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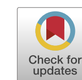
Discovery of new thienopyrimidine derivatives as potent and orally efficacious phosphoinositide 3-kinase inhibitors



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A B S T R A C T

A series of new thienopyrimidine derivatives has been discovered as potent PI3K inhibitors. The systematic SAR studies for these analogues are described. Among them, **8a** and **9a** exhibit nanomolar enzymatic potencies and sub-micromolar cellular anti-proliferative activities. **8a** displays favorable pharmacokinetic profiles, while **9a** easily undergoes deacetylation to yield a major metabolite **8a**. Furthermore, **8a** and **9a** potently inhibit tumor growth in a dose-dependent manner in the NCI-H460 xenograft model with an acceptable safety profile.

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1. Introduction

Phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases that are involved in many essential cellular functions including cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking.[1–3] Depending upon their sequence homology and substrate preferences, PI3Ks are divided into three distinct classes (I, II & III).[3] The class I PI3Ks are most intensively studied to date and consist of a regulatory subunit and a catalytic subunit. The catalytic subunit occurs in four isoforms designated as p110α, p110β, p110γ and p110δ. Signaling from receptor tyrosine kinases and G-protein-coupled receptors, the class I PI3Ks catalyze the phosphorylation of the 3′-hydroxyl group of phosphatidylinositol 4,5-biphosphate (PIP2) to generate phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 functions as a potent secondary cellular messenger to initiate a signal transduction cascade leading to activation of the serine/threonine kinase AKT (also known as protein kinase B or PKB).[3] The activated AKT in turn triggers the downstream signaling events that ultimately stimulates mammalian target of rapamycin (mTOR) that plays a key role in regulating cell growth, survival and proliferation.[4] Moreover, phosphatase and tensin homologue (PTEN), a lipid phosphatase that catalyzes the dephosphorylation of PIP3, is identified as a major negative regulator of the PI3K pathway.[5]

The PI3K pathway is one of the most frequently aberrantly activated signaling pathways in human cancers.[3,6] Molecular alterations in this pathway are significantly associated with tumorigenesis.[7] According to a recent analysis on 19,784 consecutive tumor samples (>40 cancer types), 38% of patients had at least one alternation in the PI3K pathway components.[8] Inhibition of this pathway therefore provides a promising approach to discover novel therapeutics for cancer treatment. A number of dual PI3K/mTOR, pan-PI3K and isoform selective PI3K inhibitors have entered into clinical trials, alone or in combination, in both solid tumors and hematologic malignancies.[9–12] In 2014, FDA approved the first-in-class PI3Kδ inhibitor Idelalisib for the treatment of patients with three types of hematologic cancers (CLL, FL and SLL).[13] In 2017, the class I PI3K inhibitor copanlisib received an accelerated approval from FDA for the treatment of relapsed follicular lymphoma based on a single-arm trial that included only 104 patients (Fig. 1).[14] Copanlisib showed preferential activity against PI3Kα and p110δ as compared with PI3Kβ and p110γ.[15] Extensive efforts to develop PI3K inhibitors to treat solid tumors are still ongoing. However, emerging clinical data showed those PI3K inhibitors

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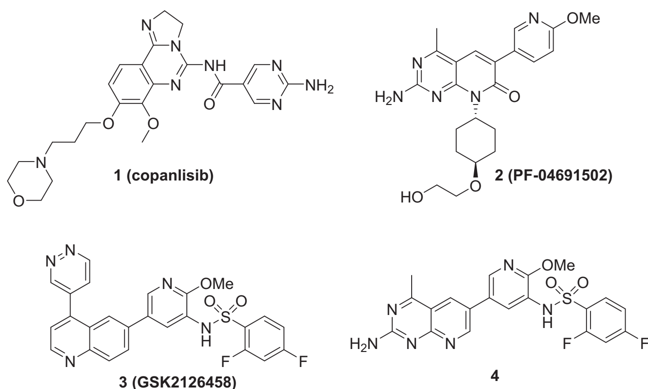


Fig. 1. Selected PI3K inhibitors (**1**–**4**).

had limited single-agent activities in solid tumors and none has yet reached a regulatory approval.[16] Clearly, challenges remain for PI3K inhibitors to become a significant component of the anti-cancer portfolio. To address these challenges, future directions for clinical development of PI3K inhibitors are getting a greater focus on patient selection, rational combination as well as understanding of immune modulation.[16–18] From medicinal chemistry point of view, identification of more structurally diversified PI3K inhibitors would provide opportunities to differ their pharmacological and safety profiles, thereby facilitating discovery of inhibitors targeting PI3K pathway with better clinical outcomes.

