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Studies on the Biosynthesis of Chetomin: Enantiospecific Synthesis of a Putative, Late-Stage Biosynthetic Intermediate

Timothy R. Welch^a and Robert M. Williams^{a,b,*}

^aDepartment of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

^bUniversity of Colorado Cancer Center, Aurora, CO 80045, USA

Abstract

The enantiospecific synthesis of desthiiochetomin, a putative biosynthetic intermediate of the epidithiodioxopiperazine natural product chetomin, is described. A diastereoselective *N*-alkylation was employed to form the key C3-N1' bond of the heterodimeric indoline core, followed by peptide coupling and dioxopiperazine cyclization with the requisite *N*-methyl amino acids. A related sarcosine-derived dioxopiperazine was prepared in the same manner. The first proposed biosynthesis of chetomin is also detailed in the text.

Keywords

Aspergillus versicolor; biosynthesis; prenylated indole alkaloid

1. Introduction

Epidithiodioxopiperazines are a unique class of fungal metabolites characterized by a sulfur-bridged dioxopiperazine. All natural epidithiodioxopiperazines discovered to date—including chetomin (**1**, Figure 1), gliotoxin (**2**) and sirodesmin PL (**3**)—are derived from at least one aromatic amino acid.¹ This class of alkaloids has received considerable attention from the scientific community since the seminal discovery of gliotoxin in 1936,² largely due to the potent biological activity inherent in the core structure and the synthetic challenge posed by their complex molecular architectures. Advances in genomics have contributed to our understanding of the biogenetic origins of gliotoxin and the class as a whole, providing inspiration to synthetic chemists hoping to channel some of the efficiency with which Nature is able to achieve similar bond formations.

Chetomin (**1**) is a rare heterodimeric indole alkaloid possessing an unsymmetrical dimeric structure joined by a C3-N1' linkage between two tryptophan fragments.^{3,4} The densely functionalized molecule contains five tetra-substituted carbons and six stereogenic centers, in addition to two epidithiodioxopiperazine rings that are sensitive to oxidative, reductive, basic and strongly acidic conditions. Until recently, no direct synthetic method for the requisite C3-N1' bond formation existed.^{5,6} Although sixty-eight years have passed since its isolation, chetomin has not yet succumbed to a total synthesis.

Chetomin was first described as an antibiotic fungal metabolite of *Chaetomium cochliodes*, although it has recently received renewed interest as a cancer chemotherapeutic agent with

activity against the transcription factor hypoxia inducible factor 1 (HIF-1).⁷ Expression of HIF-1 is essential to the growth and progression of oxygen-deprived solid tumors. Chetomin binds to the CH1 domain of the HIF-1 co-activator p300 and extracts a zinc atom from the protein, inhibiting the binding of HIF-1 to p300 despite extensive surface interactions between the two proteins.⁸

Chetomin is thus able to attenuate the transcriptional activity of HIF-1, both *in vitro* and *in vivo*. Administration of chetomin to mice bearing human xenograft tumors (HCT116 and PC3) suppressed tumor growth.⁷ Herein, we report a concise enantiospecific synthesis of a putative, late-stage biosynthetic intermediate of chetomin, the desthio carbon skeleton of the natural metabolite, namely compound **7**.

2. Results and Discussion

2.1 Proposed biosynthesis

Putative gene clusters for gliotoxin (**2**) and sirodesmin PL (**3**) have been identified from *Aspergillus fumigatus* and *Leptosphaeria maculans*.^{9–11} While whole genome sequencing and bioinformatics studies of the fungus that produces chetomin have not to our knowledge been conducted, it is reasonable to suggest that related enzymes responsible for the catalysis of analogous reactions exist in *Chaetomium* sp., herein labeled “CheX” (Scheme 1). The biogenetic origin of the C3-N1' linkage is not well understood, although Baran and coworkers have summarized numerous possibilities leading to tryptophan-derived heterodimer **5**.¹² In accordance with studies from the Walsh group, a nonribosomal peptide synthetase “CheP” likely catalyzes the peptide coupling reactions with serine (**6**) and subsequent dioxopiperazine cyclizations.¹³ “CheN” could be responsible for *N*-methylation at this stage in the biosynthesis to give desthiochetomin (**7**).¹¹

