CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Expanding the Rubterolone Family - Intrinsic Reactivity and Directed Diversification of PKS-derived Pyrans

Authors: Huijuan Guo, Rene Benndorf, Stefanie König, Daniel Leichnitz, Christiane Weigel, Gundela Peschel, Patrick Berthel, Marcel Kaiser, Christoph Steinbeck, Oliver Werz, Michael Poulsen, and Christine Beemelmanns

To be cited as: *Chem. Eur. J.* 10.1002/chem.201802066

Link to VoR: http://dx.doi.org/10.1002/chem.201802066

Supported by
ACES

WILEY-VCH

10.1002/chem.201802066

WILEY-VCH

Expanding the Rubterolone Family – Intrinsic Reactivity and Directed Diversification of PKS-derived Pyrans

Huijuan Guo,[a] René Benndorf,[a] Stefanie König,[b] Daniel Leichnitz,[a] Christiane Weigel,[a] Gundela Peschel,[a] Patrick Berthel,[a] Marcel Kaiser,[c,d] Christoph Steinbeck,[e] Oliver Werz,[b] Michael Poulsen,[f] and Christine Beemelmanns[a]*

Dedicated to Prof. Hans-Ulrich Reissig.

Abstract: We characterized two key biosynthetic intermediates of the intriguing rubterolone familiy (tropolone alkaloids) that contain a highly reactive pyran moiety (in equilibrium with the hydrolyzed 1,5-dione form) and undergo spontaneous pyridine formation in the presence of primary amines. We exploited the intrinsic reactivity of the pyran moiety and isolated several new rubterolone derivatives, two of which contain a unique thiazolidine moiety. Three rubterolone derivatives were chemically modified with fluorescence and biotin tags using peptide coupling and click reaction. Overall, eight derivatives were fully characterized by HRMS/MS and 1D and 2D NMR spectroscopy and their antimicrobial, cytotoxic, anti-inflammatory and antiparasitic activities evaluated.

Introduction

Bacteria produce an extraordinary array of natural products, which serve as prolific source for drug discovery and formed the basis for much of the chemistry and biology investigated in academia.[1,2,3] The complex architecture of natural products prompted major advances in both analytical[4] and synthetic chemistry,[5,6] and more recently in genome sequencing techniques to elucidate biosynthetic origins.[7] After decades of declining enthusiasm in the field of natural product-based drug discovery, ecology-driven approaches and efficient OMICs-based dereplication strategies have reignited research interests and led to the identification of many new natural products with unique architectures at unprecedented discovery rates.[8,9,10]

[a] Dr. Christine Beemelmanns, Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute, Beutenbergstraße 11a, 07745 Jena, Germany, Christine.beemelmanns@hki-jena.de
[a] Dr. Huijuan Guo, René Benndorf, Daniel Leichnitz, Christiane Weigel, Dr. Gundela Peschel, Patrick Berthel, Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute, Beutenbergstraße 11a, 07745 Jena, Germany.
[b] Prof. Oliver Werz, Stefanie König, Institute of Pharmacy, Friedrich-Schiller-University Jena, Philosophenweg 14, 07743 Jena, Germany.
[c] Dr. Marcel Kaiser, Swiss Tropical and Public Health Institute, Parasite Chemotherapy, Socinstraße 57, 4002 Basel.
[d] Dr. Marcel Kaiser, University of Basel, Petersplatz 1, 4003 Basel, Switzerland.
[e] Prof. Christoph Steinbeck, Institute for Analytical Chemistry, Friedrich-Schiller-University Jena, Lessingstr. 8, 07743 Jena, Germany
[f] Prof. Michael Poulsen, Centre for Social Evolution, University of Copenhagen, 2100 Copenhagen East, Denmark

Supporting information for this article is given via a link at the end of the document.

We have recently applied ecologically relevant bacterial-fungal interaction studies to understand the stability of the ancient symbiotic fungus-growing termite ecosystem. Based on these, we identified several novel bioactive compound classes exhibiting broad ranges of different bioactivities. Most recent examples include the geldanamycin derivative natalamycin A,[11] a group of new depsipeptides named dentigerumycins,[12] the polyeneic and glycosylated macrolactam macrotermycins,[13] and a rare group of glycosylated tropolone-containing natural products, named rubterolones A–D (**1**–**4**).[14] We were particularly intrigued by the complex hybrid structure of rubterolones that feature a tropolone moiety, a fused cyclopentanone ring, an O,C-condensated sugar and a highly substituted pyridine (drawn as dihydropyridine tautomer) or pyridinium inner salt moiety. Rubterolones are structurally related to the recently identified rubrolone B (**5**)[15] and isarubrolones (**6**),[16] which are all members of the widely distributed pyridine alkaloid family possessing a broad range of bioactivities.[17]

