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Bioorganic & Medicinal Chemistry 14 (2006) 6832–6846
Bioorganic & Medicinal Chemistry

Synthesis and SAR of indazole-pyridine based protein kinase B/Akt inhibitors

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Received 1 June 2006; revised 12 June 2006; accepted 19 June 2006
Available online 14 July 2006

Abstract—A series of heteroaryl-pyridine containing inhibitors of Akt are reported. The synthesis and structure–activity relationships are discussed, leading to the discovery of a indazole-pyridine analogue (K_i = 0.16 nM). These compounds bind in the ATP binding site, are potent, ATP competitive, and reversible inhibitors of Akt activity. No selectivity amongst the Akt isoforms is observed for this analogue, but there is good selectivity against an panel of other kinases. It is least selective for other members of the AGC family of kinases but is nonetheless 40-fold selective for Akt over PKA. The compound shows cellular activity and significantly slows tumor growth in vivo.

1. Introduction

Akt1 (also called protein kinase B, PKB)[1–3] is a serine/threonine protein kinase that exhibits elevated activity in a large proportion of human malignancies.[4,5] Akt1 was discovered as the human homologue of the transforming gene in the Akt-8 oncogenic virus which was isolated from a spontaneous thymoma in the AKR mouse.[6,7] Two additional Akt isoforms, Akt2 and Akt3, have been identified. The three Akts are approximately 85% homologous in protein sequence.[8–10] Sequence homology in the ATP binding site is 100% except for one non-crucial amino acid in Akt3. Akt is a member of the AGC family of kinases and has a high degree of homology with PKA and PKC.[11]

Akt is activated by phosphorylation in response to a number of mitogenic stimuli. Fully activated Akt is phosphorylated at two sites: Thr 308 and Ser 473. All three Akt isoforms are either overexpressed or activated in a variety of human tumors including lung, breast, prostate, ovarian, gastric, and pancreatic carcinomas.[12–14] Increased levels of Akt expression also correlate with disease progression. The central role of Akt in growth and survival pathways provides the rationale for inhibiting Akt in the treatment of cancer. Several Akt inhibitors have been reported.[15–21]

Herein, we report the development of a series of Akt kinase inhibitors. These compounds are potent, ATP competitive, reversible inhibitors of Akt. Our efforts have resulted in the discovery of the indazole-pyridine compound **4**. The compound is a potent (Akt1 K_i = 0.16 nM) and selective Akt inhibitor (greater than 20-fold selective for Akt over more than 35 other kinases), and causes significant delay in the growth of tumors in mouse xenograft models.[22]

2. Chemical synthesis

Compound **1** (Fig. 1) was identified as a lead compound from a high-throughput screening assay (Akt1

Keywords: Akt; Protein kinase B; Serine/threonine kinase; Indazole.
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doi:10.1016/j.bmc.2006.06.047

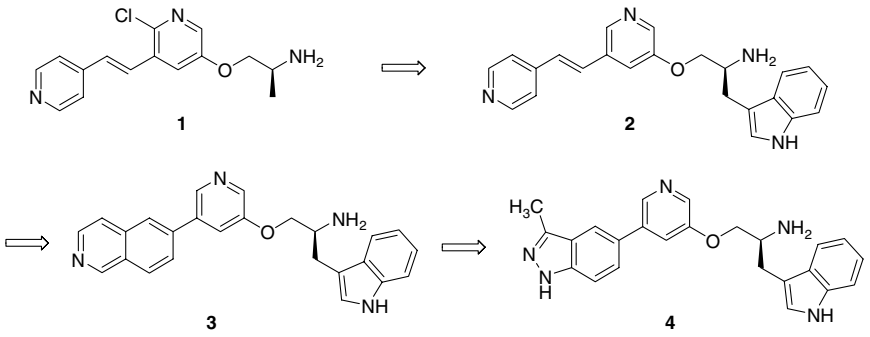


Figure 1. Hit to lead progression.

K_i = 5 μM). The chlorine was removed for simplicity and investigation of the ether-linked side-chain requirements was undertaken. These efforts have been reported previously.[16] That research led to the discovery of compound **2** with the indole containing side chain. Compound **2** (Akt1 K_i = 14 nM) represents an increase in the Akt1 activity of greater than 350-fold when compared to the initial screening hit.

The details of restricting rotation about the olefin linkage of **2**, resulting in compound **3** with significantly improved Akt1 potency (Akt1 K_i = 0.99 nM), were discussed in an earlier communication from our laboratories.[17] Extensive SAR studies to investigate replacements for the isoquinoline ring in **3** have yielded the highly active indazole containing Akt inhibitor **4** (Akt1 K_i = 0.16 nM). These studies are detailed here.

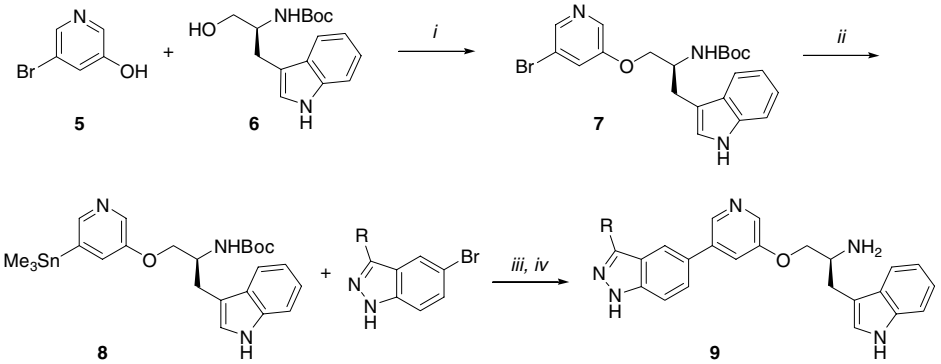
The general synthesis of the compounds is outlined in Scheme 1. The side-chain ether linkage is made via a Mitsunobu reaction between *N*-Boc-tryptophanol (**6**) and 3-bromo-5-hydroxypryidine (**5**). The aryl or heteroaryl moieties are introduced using the Stille reaction rather than alternate methods such as the Suzuki reaction since, in general, the Stille reaction proved to be more effective. Finally, removal of the Boc protecting group yielded the desired Akt inhibitors. Deprotection with HCl was usually unsuccessful. It appears that protonation, and subsequent precipitation of the compounds, occurs faster than deprotection. TFA in CH_2Cl_2 leads to the desired deprotected amines.

The preparation of compound **3** required the synthesis of 6-bromoisoquinoline. The 6-bromoisoquinoline was initially prepared according to the procedure reported by Hendrickson and Rodriguez.[23] This method suffers from long reaction times (>4 days) and modest yields. We have thus found the synthesis described by Miller and Frincke to be preferable.[24]

The SAR studies carried out to investigate the importance of the isoquinoline moiety are summarized in Table 1. The aromatic starting materials required for the preparation of compounds **37**, **38**, **43**, **44**, **46**, and **47** are commercially available.

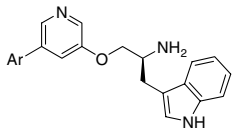
Example **39** requires the preparation of 6-bromocinnoline (**16**). The synthesis is outlined in Scheme 2. Acetylation of 2-aminoacetophenone (**10**) followed by bromination with bromine in acetic acid gives **12**. De-acetylation and diazotization result in cyclization to the cinnolinone **13**.[25] Upon treatment with phosphorus oxychloride, the 4-chlorocinnolinone **14** is formed. Displacement of the chlorine with hydrazine gives compound **15**. Heating the hydrazino intermediate in the presence of aqueous $CuSO_4$ leads to removal of the hydrazine and isolation of the desired 6-bromocinnoline **16**.

The three isoquinolines (**40**–**42**) with substitutions in the 1-position derive from 6-bromo-1-hydroxyisoquinoline (**17**) which was prepared according to a literature procedure (Scheme 3).[26] Treatment of **17** with phosphorus



Scheme 1. Reagents and conditions: (i) DEAD, PPh_3, THF, 0 °C to rt, overnight, 89%; (ii) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, 75 °C, 1.5 days, 34%; (iii) $Pd_2(dba)_3$, P(*o*-tol)$_3$, TEA, 110 °C, 4 h, 49%; (iv) TFA, CH_2Cl_2, rt, 3 h, 81%.

Table 1. Structures and in vitro Akt1 kinase binding[a]



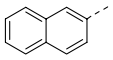
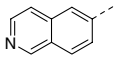
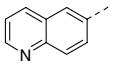
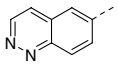
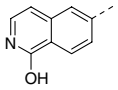
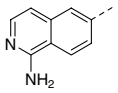
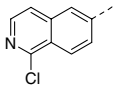
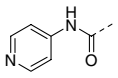
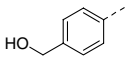
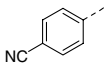
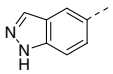
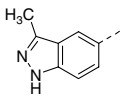
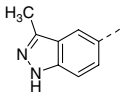
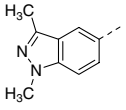
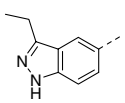
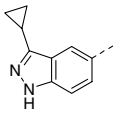
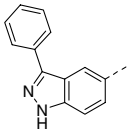
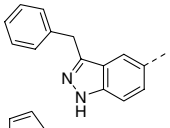
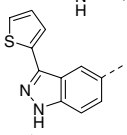
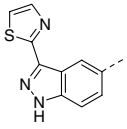
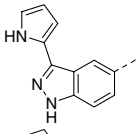
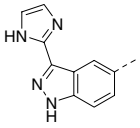
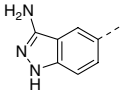
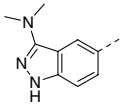
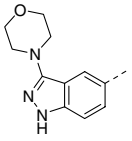
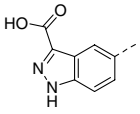
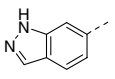
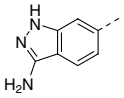
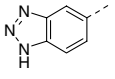
Compound	Ar	Akt1 K_i (nM)
37		1117
3[b]		0.99
38		312
39		215
40[c]		1022
41[c]		188
42[c]		473
43		331
44[b]		245
45[b]		1659
46		4022
47[b]		1503
48		0.99
4	 (*S*-isomer)	0.16
49	 (*R*-isomer)	28
50		685
51		1.15

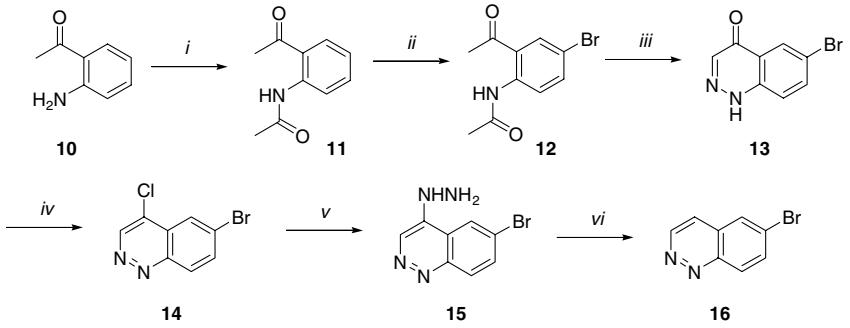
Table 1 (*continued*)

Compound	Ar	Akt1 K_i (nM)
52		2.6
53		3.9
54		174
55		1.3
56		9.8
57		1.2
58		9.8
59		2.9
60		18
61		18
62		1848
63		237
64		1232
65		92

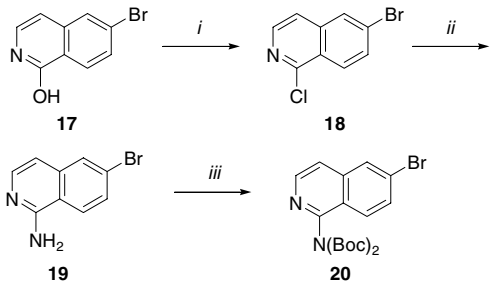
[a] Values were measured against Akt1 with ATP concentrations of 10 μM.[22,36]

[b] Compound was reported in Ref. 17. The data are shown here for the ease of the reader.

[c] Compound was reported in Ref. 18. The data are shown here for the ease of the reader.



