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ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 2441–2452
Bioorganic & Medicinal Chemistry

Design and synthesis of pyridine–pyrazolopyridine-based inhibitors of protein kinase B/Akt

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Received 2 November 2006; revised 10 January 2007; accepted 11 January 2007
Available online 17 January 2007

Abstract—Thr-211 is one of three different amino acid residues in the kinase domain of protein kinase B/Akt as compared to protein kinase A (PKA), a closely related analog in the same AGC family. In an attempt to improve the potency and selectivity of our indazole–pyridine series of Akt inhibitors over PKA, efforts have focused on the incorporation of a chemical functionality to interact with the hydroxy group of Thr-211. Several substituents including an oxygen anion, amino, and nitro groups have been introduced at the C-6 position of the indazole scaffold, leading to a significant drop in Akt potency. Incorporation of a nitrogen atom into the phenyl ring at the same position (i.e., **9f**) maintained the Akt activity and, in some cases, improved the selectivity over PKA. The structure–activity relationships of the new pyridine–pyrazolopyridine series of Akt inhibitors and their structural features when bound to PKA are also discussed.

1. Introduction

Protein kinase B, also known as Akt, is a 57-kDa serine/threonine kinase that plays critical roles in anti-apoptotic processes.[1] Overexpression of Akt can result from inactivation of tumor suppressor PTEN and has been correlated with an increasing number of human cancers.[2] Akt is also responsible for promoting survival signals that downregulate apoptotic pathways and contribute to cancer progression.[3] Correlation between resistance to chemotherapy and Akt activation has also been observed in prostate cancer cell lines and in human tumor tissue.[4] Inhibition of Akt alone or in combination with other standard cancer chemotherapeutics results in increased programmed death of cancer cells, leading to decreased tumor growth and tumor resistance to chemotherapy.

As summarized in two review articles,[5,6] a significant number of small molecule inhibitors of Akt have been developed and shown to sensitize tumor cells to apoptotic stimuli. Some of these Akt inhibitors slowed the tumor growth in animal models. We have reported several series of potent and ATP competitive inhibitors of Akt.[7] These single-digit nanomolar inhibitors have demonstrated very good selectivity over more distinct members of protein kinase family but are less selective against some of the highly homologous kinases, especially the closely related protein kinase A (PKA). By using structure-based approaches, Breitenlechner et al. discovered several nanomolar Akt selective inhibitors over PKA.[8] Herein, to further improve the potency and selectivity of our indazole–pyridine series of inhibitors, we have incorporated a variety of substituents or chemical moieties at the C-6 position of the indazole scaffold to interact with the hydroxy group of Thr-211, one of the three different amino acid residues in the kinase domain of Akt as compared to PKA. These efforts have resulted in the discovery of a new series of potent and selective pyrazolopyridine inhibitors of Akt. An X-ray structure of our reference inhibitor **1** bound to PKA provided guidance in these efforts.

Keywords: Protein kinase B; Akt inhibitor; Serine/threonine kinase; Pyrazolopyridine.
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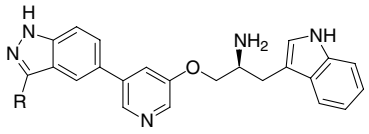
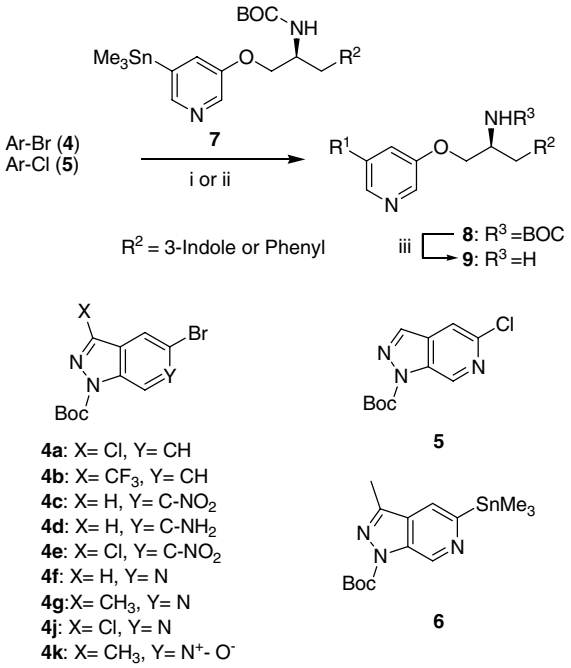
doi:10.1016/j.bmc.2007.01.010



1: R= H
2: R= Cl
3: R= CF_3

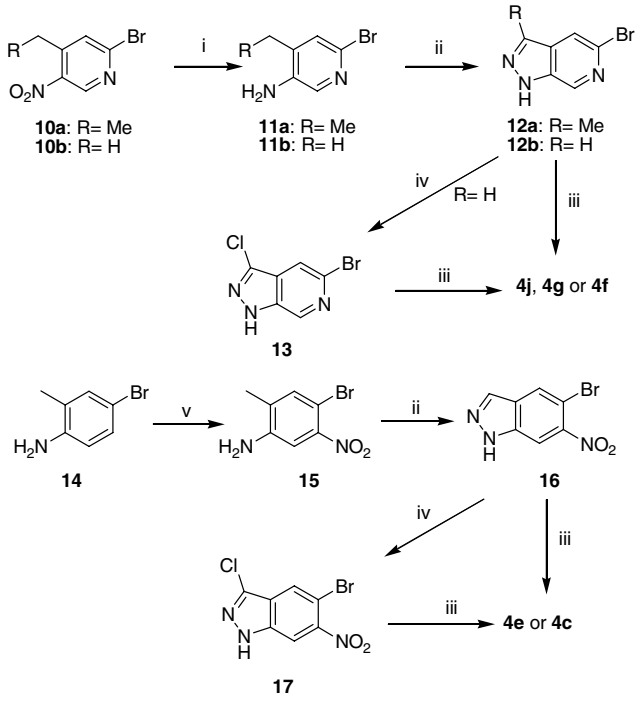
2. Chemical synthesis

A general synthesis of the indazole–pyridine series of Akt inhibitors and pyrazolo[3,4-c]pyridine–pyridine-based inhibitors is depicted in Scheme 1. Stille reactions of either an arylbromide **4** or arylchloride **5** with trimethylstannane **7**,[9] under the catalysis of tri-*o*-tolylphosphine and $Pd_2(dba)_3$ (for bromide **4**) or bis(tri-*tert*-butylphosphine)palladium (0) (for chloride **5**), provided compound **8**. While the typical yields for the coupling of bromoindazoles **4a** and **4b** with **7** were around 70%, the reactions of **4c**–**4j**, under the same conditions, were less efficient, affording less than 35% of desired products. In the case of **4g**, the best catalysis was found to be either bis(tri-*tert*-butylphosphine)palladium (0) or $Pd_2(dba)_3$, leading to desired product in 20% yield. Other ligands including Nolan's,[10] BINAP, and tri-2-furylphosphine did not furnish any desired product. To improve the coupling reaction, we also explored reversal of the Stille coupling partners. However, we were not able to synthesize trimethylstannane **6** by either the standard metal-exchange/Me_3SnCl procedure or a

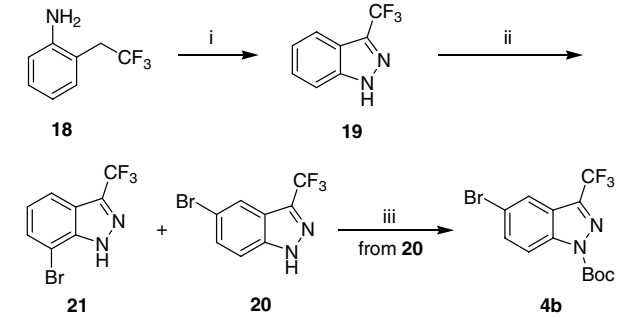


4a: X= Cl, Y= CH
4b: X= CF_3, Y= CH
4c: X= H, Y= C-NO_2
4d: X= H, Y= C-NH_2
4e: X= Cl, Y= C-NO_2
4f: X= H, Y= N
4g:X= CH_3, Y= N
4j: X= Cl, Y= N
4k: X= CH_3, Y= N^+- O^-

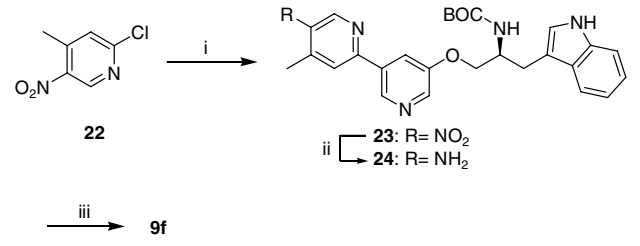
Scheme 1. Reagents and conditions for Ar–Br: (i) $Pd_2(dba)_3$, P(*o*-tol)$_3$, Et_3N, DMF, 80 °C, 6 h; for Ar–Cl: (ii) bis(tri-*tert*-butylphosphine)palladium (0), CsF, dioxane, 90 °C, overnight, 30%; (iii) CF_3CO_2H, CH_2Cl_2, yield: 40–90%.



