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Identification of NVP-BKM120 as a Potent, Selective, Orally Bioavailable Class I PI3 Kinase Inhibitor for Treating Cancer

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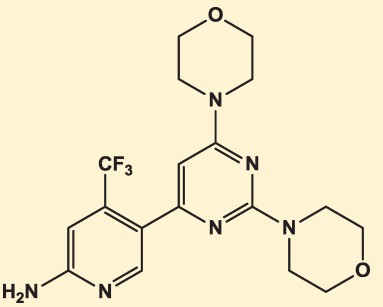
Supporting Information

ABSTRACT: Phosphoinositide-3-kinases (PI3Ks) are important oncology targets due to the deregulation of this signaling pathway in a wide variety of human cancers. Herein we describe the structure guided optimization of a series of 2-morpholino, 4-substituted, 6-heterocyclic pyrimidines where the pharmacokinetic properties were improved by modulating the electronics of the 6-position heterocycle, and the overall druglike properties were fine-tuned further by modification of the 4-position substituent. The resulting 2,4-bismorpholino 6-heterocyclic pyrimidines are potent class I PI3K inhibitors showing mechanism modulation in PI3K dependent cell lines and *in vivo* efficacy in tumor xenograft models with PI3K pathway deregulation (A2780 ovarian and U87MG glioma). These efforts culminated in the discovery of **15** (NVP-BKM120), currently in Phase II clinical trials for the treatment of cancer.



KEYWORDS: NVP-BKM120, phosphoinositide-3-kinase, PI3K/AKT3 pathway

The phosphoinositide-3-kinase (PI3K) family of lipid kinases is involved in a diverse set of cellular functions, including cell growth, proliferation, motility, differentiation, glucose transport, survival, intracellular trafficking, and membrane ruffling.[1] PI3K's can be categorized into class I, II, or III, depending on their subunit structure, regulation, and substrate selectivity.[2] Class IA PI3K's are activated by receptor tyrosine kinases and consist of a regulatory subunit (p85) and a catalytic subunit (p110). There are three catalytic isoforms: p110α, β, and δ. A single class IB PI3K, activated by GPCRs, consists of only one member: a p110γ catalytic subunit and a p101 regulatory subunit. The primary *in vivo* substrate of the class I PI3K's is phosphatidylinositol (4,5) diphosphate (PtdIns(4,5)P2), which upon phosphorylation at the 3-position of the inositol ring to form phosphatidylinositol triphosphate (3,4,5)P3 (PIP3) serves as a second messenger by activating a series of downstream effectors that mediate the cellular functions mentioned above. The PI3K isoforms have different distributions and share similar cellular functions, which are context dependent. In particular, p110α pathway deregulation has been demonstrated in ovarian, breast, colon, and brain cancers.[3,4] Inhibitors of PI3Kα represent an intriguing therapeutic modality for these indications, and as such, there is much interest in generating suitable molecules to test this hypothesis in the clinic.[5−10]

We have previously reported on a series of 6-hydroxyphenyl-2-morpholino pyrimidines,[11] as potent pan class I PI3K inhibitors that exhibit high selectivity toward protein kinases (serine/threonine and tyrosine kinases). We have further reported on non-phenol containing heterocyclic, morpholino pyrimidines[12] such as compound **1** which demonstrate *in vivo* PI3K pathway modulation and modest tumor growth inhibition. Described herein are our efforts to identify potent morpholino pyrimidinyl inhibitors of class I PI3Ks that exhibit potency and pharmacokinetic properties which allow for maximal pathway modulation *in vivo* and have druglike properties suitable for clinical development. These efforts culminated in the identification of **15**, NVP-BKM120.

Aminopyrimidine **1** and analogues such as **3** (Figure 1) exhibit low or sub-nanomolar biochemical potency and sub-micromolar cellular potency against PI3Kα. Even with high rodent CL values, such analogues can demonstrate PI3K pathway modulation in mouse xenograft models.[12] During our exploration of the C_6 position, it was noted that C_6 aminopyridine analogue **4**, while being less potent than **3** against PI3Kα (>10× potency loss), exhibited a markedly reduced (>9×) rat CL value, increased %F, and increased oral AUC. Thus, superior pharmacokinetic properties were achievable within this scaffold and the challenge remaining was to retain this kind of pharmacokinetic profile while optimizing all the other attributes (potency, solubility, permeability, safety) necessary for advancement. To address this challenge, the approach taken focused on modifying the electronic properties of the C_6

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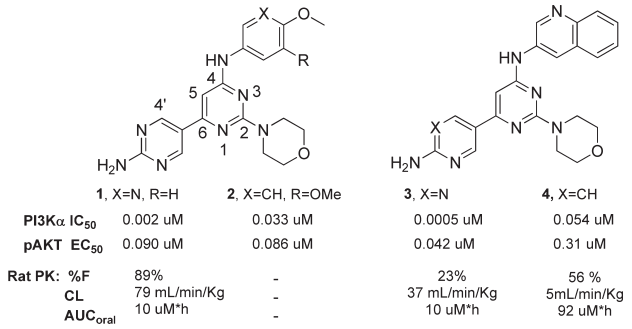

Figure 1. PI3Kα enzymatic potency and rat PK properties of 6-substituted, 4-(aminopyrid-3-yl), 2-morpholino pyrimidines.