Two groups recently provided evidence suggesting that the incorporation of sulfur to gliotoxin (**2**) begins with bis-hydroxylation of a dioxopiperazine ring.^{14,15} It is likely that a “CheC”-mediated bishydroxylation of **7** similarly proceeds to tetraol **8** in the biosynthesis of chetomin. Elimination of water to generate pairs of iminium ions (**9**) could be followed by nucleophilic attack of the cysteine thiolate residues of two glutathione (GSH) molecules, catalyzed by a specialized glutathione *S*-transferase “CheG” to afford intermediate **10**.^{14–16} Sequential “CheJ” peptidase and “CheI” thioesterase activity is proposed to reveal the free dithiols (**11**).¹⁴ Oxidation to the disulfides could be catalyzed by “CheT” to complete the biosynthesis of chetomin (**1**).¹⁷

2.2 Dioxopiperazine synthesis

Our retrosynthetic analysis revealed two disconnections key to a convergent synthesis of dioxopiperazine **7**; (i) coupling of two equivalents of a suitably protected *N*-Me-*L*-Ser derivative to assemble both dioxopiperazine rings and (ii) *N*-alkylation of an *N*-Me-*L*-Trp derivative with bromopyrroloindoline **13** to form the C3-N1' linkage. To arrive at the correct stereochemistry at C3, it would be necessary to employ a *D*-tryptophan-derived bromopyrroloindoline in this alkylation. According to reports from Espejo and Rainier,⁶ the methyl ester was expected to epimerize to the thermodynamically more favorable *endo*-position following *N*-alkylation, thus establishing the required configuration at that position.

N,N'-Boc-*D*-Trp-OMe was prepared from *D*-tryptophan by known procedures (Scheme 2). Bromocyclization proceeded stereoselectively to *exo*-bromopyrroloindoline **13** in good yield, and the requisite C3-N1' bond was constructed between *N*-Me, Boc-*L*-Trp-OMe and bromopyrroloindoline **13** following addition of KO^tBu to give the *endo*-intermediate, along with recovered starting material (**13**, 22%). Subsequent treatment with TFA resulted in

global Boc-deprotection to key intermediate **14**. T3P-mediated peptide coupling with *N*-Me,Fmoc-Ser(OTBS) consistently provided tetrapeptide **15** in modest yield with minimal purification necessary. Gentle heating of the tetrapeptide in THF and morpholine resulted in concomitant deprotection of the Fmoc group and cyclization to the dioxopiperazine, leaving deprotection of the silyl ethers to complete the synthesis of desthiiochetomin (**7**), a putative biosynthetic intermediate of chetomin (**1**).

2.3 Sarcosine-derived dioxopiperazine synthesis

In the course of these experiments, a related *N*-methyl dioxopiperazine (**17**) was prepared from sarcosine (Scheme 3). *N*-Me, Fmoc-glycine (**16**) was coupled to key intermediate **14** used in the above synthesis using analogous T3P-mediated coupling conditions to afford the tetrapeptide. Concomitant Fmoc-deprotection and cyclization provided dioxopiperazine **17** in good yield. This compound served as a useful model for dioxopiperazine cyclization with *N*-methyl amino acids in place and is also a potential synthetic precursor to chetomin (**1**).

3 Conclusion

In summary, we have detailed a proposed biosynthesis of the epidithiodioxopiperazine chetomin (**1**). A convergent and efficient enantioselective synthetic route was developed for a putative biosynthetic intermediate in this pathway, desthiiochetomin (**7**), and for a related sarcosine-derived analogue (**17**). Ongoing efforts in our laboratory are focused on the conversion of dioxopiperazines **7** and **17** into chetomin (**1**), and on experimentally validating the proposed biogenesis by utilizing isotopically labeled **7** for biosynthetic precursor and incorporation studies.

