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# Bezerramycins A–C, Antiproliferative Phenoxazinones from *Streptomyces griseus* Featuring Carboxy, Carboxamide or Nitrile Substituents

**Patrícia Bezerra Gomes,[a] Markus Nett,[a] Hans-Martin Dahse,[a] Isabel Sattler,[a] Karin Martin,[a] and Christian Hertweck*[a,b]**

**Keywords:** *Streptomyces griseus* / Antiproliferative activity / Phenoxazinone / Natural products / Biosynthesis

Three new phenoxazinone antibiotics, named bezerramycins A–C (**1**–**3**), were isolated from a *Streptomyces griseus* strain (HKI 0545, DSM 41823) together with the known metabolite elloxazinone B (**4**). Their structures were elucidated by one- and two-dimensional NMR techniques ($^1$H, $^{13}$C, HSQC, $^1$H-$^1$H COSY and HMBC) as well as mass spectrometry. One of the isolated phenoxazinones (bezerramycin C) features a nitrile moiety, which is scarce in natural products. All compounds were evaluated for their antiproliferative and cytotoxic activities. Those featuring a hydroxymethyl substituent at C-8 were found to exhibit moderate antiproliferative properties against vascular endothelium cells (HUVEC) ($GI_{50}$ = 14.5–20 μM). A biosynthetic model for the isolated compounds is discussed.

## Introduction

Phenoxazinones from microbial sources represent a family of anticancer agents sharing a tricyclic iminoquinone core structure.[1–5] Many phenoxazinone antibiotics exert their biological effects through a sequence-selective intercalation into DNA, and hydrogen bonding between the 2-amino group and O-4′ or O-5′ of the cytosine C-5 residue likely contributes to the high antiproliferative activity.[6] Perhaps the most extensively studied phenoxazinone antibiotics are the actinomycins. These yellow- to red-coloured chromopeptides were the first antibiotics discovered in streptomycetes (e.g. *Streptomyces antibioticus*) and still represent one of the most potent antineoplastic natural product families.[4,7] Even though their clinical application is limited because of the side effects associated with myelosuppression and cardiotoxicity, actinomycin D has found broad application as an investigative tool in cell biology to inhibit transcription.[7,8] In recent years, several structural variations of the 2-aminophenoxazin-3-one scaffold have been identified in actinobacterial metabolites, which primarily differ in their substitution pattern at C-1, C-2, C-8 and C-9.[4,9,10] Here, we report the isolation and structure elucidation of three new antiproliferative phenoxazinone antibiotics (**1**–**3**) along with the known aminophenoxazinone elloxazinone B (**4**).[11] In addition to the biological activities, the finding of congeners featuring carboxy, carboxamide, or rare nitrile substituents is intriguing from a biosynthetic point of view.

## Results and Discussion

In order to study the health impact of moisture damage and microbial growth in indoor environments, we have investigated the chemical constituents of the mycelium of *Streptomyces griseus* (HKI 0545, DSM 41823) isolated from a plaster of an old building (kindly provided by Dr. Wolfgang Lorenz at the Institut für Innenraumdiagnostik, Düsseldorf). Extracts of the strain showed antiproliferative activities and revealed obvious spots on silica gel plates ($CHCl_3$/MeOH, 9:1 and BuOH/EtOAc/$H_2O$, 4:5:1) with UV-light detection (254 and 366 nm) and after staining with anisaldehyde/$H_2SO_4$. In order to isolate significant amounts of these compounds, cultivation of the producing organism was carried out in a 300 L fermentor in soybean/glucose medium (20 g L$^{-1}$ soybean, 20 g L$^{-1}$ glucose, 5 g L$^{-1}$ NaCl and 3 g L$^{-1}$ $CaCO_3$) at 28 °C for 120 h, with 30 L min$^{-1}$ aeration and stirring at 200 rpm. The culture filtrate was separated from the mycelium by filtration and subjected to an amberchrom-161M resin column using MeOH/$H_2O$ as eluent, and the relevant fractions were concentrated under reduced pressure and lyophilized. The mycelium (30 g) was extracted with 2 L of methanol and separated by repeated column chromatography on silica gel (eluted with $CHCl_3$/MeOH) and gel permeation chromatography on Sephadex LH-20 (eluted with MeOH) to yield 3.6 mg of **1**, 1 mg of **2**, 1 mg of **3**, and 11.4 mg of **4**. The latter was identified as elloxazinone B (**4**) by a comparison of its spectroscopic data with those published in the literature.[11]