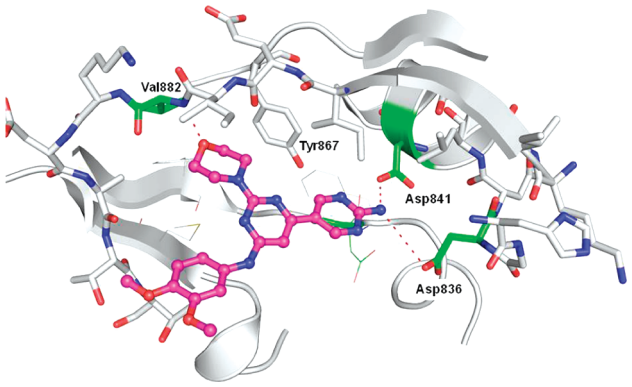

Figure 2. Structure of **2** in PI3Kγ.

aminopyridine and C_6 aminopyrimidine moieties. It was hypothesized that electron withdrawing substituents would improve potency in the aminopyridines.[13] In parallel, a series of substituted pyrimidines was surveyed, assessing the impact of substitution on PK.

To guide the C_6 aminoheterocycle modifications, we looked to the cocrystal structure of aminopyrimidine **2** (X = CH, R = OCH_3) in PI3Kγ to gain an understanding of the aminopyrimidine binding interactions.[14] Given the high homology between the α and γ isoforms and the nanomolar potency of **2** against the two isoforms,[15] p110γ was used as a surrogate for p110α. The cocrystal structure of **2** in the ATP binding site of PI3Kγ (Figure 2) indicates the key binding contacts being made by the aminopyrimidine as well as the morpholine group. The aminopyrimidine interacts *via* hydrogen bond interactions with Asp836, Asp841, and Tyr867. The C_4' position of the aminopyrimidine appears to provide a vector to a region of the active site where small groups would be tolerated. The morpholine oxygen forms a known hydrogen bond to the hinge Val882 NH.[16,17] The central pyrimidine C_4 substituent extends out toward solvent and does not appear to make any specific hydrogen bonds. These latter two features are consistent with earlier structures of morpholino pyrimidines.[11,12]

With this structural insight, our strategy to find optimal C_6 aminoheterocycles was to substitute the C_4' position of the C_6 aminopyrimidine or the C_4' position of the C_6 aminopyridine with small groups that could modulate the electronic properties of the heterocycle. Additionally, it was envisioned that the C_4' substitution would enforce the nonplanar conformation between the central pyrimidine and the C_6 heterocycle, which could disrupt intermolecular crystal packing and improve aqueous solubility. Finally, upon identification of preferred C_6 aminoheterocycles, further optimization at the central pyrimidine C_4 position to modulate druglike properties and maintain potency was anticipated, since the cocrystal structure indicated this position was partially solvent exposed and would tolerate a range of substituents.

C_4' modified, C_6 pyridyl or pyrimidyl substituted 2-morpholino 4-aminoquinolyl pyrimidines, synthesized as previously described,[12] were initially screened in biochemical PI3K assays, and compounds with PI3Kα IC_{50} values < 100 nM were tested in the A2780 ovarian carcinoma cell line (where the PI3K pathway is deregulated due to PTEN deletion) for inhibition of cell proliferation and phosphorylation of AKT^{Ser473} as target modulation readout.

The results of the C_4' modified, C_6 substituent survey (Table 1) indicate that the biochemical potency of the C_6 aminopyridine can be improved by introduction of an electron withdrawing group at the C_4' position, as is evident in the 3×, 12×, and 20× biochemical potency improvement in CF_3, CN, and Cl replacement of H. Additionally, substitution at the C_4' position of the aminopyridine does not compromise the rat PK properties, as the CL and AUC are minimally impacted with the CF_3 substitution, **7** vs **4**. In contrast to the trends in C_6 aminopyridines, substitution at the C_4' position of the C_6 aminopyrimidine does not markedly increase the enzymatic or cellular potency. However, substitution at the C_4' position of the C_6 aminopyrimidine can improve the PK properties, as is evident in **10**, where the rat CL is reduced 3-fold and oral AUC increased 3-fold relative to **3**.

