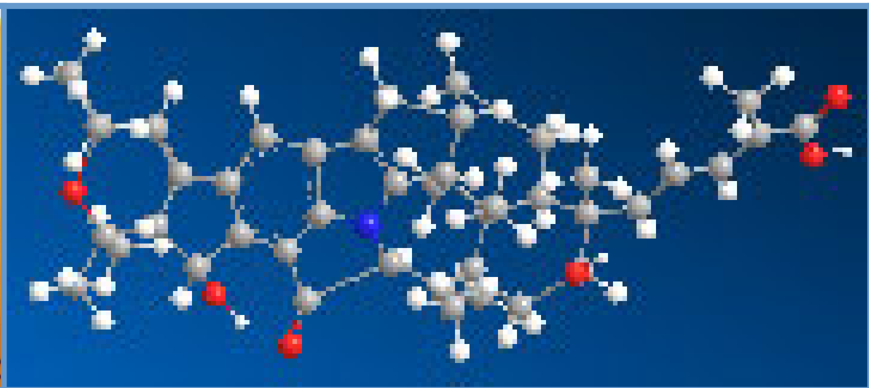
New anti-infective and neurotrophic terpenoids from cultures and “fruiting bodies*” of African, Asian and European Basidiomycota

*basidiomata



Keynote lecture CLAM2023
Panama City
August 2023

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

HZI HELMHOLTZ Centre for Infection Research

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

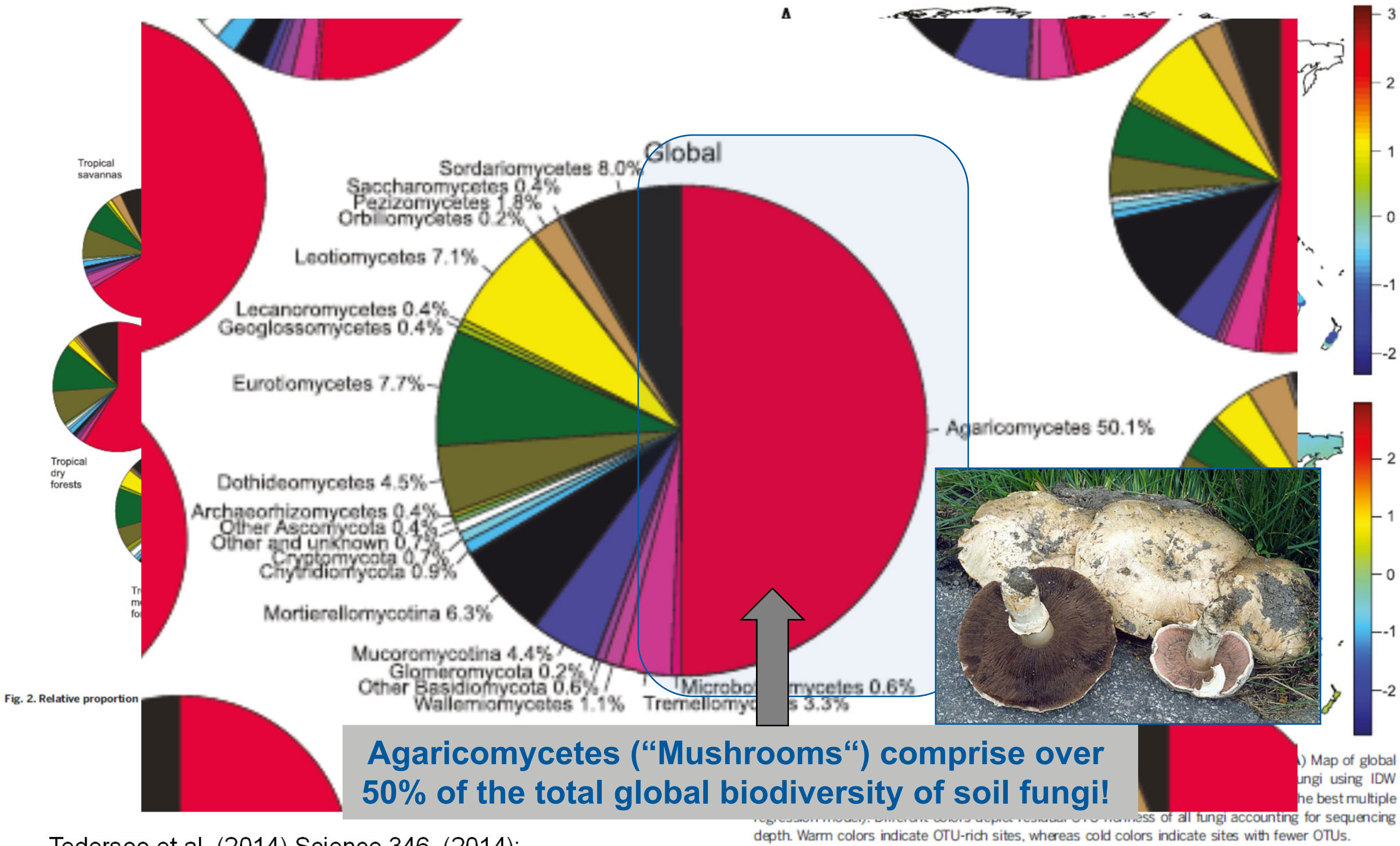
Agro indications

- 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**

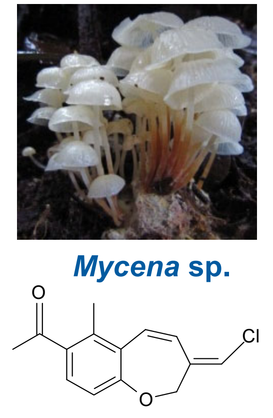
Global diversity of soil fungi



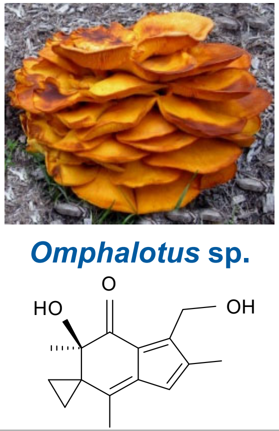
Agaricomycetes (“Mushrooms“) comprise over 50% of the total global biodiversity of soil fungi!

Tedersoo et al. (2014) Science 346, (2014);
DOI: 10.1126/science.1256688

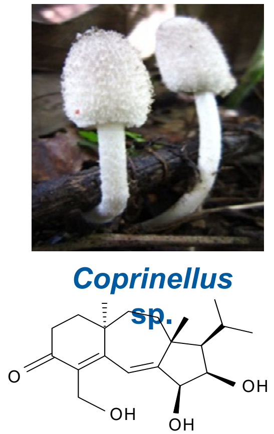
Important metabolites from Basidiomycota



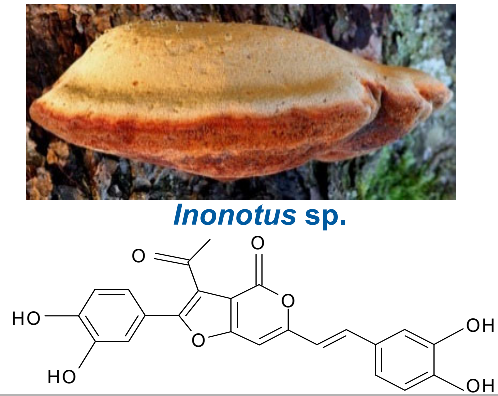
Mycena sp.



Omphalotus sp.

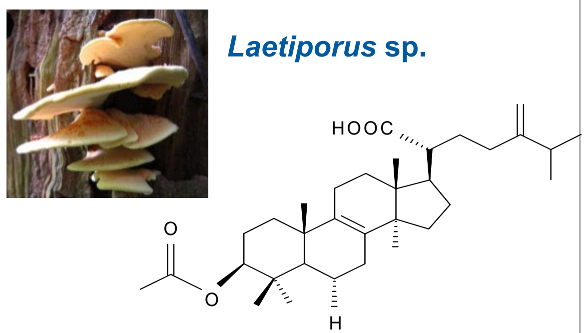


Coprinellus sp.

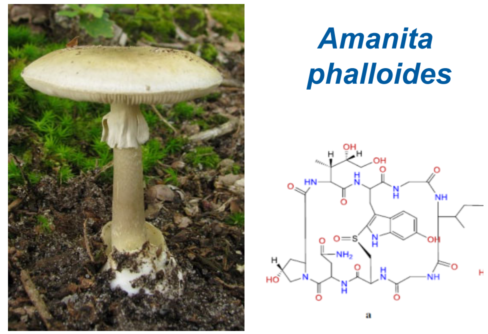


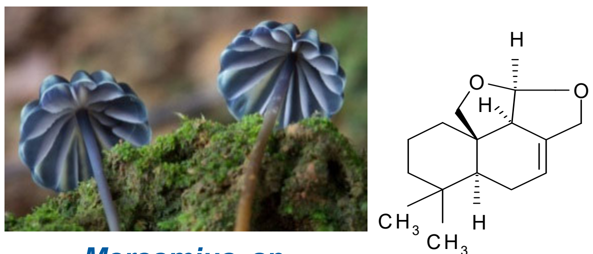
Inonotus sp.

Clitopilus sp.

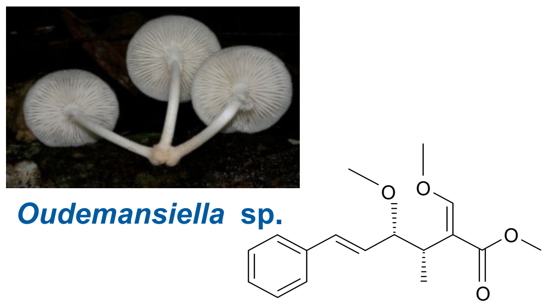


Laetiporus sp.

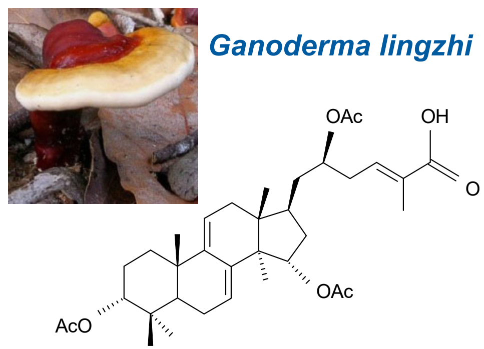

Amanita phalloides



Marasmius sp.



Oudemansiella sp.

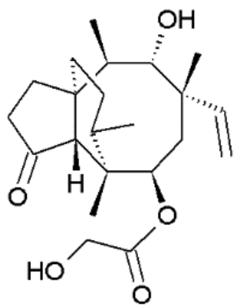


Ganoderma lingzhi

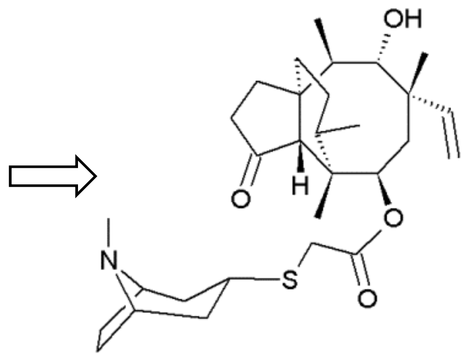
Images by Benjarong Thongbai

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 (inhibitors of protein synthesis)
  Target site different from that of all presently marketed antibiotics

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) | Nabriva Therapeutics - Mozilla Firefox

Datei Bearbeiten Ansicht Chronik Lesezeichen Extras Hilfe

E-Mail | Corallina officinalis - Google | Editorial Manager® | Editorial Manager® | MDPI | Editor Pre Peer-Review | MDPI | Editor Pre Peer-Review | Nabriva Therapeutics Receive

https://investors.nabriva.com/news-releases/news-release-details/nabriva-therapeutics-receives-us-fda-approval-xenleta

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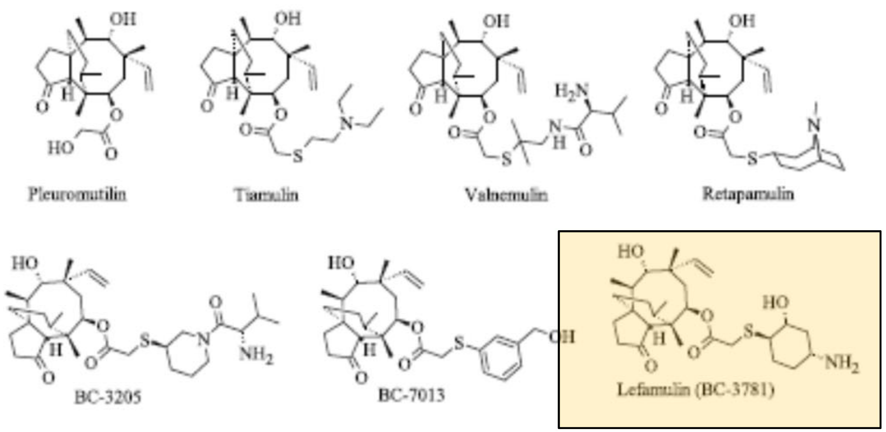
Nabriva Therapeutics Receives U.S. FDA Approval of Xenleta™ (lefamulin) to Treat

Pneumonia (CABP)

560 Fungal Diversity (2022) 116:547–614

Fig. 8 Chemical structures of pleuromutilin and its derivatives



Review | Open Access | Published: 15 September 2022

Ten decadal advances in fungal biology leading towards human well-being

Ausana Mapook, Kevin D. Hyde, Khadija Hassan, Blondelle Matio Kemkuignou, Adéla Čmoková, Frank Surup, Eric Kuhnert, Pathompong Paomephan, Tian Cheng, Sybren de Hoog, Yinggai Song, Ruvishika S. Jayawardena, Abdullah M. S. Al-Hatmi, Tokameh Mahmoudi, Nadia Ponts, Lena Studt-Reinhold, Florence Richard-Forget, K. W. Thilini Chethana, Dulanjalee L. Harishchandra, Peter E. Mortimer, Huili Li, Saisamorm Lumyong, Worawoot Aiduang, Jaturong Kumla, ... Marc Stadler + Show authors

Fungal Diversity 116, 547–614 (2022)

Did the Iceman already known about the therapeutic potential of fungi ?

Fomes fomentarius
Medicinal mushroom, firestarter

Fomitopsis betulina
Medicinal mushroom

The mummy found in the Ötztal Valley carried two fungal materials along in a bag, which may have served as “herbal remedies”

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

Asian medicinal mushrooms

Source of fungal images: *http://www.mycokey.org*

Bioactive principles of many medicinal mushrooms

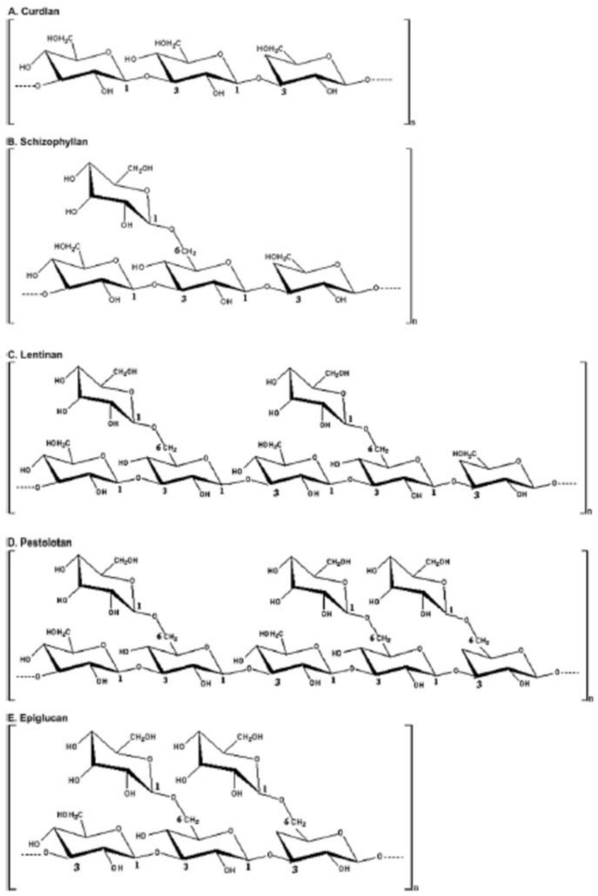
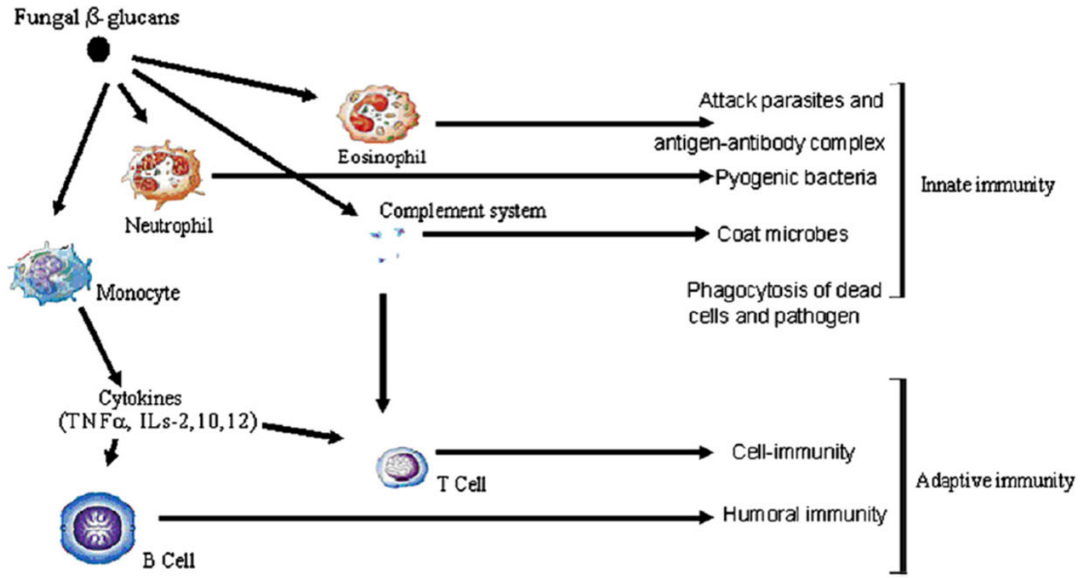


Fig 1 – Examples of structures of β-(1→3)(1→6) glucans showing branching patterns of their repeating units.



