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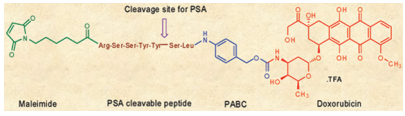
Prodrugs for Prostate Cancer

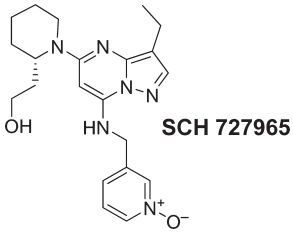
The protein-specific antigen (PSA) protein is a molecular target that is found in abundance in prostate cancer. It is the best tumor marker for this disease. Because of the adverse effects of the cancer-therapeutic doxorubicin, specific targeting is desirable. Elsadek et al. (DOI: 10.1021/ml100060m) now describe the synthesis and characterization of the peptide-conjugate prodrug of doxorubicin. Many compounds have an *N*-maleimide function for reaction with a specific cysteine in human serum albumin.



One specific compound is designed to be a protein-bound protease-activated prodrug, which accumulates in tumors due to enhanced permeability retention and then is cleaved by a protease-specific antigen to release active doxorubicin. This prodrug is stable and has antiproliferative effects in a PSA-specific prostate cancer cell line, making it a worthy candidate for further preclinical studies.

A Potent CDK Inhibitor as a Cancer Therapeutic

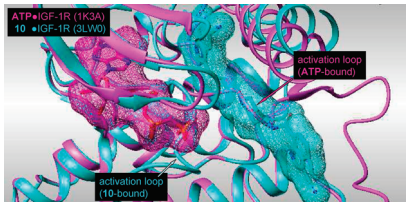
Cyclin-dependent kinases are a family of serine/threonine kinases atypically activated in all human cancers. Inhibition of these kinases is, therefore, a strategy used to develop cancer therapeutics. Paruch et al. (DOI: 10.1021/ml100051d) describe the synthesis of a series of pyrazolopyridimine scaffold inhibitors and subsequent characterization.



The authors used a functional in vivo screen to assess the efficacy of the small molecules and identified a particularly promising one, dinaciclib. This drug is currently in phase II clinical trials.

Allosteric Kinase Inhibitors

The insulin-like growth factor I receptor belongs to the receptor tyrosine kinase family and is a potential target in cancer therapy. Heinrich et al. (DOI: 10.1021/ml100044h) describe the discovery, structure−activity relationship analysis, and cocrystallization of novel allosteric inhibitors of the kinase activity of this enzyme.



Small molecule inhibitors of this enzyme suffer from cross-reactivity to the insulin receptor ATP-binding site because of the similarity to the kinase ATP-binding site. Therefore, competitive inhibitors of kinase activity also potentially inhibit insulin receptor signaling. Because the inhibitors described by the authors bind at an allosteric site, they do not impact insulin receptor signaling at physiological concentrations. Therefore, these small molecules are useful as tools for dissecting activity and as starting points for therapeutics.

DOI: 10.1021/ml1001739 | *ACS Med. Chem. Lett.* **2010**, *1*, 188–188