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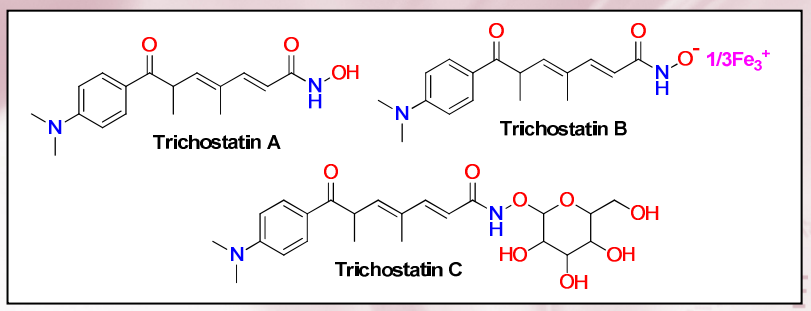
Histones

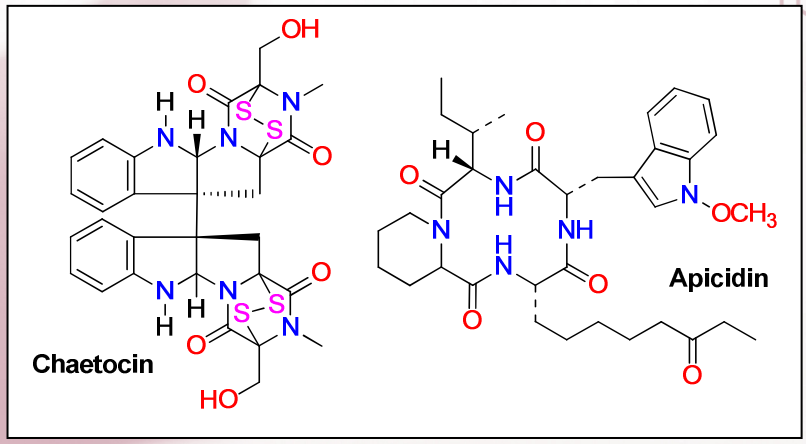
New Generation Targets

In the cell, the acidic nature of DNA is balanced by the basic histone proteins that shape, package and manage our genetic code. There are five broad classes of histones and each contains a number of variants whose functions are slowly being unravelled. Research has recently demonstrated the importance of post-translational modifications to histones, including the addition of methyl and acetyl groups, phosphate and even other proteins like ubiquitin.

The search for inhibitors from microbes has yet again proven their versatility in producing metabolites that are able to regulate eukaryotic cells by highly selective interaction with histones.



Trichostatin A was discovered by researchers at Shionogi and Co. in 1976 from *Streptomyces hygroscopicus*. It was named for its ability to inhibit the growth of the fungal pathogen *Trichophyton* spp. Research on histone deacetylase (HDAC) demonstrated that **trichostatin A** was a potent inhibitor of Class I and II HDAC. The discovery of trichostatin A became the template for medicinal chemists to develop vorinostat.



Interestingly, microbes also recognise the merits of "pro-drugs", storing **trichostatin A** in an inactive state awaiting activation. For **trichostatin B**, a ferric complex of trichostatin A, activation is achieved by Fe^{3+} ion scavenging while **trichostatin C**, a glycosyl ester of trichostatin A, is activiated by hydrolysis. The pharmacology of these metabolites has received scant attention.

While **trichostatin A** is active across all HDAC classes, the fungal metabolite **apicidin** offers selectivity towards HDAC class II and III. **Apicidin** is a cyclic tetrapeptide isolated from several *Fusarium* species.

In 2005 **chaetocin**, a polythiodiopiperazine metabolite isolated from the fungus Chaetomium globosum**,** was found to be a specific inhibitor of a lysine specific histone methyltransferase. While there are a number of polythiodioxopiperazines produced by fungi, currently only **two**, **gliotoxin** and **chaetocin** readily available to researchers. At BioAustralis, we recognise the need to expand this class and anticipate releasing the melinacidins and related metabolites in the near future.

Despite the ample evidence that microbes have harnessed the regulation of histones as a key site for secondary metabolite activity there

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has been no systemic study of microbial metabolites as the source of new actives. Perhaps the possibility that longevity can be sustained by regulation of Class III HDACs through sirtuins suggests that microbes may hold a secret to the "fountain of youth".

The opportunities: The search for new selective actives, tools exploring the selectivity of histone classes and sub-classes, analogue synthesis and structure-activity relationships against new sites using unusual structural "scaffolds".

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3. Potent and specific inhibition of mammalian histone deacetylase both *in vivo* and *in vitro* by trichostatin A. Yoshida M.et al. *J. Biol. Chem.* **1990**, 265, 17174.
4. Trichostatin C, a glucopyranosyl hydroxamate. Tsuji N. et al. *J. Antibiot.* **1978**, 31, 939.
5. Apicidin is a histone deacetylase inhibitor with anti-invasive and anti-angiogenic potentials. Kim S.H. et al. *Biochem. Biophys. Res. Commun.* **2004**, 315, 964.
6. Apicidin, a histone deacetylase inhibitor, inhibits proliferation of tumor cells via induction of p21WAF1/Cip1 and gelsolin. Han J.W. et al. *Cancer Res*. **2000**, 60, 6068.

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