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Synthesis, spectroscopic, physicochemical and structural characterization of tetrandrine-based macrocycles functionalized with acridine and anthracene groups: DNA binding and anti-proliferative activity

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ABSTRACT

In this work, we report on the synthesis of two new mono-alkylated tetrandrine derivatives with acridine and anthracene units, **MAcT** and **MAnT**. The compounds were fully characterized by physicochemical techniques and single-crystal X-ray diffraction analysis. In addition, both derivatives were studied as nucleotide receptors and double-stranded DNA binders in aqueous phosphate buffer at pH = 7.2 using UV–vis and fluorescence spectroscopy. According to the molecular recognition studies, **MAcT** and **MAnT** exhibit high affinity ($K \sim 10^5\,M^{-1}$) and selectivity for ds-DNA, presumably in an intercalation mode. Finally, the anti-proliferative effects of the tetrandrine derivatives on different cancer cell lines were explored, revealing promising activities. Particularly, the mono-anthracene tetrandrine derivative **MAnT** showed an IC_{50} of 2.74 μg/mL on the HeLa cervical cancer cell line, representing a value 3.3 times smaller than that obtained for unsubstituted tetrandrine. Examination of the cytotoxic effects on the HeLa cell line by inverted microscopy suggests that the cell death mechanism consists basically in apoptosis. The molecular modelling of three ds-DNA-**MAcT** complexes, suggested that the macrocycles may use an intercalation binding mode towards DNA. **MAcT** is predicted to bind into the major groove of the ds-DNA providing non-covalent interactions such as electrostatic, van der Waals and hydrophobic interactions that lead to selectivity. Overall experimental data supports the mode of action of **MAnT** and **MAcT** as cytotoxic compounds against cancer cell lines via a DNA interaction mechanism.

1. Introduction

S, *S*-(+)-Tetrandrine is an alkaloid isolated from plants of the menispermaceae family that exhibits a broad range of pharmacological activities including anti-inflammatory, analgesic, antimicrobial and anti-cancer properties, among others [1,2]. With respect to the anti-cancer activity, both *in vitro* and *in vivo* experiments have shown the effectiveness of this alkaloid toward different cancer cell lines [1–3]. However, the complete understanding of the mechanisms and molecular targets involved in the anti-cancer drug activity of tetrandrine requires further research.

The structural modification of this alkaloid is the strategy of choice to improve the physicochemical and pharmacological properties, as well as to reduce the toxicity. In this regard, in the past our research group reported a series of bis-alkylated tetrandrine derivatives that have been found to be effective dicationic hosts in water for carboxylates, nucleotides, and DNA [4–8]. More recently, a few works have been reported tetrandrine derivatives by incorporating halogen atoms or other substituents into the aromatic rings within the macrocyclic structure as well as by alkylation of the nitrogen atoms, the evaluation of their anti-proliferative activity against several cancer cell lines and the capacity to reverse multidrug resistance (MDR) in cancer [9–17].

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