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Design, synthesis and structure-activity relationship study of piperazinone-containing thieno[3,2-*d*]pyrimidine derivatives as new PI3Kδ inhibitors

Ning-Yu Wang[a,*,1], Wei-Qiong Zuo[b,1], Rong Hu[a], Wan-Li Wang[a], Yong-Xia Zhu[b], Ying Xu[b], Luo-Ting Yu[b], Zhi-Hao Liu[b,*]

[a] School of Life Science and Engineering, Southwest Jiaotong University, Chengdu, China
[b] Lab of Medicinal Chemistry, Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center, Chengdu, China

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ABSTRACT

Two classes of piperazinone-containing thieno[3,2-*d*]pyrimidines were designed and synthesized as new PI3Kδ inhibitors in this study. Detailed SAR study with respect to the piperazinone substituents at the 6-position of thieno[3,2-*d*]pyrimidine core demonstrated that piperazinone-containing thieno[3,2-*d*]pyrimidines would be more potent and selective for PI3Kδ than their piperazine counterparts, which led to the discovery of several potent PI3Kδ inhibitors with comparable or better antiproliferative activity against a panel of non-Hodgkin lymphoma (NHL) cell lines as compared with idelalisib. Our study will promote the development of new PI3Kδ inhibitors based on piperazinone-containing thieno[3,2-*d*]pyrimidine scaffold.

The phosphatidylinositol 3-kinases (PI3Ks) family contains a panel of lipid kinases which regulate many physiological functions and cellular processes, including cell proliferation, survival and metabolism.[1] The amplification or mutation of PI3Ks are always associated with different diseases, including various cancers[2] and autoimmune diseases,[3] implying that PI3K pathways would be promising drug targets. Up to now, a number of small molecules targeted at PI3Ks have been developed[4] and their clinical benefit for cancer patients have been extensively validated.[5] Current reported PI3K inhibitors could be divided into two classes: pan PI3K inhibitors and isoform-selective PI3K inhibitors.[4] Although the former class, including pan-class I PI3K inhibitors and pan-PI3K/mTOR inhibitors, have demonstrated remarkable anticancer activity in preclinical models of solid tumor and leukemia, most cancer patients cannot achieve satisfactory clinical efficiency from them owing to their dose-limiting toxicities or inadequate responses in the clinic.[6,7] While isoform-selective PI3K inhibitors, which only target at one or several PI3K isoforms closely related to specific cancer types, have achieved impressive efficiency in clinical, including PI3Kδ inhibitors in B cell malignancies and PI3Kα inhibitors in advanced breast cancer.[8]

The PI3Kδ isoform mainly expresses in leukocytes and is crucial for the survival of leukocytes as well as their malignant counterpart.[9] It was thus thought to be a promising target for the treatment of lymphomas. A number of PI3Kδ inhibitors have been disclosed in recent years,[10] and some of them have entered advanced clinical trials or even been approved, such as idelalisib, duvelisib and umbralisib (Fig. 1a). However, several disadvantages, including significant toxicity, poor target selectivity as well as unsatisfactory pharmacokinetic profiles, have prevented their wide application or clinical development. More potent PI3Kδ inhibitors with new chemotypes are thus needed to be developed to provide us more drug candidates.

Thienopyrimidine derivatives have represented a classical chemotype of PI3K inhibitors, including pan-PI3K inhibitors as well as isoforms selective PI3K inhibitors (Fig. 1b).[11] Previous reports have demonstrated that the substituent at 6-position of thienopyrimidine core is important for the PI3Kδ isoform selectivity, mainly due to the "tryptophan shelf" effect that a small amino acid, threonine, at position 750 in PI3Kδ is substituted by a larger, charged amino acid, lysine or arginine, in the other three Class I isoforms (Fig. 2).[12–15] This subtle difference in residues results in the substantial different drug-target interactions between the piperazine ring of GDC-0941 and PI3Kδ as well as other PI3K isoforms,[16] and thus makes it possible to develop selective PI3Kδ inhibitors by minor structural modifications from a pan-PI3K inhibitor. In this study, a series of thienopyrimidine derivatives implanting two kinds of piperazinone motifs at 6-position were designed as novel PI3Kδ inhibitors. We thought that the relative rigid and tortuous feature of piperazinone would facilitate the terminal fragment accessing the tryptophan shelf of PI3Kδ while impair its binding with

* Corresponding authors.
E-mail addresses: wangny-swjtu@swjtu.edu.cn (N.-Y. Wang), liuzhihao@scu.edu.cn (Z.-H. Liu).
[1] These authors contributed equally to this work.

