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Design and Synthesis of Novel DFG-Out RAF/Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) Inhibitors. 1. Exploration of [5,6]-Fused Bicyclic Scaffolds†

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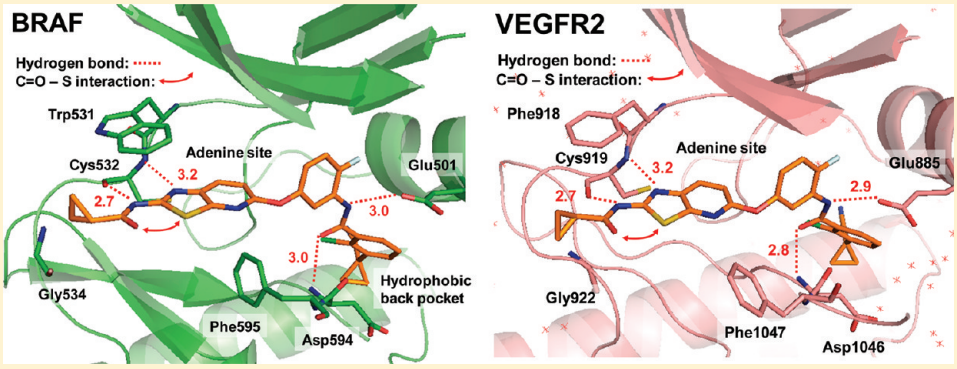
Supporting Information



ABSTRACT: To develop RAF/VEGFR2 inhibitors that bind to the inactive DFG-out conformation, we conducted structure-based drug design using the X-ray cocrystal structures of BRAF, starting from an imidazo[1,2-*b*]pyridazine derivative. We designed various [5,6]-fused bicyclic scaffolds (ring A, **1**−**6**) possessing an anilide group that forms two hydrogen bond interactions with Cys532. Stabilizing the planarity of this anilide and the nitrogen atom on the six-membered ring of the scaffold was critical for enhancing BRAF inhibition. The selected [1,3]thiazolo[5,4-*b*]pyridine derivative **6d** showed potent inhibitory activity in both BRAF and VEGFR2. Solid dispersion formulation of **6d** (**6d-SD**) maximized its oral absorption in rats and showed significant suppression of ERK1/2 phosphorylation in an A375 melanoma xenograft model in rats by single administration. Tumor regression (T/C = −7.0%) in twice-daily repetitive studies at a dose of 50 mg/kg in rats confirmed that **6d** is a promising RAF/VEGFR2 inhibitor showing potent anticancer activity.

INTRODUCTION

Signal transduction in the mitogen-activated protein kinase (MAPK) or Ras/RAF/MEK/ERK pathway plays critical roles in cellular activities, including proliferation, differentiation, and survival. The pathway is controlled by extracellular signals through membrane receptors such as receptor tyrosine kinases (RTK)[1] and is activated by oncogenic mutations in many types of cancer.[2] For example, there are many reports demonstrating the correlation between RAS mutations and malignant tumors.[3] According to these reports, the RAS gene is activated by mutations at codon 12, 13, or 61 in various carcinomas, including pancreatic cancer (~90%), non-small-cell lung cancer (~35%), and liver cancer (~30%), and so on. It is also known that BRAF mutation, particularly V600E, occurs in various carcinomas, including malignant melanoma (~60%), thyroid cancer (~30%), and colon cancer (~15%).[4,5] BRAF(V600E) kinase has approximately 13-fold more potent MEK phosphorylation activity than does wild-type BRAF kinase, and the BRAF mutation is deeply involved in the growth of these cancers.[6] Hence, targeting the Ras/RAF/MEK/ERK pathway may be a legitimate approach to cancer treatment.[7,8]

However, angiogenesis is also a critical process in solid tumor progression because the tumors require significantly more oxygen,

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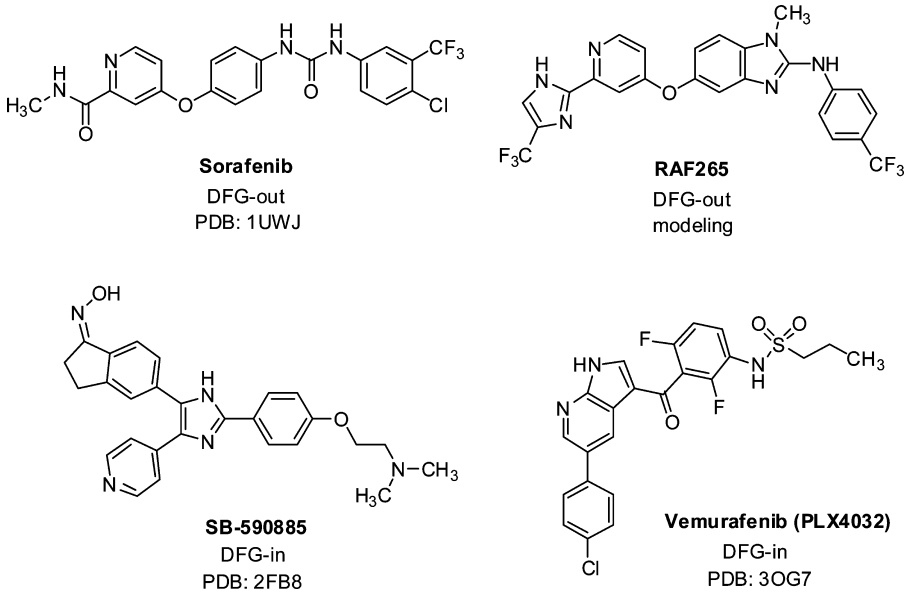

Figure 1. Various BRAF inhibitors and their binding to the BRAF protein.

glucose, and other nutrients to sustain their rapid growth than do normal tissues.[9] Many cancer tissues secrete vascular endothelial growth factor (VEGF) to promote angiogenesis from adjacent blood vessels.[10] The VEGF receptor 2 (VEGFR2) is expressed on the surface of blood vessels, and it plays an important role in tumor angiogenesis. VEGF/VEGFR2 inhibition has been demonstrated as a cancer treatment method by using bevacizumab,[11] a monoclonal antibody against VEGF, and several small molecule inhibitors of VEGFR2, such as sunitinib,[12] axitinib,[13] and pazopanib.[14]

Sorafenib[15] (Figure 1) was initially developed as a C-RAF (RAF-1) inhibitor, although its actual profile is a multikinase inhibitor against VEGFR2, VEGFR3, and PDGFR-β kinases involved in angiogenesis. Efficacy in the clinical studies was thought to be primarily derived from inhibition of tumor angiogenesis.[16] Sorafenib was approved by the Food and Drug Administration (FDA) for the treatment of hepatocellular carcinoma and renal cell carcinoma with its efficacy likely due to its antiangiogenesis activity.[17] However, sorafenib showed insufficient efficacy in metastatic melanoma phase 3 clinical trials, most likely because of insufficient RAF inhibition in melanoma tissues.[18] One possible explanation may be that metastatic melanoma is independent of angiogenesis. Another explanation may be that the potency of sorafenib is insufficient for RAF inhibition in melanoma tissues. Therefore, more potent dual inhibitors against RAF and VEGFR2 may be beneficial for patients suffering from various tumors, including metastatic melanoma.

Over the past decade, efforts have been made to develop drugs and optimize the effects of RAF kinase inhibitors by using X-ray cocrystal structures of the BRAF protein with various ligands. Sorafenib is the first reported RAF kinase inhibitor that binds to the DFG-out "inactive" conformation of BRAF and BRAF(V600E).[19] Another RAF inhibitor, RAF265, has also been reported as a RAF/VEGFR dual kinase inhibitor.[20] These two compounds are classified as type II inhibitors,[21] which bind to the DFG-out "inactive" conformation at the ATP binding site and occupy the hydrophobic "back pocket" in kinases. In contrast, vemurafenib (PLX4032)[8b,22] and SB-590885[23] are classified as type I inhibitors, which bind to the DFG-in "active" conformation of the ATP binding site. These type I inhibitors of RAF are highly BRAF selective against other kinases, particularly VEGFR2.

Imidazo[1,2-*b*]pyridazine derivative **1a**[24] was identified as a hit compound by kinase screening of our chemical library (Figure 2A). Compound **1a** showed significant inhibitory activities against BRAF and VEGFR2, with IC_{50} values of 43 nM and 3.1 nM, respectively. A molecular model was constructed using the docking program GOLD, version 3.2,[25a] and the cocrystal structure model of sorafenib[19] with BRAF(V600E) was used to examine the binding mode of imidazo[1,2-*b*]pyridazines. Although the pyranyl group of **1a** did not fit in this model (vide infra), the simplified acetyl derivative **1b** overlapped well with sorafenib in the DFG-out conformation of BRAF(V600E) (Figure 2B). An amide proton at the 2-position and a nitrogen atom at the N-1 position of 2-aminoimidazo[1,2-*b*]pyridazine were considered significant because they could interact with the backbone C═O and NH of Cys532 in the kinase hinge region of the BRAF(V600E) protein. On the basis of this modeling, novel DFG-out RAF inhibitors bearing [5,6]-fused bicyclic rings (ring A, **1**−**6**, Figure 3) were designed. An acyl group (R^1), which is smaller than pyran (**1a**), was considered suitable because of space constraints in the binding site between the indole side chain of Trp531 and Gly534. Additionally, the benzamide moiety (ring C) linked to a central phenoxy group (ring B) was also thought to be significant for binding with the DFG-out conformation of BRAF. The amide NH between rings B and C can interact with the carboxylate side chain of Glu501, and the C═O group of the amide interacts with the backbone NH of Asp594 in the DFG motif. The benzamide group (ring C) should occupy the hydrophobic back-pocket region, where the phenyl group of Phe595 exists in the DFG-in conformation (Figure 3).

In this paper, the synthesis and structure−activity relationships (SARs) of novel DFG-out RAF/VEGFR2 inhibitors bearing various [5,6]-fused bicyclic scaffolds will be described.

