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# 3,5-Bis(aminopyrimidinyl)indole Derivatives: Synthesis and Evaluation of Pim Kinase Inhibitory Activities

**Jinho Lee,* Kunal N. More, Seun-Ah Yang,† and Victor S. Hong**

*Department of Chemistry, Keimyung University, Daegu 704-701, Korea. *E-mail: jinho@kmu.ac.kr*
*†The Center for Traditional Microorganism Resources (TMR), Keimyung University, Daegu 704-701, Korea*
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Pim kinases are promising targets in the treatment of hematopoietic and solid cancers. Meridianin C was chosen as a starting point to discover novel pim kinase inhibitors. Using known pim kinase's structural information, aminopyrimidine was introduced to provide the hydrogen-bonding interactions with the conserved lysine residue in the ATP binding pocket of all three Pim kinases. Synthesized 3,5-bis(aminopyrimidinyl)indole derivatives showed pan-pim inhibitory activity. Aminoalkyl substituent was attached on the aminopyrimidine to further enhance the potency and physicochemical properties of compound. The research reveals a significative way of designing compounds with high potency and kinase selectivity for pan-pim kinases.

**Key Words :** 3,5-Bis(aminopyrimidinyl)indole, Pim kinase, Inhibitor

## Introduction

Pim proteins comprising isoforms as Pim-1, Pim-2, and Pim-3 are homologous constitutively active serine/ threonine kinases in Jak/Stat pathway, one of key survival signaling pathways along with PI3K/Akt pathway.[1] Many cell functions are regulated by pim kinases such as cell growth, differentiation, proliferation and apoptosis.[2,3] Earlier data indicated that pim kinase overexpression and dysfunction lead to many hematological cancers; recent data reveal diverse biological roles in solid tumor malignancies including colon, pancreatic, and prostate cancer. Pim kinases are upregulated during human cancer onset and metastatic progression, and also promote chemoresistance of cancer cells through BAD inactivation and hypoxia-induced drug resistance.[4-6] Thus pim kinases are very promising targets for the treatment of cancers.[7,8]

Crystal structures of Pim-1 and Pim-2 in apo and inhibitor-bound form showed unique feature among the protein kinases as having distinct hinge region bearing proline (Pro123 in Pim-1) in place of hydrogen bond donating amino acids, which sacrifices one hydrogen bond interaction to adenine ring of ATP.[5,9] Pim family consists of structurally homologous members with Pim-1 and Pim-2 sharing 61% similarity while Pim-1 and Pim-3 having 71% similarity at the amino acid level.[2] This offers a unique opportunity to generate highly specific small molecule inhibitors against all three pim kinases. Several small molecule inhibitors for pan-pim kinases are at different stages of preclinical and clinical trials for the treatment of several solid and blood cancers.[8]

In this study, we report on the selective inhibitors of pan-pim kinases using the meridianin C as the starting molecule for inhibitor design. The previous reports showed marine alkaloid meridianin C (**A**), 4-(5-bromo-1*H*-indol-3-yl)pyrimidin-2-amine, has the inhibitory activity against several protein kinases.[10] Also, a series of 3,5-disubstituted indole derivatives (**B**) were reported to be pan-pim kinase inhibitors (Figure 1).[11] We found that meridianin C inhibited Pim-1 kinase with $IC_{50}$ value of 1.44 μM. Based on the previous result that 2-aminopyrimidine could interact with the side chain of Lys67 of Pim-1 kinase,[12] meridianin C was converted to 3,5-bis(aminopyrimidinyl)indole by replacing bromo group with 2-aminopyrimidine. This novel class of pim inhibitors served as a hit compound and was then modified as selective inhibitors against all pim family kinases.

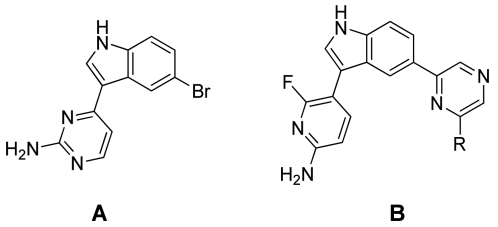
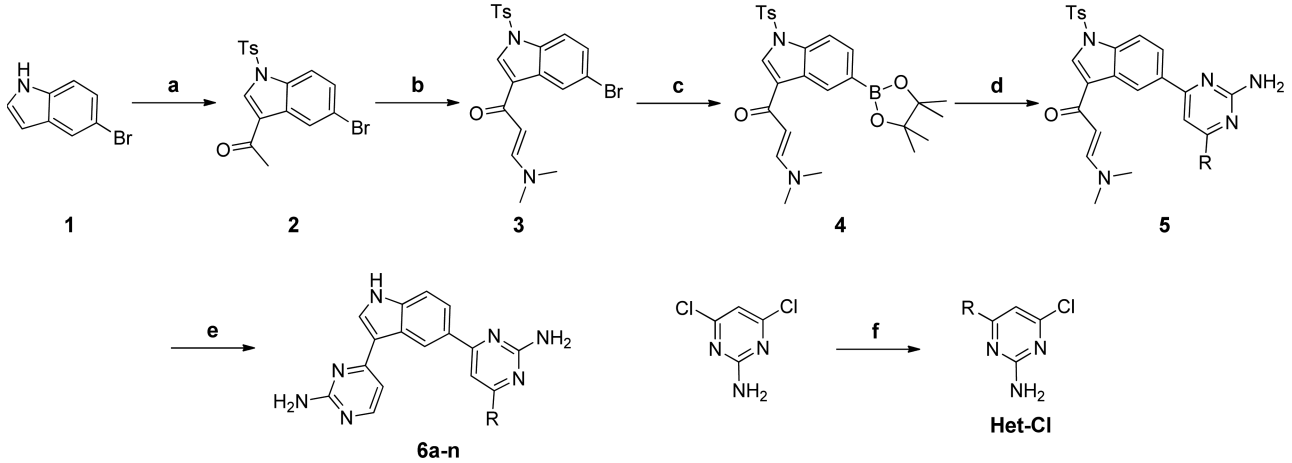



