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Physico-chemical characterization, permeability and molecular dynamics simulations of two series of structurally related macrocycles

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Aim

To characterize the physico-chemical profile and permeability of two series of macrocycles (MCs): temsirolimus, everolimus (ascomycin class) and rifabutin, rifampicin, rifapentine, rifamixin (ansamycin class) and to predict the influence of the environment on low energy conformations.

Methods

Experimental and *in silico* tools were used.

pK_a values were calculated with MoKa v.2.5.4. (www.moldiscovery.com).

Four chromatographic lipophilicity indexes were measured. The following stationary phases were used: a) Supelcosil TM LC-ABZ alkylamide column; b) PLRP-S polymeric reversed phase column; c) ZIC-HILIC column (sulfoalkylbetaine phase on a silica gel support) and d) ZIC-cHILIC column (phosphorylcholine phase covalently attached to porous silica). The mobile phase consisted of 20 mM ammonium acetate buffer at pH 7.0 and acetonitrile in varying proportions.

Permeability was measured with an MDCK cell-based permeability assay.

Molecular Dynamics (MD) were performed using AMBER (ver. 14, www.amber.org) with standard protocols.

Results

We determined ionization constants (pK_a), logarithm of the retention factors (log k), permeability coefficients (P_{app}). Temsirolimus and everolimus are neutral at pH = 7.0 and have similar lipophilicity in the four investigated systems. Conversely, the ionization profiles of ansamycins are complex and markedly influence lipophilicity expressed as the logarithm of the retention factors and permeability. MD simulations provide insights in the evaluation of low energy conformational ensembles of macrocycles in apolar (chromatographic systems a) and b)) and polar (chromatographic systems c) and d)) media.

Conclusion

The determination of the physico-chemical profile of MCs requires a wise application of the lessons learnt from small organic molecules but also additional specific tools. This is due to the MCs conformational variability, which is influenced by different bioenvironments in a larger extent than small organic drugs.