Discovery of Novel Benzimidazoles as Potent Inhibitors of TIE-2 and VEGFR-2 Tyrosine Kinase Receptors

Masaichi Hasegawa,* Naohiko Nishigaki, Yoshiaki Washio, Kazuya Kano, Philip A. Harris, Hideyuki Sato, Ichiro Mori, Rob I. West, Megumi Shibahara, Hiroko Toyoda, Liping Wang,‡ Robert T. Nolte,‡ James M. Veal,†,‡ and Mui Cheung‡

Tsukuba Research Laboratories, GlaxoSmithKline K.K., 43 Wadai, Tsukuba, Ibaraki 300-4247, Japan, and GlaxoSmithKline Inc., Five Moore Drive, Research Triangle Park, North Carolina 27709

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We herein disclose a novel chemical series of benzimidazole-ureas as inhibitors of VEGFR-2 and TIE-2 kinase receptors, both of which are implicated in angiogenesis. Structure−activity relationship (SAR) studies elucidated a critical role for the N1 nitrogen of both the benzimidazole (segment E) and urea (segment B) moieties. The SAR results were also supported by the X-ray crystallographic elucidation of the role of the N1 nitrogen and the urea moiety when the benzimidazole-urea compounds were bound to the VEGFR-2 enzyme. The left side phenyl ring (segment A) occupies the backpocket where a 3-hydrophobic substituent was favored for TIE-2 activity.

Introduction

Angiogenesis is the process of blood vessel sprouting, generating capillaries from existing vasculature. It occurs during tissue growth from embryonic development through to maturity, after which the process enters a period of relative quiescence during adulthood. Angiogenesis is also activated during wound healing and at certain stages of the female reproductive cycle. Pathological angiogenesis is involved with several disease states including various retinopathies, ischemic diseases, atherosclerosis, chronic inflammatory disorders, and cancer.[1]

In cancer, the growth of solid tumors has been shown to be angiogenesis-dependent. Consequently, manipulating the pro-angiogenic pathways is a strategy being widely pursued to provide new therapeutics in this area of unmet medical need. The role of tyrosine kinases in angiogenesis and in the vascularization of solid tumors has drawn considerable interest. Until recently, investigations in this area have focused on vascular endothelial growth factor (VEGF) and its three receptors, VEGFR-1, VEGFR-2 (KDR/Flk-1), and VEGFR-3. The VEGFR family consists of protein tyrosine kinases (PTKs) that catalyze the phosphorylation of specific tyrosine residues in proteins.[2] Of the three PTK receptors for VEGF involved in angiogenesis, VEGFR-2 has received the most attention to date. The kinase domain of this receptor functions by transferring a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of VEGFR-2, leading ultimately to the initiation of angiogenesis.[3] Indeed, a number of angiogenesis inhibitors involving inhibition of VEGFR-2 are currently in various stages of clinical studies.[4]

Angiopoietin 1 (Ang1), a ligand for the endothelium-specific receptor tyrosine kinase TIE-2 (tyrosine kinase containing Ig and EGF homology domains), has been identified as a novel angiogenic factor.[5] TIE is used to identify a class of receptor tyrosine kinases, which are exclusively expressed in vascular endothelial cells and early hemopoietic cells. Precedents exist in the literature for the development of TIE-2 inhibitors: a pyrazolo[3,4-*d*]pyrimidine series of compounds was reported to inhibit TIE-2 and LCK,[6] and a natural terpenoid from the plant *Acacia aulacocarpa* was reported to inhibit TIE-2.[7] None of the compounds identified in these studies were found suitable for further development as potential drug candidates.

Many researchers have been pursuing VEGFR-2 or TIE-2 kinase domain inhibitors to discover novel anti-angiogenic drugs. The growing interest in this strategy for cancer treatment stems from the envisioned favorable toxicity profile. Because VEGFR-2 and TIE-2 are located only in endothelial cells, an angiogenesis inhibitor would not be expected to affect normal proliferative cells, unlike conventional cytotoxic chemotherapy.

VEGF and its receptor VEGFR-2 play roles during the early stages of vascular development (namely, cell proliferation, migration, and tube formation), whereas Ang1 and its receptor TIE-2 function in the later stages of vascular development, such as vessel maturation and sprouting.[8] Because VEGFR-2 and TIE-2 are involved in angiogenesis at different time points, we hypothesized that inhibiting VEGFR-2 and TIE-2 simultaneously would be even more effective than the inhibition of either one of these kinases. To our knowledge, there has only been a single report of a dual inhibitor of TIE-2/VEGFR-2.[4f] In this paper, we report the discovery of a novel class of potent low-molecular-weight dual TIE-2/VEGFR-2 inhibitors.

An initial high-throughput screening effort enabled us to identify a series of benzimidazole-urea compounds having dual inhibitory activity against TIE-2 and VEGFR-2. The prototypical compound **15**, originally targeted as an anthelmintic agent,[9] showed moderate VEGFR-2 and weak TIE-2 inhibitory activities.

Several reports have previously described the activity of inhibitors having the diphenyl urea motif against such kinases as Raf, p38, and PDGFR.[10] None, however, centered on the structure−activity relationship (SAR) studies for TIE-2 or VEGFR-2. Regan and co-workers[10f] elucidated the X-ray crystal structure of the binding mode of **55** (BIRB796) in p38α. The X-ray crystal structure suggested that the urea moiety of **55** forms hydrogen bonds with Phe168 and Glu70, two residues that did not interact with ATP. As depicted in Figure 1a, we surmised that the urea moiety of **15** might have a similar binding mode to that of **55** and decided to expand our understanding of the SAR of **15** based on this premise. We further hypothesised

* To whom correspondence should be addressed. Tel.: +81-27-364-0667. Fax: +81-27-364-1573. E-mail: masaichi.hasegawa@gsk.com.
† Current address: Informatics and Computational Chemistry, Serenex, Inc., Durham, NC 27701.
‡ GlaxoSmithKline, Inc., North Carolina.

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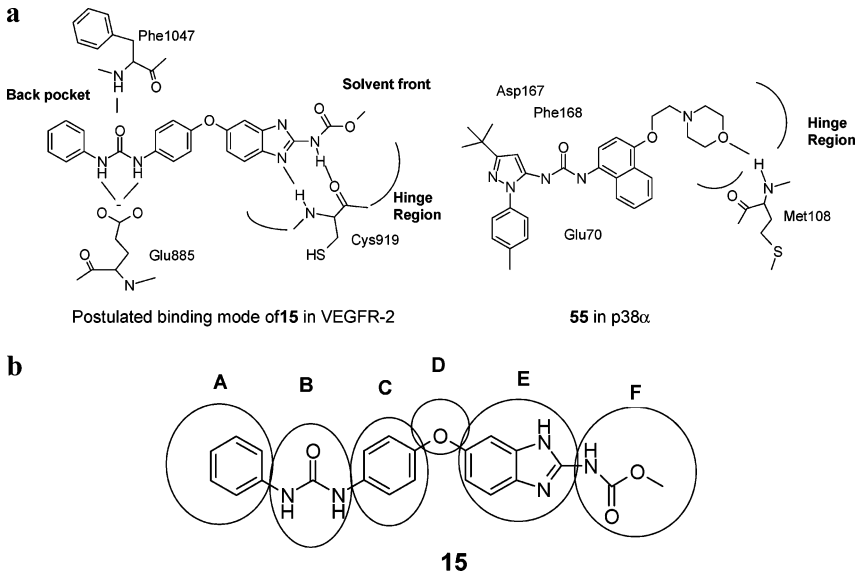
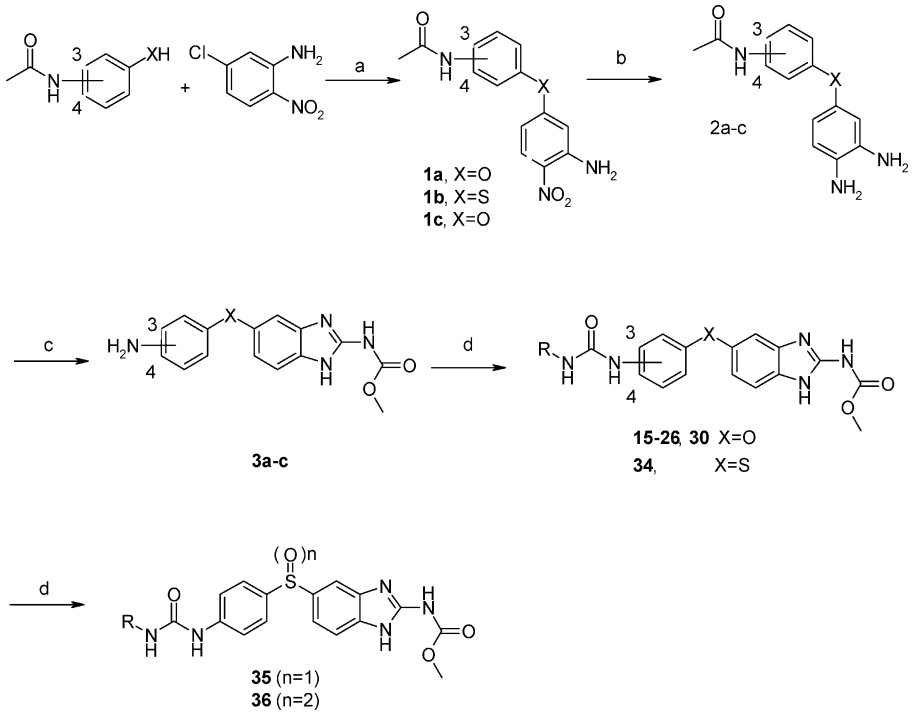


Figure 1. (a) Binding hypothesis of **15** in VEGFR-2 based on the X-ray crystallographic complex of **55** and human p38α. (b) Compound **15** consists of several critical components and was divided into six segments (A−F) to facilitate the understanding of respective contributions to inhibitory potency at the target enzymes. Segment A, the backpocket region; segment B, the urea moiety that has hydrogen bonding interaction with Phe1407 and/or Glu885 of VEGFR-2; segment C, the inner hydrophobic region; segment D, the center linkage region; segment E, the scaffold and hinge-binding region; and segment F, the solvent front region.

Scheme 1[a]



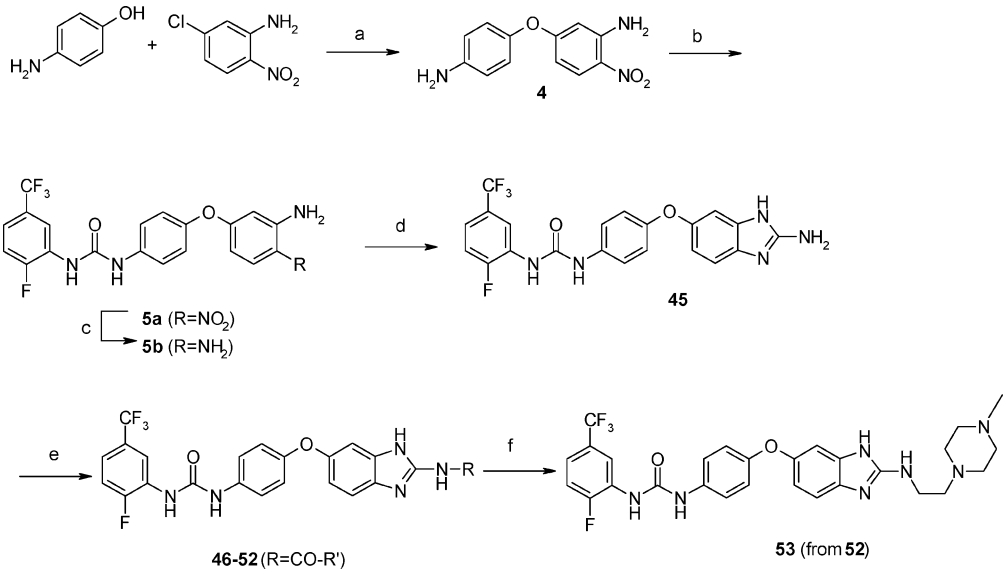
[a] Reagents: (a) NaH, DMF; (b) $Na_2S_2O_4$ or Pd−C, H_2, EtOH; (c) MeOC(O)NHC(SMe)NC(O)OMe (1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea), EtOH, HCl; (d) isocyanate (R-NCO), THF; (e) mCPBA, AcOH.

that the benzimidazole of **15** may position itself in the pocket, where the adenine of ATP is bound to the beta-strand of the target kinase.

Chemistry

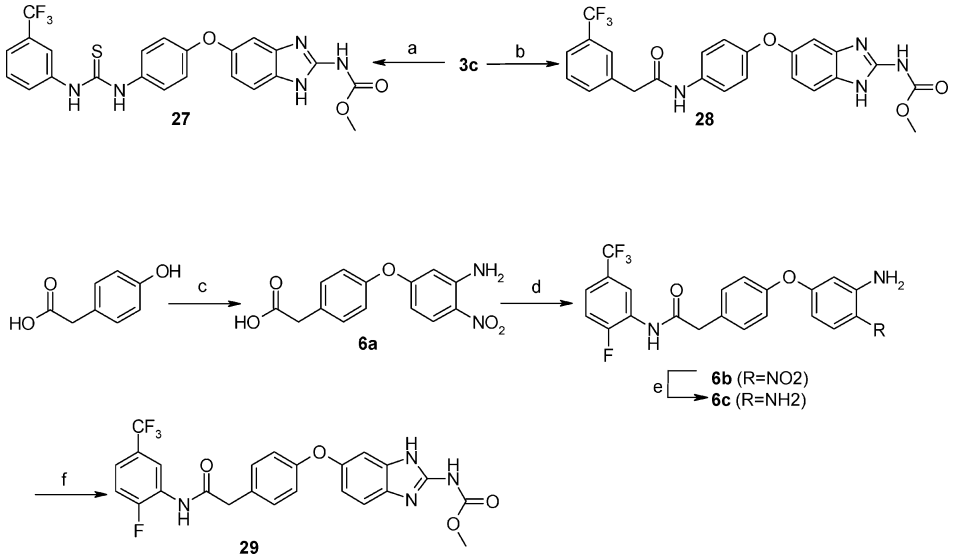
To facilitate synthetic investigations and subsequent SAR analysis, we decided to divide **15** into six segments (see Figure 1b). To modify segment **A**, target compounds were prepared according to the synthesis shown in Scheme 1. In this scheme, the aryl group R is incorporated upon urea formation. 4-Acetamidophenol (X = O) in DMF was reacted with 5-chloro-2-nitroaniline in the presence of NaH to provide 5-(4-acetamidophenoxy)-2-nitroaniline (**1c**), the nitro group of which was reduced with $Na_2S_2O_4$ to provide diamine **2c**. Compound **2c** was refluxed with 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea in ethanol, leading to an acetylated carbamate intermediate,[11] which on deacetylation in HCl gave methyl (5-(4-aminophenoxy)-1*H*-benzimidazol-2yl)carbamate (**3c**). This was then reacted with the appropriate phenyl isocyanate to give the target benzimidazoles **15**−**26**. Diphenylthioether derivative **34** was obtained using a similar procedure. Subsequent oxidation with mCPBA led to **35** and **36**, respectively. The 3-(arylurea)-

Scheme 2[a]



[a] Reagents: (a) NaH, DMF; (b) 2-F-5-CF_3PhNCO (2-fluoro-5-trifluoromethylphenylisocyanate), THF; (c) Pd−C, H_2, EtOH; (d) BrCN, MeOH; (e) RCO_2H, Et_3N, HBTU (*O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluoro-phosphate), HOBt (*N*-hydroxybenzotriazole), DMF; (f) $LiAlH_4$, THF.

Scheme 3[a]



[a] Reagents: (a) 3-CF_3PhNCS (3-trifluoromethyl-phenylisothiocyanate), THF; (b) 3-$CF_3PhCH_2CO_2H$ (3-trifluoromethylphenylacetic acid), HBTU, HOBt, Et_3N, DMF; (c) NaH, 5-Cl-2-NO_2PhNH_2 (5-chloro-2-nitroaniline), DMSO; (d) HBTU, HOBt, Et_3N, 2-F-5-CF_3PhNH_2, DMF; (e) Pd−C, H_2, EtOH; (f) MeOC(O)NHC(SMe)NC(O)OMe, EtOH.

