Natural Product Research: Formerly Natural Product Letters
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gnpl20

A new cyclododeca[d]oxazole derivative from Streptomyces spp. CIBYL1

Xiang Pu [a b], Guangzhou Li [a c d], Tao Yang [a], Guoyou Li [a], Jinhai Yi [c d], Guolin Zhang [a] & Yinggang Luo [a]

[a] Center for Natural Products Research, Chengdu Institute of Biology of the Chinese Academy of Sciences, Chengdu 610041, People's Republic of China

[b] Graduate University of the Chinese Academy of Sciences, Beijing 100049, People's Republic of China

[c] Institute of Chinese Materia Medica, Sichuan Academy of Chinese Medicine Sciences, Chengdu 610041, People's Republic of China

[d] School of Chinese Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengu 610075, People's Republic of China

Version of record first published: 01 May 2012.

To cite this article: Xiang Pu , Guangzhou Li , Tao Yang , Guoyou Li , Jinhai Yi , Guolin Zhang & Yinggang Luo (2012): A new cyclododeca[d]oxazole derivative from Streptomyces spp. CIBYL1, Natural Product Research: Formerly Natural Product Letters, DOI:10.1080/14786419.2012.682997

To link to this article: http://dx.doi.org/10.1080/14786419.2012.682997

Natural Product Research
2012, 1–6, iFirst

A new cyclododeca[d]oxazole derivative from *Streptomyces* spp. CIBYL1

Xiang Pu[ab], Guangzhou Li[acd], Tao Yang[a], Guoyou Li[a], Jinhai Yi[cd], Guolin Zhang[a] and Yinggang Luo[a]*

[a]*Center for Natural Products Research, Chengdu Institute of Biology of the Chinese Academy of Sciences, Chengdu 610041, People's Republic of China;* [b]*Graduate University of the Chinese Academy of Sciences, Beijing 100049, People's Republic of China;* [c]*Institute of Chinese Materia Medica, Sichuan Academy of Chinese Medicine Sciences, Chengdu 610041, People's Republic of China;* [d]*School of Chinese Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengu 610075, People's Republic of China*

(*Received 19 July 2011; final version received 4 March 2012*)

A novel secondary metabolite, *N-trans*-cinnamoyl 2-amino-3a,4,5,6,7,8,9,10,11,12,13,13a-dodecahydrocyclododeca[d]oxazole (**1**), was isolated from *Streptomyces* spp. CIBYL1, along with five known compounds, pimprinine (**2**), (3*R*,4*S*,5*R*,6*R*)-3,4,5,6-tetrahydro-4-hydroxy-3,5,6-trimethyl-2H-pyran-2-one (**3**), indolyl-3-carboxylic acid (**4**), 2-phenylacetamide (**5**) and di(1*H*-pyrrol-2-yl)methanone (**6**). The structures of these metabolites were elucidated on the basis of extensive analysis of spectroscopic data, including OR, IR, HRMS, 1D and 2D NMR data and chemical derivation.

Keywords: *Streptomyces*; cyclododecane; oxazole

1. Introduction

The bacteria of the genus *Streptomyces* are prolific microorganisms for their production of intriguing secondary metabolites. Of them, most are pharmaceutically important natural products with different biological activities, including antimicrobial, antimalarial, cytotoxic and antitumour properties (Chen, Smanski, & Shen, 2010). The immense diversity of *Streptomyces*, along with its under-utilisation is another fundamental reason for attracting researchers to discover novel secondary metabolites. During the past decades, there has been increasing number of novel metabolites isolated from *Streptomyces* with the potent bioactivity by using the combination of chemical, biological and engineering methods (Cragg, Grothaus, & Newman, 2009; Walsh & Fischbach, 2010). Inspired by the impressive pharmaceutical potency of the secondary metabolites from *Streptomyces*, we initiated a programme aiming at the discovery of new antitumour chemical entities from microorganisms. We collected a large number of microorganisms, and they were grown and fermented. All fermentation broths were screened and the ethyl acetate-soluble fraction of the fermentation broth of *Streptomyces* spp. CIBYL1 was found to be active ($GI_{50} = 40\,\mu g\,mL^{-1}$) against human hepatic cancer cells HepG2. Bioassay-guided chemical investigations on this extract afforded a novel secondary metabolite and five known compounds. Herein, we report the isolation and structure elucidation of these metabolites.

