



A Conformational Isomer of Soulattrolide from the Stem Bark of *Calophyllum symingtonianum* and Its Antibacterial Activity

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Abstract – *Calophyllum symingtonianum* (Guttiferae), an evergreen broad-leaved tree that usually grows in hill forests, can be found distributed in the Malay Peninsula. The barks, leaves, flowers and seeds are often used medicinally to treat diarrhea and rheumatism. In the present study, we isolated two inophyllum type coumarins, 12-O-ethylinophyllum D (**1**) and iso-soultrolide (**2**) from the stembarks of *C. symingtonianum* together with their antibacterial activity. The compounds were isolated by chromatographic methods on a silica gel. The structures were established by spectroscopic methods including UV, IR, (1D and 2D) NMR and mass spectrometry as well as by comparison with several literature sources. The antibacterial activity of those compounds was tested using a disc-diffusion assay against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Both compounds exhibited mild inhibition against *P. aeruginosa* with both 111 µg/ml MIC value. Compound **2** also inhibits *S. aureus* with 25 µg/ml MIC value.

Keywords – *Calophyllum symingtonianum*, Guttiferae, Coumarins, Antibacterial.

Introduction

Calophyllum symingtonianum (Guttiferae) is an evergreen broad-leaved tree distributed in the Malay Peninsula. It usually grows in hill forests, at an altitude of 100 – 150 m.¹ The latex from the bark of several species of *Calophyllum* genus is also used to numb fish and mixed with rice to kill rats. A decoction of the bark and the latex of some species such as *C. inophyllum* is often used medicinally (internally against diarrhea, after childbirth and externally against skin and eye diseases and rheumatism) while the

leaves, flowers and seeds are sometimes used in local medicine.² This paper describes the isolation, structure elucidation and antibacterial activity of compound **2** from the stembark of *Calophyllum symingtonianum*.

Experimental

General experimental procedures – The NMR spectra (¹H NMR: 400 MHz, ¹³C NMR: 100 MHz) were recorded on a BRUKER 400 MHz NMR Spectrometer using CDCl₃ as solvent in Standards and Industrial Research Institute of Malaysia (SIRIM). The ESI-MS spectra were recorded on a Waters Acquity UPLC/SQD mass spectrometer in University College London, UK. IR spectra were measured on a Perkin Elmer FT-IR Spectrum GX spectrophotometer. UV spectra were obtained on a Perkin

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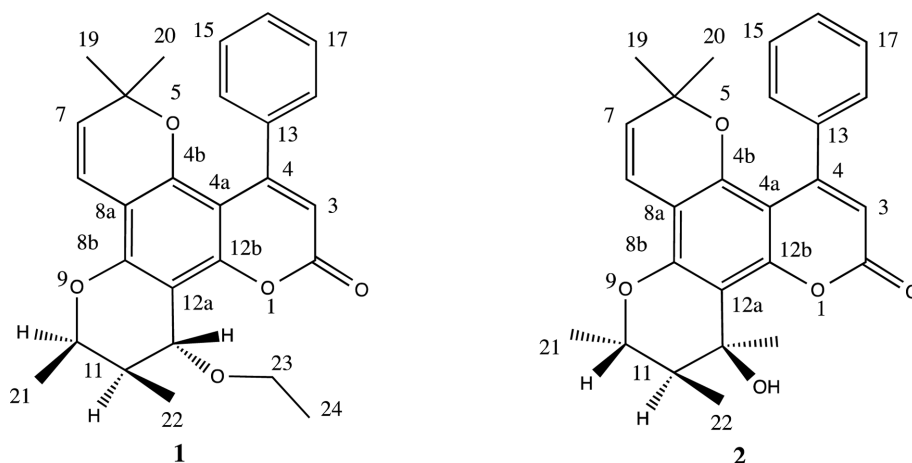


Fig. 1. Structures of compounds **1** and **2** isolated from *Calophyllum symingtonianum*.