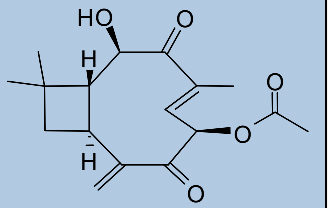
Review

Medicinal importance of fungal β-(1→3), (1→6)-glucans

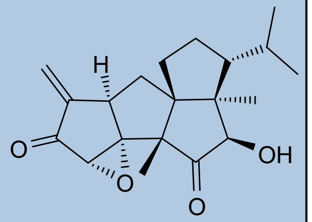
Jiezhong CHEN[a,], Robert SEVIOUR[b]*

Beta-glucans have been identified from over 100 species of medicinal mushroooms but are not well-suited for classical MedChem-driven drug development

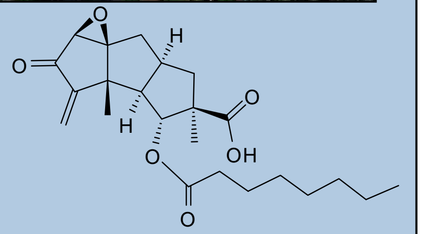
Unique terpenoids from basidiomycetes

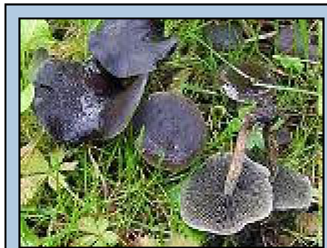
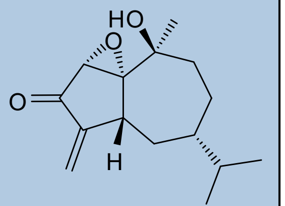
Naematolon (*Hypholoma*)

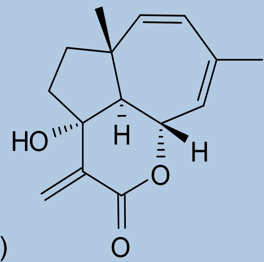
Crinipellin A (*Crinipellis*)

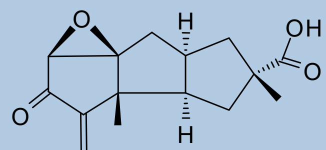
Phellodonic acid (*Phellodon*)

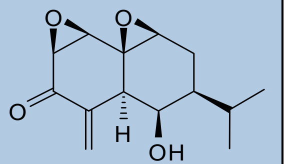
Fimicolon *Panaeolus*)

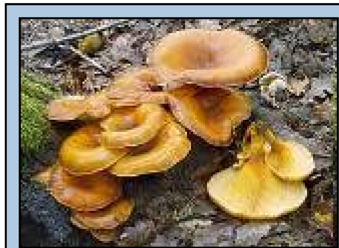
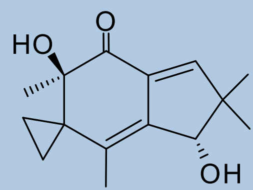
Fulvoferruginin (*Marasmius*)

Complicatic acid (*Stereum*)

Panellon (*Panellus*)

Illudin-M (*Omphalotus*)

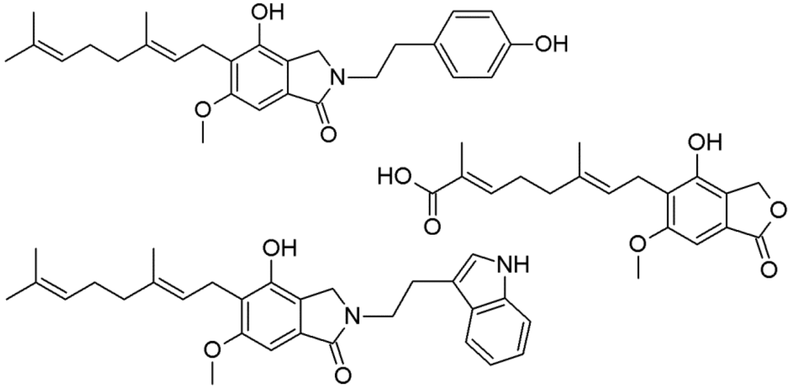
Several hundreds of unique biologically active terpenoids are known from cultures of Basidiomycetes

Source of fungal images: *http://www.mycokey.org*

Evaluation of *Hericium* spp. for antimicrobial & neutrotrophic activities


fruiting bodies extraction
(*H. erinaceus* & *coralloides*)

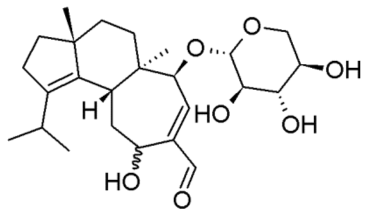
9 hericenones and
hericenone-type compounds



new derivatives from *H. coralloides*


submerged fermentation (different media)
(*H. erinaceus, coralloides* & *alpestre*)

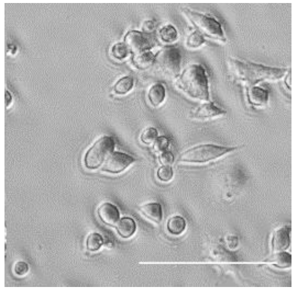
16 cyathane diterpenoids (erinacines)



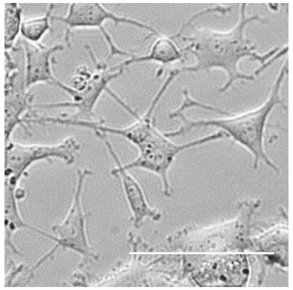
new erinacine

Highly interesting neurotrophic effects

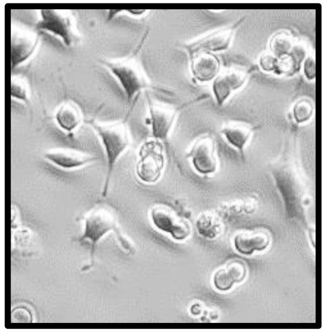
Treatment of PC12 cells with conditioned 1321N1 culture medium



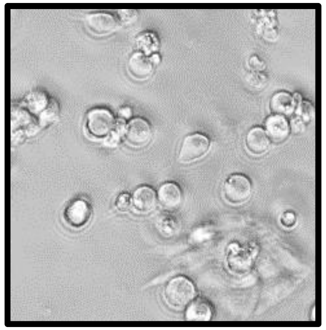
(-) DMSO & 1321N1 medium



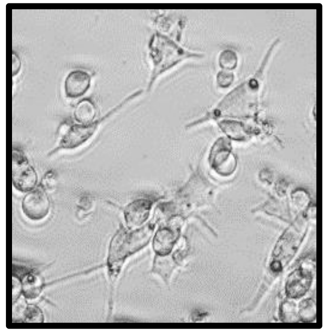
(+) salivary gland extract



A



B

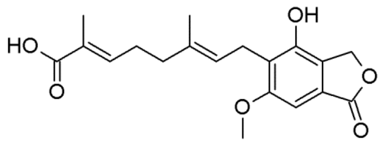


C

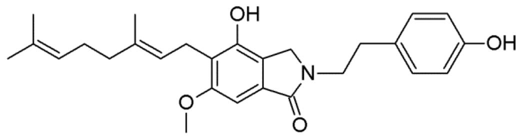
Zeljka Rupcic

Kathrin Wittstein

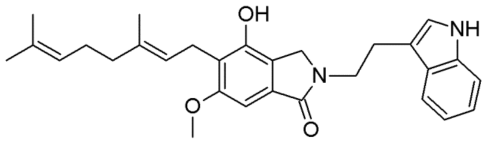
Monique Rascher



corallocin A



corallocin B



corallocin C
(strongest neuritogenic activity of all tested compounds)

HZI HELMHOLTZ Centre for Infection Research

Neurotrophins from *Hericium* cultures

Zeljka Rupcic

Kathrin Wittstein

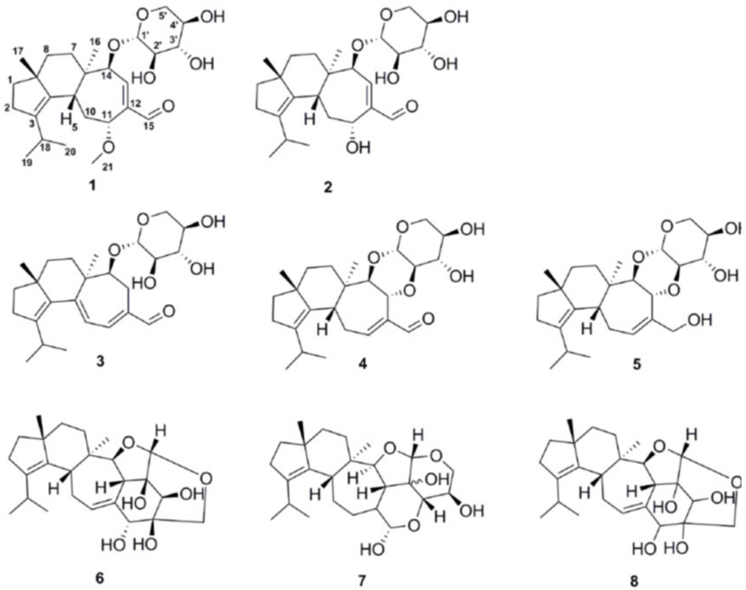
International Journal of
Molecular Sciences

MDPI

Article

Two New Cyathane Diterpenoids from Mycelial Cultures of the Medicinal Mushroom *Hericium erinaceus* and the Rare Species, *Hericium flagellum*

Zeljka Rupcic [1,2,†], Monique Rascher [1,2,3,†], Sae Kanaki [1,4], Reinhard W. Köster [3], Marc Stadler [1,2,*] and Kathrin Wittstein [1,2,*]



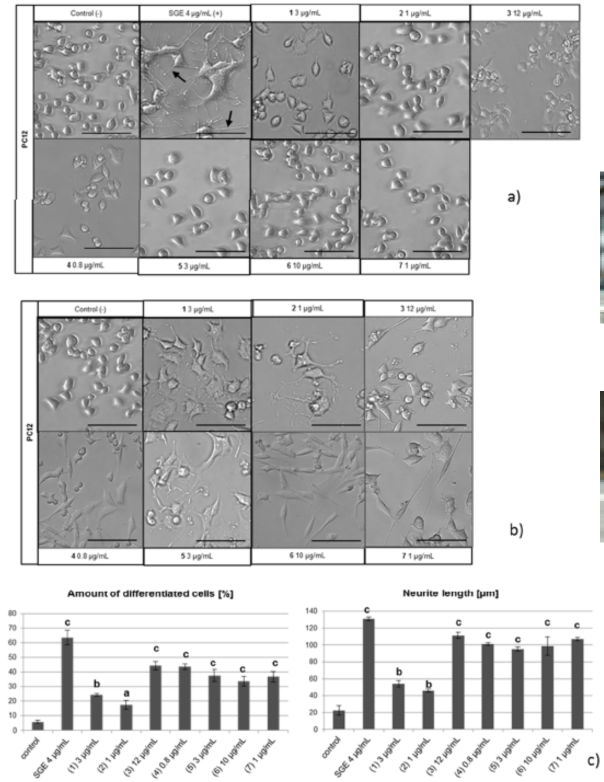
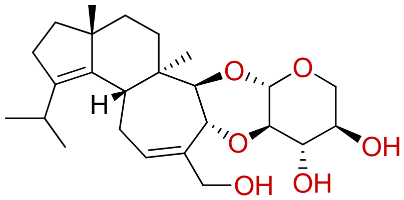


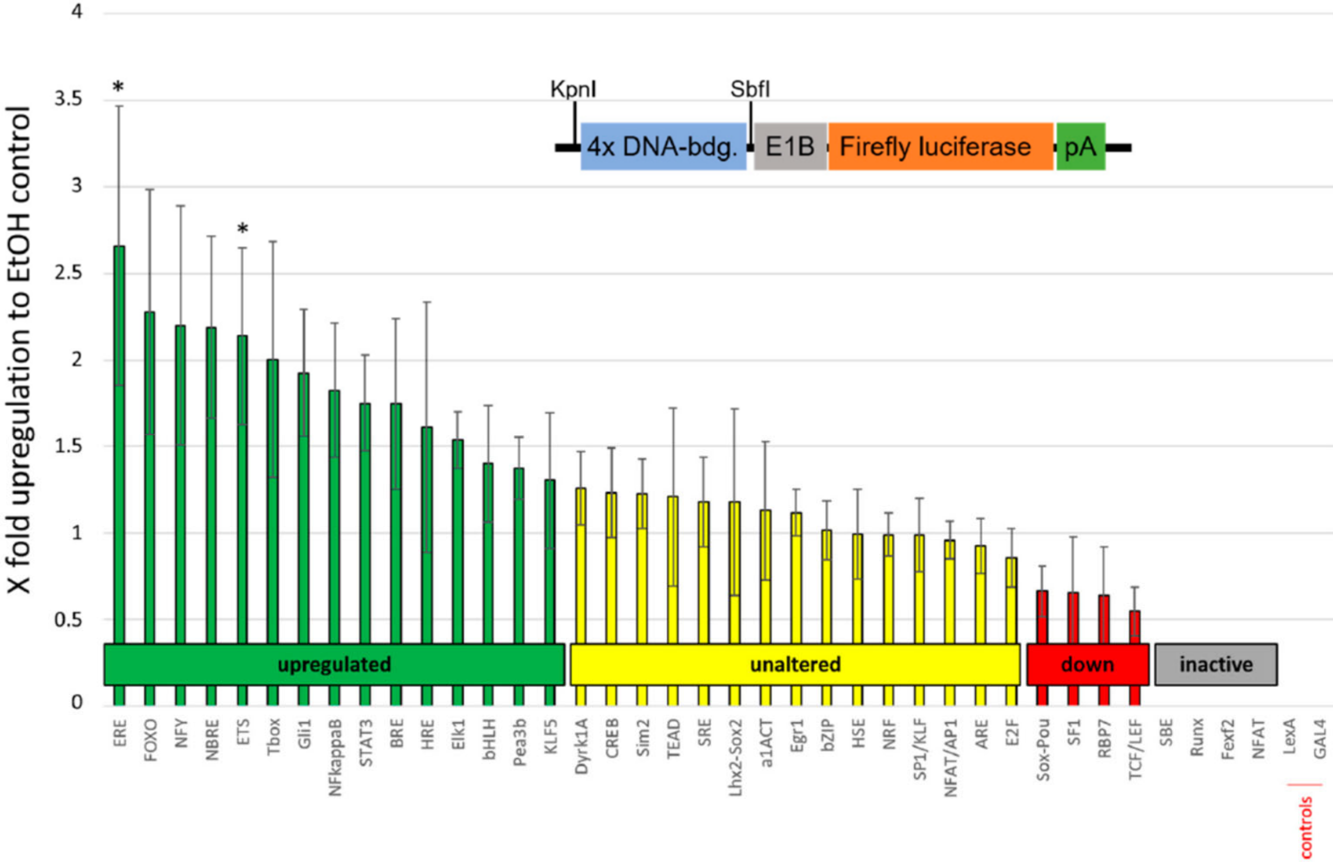
Figure 3. Morphological differentiation of PC12 cells incubated with erinacines Z1, Z2, A, B, C, E, and CJ14.258 (**1–7**) (**a**) or conditioned medium produced by 1321 N1 cells; (**b**) (−): negative control, no additive; (−) Ethanol: negative control with ethanol; (−) 1321N1 medium: negative control with 1321N1 medium; (+) SGE: positive control with salivary gland extract (contains *NGF*). Differentiated cells are marked with an arrow; (**c**) a quantification of analyses with the amount of differentiated cells [%] or neurite length [µm]. Scale bar 100 µm (±SEM; a, $p < 0.01$; b, $p < 0.001$; c, $p < 0.0001$).

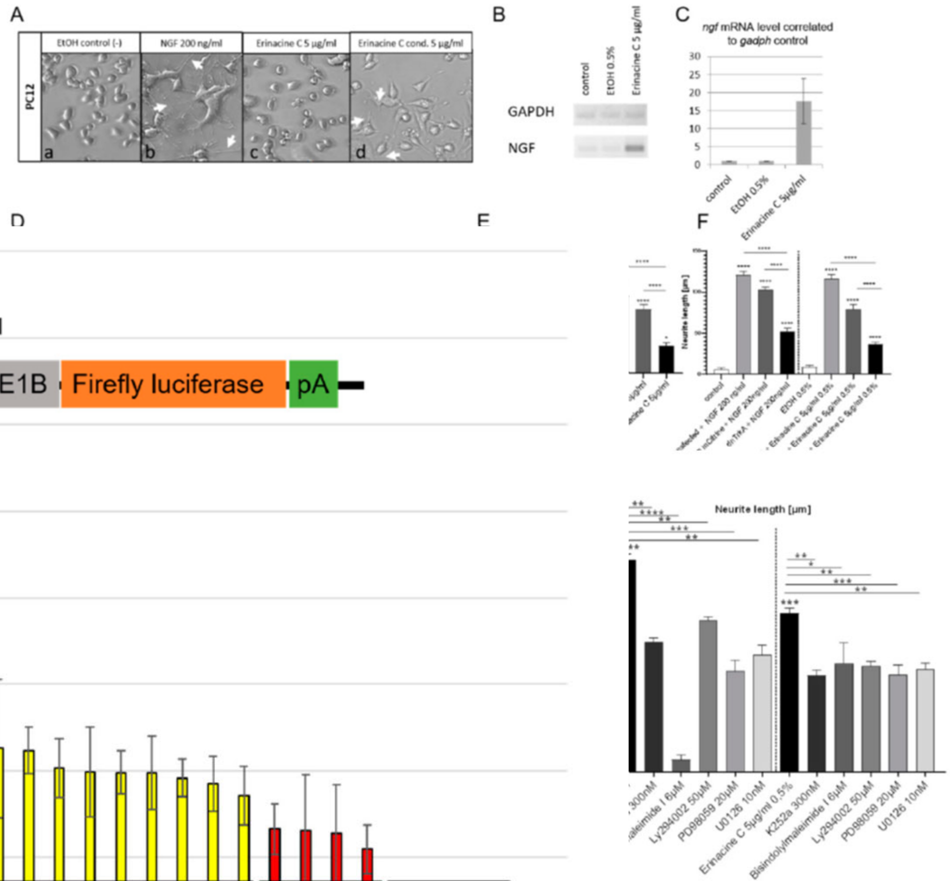
Monique Rascher

Sae Kanaki

Studies toward the mode of action of erinacines







M. Rascher et al. (2020) Biomolecules 10:440

Strong evidence for the identity of the molecular target site (may facilitate optimization of the compound class)

biomolecules

MDPI

Article

Erinacine C Activates Transcription from a Consensus ETS DNA Binding Site in Astrocytic Cells in Addition to NGF Induction

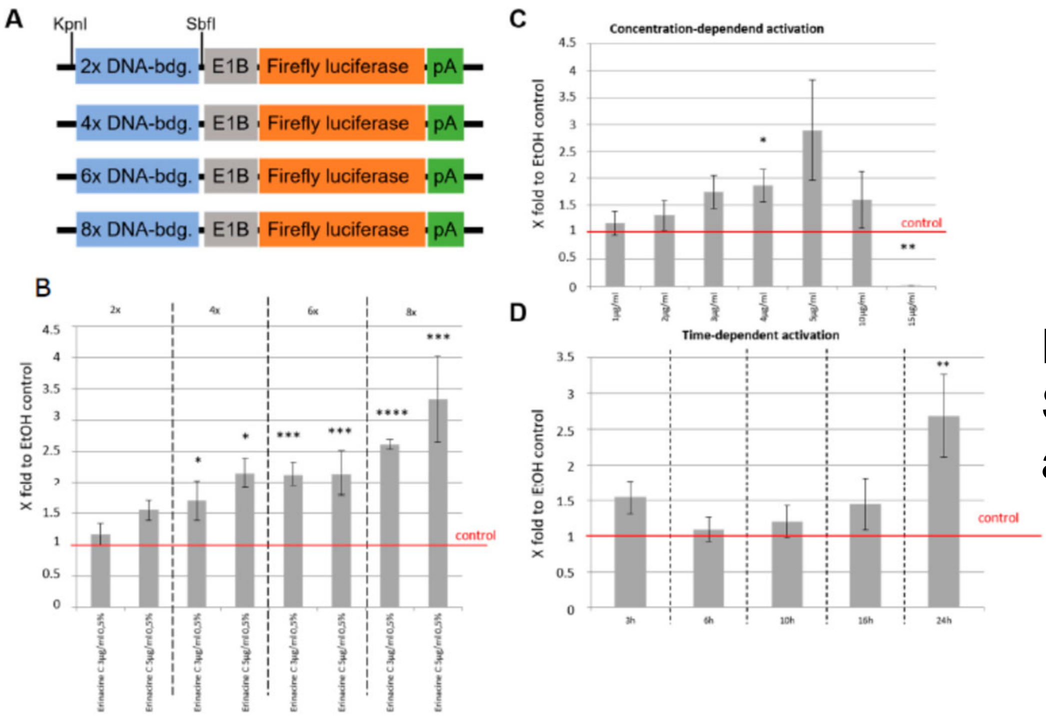


Figure 5. Erinacine C activates ETS-reporter construct in a concentration dependent manner. (A) Series

Zeljka Rupcic

Kathrin Wittstein

Monique Rascher

ETS (Erythroblast Transformation Specific) transcription factors are addressed by erinacine C

Impressions from field work in Thailand

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

A novel terpene lactam from a new species of *Panus*

Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Lentinulactam, a hirsutane sesquiterpene with an unprecedented lactam modification

Soleiman E. Helaly [a,b,c,1], Christian Richter [a,b,1], Benjarong Thongbai [d], Kevin D. Hyde [d], Marc Stadler [a,b,*]

[a] Department of Microbial Drugs, Helmholtz Centre for Infection Research, Inhoffenstrasse 7, 38124 Braunschweig, Germany
[b] German Centre for Infection Research (DZIF), Partner Site Hannover/Braunschweig, Inhoffenstrasse 7, 38124 Braunschweig, Germany
[c] Department of Chemistry, Faculty of Science, Aswan University, Aswan 81528, Egypt
[d] Center of Excellence in Fungal Research, Mae Fah Luang University, Chiang Rai 57100, Thailand

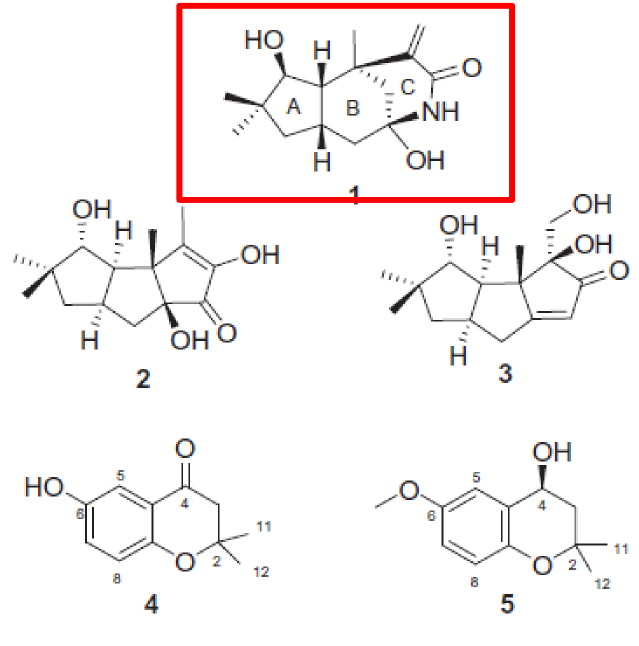


Fig. 1.

