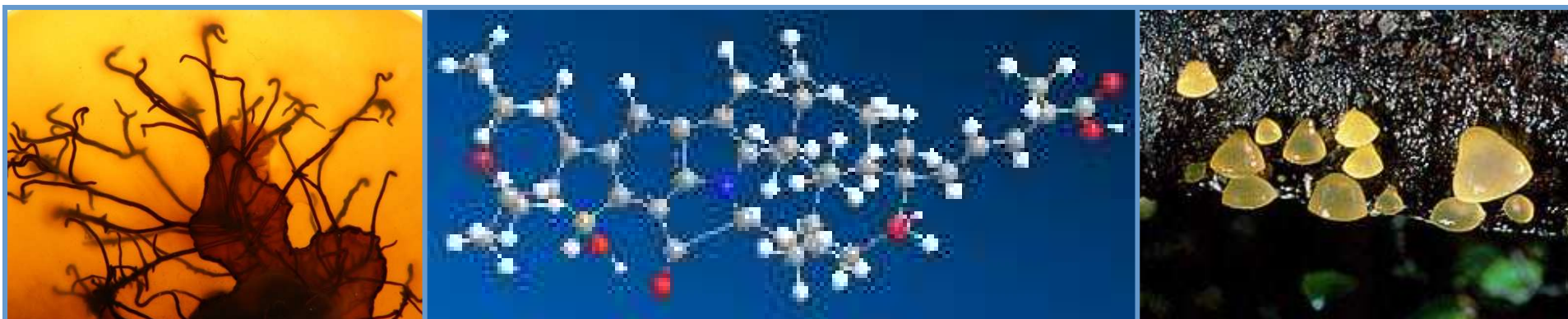


Bioactive secondary metabolites from fungi with special emphasis on anti-infectives



**Plenary talk, HRH-Hub conference, Ogbomosho, Nigeria,
29 Oct. 2025**

Marc Stadler, Dept. Microbial Drugs, HZI Braunschweig, Germany;
marc.stadler@helmholtz-hzi.de

HZI **HELMHOLTZ**
Centre for Infection Research

Strong competition in tropical rainforests

Amauroderma sp.
(Basidiomycota, Ganodermataceae)

Squamotubera leratii
(Ascomycota, Xylariaceae)

Image by Thomas Læssøe (Khao Yai NP, Thailand, 2007)

Fungal metabolites as drugs & pesticides

Pharma indications

- **Antibacterial** (**Penicillins, Cephalosporins**) & **antimycotic** (**Caspofungin, Micafungin**) antibiotics A
- **Immunosuppressive** agents (e.g. **Cyclosporin, Mycophenolic acid**) A
- **CNS-active** drugs (e.g. **Ergotamine**) A
- **Cardiovascular** drugs (e.g. cholesterin-lowering **Statins**) A

Agro indications

- **Fungicides** (e.g. **Strobilurins**) B
- **Antiparasitic** agents (e.g. **emodepsin**) A

Fungal metabolites continue to be of great value as lead structures for development of new drugs & pesticides

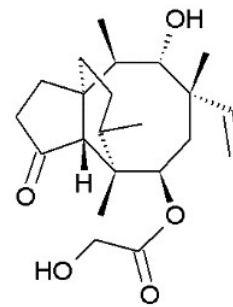
A: From Ascomycota

B: From Basidiomycota

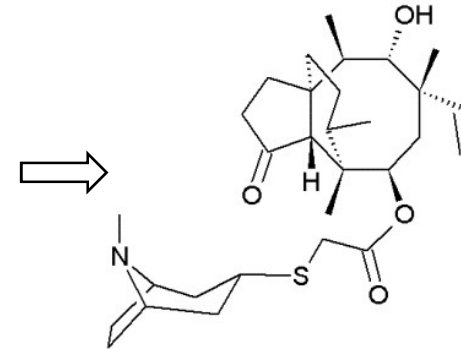
A „novel“ class of antibiotics



Clitopilus prunulus (Entolomataceae)



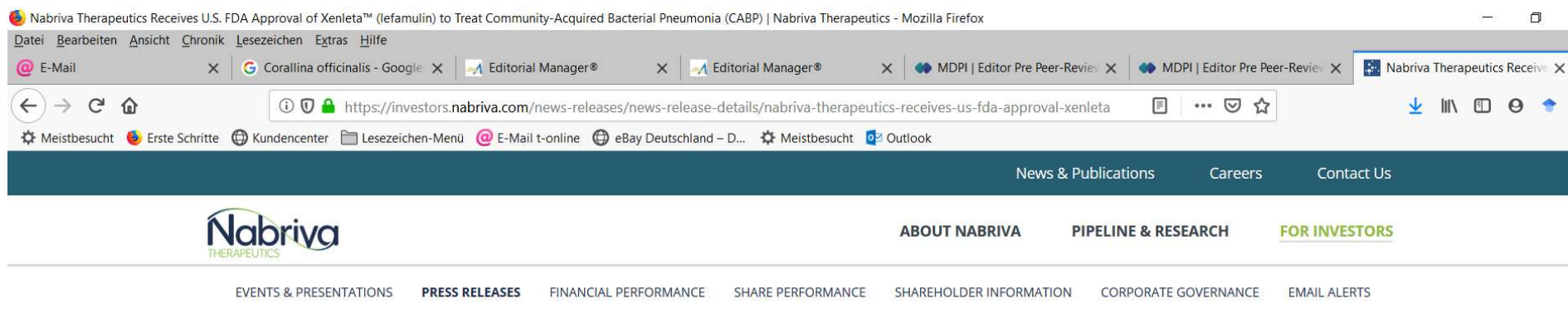
Pleuromutilin



Retapamulin (Altabax®/Altargo®)
(semisynthetic derivative
of pleuromutilin)

- ❑ First discovered from cultures of „**Pleurotus**“ spp. in 1951
- ❑ **Chemotaxonomic marker metabolite** for the genus **Clitopilus**!
- ❑ Highly efficient against Gram-positive bacteria (inhibitor of protein synthesis)
- ❑ Only In 2007, Retapamulin was approved for treatment of skin infections (further derivatives are in development)

First systemic pleuromutilin type antibiotic was approved by the US FDA in August of 2019 !

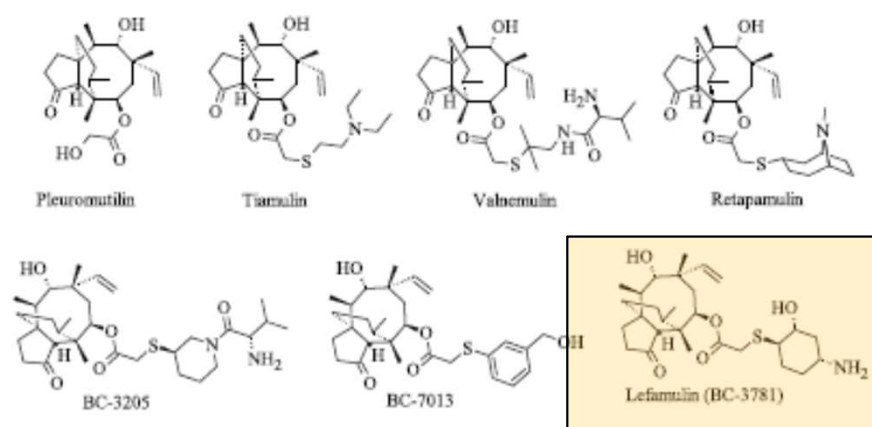


Nabriva Therapeutics Receives U.S. FDA Approval of Xenleta™ (lefamulin) to Treat Community-Acquired Bacterial Pneumonia (CABP)

560

Fungal Diversity (2022) 116:547–614

Fig. 8 Chemical structures of pleuromutilin and its derivatives



reatment Option for Adult Patients with CABP

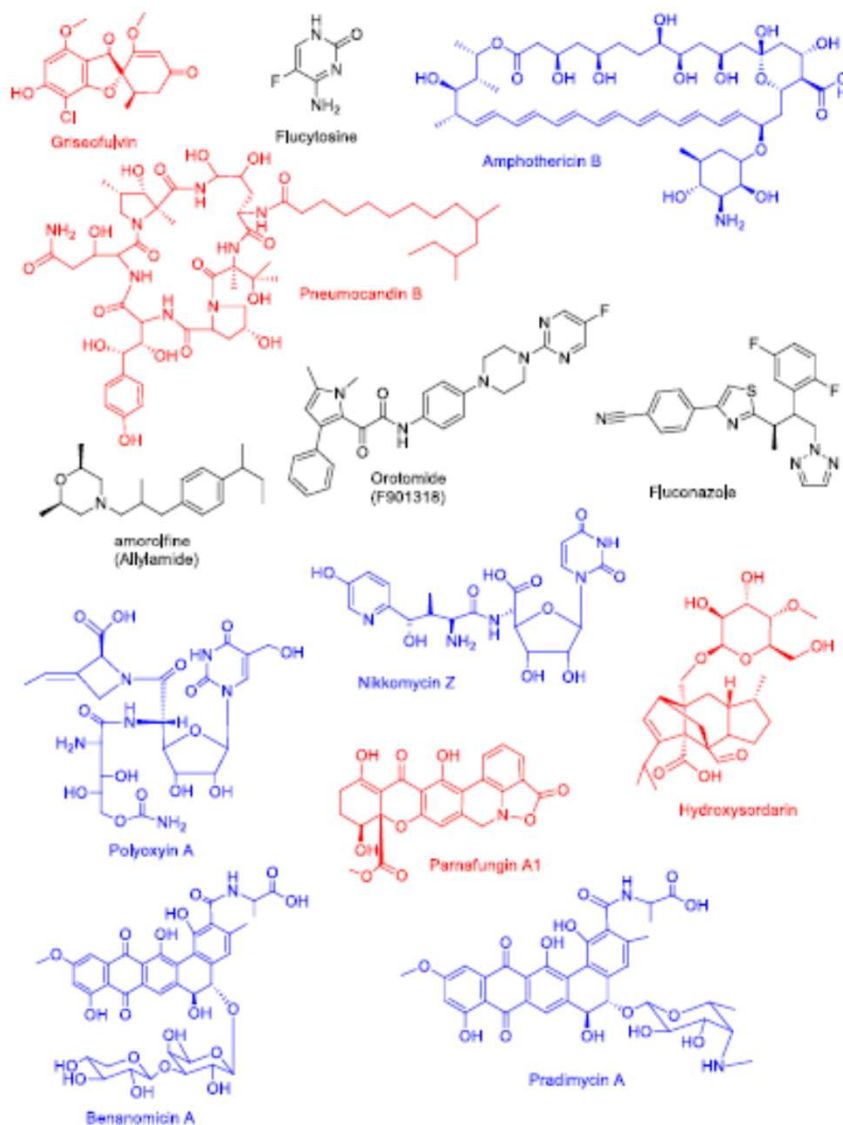


Antimycotic agents on the market/ under development

556

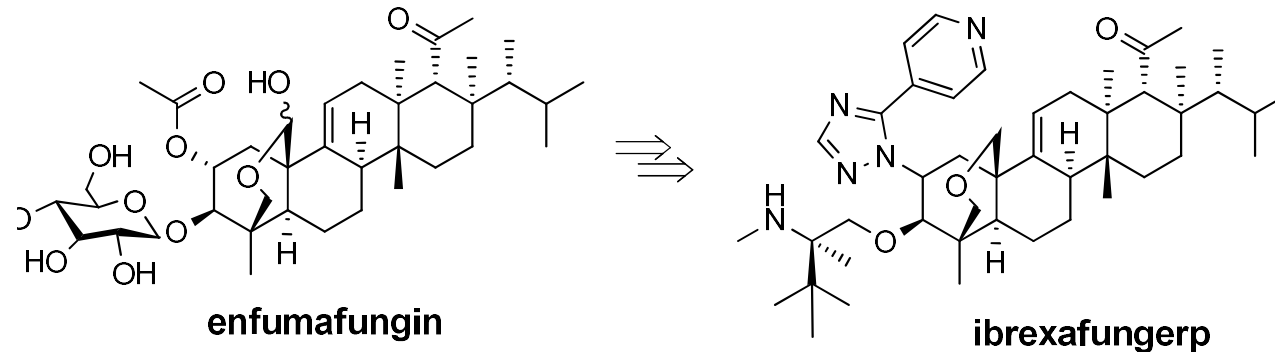
Fungal Diversity (2022) 116:547–614

Fig. 5 Antimycotic agents approved or under development for treatment of fungal infections. Fungal metabolites are printed in red and metabolites from Actinobacteria are printed in blue; the others are of synthetic origin



Many of them are derived from bacteria or fungi (as in case of the antibacterials)

Ibrexafungerp, a semisynthetic enfumafungin



- First newly FDA-approved antimycotic in ages
- (1,3)- β -D-glucan synthase inhibitor
- Indications: e.g. invasive candidiasis, invasive aspergillosis

First drug ever approved that is derived from a fungal endopyhte!

Impressions from field work in Thailand



Post IMC10 Foray, Mushroom Research Centre, Chiang Mai Prov., Thailand (2014)

New pleurotins from *Hohenbuehelia grisea*



H. grisea (Thailand)



Birthe Sandargo



Benjarong Thongbai



Frank Surup

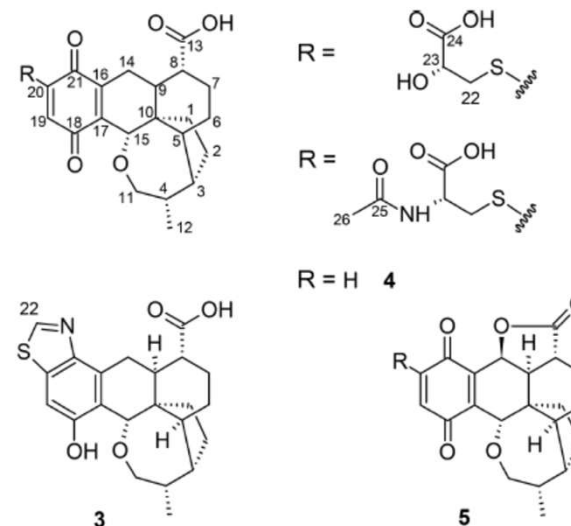





Figure 1. Structures of new compounds thiopleurotinic acid A (1), thiopleurotinic acid B (2), and pleurothiazole (3) and parental metabolites dihydropleurotinic acid (4) and pleurotin (5).

Article

Antiviral 4-Hydroxypleurogrisein and Antimicrobial Pleurotin Derivatives from Cultures of the Nematophagous Basidiomycete *Hohenbuehelia grisea*

Birthe Sandargo ^{1,2}, Benjarong Thongbai ^{1,2}, Dimas Praditya ^{3,4} , Eike Steinmann ^{3,5}, Marc Stadler ^{1,2,*}  and Frank Surup ^{1,2,*} 

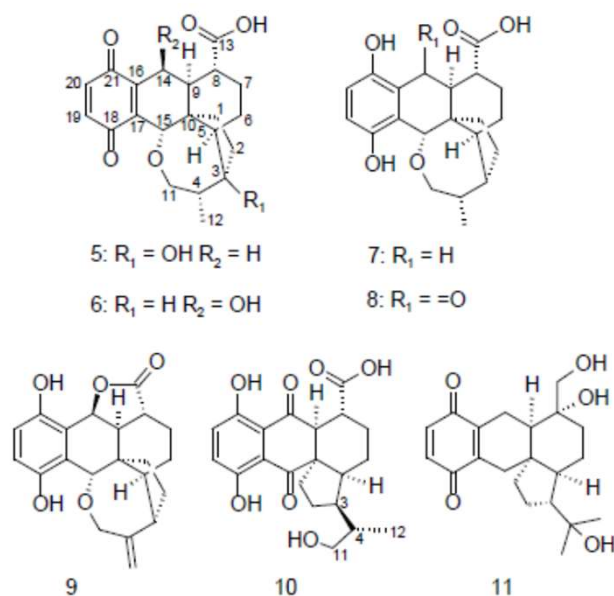
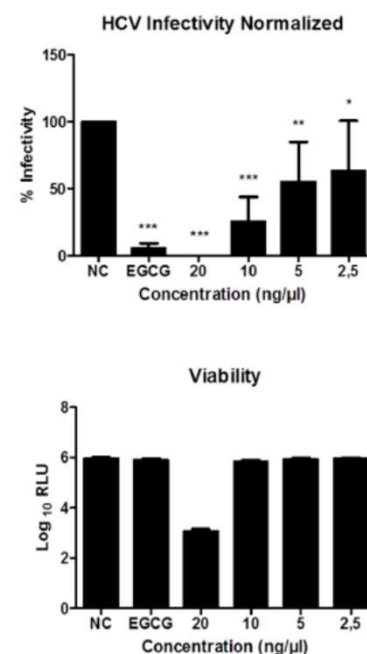


Figure 2. Chemical structures of newly isolated compounds 5–11.



Impressions from field work in Kakamega, Kenya (Sept. 2014)



Expedition in the course of a project funded by AvH and ERAFRICA, 2014-2018

Mycology

→ Novel producer strains



Collection
of fungi



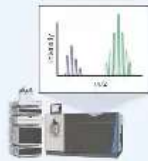
Isolation &
identification
of strains



Cultivation &
extraction

NP Chemistry

→ Novel natural products



Screening



Isolation of
compounds



Identification
of novel
compounds

Biotests

→ Novel antiinfectives



MIC



Nematode



Cytotoxic



Neurotrophic



Biofilm



Topo I

Microbiology

→ HZI strain collection



Deposition of
new strains



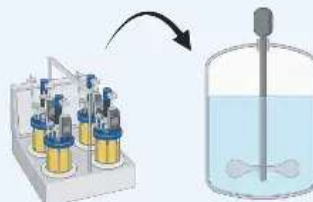
Storage



Strain & cell bank
supply

Biotechnology

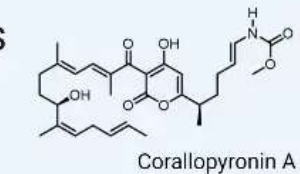
→ production of antiinfective candidates



USP development,
optimization & scale up



DSP development,
optimization & scale up



Multigramm production of
drug substance

New biotechnology platform at HZI (operative since 2021)

Upstream Processing Equipment



Shake flask cultivations

- RAMOS (50 mL; 200 mL)
- Transfer from shake flask to bioreactor
- Media development



Multifermenter

- DASGIP (1.5 L)
- Process development in laboratory scale



Stainless steel bioreactors

- Six vessels (10 L)
- Process implementation
- Optimization for technical scale



Pilot scale bioreactors

- 4 x 150 L; 2 x 350 L
- Material supply for e.g. preclinical studies
- Process transfer to CRO's

Downstream Processing Equipment



Biomass separation

- Tube centrifuge
- Filtration



Extraction

- Fluidized bed
- Liquid-liquid



Concentration

- Rotary evaporator
- High vacuum



Product separation

- MPLC
- Preparative HPLC

Only facility in European academia that can handle production of 100 g scale amounts of pure natural products

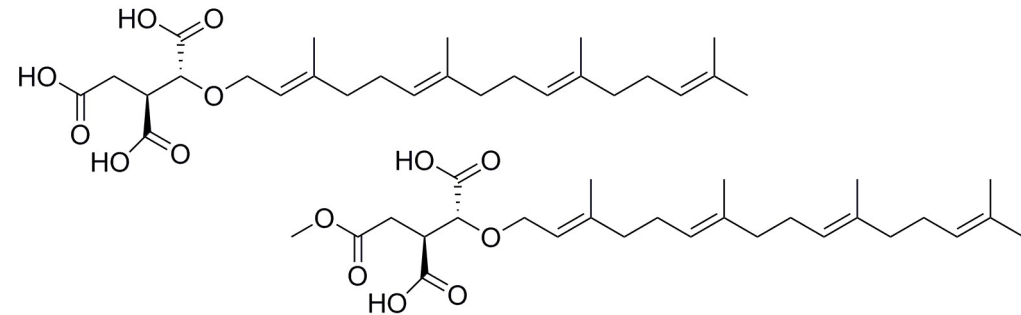
First compound that can destroy pre-formed biofilm in *Candida albicans*



***Microporus* sp.**
(new species, Kakamega, Kenia)



Clara Chepkirui



Microporenic Acids A and B

Antibiofilm Activity (*S. aureus* & *C. albicans*)

Organism	Biofilm inhibition %	Preformed biofilm inhibition
<i>S. aureus</i>	86% (256 $\mu\text{g mL}^{-1}$)	49% (256 $\mu\text{g mL}^{-1}$)
	54% (64 $\mu\text{g mL}^{-1}$)	37% (128 $\mu\text{g mL}^{-1}$)
	28% (16 $\mu\text{g mL}^{-1}$)	1.5% (64 $\mu\text{g mL}^{-1}$)
<i>C. albicans</i>	-	72% (16 $\mu\text{g mL}^{-1}$)
		52% (8 $\mu\text{g mL}^{-1}$)

