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Titolo	TUMOR TARGETING VIA INTEGRIN LIGANDS: SYNTHESIS AND BIOLOGICAL EVALUATION OF RGD PEPTIDOMIMETIC-DRUG CONJUGATES [Tesi di dottorato]
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Sommario	Peptides and peptidomimetics bearing the Arg-Gly-Asp peptide sequence have been demonstrated to bind with high affinity to ?v?3 Integrin, a heterodimeric transmembrane receptor overexpressed in several tumor cells. For these reasons, integrin ligands have been coupled to a variety of anticancer drugs, aiming at the selective delivery of the payload at the tumor site. This PhD work describes the conjugation of the peptidomimetic ?v?3 Integrin ligand cyclo [DKP-RGD] to different anticancer drugs (i.e. paclitaxel, daunorubicin and camptothecin) through peptide and disulfide linkers. The resulting small molecule-drug conjugates (SMDCs) are selective ?v?3 binders and are able to release the drug upon exposure to lysosomal enzymes (e.g. cysteine proteases) or intracellular reducing agents (e. g. glutathione). Cell proliferation assays against isogenic human cancer cells expressing ?v?3 at different levels (?v?3 +/?v?3 ?) have been performed to evaluate the selective cytotoxic activity of RGD-based SMDCs against integrin-positive cancer cells. Fairly effective integrin targeting was displayed by the cyclo[DKP-RGD]-Val-Ala-PTX conjugate (compound 80), which was found to differentially inhibit proliferation in antigen-positive CCRF CEM ?v?3 versus antigen-negative isogenic CCRF-CEM cells. Next-generation cyclo[DKP-RGD]-Drug conjugates were prepared, aiming at improving the targeting effect shown by the cyclo[DKP-RGD]-Val-Ala-PTX conjugate as well as

	to deeply analyze the SMDC’s interactions with cancer cells.
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