Elmer Lambda 35 UV/VIS spectrophotometer in MeOH.

Plant materials – The plant material was collected from Pandan river, Kuantan Pahang, Malaysia in May 2010 and identified by Dr. Shamsul Khamis, Institute of Bioscience, Universiti Putra Malaysia. A voucher specimen (No. MT26) has been deposited in the Herbarium of Faculty of Pharmacy, International Islamic University Malaysia.

Extraction and isolation – The air dried stembarks of *C. symingtonianum* were powdered (1.7 kg) and extracted under reflux by *n*-hexane, dichloromethane and methanol, successively. After filtration, the solvent was evaporated in vacuum. An aliquot of the dichloromethane extract (20 g) was subjected to vacuum liquid chromatography (silica gel 230 - 400 mesh (400 g), *n*-hexane/diethyl ether 1:1) to give 3 fractions. Fraction 3 was purified with column chromatography on silica gel (70 - 230 mesh) using the same mobile phase to obtain 23 fractions. Fractions 5 - 23 were combined and purified using silica gel (70 - 230 mesh) to obtain compound **1** (19 mg) and compound **2** (20 mg).

12-O-ethylinophyllum D (1, Fig. 1). Yellowish oil. UV (MeOH) λ_{max} , nm: 210, 230, 270. IR ν_{max} , cm^{-1} : 3435, 1733, 1381. ESI-MS: m/z 433 $[\text{M}+\text{H}]^+$ ($\text{C}_{27}\text{H}_{29}\text{O}_5$); ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (100 MHz, CDCl_3) (Table 1 and 2).

10,11-diastereomer of inophyllum B (2, Fig. 1). Yellowish oil. UV (MeOH) λ_{max} , nm: 210, 278, 317. IR ν_{max} , cm^{-1} : 3426, 1733, 1383. ESI-MS: m/z 405 $[\text{M}+\text{H}]^+$ ($\text{C}_{25}\text{H}_{25}\text{O}_5$). ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (100 MHz, CDCl_3) (Table 1 and 2).

Antibacterial assay – Antibacterial activity by disc diffusion method was carried out as described in the literature.³ Discs impregnated with compounds **1** and **2**

along with chloramphenicol as a positive control were placed on the Mueller-Hinton agar surface previously inoculated with bacterial strains. All tests were conducted in triplicates to ensure the consistency of the results.

The MIC was determined using the method described by Irith et al.⁴ using 96-well plates. The concentration of compounds on the first well was 1 mg/mL and a serial dilution was conducted to obtain different concentrations such as 333.3, 111.1, 37.0, 12.3, 4.1, 1.4 and 0.46 $\mu\text{g/mL}$ in the subsequent wells. The MBC (minimum bactericidal concentration) was determined by spreading the treated culture broth from the wells containing the concentrations of equal to and higher than the MIC values on agar plates. The lower concentration of the fraction required to kill the tested microorganisms after 24 hours of incubation was reported as the MBC.

Result and Discussion

The air dried stem barks of *C. symingtonianum* were powdered (1.7 kg) and extracted under reflux by *n*-hexane, dichloromethane and methanol, successively. Vacuum liquid chromatography (VLC) of an aliquot of the dichloromethane extract followed by column chromatography of a VLC fraction on silica gel gave compound **1** (19 mg) and compound **2** (20 mg).

