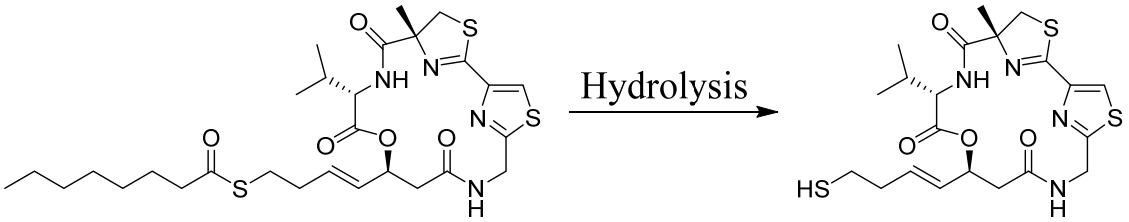
LARGAZOLE, A PROMISING SCAFFOLD FOR HDAC INHIBITORS

Matteo Borgini[a], Giulio Poli[a], Maurizio Botta[a,b]

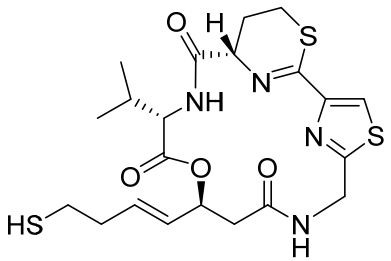
[a] Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Italy
[b] Lead Discovery Siena S.r.l., Castelnuovo Berardenga, Siena, Italy
borgini.m4@gmail.com

Largazole is a marine cyanobatcerium metabolite (*Symploca* genus) isolated by Luesch and co-workers, with novel chemical scaffold. It consists of a strained 16-membered cyclic depsipeptide bearing a thioester moiety that, in physiological condition, is hydrolyzed leaving the active HDAC inhibitor Largazole-SH.



Largazole Largazole-SH

Largazole showed a sub-nanomolar inhibition potency with high selectivity for class I HDAC. Furthermore, its selective cytotoxicity for cancer cell lines (e.g.: MDA-MB-231 GI_{50} = 7.7 nm) compared to non-transformed cells (e.g.: NMuMG GI_{50} = 122 nm),[1,2] pushes us towards the search for new derivatives with greater potency and improved HDAC isoform selectivity.



5,6-dihydro-4H-1,3-thiazine derivative

The synthesis of Largazole, along with its chemical challenges, is presented, as well as its adaptation for the preparation of 5,6-dihydro-4H-1,3-thiazine derivative which, among the planned derivatives, is of great interest for its anticipated HDAC isoform selectivity.

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[1]. Kim B, Park H, Salvador LA, Serrano PE, Kwan JC, Zeller SL, Chen QY, Ryu S, Liu Y, Byeon S, Luesch H, Hong J. *Bioorg Med Chem Lett.* **2014** Aug 15;24(16):3728-31

[2]. Taori K, Paul V.J. and Luesch H *J. Am. Chem. Soc.*, **2008**, *130* (6), pp 1806–1807