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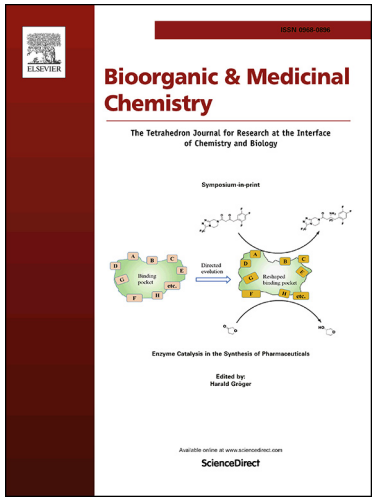

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Novel 4-(2-Pyrimidinylamino)benzamide Derivatives as Potent Hedgehog Signaling Pathway Inhibitors

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Footnotes

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Abstract: A series of novel hedgehog signaling pathway inhibitors have been designed and synthesized based on our previously reported scaffold of 4-(2-pyrimidinylamino)benzamide. The Hh signaling pathway inhibitory activities were evaluated by Gli-luciferase reporter method and most compounds showed more potent inhibitory activities than vismodegib. Three compounds were picked out to evaluated *in vivo* for their PK properties, and compound **23b** bearing a 2-pyridyl A-ring and (morpholin-4-yl)methylene at 3-position of D-ring demonstrated satisfactory PK properties. This study suggested the 4-(2-pyrimidinylamino)benzamides were a series of potent Hh signaling pathway inhibitors, deserving to further structural optimization.

Keywords: hedgehog signaling pathway inhibitors, 4-(2-pyrimidinylamino)benzamide, SAR, in vivo.

1. Introduction

Hedgehog (Hh) signaling plays an essential role in embryonic morphogenesis and tissue patterning, and is generally silent in the adult. However, aberrantly constitutive activation of Hh signaling was identified in the development of many tumors, such as basal cell carcinoma (BCC), medulloblastoma (MB) and rhabdomysarcoma (RMS), and hematological and solid tumors such as leukemia, lymphoma, glioblastoma, melanoma, esophageal, lung, gastric, pancreatic, hepatocellular, colorectal, prostate, and ovarian cancer. [1, 2] Thus, Hh signaling pathway emerged as an attractively therapeutic target for treatment of cancers, and many small molecules were designed to block this Hh signaling pathway. Vismodegib (GDC-0449, **1**), the first-in-class FDA approved Hh inhibitor, was very clinically efficient in treating locally advanced or metastatic BCC. Sonidegib (LDE-225, **2**), another FDA approved Hh inhibitor, also showed significant median progress-free survival in the BCC clinical therapy. Other Hh inhibitors such as taladegib (LY-2940680, **3**), itraconazole (**4**), arsenic trioxide, were currently studies in clinical trials (Figure 1). Although the proof-of-concept of Hh inhibitors were confirmed in BCC, it is still believed Hh inhibitors have huge therapeutic potential against MB and RMS, either by single or combination therapy. [3-5] Consequently, it is imperative to develop new chemical structures of Hh inhibitors to further enable the medicinal investigation.

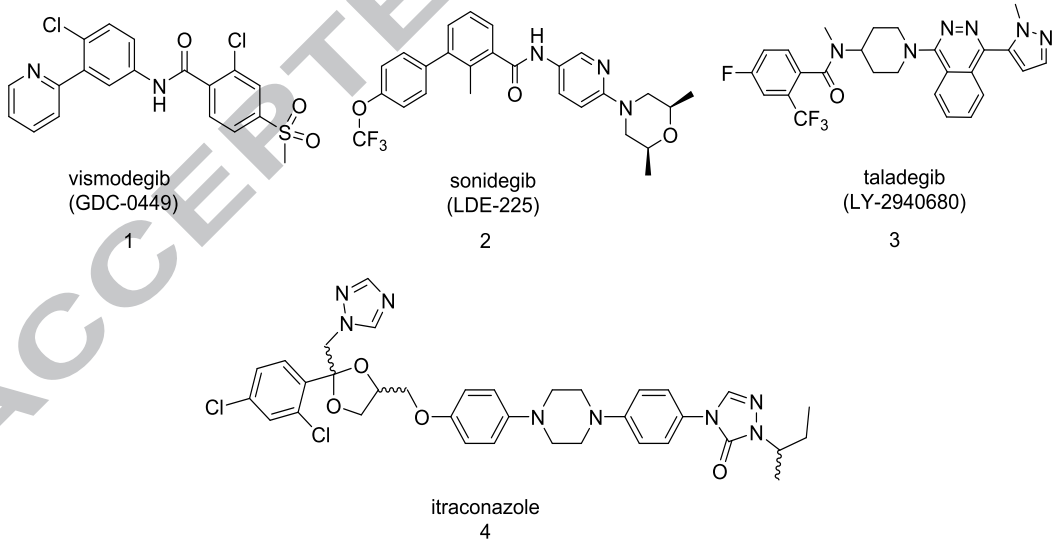
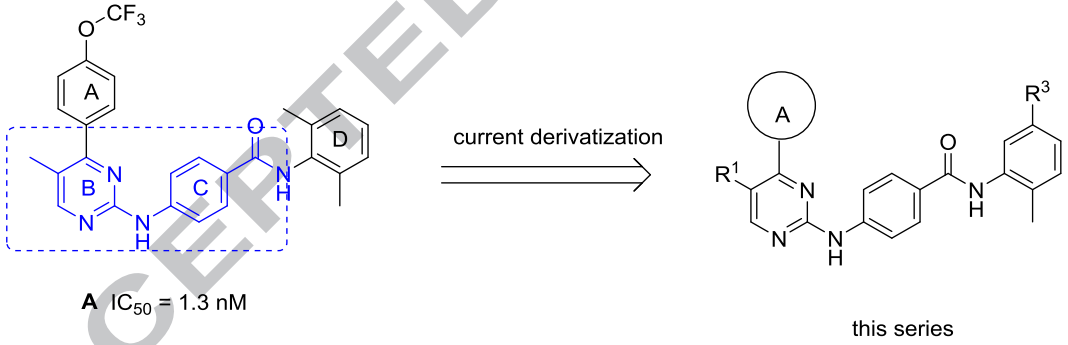


Figure 1. Representative chemical structures of reported Hh signaling inhibitors.

Our group was interested in developing new chemotypes of Hh inhibitors, and

recently a new series of 4-(2-pyrimidinylamino)benzamide derivatives were firstly identified as potent Hh inhibitors, exemplified by compound **A** which inhibited the Hh signaling pathway with IC_{50} value of 1.3 nM.[6] Based on this skeleton of 4-(2-pyrimidinylamino)benzamide, a subsequent structure activity relationship was extensively investigated, [7, 8, 9, 10] and several new scaffolds such as pyrrolo[2,1-f][1,2,4]triazine, [11] thieno[2,3-d]pyrimidines, furo[3,2-d]pyrimidines, purines, [12] and others were derivatized [13]. In particular, in the series of 4-(2-pyrimidinylamino)benzamides, some representative analogues displayed potent Hh inhibition and antitumor efficacy in vitro and in vivo, as well as satisfactory PK profiles in rats. [14] On the basis of these previous encouraging results, we intend to continuously investigate 4-(2-pyrimidinylamino)benzamide core. In particular, it was previously concluded that different substituents on A-ring, B-ring and D-ring could remarkably affect the inhibitory activity of Hedgheg signaling pathway. Thus, a new series of derivatives bearing the 4-(2-pyrimidinylamino)benzamide skeleton were synthesized, mainly structural modification on A-ring, B-ring and D-ring. (Figure 2). Herein, we reported the preparation and biological evaluation of new 4-(2-pyrimidinylamino)benzamides as potent Hh inhibitors.



