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Design, synthesis and biological evaluation of 7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine derivatives as selective Btk inhibitors with improved pharmacokinetic properties for the treatment of rheumatoid arthritis

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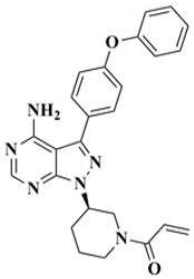
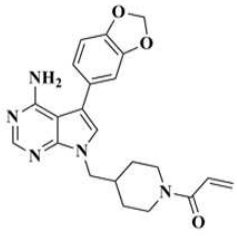


Ibrutinib
Btk IC_{50} = 0.81 nM
hERG IC_{50} = 0.97 μM
ClogP = 4.07
aqueous solubility < 0.01 mg/ml
F % in rats: 18-23%

structure-based design
PK studies and preliminary druglikeness evaluation



B16
Btk IC_{50} = 21.70 nM
hERG IC_{50} = 11.10 μM
ClogP = 2.53
aqueous solubility ≈ 0.1 mg/ml
F% in SD rat: 49.15%