■ CHEMISTRY

Imidazo[1,2-*b*]pyridazine[26] derivatives **1a**−**n** were prepared as shown in Schemes 1 and 2. Compounds **1a**−**g** with various acyl

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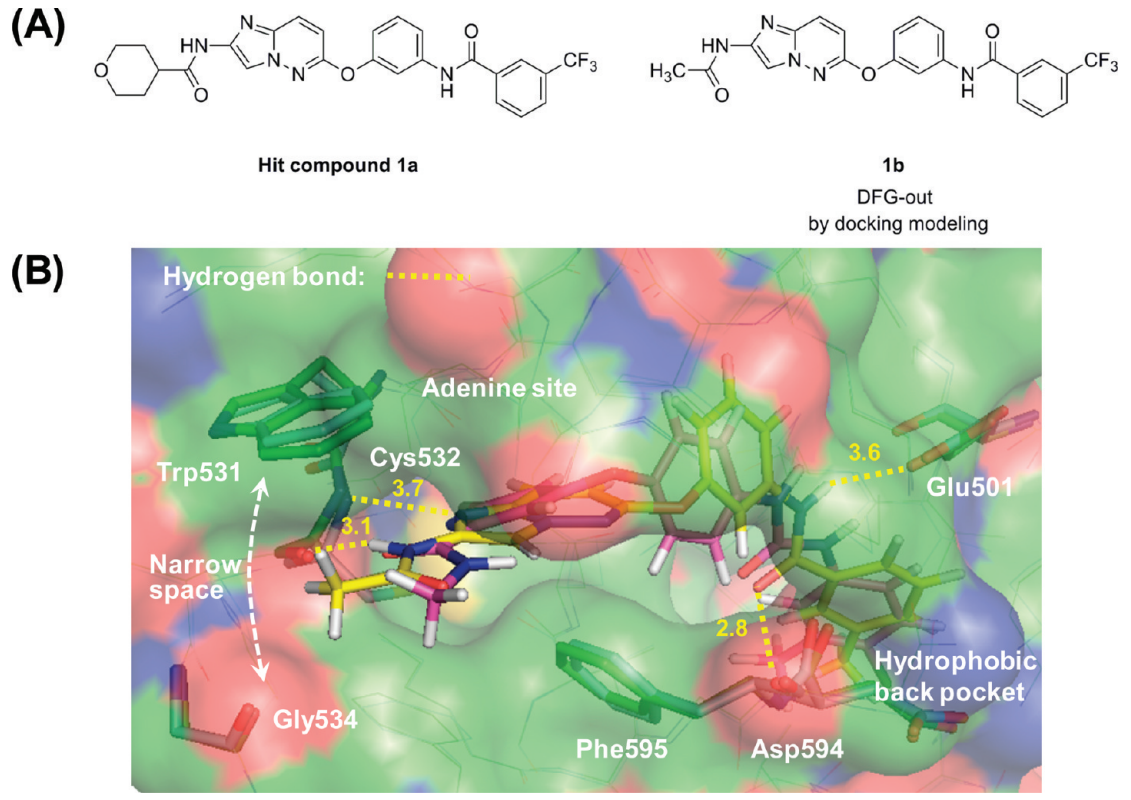

Figure 2. Design concept: (A) structures of hit compound **1a** and its analogue **1b**; (B) overlap modeling of **1b** (yellow) and sorafenib (purple) bound to BRAF(V600E) (PDB code 1UWJ).

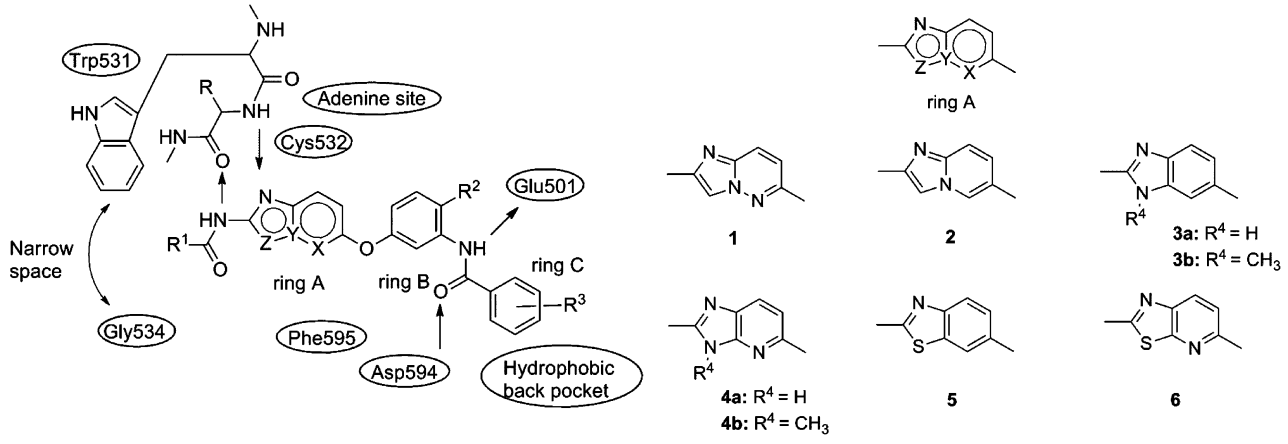

Figure 3. Design of our DFG-out-type RAF inhibitors (left). Design of the [5,6]-fused bicyclic ring A (right).

groups (R^1) were synthesized using the commercially available ethyl 6-iodoimidazo[1,2-*b*]pyridazine-2-carboxylate **7** as the starting material. S_NAr displacement reaction of **7** with 3-aminophenol in the presence of potassium carbonate gave the phenoxylated derivative **8** in 50% yield. Condensation of **8** with 3-(trifluoromethyl)benzoic acid using (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling reagents afforded benzamide **9** in 86% yield. Hydrolysis of **9** with 8 N NaOH gave the corresponding carboxylic acid in 91% yield. Subsequent Curtius rearrangement of the resulting carboxylic acid using diphenylphosphorylazide (DPPA) and *tert*-butanol gave the Boc-protected amine in 89% yield. The Boc group was deprotected using 4 N HCl in EtOAc to provide 2-aminoimidazo[1,2-*b*]pyridazine derivative **10** in 67% yield. Finally, the 2-amino group was acylated by the corresponding carboxylic acids (**a**, **c**, and **d**) using EDCI and HOBt as the coupling agents or the corresponding acid chlorides (**b**, **e**, **f**, and **g**) to give the desired acylated 2-aminoimidazo[1,2-*b*]pyridazine derivatives **1a**–**g** in 42–81% yield (Scheme 1).

Cyclopropylcarbonyl-2-aminoimidazo[1,2-*b*]pyridazine derivatives **1h**–**n** were synthesized via a different route, for efficiently introducing various substituents (R^3) (Scheme 2). The reaction of commercially available 6-iodopyridazine-3-amine **11** with ethyl (chloroacetyl)carbamate in the presence of disodium hydrogen phosphate gave ethyl 6-iodoimidazo[1,2-*b*]pyridazine-2-carbamate **12** in 76% yield. Hydrolysis of ethyl carbamate with aqueous barium hydroxide, followed by acylation of the resulting

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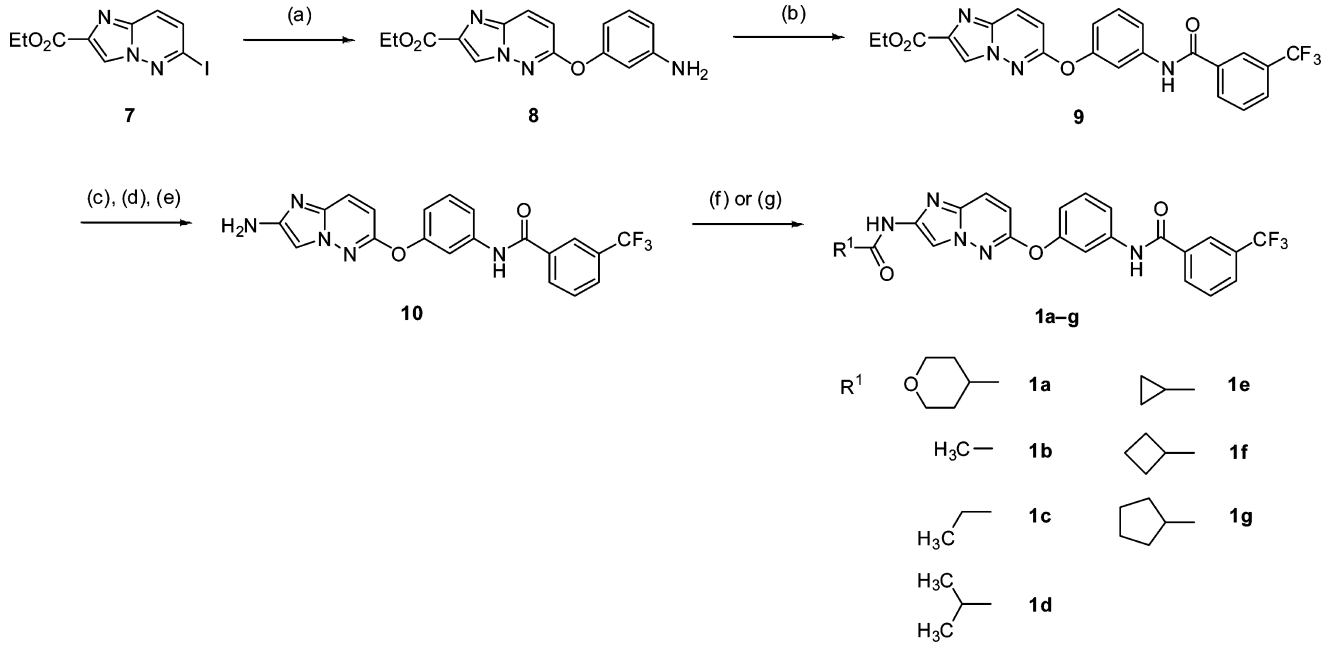
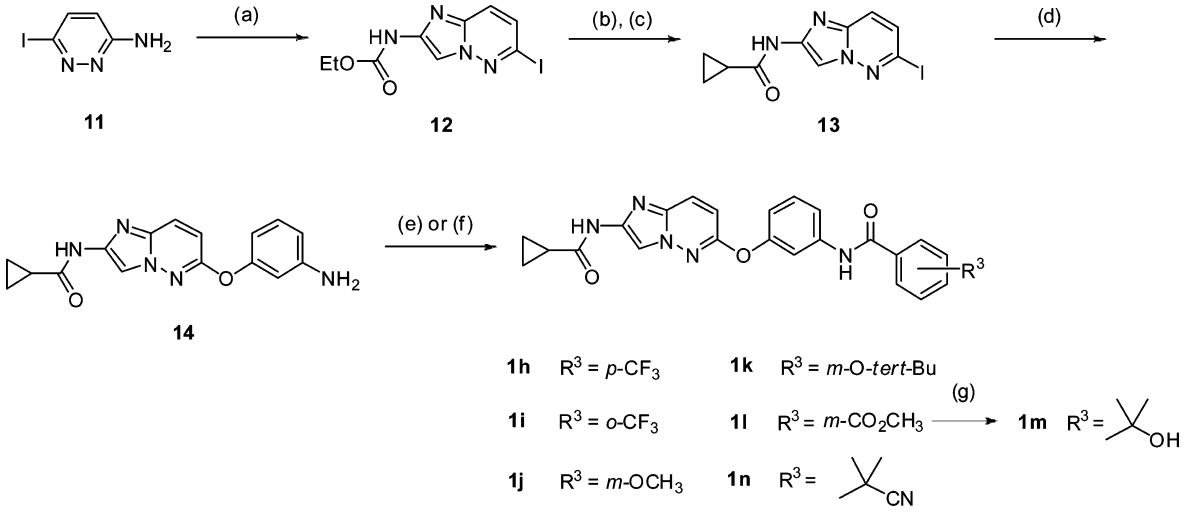
Scheme 1. Synthesis of N-Acylated 2-Aminoimidazo[1,2-*b*]pyridazines 1a–f[a]



