MED 001

Novel High Affinity Histone Deacetylase Inhibitors as Potential Radiotracers for PET

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Introduction

- Histone deacetylases (HDACs) deacetylate histone side chains
- **Class I HDACs 1, 2** and **3** are overexpressed in several types of cancer, neurodegenerative diseases and inflammation
- Deacetylation causes transcriptional silencing
  → Inhibition of HDACs leads to anticancer effects
- Structure of a HDAC inhibitor (HDACi) contains a cap group, a linker and a zinc-binding group (ZBG)
- Hydroxamic acids and *ortho*-aminoanilides emerged as valuable ZBGs (Figure 1)
- Advantages of ***o*-aminoanilides:**
  Class I selective HDACi, non mutagenic

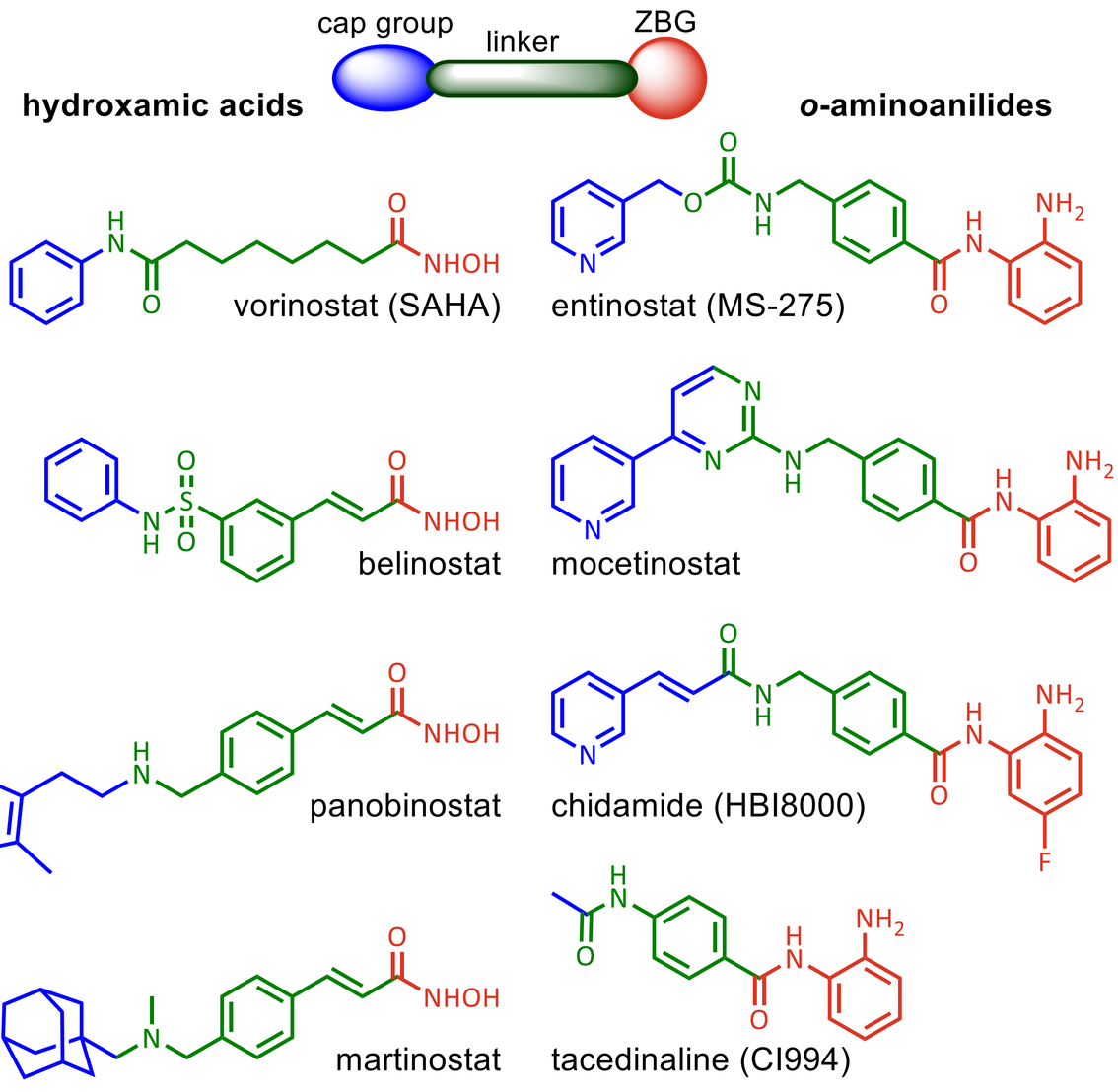
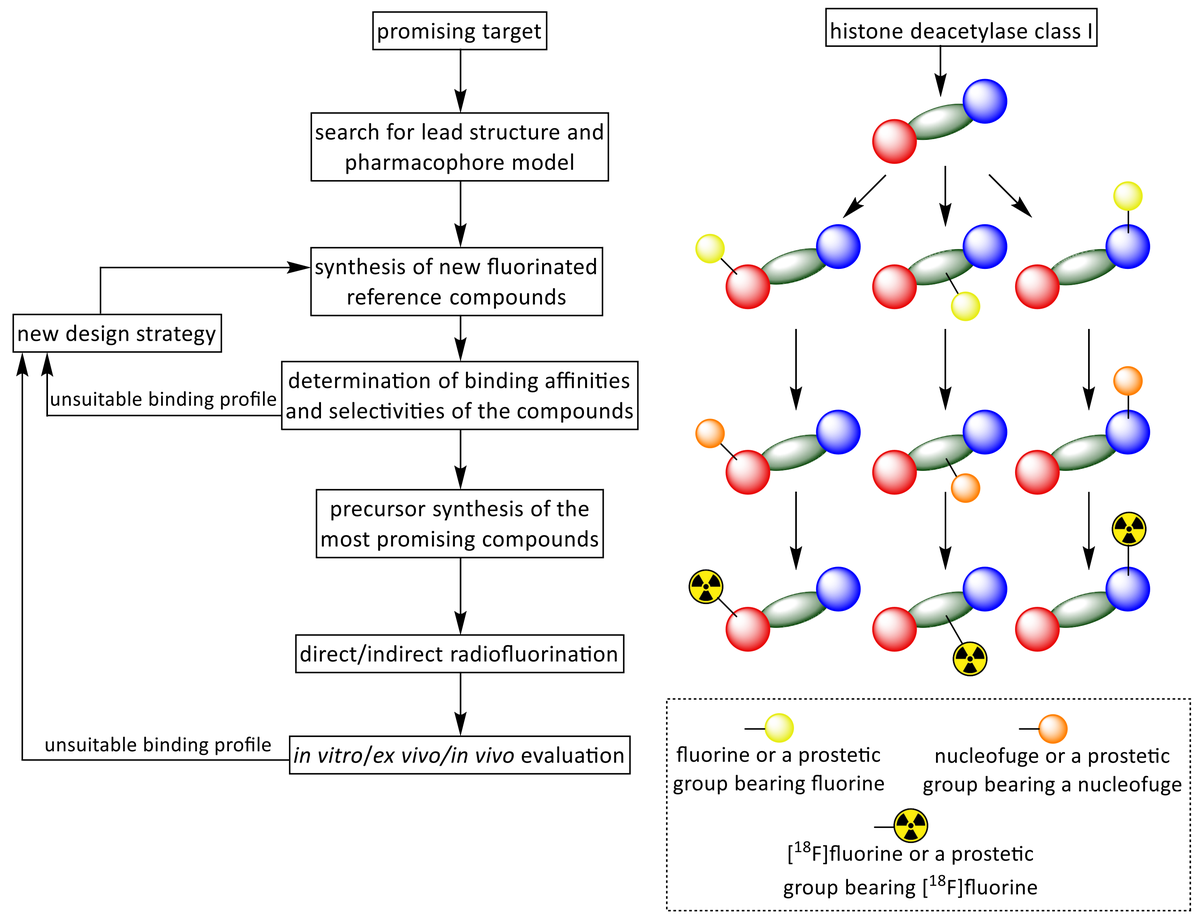


