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Discovery of a Novel Series of 7-azaindole scaffold derivatives as PI3K inhibitors with potent activity

Chengbin Yang,^{†,‡} Xi Zhang,^{‡,‡} Yi Wang,[‡] Yongtai Yang,[†] Xiaofeng Liu,[†] Mingli Deng,[†] Yu Jia,[†] Yun Ling,[†] Ling-hua Meng,^{*,‡} Yaming Zhou^{*,†}

[†] Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials, Department of Chemistry, Fudan University, Shanghai, 200433, China.

[‡] Division of Anti-tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences

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ABSTRACT: The phosphoinositide 3-kinase (PI3K) inhibitors potently inhibit the signaling pathway of PI3K/AKT/mTOR, which provides a promising new approach for the molecularly targeted cancer therapy. In this work, a novel series of 7-azaindole scaffold derivatives was discovered by the fragment-based growing strategy. The structure-activity relationship (SAR) profiles identified that the 7-azaindole scaffold derivatives exhibit potent activity against PI3K at molecular and cellular levels as well as cell proliferation in a panel of human tumor cells.

The phosphatidylinositol 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) pathway is an important intracellular signaling pathway in regulating multiple cellular processes including metabolism, survival and proliferation.¹ This pathway is frequently deregulated by various genetic and epigenetic mechanisms in a wide range of tumors.^{1–3} Guided by the strategy of “drugging the cancer kinome”, design and synthesis of small molecules that are able to target the key components within this pathway may result in tumor suppression.⁴ The PI3K is a family of lipid and protein kinases, which can be categorized into three classes (I, II, and III). Class I PI3Ks contain four catalytic isoforms (p110 alpha, p110 beta, p110 gamma and p110 delta),⁵ converting phosphatidylinositol-4,5-bisphosphate (PtdIns (4, 5) P2) to PtdIns (3,4,5) P3. Deregulation of PI3K will lead to elevated PtdIns (3,4,5) P3 levels and activation of downstream AKT, which are often found in cancer cells favoring cell survival and spreading.⁶ In this context, the PI3K activity contributes significantly to cellular transformation and the development of cancer. Small molecules targeting one particular PI3K isoform or multiple isoforms have been emerged as promising anti-cancer drug candidates for targeted therapy.^{7–11}

A number of inhibitors have been reported so far (Figure 1),^{12–20} which can be classified into two categories,²¹ pan-PI3K inhibitors targeting all p110 isoforms,^{22–23} and isoform-specific PI3K inhibitors targeting a specific p110 isoform.^{22, 24} Some of them have entered clinical trials as targeted anticancer drugs, in which GSK2126458 (GlaxoSmithKline) has attracted considerable interest.¹² X-ray co-crystal structure with PI3K γ and GSK2126458 revealed that it fits well at the active site of PI3K and forms key hydrogen bonds using its quinoline, sulfonamide, and methoxypyridine moieties with Val882, Lys833, and an active water molecule respectively (Figure 2).

Although it possesses a high ligand efficiency and exhibits remarkable potency in vitro and in vivo, GSK2126458 itself exhibits a low water-solubility and unfavorable safety profile. Owing to these issues, N-(2,5-disubstituted-pyridin-3-yl)phenylsulfonamides (Amgen, Figure 1) have been developed.¹³ The quinoline core was