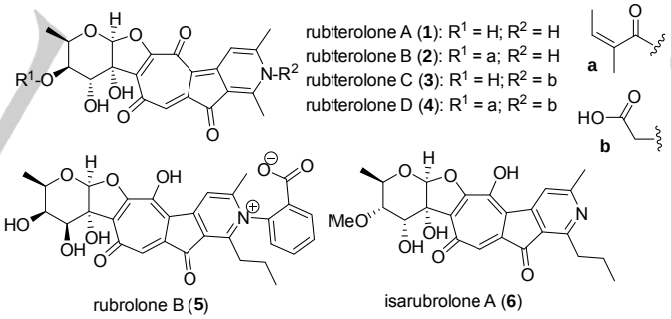


Figure 1. Structures of the glycosylated tropolone-containing natural products from *Actinomadura* sp. 5-2, named rubterolones (**1**–**4**), and structurally related derivatives (**5**, **6**).

Analysis of the biosynthesis of this intriguing compound class and complementing feeding experiments led by us and others[15,16] suggested that the tropolone and cyclopentanone containing carbon skeleton is of type II polyketide origin. The labelling pattern is also consistent with a series of complex oxidative rearrangements induced by the cluster-encoded oxygenases. Furthermore, Huang et al. suggested that pyridine formation in rubrolones should occur prior to glycosylation, which is catalyzed by the glycosyl transferase RubS7.[15]

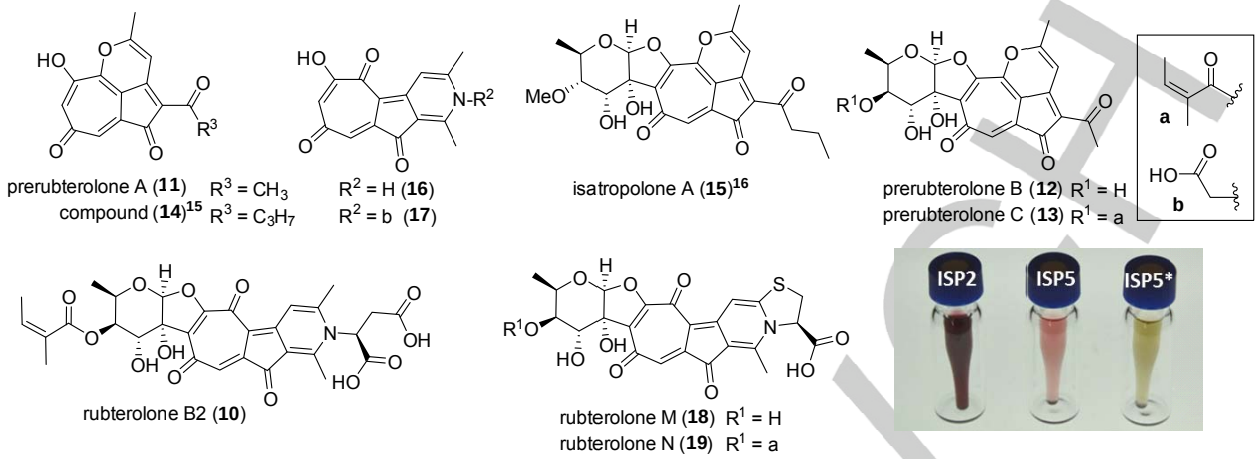


Figure 2. Structures of newly detected biosynthetic intermediates (**11**–**13**, **16**, **17**) and rubterolone derivatives (**10**, **18**, **19**) reported in this study and from the literature (**12**-**15**).[15,16]

In vitro transformations and genetic analyses of the *rub* and *ist* pathways showed that a condensed form of a 1,5-dicarbonyl derivative (in equilibrium with the hydrolyzed open 1,5-dione form; from now on referred to as pyran or 1,5-dione) is a key biosynthetic intermediate of rubrolones (**5**) and isarubrolones (**6**) that undergoes spontaneous pyridine formation in the presence of primary amines. We were intrigued by the intrinsic reactivity of the proposed pyran core structure (**11** and **14**) and whether or not the timing of the pyridine formation is essential for decorating enzymes in the *rbl* pathway. Thus, we set out to identify possible biosynthetic intermediates of rubterolones and to use their intrinsic reactivity to generate a rubterolone library amiable for chemical transformations and activity testing.