Scheme 2. Reagents and conditions: (i) H_2, Raney Ni, THF, yield: 85–100%; (ii) $NaNO_2$, HOAc, H_2O, rt, 3 days, yield: 63–86%; (iii) $(Boc)_2O$, Et_3N, DMAP, CH_3CN, rt, overnight, yield: 90–100%; (iv) 10–13% NaClO, H_2O, NaOH, 0 °C, 5 h, yield: 77–95%; (v) KNO_3, H_2SO_4, rt, overnight, 95%.



Scheme 3. Reagents and conditions: (i) $NaNO_2$, HOAc, H_2O, rt, 3 days, yield: 49% (as a 1:1 mixture with an uncharacterized side-product); (ii) NBS, CH_3CN, rt, 2 days, yields: 35% of **20** and 6% of **21**; (iii) $(Boc)_2O$, Et_3N, DMAP, CH_3CN, rt, yield: 86%.



Scheme 4. Reagents and conditions: (i) compound **7** (R^2 = 3-indole), $Pd_2(dba)_3$, P(2-Fur)$_3$, Et_3N, DMF, 75 °C, 8 h, yield: 64%; (ii) H_2, Raney Ni, THF, rt, 3 h, yield: 89%; (iii) a—$NaNO_2$, HOAc, H_2O, rt, 3 days, yield: 30%; b—CF_3CO_2H, CH_2Cl_2, yield: 40%.

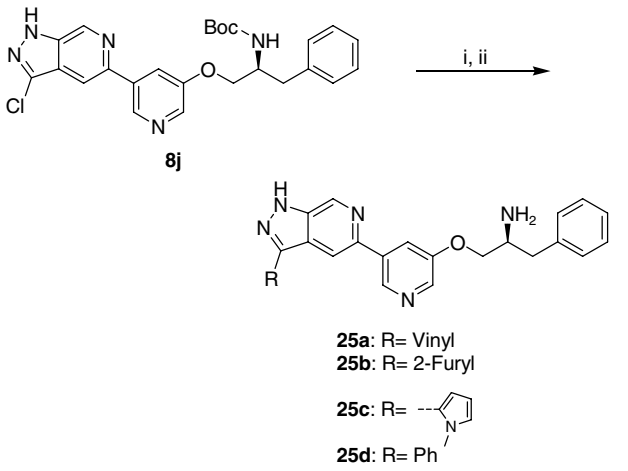
palladium-catalyzed reaction [$Pd(PPh_3)_4/Me_3SnSnMe_3$/toluene/100 °C]. The Stille reaction of arylchloride **5** with **7**, using tri-*o*-tolylphosphine, tri-2-furylphosphine, Xantphos, and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl (Cy-MAP) as ligands, failed to provide any coupled product as well. Boc-deprotection of compound **8** with trifluoroacetic acid afforded **9**.

As shown in Scheme 2, aryl bromides **4c–j** were synthesized by oxidative cyclization of appropriately substituted 3-amino-4-methylpyridine (e.g., **11**) or *ortho*-aminotoluene (e.g., **15**). Intermediates **11a** and **11b** were in turn prepared by reduction of nitro-precursor **10**. Nitration of commercially available **14** with one equivalent of KNO_3 in concentrated H_2SO_4 afforded intermediate **15** in nearly quantitative yield. Treatment of **12** or **16** with aqueous sodium hypochlorite provided 3-chloropyrazolopyridine **13** or indazole **17**. Boc-protection of **12**, **13**, **16**, and **17** then furnished compound **4**.

The synthesis of 3-trifluoromethylindazole **4b** is described in Scheme 3. Starting material **18** was prepared as a 1:4 mixture with aniline according to a literature procedure.[11] Treatment of the mixture with sodium nitrite in acetic acid as described in Scheme 2 provided indazole **19** in 49% yield as a 1:1 mixture with an uncharacterized side product. Bromination of the impure **19** with *N*-bromosuccinimide afforded 35% of 5-bromo derivative **20** and 6% of 7-bromo analog **21**. Boc-protection of **20** provided **4b**, which was converted to **3** as described in Scheme 1.

Due to the poor yields of the Stille coupling of **7** with both chloride **5** and bromide **4f**, an alternative synthetic route as shown in Scheme 4 was also investigated. The commercially available chloride **22** was first coupled with trimethylstannane **7** (R^2 = 3-indole), under the catalysis of $Pd_2(dba)_3$ and tri-2-furylphosphine, affording **23** in 64% yield. Reduction of **23**, followed by oxidative cyclization of **24** with sodium nitrite, gave, after Boc-deprotection, **9f** in 12% overall yield from **23**.

Syntheses of 3-substituted pyrazolopyridine analogs **25a–d** are described in Scheme 5. The 3-chloro-functionality in **8j**, prepared according to the general protocol described in Scheme 1, readily underwent Stille reaction with a variety of tin reagents in modest to good yields, using Cy-MAP as ligand. Boc-deprotection of the coupled products afforded **25a–d**.



Scheme 5. Reagents and conditions: (i) a—tributylvinyltin, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, $Pd_2(dba)_3$, Et_3N, DMF, 85 °C, 3 h, Yield: 64%; b—tributylvinyltin was replaced with 2-tributylstannylfuran, yield: 70%; c—replaced with *N*-methyl-2-tributylstannylpyrrole, yield: 37%, d—replaced with tributylphenyltin, yield: 52%; (ii) CF_3CO_2H, CH_2Cl_2, yield: 60–80%.

3. Results and discussion

We previously reported our indazole–pyridine series of compounds as exemplified by **1** as very potent Akt inhibitors (K_i = 1 nM for **1**).[7g] Major drawbacks of this series of Akt inhibitors as clinically useful agents include short half-life in animals and poor oral bioavailability. Substitution at C-3 position of the indazole scaffold by alkyl, aryl, and amino groups failed to provide Akt inhibitors with improved pharmacokinetic properties. Herein, relatively more inert chloro- and trifluoromethyl groups were also introduced at the same position of the indazole, in an effort to block the potentially labile site of metabolism.

To structurally understand the binding mode of our indazole–pyridine series of Akt inhibitors and to find potential sites of modification to improve selectivity over other closely related protein kinases, we crystallized our reference compound **1** with PKA, a highly homologous protein kinase of Akt in the same AGC family. The structure was resolved at 2.2 Å and is illustrated in Figure 1. Corresponding residues for Akt in the ATP binding site are shown on left. As shown in Figure 1, four key hydrogen bonding interactions of **1** (Val-123, Glu-121, Lys-72, and Asn-171/Asp-184) are important for its high-affinity to PKA (IC_{50} = 18 nM). The hydrophobic indole moiety in **1** fits nicely underneath the glycine-rich loop. As indicated on the left, Akt has three different amino residues, namely Thr-211, Met-173, and Ala-123, in the ligand-binding domain. It was thought that introduction of an appropriate functionality at

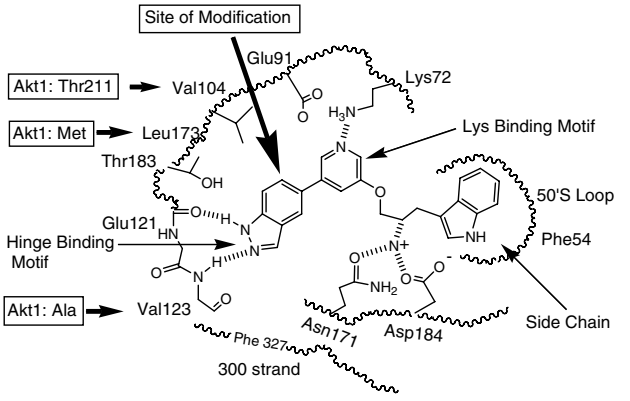
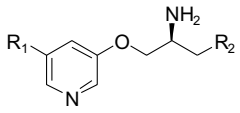


Figure 1. An illustration of the X-ray structure of **1** bound to protein kinase A. Shown on left are the corresponding amino acid residues in Akt.

