Discovery and structure of a new inhibitor scaffold of the autophagy initiating kinase ULK1

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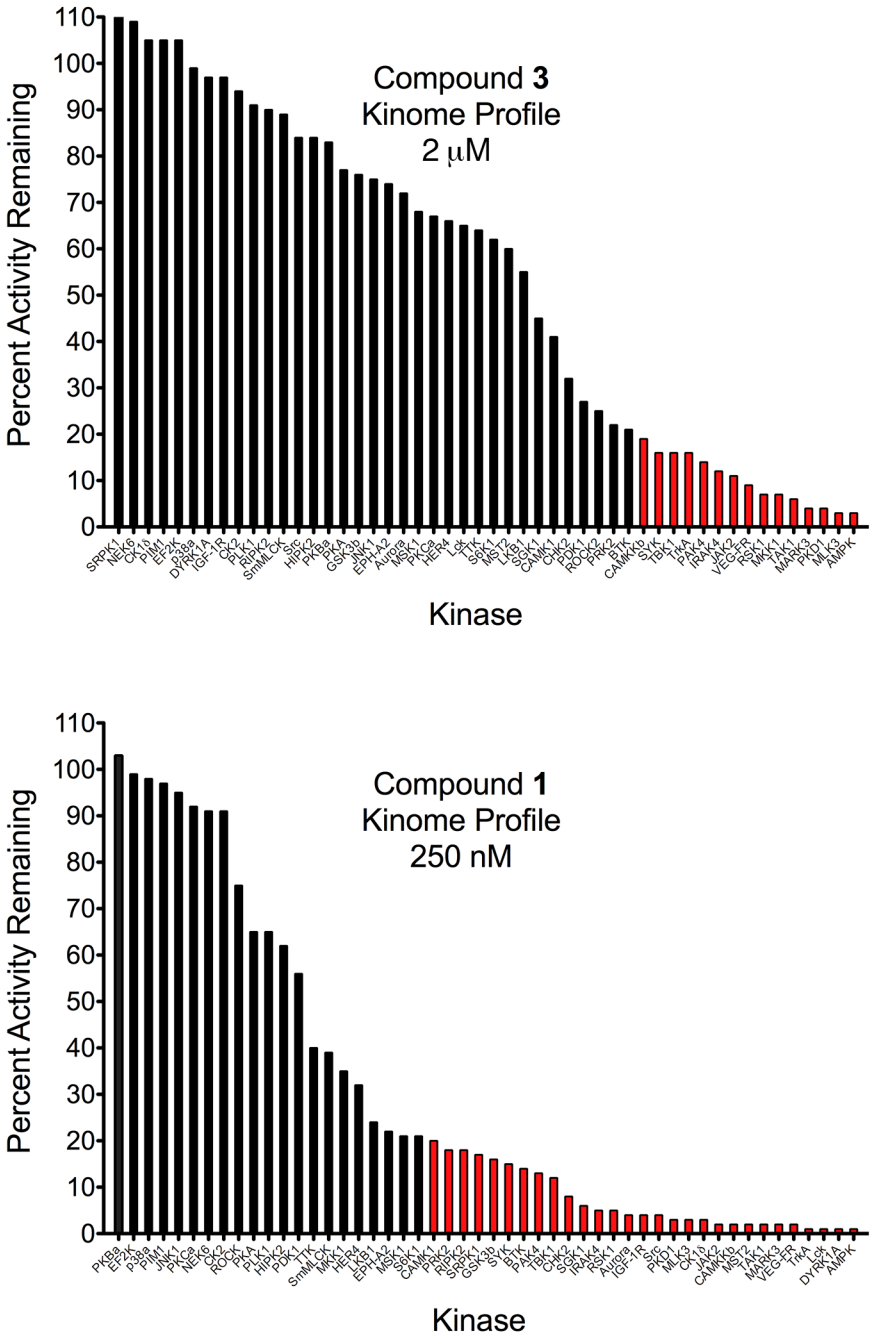
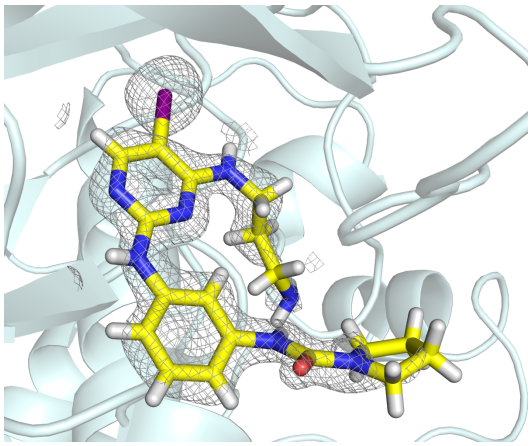
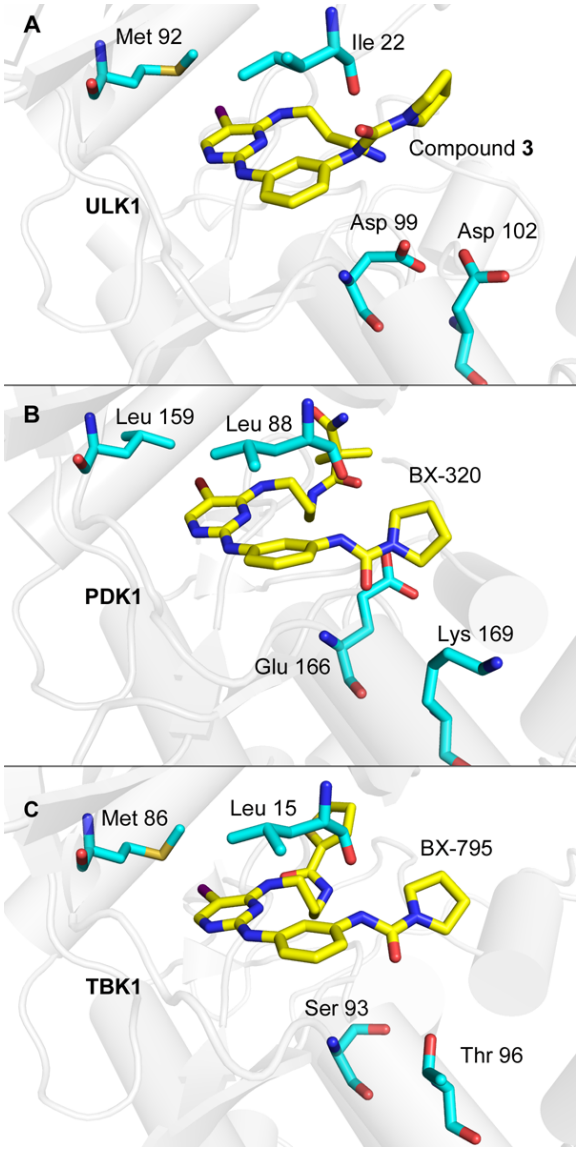
Supplementary Information