[a] Leibniz Institute for Natural Product Research and Infection Biology (HKI)
Beutenbergstr. 11a, 07745 Jena, Germany
Fax: +49-3641-5320804
E-mail: Christian.Hertweck@hki-jena.de
[b] Friedrich Schiller University,
Jena, Germany

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The UV spectrum and the NMR spectroscopic data of compound **1**, named bezerramycin A (Figure 1), are very similar to those of the known compound elloxazinone B (**4**),[11] suggesting that **1** also belongs to the group of phenoxazinone antibiotics. Its empirical formula was assigned to be $C_{14}H_{11}N_3O_4$ by HR-ESI-MS (*m*/*z* = 284.0681 for $[M - H]^-$; calcd. 284.0666 for $C_{14}H_{10}N_3O_4$), which indicated eleven degrees of unsaturation. The $^{13}C$ NMR spectra of **1** and **4** differ in signals for the quaternary carbon atom of the carboxylic acid in **4** ($\delta_C$ = 167.0 ppm), which is replaced by a methylene group resonating at $\delta_C$ = 62.0 ppm in **1**. The $^1H$ NMR spectrum ([D$_6$]DMSO, 500 MHz) of **1** exhibits nine signals corresponding to one aliphatic methylene group and four aromatic protons. The remaining four signals did not give any correlation in the HSQC experiment and must thus be attached to heteroatoms. The $^{13}C$ NMR spectrum ([D$_6$]DMSO, 125 MHz) shows the signals of fourteen carbon atoms (Table 1). A $^{13}C$ NMR DEPT spectrum reveals four methine groups ($\delta_C$ = 127.8, 125.1, 115.3 and 103.9 ppm) as well as one methylene group ($\delta_C$ = 62.0 ppm), which are in agreement with the $^1H$ NMR spectroscopic data. The chemical shift of the $CH_2$ group suggested the presence of an OH group attached to it. The HMBC spectrum provided the crucial information for the presence of a $CH_2$ group attached to C-8 (Figure 2) in ring A. The connectivities from 7-H and 9-H to C-14 and C-8 together with the coupling constants of the protons 6-H, 7-H and 9-H (Table 1) support the substitution pattern of ring A. Results from the $^1H$-$^{13}C$ HMBC experiment allowed for the deduction of the structure of ring C. It shows correlations between the methine proton (4-H) to C-2, C-4a and C-10a (Figure 2). The assignment of the protons resonating at $\delta_H$ = 7.63, 9.92, 8.02 and 10.43 ppm is supported by comparison with the data for elloxazinone B. In analogy to the NMR assignments of elloxazinone B (**4**),[11] we attribute the chemical shifts of $\delta_H$ = 7.63 and 9.92 ppm of **1** to the amide group, whereas the chemicals shifts of $\delta_H$ = 8.02 and 10.43 ppm belong to the amine group.

For **2** (named bezerramycin B, Figure 1) an empirical formula of $C_{16}H_{12}N_2O_6$ was deduced from HR-ESI-MS (*m*/*z* = 327.0592 $[M - H]^-$; calcd. 327.0612 for $C_{16}H_{11}N_2O_6$), which indicates twelve double-bond equivalents. The $^{13}C$ NMR spectrum shows the signals of fourteen carbon atoms (Table 1). The DEPT spectrum exhibits four methine ($\delta_C$ = 104.2, 115.5, 127.0, and 130.6 ppm), one methylene ($\delta_C$ = 61.8 ppm) and one methyl carbon atom ($\delta_C$ = 22.8 ppm), which are in agreement with the $^1H$ NMR spectroscopic data. Analysis of the 1D and 2D NMR spectroscopic data and comparison with that of **1** revealed that **2** is also a member of the phenoxazinone family. The NMR spectroscopic data of **2** are similar to those of **1**, the differences being that the amide group (C-11) in **1** is replaced by a carboxylate moiety in **2**, and the NH group linked to C-2 in **1** is attached to an acetyl group in **2**. The presence of an acetyl group was supported by the observed HMBC correlation between 14-H and C-13 (Figure 2). However, the signals of the quaternary carbon atoms C-1 and C-2 are not detectable, likely due to a keto/enol tautomerism. Yet, NMR spectroscopic data of **2** are similar to those reported for the antibiotic exfoliazone (**5**) isolated from *Streptomyces exfoliatus*.[12] A comparison of the $^1H$ and $^{13}C$ NMR spectroscopic data revealed that these two compounds have similar structures. The only difference is that **2** has a carboxylic acid moiety at C-1, whereas **5** has a hydrogen atom in this position.

