Allosteric small-molecule kinase inhibitors

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Small-molecule kinase inhibitors are invaluable targeted therapeutics for the treatment of various human diseases, especially cancers. While the majority of approved and developed preclinical small-molecule inhibitors are characterized as type I or type II inhibitors that target the ATP-binding pocket of kinases, the remarkable sequential and structural similarity among ATP pockets renders the selective inhibition of kinases a daunting challenge. Therefore, targeting allosteric pockets of kinases outside the highly conserved ATP pocket has been proposed as a promising alternative to overcome current barriers of kinase inhibitors, including poor selectivity and emergence of drug resistance. In spite of the small number of identified allosteric inhibitors in comparison with that of inhibitors targeting the ATP pocket, encouraging results, such as the FDA-approval of the first small-molecule allosteric inhibitor trametinib in 2013, the progress of more than 10 other allosteric inhibitors in clinical trials, and the emergence of a pipeline of highly selective and potent preclinical molecules, have been reported in the past decade. In this article, we present the current knowledge on allosteric inhibition in terms of conception, classification, potential advantages, and summarized debatable topics in the field. Recent progress and allosteric inhibitors that were identified in the past three years are highlighted in this paper.

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