**Figure 1.** Structure of meridianin C (**A**) and 3,5-disubstituted indole derivatives (**B**).

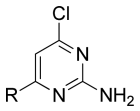
## Results and Discussion

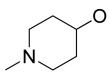
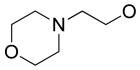
**Chemistry.** 3,5-Bis(2-aminopyrimidin-4-yl)indole derivatives were synthesized as shown in Scheme 1. A 2-aminopyrimidine ring at 3-position of indole was synthesized by Bredereck cyclization[13] while the other at 5-position was introduced by Suzuki type coupling. First, acetyl group was introduced at 3-position of indole by Friedel-Crafts acylation after the protection of indolyl NH with tosyl. The reaction of compound **2** with *N,N*-dimethylformamide diethyl acetal gave compound **3**,[14] which has undergone Miyaura borylation at C-5 position to give pinacolatoboronated compound **4**. The palladium catalyzed coupling with the corresponding substituted 6-chloro-2-aminopyrimidines (Het-Cl) followed by the concurrent cyclization and deprotection with guani-




**Scheme 1.** *Reagents and experimental conditions*. a) i) NaH, TsCl, DMF 0 °C to RT, ii) AcCl, $AlCl_3$, $CS_2$, under $N_2$, b) DMF-DEA, DMF, microwave, c) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, 1,4-dioxane, microwave, d) Het-Cl, $PdCl_2(PPh_3)_2$, 2 M $K_2CO_3$, 1,4-dioxane:EtOH (2:3), microwave, e) guanidine carbonate, $K_2CO_3$, 2-methoxyethanol, microwave, f) NaH, RH, 1,4-dioxane, microwave or amine, $K_2CO_3$, DMF.

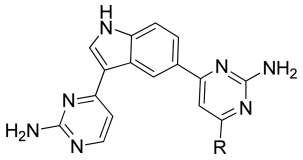
**Table 1.** Structure, synthetic methods and spectral data of Het-Cl

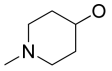
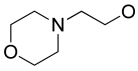


