TGFbR1 ATP Binding Site: a Magnet for Fragments

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Fragments have been shown to be a useful starting point for medicinal chemistry programs. The kinase domain of TGFβR1 was screened by thermal shift assay for binding to fragments from the BMS fragment deck with a 1° C shift as a cutoff. Approximately 400 hits were found with the largest shift being 9.5° C followed by a continuum starting at 6.4° C. The top 91 hits (≥ 2.6° C) were then soaked into uncomplexed TGFβR1 kinase domain crystals. Previous experience had shown that a hit rate in crystallography as high as 20% for compounds pre-screened by a biophysical method was exceptional, although another kinase domain had shown a 50% hit rate, but TGFβR1 kinase domain crystals bound 90% of the top hit compounds with all compounds binding in the ATP binding site. An analysis of the various binding modes observed will be presented.