Enhancement of the antiproliferative effect of the abietane diterpenoid ferruginol by amination of position 18

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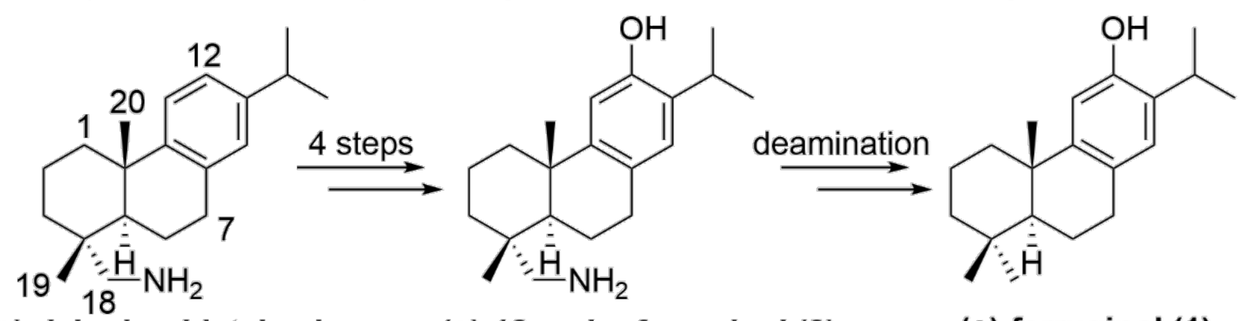
INTRODUCTION

The family of abietane-type diterpenoids has long attracted natural product researchers, organic and medicinal chemists leading to significant discoveries [1]. In our group, we have developed a number of studies towards the semisynthesis of a variety of aromatic abietanes as well as biological screenings. The diterpene ferruginol (**1**, F) is a very simple phenolic abietane which has demonstrated a plethora of promising biological and pharmacological properties, including antibacterial, antifungal, antiparasitic, antiviral [2].

Some years ago, we developed a multigram semisynthetic procedure to obtain ferruginol from the commercially available (+)-dehydroabietylamine *via* the intermediate 18-aminoferruginol (**2**, 18AF) (Scheme 1) [3]. First step is the protection of the amino group as phthalimide, acylation of Friedel-Crafts and Baeyer-Villiger, and overall deprotection with hydrazine gives 18AF, whose deamination gives **1**.

Herein, we present the results obtained in terms of antiproliferative activities for these two molecules in four breast cancer cell lines SUM149, MDA-MB231, T47D, MCF07 and one melanoma cell line SK-MEL28 [4,5] as well as a primary cell line (BJ) to measure its selectivity. Non-tumorigenic cell line BJ was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). BJ cells are fibroblasts established from skin taken from normal foreskin from a neonatal male.



(+)-dehydroabietylamine **(+)-18-aminoferruginol (2)** **(+)-ferruginol (1)**

Scheme 1. Synthesis of ferruginol

RESULTS

Our preliminary data using SK-MEL28 indicate that 18-AF induces caspase-3/7 activity (6.5x at 72h; $p<0.0001$) without changes in the mitochondrial membrane potential thus reversing the cytotoxic mechanism of the parent molecules ferruginol (depolarization of mitochondrial membrane, $p<0.01$ at 72h; no caspases 3/7 activation) and therefore making it more similar to the drug control paclitaxel (GI50=10 nM; caspases 3/7 activation $p<0.0001$)[5].

Table1 shows that amination of ferruginol in position 18 leads to a general enhancement (from 1.6 to *c.a.* 5 times) of the antiproliferative activity and lower toxicity to normal cells (BJ) thus increasing selectivity. It seems that the highest enhancement occurs in the melanoma cell line.

Table 1: Antiproliferative activity (GI50, μM) of compounds **1** and **2** in a panel of human cell lines.

	SUM149*	MDA-MB231*	T47D*	MCF07*	SK-MEL28**	BJ*
1	>50	8.3±14.4	>100	19.0±1.5	47.5	>50
2	4.4±0.3	5.1±0.6	>50	10.0±1.5	9.8	75.0±6.2

(*)= CellTitreGlo® assay (72h). The positive control used was staurosporine (1 uM)[4]; (**) SRB assay (48h). The positive control was paclitaxel (10 nM)[5].

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