Compound **1** (Fig. 1) was obtained as yellowish oil. The ^1H -NMR and ^{13}C -NMR data of **1** (Table 1) in conjunction with the DEPT 135 spectrum proved the presence of 27 C-atom signals corresponding to five Me, one sp^3CH_2 , three sp^3CH , eight sp^2CH groups, and one sp^3 and nine sp^2 quaternary C-atoms. The ESI-MS displayed the $[\text{M}+\text{H}]^+$ at m/z 433 which, in conjunction with the data of other spectra, suggested the molecular

Table 1. ¹H NMR (60, 100 & 400 MHz) spectroscopic data of compounds **1** – **7** (CDCl₃, δ, ppm, J/Hz)

Proton	1*	2*	Soulattrolide (3)** ⁶	Inophyllum A (4 *** ⁶	Inophyllum B (5)* ⁸	Inophyllum D (6)* ⁵	Inophyllum P (7)* ⁸
3	5.96 (1H, s)	5.94 (1H, s)	5.94 (1H, s)	5.96 (1H, s)	5.97 (1H, s)	5.98 (1H, s)	5.97 (1H, s)
7	5.33 (1H, d, J = 10.0)	5.30 (1H, d, J = 10.0)	5.35 (1H, d, J = 10.0)	5.37 (1H, d, J = 10.0)	5.37 (1H, d, J = 10.0)	5.36 (1H, d, J = 10.0)	5.37 (1H, d, J = 10.0)
8	6.54 (1H, d, J = 10.0)	6.51 (1H, d, J = 10.0)	6.53 (1H, d, J = 10.0)	6.55 (1H, d, J = 10.0)	6.53 (1H, d, J = 10.0)	5.66 (1H, d, J = 10.0)	6.54 (1H, d, J = 10.0)
10	4.56 (1H, dq, J = 6.4, 1.6)	4.63 (1H, dq, J = 6.4, 1.6)	4.31 (1H, m, J = 7.0, 10.0)	4.43 (1H, m, J = 7.0, 3.3)	3.96 (1H, dq, J = 6.4, 9.1)	4.56 (1H, dq, J = 6.7, 2.0)	4.29 (1H, dq, J = 6.3, 10.6)
11	2.07 (1H, ddq, J = 7.2, 2.0, 2.0)	3.01 (1H, ddq, J = 7.2, 2.0, 2.0)	1.78 (1H, m, J = 3.2, 10.0)	2.27 (1H, m)	1.97 (1H, ddq, J = 6.8, 9.1, 7.8)	1.99 (1H, ddq, J = 7.2, 2.0, 2.0)	1.79 (1H, ddq, J = 3.3, 7.0, 10.6)
12	4.54 (1H, d, J = 2.0)	4.88 (1H, d, J = 1.4)	5.04 (1H, d, J = 3.2)	5.17 (1H, d, J = 5.4)	4.79 (1H, d, J = 7.8)	4.95 (1H, d, J = 2.0)	5.04 (1H, d, J = 3.3)
14	7.22 (1H, m)	7.23 (1H, m)				7.31-7.33 (1H, m)	
15	7.35 (1H, m)	7.35 (1H, m)				7.29-7.30 (1H, m)	
16	7.35 (1H, m)	7.35 (1H, m)	7.30 (5H, m)	7.30 (5H, m)	7.41, 7.31 (5H, m)	7.31-7.33 (1H, m)	7.42, 7.30 (5H, m)
17	7.35 (1H, m)	7.35 (1H, m)				7.29-7.30 (1H, m)	
18	7.22 (1H, m)	7.23 (1H, m)				7.31-7.33 (1H, m)	
19	0.90 (3H, s)		0.93 (6H, s)	0.94 (6H, s)	0.97 (3H, s)		
20	0.93 (3H, s)	0.89 (6H, s)			0.91 (3H, s)	0.95 (6H, s)	0.93 (6H, s)
21	1.42 (3H, d, J = 6.8)	1.56 (3H, d, J = 6.4)	1.44 (3H, d, J = 7.0)	1.43 (3H, d, J = 7.0)	1.47 (3H, d, J = 6.4)	1.45 (3H, d, J = 6.7)	1.44 (3H, d, J = 6.3)
22	0.79 (3H, d, J = 7.2)	0.90 (3H, d, J = 7.6)	1.16 (3H, d, J = 7.2)	1.17 (3H, d, J = 7.2)	1.18 (3H, d, J = 6.8)	0.83 (3H, d, J = 7.2)	1.17 (3H, d, J = 7.0)
23	3.85 (2H, q, J = 7.2)	---	---	---	---	---	---
24	1.28 (3H, t, J = 6.8)	---	---	---	---	---	---

