Design, Synthesis, and Evaluation of Orally Active Benzimidazoles and Benzoxazoles as Vascular Endothelial Growth Factor-2 Receptor Tyrosine Kinase Inhibitors

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Inhibition of the VEGF signaling pathway has become a valuable approach in the treatment of cancers. Guided by X-ray crystallography and molecular modeling, a series of 2-aminobenzimidazoles and 2-aminobenzoxazoles were identified as potent inhibitors of VEGFR-2 (KDR) in both enzymatic and HUVEC cellular proliferation assays. In this report we describe the synthesis and structure−activity relationship of a series of 2-aminobenzimidazoles and benzoxazoles, culminating in the identification of benzoxazole **22** as a potent and selective VEGFR-2 inhibitor displaying a good pharmacokinetic profile. Compound **22** demonstrated efficacy in both the murine matrigel model for vascular permeability (79% inhibition observed at 100 mg/kg) and the rat corneal angiogenesis model (ED_{50} = 16.3 mg/kg).

Introduction

Angiogenesis, the formation of new blood vessels from existing vasculature, is a normal physiological event that occurs during embryonic growth, wound healing and the menstrual cycle. Abnormal regulation of angiogenesis has been implicated in the pathogenesis of several disorders including diabetic retinopathy,[1] rheumatoid arthritis,[2] age-related macular degeneration,[3] and cancer.[4,5] As angiogenesis is required for tumor growth and metastasis, the concept of limiting the growth of a solid tumor by restricting the blood supply has been evaluated in human cancer and has proven successful.[6]

Vascular endothelial growth factor (VEGF[a]) is a known promoter of angiogenesis, and the increased expression of VEGF has been implicated in tumor growth and metastasis.[4,5] VEGF signaling through its receptor tyrosine kinase VEGFR-2 (or KDR, kinase insert domain receptor) promotes several events required for the formation of new blood vessels, such as endothelial cell survival, proliferation, migration, and vascular permeability.

Inhibition of the VEGF signaling pathway has become a valuable approach in the treatment of cancers. For example, the use of the neutralizing monoclonal antibody to VEGF, bevacizumab (Genentech), has demonstrated a prolonged survival in colorectal cancer patients.[7] The compounds in Figure 1 represent the structural diversity of small molecule, ATP-competitive, KDR inhibitors under clinical investigation. In particular, sunitinib (SU-11248)[8] and sorafenib (Bay 43-9006, **2**;[9] a dual raf-KDR inhibitor) have recently been approved for the treatment of cancers.[10]

Our independent medicinal chemistry efforts in finding a selective VEGFR inhibitor led to motesanib diphosphate (AMG 706, **1**), currently in phase II clinical trials for the treatment of various cancers.[10e] We were also interested in identifying a second generation of KDR inhibitor belonging to a completely different structural class from the nicotinamide. Urea **2** was originally described solely as a raf inhibitor, however, we serendipitously discovered that it inhibited KDR as well, with a K_i of 2 nM.[11] As a means to understand the binding mode and generate a new chemotype for KDR inhibition, we docked **2** into the cocrystal structure of **1** and KDR[12] to identify the key interactions between this molecule and the protein. One of the key features of the cocrystal structure of **1** bound KDR is the reorganization of Phe 1047 (of the Asp 1046, Phe 1047, Gly 1048 triad, the "DFG" motif) to induce the inactive "DFG-out" conformation, similar to that observed upon binding of imatinib to its target kinase Abl.[13] This conformational change inhibits the ability of the kinase to bind ATP productively and accommodates the binding of an appropriately substituted inhibitor into an extended lipophilic pocket. On the basis of the presumed *cis*-conformation of the urea moiety and the size of the terminal aryl group, we reasoned that **2** would also bind KDR in a DFG-out fashion.

The docking of **2** in the crystal structure of **1** bound to KDR is depicted in Figure 2. The pyridine ring of **2** is positioned to overlay with the 4-aminomethylpyridine moiety of the nicotinamide to satisfy the critical interaction between the ring nitrogens and the Cys 919-NH in the kinase hinge region. This positioning also allows the amide-NH of **2** to engage in a second hydrogen bond with the backbone amide-CO of Cys 919. The biaryl-ether linkage projects the substituted phenyl ring into the lipophilic pocket neighboring the ATP binding site, adjacent to the gatekeeper residue, Val 916. This portion of **2** overlays well with the nicotinamide moiety. Further, this model places the urea carbonyl and its internal NH within hydrogen bond distances to the backbone of Asp 1046 and side chain of Glu 885, respectively, similar to the amide of **1**. The preferred *cis*-conformation of the urea places terminal aryl of **2** in a second

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[a] Abbreviations: VEGF, vascular endothelial growth factor; KDR, kinase insert domain receptor; HUVEC, human umbilical vein endothelial cells.

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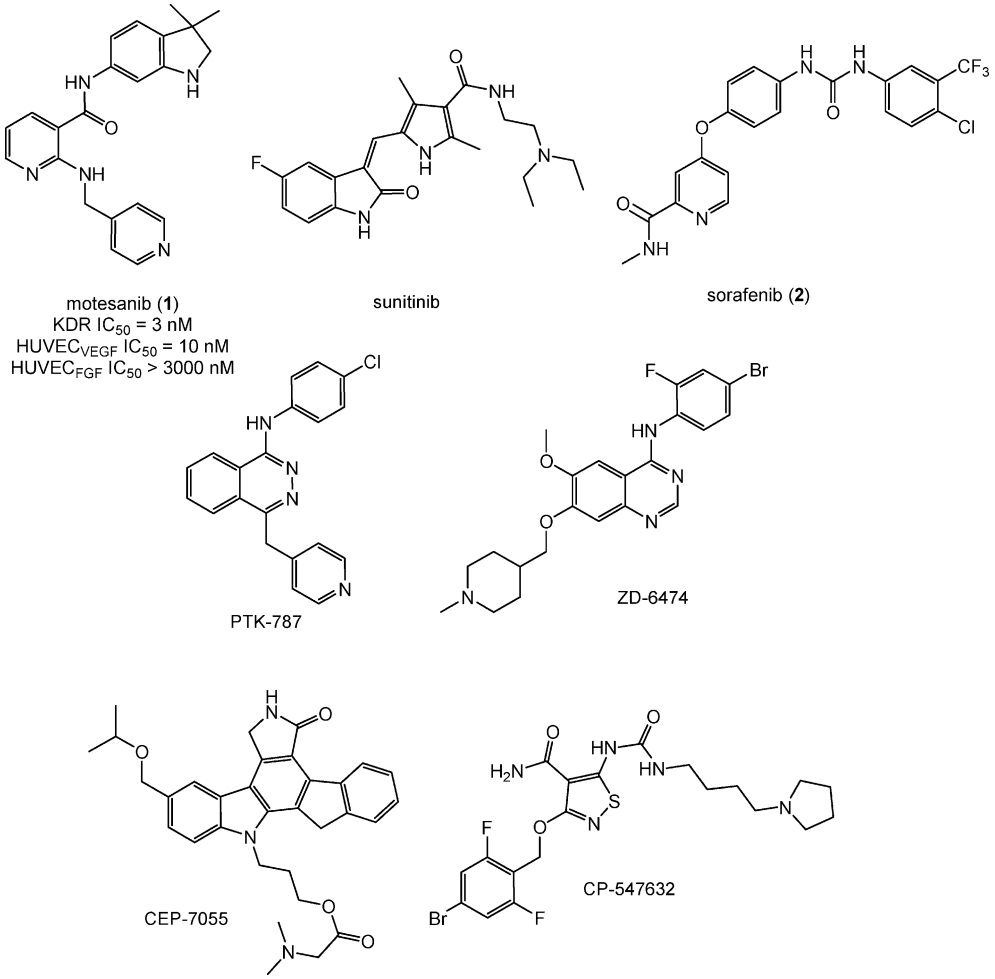


Figure 1. KDR inhibitors under clinical investigation.

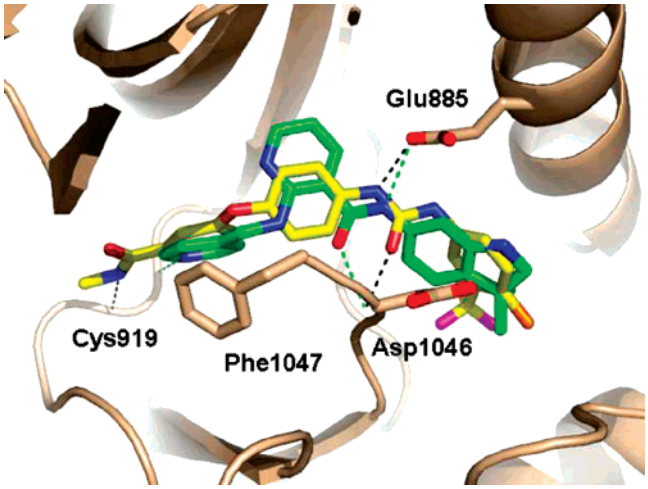


Figure 2. Model of urea **2** (yellow) overlaid with cocrystal structure of nicotinamide **1** (green) and KDR.

lipophilic pocket created by the movement of Phe 1047, similarly placed as the 3,3-dimethylindoline portion of the nicotinamide.

Based on the above model, we proposed the cyclization of **2** to the corresponding 2-aminobenzimidazole to enhance conformational rigidity while maintaining the key hydrogen-bonding interactions. Reduced flexibility is expected to improve potency and oral bioavailablity.[14]

To test this hypothesis, compound **3**[15] was prepared and found to be a potent KDR enzyme inhibitor, with a K_i of 9 nM (Figure 3). The cellular activity was assessed by measuring the inhibition of VEGF-stimulated cellular proliferation of human umbilical vein endothelial cells (HUVEC). Surprisingly, lead compound **3** exhibited weak cellular activity ($IC_{50} \geq 1140$ nM). Guided by structural information, we varied the three main components of compound **3** (aniline ring, heterocyclic core, and hinge binding element) to improve the cellular potency. Herein, we describe the synthesis, structure−activity relationship, and pharmacological characterization of this new class of KDR inhibitors, which culminated in the identification of a potent, selective, and orally active 2-aminobenzoxazole **22** that demonstrated suppression of capillary formation in a rat-corneal model of angiogenesis.

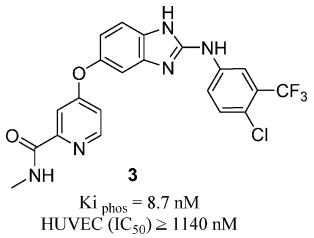
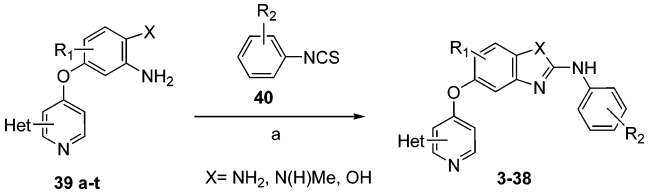


Figure 3. Lead compound **3**.

Chemistry

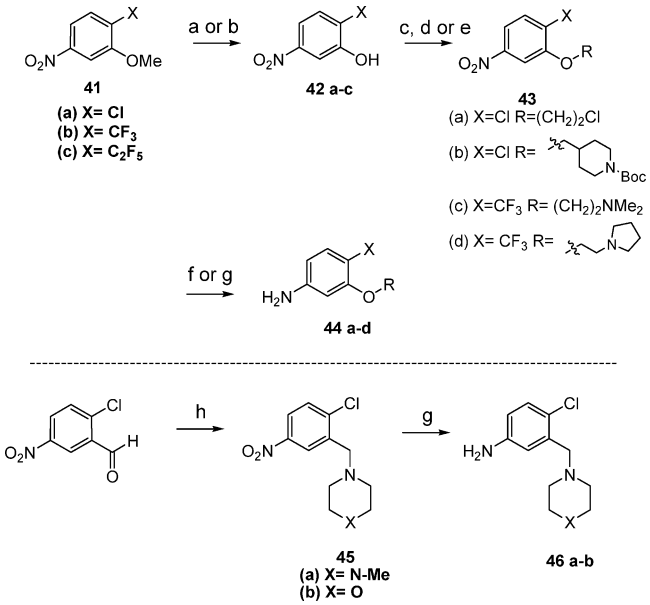
The benzo-1,3-azoles described in this paper were prepared according to the general method represented in Scheme 1. Benzimidazoles **3**−**19** were prepared in a two-step, one-pot protocol by treatment of bis-anilines **39a**−**i** with isothiocyanates

Scheme 1. General Synthesis of 2-Aminobenzimidazoles and 2-Aminobenzoxazoles **3**−**38**[a]



[a] Reagents: (a) EDC, CH_3CN.

Scheme 2. Preparation of Substituted Anilines[a]



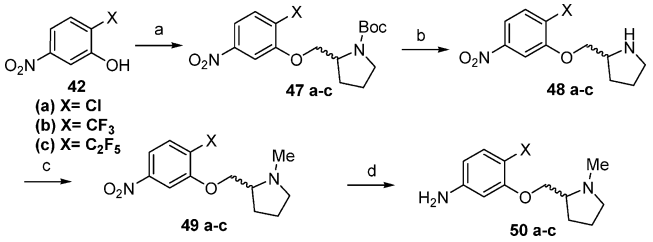
[a] Reagents and conditions: (a) pyridine·HCl, 210 °C; (b) HOAc, HBr, 140−180 °C; (c) R-Cl, K_2CO_3, $Bu_4N^+I^-$, acetone; (d) R-Cl, K_2CO_3, DMF; (e) triphenylphosphine, DIAD, R-OH, THF; (f) Pd/C, H_2, ethyl acetate or MeOH; (g) $SnCl_2$, EtOH; (h) amine, $NaBH(OAc)_3$, CH_2Cl_2.

40 to afford thiourea intermediates that were directly cyclized to the desired products employing 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (EDC). In a sequence similar to that used to prepare the benzimidazoles, treatment of amino-phenols **39j**−**t** with thioisocyanates **40** and direct cyclization of the urea intermediates with EDC afforded the benzoxazoles **20**−**38** in good yields. The thiourea intermediates were not isolated, but rather cyclized directly to the desired core structure in situ. This convergent route allowed for rapid analoging of the 2-aniline moiety, as each variation could be introduced by simply employing the corresponding thioisocyanate.

The anilines required for the synthesis of the arylthioisocyanates **40** were prepared via one of the methods described in Schemes 2 and 3. Compounds containing an ether-linked tether to the amino group were synthesized from the corresponding nitro anisole **41**. Demethylation of **41** using strongly acidic conditions afforded phenols **42** with excellent yields. Compounds **43** were prepared by either a Mitsunobu etherification or alkylation of the phenol with generally high yields. Reduction of the nitro groups using either $SnCl_2$ or catalytic hydrogenation afforded anilines **44a**−**d**.

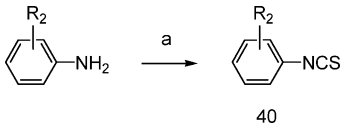
Alternatively, anilines **46** containing an all-carbon tether to the amino group were prepared from 2-chloro-5-nitrobenzaldehyde in two steps. Reductive amination of the benzaldehyde with the appropriate amine afforded intermediate **45**. Reduction of the nitro arenes with $SnCl_2$-generated anilines **46** in good yields.

Scheme 3. Preparation of *N*-Methylpyrrolidine-Substituted Anilines[a]



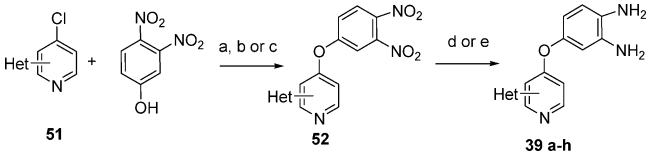
[a] Reagents and conditions: (a) (*S* or *R*)-(−)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol, triphenylphosphine, DIAD, THF; (b) TFA, CH_2Cl_2; (c) $NaBH_3CN$, CH_2O, CH_3CN; (d) Pd/C, H_2, MeOH and dioxane/ethyl acetate or $SnCl_2$, EtOH.

Scheme 4. Synthesis of Thioisocyanates[a]



[a] Reagents: (a) 1,1'-thiocarbonyldiimidazole, CH_3CN.

Scheme 5. Preparation of Phenylene Diamines[a]



[a] Reagents and conditions: (a) neat, 145−170 °C; (b) NEt_3/TFA; (c) HCl, 145−150 °C; (d) Pd/C, H_2, MeOH and/or ethyl acetate; (e) Zn, AcOH, THF.

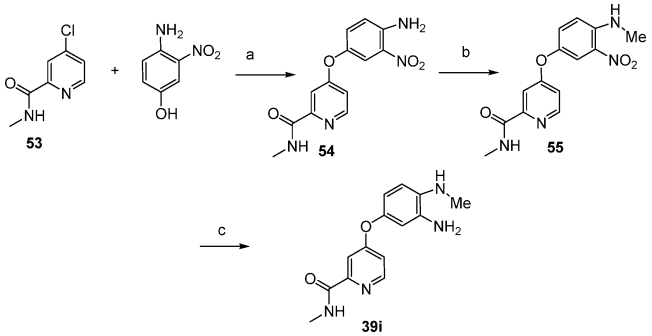
Anilines containing the *N*-methylpyrrolidine amino group were prepared using a variation to the chemistry described above (Scheme 3). Etherification of the phenols **42** with the *N*-Boc-pyrrolidinol using Mitsunobu conditions afforded the nitro intermediates **47** with good yields. Compounds **47** were deprotected using TFA and the free amine subjected to reductive amination conditions to yield compounds **49** in good yields. Subsequent reduction of the nitro groups to the corresponding anilines (using either catalytic hydrogenation for the perfluorinated compounds or $SnCl_2$ for the halogenated compound) afforded compounds **50** in excellent yields.

Some arylthioisocyanates were commercially available, however, the remaining were prepared from condensation of the corresponding aniline with 1,1′-thiocarbonyldiimidazole (Scheme 4). Intermediates **40** were either purified before use or used crude in the cyclization sequence (as a 1:2 mixture with imidazole).

The phenylene diamines **39a**−**h**, required for the synthesis of benzimidazoles **3**−**18** described in Tables 1−3, were prepared according to the generic route shown in Scheme 5. The substitution reactions of 3,4-dinitro phenol with the chlorinated heterocycles **51** afforded the biarylether **52**.[16] Subsequent reduction of the nitro groups using either catalytic hydrogenation or zinc dust afforded the desired phenylene diamines **39a**−**h** in good to excellent yields.

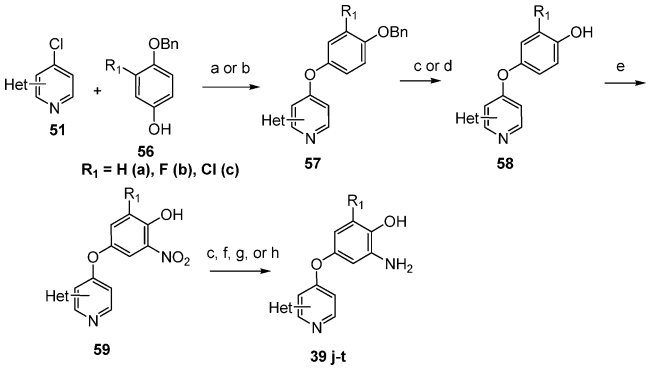
Scheme 6 depicts the synthesis of the *N*-methylphenylene diamine **39i**, a precursor to *N*-methylbenzimidazole **19** (Table 4). The substitution reaction of the 4-chloropyridine carboxamide **53** with 4-amino-3-nitro phenol afforded aniline **54**. Regioselective monomethylation was achieved in a one-pot procedure by employing in situ protection of the amine with the trifluoroacetate group, followed by methylation with dimethyl sulfate to afford compound **55** in excellent yield. Reduction of the nitro

Scheme 6. Synthesis of Intermediate **39i**[a]



[a] Reagents and conditions: (a) KO*t*-Bu, K_2CO_3, DMSO, rt−110 °C; (b) (i) TFAA, (ii) TBACl, Me_2SO_4, (iii) NaOH, H_2O; (c) Pd/C, H_2, MeOH/ethyl acetate.

Scheme 7. Preparation of Aminophenols[a]



[a] Reagents and conditions: (a) NaH, DMF, rt−85 °C; (b) NEt_3/TFA, 150 °C; (c) Pd/C, H_2, MeOH, ethyl acetate; (d) TFA, heat; (e) HNO_3, AcOH; (f) Fe, HCl, EtOH; (g) Zn, AcOH, THF; (h) $SnCl_2$, EtOH.

group of **55**, achieved using $SnCl_2$, then yielded the desired monomethylated bisaniline **39i**.

The amino phenol moieties required for the synthesis of 2-aminobenzoxazoles **20**−**38** described in Tables 4−6 were prepared according to the method described in Scheme 7. Chlorinated nitrogen-containing heterocycles **51** were treated with the preformed sodium phenolate of a 4-benzyloxyphenol to yield biarylethers **57** in generally good yields. Debenzylation of **57** was accomplished using either catalytic hydrogenation or trifluoroacetic acid (TFA; depending on the substrate) to give corresponding phenols **58**. The benzyl groups of compounds **57c** and **57d** (R_1 = Cl; heterocycle = quinoline and pyridine carboxamide, respectively) were removed under the TFA conditions. Regioselective nitration of phenols **58** using nitric acid afforded compounds **59** in good yields. Reduction of the nitro groups yielding amino phenols **39j**−**t** proceeded in generally excellent yields.

Structural Information on Lead Compound 3. A crystal structure of **3** bound to KDR (Figure 4) confirmed the proposed binding mode and allowed us to use structural information to guide our medicinal chemistry efforts. As shown in Figure 4, compound **3** binds largely as predicted based on our model of compound **2** within the AMG 706/KDR structure. Hydrogen bonds between the hinge-region Cys 919 are observed with both the nitrogen of the pyridine and the carboxamide-NH. The benzimidazole core is oriented in the hydrophobic pocket flanked by Val 917. The endocyclic nitrogen of the benzimidazole hydrogen bonds with the NH of Asp 1046 and either the exocyclic or the endocyclic NH may interact with the side chain of Glu 885. Also consistent with the modeling studies, the aniline aryl ring occupies the second hydrophobic pocket

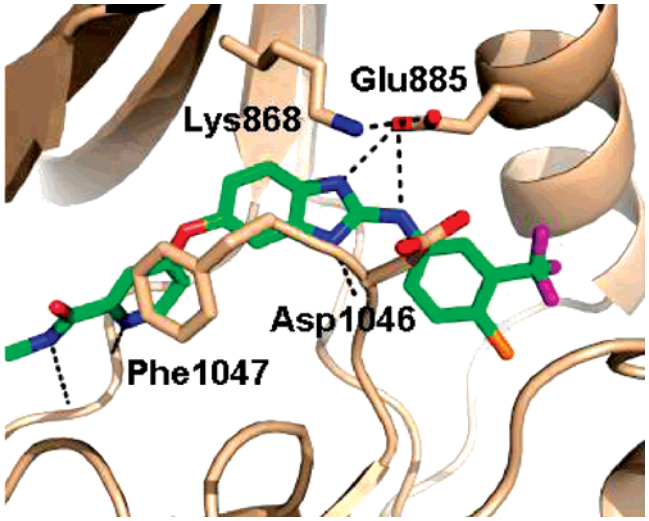


Figure 4. Crystal structure of **3** bound to KDR. Asp 1046, Phe 1047, and Gly 1048 (not shown for clarity) constitute the residues of the "DFG" motif. Potential hydrogen-bond interactions are indicated by dotted lines.