Scheme 2. Reagents and conditions: (i) AcCl, TEA, CH_2Cl_2, rt, 3 h, 100%; (ii) Br_2, HOAc, 75 min, 89%; (iii) a—HCl (aq), THF, reflux, 1 h; b—6 N HCl, $NaNO_2$, 0 °C, 2 h then overnight at rt then reflux 6 h, 54%; (iv) $POCl_3$, 100 °C 2 h, 43%; (v) $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 3 days, 100%; (vi) $CuSO_4$, H_2O, reflux, 2 h, 24%.

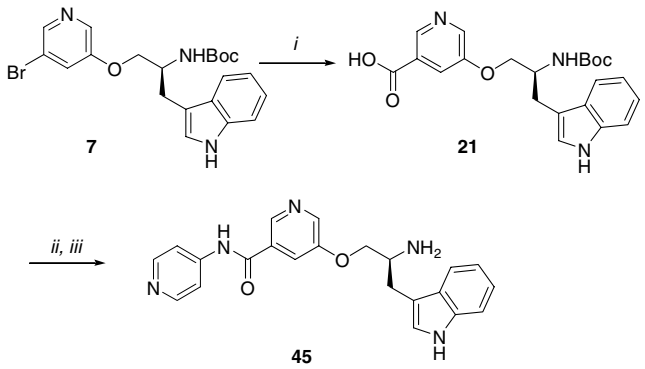


Scheme 3. Reagents and conditions: (i) $POCl_3$, 100 °C, 4 h, 62%; (ii) acetamide, K_2CO_3, 180 °C, 5 h, 65%; (iii) Boc_2O, DMAP, TEA, CH_3CN, rt, 2 h, 71%.

oxychloride yields 6-bromo-1-chloroisoquinoline (**18**). The chloride is displaced with acetamide which undergoes hydrolysis to give 1-amino-6-bromoisoquinoline (**19**). The amino group is bis protected with di-*tert*-butyl dicarbonate to give **20** prior to the Stille coupling reaction.

Synthesis of the amide linkage (**45**) begins with carbonylation of the bromopyridine intermediate **7** to give carboxylic acid **21** (Scheme 4). Carbodiimide activation of the carboxyl group followed by addition of 4-aminopyridine and removal of the Boc protecting group yields **45**.

5-Bromoindazole (**23**) which is used for the preparation of compound **48** is prepared by the reaction of 5-bromo-



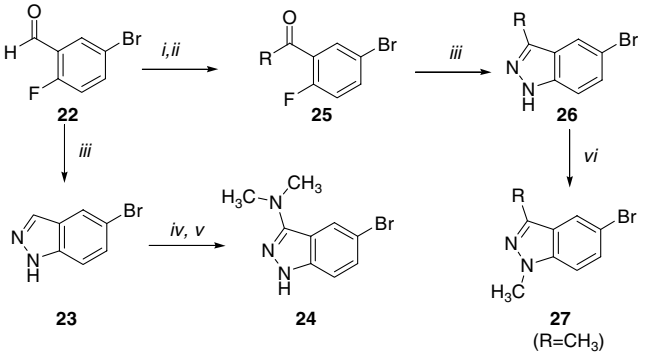
Scheme 4. Reagents and conditions: (i) $PdCl_2$·dppf, CO, THF/H_2O, 100 °C, 19 h, 76%; (ii) 4-aminopyridine, EDCI, HOBt, DMF, rt, overnight, 18%; (iii) HCl/dioxane, CH_2Cl_2, 2 h, rt, 31%.

2-fluorobenzaldehyde (**22**) with hydrazine (Scheme 5). A series of compounds having substitutions at the 3-position of the indazole are shown in Table 1.

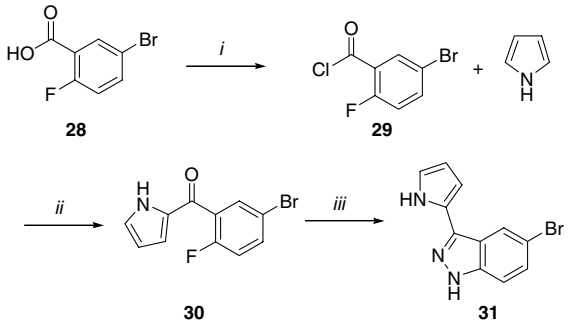
Carbon substitutions in the 3-position of the indazoles (**4**, **49**, **51**, **52**, **53**, **54**, **55**, **56**, and **58**) are prepared by anion addition (Grignard reagents or lithiated species) to 5-bromo-2-fluorobenzaldehyde (**22**) (Scheme 5). The resulting alcohol is oxidized with manganese dioxide to give the corresponding ketone **25**. The indazole **26** is then formed by refluxing the ketone in hydrazine.

The pyrrole-substituted indazole required for the synthesis of **57** is prepared as outlined in Scheme 6. The acid chloride **29** is obtained by treatment of 5-bromo-2-fluorobenzoic acid (**28**) with thionyl chloride. Friedel–Crafts reaction of **29** with pyrrole gives the requisite ketone **30** which is converted to the indazole **31** under the usual treatment with hydrazine.

Coupling of the 5- or 6-bromo-3-aminoindazole with the stannylpyridine intermediate **8** using the usual Stille conditions fails to give the desired product (**59** or **64**). These compounds are therefore obtained by doing the Stille reaction prior to formation of the indazole. Reaction of stannane **8** with 5-bromo-2-fluorobenzonitrile (**32**) followed by formation of the indazole ring system gives



Scheme 5. Reagents and conditions: (i) RMgBr, Et_2O, 0 °C, 1 h, 85–99%; (ii) MnO_2, *p*-dioxane, reflux, 4 h, 78–85%; (iii) $H_2NNH_2{\cdot}H_2O$, reflux, 9 h, 60–95%; (iv) fuming HNO_3, Ac_2O, HOAc, −5 °C, 45 min, 94%; (v) Me_2NH, THF, reflux, overnight, 45%; (vi) NaH, DMF, CH_3I, rt, 2 h, 67%.



Scheme 6. Reagents and conditions: (i) $SOCl_2$, reflux, 2 h; (ii) $AlCl_3$, 1,2-dichloroethane, 0 °C to rt, overnight, 31%; (iii)) $H_2NNH_2{\cdot}H_2O$, reflux, 9 h, 95%.

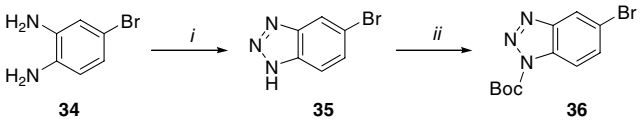
compound **59** (Scheme 7). The 3-aminoindazole attached to the pyridine ring at the indazole 6-position (**64**) can be prepared in the same manner as described for compound **59** by starting with 4-bromo-2-fluorobenzonitrile.

The 5-bromo-3-dimethylaminoindazole required for the synthesis of **60** and 5-bromo-3-morpholinoindazole used in the preparation of **61** are prepared according to the procedure reported by Wrzeciono et al.[27] Compound **26** (R = CH_3) is treated with iodomethane in the presence of base to give the 5-bromo-1,3-dimethylindazole analogue **27** (Scheme 5). The 6-substituted compounds (**63** and **64**) are prepared as described for compounds **48** and **59**, respectively, replacing the 5-bromobenzene starting materials with the corresponding 4-bromobenzene reagents.

The 5-bromobenztriazole (**35**) necessary for the synthesis of **65** is obtained in two steps from 4-bromo-1,2-diaminobenzene (**34**) (Scheme 8). Diazotization of the diamine **34** yields the benztriazole **35**. The ring nitrogen is protected with a Boc group (**36**) prior to Stille coupling.[28]

3. Results and discussion

Compound **1** (Fig. 1) was identified as a hit from a high-throughput screening assay (Akt1 K_i = 5 μM). The SAR



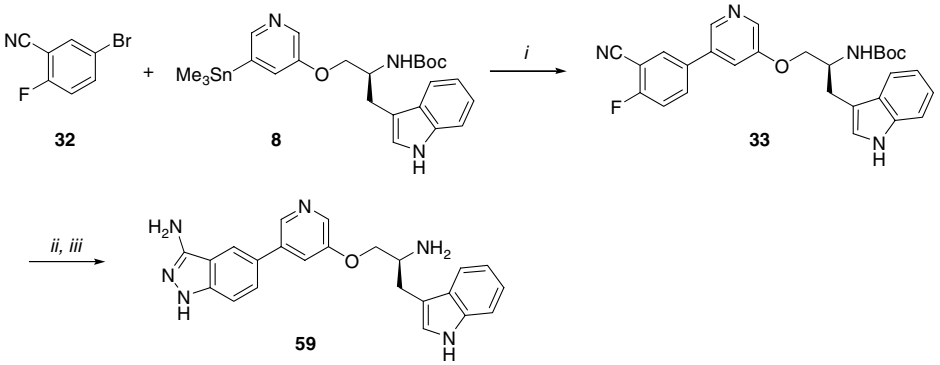
Scheme 8. Reagents and conditions: (i) $NaNO_2$, H_2SO_4, 30 min, 72%; (ii) a—phosgene, THF, −20 °C, 1 h, then rt, 2 h; b—*t*-BuOH, THF, −20 °C to rt, overnight, 76%.

efforts that resulted in the discovery of the indole containing side chain (**2**, Akt1 K_i = 14 nM) and the work leading to the isoquinoline containing compound (**3**, Akt1 K_i = 0.99 nM) have been reported previously.[16,17] We now report the SAR studies leading to the discovery of the indazole moiety as a replacement for the isoquinoline. The 3-methylindazole analogue **4** (Akt1 K_i = 0.16 nM) is the most potent Akt inhibitor obtained from this work. It shows good selectivity and has shown in vivo efficacy in several mouse tumor models.[22]

The ring nitrogen in both the pyridine ring of **2** and the isoquinoline ring of **3** appears to be well oriented to interact favorably in the hinge binding region of the ATP binding site. This hinge binding interaction is a common motif observed for most ATP competitive kinase inhibitors.

The details of our efforts investigating replacements of the olefin linkage have been reported earlier.[17] In summary, we found that if the olefin link in **2** is removed, the activity of the compounds decreases (**44** Akt1 K_i = 245 nM). The pyridine is too far away from the hinge binding region to be optimal if the other favorable molecular interactions are maintained in the ATP binding site. Attempts to interact with the hinge binding region with substituted phenyl rings were unsuccessful (**46**, Akt1 K_i = 4022 nM; **47**, Akt1 K_i = 1503 nM). Exchanging the olefin with an amide linkage, likewise, leads to a loss of Akt1 activity (**45**, Akt1 K_i = 1659 nM).

Restricting rotation about the olefin linkage of **2**, however, results in compound **3** with significantly improved Akt1 potency (Akt1 K_i = 0.99 nM).[17] This represents an improvement in activity of 14-fold versus compound **2** and an increase in activity of greater than 5000-fold over the initial hit (**1**).



Scheme 7. Reagents and conditions: (i) $Pd_2(dba)_3$, P(*o*-tol)$_3$, TEA, 110 °C, 4 h, 49%; (ii) $H_2NNH_2{\cdot}H_2O$, reflux, 5 h, 84%; (iii) TFA, CH_2Cl_2, rt 3 h, 81%.

Efforts were, therefore, undertaken to investigate the importance of the isoquinoline nitrogen and the requirements with respect to its regiochemical orientation. As would be predicted, the presence of the nitrogen atom is essential for Akt inhibitory activity. Replacing the isoquinoline with a naphthyl (**37**) results in a large decrease in potency (Akt1 K_i = 1117 nM). Removal of the isoquinoline nitrogen eliminates the ability to hydrogen bond to the protein backbone. Likewise, the position of the nitrogen atom in the hinge binding interaction is important. The quinoline analogue (**38**) shows decreased Akt activity (Akt1 K_i = 312 nM) as does the isoquinoline analogue connected to the pyridine through the isoquinoline 5-position (**43**, Akt1 K_i = 331 nM). Not only are the presence and position of the nitrogen important, there also appears to be a sensitivity to the basicity of the nitrogen in heteroaromatic ring. The less basic cinnoline rings system (**39**) maintains a nitrogen in the same spatial orientation as the isoquinoline but shows decreased Akt1 activity (Akt1 K_i = 215 nM) similar to either the quinoline (**38**, Akt1 K_i = 312 nM) or the 5-substituted isoquinoline (**43**, Akt1 K_i = 331 nM) analogues.