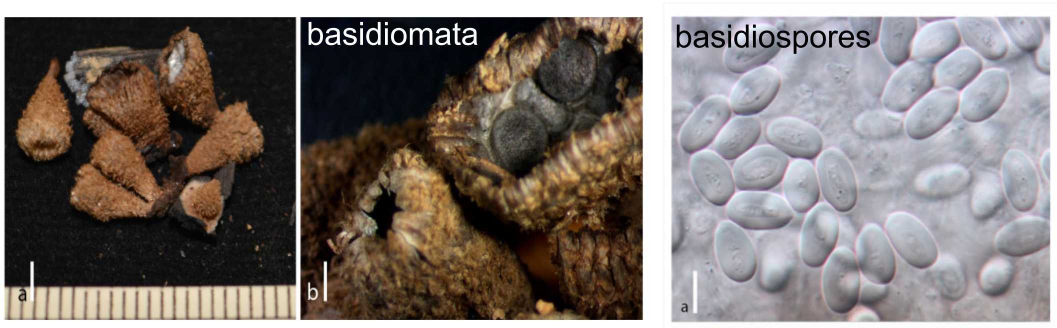
Panus subfasciatus Thongbai et al., sp. nov

Christian Richter

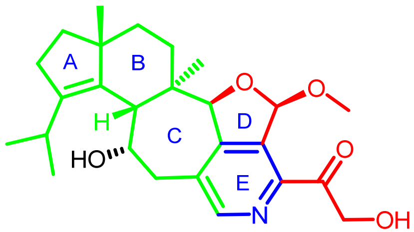
Soleiman Helaly

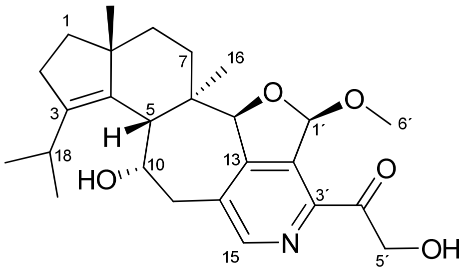
Benjarong Thongbai

Novel cyathane-pyridine terpenoids from *Cyathus*

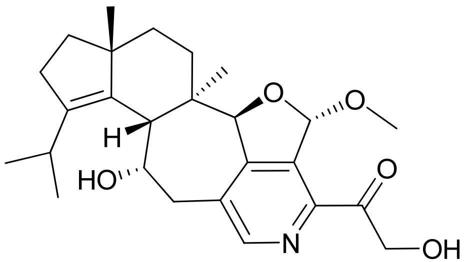


Cyathus pyristriatus sp. nov. (ined.)

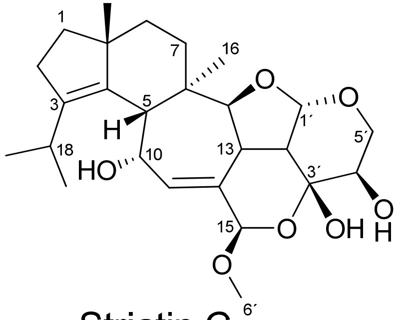




Pyristriatin A



Pyristriatin B



Striatin C

- First cyathane natural products (and first fungal terpenes) featuring a pyridine ring
- **Broad antimicrobial** and **moderate cytotoxic activities**

New terpenes from a Thai *Marasmius* sp.

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Analogs of the carotane antibiotic fulvoferruginin from submerged cultures of a Thai *Marasmius* sp.

Birthe Sandargo[1], Leon Kaysan[1,2], Rémy B. Teponno[1,3], Christian Richter[1], Benjarong Thongbai[1], Frank Surup[1] and Marc Stadler[*1,4]

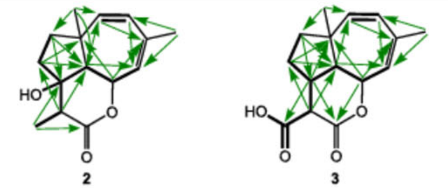


Figure 2: KEY HMBC (arrows) and COSY (thick bonds) correlations of compounds **2** and **3**.

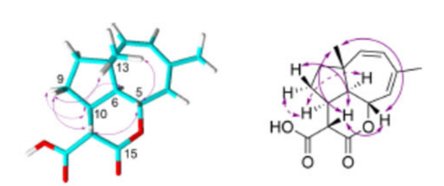
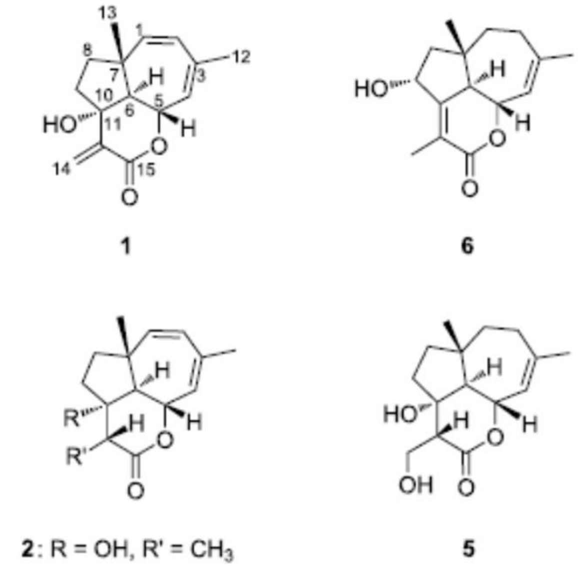


Figure 3: Key ROESY correlations of metabolite **3**.



2: R = OH, R' = CH_3
3: R = H, R' = COOH
4: R = OH, R' = CH_2OH

Figure 1: Structures of fulvoferruginin (**1**) and the newly isolated derivatives fulvoferruginins B–F (**2–6**).

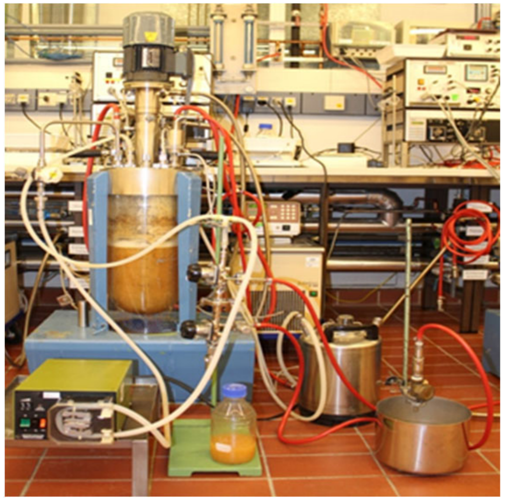
HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

New pleurotins from *Hohenbuehelia grisea*

H. grisea (Thailand)

Frank Surup

Birthe Sandargo



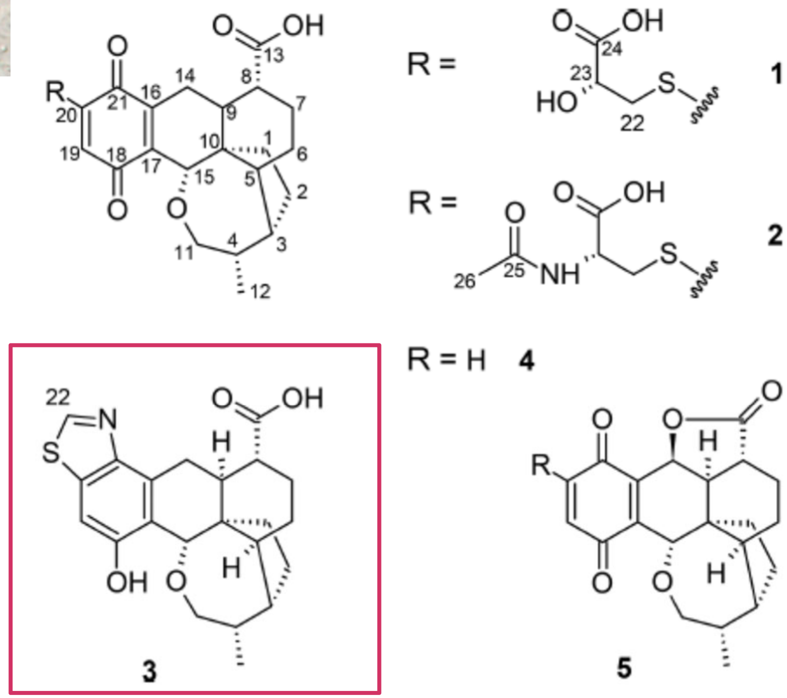


Figure 1. Structures of new compounds thiopleurotinic acid A (1), thiopleurotinic acid B (2), and pleurothiazole (3) and parental metabolites dihydropleurotinic acid (4) and pleurotin (5).

molecules
MDPI

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,*]

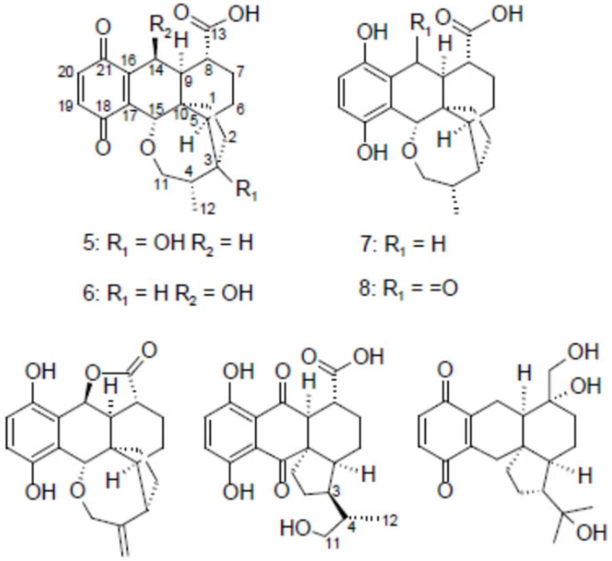
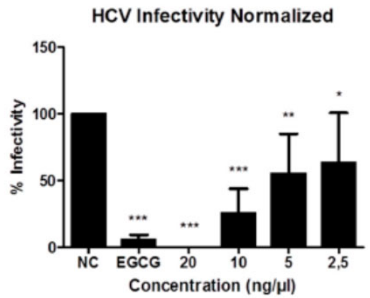
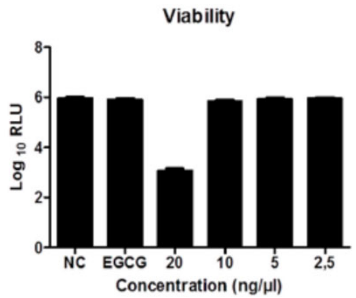


Figure 2. Chemical structures of newly isolated compounds **5**–**11**.

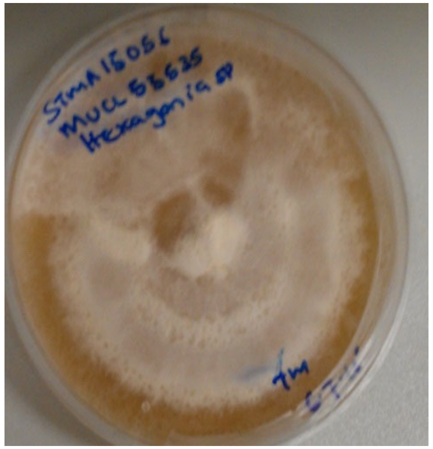




Impressions from field work in Kakamega, Kenya (Sept. 2014)

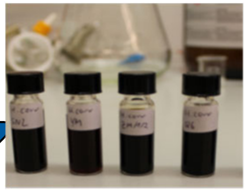
Expedition in the course of a project funded by AvH and ERAFRICA, 2014-2018

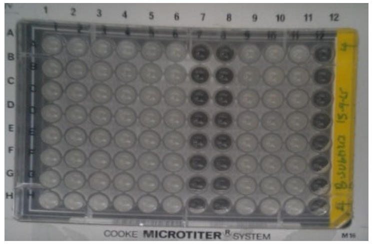
Methodology



Pre-screening

Extraction

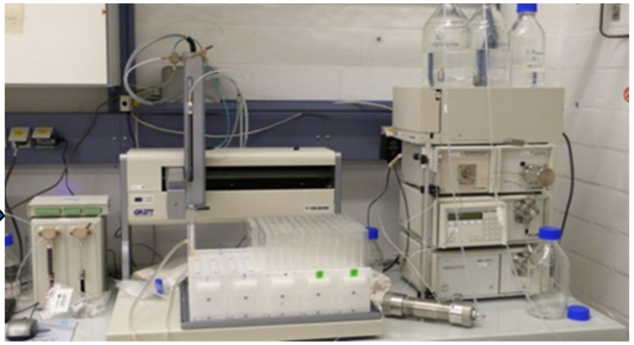




HPLC-MS analysis/ database search

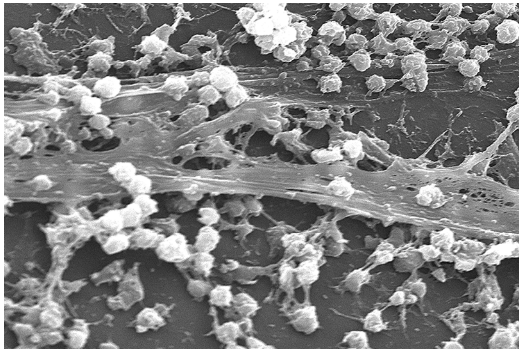
Semi-preparative and preparative HPLC

Large scale fermentation



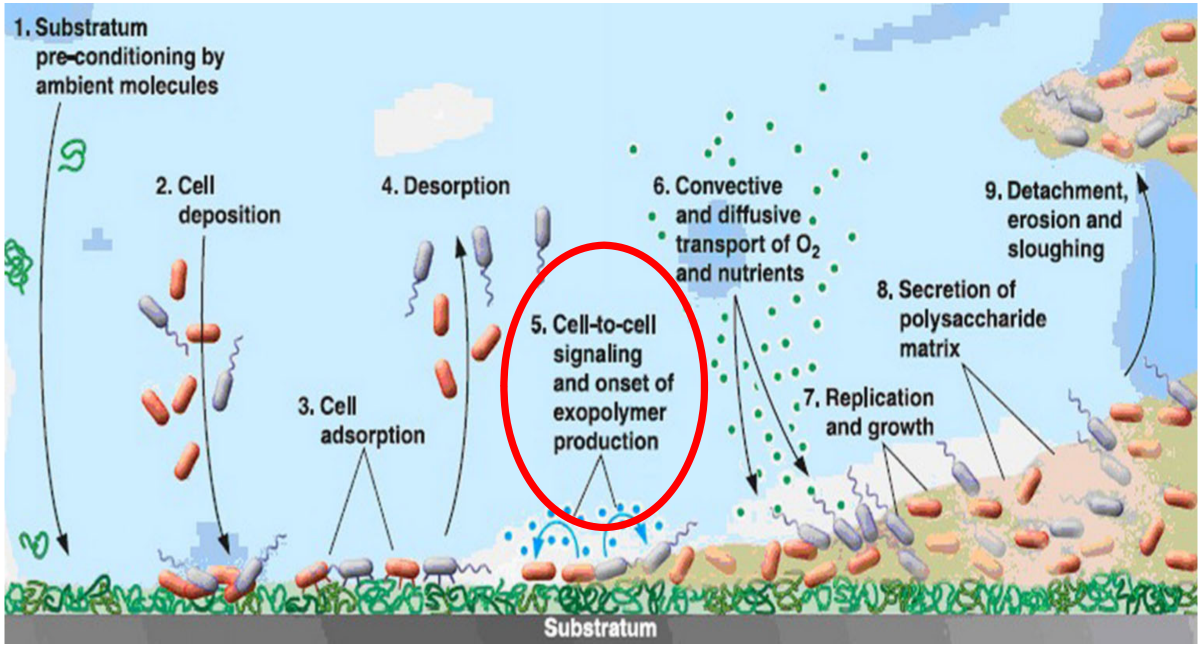
Structure elucidation

New compounds with anti-biofilm activity



Rodney M. Donlan, Ph.D.; Janice Carr

***S. aureus* biofilm**



Processes of biofilm formation

Simoes et al. 2010,
Lwt-Food Sci Technol 43, 573.

