Syntheses of Potent, Selective, and Orally Bioavailable Indazole-Pyridine Series of Protein Kinase B/Akt Inhibitors with Reduced Hypotension

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Compound **7** was identified as a potent (IC_{50} = 14 nM), selective, and orally bioavailable (F = 70% in mouse) inhibitor of protein kinase B/Akt. While promising efficacy was observed in vivo, this compound showed effects on depolarization of Purkinje fibers in an in vitro assay and CV hypotension in vivo. Guided by an X-ray structure of **7** bound to protein kinase A, which has 80% homology with Akt in the kinase domain, our efforts have focused on structure−activity relationship (SAR) studies of the phenyl moiety, in an attempt to address the cardiovascular liability and further improve the Akt potency. A novel and efficient synthetic route toward diversely substituted phenyl derivatives of **7** was developed utilizing a copper-mediated aziridine ring-opening reaction as the key step. To improve the selectivity of these Akt inhibitors over other protein kinases, a nitrogen atom was incorporated into selected phenyl analogues of **7** at the C-6 position of the methyl indazole scaffold. These modifications resulted in the discovery of inhibitor **37c** with greater potency (IC_{50} = 0.6 nM vs Akt), selectivity, and improved cardiovascular safety profile. The SARs, pharmacokinetic profile, and CV safety of selected Akt inhibitors will be discussed.

Introduction

Protein kinase B, also known as Akt, comprises three closely related, highly conserved cellular homologues, namely, PKBα (Akt1), PKBβ (Akt2), and PKBγ (Akt3).[1] All three mammalian isoforms of the 57 kDa serine/threonine kinase are composed of an N-terminal pleckstrin homology (PH[a]) domain, a highly homologous kinase domain and a C-regulatory domain. In unstimulated cells, the inactive PKB/Akt is not phosphorylated on T308 and S473 and resides mainly in the cytosol.[2] After activation of receptor tyrosine kinases (RTK) by growth factor (GF) and/or other extracellular stimuli, phosphatidylinositol 3-kinase (PI3K) is recruited and activated to generate, through a cascade of biological interactions,[3] its lipid product phosphatidylinositol (3,4,5) trisphosphate (PIP3). The binding of PIP3 to the PH domain of Akt causes a conformational change of the protein and facilitates its translocation to the plasma membrane. On the surface of membrane, Akt is phosphorylated on T308 by PDK-1 and on S473 by an uncharacterized protein kinase (also referred to PDK-2). The fully activated kinase then translocates to subcellular compartments where it phosphorylates an increasing number of downstream substrates that are key elements of diverse cellular processes including proliferation and survival.

Protein kinase B/Akt is a central node of the PI3K/Akt signaling pathway that is believed to be the most frequently mutated or overexpressed signaling abnormality in human cancers.[4] A plethora of evidence has demonstrated frequent hyperactivation of Akt kinase in a wide assortment of human solid tumors and hematological malignancies.[5] Akt signaling inactivates a number of proapoptotic proteins, including BAD, procaspase-9, and Forkhead (FOXO) transcription factors.[6] Akt also activates transcription factors that upregulate anti-apoptotic genes, such as cyclic-AMP response element-binding protein (CREB). Akt can inactivate tumor suppressor protein p53 through mdm2, leading to centrosome hyperamplification and chromosome instability in cancer. Furthermore, in genetically modified mouse models, aberrant Akt signaling contributes to malignancy, either alone or in cooperation with other genetic alterations.[7] Therefore, inhibition of Akt alone, or in combination with other standard cancer chemotherapeutics, is widely considered as an example of targeted molecular therapeutics for the treatment of cancers. There have been more than 20 companies and academic centers declaring active programs that target the PI3K/Akt signaling pathways.[6] Because a number of the downstream targets of Akt kinase are important for normal cellular functions and, in particular, signaling by insulin, a sufficient therapeutic index is required to warrant clinical implementation.[8]

Many small molecule inhibitors of Akt have been developed and described in detail in several review articles.[2,9,10] Some of these Akt inhibitors have been shown to sensitize tumor cells to apoptotic stimuli and to slow tumor growth in vivo. Figure 1 shows the compound progression at Abbott in search for small molecule inhibitors of Akt. High-throughput screening of the Abbott compound collections identified a 5 μM hit **1**. The structure−activity relationship (SAR) studies at the *trans*-3,4′-bispyridinylethylene of **1** and derivatization of the alkylamine led to a double-digit nanomolar Akt inhibitor **2**.[11] Several conformationally locked structures of **1** at the stilbene double bond were evaluated, providing compound **3** with a 10-fold

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[a] Abbreviations: CV, cardiovascular; SAR, structure−activity relationship; RTK, receptor tyrosine kinase; GF, growth factor; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol (3,4,5) trisphosphate; PH, pleckstrin homology; CREB, cyclic-AMP response element-binding protein; TFA, trifluoroacetic acid; Boc, *tert*-butoxycarbonyl; DEAD, diethyl azocarboxylate; DBAD, di-*t*-butyl azocarboxylate; ADP, Action Potential Duration.

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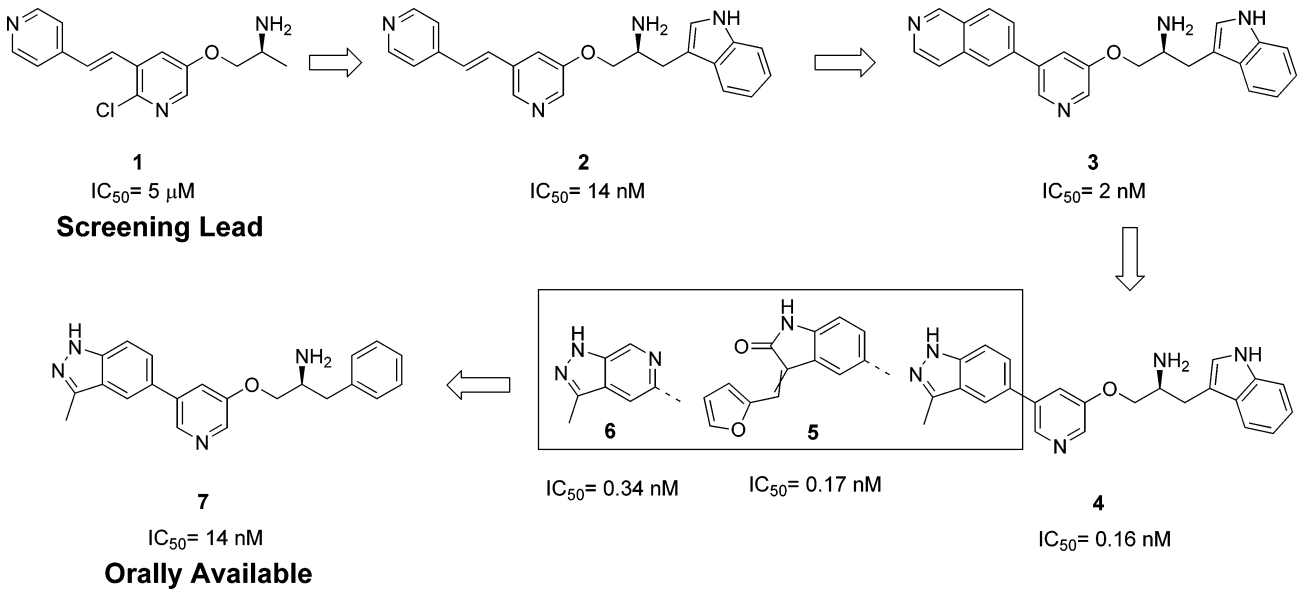


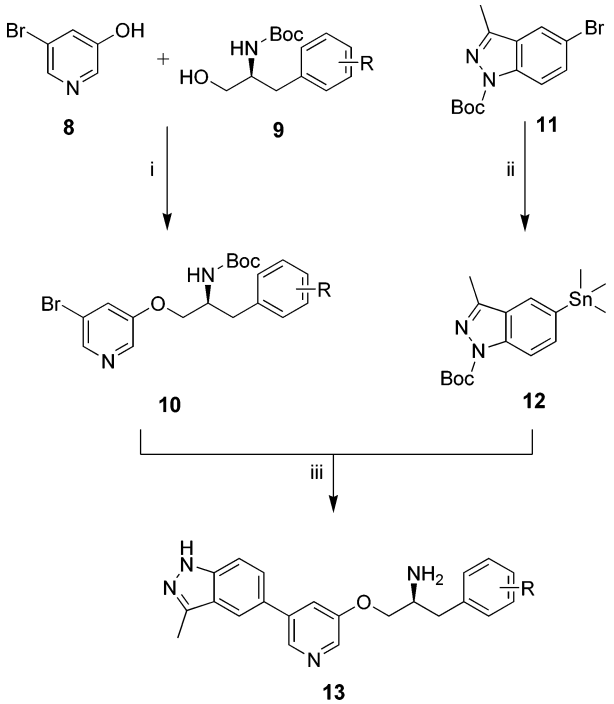
Figure 1. Abbott compound progression of Akt inhibitors.

boost in potency against Akt.[12] Further SAR studies[13] at the isoquinoline scaffold, as well as the pyridine ring of **3**, afforded analogues that significantly slowed the tumor growth in vivo, but were accompanied by toxicity. Metabolism at the C-1 position of the isoquinoline was found to be responsible for the poor pharmacokinetic profile of this series of Akt inhibitors, however, blocking this site failed to provide potency against Akt. Investigations on alternative heterocyclic pharmacophores for the metabolically labile isoquinoline led to the discovery of indazole-pyridine based Akt inhibitors **4**,[14] oxindole-pyridine based **5**,[15] and pyrazolopyridine-pyridine derivative **6**.[16] The selected inhibitors displayed excellent selectivity over a majority of families of protein kinases and showed significant in vivo efficacy in a number of mouse xenograft models. More recently, an orally available analog **7** (F = 70% in mice) was also identified[17] by replacing the indole moiety in **4** with a phenyl group. Despite a nearly 100-fold loss in potency as compared to **4**, compound **7** showed a comparable efficacy in vivo as **4** at higher doses.[14a] However, compound **7** displayed an IC_{50} of 13.4 μM in a patch clamp assay for hERG and showed prominent effect on Purkinje fiber repolarization at 20 μM. In both unconscious rats and unconscious dogs, **7** caused acute hypotension. In this report, we disclose our progress on identifying a drug-like Akt inhibitor with reduced hypotensive effect.

Chemistry. The Akt inhibitors with a general structure **13** were prepared by three alternative synthetic routes. Outlined in Scheme 1 is the first and general protocol (method A). The ether linkage in compound **10** was constructed via a Mitsunobu reaction between bromopyridinol **8** and *t*-butylcarboxyaminoalcohol **9**. A Stille reaction of the bromide **10** with trimethylstannane **12**, which was prepared from the known bromoindazole **11**,[14b] afforded, after Boc-deprotection with TFA, Akt inhibitors **13**. The yield in each step of method A was generally high, but synthesis of the final compounds from **9** required three chemical transformations and was limited by the commercial availability of Boc-aminoalcohols.

Scheme 2 illustrates an alternate approach to compound **13** from the same starting materials (method B). Bromide **8** was first coupled with trimethylstannane **12** through a Stille reaction, providing phenol **14**. Mitsunobu coupling of **14** with a Boc-protected aminoalcohol **9** in the presence of diethyl azocarboxylate (DEAD) frequently failed to afford **15**, but a replacement with di-*t*-butyl azocarboxylate (DBAD) provided the desired product, although in poor to modest yields. Finally, removal of the Boc-protecting group under acid conditions yielded **13**. Method B allowed quicker access to **13** from the shared intermediate **14**, but the yield for the Mitsunobu step was significantly lower, averaging 20%.

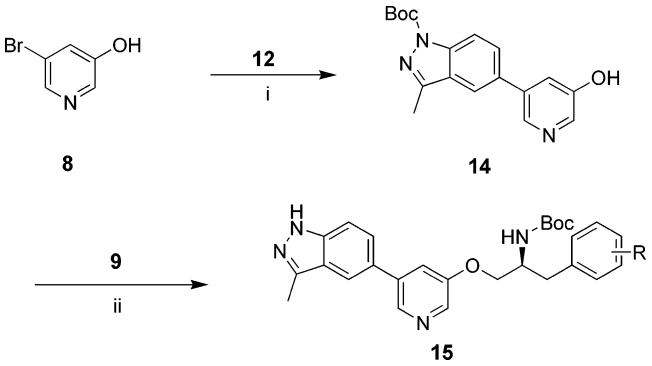
Scheme 1. Method A[a]



[a] Reagents and conditions: (i) DEAD, Ph_3P, THF; (ii) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, 80 °C, 80%; (iii) (a) $Pd_2(dba)_3$, $(o\text{-tol})_3P$, TEA, 80 °C, 5 h; (b) TFA, CH_2Cl_2, rt, 1 h.

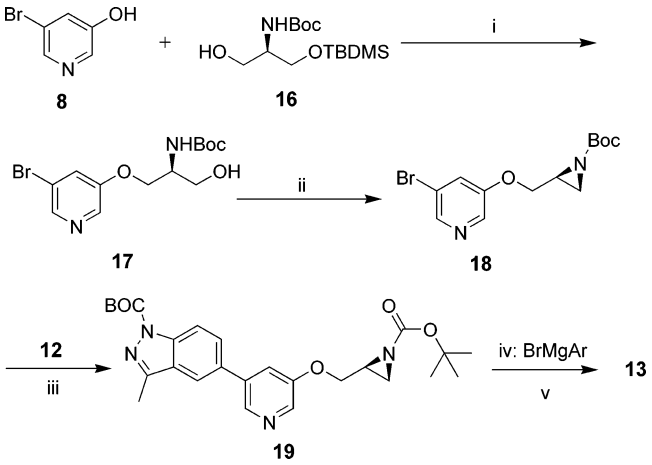
Shown in Scheme 3 is a novel and more diversified synthetic route to **13**, utilizing a copper-mediated aziridine ring-opening reaction as the key step. Mitsunobu reaction of **8** with an optically pure and protected aminoalcohol **16**,[18] followed by silyl deprotection with TBAF, afforded ether-alcohol **17**. A ring-closure reaction of **17** proceeded smoothly under Mitsunobu conditions to provide aziridine **18**. All dialkyl azodicarboxylates worked in the Mitsunobu step, but for easier purification, DEAD

Scheme 2. Method B[a]



[a] Reagents and conditions: (i) $Pd_2(dba)_3$, $(o\text{-tol})_3P$, TEA, 72%; (ii) DBAD, Ph_3P, THF, ~20%.

Scheme 3. Method C[a]



[a] Reagents and conditions: (i) (a) DEAD, Ph_3P, THF, 99%; (b) TBAF, THF, 93%; (ii) DEAD, Ph_3P, THF, 92%; (iii) $Pd_2(dba)_3$, $(o\text{-tol})_3P$, DMF, 65%; (iv) $CuBr{-}SMe_2$, THF, −78 °C to 0 °C; (v) CF_3CO_2H, CH_2Cl_2.