Metabolites of the “Orange Pingpong Bat Fungus”



01737964 © Adrian Davies / naturepl.com

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The future's orange in woodlands as 'ping pong bat' mushrooms could threaten native species

Brightly coloured invader that may have arrived on breeze from Spain among new species thriving in UK, possibly because of climate change

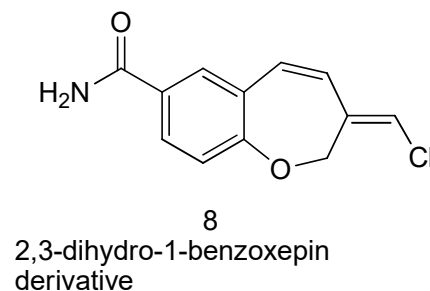
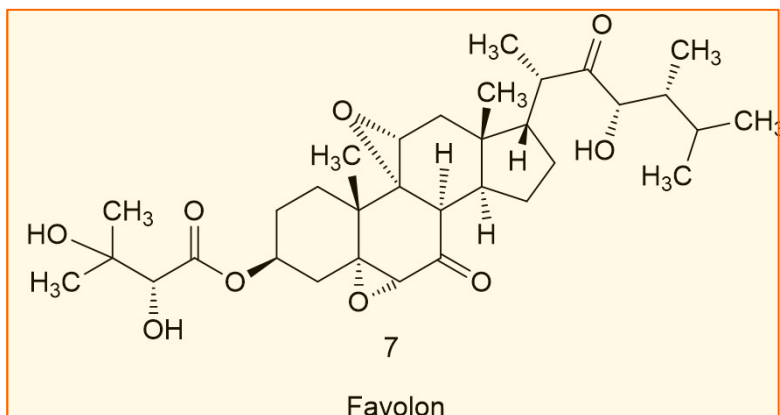


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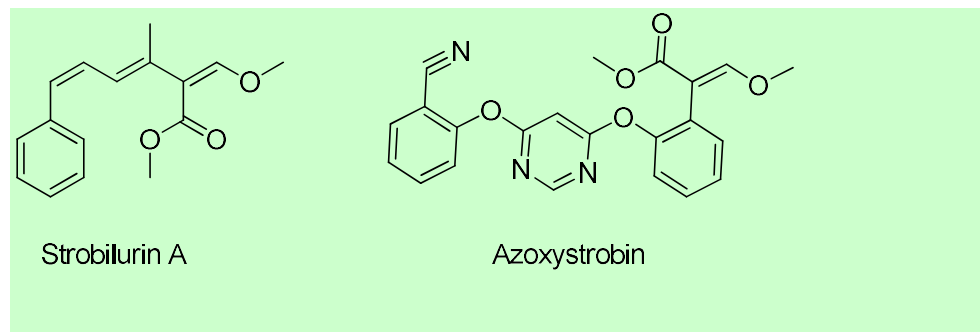
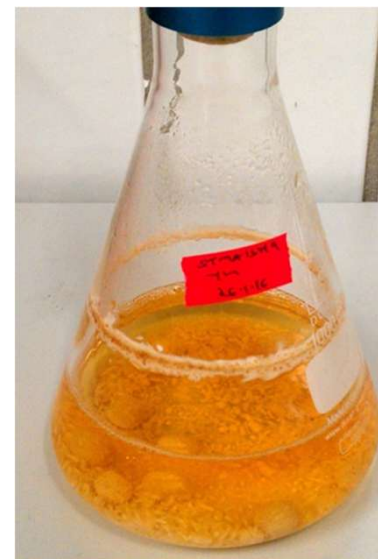
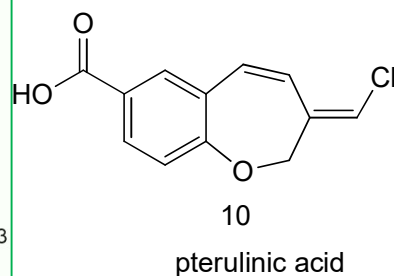
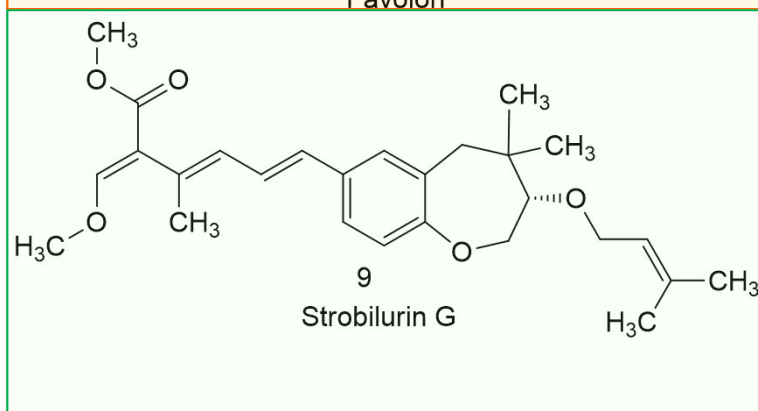


Favolaschia calocera, known as the ping pong bat fungus, was first discovered in the UK in 2012 and has been spreading

Metabolites of the “Orange Pingpong Bat Fungus”



Clara Chepkirui



Favolone – promising lead for a new antimycotic agent?

Compounds	Antifungal activity MIC (µg/ml)		Cytotoxicity-L929 IC ₅₀ (µg/mL)	
	<i>Candida tenuis</i> - MUCL29892	<i>Mucor plumbeus</i> - MUCL49355	Mouse fibroblast- L929	HeLa- (KB3.1)
1	≤ 9.37	≤ 18.75	15.00	5.50
2	≤ 4.68	≤ 9.37	18.00	6.00
3	≤ 4.68	≤ 9.37	0.28	0.51
4	≤ 4.68	≤ 9.37	1.10	5.50
Favolone	≤ 2.34	≤ 2.34	-	-
Nystatin ^c	≤ 2.34	≤ 4.68	-	-
Epothilone B ^c	-	-	-	0.00022
Epothilone A ^c	-	-	0.0038	-
Methanol ^c	-	-	-	-

1-4: New Strobilurins

[a] No antibacterial activities were observed for all the compounds against *E. coli* (DSM498) and *B. subtilis* (DSM10) at concentration ≥ 300µg/mL.

[b] Nystatin- antifungal reference. Epothilone A and B cytotoxicity test references. Methanol- negative control, - no activity.

Table 1. Antifungal activity of favolon in the agar diffusion assay.

Organism	Diameter of inhibition zone (mm)		
	µg/disc*		
	0.1	1	10
<i>Absidia glauca</i> (+)	—	—	—
<i>A. glauca</i> (—)	—	—	—
<i>Alternaria porri</i>	19i	23i	26i
<i>Aspergillus ochraceus</i>	11i	19i	20i
<i>Botrytis cinerea</i>	16i	20i	26i
<i>Cladosporium cladosporioides</i>	16i	22i	26i
<i>Epicoccum purpurascens</i>	—	15i	19i
<i>Fusarium fujikuroi</i>	19i	22i	22i
<i>Fusarium oxysporum</i>	15	25	25
<i>Mucor miehei</i>	24	30	30
<i>Nematospora coryli</i>	—	—	—
<i>Neurospora crassa</i>	+	+	+
<i>Paecilomyces varioti</i>	20	30	30
<i>Penicillium islandicum</i>	25	34	34
<i>P. notatum</i>	12	23	25
<i>Pythium ultimum</i>	+	+	+
<i>Rhodotorula glutinis</i>	—	—	—
<i>Saccharomyces cerevisiae</i> is 1**	—	—	—
<i>Ustilago nuda</i>	—	9	11
<i>Zygorhynchus moelleri</i>	15i	22i	25i

—: no inhibition zone, +: inhibition zone just visible,
*: diameter = 6 mm, **: Gift of Prof. LACROUTE, STRASBOURG,
F, i: inhibition incomplete.

Data from Anke et al. (J. Antibiotics 1995)

Favolascha represents the dangerous **Neomycota**
Due to global warming & globalisation, these fungi now invade
temperate climates and are a big threat for our ecosystems!

The *Favolaschia* species that invades Europe is different from *F. calocera*

Citation: Zhang, Q.-Y.; Dai, Y.-C. Taxonomy and Phylogeny of the *Favolaschia calocera* Complex (Mycenaceae) with Descriptions of Four New Species. *Forests* **2021**, *12*, 1397. <https://doi.org/10.3390/f12101397>

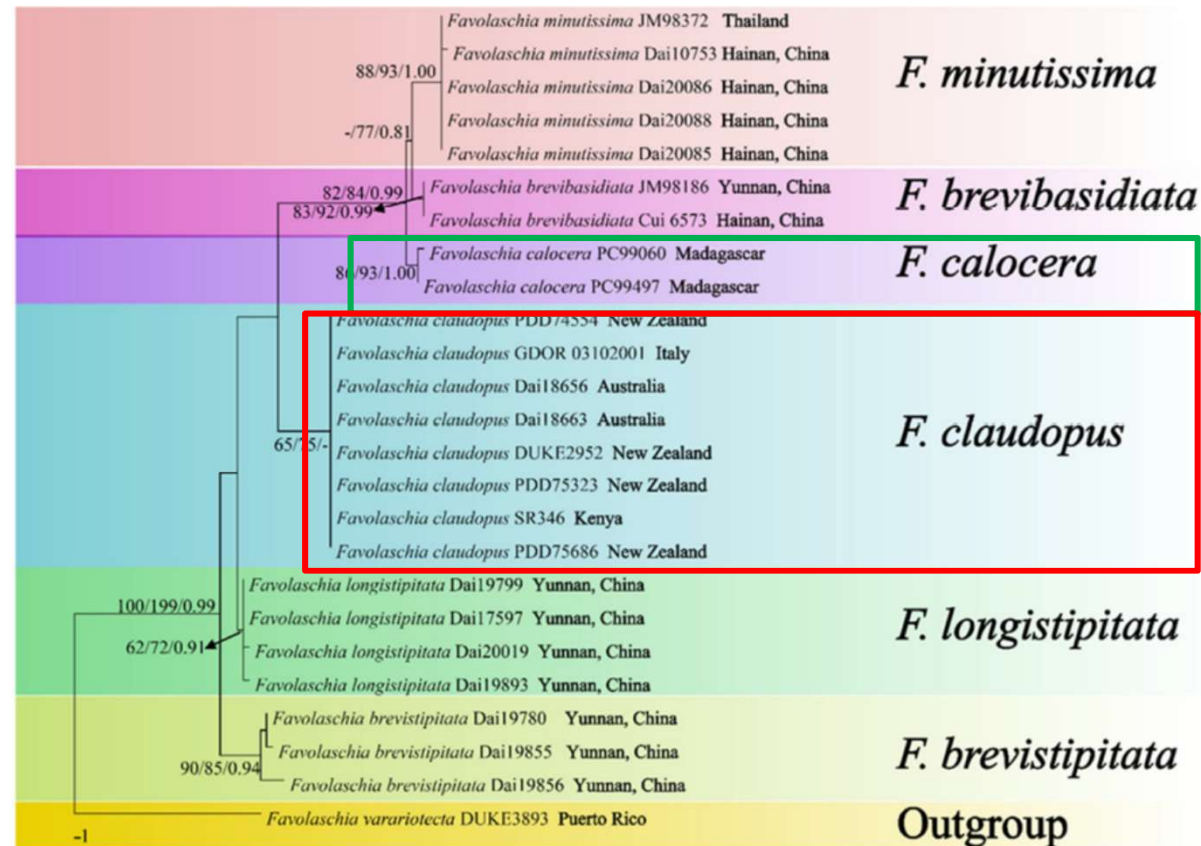


Figure 2. Maximum parsimony tree illustrating the phylogeny of the *Favolaschia calocera* complex based on ITS + nLSU + mt-SSU + nu-SSU + TEF1 sequences. Branches are labelled with parsimony bootstrap values higher than 50%, and Bayesian posterior probabilities more than 0.70.

***Favolaschia claudopus* has already been found in our neighbour countries (B, NL) and will soon reach Germany from New Zealand !**

New terpenoids from a tropical genus of Mycenaceae

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Article

Heimiomycins A–C and Calamenens from the African Basidiomycete *Heimiomyces* sp.

Tian Cheng,[⊥] Clara Chepkirui,[⊥] Cony Decock, Josphat C. Matasyoh, and Marc Stadler*



Cite This: <https://dx.doi.org/10.1021/acs.jnatprod.0c00486>



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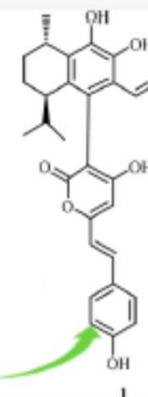


Article Recommendations



Supporting Information

ABSTRACT: Three previously undescribed compounds named heimiomycin A–C (1–3), featuring a unique scaffold with calamenene connected to a hydroxystyryl-pyrone moiety, along with the new calamenene derivatives 4 and 5 and phenanthridine derivative (6) were obtained from a culture of a *Heimiomyces* sp. This is the first report of the occurrence of calamenene-type terpenoids in fungi. Compound 3 exhibited antimicrobial activity against Gram-positive bacteria and *Mucor hiemalis*. Compounds 1 and 3 displayed moderate cytotoxicity against KB 3.1 and L929 cell lines, respectively.



low to legitimately share published articles.

New terpenoids from a tropical genus of Mycenaceae



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Article

Calamene-Type Sesqui-, Mero-, and Bis-sesquiterpenoids from Cultures of *Heimiomyces* sp., a Basidiomycete Collected in Africa

Sebastian Pfützte, Atchana Khamsim, Frank Surup, Cony Decock, Josphat C. Matasyoh, and Marc Stadler*

Cite This: <https://doi.org/10.1021/acs.jnatprod.2c01015>

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Article Recommendations

Supporting Information

ABSTRACT: New meroterpenoids bis-heimiomycins A–D (1–4) and heimiomycins D and E (5 and 6) were isolated from solid rice cultures of *Heimiomyces* sp., while new calamene-type sesquiterpenoids heimiocalamene A (7) and B (8) were isolated from shake cultures, respectively. Structures of 9 the metabolites were elucidated by 1D and 2D NMR in addition to 10 HRESIMS data. While relative configurations were assigned by ROESY data, 11 absolute configurations were derived from the structurally related, previously 12 described calamenes, which we herein name heimiocalamenes C–E (9–11). 13 A plausible biosynthetic pathway was proposed for 1–6, with a radical 14 reaction connecting their central para-benzoquinone building block to 15 calamene-sesquiterpenoids. Based on the assumption of a common 16 biosynthesis, we reviewed the structure of the known nitrogen-containing derivative 11, calling the validity of the originally



Photo by Sabine Peacock

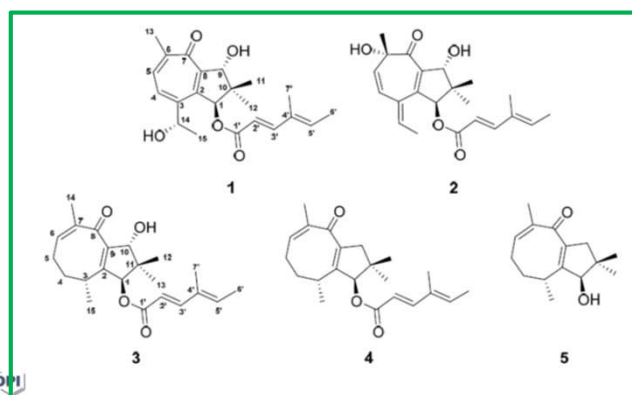


Article

Heimionones A–E, New Sesquiterpenoids Produced by *Heimiomyces* sp., a Basidiomycete Collected in Africa

Sebastian Pfützte^{1,2}, Atchana Khamsim^{1,2}, Frank Surup^{1,2}, Cony Decock³, Josphat C. Matasyoh⁴ and Marc Stadler^{1,2,*}

From shake cultures



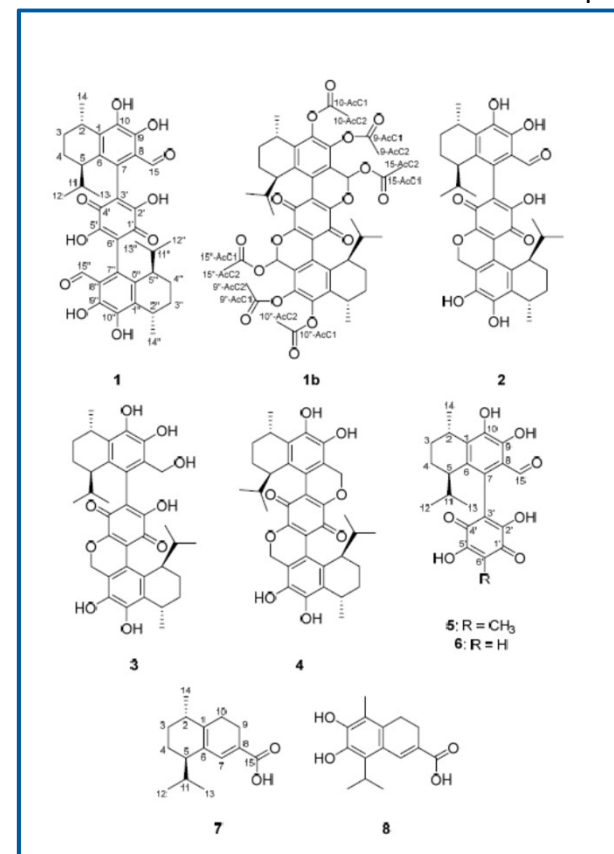
From solid state culture after 7 months of growth



Sebastian Pfützte



Frank Surup



Heimiomyces: cultured and studied on its secondary metabolites for the first time

Even German forests harbour many basidiomycetes that are yet untapped for secondary metabolites



Antiviral Meroterpenoid Rhodatin and Sesquiterpenoids Rhodocoranes A–E from the Wrinkled Peach Mushroom, *Rhodotus palmatus*

Birthe Sandargo,^{†,‡} Maira Michehl,^{†,‡,§} Dimas Praditya,^{§,||} Eike Steinmann,^{§,⊥} Marc Stadler,^{†,‡,Ⓜ} and Frank Surup^{*,†,‡,Ⓜ}

[†]Department of Microbial Drugs, Helmholtz Centre for Infection Research GmbH, Inhoffenstraße 7, 38124 Braunschweig, Germany

[‡]German Centre for Infection Research (DZIF), partner site Hannover-Braunschweig, 38124 Braunschweig, Germany

[§]TWINCORE-Centre for Experimental and Clinical Infection Research (Institute of Experimental Virology), Feodor-Lynen-Straße 7-9, 30625 Hannover, Germany

^{||}Research Center for Biotechnology, Indonesian Institute of Science, Jl. Raya Bogor KM 46, Cibinong, Indonesia

[⊥]Department of Molecular and Medical Virology, Ruhr-University Bochum, 44801 Bochum, Germany

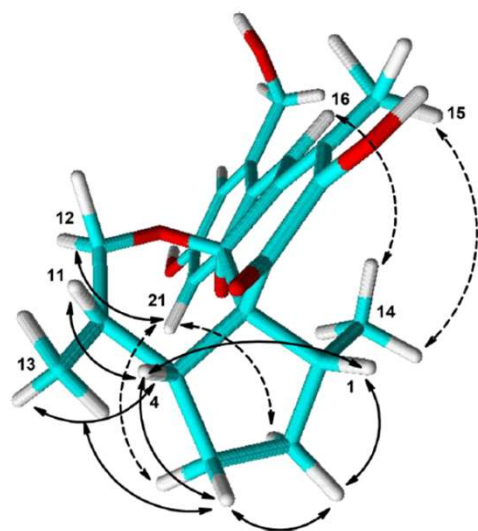
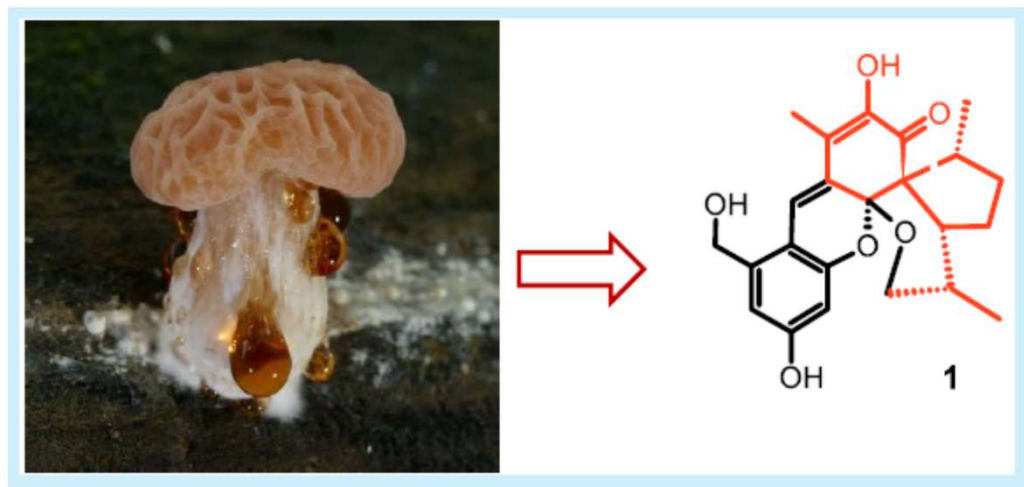


Figure 3. Key ROE correlations of rhodatin (1). Correlations above the molecular main plane are indicated with solid arrows, and correlations below with dashed arrows.



