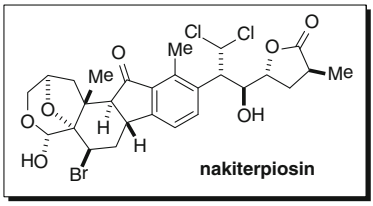
Chapter 2
Nakiterpiosin

Shuanhu Gao and Chuo Chen



2.1 Background

For decades, ranchers in central Idaho were puzzled by a mysterious birth defect in their flocks of sheep. A percentage of their lambs, ranging from 1 % to 20 %, were born with only one eye. The Poisonous Plant Research Laboratory of the US Department of Agriculture started to investigate this "malformed lamb disease" in 1954. During the 11 years of work, they found that ewes grazing on corn lily (*Veratrum californicum*) on the *14th* day of gestation gave birth to cyclopic lambs, while the ewes were left unaffected [1]. They further found that cyclopamine (**3**) was responsible for the one-eyed face malformation and veratramine (**4**) led to leg deformity (Chart 2.1). The molecular target of **3** was identified 30 years later to be smoothened (Smo) [2]. Smo is a seven-pass transmembrane protein that regulates the activity of the Hedgehog (Hh) signal transduction pathway. Since Hh signaling is central to stem cell differentiation and tissue homeostasis, and 10 % of basal cell carcinoma and medulloblastoma patients carry hyperactive mutant Smo, small

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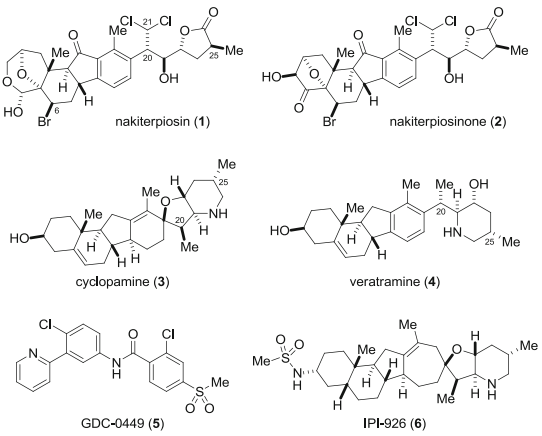


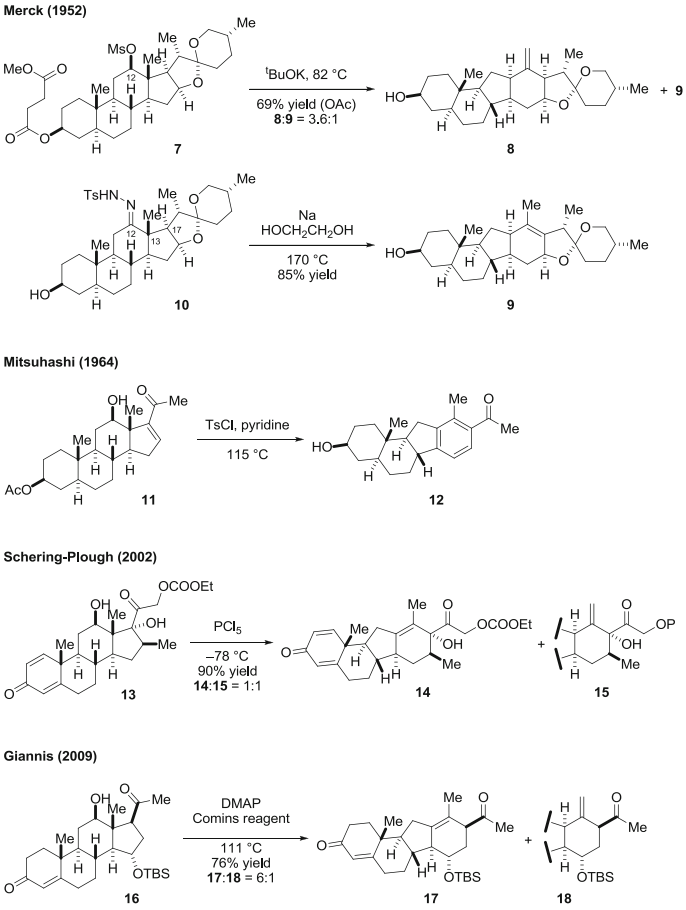
Chart 2.1 C-nor-D-homosteroids and the first two Hedgehog antagonists in clinical trials

molecules that suppress Hh signaling have been pursued as a new class of therapeutics for cancer and neurodegenerative diseases [3]. Several small-molecule Smo inhibitors, including vismodegib (or GDC-0449, **5**) by Genentech [4], IPI-926 (**6**, a cyclopamine derivative) by Infinity Pharmaceuticals [5], BMS-833923 (XL139) by Bristol-Myers Squibb [6], LDE225 and LEQ506 by Novartis [7], PF-04449913 by Pfizer, and TAK-441 by Millennium Pharmaceuticals, are now under clinical evaluation [8].

