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Synthesis of decasubstituted pillar[5]arene derivatives containing *L*-alanine fragments: self-assembly, cytotoxicity, clonogenic assay and gene expression

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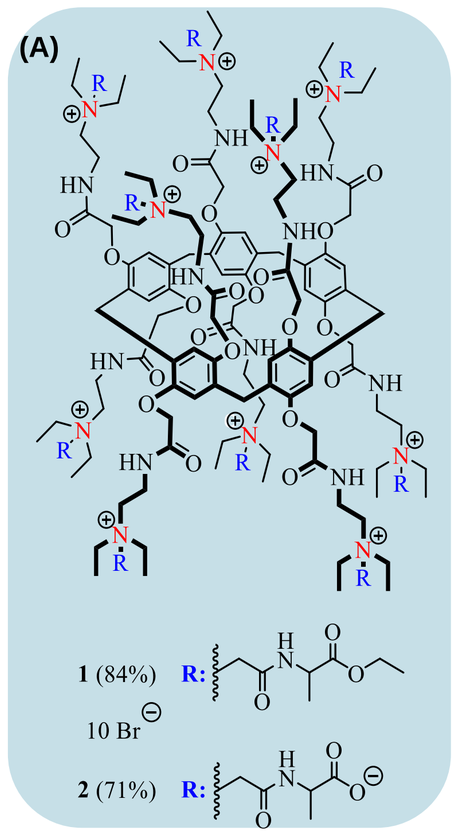
INTRODUCTION

Macrocyclic receptors represent a promising platform for constructing "drug-in-drug" and "drug-free" therapeutic systems due to their capacity to form stable inclusion complexes within their cavities, thereby offering a viable strategy to overcome drug resistance.

This study presents a synthetic methodology for obtaining ester and betaine derivatives of pillar[5]arene functionalized with *L*-alanine residues and a quaternary ammonium moiety bearing diethyl substituents. We elucidated the effect of the macrocycle's spatial configuration on self-assembly behavior, evaluate the cytotoxic potency of the synthesized compounds, and delineate the structure-activity relationship governing their inhibitory effect on cell colony formation and expression of p53-dependent genes.

Table 1. Half-maximal inhibitory concentration (IC_{50}, μM) values of pillar[5]arene derivatives **1** and **2** in tumor (MCF7, Huh7) and non-tumor (BEAS-2B) cell lines.

Compound \ Cell line	MCF7	Huh7	BEAS-2B
1	2.4 ± 0.6	2.3 ± 0.2	3.2 ± 2.0
2	25.1 ± 3.0	78.2 ± 16.3	175.6 ± 24.4



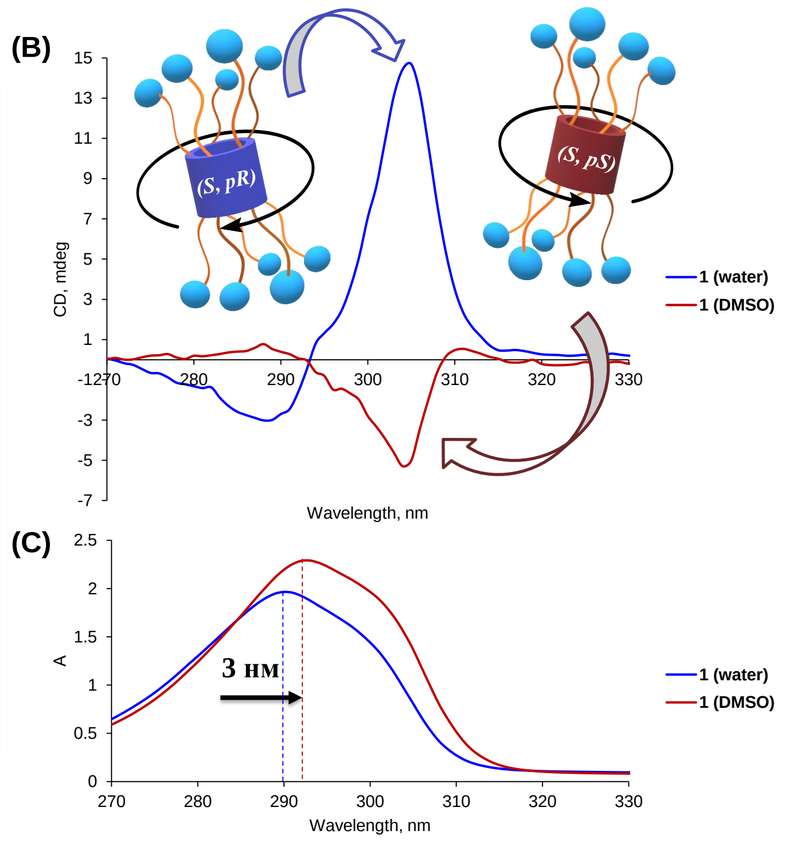


Figure 1. Structures of pillar[5]arene **1**, **2** (A); CD (B) and UV-vis (C) spectra of pillar[5]arene **1** at 1 × 10^{-4} M in water and DMSO.

