## Proposed EC/sub-subclass:

Not provided in the source material.

## Accepted name:

Bruton’s tyrosine kinase

## Synonyms:

BTK; Bruton tyrosine kinase (no additional synonyms were listed in the source material).

## Phylogeny

BTK belongs to the Tec family of non-receptor tyrosine kinases (with ITK, BMX, TEC and TXK) and is evolutionarily conserved across vertebrates (Singh et al., 2018; McDonald et al., 2021). Large-scale kinome analyses place BTK in a distinct branch from the Src, AGC and CMGC kinase families, and its multidomain organisation distinguishes it from receptor tyrosine kinases and other non-receptor classes (Hendriks et al., 2014).

## Reaction catalyzed

ATP + [protein]-tyrosine ⇌ ADP + H⁺ + [protein]-O-phosphotyrosine (Buggy & Elias, 2012; Wen et al., 2021).

## Cofactor requirements

Mg²⁺ is required for ATP coordination and phosphoryl transfer (Xing & Huang, 2014).

## Substrate Specificity

BTK phosphorylates tyrosine residues in proteins engaged in B-cell receptor and Toll-like receptor signalling. Documented physiological substrates include PLCγ2, BLNK, TIRAP and NLRP3, indicating that recognition depends on both local sequence and protein-protein interaction determinants (Buggy & Elias, 2012; Zain & Vihinen, 2021; Singh et al., 2018).

## Structure

BTK is modular: PH–TH (zinc-binding)–SH3–SH2–kinase domains (Lou et al., 2012; Xing & Huang, 2014).  
• The PH domain binds PIP₃ to target BTK to the plasma membrane (Buggy & Elias, 2012).  
• Activation loop Tyr551 and autophosphorylation site Tyr223 (in SH3) regulate activity (Xing & Huang, 2014).  
• Cys481 in the catalytic cleft is the covalent binding site for several inhibitors (Xing & Huang, 2014).  
• Crystal structures show active and “αC-helix-out” inactive conformations, highlighting flexibility of the αC-helix and DFG motif (Xing & Huang, 2014).

## Regulation

Activation is initiated by phosphorylation of Tyr551 by upstream kinases such as SYK or LYN, followed by BTK autophosphorylation on Tyr223, which stabilises the active state (Buggy & Elias, 2012; Singh et al., 2018). BTK also operates as a scaffold, inducing phosphorylation-dependent degradation of TIRAP to modulate TLR9 signalling and phosphorylating NLRP3 during inflammasome activation (Buggy & Elias, 2012; McDonald et al., 2021). These mechanisms ensure stimulus-dependent and temporally restricted activity.

## Function

BTK is indispensable for adaptive and innate immune signalling.  
• B cells – transduces B-cell receptor signals that govern development, proliferation, survival and NF-κB activation via PLCγ2 and PKC-dependent pathways (Buggy & Elias, 2012; Wen et al., 2021).  
• Innate immunity – modulates Toll-like receptor signalling and cytokine production (McDonald et al., 2021; Weber et al., 2017).  
• Inflammasome – phosphorylates and promotes activation of NLRP3 (Zain & Vihinen, 2021; McDonald et al., 2021).  
Expression is high in B cells, mast cells, monocytes and macrophages, but minimal in T cells and plasma cells (Crofford et al., 2016; Hendriks et al., 2014).

## Inhibitors

Irreversible covalent inhibitors (e.g., ibrutinib) bind Cys481 and produce sustained BTK inhibition in B-cell malignancies. Second-generation inhibitors (acalabrutinib, zanubrutinib) improve selectivity while retaining efficacy (Xing & Huang, 2014; Wen et al., 2021; Ringheim et al., 2021).

## Other Comments

Loss-of-function mutations cause X-linked agammaglobulinemia, whereas BTK overactivation contributes to B-cell cancers and autoimmune diseases. Its dual role in BCR and TLR pathways and in NLRP3 regulation makes BTK a broad therapeutic target, and ongoing work is refining substrate mapping and allosteric control (Buggy & Elias, 2012; Singh et al., 2018; Rozkiewicz et al., 2023).

## References

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