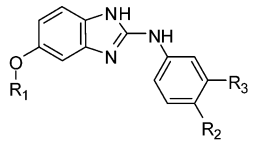
created by the rearrangement of the protein into the "DFG-out" conformation. The *meta*-trifluoromethyl substituent orients toward a small lipophilic pocket away from the solvent exposed portion of the protein.

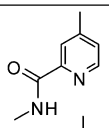
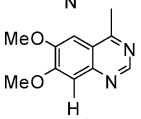
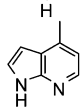
Results and Discussion

All compounds depicted in Tables 1−6 were screened for inhibition of KDR tyrosine kinase activity with select compounds further assayed in the HUVEC cellular assay. Our initial work focused on exploring variants to the pyridine carboxamide moiety of the 2-aminobenzimidazole **3** (Table 1). As shown in Table 1, removal of the carboxamide group (**4** vs **3**) led to an 18-fold reduction in enzyme potency, presumably due to the loss of the hydrogen-bond interaction between the NH of the carboxamide and the carbonyl of Cys 919. By incorporating nitrogen-containing heterocycles with a hydrogen-bond donor and acceptor appropriately spaced to interact with the hinge greater potency was realized. For example, quinazoline **5** (with the proton of C8 engaged in a hydrogen bond with the carbonyl of Cys 919)[17] and azaindole-substituted **6** showed improved enzyme potency by 20-fold and 3-fold, respectively, compared to pyridine **4**. Compound **5** displayed improved potency in the cellular assay (IC_{50} = 49 nM), however, this was insufficient for advancement of this compound. Although **3** and **6** exhibited modest to good enzyme potencies, they lacked the desired activity in the HUVEC cellular proliferation assay.

In an effort to improve the solubility and potentially improve cellular potency of the 2-aminobenzimidazoles, analogs containing a basic amine were investigated (Table 2). Guided by the structural information, we attached the amine from the 3-position of the phenyl ring with a 2- to 4-atom tether to direct the group toward bulk solvent. As exemplified by compound **7**, no significant change was observed at the enzyme level compared to parent compound **3**, however, the enzyme to cellular shift was 36-fold, resulting in a cellular potency of 146 nM. As shown by compounds **7**−**10**, varying the amino moiety (e.g., acyclic vs cyclic), the tether linkage (e.g., O-linked vs C-linked), and the group at the 4-position (e.g., Cl vs CF_3, vs C_2H_5) resulted in relatively small differences in the cellular potencies, with enzyme-to-cell shifts ranging from 10- to 40-fold. Other aniline substitution patterns (i.e., 3,5-substituted, **11**) proved suboptimal for potency.

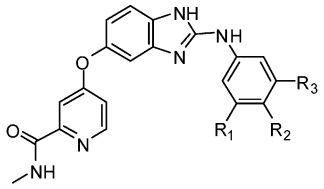
Table 1. Investigation of the Hinge-Binding Moiety[a]

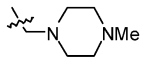
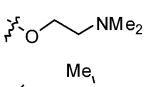
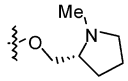
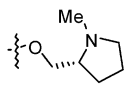
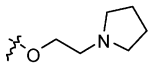


Compound	R1	R2	R3	$K_{i\ phos}$ (nM)	V-HUVEC[b] IC50 (nM)
3		Cl	CF_3	9	>1140
4		Cl	CF_3	160	3896
5		Cl	H	8	49
6		Cl	CF_3	48	2270

[a] Enzyme binding and cellular IC_{50} data are determined by one single experiment. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells.

Table 2. Investigation of Amino Group to Improve Cellular Potency[a]

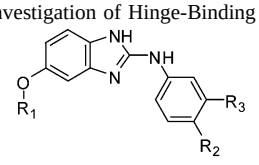


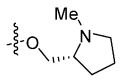
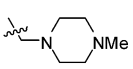
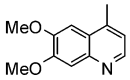
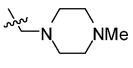
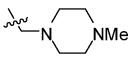
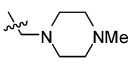
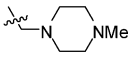
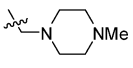
Compound	R1	R2	R3	$K_{i\ phos}$ (nM)	V-HUVEC[b] IC50 (nM)
3	H	Cl	CF_3	9	1140
7	H	Cl		4[c]	146
8	H	CF_3		3	65
9	H	CF_3		2	84
10	H	C_2F_5		9	93
11	CF_3	H		287	n.d.[d]

[a] Enzyme binding and cellular IC_{50} data are determined by one single experiment, except where noted. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells. [c] $N = 2$ for enzyme binding (3.9 nM ± 3.0 nM). [d] n.d.= not determined.

Encouraged by the improved cellular potency of compounds **7**−**10** compared to the parent compound **3**, we investigated the effect of substituting the pyridine carboxamide with other nitrogen-containing heterocycles (Table 3). Consistent with previous observations (i.e., quinazoline **5**, Table 1), compounds **12**−**14** containing the quinoline moiety were more potent at the cellular levels than the analogs bearing a pyrrolopyrimidine (**15**), an azaindole (**16**), or a 2-aminopyrimidine (**17**). The

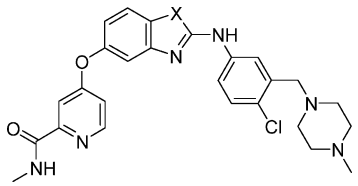
Table 3. Further Investigation of Hinge-Binding Moiety[a]



Compound	R1	R2	R3	$K_{i\ phos}$ (nM)	V-HUVEC[b] IC50 (nM)
12		CF_3		1	32[c]
13		Cl		2	40
14		Cl		0.2	17[d]
15		Cl		17	645
16		Cl		3	143
17		Cl		40	1028
18		Cl		128	n.d.[e]

[a] Enzyme binding and cellular IC_{50} data are determined by one single experiment, except where noted. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells. [c] $N = 2$ for IC_{50} determination (32.4 nM ± 5.4 nM). [d] $N = 2$ for IC_{50} determination (16.6 nM ± 4.6 nM). [e] n.d.= not determined.

Table 4. Investigation of the 1,3-Azole Core[a]

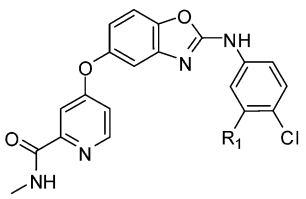


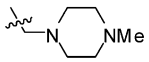
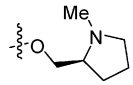
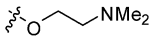
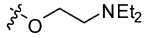
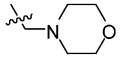
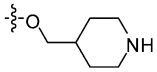
cmpd	X	$K_{i\ phos}$ (nM)	V-HUVEC[b] IC_{50} (nM)
7	NH	4	146
19	N−Me	10	31
20	O	4	36

[a] Enzyme binding and cellular IC_{50} data are determined by one single experiment. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells.

improved potency observed with quinoline derivatives **12**−**14** reflected a slight decrease in enzyme-to-cell shift. Modifying either the bicyclic pyrollopyrimidine **15** or the azaindole **16** to the monocylic 2-aminopyridine **17** resulted in a loss of potency at the enzyme and cellular level. Although this is consistent with data in other series (ex: benzoxazole series (vide infra) and unpublished results), it could not be rationalized by structural information. As anticipated based on earlier studies, removal of the hydrogen-bond donor to the hinge region resulted in a 3-fold decline in enzyme potency (**17** vs **18**). The 2-aminobenzimidazole **14**, containing a 6,7-dimethoxyquinoline moiety, displayed the best overall potency with a 10-fold increase in enzyme affinity (K_i = 0.2 nM) compared to the

Table 5. Investigation of Pendant Tertiary Amines on the Aniline Moiety[a]



Compound	R_1	$K_{i\ phos}$ (nM)	V-HUVEC[b] IC50 (nM)
20		4	36
21	H	12	766
22		3[c]	15[d]
23		4	88
24		5	34
25		4	117
26		3	94

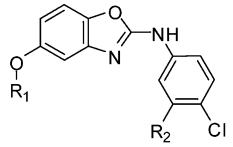
[a] Enzyme binding and cellular IC_{50} data are determined by one single experiment, except where noted. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells. [c] $N = 2$ for K_i determination (2.8 nM ± 1.6 nM). [d] $N = 3$ for IC_{50} determination (15.3 nM ± 5.2 nM).

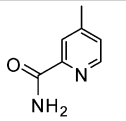
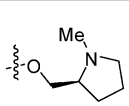
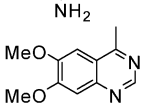
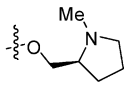
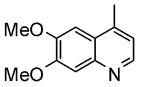
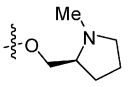
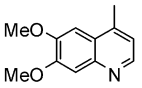
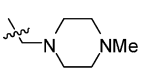
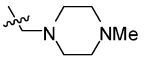
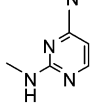
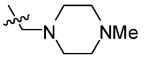
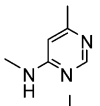
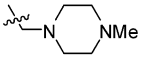
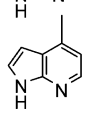
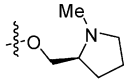
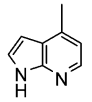
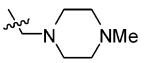
unsubstituted quinoline **13** ($K_i = 2$ nM). This improved enzyme potency could result from an increased donor character of the C8-hydrogen of the 6,7-dimethoxyquinoline moiety binding the hinge region. In addition, compound **14** displayed an IC_{50} of 17 nM in the HUVEC assay. Although cellular efficacy was greatly improved by adding a tertiary amino group and varying the nitrogen-containing heterocycle, the shift between enzyme potency and cellular potency was difficult to predict and often greater than 10-fold.

The crystal structure of **3** bound to KDR illustrates the hydrogen bond between either the exocyclic or the endocyclic NH of the benzimidazole and the side chain of Glu 885. To evaluate the possibility of removing the endocyclic hydrogen-bond donor, we methylated the benzimidazole core. Indeed, the *N*-methylbenzimidazole **19** provided a K_i of 10 nM on phosphorylated KDR and an IC_{50} of 31 nM in the cellular assay, exhibiting only a 3-fold enzyme-to-cell shift (compared to the 36-fold shift observed with the parent compound **7**; Table 4). This result indicates that a possible hydrogen bond between the endocyclic NH and the Glu 885 can be removed due to an interaction between Glu 885 and the exocyclic NH. Encouraged by this data, we altered the aminobenzimidazole core to a 2-aminobenzoxazole, as exemplified by compound **20**. Compound **20** displayed good potency at the enzyme ($K_i = 4$ nM) and cellular ($IC_{50} = 36$ nM) levels. Based on this finding, we elected to investigate other structural variants in the 2-aminobenzoxazole series.

The overall structure−activity relationship of the 2-aminobenzoxazoles followed a similar pattern as that of the corresponding 2-aminobenzimidazoles (Tables 5 and 6). As observed in the 2-aminobenzimidazole series, addition of a pendant basic amine was preferred to achieve good cellular potency (Table 5). For example, simply substituted **21** exhibited a K_i of 12 nM in the enzyme assay, but displayed an IC_{50} of 766 nM in the cellular assay. Appendage of a basic amine (**20**) improved the enzyme potency 3-fold ($K_i = 4$ nM), with a 20-fold improvement in cellular potency ($IC_{50} = 36$ nM). A brief examination of tertiary amine substituents indicated a variety of groups are tolerated (**22**−**26**). In particular, compounds containing an *N*-methylpyrrolidine (**22**), an *N*,*N*-diethylaminoethyl (**24**), or an *N*-methylpiperazine (**20**) substituent are optimum for achieving good cellular potency.

Table 6. Benzoxazoles: Investigation of the Hinge-Binding Element[a]

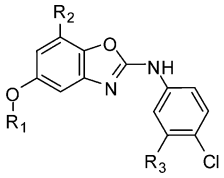


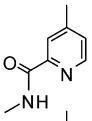
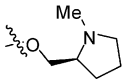
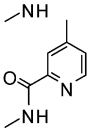
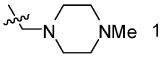
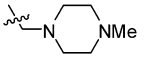
Compound	R1	R2	$K_{i\ phos}$ (nM)	V-HUVEC[b] IC50 (nM)
27			3	18
28			0.5	6
29			0.5	7
30			0.5[c]	10
31			4[d]	26
32			25	303
33			20	289
34			2[e]	5
35			2	52

[a] Enzyme binding and cellular IC_{50} data are determined by one single experiment, except where noted. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells. [c] $N = 2$ for K_i determination (0.5 nM ± 0.1 nM). [d] $N = 2$ for K_i determination (3.6 nM ± 2.3 nM). [e] $N = 2$ for K_i determination (1.6 nM ± 0.5 nM).

To further improve the cellular potency, we also explored the hinge binding moiety (Table 6). As shown previously, when combined with the appropriate tertiary amine pendant, compounds containing a pyridine carboxamide were potent KDR inhibitors (compounds **20**, **22**, and **24** in Table 5 and compound **27** in Table 6). Similar to the benzimidazole series, compounds **28**−**30** illustrate that a dimethoxyquinoline and quinazoline heterocycles were optimal. Although removal of the 6- and

Table 7. Investigation of Substitution on Benzoxazole Core[a]



Compound	R1	R2	R3	$K_{i\ phos}$ (nM)	V-HUVEC[b] IC50 (nM)
36		F		3	31
37		Cl		10	35
38		Cl		2	52

[a] Enzyme binding and cellular IC_{50} data are determined by one single experiment. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells.

7-methoxy groups resulted in an 8-fold drop in enzyme potency, the cellular activities were comparable (**30** vs **31**). As observed in the benzimidazole series, compounds with an amino pyrimidine hinge binding moiety exemplified exhibited a loss in cellular activity (**32** and **33**). Finally, good cellular potency can also be achieved with an azaindole binding the hinge and an appropriately substituted aniline (compound **34**).

In an attempt to improve the enzyme potency further, we returned to the crystal structure. Based on the structure of **3** with KDR, we noted a small to medium sized lipophilic pocket that could be accessed by placing a substituent at the 7-position of the bicyclic core (Figure 5). We proposed that placement of a substituent at this position could increase potency. We

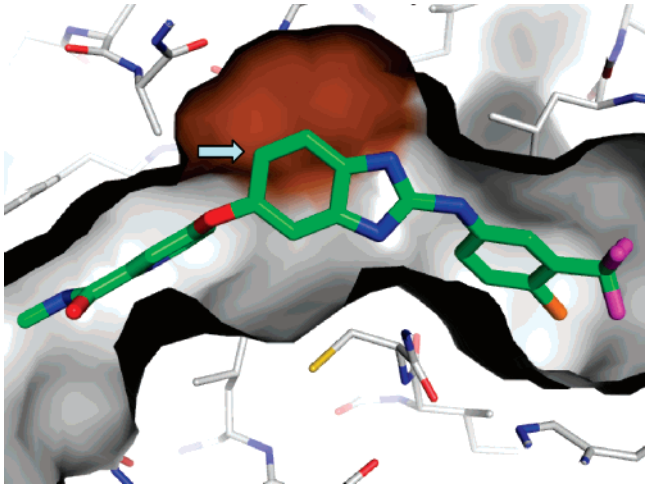


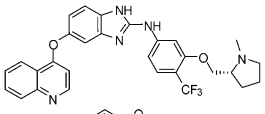
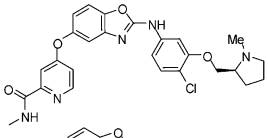
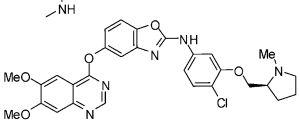
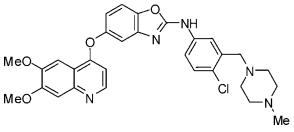
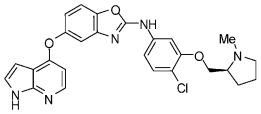
Figure 5. Surface diagram of compound **3** bound to KDR. The 7-position is indicated by the arrow.

therefore prepared the 7-fluoro and 7-chloro derivates. Surprisingly, as shown by compounds **36**−**38** (Table 7), substitution at the 7-position of the benzoxazole did not yield any significant improvement in enzyme or cellular potencies compared to the corresponding unsubstituted analogs.

Pharmacokinetic Studies

Several 2-aminoazoles with suitable inhibitory activity in the kinase enzyme and cellular proliferation assays were evaluated for their in vivo pharmacokinetics in male Sprague−Dawley rats (Table 8). Compounds were administered by both intravenous (i.v.) and oral (p.o.) dosing routes. Compounds **12** and **34** displayed reasonable clearance values (Cl = 1.0 and 1.24 L/h/kg, respectively), but had a low oral bioavailablity (24 and 17 %*F*, respectively). Dimethoxyquinazoline (**28**), dimethoxyquinoline (**30**), and pyridine carboxamide (**22**) had improved bioavailability (40−67 %*F*). In general, the 2-aminoazoles tested exhibited moderate to high Cl and a high volume of distribution

Table 8. PK Studies of Leading Compounds[a]

Compound	Structure	V-HUVEC[b] IC_{50} (nM)	Cl (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	*F*%
12		32	1.0	5.8	4.8	24
22		15	3.40[c]	8.40[c]	1.80[c]	40[d]
28		6	0.89	6.88	6.14	60
30		10	1.63	12.1	5.53	67
34		5	1.24	5.02	2.87	17

[a] IV dosing at 1 mpk (DMSO), with $n = 3$ male Sprague−Dawley rats. Oral dosing at 10 mpk (Ora-Plus, pH 2), with $n = 2$ rats. [b] Human umbilical vein endothelial cells. [c] $n = 2$ rats. [d] Oral dosing at 3 mpk.

Table 9. Cellular Selectivity Profile of Selected Compounds in VEGF- and FGF-Induced Cellular Proliferation[a]

cmpd	V-HUVEC[b] IC_{50} (nM)	F-HUVEC[b] IC_{50} (nM)
22	15[c]	420[d]
28	6	55
30	10	101

[a] Cellular IC_{50} data are determined by one single experiment, except where noted. See Experimental Section for a description of the assay conditions. [b] Human umbilical vein endothelial cells. [c] $N = 3$ for IC_{50} determination (15.3 nM ± 5.2 nM). [d] $N = 3$ for IC_{50} determination (420 nM ± 100 nM).

after i.v. dosing. Compounds **22**, **28**, and **30** all exhibited acceptable half-lives and oral bioavailability for further in vivo evaluation.

Selectivity. To evaluate compounds in an in vivo setting, it was critical to understand the kinase selectivity profile. To measure the selectivity of this series in a cellular assay, compounds **22**, **28**, and **30** were evaluated in a fibroblast growth factor (b-FGF)-driven HUVEC proliferation assay (Table 9). While compounds **28** and **30** displayed moderate selectivity (10-fold) for VEGF-driven cellular proliferation, compound **22** exhibited the best selectivity (28-fold) over FGF-induced HUVEC proliferation ($IC_{50(V-HUVEC)} = 15$ nM, $IC_{50(F-HUVEC)} = 420$ nM).

Compound **22** was further profiled against an extended panel of kinase enzymes, including receptor tyrosine kinases and serine/threonine kinases. As summarized in Table 10, compound **22** exhibited excellent enzymatic selectivity. Within the protein tyrosine kinase family, **22** showed excellent levels of selectivity (>100-fold) over Tie-2, FGF, Src, IGFR-1, and EGFR. Similar selectivity was seen over kinases in the serine/threonine group (MAP, GSK3-b, CDK). As expected, due to the close homology of KDR to cFMS and cKit, only modest selectivity was observed (16-fold and 6-fold, respectively). Based on its favorable selectivity profile in both the enzyme and the cellular assays and pharmacokinetics, compound **22** was further examined in our animal efficacy models.

Animal Efficacy Models. Vascular Permeability. The in vivo activity of compound **22** on VEGF-induced vascular permeability was assessed in a modified Miles assay[18] (Figure 6). For this assay, HEK 293 cells, transfected with murine VEGF or vector control were mixed with Matrigel and injected subcutaneously into CD-1 Nu/Nu mice. Compound **22** was administered orally 22 h after injection of the cells at 10, 30, and 100 mg/kg doses. Six hours after administration of compound, vascular permeability in the skin overlying the Matrigel plug was measured by the quantization of extravasated Evan's blue dye. In mice dosed with **22**, linear pharmacokinetics was observed. Although the responses at 10 and 30 mg/kg were not statistically significant, a strong inhibition of vascular permeability at 100 mg/kg (79%) was observed.

Angiogenesis. To evaluate the in vivo VEGF-mediated anti-angiogenic activity of compound **22**, a rat corneal model of angiogenesis was performed (Figure 7). A disk infused with rHu-VEGF was placed in the rat cornea to stimulate blood vessel formation from the limbal vessels of the eye toward the disk. The rats were then treated with **22** at doses of 1, 3, 10, and 30 mg/kg once a day orally. Treatment began on the day of implantation and continued for 7 days. Two vascular endpoints were evaluated: the number of blood vessels at the midpoint between the limbus and the disk and the mean blood vessel area. Benzoxazole **22** significantly reduced both vascular endpoints in a dose-concentration-dependent manner, with an estimated ED_{50} of 16.3 mg/kg. Terminal PK analysis estimated the $AUC_{(0-24\,h)}$ at the ED_{50} as 17.03 μM·h.

Crystal Structure of 22 Bound to KDR. To confirm the binding mode of **22**, the crystal structure of the benzoxazole

Table 10. Selectivity Profile of **22**[a]

enzyme inhibition IC_{50} (μM)			
PTK group I	*PTK group VI*	*PTK group X*	*CMGC group I*
Src = 0.72	Zap-70 > 25	EGFR > 25	CDK5p25 > 40
LCK = 1.14			CDK1 > 40
PTK group XIII	*PTK group XIV*	*PTK group XV*	*CMGC group II*
Tie-2 = 3.18	KDR = 0.005[b]	FGF = 4.37	p38α > 40
	cFMS = 0.08		p38β > 40
	cKIT = 0.03	*OPK group VII*	JNK1 > 40
PTK group XVI		E2K2 > 40	JNK2 > 40
IGFR-1 = 4.01			JNK3 > 40
	PTK group XXI	*CMGC group III*	
	cMet = 13.7	GSK3-b > 40	

[a] IC_{50} data are determined by one single experiment. See Experimental Section for a description of the assay conditions. [b] $N = 2$ for IC_{50} determination (4.6 nM ± 2.8 nM).

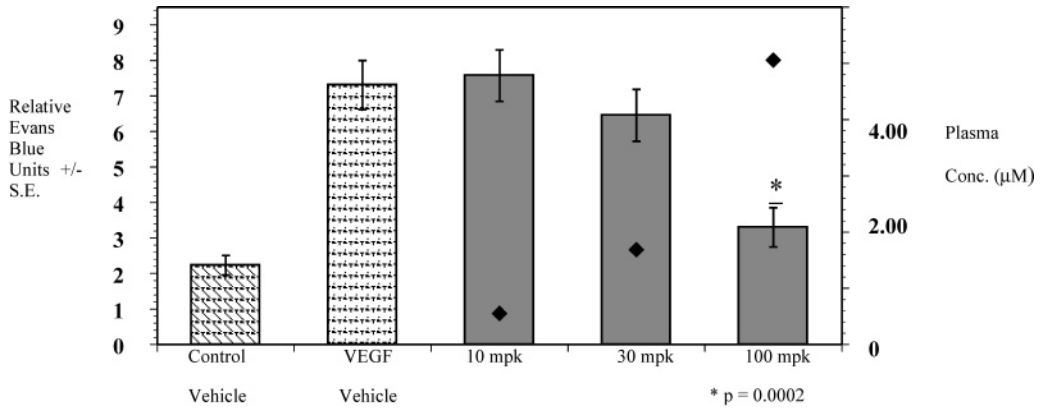


Figure 6. Effect of **22** on VEGF-induced vascular permeability in mice. (◆) Indicates drug concentration.

