Bioorganic & Medicinal Chemistry Letters 27 (2017) 2721–2726

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Identification of quinazoline based inhibitors of IRAK4 for the treatment of inflammation

Graham F. Smith [a,*], Michael D. Altman [b], Brian Andresen [b], James Baker [b], Jason D. Brubaker [c], Hongmin Chen [b], Yiping Chen [b], Matthew Childers [b], Anthony Donofrio [b], Heidi Ferguson [b], Christian Fischer [b], Thierry O. Fischmann [b], Craig Gibeau [b], Alexander Hicks [d], Sue Jin [b], Sam Kattar [b], Melanie A. Kleinschek [e], Erica Leccese [b], Charles Lesburg [b], Chaomin Li [b], Jongwon Lim [b,*], Duan Liu [b], John K.F. Maclean [f], Faruk Mansoor [b], Lilly Y. Moy [b], Erin F. Mulrooney [b], Antoaneta S. Necheva [b], Jeremy Presland [b], Larissa Rakhilina [b], Ruojing Yang [b], Luis Torres [b], Jie Zhang-Hoover [b], Alan Northrup [b]

[a] AstraZeneca, 35 Gatehouse Drive, Waltham, MA 02451, United States
[b] Merck & Co., Inc., 33 Avenue Louis Pasteur, Boston, MA 02115, United States
[c] Blueprint Medicines, 38 Sidney St Suite 200, Cambridge, MA 02139, United States
[d] Oncorus, 50 Hampshire St. Suite 401, Cambridge, MA 02139, United States
[e] Theravance Biopharma US, Inc., 901 Gateway Boulevard, South San Francisco, CA 94080, United States
[f] Redx Pharma, Block 33, Mereside, Alderley Park, Macclesfield SK10 4TG, United Kingdom

ARTICLE INFO

Article history:
Received 14 March 2017
Revised 14 April 2017
Accepted 15 April 2017
Available online 18 April 2017

Keywords:
IRAK4
Quinazoline
Serine-threonine kinase
Kinase inhibitor
Inflammatory disease

ABSTRACT

Interleukin-1 receptor associated kinase 4 (IRAK4) has been implicated in IL-1R and TLR based signaling. Therefore selective inhibition of the kinase activity of this protein represents an attractive target for the treatment of inflammatory diseases. Medicinal chemistry optimization of high throughput screening (HTS) hits with the help of structure based drug design led to the identification of orally-bioavailable quinazoline based IRAK4 inhibitors with excellent pharmacokinetic profile and kinase selectivity. These highly selective IRAK4 compounds show activity *in vivo* via oral dosing in a TLR7 driven model of inflammation.

Interleukin-1 receptor associated kinase 4 (IRAK4) is an intracellular serine-threonine kinase belonging to the IRAK family of kinases which includes IRAK1, IRAK2, IRAK-M, and IRAK4.[1–4] IRAK4 is an innate immune system target downstream of multiple signaling receptors including IL-1R, IL-18R, IL-33R and the Toll-like-receptors (TLRs). The observed phenotype of IRAK4-deficient patients suggests that a favorable clinical safety profile is possible with its pharmacological inhibition. MyD88 and IRAK4 deficient patients are susceptible to pyrogenic bacterial infections in infancy and early childhood which they outgrow during adolescence.[5,6] Selective inhibition of IRAK4 could therefore be of potential utility in multiple inflammatory diseases such as rheumatoid arthritis,[7,8] irritable bowel disease,[9,10] asthma and systemic lupus erythematosus.[11,12]

IRAK4 kinase inhibitors from multiple chemical classes have been reported previously in the literature by both Merck,[13–16] and others to date.[17–25] However at the onset of this work, as we assessed the current chemical tools available to validate the proposed IRAK4 inhibition anti-inflammatory mechanisms *in vivo*, each of these tools had issues of either kinase selectivity or pharmacokinetic properties making them unsuitable for significant *in vivo* mechanistic validation work. In order to de-risk downstream drug discovery it is preferable to have at least 2 chemical tools with orthogonal chemotypes, SAR and development risks to proceed with target validation and later drug discovery programs.[26,27]

At this early stage in the IRAK4 discovery program we had gathered a wealth of IRAK4 kinase inhibition data from several HTS campaigns in various assay formats since the IRAK4 program had

* Corresponding authors at: Tel.: +1 617 992 2012 (J. Lim).
E-mail addresses: Graham.smith@astrazeneca.com (G.F. Smith), jongwon_lim@merck.com (J. Lim).

http://dx.doi.org/10.1016/j.bmcl.2017.04.050
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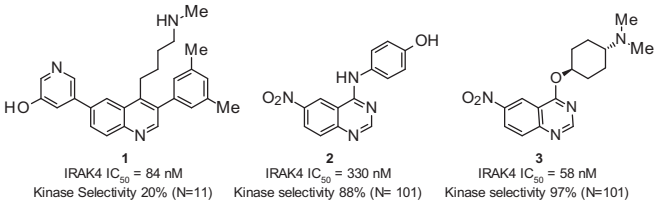

