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"Click-chemistry" を使用した新規 class IIa HDAC 選択的阻害薬の創製

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Background: Histone deacetylases (HDACs) are Zn^{2+}dependent enzymes that remove acetate from (non-)histone proteins thus epigenetically regulating essential cellular functions such as cell proliferation and apoptosis. Overexpression of HDACs is associated with the development of various cancers, autoimmune and neurodegenerative diseases. Class IIa HDACs e.g. HDAC4 are linked with the development of highly malignant tumours including oesophageal, colon and gastric cancer. However, little is known about their molecular mechanisms and therapeutic potential due to the lack of chemical probes. Currently, only 3 inhibitors are tested in pre-clinical trials. In this study the click chemistry approach was employed for a rapid generation of a focused library for class IIa HDAC inhibitors. **Method:** Several alkynes containing Zn^{2+} coordinating N-heteroaromatic cycles with a trifluoromethyl group were synthesized and reacted with a number of azides on a 96-well plate to construct a library of triazoles via a Cu(I)-catalysed 1,3-dipolar cycloaddition. The products are evaluated in a high throughput enzyme activity screening using a fluorogenic substrate for class IIa HDACs at 30°C. The inhibition values were calculated from the fluorescence readings of inhibited wells relative to those of the control wells at 10μM after 30, 60 and 120min. **Results:** Several compounds were found to inhibit HDAC4 activity by >70% at 10μM after 120min. A steady increase of the inhibition values over time was indicative of a slow binding mechanism. **Conclusion:** Novel HDAC4 inhibitors were generated by click chemistry approach to provide new probes for further biological studies as well as for the development of class IIa HDAC drug candidates.