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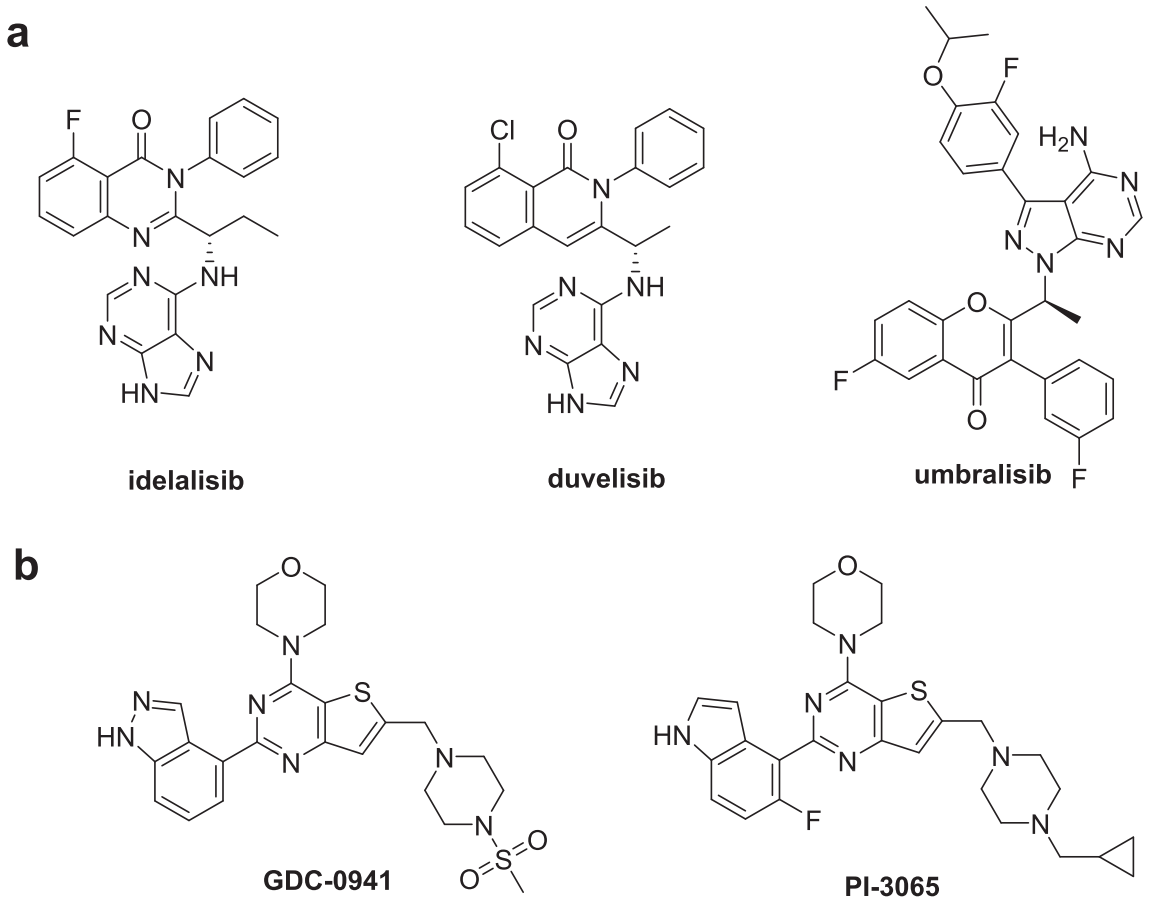


Fig. 1. Structure of representative PI3K inhibitors. (a). The structure of PI3Kδ inhibitors idelalisib, duvelisib and umbralisib; (b). The structure of thienopyrimidine PI3K inhibitors, including pan-PI3K inhibitor GDC-0941 and PI3Kδ inhibitor PI-3065.

