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Synthesis of new apicidin derivatives as Histone deacetylase(HDAC) inhibitors

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ABSTRACT

Histone deacetylase(HDAC), a neuclear enzyme that regulates gene trascription and the assembly of newly synthesized chromatin, has received much attention in recent literature. The explosion of activity in this field has yielded the cloning of a mammalian gene which encodes a complementary histone acetyl trasferases. Several cyclic tetrapeptide inhibitors of HDAC has been reported to affect the hyperacetylation of mammalian and plant histones.

Apicidin, a natural product HDAC inhibitor recently isolated at Merck Research Laboratories, induces therapeutic applications as a broad spectrum antiprotozoal agent to multi-drug resistant malaria and a potential antitumor agnet. The biological activity of apicidin appears to be attributable to inhibition of apicocomplexan HDAC at low nanomolar concentrations.

In the present work about the synthesis and biological activities of new apicidin derivatives which are analogues of apicidin isolated from *Fusarium sp.*, we have discovered that apicidin and some derivatives have mild antitumor activity, which caused the change of tumor cells morphology to return to normal cells. As part of our program toward the development of new antitumor agents, we synthesized its derivatives systemically, and then studied their structure-activity relationships. At present, we modified the ketone moiety of apicidin to various imine derivatives in consideration of interaction with HDAC.