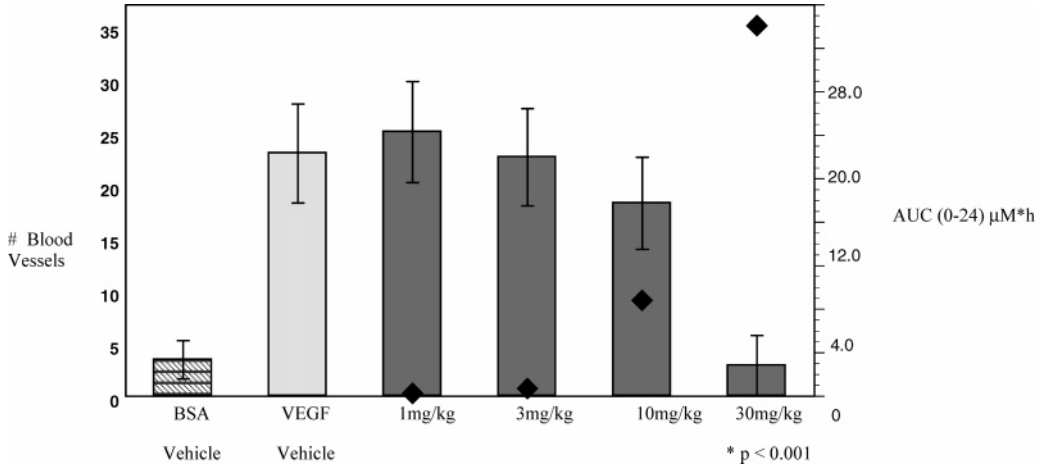


Figure 7. Inhibition of VEGF-induced angiogenesis in rats by **22**. (◆) Indicates drug concentration.

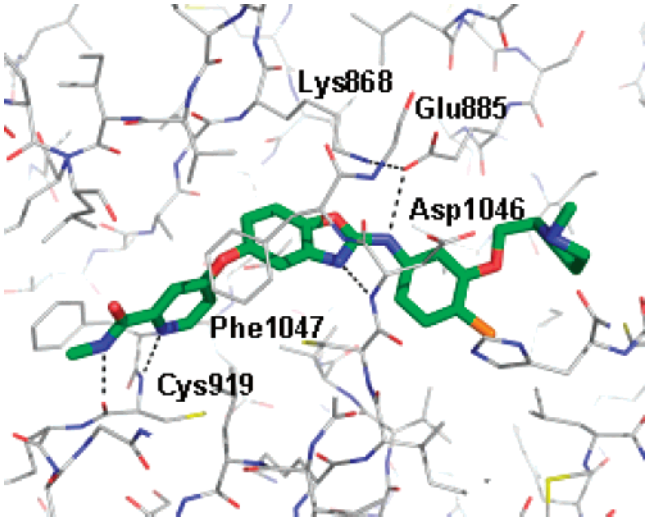


Figure 8. Crystal structure of **22** bound to KDR.

complexed with KDR was obtained. As shown in Figure 8, compound **22** binds largely as predicted based on our structure of compound **3** bound to KDR. Hydrogen bonds between the hinge-region Cys 919 are observed with both the nitrogen of the pyridine and the carboxamide-NH. The benzoxazole core is oriented in the hydrophobic pocket flanked by Val 917. The endocyclic nitrogen of the aminobenzoxazole hydrogen bonds with the NH of Asp 1046 and the exocyclic NH picks up a key interaction with side chain of Glu 885. The aniline aryl ring occupies the second hydrophobic pocket with the *N*-methyl pyrrolidine side chain directed to a solvent-exposed portion of the protein.

Conclusion

Guided by X-ray crystallography and molecular modeling, we identified a new class of KDR inhibitors: 2-aminobenzimidazoles. While the 2-aminobenzimidazoles were potent enzyme inhibitors, achieving good cellular potency remained a challenge. A detailed understanding of the key interactions between the ligand and the receptor prompted the replacement of the 2-aminobenzimidazole core by a 2-aminobenzoxazole. Optimization of the hinge binding heterocycle as well as the aryl ring occupying the second hydrophobic pocket resulted in several benzoxazoles with good enzyme and cellular potencies. Among them, compound **22** emerged as the best candidate for in vivo evaluation. Compound **22** showed on mechanism in vivo activity upon oral dosing in both the mouse Matrigel and the rat corneal models. Although compound **22** is less efficacious in the rat corneal model compared to motesanib,[19] it represents one step toward identification of a novel series of potent KDR inhibitors with strong antitumor activity in vivo. Reports detailing the discovery of these compounds will be published hereafter.

Experimental Section

General Considerations. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. All final compounds were purified to >95% purity, as determined by high-performance liquid chromatography (HPLC: **A**, Zorbax SB-C8, 4.6 × 150 mm, 15 min; flow rate = 1.5 mL/min; gradient = 0 to 100% 0.1% TFA in CH_3CN/100 to 0% 0.1% TFA in water; **B**, Zorbax SB-C8, 4.6 × 150 mm, 12 min; flow rate = 1.5 mL/min; gradient = 10 to 90% 0.1% formic acid in CH_3CN/90 to 10% 0.1% formic acid in water; **C**, Phenomenex Synergi, 2 × 50 mm, 3 min, flow rate = 1.0 mL/min; gradient = 5 to 95% 0.1% formic acid in CH_3CN/95 to 5% 0.1% formic acid in water). Silica gel chromatography was performed using either glass columns packed with silica gel (230−400 mesh), prepacked silica gel cartridges (Isco or Biotage), or preparative thin-layer chromatography plates (Analtech, 1000 microns). NMR spectra were determined using a Varian 300 or 400 MHz spectrometer. Preparative reverse-phase HPLC was performed using Gilson 306 gradient elution pump, YMC ODS-AQ reverse-phase silica gel column and a Gilson variable wavelength UV/vis-155 detector. High-resolution mass spectrometry (HRMS) was performed using an Agilent MSD-TOF mass spectrometer equipped with an ESI dual channel source. The instrument was calibrated using Agilent ESI-MS tuning mixture (ES Tuning Mix PN G2421A). The tuning mixture was continuously infused on the second ESI channel, and the 622.02895 Da ion was used to provide a lock-mass correction to the calibration function. All samples were diluted to an appropriate concentration so that the number of counts per scan was less that 10e5 to prevent dead-time distortion of the measurement.

4-((2-((4-Chloro-3-(trifluoromethyl)phenyl)amino)-1*H*-benzimidazol-5-yl)oxy)-*N*-methyl-2-pyridinecarboxamide (3). To a solution of 4-(3,4-diamino-phenoxy)-pyridine-2-carboxylic acid methylamide (0.07 g, 0.27 mmol) in CH_3CN (20 mL) was added dropwise, over 5 min, a solution of 1-chloro-4-isothiocyanato-2-trifluoromethyl-benzene (0.055 g, 0.27 mmol) in CH_3CN (10 mL). The reaction was stirred 18 h at rt. The reaction was diluted with additional CH_3CN (10 mL), followed by addition of EDC (0.078 g, 0.41 mmol). The reaction was heated at 80 °C for 3 h, allowed to cool to rt, and concentrated in vacuo. The crude mixture was dissolved in EtOAc and water. The layers were separated, and the

organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a hexane−EtOAc gradient to yield the title compound as a white solid (74 mg, 59%). ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.42 (s, 0.5H), 11.37 (s, 0.5H), 10.13 (s, 0.5H), 10.09 (s, 0.5H), 8.70−8.80 (m, 1H), 8.45−8.48 (m, 1H), 8.31−8.32 (m, 1H), 8.10−8.14 (m, 1H), 7.62−7.65 (m, 1H), 7.46 (d, J = 8.4, Hz, 0.5H), 7.30−7.40 (m, 2.5H), 7.10−7.14 (m, 1H), 6.84−6.88 (m, 1H), 2.75 (d, J = 1.6 Hz, 1.5H), 2.74 (d, J = 2.0 Hz, 1.5H); HRMS calcd for $C_{21}H_{15}ClF_3N_5O_2$ $(M + H)^+$, 462.0939; found, 462.0943; HPLC purity = 98% (system A), 98% (system B).

(4-Chloro-3-trifluoromethyl-phenyl)-[5-(pyridin-4-yloxy)-1*H*-benzimidazol-2-yl]-amine (4). Starting with 4-(3,4-diamino-phenoxy)-pyridine (273 mg, 1.36 mmol), 228 mg (42%) of the title compound was obtained as a white solid according to the method described for the synthesis of **3**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.37 (s, 0.5H), 11.32 (s, 0.5H), 10.10 (s, 0.5H), 10.06 (s, 0.5H), 8.38−8.45 (m, 2H), 8.30−8.35 (m, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 8.8, 3.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 0.5H), 7.35 (d, J = 8.4 Hz, 0.5 H), 7.18 (d, J = 2.0 Hz, 0.5H), 7.08 (d, J = 2.0 Hz, 0.5H), 6.80−6.90 (m, 3H); HRMS calcd for $C_{19}H_{12}ClF_3N_4O$ $(M + H)^+$, 405.0725; found, 405.0725; HPLC purity = 100% (system B), 100% (system C).

(4-Chloro-phenyl)-[5-(6,7-dimethoxy-quinazolin-4-yloxy)-1*H*-benzoimidazol-2-yl]-amine (5). A solution of 4-amino-3-nitro-phenol (0.80 g, 5.34 mmol, 1.2 equiv) in DMSO (3.80 mL) was treated with KO*t*-Bu (0.60 g, 5.34 mmol) and the mixture was stirred at rt for 2 h. To this solution, 4-chloro-6,7-dimethoxyquinazoline (1.00 g, 4.45 mmol) and K_2CO_3 (0.33 g, 2.4 mmol) were added, and the mixture was heated at 110 °C for 16 h. The mixture was allowed to cool to rt, diluted with EtOAc, and washed with $NaHCO_3$ (satd). To remove the emulsion, the mixture was filtered through Celite, and then the organic layer was washed with brine, 1 N NaOH, and then brine again. The organic portion was dried with Na_2SO_4, filtered, and evaporated to give 4-(6,7-dimethoxyquinazolin-4-yloxy)-2-nitro-phenylamine as an orange solid (1.0 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.86 (d, J = 3.0 Hz, 1H), 7.50−7.55 (m, 3H), 7.44 (dd, J = 9.1, 2.5 Hz, 1H), 7.36 (s, 1H), 7.10 (d, J = 9.1 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H).

A flask was charged with 4-(6,7-dimethoxyquinazolin-4-yloxy)-2-nitro-phenylamine (1.00 g, 2.90 mmol) and the solid was dissolved in a mixture of EtOH (200 mL) and glacial acetic acid (10 mL) and placed under nitrogen. Pd/C was added, the reaction mixture was blanketed with H_2, and the mixture was shaken under H_2 for 18 h at 55 psi. The catalyst was removed by filtration through Celite and the solution was concentrated in vacuo. The residue was dissolved in MeOH/water, NH_4OH was added to adjust to pH 10, and the solvent was evaporated. Partial purification of the residue by column chromatography using a gradient of 0−100% of a 90:10:1 CH_2Cl_2/MeOH/NH_4OH eluent afforded 4-(6,7-dimethoxy-quinazolin-4-yloxy)-benzene-1,2-diamine (impure). A portion of this (60 mg, est 1.44 mmol) was subjected to the conditions used to prepare **3** to yield the title compound as a yellow solid (22 mg, 34%). ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.05−11.15 (m, 1H), 9.71 (s, 0.5H), 9.66 (s, 0.5H), 8.48−8.55 (m, 1H), 7.75−7.85 (m, 2H), 7.57 (s, 1H), 7.15−7.40 (m, 5H), 6.80−6.95 (m, 1H), 3.97 (s, 6H); HRMS calcd for $C_{23}H_{18}ClN_5O_3$ $(M + H)^+$, 448.1170; found, 448.1169; HPLC purity = 100% (system A), 99% (system B).

(4-Chloro-3-trifluoromethyl-phenyl)-[6-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-1*H*-benzimidazol-2-yl]-amine (6). Starting with 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-benzene-1,2-diamine (82 mg, 0.34 mmol), 58 mg (39%) of the title compound was obtained according to the method described for the synthesis of **3**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.60−11.65 (m, 1H), 11.30 (s, 0.5H), 11.20 (s, 0.5H), 10.10 (s, 0.5H), 10.00 (s, 0.5H), 8.28−8.35 (m, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.95−8.05 (m, 1H), 7.60−7.65 (m, 1H), 7.42 (d, J = 7.7 Hz, 0.5H), 7.35 (d, J = 7.7 Hz, 0.5H), 7.28−7.30 (m, 1H), 7.15−7.20 (m, 0.5H), 7.05−7.10 (m, 0.5H), 6.85−6.90 (m, 1H), 6.35 (d, J = 5.8 Hz, 0.5H), 6.30 (d, J = 5.8 Hz, 0.5H), 6.15−6.20 (m, 1H); Anal. ($C_{21}H_{13}ClF_3N_5O$·0.33 CH_3OH) C, H, N.

4-{2-[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-1*H*-benzimidazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (7). To a cooled (0 °C) solution of 1-(2-chloro-5-amino-benzyl)-4-methyl-piperazine (252 mg, 1.05 mmol) in CH_3CN (10 mL) was added 1,1′-thiocarbonyldiimidazole (225 mg, 1.26 mmol). The reaction mixture was allowed to warm to rt and stirred for 18 h. The mixture was added dropwise to a solution of 4-(3,4-diamino-phenoxy)-pyridine-2-carboxylic acid methylamide (271 mg, 1.05 mmol) in CH_3CN (20 mL) at rt and stirred 18 h. The reaction mixture was further diluted with CH_3CN (15 mL), then EDC (0.20 g, 1.05 mmol) was added, and the vessel was heated at 80 °C for 3 h. The mixture was allowed to cool to rt, concentrated in vacuo, and the residue was dissolved in EtOAc and water. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The mixture was purified by a combination of silica gel column chromatography and silica gel prep plates to obtain the title compound (231 mg, 43%). ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.11 (s, 0.5H), 11.05 (s, 0.5H), 9.74 (s, 0.5H), 9.69 (s, 0.5H), 8.70−8.80 (m, 1H), 8.45−8.50 (m, 1H), 7.85−7.90 (m, 1H), 7.70−7.75 (m, 1H), 7.30−7.45 (m, 3H), 7.10−7.15 (m, 2H), 6.80−6.90 (m, 1H), 3.50−3.54 (m, 2H), 2.75 (s, 1.5H), 2.74 (s, 1.5H), 2.30−2.50 (m, 8H), 2.17 (s, 1.5H), 2.13 (s, 1.5H); Anal. ($C_{26}H_{28}ClN_7O_2$·H_2O·0.5CH_3OH) C, H, N.

4-((2-((3-((2-(Dimethylamino)ethyl)oxy)-4-(trifluoromethyl)-phenyl)amino)-1*H*-benzimidazol-5-yl)oxy)-*N*-methyl-2-pyridinecarboxamide (8). Starting from 4-(3,4-diamino-phenoxy)-pyridine-2-carboxylic acid methylamide (217 mg, 0.84 mmol) and [2-(5-isothiocyanato-2-trifluoromethyl-phenoxy)-ethyl]-dimethyl-amine (prepared following the procedure outlined for **40d** from 3-(2-dimethylamino-ethoxy)-4-trifluoromethylaniline (209 mg, 0.84 mmol) and used crude), 210 mg (48%) of the title compound was obtained as a tan solid according to the method described for the synthesis of **3**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.33 (s, 0.5H), 11.27 (s, 0.5H), 10.04 (s, 0.5H), 9.98 (s, 0.5H), 8.75−8.76 (m, 1H), 8.46−8.47 (m, 1H), 7.68−7.70 (m, 1H), 7.32−7.52 (m, 4H), 7.13−7.20 (m, 2H), 6.84−6.87 (m, 1H), 4.18−4.21 (m, 2H), 2.75 (d, J = 4.8 Hz, 3H), 2.50−2.54 (m, 2H), 2.20−2.30 (m, 6H); Anal. ($C_{25}H_{25}F_3N_6O_3$·0.66 H_2O·CH_3OH) C, H, N.

***N*-Methyl-4-((2-((3-((((2*R*)-1-methyl-2-pyrrolidinyl)methyl)-oxy)-4-(trifluoromethyl)phenyl)amino)-1*H*-benzimidazol-5-yl)-oxy)-2-pyridinecarboxamide (9).** Starting from 4-(3,4-diamino-phenoxy)-pyridine-2-carboxylic acid methylamide (83 mg, 0.32 mmol), 109 mg (63%) of the title compound was obtained according to the method described for the synthesis of **3**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.35 (s, 0.5 H), 11.28 (s, 0.5H), 10.05 (s, 0.5H), 9.99 (s, 0.5H), 8.75 (s, 1H), 8.45−8.47 (m, 1H), 7.69 (s, 1H), 7.30−7.50 (m, 4H), 7.10−7.25 (m, 2H), 6.80−6.90 (m, 1H), 4.05−4.15 (m, 1H), 3.85−3.95 (m, 1H), 2.90−3.00 (m, 1H), 2.70−2.75 (m, 3H), 2.60−2.70 (m, 1H), 2.35−2.45 (m, 3H), 2.15−2.25 (m, 1H), 1.90−2.00 (m, 1H), 1.55−1.75 (m, 3H); Anal. ($C_{27}H_{27}F_3N_6O_3$·1.5 H_2O) C, H, N.

(*R*)-4-{2-[3-(1-Methyl-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenylamino]-1*H*-benzimidazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (10). To a cooled (0 °C) solution of (*R*)-1-methyl-2-(5-amino-2-pentafluoroethyl-phenoxymethyl)-pyrrolidine (312 mg, 0.96 mmol) in CH_2Cl_2 (3 mL) was added 1,1′-thiocarbonyldiimidazole (180 mg, 1.00 mmol). The reaction was allowed to warm to rt and stirred for 18 h. The mixture was concentrated in vacuo, the residue was dissolved in CH_3CN (7 mL), and 4-(3,4-diamino-phenoxy)-pyridine-2-carboxylic acid methylamide (312 mg, 0.96 mmol) was added. The reaction mixture stirred at rt an additional 16 h, followed by the addition of EDC (276 mg, 1.44 mmol) and CH_3CH (20 mL). The mixture was heated at 80 °C for 3 h, allowed to cool to rt, and concentrated in vacuo. The residue was taken up into CH_2Cl_2, washed with water and brine, dried with Na_2SO_4, filtered, and evaporated. The crude material

was purified by column chromatography using 0−50% of a 90:10:1 CH_2Cl_2/MeOH/NH_4OH solution as the eluent to yield the title compound as an off-white solid (170 mg, 29%). ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.25−11.40 (m, 1H), 9.95−10.05 (m, 1H), 8.70−8.80 (m, 1H), 8.46 (d, J = 5.8 Hz, 1H), 7.71 (s, 1H), 7.30−7.50 (m, 4H), 7.10−7.20 (m, 2H), 6.80−6.90 (m, 1H), 3.80−3.90 (m, 1H), 2.90−3.00 (m, 1H), 2.76 (d, J = 4.8 Hz, 3H), 2.55−2.60 (m, 1H), 2.38 (s, 1.5H), 2.35 (s, 1.5H), 2.15−2.25 (m, 1H), 1.90−2.05 (m, 1H), 1.55−1.70 (m, 3H). Anal. ($C_{28}H_{27}F_5N_6O_3$·CH_3OH·0.50H_2O) C, H, N.

***N*-Methyl-4-((2-((3-((2-(1-pyrrolidinyl)ethyl)oxy)-5-(trifluoromethyl)phenyl)amino)-1*H*-benzimidazol-5-yl)oxy)-2-pyridinecarboxamide (11).** A flask was charged with 3-(2-pyrrolin-1-yl-ethoxy)-5-trifluoromethyl-phenylamine (0.56 m, 2.0 mmol) and CH_2Cl_2 (10 mL) and cooled in an ice bath. To this solution, 1,1-thiocarbonyldiimidazole (463 mg, 2.6 mmol) was added and the reaction was allowed to warm to rt. After 4 h, the solvent was concentrated in vacuo and the residual yellow solid was titrated with acetone to afford 1-[2-(3-thioisocyanato-5-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine as a 1/1 mixture with imidazole (242 mg). This mixture was used directly in the cyclization step following the procedure described for the synthesis of **3** using 4-(3,4-diamino-phenoxy)-pyridine-2-carboxylic acid methylamide (0.20 g, 0.63 mmol). The title compound was obtained as a yellow solid (0.20 g, 58%). ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.32 (s, 0.5 H), 11.28 (s, 0.5H), 9.93 (s, 0.5H), 9.88 (s, 0.5H), 8.70−8.80 (m, 1H), 8.46 (d, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.65 (s, 1H), 7.45−7.50 (m, 0.5H), 7.30−7.40 (m, 2H), 7.20−7.25 (m, 0.5H), 7.12 (dd, J = 5.5, 2.6 Hz, 1H), 6.82−6.90 (m, 1H), 6.78 (s, 1H), 4.10−4.18 (m, 1H), 2.77−2.85 (m, 2H), 2.76 (d, J = 5.1 Hz, 3H), 2.52−2.58 (m, 4H), 1.60−1.72 (m, 4H); Anal. ($C_{27}H_{27}F_3N_6O_3$·H_2O·0.50CH_3OH) C, H, N.

***N*-(3-((((2*R*)-1-Methyl-2-pyrrolidinyl)methyl)oxy)-4-(trifluoromethyl)phenyl)-5-(4-quinolinyloxy)-1*H*-benzimidazol-2-amine (12).** Starting with 4-(quinolin-4-yloxy)-benzene-1,2-diamine (200 mg, 0.80 mmol), 121 mg (28%) of the title compound was obtained according to the method described for the synthesis of **3**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.35 (s, 0.5H), 11.25 (s, 0.5H), 10.05 (s, 0.5H), 9.95 (s, 0.5H), 8.60−8.65 (m, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.78−7.85 (m, 1H), 7.70 (s, 1H), 7.60−7.68 (m, 1H), 7.40−7.55 (m, 3H), 7.30 (s, 0.5H), 7.20 (s, 0.5H), 6.90−6.95 (m, 1H), 6.50−6.60 (m, 1H), 4.10−4.20 (m, 1H), 3.90−4.00 (m, 1H), 2.90−3.00 (m, 1H), 2.60−2.70 (m, 1H), 2.39−2.42 (m, 3H), 2.20−2.30 (m, 3H), 1.95−2.05 (m, 1H), 1.50−1.80 (m, 3H); Anal. ($C_{29}H_{26}F_3N_5O_2$·1.5H_2O) C, H, N.

[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[5-(quinolin-4-yloxy)-1H-benzimidazol-2-yl]-amine (13). Starting with 4-(quinolin-4-yloxy)-benzene-1,2-diamine (200 mg, 0.80 mmol), 20 mg (5%) of the title compound was obtained according to the method described for the synthesis of **7**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.10 (s, 0.5 H), 11.05 (s, 0.5 H), 9.75 (s, 0.5H), 9.65 (s, 0.5H), 8.60−8.70 (m, 1H), 8.34 (d, J = 7.4 Hz, 1H), 8.00 (d, J = 7.4 Hz, 1H), 7.85−7.90 (m, 1H), 7.75−7.80 (m, 1H), 7.70−7.80 (m, 1H), 7.60−7.70 (m, 1H), 7.30−7.50 (m ,2H), 7.25 (s, 0.5H), 7.15 (s, 0.5H), 6.80−6.95 (m, 1H), 6.50−6.60 (m, 1H), 3.55 (s, 2H), 2.20−2.60 (m, 8H), 2.18 (s, 1.5H), 2.15 (s, 1.5H); HRMS calcd for $C_{28}H_{27}ClN_6O$ $(M + H)^+$, 499.2008; found, 499.2005; HPLC purity 99% (system A), 99% (system B).

