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Structure guided optimization of a fragment hit to imidazopyridine inhibitors of PI3K

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ABSTRACT

PI3 kinases are a family of lipid kinases mediating numerous cell processes such as proliferation, migration and differentiation. The PI3 Kinase pathway is often de-regulated in cancer through PI3Kα overexpression, gene amplification, mutations and PTEN phosphatase deletion. PI3K inhibitors represent therefore an attractive therapeutic modality for cancer treatment. Herein we describe how the potency of a benzothiazole fragment hit was quickly improved based on structural information and how this early chemotype was further optimized through scaffold hopping. This effort led to the identification of a series of 2-acetamido-5-heteroaryl imidazopyridines showing potent in vitro activity against all class I PI3Ks and attractive pharmacokinetic properties.

Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid and serine/threonine kinases involved in a diverse set of cellular functions.[1] PI3Ks can be categorized in class I, II or III, depending on their subunit structure, regulation and substrate selectivity.[2] Class IA PI3Ks are heterodimers composed of a catalytic p110 subunit (α, β and δ isoforms) constitutively associated with a regulatory subunit that can be p85α, p55α, p50α, p85β or p55γ. The Class IB has one family member, a heterodimer composed of a catalytic p110γ subunit associated with one of two regulatory subunits, p101 or p84. Class IA PI3Ks are activated by tyrosine kinases while Class IB is activated by G protein-coupled receptors, therefore linking upstream receptors with downstream cellular activities including cell growth, proliferation, survival, chemotaxis, cellular trafficking, membrane ruffling and glucose homeostasis,[1] motility, metabolism, inflammatory and allergic responses, transcription and translation.[2,3] PI3Ks catalyze the transfer of phosphate to the D-3′ position of inositol lipids to produce phosphoinositol-3-phosphate (PIP), phosphoinositol-3,4-diphosphate (PIP_2) and phosphoinositol-3,4,5-triphosphate (PIP_3), second messengers in numerous signaling cascades.[4] In many cases, PIP_2 and PIP_3 recruit AKT to the plasma membrane where it acts as a nodal point for many intracellular signaling pathways important for growth and survival.[5,6] Aberrant regulation of PI3K, which often increases survival through AKT activation, is one of the most prevalent events in human cancer[7] and can occur at multiple levels.[8,9] In particular, p110α pathway deregulation has been demonstrated in ovarian, breast, colon and brain cancers.[10,11] These observations support the inhibition of Class I PI3 kinases as a potential treatment for a variety of tumor types and other proliferative diseases,[12,13] hence the interest during the last 10 years in generating suitable molecules to test this hypothesis in the clinic.[14,15,16,17,18]

In the course of our efforts to identify a backup series for our 2-morpholino pyrimidines front runners[19] and NVP-BKM120 (**1**, Fig. 1)[20] we conducted a second HTS campaign on an expanded compound collection and fragment library. Through this effort, several hits were identified and compound **2** (a fragment with MW = 250.2, Fig. 1) was selected for follow up. Compound **2** had reasonable potency against PI3Kα and good ligand efficiency (IC_{50} = 2.2 μM, LE = 0.47). It appeared to be approximately equipotent against the γ isoform and less potent against the β and δ isoforms, PI4K and VPS34.[21] We were therefore intrigued by the opportunity to explore this selectivity potential.

In silico profiling of **2** (PSA = 96, cLog*P* = 2.0, $logD_{7.4}$ = 1.5, 1 HBD, 3 HBA, good predicted passive permeability) did not show any significant alerts. One significant advantage in the follow up

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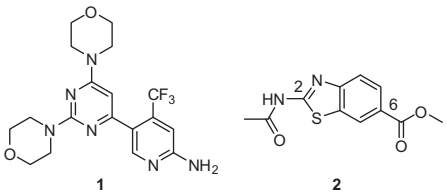


Figure 1. Clinical candidate **1** (NVP-BKM120) and benzothiazole fragment hit **2**.

was the availability of a co-crystal structure of **2** in p110γ obtained shortly after hit triaging.

Figure 2 shows an overlay of compound **2** with NVP-BKM120 (**1**, Fig. 1), the lead compound from the 2-morpholinopyrimidine series,[20] in a homology model of p110α. This model was generated based on the co-crystal structures of both compounds in p110γ[22].It is worth noting that the 2-acetamidobenzothiazole scaffold provides one additional contact with the hinge binding domain of the ATP binding site in comparison to the morpholine. The acetamide NH acts as a H bond donor and the benzothiazole N acts as a H bond acceptor with VAL851 backbone carbonyl and NH, respectively. The third hydrogen bond interaction is provided by the carbonyl of the ester substituent in the 6-position with the OH of TYR836. The benzothiazole spans two key regions of the active site (hinge domain and catalytic region) more efficiently than the 2-morpholinopyrimidine series, where the central pyrimidine ring has mainly a scaffolding function. The ester interaction is likely inefficient, but the 6-position of the benzothiazole provides a good vector for growth in the direction of the 'affinity pocket', accessing the same area of the binding site as the one occupied by the aminopyridine in the 2-morpholinopyrimidine series. This indicated the potential for hybridizing the two chemotypes.