Results and Discussion

Actinomadura sp. 5-2 (from now on named as 5-2) was cultured on ISP2 agar plates (static, 30 °C) or in ISP2 broth (120 rpm, 30 °C). The produced spores were transferred to the respective liquid media (ISP2) or agar plates, which were again incubated for a given time period at 30 °C (Supporting Information). To determine the influence of carbon and nitrogen sources on the production levels of the proposed 1,5-dicarbonyl (**I**) or pyran (**11**) intermediates (Fig. 3), strain 5-2 was grown on different solid and liquid media. During fermentation ammonium (NH_4^+) concentrations were monitored using QUANTOFIX® Ammonium. Metabolite extracts were obtained using an established solid phase extraction (C-18) protocol of culture supernatants and analyzed by UHPLC-MS. Subsequent comparative LC-MS analysis of metabolite extracts quickly revealed that in complex ISP media (ISP1–7) rubterolones were constantly produced. In particular, cultivation in nutrient rich ISP2 medium stimulated angelic acid modification (C-20) of derivatives **1** and **3** resulting in the predominant formation of derivative B (**2**) and D (**4**); whereas less complex media (ISP5 medium) afforded mainly a mixture of derivatives **1** and **2**. The constant production of rubterolones *in vivo* is presumably induced by the dominant presence of NH_4^+ (10–25 mg/mL, 0.5–1.3 M, Fig. S1, S3, S4) within in all tested ISP media. Interestingly, complex media (ISP1–ISP4 and ISP6) also resulted in the formation of glycine-rubterolone conjugates (**3**, **4**) indicating that glycine production in strain 5-2 might be a dominant metabolic trait. An analogous observation was made by Huang *et al.* in *Streptomyces* sp. KIB-H033, where anthranilic acid conjugate (**5**) was almost exclusively formed during fermentation. To decrease NH_4^+ concentrations and thereby prevent spontaneous pyridine formation, we then modified ISP5 medium by replacing L-asparagine (Asn) with L-aspartic acid (Asp) (named ISP5*) as ammonia is enzymatically released by deamination of glutamine and/or asparagine within the cell.[18] As expected, cultivation in ISP5* was accompanied by low NH_4^+ concentrations (NH_4^+ ~ 0 mg/mL, pH 6.95-7.00, Fig. S3) and a colour shift of the cultivation broth from pink (ISP5) to light-orange (ISP5*). Analysis of the enriched culture extracts (C-18 SPE) by UHPLC-MS revealed the appearance of three new metabolites (UV-Vis adsorption at λ_{max} 244, 286, 358 nm; corresponding *m*/*z* values 271.0601, 415.1031, 497.1443). Subsequent large scale cultivation (2 L ISP5*) and MS-guided purification resulted in the isolation of three pyran-containing prerubterolone A (**11**, *m*/*z* 271.0601), B (**12**, *m*/*z* 415.1031) and C (**13**, *m*/*z* 497.1443). Although prerubterolones are prone to decomposition, we were able to determine the planar structures of derivatives A (**11**) and C (**13**) based on HRMS analysis and comparative 1D and 2D NMR spectroscopy.

We then tested whether the isolated pyran intermediates **11**–**13** transform spontaneously into the pyridine-containing rubterolones (**1**-**4**, **16**, **17**). Treatment of enriched culture extracts with 10% NH_4OH or 100 mM glycine, respectively, resulted in an immediate color change of the reaction mixture from orange to pink, which was indicative for rubterolone formation.

