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Next generation irreversibile inhibitors: From design to clinical development

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Afatinib, a first line agent against certain cancers, represents a next generation of irreversible inhibitors. The modular design strategy used in creating such inhibitors begins with an optimization of non-covlent interactions between the inhibitor and the target binding pocket, often with molecules lacking the irreversible "warhead". Optimization includes selectivity increasing the noncovalent residence time of the inhibitor within the target binding pocket. Incorporating a long residence time permits the selection of a less reactive warhead. Unfortunately, *in vitro* evaluations of next generation irreversible inhibitors produce paradoxical behavior as pre-covelant binding is improved and the selected warhead is made less reactive, standard methods report those inhibitors as more loosely bound and more reactive to the target. These observations arise from a breakdown in the steady state assumption of standard methods. An alternative target engagement theory is proposed which views the pre-covalent inhibitor-target complex as a competition between the rate of dissociation and the rate of covalent reaction. A case study is presented illustrating some useful steps to advance from early discovery to Phase 1 trial design.

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