Table 1. Enzyme and cellular assay results for compounds **1**–**3** and **9**



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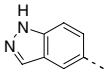
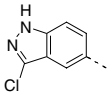
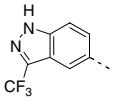
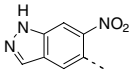
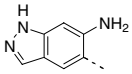
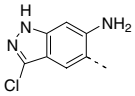
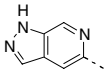
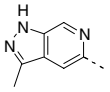
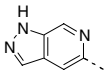
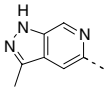
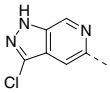
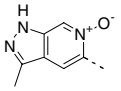
Compound	R^1	R^2	Akt1 IC_{50}[a] (nM)	PKA IC_{50}[a] (nM)	MTT (MiaPaCa) EC_{50}[a] (μM)
1		3-Indole	1.5	18	0.82
2		3-Indole	1.0	6.8	0.38
3		3-Indole	1.8	16	1.29
9c		3-Indole	953	nd[b]	2.94
9d		3-Indole	51	nd	nd
9e		3-Indole	7.1	58	0.33
9f		3-Indole	0.6	110	1.16
9g		3-Indole	0.34	15	0.041
9h		Ph	223	nd	1.69
9i		Ph	25	32	0.68
9j		Ph	59	46	nd
9k		Ph	104	nd	nd

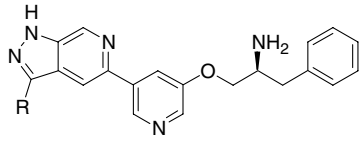
[a] Values are means of two or more experiments. All compounds were tested under 5 μM ATP.
[b] Not determined.

the C-6 position of the indazole scaffold would interact with the hydroxyl group of Thr-211 and would improve the binding affinity to Akt.

As shown in Table 1, both chloro-analog **2** and trifluoromethyl-analog **3** displayed a similar profile of activity as compound **1**. Installation of a nitro group at the C-6 position of the indazole moiety resulted in nearly three orders of magnitude loss of potency against Akt, suggesting a limited space between the indazole and protein. Reduction of the nitro to an amino group partially restored the potency as exemplified by both **9d** and **9e**, the latter with a chlorine at the C-3 position of the indazole. Since it appeared that a hydrogen bond accepting group was preferred and due to space constraints, we next incorporated a nitrogen atom into the phenyl ring of the indazole at the same position. The resulting pyrazolopyridine analog **9f** demonstrated a sub-nanomolar IC_{50} to Akt and was more than 100-fold selective over PKA. A 3-methyl analog **9g** showed excellent potency against Akt as well (IC_{50} = 0.34 nM).

In a previous investigation, the pharmacokinetic profile of the indazole–pyridine series of Akt inhibitors was successfully improved through a replacement of the indole side-chain moiety with a phenyl group.[7f]

Table 2. Enzyme and cellular assay results for compounds **9h–j** and **25**



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Compound	R	Akt1 IC_{50}[a] (nM)	PKA IC_{50}[a] (nM)	MTT (MiaPaCa) EC_{50}[a] (μM)
9h	H	223	nd[b]	1.69
9i	CH_3	25	32	0.68
9j	Cl	59	46	nd[b]
25a	Vinyl	13	32	0.66
25b	2-Furyl	6.1	274	1.2
25c		228	nd[b]	nd
25d	Ph	8.3	371	0.584

[a] Values are means of two or more experiments. All compounds were tested under 5 μM ATP.
[b] Not determined.

Therefore, analogs of the current pyrazolopyridine series with a phenyl-containing side chain were synthesized and the results are summarized in Tables 1 and 2. Unlike analogs with an indole side chain, compounds **9h–j** with a phenyl group are much less potent. There was no selectivity against PKA observed as well. In addition, the 3-methylpyrazolopyridine analog **9i** was 9-fold more potent than the un-substituted **9h**. An *N*-oxide analog **9k**, where the oxygen anion serves as a hydrogen bond acceptor, is 4-fold less potent than compound **9i**.

Table 2 summarizes our preliminary investigation at the C-3 position of the pyrazolopyridine scaffold containing a phenyl side chain. Surprisingly, 2-furyl (**25b**) and phenyl (**25d**) analogs were 20-fold more potent than the sterically similar *N*-methyl-pyrrol-2-yl derivative (**25c**). Smaller substituents such as vinyl- (**25a**), chloro- (**9j**), and methyl- (**9i**) only showed slightly reduced potency against Akt as compared to **25b** or **25d**. Compounds **25b** and **25d** were 10-fold more selective versus PKA than compounds **9i**, **9j**, and **25a**. The best selectivity was observed for compound **9f** with an indole side-chain. Also included in Tables 1 and 2 are the MTT data of our Akt inhibitors in MiaPaCa-2 human pancreatic cancer cells as an indication of their anti-proliferative activity. The majority of these compounds showed correlations between Akt activity and cytotoxicity. A combination of factors including cell penetration and selectivity would complicate the direct comparison of enzyme and cellular activity.

Displayed in Table 3 is a head-to-head comparison of the selectivity profile between **9f** and **1**. Compound **9f** demonstrates 10-fold higher selectivity than compound **1** against PKA. The Akt selectivity of **9f** over other selected protein kinases in AGC, CAMK, and TK families is similar to that of compound **1**, varying from modest to excellent.

The X-ray structure of **9f** in complex with PKA was resolved at 2.7 Å and is shown in Figure 2 (left). As for the case of compound **1**, four hydrogen bond interactions of **9f** to the ligand-binding domain of PKA were observed, with the hydrophobic indole positioned underneath the glycine-rich loop. Overlap of the two Akt inhibitors in PKA complex as shown in the right, however, shows visible differences between the two ligands. Due to the structural difference between the pyrazolopyridine scaffold (in purple) versus indazole (in green), the middle pyridine of **9f** orients slightly forward as compared to compound **1**, leading to more significant change in the orientation of the side-chain indole. Precise positioning of the indole underneath the hydrophobic glycine-rich loop is known to be critical to binding affinity.[7a,f] Overall, these changes must be detrimental for compound **9f** on the binding affinity to PKA and resulted in a 6-fold loss in potency. For Akt, however, the hydroxyl group of Thr-211 may interact with the N-6 of the pyrazolopyridine scaffold in **9f**, leading to an improved affinity to Akt. Because of the formation of an extra hydrogen bond interaction, or perhaps due to the size difference between the pyrazolopyridine and indazole, compound **9f** also repositioned in Akt complex and compromised the predicted boost in potency against Akt.

Table 3. Fold-selectivity of Akt inhibitors **9f** and **1** for Akt1 over selected kinases

Kinase family	Kinase	IC_{50} (fold selectivity)	
		Compound **9f**	Compound **1**
AGC	Akt1	1	1
	PKA	180	18
	PKCγ	130	180
	PKCδ	100	220
	CDK1	110	250
	CDK2	10	42
	ERK2	>8750	630
	CK2	3310	5300
	SGK	240	780
CAMK	MAPK	1250	8100
TK	KDR	>12,500	>920
	SRC	>10,000	5000

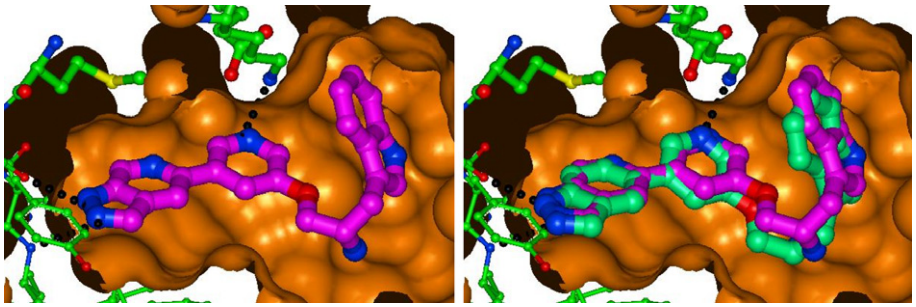

Figure 2. (Left) X-ray structure of **9f** in protein kinase A at 2.7 Å. (Right) Overlap of **9f** (shown in purple) with the crystal structure of **1** (shown in green) in PKA.[12]

4. Conclusion

In an effort to search for additional interactions with Thr-211 of Akt, we have explored the SAR at the C-6 position of the indazole scaffold of compound **1**. Introduction of an oxygen anion, amino and nitro groups at this position led to a significant drop in potency against Akt. Incorporation of a nitrogen atom into the phenyl ring provided a new series of potent and selective pyridine–pyrazolopyridine-based inhibitors. The Akt selectivity of this series of compounds over PKA is significantly dependent on the C-3 substitution of the pyrazolopyridine scaffold, as well as the side-chain structures. Compound **9f** was 180-fold selective over the closely related protein kinase A, which is 10-fold higher than the corresponding indazole–pyridine-based inhibitor **1** against PKA. However, the boosted potency against Akt was less than predicted and the deleterious effect on PKA is not conclusive from their X-ray structures. Compound **9f** showed a similar selectivity profile as compound **1** against other selected AGC, CAMK, and TK families of protein kinases. It is interesting that the SAR at the C-3 position of the pyrazolopyridine scaffold is significantly different from the corresponding indazole series. Better potency and selectivity were obtained with larger groups such as phenyl and 2-furyl (**25d** and **25b**) while less tolerance was observed with the same changes in the indazole series.[7g] Despite lack of structural evidence, it is reasonable to assume the existence of an additional hydrogen bond interaction with Thr-211 for compounds **9d**–**f**. However, formation of the extra hydrogen bond may change the conformation and/or orientation of the inhibitor in protein and compromise the overall binding affinity. In vivo evaluations, including pharmacokinetics and mouse MiaPaCa xenograft models, will be published in due course.