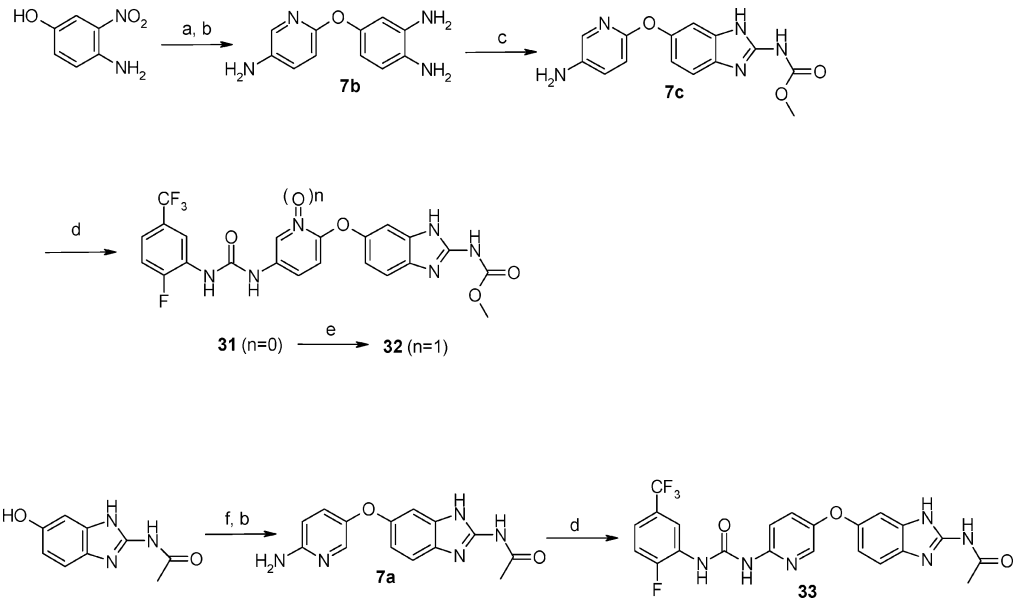
phenoxy derivative **30** was also synthesized according to the same procedure, using 3-acetamidophenol in the initial coupling.

Scheme 2 depicts segment **F** modification. In contrast to Scheme 1, the left-hand side synthesis precedes the right-hand portion to introduce diverse functionality in segment **F**. 4-Aminophenol in DMF was treated with 5-chloro-2-nitroaniline in the presence of NaH to give 5-(4-aminophenoxy)-2-nitroaniline (**4**), which was coupled with 2-fluoro-5-trifluoromethylphenylisocyanate to provide **5a**. Compound **5a** was hydrogenated in the presence of Pd/C to give diamine **5b**, which was reacted with cyanogen bromide to give benzimidazole **45**. Condensation of **45** with the appropriate carboxylic acids in the presence of triethylamine, HBTU (*O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluoro-phosphate), and HOBt (*N*-hydroxybenzotriazole) gave amides **46**−**52**. Reduction of **52** with lithium aluminum hydride gave **53**.

We wanted to understand the significance of the urea moiety for binding and thus decided to include the following modifications with regards to segment **B**. As shown in Scheme 3, we first synthesized benzylamide **28** using aniline **3c** via treatment with 3-trifluoromethylphenylacetic acid in the presence of HBTU. Thiourea **27** was obtained using 3-trifluoromethylphenylisothiocyanate, following a similar procedure used for the synthesis of urea analogues (e.g., Scheme 1). Reverse amide **29** was synthesized via a four-step sequence, as shown also in Scheme 3. Thus, 4-hydroxyphenylacetic acid was first reacted with 5-chloro-2-nitroaniline in the presence of NaH to give **6a**, which on coupling with 2-fluoro-5-(trifluoromethyl)aniline in the presence of HBTU, HOBt, and Et_3N gave **6b.** Reduction of the nitro group of **6b** gave **6c**, which was further reacted with 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea to give **29**.

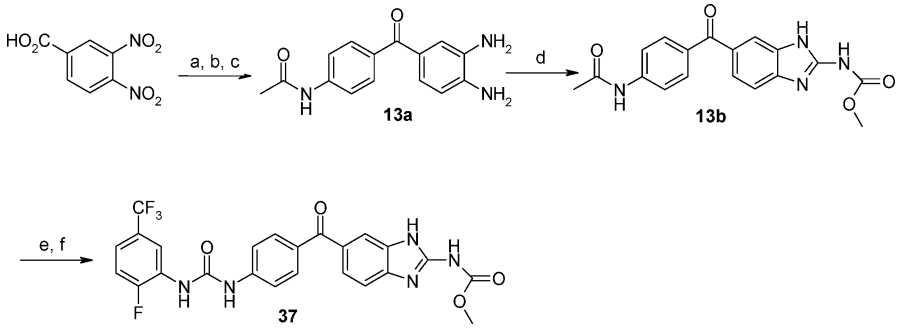
Modification of segment C via incorporation of a pyridine ring was carried out as shown in Scheme 4. The synthesis of analogues **31** and **32** began with the coupling of 2-chloro-5-nitropyridine with 2-nitro-4-hydroxyaniline. The product of this reaction was reduced via catalytic hydrogenation, resulting in

Scheme 4[a]



[a] Reagents: (a) 2-Cl-5-NO_2Py (2-chloro-5-nitropyridine), K_2CO_3, DMF; (b) H_2 Pd/C, EtOH; (c) MeOC(O)NHC(SMe)NC(O)OMe, THF; (d) 2-F-5-CF_3PhNCO, THF; (e) mCPBA, CH_2Cl_2; (f) $CsCO_3$, 5-Br-2-NO_2Py (5-bromo-2-nitropyridine), DMF.

Scheme 5[a]



[a] Reagents: (a) $(COCl)_2$; (b) acetoanilide, $AlCl_3$, CH_2Cl_2; (c) Zn, AcOH; (d) MeOC(O)NHC(SMe)NC(O)OMe, THF; (e) HCl; (f) 2-F-5-CF_3PhNCO, THF.

triamine **7b**. Intermediate **7c** was next obtained from **7b** and, using procedures described previously, was converted to urea **31**. The *N*-oxide derivative **32** was obtained via mCPBA oxidation of **31**.

2-*N*-Acetyl-5-hydroxybenzimdazole was treated with 5-bromo-2-nitropyridine in the presence of Cs_2CO_3, and the product of this reaction was hydrogenated over Pd−C to provide **7a**. Coupling of **7a** with 2-fluoro-5-(trifluoromethyl)phenylisocyanate led to urea **33**.[9]

The synthesis of a carbonyl-linked analogue is depicted in Scheme 5. Friedel−Crafts condensation of 3,4-dinitrobenzoic acid with acetanilide was carried out in the presence of $AlCl_3$ to give a biaryl ketone intermediate, which was reduced with zinc to give diamine **13a**. Cyclization with 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea gave **13b**. Benzophenone **37** was obtained following hydrolysis of **13b** and coupling with 2-fluoro-5-(trifluoromethyl)phenylisocyanate,.

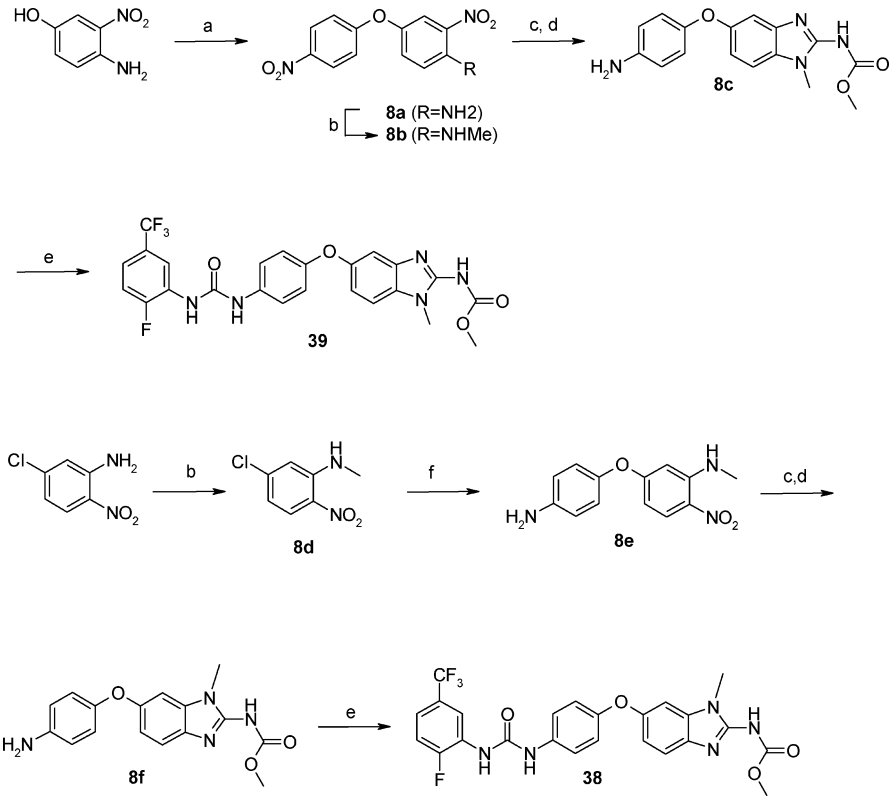
In addition to the synthetic routes mentioned above, further modifications around segment **B** were also undertaken. Scheme 6 illustrates one such method. 2-Nitro-4-hydroxyaniline was reacted with 4-fluoronitrobenzene with NaH to give bisarylether **8a**, followed by methylation to give **8b**. Subsequent hydrogenation and cyclization with pseudothiourea derivative afforded **8c**. This was followed by reaction with 2-fluoro-5-(trifluoromethyl)-phenyl isocyanate to give **39**.

The *N*-methyl-6-phenoxybenzimidazole derivative **38** was synthesized as follows: *N*-methyl-5-chloro-2-nitroaniline (**8d**), derived from 2-nitro-5-chloroaniline, was reacted with 4-aminophenol to provide **8e**. Following a procedure similar to that for the synthesis of **39**, intermediate **8f** was obtained, which was reacted with 2-fluoro-5-(trifluoromethyl)phenyl isocyanate to afford **38**.

Benzthiazole and benzoxazole derivatives were prepared as follows (see Scheme 7). 4-(4-Nitrophenoxy)aniline (**10**), derived from 4-fluoronitrobenzene and 4-aminophenol, was cyclized with KSCN and Br_2 in the presence of acid to provide thiazole **10a**.[12] Subsequent reaction with $ClCO_2Me$ gave **10d**. Reduction with $SnCl_2$ gave **10e**, and finally, reaction with 2-fluoro-5-(trifluoromethyl)phenyl isocyanate afforded **40**. The corresponding sulfonamide derivative **54** was obtained by the coupling of $ClSO_2Me$ with intermediate **10a**, using the same procedure. The benzoxazole derivative **41** was prepared as follows. 4-Aminophenol was coupled with 2-benzyloxy-4-fluoro-1-nitrobenzene to give ether **11**, which was then treated with 2-fluoro-5-(trifluoromethyl)phenylisocyanate to afford urea **12a**. Hydrogenation with concurrent debenzylation and subsequent cyclization with BrCN gave **12b**. This was followed by reaction with $ClCO_2Me$ to provide benzoxazole **41**.[13]

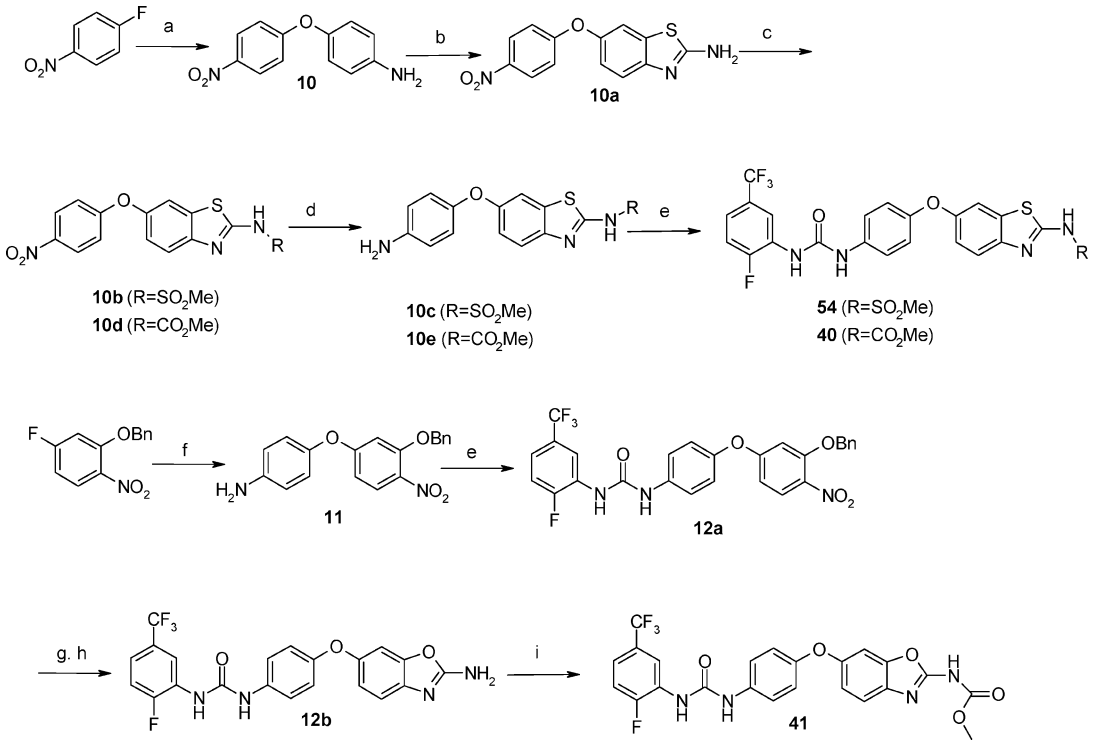
A 4-aza-1,3-benzimidazole derivative was synthesized according to the procedure shown in Scheme 8. 2-Amino-6-chloro-

Scheme 6[a]



[a] Reagents: (a) NaH, 4-F−NO_2Ph, DMF; (b) MeI, NaH, DMF; (c), H_2, Pd−C, MeOH; (d) MeOC(O)NHC(SMe)NC(O)OMe, MeOH or AcOH; (e) 2-F-5-CF_3PhNCO, THF; (f) 4-aminophenol, NaH, DMF.

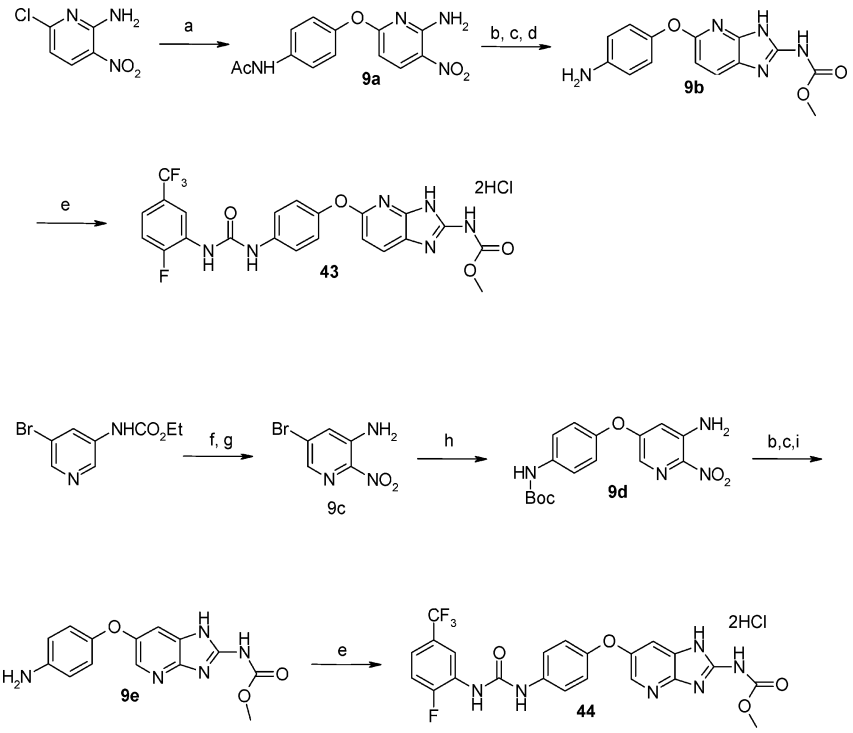
Scheme 7[a]



[a] Reagents: (a) 4-aminophenol, NaH, DMF; (b) KSCN, Br_2, AcOH; (c) $ClCO_2Me$ or $ClSO_2Me$, pyridine, DMF; (d) Zn, AcOH or $SnCl_2$; (e) 2-F-5-CF_3PhNCS, THF; (f) 4-aminophenol, NaH, DMF; (g) H_2, Pd−C, MeOH; (h) BrCN, MeOH; (i) $ClCO_2Me$, pyridine.