[4-Chloro-3-(4-methylpiperazin-1-ylmethyl)-phenyl]-[5-(6,7-dimethoxyquinolin-4-yloxy)-1*H*-benzimidazol-2-yl]-amine (14). Starting with 4-(6,7-dimethoxyquinolin-4-yloxy)-benzene-1,2-diamine (120 mg, 0.38 mmol), 38 mg (18%) of the title compound was obtained according to the method described for the synthesis of **7**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.0 Hz, 1H), 7.50−7.65 (m, 2H), 7.35−7.50 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.20−7.28 (m, 4H), 6.93 (dd, J = 8.0, 2.0 Hz, 1H), 6.40 (d, J = 5.0 Hz, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.70 (s, 2H), 2.60−2.80 (m, 8H), 2.35 (s, 3H); HRMS calcd for $C_{30}H_{31}ClN_6O_3$ $(M + H)^+$, 559.2219; found, 559.2223; HPLC purity 99% (system A), 96% (system B).

[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[6-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-1*H*-benzimidazol-2-yl]-amine (15). Starting with 4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yloxy)-benzene-1,2-diamine (100 mg, 0.40 mmol), 15 mg (8%) of the title compound was obtained according to the method described for the synthesis of **3**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 12.08−12.14 (m, 1H), 11.00 (s, 0.5H), 10.94 (s, 0.5H), 9.65 (s, 0.5H), 9.60 (s, 0.5H), 8.23−8.26 (m, 1H), 7.84−7.92 (m, 1H), 7.68−7.74 (m, 1H), 7.24−7.40 (m, 3H), 7.12−7.17 (m, 1H), 6.80−6.88 (m, 1H), 6.24−6.30 (m, 1H), 3.50 (s, 2H), 2.20−2.50 (m, 8H), 2.15 (s, 1.5H), 2.10 (s, 1.5H); HRMS calcd for $C_{25}H_{25}ClN_8O$ $(M + H)^+$, 489.1912; found, 489.1911; HPLC purity 95% (system B), 100% (system C).

[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[6-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-1*H*-benzimidazol-2-yl]-amine (16). Starting with 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-benzene-1,2-diamine (106 mg, 0.44 mmol), 84 mg (39%) of the title compound was obtained according to the method described for the synthesis of **3**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 11.60−11.70 (m, 1H), 11.05 (s, 0.5H), 10.95 (s, 0.5H), 9.70 (s, 0.5H), 9.65 (s, 0.5H), 7.95−8.05 (m, 1H), 7.85−7.90 (m, 1H), 7.75 (d, J = 3.2 Hz, 1H), 7.30−7.40 (m, 2H), 7.12 (d, J = 2.1 Hz, 0.5H), 7.07 (d, J = 2.1 Hz, 0.5H), 6.80−6.90 (m, 1H), 6.35 (d, J = 5.5 Hz, 0.5H), 6.30 (d, J = 5.5 Hz, 0.5H), 6.15−6.20 (m, 1H), 3.52 (s, 1H), 3.50 (s, 1H), 2.20−2.50 (m, 8H), 2.18 (s, 1.5 H), 2.15 (s, 1.5H); Anal. ($C_{26}H_{26}ClN_7O$·2H_20) C, H, N.

[4-Chloro-3-(4-methylpiperazin-1-ylmethyl)phenyl]-[5-(2-methylamino-pyrimidin-4-yloxy)-1*H*-benzimidazol-2-yl]-amine (17). To a solution of 4-(2-methanesulfonyl-pyrimidin-4-yloxy)-benzene-1,2-diamine (**39h**; 400 mg, 1.4 mmol) in anhydrous THF (4 mL) was added CH_3NH_2 (2 M in THF, 1 mL, 2.0 mmol). The solution was heated to 80 °C for 1 h, and the mixture was allowed to cool to rt and concentrated in vacuo. The material was purified by column chromatography (0−10% MeOH/CH_2Cl_2 with 1% NH_4-OH) to yield 4-(2-methylamino-pyrimidin-4-yloxy)-benzene-1,2-diamine (300 mg, 92%), which was used directly in the next step.

To a solution of 4-(2-methylamino-pyrimidin-4-yloxy)-benzene-1,2-diamine (300 mg, 1.3 mmol) in anhydrous CH_3CN (20 mL) was added dropwise a solution of 1-(2-chloro-5-isothiocyanato-benzyl)-4-methyl-piperazine (405 mg [residual imidazole present], 1.3 mmol) in anhydrous CH_3CN (10 mL). The solution was stirred for 16 h at rt, then EDC (250 mg, 1.3 mmol) was added, and the reaction mixture was heated at 80 °C for 2 h. The mixture was allowed to cool to rt and concentrated in vacuo. The residue was dissolved in a mixture of CH_2Cl_2/MeOH (50 mL) and washed with H_2O, $NaHCO_3$ (satd), and brine. The aqueous layers were back-extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The material was purified by column chromatography (0−10% MeOH/CH_2Cl_2 with 1% NH_4-OH) followed by preparative TLC and reverse-phase HPLC (5−100% H_2O/CH_3CN with 0.1% TFA) to yield the title compound (57 mg, 9%). ^{1}H NMR (400 MHz, 325K, DMSO-d_6) δ 10.85−11.00 (bs, 1H), 9.45−9.55 (bs, 1H), 8.10 (d, J = 5.3 Hz, 1H), 7.81 (dd, J = 8.5, 2.3 Hz, 1H), 7.76 (d, J = 2.6 Hz, 1H), 7.25−7.35 (m, 2H), 7.07 (s, 1H), 6.70−6.90 (m, 2H), 5.95−6.00 (m, 1H), 3.55 (s, 2H), 2.71 (d, J = 4.6 Hz, 3H), 2.45−2.55 (m, 8H), 2.24 (s, 3H); Anal. ($C_{24}H_{27}ClN_8O$·H_2O·1.66CH_3OH) C, H, N.

[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[5-(2-methylsulfanyl-pyrimidin-4-yloxy)-1*H*-benzimidazol-2-yl]-amine (18). Starting with 4-(2-methylsulfanyl-pyrimidin-4-yloxy)-benzene-1,2-diamine (400 mg, 1.6 mmol), 13 mg (2%) of the title compound was obtained according to the method described for the synthesis of **7**. ^{1}H NMR indicates a mixture of tautomers (400 MHz, DMSO-d_6) δ 10.95−11.10 (m, 1H), 9.70 (s, 0.5 H), 9.60 (s, 0.5H), 8.40−8.45 (m, 1H), 7.80−7.90 (m, 1H), 7.70−7.78 (m, 1H), 7.25−7.40 (m, 2H), 7.05−7.18 (m, 1H), 6.75−6.90 (m, 1H), 6.55−6.70 (m, 1H), 3.55 (s, 2H), 2.30−2.50 (m, 1H), 2.20 (s, 3H); HRMS

calcd for $C_{24}H_{26}ClN_7OS$ $(M + H)^+$, 496.1681; found, 496.1682; HPLC purity = 99% (system B), 99% (system C).

4-{2-[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-1-methyl-1*H*-benzimidazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (19). Starting with 4-(3-amino-4-methylamino-phenoxy)-pyridine-2-carboxylic acid methylamide (25 mg, 0.92 mmol), 5 mg (10%) of the title compound was obtained as an off-white solid according to the method described for the synthesis of **7**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.70−8.76 (m, 1H), 8.46 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 9.2, 2.5 Hz, 1H), 7.85 (d, J = 2.6 Hz, 1 H), 7.40 (d, J = 8.4 Hz, 1H), 7.30−7.35 (m, 2H), 7.17 (d, J = 2.2 Hz, 1H), 7.10−7.14 (m, 1H), 6.88 (d, J = 8.5, 2.2 Hz, 1H), 3.74 (s, 3H), 3.51 (s, 2H), 2.75 (d, J = 4.7 Hz, 3H), 2.30−2.50 (m, 8H), 2.11 (s, 3H); HRMS calcd for $C_{27}H_{30}ClN_7O_2$ $(M + H)^+$, 519.2149; found, 520.2222; HPLC purity = 100% (system A), 99% (system B).

4-{2-[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-benzoxazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (20). To a cooled (0 °C) solution of 1-(2-chloro-5-amino-benzyl)-4-methyl-piperazine (1.87 g, 7.79 mmol) in CH_2Cl_2 (30 mL) was added 1,1′-thiocarbonyldiimidazole (2.08 g, 11.69 mmol). The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was concentrated to a small volume and partially purified by short column silica gel chromatography using 1:3 EtOAc/hexanes as the eluent to obtain 1-(2-chloro-5-isothiocyanato-benzyl)-4-methyl-piperazine. A portion of this (350 mg, 0.68 mmol) and 4-(3-amino-4-hydroxy-phenoxy)-pyridine-2-carboxylic acid methylamide (147 mg, 0.57 mmol) were used to prepare the title compound according to the method described for the synthesis of **7** (63 mg, 22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.70−8.80 (m, 1H), 8.45−8.50 (m, 1H), 7.75−7.80 (m, 2H), 7.65−7.70 (m, 1H), 7.30−7.45 (m, 3H), 7.15−7.20 (m, 1H), 6.95−7.00 (m, 1H), 3.52 (s, 2H), 2.75−2.77 (m, 3H), 2.30−2.50 (m, 8H), 2.14 (s, 3H); HRMS calcd for $C_{26}H_{27}ClN_6O_3$ $(M + H)^+$, 507.1906; found, 507.1906; HPLC purity 100% (system A), 100% (system B).

4-((2-((4-Chlorophenyl)-amino)-1,3-benzoxazol-5-yl)oxy)-*N*-methyl-2-pyridinecarboxamide (21). Starting from 4-(3-amino-5-fluoro-4-hydroxyphenoxy)-pyridine-2-carboxylic acid methylamide (100 mg, 0.39 mmol), 39 mg (25%) of the title compound was obtained according to the method described for the synthesis of **7**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.70−8.80 (m, 1H), 8.50 (d, J = 5.6 Hz, 1H), 7.75−7.80 (m, 2H), 7.62 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 5.6 Hz, 2H), 7.35−7.38 (m, 2H), 7.15−7.18 (m, 1H), 7.00 (dd, J = 8.5, 1.7 Hz, 1H), 2.78 (d, J = 4.8 Hz, 3H); Anal. ($C_{20}H_{15}ClN_4O_3$) C, H, N.

4-((2-((4-Chloro-3-((((2*S*)-1-methyl-2-pyrrolidinyl)methyl)oxy)-phenyl)amino)-1,3-benzoxazol-5-yl)oxy)-*N*-methyl-2-pyridinecarboxamide (22). To a 0 °C solution of (*S*)-4-chloro-3-(1-methyl-pyrrolidin-2-ylmethoxy)-phenylamine (3.11 g, 12.92 mmol) in CH_2Cl_2 (30 mL) was added 1,1′-thiocarbonyldiimidazole (2.87 g, 16.15 mmol). The reaction was allowed to warm to rt and stirred for 2 h. The reaction was concentrated and purified by short column silica gel chromatography using 1:3 EtOAc/hexanes as the eluent to yield (*S*)-2-((2-chloro-5-isothiocyanatophenoxy)methyl)-1-methylpyrrolidine. A portion of this (1.80 g, 6.37 mmol) and 4-(3-amino-4-hydroxy-phenoxy)-pyridine-2-carboxylic acid methylamide (1.90 g, 7.32 mmol) were used to prepare the title compound according to the method described for the synthesis of **7** (1.96 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.77 (q, J = 5.2 Hz, 1H), 8.49 (d, J = 6.4 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.57−7.58 (m, 1H), 7.32−7.41 (m, 4H), 7.14−7.16 (m, 1H), 6.96−6.99 (m, 1H), 3.91−4.02 (m, 2H), 2.92−2.98 (m, 1H), 2.76 (d, J = 5.2 Hz, 3H), 2.62−2.68 (m, 1H), 2.40 (s, 3H), 2.16 −2.28 (m, 1H), 1.90−2.02 (m, 1H), 1.58−1.74 (m, 3H); Anal. ($C_{26}H_{26}ClN_5O_4 \cdot 0.50\,H_2O \cdot 0.50CH_3OH$) C, H, N.

4-{2-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenylamino]-benzoxazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (23). Starting from 4-{2-[4-chloro-3-(2-chloro-ethoxy)-phenylamino]-benzoxazolo-5-yloxy}-pyridine-2-carboxylic acid methylamide (as a mixture with the bromo) (0.17 g, 0.36 mmol), 89 mg (50%) of the title compound was obtained as a light yellow solid according to the method described for the synthesis of **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.76−8.79 (m, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.33−7.38 (m, 4H), 7.14−7.16 (m, 1H), 6.98 (dd, J = 8.4, 2.4 Hz, 1H), 4.12 (t, J = 6.0 Hz, 2H), 2.75 (d, J = 4.8 Hz, 3H), 2.67−2.70 (m, 2H), 2.24 (s, 6H); Anal. ($C_{24}H_{24}ClN_5O_4 \cdot CH_3OH$) C, H, N.

4-{2-[4-Chloro-3-(2-diethylamino-ethoxy)-phenylamino]-benzoxazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (24). To a stirring rt solution of 4-(3-amino-4-hydroxy-phenoxy)-pyridine-2-carboxylic acid methylamide (1.51 g, 5.824 mmol) in DMF (8 mL) and CH_3CN (80 mL) was added 1-chloro-2-(2-chloro-ethoxy)-4-isothiocyanato-benzene (1.39 g, about 5.3 mmol-mixed with the bromo adduct). The reaction mixture was stirred over 4 days at rt, and EDC (1.02 g, 5.30 mmol) was added. The mixture was heated at 50 °C for 16 h and allowed to cool to rt. The solvent was evaporated, and the mixture was diluted with 1 N NaOH and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Silica gel chromatography of the crude residue yielded 4-{2-[4-chloro-3-(2-chloro-ethoxy)-phenylamino]-benzoxazolo-5-yloxy}-pyridine-2-carboxylic acid methylamide (as a mixture with the bromo). A portion of this mixture (156 mg, 0.33 mmol) was combined with excess diethylamine (0.5 mL) and DMSO (1 mL) in a sealed tube, and the mixture was heated with stirring for 2 days at 85 °C. The mixture was allowed to cool to rt and treated with 1 N NaOH and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude residue by thin layer silica gel chromatography yielded the title compound as a light yellow solid (105 mg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.76−8.79 (m, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.32−7.40 (m, 4H), 7.14−7.16 (m, 1H), 6.98 (dd, J = 8.4, 2.8 Hz, 1H), 4.08 (t, J = 5.6 Hz, 2H), 2.80−2.90 (m, 2H), 2.76 (d, J = 4.8 Hz, 3H), 2.56 (q, J = 7.2 Hz, 4H), 0.96 (t, J = 7.2 Hz, 6H). Anal. ($C_{26}H_{28}ClN_5O_4 \cdot H_2O$) C, H, N.

4-((2-((4-Chloro-3-(4-morpholinylmethyl)phenyl)amino)-1,3-benzoxazol-5-yl)oxy)-*N*-methyl-2-pyridinecarboxamide (25). Starting from 4-(3-amino-4-hydroxy-phenoxy)-pyridine-2-carboxylic acid methylamide (324 mg, 1.25 mmol), 263 mg (45%) of the title compound was obtained as an off-white solid according to the method described for the synthesis of **7**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.77 (q, J = 4.8 Hz, 1H), 8.49 (d, J = 5.6 Hz, 1H), 7.84 (d, J = 2.8 Hz, 1H), 7.77 (dd, J = 8.8, 3.2 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 10.4, 2.8 Hz, 1H), 7.14−7.16 (m, 1H), 6.97 (dd, J = 8.8, 2.0 Hz, 1H), 3.60−3.62 (m, 4H), 3.54 (s, 2H), 2.76 (d, J = 5.2 Hz, 3H), 2.42−2.47 9 m, 4H); Anal. ($C_{25}H_{24}ClN_5O_4 \cdot 0.33CH_3OH$) C, H, N.

4-{2-[4-Chloro-3-(piperidin-4-ylmethoxy)-phenylamino]-benzoxazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (26). To a cooled (0 °C) solution of 4-(5-amino-2-chloro-phenoxymethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (54 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) was added 1,1′-thiocarbonyldiimidazole (28 mg, 0.16 mmol). The reaction was allowed to warm to rt and stirred for 18 h. 4-(3-Amino-4-hydroxy-phenoxy)-pyridine-2-carboxylic acid methylamide (41 mg, 0.16 mmol) was added, and the reaction mixture was stirred an additional 16 h. EDC (45 mg, 0.24 mmol) was added, and the mixture was stirred at rt for 3 h. The reaction mixture was partially purified by prep HPLC to obtain 4-{2-chloro-5-[5-(2-methylcarbamoyl-pyridin-4-yloxy)-benzoxazol-2-ylamino]-phenoxymethyl}-piperidine-1-carboxylic acid *tert*-butyl ester. This intermediate was stirred with TFA (2 mL) at rt for 3 h and concentrated in vacuo. The residue was taken up into ethyl acetate, washed with 1 N NaOH and $NaHCO_3$ (satd), dried with Na_2SO_4, filtered, and evaporated. Purification by prep HPLC yielded the title compound as a white solid (13 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (bs, 1H), 8.76−8.82 (m ,1H), 8.50 (d, J = 5.9 Hz, 1H), 8.00−8.30 (bs, 1H), 7.58−7.64 (m, 2H), 7.32−7.42 (m, 4H), 7.15−7.18 (m, 1H), 6.99 (dd, J = 8.7, 2.4 Hz, 1H),

3.95 (d, J = 5.8 Hz, 2H), 3.24−3.30 (m, 2H), 2.54−2.84 (m, 2H), 2.75 (d, J = 4.9 Hz, 3H), 2.02−2.14 (m, 1H), 1.90−1.98 (m, 2H), 1.42−1.58 (m, 2H); HRMS calcd for $C_{26}H_{26}ClN_5O_4$ $(M + H)^+$, 508.1746; found, 508.1747; HPLC purity 99% (system A), 96% (system B).

4-{2-[4-Chloro-3-((2*S*)-1-methyl-pyrrolidin-2-ylmethoxy)-phenylamino]-benzooxazol-5-yloxy}-pyridine-2-carboxylic Acid Amide (27). Starting with 4-(3-amino-4-hydroxy-phenoxy)-pyridine-2-carboxylic acid amide (0.22 g, 0.88 mmol), 160 g (37%) of the title compound was obtained as a white solid according to the method described for the synthesis of **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.08−8.12 (m, 1H), 7.65−7.70 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.30−7.40 (m, 4H), 7.17 (dd, J = 8.4, 5.2 Hz, 1H), 6.98 (dd, J = 8.4, 2.4 Hz, 1H), 3.90−4.02 (m, 2H), 2.90−2.98 (m, 1H), 2.60−2.70 (m, 1H), 2.40 (s, 3H), 2.15−2.25 (m, 1H), 1.90−2.02 (m, 1H), 1.58−1.72 (m, 3H); Anal. ($C_{25}H_{24}ClN_5O_4$·CH_3OH) C, H, N.

***S*-[4-Chloro-3-(1-methyl-pyrrolidin-2-ylmethoxy)-phenyl]-[5-(6,7-dimethoxy-quinazolin-4-yloxy)-benzoxazol-2-yl]-amine (28).** Starting with 2-amino-4-(6,7-dimethoxyquinazolin-4-yloxy)-phenol (0.22 g, 0.70 mmol), 125 mg (32%) of the title compound was obtained as a tan solid according to the method described for the synthesis of **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.51 (s, 1H), 7.50−7.60 (m, 3H), 7.30−7.40 (m, 4H), 7.00−7.10 (m, 1H), 3.85−4.05 (m, 8H), 2.95−3.00 (m, 1H), 2.60−2.80 (m, 1H), 2.42 (s, 3H), 2.20−2.30 (m, 1H), 1.90−2.05 (m, 1H), 1.60−1.80 (m, 3H); HRMS calcd for $C_{29}H_{28}ClN_5O_5$ $(M + H)^+$, 562.1852; found, 562.1848; HPLC purity = 95% (system A), 99% (system B).

***S*-[4-Chloro-3-(1-methylpyrrolidin-2-ylmethoxy)-phenyl]-[5-(6,7-dimethoxyquinolin-4-yloxy)-benzoxazol-2-yl]-amine (29).** Starting with 2-amino-4-(2,3-dimethoxyquinolin-4-yloxy)phenol (200 mg, 0.64 mmol), 50 mg (14%) of the title compound was obtained as a tan solid according to the method described for the synthesis of **22**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.42 (d, J = 5.0 Hz, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.55 (m, 1H), 7.50 (s, 1H), 7.35−7.40 (m, 4H), 7.00 (dd, J = 7.3, 2.3 Hz, 1H), 6.40 (d, J = 5.0 Hz, 1H), 3.90−4.05 (m, 8H), 2.95−3.00 (m, 1H), 2.60−2.70 (m, 1H), 2.40 (s, 3H), 2.15−2.25 (m, 1H), 1.95−2.05 (m, 1H), 1.60−1.80 (m, 3H); HRMS calcd for $C_{30}H_{29}ClN_4O_5$ $(M + H)^+$, 560.1826; found, 561.18992; HPLC purity = 99% (system A), 99% (system B).

5-((6,7-Bis(methoxy)-4-quinolinyl)oxy)-*N*-(4-chloro-3-((4-methyl-1-piperazinyl)methyl)phenyl)-1,3-benzoxazol-2-amine (30). Starting from 2-amino-4-(6,7-dimethoxyquinolin-4-yloxy)phenol (220 mg, 0.70 mmol), 34 mg (9%) of the title compound was obtained as a tan solid according to the method described for the synthesis of **20**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.42 (d, J = 3.6 Hz, 1H), 7.80−7.85 (m, 2H), 7.60 (d, J = 8.9 Hz, 1H), 7.50 (s, 1H), 7.30−7.40 (m, 3H), 7.00−7.05 (m, 1H), 6.45 (d, J = 3.6 Hz, 1H), 3.90 (s, 6H), 3.50 (s, 2H), 2.20−2.50 (m, 8H), 2.15 (s, 3H); HRMS calcd for $C_{30}H_{30}ClN_5O_4$ $(M + H)^+$, 560.2059; found, 560.2058; HPLC purity 99% (system A), 99% (system B).

([4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[5-(quinolin-4-yloxy)-benzoxazol-2-yl]-amine) (31). Starting from 2-amino-4-(quinolin-4-yloxy)-phenol (150 mg, 0.59 mmol), 50 mg (17%) of the title compound was obtained according to the method described for the synthesis of **20**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 4.2 Hz, 1H), 8.38−8.42 (m, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.74−7.79 (m, 1H), 7.57−7.67 (m, 4H), 7.32−7.39 (m, 2H), 7.31 (d, J = 2.1 Hz, 1H), 6.95 (dd, J = 8.3, 2.8 Hz, 1H), 6.54 (d, J = 4.2 Hz, 1H), 3.65 (s, 2H), 2.50−2.70 (m, 8H), 2.30 (s, 3H); HRMS calcd for $C_{28}H_{26}ClN_5O_2$ $(M + H)^+$, 500.1848; found, 500.1847; HPLC purity 98% (system A), 94% (system B).