4 Experimental section

4.1 General

Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. All air or moisture sensitive reactions were performed under a positive pressure of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran (THF), toluene, diethyl ether (Et₂O), dichloromethane, benzene (PhH), acetonitrile, triethylamine (Et₃N), pyridine, diisopropyl amine, methanol (MeOH), dimethylsulfoxide (DMSO), and *N,N*-dimethylformamide (DMF) were obtained from a dry solvent system (Ar degassed solvents delivered through activated alumina columns, positive pressure of argon). Column chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh).

¹H NMR and ¹³C NMR spectra were recorded on Varian 300 or 400 MHz spectrometers. Chemical shifts are reported in ppm relative to CHCl₃ at δ 7.26 (¹H NMR) and δ 77.23 (¹³C NMR). Mass spectra were obtained on Fisons VG Autospec. IR spectra were obtained from thin films on a NaCl plate using a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were collected at 589 nm on a Rudolph Research automatic polarimeter Autopol III.

4.1.1 Bromopyrroloindoline (13)—To a solution of *N,N'*-Boc₂-D-Trp-OMe (18.53 g, 44.3 mmol) in CH₂Cl₂ (1000 mL) was added NBS (7.89 g, 44.3 mmol) and PPTS (11.12 g, 44.3 mmol). The resulting solution was allowed to stir at r.t. O/N. The reaction mixture was washed with brine and the organic layer dried (Na₂SO₄) and concentrated. Purification of the crude residue by SiO₂ chromatography (30% EtOAc in hexanes) gave the desired product in 96% yield (21.20 g). [α]_D = +150.0 (CH₂Cl₂); ¹H-NMR (400 MHz; CDCl₃): δ 7.53–7.52 (bs, 1H), 7.34–7.24 (m, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.37 (s, 1H), 3.86 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.71 (s, 3H), 3.18 (dd, *J* = 12.6, 6.3 Hz, 1H), 2.79 (dd, *J* = 12.6, 10.3 Hz,

1H), 1.56 (s, 9H), 1.37 (bs, 9H); 13-C NMR (101 MHz; cdcl₃): δ 171.46, 171.41, 171.0, 152.1, 141.5, 130.6, 124.37, 124.35, 123.2, 83.8, 82.2, 59.4, 52.3, 36.4, 28.6, 28.2, 24.1, 21.0, 14.2; IR (NaCl, film) 2980, 1719, 1395, 1334, 1163, 753 cm⁻¹; HRMS (ESI-APCI): [M+Na]⁺ 519.1107 calcd for C₂₂H₂₉BrN₂NaO₆, found: 519.1102.

4.1.2 (2S,3aS,8aS)-1,8-di-tert-butyl 2-methyl 3a-(3-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-1-yl)-3,3a-dihydro-pyrrolo[2,3-b]indole-1,2,8(2H,8aH)-tricarboxylate (S1)—KOrBu (3.04 g, 27.2 mmol) was added to a solution of bromopyrroloindoline **13** (10.08 g, 20.3 mmol) and *N*-Me, Boc-Trp-OMe (4.50 g, 13.6 mmol) in CH₃CN (1000 mL) at 0°C and stirred 1h under Ar. NaHCO₃ was added and the product extracted in CH₂Cl₂, washed with brine, dried (Na₂SO₄), and concentrated. Purification by SiO₂ chromatography (10–20% EtOAc in hexanes) afforded pure dipeptide **S1** (5.41 g, 53% yield). [α]_D = −3.1 (CH₂Cl₂); ¹H-NMR (400 MHz; CDCl₃): δ 7.68–7.67 (bs, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.35–7.32 (m, 2H), 7.23 (s, 1H), 7.16–7.08 (m, 3H), 6.84 (d, J = 15.2 Hz, 1H), 6.74 (d, J = 3.3 Hz, 1H), 4.87–4.86 (bs, 1H), 4.73–4.56 (broad, 2H), 3.69 (broad, J = 7.1 Hz, 3H), 3.49–3.43 (m, 1H), 3.29 (dd, J = 15.0, 4.9 Hz, 1H), 3.20 (s, 3H), 3.02–2.91 (m, 2H), 2.67–2.59 (m, 3H), 1.57–1.11 (m, 27H); 13-C NMR (101 MHz; cdcl₃): δ 171.7, 170.9, 151.9, 134.7, 130.97, 130.82, 129.9, 125.0, 123.3, 122.2, 119.88, 119.86, 119.2, 111.6, 110.6, 82.0, 79.9, 72.59, 72.57, 59.9, 59.32, 59.30, 52.12, 52.09, 52.05, 52.00, 51.97, 34.6, 31.5, 28.19, 28.17, 25.2, 22.6, 20.7, 14.1; IR (NaCl, film) 2978, 1703, 1482, 1394, 1157, 738 cm⁻¹; HRMS (ESI-APCI): [M+Na]⁺ 771.3581 calcd for C₄₀H₅₂N₄NaO₁₀, found: 771.3600.

