Design and synthesis of anti-cancer cyclopeptides containing triazole skeleton

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Abstract We describe the design and synthesis of some hypothetical heptapeptides specifically to overcome the neoplastic activity of ras oncogene and their anti-cancer activities were studied. To improve the anti-cancer activity of the synthesized peptides, their structure modifications were done based on a sequential Ugi/Huisgen 1,3-Dipolar cyclization reaction. The cyclopeptides which contained triazole skeleton showed significant anti-cancer activity against cancer cells with mutated ras oncogene such as A549, PC3 and C26 cells. This study clearly shows the importance of triazole skeleton in biological activity of the peptides. It might be possible to overcome the difficulties involved in making complex peptides by employing this elegant chemistry.

Keywords Ugi ligation · Ligation of peptides · Anti-cancer activity · Cyclopeptides · Click reaction · Huisgen 1,3-Dipolar reaction

Introduction

Several monoclonal antibodies such as Rituximab (anti-CD:?.O antibody) and Herceptin (anti-HER-2 antibody) have been approved for the treatment of some cancers. The efficacy of chis cancer immunotherapy is, however, limited by its large size and its nonspecific binding to the reticuloendothelial system that causes many undesirable side effects (Aina et al. 2007). Furthermore, the drug research and development has become very expensive and the number of approved drugs has been declining in recent years. Therefore, the demands for alternative approaches are very high. This has contributed to the revival of peptides as potential therapeutic drugs. A large number of peptide-based drugs are now being marketed because new synthetic strategies have been developed in recent years (Vlieghe et al. 2010).

One classical strategy used in drug design is based on the structure of receptor-binding pocket, called "rational structure-based design" (Shoichet et al. 1993; Voltzstein et al. 1993). Most peptide drugs are designed this way. Here we have used a novel strategy based on DNA-protein binding criteria to design anti-cancer drugs. We focused our interest on finding specific DNA–protein binding sites along the promoter elements of ras oncogene. The precise interactions between amino acid motifs of our designed peptides and ras-specifie regulatory sites within the CpG islands might interfere with ras activity at transcriptional level. The most active peptide is then selected based on its in vitro anti-cancer activity to optimize its pharmaceutical value by means of different chemical approaches. One such approach would be the reduction of conformational space by cyclization.

Several hypothetical heptapeptides were designed based on DNA-protein binding criteria known for regulation of gene expression at transcriptional level. These peptides designed to perhaps suppress ras oncogenic activities in human cancer cells. The designed peptides 1-4 were tested for their anti-cancer activities against A549, human lung

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