Boosting of retinol activity using novel lecithin:retinol acyltransferase inhibitors

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Meet Dr Dominik Imfeld at IFSCC

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Poster session: **Delivering on Efficacy**

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Abstract

There is an ongoing desire in the cosmetic industry to boost the efficacy of retinol (ROH) in order to be able to reduce the concentration thereof in topical compositions and thus to overcome stability issues of retinol. In the epidermis, retinol is metabolized to retinoic acid. However, substantial amounts of ROH are also converted to retinyl esters as storage reserves. Lecithin:retinol acyltransferase (LRAT) is the main enzyme catalyzing the esterification of ROH to retinyl esters and, hence, is of central importance for retinol homeostasis. As ROH stimulates fibroblasts to synthesize collagen fibres and inhibits collagen-degrading enzymes, the inhibition of LRAT presents an intriguing strategy for anti-aging ingredients by increasing the available retinol in the skin. We synthesized several derivatives mimicking natural lecithin substrates as potential LRAT inhibitors. By exploring various chemical modifications of the core scaffold consisting of a central amino acid and an N-terminal acylsulfone, we tested 10 different compounds in a biochemical assay, resulting in two compounds 1 = DODS-(D,L)-F(3AMD-Pzd(N-SO2Me) and 2 = DECS-(D,L)-F(3AMD-Pzd(N-SO2Me) with IC50 values of 21.1 and 32.7 µM, respectively (DODS = dodecansulfonyl and DECS = decansulfonyl). We recently demonstrated that these two LRAT-inhibitors (1 and 2) were able to boost the effect of ROH) on *ex vivo* human skin resulting in a significant and synergistic increase in collagen III staining in the dermis (IFSCC 2021).

Now we used computational methods, to investigate their structure-activity relationship (SAR). As no crystal structures are available for LRAT, a structural model had to be established and validated. The combination of the structural model obtained from AlphaFold together with the AutoDock Vina docking engine produced the most consistent results. AlphaFold is a novel machine learing approach solving a 50 years old challenge to predict the three-dimensional protein structure solely based on the primary amino acid sequence. Using the validated model, the stereoisomers of inhibitors 1 and 2 were docked to the active site of LRAT. Based on the introduced characteristics of binding modes of different lecithin derivatives, we selected poses of the inhibitors in accordance with this rationale by visual inspection.

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Interestingly, the acyl chain length of our LRAT inhibitors affected their inhibitory activity with the shorter variants being more active in accordance with the substrate specificity reported by Horchani et al. [Ref]. Using molecular modeling, the above-described SAR could be investigated in structural setting. The influence of the length of the acyl side chain, which presented best inhibition with 8-12 carbon atoms, could be explained by the size of the respective hydrophobic pocket where it resides. The binding mode of inhibitor 1 showed that the C12 fatty acid nearly completely occupied the hydrophobic pocket. In contrast, the binding mode of the inhibitor with C16 acyl moiety could not be completely accommodated in the hydrophobic pocket. Hence, longer acyl moieties result in reduced inhibition likely due to steric limitations. The loss of inhibition by compounds without the amidino group could be explained by the lack of a potent ionic interaction in the active site. The mildly reduced inhibition resulting from the removal of the sulfomethyl moiety attached to the piperazine ring might be caused by the lack of hydrogen bonding interactions (to Arg55 or Tyr118). Inhibitor 1 linked to the N-terminus and a piperazine moiety with a methylsulfonamide modification at the C-terminus of modified phenylalanine moiety was found to be a particularly effective LRAT inhibitor computationally and was consistent with the experimental data.

Using molecular modeling, we could identify the SAR of this compound series by investigating key ligand-protein contacts such as the size of the hydrophobic pocket the acyl moieties residue in and an ionic interaction of the amidino group. Overall, LRAT inhibition using the reported compounds based on a common scaffold is a very promising approach to further boost the efficacy of ROH in future products, delivering superior anti-aging results.

Brief summary

With this research we leverage our competence in the retinol pathway.

The Lrat-Inhibitors are new compounds with the functionality of retinol boosters. The success of this work is based on a colaboraion of in silico design technologies with biology. For in silico design this is an excellent case study using the latest technology, the AlphaFold to virtually simulate the structure of an enzyme (LRAT) and with the structural model it was possible to identify inhibitors binding to the enzyme.

The outcome are new DSM patented Lrat Inhibitors with confirmed retinol boosting activity on human skin. The candidates are considered as a preview for future retinol boosters that could bring retinol based anti aging products to the next level.

Ref: Horchani H, Bussieres S, Cantin L, Lhor M, Laliberte-Gemme JS, Breton R, et al. Enzymatic activity of Lecithin:retinol acyltransferase: a thermostable and highly active enzyme with a likely mode of interfacial activation. Biochim Biophys Acta. 2014;1844(6):1128-36.