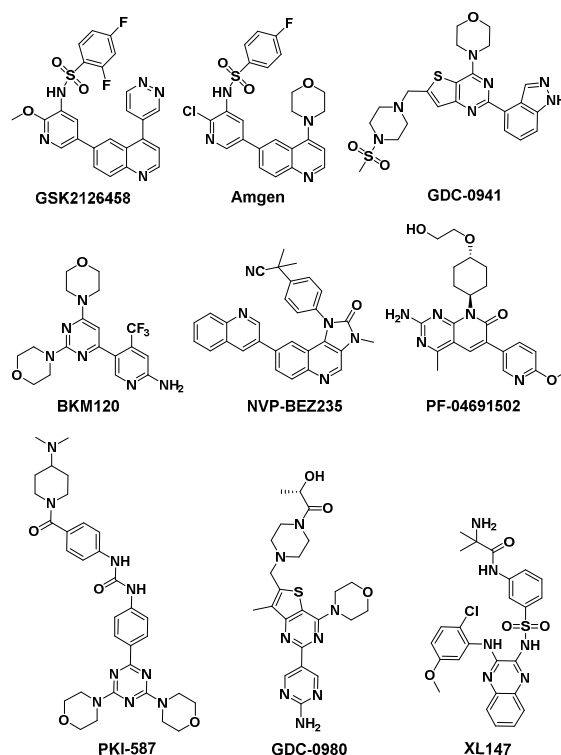
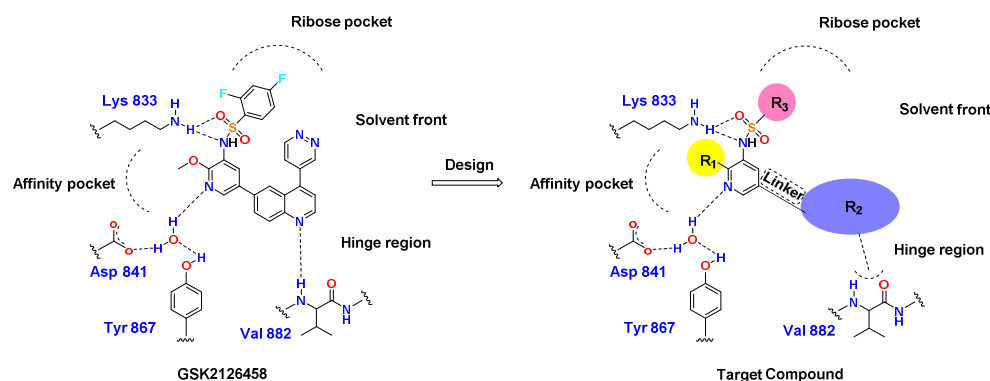


Figure 1. Chemical structures of representative PI3K inhibitors in

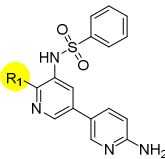
clinical trials.

**Figure 2.** A view of our design strategy derives from the X-ray crystallographic results of GSK2126458 with p110 γ protein (PDB Code: 3L08).

retained to form hydrogen bond with Val822 hinge region and to project other moieties appropriately thereby accessing additional interactions. To optimize the ligand efficiency as well as other drug-like properties, structure–activity relationship (SAR) investigation was carried out with the interest on the quinoline region, leading to the generation of a structurally novel thienopyrimidine series as potent PI3K inhibitors.²⁵

Taking the above achievements in consideration, in this paper, we describe our research progress on optimizing the potency by replacement of quinoline fragment with a series of heterocycles. Started from 2-aminopyridine, structurally novel 7-azaindole series compounds were revealed as potent PI3K inhibitors, in which B13, B14, C1 and C2 inhibit PI3K kinase activity at subnanomolar concentration and display potent anti-proliferative activity in a panel of human tumor cells.

Table 1. SAR studies of the substitution of pyridine at 2-position.

		
Compound	R1	PI3K γ IC ₅₀ (nM)
A1	H	1593
A2	H ₂ N-	2966
A3	H ₃ C-O-	2062
A4	H ₃ C-	381
A5	Cl-	375

Our SAR investigations were started from N-(5-(6-aminopyridin-3-yl)pyridin-3-yl)benzenesulfonamide (A1), which was synthesized in our lab (Section 3 synthesis, SI). Introduction of small molecular substituents in pyridine ring at 2-position was firstly evaluated (Table 1). When pyridine H was replaced by amino and methoxyl group, it gave compound A2 and A3, respectively, which displayed a slight drop of potency against PI3K γ (2 and 1.3 fold decrease relative to A1 respectively). In contrast, introduction of methyl group (A4) significantly enhanced the inhibitory activity (5-fold increase). Meanwhile, it is also noted that introduction of chloro group

