Cover Profile
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SAR Studies of the Leupyrrins: Design and Total Synthesis of Highly Potent Simplified Leupylogs


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Invited for the cover of this issue is the group of Dirk Menche at the University of Bonn. The image depicts the natural product leupyrrin A_1 and a synthetic leupylog in balance on an IC50 weighing scale. Read the full text of the article at 10.1002/chem.202002622.

What prompted you to investigate this topic?

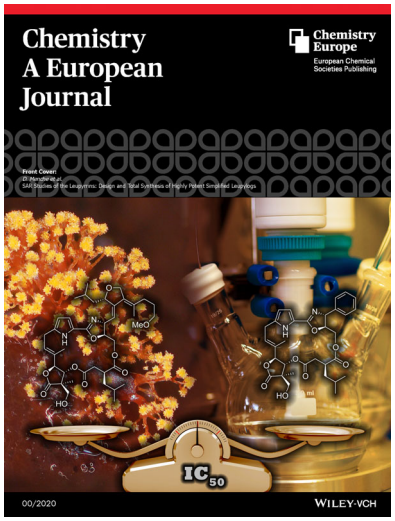
Leupyrrins exhibit very potent antifungal activities, antiproliferative, and anti-HIV properties. They efficiently inhibit DNA, RNA, and protein syntheses without disrupting other cellular systems. Nevertheless, its biological target as well as its pharmacophore is unknown yet. After the elucidation of the full stereochemistry of these complex macrodiolides and the total synthesis of leupyrrin A_1 and B_1 it was our intention to explore the molecular processes behind these fascinating secondary metabolites. An improved knowledge of the detailed mechanisms will help to evaluate practical applications in basic research, medicine, and agriculture.

What is the most significant result of this study?

The first set of relevant SAR data for the leupyrrins revealed the high importance of the macrocyclic core, a certain flexibility of the diacid fragment, and high tolerance of the side chain. The leupylogs, which are characterized by a substitution of dihydrofuran side chain by a mere aryl substituent, retain the potent biological activity of the parent natural products. This demonstrates that the overall structure can be simplified, which is quite remarkable as few such examples have been described in the context of complex natural macrolides. Moreover, the results suggest that the pyrroleoxazoline subunit seems to be a crucial element of their pharmacophore.

What was the inspiration for this cover design?

We wanted to highlight that structurally simplified leupylogs can exhibit similar highly potent antifungal activities as the authentic leupyrrins. Hence, natural product leupyrrin A_1 and a synthetic leupylog are in balance on an IC_{50} weighing scale. In addition, we wanted to emphasize the different origins of these antifungal agents. The leupyrrins are secondary metabolites from the myxobacterium Sorangium cellulosum, represented by its fruiting bodies in the background. The flask depicts synthetic endeavors in our laboratories which have led to the discovery of leupylogs. The cover was designed by Philipp Wollnitzke.



COVER PROFILE

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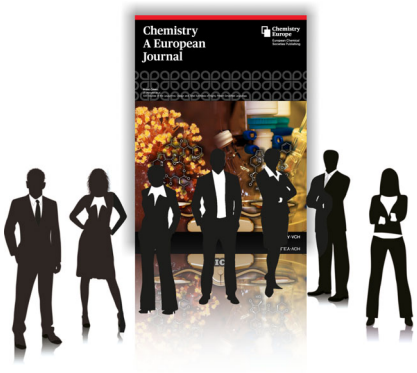

"The first set of relevant SAR data for the leupyrrins revealed the high importance of the macrocyclic core, a certain flexibility of the diacid fragment, and high tolerance of the side chain. The leupylogs, which are characterized by a substitution of dihydrofuran side chain by a mere aryl substituent, retain the potent biological activity of the parent natural products." Read more about the story behind the cover in the Cover Profile and about the research itself on page ■■ ff. (DOI: 10.1002/chem.202002622).