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Scaffold hopping approach to a new series of smoothened antagonists

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ABSTRACT

The hedgehog (Hh) signaling pathway is a key regulator during embryonic development, while in adults, it has limited functions such as stem cell maintenance and tissue repair. The aberrant activity of the Hh signaling in adults has been linked to numerous human cancers. Inhibition of Hh signaling therefore represents a promising approach toward novel anticancer therapies. The Smoothened (Smo) receptor mediates Hh signaling. Here we report a new series of Smo antagonists which were obtained by a scaffold hopping strategy. Compounds from this new scaffold demonstrated decent inhibition of Hh pathway signaling. The new scaffold can serve as a starting point for further optimization.

The hedgehog (Hh) signaling pathway is a key developmental pathway which regulates patterning, growth and cell migration during embryonic development, but in adults it is limited to tissue maintenance and repair. Under normal conditions, the endogenous ligands sonic hedgehog, Indian hedgehog and desert hedgehog bind to their receptor Patched (Ptch), relieving the inhibitory effect of Ptch on Smoothened (Smo). Smo activation triggers a series of events which ultimately lead to specific gene expression mediated by the Gli family transcription factors.[1] Aberrant Hh signaling has been linked to numerous human cancers. Mutational inactivation of the inhibitory pathway components such as Ptch leads to constitutive ligand-independent activation of the Hh signaling pathway, resulting in cancers such as basal cell carcinoma and medulloblastoma.[2] Ligand-dependent activation of Hh signaling is involved in prostate cancer, pancreatic cancer, breast cancer and some blood cancers.[3] Therefore, inhibition of aberrant Hh signaling represents a promising approach toward novel anticancer therapy.[4]

Cyclopamine (Fig. 1), a naturally occurring alkaloid, was the first reported Hh signaling pathway inhibitor,[5] and it was later identified as a Smo antagonist.[6] A cyclopamine derivative, IPI-926 (Fig. 1), which demonstrated better potency, stability and other pharmaceutical properties than cyclopamine, had entered clinical development.[7] Numerous synthetic Smo antagonists had been reported in recent years.[8] The most advanced in the class, GDC-0449 (Vismodegib, Fig. 1), was approved by FDA in January 2012 for the treatment of basal cell carcinoma which was not suitable for operation.[9] This approval showcased the first embryonic pathway inhibitor for the treatment of human cancer. Other Smo antagonists are in different stages of development (Fig. 1).

We have investigated numerous templates in pursuit of novel Smo receptor antagonists. Both GDC-0449[8c] and NVP-LDE225[8h] were the results of optimization campaigns based on initial screening hits. The central amide bonds were reversed, yet both molecules maintained excellent potency. This observation indicated that the central amides were place-holders, unlikely to have participated in significant interactions with the Smo receptor. This assumption was reinforced by Pfizer compound **1**[10] (Fig. 2) and a series of Amgen compounds.[8g] GDC-0449 possessed all sp2-hybridized carbons, resulting in a high melting point (264 °C) and poor solubility (9.5 μg/mL). Enhanced solubility was achieved by adding an *ortho*-chloro group to the right side ring to introduce tilt and reduce planarity of the aryl amide.[8c] It is well documented in the literature that planarity and molecular topology have significant impacts on absorption, metabolism and toxicity.[11] In order to improve the physical–chemical properties, we proposed introducing the saturation ring as the place-holder (introducing sp3-hybridized carbons, reducing planarity), as featured in compound **1**. We also proposed tying the long tail featured

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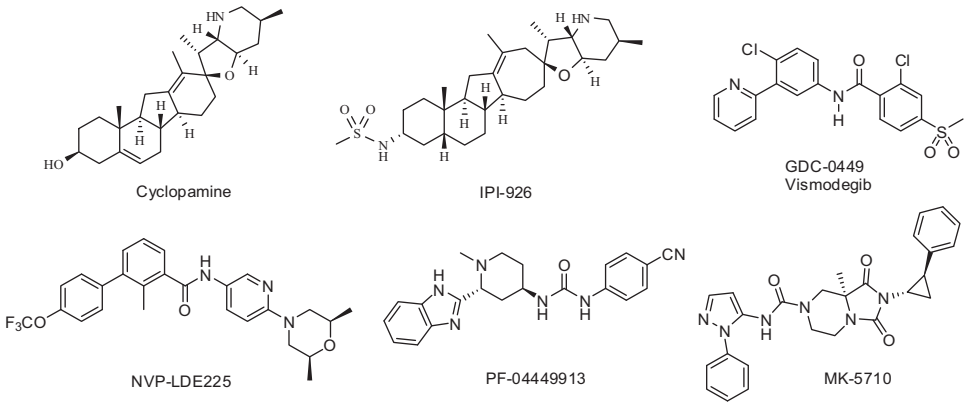


Figure 1. Smoothened antagonists in advanced development.