While the biochemical and PK parameters can be improved with C_4' substitution on the C_6 aminoheterocycle, all compounds with the C_4 aminoquinoline exhibit low aqueous solubility, as well as low Caco-2 permeability.[18] The low solubility and permeability potentially could play a role in the lack of correlation between the biochemical potency and cellular activity. Additionally, this solubility range would not be sufficient for further development if concentrations in excess of the cell activity (0.1−1 μM) would need to be achieved *in vivo* for efficacy, as well as not sufficient to assess the safety profile of the compound.

With these considerations in mind, we further explored C_4 position SAR with the preferred C_4' substituted C_6 aminoheterocycles, to arrive at potent PI3K inhibitors with improved solubility. From earlier work[12] it was known that the C_4 position could tolerate a wide range of moieties. Additionally, it was known that a morpholine group at the C_4 position maintained reasonable potency while improving solubility relative to the aminoquinoline (compound **12**, Table 2). As such, compounds which contained the C_4 morpholine and the C_4' substituted C_6 aminopyridines or aminopyrimidines were prepared. The properties of these analogues are shown in Table 2.

All bis morpholino compounds demonstrate biochemical activity against PI3K in the nanomolar range, mechanism modulation <300 nM, and inhibition of cell proliferation approximately between 0.5 and 1.5 μM. Additionally, the solubility at pH 7 was markedly improved for all bis morpholino compounds (at least 10−1000×) relative to the C_4 aminoquinoline analogues. This increased solubility, along with the high permeability, *vide infra*, may account for the comparable cellular potency of the bismorpholino compounds in Table 2 relative to the more biochemically potent but less soluble aminoquinoline compounds in Table 1. The additional morpholine at the C_4 position did not compromise the rat PK parameters,[19] as, for both C_6 substituted aminopyridines as well as C_6 substituted aminopyrimidines in

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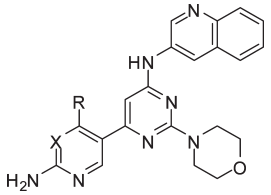
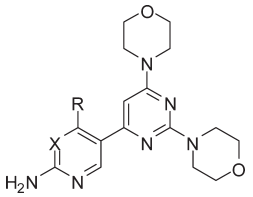
Table 1. Selected C_6 Aminopyridyl/Pyrimidyl Analogue SAR



entry	X	R	PI3Kα IC_{50}[a] (μM)	prolif EC_{50}[b] (μM)	pAKT^{Ser473} EC_{50}[b] (μM)	CL[c]	AUC[d]	V_{ss}[e]
3	N	H	<0.002 ± 0.004 (15)	0.146 ± 0.10 (6)	0.042 ± 0.01 (4)	37 ± 5.7	7 ± 2.6	1.9 ± 0.2
4	CH	H	0.11 ± 0.15 (16)	0.54 ± 0.19 (10)	0.31 ± 0.09 (3)	5 ± 0.8	92 ± 22	0.8 ± 0.1
5	CH	Cl	0.0024 ± 0.0004 (2)	0.28 ± 0.14 (4)	0.29			
6	CH	CN	0.0041 ± 0.0001 (2)	0.19 ± 0.05 (4)	1.3 ± 0.78 (2)			
7	CH	CF_3	0.021 ± 0.010 (9)	0.083 ± 0.24 (17)	0.45 ± 0.22 (7)	8 ± 0.3	114 ± 19	2.6 ± 0.4
8	N	NH_2	0.0026 ± 0.0001 (2)	0.17	0.18			
9	NH	O	0.0074 ± 0.0008 (2)	3.2 ± 1.2 (4)				
10	N	CF_3	0.0022 ± 0.002 (8)	0.58 ± 0.49 (12)	0.43 ± 0.11 (4)	11. ± 3 2	26 ± 3.4	2.8 ± 0.8
11	N	CH_3	0.008 ± 0.009 (8)	0.19 ± 0.11 (8)	0.09			

[a] ATP depletion assay; the value in parentheses is the number of replicates. [b] A2780 cell line. [c] Rat, IV, 5 mg/kg dose, mL/(min·kg). [d] Rat, oral, 20 mg/kg dose, μM·h. [e] Rat, IV, 5 mg/kg dose, L/kg.

