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Indolinone based phosphoinositide-dependent kinase-1 (PDK1) inhibitors. Part 1: Design, synthesis and biological activity

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Abstract—HTS screening identified **1** with micromolar inhibitory activity against PDK1. Optimization of **1** afforded **4i (BX-517)** which has single-digit nanomolar activity against PDK1 and excellent selectivity against PKA.

Protein kinases are critical regulators of cellular processes in normal tissues and disease. A number of small molecule kinase inhibitors such as Iressa, Gleevec, and Sorafenib have been approved for the treatment of cancer. Compounds targeting other kinases are in development.[1] One promising protein kinase target for the development of new cancer drugs is phosphoinositide-dependent kinase-1 (PDK1). PDK1 is required for the activation of Akt, which plays a key role in processes such as tumor cell growth, protection from apoptosis, stimulation of epithelial to mesenchymal transition (EMT), and tumor angiogenesis.[2] The Akt family of Ser/Thr protein kinases is comprised of three highly homologous members (AKT1, AKT2, and AKT3), all of which require PDK1 for activation. PDK1 activates Akt by phosphorylating its activation loop (e.g., on residue Thr 308 of AKT1), which initiates a conformational change to the active protein.[3]

Numerous studies demonstrate that Akt is highly activated in many common tumor types, including melanoma and breast, lung, gastric, prostate, hematological, and ovarian cancers. Activation of Akt by PDK1 is promoted by phosphoinositide 3-kinase (PI3K) activity in cells, resulting in the production of PtdIns-3,4-P_2 or PtdIns-3,4,5-P_3 that recruit Akt and PDK1 to the plasma membrane through interaction with their pleckstrin homology domains.[4] PI3K and Akt activity become highly elevated in many tumors through the up-regulation or mutation of upstream signaling molecules such as EGF receptors, Ras, Src, and c-ABL, or by over-expression of PI3K itself.[2a–c] Loss of the tumor suppressor PTEN/MMAC1, which negatively regulates PI3K activity, is also a common mechanism of Akt activation in tumor cells.[5]

In addition to Akt, PDK1 has been shown to be a critical activator of other kinases in the AGC kinase superfamily that are important promoters of cancer progression, including protein kinase C (PKC), serum and glucocorticoid-regulated kinase (SGK), and p70 ribosomal S6 kinase (S6K1).[2] These kinases have a homologous region in their activation loops containing a consensus substrate recognition site for PDK1.[6]

The role of PDK1 in several distinct signaling pathways that are important for tumor progression provides further rationale for the development of small molecule PDK1 inhibitors as anticancer drugs. Previously, we reported on the discovery and characterization of aminopyrimidines with potent inhibitory activity against PDK1.[7] Several additional reports of small molecule Akt inhibitors have also appeared in the literature.[8]

High-throughput screening using a PDK1 mediated AKT2 activation assay (cAKT2[9]) identified **1** as a 1.8 μM inhibitor (Fig. 1). This assay can identify inhibitors of Akt activation as well as inhibitors of AKT2 or

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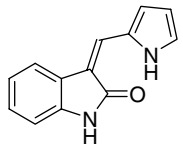


1
IC_{50} cAKT = 2.3 μM
IC_{50} PDK1 = 0.52 μM
IC_{50} P-AKT PC-3 ~ 32 μM
IC_{50} PKA = 16 μM

Figure 1. Biological activity of **1**.

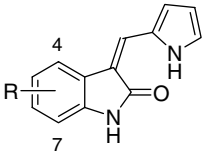
PDK1 activity. Further testing determined that **1** blocks PDK1 kinase activity[10] and inhibits the activation of Akt in tumor cells in vitro.[7,11] Compound **1** was previously reported to be an inhibitor of VEGF receptors,[12] CDK4,[13] and other kinases.[14] We found that **1** also inhibits PKA although with 9-fold less potency. Due to the close homology of PKA with PDK1, PKA was used as an initial measure of kinase selectivity. The goal was to achieve 50-fold selectivity or higher. Herein we disclose the optimization of **1**, leading to **4i (BX-517)**, a potent and selective inhibitor of PDK1.[15]

