POSTERS

Drug Design

COMBINED *IN SILICO* APPROACHES FOR DRUG DESIGN AND PHARMACOKINETIC OPTIMIZATION OF A SET OF CARNOSINE ANALOGUES AS POTENT AND SELECTIVE CARBONYL QUENCHERS

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Reactive carbonyl species (RCS) are important cytotoxic mediators and represent a novel drug target since supposed to play a pathogenic role in several diseases including renal, hepatic, neurodegenerative diseases, diabetes, and atherosclerosis. Taking RCS and carbonylation damage as a new drug target, we recently found that L-carnosine (β-alanyl-L-histidine), an endogenous dipeptide present in mM concentrations in some tissues, is a selective detoxifying agent of RCS, [1] which is actively absorbed by hPepT1, but is rapidly hydrolyzed in human serum by carnsosinase, a specific dipeptidase. Hence, the rational design of new carnosine analogues should (1) increase the quenching activity of carnosine, maintaining its selectivity (2) confer plasma stability against human serum carnosinase, and (3) conserve an optimal recognition by hPepT1. The computational approaches proved successful for each mentioned objective affording valuable tools for the rational design of novel derivatives. In particular, (1) quanto-mechanical calculations, conformational analyses and physicochemical predictions cooperated to design more active and specific carnosine derivatives [2], while (2) homology modeling techniques and docking simulations were exploited to generate reliable models for human serum carnosinase [3] and hPepT1 [4], whose experimental structures were not yet resolved, in order to conveniently rationalize and predict the plasma stability and the active absorption of novel derivatives. When the introduced modifications were so significant to prevent the active transport, the marked hydrophilicity of carnosine analogues was modulated by designing ester- and carbamate-based prodrugs whose hydrolysis was predicted *in silico* by docking simulations with the major human carboxylesterases (hCES1 and hCES2)[5]. Globally, this study shows how drug design principles and homology modeling techniques can be synergically exploited to enhance both ligand activity and pharmacokinetic properties by simulating the main biological targets influencing the carnosine bioavailability. And indeed, such computational approaches supported the design, synthesis and biological evaluation of a significant number of carnosine derivatives which can be subdivided in two main classes: (1) compounds which are quite different compared to carnosine and are endowed by a greater activity even conserving an adequate selectivity (as seen in arylderivatives, [2]) and (2) compounds which are strictly related to carnosine (e.g. D-carnosine derivatives), conserve a comparable activity and reach a significant bioavailability.

References

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