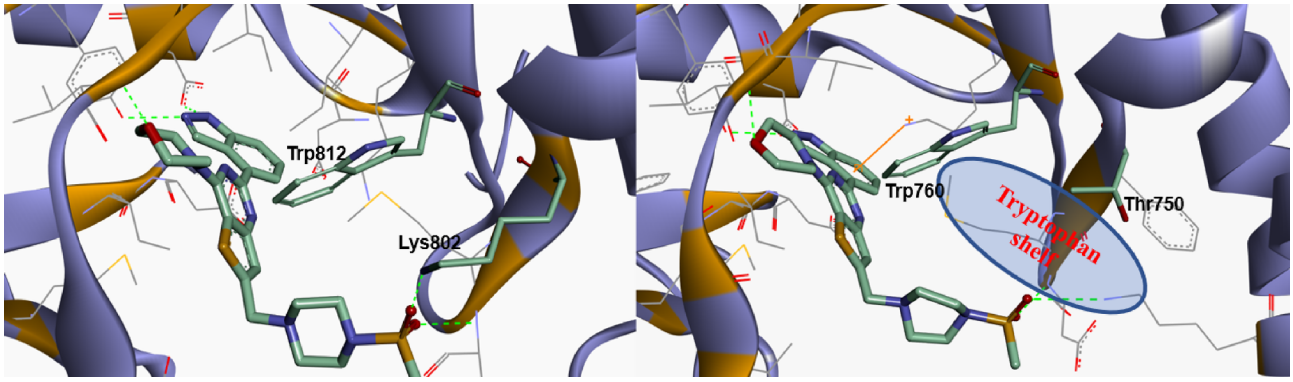
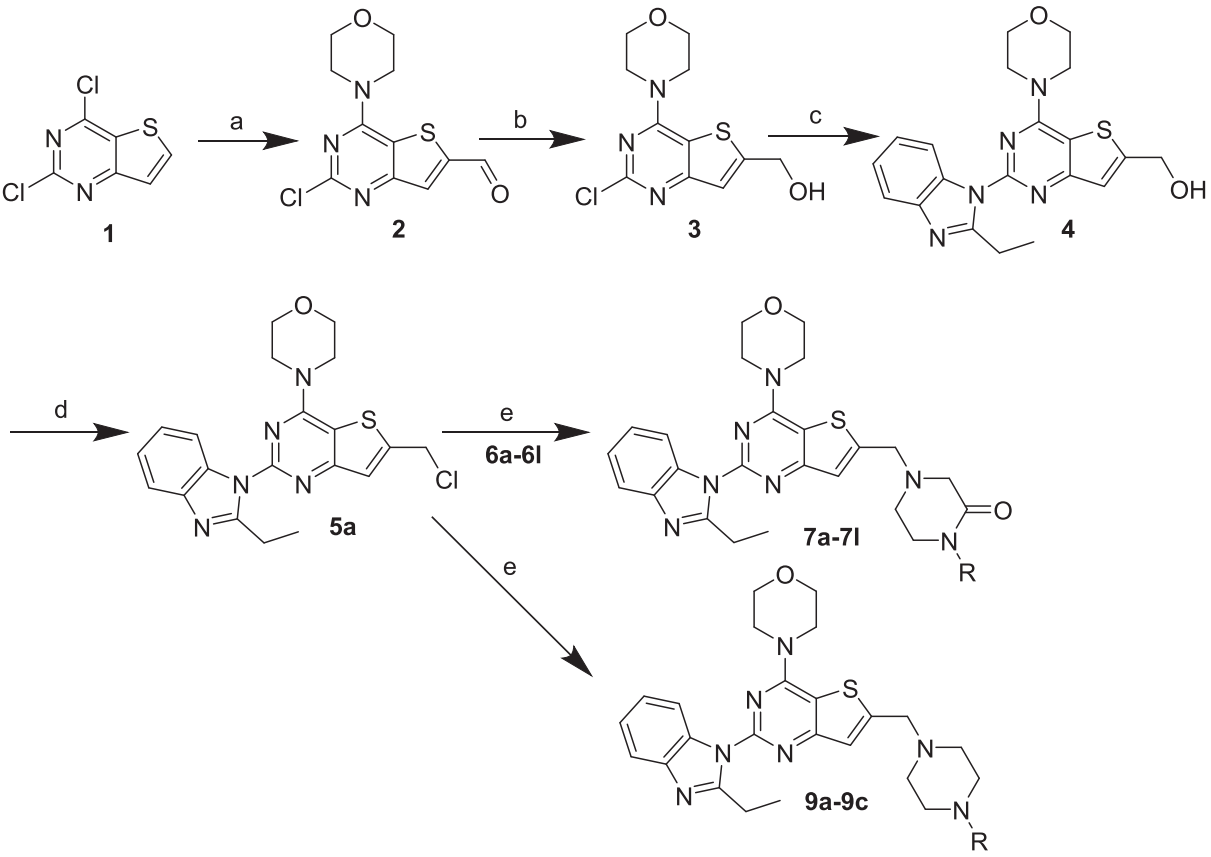


Fig. 2. Cocrystal structure of PI3Kγ + GDC-0941 (left, PDB ID: 3DBS)[15] and PI3Kδ + GDC-0941 (right, PDB ID: 2WXP)[16] demonstrate the "tryptophan shelf" formed in PI3Kδ.

other PI3K isoforms. Here we report the synthesis, structure-activity relationship (SAR) study and the preliminary biological evaluation with respect to this kind of PI3Kδ inhibitors to validate their potential as anticancer agents.

The synthesis route of thienopyrimidine derivatives **7a-7l, 8a-8ab** and **9a-9c** is shown in Scheme 1 and Scheme 2. To prepare the two kinds of piperazinone-containing thieno[3,2-*d*]pyrimidines reported in our study, an alternative synthesis route was designed based on previous studies.[17–18] Briefly, compound **1** underwent nucleophilic substitution with morpholine and formylation with dimethylformamide to afford aldehyde **2**, which was reduced by sodium borohydride to provide alcohol **3**. Then C—N coupling of compound **3** and 2-ethylbenzo[*d*] imidazole afford **4**, which was then chloridized with thionyl chloride to provide the critical common intermediates **5a**. **5a** reacted with different 1-substituted piperazin-2-ones (**6a-6l,** Supplementary data Table 1) or 1-substituted piperazines in the presence of *N,N*-diisopropylethylamine to provide **7a-7l** and **9a-9c**, or it underwent nucleophilic substitution with 4-methylpiperazin-2-one or *tert*-butyl 3-oxopiperazine-1-carboxylate to produce the title compounds **8a** and **8x**(Scheme 2).