[a]Reagents and conditions: (a) 3-aminophenol, K_2CO_3, DMF, 150 °C, 5 h (50%); (b) 3-(trifluoromethyl)benzoic acid, EDCI·HCl, HOBt, DMF, room temp, 3 h (86%); (c) 8 N NaOH aq, MeOH, H_2O, room temp, 4 h (91%); (d) DPPA, Et_3N, ^{t}BuOH, 100 °C, 14 h (89%); (e) 4 N HCl/EtOAc, MeOH, room temp, 14 h (67%); (f) R^1CO_2H (**a**, **c**, and **d**), EDCI·HCl, HOBt, DMF, room temp (42–81%); (g) R^1COCl (**b**, **e**, **f**, and **g**), Et_3N, THF, room temp (54–75%).

Scheme 2. Synthesis of Cyclopropyl Carbonylated 2-Aminoimidazo[1,2-*b*]pyridazines 1g–n[a]



[a]Reagents and conditions: (a) ethyl (chloroacetyl)carbamate, Na_2HPO_4, DMF, 110 °C, 4 h (76%); (b) $Ba(OH)_2·8H_2O$, H_2O, NMP, 120 °C, 12 h (71%); (c) cyclopropanecarbonyl chloride, DMA, room temp, 16 h (98%); (d) 3-aminophenol, K_2CO_3, DMF, 150 °C, 24 h (80%); (e) R^3-$C_6H_4CO_2H$ (**h**, **l**, and **n**), EDCI, HOBt, DMF, room temp (68–77%); (f) R^3-C_6H_4COCl (**i**, **j**, and **k**), NMP, room temp (43–75%); (g) 1.4 M methylmagnesium bromide in THF, toluene, room temp, 12 h (19%).

amine with cyclopropanecarbonyl chloride, was performed in two steps to afford 2-cyclopropylcarbonylamino-6-iodoimidazo-[1,2-*b*]pyridazine **13** in 70% yield. The reaction of **13** with 3-aminophenol in the presence of potassium carbonate afforded the 6-phenoxylated derivative **14** in 80% yield. Amide-forming reactions of **14** with the corresponding benzoic acids were carried out in the presence of EDCI and HOBt to give **1h**, **1l**, and **1n** in 68–77% yield or with the corresponding acid chlorides to give **1i**, **1j**, and **1k** in 43–75% yield. The tertiary alcohol derivative **1m** was synthesized in 19% yield by the treatment of methyl ester **1l** with methylmagnesium bromide.

Benzoic acids **15n–q** were prepared by the method shown in Scheme 3. The synthesis of 3-(1-cyano-1-methylethyl)benzoic acid **15n** began with cyanation of the corresponding commercially available methyl-3-(bromomethyl)benzoate **16** with potassium cyanide in the presence of 18-crown-6, and benzyl cyanide **17** was obtained in 91% yield. Compound **17** was dimethylated using iodomethane in the presence of sodium

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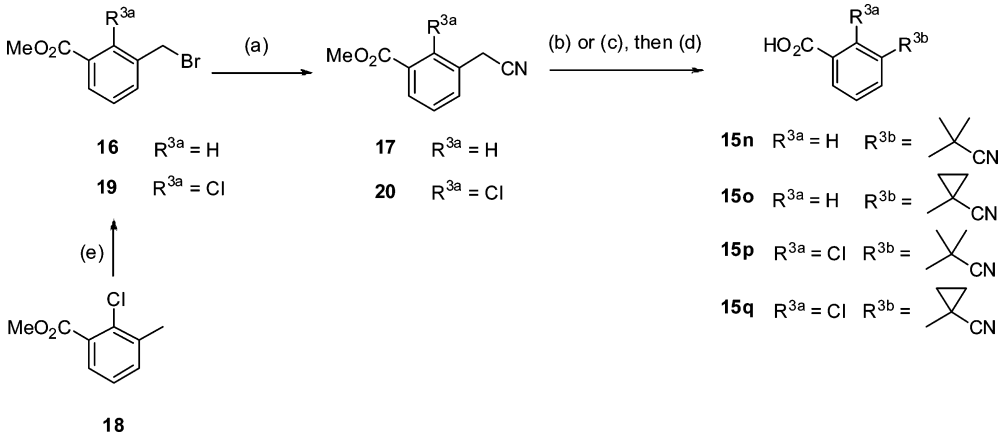
Scheme 3. Synthesis of Benzoic Acids 15n−q[a]



[a]Reagents and conditions: (a) potassium cyanide, 18-crown-6, CH_3CN, room temp, 3 days (91%) or sodium cyanide, DMF, 80 °C, 1 h (79%); (b) NaH, DMSO, room temp, then MeI, room temp (79−88%); (c) NaH, DMSO, room temp, then 1,2-dibromoethane, room temp (57−76%); (d) $LiOH·H_2O$, THF, MeOH, H_2O, room temp (61−98%); (e) NBS, AIBN, CH_3CN, 90 °C, 26 h (66%).

hydride, followed by hydrolysis with aqueous lithium hydroxide, to give the desired benzoic acid **15n** in 77% yield in two steps. Cyclopropyl derivative **15o** was synthesized in two steps from benzyl cyanide **17** by a similar method using 1,2-dibromoethane; the obtained yield was 46% yield. 2-Chlorobenzoic acid (R^{3a} = Cl) derivatives **15p** and **15q** were synthesized using similar methods adopted for **15n** and **15o**. Bromination of the commercially available 3-methylbenzoate derivative **18** with *N*-bromosuccinimide (NBS) in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN) gave the benzyl bromide derivative **19** in 66% yield. Cyanation of **19** using sodium cyanide in *N*,*N*-dimethylformamide afforded benzyl cyanide **20** in 79% yield. Subsequent alkylation of **20** with iodomethane or 1,2-dibromoethane in the presence of sodium hydride afforded the corresponding alkylated derivatives, which were hydrolyzed using aqueous lithium hydroxide to give the desired benzoic acids **15p** and **15q** in 52−80% yield in two steps.

Imidazo[1,2-*a*]pyridine derivative[27] **2** was synthesized using the method described in Scheme 4. The reaction of 5-bromo-2-nitropyridine **21** with 3-nitrophenol in the presence of cesium carbonate and subsequent hydrogenation using 10% palladium/carbon provided aminophenoxylated aminopyridine **22** as the dihydrochloride salt (yield of 54%, two steps) after treatment of the product with 4 N HCl in EtOAc. Regioselective amide formation between **22** and 3-(1-cyano-1-methylethyl)benzoyl chloride, prepared in situ from **15n** using oxalyl chloride, gave benzamide **23** in 66% yield. Tosylation of the 2-amino group on the pyridine ring, followed by alkylation with 2-iodoacetamide at the nitrogen atom on the pyridine ring, provided the precursor **24** (yield, 63%) for the imidazo[1,2-*a*]pyridine scaffold in two steps. The ring formation reaction of **24** proceeded in the presence of trifluoroacetic anhydride (TFAA) in dichloromethane to give imidazo[1,2-*a*]pyridine-2-trifluoroacetamide **25** in 52% yield. Cleavage of the trifluoroacetyl group with 1 N NaOH and subsequent acylation of the resulting amino group using cyclopropanecarbonyl chloride gave the desired compound **2** (yield, 43%) in two steps.