| Het-Cl | R | Method[a] | Yield and $^1$H NMR data |
|---|---|---|---|
| 4-chloro-6-(2-(dimethyl-amino)ethoxy)pyrimidin-2-amine | $Me_2N(CH_2)_2O$ | A | Yield: 99%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.04 (s, 1H), 5.35 (br, 2H), 4.28 (t, *J* = 5.8 Hz, 2H), 2.57 (t, *J* = 5.6 Hz, 2H), 2.22 (s, 6H) |
| 4-chloro-6-(2-(diethyl-amino)ethoxy)pyrimidin-2-amine | $Et_2N(CH_2)_2O$ | B | Yield: 99%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.44 (s, 1H), 4.44 (t, *J* = 6.0 Hz, 2H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.64 (q, *J* = 7.2 Hz, 4H), 1.06 (t, *J* = 7.2 Hz, 6H) |
| 4-chloro-6-(3-(dimethylamino)prop-oxy)pyrimidin-2-amine | $Me_2N(CH_2)_3O$ | A | Yield: 98%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.88 (s, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 2.21 (t, *J* = 7.2 Hz, 2H), 2.06 (s, 6H), 1.72 (pent, *J* = 6.9 Hz, 2H) |
| 4-chloro-6-(3-(diethylamino)prop-oxy)pyrimidin-2-amine | $Et_2N(CH_2)_3O$ | B | Yield: 46%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.99 (s, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 2.47 (q, *J* = 7.2 Hz, 6H), 1.81 (pent, *J* = 6.8 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 6H) |
| 6-chloro-$N^4$-(2-(dimethyl-amino)ethyl)pyrimidine-2,4-diamine | $Me_2N(CH_2)_2NH$ | A | Yield: 91%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.74 (s, 1H), 5.45 (s, 2H), 3.30 (br, 2H), 2.45 (t, *J* = 6.0 Hz, 2H), 2.20 (s, 6H) |
| 6-chloro-$N^4$-(2-(diethyl-amino)ethyl)pyrimidine-2,4-diamine | $Et_2N(CH_2)_2NH$ | A | Yield: 39%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.72 (s, 1H), 5.44 (s, 2H), 3.23 (br, 2H), 2.56 (t, *J* = 6.0 Hz, 2H), 2.49 (q, *J* = 7.06 Hz, 4H), 0.96 (t, *J* = 7.2 Hz, 6H) |
| 6-chloro-$N^4$-(3-(dimethylamino)pro-pyl)pyrimidine-2,4-diamine | $Me_2N(CH_2)_3NH$ | A | Yield: 47%; $^1$H NMR ($CDCl_3$+$CD_3OD$, 400 MHz) δ 5.77 (s, 1H), 3.30 (br, 2H), 2.37 (t, *J* = 6.8 Hz, 2H), 2.24 (s, 6H), 1.73 (pent, *J* = 6.7 Hz, 2H) |
| 6-chloro-$N^4$-(3-(diethylamino)pro-pyl)pyrimidine-2,4-diamine | $Et_2N(CH_2)_3NH$ | A | Yield: 40%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.72 (s, 1H), 5.49 (s, 2H), 3.33 (br, 2H), 2.53 (q, *J* = 7.06 Hz, 6H), 1.71 (pent, *J* = 6.3 Hz, 2H), 1.04 (t, *J* = 7.2 Hz, 6H) |
| 6-chloro-$N^4$-(2-(dimethylamino)ethyl)-$N^4$-methylpyrimidine-2,4-diamine | $Me_2N(CH_2)_2NCH_3$ | A | Yield: 55%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.88 (s, 1H), 4.92 (s, 2H), 3.60 (br, 2H), 3.01 (s, 3H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.29 (s, 6H) |
| 4-chloro-6-(1-methylpiperidin-4-yloxy)pyrimidin-2-amine |  | B | Yield: 49%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.09 (s, 1H), 5.37 (s, 2H), 5.05-5.03 (m, 1H), 2.67 (br, 2H), 2.31 (s, 6H), 2.06-1.98 (m, 2H), 1.87-1.79 (m, 2H) |
| 4-chloro-6-(4-methylpiperazin-1-yl)pyrimidin-2-amine |  | A | Yield: 79%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.96 (s, 1H), 4.97 (s, 2H), 3.59 (s, 4H), 2.43 (t, *J* = 5.2 Hz, 4H), 2.32 (s, 3H) |
| 4-chloro-6-(2-morpholinoe-thoxy)pyrimidin-2-amine |  | B | Yield: 80%; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 5.02 (t, *J* = 5.4 Hz, 2H), 4.35 (t, *J* = 8.4 Hz, 4H), 3.36 (t, *J* = 5.4 Hz, 2H), 3.17 (s, 4H) |
| 4-chloro-6-(cyclopentyloxy)pyrimi-din-2-amine |  | B | Yield: 48%; $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.03 (s, 1H), 5.80 (br, 2H), 5.32-5.29 (m, 1H), 1.89 (br, 2H), 1.76 ( br, 4H), 1.60 (br, 2H) |
| 4-chloro-6-(cyclohexyloxy)pyrimi-din-2-amine |  | B | Yield: 60%; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.12 (s, 2H), 5.0-4.93 (m, 1H), 1.95-1.92 (m, 2H), 1.79-1.75 (m, 2H), 1.59-1.25 (m, 6H). |

[a]Details of method A and B are in the section "General Method for Preparation of Het-Cl"

**Table 2.** Pim-kinase inhibitory activity of the synthesized compounds



| | R | IC$_{50}$ (μM) | | |
|---|---|---|---|---|
| | | Pim-1 | Pim-2 | Pim-3 |
| **6a** | $Me_2N(CH_2)_2O$ | 0.30 | 1.40 | 0.50 |
| **6b** | $Et_2N(CH_2)_2O$ | 0.14 | 0.84 | 0.27 |
| **6c** | $Me_2N(CH_2)_3O$ | 0.058 | 0.52 | 0.16 |
| **6d** | $Et_2N(CH_2)_3O$ | 0.11 | 0.38 | 0.081 |
| **6e** | $Me_2N(CH_2)_2NH$ | 0.31 | 1.35 | 0.47 |
| **6f** | $Et_2N(CH_2)_2NH$ | 0.15 | 1.07 | 0.33 |
| **6g** | $Me_2N(CH_2)_3NH$ | 0.18 | 0.74 | 0.24 |
| **6h** | $Et_2N(CH_2)_3NH$ | 0.067 | 3.16 | 0.61 |
| **6i** | $Me_2N(CH_2)_2NCH_3$ | 0.44 | N.D. | N.D. |
| **6j** |  | 0.14 | 1.49 | 0.39 |
| **6k** |  | 0.17 | 3.29 | 0.74 |
| **6l** |  | 0.36 | 0.81 | 0.37 |
| **6m** |  | 0.78 | 2.95 | 1.26 |
| **6n** |  | 2.53 | >10 | 5.07 |

dine under basic condition provided the final compound **6**.

The substituted 6-chloro-2-aminopyrimidines (Het-Cl) were synthesized in two different methods depending on the reactivity of RH. Microwave assisted reaction was used when RH had low reactivity (Table 1).