Table 2. Selected 2,4-Bismorpholino Pyrimidyl Analogue SAR



entry	X	R	PI3Kα IC_{50}[a] (μM)	pAKT^{Ser473} EC_{50}[b] (μM)	prolif EC_{50}[b] (μM)	CL[c]	AUC[d]	V_{ss}[e]	%F	sol[f]
12	N	H	0.0184 ± 0.001 (2)	0.10	0.93 ± 0.11 (2)					25
13	CH	Cl	0.034 ± 0.006 (6)	0.11	1.77 ± 0.68 (4)	22 ± 5	29 ± 6	1.11 ± 0.7	69 ± 14	45
14	CH	CN	0.068 ± 0.014 (5)	0.10 ± 0.10 (3)	0.51 ± 0.48 (3)	11 ± 2	86 ± 5	1.6 ± 0.1	98 ± 6	11
15	CH	CF_3	0.030 ± 0.017 (24)	0.055 ± 0.02 (11)	0.52 ± 0.50 (30)	3 ± 0.4	178 ± 3	3.1 ± 0.4	50 ± 7	132
16	N	NH_2	0.023 ± 0.011 (10)	0.079 ± 0.03 (11)	1.46 ± 2.0 (33)	9 ± 0.1	64 ± 7	4.5 ± 0.9	68 ± 14	8
17	NH	O	0.015 ± 0.008 (8)	0.073 ± 0.01 (2)	0.68 ± 0.22 (4)	24 ± 4	24 ± 3	2.8 ± 1.2	56 ± 15	22
18	N	CF_3	0.014 ± 0.006 (14)	0.070 ± 0.03 (3)	0.45 ± 0.10 (3)	11 ± 2	62 ± 5	2.1 ± 0.2	83 ± 3	61

[a] ATP depletion assay; the value in parentheses is the number of replicates. [b] A2780 cell line. [c] Rat, IV,[19] mL/(min·kg). [d] Rat, oral,[19] μM·h. [e] Rat, IV,[19] L/kg. [f] Solubility at pH 7, μM

Table 2, low to moderate CL and moderate to high %F were observed. All bismorpholino compounds in Table 2 exhibit high stability in both rat and human liver microsomes, with $Cl_{int} \leq 9$ μL/min/mg in both species.

Compound **15** was of particular interest, as the solubility was the highest (170 μM on crystalline material) and it was among the most potent bismorpholine compounds in cell based assays (50 nM target modulation; 500 nM cell proliferation). Figure 3 shows the cocrystal structure of **15** in PI3Kγ.[20] The binding mode was as expected with one of the morpholines binding to the hinge at Val882 and the aminopyridine group interacting *via* hydrogen bonds to Asp836, Asp841, and Tyr867.

The biochemical activity of **15** was assessed across class I PI3K's, related lipid kinases, and against more than 200 protein kinases. Some of the data are shown in Table 3. Compound **15** exhibited 50−300 nM activity for class I PI3K's, including the most common p110α mutants. Additionally, **15** exhibited lower potency against class III and class IV PI3K's, where 2, 5, >5, and >25 μM biochemical activity was observed for inhibition of VPS34, mTOR, DNAPK, and PI4K, respectively. No significant activity was observed against the protein kinases tested.

In vitro evaluation of **15** across a range of PI3K deregulated cell lines from a variety of tumor types, including ovarian, glioblastoma, breast, and prostate, was conducted (Table 4). Across all cell lines, pathway modulation and antiproliferative activity was consistent with cellular PI3K inhibition.

The behavior consistent with selective *in vitro* inhibition of class I PI3K's translated to *in vivo* settings in two models of PI3K-AKT pathway driven cancers: the A2780 ovarian carcinoma and the U87MG glioma model, which carry a PTEN deletion. In A2780 xenograft tumors (Figure 4), oral dosing of **15** at 3, 10, 30, 60, and 100 mg/kg resulted in a dose dependent modulation of

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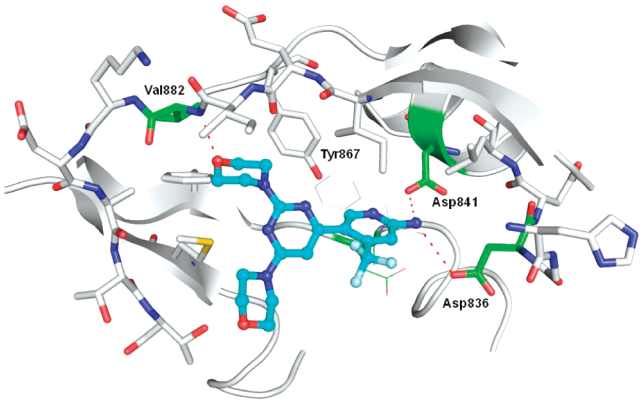

Figure 3. Structure of **15**, NVP-BKM120, in PI3Kγ.

