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Five-membered heteroaromatic ring fused-pyrimidine derivatives: Design, synthesis, and hedgehog signaling pathway inhibition study

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ABSTRACT

A series of novel five-membered heteroaromatic ring fused-pyrimidine derivatives including purines, pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines and furo[3,2-*d*]pyrimidines have been identified to be potent inhibitors of hedgehog signaling pathway. The synthesis and SAR of these compounds are described. Among this new series of hedgehog signaling pathway inhibitors, most compounds exhibited significant inhibitory activity compared to vismodegib, indicating that the five-membered heteroaromatic ring fused-pyrimidines stand out as encouraging scaffolds among the currently reported structural skeletons for hedgehog signaling pathway inhibitors, deserving more exploration and further investigation.

Hedgehog (Hh) signaling pathway has been found to be a key signal transduction cascade which significantly affects embryonic morphogenesis, tissue patterning, angiogenesis and tumorigenesis.[1] The Hh signaling transduction is initiated by binding of the Hh-protein, such as sonic hedgehog (Shh), Indian hedgehog (Ihh), desert hedgehog (Dhh), to its cellular membrane receptor patched (Ptch), thereafter leading to the relief of suppressed GPCR-like receptor smoothened (Smo). The activated Smo can trigger a downstream signaling cascade, leading to activation of Gli-transcription factors. And then the active Gli-1 and Gli-2 move into the nucleus where they induce the target genes to regulate proliferation, differentiation, and survival.[2] Usually, the Hh signaling is inactive in adulthood; however, when mutations or hyper-activations in this signaling pathway occur, it becomes aberrantly activated and consequently leads to tumor growth and aggravation. For examples, loss-of-function mutations in Ptch1 occur in a majority of basal cell carcinoma (BCC) and approximately 30% of sporadic medulloblastoma cases, while Hh overexpression by an autocrine or paracrine manner in this pathway identified in the past few years is implicated in many other cancer types, such as lung, pancreatic, gastric, colorectal, prostate, breast and melanoma tumors.[3] Hence, inhibition of Hh signaling pathway is considered to be an attractive therapeutic strategy for anticancer intervention.[4] In 2012, the small molecule Hh signaling pathway inhibitor vismodegib (GDC-0449) was approved by FDA for its significantly clinical efficacy in phase II clinical evaluation of metastatic and locally advanced BCC. Subsequently, the Hh signaling pathway inhibitors NVP-LDE225 and LY-2940680 were also quickly advanced into clinical phase III and phase II, respectively, to validate their clinical profiles for cancer therapy (Fig. 1).[5]

We have reported a novel series of potent 4-(2-pyrimidinylamino)benzamide-based inhibitors of Hh signaling pathway recently, such as **1**, which exhibited highly effective inhibition with an IC_{50} = 1.3 nM in Gli-luciferase reporter assay.[6] In the course of extensively structural modification, we have described the SAR details, and identified several compounds showing satisfactory potency and significant pharmacokinetic properties. In addition, on the basis of 4-(2-pyrimidinylamino)benzamide core, using conceptual cyclization strategy, we have also developed two new pyrimidine-based scaffolds, pyrrolo[2,1-*f*][1,2,4]triazines and dihydro-5*H*-pyrano[2,3-*d*]pyrimidines.[7] And in the comparison of these two nucleuses derivatizing analogues, it showed that pyrrolo[2,1-*f*][1,2,4]triazines exhibited more potent inhibition than dihydro-5*H*-pyrano[2,3-*d*]pyrimidines. For examples, pyrrolo[2,1-*f*][1,2,4]triazine **2** (IC_{50} = 1.6 nM) displayed over three-fold more effective than dihydro-5*H*-pyrano[2,3-*d*]pyrimidine **3** (IC_{50} = 5.2 nM). From these discoveries, with substitution of the

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0960-894X/

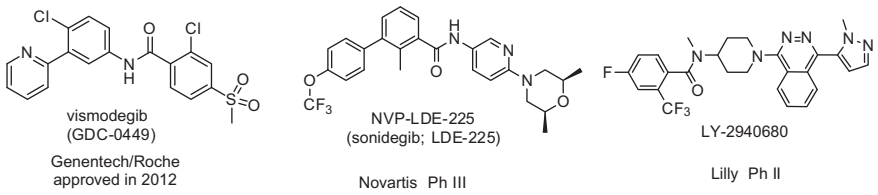


Figure 1. Chemical structure of several Hh signaling pathway inhibitors.

pyrimidine extensively explored, we became interested in preparing other five-membered ring fused-pyrimidine heterocyclic cores, such as purines, pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines and furo[3,2-*d*]pyrimidines. These novel alternative scaffolds would allow us to maintain the optimized substitute profile, while potentially attempting to improve the developability characteristics, by altering lipophilicity of the core skeleton. Accordingly, herein we describe the synthesis of several novel scaffolds of five-membered heteroaromatic ring fused-pyrimidine, and their inhibition toward the Hh signaling pathway (Fig. 2).

