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γ-Pyrone natural products—A privileged compound class provided by nature

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ABSTRACT

In "Biology Oriented Synthesis" (BIOS), the inherent biological relevance of natural products is employed for the design and synthesis of compound libraries. Towards this end, library generation in BIOS is focused on compound classes from biologically relevant space such as the natural product space or also the drug space and only scaffolds of these areas of proven relevance are employed for synthesis of small focused libraries with limited diversity. We here present a short overview of γ-pyrone natural products, highlighting their biological properties and their potential applicability in a BIOS of a compound library.
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1. Introduction

Natural products have influenced the development of chemical treatments of diseases or other pathological misconditions since ancient times and are still one of the major driving forces behind the invention of novel pharmaceuticals.[1] Their importance for modern drug discovery stems from their inherent biological relevance which Nature has encoded in their molecular structures. Consequently, their systematic study has stimulated the scientific progress in various disciplines such as chemistry, pharmacology, biology or even medicine.

Historically, several phases of natural product based drug discovery can be differentiated: in the beginning, due to an only limited understanding of the molecular principles of drug action, natural products were mainly applied as they were found in nature, either directly within herbal preparations or after isolation from the producing organism. Consequently, most scientific and also industrial investigations were devoted to the establishment of efficient routes towards purification or to a much lesser extent towards synthesis of these biologically active entities and their formulation into drugs. Later on, with the progress in the life sciences, the focus of medicinal chemistry research turned towards the synthesis of structural analogs of natural products, aiming at improving key factors of drug action such as pharmacokinetics, potency or toxicity.

With the implementation of high-throughput (HTS) and phenotypic screens in pharmaceutical chemistry, which came along with a change of the workflow of drug discovery, a need for proper compound libraries arose.[2] First, unbiased combinatorial compound libraries were generated, driven by the huge advancement in parallel synthesis and subjected to screens. However, already shortly after the extensive implementation of the necessary infrastructure in industrial and academic research, it became clear that this approach suffers from the enormous range of chemical compounds comprising 'chemical space' that in principle can be covered by chemical synthesis.[3] Consequently, different concepts for identifying such regions of chemical space which should provide biologically active compounds have evolved.[4] We have recently introduced an approach that we have termed as 'biology oriented synthesis' (BIOS).[5] In BIOS, the inherent biological relevance of natural products is employed for the design and synthesis of compound libraries based on natural product scaffolds. It, therefore, combines the successful approach of using natural products as starting points for drug design[6] with the generation of compound libraries for chemical biology and medicinal chemistry research.

2. Biology oriented synthesis (BIOS)

In principle, a vast number of chemical compounds can be generated by parallel synthesis. Consequently, a concept which would allow a preselection of scaffolds before synthesis of such structures that would yield libraries with a relatively high fraction of biologically active compounds would be advantageous. Several different approaches towards this aim such as diversity-oriented synthesis (DOS)[7] or computer-based methods[8] have been described before.

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We have recently proposed biology oriented synthesis (BIOS) as an alternative approach to this problem which is based on natural products as a source of inspiration for library synthesis.[5] Natural products represent defined chemical entities within chemical space and often are biologically active. Nevertheless, only a small fraction of the vast chemical space has been surveyed by nature on its venture for low molecular weight natural products with such biological activity. Interestingly, the same observation proves true for the protein targets of natural products. During evolution, again only a limited fraction of all possible amino acid combinations have been probed by nature. This is even more apparent if the three-dimensional folds of proteins are considered which are even stronger conserved during evolution. Consequently, both the natural product space as well as the protein structure space exploited by nature are limited in size and are highly conserved. High affinity-binding between proteins and ligands relies on a complementary interaction. This implies that also the structure space of proteins and of their ligands has to be highly complementary. Although the chemical space filled out by natural products does not represent the only region compatible with the protein structure space, the number and size of such regions in chemical space should be limited. Thus, the natural product space is enriched with bioactive structures and includes therefore promising starting points for the development of novel bioactive small molecules.

