Simultaneous Production of Psilocybin and a Cocktail of β-Carbol ine Monoamine Oxidase Inhibitors in “Magic” Mushrooms

Felix Blei[a], Sebastian Dörner[a], Janis Fricke[a], Florian Baldeweg[a], Felix Trottmann[b], Anna Komor[b], Florian Meyer[c], Christian Hertweck[bd] and Dirk Hoffmeister*[a]

Abstract: The psychotropic effects of Psilocybe “magic” mushrooms are caused by the L-tryptophan-derived alkaloid psilocybin. Despite their significance, the secondary metabolome of these fungi is poorly understood in general. Our analysis of four Psilocybe species identified harmine, harmine, and a range of other L-tryptophan-derived β-carbolines as their natural products, which was confirmed by 1D and 2D NMR spectroscopy. Stable-isotope labeling with 13C1L-L-tryptophan verified the β-carbolines as biosynthetic products of these fungi. In addition, MALDI-MS imaging showed that β-carbolines accumulate toward the hyphal apices. As potent inhibitors of monoamine oxidases, β-carbolines are neuroactive compounds and interfere with psilocybin degradation. Therefore, our findings represent an unprecedented scenario of natural product pathways that diverge from the same building block and produce dissimilar compounds, yet contribute directly or indirectly to the same pharmacological effects.

Introduction

Since ancient times, vision-inducing, consciousness-altering natural products, so-called entheogens, have been used for spiritual purposes. The producing plants or fungi have accompanied humankind and impacted the genesis of culture and religion.[1] Indisputably, mushrooms producing psilocybin (1), Scheme 1) rank among the most prominent entheogens and were considered the “flesh of the gods” (teonanacatl) by the Aztecs.[1] Numerous species within the fungal genus Psilocybe and other genera biosynthesize 1 which represents the phos-
baceocystin, and norpsilocin were discovered.\textsuperscript{[5]} Compound 2 interferes with serotonergic neurotransmission because it acts as a partial agonist primarily on the 5-hydroxytryptamine (5-HT)\textsubscript{2A} receptor.\textsuperscript{[5]} The perceptual and somatic effects include synesthesia, visual hallucinations, dilated pupils, and others.\textsuperscript{[5]}

The effects last for several hours before they subside when 2 is eliminated both renally through O-glucuronolysis and by formation of 4-hydroxyindol-3-yl-acetaldehyde (Scheme 1). The latter process is catalyzed by the monoamine oxidase isozyme A (MAO A).\textsuperscript{[7]} a mitochondrial flavin-dependent enzyme that oxidatively deaminates serotonin and other biogenic and neuroactive amines. Consequently, MAO inhibitors generally increase the pharmacological effects of such bioactive amines.

Another entheogen that has traditionally been consumed in spiritual and healing ceremonies is a psychotropic brew, known by its vernacular name ayahuasca, a Quechua term literally meaning “vine of the souls”. Unlike Psilocybe mushrooms, it is not the product of a single biological species. Rather, ayahuasca consists of leaves of \textit{N,N}-dimethyltryptamine (DMT, 3, Scheme 1) producers, e.g., \textit{Psychotria viridis} (Rubiaceae, coffee family).\textsuperscript{[9]} Compound 3 is inactive when taken up orally, but becomes neuroactive in the presence of MAO A inhibitors that prevent 3 degradation in the human gut (Scheme 1). Such inhibitors are present in ayahuasca as well, because its second ingredient is the bark of the jungle vine \textit{Banisteriopsis caapi} (Malpighiaceae), which produces \( \beta \)-carbolines, which are strong reversible MAO inhibitors.\textsuperscript{[9]} Ayahuasca’s synergism, caused by two separate species, has empirically been discovered in pre-Columbian times by South American natives.\textsuperscript{[9]} It compensates the fact that synchronous production of a bioactive compound and the inhibitor of its own degradation as enhancer in one single species is unprecedented for psychotropic natural products.

