Design, synthesis and structure activity relationship of potent *pan*-PIM kinase inhibitors derived from the pyridyl carboxamide scaffold

Gisele A. Nishiguchi, Matthew T. Burger, Wooseok Han, Jiong Lan, Gordana Atallah, Victoriano Tamez, Mika Lindvall, Cornelia Bellamacina, Pablo Garcia, Paul Feucht, Tatiana Zavorotinskaya, Yumin Dai, Kent Wong

PII: S0960-894X(16)30256-6
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.03.037
Reference: BMCL 23680

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 7 January 2016
Revised Date: 9 March 2016
Accepted Date: 10 March 2016

Please cite this article as: Nishiguchi, G.A., Burger, M.T., Han, W., Lan, J., Atallah, G., Tamez, V., Lindvall, M., Bellamacina, C., Garcia, P., Feucht, P., Zavorotinskaya, T., Dai, Y., Wong, K., Design, synthesis and structure activity relationship of potent *pan*-PIM kinase inhibitors derived from the pyridyl carboxamide scaffold, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.03.037

Design, synthesis and structure activity relationship of potent *pan*-PIM kinase inhibitors derived from the pyridyl carboxamide scaffold

Gisele A. Nishiguchi [a,*], Matthew T. Burger [a], Wooseok Han [a], Jiong Lan [a], Gordana Atallah [a], Victoriano Tamez [a], Mika Lindvall [a], Cornelia Bellamacina [a], Pablo Garcia [b], Paul Feucht [b], Tatiana Zavorotinskaya [b], Yumin Dai [b], Kent Wong [a]

[a] *Global Discovery Chemistry, Novartis Institutes for Biomedical Research, 4560 Horton Street, Emeryville, California 94608, United States*

[b] *Oncology, Novartis Institutes for Biomedical Research, 4560 Horton Street, Emeryville, California 94608, United States*

Abstract: The Pim proteins (1, 2 and 3) are serine/threonine kinases that have been found to be upregulated in many hematological malignancies and solid tumors. As a result of overlapping functions among the three isoforms, inhibition of all three Pim kinases has become an attractive strategy for cancer therapy. Herein we describe our efforts in identifying potent *pan*-Pim inhibitors that are derived from our previously reported pyridyl carboxamide scaffold as part of a medicinal chemistry strategy to address metabolic stability.

The Pim kinases (Pim-1, Pim-2 and Pim-3) have emerged as attractive pharmacologic targets in cancer therapy given their roles in cell-cycle progression, cell survival and tumorogenesis.[1] Pim oncogenes are known to be overexpressed and dysregulated in a variety of cancers and more recent evidence points to hematologic malignancies as a potential oncology indication.[2] The Pim kinases are a family of serine/threonine kinases that are constitutively active and lack regulatory domains, hence they are regulated at both the transcriptional and translational levels.[3] They share a high level of sequence

* Corresponding Author at present address: 250 Massachusetts Avenue, Cambridge, MA 02139. Tel.: +1 617 871 3463. E-mail address: gisele.nishiguchi@novartis.com (G. A. Nishiguchi).

homology within the family (>61%)[4] and are differentiated from other kinases by a unique structure of their active site, which provides the opportunity for small molecule designs to generate highly selective kinase inhibitors.[5] At the same time, the Pim kinases are characterized by significantly different ATP K_m's within their own family (ATP K_m for Pim-2 is 4 μM compared to 160 μM and 40 μM for Pim-1 and Pim-3 respectively), which makes it challenging to obtain cellular potent *pan*-PIM inhibitors, especially for cell lines that are Pim-2 dependent.[6] Functional similarities and compensatory roles in oncogenesis among the Pim kinase isoforms have been reported,[7] which emphasizes the significance of targeting all three members of the Pim family for effective inhibition. Several cellular active and novel *pan*-PIM kinase inhibitors have now emerged,[8] offering the opportunity to evaluate the therapeutic benefits of *pan*-Pim inhibition in the clinic.