Benzimidazole derivatives[28] **3a**,**b** were synthesized as shown in Scheme 5. For synthesis of the N-methylated compound **3b**, introduction of a methyl group was regiocontrolled at the first step by the regioselective S_NAr displacement of 2,4-difluoronitrobenzene **26** using 40% aqueous methylamine solution. When *N*,*N*-dimethylformamide was used as a cosolvent in this reaction, methylamine was allowed to react with the 2- and 4-fluorine groups of **26** to provide a complex mixture of 2-methylamino, 4-methylamino, and 2,4-bis(methylamino) products. However, in the absence of *N*,*N*-dimethylformamide, the desired 2-methylamino derivative **27b** precipitated from the reaction mixture. Thus, the N-methylated starting material **27b** could be selectively synthesized in 99% yield. Commercially available 2-amino-4-fluoronitrobenzene **27a** and the prepared **27b** were allowed to react with *tert*-butyl (3-hydroxyphenyl)-carbamate in the presence of potassium carbonate to afford phenoxylated derivatives **28a**,**b** in 69% and 100% yields, respectively. Hydrogenation of the nitro group in **28a**,**b** using palladium/carbon gave the corresponding diamines in quantitative yield. Subsequent treatment of the resulting diamines with cyanogen bromide provided benzimidazol-2-amines in 69−100% yield, which were acylated using cyclopropanecarbonyl chloride to afford cyclopropyl carbonylated 2-aminobenzimidazoles **29a**,**b** in 98% and 65% yields, respectively. After the Boc groups of **29a**,**b** were cleaved by TFA (88% yield), an amide coupling reaction between the deprotected compounds and **15n** was carried out in the presence of EDCI and 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) to obtain the target benzimidazole derivatives **3a**,**b** in 69% and 38% yields, respectively.

The synthesis of imidazo[4,5-*b*]pyridine derivatives[29] **4a**,**b** is shown in Scheme 6. Substituted benzoyl chloride, prepared by the reaction of **15n** with oxalyl chloride in situ, was allowed to react with 3-aminophenol under Schotten−Baumann conditions to provide the intermediate phenol **30** in 95% yield in two steps. The regioselective reaction of 2,6-dichloro-3-nitropyridine **31** with *tert*-butylamine proceeded at the 2-position to give the *tert*-butylaminated compound **32a** in 99% yield. Subsequent coupling of **32a** with **30** in the presence of potassium carbonate afforded the coupled product **33a** in 72% yield. The nitro group of **33a** was hydrogenated using palladium/carbon, and the resulting aniline was treated with cyanogen bromide to provide the imidazo[4,5-*b*]pyridine-2-amine derivative **34a** in 82% yield in two steps. Subsequent acylation of the 2-amino group of **34a** with cyclopropanecarbonyl chloride, followed by cleavage of the *tert*-butyl group with TFA, provided the desired imidazo[4,5-*b*]pyridine derivative **4a** in 79% yield in two steps.

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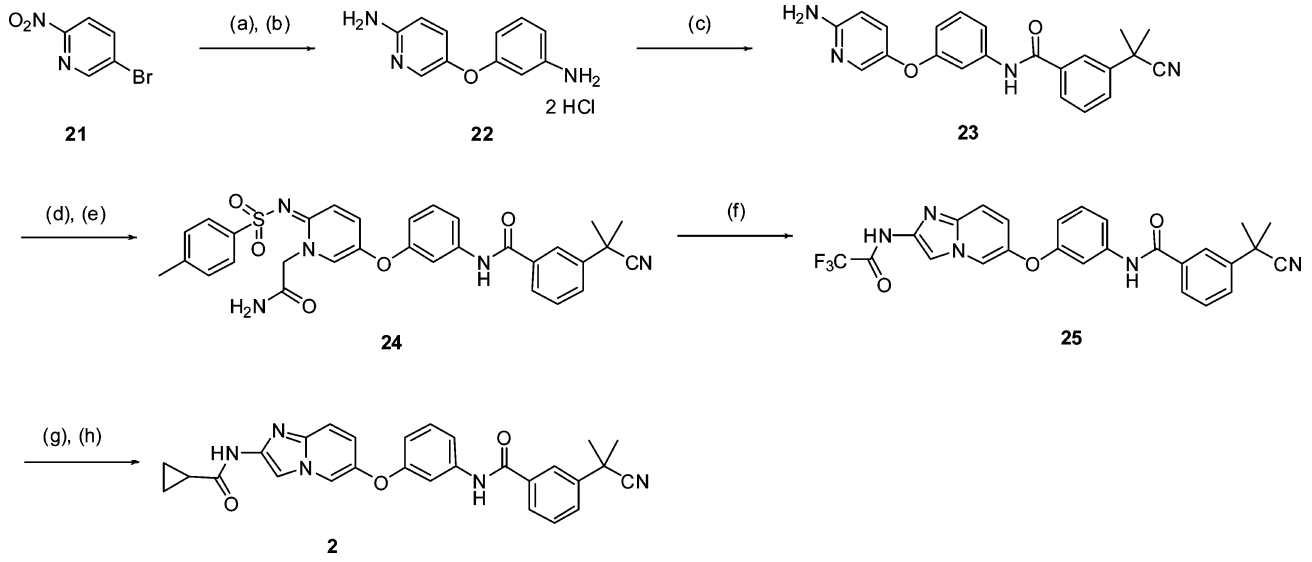
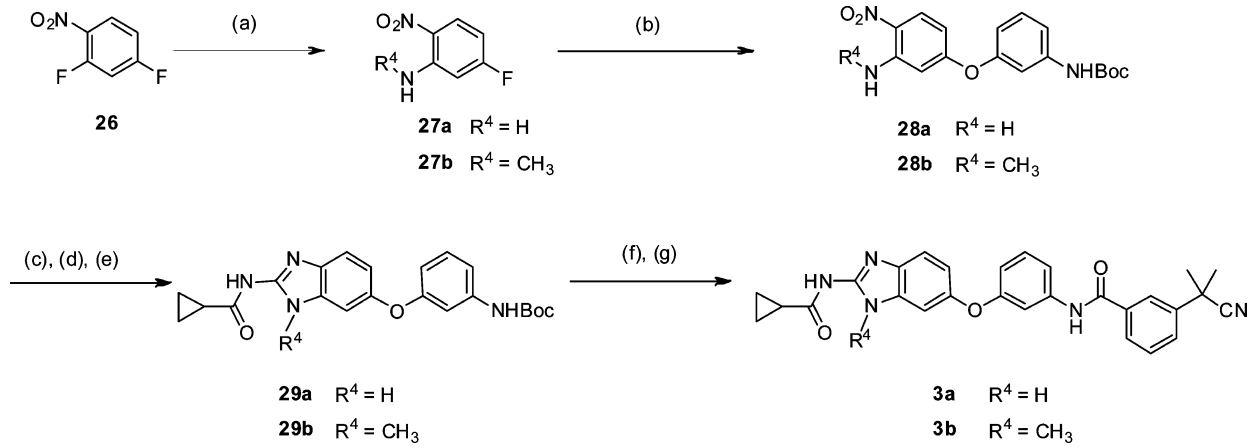
Scheme 4. Synthesis of Imidazo[1,2-*a*]pyridine 2[a]



[a]Reagents and conditions: (a) 3-nitrophenol, Cs_2CO_3, DMF, room temp, 12 h (54%); (b) H_2, 10% Pd/C, MeOH, THF, EtOAc, room temp, 20 h, then 4 N HCl/EtOAc (quant); (c) 3-(1-cyano-1-methylethyl)benzoyl chloride, DMA, room temp, 18 h (66%); (d) 4-methylbenzenesulfonyl chloride, pyridine, 80 °C, 2 days (99%); (e) 2-iodoacetamide, DIEA, DMF, room temp, 48 h (63%); (f) TFAA, CH_2Cl_2, room temp, 16 h (52%); (g) 1 N NaOH aq, EtOH, 45 °C, 12 h (quant); (h) cyclopropanecarbonyl chloride, DMA, room temp, 8 h (43%).

Scheme 5. Synthesis of 1*H*-Benzimidazole 3a,b[a]



[a]Reagents and conditions: (a) 40% methylamine solution, 0 °C, 1.5 h (99%); (b) *tert*-butyl (3-hydroxyphenyl)carbamate, K_2CO_3, DMF, 80−100 °C (69−100%); (c) H_2, 10% Pd/C, THF, MeOH, room temp (quant); (d) BrCN, THF, room temp (69−100%); (e) cyclopropanecarbonyl chloride, DMAP, pyridine, room temp (65−98%); (f) TFA, reflux (88%); (g) **15n**, EDCI·HCl, DMAP, pyridine (38−69%).

The corresponding N-methylated derivative **4b** was prepared using a method similar to that used to generate **4a**. Regioselective amination of 2,6-dichloro-3-nitropyridine **31** with methylamine provided the 2-methylaminated product **32b** in 78% yield. The coupling reaction of **32b** with **30** in the presence of potassium carbonate gave **33b** in 88% yield. Reduction of the nitro group of **33b** and subsequent treatment with cyanogen bromide provided the 1-methylimidazo[4,5-*b*]pyridine-2-amine derivative **34b** in 80% yield in two steps. Finally, acylation of **34b** with cyclopropanecarbonyl chloride provided the desired N-methylated imidazo[4,5-*b*]pyridine derivative **4b** in 56% yield.

The synthesis of 1,3-benzothiazole derivative[30] **5** is shown in Scheme 7. The reaction of 4-fluoronitrobenzene **35** with 3-aminophenol in the presence of potassium carbonate gave the phenoxylated aniline derivative **36** in 95% yield. Condensation of **36** with **15n** using EDCI in the presence of DMAP in pyridine provided benzamide **37** in 99% yield. Reduction of the nitro group of **37** under hydrogenation conditions using palladium/carbon gave aniline **38** in 98% yield. The thiazole ring was constructed by the reaction of **38** with potassium thiocyanate and bromine in acetic acid, and the obtained yield was 87%. The obtained 2-amino-1,3-benzothiazole derivative was acylated using cyclopropanecarbonyl chloride to afford the desired 1,3-benzothiazole derivative **5** in 88% yield.

