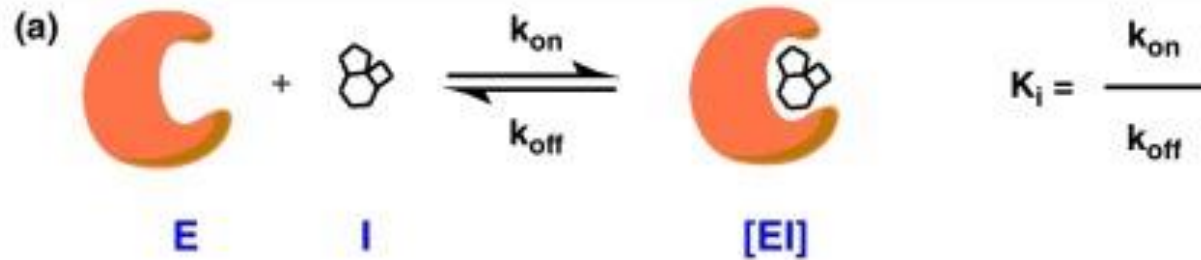




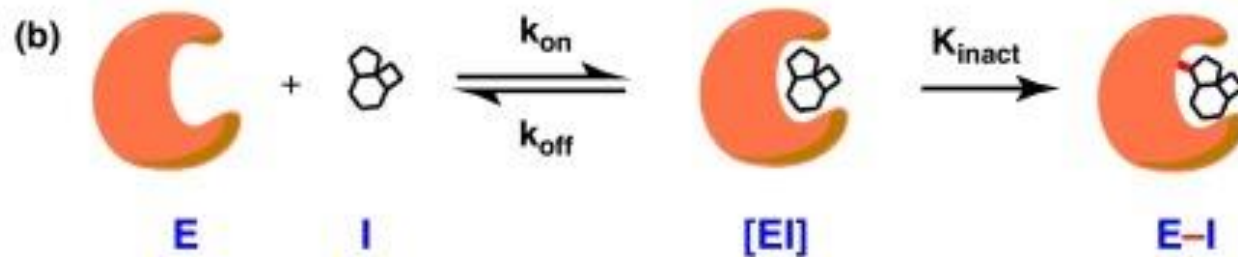
Methods in Drug Development

Covalent Drugs

Principle of covalent drugs

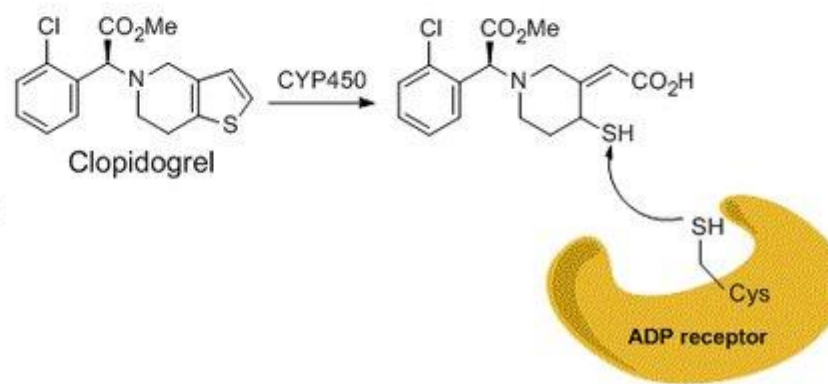
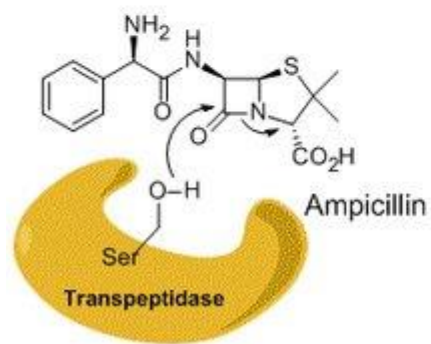
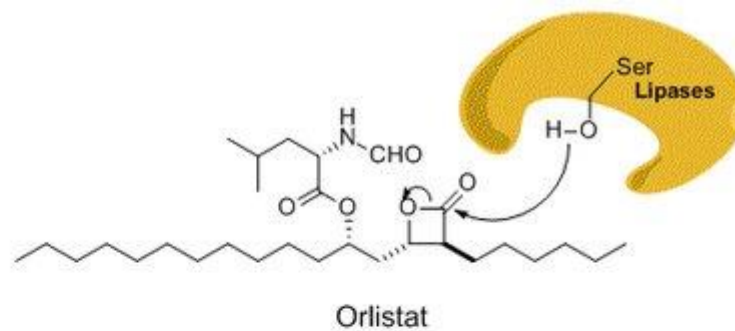
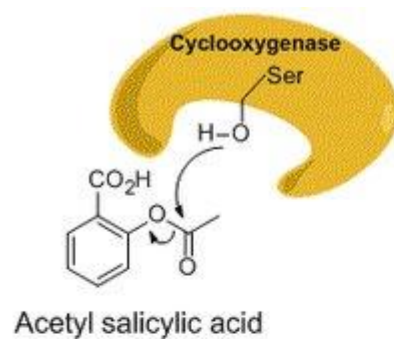