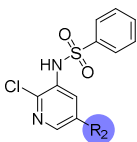
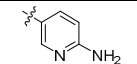
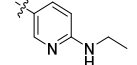
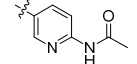
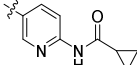
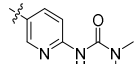
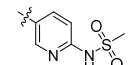
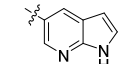
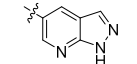
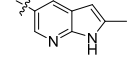
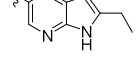
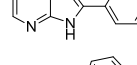
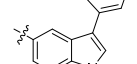
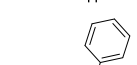
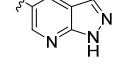
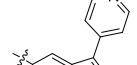
(A5) led a similar potency improvement as A4. These results suggested that a small and greasy moiety would be more favorable in pyridine group at this site. Considering that the chloro group was more preferred at this site,²⁶ we carried out our next stage of structural optimization on scaffold A5.

Previous studies suggested that the inhibitory activity would be associated with hydrogen bonding interaction in the hinge region.^{12,13,25} 2-aminopyridine motif is possible to form two kinds of hydrogen bonds. One is pyridine N as the proton acceptor that interacts with NH group, the other one is NH₂ as proton donor that interacts with C=O of Val 882 (Figure 2). Therefore, we focused the SAR studies on the optimization of 2-aminopyridine at this stage. As shown in Table 2, compound B1 displayed a significant drop of potency (~ 4-fold decrease vs A5) after the introduction of ethyl onto amino group. However, in case of carbonyl derivatives, B2 and B3 remained the PI3K γ inhibitive activity similar as that of A5. Compound B4 exhibited a prominent improvement (~ 6-fold increase vs A5). In contrast, in case of sulphonyl group, B5 displayed a significant drop in potency (~ 13-fold decrease). If hydrogen bonding interaction plays a key role to the potency in this hinge region, the introduction of electron-withdrawing group should contribute to the enhancement of N-H...O in principle. While, the negative result of B5 indicates that there are other factors affecting the hydrogen bond. Besides the electronegativity of proton donor, the spatial direction could also greatly affect the interaction, which is subject to the structural flexibility. In this consideration, we carried out conformational calculation. The results revealed that carbonyl group forms intramolecular hydrogen bond with pyridine H at 3-position, generating a six-membered ring coplanar with the pyridine, thus restraining the direction of proton donor NH (Fig. S1, SI). In contrast, B5 displayed the structural flexibility with at least four potential conformers, which could influence the spatial direction. All the above results suggested that a rigid ligand efficiency with proper hydrogen bond donor would be more beneficial for the hydrogen bonding interaction in this hinge region.

7-azaindole, which is a kind of widely studied pharmacophore,²⁷⁻²⁹ seems to meet the aforementioned requirements. Therefore, it was chosen for the following SAR studies. Compound B6 exhibited an increase of potent activity against PI3K γ (~4 fold increase vs. A5). In comparison, compound B7 displayed a further moderate increase in potency after pyrrolic CH at 2-position replaced by nitrogen based on the bioisostere.

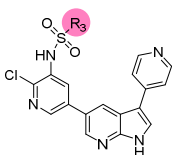



Then, the effect of substitute group (methyl, ethyl, and aromatic group) at the 2-position of 7-azaindole was assessed

Table 2. SAR studies of pyridine at 5-position.

		
Compound	R ₂	PI3K γ IC ₅₀ (nM)
A5		375
B1		1491
B2		420
B3		445
B4		68
B5		4752
B6		97
B7		37
B8		63
B9		155
B10		268
B11		15
B12		17
B13		0.5
B14		7

respectively, which shows a gradual decrease in potency from B8 to B10, indicating that this position is not well tolerated with bulk group. Interestingly, when the aromatic

Table 3. SAR studies of compound B13 and C1, C2.

