Synthetic remodeling of the chartreusin pathway to tune antiproliferative and antibacterial activities.

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Abstract

Natural products of the benzonaphthopyranone class, such as chartreusin, elsamicin A, gilvocarcin, and polycarcin, represent potent leads for urgently needed anticancer therapeutics and antibiotics. Since synthetic protocols for altering their architectures are limited, we harnessed enzymatic promiscuity to generate a focused library of chartreusin derivatives. Pathway engineering of the chartreusin polyketide synthase, mutational synthesis, and molecular modeling were employed to successfully tailor the structure of chartreusin. For the synthesis of the aglycones, improved synthetic avenues to substituted coumarin building blocks were established. Using an engineered mutant, in total 11 new chartreusin analogs (desmethyl, methyl, ethyl, vinyl, ethynyl, bromo, hydroxy, methoxy, and corresponding (1→2) abeo-chartreusins) were generated and fully characterized. Their biological evaluation revealed an unexpected impact of the ring substituents on antiproliferative and antibacterial activities. Irradiation of vinyl- and ethynyl-substituted derivatives with blue light resulted in an improved antiproliferative potency against a colorectal cancer cell line. In contrast, the replacement of a methyl group by hydrogen caused a

drastically decreased cytotoxicity but markedly enhanced antimycobacterial activity. Furthermore, mutasynthesis of bromochartreusin led to the first crystal structure of a chartreusin derivative that is not modified in the glycoside residue. Beyond showcasing the possibility of converting diverse, fully synthetic polyphenolic aglycones into the corresponding glycosides in a whole-cell approach, this work identified new chartreusins with fine-tuned properties as promising candidates for further development as therapeutics.

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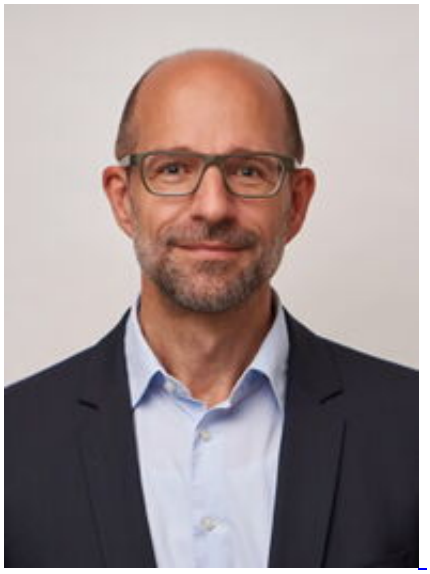

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