Synthesis and citotoxicity activity of new aza-analogues of angucyclinones from (-)-shikimic acid

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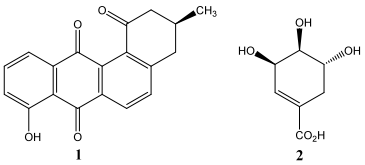
INTRODUCTION

The synthesis of heterocyclic quinones is an attractive research area in organic synthesis due to the well-known biological activities of these compounds isolated from several natural sources.

There are several natural products which contain a tetrahydrobenzo[*a*]anthraquinone skeleton. Most of these are named as angucyclines[1], which are well-known for their broad range of biological properties including antifungal, antiviral, antibiotic, antitumor, platelet aggregation and enzyme inhibitory behavior[1-3], a representative example is provided by (+)-ochromycinone (**1**). These compounds, which are secreted by Actinomycetes are, after the tetracyclines and anthracyclines, the third class of natural antibiotics featuring a carbotetracyclic skeleton. On the other hand, (-)-shikimic acid (**2**), is a natural products has been used as a versatile chiral building block for the synthesis of many targets including therapeutic drugs, due that this compounds has three stereocenter with a specific configuration.[4]



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RESULTS AND DISCUSSION

In this work, we described to the synthesis of five new aza-angucyclinones starting from (-)-shikimic acid. These were synthesized using as synthetic strategy the Diels-Alder cycloaddition reaction between azadiene **4** and 1,4-benzoquinone, 1,4-naphthoquinone, acetyl-juglone and naphthazarin (Scheme 1). Furthermore we reported herein the *in vitro* testing of **5-9** to include normal and tumor cell lines in order to determine the broadness of the activity. The antitumoral activities of compounds were assayed against four cells lines (MCF-7, PC3, HT-29 and CoN) (Table 1).

Scheme 1. Reagents and conditions. (a) Ref 5; (b) N,N-dimthylhydrazine; c) 1,4-benzoquinone, CH_3CN; d) 1,4-naphthoquinone, acetyl-juglone or naphthazarin in CH_3CN.

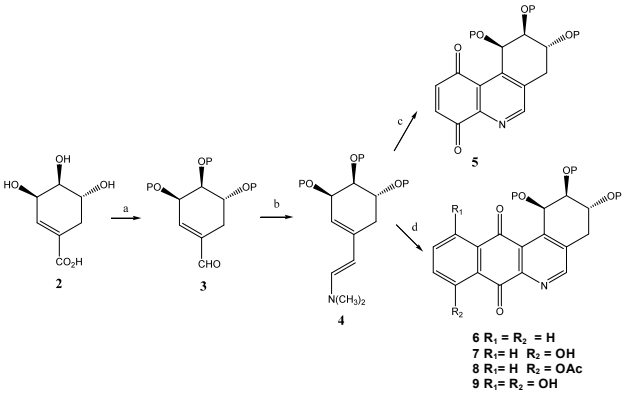

Table 1. Antitumoral activity, IC50 (μM)

Compound	MCF-7	PC-3	HT-29	CoN
5	>100	10±0,7	15±0,9	>100
6	5±0,3	5±0,7	15±0,8	10±0,5
7	10±0,5	1.2±0,4	20±0,7	1.2±0,7
8	15±0,8	25±0,7	10±0,7	2.5±0,5
9	20±0,7	5±0,7	18±0,5	15±0,7

CONCLUSION

In summary, we described here the synthesis of new aza-angucyclinones and anticancer evaluation of them. As compared with the tumor cell lines analyzed, we found that all the synthesized compounds shown antitumoral effect in most of the cells lines (Table 1).

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