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Case study: Pharmaceutical

Pharmacophore identification and lead optimization for novel antifungals

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Customer Type

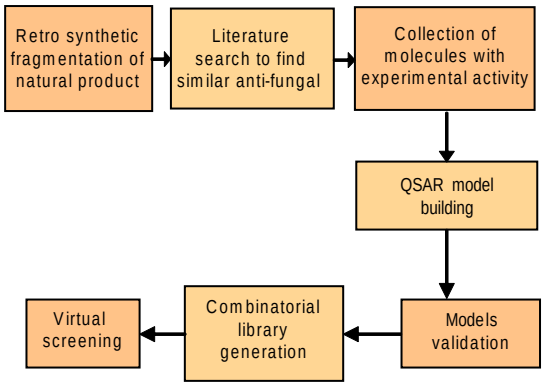
A leading pharmaceutical company

Software modules

QSARPlus

LeadGrow

VLife Engine



Application

NCE Design

Techniques

QSAR analysis

Combinatorial library

Virtual screening

Background:

Natural products play an important role in drug discovery and have been used for the treatment of various diseases for decades. They constitute a leading source of novel molecules for the development of new drug candidates to treat life threatening infections and other human disorders. To identify such potential drug candidates from nature, different methods have been developed and routinely used in natural product discovery laboratories.

Design challenge:

Customer has shared a proprietary anti-aspergillus compound obtained from vegetative origin under NDA. The objective of the present study was to develop NCE's with at least anti-aspergillus activity using given natural product.

Retro-synthetic fragmentation approach was followed to simplify the given tetra cyclic natural product structure. These fragments were searched for similarity with known anti-fungals to get class of anti-fungal compounds with their anti-candida as well as anti-aspergillus activities. A ligand based drug design approach was then utilized to develop new potential anti-fungal candidates.

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VLifeMDS

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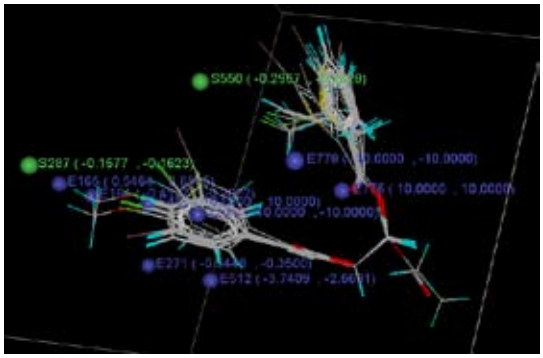

Fig. A: Plot of kNN MFA identified key steric and electrostatic field points

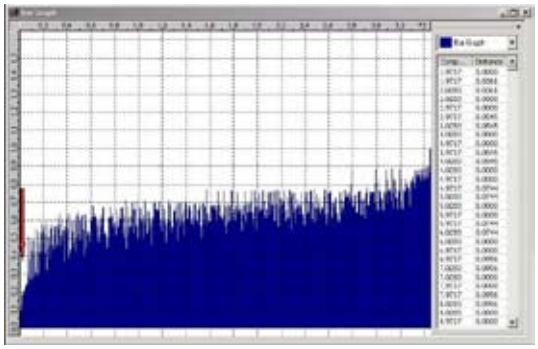

Fig. B: Diversity plot of the combinatorial library generated library

Project work:

The study was done on a series of substituted-lead derivatives with anti-fungal activity reported against yeast (i.e. *candida* species) and filamentus fungus (*aspergillus* species). The activity was expressed in terms of IC50 values.

Both 2D QSAR and 3D QSAR approaches were followed for building quantitative models. For 2D QSAR analysis, various 2D descriptors were calculated. Quantitative models were built using simulated annealing variable selection coupled with regression method.

For kNN MFA (3D QSAR) analysis, a template based alignment of lower energy conformers of the set of molecules was used.

Result analysis:

The above study resulted in statistically significant 2D QSAR and 3D QSAR models for both anti-candida and anti-aspergillus activities.

Developed kNN MFA models revealed various molecular features requirement for both the activities and thus aided in generation of diverse combinatorial library. The generated library was then screened using QSAR models. 4 of 45 suggested novel molecules were found to be potent with experimental activity (IC50 <1µg/ ml) against both *candida* and *aspergillus*.

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