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Novel MDR-reversing inhibitors of MRP subtypes related to antiretroviral drug resistance and CD4 cell counts

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Introduction

Transmembrane efflux pumps play an increasing role in the success of ART. The occurrence of increasing mRNA levels of the efflux pump proteins P-gp and MRP subtypes has been associated with ART therapeutics like PIs and NNRTIs. Moreover, a relation has been suggested of MRP subtypes and CD4 cell counts. So there is a challenge to find selective MRP inhibitors which may reduce MRP-induced drug resistances as well as discussed effects on CD4 cells. We developed novel nonpeptidic inhibitors of important MRP subtypes related to both MRP-mediated resistances as well as reduced cell counts.

Materials and methods

The molecular structures of the various efflux pumps guided the development of both symmetric and nonsymmetric inhibitors dedicated to selectively inhibit the relevant MRP-subtypes. Inhibiting properties were evaluated in exclusively P-gp as well as MRP-overexpressing cell lines in comparison to nonexpressing parental cell lines with fluorescent substrates using flow cytometry.

Results

Our inhibitors with allover symmetric substitution patterns are excellent P-gp inhibitors, while a reduction of those symmetric elements concerning their number and exact positioning significantly lowers the P-gp inhibition whereas the MRP1 inhibition is found mainly increased. So selective inhibitors are demonstrated to influence the efflux pump type-related antiretroviral drug resistance.

Conclusions

The success of ART may be mainly increased by selective MRP inhibitors which reduce the MRP-related effects on drug resistance as well as on discussed cell counts. Structure-guided studies of the efflux pump inhibition helped to design novel selective inhibitors with structure-reasoned effects of the nonsymmetric substitution patterns. So far only nonselective inhibitors have been used in ART with undesired effects on transporter-related pharmacokinetics. Selective inhibitors will mean a progress in ART especially with less limiting side effects.

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