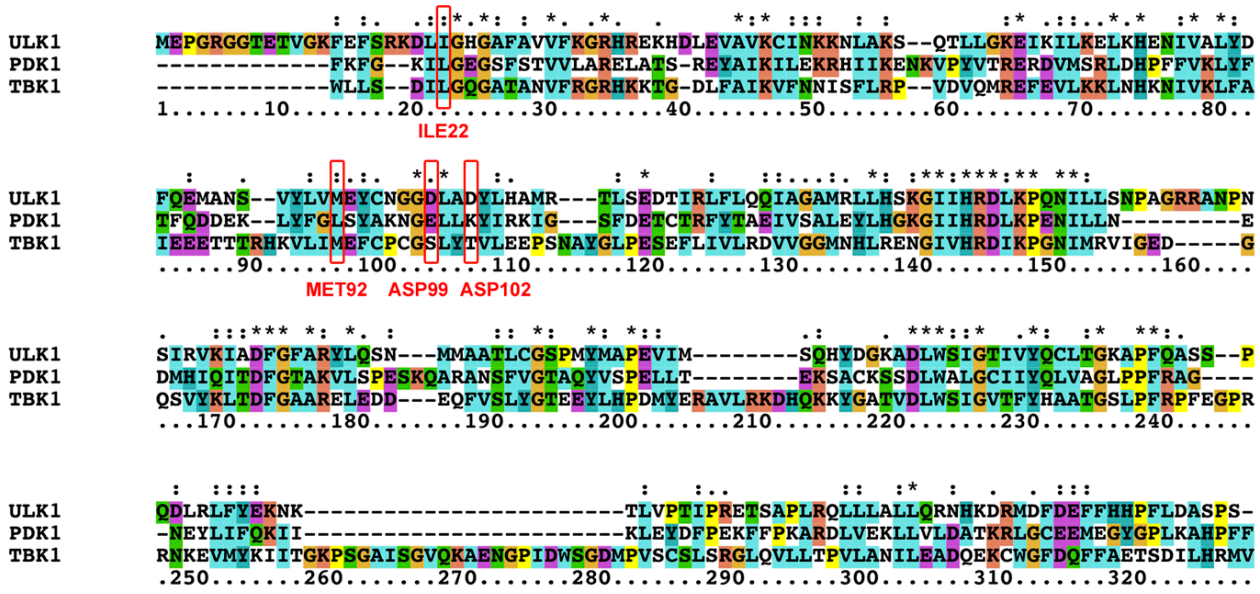
Supplementary Figure 1. Kinome profiling of compounds 3 and 1. (Top) 50 kinases were tested with 2 μM compound **3**. Kinases that were inhibited on average by 80% or more at this concentration are highlighted in red. (Bottom) For comparison, our previously reported profiling of compound **1,** tested at 250 nM, is shown.



Supplementary Figure 2. Compound 3 bound to ULK1. The electron density is shown as an Fo-Fc omit map, contoured at 3σ. The weaker density around the pyrrolidine group suggests its flexibility within the active site in this structure.



Supplementary Figure 3. Structures of kinases bound to the BX-795 scaffold. Key residues that are in close proximity to the inhibitor and show variability between the three kinases are highlighted. The inhibitor is shown in yellow and the kinase sidechains in cyan. (A) Structure of ULK1 (this study). Hydrogen atoms have been omitted for clarity. (B) Structure of PDK1[1]. (C) Structure of TBK1[2].



Supplementary Figure 4. Alignment of ULK1, PDK1, and TBK1. Residues mentioned in the text are highlighted with red boxes. The labels refer to the residue in ULK1. Alignment was performed using ClustalX[3].

References

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[3] F. Jeanmougin, J.D. Thompson, M. Gouy, D.G. Higgins, T.J. Gibson, Multiple sequence alignment with Clustal X, Trends Biochem. Sci., 23 (1998) 403-405.