Development of novel HDAC inhibitors with improved selectivity to target inflammatory airway diseases

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Histone deacetylases (HDACs) are known to be epigenetic drug targets. HDAC inhibitors are used to treat cancer, and also have potential to treat other diseases such as inflammatory airway diseases. However, currently marketed HDAC inhibitors lack selectivity for the various HDAC isoenzymes. Several studies have shed more light on the role of HDAC isoenzymes in the NF-κB pathway [1]. This indicates that the development of isoenzyme selective HDAC inhibitors provides opportunities to suppress inflammatory reactions.

Aims

We aim to develop novel HDAC inhibitors with improved selectivity among class I HDACs with improved anti-inflammatory activity.

Results / Conclusions

We designed and synthesized HDAC inhibitors with variations in the 'lid' region and tested inhibition of these compounds for HDAC1,2 and 3. Differences in binding were explained by docking studies and revealed that small structural differences despite structural conservatism could be employed to gain differences in binding. Biological characterizations using a NF-kB reporter gene assay and QPCR indicated that HDAC 1 inhibition is an important feature for anti-inflammatory effects.

References:

1. Leus, N. G. J.; Van Der Wouden, P. E.; Van Den Bosch, T.; Hooghiemstra, W. T. R.; Ourailidou, M. E.; Kistemaker, L. E. M.; Bischoff, R.; Gosens, R.; Haisma, H. J.; Dekker, F. J. HDAC 3-selective inhibitor RGFP966 demonstrates anti-inflammatory properties in RAW 264.7 macrophages and mouse precision-cut lung slices by attenuating NF-κB p65 transcriptional activity. Biochem. Pharmacol. 2016, 108, 58–74, doi:10.1016/j.bcp.2016.03.010.