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“Modifications of the benzoquinone core of the natural macrolactam - geldanamycin and their influence on anticancer properties.”

Abstract

Ansamycin antibiotics have a relatively flat aromatic core and an aliphatic chain - ansamycin bridge and are known for their antibacterial, antiviral and antitumor activity. One of the representatives of the benzenoid ansamycins is geldanamycin, which inhibits the activity of heat shock proteins (Hsp90). The aim of the doctoral dissertation was to obtain various types of new geldanamycin derivatives and to determine the influence of the type of modification on the structure-activity relationship. I functionalised the C(17) arm by introducing amine substituents of various chemical nature. The assumption was to check how the disruption of the macrocyclic structure of the bridge affects its orientation towards the aromatic core and biological activity. In order to improve the solubility, I obtained a series of analogs containing a quaternary ammonium salt moiety. The arm at position C(17) was also functionalized using the Huisgen and Heck reactions. To test possible other potential ways of binding geldanamycin derivatives to Hsp90 and to reduce toxicity, cascade heterocyclization of the geldanamycin core to benzoxazole systems was planned. Based on the analysis of NMR and FT-IR spectra, as well as crystallographic methods, it was important to determine the structures and conformation of the derivatives. The last part of the work was to establish the structure-biological activity correlation (SAR), by confronting the determined physicochemical parameters of the obtained derivatives with the method of their binding in NBD Hsp90 and the obtained data on antitumor activity.