The compounds in Tables 1–4 were synthesized by condensation of indolinones **5** and pyrroles **6** as shown in Scheme 1 affording exclusively the *Z*-isomer as shown.[12] The reaction with aldehydes was facile; however, the reaction with ketones required more drastic conditions. Indolinones **5** and pyrroles **6** are commercially available or were prepared according to the literature.[16]

The cyano (**3h**) and nitro (**7**) analogs were further elaborated as shown in Scheme 2. The cyano analog was converted to the tetrazole (**3f**) analog under standard reaction conditions. The amino analog (**8**) was reacted with methanesulfonyl chloride to afford sulfonamide **3j** or with trimethylsilyl isocyanate to afford the urea analogs (**3l**, **4i**–**l**).

To guide the optimization, a model of **1** bound to PDK1 was built. The model was based on an X-ray structure of

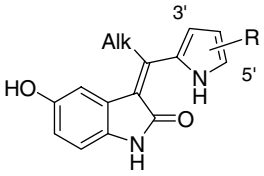
Table 1. PDK1 activity of methyl and hydroxyl analogs on the indolinone ring



Compound	R	cAKT2 IC_{50}[a] (nM)
1	H	1800
1a	4-Me	510
1b	5-Me	2700
1c	7-Me	>26,000
1d	4-OH	1000
1e	5-OH	340
1f	6-OH	900
1g	7-OH	>26,000

[a] Values are means of multiple experiments ($n \geqslant 2$), standard deviation is <30% of the mean.

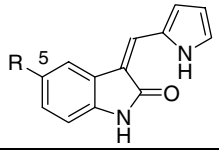
Table 2. PDK1 activity of methyl analogs on the pyrrole ring and alkene



Compound	Alk	R	cAKT2 IC_{50}[a] (nM)
1e	H	H	340
2a	Me	H	80
2b	H	3′-Me	280
2c	H	4′-Me	280
2d	H	5′-Me	680
2e	H	5′-Et	2300
2f	H	3′,5′-Me	1100

[a] Values are means of multiple experiments ($n \geqslant 2$), standard deviation is <30% of the mean.

Table 3. PDK1 activity of analogs substituted at the 5-position of the indolinone ring



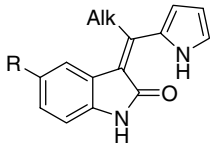
Compound	R	cAKT2 IC_{50}[a] (nM)
1e	OH	340
3a	OMe	580
3b	SO_2NH_2	290
3c	CO_2Me	670
3d	CO_2H	260
3e	$CONH_2$	120
3f	5-Tetrazole	200
3g	NH_2	580
3h	CN	990
3i	CH_2NH_2	1000
3j	$NHSO_2Me$	530
3k	NHCOMe	55
3l	$NHCONH_2$	18

[a] Values are means of multiple experiments ($n \geqslant 2$), standard deviation is <30% of the mean.

1 bound to a related Ser/Thr kinase. The model predicts that the indolinone amide and pyrrole interact with the hinge region of PDK1 similar to the binding conformation of other indolinone based inhibitors bound to other kinases.[17] Based on the predicted binding conformation, substitution on the 7-position of the indolinone or the 5′-position of the pyrrole should be disfavored for steric reasons. Substitution on the 5- or 6-position of the indolinone could lead to interaction with Lys 111 and/or Thr 222. Substitution on the 4-position of the indolinone, the alkene, or the 3′- or 4′-position of the pyrrole could lead to interaction with Glu 166.

Initially, methyl and hydroxyl groups were placed on different positions of **1** to identify sites amenable to substitution. The results for the indolinone ring are shown in Table 1. Substitution at the 7-position was not tolerated (**1c** and **1g**). Methyl substitution on the 4-position

Table 4. PDK1 activity of alkene analogs



Compound	R	Alk	cAKT2 IC_{50}[a] (nM)
3b	SO_2NH_2	H	290
4a	SO_2NH_2	Me	67
4b	SO_2NH_2	Et	14
4c	SO_2NH_2	Ph	29
4d	SO_2NH_2	CO_2Et	34
4e	SO_2NH_2	CO_2H	4200
4f	SO_2NH_2	$CONH_2$	3900
4g	SO_2NH_2	CONHEt	6100
4h	SO_2NH_2	$CONEt_2$	5400
3l	$NHCONH_2$	H	18
4i	$NHCONH_2$	Me	5
4j	$NHCONH_2$	Et	3
4k	$NHCONH_2$	Ph-3–NH_2	9
4l	$NHCONH_2$	4-Pyridine	10

[a] Values are means of multiple experiments ($n \geqslant 2$), standard deviation is <30% of the mean.