New carbon skeleton; antiviral activities

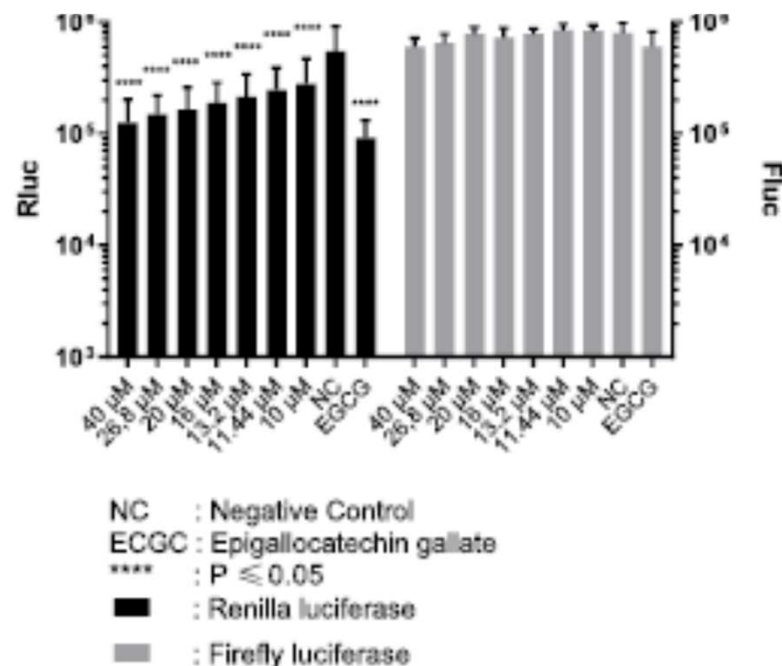
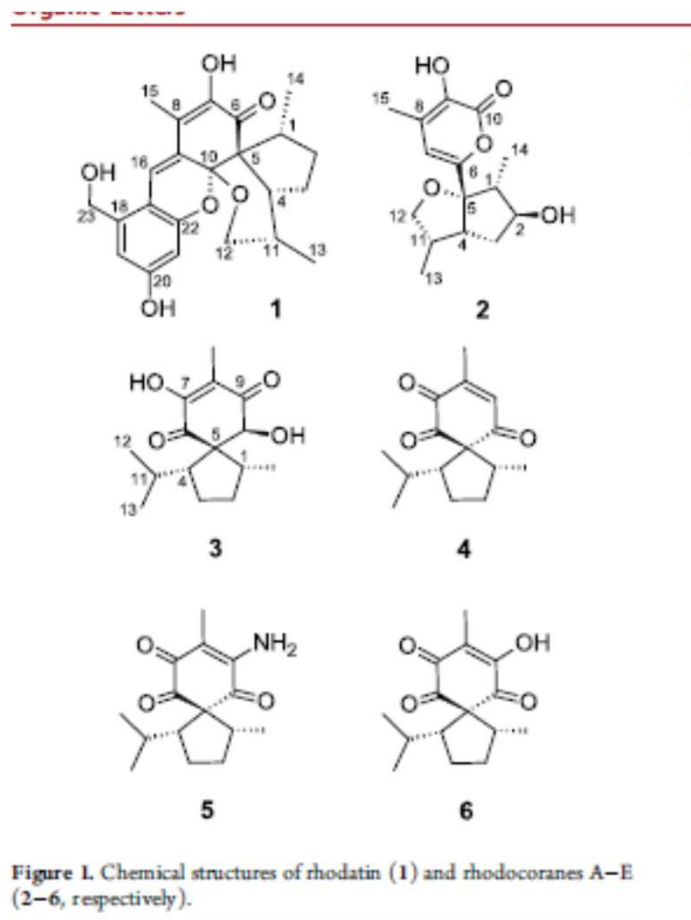


Figure 4. Antiviral activity of rhodatin (1). Huh-7.5 cells were inoculated with RLuc-Jc1 reporter viruses in the presence of rhodatin. Infected cells were lysed for 3 days, and reporter virus infection was determined by Renilla luciferase activity (RLuc). Cell viability was measured by determination of firefly luciferase (Fluc), which is stably expressed in the target cells.

Significant antiviral activity (HCV)

Several new acorane sesquiterpenoids were obtained concurrently

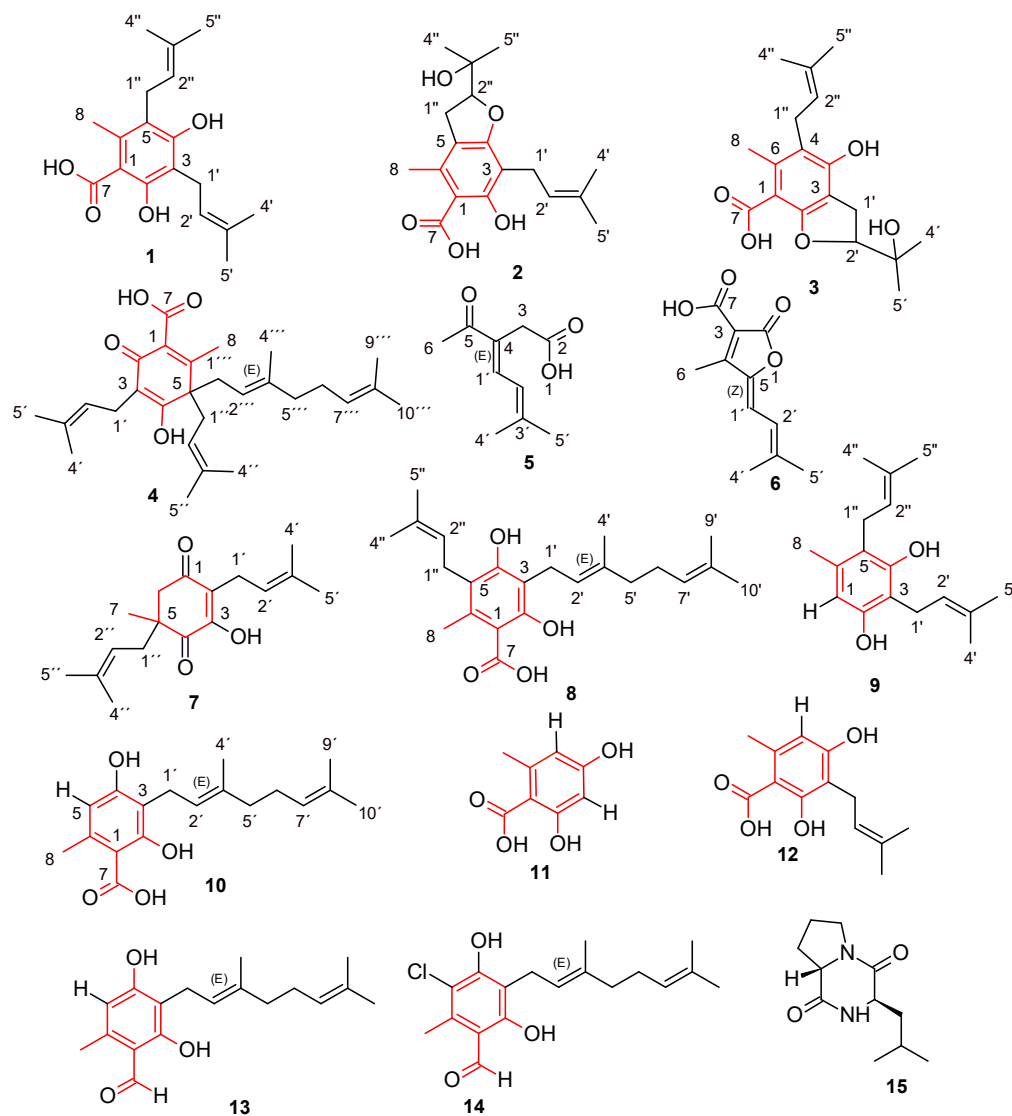
Kakamega rainforest (February 2023)



Meroterpenoids from *Amylosporus* spp.



Blondelle Matio



— Orsellinic acid-derived carbons



Grass symbionts
Growth time of cultures
in the lab: 4 months

Meroterpenoids from *Amylosporus* spp.



Blondelle Matio



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Article

Terpenoids and Meroterpenoids from Cultures of Two Grass-Associated Species of *Amylosporus* (Basidiomycota)

Blondelle Matio Kemkuignou,[‡] Ashaimaa Y. Moussa,[‡] Cony Decock, and Marc Stadler*

Cite This: <https://doi.org/10.1021/acs.jnatprod.1c00975>

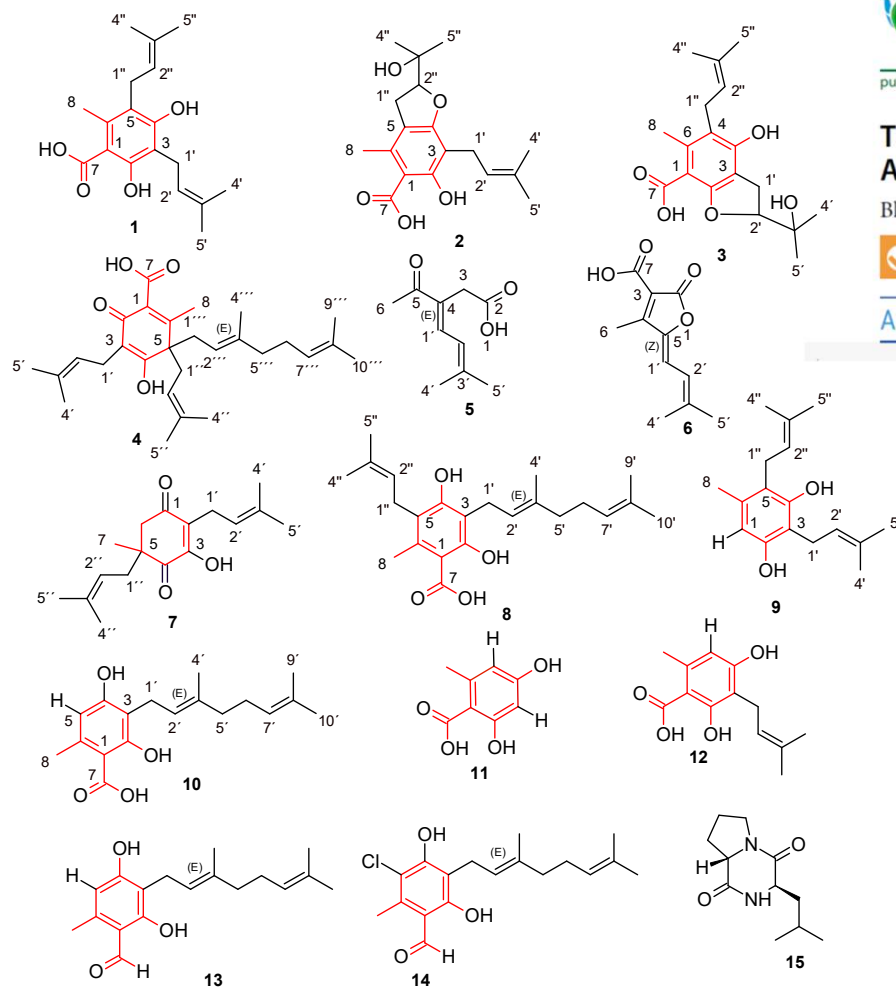
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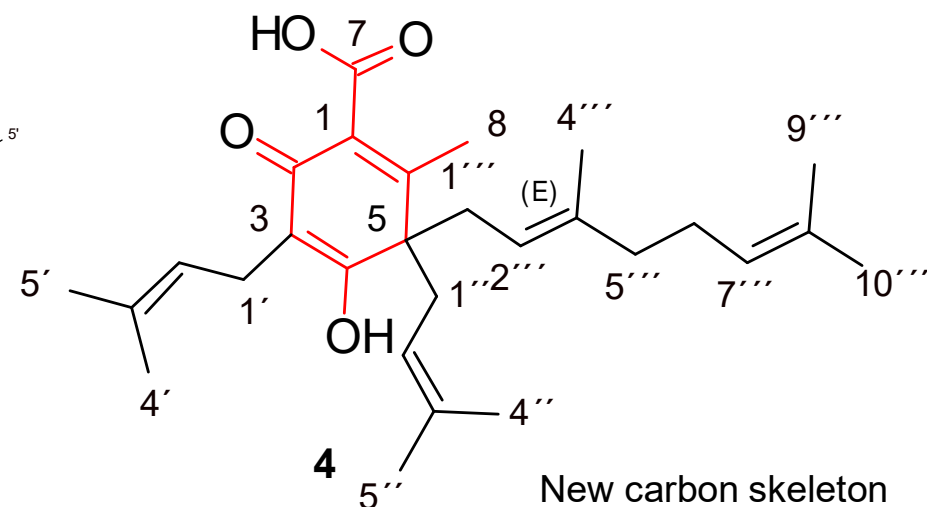
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Supporting Information



— Orsellinic acid-derived carbons



Impressions from field work (Arabuko Sokoke NP, Kenya, May 2022)



Project funded by the EU
(H2020-MSCA-RISE Mycobiomics)
and **AvH Foundation**



Alexander von
HUMBOLDT
STIFTUNG

Many of the strains we isolated seem to represent hitherto undescribed species
⇒ **Good chances to find novel bioactive metabolites**

Model Basidiomycetes: the largest organisms on Earth ?*

*Smith et al. 1992. Nature 356:428-431



Armillaria gallica Marxm. & Romagn.



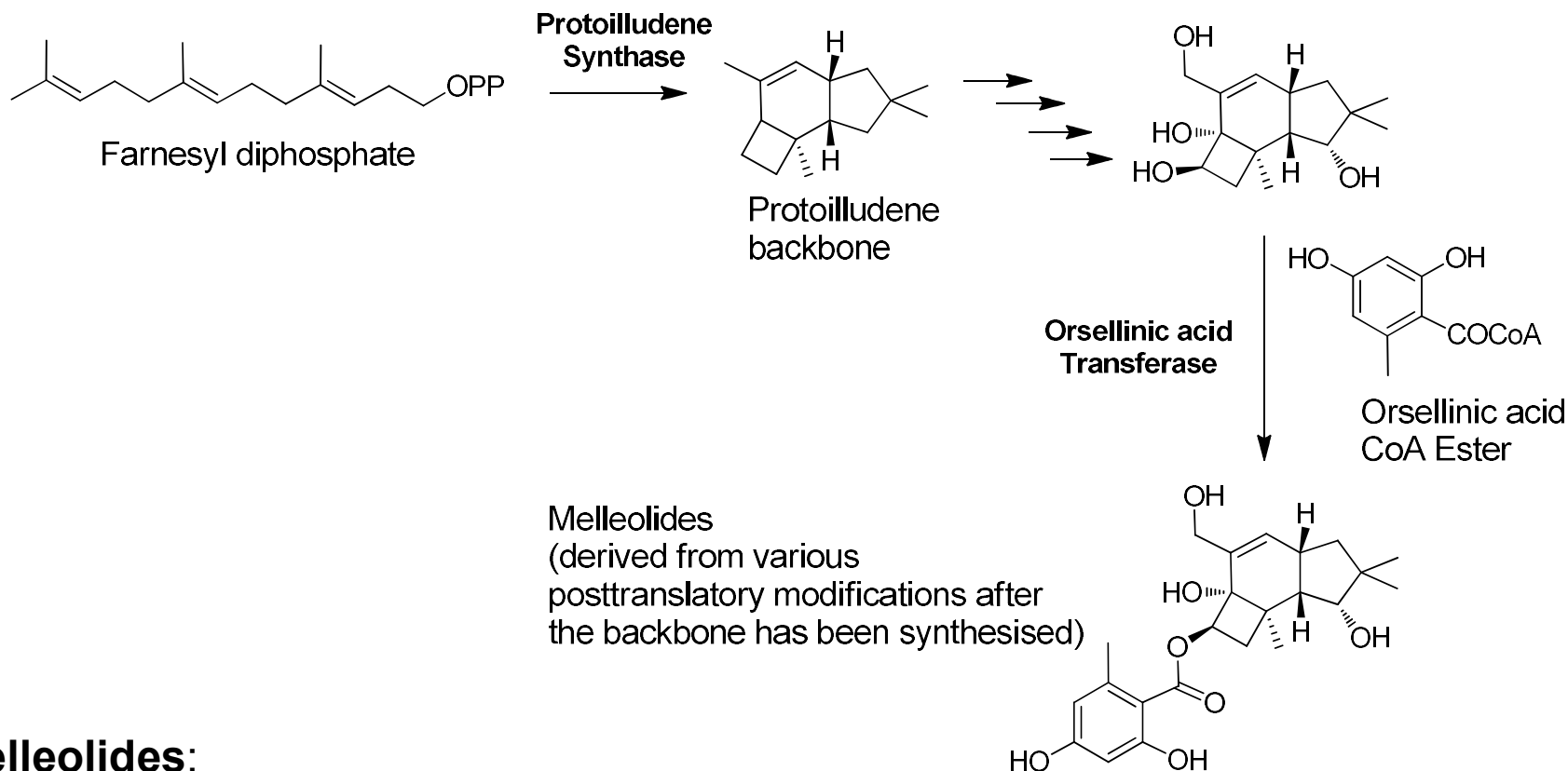
Culture with rhizomorphs (by B. Schmieschek)



http://botit.botany.wisc.edu/toms_fungi/apr2002.html

- **Cosmopolitan saprotrophic edible mushrooms**
- **Notorious forest parasites**

Hypothetical scheme for melleolide biosynthesis



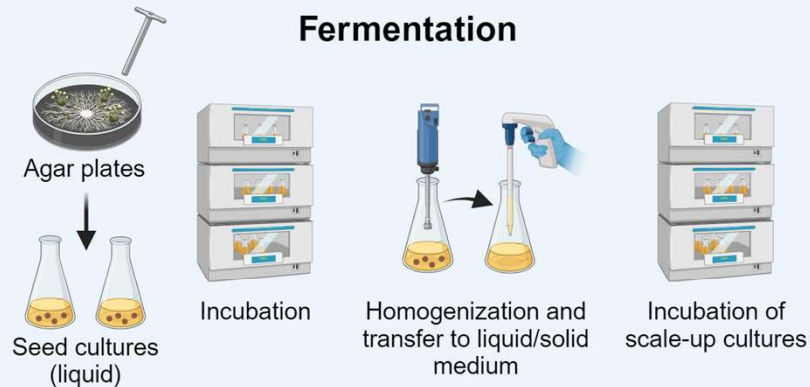
Melleolides:

- Esters of aromatic polyketides (orsellinic acid) with a protoilludane sesquiterpene backbone
- Specific for *Armillaria* species
- Antibiotic, anticancer and other biological activities