The Boc group of **8x** was removed by trifluoroacetic acid in dichloromethane to provide **5b**, which was nucleophilic substituted with 2,2,2-trifluoroethyl methanesulfonate in acetonitrile to produce **8b**. And reduction amination of **5b** with different aldehydes or ketones in dichloromethane by sodium triacetoxyborohydride produced **8c-8k**. **8k** was then underwent deprotection of ethylene glycol with concentrated hydrochloric acid to afford ketone **8l**, which was reduced by sodium



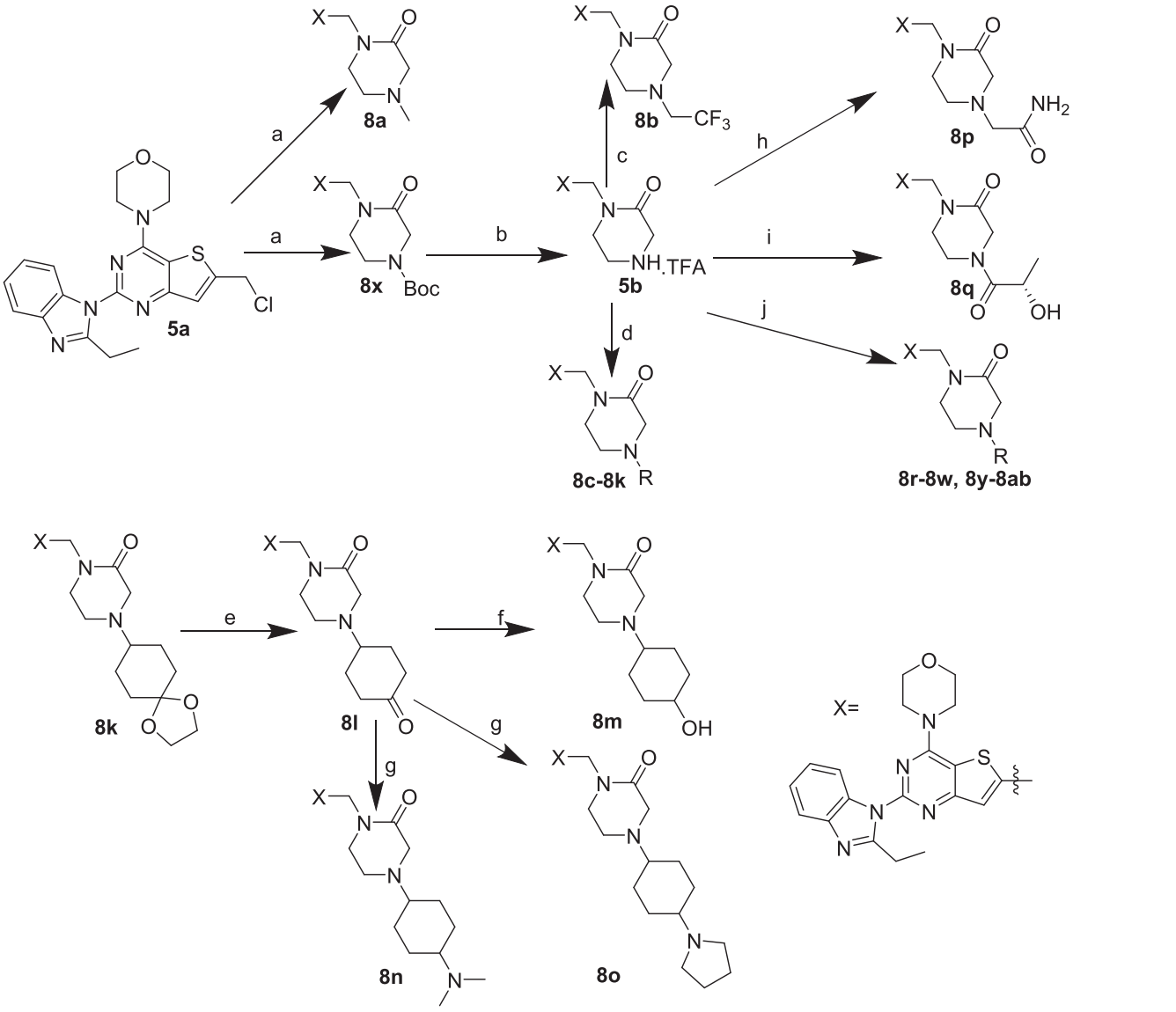
Scheme 1. Synthesis of thieno[3,2-*d*]pyrimidine derivatives **7a-7l** and **9a-9c**. Reagents and conditions: a. (i) Morpholine, MeOH, rt; (ii) *n*-BuLi, DMF, THF, −78 °C; b. $NaBH_4$, MeOH; c. $Pd_2(dba)_3$, XPhos, Cs_2CO_3, 1,4-Dioxane, 110 °C; d. $SOCl_2$, DCM; e. DIPEA, i-PrOH, reflux.

borohydride to provide alcohol **8m**, or underwent reduction amination with dimethylamine hydrochloride or pyrrolidine to provide **8n** and **8o**. The acetamide **8p** was prepared by nucleophilic substitution of **5b** with iodoacetamide in acetonitrile, while **8q** was got by condensation reaction of **5b** with L-lactic acid. Finally, **5b** underwent acylation with different acyl chlorides or sulfonylation with different sulfonyl chlorides to produce **8r-8w**, **8y-8ab**.

