DEVELOPMENT OF INHIBITORS OF THE MOLECULAR CHAPERONE HSP90

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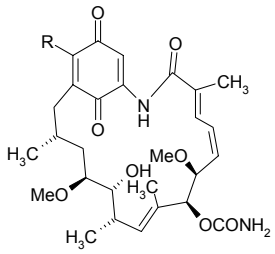
In the 90th of the last century it could be shown, that heat-shock proteins or chaperones can protect proteins from unfolding and aggregation caused by cell stress. HSP90 is an ATP-dependent chaperone protein essential for the maturation and activity of a diverse group of proteins involved in signal transduction, cell cycle regulation and apoptosis. It was observed, that blocking of HSP90 can interrupt regulatory mechanism of the cell. Tumour cells suffer from cell stress, caused by immune system or anti tumour therapy, so heat-shock proteins like HSP90 show an increased activity. Therefore antagonists of HSP90 seem to be good anticancer candidates. The ATPase activity can be inhibited with some selectivity by various antibiotics such as geldanamycin **1a** and its derivatives (see figure 1). Recent studies with geldanamycin derivatives suggest that cancer cells are particularly sensitive to HSP90 inhibition, because HSP90 has different conformations in healthy and tumour cells [1].



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1a -OCH_3
1b -$NHCH_2CH{=}CH_2$

Figure 1: Structures of geldanamycin 1a and 17-AAG 1b

As naturally derived structures the benzoquinone ansamycins like geldanamycin are difficult to synthesise. Therefore it seems to be useful to develop small, easy to synthesise molecules as HSP90-binders.

X-ray investigations show that HSP90 inhibitors bind to the ATP-binding site at the N-terminus of HSP90. A seven-stranded beta sheet forms the backbone of the protein and four alpha helices are arranged such they form a compact cavity in which resides the ATP binding site (see figure 2) [2].

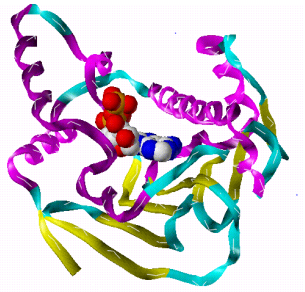
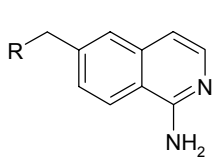


Figure 2: Structure of the ADP/ATP- binding site of HSP90 with an ADP bounded inside

Starting from the published structures of both unliganded protein and HSP90-complexes with a variety of inhibitors, we used Molecular Modelling methods to design isoquinolin-1-ylamin **2** and 4-amino-1H-quinazolin-2-one derivatives **3** as potential new HSP90 binders (see figure 3).

As the next step, we will synthesise the predicted structures by a modified Heck reaction. The binding affinity of the structures to HSP90 will be tested in a malachite green ATPase assay. Promising candidates will be tested for their antitumour activity by the NCI in an in vitro human tumour cell line test [3].



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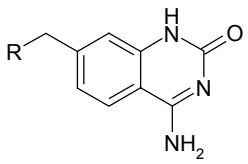

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Figure 3: Structures of the possible new HSP90 binders

[1] A. Maloney and P. Workman, Expert Opin. Biol. Ther. **2002**, 2, S. 3;
[2] J. Jez, J.-H. Chen, G. Rastelli, R. Stroud, D. Santi, Chem. Biol. **2003**, 10, S. 361.
[3] National Cancer Institute, Bethesda, Maryland, USA.