The novel five-membered heteroaromatic ring fused-pyrimidine derivatives (**18a–18b**, **20a–20d**, **21a–21b**, **26a–26c**, **30a–30d**, **44a–44d** and **45a–45c**) were prepared as depicted in Schemes 1–4.

Scheme 1 detailed the synthesis of the desired purines (**18a–18b**, **20a–20d** and **21a–21b**). We first prepared the four building blocks **6**, **9**, **13a** and **13b**, shown in Scheme 1-A. Condensation of 4-nitrobenzoic acid **4** with 2,6-dimethylaniline, 3-amino-4-methylphenol and 3-amino-4-methylbenzyl alcohol provided intermediates **5**, **7** and **10**, respectively. Reduction of **5** using catalytic hydrogenation by hydrogen in the presence of 10% Pd/C led to the block **6**, while block **9** was obtained including nucleophilic substitution of **7** with commercially available 4-(2-chloroethyl)morpholine hydrochloride, then following a similar catalytic hydrogenation procedure. And blocks **13** were synthesized from **10** by three steps, through chlorination of **10** with thionyl chloride to give **11**, which was subsequently substituted by cyclic amines and then catalytically hydrogenated in a similar procedure. With success in accomplishing the building blocks, we then focused on coupling of the above blocks with 2-chloro-6-(4-trifluoromethoxyphenyl)purine (Scheme 1-B). However, straight Suzuki C–C coupling of block **6** with 2,6-dichloro-9*H*-purine **14** gave complex mixtures and was difficult to isolate the desired product **16a**. Considering that such difficulty was likely due to the presence of free NH group in purine backbone, we decided to introduce protecting group at 9-position of purine. In this regard, 2,6-dichloro-9-(4-methoxybenzyl)purine **15** was prepared by a general 4-methoxybenzyl protection procedure, which was subsequently reacted with 4-trifluoromethoxyphenylboronic acid under Pd-catalyzed condition to afford Suzuki coupling product **16**. And then the coupling reaction between **16** and the above aniline-blocks under $Pd(OAc)_2$/BINAP/Cs_2CO_3 catalytic system proceeded smoothly and afforded 4-methoxybenzyl protected products **19a–19d**. Deprotection of **19a–19d** with TFA provided the target compounds **20a–20d**, and methylation of **20a–20b** with methyl iodide gave target compounds **21a–21b**. Besides, the coupling of **16** with other aniline-like materials 1*H*-indazol-5-amine and 5-aminoindolin-2-one, followed deprotection, afforded another target compounds **18a–18b** (Scheme 1).

Scheme 2 depicted the synthesis of the desired pyrrolo[2,3-*d*]pyrimidines (**26a–26c**). The similar synthetic procedures were employed. Briefly, from the commercially available 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **22** and 4-trifluoromethoxyphenylboronic acid, the Suzuki coupling product **23** was constructed. Subsequently the free NH group of **23** was protected by another alternative protection group *p*-toluenesulfonyl, to give product **24**. Coupling of **24** with block **6** led to intermediate