*Corresponding author. Email: yinggluo@cib.ac.cn

ISSN 1478–6419 print/ISSN 1478–6427 online

http://dx.doi.org/10.1080/14786419.2012.682997
http://www.tandfonline.com

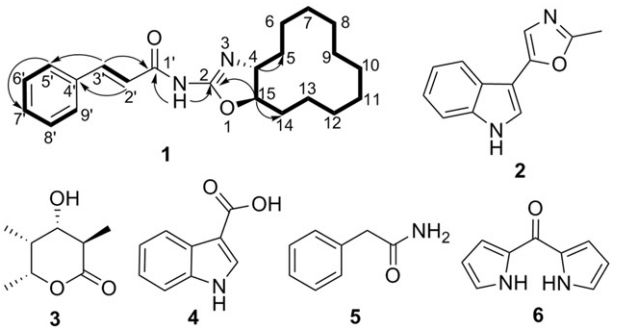

Figure 1. Secondary metabolites from *Streptomyces* spp. CIBYL1 and key HMBC (curved arrows) and ^{1}H–^{1}H COSY (bold bonds) correlations of compound **1**.

2. Results and discussion

To isolate the bioactive compounds from the fermentation broth of *Streptomyces* spp. CIBYL1, we performed a large-scale fermentation of the bacteria. The fermentation broth (20 L) was harvested by centrifugation. The supernatant was extracted with EtOAc (three times) while the mycelia mass was extracted with acetone (two times) and the crude extracts were obtained. Based on the thin layer chromatography (TLC) analysis, the two organic extracts displayed same spots and they were combined as a whole residue which was separated over silica gel column chromatography (CC) to offer a novel secondary metabolite **1** and five known compounds **2**–**6** (Figure 1).

Compound **1** was isolated as colourless needle. Its molecular formula $C_{22}H_{30}N_2O_2$ was provided by the $[M+Na]^+$ ion at m/z 377.2200 in its HR-ESI-MS (positive mode). The infrared (IR) absorption bands revealed the presence of amine (3443 cm^{-1}) , aliphatic (2924 and 2853 cm^{-1}) and phenyl (1598 and 1452 cm^{-1}) groups, as well as ether (1233 cm^{-1}) and unsaturated double bonds (1647 cm^{-1}). The ^{1}H NMR ($CDCl_3$) signals of compound **1** at δ 7.69 (d, $J = 15.4$ Hz, 1H), 6.75 (d, $J = 15.4$ Hz, 1H), 7.50 (m, 2H), 7.39 (m, 2H) and 7.38 (m, 1H) suggested that the presence of a cinnamoyl group. Acid hydrolysis of compound **1** generated cinnamic acid, which confirmed the presence of a cinnamoyl moiety. A 1,2-disubstituted cyclododecane moiety was deduced from its characteristic ^{1}H NMR signals in $CDCl_3$ at δ 4.12 (dt, $J = 11.4$, 3.6 Hz, 1H), 3.76 (m, 1H), 1.98 (m, 4H), 1.85 (m, 4H), 1.72 (m, 2H), 1.67 (m, 1H), 1.60 (m, 1H), 1.36 (m, 4H) and 1.22 (m, 4H) (Cao & Qu, 2010; Han et al., 2007), which was supported by $^{1}H-^{1}H$ COSY (Figure 1) and HSQC data. The ^{1}H NMR signal at δ 7.00 (br s, 1H) was assigned to a secondary amino group in view of no proton–carbon correlation signal was observed in the HSQC experiment, which was confirmed by its disappearance in D_2O exchange experiment. This secondary amino group was connected with the above-mentioned cinnamoyl group to form an amide in view of the IR absorption band at 1709 cm^{-1}. Thus, a 2-amino oxazole moiety was deduced in view of the ^{13}C NMR signal at δ 154.1 and one remaining N from the above-mentioned information.

The three moieties, cinnamoyl group, 2-amino oxazole and 1,2-disubstituted cyclododecane, were linked by extensive analyses of 2D NMR experiments (Figure 1). The HMBC cross-signals of the amide NH (δ_H 7.00) to C-1′ (δ_C 168.2) revealed the connectivity of cinnamoyl and 2-amino oxazole. Meanwhile, the HMBC correlations of the amide NH (δ_H 7.00) to C-2 (δ_C 154.1) and H-15 (δ_H 4.12) to C-2 (δ_C 154.1) indicated that 2-amino oxazole moiety fused with cyclododecane. The relative configurations of

C-4 and C-15 were determined as *trans*-orientation in view of the small coupling constant 3.6 Hz of H-4 and H-15 (Betanocor, León, Prange, Salazar, & Suárez, 1989; Han et al., 2007; Sharpless, Teranishi, & Bäckvall, 1977; Wolinsky, Thorstenson, & Killinger, 1978). The double bond of cinnamoyl group must be *trans*-geometry in view of the large coupling constant 15.4 Hz of H-2′ and H-3′ (Yu & Yang, 1999). Thus, compound **1** was elucidated as *N*-*trans*-cinnamoyl 2-amino-3a,4,5,6,7,8,9,10,11,12,13,13a-dodecahydrocyclododeca[-d]oxazole (Figure 1).