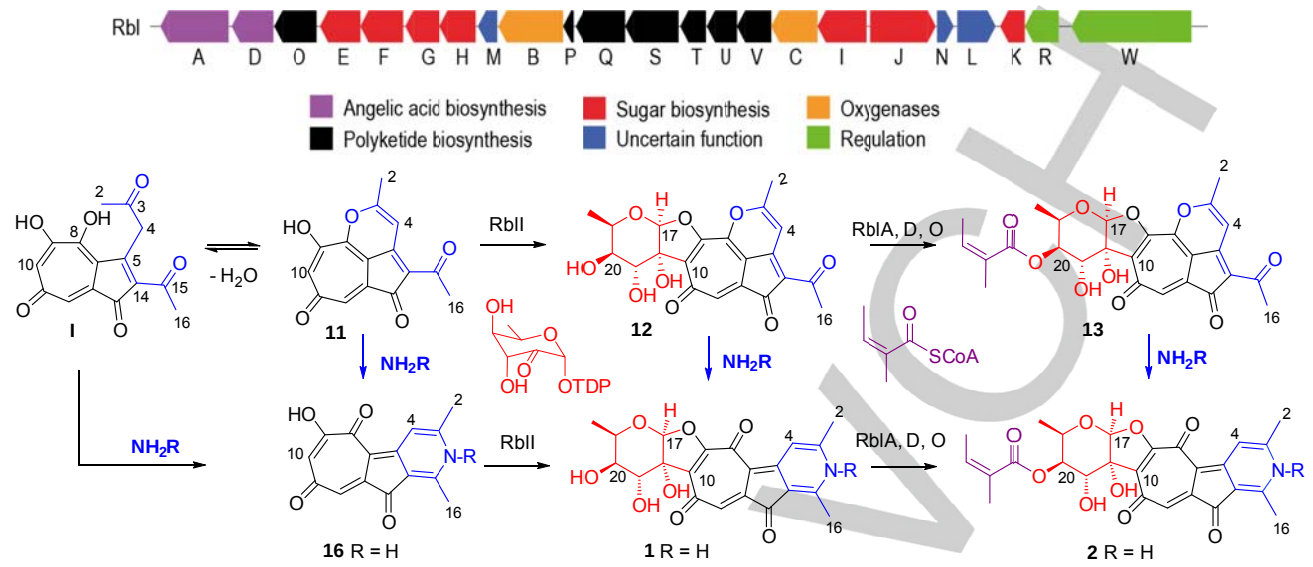


Figure 3. Gene map of *rbl* biosynthetic cluster and B) proposed biosynthetic pathway of rubterolones (**1**, **2** and **16**) starting from 1,5-dicarbonyl precursor (**I**). High concentrations of primary amines induce spontaneous pyridine formation (drawn as dihydropyridine tautomer) in prerubterolones (**11**–**13**).[14]

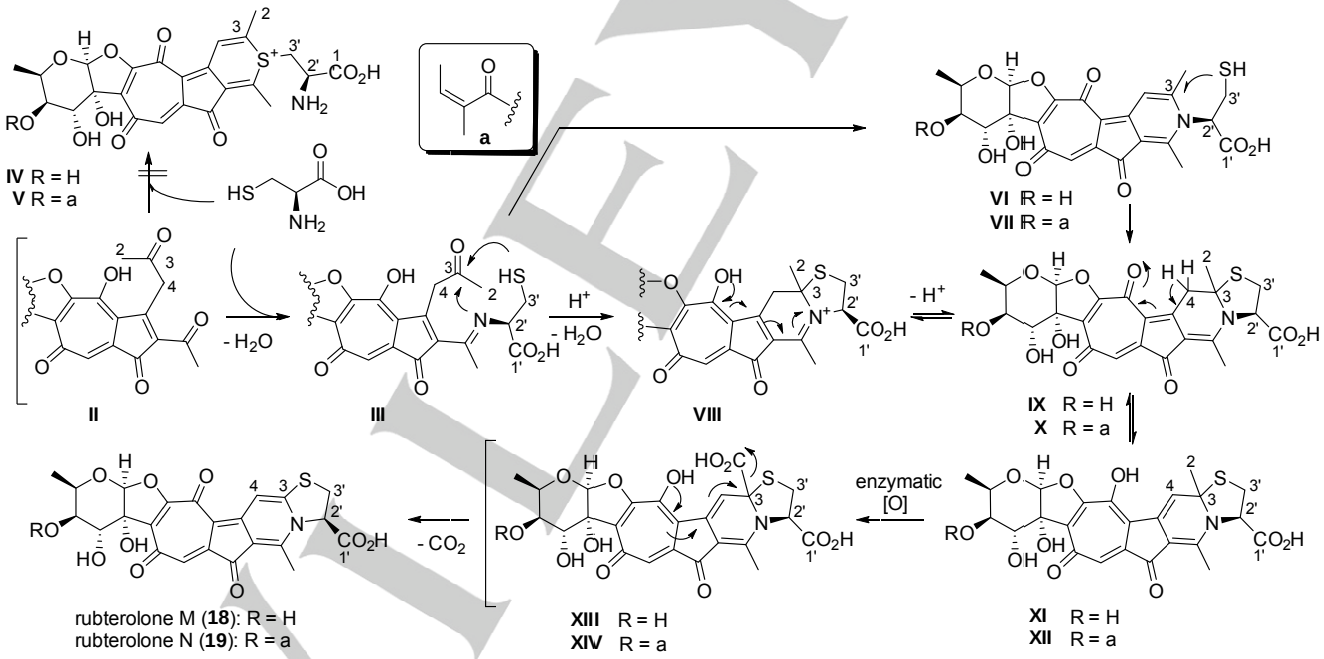


Figure 4. Proposed mechanisms for rubterolone M (**18**) and N (**19**) formation via intramolecular thiazolidine formation (**VIII**-**X**) and putative oxidation and decarboxylation of the tertiary CH_3-group (C-2) based on *in vitro* conversion of prerubterolones-containing fractions with L-cysteine. Formation of thiopyrylium derivatives **IV**/**V** were not observed (pathway B).