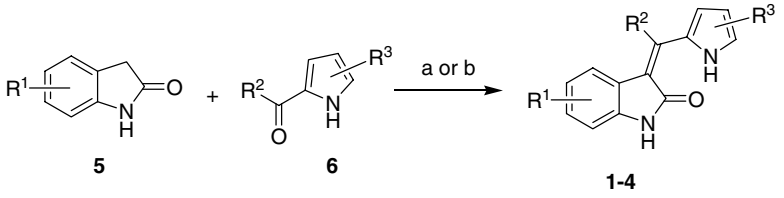
improved potency ca. 4-fold (**1a**). Hydroxyl substitution on the 5-position improved potency 5-fold while substitution on the 6-position had little effect (**1e** and **1f**). These data support the predictions based on the model.

The results for the alkene and pyrrole ring are shown in Table 2. In this case, the study was conducted on the more potent 5-hydroxy analog **1e**. Methyl substitution on the alkene improved potency 4-fold (**2a** vs **1e**). Substitution on the pyrrole 3′- or 4′-position was tolerated (**2b** and **2c**). Methyl substitution on the 5′-position reduced potency somewhat; however, ethyl substitution or 3′, 5′-dimethyl substitution reduced potency more significantly (**2d–f**).

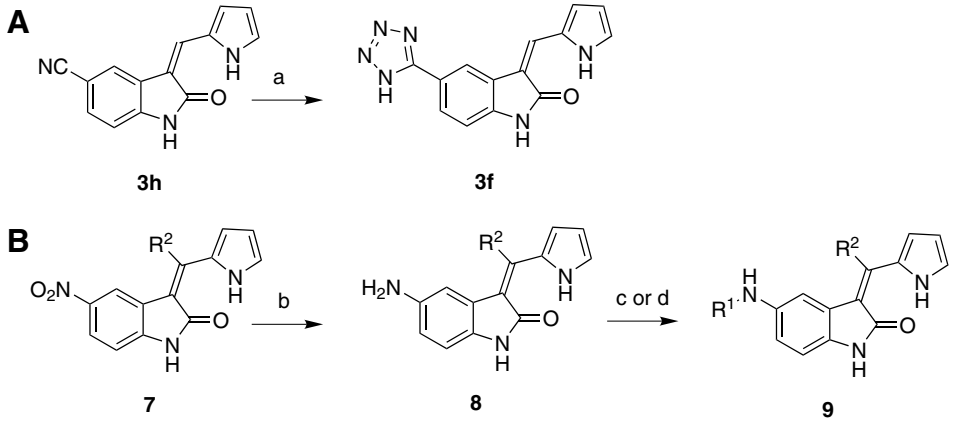
Based on the model of **1** bound to PDK1 the 5-hydroxyl group of **2a** could interact with Lys 111 and/or Thr 222. In order to optimize this interaction, a series of inhibitors with varied substitution at the 5-position were prepared. The results are shown in Table 3.

Three analogs were more potent than **1e**. The amide (**3e**) was 3-fold more potent, the acetamide (**3k**) 6-fold, and the urea (**3l**) 19-fold. The amide, acetamide, and urea analogs have a carbonyl that can interact with the side-chains of Lys 111 and Thr 222. Based on the relative potency of these three analogs, it appears that the optimal position of the carbonyl is on the second atom from the indolinone core. With the exception of the cyano (**3h**) and aminomethyl (**3i**) analogs, the remaining analogs were equipotent with **1e**. The binding pocket for the substituents on the 5-position appears to be highly accommodating since none of the analogs is more than 3-fold less potent than **1e**. This is not surprising since the indolinone inhibitors bind into the same channel as ATP. Substituents on the 5-position of the indolinone should roughly occupy the same space as the phosphate tail of ATP.[17]

Several analogs with either sulfonamide or urea on the 5-position of the indolinone ring were prepared investigating substitution on the alkene. The results are shown in Table 4. In the sulfonamide series, methyl substitution improved potency 4-fold (**4a** vs **3b**).

