Tetrahedron 72 (2016) 775–778

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Polycyclic tetrahydroxanthones from *Streptomyces chrestomyceticus* BCC 24770

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ARTICLE INFO

Article history:
Received 30 October 2015
Received in revised form 14 December 2015
Accepted 21 December 2015
Available online 22 December 2015

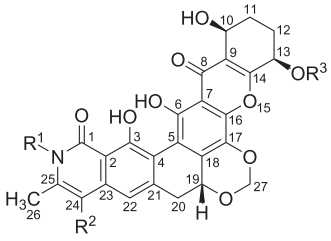
Keywords:
Antifungal activity
Streptomyces chrestomyceticus
Polycyclic tetrahydroxanthone
Secondary metabolite

ABSTRACT

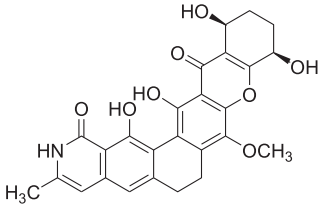
Three polycyclic tetrahydroxanthones, chrestoxanthones A–C, together with known albofungin and chloroalbofungin were isolated from the actinomycete *Streptomyces chrestomyceticus* BCC 24770. Their structures were elucidated by extensive spectroscopic analyses. Chrestoxanthone A was active against *Curvularia lunata* and *Alternaria brassicicola*, while all other isolated metabolites displayed broad antifungal activities against *C. lunata*, *A. brassicicola*, *Colletotrichum capsici*, and *Colletotrichum gloeosporioides*.

1. Introduction

Streptomyces, the largest genus of Actinobacteria, is especially known as a rich source of bioactive secondary metabolites and clinically useful antibiotics including streptomycin, daptomycin, chloramphenicol, fosfomycin, and oxytetracycline.[1,2] Streptomyces contain over 770 species[3] and produce more than 7600 different bioactive secondary metabolites.[4] *Streptomyces chrestomyceticus* is a streptomyces species that has been reported to produce pyrrolostatin (a lipid peroxidation inhibitor),[5] and antibiotic aminosidine (or paromomycin).[6] In our ongoing research on novel bioactive compounds from Thai actinomycetes, *S. chrestomyceticus* BCC 24770 was isolated from soil sample collected at Srinagarindra Dam, Kanchanaburi Province. Its crude extract from liquid medium culture showed antifungal activities against *Curvularia lunata*, *Alternaria brassicicola*, *Colletotrichum capsici*, and *Colletotrichum gloeosporioides* with MIC values of 3.13, ≤1.56, ≤3.13, and ≤3.13 μg/mL, respectively. Further study of the large scale fermentation led to the isolation and structure elucidation of three new polycyclic tetrahydroxanthones, chrestoxanthones A–C (**1**, **2**, and **5**), together with known albofungin (**3**)[7–10] and chloroalbofungin (**4**).[10,11] Among these isolated metabolites, albofungin and chloroalbofungin showed strong activities against all four tested pathogenic fungi with similar MIC values.



1 R^1, R^2 = H, R^3 = CH_3
2 R^1, R^2, R^3 = H
3 R^1 = NH_2, R^2 = H, R^3 = CH_3 (albofungin)
4 R^1 = NH_2, R^2 = Cl, R^3 = CH_3 (chloroalbofungin)



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http://dx.doi.org/10.1016/j.tet.2015.12.045
0040-4020/

2. Results and discussion

Fractionation of the EtOAc extract from the culture of BCC 24770 utilizing Sephadex LH-20 column chromatography afforded 12 fractions. Fraction five was further separated by Sephadex column chromatography into sub-fractions. Sub-fraction 5–4 was subsequently purified by reversed-phase HPLC yielding compound **5**. Compounds **1**–**3** were obtained from fraction 9, while fraction 11 gave compounds **3** and **4** after purification by reversed-phase HPLC.

Chrestoxanthone A (**1**) was isolated as a yellow-brown solid. The molecular formula of $C_{27}H_{23}NO_9$, established from the quasimolecular ion peak at *m/z* 506.1441 $[M+H]^+$ in the HRESIMS, indicated the lack of one nitrogen and one hydrogen when compared to that of known albofungin (**3**). The ^{13}C NMR spectrum of **1** (Table 1) revealed resonances of a conjugated ketone carbonyl (δ_C 182.6), an amide carbonyl (δ_C 167.3), two olefinic/aromatic methine (δ_C 114.4 and 105.3), 14 quaternary sp^2 carbons/oxycarbons (δ_C 165.6–109.9), one dioxymethylene (δ_C 91.1), three oxymethines (δ_C 75.2, 72.6, and 59.3), a methoxy (δ_C 58.2), three methylenes (δ_C 36.4, 28.4, and 23.3), and a methyl group (δ_C 19.0). The ^{13}C and ^1H NMR spectra of **1** and **3** in DMSO-d_6 were found to be closely similar, with the exception that two N–NH_2 protons in **3** (δ_H 5.90) was replaced by an amide NH proton in **1** (δ_H 11.83), indicating that the *N*-amino isoquinolin-1(2*H*)-one moiety of albofungin (**3**) was substituted by isoquinolin-1(2*H*)-one in **1**. The isoquinolin-1(2*H*)-one unit of **1** was confirmed by HMBC correlations from NH to C-2 and C-24; from 3-OH to C-2, C-3, and C-4; from H-22 to C-1, C-2, C-4, C-23, and C-24; from H-24 to C-2, and C-26; from H_3-26 to C-24, and C-25. The spin system –CH(OH)–CH_2–CH_2–CH– and key HMBC correlations from 6-OH to C-5, C-6, and C-7; from 10-OH to C-9; from H-12 to C-14; and from 13-OCH_3 to C-13 supported the existence of tetrahydroxanthone moiety. The connectivity between isoquinolin-1(2*H*)-one and tetrahydroxanthone subunits, and the remaining two rings were deduced by the spin system –CH_2–CH– and HMBC correlations from H-19 to C-17; from H_2-20 to C-4, C-18, C-21, and C-22; and from H_2-27 to C-17 and C-19.