A IC_{50} = 1.3 nM

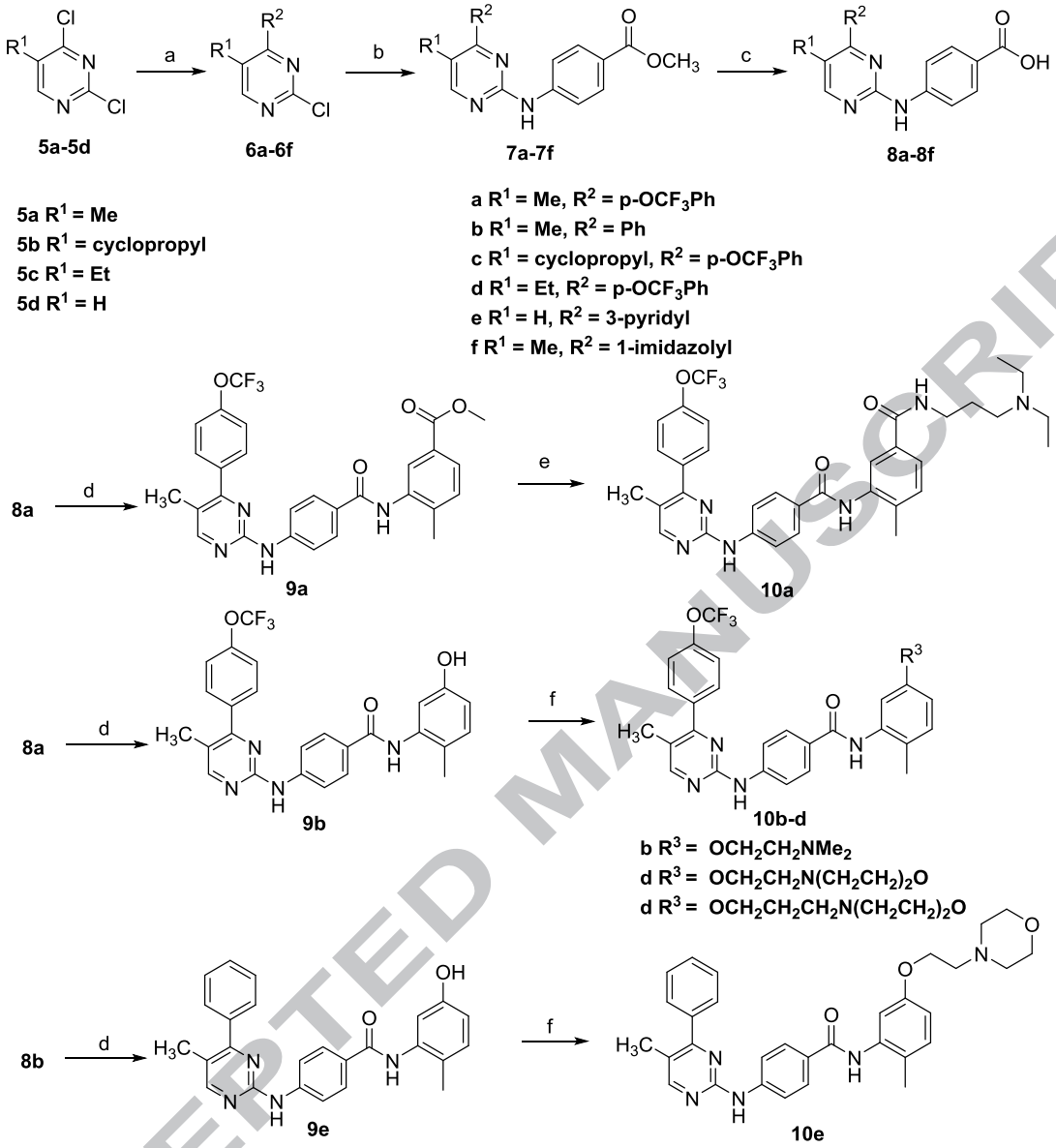
Figure 2. Current design of new 4-(2-pyrimidinylamino)benzamide derivatives

2. Chemistry

The title 4-(2-pyrimidinylamino)benzamides were prepared through the routes as shown in Scheme 1, 2 and 3.

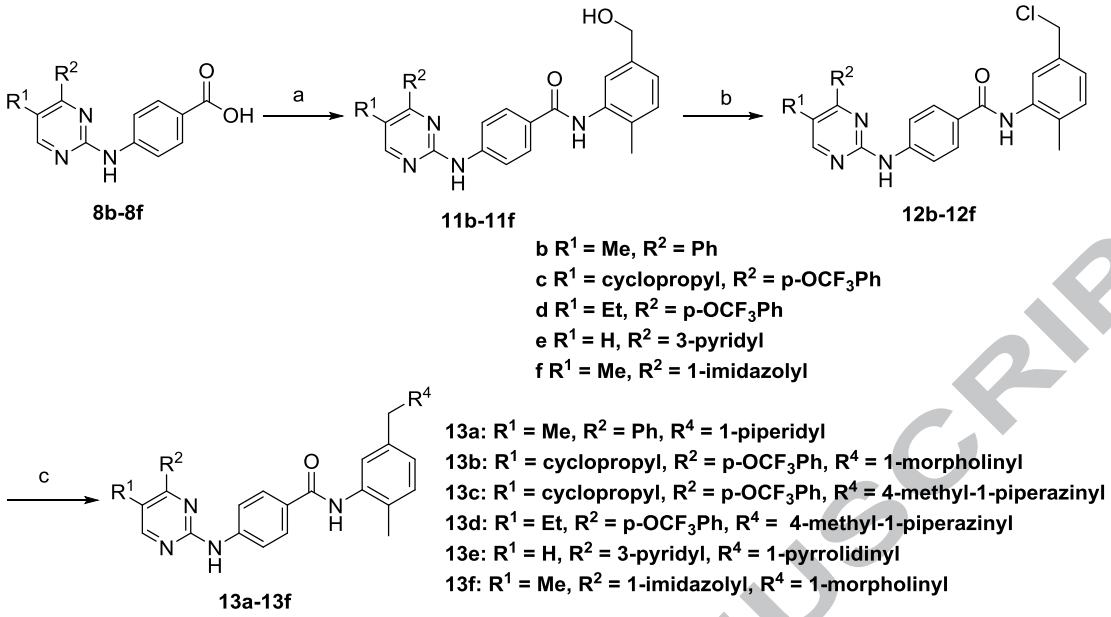
As depicted in Scheme 1, the intermediates **6a-6e** were constructed by Suzuki coupling reaction of the commercially available 5-methyl-2, 4-dichloropyrimidine (**5a**) and 4-trifluoromethoxyphenylboronic acid or phenylboronic acid, or 3-pyridylboronic acid

under the condition of Pd-catalyst and basic atmosphere in reflux dioxane, and **6f** was prepared by **5a** and imidazole in the refluxing acetonitrile solution. Subsequently, **6a-6f** were treated with methyl 4-aminobenzoate by the Buchwald-Hartwig coupling condition of $Pd(OAc)_2$ catalyst and BINAP and Cs_2CO_3 to generate **7a-7f**, which were hydrolyzed by alkaline condition to afford free acids **8a-8f**. Treatment of **8a** with methyl 3-amino-4-methylbenzoate or 3-amino-4-methylphenol gave intermediates **9a-9b**. **9a** directly reacted with 3-diethylaminopropylamine under 150 ^{o}C microwave for 2h to release compound **10a**, whereas **9b** was treated with 4-(2-chloroethyl)morpholine, 4-(3-chloropropyl)morpholine or 2-chloroethyl diethylamine to give compounds **10b-10d**. Similarly, acylation of **8b** with 3-amino-4-methylbenzyl alcohol gave rise to **9e**, which was followed by substitution with 4-(2-chloroethyl)morpholine to produce **10e**. (Scheme 1)