5. Experimental

5.1. General procedure

The NMR spectra were obtained on Varian M-300, Bruker AMX-400, and Varian U-400 magnetic resonance spectrometers (300/400 MHz for ^{1}H and 75/100 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) 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 obtained 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; 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 $MgSO_4$.

5.2. Chemistry

5.2.1. *tert*-Butyl 5-bromo-3-chloro-1H-indazole-1-carboxylate (4a). 5-Bromo-1*H*-indazole[7g] (10.0 g, 50.8 mmol) was suspended in a solution of NaOH (8.13 g, 0.203 mol) in water (250 mL). This suspension was heated until a transparent solution formed. After cooling with an ice-water bath to 5 °C, sodium hypochlorite solution (10–13% chlorine, 43.26 g, 60.7 mmol) was added. The reaction mixture was stirred at 0–5 °C for 5 h and was neutralized with 1 M aq HCl. The reaction mixture was extracted with ethyl acetate and the combined organic phases were washed with water and concentrated. The residual solid was dissolved in 400 mL of acetonitrile. Triethylamine (24 mL, 172.7 mmol), DMAP (620 mg, 5.08 mmol), and BOC anhydride (16.63 g, 76.2 mmol) were then added. The formed dark-red solution was stirred at rt for 5 h and was concentrated. The residue was partitioned between ethyl acetate and brine. The organic phase was washed with water and concentrated. The residual solid was purified by flash chromatography (silica gel, 5% EtOAc in hexane) to give **4a** (11.3 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 9H), 7.67 (dd, J = 8.99, 1.87 Hz, 1H), 7.85 (d, J = 1.70 Hz, 1H), 8.06 (d, J = 8.82 Hz, 1H). MS (DCI) m/z: 332 $(M+H)^{+}$.

5.2.2. 3-(Trifluoromethyl)-1H-indazole (19). A solution of 2-(2′,2′,2′-trifluoroethyl)aniline (**18**) as a 1:4 mixture with aniline (16.5 g)[10] in glacial acetic acid (990 mL) was treated with a solution of sodium nitrite (11.1 g, 0.161 mol) in water (25 mL). The reaction mixture was stirred for 15 min and allowed to stand at rt for 3 days. Volatiles were removed and the residual oil was partitioned between EtOAc and aq $NaHCO_3$ solution. The organic layer was washed with aq $NaHCO_3$ solution and concentrated. The residue was separated by flash chromatography (silica gel, 15–30% gradient EtOAc in hexane) to give a 1:1 mixture of **19** with an uncharacterized side-product (3.40 g). This material was directly used in the next step without further separation.

5.2.3. 5-Bromo-3-(trifluoromethyl)-1H-indazole (20) and 7-bromo-3-(trifluoromethyl)-1H-indazole (21). The mixture of compound **19** (3.3 g) was dissolved in anhyd CH_3CN (50 mL). *N*-Bromosuccinimide (15.8 g, 88.64 mmol) was then added and the reaction mixture was stirred at rt for 2 days. Ethyl acetate (200 mL) was added and the mixture was washed with 5% aq $NaHSO_3$ solution (200 mL). The organic phase was washed with brine and concentrated. The residue was separated by flash chromatography (silica gel, 10–40% gradient EtOAc in hexane) to give 1.67 g of compound **20** (35%) and 302 mg of **21** (6%). Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.50 Hz, 1H), 7.60 (dd, J = 1.70, 8.48 Hz, 1H), 8.03 (s, 1H), 10.58 (br s, 1H); MS(DCI) *m*/*z*: 264, 266 $(M+H)^+$. Compound **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 8.14 Hz, 1H), 7.65 (d, J = 7.46 Hz, 1H), 7.83 (d, J = 8.48 Hz, 1H), 10.42 (br s, 1H). MS(DCI) *m*/*z*: 264, 266 $(M+H)^+$.

5.2.4. *tert*-Butyl 5-bromo-3-trifluoromethyl-1H-indazole-1-carboxylate (4b). To a solution of **20** (1.66 g, 6.26 mmol) in anhyd acetonitrile (50 mL) were added triethylamine (3.0 mL, 21.28 mmol), DMAP (153 mg, 1.25 mmol), and BOC anhydride (2.05 g, 9.40 mmol). The dark-red solution was stirred at rt for 5 h and was partitioned between ethyl acetate and brine. The organic phase was washed with brine and concentrated. The residual solid was purified by flash chromatography (silica gel, 5–10% gradient EtOAc in hexane) to give **4b** (1.97 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 9 H), 7.70 (dd, J = 8.99, 1.87 Hz, 1H), 7.99 (s, 1H), 8.12 (d, J = 9.16 Hz, 1H). MS(DCI) *m*/*z*: 382, 384 $(M+NH_4)^+$.

5.2.5. 4-Bromo-2-methyl-5-nitroaniline (15). A solution of 4-bromo-2-methylaniline hydrochloride (11.12 g, 50 mmol) in 40 mL of concn H_2SO_4 was added in one portion to an ice-cold solution of KNO_3 (5.05 g, 50 mmol) in 100 mL of concentrated H_2SO_4. The resulting solution was stirred overnight at rt before being poured over 1.25 L of crushed ice and neutralized with concentrated ammonium hydroxide (350 mL). The formed yellow solid was collected by filtration, washed with water, and dried to give 11.05 g of **15** (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.92 (br s, 2H), 7.21 (s, 1H), 7.36 (s, 1H). MS(DCI) *m*/*z*: 248, 250 $(M+NH_4)^+$.

5.2.6. 5-Bromo-6-nitro-1H-indazole (16). To a solution of **15** (10.9 g, 47.17 mmol) in glacial acetic acid (1 L) was added a solution of sodium nitrite (3.25 g, 47.17 mmol) in water (10 mL) at rt. The solution was stirred for 15 min and allowed to stand at rt for 3 days. Volatiles were removed under vacuum and the residue was stirred with 100 mL of water. The formed solid was collected by filtration, washed with water, and dried. The crude product was recrystallized from a mixture of ethanol and water to give **16** (7.22 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.33 (s, 1H), 8.35 (s, 1H), 13.84 (br s, 1H). MS(DCI) *m*/*z*: 241, 243 $(M+1)^+$.

5.2.7. *tert*-Butyl 5-bromo-6-nitro-1H-indazole-1-carboxylate (4c). To a suspension of **16** (1.26 g, 5.21 mmol) in acetonitrile (50 mL) were added triethylamine (2.47 mL, 17.75 mmol), DMAP (64 mg, 0.521 mmol), and di-*t*-butyl dicarbonate (1.71 g, 7.81 mmol). The formed dark-red solution was stirred at rt for 15 h and was concentrated. The residue was partitioned between ethyl acetate and brine. The organic phase was concentrated and the residual solid was purified by flash chromatography (silica gel, 20–50% gradient EtOAc in hexane) to give **4c** (1.64 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 9H), 8.11 (s, 1H), 8.22 (s, 1H), 8.67 (s, 1H). MS(DCI) *m*/*z*: 359, 361 $(M+NH_4)^+$.

5.2.8. *tert*-Butyl 5-bromo-6-amino-1H-indazole-1-carboxylate (4d). To a solution of **4c** (0.5 g, 1.46 mmol) in THF (10 mL) was added Raney 2800 nickel (0.2 g, slurry in water) at rt. This suspension was purged with hydrogen and stirred under hydrogen (balloon) for 6 h. Solid material was filtered off and the filtrate was concentrated. The residual solid was purified by flash chromatography (silica gel, 20–50% gradient EtOAc in hexane) to give **4d** (446 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 9H), 7.83 (s, 1H), 7.96 (s, 1H), 8.16 (s, 1H), 8.52 (s, 1H), 8.86 (d, J = 1.70 Hz, 1H). MS(DCI) *m*/*z*: 312, 314 $(M+1)^+$, 328, 330 $(M+NH_4)^+$.