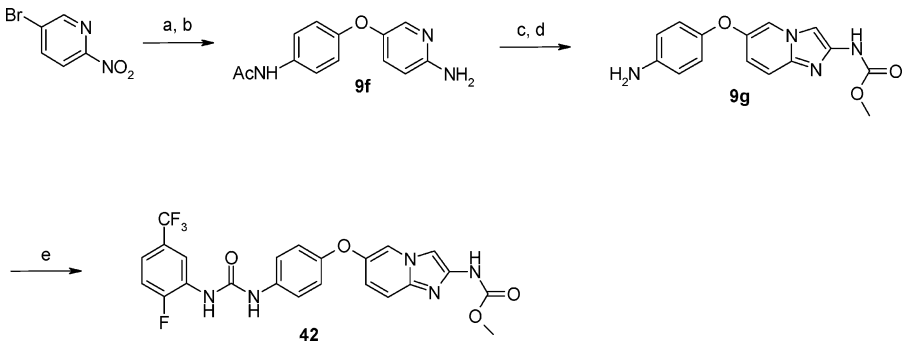
3-nitropyridine was coupled with 4-acetylaminophenol and K_2CO_3 to provide bisarylether **9a**. Using methods similar to those shown in previous schemes, hydrogenation, cyclization, and hydrolysis provided **9b**, which was then reacted with 2-fluoro-5-(trifluoromethyl)phenylisocyanate to yield **43**. The synthetic sequence leading to the 7-aza-1,3-benzimidazole derivative **44** is also shown in Scheme 8. Nitration of ethyl *N*-(5-bromopyridin-3-yl)carbamate with fuming HNO_3 was followed by hydrolysis to give pyridine **9c**. Reaction with 4-Boc-aminophenol gave **9d**, which was then followed by the standard

Scheme 8[a]



[a] Reagents: (a) 4-acetylaminophenol, K_2CO_3, DMF; (b) H_2, Pd−C, MeOH; (c) MeOC(O)NHC(SMe)NC(O)OMe, MeOH; (d) HCl, (e) 2-F-5-CF_3PhNCO, HCl, THF; (f) fuming HNO_3, concd H_2SO_4; (g) KOH, EtOH; (h) 4-Boc-aminophenol, $CsCO_3$, DMF; (i) HCl.

Scheme 9[a]



[a] Reagents: (a) 4-acetamidophenol, $CsCO_3$, DMF; (b) H_2, Pd−C, MeOH; (c) $ClCH_2CONHCO_2Me$, DMF; (d) HCl, H_2O; (e) 2-F-5-CF_3PhNCO, THF.

hydrogenation, cyclization, and hydrolysis sequence to give aniline **9e**. Reaction with 2-fluoro-5-(trifluoromethyl)phenylisocyanate yielded the 7-aza-1,3-benzimidazole derivative **44**.

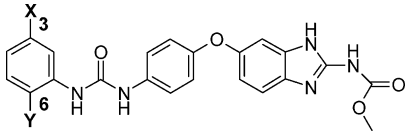
The pyrrolo[2,3-*a*]pyridine derivative **42** was prepared as shown in Scheme 9. Bisarylether **9f**, derived from 5-bromo-2-nitroaniline, was cyclized with $ClCH_2CONHCO_2Me$. Hydrolysis of the resultant intermediate gave aniline **9g**.[14] Reaction with 2-fluoro-5-(trifluoromethyl)phenylisocyanate gave urea **42**.

Biological Results

Baculovirus-expressed recombinant constructs of the intracellular domains of human TIE-2 tagged by GST WERE were used to assay TIE-2 enzyme inhibition (TIE-2 (E)). The protocol measured the ability of the purified enzyme to catalyze the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, D1-15 (biotin-C6-LEARLVAYEGWVAGKKKamide). Similarly, baculovirus expressed recombinant constructs of the intracellular domains of human VEGFR2 tagged by GST WERE were used to measure the ability of the purified enzyme to catalyze the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, (biotin-aminohexyl-EEEEYFELVAKKKK-NH_2; VEGFR-2 (E)). The TIE-2 cellular autophosphorylation assay (TIE-2 (C)) used an ELISA method and a TIE-2 intracellular domain/c-fms extracellular domain (TIE-2/c-fms) chimeric protein expressed in mouse 3T3 cells. This assay measured the autophosphorylation level of TIE-2 protein expressed in cells.

Segment A Modification: The assay results for segment A modified compounds are listed in Table 1. Compound **15**, the prototypical compound, exhibited weak TIE-2 and moderate VEGFR-2 inhibitory activity. Introduction of a trifluoromethyl (CF_3) substituent in the 3-position (**16**) resulted in a 600-fold increase in inhibitory activity against TIE-2 and an approximate 6-fold increase against VEGFR-2. A similar effect is observed with the ethyl analogue **19**, the bromo analogue **20**, and the chloro analogue **21**. However, in the case of the ethyl analogue **19**, there was a significant decline in cell potency. Potency against both TIE-2 and VEGFR-2 was little changed compared to compound **16** when a fluoro group (**17**) or a chloro group (**18**) were introduced at the 6-position. Introduction of a fluoro group to the 3-position (**22**) was less effective than Br, CF_3, or

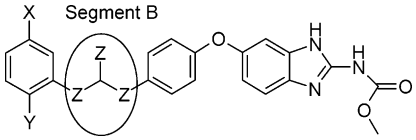
Table 1. Assay Results from Segment A Modification



cpd	X	Y	IC_{50} values (in nM) versus TIE-2 (E)	VEGFR-2 (E)	TIE-2 (C)
15	H	H	3200	32	NT[a]
16	CF_3	H	5.2	5.0	2.6
17	CF_3	F	6.9	3.5	8.7
18	CF_3	Cl	6.3	3.3	10
19	Et	H	18	2.9	170
20	Br	H	13	1.1	8.0
21	Cl	H	40	6.3	50
22	F	F	390	7.6	71
23	SCF_3	H	10	1.3	41
24	SCH_3	H	58	5.4	56
25	NH_2	F	2190	190	NT
26	CO_2H	H	>10 000	603	NT

[a] Not tested.

Table 2. Assay Results from Segment B Modification



cpd	segment B	X	Y	IC_{50} values (in nM) versus TIE-2 (E)	VEGFR-2 (E)	TIE-2 (C)
17	NH(C═O)NH	CF_3	F	6.9	3.5	8.7
27	NH(C═S)NH	CF_3	H	3200	105	680
28	CH2(C═O)NH	CF_3	H	3200	NT[a]	NT
29	NH(C═O)CH_2	CF_3	F	5400	16	NT

[a] Not tested.

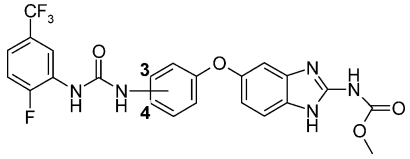
Cl, suggesting the importance of the substituent size. Hydrophilic substituents such as NH_2 (**25**) or CO_2H (**26**) resulted in inactive compounds. The trend in the SAR of the compounds with regard to TIE-2 inhibition was quite similar to that against VEGFR-2, although the compounds in question generally showed greater inhibitory potency against the TIE-2 enzyme. Cellular activity generally correlated well with enzyme activity, suggesting satisfactory cell membrane permeability properties for these compounds.

Segment B Modification: For compounds where a variety of linker groups (segment **B**) were introduced, segment **A** was maintained either as the 6-fluoro-3-trifluoromethylphenyl or 3-trifluoromethylphenyl group. (Table 2). Replacement of the urea moiety with a thiourea resulted in **27**, which was inactive against TIE-2 and showed greatly reduced activity against VEGFR-2. The acetamide linker compounds **27** and **28** also resulted in inactive compounds against the TIE-2 enzyme, although **29** did show good inhibitory potency against VEGFR-2.

Segment C Modification (Part A): Repositioning of the arylurea moiety from the 4-position of the phenoxy moiety to the 3-position gave **30**, which retained considerable potency against both TIE-2 and VEGFR-2, in spite of the fact that such a rearrangement should significantly change the configuration (Table 3).

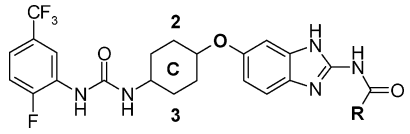
Segment C Modification (Part B): When the phenyl moiety of **17** was replaced by a 2-pyridyl group, the activity against both enzymes and cell of the resultant **31** was slightly weakened, whereas the 3-pyridyl compound **33** maintained potency comparable to that shown by the phenyl analogue **17** (Table 4). The *N*-oxide **32** reduced both enzyme and cellular activities although the effect was more pronounced against VEGFR-2. This was also observed when the oxygen linker was replaced by a sulfoxide or sulfone (vide infra).

Table 3. Assay Results from Segment C Modification (Part A)



cpd	attachment	IC_{50} values (in nM) versus TIE-2 (E)	VEGFR-2 (E)	TIE-2 (C)
17	4	6.9	3.5	8.7
30	3	28	17	81

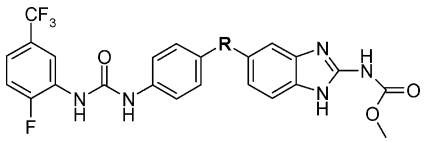
Table 4. Assay Results from Segment C Modification (Part B)



cpd	C-segment	R	IC_{50} values (in nM) versus TIE-2 (E)	VEGFR-2 (E)	TIE-2(C)
17	Ph	OMe	6.9	3.5	8.7
31	2-Py	OMe	20	16	81
32	2-Py(N═O)	OMe	71	230	350
33	3-Py	Me	2.9	NT[a]	6.4
48	Ph	Me	2.6	2.6	3.3

[a] Not tested.

Table 5. Assay Results from Segment D Modification

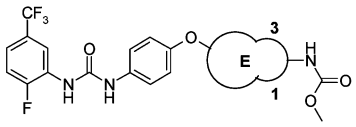


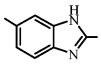
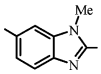
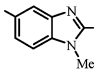
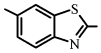
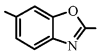
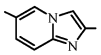
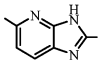
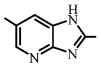
cpd	R	IC_{50} values (in nM) versus TIE-2 (E)	VEGFR-2 (E)	TIE-2 (C)
17	O	6.9	3.5	8.7
34	S	10	10	76
35	SO	69	9500	60
36	SO_2	120	>20 000	160
37	CO	11	26	NT[a]

[a] Not tested.

Segment D Modification: The sulfur-linked compound **34** retained potency against both enzymes when compared with the oxygen-linked analogue **17**, although cellular activity was considerably reduced. Sulfoxide and sulfone analogues, **35** and **36**, respectively, showed a significant reduction in TIE-2 enzyme and cellular activity when compared with the sulfur analogue and were virtually inactive against VEGFR-2 (Table 5). As was seen with the comparison of TIE-2 and VEGFR-2 activities for the *N*-oxide analogue **32** described above, analogues **35** and **36** gave further indications that the region of the TIE-2 and VEGFR-2 enzymes where the sulfoxide and sulfone moieties project into show significant differences. A carbonyl linker such as in compound **37** also decreased the enzyme activity against VEGFR-2 and yet left the activity against TIE-2 virtually unchanged. Here, the less pronounced drop in activity against each enzyme could be explained by the fact that the carbonyl

Table 6. Assay Results from Segment E Modification



		IC_{50} values (in nM) versus		
cpd	segment E	TIE-2 (E)	VEGFR-2 (E)	TIE-2 (C)
17		6.9	3.5	8.7
38		60	27	41
39		5600	420	NT [a]
40		6.5	2.1	7.2
41		8.9	4.8	3.7
42		3.4	3.4	1.5
43		5.6	2.3	6.5
44		130	5.4	91

[a] Not tested.

moiety is not as large as the sulfoxide and sulfone moieties, thus, the resultant compound was unable to discriminate differences in the enzyme sites.

Segment E Modification: Table 6 summarizes the results of the segment **E** [5+6] fused ring modification. The 3-*N*-methylated derivative **38** still retained activity against both enzymes and in the cell, yet the 1-methylated analogue **39** abrogated the enzyme activity considerably, more so against TIE-2 than against VEGFR-2. Replacement of the nitrogen in the 3-position of the benzimidazole moiety by sulfur, oxygen, or a methylene group (such as **40**−**42**) retained potency comparable to that of **17**, suggesting that the nitrogen at the 3-position of the benzimidazole ring system might not be necessary for binding. Compounds **43** and **44** showed the impact of the position of the nitrogen in the imidazopyridine system on enzyme and cell activity. While compound **43** was active against both enzymes and in the cell, compound **44** was somewhat less active against TIE-2, both against the enzyme and in the cellular assay.

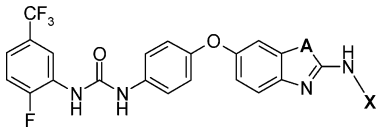
Segment F Modification: Finally, the right terminus (segment **F**) was probed by introducing a variety of functionalities. The inhibitory activities of the resultant compounds are listed in Table 7. Overall, all modifications employed affected activity against both TIE-2 and VEGFR-2 quite evenly. Amides (**46**−**53**) were generally found to show comparable activity to that of the parent carbamate **45**, regardless of size and hydrophilicity. An exception was **48**, where the bulky *ortho*-substituent probably distorted the binding conformation of the molecule. Compound **52** containing a carbonyl moiety was hydrogenated to the piperazinoethyl derivative **53**, which demonstrated weaker potency than **52** across the respective assay systems, indicating the potentially important role of the carbonyl group. Furthermore, conversion of the carbamate to a sulfonamide analogue **(54)** proved to be detrimental for TIE-2 and VEGFR-2 inhibitory activity. Because the benzthiazole derivative **40** (Table 6) exhibited the same activity as that of **17**, it is possible to conclude that the replacement of the carbonyl with SO_2 was responsible for the loss of potency in this case.

Structural Results and SAR Discussion

We have described herein the modification of the benzimidazole-urea scaffold that resulted in a series of analogues exhibiting dual inhibitory activity against both TIE-2 and VEGFR-2. Furthermore, the TIE-2 enzyme activity of the analogues correlated well with their activity in the cell, suggesting the high cellular permeability of the compounds. Interestingly, the modification of this benzimidazole-urea series resulted in a much flatter structure−activity relationship profile for VEGFR-2 compared to TIE-2. The only exception observed was that VEGFR-2 activity was more susceptible to change in the structure of segment **D** (Table 5). Three critical elements for TIE-2 inhibitory activity were identified: the urea, the *meta*-hydrophobic substituent at the left-hand phenyl ring, and the proton-acceptor nitrogen confined in the [5+6] heterocyclic system. An X-ray crystal structure of VEGFR-2 with compound **17** bound at the ATP site was solved at a resolution of 2.05 Angstroms and has an R-factor of 18.7%, with a free-R of 23.1%. The crystal structure was deposited into the protein data bank (code number: 2OH4). Figure 2 illustrates the complex and shows that the urea is sandwiched between Asp1046 and Glu885 and that the nitrogen at the 1-position in the benzimidazole is bound in the hinge region. Asp1046 is considered to be a key part of the Asp-Phe-Gly motif at the end of the activation loop.[10f] This allowed for the hydrogen bond interactions of the two amide hydrogens with Glu885 and the carbonyl group with Asp1046. This might explain why the urea moiety was essential to observe potent inhibition of VEGFR-2, and such interactions may well be required for potency against TIE-2. This also might explain why replacement by methylene group resulted in inactive compounds (**28** and **29**) against VEGFR-2 (Table 2). The linker oxygen lay around Val916 and was found to act as a "linchpin" that dictated the angle between segments **A**−**B**−**C** and **E**−**F**, both of which were planar and inflexible. This binding mode may potentially rationalize the fact that the change of oxygen to a sulfone moiety abrogated the inhibitory activity against VEGFR-2 (**36**, Table 5). The fact that inhibitory activity was retained against TIE-2 implies that there are conformational differences between the two kinases around the area where the sulfone resided, thus creating an opportunity to exploit selectivity in the two enzymes.

The nitrogen at the 1-position of the benzimidazole ring interacts with Cys919 at the ATP binding site, which supports the finding that N1-methylation was detrimental for activity, whereas N3-methylation was acceptable (Table 6). As long as the N-1 hydrogen bond acceptor was present, all the analogues containing the [6+5] heterocycles, including benzimidazoles, maintained strong potency against both enzymes. The only exception was compound **44**, which still retained potency against VEGFR-2. The 1- and 7-nitrogen in the pyridine moiety of **44** when docked in a model was located near Ala905 in TIE-2,

Table 7. Assay Results from Segment F Modification



cpd	X	A	IC_{50} values (in nM) versus TIE-2 (E)	VEGFR-2 (E)	TIE-2 (C)
45	H	NH	60	15	1100
17	(CO)OMe	NH	6.9	3.5	8.7
46	(CO)Me	NH	2.6	2.6	3.3
47	(CO)Ph	NH	13	42	120
48	(CO)-2-(2-(*N*-pyrrolo)Ph)	NH	1300	510	NT[a]
49	(CO)-2-furyl	NH	5.2	5.1	6.2
50	(CO)-3-Py	NH	16	16.5	20
51	$(CO)CH_2OCH_2CH_2OMe$	NH	3.0	5.4	2.8
52	$(CO)CH_2$-4-(NMe-piperazino)	NH	4.9	1.5	5.9
53	CH_2CH_2-4-(NMe- piperazino)	NH	130	33	430
54	SO_2Me	S	3200	4000	NT

[a] Not tested.