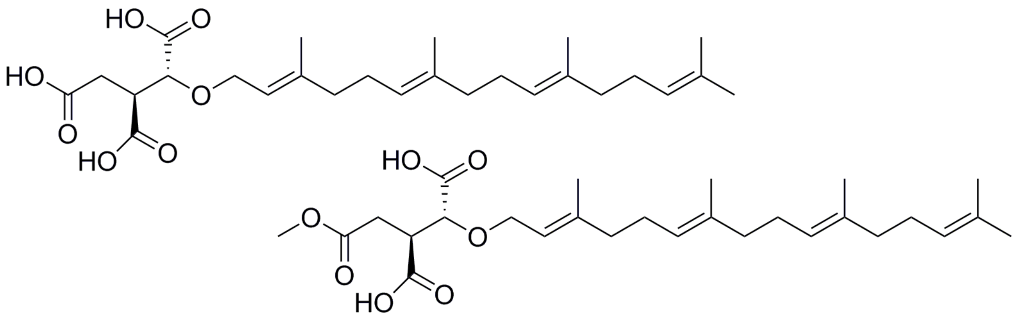
Inhibitors of biofilm formation and quorum sensing

- **no interference with bacterial growth**
- **phenotype changes with no /minimal selective pressure**
- **resistences unlikely or very slow**

- **valid potential alternatives to classical antibiotics!**

New compounds with anti-biofilm activity

Microporus sp.
(new species, Kakamega, Kenia)



Microporenic Acids A and B

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

Clara Chepkirui

Organism	Biofilm inhibition %	Preformed biofilm inhibition
S. aureus	86% (256 µg mL⁻¹) 54% (64 µg mL⁻¹) 28% (16 µg mL⁻¹)	49% (256 µg mL⁻¹) 37% (128 µg mL⁻¹) 1.5% (64 µg mL⁻¹)
C. albicans	-	72% (16 µg mL⁻¹) 52% (8 µg mL⁻¹)

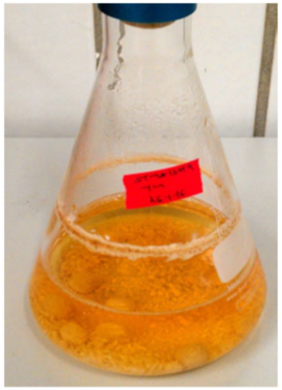
Activity of Microporenic Acid A

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

HZI HELMHOLTZ Centre for Infection Research

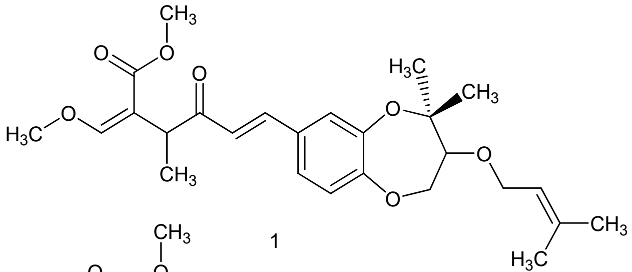
New natural fungicides from *Favolaschia calocera*

F. calocera

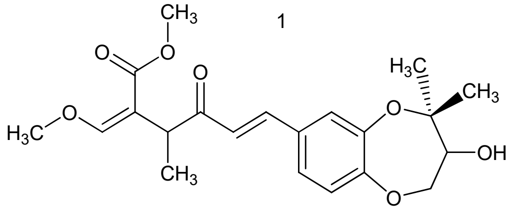


Simone Heitkämper

Clara Chepkirui



1



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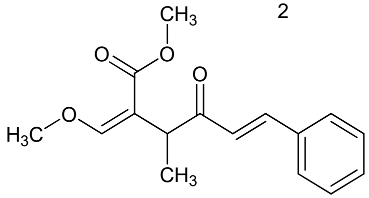

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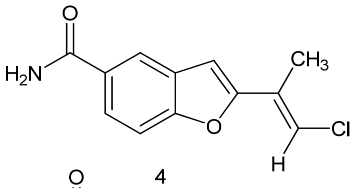

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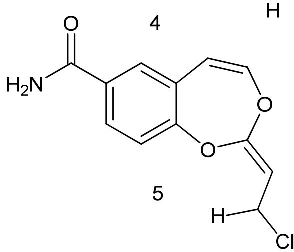
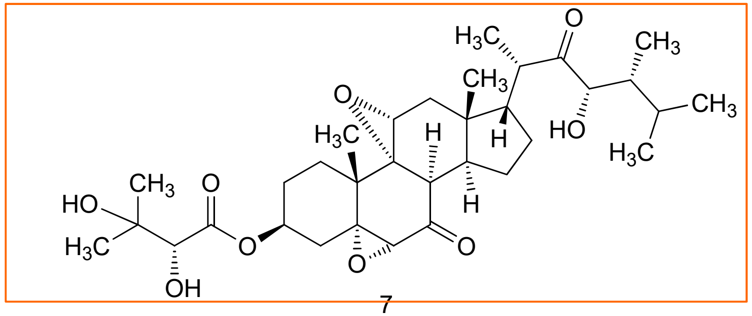


5

Strobilurins and benzoxepins:

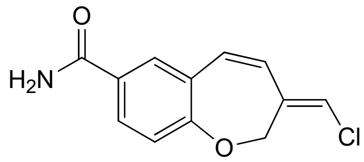
Lead structures for agrochemical applications (fungicides)

Favolaschia: 3 different potent chemical weapons

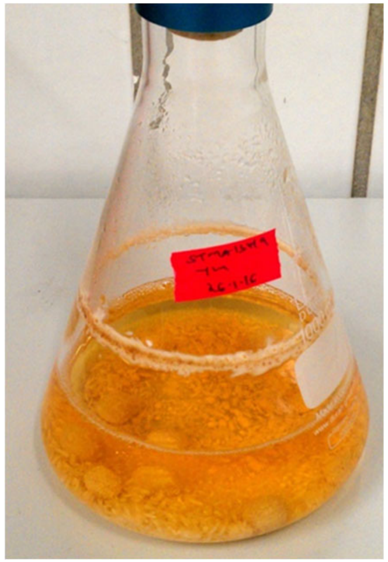


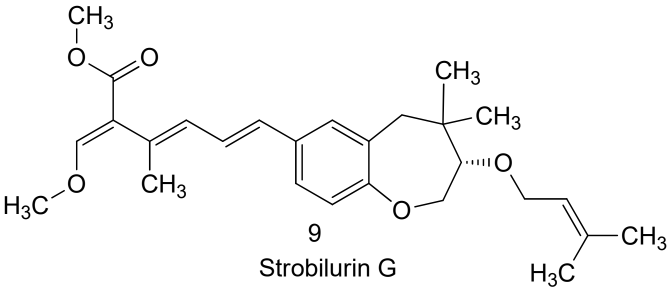
7

Favolon

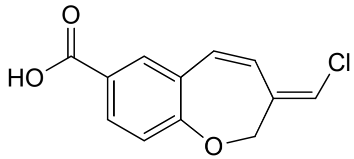


8
2,3-dihydro-1-benzoxepin derivative





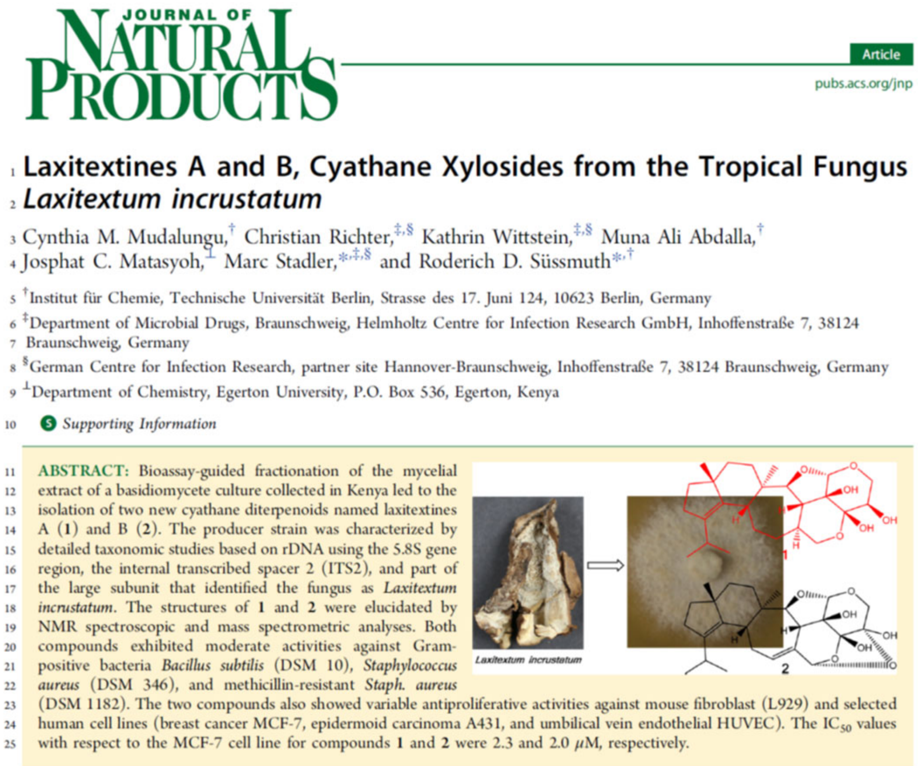
9
Strobilurin G



10
pterulinic acid

- Strobilurins and favolon, as well as benzoxazepins are **very potent antifungal agents**
- ***Favolascha* species are very dangerous Neomycota**
- **Due to global warming they invade temperate climates and are a threat for any other fungus!**

Secondary metabolites from *Laxitextum incrustratum*


JOURNAL OF NATURAL PRODUCTS

Article

pubs.acs.org/jnp

Laxitextines A and B, Cyathane Xylosides from the Tropical Fungus *Laxitextum incrustatum*

Cynthia M. Mudalungu,[†] Christian Richter,[‡,§] Kathrin Wittstein,[‡,§] Muna Ali Abdalla,[†] Josphat C. Matasyoh,[⊥] Marc Stadler,[*,‡,§] and Roderich D. Süssmuth[*,†]

[†]Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 124, 10623 Berlin, Germany

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

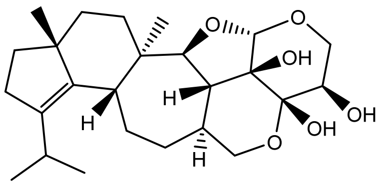
[§]German Centre for Infection Research, partner site Hannover-Braunschweig, Inhoffenstraße 7, 38124 Braunschweig, Germany

[⊥]Department of Chemistry, Egerton University, P.O. Box 536, Egerton, Kenya

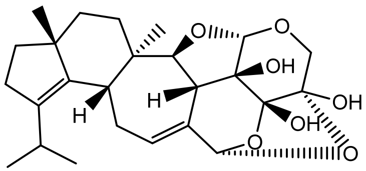
Supporting Information

ABSTRACT: Bioassay-guided fractionation of the mycelial extract of a basidiomycete culture collected in Kenya led to the isolation of two new cyathane diterpenoids named laxitextines A (**1**) and B (**2**). The producer strain was characterized by detailed taxonomic studies based on rDNA using the 5.8S gene region, the internal transcribed spacer 2 (ITS2), and part of the large subunit that identified the fungus as *Laxitextum incrustatum*. The structures of **1** and **2** were elucidated by NMR spectroscopic and mass spectrometric analyses. Both compounds exhibited moderate activities against Gram-positive bacteria *Bacillus subtilis* (DSM 10), *Staphylococcus aureus* (DSM 346), and methicillin-resistant *Staph. aureus* (DSM 1182). The two compounds also showed variable antiproliferative activities against mouse fibroblast (L929) and selected human cell lines (breast cancer MCF-7, epidermoid carcinoma A431, and umbilical vein endothelial HUVEC). The IC_{50} values with respect to the MCF-7 cell line for compounds **1** and **2** were 2.3 and 2.0 μM, respectively.

Cynthia Mudalungu



laxitextine A



laxitextine B

- Moderate activity against Gram-positive bacteria
- Antiproliferative effects (human and mouse fibroblast cell lines)

Laxitextum belongs to the Hericiaceae (phylogenetically related to *Hericium*)

Active principles of an African relative of an Asian TM fungus (1)

Phytochemistry Letters 25 (2018) 141–146

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Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

An unprecedented spiro [furan-2,1'-indene]-3-one derivative and other nematicidal and antimicrobial metabolites from *Sanghuangporus* sp. (Hymenochaetaceae, Basidiomycota) collected in Kenya

Clara Chepkirui[a], Tian Cheng[a], Josphat Matasyoh[b], Cony Decock[c], Marc Stadler[a,*]

[a] Department of Microbial Drugs, Helmholtz Centre for Infection Research and German Centre for Infection Research (DZIF), Partner Site Hannover/Braunschweig, Inhoffenstrasse 7, 38124 Braunschweig, Germany
[b] Egerton University, Department of Chemistry, P.O BOX 536, 20115, Njoro, Kenya
[c] Mycothéque de l' Universite catholique de Louvain (BCCM/MUCL), Place Croix du Sud 32 bte L7.05.06, B-1348 Louvain-la-Neuve, Belgium

Table 2
Antimicrobial and nematicidal activities of compounds **1-7**.

Test strains	1	2	3	4	5	6	7	Reference
Antimicrobial activities MIC (μg/mL)								
Bacillus subtilis DSM 10	/	/	/	6.25	/	/	/	2.3[a]
Micrococcus luteus DSM 1790	25	25	100	25	≤100	/	/	8.3[a]
Escherichia coli DSM 498	/	/	/	/	/	/	/	2.3[a]
Candida tenuis MUCL 29982	/	/	/	50	/	/	/	2.3[b]
Mucor plumbeus MUCL 49355	100	/	/	12.5	100	/	/	9.4[b]
Nematicidal activities LD_{50} (μg/mL)								
Caenorhabditis elegans	12.5	12.5	25	/	/	/	/	≤3.1[c]

/ No activity; stock solution 100 μg/mL.
[a] Ciprofloxacin.
[b] Nystatin.
[c] Ivermectin.

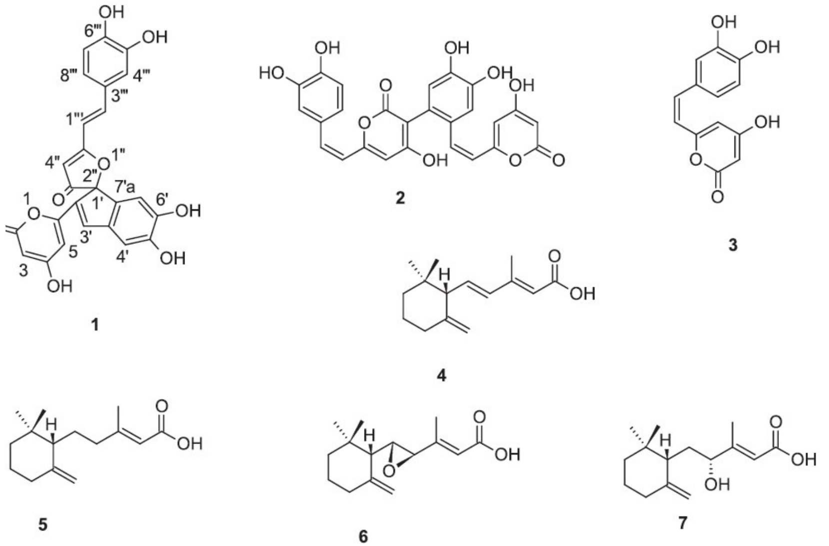
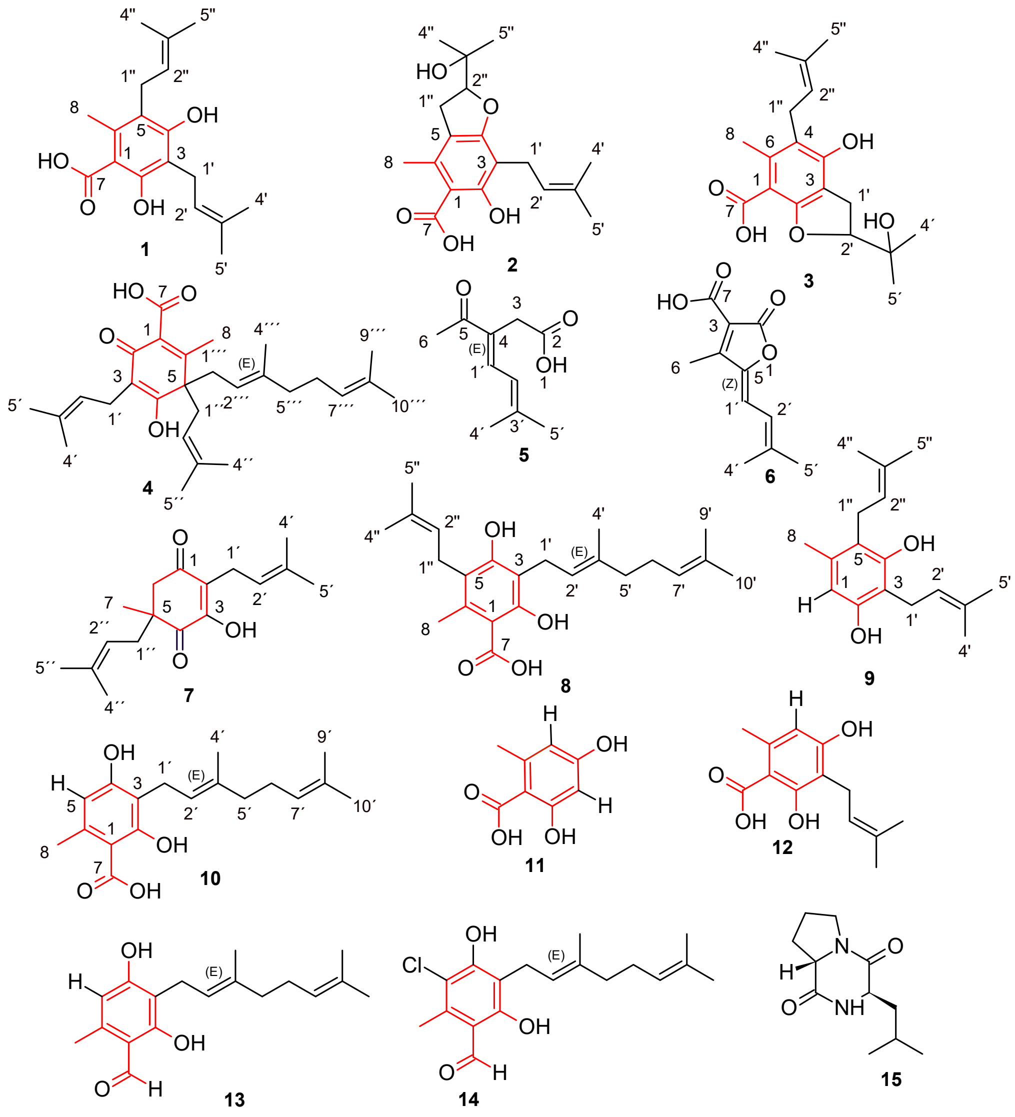


Fig. 2. Chemical structures of 1–7.

Chepkirui et al. (2018) Phytochemistry Lett 25: 141-146.

Meroterpenoids from *Amylosporus* spp.

Blondelle Matio



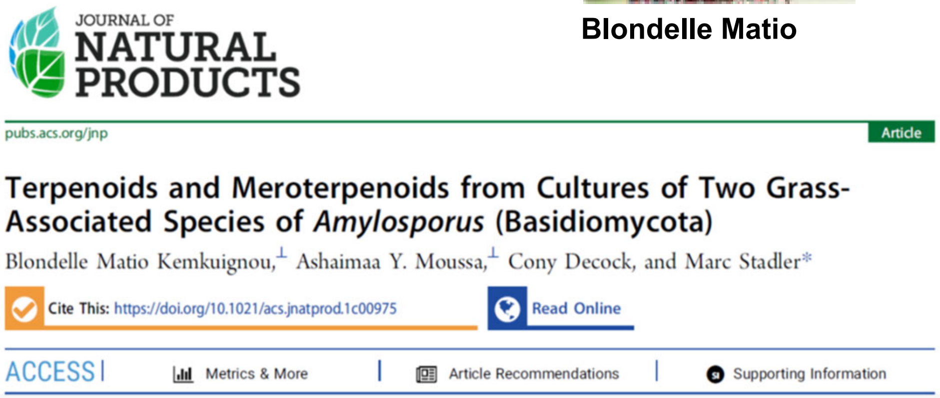
Orsellinic acid-derived carbons

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

B. Matio et al. (2022) J. Nat Prof.

Meroterpenoids from *Amylosporus* spp.

