Synthesis and biomedical applications of tumor targeting integrin ligands and conjugates

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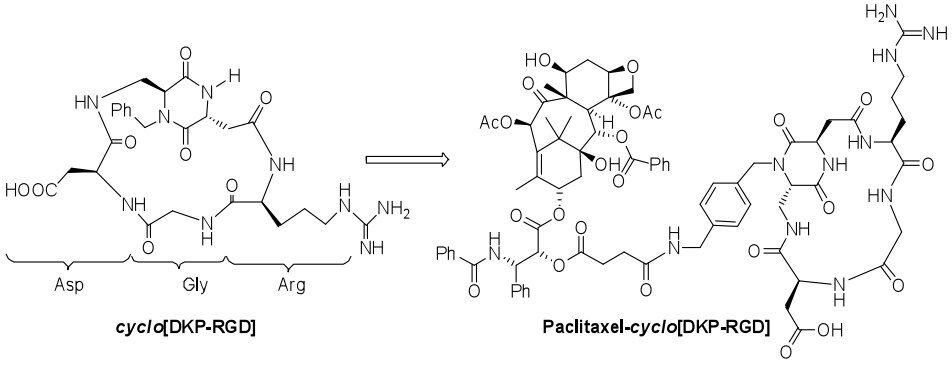
The importance and specificity of protein associations in cellular events and in the etiology of many pathologic processes raised interest on protein-protein interactions as attractive targets for therapeutic intervention. In cancer, several cell surface protein receptors, such as the $\alpha_V\beta_3$, $\alpha_V\beta_5$ and $\alpha_5\beta_1$ integrins, are considered specific molecular indicators of tumor angiogenesis, progression and metastasis. In addition, these receptors represent an interesting target for tumor-homing peptides, which can act as vectors of cytotoxic payload directly to tumour cells.

We have recently investigated the synthesis and the biological properties of a new class of cyclic peptidomimetics containing a bifunctional diketopiperazine (DKP) scaffold and the tripeptide sequence Arg-Gly-Asp (RGD)[1] or *iso*Asp-Gly-Arg (*iso*DGR)[2] as potent integrin ligands. The interaction of *cyclo*[DKP-RGD] ligands with intact cancer cells was investigated[3] and these ligands showed effective inhibition of angiogenesis in HUVEC cells without affecting cell viability and proliferation.[4]

A small number of *cyclo*[DKP-RGD]-Paclitaxel conjugates were synthesized and the cytotoxicity and targeting properties of these constructs were determined.[5]



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