Figure 1: HTS hit (**1a**), tool compound (**1b**) and strategies to mitigate clearance

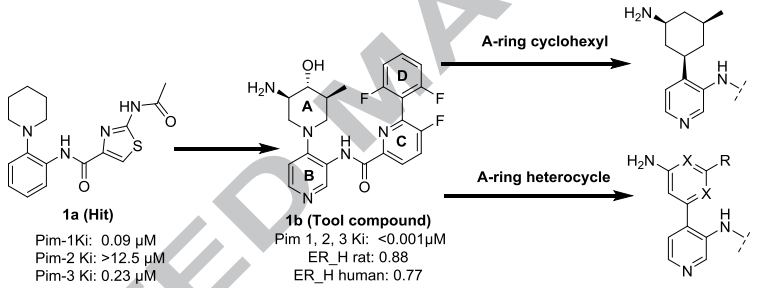
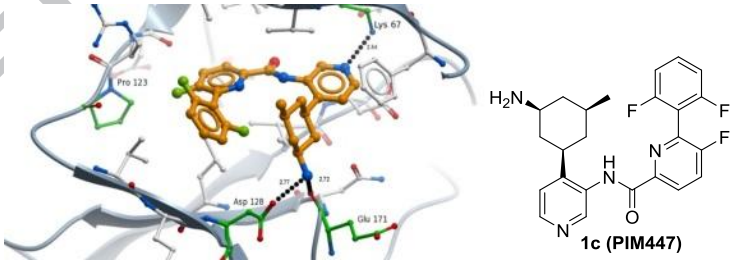


Figure 2: X-ray structure of PIM447 (**1c**) in Pim-1 (PDB: 5DWR).

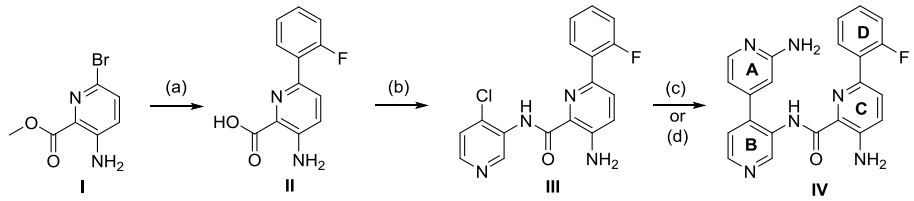


We previously reported the optimization of a singleton HTS hit (**1a**) that led to the discovery of **1b** (Figure 1), a highly potent and selective *pan*-Pim inhibitor with demonstrated efficacy on Pim-2 driven multiple myeloma (KMS-11) and acute myeloid leukemia (EOL-1) subcutaneous tumor mouse models.[8j] Compound **1b** served as an *in-vivo* tool for *pan*-Pim target validation. More recently, we also disclosed the

discovery of PIM447 (**1c**, Figure 2), a compound currently in several clinical trials belonging to the aminocyclohexyl pyridyl carboxamide chemical series.[8c] This series emerged from a medicinal chemistry strategy to investigate the effect of the A-ring carbon-linker on *in-vitro* liver microsomal stability. The high hepatic extraction ratio (ER_H) in both rat and human liver microsomes for the tool compound **1b** combined with the extensive metabolism that takes place in the piperidine A-ring according to met ID studies in human liver microsomes, posed both developability and toxicity risks.[8c] Therefore, in conjunction to the cyclohexyl strategy that led to **1c**, an alternative series was investigated that explored heteroaryl moieties as the A-ring with the similar goal of assessing the effect of this modification on the microsomal stability (Figure 1). However, such a strategy would require the removal of the basic amine and *a priori*, it was unknown if that would be tolerated from a potency perspective and the effect it would have on the physicochemical properties of the compounds. Therefore, we anticipated that the A-ring aromatization strategy would require potency and physicochemical properties re-optimization due to potentially distinct A-ring conformation and the lower basicity of a heteroaryl amine relative to **1b**. Herein, we describe our medicinal chemistry strategy and our findings in the generation of a potent *pan*-Pim inhibitor series.

