Bioorganic & Medicinal Chemistry Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design and synthesis of novel 3-sulfonylpyrazol-4-amino pyrimidines as potent anaplastic lymphoma kinase (ALK) inhibitors

Peilong Zhang [a,c], Jiaqiang Dong [b,*], Boyu Zhong [b], Deyi Zhang [b], Hongbin Yuan [b], Can Jin [b], Xiangyuan Xu [b], Hailong Li [b], Yong Zhou [b], Zhi Liang [b], Minghua Ji [b], Tao Xu [b], Guowei Song [b], Ling Zhang [b], Gang Chen [b], Xuejing Meng [b], Desheng Sun [b], Joe Shih [b], Ruihao Zhang [b], Guojun Hou [b], Chengcheng Wang [b], Ying Jin [b], Qiong Yang [b]

[a] Department of Applied Chemistry, Beijing Institute of Technology, Zhongguancun South Street, Beijing 100081, China
[b] Crown Bioscience Inc. (Taicang), 6 Beijing West Road, Taicang Economic Development Area, Taicang 215400, China
[c] Beijing Pearl Biotech Ltd, No. 203, Section 2, Wangjing Lize Zhongyuan, Chaoyang District, Beijing 100102, China

ARTICLE INFO

Article history:
Received 27 January 2016
Revised 24 February 2016
Accepted 7 March 2016
Available online xxxx

Keywords:
ALK
Kinase
Anti-tumor
NSCLC
Pyrimidine

ABSTRACT

Anaplastic lymphoma kinase (ALK) is a highly attractive therapeutic target for the treatment of some non-small cell lung cancer patients. This Letter describes the further SAR exploration on the novel 3-sulfonylpyrazol-4-amino pyrimidine scaffold. This work identified a compound **53** with very good in vitro/in vivo efficacies, good DMPK properties together with better hERG tolerability and it is currently being profiled for the evaluation as a potential pre-clinical candidate.

Anaplastic lymphoma kinase (ALK) is one of receptor tyrosine kinases and belongs to the insulin receptor superfamily. The expression of ALK in adults is low and is only found in a subset of neural cells of healthy bodys.[1] So far, no essential physiological role of ALK in the normal body was found, however, ALK fusion proteins have been connected with many human cancers.[2,3] Nucleophosmin (NPM)—ALK fusion protein was firstly identified in 1994 in around 75% of anaplastic large cell lymphoma (ALCL) patients with a t(2;5) chromosomal translocation.[4] ALK fusion genes were also detected in breast cancer, ovarian cancer, inflammatory myofibroblastic tumors (IMT) and pediatric neuroblastoma, etc.[5–10] Most notably, the oncogenic fusion gene echimoderm micro-tubule-associated protein-like 4 (EML4)—ALK was identified in around 5% non-small cell lung cancer (NSCLC) patients in 2007.[11] Since then, ALK has been attracted as a promising anti-tumor drug target in pharmaceutical industry and academic fields.[12–14]

The strong correlation between ALK overexpression and tumorigenesis has been confirmed by the successful discovery of ALK inhibitors with structural diversity.[15] To date, there have been three drugs on the market for the treatment of ALK-positive NSCLC patients (Fig. 1). Crizotinib (**1**, Pfizer) was the first agent and used currently as the first-line drug against ALK.[16,17] However, the emergence of drug resistance during crizotinib treatment promoted the discovery of second generation ALK inhibitors. Now ceritinib (**2**, Novartis)[18] and alectinib (**3**, Roche)[19] have been approved and used in crizotinib-resistant NSCLC cases.

Previously, we discovered a novel series of 2-arylamino-4-pyrazolamino pyrimidines as potent ALK inhibitors. Based on the extensive investigation on the SAR of left side-chain, we delivered several inhibitors with good in vitro potency, favorable pharmacokinetic (PK) property and significant anti-tumor efficacy, exemplified by compound **4**.[20]

Recently, we have determined the co-crystal structure of **4** bound in ALK kinase domain with a 2.1 Å of resolution (PDB code: 5IMX). As shown in Figure 2, the X-ray crystallographic analysis indicated that the pyrimidine and the amino nitrogen atoms of the ligand form bidentate hydrogen bonds at the hinge region with the backbone nitrogen and the carbonyl oxygen of the residue Met1199, respectively. The chlorine in pyrimidine sits adjacent to gatekeeper residue Leu1196. The sulfonyl is directed toward the catalytic Lys1150 while the isopropyl group of sulfone binds in a deep pocket of the ALK protein. In addition, the piperidine ring

* Corresponding author.
E-mail address: djiaqiang@163.com (J. Dong).

http://dx.doi.org/10.1016/j.bmcl.2016.03.017
0960-894X/

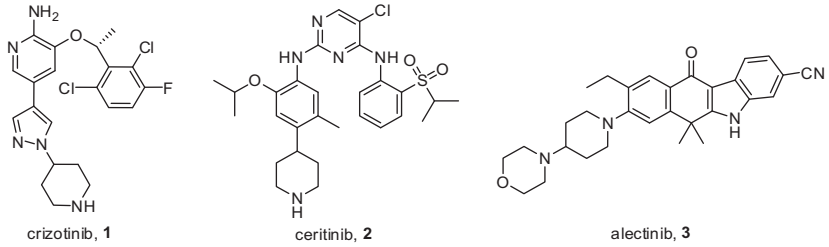

Figure 1. Current ALK inhibitors on the market.