Product formation was confirmed by comparative LC-MS analysis using natural rubterolones A–D (**1**–**4**) as standards (Supporting Information Fig. S4). These results suggest that derivatives **11**–**13**, or the respective 1,5 dicarbonyl derivatives, are indeed the biosynthetic precursors of rubterolones, which are then - depending on the culture conditions - glycosylated and further modified at C-20 (Fig. 3).

Interestingly, glycosyltransferase RblI appears to be capable of transforming both pyran **11** and pyridine derivative **16** into **12** and **1**, respectively. We then used the intrinsic reactivity of the 1,5 dicarbonyl (pyran) intermediates to perform a precursor-directed expansion of the rubterolone family and to produce larger quantities of rubterolone-conjugates for biological testing. We have previously reported that supplementation of glycine or lysine to the culture broth of 5-2 resulted in the formation of the corresponding amino acid-rubterolone conjugates C–L (Supporting Information, Table S1).[13] We therefore extended these cultivation experiments using other amino acids. After a detailed analysis of the first cultivation studies, we noted that the use of glutamine in ISP5 and the use of aspartic acid in ISP5* medium induced the formation of minor amounts of the glutamine-rubterolone (A1 (**7**), B1 (**8**)) and aspartic acid-rubterolone derivative (A2 (**9**), B2 (**10**), respectively (Fig. 2, Supporting Information, Table S1).

Interestingly, when we supplemented L-cysteine to the culture broth of 5-2 using ISP5*, the proposed condensation products **VI/VII** and **XI/XII** (*m/z* 518.1 and 600.2, Fig. 4) were not detected by UHPLC-MS analysis (Fig. S5), but two unknown metabolites (*m/z* 502.1 and 584.2) were observed. Subsequent semipreparative HPLC purification afforded thiazolidine-containing rubterolone derivatives M (**18**) and N (**19**), which were both fully characterized by ESI-HRMS and comparative 1D and 2D NMR spectroscopy. ^{1}H NMR, COSY and HSQC analysis clearly indicated additional methylene ($\delta_{H2\text{-}3'}$ 4.00 ppm/$\delta_{C\text{-}3'}$ 33.70 ppm), methine ($\delta_{H\text{-}2'}$ 5.92 ppm/$\delta_{C\text{-}2'}$ 66.97 ppm) and carbonyl ($\delta_{C\text{-}1'}$ 167.40 ppm) groups, which was accompanied by a significant chemical shift of C-3 (δ_C 161.3 ppm) compared to rubterolone B2 (**10**) ($\delta_{C\text{-}3}$ 157.8 ppm). Overall, our NMR analysis indicate the presence of a thiazolidine-4-carboxylic acid moiety, which was verified by strong HMBC correlations from H-24 to C-3, C-23, and C-25 that confirm the connection between pyridine and the thiazolidine-4-carboxylic acid moiety. The stereochemistry of sugar moiety was deduced from NOESY correlation of H-17 to H-21, and comparative analysis of ^{13}C shifts amongst all identified rubterolones (Supporting information,Table S13 and S14). Additionally, we confirmed our structural proposal and NMR assignments by calculation of ^{13}C chemical shifts using density functional theory (DFT) with Gaussian 09 following the procedures described in the literature (Supporting information, Table S2).[19]

Unexpectedly, rubterolone M (**18**) and N (**19**) lacked the PKS-derived methyl group at C-2. As depicted in Fig. 4, we propose the following biosynthetic mechanism: In the first consecutive steps, spontaneous imine formation (**III**) is followed by thiazolidine formation (**VIII**) and tautomerization (**IX/X**). We speculate that subsequent oxidation of C-2 (intermediates **XI/XII**) via the encoded oxygenases (*rbt*B/C)[14] or related enzymes and spontaneous decarboxylation and tautomerization leads to the production of the isolated compounds **18** and **19**.

So far we were not able to isolate or characterize any possible intermediates, such as the likely unstable thiopyrylium derivatives **IV/V**, dihydropyridine derivatives **VI/VII** or thiazolidine derivatives **IX/X** from culture extracts. However, *in vitro* reaction of prerubterolones-containing fractions with L-cysteine under mild basic reaction conditions indicated the formation of putative derivatives **VI/IX/XI** (*m/z* = 518.1) and **VII/X/XII** (*m/z* = 600.2) within one hour (Supporting Information, Fig. S5).