Figure 1: Schematic pharmacophore model and published hydroxamic acid and benzanilide HDACi [3]

Strategy



Scheme 1: Strategy for the development of novel ^{18}F-PET tracers

Results

- The inhibitory activities (IC_{50}) of HDACi were determined based on a modified in-house *in vitro* fluorogenic binding assay
- Highly potent HDACi were synthesized (Table 1)

Table 1: Inhibitory activity (IC_{50}) of reference compounds and corresponding fluorinated derivatives towards HDACs

	IC_{50} [nM]		
Compound	**HDAC1***	**HDAC2***	**HDAC3***
Vorinostat**	123.45 ± 14.65	200.57 ± 16.68	129.25 ± 5.85
Tacedinaline**	636.33 ± 114.32	696.30 ± 10.50	262.55 ± 30.65
LSH-A30	4.40 ± 0.10	44.67 ± 6.89	> 1110
OC59	4.78 ± 0.39	64.29 ± 4.46	> 1110
OC70	4.83 ± 0.56	39.85 ± 3.18	> 1110

* 1 hour preincubation of the test compound and the respective enzyme

** commercially available HDACi

Aim

- **Development** of novel, highly affine and selective fluorine-containing **class I HDACi** (Scheme 1)
- Synthesis of **18-fluorine labelled *o*-aminoanilide inhibitors** for diagnostic imaging of tumors by positron emission tomography (PET)

Outlook and Future Perspectives

- Three novel, highly potent fluorinated class I HDACi were developed: **LSH-A30, OC59** and **OC70**
- Synthesis of the corresponding precursor for direct or indirect radiofluorination
- A fully automated radiosynthesis procedure will be established
- *In vitro* and *in vivo* evaluation of the selected ^{18}F-labelled compounds

DRESDEN concept

Europäische Union

Europa fördert Sachsen. ESF Europäischer Sozialfonds

Freistaat Sachsen

Diese Maßnahme wird mitfinanziert durch Steuermittel auf Grundlage des von den Abgeordneten des Sächsischen Landtags beschlossenen Haushaltes.

References

[1] Chuang et al.: *Trends Neurosci.* **2009**, *32*, 591
[2] Lane and Chabner: *J. Clin. Oncol.* **2009**, 27, 5459
[3] Roche and Bertrand: *Eur. J. Med. Chem.* **2016**, *121*, 451