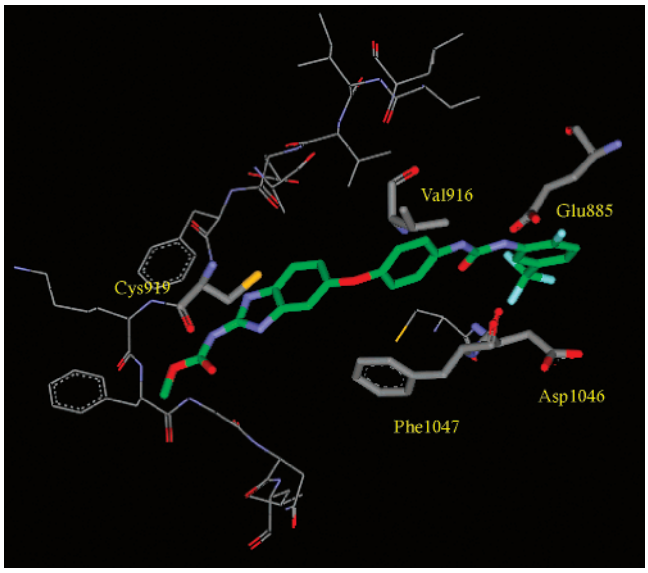


Figure 2. The structure of VEGFR-2 ATP binding domain in complex with compound **17** (green). The urea part of the compound **17** is sandwiched between the activation loop of Asp1046 and Glu885, and the nitrogen at the 1-position of the benzimidazole is bound in the hinge region of Cys919.

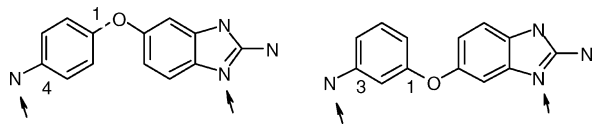


Figure 3.

corresponding to Cys919 in VEGFR-2, and yet there still is uncertainty how the difference affects the selectivity. Why the repositioned compound **30** retains the potency may be explained by the docked structure (Table 3). The rearrangement (1,4 to 1,3) would cause the benzimidazole to align the molecule favorably (Figure 3).

The right terminus (segment **F**) extended to the solvent front region, giving consistent rationale that most of the analogues with appropriate substituents gave favorably inhibitory activity against both TIE-2 and VEGFR-2 (Table 7). Of high interest is that the left terminus (segment **A**) was predicted to penetrate through the Asp-Glu channel, extending to the backpocket. Although the model of the complex could not exactly explain how the 3-substituent in segment **A** played a pivotal role, it was apparent that there was enough space that could accommodate a trifluoromethyl moiety surrounded by Val 899 and Cys1045 (Table 1).

A representative compound **18** was administered orally to mouse (10 mg/kg) to show a moderate C_{max} of 0.36 μg/mL at 2 h and a moderate AUC of 2.54 μg hr/mL, indicating that this urea-benzimidazole series can be employed as a systemically active drug. Overall, solubility of all analogues synthesized was poor despite the high cell activity. However, as described earlier, solubilizing functionalities could be attached off the benzimidazole region, which extended to the solvent front area without affecting enzyme and cell activities. For example, compound **52** (see Table 7) has good potency, with a solubility in PBS (phosphate-buffered saline) of approximately 200 ug/mL.

Conclusion

A novel series of benzimidazole-ureas were found to inhibit both VEGFR-2 and TIE-2 kinases, each of which plays a major role in angiogenesis. The lead molecule **15** was divided into six segments and optimized accordingly. Structure−activity relationship studies elucidated a critical role of the N1 of the benzimidazole (segment **E**) and the urea moiety (segment **B**). This result was supported by the X-ray crystallographic elucidation of the complex of **17** in VEGFR-2 where the N1 and the urea moieties made key hydrogen bonding interactions with the enzyme. The left side phenyl ring (segment **A**) fits the backpocket where the 3-hydrophobic substituent was favored for the TIE-2 activity. The other side (segment **E**) is bent toward the solvent front where any substituent was tolerated insofar as the carbonyl moiety existed aligning with the exo-NH_2 and the benzimidazole ring. The central linker proved to be the key part, interacting in the "hinge" region of the enzyme.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AVANCE-400. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), dd (doublet-doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), brs (broad singlet), brd (broad doublet), and brdd (broad doublet-doublet). LC-MS analyses were performed with a Waters 2695 equipped with a diode array detector and ZQ2000 on a Waters XTerra MS C_{18} 2.5 μm (φ2.1 × 20 mm) column eluted with a gradient mixture of H_2O−acetonitrile with formic acid and ammonium acetate. All compounds analyzed were >90% pure.

Elemental analyses (C, H, N) were performed by Atlantic Microlab, Inc., GA. Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light or LC-MS. Flash column chromatography was performed on silica gel (230−400 mesh, Merck) unless otherwise mentioned. The sequence data of TIE-2, VEGFR-2, and P38α were citated from Swiss-Prot entry Q02763(TIE2_HUMAN), P35968(VGFR2_HUMAN), and Q16539(MK14_Human), and VEGFR-2 is synonym of VGFR2 in Swiss-Prot entry.

5-(4-Acetamidophenoxy)-2-nitroaniline (1c). To a solution of 4-acetamidophenol (7.56 g, 50 mmol) in DMF (20 mL) was added 60% NaH (2.2 g) followed by 5-chloro-2-nitroaniline (9.06 g, 50 mmol). The mixture was heated to 120 °C overnight. After cooling, 800 mL of water was added and the resultant solid was collected by filtration. Desiccation in vacuo gave intermediate **1c** as a brown solid (13.75 g, 96%): ^{1}H NMR (DMSO-d_6) δ 7.37 (2H, d, J = 9.0 Hz), 6.84 (2H, d, J = 8.8 Hz), 6.48 (1H, d, J = 7.2 Hz), 6.23 (1H, s), 6.06 (1H, d, J = 7.2 Hz), 4.35−4.75 (mbr, 4 H), 2.02 (s, 3H); MS m/z 286 (M − 1).

5-(3-Acetamidophenoxy)-2-nitroaniline (1a). Following the procedure utilized for the synthesis of **1c** and using 3-acetamidophenol, **1a** was obtained as a yellow solid (90%): ^{1}H NMR (DMSO-d_6) δ 10.15 (s, 1 H), 8.00 (d, J = 9 Hz, 1 H), 7.36−7.49 (m, 5 H), 6.82 (d, J = 8 Hz, 1 H), 6.38 (s, 1 H), 6.30 (d, J = 9 Hz, 1 H), 2.04 (s, 3 H); LC-MS m/z 286 (M − 1).

5-(4-Acetamidophenylthio)-2-nitroaniline (1b). 5-Chloro-2-nitroaniline (15.7 g, 90.8 mmol) and potassium *tert*-butoxide (10.2 g, 90.8mmol) was added to a solution of 4-acetamidothiophenol (14.5 g, 86.5 mmol) in 2-propanol (600 mL). The mixture was refluxed for 4 h. After cooling, water was added and the resultant solid was collected by filtration. Desiccation in vacuo gave **1b** as a yellow solid (24.65 g, 94%): ^{1}H NMR (DMSO-d_6) δ 10.24 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.45 (s, 2H), 6.54 (d, J = 2.0 Hz, 1H), 6.29 (dd, J = 8.8 and 2.0 Hz, 1H), 2.09 (s, 3H); MS m/z 304 (M + 1).

4-(4-Acetamidophenoxy)phenylene-1,2-diamine (2c). $Na_2S_2O_4$ (28.2 g, 160 mmol) was added to a solution of 5-(4-acetamidophenoxy)-2-nitroaniline (**1c**; 13.7 g, 48 mmol) in EtOH (600 mL) and H_2O (150 mL). The yellow mixture was refluxed with vigorous stirring until the color disappeared. After cooling, the mixture was washed with brine and the product was extracted with EtOAc. The EtOAc layer was dried over $MgSO_4$, filtered, and evaporated to give intermediate **2c** as a brown film (10.2 g, 83%): ^{1}H NMR (DMSO-d_6) δ 7.46 (d, J = 9.1 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 6.48 (d, J = 8.3 Hz, 1H), 6.22 (d, J = 2.8 Hz, 1H), 6.06 (dd, J = 8.3 and 2.8 Hz, 1H), 4.58 (brs, 4H), 2.00 (s, 3H); MS m/z 258 (M + 1).

4-(3-Acetamidophenoxy)phenylene-1,2-diamine (2a). Compound **1a** was used instead of **1c** according to the procedure described for the synthesis of **2c** to give intermediate **2a** (78%): ^{1}H NMR (DMSO-d_6) δ 7.24 (brd, J = 8.1 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 7.08 (t, J = 2.3 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 6.23 (d, J = 2.5 Hz, 1H), 6.08 (dd, J = 8.3 and 2.5 Hz, 1H), 1.98 (s, 3H); MS m/z 258 (M + 1).

***N*-[4-(3,4-Diaminophenylsulfanyl)-phenyl]acetamide (2b).** $Na_2S_2O_4$ (56.4 g, 323.2mmol) was added to a solution of 5-(4-acetamidothiophenoxy)-2-nitroaniline (**1b**; 24.5 g, 80.8mmol) in EtOH (1200 mL) and H_2O (300 mL). The reaction mixture was refluxed with vigorous stirring for 2 h. After cooling, EtOH was removed by evaporation and product was extracted with EtOAc. The EtOAc layer was washed with water and brine then dried over $MgSO_4$, filtered, and evaporated to give **2b** as a brown film (21.3 g, 97%): ^{1}H NMR (DMSO-d_6) δ 9.90 (s, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 4.77 (brs, 2H), 4.62 (brs, 2H), 1.99 (s, 3H); MS m/z 274 (M + 1).

Methyl (5-(4-Aminophenoxy)-1*H*-benzimidazol-2-yl)carbamate (3c). A mixture of 4-(4-acetamidophenoxy)phenylene-1,2-diamine (**2c**; 750 mg, 2.9 mmol) and 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (600 mg, 2.9 mmol) in EtOH (13 mL) was refluxed overnight. After cooling to rt, diethyl ether was added to form a solid (830 mg), which was collected by filtration. HCl (1 N, 150 mL) was poured into the solid (7.7 g, 23 mmol). The mixture was heated to reflux (105 °C) for 2 h. After cooling, aq NH_3 (30%, 20 mL) was added. The precipitate thus formed was collected by filtration with suction and dried in vacuo. The solid material was then suspended in MeOH (150 mL) and heated to 70 °C for 30 min with stirring to dissolve a minor byproduct. After cooling, the insoluble material was collected by filtration and dried in vacuo to give **3c** as a brown solid (6.75 g, 99%): ^{1}H NMR (DMSO-d_6) δ 11.40 (brs, 2H), 7.35 (d, J = 8.5 Hz, 1H), 6.85 (s, 1H), 5.72 (m, 3H), 6.57 (d, J = 8.5 Hz, 2H), 5.4 (brs, 2H), 3.75 (s, 3H); MS m/z 299 (M + 1).

Methyl (5-(3-Aminophenoxy)-1*H*-benzimidazol-2-yl)carbamate (3a). Following the procedure described for the synthesis of **3c** and using intermediate **2a**, intermediate **3a** was obtained in 60% yield: ^{1}H NMR (DMSO-d_6) δ 11.6 (brs, 2H), 7.36 (d, J = 8.6 Hz, 1H), 7.01 (brs, 1H), 6.92 (t, J = 8.6 Hz, 1H), 6.77 (dd, J = 8.6 and 2.3 Hz, 1H), 6.23 (d, J = 8.6 Hz, 1H), 6.09 (m, 2H), 5.13 (brs, 2H), 3.74 (s, 3H); MS m/z 244 (M − 1).

Methyl (5-(4-Aminophenylthio)-1*H*-benzimidazol-2-yl)carbamate (3b). A mixture of 4-(4-acetamidothiophenoxy)phenylene-1,2-diamine (**2b**; 21.3 g, 78 mmol) and 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (17 g, 82mmol) in EtOH (400 mL) was refluxed overnight. After cooling to rt, diethyl ether was added and the solid (16 g) was collected by filtration and washed with EtOH−Et_2O. HCl (1 N, 450 mL) was poured on the solid, and the mixture was heated to reflux (105 °C) for 2 h. After cooling, aq NH_3 (30%) was added to basify the solution. The precipitate thus formed was collected by filtration with suction and dried in vacuo. The solid material was then suspended in MeOH and heated to 70 °C for 30 min with stirring to dissolve a minor byproduct. After cooling, the unsolved material was collected by filtration and dried in vacuo to give **3b** (11.75 g, 48%): ^{1}H NMR (DMSO-d_6) δ 11.60 (brs, 2H), 7.29 (d, J = 8.3 Hz, 1H), 7.18 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.3 Hz, 1H), 6.57 (d, J = 8.4 Hz, 2H), 5.39 (s, 2H), 3.73 (s, 3H); MS m/z 315 (M + 1).

5-(4-Aminophenoxy)-2-nitroaniline (4). To a solution of 4-aminophenol (5.0 g, 46 mmol) in DMF (120 mL) was slowly added 60% NaH (2.0 g, 50 mmol), followed by 5-chloro-2-nitroaniline (8.7 g). The mixture was heated to 90 °C and stirred overnight. The reaction mixture was poured onto aq NH_4Cl to form a solid, which was collected by filtration, washed with hexane, and dried to give **4** as a yellow solid (12.0 g, 99%): ^{1}H NMR (DMSO-d_6) δ 5.11 (2H, s), 6.25 (2H, m), 6.62 (2H, d, J = 8.8 Hz), 6.82 (2H, d, J = 8.8 Hz), 7.45 (2H, s), 7.95 (d, 1H, J = 8.8 Hz); MS m/z 244 (M − 1).

5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-2-nitroaniline (5a). A mixture of 2-fluoro-5-(trifluoromethyl)phenylisocyanate (10.0 g, 48.8 mmol) and **4** (11.6 g, 47.3 mmol) in dry THF (200 mL) was stirred overnight at rt. After treatment with activated carbon, the solvent was evaporated. Purification of the crude material by column chromatography (hexane−EtOAc) afforded **5a** as a yellow solid (21.6 g, >98%): ^{1}H NMR (DMSO-d_6) δ 9.28 (1H, s), 8.91 (1H, s), 8.62 (1H, d, J = 7.6 Hz), 8.00 (1H, d, J = 9.3 Hz), 7.56 (2H, d, J = 9.1 Hz), 7.48 (3H, m), 7.40 (1H. sbr), 7.14 (2H, d, J = 9.1 Hz), 6.32 (2H, m); MS m/z 449 (M − 1).

4-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)phenylene−1,2-diamine (5b). Pd/C (5%, 3.0 g) was introduced to a solution of **5a** (21.6 g, 48 mmol) in EtOH (200 mL) under an argon atmosphere. The starting material was hydrogenated under a H_2 atm for 3 days while being stirred. The reaction mixture was then filtered through a celite pad and the filtrate was evaporated to give crude **6** as a black film. This crude material was chromatographed through silica gel (hexane−EtOAc) to give purified **5b** (13.0 g, 64%): ^{1}H NMR (DMSO-d_6) δ 9.05 (1H, s), 8.82 (1H, s), 8.62 (1H, d, J = 7.2 Hz), 7.45 (1H, m), 7.37 (3H, m), 6.84 (2H, d, J = 9.1 Hz), 6.48 (1H, d, J = 8.1 Hz), 6.23 (1H, s), 6.07 (1H, d, J = 8.4 Hz), 4.20−4.70 (4H, mbr); MS m/z 421 (M + 1).

[4-(3-Amino-4-nitrophenoxy)phenyl]acetic Acid (6a). To a solution of 4-hydroxyphenylacetic acid (76 mg, 0.50mmol) in

DMSO (2 mL) was added 60% NaH (40 mg) followed by 5-chloro-2-nitroaniline (86 mg, 0.50mmol). The mixture was heated at 150 °C for 20 min by a microwave reactor. After cooling, water and diluted HCl were added and the resultant solid was collected by filtration. Desiccation in vacuo gave **6a** as a brown solid (108.7 mg, 75%): ^{1}H NMR (DMSO-d_6) δ 12.39 (brs, 1H), 8.01 (d, J = 9.4 Hz, 1H), 7.50 (s, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.36 (s, 1H), 6.29 (d, J = 9.4 Hz, 1H), 3.61 (s, 2H); MS m/z 287 (M − 1).

