IPAP18 Innovations in Pharmacy ADVANCES & PERSPECTIVES

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#IPAP18 Posters

SYNTHESIS AND BIOLOGICAL EVALUATION OF A HISTONE DEACETYLASE INHIBITOR, ANALOGOUS OF SCRIPTAID

Yasmine SERI, José M. ZAPICO, Claire CODERCH, Beatriz de PASCUAL-TERESA and Ana RAMOS.

GOBIERNO DE ESPAÑA · MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD · Instituto de Salud Carlos III
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Previous studies

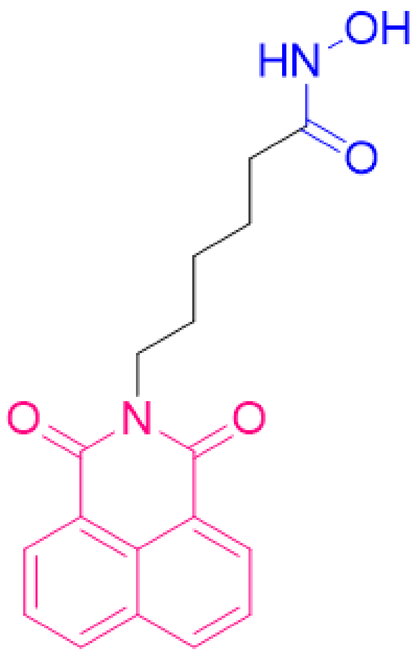


Figure 1. Chemical structure of scriptaid

A series of HDAC inhibitors has been synthesized through the years, but only some of them showed good results with low toxicity. It is the case of Scriptaid.

Scriptaid is **a potent histone deacetylase inhibitor** belonging to the **hydroxamic acid group**, preferentially inhibiting the Class I HDAC (1,2,3). [1,2]

This compound **induces the inhibition of cellular growth in several tumour cells**.[1]

On the other hand, Scriptaid shows a **potent anti-Toxoplasma gondii activity in vitro.**[2]

Objectives

- Synthesis of a derivative of scriptaid in a new and effective way, as a possible new antitumoral and antiparasitic agent.
- The **naphtalimide moiety** of our molecule **5c** is similar to the one of scriptaid but with an **additional methoxy group**. **It acts as the capping group**, and is connected to the **hydroxamic ZBG**, through a **5 carbon atom alkyl chain.**