Previous studies have demonstrated that a benzo[*d*]imidazole fragment substituted at 2-position of thieno[3,2-*d*]pyrimidine core could fit well into the affinity pocket of PI3Kδ to achieve moderate to good PI3Kδ inhibitory activity and selectivity.[12,14,18] More importantly, the benzo[*d*]imidazole motif could also significantly attenuate CYP3A4 time-dependent inhibition to avoid the drug-drug interactions (DDI) risk,[12] which makes benzo[*d*]imidazoles an preferred class of substituents for 2-position of thieno[3,2-*d*]pyrimidine core. 2-Ethylbenzo[*d*]imidazole motif was thus selected to incorporate in the 2-position of thieno[3,2-*d*]pyrimidine core in this study. Several 4-(thieno[3,2-*d*]pyrimidin-6-ylmethyl)piperazin-2-ones (**7a-7l**) harboring alkyls or aryls in the 1-position of piperazinone with different size were firstly prepared, And the potency of these compounds for PI3Kδ and PI3Kα were tested to evaluate their potency and PI3Kδ selectivity. As shown in Table 1, a hydrophobic alkyl group on 1-position of piperazinone (**7b-7g** VS **7h-7i**) seemed to be essential for the potency against PI3Kδ and the increase in the size would benefit the potency and the δ/α selectivity as well. An alkyl or cycloalkyl with 3–5 carbons seemed to be the best substituent for both the PI3Kδ potency and the δ/α selectivity. When an aryl was introduced to this position, a substantial loss of potency for PI3Kδ as well as the δ/α selectivity was observed. This could be partly attributed to the high rigidity of 1-aryl-piperazin-2-one motif that might compromise the fitness of these compounds for PI3Kδ. The preliminary SAR study yielded several potent PI3Kδ inhibitors with low nanomolar IC_{50} and moderate to good δ/α selectivity, which demonstrated the possibility to develop PI3Kδ inhibitors based on piperazinone motifs.

The lactam nitrogen in 4-(thieno[3,2-*d*]pyrimidin-6-ylmethyl)piperazin-2-one series (**7a-7l**) prevent its modification for extensive SAR study. We thus designed the 1-(thieno[3,2-*d*]pyrimidin-6-ylmethyl)piperazin-2-one series (**8a-8ab**) which allowed the introduction of more diverse fragments to optimize the potency and selectivity. When alkyls or cycloalkyls were introduced to the 4-position of piperazinone (**8a-8f**), all compounds exhibited excellent potency for PI3Kδ with moderate to good δ/α selectivity. And an alkyl or cycloalkyl with 3–5 carbons also seemed to be the best substituent for both the PI3Kδ potency and the δ/α selectivity, which was consistent with the 4-(thieno[3,2-*d*]pyrimidin-6-ylmethyl)piperazin-2-one series. The replacement of cyclohexyl in **8f** with hexatomic heterocycles (**8g-8i**) resulted in negligible to moderate improvement in both PI3Kδ potency and δ/α selectivity, while the introduction of substituents with hydrogen receptors (**8j-8m**) at the *para*-position of cyclohexyl substantially benefit the PI3Kδ potency. We speculated that these four compounds might form an additional hydrogen bond with PI3Kδ via this fragment to contribute the PI3Kδ potency but only **8k** and **8m** could form a hydrogen bond with PI3Kα, which resulted in a better δ/α selectivity for **8j** and **8l**. A basic substituent at the *para*-position of cyclohexyl (**8n, 8o**) would be harmful to the PI3Kδ potency, which could also be validated by **8g**. The position of the piperazinone carbonyl seemed to be inessential for the PI3Kδ potency or the δ/α selectivity (**7b**&**8a**, **7e**&**8d**, **7f**&**8e**, **7g**&**8m**, **7h**&**8p**), though the presence of this carbonyl seemed to be critical for both PI3Kδ potency and selectivity (**7f**, **8e**&**9c**).

Next, a series of acyls and sulfonyls were introduced to the 4-position of piperazinone. Almost all of these acyl and sulfonyl derivatives exhibited excellent PI3Kδ potency with single-digit nanomolar IC_{50}s, while the acyl panel displayed much better δ/α selectivity as compared with the sulfonyl panel. A possible explanation for this phenomenon



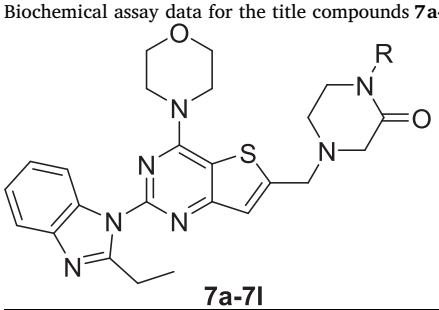
Scheme 2. Synthesis of thieno[3,2-*d*]pyrimidine derivatives **7a-7l** and **9a-9c**. Reagents and conditions: a. *t*-BuOK, THF, 0 °C; b. TFA, DCM, rt; c. 2,2,2-trifluoroethyl methanesulfonate, K_2CO_3, MeCN, reflux; d. aldehydes or ketones, DCM, sodium triacetoxyborohydride; e. DCM, THF, concentrated HCl(aq); f. $NaBH_4$, MeOH, 0 °C-r.t.; g. dimethylamine hydrochloride(**8n**) or pyrrolidine(**8o**), DCM, sodium triacetoxyborohydride; h. iodoacetamide, MeCN, reflux; i. L-lactic acid, HOBT, EDCI, TEA, DCM; j. acyl chlorides or sulfonyl chlorides, TEA, DCM.