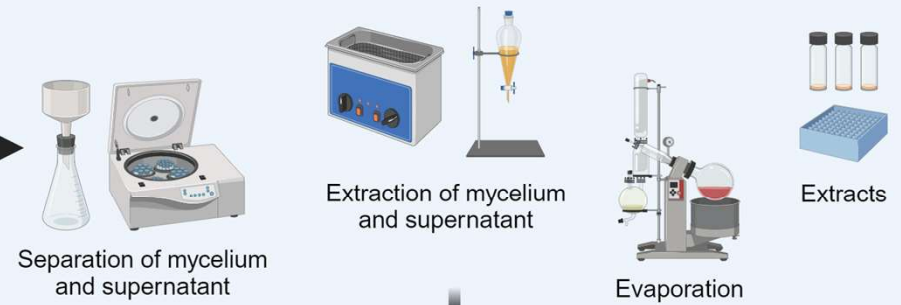


General workflow

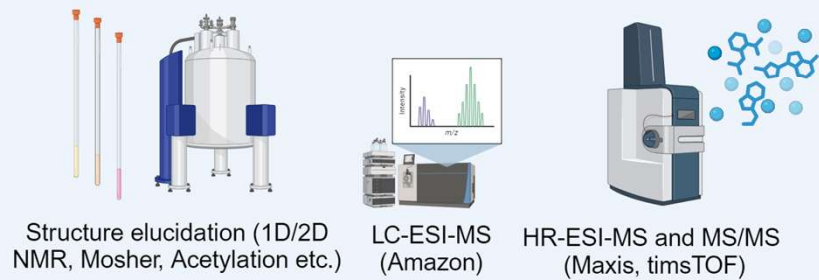
Fermentation



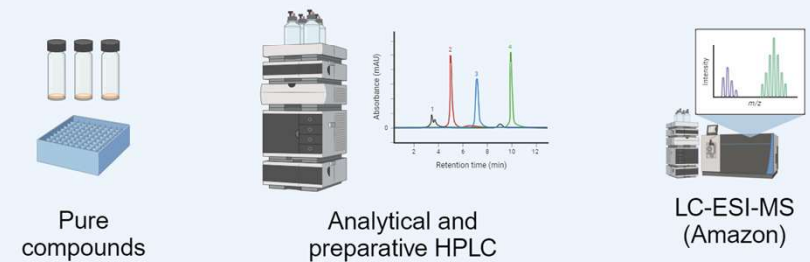
Harvest and Extraction



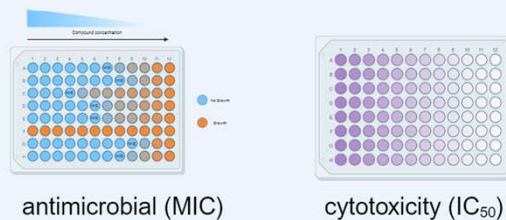
Chemical Characterization and Metabolomics



Analytics and Purification



Evaluation of Bioactivities



New melleolide-type meroterpenoids from *A. ostoyae*



Armillaria ostoyae

- collected in Rhineland-Palatinate from a dead trunk of *Pseudotsuga menziesii* in 2013
- most prolific producer of in-house strain collection (previous screening)
- In-depth investigation on secondary metabolism



Sebastian Pfütze



Frank Surup



Esteban Charria



Esther Schulzke



Rita Toshe



Artit Khonsanit
Tony



Natural Products

Depicting the Chemical Diversity of Bioactive Meroterpenoids Produced by the Largest Organism on Earth

Sebastian Pfütze*, Esteban Charria-Girón*, Esther Schulzke, Rita Toshe, Artit Khonsanit, Raimo Franke, Frank Surup, Mark Brönstrup, and Marc Stadler*

Abstract: In this investigation, we explored the diversity of melleolide-type meroterpenoids produced by *Armillaria ostoyae*, one of the largest and oldest organisms on Earth, using extracts from liquid and solid fermentation media. The study unveiled three unprecedented dimeric bismelleolides and three novel fatty-acid-substituted congeners, along with 11 new and 21 known derivatives. The structures were elucidated by 1D and 2D NMR spectroscopy and HRESI-MS, and ROESY spectral analysis for relative configurations. Absolute configurations were determined from crystal structures and through ECD spectra comparison. A compound library of melleolide-type meroterpenoids facilitated metabolomics-wide associations, revealing production patterns under different culture conditions. The library enabled assessments of antimicrobial and cytotoxic activities, revealing that the $\Delta^{2,4}$ double bond is not crucial for antifungal activity. Cytotoxicity was linked to the presence of an aldehyde at C1, but lost with hydroxylation at C13. Chemoinformatic analyses demonstrated the intricate interplay of chemical modifications on biological properties. This study marks the first systematic exploration of *Armillaria* spp. meroterpenoid diversity by MS-based untargeted metabolomics, offering insight into structure–activity relationships through innovative chemoinformatics.

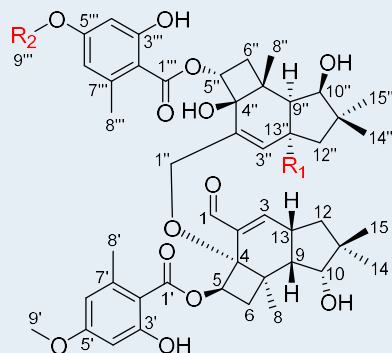
Introduction

The phylum Basidiomycota comprises ca. 40,000 species and represents the second largest division within the Eumycota after the Ascomycota.^[1] Taxa belonging to this phylum are well known as creative producers of bioactive natural products.^[2] Even though most of the fungal natural product-derived drugs on the market were originally isolated from species of the Ascomycota, some of them were obtained from Basidiomycota.^[3] For instance, the pleuromutilins are a family of sesquiterpenoid antibiotics produced by *Clitopilus* spp. (Agaricales, Basidiomycota) that are the most recent antibacterial drug class to make it to the market.^[4]

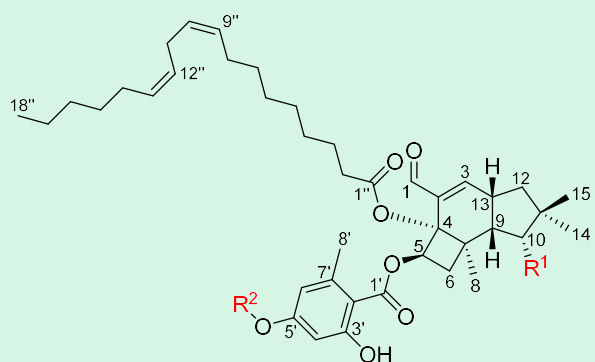
An important representative of the Basidiomycota is *Armillaria* (Physalacriaceae—also known as honey mushrooms), a globally distributed genus of plant pathogens whose species infect trees by causing butt and root diseases that can lead to entire forest diebacks.^[5,6] In particular, the ability to form thickened mycelium strands (rhizomorphs), that allow *Armillaria* spp. to exploit large areas in the search for essential nutrients, is of great importance for their pathogenicity. *Armillaria bulbosa* and *A. ostoyae* have become famous for being among the largest and oldest organisms on Earth. This is owing to the facts that *i)* genetic studies on their occurrence in some large forests of Northeastern North America revealed that the same mycelium can cover up to several thousands of square km and, *ii)* extrapolating their growth speed, these fungal mycelia are estimated to have reached an age of several thousand years.^[7,8]



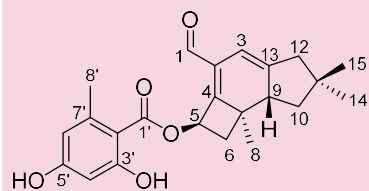
New melleolide-type meroterpenoids from *A. ostoyae*



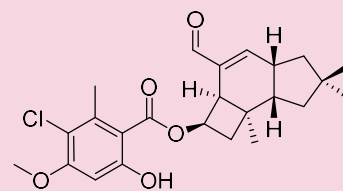
- 1: $R_1 = H$; $R_2 = CH_3$ (bismelleolide BH)
2: $R_1 = H$; $R_2 = H$ (bismelleolide EH)
3: $R_1 = OH$; $R_2 = CH_3$ (bismelleolide CH)



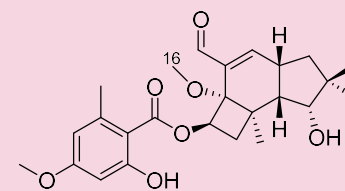
- 4: $R^1 = H$; $R^2 = H$ (melleolide linoleate)
5: $R^1 = H$; $R^2 = CH_3$ (armillarine linoleate)
6: $R^1 = OH$; $R^2 = CH_3$ (melleolide H linoleate)



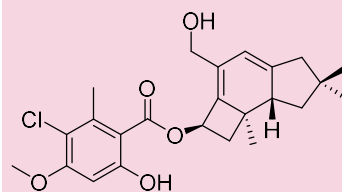
7 (5'-O-desmethyllumillaridin)



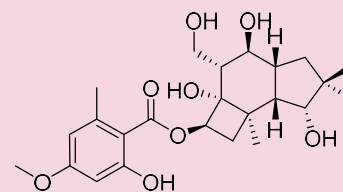
8 (4-dehydroxyarmillaridin)



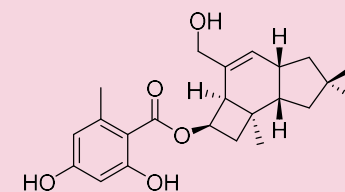
9 (4-methoxymelleolide H)



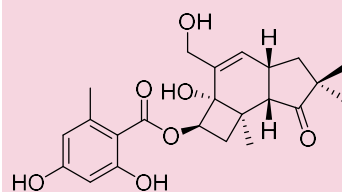
10 (1-hydroxyarmillaricin)



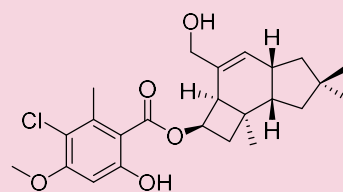
11 (10-hydroxy-5'-O-methylarmillane)



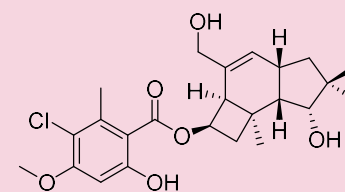
12 (4-dehydroxymelleolide F)



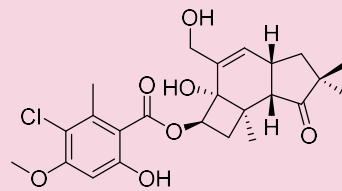
13 (10-ketomelleolide E)



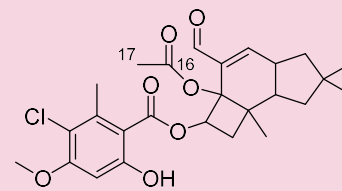
14 (4,10-dehydroxymelleolide I)



15 (4-dehydroxymelleolide I)



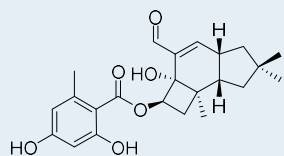
16 (10-ketomelleolide I)



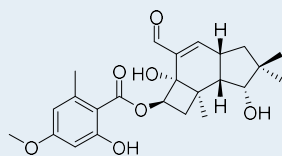
17 (4-acetyllumillaridin)



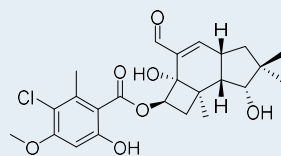
Known melleolide-type meroterpenoids from *A. ostoyae*



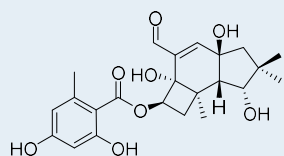
18 (melleolide)



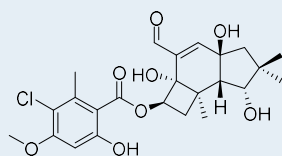
19 (melleolide H)



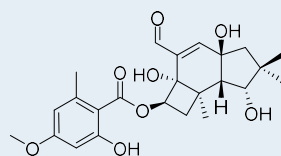
20 (melleolide J)



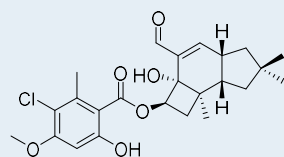
21 (melledonal A)



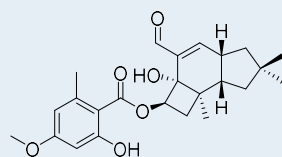
22 (melledonal C)



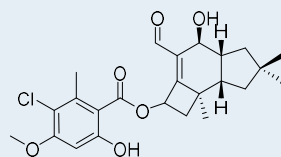
23 (5'-O-methylmelledonal)



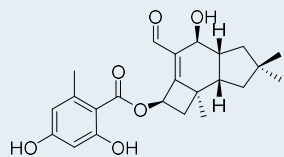
24 (armillaridin)



25 (armillararin)

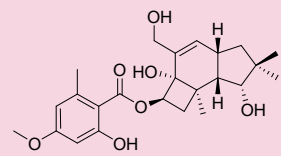


26 (arnamial)

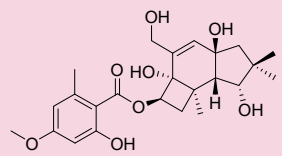


27 (dehydroarmillylorsellinate)

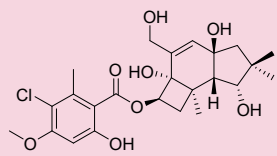
Aldehydes



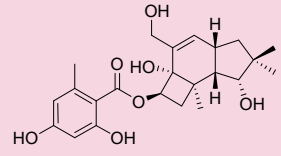
28 (melleolide B)



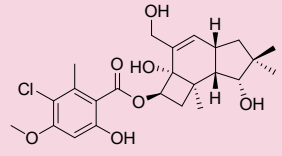
29 (melleolide C)



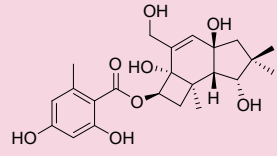
30 (melleolide D)



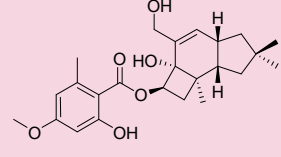
31 (melleolide E)



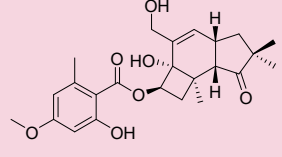
32 (melleolide I)



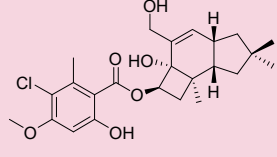
33 (melledonol)



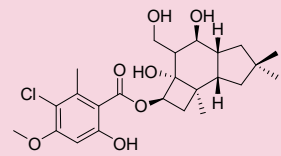
34 (10-dehydroxy-melleolide B)



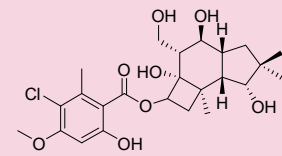
35 (10-oxo-melleolide B)



36 (A52a)



37 (5'-methoxy-6'-chloroarmillane)



38 (10-hydroxy-5'-methoxy-6'-chloroarmillane)

Alcohols

→ together with the new derivatives, ~40% of all melleolides described in literature were isolated only from cultures of *A. ostoyae*



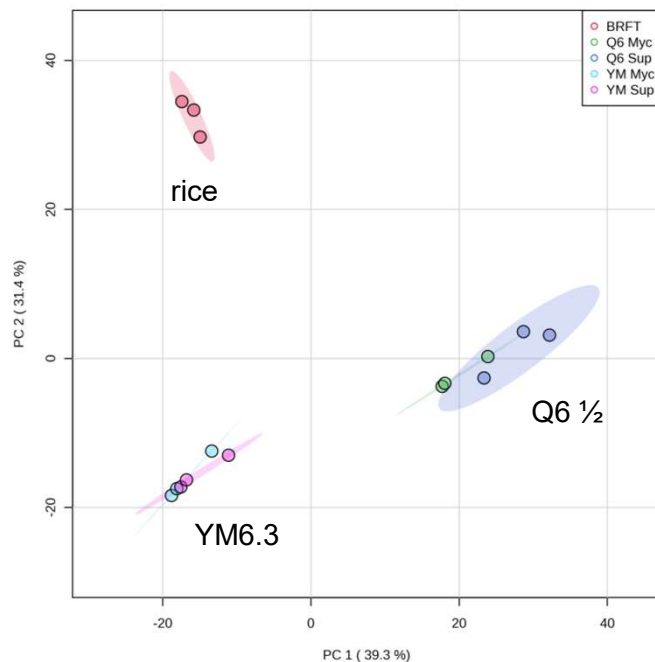
A. ostoyae – metabolomics

- assessment of melleolide production in *A. ostoyae* under different cultivation conditions (three different media: rice, Q6 ½, YM6.3)
- analysis of extracts by tandem mass spectrometry (timsTOF)
- at **first principal component analysis (PCA)** to obtain overall picture of metabolomes observed in each extract

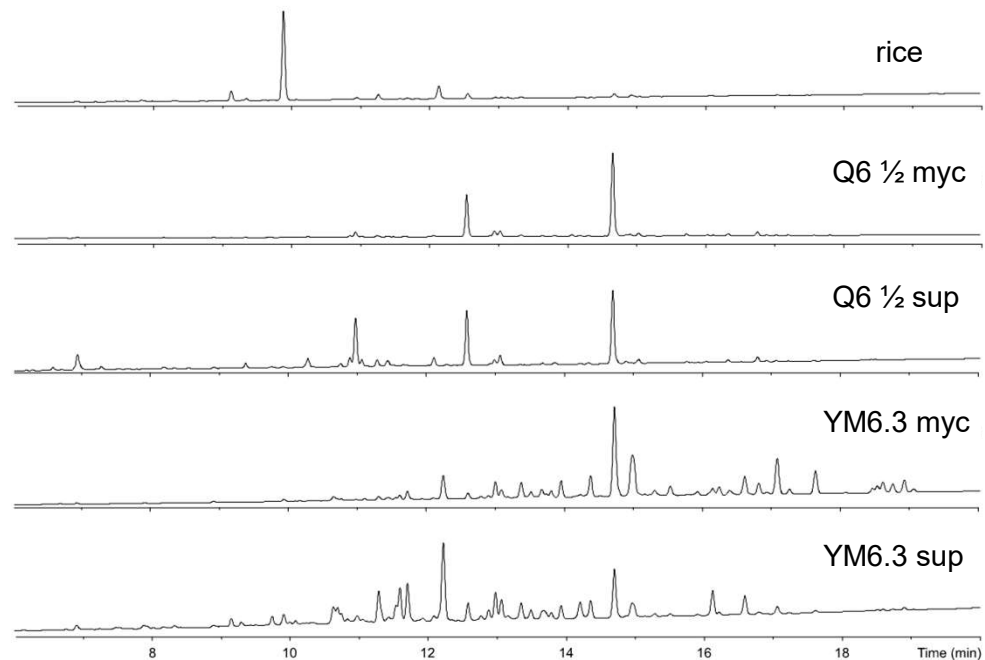


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PCA scores plot



HPLC-UV/Vis chromatograms (210 nm) of different extracts





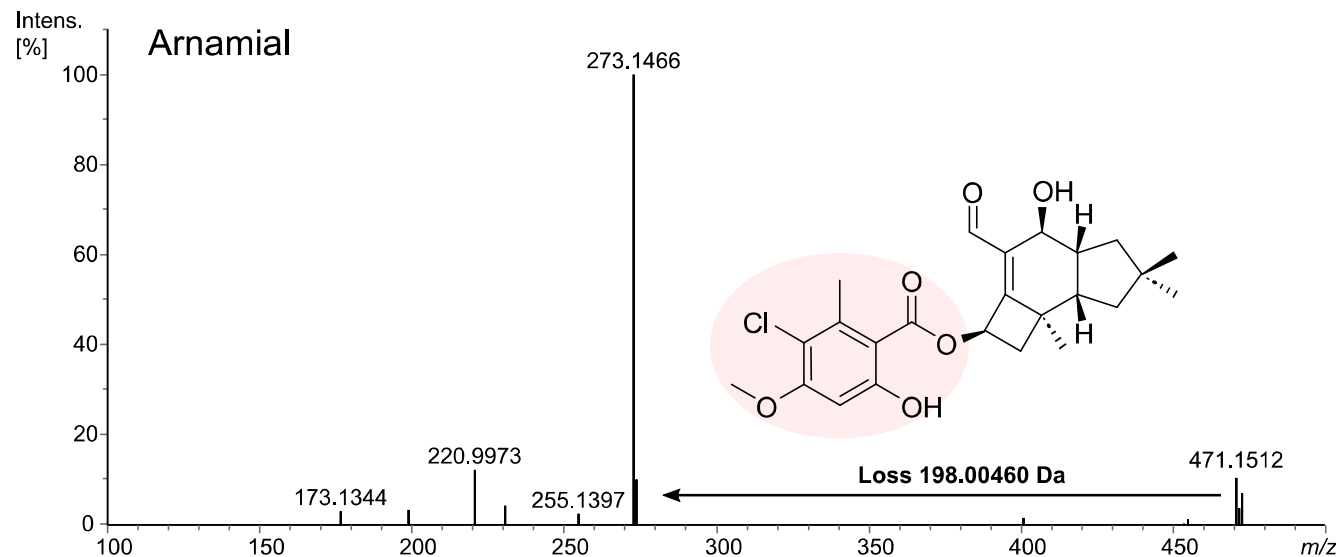
A. ostoyae – metabolomics

- tandem mass spectrometry analysis (timsTOF) of isolated pure compounds and evaluation of their fragmentation patterns
- distinctive patterns observed → characteristic neutral losses corresponding to loss of orsellinic acid (OA) moiety
- identification of chlorination and O-methylation in OA, as well as presence of hydroxylations, fatty acid side chains, dimerisation etc.