Pharmacokinetic examination of the isoquinoline compound **3** suggested metabolic liabilities with the molecule.[29] The 1-position of the isoquinoline appears to be prone to oxidative metabolism. The 1-hydroxy compound was prepared (**40**) and was found to have little activity (Akt1 K_i = 1022 nM). Attempts to prevent oxidative metabolism by blocking the 1-position likewise resulted in compounds with diminished Akt1 activity (**41**, Akt1 K_i = 188 nM and **42**, Akt1 K_i = 473 nM). Details of the SAR studies investigating the isoquinoline moiety are reported elsewhere.[18]

We desired to find an alternative to the isoquinoline ring. Replacement of the isoquinoline with indazole (**48**) was found to give a compound with equal potency to **3** (Akt1 K_i = 0.99 nM) while eliminating the oxidative liabilities of the isoquinoline. In addition, it was found that the indazole compound **48** exhibited an improved selectivity profile versus other kinases (see Table 2).

Many of the compounds were examined for their selectivity for Akt over other kinases. Akt1, Akt2, and Akt3 are approximately 85% homologous in protein sequence, and as a result, little selectivity is observed amongst the Akt isoforms. Selected compounds were tested against a panel of no fewer than 15 kinases. (See Table 2 for some representative examples.) Akt is a Ser/Thr kinase and, as would be expected, the compounds are highly selective for Akt when compared to tyrosine kinases (>1000-fold). The compounds are least selective for the closely related AGC family of kinases (e.g., PKA and PKC). Compound **3** was only 2-fold selective for Akt over PKA, whereas **48** showed a selectivity of nearly 20-fold. The Akt activity, the better selectivity profile, and the improved metabolic profile of the indazole compound **48** prompted us to further investigate the SAR about the indazole ring.

Table 2. Selectivity of Akt inhibitors for selected kinases[a]

Family	Kinase	K_i, nM (selectivity)		
		Compound **3**	Compound **48**	Compound **4**[b]
AGC	Akt1	0.99	0.99	0.16
	PKA	2.1 (2.1)	19 (19)	6.3 (40)
	PKCδ	225 (225)	222 (222)	33 (200)
	PKCγ	314 (314)	182 (182)	24 (150)
	SGK	270 (270)	777 (777)	82 (512)
CMGC	CDK2	82 (82)	42 (42)	24 (150)
	CDC2	85 (85)	257 (257)	127 (794)
	ERK2	524 (524)	633 (633)	340 (2100)
	CK2	13,600 (13,600)	5270 (5270)	2400 (15,000)
CAMK	MAPK	13,800 (13,800)	8160 (8160)	3300 (21,000)
TK	SRC	2180 (2180)	5000 (5000)	2600 (16,000)

[a] K_i value is shown (nM). The fold selectivity is shown in parentheses.
[b] Some of the selectivity data for compound **4** have been reported in Ref. 22. The data are re-reported here for the ease of the reader.

A number of compounds were prepared with substitutions in the 3-position of the indazole. A variety of groups were tolerated on the indazole. The thiazole **56** and imidazole **58** analogues had Akt1 K_i values of 9.8 nM. The phenyl analogue **53** had intermediate activity (Akt1 K_i = 3.9 nM). The thiophene **55** (Akt1 K_i = 1.3 nM) and pyrrole **57** (Akt1 K_i = 1.2 nM) analogues both had Akt1 activity less than 2 nM. Methyl **4** (Akt1 K_i = 0.16 nM), ethyl **51** (Akt1 K_i = 1.1 nM), and cyclopropyl **52** (Akt1 K_i = 2.6 nM) analogues all had Akt1 K_i values less than 3 nM. Introduction of a methylene linkage between the indazole and the phenyl ring (**54**) resulted in decreased activity (Akt1 K_i = 174 nM).

An unsubstituted amino group **59** in the 3-position was tolerated (Akt1 K_i = 2.9 nM) but the activity decreased to some extent with substituted amines. Dimethylamino **60** and morpholino **61** both showed Akt1 K_i values of 18 nM. Introduction of a carboxylic acid (**62**), on the other hand, was unfavorable. There was a dramatic decrease in the Akt1 inhibitory activity (Akt1 K_i = 1848 nM).

The indazole interacts with the hinge binding region of the enzyme through a hydrogen bond donor–acceptor relationship.[16,17,22] The free N–H of the indazole is essential for this interaction. Methylation of the N-1 position (**50**) disrupts that binding possibility and results in a dramatic decrease in activity (Akt1 K_i = 685 nM).

A stereochemical preference is observed for the ether-linked side chain. Both enantiomers of the tryptophanol side chain were prepared. The *S*-stereoisomer of the ether side-chain **4** (Akt1 K_i = 0.16 nM) is preferred over the *R*-enantiomer **49** (Akt1 K_i = 28 nM).[30]

The attachment in the 5-position of the indazole to the pyridine (**48**) is optimal for Akt activity. Attachment in the 6-position of the indazole (**63**) results in a loss of Akt activity (Akt1 K_i = 237 nM). The orientation of the hydrogen bond donor–acceptor arrangement with this connectivity cannot align properly in the hinge

binding site. Attempts to provide a possibility for the desired interaction led to the introduction of an amino group in the 3-position (**64**). The compound, however, showed little Akt activity (Akt1 K_i = 1232 nM).

As was the case for the isoquinoline analogues, the indazole analogues also seem to exhibit a balance between geometric requirements and electronic requirements. The cinnoline analogue (**39**, Akt1 K_i = 215 nM) was much less active than the isoquinoline analogue (**3**, Akt1 K_i = 0.99 nM) even though the hinge binding nitrogen atoms should be in the same spatial orientation. Replacing the indazole (**48**, Akt1 K_i = 0.99 nM) with benztriazole (**65**) maintains a similar spatial relationship of the nitrogen atoms but results in a nearly 100-fold loss of Akt activity (Akt1 K_i = 92 nM).

The 3-methylindazole compound **4** was chosen for further investigation. Not only was this compound the most potent of the inhibitors against Akt1 (Akt1 K_i = 0.16 nM) but it also showed a favorable selectivity profile (Table 2). There is little selectivity within the Akt isoforms. Compound **4** is least selective against closely related kinases in the AGC family, nonetheless, it is 40-fold selective against PKA. The inhibitor **4** also demonstrated cellular growth inhibition activity against MiaPaCa cells (Soft Agar EC_{50} = 44 nM; MTT EC_{50} = 100 nM; GSK3-P EC_{50} = 300 nM).

Although the 3-methylindazole compound **4** suffered from a short half-life ($t_{1/2}$ = 0.6 h in mouse) and no oral bioavailability, it was examined for in vivo efficacy in several mouse tumor models. The compound was dosed subcutaneously at 7.5 and 15 mg/kg/day for 14 days. Dosing was limited to 14 days due to skin irritation at the injection site. The inhibitor was found to significantly slow the growth of the tumors. The details of these tumor studies have been previously reported.[22]

4. Conclusion

We have prepared a series of heteroaryl-pyridine containing inhibitors of Akt leading to the discovery of the indazole-pyridine **4**. These compounds bind in the ATP binding site, are potent, ATP competitive,[31] and reversible inhibitors of Akt activity.[32] Compound **4** is highly potent against Akt1 (K_i = 0.16 nM). No selectivity amongst the Akt isoforms is observed for this analogue, but it shows good selectivity against a panel of other kinases. It is least selective for other members of the AGC family of kinases but is nonetheless 40-fold selective for Akt over closely related PKA. The compound shows cellular activity and significantly slows tumor growth in vivo when dosed subcutaneously. The in vivo dosing, however, is limited as a result of severe irritation at the injection site. Discussions of oral bioavailability and half-life issues are addressed in other communications from our laboratories.[33]

5. Experimental

5.1. General procedures

^{1}H NMR spectra were recorded on a Varian Mercury 300 (300 MHz) spectrometer or a Varian Unity Inova 500 (500 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. 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; APCI (atmospheric pressure chemical ionization) was performed on a Finnigan Navigator MS run as flow injection acquisition. Elemental analyses were performed by Robertson Microlit, Madison, NJ. Flash chromatography was carried out using Merck 50–200 mm silica gel. All solvents and reagents were obtained from commercial sources and used without further purification, except where noted.

5.2. Chemistry

5.2.1. (*S*)-[2-(5-Bromo-pyridin-3-yloxy)-1-(1*H*-indol-3-ylmethyl)-ethyl]-carbamic acid *tert*-butyl ester (7). A solution of 3-bromo-5-hydroxypyridine[34] (2.0 g, 11.5 mmol), L-Boc-tryptophanol (3.67 g, 12.6 mmol), and triphenylphosphine (4.53 g, 17.3 mmol) in 50 mL THF at 0 °C was treated dropwise with DEAD (3.01 g, 17.3 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction mixture was concentrated and purified by flash column chromatography on silica gel with 20% EtOAc/hexane to provide the desired product **7** (4.55 g, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.8 (br s, 1H), 8.27 (m, 2H), 7.65 (m, 1H), 7.56 (d, J = 8 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 6.9–7.1 (m, 4H), 4.0 (M, 2H), 2.9–3.0 (m, 3H), 1.35 (s, 9H). MS (DCI/NH_3): m/z $(M+H)^+$ 446, 448.

5.2.2. (*S*)-[1-(1*H*-Indol-3-ylmethyl)-2-(5-trimethylstannanyl-pyridin-3-yloxy)-ethyl]-carbamic acid *tert*-butyl ester (8). A solution of **7** (1 g, 2.23 mmol) in DMA (15 mL) was treated with hexamethylditin (1.8 mL, 5.6 mmol) and $Pd(PPh_3)_4$ (0.4 g, 0.2 mmol). The reaction mixture was heated to 75 °C for 1.5 days. The mixture was added to water and extracted three times with ethyl acetate. The combined extracts were concentrated and the residue was purified by flash column chromatography on silica gel with 1:1 hexanes/ethyl acetate to provide the desired product **8** (0.4 g, 34 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.8 (br s, 1H), 8.17 (d, J = 3 Hz, 1H), 8.15 (s, 1H), 7.54 (d, J = 8 Hz, 1H), 7.38 (s, 1H), 7.33 (d, J = 8 Hz, 1H), 6.9–7.1 (m, 4H), 4.0 (m, 2H), 2.9–3.0 (m, 3H), 1.36 (s, 9H), 0.29 (s, 9H). MS (DCI/NH_3): m/z $(M+H)^+$ 528, 530, 532.

5.2.3. (*R*)-[2-(5-Bromo-pyridin-3-yloxy)-1-(1*H*-indol-3-ylmethyl)-ethyl]-carbamic acid *tert*-butyl ester. The *R*-enantiomer of **7** (required for the synthesis of **49**) is

prepared in the same manner described for **7** using D-Boc-tryptophanol in place of the L-Boc-tryptophanol. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.8 (br s, 1H), 8.27 (m, 2H), 7.65 (m, 1H), 7.56 (d, J = 8 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 6.9–7.1 (m, 4H), 4.0 (M, 2H), 2.9–3.0 (m, 3H), 1.35 (s, 9H). MS (DCI/NH_3): m/z $(M+H)^+$ 446, 448.

5.2.4. (*R*)-[1-(1*H*-Indol-3-ylmethyl)-2-(5-trimethylstannanyl-pyridin-3-yloxy)-ethyl]-carbamic acid *tert*-butyl ester. The *R*-enantiomer of **8** is prepared in the same manner described for **8** using D-Boc-tryptophanol pyridyl ether in place of example **7**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.8 (br s, 1H), 8.17 (d, J = 3 Hz, 1H), 8.15 (s, 1H), 7.54 (d, J = 8 Hz, 1H), 7.38 (s, 1H), 7.33 (d, J = 8 Hz, 1H), 6.9–7.1 (m, 4H), 4.0 (m, 2H), 2.9–3.0 (m, 3H), 1.36 (s, 9H), 0.29 (s, 9H). MS (DCI/NH_3): m/z $(M+H)^+$ 528, 530, 532.

