Kinase inhibitors

Since the original discovery just over 50 years ago that the activity of the enzyme glycogen phosphorylase is regulated by the addition and removal of a phosphate group, reversible phosphorylation has come to be recognized as the major signaling mechanism of the cell. Two key groups of enzymes are involved in this process: kinases, which transfer a phosphate group from ATP to a protein or other biomolecule, and phosphatases, which remove these phosphate groups. The human genome contains approximately 520 protein kinases that transfer phosphates to serine, threonine or tyrosine residues within target proteins. Collectively, these kinases—referred to as the human kinome—play a role in regulating nearly every cellular process.

In 1978, a prominent role for kinases in disease was first recognized when the cancer-causing agent of Rous sarcoma virus, vSrc, was discovered to be a protein kinase. Kinases have now been implicated in nearly every known cancer and in a wide range of other diseases, from neurological to metabolic disorders. However, the race to identify kinase inhibitors as potential drugs has been slow. Vascular endothelial growth factor (VEGF), which was discovered to potently inhibit kinases in cells despite high endogenous ATP concentrations, is one example of an ATP-competitive inhibitor. In the intervening two decades, intensive pharmaceutical, biotechnology and academic research efforts have focused on discovering small-molecule kinase inhibitors, resulting in 11 inhibitors approved for clinical use so far. Notably, imatinib (Gleevec), which was approved for use in the United States in 2001 against a form of leukemia, was the first drug specifically developed to target a kinase.

As a result of these efforts, it has become clear that there are many ways to inhibit a kinase—with inhibitors binding at a variety of locations to both active and inactive kinase conformations. In this primer, we highlight the different mechanisms employed by kinase inhibitors.

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KEY RESOURCES

Modes of kinase inhibition

Type I

Kinases can adopt both active and inactive conformations. In the active conformation, three sequential amino acids (Asp-Phe-Gly, referred to as the DFG motif and shown in pink) in the activation loop are in the ‘DFG-in’ conformation, which allows substrate access to the active site. Type I inhibitors bind in an ATP-mimetic manner to the ATP binding pocket of this DFG-in conformation. These ATP-competitive inhibitors prevent kinase activity by blocking ATP binding. Depicted here is the type I inhibitor PD166326 bound to ABL1 (Protein Data Bank (PDB) code 10PK).

Covalent

Covalent inhibitors identified so far occupy the ATP binding pocket, much like type I inhibitors. Once bound, they form a covalent bond with an active site residue—usually a cysteine. In the case depicted above, the 6-acrylamide group of the 34-JAB inhibitor has reacted with Cys797 in the active site of the epidermal growth factor receptor (EGFR) (PDB code 2J5F).

Type II

In the inactive kinase conformation, the positioning of the DFG motif in the ‘DFG-out’ conformation blocks substrate access to the active site. Type II inhibitors bind to this DFG-out conformation, occupying both the ATP binding site and an adjacent hydrophobic pocket that is created by the movement of the DFG motif. These compounds inhibit kinases by preventing ATP binding and also by stabilizing the inactive kinase conformation. Depicted here is the type II inhibitor imatinib (Gleevec) bound to ABL1 (PDB code 1IEP).

Allosteric

Allosteric inhibitors, or allosteric activators, are ‘non-ATP-competitive’. The compounds bind outside of the ATP binding site at a location in which binding modulates the catalytic activity of the kinase. Allosteric inhibitors have been reported that bind distantly from the kinase domain or very close to the active site. As shown here, PD334581 binds to the DFG-out conformation of MEK2 at an allosteric site near a bound molecule of ATP (PDB code 1S9I).
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