Blondelle Matio


JOURNAL OF NATURAL PRODUCTS
pubs.acs.org/jnp
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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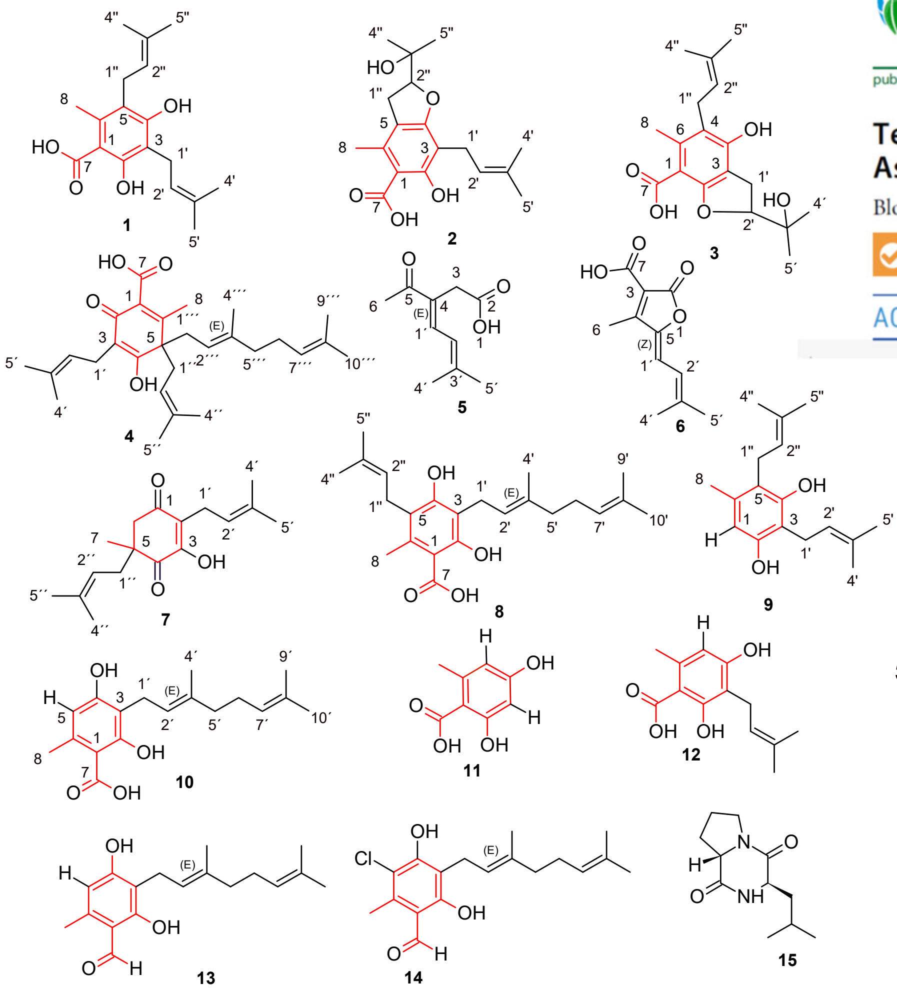
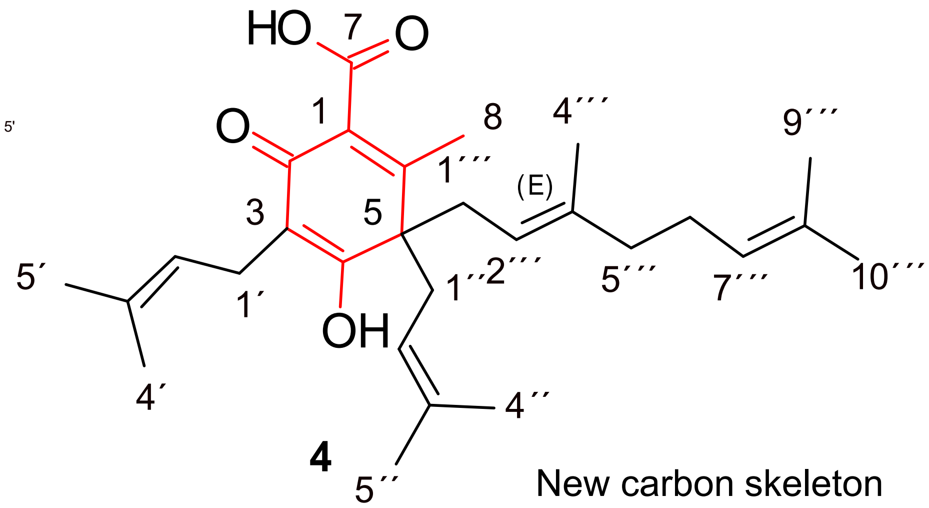


Orsellinic acid-derived carbons



New carbon skeleton

B. Matio et al. (2022) J. Nat Prof.

New terpenoids from a tropical genus of Mycenaceae

Sebastian Pfütze

Frank Surup

JOURNAL OF NATURAL PRODUCTS
pubs.acs.org/jnp Article

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

Sebastian Pfütze, Atchara Khamsim, Frank Surup, Cony Decock, Josphat C. Matasyoh, and Marc Stadler*

Cite This: https://doi.org/10.1021/acs.jnatprod.2c01015 Read Online
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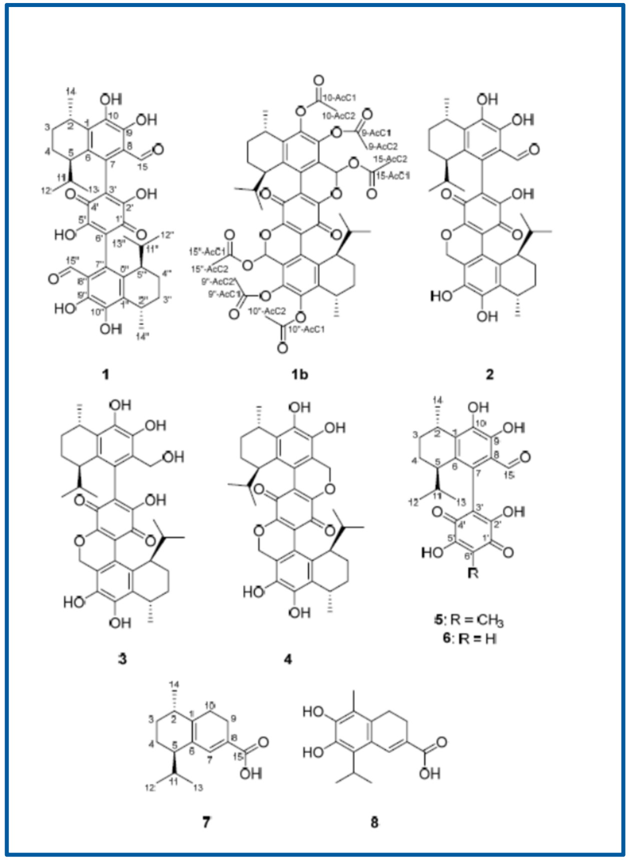
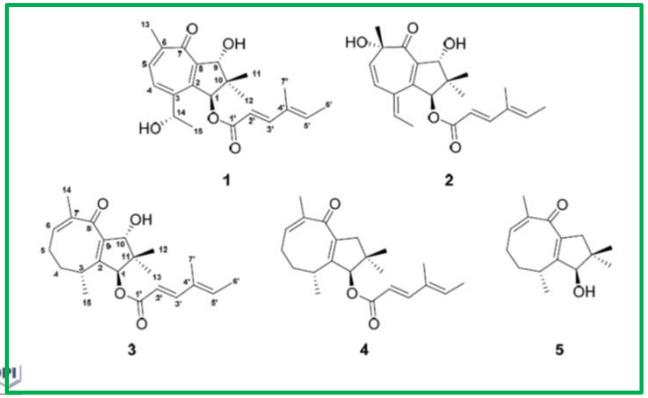
ABSTRACT: New meroterpenoids bis-heimiomycins A–D (**1–4**) and heimiomycins D and E (**5** and **6**) were isolated from solid rice cultures of *Heimiomyces* sp., while new calamene-type sesquiterpenoids heimiocalamene A (**7**) and B (**8**) were isolated from shake cultures, respectively. Structures of the metabolites were elucidated by 1D and 2D NMR in addition to HRESIMS data. While relative configurations were assigned by ROESY data, absolute configurations were derived from the structurally related, previously described calamenes, which we herein name heimiocalamenes C–E (**9–11**). A plausible biosynthetic pathway was proposed for **1–6**, with a radical reaction connecting their central *para*-benzoquinone building block to calamene-sesquiterpenoids. Based on the assumption of a common biosynthesis, we reviewed the structure of the known nitrogen-containing derivative **11**, calling the validity of the originally

From solid state culture after 7 months of growth



From shake cultures



molecules MDPI
Article

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

Sebastian Pfütze [1,2], Atchara Khamsim [1,2], Frank Surup [1,2], Cony Decock [3], Josphat C. Matasyoh [4] and Marc Stadler [1,2,*]

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

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

Organic Letters

Letter

Cite This: *Org. Lett.* 2019, 21, 3286−3289

pubs.acs.org/OrgLett

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

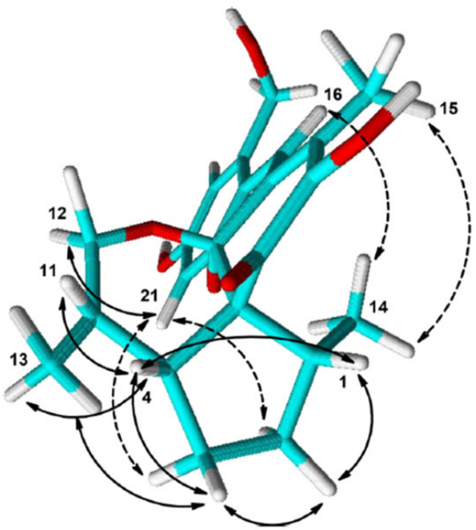
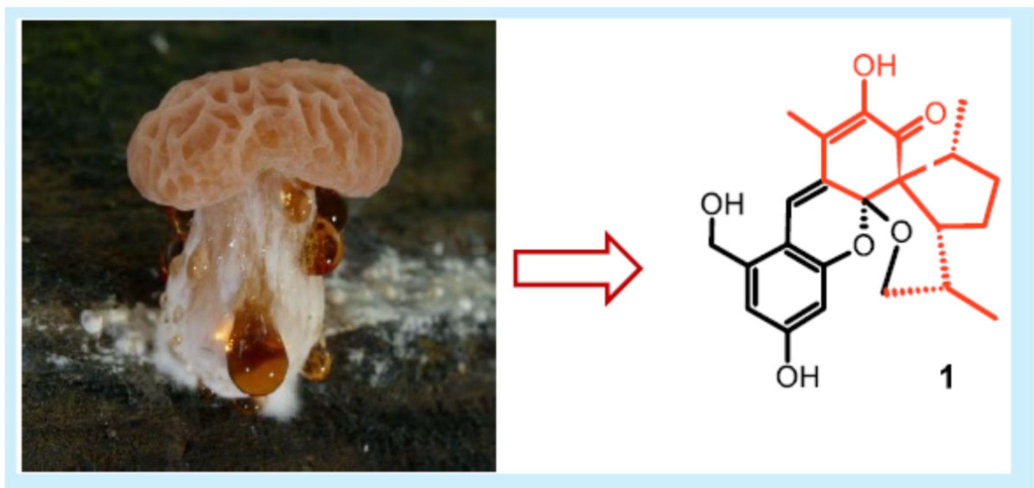


Figure 3. Key ROE correlations of rhodatin (1). Correlations above the molecular main plane are indicated with solid arrows, and correlations below with dashed arrows.



New carbon skeleton; antiviral activities

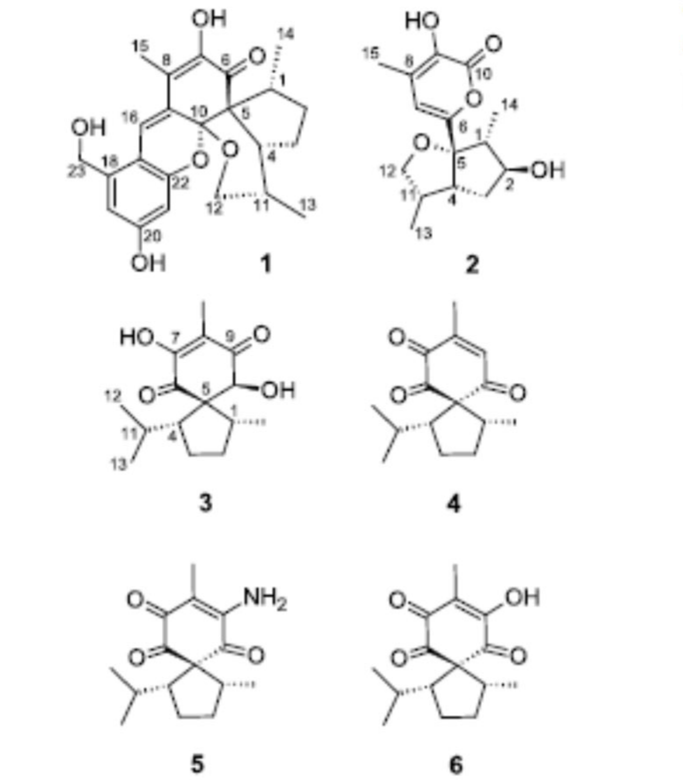


Figure 1. Chemical structures of rhodatin (1) and rhodocoranes A–E (2–6, respectively).

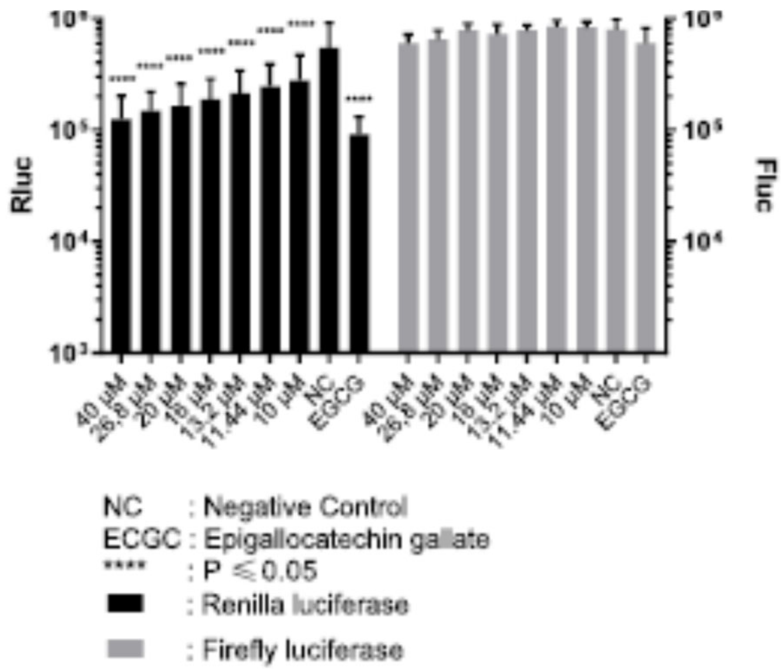


Figure 4. Antiviral activity of rhodatin (1). Huh-7.5 cells were inoculated with RLuc-Jc1 reporter viruses in the presence of rhodatin. Infected cells were lysed for 3 days, and reporter virus infection was determined by Renilla luciferase activity (Rluc). Cell viability was measured by determination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

Significant antiviral activity (HCV)

Several new acorane sesquiterpenoids were obtained concurrently

JOURNAL OF NATURAL PRODUCTS

Note

Cite This: J. Nat. Prod. 2020, 83, 720–724

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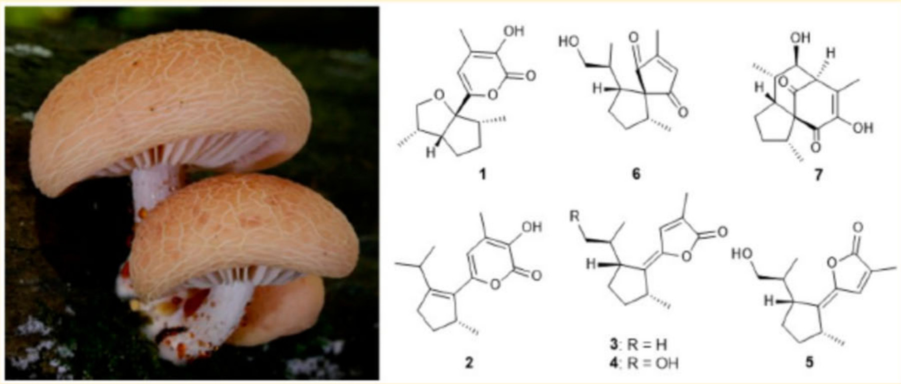
Antifungal Sesquiterpenoids, Rhodocoranes, from Submerged Cultures of the Wrinkled Peach Mushroom, *Rhodotus palmatus*

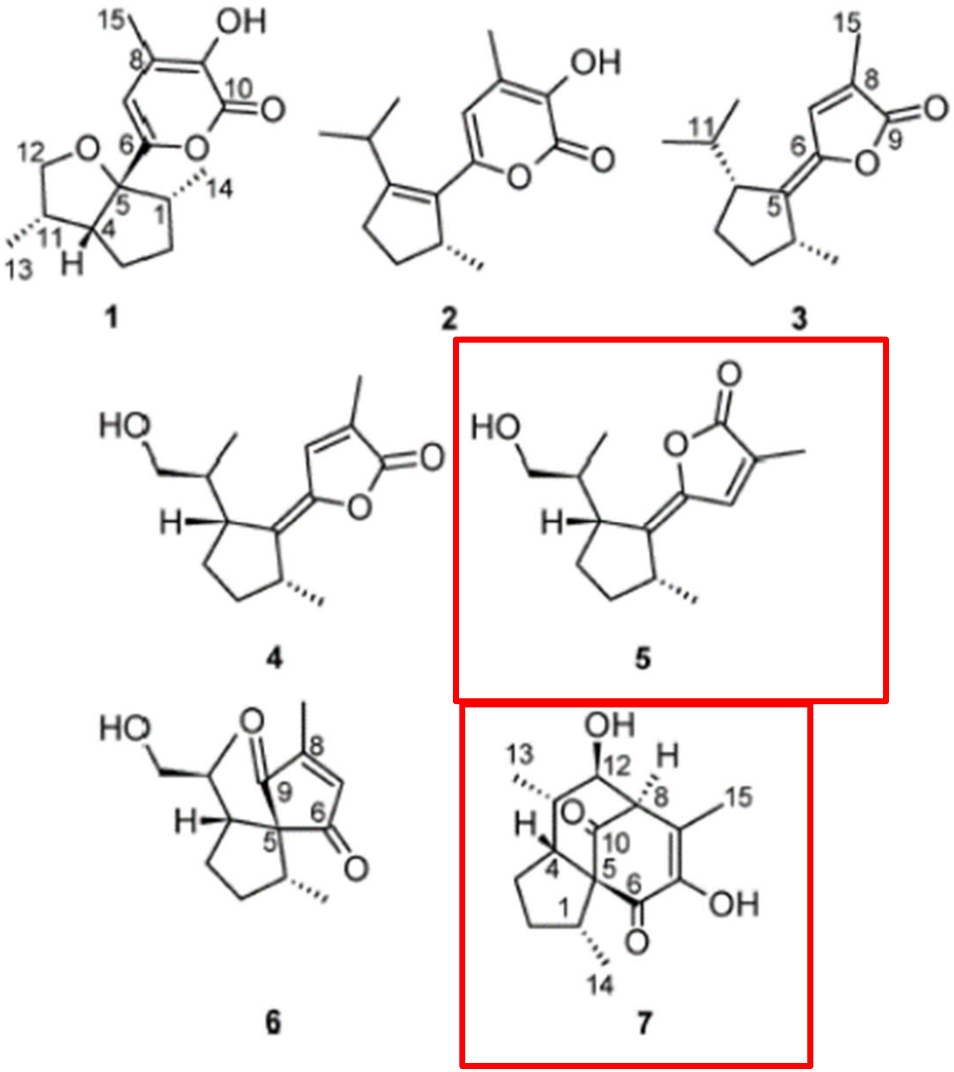
Birthe Sandargo,[†,§] Maira Michehl,[†,§,‡] Marc Stadler,[†,§] and Frank Surup*[,†,§]

[†]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

Supporting Information



ABSTRACT: Seven previously unknown sesquiterpenoids and norsesquiterpenoids, rhodocoranes F–L (**1**–**7**), were isolated from the fermentation broth of the basidiomycete *Rhodotus palmatus*. Their structures were elucidated utilizing 1D and 2D NMR techniques as well as HRESIMS; they are unusual noracorane, spiro[4.4]nonene, and acorane-type sesquiterpenoids. They include the first naturally occurring cyclopentylidenefuranones (**3**–**5**) and the new tricyclic scaffold of **7**. Metabolites **1**–**7** exhibited a general mild antimycotic activity, while **1**–**3** also displayed cytotoxic effects.



Novel natural carbon skeletons!