The third compound, bezerramycin C (**3**, Figure 1) also proved to be a congener of phenoxazinones **1**, **2** and **4** according to its UV spectrum. Its empirical formula ($C_{16}H_{11}N_3O_4$) was deduced from HR-ESI-MS (*m*/*z* = 332.0655 $[M + Na]^+$; calcd. 332.0642 for $C_{16}H_{11}N_3NaO_4$), which indicated a molecule with thirteen degrees of unsaturation. A comparison of the overall NMR spectroscopic data (Table 1), in particular $^1H$ and $^{13}C$ NMR, $^1H$-$^1H$ COSY and HMBC (Figure 2) revealed that bezerramycin C (**3**) differs from bezerramycin B (**2**) only in having a nitrile group at C-1 in **3**, whereas **2** has a carboxylic acid group in

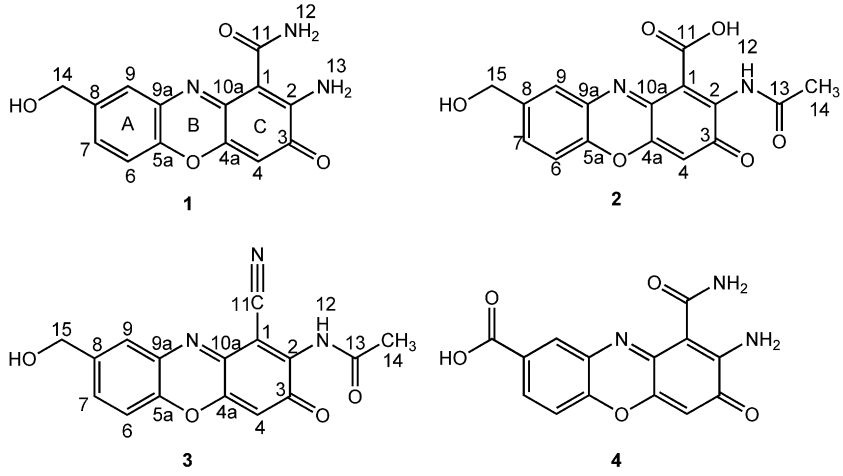



Figure 1. Structures of bezerramycins A–C (**1**–**3**) and elloxazinone B (**4**).

Table 1. NMR spectroscopic data for **1**–**3** in [$D_6$]DMSO ($\delta$ in ppm, $J$ in Hz).

