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Cytotoxic peptide-drug conjugates based on cryptophycins

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Anticancer chemotherapeutics like paclitaxel interfere with microtubule dynamics and prevent microtubules from forming correct mitotic spindles, which causes cell-cycle arrest and apoptosis. Cryptophycins are a class of 16-membered highly cytotoxic macrocyclic depsipeptides isolated from cyanobacteria.[1] The biological activity is based on their ability to interact with tubulin. Strong antiproliferative activities with 100- to 1000-fold increased potency compared to paclitaxel and vinblastine have been observed.[2] Cryptophycins are highly promising drug candidates, since their biological activity is not negatively affected by P-glycoprotein, a drug efflux system commonly found in multdrug resistant cancer cell lines and solid tumors. Cryptophycin-52 had been investigated in phase II clinical trials, but failed because of its high neurotoxicity.[3]

We have developed efficient strategies for the synthesis of cryptophycins and their analogues [2] for structure-activitiy relationship data, taking specific emphasis on the synthetically most challenging unit A.[4] In addition, new interesting functionalities have been introduced in different positions for SAR studies and application in bioconjugation for targeted delivery.[4,5]

The quasi-isosterism of 1,4-disubstituted 1*H*-1,2,3-triazoles and trans-amide bonds is still under debate. Therefore, we additionally synthesized an analogue of cryptophycin-52 where the trans-amide bond between units B and C is replaced by a 1,4-disubstituted 1H-1,2,3-triazole. The cytotoxic activity is largely retained for this “clicktophycin”, generated by a [3+2] “click” cycloaddition reaction. Consequently, this proves the bio-equivalence of 1,4-disubstituted 1*H*-1,2,3-triazoles and trans-amide bonds even in complex compounds.[6]

An azide-functionalized cryptophycin was connected by copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) to a fluorescently labeled cyclic RGD-peptide for internalization studies. The cyclic RGD-peptide was designed to act as the homing device, because it binds to integrin $\alpha_V\beta_3$, which is highly expressed e.g. on some tumor cells. Confocal fluorescence microscopy proves the internalization and final lysosomal localization of the cryptophycin conjugate.[7]

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