- K_i measures the ability of a non-covalent inhibitor to interact with a target

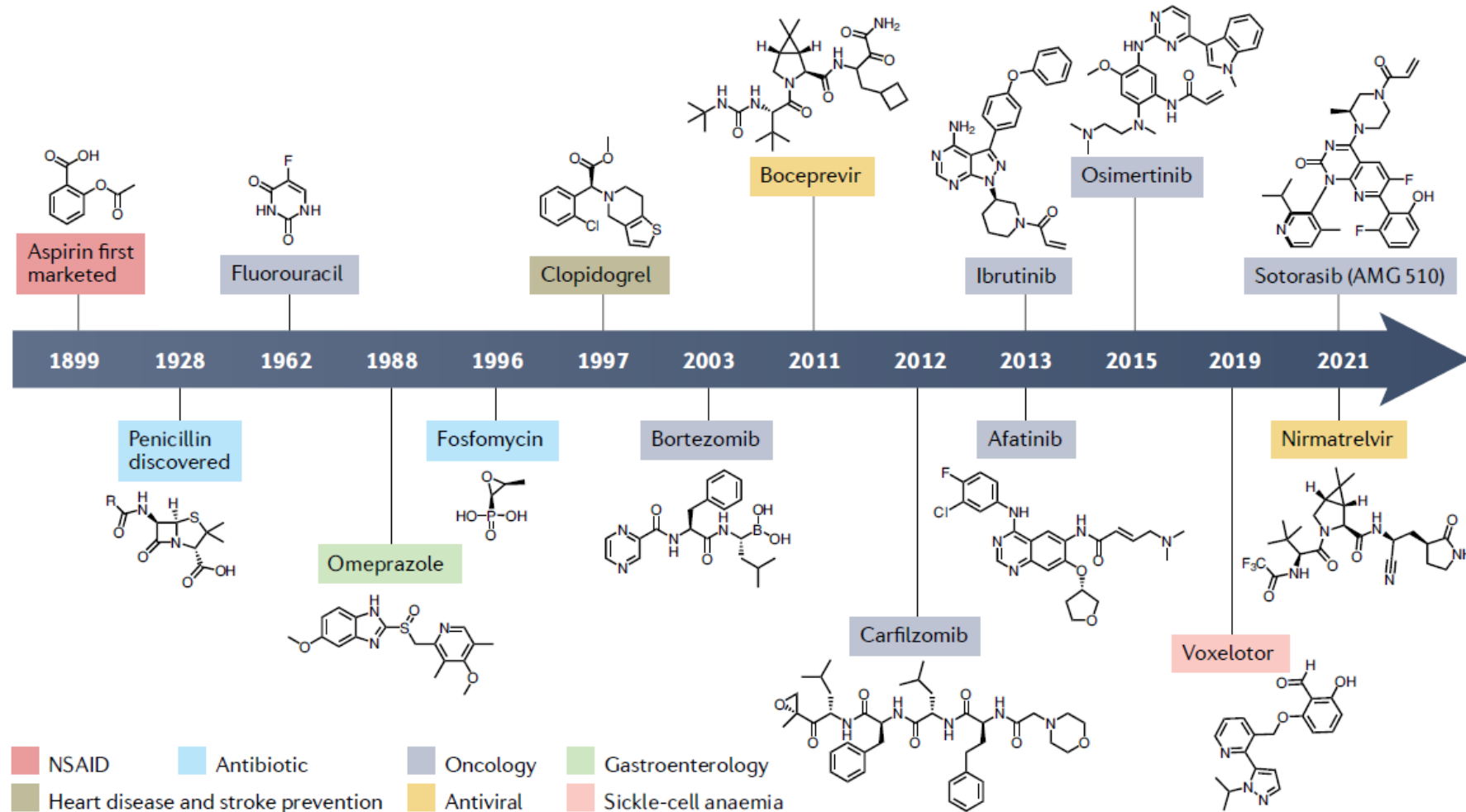


- K_{inact}/K_i describes the ability of a covalent irreversible inhibitor to interact with and neutralize a target

Many «old» drugs are covalent drugs

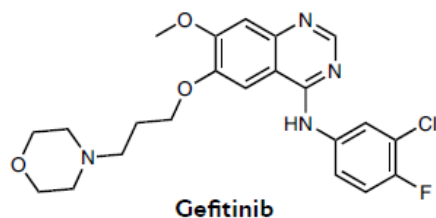
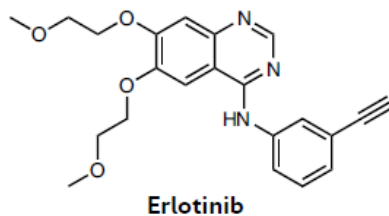


