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Research paper

# Discovery of novel 4-(2-pyrimidinylamino)benzamide derivatives as highly potent and orally available hedgehog signaling pathway inhibitors

Minhang Xin [a, *], Liandi Zhang [b], Qiu Jin [b], Feng Tang [b], Jun Wen [b], Liyun Gu [b], Lingfei Cheng [b], Yong Zhao [b]

[a] Department of Medicinal Chemistry, School of Pharmacy, Health Science Center, Xi'an Jiaotong University, No 76, Yanta West Road, Xi'an 710061, PR China
[b] Jiangsu Simcere Pharmaceutical Co. Ltd., No 699-18, Xuan Wu District, Nanjing 210042, PR China

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ABSTRACT

A series of novel hedgehog signaling pathway inhibitors have been designed by structural modification based on the former reported scaffold of 4-(2-pyrimidinylamino)benzamide. The SAR for this series was described and many derivatives showed potent inhibitory activity. Among these compounds, compounds **12af** and **12bf** were identified to have high potency and optimal PK profiles. Although both of compounds **12af** and **12bf** did not show strong antitumor efficacy in LS-174T nude mice model, they were promising candidates as Hh signaling inhibitors due to great potency against Hh signaling pathway and outstanding PK properties, deserving further evaluation in other Hh signaling operative tumor models.



## 1. Introduction

Hedgehog (Hh) signaling pathway plays a critical role in regulation of the cell growth, embryonic morphogenesis, tissue patterning, and angiogenesis process [1]. Generally, Hh signaling is silence in the adult human; however, when tumor occurred, Hh signaling pathway became aberrantly activated. Strong evidences suggested that abnormal activation of Hh pathway has been linked to pathogenesis of a variety of human tumor types, such as basal cell carcinoma (BCC), medulloblastoma (MB), rhabdomyosarcoma (RMS), lymphoma, leukemia, lung, pancreatic, hepatocellular, gastric, esophageal, colorectal, ovarian, prostate, melanoma and glioblastoma [2]. Thus, Hh signaling pathway inhibitor is considered to have therapeutic potential for combating many human tumors.

Until now, there are many Hh signaling pathway inhibitors have been reported [3]. Two agents, vismodegib (GDC-0449, **1**) and sonidegib (LDE-225, **2**), have been approved by FDA for treatment of locally advanced BCC [4,5]. Besides, other Hh inhibitors, including taladegib (LY-2940680, **3**) [6], glasdegib (PF-04449913, **4**) [7] and BMS-833923 (XL-139, **5**) [8], are evaluated for their therapeutic use in clinical trials. Obviously, although Hh inhibitors have already been proved to be clinically significant effective in BCC treatment, they still remained to be undefined for their therapeutic potential against other solid and hematological tumors such as lymphoma, leukemia, hepatocellular and so on [9]. Therefore, there is still enthusiastic interest to develop new classes of Hh inhibitors for enlarging their medicinal use (see Fig. 1).

Recently, we have reported our medicinal chemistry effort on the discovery of a novel series of highly potent Hh inhibitors, which contained a central backbone of 4-(2-pyrimidinylamino)benzamide [10]. Subsequently, the systematic SAR of the A-ring, B-ring, C-ring and D-ring of *N*-(2-pyrimidinylamino) benzamide core has been established [11,12]. Furthermore, using scaffold hopping strategy, the structural modification on the B-ring has been explored, and several interesting novel scaffolds such as pyrrolo [2,1-*f*][1,2,4] triazine, thieno [2,3-*d*]pyrimidines, furo [3,2-*d*]pyrimidines, purines, and 6,7-dihydro-5*H*-pyrano [2,3-*d*]pyrinidine have first been developed [13–15]. Although these new scaffolds showed potent Hh signaling inhibitory activity in vitro, they displayed unsatisfactory physic-chemical properties and insufficient pharmacokinetic profiles, and that block their further investigation. Thus, our drug

* Corresponding author.
*E-mail address:* xmhcpu@163.com (M. Xin).

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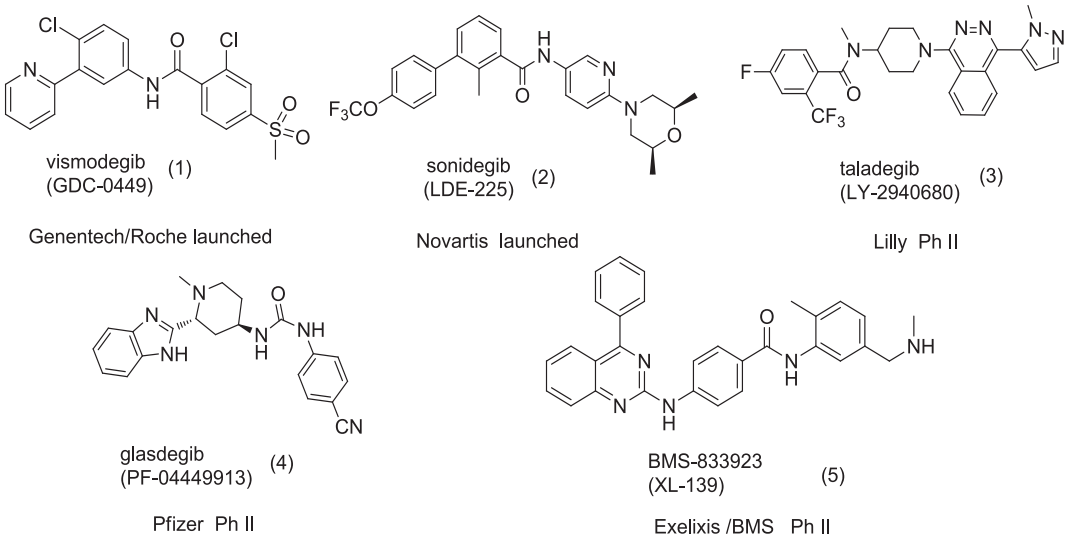


