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Conformationally restricted quinazolone derivatives as PI3K δ -selective inhibitors: the design, synthesis and biological evaluation†

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A series of structurally novel quinazolone-based PI3K δ -selective inhibitors were designed and synthesized via the approach of conformational restriction. The majority of them exhibited two-digit to single-digit nanomolar IC₅₀ values against PI3K δ , along with low micromolar to submicromolar GI₅₀ values against human malignant B-cell line SU-DHL-6. The representative compound, with the most potent PI3K δ inhibitory activity (IC₅₀ = 6.3 nM) and anti-proliferative activity (GI₅₀ = 0.21 μ M) in this series, was further evaluated for its PI3K δ selectivity, capability to down-regulate PI3K signaling in SU-DHL-6 cells, *in vitro* metabolic stability, and pharmacokinetic (PK) properties. The experimental results illustrated that this compound, as a promising lead, merits extensive structural optimization for exploring novel PI3K δ -selective inhibitors as clinical candidates.

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1. Introduction

Phosphoinositide 3-kinases (PI3Ks), catalyzing the transformation of phosphatidylinositol 4,5-bisphosphate (PIP₂) to the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP₃),¹ play an essential role in major cellular activities, such as survival, growth, proliferation and metabolism.^{2,3} The medicinal potential of PI3Ks as therapeutic targets for human malignancies has been validated by an increasing amount of research, as well as the clinical development of numerous inhibitors that ablate aberrant PI3K signaling.^{4–6} According to their kinase specificity, they are divided into three classes, including pan-class I PI3K inhibitors, PI3K/mTOR dual inhibitors, and subtype-selective PI3K modulators.

Throughout the PI3K family, class I PI3Ks have been most deeply studied.⁷ Despite their high sequence homology in catalytic domains, the four isoforms belonging to class I PI3Ks, termed as PI3K α , β , γ and δ , are involved in differentiated biological functions.^{4,8} Distinct from PI3K α and PI3K β that are

ubiquitously expressed, the latter two class I PI3K subtypes are predominantly distributed in leucocytes.^{9–12} As a vital effector of B-cell receptor-mediated signaling, PI3K δ is frequently up-regulated in leukemic blasts from patients with B-cell malignancies and drives the proliferation, survival, and trafficking of malignant cells to lymphoid.^{13–15} Additionally, PI3K δ is overexpressed in rheumatoid arthritis (RA) synovium¹⁶ and critical to the etiology of allergic responses¹⁷ and inflammatory arthritis.¹⁸ Thus, PI3K δ inhibition has been identified as a viable avenue for battling B-cell malignancies,^{19,20} inflammatory conditions,²¹ and autoimmune diseases.²² Importantly, PI3K δ -selective inhibition is anticipated to circumvent the side effects related to concomitant suppression of the four class I PI3Ks, including hyperglycemia, maculopapular rashes, and gastrointestinal intolerance.^{23–26}

With intense efforts in exploring PI3K δ -selective inhibitors, idelalisib 1 (Fig. 1), bearing the trade name Zydeler, has been marketed in 2014 for treating relapsed chronic lymphocytic leukemia, follicular non-Hodgkin lymphoma, and small lymphocytic lymphoma.²⁷ Besides, duvelisib 2,²⁸ a structural analog of 1, has recently been approved for treating hematopoietic malignancies as a δ -weighted PI3K δ / γ dual inhibitor. Other clinically investigated PI3K δ -selective inhibitors embrace tenalisib 3, umbralisib 4, setalisib 5,²⁹ dezapelisib 6, nemiralisib 7,³⁰ and leniolisib 8³¹ (Fig. 1) (<https://www.pharmacodia.com/cn>). Among them, 3–6 also share some structural similarities to 1 and feature a propeller-shaped conformation. The pharmacophore of 1–6 is characterized by a bicyclic heteroaromatic core, a hydrophobic aryl group directly attached to it, and a hinge binder (HB),

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Fig. 1 PI3K δ -selective inhibitors approved or under clinical development.