Five known compounds were isolated from *Streptomyces* spp. CIBYL1. Their structures were elucidated on the basis of spectroscopic data analyses and comparison with spectral data reported in the literature. They were identified as 5-(1*H*-indol-3-yl)-2-methyloxazole (pimprinine, **2**, Figure 1) (Joshi, Taylor, Bhate, & Karmarkar, 1963; Kelly, Fu, & Xie, 1999), (3*R*,4*S*,5*R*,6*R*)-3,4,5,6-tetrahydro-4-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-one (**3**, Figure 1) (Brown, Cortes, Cutter, Leadlay, & Staunton, 1995; Kinoshita, Khosla, & Cane, 2003; Marsden et al., 1998), indolyl-3-carboxylic acid (**4**, Figure 1) (Li, Mao, & Yi, 2000), 2-phenylacetamide (**5**, Figure 1) (Dillman & Cardellina, 1991) and di(1*H*-pyrrol-2-yl)methanone (**6**, Figure 1) (Katritzky, Suzuki, Singh, & He, 2003; Plater, Aiken, & Bourhill, 2002). Among them, compound **2** displayed promising anticonvulsant activity in both minimum and maximum electric seizure threshold test in mice (Naik, Harindran, & Varde, 2001). Both compounds **2** and **4** are structurally related to potent antitumour properties in view of the presence of privileged indolyl moiety that plays a vital role in many biologically interesting natural products and useful therapeutic agents (Prudhomme, 2000). Compound **3**, a characteristic polyketide, is a simple biosynthetic intermediate on the pathway to erythromycin antibiotic (Brown et al., 1995; Kinoshita et al., 2003; Marsden et al., 1998). The primary benzamide **5** has long been known as a metabolite of phenylalanine. The occurrence of **5** in *Actinomycete* is of general interest considering that primary benzamides are rare as natural products (Dillman & Cardellina, 1991; Jaroszewski et al., 2005). It is the first report of the production of the dipyrrol ketone **6** (a wildly used material for the synthesis of porphyrins; Khoury, Jaquinod, & Smith, 1997; Plater et al., 2002; Shi, Wheelhouse, Sun, & Hurley, 2001) in microorganisms.

3. Experimental

3.1. *General procedure*

Melting points were determined on an X-6 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter using $CHCl_3$ as solvent. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer using a KBr disc and ν_{max} is given in cm^{-1}. Ultraviolet (UV) spectra were recorded in MeOH (1 mg/50 mL) on a Perkin-Elmer Lambda 35 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on an Avance Bruker 600 spectrometer (600 MHz for ^1H NMR and 150 MHz for ^{13}C NMR) at room temperature. The chemical shifts (δ) are reported in ppm using tetramethylsilane as an internal standard, and the coupling constants (J) are given in Hertz (Hz). High-resolution electrospray ionisation mass spectra (HR-ESI-MS) and ESI-MS spectra were obtained on a Bruker Bio TOF IIIQ (quadrupole time-of-flight) mass spectrometer. CC was performed on self-packed open column with silica gel from Qingdao Haiyang Chemical Engineering Company (QHCEC, P.R. China). TLC analyses were carried out on plates precoated with 10–40 μm of silica gel GF_{254} from QHCEC and visualised under a UV lamp at 254 nm or 365 nm, visualised by spraying 8% phosphomolybdic acid–ethanol solution (w/v) or 5% vanillin–H_2SO_4 (w/v) followed by heating, or visualised by iodine (I_2). Fractions from all columns were generally collected by an auto-collected apparatus and combined according to TLC analyses.

3.2. *Bacterial strain and materials*

According to standard procedure, *Streptomyces* spp. CIBYL1 strain was isolated from the soil near our campus (104°4′21″ E, 30°37′47″ N). It was grown and maintained on Gause's no. 1 medium (consisting of autoclaved 2% soluble starch, 0.1% KNO_3, 0.05% K_2HPO_4, 0.05% NaCl, 0.05% $MgSO_4 \cdot 7H_2O$, 0.01% $FeSO_4 \cdot 7H_2O$ and 2% agar in tap water, pH 7.2–7.4) at 30°C until they were well sporulated (usually 168 h).