5.2.5. *N*-(2-Acetyl-phenyl)-acetamide (11). A solution of 2′-aminoacetophenone (5.0 g, 37 mmol) in dichloromethane (150 mL) at room temperature was treated with triethylamine (5.3 mL, 40 mmol) and acetyl chloride (3.2 mL, 45 mmol). The reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with ethyl acetate (2×). The combined extracts were rinsed with brine (1×), dried over $MgSO_4$, and concentrated to provide the desired product **11** of sufficient purity to carry on with no additional purification (6.5 g, 100%).

5.2.6. *N*-(2-Acetyl-4-bromo-phenyl)-acetamide (12). A solution of **11** (6.5 g, 37 mmol) in acetic acid (100 mL) at room temperature was treated with Br_2 (4 mL, 84 mmol) and stirred for 75 min. The reaction mixture was poured into water (200 mL) and filtered. The solid was washed with water (2×) and hexanes (2×) then dissolved in diethyl ether. The Et_2O solution was washed with brine (1×), dried over $MgSO_4$, and concentrated to provide the desired product **12** (8.5 g, 89%). The product was carried on with no additional purification.

5.2.7. 6-Bromo-1*H*-cinnolin-4-one (13). A solution of **12** (6.28 g, 24.4 mmol) in THF (75 mL) was treated with concentrated HCl (aq) (15 mL) and water (15 mL). The reaction was heated at reflux for 1 h then concentrated to remove the THF. The aqueous solution was treated with additional water (5 mL) and concd HCl (5 mL). The solution was cooled to 0 °C, then treated with a solution of $NaNO_2$ (1.85 g, 26.84 mmol) in water (10 mL) in five portions. The reaction mixture was warmed to room temperature gradually over a 2 h period then stirred overnight at room temperature. The reaction mixture was heated to reflux for 6 h and filtered. The resulting solid was washed with water (50 mL) and diethyl ether (50 mL) then dried under vacuum to provide the desired product **13** (3.0 g, 54%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.65 (br s, 1H), 8.12 (d, J = 2 Hz, 1H), 7.94 (dd, J = 9, 2 Hz, 1H), 7.82 (s, 1H), 7.57 (d, J = 9 Hz, 1H). MS (ESI): m/z $(M+H)^+$ 225, 227.

5.2.8. 6-Bromo-4-chloro-cinnoline (14). A solution of **13** (0.4 g, 1.8 mmol) in $POCl_3$ (2.5 mL) was heated to 100 °C for 2 h, then poured slowly onto ice. The aqueous solution was cooled to 0 °C and adjusted to pH 5–7 with 50% NaOH. The solution was extracted with ethyl acetate (2×), and the combined organic layers were concentrated. The residue was purified by flash column chromatography on silica gel with 4:1 hexanes/EtOAc to provide the desired product **14** (0.190 g, 43%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.64 (s, 1H), 8.51 (d, J = 9 Hz, 1H), 8.42 (d, J = 2 Hz, 1H), 8.22 (dd, J = 9, 2 Hz, 1H). MS (ESI): m/z $(M+H)^+$ 243, 245, 247.

5.2.9. (6-Bromo-cinnolin-4-yl)-hydrazine (15). A solution of **14** (2.6 g, 10.6 mmol) in ethanol (70 mL) was treated with hydrazine monohydrate (3 mL, 90% solution), stirred at room temperature for 3 days, and filtered. The solid was washed with water (50 mL) and diethyl ether (50 mL) and dried under vacuum to provide the desired product **15** (2.5 g, 100%). The material was carried on with no additional purification.

5.2.10. 6-Bromo-cinnoline (16). A solution of **15** (3.5 g, 14 mmol) in water (50 mL) was heated to reflux then treated dropwise with a solution of $CuSO_4$ (2.8 g, 17.5 mmol) in water (20 mL). The reaction mixture was heated at reflux for 2 h. The mixture was cooled to room temperature and adjusted to pH 7 with saturated $NaHCO_3$ (aq). The reaction mixture was extracted with ethyl acetate (2×). The combined extracts were rinsed with brine, dried over $MgSO_4$, and concentrated. The material was purified by flash column chromatography on silica gel with 1:1 hexanes/EtOAc to provide the desired product **16** (0.7 g, 24%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.41 (d, J = 6 Hz, 1H), 8.51 (d, J = 9 Hz, 1H), 8.26 (d, J = 2 Hz, 1H), 8.21 (d, J = 6 Hz, 1H), 7.98 (dd, J = 9, 2 Hz, 1H). MS (ESI): m/z $(M+H)^+$ 209, 211.

5.2.11. 6-Bromo-1-chloro-isoquinoline (18). A solution of 6-bromo-1-hydroxyisoquinoline[35] (9.205 g, 41.0 mmol) in $POCl_3$ (100 mL) was heated at 100 °C for 4 h. The reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc and the organic layer was washed successively with 5% $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluting with 30% CH_2Cl_2/hexane to give the desired compound **18** (6.176 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.30 (d, J = 6 Hz, 1H), 8.22 (d, J = 9 Hz, 1H), 8.04 (d, J = 2 Hz, 1H), 7.77 (dd, J = 9, 2 Hz, 1H), 7.52 (d, J = 6 Hz, 1H). MS (DCI/NH_3): m/z $(M+H)^+$ 242, 244, 246.

5.2.12. 6-Bromo-isoquinolin-1-ylamine (19). A mixture of the chloride **18** (264 mg, 1.09 mmol), acetamide (1.3 g), and K_2CO_3 (0.45 g) was heated at 180 °C for 5 h. After cooling to rt, the mixture was dissolved in ethyl acetate and washed successively with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (100:5:0.5) to give the desired compound **19**

(159 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.96 (d, J = 6 Hz, 1H), 7.88 (d, J = 2 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 7.57 (dd, J = 9, 2 Hz, 1H), 6.96 (d, J = 6 Hz, 1H), 5.4 (br s, 2H). MS (DCI/NH_3): m/z $(M+H)^+$ 223, 225.

5.2.13. (6-Bromo-isoquinolin-1-yl)-bis-carbamic acid *tert*-butyl ester (20). A solution of **19** (616 mg, 2.76 mmol), Boc_2O (1.81 g), DMAP (67 mg), and triethylamine (1.15 mL) in acetonitrile (15 mL) was stirred at rt for 2 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel eluting with 30% EtOAc/hexane to give the desired compound **20** (1.18 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.45 (d, J = 6 Hz, 1H), 8.06 (d, J = 2 Hz, 1H), 7.83 (d, J = 9 Hz, 1H), 7.71 (dd, J = 9, 2 Hz, 1H), 7.57 (d, J = 6 Hz, 1H) 1.32 (s, 18H). MS (DCI/NH_3): m/z $(M+H)^+$ 423, 425.

5.2.14. (*S*)-5-[2-*tert*-Butoxycarbonylamino-3-(1*H*-indol-3-yl)-propoxy]-nicotinic acid (21). A solution of **7** (1.30 g, 3.02 mmol) and $PdCl_2$·dppf (123 mg) in 12 mL 1:1 THF/water was heated at 100 °C under CO (800 psi) for 19 h. The reaction mixture was cooled to room temperature and diluted with water. The mixture was extracted with dichloromethane (3×) and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated to provide the desired product **21** (912 mg, 76%) that was carried on with no further purification.

5.2.15. (*S*)-{1-(1*H*-Indol-3-ylmethyl)-2-[5-(pyridin-4-yl carbamoyl)-pyridin-3-yloxy]-ethyl}-carbamic acid *tert*-butyl ester (Boc-protected 45). A solution of **21** (410 mg, 1.0 mmol), 4-aminopyridine (100 mg, 1.0 mmol), EDC (960 mg), and HOBt (680 mg) in DMF (10 mL) was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel with ethyl acetate/methanol (8:1) to provide the desired product (87 mg, 18%). MS (DCI/NH_3): m/z $(M+H)^+$ 488.

5.2.16. (*S*)-5-[2-Amino-3-(1*H*-indol-3-yl)-propoxy]-*N*-pyridin-4-yl-nicotinamide (45). A solution of Boc-protected **45** (85 mg, 0.17 mmol) in dichloromethane (20 mL) at room temperature was treated with 4 N HCl in dioxane (5 mL), stirred for 2 h, and concentrated. The residue was dissolved in water (1.5 mL) and lyophilized to provide the desired product **45** as the dihydrochloride salt (25 mg, 31%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.32 (br s, 1H), 11.04 (br s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.69 (d, J = 6.8 Hz, 2H), 8.59 (d, J = 2.7 Hz, 1H), 8.15 (br s, 2H), 8.08 (d, J = 6.8 Hz, 2H), 7.85 (dd, J = 2.7, 1.4 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.12 Hz, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.10 (m, 1H), 7.01 (m, 1H), 4.33 (m, 1H), 4.16 (m, 1H), 3.87 (m, 1H), 3.16 (m, 2H). MS (DCI/NH_3): m/z $(M+H)^+$ 388.

5.2.17. 5-Bromo-1*H*-indazole (23). A mixture of 5-bromo-2-fluorobenzaldehyde (10 g, 49.2 mmol) and 98% hydrazine (20 mL) was heated at reflux for 5 h, poured over ice, and filtered. The solid was recrystallized from H_2O/methanol to provide the desired product **23** (3.7 g, 38%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.25 (br s, 1H), 8.05 (s, 1H), 8.00 (s, 1H), 7.4–7.5 (m, 2H). MS (DCI/NH_3): m/z $(M+H)^+$ 197, 199.

5.2.18. 1-(5-Bromo-2-fluoro-phenyl)-ethanone (25) (R = CH_3)

5.2.18.1. Step 1. A solution of 5-bromo-2-fluorobenzaldehyde (24.75 g; 122 mmol) in Et_2O (125 mL) at 0 °C was treated with 3.0 M MeMgBr in Et_2O (43 mL, 129 mmol). The mixture was stirred for 30 min. then carefully diluted with water and acidified with 10% HCl (aq). The aqueous layer was extracted with Et_2O. The combined extracts were rinsed successively with 10% HCl (aq), water, and brine, dried ($MgSO_4$), and evaporated to give 1-(5-bromo-2-fluorophenyl)ethanol (26.6 g; 99%) of sufficient purity to carry on to the next step.

5.2.18.2. Step 2. A solution of 1-(5-bromo-2-fluorophenyl)ethanol (26.6 g; 121 mmol) and manganese(IV) oxide (53 g; 610 mmol) in *p*-dioxane (500 mL) was heated at reflux for 4 h. The reaction mixture was cooled and filtered through Celite®. The filtrate was evaporated and purified by flash chromatography (5–10% Et_2O/hexane) to yield the desired product **25** (R = CH_3) as a nearly colorless oil that solidified upon standing (20.5 g; 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.99 (dd, J = 6, 3 Hz, 1H), 7.60–7.64 (m, 1H), 7.0–7.1 (m, 1H), 2.63 (s, 3H). MS (DCI/NH_3): m/z $(M+H)^+$ 217, 219.

5.2.19. 5-Bromo-3-methyl-1*H*-indazole (26) (R = CH_3). A solution of **25** (R = CH_3) (10 g; 46 mmol) in 25 mL of hydrazine monohydrate was heated at reflux for 9 h. The reaction mixture was poured over ice and the resulting precipitate was collected. The product was purified by flash chromatography (1:1 Et_2O/hexane) to give the desired indazole **26** (R = CH_3) as a white solid (5.8 g; 60%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.8 (br s, 1H), 7.95 (s, 1H), 7.43 (s, 2H), 2.47 (s, 3H). MS (DCI/NH_3): m/z $(M+H)^+$ 211, 213.

5.2.20. 5-Bromo-1,3-dimethyl-1*H*-indazole (27) (R = CH_3). To a solution of 60% NaH (115 mg; 2.84 mmol) in 10 mL DMF was added indazole **26** (R = CH_3) (500 mg; 2.37 mmol). After 15 min at rt iodomethane (465 mg; 3.21 mmol) was added and the reaction mixture was stirred for 2 h. The reaction mixture was treated with water and extracted into EtOAc (3×). The combined extracts were rinsed with brine (2×), dried over $MgSO_4$, and evaporated. The product was purified by flash chromatography (1:1 Et_2O/hexane) to give the desired *N*-methylindazole **27** (R = CH_3) as a white solid (360 mg; 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.79 (d, J = 2 Hz, 1H), 7.43 (dd, J = 9, 2 Hz, 1H), 7.21 (d, J = 9 Hz, 1H), 3.98 (s, 3H), 2.53 (s, 3H). MS (DCI/NH_3): m/z $(M+H)^+$ 225, 227.