[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[5-(2-methylamino-pyrimidin-4-yloxy)-benzoxazol-2-yl]-amine (32). To a solution of 2-amino-4-(2-methylamino-pyrimidin-4-yloxy)-phenol (0.14 g, 0.62 mmol) in CH_3CN (30 mL) was added dropwise over 5 min a solution 1-(2-chloro-5-isothiocyanato-benzyl)-4-methyl-piperazine (0.17 g, 0.62 mmol) in CH_3CN (10 mL). The reaction mixture was stirred 18 h at rt. The reaction mixture was diluted with CH_3CN (10 mL), then EDC (0.12 g, 0.62 mmol) was added, and the mixture was heated at 80 °C for 3 h. The mixture was allowed to cool to rt and concentrated in vacuo, and the residue was dissolved in EtOAc and water. The layers were separated, and the organic layer washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by a combination of silica gel column chromatography and silica gel prep plates to obtain the title compound (125 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.12 (bs, 1H), 7.75−7.80 (m, 2H), 7.51 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 6.85−7.00 (m, 2H), 5.90−6.20 (m, 1H), 3.53 (s, 2H), 2.60−2.70 (m, 4H), 2.30−2.50 (m, 7H), 2.17 (s, 3H); Anal. ($C_{24}H_{26}ClN_7O_2$·H_2O) C, H, N.

[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[5-(6-methylamino-pyrimidin-4-yloxy)-benzoxazol-2-yl]-amine (33). Starting with 2-amino-4-(6-methylamino-pyrimidin-4-yloxy)-phenol (132 mg, 0.57 mmol), 80 mg (30%) of the title compound was obtained as a yellow solid according to the method described for the synthesis of **32**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.11 (bs, 1H), 7.76−7.80 (m, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.25−7.30 (m, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 5.74 (s, 1H), 3.52 (s, 2H), 2.74 (bs, 3H), 2.30−2.50 (m, 8H), 2.15 (s, 3H); Anal. ($C_{24}H_{26}ClN_7O_2$·H_2O·0.50CH_3OH) C,H,N.

***N*-(4-Chloro-3-(((2*S*)-1-methyl-2-pyrrolidinyl)methoxy)phenyl)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-1,3-benzoxazol-2-amine (34).** Starting with 4-(1*H*-indol-4-yloxy)-2-aminophenol (130 mg, 0.50 mmol), 79 mg (32%) of the title compound was obtained according to the method described for the synthesis of **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 10.90 (s, 1H), 8.05 (d, J = 5.8 Hz, 1H), 7.55−7.60 (m, 2H), 7.35−7.45 (m, 3H), 7.30 (d, J = 2.0 Hz, 1H), 6.95 (dd, J = 7.7, 2.0 Hz, 1H), 6.38 (d, J = 5.8 Hz, 1H), 6.20−6.25 (m, 1H), 4.00−4.05 (m, 1H), 3.92−3.97 (m, 1H), 2.92−2.98 (m, 1H), 2.62−2.70 (m, 1H), 2.40 (s, 3H), 2.16−2.25 (m, 1H), 1.90−2.04 (m, 1H), 1.58−1.78 (m, 3H); HRMS calcd for $C_{26}H_{24}ClN_5O_3$ $(M + H)^+$, 490.1640; found, 490.1642; HPLC purity = 99% (system B), 100% (system C).

***N*-(4-Chloro-3-((4-methyl-1-piperazinyl)methyl)phenyl)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-1,3-benzoxazol-2-amine (35).** Starting with 4-(1*H*-indol-4-yloxy)-2-aminophenol (0.13 g, 0.50 mmol), 116 mg (48%) of the title compound was obtained according to the method described for the synthesis of **32**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 10.85 (s, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.30−7.35 (m, 1H), 7.25 (s, 1H), 6.90−7.0 (m, 1H), 6.38 (d, J = 5.6 Hz, 1H), 6.20−6.25 (m, 1H), 3.55 (s, 2H), 2.30−2.50 (m, 8), 2.15 (s, 3H); Anal. ($C_{26}H_{25}ClN_6O_2$·0.50CH_3OH) C, H, N.

4-((2-((4-Chloro-3-(((2*S*)-1-methyl-2-pyrrolidinyl)methoxy)-phenyl)amino)-7-fluoro-1,3-benzoxazol-5-yl)oxy)-*N*-methyl-2-pyridinecarboxamide (36). Starting from 4-(3-amino-5-fluoro-4-hydroxyphenoxy)-pyridine-2-carboxylic acid methylamide (256 mg, 0.93 mmol) and 2-(2-chloro-5-isothiocyanato-phenoxymethyl)-1-methyl-pyrrolidine (249 mg, 0.88 mmol), 244 mg (53%) of the title compound was obtained according to the method described for the synthesis of **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.79 (q, J = 5.2 Hz, 1H), 8.50 (d, J = 6.0 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.39−7.42 (m, 2H), 7.29−7.32 (m, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.17−7.19 (m, 1H), 7.11−7.14 (m, 1H), 3.90−4.06 (m, 2H), 2.90−3.00 (m, 1H), 2.76 (d, J = 4.8 Hz, 3H), 2.62−2.70 (m, 1H), 2.40 (s, 3H), 2.18−2.28 (m, 1H), 1.92−2.08 (m, 1H), 1.58−1.76 (m, 3H); Anal. ($C_{26}H_{25}ClFN_5O_4$·H_2O) C, H, N.

4-{7-Chloro-2-[4-chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-benzoxazol-5-yloxy}-pyridine-2-carboxylic Acid Methylamide (37). Starting with 4-(3-amino-5-chloro-4-hydroxy-phenoxy)-pyridine-2-carboxylic acid methylamide (63 mg, 0.21 mmol), 24 mg (21%) of the title compound was obtained according to the method described for the synthesis of **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.75−8.80 (m, 1H), 8.40−8.50 (m, 1H), 7.80−7.90 (m, 1H), 7.70−7.80 (m, 1H), 7.30−7.50 (m,

3H), 7.05−7.10 (m, 2H), 3.51 (s, 2H), 2.76 (d, J = 4.8 Hz, 3H), 2.20−2.50 (m, 8H), 2.15 (s, 3H); Anal. ($C_{26}H_{26}Cl_2N_6O_3 \cdot 1.50CH_3OH$) C, H, N.

[4-Chloro-3-(4-methylpiperazin-1-ylmethyl)-phenyl]-[7-chloro-5-(quinolin-4-yloxy)-benzoxazol-2-yl]-amine (38). Starting with 2-chloro-4-(quinolin-4-yloxy)phenol (843 mg, 3.10 mmol), 844 mg of a yellow solid was obtained (as a 1:1 mixture of starting material and 2-chloro-6-nitro-4-(quinolin-4-yloxy)phenol) according to the method described for the synthesis of **59a**. This crude mixture was combined with Fe (3.2 g, excess), 6 N HCl (2 drops), water (5 mL), and EtOH (24 mL) and refluxed for 2.5 h. The hot mixture was filtered through Celite and concentrated in vacuo. The residue was partially purified by prep HPLC to give 2-amino-6-chloro-4-(quinolin-4-yloxy)phenol (31 mg, 0.10 mmol, 9%), which was dissolved into CH_3CN and subjected to the procedure described for the synthesis of **20**. The title compound was obtained as a white solid (11 mg, 21%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.65−8.70 (m, 1H), 8.32 (d, J = 8.8 Hz, 1H), 8.00−8.05 (m, 1H), 7.80−7.85 (m, 2H), 7.70−7.78 (m, 1H), 7.60−7.70 (m, 1H), 7.40−7.45 (m, 2H), 7.25−7.30 (m, 1H), 6.65−6.70 (m, 1H), 3.52 (s, 2H), 2.20−2.60 (m, 8H), 2.15 (s, 3H); HRMS calcd for $C_{28}H_{25}C_{l2}N_5O_2$ $(M + H)^+$, 534.1458; found, 534.1458; HPLC purity = 95% (system A), 95% (system B).

4-(3,4-Diamino-phenoxy)-pyridine-2-carboxylic Acid Methylamide (39a). A flask was charged with 4-(3,4-dinitro-phenoxy)-pyridine-2-carboxylic acid methylamide (0.71 g, 2.23 mmol), MeOH (40 mL), and EtOAc (80 mL). To the argon-degassed solution was added 10% Pd/C (0.20 g). The reaction was vigorously stirred for 42 h at rt under 1 atm of H_2 gas. The reaction was filtered through Celite and the solvent was removed in vacuo to obtain the title compound (71 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70−8.75 (m, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 2.8 Hz, 1H), 7.04−7.06 (m, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.27 (d, J = 2.8 Hz, 1H), 6.16 (dd, J = 8.4, 2.8 Hz, 1H), 4.76 (bs, 1H), 4.51 (bs, 2H), 2.75 (d, J = 4.4 Hz, 3H).

4-(6,7-Dimethoxyquinolin-4-yloxy)-benzene-1,2-diamine (39b). Starting with 4-(3,4-dinitrophenoxy)-6,7-dimethoxyquinoline (0.256 g, 0.74 mmol), 122 mg (57%) of the title compounds was obtained according to the method described for the synthesis of **39m**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 5.5 Hz, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.40 (d, J = 5.5 Hz, 1H), 6.35 (d, J = 2.7 Hz, 1H), 6.25 (dd, J = 8.2, 2.7 Hz, 1H), 4.40−4.80 (bm, 4H), 3.90 (m 6H).

4-(Quinolin-4-yloxy)-benzene-1,2-diamine (39c). A flask was charged with 4-(3,4-dinitro-phenoxy)-quinoline (400 mg, 1.2 mmol), and the compound was dissolved in THF. The mixture was cooled to 0 °C and AcOH (1.5 mL) and zinc dust (2.5 g, 38 mmol) were added sequentially. The mixture was allowed to warm to rt, stirred for 1 h, filtered through a pad of silica gel, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 1 M NaOH. The organic phases were dried, filtered, and evaporated to give the title compound as a brown-orange oil (210 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 5.7 Hz, 1H), 8.24−8.27 (m, 1H), 7.74−7.79 (m, 1H), 7.56−7.62 (m, 1H), 6.53−6.58 (m, 2H), 6.37 (d, J = 3.8 Hz, 1H), 6.25 (dd, J = 7.6, 2.8 Hz, 1H), 5.75 (bs, 2H), 5.50 (bs, 2H).

4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yloxy)benzene-1,2-diamine (39d). Starting with 4-(3,4-dinitro-phenoxy)-7,7a-dihydro-4a*H*-pyrrolo[2,3-*d*]pyrimidine (0.16 g, 0.53 mmol), 284 mg (118%) of the title compound was obtained according to the method described for the synthesis of **39o**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (bs, 1H), 8.25 (s, 1H), 7.30−7.35 (m, 1H), 6.50 (d, J = 7.0 Hz, 1H), 6.35 (s, 1H), 6.20−6.25 (m, 1H), 6.10−6.12 (m, 1H), 4.36−4.70 (bm, 4H).

4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-benzene-1,2-diamine (39e). Starting with 4-(3,4-dinitro-phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (0.284 g, 0.95 mmol), 190 mg (83%) of the title compound was obtained according to the method described for the synthesis of **39o**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (bs, 1H), 7.97 (d, J = 5.8 Hz, 1H), 7.24−7.28 (m, 1H), 6.51 (d, J = 8.3 Hz, 1H), 6.32 (d, J = 3.3 Hz, 1H), 6.29 (d, J = 5.8 Hz, 1H), 6.16−6.21 (m, 2H), 4.70 (bs, 2H), 4.40 (bs, 2H).

4-(3,4-Diamino-phenoxy)-pyridine (39f). Starting with 4-(3,4-dinitro-phenoxy)-pyridine (1.36 g, 5.21 mmol), 0.97 g (92%) of the title compound was obtained as a dark brown solid according to the method described for the synthesis of **39o**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32−8.38 (m, 2H), 6.75−6.83 (m, 2H), 6.51 (d, J = 8.0 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 6.14 (dd, J = 8.0, 2.4 Hz, 1H), 4.40−4.80 (bm, 4H).

4-(2-Methylsulfanyl-pyrimidin-4-yloxy)-benzene-1,2-diamine (39g). A flask was charged with 4-(3,4-dinitro-phenoxy)-2-methylsulfanyl-pyrimidine (1.00 g, 3.20 mmol) and the solid was dissolved in MeOH (10 mL). To the argon-degassed solution, a catalytic amount of Pd/C (10% by wt) was added, and the mixture was shaken under H_2 at 60 psi until the reaction was complete. The mixture was filtered through a pad of Celite and the material was purified using column chromatography (0−100% EtOAc in hexanes) to give the title compound (500 mg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 6.0 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.33 (d, J = 6.0 Hz, 1H), 6.37 (d, J = 3.0 Hz, 1H), 6.24 (dd, J = 7.5, 3.0 Hz, 1H), 2.40 (s, 3H).

4-(2-Methylsulfonyl-pyrimidin-4-yloxy)-benzene-1,2-diamine (39h). Starting with 4-(3,4-dinitro-phenoxy)-2-methylsulfonyl-pyrimidine (1.0 g, 2.9 mmol), 0.80 g (97%) of the title compound was obtained according to the method described for the synthesis of **39a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 5.4 Hz, 1H), 7.15 (d, J = 5.4 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.35−6.40 (m, 1H), 6.25 (dd, J = 8.2, 3.0 Hz, 1H), 4.80 (s, 2H), 4.50 (s, 2H), 3.30 (s, 3H).

4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carboxylic Acid Methylamide (39i). Starting from 4-(4-methylamino-3-nitrophenoxy)-pyridine-2-carboxylic acid methylamide (100 mg, 0.33 mmol), the title compound was obtained using the method described in **39a** (28 mg, 31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70−8.80 (m, 1H), 8.41 (d, J = 5.5 Hz, 1H), 7.31 (d, J = 2.5 Hz, 1H), 7.06 (dd, J = 5.5, 2.5 Hz, 1H), 6.38 (d, J = 8.0 Hz, 1H), 6.25−6.35 (m, 2H), 4.80 (s, 2H), 4.60−4.65 (m, 1H), 2.76 (d, J = 4.8 Hz, 3H), 2.72 (d, J = 5.1 Hz, 3H).

4-(3-Amino-4-hydroxyphenoxy)-pyridine-2-carboxylic Acid Methylamide (39j). Starting from 4-(4-hydroxy-3-nitrophenoxy)-pyridine-2-carboxylic acid methylamide (185 mg, 0.69 mmol), 148 mg (89%) of the title compound was obtained as a white foam according to the method described for the synthesis of **39o**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.70−8.80 (m, 1H), 8.43 (d, J = 4.8 Hz, 1H), 7.30−7.35 (m, 1H), 7.06−7.20 (m, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.30−6.40 (m, 1H), 6.10−6.20 (m, 1H), 4.82 (s, 2H), 2.76 (d, J = 4.8 Hz, 3H).

4-(3-Amino-5-fluoro-4-hydroxyphenoxy)-pyridine-2-carboxylic Acid Methylamide (39k). Starting from 4-(3-fluoro-4-hydroxy-5-nitrophenoxy)-pyridine-2-carboxylic acid methylamide (0.61 g, 1.98 mmol), 495 mg (90%) of the title compound was obtained according to the method described for the synthesis of **39o**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.70−8.80 (m, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.09−7.11 (m, 1H), 6.25 (dd, J = 11.2, 2.8 Hz, 1H), 6.20−6.21 (m, 1H), 5.21 (s, 2H), 2.76 (d, J = 5.2 Hz, 3H).

2-Amino-4-(6,7-dimethoxyquinolin-4-yloxy)phenol (39l). Starting from 4-(6,7-dimethoxyquinolin-4-yloxy)-2-nitrophenol (440 mg, 1.28 mmol), 220 mg (59%) of the title compound was obtained according to the method described for the synthesis of **39m**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (bs, 1H), 8.42 (d, J = 5.2 Hz, 1H), 7.45 (s, 1H), 7.35 (s, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.40−6.45 (m, 2H), 6.24 (dd, J = 8.8, 3.3 Hz, 1H), 4.80 (bs, 2H), 3.90 (s, 3H).

2-Amino-4-(quinolin-4-yloxy)-phenol (39m). To a cooled (0 °C) solution of 2-nitro-4-(quinolin-4-yloxy)-phenol (200 mg, 0.79 mmol) in THF (50 mL) and AcOH (0.88 mL), zinc dust (2.3 g, 35.2 mmol) was added. The mixture was stirred at rt for 1.5 h and filtered through a Celite pad. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, washed with 1 M NaOH, dried, filtered, and concentrated in vacuo to give the title compound as a

brown solid (150 mg, 86%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 9.5 Hz, 1H), 7.95 (d, J = 9.5 Hz, 1H), 7.70−7.80 (m, 1H), 7.55−7.60 (m, 1H), 6.70 (d, J = 9.5 Hz, 1H), 6.55 (d, J = 4.8 Hz, 1H), 6.40−6.45 (m, 1H), 6.20−6.30 (m, 1H), 4.80 (s, 2H).

4-(3-Amino-5-chloro-4-hydroxyphenoxy)-pyridine-2-carboxylic Acid Methylamide (39n). Starting with 4-(3-chloro-4-hydroxy-5-nitrophenoxy)-pyridine-2-carboxylic acid methylamide (394 mg, approx 1.21 mmol), 66 mg (19%) of the title compound was obtained as a brown solid according to the method described for the synthesis of **46a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80−8.90 (bs, 1H), 8.70−8.80 (m, 1H), 8.47 (d, J = 5.3 Hz, 1H), 7.35 (d, J = 2.5 Hz, 1H), 7.10−7.12 (m, 2H), 6.39 (d, J = 2.9 Hz, 1H), 6.34 (d, J = 2.9 Hz, 1H), 5.20 (bs, 2H), 2.76 (d, J = 4.9 Hz, 3H).

2-Amino-4-(2-methylamino-pyrimidin-4-yloxy)-phenol (39o). A flask was charged with 4−(2-methylamino-pyrimidin-4-yloxy)-2-nitro-phenol (0.16 g, 0.620 mmol), and the solid was dissolved in MeOH (7 mL) and EtOAc (15 mL). To the argon-degassed solution was added 10% by weight Pd/C (0.08 g). The reaction was stirred vigorously at rt under 1 atm H_2 gas for 18 h. The reaction was filtered through a Celite plug and concentrated in vacuo to yield the title compound (144 mg, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.05 (s, 1H), 6.98 (s, 1H), 6.59 (d, J = 8.4 Hz, 1H), 6.31 (s, 1H), 6.10−6.15 (m, 1H), 5.73−6.00 (m, 1H), 4.69 (s, 2H), 2.69 (d, J = 4.0 Hz, 3H).

2-Amino-4-(6-methylamino-pyrimidin-4-yloxy)-phenol (39p). Starting with 4−(6-methylamino-pyrimidin-4-yloxy)-2-nitro-phenol (0.15 g, 0.57 mmol), 133 mg (100%) of the title compound was obtained as a tan solid according to the method described for the synthesis of **39o**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.09 (s, 1H), 7.17 (q, J = 4.8 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 2.8 Hz, 1H), 6.10 (dd, J = 8.4, 2.8 Hz, 1H), 5.56 (s, 1H), 4.70 (s, 2H), 2.70 (s, 3H).

4-(1*H*-Indol-4-yloxy)-2-aminophenol (39q). Starting with 4-(1*H*-indol-4-yloxy)phenol (0.80 g, 3.53 mmol), 400 mg (41%) of 4-(1*H*-indol-4-yloxy)-2-nitrophenol was obtained according to the method described for the synthesis of **59e**. This compound (400 mg, 1.46 mmol) was subjected to the conditions used in the preparation of **39o** to yield the title compound (400 mg, 113%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 9.08 (s, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.30−7.35 (m, 1H), 6.65 (d, J = 7.4 Hz, 1H), 6.40 (d, J = 1.8 Hz, 1H), 6.35 (d, J = 5.6 Hz, 1H), 6.20−6.25 (m, 2H), 4.80 (s, 2H).

4-(3-Amino-4-hydroxy-phenoxy)-pyridine-2-carboxylic Acid Amide (39r). Starting with 4-(4-hydroxy-phenoxy)-pyridine-2-carboxylic acid amide (6.22 g, 27.0 mmol), 4-(4-hydroxy-3-nitro-phenoxy)-pyridine-2-carboxylic acid amide was obtained according to the method described for the synthesis of **59e**. A portion of this material (0.27 g, 0.98 mmol) was subjected to the conditions for the preparation of **39o** to yield the title compound (0.22 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 8.05−8.10 (m, 1H), 7.65−7.68 (m, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.08 (dd, J = 5.6, 2.8 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 6.16 (dd, J = 8.4, 3.2 Hz, 1H), 4.82 (s, 2H).

2-Amino-4-(6,7-dimethoxyquinazolin-4-yloxy)-phenol (39s). Starting with 4-(6,7-dimethoxyquinazolin-4-yloxy)-2-nitrophenol (0.48 g, 1.40 mmol), 0.22 g (51%) of the title compound was obtained according to the method described for the synthesis of **39o**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.50 (s, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 6.65 (d, J = 9.0 Hz, 1H), 6.40 (d, J = 3.0, 1H), 6.20 (dd, J = 9.0, 3.0 Hz, 1H), 4.70 (bs, 2H), 3.95 (s, 3H), 3.90 (s, 3H).

1-(2-Chloro-5-isothiocyanato-benzyl)-4-methyl-piperazine (40a). Starting from 1-(2-chloro-5-amino-benzyl)-4-methyl-piperazine (1.87 g, 7.79 mmol), 2.03 g (93%) of the title compound was obtained (as a mixture with imidazole; 3.71 g total) according to the method described for the synthesis of **40d**. The compound was used without further purification. ^{1}H NMR of the isothiocyanate (400 MHz, DMSO-d_6) δ 7.44−7.52 (m, 2H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H), 3.51 (s, 2H), 2.32−2.46 (m, 8H), 2.17 (s, 3H).

(*R*)-2-((5-Isothiocyanato-2-(trifluoromethyl)phenoxy)methyl)-1-methylpyrrolidine (40b). Starting from (*R*)-3-(1-methyl-pyrrolidin-2-ylmethoxy)-4-trifluoromethyl-phenylamine (225 mg, 0.82 mmol), 94 mg (36%) of the title compound was obtained as an off-white solid according to the method described for the synthesis of **40d**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, J = 8.1 Hz, 1H), 7.38−7.41 (m, 1H), 7.08−7.12 (m, 1H), 4.08−4.14 (m, 1H), 3.93−4.00 (m, 1H), 2.91−2.98 (m, 1H), 2.52−2.60 (m, 1H), 2.34 (s, 3H), 2.12−2.26 (m, 1H), 1.88−2.00 (m, 1H), 1.50−1.75 (m, 3H).

1-Chloro-2-(2-chloro-ethoxy)-4-isothiocyanato-benzene (40c). Starting from 4-chloro-3-(2-chloro-ethoxy)-phenylamine (2.54 mg, 11.5 mmol), 2.79 g (98%) of the title compound was obtained (as a 2:1 mixture with the bromide) as a beige solid according to the method described for the synthesis of **40d**. ^{1}H NMR of the major product (400 MHz, DMSO-d_6) δ 7.49 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 8.4, 2.4 Hz, 1H), 4.36 (t, J = 5.2 Hz, 2H), 3.95 (t, J = 5.2 Hz, 1H). ^{1}H NMR of the minor product (400 MHz, DMSO-d_6) δ 7.49 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 8.4, 2.4 Hz, 1H), 4.24 (t, J = 5.2 Hz, 2H), 3.81 (t, J = 5.2 Hz, 1H).