Table 1. Comparison of Akt1 Enzyme Assay and Pharmacokinetic Profile in Mice for Compounds **4**, **7**, and **34**−**36**

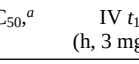
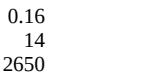
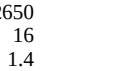
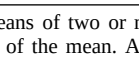
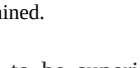
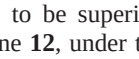
cmpd	Akt1 IC_{50},[a] nM	IV $t_{1/2}$ (h, 3 mg/kg)	PO F (%, 10 mg/kg)	PO auc (μM·h, 10 mg/kg)
4	0.16	0.6	0	0
7	14	1	70	2.0
34	2650	nd[b]	nd[b]	nd[b]
35	16	0.5	0	0
36	1.4	1.15	0	0

[a] Values are means of two or more experiments; all assays generated data within 2-fold of the mean. All compounds were tested under 5 μM ATP. [b] Not determined.

was considered to be superior. A Stille reaction of **18** with trimethylstannane **12**, under the catalysis of $Pd_2(dba)_3$ and tri-*o*-tolylphosphine, afforded compound **19** in an average of 65% yield. Other catalytic systems, including $Pd(PPh_3)_4$ and $Pd(dppf)_2Cl_2$, were also explored, but gave lower yields. Treatment of the aziridine **19** with an arylmagnesium bromide in the presence of $CuBr{-}SMe_2$ afforded, after Boc-deprotection, **13** in modest to excellent yields. The Grignard reagents were prepared from bromides by classical Mg/I_2 protocol or from iodides by an exchange methodology with isopropylmagnesium chloride. In the latter cases, an ester functionality is compatible in the reaction.

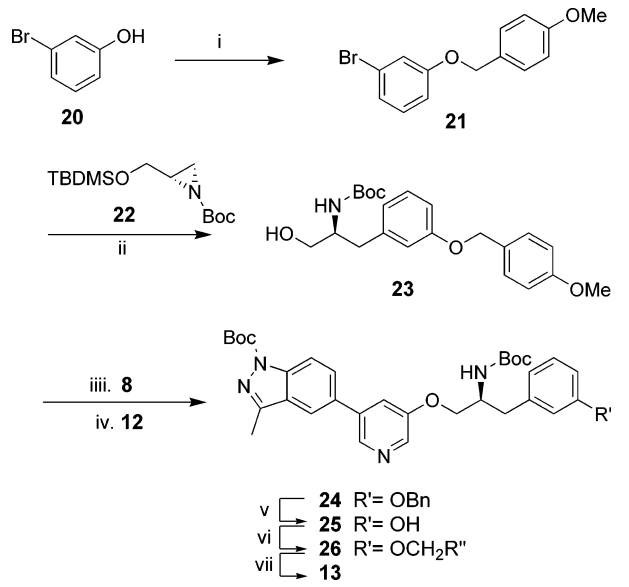
The synthesis of aryl ether analogues (**13ar**−**13aw** of Table 2) are described in Scheme 4. A copper-mediated opening of aziridine **22**[18] with a Grignard reagent of **21** afforded, after deprotection of TBDMS, intermediate alcohol **23**. Compound **21** was in turn prepared from 3-bromophenol **20** through alkylation. The Mitsunobu reaction of **23** with hydroxypyridine **8**, followed by Stille reaction with trimethylstannane **12**, as described in Scheme 1, furnished **24**. Removal of the benzyl protecting group in **24** under hydrogenation conditions provided phenol **25**, that was coupled with appropriate alcohols under Mitsunobu conditions, followed by acidic hydrolysis, to give **13ar**−**13aw**.

Table 2. Enzyme and Cellular Assay Results for Compounds **13**

cmpds	R	Akt1 IC_{50},[a] nM	MTT (MiaPaCa) EC_{50},[a] μM
7	H	14	0.64
13a	3-F	8.4	0.26
13b	2,3-F_2	8.5	0.18
13c	2,4-F_2	21.0	0.93
13d	2,6-F_2	65.5	nd[b]
13e	2,3,4-F_3	12	0.29
13f	2,4,6-F_3	31	nd
13g	2-Cl	29	0.38
13h	3-Cl	5.9	0.45
13i	4-Cl	11	0.44
13j	2-Br	23	0.34
13k	3-Br	2.1	0.37
13l	4-Br	5.0	0.7
13m	3-I	0.9	0.81
13n	3-Cl-4-F	3.1	0.67
13o	4-Cl-3-F	3.6	0.27
13p	2,3-$(Cl)_2$	5.6	0.21
13q	3,4-$(Cl)_2$	1.8	0.49
13r	3,5-$(Cl)_2$	20.7	1.0
13s	4-Br-2-F	10.0	0.9
13t	4-Br-3-F	1.3	0.43
13u	2-Br-4,6-F_2	49	nd
13v	5-F-2-Me	3.9	0.24
13w	4-Br-3-Me	2.5	1.26
13x	4-F-3-Me	11	1.07
13y	4-F-2-Me	6.0	0.34
13z	3-F-4-Me	2.4	0.33
13aa	2,4,6-$(Me)_3$	39	1.61
13ab	5-F-2-OMe	7.7	0.23
13ac	3-CF_3	1.2	0.6
13ad	4-CF_3	18	nd
13ae	3,5-$(CF_3)_2$	57	nd
13af	3-CF_3, 4-F	1.8	0.6
13ag	3-CF_3, 5-F	13.3	1.38
13ah	3-CF_3, 6-F	1.2	0.97
13ai	4-CF_3, 3-F	3.1	1.43
13aj	4-CF_3, 2-F	12.1	2.9
13ak	2-OCF_3	15.3	0.23
13al	3-OCF_3	3.3	0.83
13am	4-OCF_3	20.3	1.7
13an	3-Ph	126	nd
13ao	3,4-OCH_2O-	42	0.58
13ap	2,3-OCF_2O-	14	0.68
13aq	3,4-OCF_2CF_2O-	13	3.7
13ar		751	13
13as		290	2.74
13at		6.8	0.25
13au		1360	16.5
13av		78	1.25
13aw		47	4.8

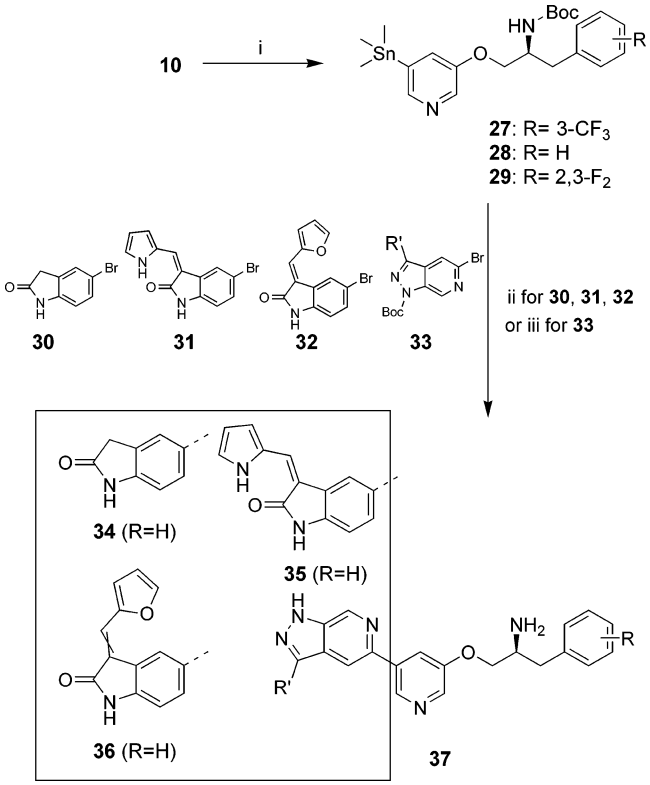
[a] Values are means of two or more experiments; all assays generated data within 2-fold of the mean. Enzyme assays were conducted under 5 μM ATP. [b] Not determined.

Scheme 4[a]



[a] Reagents and conditions: (i) 4-MeOBnCl, Cs_2CO_3, DMF, 80%; (ii) (a) Mg, THF, I_2; (b) CuBr−SMe_2, THF, −78 °C to 0 °C; (c) TBAF, THF, 91%; (iii) Ph_3P, DEAD, THF, 75%; (iv) $Pd_2(dba)_3$, (*o*-tol)$_3$P, DMF, 76%; (v) 10% Pd/C, H_2, MeOH, 83%; (vi) $HOCH_2R''$, DBAD, Ph_3P, THF; (vii) CF_3CO_2H, CH_2Cl_2.

Scheme 5[a]



[a] Reagents and conditions: (i) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, 115 °C; (ii) (a) $Pd_2(dba)_3$, (*o*-tol)$_3$P, TEA, 80 °C, 5 h; (b) TFA, CH_2Cl_2, rt, 1 h; (iii) (a) $Pd[P(t\text{-}Bu)_3]_2$, CsF, dioxane, 80 °C, 15 h; (b) TFA, CH_2Cl_2, rt, 1 h.

Outlined in Scheme 5 are the syntheses of Akt inhibitors **34**−**37**. Bromide **10** in which R is hydrogen, 3-trifluoromethyl, or 2,3-difluorophenyl groups, were prepared as described in Scheme 1 via Mitsunobu protocol. Palladium-catalyzed reaction of the bromides **10** with hexamethylditin furnished trimethylstannanes **27**−**29**. Stille coupling of **28** with bromides **30**−**32**[15] under the catalysis of $Pd_2(dba)_3$ and (*o*-tol)$_3$P, followed by Boc-deprotection, provided **34**−**36**, while the reaction of **27** and **29** with **33**[16] in the presence of bis(tri-*tert*-butylphosphine)palladium(0) provided **37**.

Results and Discussion

When the side chain indole moiety of **4** was replaced with a phenyl group, the resulting Akt inhibitor **7** displayed an improved pharmacokinetic profile in several species (mouse, rat, and dog).[17] Despite a relatively short half-life (IV $t_{1/2} = 1$ h in mouse), as shown in Table 1, compound **7** showed 70% oral bioavailability in mice with respectable plasma drug exposure (PO auc = 2.0 μM·h, 10 mg/kg). Encouraged by this initial success, we next adopted the same strategy into other interesting series of Akt inhibitors. The indole moiety in three oxindole-pyridine based Akt inhibitors (e.g., **5**[15]) was replaced with a phenyl group, leading to **34**−**36**. As shown in Table 1, the modification to **34** demonstrated a 1000-fold drop in potency against Akt1, while **35** and **36** retained good activities. PK screening of **35** and **36** in mice, however, revealed lack of oral bioavailability for both compounds.

There were several limitations with the orally bioavailable **7** as a clinically useful agent. Despite significant efficacy in multiple animal models,[14a] this compound showed a relatively poor therapeutic index. In an in vitro assay, compound **7** caused depolarization of Purkinje fibers at 20 μM, which is less than 10-fold of the plasma concentration at therapeutic dose. Compound **7** also induced severe hypotension at 4-fold efficacious C_{max} in both dog and rat. In addition, **7** is 100-fold less active than **4** against Akt1 and significantly less selective over other protein kinases. Therefore, our initial goals were, through substitutions of the phenyl group in **7**, to identify an orally bioavailable Akt inhibitor with (i) reduced hypotension, (ii) less activity in the Purkinje assay, and (iii) improved in vitro potency against Akt, as well as selectivity over other protein kinases.

Armed with an X-ray structure of **4** bound to PKA,[14a] which is a closely related analogue of Akt in the same AGC family of protein kinases and has only three different amino acid residues in the kinase domain, we initially planned to modify the phenyl group of **7** in a way to mimic indole. The indole scaffold of **4** lies nicely underneath the glycine-rich loop in PKA and results up to 100-fold higher potency against Akt1 (Figure 2, right). An X-ray structure of **7** bound to PKA, however, displayed relatively low electron density of the phenyl group, suggesting a less tightly bound phenyl moiety in the ligand−protein complex. An overlap of **4** (green) and **7** (blue) in the protein, as shown on the left of Figure 2, reveals the phenyl group (blue) positioned away from the glycine-rich loop. Thus, it seems difficult to predict patterns of substitutions helpful in locking the loosely bound phenyl group into the same position as the indole. Due to this challenge, we decided to synthesize a number of diversely substituted phenyl derivatives of **7** to screen for more potent and selective analogs with reduced hypotension. Accordingly, we developed a novel and efficient synthetic route (Scheme 3/method C), with which diversified analogs of **7** could be synthesized in two steps from intermediate **19** and readily available aryl halides.

Table 2 summarizes selected data of compound **13** in an Akt enzymatic assay, as well as in an MTT assay as an indication of their cytotoxicity in MiaPaCa cells. As predicted from the X-ray structure of **7** bound to PKA, there was no clear trend of SAR observed for the phenyl group with a wide variety of substituents. Substitutions by one, two, or three fluorines on the phenyl ring had minimal impact (**13a**, **13b**, and **13e**) unless both hydrogen atoms *ortho* to the C-1 position were replaced

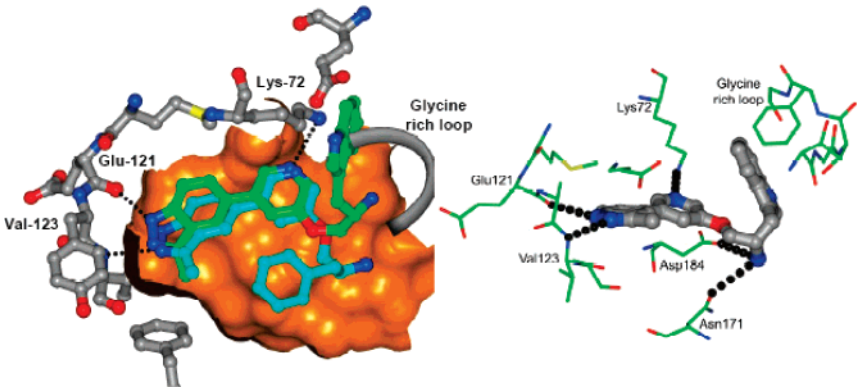


Figure 2. X-ray structures of **4** bound to PKA (right) and an overlap with **7** in the protein complex (left).[19]

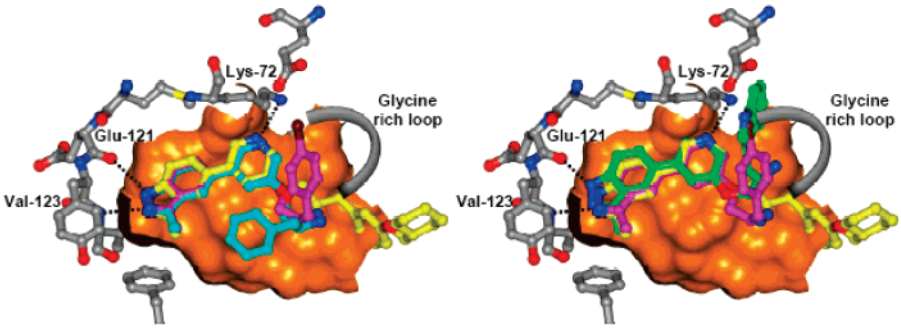


Figure 3. Left: overlap of the X-ray structures of Akt inhibitor **7** (blue) in protein kinase A with **13l** (purple) and **13au** (yellow). Right: overlap of **4** (green) with **13l** (purple) and **13au** (yellow).