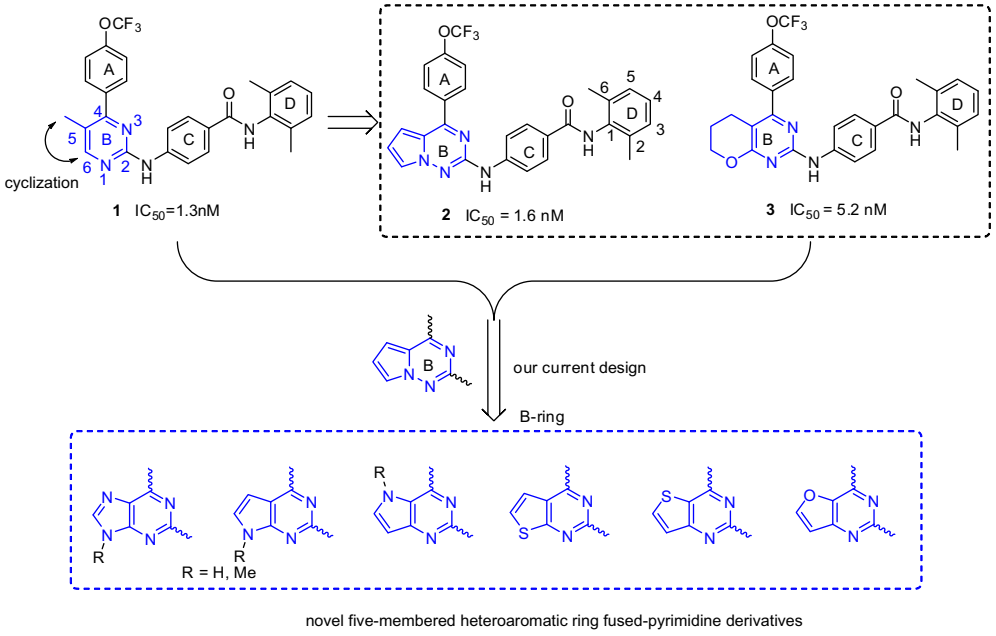
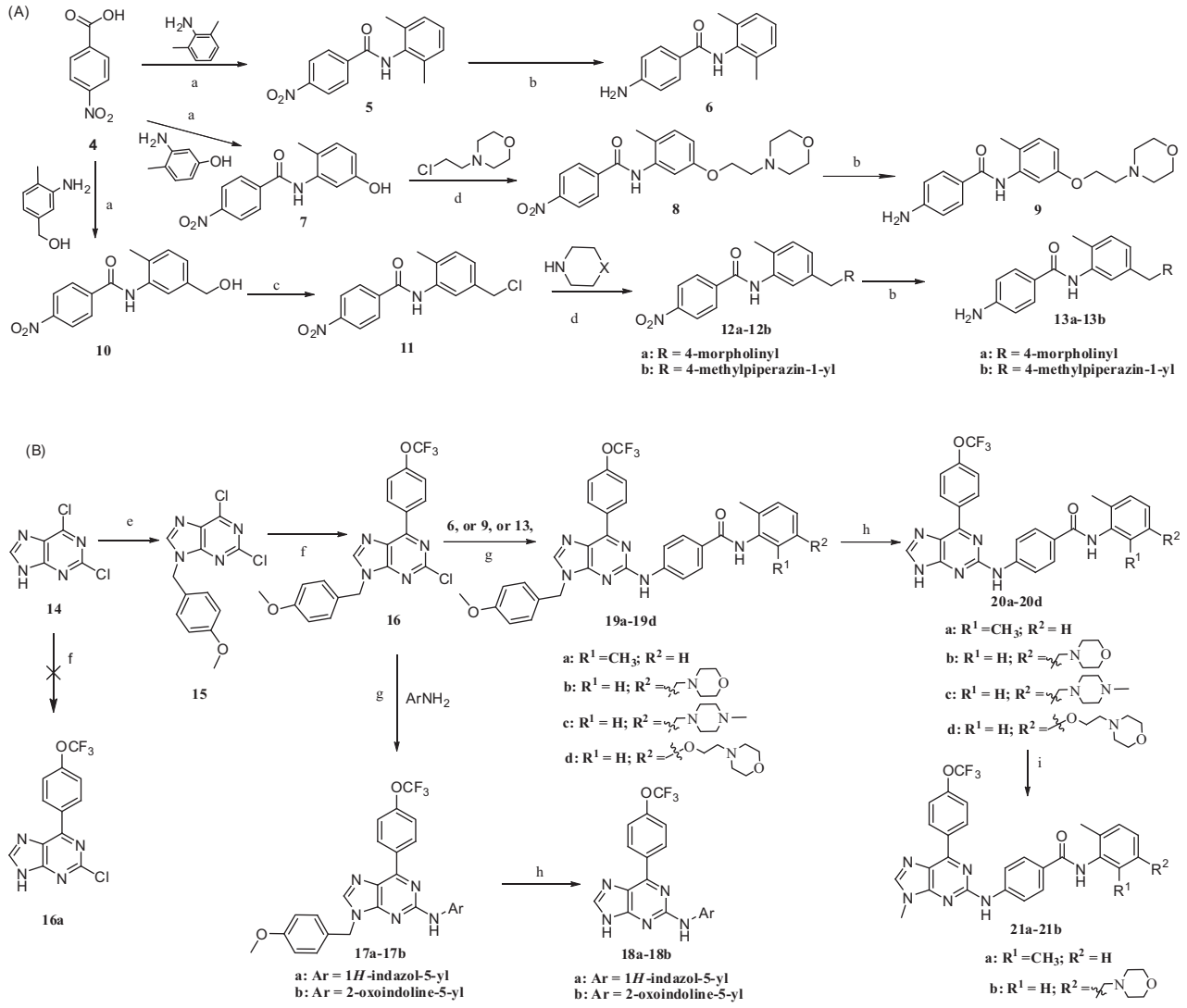
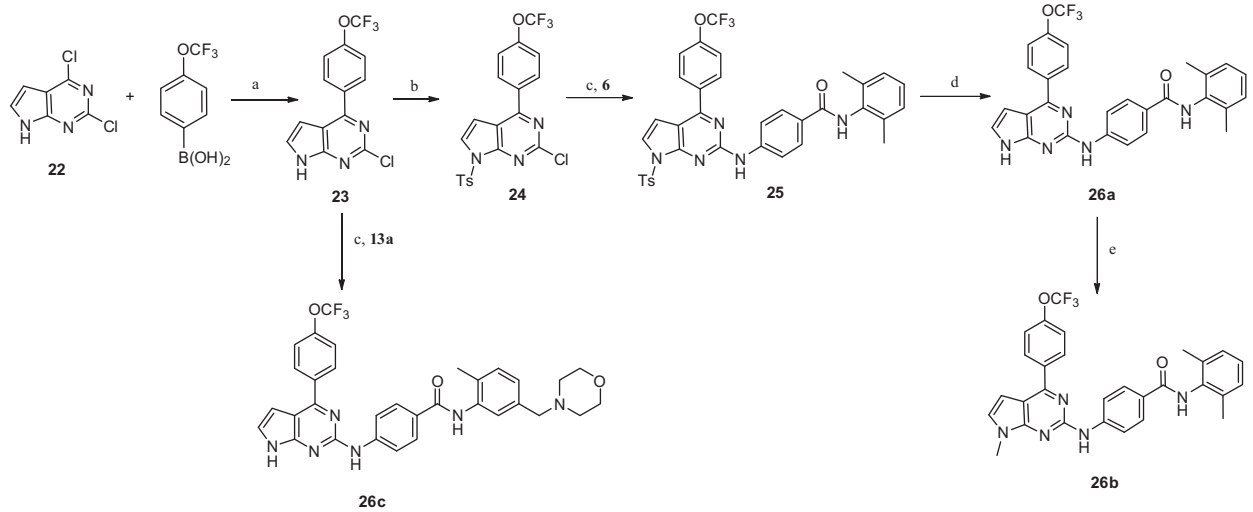