The synthesis of thiazolo[5,4-*b*]pyridine[31] derivatives **6a−c** is shown in Scheme 8. Reaction of commercially available 2-chloro-5-nitropyridine **39** with Boc-protected aminophenol in the presence of potassium carbonate provided a coupled product, and subsequent reduction of the nitro group under standard hydrogenation conditions provided the corresponding aniline **40** in 77% yield in two steps. Fused 1,3-thiazole ring construction

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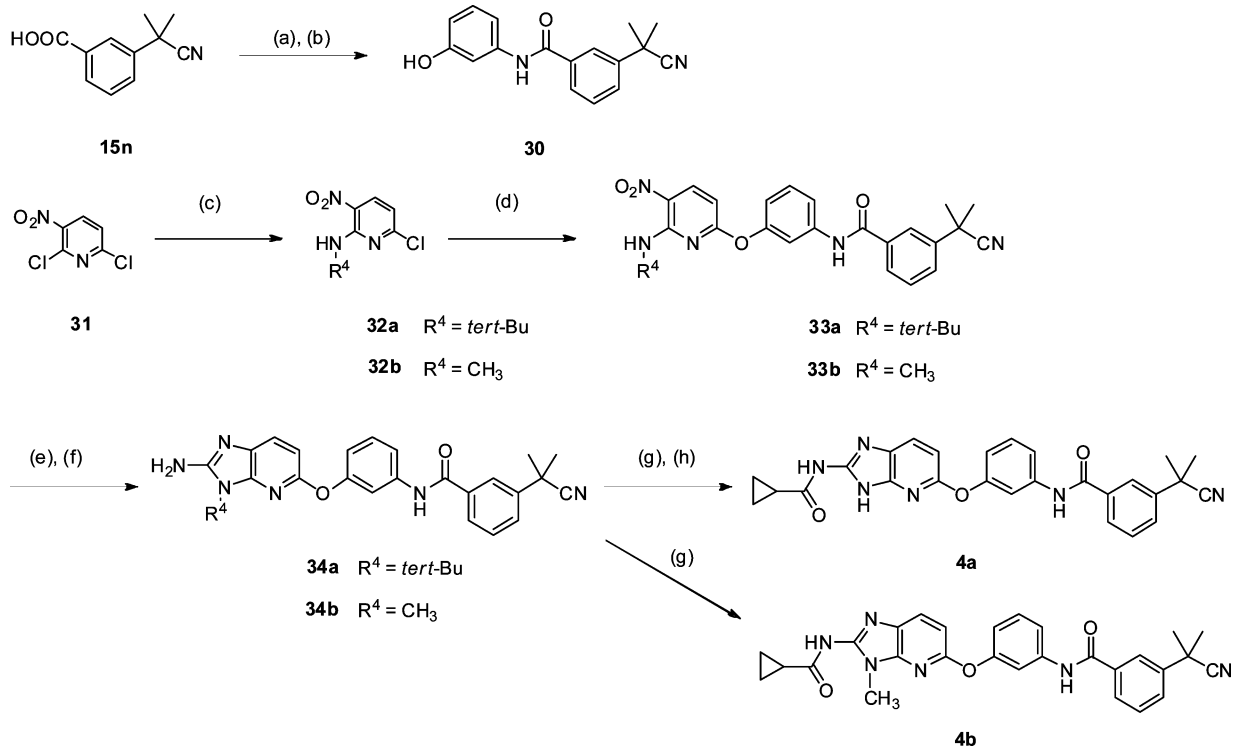
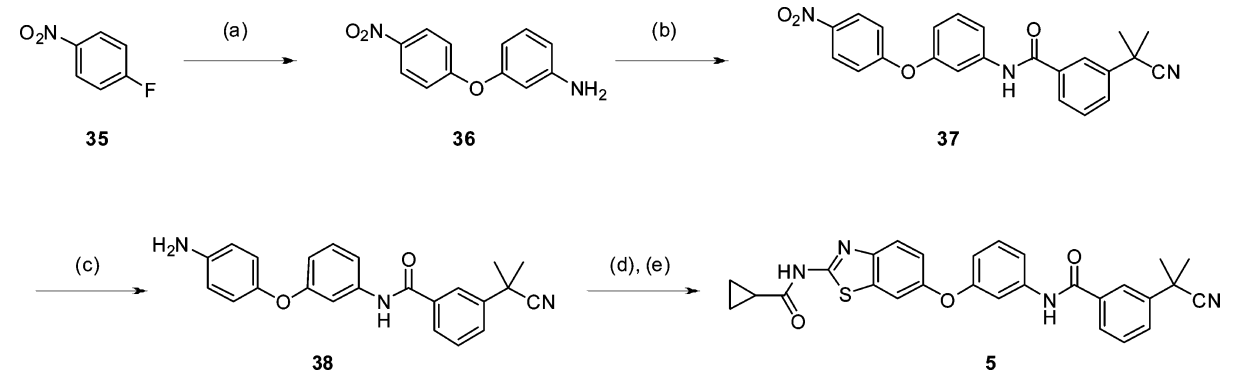
Scheme 6. Synthesis of Imidazo[4,5-*b*]pyridine 4[a]



[a]Reagents and conditions: (a) $(COCl)_2$, cat. DMF, THF, room temp; (b) 3-aminophenol, $NaHCO_3$, H_2O, THF, room temp (96% in two steps); (c) *tert*-butylamine, toluene, or methylamine, THF, room temp (78−99%); (d) **30**, K_2CO_3, DMF, room temp, 18 h (72−88%); (e) H_2, 10% Pd/C, MeOH, THF, room temp, 12 h; (f) BrCN, THF, room temp, 18 h (80−82% in two steps); (g) cyclopropanecarbonyl chloride, DMAP, pyridine, room temp (56−96%); (h) TFA, 80 °C, 2 h (82%).

Scheme 7. Synthesis of 1,3-Benzothiazole 5[a]



[a]Reagents and conditions: (a) 3-aminophenol, K_2CO_3, DMF, 80 °C, 8 h (95%); (b) **15n**, EDCI·HCl, DMAP, pyridine, room temp, 4 h (99%); (c) H_2, 10% Pd/C, THF, MeOH, room temp, 14 h (98%); (d) KSCN, Br_2, AcOH, room temp, 4 h (87%); (e) cyclopropanecarbonyl chloride, DMAP, pyridine, room temp, 6 h (88%).

using potassium thiocyanate and bromine under conditions similar to those used to generate 1,3-benzothiazole afforded the 2-aminothiazolo[5,4-*b*]pyridine derivative **41** in 88% yield. Acylation of the 2-amino group with cyclopropanecarbonyl chloride in pyridine gave the precursor **42** for introducing benzamide moieties, in 86% yield. Deprotection of the Boc group using TFA and subsequent condensation using benzoic acid derivatives **15n−p** under the standard conditions provided the desired thiazolo[5,4-*b*]pyridine derivatives **6a−c** in 46−87% yield.

Compound **6d** was synthesized using a method similar to that used for **6a−c** in Scheme 9. Compound **15q** was converted into the corresponding acid chloride in situ using oxalyl chloride, and the obtained acid chloride was allowed to react with 3-amino-4-fluorophenol in the presence of aqueous sodium bicarbonate to give an intermediate phenol **43** in 100% yield. Compound **43** was allowed to react with 2-chloro-5-nitropyridine **39** in the presence of potassium carbonate to give a coupled product in 93% yield, and subsequent reduction of the nitro group using reduced iron and calcium chloride in aqueous ethanol provided aniline **44** in 69% yield. Cyclization of **44** using potassium thiocyanate and bromine in acetic acid gave thiazolo[5,4-*b*]pyridin-2-amine **45** in 69% yield.

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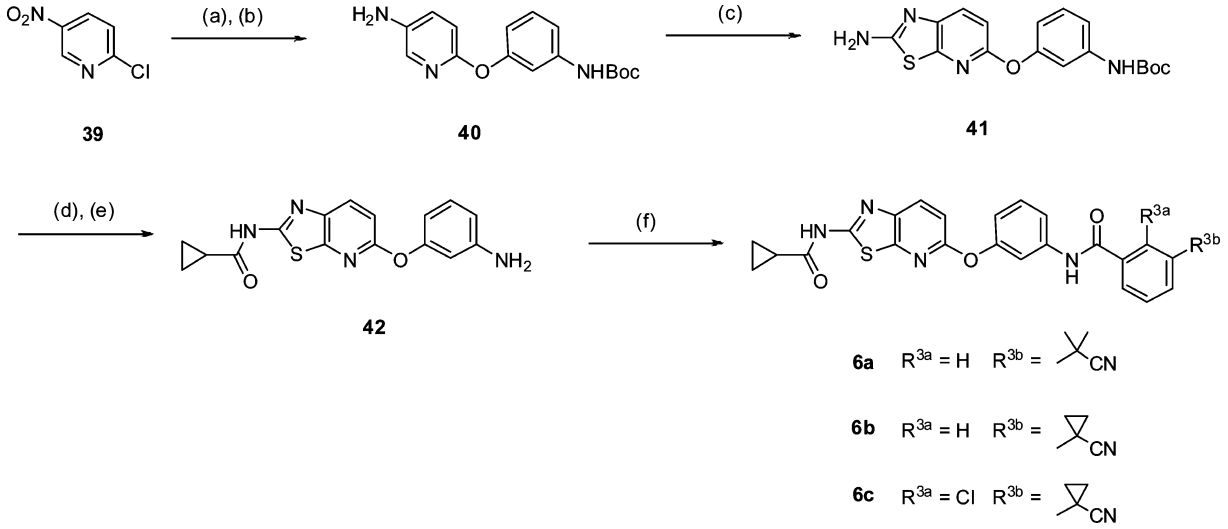
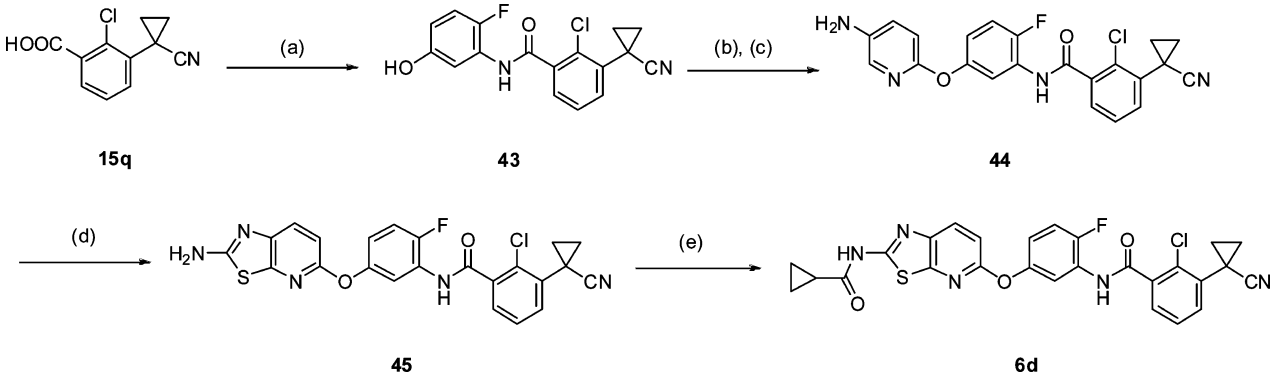
Scheme 8. Synthesis of [1,3]Thiazolo[5,4-*b*]pyridine 6a−c[a]



[a]Reagents and conditions: (a) *tert*-butyl (3-hydroxyphenyl)carbamate, K_2CO_3, DMF, 70 °C, 2 h; (b) H_2, 10% Pd/C, EtOH, THF, room temp, 7 h (77% in two steps); (c) KSCN, Br_2, AcOH, room temp, 1.5 h (88%); (d) cyclopropanecarbonyl chloride, pyridine, room temp, 1 h (86%); (e) TFA, anisole, 0 °C, 1 h (79%); (f) **15n,o**, $SOCl_2$, DMAP, toluene, then pyridine (46−58%), or **15p**, HATU, pyridine, room temp (87%).