2-[4-(3-Amino-4-nitrophenoxy)phenyl]-N-(2-fluoro-5-trifluoromethylphenyl)acetamide (6b). HBTU (910 mg, 2.4 mmol) and HOBT (562 mg, 2.4 mmol) were added to a solution of **6a** (576 mg, 2.0 mmol) and 2-fluoro-5-(trifluoromethyl)aniline (0.26 mL, 2.0 mmol) in DMF (5 mL). To it was added 60% NaH (40 mg) followed by 5-chloro-2-nitroaniline (86 mg, 0.5 mmol). The mixture was heated at 80 °C overnight. After cooling, aq $NaHCO_3$ was added and the product was extracted with EtOAc. The EtOAc layer was washed with 1 N HCl, water, and brine, dried over $MgSO_4$, and then evaporated to give a crude solid, which was purified with SPE (silica gel and NH_2), resulting in a yellow solid that was further recrystallized from hexane−EtOAc to give **6b** (338 mg, 38%): ^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1H), 8.46 (d, J = 7.3 Hz, 1H), 8.00 (d, J = 9.4 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.50 (s, 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 6.36 (d, J = 2.8 Hz, 1H), 6.29 (dd, J = 9.4 and 2.8 Hz, 1H), 3.83 (s, 2H); MS m/z 450 (M + 1).

2-[4-(3,4-Diaminophenoxy)phenyl]-*N*-(2-fluoro-5-trifluoromethylphenyl)acetamide (6c). Pd/C (5%, 3.0 g) was introduced to a solution of **6b** (300 mg, 0.67 mmol) in EtOH (25 mL) under argon. The starting material was hydrogenated. The reaction mixture was then filtered through a celite pad and evaporated to give **6c** (210 mg, 75%): ^{1}H NMR (DMSO-d_6) δ 10.26 (s, 1H), 8.43 (d, J = 7.6 Hz, 1H), 7.50−7.53 (m, 2H), 7.25 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.49 (d, J = 8.3 Hz, 1H), 6.23 (d, J = 2.7 Hz, 1H), 6.08 (dd, J = 8.3 and 2.7 Hz, 1H), 4.64 (brs, 2H), 4.33 (brs, 2H), 3.71 (s, 2H); MS m/z 420 (M + 1).

***N*-(5-(2-Amino-5-pyridyloxy)-1*H*-benzimidazol-2-yl)acetamide (7a).** To a mixture of 5-hydroxy-2-acetylaminobenzimidazole (382 mg, 2 mmol) and Cs_2CO_3 (978 mg, 3 mmol) in DMF (20 mL) was added 5-bromo-2-nitropyridine (550 mg, 2 mmol) at rt. After 2 h of stirring, the mixture was poured into water and extracted with EtOAc. The organic solvent was washed with water and brine and then evaporated to obtain a crude product, which was passed through a short silica gel column using $CHCl_3$−MeOH as the eluent. The product (314 mg) was hydrogenated with Pd−C (10%, 100 mg) in MeOH. After the reaction was complete, the catalyst was filtered off, and the filtrate was evaporated. The crude mixture was purified by silica gel column chromatography to give **7a** (47 mg, 17%): ^{1}H NMR (DMSO-d_6) δ 11.92 (m, 1H) 11.56 (brs, 1H) 7.72 (d, 1H) 7.36 (m, 1H), 7.16 (dd, 1H, 3.04 5.76 Hz), 6.92 (m, 1H), 6.74 (dd, 1H, 6.28 2.28 Hz), 6.47 (dd, 1H, 8.84 Hz), 5.80 (brs, 2H), 2.14 (s, 3H); MS m/z 284 (M + 1).

5-Nitro-2-(4-amino-3-nitrophenoxy)pyridine (7b). 2-Nitro-4-hydroxyaniline (4.62 g, 30 mmol) was reacted with 2-chloro-5-nitropyridine (4.75 g, 30 mmol) and K_2CO_3 (6.22 g, 45 mmol) in DMF (200 mL) at rt for 3 h. The solid was filtered off and washed with EtOAc. To the residue, water was added, and then extracted with EtOAc (200 mL). On evaporation of the organic solvent, precipitate was formed. This was filtered and washed with water to give **7b** (7.12 g, 86%): ^{1}H NMR (DMSO-d_6) δ 9.03 (d, J = 2.8 Hz, 1H), 8.62 (dd, J = 6.0 and 3.0 Hz, 1H), 7.80 (d, J = 2.8 Hz ,1H) 7.54 (brs, 2H), 7.37 (dd, J = 6.3 and 2.8 Hz ,1H), 7.28 (d, J = 9.1 Hz, 1H), 7.11 (d, J = 9.1 Hz ,1H); MS m/z 217 (M + 1).

Methyl *N*-(5-(5-Aminopyridine-2-yl)-1*H*-benzimidazol-2-yl)-carbamate (7c). Compound **7b** (1 g, 3.62 mmol) was hydrogenated over 5% Pd−C (200 mg) in MeOH (20 mL). After filtration of the catalyst, a mixture of the product and 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (1.57 g, 7.6 mmol) in MeOH (25 mL) was refluxed for 5 h. After cooling, aq HCl (2 N, 80 mL) was added to the mixture, which was stirred at rt for 2 h. The solid formed was collected by filtration to give **7c** as an off-white solid (0.79 g, 73%): ^{1}H NMR (DMSO-d_6) δ 11.56 (brs, 1H), 7.51 (d, J = 2.8 Hz 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 5.6 and 3.0 Hz 1H), 6.67 (d, J = 2.0 Hz, 1H), 6.73 (dd, J = 6.3 and 2.2 Hz, 1H), 6.69 (d, J = 8.56 Hz, 2H), 5.02 (brs, 2H), 3.74 (s, 3H); MS m/z 300 (M + 1).

4-(4-Nitrophenoxy)-2-nitroaniline (8a). To a solution of 4-hydroxy-2-nitroaniline (3.08 g, 20.0 mmol) in DMF (30 mL) was added NaH (60%, 880 mg, 22.0 mmol) followed by 1-fluoro-4-nitrobenzene (2.33 mL, 22.0 mmol). The mixture was stirred at 90 °C overnight. After cooling, the mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and silica-gel column chromatography (hexane−EtOAc), **8a** was obtained (4.56 g, 83%): ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 9.4 Hz, 2H), 7.90 (d, J = 2.8 Hz, 1H), 7.19 (dd, J = 9.1 and 2.8 Hz, 1H), 7.01 (d, J = 9.4 Hz, 2H), 6.91 (d, J = 9.1 Hz, 1H), 6.11 (brs, 2H); MS m/z 274 (M − 1).

***N*-Methyl-4-(4-nitrophenoxy)-2-nitroaniline (8b).** To a mixture of NaH (60%, 320 mg, 8.0 mmol) in DMF (30 mL) was added a solution of **8a** (2.00 g, 7.3 mmol) in DMF (30 mL) at 0 °C followed by an excess amount of MeI (2.0 mL). The mixture was stirred at 0 °C for 1.5 h and then at rt overnight. The mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and sequence purification on silica gel column chromatography, **8b** was obtained in quantitative yield (2.10 g): ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 9.4 Hz, 2H), 8.08 (br, 1H), 7.97 (d, J = 2.8 Hz, 1H), 7.30 (dd, J = 9.1 and 2.8 Hz, 1H), 7.00 (d, J = 9.4 Hz, 2H), 6.94 (d, J = 9.4 Hz, 1H), 3.08 (d, J = 5.3 Hz, 3H).

Methyl (1-Methyl-5-(4-aminophenoxy)-benzimidazol-2-yl)-carbamate (8c). To a mixture of **8b** (2.10 g, 2.27 mmol) in MeOH (100 mL) was added a catalytic amount of 5% Pd−C and stirred at rt under H_2 atm. After 7 h, the catalyst was removed by filtration and the solvent was evaporated off. The residual mixture was dissolved in MeOH (50 mL) and 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (3.0 g, 14.5 mmol) was added. The resultant mixture was refluxed overnight. The solvent was removed by evaporation, and sequence purification on a silica gel column chromatography ($CHCl_3$−MeOH) gave **8c** (87.3 mg, 4%): ^{1}H NMR (DMSO-d_6) δ 11.12 (brs, 1H), 7.06 (d, J = 8.6 Hz, 1H), 6.86 (m, 4H), 6.68 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 3.61 (brs, 2H), 3.57 (s, 3H); MS m/z 313 (M + 1).

***N*-Methyl-5-chloro-2-nitroaniline (8d).** To a solution of 5-chloro-2-nitroaniline (1.73 g, 10.0 mmol) in DMF (40 mL) was added NaH (60%, 880 mg, 22.0 mmol) at 0 °C followed by an excess amount of MeI (3.0 mL). The mixture was stirred at 0 °C for 1 h and then at rt overnight. The mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column ($CHCl_3$−MeOH), **8d** was obtained in quantitative yield (1.86 g): ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 9.1 Hz, 1H), 8.08 (s, 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 9.1 and 2.0 Hz, 1H), 3.02 (d, J = 5.1 Hz, 3H).

4-(3-Methylamino-4-nitrophenoxy)aniline (8e). To a mixture of NaH (60%, 440 mg, 11.0 mmol) in DMF (30 mL) was added a solution of 4-aminophenol (1.20 g, 11.0 mmol) in DMF (15 mL) followed by **8d** (2.02 g, 10.0 mmol) in DMF (20 mL). The mixture was stirred at 90 °C overnight. After cooling, the mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column, **8e** was obtained (2.44 g, 94%): ^{1}H NMR (DMSO-d_6) δ 8.22 (br, 1H), 8.13 (d, J = 9.6 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.19 (m, 2H), 3.69 (br, 2H), 2.90 (d, J = 5.1 Hz, 3H); MS m/z 260 (M + 1).

Methyl (3-Methyl-5-(4-aminophenoxy)-benzimidazol-2-yl)-carbamate (8f). 4-(3-Methylamino-4-aminophenoxy)aniline (520 mg, 2.0 mmol), obtained from the hydrogenation of **8e**, 1,3-bis-(methoxycarbonyl)-2-methyl-2-thiopseudourea (1.03 g, 5.0 mmol), and AcOH (2.0 mL) were stirred at 85 °C for 5.5 h. After cooling, 2 N HCl aq (25 mL) was added, and the mixture was stirred at 65 °C for 2 h. The mixture was passed through a celite pad to remove

the catalyst, and the solvent was removed by evaporation. The residue was then extracted with EtOAc. The organic layer was washed with aq NH_4OH and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column ($CHCl_3$−MeOH), **8f** (529.1 mg, 85%) was obtained: ^{1}H NMR ($CDCl_3$) δ 7.11 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.81 (dd, J = 8.6 and 2.3 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.69 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H) and 3.51 (s, 3H), NH2 and NH not detected; MS m/z 313 (M + 1).

3-Nitro-6-(4-acetamidophenoxy)pyridine-2-ylamine (9a). To a solution of 2-amino-6-chloro-3-nitropyridine (2.77 g, 16.0 mmol) in DMF (55 mL) was added 4-acetylaminophenol (2.67 g, 17.5 mmol) followed by K_2CO_3 (3.3 g, 5.0 mmol), and the resultant mixture was stirred at rt for 2 h. The solvent was removed by evaporation. To the residue, water was added, resulting in a precipitate, which was collected by filtration, washed with water and EtOAc, and then dried under reduced pressure to **9a** (4.32 g, 94%): ^{1}H NMR (DMSO-d_6) δ 10.03 (s, 1H), 8.39 (d, J = 9.1 Hz, 1H), 8.05 (brs, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.27 (d, J = 9.1 Hz, 1H), 2.06 (s, 3H); MS m/z 289 (M + 1).

Methyl (5-(4-Aminophenoxy)-3,4-diazaindole-2-yl)carbamate (9b). Compound **9a** (2.02 g, 7.0 mmol) was first hydrogenated with 5% Pd−C in MeOH (70 mL). The catalyst was then removed by filtration. To the filtrate was added 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (1.73 g, 8.4 mmol), and the resultant mixture was stirred at 75 °C. After 8 days, AcOH (15 mL) was added and the mixture was stirred at 80 °C overnight. Additional 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (1.73 g, 8.4 mmol) was added, and the mixture was again stirred at 80 °C overnight. After cooling, the mixture was poured into aq $NaHCO_3$. The precipitate that formed was collected by filtration, washed with EtOAc, and dried under reduced pressure to give methyl (5-(4-acetoamidophenoxy)-3,4-diazaindolin-2-yl)carbamate (983.0 mg, 41%). To this intermediate (102 mg, 0.3 mmol) in water (3 mL) was added 2 N HCl (3.0 mL), and the resultant mixture was then refluxed for 1 h followed by stirring at rt for another hour. The mixture was extracted with EtOAc. The organic layer was washed with aq NH_4OH and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column (hexane−EtOAc), **9b** (33.6 mg, 37%) was obtained: ^{1}H NMR (DMSO-d_6) δ 7.68 (brd, J = 8.6 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 6.53 (brs, 1H), 4.92 (brs, 2H), 3.73 (brs, 3H), two NH not detected; MS m/z 342 (M + 1).

5-Bromo-2-nitropyridine-3-ylamine (9c). To a mixture of concd H_2SO_4 (3.0 mL) and fuming HNO_3 (2.1 mL), 3-bromo-5-(ethoxycarbonyl)aminopyridine (20 g, 99 mmol) was added portionwise at 0 °C. After stirring at 0 °C for 5 min, the mixture was stirred at rt overnight. The mixture was poured into iced water then basified with aq. NH_4OH. The mixture was extracted with EtOAc. The organic layer was washed with aq NH_4OH and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column (hexane−EtOAc), 5-bromo-3-(ethoxycarbonyl)amino-2-nitropyridine (1.57 g, 54%) was obtained. To a portion of this intermediate (1.57 g, 5.4 mmol) in EtOH (2.5 mL) was added KOH (813 mg, 14.5 mmol) in water (12.5 mL), and the mixture was stirred at 90 °C for 1 h and then at rt for 1 h. Water was added and precipitate was formed, which was collected by filtration, washed with water, and then dried under reduced pressure to give **9c** (1.08 g, 92%): ^{1}H NMR (DMSO-d_6) δ 7.84 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H) and 7.45 (brs, 2H); MS m/z 216, 218 (M − 1).

2-Nitro-5-(4-(*tert*-butoxycarbonylamino)phenoxy)pyridine-3-ylamine (9d). To a solution of **9c** (436 mg, 2.0 mmol) in DMF (10 mL) at 0 °C was added Cs_2CO_3 (977 mg, 3.0 mmol) followed by 4-(*tert*-butoxycarbonyl)aminophenol (459 mg, 2.2 mmol) in DMF (10 mL). The mixture was stirred at rt for 3 days. The mixture was extracted with EtOAc. The organic layer was washed with aq $NaHCO_3$ and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column (hexane−EtOAc), **9d** was obtained (624 mg, 90%): ^{1}H NMR (DMSO-d_6) δ 9.51 (brs, 1H), 7.63 (d, J = 2.5 Hz, 1H), 7.56 (brd, J = 9.1 Hz, 2H), 7.34 (brs, 2H), 7.14 (d, J = 9.1 Hz, 2H), 6.70 (d, J = 2.5 Hz, 1H), 1.49 (s, 9H); MS m/z 347 (M + 1).

Methyl (6-(4-Aminophenoxy)-3,4-diazaindole-2-yl)carbamate (9e). Using the procedures described for the synthesis of **2c** and **3c** and utilizing **9d** gave methyl (5-(4-(*tert*-butoxycarbonyl)aminophenoxy)-3,7-diazaindole-2-yl)carbamate. To a solution of the carbamate (160.8 mg, 0.4 mmol) in MeOH (10 mL) was added 2 N HCl (10 mL), and the mixture was then stirred at rt overnight. The solution was removed by evaporation, and the residue was extracted with EtOAc. The organic layer was washed with aq $NaHCO_3$ and brine, dried over Na_2SO_4, and then evaporated. The residual solid was washed with EtOAc and dried under reduced pressure to give **9e** (95.3 mg, 80%): ^{1}H NMR (DMSO-d_6) δ 7.89 (br, 1H), 7.20 (br, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 4.93 (br, 2H), 3.71 (br, 3H), two NH not detected; MS m/z 300 (M + 1).

5-(4-Acetamidophenoxy)pyridine-2-ylamine (9f). To a solution of 5-bromo-2-nitropyridine (2.03 g, 10.0 mmol) in DMF (30 mL) at 0 °C was added Cs_2CO_3 (4.9 g, 15.0 mmol) followed by 4-acetylaminophenol (1.66 g, 11.0 mmol) in DMF (30 mL), and the mixture was then stirred at rt overnight. The mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and sequence purification on silica gel column and then recrystallization from EtOAc, 5-(4-acetamidophenoxy)-2-nitropyridine (1.62 g, 59%) was obtained. Hydrogenation of 5-(4-acetamidophenoxy)-2-nitropyridine (879 mg, 3.22 mmol) with 5% Pd−C in MeOH (80 mL) gave **9f** (576 mg, 74%): ^{1}H NMR (DMSO-d_6) δ 9.87 (brs, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.50 (d, J = 9.1 Hz, 2H), 7.16 (dd, J = 8.8 and 3.0 Hz, 1H), 6.84 (d, J = 9.1 Hz, 2H), 6.47 (d, J = 8.8 Hz, 1H), 5.84 (br, 2H), 2.00 (s, 3H); MS m/z 244 (M + 1).