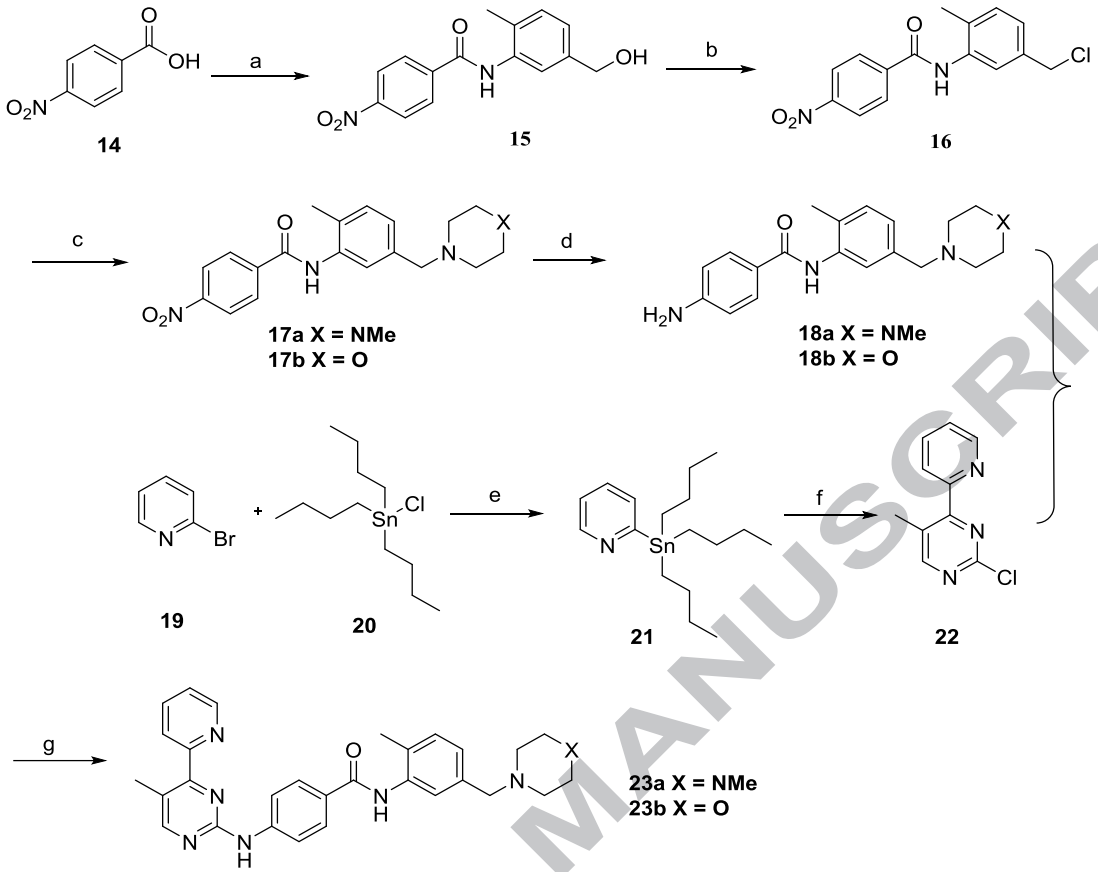
Scheme 1. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, TEA, DMF/H_2O, 80 °C, 6-12h, 42-89 %, for **6a-6e**; CH_3CN, 65 °C, 40h, 89 % for **6f**; (b) $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, reflux, 3-8h °C, 43-94 %; (c) NaOH, MeOH/H_2O, reflux overnight, 85-100 %; (d) $SOCl_2$, TEA, DCM, overnight, 7-30 %; (e) Microwave, 150 °C, 2h, 51 %; (f) DMF, K_2CO_3, DMF, 2h, 80°C, 39-54 %.

The compounds **13a-13f** were synthesized as shown in Scheme 2. The free acids **8b-8f** reacted with 3-amino-4-methylbenzyl alcohol to provide **11b-11f**, which were subsequently chlorinated by thionyl chloride to yield **12b-12f**, followed by nucleophilic substitution with piperidine, morpholine, N-methylpiperazine, or pyrrolidine to prepare the desired product **13a-13f**. (Scheme 2)



Scheme 2. Reagents and conditions: (a) HATU, DMF, DIPEA, rt, 16h, 45-80 %; (b) $SOCl_2$, CH_2Cl_2, rt, 5h, 65-94 %; (c) CH_3CN, K_2CO_3, reflux, 6h, 44-76 %.

As outlines in Scheme 3, the compounds **23a-23b** were synthesized by alternative route. Acylation of p-nitrobenzoic acid **14** with 3-amino-4-methylbenzyl alcohol delivered intermediate **15**. Subsequent chlorination of **15** provided **16**, which was treated with morpholine or N-methylpiperazine, followed by catalytic hydrogenation to afford intermediate **18a-18b**. Although 3-pyridyl substituted **6b** was successfully prepared by the Suzuki coupling reaction, it is difficult to construct **22** by similar Suzuki coupling reaction of 2-pyridylboronic acid/ pinacol ester and **5a**. After several reaction conditions attempted, **22** was finally synthesized by Stille coupling reaction in 34 % yield based on the firstly successful preparation of 2-(tributylstannyl)pyridine reagent in the presence of n-BuLi. Accordingly, treatment of **22** with **18a-18b** under Buchwald-Hartwig coupling conditions produced the compounds **23a-23b**. (Scheme 3)



Scheme 3. Reagents and conditions: (a) (1) $SOCl_2$, reflux, 3h; (2) 3-amino-4-methylbenzyl alcohol, THF, DIPEA, rt, 26h; 99 %; (b) $SOCl_2$, CH_2Cl_2, rt, 2.5h, 100 %; (c) morpholine or 4-methylpiperazine, DMF, K_2CO_3, 85 ^oC, 2.5h, 78-100 %; (d) 10 %Pd/C, H_2, rt, 24h, 85-94 %; (e) n-BuLi, THF, -78 ^oC, 3h, 38%; (f)Toluene, $Pd(PPh_3)_4$, 150 ^oC, 2h, 34 %; (g) $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, reflux, 2.5h , 43-56%.

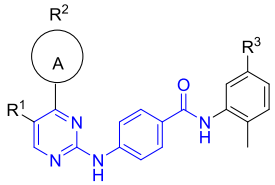
3. Result and discussion

3.1 Hh signaling inhibitory activity

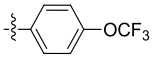
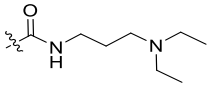
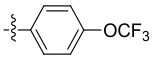
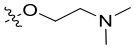
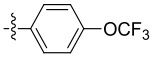
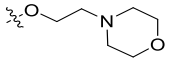
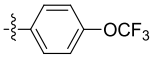
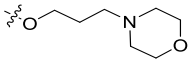
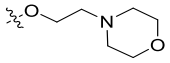
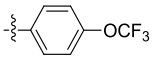
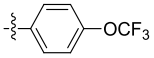
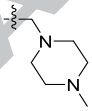
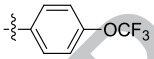
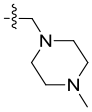
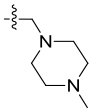
The Hh signaling inhibitory activities for all newly prepared 4-(2-pyrimidinylamino)benzamides were evaluated by the luciferase reporter in NIH3T3 cell with a stably transfected Gli-reporter construct (Gli-luciferase reporter cell lines), and vismodegib was used as positive control drugs. As shown in Table 1, all the 4-(2-pyrimidinylamino)benzamides displayed excellent inhibitory effects against Hh signaling pathway with the IC_{50} values range from 0.62 nM to 28.99 nM, while vismodegib showed an IC_{50} value of 7.17 nM. Compound **10a** with an N-(3-diethylamino)propylaminocarbonyl group at 3-postion of D-ring shown the most