5.2.21. 5-Bromo-2-fluoro-benzoic acid (28). A solution of 5-bromo-2-fluorobenzaldehyde (810 mg; 4.0 mmol) in 5 mL MeOH was treated with 3 mL of 15% NaOH (aq) and 5 mL of 30% H_2O_2. The reaction mixture was stirred at rt for 2 h. The mixture was acidified with

10% HCl (aq) and the resulting precipitate was collected, rinsed with water, and dried to yield the desired product **28** (670 mg; 77%) which was carried on with no further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.6 (br s, 1H), 7.96 (dd, J = 6, 3 Hz, 1H), 7.8-7.9 (m, 1H), 7.3-7.4 (m, 1H). MS (DCI/NH_3): m/z $(M+H)^+$ 219, 221.

5.2.22. (5-Bromo-2-fluoro-phenyl)-(1*H*-pyrrol-2-yl)-methanone (30). The carboxylic acid **28** (665 mg; 3.0 mmol) was dissolved in thionyl chloride (7 mL) and heated at reflux for 2 h. The reaction mixture was concentrated and azeotroped with toluene. The resulting acid chloride **29** and pyrrole (203 mg; 3.0 mmol) were taken up in 1,2-dichloroethane (15 mL) and cooled to 0 °C. $AlCl_3$ (420 mg; 3.15 mmol) was added portionwise then stirred overnight while gradually warming to rt. The reaction mixture was poured over ice and acidified with 1 N HCl then stirred at rt for 1.5 h. The solution was extracted with CH_2Cl_2 (3×). The combined extracts were rinsed with water and saturated $NaHCO_3$ (aq), dried over Na_2SO_4, and evaporated. The product **30** was isolated by flash chromatography (10% EtOAc/hexane) as a purple solid (252 mg; 31%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.2 (br s, 1H), 7.7–7.8 (m, 2H), 7.35 (t, J = 9 Hz, 1H), 7.25–7.3 (m, 1H), 6.6–6.7 (m, 1H), 6.2–6.3 (m, 1H). MS (DCI/NH_3): m/z $(M+H)^+$ 268, 270.

5.2.23. 5-Bromo-3-(1*H*-pyrrol-2-yl)-1*H*-indazole (31). Conversion of the ketone **30** to the indazole **31** was carried out as described for example **26**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.1 (br s, 1H), 11.4 (br s, 1H), 8.18 (s, 1H), 7.45–7.5 (m, 2H), 6.85–6.9 (m, 1H), 6.7–6.75 (m, 1H), 6.15–6.2 (m, 1H). MS (DCI/NH_3): m/z $(M+H)^+$ 262, 264.

5.2.24. 5-Bromo-1*H*-benzotriazole (35). 4-Bromo-1,2-benzenediamine (262 mg; 1.4 mmol) in 4 mL of 10% H_2SO_4 (aq) was treated with an aqueous solution of $NaNO_2$ (120 mg; 1.7 mmol in 1 mL H_2O). A tan precipitate formed almost immediately. The reaction mixture was stirred for 30 min. The mixture was diluted with water and extracted into EtOAc (3×). The combined extracts were rinsed with brine, dried over Na_2SO_4, and evaporated. The product was isolated by flash chromatography (5% MeOH/CH_2Cl_2). The product was obtained as a tan solid (200 mg; 72%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 15.95 (br s, 1H), 8.21 (s, 1H), 7.92 (d, J = 9 Hz, 1H), 7.59 (d, J = 9 Hz, 1H). MS (DCI/NH_3): m/z $(M+H)^+$ 196, 198.

5.2.25. 5-Bromo-benzotriazole-1-carboxylic acid *tert*-butyl ester (36). The Boc group was introduced onto the benztriazole **35** nitrogen as described by Katritzky et al.[28]

5.2.26. (*S*)-[2-[5-(3-Cyano-4-fluoro-phenyl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethyl]-carbamic acid *tert*-butyl ester (33). A solution of 5-bromo-2-fluorobenzonitrile (246 mg; 1.23 mmol) and stannyl material **8** (595 mg; 1.12 mmol) in DMF (10 mL) was treated with $Pd_2(dba)_3$ (113 mg; 0.123 mmol),tri-*o*-tolylphosphine (80 mg; 0.246 mmol), and triethylamine (156 mg; 1.54 mmol) then heated at 110 °C for 4 h. The reaction mixture was partitioned between brine and EtOAc, filtered through Celite®, and extracted with EtOAc. The extracts were rinsed with brine and dried over $MgSO_4$. The product was purified by flash chromatography (1:1 EtOAc/hexane) to provide the desired product **33** (265 mg; 49%). ^{1}H NMR (300 MHz DMSO-d_6), δ ppm 10.8 (br s, 1H), 8.54 (s, 1H), 8.35–8.4 (m, 1H), 8.31–8.33 (m, 1H), 8.10–8.20 (m, 1H), 7.55–7.70 (m, 3H), 7.33 (d, J = 8 Hz, 1H), 7.15–7.20 (m, 1H), 6.90–7.10 (m, 3H), 4.1–4.15 (m, 2H), 2.8–3.05 (m, 3H), 1.36 (s, 9H). MS (ESI): m/z $(M+H)^+$ 487.

5.2.27. (*S*)-[2-[5-(3-Amino-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethyl]-carbamic acid *tert*-butyl ester (Boc-protected 59). A mixture of **33** (120 mg, 0.25 mmol) in 5 mL of 98% hydrazine was heated to reflux for 5 h then poured over ice. The solution was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (7% MeOH/CH_2Cl_2) provided the desired product Boc-protected **59** (103 mg, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.5 (br s, 1H), 10.8 br s, 1H), 8.48 (d, J = 2 Hz, 1H), 8.20 (d, J = 3 Hz, 1H), 8.10 (s, 1H), 7.55–7.60 (m, 3H), 7.30–7.35 (m, 3H), 7.15–7.18 (m, 1H), 6.90–7.05 (m, 2H), 5.43 (s, 2H), 4.05–4.15 (m, 2H), 2.90–3.05 (m, 3H), 1.36 (s, 9H). MS (ESI): m/z $(M+H)^+$ 499.

5.2.28. (*S*)-5-{5-[2-Amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-1*H*-indazol-3-ylamine (59). A solution of Boc-protected **59** (95 mg; 0.19 mmol) in 5 mL CH_2Cl_2 was treated with 0.5 mL TFA and stirred at rt for 3 h. The reaction mixture was concentrated and the product was purified by reverse-phase HPLC on a C18 column with 0–100% CH_3CN/H_2O/0.1%TFA to provide the desired product **59** as a TFA salt (114 mg; 81%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.04 (s, 1 H) 11.92 (br s, 1H), 8.57 (d, J = 1.70 Hz, 1H), 8.32 (d, J = 2.71 Hz, 1H), 8.18 (m, 4H), 7.66 (s, 1H), 7.63 (d, J = 7.46 Hz, 1H), 7.42 (s, 1H), 7.38 (m, 1H), 7.30 (d, J = 2.37 Hz, 1H), 7.12 (m, 4H), 4.36 (m, 1H), 4.18 (dd, J = 10.51, 5.76 Hz, 1H), 3.84 (m, 1H), 3.17 (d, J = 7.12 Hz, 2H). MS (ESI): m/z $(M+H)^+$ 399. Anal. Calcd for $C_{23}H_{22}N_6O$·2.9TFA: C, 47.44; H, 3.44; N, 11.53. Found: C, 47.87; H, 3.49; N, 11.19.

5.2.29. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-(5-naphthalen-2-yl-pyridin-3-yloxy)-ethylamine (37). Stille reaction with 2-bromonaphthalene and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **37**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.02 (s, 1H), 8.74 (s, 1H), 8.38 (s, 1H), 8.30 (s, 1H), 8.18–8.21 (m, 2H), 8.04 (d, J = 8 Hz, 1H), 7.97–8.01 (m, 2H), 8.85 (d, J = 8 Hz, 1H), 7.81 (s, 1H), 7.62 (d, J = 8 Hz, 1H), 7.50–7.58 (m, 1H), 7.35–7.39 (m, 1H), 7.23–7.31 (m, 1H), 7.08–7.12 (m, 1H), 6.96–7.03 (m, 2H), 4.18–4.41 (m, 2H), 3.82–3.87 (m, 1H), 3.17–3.21 (m, 2H). MS (ESI): m/z $(M+H)^+$ 394.

5.2.30. (*S*)-2-(1*H*-indol-3-yl)-1-{[(5-isoquinolin-6-ylpyridin-3-yl)oxy]methyl}ethylamine (3). Stille reaction with 6-bromoisoquinoline and stannyl material **8** (as de-

scribed for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **3**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.02 (br s, 1H), 9.52 (s, 1H), 8.76 (d, J = 3 Hz, 1H), 8.62 (d, J = 8 Hz, 1H), 8.44–8.46 (m, 2H), 8.38 (d, J = 9 Hz, 1H), 8.11–8.20 (m, 3H), 8.04–8.08 (m, 1H), 7.83–7.86 (m, 1H), 7.62 (d, J = 9 Hz, 1H), 7.37–7.40 (m, 1H), 7.31 (d, J = 3 Hz, 1H), 7.08–7.12 (m, 1H), 6.99–7.03 (m, 1H), 4.37–4.41 (m, 1H), 4.18–4.23 (m, 1H), 3.86–3.91 (m, 1H), 3.16–3.20 (m, 2H). MS (ESI): m/z (M+H)$^+$ 395. Anal. Calcd for $C_{25}H_{22}N_4O{\cdot}2TFA{\cdot}H_2O$: C, 49.35; H, 3.61; N, 7.43; F, 22.67. Found: C, 49.04; H, 3.55; N, 7.42; F, 22.28.

5.2.31. (*S*)-2-(1*H*-indol-3-yl)-1-{[(5-quinolin-6-ylpyridin-3-yl)oxy]methyl}ethylamine (38). Stille reaction with 6-bromoquinoline and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **38**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.02 (s, 1H), 8.97-9.00 (m, 1H), 8.74 (d, J = 3 Hz, 1H), 8.50–8.54 (m, 1H), 8.39–8.42 (m, 2H), 8.18–8.23 (m, 3H), 8.13–8.17 (m, 1H), 7.81–7.83 (m, 1H), 7.61–7.66 (m, 2H), 7.39 (d, J = 8 Hz, 1H), 7.31 (d, J = 3 Hz, 1H), 7.07–7.10 (m, 1H), 6.99–7.02 (m, 1H), 4.38–4.41 (m, 1H), 4.21–4.24 (m, 1H), 3.79–3.83 (m, 1H), 3.16–3.19 (m, 2H). MS (ESI): m/z (M+H)$^+$ 395.

5.2.32. (*S*)-2-[(5-cinnolin-6-ylpyridin-3-yl)oxy]-1-(1*H*-indol-3-ylmethyl)ethylamine (39). Stille reaction with 6-bromocinnoline (**16**) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **39**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.04 (s, 1H), 9.43 (d, J = 6 Hz, 1H), 8.78 (d, J = 2 Hz, 1H), 8.60 (d, J = 8 Hz, 1H), 8.45–8.49 (m, 2H), 8.30–8.34 (m, 1H), 8.26 (d, J = 6 Hz, 1H), 8.21–8.25 (m, 2H), 7.89 (t, J = 2 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 7.39 (d, J = 8 Hz, 1H), 7.31 (d, J = 2 Hz, 1H), 7.08–7.12 (m, 1H), 7.01–7.04 (m, 1H), 4.38–4.42 (m, 1H), 4.22–4.26 (m, 1H), 3.83–3.88 (m, 1H), 3.17–3.20 (m, 2H). MS (ESI): m/z (M+H)$^+$ 396.