Consequently, library generation in BIOS is focused on compound classes from biologically relevant space such as the natural product space or also the drug space and only scaffolds of these areas of proven relevance are employed for synthesis of small focused libraries with limited diversity (see Fig. 1). Successful examples of the feasibility of this concept have already been reported by us in the literature.[9] BIOS thereby bases on and extends two previously proposed concepts, that is, on the one hand a 'structural classification of natural products' (SCONP) which arranges and correlates the scaffolds of natural products in a hierarchical manner,[10a] on the other hand in 'protein structure similarity clustering' (PSSC), clusters of proteins with structurally similar ligand sensing cores are created by bio- and cheminformatic methods.[10b] If a ligand for one member of the cluster is already known, the scaffold of this ligand can be expected to be a prevalidated starting point for the library synthesis of ligands of the other members of the cluster.

Consequently, BIOS requires a thorough analysis of diverse natural product classes in order to identify those scaffolds most worthwhile for compound collection synthesis that is natural product classes with as much as possible diverse biological activities. We therefore wish to present a summary of the biological activities of a selected number of γ-pyrone natural products, highlighting them as a promising scaffold for BIOS based library synthesis.

However, to obtain a more reliable analysis, we have included only those γ-pyrone natural products in which at least one member displays some kind of biochemical activity, such as enzyme inhibition. We have omitted those classes, for which only phenotypic data is available as phenotypic effects can be generated by a multitude of actions which hampers analysis.

3. γ-Pyrone based natural products

γ-Pyrone based natural products constitute a large class of biologically active compounds and are found in all three kingdoms of life. Since the first isolation of the structurally rather simple γ-pyrone poppy acid from *Papaver somniferum* by F.W. Sertürner in 1805,[11] numerous additional γ-pyrone natural products were isolated. Most of these were derived from marine organisms in which they seem to play an important role as allomones or defense compounds. Consequently, up to date, most biological studies with γ-pyrones have been devoted towards their biological function in a marine ecosystem. Nevertheless, also several studies of their biochemical activity on certain cellular proteins have already been performed and are the basis of the present discussion for which we have summarized several γ-pyrone natural product classes. This however implies that only a subfraction of the fascinating γ-pyrone natural product chemistry is presented. For a broader presentation, the interested reader is referred to previously published reviews. Unfortunately, no general review covering all aspects of γ-pyrone based natural products has yet been published, nevertheless certain features of either the chemistry or biology of γ-pyrones were already summarized before.[12]