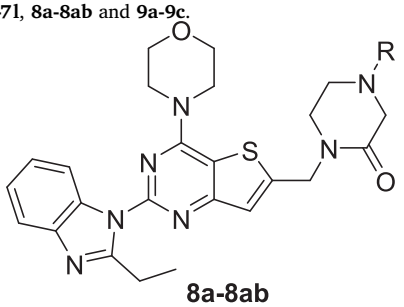
would be that the bond angle of the two single bonds for sulfonyl is significantly smaller than that for acyl, which facilitate their interaction with PI3Kα and finally led to worse δ/α selectivity. Moreover, our sulfonyl piperazinone derivatives also exhibited better PI3Kδ potency and δ/α selectivity as compared with their sulfonyl piperazine counterparts (**8y**&**9a**, **8ab**&**9b**) in spite of to a less extent.

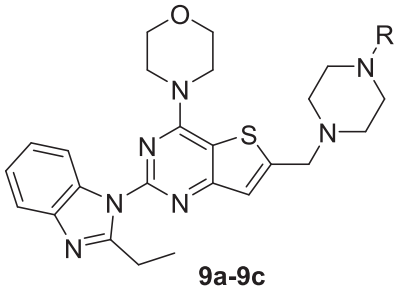
Our SAR study have demonstrated that piperazinone would be a promising motif to design new PI3Kδ inhibitors with better PI3Kδ potency and δ/α selectivity, regardless of the position of the carbonyl of piperazinone. To interpret the importance of piperazinone motif for PI3Kδ potency and δ/α selectivity, two structurally similar compounds **8e** and **9c** were selected to dock into the hinge and affinity pocket of PI3Kδ. As shown in Fig. 3, the O atom of morpholine and N atom of benzimidazole of both compounds formed two crucial hydrogen bonds with Val828 and Lys779 of PI3Kδ, respectively. And the piperazinone fragment in **8e** and the piperazine fragment in **9c** could stack on the "tryptophan shelf" formed by Thr750 and Trp760 in PI3Kδ, which endow the PI3Kδ selectivity of both compounds over other PI3K isoforms. It seemed that the relative rigid piperazinone fragment of **8e** could adopt a favorable packing interaction with the indole ring of Trp760 over its piperazine counterpart **9f** via the methylene groups of piperazinone and cyclopentyl, which would be a possible explanation for the substantial better PI3Kδ potency of **8e** than **9c**.

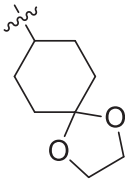
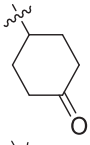
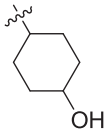
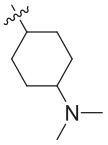
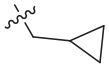
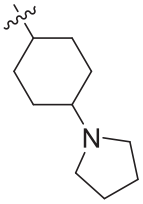
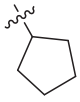
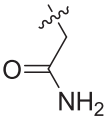
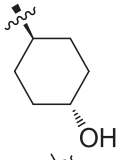
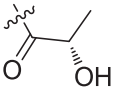
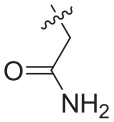
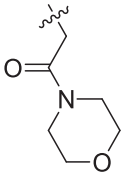
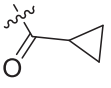
The preliminary optimization with respect to piperazinone-containing thieno[3,2-*d*]pyrimidines have provide us several compounds with comparable or even better PI3Kδ potency as compared with idelalisib, several potent and selective piperazinone PI3Kδ inhibitors (**7f**, **8e**, **8l**, **8s**, **8t**) were selected to further evaluate their PI3K isoforms selectivity as well as the antiproliferative activity (Table 2). All of these compounds also exhibited good δ/β and δ/γ selectivity with SI of > 100, implying that the PI3Kδ isoforms selectivity of piperazinone-containing thieno[3,2-*d*]pyrimidines is not restricted to PI3Kα. Four non-Hodgkin lymphoma (NHL) cell lines, including three diffuse large B-cell lymphoma (DLBCL) cell lines (SU-DHL-6, OCI-LY-3, OCI-LY-10) and one mantle cell lymphoma (MCL) cell line (JEKO-1), as well as three normal cell lines (Vero, LO-2 and HEK-293) were selected to evaluate the antiproliferative activity of the abovementioned PI3Kδ inhibitors by MTS assay. All these compounds exhibited similar

Table 1
Biochemical assay data for the title compounds **7a-7l**, **8a-8ab** and **9a-9c**.