5.2.33. 6-{5-[(*S*)-2-Amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-2*H*-isoquinolin-1-one (40). Stille reaction with 6-bromo-1-hydroxyisoquinoline (**17**) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **40**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.30 (br s, 1H), 11.04 (br s, 1H), 8.66–8.68 (m, 1H), 8.41 (d, J = 3 Hz, 1H), 8.27 (d, J = 8 Hz, 1H), 8.17–8.20 (m, 2H), 8.02–8.03 (m, 1H), 7.76–7.81 (m, 2H), 7.62 (d, J = 8 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.29–7.31 (m, 1H), 7.20–7.26 (m, 1H), 7.07–7.12 (m, 1H), 6.98–7.04 (m, 1H), 6.60 (d, J = 8 Hz, 1H), 4.14–4.39 (m, 2H), 3.33–3.38 (m, 1H), 3.13–3.16 (m, 2H). MS (ESI): m/z (M+H)$^+$ 411. Anal. Calcd for $C_{25}H_{22}N_4O{\cdot}2TFA$: C, 54.54; H, 3.78; N, 8.78. Found: C, 54.54; H, 4.00; N, 8.56.

5.2.34. 1-Amino-6-{5-[(*S*)-2-amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-isoquinoline (41). Stille reaction with 1-bis-Boc-amino-6-bromoisoquinoline (**20**) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **41**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.77 (s, 1H), 8.55 (d, J = 8.6 Hz, 1H), 8.45 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 1.5 Hz, 1H), 8.05 (dd, J = 8.6, 1.8 Hz, 1H), 7.83 (dd, J = 1.8, 2.5 Hz, 1H), 7.61 (m, 2H), 7.38 (d, J = 7.1 Hz, 1H), 7.24 (s, 1H), 7.12 (m, 1H), 7.02 (m, 1H), 4.44 (dd, J = 10.4, 3.1 Hz, 1H), 4.30 (dd, J = 10.4, 5.8 Hz, 1H), 4.01 (m, 1H), 3.32 (m, 2H). MS (DCI/NH$_3$): m/z (M+H)$^+$ 410.

5.2.35. 6-{5-[(*S*)-2-amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-1-chloro-isoquinoline (42). Stille reaction with 6-bromo-1-chloroisoquinoline (**18**) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **42**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.03 (br s, 1H), 8.75 (d, J = 1.6 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.84 (m, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.10 (m, 1H), 7.01 (m, 1H), 4.38 (dd, J = 10.6, 3.1 Hz, 1H), 4.22 (dd, J = 10.4, 6.2 Hz, 1H), 3.88 (m, 1H), 3.18 (m, 2H). MS (ESI): m/z (M+H)$^+$ 429, 431.

5.2.36. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-(5-isoquinolin-5-yl-pyridin-3-yloxy)-ethylamine (43). Stille reaction with 5-bromoisoquinoline and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **43**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.02 (br s, 1H), 9.53 (s, 1H), 8.52 (d, J = 8 Hz, 1H), 8.49 (d, J = 4 Hz, 1H), 8.37 (d, J = 3 Hz, 1H), 8.30–8.34 (m, 1H), 8.15–8.19 (m, 2H), 7.84–7.88 (m, 2H), 7.68 (d, J = 8 Hz, 1H), 7.56–7.60 (m, 2H), 7.47 (d, J = 8 Hz, 1H), 7.28 (d, J = 4 Hz, 1H), 7.60–7.12 (m, 1H), 6.94–6.99 (m, 1H), 4.12–4.32 (m, 2H), 3.82–3.87 (m, 1H), 3.13–3.17 (m, 2H). MS (ESI): m/z (M+H)$^+$ 395.

5.2.37. (*S*)-2-{[5-(1*H*-indazol-5-yl)pyridin-3-yl]oxy}-1-(1*H*-indol-3-ylmethyl)-ethylamine (48). Stille reaction with 5-bromoindazole (**23**) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **48**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.22 (br s, 1H), 11.04 (br s, 1H), 8.62 (d, J = 2 Hz, 1H), 8.33 (d, J = 3 Hz, 1H), 8.13–8.21 (m, 3H), 8.12 (s, 1H), 7.67–7.72 (m, 3H), 7.64 (d, J = 8 Hz, 1H), 7.39 (d, J = 8Hz, 1H), 7.30 (d, J = 2 Hz, 1H), 7.06–7.13 (m, 1H), 6.98–7.04 (m, 1H), 4.14–4.39 (m, 2H), 3.33–3.38 (m, 1H), 3.13–3.16 (m, 2H). MS (ESI): m/z (M+H)$^+$ 384. Anal. Calcd for $C_{23}H_{21}N_5O{\cdot}2TFA{\cdot}H_2O$: C, 51.52; H, 4.00; N, 11.13. Found: C, 51.80; H, 3.61; N, 11.03.

5.2.38. (*S*)-2-([3,4′]Bipyridinyl-5-yloxy)-1-(1*H*-indol-3-ylmethyl)-ethylamine (44). Stille reaction with 4-bromopyridine and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **44**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.85 (d, J = 6.8 Hz, 2H), 8.73 (d, J = 1.7 Hz, 1H), 8.53 (d, J = 2.7 Hz, 1H), 8.20 (d, J = 6.8 Hz, 2H), 7.84 (t, J = 1.7 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.24 (s, 1H), 7.12 (t, J = 6.8 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 4.44

(dd, J = 10.8, 3.4 Hz, 1H), 4.30 (dd, J = 10.5, 5.8 Hz, 1H), 4.01 (m, 1H), 3.33 (m, 2H). MS (APCI): m/z $(M+H)^+$ 345. Anal. Calcd for $C_{21}H_{20}N_4O{\cdot}2.7TFA$: C, 48.61; H, 3.51; N, 8.59. Found: C, 48.69; H, 3.50; N, 8.46.

5.2.39. (*S*)-(4-(5-(2-Amino-3-(1*H*-indol-3-yl)-propoxy)-pyridin-3-yl)-phenyl)-methanol (46). Stille reaction with 4-bromobenzyl alcohol and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **46**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.03 (s, 1H), 8.51 (d, J = 1.56 Hz, 1H), 8.30 (d, J = 2.81 Hz, 1H), 7.64 (dd, J = 10.61, 8.42 Hz, 3H), 7.59 (m, 1H), 7.43 (d, J = 8.42 Hz, 2H), 7.37 (d, J = 8.11 Hz, 1H), 7.28 (d, J = 2.18 Hz, 1H), 7.09 (t, J = 7.02 Hz, 1H), 6.99 (t, J = 7.02 Hz, 1H), 5.29 (s, 1H), 4.55 (s, 2H), 4.29 (m, 1H), 4.16 (dd, J = 10.29, 5.93 Hz, 1H), 3.72 (m, 1H), 3.15 (m, 4H). MS (ESI): m/z $(M+H)^+$ 374.

5.2.40. 4-(5-{[(*S*)-2-amino-3-(1*H*-indol-3-yl)propyl]oxy}-pyridin-3-yl)benzonitrile (47). Stille reaction with 4-bromobenzonitrile and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **47**. ^{1}H NMR (300 MHz,DMSO-d_6) δ ppm 11.02 (s, 1H), 8.63 (d, J = 1.9 Hz, 1H), 8.42 (d, J = 2.8 Hz, 1H), 8.21 (br s, 2H), 7.99-7.92 (m, 4H), 7.73 (t, J = 1.9 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.10 (m, 1H), 7.01 (m, 1H), 4.36 (dd, J = 10.6, 3.1 Hz, 1H), 4.19 (dd, J = 10.9, 5.9 Hz, 1H), 3.89–3.82 (m, 1H), 3.16 (d, J = 7.2 Hz, 2H). MS (DCI/NH_3): m/z $(M+H)^+$ 369.

5.2.41. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (4). Stille reaction with 5-bromo-3-methylindazole (**26** R = CH_3) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **4**. The product obtained was converted to the HCl salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.8 (br s, 1H), 11.06 (s, 1H), 8.76 (s, 1H), 8.44 (m, 3H), 8.17 (s, 1H), 8.01 (s, 1H), 7.73 (dd, J = 9, 2 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.32 (d, J = 2 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 4.26–4.46 (m, 2H), 3.78–3.88 (m, 1H), 3.19–3.22 (m, 2H), 2.56 (s, 3H). MS (ESI): m/z $(M+H)^+$ 398. Anal. Calcd for $C_{24}H_{23}N_5O{\cdot}2.25HCl$: C, 59.62; H, 5.31; N, 14.60, Cl, 16.63. Found: C, 59.62; H, 5.31; N, 14.28, Cl, 16.22.

5.2.42. (*R*)-1-(1*H*-Indol-3-ylmethyl)-2-[5-(3-methyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (49). Stille reaction with 5-bromo-3-methylindazole (**26** R = CH_3) and stannyl material (the *R*-enantiomer of **8**) (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **49** as the TFA salt that was subsequently converted to the HCl salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.8 (br s, 1H), 11.06 (s, 1H), 8.76 (s, 1H), 8.44 (m, 3H), 8.17 (s, 1H), 8.01 (s, 1H), 7.73 (dd, J = 9, 2 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.32 (d, J = 2 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 4.26–4.46 (m, 2H), 3.78–3.88 (m, 1H), 3.19–3.22 (m, 2H), 2.56 (s, 3H). MS (ESI): m/z $(M+H)^+$ 398. Anal. Calcd for $C_{24}H_{23}N_5O{\cdot}2.0HCl{\cdot}0.75H_2O$: C, 59.57; H, 5.52; N, 14.47, Cl, 14.65. Found: C, 59.73; H, 5.36; N, 14.32, Cl, 14.74.

5.2.43. (*S*)-2-[5-(1,3-Dimethyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethylamine (50). Stille reaction with 5-bromo-1,3-dimethylindazole (**27** R = CH_3) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **50**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.04 (s, 1H) 8.66 (d, J = 1.70 Hz, 1H) 8.34 (d, J = 2.71 Hz, 1H) 8.18 (m, 3H) 8.08 (s, 1H) 7.73 (m, 2H) 7.63 (d, J = 7.80 Hz, 1H) 7.39 (d, J = 7.80 Hz, 1H) 7.30 (d, J = 2.37 Hz, 1H) 7.10 (t, J = 7.12 Hz, 1H) 7.01 (t, J = 7.46 Hz, 1H) 4.37 (m, 1H) 4.20 (dd, J = 10.51, 6.10 Hz, 1H) 4.00 (s, 3H) 3.86 (s, 1H) 3.18 (m, 2H) 2.54 (s, 3H). MS (ESI): m/z $(M+H)^+$ 412. Anal. Calcd for $C_{25}H_{25}N_5O{\cdot}2.8TFA$: C, 50.29; H, 3.83; N, 9.58. Found: C, 50.36; H, 3.84, N, 9.60.

5.2.44. (*S*)-2-[5-(3-Ethyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethylamine (51). Stille reaction with 5-bromo-3-ethylindazole (**26** R = Et) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **51**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.80 (m, 1H) 11.04 (d, J = 2.03 Hz, 1H) 8.63 (d, J = 1.70 Hz, 1H) 8.33 (d, J = 2.71 Hz, 1H) 8.16 (m, 2H) 8.08 (s, 1H) 7.72 (m, 1H) 7.63 (m, 3H) 7.38 (d, J = 7.80 Hz, 1H) 7.30 (d, J = 2.37 Hz, 1H) 7.11 (t, J = 7.46 Hz, 1H) 7.01 (t, J = 7.46 Hz, 1H) 4.37 (m, 1H) 4.19 (dd, J = 10.85, 6.10 Hz, 1H) 3.86 (m, 1H) 3.17 (m, 2H) 2.99 (q, J = 7.57 Hz, 2H) 1.35 (t, J = 7.63 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 412. Anal. Calcd for $C_{25}H_{25}N_5O{\cdot}2.7TFA$: C, 50.76; H, 3.88; N, 9.74. Found: C, 51.09; H, 3.88; N, 9.66.