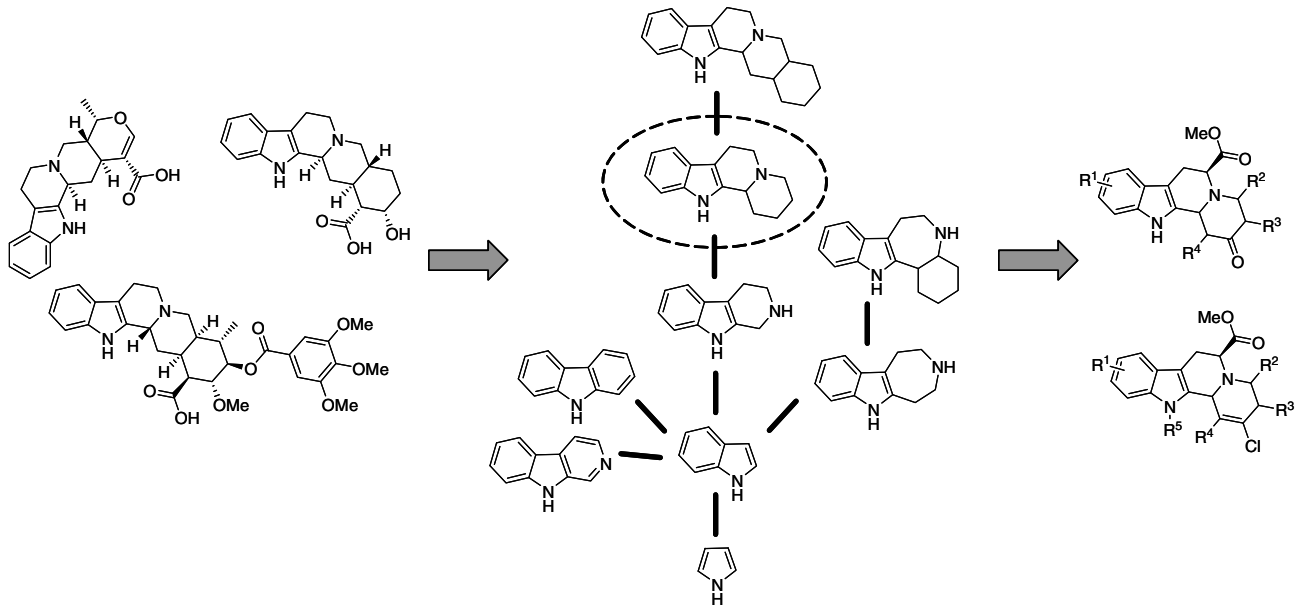


Figure 1. Schematic workflow of biology oriented synthesis (BIOS). Natural product classes are analyzed for their diverse biological activities, resulting in the identification of suitable natural product scaffolds. Additional guidance to this selection step can be provided by the structural classification of natural products (SCONP). Focused library synthesis of such identified scaffolds then generates a BIOS-based compound library.

To highlight the diverse biological activities of γ-pyrone natural products which can even be found within a subfamily, we have summarized all structurally related members of three major γ-pyrone natural product families, that is, the colletotrichins, the nitrophenyl pyrones and the actinopyrones.

4. Colletotrichins

Acetylcolletotrichin (**1**) was isolated in 1966 as the first member of the colletotrichin family from green plants infected by the plant pathogenic fungus *Colletotrichum capsici*.[13] However, acetylcolletotrichin was renamed to colletotrichin A in 1979 after a reisolation from the same biomaterial.[14] Additionally, colletotrichin A was also isolated together with the analogs colletotrichin B (**2**) and C (**3**) from the plant pathogenic fungus *Colletotrichum nicotianae* and were identified as the disease causing agents as application to tobacco leaves caused the same disease symptoms as those from the fungus.[15]

All colletotrichins feature a γ-pyrone moiety fused to a diversely substituted decaline residue (see Fig. 2). Their biosynthesis was exemplarily studied with colletotrichin A, using ^{13}C NMR and ^{13}C-labeled precursors.[16] Besides their role in plant pathology, colletotrichin A was also tested in several bioassays, revealing a pronounced toxicity. For example, an LD_{50} of 16 mg/kg was determined for its intraperitoneal injection into rats.[13] Additionally, colletotrichin A was found as an inhibitor mitochondrial respiration[17] and caused rapid membrane damage to plant cells.[18]

Several years later, the structurally related compounds candelalide A (**4**), B (**5**) and C (**6**) were isolated by a Merck research group from the fermentation broths of *Sesquicillium candelabrum*. These γ-pyrones were recognized as potent blockers of the voltage-gated potassium channel Kv1.3 which represents a promising target for suppressing activation and proliferation of T cells. Using ^{86}Rb efflux experiments in CHO-Kv1.3 cells, IC_{50} values of 3.7, 1.2 and 2.5 μM for candelide A, B and C, respectively, were determined.[19]

The same group also isolated nalanthalide (**7**) from *Nalanthamala sp.*, MF 5638 or *Chaunopycnis alba*, MF 6799. Nalanthalide (**7**) is also an antagonist of the Kv1.3 channel (IC_{50} of 3.9 μM).[20] Moreover, electrophysiological measurements revealed a depolarization of human T-cells with an EC_{50} of 500 nM after nalanthalide application.[20b]

Structurally similar to nalanthalide is colletochin (**8**), which was isolated from *Colletotrichum nicotinae* and which might be a biosynthetic precursor to the colletotrichins.[21]