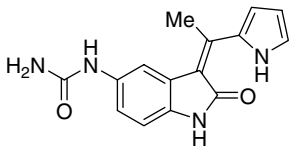


Scheme 1. Synthesis of indolinones **1–4**. Reagents and conditions: (a) pyrrolidine, EtOH, 60 °C (11–68%); (b) cat. piperidine, 130 °C (3–45%).



Scheme 2. Elaboration of cyano and nitro analogs. Reagents and condition: (a) Bu_3SnCl, NaN_3, toluene, reflux (25%); (b) Pd/C, MeOH, H_2 (40 PSI, 85%); (c) $MeSO_2Cl$, satd $NaHCO_3$, THF (7%); (d) TMSN=C=O, THF (89%).

Table 5. Properties of **4i**



4i

Assays	IC_{50} (nM)	ADME
cAKT2[8]	5[a]	Sol. PBS[c] 2 mg/L
PDK1[9]	6[a]	$t_{1/2}$[d] 24 min
P-AKT PC-3[10]	100–1000[b]	Cl[d] 31 mL/min/kg
PKA[a]	1600	%F[e] <1%

[a] Values are means of multiple experiments ($n \geqslant 2$), standard deviation is <30% of the mean.
[b] Determined from 10 experiments.
[c] Determined from 1 experiment.
[d] Dosed 2 mg/kg iv in three rats.
[e] Dosed 10 mg/kg po in three rats.

Ethyl was 4-fold more potent than methyl (**4b** vs **4a**), while phenyl (**4c**) and carboethoxy (**4d**) showed no improvement over methyl. The acid (**4e**) and the amide (**4f–h**) analogs were much less potent. Modeling suggests that the poor potency of the acid analog (**4e**) may be due to a negative interaction with Glu 166. For the amide analogs (**4f–h**), the poor potency may be due to steric interactions between the substituents on the amide and the 4-proton of the indolinone and the 3′-proton of the pyrrole. In the urea series, methyl substitution improved potency 4-fold affording single-digit nanomolar activity (**4i** vs **3l**). Unlike the sulfonamide series, ethyl (**4j**) did not improve potency further. Aniline (**4k**) and pyridyl (**4l**) analogs also did not improve potency.

Based on potency and ease of synthesis **4i**[18] was selected for further evaluation (Table 5). **4i** had similar activity in the PDK1 assay and in the PDK1 mediated AKT2 activation assay (cAKT2) supporting that these indolinone inhibitors blocked Akt activity by inhibiting PDK1. Additionally, **4i** blocked AKT2 activation in cells with submicromolar potency. The PKA selectivity was 320-fold, exceeding the goal of the project. Because of the close homology of PKA with PDK1, we hypothesized that a compound with high selectivity against PKA would also have high selectivity against other kinases. This was borne out by further profiling. **4i** was 100-fold selective or better against a panel of seven additional Ser/Thr and Tyr kinases.[19] Not all properties of **4i** were optimal. **4i** has poor solubility in aqueous media and has a poor ADME profile.

An X-ray structure of **4i** and PDK1 is shown in Figure 2. The binding conformation of **4i** is similar to that predicted by the model. The indolinone core occupies the same site as the adenosine of ATP and the inhibitor makes three critical H-bonds to the backbone of the hinge region. The nitrogen of the indolinone interacts with the carbonyl of Ser 160 (2.9 Å), the carbonyl interacts with the amide of Ala 162 (2.8 Å) and the pyrrole nitrogen interacts with the carbonyl of Ala 162 (2.9 Å). The 5-urea group interacts with Lys 111 (3.2 Å) and Thr 222 (2.8 Å). A superposition of **2a** and **4i** is shown in Figure 3. The 5-hydroxyl group of **2a** forms a water mediated H-bond with the side chains of Lys 111 and Thr 222, whereas the urea group of **4i** interacts with these two residues directly explaining the greater potency of **4i**. In addition, the interaction