Figure 2. Novel five-membered heteroaromatic ring fused-pyrimidine derivatives design.



Scheme 1. Reagents and conditions: (a) (1) $SOCl_2$, reflux for 3 h; (2) THF, DIPEA, rt for 26 h, 2,6-dimethylaniline for **5**, 46%; 3-amino-4-methylphenol for **7**, 100%; 3-amino-4-methylbenzyl alcohol for **10**, 100%; (b) 10% Pd/C, H_2, rt for 24 h, 84–96%; (c) $SOCl_2$, CH_2Cl_2, rt for 2.5 h, 100%; (d) DMF, K_2CO_3, 85 °C for 2.5 h, 4-(2-chloroethyl)morpholine hydrochloride for **8**, 24%; morpholine for **12a**, 100%; 1-methylpiperizine for **12b**, 78%; (e) 4-methoxybenzyl chloride, K_2CO_3, DMF, rt, overnight, 50%; (f) 4-trifluoromethoxyphenylboronic acid, $Pd(PPh_3)_2Cl_2$, TEA, DMF, H_2O, 80 °C for 4 h, 48%; (g) $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, 150 °C, microwave for 4 h, 12–81% ; (h) TFA, reflux for 4 h, 34–79%; (i) CH_3I, K_2CO_3, DMF, rt for 6 h, 55–100%.



Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, TEA, DMF, H_2O, 80 °C for 4 h, 41%; (b) TsCl, NaOH, acetone/H_2O, rt for 3 h, 87%; (c) $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, 150 °C, microwave for 4 h, 39–46%; (d) NaOH, CH_3OH, reflux for 1 h, 81%; (e) CH_3I, K_2CO_3, DMF, rt for 6 h, 53%.