4-(2-Chloro-5-isothiocyanato-benzyl)-morpholine (40d). To a 0 °C solution of 4-chloro-3-morpholin-4-ylmethyl-phenylamine (0.33 g, 1.46 mmol) in 10 mL of CH_2Cl_2 was added 1,1′-thiocarbonyldiimidazole (0.39 g, 2.18 mmol). The reaction was allowed to warm to rt and stirred for 1 h. The mixture was concentrated down to a small volume and purified by short column silica gel chromatography using EtOAc as the eluent to obtain the title compound (0.36 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48−7.52 (m, 2H), 7.34−7.38 (m, 1H), 3.56−3.60 (m, 4H), 3.50−3.52 (s, 2H), 2.38−2.42 (m, 4H).

1-Chloro-4-isothiocyanato-2-(2-methoxyethoxy)benzene (40e). Starting with 1-chloro-2-(2-methoxyethoxy)-4-nitrobenzene (1.30 g, 5.60 mmol), 4-chloro-3-(2-methoxyethoxy)phenylamine was obtained by the method described for the synthesis of **46a**. A portion of this material (0.20 g, 1.00 mmol) was converted to the title compound using the procedure described for the synthesis of **40d** (180 mg, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 6.0 Hz, 1H), 7.35 (s, 1H), 7.00−7.05 (m, 2H), 4.20−4.25 (m, 2H), 3.65−3.75 (m, 2H), 3.30 (s, 3H).

5-Nitro-2-trifluoromethylanisole (41b). To a cooled (−40 °C) solution of pyridine (140 mL), trifluoromethyl iodide (from a gas cylinder that had been kept in freezer overnight) was bubbled in over a 20 min period. To this solution was added 2-iodo-5-nitroanisole (29.76 g, 107 mmol) and copper powder (81.33 g, 128 mol), and the vessel sealed. The reaction was stirred vigorously for 22 h at 140 °C. The reaction was cooled to −50 °C, and the vessel was carefully opened and poured onto ice and Et_2O and allowed to warm slowly to rt. The layers were separated, and the organic layer was washed with 1 N HCl (×3) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified on a short silica gel column (4.5:1 hexanes/CH_2Cl_2) to provide the title compound as a yellow oil (10.72 g, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85−8.00 (m, 3H), 4.02 (s, 3H).

2-Methoxy-4-nitro-1-pentafluoroethylbenzene (41c). To a cooled (0 °C) suspension of zinc powder (54.15 g, 828 mmol) in DMF (200 mL), pentafluoroethyl iodide (excess) was bubbled through while the mixture was gradually allowed to warm to rt. The reaction mixture was stirred at rt for 6 h, at which point the bubbling ceased. The solution was transferred to an addition funnel and added dropwise to a slurry of CuBr (66.57 g, 464 mmol) in DMF (200 mL) over 30 min, keeping the temperature below 30 °C. To this mixture, 2-nitro-5-iodoanisole (50.0 g, 179.2 mmol) was added and the reaction mixture was heated to 70 °C for 6 h, then allowed to cool to rt and stirred for 8 h. The reaction mixture was poured into a mixture of ice water (600 mL), 6 N HCl (500 mL), and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with water then $NaHCO_3$ (satd) and brine. The solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexanes/ethyl acetate as the eluent) to give the title

compound as a yellow oil (41.0 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70−7.86 (m, 3H), 3.85 (s, 3H).

2-Chloro-5-nitrophenol (42a). To a flask containing HOAc (78 mL) and 48% HBr (97 mL) was added 2-chloro-5-nitroanisole (9.7 g, 49.1 mmol). The mixture was heated for 18 h at 140 °C. The reaction mixture was allowed to cool to rt, diluted with ice water, and extracted with EtOAc once the ice had melted. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum to yield the title compound as yellow-light brown solid (8.3 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.32 (s, 1H), 7.74 (d, J = 1.6 Hz, 1H), 7.62−7.67 (m, 2H).

5-Nitro-2-trifluoromethylphenol (42b). A round-bottom flask was charged with 5-nitro-2-trifluoromethylanisole (10.7 g, 48.5 mmol) and pyridine hydrochloride (44.9 g, 388 mmol) and heated at 210 °C for 2 h. The reaction mixture was allowed to cool to rt and dissolved into 6 N HCl and EtOAc. The layers were separated, and the organic layer was washed 4× with 2 N HCl and once with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The title compound was obtained as a dark red solid (8.98 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 7.60−7.85 (m, 3H).

5-Nitro-2-pentafluoroethylphenol (42c). A round-bottom flask was charged with 2-methoxy-4-nitro-1-pentafluoroethylbenzene (9.35 g) and pyridine hydrochloride and heated at 210 °C for 1 h. The mixture was allowed to cool to rt and dissolved in EtOAc and 2 N HCl (>500 mL). The organic layer was washed with 2 N HCl (2×) and concentrated in vacuo. The residue was dissolved in hexanes and Et_2O and washed with 2 N HCl and then brine. The organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo, and dried under high vacuum to provide 5-nitro-2-pentafluoromethylphenol as a dark brown oil (8.77 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H), 7.60−7.70 (m, 3H).

1-Chloro-2-(2-chloro-ethoxy)-4-nitro-benzene (43a). A flask was charged with 2-chloro-5-nitrophenol (4 g, 23 mmol), 1-bromo-2-chloroethane (9 mL, 115 mmol), K_2CO_3 (8 g, 58 mmol), and DMF (50 mL) and heated at 80 °C for 18 h. The reaction mixture was allowed to cool to rt, diluted with water, and extracted several times with EtOAc. The combined organic layers were washed with 1 N NaOH and concentrated in vacuo to yield the title compound in a 2:1 ratio with the bromo adduct (3.9 g). ^{1}H NMR of the major product (400 MHz, DMSO-d_6) δ 7.92−7.94 (m, 1H), 7.84 (d, J = 3.0 Hz, 1H), 7.76 (s, 1H), 4.52 (t, J = 5.5 Hz, 2H), 4.00 (t, J = 5.5 Hz, 2H); ^{1}H NMR of the minor product (400 MHz, DMSO-d_6) δ 7.92−7.94 (m, 1H), 7.86 (d, J = 3 Hz, 1H), 7.72 (s, 1H), 4.58 (t, J = 5.5 Hz, 2H), 3.85 (t, J = 5.5 Hz, 2H).

4-(2-Chloro-5-nitro-phenoxymethyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (43b). To a cooled solution (−20 °C) of 2-chloro-5-nitro phenol (10 g, 63.497 mmol), *N*-boc-4-piperidine methanol (13.67 g, 63.49 mmol), and PPh_3 (16.63 g, 63.49 mmol) in THF (130 mL) was added a solution of DIAD (12.75 mL, 64.76 mmol) in THF (50 mL) dropwise over 1.5 h. The reaction mixture was allowed to warm to rt and stirred for 18 h. The mixture was concentrated in vacuo, and the residue was dissolved in Et_2O and washed with water and then $NaHCO_3$ (satd). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was treated with a mixture of hexanes and EtOAc (1:1), and the solid was filtered. The filtrate was evaporated and the residue was purified by silica gel column chromatography to yield the title compound as a yellow solid (5.59 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 2.5 Hz, 1H), 7.80−7.83 (m, 1H), 7.73 (d, J = 7.8 Hz, 1H), 4.08 (d, J = 6.3 Hz, 2H), 3.90−4.00 (m, 2H), 2.60−2.80 (m, 2H), 1.90−2.05 (m, 1H), 1.70−1.80 (m, 2H), 1.37 (s, 9H), 1.10−1.25 (m, 2H).

1-Nitro-3-(2-dimethylamino-ethoxy)-4-trifluoromethylbenzene (43c). A sealed tube was charged with 5-nitro-2-trifluoromethylphenol (3.48 g, 16.8 mmol), 2-(dimethylamino)ethylchloride hydrochloride (5.32 g, 37.0 mmol), K_2CO_3 (9.76 g, 70.7 mmol), tetrabutylammonium iodide (0.5 g, 1.34 mmol), acetone (114 mL), and water (33 mL). The mixture was heated at 105 °C for 24 h, and then the temperature was raised and the mixture was heated at 120 °C for 24 h. The reaction mixture was cooled to rt and partially concentrated. The solution was diluted with brine and 6 N NaOH and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography yielded the title compound as a light brown oil (1.26 g, 27%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.90−7.92 (m, 2H), 4.34 (t, J = 5.6 Hz, 2H), 2.69 (t, J = 5.6 Hz, 2H), 2.23 (s, 6H).

1-Chloro-2-(2-methoxyethoxy)-4-nitrobenzene (43d). To a solution of 5-nitro-2-chlorophenol (1.00 g, 5.80 mmol) and 2-methyloxychloroethane (2.60 mL, 28.8 mmol) in DMF (20 mL) was added K_2CO_3 (2.40 g, 17.4 mmol). The suspension was heated at 80 °C for 18 h. After cooling to rt, the mixture was filtered, the salts were washed with EtOAc, and the solvent was concentrated in vacuo. The residue was dissolved in EtOAc, washed with 1 N NaOH and water, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified on silica gel using a hexanes/EtOAc gradient (100/0 to 50/50) to give the title compound (1.3 g, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 2.6 Hz, 1H), 7.85 (dd, J = 9.1, 2.6 Hz, 1H), 7.75 (d, J = 9.1 Hz, 1H), 4.35−4.40 (m, 2H), 3.70−3.75 (m, 2H), 3.35 (s, 3H).

4-Chloro-3-(2-chloro-ethoxy)-phenylamine (44a). To an argon-degassed solution of 1-chloro-2-(2-chloro-ethoxy)-4-nitro-benzene (2.9 g, <12.5 mmol due to contamination with the bromide) in EtOAc (50 mL) was added Pd/C (10% by wt, 1 g). The reaction was stirred under H_2 for 18 h, then filtered through Celite, and concentrated in vacuo to yield the title compound (as a mixture with the bromo adduct) (2.54 g, approx 92%). ^{1}H NMR of the major product (400 MHz, DMSO-d_6) δ 7.01 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 2.8 Hz, 1H), 6.19 (dd, J = 8.4, 2.8 Hz, 1H), 5.70 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.91 (t, J = 5.2 Hz, 2H). ^{1}H NMR of the minor product (400 MHz, DMSO-d_6) δ 7.01 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 2.8 Hz, 1H), 6.19 (dd, J = 8.4, 2.8 Hz, 1H), 5.70 (bs, 2H) 4.23 (t, J = 5.2 Hz, 2H), 3.77 (t, J = 5.2 Hz, 2H).

4-(5-Amino-2-chloro-phenoxymethyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (44b). Starting from 4-(2-chloro-5-nitro-phenoxymethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (1.00 g, 2.69 mmol), 54 mg (6%) of the title compound was obtained according to the method described for the synthesis of **46a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 (d, J = 8.7 Hz, 1H), 6.28 (d, J = 2.4 Hz, 1H), 6.10 (dd, J = 8.8, 2.4 Hz, 1H), 3.95−4.00 (m, 2H), 5.20 (s, 2H), 3.75 (d, J = 6.3 Hz, 2H), 2.60−2.80 (m, 2H), 1.80−1.95 (m, 1H), 1.70−1.80 (m, 2H), 1.37 (s, 9H), 1.10−1.20 (m, 2H).

3-(2-Dimethylamino-ethoxy)-4-trifluoromethylaniline (44c). A flask was charged with 1-nitro-3-(2-dimethylamino-ethoxy)-4-trifluoromethylbenzene (1.26 g, 4.51 mmol) and dissolved in MeOH (50 mL). To the nitrogen-degassed solution was added 10% Pd/C (0.10 g). The reaction was stirred vigorously at rt under 1 atm of H_2 gas for 18 h. The reaction was filtered through Celite and concentrated in vacuo to yield the title compound as a gray solid (1.03 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 (d, J = 7.7 Hz, 1H), 6.27 (s, 1H), 6.13 (d, J = 7.7 Hz, 1H), 5.78 (s, 2H), 3.99 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.19 (s, 3H).

3-(2-Pyrrolin-1-yl-ethoxy)-5-trifluoromethyl-phenylamine (44d). A flask charged with 1-methoxy-3-nitro-5-trifluoromethyl-benzene (10 g, 45.2 mmol) and pyridine·HCl (41.8 g) was heated at 210 °C open to the air. After 2.5 h, the reaction mixture was allowed to cool to rt and partitioned between 1 N HCl and EtOAc. The organic portion was washed with 1 N HCl and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to form 3-nitro-5-trifluoromethylphenol (42b) as an off-white solid. A portion of this material (2.00 g, 9.66 mmol) was combined with 1-(2-chloroethyl)pyrrolidine hydrochloride (3.40 g, 19.3 mmol), K_2CO_3 (5.34 g, 38.64 mmol), and DMF (30 mL) and heated at 90 °C for 3 d. The reaction mixture was allowed to cool to rt, taken up in EtOAc, and washed with 2 N NaOH and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The aqueous layer was acidified, extracted with EtOAc, dried with $MgSO_4$, filtered, concentrated in vacuo, and combined with the other portion. The crude 1-[2-(3-nitro-5-trifluoromethyl-phenoxy)ethyl]-pyrrolidine was reduced to the amine following the procedure outlined for **58e**. The title compound was obtained as a tan solid (560 mg, 21% over 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.41 (s, 1H), 6.32 (s, 1H), 6.28

(s, 1H), 5.55 (s, 2H), 3.98 (t, $J = 5.5$ Hz, 2H), 2.72 (t, $J = 5.9$ Hz, 2H), 2.50−2.55 (m, 4H), 1.60−1.68 (m, 4H).

1-(2-Chloro-5-nitro-benzyl)-4-methyl-piperazine (45a). To a rt solution of 2-chloro-5-nitrobenzaldehyde (3.28 g, 17.7 mmol) and 1-methylpiperazine (1.77 g, 17.7 mmol) in CH_2Cl_2 (60 mL) was added $NaBH(OAc)_3$ (5.24 g, 24.7 mmol). The reaction mixture was stirred overnight at rt. The mixture was allowed to cool to rt, and 2 N NaOH (150 mL) was added and the mixture was stirred for 10 min. The reaction mixture was diluted with CH_2Cl_2 and additional 2 N NaOH. The layers were separated, the CH_2Cl_2 layer was washed with 2 N NaOH, and the aqueous layers were back-extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were extracted with 2 N HCl, which was then basified to pH > 12 by treatment with solid NaOH. This aqueous layer was extracted with EtOAc, and the EtOAc layers were combined, washed with a mix of brine and 2 N NaOH, dried over Na_2SO_4, filtered, and concentrated in vacuo. The title compound was isolated as an amber oil (4.24 g, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (d, $J = 3.0$ Hz, 1H), 8.11 (dd, $J = 8.7$, 3.3 Hz, 1H), 7.72 (d, $J = 8.7$ Hz, 1H), 3.62 (s, 2H), 2.42−2.50 (m, 4H), 2.30−2.40 (m, 4H), 2.16 (s, 3H).

4-(2-Chloro-5-nitro-benzyl)-morpholine (45b). Starting from 2-chloro-5-nitrobenzaldehyde (6.14 g, 33.0 mmol), 5.96 g (70%) of the title compound was obtained as a yellow solid according to the method described for the synthesis of **45a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, $J = 3.2$ Hz, 1H), 8.12 (dd, $J = 8.8$, 3.2 Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 3.64 (s, 2H), 3.57−3.60 (m, 4H), 2.43−2.46 (m, 4H).

1-(2-Chloro-5-amino-benzyl)-4-methyl-piperazine (46a). To a solution of 1-(2-chloro-5-nitro-benzyl)-4-methyl-piperazine (1.04 g, 3.86 mmol) in EtOH (30 mL) was added $SnCl_2$ (2.2 g, 11.6 mmol), and the reaction mixture was heated at 70 °C for 4.5 h. An additional amount of $SnCl_2$ (0.7 g, 3.7 mmol) was added, and the reaction was heated at 80 °C for 1 h. The reaction was allowed to cool to rt and quenched with 1 N aqueous K_2CO_3. The white slurry was filtered through a Celite plug, the ethanol was evaporated, and the resulting aqueous suspension was diluted with EtOAc and 1 N NaOH. The layers were separated, and the organic layer was washed with a brine/1 N NaOH mixture. The aqueous layers were back-extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the title compound as a light orange solid (793 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.97 (d, $J = 8.4$ Hz, 1H), 6.66 (s, 1H), 6.41 (d, $J = 8.4$ Hz, 1H), 5.18 (s, 2H), 3.32 (s, 2H), 2.28−2.42 (m, 8H), 2.13 (s, 3H).

4-Chloro-3-morpholin-4-ylmethyl-phenylamine (46b). Starting from 4-(2-chloro-5-nitro-benzyl)-morpholine (5.96 g, 23.2 mmol), 2.60 mg (49%) of the title compound was obtained as a light orange solid according to the method described for the synthesis of **46a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.98 (d, $J = 8.4$ Hz, 1H), 6.80 (d, $J = 2.8$ Hz, 1H), 6.42 (dd, $J = 8.4$, 2.8 Hz, 1H), 5.18 (s, 2H), 3.54−3.58 (m ,4H), 3.37 (s, 2H), 2.35−2.39 (m, 4H).

(*S*)-2-(2-Chloro-5-nitro-phenoxymethyl)-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (47a). To a cooled solution (−15 °C) of 2-chloro-5-nitrophenol (5.06 g, 29.17 mmol), (*S*)-(−)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol (5.87 g, 29.17 mmol), and triphenylphosphine (7.65 g, 29.17 mmol) in THF (50 mL) was added a solution of DIAD (6.02 g, 29.75 mmol) in THF dropwise over 75 min. Upon the complete addition, the reaction mixture was allowed to warm to rt and stirred for 18 h. The mixture was concentrated in vacuo, and the residue was treated with a mixture of Et_2O and hexanes. The suspension was sonicated and the solid was filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by silica gel column chromatography using 7% EtOAc in hexanes to yield the title compound as a thick yellow oil (8.94 g, 97%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91−7.96 (m, 1H), 7.80−7.86 (m, 1H), 7.72−7.76 (m, 1H), 4.16−4.30 (m, 2H), 4.02−4.10 (m, 1H), 3.24−3.30 (m, 2H), 1.90−2.10 (m, 3H), 1.74−1.84 (m, 1H), 1.36 (s, 9H).

(*R*)-2-(5-Nitro-2-trifluoromethyl-phenoxymethyl)-1-(*tert*-butoxycarbonyl)pyrrolidine (47b). To a cooled solution (−20 °C) of 5-nitro-2-trifluoromethylphenol (5.50 g, 26.55 mmol), (*R*)-(+)-(*tert*-butoxy-carbonyl)-2-pyrrolidinemethanol (5.34 g, 26.55 mmol), and PPh_3 (6.96 g, 26.55 mmol) in THF (46 mL) was added a solution of DEAD (4.71 g, 27.08 mmol) in THF (23 mL) dropwise over 1.5 h. The reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction was concentrated in vacuo and treated with a small mixture of hexanes and Et_2O. After sonication, the solids were filtered off, and the filtrate was concentrated in vacuo. The crude mixture was dissolved in a small amount of EtOAc, then diluted with hexanes, and washed with 0.1 N HCl, 2 N NaOH, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using 5% EtOAc in hexanes as the eluent to yield the title compound as a light yellow oil (6.36 g, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85−8.05 (m, 3H), 4.20−4.35 (m, 2H), 4.00−4.10 (m, 1H), 3.20−3.30 (m, 2H), 1.70−2.05 (m, 4H), 1.37 (s, 9H).

(*R*)-2-(5-Nitro-2-pentafluoroethyl-phenoxymethyl)-1-(*tert*-butoxycarbonyl)pyrrolidine (47c). A flask was charged with 5-nitro-2-pentafluoroethyl-phenol (945.0 mg, 3.7 mmol), PPh_3 (965.0 mg, 3.7 mmol), *R*-(+)-(1-*tert*-butoxycarbonyl)-2-pyrrolidine-methanol (740 mg, 3.7 mmol), and THF (9 mL). The mixture was stirred to dissolve the solids and cooled to −20 °C. DIAD (738 μL, 3.8 mmol) in THF (4 mL) was added over 2 h, keeping the reaction temperature between −10 to −20 °C. The reaction was allowed to warm to rt and stirred for 19 h. The THF was concentrated in vacuo, and the crude mixture was dissolved in ethyl acetate, washed with water and brine, dried with $MgSO_4$, filtered, and evaporated. The mixture was purified by column chromatography using EtOAc/hexanes as the eluent. The title compound was obtained as a viscous liquid (937 mg, 58%). ^{1}H NMR (rotamers) (400 MHz, DMSO-d_6) δ 8.00−8.05 (m, 1H), 7.80−7.95 (m, 2H), 4.20−4.30 (m, 2H), 4.00−4.10 (m, 1H), 3.20−3.20 (m, 2H), 1.70−2.00 (m, 4H), 1.36−1.38 (m, 9H).

(*S*)-2-(2-Chloro-5-nitro-phenoxymethyl)-pyrrolidine (48a). (*S*)-2-(2-Chloro-5-nitro-phenoxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (6.94 g, 19.45 mmol) was stirred in CH_2Cl_2 (30 mL) and TFA (20 mL) for 3 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in 0.1 N HCl. The solution was basified to pH > 12 with solid NaOH and extracted with EtOAc (×3). The organic layers were combined, washed with 1 N NaOH and then a mixture of brine and 1 N NaOH, dried over Na_2SO_4, filtered, and concentrated to dryness. The title compound was obtained as a yellow solid (4.82 g, 97%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87−7.90 (m, 1H), 7.80−7.84 (m, 1H), 7.30 (d, $J = 8.8$ Hz, 1H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.43−3.49 (m, 1H), 2.79−2.84 (m, 2H), 1.47−1.90 (m, 4H).

(*R*)-2-((5-Nitro-2-(trifluoromethyl)phenoxy)methyl)-pyrrolidine (48b). To a solution of (*R*)-*tert*-butyl 2-((5-nitro-2-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate (6.36 g, 16.29 mmol) in CH_2Cl_2 (20 mL), TFA (20 mL) was added. After stirring for 1 h at rt, the mixture was concentrated in vacuo and treated with 6 N NaOH until pH 10. The mixture was taken up into ethyl acetate and washed with brine, and the organic layer was dried over Na_2SO_4, filtered, and evaporated. The title compound was obtained as a dark yellow oil (4.16 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.87−7.92 (m, 2H), 4.05−4.15 (m, 2H), 3.40−3.50 (m, 1H), 3.31 (bs, 1H), 2.47−2.50 (m, 2H), 1.80−1.89 (m, 1H), 1.58−1.77 (m, 2H), 1.46−1.56 (m, 1H).

(*R*)-2-(5-Nitro-2-pentafluoroethyl-phenoxymethyl)-pyrrolidine (48c). To a solution of 2-(5-nitro-2-pentafluoroethyl-phenoxymethyl)-1-(*tert*-butoxycarbonyl)pyrrolidine (727 mg, 1.77 mmol) in CH_2Cl_2 (5 mL), TFA (2.5 mL) was added and stirred at rt for 1 h. The mixture was diluted with CH_2Cl_2 (20 mL) and neutralized with satd $NaHCO_3$ and then 2 N NaOH. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to yield the title compound as a yellow solid (603 mg, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (bs, 1H), 7.97−8.04 (m, 1H), 7.89−7.94 (m, 1H), 4.45−4.50 (m, 1H), 4.35−4.40

(m, 1H), 3.85−3.95 (m, 1H), 3.10−3.25 (m, 2H), 2.05−2.18 (m, 1H), 1.70−2.00 (m, 3H).

