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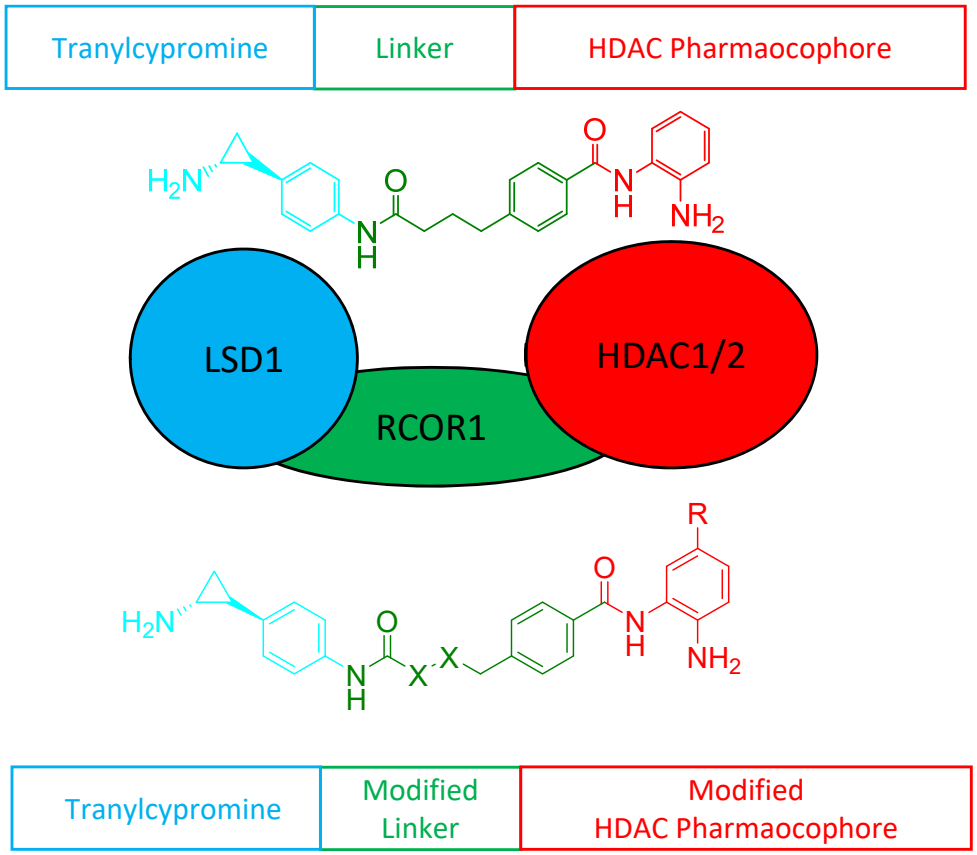
Inhibiting the CoREST complex with dual HDAC1,2 - LSD and protein-protein interaction inhibitors



The CoREST complex is one of seven nuclear histone deacetylase complexes. The ternary chromatin modifying corepressor is composed of the two epigenetic components HDAC1 (or its homologue HDAC2) and the histone demethylase LSD1, which are connected through the scaffold protein RCOR 1. The epigenetic bifunctionality of the CoREST complex through HDAC mediated deacetylation of H4K9 and demethylation of H4K4 by LSD1, results in transcriptional repression and decreased gene activity. The overexpression of the CoREST complex is associated with cancer e.g. breast cancer and acute myeloid leukemia. Corin, the projects lead structure, is a dual inhibitor that has low nanomolar IC_{50} values against HDAC1, 2 and LSD1 in the CoREST complex.

One aim of the project is the optimization of the lead structure through modification of the linker moiety, the HDAC pharmacophore and the replacement of the tranylcypromine pharmacophore with other LSD1 inhibitor motifs. Besides the strategy of dually inhibiting the CoREST complex, another approach is to inhibit the formation or the protein-protein interaction of the complex. In collaboration with the Gohlke group, the development of a CoREST selective protein-protein interaction inhibitors is planned.

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