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Design and synthesis of novel selective anaplastic lymphoma kinase inhibitors

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ABSTRACT

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase belonging to the insulin receptor superfamily. Expression of ALK in normal human tissues is only found in a subset of neural cells, however it is involved in the genesis of several cancers through genetic aberrations involving translocation of the kinase domain with multiple fusion partners (e.g., NPM-ALK in anaplastic large cell lymphoma ALCL or EML4-ALK in non-small cell lung cancer) or activating mutations in the full-length receptor resulting in ligand-independent constitutive activation (e.g., neuroblastoma). Here we are reporting the discovery of novel and selective anaplastic lymphoma kinase inhibitors from specific modifications of the 2,4-diaminopyridine core present in TAE684 and LDK378. Synthesis, structure activity relationships (SAR), absorption, distribution, metabolism, and excretion (ADME) profile, and in vivo efficacy in a mouse xenograft model of anaplastic large cell lymphoma are described.

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase of the insulin receptor superfamily and expression of ALK in normal human tissues is only found in a subset of neural cells.[1] It is involved however in the genesis of several cancers through genetic aberrations involving translocation of the kinase domain with multiple fusion partners or activating mutations that result in ligand-independent constitutive activation.[2–4] To date, no essential role has been found for ALK in mammals. Mice deficient in ALK have normal development and display an anti-depressive profile with enhanced performance in hippocampus-dependent tasks potentially due to increased hippocampal progenitor cells.[5]

Deregulation of ALK was first identified in anaplastic large cell lymphoma (ALCL) where the tyrosine kinase domain is fused to nucleophosmin (NPM), a product of recurrent t(2;5)(p23;q35) chromosome translocation.[6] Subsequently, chromosome rearrangements resulting in ALK fused to various partner genes have been found in nearly 70% of ALCL, 40–60% of inflammatory myofibroblastic tumors (IMT),[7] a few dozen cases of diffuse large B-cell lymphoma (DLBCL), and most recently in 2–7% of non-small cell lung cancer (NSCLC).[8–10] Among fusion partner genes identified to date, NPM is the most common partner in ALCL and echinoderm microtubule-associated protein-like-4 (EML4) is the main partner in NSCLC. In addition to the chromosome rearrangements that result in ALK fusion genes, amplification of ALK gene and activating point mutations in the full length ALK gene have recently been reported in neuroblastoma,[11–13] inflammatory breast cancer,[14] and ovarian cancer.[15]

To date, **3** (crizotinib, Xalkori®)[16,17] has been approved for the treatment ALK-positive NSCLC and **2** (LDK378, ceritinib, Zykadia®)[18] was approved for the treatment of crizotinib-resistant NSCLC patients. Both **4** (alectinib) and **5** (AP26113) have obtained the breakthrough therapy designation by the FDA for their activity in crizotinib-resistant NSCLC patients. Figure 1 represents a selected subset of ALKi currently FDA approved or in clinical trials.[18–25]

In a previous communication, we presented the modifications we made around TAE684 (**1**) that led to the discovery of LDK378 (**2**).[18] We present additional medicinal chemistry efforts performed on this scaffold; focusing in this communication on the replacement of the pyrimidine ring present in compound **2** in the aim of optimizing hinge interactions.

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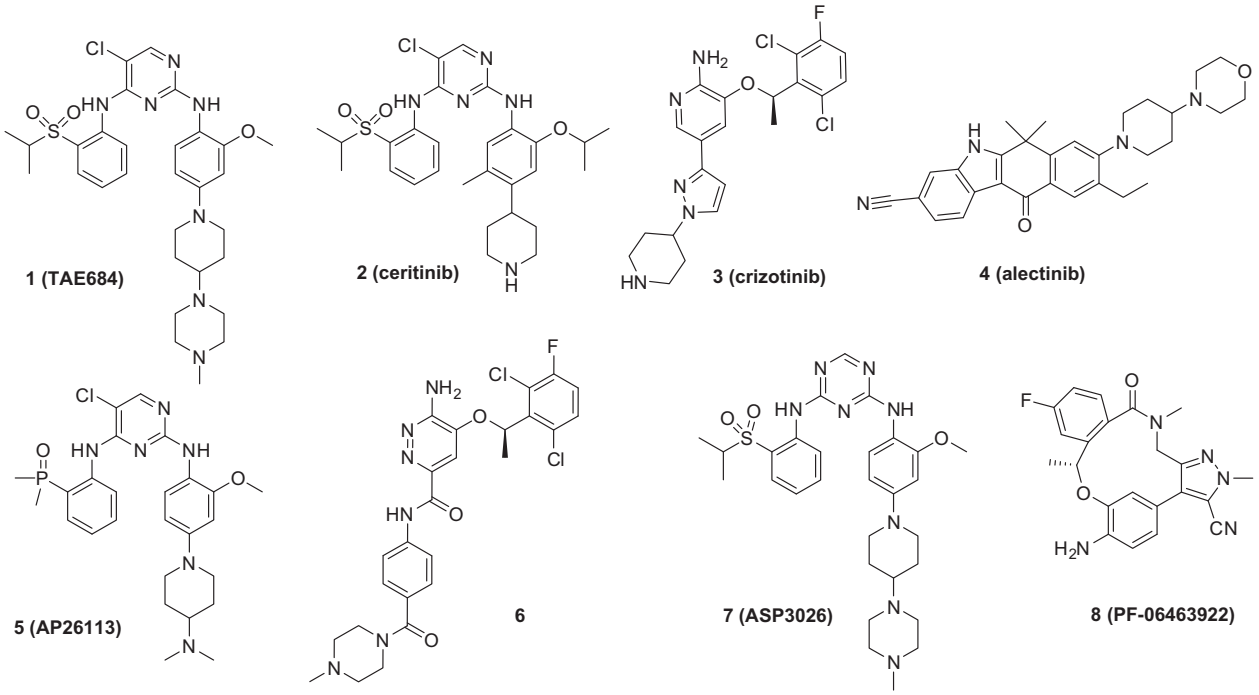

Figure 1. Selected examples of ALKi.