potent inhibitory activity with an IC_{50} value of 0.62 nM, while compound **10b** with a (2-dimethylamino)ethoxy group showed retained inhibitory activity with an IC_{50} value of 1.07 nM. Replacement of the terminal diethylamino tail with morpholine group resulted in compound **10c** showing tolerable inhibition against Hh signaling pathway (IC_{50} = 2.45 nM). Extending the ethoxy linker to propoxy led to compound **10d** also shown the inhibitory effect remained (IC_{50} = 2.14 nM). The derivatives **10e** and **13a** with a phenyl group in A-ring were investigated. Compound **10e** tailed a 2-(morpholin-4-yl)ethoxy at 3-position of D-ring showing slightly lower inhibitory activity (IC_{50} = 4.28 nM) compared to **10b**, while compound **13a** bearing a (piperidin-1-yl)methylene group afforded reserved inhibitory activity (IC_{50} = 1.94 nM). Additionally, an attempt of cyclopropyl or ethyl instead of the methyl group at 5-position of B ring led to the preparation of representative compounds **13b**, **13c** and **13d**. Although the cyclopropyl analogue **13b** linked the (morpholin-4-yl)methylene at D-ring showed descreased inhibitory activity with an IC_{50} value of 11.95 nM, both the cyclopropyl analogue **13c** and the ethyl analogue **13d** tailed the (4-methylpiperazin-1-yl)methylene demonstrated potent activity with the IC50 value of 1.54 and 2.21 nM, respectively, compared with **13a**. Moreover, several representative heteroaryl groups as A-ring moiety were investigated, exemplified by **13e-13f,** and **23a-23b**. Compound **13e** with 3-pyridyl group and **13f** with 1-imidazolyl group at A-ring showed lower inhibitory activity (IC_{50} = 28.99 and 21.11 nM, respectively), while the 2-pyridyl substituted **23a** attached (4-methylpiperazin-1-yl)methylene group at 3-position of D-ring showed equivalent potency compared with vismodegib and compound **23b** attached the (morpholin-4-yl)methylene group showed more potent inhibition. Building on the above evaluation, this series of 4-(2-pyrimidinylamino)benzamide derivatives were certainly potent Hh signaling pathway inhibitors, and most of them showed more potent inhibitory activities than vismodegib.

Table 1. Hh signaling pathway inhibition of 4-(2-pyrimidinylamino)benzamide derivatives



13a-13n

compds	R^1	R^2 (A-ring)	R^3	Gli-luc reporter IC_{50} (nM)
10a	Me			0.62±0.14
10b	Me			1.07±0.34
10c	Me			2.45±1.44
10d	Me			2.14±0.72
10e	Me			4.28±1.60
13a	Me			1.94±0.65
13b				11.95±4.3
13c				1.54±0.40
13d	Et			2.21±0.90
13e	H			28.99±12.33
13f	Me			21.11±3.86
23a	Me			7.37±1.74
23b	Me			1.89±0.50
vismodegib	-	-	-	7.17±2.18

3.2 The calculated drug-like data for compounds

The rule of **5** is usually used to predict the drug-like properties of compounds. Considering all the derivatives showed moderate to high potency, all compounds were calculated for their molecular weights, numbers of H-donors, numbers of H-acceptors,

and ClogP values to examine their drug-like properties. The calculated data were shown in Table 2. Obviously, only four compounds (including **13e**, **13f**, **23a** and **23b**) met the rule of 5. In particularly, compound **13e** and **23b** showed the lowest ClogP values. (Table 2)

Table 2. The calculated data for compounds [a]

compds	Molecular weight	numbers of H-donors	numbers of H-acceptors	ClogP
10a	634	3	12	6.94
10b	607	2	12	6.37
10c	621	2	12	6.68
10d	565	2	11	6.35
10e	**523**	**2**	**8**	**5.22**
13a	**491**	**2**	**6**	6.05
13b	603	2	11	6.37
13c	616	2	11	6.93
13d	604	2	11	6.90
13e	**480**	**2**	**8**	**3.19**
13f	**467**	**2**	**8**	**3.70**
23a	**507**	**2**	**8**	**4.16**
23b	**494**	**2**	**8**	**3.60**
vismodegib	**420**	**1**	**6**	**2.74**

[a] The data were calculated by Chemdraw 14.0;

3.3 Pharmacokinetic (PK) profiles of selective compounds *in vivo*

Based on the Hh signaling pathway inhibitory activities and the calculated drug-like datas of all the 4-(2-pyrimidinylamino)benzamide derivatives, compounds **13e** and **23b** were selected to examine their pharmacokinetic (PK) profiles in vivo. In addition, considering the structural diversity, compound **10e** was also included for comparation. The PK data were illustrated in Table 3, and three compounds showed different PK

parameters after administration to SD rats by intravenous injection (iv) with a dose of 1 mg/kg. compound **10e** bearing a 2-(morpholin-4-yl)ethoxy substituent at 3- position of D-ring showed a low peak-plasma-concentration (C_{max} = 863 ng/mL) and low plasma exposure (AUC = 787 hr×ng/mL) which means it may be administrated by a high dose as so to afford in vivo antitumor efficacy, whereas compound **10e** had a large volume of distribution (V_z = 2745 mL/kg) because of the high lipophilicity (ClogP = 5.22). In addition, compound **10e** exhibited a clearance of 1288 mL/hr/kg and a half time of 1.44 h. Unfortunately, although compound **13e** possessed the lowest ClogP value, it showed the lowest biggest area-under-curve (AUC = 521 hr×ng/mL) and half time ($t_{1/2}$ = 0.25 h), and higher clearance (Cl = 2016 mL/hr/kg) which means this compound may be easily eliminated or metabolized. Compound **23b** displayed satisfactory area-under-curve (AUC = 1370 hr×ng/mL) and peak-plasma-concentration (C_{max} = 1544 ng/mL), whose clearance (Cl = 736 mL/hr/kg) and half time ($t_{1/2}$ = 0.84 h) were moderate, although its PK profiles were not better than vismodegib. In the light of the in vivo PK properties evaluation, compound **23b** was the preferable compound for further evaluation. (Table 3)

Table 3. Pharmacokinetic properties for represented compound**s** in SD rats [a]

compds	C_{max} (ng/mL)	AUC (hr*ng/mL)	V_z (mL/kg)	Cl (mL/hr/kg)	$T_{1/2}$ (h)
10e	863±166	787±128	2745±1068	1288±230	1.44±0.29
13e	2520±701	521±136	700±124	2016±605	0.25±0.03
23b	1544±211	1370±174	888±54	736±95	0.84±0.02
vismodegib	1250±94	2456±354	954±95	406±66	1.64±0.12

[a] compound (including GDC-0449) was formulated using 5%DMA+5% Tween-80, iv 1mg/kg;

4. Conclusion

A series of new 4-(2-pyrimidinylamino)benzamide derivatives have been designed and synthesized. Their Hh signaling pathway inhibitory effects were evaluated and most derivatives exhibited more potent Hh signaling inhibitory activity than vismodegib. Subsequently, on base of the calculated drug-like data, three compounds were profiled *in vivo* for their PK properties, and compound **23b** bearing a 2-pyridyl A-ring and (morpholin-4-yl)methylene at 3-position of D-ring afforded optimal PK properties. This study suggested the 4-(2-pyrimidinylamino)benzamides were a series of potent Hh

signaling pathway inhibitors, deserving to further structural optimization for develop new chemotype drug-candidate.