5.2.45. (*S*)-2-[5-(3-Cyclopropyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethylamine (52). Stille reaction with 5-bromo-3-cyclopropylindazole (**26** R = cyclopropyl) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **52**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.73 (m, 1H) 11.03 (d, J = 2.03 Hz, 1H) 8.63 (d, J = 1.36 Hz, 1H) 8.33 (d, J = 2.37 Hz, 1H) 8.19 (m, 2H) 8.12 (s, 1H) 7.73 (m, 1H) 7.65 (m, 2H) 7.56 (d, J = 8.48 Hz, 1H) 7.38 (d, J = 8.14 Hz, 1H) 7.30 (d, J = 2.37 Hz, 1H) 7.10 (t, J = 6.95 Hz, 1H) 7.01 (t, J = 7.46 Hz, 1H) 4.37 (dd, J = 10.68, 3.22 Hz, 1H) 4.19 (dd, J = 10.68, 5.93 Hz, 1H) 3.86 (m, 1H) 3.15 (m, 2H) 2.36 (m, 1H) 1.02 (m, 4H). MS (ESI): m/z $(M+H)^+$ 424. Anal. Calcd for $C_{26}H_{25}N_5O{\cdot}2.6TFA$: C, 52.05; H, 3.86; N, 9.73. Found: C, 52.03; H, 3.89; N, 9.69.

5.2.46. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-[5-(3-phenyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (53). Stille reaction with 5-bromo-3-phenylindazole (**26** R = phenyl) and stannyl material **8** (as described for **33**) followed

by deprotection of the Boc group with TFA (as described for **59**) yielded **53**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.45 (br s, 1H) 11.03 (s, 1H) 8.68 (d, J = 1.70 Hz, 1H) 8.36 (d, J = 2.71 Hz, 1H) 8.30 (s, 1H) 8.16 (m, 2H) 8.08 (s, 1H) 8.05 (s, 1H) 7.76 (m, 1H) 7.72 (s, 2H) 7.62 (d, J = 7.46 Hz, 1H) 7.43–7.55 (m, 3H) 7.39 (m, 1H) 7.30 (d, J = 2.37 Hz, 1H) 7.09 (t, J = 7.46 Hz, 1H) 7.00 (t, J = 7.46 Hz, 1H) 4.38 (m, 1H) 4.19 (dd, J = 10.51, 5.76 Hz, 1H) 3.87 (m, 1H) 3.17 (m, 2H). MS (ESI): m/z (M+H)$^+$ 460. Anal. Calcd for $C_{29}H_{25}N_5O{\cdot}3$TFA: C, 52.44; H, 3.52; N, 8.74. Found: C, 52.91; H, 3.68; N, 8.80.

5.2.47. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-[5-(3-thiophen-2-yl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (55). Stille reaction with 5-bromo-3-(thiophen-2-yl)indazole (**26** R = thiophen-2-yl) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **55**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.39 (s, 1H) 11.06 (s, 1H) 8.67 (s, 1H) 8.34 (m, 4H) 7.91 (d, J = 2.76 Hz, 1H) 7.73 (m, 3H) 7.64 (d, J = 7.98 Hz, 1H) 7.59 (d, J = 6.14 Hz, 1H) 7.39 (d, J = 7.98 Hz, 1H) 7.31 (d, J = 2.15 Hz, 1H) 7.23 (dd, J = 5.22, 3.68 Hz, 1H) 7.10 (t, J = 7.06 Hz, 1H) 7.00 (t, J = 7.52 Hz, 1H) 4.38 (m, 1H) 4.23 (dd, J = 10.43, 5.83 Hz, 1H) 3.86 (br s, 1H) 3.21 (d, J = 7.06 Hz, 2H). MS (ESI): m/z (M+H)$^+$ 466.

5.2.48. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-[5-(3-thiazol-2-yl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (56). Stille reaction with 5-bromo-3-(thiazol-2-yl)indazole (**26** R = thiazol-2-yl) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **56**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 13.74 (s, 1H) 11.04 (s, 1H) 8.60 (s, 2H) 8.38 (d, J = 2.18 Hz, 1H) 8.28 (s, 2H) 8.04 (d, J = 3.43 Hz, 1H) 7.79 (d, J = 3.12 Hz, 1H) 7.78 (s, 2H) 7.73 (s, 1H) 7.64 (d, J = 7.80 Hz, 1H) 7.38 (d, J = 8.11 Hz, 1H) 7.31 (d, J = 1.56 Hz, 1H) 7.09 (t, J = 7.49 Hz, 1H) 7.01 (t, J = 7.49 Hz, 1H) 4.38 (dd, J = 10.45, 2.65 Hz, 1H) 4.22 (dd, J = 10.29, 5.93 Hz, 1H) 3.86 (m, 1H) 3.19 (d, J = 7.18 Hz, 2H). MS (ESI): m/z (M+H)$^+$ 467.

5.2.49. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-{5-[3-(1*H*-pyrrol-2-yl)-1*H*-indazol-5-yl]-pyridin-3-yloxy}-ethylamine (57). Stille reaction with 5-bromo-3-(pyrol-2-yl)indazole (**31**) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **57**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.10 (br s, 1H) 11.38 (s, 1H) 11.03 (s, 1H) 8.68 (s, 1H) 8.35 (d, J = 2.37 Hz, 1H) 8.26 (s, 1H) 8.15 (br s, 2H) 7.67 (m, 4H) 7.38 (d, J = 8.14 Hz, 1H) 7.30 (d, J = 2.03 Hz, 1H) 7.10 (t, J = 7.46 Hz, 1H) 7.01 (t, J = 7.46 Hz, 1H) 6.86 (m, 2H) 6.21 (m, 1H) 4.38 (m, 1H) 4.20 (dd, J = 10.51, 5.76 Hz, 1H) 3.87 (m, 1H) 3.18 (m, 2H). MS (ESI) m/z (M+H)$^+$ 449. Anal. Calcd for $C_{27}H_{24}N_6O{\cdot}2.5$TFA: C, 52.39; H, 3.64; N, 11.46. Found: C, 52.26; H, 3.67; N, 11.39.

5.2.50. (*S*)-(5-{5-[2-Amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-1*H*-indazol-3-yl)-dimethyl-amine (60). Stille reaction with 5-bromo-3-(*N*,*N*-dimethylamino)indazole (**24**) (prepared as described in Wrzeciono et al.[27]) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **60**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.04 (s, 1H) 11.03 (s, 1H) 8.62 (d, J = 1.36 Hz, 1H) 8.33 (d, J = 2.37 Hz, 1H) 8.17 (m, 2H) 8.07 (s, 1H) 7.73 (s, 1H) 7.61 (m, 2H) 7.45 (d, J = 8.82 Hz, 1H) 7.38 (d, J = 8.14 Hz, 1H) 7.30 (d, J = 2.37 Hz, 1H) 7.10 (t, J = 7.12 Hz, 1H) 7.01 (t, J = 6.95 Hz, 1H) 4.36 (m, 1H) 4.19 (m, 1H) 3.86 (s, 1H) 3.16 (m, 2H) 3.04 (s, 6H). MS (ESI): m/z (M+H)$^+$ 427. Anal. Calcd for $C_{25}H_{26}N_6O{\cdot}3.5$TFA: C, 46.55; H, 3.60; N, 10.18. Found: C, 46.71; H, 3.65, N, 10.02.

5.2.51. (*S*)-1-(1*H*-Indol-3-ylmethyl)-2-[5-(3-morpholin-4-yl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-ethylamine (61). Stille reaction with 5-bromo-3-(morpholin-4-yl)indazole (prepared as described in Wrzeciono et al.[27]) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **61**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.21 (s, 1H) 11.03 (s, 1H) 8.65 (d, J = 1.70 Hz, 1H) 8.33 (d, J = 2.71 Hz, 1H) 8.17 (m, 2H) 8.09 (s, 1H) 7.72 (m, 1H) 7.62 (m, 2H) 7.48 (d, J = 8.82 Hz, 1H) 7.38 (d, J = 7.80 Hz, 1H) 7.30 (d, J = 2.37 Hz, 1H) 7.10 (t, J = 7.46 Hz, 1H) 7.01 (t, J = 7.46 Hz, 1H) 4.35 (m, 1H) 4.19 (dd, J = 10.68, 5.93 Hz, 1H) 3.88 (m, 1H) 3.81 (m, 4H) 3.35 (m, 4H) 3.16 (d, J = 7.12 Hz, 2H). MS (ESI): m/z (M+H)$^+$ 469. Anal. Calcd for $C_{27}H_{28}N_6O_2{\cdot}3.4$TFA: C, 47.41; H, 3.70; N, 9.82. Found: C, 47.10; H, 3.86; N, 9.95.

5.2.52. (*S*)-2-[5-(1*H*-Indazol-6-yl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethylamine (63). Stille reaction with 6-bromoindazole and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **63**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 13.28 (br s, 1H) 10.97 (s, 1H) 8.53 (s, 1H) 8.31 (s, 1H) 8.11 (s, 1H) 7.81–7.86 (m, 3H) 7.65 (s, 2H) 7.58 (d, J = 7.5 Hz, 1H) 7.41 (d, J = 7.5 Hz, 1H) 7.34 (d, J = 7.5 Hz, 1H) 7.24 (s, 1H), 6.95–7.05 (m, 2H) 4.13 (m, 2H) 3.60 (m, 1H) 2.97 (m, 2H). MS (ESI): m/z (M+H)$^+$ 384.

5.2.53. (*S*)-2-{5-[3-(1*H*-Imidazol-2-yl)-1*H*-indazol-5-yl]-pyridin-3-yloxy}-1-(1*H*-indol-3-ylmethyl)-ethylamine (58). Stille reaction with 5-bromo-3-(imidazol-2-yl)indazole (**26** R = imidazol-2-yl) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **58**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 14.36 (s, 1H) 11.04 (s, 1H) 8.72 (s, 1H) 8.61 (s, 1H) 8.39 (d, J = 2.50 Hz, 1H) 8.26 (br s, 3H) 7.86 (s, 2H) 7.83 (s, 1H) 7.76 (s, 1H) 7.63 (d, J = 8.11 Hz, 1H) 7.38 (d, J = 8.11 Hz, 1H) 7.30 (d, J = 2.18 Hz, 1H) 7.09 (t, J = 7.49 Hz, 1H) 7.00 (t, J = 7.49 Hz, 1H) 4.37 (dd, J = 10.45, 2.96 Hz, 1H) 4.22 (dd, J = 10.45, 5.77 Hz, 1H) 3.86 (s, 1H) 3.19 (d, J = 7.17 Hz, 2H). MS (ESI): m/z (M+H)$^+$ 450.

5.2.54. (*S*)-2-[5-(1*H*-Benzotriazol-5-yl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethylamine (65). Stille reaction with *N*-Boc-5-bromobenztriazole (**36**) and stannyl material **8** (as described for **33**) followed by deprotection of

the Boc group with TFA (as described for **59**) yielded **65**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.03 (s, 1H) 8.66 (d, J = 1.36 Hz, 1H) 8.38 (d, J = 2.71 Hz, 1H) 8.27 (m, 1H) 8.18 (m, 3H) 8.01 (m, 1H) 7.78 (m, 1H) 7.63 (d, J = 7.80 Hz, 1H) 7.38 (d, J = 8.14 Hz, 1H) 7.30 (d, J = 2.37 Hz, 1H) 7.10 (t, J = 7.12 Hz, 1H) 7.01 (t, J = 6.95 Hz, 1H) 4.38 (dd, J = 10.68, 2.88 Hz, 1H) 4.21 (dd, J = 10.68, 6.27 Hz, 1H) 3.86 (m, 1H) 3.17 (d, J = 7.12 Hz, 2H). MS (ESI): m/z (M+H)$^+$ 385.

5.2.55. (*S*)-2-[5-(3-Benzyl-1*H*-indazol-5-yl)-pyridin-3-yloxy]-1-(1*H*-indol-3-ylmethyl)-ethylamine (54). Stille reaction with 5-bromo-3-benzylindazole (**26** R = benzyl) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded **54**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.03 (s, 1H) 8.55 (d, J = 1.70 Hz, 1H) 8.32 (d, J = 2.71 Hz, 1H) 8.15 (m, 3H) 7.98 (s, 1H) 7.61 (m, 4H) 7.29 (m, 7H) 7.08 (m, 1H) 7.02 (t, J = 7.12 Hz, 1H) 4.42 (dd, J = 10.68, 5.93 Hz, 1H) 4.35 (s, 2H) 4.17 (dd, J = 10.68, 5.93 Hz, 1H) 3.86 (m, 1H) 3.17 (m, 2H). MS (ESI): m/z (M+H)$^+$ 474. Anal. Calcd for $C_{30}H_{27}N_5O$·3.9TFA: C, 49.44; H, 3.39; N, 7.63. Found: C, 49.07; H, 3.75; N, 7.42.