Considering the presence of proline at ATP binding hinge region of pim kinases, most pim kinase inhibitors were designed to utilize the interaction with the conserved lysine (Lys67 in Pim-1) in the ATP binding pocket instead.[11,15-18] Also, another hydrogen bonding interaction with Glu89 *via* water molecule was noticed as an important factor for the inhibitor binding.[19] Since aminopyrimidine was reported to make two hydrogen bonds with the side chains of Lys33 and Glu51 of CDK2,[12] aminopyrimidine was attached at 5-position of indole to provide meridianin C with the functionality that interacts with the side chains of both Lys67 and Glu89 of Pim-1. In addition, aminoalkyl groups were introduced to the aminopyrimidine for both the enhancement of potency through the additional interaction with enzyme and the improvement of physicochemical properties.

In general, the introduction of aminoalkyl substituted aminopyrimidine to meridianin C improved the potency against Pim-1 kinase about an order of magnitude (Table 2). All compounds were found to be more potent against Pim-1 and Pim-3 as compared to Pim-2. It was reported that Pim-2 inhibition was more difficult to achieve than Pim-1 and Pim-3, likely due to its low $K_m$ value for ATP.[15,20] The potencies of compounds against Pim-1 kinase were influenced by several factors such as carbon chain length of the aminoalkyl group, the types of substituent at amine, and the linker between aminoalkyl group and aminopyrimidine. Compound **6c** with 3-(*N,N*-dimethylamino)propoxy and **6h** with 3-(*N,N*-diethylamino)propylamino were the most potent against Pim-1 kinase. However, compound **6d** with 3-(*N,N*-diethylamino)-propoxy showed the highest potencies against both Pim-2 and Pim-3 kinases. The effect of substitutions with cyclic amine attached either directly or remotely was not noticeable (**6j**, **6k**, **6l**). Hydrophobic cycloalkyl was tolerated as a substituent with ring size dependency (**6m** *vs*. **6n**).

**Table 3.** The effect of compound **6c** on enzyme activity of a panel of 14 protein kinases. Percent activity of kinase at 1 μM concentration of **6c**

| Kinase | Type of kinase | % activity |
|---|---|---|
| Aurora-A | serine-threonine | 100 |
| CDK2/cyclinA | serine-threonine | 106 |
| cSRC | nonreceptor tyrosine kinase | 89 |
| Flt3 | receptor tyrosine kinase | 92 |
| GSK3β | serine-threonine | 98 |
| IRAK4 | serine-threonine | 86 |
| JAK2 | nonreceptor tyrosine kinase | 100 |
| JNK3 | serine-threonine | 94 |
| KDR | receptor tyrosine kinase | 89 |
| MAPK2 | serine-threonine | 76 |
| Met | receptor tyrosine kinase | 87 |
| Plk1 | serine-threonine | 110 |
| SAPK2a | serine-threonine | 96 |
| TAK1 | serine-threonine | 94 |

The selectivity of compound **6c** against other 14 kinases was evaluated at 1 μM concentration (Table 3). Compound **6c** is among the most potent compounds in the enzymatic assays against Pim-1 kinase. Compound **6c** did not show any significant inhibition against all the tested kinases including serine-threonine kinases or receptor/non-receptor tyrosine kinases.

Compound **6c** for its antiproliferative activity against three leukemia cell lines, MV4-11, Jurkat, and K562, was further

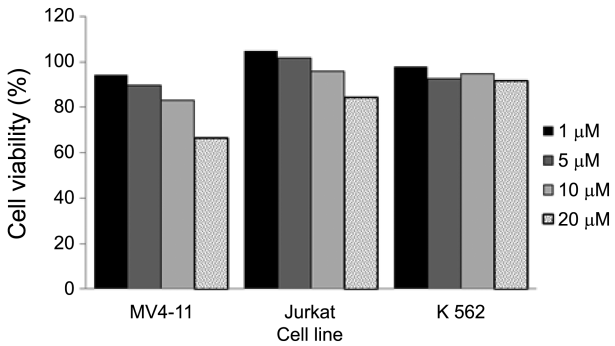



**Figure 2.** Dose–dependent inhibitory effect of **6c** on three human leukemiea cell lines (MV-4-11, Jurkat, K562).

studied (Figure 2). MV4-11 cells, which have an ITD mutation in the Flt3 receptor, were reported to be more sensitive to pim inhibitors than K562 cells that overexpress the anti-apoptotic Bcr-Abl.[21-24] Correspondingly, compound **6c** showed growth inhibition in a dose dependent manner and about 34% inhibition of MV4-11cells at 20 μM concentration, but did not inhibit the proliferation of K562 cells. These results suggested that our modified 3,5-bis(aminopyrimidinyl)-indole is a promising leading structure as a pan-pim kinase inhibitor. Further optimization based on X-ray structure and binding interactions may lead to very potent and selective pim kinase inhibitors.