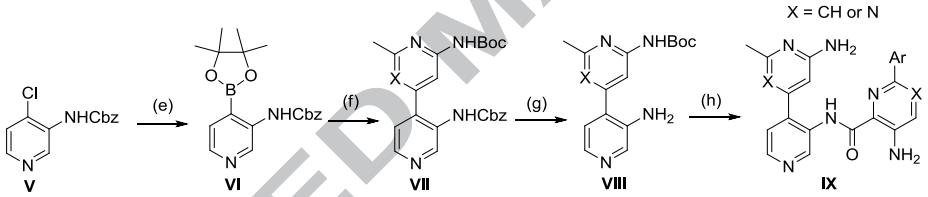
Based on the published crystal structure illustrating the binding mode of **1c** in Pim-1 (Figure 2),[8c] the basic amine makes two hydrogen bonds to the Asp128 side chain carboxylate and the Glu171 backbone carbonyl in the ribose patch. We postulated that we could mimic these interactions with a heteroaryl-NH_2 moiety while also providing vectors in which we could further explore the surrounding region of the pocket by substituting off the heteroaryl.

With this strategy in mind, Schemes 1 and 2 illustrate general methods for how compounds were synthesized. Introduction of the D-ring on intermediate **I** via Suzuki-Miyaura coupling followed by hydrolysis of the methyl ester afforded carboxylic acid **II** (Scheme 1). This intermediate was reacted with 4-chloropyridin-3-amine in the presence of EDC and HOAt at room temperature to provide intermediate **III**. Carbon-carbon bond formation to install the A-ring was achieved via Suzuki-Miyaura reaction utilizing $Pd(dppf)Cl_2$-DCM as the catalyst and the corresponding boronic ester or boronic acid, or alternatively via conversion of **III** to the corresponding boronic ester, followed by Suzuki-Miyaura reaction with a heteroaryl halide. Individual A-ring boronic esters and halides were synthesized as previously described.[9]



Scheme 1. Representative example for the synthesis of compounds illustrated in Tables 1 and 2 . Reagents and Conditions: (a) (i) 2-fluorophenylboronic acid, Pd(dppf)Cl_2-DCM, DME/2M Na_2CO_3, 120 ^oC; (ii) LiOH; (b) 4-chloropyridin-3-amine, HOAt, EDCI, DCM or DMF; (c) heteroarylboronic acid, Pd(dppf)Cl_2-DCM, dioxane/2M Na_2CO_3, 120 ^oC; (d) (i) KOAc, bis(pinacolato)diboron, Pd(dppf)Cl_2-DCM, dioxane, 120-150 ^oC; (ii) heteroarylhalide, Pd(dppf)Cl_2-DCM, DME/2M Na_2CO_3, 110 ^oC

Alternatively, C and D ring diversification was introduced by first making the boronic ester of the Cbz protected chloro-aminopyridine **V** to give boronic ester **VI**, followed by cross-coupling with the corresponding heteroaryl halide to afford intermediate **VII** (Scheme 2). Deprotection of the Cbz under hydrogenolysis conditions followed by amide bond formation in the presence of HOAt and EDC afforded final compound **IX** after Boc group deprotection and HPLC purification.



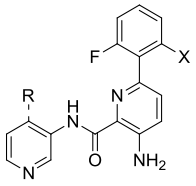
Scheme 2. Representative example for the synthesis of compounds illustrated in Table 3. Reagents and Conditions: (e) bis(pinacolato)diboron, $Pd_2(dba)_3$, PCy_3, KOAc, dioxane, 90 ^oC; (f) heteroaryl halide, Pd(dppf)Cl_2-DCM, DME/2M Na_2CO_3, 90 ^oC; (g) H_2, Pd/C; (h) (i) HOAt, EDC, NMP and carboxylic acid; (ii) TFA