Esteban Charria Girón

Reference MS/MS spectrum



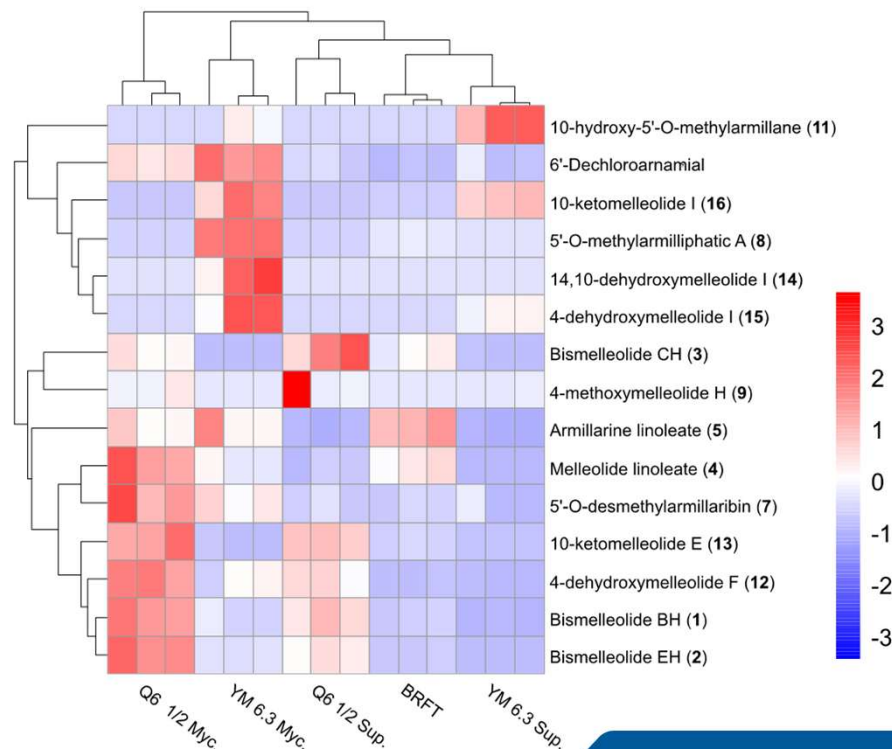
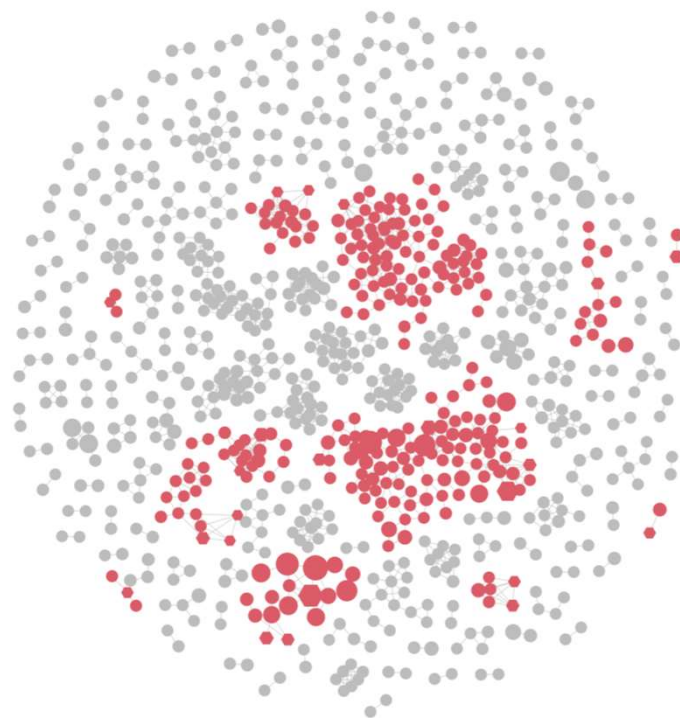


A. ostoyae – metabolomics

- for feature based molecular network (**FBMN**) analyses UHPLC-DAD-IM-MS/MS data pre-processed with **MetaboScape** software
- detected features organized into 156 molecular families (MFs), with 22 MFs belonging to compound class of “melleolides”
- grouping of new “melleolides” by hierarchical clustering to show effect of cultivation conditions on metabolome in a **heatmap**



Esteban Charria Girón



Paradigm shift in agrochemistry ?

- In the past decades, the Big Agro companies have essentially given up their internal R&D activities on natural products and biocontrol.
- Unfortunately, this has now led to serious problems regarding the development of innovative products that can help to satisfy the need of their customers

...increasing resistances against strobilurins; problematic use of azoles in both, agrochemistry and antimycotic therapy

Fungi and their secondary metabolites could fill some innovation gaps because mycologists have made substantial progress in the past years!

Nematode antagonists can yield interesting chemistry

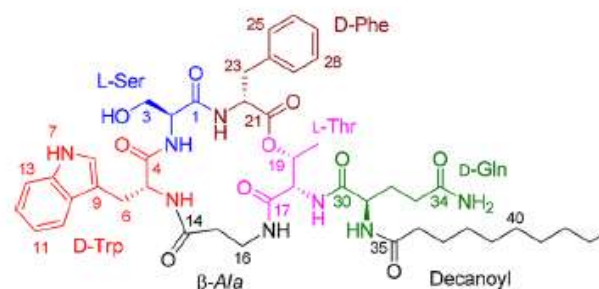


¹ Nematicidal Cyclic Lipodepsipeptides and a Xanthoci ² from a Phaeosphariaceae Fungus Parasitizing Eggs ³ Parasitic Nematode *Heterodera filipjevi*

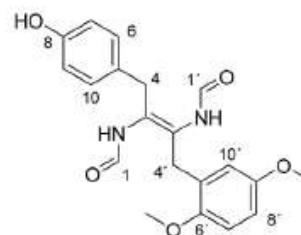
⁴ Soleiman E. Helaly,^{†,*} Samad Ashrafi,[§] Rémy B. Teponno,^{†,‡} Steffen Bernecker,[†]
⁵ Abdelfattah A. Dababat,^{||} Wolfgang Maier,[§] and Marc Stadler^{*,†,§}



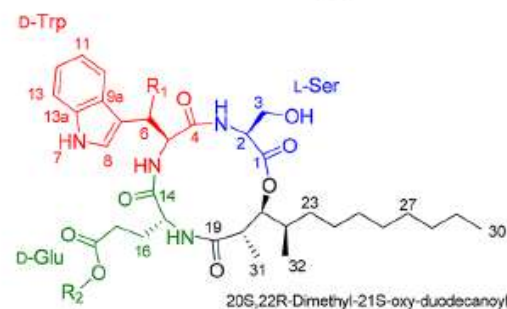
Metabolites of new nematode
antagonistic fungus
that represents a new genus



Ophiotine (1)



Xanthomide Z (2)



Arthrichitin (3): $R_1 = \text{=O}$; $R_2 = \text{H}$
Arthrichitin B (4): $R_1 = \text{H}_2$; $R_2 = \text{H}$
Arthrichitin C (5): $R_1 = \text{=O}$; $R_2 = \text{CH}_3$



Soleiman Helaly



Remy B. Teponno

Species of a new genus of root endophytes attack nematodes and thereby protect the host plants!

Ashrafi et al. *IMA Fungus* (2023) 14:6
<https://doi.org/10.1186/s43008-023-00113-w>

IMA Fungus



RESEARCH

Open Access

Polydomus karssenii gen. nov. sp. nov.
 is a dark septate endophyte with a bifunctional
 lifestyle parasitising eggs of plant parasitic cyst
 nematodes (*Heterodera* spp.)

Samad Ashrafi^{1,2*}, Jan-Peer Wennrich^{3,4}, Yvonne Becker¹, Jose G. Maciá-Vicente⁵, Anke Brißke-Rode¹,
 Matthias Daub⁶, Torsten Thünen², Abdelfattah A. Dababat⁷, Maria R. Finckh⁸, Marc Stadler^{3,4} and
 Wolfgang Maier¹

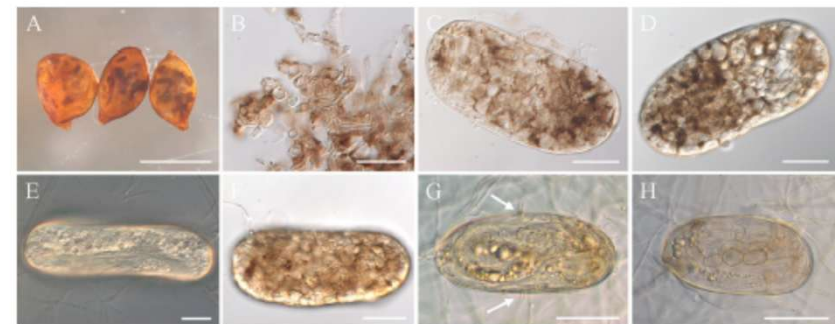
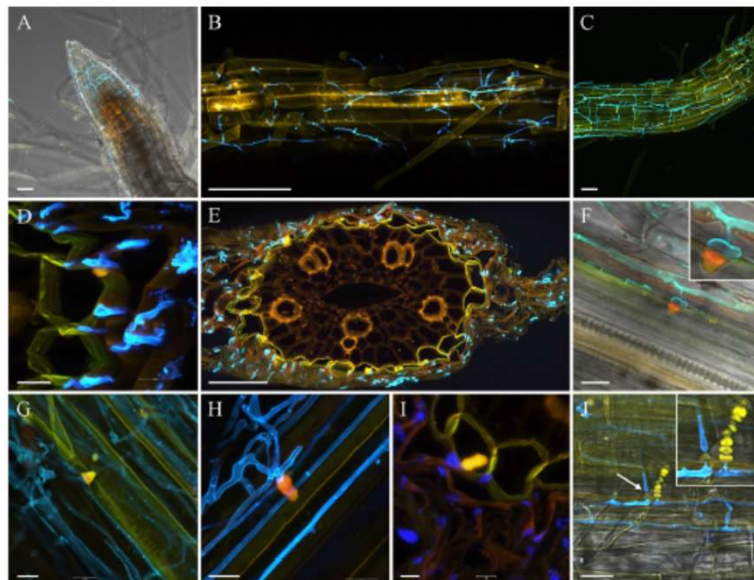


Fig. 4 Pathogenicity of *Polydomus karssenii* DSM 106875. Inward nematode eggs and roots. **a** Symptomatic eggs of *Heterodera filiformis* obtained



New metabolites from *Polydomus*



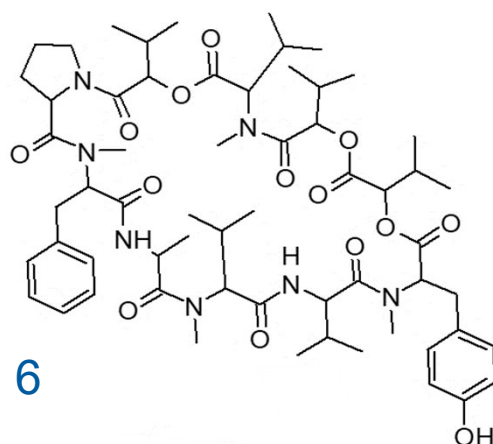
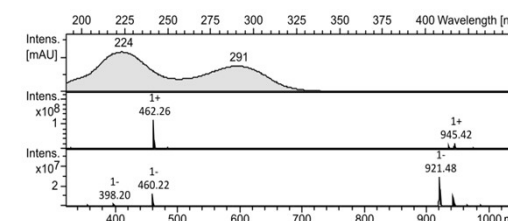
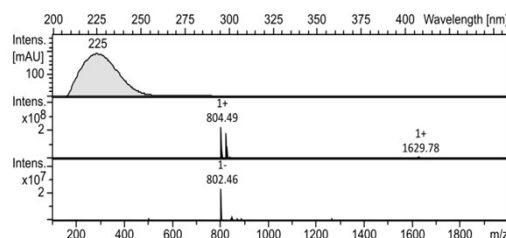
JP Wennrich



Frank Surup

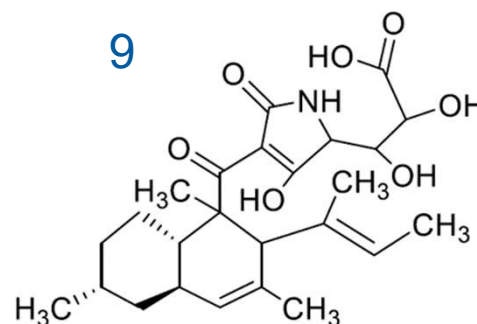
Table 1. Compounds isolated from *Polydomus*

Compound	[M + H] ⁺ ion at m/z	Formula (Ion)
4	804.49	C ₄₄ H ₆₂ N ₅ O ₉
5	818.52	C ₄₅ H ₆₄ N ₅ O ₉
13	788.50	C ₄₄ H ₆₁ N ₅ O ₈
7	430.25	C ₂₅ H ₃₅ NO ₅
8	448.23	C ₂₄ H ₃₃ NO ₇
9	462.26	C ₂₅ H ₃₅ NO ₇
10	446.27	C ₂₅ H ₃₅ NO ₆
11	476.27	C ₂₆ H ₃₇ NO ₇
12	502.28	C ₂₈ H ₄₉ NO ₇
6	1132.65	C ₆₀ H ₈₉ N ₇ O ₁₄



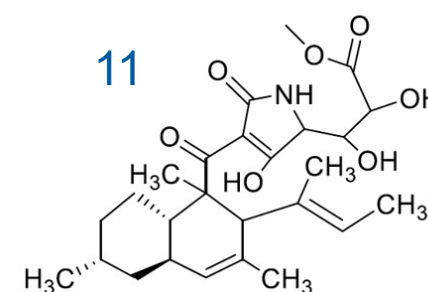
6

Exact Mass: 1131,65
Sum Formula: C₆₀H₈₉N₇O₁₄



9

Exact mass: 461.56
Sum Formula: C₂₅H₃₅NO₇



11

Exact Mass: 475,26
Sum Formula: C₂₆H₃₇NO₇

Laburnicola nematophila

(Didymosphaeriaceae, Pleosporales)

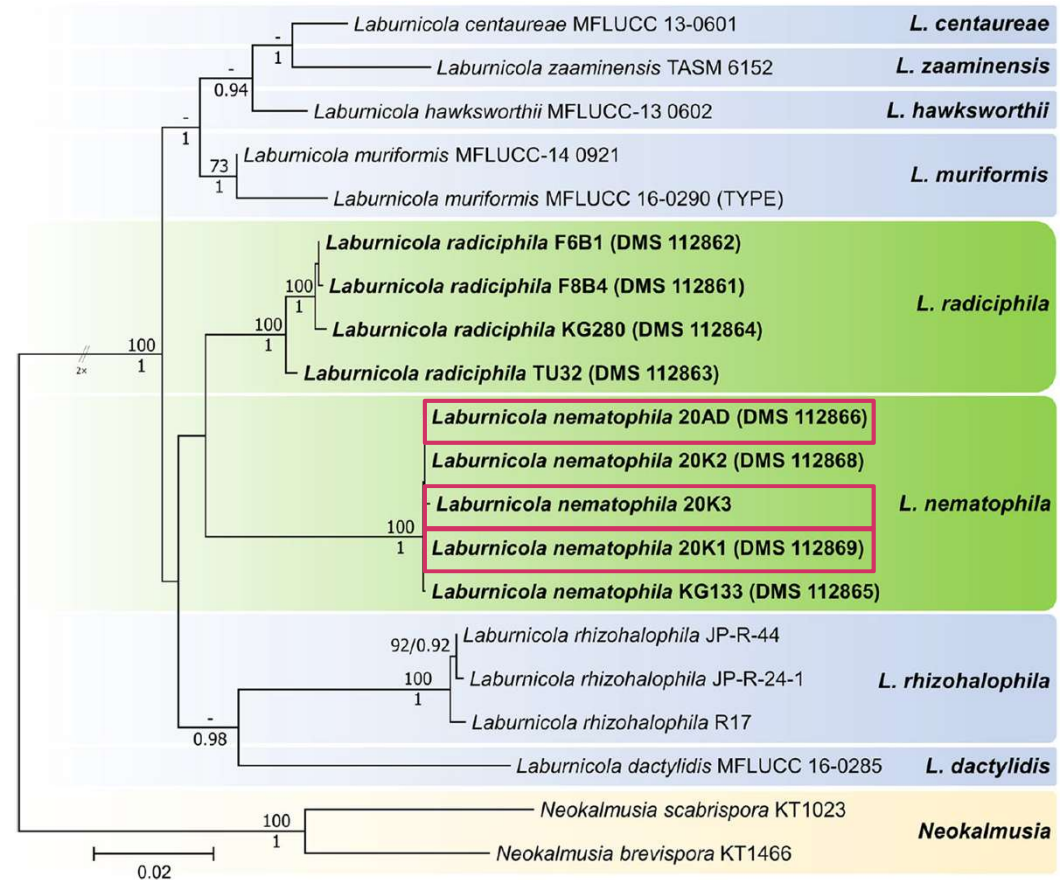
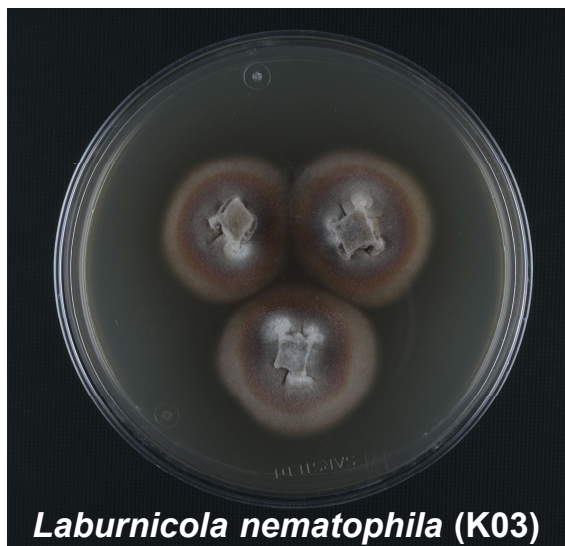


Fig. Maximum likelihood (RAxML) tree of sequences of *Laburnicola* species. The ML and Bayesian analysis were performed using the combined data set of four loci (ITS, LSU, SSU, and TEF1).