(**13d** vs **13a**−**13e**). For other halides, substitution at the *meta*-position was statistically more potent (**13h**, **13k**, **13m**), while *ortho*-substituted analogues showed reduced potency (**13g**, **13j**). The Akt1 potency of 3-substituted derivatives correlated well with the size of the halides (I > Br > Cl > F), with the iodo-analog **13m** being the most active (Akt1 IC_{50} = 0.9 nM). As demonstrated with compounds **13n**, **13o**, **13q**, and **13t**, 3,4-bis-halogen-substituted analogues with at least one nonfluorine, showed higher Akt potency than other substitution patterns, with IC_{50} values of low single-digit nanomolar. Again, bis-substitutions ortho to methylene (e.g., **13u**) were detrimental. Likewise, bis-halogen/methyl-substituted analogues showed a similar pattern of activity, with C-3,4 analogs (**13w**, **13z**) being more potent and 2,6-substitutions (**13aa**) being the least active. 2-Methoxy analogue **13ab** showed a similar profile of activity as compared to the corresponding methyl derivative (**13v**). It is interesting that *meta*-trifluoromethyl analogue **13ac** is 10-fold more active than the *para*-derivative **13ad**, showing an IC_{50} of 1.2 nM against Akt1. While addition of fluorine to **13ac** at the 4- (**13af**) or 6-position (**13ah**) showed little impact, 5-fluoro-3-trifluoromethyl analogue **13ag** displayed an order of magnitude diminished binding affinity to Akt1. As observed for mono-halogen compounds, C-3 substitution (**13al**) showed highest Akt activity among the three mono-trifluoromethoxy-analogs (**13ak**−**13am**). A phenyl group seems to be too bulky at the C-3 position of the phenyl group (**13an**). A bicyclic structure as indicated in compounds **13ao**−**13aq** appeared to be detrimental as well.

Compounds **13ar**−**13aw** demonstrate our efforts toward incorporation of a chemical functionality to interact with the protein through hydrogen bonding. SAR studies on the phenyl group of **7** have shown the C-3 position optimal for attachment of a linker. Further encouraged by the high potency of 3-trifluoromethoxy analogue **13al** (Akt1 IC_{50} = 3.3 nM), a straight or branched alkoxy group was considered to be an appropriate tether. Thus, a morpholine group, in which both nitrogen and oxygen can be hydrogen bond acceptors, was attached to the C-3 position of the phenyl group with a methylene-ether linkage. As shown in Table 2, compound **13ar** was a rather weak Akt inhibitor, suggesting a limited space in this area of the protein. An amino group, as exemplified by **13as**, appeared to be slightly beneficial. Interestingly, compound **13at**, with one methylene shorter linkage, showed a 2 orders of magnitude boost in Akt potency. Removal (**13au**) or methylation (**13av**) of the piperidine nitrogen in **13at** showed much diminished potency. A shorter tether between the amino and the phenyl group, as illustrated with compound **13aw**, was also detrimental. Despite a lack of structural confirmation, the sum of the above data implies formation of a hydrogen bond between the piperidine nitrogen of **13at** and the protein.

Through the synthesis of a wide variety of substituted phenyl analogues, we have identified a number of Akt inhibitors with an order of magnitude improved potency with respect to **7**. However, little is known about the structural requirements for even more potent compounds. Figure 3 shows a comparison of the crystal structures of selected Akt inhibitors in PKA, attempting to illustrate conformational requirement for a higher binding affinity to Akt. On the left of the figure is an overlap of the X-ray structures of **7** (blue) bound to PKA, with **13l** (purple) and **13au** (yellow). Despite large variations in the potency (PKA IC_{50} = 16 nM for **7**, 15 nM for **13l**, and >3μM for **13au**), the indazole, pyridine ring, and primary amino group overlap quite well for all three Akt inhibitors. The major difference appears on the orientations of the phenyl group, with an unsubstituted ring (**7**) hovering away from, and the 4-bromo analog (**13l**) underneath, the glycine-rich loop. The 3-cyclohexylmethoxy group in **13au** seems to be too bulky for this area, extending into a deeper binding cavity. Together with the lost potency of **13au**, the hydrophobic interaction with the glycine-rich loop is thus considered to be critical for a higher binding affinity to PKA.

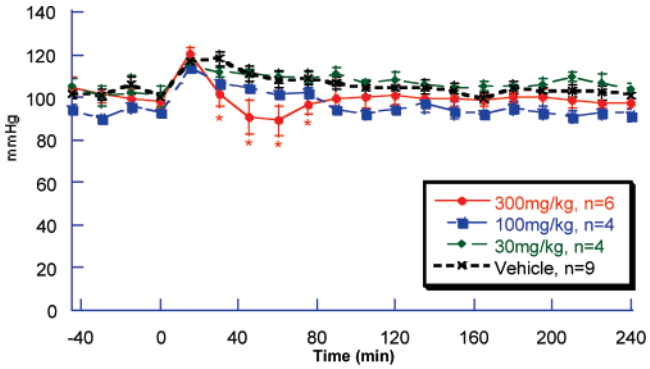


Figure 4. Effect of **13o** on mean arterial pressure in conscious mice following oral administration. Compound **13o** induced a slight effect at 300 mg/kg.

As shown on the right of Figure 3, the 4-bromophenyl group of **13l** is in the proximity of the indole pharmacophore of the more potent **4** (green, PKA $IC_{50} = 6$ nM). After a comparison of their Akt (**4** ≫ **13l** > **7** ≫ **13au**) and PKA activity (**4** > **13l** = **7** ≫ **13au**), along with their side chain orientations in the X-ray structures, it is reasonable to conclude (1) the space underneath the glycine-rich loop of PKA is limited but big enough to accommodate small substituents to a phenyl group without significant impact on the activity, (2) the hydrophobic interaction with the glycine-rich loop is critical for a higher binding affinity, and (3) cocrystallization of this series of Akt inhibitors with PKA has limited utility in predicting structures of highly potent Akt inhibitors.

Also included in Table 2 are the MTT data of our Akt inhibitors in MiaPaCa-2 human pancreatic cancer cells as an indication of their antiproliferative activity. The majority of these compounds showed correlations between Akt activity and cytotoxicity, while a few displayed either unexpectly strong (**13b**) or weak (**13m**, **13w**, and **13ai**) cytoxicity. A combination of factors including cell penetration and selectivity profile would complicate the direct comparison of enzyme and cellular potency.

We next needed to assess the hypotensive effect of these phenyl analogues of **7**. Due to limited throughput and the high cost of in vivo dog cardiovascular evaluation, an in vitro assay, namely, femoral artery relaxation assay (FAR), was evaluated as an initial screening assay for reduced risk of in vivo CV toxicity (i.e., hypotension). In this assay, isolated slices of dog femoral artery were placed on a strain gauge. Relaxations under eight concentrations of Akt inhibitor or vehicle were then assessed. However, little correlation between the FAR data and the later in vivo dog cardiovascular risk was observed. Compounds that had little or no effect on the isolated femoral arteries, such as **35** ($EC_{50} = 354$ μM), showed acute hypotension in unconscious dog (30 mmHg at IV 25 mg/kg). On the other hand, compounds that showed profound effects in the isolated arteries, for example **13o** ($EC_{50} = 6.0$ μM), had modest in vivo toxicity (12 mmHg at IV 30 mg/kg), particularly when administered orally (Figure 4). Therefore, we turned to a more reliable in vivo model with reasonable throughput, cost, and compound requirements. After evaluation of several practical models in literature, we initiated studies in telemetry-instrumented rats and later to telemetry-instrumented mice as they became available. As demonstrated in Figure 4, **13o** caused minimal hypotension in conscious mice after an oral administration up to 300 mg/kg, correlating with the unconscious dog results.

Illustrated in Figure 5 is a dog pharmacokinetic profile of **13o**. After oral administration, this compound showed a

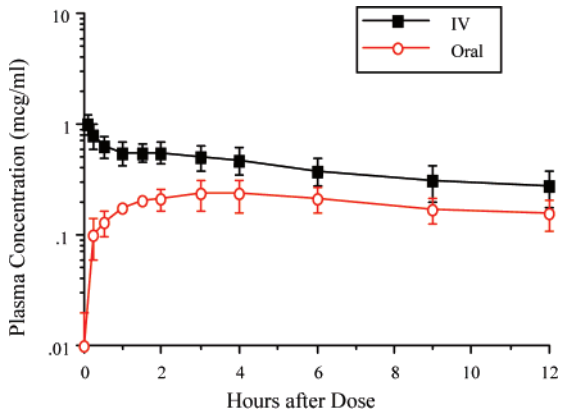


Figure 5. Dog pharmacokinetics of compound **13o** at 2.5 mg/kg.

Table 3. Fold Selectivity of Selected Akt Inhibitors over Other Selected Protein Kinases[a]

family	kinase	**4**	**7**	**13o**	**37c**
AGC	Akt1	1	1	1	1
	PKA	40	1.4	2.4	22
	PKCγ	150	110	250	130
	PKCδ	200	32	320	120
CMGC	CDK2	150	4.2	5.3	110
	ERK2	2100	24	6.0	620
	GSK3β	260	10	27	9000
	MAPK	21 000	100	360	3100
	CK2	15 000	490	400	4200
TK	KDR	19 000	>330	>1500	>1800
	Flt1	22 000	>200	>880	>7900
	cKIT	7300	>530	>2300	>2900
	SRC	16 000	1200	1600	3000
CAMK	Chk1	15 000	235	1000	7400
	RSK2	68	53	3000	57

[a] All compounds were tested at 5 μM ATP.

Table 4. Enzyme and Cellular Assay Results for Compounds **37**

cmpds	R′	R	Akt1 IC_{50},[a] nM	PKA IC_{50},[a] nM	MTT (MiaPaCa) EC_{50},[a] μM
37a	H	3-CF_3	7.2	78	2.39
37b	Cl	3-CF_3	2.9	15	1.38
37c	CH_3	3-CF_3	0.6	13	0.37
13ac	NA[b]	3-CF_3	1.2	5	0.6
37d	CH_3	2,3-F_2	5	7	0.26
13b	NA[b]	2,3-F_2	8.5	9	0.18

[a] Values are means of two or more experiments; all assays generated data within 2-fold of the mean. Kinase assays were conducted under 5 μM ATP. [b] Not applicable.

respectable plasma drug exposure in dog with 40% bioavailability. A similar type of pharmacokinetic properties for this compound were also observed in other species such as mouse (PO $F = 84\%$) and rat (PO $F = 38\%$).

As shown in a head-to-head comparison in Table 3, compound **13o** displayed a similar type of selectivity profile as **7**, which is relatively less selective as compared to compound **4** against the majority of protein kinase.

Thus, through the synthesis of a number of phenyl derivatives of our lead Akt inhibitor **7**, we have identified **13o** as a next generation lead with better in vitro potency and improved pharmacokinetic and CV safety profiles. Higher selectivity, however, still remained as one of major criteria to be further improved for a potentially wider therapeutic window. In a previous report,[16] we have discribed that incorporation of a nitrogen atom into the C-6 position of the indazole scaffold may increase the selectivity profile, especially against PKA. Table 4 summarizes our further investigation of this modification. We

Table 5. Comparison of Important Akt Inhibitors

				PK in mouse (10 mg/kg)			toxicity		
cmpds	Akt1 IC_{50},[a] nM	MTT (MiaPaCa) EC_{50},[a] μM	selectivity vs other kinase	$t_{1/2}$, h	PO *F*, %	PO auc, μM·h	mouse skin	mouse MAP decrease (mmHg)	canine purkinje (APD prolongation)[c]
4	0.16	0.082	excellent	0.6	0	0	severe	60 (infusion at 0.48 mg/kg/min)[b]	2.4% at 20 μM
7	14	0.64	good	1.0	70	2.0	no	31 (PO at 150 mg/kg)	severe depolarization at 20 μM
13o	3.6	0.27	good	2.1	84	2.3	no	clean (PO at 150 mg/kg)	−1.3% at 20 μM
37c	0.6	0.37	excellent	1.84	25	1.7	no	clean (PO at 150 mg/kg)	−4% at 20 μM

[a] Values are means of two or more experiments. Kinase assays were conducted under 5 μM ATP. [b] Dog study. [c] APD: action potential duration.

chose to incorporate a nitrogen atom into a more potent analog **13ac** and a more cytotoxic **13b** identified in Table 2.

As demonstrated in Tables 3 and 4, incorporation of a nitrogen atom into the C-6 position of the indazole moiety of **13ac** led to the identification of compound **37c** with improved potency against Akt (IC_{50} = 0.6 nM). A 5-fold boost on the selectivity over PKA was also observed. Screening of **37c** in selected protein kinases across several different families, as shown in Table 3, revealed a comparable selectivity profile to our highly selective benchmark **4**. The 3-methyl group of the aza-indazole seemed to be important; elimination (**37a**) or replacement with a chlorine (**37b**) resulted in reduced potency, as well as selectivity. No significant improvement over Akt selectivity was observed, however, for incorporation of a nitrogen atom into **13b** at the same position.

Table 5 summarizes selected properties of our representative Akt inhibitors. Compound **4** was highly potent in both enzyme and cellular assays, but lacked both oral bioavailability and sufficient cardiovascular safety. Compound **7** improved the pharmacokinetic property but with a sacrifice of potency and selectivity. In addition, the CV toxicity issue remained unsolved. The SAR studies on the phenyl group of **7** resulted in the more potent and orally bioavailable **13o** with reduced hypotension. Further improvement on selectivity by introducing a nitrogen atom at the C-6 position of the indazole led to the discovery of **37c**. Compound **37c** displayed excellent potency against Akt1 with an IC_{50} of 0.6 nM and improved selectivity over other protein kinases. Compound **37c** was orally bioavailable in mice (*F* = 25%), with a longer half-life ($t_{1/2}$ = 1.8h) and similar plasma exposure (auc = 1.7 μM·h) at 10 mg/pk as compared to **7**. As was observed for **13o**, no statistically meaningful hypotension was observed for compound **37c** when dosed orally in conscious mice up to 150 mg/kg. Both compounds were negative in a dog Purkinje assay, indicating relatively less risk of cardiovascular QT prolongation.