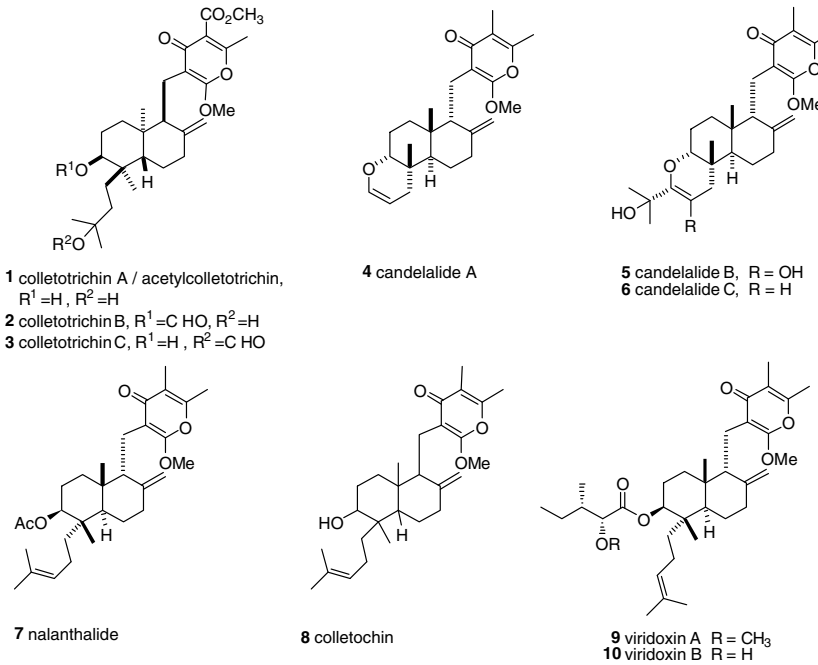
The fungus *Metarhizium flavoviride* produces Viridoxin A (**9**) and B (**10**) which display potent insecticidal toxicity with LC_{50}s of 39.7 ppm and 50.7 ppm, respectively, versus Colorado potato beetles (*Leptinotarsa decemlineata*, *Coleoptera*). Hydrolysis of viridoxins generates colletochin (**8**) which interestingly did not show any insecticidal toxicity even at a dosage of 1000 ppm indicating a crucial role of the α-hydroxy moiety for biological activity.[22]

Due to their interesting biological activities, also synthesis of (−)-candelide A and (−)-nalanthalide were reported.[23]

5. Nitrophenyl pyrones

All members of this γ-pyrone natural product class are produced by *Streptomyces* strains. As the name indicates, almost all member features beside the obligate γ-pyrone residue a nitrophenyl moiety. However, usually also two additional γ-pyrones lacking the nitrophenyl moiety, that is, aureothamine (**12**) and aureonitrile (**13**), are also categorized in this category due to their structural similarity and analogous biosynthesis. Besides the γ-pyrone and nitrophenyl moieties, several members also embody a furan ring attached to the γ-pyrone core motif (see Fig. 3).

Aureothin (**11**) is the most famous member of this γ-pyrone natural product subclass and was isolated from *Streptomyces thioluteus*[24] after re-investigating a previous isolation of aureothricin in 1949 from Umezawa et al.[25] In 1976, it was shown that the previously known antibiotic mycolutein which was isolated from the bacterial culture MA-2465 was identical to aureothin.[26] Moreover, it was isolated from *Streptomyces luteoreticuli* in which also its biosynthesis was studied.[27] Furthermore, key enzymes of the late stages of biosynthesis have been cloned and analyzed.[28] Aureothin was evaluated in various biological assays and exhibited antitumor, antifungal, insecticidal, and complex I inhibiting properties



1 colletotrichin A / acetylcolletotrichin, R^1 =H , R^2 =H
2 colletotrichin B, R^1 =C HO, R^2 =H
3 colletotrichin C, R^1 =H , R^2 =C HO

4 candelalide A

5 candelalide B, R = OH
6 candelalide C, R = H

7 nalanthalide

8 colletochin

9 viridoxin A R = CH_3
10 viridoxin B R = H

Figure 2. Chemical structures and producing organism of colletotrichins.

and most strikingly a very potent anti-*Heliobacter pylori* activity.[24,26,29]