Laburnicola nematophila



<http://pubs.acs.org/journal/acsodf>

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Article

Laburnicotides A–F: Acyclic N-Acetyl Oligopeptides from the Nematode-Cyst-Associated Fungus *Laburnicola nematophila*

Caren Holzenkamp,[○] Jan-Peer Wennrich,[○] Jackson M. Muema, Samad Ashrafi, Wolfgang Maier, Laburnicotides A–F: Acyclic N-Acetyl Oligopeptides from the Nematode-Cyst-Associated Fungus *Laburnicola nematophila*

Caren Holzenkamp,[○] Jan-Peer Wennrich,[○] Jackson M. Muema, Samad Ashrafi, Wolfgang Maier, Marc Stadler,* and Sherif S. Ebada*



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doi.org/10.1002/cbdv.202401152

Research Article

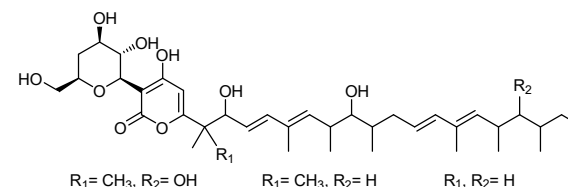


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Laburnicolamine: A Rare Penillic Acid Congener from the Nematode Cyst-Associated Fungus *Laburnicola nematophila*

Laburnicolamine: A Rare Penillic Acid Congener from the Nematode Cyst-Associated Fungus *Laburnicola nematophila*

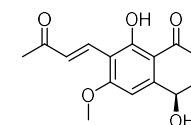
Jan-Peer Wennrich,^{+, [a, b]} Caren Holzenkamp,^{+, [a, b]} Samad Ashrafi,^[c, d] Wolfgang Maier,^[c] Hao Wang,^[e] Mahmoud A. A. Ibrahim,^[f, g] Sherif S. Ebada,^{*, [a, h]} and Marc Stadler^{*, [a, b]}



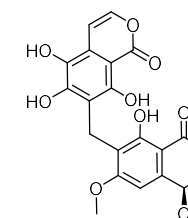
17 dactylfungin C

18 dactylfungin D

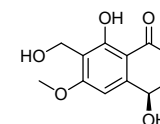
19 YM-202204



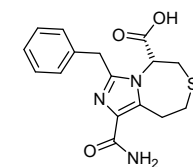
21 laburnicolone



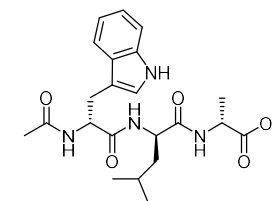
20 laburnicolin



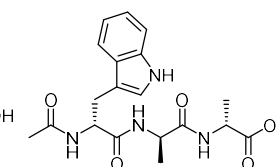
22 10-norparvulenone



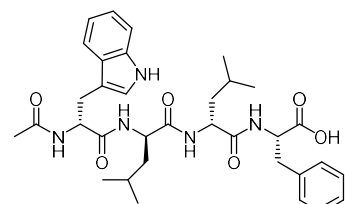
23 laburnicolamine



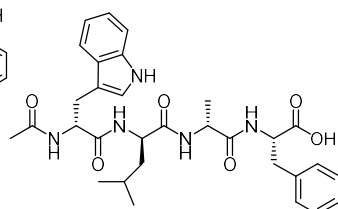
28 laburnicotide E



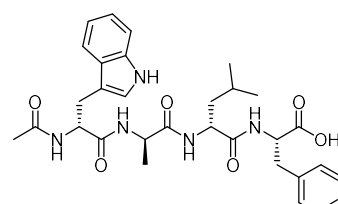
29 laburnicotide F



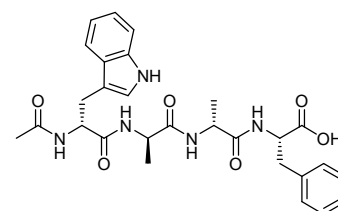
24 laburnicotides A



25 laburnicotides B



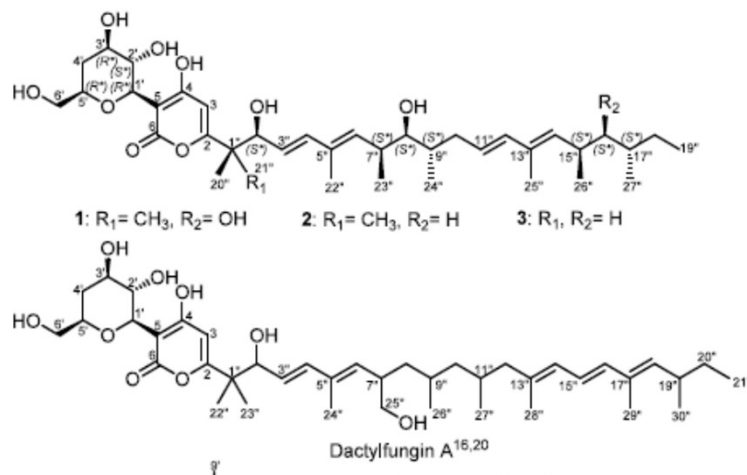
26 laburnicotides C



27 laburnicotides D

Re-discovery of Dactylfungins (1)

Miroslav Kolarik



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Article

Dactylfungins and Tetralones: Bioactive Metabolites from a Nematode-Associated *Laburnicola nematophila*

Jan-Peer Wennrich, Caren Holzenkamp, Miroslav Kolarik, Wolfgang Maier, Attila Mándi, Tibor Kurtán, Samad Ashrafi, Sherif S. Ebada,* and Marc Stadler*

Cite This: *J. Nat. Prod.* 2024, 87, 1860–1871

Read Online

Organisms	ID	MIC $\mu\text{g mL}^{-1}$			
		1	2	3	P
<i>Aspergillus fumigatus</i>	ATCC 204305	0.26	0.52	8.3	0.31 ^A
<i>A. fumigatus</i>	CCF 3522		0.52		0.31 ^A
<i>A. fumigatus</i>	CCUG 75301			-	0.31 ^A
<i>A. fumigatus</i> (azole resistant)	CCF 6651	-	2.08	0.52	0.16 ^A
<i>A. fumigatus</i> (azole resistant)	CCF 6674	16.6	0.52	0.52	2.5 ^A
<i>C. albicans</i>	CCM 8215	-	-	8.3	1.25 ^A
<i>Cryptococcus neoformans</i>	CCF 1081	-	4.15	4.15	2.5 ^A
<i>Mucor plumbeus</i>	CCF 2612	-	-	1.04	0.31 ^A

N: nystatin, A: amphotericin B

New derivatives with enhanced effects against azole resistant *A. fumigatus*



JP Wennrich

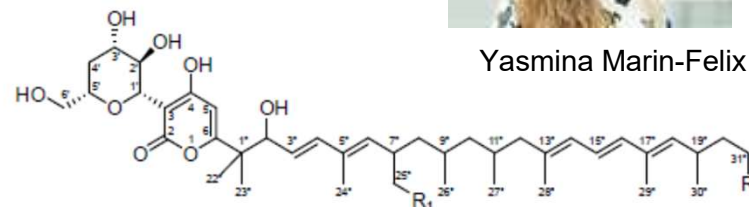
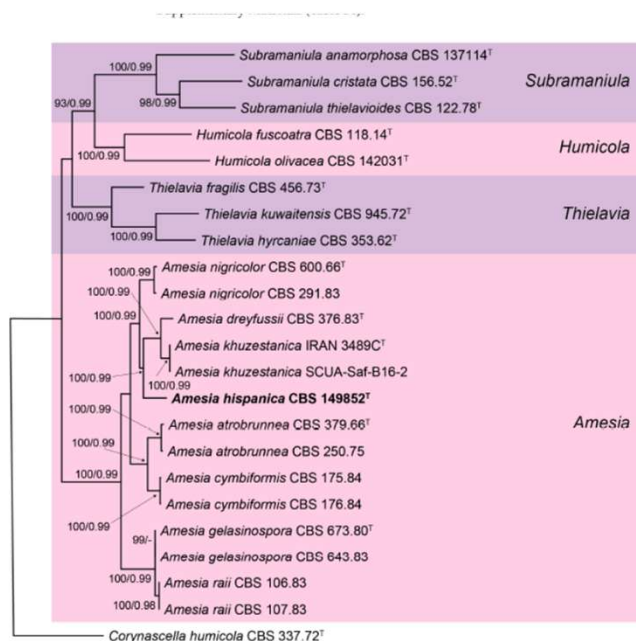
Re-discovery of Dactylfungins (2)



Yasmina Marin-Felix



Adéla Wennrich
(née Cmokova)

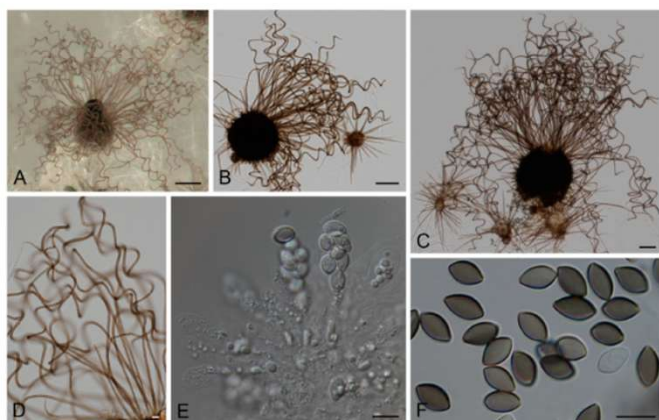


- 1 R₁=OH, R₂=H
2 R₁=OH, R₂=OH
3 R₁=H, R₂=H

no inhibition observed under test conditions, nt: not tested.

Bioassay	Test Organism/Cell Line	Compound				Positive Control
		1	2	3	4	
MIC (µg/mL)	<i>Rhizopus arrhizus</i>	100	100	50	nt	16.65 ¹
	<i>Cryptococcus neoformans</i> *	6.25	-	-	nt	2.08 ¹
	<i>Aspergillus fumigatus</i>	6.25	25	100	nt	33.3 ¹
	<i>Schizosaccharomyces pombe</i>	-	-	4.2	-	8.3 ²
	<i>Wickerhamomyces anomalus</i>	-	-	-	-	8.3 ²
	<i>Mucor hiemalis</i>	-	-	66.6	-	8.3 ²
	<i>Candida albicans</i>	-	-	-	-	8.3 ²
	<i>Rhodotorula glutinis</i>	66.6	-	4.2	66.6	4.2 ²
	<i>Acinetobacter baumannii</i>	-	-	-	-	0.26 ³
	<i>Escherichia coli</i>	-	-	-	-	1.7 ⁴
	<i>Bacillus subtilis</i>	-	66.6	-	66.6	8.3 ⁴
	<i>Mycobacterium smegmatis</i>	-	-	-	-	1.7 ⁵
	<i>Staphylococcus aureus</i>	-	-	-	-	0.42 ⁴
	<i>Pseudomonas aeruginosa</i>	-	-	-	-	0.21 ⁶
	<i>Chromobacterium violaceum</i>	-	-	-	-	0.42 ⁴
IC ₅₀ (µM)	L929	-	-	32.1	5.5	0.00134 ⁷
	KB 3.1	-	-	19.0	4.9	0.00006 ⁷

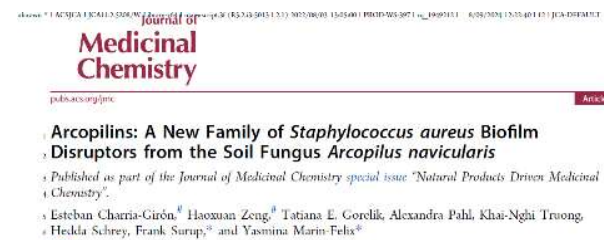
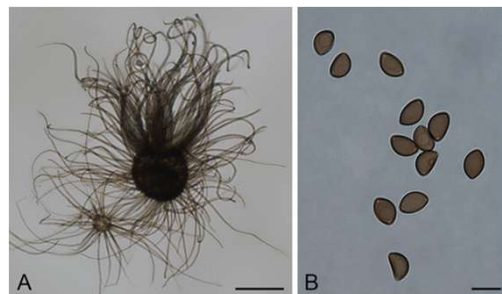
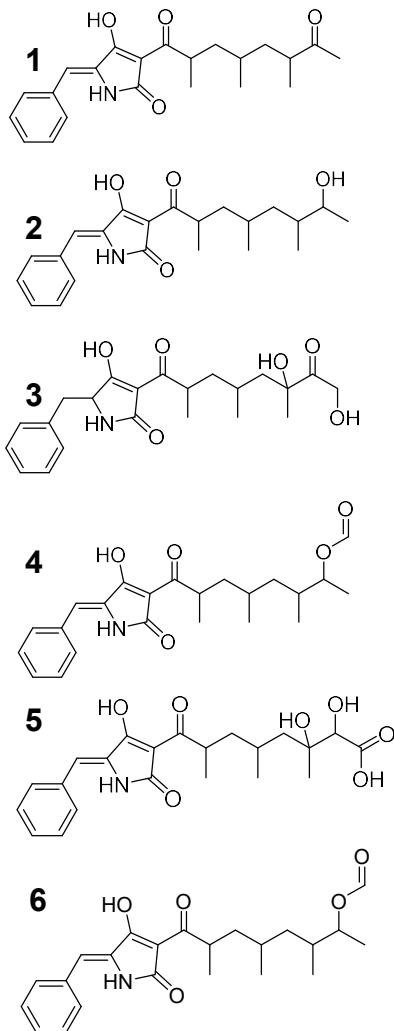
* The minimum inhibitory concentration (MIC) against *Cryptococcus neoformans* was positively scored in case of 50% inhibition. MIC against other microorganisms was considered positive at 100% inhibition.



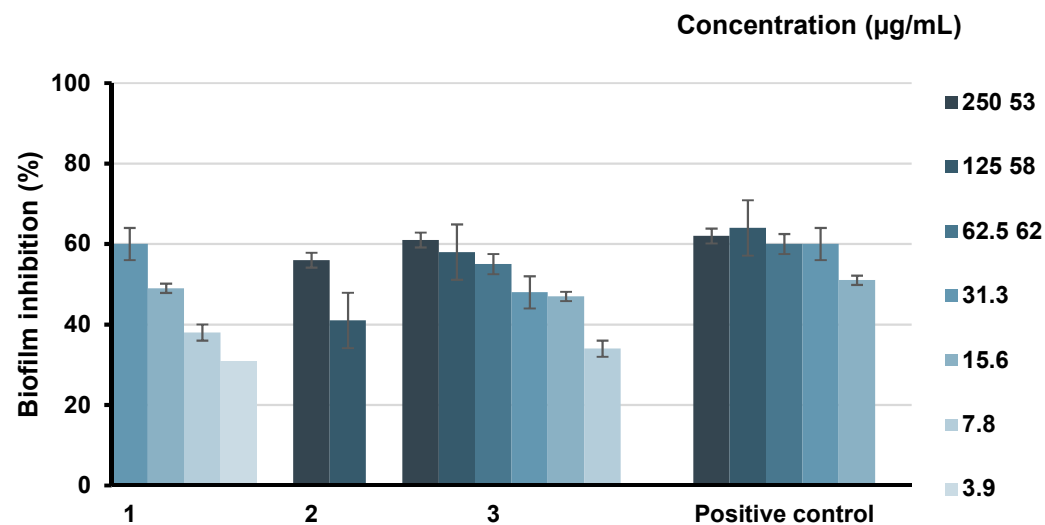
Strong effects against fungal pathogens

Arcopilus navicularis as source of biofilm inhibitors

Arcopilins A-G

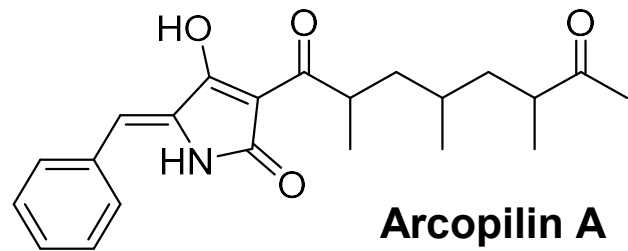


Dispersion of preformed biofilm of *Staph. aureus*



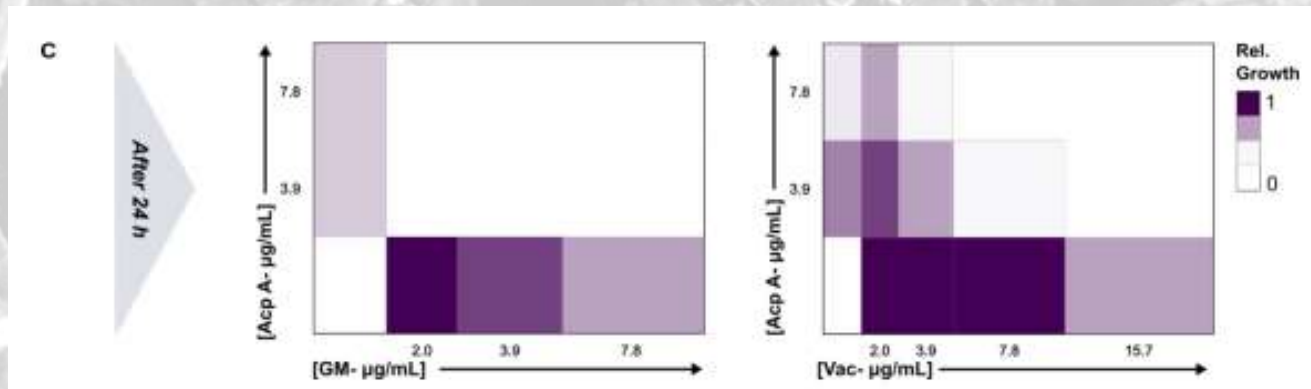
Potential of antibiotic effects
(gentamicin 115x; vancomycin 31x)

Arcopilus navicularis as source of biofilm inhibitors



Gentamicin

Vancomycin



Arp A potentiates the bactericidal activity of gentamicin and vancomycin up to 115- and 31-fold times, respectively

A new endophyte genus from Algeria



Sarah Raouia Noumeur

Mycological Progress (2020) 19:589–603
https://doi.org/10.1007/s11557-020-01581-9

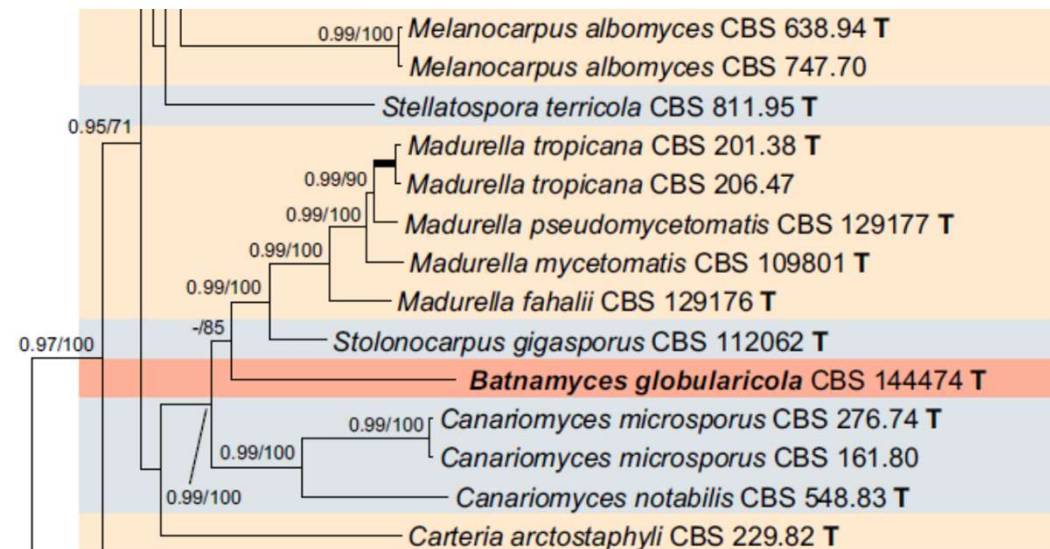
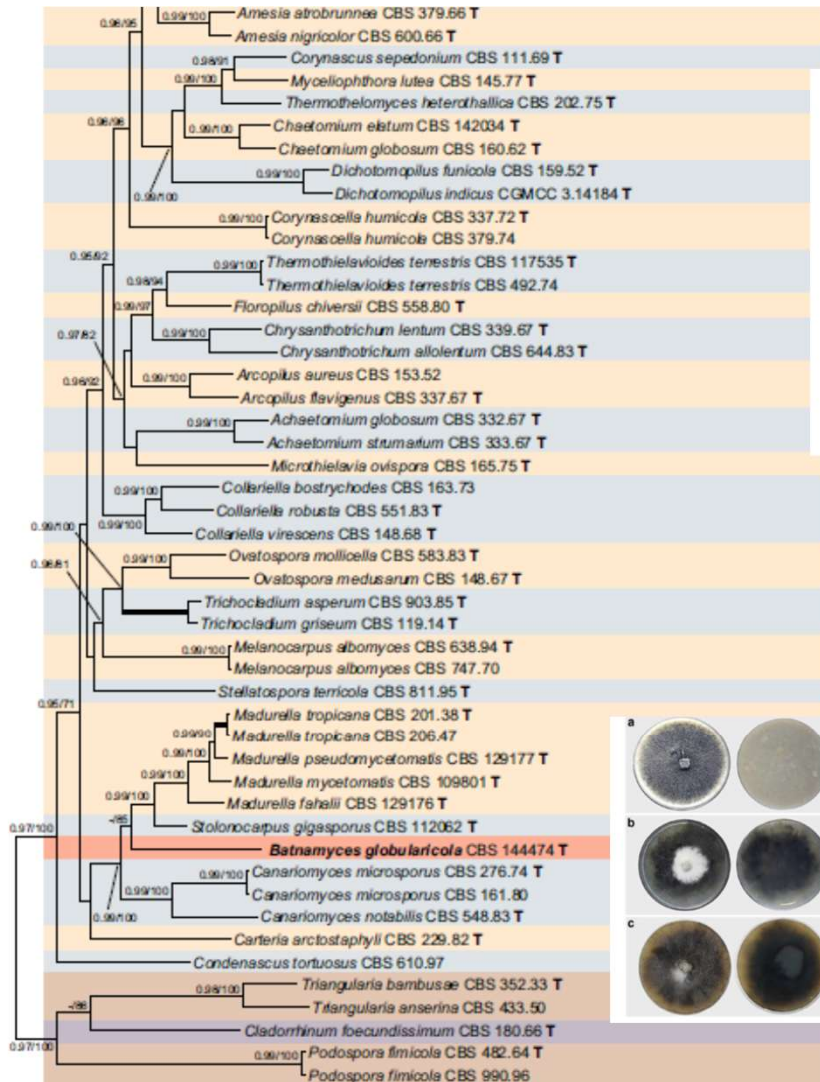


ORIGINAL ARTICLE



Diketopiperazines from *Batnamyces globulariicola*, gen. & sp. nov. (Chaetomiaceae), a fungus associated with roots of the medicinal plant *Globularia alypum* in Algeria

Sara R. Noumeur^{1,2} · Rémy B. Teponno^{1,3} · Soleiman E. Helaly^{1,4} · Xue-Wei Wang⁵ · Daoud Harzallah⁶ · Jos Houbraken⁷ · Pedro W. Crous⁷ · Marc Stadler¹



Close to pathogens like *Madurella* and also thermophilic!