In summary, we have developed a facile synthesis of substituted arylether-indazole-pyridine based protein kinase B/Akt inhibitors utilizing a novel copper-mediated aziridine ring opening methodology. This new synthetic protocol enabled a convergent synthesis of a wide variety of substituted aryl ether analogues and resulted in the discovery of our next generation lead **13o** and **13ac**. Compound **13ac** was further optimized into **37c** through incorporation of a nitrogen into the benzene ring of the methyl indazole scaffold. Compound **37c** demonstrated significant improvement in potency, selectivity, and cardiovascular safety as compared to the previous Akt inhibitors of this series.

Experimental Section

General Procedure. The NMR spectra were obtained on Varian M-300, Bruker AMX-400, Varian U-400, and Varian Unity Inova 500 magnetic resonance spectrometers (300/400/500 MHz for ^{1}H and 75/100/125 MHz for ^{13}C) with deuteriochloroform as solvent and internal standard unless otherwise indicated. The chemical shifts are given in delta (δ) values, and the coupling constants (*J*) are given in hertz (Hz). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Mass spectra were performed as follows: ESI (electrospray ionization) was performed on a Finnigan SSQ7000 MS run as a flow injection acquisition; DCI (desorption chemical ionization) was performed on a Finnigan SSQ7000 MS using a direct exposure probe with ammonia gas; and APCI (atmospheric pressure chemical ionization) was performed on a Finnigan Navigator MS run as flow injection acquisition. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, New Jersey. All manipulations were performed under nitrogen atmosphere unless otherwise mentioned. All solvents and other reagents were obtained from commercial sources and used without further purification, except where noted. Flash column chromatography was performed on silica gel 60 (Merck, 230−400 mesh) using the indicated solvent. For routine aqueous workup, the reaction mixture was partitioned between brine and EtOAc, and the organic layer was washed with brine and dried over $MgSO_4$.

***tert*-Butyl 3-Methyl-5-(trimethylstannyl)-1*H*-indazole-1-carboxylate (12).** A 250 mL round-bottom flask (RBF) was charged with bromide **11** (10.0 g, 32.14 mmol)[14b] and $Pd(PPh_3)_4$ (3.7 g, 3.21 mmol) and was purged with N_2. Toluene (120 mL) and hexamethylditin (15.8 g, 48.20 mmol) were added, and the reaction mixture was heated under N_2 at 115 °C for 3 h. After cooling, solid material was filtered off and the filtrate was concentrated. The residue was separated by flash chromatography (8−20% gradient EtOAc in hexane) to give **12** as a white solid. Yield: 10.1 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.35 (s, 9H), 1.72 (s, 9H), 2.61 (s, 3H), 7.60 (d, *J* = 8.14 Hz, 1H), 7.75 (s, 1H), 8.08 (d, *J* = 8.14 Hz, 1H). MS (DCI): *m/z* 397 $(M + H)^+$.

General Procedure for Synthesis of Compound 13 through the Stille Reaction of Aryl Bromide 10 with Trimethylstannane 12 (Method 1). Step A. A 1 L RBF was charged with 3-bromo-5-hydroxypyridine (**8**, 79.6 mmol),[20] a Boc-protected amino-alcohol **9** (79.6 mmol), and Ph_3P (25.05 g, 95.52 mmol) and was purged with nitrogen. THF (250 mL) was added at 0 °C. After stirring at the same temperature for 10 min, diethyl azodicarboxylate (DEAD, 15.04 mL, 95.52 mmol) was added via syringe. The reaction mixture was stirred at 0 °C for 1 h and at rt overnight. Volatiles were removed by rotary evaporator, and the residue was separated by flash chromatography to provide product **10**.

Step B. A RBF equipped with a septum was charged with bromide **10** (0.395 mmol), trimethylstannane **12** (0.395 mmol), $Pd_2(dba)_3$ (36 mg, 0.0395 mmol), and $(o\text{-tol})_3P$ (36 mg, 0.118 mmol) and was purged with N_2. Anhydrous DMF (10 mL) and Et_3N (165 μL, 1.18 mmol) were added via syringe. The solution was purged with N_2 again and was heated at 70 °C overnight. After cooling, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with brine and concentrated. The residue was separated by flash chromatography to afford the coupled product **15**.

Step C. Compound **15** (0.2 mmol) was dissolved in CH_2Cl_2 (5 mL) and was treated with trifluoroacetic acid (1 mL) at 0 °C. After stirring at 0 °C for 5 min, the solution was allowed to warm up to rt for 1 h. CH_3CN (10 mL) was added, and the solution was concentrated. The residue was purified by HPLC (Zorbax, C-18, 250 × 2.54 column; mobile phase A, 0.1% TFA in H_2O; B, 0.1% TFA in CH_3CN; 0−100% gradient) to provide compound **13** as TFA salt. A HCl salt of compound **13** was obtained by dissolving the TFA salt in a mixture of methylene chloride and methanol and precipitating with 1 M HCl solution in ether. Removal of the volatiles afforded **13** as HCl salt.

***tert*-Butyl 5-(5-Hydroxypyridin-3-yl)-3-methyl-1*H*-indazole-1-carboxylate (14).** A 1 L RBF equipped with a septum was charged with bromide **8** (5.2 g, 30.3 mmol), trimethylstannane **12** (10.0 g, 25.2 mmol), $Pd_2(dba)_3$ (2.3 g, 2.52 mmol), and $(o\text{-tol})_3P$ (2.3 g, 7.6 mmol) and was purged with N_2. Anhydrous DMF (250 mL) and Et_3N (7 mL, 50 mmol) were added via syringe. The solution was purged with N_2 again and was heated at 80 °C for 3 h. After cooling, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with brine and concentrated. The residue was separated by flash chromatography (30−100% gradient EtOAc in hexane) to afford **14**. Yield: 5.9 g (72%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.66 (s, 9H), 2.59 (s, 3H), 7.50 (d, J = 2.37 Hz, 1H), 7.88−7.93 (m, 1H), 8.12 (d, J = 8.82 Hz, 1H), 8.15−8.18 (m, 2H), 8.46 (d, J = 1.70 Hz, 1H), 10.07 (br s, 1H). MS (DCI): m/z 326 $(M + 1)^+$.

General Synthesis of Compound 13 through Mitsunobu Reaction of 14 (Method 2). A 100 mL RBF was charged with **14** (101 mg, 0.31 mmol), an appropriate alcohol **9** (0.31 mmol), and Ph_3P (199 mg, 0.76 mmol) and was purged with N_2. THF (10 mL) was added at 0 °C. After stirring at the same temperature for 10 min, di-*t*-butyl azodicarboxylate (DBAD, 175 mg, 0.76 mmol) was added. The reaction mixture was stirred at rt overnight. Volatiles were removed by rotary evaporator, and the residue was separated by flash chromatography to provide product **15**. Boc-deprotection of **15**, as described in method 1/step C, provided Akt inhibitor **13**.

(1*S*)-[2-(5-Bromo-pyridin-3-yloxy)-1-hydroxymethyl-ethyl]-carbamic Acid *tert*-Butyl Ester (17). A 100 mL RBF was charged with 3-bromo-5-hydroxypyridine (**8**, 1.20 g, 6.87 mmol),[20] (*R*)-[1-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-hydroxy-ethyl]-carbamic acid *tert*-butyl ester (**16**, 2.1 g, 6.87 mmol),[18] and Ph_3P (2.34 g, 8.93 mmol) and was purged with N_2. THF (30 mL) was added at 0 °C. After stirring at 0 °C for 10 min, diethyl azodicarboxylate (DEAD, 1.41 mL, 8.93 mmol) was added via syringe. The reaction mixture was stirred at 0 °C for 0.5 h and at rt for 2 h. The reaction mixture was concentrated, and the residue was separated by flash chromatography (5−25% gradient EtOAc in hexane) to provide the coupled product (3.14 g, 99%). This product (3.14 g, 6.8 mmol) was dissolved in THF (40 mL) and was treated with TBAF (7.14 mL, 7.14 mmol) at rt for 1 h. Solvent was removed and the residual oil was purified by flash chromatography (40−80% gradient EtOAc in hexane) to give alcohol **17** (2.19 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.77−3.95 (m, 2H), 3.98−4.20 (m, 3H), 5.09 (br s, 1H), 7.40 (t, J = 2.20 Hz, 1H), 8.25 (d, J = 2.37 Hz, 1H), 8.30 (d, J = 1.36 Hz, 1H). MS (DCI): m/z 347, 349 $(M + 1)^+$.

(2*S*)-2-(5-Bromo-pyridin-3-yloxymethyl)-aziridine-1-carboxylic Acid *tert*-Butyl Ester (18). Ph_3P (15.95 g, 60.82 mmol) was dissolved in 9:1 THF/CH_3CN (300 mL) and cooled to 4 °C with an ice/water bath. DEAD (9.58 mL, 60.82 mmol) was added slowly. After stirring for 15 min at the same temperature, a solution of **17** (17.6 g, 50.68 mmol) in THF (60 mL) was added slowly. The solution was allowed to warm to rt and stirred overnight. The solution was concentrated and the residual oil was purified by flash chromatography (20−40% gradient EtOAc in hexane) to give aziridine **18** (15.4 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.22 (d, J = 3.73 Hz, 1H), 2.41 (d, J = 6.10 Hz, 1H), 2.78−2.84 (m, 1H), 4.05−4.17 (m, 2H), 7.42−7.44 (m, 1H), 8.27 (s, 1H), 8.31 (s, 1H). MS (DCI): m/z 329, 331 $(M + 1)^+$.

5-[5-((2*S*)-1-*tert*-Butoxycarbonyl-aziridin-2-ylmethoxy)-pyridin-3-yl]-3-methyl-indazole-1-carboxylic Acid *tert*-Butyl Ester (19). A 100 mL RBF was charged with aziridine **18** (950 mg, 2.88 mmol), trimethylstannane **12** (1.14 g, 2.88 mmol), $Pd_2(dba)_3$ (263 mg, 0.288 mmol), and tri-*o*-tolylphosphine (263 mg) and was purged with N_2. Anhydrous DMF (35 mL) and Et_3N (1.2 mL) were added via syringe. The solution was purged with N_2 again and was heated at 72 °C for 4 h. After cooling, ethyl acetate (150 mL) was added. The mixture was washed with brine (200 mL) and water (200 mL). The ethyl acetate solution was concentrated and the residual oil was separated by flash chromatography (50−80% gradient EtOAc in hexane) to give **19** (634 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.74 (s, 9H), 2.28 (d, J = 3.73 Hz, 1H), 2.44 (d, J = 6.44 Hz, 1H), 2.65 (s, 3H), 2.88 (dd, J = 6.10, 3.73 Hz, 1H), 4.23 (d, J = 4.75 Hz, 2H), 7.49−7.51 (m, 1H), 7.73 (dd, J = 8.82, 1.70 Hz, 1H), 7.82 (s, 1H), 8.20 (d, J = 8.48 Hz, 1H), 8.33 (d, J = 2.37 Hz, 1H), 8.53 (s, 1H). MS (APCI): m/z 481 $(M + 1)^+$.

General Synthesis of 13 through Opening of Aziridine 19 (Method 3). To a suspension of CuBr−SMe_2 (25 mg, 0.12 mmol) and aziridine **19** (100 mg, 0.21 mmol) in THF (6 mL) was added substituted phenylmagnesium bromide (0.8 mmol) at approximately −35 °C. The formed clear solution was allowed to warm up to −20 °C within 40 min and was quenched with water. The mixture was partitioned between EtOAc and brine. The organic layer was concentrated and the residue was separated by flash chromatography to provide a Boc-protected **13**, which was deprotected as described in method 1/step C to afford **13**.

(1*S*)-1-(3-Fluoro-benzyl)-2-(5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy)-ethylamine (13a). The title compound was synthesized as 2× TFA salt by method A. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.55 (s, 3H), 3.08 (m, 2H), 3.91 (s, 1H), 4.15 (dd, J = 10.61, 5.93 Hz, 1H), 4.32 (dd, J = 10.61, 3.12 Hz, 1H), 7.12 (m, 1H), 7.20 (m, 2H), 7.40 (m, 1H), 7.57 (d, J = 8.73 Hz, 1H), 7.69 (dd, J = 8.42, 1.56 Hz, 1H), 7.71 (d, J = 1.87 Hz, 1H), 8.07 (s, 1H), 8.29 (s, 3H), 8.31 (d, J = 2.81 Hz, 1H), 8.62 (s, 1H). MS (ESI): m/z 377 $(M + H)^+$.

(1*S*)-1-(2,3-Difluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13b). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.30 (m, 2H), 4.03 (m, 1H), 4.32 (dd, J = 10.8, 4.5 Hz, 1H), 4.48 (dd, J = 10.8, 3.0 Hz, 1H), 7.19 (m, 3H), 7.62 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 8.12 (s, 2H), 8.44 (s, 1H), 8.74(s, 1H). MS (DCI/NH_3): m/e 395 $(M + 1)^+$.

(1*S*)-1-(2,4-Difluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13c). The title compound was synthesized as TFA salt by method A. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.10 (m, 2H), 3.96 (m, 1H), 4.27 (dd, J = 10.8, 4.5 Hz, 1H), 4.43 (dd, J = 10.8, 3.0 Hz, 1H), 7.01 (m, 2H), 7.40 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 8.08 (s, 1H), 8.37 (s, 1H), 8.67 (s, 1H). MS (DCI/NH_3): m/e 395 $(M + 1)^+$.

(1*S*)-1-(2,6-Difluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13d). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.31 (m, 2H), 3.97 (m, 1H), 4.24 (dd, J = 10.8, 4.5 Hz, 1H), 4.42 (dd, J = 10.8, 3.0 Hz), 7.06 (m, 2H), 7.40(m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 8.04 (s, 1H), 8.31 (s, 1H), 8.41 (s, 1H). MS (DCI/NH_3): m/e 395 $(M + 1)^+$.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(2,3,4-trifluoro-benzyl)-ethylamine (13e). The title compound was synthesized as 2× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.62 (s, 3H), 3.23 (m, 2H), 4.00 (m, 1H), 4.31 (dd, J = 10.61, 5.30 Hz, 1H), 4.46 (dd, J = 10.61, 3.12 Hz, 1H), 7.17 (m, 2H), 7.62 (d, J = 8.73 Hz, 1H), 7.73 (dd, J = 8.74, 1.56 Hz, 1H), 8.02 (s, 1H), 8.08 (s, 1H), 8.40 (s, 1H), 8.69 (s, 1H). MS (DCI/NH_3): m/e 413 $(M + 1)^+$. Anal. ($C_{22}H_{19}F_3N_4O\cdot 2.8$TFA) C, H, N.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(2,4,6-trifluoro-benzyl)-ethylamine (13f). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz,

CD_3OD): δ 2.63 (s, 3H), 3.19 (m, 2H), 3.97 (m, 1H), 4.32 (dd, J = 10.61, 4.99 Hz, 1H), 4.49 (dd, J = 10.61, 3.12 Hz, 1H), 6.95 (t, J = 8.27 Hz, 2H), 7.63 (d, J = 8.73 Hz, 1H), 7.74 (dd, J = 8.74, 1.56 Hz, 1H), 8.08 (d, J = 2.18 Hz, 1H), 8.10 (s, 1H), 8.41 (s, 1H), 8.72 (s, 1H). MS (APCI): m/z 411 $(M - 1)^+$. Anal. ($C_{22}H_{19}F_3N_4O$·3.0TFA) C, H, N.

