Discovery of small molecule inhibitors of Fascin 1 using fragment-based drug discovery

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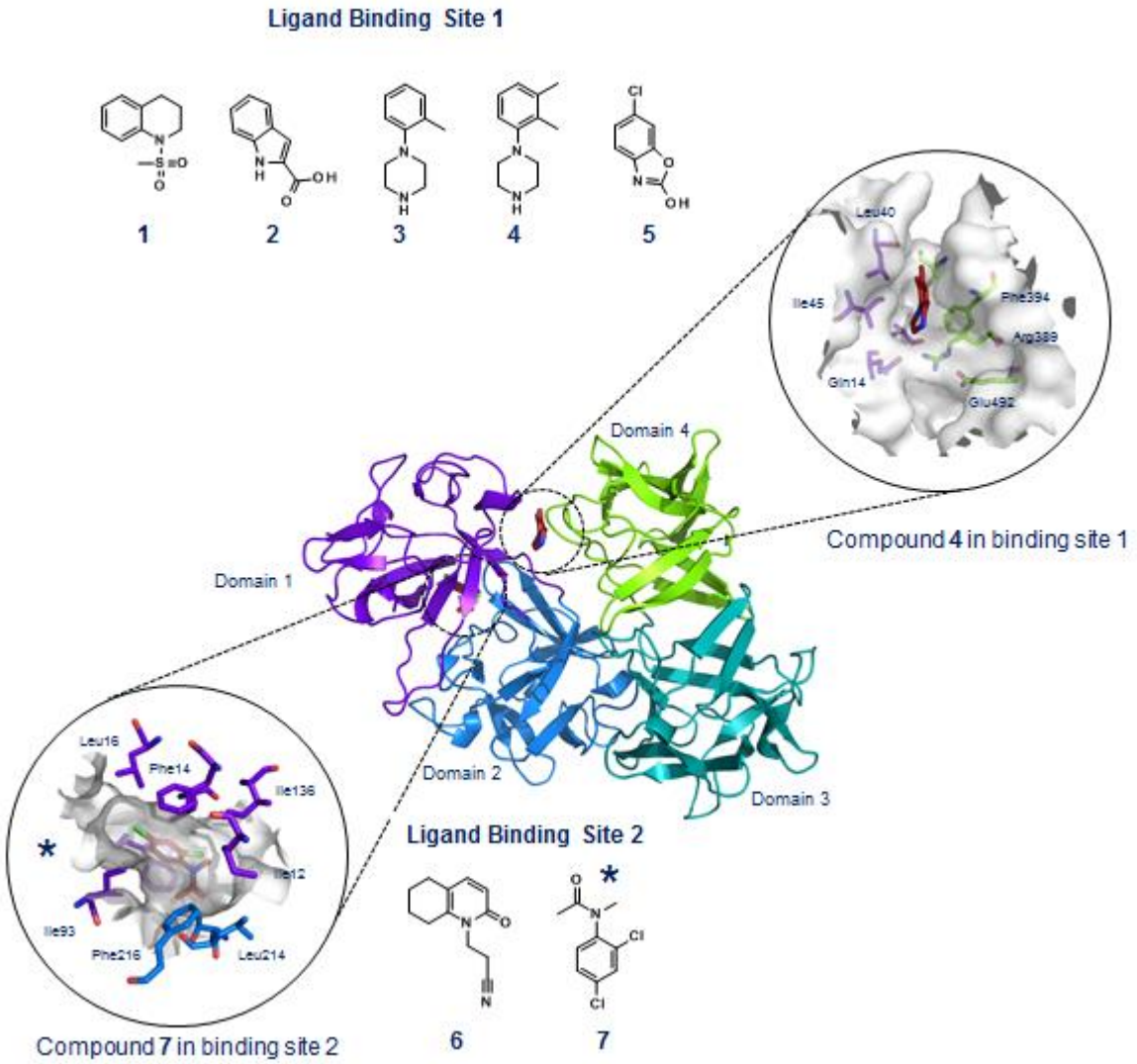
Fascin 1 binds and cross-links filamentous actin (F-actin) into parallel bundles that are used in the formation of dynamic cellular protrusions (such as lamellipodia and filopodia) used during cell migration, and in the formation of invadopodia used by tumor cell lines to degrade the tumor extracellular matrix (ECM). Fascin 1 is overexpressed in a range of aggressive and invasive tumors and is believed to play a critical role in cancer cell metastasis. Utilising our in-house fragment collection (~1000 compounds) coupled with biophysical assays and X-ray crystallography, we identified novel fascin 1 inhibitors binding in multiple ligand binding sites the best of which show nanomolar affinity in biochemical binding and bundling assays. We will show several series of compounds binding at different sites, finally settling on compounds which caused a large conformational twist of one of the domains.[1] BDP-00013176 (K_d=85nM, IC_{50}=240nM) has activity in a number of cell based invasion assays including both 2D and 3D cultures, demonstrating the potential of fascin inhibition as a valid target for preventing invasion and metastasis.



(1) Francis *et al.* (2019) Structure-based design, synthesis and biological evaluation of a novel series of isoquinolone and pyrazolo[4,3-c]pyridine inhibitors of fascin 1 as potential anti-metastatic agents. *Biorg Med Chem Lett* ***8****,1023-1029*