(*S*)-2-(2-Chloro-5-nitro-phenoxymethyl)-1-methylpyrrolidine (49a). To a solution of (*S*)-2-(2-chloro-5-nitro-phenoxymethyl)-pyrrolidine (4.82 g, 18.77 mmol) in CH_3CN (167 mL) was added 37% aqueous formaldehyde (7.58 mL) and $NaCNBH_3$ (1.887 g, 30.03 mmol) at rt. The mixture was stirred at rt for 1 h, with the reaction pH adjusted every 10 min to about 7 by adding small amounts of HOAc. The reaction mixture was concentrated in vacuo and dissolved in 2 N NaOH (aq) and Et_2O. The layers were separated, and the organic layer was washed with 2 N NaOH, and extracted with 1 N HCl. The combined acidic aqueous layers were basified to pH > 12 with solid NaOH and extracted with EtOAc (×3). The EtOAc layers were combined and washed with 2 N NaOH and a mixture of brine and 2 N NaOH. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the title compound (3.42 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89−7.91 (m, 1H), 7.80−7.84 (m, 1H), 7.71−7.74 (m, 1H), 4.12−4.14 (m, 2H), 2.93−2.98 (m, 1H), 2.60−2.70 (m, 1H), 2.40 (s, 3H), 2.18−2.40 (m, 1H), 1.90−2.0 (m, 1H), 1.60−1.76 (m, 3H).

(*R*)-1-Methyl-2-((5-nitro-2-(trifluoromethyl)phenoxy)methyl)-pyrrolidine (49b). To a solution of (*R*)-2-((5-nitro-2-(trifluoromethyl)phenoxy)methyl)pyrrolidine (4.16 g, 14.33 mmol) in CH_3CN (128 mL), formaldehyde (5.8 mL, 37% aqueous) was added and the mixture was stirred. Sodium cyanoborohydride (1.44 g, 22.9 mmol) was added (exotherm observed), and the reaction was stirred at rt. The pH was monitored every 15 min and adjusted to ∼7 with AcOH. After 45 min, the mixture was concentrated in vacuo and the residue was dissolved in Et_2O and washed with 6 N NaOH, 1 N NaOH, and 2 N HCl (3×). The acid washings were combined, adjusted to ∼pH 10 with solid Na_2CO_3, and extracted with EtOAc (×2). The EtOAc fractions were combined, dried with Na_2SO_4, and purified with flash chromatography (SiO_2, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH) to afford the title compound (3.16 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80−8.00 (m, 3H), 4.00−4.15 (m, 1H), 4.20−4.30 (m, 1H), 2.90−3.00 (m, 1H), 2.60−2.70 (m, 1H), 2.37 (S, 3H), 2.10−2.20 (m, 1H), 1.80−2.00 (m, 1H), 1.50−1.75 (m, 3H).

(*R*)-1-Methyl-2-(5-nitro-2-pentafluoroethyl-phenoxymethyl)-pyrrolidine (49c). To a solution of 2-(5-nitro-2-pentafluoroethyl-phenoxymethyl)-pyrrolidine (603.0 mg, 1.8 mmol) and formaldehyde (37% in water, 1 mL) in CH_2Cl_2 (25 mL), $NaBH(OAc)_3$ (600 mg, 2.8 mmol) was added. The mixture was stirred at rt for 15 h. The reaction mixture was quenched with water, and the organic layer was washed with 2 N NaOH, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography to give the title compound as a yellow solid (455 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.90−7.94 (m, 1H), 7.84−7.85 (m, 1H), 4.24−4.30 (m, 1H), 3.98−4.04 (m, 1H), 2.90−2.98 (m ,1 H), 2.54−2.62 (m, 1H), 2.34 (s, 3H), 2.16−2.22 (m, 1H), 1.90−2.00 (m, 1H), 1.56−1.72 (m 3H).

(*S*)-4-Chloro-3-(1-methyl-pyrrolidin-2-ylmethoxy)-phenylamine (50a). A flask charged with (*S*)-2-(2-chloro-5-nitro-phenoxymethyl)-pyrrolidine (3.42 g, 12.63 mmol), $SnCl_2$ (7.19 g, 37.9 mmol), and EtOH (45 mL) was heated at 75 °C for 11 h. The reaction mixture was allowed to cool to rt, treated with 15 mL 1 N K_2CO_3, and stirred 40 min. The suspension was filtered through Celite and the ethanol was evaporated. The remaining aqueous solution was diluted with 1 N NaOH and EtOAc. The layers were separated, and the organic layer was washed with 1 N NaOH and a mixture of brine and 1 N NaOH. The aqueous layers were extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the title compound as a brown solid (2.77 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93−6.95 (m, 1H), 6.29−6.30 (m, 1H), 6.08−6.11 (m, 1H), 5.20 (s, 2H), 3.75−3.85 (m, 2H), 2.91−2.94 (m, 1H), 2.53−2.61 (m, 1H), 2.37 (s, 3H), 2.14−2.21 (m, 1H), 1.88−1.98 (m, 1H), 1.63−1.70 (m, 2H), 1.53−1.57 (m, 1H).

(*R*)-3-((1-Methylpyrrolidin-2-yl)methoxy)-4-(trifluoromethyl)-benzenamine (50b). To a degassed solution of (*R*)-1-methyl-2-((5-nitro-2-(trifluoromethyl)phenoxy)methyl)pyrrolidine (3.16 g, 10.89 mmol) in dioxane (80 mL) and methanol (80 mL), Pd/C (10 wt %, 650 mg) was added. The mixture was stirred under H_2 for several days until the starting material was consumed. The reaction mixture was filtered through Celite and concentrated in vacuo to yield the title compound as a light yellow solid (2.98 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (d, J = 8.4 Hz, 1H), 6.25−6.30 (m, 1H), 6.13 (dd, J = 8.4, 1.6 Hz, 1H), 5.75 (bs, 2H), 3.88−3.94 (m, 1H), 3.70−3.88 (m, 1H), 2.90−2.97 (m, 1H), 2.50−2.58 (m, 1H), 2.33 (s, 3H), 2.13−2.22 (m, 1H), 1.88−1.98 (m, 1H), 1.62−1.72 (m, 2H), 1.50−1.58 (m, 1H).

(*R*)-1-Methyl-2-(5-amino-2-pentafluoroethyl-phenoxymethyl)-pyrrolidine (50c). Starting from (*R*)-1-methyl-2-(5-nitro-2-pentafluoroethyl-phenoxymethyl)-pyrrolidine (455 mg, 1.28 mmol), 313 mg (75%) of the title compound was obtained according to the method described for the synthesis of **58e**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, J = 8.5 Hz, 1H), 6.28 (d, J = 1.5 Hz, 1H), 6.19 (dd, J = 8.5, 1.8 Hz, 1H), 5.79 (s, 2H), 3.90−3.95 (m, 1H), 3.60−3.70 (m, 1H), 2.90−2.95 (m, 1H), 2.32 (s, 3H), 2.15−2.20 (m, 1H), 1.90−2.00 (M, 1H), 1.60−1.70 (m, 2H), 1.50−1.60 (m, 1H).

4-(3,4-Dinitrophenoxy)pyridine-2-carboxylic Acid Methylamide (52a). A 50 mL flask was charged with 3,4-dinitrophenol (12.3 g, 66.8 mmol) and 4-chloro-pyridine-2-carboxylic acid methylamide[20] (**53**; 7.79 g, 45.7 mmol) and fitted with a running water condenser. The mixture was heated at 150 °C for 1 h and at 170 °C for 16 h. The flask was allowed to cool to rt, and the crude mixture was dissolved in CH_2Cl_2 and 2 N NaOH (aq). The layers were separated, and the organic layer was washed with a mix of brine and 2 N NaOH. The aqueous layers were back-extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using a hexanes to hexanes/EtOAc gradient to yield the title compound (93.5 mg, 15%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.80−8.88 (m, 1H), 8.63 (d, J = 5.7 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.70 (dd, J = 9.0, 2.4 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.40−7.43 (m, 1H), 2.81 (d, J = 4.5 Hz, 3H).

4-(3,4-Dinitrophenoxy)-6,7-dimethoxyquinoline (52b). A flask was charged with 6,7-dimethoxy-4-chloroquinoline (0.35 g, 1.6 mmol) and 3,4-dinitrophenol (0.85 g, 4.6 mmol) and heated at 150 °C for 4 h. The reaction mixture was allowed to cool at rt suspended in methanol. The suspension was stirred with methanol for 3 h at which point the precipitate was filtered and washed with fresh methanol to afford the title compound (256 mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J = 6.3 Hz, 1H), 8.65 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 7.98 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 7.34 (d, J = 6.3 Hz, 1H), 4.03 (s, 3H), 3.95 (s, 3H).

4-(3,4-Dinitro-phenoxy)-quinoline (52c). A flask charged with 4-chloroquinoline (4.3 g, 26.3 mmol) and 3,4-dinitrophenol (4.5 g, 24.4 mmol) was heated (neat) at 150 °C for 30 min. The mixture was allowed to cool to rt, and the residue was dissolved in CH_2Cl_2, washed with 2 M NaOH, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in EtOAc and filtered through a pad of silica gel, and the solvent was concentrated in vacuo to give the title compound as a brown solid (2.6 g, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 5.6 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.18−8.21 (m, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.83−7.88 (m, 1H), 7.64−7.73 (m, 2H), 7.20 (d, J = 5.6 Hz, 1H).

4-(3,4-Dinitro-phenoxy)-7,7a-dihydro-4a*H*-pyrrolo[2,3-*d*]pyrimidine (52d). A flask was charged with 4-chloro-7,7a-dihydro-4a*H*-pyrrolo[2,3-*d*]pyrimidine (1.66 g, 10.8 mmol), 3,4-dinitrophenol (2.4 g, 13 mmol), and a TFA/TEA mixture (1.1 mL), and the reaction mixture was heated at 150 °C for 2 h. The mixture was allowed to cool to rt and a green solid formed. This material was purified on silica gel using a hexane/EtOAc gradient (100/0 to 50/50) to give the title compound (460 mg, 14%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36−8.38 (m, 2H), 8.34 (s, 1H), 8.30 (d, J = 2.9 Hz, 1H), 7.90 (dd, J = 8.7, 2.9 Hz, 1H), 7.56−7.89 (m, 1H), 6.73−6.76 (m, 1H).

4-(3,4-Dinitro-phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (52e). To cooled solution of $POCl_3$ (50 mL) was added 1*H*-pyrrolo[2,3-*b*]-pyridine 7-oxide[21] (6.60 g, 55.0 mmol) in portions. Upon complete addition, the mixture was heated to reflux for 5 h and allowed to cool to rt. The $POCl_3$ was evaporated under high vacuum with gentle heating (40−50 °C) to give a black residue. The residue was diluted with water (50 mL), and the pH was adjusted to 8−9 with Na_2CO_3 (first with solid, and then a saturated aqueous solution). The resulting precipitate was collected by filtration, washed with cold H_2O, and dried in a vacuum oven (50 °C) to give 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine as a tan powder (7.7 g, regioisomeric mixture). A portion of this mixture (0.85 g, 5.50 mmol) was combined with 3,4-dinitrophenol (1.23 g, 6.7 mmol), and the mixture was heated at 150 °C for 8 h. The reaction mixture was allowed to cool to rt, and the resulting solid was dissolved in 12 N NaOH and CH_2Cl_2. The aqueous layer was extracted several times with CH_2Cl_2. The insoluble material was solubilized in acetone, and the acetone solution was diluted with CH_2Cl_2 and washed with water. The combined CH_2Cl_2 layers were dried and concentrated in vacuo. The crude material was purified on silica gel using a CH_2Cl_2/EtOH gradient (100/0 to 90/10) to yield the title compound (350 mg, 21%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (bs, 1H), 8.23−8.29 (m, 2H), 7.99 (d, J = 2.9 Hz, 1H), 7.46−7.49 (m, 2H), 6.89 (d, J = 5.5 Hz, 1H), 6.25−6.35 (m, 1H).

(3,4-Dinitro-phenoxy)-pyridine (52f). A flask charged with 4-chloropyridine (2.45 g, 21.5 mmol) and 3,4-dinitrophenol (4.56 g, 247 mmol) was fitted with a condenser and heated (open to the air) at 145 °C. After 45 min, 4 N HCl/dioxane (2.1 mL) was added, and the mixture was heated for an additional 25 min and allowed to cool to rt. The material was dissolved in a mixture of EtOAc and 0.5 N HCl/water, and the aqueous layer was basified with 6 N NaOH. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound as a beige solid (1.36 g, 21%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58−8.62 (m, 2H), 8.32 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.63 (dd, J = 8.8, 2.4 Hz, 1H), 7.22−7.26 (m, 2H).

4-(3,4-Dinitro-phenoxy)-2-methylsulfanyl-pyrimidine (52g). A flask charged with 3,4-dinitrophenol (6.10 g, 38.0 mmol) and 2-thiomethyl-4-chloro-1,2-pyrimidine (7.02 g, 38.0 mmol) was heated at 150 °C for 2 h. The mixture was allowed to cool to rt, and the resulting solid was finely ground and washed several times with methyl-*t*-butylether. The solid was suspended in 2 N NaOH, recovered by filtration, washed with water and dried under vacuum over P_2O_5 to give the title compound (11.26 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 5.2 Hz, 1H), 8.37 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 2.6 Hz, 1H), 7.88 (dd, J = 9.0, 2.6 Hz, 1H), 7.02 (d, J = 5.2 Hz, 1H), 2.35 (s, 3H).

4-(3,4-Dinitro-phenoxy)-2-methylsulfonyl-pyrimidine (52h). To a cooled solution (0 °C) of 4-(3,4-dinitro-phenoxy)-2-methylsulfanyl-pyrimidine (0.50 g, 1.60 mmol) in CH_2Cl_2 (100 mL) was added *m*-CPBA (0.70 g, 4.00 mmol). The solution was allowed to warm to rt and stirred for 16 h. The reaction mixture was washed with satd $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound (0.43 g, 78%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.03 (d, J = 5.8 Hz, 1H), 8.40−8.42 (m, 2H), 7.98 (dd, J = 9.2, 2.5 Hz, 1H), 7.65 (d, J = 5.8 Hz, 1H), 3.30 (s, 3H).

4-(4-Amino-3-nitro-phenoxy)-pyridine-2-carboxylic Acid Methylamide (54). A solution of 4-amino-3-nitrophenol (97.6 g, 633 mmol) in DMSO (39 g) was treated with KO*t*-Bu (71.0 g, 633 mmol), and the mixture was stirred at rt for 2 h. The contents of the flask were treated with 4-chloro-*N*-methyl-2-pyridine-2-carboxylic acid methylamide (90 g, 527.5 mmol) and K_2CO_3 (38.6 g, 460 mmol) and heated at 110 °C for 16 h. To the stirred mixture, water (200 mL) was added slowly. The precipitate was filtered, washed with water (400 mL), and dried in a vacuum oven overnight to give the title compound as a purple solid (190 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80−8.82 (m, 1H), 8.49 (d, J = 5.7 Hz, 1H), 7.90 (s, 1H), 7.78 (s, 2H), 7.35−7.40 (m, 2H), 7.13−7.16 (m, 2H), 2.80 (s, 3H).

4-(4-Methylamino-3-nitrophenoxy)-pyridine-2-carboxylic Acid Methylamide (55). To a cooled (0 °C) flask containing CH_2Cl_2 (18 mL) and 4-(4-amino-3-nitro-phenoxy)-pyridine-2-carboxylic acid methylamide (1.0 g, 3.5 mmol), trifluoroacetic anhydride (0.93 mL, 6.59 mmol) was added dropwise over 15 min and the mixture was stirred for 45 min. To this cooled solution, tetrabutylammonium chloride (0.48 g, 1.73 mmol), dimethyl sulfate (0.66 mL, 6.94 mmol), and 50% NaOH/water (by wt, 14 mL) were added. The mixture was allowed to warm to rt and stirred 16 h. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The title compound was obtained as an orange solid after crystallization from 3:1 EtOH/water (0.87 g, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90−8.95 (m, 1H), 8.65 (d, J = 5.7 Hz, 1H), 8.35−8.45 (m, 1H), 8.04 (d, J = 2.8 Hz, 1H), 7.67 (dd, J = 9.4, 2.7 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.27−7.35 (m, 2H), 3.14 (s, 3H), 2.92 (s, 3H).

4-Benzyloxy-3-chlorophenol (56c).[22] To a solution of 4-benzyloxy-3-chlorobenzaldehyde (4 g, 16.2 mmol) in CH_2Cl_2 (65 mL), *m*-CPBA (3.63 g, 77% max, 21.05 mmol) was added, and the reaction mixture was stirred at rt for 5 days. The mixture was washed with a $Na_2S_2O_3$ solution and then $NaHCO_3$ (satd) and concentrated in vacuo. The residue was suspended in MeOH (150 mL), NaOMe (0.5 M in MeOH, 60 mL) was added, and the mixture was stirred for 1 h. The mixture was concentrated, and the residue was dissolved in water and extracted with a mixture of Et_2O/EtOAc. The aqueous layer was acidified and extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered, and evaporated. The mixture was purified by column chromatography using CH_2Cl_2 as the eluent to yield the title compound as an off-white solid (3.32 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.27−7.44 (m, 5H), 7.02 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 2.9 Hz, 1H), 6.65 (dd, J = 8.8, 2.9 Hz, 1H).

4-(4-Benzyloxy-phenoxy)-pyridine-2-carboxylic Acid Methylamide (57a). To a stirred slurry of NaH (2.24 g of 60% oil dispersion, 55.9 mmol) in DMF (40 mL) was added 4-benzyloxyphenol (11.2 g, 55.9 mmol). The mixture was stirred at rt for 10 min, followed by addition of 4-chloro-pyridine-2-carboxylic acid methylamide (3.18 g, 18.6 mmol). The reaction mixture was stirred at rt for 5 min, then heated to 75 °C for 2 h, and finally at 85 °C for 6 h. The reaction was allowed to cool to rt, quenched with saturated aqueous $NaHCO_3$, then diluted with Et_2O and 6 N NaOH. The layers were separated, and the organic layer was washed with 6 N NaOH and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the title compound as a light salmon-colored solid (6.45 g, 103%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66−8.69 (m, 1H), 8.47 (d, J = 5.6 Hz, 1H), 7.40−7.47 (m, 2H), 7.29−7.40 (m, 4H), 7.09−7.17 (m, 5H), 5.12 (s, 2H), 2.76 (d, J = 4.8 Hz, 3H).

4-(4-(Benzyloxy)phenoxy)quinoline (57b). Starting from 4-chloroquinoline (3.0 g, 18.4 mmol), 3.8 g (63%) of the title compound was obtained as a tan solid according to the method described for the synthesis of **57a**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.64 (d, J = 5.7 Hz, 1H), 8.27−8.32 (m, 1H), 7.95 (d, J = 9.5 Hz, 1H), 7.76−7.82 (m, 1H), 7.58−7.65 (m, 1H), 7.42−7.48 (m, 2H), 7.36−7.42 (m, 2H), 7.30−7.35 (m, 1H), 7.20−7.26 (m, 2H), 7.10−7.16 (m, 2H), 6.50 (d, J = 5.7 Hz, 1H, 5.12 (s, 2H).

4-(4-(Benzyloxy)-3-chlorophenoxy)quinoline (57c). Starting with 4-chloroquinoline (725 mg, 5.0 mmol) and 4-benzyloxy-3-chlorophenol (3 g, 12.78 mmol), 1.37 g (76%) of the title compound was obtained as a pink solid according to the method described for the synthesis of **57a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 5.7 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.79−7.82 (m, 1H), 7.61−7.64 (m, 1H), 7.46−7.54 (m, 3H), 7.30−7.42 (m, 4H), 7.24−7.30 (m, 1H), 6.58 (d, J = 5.1 Hz, 1H), 5.23 (s, 2H).

4-(4-(Benzyloxy)-3-chlorophenoxy)-pyridine-2-carboxylic Acid Methylamide (57d). Starting with 4-chloro-pyridine-2-carboxylic acid methylamide (367 mg, 2.15 mmol), 609 mg (87%) of the title compound was obtained as a brown solid according to the method described for the synthesis of **57a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75−8.85 (m, 1H), 8.48−8.50 (m, 1H), 7.46−7.50 (m, 3H),

7.38−7.44 (m, 2H), 7.32−7.37 (m, 3H), 7.51−7.55 (m, 1H), 7.19−7.30 (m, 1H), 5.23 (s, 2H), 2.77 (d, J = 4.8 Hz, 3H).

[4-(4-Benzyloxy-phenoxy)-pyrimidin-2-yl]-methyl-amine (57e). To a stirred rt slurry of NaH (0.5 g of 60% oil dispersion, 12.6 mmol) in DMF (15 mL) was added 4-benzyloxyphenol (2.40 g, 12.0 mmol). The mixture was stirred for 10 min before 2,4-dichloropyrimidine (1.79 g, 12.0 mmol) was added. A mild exotherm occurred. The reaction mixture was stirred for 2 h, quenched with saturated aqueous $NaHCO_3$, and diluted with EtOAc and the layers were separated. The organic layer was washed with 2 N NaOH and brine, then dried over Na_2SO_4, filtered, and concentrated in vacuo to yield crude 4-(4-benzyloxy-phenoxy)-2-chloro-pyrimidine (4.0 g contaminated with minor 4-Cl impurity). A portion of this material (2.03 g, approx 6.49 mmol) was dissolved in 10 mL of DMSO in a sealed tube at 0 °C, and 2 N methylamine (in THF) was added (4.9 mL, 9.7 mmol) and the tube was sealed. The mixture was allowed to warm to rt, stirred for 2 h, and then heated to 70 °C for 2 h. The reaction mixture was allowed to cool to rt and concentrated in vacuo. The crude solution was diluted with Et_2O, and washed with 1 N NaOH, water, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by silica gel column chromatography using a hexanes/EtOAc gradient to yield the title compound as a white solid (1.67 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (bs, 1H), 7.30−7.50 (m, 5H), 7.00−7.10 (m, 5H), 5.90−6.10 (m ,1H), 5.08 (s, 2H), 2.60−2.70 (bs, 3H).

6-(4-(Benzyloxy)phenoxy)-*N*-methylpyrimidin-4-amine (57f). Starting with 4,6-dichloropyrimidine (4.10 g, 27.6 mmol), 2.89 g (34%) of the title compound was obtained according to the method described for the synthesis of **57a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (bs, 1H), 7.22−7.48 (m, 6H), 7.00−7.08 (m, 4H), 5.68 (s, 1H), 5.08 (s, 2H), 2.73 (s, 3H).

4-(4-Benzyloxy-phenoxy)-pyridine-2-carboxylic Acid Amide (57g). Starting with 4-chloro-pyridine-2-carboxylic acid amide[23] (4.27 g, 27.26 mmol), 8.90 g (102%) of the title compound was obtained according to the method described for the synthesis of **57a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 5.6 Hz, 1H), 8.09−8.12 (m, 1H), 7.68−7.70 (m, 1H), 7.44−7.48 (m, 2H), 7.38−7.42 (m, 2H), 7.30−7.36 (m, 2H), 7.10−7.18 (m, 5H), 5.15 (s, 2H).

4-(4-Benzyloxyphenoxy)-6,7-dimethoxyquinazoline (57h). Starting with 4-chloro-6,7-dimethoxyquinazoline (2.30 g, 11.1 mmol), 2.0 g (46%) of the title compound was obtained according to the method described for the synthesis of **57a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 7.52 (s, 1H), 7.40−7.50 (m, 2H), 7.30−7.40 (m, 3H), 7.20 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H), 5.13 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H).