Table 3. Biochemical Activity of 15, NVP-BKM120, against Class I, III, IV, PI3, and Related Kinases

class	enzyme	IC_{50} (μM)	enzyme	IC_{50} (μM)
Class I PI3K's[a]	p110α	0.052 ± 0.037	p110β	0.166 ± 0.029
	p110α−H1047R	0.058 ± 0.002	p110δ	0.116
	p110α−E545K	0.099 ± 0.006	p110γ	0.262 ± 0.094
Class III PI3K's[b]	VPS34	2.4 ± 1.5		
Class IV PI3K's	mTOR[c]	4.6 ± 1.9	DNAPK[d]	>5
PI4K[b]	PI4Kβ	>25		

[a] Filter binding assay. [b] ATP depletion assay. [c] TR-FRET assay. [d] Promega SignaTECT.

Table 4. Cellular Activity of 15 across Multiple Cell Lines with PI3K Pathway Deregulation

cell line	genotype	$pAKT^{Ser473}$ EC_{50} (μM)	GI_{50} (nM)
A2780	PTEN del	0.074	0.635
U87MG	PTEN del	0.13	0.698
MCF7	E545K−PIK3CA	<0.100	0.158
DU145	LKB1 mutant	0.073	0.435

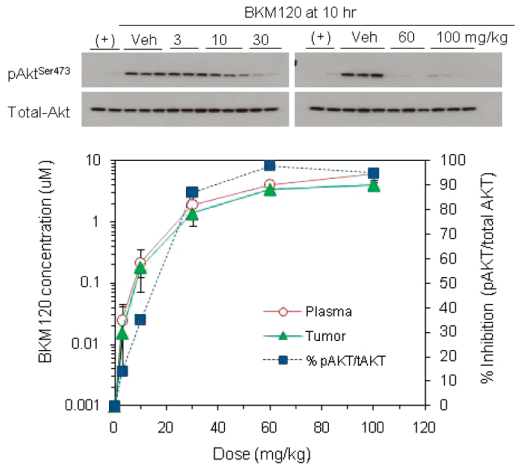

Figure 4. $pAKT^{ser473}$ inhibition and plasma exposure of **15**, NVP-BKM120, in an A2780 xenograft model.

$pAKT^{Ser473}$. Partial inhibition of $pAKT^{ser473}$ was observed at 3 and 10 mg/kg, and near complete inhibition was observed at

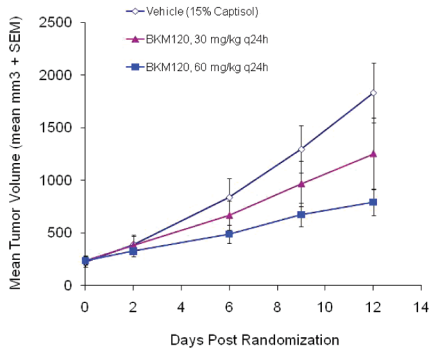

Figure 5. Efficacy of compound **15**, NVP-BKM120, in an A2780 xenograft model.

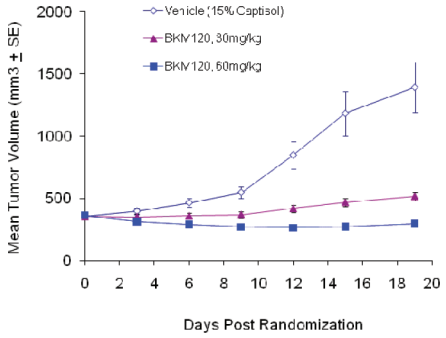

Figure 6. Antitumor activity of **15**, NVP-BKM120, against the subcutaneous U87MG glioma tumor model.

doses of 30, 60, or 100 mg/kg, respectively. Inhibition of pAKT (normalized to total AKT) tracked well with both plasma and tumor drug exposure. pAKT modulation was also time dependent, with >90% target modulation achieved with the 60 and 100 mg/kg dose at the 10 h time point when the plasma and tumor exposure was ca. 2 μM.[21]

Consistent with the mechanism modulation observed, significant tumor growth inhibition was obtained in the A2780 tumor model at 60 mg/kg upon multiple dosing (Figure 5). Efficacy was associated with significant inhibition of the PI3K pathway, as assessed by reduction in $pAkt^{Ser473}$, for up to 16 h.

As was the case *in vitro*, **15** displays *in vivo* activity across a range of PI3K pathway deregulated tumor xenograft models.[22] In the established U87MG glioma model, significant single agent activity was obtained with **15** at daily oral doses of 30 and 60 mg/kg (Figure 6) in a well tolerated manner.[23] This activity in the U87MG model, coupled with the high permeability and lack of efflux exhibited by **15**,[24] suggests that **15** may have utility in PI3K-driven gliomas.

