159.6, 157.0, 155.2, 136.5, 129.4, 110.0, 109.9, 108.8, 107.2, 106.6, 106.5, 56.0; EIMS: m/z 430 (0.5, $[M+TMS]^{+\bullet}$), 418 (2), 417 (14), (416 (32), 415 (100), 400 (11), 372 (2), 357 (8), 355 (12), 299 (16), 298 (58), 283 (19), 269 (18), 253 (14), 227 (13), 187 (12), 165 (7), 74 (6), 73 (8); HRMS (ESI): *m/z* calcd for $C_{15}H_9O_6$ $[M-H]^-$: 285.04046; found: 285.04129.

Synthesis of 1-hydroxy-6-(hydroxymethyl)-8-methoxy-3-methyl-9*H*-xanthen-9-one (5) and 8-hydroxy-3-(hydroxymethyl)-1-methoxy-9*H*-xanthen-9-one (6): In a typical experiment, 4 mL of a solution of NaOH 2M in H_2O/MeOH (9:1) was added to compound **7** (210 mg, 660 µmol) in a 10 mL MW reaction vessel. The reaction mixture was microwave heated at 130 °C for 5 minutes. The mixture was cooled to room temperature, and HCl 5% were added until a pH of 4-5. The precipitate was collected by filtration under reduced pressure. Compound **5** was obtained as a pale yellow solid (175 mg, 93 %).

Compound 5: pale yellow solid; mp: 179–180 °C; IR (KBr): $\tilde{\nu}$ = 3472, 2983, 2920, 2853, 1655, 1607, 1559, 1504, 1477, 1464, 1428, 1361, 1327, 1298, 1265, 1224, 1210, 1133, 1112, 1091, 1069, 1005, 983, 963, 904, 826 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ = 13.06 (s, OH), 7.06 (s, H), 6.95 (s, H), 6.82 (s, H), 6.60 (s, H), 5.59 (t, *J* = 3.4 Hz, OH), 4.64 (*d*, *J* = 3.4 Hz, 2H), 3.91 (*s*, 3H), 2.38 (*s*, 3H); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 181.0, 161.0, 160.1, 157.4, 154.8, 152.9, 148.2, 111.0, 108.7, 106.8, 106.7, 106.1, 103.9, 62.3, 56.3, 21.9; EIMS: m/z 431 (1, $[M+TMS]^{+\bullet}$), 416 (15), 415 (26), 311 (22), 310 (17), 283 (60), 253 (20), 237 (15), 89 (32), 73 (100), 59 (42); HRMS (ESI): *m/z* calcd for $C_{16}H_{15}O_5$ $[M+H]^+$: 287.09140; found: 287.09283.

Compound 6: pale yellow solid (311 mg, 90 %); mp: 236–238 °C; IR (KBr): $\tilde{\nu}$ = 3471, 2920, 2851, 1655, 1607, 1558, 1504, 1476, 1464, 1428, 1361, 1327, 1264, 1224, 1209, 1133, 1111, 1091, 1068, 826, 790 cm^{-1}; ^1H NMR (400. 14 MHz, DMSO-d_6): δ = 13.12 (s, OH), 7.64 (t, *J* = 8.3, 1H), 7.06 (d, *J* =1.2 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.74 (dd, *J* = 8.3, 0.9 Hz, 1H), 5.56 (t, *J* = 5.8 Hz, OH), 4.64 (d, *J* = 5.6, 2H), 3.92 (s, 3H, OCH_3); ^{13}C NMR (100.63 MHz, DMSO-d_6): δ = 181.6, 161.3, 160.2, 157.5, 155.0, 153.2, 136.8, 110.4, 108.8, 108.8, 106.6, 106.2, 104.0, 62.4, 56.4; EIMS: m/z 416 (0.5, $[M+TMS]^{+\bullet}$), 401 (52), 341 (21), 315 (21), 314 (18), 312 (20), 311 (18), 299 (30), 298 (16), 297 (36), 296 (16), 287 (16), 286 (18), 285 (27), 272 (18), 270 (28), 269 (72), 253 (15), 252 (25), 239 (27), 237 (16), 223 (19), 89 (31), 73 (100), 59 (31); HRMS (ESI): *m/z* calcd for $C_{15}H_{13}O_5$ $[M+H]^+$: 273.07685; found: 273.07611.