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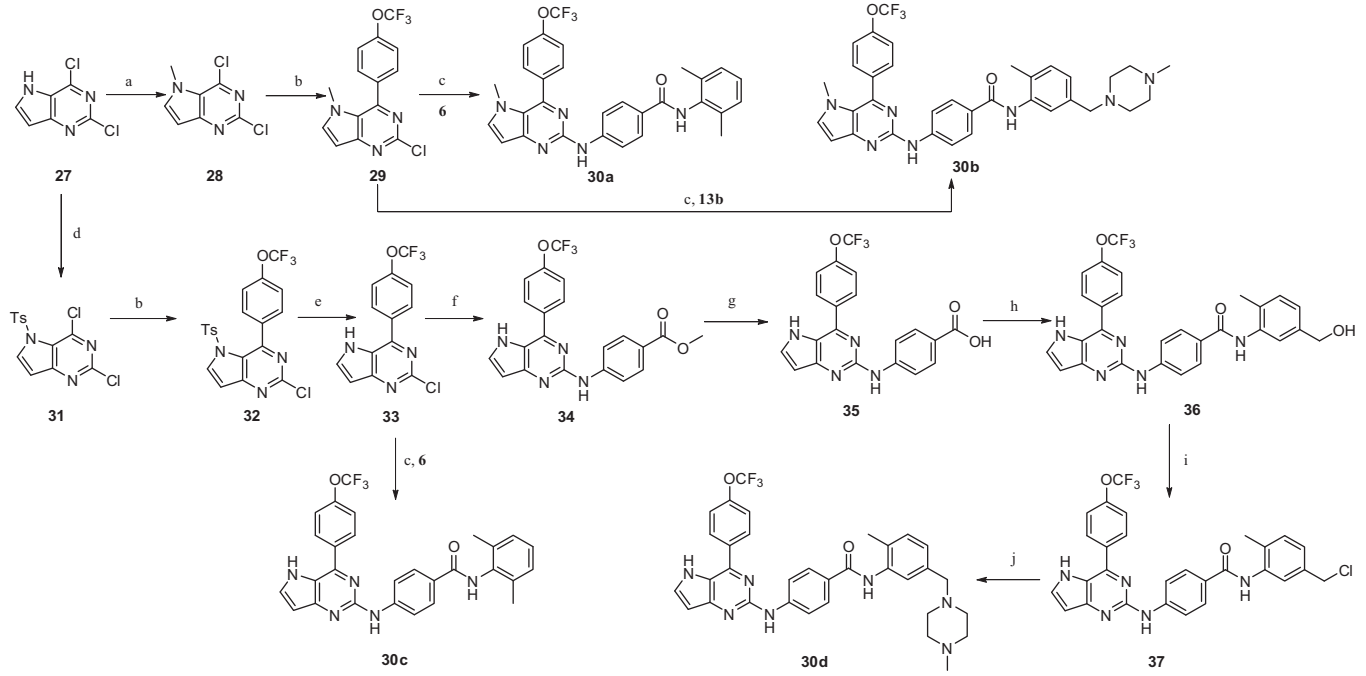
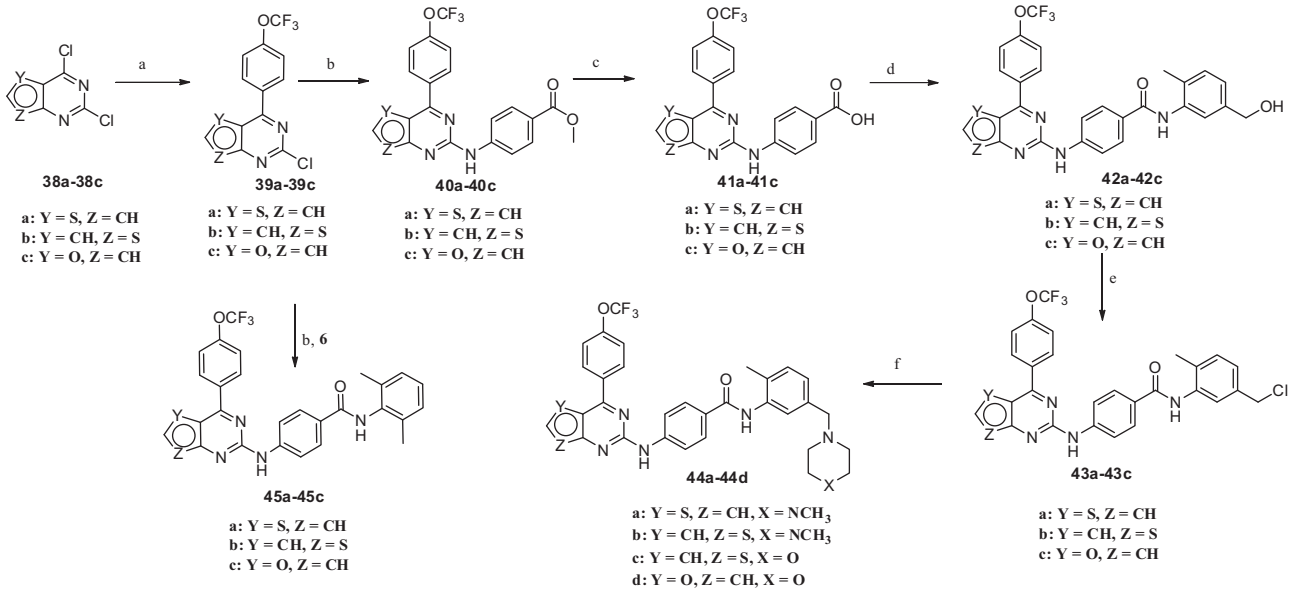


