Pharmacology & Therapeutics 156 (2015) 59–68

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Allosteric small-molecule kinase inhibitors

Peng Wu [a,*], Mads H. Clausen [a,b], Thomas E. Nielsen [c]

[a] Department of Chemistry, Technical University of Denmark, Kgs. Lyngby DK-2800, Denmark
[b] Center for Nanomedicine and Theranostics, Technical University of Denmark, Kgs. Lyngby DK-2800, Denmark
[c] Protein and Peptide Chemistry, Novo Nordisk A/S, Måløv DK-2760, Denmark

ARTICLE INFO

Available online 24 October 2015

Keywords:
Allosteric inhibitors
Serine/threonine kinase
Tyrosine kinase
MEK inhibitors
Type III inhibitors
Type IV inhibitors

ABSTRACT

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 conversed 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.

© 2015 Elsevier Inc. All rights reserved.

Contents

Abbreviations: AGC, containing protein kinase A, protein kinase G, protein kinase C families; ATP, adenosine 5′-triphosphate; CAMK, calcium/calmodulin-dependent protein kinases; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; DFG, aspartate-phenylalanine-glycine residues; FAK, focal adhesion kinase; FDA, United States Food and Drug Administration; IGF-1R, insulin-like growth factor-1 receptor; IKK, IκB kinase; IRE1, inositol requiring enzyme 1; ITK, interleukin-2-inducible T-cell kinase; JNK, c-Jun N-terminal kinase; LIMK, LIM (Lin11, Isl1 & Mec3) domain-containing kinase; MAPK, mitogen-activated protein kinase; MAPKK, mitogen-activated protein kinase kinase; MEK, mitogen/extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; PAK1, p21-activated kinase 1; PDK1, phosphoinositide-dependent kinase1; PH domain, pleckstrin homology domain; PIF, PDK1-interacting fragment; PI3K, phosphatidylinositol 3-kinase; PIKK, phosphatidylinositol 3-kinase-like protein kinases; PKB, protein kinase B (also known as Akt); PKC, protein kinase C; RIP1, receptor-interacting protein kinase 1; SMKIs, small-molecule kinase inhibitors; STE, homologs of yeast Sterile 7, Sterile 11, and Sterile 20 kinases; TK, tyrosine kinase; TKL, tyrosine kinase-like.

* Corresponding author at: Department of Chemistry, Technical University of Denmark, Kgs. Lyngby DK-2800, Denmark. Tel.: +45 5239 9298; fax: +45 4525 2116.
E-mail address: penwu@kemi.dtu.dk (P. Wu).

http://dx.doi.org/10.1016/j.pharmthera.2015.10.002
0163-7258/© 2015 Elsevier Inc. All rights reserved.

1. Introduction: kinase inhibition

Kinases transfer the gamma phosphate of ATP onto hydroxyl bearing substrates including proteins, lipids, and sugars, and are implicated in various cellular and extracellular activities (Johnson & Lewis, 2001). Overexpression and dysregulation of kinases are directly associated with many human diseases. Inhibition of kinases by small molecules can severely impair activation of crucial cellular signaling pathways. Initiated by pioneering work performed before the 1980s, small molecule kinase inhibitors (SMKIs) entered the clinical stage in the 1990s, followed by a "sprouting decade of kinase inhibitors" research from 2001 to 2010 that was effectively kicked off by the FDA-approval of imatinib for the treatment of patients with chronic myeloid leukemia. As of October 2015, a total of 28 FDA-approved SMKIs (Wu et al., 2015a), together with a few more approved by drug administrations of other countries, are on the market. Encouraged by the success of SMKIs in clinical settings, kinases are now being intensively studied as key therapeutic targets in drug discovery (Fabbro et al., 2015), especially for the treatment of different types of human cancers (Wu et al., 2015b). In parallel, kinases have been indicated as potent therapeutic targets in treating inflammatory diseases, cardiovascular diseases, diabetes, and also in neurological disorders, such as Alzheimer's and Parkinson's disease (Rask-Andersen et al., 2014).

However, a few factors collectively undermine the clinical applications of SMKIs. Many reported kinase inhibitors, including approved drugs, suffer from undesired selectivity profiles (Davis et al., 2011; Norman et al., 2012). Low specificity towards the target kinase and a lack of selectivity for structurally related kinase families may lead to side effects and off-target toxicity in clinical settings. In addition, the emergence of resistance due to site mutations in the ATP binding pocket also limits the use of SMKIs in cancer treatment. Since most developed SMKIs target the highly conserved ATP binding pocket, an alternative inhibition approach that targets other less-conserved allosteric pockets in the kinase domain, or other remote sites, is being actively pursued (Foda & Seeliger, 2014).