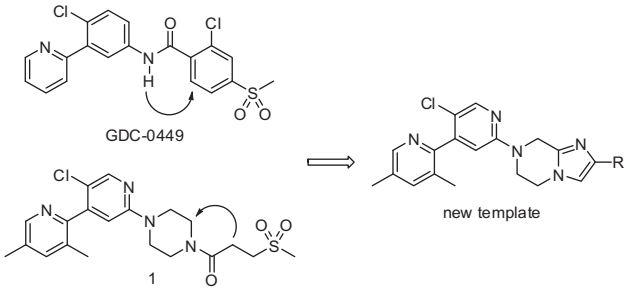
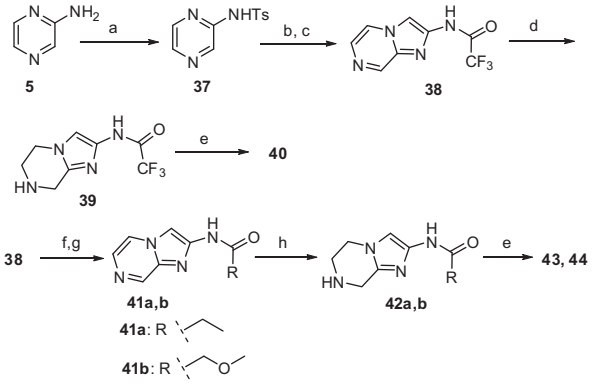


Figure 2. Scaffold hopping approach to a novel series of smoothened antagonists.

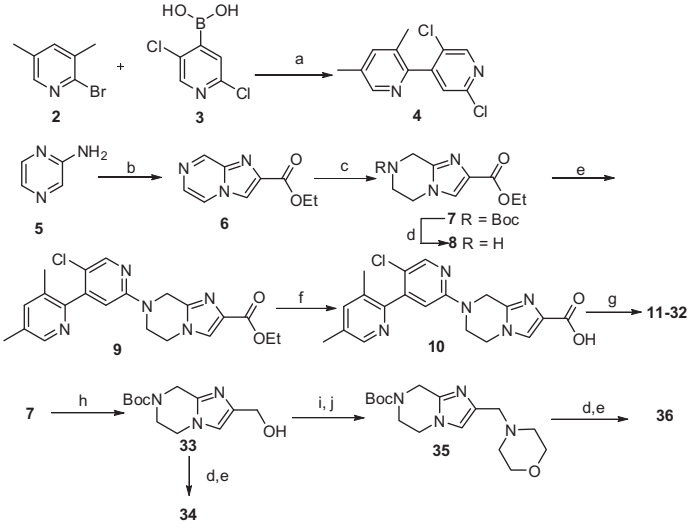
in compound **1** to decrease rotatable bonds as a way to enhance absorption and metabolic stability.[12] The scaffold hopping strategy led us to a novel template shown in Figure 2.

The general synthetic route used to prepare compounds **9**–**36** was shown in Scheme 1. Commercially available pyrazin-2-amine **5** was reacted with ethyl 3-bromo-2-oxopropanoate in DME at room temperature and then refluxed in EtOH to give intermediate **6**. Hydrogenation of intermediate **6** under Pd/C with Boc_2O/EtOH provided intermediate **7**. Removal of the Boc-protecting group of



Scheme 2. Reagents and conditions: (a) TsCl, pyridine, rt, 80 min, 72%; (b) 2-iodoacetamide, DMF, rt, 28 h, 64%; (c) trifluoroacetic anhydride, DCM, reflux, 2 h, 97%; (d) 10% Pd/C, H_2, MeOH, rt, 10 h, 25%; (e) Compound **4**, CsF, DMSO, 120 °C, 48 h, 18–26%; (f) NH_4OH, MeOH, 70 °C, 6 h, 44%; (g) corresponding acid, HATU, DIPEA, DMF, rt, 24 h, 44–52%; (h) PtO_2, H_2, MeOH, rt, 48 h, 73%.

intermediate **7** in the presence of HCl/EtOAc led to intermediate **8**, which was used to displace the 2-position chlorine of bipyridine **4** to yield ester **9**. Compound **4** was obtained by Suzuki coupling of



Scheme 1. Reagents and conditions: (a) $Pd(dppf)Cl_2$, $K_3PO_4{\cdot}3H_2O$, dioxane, H_2O, 110 °C, 16 h, 41%; (b) ethyl 3-bromo-2-oxopropanoate, DME, rt, 2.5 h, then EtOH, reflux, 2.5 h, 27%; (c) 10% Pd/C, EtOH, Boc_2O, H_2, 24 h, 63%; (d) HCl/EtOAc, rt, 3 h, 83–95%; (e) compound **4**, CsF, DMSO, 120 °C, 48 h, for **9**, 85%; for **34**, 16%; (f) LiOH, THF, H_2O, rt, 12 h, 70%; (g) HATU, DIPEA, DMF, rt, 16 h, for **11**–**28**, 26–72%; alcohol, $SOCl_2$, reflux for **29** (45%) and **30** (36%); DCC, HOBt, DMAP, DCM, 6–36 h for **31** (25%) and **32** (66%); (h) $LiAlH_4$, THF, 0 °C, 30 min, 70%; (i) MsCl, TEA, DCM, rt, 30 min; (j) morpholine, Na_2CO_3, ACN, 100 °C, 2 h, two steps, 43%.