5. Experimental

5.1 General methods

^{1}H-NMR spectra (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Bruker BioSpin AG (Ultrashield Plus AV 400) spectrometer. Mass spectra (MS) were recorded on an Agilent technologies 6120 quadrupole LC/MS spectrometer. The purity of the compounds was verified by the HPLC study using a mixture of solvent methanol/water or acetonitrile/water at the flow rate of 2 mL/min and peak detection at 254 nm under UV. Column chromatography was carried out on silica gel (200–300 mesh). All the reactions were monitored using thin layer chromatography (TLC) on silica gel plates. All the reagents were purchased from commercial sources and used without further purification unless especially stated.

5.1.1 4-((5-Methyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)benzoic acid (8a)

It was synthesized as we recently described,[6] as white product (720 mg, 56 %).

5.1.2 4-((5-Methyl-4-phenyl)pyrimidin-2-yl)amino)benzoic acid (8b)

It was prepared according to the method we recently reported, [6] as white product (100 mg, 87 %).

5.1.3 4-((5-Cyclopropyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)benzoic acid (8c)

It was synthesized as we recently described [6], as white product (350 mg, 68 %).

5.1.4 4-((5-Ethyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)benzoic acid (8d)

It was synthesized as we recently described [6], as white product (75 mg, 74 %).

5.1.5 4-((4-(Pyridin-3-yl)pyrimidin-2-yl)amino)benzoic acid (8e)

It was synthesized as we recently described [6], as yellow product (126 mg, 84 %).

5.1.6 2-Chloro-4-(1*H*-imidazol-1-yl)-5-methylpyrimidine (6f)

The solution of **5a** (300 mg, 1.85 mmol) and 1H-imidazole (151 mg, 2.22 mmol) in

MeCN (10 mL) was heated to 65ºC and refluxed for 40h. Then the mixture was cooled to room temperature and concentrated. The residue was purified by chromatography (EtOAc/petroleum ether, 5:1) to give **6f** (319 mg, 89 %), MS (ESI) m/z: $[M+H]^+$ = 195.1. ^{1}H NMR (400M, DMSO-d_6) δ 8.83 (s, 1H, ArH), 8.35 (s, 1H, ArH), 7.84-7.80 (m, 1H, ArH), 7.19 (s, 1H, ArH), 2.44 (s, 3H, $ArCH_3$) ppm.

5.1.7 4-((4-(1*H*-imidazol-1-yl)-5-methylpyrimidin-2-yl)amino)benzoic acid (8f)

It was synthesized as we described [6], as yellow product (484 mg, 68 %).

5.1.8 Methyl 4-methyl-3-(4-((5-methyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl) amino) benzamido)benzoate (9a)

A solution of **8a** (200 mg, 0.51 mmol) in $SOCl_2$ (5 mL) was refluxed for 30 min, then the mixture was concentrated to afford acyl chloride intermediate. The residue was dissolved in drug DCM (5 mL) in ice bath, and methyl 3-amino-4-mehtylbenzoate (128 mg, 0.75mmol) and TEA (150mg, 1.53 mmol) were added. The mixture was warmed to room temperature, and stirred overnight. The reaction mixture was concentrated, and the residue was purified by chromatography (DCM/ MeOH, 80:1) to give compound **9a** (161 mg, 58 %) as white solid. MS (ESI) m/z: $[M+H]^+$ = 537.2. ^{1}H NMR (400M, DMSO-d_6) δ 10.00 (s, 1H, NH), 9.79 (s, 1H, NH), 8.53 (s, 1H, ArH), 8.01 (s, 1H, ArH), 7.94 (s, 4H, ArH), 7.88 (d, 2H, *J* = 8.4 Hz, ArH), 7.75 (d, 1H, *J* = 8.0Hz, ArH), 7.55 (d, 2H, *J* = 8.0 Hz, ArH), 7.43 (d, 1H, *J* = 8.0 Hz, ArH), 3.85 (s, 3H, OCH_3), 2.32 (s, 3H, $ArCH_3$), 2.26 (s, 3H, $ArCH_3$) ppm.

5.1.9 N-(3-(Diethylamino)propyl)-4-methyl-3-(4-((5-methyl-4-(4-(trifluoromethoxy) phenyl)pyrimidin-2-yl)amino)benzamido)benzamide (10a)

A mixture of **9a** (160 mg, 0.3 mmol) and N, N-diethyl-1, 3-propyldiamine (153 mg, 1.5 mmol) in the tube were stirred at 150 ºC by microwave machine, then the mixture was concentrated and purified by chromatography (DCM/ MeOH, 50:1) to give compound **10a** (46 mg, 25 %) as white solid. MS (ESI) m/z: $[M+H]^+$ = 635.2. ^{1}H NMR (400M, DMSO-d_6) δ 9.99 (s, 1H, CONH), 9.79 (s, 1H, NH), 8.53 (s, 2H, ArH), 7.94 (s, 4H, ArH), 7.88 (d, 2H, *J* = 8.4 Hz, ArH), 7.82 (s, 1H, ArH), 7.64 (d, 2H, *J* = 8.0 Hz, ArH), 7.55 (d, 2H, *J* = 8.4 Hz, ArH), 7.36 (d, 1H, *J* = 7.6 Hz, ArH), 3.32-3.24 (m, 2H, NCH_2), 2.48-2.40 (m, 6H, $CH_2N(CH_2)_2$), 2.27 (s, 3H, $ArCH_3$), 2.26 (s, 3H, $ArCH_3$), 1.63 (m, 2H, CH_2), 0.99-0.89 (m, 6H, $(CH_3)_2$) ppm, HPLC: 94.39 %.

5.1.10

N-(5-Hydroxy-2-methylphenyl)-4-((5-methyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)benzamide (9b)

9b was synthesized by the similar preparation of **9a**, as white solid (45 mg, 14 %). MS (ESI) m/z: $[M+H]^+$ = 495.2. ^{1}H NMR (400M, DMSO-d_6) δ 9.98 (s, 1H, CONH), 9.49 (s, 1H, NH), 9.25 (s, 1H, PhOH), 8.52 (s, 1H, ArH), 7.91 (s, 4H, ArH), 7.86 (d, 2H, *J* = 8.4 Hz, ArH), 7.54 (d, 2H, *J* = 8.4 Hz, ArH), 7.02 (d, 1H, *J* = 8.4 Hz, ArH), 6.84 (d, 1H, *J* = 2.0 Hz, ArH), 6.56 (dd, 1H, *J* = 8.0, 2.4 Hz, ArH), 2.25 (s, 3H, $ArCH_3$), 2.21 (s, 3H, $ArCH_3$) ppm.

5.1.11

N-(5-(2-(Dimethylamino)ethoxy)-2-methylphenyl)-4-((5-methyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)benzamide (10b)

To a solution of **8a** (58 mg, 0.12 mmol) in DMF (5 mL), K_2CO_3 (24 mg, 1.8 mmol) and N, N-dimethyl-2-chloroethylamine hydrochloride (17 mg, 0.12 mmol) were added. The mixture was refluxed at 80 ºC for 2h. The reaction mixture was concentrated and purified by chromatography (DCM/ MeOH, 50:1) to give compound **10b** (31 mg, 54 %) as white solid. MS (ESI) m/z: $[M+H]^+$ = 566.3. ^{1}H NMR (400M, DMSO-d_6) δ 9.99 (s, 1H, CONH), 9.58 (s, 1H, NH), 8.52 (s, 1H, ArH), 7.92 (s, 4H, ArH), 7.87 (d, 2H, *J* = 8.0 Hz, ArH), 7.55 (d, 2H, *J* = 8.0 Hz, ArH), 7.15 (d, 1H, *J* = 8.4 Hz, ArH), 7.00 (s, 1H, ArH), 6.76 (d, 1H, *J* = 8.0 Hz, ArH), 4.03 (s, 2H, *J* = 9.2 Hz, OCH_2), 2.70-2.64 (m, 2H, *J* = 5.2 Hz, NCH_2), 2.26 (s, 9H, $N(CH_3)_2$+$ArCH_3$), 2.16 (s, 3H, $ArCH_3$) ppm. HPLC: 92.51 %.

