Identification of Novel Aromatase Inhibitors Using Pharmacophore Modeling

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Abstract: Pharmacophore modeling has become established as one of the most successful computational tools in modern drug design. This work describes how ligand- and structure-based pharmacophore modeling can be used to identify novel anti-breast cancer drugs.

Human aromatase (CYP19), a cytochrome P450 enzyme present in breast tissue, catalyzes the biosynthesis of estrogens from androgens. It is an important pharmacological target in anti-cancer therapy because intratumoral aromatase produces estrogen necessary for tumor growth in breast cancer tissues. Suppression of estrogen biosynthesis via aromatase inhibition represents an effective treatment for hormone-sensitive breast cancer, and several classes of aromatase inhibitors have been developed. However, important side effects associated with prolonged clinical use call for new CYP19 inhibitors.

The recent elucidation of the crystal structure of aromatase provides an excellent opportunity for designing the next generation of inhibitors. We will demonstrate the power of structure- and ligand-based pharmacophore modeling in identifying novel anti-breast cancer drugs.