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[Protein Sci.](#) 2010 Mar;19(3):429-39. doi: 10.1002/pro.321.

Structures of human Bruton's tyrosine kinase in active and inactive conformations suggest a mechanism of activation for TEC family kinases

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Affiliations

PMID: 20052711 PMCID: [PMC2866269](#) DOI: [10.1002/pro.321](#)

Abstract

Bruton's tyrosine kinase (BTK), a member of the TEC family of kinases, plays a crucial role in B-cell maturation and mast cell activation. Although the structures of the unphosphorylated mouse BTK kinase domain and the unphosphorylated and phosphorylated kinase domains of human ITK are known, understanding the kinase selectivity profiles of BTK inhibitors has been hampered by the lack of availability of a high resolution, ligand-bound BTK structure. Here, we report the crystal structures of the human BTK kinase domain bound to either Dasatinib (BMS-354825) at 1.9 Å resolution or to 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolopyrimidin-7-yl-cyclopentane at 1.6 Å resolution. This data provides information relevant to the development of small molecule inhibitors targeting BTK and the TEC family of nonreceptor tyrosine kinases. Analysis of the structural differences between the TEC and Src families of kinases near the Trp-Glu-Ile motif in the N-terminal region of the kinase domain suggests a mechanism of regulation of the TEC family members.

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Figures

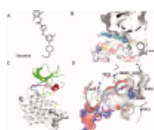


Figure 1 BTK-KD Y551E/Dasatinib crystal structure. A:...

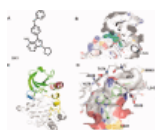


Figure 2 BTK-KD/B43 crystal structure. A: Chemical...

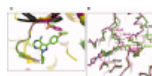


Figure 3 Differences between the "inactive" B43...



Figure 4 Mechanism of kinase activation. A:...

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PMID- 20052711
OWN - NLM
STAT- MEDLINE
DCOM- 20100520
LR - 20240516
IS - 1469-896X (Electronic)
IS - 0961-8368 (Print)
IS - 0961-8368 (Linking)
VI - 19
IP - 3
DP - 2010 Mar
TI - Structures of human Bruton's tyrosine kinase in active and inactive conformations suggest a mechanism of activation for TEC family kinases.
PG - 429-39
LID - 10.1002/pro.321 [doi]
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 AU - Baker DP
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 AU - Silvian LF
 LA - eng
 SI - PDB/3GEN
 SI - PDB/3K54
 PT - Journal Article
 PL - United States
 TA - Protein Sci
 JT - Protein science : a publication of the Protein Society
 JID - 9211750
 RN - 0 (4-amino-5-(4-phenoxyphenyl)-7H-pyrrolopyrimidin-7-ylcyclopentane)
 RN - 0 (Protein Kinase Inhibitors)
 RN - 0 (Pyrimidines)
 RN - 0 (Pyrroles)
 RN - 0 (Thiazoles)
 RN - EC 2.7.1.- (Tec protein-tyrosine kinase)
 RN - EC 2.7.10.1 (Protein-Tyrosine Kinases)
 RN - EC 2.7.10.2 (Agammaglobulinaemia Tyrosine Kinase)
 RN - EC 2.7.10.2 (BTK protein, human)
 RN - EC 2.7.10.2 (Btk protein, mouse)
 RN - RBZ1571X5H (Dasatinib)
 SB - IM
 MH - Agammaglobulinaemia Tyrosine Kinase
 MH - Amino Acid Sequence
 MH - Crystallography, X-Ray
 MH - Dasatinib
 MH - Enzyme Activation
 MH - Humans
 MH - Molecular Sequence Data
 MH - Protein Conformation
 MH - Protein Kinase Inhibitors/chemistry

MH - Protein-Tyrosine Kinases/antagonists & inhibitors/*chemistry/*metabolism
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MH - Pyrroles/chemistry
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PMC - PMC2866269
EDAT- 2010/01/07 06:00
MHDA- 2010/05/21 06:00
PMCR- 2011/03/01
CRDT- 2010/01/07 06:00
PHST- 2010/01/07 06:00 [entrez]
PHST- 2010/01/07 06:00 [pubmed]
PHST- 2010/05/21 06:00 [medline]
PHST- 2011/03/01 00:00 [pmc-release]
AID - 10.1002/pro.321 [doi]
PST - ppublish
SO - Protein Sci. 2010 Mar;19(3):429-39. doi: 10.1002/pro.321.