* at 400 MHz; ** 100 MHz; *** at 60 MHz

formula $C_{27}H_{28}O_5$ for **1**. The 1H -NMR and ^{13}C -NMR data of **1** were identical to those of the coumarin 12-*O*-ethylinophyllum D isolated from the plant *Callophyllum inophyllum*.⁵ This is the first report of 12-*O*-ethylinophyllum D from the plant *Callophyllum symingtonianum*.

Compound **2** (Fig. 1) was obtained as a 7:3 mixture with compound **1**. The ^{13}C -NMR spectra of **2** (Table 1) showed 25 C-atom signals corresponding to four Me, three sp^3 CH, eight sp^2 CH groups, and one sp^3 and nine sp^2 quaternary C-atoms. The 1H -NMR spectrum of **2** (Table 1) exhibited a singlet for two Me at δ 0.89 (Me-19 and 20), two Me doublets at δ 1.56 (J = 6.4 Hz, Me-21) and δ 0.90 (J = 7.6 Hz, Me-22), three olefinic H-atom signals at δ 5.30 (d , J = 10.0 Hz, H-7), δ 6.51 (d , J = 10.0 Hz, H-8) and δ 5.94 (s , H-3), signals due to a mono-substituted benzene ring at δ 7.35 (m , H-15,16 and 17), 7.23 (m , H-14 and 18), and three sp^3 CH signals at δ 4.63 (dq , J = 6.4 and 1.6 Hz, H-10), δ 4.88 (d , J = 1.4 Hz, H-12) and δ 3.01 (ddq , J = 7.2, 2.6 and 2.0 Hz, H-11). The

ESI-MS displayed the $[M+H]^+$ at m/z 405 which, in conjunction with the data of other spectra, suggested the molecular formula $C_{25}H_{24}O_5$ for **2**.

The NMR spectra of **2** were similar to those of **1**, except for one sp^3 CH_2 signal and one sp^3 CH_3 that was appeared as weak signal in spectra of **2**. The structure elucidation of compound **2** was performed following logical and systematic processes. The 1H - and ^{13}C -NMR spectra of compound **2** is not identical but similar to that of the coumarins soulattrolide (**3**)^{6,7} and its enantiomer inophyllum P (**7**)⁸, inophyllums A (**4**)^{6,7,9,10}, B (**5**)^{6,8,9,10}, D (**6**)^{5,8} and discrepancies appearing solely among the three tetrahedral stereocenters of the chromanol ring protons (H-10, H-11, H-12, H-21 and H-22) and carbons (C-10, C-11, C-12, C-21 and C-22). The chemical shift of H-11 of the compound **2** resonated at significant lower field compare to the reported inophyllums (3.01 ppm vs 1.79 – 2.27 ppm), difference in chemical shift of H-10 among **2** and known inophyllums is noticeable (4.63 ppm vs 4.29 –