2. Understanding allosteric kinase inhibitors

The majority of non-covalent SMKIs are ATP-competitive inhibitors, classified as either type I or type II inhibitors, by reference to the conformation of the highly conserved aspartate-phenylalanine-glycine (DFG)-motif in the beginning of the activation loop in the C-lobe of the kinase domain (Wu et al., 2015a). Type I inhibitors, such as gefitinib (Iressa®), bind in the ATP pocket of the active kinase form with a "DFG-in" conformation. Type II inhibitors, such as imatinib (Gleevec®), bind in the hinge region of the ATP pocket and a less conserved allosteric region that is formed following the conformational change to the "DFG-out" motif, and stabilize the inactive form of the kinase. In contrast, allosteric inhibitors are defined as molecules that bind outside the ATP-binding pocket with no interaction with the hinge region that connects the N- and C-lobes of the kinase domain. Allosteric inhibitors can be classified as type III inhibitors, such as cobimetinib, which bind in an adjacent allosteric site that does not overlap with the ATP binding pocket/hinge region (Rice et al., 2012) (Fig. 1A), or type IV inhibitors, such as GNF2, which bind to an allosteric site that is distant from the ATP binding pocket (Zhang et al., 2010) (Fig. 1B). There are different definitions for other types of non-covalent SMKIs, which are referred to as type V inhibitors in this paper. Type V inhibitors include a small group of bivalent or bisubstrate inhibitors (Lamba & Ghosh, 2012; Gower et al., 2014), and a few inhibitors with hybrid type I and II features (Okamoto et al., 2015), which have also been referred to as type 1½ inhibitors (Zuccotto et al., 2010). Even though most allosteric SMKIs are non-ATP competitive, as they bind into a site that does not overlap with the ATP-binding site, some allosteric SMKIs may still be ATP-competitive due to stabilization of the inactive conformation of their binding kinases (Cowan-Jacob et al., 2014).

The field of allosteric kinase inhibition has evolved rapidly in the past few years with the FDA-approval of trametinib as the first allosteric SMKI, the progression of more than 10 other allosteric inhibitors of MEK and Akt in clinical trials, and examples of allosteric inhibitors of LIMK2, PAK, IRE1, and RIP1 being reported for the first time.

The comparatively low sequence homology of allosteric sites provides unique opportunities for more specific inhibition and minimal off-target pharmacology (Fang et al., 2013). Other advantages of allosteric inhibitors over traditional ATP-competitive type I and II inhibitors include the potential to overcome mutation-associated drug-resistance, especially mutations in the ATP-binding site that confer resistance to almost all related ATP-competitive inhibitors, such as the frequently occurring T315I mutations in the gatekeeper residue Abl (Gibbons et al., 2012) In addition, SMKIs may not need to exhibit nanomolar affinity to compete with the high intracellular ATP concentrations, making it easier to identify weak binding inhibitors, ranging from fragments to hit and lead compounds, and treatment of indications beyond cancer may be feasible. Furthermore, allosteric SMKIs can find utility as selective chemical probes to facilitate mechanistic studies on molecular function. With these attractive features, allosteric inhibitors are now being extensively studied as a new generation of SMKIs.

As previous articles have analyzed the structural basis (Fang et al., 2013), and discussed the potential and opportunities (Cowan-Jacob et al., 2014), for allosteric inhibition, this review will highlight recent development on small-molecule allosteric inhibitors that have already progressed in clinical trials and inhibitors that were revealed in the past three years. Inhibitors that disrupt protein–protein interactions are not covered in this discussion.

3. Allosteric serine/threonine kinase inhibitors

The signaling cascades of Ras-Raf-mitogen/extracelluar signal-regulated kinase (MEK) pathway (Samatar & Poulikakos, 2014) and phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway are among the most frequently dysregulated signaling networks in human malignancies (Fruman & Rommel, 2014; Houédé & Pourquier, 2015). A large number of structurally diverse small molecules have been reported as inhibitors of key kinases along both pathways. The serine/threonine kinases MEK and Akt are among the most thoroughly-investigated targets for which allosteric inhibitors have been developed (Fasano et al., 2014).

3.1. MAPKK and MAPK inhibitors

MEK, a member of the mitogen-activated protein kinase kinase (MAPKK) family, is a dual specificity threonine/tyrosine kinase that plays a critical role in the Raf-Ras-MEK signaling pathway. A collection of highly selective and potent allosteric non-ATP competitive MEK inhibitors are currently in clinical trials of different phases for the treatment of non-small cell lung cancer (NSCLC) (Zhao & Adjei, 2014).

The MEK1/2 inhibitor trametinib (**1**, Mekinist®, originally developed by GlaxoSmithKline, but owned by Novartis starting from May 2015) is the first and only approved allosteric SMKI, whose structural-activity relationship and pharmacological profile have been widely studied (Abe et al., 2011). Trametinib was approved by FDA in May 2013 as a single-agent for the treatment of patients with either B-Raf V600E or V600K mutated metastatic melanoma. Most common adverse reactions of trametinib in more than 20% of patients are rash, diarrhea, and lymphedema, which are also common adverse reactions for many other approved SMKIs. To overcome the observed progression using single-agent trametinib, which usually occurs within 7 months, combination strategies using the B-Raf inhibitor dabrafenib was evaluated and shown to delay the emergence of resistance and significantly improve survival without increased overall toxic effects (Long et al., 2014; Robert et al., 2015). FDA approved the combination of dabrafenib and

Download English Version:

https://daneshyari.com/en/article/5843920

Download Persian Version:

https://daneshyari.com/article/5843920

Daneshyari.com