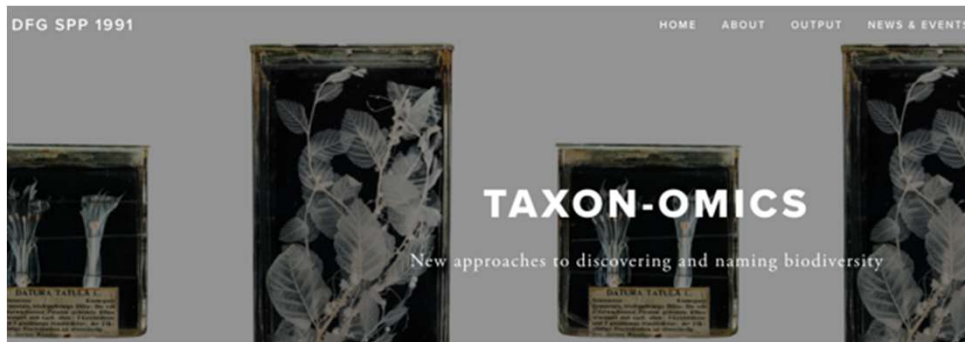
Characterized by phylogenetic methods and new secondary metabolites

Xylariales HQ Genomes Project

- Genome sequencing of 12 representatives of Hypoxylaceae and the ex-epitype strain of *Xylaria hypoxylon*
- **High genome quality** (between 16 and 88 contigs) with N50 ranging from 1,165,420 bp to 5,039,066 bp based on **third generation techniques (Oxford nanopore/ONP) and PACBIO** polished with Illumina
- Gene prediction and annotation using Augustus and Genemark
- Between 8,988 and 11,762 genes per genome



Eric Kuhnert



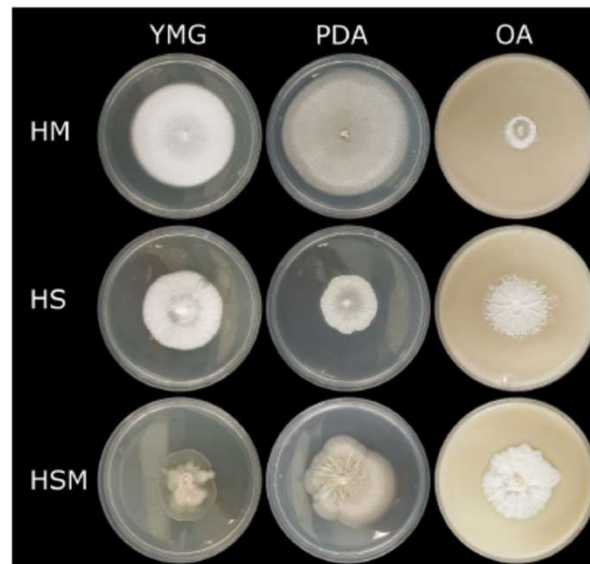
Collaboration with Russell Cox and J. Kalinowski in the course of DFG SPP 1991 „Taxon-omics“
Genome data provided by CEBITEC Bielefeld and DSMZ

1st in Class phylogenomic study on an ascomycete family using 3rd generation genome data

Table 1 Details of the genome sequences generated for the selected Xylariales

Organism	Strain	Sequencing method	Genome size (bp)	Contigs	N50 (bp)	Annotated genes ^a	GC (%)
<i>Annulohypoxylon truncatum</i>	CBS 140778	ONT/ILU	38,511,861	64	1,760,563	11,384	46.5
<i>Daldinia concentrica</i>	CBS 113277	ONT/ILU	37,605,921	69	2,728,111	11,205	43.8
<i>Entonaema liquescens</i>	ATCC 46302	ONT/ILU	39,197,785	31	3,541,465	10,384	43.4
<i>Hypomontagnella monticulosa</i>	MUCL 54604	ONT/ILU	42,889,121	30	3,439,634	12,475	46.0
<i>Hypomontagnella spongiphila</i>	MUCL 57903	ONT/ILU	42,173,915	16	5,039,066	12,622	46.2
<i>Hypomontagnella submonticulosa</i>	DAOMC 242471	ONT/ILU	41,574,079	125	657,615	11,692	46.3
<i>Hypoxylon fragiforme</i>	MUCL 51264	PB	38,198,373	36	3,581,784	10,557	46.2
<i>Hypoxylon lienhwacheense</i>	MFLUCC 14-1231	ONT/ILU	35,785,595	61	1,602,745	9,942	45.4
<i>Hypoxylon pulicicidum</i>	ATCC 74245	ONT/ILU	43,543,700	24	3,855,590	12,174	44.8
<i>Hypoxylon rickii</i>	MUCL 53309	ONT/ILU	41,846,710	81	3,963,481	11,101	46.4
<i>Hypoxylon</i>							44.1
<i>Ja</i>							45.8
<i>P</i>							44.9
<i>X</i>							40.7

Fig. 7 Culture morphology of various members of the *Hypomontagnella monticulosa* species complex after 16 days of growth on different media (YMG, PDA, OA). HM – *Hypom. monticulosa* MUCL 54604, HS – *Hypom. spongiphila* MUCL 57903, HSM – *Hypom. submonticulosa* DAOMC 242471



Hypomontagnella spongiphila, the first fungal species that was erected based on phylogenomic comparison data

[Open Access](#) | [Published: 25 May 2020](#)

High quality genome sequences of thirteen Hypoxylaceae (Ascomycota) strengthen the phylogenetic family backbone and enable the discovery of new taxa

[Daniel Wibberg](#), [Marc Stadler](#), [Christopher Lambert](#), [Boyke Bunk](#), [Cathrin Spröer](#), [Christian Rückert](#), [Jörn Kalinowski](#), [Russell J. Cox](#) & [Eric Kuhnert](#) ✉

[Fungal Diversity](#) **106**, 7–28 (2021)

8019 Accesses | **57** Citations | **5** Altmetric | [Metrics](#)



Secondary metabolite biosynthetic diversity in the fungal family *Hypoxylaceae* and *Xylaria hypoxylon*

E. Kuhnert^{1*}, J.C. Navarro-Muñoz², K. Becker^{1,3}, M. Stadler³, J. Collemare², and R.J. Cox¹

¹Centre of Biomolecular Drug Research (BMWZ), Institute for Organic Chemistry, Leibniz University Hannover, Schneiderberg 38, 30167, Hannover, Germany;

²Westerdijk Fungal Biodiversity Institute, Uppsalalaan 8, 3584 CT, Utrecht, The Netherlands; ³Department Microbial Drugs, Helmholtz Centre for Infection Research (HZI), German Centre for Infection Research (DZIF), partner site Hannover-Braunschweig, Inhoffenstrasse 7, 38124, Braunschweig, Germany

*Correspondence: E. Kuhnert, eric.kuhnert@oci.uni-hannover.de

Table 3. Classes of biosynthetic gene clusters (BGC) and number of representatives identified in the genomes of *X. hypoxylon* and selected *Hypoxylaceae* by manual genome mining. Frequency and total number of BGCs are colour coded (green to red – rare to common, light blue to dark blue – low number to high number).

BGC-type		Organism													
class	subclass	<i>X. hypoxylon</i>	<i>H. rubiginosum</i>	<i>H. fragiforme</i>	<i>H. rickii</i>	<i>H. pulicidum</i>	<i>A. truncatum</i>	<i>J. multififormis</i>	<i>Hypom. submonticulosa</i>	<i>Hypom. spongiphila</i>	<i>Hypom. monticulosa</i>	<i>H. lien-hwachense</i>	<i>P. hunteri</i>	<i>D. concentrica</i>	<i>Daldinia sp.</i>
PKS	nrPKS	10	8	6	7	7	6	6	3	5	5	2	4	5	4
	hrPKS	26	23	13	16	18	19	20	18	23	23	10	8	16	22
	prPKS	7	3	3	3	4	2	2	1	4	2	1	3	2	3
	Collaborative ¹	-	5	2	1	4	-	2	5	6	7	-	1	-	1
	Type III	2	1	1	1	1	1	1	1	1	1	1	1	1	1
Mero-terpenoid	Broken ²	4	-	-	-	-	1	1	-	1	1	-	1	-	-
	PKS	2	2	1	(1)	1	1	1	-	1	-	-	-	-	-
PKS-NRPS	Indole	-	(1)	-	-	1	-	-	-	-	-	-	-	-	-
	Broken ²	6	2	2	3	4	2	4	-	1	1	1	1	1	1
NRPS	Siderophore	2	2	2	3	2	2	2	2	2	2	2	2	2	2
	Other	5	5	1	2	3	3	2	2	2	3	2	2	3	4
NRPS-like ³	TE-release	-	2	-	3	3	4	1	1	-	-	-	1	2	1
	Red-release (clustered)	2	5	1	4	1	1	4	4	9	5	1	4	3	5
	Red-release (unclustered)	12	6	10	6	9	7	4	6	7	7	5	4	7	6
Alkaloid	NRPS-PKS	1	-	-	-	-	-	-	1	-	-	-	-	-	-
	Ergot alkaloid	-	-	-	-	-	1	-	-	1	1	-	-	-	-
	Other ⁴	-	1	-	-	-	-	1	-	-	-	-	-	1	1
Alkyl ⁵	FAS	1	1	1	1	1	1	1	2	2	2	1	1	1	1
citrates	PKS	-	-	-	-	-	-	-	-	-	-	1	-	-	-
	Other	10	9	10	9	12	12	8	7	9	10	3	4	8	8
Terpene ⁶	Labdane	4	2	-	4	1	3	1	2	-	-	-	-	3	-
	Triterpenoid	1	1	-	-	-	-	-	-	-	-	-	-	-	-
RiPP		-	1	-	-	1	-	-	1	1	1	-	-	-	-
Total ⁷		83	75	43	58	64	59	57	50	69	64	25	33	48	55

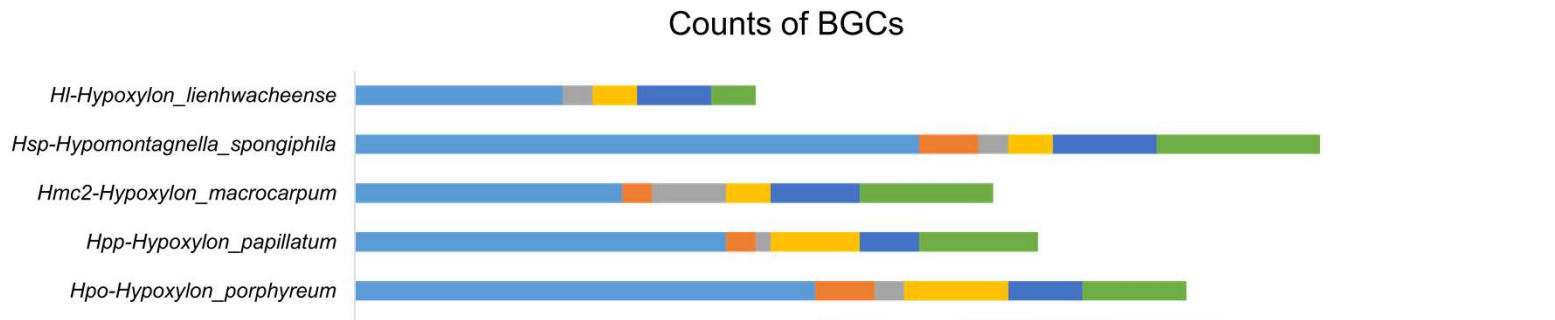
rare common

Several BGC analogues putatively encoding for metabolites that were never before found in Xylariales detected

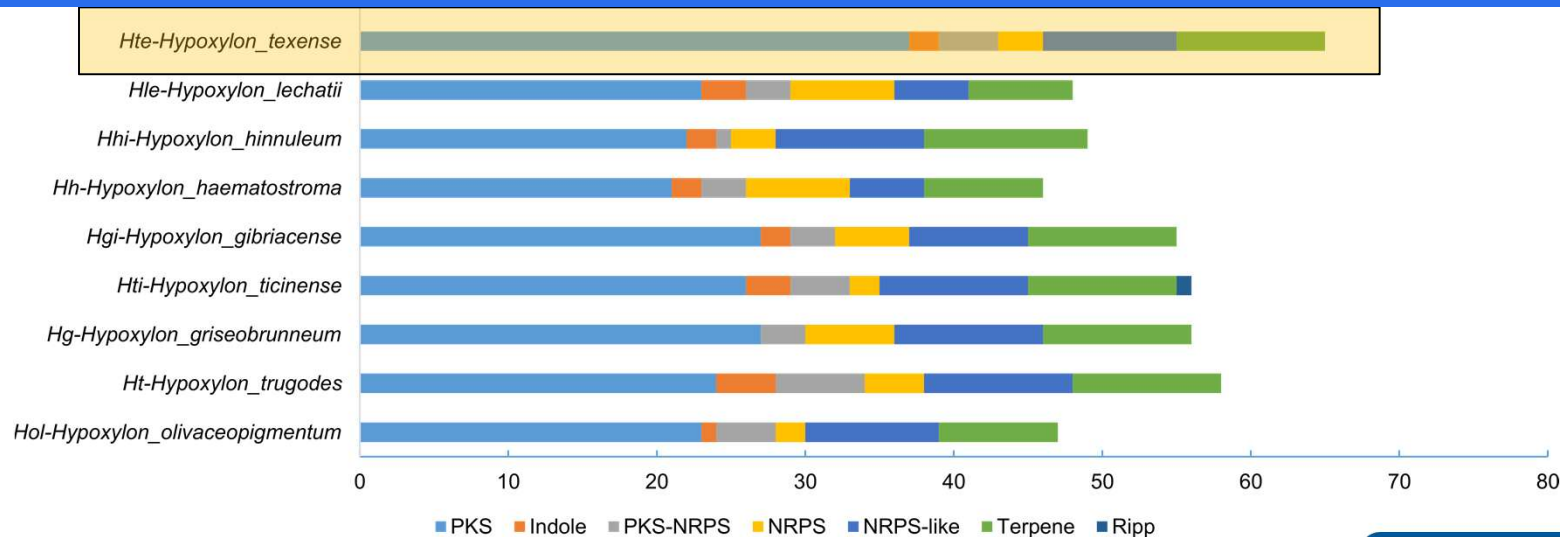
The majority of BGC detected could not be associated with any known class of fungal metabolites

DFG SPP1991, project Hypoxylomics (2022-2025)

50 further high quality genomes generated (ONP) & annotated
Examples with BGC counts see below



Hypoxylon texense genome: 10 contigs, nine of which represent the chromosome and the tenth the mitochondrion!





Haoxuan Zeng

Article

Inhibitory Effects of the Fungal Pigment Rubiginosin C on Hyphal and Biofilm Formation in *Candida albicans* and *Candida auris*

Haoxuan Zeng ^{1,2}, Marc Stadler ^{1,2}, Wolf-Rainer Abraham ¹, Mathias Müssen ^{3,*} and Hedda Schrey ^{1,2,*}

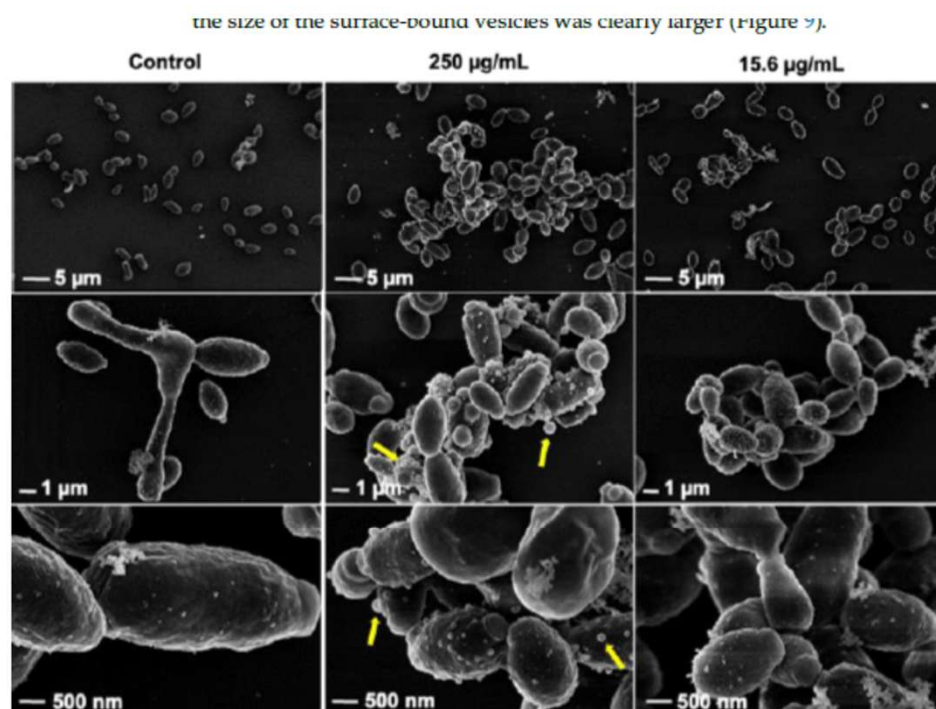


Figure 9. Effects of Rub C on the planktonic cells of *C. auris*, as shown by SEM micrographs. Cells were incubated with Rub C in RPMI 1640 (supplemented with 0.165 mM MOPS) at 37 °C and exposed to Rub C with indicated concentrations. Differences with regard to cell morphology and vesicles are observed in the samples treated with 250 µg/mL Rub C (yellow arrows).

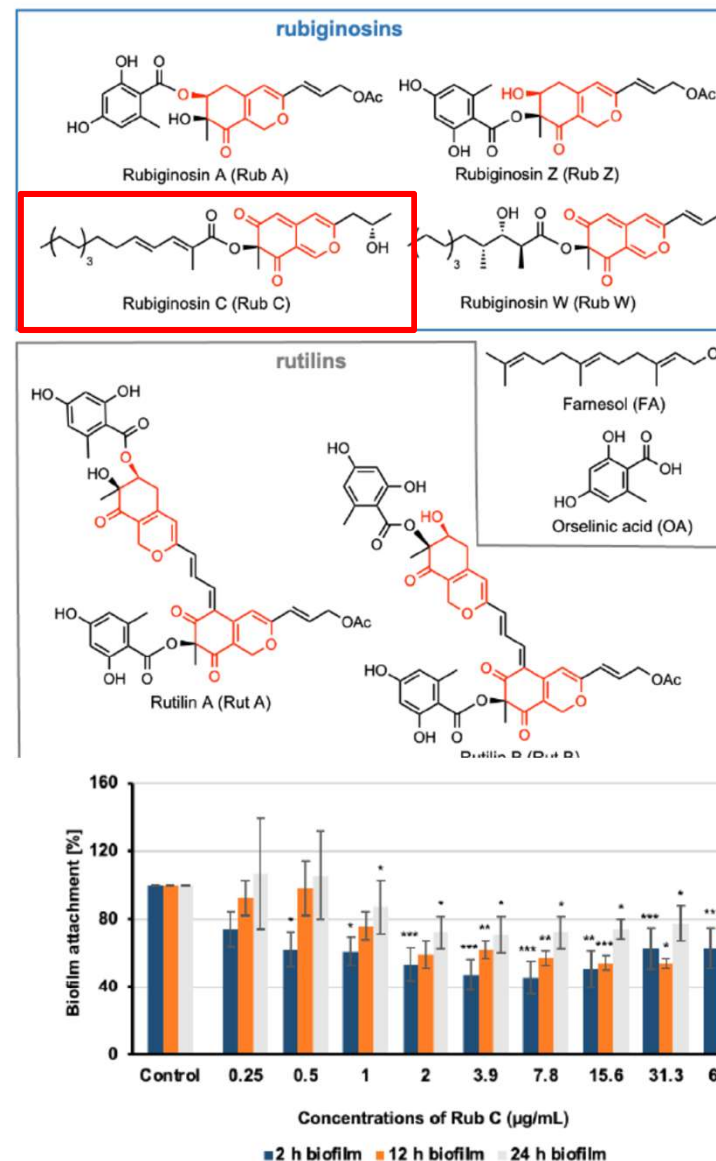


Figure 4. Effect on biofilm formation of pre-grown *C. auris* biofilms of different developmental stages (2 h, 12 h, and 24 h) after 24 h treatment with Rub C. The solvent methanol served as solvent control. Error bars indicate SD of duplicates in two biological repeats; *p* values: * *p* < 0.05, ** *p* < 0.01, *** *p* < 0.001.