Structurally, **3** and **4** belong to a special class of steroids in which the C-ring is contracted and D-ring expanded by one carbon via a C-13 → C-12 migration. For decades, the C-nor-D-homosteroids were found only in plants. It was not until 2003 that the first marine-originated members, nakiterpiosin (**1**) and nakiterpiosinone (**2**), were reported by Uemura and coworkers [9] as part of a study of coral black disease. From 1981 to 1985, large patches (up to 1,000 m in length) of cyanobacteriosponges *Terpios hoshinota* were observed in Okinawa [10]. These thin, encrusting sponges aggressively compete with corals for space by epizoism. Uemura and coworkers hypothesized that *T. hoshinota* killed the covered corals by secreting toxic compounds. Searching for these toxins, they isolated 0.4 mg of **1** and 0.1 mg of **2** from 30 kg of the sponges. Both compounds inhibited the growth of P388 mouse leukemia cells with an IC_{50} of 10 ng/mL.

2.2 Synthesis of the 6,6,5,6 Steroidal Skeleton

The unique molecular skeleton of the C-nor-D-homosteroids represents significant challenges for organic chemists. The structure elucidation and the total synthesis of cyclopamine (**3**, also known as 11-deoxojervine), jervine (11-oxo-**3**), and veratramine (**4**) are important milestones in steroid chemistry. Many synthetic strategies were developed in the 1960s–1970s for these targets. Notably, Masamune



Scheme 2.1 The biomimetic approaches to C-nor-D-homosteroids

and Johnson documented the synthesis of jervine and veratramine, respectively, in 1967 [11, 12]. Together with Masamune's previous report of the conversion of jervine to cyclopamine by a Wolff reduction, these reports are the first syntheses of these three steroidal alkaloids [13]. In addition, a formal synthesis was reported by Kutney in 1975 [14] and an efficient approach by Giannis in 2009 [15]. The development of the synthetic approaches to this unique 6,6,5,6 steroidal skeleton is summarized below.

2.2.1 The Biomimetic Approaches

The biomimetic approach to the core skeleton of C-nor-D-homosteroid was first developed by the Merck research group (Scheme 2.1) [16]. In the Merck procedure,

the C-12 position of hecogenin was first activated as a mesylate (**7**) or a tosylhydrozone (**10**). While treating **7** with a base gave a mixture of rearranged products **8** and **9**, thermolysis of **10** gave only **9**. It was proposed that the C-13 → C-12 migration of **10** was accompanied by a concerted deprotonation of H-17 to provide **9** selectively. This method was later modified by Mitsuhashi [17], Schering-Plough [18], and Giannis [19]. In particular, Giannis has demonstrated that a combination of the Comins reagent and DMAP effectively promotes the rearrangement of a series of steroid derivatives that fail to undergo rearrangement under other reported conditions. It should also be noted that ketone **12** served as the common intermediate for Masamune and Johnson in their synthesis of 11-oxo-**3** and **4**. Ketone **12** was initially obtained from the degradation of **4** by Masamune [20]. Mitsuhashi prepared **11** by degrading hecogenin.