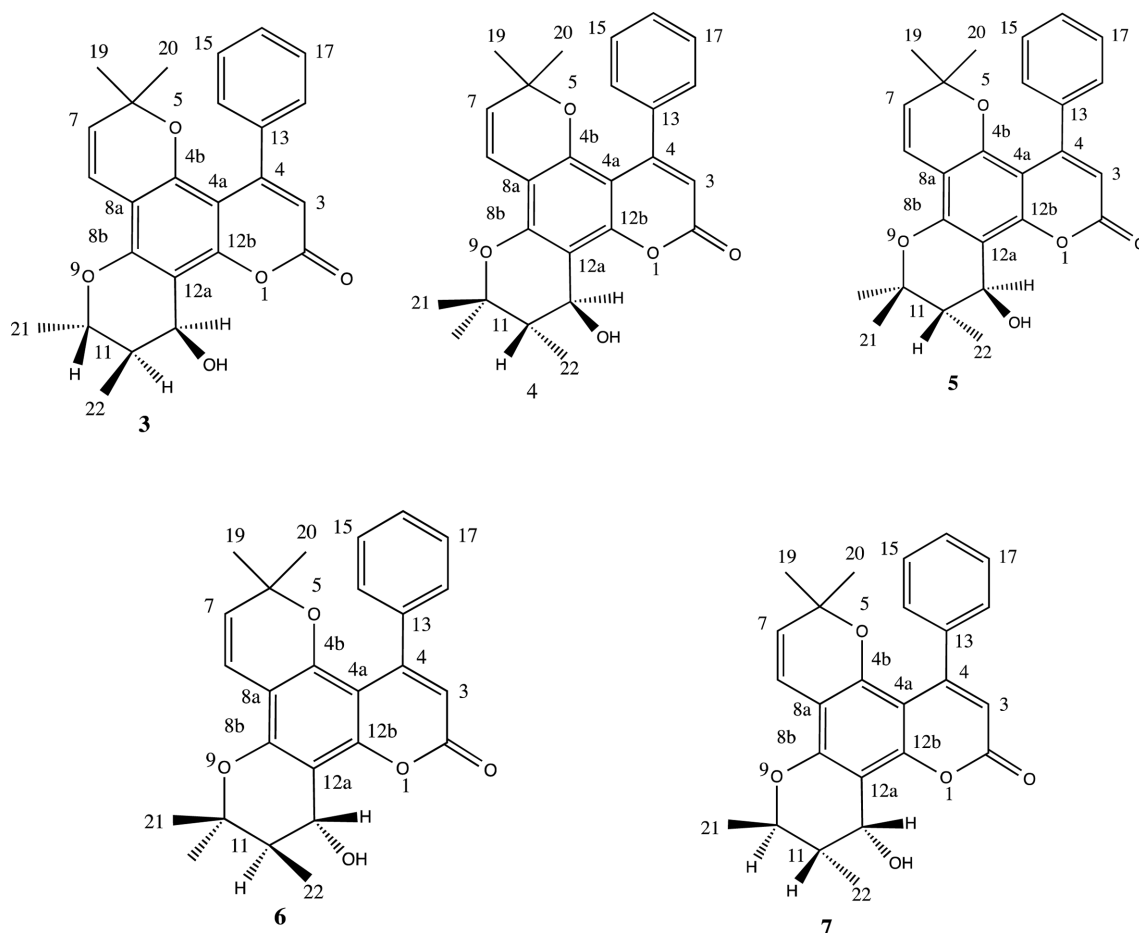
Table 2. ^{13}C NMR (100 MHz) spectroscopic data of compounds **1**, **2**, **4** - **7** ($CDCl_3$, δ , ppm)

Carbon	1	2	Inophyllum A (4) ⁸	Inophyllum B (5) ⁸	Inophyllum D (6) ⁵	Inophyllum P (7) ⁸
2	160.6	160.7	160.3	160.6	160.5	160.1
3	112.1	111.6	111.4	111.7	111.9	111.5
4	156.1	156.4	156.2	156.3	156.3	156.4
4a	103.5	103.2	103.1	103.1	103.4	103.6
4b	151.2	151.3	150.9	151.1	151.1	150.9
6	77.0	77.0	76.8	76.7	77.1	77.2
7	127.1	127.0	127.1	127.1	127.2	127.6
8	116.1	116.1	115.9	116.0	115.9	115.9
8a	105.9	106.0	106.3	106.0	106.0	106.3
8b	154.9	154.7	152.5	153.7	153.9	153.7
10	71.0	69.2	75.7	73.0	71.2	76.9
11	34.5	31.9	35.5	38.2	37.2	40.4
12	71.9	71.7	62.6	61.8	64.6	67.1
12a	102.0	101.6	105.5	106.1	103.9	106.1
12b	154.0	154.6	154.0	153.6	154.6	154.1
13	140.2	140.2	139.9	140.0	139.9	139.9
14	127.1	127.0	127.2	127.3	127.3	127.3
15	127.4	127.4	127.2	127.3	127.4	127.3
16	127.6	127.5	127.5	127.6	127.6	127.4
17	127.4	127.4	127.2	127.3	127.4	127.3
18	127.1	127.0	127.2	127.3	127.3	127.3
19	26.7	27.0	26.7	26.9	27.0	26.5
20	27.0	26.9	26.7	26.8	27.0	26.9
21	17.9	17.5	16.0	18.8	17.1	18.9
22	9.1	9.5	9.7	12.5	9.1	15.0
23	64.8	---	---	---	---	---
24	15.9	---	---	---	---	---