Scheme 9. Synthesis of [1,3]Thiazolo[5,4-*b*]pyridine 6d[a]



[a]Reagents and conditions: (a) $(COCl)_2$, cat. DMF, THF, room temp, 2.5 h, then 3-amino-4-fluorophenol, $NaHCO_3$, THF, H_2O, room temp, 1 h (100%); (b) **39**, K_2CO_3, DMF, room temp, 4 h (93%); (c) Fe(0), $CaCl_2$, EtOH, H_2O, 80 °C, 18 h (69%); (d) KSCN, Br_2, AcOH, room temp, 6 h (69%); (e) cyclopropanecarbonyl chloride, pyridine, THF, room temp, 3 h (96%).

Acylation of **45** with cyclopropanecarbonylchloride afforded the desired compound **6d** in 96% yield.

Compound **6e**, which was chlorinated at ring B, was prepared by the synthetic route shown in Scheme 10. Reaction of **39** with 3-amino-4-chlorophenol in the presence of potassium carbonate provided the phenoxylated compound **46** in 85% yield. Protection of the anilino group of **46** by a trifluoroacetyl group using trifluoroacetic anhydride, followed by reduction of the nitro group using reduced iron in acetic acid, gave the trifluoroacetylated compound **47** in 79% yield in two steps. Cyclization of **47** using potassium thiocyanate and bromine in acetic acid and subsequent acylation with cyclopropanecarbonyl chloride provided the 2-acylated aminothiazolo[5,4-*b*]pyridine derivative **48** in 42% yield in two steps. Deprotection of the trifluoroacetyl group was achieved using sodium borohydride in mixed solvent of methanol and ethanol to give the corresponding aniline in 75% yield. Condensation with **15q** under standard conditions provided the desired thiazolo[5,4-*b*]-pyridine derivative **6e** in 64% yield.

RESULTS AND DISCUSSION

To develop novel RAF/VEGFR2 inhibitors, we identified an initial lead compound imidazo[1,2-*b*]pyridazine[24] derivative **1a** from screening. Compound **1a** showed good potency against VEGFR2 and BRAF(V600E), with IC_{50} values of 3.1 and 43 nM, respectively. However, Western blotting assay for assessing the phosphorylation level of the downstream MEK1/2 (pMEK) in HT-29 colon cancer cells revealed that its cellular activity based on BRAF(V600E) inhibition was insufficient (IC_{50} = 3800 nM). Thus, our initial medicinal chemistry efforts were directed at exploring the alkylamide side chain (R^1) and hydrophobic "back pocket" benzamide moiety (R^3) using the imidazo[1,2-*b*]pyridazine scaffold **1** to enhance both BRAF(V600E) and cellular pMEK inhibitory activities.

Imidazo[1,2-*b*]pyridazines **1a−g**, with various *N*-acyl groups (R^1) at the 2-position, were evaluated as shown in Table 1. BRAF(V600E) modeling suggested that the R^1 group exists in the narrow space formed by the indole ring of Trp531 and Gly534 and that the optimal size of the R^1 group for fitting into

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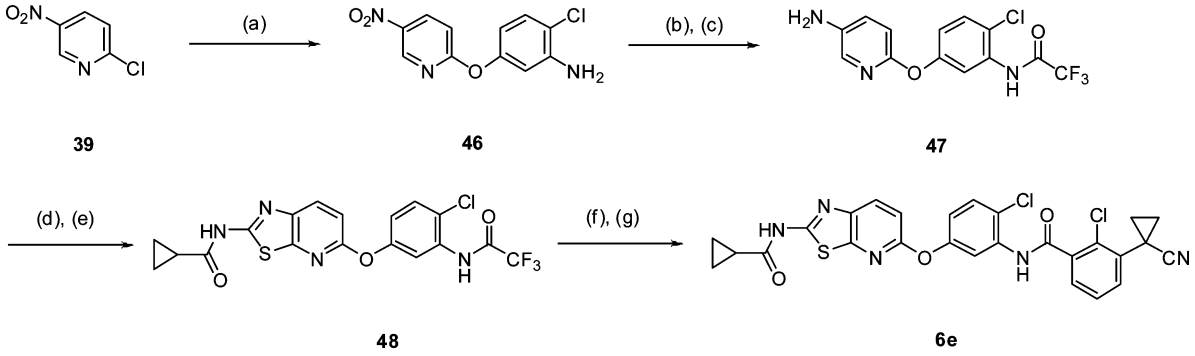
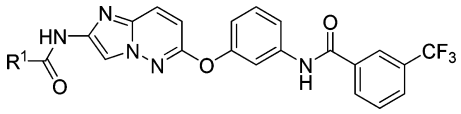
Scheme 10. Synthesis of [1,3]Thiazolo[5,4-*b*]pyridine 6e[a]



[a]Reagents and conditions: (a) 3-amino-4-chlorophenol, K_2CO_3, DMF, room temp, 16 h (85%); (b) TFAA, THF, room temp, 1 h (87%); (c) Fe(0), AcOH, 60 °C, 3 h (91%); (d) KSCN, Br_2, AcOH, room temp, 16 h (72%); (e) cyclopropanecarbonyl chloride, pyridine, room temp, 1 h (59%); (f) $NaBH_4$, MeOH, EtOH, room temp, 1 h (75%); (g) **15q**, $(COCl)_2$, DMF, THF, then DMA, room temp, 2 h (64%).

Table 1. Structure–Activity Relationship of *N*-Acyl Groups at 2-Amino Position (R^1)



Compound	R^1	Kinase IC_{50} (nM)[a]		Cellular pMEK[b] IC_{50} (nM)
		BRAF(V600E)	VEGFR2	
1a		43 (26–73)	3.1 (2.8–3.3)	3800
1b		4.1 (3.7–4.6)	1.1 (0.92–1.3)	130
1c		6.9 (6.2–7.6)	1.7 (1.4–1.9)	480
1d		31 (29–33)	4.2 (3.8–4.6)	N.D.[c]
1e		7.6 (6.0–9.6)	1.9 (1.5–2.3)	310
1f		28 (22–34)	4.8 (4.3–5.3)	N.D.[c]
1g		44 (37–52)	9.3 (8.1–11)	N.D.[c]

[a]n = 2. Values in parentheses indicate the 95% confidence interval. [b]Concentration producing 50% inhibition (IC_{50}) values against RAF substrate MEK phosphorylation in HT-29 ($BRAF^{V600E}$) cultured human colon cancer cell lines. [c]Not determined.

this narrow space would be smaller than that of a pyranyl group. Therefore, we examined the SAR of R^1 groups to determine their BRAF preference and their potency against cellular pMEK activity. Replacement of the pyranyl group in **1a** with a methyl group in **1b** resulted in significantly increased BRAF(V600E) inhibitory activity, with an IC_{50} of 4.1 nM. Compounds bearing alkyl groups larger than those in **1b**, such as ethyl (**1c**) and isopropyl (**1d**) groups, exhibited decreased BRAF(V600E) inhibitory activities, with IC_{50} values of 6.9 and 31 nM, respectively. Thus, **1b** and **1c** revealed more potent cellular pMEK activity than did **1a**. These results are consistent with those of our modeling studies, suggesting that decreasing the size of the *N*-acyl groups (R^1) generally increased BRAF and the cellular pMEK inhibitory activity. Because the R^1 group is located near a hinge in our BRAF model, bulky groups may be unfavorable for binding the BRAF protein.

Compounds **1e–g** having a cycloalkyl group as R^1 were further evaluated. Similar to the alkyl side chain in **1b–d**, decreasing the ring size from cyclopentyl (**1g**) to cyclopropyl (**1e**) enhanced the BRAF(V600E) inhibitory activity. Additionally, the cyclopropyl derivative **1e** showed potent cellular pMEK activity with an IC_{50} of 310 nM. However, substitution of the *N*-acyl group (R^1) had negligible impact on the VEGFR2 inhibition, with compounds **1a–g** showing nanomolecular-order inhibitory activity against VEGFR2. Since the acetyl group of **1b** was found to be sensitive to deacetylation[32a] by liver microsomes in an in vitro metabolism study (data not shown, but this result was utilized in our next prodrug study[32b]), we chose the cyclopropyl group (**1e**) as the representative R^1 group.

Next, we investigated the effect of substituting R^3 groups in the "back pocket" of the benzene ring (ring C); the results are summarized in Table 2. Our initial goal was to examine the substitution position of the trifluoromethyl group against BRAF(V600E). Alternating between the meta (**1e**), para (**1h**), and ortho (**1i**) positions resulted in decreased BRAF inhibitory activity, suggesting that meta substitution may be favorable for inhibiting the BRAF protein.