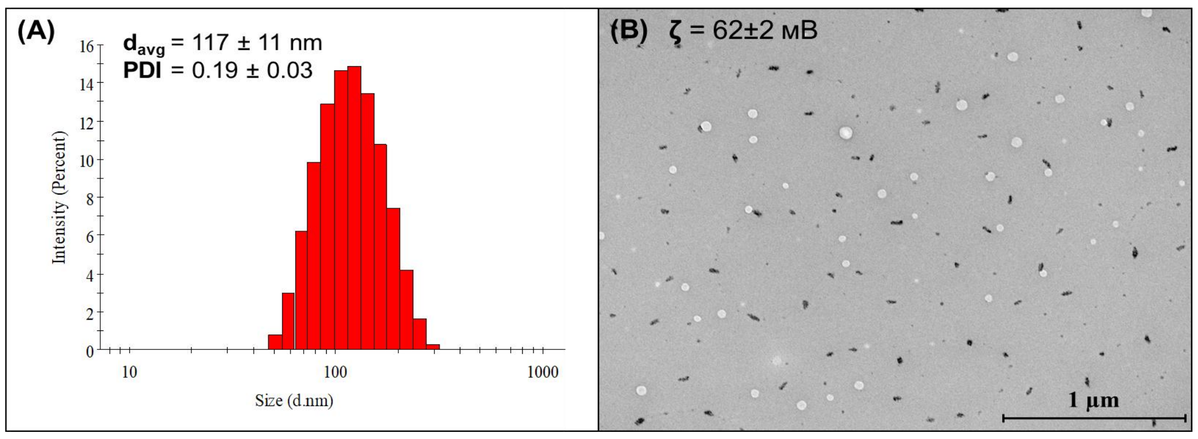


Figure 2. Size distribution by intensity of particles formed by macrocycle **1** in water (1 × 10^{-4} M) (A); TEM image of particles formed by pillar[5]arene **1** (B).