2.2.2 The Ring-by-Ring Approaches

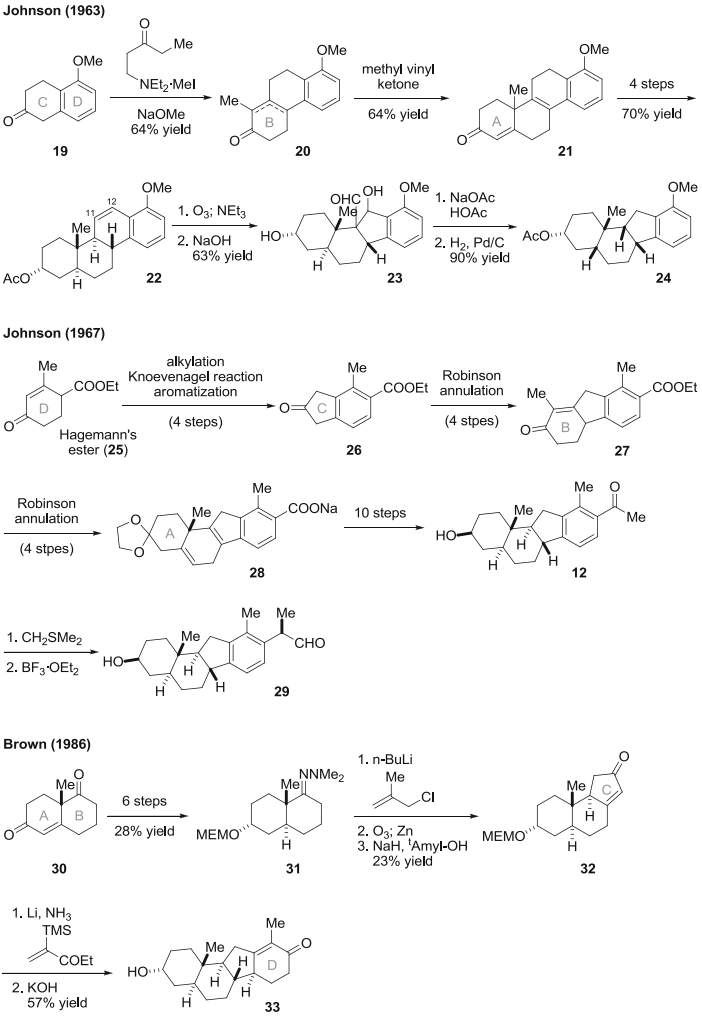
Johnson has developed two linear approaches to synthesize the C-nor-D-homosteroid skeleton (Scheme 2.2). In his first approach [21], tetralone **19**, obtained from reduction of 2,5-dimethoxynaphthalene, was used as the source of the C,D-rings. The B- and A-rings were constructed by sequential Robinson annulations (**19** → **20** → **21**). The C11,12 olefin was then introduced to provide **22**. Ozonolysis of **22** followed by an aldol reaction of the resulting dialdehyde gave **23**. Subsequent deformylation and deoxygenation afforded the cyclopamine skeleton **24**.

In Johnson's second approach [12b], the C-ring was introduced directly with the desired ring size. Starting from Hagemann's ester (**25**), which served as the source of the D-ring, a Knoevenagel condensation was used to introduce the C-ring (**25** → **26**). After decarboxylation and D-ring aromatization, the B- and A-rings were introduced stepwise by Robinson annulations (**26** → **27** → **28**). A series of reduction and aromatization reactions were then performed to deliver racemic **12**. Johnson's asymmetric synthesis of veratramine (**4**) was accomplished by adopting Mitsuhashi's procedure [17a]. Finally, the side chain of **12** was functionalized by an epoxide–aldehyde rearrangement.

In contrast to the Johnson's D → A-ring construction approach, Brown devised an A → D-ring construction approach [22]. Starting from Wieland–Miescher ketone (**30**), a common source of the A, B-rings in the de novo synthesis of steroids, the C-ring was introduced via hydrazone allylation, ozonolysis, aldol condensation, and olefin isomerization (**31** → **32**). The D-ring was assembled by a reductive alkylation of enone **32** followed by an aldol condensation to give **33** after deprotection.