3.3. *Fermentation of* Streptomyces *spp. CIBYL1*

The strain *Streptomyces* spp. CIBYL1 was grown and fermented in a large-scale fermentation procedure. The seed culture was prepared as follows. The seed medium consisting of autoclaved glucose 0.5%, soluble starch 2.5%, yeast extract 0.5%, beef extract 0.3%, peptone 0.5%, $CaCO_3$ 0.4%, pH 7.0 (50 mL in a 250-mL flask) was inoculated with spores, and the mixture were incubated on a rotary shaker at 280 rpm and 28°C for 48 h. Then the seed culture (50 mL) was transferred into the fermentation medium consisting of autoclaved sucrose 1%, glycerin 2%, bean powder 1%, corn powder 1%, yeast extract 0.3%, peptone 0.3%, $MgSO_4{\cdot}7H_2O$ 0.005%, $CaCO_3$ 0.02%, NaCl 0.04%, pH 7.0 (500 mL in a 2-L flask), and the mixture was incubated on a rotary shaker at 280 rpm and 28°C for 144 h. Both seed and production media were sterilised by autoclaving at 121°C for 35 min in a steriliser.

3.4. *Extraction and isolation of secondary metabolites*

The fermentation broth (20 L) was harvested by centrifugation at 3800 rpm at 4°C for 20 min to separate the supernatant from the mycelia. The supernatants were collected and extracted with EtOAc (20 L per times, three times) at room temperature. The mycelia were subjected to soak with acetone (1 L per times, twice). All organic solvents were removed under vacuum to offer two residues which were combined according to the TLC analysis. All organic solvents were removed under vacuum to offer two residues which were combined according to the TLC analyses.

The combined crude extract (67.312 g) was chromatographed over a silica gel (600 g, 200–300 mesh) CC eluted by the mixture of petroleum ether and EtOAc (5 : 1 and 1 : 1, each 1500 mL) and by $CHCl_3$–MeOH mixtures (10 : 1, 5 : 1, 2 : 1 and 0 : 1, each 1500 mL) to offer nine fractions. The third fraction (872 mg) was separated over silica gel (60 g, 200–300 mesh) by the elution of the mixture of $CHCl_3$–MeOH (100 : 1, 1500 mL; 50 : 1, 20 : 1 and 10 : 1, each 1000 mL; and 0 : 1, 500 mL). Compounds **2** (12 mg, $R_f = 0.7$, $CHCl_3$–MeOH (20 : 1)) and **3** (10 mg, $R_f = 0.4$, $CHCl_3$–MeOH (20 : 1)) were crystallised from the elution solution of 50–300 and 901–1500 mL, respectively. Compound **4** (6 mg, $R_f = 0.5$, $CHCl_3$–MeOH (10 : 1)) was obtained as crystal from the elution solution of 160–500 mL of the fourth fraction (522 mg) which was separated over silica gel (30 g, 200–300 mesh) by the elution of $CHCl_3$–MeOH (200 : 1, 100 : 1, 50 : 1, 40 : 1 and 30 : 1, each 500 mL). The fifth fraction (2.2 g) was separated over silica gel (110 g, 200–300 mesh) by the elution of $CHCl_3$–MeOH (50 : 1, 4000 mL; 40 : 1, 2000 mL; 20 : 1, 2000 mL and 10 : 1, 1000 mL). Compounds **5** (34 mg, $R_f = 0.4$, $CHCl_3$–MeOH (15 : 1)) and **6** (68 mg, $R_f = 0.3$, $CHCl_3$–MeOH (15 : 1)) were crystallised from the elution solution of 50–350 and 1501–2800 mL, respectively. The sixth fraction (5.33 g) was separated by CC over silica gel (200 g, 200–300 mesh) with the elution of $CHCl_3$–MeOH (50 : 1, 30 : 1, 15 : 1 and 5 : 1, each 1000 mL) to offer eight sub-fractions. The third sub-fraction (1.8 g) was separated on silica gel (90 g, 200–300 mesh) with the elution of the mixture of petroleum ether and acetone (5 : 1, 2.5 : 1, 1 : 1 and 0 : 1, each 300 mL). Compound **1** (4 mg, $R_f = 0.6$, $CHCl_3$–MeOH (30 : 1)) was crystallised from the elution solution of 1–300 mL.

