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DEVELOPMENT OF CROSS METATHESIS FOR THE DESIGN OF HDAC INHIBITORS

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Epigenetic histones post translational modifications are key players in the regulation of gene expression. Amongst all possible modifications, the N-acetylation of the lysine side chains located at the N-terminal tail of histones is involved in the relaxation of chromatine and contributes to gene transcription. This acetylation status is controlled by histone acetyl transferases (HAT) and histone deacetylases (HDAC and SIRT). The abnormal expression of HDAC has been linked to the progression of several human diseases such as cancers. Therefore, the development of HDAC inhibitors has emerged as a valuable therapeutic strategy, with currently four compounds approved by the FDA and a fifth one in China. Recent data suggested that combination therapies with HDAC inhibitors may contribute to better clinical results.

HDACs are zinc-dependant enzymes grouped in a family of 11 proteins (HDAC1-11), grouped in three classes: class I (HDAC1-3,8), class II (HDAC4-7,9,10) and class IV (HDAC11). The fourth group of deacetylases contains the class III NADH+-dependant sirtuins (SIRT1-7). The standard pharmacophore for HDAC inhibitors involves a zinc-binding group (ZBG) linked through a spacer to a "cap" group in interaction with the external solvent accessible surface. We were interested in alternative chemistries to access HDAC inhibitors in which the intermediate spacer could be build out of two similar building blocks, one bearing the ZBG and on bearing the cap group. By selecting linear alkyl-based spacer, cross metathesis appeared to be a short and flexible strategy, provided it supports the presence of highly oxophile functional groups such as carbonyl groups.

This poster summarizes our findings in the application of cross metathesis and the biological evaluations of some of the compounds obtained.

1) Bioorg. Med. Chem. Lett. 2016, 26, 154.
2) Bioorg. Med. Chem. Lett. 2016, 26, 4955.
3) Eur. J. Med. Chem. 2016, 121, 451.