Besides 1 and its congeners, other amino-acid derived natural products have not been reported yet from \textit{Psilocybe} mushrooms. Therefore, their secondary metabolites appear surprisingly little understood, despite 60 years of intensive research. We addressed this knowledge gap and describe here an in-depth re-analysis of natural-product profiles of five \textit{Psilocybe} species. In all of them, we identified \( \beta \)-carbolines as their products, i.e., a metabolic profile reminiscent of the active principles of ayahuasca.

Results and Discussion

In the course of metabolic profiling of carpophores of \textit{Psilocybe mexicana}, we routinely extracted with methanol, using a published protocol.\textsuperscript{[4c]} and analyzed the crude extracts by LC-HR-ESI-MS. As expected, 1, its immediate biosynthetic precursors baeocystin and norbaceocystin, and low amounts of its dephosphorylated follow-up compound 2 were detected. However, we also identified two very minor mass spectrometric signals that showed retention times and masses dissimilar to those of authentic standards of 1 and its precursors (Figure 1 A). These signals appeared at \( t_{\text{R}} = 4.53 \text{ min} \) (m/z = 183.0916 [M+H]\textsuperscript{+}) and at \( t_{\text{R}} = 4.89 \text{ min} \) (m/z = 213.1022 [M+H]\textsuperscript{+}). We hypothesized that \( \beta \)-carbolines may account for these signals as the observed masses are in good agreement with that of harmine (4, Figure 1) and harmine (5).\textsuperscript{[11,12]} Upon exposure to UV light, \( \beta \)-carbolines fluoresce.\textsuperscript{[13]} Therefore, we repeated the analysis, this time using an acidic aqueous mushroom extract and an HPLC instrument interfaced to a fluorescence detector, excitation was at \( \lambda = 340 \text{ nm} \), emission was recorded at \( \lambda = 410 \text{ nm} \). The signals were detected again, and authentic 4 and 5 standards showed identical retention times and masses (Figure 1 B).

We analyzed acidic aqueous extracts of other \textit{Psilocybe} species by HPLC and fluorescence detection (Figure 1 C) to investigate if \( \beta \)-carbolines were present in those fungi as well. Compound 4 and, in lower quantities, 5 were found (\( t_{\text{R}} = 2.98 \text{ and } 3.16 \text{ min} \) in carpophores of \textit{P. cyanescens}, \textit{P. semilanceata}, and of two \textit{P. cubensis} isolates, as well as in \textit{P. mexicana} (both scle- rotia and mycelium), and in \textit{P. cubensis} mycelium. In addition to the above-mentioned \( \beta \)-carbolines, we detected norharmane (6, \( t_{\text{R}} = 2.85 \text{ min} \), Figure 1) and perlolyrine (7, \( t_{\text{R}} = 3.49 \text{ min} \), and identified them by their masses (m/z = 169.0763 and 265.0974 [M+H]\textsuperscript{+}) and by comparison with synthetic standards. The latter compound is known as a plant alkaloid from \textit{Codonopsis pilosula} (Campanulaceae, bellflower family).\textsuperscript{[10]} Overall, the \( \beta \)-carbonate pattern was quantitatively and qualitatively inhomogeneous among species, yet indicated that their occurrence is more widespread within the genus \textit{Psilocybe} and independent of the developmental stage. For final evidence that \textit{Psilocybe} fungi contain \( \beta \)-carbolines, we purified the two major compounds from \textit{P. cubensis} carpophores. Subsequent 1D and 2D NMR spectroscopy resulted in spectra (Figures S1–S10, Table S1, Supporting Information) that were identical to reported data for 4 and 5.\textsuperscript{[13]}