In accordance with this, *in vitro* reaction of *N*-protected cysteine and prerubterolones did not result in detectable amounts of condensation and cyclization products (Supporting Information Fig. S5).

We then investigated the incorporation of synthetic primary amines by supplementing the cultivation broth with synthetic amines. To our surprise, strain 5-2 tolerates the presence of several primary amines without growth deficiencies and allows for the formation of amine-rubterolone conjugates. Sterically less-demanding and highly nucleophilic amines (allylamine, benzylamine, and 4-bromobenzyl amine) almost exclusively afforded the respective amine-rubterolone conjugates A3–B7 (**20**–**29**). In contrast, sterically more demanding cyclopentylamine yielded the respective product **22** and **23** only in trace amounts.

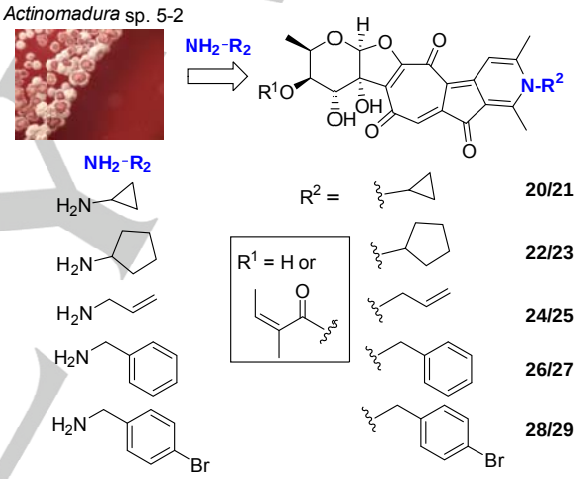


Figure 5. Structures of the rubterolone-amine conjugates (**20**–**29**) and corresponding angelate esters (**21**, **23**, **25**, **27**, **29)** from *Actinomadura* sp. 5-2.

We next evaluated the biological activity of our extended rubterolone compound library. Similar to previous reports for rubrolone B[15] and isarubrolones[16] rubterolones A–D did not display significant antimicrobial activity against bacterial and fungal test strains, cytotoxic activity against human cells or antiprotozoal activity (Supporting Information). Although pyran intermediates were reported to have promising activities against *Leishmania donovani*, the causative agent of visceral leishmaniasis, we did not pursue antiprotozoal activity tests of **11**–**13** due to their intrinsic chemical instability and based on experiments suggesting that pyran derivatives do not reach the intracellular pathogen in *Leishmania*-infected macrophages.[16] We therefore focused on anti-inflammatory activity assays as part of our screening efforts (Fig. 6). Indeed, rubterolone D moderately decreases the cellular level of prostaglandin E_2 (PGE_2) in human monocytes (61% related to DMSO control). Furthermore, rubterolone N and prerubterolone C inhibit the

activity of microsomal prostaglandin E_2 synthase-1 (mPGES1), with 81% and 68% related to DMSO control, respectively. None of the compounds caused significant cytotoxicity against the monocytes (Supporting Information, Table S3).

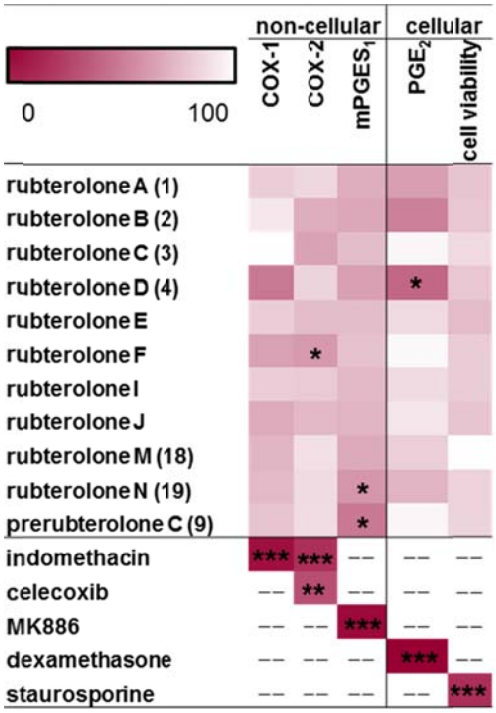


Figure 6. Biological evaluation of rubterolones (10 µM) for inhibition of cyclooxygenase (COX)-1 and -2 and mPGES-1 in cell-free assays and for inhibition of PGE_2 formation in human monocytes as well as cytotoxic effects against these cells. Data (means, n = 3) are expressed as a heat map; ***p < 0.001; **p < 0.01; *p < 0.05; compound vs. vehicle control, one-way ANOVA + Bonferroni.