New terpenoids from one of the most common European mushrooms

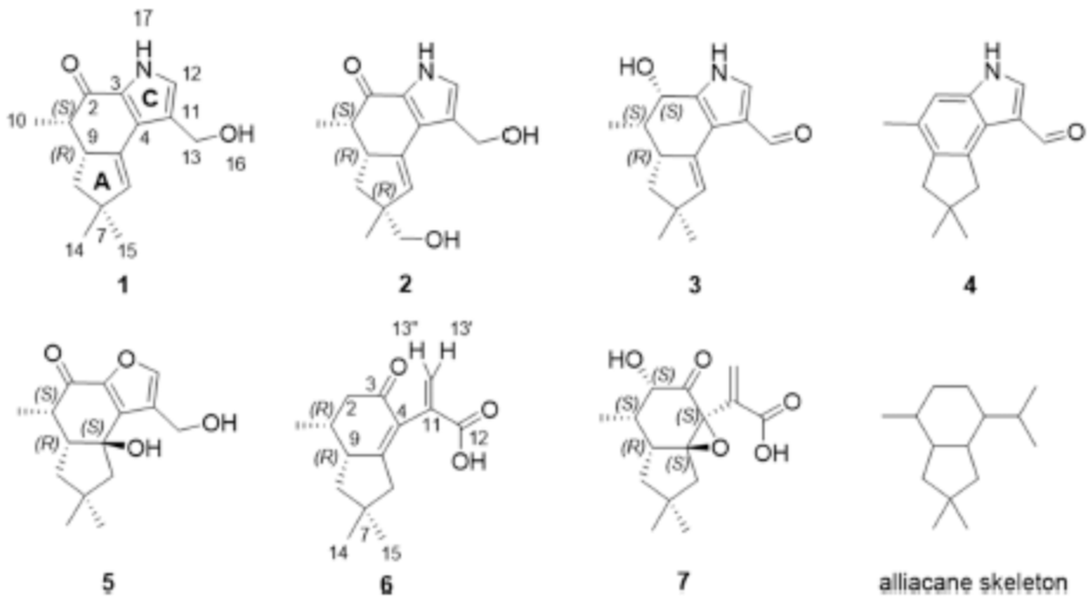
JOURNAL OF NATURAL PRODUCTS
pubs.acs.org/jnp Article

Alliacane-Type Secondary Metabolites from Submerged Cultures of the Basidiomycete *Clitocybe nebularis*

Hedda Schrey, Tarek Scheele, Conrad Ulonska, Dana Leoni Nedder, Tim Neudecker, Peter Spiteller, and Marc Stadler*

Hedda Schrey

Dana Nedder



https://www.mycokey.com
Jens H. Petersen

The CBS strain was supposed to be a *Laccaria* sp. (confusion by the depositor?)
The identity was proven by isolation and study of a fresh culture that produced the same compounds

J. Nat. Prod. 2022, 85, 10, 2363–2371

Kakamega rainforest (February 2023)

Novel triterpenes from a *Laetiporus* sp.

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

Short communication

Two cytotoxic triterpenes from cultures of a Kenyan *Laetiporus* sp. (Basidiomycota)

Clara Chepkirui[a,b], Josphat Clement Matasyoh[c], Cony Decock[d], Marc Stadler[a,b,*]

[a] Helmholtz Centre for Infection Research GmbH (HZI), Department Microbial Drugs, Inhoffenstraße 7, 38124 Braunschweig, Germany
[b] German Centre for Infection Reseach Association (DZIF), Partner site Hannover-Braunschweig, Inhoffenstraße 7, 38124 Braunschweig, Germany
[c] Egerton University, Department of Chemistry, P.O BOX 536, 20115, Njoro, Kenya
[d] Mycothéque de l' Universite catholique de Louvain (BCCM/MUCL), Place Croix du Sud 3, B-1348 Louvain-la-Neuve, Belgium

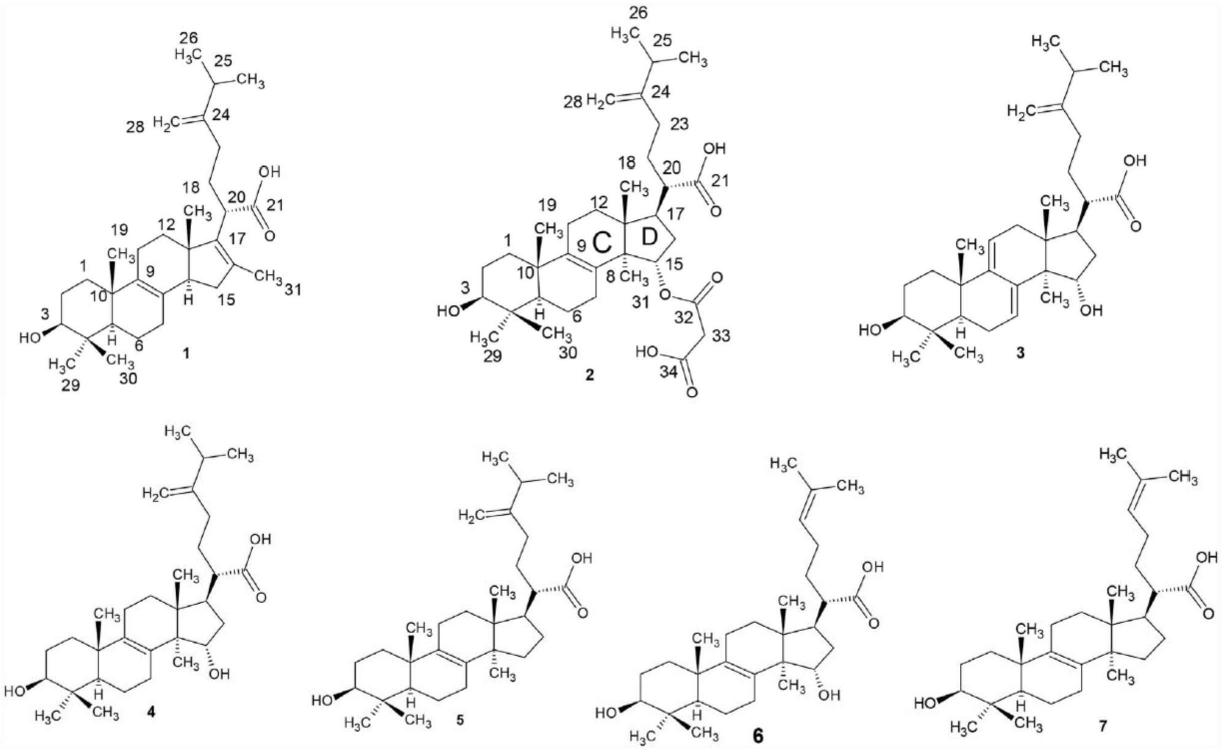
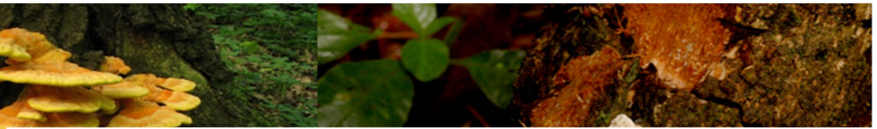


Fig. 1. Chemical structures of compounds 1–7.

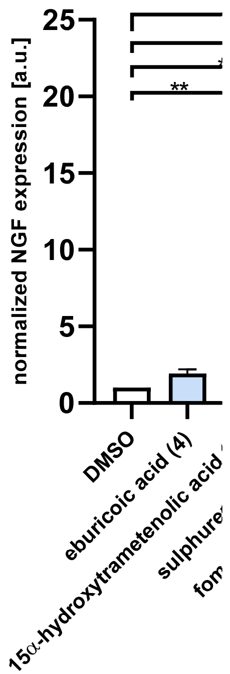
HZI HELMHOLTZ Centre for Infection Research

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

Triterpenoids show significant BDNF and NGF enhancement!



A. *Laetiporus su*



International Journal of *Molecular Sciences*

MDPI

Article

Neurotrophic and Immunomodulatory Lanostane Triterpenoids from Wood-Inhabiting Basidiomycota

Khadija Hassan [1,2], Blondelle Matio Kemkuignou [1,2], Marco Kirchenwitz [3], Kathrin Wittstein [1,2], Monique Rascher-Albaghdadi [1,4], Clara Chepkirui [1,2], Josphat C. Matasyoh [5], Cony Decock [6], Reinhard W. Köster [4], Theresia E. B. Stradal [3] and Marc Stadler [1,2,*]

[1] Department of Microbial Drugs, Helmholtz Centre for Infection Research (HZI), German Centre for Infection Research (DZIF), Partner Site Hannover/Braunschweig, Inhoffenstrasse 7, 38124 Braunschweig, Germany

[2] Institute of Microbiology, Technische Universität Braunschweig, Spielmannstraße 7, 38106 Braunschweig, Germany

[3] Department of Cell Biology, Helmholtz Centre for Infection Research, Inhoffenstrasse 7, 38124 Braunschweig, Germany

[4] Department of Cellular and Molecular Neurobiology, Zoological Institute, Technische Universität Braunschweig, Spielmannstraße 7, 38106 Braunschweig, Germany

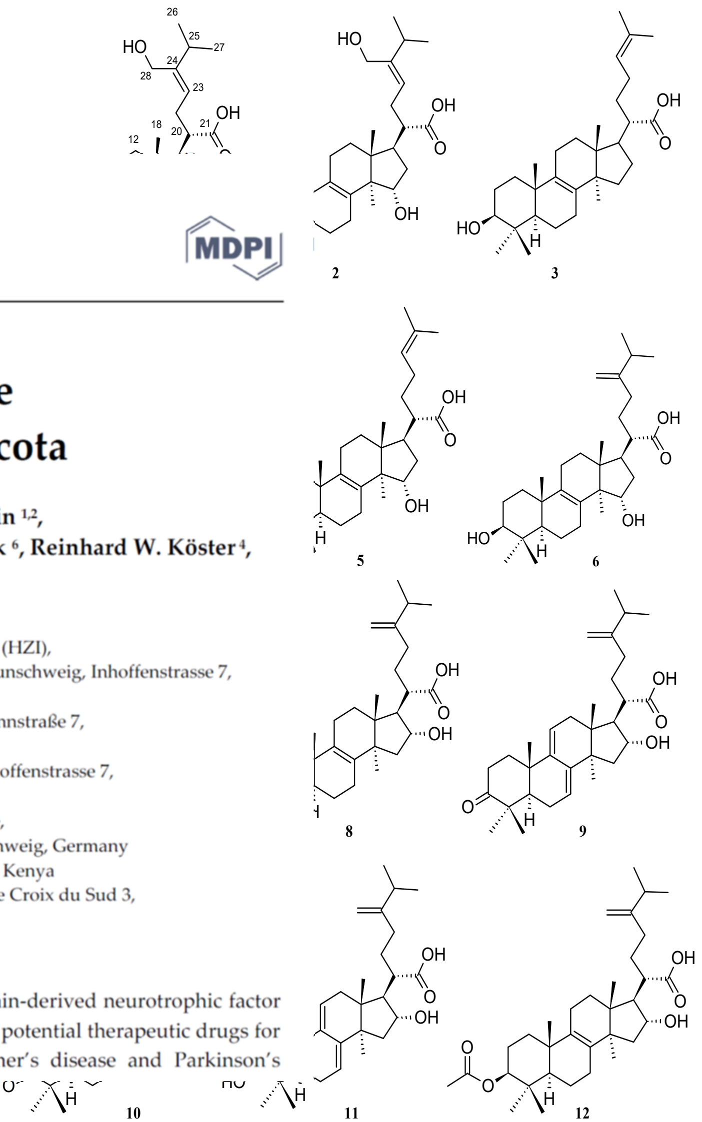
[5] Department of Chemistry, Egerton University, P.O. Box 536, Njoro 20115, Kenya

[6] Mycothèque de l'Université Catholique de Louvain (BCCM/MUCL), Place Croix du Sud 3, B-1348 Louvain-la-Neuve, Belgium

* Correspondence: marc.stadler@helmholtz-hzi.de; Tel.: +49-531-6181-4240

Citation: Hassan, K.; Matio Kemkuignou, B.; Kirchenwitz, M.; Wittstein, K.; Rascher-Albaghdadi, M.; Chepkirui, C.; Matasyoh, J.C.; Decock, C.; Köster, R.W.; Stradal, T.E.B.; et al. Neurotrophic and Immunomodulatory Lanostane Triterpenoids from Wood-Inhabiting Basidiomycota. *Int. J. Mol. Sci.* **2022**, 23, 13593. https://doi.org/10.3390/ijms232113593

Abstract: Neurotrophins such as nerve growth factor (ngf) and brain-derived neurotrophic factor (bdnf) play important roles in the central nervous system. They are potential therapeutic drugs for the treatment of neurodegenerative diseases, including Alzheimer's disease and Parkinson's

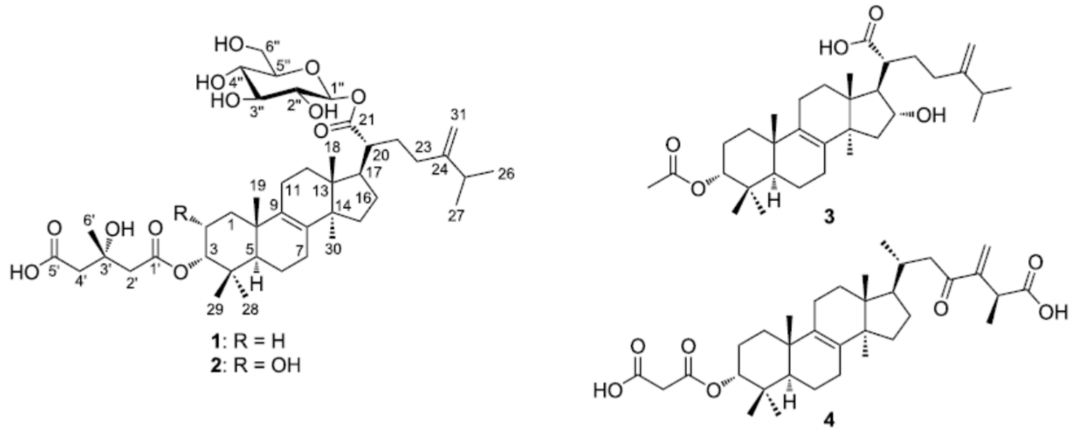


Constituents of many medicinal and edible mushrooms

Lanostane triterpenoids: Characteristic metabolites of polypores

Two new lanostanoid glycosides isolated from a Kenyan polypore *Fomitopsis carnea*

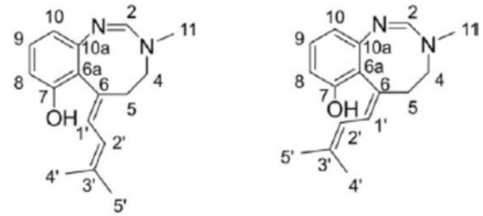
Winnie Chemutai Sum[1,3], Sherif S. Ebada[1,4], Didsanutda Gonkhom[5], Cony Decock[6], Rémy Bertrand Teponno[*1,2], Josphat Clement Matasyoh[7] and Marc Stadler[*1,3,§]



Almost every polypore can produce different combinations of lanostane triterpenoids in their basidiomata and cultures

New compounds from *Laccaria* basidiomes

Hedda Schrey



E-proxamidine (**1a**) *Z*-proxamidine (**1b**)

Figure 1. Structures of *E*- (**1 a**) and *Z*-proxamidine (**1 b**).

Phytochemistry 160 (2019) 85–91

Contents lists available at ScienceDirect

Phytochemistry

journal homepage: www.elsevier.com/locate/phytochem

Nematicidal anthranilic acid derivatives from *Laccaria* species

Hedda Schrey[a], Freya Janina Müller[a], Philipp Harz[a], Zeljka Rupcic[b], Marc Stadler[b], Peter Spiteller[a,*]

[a] Institute for Organic and Analytical Chemistry, University of Bremen, Leobener Straße 7, 28359, Bremen, Germany
[b] Department of Microbial Drugs, Helmholtz Centre for Infection Research, Inhoffenstraße 7, 38124, Braunschweig, Germany

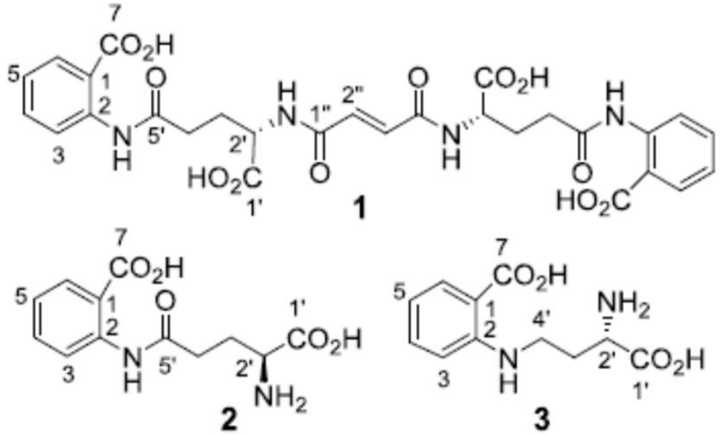
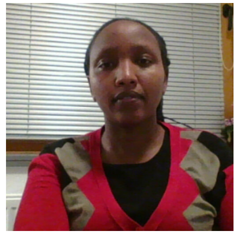


Fig. 1. Structures of laccanthrilic acids A–C (**1–3**).

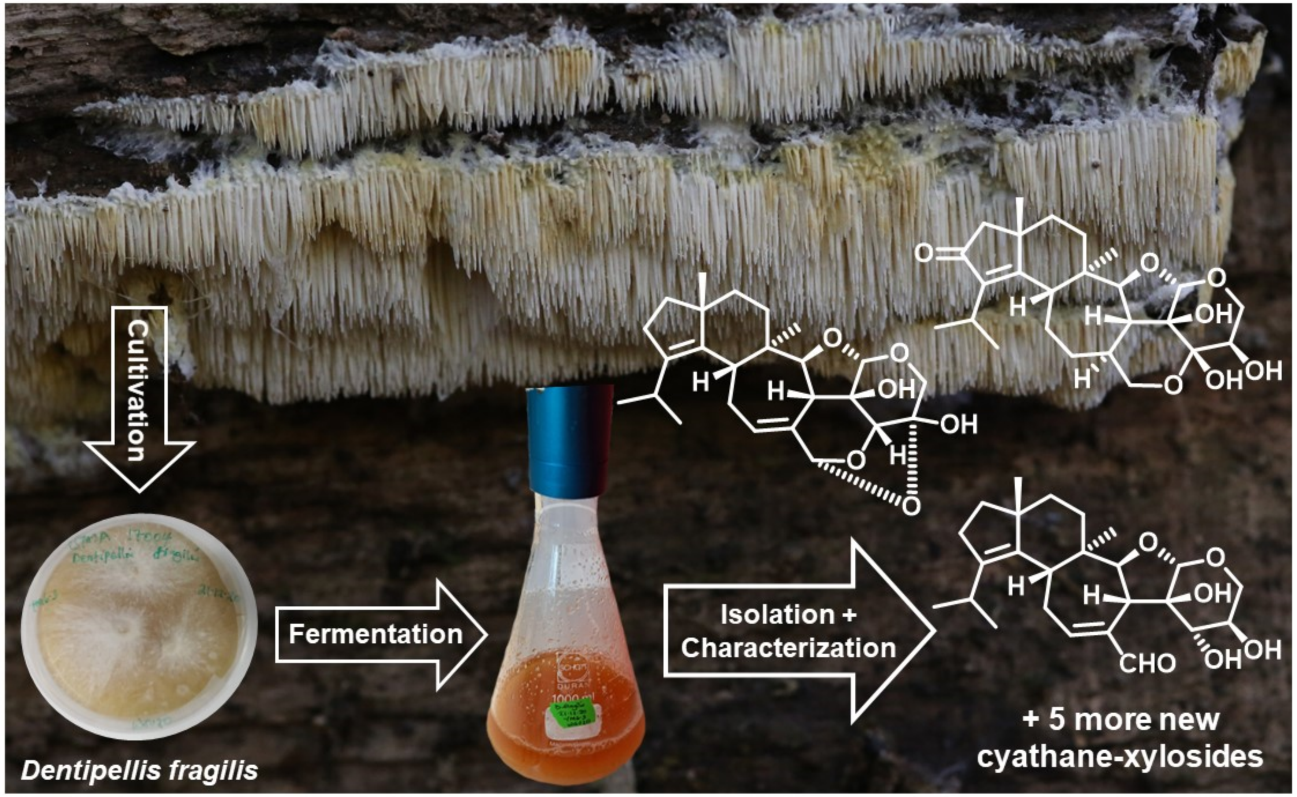
Very interesting chemistry in the tiny fruitbodies

Less risk that the students are eating the material!