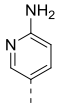
The compounds were tested in Pims-1, 2 and 3 biochemical assays where each Pim isoform was screened with ATP concentrations at or below its corresponding ATP K_m and obtained K_i's are reported. Based on our previous work in this scaffold, Pim-2 biochemical potency was the most challenging among the three isoforms, so we focused on obtaining potent Pim-2 activity. By introducing a 4-pyridine as the A-ring (**2b**), a significant reduction of Pim-2 biochemical potency was observed relative to the aminopiperidine A-ring (**2a**). With the goal of obtaining the hydrogen bond interactions in the ribose patch, the amino substituent at the 2-position of the pyridine (**2c**) was introduced and gratifyingly, a 10-fold increase in potency was observed, to achieve a compound with reasonable activity for Pim-2. Slightly improved potency

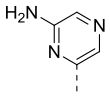
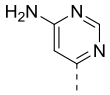
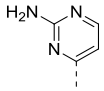
was obtained with the corresponding difluorophenyl D-ring (**2g**). Compounds **2d** and **2e** where the amino group is moved around the heteroaromatic ring were not as potent, presumably due to suboptimal interaction with the ribose patch residues (Glu171 and/or Asp128).

Investigation of other A-ring heterocycles (Table 1) that could maintain similar orientation of the amino group of **2c** such as in compounds **2f**, **2h** and **2i** enabled us to identify the 4-amino-substituted pyrimidine as an additional heterocycle (**2h**) with a slightly lower clogP than the corresponding pyridine matched-pair (cLogP: 2.3 vs 2.7). While the K_i's of compounds **2g** and **2h** are reasonable, further improvement in potency was desired, given that based on our previous experience with this chemotype, picomolar biochemical inhibition would be needed for efficacious cellular inhibition.

Table 1 – A-ring heteroaryl SAR

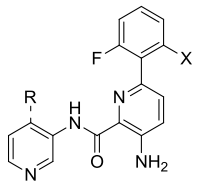


Compound	R	X	Pim-1 K_i (μM)	Pim-2 K_i (μM)	Pim-3 K_i (μM)
2a		H	<0.001	<0.003	<0.003
2b		H	0.008	0.317	0.021
2c		H	<0.001	0.035	0.003
2d		H	0.004	0.158	0.012
2e		F	0.028	0.187	0.036

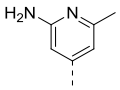
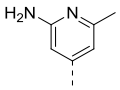
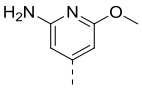
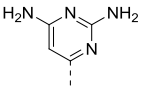
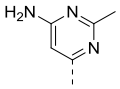
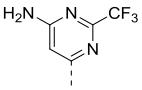
2f		H	0.003	0.094	0.006
2g		F	0.002	0.008	<0.003
2h		F	0.004	0.027	0.005
2i		F	0.006	0.050	0.005

Additional potency improvement could be achieved by designing and synthesizing compounds with various substitutions on the heteroaryl A-ring which probed the hydrophobic dimple under the glycine rich loop (Table 2). Similar to the aminocyclohexyl and aminopiperidine chemical series, small hydrophobic substituents, such as methyl, located at the 6-position of the pyridine A-ring provided a >3-fold increase in Pim-2 biochemical potency (**2g** vs **3b**). As shown in Table 2, methyl (**3b**), methoxy (**3c**) and trifluoromethyl (**3f**) substituents were efficient in driving the biochemical potency further in both the pyridine and pyrimidine heterocycles. Polarity in this region, represented by compound **3d** with the amino group was detrimental to potency.

