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210 - Chemical tools for unraveling the substrate specificity of the lysine deacetylase (KDAC) enzymes

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The lysine deacetylase (KDAC) enzymes catalyze hydrolytic removal of acyl functionalities from the ϵ -amino group of lysine residues in a variety of proteins including histones, and KDAC-mediated deacetylation of proteins has been established as a key epigenetic and metabolic regulator. Recent studies have highlighted lysine acetylation as a general post-translational modification (PTM), and a growing list of non-histone proteins has been identified as substrates for the KDACs, thereby extending their potential impact on cellular function. Furthermore, other acyl groups (e.g., crotonyl, malonyl, succinyl, glutaryl, myristoyl and 3-phosphoglyceroyl) have been identified as lysine PTMs, and both zinc- and NAD⁺-dependent KDACs have demonstrated capability to remove such modifications. These findings suggest that KDACs with impaired deacetylase activity might in fact be functional deacylases catalyzing hydrolysis of other acylamides.

To address these interesting observations, we have synthesized a library of substrates containing different peptide scaffolds functionalized with a number of *N*- ϵ -acyl moieties. Library synthesis and its evaluation against a panel of human KDACs including zinc-dependent HDACs 1–11 as well as NAD⁺-dependent sirtuins (SIRT1–7) will be discussed.

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