Scheme 3. Reagents and conditions: (a) CH_3I, K_2CO_3, DMF, rt for 6 h, 88%; (b) 4-trifluoromethoxyphenylboronic acid, $Pd(PPh_3)_2Cl_2$, TEA, DMF, H_2O, 80 °C for 4 h, 54–58%; (c) $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, 150 °C, microwave for 4 h, 36–58%; (d) TsCl, NaOH, acetone/H_2O, rt for 3 h, 97%; (e) NaOH, CH_3OH, reflux for 1 h, 95%; (f) methyl 4-aminobenzoate, $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, 150 °C, microwave for 4 h, 31%; (g) NaOH, MeOH/H_2O, reflux overnight, 99%; (h) 3-amino-4-methylbenzyl alcohol, HATU, DMF, DIPEA, 80 °C for 5 h, 38%; (i) $SOCl_2$, CH_2Cl_2, rt for 2.5 h, 99%; (j) *N*-methylpiperazine, DMF, K_2CO_3, 85 °C for 2.5 h, 58%.

25, which was further deprotected to afford the target compound **26a**. Methylation on the NH of **26a** provided methylated compound **26b**. Alternately, compound **26c** was achieved straightly using non-protected **23** as reactive reagent in 39% yield (Scheme 2).

Synthesis of pyrrolo[3,2-*d*]pyrimidine analogues **30a**–**30d** was illustrated in Scheme 3. Treatment of commercially available 2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine **27** with methyl iodide or *p*-toluenesulfonyl chloride under basic condition gave *N*-methyl product **28** and *N*-*p*-toluenesulfonyl product **31**, respectively. At this point, coupling of **28** using the above similar Suzuki condition afforded compound **29**, which was subsequently treated with **6** or **13b** under Buchwald–Hartwig coupling condition to yield target compounds **30a** and **30b**, respectively. Alternately, target compound **30c** was practically assembled from **31** by three steps, which were Suzuki coupling of **31** with 4-trifluoromethoxyphenylboronic acid to give **32**, followed by



Scheme 4. Reagents and conditions: (a) 4-trifluoromethoxyphenylboronic acid, $Pd(PPh_3)_2Cl_2$, TEA, DMF, H_2O, 80 °C for 4 h, 2,4-dichlorothieno[3,2-*d*]pyrimidine for **39a** (76%); 2,4-dichlorothieno[2,3-*d*]pyrimidine for **39b** (75%); 2,4-dichlorofuro[3,2-*d*]pyrimidine for **39c** (70%); (b) methyl 4-aminobenzoate, $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, 150 °C, microwave for 4 h, 43–77%; (c) NaOH, MeOH/H_2O, reflux overnight, 90–100%; (d) 3-amino-4-methylbenzyl alcohol, HATU, DMF, DIPEA, 80 °C for 5 h, 64–89%; (e) $SOCl_2$, CH_2Cl_2, rt for 2.5 h, 42–94%; (f) *N*-methylpiperazine or morpholine, DMF, K_2CO_3, 85 °C for 2.5 h, 48–62%.