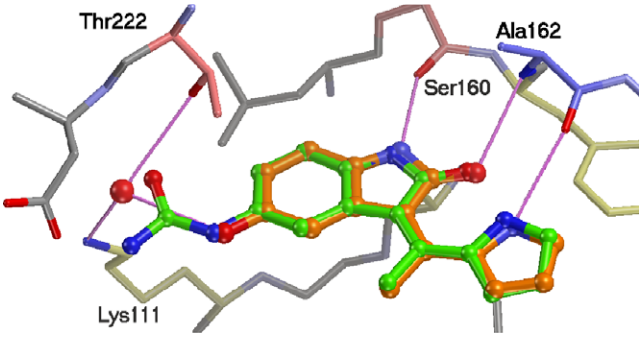


Figure 3. **4i** (green carbon atoms) superimposed on the X-ray structure of **2a** (orange) bound to PDK1, PDB entry 2PE0. The pink lines show the water mediated H-bonds formed by the 5-OH group on **2a** to the side chains of Lys 111 and Thr 222. The figure also shows the H-bonds to the hinge residues, Ser 160 and Ala 162.

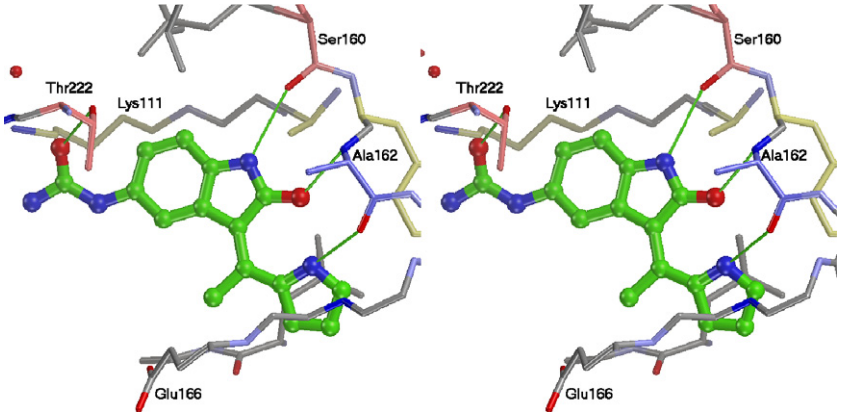


Figure 2. Divergent stereo view of the X-ray structure of **4i** bound to PDK1, PDB entry 2PE1. The three H-bonds from the inhibitor to Ser 160 and Ala 162 are typical for indolinone based kinase inhibitors. The urea accepts an H-bond from the side chain of Lys 111 and Thr 222 conferring selectivity for PDK1.

between the 5-urea group of **4i** and Thr 222 may explain the selectivity shown by **4i**. Other kinases have a different amino acid in place of Thr. However, PKA also has a Thr residue suggesting a different mechanism of selectivity. Preliminary modeling studies indicate that the reduced affinity of **4i** in PKA may stem from steric factors. The gatekeeper residue in PKA is Met 120. This bulky residue points downward from the hinge region into the adenosine binding site and may preclude binding of **4i**. On the other hand, PDK1 has Leu 159 in the gatekeeper position. This shorter residue may provide enough room to accommodate the urea group from our inhibitors.

In summary, starting from **1**, a non-selective kinase inhibitor with moderate activity against PDK1, we designed and synthesized **4i**, a potent and selective inhibitor of PDK1. Key steps of the optimization were the addition of a urea group to the 5-position of the indolinone which improved activity 100-fold, and of a methyl group to the alkene which improved activity 4-fold further. Because of the close homology of PKA and PDK1, we did not expect to find selectivity for PKA. However, **4i** was highly selective against PKA although the reason for this selectivity is still not clearly understood. Further optimization based on **4i** will be described in the following paper.

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10. *PDK1 (^{33}P-filter paper):* PDK1 inhibitory activity is measured directly using PDK1, a peptide substrate, ^{33}P-ATP, and compound followed by capture on P81 phospho-cellulose paper and detection by phorphor-imaging.
11. *P-AKT in PC-3 cells:* Inhibition of Akt phosphorylation in cells is measured by incubating compounds with cells, followed by lysis and standard immunoblotting techniques using phosphospecific antibodies to Akt P-Thr 308.
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