Biosynthetically, \( \beta \)-carbolines derive from tryptamine and have been isolated from plants, bacteria, and various fungi including basidiomycetes.\textsuperscript{[10,14]} To confirm that the compounds are intrinsic \textit{Psilocybe} products, we carried out stable-isotope labeling with \textsuperscript{13}C\textsubscript{14}-L-tryptophan and \textit{P. mexicana} mycelium in liquid axenic culture under controlled laboratory conditions, along with an unlabeled control, and detected 4, 6, and 7 again. In the stable-isotope-treated cultures, the masses of the carbolines expectedly increased by ten mass units (Figure 2). This is compatible with the incorporation of ten \textsuperscript{13}C\textsubscript{14} atoms, i.e., a \textsuperscript{13}C\textsubscript{14}-\( \beta \)-tryptamine moiety. Thus, we had excluded a carboline source other than \textit{Psilocybe}’s intrinsic cellular metabolism.

We detected two further compounds in minor quantities. The first one whose mass was identical to that of harmal (8, m/z = 199.0869 [M+H]\textsuperscript{+}) was eluted at \( t_{\text{R}} = 4.26 \text{ min} \). However, authentic 8 showed an shorter retention time (\( t_{\text{R}} = 3.99 \text{ min} \), Figure 2), which points to an isomer of 8 as \textit{Psilocybe} metabolite. \textit{P. mexicana} mycelium also contained a compound at \( t_{\text{R}} = 4.89 \text{ min} \) (m/z = 213.1025 [M+H]\textsuperscript{+}). Even though this molecular mass is identical to that of 5, the retention time was not, as this unidentified compound virtually co-eluted with 4 at \( t_{\text{R}} = 4.53 \text{ min} \).

This mass is consistent with that of cordyssins C and D (9 and 10), i.e., enantiomeric \( \beta \)-carbolines described from the carpellifer fungus \textit{Ophiocordyceps sinensis}.\textsuperscript{[15]} Comparison with a synthesized mixture of 9 and 10 confirmed that one of those compounds, or both, is a \textit{P. mexicana} metabolite as well.
Psilocybe cubensis FSU12410 mycelia and carpophores were used to quantify the concentration of 4, i.e., the major \( \beta \)-carboline in the fungal biomass (Figure 1C, Table S2, Supporting Information). Although mycelia showed a concentration of 21 mg g\(^{-1}\) dried biomass, we found a 100-fold lower concentration in the carpophores (0.2 mg g\(^{-1}\)). Sclerotia of \( P. \) mexicana contained 1.4 mg g\(^{-1}\) 4 and 1.6 mg g\(^{-1}\) 5. Next, we used MALDI imaging to investigate the spatial distribution of 4 in fungal mycelium. An actively growing \( P. \) cubensis culture was screened for a compound with \( m/z \) 183.1 (± 0.7) Da, which corresponds to 4 (Figure 3). The signals of maximum intensity localized to the hyphal tips while more mature areas showed low abundance.

Considered divine by native Central Americans, Psilocybe mushrooms produce one natural product that has been used both as recreational drug and an immensely valuable carcinogenic producer, currently in advanced clinical trials, to treat anxiety and depression.\(^{16}\) Despite their history and importance, the mushrooms’ capacity to make further compounds has received deceptively little attention. We identified five \( Psilocybe \) species as \( \beta \)-carboline producers. This capacity of \( 1 \)-producing mushrooms is remarkable in the light of the synergistic pharmacology. 4 and 5 are potent reversible inhibitors of mammalian brain and liver MAO A \( (K_i = 8.9 \text{ and } 0.5 \text{ nM}) \), for brain, \( K_i = 9.9 \) and 0.2 nM for liver.\(^{17}\) Human placental MAO A is inhibited at \( K_i = 7.2 \mu \text{M}.\(^{18}\) Furthermore, tetrahydro-\( \beta \)-carbolines do not inhibit MAO A, yet represent neuroactive natural products as well as they moderately inhibit serotonin reuptake.\(^{19}\)