The observed anti-inflammatory activity profile of rubterolone-conjugates prompted us to synthesize rubterlone-conjugates containing a fluorophore or biotin tag. As an example (Fig. 7), rubterolone D (**4**) containing a carboxylic acid moiety was subjected to peptide coupling reactions and reacted with dansyl cadaverine, a wide-spread applicable chemical probe used e.g. in cell membrane studies.[20] Using the same cadaverine linker, we also synthesized biotin-modified rubterolone D (**32**). Rubterolone derivative **4a** carrying a propargyl containing side chain was furthermore subjected to click reaction using a biotin-PEG_3 azide affording biotin-PEG_3 conjugated rubterolone D (**33**).

Conclusions

Based on our recent discovery of rubterolones and the analysis of their biosynthetic assembly line, we identified three highly reactive biosynthetic precursors, named pre-rubterolones. We used the intrinsic reactivity of the pyran moiety (1,5-dicarbonyl unit) of pre-rubterolones and functional group transformations to generate a structurally diverse rubterolone compound library including derivatives containing chemical tags suitable for target identification. Furthermore, we observed that fermentation in the presence of cysteine afforded the formation of two new thiazolidine-containing derivatives **18**–**19**. Biological activity tests revealed anti-inflammatory activity profile of rubterolone derivatives, which prompted us to synthesize rubterolone-conjugates containing a fluorophore or biotin tag suitable for future target identification.

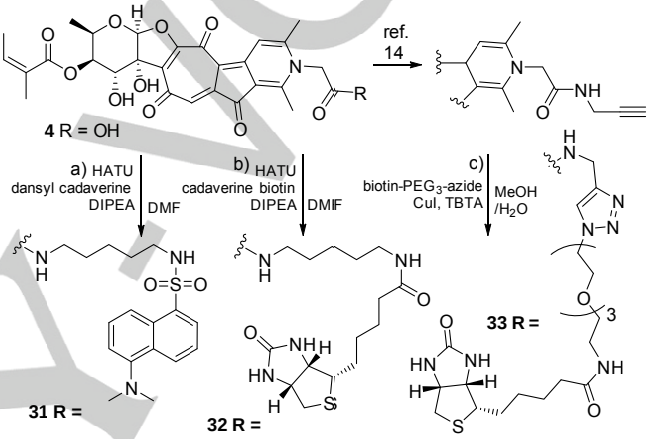


Figure 7. Chemical derivatization of rubterolone D (**4**) by introduction of a dansyl cadaverine tag (**31**) or biotin cadaverine tag (**32**) using peptide coupling and a biotin-PEG_3 tag using click chemistry.

Experimental Section

Supplementary Information (SI) available: fermentation procedures; isolation procedures, ESI-HRMS, ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra as well as chemical modifications.

Acknowledgements

We are grateful for financial support from the German Research Foundation (DFG, CRC1127 ChemBioSys, and BE 4799/2-1) and the Daimler Benz foundation to CB, and the Villum Kann Rasmussen Foundation for a Young Investigator Fellowship (VKR10101) to MP. RB is generously supported by the International Leibniz Research School for Microbial and Biomolecular Interactions (ILRS). RB and SK are generously supported by the School for Microbial Communication (JSMC, DFG). We thank Mrs. Heike Heinecke (HKI) for recording NMR spectra, Mrs. Andrea Perner (HKI) for HRMS measurements, and the Oerlemans family (Mookgophong) for permission to sample the colony from which *Actinonmadura* sp. 5-2 was isolated.

Keywords: Tropolone alkaloids • Natural Products • Biosynthetic Pathway • Polyketides • Chemical Probes