3.5. *N-trans-cinnamoyl 2-amino-3a,4,5,6,7,8,9,10,11,12,13,13a-dodecahydrocyclododeca[d]oxazole (1)*

Colourless needle. $[\alpha]_D^{20} = +10$ (*c* 0.03, $CHCl_3$). IR: 3443, 2924, 2853, 1709, 1647, 1598, 1452, 1385, 1350, 1259, 1233, 875, 848, 800, 765, 751 and 620 cm^{-1}. HR-ESI-MS (positive mode): *m/z* 377.2200 $[M+Na]^+$ (calcd for $C_{22}H_{30}N_2O_2Na$, 377.2199). ^1H NMR ($CDCl_3$): δ 7.69 (d, $J = 15.4$ Hz, 1H, H-3′), 7.50 (m, 2H, H-5′ and 9′), 7.39 (m, 2H, H-6′ and 8′), 7.38 (m, 1H, H-7′), 7.00 (br s, 1H, −NH, D_2O exchangeable), 6.75 (d, $J = 15.4$ Hz, 1H, H-2′), 4.12 (dt, $J = 11.4$, 3.6 Hz, 1H, H-15), 3.76 (m, 1H, H-4), 1.98 (m, 4H, H-5 and 14), 1.85 (m, 4H, H-6a, H-7a and 13), 1.72 (m, 2H, H-12), 1.67 (m, 1H, H-6b), 1.60 (m, 1H, H-7b), 1.36 (m, 4H, H-8 and 11) and 1.22 (m, 4H, H-9 and 10). ^{13}C NMR ($CDCl_3$): δ 168.2 (C-1′), 154.1 (C-2), 143.5 (C-3′), 134.7 (C-4′), 130.1 (C-5′,9′), 128.9 (C-6′,8′), 127.9 (C-7′), 119.6 (C-2′), 56.5 (C-15), 49.8 (C-4), 32.8 (C-14), 31.0 (C-5), 26.3 (C-6, 13), 25.5 (C-7, 12), 25.4 (C-8, 11) and 24.6 (C-9, 10). The NMR data assignments were confirmed by 2D NMR experiments including ^1H–^1H COSY, HSQC and HMBC.

3.6. *Acid hydrolysis of compound 1*

To a dried round-bottom flask was added 3 mg of compound **1** and 5 mL of 8 N HCl with stirring, in an atmosphere of argon. The mixture was heated to 100°C for 8 h. H_2O (5 mL) was added into the reaction mixture to quench the reaction. The resultant mixture was extracted three times with 10 mL of $CHCl_3$ at room temperature. The organic layer was separated, combined, washed with brine and dried over anhydrous $MgSO_4$. The $CHCl_3$ solution was concentrated under vacuum to offer a residue, which was purified by CC over silica gel with the elution of the mixture of petroleum ether and ethyl acetate (80 : 1) to give **1a**. Compound **1a** was identified as *trans*-cinnamic acid by the ^1H NMR analysis and by the comparison of physicochemical data with authentic sample. The remaining aqueous solution was neutralised with 4 N NaOH and extracted three times with 10 mL of $CHCl_3$. The organic layer was processed following the above-mentioned procedure. However, the expected product was not observed in the ^1H NMR spectrum of the residue.

Acknowledgements

We are grateful to the forefront programme and 'Western Light' joint project from the Chinese Academy of Sciences for the partial financial support.

References

Betancor, C., León, E.I., Prangé, T., Salazar, J.A., & Suárez, E. (1989). 2-Oxazolines (4,5-dihydro-oxazoles) by organoselenium-induced cyclisation of allylic ureas. *Journal of the Chemical Society, Chemical Communications,* 450–452.

Brown, M.J.B., Cortes, J., Cutter, A.L., Leadlay, P.F., & Staunton, J. (1995). A mutant generated by expression of an engineered DEBS1 protein from the erythromycin-producing polyketide synthase (PKS) in *Streptomyces coelicolor* produces the triketide as a lactone, but the major product is the nor-analogue derived from acetate as starter acid. *Journal of the Chemical Society, Chemical Communications,* 1517–1518.

Cao, J.L., & Qu, J. (2010). Desymmetrization of meso-1,2-diols via the dynamic kinetic resolution of its monodichloroacetates. *The Journal of Organic Chemistry, 75*, 3663–3670.

Chen, Y., Smanski, M.J., & Shen, B. (2010). Improvement of secondary metabolite production in streptomyces by manipulating pathway regulation. *Applied Microbiology and Biotechnology, 86*, 19–25.