2.2.3 Miscellaneous

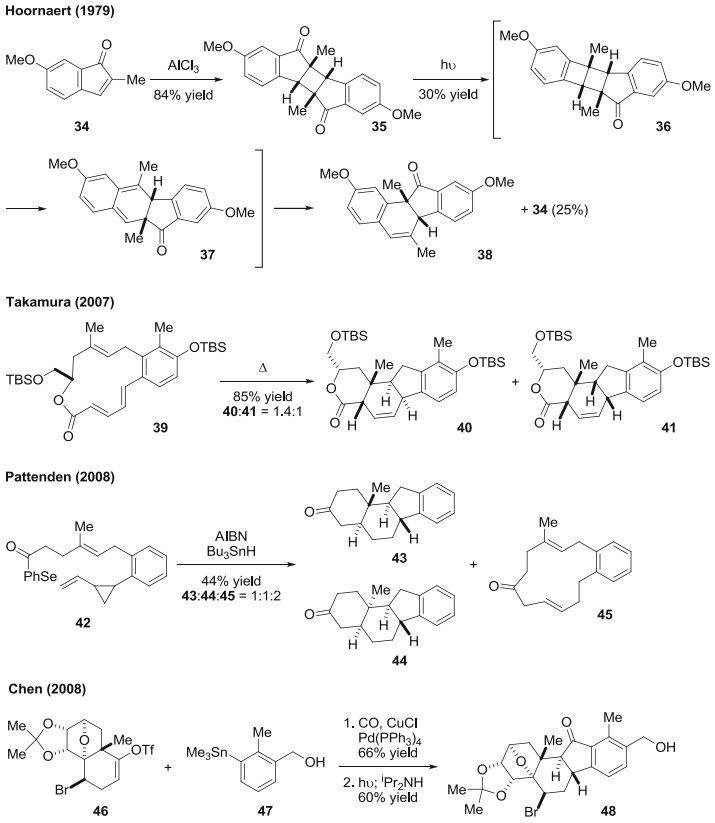
During the synthesis of an indenone derivative, Hoornaert found that $AlCl_3$ catalyzed the dimerization of indenone **34** to form truxone **35** (Scheme 2.3) [23]. Attempts to



Scheme 2.2 The ring-by-ring approaches to C-nor-D-homosteroids

induce the retrodimerization of **35** by photolysis resulted in a decarbonylation through a Norrish type I cleavage to give **36**. The subsequent photolytic, disrotatory retro-electrocyclization reaction and a thermal, suprafacial 1,5-sigmatropic benzoyl shift afforded **38** that bears a C-nor-D-homosteroid skeleton.

The thermally and Lewis acid-promoted transannular Diels–Alder reactions have proven to be a powerful tool for the synthesis of steroids and other natural products [24]. A research team led by Takamura, Arimoto, and Uemura utilized this reaction to assemble the polycyclic skeleton of nakiterpiosin (**1**) [25]. Heating macrolide **39** at 160 °C gave **40** and **41** as a mixture of diastereomers in good yields.



Scheme 2.3 Miscellaneous approaches to C-nor-D-homosteroids

Pattenden reported a tandem cyclization approach for the synthesis of estrone in 2004. Later, they further demonstrated that this strategy could be used to generate the veratramine skeleton [26].

We recently developed a convergent approach that comprises a carbonylative Stille coupling [27, 28] and a photo-Nazarov cyclization reaction [29–31] for the synthesis of nakiterpiosin [32]. Several highly acid- and base-sensitive functional groups were tolerated under these nearly neutral reaction conditions. We found that using a stoichiometric amount of $Pd(PPh_3)_4$ and 1 atmosphere of CO, triflate **46**, and stannane **47** could be coupled to give the corresponding enone in 66 % yield. The steric hindrance of both coupling components rendered the carbonylative coupling significantly challenging. The employment of CuCl as an additive and DMSO as the solvent accelerated the reaction considerably, thus making the desired reaction outcompete the decomposition pathways. Attempts to add LiCl to facilitate the reaction led to the elimination of the bromide. The beneficial role of CuCl in Stille reactions was first discovered by Liebeskind and later studied by Corey [33].

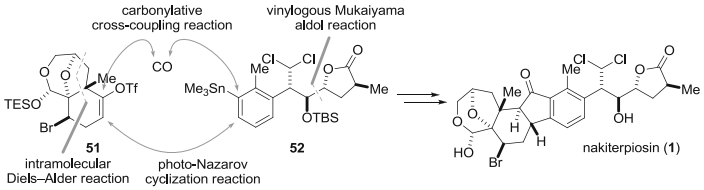


Chart 2.2 The synthetic strategy for nakiterpiosin

It is believed that the copper salts facilitate transmetalation by generating a highly reactive organocuprate intermediate.

