Evidence of molecular mode of action of 3-alkylpyridine marine alkaloid analogs against human cancer cell lines

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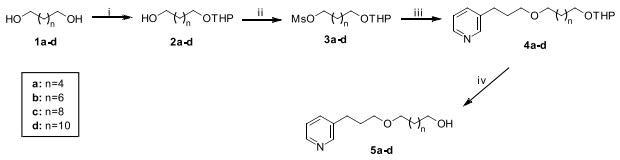
Introduction

Cancer continues to be one of the most important health problems worldwide, and the identification of novel drugs and treatments to address this disease is urgent. During recent years, marine organisms have proven to be a promising source of new compounds with action against tumoral cell lines[1]. Here, we describe the synthesis and anticancer activity of two most active synthetic 3-alkylpyridine alkaloid (3-APA) analogs against HeLa (cervix adenocarcinoma), RKO AS-45-1 (colon carcinoma), and BT-549 (breast ductal carcinoma) tumoral cell lines.

Results and Discussion

3-APA analogs were synthesized in four steps and with good yields. The key step for the synthesis of these compounds is a Williamson etherification under phase-transfer conditions (Figure 1).



Reagents, conditions, and yields: (i) $NaHSO_4$, DHP, DMSO, hexane, 40°C, 16h, 74%–89%; (ii) MsCl, Et_3N, CH_2Cl_2, RT, 10h, 77%–87%; (iii) 3-(pyrid-3-yl)propan-1-ol, NaOH/H_2O, $Bu_4N^+Br^-$, Et_2O, RT, 72h, 57%–73%; (iv) MeOH, HCl, RT, 12h, 71%–100%.
Figure 1. Synthesis of 3-APA analogs **4a–d** and **5a–d**.

Biological assays demonstrated both compounds with an alkyl chain of ten carbon atoms (**4c** and **5c**) were the most active against the three tumoral cell lines. Cytotoxic activity (Table 1), apoptosis (Figure 2), mutagenicity (Figure 3), and cytoskeleton assembly (Figure 4) assays showed that both compounds are mutagenic and induce apoptosis. In addition, Compound **5c** altered the cellular actin cytoskeleton in RKO-AS-45-1 cells.

Table 1. *In vitro* cytotoxic activity of two new 3-APA analogs **4c** and **5c** against tumoral human cell lines.

Compounds	IC50 (μM) ± SD[a]		
	RKO[b]	HeLa[b]	BT-549[c]
4c	5.1 ± 1.1	4.0 ± 0.8	24.6 ± 4.8
5c	19.1 ± 4.4	19.1 ± 4.4	60.5 ± 12.3
Etoposide	1.4 ± 0.6	1.4 ± 0.6	22.22 ± 4.1

(a) average ± standard deviation; (b) MTT assay; (c) SRB assay

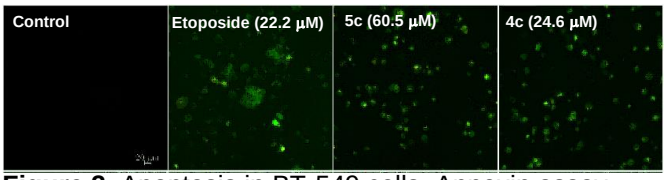


Figure 2. Apoptosis in BT-549 cells. Annexin assay.

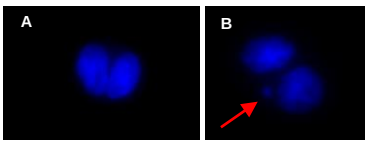


Figure 3. Mutagenicity in HeLa cells: A) non-treated cells; B) **4c** at 2.5 μM. Micronucleous assay. The red arrow indicates micronucleous formation.

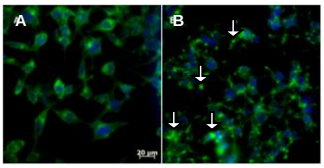


Figure 4. Effect of **5c** on the actin cytoskeleton of RKO cells: A) non-treated cells; B) **5c** at 19.1 μM. The arrows indicate that the treatment caused an accentuated alteration of the cellular actin network (green fluorescence).

Conclusions

The results suggest that compounds **4c** and **5c** may be novel prototype anticancer agents.

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[1] Gonçalves, *et. al. Marine Drugs*, **2014**, *12(8), 4361*.