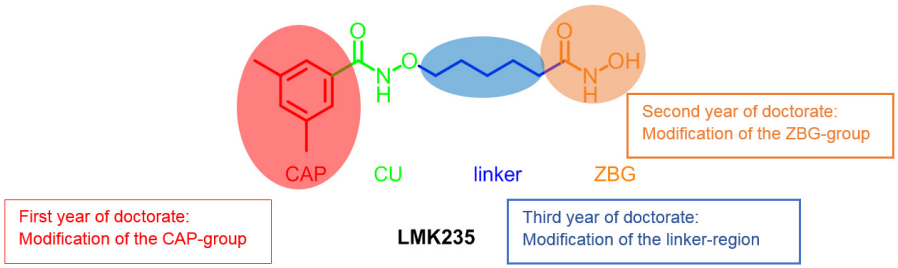
Yodita Asfaha

Synthesis and biological evaluation of novel selective inhibitors of class IIa HDACs



Within the scope of my doctoral thesis, derivates of N-((6-(hydroxyamino)-6-oxohexyl)oxy)-3,5-dimethylbenzamide (LMK 235) will be synthesized (Figure 1). LMK 235 showed similar inhibition of cellular Histone deacetylases (HDACs) in a pan-HDAC assay compared to vorinostat, an approved pan-inhibitor, but enhanced cytotoxic effects against human cell lines A2780, Cal27, Kyse510 and MDA-MB231. A novel HDAC isoform profile assay also revealed that LMK 235 showed nanomolar inhibition of HDAC 4 and HDAC 5, where vorinostat inhibits HDAC4 and HDAC5 in a higher micromolar range. Based on LMK 235, derivates with modifications on the cap-group, linker region and zinc-binding group should be synthesised in order to enhance the selectivity towards class IIa HDACs. All synthesized compounds will be biological evaluate in collaboration with Prof. Kassack.

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GRK2158 is funded by DFG