Table 2: Selected SAR of analogs targeting potency improvement via A-ring substitutions along with rat and human hepatic extraction ratios

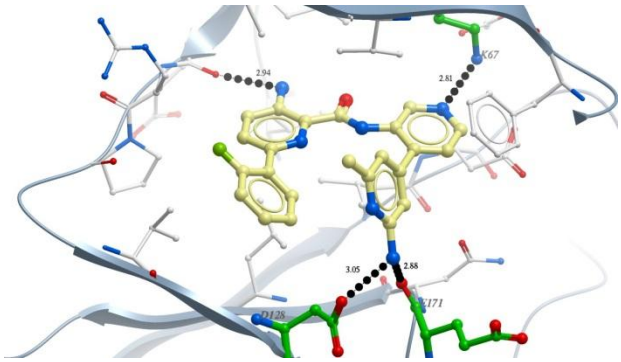


Compound	R	X	Pim-1 K_i (μM)	Pim-2 K_i (μM)	Pim-3 K_i (μM)	ER_H rat/human	cLogP

2g		F	<0.001	0.009	<0.003	-	2.7
3a		H	<0.001	0.004	<0.003	0.95/0.95	3.1
3b		F	<0.001	<0.003	<0.003	0.94/0.96	3.2
3c		F	<0.001	0.004	<0.003	-	3.6
3d		H	0.017	0.120	0.015	-	2.1
3e		F	<0.001	<0.003	<0.003	0.82/0.82	2.8
3f		F	<0.001	<0.003	<0.003	0.91/0.77	3.2

We were able to obtain an X-ray co-crystal structure of compound **3a** and confirm the binding mode in Pim-1. As shown in Figure 3, the A-ring pyridine amine forms a H-bond with the sidechain of amino acid Asp128 and interacts with the backbone amide at residue Glu171 while the methyl group occupies the hydrophobic dimple under the P-loop (top of protein omitted for clarity). The C-ring amino-pyridine makes a single hydrogen bond to the hinge and the pyridine B-ring nitrogen interacts with the Lys67 residue in a similar fashion as in the binding mode of **1c**. The lower hinge is occupied by the 2-fluorophenyl moiety.

Figure 3. X-ray structure of **3a** in Pim-1 (2.1Å, PDB: 5IIS).

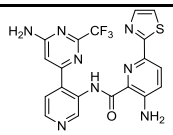
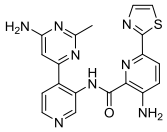
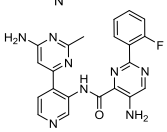


Having achieved picomolar potency across all three Pim isoforms, we evaluated the *in vitro* liver microsomal stability for the series. Compounds were incubated with rat or human liver microsomes at 1 μM for 30 min and hepatic extraction ratios (ER_H) were determined using a well-stirred liver model.[10] As illustrated in Table 2, compounds tested displayed high ER_H in rat and human microsomes. Both pyridine and pyrimidine heterocycles had similar poor metabolic stability independent of the methyl or trifluoromethyl substituent. We hypothesized that perhaps the lipophilicity of our compounds was driving the low microsomal stability. By comparing the measured logD for this series with the measured logD of the aminocyclohexyl series, we were in a more lipophilic space (logD for **3f** is 4.3 and logD for **1c** is 1.1). Therefore, we focused our strategy around lowering the cLogP and assessing whether such an approach would improve the microsomal stability. Towards designing more polar compounds, we had previously established that both the A and B rings were optimized for potency with little opportunity for further polarity introduction. We turned our attention towards the much less explored C and D rings where efforts focused upon the incorporation of polar heterocycles to reduce hydrophobicity.

We designed and synthesized several combinations of A/B rings with more polar C/D rings, with the goal of lowering the cLogP into a range of 1-2. Several representative examples are illustrated in Table 3 along with their rat and human extraction ratios. The replacement of the difluorophenyl moiety by a thiazole ring, analog **4a**, was well-tolerated based on biochemical assays however the ER_H was not improved relative to **3f** albeit the lower cLogP. A slightly improved human ER_H was observed with the methylpyrimidine A-ring combination with thiazole D-ring **4b**, however this came at the expense of Pim-2 biochemical potency. By switching the polar strategy towards the C-ring, the addition of one nitrogen

lowered the cLogP to 2 (compound **4c**) and this modification provide compounds trending towards more acceptable human ER_H (0.58), although detrimental to Pim-2 biochemical potency.