(1*S*)-1-(2-Chloro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13g). The title compound was synthesized as 2× TFA salt by method A. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.55 (s, 3H), 3.22 (m, 2H), 3.89 (m, 1H), 4.15 (m, 1H), 4.31 (m, 1H), 7.35 (m, 2H), 7.48 (m, 3H), 7.58 (d, J = 8.82 Hz, 1H), 7.70 (m, 2H), 8.08 (s, 1H), 8.31 (d, J = 2.71 Hz, 2H), 8.64 (d, J = 1.70 Hz, 1H), 12.84 (br s, 1H). MS (ESI): m/e 393 $(M + H)^+$.

(1*S*)-1-(3-Chloro-benzyl)-2-(5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy)-ethylamine (13h). The title compound was synthesized as 2× TFA salt by method A. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.55 (s, 3H), 3.06 (d, J = 7.49 Hz, 2H), 3.92 (m, 1H), 4.16 (m, 1H), 4.33 (dd, J = 10.92, 3.12 Hz, 1H), 7.31 (d, J = 7.49 Hz, 1H), 7.37 (m, 2H), 7.45 (s, 1H), 7.58 (d, J = 8.73 Hz, 1H), 7.70 (dd, J = 8.73, 1.56 Hz, 1H), 7.77 (s, 1H), 8.08 (s, 1H), 8.23 (s, 3H), 8.34 (d, J = 2.50 Hz, 1H), 8.65 (s, 1H). MS (ESI): m/z 393 $(M + H)^+$.

(1*S*)-1-(4-Chloro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13i). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.63 (s, 3H), 3.16 (dd, J = 7.63, 2.54 Hz, 2H), 3.98 (m, 1H), 4.30 (dd, J = 10.51, 5.42 Hz, 1H), 4.45 (dd, J = 10.51, 3.05 Hz, 1H), 7.34 (d, J = 8.81 Hz, 2H), 7.39 (d, J = 8.81 Hz, 2H), 7.63 (d, J = 8.81 Hz, 1H), 7.74 (dd, J = 8.81, 1.70 Hz, 1H), 8.11 (m, 2H), 8.43 (d, J = 2.03 Hz, 1H), 8.73 (s, 1H). MS (APCI): m/z 393 $(M + 1)^+$. Anal. ($C_{22}H_{21}ClN_4O$·3TFA) C, H, N.

(1*S*)-Bromo-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13j). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.62 (s, 3H), 3.37 (m, 2H), 4.10 (m, 1H), 4.30 (dd, J = 10.61, 4.99 Hz, 1H), 4.43 (dd, J = 10.61, 3.12 Hz, 1H), 7.25 (t, J = 6.71 Hz, 1H), 7.37 (t, J = 6.86 Hz, 1H), 7.42 (m, 1H), 7.63 (d, J = 8.74 Hz, 1H), 7.66 (d, J = 8.11 Hz, 1H), 7.73 (dd, J = 8.73, 1.56 Hz, 1H), 8.03 (d, J = 1.87 Hz, 1H), 8.09 (s, 1H), 8.40 (s, 1H), 8.70 (s, 1H). MS (APCI): m/z 438 $(M + 1)^+$. Anal. ($C_{22}H_{21}BrN_4O$·2.9TFA) C, H, N.

(1*S*)-1-(3-Bromo-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13k). The title compound was synthesized as 2× HCl salt by method A. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.57 (s, 3H), 3.08 (m, 2H), 4.27 (dd, J = 10.85, 5.43 Hz, 1H), 4.43 (m, 1H), 7.34 (m, 2H), 7.49 (dt, J = 7.54, 1.65 Hz, 1H), 7.61 (m, 2H), 7.77 (dd, J = 8.65, 1.53 Hz, 1H), 8.14 (s, 1H), 8.22 (s, 1H), 8.49 (s, 2H), 8.82 (s, 1H). MS(DCI): m/z 437, 439 $(M + H)^+$.

(1*S*)-1-(4-Bromo-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13l). This compound was prepared as 2× TFA salt by general method B. ^{1}H NMR (300 MHz, CF_3CO_2D): δ 3.16 (s, 3H), 3.46 (m, 2H), 4.48 (m, 1H), 4.86 (m, 2H), 7.34 (m, 2H), 7.70 (m, 2H), 8.24 (m, 2H), 8.57 (m, 2H), 8.86 (m, 1H), 9.07 (m, 1H). MS (ESI): m/e 437 $(M + 1)$.

(1*S*)-1-(3-Iodo-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13m). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.12 (m, 2H), 3.96 (m, 1H), 4.24 (dd, J = 10.8, 4.5 Hz, 1H), 4.40 (dd, J = 10.8, 3.0 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.75 (s, 1H), 7.92 (s, 1H), 8.07 (s, 1H), 8.36 (s, 1H), 8.65 (s, 1H). MS (DCI/NH_3): m/e 485 $(M + 1)^+$.

(1*S*)-1-(3-Chloro-4-fluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13n). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.15 (t, J = 7.12 Hz, 2H), 3.98 (m, 1H), 4.28 (dd, J = 10.51, 5.42 Hz, 1H), 4.44 (dd, J = 10.51, 3.05 Hz, 1H), 7.23 (d, J = 8.48 Hz, 1H), 7.30 (m, 1H), 7.51 (dd, J = 7.12, 2.03 Hz, 1H), 7.62 (d, J = 8.81 Hz, 1H), 7.72 (dd, J = 8.48, 1.36 Hz, 1H), 7.99 (s, 1H), 8.08 (s, 1H), 8.39 (s, 1H), 8.68 (s, 1H). MS (APCI): m/z 411 $(M + 1)^+$. Anal. ($C_{22}H_{20}ClFN_4O$·2.7TFA) C, H, N.

(1*S*)-1-(4-Chloro-3-fluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13o). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.63 (s, 3H), 3.17 (t, J = 6.95 Hz, 2H), 4.00 (m, 1H), 4.28 (dd, J = 10.51, 5.43 Hz, 1H), 4.44 (dd, J = 10.51, 3.05 Hz, 1H), 7.17 (dd, J = 8.14, 1.70 Hz, 1H), 7.29 (dd, J = 10.00, 1.87 Hz, 1H), 7.49 (t, J = 7.97 Hz, 1H), 7.62 (d, J = 8.82 Hz, 1H), 7.73 (d, J = 7.12 Hz, 1H), 8.01 (m, 1H), 8.09 (s, 1H), 8.40 (d, J = 2.37 Hz, 1H), 8.68 (d, J = 1.70 Hz, 1H). MS (APCI): m/z 411 $(M + 1)^+$. Anal. ($C_{22}H_{20}ClFN_4O$·2.7TFA) C, H, N.

(1*S*)-1-(2,3-Dichloro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13p). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (300 MHz, CD_3OD): δ 2.63 (s, 3H), 3.40 (dd, J = 7.32, 5.13 Hz, 2H), 4.10 (m, 1H), 4.33 (dd, J = 10.62, 4.76 Hz, 1H), 4.47 (dd, J = 10.99, 2.93 Hz, 1H), 7.30 (t, J = 7.69 Hz, 1H), 7.39 (d, J = 7.32 Hz, 1H), 7.52 (d, J = 7.69 Hz, 1H), 7.63 (d, J = 8.79 Hz, 1H), 7.74 (d, J = 8.79 Hz, 1H), 8.11 (s, 2H), 8.45 (s, 1H), 8.75 (s, 1H). MS (APCI): m/z 427 $(M + 1)^+$. Anal. ($C_{22}H_{20}Cl_2N_4O$·3.5TFA) C, H, N.

(1*S*)-1-(3,4-Dichloro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13q). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.16 (m, 2H), 3.99 (m, 1H), 4.27 (dd, J = 10.8, 4.5 Hz, 1H), 4.43 (dd, J = 10.8, 3.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.56 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 8.08 (s, 1H), 8.39 (s, 1H), 8.68 (s, 1H). MS (DCI/NH_3): m/e 428 $(M + 1)^+$.

(1*S*)-1-(3,5-Dichloro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13r). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (300 MHz, CD_3OD): δ 2.63 (s, 3H), 3.18 (dd, J = 7.32, 3.30 Hz, 2H), 4.02 (m, 1H), 4.32 (dd, J = 10.44, 5.31 Hz, 1H), 4.47 (dd, J = 10.62, 2.93 Hz, 1H), 7.37 (s, 1H), 7.39 (d, J = 8.06 Hz, 1H), 7.63 (d, J = 8.79 Hz, 1H), 7.74 (d, J = 8.06 Hz, 1H), 8.10 (s, 3H), 8.44 (s, 1H), 8.73 (s, 1H). MS (APCI): m/z 427 $(M + 1)^+$. Anal. ($C_{22}H_{20}Cl_2N_4O$·3.2TFA) C, H, N.

(1*S*)-1-(4-Bromo-2-fluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13s). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.22 (m, 2H), 4.00 (m, 1H), 4.34 (dd, J = 10.61, 5.30 Hz, 1H), 4.49 (dd, J = 10.61, 3.12 Hz, 1H), 7.33 (t, J = 8.11 Hz, 1H), 7.37 (d, J = 1.56 Hz, 1H), 7.41 (m, 1H), 7.64 (d, J = 8.73 Hz, 1H), 7.75 (dd, J = 8.74, 1.56 Hz, 1H), 8.13 (s, 1H), 8.19 (s, 1H), 8.46 (s, 1H), 8.77 (s, 1H). MS (ESI): m/z 456 $(M + 1)^+$. Anal. ($C_{22}H_{20}BrFN_4O$·2.8TFA) C, H, N.

(1*S*)-1-(4-Bromo-3-fluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13t). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.18 (m, 2H), 4.01 (m, 1H), 4.32 (dd, J = 10.61, 5.62 Hz, 1H), 4.46 (dd, J = 10.61, 2.81 Hz, 1H), 7.11 (dd, J = 8.11, 1.56 Hz, 1H), 7.26 (dd, J = 9.36, 1.87 Hz, 1H), 7.62 (d, J = 7.18 Hz, 1H), 7.63 (d, J = 8.42 Hz, 1H), 7.74 (dd, J = 8.73, 1.56 Hz, 1H), 8.10 (d, J = 4.06 Hz, 2H), 8.43 (s, 1H), 8.72 (s, 1H). MS (ESI): m/z 456 $(M + 1)^+$. Anal. ($C_{22}H_{20}BrFN_4O$·2.6TFA) C, H, N.

(1*S*)-1-(2-Bromo-4,6-difluoro-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13u). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.32 (m, 1H), 3.48 (m, 1H), 4.03 (m, 1H), 4.34 (dd, J = 10.45, 4.84 Hz, 1H), 4.48 (dd, J = 10.61, 3.43 Hz, 1H), 7.13 (t, J = 8.11 Hz, 1H), 7.40 (d, J = 8.11 Hz, 1H), 7.63 (d, J = 8.73 Hz, 1H), 7.74 (dd, J = 8.73, 1.56 Hz, 1H), 8.09 (s, 1H), 8.11 (s, 1H), 8.42 (s, 1H), 8.73 (s, 1H). MS (APCI): m/z 474 $(M + 1)^+$. Anal. ($C_{22}H_{19}BrF_2N_4O$·3TFA) C, H, N.

(1*S*)-1-(5-Fluoro-2-methyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13v). The title compound was

synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.36 (s, 3H), 2.62 (s, 3H), 3.16 (dd, J = 14.19, 6.71 Hz, 1H), 3.23 (m, 1H), 3.97 (m, 1H), 4.29 (dd, J = 10.45, 4.84 Hz, 1H), 4.42 (dd, J = 10.61, 3.12 Hz, 1H), 6.95 (td, J = 8.42, 2.81 Hz, 1H), 7.04 (dd, J = 9.67, 2.81 Hz, 1H), 7.25 (dd, J = 8.42, 5.93 Hz, 1H), 7.63 (d, J = 8.74 Hz, 1H), 7.73 (dd, J = 8.73, 1.56 Hz, 1H), 8.05 (s, 1H), 8.09 (s, 1H), 8.42 (s, 1H), 8.71 (s, 1H). MS (APCI): m/z 391 (M + 1)$^+$. Anal. ($C_{23}H_{23}FN_4O$·2.6TFA) C, H, N.

(1*S*)-1-(4-Bromo-3-methyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13w). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.37 (s, 3H), 2.63 (s, 3H), 3.11 (m, 2H), 3.97 (m, 1H), 4.29 (dd, J = 10.61, 5.62 Hz, 1H), 4.44 (dd, J = 10.61, 3.12 Hz, 1H), 7.07 (dd, J = 8.11, 1.87 Hz, 1H), 7.27 (s, 1H), 7.54 (d, J = 8.11 Hz, 1H), 7.63 (d, J = 8.73 Hz, 1H), 7.73 (d, J = 8.73 Hz, 1H), 8.06 (s, 1H), 8.10 (s, 1H), 8.41 (s, 1H), 8.71 (s, 1H). MS (ESI): m/z 452 (M + 1)$^+$. Anal. ($C_{23}H_{23}BrN_4O$·2.7TFA) C, H, N.

(1*S*)-1-(4-Fluoro-3-methyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13x). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.24 (s, 3H), 2.63 (s, 3H), 3.11 (dd, J = 7.64, 3.90 Hz, 2H), 3.94 (m, 1H), 4.29 (dd, J = 10.61, 5.62 Hz, 1H), 4.44 (dd, J = 10.61, 2.81 Hz, 1H), 7.03 (m, 1H), 7.16 (m, 1H), 7.21 (d, J = 7.18 Hz, 1H), 7.63 (d, J = 8.73 Hz, 1H), 7.74 (d, J = 1.87 Hz, 1H), 8.06 (s, 1H), 8.10 (s, 1H), 8.42 (s, 1H), 8.71 (s, 1H). MS (APCI): m/z 392 (M + 1)$^+$. Anal. ($C_{23}H_{23}FN_4O$·3TFA) C, H, N.