Replacement of the trifluoromethyl group with methoxy (**1j**) and *tert*-butoxy (**1k**) groups helped in maintaining strong BRAF(V600E) inhibitory activities comparable to that of **1e**. Additionally, **1k** showed slightly increased cellular pMEK inhibition, with an IC_{50} of 120 nM. In our model, wherein **1k** was bound to BRAF, the *tert*-butoxy group of **1k** could occupy the lipophilic space formed by Val504, Leu505, Ile513, Leu514, and Thr508 in the back pocket to result in lipophilic van der Waals interactions with the BRAF protein. On the basis of BRAF inhibition studies, we assumed that bulky lipophilic groups may stabilize the DFG-out binding conformation and increase cellular activity. Therefore, to confirm our assumption, we examined the introduction of bulky 1-hydroxy-1-methylethyl (**1m**) and 1-cyano-1-methylethyl (**1n**) groups. Although **1m** showed reduced cellular pMEK inhibitory activity compared to **1k**, the more lipophilic 1-cyano-1-methylethyl derivative **1n** demonstrated the most potent cellular activity among all the derivatives in the imidazo[1,2-*b*]pyridazine series, with an IC_{50} of 55 nM. These results indicated that the lipophilic back pocket moiety is a key pharmacophore of the DFG-out type BRAF inhibitor for its potent pMEK inhibitory activity.

All the imidazo[1,2-*b*]pyridazine derivatives **1e–n** showed more potent activities against VEGFR2 than against BRAF(V600E). These results implied that VEGFR2 has a wider range of molecular recognition in the back pocket than does BRAF(V600E). Therefore, we moved to the exploration of alternative [5,6]-fused bicyclic scaffolds to strengthen the BRAF inhibitory activity.

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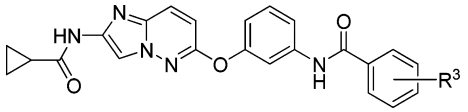
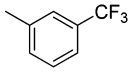
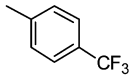
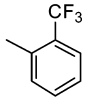
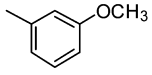
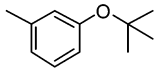
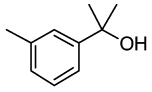
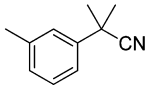
Table 2. Structure–Activity Relationship of Back Pocket Region (R^3)



Compound	R^3	Kinase IC_{50} (nM)[a]		Cellular pMEK[b] IC_{50} (nM)
		BRAF(V600E)	VEGFR2	
1e		7.6 (6.0–9.6)	1.9 (1.5–2.3)	310
1h		81 (69–96)	1.9 (1.7–2.0)	N.D.[c]
1i		3700 (3100–4400)	1.4 (1.3–1.6)	N.D.[c]
1j		18 (16–22)	0.31 (0.27–0.35)	>500
1k		15 (13–16)	1.8 (1.6–2.0)	120
1m		10 (9.7–10)	0.82 (0.77–0.87)	530
1n		14 (12–17)	1.5 (1.3–1.7)	55

[a] n = 2. Values in parentheses indicate the 95% confidence interval. [b] Concentration producing 50% inhibition (IC_{50}) values against RAF substrate MEK phosphorylation in HT-29 ($BRAF^{V600E}$) cultured human colon cancer cell lines. [c] Not determined.

To identify the appropriate scaffolds (ring A), novel [5,6]-fused bicyclic derivatives **2**–**6**, which had the same phenoxylated back pocket moiety as does **1n**, were designed and evaluated (Table 3). Replacement of imidazo[1,2-*b*]pyridazine (**1n**) with imidazo[1,2-*a*]pyridine (**2**) resulted in approximately 3-fold reduction of the BRAF(V600E) and cellular pMEK inhibitory activities. Similar tendencies were observed between benzimidazole (**3a**) and imidazo[4,5-*b*]pyridine (**4a**) as well as between 1,3-benzothiazole (**5**) and [1,3]thiazolo[5,4-*b*]pyridine (**6a**). These results suggested that the nitrogen atom adjacent to the phenoxy group contributes to the enhanced BRAF(V600E) inhibitory activities.

Additionally, alternating the fusion position of the imidazole rings, such as **2** to **3a** or **1n** to **4a**, maintained the BRAF(V600E) inhibitory activity but reduced the cellular pMEK inhibitory activity. Since the additional proton doner (NH) at the N-3 position in **3a** and **4a** plausibly diminish those cellular permeability, we examined the introduction of a methyl group at the N-3 position to mask the proton donor. However, the N-methylated derivatives **3b** and **4b** showed dramatically decreased BRAF(V600E) inhibitory activity, with IC_{50} values of 960 and 200 nM, respectively. Because the intermediate N-methylated imidazo[5,4-*d*]pyridine-2-amine **34b** showed stronger BRAF(V600E) inhibitory activity (IC_{50} = 35 nM) than did **4b**, we assumed that the steric hindrance between the *N*-3-methyl group and the 2-cyclopropylcarboxamide moiety of **4b** disrupted the planarity of the *C*-2 carboxamide with ring A and might reduce BRAF inhibition. To confirm our hypothesis, we calculated the stable dihedral angles of the amides in **3a**,**b** and **4a**,**b** using the MOE program[25] (see Experimental Section) to determine their minimum potential energies (Figure 4). We found that the N-methylated derivatives **3b** and **4b** preferred torsional conformations (energy, 3.2–4.2 kcal/mol) to the planar conformations of **3a** and **4a**. Accordingly, we focused on identifying scaffolds that could stabilize the planarity of the *C*-2 carboxamide group with ring A to enhance the BRAF inhibitory activity.

To stabilize this planarity, we designed fused 1,3-thiazole scaffolds, 1,3-benzothiazole (**5**) and [1,3]thiazolo[5,4-*b*]pyridine (**6**). On the basis of the intramolecular interactions between the carbonyl group and sulfur by using the d-orbital of the sulfur atom,[33] we hypothesized that the planar conformations of the *C*-2 carboxamide with their scaffolds may be stabilized more effectively than those of the scaffolds **1**–**4**. As expected, **5** and **6a** showed greater BRAF(V600E) inhibitory activity than did the corresponding imidazole derivatives **3a** and **4a**. Particularly, the [1,3]thiazolo[5,4-*b*]pyridine derivative **6a** demonstrated the most potent BRAF(V600E) and cellular pMEK activities, with IC_{50} values of 5.6 and 6.2 nM, respectively. The inhibitory

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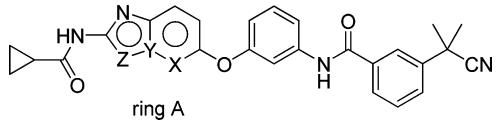
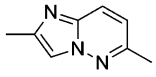
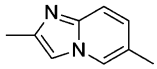
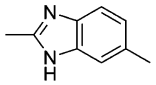
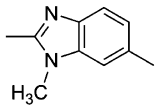
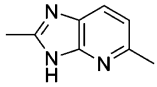
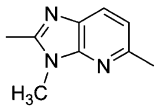
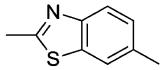
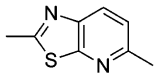
Table 3. Structure–Activity Relationship of Novel [5,6]-Fused Bicyclic Ring A



Compound	Ring A	Kinase IC_{50} (nM)[a]		Cellular pMEK[b] IC_{50} (nM)
		BRAF(V600E)	VEGFR2	
1n		14 (12–17)	1.5 (1.3–1.7)	55
2		49 (38–63)	1.8 (1.5–2.1)	200
3a		41 (37–45)	8.1 (7.0–9.3)	500
3b		960 (900–1000)	5.5 (5.1–6.2)	N.D.[c]
4a		17 (13–22)	3.1 (2.8–3.3)	140
4b		200 (140–290)	2.4 (2.1–2.6)	N.D.[c]
5		25 (23–28)	14 (13–16)	240
6a		5.6 (4.6–6.7)	2.8 (2.3–3.3)	6.2

[a] $n = 2$. Values in parentheses indicate the 95% confidence interval. [b] Concentration producing 50% inhibition (IC_{50}) values against RAF substrate MEK phosphorylation in HT-29 ($BRAF^{V600E}$) cultured human colon cancer cell lines. [c] Not determined.

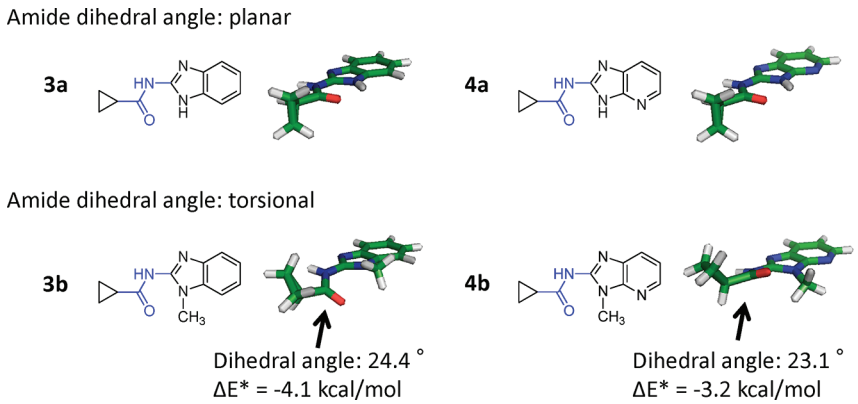


Figure 4. Stable dihedral angles of amides linked to ring A (**3**, **4**) are calculated using ligand-based analysis to determine their minimal potential energies. Compounds calculated are simplified analogues without the phenoxy moiety. Fused imidazoles without the methyl group (**3a**, **4a**) are categorized in the planar group. Fused imidazoles with a methyl group (**3b**, **4b**) are categorized in the torsional group owing to steric hindrance between 3-methyl and carbonyl. Dihedral angles (deg) and their internal energy gains (ΔE^*) from their planar conformations are shown.

potency of **6a** against BRAF(V600E) reached a level comparable to that against VEGFR2. Thus, we selected [1,3]thiazolo [5,4-*b*]pyridine scaffold **6** as one of the most appropriate scaffolds for dual inhibition against BRAF(V600E) and VEGFR2.