commonly the purine moiety tethered to the core through a short spacer³² (Fig. 2). In addition to being in contact with the hinge region *via* HB, these propeller-shaped molecules occupy the allosteric selectivity pocket of the PI3K δ enzyme *via* the bicyclic heteroaromatic core, thereby also termed as the ATP-competitive allosteric inhibitors.³³

In view of the advantage of selectively targeting PI3K δ for treating B-cell malignancies, our group has initiated a medicinal chemistry campaign to explore PI3K δ -specific inhibitors with structural novelty and favorable biological profiles. As a frequently applied drug design tactic, conformational restriction may be beneficial for optimizing the biological activity, target specificity, and metabolic stability.³⁴ On considering the importance of the quinazolone of 1 for opening the allosteric pocket and the *S*-configuration for the enzymatic activity, our work prioritized maintaining the quinazolone and incorporating *S*-pyrrolidine as the spacer between the template and HB to replace the conformationally-flexible

S-propylamine (Fig. 3). Besides, the *N*-3 position of the quinazolone, located near the mouth of the active site, was substituted with benzyl, cycloalkyl and alkyl to further increase the structural novelty. Studies also illustrated that modification at this site was capable of modifying the potency and selectivity.³⁵ Furthermore, 4-amino-5-carbonitrile pyrimidine was introduced as a ring-opening surrogate to purine, since the amino and carbonitrile, similar to the 9-*NH* and 7-*N* of purine, could serve as the H-bond donor and acceptor, respectively. As for compounds with purine as HB, we also investigated the impact of C-2 fluoro (the bioisostere of hydrogen) at the purine moiety on the binding affinity. Herein, we demonstrated our proof-of-concept study attempted to validate the design rationale of these conformationally restricted quinazolone derivatives, which has led to the discovery of compound 38 as a promising lead for further structural elaboration.

2. Results and discussion

2.1. Chemistry

The synthesis of target compounds 29–38 is depicted in Scheme 1. 2-Nitrobenzoic acid 9 or 2-fluoro-6-nitrobenzoic acid 10, as the starting material, was firstly converted into acyl chloride and condensed with various amines to afford corresponding amides 11–16. Their subsequent reaction with thionyl chloride furnished imidoyl chlorides, which were subjected to Mumm rearrangement³⁶ after treatment with (*S*)-1-*N*-Boc-proline under basic conditions to provide imides 17–22. Afterwards, one-pot reduction of the nitro functionality and intramolecular cyclization afforded quinazolone

Fig. 2 The general pharmacophore of PI3K δ allosteric inhibitors.

Fig. 3 The design rationale of target compounds.

Scheme 1 Reagents and conditions: (a) (1) DMF, SOCl₂, reflux; (2) corresponding amine, TEA, DCM, 0 °C to rt, 83–94%; (b) (1) DMF, SOCl₂, reflux; (2) TEA, (S)-1-*N*-Boc-proline, DCM, 0 °C to rt, N₂, 57–71%; (c) Zn, HAc, rt to 40 °C, 56–70%; (d) (1) TFA, DCM, 0 °C to rt; (2) 6-chloro purine, 6-chloro-2-fluoro-9*H*-purine or 4-amino-5-carbonitrile-6-chloro pyrimidine, DIPEA, *t*-BuOH, 80 °C, N₂, 52–81%.

intermediates 23–28. Following the removal of the Boc-protecting group, the newly formed *S*-pyrrolidine derivatives, without purification, underwent S_NAr reaction with 6-chloro purine, 6-chloro-2-fluoro-9*H*-purine, or 4-amino-5-carbonitrile-6-chloro pyrimidine to generate 29–38 as the target compounds.