The closely related analog *N*-acetyl aureothamine (**12**) is produced by *Streptomyces netropsis* and displayed potent and selective anti-*Heliobacter pylori* activity and cytotoxicity (5.0 μg/mL) in HeLa cells.[29c]

The structurally very similar derivative aureonitrile (**13**) is not a natural product in its original sense but was obtained by mutasynthesis of the aureothin biosynthesis cluster. Importantly, this derivative showed an enhanced cytostatic effect in comparison to the parent compound aureothin.[30]

Spectinabilin (**14**) also known as neoaureothin was isolated from *Streptomyces spectabilis* and *orinoci*.[31] Biomimetic synthesis studies with Spectinabilin[32] and fermentation studies with *Streptomyces orinoco* suggest that spectinabilin represents the biosynthetic precursor of SNF-4435C (**18**) and D (**19**) to which it is transformed non-enzymatically by photochemical reactions.[33] Spectinabilin displays potent inhibition of NADH fumarate reductase (NFRD) with an IC_{50} value of 15 nM.[34]

Luteothin (**15**) was isolated as one of the metabolites of *Streptomyces luteoreticuli*. No further characterization or determination of biological activities was disclosed.[35,24b]

Orinocin (**16**) has been isolated from *Streptomyces orinoci* in which also its biosynthesis was studied. Interestingly, it seems that this nitrophenyl γ-pyrone is also biosynthetically derived from spectinabilin (**14**) by an unusual excision of three propionate units.[33]

Recently, a new auroeothin derivative named alloaureothin (**17**) was isolated from Streptomyces sp. MM23, exhibiting a growth inhibitory effect against human fibrosarcoma HT1080 cells with an IC_{50} of 30 μM.[36]

The structurally unique natural products SNF4435C (**18**) and D (**19**) were isolated from the culture broth of *Streptomyces spectabilis*[37] and are biosynthetically derived from spectinabilin (**14**).[32,33] Both compounds demonstrated potent immunosuppressive activity in vitro and selectively suppressed B-cell proliferation versus T-cell proliferation with IC_{50} values of 0.8 μM for **18** and 0.2 μM for **19**, respectively.[37a] Additionally, these compounds also revert multidrug resistance in tumor cells, turning them into interesting candidates for the development of anticancer compounds.[38]

As a consequence of their various biological activities, extensive synthetic studies of members of this compound class have been undertaken. Up to date, syntheses of aureothin (**11**),[39,32c] *N*-acetylaureothamine (**12**),[32c,39b,39c] spectinabilin (**14**),[32] aureonitrile (**15**),[39c] orinocin (**16**),[33] and SNF4435C (**18**) and D (**19**)[32] have been reported.

6. Actinopyrones

The group of Yano isolated the physiologically active substances actinopyrone A (**20**), B (**21**) and C (**22**) in 1986 from *Streptomyces pactum* and elucidated their coronary vasodilating and microbial activity (see Fig. 4).[40] In a later study, an additional very potent anti-*Helicobacter pylori* activity with a MIC value of 0.0001 μg/mL was determined.[29d]

A structurally related compound is kalkipyrone (**22**) which differs from actinopyrone B (**21**) only by its slightly shortened alkyl side chain. It was isolated from the marine cyanobacteria *Lyngbya*