The Nazarov cyclization of vinyl aryl ketones involves a disruption of the aromaticity, and therefore, the activation barrier is significantly higher than that of the divinyl ketones. Not surprisingly, the Lewis acid-catalyzed protocols [30] resulted only in decomposition to the enone derived from **46**, **47**, and CO. Pleasingly, however, photolysis [31] readily delivered the desired annulation product **48** in 60 % yield. The photo-Nazarov cyclization reaction of aryl vinyl ketones was first reported by Smith and Agosta. Subsequent mechanistic studies by Leitich and Schaffner revealed the reaction mechanism to be a thermal electrocyclization induced by photolytic enone isomerization. The mildness of these reaction conditions and the selective activation of the enone functional group were key to the success of this reaction.

2.3 Synthesis of Nakiterpiosin

As described above, our synthetic strategy involves the convergent construction of the central cyclopentanone ring with a carbonylative cross-coupling reaction and a photo-Nazarov cyclization reaction (Chart 2.2). The electrophilic coupling component **51** was synthesized by an intramolecular Diels–Alder reaction [34] and the nucleophilic coupling component **52** by a vinylogous Mukaiyama aldol reaction [35].

The structure of nakiterpiosin was originally assigned as **49** by Uemura based on NMR experiments [9]. Puzzled by the inconsistency of the C-20 stereochemistry of **49** with that of cyclopamine (**3**) and veratramine (**4**), we first set out to probe the relative stereochemistry of nakiterpiosin. Our model studies indicated the potential misassignment of the C-6, C-20, and C-25 stereogenic centers [32]. We next considered the biogenesis of the halogen atoms of nakiterpiosin to rationalize the C-6 and C-20 stereochemistry (Chart 2.3) [36]. We envisioned that the C-21 chlorine atoms of nakiterpiosin might be introduced by radical chlorination, and the C-6 bromine atom by bromoetherification (as shown in **50**) to result in retention of the C-20 configuration and the anti C-5,6 bromohydrin stereochemistry. Taken together, these considerations led us to propose **1** as the correct structure of nakiterpiosin, which was later confirmed via the total synthesis of **49** and **1**.

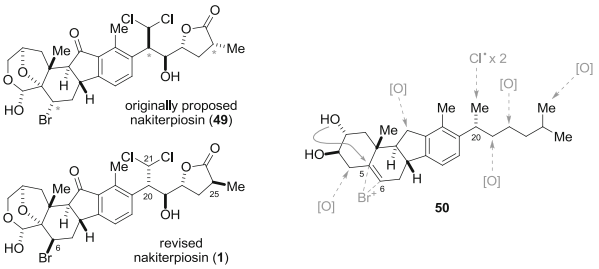
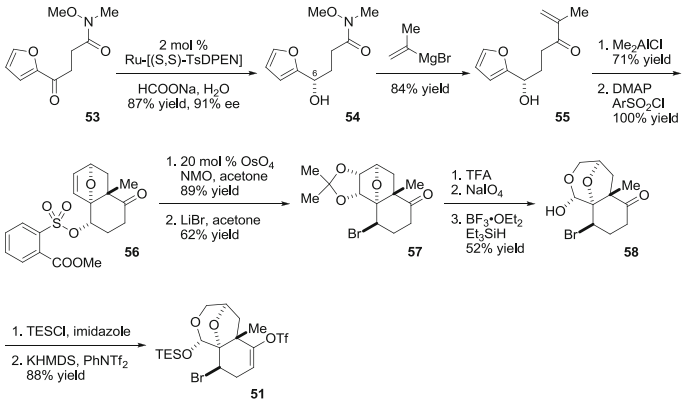