Methyl (6-(4-Aminophenoxy)azaindolizine-2-yl)carbamate (9g). To a solution of **9f** (170.2 mg, 0.7 mmol) in DMF (2 mL) was added *N*-(methoxycarbonyl)chloroacetoamide (159.0 mg, 1.1 mmol). The mixture was stirred at 80 °C overnight. Additional *N*-(methoxycarbonyl)chloroacetoamide (159.0 mg, 1.1 mmol) was added, and the mixture was further stirred at 80 °C overnight. After cooling, the mixture was extracted with EtOAc. The organic layer was washed with aq $NaHCO_3$ and brine and dried over Na_2SO_4. After sequence purification on a silica gel column chromatography ($CHCl_3$−MeOH), methyl (6-(4-acetoamidophenoxy)azaindolizine-2-yl)carbamate (51.7 mg, 22%) was obtained. To a solution of this carbamate (34.0 mg, 0.1 mmol) in water (2 mL) was added 2 N HCl (aq, 2.0 mL), and the mixture was then refluxed for 1 h followed by 1 h of stirring at rt. To the mixture was added aq NH_4OH. The precipitate that formed was collected by filtration, washed with water, and dried under reduced pressure to give **9g** (22.0 mg, 74%): ^{1}H NMR (DMSO-d_6) δ 10.22 (brs, 1H), 8.24 (brs, 1H), 7.83 (brs, 1H), 7.35 (d, J = 9.6 Hz, 1H), 6.98 (dd, J = 9.6 and 2.5 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 4.97 (brs, 2H), 3.67 (s, 3H); MS m/z 299 (M + 1).

4-(4-Nitrophenoxy)aniline (10). To a mixture of NaH (60%, 880 mg, 22.0 mmol) in DMF (40 mL) was added a solution of 4-aminophenol (2.40 g, 22.0 mmol) in DMF (30 mL) followed by 1-fluoro-4-nitrobenzene (2.12 mL, 20.0 mmol). The mixture was stirred at 90 °C overnight. After cooling, the mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column (hexane−EtOAc), **10** was obtained in a quantitative yield (4.60 g): ^{1}H NMR (DMSO-d_6) δ 8.17 (d, J = 9.1 Hz, 2H), 6.96 (d, J = 9.1 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 3.71 (brs, 2H); MS m/z 229 (M − 1).

6-(4-Nitrophenoxy)benzthiazole-2-ylamine (10a). To a solution of **10** (1.15 g, 5.0 mmol) in AcOH (5 mL) was added KSCN (729 mg, 7.5 mmol). The mixture was cooled to 0 °C and a solution of Br_2 (256 μL, 5.0 mmol) in AcOH (6 mL) was added. The mixture was then stirred at room temperature overnight. The mixture was poured into H_2O, basified with NH_4OH (aq), and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column (hexane−EtOAc), **10a** was obtained (941.5

mg, 66%): ^{1}H NMR (DMSO-d_6) δ 8.23 (d, J = 9.1 Hz, 2H), 7.60 (d, J = 2.5 Hz, 2H), 7.54 (brs, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 9.1 Hz, 2H), 7.04 (dd, J = 8.8 and 2.5 Hz, 1H); MS m/z 288 (M + 1).

***N*-(6-(4-Nitrophenoxy)benzthiazole-2-yl)methanesulfonyl Amide (10b).** To a solution of **10a** (1.15 g, 4.0 mmol) in pyridine (10 mL) was added mesyl chloride (1.55 mL, 20 mmol) at 0 °C, and the mixture was stirred overnight, gradually warming to rt. Potassium carbonate (5.5 g, 40 mmol) in water (20 mL) and MeOH (20 mL) was added, and the mixture was stirred for 4 days at 60 °C. MeOH was evaporated, the desired compound was extracted with EtOAc (3×), and the organic layer was washed with water and brine and dried over $MgSO_4$. After purification by column chromatography (EtOAc−CH_2Cl_2) and crystallization from EtOAc−hexane, **10b** was obtained as a yellow solid (290 mg, 20.5%): ^{1}H NMR (DMSO-d_6) δ 8.25 (d, J = 9.1 Hz, 2H), 7.69 (brs, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.19 (brs, 2H), 7.13 (d, J = 9.3 Hz, 2H), 2.97 (s, 3H); MS m/z 366 (M + 1).

***N*-(6-(4-Aminophenoxy)benzthiazole-2-yl)methanesulfonyl Amide (10c).** To a solution of **10b** (100 mg, 0.27 mmol) in acetic acid (1 mL) was added Zn (54 mg, 0.81 mmol), and the mixture was stirred overnight at rt. Acetic acid was removed by evaporation and the residue was dissolved in DMF and then filtered. Filtrate was purified by SPE (SCX) tube (washed with MeOH/DMF and eluted with NH_3/MeOH). NH_3/MeOH eluent was collected to provide **10c** (72 mg 79.5%): ^{1}H NMR (DMSO-d_6) δ 7.32 (d, J = 2.5 Hz, 1H), 7.28 (brs, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.90 (dd, J = 8.8 and 2.5 Hz, 1H), 6.75 (d, J = 8.8 Hz, 2H), 6.68 (brs, 1H), 6.58 (d, J = 8.8 Hz, 2H), 2.95 (s, 3H); MS m/z 336 (M + 1).

Methyl (6-(4-Nitrophenoxy)benzthiazole-2-yl)carbamate (10d). To a mixture of **10a** (430.5 mg, 1.5 mmol) in pyridine (6 mL) and DMF (9 mL) was dropwise added an excess amount of $ClCO_2Me$ (ca. 0.8 mL) at rt. To the mixture was added water. The precipitate that formed was collected by filtration, washed with water and MeOH, and dried under reduced pressure to give **10d** (503.7 mg, 97%): ^{1}H NMR (DMSO-d_6) δ 12.18 (brs, 1H), 8.25 (d, J = 9.1 Hz, 2H), 7.89 (d, J = 2.5 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.25 (dd, J = 8.8 and 2.5 Hz, 1H), 7.15 (d, J = 9.1 Hz, 2H), 3.79 (s, 3H); MS m/z 346 (M + 1).

Methyl (6-(4-Aminophenoxy)benzthiazole-2-yl)carbamate (10e). To a solution of **10d** (172.7 mg, 0.5 mmol) in DMF (5 mL) was added $SnCl_2$ (474.0 mg, 2.5 mmol) and the mixture was stirred at rt for 4 days. The mixture was extracted with EtOAc, and the organic layer was washed with aq $NaHCO_3$, dried over Na_2SO_4, and the solvent was removed. The residue was dissolved in a small amount of DMF, was charged on SCX column chromatography, then washed with MeOH and eluted with NH_3−MeOH to give **10e** (69.2 mg, 44%): ^{1}H NMR (DMSO-d_6) δ 11.99 (brs, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 6.97 (dd, J = 8.6 and 2.5 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 4.98 (brs, 2H), 3.76 (s, 3H); MS m/z 316 (M + 1).

4-(3-Benzyloxy-4-nitrophenoxy)aniline (11). To a mixture of 60% NaH (440 mg, 11.0 mmol) in DMF (20 mL) was dropwise added 4-aminophenol (1.20 g, 11.0 mmol) in DMF (15 mL) followed by 2-benzyloxy-4-nitro-1-fluorobenzene (obtained from the benzylation of 5-fluoro-2-nitrophenol with benzylbromide; 2.47 g, 10.0 mmol) in DMF (15 mL). The mixture was stirred at rt for 10 min and then at 80 °C overnight. After cooling, the mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column chromatography (hexane−EtOAc), **11** (3.30 g, 98%) was obtained: ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 9.1 Hz, 1H), 7.37 (m, 5H), 6.85 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 2.5 Hz, 1H), 6.47 (dd, J = 9.1 and 2.5 Hz, 1H), 5.14 (s, 2H), 3.70 (brs, 2H); MS m/z 337 (M + 1).

***N*-(4-(3-Benzyloxy-4-nitrophenoxy)phenyl)(2-fluoro-5-(trifluoromethyl)phenylamino)formamide (12a).** To a mixture of **11** (1.34 g, 4.0 mmol) in THF (40 mL) was added 2-fluoro-5-(trifruolomethyl)phenyl isocyanate (636 μL, 4.4 mmol) and the mixture was stirred at rt overnight. To the mixture was added MeOH, after which the solvent was removed by evaporation. The residue was purified on a silica gel column ($CHCl_3$−MeOH) to give **12a** in a quantitative yield (2.17 g): ^{1}H NMR (DMSO-d_6) δ 8.60 (brdd, J = 7.3 and 2.0 Hz, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.44−7.26 (m, 6H), 7.18 (m, 1H), 7.05 (brs, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.94 (brs, 1H), 6.67 (d, J = 2.5 Hz, 1H), 6.51 (dd, J = 9.1 and 2.5 Hz, 1H), 5.16 (s, 2H); MS m/z 542 (M + 1).

6-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenyloxy)benzoxazol-2-ylamine (12b). After hydrogenation of **12a** (542 mg, 1.0 mmol) with 5% Pd−C in MeOH (10 mL), BrCN (800 mg, 7.6 mmol) was added and stirred at rt for 4 days. To the mixture was added $NaHCO_3$ (aq), and the mixture was stirred for 1 day. The mixture was extracted with EtOAc. The organic layer was washed with aq $NaHCO_3$ and brine and dried over Na_2SO_4. After solvent removal and sequence purification on a silica gel column ($CHCl_3$−MeOH), **12b** was obtained (237 mg, 53%): ^{1}H NMR (DMSO-d_6) δ 9.30 (brs, 1H), 9.01 (brs, 1H), 8.60 (brd, J = 7.8 Hz, 1H), 7.49 (m, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.38 (m, 1H), 7.35 (brs, 2H), 7.16 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 8.3 and 2.3 Hz, 1H); MS m/z 447 (M + 1).

4-(4-(Acetamido)phenylcarbonyl)-1,2-diaminobenzene (13a). A mixture of 3,4-dinitrobenzoyl chloride (4 mmol; obtained from 3,4-dinitrobenzoic acid and $(COCl)_2$), acetoanilide (540 mg, 4 mmol), and $AlCl_3$ (1.6 g) in CH_2Cl_2 was heated at 40 °C for 24 h. The slurry was washed with aq HCl, and the product was extracted with ether. It was washed with aq K_2CO_3, dried, and evaporated. Purification by column chromatography on silica gel (hexane−EtOAc) provided 87 mg of the dinitro intermediate: MS m/z 328 (M − 1). This compound (87 mg, 0.26 mmol) was treated with Zn (60 mg) in acetic acid (10 mL) for 2 h at rt to give **13a** (36 mg, 33%): ^{1}H NMR (DMSO-d_6) δ 7.68 (2H, d, J = 8.6 Hz), 7.57 (2H, d, J = 8.6 Hz), 7.04 (1H, d, J = 2.0 Hz), 6.88 (1H, dd, J = 8.1 and 2.0 Hz), 6.53 (2H, d, J = 8.1 Hz), 5.41 (brs, 2H), 4.70 (sbr, 2H), 2.14 (s, 3H).

Methyl *N*-(5-(4-Acetamidobenzoyl)-1*H*-benzimidazol-2-yl)-carbamate (13b). Using the method for **2**, **13b** was prepared from **13a** in 40% yield: ^{1}H NMR (DMSO-d_6) δ 10.30 (1H, s), 7.73 (4H, m), 7.82 (1H, sbr), 7.53 (2H, m), 3.78 (3H, s), 2.10 (3H, s); MS m/z 353 (M + 1).

General Procedure A. Methyl *N*-(5-(4-(Phenylaminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (15). A mixture of **3c** (101 mg, 0.34 mmol) and phenyl isocyanate (46 mg, 0.40 mmol) in dry THF (2 mL) was stirred at rt overnight. Et_2O was added. The solid formed was collected by filtration to provide **15** (88.7 mg, 62%): ^{1}H NMR (DMSO-d_6) δ 8.89 (s, 1H), 7.44 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 8.0 Hz, 2H), 7.20 (brs, 1H), 7.07 (brs, 1H), 6.99 (d, J = 2.3 Hz, 1H), 6.95 (m, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.79 (dd, J = 8.6 and 2.3 Hz, 1H), 3.74 (s, 3H); LC-LC-MS m/z 418 (M + 1), 93.5%.

Methyl *N*-(5-(4-((3-(Trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (16). General procedure A was utilized. Compound **3c** and 3-trifluoromethyphenyl isocyanate gave a brown solid (66%): ^{1}H NMR (DMSO-d_6) δ 11.80 (brs, 2H), 9.04 (s, 1H), 8.78 (s, 1H), 8.01 (s, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.00 (s, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.79 (d, J = 8.0 Hz, 1H), 3.74 (s, 3H); LC-LC-MS m/z 486 (M + 1), 98.6%.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenoxy)-1*H*-benzimidazol-2-yl)carbamate (17). General procedure A was utilized using **3c** and 2-fluoro-5-trifluoromethylphenyl isocyanate, leading to **17** as a brown solid (70%): ^{1}H NMR (DMSO-d_6) δ 11.60 (brs, 2H), 9.13 (s, 1H), 8.85 (d, 1H), 8.62 (d, J = 2.5 Hz, 1H), 7.49 (m, 1H), 7.44 (d, J = 8.9 Hz, 2H), 7.40−7.35 (m, 2H), 7.01 (d, J = 2.3 Hz, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.79 (dd, J = 8.6 and 2.5 Hz, 1H), 3.74 (s, 3H); LC-MS m/z 418 (M + 1), 99.3%. Further treatment with HCl in methanol gave HCl salt: $C_{23}H_{17}F_4N_5O_4 \cdot HCl \cdot H_2O$. Elemental analysis (C, H, N): C calcd 49.52, found 49.25; H calcd 3.61, found 3.58; N calcd 12.55, found 12.44.

Methyl *N*-(5-(4-((2-Chloro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (18). General procedure A was utilized using **3c** and 2-chloro-5-trifluoromethylphenyl isocyanate leading to **18** as a brown solid (69%): ^{1}H NMR (DMSO-d_6) δ 12.0−11.2 (brs, 2H), 9.53 (s, 1H), 8.65 (d, 1H), 8.57 (s, 1H), 7.71 (d, 1H), 7.45 (d, 2H), 7.37 (m, 2H), 7.01 (s, 1H), 6.94 (d, 2H), 6.80 (dd, 1H), 3.75 (s, 3H); LC-MS *m*/*z* 520 (M + 1), 522 (M + 3), 99.9%. Further treatment with HCl in methanol gave HCl salt: $C_{23}H_{18}F_3N_5O_4 \cdot HCl \cdot H_2O$. Elemental analysis (C, H, N): C calcd 48.10, found 47.83; H calcd 3.51, found 3.47; N calcd 12.20, found 12.23.

Methyl *N*-(5-(4-((3-Ethylphenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (19). General procedure A was utilized using **3c** and 3-ethylphenyl isocyanate leading to **19** as a brown solid (71%): ^{1}H NMR (DMSO-d_6) δ 11.60 (brs, 2H), 8.71 (s, 1H), 8.67 (s, 1H), 7.42 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.31−6.98 (m, 4H), 6.92 (d, J = 9.0 Hz, 2H), 6.83−6.77 (m, 2H), 3.75 (s, 3H), 2.57 (m, 2H), 1.17 (t, 3H); LC-MS *m*/*z* 446 (M + 1), 96.5%.

Methyl *N*-(5-(4-((3-Bromophenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (20). General procedure A was utilized using **3c** and 3-bromophenyl isocyanate leading to **20** as a brown solid (64%): ^{1}H NMR (DMSO-d_6) δ 12.2−11.0 (brs, 2H), 9.11 (s, 1H), 8.93 (s, 1H), 7.84 (s, 1H), 7.42 (d, J = 9.1 Hz, 2H), 7.37 (d, J = 8.6 Hz, 1H), 7.31 (m, 1H), 7.22 (t, J = 8.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 3.0 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 6.79 (dd, J = 7.5 and 2.5 Hz, 1H), 3.74 (s, 3H); LC-MS *m*/*z* 496 (M + 1), 498 (M + 3), 99.7%.

Methyl *N*-(5-(4-((3-Chlorophenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (21). General procedure A was utilized using **3c** and 3-chlorophenyl isocyanate leading to **21** as a brown solid (75%): ^{1}H NMR (DMSO-d_6) δ 11.60 (brs, 2H), 9.00 (s, 1H), 8.83 (s, 1H), 7.70 (m, 1H), 7.42 (d, J = 9.0 Hz, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.32−7.24 (m, 2H), 7.01 (m, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.80 (dd, J = 7.5 and 2.5 Hz, 1H), 3.75 (s, 3H); LC-MS *m*/*z* 452 (M + 1), 454 (M + 3), 99.9%.