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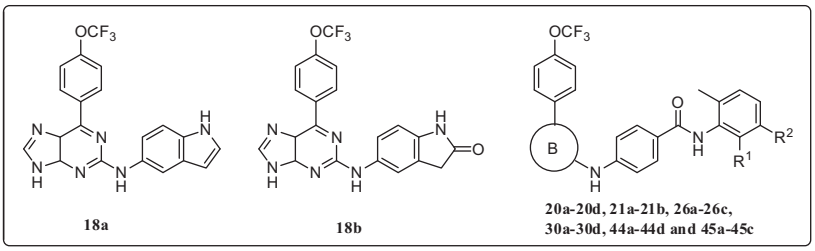
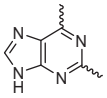
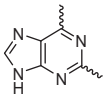
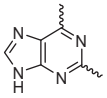
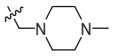
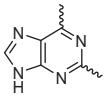
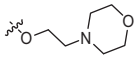
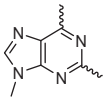
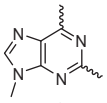
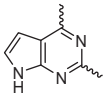
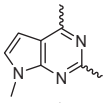
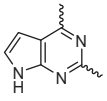
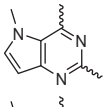
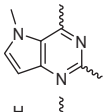
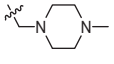
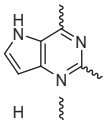
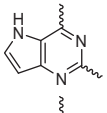
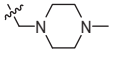
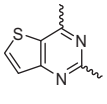
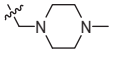
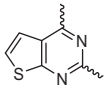
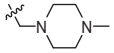
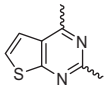
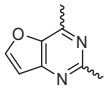
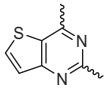
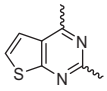
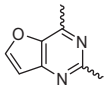
Table 1
The IC_{50} of target compounds against Gli-luc reporter



Compds	B ring	R^1	R^2	Gli-luc reporter IC_{50} (nM)
18a	—	—	—	398.8
18b	—	—	—	>1000
20a		Me	H	512.2
20b		H		0.69
20c		H		0.90
20d		H		2.98
21a		Me	H	116.1
21b		H		0.35
26a		Me	H	6.85
26b		Me	H	2.58
26c		H		6.04
30a		Me	H	1.17
30b		H		5.10
30c		Me	H	12.84
30d		H		1.39
44a		H		9.39

(*continued on next page*)

Table 1 (*continued*)

Compds	B ring	R^1	R^2	Gli-luc reporter IC_{50} (nM)
44b		H		3.36
44c		H		1.75
44d		H		1.13
45a		Me	H	3.61
45b		Me	H	0.60
45c		Me	H	1.78
GDC-0449				7.17

deprotection to yield **33**, and next by Buchwald–Hartwig coupling to afford **30c**. Otherwise, *N*-methylpiperazine derivative **30d** was prepared from intermediate **33** involving five steps. Coupling of **33** with methyl 4-aminobenzoate using the above Buchwald–Hartwig condition gave **34**, which was subsequently hydrolyzed to free acid **35**. Condensation **35** with 3-amino-4-methylbenzyl alcohol provided **36**, followed by chlorination with thionyl chloride to afford **37**, and next by nucleophilic substitution with *N*-methylpiperazine to provide **30c** (Scheme 3).

The representative compounds of other scaffolds including thieno[2,3-*d*]pyrimidine, thieno[3,2-*d*]pyrimidine and furo[3,2-*d*]pyrimidine were prepared as described in Scheme 4. Employing similar synthetic procedures, analogues **44a**–**44d** and **45a**–**45c** were synthesized. Beginning with appropriately commercially available materials (2,4-dichlorothieno[3,2-*d*]pyrimidine **38a**, 2,4-dichlorothieno[2,3-*d*]pyrimidine **38b** and 2,4-dichlorofuro[3,2-*d*]pyrimidine **38c**), the desired compounds **44a**–**44d** were accomplished in six steps, including Suzuki coupling reaction (to give **39a**–**39c**), Buchwald–Hartwig coupling reaction (to give **40a**–**40c**), hydrolysis (to give **41a**–**41c**), condensation (to give **42a**–**42c**), chlorination (to give **43a**–**43e**), and subsequently nucleophilic substitution with morpholine or *N*-methylpiperazine (to give **44a**–**44d**). While compounds **45a**–**45c** were constructed by Suzuki-coupling of intermediates **39a**–**39c** with the above building block **6**, respectively (Scheme 4).