4.1.3 (2S,3aS,8aS)-methyl 3a-(3-((S)-3-methoxy-2-(methylamino)-3-oxopropyl)-1H-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (14)—TFA (11 mL) was slowly added to a solution of Boc-protected material **S1** obtained above (4.11 g, 5.49 mmol) in CH₂Cl₂ (110 mL) at 0°C. The reaction mixture was allowed to warm to r.t. as it stirred O/N. NaHCO₃ was added and the product extracted into CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and concentrated to afford the deprotected product **14** (2.35 g, 96% yield), that was immediately used for the subsequent transformation without further purification. [α]_D = +73.3 (CH₂Cl₂); ¹H-NMR (300 MHz; CDCl₃): δ 7.61–7.58 (m, 1H), 7.46–7.43 (m, 1H), 7.18–7.05 (m, 6H), 6.77 (t, J = 7.4 Hz, 1H), 6.68 (dd, J = 7.9, 0.9 Hz, 1H), 5.51 (s, 1H), 4.55 (bs, 1H), 4.21 (d, J = 7.6 Hz, 1H), 3.61 (d, J = 9.5 Hz, 3H), 3.53–3.46 (m, 2H), 3.36 (d, J = 1.1 Hz, 3H), 3.10–2.93 (m, 4H), 2.35 (s, 3H); 13-C NMR (101 MHz; cdcl₃): δ 174.7, 173.8, 149.69, 149.66, 135.26, 135.23, 130.4, 129.7, 127.58, 127.54, 125.3, 125.00, 124.89, 121.8, 119.5, 119.30, 119.13, 112.1, 110.74, 110.71, 109.55, 109.49, 82.0, 75.72, 75.69, 63.71, 63.69, 60.2, 52.1, 51.7, 40.76, 40.70, 34.68, 34.62, 28.91, 28.81; IR (NaCl, film) 2950, 1734, 1459, 1206, 742 cm⁻¹; HRMS (ESI-APCI): [M+H]⁺ 449.2189 calcd for C₂₅H₂₉N₄O₄, found: 449.2179.

4.1.4 Tetrapeptide (15)—Diamine **14** (327 mg, 0.73 mmol), *N*-Me,Fmoc-L-Ser(OTBS)-OH (663 g, 1.46 mmol), T3P (50% by weight in DMF, 1.07 g, 1.68 mmol), DIPEA (0.635 mL, 5.0 mmol), and CH₂Cl₂ (7.3 mL) were combined and stirred under Ar O/N at 35°C. Water was added, the product extracted in EtOAc, the combined extracts washed with brine, dried (Na₂SO₄), concentrated, and flashed through a plug of silica gel (35% EtOAc in hexanes) to afford tetrapeptide **15** (351 mg, 36% yield), carried forward as such without additional purification.