**Conclusions**

Psilocybe mushrooms produce an ayahuasca-like and potentially similarly synergistic set of metabolites that may impact upon onset and duration of their effects. Remarkably, both pathways originate from the same generic building block, \( \text{L} \)- tryptophan, yet take different routes leading to dissimilar compounds whose bioactivities in return contribute directly and indirectly to the same pharmacology (Scheme 1). This is a unique case in fungal chemistry and distantly related to the bacterium \( Streptomyces clavuligerus \) that synchronously produces both the \( \beta \)-lactam antibiotic cephamycin and the \( \beta \)-lactamase inhibitor clavulanic acid.\(^{20}\)

Despite the co-occurrence of 1 and MAO inhibitors in Psilocybe, numerous studies with pure synthetic compounds have shown that the somatic, endocrinic, and psychotropic effects are the sole consequence of 1 uptake.\(^{21}\) Future pharmacologi-
Psilocybe l

For im-
malt carpophores.
was carried out as described.
and
result
6
1
Carpo-
were collect-
agar,p H5 .6) at
t
are hypothesized to fulfill a
coelut-
FSU13617 was grown in 50 mL liquid MEP
were purchased from Sigma. Compounds
2020
were synthesized (below).

P. cyanescens
and
T
www.chemeurj.org
2
mycelium.T he image was taken
13
were deposited in the Jena Microbial Resource Collection
3m onths. Carpophore production with
P. mexicana
and dikaryotic isolates thereof

Figure 2. LC-MS analysis of P. mexicana mycelial extracts after 13C-stable-isotope labeling. The generic labeling pattern is shown by red carbon atoms. UHPLC chromatograms were recorded at λ = 300 nm. Top trace: overlaid chromatograms of standards 4–10. Center trace: culture grown with unlabeled L-tryptophan (control). Bottom trace: culture grown in the presence of 13C14NL-tryptophan. Below, HR-ESI-MS spectra are shown. Blue: spectra for tR = 4.26–4.28 min with coeluting 6 and the isomer of 8 (panel A: unlabeled, panel B: 13C-labeled situation). Green: spectra for tR = 4.50–4.52 min showing 4 and 9/10 coelut-
ing, panel C: unlabeled, panel D: 13C-labeled. Red: spectra for tR = 4.94 min showing 7, panel E: unlabeled, panel F: 13C-labeled. Upper right: UV/Vis spectra of 4 and collective spectra of the β-carbolines, detected at tR = 4.50 min.

Figure 3. MALDI-MS imaging of P. cubensis mycelium. The image was taken to detect m/z 183.1(±0.7) Da, i.e., the mass of 4 [M+H]+, and a portion was overlaid on a photograph of the mycelium. Peripheral areas of the mycelium showed highest abundance (red). The image was digitally optimized for brightness which sets the maximum intensity to 60% of the initial image.

Experimental Section
Materials and microbiological methods

Chemicals, solvents, and media components were pur-
chased from Cambridge Isotope Laboratories, Deutero, Sigma–Aldrich, Roth, and VWR. Reference compounds of 4 and 5 were purchased from Sigma. Compounds 1, 2, baecystin, and norbaecystin were purified from P. cubensis carpophores. Reference compounds of 6–10 were synthesized (below). Psilocybe isolates (Table S3, Supporting Information) were maintained on
malt extract/peptone (MEP) solid medium (30 g L−1 malt extract, 3 g L−1 soy peptone, 18 g L−1 agar, pH 5.6) at t = 23 °C in the dark. P. mexicana sclerotia were produced in preserving jars filled with rye, supplemented with cow manure and straw, and kept in the dark for
3 months. Carpophore production with P. cubensis and P. mexicana was carried out as described. Carpophor-

Stable-isotope labeling

P. mexicana FSU13617 was grown in 50 mL liquid MEP medium amended with 1 mm 13C14NL-tryptophan (or 1 mm unlabeled L-tryptophan for control), for 14 d. The biomass
was harvested by filtration, lyophilized, homogenized and extract-
ed with 20% (v/v) acetic acid in water. After filtration, the liquid
was evaporated under reduced pressure, and the residue was
solved in MeOH, filtered, and used for LC/MS (below).

