SUNLIGHT- OR UVA-LIGHT-MEDIATED SYNTHESIS OF VORINOSTAT AND BUFEXAMAC

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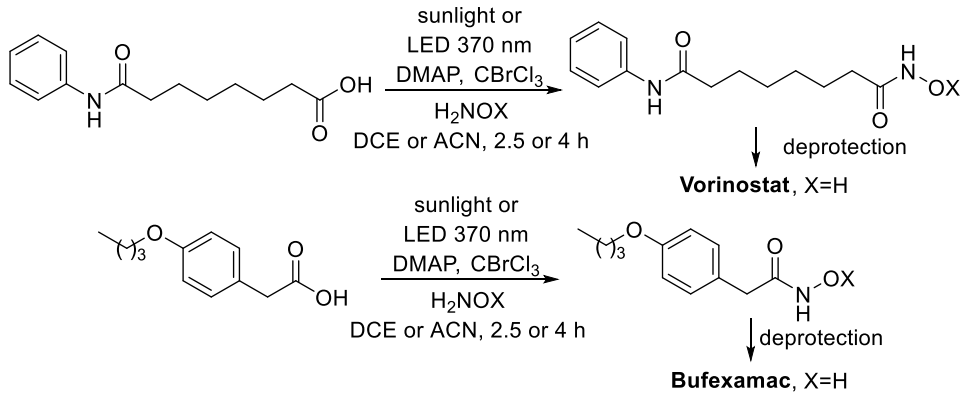
Hydroxamic acids constitute a class of compounds widely known for their biological properties and applications in medicinal chemistry. Their most interesting feature is their ability to inhibit histone deacetylases (HDACs) and exhibit potent activity as anticancer agents. Many hydroxamic acids serve as antibacterial, antifungal and/or anti-inflammatory mediators, while three of them, namely vorinostat, belinostat and panobinostat, are approved drugs for the treatment of primary cutaneous T-cell lymphoma, peripheral T-cell lymphoma and multiple myeloma, respectively. Moreover, bufexamac, an identified class IIb HDAC inhibitor, is a non-steroidal anti-inflammatory drug used to reduce the symptoms of inflammation of the skin in diseases such as atopic eczema and inflammatory dermatoses. We demonstrate herein the light-driven coupling of carboxylic acids with protected hydroxylamines leading to the synthesis of benzyl- or tetrahydropyranyl- protected hydroxamic acids. Key-point for the achievement of the reaction is a charge transfer complex intermediate generated by the interaction of 4-dimethylaminopyridine with a halomethane, mostly $CBrCl_3$, which absorbs either sunlight or light from a LED irradiation source. The photocatalytic protocol was efficiently applied to a variety of carboxylic acids leading to different protected hydroxamic acids. Vorinostat and bufexamac were synthesised as depicted in the Scheme.



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