5.1.12

4-((5-Methyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)-N-(2-methyl-5-(2-morpholinoethoxy)phenyl)benzamide (10c)

10c was synthesized by the similar preparation of **10a**, as white solid (17 mg, 47 %). MS (ESI) m/z: $[M+H]^+$ = 608.3. ^{1}H NMR (400M, DMSO-d_6) δ 10.00 (s, 1H, CONH), 9.65 (s, 1H, NH), 8.52 (s, 1H, ArH), 7.96 (m, 4H, ArH), 7.87 (d, 2H, *J* = 8.4 Hz, ArH), 7.55 (d, 2H, *J* = 8.4 Hz, ArH), 7.15 (d, 1H, *J* = 8.4 Hz, ArH), 7.00 (s, 1H, ArH), 6.76 (d, 1H, *J* = 8.0 Hz, ArH), 4.09-4.04 (m, 2H, OCH_2), 3.93-3.84 (m, 4H, morpholine-H), 2.71 (m, 2H, NCH_2), 2.54-2.47 (m, 4H, morpholine-H), 2.26 (s, 3H, $ArCH_3$), 2.16 (s, 3H,

$ArCH_3$) ppm. HPLC: 95.04%.

5.1.13

4-((5-Methyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)-N-(2-methyl-5-(3-morpholinopropoxy)phenyl)benzamide (10d)

10d was synthesized by the similar preparation of **10a**, as white solid (27 mg, 42 %). MS (ESI) m/z: $[M+H]^+$ = 622.3. ^{1}H NMR (400M, MeOD) δ 8.43 (s, 1H, ArH), 7.92 (s, 4H, ArH), 7.84 (d, 2H, *J* = 8.4 Hz, ArH), 7.44 (d, 2H, *J* = 8.4 Hz, ArH), 7.17 (d, 1H, *J* = 8.4 Hz, ArH), 7.00 (d, 1H, *J* = 2.4 Hz, ArH), 6.78 (dd, 1H, *J* = 8.4, 2.4 Hz, *J* = 6.0 Hz, ArH), 4.03 (t, 2H, *J* = 4.4 Hz, OCH_2), 3.73 (t, 4H, *J* = 4.4 Hz, CH_2OCH_2), 2.68-2.60 (m, 6H, $N(CH_2)_3$), 2.31 (s, 3H, $ArCH_3$), 2.22 (s, 3H, $ArCH_3$), 2.04-1.96 (m, 2H, CH_2) ppm. HPLC: 97.06%.

5.1.14

4-((5-Methyl-4-phenylpyrimidin-2-yl)amino)-N-(2-methyl-5-(2-morpholinoethoxy)phenyl)benzamide (10e)

10e was synthesized by the similar preparation of **10a**, as white solid (50 mg, 39 %). MS (ESI) m/z: $[M+H]^+$ = 524.3. ^{1}H NMR (400M, DMSO-d_6) δ 9.95 (s, 1H, CONH), 9.55 (s, 1H, NH), 8.50 (s, 1H, ArH), 7.95 (m, 4H, ArH), 7.72 (d, 2H, *J* = 7.2 Hz, ArH), 7.59-7.53 (m, 3H, ArH), 7.15 (d, 1H, *J* = 8.4 Hz, ArH), 7.01 (d, 1H, *J* = 2.4 Hz, ArH), 6.76 (dd, 1H, *J* = 8.4, 2.4 Hz, ArH), 4.07 (t, 2H, *J* = 5.2 Hz, OCH_2), 3.59 (t, 4H, *J* = 4.4 Hz, morpholine-H), 2.69 (t, 2H, *J* = 5.2 Hz, NCH_2), 2.54-2.46 (m, 4H, morpholine-H), 2.26 (s, 3H, $ArCH_3$), 2.16 (s, 3H, $ArCH_3$) ppm. HPLC: 96.28 %.

5.1.15

4-((5-Methyl-4-phenylpyrimidin-2-yl)amino)-N-(2-methyl-5-(piperidin-1-ylmethyl)phenyl)benzamide (13a)

13a was synthesized by the similar preparation of **13b**, as white solid (22 mg, 76 %). MS (ESI) m/z: $[M+H]^+$ = 492.3. ^{1}H NMR (400M, DMSO-d_6) δ 9.95 (s, 1H, CONH), 9.64 (s, 1H, NH), 8.50 (s, 1H, ArH), 7.96-7.90 (m, 4H, ArH), 7.72 (d, 2H, *J* = 7.2 Hz, ArH), 7.59-7.55 (m, 3H, ArH), 7.29-7.23 (m, 2H, ArH), 7.13-7.07 (m, 1H, ArH), 3.34 (s, 2H, $PhCH_2N$), 2.37-2.30 (m, 4H, piperidine-H), 2.26 (s, 3H, $ArCH_3$), 2.21 (s, 3H, $ArCH_3$), 1.54-1.47 (m, 4H, piperidine-H), 1.28-1.20 (m, 2H, piperidine-H) ppm. HPLC: 97.79 %.

5.1.16

4-((5-Cyclopropyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)-N-(5-(hydroxymethyl)-2-methylphenyl)benzamide (11c)

To a solution of **8c** (150 mg, 0.36 mmol) and 3-amino-4-methylbenzyl alcohol (85 mg, 0.62 mmol) in DMF (10mL), HATU (274 mg, 0.72 mmol) and DIPEA (130 mg, 1.1 mmol) were added, and then the mixture was warmed at 80 ºC and stirred for 15 h. The reaction mixture was poured into ice water (50 mL) followed by extraction with EtOAc. The organic layer was dried by Na_2SO_4 and concentrated. The residue was purified by chromatography (DCM/ MeOH, 80:1) to generate **11c** (160 mg, 82 %) as a white solid, MS (ESI) m/z: $[M+H]^+$ = 535.2. ^{1}H-NMR (400 M, DMSO-d_6) δ 10.02 (s, 1H, CONH), 9.66 (s, 1H, NH), 8.40 (s, 1H, ArH), 8.01 (d, 2H, *J* = 8.4 Hz, ArH), 7.94 (s, 4H, ArH), 7.55 (d, 2H, *J* = 8.4 Hz, ArH), 7.30 (s, 1H, ArH), 7.22 (d, 1H, *J* = 8.4 Hz, ArH), 7.11 (d, 1H, *J* = 8.4 Hz, ArH), 5.21-5.15 (m, 1H, OH), 4.49 (s, 2H, $ArCH_2O$), 2.21 (s, 3H, $ArCH_3$), 1.94-1.88 (m, 1H, ArCH), 0.94-0.85 (m, 2H, CH_2), 0.75-0.67 (m, 2H, CH_2) ppm.