5.2.9. 5-Bromo-3-chloro-6-nitro-1H-indazole (17). Two grams of compound **16** was dissolved in a hot solution of NaOH (1.32 g) in water (40 mL). The formed solution was cooled in an ice-water bath and sodium hypochlorite solution (10–13% chlorine, 7.04 g, 9.92 mmol) was added. The reaction mixture was stirred at 0 °C for 5 h and neutralized with 1 M aq HCl solution. This mixture was extracted with ethyl acetate and the combined organic phases were washed with water and concentrated. The residual solid was purified by flash chromatography (silica gel, 20–50% gradient EtOAc in hexane) to afford **17** (2.19 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.39 (s, 1H), 14.09 (br s, 1H). MS(DCI) *m*/*z*: 275, 277, 279 $(M+1)^+$.

5.2.10. *tert*-Butyl 6-amino-5-bromo-3-chloro-1H-indazole-1-carboxylate (4e). To a solution of **17** (2.10 g, 7.59 mmol) in acetonitrile (55 mL) were added triethylamine (3.6 mL, 25.8 mmol), DMAP (93 mg, 0.759 mmol), and di-*t*-butyl dicarbonate (2.48 g, 11.38 mmol). The yellow solution was stirred at rt for

15 h and concentrated. The residue was partitioned between ethyl acetate and brine. The organic phase was washed with brine and concentrated. The residue was purified by flash chromatography (silica gel, 5–20% gradient EtOAc in hexane) to give **4e** (2.9 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 9H), 8.07 (s, 1H), 8.63 (s, 1H). MS(DCI) *m*/*z*: 393, 395 $(M+1)^+$.

5.2.11. 2-Bromo-4-ethyl-5-nitropyridine (10a). To a flask containing 41.2 mL of 48% HBr was added 4-ethyl-5-nitropyridin-2-amine (10.0 g, 59.8 mmol) in small portions with vigorous stirring. The formed thick paste was cooled in a dry-ice/isopropanol bath to ~−30 °C. A cooled solution of Br_2 (8.58 mL, 167.5 mmol) was added maintaining the temperature below −10 °C and stirred for 1.5 h. A solution of sodium nitrite (11.14 g, 161.5 mmol) in 23 mL of water was then added slowly, and the reaction mixture was warmed to +15 °C over a period of 1 h and stirred for an additional 45 min. The reaction mixture was cooled to −20 °C and an aqueous solution of NaOH (43.2 g in 193 mL water) was added maintaining the temperature below 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. The aqueous layer was extracted with ethyl acetate and the combined organic phases were concentrated on a rotary evaporator. The residual oil was purified by flash chromatography eluting with 6% EtOAc in hexanes to provide **10a** (7.5 g, 54%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (t, J = 7.46 Hz, 3H), 2.89 (q, J = 7.23 Hz, 2H), 7.92 (s, 1H), 8.95 (s, 1H). MS (DCI) *m*/*z*: 232 $(M+H)^+$.

5.2.12. 6-Bromo-4-ethylpyridin-3-amine (11a). A solution of **10b** (2.5 g, 10.8 mmol) in THF (50 mL) was treated with Raney Ni (1.25 g) under hydrogen (balloon) for 18 h. The catalyst was filtered off and the filtrate concentrated. The residual solid was purified by flash chromatography on silica gel eluting with 50% EtOAc in hexanes to provide **11a** (1.97 g, 90%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.22 (t, J = 7.46 Hz, 3H), 2.52 (q, J = 7.46 Hz, 2H), 7.16 (s, 1H), 7.69 (s, 1H). MS (DCI) *m*/*z*: 202 $(M+H)^+$.

5.2.13. *tert*-Butyl 5-bromo-3-methyl-1H-pyrazolo[3,4-c]pyridine-1-carboxylate (4g). To a solution of **11a** (6.06 g, 30.15 mmol) in glacial acetic acid (450 mL) was added a solution of sodium nitrite (2.08 g) in water (3.8 mL). This solution was stirred for 15 min and allowed to stand at rt for 1 day. Volatiles were removed on Rotavap and the residue was partitioned between ethyl acetate (200 mL) and saturated sodium bicarbonate solution (200 mL). The organic phase was washed with brine and concentrated. The crude solid **12a** was dissolved in 250 mL of anhyd acetonitrile. Di-*t*-butyl dicarbonate (9.87 g), triethylamine (12.61 mL), and DMAP (369 mg) were then added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated on a rotary evaporator and the residue diluted with ethyl acetate (200 mL) and washed with water (200 mL). The organics were concentrated and the residue was purified by flash chromatography (silica gel, 5–10% gradient EtOAc in hexanes) to provide **4g** (7.5 g, 80%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.72 (s, 9H), 2.59 (s, 3H), 8.05 (s, 1H), 9.15 (d, J = 1.02 Hz, 1H). MS (DCI) *m*/*z*: 313 $(M+H)^+$.

5.2.14. 5-Bromo-1H-pyrazolo[3,4-c]pyridine (12b). A solution of **11b** (3.76 g, 20.11 mmol), which was prepared according to the procedure for **11a** substituting **10b** for **10a**, in glacial acetic acid (300 ml) was treated with a solution of sodium nitrite (1.39 g, 20.11 mmol) in water (2.5 ml). The reaction mixture was stirred at rt for 15 min and allowed to stand at ambient temperature for 3 days. The acetic acid was removed under reduced pressure and the residue was partitioned between EtOAc and aq sodium bicarbonate solution. The organic phase was washed with water and concentrated. The residual solid was purified by flash chromatography to give **12b** (3.9 g, 99%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.99 (s, 1H), 8.15 (s, 1H), 8.80 (s, 1H). MS (DCI) *m*/*z*: 199 $(M+H)^+$.

5.2.15. *tert*-Butyl 5-bromo-1H-pyrazolo[3,4-c]pyridine-1-carboxylate (4f). Compound **4f** was prepared according to the procedure for **4g** by substituting **12b** for **12a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, 9H), 7.70 (s, 1H), 8.20 (s, 1H), 9.40 (s, 1H). MS (DCI) *m*/*z*: 298, 300 $(M+H)^+$.

5.2.16. 5-Bromo-3-chloro-1H-pyrazolo[3,4-c]pyridine (13). Compound **12b** (4.0 g, 20.2 mmol) was suspended in a solution of sodium hydroxide (3.23 g, 80.8 mmol) in water (120 ml). The suspension was heated until a transparent solution formed. The solution was cooled in an ice-water bath for 15 min before sodium hypochloride solution (10–13% chlorine, 13.6 mL) was added. Some solid material precipitated after the addition of sodium hypochloride and re-dissolved into solution within 1 h of stirring. The reaction mixture was stirred at 0 °C for 5 h before being neutralized with diluted HCl. The mixture was extracted with ethyl acetate and the combined organic phases were washed with water and concentrated. The residual solid was purified by flash chromatography to give **13** (3.6 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 8.81 (s, 1H). MS (DCI) *m*/*z*: 233 $(M+H)^+$.

5.2.17. *tert*-Butyl 5-bromo-3-chloro-1H-pyrazolo[3,4-c]pyridine-1-carboxylate (4j). To a suspension of **13** (1.4 g, 6.07 mmol) in acetonitrile (50 ml) were added triethylamine (2.5 ml), DMAP (73 mg, 0.6 mmol), and di-*t*-butyl dicarbonate (1.98 g, 9.1 mmol). The reaction mixture was stirred at room temperature for 0.5 h and concentrated. The residue was partitioned between ethyl acetate and brine. The organic phase was washed with water and concentrated. The residual solid was purified by flash chromatography to give **4j** (1.49 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 9H), 7.83 (s, 1H), 9.32 (s, 1H). MS (DCI) *m*/*z*: 333 $(M+H)^+$.

5.2.18. 5-Bromo-1-(*tert*-butoxycarbonyl)-3-methyl-1H-pyrazolo[3,4- c]pyridine 6-oxide (4k). To a solution of compound **4g** (500 mg, 1.6 mmol) in dichloromethane (25 mL) was added *m*-CPBA (861 mg, 3.85 mmol). This solution was stirred at rt for 16 h and partitioned

between ethyl acetate and aq $NaHCO_3$ solution. The organic phase was washed with water and concentrated. The residual oil was purified by flash chromatography (EtOAc) to provide **4k** (150 mg, 28%). ^1H NMR (300 MHz, CD_3OD) δ 1.63 (s, 9H), 3.31 (s, 3H), 8.55 (d, $J = 0.68$ Hz, 1H), 8.93 (d, $J = 0.68$ Hz, 1H). MS (DCI) *m/z*: 329 $(M+H)^+$.

5.2.19. *tert*-Butyl 5-chloro-1H-pyrazolo[3,4-c]pyridine-1-carboxylate (5). Compound **5** was prepared according to the procedure for **4g** by substituting 2-chloro-4-methyl-5-nitropyridine for 2-bromo-4-ethyl-5-nitropyridine. ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 9H), 7.69 (s, 1H), 8.19 (s, 1H), 9.34 (s, 1H). MS (DCI) *m/z*: 254 $(M+H)^+$.

