Structure Based Drug Design of Novel Inhibitors of cGMP Phosphodiestearse, PDE5

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PDE5, a cGMP specific PDE, has been recognised in recent years as an important therapeutic target. It is composed of the conserved C-terminal, zinc containing, catalytic domain, which catalyses the cleavage of cGMP, and an N-terminal regulatory portion, which contains two GAF domain repeats [1]. Each GAF domain contains a cGMP-binding site, one of high affinity and the other of lower affinity [2]. PDE5 activity is regulated through binding of cGMP to the high and low affinity cGMP binding sites followed by phosphorylation, which occurs only when both sites are occupied [3]. PDE5 is found in varying concentrations in a number of tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The protein is a key regulator of cGMP levels in the smooth muscle of the erectile corpus cavernosal tissue. Inhibition of PDE5 inhibits the breakdown of cGMP allowing the levels of cGMP, and hence smooth muscle relaxation, to be maintained [2]. Sildenafil, the active ingredient of Viagra® and a potent inhibitor of PDE5, has attracted widespread attention for the effective treatment of male erectile dysfunction.

We present here the application of the structures of PDE5 [4-9] to design novel inhibitors. The use of the complexes provides additional important structural information on the binding modes of multiple series of inhibitors. The structures also highlight the diverse chemical nature of inhibitors within this gene target and wider gene family, and the subtle structure activity relationships which assist the design of more potent and specific inhibitors to treat the many diseases where PDE's play a role.

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