4.1.5 (3S,5aR,10bS,11aS)-3-(((tert-butyldimethylsilyl)oxy)methyl)-10b-(3-(((2S,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1,4-dimethyl-3,6-dioxopiperazin-2-yl)methyl)-1H-indol-1-yl)-2-methyl-2,3,5a,6,11,11a-hexahydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(10bH)-dione (S2)—Tetrapeptide **15** (300 mg, 0.227

mmol) and morpholine (2.3 mL) were dissolved in THF (9 mL) and heated to 35°C. After stirring O/N, the reaction mixture was concentrated and purified by SiO₂ chromatography (4% MeOH in CH₂Cl₂) to afford pure dioxopiperazine **S2** (153 mg, 83% yield). [α]_D = +80.0 (CH₂Cl₂); ¹H-NMR (300 MHz; CDCl₃): δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.30 (s, 1H), 7.15 (td, *J* = 7.7, 1.0 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.99–6.94 (m, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.69–6.63 (m, 2H), 5.91 (d, *J* = 2.6 Hz, 1H), 5.59 (d, *J* = 2.6 Hz, 1H), 4.57–4.52 (m, 1H), 4.26–4.19 (m, 2H), 4.03 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.87–3.77 (m, 2H), 3.68–3.61 (m, 2H), 3.40 (dd, *J* = 9.4, 5.6 Hz, 2H), 3.26–3.21 (m, 1H), 2.99 (d, *J* = 9.6 Hz, 6H), 2.71 (s, 3H), 2.60–2.55 (m, 1H), 0.84 (s, 9H), 0.74 (s, 9H), –0.01–0.08 (m, 12H); ¹³C NMR (101 MHz; cdcl₃): δ 166.0, 164.56, 164.55, 164.35, 146.7, 135.6, 130.1, 129.5, 123.1, 122.6, 120.4, 119.5, 112.1, 111.2, 109.7, 82.7, 65.1, 64.2, 63.7, 63.3, 60.6, 56.8, 41.5, 33.8, 33.1, 31.1, 30.7, 25.9, 25.5, 18.4, 18.0, –5.38, –5.40, –5.71, –5.74; IR (NaCl, film) 2930, 2857, 1654, 1462, 1255, 1112 cm^{–1}; HRMS (ESI-APCI): [M+H]⁺ 815.4348 calcd for C₄₃H₆₃N₆O₆Si₂, found:815.4349.

4.1.6 (3S,5aR,10bS,11aS)-3-(hydroxymethyl)-10b-(3-(((2S,5S)-5-(hydroxymethyl)-1,4-dimethyl-3,6-dioxopiperazin-2-yl)methyl)-1H-indol-1-yl)-2-methyl-2,3,5a,6,11,11a-hexahydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(10bH)-dione (7)—Dioxopiperazine **S2** obtained above (23.2 mg, 0.028 mmol) was dissolved in CH₂Cl₂ (0.5 mL) and TFA (0.050 mL) added. The resulting solution was allowed to stir O/N at r.t. The reaction mixture was concentrated and the crude residue purified by pTLC (5% MeOH in CH₂Cl₂) to afford the title compound **7** (8.2 mg, 51% yield). [α]_D = +133.4 (CH₂Cl₂); ¹H-NMR (400 MHz; CDCl₃): δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.41 (s, 1H), 7.33 (td, *J* = 7.7, 1.2 Hz, 1H), 7.23–7.19 (m, 1H), 7.15–7.11 (m, 2H), 6.90–6.84 (m, 3H), 6.13 (s, 1H), 4.75 (dd, *J* = 11.3, 6.0 Hz, 1H), 4.44 (dd, *J* = 12.2, 2.2 Hz, 1H), 4.39 (t, *J* = 4.7 Hz, 1H), 4.14 (dd, *J* = 12.2, 4.2 Hz, 1H), 4.10 (t, *J* = 2.0 Hz, 1H), 3.86–3.72 (m, 3H), 3.46 (dd, *J* = 15.0, 4.9 Hz, 1H), 3.21 (s, 3H), 3.08 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.04 (s, 3H), 2.96 (s, 3H), 2.89 (dd, *J* = 14.8, 11.3 Hz, 1H), 2.66 (dd, *J* = 11.1, 6.5 Hz, 1H); ¹³C NMR (101 MHz; cdcl₃): δ 167.6, 166.04, 165.98, 165.5, 146.5, 135.3, 130.4, 129.7, 127.8, 123.9, 123.4, 122.7, 120.44, 120.28, 119.5, 112.3, 110.3, 109.6, 82.9, 73.7, 62.9, 62.5, 61.7, 61.4, 59.4, 57.6, 40.1, 32.8, 32.5, 30.1, 28.3; IR (NaCl, film) 3383, 2927, 1652, 1458, 1215, 1072 cm^{–1}; HRMS (ESI-APCI): [M+H]⁺ 587.2618 calcd for C₃₁H₃₅N₆O₆, found:587.2619.