Cragg, G.M., Grothaus, P.G., & Newman, D.J. (2009). Impact of natural products on developing new anti-cancer agents. *Chemical Reviews, 109*, 3012–3043.

Dillman, R.L., & Cardellina II, J.H. (1991). Aromatic secondary metabolites from the sponge *Tedania ignis*. *Journal of Natural Products, 54*, 1056–1061.

Han, X.Y., Wang, M.A., Li, T.G., Liang, X.M., Dong, Y.H., Chen, F.H., & Wang, D.Q. (2007). Synthesis and conformation analysis of *cis*-1,2-disubstituted cyclododecanes. *Chinese Journal of Structure Chemistry, 26*, 625–631.

Jaroszewski, J.W., Stærk, D., Holm-Møller, S.B., Jensen, T.H., Franzyk, H., & Somanadhan, B. (2005). *Naravelia zeyanica*: occurrence of primary benzamides in flowering plants. *Natural Product Research, 19*, 291–294.

Joshi, B.S., Taylor, W.I., Bhate, D.S., & Karmarkar, S.S. (1963). The structure and synthesis of pimprinine. *Tetrahedron, 19*, 1437–1439.

Katritzky, A.R., Suzuki, K., Singh, S.K., & He, H.Y. (2003). Regiospecific *C*-acylation of pyrroles and indoles using *N*-acylbenzotriazoles. *The Journal of Organic Chemistry, 68*, 5720–5723.

Kelly, T.R., Fu, Y., & Xie, R.L. (1999). Structure revision of the APHEs through synthesis. *Tetrahedron Letters, 40*, 1857–1860.

Khoury, R.G., Jaquinod, L., & Smith, K.M. (1997). Rational approach to the synthesis of meso-meso (5,5′) linked bis-porphyrins. *Chemical Communications,* 1057–1058.

Kinoshita, K., Khosla, C., & Cane, D.E. (2003). Precursor-directed biosynthesis: stereospecificity for branched-chain diketides of the β-ketoacyl-ACP synthase domain 2 of 6-deoxyerythronolide B synthase. *Helvetica Chimica Acta, 86*, 3889–3907.

Li, W., Mao, S., & Yi, Y. (2000). Studies on the chemical constitutions of the sponge *Suberites tylobtusa* Levi. *Chinese Marine Medicine, 19*(3), 1–4.

Marsden, A.F.A., Wilkinson, B., Cortés, J., Dunster, N.J., Staunton, J., & Leadlay, P.F. (1998). Engineering broader specificity into an antibiotic-producing polyketide synthase. *Science, 279*, 199–202.

Naik, S.R., Harindran, J., & Varde, A.B. (2001). Pimprinine, an extracellular alkaloid produced by *Streptomyces* CDRIL-312: fermentation, isolation and pharmacological activity. *Journal of Biotechnology, 88*(1), 1–10.

Plater, M.J., Aiken, S., & Bourhill, G. (2002). A new synthetic route to donor–acceptor porphyrins. *Tetrahedron, 58*, 2405–2413.

Prudhomme, M. (2000). Recent developments of rebeccamycin analogues as topoisomerase I inhibitors and antitumor agents. *Current Medicinal Chemistry, 7*, 1189–1212.

Sharpless, K.B., Teranishi, A.Y., & Bäckvall, J.E. (1977). Chromyl chloride oxidations of olefins. Possible role of organometallic intermediates in the oxidations of olefins by oxo transition metal species. *Journal of the American Chemical Society, 99*, 3120–3128.

Shi, D.F., Wheelhouse, R.T., Sun, D., & Hurley, L.H. (2001). Quadruplex-interactive agents as telomerase inhibitors: synthesis of porphyrins and structure–activity relationship for the inhibition of telomerase. *Journal of Medicinal Chemistry, 44*, 4509–4523.

Yu, D.Q., & Yang, J.S. (1999). NMR spectroscopic analysis. *Analytical chemistry handbook* (2nd ed., p. 40). Beijing: Chemical Industry Press.

Walsh, C.T., & Fischbach, M.A. (2010). Natural products version 2.0: connecting genes to molecules. *Journal of the American Chemical Society, 132*, 2469–2493.

Wolinsky, J., Thorstenson, J.H., & Killinger, T.A. (1978). α,α'-Dibromocycloalkanols and 3-bromocycloalkene oxides. *The Journal of Organic Chemistry, 43*, 875–881.