		
Compound	R ₃	PI3K γ IC ₅₀ (nM)
B13		0.5
C1		0.7
C2		0.7

group was moved from 2- to 3-position, the resulting compound B11 displayed a prominent increase in potency (~ 18 fold increase vs B10, ~ 6 fold increase vs B6). Similarly, compound B12 is also more potent than B7. These results suggested that the aromatic substitution of 7-azaindole core at 3-position was well tolerated. Of particular note, further replacement of phenyl group of 7-azaindole at the 3-position with pyridine group led to the isolation of compound B13 and B14. These two compounds displayed a pronounced increase in potency especially compound B13, which is an exceptionally potent PI3K γ inhibitor with an IC₅₀ of 0.5 nM. The potency enhances almost ~30 compared with B11. We ascribed the enhancement to the replacement of phenyl group with pyridine group at the 3-position of 7-azaindole, which contributed to the optimization of pharmacological parameters.³⁰ Furthermore, optimization of the benzenesulfonamide segment was then explored by introduction of fluorine at 2- and 4-position, respectively (Table 3). The resulting compound C1 and C2 displayed similar inhibitory activity as that of B13, indicating that scanning the position of fluorine on benzenesulfonamide failed to effectively modulate the inhibitory potency significantly.

Table 4 The inhibitory activity of compounds on isoforms of class I PI3K

Compound	IC ₅₀ (nM)			
	PI3K α	PI3K β	PI3K γ	PI3K δ
B6	35	35	97	1
B7	51	29	37	1
B11	2	39	15	1
B12	2	6	17	1
B13	1	2	0.5	0.6
B14	1	4	7	0.7
C1	1	3	0.7	0.5
C2	1	2	0.7	0.4
Amgen ¹³	4.6±3	13±10	4.3±2	8.1±3

Table 5. Anti-proliferative effect of compounds against a panel of human cancer cell ^a.

Compound	GI ₅₀ (μM) ^b					
	NCI-H460	MCF7	T47D	U87MG	KARPAS-422	Pfeiffer
NVP-BEZ235	0.61±0.15	0.06±0.03	0.30±0.01	0.28±0.02	ND	ND
CAL-101	ND	ND	ND	ND	0.68±0.29	0.74±0.26
B6	>10	>10	>10	>10	6.71±1.32	5.50±1.58
B7	7.61±0.30	7.40±0.62	4.40±0.41	8.94±1.86	1.09±0.19	1.16±0.43
B11	>10	>10	7.72±1.56	>10	1.83±0.59	1.52±0.44
B12	8.65±0.79	7.37±0.51	4.19±0.29	>10	1.23±0.31	1.30±0.58
B13	3.90±0.25	2.14±0.75	1.50±0.41	8.95±1.28	0.12±0.03	0.10±0.03
B14	2.50±0.29	0.69±0.16	0.52±0.09	3.12±0.48	0.17±0.05	0.15±0.06
C1	>10	2.50±0.06	1.79±0.18	7.13±1.55	0.35±0.10	0.29±0.15
C2	6.19±0.49	2.91±0.05	1.30±0.04	>10	0.37±0.09	0.41±0.21

^a. Cell proliferation was detected by SRB or CCK-8 Assay as described in supporting information.

^b. GI₅₀ values are average ± SD of at least three independent experiments in triplicate.

ND: Not detected.

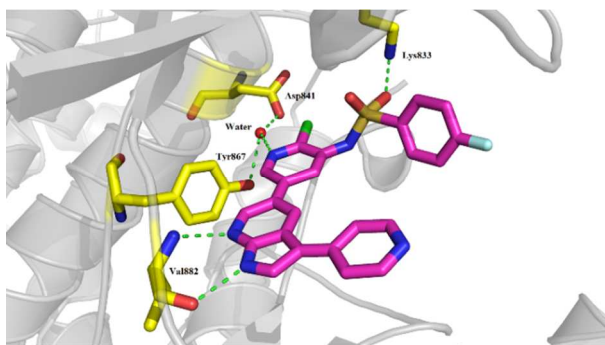


Figure 3. Predicted binding mode for C2 (shown in stick representation with carbon atoms colored gray) with PI3K γ (PDB ID: 3L08). Hydrogen bonds are shown in green dashed lines to the hinge region (Val882), Lys833, and the conserved water molecule bridge. Images generated using PyMol.