Table 3. Epimers and diastereomers of the known inophyllums 4 – 7*

Known Inophyllums	10-Epimer	11-Epimer	12-Epimer	10,11-Diastereomer	11,12-Diastereomer	10,12-Diastereomer	10,11,12-Diastereomer
Inophyllum A (4)	Inophyllum 2	Inophyllum B (5)	Inophyllum D (6)	Inophyllum 10	Inophyllum P (7)	Inophyllum 8	Inophyllum 9
Inophyllum B (5)	Inophyllum 10	Inophyllum A (4)	Inophyllum P (7)	Inophyllum 2	Inophyllum D (6)	Inophyllum 9	Inophyllum 8
Inophyllum D (6)	Inophyllum 8	Inophyllum P (7)	Inophyllum A (4)	Inophyllum 10	Inophyllum B (5)	Inophyllum 2	Inophyllum 10
Inophyllum P (7)	Inophyllum 9	Inophyllum D (6)	Inophyllum B (5)	Inophyllum 8	Inophyllum A (4)	Inophyllum 10	Inophyllum 2

*Bolded inophyllums are new

**Fig. 2.** Structures of reported inophyllums 3 - 7.

4.56 ppm) whereas it is significant in the inophyllum B (4.63 ppm vs 3.96 ppm), chemical shift of H-12 differs considerably (4.88 ppm vs 4.79 – 5.17 ppm), resonance of H-21 of **2** appeared slightly at the downfield (1.56 ppm vs 1.43 – 1.47 ppm) whereas H-22 of **2** resonated at noticeable higher field like the inophyllum D (0.90 ppm vs 0.83 ppm) compare to the other inophyllums (0.90 ppm vs 1.16 – 1.18 ppm) (Table 1). Similarly, differences in chemical shifts of the compound **2** and the known inophyllums are also observable among the chromanol ring carbons (C-10, C-11, C-12, C-21 and C-22) (Table 2).

A systematic analysis suggested the existence of eight possible diastereomeric/epimeric inophyllums having three tetrahedral stereocenters at C-10, C-11 and C-12 of which four inophyllums A (**4**), B (**5**), D (**6**) and P (**7**) have already been reported. Compound **2** may be a stereoisomeric (diastereomer/epimer or an enantiomer thereof) inophyllum of one of these known inophyllums. Logical approach on the known inophyllums A, B, D and P for their **10**-epimers, **11**-epimers, **12**-epimers, **10,11**-diastereomers, **11,12**-diastereomers, **10,12**-diastereomers and **10,11,12**-diastereomers explored the remaining four inophyllums **2**,