The stereochemistry of **1** was deduced on the basis of $^3J_{H\text{-}H}$ coupling constant and circular dichroism (CD) spectral data. The small coupling constants, $J_{H\text{-}10,H\text{-}11\alpha}$ of 3.3 Hz and $J_{H\text{-}10,H\text{-}11\beta}$ of 3.7 Hz, indicated pseudo-equatorial position of H-10, while the coupling constants of 8.1 and 7.6 Hz between H-13 and H_2-12 suggested pseudo-axial position of H-13. A large negative value of optical rotation for **1** $[\alpha]_D^{27}$ −621° (DMSO) was similar to that reported for albofungin $[\alpha]_D^{20}$ −670° (DMF).[7] The CD spectrum of **1** exhibited positive Cotton effects at 200–220, 251–272, and 281–302 nm regions, and negative Cotton effects at 220–251, 272–281, and 302–375 nm regions as shown in Fig. 1. Since the CD spectral patterns of **1** and albofungin (**3**)[9] were quite similar, therefore the absolute stereochemistry of **1** was assigned as depicted.

Chrestoxanthone B (**2**) was purified as a yellow-brown solid. The HRESIMS spectrum of **2** exhibited the $[M+Na]^+$ peak at *m/z*

Table 1
NMR Spectroscopic Data of **1**, **2** [^1H (500 MHz) and ^{13}C (125 MHz)], and **5** [^1H (400 MHz) and ^{13}C (100 MHz)] in DMSO-d_6

Position	**1**		**2**		**5**	
	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C
1		167.3		167.3[c]		167.6[f]
2		109.9		109.9		109.6
3		158.5		158.5		158.7
4		113.5		113.6		114.7
5		110.3[a]		110.3[d]		115.2[g]
6		150.0		150.1		153.1
7		112.1[a]		111.9[d]		109.6[g]
8		182.6		182.7		182.9
9		120.8		120.1		119.8
10	4.82, ddd (4.6, 3.7, 3.3)	59.3	4.83, ddd (4.6, 3.6, 3.4)	59.5	4.83, m	59.6
11	α 1.72, m	28.4	α 1.71, dddd (13.3, 13.3, 3.4, 2.7)	28.7	α 1.73, dd (13.3, 13.3)	29.1
	β 1.82, dq (13.9, 3.7)		β 1.81, m		β 1.82, m	
12	2.06, m	23.3	α 1.94, m	27.1	α 1.97, m	27.2
			β 2.07, dddd (13.3, 12.4, 9.7, 2.3)		β 2.10, ddd (13.3, 12.8, 9.7)	
13	4.43, dd (8.1, 7.6)	75.2	4.57, ddd (9.7, 7.1, 6.6)	66.0	4.62, ddd (9.7, 7.0, 6.7)	66.4
14		165.6		167.6[c]		167.7[f]
16		143.2		143.3		148.2[h]
17		130.8		130.8		136.0
18		130.5		130.3		147.5[h]
19	4.95, dd (13.1, 4.6)	72.6	4.95, dd (13.1, 4.7)	72.6	–[i]	23.9
20	α 2.74, dd (13.9, 13.1)	36.4	α 2.74, dd (13.7, 13.1)	36.5	2.89 (br m)	30.7
	β 3.20, dd (13.9, 4.6)		β 3.20, dd (13.7, 4.7)			
21		141.4		141.4		141.6
22	6.97, s	114.4	6.97, s	114.4	6.92, s	113.3
23		139.5[b]		139.5[e]		139.2
24	6.42, s	105.3	6.42, s	105.4	6.41, s	105.6
25		139.4[b]		139.4[e]		139.2
26	2.25, s	19.0	2.25, s	19.0	2.24, s	19.2
27	5.61, d (5.9)	91.1	5.59, d (5.9)	91.0		
	5.41, d (5.9)		5.41, d (5.9)			
NH	11.83, s		11.80, br s		11.73, s	
3-OH	13.83, s		13.82, s		13.81, s	
6-OH	12.94, s		13.04, s		13.23, s	
10-OH	5.18, d (4.6)		5.13, d (4.6)		5.11, br m	
13-OH			5.92, d (7.1)		5.94, d (7.0)	
13-OCH_3	3.55, s	58.2				
17-OCH_3					3.87, s	62.1

[a–h] Assignments are interchangeable.
[i] Proton signals were unable to be determined.