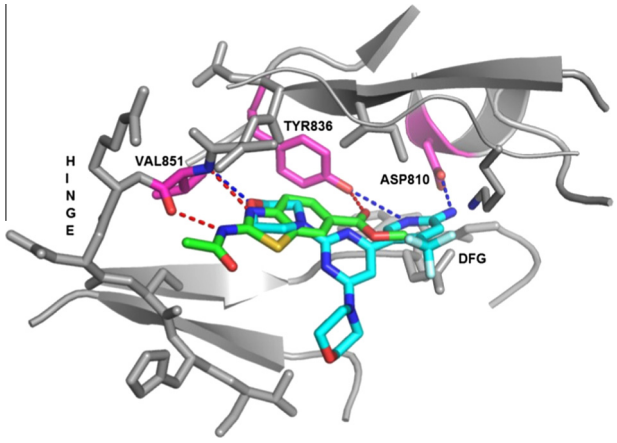
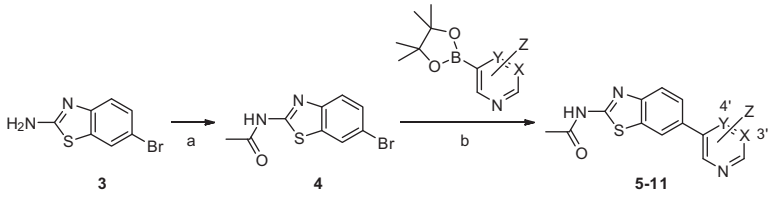


Figure 2. Model of compound **2** and NVP-BKM120 (**1**) in p110α.

We therefore proceeded to synthesize a series of benzothiazoles having six-membered rings at the 6-position. The analogs were easily obtained from commercially available 2-amino-6-bromo benzothiazole **3** by acetylation and Suzuki coupling with various heterocyclic boronic esters, either commercially available or synthesized as previously described[23] (Scheme 1). Some of the results obtained are summarized in Table 1.

Replacement of the ester in compound **2** with a 3-pyridyl (**5**) gave a 20-fold potency improvement in the biochemical assay, and showed some pathway modulation (IC_{50} for the inhibition of AKT phosphorylation on SER473 in the A2780 ovarian carcinoma cell line was 0.5 μM). Aminopyridine **6** maintained high Ligand Efficiency (LE = 0.5) and was almost 35-fold more potent than **2**. Consequently, mechanism modulation was enhanced to a level sufficient to observe a signal in our functional assay (inhibition of cell proliferation EC_{50} = 2.9 μM). Interestingly, aminopyrimidine **7** was comparable to **6**, indicating that the SAR was not tracking with the earlier 2-morpholinopyrimidine series, where 6-aminopyrimidine analogs were 50 to 100-fold more potent than the pyridines.[19] Furthermore, a CF_3 group in the 4′-position of **8**, the preferred position for substitution in the 2-morpholinopyrimidine series,[19,20] was not tolerated. On the other hand, various substituents were tolerated in the 3′-position (e.g, **9**–**11**). The 3′-CF_3 analog **9** was the most potent with almost 10-fold biochemical potency improvement compared to **6** and with a two- and seven-fold improvement in mechanism modulation and inhibition of cell proliferation, respectively. It is worth noting, however, that neither LE nor LLE (0.47 and 4.9) were improved for **9** compared to **6** (LLE = 4.8).

Thus, this hybridization approach led to the quick identification of novel, potent PI3Kα inhibitors. Potency against the other isoforms was also improved, and the series was not as selective as initially observed for compound **2** (e.g. PI3Kβ IC_{50} was 0.030 μM for **6**) but was still an interesting starting point for pan Class I PI3K inhibitors. Both compounds **6** and **9** had good microsomal stability and permeability, with low efflux potential in the Caco-2 assay.[24] The compounds were advanced to rat PK (Table 5) where they demonstrated oral exposure. However, based on our understanding of PK/PD efficacy relationship in this series, this exposure would not have sufficed for inhibiting tumor growth in our in vivo mouse xenograft model. In addition, low solubility (4.2 and 1.5 μM) and CYP450 inhibition (IC_{50} for 3A4 = 0.05 and 0.8 μM) were significant issues. To address solubility, we introduced basic amines in the 2-position (solvent exposed). Some of the results are shown in Table 2. We observed potency loss, but to a lesser extent when more than one carbon tether was introduced on the amide (compare **6** with **13**), and up to 80-fold improvement in solubility (**6** vs **14**). Tracking with the 2-acetamido series, the 3′-CF_3 aminopyridines were more potent than the unsubstituted aminopyridines (10 to 20-fold, **14** vs **13**). Morpholine was also used as solubilizing group (compound **15**), but was less effective. Due to lower efficiency (no potency improvement accompanied the increase in MW) and increased efflux potential (e.g. Caco-2 for compound **11** = A–B 6.7, B–A 18, B/A 2.7), this series was promptly abandoned.



Scheme 1. Synthesis of 6-heteroaryl substituted 2-acetamido benzothiazoles. Reagents and conditions: (a) Ac_2O, THF, rt; (b) 2 M Na_2CO_3, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, DME, microwave, 115 °C, 10 min.