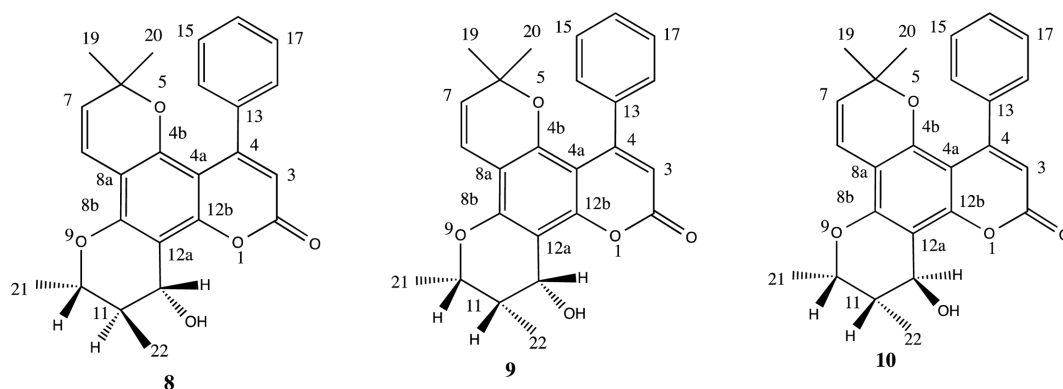


Fig. 3. Some probable structures of the compound 2.

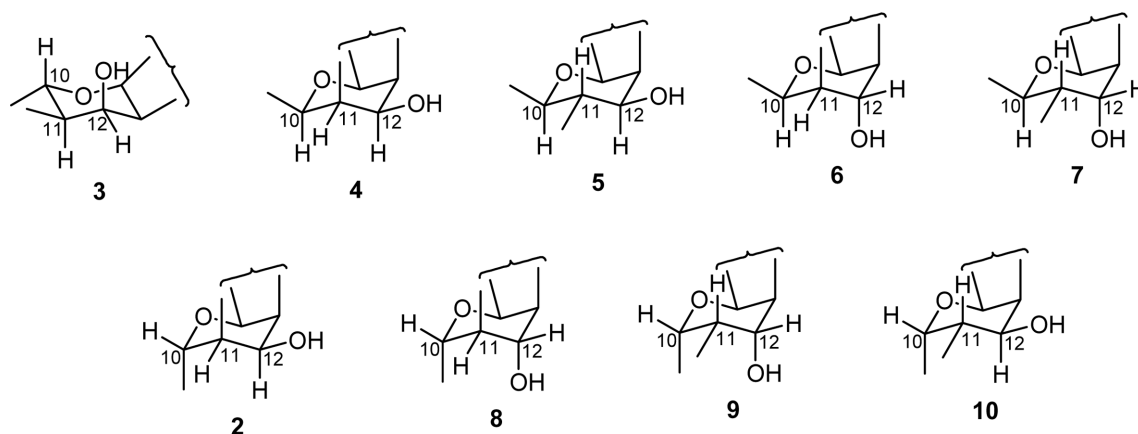


Fig. 4. Chromanol ring conformational structures of reported inophyllums 3 - 7 and probable structures of the compound 2 (2, 8 - 10).

8, 9 and 10 of this series yet to be reported along with the mutual interconversions of the known inophyllums (Table 3, Fig. 1, Fig. 2, Fig. 3 and Fig. 4). Undoubtedly, the isolated compound 2 of the present study might be one of these unexplored inophyllums, namely 2, 8, 9 or 10, or an enantiomer thereof.

Inophyllum 10 or its enantiomer should be eliminated as the coupling constant $J_{11,12}$ (2.0 Hz) and vice versa (1.4 Hz) of the isolated compound 2 is smaller than it is expected for the structure 10 (Table 1, Fig. 3 and Fig. 4).

All of the known inophyllums (4 - 7) bear a phenyl group at C-4 and a α - or β -equatorial-methyl group at C-10 (Fig. 2). On the other hand, the new inophyllum might have α -axial-methyl group at C-10 suggesting that it might be the C-10 epimer of one of the known inophyllums 4 - 7. Again, the chemical shift of H-11 of the new inophyllum resonated at significant lower field compare to the reported inophyllums (3.01 ppm vs 1.79 - 2.27 ppm) (Table 1), indicating epimerization at C-11 of one of the known inophyllums (4 - 7) will give the new inophyllum.