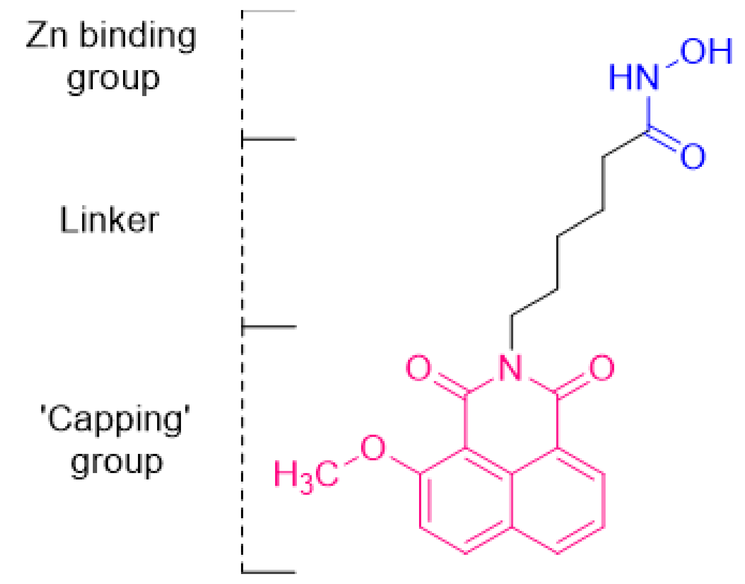
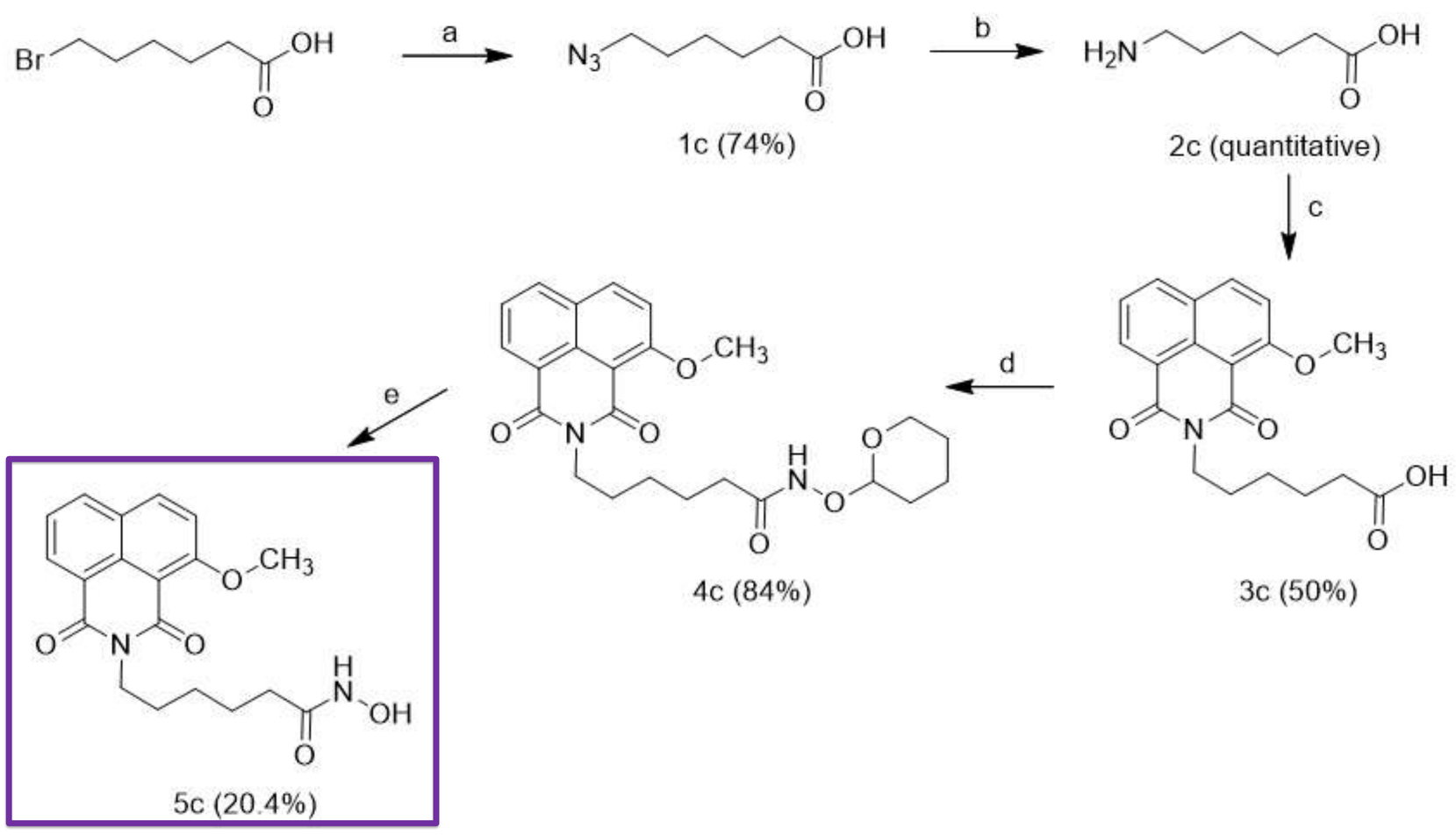


Figure 2. Chemical structure of **5c**

Synthesis



Scheme 1 Reagents: (a) NaN_3, DMF, 60°C, 12h; (b) Pd black, methanol, rt, 24h; (c) 2-methoxy-1,8-naphthalic anhydride, ethanol, MW, 100 °C, 48h; (d) NH_2OTHP, HOBt, EDCI, NMM, DMF, rt, 12 h; (e) CH_3COCl, methanol, 0 °C, 5-10 min.

Results and discussion

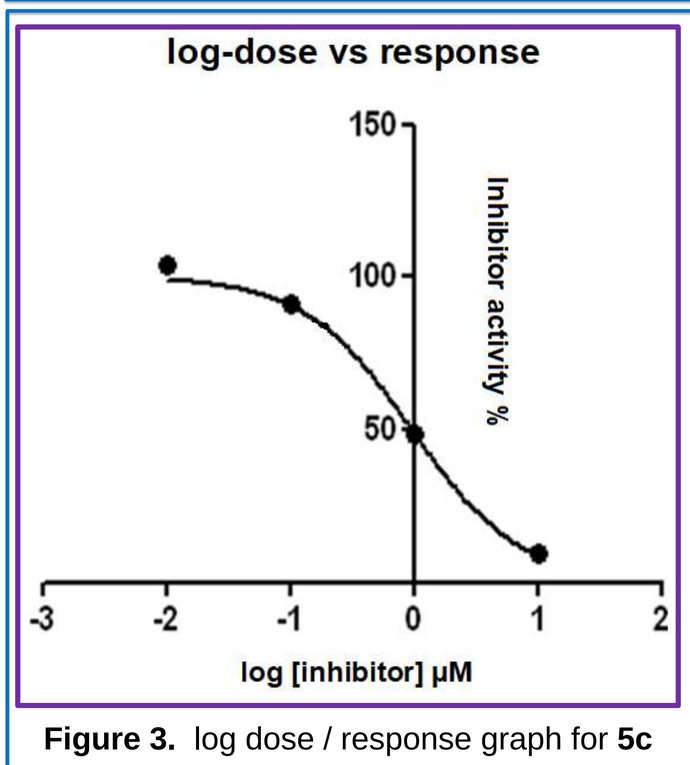


Figure 3. log dose / response graph for **5c**

A successful synthesis of **5c**, a derivative of Scriptaid, has been described in a **five-step pathway**.

