# Case study: Pharmaceutical

## Development of dual active antifungals

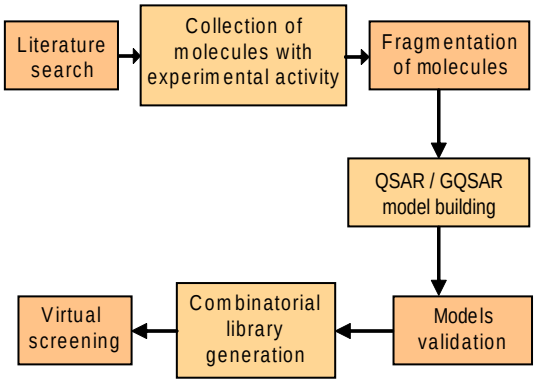
Dr. Subhash Ajmani, Kamlakar Jadhav

### Customer type

**A leading pharmaceutical company**

### Software modules

**QSARPlus**
**GQSAR**
**LeadGrow**
**VLife Engine**




### Application

**Lead optimization**

### Techniques

**QSAR analysis**
**GQSAR analysis**
**Combinatorial library**
**Virtual screening**

## Background:

Invasive fungal infections are increasing in prevalence and severity causing significant morbidity and mortality in patients whose immune systems have been compromised by disease or medical treatment. Nearly all of these infections are caused by the *Candida* and *Aspergillus* species. Thus, there is a significant need for novel anti-fungal agents with broad spectrum of activity.

## Design challenge:

The mandate given by the customer was to design novel azole based molecules with both anti-candida and anti-aspergillus activities. This was translated into a main objective of developing a dual-response QSAR model and thus to get an insight into the structural sites/ features influencing both activities.

This study also involved the application of the unique GQSAR method developed by us.

GQSAR provides flexibility to establish relationship of activity with molecular sites/ features of interest and to capture interaction amongst them.

GQSAR uses descriptors evaluated for the predefined set of fragments (groups) of a molecule rather than the whole molecule. This method provides models with the predictive ability similar or better to conventional methods. In addition, it provides hints for sites of improvement and thus to design new molecules.

**VLife Sciences Technologies Pvt. Ltd.**
Pride Purple Coronet, 1st Floor,
Baner Road, Pune - 411 045, India

Phone: +91 20 2729 1590
Web: www.vlifesciences.com
E-mail: products@vlifesciences.com

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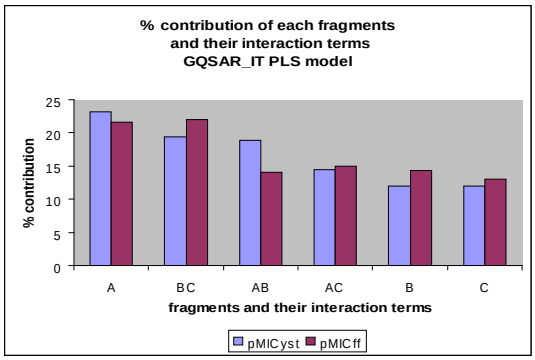


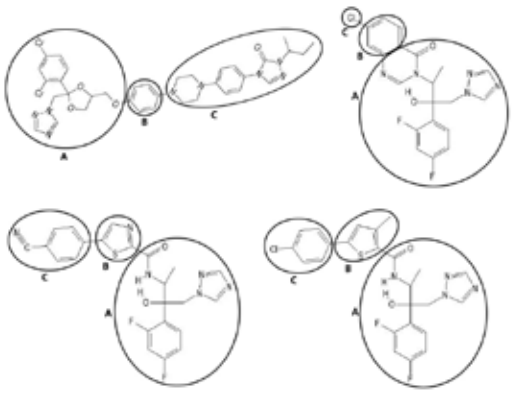

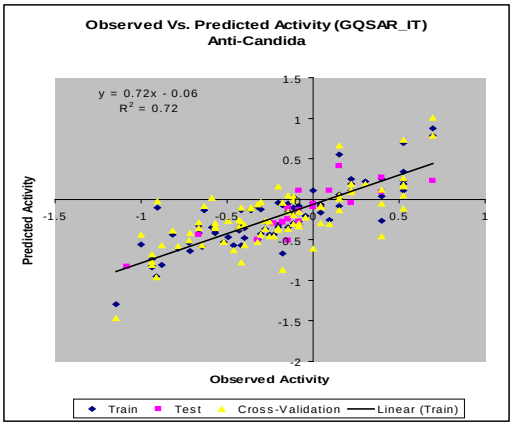


## Project work:

The study was done on a series of Heterocyclecarboxamide and 3-substituted-4(3H)-quinazolinones derivatives along with other standard anti-fungal molecules such as itraconazole, voriconazole etc.

This non-congeneric set of molecules was fragmented with a predefined set of chemical rules into three fragments. Various 2D descriptors were calculated and QSAR models were developed using stepwise and simulated annealing variable selection along with multiple regression or PLS regression methods.

## Result analysis:

QSAR and GQSAR models for individual activity and dual response to anti-candida and anti-aspergillus were generated using simple 2D descriptors.

Dual-response QSAR/ GQSAR models allowed the investigation of comparative molecular site/ features required for both these responses. This information led to the generation of combinatorial library and its screening leading to novel potent molecules with dual activity.

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