The chemical shifts of C-10 and C-11 of new inophyllum resonated at relatively higher fields compare to the reported inophyllums (69.2 ppm vs 71.2 - 76.9 ppm and 31.9 ppm vs 35.5 - 40.4 ppm, respectively) also supported the epimerizations at C-10 and C-11 for the new inophyllum. H-22 methyl of the new inophyllum resonated at significant higher field like the inophyllum D (0.90 ppm vs 0.83 ppm) having axial orientation compared to the other inophyllums (0.90 ppm vs 1.16 - 1.18 ppm) having equatorial orientation (Table 1, Fig. 4). The almost identical chemical shifts of C-22 for the compound 2 and the inophyllum D (6) (9.5 ppm vs 9.1 ppm) also supported the axial orientation of the C-22 methyl of the new inophyllum. So, one of the known inophyllums 4 - 7 might epimerize at C-10 and C-11 to yield the new inophyllum, i.e. the compound 2 is a 10,11-diastereomer or enantiomer thereof of one of the reported inophyllums 4 - 7 having the axial orientation of the C-22 methyl. The structure 9 should be eliminated as the methyl group at C-11 having equatorial orientation (Fig. 3 and Fig. 4). Structures 2 and 8 are the 10,11-

Table 4. Antibacterial activity of the isolated compounds

Microorganisms	Compound 1		Compound 2		Chloramphenicol
	Inhibition zone (cm)	MIC ($\mu\text{g/mL}$)	Inhibition zone (cm)	MIC ($\mu\text{g/mL}$)	Inhibition (cm)
<i>Staphylococcus aureus</i>	-	-	1.30 \pm 0.57	2.5 \pm 0.28	2.8 \pm 0.50
<i>Bacillus cereus</i>	-	-	-	-	2.7 \pm 0.76
<i>Escherichia coli</i>					3.8 \pm 0.50
<i>Pseudomonas aeruginosa</i>	0.70 \pm 0.28	1.11 \pm 0.50	1.0 \pm 0.50	1.11 \pm 0.50	2.4 \pm 0.57

-: No activity; \pm : Standard deviation

diastereomers of inophyllums B (**5**) and P (**7**), respectively having axial orientation of the methyl group at C-11 (Fig. 3 and Fig. 4, Table 3). Comparison of ^1H NMR values of H-10 and H-11 among the new inophyllum (4.63 and 3.01 ppm), inophyllum B (**5**) (3.96 and 1.97 ppm) and inophyllum P (**7**) (4.29 and 1.79 ppm) indicated that the 10,11-diastereomer of inophyllum B (**5**) or its enantiomer, i.e. compound **2** is the most probable structure for the new isolated inophyllum. A 1D NOE or 2D NOESY was essential to confirm this, but we could not record these spectra due to the scarcity of the sample.

The absolute configuration of inophyllum B (**5**) has been assigned as (10*R*,11*S*,12*S*).¹¹ Since the compound **2** is known to be the 10,11-diastereomer of inophyllum B (**5**), the absolute configuration of inophyllum **2** must be (10*S*,11*R*,12*S*) and, accordingly, compound **2**, 10,11-diastereomer of inophyllum B, was established as (10*S*, 11*R*,12*S*)-12-hydroxy-11,12-dihydro-6,6,10,11-tetramethyl-4-phenyl-2*H*,6*H*,10*H*-dipyran[2,3-f:2',3'-*h*]chromen-2-one, a new conformation of coumarin named as isosoulattrolide.

Compounds **1** and **2** exhibited antibacterial activities. *Staphylococcus aureus* was more susceptible to the compound **2** as indicated by the zone of inhibition of 1.3 cm at 30 $\mu\text{g/disc}$ and MIC value of 25 $\mu\text{g/mL}$, while the positive control chloramphenicol showed the zone of inhibition of 2.8 cm at the same concentration (Table 4).

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