As previously reported, we disclosed a series of 2-amino-4-methylpyrido[2,3-*d*]pyrimidine derivatives as potent PI3K inhibitors, in which the key aminopyridopyrimidine, sulfonamide and pyridyl nitrogen moieties interacts with Val 882, Lys 833, and a conserved water molecule respectively in the ATP binding pocket.[19] Among them, the representative compound **4** provided potent inhibition of PI3Kα with an IC_{50} of 2.0 nM and a reasonable U87 cell IC_{50} of 0.63 μM (Fig. 1). However, **4** could not achieve tumor growth inhibition in in vivo xenograft models at various doses, probably due to its undesirable ADME properties originated from poor physicochemical properties. In this paper, we explored various 6,6- and 6,5-bicycles (**5**–**9**) as alternatives to the pyridopyrimidine core in the previous scaffold and further optimization led to the discovery of a series of new thienopyrimidine derivatives (**8a** and **9a**) that demonstrated excellent enzymatic, cellular and in vivo antitumor activities.

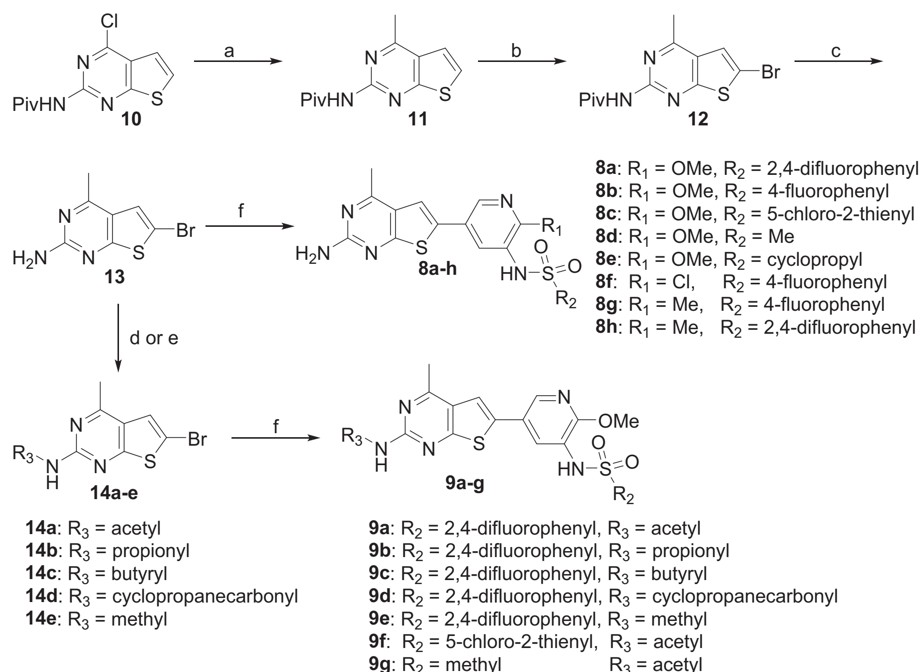
2. Results and discussion

2.1. Chemistry

The representative synthetic approach for thienopyrimidine derivatives **8a–h** and **9a–g** was described in Scheme 1. The starting material **10** was prepared according to the reported methods.[20] Treatment of **10** with methylboronic acid afforded **11**, which was brominated with NBS and then deprotected to afford the key intermediate **13**. **13** was then converted to **14a–e** by either acylation or methylation. Finally, **13** and **14a–e** were coupled with various aryl boronic esters to yield target compounds **8a–h** and **9a–g**.

2.2. Enzymatic and cellular assays

Our initial structural modification focused on replacement of the pyridopyrimidine core of compound **4** with different 6,6- and 6,5-bicycles as these bicycles were envisioned to adopt similar binding topologies that could maintain major interactions with the PI3K kinase (Table 1). Pyridopyrimidinone **5** and **6** were firstly synthesized for evaluation. As shown in Table 1, both compounds displayed effective kinase inhibition with single-digit nanomolar potencies against PI3Kα, comparable to **4**. Notably, compound **5** was inactive in a U87 cellular assay (IC_{50} > 50 μM). We reasoned that the NH proton of the pyridopyrimidinone in **5** deleteriously affected its membrane permeability. Pteridin-7(8*H*)-one **7** demonstrated similar PI3Kα and cellular potencies relative to **4** and **6**,



Scheme 1. Synthesis of compounds **8a–h** and **9a–g**. Reagents and conditions. (a) methylboronic acid, 2 M K_2CO_3, $PdCl_2$(dppf), 1,4-dioxane, 105 °C, 3 h, Ar, 42%; (b) NBS, DMF, rt, 4 h, 76%; (c) 2 M NaOH, EtOH, 90 °C, 1.5 h, 82%; (d) acyl chloride, pyridine, DMF, rt, 4 h, 52–60%; (e) MeI, NaH, DMF, rt, 4 h, 28%; (f) aryl boronic ester, $PdCl_2$(dppf), 2 M K_2CO_3, dioxane, 100 °C, Ar, 4–6 h, 20–59%.

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