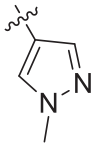
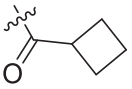
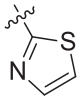
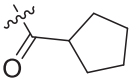
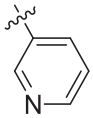
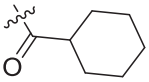
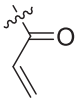
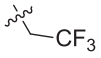
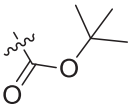
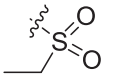
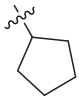
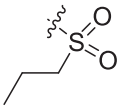
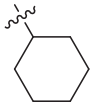
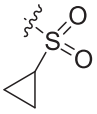
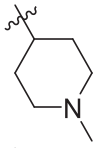
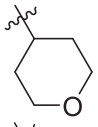
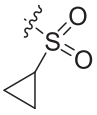
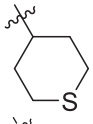
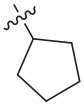
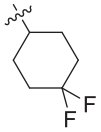




Cpd	R	PI3Kδ IC_{50}(nM)[a]	PI3Kα/δ Selectivity[b]	Cpd	R	PI3Kδ IC_{50}(nM)	PI3Kα/δ selectivity
7a	H	20	13	**8k**		2.2	13
7b	Me	4.9	53	**8l**		1.6	184
7c	Et	4.1	10	**8m**		1.6	18
7d		5.7	7.7	**8n**		14 ±	36
7e		2.5	49	**8o**		14	8
7f		2.1	119	**8p**		6.2	25
7g		2.1	35	**8q**		3.6	49
7h		12	7.1	**8r**		3.2	35
7i		15	11	**8s**		1.1	76

(*continued on next page*)

Table 1 (*continued*)

Cpd	R	PI3Kδ IC_{50}(nM)[a]	PI3Kα/δ Selectivity[b]	Cpd	R	PI3Kδ IC_{50}(nM)	PI3Kα/δ selectivity
7j		3.4	24	**8t**		1.4	84
7k		82	7.7	**8u**		2.0	95
7l		13	12	**8v**		7.9	43
8a	Me	4.5	48	**8w**		2.9	47
8b		6.3	32	**8x**		12	52
8c		2.1	53	**8y**		2.2	10
8d		2.2	64	**8z**		4.4	10
8e		2.9	84	**8aa**		3.5	4
8f		12	21	**8ab**		1.2	38
8g		15	25	**9a**		4.1	2.4
8h		6.2	61	**9b**		4.8	13
8i		4.8	56	**9c**		42	31
8j		3.8	71	**Idelalisib[c]**		4.7	> 106

[a] IC_{50} values for PI3Kδ and PI3Kα are the mean value of at least two independent measurements.
[b] The PI3Kα/δ selectivity was calculated as the ratio of the IC_{50} values of a compound to PI3Kα and PI3Kδ.
[c] Idelalisib is a selective PI3Kδ inhibitor with reported IC_{50}s of 820 nM, 565 nM, 2.5 nM and 89 nM against PI3Kα, β, δ and γ, respectively.[19]

antiproliferative profile that the SU-DHL-6 cells and JEKO-1 cells were highly sensitive to our PI3Kδ inhibitors, while the OCI-LY-10 cells were insensitive. Moreover, the five piperazinone-containing thieno[3,2-*d*] pyrimidines as well as idelalisib did not display obvious cytotoxicity against all the three normal cell lines at a concentration of 20 μM, implying their good safety profiles.

In this study, piperazinone motif was introduced into the thieno [3,2-*d*]pyrimidines core to prepare new PI3Kδ inhibitors by utilizing the different residues surrounding the solvent exposed entrance between PI3Kδ and other PI3K isoforms. Detailed SAR study demonstrated that both the 4-(thieno[3,2-*d*]pyrimidin-6-ylmethyl)piperazin-2-one and 1-(thieno[3,2-*d*]pyrimidin-6-ylmethyl)piperazin-2-one