**Fig. 1.** Representative structures of clinical Hh signaling pathway inhibitors.

development attention was turned back towards the 4-(2-pyrimidinylamino)benzamide scaffold, which is proved to be a privileged skeleton and more druggable, and widely emerging in the drugs and drug candidates. Herein, in this report we reported our further structural derivatizations on the 4-(2-pyrimidinylamino)benzamide skeleton, and also reported the PK evaluations of these analogues in vivo. After the path to candidate nomination, compound **16b** was finally picked out as a drug candidate, which displayed highly potent inhibitory activity against Hh signaling in vitro, improving PK properties, and good anticancer activity in vivo (Fig. 2).

## 2. Chemistry

The novel 4-(2-pyrimidinylamino)benzamide derivatives were synthesized, as summarized in Table 1. The synthetic routes for all the target compounds were illustrated in Schemes 1–3.

As illustrated in Scheme 1, The commercially available 5-substituted 2,4-dichloropyrimidine (**6**) was treated with 4-trifluoromethoxyphenylboronic acid under Suzuki coupling condition of $Pd(PPh_3)_2Cl_2$ and 2 M aq $Na_2CO_3$ in reflux dioxane to give product **7**, which was subsequently treated with methyl 4-aminobenzoate under the Buchwald-Hartwig coupling condition of $Pd(OAc)_2$/BINAP/$Cs_2CO_3$ in reflux dioxane to yield benzoate **8**. Hydrolysis of **8** under basic condition of NaOH afforded free acid **9**. Condensation **9** with 3-amino-4-methylbenzyl alcohol gave benzamide **10**, which was followed by chlorination with thionyl chloride reagent to generate intermediate **11**. Then the target compounds **12a** and **12b** were conveniently synthesized by treating **11** with appropriate secondary amines using the nucleophilic substitution (Scheme 1).

The similar methods were used to prepare compounds **15** and **17**, which were depicted in Scheme 2. The picolinamides **15a-b** and nicotinamide **15c** were synthesized starting from the material **7**. After Buchwald-Hartwig coupling **7** with 5-aminopicolinic acid or 6-aminonicotinic acid, the picolicolinic acid intermediate **12a-b,** and the nicotinic acid intermediate **12c** were prepared, which were subsequently reacted with benzyl alcohol under the HATU/DIPEA catalytic condition to yield the intermediate **13**. The hydroxyl group of **13** was chlorinated, followed by substitution with morpholine to provide the desired product **15**. Likewise, the benzamide **17** was prepared starting from the intermediate **8b**. Using the similar procedures including acylation, chlorination, nucleophilic substitution, the desired products **17** were achieved (Scheme 2).

The synthetic approach to acquire the target product **28** was illustrated in Scheme 3. Claisen condensation of cyclopropylacetate with formate in the presence of LDA gave the β-keto ester **19**. Treating **19** with thiocarbamide followed by transformation of 2-thiocarbonyl group to 2-carbonyl group afforded pyrimidinedione **21**. Subsequent chlorination of **21** with $POCl_3$ followed by Suzuki coupling procedure provided the key intermediate **23**. Afterwards, following several procedures similar to that for preparation of **12a**, the target compound **28** was prepared (Scheme 3).

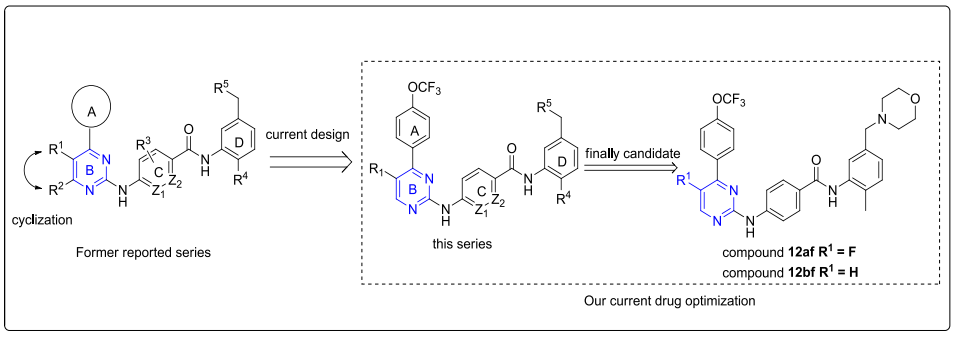


**Fig. 2.** Our new compounds design.