Table 3: Biochemical activity, rat and human hepatic extraction ratios of compounds with lower cLogP

Compound	Structure	Pim-1 K_i (μM)	Pim-2 K_i (μM)	Pim-3 K_i (μM)	ER_H rat/human	cLogP
4a		<0.001	<0.003	<0.003	0.89/0.87	1.5
4b		<0.001	0.009	<0.003	0.81/0.64	1.1
4c		<0.001	0.007	<0.003	0.80/0.58	2.0

In general, it was extremely challenging to find the appropriate balance between physicochemical properties and potency while addressing the metabolic stability for the heteroaryl series. Furthermore, the potencies of the A-ring heteroaryl compounds in a cell proliferation assay were inferior by ~10 fold (compound **4a** KMS-11 luc EC_{50} 1.5 μM) compared to the earlier aminocyclohexyl series (compound **1c** KMS-11 luc EC_{50} 0.17 μM). This result coupled with the high rat and human intrinsic clearance and low aqueous solubility contributed to a no-go decision to progress this series into further pre-clinical studies. In retrospect, the basic amine present in both the aminopiperidine and aminocyclohexyl scaffolds (Figure 1) proved instrumental in retaining the desired potency and physicochemical properties that could not be replicated using the described heteroaryl approach.

In conclusion, replacement of the A-ring cyclohexyl moiety in the pyridyl carboxamide scaffold with various amino heterocycles generated a novel chemical series of potent *pan*-Pim inhibitors. The potency of this series was optimized by utilizing structure-based drug design as well as previous SAR from a related chemical series. A new X-ray structure was determined for a representative example of this series which confirmed the binding mode for the scaffold as well as the key contacts that the heteroaryl amine makes with the protein. While weak cellular potency and poor metabolic stability prevented further advancement for these compounds, this SAR investigation proved to be a

complementary medicinal chemistry optimization effort that aided in the discovery of PIM447, a compound currently in several Phase I clinical trials.

Acknowledgments

The authors would like to thank Weiping Jia and Dhazi Tang for analytical chemistry support.

Supplementary Data

Supplementary Data (synthesis of compounds and assay experimental details) associated with this article can be found in the online version, at http://XXX

References and Notes

1. (a) Nawijn, M.C.; Alendar, A.; Berns, A. *Nat. Rev. Cancer* **2011**, *11*, 23-34; (b) Warfel, N.A.; Kraft, A. S. *Pharmacol. Ther*. **2015**, *151*, 41-49; (c) Le, B. T.; Kumarasiri, M.; Adams, J. R.; Yu, M.; Milne, R.; Sykes, M. J.; Wang, S. *Future Med. Chem.* **2015**, *7*(1), 35-53.
2. (a) Keane, N.A.; Reidy, M.; Natoni, A.; Raab, M. S.; O'Dwyer, M. *Blood Cancer J.* **2015** *5* e325, doi: 10.1038/bcj.20515.46; (b) Alvarado, Y.; Giles, F.J.; Swords, R. T. *Expert. Rev. Hematol*. **2012** Feb; 5(1): 81-96; (c) Garcia, P.B.; Langowski, J.L.; Wang, Y.; Chen, M.; Castillo, J.; Fanton, C.; Ison, M.; Zavorotinskaya, T.; Dai, Y.; Lu, J.; Niu, X. H.; Basham, S.; Chan, J.; Yu, J.; Doyle, M.; Feucht, P.; Warne, R.; Narberes, J.; Tsang, T.; Fritsch, C.; Kauffmann, A.; Pfister, E.; Drueckes, P.; Trappe, J.; Wilson, C.; Han, W.; Lan, J.; Nishiguchi, G.; Lindvall, M.; Bellamacina, C.; Aycinena, J. A.; Zang, R.; Holash, J.; Burger, M. T. *Clin. Cancer Res*. **2014**, Apr 1, 20(7): 1834-45; (d) Mondello, P.; Cuzzocrea, S.; Mian, M. *J. Hematol. Oncol*. **2014,** *7*, 95; (e) Lu, J.; Zavorotinskaya, T.; Dai, Y.; Niu, X. H.; Castillow, J.; Sim, J.; Yu, J.; Wang, Y.; Langowski, J. L.; Holash, J.; Shannon, K.; Garcia, P. D. *Blood* **2013**, *122*, 1610-1620.
3. Brault, L.; Gasser, C.; Bracher, F.; Huber, K.; Knapp, S.; Schwaller, J. *Haematologica* **2010**, *95*, 1004-1015.
4. Baytel, D.; Shalom, S.; Madgar, I.; Weissenberg, R.; Don, J. *Biochim. Biophys. Acta* **1998**, *1442*, 274-285.

