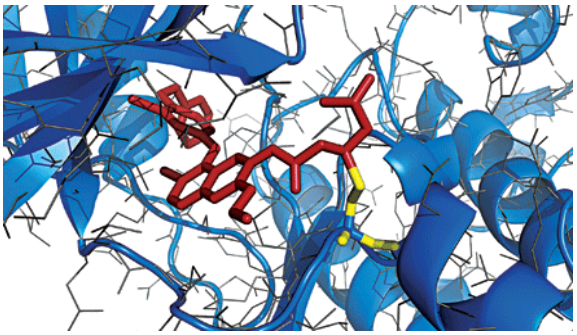
Irreversible inhibitors may provide unique benefits in drug development.

The pharmaceutical industry has by and large avoided developing drugs “interested in marriage” and instead has pursued “dating” as a model of the drug-target interaction ("marriage" and "dating" represent two different cases of synthesis process. "Marriage" can be explained by the next scheme: C + KX = CKX , where C is some compound , KX is inhibitor (K) + functional part, that must be delivered. "Dating" is: C + KX = CX + K). Covalent drugs, companies have feared, would be so desperate for a mate that they would bond with the wrong proteins. The result would undoubtedly be toxicity. Covalent drugs that form irreversible chemical bonds with their protein targets provide many advantages, according to their developers. (By contrast, covalent inhibitors that form reversible bonds—those that repeatedly marry, divorce, and remarry—behave more like non-covalent drugs, particularly if they divorce quickly.) One strength stems from the drugs’ very nature: The marriage between drug and target permanently prevents the protein molecule from wreaking



havoc. Knowledge of three-dimensional target structures allows companies to design irreversible inhibitors that bind reversibly to protein active sites, providing time for nearby chemical reactions that permanently bond drugs to targets. The reversible binding makes the drug’s concentration at the target effectively sky-high, helping drive the chemical reaction of a nucleophilic amino acid on the protein with a modestly electrophilic moiety on the drug.(Example: Neratinib (red), Irreversible inhibitor, forms a covalent bond with a cysteine (yellow) of epidermal growth factor receptor (blue).)