History of covalent drugs

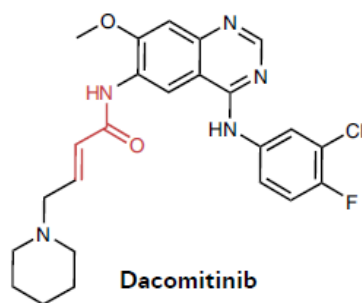
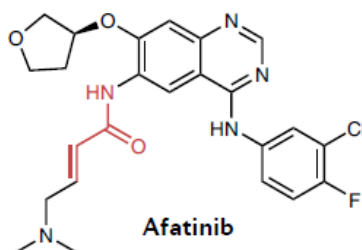
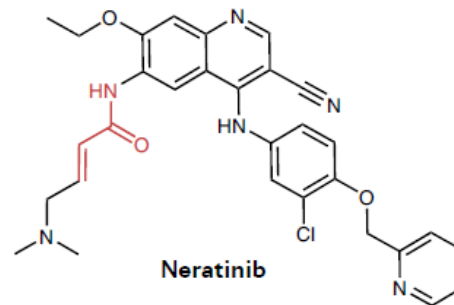


EGFR inhibitors

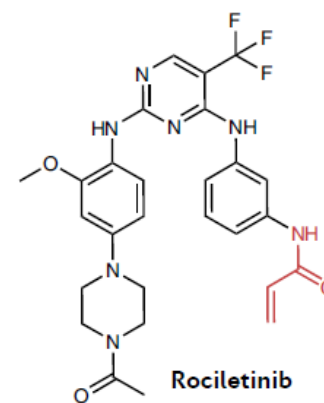
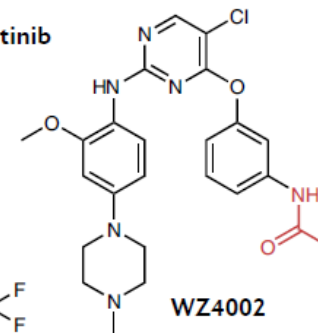
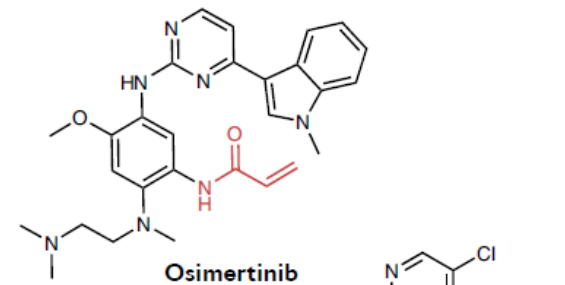
a Reversible first-generation EGFR inhibitors



