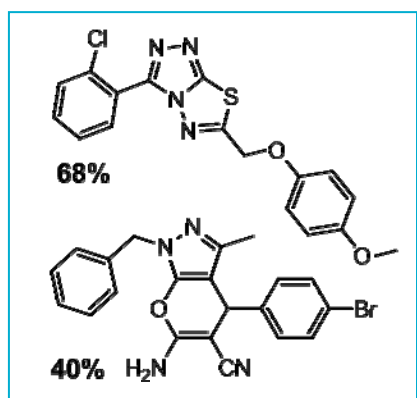


Kinase Inhibition - New Chemotypes for p38 MAP Kinase

p38 mitogen-activated protein kinase (MAPK) has a vital role in the production of pro-inflammatory cytokines such as TNF- α and IL-1 β . The inhibition of this enzyme has potential therapeutic value against overactive immune responses associated with rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel diseases.

To discover novel p38 inhibitors, three ligands in their bioactive conformations were extracted from the available p38 complex X-ray structures. Molecular Fields were added and used as seeds to search our Field database, which at that time was comprised of 2M commercially available compounds (Figure 1).

58 diverse chemotypes were selected for biological testing, using Field similarity to known inhibitors. Structures with a similar scaffold to previously reported p38 inhibitors were first removed. Of these 11 (19%) showed $\geq 20\%$ inhibition of p38 at 10 μ M. Analogues of two distinct chemical series (shown below with their % inhibition) from the 11 actives were chosen for synthesis on the basis of patentability and chemical tractability. The testing of these compounds resulted in a potential lead compound with a pIC₅₀ of 6.4.¹



Further modelling with FieldAlign afforded a likely binding model for the thiazidazole series. Opposite is the thiazidazole above, overlaid in Field space with the ligand embedded in solvent accessible surface of the p38/ligand complex X-ray structure 1M7Q.pdb.

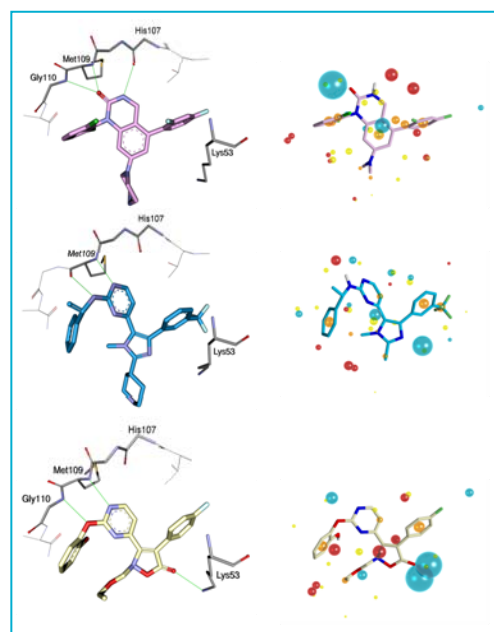
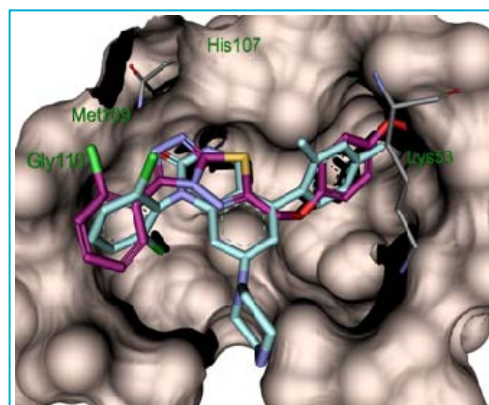


Figure 1. Ligands from PDB codes 1M7Q (top), 1OUK (middle) and 1YW2 (bottom).

Left: ligand as present in the PDB file showing the selected protein residues and H-bonds

Right: ligand used as search query including field point patterns.

Key to Field point colors:
Blue = Negative, Red = Positive,
Orange = Hydrophobic, Yellow = Surface.



¹ Cheeseright, T. C.; Holm, M.; Lehmann, F.; Luik, S.; Göttert, M.; Melville, J. L.; Laufer, S. Novel Lead Structures p38 MAP Kinase via FieldScreen Virtual Screening. *J. Med. Chem.* **2009**, *52*, 4200-4209.