## Conclusion

A novel series of 3,5-bis(aminopyrimidinyl)indole derivatives were synthesized and evaluated against Pim kinases. meridianin C was chosen as a hit structure and its substituent was modified to discover potent and selective pan-pim kinase inhibitors. Substitution at C-5-position by 2-amino-pyrimidine having hydrophilic aminoalkyl chain improved the potency. SAR of substituents at C-4 position of 2-amino-pyrimidine suggested that aminoalkyl moiety, with the adequate chain length and substituent, could provide compound with the high potency and selectivity. This study suggests the 3,5-bis(aminopyrimidinyl)indole moiety is a very interesting scaffold which can be further optimized for more potent inhibitors of pim kinases.

## Experimental

**General Information.** All reactions were performed using commercially available reagents and solvents without further purification under proper conditions as stated. CEM Discover BenchMate had been used for microwave assisted reactions. Reaction completion was monitored on E. Merck silica gel F254 TLC plates. Purifications of synthesized compounds were performed by flash column chromatography using Merck Silica Gel 60 (230-400 mesh). Melting points were determined in open capillary tubes on a Stuart apparatus and are uncorrected. Synthesized compounds were characterized by $^{1}$H and $^{13}$C NMR on a Bruker AVANCE 400 ($^{1}$H: 400 MHz, $^{13}$C: 100 MHz) spectrometer and chemical shift δ were measured in ppm with TMS as reference standard. Mass spectra were obtained using Waters ACQUITY UPLC, Micromass Quattro micro™ API.

**3-(Dimethylamino)-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-indole-3-yl)prop-2-en-1-one (4).** To Ar gas purged 1,4-dioxane (2 mL) in microwave reaction vessel were added compound **3**[14] (1.00 g, 2.24 mmol), bis(pinacolato)diboron (0.624 g, 2.46 mmol), potassium acetate (0.658 g, 0.067 mmol), and $PdCl_2$(dppf) (0.049 g, 0.067 mmol). The reaction mixture was heated in the microwave reactor at power 100 W and 110 °C for 10 min. After solvents were removed under reduced pressure, the residue was loaded directly on the flash column for purification. The purification by flash chromatography eluted with DCM:EA (3:1) mixture provided the compound **4** (620 mg) in 57% yield; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 8.81 (s, 1H), 8.06 (s, 1H) 7.93 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 7.81-7.77 (m, 4H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.60 (d, *J* = 12.4 Hz, 1H), 3.17 (br, 3H), 2.96 (br, 3H), 2.35 (s, 3H) 1.33 (s, 12H).

**General Method for Preparation of Het-Cl.** Introduction of substituent at 4-position of 2-amino-4,6-dichloropyrimidine was performed in two methods.

**Method A:** 2-Amino-4,6-dichloropyrimidine and 1.2 equivalent corresponding alcohol or amine were reacted in DMF using 1.2 equivalent of $K_2CO_3$ as base. After stirring overnight at 80 °C (or RT), solvent was removed under reduced pressure. After filtering off the precipitate formed by treatment the residue with DCM:methanol (95:5) mixture, removal of solvent of the filtrate provided Het-Cl. Compounds were used without further purification.

**Method B:** 2-Amino-4,6-dichloropyrimidine and 1.1 equivalent corresponding alcohol or amine were reacted in 1,4-dioxane using 3 equivalent of NaH as base. The reaction mixture was heated in the microwave reactor at power 100 W and 50 °C (or 80 °C) for 10 min. After solvents were removed under reduced pressure, the residue was dissolved in ethyl acetate. Organic layer was washed with saturated $Na_2CO_3$ solution and dried over $MgSO_4$. Filtration and removal of solvent of the filtrate provided Het-Cl. Compounds were used without further purification.

**General Method for Preparation of 6a to 6n.**

**1-(5-(2-Amino-6-(2-(dimethylamino)ethoxy)pyrimidin-4-yl)-1-tosyl-1*H*-indol-3-yl)-3-(dimethylamino)prop-2-en-1-one (5a).** To Ar gas purged 1,4-dioxane:ethanol (1:1.5) mixture (2.5 mL) in microwave reaction vessel were added compound **4** (0.20 g, 0.40 mmol), 4-chloro-6-(2-(dimethylamino)ethoxy)pyrimidin-2-amine (0.11 g, 0.49 mmol), bis-(triphenylphosphine) palladium(II) dichloride (0.010 g, 0.012 mmol), and aqueous 2 M $K_2CO_3$ solution (1.0 mL, 2.0 mmol). The reaction mixture was heated in the microwave reactor at power 100 W and 110 °C for 10 min. After removal of solvent, the residue was purified by flash column chromatography using eluent ($CHCl_3$:MeOH:$NH_4OH$ 100:10:1) to provide the compound **5a** in 29% yield; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.11 (s,1H), 7.98-7.92 (m, 2H), 7.79 (d, *J* = 0.8 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 6.56 (s, 1H), 5.61 (d, *J* = 12.4, 1H), 5.25 (s, 2H), 4.41 (t, *J* = 5.0 Hz, 2H), 3.12 (br, 3H), 2.94 (br, 3H), 2.72 (t, *J* = 5.4 Hz, 2H), 2.34 (s, 6H), 2.33 (s, 3H).