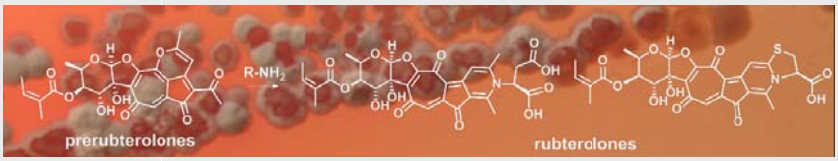
[1] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, *79*, 629; b) B. B. Mishra, V. K. Tiwari, *Eur. J. Med. Chem.* **2011**, *46*, 4769.
[2] A. L. Harvey, R. Edrada-Ebel, R. J. Quinn, *Nat. Rev. Drug Discov.* **2015**, *14*, 111.
[3] D. A. Dias, S. Urban, U. Roessner, *Metabolites* **2012**, *2*, 303.
[4] a) J. Galbá, I. Sanz-Vicente, J. Navarro, S. de Marcos *Methods Appl. Fluoresc.* **2016**, *4*, 042005; b) R. Duval, C. Duplais, *Nat. Prod. Rep.* **2017**, *34*, 161.
[5] N. I. Vasilevich, R. V. Kombarov, D. V. Genis, M. A. Kirpichenok, *J. Med. Chem.* **2012**, *55*, 7008.
[6] N. Vasudevan, K. Kashinath, D. S. Reddy, *Org. Lett.* **2014**, *16*, 6148.
[7] K. L. Dunbar, D. H. Scharf, A. Litomska, C. Hertweck, *Chem. Rev.* **2017**, *117*, 5521.
[8] E. M. Molloy, C. Hertweck, *Curr. Opin. Microbiol.* **2017**, *39*, 121.
[9] H. Machado, R. N. Tuttle, P. R. Jensen, *Curr. Opin. Microbiol.* **2017**, *39*, 136.
[10] a) C. Beemelmanns, H. Guo, M. Rischer, M. Poulsen, *Beilstein J. Org. Chem.* **2016**, *12*, 314; b) O. Genilloud, *Nat. Prod. Rep.* **2017**, *34*, 1203.
[11] K. H. Kim, T. R. Ramadhar, C. Beemelmanns, S. Cao, M. Poulsen, C. R. Currie, J. Clardy, *Chem. Sci.* **2014**, *5*, 4333.
[12] T. P. Wyche, A. C. Ruzzzini, C. Beemelmanns, K. H. Kim, J. L. Klassen, S. Cao, M. Poulsen, T. S. Bugni, C. R. Currie, J. Clardy *Org. Lett.* **2017**, *19*, 1772.
[13] C. Beemelmanns, T. R. Ramadhar, K. H. Kim, J. L. Klassen, S. Cao, T. P. Wyche, Y. Hou, M. Poulsen, T. S. Bugni, C. R. Currie, J. Clardy *Org. Lett.* **2017**, *19*, 1000.
[14] H. Guo, R. Benndorf, D. Leichnitz, J. L. Klassen, J. Vollmers, H. Görls, M. Steinacker, C. Weigel, H. M. Dahse, A. K. Kaster, Z. W. de Beer, M. Poulsen, C. Beemelmanns, *Chem. Eur. J.* **2017**, *23*, 9338.
[15] a) Y. Yan, J. Yang, Z. Yu, M. Yu, Y. Ma, L. Wang, C. Su, J. Luo, G. P. Horsman, S. Huang, *Nat. Commun.* **2016**, *7*, 13083; b) Y. Yan, Y. Ma, J. Yang, G. P. Horsman, D. Luo, X. Ji, S. Huang, *Org. Lett.* **2016**, *18*, 1254.
[16] X. Cai, Y.-M. Shi, N. Pöhlmann, O. Revermann, I. Bahner, S. J. Pidot, F. Wesche, H. Lackner, C. Büchel, M. Kaiser, C. Richter, H. Schwalbe, T. P. Stinear, A. Zeeck, H. B. Bode, *Angew. Chem. Int. Ed.* **2017**, *56*, 4945.
[17] a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257; b) T. L. S. Kishbaugh, *Curr. Top. Med. Chem.* **2016**, *16*, 3274.
[18] a) A. Kavitha, M. Vijayalakshmi, *Zeitschrift für Naturforschung C* **2014**, *65*, 528; b) J. J. Cachumba, F. A. Antunes, G. F. Peres, L. P. Brumano, J. C. Santos, S. S. Da Silva, *Braz. J. Microbiol.* **2016**, *47*, 77.
[19] A. V. Buevich, M. E. Elyashberg, *Magn. Reson. Chem.* **2017**, *1*, 1.
[20] J. H. Pincus, S.-I. Chung, N. M. Chace, M. Gross, Arch. Biochem. Biophys. **1975**, *169*, 724.

10.1002/chem.201802066

WILEY-VCH

Table of Contents

FULL PAPER



We characterized two key biosynthetic intermediates containing a highly reactive pyran moiety that undergoes spontaneous pyridine formation in the presence of primary amines. We exploited the intrinsic reactivity of the pyran moiety, synthesized chemical probes and tested the antimicrobial, cytotoxic, anti-inflammatory and antiparasitic activities of eleven rubterolone derivatives.

*Huijuan Guo, René Benndorf, Stefanie König, Daniel Leichnitz, Christiane Weigel, Gundela Peschel, Patrick Berthel, Marcel Kaiser, Christoph Steinbeck[e] Oliver Werz, Michael Poulsen, and Christine Beemelmanns**

Page No. – Page No.

Expanding the Rubterolone Family – Intrinsic Reactivity and Directed Diversification of PKS-derived Pyrans