5.2.56. 5-{5-[(*S*)-2-Amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-1*H*-indazole-3-carboxylic acid (62)

5.2.56.1. Step 1. 1*H*-Indazole-3-carboxylic acid methyl ester. A solution of 3-carboxyindazole (2.0 g; 12.3 mmol) and concd HCl (2 mL) in MeOH (50 mL) was heated at reflux overnight. The reaction mixture was concentrated, diluted with 2 N NaOH (aq), and extracted with EtOAc. The extracts were rinsed with brine, dried over $MgSO_4$, and concentrated to provide methyl indazole-3-carboxylate. ^{1}H NMR (300 MHz, DMSO-d_6) δ: ppm 13.9 (br s, 1H), 8.09 (d, J = 8 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 3.93 (s, 3H). MS (ESI): m/z (M+H)$^+$ 177.

5.2.56.2. Step 2. 5-Iodo-1*H*-indazole-3-carboxylic acid methyl ester. A solution of the ester from step 1 (300 mg; 1.7 mmol), bis(trifluoroacetoxy)iodobenzene (800 mg; 1.9 mmol), and iodine (253 mg; 1.0 mmol) in CH_2Cl_2 (10 mL) was stirred overnight at rt. The reaction mixture was treated with sodium bisulfite (aq). The resulting precipitate was collected, rinsed with water and hexane, and dried under vacuum to provide methyl 5-iodoindazole-3-carboxylate (180 mg; 36%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: ppm 14.1 (br s, 1H), 8.43 (s, 1H), 7.71 (d, J = 9 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 3.94 (s, 3H). MS (ESI): m/z (M+H)$^+$ 303.

5.2.56.3. Step 3. 5-{5-[(*S*)-2-Amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-1*H*-indazole-3-carboxylic acid (62). Stille reaction with methyl 5-iodo-indazole-3-carboxylate (from step 2) and stannyl material **8** (as described for **33**) followed by deprotection of the Boc group with TFA (as described for **59**) yielded the methyl ester of **62**. A solution of ester (150 mg; 0.34 mmol) and 1 N NaOH (5 mL) in MeOH (1 mL) was heated at reflux for 6 h. The reaction mixture was concentrated and purified by reverse-phase HPLC on a C18 column with 0–100% CH_3CN/H_2O/0.1% TFA to provide the desired product **62** as the trifluoroacetate salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 13.64 (m, 1H) 11.03 (s, 1H) 8.59 (s, 1H) 8.37 (s, 1H) 8.32 (s, 1H) 8.26 (s, 3H) 7.77 (m, 2H) 7.71 (s, 1H) 7.63 (d, J = 7.80 Hz, 1H) 7.38 (d, J = 8.11 Hz, 1H) 7.30 (d, J = 1.87 Hz, 1H) 7.10 (t, J = 7.33 Hz, 1H) 7.01 (t, J = 7.33 Hz, 1H) 4.37 (dd, J = 10.29, 2.50 Hz, 1H) 4.21 (dd, J = 10.29, 5.93 Hz, 1H) 3.86 (m, 1H) 3.18 (d, J = 7.49 Hz, 2H). MS (ESI): m/z (M+H)$^+$ 428.

5.2.57. (*S*)-6-{5-[2-Amino-3-(1*H*-indol-3-yl)-propoxy]-pyridin-3-yl}-1*H*-indazol-3-ylamine (64). The product was prepared as described for compound **59** using 4-bromo-2-fluorobenzonitrile in place of the 5-bromo-2-fluorobenzonitrile. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (br s, 1H) 11.03 (s, 1H) 8.60 (d, J = 1.36 Hz, 1H) 8.37 (d, J = 2.37 Hz, 1H) 8.17 (s, 4H) 7.88 (d, J = 8.14 Hz, 1H) 7.71 (s, 1H) 7.63 (m, 2H) 7.34 (m, 3H) 7.07 (m, 2H) 4.35 (m, 1H) 4.19 (s, 1H) 3.91 (d, J = 30.85 Hz, 1H) 3.16 (d, J = 5.42 Hz, 2H). MS (ESI): m/z (M+H)$^+$ 399. Anal. Calcd for $C_{23}H_{22}N_6O$·3.5TFA: C, 45.18;H, 3.22; N, 10.54, F, 25.01. Found: C, 44.83; H, 3.19; N, 10.40, F, 25.01.

5.3. Biology/testing

Details of the biological assays and testing protocols have been reported previously.[22,36]

References and notes

1. Li, Q.; Zhu, G.-D. *Curr. Top. Med. Chem.* **2002**, *2*, 939–971.
2. Graff, J. R. *Expert Opin. Ther. Targets* **2002**, *6*, 103–113.
3. Nicholson, K. M.; Anderson, N. G. *Cell. Signal.* **2002**, *14*, 381–395.
4. Vivanco, I.; Sawyers, C. L. *Nat. Rev. Cancer* **2002**, *2*, 489–501.
5. Luo, J.; Manning, B. D.; Cantley, L. C. *Cancer Cell* **2003**, *4*, 257–262.
6. Jones, P. F.; Jakubowicz, T.; Pitossi, F. J.; Maurer, F.; Hemmings, B. A. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 4171–4175.
7. Bellacosa, A.; Testa, J. R.; Staal, S. P.; Tsichlis, P. N. *Science* **1991**, *254*, 274–277.
8. Coffer, P. J.; Jin, J.; Woodgett, J. R. *Biochem. J.* **1998**, *335*, 1–13.
9. Masure, S.; Haefner, B.; Wesselink, J.-J.; Hoefnagel, E.; Mortier, E.; Verhasselt, P.; Tuytelaars, A.; Gordon, R.; Richardson, A. *Eur. J. Biochem.* **1999**, *265*, 353–360.
10. Nakatani, K.; Sakaue, H.; Thompson, D. A.; Weigel, R. J.; Roth, R. A. *Biochem. Biophys. Res. Commun.* **1999**, *257*, 906–910.
11. Hanks, S. K.; Hunter, T. *FASEB* **1995**, *9*, 576–596.
12. Staal, S. P. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 5034–5037.
13. Zinda, M. J.; Johnson, M. A.; Paul, J. D.; Horn, C.; Konicek, B. W.; Lu, Z. H.; Sandusky, G.; Thomas, J. E.; Neubauer, B. L.; Lai, M. T.; Graff, J. R. *Clin. Cancer Res.* **2001**, *7*, 2475–2479.
14. Yuan, Z. Q.; Sun, M.; Feldman, R. I.; Wang, G.; Ma, X.; Jiang, C.; Coppola, D.; Nicosia, S. V.; Cheng, J. Q. *Oncogene* **2000**, *19*, 2324–2330.
15. Reuveni, H.; Livnah, N.; Geiger, T.; Klein, S.; Ohne, O.; Cohen, I.; Benhar, M.; Gellerman, G.; Levitzki, A. *Biochemistry* **2002**, *41*, 10304–10314.

16. Li, Q.; Li, T.; Zhu, G.-D.; Gong, J.; Claiborne, A.; Dalton, C.; Luo, Y.; Johnson, E. F.; Shi, Y.; Liu, X.; Klinghofer, V.; Bauch, J. L.; Marsh, K. C.; Bouska, J. J.; Arries, S.; De Jong, R.; Oltersdorf, T.; Stoll, V. S.; Jakob, C. G.; Rosenberg, S. H.; Giranda, V. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1679–1685.
17. Li, Q.; Woods, K. W.; Thomas, S.; Zhu, G.-D.; Packard, G.; Fisher, J.; Li, T.; Gong, J.; Dinges, J.; Song, X.; Abrams, J.; Luo, Y.; Johnson, E. F.; Shi, Y.; Liu, X.; Klinghofer, V.; De Jong, R.; Oltersdorf, T.; Stoll, V. S.; Jakob, C. G.; Rosenberg, S. H.; Giranda, V. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2000–2007.
18. Zhu, G.-D.; Gong, J.; Claiborne, A.; Woods, K. W.; Gandhi, V. B.; Thomas, S.; Luo, Y.; Liu, X.; Shi, Y.; Guan, R.; Magnone, S. R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Shoemaker, A.; Oleksijew, A.; Stoll, V. S.; DeJong, R.; Oltersdorf, T.; Li, Q.; Rosenberg, S. H.; Giranda, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3150–3155.
19. Breitenlechner, C. B.; Wegge, T.; Berillon, L.; Graul, K.; Marzenell, K.; Friebe, W.-G.; Thomas, U.; Schumacher, R.; Huber, R.; Engh, R. A.; Masjost, B. *J. Med. Chem.* **2004**, *47*, 1375–1390.
20. Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Hartman, G. D.; Huff, J. R.; Huber, H. E.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 761–764.
21. Zhao, Z.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Hartman, G. D.; Huff, J. R.; Huber, H. E.; Duggan, M. E.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 905–909.
22. Luo, Y.; Shoemaker, A. R.; Liu, X.; Woods, K. W.; Thomas, S. A.; de Jong, R.; Han, E. K.; Li, T.; Stoll, V. S.; Powlas, J. A.; Oleksijew, A.; Mitten, M. J.; Shi, Y.; Guan, R.; McGonigal, T. P.; Klinghofer, V.; Johnson, E. F.; Leverson, J. D.; Bouska, J. J.; Mamo, M.; Smith, R. A.; Gramling-Evans, E. E.; Zinker, B. A.; Mika, A. K.; Nguyen, P. T.; Oltersdorf, T.; Rosenberg, S. H.; Li, Q.; Giranda, V. L. *Mol. Cancer Ther.* **2005**, *4*, 977–986.
23. Hendrickson, J. B.; Rodriguez, C. *J. Org. Chem.* **1983**, *48*, 3344–3346.
24. Miller, R. B.; Frincke, J. M. *J. Org. Chem.* **1980**, *45*, 5312–5315.
25. Fernandez, M.; Lopez, F.; Tapia, R.; Valderrama, J. A. *Synth. Commun.* **1989**, *19*, 3087–3095.
26. Takaki, K.; Okamura, A.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1978**, *43*, 402–405.
27. Wrzeciono, U.; Majewska, K.; Dudzinska-Usarewicz, J.; Bernas, M. *Pharmazie* **1986**, *41*, 472–474.
28. Katritzky, A. R.; Fali, C. N.; Li, J.; Ager, D. J.; Prakash, I. *Synth. Commun.* **1997**, *27*, 1623–1630.
29. The isoquinoline compound **3** was found to be metabolized by liver S9 fractions from mouse, monkey and human, but not by microsomal fractions. Menadione could inhibit the oxidative metabolism of **3**, implying aldehyde oxidase was the cytosolic enzyme responsible.
30. The *R*-isomer of **3** (Akt1 K_i = 30 nM) showed a decrease in activity compared to **3**, similar to that observed for **49** as compared to **4**.
31. IC_{50} values were determined at varying ATP concentrations from 5 μM to 1 mM. A shift in IC_{50} consistent with a competitive inhibition mode and the experimentally determined K_m was observed.
32. Reversible inhibition was established by preincubating enzyme with inhibitor (>5-fold IC_{50}) prior to dilution into reaction buffer (<1/5 IC_{50}) and observing recovery of enzyme activity (>80%) versus a control in which the high inhibitor concentration was maintained.
33. Thomas, S. A.; Li, T.; Woods, K. W.; Song, X.; Packard, G.; Fischer, J. P.; Diebold, R. B.; Liu, X.; Shi, Y.; Klinghofer, V.; Johnson, E. F.; Bouska, J. J.; Olson, A.; Guan, R.; Magnone, S. R.; Marsh, K.; Luo, Y.; Rosenberg, S. H.; Giranda, V. L.; Li, Q. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3740–3744.
34. Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458–7464.
35. Eloy, F.; Deryckere, A. *J. Heterocycl. Chem.* **1970**, *11*, 1191–1193.
36. Luo, Y.; Smith, R. A.; Guan, R.; Liu, X.; Klinghofer, V.; Shen, J.; Hutchins, C.; Richardson, P.; Holzman, T.; Rosenberg, S. H.; Giranda, V. L. *Biochemistry* **2004**, *43*, 1254–1263.