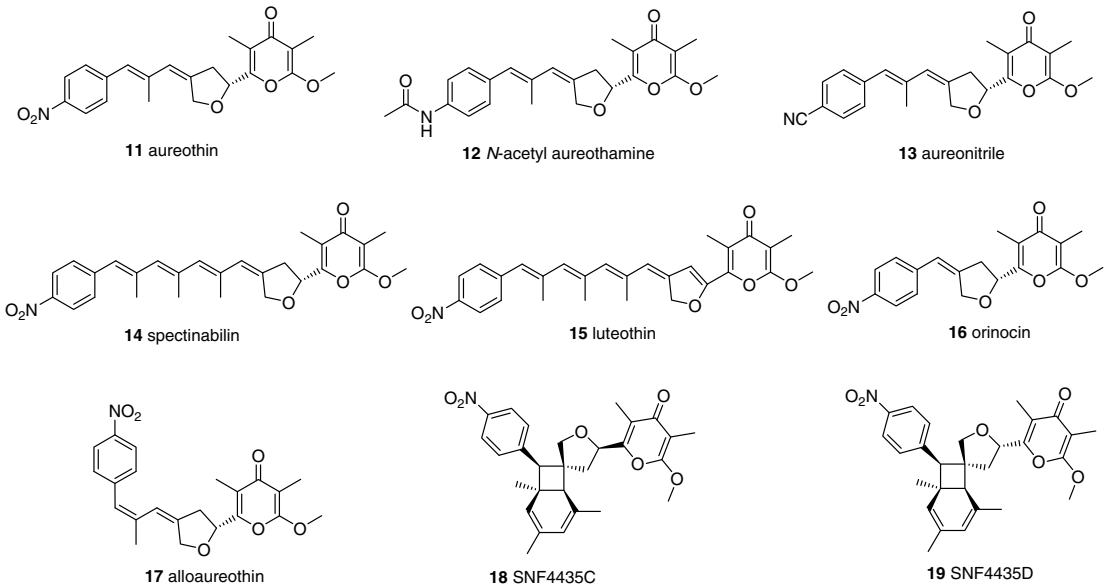


Figure 3. Chemical structures of the nitrophenyl γ-pyrone family.

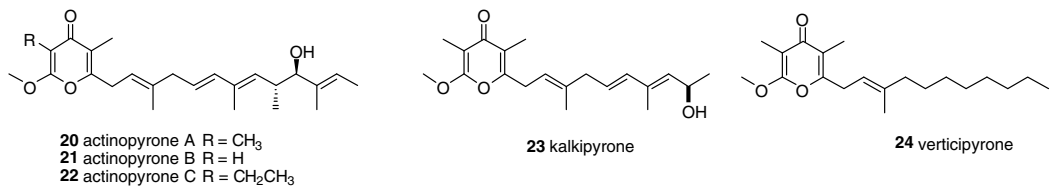


Figure 4. Chemical structures of the actinopyrone γ-pyrone family.

majuscule and *Tolypothrix sp* and displayed potent toxicity in the brine shrimp assay (LD_{50} 1 μg/mL) and ichthyotoxicity to goldfish (LD_{50} 2 μg/mL). and was also tested against NCI's 60 human tumor cell lines, but only modest inhibitory effects against several renal and melanoma cell lines were observed.[41]

Verticipyrone (**23**) was isolated from the fermentation broth of the fungal strain *Verticillium sp*. and inhibits NADH-fumarate reductase (NFRD) of *Ascaris suum* with an IC_{50} of 4.1 nM and also shows selective of complex I from helminth mitochondria. Furthermore, **25** showed anthelmintic activity against *Caenorhabditis elegans* and *Artemia salina*, suggesting its use as an antiparasitic agent.[34]

Due to their important biological activities, also total synthesis of these natural products has been reported. A first total synthesis of actinopyrone A appeared in 2006, allowing the correct assignment of its stereocenters.[42] Additionally, a total synthesis and also biological evaluation of close analogs of verticipyrone was published in 2007.[43] Moreover, this study also allowed the identification of an analog which inhibited NADH-fumarate reductase from *Ascariis suum* with an IC_{50} of 0.30 nM.

7. Conclusions

The present summary of γ-pyrone natural products highlights their potent and manifold biological activities, rendering them to interesting targets for total synthesis but especially for biology oriented synthesis (BIOS). Therefore, the generation of a library of γ-pyrones generated under the BIOS principle is highly desirable and is currently pursued in our laboratory. It will be interesting to validate their potential in various biological screens, aiming at finding new targets for this important natural product class.

Note added in proof

The group of John Boukouvalas has recently reported that the structure of ottensinin was originally misassigned. Instead, they showed that ottensin is built up of a g-pyrone moiety attached to a decalin system, thereby adding a new member to the colletotrichin group.[44]

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