Fig. 1. HTS Hits from refiltering HTS screening data.

been run in both the Schering-Plough and Merck organizations and also on several research sites. Rather than run a new hit finding HTS campaign we merged all the previous screening data, from across sites and legacy organizations, and mined it for new chemical matter. By looking at some weaker hits and ruling out all previously known IRAK4 chemotypes, internal and external, we found several potential new leads. These compounds were then further filtered using a specific small panel of 11 kinases which had caused frequent kinome selectivity problems in our previous IRAK4 medicinal chemistry projects. Kinase selectivity is reported as a percentage of kinases screened (N) which are greater than 100 fold weaker than the on target IC_{50}. The outcome of this exercise was just 2 molecules, **1** and **2**,[28] shown in Fig. 1 which became the starting chemical matter for our current IRAK4 medicinal chemistry series optimization.

We were lucky to be enabled throughout this program by strong structure based drug design support aided by X-ray crystal

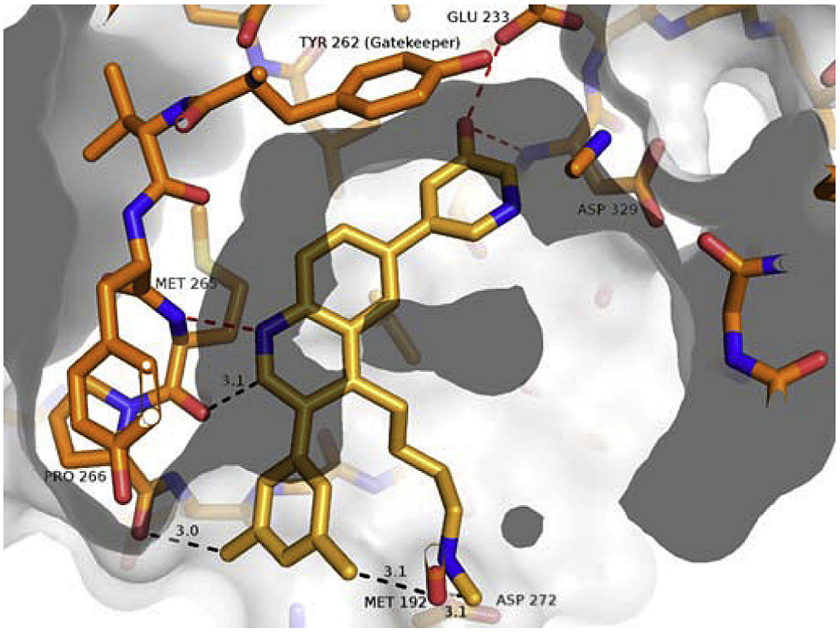

Fig. 2. Compound **1** bound to IRAK4 showing key binding interactions with hinge, gatekeeper TYR 262 and ASP 272. The H-bond between ASP 272 and the secondary amine is hidden under MET 192 carbonyl. PDB code 5T1S.

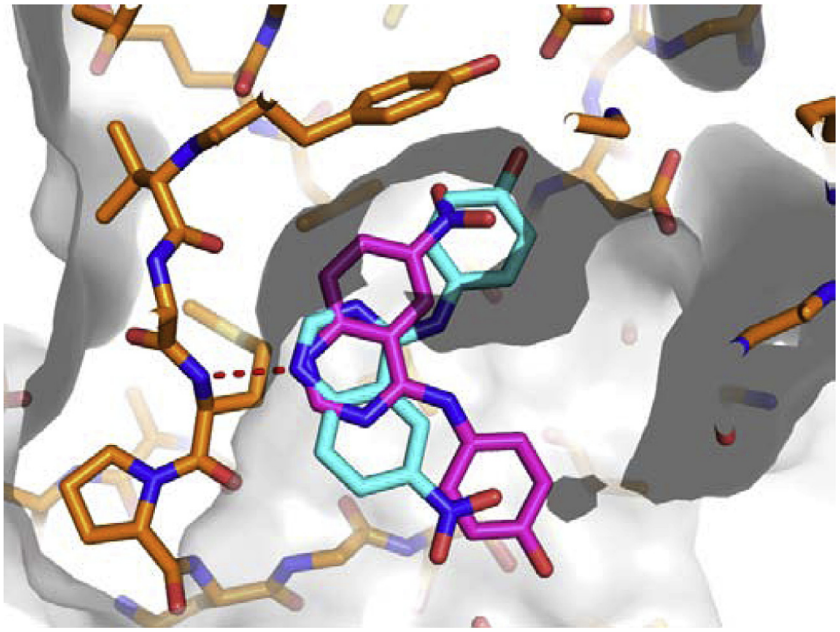

Fig. 3. Compound **2** docked into IRAK 4 showing its two favored poses.