5. Qian, K. C.; Wang, L.; Hickey, E. R.; Studts, J.; Barringer, K.; Peng, C.; Kronkaitis, A.; Li, J.; White, A.; Mische, S.; Farmer, B. *J. Biol. Chem.* **2005**, *280*, 6130-6137.

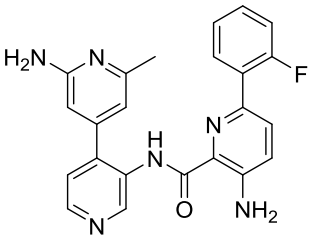
6. (a) Qian, K.; Wang, L.; Cywin, C. L.; Farmer, II, B. T.; Hickey, E.; Homon, C.; Jakes, S.; Kashem, M. A.; Lee, G.; Leonard, S.; Li, J.; Magboo, R.; Mao, W.; Pack, E.; Peng, C.; Prokopowicz, III, A.; Welzel, M.; Wolak, J.; Morwick, T. *J. Med. Chem.* **2009**, *52*, 1814-1827; (b) See Supplementary material for details on biochemical assays.

7. (a) Mikkers, H.; Nawijn, M.; Allen, J.; Brouwers, C.; Verhoeven, E.; Jonkers, J.; Berns, A. *Mol. Cell Biol.* **2004**, 24, 6104-6115; (b) van der Lugt, N. M.; Domen, J.; Verhoeven, E.; Linders, K.; vad der Gylden, H.; Allen, J.; Berns, A. *EMBO J*. **1995**, *14*, 2536.