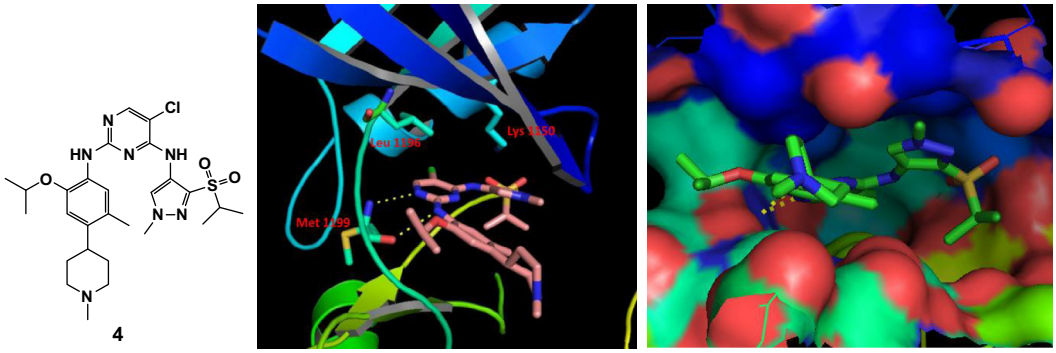

Figure 2. Co-crystal structure of **4** complexed to the ALK kinase domain. Hydrogen bonds are represented as dashed lines. Left panel shows the interaction of compound **4** (stick model) with three key residues Met1199, Leu1196 and Lys1150 of the ALK (cartoon diagram), and the right panel shows a surface view of the protein with the structure **4** in its protein binding pocket. PDB code: 5IMX.

extends to the solvent area. The mode of interaction between **4** and ALK is highly similar to what was observed in the reported complex of ALK bound 2,4-diamino pyrimidines[21,22] and provides a good tool for our further SAR expansion.

In this Letter, we will report our work on the further exploration and optimization of this scaffold. As shown in Figure 3, we attempt to investigate the effects of substitution at gate keeper area, the modification of pyrazole motif and further optimization of left piperidine, aiming to improve the potency and drug-like properties of previously reported ALK inhibitors (Fig. 4).

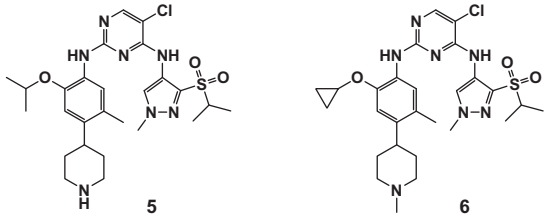

Figure 4. The structures of previously reported ALK inhibitors **5** and **6**.

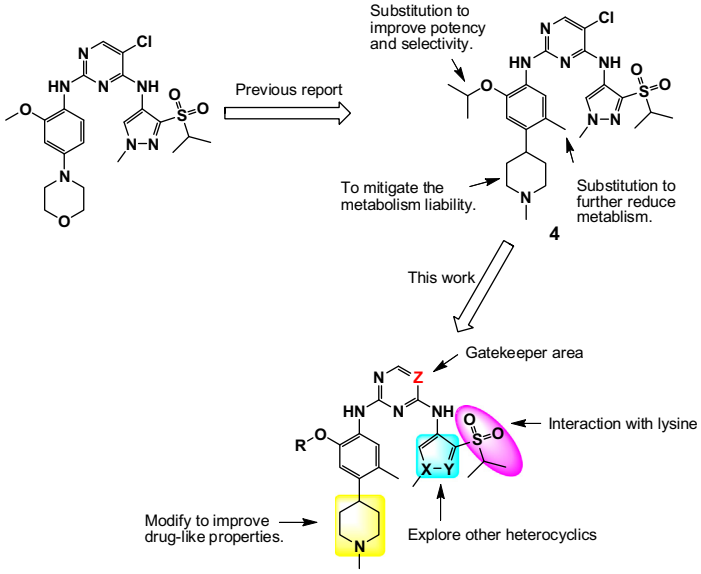

Figure 3. Previous work and current proposal of new ALK inhibitors.