2.2. PI3Kδ inhibitory activity

To validate the design rationale summarized in Fig. 3, all the target compounds were evaluated for their PI3Kδ inhibitory activity with 1 and PI-103 (a pan-class I PI3K/mTOR inhibitor) as the positive references. The majority of them exhibited favorable enzymatic activity with IC₅₀ values ranging from two-digit to

single-digit nanomolar levels (Table 1). Among these, compounds 32–34, 37 and 38 displayed IC_{50} values below 50 nM. In particular, the 4-amino-5-carbonitrile pyrimidine de-

rivative 38 exerted the most potent PI3K δ inhibitory activity (IC_{50} = 6.3 nM) in this series, which was comparable to that of 1.

Table 1 The PI3K δ inhibitory and anti-proliferative activities of the target compounds

Cpd.
	R_1	R_2	HB	PI3K δ^a (IC_{50} , nM)	SU-DHL-6 a (GI_{50} , μ M)
29	H			498 $\pm$ 52	0.58 $\pm$ 0.057
30	F			58 $\pm$ 5.7	0.48 $\pm$ 0.071
31	F			635 $\pm$ 81	0.63 $\pm$ 0.085
32	F			38 $\pm$ 4.2	2.65 $\pm$ 0.233
33	F			33 $\pm$ 4.9	0.51 $\pm$ 0.049
34	F			42 $\pm$ 6.4	0.64 $\pm$ 0.092
35	F			91 $\pm$ 9.2	0.38 $\pm$ 0.042
36	F			178 $\pm$ 15.6	1.89 $\pm$ 0.240
37	F			22 $\pm$ 3.5	0.33 $\pm$ 0.035
38	F			6.3 $\pm$ 0.78	0.21 $\pm$ 0.028
1				3.2 $\pm$ 0.28	0.02 $\pm$ 0.013
PI-103				5.8 $\pm$ 0.71	—

^a Results shown as mean $\pm$ SD (n = 2).

Table 2 The PI3K δ subtype specificity of compounds **37** and **38**

Cpd.	PI3K δ^a (IC ₅₀ , nM)	PI3K α^a (IC ₅₀ , nM)	PI3K β^a (IC ₅₀ , nM)	PI3K γ^a (IC ₅₀ , nM)
37	22 $\pm$ 3.5	4941 $\pm$ 348 (225-fold ^b)	6237 $\pm$ 508 (284-fold ^b)	587 $\pm$ 41.0 (27-fold ^b)
38	6.3 $\pm$ 0.78	8591 $\pm$ 624 (1364-fold ^b)	1554 $\pm$ 132 (247-fold ^b)	354 $\pm$ 21.9 (56-fold ^b)
1	3.2 $\pm$ 0.28	822 $\pm$ 48.1 (257-fold ^b)	281 $\pm$ 33.2 (88-fold ^b)	60 $\pm$ 4.2 (19-fold ^b)

^a Results shown as mean $\pm$ SD ($n = 2$). ^b Selectivity fold.

Additionally, some valuable preliminary structure–activity relationships (SARs) were deduced. The introduction of the fluoro substituent at the C-5 position of the quinazolone template was beneficial for improving the activity, as illustrated by the enhancement in potency when comparing **30** to its C-5 unsubstituted counterpart **29**. In contrast, the C-2 fluoro replacement at the purine moiety was detrimental to binding affinity. Both compounds **35** and **36**, bearing a C-2 fluoro replacement at the purine, demonstrated weakened activity in contrast to corresponding C-2 unsubstituted counterparts **30** and **32**. The type of HB served as another potential factor affecting PI3K δ inhibitory activity. For instance, replacement of the purine HB of **32** with the 4-amino-5-carbonitrile pyrimidine surrogate culminated in the most potent PI3K δ inhibitor throughout the series. Besides, the 4-amino-5-carbonitrile pyrimidine derivative **37** was more potent than the purine counterpart **30** as well. In respect of the *N*-3 replacement of the

quinazolone scaffold, bulkier hydrophobic substituents were envisioned to be desirable. Accordingly, compounds **30**, **32** and **33**, with a bulkier *N*-3 replacement, exerted considerably improved enzymatic activity compared to that of the *N*-3 cyclobutyl counterpart **31**.