New genus justified by chemotaxonomic evidence & molecular phylogeny

Mycological Progress (2019) 18:187–201
<https://doi.org/10.1007/s11557-018-1452-z>

ORIGINAL ARTICLE

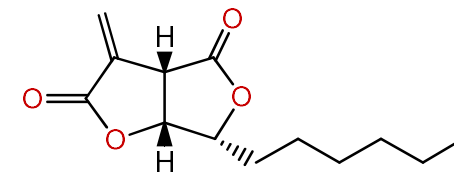
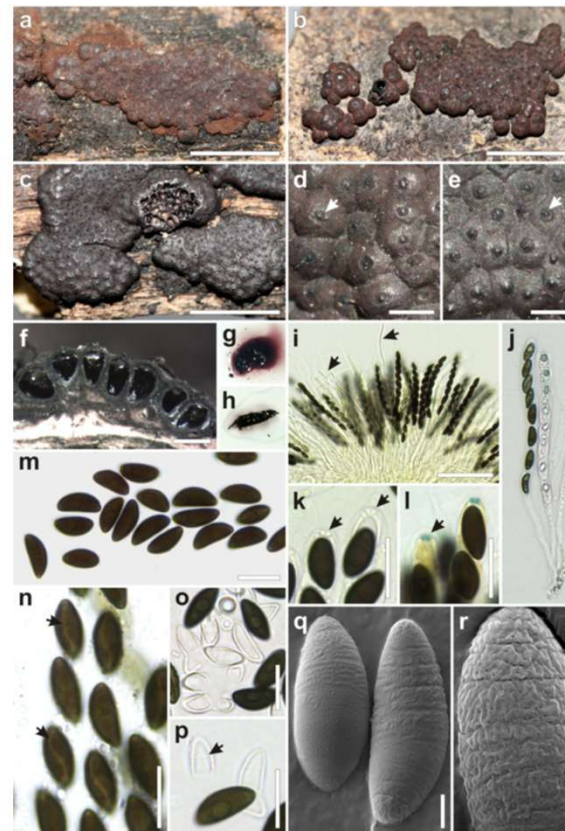
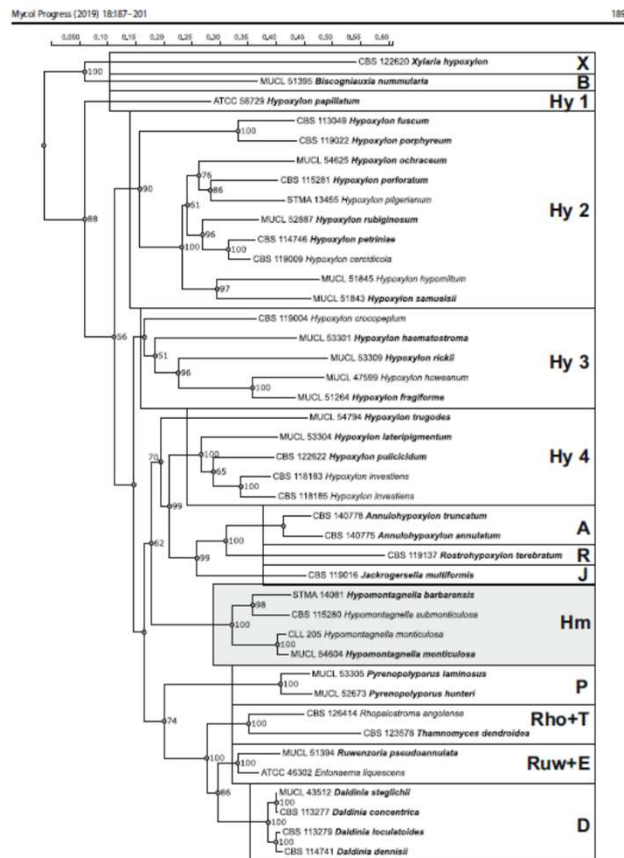


Hypomontagnella (Hypoxylaceae): a new genus segregated from *Hypoxylon* by a polyphasic taxonomic approach

Christopher Lambert^{1,2} · Lucie Wendt^{1,2} · Adriana I. Hladki³ · Marc Stadler^{1,2} · Esteban Benjamin Sir³



Christopher Lambert

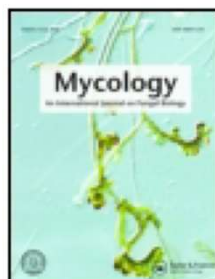


Sporothriolides =
 Genus-specific marker
 metabolites with
**selective antifungal
 effects**

Preliminary data: Sporothriolide is a selective antifungal agent!

Table 3. Minimal inhibitory concentrations (MIC) of sporothriolide (**1**), dihydrosporothriolide (**2**) and isosporothric acid (**4**), all solved in MeOH, and control drugs. [a] Oxytetracyclin hydrochloride, [b] Gentamycin, [c] Nystatin, [d] Amphotericin B, [e] Polymyxin B sulphate; -: no inhibition; n.t.: not tested. The cell density was adjusted to 8×10^6 cells/ml. * spores from agar plate were applied without justification.

Test organisms	MIC [$\mu\text{g/ml}$]			
	1	2	4	Reference
<i>Mucor hiemalis</i> * (DSM 2656)	4.2	n.t.	n.t.	5.25 [c]
<i>Candida albicans</i> (DSM 1665)	16.6	—	—	8.3–33.3 [c]
<i>Nematospora coryli</i>	8.3	n.t.	n.t.	67.0 [c]
<i>Pichia anomala</i> (DSM 8766)	33.3	—	—	8.3–33.3 [c]
<i>Rhodotorula glutinis</i> (DSM 10134)	16.6	n.t.	n.t.	16.7 [c]
<i>Schizosaccharomyces pombe</i> (DSM 70572)	8.3	n.t.	n.t.	41.5 [c]
<i>Trichosporon oleaginosus</i> (DSM 11815)	16.6	n.t.	n.t.	4.2 [c]
<i>Bacillus subtilis</i> (DSM 10)	—	—	—	33.3 [a]
<i>E. coli</i> (DSM 1116)	—	—	—	0.83 [a]
<i>Pseudomonas aeruginosa</i> (DSM 50071)	—	—	—	16.6 [b]



Mycology: An International Journal on Fungal Biology

Publication details, including instructions for authors and subscription information:
<http://www.tandfonline.com/loi/tmyc20>

Sporothriolide derivatives as chemotaxonomic markers for *Hypoxyton monticulosum*

Frank Surup^{ab}, Eric Kuhnert^{ab}, Erik Lehmann^{ab}, Simone Heitkämper^{ab}, Kevin D. Hyde^c, Jacques Fournier^d & Marc Stadler^{ab}

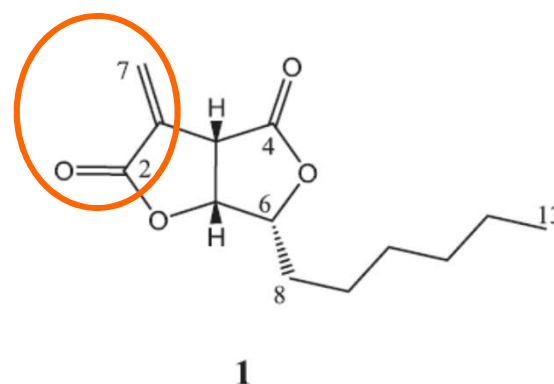
^a Department Microbial Drugs, Helmholtz-Centre for Infection Research, Inhoffenstrasse 7, 38124 Braunschweig, Germany

^b German Centre for Infection Research (DZIF), Inhoffenstraße 7, 38124 Braunschweig, Germany

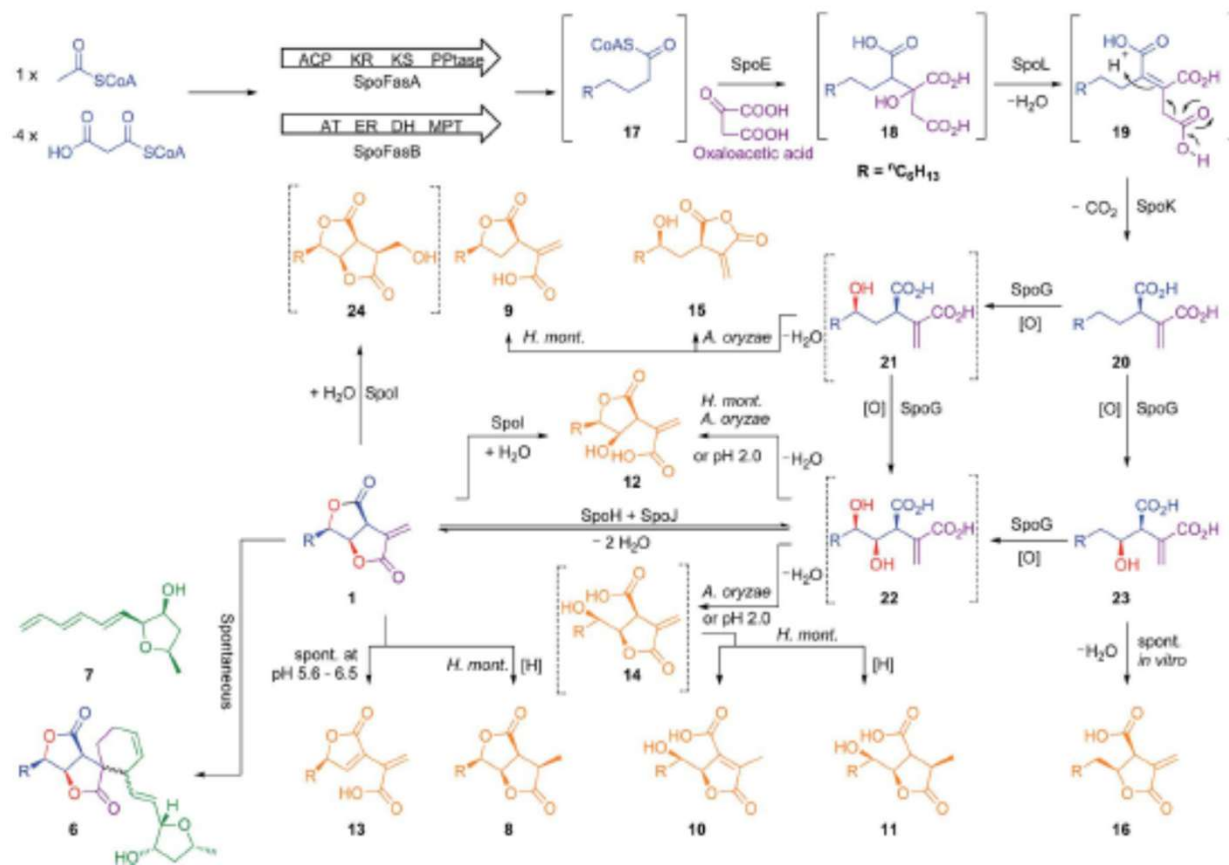
^c Institute of Excellence in Fungal Research and School of Science, Mae Fah Luang University, Chiang Rai 57100, Thailand

^d Las Muros, F-09420 Rimont, France
 Published online: 26 Jun 2014.

Surprisingly, no cytotoxicity and no antibacterial effects were observed, **despite the presence of an exo-methylene keto moiety !**



Biosynthesis of sporothriolides and sporochartins



Scheme 1 Proposed biosynthesis of sporothriolide **1** and sporochartines **6**. Orange compounds result from shunt steps. Compounds in solid square brackets were not experimentally observed and those in dashed brackets were observed during experiments but structures could not be confirmed by NMR. Abbreviations: AT, acyl transferase; ER, enoyl reductase; MPT, malonyl palmitoyl transferase; ACP, acyl carrier protein; KR, ketoreductase; KS, ketosynthase; PPTase, phosphopantetheinyl transferase.

Several key enzymes identified by heterologous expression

Alkyl citrates and their biosynthesis

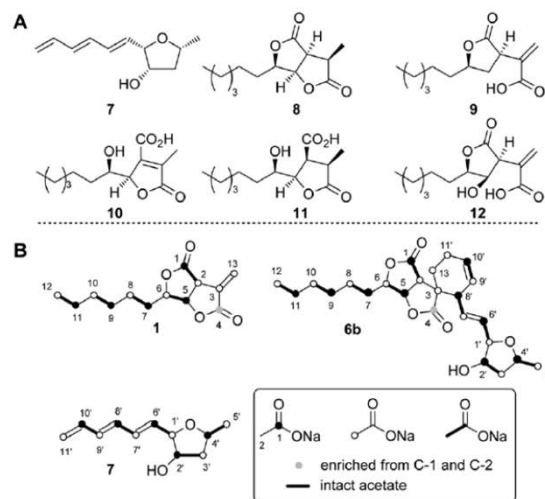


Fig. 2 (A) Isolated compounds from *H. spongiphila* CLL 205. Isotope labelled compounds from [1-¹³C], [2-¹³C] and [1,2-¹³C] acetate feeding experiments.

Feeding experiments

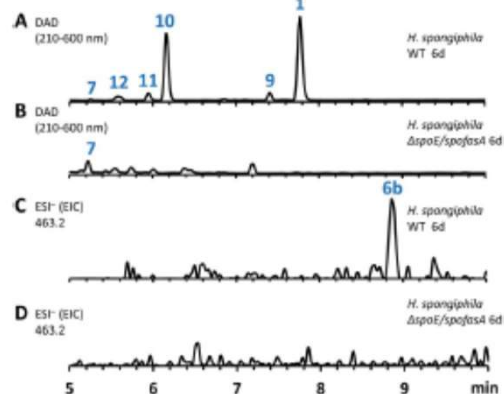


Fig. 4 HPLC analysis of crude extracts from *H. spongiphila* CLL 205 grown under producing conditions of **1**: (A), Diode Array Detector (DAD) chromatogram of wild-type (WT); (B), DAD chromatogram of $\Delta spoE/spofasA$; (C), extracted ion chromatogram (EIC of **6b**, ESI⁻, 463.2, M + HCOO⁻) of WT extract; (D), EIC of $\Delta spoE/spofasA$ transformant showing absence of **6b**.

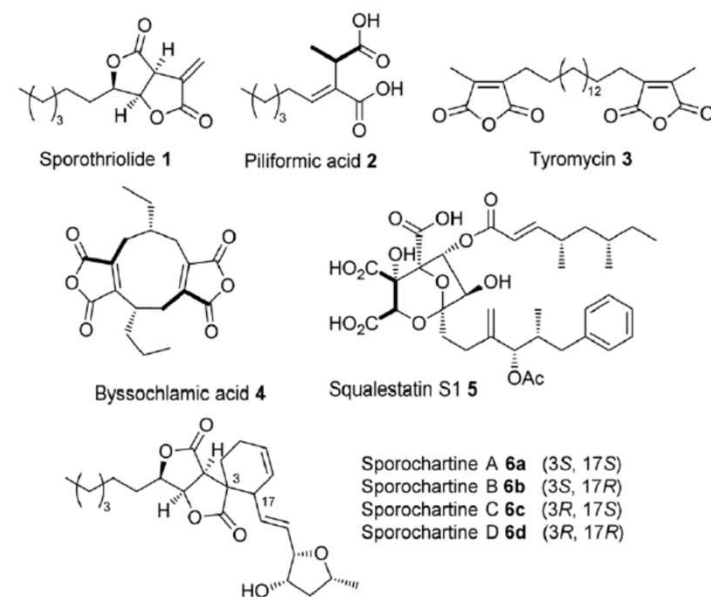


Fig. 1 Structures of γ -lactone and alkyl citrate metabolites from fungi.

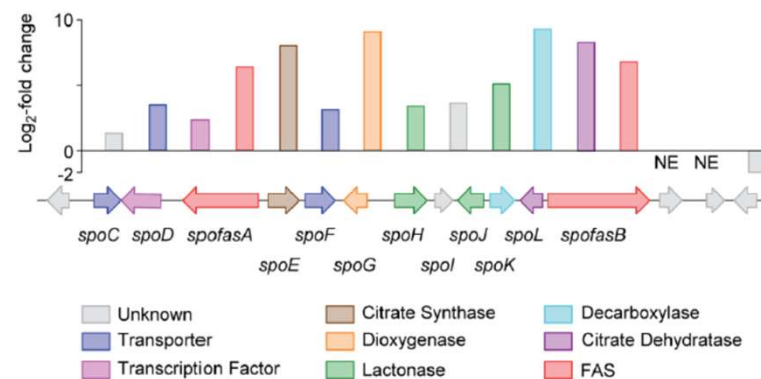


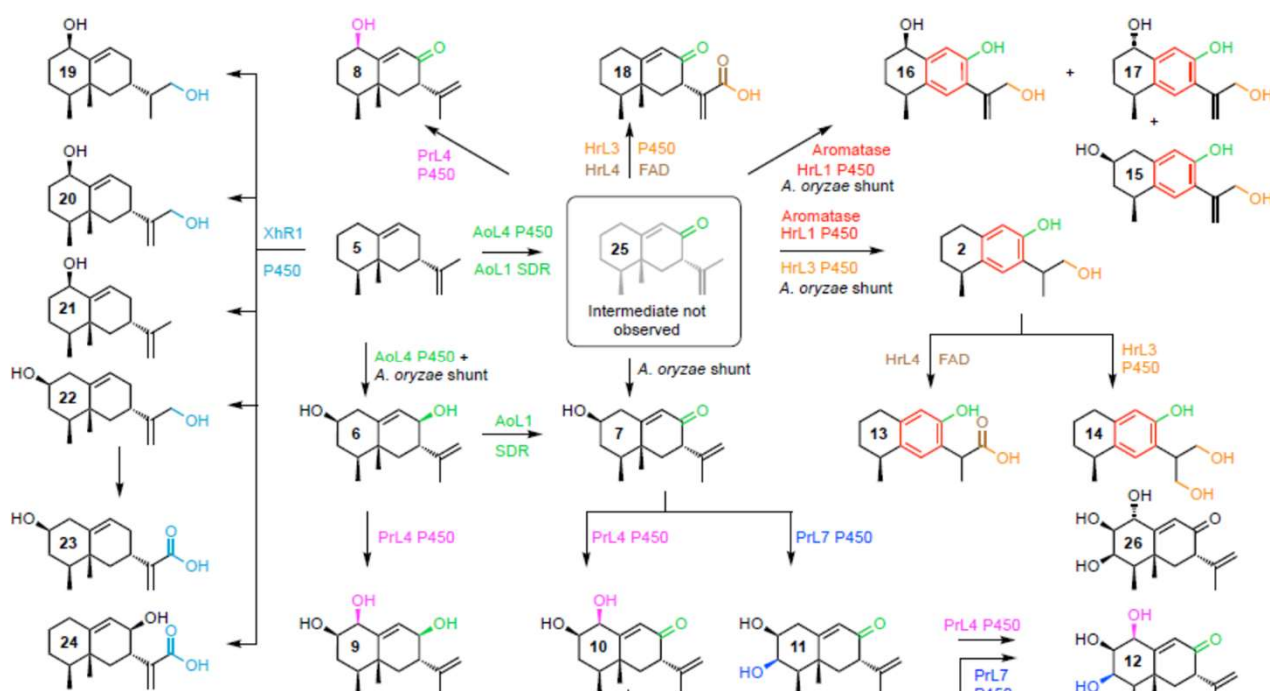
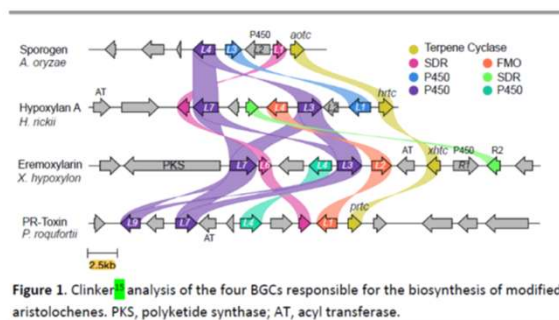
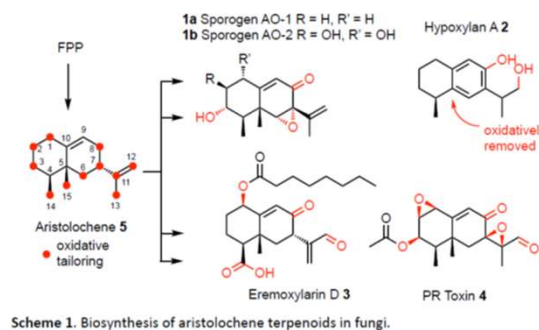
Fig. 3 Transcriptome analysis of the sporothriolide BGC from *H. monticulosa* MUCL 54604. Log₂-fold changes are calculated between producing and non-producing conditions. NE, no expression.

Transcriptome studies (and concurrent HPLC analysis)

Rapid Screening for Terpene Tailoring Enzymes for use in Total Biosynthesis

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Total Biosynthesis yields deliberately designed new terpene scaffolds

Group photo of Department MWIS, June 2023



Ca. 60 people from > 15 countries

Africa trip June 2025

Mycobiomics

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