Synthesis of (2,6-dihydroxy-4-methylphenyl)(4-(hydroxymethyl)-2,6-dimethoxyphenyl)methanone (7) and (2,6-dihydroxyphenyl)(4-(hydroxymethyl)-2,6-dimethoxyphenyl)methanone (8): In a round-bottom flask of 50 mL, compound **25** (1.1 g, 2.11 mmol) was dissolved in 24 mL of MeOH. *p*-TsOH (603 mg, 3.17 mmol) was added and the mixture turned red. The reaction mixture was stirred at 50 °C for 5 hours. H_2O was added to the mixture and the solution was extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by silica gel flash chromatography (hexane/EtOAc/formic acid 7:3:0.1). Compound **7** was obtained as a yellow solid (300 mg, 45 %).

Compound 7: yellow solid; mp: 170–171°C; IR (KBr): $\tilde{\nu}$ = 3269, 3020, 2937, 1637, 1612, 1589, 1496, 1460, 1415, 1357, 1326, 1299, 1258, 1229, 1216, 1197, 1065, 1035, 1006, 961, 923, 914, 822, 719, 622 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ = 11.59 (s, 2OH), 6.64 (s, 2H), 6.10 (s, 2H), 5.28 (t, *J* = 4.8 Hz, OH), 4.51 (d, *J* = 4.8 Hz, 2H), 3.65 (s, 6H s), 2.16 (s, 3H); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 198.8, 162.3, 155.7, 148.4, 144.8, 120.4, 109.1, 107.6, 101.9, 63.0, 55.7, 21.7; EIMS: m/z 535 (2, $[M+TMS]^{+\bullet}$), 520 (1), 519 (13), 416 (10), 415 (28), 283 (15), 282 (14), 281 (54), 267 (10), 209 (13), 191 (10), 163 (11), 149 (15), 147 (11), 89 (15), 75 (15), 73 (100); HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_6$ $[M+H]^+$: 319.11761; found: 319.11894.

Compound 8: yellow solid (292 mg, 39 %); mp: 111–113 °C; IR (KBr): $\tilde{\nu}$ = 3545, 3385, 2940, 2360, 2342, 1589, 1456, 1418, 1351 1275, 1255, 1239, 1121, 827, 766, 752, 710 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6): δ = 11.59 (s, 2OH), 7.26 (t, *J* = 8.2, H), 6.65 (s, 2H), 6.27 (d, *J* = 8.2, 2H), 5.32 (s, OH), 4.52 (s, 2H), 3.67 (s, 6H); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 199.6, 162.4, 155.8, 145.0, 137.2, 120.4, 111.2, 107.0, 101.9, 63.1, 55.7; EIMS: m/z 520 (1, $[M+TMS]^{+\bullet}$), 505 (2), 402 (14), 401 (30), 312 (13), 311 (10), 270 (12), 269 (28), 268 (26), 267 (100), 265 (14), 244 (12), 195 (10), 177 (17), 149 (15), 147 (11), 90 (12), 75 (11), 73 (83); HRMS (ESI): *m/z* calcd for $C_{16}H_{15}O_6$ $[M-H]^+$: 303.08741; found: 303.0881.

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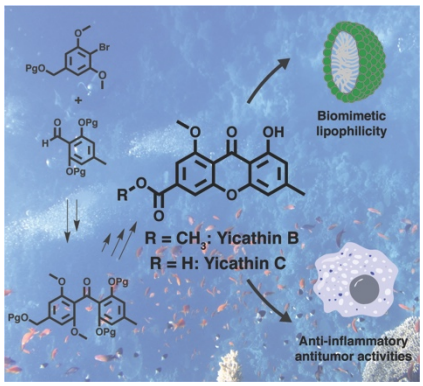

Total synthesis of two new marine xanthones - Yicathin B and C - and six additional analogues were reported for the first time. Lipophilicity of the synthetized compounds were evaluated using biomimetic models. In vitro antitumor and anti-inflammatory activities of Yicathins and its analogues were also evaluated.