Natural product extraction

Initially, mycelia and carpophores were lyophilized, ground, and
extracted with anhydrous MeOH, as described to extract 1 gently
and to minimize its artificial dephosphorylation to 2. For
improved carboline yields, the fungal biomasses (mycelia, carp-

P. semilanceata
(AUCs) in the extracted ion chromatograms were determined and referenced to a standard curve recorded with authentic 4.

**Chromatographic purification of 4 and 5**

Preparative HPLC was performed using an Agilent 1260 instrument equipped with Phenomenex Luna C18 column (250 x 21.2 mm, 10 μm particle size), and run with 0.1% trifluoroacetic acid (TFA) in water (solvent A) and acetonitrile (ACN, solvent B). The flow was 20 mL.min⁻¹. A linear gradient was applied with an increase from 10 to 100% B within 20 min. β-Carbolines were further purified by semipreparative HPLC using an Agilent 1200 instrument equipped with a Zorbax Eclipse XDB-C18 column (25 x 9.4 mm, 5 μm), and the same solvents, applying a flow of 2 mL.min⁻¹ and a linear gradient from 10 to 100% B within 10 min. The final purification was accomplished with the same solvents and instrument, but using a Phenomenex Synergi RP-80 column (25 x 10 mm, 4 μm) and a gradient that included an initial hold at 30% B for 1 min, an increase to 65% B within 10 min, and to 100% B within further 20 sec. This procedure yielded 3.5 mg of 4 and 14.4 mg of 5, which were dissolved in [D₆]DMSO for subsequent NMR analysis (below).

**HPLC and mass spectrometry**

HPLC and mass spectrometry were performed on a Thermo Accela liquid chromatograph equipped with a C₈ column (Grom-Sil 100 ODS-0 AB, 250 x 4.6 mm, 3 μm) fitted to an Exactive Orbitrap spectrometer, using electrospray ionization. The respective diode array detectors covered the wavelength range of λ = 200–400 nm. Initially, HPLC-UV chromatograms were extracted at λ = 280 nm (to detect 1), later at λ = 300 nm to detect β-carbolines. Conditions for HPLC included solvents 0.1% TFA in water (A) and 0.1% TFA in ACN (B) at a flow rate of 0.4 mL.min⁻¹. The gradient was: initial hold at 10% B for 1 min, and linear increase to 98% B within 4 min.

Standard analytical runs were performed on a Thermo Vanquish Horizon UHPLC system equipped with a diode array and a fluorescence detector. This instrument was equipped with a Phenomenex Kinetex XB-C₈ column (100 x 2.1 mm, 1.7 μm particle size). For fluorescence detection, excitation and emission were at λ = 340 and 410 nm, respectively. Solvents were 0.1% formic acid (FA) in water (A) and ACN (B) at a flow rate of 1 mL.min⁻¹. The gradient was: initial hold at 5% B for 1 min, and linear increase to 100% B within 15 min. Chromatography and mass spectrometry to quantify the concentration of 4 was done on an Agilent 1290 Infinity II UHPLC instrument with a diode array detector (DAD) and interfaced to a 6130 quadrupole mass detector, run in ESI mode. The chromatograph was equipped with a Phenomenex Luna Omega Polar C₁₈ 50 x 2.1 mm (1.6 μm particle size) and a guard column. Separation was at 25 °C and a flow of 0.5 mL.min⁻¹. Mobile phase A was 0.1% aqueous FA, phase B was ACN+0.1% FA. A linear gradient was applied (% B): initially 1%, within 3 min to 10%, and within further 1 min to 100%. UV/Vis spectra were recorded with the diode-array detector during LC-MS analyses. Samples were dissolved in MeOH.

