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Synthesis and Evaluation of Aliphatic-chain Hydroxamates Capped with Osthole Derivatives as Histone Deacetylase Inhibitors

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Our previous studies have demonstrated that osthole, a Chinese herbal compound, could be incorporated into the hydroxycinnamide scaffold of LBH-589, a potent HDAC inhibitor, as an effective hydrophobic cap; the resulting compounds showed significant potency against several HDAC isoforms. Here, we presented a series of osthole derivatives fused with the aliphatic-hydroxamate core of suberoylanilide hydroxamic acid (SAHA), a clinically-approved HDAC inhibitor. Several compounds showed potent activity against nuclear HDACs comparable. Further assays against individual HDAC isoforms revealed that some compounds showed not only SAHA-like activity towards HDAC1, -4 and -6, they inhibited HDAC8 by log difference than SAHA and thus exhibited a broader HDAC inhibition spectrum. Among them, compound **6g** showed multiple significant cellular effects towards human prostate cancer cells.