| Position | **1** | | **2** | | **3** | |
|---|---|---|---|---|---|---|
| | $\delta_H$[a] | $\delta_C$[b] | $\delta_H$[a] | $\delta_C$[b] | $\delta_H$[a] | $\delta_C$[b] |
| 1 | – | 95.8 ($C_{quat}$) | – | –[c] | – | 92.2 ($C_{quat}$) |
| 2 | – | 145.9 ($C_{quat}$) | – | –[c] | – | 145.4 ($C_{quat}$) |
| 3 | – | 178.3 ($C_{quat}$) | – | 180.4 ($C_{quat}$) | – | 180.7 ($C_{quat}$) |
| 4 | 6.48, s | 103.9 (CH) | 6.27, s | 104.2 (CH) | 6.47, s | 106.6 (CH) |
| 4a | – | 150.6 ($C_{quat}$) | – | 147.1 ($C_{quat}$) | – | 145.7 ($C_{quat}$) |
| 5a | – | 140.2 ($C_{quat}$) | – | 141.5 ($C_{quat}$) | – | 140.5 ($C_{quat}$) |
| 6 | 7.49, d (8.4) | 115.3 (CH) | 7.45, d (8.4) | 115.5 (CH) | 7.47, d (8.5) | 115.6 (CH) |
| 7 | 7.46, dd (8.6, 1.9) | 127.8 (CH) | 7.56, dd (8.5, 1.9) | 130.6 (CH) | 7.57, dd (8.5, 1.9) | 130.5 (CH) |
| 8 | – | 140.3 ($C_{quat}$) | – | 140.1 ($C_{quat}$) | – | 141.1 ($C_{quat}$) |
| 9 | 7.77, d (1.8) | 125.1 (CH) | 7.69, d (1.8) | 127.0 (CH) | 7.80, d (1.7) | 127.2 (CH) |
| 9a | – | 131.2 ($C_{quat}$) | – | 132.4 ($C_{quat}$) | – | 132.8 ($C_{quat}$) |
| 10a | – | 151.7 ($C_{quat}$) | – | 148.1 ($C_{quat}$) | – | 149.6 ($C_{quat}$) |
| 11 | – | 170.1 ($C_{quat}$) | – | 164.6 ($C_{quat}$) | – | 116.3 ($C_{quat}$) |
| 12 | 7.63, 9.92, s | – | – | – | – | – |
| 13 | 8.02, 10.43, s | – | – | 168.8 ($C_{quat}$) | – | 164.6 ($C_{quat}$) |
| 14 | 4.58, s | 62.0 ($CH_2$) | 1.98, s | 22.8 ($CH_3$) | 2.43, s | 21.9 ($CH_3$) |
| 15 | – | – | 4.58, s | 61.8 ($CH_2$) | 4.60, s | 61.8 ($CH_2$) |

[a] Recorded at 500 MHz. [b] Recorded at 125 MHz. [c] Signals not detectable.

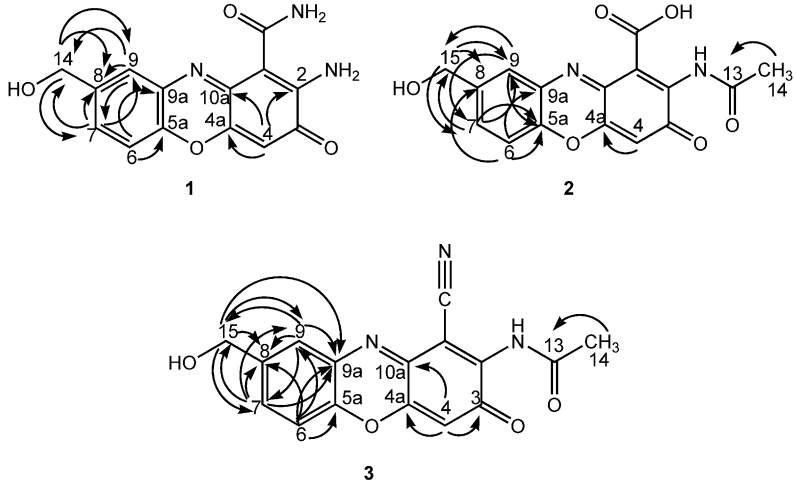



Figure 2. Selected HMBC correlations for **1**–**3**.

this position. The resonance at $\delta$ = 116.3 ppm in the $^{13}C$ NMR spectrum and the characteristic band at 2325 $cm^{-1}$ in the IR spectrum is consistent with the presence of a nitrile moiety.

