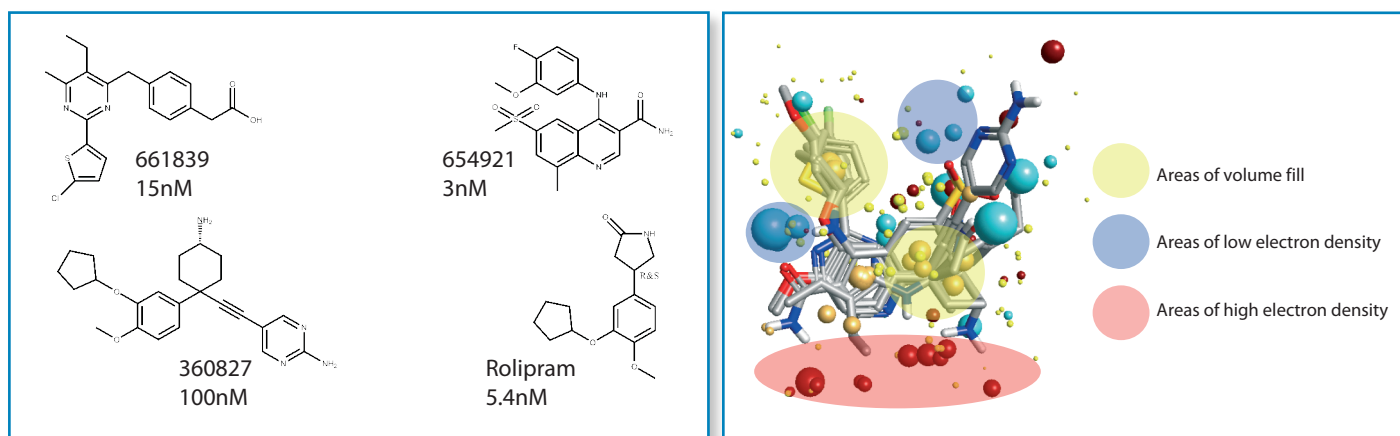


CASE STUDY

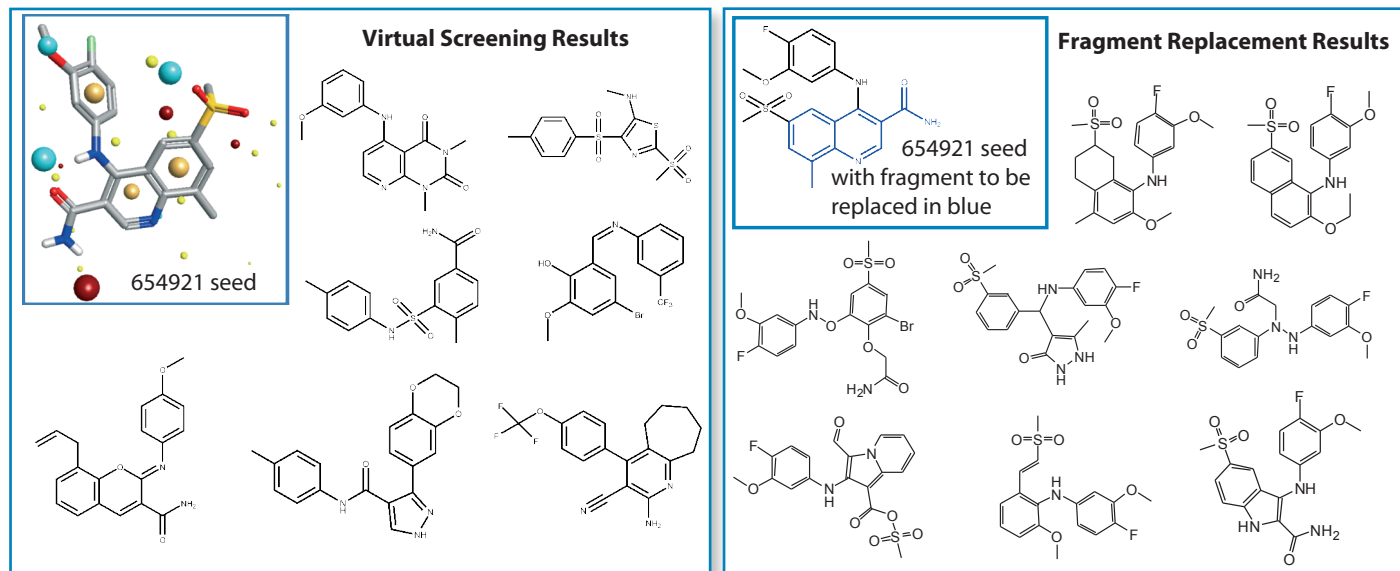
Novel Lead Generation - PDE4B inhibitors for COPD

Chronic obstructive pulmonary disease (COPD) is a common, progressive disorder of increasing prevalence in industrialized countries. COPD is an all-inclusive term that refers to a set of symptoms including chronic cough, expectoration, exertional dyspnea and a significant, progressive reduction in expiratory airflow that may or may not be partly reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Several drugs have been marketed so far, and several molecular targets have been considered so far for therapeutic intervention.

This project explored the SAR of known PDE4B inhibitors extracted from Thomson Reuters' Integrity database and used this to derive models that enabled scaffold hopping. We first assumed that all molecules act at the same site on the same target. Cresset's FieldTemplater used the five chosen compounds above to find a common Field pattern across 200 representative conformations of each compound.



Two separate experiments were then performed using the most active 654921 seed structure; firstly a virtual screening to identify bioisosteres from the Cresset databases (containing 4.5M drug and drug-like compounds), and secondly a fragment replacement of a section of the 654921 molecule. Some of the results of these experiments are shown below:



The project reported in this case study was originally presented as a joint poster between Thomson Reuters Scientific and Cresset at the EFMC Conference in Brussels in Sep 2010
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For more information please visit www.cresset-group.com