Methyl *N*-(5-(4-((2,5-Difluorophenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (22). General procedure A was utilized using **3c** and **2**, 5-difluorophenyl isocyanate, leading to **22** as a brown solid (90%): ^{1}H NMR (DMSO-d_6) δ 12.0−11.0 (brs, 2H), 9.09 (s, 1H), 8.71 (s, 1H), 8.04 (m, 1H), 7.42 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.29 (m, 1H), 7.00 (d, J = 2.5 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 6.82 (m, 1H), 6.79 (dd, J = 8.5 and 2.5 Hz, 1H), 3.74 (s, 3H); LC-MS *m*/*z* 454 (M + 1), 94.4%.

Methyl *N*-(5-(4-((3-(Trifluoromethylthio)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (23). General procedure A was utilized using **3c** and 3-trifluoromethylthiophenyl isocyanate leading to **23** as a brown solid (69%): ^{1}H NMR (DMSO-d_6) δ 12.2−11.2 (brs, 2H), 8.96 (s, 1H), 8.73 (s, 1H), 7.98 (s, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.46−7.42 (m, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.79 (dd, J = 8.5 and 2.0 Hz, 1H), 3.74 (s, 3H); LC-MS *m*/*z* 518 (M + 1), 99.1%.

Methyl *N*-(5-(4-((3-Methylthiophenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (24). General procedure A was utilized using **3c** and 3-methylthiophenyl isocyanate leading to **24** as a brown solid (77%): ^{1}H NMR (DMSO-d_6) δ 12.2−11.2 (brs, 2H), 8.67 (s, 1H), 8.64 (s, 1H), 7.46 (s, 1H), 7.41 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.78 (dd, J = 8.5 and 2.2 Hz, 1H), 3.74 (s, 3H), 2.45 (s, 3H); LC-MS *m*/*z* 464 (M + 1), 99.9%.

Methyl *N*-(5-(4-((2-Fluoro-5-aminophenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (25). General procedure A was utilized using **3c** and 2-fluoro-5-nitrophenyl isocyanate leading to *N*-(5-(4-((2-fluoro-5-nitrophenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate as a yellow solid (90%). The HCl salt of the compound (95 mg, 0.18 mmol) and $SnCl_2$ (350 mg, 1.5 mmol) in DMF (3 mL) were stirred overnight. The mixture was washed with aq $NaHCO_3$, extracted with AcOEt, dried over MgSO4, and evaporated to give a crude product. It was eluted through SCX ion exchange column with MeOH−NH_3 to give **25** as a brown solid (33 mg, 41%): ^{1}H NMR (DMSO-d_6) δ 11.65 (sbr, 2H), 8.99 (s, 1H), 8.22 (s, 1H), 7.44 (dd, J = 7.0 and 2.0 Hz, 1H), 7.41 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 6.99 (brs, 1 H), 6.91 (d, J = 9.0 Hz, 2H), 6.85 (dd, J = 11 and 9.0 Hz, 1H), 6.78 (dd, J = 9.0 and 2.0 Hz, 1H), 6.10 (m, 1H), 3.74 (s, 3H); MS *m*/*z* 451 (M + 1), 95%.

Methyl *N*-(5-(4-((3-Carboxyphenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (26). General procedure A was utilized using **3c** and 3-ethoxycarbonylphenyl isocyanate leading to *N*-(5-(4-((3-ethoxycarbonylphenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate as a brown solid (82%). Hydrolysis of the product (100 mg) with 1 N NaOH (1 mL) in EtOH (1 mL) and THF (2 mL) gave **26** as an off-white solid (84 mg, 90%): ^{1}H NMR (DMSO-d_6) δ 12.2−11.2 (brs, 2H), 8.97 (brs, 1H), 8.77 (brs, 1H), 8.12 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.38 (m, 2H), 7.00 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 8.5 and 2.5 Hz, 1H), 3.74 (s, 3H); MS *m*/*z* 462 (M + 1), 96.9%.

Methyl *N*-(5-(4-((3-(Trifluoromethyl)phenyl)aminothiocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (27). General procedure A was utilized using **3c** and 3-trifluoromethylphenyl isothiocyanate leading to **27** as a brown solid (60%): ^{1}H NMR (DMSO-d_6) δ 12.0−11.2 (brs, 2H), 9.95 (s, 1H), 9.92 (s, 1H), 7.95 (s, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.39 (m, 1H), 7.38 (d, J = 9.0 Hz, 2H), 7.06 (s, 1H), 6.93 (d, J = 9.0 Hz, 2H), 6.81 (dd, J = 8.5 and 2.2 Hz, 1H), 3.75 (s, 3H); MS *m*/*z* 502 (M + 1), 95.0%.

Methyl (5-(4-((2-(3-Trifluoromethyl)phenyl)acetylamido)phenoxy)-1*H*-benzoimidazol-2-yl)carbamate (28). A mixture of **3c** (130 mg, 0.44 mmol), 3-trifluoromethylphenylacetic acid (135 mg, 0.65 mmol), HBTU (250 mg, 0.65 mmol), and triethylamine (130 mg, 1.3 mmol) in DMF (2.5 mL) was stirred for 4 h. The precipitate formed was collected by filtration and dried in vacuo. It was loaded on a SCX ion exchange column, washed with MeOH, and eluted with MeOH−NH_3. The solution stood still to form a precipitate. Filtration afforded **28** (9.4 mg, 5%): ^{1}H NMR (DMSO-d_6) δ 10.2 (s, 1H), 7.70 (s, 1H), 7.62 (m, 3H), 7.55 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 8.8 and 2.5 Hz, 1H), 3.76 (m, 2H), 3.74 (s, 3H); LC-MS *m*/*z* 485 (M + 1), 99.0%.

Methyl (6-(4-(2-(2-Fluoro-5-(trifluoromethyl)phenylamino)-2-oxoethyl)phenoxy)-1*H*-benzoimidazol-2-yl)carbamate (29). A mixture of **6c** (210 mg, 0.5 mmol) and 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (108 mg, 0.53 mmol) in EtOH (5 mL) was refluxed overnight. After cooling, the insoluble material was collected by filtration and dried in vacuo to give desired compound **29** (174 mg, 68%): ^{1}H NMR (DMSO-d_6) δ 11.63 (brs, 2H), 10.28 (s, 1H), 8.44 (d, J = 7.6 Hz, 1H), 7.51−7.54 (m, 2H), 7.39 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 6.80 (dd, J = 8.6 and 2.3 Hz, 1H), 3.74 (brs, 5H); LC-MS *m*/*z* 503 (M + 1), 98.8%.

Methyl *N*-(5-(3-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)carbamate (30). General procedure A was utilized using **3a** and 2-fluoro-5-(trifluoromethyl)phenyl isocyanate leading to **30** as a brown solid (44%): ^{1}H NMR (DMSO-d_6) δ 11.67 (brs, 2H), 9.23 (s, 1H), 8.80 (s, 1H), 8.54 (d, J = 2.5 Hz, 1H), 7.48 (t, J = 2.3 Hz, 1H), 7.41 (m, 2H), 7.26 (t, J = 2.3 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 3.75 (s, 3H); LC-MS *m*/*z* 504 (M + 1), 94%.

Methyl *N*-(5-(5-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)-2-pyridyloxy)-1*H*-benzimidazol-2-yl)carbamate (31). General procedure A was used utilizing **7c** and 2-fluoro-5-trifluoromethylphenyl isocyanate leading to **31** as a brown solid (47%): ^{1}H NMR (DMSO-d_6) δ 12.0−11.1 (brm, 2H), 9.21(s, 1H), 8.96 (d, J = 2.76 Hz, 1H), 8.58 (dd, J = 5.3 and 2.0 Hz, 1H), 8.15 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 6.1 and 2.8 Hz 1H), 7.51 (t, J

= 11 Hz, 1H), 7.41−7.38 (m, 2H), 7.11 (d, *J* = 2 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.82 (dd, *J* = 6.0 and 2.3 Hz, 1H), 3.75 (s, 3H); LC-MS *m*/*z* 505 (M + 1), 98.8%.

Methyl *N*-(5-(5-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)-1-oxo-2-pyridyloxy)-1*H*-benzimidazol-2-yl)carbamate (32). A mixture of **31** (99 mg, 0.20 mmol) and mCPBA (530 mg) in CH_2Cl_2 (2 mL) was stirred overnight. It was loaded on a SCX ion change column, washed with MeOH, and eluted with MeOH−NH_3 to yield **32** (20 mg, 19%): ^{1}H NMR (DMSO-d_6) δ 12.2−11.2 (brs, 2H), 9.42 (s, 1H), 9.06 (s, 1H), 8.68 (s, 1H), 8.53 (d, *J* = 6.0 Hz, 1H), 7.53 (t, *J* = 9.0 Hz, 1H), 7.45 (brs, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 1H), 7.02 (s, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 3.75 (s, 3H); LC-MS *m*/*z* 521 (M + 1), 98.0%.

***N*-(5-(2-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)-5-pyridyloxy)-1*H*-benzimidazol-2-yl)acetamide Dihydrochloride (33).** General procedure A was utilized using **7a** and 2-fluoro-5-trifluoromethylphenyl isocyanate giving a free form of **33** as a brown solid (14%). Treatment with HCl−MeOH gave **33**: ^{1}H NMR (DMSO-d_6) δ 12.42 (brs, 1H), 10.64 (brs, 1H), 9.97 (s, 1H), 8.66 (dd, *J* = 5.3 and 2.0 Hz, 1H), 8.11 (d, *J* = 3.0 Hz, 1H), 7.68−7.61 (m, 1H), 7.60−7.48 (m, 3H), 7.47−7.41 (m, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 7.04 (dd, *J* = 6.3 and 2.3 Hz, 1H), 2.24 (s, 3H); LC-MS *m*/*z* 489 (M + 1), 93%.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenylthio)-1*H*-benzimidazol-2-yl)carbamate (34). General procedure A was utilized using **3b** and 5-fluoro-3-trifruolomethylphenyl isocyanate (1.90 g, 9.25 mmol) leading to **34** (4.12 g, 94%): ^{1}H NMR (DMSO-d_6) δ 11.70 (drs, 2H), 9.29 (s, 1H), 8.91 (s, 1H), 8.61 (d, 1H *J* = 6.9 Hz), 7.30−7.55 (m, 6H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 1H), 3.76 (s, 3H); LC-MS *m*/*z* 520 (M + 1), 97.7%. Further treatment with HCl in methanol gave HCl salt: $C_{23}H_{18}F_4N_5O_3S\cdot HCl\cdot H_2O$. Elemental analysis: C calcd 48.13, found 48.24; H calcd 3.51, found 3.40; N calcd 12.20, found 12.10.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenylsulfinyl)-1*H*-benzimidazol-2-yl)carbamate (35). To **34** (100 mg, 0.19 mmol) in acetic acid (ca. 5 mL), mCPBA (26 mg, 0.21mmol) was added at 0 °C, and this mixture was stirred at rt overnight. To the mixture was added $NaHCO_3$ (aq), and the solid formed was collected by filtration. The solid was purified on a NH_2 SiO_2 column (CH_2Cl_2/MeOH = 15:1) to give **35** as a colorless solid (37 mg, 36%): ^{1}H NMR (DMSO-d_6) δ 9.49 (brs, 1H), 9.00 (brs, 1H), 8.58 (brd, *J* = 7.1 Hz, 1H), 7.72 (brs, 1H), 7.60 (m, 4H), 7.50 (m, 2H), 7.41 (m, 1H), 7.33 (dd, *J* = 8.3 and 1.5 Hz, 1H), 3.75 (s, 3H); LC-MS *m*/*z* 536 (M + 1), 94.9%.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenylsulfonyl)-1*H*-benzimidazol-2-yl)carbamate (36). To a solution of **35** (100 mg, 0.19 mmol) in acetic acid (2 mL) was added mCPBA (92 mg, 0.53 mmol) in CH_2Cl_2 (1 mL) and stirred overnight. Aqueous $NaHCO_3$ was added to precipitate an off-white solid. It was collected by filtration, washed with water, and dried in vacuo to give **36** as an off-white solid (80 mg, 76%): ^{1}H NMR (DMSO-d_6) δ 12.29 (brs, 1H), 11.59 (brs, 1H), 9.70 (s, 1H), 9.07 (d, *J* = 2.5 Hz, 1H), 8.56 (dd, *J* = 7.3 and 2.5 Hz, 1H), 7.96 (brs, 1H), 7.85 (d, *J* = 9.1 Hz, 2H), 7.66 (d, *J* = 9.1 Hz, 2H), 7.63 (dd, *J* = 8.6 and 2.0 Hz, 1H), 7.61−7.46 (m, 2H), 7.42 (m, 1H), 3.78 (s, 3H); LC-MS *m*/*z* 552 (M + 1), 96.1%.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenylcarbonyl)-1*H*-benzimidazol-2-yl)carbamate (37). Compound **13b** was deacetylated with HCl and, using general procedure A, was reacted with 2-fluorol-5-(trifluoromethyl)-phenyl isocyanate to give **37** as a brown solid (20%): ^{1}H NMR (DMSO-d_6) δ 12.5−11.2 (brs, 2H), 9.59 (s, 1H), 9.04 (s, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 7.83 (brs, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.55−7.50 (m, 3H), 7.44 (m, 1H), 3.78 (s, 3H); LC-MS *m*/*z* 516 (M + 1), 92%.

Methyl *N*-(6-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenoxy)-1-methyl-1*H*-benzimidazol-2-yl)carbamate (38). General procedure A was utilized using **8f** and 2-fluoro-5-trifluoromethylphenyl isocyanate leading to **38** as ivory needles (99%): ^{1}H NMR (DMSO-d_6) δ 9.22 (brs, 1H), 8.93 (brs, 1H), 8.61 (brd, *J* = 6.3 Hz, 1H), 7.50 (m, 1H), 7.45 (d, *J* = 9.1 Hz, 2H), 7.38 (m, 2H), 7.14 (brd, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 9.1 Hz, 2H), 6.83 (brdd, *J* = 8.3 and 2.0 Hz, 1H), 3.62 (brs, 3H), 3.46 (brs, 3H); LC-MS *m*/*z* 518 (M + 1), 99.6%.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenoxy)-1-methyl-1*H*-benzimidazol-2-yl)carbamate (39). General procedure A was utilized using **8c** and 2-fluoro-5-trifluoromethylphenyl isocyanate leading to **39** as a solid (98%): ^{1}H NMR (DMSO-d_6) δ 8.66 (brd, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 9.1 Hz, 2H), 7.23 (m, 1H), 7.15 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.96−6.90 (m, 2H), 6.96 (d, *J* = 9.1 Hz, 2H), 3.78 (s, 3H), 3.59 (s, 3H), three NH were not detected; LC-MS *m*/*z* 518 (M + 1), 94.4%.

Methyl *N*-(6-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-benzthiazol-2-yl)carbamate (40). General procedure A was utilized using **10e** and 2-fluoro-5-trifluoromethylphenyl isocyanate leading to **40** as a colorless powder (95%): ^{1}H NMR (DMSO-d_6) δ 12.05 (brs, 1H), 9.18 (s, 1H), 8.87 (d, *J* = 2.8 Hz, 1H), 8.62 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.66 (m, 1H), 7.61 (brs, 1H), 7.50 (m, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.38 (m, 1H), 7.07 (dd, *J* = 8.6 and 2.0 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.77(s, 3H); LC-MS *m*/*z* 521 (M + 1), 99.9%.

Methyl *N*-(6-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy) benzoxazol-2-yl)carbamate (41). To a mixture of **12b** (67.0 mg, 0.15 mmol) in pyridine (2 mL) was added dropwise an excess amount of $ClCO_2Me$ (ca. 0.23 mL) at rt. To the mixture was added water, and the mixture was stirred at rt overnight. The mixture was extracted with EtOAc. The organic layer was washed with $NaHCO_3$ (aq) and brine and dried over Na_2SO_4. After evaporation, residual solid was washed with MeOH and dried under reduced pressure to give **41** as a solid (46.1 mg, 61%): ^{1}H NMR (DMSO-d_6) δ 11.59 (brs, 1H), 9.16 (s, 1H), 8.86 (s, 1H), 8.62 (brd, *J* = 7.3 Hz, 1H), 7.50 (m, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.39 (m, 1H), 7.26 (brs, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.92 (brd, *J* = 8.6 Hz, 1H), 3.70 (s, 1H); LC-MS *m*/*z* 505 (M + 1), 96.9%.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenoxy)-3a-aza-2-indolyl)carbamate (42). General procedure A was utilized using **9g** and 2-fluoro-5-trifluoromethylphenyl isocyanate leading to **42** as a solid (79%): ^{1}H NMR (DMSO-d_6) δ 10.27 (brs, 1H), 9.26 (brs, 1H), 8.95 (brs, 1H), 8.60 (brd, *J* = 7.6 Hz, 1H), 8.47 (m, 1H), 7.87 (brs, 1H), 7.50 (m, 1H), 7.47 (d, *J* = 9.1 Hz, 2H), 7.42 (d, *J* = 9.6 Hz, 1H), 7.38 (m, 1H), 7.05 (dd, *J* = 9.6 and 2.3 Hz, 1H), 7.02 (d, *J* = 9.1 Hz, 2H), 3.68 (s, 3H); LC-MS *m*/*z* 504 (M + 1), 97.8%.