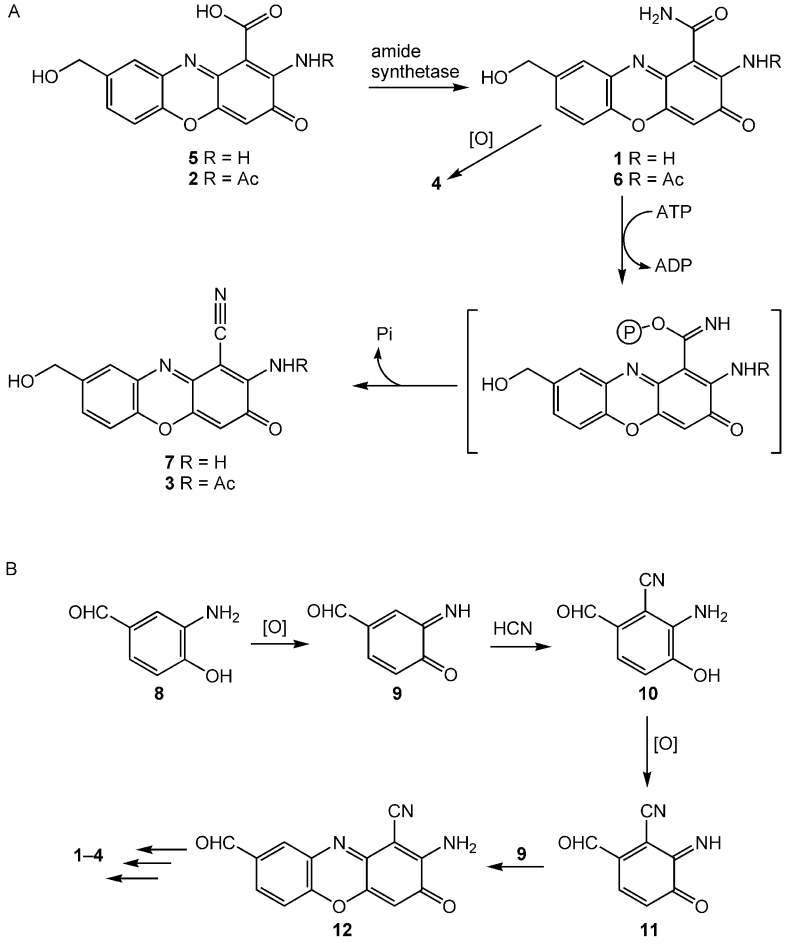
To date, a number of phenoxazinones have been reported as antibiotics from a variety of *Streptomyces* species, such as *Streptomyces thioluteus*, *Streptomyces exfoliatus*, *Streptomyces halstedii*, *Steptomyces michiganensis* and *Streptomyces* sp. WRAT-210.[12–16] Phenoxazinones frequently encountered in *S. griseus* strains include the grixazones and the elloxazinones,[11,17] all of which lack C-9 functionalization. Whereas the grixazones bear an *N*-acetylated cysteine moiety at C-1 through a thioether bond, the elloxazinones possess a carboxamide function in this position. Due to oxidative coupling of different *o*-aminophenol precursors, grixazones and elloxazinones differ in the oxidation state of their C-8 substituents, having either an aldehyde, acid or ester group in this position.[4] Notably, a nitrile-substituted phenoxazinone is fully unprecedented. Natural products featuring nitrile moieties are relatively rare in nature (ca. 120 out of >170000).[18] Among the few examples of bacterial origin are the enediyne-derived cyanosporasides, the phenazine benthocyanin C, and the macrolide borrelidin.[19–21] In saframycin A and related tetrahydroisoquinoline antibiotics the nitrile residue was shown to contribute to the potent antiproliferative activity of this class of compounds. In the presence of reduced cofactors the nitrile moiety is converted into an electrophilic iminium ion that alkylates the guanine residues of double-stranded DNA.[22] Still, the biosynthetic origin of the nitrile group in many bacterial metabolites remains elusive. For example, analysis of the saframycin gene cluster in *Streptomyces lavendulae* did not reveal any candidate gene that might be involved in nitrile formation.[23] In borrelidin biosynthesis, it was postulated that the nitrile functional group derives from enzymatic oxidation of a carbon atom, with subsequent transamination, aldoxime formation, and dehydration.[24] In analogy, the nitrile nitrogen atom of **3** could be introduced by transamination of a C-1 formyl precursor of **2** or **5**. The ensuing amine would undergo two oxidations to an *N*,*N*-

dihydroxy species, followed by successive dehydration to the nitrile. However, due to the presence of carboxylate-, amino- and nitrile-substituted congeners, two distinct biosynthetic routes for nitrile formation are more likely.