8. (a) Wu, B.; Wang, H-L.; Cee, V. J.; Lanman, B. A.; Nixey, T.; Pettus, L.; Reed, A. B.; Wurz, R. P.; Guerrero, N.; Sastri, C.; Winston, J.; Lipford, J. R.; Lee, M. R.; Mohr, C.; Andrews, K. L.; Tasker, A. S. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 775-780; (b) Flanders, Y.; Dumas, S.; Caserta, J.; Nicewonger, R.; Baldino, M.; Lee, C.-S.; Baldino, C. M. *Tetrahedron Lett.* **2015**, *56*, 3186–3190; Hu, H.; Wang, X.; Chan, G. K. Y.; Chang, J. H.; Do, S.; Drummond, J.; Ebens, A.; Lee, W.; Ly, J.; Lyssikatos, J. P.; Murray, J.; Moffat, J. G.; Chao, Q.; Tsui, V.; Wallweber, H.; Kolesnikov, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5258–5264; (c) Burger, M. T.; Nishiguchi, G.; Han, W.; Lan, J.; Simmons, R.; Atallah, G.; Ding, Y.; Tamez, V.; Zhang, Y.; Mathur, M.; Muller, K.; Bellamacina, C.; Lindvall, M. K.; Zang, R.; Huh, K.; Feucht, P.; Zavorotinskaya, T.; Dai, Y.; Basham, S.; Chan, J.; Ginn, E.; Aycinena, A.; Holash, J.; Castillo, J.; Langowski, J. L.; Wang, Y.; Chen, M. Y.; Lambert, A.; Fritsch, C.; Kauffmann, A.; Pfister, E.; Vanasse, K. G.; Garcia, P. D. *J. Med. Chem.* **2015**, *58*, 8373–8386; (d) Wurz, R. P.; Pettus, L. H.; Jackson, C.; Wu, B.; Wang, H.-L.; Herberich, B.; Cee, V.; Lanman, B. A.; Reed, A. B.; Chavez Jr., F.; Nixey, T.; Laszlo III, J.; Wang, P.; Nguyen, Y.; Sastri, C.; Guerrero, N.; Winston, J.; Lipford, J. R.; Lee, M. R.; Andrews, K. L.; Mohr, C.; Xu, Y.; Zhou, Y.; Reid, D. L.; Tasker, A. S. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 847–855; (e) Wang, H.-L.; Cee, V. J.; Chavez, F.; Lanman, B. A.; Reed, A. B.; Wu, B.; Guerrero, N.; Lipford, J. R.; Sastri, C.; Winston, J.; Andrews, K. L.; Huang, X.; Lee, M. R.; Mohr, C.; Xu, Y.; Zhou, Y.; Tasker, A. S. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 834–840; (f) Lee, J.; Park, J.; Hong, V. S. *Chem. Pharm. Bull. (Tokyo).* **2014**, *62*, 906–914; (g) Wang, X.; Magnuson, S.; Pastor, R.; Fan, E.; Hu, H.; Tsui, V.;

Deng, W.; Murray, J.; Steffek, M.; Wallweber, H.; Moffat, J.; Drummond, J.; Chan, G.; Harstad, E.; Ebens, A. J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3149–3153; (h) Haddach, M.; Michaux, J.; Schwaebe, M. K.; Pierre, F.; O'Brien, S. E.; Borsan, C.; Tran, J.; Raffaele, N.; Ravula, S.; Drygin, D.; Siddiqui-Jain, A.; Darjania, L.; Stansfield, R.; Proffitt, C.; Macalino, D.; Streiner, N.; Bliesath, J.; Omori, M.; Whitten, J. P.; Anderes, K.; Rice, W. G.; Ryckman, D. M. *ACS Med. Chem. Lett.* **2012**, *3*, 135–139; (i) Dakin, L. a.; Block, M. H.; Chen, H.; Code, E.; Dowling, J. E.; Feng, X.; Ferguson, A. D.; Green, I.; Hird, A. W.; Howard, T.; Keeton, E. K.; Lamb, M. L.; Lyne, P. D.; Pollard, H.; Read, J.; Wu, A. J.; Zhang, T.; Zheng, X. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4599–4604; (j) Burger, M. T.; Han, W.; Lan, J.; Nishiguchi, G.; Bellamacina, C.; Lindvall, M.; Atallah, G.; Ding, Y.; Mathur, M.; Mcbride, C.; Beans, E. L.; Muller, K.; Tamez, V.; Zhang, Y.; Huh, K.; Feucht, P.; Zavorotinskaya, T.; Dai, Y.; Holash, J.; Castillo, J.; Langowski, J.; Wang, Y.; Chen, M. Y.; Garcia, P. D. *ACS Med. Chem. Lett.* **2013**, *4*, 1193–1197; (k) Be, B. T; *Future Med. Chem.* **2015**, *7*(1):35-53.

9. Burger, M.; Lindvall, M.; Han, W.; Lan, J.; Nishiguchi, G.; Shafer, C.; Bellamacina, C.; Huh, K.; Atallah, G.; McBride, C.; Antonios-McCrea, W.; Zavorotinskaya, T.; Walter, A.; Garcia, P. D. U.S. Patent 2014/0249135 A1.
10. See Supplementary Information



Pim-1 Ki: <0.001 μM
Pim-2 Ki: 0.004 μM
Pim-3 Ki: <0.003 μM