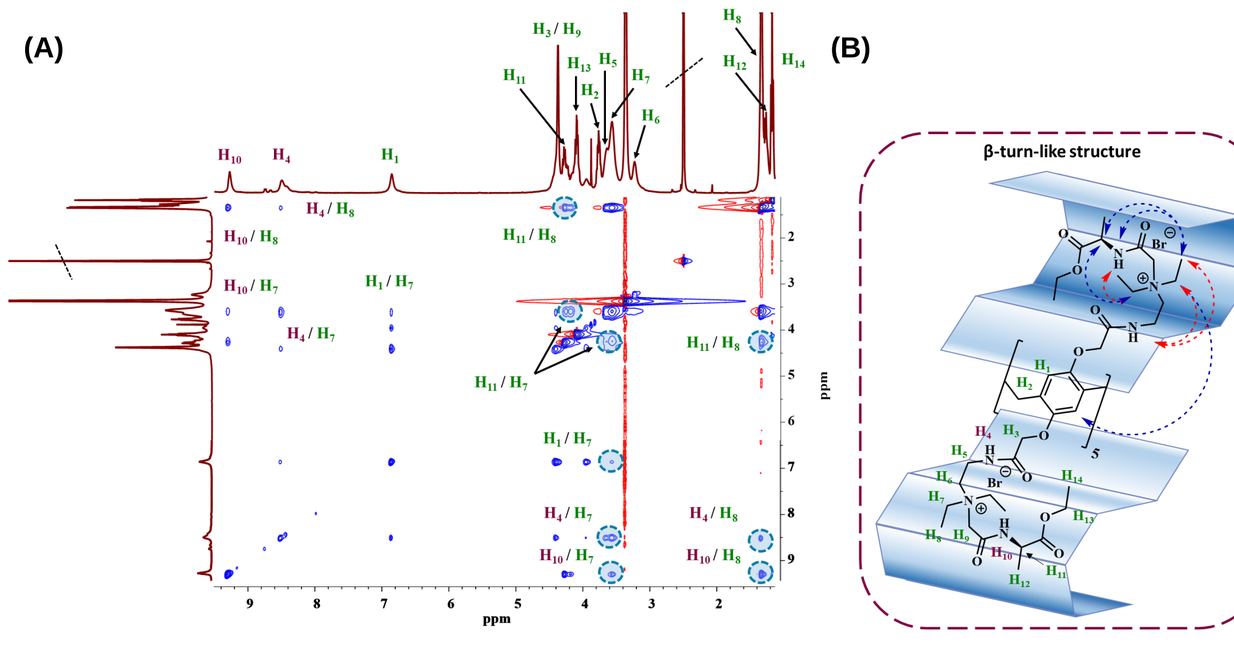


Figure 3. Fragment of the 2D ^{1}H–^{1}H NOESY NMR spectrum of pillar[5]arene **1** (DMSO, 298 K, 400 MHz) (A); schematic representation of proximal atomic arrangements in pillar[5]arene 1 during self-assembly (B).

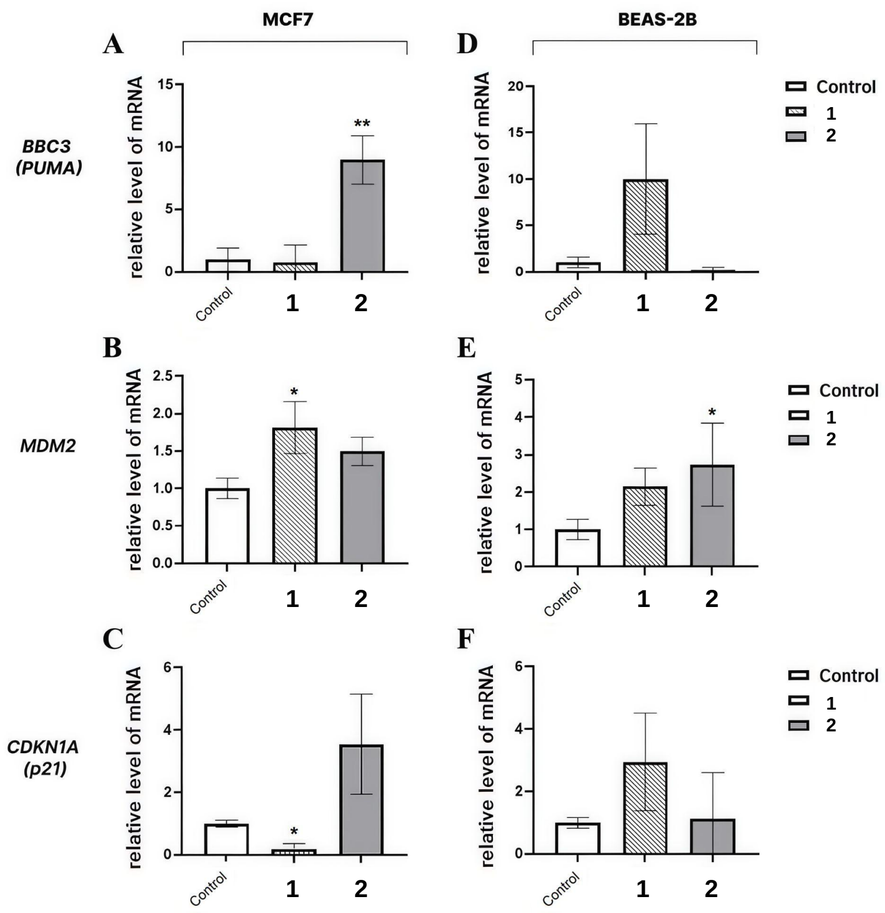


Figure 4. Effect of pillar[5]arene derivatives on the expression of p53-dependent genes in tumor and non-tumor cells.

CONCLUSION

In this study, novel pillar[5]arene derivatives with *L*-alanine moieties were synthesized. Dynamic light scattering method, TEM and 2D NOESY NMR spectroscopy demonstrated the formation of a colloidal system with a smaller particle size and a low polydispersity index by macrocycle **1**. The synthesized pillar[5]arenes demonstrated selective cytotoxic activity against tumor cells. The results of the clonogenic assay indicate that the macrocycles exert a cytostatic effect on the tumor lineage, with no observed limitations to BEAS-2B colony growth. The betaine derivative **2** increased BBC3 gene expression in MCF7 cells by 9-fold, while the ester derivative **1** reduced expression of the p53-dependent CDKN1A gene by 3.5-fold in the same cell line.

Esters emerging as promising candidates due to their nanoscale uniformity and low-dose efficacy. Betaines, though less cytotoxic, uniquely alter pro-apoptotic gene expression. This work highlights structure-dependent bioactivity, offering new avenues to circumvent drug resistance