In the first scenario, an amide synthetase would convert the putative precursor 2-amino-1-carboxy-8-hydroxymethyl-3*H*-phenoxazin-3-one (**5**) into bezerramycin A (**1**). Subsequent ATP-dependent dehydration would eventually give the corresponding nitrile **7** (Scheme 1A). The *N*-acetyl derivatives **2**, **6** and **3** would result from acetyl transfer onto the adjacent amine moiety. In another conceivable pathway, nitrile incorporation would occur prior to the formation of the phenoxazinone core. After *o*-aminophenol oxidation of **8**, cyanide could be coupled through a nucleophilic addition to the resulting quinone imine **9** (Scheme 1B), paralleling the proposed incorporation of *N*-acetylcysteine in the grixazone biosynthesis.[25] Oxidation of the putative intermediate 2-amino-6-formyl-3-hydroxybenzonitrile (**10**) and subsequent condensation of the resulting **11** with another molecule of quinone imine **9** would result in the formation of 2-amino-1-cyano-8-formyl-3*H*-phenoxazin-3-one (**12**). Reduction of the formyl group and *N*-acetylation would yield bezerramycin C (**3**), and its stepwise hydrolysis would provide access to bezerramycin A and B. The first proposed biosynthetic pathway to the nitrile moiety seems to be the most plausible. In the second pathway cyanide formation is required. As cyanide production is a process rarely found in prokaryotes (except for *Pseudomonas* spp.) because of the inherent toxicity,[26] the second biosynthetic route would be less probable. Furthermore, as carboxylate- and carboxamide-substituted analogues have been reported previously,[4] an extension of the pathway to the nitrile by dehydration appears more likely. Future molecular studies may shed more light on the exact mechanisms of nitrile formation.

Finally, all compounds **1**–**4** were evaluated for their antiproliferative activities against the cell lines K-562 (human chronic myeloid cells) and HUVEC (vascular endothelium cells) as well as for their cytotoxic effects against HeLa cells (human cervix carcinoma) (Table 2).[27,28] Whereas **4** reportedly displays potent activities towards hepatocellular adenocarcinoma (Hep-G2) and human breast carcinoma (MCF-7) cells at very low concentrations ($GI_{50}$ = 3.3 and 0.02 μM, respectively),[11] we could not detect any significant bioactivity for the tumor cell lines used in our study, thus suggesting a high cell line selectivity of this compound. The bezerramycins A–C (**1**–**3**) show moderate antiproliferative activities ($GI_{50}$ = 14.5–20.0 μM) against HUVEC and weak and no activities against K-562 cells ($GI_{50}$ > 49.0 μM). Weak or no cytotoxicity (HeLa cells) was observed for the tested compounds.




Scheme 1. Hypothetical pathways for the generation of the nitrile moiety in bezerramycin C.

Table 2. Antiproliferative ($GI_{50}$) and cytotoxic ($CC_{50}$) activities (in μM) of bezerramycins A–C (**1**–**3**) and elloxazinone B (**4**).

| Compound | K-562 ($GI_{50}$) | HUVEC ($GI_{50}$) | HeLa ($CC_{50}$) |
|---|---|---|---|
| **1** | >175.4 | 20.0 | >175.4 |
| **2** | 49.0 | 14.9 | 118.5 |
| **3** | >161.8 | 14.5 | >161.8 |
| **4** | 131.7 | >167.2 | >167.2 |

## Conclusions

Natural phenoxazinones containing a tricyclic iminoquinone system have been isolated from various microorganisms, especially from a variety of *Streptomyces* species. The iminoquinone moiety is an important structural characteristic of several antineoplastic drugs and plays a significant role in the nucleus of actinomycins, which target DNA as intercalating agents.[6] In the course of this study, we have isolated and identified three novel phenoxazinones named bezerramycins A–C (**1**–**3**) from *Streptomyces griseus* together with the known elloxazinone B (**4**). The new bezerramycins primarily differ in their carboxy, carboxamide and nitrile substituents at C-1. To the best of our knowledge, this is the first report of a nitrile-substituted phenoxazinone metabolite. The cooccurence of carboxy-, carboxamide- and nitrile-substituted congeners is intriguing as it implies a biogenetic relationship. According to their structures, the most plausible route to the nitrile moiety in bezerramycin C would involve an amide synthetase, ATP-dependent dehydration with subsequent acetylation. The novel bezerramycins A–C display significant antiproliferative activities against HUVEC cells and weak or no cytotoxicity against HeLa cells.

**Supporting Information** (see footnote on the first page of this article): All experimental details and NMR spectra of bezerramycins.

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