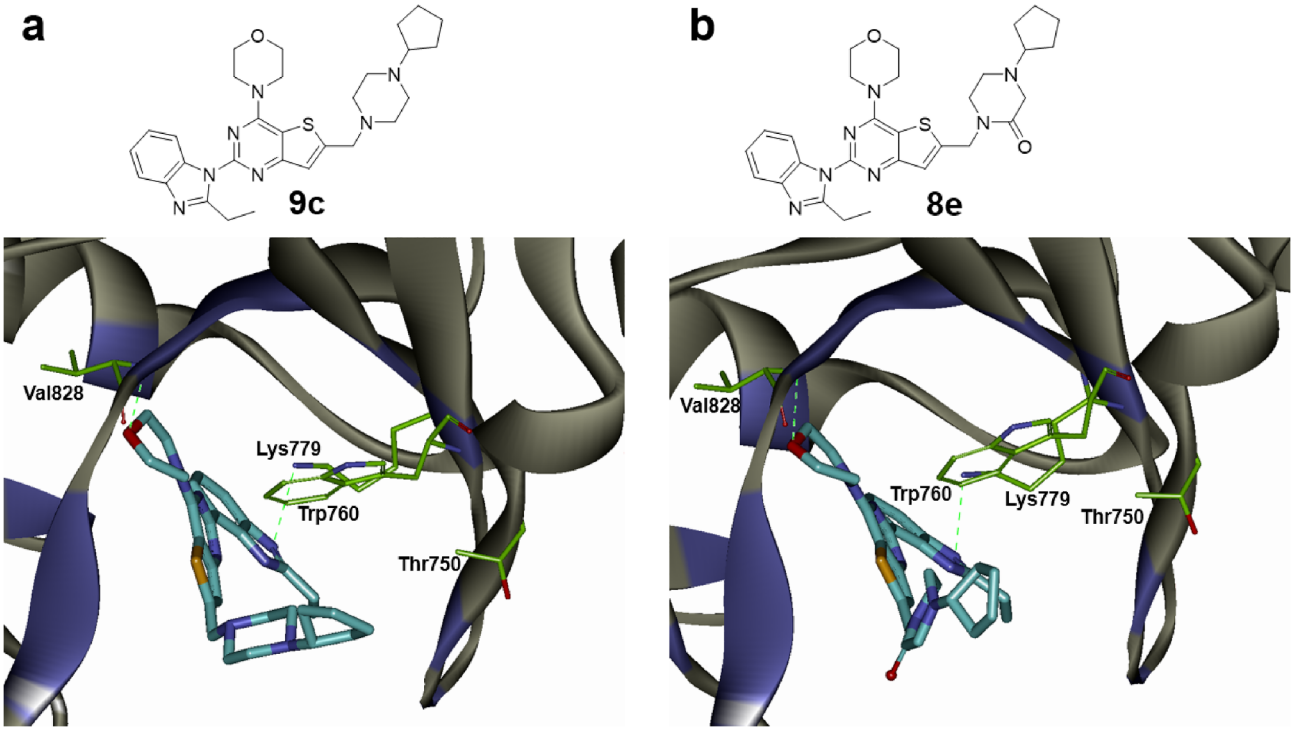


Fig. 3. Models comparing the interaction of PI3Kδ and piperazine or piperazinone-containing thieno[3,2-*d*]pyrimidine derivatives. (a) The flexible piperazine fragment of **9c** attenuate its interaction with the indole ring of Trp760. (b) The relative rigid piperazinone fragment of **8e** would facilitate its packing interaction with the indole ring of Trp760 via the methylene groups of piperazinone and cyclopentyl.

Table 2
The PI3K isoforms selectivity and antiproliferative activity of five potent PI3Kδ inhibitors.[a]

Cmpds	PI3K isoforms potency (IC_{50}: nM)				Antiproliferative activity (IC_{50}: μM)						
	PI3Kδ	PI3Kα	PI3Kβ	PI3Kγ	OCI-LY-3	OCI-LY-10	SU-DHL-6	JEKO-1	Vero	LO-2	HEK-293
Idelalisib	4.7 ± 1.9	> 500	> 500	245 ± 52	5.2 ± 2.4	> 10	0.12 ± 0.05	0.12 ± 0.06	> 20	> 20	> 20
7f	2.1 ± 0.9	250 ± 37	> 500	> 500	2.8 ± 1.5	> 10	0.18 ± 0.07	0.17 ± 0.02	> 20	> 20	> 20
8e	2.9 ± 0.5	243 ± 54	> 500	370 ± 65	6.9 ± 1.7	> 10	0.53 ± 0.39	0.56 ± 0.31	> 20	> 20	> 20
8l	1.6 ± 0.6	295 ± 72	232 ± 61	266 ± 73	8.6 ± 4.6	> 10	0.57 ± 0.16	0.47 ± 0.13	> 20	> 20	> 20
8s	1.1 ± 0.5	84 ± 13	137 ± 24	185 ± 43	2.2 ± 0.9	7.6 ± 4.2	0.10 ± 0.04	0.19 ± 0.08	> 20	> 20	> 20
8t	1.4 ± 0.3	117 ± 26	165 ± 12	303 ± 81	1.5 ± 0.3	> 10	0.08 ± 0.02	0.12 ± 0.03	> 20	> 20	> 20

[a]IC_{50} values for PI3K isoforms potency and antiproliferative activity are the mean of three independent measurements and represent as mean ± SD.

derivatives would be more potent and selective for PI3Kδ than their piperazine counterparts, which led to the discovery of several highly selective PI3Kδ inhibitors with single-digit nanomolar of IC_{50}s. And the molecular modeling results further confirmed that the relative rigid piperazinone fragment indeed facilitated the interaction of PI3Kδ with the inhibitor by favorable packing interactions. These piperazinone PI3Kδ inhibitors also exhibited comparable antiproliferative activity against a panel of NHL cell lines as compared with idelalisib while without obvious cytotoxicity against normal cell lines. This study thus provided us a start point to develop new PI3Kδ inhibitors based on piperazinone motifs and the optimization with respect to thieno[3,2-*d*] pyrimidine core as well as the benzo[*d*]imidazole motif would further improve the drug-like property of this chemotype.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127479.

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