**MALDI-MS imaging**

P. cubensis mycelium was directly grown on indium tin oxide (ITO)-coated glass slides for Imaging MS. ITO glass slides were placed inside petri dishes and covered with 20 mL of MEP agar to form a thin layer on which cultures were grown at room temperature for up to 4 d. Subsequently, the slides were dried overnight at 37 °C and sprayed with 2.5 mL of universal MALDI matrix (1:1 mixture of 2,5-dihydroxybenzoic acid and α-cyano-4-hydroxycinnamic acid) dissolved at 20 mgmL⁻¹ in a mixture of acetonitrile, methanol and water (70:25:5), using the automatic ImagePrep device 2.0 (Bruker Daltonics) with 60 consecutive cycles (a 180° rotation of the sample after 30 cycles was performed) of 31 seconds (1 s spraying, 10 s incubation time, and 20 s of active drying). Samples were then analyzed on an UltraflexXTreme MALDI TOF/TOF instrument (Bruker Daltonics), operated in the positive reflector mode using flexControl 3.0. The analysis was performed from 100 Da to 3,000 Da, accumulating 500 shots by taking 10 random shots at each raster position (raster width 200 μm). The acquisition method was externally calibrated using the Peptide Calibration Standard II (Bruker Daltonics). Spectra were processed with baseline subtraction in flexAnalysis 3.3. Images were obtained using root mean square normalization and brightness optimization.

**Nuclear magnetic resonance spectroscopy**

NMR spectra were recorded on a Bruker Avance III 600 MHz spectrometer at 300 K. The solvent was [D₆]DMSO 1H and 13C NMR chemical shifts were referenced relative to residual protons present in deuterated DMSO at δ_H = 2.49 ppm and δ_C ≈ 39.5 ppm.

**Syntheses of reference compounds**

To synthesize 6, we followed the protocol by Snyder et al.[22] but substituted ethyl acetate by formaldehyde. The synthesis of 7 was carried out as described.[18] For 8 synthesis, a published procedure was applied,[23] but replacing HBr by HCl. A mixture of 9 and 10 was synthesized following a published procedure.[24]

**Acknowledgements**

We gratefully acknowledge A. Perner, H. Heinecke, S. Schieferdecker, and V. Valiante (Leibniz Institute for Natural Product Research and Infection Biology—Hans Knöll Institute, Jena) for recording high-resolution mass and NMR spectra, and for providing [13C]1-L-tryptophan, respectively. This work was funded by the Deutsche Forschungsgemeinschaft (DFG, grant HO2515/7-1 to D.H.) and by the DFG Collaborative Research Center CRC 1127 (ChemBioSys, to C.H. and D.H.).

**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** alkaloids · ayahuasca · beta-carboline · natural products · psilocybin