Related to *Hericium* => similar metabolites



Winnie Sum



antibiotics MDPI

Article

Antimicrobial and Cytotoxic Cyathane-Xylosides from Cultures of the Basidiomycete *Dentipellis fragilis*

Winnie Chemutai Sum [1,†], Nico Mitschke [1,2,†], Hedda Schrey [1], Kathrin Wittstein [1], Harald Kellner [3], Marc Stadler [1,4,*] and Josphat Clement Matasyoh [5,*]

Moderate antimicrobial and cytotoxic effects
Tests for neurotrophic activities pending

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

pubs.acs.org/JAFC Article

Hericioic Acids A–G and Hericiofuranoic Acid; Neurotrophic Agents from Cultures of the European Mushroom *Hericium flagellum*

Winnie Chemutai Sum, Sherif S. Ebada, Marco Kirchenwitz, Harald Kellner, Mahmoud A. A. Ibrahim, Theresia E. B. Stradal, Josphat Clement Matasyoh, and Marc Stadler*

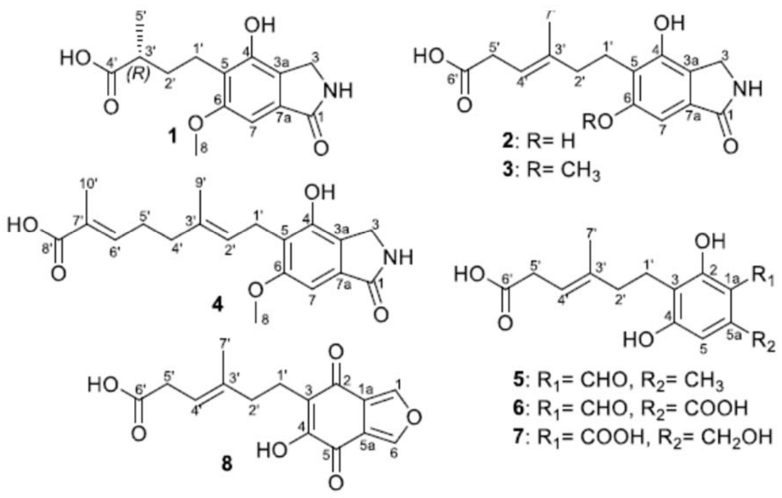


Figure 1. Chemical structures of 1–8.

Journal of Agricultural and Food Chemistry pubs.acs.org/JAFC Article

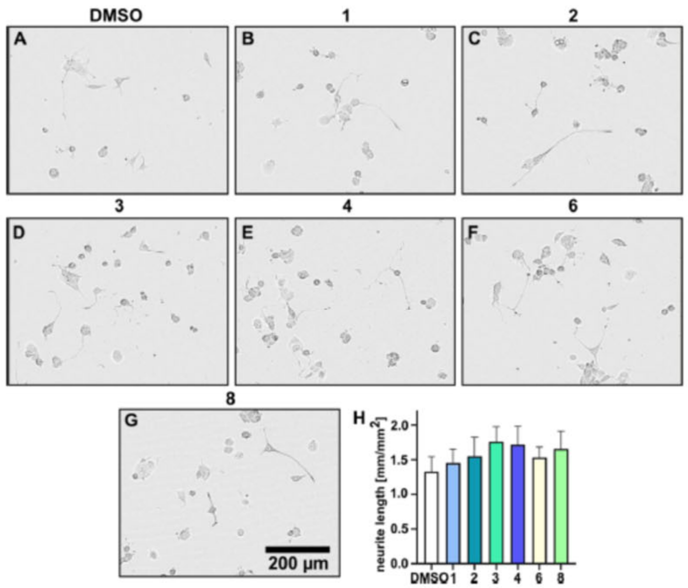
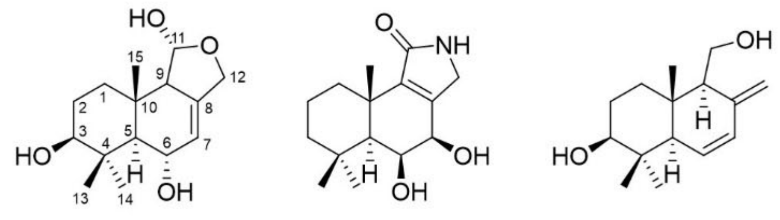


Figure 5. PC-12 cells were treated with (A) DMSO, (B–F) 1 mg/mL hericioic acids (**1–4**, **6**), and (G) hericiofuranoic acid (**8**) supplemented with 5 ng/mL NGF. Phase contrast images show neurite outgrowth after 48 h of treatment. (H) Bar graph displays the mean neurite length ± SEM, from five independent experiments.

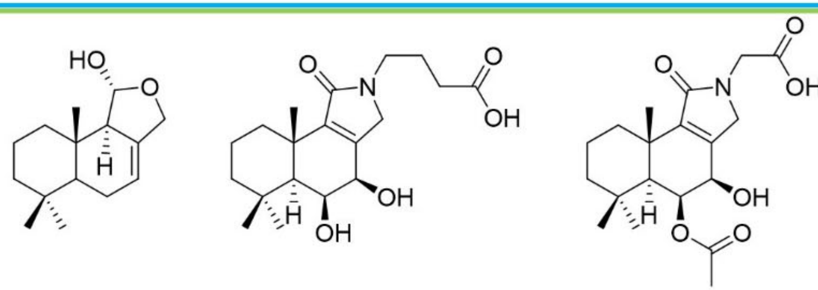
Terpene alkaloids from tropical mushrooms

Perenniporia centrali-africana

Cerrena sp. nov.



1 2 3



4 5 6

molecules

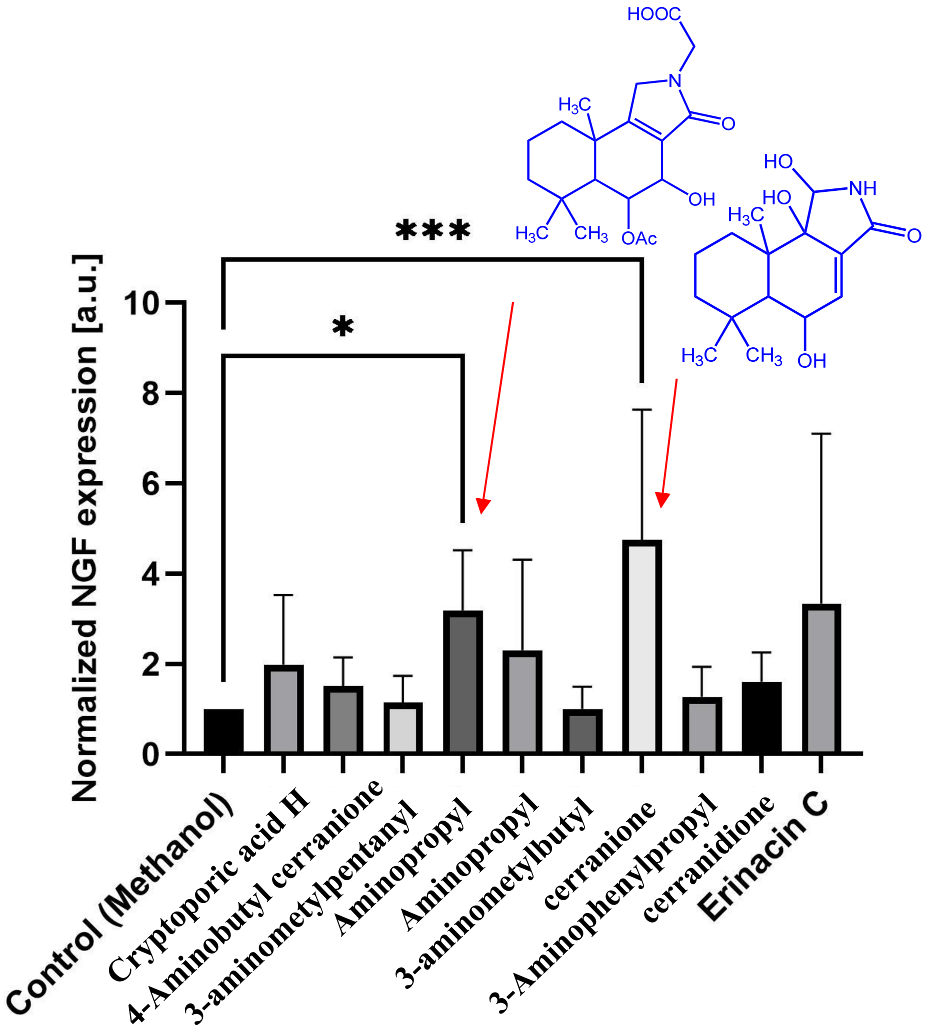
MDPI

Article

Drimane-Type Sesquiterpenoids Derived from the Tropical Basidiomycetes *Perenniporia centrali-africana* and *Cerrena* sp. nov

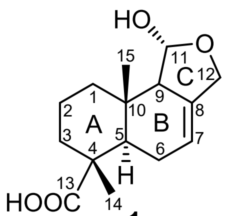
Paomephan Pathompong [1,2,†], Sebastian Pfütze [2,3,†], Frank Surup [2,3], Thitiya Boonpratuang [4], Rattaket Choeyklin [4,5], Josphat C. Matasyoh [6], Cony Decock [7], Marc Stadler [2,3,*] and Chuenchit Boonchird [1,*]

Further unpublished drimane derivatives from *Cerrena* sp.

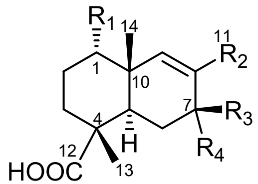


Pathompong Paomephan et al. (only published in the PhD thesis Mahidol Univ., Thailand (2022)

New terpenoids from solid cultures of *Abundisporus violaceus*



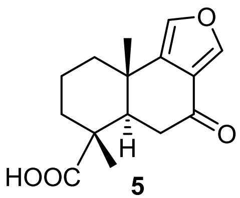
1



2: R_1, R_4= H, R_2= COOH, R_3= OH

3: R_1, R_4= H, R_2= CH_2OH, R_3= OH

4: R_1= OH, R_2= CH_2OH, R_3,R_4= =O



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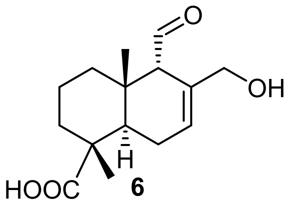

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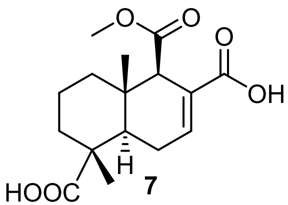
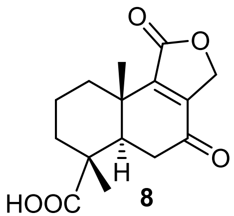


7

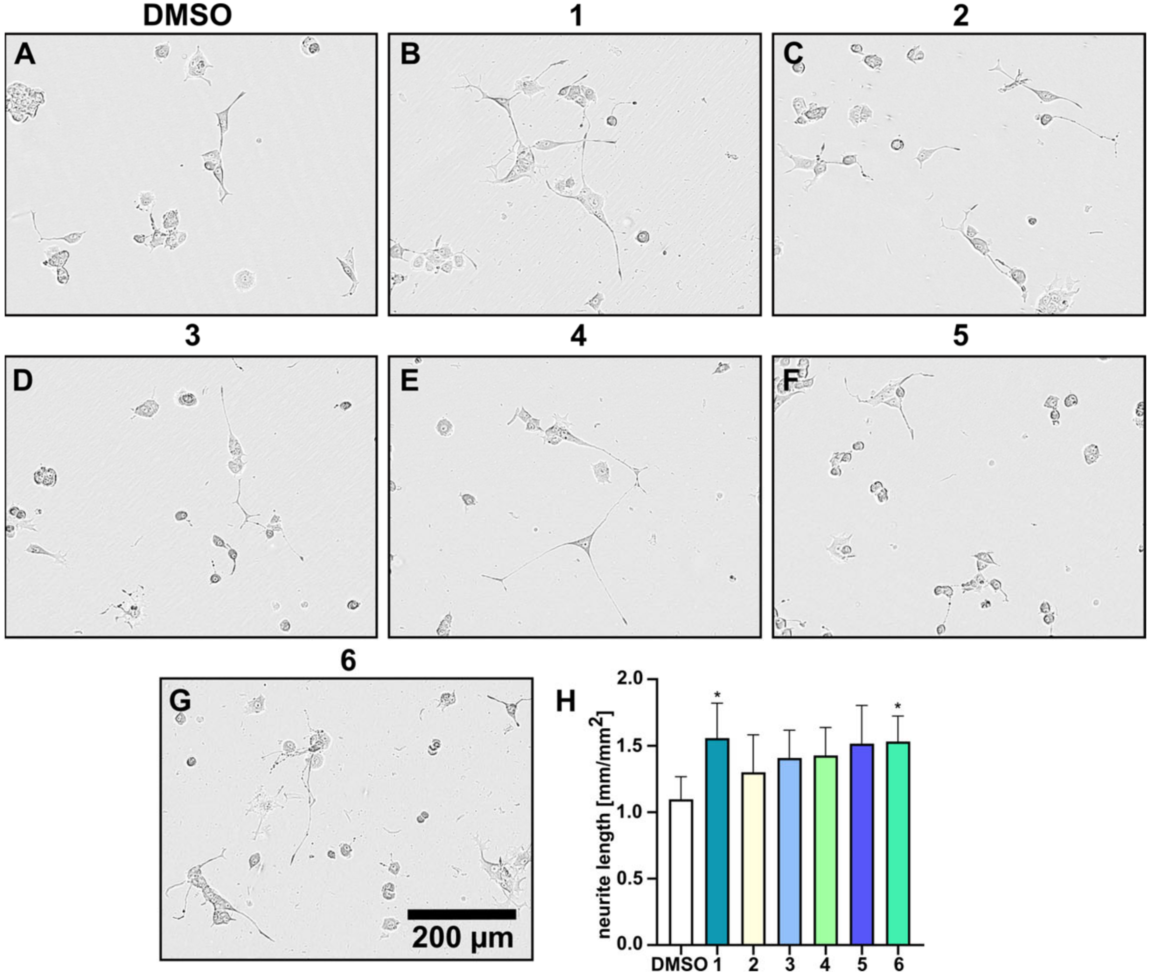


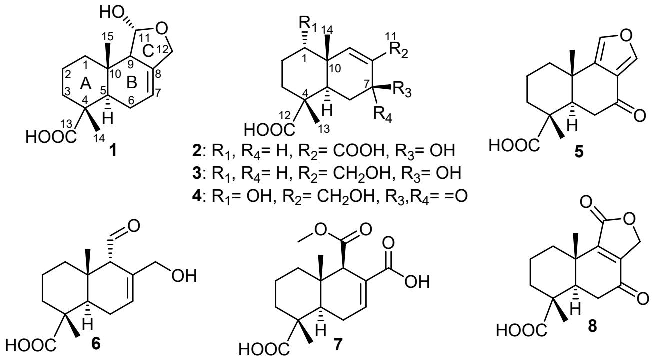
8

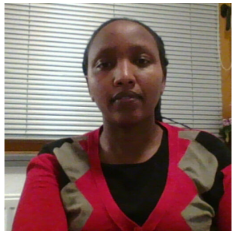
Eight new drimanes were isolated from solid cultures on rice

Fermentation time: 68 days

Terpenoids from *Abundisporus violaceus are* NGF enhancers



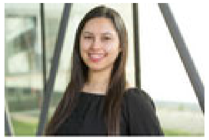




Winnie Sum

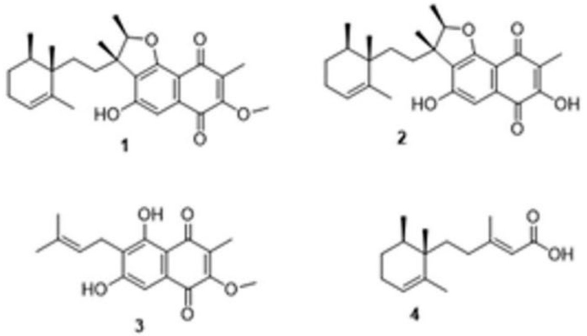
Endofungal bacteria of tropical Basidiomycota also produce interesting molecules

Khadija Hassan



Natalia Llanos-Lopez

Yasmina Marin-Felix



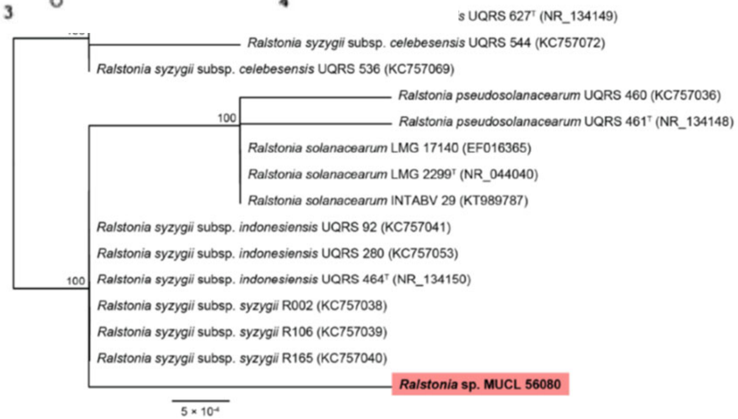


Figure 2. RAxML phylogram obtained from 16S sequences of taxa included in *Ralstonia solanacearum* species complex. Bootstrap support values ≥ 70 are indicated along branches. Branch lengths are proportional to distance. Ex-type strains are indicated with ^{T}. The maximum-likelihood (ML) analyses employed RAxML on the CIPRES portal (www.phylo.org, accessed on 12 May 2022) using RAxML-HPC BlackBox v8.2.12 with default parameters. Our strain studied is highlighted using pink colour.

biomolecules MDPI

Article

Meroterpenoids Possibly Produced by a Bacterial Endosymbiont of the Tropical Basidiomycete *Echinochaete brachypora*

Khadija Hassan [1,2], Clara Chepkirui [1,3], Natalia Andrea Llanos-López [1,2], Josphat C. Matasyoh [4], Cony Decock [5], Yasmina Marin-Felix [1,2,*] and Marc Stadler [1,2,*]

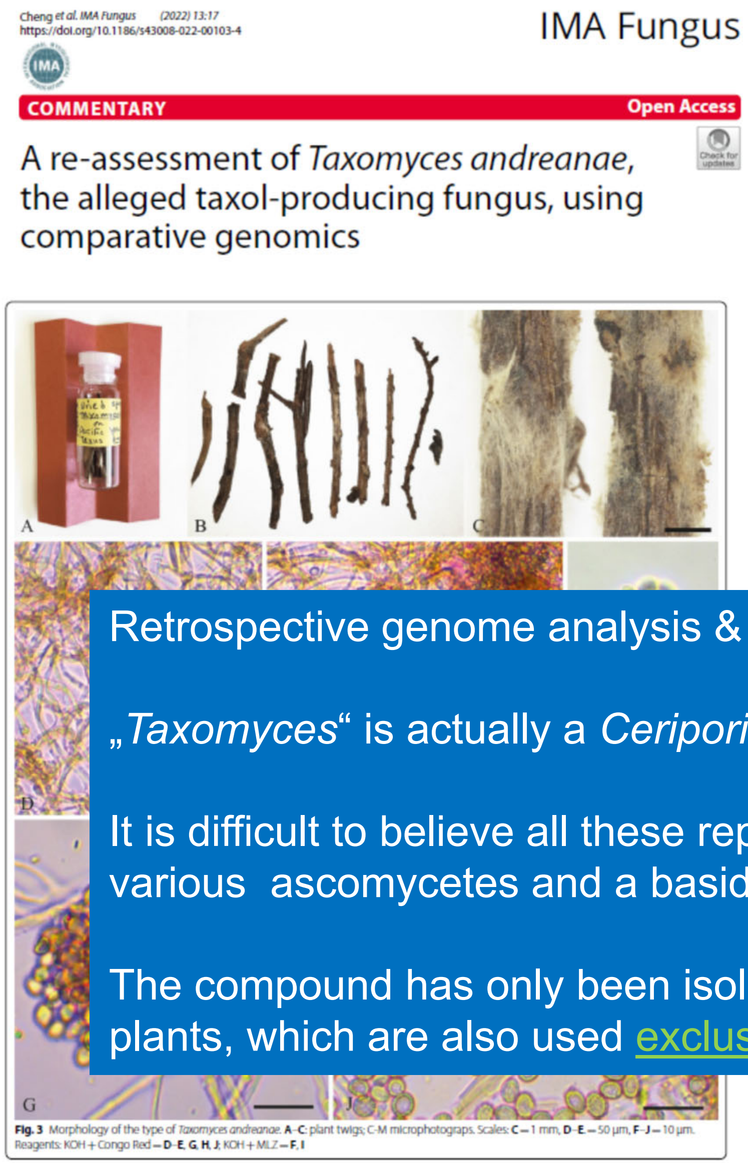
Impressions from field work (Arabuko Sokoke NP, Kenya, May 2022)