(1*S*)-1-(4-Fluoro-2-methyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13y). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.40 (s, 3H), 2.62 (s, 3H), 3.15 (dd, J = 14.19, 6.40 Hz, 1H), 3.22 (m, 1H), 3.94 (m, 1H), 4.29 (dd, J = 10.61, 4.99 Hz, 1H), 4.42 (dd, J = 10.61, 2.81 Hz, 1H), 6.91 (td, J = 8.42, 2.50 Hz, 1H), 7.00 (dd, J = 9.83, 2.34 Hz, 1H), 7.26 (dd, J = 8.42, 5.93 Hz, 1H), 7.63 (d, J = 8.74 Hz, 1H), 7.73 (dd, J = 8.74, 1.25 Hz, 1H), 8.08 (s, 1H), 8.10 (s, 1H), 8.43 (s, 1H), 8.72 (s, 1H). MS (APCI): m/z 392 (M + 1)$^+$. Anal. ($C_{23}H_{23}FN_4O$·2.8TFA) C, H, N.

(1*S*)-1-(3-Fluoro-4-methyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13z). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.24 (d, J = 1.70 Hz, 3H), 2.63 (s, 3H), 3.11 (d, J = 8.14 Hz, 2H), 3.96 (m, 1H), 4.31 (dd, J = 10.51, 5.76 Hz, 1H), 4.46 (dd, J = 10.85, 3.05 Hz, 1H), 7.03 (t, J = 8.48 Hz, 1H), 7.15 (m, 1H), 7.21 (d, J = 7.46 Hz, 1H), 7.64 (d, J = 8.48 Hz, 1H), 7.74 (dd, J = 8.81, 1.70 Hz, 1H), 8.14 (m, 2H), 8.45 (d, J = 2.37 Hz, 1H), 8.75 (d, J = 1.36 Hz, 1H). MS (APCI): m/z 391 (M + 1)$^+$. Anal. ($C_{23}H_{23}FN_4O$·2.9TFA) C, H, N.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(2,4,6-trimethyl-benzyl)-ethylamine (13aa). The title compound was synthesized as 2× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.21 (s, 3H), 2.34 (s, 6H), 2.62 (s, 3H), 3.14 (dd, J = 14.19, 5.46 Hz, 2H), 3.92 (m, J = 8.73, 4.99 Hz, 1H), 4.26 (dd, J = 10.45, 4.84 Hz, 1H), 4.36 (m, 1H), 6.89 (s, 2H), 7.63 (d, J = 8.74 Hz, 1H), 7.72 (dd, J = 8.73, 1.56 Hz, 1H), 8.11 (s, 2H), 8.42 (s, 1H), 8.75 (s, 1H). MS (APCI): m/z 402 (M + 1)$^+$. Anal. ($C_{25}H_{28}N_4O$·2.5TFA) C, H, N.

(1*S*)-1-(5-Fluoro-2-methoxy-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13ab). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.16 (d, J = 7.18 Hz, 2H), 3.84 (s, 3H), 4.02 (m, 1H), 4.30 (dd, J = 10.61, 5.93 Hz, 1H), 4.45 (dd, J = 10.45, 2.96 Hz, 1H), 7.04 (m, 3H), 7.64 (d, J = 8.73 Hz, 1H), 7.74 (d, J = 8.74 Hz, 1H), 8.12 (s, 2H), 8.43 (s, 1H), 8.74 (s, 1H). MS (APCI): m/z 408 (M + 1)$^+$. Anal. ($C_{23}H_{23}FN_4O_2$·3.5TFA) C, H, N.

(1*S*)-2-(5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy)-1-(3-trifluoromethyl-benzyl)-ethylamine (13ac). The title compound was synthesized as 2× TFA salt by method A. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.55 (s, 3H), 3.16 (dd, J = 7.33, 2.34 Hz, 2H), 3.97 (s, 1H), 4.16 (dd, J = 10.61, 5.62 Hz, 1H), 4.34 (dd, J = 10.76, 3.28 Hz, 1H), 7.58 (d, J = 8.42 Hz, 1H), 7.61 (d, J = 7.49 Hz, 1H), 7.65 (s, 1H), 7.66 (s, 1H), 7.69 (dd, J = 8.74, 1.56 Hz, 1H), 7.73 (s, 1H), 7.75 (m, 1H), 8.07 (s, 1H), 8.22 (s, 3H), 8.33 (d, J = 2.50 Hz, 1H), 8.64 (d, J = 1.56 Hz, 1H). MS (ESI): m/z 427 (M + H)$^+$.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(4-trifluoromethyl-benzyl)-ethylamine (13ad). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.28 (m, 2H), 4.05 (m, 1H), 4.32 (dd, J = 10.61, 5.30 Hz, 1H), 4.47 (dd, J = 10.61, 2.81 Hz, 1H), 7.56 (d, J = 7.80 Hz, 2H), 7.63 (d, J = 8.74 Hz, 1H), 7.69 (d, J = 8.11 Hz, 2H), 7.74 (dd, J = 8.74, 1.56 Hz, 1H), 8.12 (d, J = 6.55 Hz, 2H), 8.45 (br s, 1H), 8.74 (br s, 1H). MS (APCI): m/z 428 (M + 1)$^+$. Anal. ($C_{23}H_{21}F_3N_4O$·2.7TFA) C, H, N.

(1*S*)-1-(3,5-Bis-trifluoromethyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13ae). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.62 (s, 3H), 3.35 (m, 1H), 3.42 (m, 1H), 4.12 (m, 1H), 4.31 (dd, J = 10.61, 5.30 Hz, 1H), 4.49 (dd, J = 10.61, 3.12 Hz, 1H), 7.63 (d, J = 8.73 Hz, 1H), 7.73 (dd, J = 8.74, 1.87 Hz, 1H), 7.94 (s, 1H), 8.01 (s, 2H), 8.05 (s, 1H), 8.08 (s, 1H), 8.43 (s, 1H), 8.72 (s, 1H). MS (APCI): m/z 495 (M + 1)$^+$. Anal. ($C_{24}H_{20}F_6N_4O$·2.8TFA) C, H, N.

(1*S*)-1-(4-Fluoro-3-trifluoromethyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13af). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.23 (m, 2H), 4.02 (m, 1H), 4.28 (dd, J = 10.8, 4.5 Hz, 1H), 4.44 (dd, J = 10.8, 3.0 Hz, 1H), 7.36 (t, J = 9.0 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.68 (m, 1H), 7.74 (d, J = 8.1 Hz, 1H), 8.04 (s, 1H), 8.09 (s, 1H), 8.41 (s, 1H), 8.70 (s, 1H). MS (DCI/NH_3): m/e 445 (M + 1)$^+$.

(1*S*)-1-(3-Fluoro-5-trifluoromethyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13ag). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.30 (m, 2H), 4.06 (m, 1H), 4.29 (dd, J = 10.51, 5.09 Hz, 1H), 4.45 (dd, J = 10.85, 3.05 Hz, 1H), 7.45 (dd, J = 7.80, 5.76 Hz, 2H), 7.55 (s, 1H), 7.62 (d, J = 8.81 Hz, 1H), 7.73 (d, J = 8.48 Hz, 1H), 7.98 (s, 1H), 8.07 (s, 1H), 8.42 (br s, 1H), 8.73 (br s, 1H). MS (APCI): m/z 445 (M + 1)$^+$.

(1*S*)-1-(2-Fluoro-5-trifluoromethyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13ah). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.26−3.31 (m, 1H), 3.34−3.39 (m, 1H), 4.03−4.10 (m, 1H), 4.32 (dd, J = 10.53, 5.03 Hz, 1H), 4.49 (dd, J = 10.68, 3.05 Hz, 1H), 7.38 (t, J = 9.15 Hz, 1H), 7.63 (d, J = 8.85 Hz, 1H), 7.70−7.72 (m, 1H), 7.72−7.76 (m, 1H), 7.78 (d, J = 6.71 Hz, 1H), 8.10 (d, J = 1.83 Hz, 1H), 8.11 (s, 1H), 8.43 (s, 1H), 8.73 (s, 1H). MS (ESI): m/z 445 (M + H)$^+$. Anal. ($C_{23}H_{20}F_4N_4O$·2.7TFA) C, H, N.

(1*S*)-1-(3-Fluoro-4-trifluoromethyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13ai). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.28 (m, 2H), 4.08 (m, 1H), 4.32 (dd, J = 10.8, 4.5 Hz, 1H), 4.48 (dd, J = 10.8, 3.0 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 12.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 8.13 (m, 2H), 8.44 (s, 1H), 8.74 (s, 1H). MS (DCI/NH_3): m/e 445 (M + 1)$^+$.

(1*S*)-1-(2-Fluoro-4-trifluoromethyl-benzyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13aj). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.31 (m, 2H), 4.04 (m, 1H), 4.29 (dd, J = 10.85, 5.09 Hz, 1H), 4.45 (dd, J = 10.85, 3.39 Hz, 1H), 7.54 (d, J = 8.81 Hz, 1H), 7.55 (s, 1H), 7.60 (dd, J = 4.07, 3.39 Hz, 1H), 7.63 (s, 1H), 7.72 (dd, J = 8.81, 1.70 Hz, 1H), 7.96 (s, 1H), 8.07 (s, 1H), 8.39 (s, 1H), 8.67 (s, 1H). MS (APCI): m/z 445 (M + 1)$^+$.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(2-trifluoromethoxy-benzyl)-ethylamine (13ak). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz,

CD_3OD): δ 2.62 (s, 3H), 3.28 (m, 2H), 4.00 (m, 1H), 4.24 (dd, J = 10.8, 4.5 Hz, 1H), 4.40 (dd, J = 10.8, 3.0 Hz, 1H), 7.42 (m, 4H), 7.63 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 8.01 (s, 1H), 8.09 (s, 1H), 8.39 (s, 1H), 8.70 (s, 1H). MS (DCI/NH_3): m/e 443 $(M + 1)^+$.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(3-trifluoromethoxy-benzyl)-ethylamine (13al). The title compound was synthesized as TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.22 (dd, J = 7.29, 5.26 Hz, 2H), 4.00 (m, 1H), 4.26 (dd, J = 10.51, 5.09 Hz, 1H), 4.43 (dd, J = 10.85, 3.05 Hz, 1H), 7.25 (d, J = 8.48 Hz, 1H), 7.30 (s, 1H), 7.36 (d, J = 7.46 Hz, 1H), 7.49 (t, J = 7.97 Hz, 1H), 7.62 (d, J = 8.48 Hz, 1H), 7.72 (dd, J = 8.82, 1.70 Hz, 1H), 8.00 (s, 1H), 8.08 (s, 1H), 8.40 (d, J = 2.03 Hz, 1H), 8.68 (s, 1H). MS (APCI): m/z 444 $(M + 1)^+$. Anal. ($C_{23}H_{21}F_3N_4O_2 \cdot 2.6$TFA) C, H, N.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(4-trifluoromethoxy-benzyl)-ethylamine (13am). The title compound was synthesized as 2× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.62 (s, 3H), 3.20 (t, J = 6.95 Hz, 2H), 3.98 (m, 1H), 4.28 (dd, J = 10.51, 5.42 Hz, 1H), 4.43 (dd, J = 10.51, 2.71 Hz, 1H), 7.30 (d, J = 7.80 Hz, 2H), 7.45 (d, J = 8.48 Hz, 2H), 7.62 (d, J = 8.48 Hz, 1H), 7.73 (d, J = 8.81 Hz, 1H), 8.00 (s, 1H), 8.08 (s, 1H), 8.40 (s, 1H), 8.68 (s, 1H). MS (APCI): m/z 443 $(M + 1)^+$. Anal. ($C_{23}H_{21}F_3N_4O_2 \cdot 2.4$TFA) C, H, N.

(1*S*)-1-Biphenyl-3-ylmethyl-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13an). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.61 (s, 3H), 3.25 (d, J = 7.69 Hz, 2H), 4.05 (m, 1H), 4.33 (dd, J = 10.62, 5.13 Hz, 1H), 4.46 (d, J = 10.25 Hz, 1H), 7.36 (m, 4H), 7.46 (t, J = 7.14 Hz, 1H), 7.57 (m, 6H), 8.06 (s, 2H), 8.42 (s, 1H), 8.69 (s, 1H). MS (APCI): m/z 435 $(M + 1)^+$. Anal. ($C_{28}H_{26}N_4O \cdot 3.2$TFA) C, H, N.

(1*S*)-1-Benzo[1,3]dioxol-5-ylmethyl-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13ao). The title compound was synthesized as 3× TFA salt by method C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.08 (dd, J = 7.64, 2.65 Hz, 2H), 3.92 (m, 1H), 4.32 (dd, J = 10.45, 5.77 Hz, 1H), 4.46 (dd, J = 10.61, 2.81 Hz, 1H), 5.92 (d, J = 1.87 Hz, 2H), 6.80 (d, J = 1.87 Hz, 2H), 6.85 (s, 1H), 7.64 (d, J = 8.73 Hz, 1H), 7.74 (dd, J = 8.73, 1.56 Hz, 1H), 8.12 (s, 1H), 8.14 (d, J = 1.87 Hz, 1H), 8.45 (d, J = 1.87 Hz, 1H), 8.74 (s, 1H). MS (APCI): m/z 404 $(M + 1)^+$. Anal. ($C_{23}H_{22}N_4O_3 \cdot 2.6$TFA) C, H, N.

(1*S*)-1-(2,2-Difluoro-benzo[1,3]dioxol-4-ylmethyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (13ap). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.28 (m, 2H), 4.07 (m, 1H), 4.34 (dd, J = 10.61, 4.99 Hz, 1H), 4.51 (dd, J = 10.61, 2.81 Hz, 1H), 7.17 (m, 3H), 7.64 (d, J = 8.73 Hz, 1H), 7.75 (d, J = 8.73 Hz, 1H), 8.12 (s, 1H), 8.16 (s, 1H), 8.46 (s, 1H), 8.76 (s, 1H). MS (APCI): m/z 437 $(M - 1)^+$. Anal. ($C_{23}H_{20}F_2N_4O_3 \cdot 3$TFA) C, H, N.

(1*S*)-2-[5-(3-Methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-ethylamine (13aq). The title compound was synthesized as 3× TFA salt by method B. ^{1}H NMR (500 MHz, CD_3OD): δ 2.63 (s, 3H), 3.18 (dd, J = 14.19, 7.02 Hz, 1H), 3.24 (m, 1H), 4.02 (m, J = 5.15, 2.65 Hz, 1H), 4.33 (dd, J = 10.45, 5.46 Hz, 1H), 4.47 (dd, J = 10.61, 3.12 Hz, 1H), 7.29 (m, 2H), 7.34 (s, 1H), 7.63 (d, J = 8.73 Hz, 1H), 7.74 (dd, J = 8.74, 1.25 Hz, 1H), 8.11 (s, 2H), 8.44 (s, 1H), 8.72 (s, 1H). MS (APCI): m/z 487 $(M - 1)^+$. Anal. ($C_{23}H_{20}F_2N_4O_3 \cdot 3.1$TFA) C, H, N.