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(2-(dimethylamino)ethoxy)pyrimidin-2-amine (6a).** To Ar gas purged 2-methoxyethanol (2.5 mL) in microwave reaction vessel were added compound **5a** (0.064 g, 0.12 mmol), $K_2CO_3$ (0.032 g, 0.24 mmol), and guanidine carbonate (0.042 g, 0.24 mmol). The reaction mixture was heated in the microwave reactor at power 100 W and 150 °C for 10 min. After removal of solvent, the residue was purified by flash column chromatography using eluent ($CHCl_3$:MeOH:$NH_4OH$ 100:10:1) to provide the compound **6a** (84%) as a yellowish solid: mp 166-169 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.82 (s, 1H), 9.20 (s, 1H), 8.23 (d, *J* = 2.8 Hz, 1H), 8.14 (d,

*J* = 5.2 Hz, 1H), 7.91 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 5.2 Hz, 1H), 6.64 (s, 1H), 6.56 (s, 2H), 6.47(s, 2H), 4.39 (t, *J* = 5.8 Hz, 2H), 2.67 (t, *J* = 5.8 Hz, 2H), 2.26 (s, 6H); $^{13}$C NMR (100MHz, DMSO-$d_6$) δ 171.08, 166.47, 163.98, 163.70, 162.90, 157.65, 138.74, 130.10, 129.68, 125.71, 121.56, 115.05, 112.13, 106.00, 91.65, 63.28, 57.96, 45.82; ESI MS: *m/z* = 391 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(2-(diethylamino)ethoxy)pyrimidin-2-amine (6b).** Obtained 31% overall yield in two steps as a brownish solid: mp 96-99 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ 11.81 (s, 1H), 9.22 (s, 1H), 8.21 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 5.2 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 6.60 (s, 1H), 6.54 (s, 2H), 6.47 (s, 2H), 4.32 (t, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.55 (q, *J* = 7.06 Hz, 4H), 0.98 (t, *J* = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ 171.11, 166.30, 163.93, 163.89, 163.68, 162.92, 157.52, 138.69, 130.03, 129.59, 125.70, 121.69, 121.44, 115.00, 112.05, 105.90, 91.61, 63.97, 51.55, 47.47, 12.38; ESI MS: *m/z* = 419 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(3-(dimethylamino)propoxy)pyrimidin-2-amine (6c).** Obtained 17% overall yield in two steps as a yellowish solid: mp 235-238 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$): δ 11.78 (d, *J* = 2.4 Hz, 1H), 9.21 (d, *J* = 1.2 Hz, 1H), 8.18 (d, *J* = 2.8 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 5.6 Hz, 1H), 6.60 (s, 1H), 6.51 (s, 2H), 6.45 (s, 2H), 4.29 (t, *J* = 6.8 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.17 (s, 6H), 1.86 (quint, *J* = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ 171.23, 166.26, 163.93, 163.70, 162.92, 157.49, 138.68, 130.06, 129.52, 125.70, 121.66, 121.43, 115.01, 112.03, 105.90, 91.59, 64.12, 56.14, 45.59, 27.07; ESI MS: *m/z* = 405 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(3-(diethylamino)propoxy)pyrimidin-2-amine (6d).** Obtained 36% overall yield in two steps as a brownish solid: mp 208-210 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ 11.79 (s, 1H), 9.21 (s, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 6.59 (s, 1H), 6.52 (s, 2H), 6.45 (s, 2H), 4.29 (t, *J* = 6.4 Hz, 2H), 2.54-2.45 (m, 6H), 1.83 (quint, *J* = 6.5 Hz, 2H), 0.96 (t, *J* = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ 171.29, 166.24, 163.93, 163.72, 162.92, 157.50, 138.68, 130.07, 129.53, 125.70, 121.67, 121.42, 115.01, 112.03, 105.91, 91.57, 64.19, 49.29, 46.74, 26.81, 12.12; ESI MS: *m/z* = 433 $[M+H]^+$.

**6-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-$N^4$-(2-(dimethylamino)ethyl)pyrimidine-2,4-diamine (6e).** Obtained 45% overall yield in two steps as a yellowish solid: mp 84-87 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ 11.75 (s, 1H), 9.15 (s, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 5.2 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 5.6 Hz, 1H), 6.44 (s, 1H), 6.40 (s, 2H), 5.97 (s, 2H), 5.42 (s, 1H), 3.42-3.39 (m, 2H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.23 (s, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ 167.87, 164.46, 163.85, 163.61, 163.05, 160.12, 157.46, 138.32, 130.83, 129.35, 125.74, 121.12, 114.72, 111.84, 105.88, 58.74, 45.62; ESI MS: *m/z* = 390 $[M+H]^+$.

**6-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-$N^4$-(2-(diethylamino)ethyl)pyrimidine-2,4-diamine (6f).** Obtained 29% overall yield in two steps as a brownish solid: mp 232-235 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ 11.77 (s, 1H), 9.17 (s, 1H), 8.20 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 5.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 5.6 Hz, 1H), 6.43 (s, 3H), 5.96 (s, 2H), 3.39 (s, 2H), 2.60-2.52 (m, 4H), 1.00 (t, *J* = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ 164.53, 163.86, 163.76, 163.04, 157.48, 138.30, 131.01, 129.37, 125.72, 121.12, 114.75, 111.83, 105.90, 52.14, 46.98, 12.18; ESI MS: *m/z* = 418 $[M+H]^+$.