2.3. Anti-proliferative activity

All the compounds were further evaluated against human malignant B-cell line SU-DHL-6 for their anti-proliferative efficacy with **1** as the positive reference. The majority of them displayed favorable cytotoxic activity with GI₅₀ values at the submicromolar level (Table 1). In addition to its most potent enzymatic activity, the 4-amino-5-carbonitrile pyrimidine derivative **38** also exhibited the strongest anti-proliferative activity among the target compounds with a GI₅₀ value of 0.21 μ M. By contrast to the corresponding purine counterpart **32**,

Fig. 4 The capability of compound **38** to down-regulate the phosphorylation levels of Akt and S6K1 in SU-DHL-6 cells after treatment for 2 h. The Akt and S6K1 phosphorylation levels were investigated via the Western blot assay (A). Phosphorylation levels of Akt (B) and S6K1 (C) were indicated as folds of control. The bar chart represents the quantification of the bands in the Western blot with the result shown as mean $\pm$ SD ($n = 3$). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. control (cells incubated without compound **38** or **1**).

Table 3 The *in vitro* metabolic stability of compounds **37** and **38** in HLM and RLM

Cpd.	HLM				RLM			
	$T_{1/2}$ (min)	$CL_{int(mic)}^a$ ($\mu\text{L min}^{-1} \text{mg}^{-1}$)	$CL_{int(liver)}^b$ ($\text{mL min}^{-1} \text{kg}^{-1}$)	Remaining ($T = 60 \text{ min}$)	$T_{1/2}$ (min)	$CL_{int(mic)}^a$ ($\mu\text{L min}^{-1} \text{mg}^{-1}$)	$CL_{int(liver)}^b$ ($\text{mL min}^{-1} \text{kg}^{-1}$)	Remaining ($T = 60 \text{ min}$)
37	31.1	44.6	40.1	25.5%	1.6	865.1	1557.1	0.1%
38	17.5	79.2	71.3	9.1%	15.1	91.7	165.1	6.2%
Testosterone	13.7	101.2	91.1	4.8%	0.7	2097.5	3775.6	0.0%
Diclofenac	9.6	144.3	129.9	1.2%	17.4	79.5	143.0	8.7%
Propafenone	6.6	211.1	190.0	0.2%	2.1	657.9	1184.2	0.3%

^a $CL_{int(mic)} = 0.693/\text{half-life}/\text{mg}$ microsomal protein per mL. ^b $CL_{int(liver)} = CL_{int(mic)} \times \text{mg}$ microsomal protein per g liver weight $\times$ g liver weight per kg body weight.

Fig. 5 Compound **38** (yellow) overlapped with **1** (magenta) in the PI3K δ catalytic site: A) highlighting the bicyclic heteroaromatic core; B) highlighting the short spacer.

compound **38** was approximately 6-fold and 13-fold more potent in PI3K δ inhibitory activity and anti-proliferative activity, respectively. Compared to enzymatic activity, a more obvious enhancement in anti-proliferative activity occurred. Thus, it was speculated that replacement of purine with 4-amino-5-carbonitrile pyrimidine didn't weaken the anti-proliferative activity.

2.4. PI3K δ specificity

To confirm the PI3K δ specificity of these quinazolones, compounds **37** and **38** were selected for evaluating their selectivity over PI3K α , β , and γ . The results illustrated that compound **37** exhibited comparable selectivity to **1** (Table 2). Importantly, compound **38** demonstrated superior subtype-specificity to **1**, and was 1364, 247 and 56-fold selective over PI3K α , β and γ , respectively. Given the favorable PI3K δ inhibitory activity and selectivity of **38**, 4-amino-5-carbonitrile pyrimidine was a desirable surrogate to purine as the HB.