We demonstrated that :

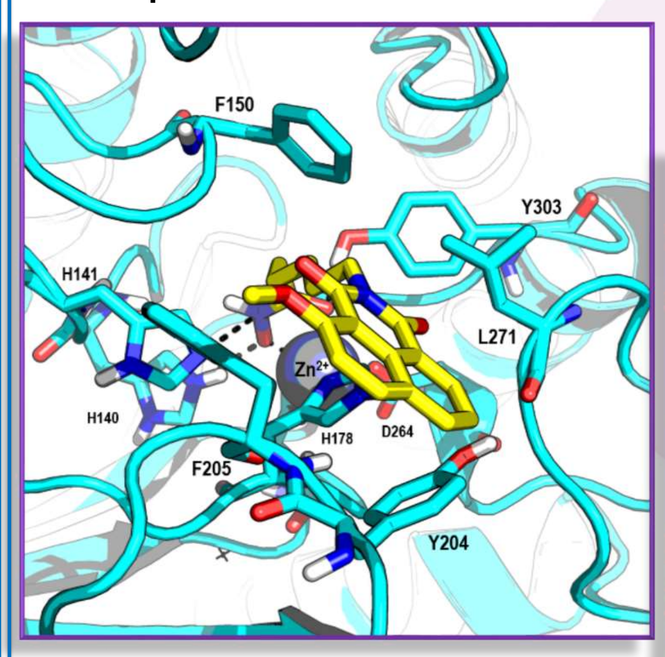
- The **amidation** reaction is **successfully completed when** :
  - **preceded by the reduction of the azide,**
  - **followed by the protection reaction**.
- Also **the transformation into the hydroxamate was successively achieved.**

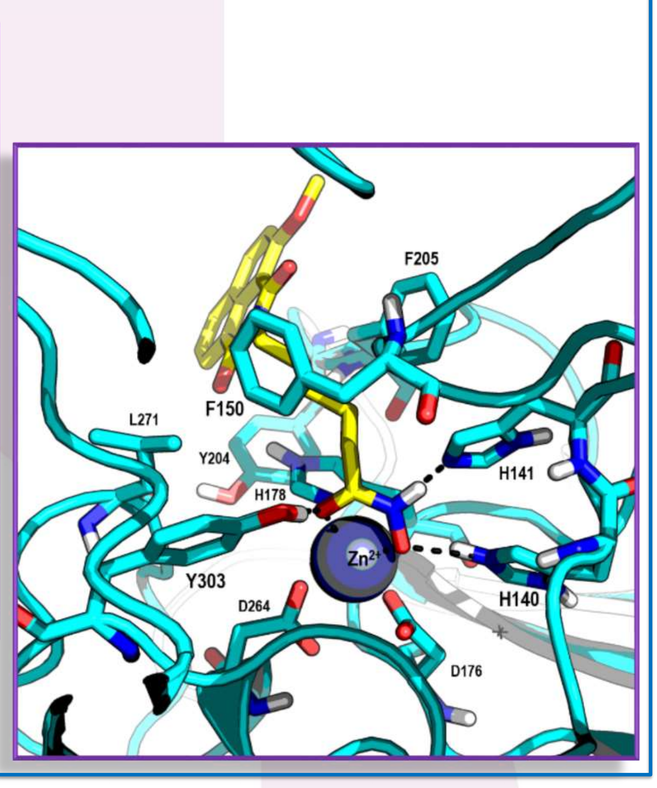
Its inhibitory activity was tested using a **Fluorimetric Activity Assay**.

- The compound is active in the low micromolar range (**IC_{50} = 0,97 µM**).
- **Potential antitumoral and antiparasitic agent.**

A docking study allowed us to propose a **mode of binding to HDAC 1**.

- The **ZBG** (hydroxamic acid group), establishes a **bidentate chelation to the catalytic Zn^{2+},** and three hydrogen bonds with the side chains of amino acids in the active site.
- The **linker** (5 carbon atom alkyl chain) establishes **van der Waals interactions with the side chains of the amino acids that make up the walls of the tunnel**.
- The **cap group interacts with the amino acids located on the surface of the protein**.





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[1] L. Giacinti, C. Giacinti, C. Gabellini, E. Rizzuto, M. Lopez and A. Giordano, *J. Cell. Physiol*. **2012**, *227*, 3426-3433.
[2] J.S. Strobl, M. Cassell, S.M. Mitchell, C.M. Reilly and D.S. Lindsay, *J. Parasitol.* **2007**, *93(3)*, 694-700.