**6-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-$N^4$-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine (6g).** Obtained 21% overall yield in two steps as a yellowish solid: mp 119-121 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ 11.74 (d, *J* = 2.0 Hz, 1H), 9.14 (s, 1H), 8.17 (d, *J* = 2.8 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.78 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 5.2 Hz, 1H), 6.57 (s, 1H), 6.37 (d, *J* = 5.6, 2H), 5.99 (s, 2H), 5.96 (s, 2H), 3.35-3.32 (m, 2H), 2.39 (t, *J* = 6.6 Hz, 2H), 2.23 (s, 6H), 1.70 (quint, *J* = 6.9 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$ + $CDCl_3$) δ 167.88, 164.58, 163.85, 163.58, 163.28, 163.03, 157.49, 138.33, 129.33, 125.72, 121.10, 114.78, 111.88, 105.97, 57.01, 45.31, 31.12, 27.33; ESI MS: *m/z* = 404 $[M+H]^+$.

**6-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-$N^4$-(3-(diethylamino)propyl)pyrimidine-2,4-diamine (6h).** Obtained 36% overall yield in two steps as a brownish solid: mp 78-81 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.79 (s, 1H), 9.14 (s, 1H), 8.22 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 5.2 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 5.2 Hz, 1H), 6.72 (s, 1H), 6.40 (s, 2H), 6.36 (s, 1H), 5.96 (s, 2H), 3.33-3.32 (m, 2H), 2.52-2.47 (m, 6H), 1.67 (quint, *J* = 7.0 Hz, 2H), 0.97 (t, *J* = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 164.64, 163.91, 163.83, 163.03, 157.62, 138.31, 131.19, 129.46, 125.72, 121.18, 121.00, 114.80, 111.92, 106.03, 50.67, 46.76, 27.18, 12.07; ESI MS: *m/z* = 432 $[M+H]^+$.

**6-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-$N^4$-(2-(dimethylamino)ethyl)-$N^4$-methylpyrimidine-2,4-diamine (6i).** Obtained 37% overall yield in two steps as a brownish solid: mp 258-261 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.80 (s, 1H), 9.17 (s, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 5.2 Hz, 1H), 6.46 (s, 2H), 6.41 (s, 1H), 6.03 (s, 2H), 6.00 (s, 1H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.07 (s, 3H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.21 (s, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 167.92, 164.25, 163.97, 163.77, 163.40, 163.01, 157.60, 138.37, 131.48, 129.50, 125.67, 121.58, 121.28, 114.89, 111.90, 105.99, 88.47, 56.91, 45.99, 35.95; ESI MS: *m/z* = 404 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(1-methylpiperidin-4-yloxy)pyrimidin-2-amine (6j).** Obtained 77% overall yield in two steps as a yellowish solid: mp 115-118 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.79 (s, 1H), 9.20 (s,

1H), 8.19 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 5.2 Hz, 1H), 7.88 (dd, *J* = 8.8,1.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 5.6 Hz, 1H), 6.58 (s, 1H), 6.49 (s, 2H), 6.46 (s, 2H), 2.66 (br, 2H), 2.19 (s, 3H), 2.17-2.12 (m, 2H), 1.99 (br, 2H), 1.73-1.66 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$+$CD_3OD$) δ 166.42, 163.39, 159.36, 159.09, 158.96, 158.93, 152.75, 134.50, 126.46, 124.53, 121.56, 117.73, 116.70, 111.16, 108.04, 103.03, 90.62, 41.83, 26.37; ESI MS: *m/z* = 417 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-amine (6k).** Obtained 62% overall yield in two steps as a yellowish solid: mp 235-240 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.80 (d, *J* = 2 Hz, 1H), 9.19 (s, 1H), 8.24 (d, *J* = 2.8 Hz, 1H), 8.15 (d, *J* = 5.2 Hz, 1H), 7.92 (dd, *J* = 8.8,1.2 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 5.6 Hz, 1H), 6.62 (s, 1H), 6.49 (s, 2H), 6.12 (s, 2H), 3.65 (s, 4H), 2.39 (t, *J* = 4.4 Hz, 4H), 2.23 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 166.95, 164.79, 164.24, 163.97, 163.45, 162.99, 157.62, 138.43, 131.31, 129.54, 125.63, 121.71, 121.37, 114.96, 111.88, 106.00, 88.87, 54.97, 46.31, 43.93; ESI MS: *m/z* = 402 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(2-morpholinoethoxy)pyrimidin-2-amine (6l).** Obtained 44% overall yield in two steps as a yellowish solid: mp 212-217 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ 11.83 (s, 1H), 9.21 (s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 5.2 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 5.2 Hz, 1H), 6.64 (s, 1H), 6.55 (s, 2H), 6.48 (s, 2H), 4.41 (t, *J* =5.8 Hz, 2H), 3.59 (t, *J* = 4.2 Hz, 4H), 2.70 (t, *J* = 5.6 Hz, 2H), 2.49 (s, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 171.03, 166.93, 166.38, 163.92, 163.63, 162.92, 157.49, 138.70, 131.50, 130.02, 129.50, 128.83, 125.70, 121.68, 121.44, 115.02, 112.03, 105.92, 91.62, 66.66, 63.07, 58.53, 54.07; ESI MS: *m/z* = 433 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(cyclopentyloxy)pyrimidin-2-amine (6m).** Obtained 18% overall yield in two steps as a brownish solid: mp 248-252 °C; $^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ 11.81 (d, *J* = 2.4 Hz, 1H), 9.21 (s, 1H), 8.21 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 5.2 Hz, 1H), 7.89 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 5.2 Hz, 1H), 6.57 (s, 1H), 6.49 (s, 4H), 5.46-5.43 (m, 1H), 1.96-1.94 (m, 2H), 1.76 (br, 4H), 1.63-1.61 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ 170.86, 166.19, 163.93, 163.68, 162.92, 157.51, 138.66, 130.12, 129.56, 125.68, 121.59, 121.44, 115.01, 112.04, 105.92, 92.08, 77.31, 32.85, 23.89; ESI MS: *m/z* = 388 $[M+H]^+$.