1-Bromo-3-(4-methoxybenzyloxy)benzene (21). A solution of 3-bromophenol (25 g, 144 mmol), *p*-methoxybenzyl chloride (22.5 g, 144 mmol), and cesium carbonate (117 g, 360 mmol) in DMF (200 mL) was stirred at rt for 18 h. Ethyl acetate (500 mL) was added, and the reaction mixture washed with brine (500 mL) and water (500 mL). The organic phase was concentrated and the residual solid was recrystallized from a 7:3 mixture of dichloromethane/ethanol to provide **21** as white solid. Yield: 33.7 g (80%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.76 (s, 3H), 5.03 (s, 2H), 6.92−6.94 (m, 1H), 6.95−6.97 (m, 1H), 6.98−7.03 (m, 1H), 7.10−7.14 (m, 1H), 7.20−7.21 (m, 1H), 7.22−7.25 (m, 1H), 7.34−7.37 (m, 1H), 7.37−7.40 (m, 1H). MS (DCI): m/z 294 $(M + H)^+$.

***tert*-Butyl 1-Hydroxy-3-(3-(4-methoxybenzyloxy)phenyl)propan-2-ylcarbamate (23).** To a suspension of magnesium turnings (1.64 g, 68 mmol) and a crystal of iodine in anhydrous THF (80 mL) was added dropwise a solution of **21** (20 g, 68 mmol) in anhydrous THF (56 mL) under nitrogen. The reaction mixture was heated under reflux until all magnesium was consumed. After cooling to rt, the formed Grignard solution was canulated into a suspension of *tert*-butyl 2-((*tert*-butyldimethylsilyloxy)-methyl)-aziridine-1-carboxylate (**22**,[18] 9.76 g, 34 mmol) and CuBr−SMe_2 (3.5 g, 17 mmol) in anhydrous THF (60 mL) at − 30 °C. The reaction mixture was stirred at −30 °C for 2 h and was quenched with aq NH_4Cl solution. Volatiles were removed and the residue was partitioned between EtOAc and brine. The organic phase was washed with water and concentrated. The residual solid was dissolved in anhydrous THF (100 mL) and cooled to 0 °C. A 1 M solution of TBAF in THF (100 mL) was then added, and the mixture was allowed to be warmed up to rt for 1 h. The dark solution was partitioned between ethyl acetate and brine. The organic phase was washed with water and concentrated. The residual oil was separated by flash chromatography on silica gel (60% EtOAc in hexane) to provide **23**. Yield: 11.97 g (91%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (s, 9H), 2.55 (d, J = 8.82 Hz, 1H), 2.78 (dd, J = 13.73, 5.26 Hz, 1H), 3.22−3.37 (m, 1H), 3.31 (s, 3H), 3.50−3.64 (m, 1H), 4.67 (t, J = 5.59 Hz, 1H), 4.97 (s, 2H), 6.57 (d, J = 8.48 Hz, 1H), 6.75−6.77 (m, 1H), 6.81 (br s, 1H), 6.85−6.83 (m, 1H), 6.92−6.94 (m, 1H), 6.94−6.97 (m, 1H), 7.16 (t, J = 7.80 Hz, 1H), 7.34 − 7.36 (m, 1H), 7.37 − 7.38 (m, 1H). MS (DCI): m/z 388 $(M + H)^+$.

***tert*-Butyl 6-(5-(2-(*tert*-Butoxycarbonylamino)-3-(3-(4-methoxybenzyloxy)phenyl)propoxy)-pyridin-3-yl)-3-methyl-1*H*-indazole-1-carboxylate (24).** A solution of **23** (12 g, 31 mmol), 5-bromopyridin-3-ol (**8**, 5.4 g, 31 mmol), and triphenylphosphine (12.2 g, 46.5 mmol) in anhydrous THF (150 mL) was cooled in an ice bath and stirred under nitrogen for 10 min. A solution of DBAD (10.7 g, 46.5 mmol) in anhydrous THF (100 mL) was added to the above solution and stirred at rt for 20 h. The solution was then concentrated and the residue was purified by flash chromatography (15% EtOAc in hexane) to give the ether formation product. This product was dissolved in anhydrous DMF (200 mL) and was added trimethylstannane **12** (9.44 g, 23.9 mmol), $Pd_2(dba)_3$ (2.98 g, 3.26 mmol), (o-tol)$_3$P (2.98 g), and triethylamine (9.1 mL). The reaction mixture was purged with N_2 and heated at 70 °C for 16 h. After cooling, the mixture was partitioned between ethyl acetate and brine. The organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash column chromatography on silica gel (50% EtOAc in hexane) to give **24**. Yield: 11.5 g (76%). ^{1}H NMR (300 MHz, CD_3OD): δ 1.40 (s, 9H), 1.72 (s, 9H), 2.61 (s, 3H), 2.85−2.92 (m, 1H), 2.93−3.01 (m, 1H), 3.74 (s, 3H), 4.08−4.19 (m, 3H), 4.85 (s, 2H), 6.78−6.84 (m, 2H), 6.84−6.88 (m, 2H), 6.88−6.91 (m, 1H), 7.14−7.18 (m, 1H), 7.19−7.25 (m, 2H), 7.64−7.68 (m, 1H), 7.82 (dd, J = 8.65, 1.86 Hz, 1H), 8.01−8.04 (m, 1H), 8.15 (d, J = 8.82 Hz, 1H), 8.24 (d, J = 2.71 Hz, 1H), 8.47 (d, J = 1.36 Hz, 1H). MS (DCI): m/z 695 $(M + H)^+$.

***tert*-Butyl 6-(5-(2-(*tert*-Butoxycarbonylamino)-3-(3-hydroxyphenyl)propoxy)pyridin-3-yl)-3-methyl-1*H*-indazole-1-carboxylate (25).** A solution of **24** (9.4 g) in methanol (95 mL) was treated with 10% Pd/C (2.85 g) under hydrogen of 60 psi at 50 °C for 6 h. Solid material was filtered off, and the methanol solution was concentrated. The dark residue was purified by flash chromatography on silica gel (50% EtOAc in hexane) to afford **25**. Yield: 6.5 g (83%). ^{1}H NMR (300 MHz, CD_3OD): δ 1.38−1.41 (m, 9H), 1.72−1.73 (m, 9H), 2.63 (s, 3H), 2.84−2.96 (m, 2H), 4.09−4.15 (m, 3H), 6.60−6.66 (m, 1H), 6.69−6.75 (m, 2H), 7.08 (t, J = 7.80 Hz, 1H), 7.67−7.71 (m, 1H), 7.86 (dd, J = 8.82, 1.70 Hz, 1H), 8.05 (d, J = 1.02 Hz, 1H), 8.17 (d, J = 8.82 Hz, 1H), 8.24 (d, J = 2.71 Hz, 1H), 8.47 (d, J = 1.70 Hz, 1H). MS (DCI): m/z 574 $(M + H)^+$.

(*S*)-1-(5-(3-Methyl-1*H*-indazol-5-yl)pyridin-3-yloxy)-3-(3-(2-morpholinoethoxy)phenyl)propan-2-amine (13ar). A solution of **25** (200 mg, 0.35 mmol), 4-(2-hydroxyethyl)-morpholine (91 mg, 0.70 mmol), and triphenylphosphine (182 mg, 0.70 mmol) in anhydrous THF (8 mL) was purged with N_2 and stirred in an ice-bath for 10 min. DBAD (160 mg, 0.70 mmol) was then added, and the reaction mixture stirred at rt for 20 h. After concentration, the residual oil was separated by flash chromatography (10% MeOH in EtOAc) to provide the ether product **26** (R″ = *N*-morpholinomethy). This product was dissolved in dichloromethane (6 mL) and was treated with trifluoroacetic acid (3 mL) at rt for 1 h. Acetonitrile (10 mL) was added, and the mixture was concentrated. The residual oil was purified by HPLC (Zorbax, C-18, 250 × 2.54 column; mobile phase A, 0.1% TFA in H_2O; mobile phase B, 0.1% TFA in CH_3CN; 0−100% gradient) to afford **13ar** (93 mg, 55%). ^{1}H NMR (400 MHz, CD_3OD): δ 2.62 (s, 3H), 3.16 (d, J = 7.67 Hz, 2H), 3.35 (s, 2H), 3.38−3.50 (m, 2H), 3.58−3.62 (m, 2H), 3.86−3.98 (m, 3H), 3.99−4.04 (m, 2H), 4.30 (dd, J = 10.74, 5.52 Hz, 1H), 4.35−4.39 (m, 2H), 4.44 (dd, J = 10.74, 3.07 Hz, 1H), 6.94−6.98 (m, 1H), 6.98−7.02 (m, 2H), 7.34 (t, J = 8.13 Hz, 1H), 7.61−7.65 (m, 1H), 7.73 (dd, J = 8.75, 1.69 Hz, 1H), 8.05−8.08 (m, 1H), 8.10 (d, J = 0.92 Hz, 1H), 8.41 (d, J = 1.84 Hz, 1H), 8.71 (s, 1H). MS (DCI): m/z 488 (M + H)$^+$. Anal. ($C_{28}H_{33}N_5O_3$·3.5TFA) C, H, N.

(*S*)-1-(5-(3-Methyl-1*H*-indazol-5-yl)pyridin-3-yloxy)-3-(3-(2-(piperidin-4-yl)ethoxy)phenyl)-propan-2-amine (13as). The title product was prepared as 3× TFA salt according to the procedure for **13ar** substituting *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate for 4-(2-hydroxyethyl)-morpholine. Yield: 158 mg (93%). ^{1}H NMR (500 MHz, CD_3OD): δ 1.35−1.46 (m, 2H), 1.71 (q, J = 6.34 Hz, 2H), 1.80−1.88 (m, 1H), 1.95 (d, J = 9.36 Hz, 2H), 2.62 (s, 3H), 2.93 (t, J = 12.79 Hz, 2H), 3.13 (d, J = 7.49 Hz, 2H), 3.32−3.37 (m, 2H), 3.93−4.03 (m, 3H), 4.26 (dd, J = 10.76, 5.46 Hz, 1H), 4.41 (dd, J = 10.60, 3.12 Hz, 1H), 6.84−6.88 (m, 2H), 6.91 (d, J = 7.80 Hz, 1H), 7.28 (t, J = 7.80 Hz, 1H), 7.62 (d, J = 8.73 Hz, 1H), 7.71 (dd, J = 8.73, 1.56 Hz, 1H), 7.96−7.98 (m, 1H), 8.07 (d, J = 0.62 Hz, 1H), 8.37 (d, J = 1.87 Hz, 1H), 8.67 (s, 1H). MS (DCI): m/z 486 (M + H)$^+$. Anal. ($C_{29}H_{35}N_5O_2$·3.3TFA) C, H, N.

(*S*)-1-(5-(3-Methyl-1*H*-indazol-5-yl)pyridin-3-yloxy)-3-(3-(piperidin-4-ylmethoxy)phenyl)-propan-2-amine (13at). The title product was prepared as 4× TFA salt according to the procedure for **13ar**, substituting *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate for 4-(2-hydroxyethyl)-morpholine. Yield: 86 mg (52%). ^{1}H NMR (400 MHz, CD_3OD): δ 1.49−1.63 (m, 1H), 2.02 (d, J = 14.12 Hz, 2H), 2.06−2.15 (m, 1H), 2.60−2.65 (m, 3H), 2.95−3.05 (m, 2H), 3.11 (dd, J = 20.71, 7.52 Hz, 2H), 3.41 (d, J = 9.82 Hz, 2H), 3.79−3.88 (m, 2H), 3.90−4.03 (m, 2H), 4.23−4.34 (m, 1H), 4.43 (dd, J = 10.59, 5.98 Hz, 1H), 6.71−6.77 (m, 1H), 6.77−6.88 (m, 1H), 6.89−6.94 (m, 1H), 7.15−7.34 (m, 1H), 7.59−7.66 (m, 1H), 7.70−7.76 (m, 1H), 8.00−8.10 (m, 1H), 8.09−8.13 (m, 1H), 8.38−8.46 (m, 1H), 8.71 (d, J = 5.22 Hz, 1H). MS (DCI): m/z 472 (M + H)$^+$.

(*S*)-1-(3-Cyclohexylmethoxy-benzyl)-2-[5-(3-methyl-1*H*-indazol-6-yl)-pyridin-3-yloxy]-ethylamine (13au). The title product was prepared as 2× TFA salt according to the procedure for **13ar**, substituting cyclohexylmethylalcohol for 4-(2-hydroxyethyl)-morpholine. Yield: 133 mg (81%). ^{1}H NMR (400 MHz, CD_3OD): δ 0.86−1.02 (m, 2H), 1.07−1.28 (m, 3H), 1.57−1.67 (m, 4H), 1.72 (d, J = 12.58 Hz, 2H), 2.57 (s, 3H), 3.05−3.15 (m, 2H), 3.55−3.70 (m, 2H), 3.86−3.97 (m, 1H), 4.26 (dd, J = 10.59, 5.37 Hz, 1H), 4.41 (dd, J = 10.59, 2.92 Hz, 1H), 6.78 (dd, J = 8.29, 2.15 Hz, 1H), 6.81 (s, 1H), 6.84 (d, J = 7.67 Hz, 1H), 7.21 (t, J = 7.82 Hz, 1H), 7.55−7.59 (m, 1H), 7.67 (dd, J = 8.90, 1.53 Hz, 1H), 8.05 (d, J = 0.61 Hz, 1H), 8.06−8.08 (m, 1H), 8.39 (d, J = 2.45 Hz, 1H), 8.68 (d, J = 1.23 Hz, 1H). MS (ESI): m/z 471 (M + H)$^+$. Anal. ($C_{29}H_{34}N_4O_2$·2.0TFA) C, H, N.

(*S*)-2-[5-(3-Methyl-1*H*-indazol-6-yl)-pyridin-3-yloxy]-1-[3-(1-methyl-piperidin-4-ylmethoxy)-benzyl]-ethylamine (13av). The title product was prepared as 3× TFA salt according to the procedure for **13ar**, substituting 1-methyl-4-(hydroxymethyl)-piperidine for 4-(2-hydroxyethyl)-morpholine. Yield: 105 mg (63%). ^{1}H NMR (500 MHz, CD_3OD): δ 1.53−1.67 (m, 2H), 1.97−2.10 (m, 3H), 2.62 (s, 3H), 2.85 (s, 3H), 2.95−3.03 (m, 2H), 3.13 (d, J = 7.80 Hz, 2H), 3.52 (d, J = 12.16 Hz, 2H), 3.78−3.88 (m, 2H), 3.92−4.00 (m, 1H), 4.25 (dd, J = 10.60, 5.30 Hz, 1H), 4.40 (dd, J = 10.60, 2.81 Hz, 1H), 6.84−6.90 (m, 2H), 6.92 (d, J = 7.80 Hz, 1H), 7.29 (t, J = 7.80 Hz, 1H), 7.61 (d, J = 8.73 Hz, 1H), 7.71 (dd, J = 8.73, 1.56 Hz, 1H), 7.95 (d, J = 1.87 Hz, 1H), 8.06 (s, 1H), 8.36 (d, J = 2.18 Hz, 1H), 8.66 (s, 1H). MS (ESI): m/z 486 (M + H)$^+$. Anal. ($C_{29}H_{35}N_5O_2$·3.6TFA) C, H, N.