With these encouraging rodent pharmacology activities, compound **15** was studied further. Profiling indicated that **15** exhibited no reversible or time dependent CYP450 (3A4, 2C9, 2D6) inhibition up to 50 μM or CYP3A4 induction up to 25 μM, exhibited high permeability with no propensity for efflux,[23] demonstrated no cardiotoxicity potential,[25] and showed a clean profile (>10 μM) against enzymes, receptors, and transporters included in internal safety and the external MDS Pharma Services panels. The melting point of **15** is 153 °C, its log *D* (pH 7.4) is 2.9, and its pK_a is 5.1. The synthesis of **15** is straightforward, proceeding in four steps for the research route (Scheme 1).

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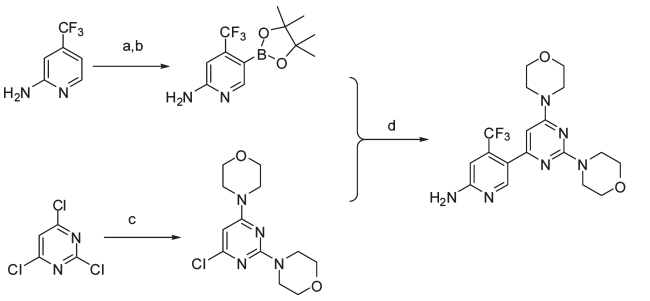
Scheme 1. Synthesis of 15



a. NBS, CH_2Cl_2, 80%; b. bispinacolatodiboron, Pd(dppf)$_2$Cl$_2$DCM, KOAc, 48%; c. morpoline, DIEA, EtOH, 80%; d. Pd(dppf)$_2$Cl$_2$DCM, DME, 2N Na_2CO_3, 95 °C, 15h, 95%

Table 5. PK Properties of 15 across Species[26]

	IV			PO
species	$t_{1/2}$[a]	CL[b]	V_{ss}[c]	%F
mouse	1.6	11	1.4	71−89
rat	11	3 ± 0.4	3.1 ± 0.4	50
dog	6.6 ± 0.8	7.3 ± 1.5	3.1 ± 0.4	>100
monkey	3.6	13	3.1	44

[a] Units of hour. [b] Units of mL/(min kg). [c] Units of L/kg.

The pharmacokinetic properties of **15** were evaluated across multiple species (Table 5). Low to moderate CL was observed for **15** across species, as CL values of 11, 3, 13, and 7 mL/(min kg) were observed in mouse, rat, dog, and monkey, respectively. Additionally, **15** exhibited medium to high oral bioavailability across species as 80%, 50%, 44%, and 100% was observed in mouse, rat, dog, and monkey, respectively.

With the favorable cellular potency, kinase selectivity, preclinical pharmacology, rodent, dog, and monkey pharmacokinetics, physical properties, and preclinical safety profile, **15** was advanced into clinical trials in 2008 and has since shown clinical activity in patients with cancer.[27] Specifically promising activity has been observed in those patients with an activated PI3K pathway.[28]

In summary, we have described the structure guided optimization of a series of 6-aminoheterocyclic, 4-substituted, 2-morpholino pyrimidines which exhibited high CL and low aqueous solubility into a compound suitable for clinical development. Modification of the aminoheterocycle with small groups that modulated the ring electronics either improved potency or reduced the *in vivo* CL values. Incorporation of a morpholine group at the C_4 central pyrimidine position increased the aqueous solubility while retaining sufficient potency, selectivity, and favorable *in vivo* properties. The combination of these modifications led to the discovery of a series of substituted 6-aminoheterocyclic, 2,4-bismorpholino pyrimidines. From this series, compound **15** (NVP-BKM120) has advanced into humans and is currently being assessed in phase II trials.[29]

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for the synthesis and characterization of all compounds, biological assay, and pharmacology model procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS

PI3K, phosphoinositide-3-kinase; DNAPK, DNA dependent protein kinase; PI4K, 1-phosphatidylinositol-4-kinase; mTOR, mammalian target of rapamycin; PTEN, phosphatase and tensin homologue; NBS, *N*-bromosuccinimide; DIEA, diisopropylethylamine; Pd(dppf)Cl_2-DCM, dichloro[1,1′-bis(diphenylphosphino)-ferrocene] palladium(II) dichloromethane adduct; DIEA, diisopropylethylamine; DME, dimethoxyethane; CYP, cytochrome P450; CL, clearance; PK, pharmacokinetics

■ REFERENCES

(1) Engelman, J. A.; Luo, J.; Cantley, L. C. The Evolution of Phosphatidylinositol 3-Kinases as Regulators of Growth and Metabolism. *Nat. Rev. Genet.* **2006**, *7*, 606–619.

(2) Katso, R.; Okkenhaug, K.; Ahmadi, K.; White, S.; Timms, J.; et al. Cellular Function of Phosphoinositide 3-Kinases: Implications for Development, Homeostasis and Cancer. *Annu. Rev. Cell Dev. Biol.* **2000**, *17*, 615–675.