4-(4-Hydroxyphenoxy)-pyridine-2-carboxylic Acid Methylamide (58a). Starting from 4-(4-benzyloxy-phenoxy)-pyridine-2-carboxylic acid methylamide (0.44 g, 1.32 mmol), 282 mg (88%) of the title compound was obtained as a pink oil according to the method described for the synthesis of **58e**. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.59 (s, 1H), 8.70−8.80 (m, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.06−7.08 (m, 1H), 6.98−7.02 (m, 2H), 6.82−6.86 (m, 2H), 2.76 (d, J = 4.8 Hz, 3H).

4-(Quinolin-4-yloxy)phenol (58b). Starting from 4-(4-(benzyloxy)phenoxy)quinoline (3.8 g, 11.6 mmol), 800 mg (30%) of the title compound was obtained according to the method described for the synthesis of **58e**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.65 (d, J = 5.8 Hz, 1H), 8.30 (d, J = 5.8 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.70−7.80 (m, 1H), 7.55−7.65 (m, 1H), 7.10 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 3.8 Hz, 1H).

2-Chloro-4-(quinolin-4-yloxy)phenol (58c). A solution of 4-(4-(benzyloxy)-3-chlorophenoxy)quinoline (1.37 g, 3.79 mmol) in TFA (10 mL) was refluxed for 20 h, and the mixture was allowed to cool to rt and concentrated in vacuo. The residue was diluted with water and basified with NH_4OH (concd) and a solid precipitated. The solid was collected and washed with water and Et_2O, yielding the title compound (983 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.66 (d, J = 4.8 Hz, 1H), 8.28 (d, J = 7.3 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.75−7.85 (m, 1H), 7.60−7.70 (m, 1H), 7.35−7.40 (m ,1H), 7.00−7.15 (m, 2H), 6.57 (d, J = 5.4 Hz, 1H).

4-(3-Chloro-4-hydroxyphenoxy)-pyridine-2-carboxylic Acid Methylamide (58d). Starting with 4-(4-(benzyloxy)-3-chlorophenoxy)-pyridine-2-carboxylic acid methylamide (0.60 g, 1.65 mmol), 578 mg (crude, mixed with salts) of the title compound was obtained as a tan solid according to the method described for the synthesis of **58c**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.70−8.85 (m, 1H), 8.47 (d, J = 5.4 Hz, 1H), 7.30−7.40 (m, 1H), 7.00−7.15 (m, 4H), 2.76 (d, J = 4.9 Hz, 3H).

4-(2-Methylamino-pyrimidin-4-yloxy)-phenol (58e). A flask was charged with [4-(4-benzyloxy-phenoxy)-pyrimidin-2-yl]-methyl-amine (0.75 g, 2.44 mmol) and the solid was dissolved in MeOH (5 mL) and EtOAc (10 mL). To the argon-degassed solution was added 10% by weight Pd/C (0.15 g). The reaction mixture was stirred vigorously at rt under 1 atm H_2 gas for 4 days, filtered through Celite, and concentrated in vacuo to yield the title compound (517 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.08 (s, 1H), 6.90−7.05 (m, 3H), 6.75 (d, J = 8.8 Hz, 2H), 5.80−6.00 (m, 1H), 2.66 (s, 3H).

4-(6-Methylamino-pyrimidin-4-yloxy)-phenol (58f). Starting with 6-(4-(benzyloxy)phenoxy)-*N*-methylpyrimidin-4-amine (1.29 g, 4.20 mmol), 833 mg (97%) of the title compound was obtained as an off-white solid according to the method described for the synthesis of **58e**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.08 (bs, 1H), 7.15−7.25 (m, 1H), 6.88−6.92 (m, 2H), 6.73−6.80 (m, 2H), 5.61 (s, 1H), 2.72 (s, 3H).

4-(4-Hydroxy-phenoxy)-pyridine-2-carboxylic Acid Amide (58g). Starting with 4-(4-benzyloxy-phenoxy)-pyridine-2-carboxylic acid amide (8.90 g, 27.78 mmol), 6.22 g (97%) of the title compound was obtained according to the method described for the synthesis of **58e**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (bs, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.08−8.12 (m, 1H), 7.65−7.70 (m, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 5.6, 2.4 Hz, 1H), 6.98−7.05 (m, 2H), 6.80−6.90 (m, 2H).

4-(1*H*-Indol-4-yloxy)phenol (58i). A mixture of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (3.10 g, 20.0 mmol), 4-benzyloxyphenol (8.10 g, 40.0 mmol) and Et_3N/TFA 1:1 mixture (3.0 mL) was heated at 150 °C for 96 h. The crude material was directly purified on silica gel without workup using a hexanes/EtOAc gradient (100/0 to 0/100) to afford 4-(4-benzyloxy-phenoxy)-1*H*-pyrrolo[2,3-*b*]-pyridine (1.20 g) as a 2:1 mixture with the phenol starting material. This material was subjected to the conditions for the synthesis of **58e** at a pressure of 60 psi to afford the title compound (0.80 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 9.55 (s, 1H), 8.10 (d, J = 6.6 Hz, 1H), 7.35−7.40 (m, 1H), 7.05 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.3 Hz, 2H), 6.40 (d, J = 6.6 Hz, 1H), 6.25−6.30 (m, 1H).

4-(4-Hydroxy-3-nitrophenoxy)-pyridine-2-carboxylic Acid Methylamide (59a). Starting from 4-(4-hydroxyphenoxy)-pyridine-2-carboxylic acid methylamide(0.28 g, 1.15 mmol), 187 mg (56%) of the title compound was obtained as a yellow foam according to the method described for the synthesis of **59e**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.70−8.80 (m, 1H), 8.50 (d, J = 5.6 Hz, 1H), 7.80 (d, J = 2.8 Hz, 1H), 7.44−7.47 (m, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 9.2 Hz, 1H), 7.14−7.16 (m, 1H), 2.77 (d, J = 4.8 Hz, 3H).

2-Nitro-4-(quinolin-4-yloxy)phenol (59b). Starting from 4-(quinolin-4-yloxy)phenol (800 mg, 3.79 mmol), 760 mg (76%) of the title compound was obtained as an orange solid according to the method described for the synthesis of **59e**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, J = 7.3 Hz, 1H), 8.25−8.30 (m, 1H), 8.02 (d, J = 9.7 Hz, 1H), 7.88 (d, J = 4.8 Hz, 1H), 7.75−7.85 (m, 1H), 7.60−7.70 (m, 1H), 7.55 (d, J = 4.8 Hz, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.25 (d, J = 12.1 Hz, 1H), 6.65 (d, J = 5.8 Hz, 1H).

4-(3-Chloro-4-hydroxy-5-nitrophenoxy)-pyridine-2-carboxylic Acid Methylamide (59d). Starting with 4-(3-chloro-4-hydroxyphenoxy)-pyridine-2-carboxylic acid methylamide (578 mg, appx 1.83 mmol), 394 mg (crude, with salts) of the title compound was obtained as an orange solid according to the method described for

the synthesis of **59e**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.40−8.50 (m, 1H), 7.38−7.45 (m, 2H), 7.00−7.25 (m, 3H), 2.75−2.80 (m, 3H).

4−(2-Methylamino-pyrimidin-4-yloxy)-2-nitro-phenol (59e). A flask was charged with 4-(2-methylamino-pyrimidin-4-yloxy)-phenol (0.20 g, 0.92 mmol) was the solid dissolved in AcOH (5 mL). To this solution was added fuming HNO_3 (64 mg, 0.92 mmol; diluted with water (∼12 μL) dropwise over 1 min. The reaction mixture was stirred at rt for 18 h, after which it was poured slowly to 40 mL saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ (satd) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using hexanes/EtOAc gradient to yield the title compound (163 mg, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.15 (s, 1H), 7.70−7.80 (m, 1H), 7.35−7.45 (m, 1H), 7.14 (d, J = 9.2 Hz, 1H), 6.95−7.05 (m, 1H), 6.10−6.20 (m, 1H), 2.48 (s, 3H).

4-(6-Methylamino-pyrimidin-4-yloxy)-2-nitro-phenol (59f). Starting with 4-(6-methylamino-pyrimidin-4-yloxy)-phenol (0.88 g, 4.06 mmol), 740 mg (69%) of the title compound was obtained as a light yellow solid according to the method described for the synthesis of **59e**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.09 (bs, 1H), 7.65 (d, J = 2.8 Hz, 1H), 7.33−7.36 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 5.82 (s, 1H), 2.76 (s, 3H).

4-(6,7-Dimethoxyquinazolin-4-yloxy)-2-nitrophenol (59h). Starting with 4-(4-benzyloxy-phenoxy)-6,7-dimethoxyquinazoline (2.0 g, 5.15 mmol), 0.76 g (2.36 mmol, 46%) of 4-(6,7-dimethoxyquinazolin-4-yloxy)-phenol was obtained according to the method described for the synthesis of **58e** (using a mixture of DMF and methanol as the solvent). This compound was converted to 4-(6,7-dimethoxyquinazolin-4-yloxy)-2-nitrophenol using the conditions described for **59e** to obtain the title compound as a yellow solid (0.48 g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (bs, 1H), 8.60 (s, 1H), 7.85−7.90 (m, 1H), 7.50−7.60 (m, 2H), 7.35−7.40 (m, 1H), 7.15−7.25 (m, 1H), 3.95−4.00 (m, 6H).

4-(3-Fluoro-4-hydroxy-5-nitrophenoxy)-pyridine-2-carboxylic Acid Methylamide (59j). To a stirred rt slurry of NaH (0.10 g of 60% oil dispersion, 4.51 mmol) in DMF (8 mL) was added 4-(benzyloxy)-3-fluorophenol (0.98 g, 4.50 mmol). The mixture was stirred at rt for 10 min before adding 4-chloro-pyridine-2-carboxylic acid methylamide (0.77 g, 4.50 mmol). The reaction mixture was stirred at rt for 10 min and then heated at 85 °C for 16 h. The reaction was allowed to cool to rt, quenched with saturated aqueous $NaHCO_3$, and then diluted with Et_2O and 6 N NaOH. The layers were separated, and the organic layer was washed with 6 N NaOH and then brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 4-(4-(benzyloxy)-3-fluorophenoxy)-pyridine-2-carboxylic acid methylamide as a 1:1 mixture with 4-chloro-pyridine-2-carboxylic acid methylamide (1.24 g). This crude material was dissolved in ethanol (20 mL). To the argon-degassed solution was added Pd/C (10% by wt, 0.40 g), and the reaction was stirred vigorously at rt under 1 atm H_2 gas for 4 days. The mixture was filtered through Celite and concentrated in vacuo to yield 4-(3-fluoro-4-hydroxyphenoxy)-pyridine-2-carboxylic acid methylamide (655 mg) as a 1:1 mixture with pyridine-2-carboxylic acid methylamide (996 mg total). The title compound was further obtained as a thick oil (611 mg, 80%) according to the method described for the synthesis of **59e**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.70−8.80 (m, 1H), 8.51 (d, J = 5.7 Hz, 1H), 7.55−7.65 (m, 2H), 7.43 (d, J = 2.4 Hz, 1H), 7.17−7.20 (m, 1H), 2.78 (d, J = 5.1 Hz, 3H).

4-(6,7-Dimethoxyquinolin-4-yloxy)-2-nitrophenol (59k). Starting from 4-chloro-6,7-dimethoxyquinoline[24] (3 g, 13.4 mmol), 6.43 g of 4-(4-(benzyloxy)phenoxy)-6,7-dimethoxyquinoline (contaminated with the phenol) was obtained according to the method described for the synthesis of **57a**. The mixture was treated with Pd/C according to the procedure described in **39o** to give 4-(6,7-dimethoxyquinolin-4-yloxy)phenol. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60(s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.50 (s, 1H), 7.35 (s, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.35 (d, J = 5.6 Hz, 1H), 3.95 (s, 6H). A portion of 4-(6,7-dimethoxyquinolin-4-yloxy)phenol (200 mg, 0.67 mmol) was converted to 4-(6,7-dimethoxyquinolin-4-yloxy)-2-nitrophenol (160 mg, 69%) using the method described in **59e**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (bs, 1H), 8.85 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 3.3 Hz, 1H), 7.70 (s, 1H), 7.52 (dd, J = 8.0, 3.3 Hz, 1H), 7.50 (s, 1H), 7.30 (d, J = 10.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 4.04 (s, 3H), 4.01 (s, 3H).

Bioligical Assays. KDR Enzyme Assay: In a 96-well plate, 5 nM of either the phosphorylated or unphosphorylated form of the KDR kinase domain was incubated with a 10-point titration of compound ranging from 3 μM to 0.15 nM and 1 μM gastrin substrate, sequence {N} EEEEA YGWLD F {C}, in 20 mM Tris-HCl pH 7.5, 10 mM $MgCl_2$, 100 mM NaCl, 1.5 mM EGTA, 1 mM DTT, 0.2 mM sodium orthovanadate, and 20 μg/mL BSA for 30 min at 25 °C. ATP was added at a final concentration of 11.8 μM and incubated for 60 min at room temperature. From this reaction mix, 5 μL was transferred to a black 96-well plate containing 80 μL of 2.75 μg/mL SA-APC (Prozyme, Inc., catalog #PJ25S) and 0.1125 nM Eu-labeled antiphosphotyrosine pT66 antibody (Perkin-Elmer) in 50 mM Tris-HCl pH 7.5, 100 mM NaCl, 0.1% BSA, 0.05% Tween-20, and incubated for 30 min at 25 °C. The plate was read on a RubyStar and data was fitted using the Levenburg−Marquardt algorithm into a four-parameter logistic equation.

Inhibition of LCK Kinase Domain. In a 96-well black polypropylene costar plate, 1 μM biotinylated gastrin substrate (sequence {N} EEEEA*Y*GWLDF {C}) and 0.5 μM ATP (at K_m) were added to a 10-point, 5-fold titration of compound ranging from 25 μM to 12.8 pM. The reaction was initiated by adding 50 pM of the GST-tagged form of the LCK kinase domain in 50 mM HEPES pH 7.5, 20 mM $MgCl_2$, 5 mM $MgCl_2$, 50 mM NaCl, 1 mM DTT, and 0.05% BSA. The reaction was incubated for 90 min at rt. The reaction was quenched by the addition of 160 μL of detection mix consisting of 50 mM TRIS pH 7.5, 100 mM NaCl, 0.05% BSA, 0.1% Tween-20, 3 mM EDTA, 40 μg/mL SA-APC (Perkin-Elmer), 25 nM Eu-labeled anti-phosphotyrosine pT66 antibody (Perkin-Elmer), and incubated at room temperature for 30 min. The plate was read on a BMG RubyStar. All enzymes were run at the apparent K_m of ATP, and peptide substrates were dependent upon enzymes: gastrin (LCK, cMet, Src, EGFR, Zap-70, IGF); biotinyl-GG-MEDIYFEFMGGKKK (Tie-2, cFMS, cKit); and biotinyl-KEAPED-LYKDFLTL (FGFR).

Inhibition of p38α, p38*β*, JNK1, JNK2, JNK3. In a 96-well black polypropylene costar plate, 100 nM biotinyl-ATF2, and 50 μM ATP(p38α, p38*β*) or 2 μM ATP(JNK1, JNK2, JNK3) were added to a 10-point, 3-fold titration of compound. Adding 1 nM p38α, 5 nM p38*β*, 0.5 nM JNK1, 1 nM JNK2, or 1.5 nM JNK3 in 50 mM Tris HCl, pH 7.5, 5 mM $MgCl_2$, 0.5 mM DTT, 0.1 mM Na_3VO_4, and 0.1 mg/mL BSA initiated the reaction. The 30 μL of reaction volume was incubated for 60 min at rt. The reaction was quenched by the addition of 30 μL of detection mix consisting of 50 mM Hepes, pH 7.5, 100 mM NaCl, 0.1% BSA, 0.05% Tween-20, 10 mM EDTA, 4nM streptavidin allophycocyanin (Prozyme), and 0.1 nM Eu-labeled antiphosphothreonine proline antibody (Perkin-Elmer).

Inhibition of CDK1, CDK2, and p25CDK5. In a 96-well black polypropylene costar plate, 0.5 μM biotinylated histone H1 and 25 μM ATP ($<K_m$) were added to a 10-point, 3-fold titration of compound. Adding 5 nM CDK1, 1 nM cyclin E_2-CDK2, or 0.2 nM of p25CDK5 in 50 mM Tris HCl, pH 7.5, 5 mM $MgCl_2$, 5 mM DTT, 5 mM *β*-glycerolphosphate, and 0.2 mg/mL BSA initiated the reaction. The 30 μL of reaction volume was incubated for 60 min at rt. The reaction was quenched by the addition of 30 μL of detection mix consisting of 100 mM Hepes, pH 7.5, 100 mM NaCl, 0.1% BSA, 0.05% Tween-20, 10 mM EDTA, 1nM streptavidin allophycocyanin (Prozyme), and 0.05 nM Eu-labeled antiphosphothreonine proline antibody (Perkin-Elmer) and incubated at rt for 60 min. The plate was read on a Discovery Plate Reader (Perkin-Elmer).

Inhibition of GSK3*β*. In a 96-well polypropylene costar plate, 0.5 μM biotinylated phosphorylated CREB-T peptide (KKRREIL-TRRP[pS]YR) and 25 μM ATP ($<K_m$) were added to a 10-point,

3-fold titration of compound. Adding 0.2 nM of GSK3β in 50 mM Tris HCl, pH 7.5, 5 mM $MgCl_2$, 5 mM DTT, 10 mM β-glycerol-phosphate, and 0.2 mg/mL BSA initiated the reaction. The 50 μL of reaction volume was incubated for 60 min at rt. The reaction was quenched by a 30-fold dilution into detection mix consisting of 100 mM Tris HCl, pH 7.5, 100 mM NaCl, 0.1% BSA, 0.05% Tween-20, 10 mM EDTA, 1 nM ruthenylated antirabbit antibody (BioVeris), 1 nM antiphosphothreonine antibody (Cell Signaling Technology), and 7.5 μg streptavidin paramagnetic beads (Dynal) and incubated with agitation at rt for 60 min. The plate was read on a M-Series M8 Analyzer (BioVeris). The proportion of substrate phosphorylated in the kinase reactions in the presence of compound compared with that phosphorylated in the presence of DMSO vehicle alone (HI control) was calculated using the formula: % control (POC) = (cmpd − average LO)/(average HI − average LO) × 100. Data (consisting of POC and inhibitor concentration in μM) was fitted to a four-parameter equation ($y = A + ((B - A)/(1 + ((x/C)\hat{}D))$), where A is the minimum y (POC) value, B is the maximum y (POC), C is the x (cmpd concentration) at the point of inflection, and D is the slope factor) using a Levenburg−Marquardt nonlinear regression algorithm. The inhibition constant (K_i) of the inhibitor was estimated from the IC_{50} (cmpd concentration at the point of inflection; C) using the Cheng−Prussof equation: $K_i = IC_{50}/(1 + S/K_m)$, where S is the ATP substrate concentration and K_m is the Michaelis constant for ATP as determined experimentally.

HUVEC Proliferation Assay. HUVEC proliferation assays were performed as previously described.[10e] Briefly HUVECs were cultured in endothelial growth medium-2 (Cambrex). One day before the assay was run, HUVEC were seeded into flat-bottom, 96-well plates (BD Falcon) at 3000 cells per well in DMEM medium with 10% qualified fetal bovine serum (FBS) and 1× penicillin, streptomycin, and L-glutamine (1× PSG). After culture for 22 h, media was removed and HUVEC were preincubated for 2 h with serial dilutions of small molecule diluted 1:400 in DMEM with 10% FBS plus 1× PSG. HUVEC were then challenged with 50 ng/mL VEGF or 20 ng/mL bFGF and incubated for 72 h at 37 °C, 5% CO_2. Cells were washed 2× with DPBS, and plates were frozen at −70 °C for 24 h. Plates were thawed, incubated with CyQuant dye (Molecular Probes), and read on a Victor 1420 Workstation (Perkin-Elmer Corporation). IC_{50} data was calculated using the Levenburg−Marquardt algorithm into a 4-parameter logistic equation (ID Business Solutions, Ltd.) and expressed in μM.

Pharmacokinetic Studies. Male Sprague−Dawley rats were dosed via femoral vein (intravenous, DMSO solution, dose 1 mg/kg) or via oral gavage (suspensions in Ora-Plus, pH adjusted to a range of 2.0−2.2 using methanesulfonic acid, dose 10 mg/kg). Concentrations of all formulations were selected as to allow for dose volumes in accordance with the highest scientific, humane, and ethical principals as defined by IACUC (Institutional Animal Care and Use Committees).[25] Serial blood samples were collected from jugular vein into heparized tubes over a 12−24 h period. Plasma was separated by centrifugation, and the sample was prepared for analysis by protein precipitation with acetonitrile. Quantitation of the test compounds was accomplished by reversed liquid chromatography with mass spectral detection in multiple reaction monitoring mode, with an appropriate internal standard. Pharmacokinetic parameters such as clearance, volume of distribution, and terminal half-life were calculated by a noncompartmental method.

Vascular Permeability Assay. Vascular permeability was induced using a modified Miles assay.[18] HEK 293 cells overexpressing murine VEGF were used to induce vascular permeability in nude mice. Briefly, 2×10^5 VEGF-expressing or vector control HEK 293 cells were mixed with Matrigel and injected subcutaneously on the ventral surface of nude mice. Approximately 22 h later, a single oral dose of compound or vehicle was administered. After 6 h, the mice received an intravenous injection of 0.1 mL 1% Evan's blue dye for 10 min prior to sacrifice. A 1 cm^2 piece of skin overlying the cells was harvested and placed in formamide at 60 °C overnight. The extracted Evan's blue dye was measured using a spectrophotometer at OD_{630}. Relative Evan's blue units refer to the % Evan's blue, as determined by the standard curve, multiplied by 10^4. Data represent mean ± standard error; $n = 5$. Statistical analysis was performed by one-way ANOVA with Bonferroni−Dunn post hoc test. $p < 0.0009$ was considered significant.

Rat Corneal Angiogenesis Model. Corneal angiogenesis was evaluated in female CD rats as described.[26] Briefly, rats weighing approximately 250 grams were randomized into one of six treatment groups. Angiogenesis was induced by surgically implanting a VEGF (or BSA control)-soaked nylon disk into the corneal stroma (n = 8/group). Rats were treated with 1, 3, 10, or 30 mg/kg orally once a day with compound or vehicle. Treatment began on the day of surgery and was continued for 7 days. Two vascular endpoints were evaluated: the number of blood vessels at the midpoint between the limbal vessels and the disk and the mean blood vessel area. After 7 days, the implanted corneas were photographed at 25× using a Nikon SV-3 Ophthalmic Slit Lamp (Nikon Ophthalmic) equipped with a Nikon D-1 digital camera back. A reference stage micrometer was photographed for calibration. The images were transferred to a desktop PC, reformatted for image analysis, and transferred to a Metamorph IA system for computerized analysis. Numerical data were generated from the digital images using the Metamorph image analysis system (Universal Imaging). Three endpoints were analyzed on each corneal image: (1) disk placement distance from the limbus, (2) number of vessels intersecting a perpendicular line at the midpoint of the disk placement distance, and (3) blood vessel area, as determined by RGB thresholding and automated pixel counting. Image analysis was performed in a blinded fashion. Values represent the group mean ± standard error. Statistical analysis was performed using one-way ANOVA followed by Fisher's protected least significant difference post hoc test.

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Supporting Information Available: Elemental analysis and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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