Chart 2.3 Structural revision and biosynthesis analysis of nakiterpiosin

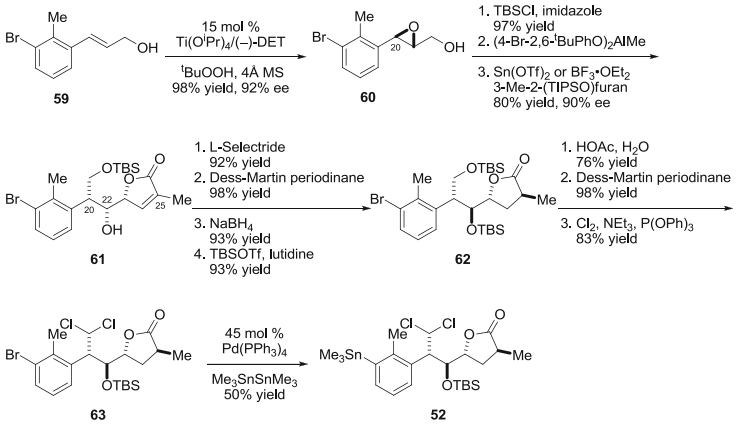


Scheme 2.4 Synthesis of the electrophilic coupling component **51**

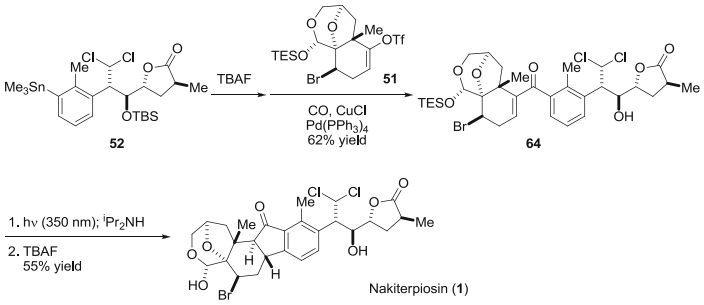
The synthesis of the electrophilic coupling component **51** commenced with a Friedel–Craft acylation of furan with succinic anhydride (Scheme 2.4) [37]. The resulting acid was converted to a Weinreb amide (**53**). The Noyori reduction [38] with the Xiao modification [39] was then used to set the C-6 stereochemistry, affording **54**. A Grignard reaction then gave the enone (**55**). The subsequent intramolecular Diels–Alder reaction proceeded with good stereochemical control [40] to give the exo product exclusively. The sterically congested C-6 hydroxyl group was then activated with an unusual, electron-deficient aryl sulfonate group to afford **56**.

To avoid the retro-Diels–Alder reaction, **56** was dihydroxylated prior to the introduction of the bromine atom (**57**). Removal of the acetonide group followed by cleavage of the diol afforded a bis-hemiacetal. Selective reduction of the less-hindered hemiacetal group gave **58**. The remaining hemiacetal was protected, and the ketone was converted to an enol triflate, thus concluding the synthesis of the electrophilic coupling component **51**.

The synthesis of the nucleophilic coupling component **52** started with the reduction of 3-bromo-2-methylbenzenecarboxylic acid, and followed with a Horner–Wadsworth–Emmons reaction of the corresponding aldehyde, and a 1,2-reduction of



Scheme 2.5 Synthesis of the nucleophilic coupling component **52**



Scheme 2.6 Completion of the synthesis of nakiterpiosin (**1**)

the resulting enoate to afford **59** (Scheme 2.5). A Sharpless epoxidation [41] was then used to set the C-20 stereochemistry, giving epoxide **60** with 92 % ee. After the protection of the hydroxyl group, a pinacol-type rearrangement using Yamamoto's catalyst [42] followed by a vinylogous Mukaiyama aldol reaction afforded **61** without significant erosion of the enantiomeric purity.

With the complete carbon framework of the side chain in place, we next sought to set its anti–anti–trans configuration. The C-25 stereochemistry could be established by either a directed hydrogenation [43] or a conjugate reduction. The C-22 stereochemistry was inverted by reduction of the C-22 ketone to afford the requisite anti–anti–trans configuration. Subsequent protection of the hydroxyl group gave **62**. To introduce the *gem*-dichloromethyl group, we selectively deprotected the primary alcohol, oxidized it to an aldehyde, and chlorinated it with $Cl_2/P(OPh)_3$ [44]. Bromide **63** was then stannylated to provide the nucleophilic coupling component **52**.

To complete the synthesis of nakiterpiosin (**1**), we first deprotected **52** and then coupled it to **51** under the previously described carbonylative conditions (Scheme 2.6). Photolysis of **64** readily provided the desired annulation product.

The subsequent deprotection of the hemiacetal concluded the synthesis of **1**. We also successfully used this convergent approach to synthesize nakiterpiosinone (**2**) and 6,20,25-*epi*-nakiterpiosin (**49**).

2.4 Biology of Nakiterpiosin

The strong growth inhibitory activity of **1** toward P388 cells prompted us to further investigate its biological functions. Our preliminary studies showed that **1** suppressed Hh signaling in NIH3T3 mouse fibroblasts with an IC_{50} of 0.6 μM, presumably by inducing the loss of primary cilium [45]. While the detailed mechanism is not clear, **1** is likely to influence the microtubule dynamics through a different mode of action from common antimitotic agents such as taxol and nocodazole. Further work is needed to elucidate its molecular target.

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