5.1.17

4-((5-Cyclopropyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)-N-(5-(chloromethyl)-2-methylphenyl)benzamide (12c)

To a solution of **11c** (110 mg, 0.2 mmol) in anhydrous DCM (20 mL), $SOCl_2$ (60 mg, 0.4 mmol) was added, and then the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated and purified by chromatography (DCM/ MeOH, 80:1) to generate **11c** (86 mg, 76 %) as a yellow solid, MS (ESI) m/z: $[M+H]^+$ = 553.2. ^{1}H-NMR (400 M, DMSO-d_6) δ 10.04 (s, 1H, CONH), 9.73 (s, 1H, NH), 8.40 (s, 1H, ArH), 8.01 (d, 2H, *J* = 8.4 Hz, ArH), 7.94 (s, 4H, ArH), 7.57 (d, 2H, *J* = 8.4 Hz, ArH), 7.44 (s, 1H, ArH), 7.30 (d, 1H, *J* = 8.4 Hz, ArH), 7.24 (d, 1H, *J* = 8.4 Hz, ArH), 4.77 (s, 2H, $ArCH_2Cl$), 2.24 (s, 3H, $ArCH_3$), 1.94-1.88 (m, 1H, ArCH), 0.94-0.85 (m, 2H, CH_2), 0.75-0.67 (m, 2H, CH_2) ppm.

5.1.18

4-((5-Cyclopropyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)-N-(2-methyl-5-(morpholinomethyl)phenyl)benzamide (13b)

To a solution of **12c** (86 mg, 0.15 mmol) in anhydrous MeCN (20 mL), morpholine (20 mg, 0.22 mmol) and K_2CO_3 were added, and then the mixture was refluxed for 6 h. The reaction mixture was filtered, concentrated and purified by chromatography (DCM/

MeOH, 80:1) to generate **13b** (18 mg, 21 %) as a white solid, MS (ESI) m/z: $[M+H]^+$ = 604.3. ^{1}H-NMR (400 M, DMSO-d_6) δ 10.01 (s, 1H, CONH), 9.66 (s, 1H, NH), 8.40 (s, 1H, ArH), 8.00 (d, 2H, *J* = 8.4 Hz, ArH), 7.93 (s, 1H, ArH), 7.57 (d, 2H, *J* = 8.0 Hz, ArH), 7.29 (s, 1H, ArH), 7.23 (d, 1H, *J* = 7.6 Hz, ArH), 7.10 (d, 1H, *J* = 7.2 Hz, ArH), 3.59-3.54 (m, 4H, morpholine-H), 3.37 (s, 2H, $ArCH_2N$), 2.39-2.34 (m, 4H, morpholine-H), 2.24 (s, 3H, $ArCH_3$), 1.94-1.88 (m, 1H, CH), 0.94-0.85 (m, 2H, CH_2), 0.75-0.67 (m, 2H, CH_2) ppm. HPLC: 96.79 %.

5.1.19

4-((5-Cyclopropyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)-N-(2-methyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)benzamide (13c)

13c was synthesized by the similar prepareation of **13b** (45 mg, 53 %) as a yellow solid, MS (ESI) m/z: $[M+H]^+$ = 617.3. ^{1}H-NMR (400 M, DMSO-d_6) δ 10.00 (s, 1H, CONH), 9.63 (s, 1H, NH), 8.39 (s, 1H, ArH), 7.99 (d, 2H, *J* = 7.6 Hz, ArH), 7.92 (s, 1H, ArH), 7.56 (d, 2H, *J* = 8.4 Hz, ArH), 7.28 (s, 1H, ArH), 7.21 (d, 1H, *J* = 8.0 Hz, ArH), 7.08 (d, 1H, *J* = 7.6 Hz, ArH), 3.45 (s, 2H, $ArCH_2N$), 2.44-2.36 (m, 8H, piperazine-H), 2.20 (s, 3H, $ArCH_3$), 1.94-1.87 (m, 1H, CH), 0.92-0.88 (m, 2H, CH_2), 0.74-0.67 (m, 2H, CH_2) ppm. HPLC: 96.19 %.

5.1.20

4-((5-Ethyl-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)-N-(2-methyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)benzamide (13d)

13d was synthesized by the similar prepareation of **13b** (28 mg, 25 %) as a yellow solid, MS (ESI) m/z: $[M+H]^+$ = 605.3. ^{1}H-NMR (400 M, DMSO-d_6) δ 10.01 (s, 1H, CONH), 9.63 (s, 1H, NH), 8.57 (s, 1H, ArH), 7.94 (d, 2H, *J* = 7.6 Hz, ArH), 7.78 (s, 1H, ArH), 7.55 (d, 2H, *J* = 8.4 Hz, ArH), 7.26 (s, 1H, ArH), 7.20 (d, 1H, *J* = 8.0 Hz, ArH), 7.07 (d, 1H, *J* = 7.6 Hz, ArH), 3.57 (s, 2H, $ArCH_2N$), 2.63-2.58 (m, 2H, $ArCH_2$), 2.54-2.48 (m, 8H, piperazine-H), 2.35 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 1.18-1.12 (m, 2H, CH_2) ppm. HPLC: 90.76 %.

5.1.21

N-(2-Methyl-5-(morpholinomethyl)phenyl)-4-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzamide (13e)

13e was synthesized by the similar prepareation of **13b** (20 mg, 44 %) as a yellow

solid, MS (ESI) m/z: $[M+H]^+$ = 481.2. ^{1}H-NMR (400 M, DMSO-d_6) δ 10.16 (s, 1H, CONH), 9.73 (s, 1H, NH), 9.39 (d, 1H, *J* = 2.0 Hz, ArH), 8.76 (dd, 1H, *J* = 8.8, 1.6 Hz, ArH), 8.70 (d, 1H, *J* = 5.2 Hz, ArH), 8.56 (d, 1H, *J* = 8.4 Hz, ArH), 7.98 (s, 4H, ArH), 7.67-7.62 (m, 2H, ArH), 7.29 (s, 1H, ArH), 7.23 (d, 1H, *J* = 7.6 Hz, ArH), 7.13-7.07 (m, 1H, *J* = 7.6 Hz, ArH), 3.59-3.55 (m, 4H, morpholine-H), 3.44 (s, 2H, $ArCH_2$), 2.39-2.33 (m, 4H, morpholine-H), 2.22 (s, 3H, $ArCH_3$) ppm. HPLC: 98.30 %.

5.1.22

4-((4-(1H-imidazol-1-yl)-5-methylpyrimidin-2-yl)amino)-N-(2-methyl-5-(pyrrolidin-1-ylmethyl)phenyl)benzamide (13f)

Similar procedure of **13b** was performed to give compound **13f** (62 mg, 46 %) as a yellow solid, MS (ESI) m/z: $[M+H]^+$ = 468.3. ^{1}H-NMR (400 M, DMSO-d_6) δ 10.14 (s, 1H, CONH), 9.68 (s, 1H, NH), 8.61 (s, 1H, ArH), 8.35 (s, 1H, ArH), 7.96 (d, 2H, *J* = 8.4 Hz, ArH), 7.87 (d, 2H, *J* = 8.8 Hz, ArH), 7.82 (s, 1H, ArH), 7.28 (s, 1H, ArH), 7.19 (d, 2H, *J* = 6.8 Hz, ArH), 7.07 (d, 1H, *J* = 7.6 Hz, ArH), 3.54 (s, 2H, $ArCH_2N$), 2.42 (s, 4H, $N(CH_2)_2$), 2.33 (s, 3H, $ArCH_3$), 2.21 (s, 3H, $ArCH_3$), 1.69 (s, 4H, $(CH_2)_2$) ppm. HPLC: 98.62 %.

5.1.234-Amino-N-(2-methyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)benzamide (18a)

It was synthesized as we recently described [11], as white product (200 mg, 85 %), MS (ESI) m/z: $[M+H]^+$ = 339.2. ^{1}H-NMR (400 M, DMSO-d_6) *δ* 9.34 (s, 1H, NH), 7.70 (d, 2H, *J* = 8.4 Hz, ArH), 7.24 (s, 1H, ArH), 7.15 (d, 1H, *J* = 7.6 Hz, ArH), 7.04 (d, 1H, *J* = 7.6 Hz, ArH), 6.58 (d, 2H, *J* = 8.4 Hz, ArH), 5.70 (s, 2H, NH_2), 3.40 (s, 2H, CH_2), 2.36-2.30 (m, 8H, piperazine-H), 2.17 (s, 3H, CH_3), 2.14 (s, 3H, CH_3) ppm.