[1] R. E. Schultes, *Amer. Anthropol.* 1940, 42, 429–443.
[2] J. Frickie, C. Lenz, J. Wick, F. Blei, D. Hofmeister, *Chem. Eur. J.* 2019, 25, 897–903.
[3] a) A. Hofmann, R. Heim, A. Brack, H. Kobel, *Experientia* 1958, 14, 107–109; b) A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, T. Petzilka, F. Troxler, *Helv. Chim. Acta* 1959, 42, 1557–1572.
[4] a) F. Y. Leung, A. G. Paul, *J. Pharm. Sci.* 1968, 57, 1667–1671; b) N. Jensen, J. Gartz, H. Laatsch, *Planta Med.* 2006, 72, 665–666; c) C. Lenz, J. Wick, D. Hofmeister, *J. Nat. Prod.* 2017, 80, 2835–2838; d) J. Frickie, F. Blei, D. Hofmeister, *Angew. Chem. Int. Ed.* 2017, 56, 12325–12355; *Angew. Chem.* 2017, 129, 12524–12527; e) F. Blei, J. Frickie, J. Wick, J. C. Slot, D. Hofmeister, *ChemBioChem* 2018, 19, 2160–2166.
[5] F. Hasler, U. Grimberg, M. A. Benz, T. Huber, F. X. Vollenweider, *Psychopharmacology* 2004, 172, 145–156.
[6] T. Passie, J. Seifert, U. Schneider, H. M. Emrich, Addict. Biol. 2002, 7, 357 – 364.
[7] F. Hasler, D. Bourquin, R. Brenneisen, T. Bär, F. X. Vollenweider, Pharm. Acta Helv. 1997, 72, 175 – 184.
[8] a) D. J. McKenna, G. H. Towers, F. Abbott, J. Ethnopharmacol. 1984, 10, 195 – 223; b) E. A. Estrella-Parra, J. C. Almanza-Pérez, F. J. Alarcón-Aguilar, Nat. Prod. Bioprospect. 2019, 9, 251 – 265.
[9] L. Rivier, J. E. Lindgren, Econ. Bot. 1972, 26, 101 – 129.
[10] J. R. F. Allen, B. R. Holmstedt, Phytochemistry 1980, 19, 1573 – 1582.
[11] F. O. Rasse-Suriani, F. S. Garcia-Einschlag, M. Rafii, T. Schmidt De León, P. M. David Gara, R. Erra-Balsells, F. M. Cabrerizo, Photochem. Photobiol. 2018, 94, 36 – 51.
[12] T. Liu, W. Liang, G. Tu, Planta Med. 1988, 54, 472 – 473.
[13] a) K. A. Shaaban, S. I. Elshahawi, X. Wang, J. Horn, M. K. Kharel, M. Leggas, J. S. Thronson, J. Nat. Prod. 2015, 78, 1723 – 1729; b) T. Zhao, S. S. Zheng, B. F. Zhang, Y. Y. Li, S. W. A. Bligh, C. H. Wang, Z. T. Wang, Food Chem. 2012, 134, 1096 – 1105.
[14] a) W. Steglich, L. Kopanski, M. Wolf, M. Moser, G. Tegtmeyer, Tetrahedron Lett. 1984, 25, 2341 – 2344; b) R. J. Jaeger, M. Lamshöft, S. Gottfried, M. Spiteller, P. Spiteller, J. Nat. Prod. 2013, 76, 127 – 134.
[15] M.-L. Yang, P.-C. Kuo, T.-L. Hwang, T.-S. Wu, J. Nat. Prod. 2011, 74, 1996 – 2000.
[16] A. M. Sherwood, T. E. Prisinzano, Expert Rev. Clin. Pharmacol. 2018, 11, 1 – 3.
[17] A. Miralles, S. Esteban, A. Sastre-Coll, D. Moranta, V. J. Asensio, J. A. García-Sevilla, Eur. J. Pharmacol. 2005, 518, 234 – 242.
[18] W. P. Gessner, A. Brosi, M. E. Bembeneck, C. W. Abell, Arch. Pharm. 1988, 321, 95 – 98.
[19] H. Komulainen, J. Tuomisto, M. M. Airaksinen, I. Kari, P. Peura, L. Pollari, Acta Pharmacol. Toxicol. 2009, 46, 299 – 307.
[20] J. M. Ward, J. E. Hodgson, FEMS Microbiol. Lett. 1993, 110, 239 – 242.
[21] H. A. Geiger, M. G. Wurst, R. N. Daniels, ACS Chem. Neurosci. 2018, 9, 2438 – 2447.
[22] H. T. Reynolds, V. Vijayakumar, E. Gluck-Thaler, H. B. Korotkin, P. B. Matheny, J. C. Slot, Evol. Lett. 2018, 2, 88 – 101.
[23] H. R. Snyder, S. M. Parmerter, R. Katz, J. Am. Chem. Soc. 1948, 70, 222 – 225.
[24] H. Song, Y. Liu, Y. Liu, L. Wang, Q. Wang, J. Agric. Food Chem. 2014, 62, 1010 – 1018.
[25] I. Nemet, L. Varga-Defterdarovic, Biogeo. Med. Chem. 2008, 16, 4551 – 4562.

Manuscript received: September 20, 2019
Accepted manuscript online: November 14, 2019
Version of record online: December 13, 2019