2.5. Western blot analysis

Compound **38**, with the most potent enzymatic and cellular activities in this series, as well as favorable PI3K δ selectivity,

was subsequently selected for the evaluation of its capability to down-regulate the PI3K signaling in the SU-DHL-6 cell line *via* Western blot assay (Fig. 4A). The lowered phosphorylation levels of Akt (S473) (Fig. 4B) and its downstream effector S6K1 (T389) (Fig. 4C) indicated the suppressed PI3K signaling. According to the results, compound **38** inhibited the phosphorylation of both Akt and S6K1 in a dose-dependent manner. Particularly, at the concentration as low as 100 nM, it was capable to remarkably attenuate the phosphorylation of both investigated signaling effectors. Hence, compound **38** can strongly ablate the PI3K signaling.

2.6. *In vitro* liver microsomal stability

Compounds **37** and **38** were subsequently incubated with human liver microsome (HLM) and rat liver microsome (RLM) to investigate their *in vitro* metabolic stability. According to the data shown in Table 3, compound **38** exhibited acceptable metabolic stability in both HLM and RLM with the elimination half-life being 17.5 and 15.1 min, respectively. In comparison, compound **37** only displayed acceptable metabolic stability in HLM with the elimination half-life being 31.1 min.

2.7. Preliminary pharmacokinetic (PK) study

We then evaluated the PK profiles of **38** in Sprague–Dawley (SD) rats following oral administration at the dosage of 10 mg kg⁻¹. Consequently, **38** exhibited an AUC_{0–last} value of 3048 ± 1470 ng min mL⁻¹ and a T_{1/2} value of 4.10 ± 1.69 h. According to the results, compound **38** needs further structural optimization to improve its PK profiles.

2.8. Molecular docking analysis

The binding mode of representative quinazalone **38** with the enzyme was then simulated on the basis of the reported crystal structure of the idelalisib–PI3Kδ complex (PDB code 4XE0).³⁵ Fig. 5 depicts the location of compound **38** overlapped with **1** in the PI3Kδ catalytic site. Despite the incorporation of the conformationally restricted *S*-pyrrolidine as the short spacer, **38** assumed a similar binding mode with the PI3Kδ catalytic site to **1**. The quinazalone core is located deeply into the allosteric selectivity pocket bearing Trp760 on one side and Met752 on the other side, while the 4-amino-5-carbonitrile pyrimidine moiety is in contact with the hinge region *via* forming two H-bonds. In addition, the *N*-3 position of the quinazalone was oriented to the solvent-exposed region, thereby being a potential site for further structural elaboration. This also accounted for the comparable PI3Kδ inhibitory activity of compounds with different substitutions at this site, including **30** and **32–34**.

3. Conclusions

Upon introduction of the conformationally restricted *S*-pyrrolidine as the spacer between the quinazalone template and HB, as well as structural alteration at the *N*-3 position, ten novel PI3Kδ-selective inhibitors were designed, synthesized, and biologically evaluated in this feasibility study. Most of them displayed two-digit to single-digit nanomolar PI3Kδ inhibitory activity. In particular, compound **38** exhibited the most remarkable PI3Kδ inhibitory activity in this series with an IC₅₀ value of 6.3 nM. Consistent with the potent enzymatic activity, it also exerted the most favorable cytotoxic efficacy against the SU-DHL-6 cell line in this series with a GI₅₀ value of 0.21 μM. Moreover, compound **38** displayed superior selectivity profile compared to **1**. At the concentration as low as 100 nM, **38** dramatically suppressed the phosphorylation of both Akt and S6K1 in the SU-DHL-6 cell line, highlighting its capability to ablate the PI3K signaling. In both HLM and RLM, **38** demonstrated acceptable *in vitro* metabolic stability. Further PK study illustrated that structural modification of **38** was demanded to improve its oral exposure. However, by virtue of its excellent potency and specificity, **38** may serve as a promising lead for extensive structural optimization attempted to explore novel PI3Kδ-selective inhibitors as clinical candidates. Based on the proof-of-concept study, our efforts to broaden the chemical diversity of these conformationally restricted quinazolones are currently underway.

Conflicts of interest

The authors confirm that this article content has no conflicts of interest.

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