2 binds to the hinge of the ALK kinase via interactions of the N1 of the pyrimidine ring and N2 from the aniline bearing the solubilizing moiety.[26] As we described previously, docking of **2** in the ALK kinase domain revealed the aminopyrimidine making contact at the hinge with the Met_{1199} residue and was within reach of the carbonyl from the Glu_{1197} towards the gatekeeper region (Fig. 2). This conformation was confirmed later on when a co-crystal was obtained.[26] We postulated it was likely feasible to introduce an extra interaction with Glu_{1197} by a simple addition of a hydrogen donor in this region. This would result into a hinge binding moieties containing three donor–acceptor interactions instead of two in the pyrimidine case.

In the aim to conduct our studies (and further test our hypothesis), we decided to include some ring systems that lack the possibility to involve a third interaction at the hinge like a quinazoline (**F**) and a pyrimidopyrimidine (**G**) in addition to the 5,6-fused ring systems like a pyrrolopyrimidine (**A**), a purine (**B**), or a pyrrazolopyrimidine (**D**). The ring systems and the anilines **I1**-**I3** we used to make the final molecules are depicted in Figure 3.

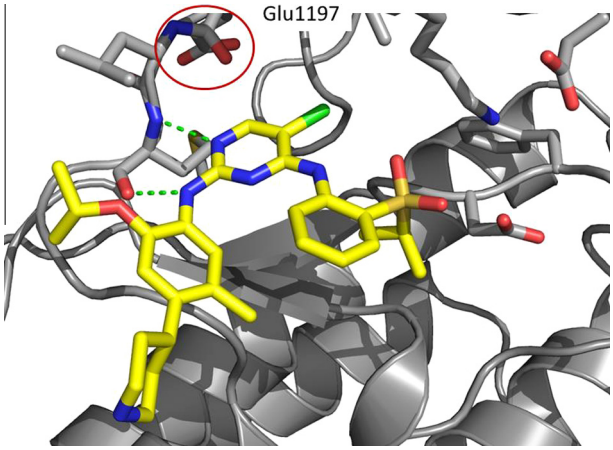

Figure 2. Co-crystal structure of **2** complexed with the ALK kinase domain depicting the proximity of Glu_{1197} to the pyrimidine ring forming interactions with Met_{1199} at the hinge moiety.[27]

The syntheses of the compounds described in this communication (**11a–e**, **12a–e**, **16a**,**b**, **20a**,**b**, **23**, **26**, **27**, **30a**,**b**, **31** and **32**) mirror the synthetic route we described for the synthesis of **2**[18] and are depicted in Schemes 1–4. For the sake of clarity, we have voluntarily restricted the analogs shown in this communication as ones bearing an unsubstituted piperidine (compounds **11a–e**, **16a**, **20a**, **31** and **32**) or *N*-Me-substituted piperidine ring (compounds **12a–e**, **16b**, **20b**, **23**, **26**, **27** and **30a**,**b**). Typically, we introduced the 2-(*iso*-propylsulfonyl)amino moiety first using simple amination conditions (usually, IPA, reflux) by condensation of **9a–e**, **14**, **17**, **21** and **28a–c** with 2-(*iso*-propylsulfonyl)aniline to afford **10a–e**, **15**, **18**, **22** and **29a–c** in moderate to excellent yields. In the case of compounds **11a–e**, **30a**,**b**, **29a–c** and **31** the synthesis was completed by a second amination reaction using selected proprietary aniline derivatives (**I1–I3**, Fig. 3) in moderate to good yields.[18,28] In the case of compounds **16a**,**b**, and **23**, an additional synthetic step was introduced on **19** and **22** in order to form the pyrrazolopyrimidine ring ($NH_2NH_2{\cdot}2HCl$, NaOAc, EtOH, 80 °C). For compounds **16a**, **26** and **27**, an additional deprotection step of the tosylate and carbamate groups was necessary to complete the synthesis. Further alkylation (typically, CH_3–I, Et_3N, DMF, MW, 100 °C, 10 min) of compounds **11a–e** afforded the derivatives **12a–e** in good yields (>70%). Reductive amination (HCHO, MeOH/THF, $NaBH_3CN$) of **16a** yielded compound **16b**. Compounds **26** and **27** required an inverted sequence of reactions in order to be synthesized (amination using 2-(*iso*-propylsulfonyl)aniline failed to produce the desired derivative, likely due to the lower reactivity of the aniline). Their synthesis was achieved by two sequential Buchwald couplings involving at first the aniline **I3** and at second the 2-(*iso*-propylsulfonyl)amino moiety. Finally, reduction of the pyridine ring (PtO_2, AcOH, TFA) of **31** yielded **32** in good yield.

As described in our previous communication,[18] ALK inhibition was directly measured in a cellular context by measuring the proliferation of Ba/F3 cells expressing NPM-ALK as a guide for our SAR.