4.1.7 (2S,3aS,8aR)-methyl 3a-(3-((S)-2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-N-methylacetamido)-3-methoxy-3-oxopropyl)-1H-indol-1-yl)-1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)acetyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (S3)—Diamine **14** (3.80, 896 mg, 2.0 mmol), N-Fmoc-sarcosine-OH (1.24 g, 4.0 mmol), T3P (50% by weight in DMF, 2.93 g, 4.6 mmol), DIPEA (1.7 mL, 10.0 mmol), and CH₂Cl₂ (20 mL) were combined and stirred under Ar O/N at 35°C. Water was added, the product extracted in EtOAc, the combined extracts washed with brine, dried (Na₂SO₄), concentrated, and flashed through a plug of silica gel (50–100% EtOAc in hexanes) to afford tetrapeptide **S3** (1.17 g, 57% yield), carried forward as such without further purification.

4.1.8 (5aR,10bS,11aS)-10b-(3-(((S)-1,4-dimethyl-3,6-dioxopiperazin-2-yl)methyl)-1H-indol-1-yl)-2-methyl-2,3,5a,6,11,11a-hexahydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(10bH)-dione (17)—Tetrapeptide **S3** (1.0 g, 0.97 mmol) and morpholine (10 mL) were dissolved in THF (40 mL) and heated to 35°C. After stirring O/N, the reaction mixture was concentrated and purified by SiO₂ chromatography (2–6% MeOH in CH₂Cl₂) to afford pure dioxopiperazine **17** (470 mg, 92% yield). [α]_D = +145.5 (CH₂Cl₂); ¹H-NMR (300 MHz; CDCl₃): δ 7.49 (t, *J* = 7.3 Hz, 1H), 7.26–7.15 (m, 2H),

7.09–6.91 (m, 3H), 6.79–6.73 (m, 2H), 6.01 (dd, $J = 51.3, 3.1$ Hz, 1H), 5.45 (dd, $J = 53.9, 3.8$ Hz, 1H), 4.57–4.49 (m, 1H), 4.18 (t, $J = 3.2$ Hz, 1H), 3.84–3.46 (m, 4H), 3.23–3.12 (m, 2H), 3.06–2.98 (m, 6H), 2.68 (ddd, $J = 15.3, 11.5, 4.2$ Hz, 1H), 2.33 (d, $J = 32.5$ Hz, 3H), 2.06–1.94 (m, 1H); ^{13}C NMR (101 MHz; cdCl_3): δ 166.3, 166.0, 164.6, 164.2, 146.7, 135.4, 130.1, 129.1, 128.1, 127.8, 124.7, 124.4, 122.8, 122.5, 120.2, 119.7, 112.4, 110.2, 108.3, 82.6, 82.0, 74.1, 62.7, 57.2, 53.5, 40.1, 39.7, 33.5, 32.9, 32.0; IR (NaCl, film) 2931, 1664, 1459, 1324, 1259 cm^{-1} ; HRMS (ESI-APCI): $[\text{M}+\text{H}]^+$ 527.2407 calcd for $\text{C}_{29}\text{H}_{31}\text{N}_6\text{O}_4$, found: 527.2402.

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Figure 1.
Structures of chetomin, gliotoxin and sirodesmin PL.

Scheme 1.
Proposed biosynthesis of chetomin.

Scheme 2.
Synthesis of postulated biosynthetic intermediate **7**.

Scheme 3.
Synthesis of sarcosine-derived dioxopiperazine.