All the newly synthesized five-membered heteroaromatic ring fused-pyrimidines, including purines (**18a**–**18b**, **20a**–**20d** and **21a**–**21b**), pyrrolo[2,3-*d*]pyrimidines (**26a**–**26c**), pyrrolo[3,2-*d*]pyrimidines (**30a**–**30d**), thieno[3,2-*d*]pyrimidines (**44a** and **45a**), thieno[2,3-*d*]pyrimidines (**44b**, **44c** and **45b**) and furo[3,2-*d*]pyrimidines (**44d** and **45c**) were evaluated for their ability to inhibit the Hh signaling pathway by using a luciferase reporter in NIH3T3 cell carrying a stably transfected Gli-reporter construct (Gli-luciferase reporter cell lines).[7] The in vitro IC_{50} values were illustrated in Table 1 and GDC-0449 was used as a positive control. In the initially designed purine derivatives, although several compounds such as **18a** (398.8 nM), **18b** (>1000 nM) and **20a** (512.2 nM) showed very weak inhibitory activity against Hh, the analogues **20b**, **20c** and **20d**, bearing basic amine side chains, exhibited significantly potency (**20b**: 0.69 nM, **20c**: 0.90 nM, **20d**: 2.98 nM). This result demonstrated the viability of purines as an alternative to our previously reported pyrrolo[2,1-*f*][1,2,4]triazine and pyrimidine scaffolds. Additionally, some purines of methyl substituted at 9-position were explored, such as compounds **21a** and **21b**. Interestingly, methyl substitution which lacked a hydrogen bond acceptor, appeared to be helpful for slightly improving inhibitory activity (**21a**: 116.1 nM vs **20a**: 512.2 nM, as well as **21b**: 0.35 nM vs **20b**: 0.69 nM). Considering purines to be good surrogate scaffold, we tried to explore other scaffolds for enlarging the scaffold alternatives. Some scaffolds such as pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines and furo[3,2-*d*]pyrimidines were designed and synthesized and the selected examples were depicted in Table 1. Two pyrrolo[2,3-*d*]pyrimidine derivatives such as **26a** and **26c** showed satisfactorily equipotent potency compared to GDC-0449 (**26a**: 6.85 nM, **26c**: 6.04 nM vs GDC-0449: 7.17 nM), while compound **26b** attaching a methyl group displayed approximate 3-fold more effective than GDC-0449. However, in pyrrolo[3,2-*d*]pyrimidines (**30a**–**30d**), it was found that the methyl **30a** showed better potency than no-methyl **30c**, while methyl **30b** when bearing *N*-methyl piperazine in D-ring displayed decreased activity compared to the no-methyl compound **30d**. Furthermore, when the N atom of five-ring adjacent to the ring junction was replaced with isosteric S or O atom, thereby derivatizing scaffolds such as thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines and furo[3,2-*d*]pyrimidines. It showed very tolerant. These analogs containing S or O on the scaffolds showed good Hh signaling inhibitory activity with IC_{50} varied from 0.60 nM to 9.39 nM. Interestingly, the biological data between **44a** and **44b** (IC_{50}: 9.39 nM vs 3.36 nM) showed that the thieno[2,3-*d*]pyrimidine one was more potent than thieno[3,2-*d*]pyrimidine one. The same cases were accounted by compounds **45a** and **45b** (IC_{50}: 3.61 nM vs 0.60 nM). In addition, Compared **45c** with **45a** (**45c**: 1.78 nM vs **45a**: 3.61 nM), it appeared the furo[3,2-*d*]pyrimidines provided a better potency than thieno[3,2-*d*]pyrimidines. Considering that thieno[2,3-*d*]pyrimidine and furo[3,2-*d*]pyrimidine scaffolds showed improving activity, the morpholine derivatives **44c** and **44d** were prepared, whereas both showed low nanomolar Hh

inhibitory activity with an IC_{50} of 1.75 nM and 1.13 nM, respectively, more potent than GDC-0449 (7.17 nM). In a word, five-membered heteroaromatic ring fused-pyrimidines appears to be good alternatives for surrogate of pyrrolo[2,1-*f*][1,2,4]triazine and pyrimidine scaffolds. The structural modification study showed most of target compounds displayed better inhibitory activities than positive control GDC-0449, of which 4 ones exhibited superior activities with an subnanomolar IC_{50} values (<1 nM).

In summary, we have designed and synthesized a series of novel five-membered heteroaromatic ring fused-pyrimidines targeting the hedgehog signaling pathway. These five-membered heteroaromatic ring fused-pyrimidine scaffolds including purine, pyrrolo[2,3-*d*]pyrimidine, pyrrolo[3,2-*d*]pyrimidine, thieno[2,3-*d*]pyrimidine, thieno[3,2-*d*]pyrimidine and furo[3,2-*d*]pyrimidine turned out to be viable alternatives to the previously reported pyrrolo[2,1-*f*][1,2,4]triazine and pyrimidine cores, showing similar inhibitive profile of Hh signaling pathway. Furthermore, structural modification study showed most compounds exerted better inhibitory activities than positive control GDC-0449. Compound **20b**, **20c**, **21b** and **45b** were found to be the most potent inhibitors with IC_{50} values below 1 nM, and deserved more exploration and further investigation. Otherwise, what is important is that this study may provide a potential route to design more effective hedgehog signaling pathway inhibitors with novel structural skeletons.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.05.066.

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