(3) Samuels, Y.; Wang, Z.; Bardelli, A.; Silliman, N.; Ptak, J.; Szabo, S.; Yan, H.; Gasdar, A.; Powell, S. M.; Riggins, G. J.; Willson, J. K.; Markowitz, S.; Kinzler, K. W.; Vogelstein, B.; Velculescu, V. E. High Frequency of Mutations of the PIK3CA Gene in Human Cancers. *Science* **2004**, *304*, 554.

(4) Leslie, N. R.; Downes, C. P. PTEN Function: How Normal Cells Control it and Tumour Cells Lose it. *Biochem. J.* **2004**, *382*, 1–11.

(5) Liu, P.; Cheng, H.; Roberts, T. M.; Zhao, J. J. Targeting the Phosphoinositide 3-Kinase Pathway in Cancer. *Nat. Rev. Drug Discovery* **2009**, *8*, 627–644.

(6) Nuss, J. M.; Tsuhako, A. L.; Anand, N. K. Emerging Therapies Based on Inhibitors of Phosphatidyl-Inositol-3-Kinases. In *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: Oxford, 2009; Vol. 44, pp 339−351.

(7) Maira, S.-M.; Stauffer, F.; Brueggen, J.; Furet, P.; Schnell, C.; Fritsch, C.; Brachmann, S.; Chene, P.; De Pover, A.; Schoemaker, K.; Fabbro, D.; Gabriel, D.; Simonen, M.; Murphy, L.; Finan, P.; Sellers, W.; Garcia-Echeverria, C. Identification and Characterization of NVP-BEZ235, a New Orally Available Dual Phosphatidylinositol 3-kinase/Mammalian Target of Rapamycin Inhibitor with Potent in Vivo Antitumor Activity. *Mol. Cancer Ther.* **2008**, *7*, 1851–1863.

(8) Folkes, A. J.; Ahmadi, K.; Alderton, W. K.; Alix, S.; Baker, S. J.; Box, G.; Chuckowree, I. S.; Clarke, P. A.; Depledge, P.; Eccles, S. A.; Friedman, L. S.; Hayes, A.; Hancox, T. C.; Kugendradas, A.; Lensun, L.; Moore, P.; Olivero, A. G.; Pang, J.; Patel, S.; Pergl-Wilson, G. H.; Raynaud, F. I.; Robson, A.; Saghir, N.; Salphati, L.; Sohal, S.; Ultsch, M. H.; Valenti, M.; Wallweber, H. J. A.; Wan, N. C.; Wiesmann, C.; Workman, P.; Zhyvoloup, A.; Zvelebil, M. J.; Shuttleworth, S. J. The Identification of 2-(1H-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine (GDC-0941) as

a Potent, Selective, Orally Bioavailable Inhibitor of Class I PI3 Kinase for the Treatment of Cancer. *J. Med. Chem.* **2008**, *51*, 5522–5532.

(9) Knight, S. D.; Adams, N. D.; Burgess, J. L.; Chaudhari, A. M.; Darcy, M. G.; Donatelli, C. A.; Luengo, J. E.; Newlander, K. A.; Parrish, C. A.; Ridgers, L. H.; Sarpong, M. A.; Schmidt, S. J.; Van Aller, G. S.; Carson, J. D.; Diamond, M. A.; Elkins, P. A.; Gardiner, C. M.; Garver, E.; Gilbert, S. A.; Gontarek, R. R.; Jackson, J. R.; Kershner, K. L.; Luo, L.; Raha, K.; Sherk, C. S.; Sung, C. M.; Sutton, D.; Tummino, P. J.; Wegrzyn, R. J.; Auger, K. R.; Dhanak, D. Discovery of GSK2126458, a Highly Potent Inhibitor of PI3K and the Mammalian Target of Rapamycin. *ACS Med. Chem. Lett.* **2010**, *1*, 39–43.

(10) Courtney, K. D.; Corcoran, R. B.; Engelman, J. A. The PI3K Pathway as Drug Target in Human Cancer. *J. Clin. Oncol.* **2010**, *28*, 1075–1083.

(11) Pecchi, S.; Renhowe, P. A.; Taylor, C.; Kaufman, S.; Merrit, H.; Wiesmann, M.; Shoemaker, K.; Knapp, M. S.; Hendrickson, T. F.; Fantl, W.; Voliva, C. F. Identification and Structure-Activity Relationship of 2-Morpholino 6-(3-hydroxyphenyl)pyrimidines, a Class of Potent and Selective PI3-kinase Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6895–6898.