**4-(3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-yl)-6-(cyclohexyloxy)pyrimidin-2-amine (6n).** Obtained 63% overall yield in two steps steps as a yellowish solid: mp 138-141 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.74 (d, *J* = 2.0 Hz, 1H), 9.20 (s, 1H), 8.15 (d, *J* = 2.8 Hz, 1H), 8.11 (d, *J* = 5.2 Hz, 1H), 7.85 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 5.2 Hz, 1H), 6.53 (s, 1H), 6.41 (s, 4H), 5.10-5.05 (m, 1H), 1.96 (br, 2H), 1.76 (br, 2H), 1.58-1.22 (m, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 170.64, 166.27, 163.91, 163.68, 162.91, 157.44, 138.65, 130.12, 129.35, 125.68, 121.59, 121.35, 115.04, 111.98, 105.93, 92.20, 72.54, 55.06, 31.96, 25.59, 24.06; ESI MS: *m/z* = 402 $[M+H]^+$.

**Biochemical Assay.** The potency of the compounds in this study was measured using a fluorescence polarization assay method. Enzyme, substrate, and ATP were prepared in kinase reaction buffer containing 10 mM Tris-HCl (pH 7.2), 10 mM $MgCl_2$, 0.05% $NaN_3$, 0.01% Triton X-100 and 2 mM DTT. In 384-well black flat bottom polystyrene plates, the IMAP PIM kinase assays were formatted using 10 μL reaction volumes consisting of 2.5 μL compound, 2.5 μL Pim-1 (1 nM) or Pim-2 (1 nM) or Pim-3 (1 nM), 2.5 μL ATP and 2.5 μL 5-FAM-labeled BAD peptide (100 nM). The final concentrations of ATP were 30 μM, 5 μM and 20 μM for Pim-1, Pim-2 and Pim-3, respectively. Following 90 min incubation at room temperature, IMAP binding reagent (Molecular Devices, solution containing 75% Buffer A: 25% Buffer B and a 1 in 600 dilution of beads) was added to each well to stop the reaction. After incubation for a 2-hr at room temperature, the fluorescence polarization was measured on an Infinity F200 plate reader (Tecan) at an excitation wavelength of 485 nm and an emission wavelength of 530 nm. The data were then fitted to a 4-parameter logistic equation shown below and $IC_{50}$s were determined using GraphPad Prism (GraphPad Software, Inc., La Jolla).

$$Y = \text{Bottom} + \frac{(Top - Bottom)}{1 + 10^{(\log IC_{50} - X) \times Hillslope}}$$

**Cell Culture Conditions and Viability Assays.** MV4-11 (human acute myelocytic leukemia cell line) cells purchased from the American Type Culture Collection (ATCC, Manassas, VA) were grown in Iscove's Modified Dulbecco's Medium (IMDM, ATCC, Manassas, VA) containing 10% fetal bovine serum (FBS, Gibco-BRL, Grand Island, NY), 100 U/mL penicillin and 100 μg/mL streptomycin at 37 °C in a 5% $CO_2$ humidified atmosphere. K562 (human erythromyeloblastoid leukemia cell line) and Jurkat clone E6-1 (human acute T cell leukemia) cells were purchased from Korean Cell Line Bank (KCBL, Seoul, Korea). K562 and Jurkat cells were grown in RPMI 1640 (Gibco-BRL, Grand Island, NY), supplemented with 10% heat inactivated FBS, 100 U/mL penicillin and 100 μg/mL streptomycin. Cell viability was measured using the CellTiter 96$^R$ $AQ_{UES}$ One Solution Cell Proliferation Assay (MTS) from Promega (Madison, WI). MV4-11 and Jurkat cells were seeded in a 96-well plate at the density 200,000 cells per well. K562 cells were seeded at 10,000 cells per well. The next day, test compounds drugs at indicated concentrations were added and incubated at 37 °C. After 24 h, 20 μL of MTS solution was added to each well, and the plates were incubated at 37 °C for 4 h. The absorbance of each well was measured at 490 nm with a microplate reader (SPECTRA max 340PC, Molecular Devices, Sunnyvale, CA).

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