5.1.24 4-Amino-N-(2-methyl-5-(morpholinomethyl)phenyl)benzamide (18b)

Similar procedure of **18a** was performed to give compound **18b** (78 mg, 94 %), MS (ESI) m/z: $[M+H]^+$ = 326.2. ^{1}H-NMR (400 M, DMSO-d_6) *δ* 9.35 (s, 1H, NH), 7.71 (d, 2H, *J* = 8.4 Hz, ArH), 7.26 (s, 1H, ArH), 7.18 (d, 1H, *J* = 7.6 Hz, ArH), 7.05 (d, 1H, *J* = 7.6 Hz, ArH), 6.60 (d, 2H, *J* = 8.4 Hz, ArH), 5.71 (s, 2H, NH_2), 3.59-3.53 (m, 4H, CH_2*2), 3.41 (s, 2H, CH_2), 2.35 (s, 4H, CH_2*2), 2.18 (s, 3H, CH_3) ppm.

5.1.25 2-Chloro-5-methyl-4-(pyridin-2-yl)pyrimidine (22)

It was synthesized similar to the procedure as we recently described [11], as yellow solid

(150 mg, 34 %), MS (ESI) m/z: $[M+H]^+$ = 206. ^{1}H-NMR (400 M, $CDCl_3$) δ 8.72 (d, 1H, *J* = 4.0 Hz, ArH), 8.55 (s, 1H, ArH), 8.10 (d, 2H, *J* = 8.0 Hz, ArH), 7.90-7.86 (m, 1H, ArH), 7.42-7.39 (m, 1H, ArH), 2.60 (s, 3H, CH_3) ppm.

5.1.26

4-((5-methyl-4-(pyridin-2-yl)pyrimidin-2-yl)amino)-N-(2-methyl-5-(4-methylpiperazin-1-ylmethyl)phenyl)benzamide (23a)

It was synthesized similar to the procedure as we recently described [6], as yellow solid (23 mg, 72 %), MS (ESI) m/z: $[M+H]^+$ = 508.3.^{1}H-NMR (400M, $CDCl_3$) δ 8.75 (d, 1H, *J* = 4.0 Hz, ArH), 8.43 (s, 1H, CONH), 8.00-7.90 (m, 2H, ArH), 7.88 (d, 2H, *J* = 8.0 Hz, ArH), 7.82 (d, 2H, *J* = 8.0 Hz, ArH), 7.64 (s, 1H, NH), 7.41-7.39 (m, 2H, ArH), 7.19 (d, 1H, *J* = 8.0 Hz, ArH), 7.08 (d, 1H, *J* = 8.0 Hz, ArH), 3.55 (s, 2H, NCH_2Ph), 2.80-2.60 (m, 8H, piperazine-H), 2.48 (s, 3H, $ArCH_3$), 2.39(s, 3H, NCH_3), 2.33 (s, 3H, $ArCH_3$) ppm, HPLC：98 %.

5.1.27

4-((5-methyl-4-(pyridin-2-yl)pyrimidin-2-yl)amino)-N-(2-methyl-5-(morpholinomethyl)phenyl)benzamide (23b)

It was synthesized as we recently described [6], as yellow solid (60 mg, 43 %), MS (ESI) m/z: $[M+H]^+$ = 495.3.^{1}H-NMR (400M,$CDCl_3$) δ 8.75 (d, 1H, *J* = 4.0 Hz, ArH), 8.44 (s, 1H, CONH), 7.99 (d 1H, *J* = 8.0 Hz, ArH), 7.95 (s, 1H, NH), 7.92-7.87 (m, 3H, ArH), 7.82 (d, 2H, *J* = 8.0 Hz, ArH), 7.63 (s, 1H, ArH), 7.41-7.38 (m, 2H, ArH), 7.19 (d, 1H, *J* = 8.0 Hz, ArH), 7.09 (d, 1H, *J* = 8.0 Hz, ArH), 3.72-3.70 (m, 4H, morpholine-H), 3.50 (s, 2H, NCH_2Ph), 2.50-2.43 (s, 7H, morpholine-H+$ArCH_3$), 2.33 (s, 3H, $ArCH_3$) ppm, HPLC: 97 %.

5.2 In vitro Gli-luciferase reporter assay to evaluate the Hh signaling pathway inhibitory activity

The Hh signaling pathway inhibitory activity for all the target compounds were used a luciferase reporter assay in NIH3T3 cells carrying a stably transfected Gli-reporter construct (Gli-luc reporter cell line), which were similar to our previous manuscript.[6] Firstly, the NIH3T3/Gli-luc cells were treated with DMEM and 10% FBS and 1μg/mL Puromycin. Secondly, The cells were seeded onto 96-well plates at 2×10^4cells/well and cultured in the condition of 5% CO_2 and 37 ºC overnight. Thirdly, after incubation, all the

prepared compounds (including GDC-0449, as an internal standard control) diluted in a serial 8×solution (0.05-300nM) containing 0.5% FBS and 0.7μg/mL Sonic Hh agonist were added to each well (n = 4 wells per concentration). The cells were incubated for an additional 48 h. Cells were incubated in media containing 0.1% DMSO with or without Sonic Hh (0% or 100% inhibition control) respectively. Lastly, cells were then harvested and lysed in reporter lysis buffer, and luciferase activities were measured using a Dual-Luciferase® Reporter Assay System (Promega E1910). The activity of the Gli reporter was defined as the ratio of Firefly/Renilla luciferase activities.

5.3 Pharmacokinetic Studies of the selected compounds in SD rats

The pharmacokinetic studies of the selected compounds were evaluated according to the procedure of our previous report.[6] Compounds were administered to 3 male SD rats (weight ranging from 180 g to 240 g) by a dose of 1 mg/kg in iv administration, and the dosing volume was 5 mL/kg. After administration, blood samples were collected at the point including 2 min, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, and 24 h for analyses, the collected blood samples were centrifuged at 4000 rpm for 5 min at 4 ^{o}C, and then analyzed after protein precipitation. LC/MS/MS analysis of compounds were performed under optimized conditions to obtain the best sensitivity and selectivity of the analyte in selected reaction monitoring mode (SRM) containing an internal standard. Plasma concentration-time data were measured by a noncompartmental approach using the software WinNonlin Enterprise, version 5.2.

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Novel 4-(2-Pyrimidinylamino)benzamide Derivatives as Potent Hedgehog Signaling Pathway Inhibitors

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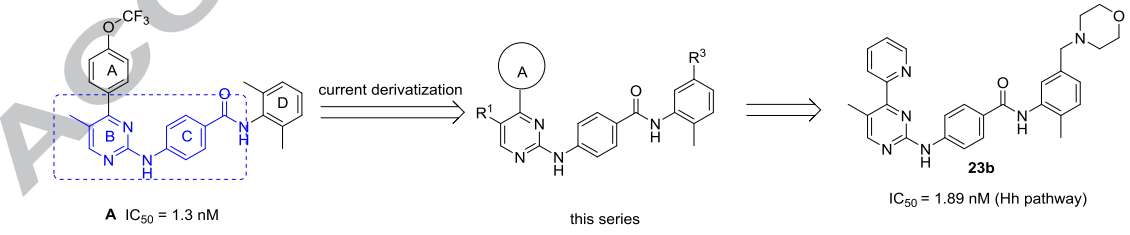
Graphical Abstract



Footnotes

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