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

Alexander von
HUMBOLDT
STIFTUNG

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

Another (in-)famous fungus turned out to be a basidiomycete

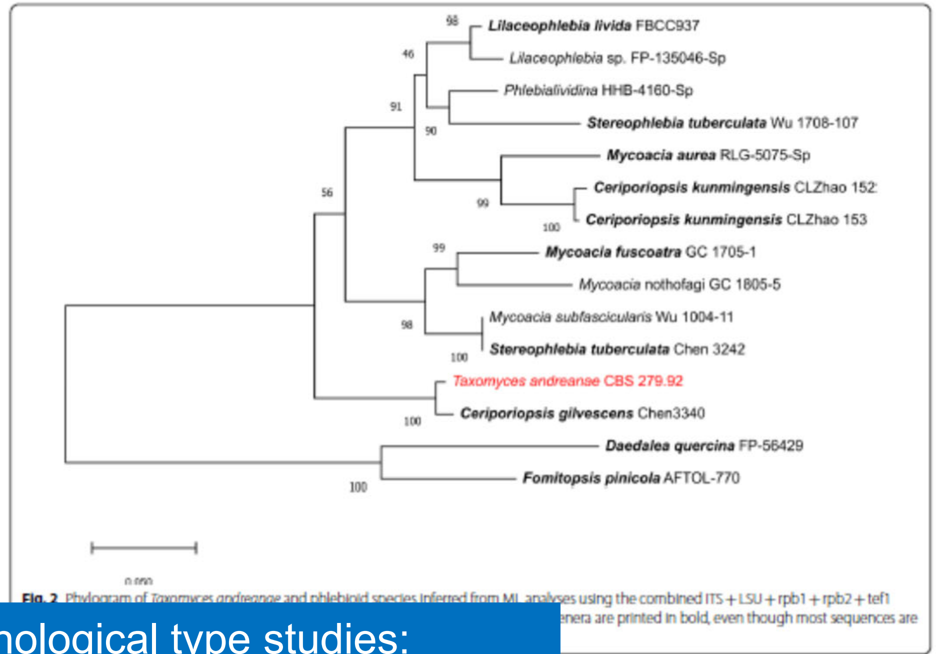

Cheng et al. IMA Fungus (2022) 13:17
https://doi.org/10.1186/s43008-022-00103-4

IMA Fungus

COMMENTARY Open Access

A re-assessment of *Taxomyces andreanae*, the alleged taxol-producing fungus, using comparative genomics

Fig. 3 Morphology of the type of *Taxomyces andreanae*. A–C: plant twigs; C-M microphotograps. Scales: C = 1 mm, D–E = 50 µm, F–J = 10 µm. Reagents: KOH + Congo Red = D–E, G, H, J; KOH + MLZ = F, I



Retrospective genome analysis & morphological type studies:

„*Taxomyces*“ is actually a *Ceriporiopsis* species !

It is difficult to believe all these reports on the occurrence of taxol in various ascomycetes and a basidiomycete

The compound has only been isolated in substantial quantities from plants, which are also used exclusively to produce it.

Tian Cheng

A new model organism to express biosynthetic gene clusters from Basidiomycota


Sebastian Pfütze


Frank Surup

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

New terpenoids from the fermentation broth of the edible mushroom *Cyclocybe aegerita*

Frank Surup[1,2], Florian Hennicke[3], Nadine Sella[4], Maria Stroot[1,2], Steffen Bernecker[1
Sebastian Pfütze[1,2], Marc Stadler*[1,2] and Martin Rühl*[4,5]

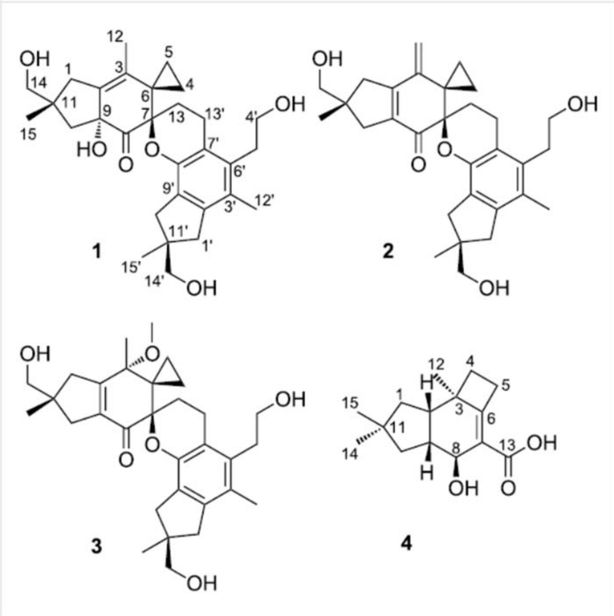


Figure 1: Structures of the isolated metabolites bovistol A (**1**), its new derivatives bovistol B (**2**) and C (**3**), as well as the new protoilludane pasteurestin C (**4**).

Readily forms fruitbodies on agar plates, and even stable fruitbody forming monokaryons are available

C. aegerita is not only a good model organism but also has an excellent taste!

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

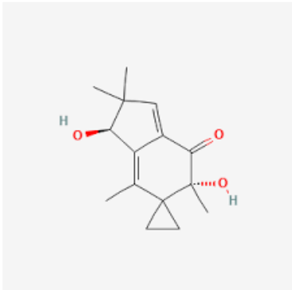
- MPLC
- Preparative HPLC

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

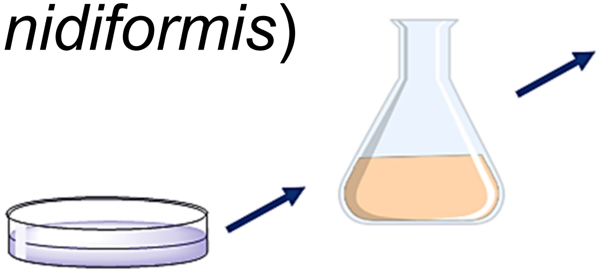
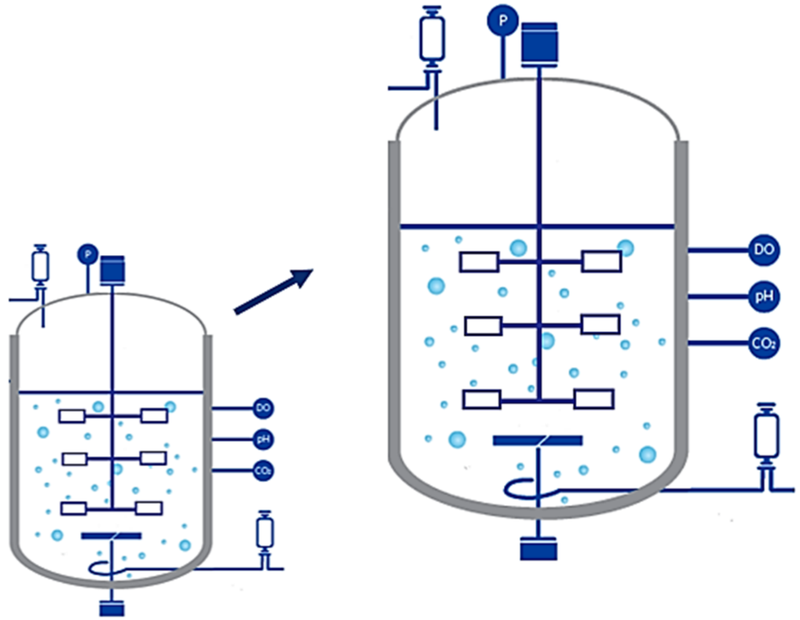
PhD project of Lillibeth Chaverra-Munoz

Lillibeth Chaverra

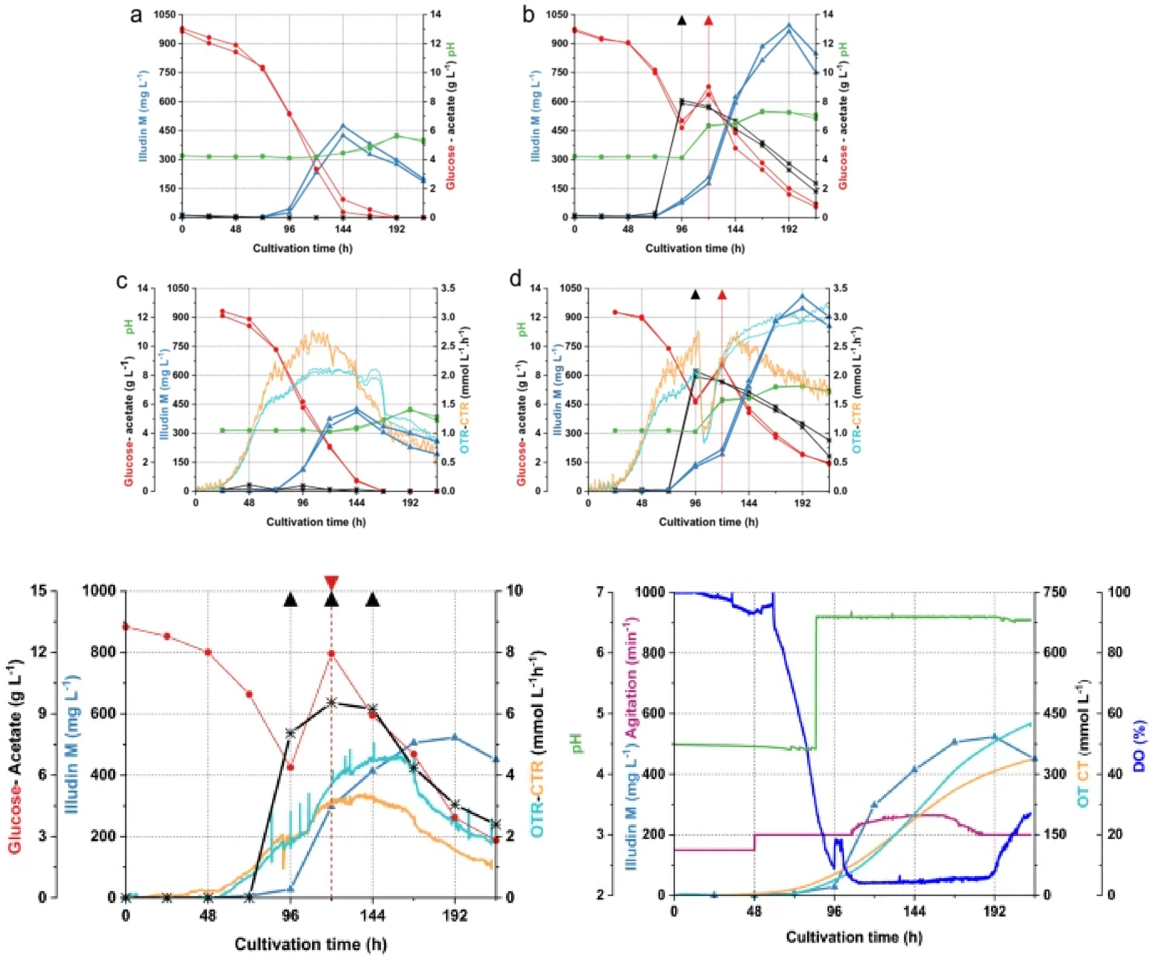
Development of a sustainable and reproducible process for biotechnological production of illudin M

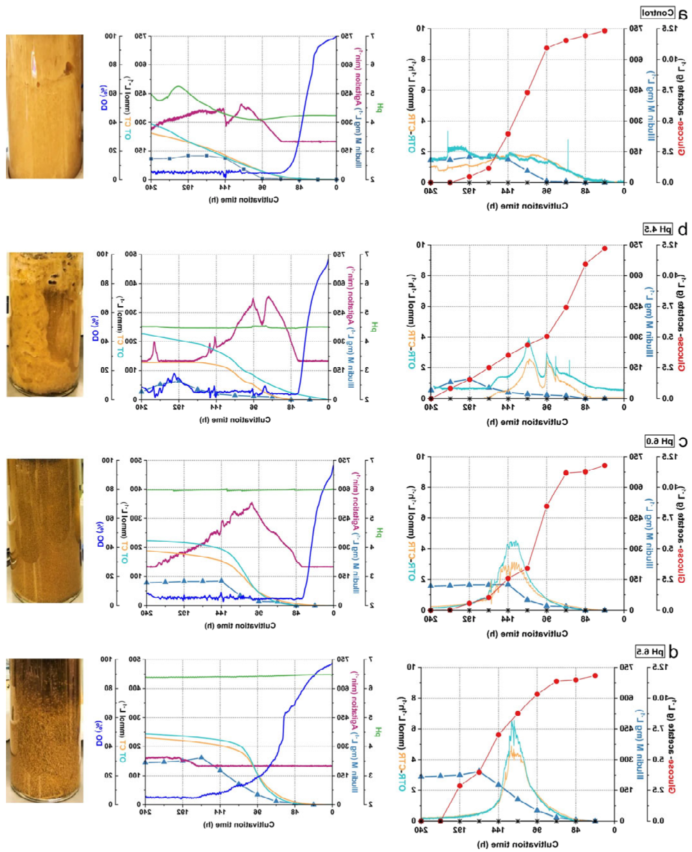


….using the „Ghost Fungus“ (*Omphalotus nidiformis*)

Titers of over 1 gram per litre were finally attained by Lilly after 2 years of meticulous empirical work





Results of a PhD thesis

Chaverra-Muñoz *et al. Microbial Cell Factories* (2022) 21:98
https://doi.org/10.1186/s12934-022-01827-z
Microbial Cell Factories

METHODOLOGY **Open Access**

Optimization of the production process for the anticancer lead compound illudin M: improving titers in shake-flasks

Lillibeth Chaverra-Muñoz[1,2], Theresa Briem[1] and Stephan Hüttel[1,2*]

https://doi.org/10.1186/s12934-022-01870-w

METHODOLOGY **Open Access**

Optimization of the production process for the anticancer lead compound illudin M: process development in stirred tank bioreactors

Chaverra-Muñoz *et al. Microbial Cell Factories* (2022) 21:165
https://doi.org/10.1186/s12934-022-01886-2
Microbial Cell Factories

METHODOLOGY **Open Access**

Optimization of the production process for the anticancer lead compound illudin M: downstream processing

Lillibeth Chaverra-Muñoz[1,2], Theresa Briem[1] and Stephan Hüttel[1,2*]

First trip abroad after the pandemics (Colombia 2021)

First output of our collaboration with Colombian scientists

metabolites MDPI

Article

Panapophenanthrin, a Rare Oligocyclic Diterpene from *Panus strigellus*

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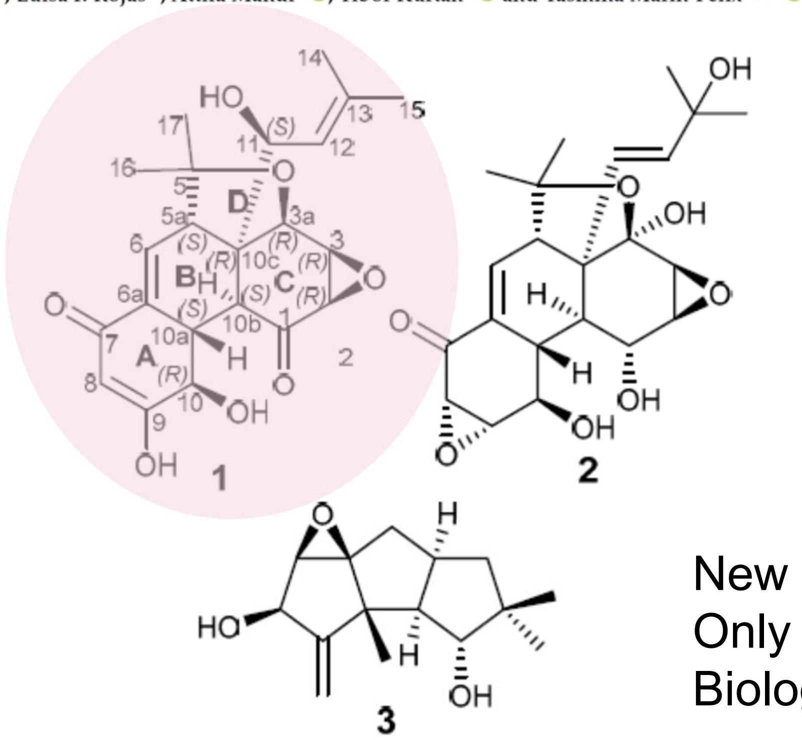
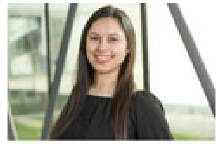


Figure 1. Chemical structures of 1–3.



Natalia Llanos-Lopez

Yasmina Marin-Felix

New derivative of an unique carbon skeleton
Only weak antibiotic activities observed
Biological evaluation in other assays ongoing

Take Home Messages

- **The (sub-)tropical species of the Basidiomycota still harbor a plethora of unprecedented bioactive metabolites**
- **Phylogenetic & taxonomic data can help substantially to identify producers of novel lead compounds**
- **Basic & applied research (e.g. taxonomy & ecology vs. bioprospecting & biotechnology) can be combined to reach multiple mutual benefits**
- **Our international, interdisciplinary research network, providing training opportunities for young scientists from all over the world, is indispensable to accomplish these tasks**
- **Latin American mycologists should also try harder to culture their basidiomycetes and study them for secondary metabolites and other beneficial aspects.**

Further reading

Review | Open Access | Published: 12 July 2023

The contribution of fungi to the global economy

Allen Grace T. Niego, Christopher Lambert, Peter Mortimer, Naritsada Thongklang, Sylvie Rapior, Miriam Grosse, Hedda Schrey, Esteban Charria-Girón, Arttapon Walker, Kevin D. Hyde & Marc Stadler

Fungal Diversity (2023)

Biotechnology Advances
Volume 37, Issue 6, 1 November 2019, 107344

Research review paper

Biological and chemical diversity go hand in hand: Basidiomycota as source of new pharmaceuticals and agrochemicals ☆

Birthe Sandargo [a b 1], Clara Chepkirui [a b 1], Tian Cheng [a b], Lillibeth Chaverra-Muñoz [a b], Benjarong Thongbai [a b], Marc Stadler [a b], Stephan Hüttel [a b]

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Issue 4, 2021

From the journal:
Natural Product Reports

Mind the mushroom: natural product biosynthetic genes and enzymes of Basidiomycota

Check for updates

Markus Gressler, [a] Nikolai A. Löhr, [a] Tim Schäfer, [a] Stefanie Lawrinowitz, [a] Paula Sophie Seibold [a] and Dirk Hoffmeister *[a]

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ZENTRUM FÜR INFEKTIONSFORSCHUNG

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ERAfrica

HORIZON 2020

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DZIF

Bundesministerium für Bildung und Forschung

DAAD Deutscher Akademischer Austausch Dienst German Academic Exchange Service

TRF

Alexander von HUMBOLDT STIFTUNG

DFG Deutsche Forschungsgemeinschaft

Bill & Melinda Gates foundation

… and all coauthors of the cited publications

….and all members of the MWIS Team!

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Marie Skłodowska-Curie Actions

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