Methyl *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenoxy)-3,4-diazaindole-2-yl)carbamate Dihydrochloride (43). General procedure A was utilized using **9b** and 2-fluoro-5-trifluoromethylphenyl isocyanate leading to the free form of **43** (75%). Treatment with HCl gave **43** as an ivory powder: ^{1}H NMR (DMSO-d_6) δ 9.24 (brs, 1H), 8.94 (brs, 1H), 8.62 (brd, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.50 (m, 1H), 7.47 (d, *J* = 9.1 Hz, 2H), 7.39 (m, 1H), 7.04 (d, *J* = 9.1 Hz, 2H), 6.71 (brd, 1H), 3.75 (s, 3H), two NH were not detected; LC-MS *m*/*z* 505 (M + 1), 98.9%.

Methyl *N*-(6-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino) phenoxy)-3,4-diaza-1*H*-indole-2-yl)carbamate Dihydrochloride (44). General procedure A was utilized using **9e** and 2-fluoro-5-trifluoromethylphenyl isocyanate leading to the free form of **44** as a brown solid (63%). Treatment with HCl resulted in **44**: ^{1}H NMR (DMSO-d_6) δ 9.22 (brs, 1H) 8.89 (brs, 1H), 8.61 (brd, *J* = 6.6 Hz, 1H), 8.08 (brs, 1H), 7.50 (m, 1H), 7.48 (d, *J* = 9.1 Hz, 2H), 7.46 (overlapped, 1H), 7.39 (m, 1H), 7.01 (d, *J* = 9.1 Hz, 2H), 3.78 (s, 3H), two NH were not detected; LC-MS *m*/*z* 419 (M + 1).

2-Amino-5-(4-((2-fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazole (45). To a solution of **5b** (1.5 g, 3.6 mmol) in MeOH (20 mL) was added BrCN (490 mg, 4.6 mmol). The reaction mixture was stirred for 1 h and then

washed with aq NaOH. The product was extracted with AcOEt, dried over $MgSO_4$, and the solvent was evaporated. Purification with SCX ion exchange column (eluted with aq NH_3 in MeOH) yielded **45** as a brown solid (1.53 g, 96%): ^{1}H NMR (DMSO-d_6) δ 10.63 (brs, 1H), 9.08 (s, 1H), 8.83 (s, 1H), 8.62 (d, J = 7.3 Hz, 1H), 7.49 (t, J = 9.5 Hz, 1H), 7.40 (d, J = 9.1 Hz, 2H), 7.38 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 9.1 Hz, 2H), 6.74 (s, 1H), 6.55 (d, 1H), 6.15 (s, 2H); LC-MS m/z 446 (M + 1), 95.1%.

General Procedure B. *N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)-phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)-acetamide (46). To a mixture of **45** (72 mg, 0.165 mmol), acetic acid (15 mg, 0.24 mmol), and triethylamine (50 mg) in DMF was added HBTU (91 mg, 0.24 mmol) and HOBT (20 mg). The reaction mixture was stirred for 4 h, poured into water, washed, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. Purification of the residue by column chromatography on silica gel (EtOAc as eluent) afforded **46** (28 mg, 36%): ^{1}H NMR (DMSO-d_6) δ 11.99 (brs, 1H), 11.51 (brs, 1H), 9.15 (s, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.62 (dd, J = 7.3 and 2.0 Hz, 1H), 7.50 (t, J = 8.6 Hz, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.38 (m, 2H), 7.04 (d, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.80 (dd, J = 8.6 and 2.0 Hz, 1H), 2.15 (s, 3H); LC-MS m/z 488 (M + 1), 94%.

***N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)benzamide (47).** General procedure B was utilized using benzoic acid leading to **47** as a brown solid (89%): ^{1}H NMR (DMSO-d_6) δ 12.6−12.2 (brs, 2H), 9.15 (s, 1H), 8.87 (d, J = 3.0 Hz, 1H), 8.62 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 7.0 Hz, 2H), 7.95 (s, 2H), 7.64−7.50 (m, 4H), 7.45 (d, J = 9.0 Hz, 2H), 7.39 (brm, 1H), 6.97 (d, J = 9.0 Hz, 2H), 6.86 (dd, J = 8.5 and 2.5 Hz, 1H); LC-MS m/z 550 (M + 1), 97.5%.

***N*-(6-(4-((2-Fluoro-5(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)-2-(1*H*-pyrrol-1-yl)benzamide (48).** General procedure B was utilized using 1-(2-carboxyphenyl)pyrrole leading to **48** as a yellow solid (53%): ^{1}H NMR (DMSO-d_6) δ 9.27 (s, 1H), 8.92 (s, 1H), 8.61 (dd, J = 7.0 and 2.0 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.54−7.46 (m, 6H), 7.38 (m, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.00 (m, 5H), 6.19 (t, J = 2.0 Hz, 2H); LC-MS m/z 615 (M + 1), 94%.

***N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)-2-furylcarboxamide (49).** General procedure B was utilized using 2-furoic acid leading to **49** as an off-white solid (94%): ^{1}H NMR (DMSO-d_6) δ 12.40 (brs, 2H), 9.16 (s, 1H), 8.88 (d, J = 3 Hz, 1H), 8.62 (dd, J = 7.5 and 2 Hz, 1H), 7.95 (s, 1H), 7.45 (m, 5H), 7.39 (m, 1H), 7.05 (d, J = 2 Hz, 1H), 6.96 (d, J = 8.5 Hz, 2H), 6.86 (dd, J = 8.5 and 2 Hz, 1H), 6.70 (dd, J = 4 and 2 Hz, 1H); LC-MS m/z 540 (M + 1), 98.9%.

***N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)-3-pyridinecarboxamide (50).** General procedure B was utilized using nicotinic acid leading to **50** as an off-white solid (98%): ^{1}H NMR (DMSO-d_6) δ12.41 (br, 2H), 9.26 (d, J = 1.5 Hz, 1H), 9.16 (s, 1H), 8.87 (m, 1H), 8.74 (dd, J = 4.8 and 1.3 Hz, 1H), 8.62 (dd, J = 5.4 and 2.0 Hz, 1H), 8.43 (m, 1H), 7.57−7.42 (m, 5H), 7.42−7.36 (m, 1H), 7.05 (d, J = 1.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 8.6 and 2.5 Hz, 1H); LC-MS m/z 551 (M + 1), 98.4%.

***N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)-2-(2-methoxyethoxy)-acetamide (51).** General procedure B was utilized using methoxyethoxyacetic leading to **51** as an off-white solid (73%): ^{1}H NMR (DMSO-d_6) δ 12.11 (brs, 1H), 11.28 (brs, 1H), 9.14 (s, 1H), 8.86 (d, J = 2.8 Hz, 1H), 8.61 (dd, J = 7.3 and 2.0 Hz, 1H), 7.38−7.52 (m, 5H), 6.98−7.14 (brs, 1H), 6.94 (d, J = 9.1 Hz, 2H), 6.82 (dd, J = 8.6 and 2.5 Hz, 1H), 4.22 (s, 2H), 3.68−3.71 (m, 2H), 3.51−3.54 (m, 2H), 3.30 (s, 3H); LC-MS m/z 562 (M + 1), 93%.

***N*-(5-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazol-2-yl)-2-(4-methylpiperazin-1-yl)acetamide (52).** General procedure B was utilized using *N*-methylpiperazinoacetic leading to **52** as an off-white solid (50%): ^{1}H NMR (DMSO-d_6) δ 11.90−12.25 (brd, 1H), 10.90−11.30 (brs, 1H), 9.13 (s, 1H), 8.85 (s, 1H), 8.62 (d, J = 7.6 Hz, 1H), 7.33−7.53 (m, 5H), 6.97−7.18 (brd, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.81 (dd, J = 8.3 and 2.2 Hz, 1H), 3.26 (s, 2H), 2.54−2.62 (brs, 4H), 2.28−2.42 (brs, 4H), 2.16 (s, 3H); LC-MS m/z 584 (M − 1), 97.0%.

2-(2-(4-Methyl-1-piperazino)ethylamino)-5-(4-((2-fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)-1*H*-benzimidazole (53). To a stirred solution of **52** (150 mg, 0.26 mmol) in dry THF (10 mL) under nitrogen was added dropwise a solution of LAH in THF (5 mL of a 1 M solution, 5 mmol). The reaction was stirred at rt for 5 h and then quenched by slow dropwise addition of EtOAc, followed by MeOH and water. The resulting white precipitate was filtered off through a celite pad and washed well with MeOH. The filtered solution was evaporated to dryness and partitioned between EtOAc and water. The aqueous phase was further extracted by EtOAc (3×), and the combined EtOAc solutions were dried over $MgSO_4$ and concentrated to give a crude product as an oil. Purification of the crude material by column chromatography (eluting with EtOAc and incremental amounts of methanolic NH_3, up to 10%) afforded **53** as an oil (86 mg, 58% yield): ^{1}H NMR (DMSO-d_6) δ 10.80 (brs, 1H), 9.10 (s, 1H), 8.84 (d, J = 2.8 Hz, 1H), 8.61 (dd, J = 7.3 and 2.0 Hz, 1H), 7.49 (t, J = 9.1 Hz, 1H), 7.35−7.43 (m, 4H), 7.08 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 2.3 Hz, 1H), 6.41 (brs, 1H), 2.25−2.45 (m, 4H), 2.15 (s, 4H), 1.76 (s, 7H); LC-MS m/z 572 (M + 1), 95%.

***N*-(6-(4-((2-Fluoro-5-(trifluoromethyl)phenyl)aminocarbonylamino)phenoxy)benzthiazol-2-yl)methanesulfonamide (54).** A mixture of 2-fluoro-5-(trifluoromethyl)phenyl isocyanate (47.4 mg, 0.23 mmol) and **10c** (72 mg, 0.21 mmol) in THF (3 mL) was stirred overnight at 45 °C. The reaction mixture was cooled to room temperature, ether was added, and a pale brown solid was generated. The solid was collected by filtration, washed with ether, and dried in vacuo to give **54** (55 mg, 50%): ^{1}H NMR (DMSO-d_6) δ 12.95 (br, 1H), 9.18 (s, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.62 (dd, J = 7.8 and 2.5 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1H), 7.50 (m, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.39 (m, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 8.6 and 2.5 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 2.99 (s, 3H); LC-MS m/z 541 (M + 1), 98.9%.

TIE-2 Enzyme Assay (TIE-E). The TIE-2 enzyme assay used the LANCE method (Perkin-Elmer) and GST-TIE-2, baculovirus expressed recombinant constructs of the intracellular domains of human TIE-2 (amino acids 773−1124, GenBank Accession No. L06139) tagged by GST. The method measured the ability of the purified enzymes to catalyze the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, D1−15 (biotin-C6-LEARLVAYEGWVAGKKKamide). This peptide phosphorylation was detected using the following procedure: for enzyme preactivation, GST-TIE-2 was incubated for 30 min at room temperature with 2 mM ATP, 5 mM $MgCl_2$, and 12.5 mM DTT in 22.5 mM HEPES buffer (pH 7.4). Preactivated GST-TIE-2 was incubated for 30 min at room temperature in 96-well plates with 1 μM D1−15 peptide, 80 uM ATP, 10 mM $MgCl_2$, 0.1 mg/mL BSA, and the test compound (diluted from a 10 mM stock in DMSO, final DMSO concentration was 2.4%) in 1 mM HEPES (pH 7.4). The reaction was stopped by the addition of EDTA (final concentration 45 mM). Streptavidin-linked APC (allophycocyanin, Molecular Probe) and Europium-labeled antiphosphorylated tyrosine antibody (Perkin-Elmer) were then added at the final concentration of 170 ng/well and 21 ng/well, respectively. The APC signal was measured using an ARVO multilabel counter. (Perkin-Elmer). The percent inhibition of activity was calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) was interpolated using nonlinear regression (Levernberg−Marquardt) and the equation, $y = V_{max}(1 - x/(K + x)) +$ Y2, where K was equal to the IC_{50}. The IC_{50} values were converted to pIC_{50} values, that is, $-\log IC_{50}$ in molar concentration. The results are represented in Table 1.

TIE-2 Autophosphorylation Assay (TIE-C). The TIE-2 autophosphorylation assay used an ELISA method and a TIE-2 intracellular domain/c-fms extracellular domain (TIE-2/c-fms)

chimeric protein expressing mouse NIH/3T3 cells. This assay measured the autophosphorylation level of TIE-2 protein expressed in cells. The cells were cultured in high glucose DMEM (Sigma) containing 10% serum at 37 °C in a humidified 10% CO_2, 90% air incubator. The test compound (diluted from a 10 mM stock in DMSO, final DMSO concentration was 0.1%) was incubated with TIE-2/c-fms expressing cells for 1 h in serum-free DMEM in 96-well plates followed by the activation of TIE-2/c-fms receptor using c-fms ligand, MCSF (macrophage colony stimulating factor). The culture media was removed by aspiration, and the cells were incubated for at least 30 min on ice with lysis buffer containing 137 mM NaCl, 2 mM EDTA, 10% glycerol, 2 mM sodium *ortho*-vanadate, and complete protease inhibitor cocktail (Roche) in 20 mM Tris-HCl (pH 8.0). The cell extracts were transferred into rat anti-c-fms antibody coated 96-well plates and incubated for 16 h at 4 °C. The extracts were removed by aspiration and the plate was incubated with biotinylated antiphosphotyrosine antibody, PT66 (Sigma) and then with HRP (horseradish peroxidase)-labeled streptavidin (PIERCE). The optical density at 450 nm derived from HRP-catalyzed TMB was measured with an ARVO multilabel counter (Perkin-Elmer). The percent inhibition of activity was calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) was interpolated using nonlinear regression (Levernberg−Marquardt) and the equation, $y = V_{max}\,(1 - x/(K + x)) + Y2$, where K was equal to the IC_{50}. The IC_{50} values were converted to pIC_{50} values, that is, $-\log IC_{50}$ in molar concentration. The results are represented in Table 1 below.

Assay Conditions: The final assay conditions were 50 mM HEPES, pH 7.5, 5% DMSO (when screening compounds), 200 μM ATP, 5 mM $MgCl_2$, 1 mM DTT, 50 μM sodium vanidate, 1 nM activated enzyme, and 200 μM peptide. IC_{50}s of compounds were measured under subsaturating ATP (200 μM) and varying concentrations of activated TIE-2 and peptide substrate (RFWKYEFWR-OH; MW 1873 Da, TFA salt). Panvera antiphosphotyrosine antibody (cat. No. P2840) and PTK Green Tracer (cat. No. P2842) were used to detect the phosphorylated peptide. Polarization was measured on a TECAN Polarion in 138-second cycles for 30 min at room temperature. IC_{50}s were then determined from the % polarization using normal calculation methods. Results are indicated below.

VEGFR-2 Enzyme Assay (VEGF-E). The VEGF enzyme assay used the LANCE method (Wallac) and GST-VEGFR-2, baculovirus-expressed recombinant constructs of the intracellular domains of human TIE-2 tagged by GST. The method measured the ability of the purified enzymes to catalyze the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, (biotin-aminohexyl-EEEEYFELVAKKKK-NH_2). This peptide phosphorylation was detected using the following procedure: GST-VEGFR-2 was incubated for 40−60 min at room temperature with 75 μM ATP, 5 mM $MgCl_2$, 0.1 mM DTT, 0.1 mg/mL BSA, and the test compound (diluted from a 10 mM stock in DMSO for desired concentration) in 100 mM HEPES buffer. The reaction was stopped by the addition of EDTA (final concentration 50 mM). Streptavidin-linked APC (allophycocyanin, Molecular Probe) and Europium-labeled antiphosphorylated tyrosine antibody (Wallac) were then added at the final concentration of 15 nM and 1nM, respectively. The APC signal was measured using an ARVO multilabel counter (Wallac Berthold, Japan). The percent inhibition of activity was calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) was interpolated using nonlinear regression (Levernberg−Marquardt) and the equation, $y = V_{max}\,(1 - x/(K + x)) + Y2$, where K was equal to the IC_{50}.

VEGFR-2 Crystallography. Protein expression, purification, and preparation of VEGFR-2 for crystallographic studies was carried out as described.[15] A crystal structure of unliganded VEGFR-2 was solved using the Amore molecular replacement program using the FGF kinase as the model. Map generation and density modification were carried out using the CCP4 program suite.[16] The structures were built using the program O[17] and refined using the program CNX.[18]

Cocrystals were prepared by adding a 3-fold molar excess of ligand (50 mM in DMSO) to the protein for 1 h prior to the start of crystallization under conditions similar to those used to grow the unliganded crystals. The crystal structure of a VEGFR-2 complexed with ligand was solved in a similar fashion to the liganded structure, except the VEGFR-2 structure was used as the search model.

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