5.2.20. General procedure for Stille reaction of trimethylstannane 7 with an aryl bromide 4 or aryl chloride 5

5.2.20.1. Method A. A round-bottomed flask equipped with a septum was charged with bromide **4** (0.395 mmol), trimethylstannane **7** (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 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 (silica gel) to afford the title compound **8**.

5.2.20.2. Method B. A round-bottomed flask was charged with the bromide **4** or chloride **5** (0.16 mmol), trimethylstannane **7** (0.24 mmol), bis(tri-*t*-butylphosphine)palladium (0) (20 mg, 0.039 mmol), and cesium fluoride (130 mg, 0.855 mmol), and was purged with N_2. Anhydrous dioxane (5 mL) was added via syringe. The solution was purged with N_2 again and heated at 80 °C for 16 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 (silica gel) to provide the title compound **8**.

5.2.21. General procedure for acidic Boc-deprotection of compound 8. To a solution of **8** (0.2 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (1 mL) at 0 °C. The solution was stirred at 0 °C for 5 min and allowed to warm up to rt for 1 h. After cooling to 0 °C again, 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 **9** as TFA salt. A HCl salt of compound **9** 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 **9** as HCl salt.

5.2.22. (*S*)-1-(5-(3-Chloro-1H-indazol-5-yl)pyridin-3-yloxy)-3-(1H-indol-3-yl)propan-2-amine (2). Compound **2** was synthesized according to general procedure Method A followed by Boc-deprotection. ^1H NMR (300 MHz, CD_3OD) δ 3.27–3.35 (m, 2H), 3.97–4.05 (m, 1H), 4.31 (dd, $J = 6.00$, 9.00 Hz, 1H), 4.46 (dd, $J = 3.00$, 9.00 Hz, 1H), 7.04 (t, $J = 7.46$ Hz, 1H), 7.13 (t, $J = 7.63$ Hz, 1H), 7.25 (s, 1H), 7.38 (d, $J = 8.14$ Hz, 1H), 7.61 (d, $J = 7.80$ Hz, 1H), 7.67 (d, $J = 9.00$ Hz, 1H), 7.75 (d, $J = 9.00$ Hz, 1H), 7.91 (d, $J = 2.03$ Hz, 1H), 7.97 (s, 1H), 8.37 (d, $J = 2.37$ Hz, 1H), 8.64 (s, 1H). MS (APCI) *m/z*: 418 $(M+H)^+$. Anal. Calcd for $C_{23}H_{20}ClN_5O \cdot 2.7TFA$: C, 47.00; H, 3.15; N, 9.65. Found: C, 47.24, H, 3.08; N, 9.87.

5.2.23. (*S*)-1-(5-(3-Trifluoromethyl-1H-indazol-5-yl)pyridin-3-yloxy)-3-(1H-indol-3-yl)propan-2-amine (3). Compound **3** was synthesized according to general procedure Method A followed by Boc-deprotection. ^1H NMR (300 MHz, CD_3OD) δ 3.32–3.36 (m, 2H), 3.97–4.04 (m, 1H), 4.31 (dd, $J = 10.51$, 5.76 Hz, 1H), 4.45 (dd, $J = 11.00$, 2.50 Hz, 1H), 7.03 (t, $J = 6.95$ Hz, 1H), 7.13 (d, $J = 7.00$ Hz, 1H), 7.24 (s, 1H), 7.38 (d, $J = 8.14$ Hz, 1H), 7.60 (d, $J = 7.80$ Hz, 1H), 7.78–7.80 (m, 2H), 7.86–7.88 (m, 1H), 8.06 (s, 1H), 8.38 (d, $J = 2.71$ Hz, 1H), 8.62 (d, $J = 1.36$ Hz, 1H). MS (APCI) *m/z*: 452 $(M+H)^+$. Anal. Calcd for $C_{24}H_{20}F_3N_5O \cdot 3TFA$: C, 45.41; H, 2.92; N, 8.83. Found: C, 45.65, H, 3.44; N, 8.89.

5.2.24. (*S*)-1-(1H-indol-3-yl)-3-(5-(6-nitro-1H-indazol-5-yl)pyridin-3-yloxy)propan-2-amine (9c). Compound **9c** was synthesized as 3× TFA salt according to general procedure Method A followed by Boc-deprotection. ^1H NMR (300 MHz, CD_3OD) δ 3.26–3.32 (m, 2H), 3.93–4.00 (m, 1H), 4.24 (dd, $J = 5.76$, 9.00 Hz, 1H), 4.37 (dd, $J = 7.46$, 3.05 Hz, 1H), 7.01 (t, $J = 7.46$ Hz, 1H), 7.10 (t, $J = 6.95$ Hz, 1H), 7.21 (s, 1H), 7.35 (d, $J = 7.80$ Hz, 1H), 7.54 (t, $J = 2.71$ Hz, 1H), 7.57 (d, $J = 8.14$ Hz, 1H), 7.90 (s, 1H), 8.26–8.29 (m, 2H), 8.34 (s, 1H), 8.38 (d, $J = 2.71$ Hz, 1H). MS (APCI) *m/z*: 429 $(M+H)^+$.

5.2.25. (*S*)-1-(1H-indol-3-yl)-3-(5-(6-amino-1H-indazol-5-yl)pyridin-3-yloxy)propan-2-amine (9d). Compound **9d** was synthesized as 3× TFA salt according to general procedure Method A followed by Boc-deprotection. ^1H NMR (300 MHz, CD_3OD) δ 3.28–3.33 (m, 2H), 3.96–4.03 (m, 1H), 4.27 (dd, $J = 5.76$, 9.00 Hz, 1H), 4.42 (dd, $J = 3.05$, 7.46 Hz, 1H), 6.96 (s, 1H), 7.03 (d, $J = 7.46$ Hz, 1H), 7.13 (d, $J = 6.95$ Hz, 1H), 7.23 (s, 1H), 7.38 (d, $J = 8.14$ Hz, 1H), 7.53 (s, 1H), 7.58 (d, $J = 7.80$ Hz, 1H), 7.84 (d, $J = 1.70$ Hz, 1H), 7.95 (s, 1H), 8.41 (d, $J = 2.71$ Hz, 1H), 8.44 (d, $J = 1.36$ Hz, 1H). MS (APCI) *m/z*: 399 $(M+H)^+$.

5.2.26. (*S*)-5-(5-(2-Amino-3-(1H-indol-3-yl)propoxy)pyridin-3-yl)- 3-chloro-1H-indazol-6-amine (9e)

5.2.26.1. Step 1. A 100-mL RBF equipped with a septum was charged with **4e** (376 mg, 1.0 mmol), **7** (R^2 = 3-indole, 530 mg, 1.0 mmol), $Pd_2(dba)_3$ (183 mg, 0.2 mmol), and $(o\text{-tol})_3P$ (183 mg, 0.6 mmol), and was purged with N_2. Anhydrous DMF (20 mL) and Et_3N (418 μL, 3.0 mmol) were added via syringe. The solution was purged with N_2 again and heated at 70 °C for 60 h. After cooling, the reaction mixture was partitioned

between ethyl acetate and brine. The organic phase was washed with brine and concentrated. The residual oil was separated by flash chromatography (silica gel, 20–80% gradient EtOAc in hexane) to provide the coupled product (232 mg, 35%) of sufficient purity to carry on to the next step.

5.2.26.2. Step 2. 150 mg of the nitro compound from step 1 was dissolved in 10 mL THF. Raney 2800 nickel (0.2 g, Aldrich, slurry in water) was added and the suspension was stirred at rt under hydrogen (balloon) for 16 h. Solid material was filtered off and the filtrate was concentrated. The residual solid was purified by flash chromatography (silica gel, 0–15% gradient MeOH in 2:1 EtOAc/hexane) to give (*S*)-*tert*-butyl 6-amino-5-(5-(2-(tert-butoxycarbonylamino)-3-(1H-indol-3-yl)propoxy)pyridin-3-yl)-3-chloro-1H-indazole-1-carboxylate (88 mg, 62%). Boc-deprotection of this compound as described in general procedure afforded **9e**. ^{1}H NMR (300 MHz, CD_3OD) δ 3.28–3.32 (m, 2H), 3.97–4.04 (m, 1H), 4.32 (dd, J = 5.76, 10.00 Hz, 1H), 4.46 (dd, J = 3.39, 10.55 Hz, 1H), 6.84 (s, 1H), 7.02 (t, J = 6.95 Hz, 1H), 7.12 (t, J = 7.12 Hz, 1H), 7.24 (s, 1H), 7.37 (d, J = 8.00, 1H), 7.38 (s, 1H), 7.59 (d, J = 7.80 Hz, 1H), 7.91–7.93 (m, 1H), 8.45 (d, J = 2.71 Hz, 1H), 8.49 (d, J = 1.70 Hz, 1H). MS (APCI) m/z: 433 $(M+H)^+$. Anal. Calcd for $C_{23}H_{21}ClN_6O$·3.1TFA: C, 44.60; H, 3.09; N, 10.69. Found: C, 44.60, H, 2.60; N, 10.54.