With these achieved subnanomolar IC₅₀, PI3K γ potency level based on the novel 7-azaindole scaffold was optimized similarly to those of quinolone series, which exhibits more potency than some PI3K inhibitors in clinical trials, such as XL147, GDC-0980, BEZ235, BKM120 and GDC-0941, as well as Amgen (Table S1, SI). To understand the mechanism at molecular level, the binding mode between the 7-azaindole scaffold and PI3K γ was then proposed by molecular simulation (Section 4 docking, SI). C2 was explored as an example. As shown in Figure 3, the pyridyl N forms a hydrogen bond with the lattice water molecule, similar to the bonding model observed in the co-crystal structure of GSK2126458 with p110 γ .¹² There is only one sulfonamide oxygen interacts with Lys833, which is different from the chelate binding mode formed by the sulfonamide nitrogen and oxygen with Lys833 in GSK2126458. Importantly, the 7-azaindole forms two hydrogen bonds with Val882, which is greatly different from that of GSK2126458, where it has only one quinolone nitrogen interacting with this hinge region.

Through the SAR investigation, compounds B6-B7, B11-B14 and C1-C2 were identified to bear decent potency against

PI3K γ and were selected for further profiling. The inhibitory activities to the four isoforms (α , β , γ , and δ) of class I PI3Ks were evaluated (Table 4, Figure S2-5, SI). According to the potency and selectivity, the tested compounds can be classified into three categories: i) isoform-specific PI3K inhibitors, including B6 and B7, they display more potent activity against PI3K δ than the rest of three isoforms; ii) pan-PI3K inhibitors, including B13, B14, C1, and C2, which similarly inhibit the four isoforms without significant selectivity; and iii) transitional ones including B11 and B12, which exhibit undistinguished potency. We believed that the overall profiles obtained from the enzyme assays would contribute greatly for the further design and synthesis of more potent inhibitors. Consistent with the potency against the PI3K, compounds B13-B14 and C1-C2 displayed activity against cell proliferation in a panel of human tumor cells originated from different tissues (Table 5). In addition, it is notable that compound B14 potently inhibited the proliferation of both PI3K δ -activated lymphoma cells (GI₅₀ = 0.17 ± 0.05 μM, 0.15±0.06 μM, for KARPAS-422, Pfeiffer, respectively) and PI3K α -activated solid tumor cells (GI₅₀ = 0.69±0.16 μM, 0.52±0.09 μM, for MCF7, T47D, respectively), which might be due to its significant activity against both PI3K δ and PI3K α (Table 4).

In summary, based on the lead compound N-(2-chloro-5-(1H-pyrrolo(2,3)pyridin-5-yl)pyridin-3-yl)benzenesulfonamide (B6), a structurally novel series of PI3K inhibitors with 7-azaindole scaffold was discovered by fragment-based searching strategy. Different from previously reported series of quinolone scaffold, this 7-azaindole scaffold forms two hydrogen bonds with the Val882. Furthermore, our SAR investigations revealed that both pan-PI3K and isoform-specific PI3K inhibitors would be possibly developed based on this novel scaffold, demonstrating its promising prospect as a lead compound for further optimization. In addition, the selected compounds demonstrated subnanomolar activities against the kinase activity of PI3K and potent anti-proliferative activities against a panel of human cancer cell lines, supporting our next phase of in-vivo evaluation.

■ ASSOCIATED CONTENT

Supporting Information

Biological assays, experimental procedures and Docking procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

* E-mail: ymzhou@fudan.edu.cn (Prof. Zhou YM.)
lhmeng@sim.ac.cn (Prof. Meng LH)

Author contributions

These two authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; SRB, sulforhodamine B; CCK-8, Cell Counting Kit-8

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