

CASE STUDY

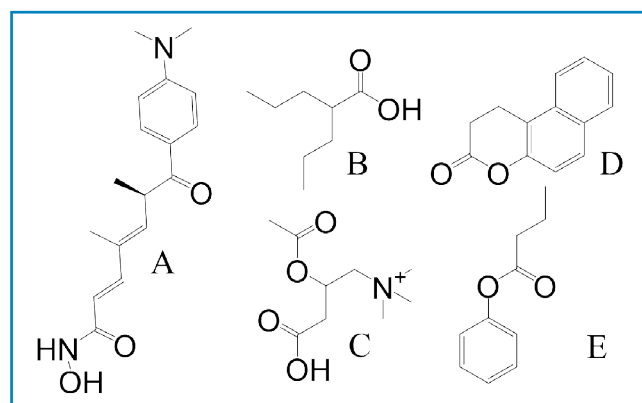
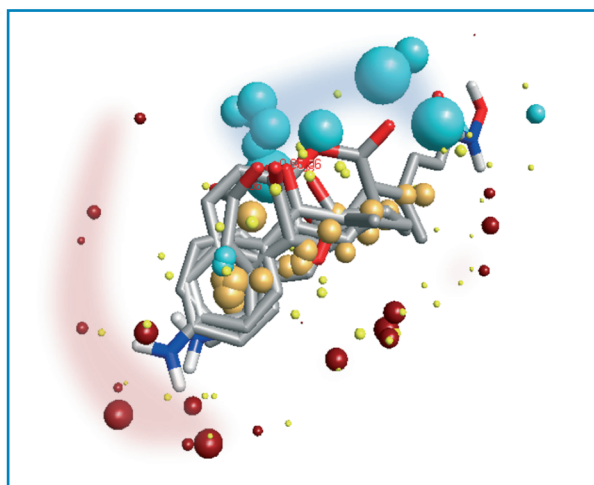
Gene Control - Reactivating the FMR1 Fragile-X Gene



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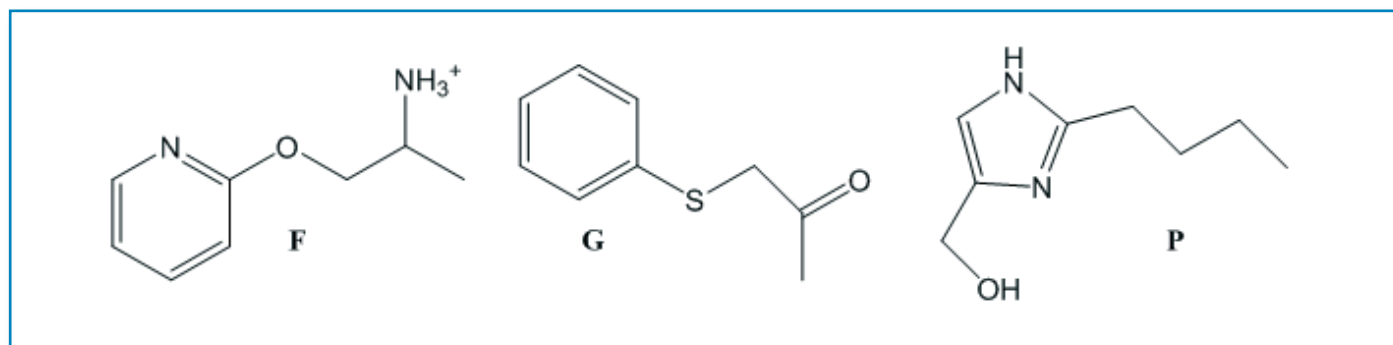
Fragile-X syndrome affects approximately 1 in 4,000 people and results in a range of physical and mental defects. The FMR1 gene codes for a protein that may control the development and subsequent plasticity of synapses. FMR1 is turned off in sufferers by histone methylation and can be reactivated by histone deacetylase (HDAC) inhibitors. Our collaborators were interested in finding new chemotypes for FRM1 reactivation and provided five known diverse HDAC inhibitors (opposite) as starting blocks for Cresset's Field technology.



Despite the diversity of the structures, FieldTemplater yielded a consistent Field template (opposite) for all five compounds. This Field template revealed the likely bioactive conformations of the five starting structures when bound to the protein target (even though an X-ray structure for the target was not available).

The Field patterns from molecules A (Trichostatin-A), C (L-acetylcarnitine) and D (Splitomycin) were used as seeds to run three FieldScreen searches on our Field database of 3.4M commercially available molecules. The structures of B (Valproate) and E (Phenylbutyrate) possessed insufficient Field information to be useful as FieldScreen seeds.

The top 200 molecules with the most similar Field patterns to the three seed structures were extracted from each of the searches (giving 600 hits in all). 18 candidates were purchased on the basis of best Field and volume fit to its seed, as well as structural diversity, ease of chemical modification and intuitive appeal. After *in-vitro* testing, three compounds showed activity around 10µM (see below), one of which has been synthesized in bulk for further investigation. Compounds F and G were detected in FieldScreen using the L-acetylcarnitine seed and compound P came out of the search using the Splitomycin seed.



The striking feature of this project is the way Field analysis has taken a set of diverse molecules and produced a further active set which are very different from the seeds but retain essential structural feature in very different arrangements. This result and the opportunity it brings could not be attained by any form of structural comparison.