5.2.27. (*S*)-1-(5-(1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-3-(1H-indol-3-yl)propan-2-amine (9f). Compound **9f** was synthesized from chloride **5** and trimethylstannane **7** (R^2 = 3-indole) according to general procedure Method B followed by Boc-deprotection. ^{1}H NMR (300 MHz, CD_3OD) δ 3.31–3.36 (m, 2H), 4.05 (dd, J = 5.76, 3.05 Hz, 1H), 4.37 (dd, J = 5.76, 10 Hz, 1H), 4.52 (dd, J = 3.39, 11.00 Hz, 1H), 7.03 (t, J = 6.95 Hz, 1H), 7.12 (t, J = 7.12 Hz, 1H), 7.26 (s, 1H), 7.38 (d, J = 8.14 Hz, 1H), 7.61 (d, J = 7.80 Hz, 1H), 8.33 (s, 1H), 8.44–8.47 (m, 2H), 8.46 (s, 1H), 9.05 (s, 1H), 9.18 (s, 1H). MS (APCI) m/z: 385 $(M+H)^+$. Anal. Calcd for $C_{22}H_{20}N_6O$·3.7TFA: C, 43.79; H, 2.96; N, 10.42. Found: C, 43.97, H, 2.58; N, 10.41.

5.2.28. An alternative approach to compound 9f (Scheme 4)

5.2.28.1. Step 1: (*S*)-*tert*-butyl 1-(1H-indol-3-yl)-3-(4-methyl-5-nitro-2,3′-bipyridin-5′-yloxy)propan-2-ylcarbamate (23). A 250-mL RBF was charged with 2-chloro-4-methyl-5-nitropyridine (**22b**) (990 mg, 5.73 mmol), **7** (R^2 = 3-indole, 3.04 g, 5.73 mmol), $Pd_2(dba)_3$ (525 mg, 0.573 mmol), and tri-2-furylphosphine (399 mg, 1.72 mmol), and was purged with N_2. Anhydrous DMF (60 mL) and triethylamine (2.40 mL) were added via syringe. The solution was purged with N_2 again and heated at 75 °C for 8 h. After cooling, the reaction mixture was partitioned between EtOAc and brine. The organic phase was washed with brine and concentrated. The residue was separated by flash chromatography (40–80% gradient EtOAc in hexane) to afford **23**. Yield: 1.86 g (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.75 (s, 3H), 3.16–3.21 (m, 2H), 4.04–4.13 (m, 2H), 4.35 (br s, 1H), 4.94 (br s, 1H), 7.04 (br s, 1H), 7.08 (t, J = 8.14 Hz, 1H), 7.19 (t, J = 7.63 Hz, 1H), 7.36 (d, J = 8.14 Hz, 1H), 7.65 (d, J = 7.80 Hz, 1H), 7.76 (s, 1H), 7.96 (s, 1H), 8.09 (s, 1H), 8.43 (d, J = 2.71 Hz, 1H), 8.86 (s, 1H), 9.25 (s, 1H). MS (APCI) m/z: 504 $(M+H)^+$.

5.2.28.2. Step 2: (*S*)-*tert*-Butyl 1-(1H-indol-3-yl)-3-(5-amino-4-methyl-2,3′-bipyridin-5′-yloxy)propan-2-ylcarbamate (24). To a solution of **23** (1.85 g, 3.67 mmol) in THF (50 mL) was added Raney 2800 nickel (1.0 g, slurry in water) at rt. This suspension was purged with hydrogen and stirred under hydrogen (balloon) for 3 days. Solid material was filtered off and the filtrate was concentrated. The residual solid was purified by flash chromatography (0–15% gradient MeOH in 2:1 EtOAc/hexane) to afford **24**. Yield: 1.56 g (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.19 (s, 3H), 3.12 (m, 2H), 3.90 (br s, 1H), 3.92–3.96 (m, 2H), 4.30 (br s, 1H), 5.11 (d, J = 7.98 Hz, 1H), 6.94 (d, J = 1.53 Hz, 1H), 7.04 (t, J = 7.36 Hz, 1H), 7.13 (t, J = 7.52 Hz, 1H), 7.30 (d, J = 7.98 Hz, 1H), 7.39 (s, 1H), 7.64 (d, J = 7.67 Hz, 1H), 7.73 (s, 1H), 8.04 (s, 1H), 8.23 (d, J = 2.76 Hz, 1H), 8.68 (d, J = 1.53 Hz, 1H), 8.70 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.92, 27.02, 28.34, 31.50, 50.20, 68.18, 79.49, 111.19, 118.11, 118.81, 119.40, 121.91, 122.35, 123.04, 127.55, 130.89, 135.89, 136.22, 136.50, 136.86, 139.68, 141.21, 144.32, 155.08, 155.40. MS (DCI) m/z: 474 $(M+H)^+$.

5.2.28.3. Step 3. To a solution of **24** (440 mg, 0.93 mmol) in glacial acetic acid (70 mL) was added a solution of sodium nitrite (64 mg, 0.93 mmol) in water (1.0 mL). The solution was stirred at rt for 1 h and aged at ambient temperature overnight. Solvent was removed under reduced pressure. The residual oil was separated 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 the coupled product (**8f**). Yield: 197 mg (30%). This product was dissolved in CH_2Cl_2 (5 mL) and treated with trifluoroacetic acid (1 mL) as described in Section 5.2.21 to give **9f** as 3× TFA salt. Yield: 80 mg (40%).

5.2.29. (*S*)-1-(1H-indol-3-yl)-3-(5-(3-methyl-1H-pyrazolo-[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-propan-2-amine (9g). Compound **9g** was synthesized from bromide **4g** and trimethylstannane **7** (R^2 = 3-indole) according to general procedure Method B followed by Boc-deprotection. ^{1}H NMR (300 MHz, CD_3OD) δ 2.68 (s, 3H), 3.32–3.37 (m, 2H), 4.01–4.09 (m, 1H), 4.38 (dd, J = 5.76, 9.00 Hz, 1H), 4.52 (dd, J = 3.05, 9.00 Hz, 1H), 7.03 (t, J = 7.46 Hz, 1H), 7.12 (t, J = 7.63 Hz, 1H), 7.26 (s, 1H), 7.38 (d, J = 8.14 Hz, 1H), 7.61 (d, J = 7.80 Hz, 1H), 8.43–8.46 (m, 2H), 8.45 (s, 1H), 9.05 (s, 1H), 9.10 (s, 1H). MS (APCI) m/z: 399 $(M+H)^+$. Anal. Calcd for $C_{23}H_{22}N_6O$·3.1TFA: C, 46.64; H, 3.36; N, 11.18. Found: C, 46.59, H, 2.72; N, 10.89.

5.2.30. (*S*)-1-(5-(1H-Pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-3-phenylpropan-2-amine (9h). Compound **9h** (36 mg) as 3× TFA salt was synthesized from bromide

4f (51 mg, 0.17 mmol) and trimethylstannane **7** (R^2 = Ph, 100 mg, 0.2 mmol) according to general procedure Method A followed by Boc-deprotection. ^{1}H NMR (300 MHz, CD_3OD) δ 3.17 (d, J = 7.46 Hz, 2H), 3.95–4.03 (m, 1H), 4.28 (dd, J = 5.43, 10.50 Hz, 1H), 4.43 (dd, J = 3.05, 10.51 Hz, 1H), 7.30–7.41 (m, 5H), 8.31 (s, 1H), 8.35–8.38 (m, 1H), 8.42–8.47 (m, 2H), 9.01 (d, J = 1.36 Hz, 1H), 9.17 (s, 1H). MS (DCI) m/z: 455 $(M+H)^+$.

5.2.31. (*S*)-1-(5-(3-Methyl-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-3-phenylpropan-2-amine (9i). Compound **9i** (26 mg) was synthesized from bromide **4g** (150 mg, 0.48 mmol) and trimethylstannane **7** (R^2 = Ph, 236 mg, 0.48 mmol) according to general procedure Method B followed by Boc-deprotection. Yield: 15%. ^{1}H NMR (400 MHz, CD_3OD) δ 2.63 (s, 3H), 3.13 (d, J = 7.67 Hz, 2H), 3.91–3.98 (m, 3H), 4.26 (dd, J = 10.43, 5.52 Hz, 1H), 4.37–4.45 (m, 1H), 7.24–7.29 (m, 1H), 7.29–7.33 (m, 3H), 7.33–7.36 (m, 1H), 8.39–8.43 (m, 3H), 9.01 (s, 1H), 9.05 (d, J = 1.23 Hz, 1H). MS (DCI) m/z: 360 $(M+H)^+$. Anal. Calcd for $C_{21}H_{21}N_5O{\cdot}2.9$ TFA: C, 46.64; H, 3.49; N, 10.15. Found: C, 46.68; H, 3.19; N, 10.12.