(*S*)-1-[3-(2-Amino-ethoxy)-benzyl]-2-[5-(3-methyl-1*H*-indazol-6-yl)-pyridin-3-yloxy]-ethylamine (13aw). The title product was prepared as 3× TFA salt according to the procedure for **13ar**, substituting *t*-butyl 2-hydroxyethylamine-1-carboxylate for 4-(2-hydroxyethyl)-morpholine. Yield: 132 mg (91%). ^{1}H NMR (500 MHz, CD_3OD): δ 2.61 (s, 3H), 3.15 (d, J = 7.49 Hz, 2H), 3.31−3.35 (m, 2H), 3.95−4.02 (m, 1H), 4.17−4.22 (m, 2H), 4.27 (dd, J = 10.60, 5.61 Hz, 1H), 4.41 (dd, J = 10.60, 2.81 Hz, 1H), 6.96 (d, J = 8.42 Hz, 1H), 6.97−7.01 (m, 2H), 7.29−7.36 (m, 1H), 7.61 (d, J = 8.73 Hz, 1H), 7.71 (dd, J = 8.73, 1.56 Hz, 1H), 7.98 (s, 1H), 8.07 (s, 1H), 8.37 (s, 1H), 8.68 (s, 1H). MS (ESI): m/z 418 (M + H)$^+$. Anal. ($C_{24}H_{27}N_5O_2$·3.5TFA) C, H, N.

(*S*)-*tert*-Butyl 1-(3-(Trifluoromethyl)phenyl)-3-(5-(trimethylstannyl)pyridin-3-yloxy)propan-2-ylcarbamate (27). A 100 mL RBF was charged with $Pd(PPh_3)_4$ (843 mg, 0.73 mmol) and bromide **10** (R= 3-CF_3, 3.47 g, 7.3 mmol) that was synthesized as described in the general synthesis of **13** (step A). After purging with N_2, anhydrous toluene (50 mL) and hexamethylditin (4.78 g, 14.6 mmol) were added via syringe. The solution was purged with N_2 again and was heated at 115 °C (oil bath) for 3 h. After cooling, the black reaction mixture was directly loaded to a silica gel column that was eluted with 30−70% gradient EtOAc in hexane to give **27**. Yield: 3.27 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.34 (s, 9H), 1.41 (s, 9H), 3.07 (d, J = 7.46 Hz, 2H), 3.90−4.03 (m, 1H), 4.20 (m, 1H), 4.91 (m, 1H), 7.27 (d, J = 3.05 Hz, 1H), 7.41 (d, J = 5.09 Hz, 2H), 7.47 (s, 2H), 8.21 (d, J = 3.05 Hz, 1H), 8.24 (s, 1H). MS (DCI): m/z 560 (M + H)$^+$.

(*S*)-1-Phenyl-3-(5-(trimethylstannyl)pyridin-3-yloxy)propan-2-amine (28). The title compound was prepared according to the procedure for **27**, substituting (*S*)-*tert*-butyl 1-phenyl-3-hydroxypropan-2-ylcarbamate for [1-hydroxymethyl-2-(3-trifluoromethyl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester. Yield: 100%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.34 (s, 9H), 1.43 (s, 9H), 3.00 (d, J = 7.46 Hz, 2H), 3.90−3.96 (m, 2H), 4.12−4.22 (m, 1H), 4.85−4.95 (m, 1H), 7.19−7.31 (m, 6H), 8.19−8.23 (m, 2H). MS (APCI): m/z 492 (M + H)$^+$.

(*S*)-1-(2,3-Difluorophenyl)-3-(5-(trimethylstannyl)pyridin-3-yloxy)propan-2-amine (29). The title compound was prepared according to the procedure for **27**, substituting (*S*)-*tert*-butyl 1-(2,3-difluorophenyl)-3-hydroxypropan-2-ylcarbamate for [1-hydroxymethyl-2-(3-trifluoromethyl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester. Yield: 72%. ^{1}H NMR (300 MHz, CD_3OD): δ 0.25 − 0.45 (m, 9H), 1.35 (s, 9H), 2.83−2.94 (m, 1H), 3.08−3.17 (m, 1H), 4.07 (d, J = 5.09 Hz, 2H), 4.13−4.22 (m, 1H), 7.04−7.09 (m, 2H), 7.08−7.16 (m, 1H), 7.50 (dd, J = 3.05, 1.02 Hz, 1H), 8.12 (s, 1H), 8.14 (d, J = 3.05 Hz, 1H). MS (DCI): m/z 528 (M + H)$^+$.

(*S*)-5-(5-(2-Amino-3-phenylpropoxy)pyridin-3-yl)indolin-2-one (34). The title compound was synthesized from **28** and **30**[15] as TFA salt, according to the general synthesis of compound **13**, method 1 (steps B and C). Yield: 26%. ^{1}H NMR (500 MHz, CD_3OD): δ 3.15 (d, J = 7.49 Hz, 2H), 3.61 (s, 2H), 3.91−3.99 (m, 1H), 4.26 (dd, J = 10.61, 5.62 Hz, 1H), 4.40 (dd, J = 10.61, 3.12 Hz, 1H), 7.04 (d, J = 8.11 Hz, 1H), 7.28−7.34 (m, 3H), 7.35−7.40 (m, 2H), 7.58 (d, J = 8.11 Hz, 1H), 7.62 (s, 1H), 7.94−7.99 (m, 1H), 8.38 (d, J = 2.50 Hz, 1H), 8.60 (d, J = 0.94 Hz, 1H). MS (ESI): m/z 360 (M + H)$^+$. Anal. ($C_{22}H_{21}N_3O_2$·2.3TFA) C, H, N.

(*S,Z*)-3-((1*H*-Pyrrol-2-yl)methylene)-5-(5-(2-amino-3-phenylpropoxy)pyridin-3-yl)indolin-2-one (35). The title compound was synthesized from **28** and **31**[15] as HCl salt according to general synthesis of compound **13**, method 1 (steps B and C). Yield: 55%. ^{1}H NMR (500 MHz, CD_3OD): δ 3.22 (d, J = 7.80 Hz, 2H), 4.01−

4.09 (m, 1H), 4.45 (dd, J = 10.29, 5.62 Hz, 1H), 4.58 (dd, J = 10.61, 2.81 Hz, 1H), 6.35−6.39 (m, 1H), 6.87 (d, J = 2.18 Hz, 1H), 7.06 (d, J = 8.11 Hz, 1H), 7.25 (s, 1H), 7.30−7.35 (m, 1H), 7.37−7.43 (m, 4H), 7.60 (dd, J = 8.11, 1.56 Hz, 1H), 7.80 (s, 1H), 8.09 (d, J = 1.25 Hz, 1H), 8.51 (d, J = 1.25 Hz, 1H), 8.53 (d, J = 2.18 Hz, 1H), 8.84 (s, 1H). MS (ESI): m/z 437 $(M + H)^+$. Anal. ($C_{27}H_{24}N_4O_3$·2.8HCl) C, H, N.

(*S*)-5-(5-(2-Amino-3-phenylpropoxy)pyridin-3-yl)-3-(furan-2-ylmethylene)indolin-2-one (36). The title compound was synthesized from **28** and **32**[15] as HCl salt according to general synthesis of compound **13**, method 1 (steps B and C). Yield: 9%. ^{1}H NMR (500 MHz, CD_3OD): δ 3.21 (d, J = 7.80 Hz, 2H), 4.02−4.09 (m, 1H), 4.43 (dd, J = 10.45, 5.77 Hz, 1H), 4.58 (dd, J = 10.45, 2.96 Hz, 1H), 6.76 (dd, J = 3.43, 1.87 Hz, 1H), 7.10 (d, J = 8.11 Hz, 1H), 7.15 (d, J = 3.43 Hz, 1H), 7.30−7.35 (m, 1H), 7.36−7.41 (m, 4H), 7.45 (s, 1H), 7.71 (dd, J = 8.11, 1.87 Hz, 1H), 8.01 (d, J = 1.56 Hz, 1H), 8.40−8.44 (m, 1H), 8.62 (d, J = 1.87 Hz, 1H), 8.79 (d, J = 1.87 Hz, 1H), 8.82 (s, 1H). MS (ESI): m/z 438 $(M + H)^+$. Anal. ($C_{27}H_{23}N_3O_3$·2.1HCl) C, H, N.

General Procedure for Synthesis of 37. A suspension of bromide **33** (0.48 mmol), trimethylstannane **27**−**29** (0.48 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (26 mg, 0.05 mmol), and cesium fluoride (218 mg, 1.44 mmol) in anhydrous dioxane (10 mL) was heated at 80 °C under nitrogen for 15 h. After cooling, the reaction mixture was partitioned between EtOAc and brine. The organic phase was washed with water, dried ($MgSO_4$), filtered, and concentrated. The residual oil was purified by flash column chromatography on silica gel to provide the Stille product. This product was dissolved in dichloromethane (6 mL), and was treated with TFA (3 mL) at rt for 1 h. Acetonitrile (10 mL) was added and the mixture was concentrated. The residual oil was purified by HPLC (Zorbax, C-18, 250 × 2.54 column; mobile phase A, 0.1% TFA in H_2O; mobile phase B, 0.1% TFA in CH_3CN; 0−100% gradient) to provide **37** as TFA salt.

(*S*)-1-(5-(1*H*-Pyrazolo[3,4-*c*]pyridin-5-yl)pyridin-3-yloxy)-3-(3-(trifluoromethyl)phenyl)propan-2-amine (37a). Yield: 37%. ^{1}H NMR (300 MHz, CD_3OD): δ 3.23−3.28 (m, 2H), 4.05 (dd, J = 4.58, 2.88 Hz, 1H), 4.27 (dd, J = 10.68, 5.26 Hz, 1H), 4.45 (dd, J = 10.51, 3.05 Hz, 1H), 7.60−7.64 (m, 3H), 7.70 (s, 1H), 8.30 (s, 1H), 8.33−8.35 (m, 1H), 8.42−8.45 (m, 2H), 8.99 (d, J = 1.70 Hz, 1H), 9.16 (s, 1H). MS (DCI): m/z 414 $(M + H)^+$.

(*S*)-1-(5-(3-Chloro-1*H*-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-3-(3-(trifluoromethyl)-phenyl)propan-2-amine (37b). Yield: 23%. ^{1}H NMR (300 MHz, CD_3OD): δ 3.23−3.28 (m, 2H), 4.00−4.07 (m, 1H), 4.24−4.29 (m, 1H), 4.43 (dd, J = 10.51, 3.05 Hz, 1H), 7.60−7.63 (m, 3H), 7.69 (s, 1H), 8.29 (d, J = 1.36 Hz, 2H), 8.42 (d, J = 2.71 Hz, 1H), 9.01 (d, J = 1.70 Hz, 1H), 9.12 (s, 1H). MS (DCI): m/z 448 $(M + H)^+$.

(*S*)-1-(5-(3-Methyl-1*H*-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-3-(3-(trifluoromethyl)-phenyl)propan-2-amine (37c). Yield: 22%. ^{1}H NMR (500 MHz, CD_3OD): δ 2.66 (s, 3H), 3.22−3.28 (m, 2H), 4.02−4.08 (m, 1H), 4.28 (dd, J = 10.60, 5.30 Hz, 1H), 4.45 (dd, J = 10.60, 3.12 Hz, 1H), 7.56−7.60 (m, 1H), 7.61−7.65 (m, 2H), 7.69 (s, 1H), 8.33−8.35 (m, 1H), 8.39 (d, J = 0.94 Hz, 1H), 8.43 (d, J = 2.49 Hz, 1H), 9.00 (d, J = 0.94 Hz, 1H), 9.07 (d, J = 1.25 Hz, 1H). MS (DCI): m/z 428 $(M + H)^+$. Anal. ($C_{22}H_{20}F_3N_5O$·2.2TFA) C, H, N.

(*S*)-1-(2,3-Difluorophenyl)-3-(5-(3-methyl-1*H*-pyrazolo[3,4-*c*]-pyridin-5-yl)pyridin-3-yloxy)propan-2-amine (37d). Yield: 4%. ^{1}H NMR (300 MHz, CD_3OD): δ 2.67 (s, 3H), 3.24−3.29 (m, 2H), 3.97−4.06 (m, 1H), 4.22−4.30 (m, 1H), 4.43 (dd, J = 10.51, 3.05 Hz, 1H), 7.15−7.20 (m, 2H), 7.22−7.29 (m, 1H), 8.24 (dd, J = 2.88, 1.86 Hz, 1H), 8.36 (d, J = 1.36 Hz, 1H), 8.39 (d, J = 2.71 Hz, 1H), 8.96 (d, J = 1.70 Hz, 1H), 9.06 (d, J = 1.02 Hz, 1H). MS (DCI): m/z 396 $(M + H)^+$. Anal. ($C_{21}H_{19}F_2N_5O$·3.0TFA) C, H, N.

Biological Assays and In Vivo Studies. All biological assays and in vivo studies were performed according to the same protocols reported previously.[14a]

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Supporting Information Available: Full combustion data available for the majority of final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Crystallization and X-ray analysis. PKA was purified, concentrated to 20 mg/mL, and complexed with PKI peptide for 1 hour and then complexed with Akt inhibitors. Crystals were transferred to cryo-solutions that contained well solution plus increasing amounts of glycerol, soaking for 1 minute in 5%, 15%, and 25% glycerol. Crystals were then frozen in a stream of 100 K nitrogen using an Oxford Cryo-stream cooling device. Diffraction data were recorded using a MAR-165 CCD detector system on a Rigaku RU-2000 rotating anode X-ray generator operating at 100 mA and 50 kV. Diffraction data were reduced using DENZO and the protein model (accession number 1YDT) with the inhibitor (H89), and the phosphorylation sites omitted from the Protein Data Bank entry 1YDT were used for initial phasing. Generation of initial electron density maps and structure refinement was achieved using CNX program package. Electron density maps were inspected on a Silicon Graphics Inc. workstation using the program QUANTA 97/2001 (Molecular Simulations Inc., San Diego, CA). Crystallographic data described in this paper have been deposited with PDB (ID for 4: 2UZU, ID for 7: 2UZT, ID for 13au: 2UZV, ID for 131: 2UZW).

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