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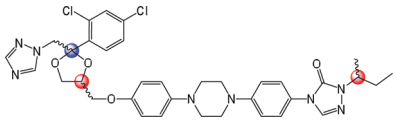
Dual Activity Drugs

Angiogenesis, which refers to the process of blood vessel formation, is associated with numerous diseases, including cancer and macular degeneration. Itraconazole, a clinically used antifungal drug, was demonstrated to possess antiangiogenic activity in a search for new pharmacological agents. Itraconazole possesses three stereocenters, which can give rise to a total of eight stereoisomers. Now, Shi et al. (DOI: 10.1021/ml1000068) synthesize and analyze the antifungal and antiangiogenic activities of all eight stereoisomers of itraconazole.

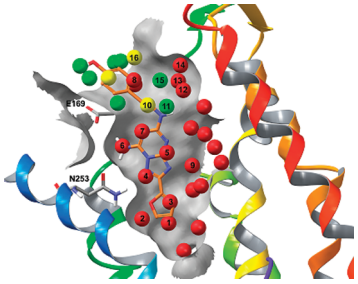
Notably, the authors find differential effects of the chiral centers on antiangiogenic and antifungal activities. These results are noteworthy because they suggest that stereoisomers might serve as superior therapeutics to the racemic mixture. In addition, these results point to different mechanisms for two distinct properties of itraconazole.



Thermodynamic Explanation of Receptor Binding

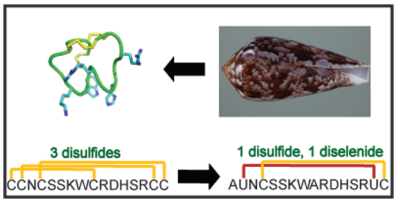
The A2A adenosine receptor shows great promise as a target for the treatment of depression, pain, and Parkinson's disease. Recently, the X-ray crystal structure of the receptor protein bound to an antagonist was resolved. This is a milestone in the search for new small molecules that modulate function. However, to date, traditional computational methods have not explained unintuitive structure−activity relationship analyses with the A2A adenosine receptor as a target. Using a novel method that estimates the free energy of water molecules in protein binding sites, Higgs et al. (DOI: 10.1021/ml100008s) now provide a rational framework for previously unintuitive structure−activity relationship results.

The authors use a process for predicting hydration site energetics, which might aid in the efficient design of new small molecules. While this method has previously been applied to kinases, proteases, and peptide binding domains, the authors now demonstrate the broad use of this approach in a membrane-bound protein.



Selenopeptide Synthesis Strategy

Neurotoxins from animals such as spiders, scorpions, marine cone-snails, and plant-derived bioactive compounds are a diverse source of natural products that show promise as drug leads. Many of these natural products are disulfide-rich natural products. A long-standing challenge has been the lack of acceptable, cost-effective strategies for large-scale oxidative folding of disulfide-rich peptides. Now, Han et al. (DOI: 10.1021/ml900017q) describe the use of a disulfide-depleted selenopeptide strategy to simplify chemical synthesis of disulfide-rich peptides. The approach described by the authors might aid in broader use of disulfide-rich peptides in drug discovery.



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