5.2.32. (*S*)-5-(5-(2-Amino-3-phenylpropoxy)pyridin-3-yl)-3-methyl-1H-pyrazolo[3,4-c]pyridine 6-oxide (9k). A suspension of **4k** (50 mg, 0.15 mmol), trimethylstannane **7** (R^2 = Ph, 75 mg, 0.15 mmol), and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in anhyd xylene (10 mL) was heated at 120 °C under nitrogen for 3 h. After cooling to rt, ethyl acetate (50 mL) was added. The mixture was washed with brine (50 mL) and water (50 ml), dried ($MgSO_4$), filtered, and concentrated. The residual oil was purified by flash column chromatography (EtOAc) to provide the corresponding coupling product. This product was dissolved in dichloromethane (6 mL) and treated with TFA (3 mL) at rt for 1 h. After concentration, the residual oil 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 **9k** (5 mg, 6%). ^{1}H NMR (400 MHz, CD_3OD) δ 2.62 (s, 3H), 3.11–3.17 (m, 2H), 3.89–3.97 (m, 1H), 4.16 (dd, J = 10.59, 5.68 Hz, 1H), 4.29–4.36 (m, 1H), 7.28–7.31 (m, 2H), 7.32– 7.36 (m, 2H), 7.36–7.39 (m, 1H), 7.87–7.90 (m, 1H), 8.08 (s, 1H), 8.42 (s, 1H), 8.51 (s, 1H), 8.87 (s, 1H). MS (DCI) m/z: 376 $(M+H)^+$.

5.2.33. (*S*)-*tert*-Butyl 5-(5-(2-(tert-butoxycarbonylamino)-3-phenylpropoxy)pyridin-3-yl)-3-chloro-1H-pyrazolo-[3,4-c]pyridine-1-carboxylate (8j: R^2 = Ph). A 100-ml RBF was charged with **4j** (1.2 g, 3.61 mmol), trimethylstannane **7** (R^2 = Ph, 1.77 g, 3.61 mmol), bis(tri-*t*-butylphosphine)palladium (0) (184 mg, 0.36 mmol), and cesium fluoride (1.37 g, 9.02 mmol), and was purged with nitrogen. Anhydrous dioxane (60 ml) was added via syringe. The suspension was purged with nitrogen again and was heated at 85 °C for 5 h. After cooling, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with water and concentrated. The residual solid was separated by flash chromatography to give **8j** (R^2 = Ph, 0.4 g, 20%). ^{1}H NMR (300 MHz, CD_3OD) δ 3.13 (s, 9H), 3.35 (s, 9H), 3.85–4.02 (m, 1H), 4.19–4.29 (m, 2H), 4.40 (dd, J = 10.85, 3.05 Hz, 2H), 7.22–7.47 (m, 5H), 8.24–8.26 (m, 1H), 8.28 (d, J = 1.36 Hz, 1H), 8.40 (d, J = 2.37 Hz, 1H), 9.00 (s, 1H), 9.12 (s, 1H). MS (DCI) m/z: 581 $(M+H)^+$.

5.2.34. (*S*)-1-(5-(3-Chloro-1H-pyrazolo[3,4-c]pyridin-5-yl)-pyridin-3-yloxy)-3-phenylpropan-2-amine (9j). Compound **9j** (30 mg) as 3× TFA salt was prepared from **8j** (31 mg) according to the general procedure for Boc-deprotection. ^{1}H NMR (300 MHz, CD_3OD) δ 3.16 (t, J = 7.29 Hz, 2H), 3.85–4.05 (m, 1H), 4.11–4.31 (m, 1H), 4.32–4.52 (m, 1H), 7.17–7.46 (m, 5H), 8.32 (s, 1H), 8.40–8.48 (m, 1H), 8.54 (s, 1H), 9.05 (s, 1H), 9.13 (s, 1H). MS (DCI) m/z: 380 $(M+H)^+$.

5.2.35. (*S*)-1-Phenyl-3-(5-(3-vinyl-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)propan-2-amine (25a). A 25-ml RBF was charged with **8j** (28 mg), tributylvinyltin (32 mg), 2-dicyclohexylphosphino-2-(*N*,*N*-dimethylamino)biphenyl (4 mg), and $Pd_2(dba)_3$ (5 mg), and was purged with nitrogen. Anhydrous DMF (4 ml) was added via syringe. The solution was purged with nitrogen again and heated at 85 °C for 3 h. After cooling, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with water and concentrated. The residue was separated by flash chromatography to give the Boc-protected coupling product which was deprotected according to the general procedure for Boc-deprotection to provide **25a**. ^{1}H NMR (300 MHz, CD_3OD) δ 3.17 (d, J = 7.12 Hz, 2H), 3.91–4.05 (m, 1H), 4.21–4.33 (m, 1H), 4.37–4.47 (m, 1H), 5.65 (d, J = 11.53 Hz, 1H), 6.30 (d, J = 16.95 Hz, 1H), 7.13 (dd, J = 17.97, 11.53 Hz, 1H), 7.23–7.47 (m, 5H), 8.35–8.42 (m, 1H), 8.44 (t, J = 2.71 Hz, 1H), 8.56 (d, J = 1.36 Hz, 1H), 9.02 (s, 1H), 9.10 (s, 1H). MS (DCI) m/z: 295 $(M+H)^+$.

5.2.36. (S)-1-(5-(3-(furan-2-yl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-3-phenylpropan-2-amine (25b). Compound **25b** as 3× TFA salt (20 mg) was synthesized from **8j** (50 mg) according to procedure for **25a** substituting 2-tributylstannylfuran for tributylvinyltin. ^{1}H NMR (300 MHz, CD_3OD) δ 3.11–3.23 (m, 2H), 3.93–4.07 (m, 1H), 4.28 (dd, J = 10.51, 5.43 Hz, 1H), 4.44 (dd, J = 10.68, 3.22 Hz, 1H), 6.68 (dd, J = 3.56, 1.86 Hz, 1H), 7.14 (d, J = 3.56 Hz, 1H), 7.25–7.44 (m, 5H), 7.77 (d, J = 1.86 Hz, 1H), 8.34–8.38 (m, 1H), 8.44 (d, J = 2.71 Hz, 1H), 8.64 (s, 1H), 9.04 (s, 1H), 9.16 (s, 1H). MS (DCI) m/z: 335 $(M+H)^+$.

5.2.37. (2*S*)-1-(5-(3-(1-Methyl-1H-pyrrol-2-yl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)-3-phenylpropan-2-amine (25c). Compound **25c** as 3× TFA salt (20 mg) was synthesized from **8j** (50 mg) according to procedure for **25a** substituting *N*-methyl-2-tributylstannylpyrrole for tributylvinyltin. ^{1}H NMR (300 MHz, CD_3OD) δ 3.11–3.23 (m, 2H), 3.93–4.07 (m, 1H), 4.28 (dd, J = 10.51, 5.43 Hz, 1H), 4.44 (dd, J = 10.68, 3.22 Hz, 1H), 6.68 (dd, J = 3.56, 1.86 Hz, 1H), 7.14 (d, J = 3.56 Hz, 1H), 7.25–7.44 (m, 5H), 7.77 (d, J = 1.86 Hz, 1H), 8.34–8.38 (m, 1H), 8.44 (d, J = 2.71 Hz, 1H), 8.64 (s, 1H), 9.04 (s, 1H), 9.16 (s, 1H). MS (DCI) m/z: 348 $(M+H)^+$.

5.2.38. (*S*)-1-Phenyl-3-(5-(3-phenyl-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-3-yloxy)propan-2-amine (25d). Compound **25d** as 3× TFA salt (28 mg) was synthesized from **8j** (50 mg) according to procedure for **25a** substituting phenyltributyltin for tributylvinyltin. ^{1}H NMR (300 MHz, CD_3OD) δ 3.08–3.20 (m, 2H), 3.74–4.09 (m, 1H), 4.12–4.31 (m, 1H), 4.41 (dd, J = 10.68, 3.22 Hz, 1H), 7.14–7.42 (m, 5H), 7.45–7.51 (m, 1H), 7.51–7.64 (m, 2H), 7.90–8.13 (m, 2H), 8.23–8.35 (m, 1H), 8.41 (s, 1H), 8.55 (d, J = 1.36 Hz, 1H), 9.02 (s, 1H), 9.17 (s, 1H). MS (DCI) *m/z*: 348 $(M+H)^+$.

Acknowledgment

We thank Dr. Thomas Penning for proofreading this manuscript and valuable suggestions.

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