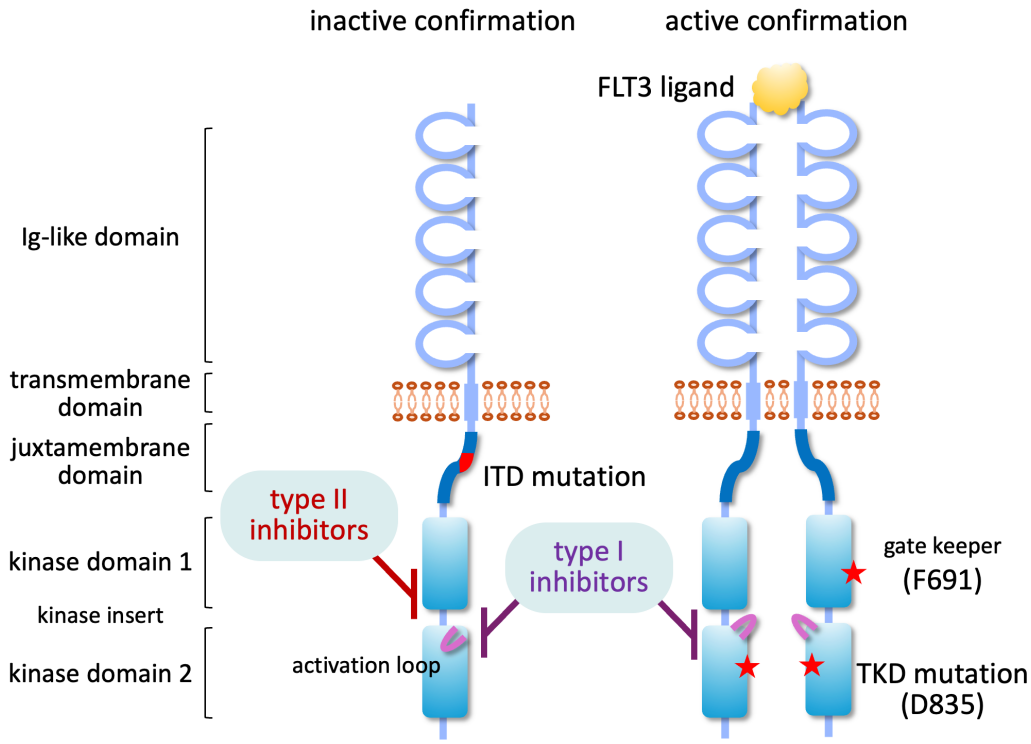
Supplementary Figure S1



Domain architecture of FLT3, highlights common ITD and TKD, and depicts representative inhibitor binding modes

FLT3 consists of five extracellular Ig-like domains, a juxtamembrane domain (JMD), two tyrosine kinase domains (TKDs), and a C-terminal region. Ligand (FL) binding induces dimerization, TKD phosphorylation, and downstream signaling essential for hematopoietic cell differentiation, proliferation, and stem cell self-renewal. In leukemic cells, FL stimulation promotes proliferation and suppresses apoptosis. Activating mutations include ITD in the JMD (20–28%) and TKD mutations such as D835 (5–10%), both leading to constitutive signaling. FLT3 inhibitors competitively bind to the ATP-binding site, thereby blocking kinase activity and inducing apoptosis. However, the conformation of the ATP-binding pocket differs between inactive and active states. Type I inhibitors bind either the ATP-binding site of constitutively active receptor (via ITD or TKD mutations) or the activation loop located between the TKDs, thereby blocking signaling. Type II inhibitors bind to a region adjacent to the ATP-binding site in the inactive kinase conformation, thereby inhibiting phosphorylation driven by ITD mutations. The F691L gatekeeper mutation arises in TKD1 and confers resistance to many FLT3 inhibitors, making it a critical therapeutic challenge.