b Covalent second-generation EGFR inhibitors



c Covalent third-generation T790M mutant-selective EGFR inhibitors



KRAS inhibitor

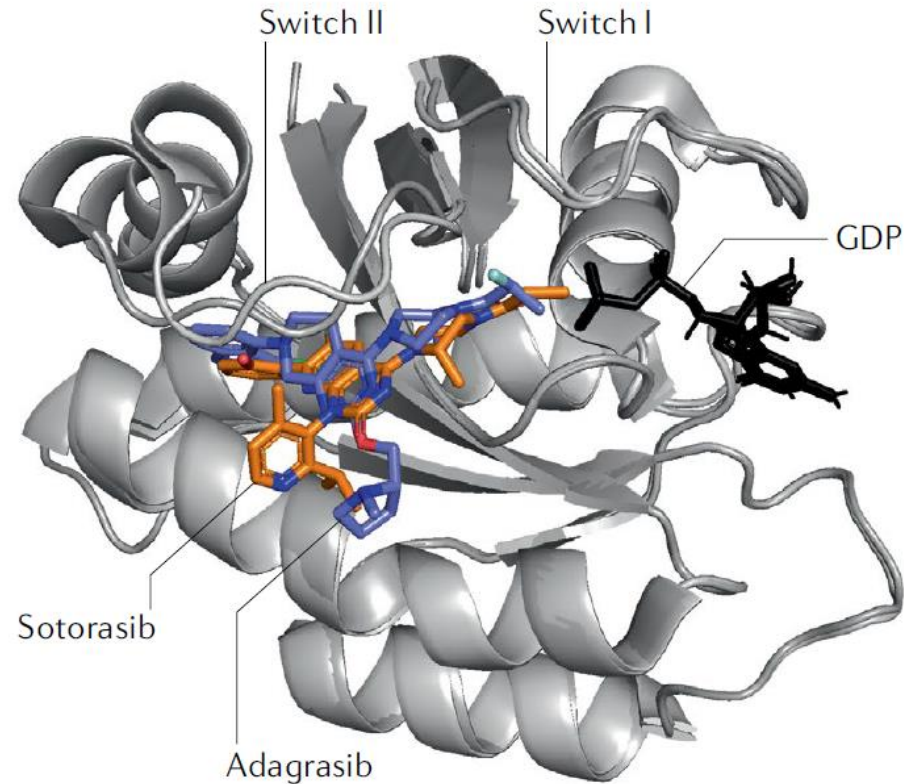
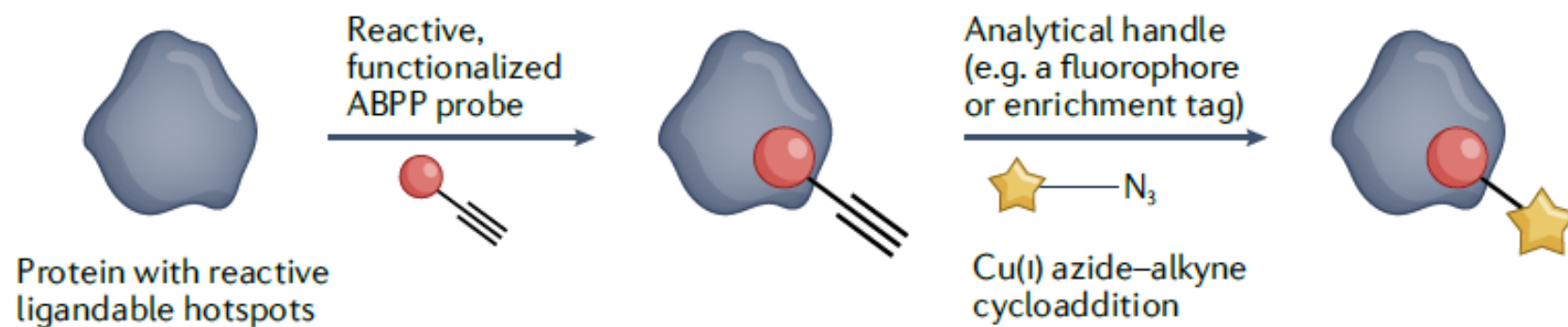


Fig. 3 | **Aligned structures of KRAS(G12C) co-crystallized with adagrasib (MRTX849) and sotorasib (AMG-510).** The covalent inhibitors adagrasib (PDB ID: 6UT0) and sotorasib (PDB ID: 6OIM) are bound to the switch II pocket, which is adjacent to the GDP-binding pocket^{93,96}.

Development of new covalent drugs



Development of new covalent drugs