(12) Burger, M. T.; Knapp, M.; Wagman, A.; Ni, Z. J.; Hendrickson, T.; Atallah, G.; Zhang, Y.; Frazier, K.; Verhagen, J.; Pfister, K.; Ng, S.; Smith, A.; Bartulis, S.; Merrit, H.; Wiesmann, M.; Xin, X.; Haznedar, J.; Voliva, C. F.; Iwanowicz, E.; Pecchi, S. Synthesis and in Vitro and in Vivo Evaluation of Phosphoinositide-3-kinase Inhibitors. *ACS Med. Chem. Lett.* **2011**, *2*, 34–38.

(13) By mimicking the electronics and H bond donating capabilities of the aminopyrimidines. see:Mautner, M. Models for Strong Interactions in Proteins and Enzymes. 1. Enhanced Acidities of Principal Biological Hydrogen Donors. *J. Am. Chem. Soc.* **1988**, *110*, 3071–3075.

(14) Structure of **2** in PI3Kγ submitted under PDB accession code 3JTP.

(15) For **2**, PI3Kα and γ IC_{50} values = 0.003 and 0.142 μM.

(16) Walker, E. H.; Pacold, M. E.; Perisic, O.; Stephens, L.; Hawkins, P. T.; Wymann, M. P.; Roger, L. Structural Determinants of Phosphoinositide-3-Kinase Inhibition by Wortmannin, LY294002, Quercetin, Myricetin and Staurosporine. *Mol. Cell* **2000**, *6*, 909–919.

(17) Knight, Z. A.; Chiang, G. G.; Alaimo, P. G.; Kenski, D. M.; Ho, C. B.; Coan, K.; Abraham, R. T.; Shokat, K. M. Isoform Specific Phosphoinositide-3-Kinase Inhibitors from an Arylmorpholine Scaffold. *Bioorg. Med. Chem.* **2004**, *12*, 4749–4759.

(18) Compound **7** has a solubility of 0.3 μg/mL, while its permeability in the Caco-2 assay is $P_{appA\text{-}B}$ (cm/s $\times 10^{-6}$) = 1.56 and $P_{appA\text{-}B}$ (cm/s $\times 10^{-6}$) = 2.15.

(19) 5 mg/kg IV dose and 20 mg/kg oral dose for all compounds except **16**, which was dosed 5 mg/kg IV and 10 mg/kg orally.

(20) Structure of **15** in PI3Kγ submitted under PDB accession code 3SD5.

(21) With >95% mouse plasma protein binding, the free plasma concentrations required for *in vivo* target modulation correlated with the cellular activity.

(22) "NVP-BKM120, a novel inhibitor of phosphoinositide 3-kinase in Phase I/II clinical trials, shows significant antitumor activity in xenograft models". Maira, M.; Menezes, D.; Pecchi, S.; Shoemaker, K.; Burger, M.; Schnell, C.; Fritsch, C.; Brachmann, S.; Nagel, T.; Sellers, W. R.; Garcia-Echeverria, C.; Wiesmann, M.; Voliva, C. F. 2010 AACR annual meeting, Washington, D.C., Abstract 4497.

(23) Female nude mice (6−8 weeks of age from Charles River) were implanted with 5×10^6 U87MG cells (in 0.2 mL 50% matrigel) s.c. into the right flank. Mice were randomized when tumors reached a mean size of 350 mm^3 (n = 12/group) and were treated with either vehicle or BKM120 at 30 or 60 mg/kg, q.d. Body weights are included in the Supporting Information for both A2780 and U87MG efficacy studies.

(24) $P_{appA\text{-}B}$ (cm/s $\times 10^{-6}$) = 42, $P_{appB\text{-}A}$ (cm/s $\times 10^{-6}$) = 21.

(25) Dofetilide binding IC_{50} > 30 μM; no significant findings in isolated rabbit heart model and dog telemetry.

(26) Mouse PK (female CD1 mice, 5 mg/kg IV, 10 mg/kg PO), rat PK (female CD rats, 5 mg/kg IV, 20 mg/kg PO), dog PK (male and female beagles, 1 mg/kg IV, 2 mg/kg PO), monkey PK (male cynomolgus monkeys, 1 mg/kg IV, 2 mg/kg PO).

(27) "Oral Pan-Class I PI3K Inhibitor BKM120 Monotherapy in Patients with Advanced Solid Tumors: an Update on Safety and Efficacy". Graña-Suárez, B.; Burris, H. A.; Anhert, J. R.; Abdul Razak, A. R.; De Jonge, M. J.; Eskens, F.; Siu, L. L.; Ru, Q. C.; Homji, N. F.; Demanse, D.; Di Tomaso, E.; Cosaert, J.; Quadt, C.; Baselga, J.; Bendell, J. C. 47th ASCO Annual Meeting, June 2001, Chicago, IL, Abstract 3043.

(28) Novartis internal data.

(29) www.clinicaltrials.gov and NVP-BKM120.