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Oligotuftsin-based peptide carriers for novel antimycobacterial active agents: Synthesis and *in vitro* evaluation

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Background: The global tuberculosis epidemic and increasing emergence of drug-resistant *Mycobacterium tuberculosis* and non-tuberculous mycobacteria call for intensive research on novel drugs and drug delivery systems (DDS) for them. DDS have been used largely for the modification of inconvenient properties (poor solubility, bioavailability, toxicity etc.) of bioactive molecules. They are also useful in targeted drug delivery.

Methods: We selected tuftsin-based oligopeptides as potential carriers for antimycobacterial salicylanilides. Tuftsin derivatives are non-toxic, non-immunogenic and biodegradable. They also stimulate immune response and enhance cellular uptake. Salicylanilides share a significant *in vitro* activity against mycobacteria including drug-resistant strains. However, they are cytotoxic and poorly soluble. These obstacles can be overcome, i.a., by employment of DDS.

Results: Peptide carriers based on repeated oligotuftsin sequence $[TKPKG]_n$ were obtained using solid-phase synthesis (Fmoc/tBu strategy, rink amide MBHA resin, diisopropylcarbodiimide/HOBt). N-Terminus and/or lysine side chain amino groups were modified by various substituents (carboxylic acids, fluorescent labels, peptide spacers, aminooxyacetic acid etc.). Carriers were cleaved from resin, purified and then coupled with salicylanilide derivatives bearing a carbonyl group via oxime bond. Obtained conjugates were purified and characterized.

Conclusions: The conjugates were evaluated for their *in vitro* extracellular antimycobacterial activity (*M. tuberculosis, M. abscessus*), intracellular activity in infected macrophages, cytotoxic and cytostatic properties and cellular uptake. In general, salicylanilide-oligotuftsin conjugates showed improved activity against both extracellular and intracellular mycobacteria, enhanced cellular uptake together with decreased toxicity. They were effective also against multidrug-resistant *M. tuberculosis* and chemoresistant *M. abscessus*. These promising *in vitro* results could stimulate further research on this field.

Biography

Martin Kratky is Postdoc fellow at the Department of Inorganic and Organic Chemistry, Faculty of Pharmacy in Hradec Kralove, Charles University – from 2012 till today He published 23 articles.

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