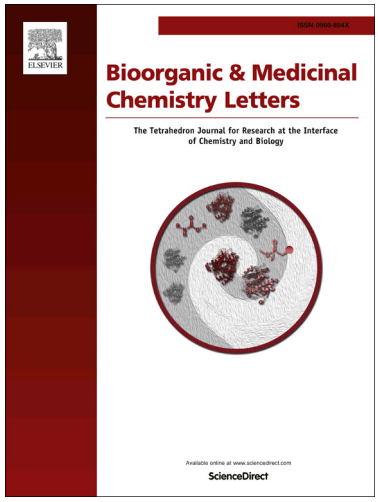

Discovery of 5-(1H-indol-5-yl)-1,3,4-thiadiazol-2-amines as potent PIM inhibitors

Bin Wu, Hui-Ling Wang, Victor Cee, Brian Lanman, Thomas Nixey, Liping Pettus, Anthony B. Reed, Ryan P. Wurz, Nadia Guerrero, Christine Sastri, Jeff Winston, J. Russell Lipford, Matthew R. Lee, Christopher Mohr, Kristin Andrews, Andrew S. Tasker

PII: S0960-894X(14)01399-7
DOI: http://dx.doi.org/10.1016/j.bmcl.2014.12.091
Reference: BMCL 22336

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 7 November 2014
Revised Date: 23 December 2014
Accepted Date: 29 December 2014

Please cite this article as: Wu, B., Wang, H-L., Cee, V., Lanman, B., Nixey, T., Pettus, L., Reed, A.B., Wurz, R.P., Guerrero, N., Sastri, C., Winston, J., Russell Lipford, J., Lee, M.R., Mohr, C., Andrews, K., Tasker, A.S., Discovery of 5-(1H-indol-5-yl)-1,3,4-thiadiazol-2-amines as potent PIM inhibitors, *Bioorganic & Medicinal Chemistry Letters* (2015), doi: http://dx.doi.org/10.1016/j.bmcl.2014.12.091

Discovery of 5-(1H-indol-5-yl)-1,3,4-thiadiazol-2-amines as potent PIM inhibitors

Bin Wu,*[a] Hui-Ling Wang,[a] Victor Cee,[a] Brian Lanman,[a] Thomas Nixey,[a] Liping Pettus,[a] Anthony B. Reed,[a] Ryan P. Wurz,[a] Nadia Guerrero,[b] Christine Sastri,[b] Jeff Winston,[b] J. Russell Lipford,[b] Matthew R. Lee,[c] Christopher Mohr,[c] Kristin Andrews,[c] and Andrew S. Tasker.[a]

Amgen Inc. One Amgen Center Drive, Thousand Oaks, California 91320-1799, USA

a) Department of Therapeutic Discovery; b) Department of Oncology; c) Department of Molecular Structure and Characterization.

* To whom correspondence should be addressed:
Bin Wu: Tel +1-805-313-5661; Fax 805-480-3016; email:binw@amgen.com

Abstract: PIM kinases are a family of Ser/Thr kinases that are implicated in tumorigenesis. The discovery of a new class of PIM inhibitors, 5-(1H-indol-5-yl)-1,3,4-thiadiazol-2-amines, is discussed with optimized compounds showing excellent potency against all three PIM isoforms.

PIM kinases are a family of serine/threonine kinases in the CAMK group (calcium/calmodulin-dependent protein kinase) that are constitutively active and are regulated at the level of transcription and translation, as opposed to the more classical post-translational phosphorylation. [1] There are three isoforms in the family, PIM1, PIM2 and PIM3, which share high homology and exhibit some functional redundancy. PIM kinases are widely expressed and are involved in a variety of biological processes, including cell survival, proliferation, differentiation and apoptosis.[2] Over-expression of PIM kinases has been reported in hematological and solid tumors such as diffuse large B-cell lymphomas (DLBCL) and prostate cancer.[3] Other evidence has also suggested that PIM kinases play a role in tumorigenesis, making it an attractive target for cancer therapy.[4] There have been several reports of both PIM1-selective and pan-PIM inhibitors, including three clinical compounds, SGI-1776, AZD1208, (structures shown in Figure 1) and LGH447 (structure not disclosed).[5,6] Considering the compensatory