Abstract

BCA 2 (Breast Cancer Associated Protein2) is a novel monomeric RING (Really Interesting New Gene 2) – type ubiquitin E3 ligase. It was found to be overexpressed in 56 % of invasive breast cancers and its expression is correlated with a positive estrogen receptor status.

The RING-type family of proteins possesses ubiquitin ligase activity and involves in protein degradation. Ubiquitylation is used to target proteins of different biological processes including proteosomal degradation or endocytosis. Polyubiquitination of target protein substrates is carried out by three classes of ubiquitin ligase enzymes, of which the diverse E3 ligase family catalyse the final step of ubiquitin transfer to specific lysyl residues of target proteins prior to proteosomal destruction. The RING-type proteins can be defined as unique linear series of conserved cysteine and histidin residues and binds two zinc atoms in a cross-brace arrangement.

Studies of zinc-ejecting compounds have led to the identification of disulfiram, which has been used for alcohol aversion therapy for alcohol aversion therapy as an alcohol dehydrogenase inhibitor.

In this thesis I describe the synthesis of three series of novel zinc-affinic compounds, in order to optimise selectivity of BCA2 inhibitors which could lead to the identification of novel more effective antitumor agents compared to disulfiram.