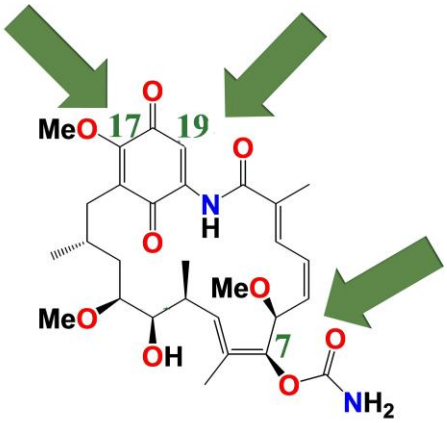
DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Geldanamycin (Fig. 1) and structurally related other ansamycin macrolides belong to natural antibiotics of great anticancer potential. Mechanism of anticancer activity for such type of natural products is closely related to the inhibiting activity of heat shock proteins as Hsp90 chaperones, which are responsible for folding of key proteins regulating crucial cellular processes. Incorporation of new polar substituents (guanidines, amidines, heterocyclic systems, phosphonates or phosphates) into geldanamycin skeleton at C(7), C(17) and C(19) positions will be aimed to improve mode of binding (Fig. 2), reduce toxicity and to increase water solubility of this type of ansa-macrolides. Thanks to incorporation of rationally designed polar structural motifs at C(17) and C(19) positions of geldanamycin skeleton, new analogs will be less susceptible to reactions with SH groups of glutathione and in result will be characterize by lower toxicity. In turn, introduced C(17) triazole-phosphonate arms "pretending" ATP will be steric hindrance blocking the access to the region of three glycines G132, G135 and G137 binding ATP at Hsp90 chaperones. Determined anticancer potency/selectivity and physico-chemical parameters together with the docking analysis of new geldanamycins at chaperone Hsp90 binding pocket will enable to reveal the desired structure of substituents, required for the achieving an compromise between anticancer potency and reduced toxicity. Performed studies on chemical transformations will show some possibilities and limitations related to reactivity of selected structural regions of geldanamycins and will enrich knowledge about the chemistry of ansa-antibiotics. Designed modifications can be a source of effective and bioavailable anticancer drug candidates built on the geldanamycin macrocyclic core.



Geldanamycin

Fig. 1 Structure of geldanamycin and key regions subjected to structure-activity relationship (SAR) studies.

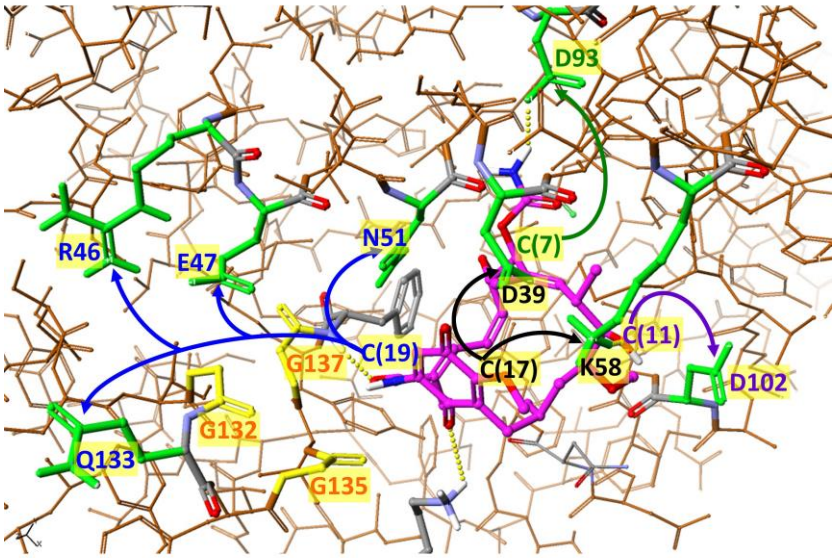


Fig. 2 Considered regions of SAR studies related to chemical modifications at C(7), C(17) and C(19) positions within geldanamycin scaffold (pink) directed to the key (green) aminoacids of the target protein – Hsp90 chaperone of ATP-ase activity (brown).