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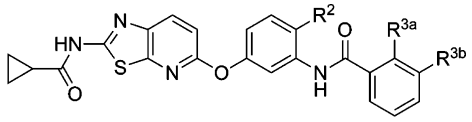
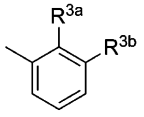
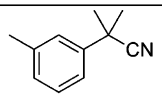
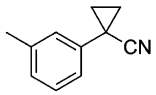
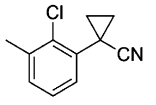
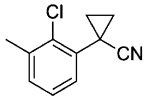
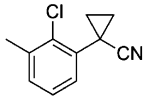
Because **6a** showed sufficient in vitro potency to act as a BRAF(V600E) and VEGFR2 dual kinase inhibitor, the pharmacokinetic (PK) profile of this compound was evaluated in mice (Table 4). However, **6a** showed poor drug exposure, with an AUC_{0-8h} of 0.393 μg h/mL, after oral administration at a dose of 10 mg/kg in mice. To improve this poor oral absorption, we initially substituted the dimethylcyanomethyl group (**6a**) with a cyanocyclopropyl group (**6b**) so that the metabolized site was blocked. The BRAF/VEGFR2 inhibitory activities remained high, and this transformation was effective in enhancing oral absorption in mice while improving metabolic stability and slightly increasing the solubility for **6b**. Additionally, we attempted to introduce an R^{3a} group at the ortho position between benzamide and the R^{3b} group to increase the solubilities of **6a**,**b** by twisting the plane of benzamide (ring B) with ring C. As expected, **6c**, with a chlorine atom at the 2-position of benzamide (ring C), showed improved solubility and oral absorption in mice while maintaining the in vitro potency. Introduction of chlorine at R^{3a} proved to be effective for enhancing the poor solubility.

Finally, we optimized the substituents (R^2) at the para or 6-position of the phenoxyl group (ring B) to enhance the metabolic stability of **6c** by blocking the metabolically labile site. The results of our modeling studies showed that because of steric restriction around the 4-position, smaller R^2 groups could be more favorable to be introduced. The 6-chlorinated [1,3]-thiazolo[5,4-*b*]pyridine derivative **6e** showed reduced in vitro potency against BRAF(V600E), but the 6-fluorinated [1,3]-thiazolo[5,4-*b*]pyridine derivative **6d** maintained sufficient in vitro potency to act as a BRAF(V600E) and VEGFR2 dual kinase inhibitor. Furthermore, **6d** showed significantly improved metabolic stability against human liver microsomes and good PK profiles in mice. Therefore, we selected **6d** as a promising candidate for further evaluation.

X-ray Cocrystal Structural Analysis of 6d with BRAF and VEGFR2. We determined the X-ray cocrystal structures of **6d** with BRAF and VEGFR2 proteins, respectively.[34] The BRAF cocrystal structure (PDB code 4DBN) revealed that **6d** occupies the ATP-binding site and stabilizes the inactive DFG-out conformation of BRAF by being accommodated to the back pocket region (Figure 5A). As expected, the [1,3]thiazolo[5,4-*b*]-pyridine-2-amine moiety is located in front of the hinge region of BRAF and forms two significant hydrogen bonds between the carbonyl of Cys532 and the NH of the 2-amide (2.7 Å) and between the NH of Cys532 and the N-3 nitrogen (3.2 Å). The cocrystal structure of BRAF supports our hypothesis that the planar conformation of the 2-amide group with the

Table 4. Structure–Activity Relationship of [1,3]Thiazolo[5,4-*b*]pyridine Derivatives 6a–e



	R^2		Kinase IC_{50} (nM)[a]		Cellular pMEK[b]	Solubility[c] (μg/mL)	Microsome stability[d] (μL/min/mg)			Mouse PK[e]
			BRAF (V600E)	VEGFR2	IC_{50} (nM)		Human	Mouse	Rat	AUC PO (μg h/mL)
6a	H		5.6 (4.6–6.7)	2.8 (2.3–3.3)	6.2	4.3	13	26	142	0.393
6b	H		3.0 (2.6–3.5)	2.2 (1.9–2.6)	31	8.0	10	−16	61	1.415
6c	H		9.0 (8.1–10)	4.0 (3.6–4.3)	29	15	51	83	83	2.951
6d	F		7.0 (6.0–8.3)	2.2 (2.0–2.4)	25	16	−7.0	80	20	1.902
6e	Cl		43 (35–54)	7.5 (6.8–8.2)	260	83	−12	44	19	3.441

[a] n = 2. Values in parentheses indicate the 95% confidence interval. [b] Concentration producing 50% inhibition (IC_{50}) values against RAF substrate MEK phosphorylation in HT-29 ($BRAF^{V600E}$) cultured human colon cancer cell lines. [c] 10 mmol/L solution of the compound in DMSO was evaluated using the JP second fluid in the disintegration test (pH 6.8) containing bile acid. The sample solution was shaken at 37 °C for 24 h, and its solubility was evaluated after filtration. [d] Metabolism clearance of each compound was examined using liver microsomes and NADPH. [e] Cassette dosing of five compounds. Values shown are the mean of data from three mice. Compounds (10 mg/kg) were administered in 0.5% methylcellulose in distilled water.

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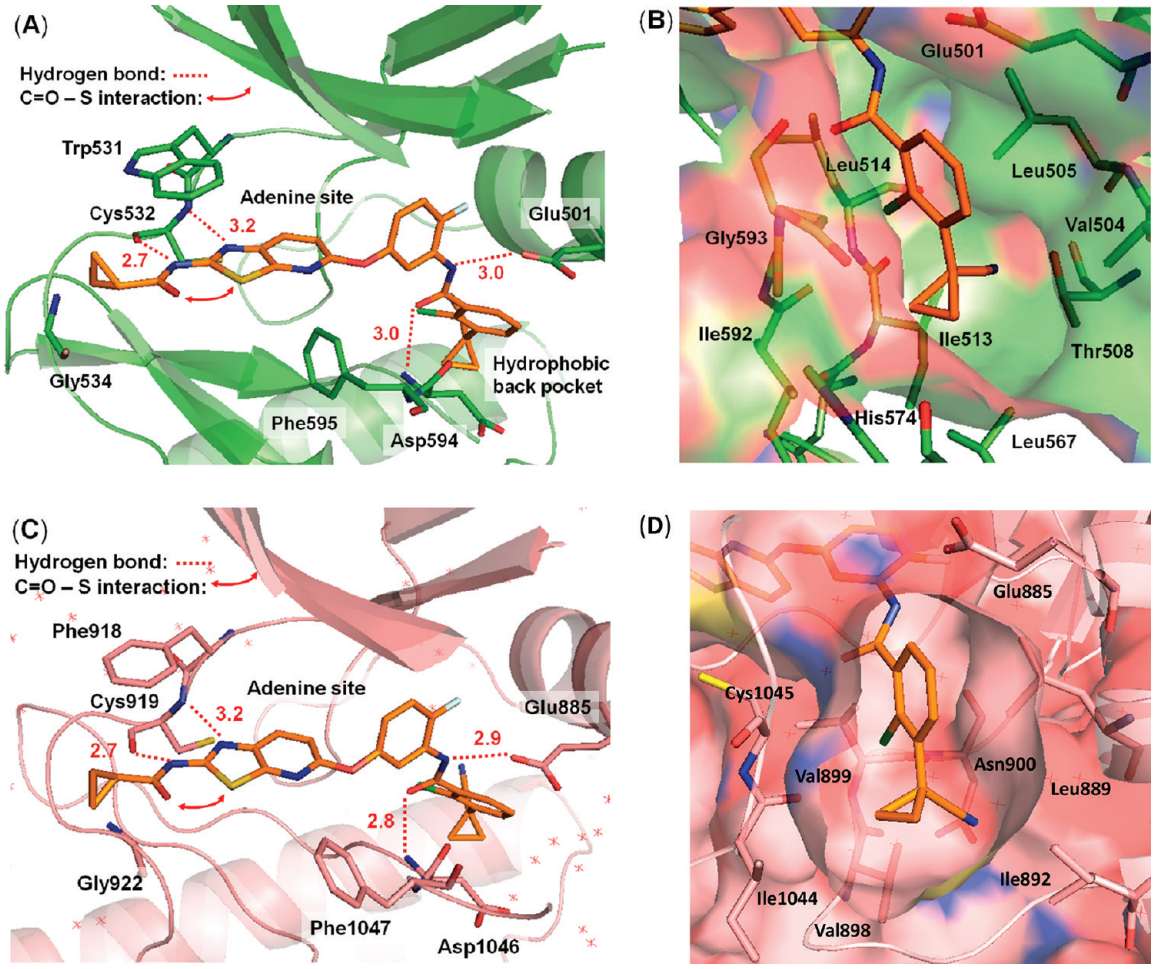

Figure 5. Cocrystal structure of **6d** with BRAF (PDB code 4DBN, 3.1 Å resolution) and VEGFR2 (PDB code 3VNT, 1.64 Å resolution): (A) DFG-out conformation of BRAF (green cartoon) is stabilized by **6d**; (B) back pocket region of BRAF (surface); (C) DFG-out conformation of VEGFR2 (magenta cartoon) is stabilized by **6d**; (D) back pocket region of VEGFR2 (surface).

[1,3]thiazolo[5,4-*b*]pyridine scaffold may be stabilized through sulfur−carbonyl interactions because the measured distance (2.8 Å) between the sulfur and oxygen atoms is shorter than the sum of the corresponding van der Waals radii of the oxygen and sulfur atoms (3.32 Å).[35] Interestingly, the indole side chain of Trp531 is located near the 2-amide bond of **6d** and possibly forms $\pi-\pi$ stacking interactions with the 2-amide. This type of interaction is not observed in the cocrystal structure[19] of sorafenib, and it may be critical for enhancing the BRAF inhibition of **6d**. Structural differences of adenine sites between 4DBN (**6d**) and 1UWJ (sorafenib) is discussed in detail using the figure that describes the overlapped structures in Supporting Information. Additionally, the biphenyl amide moiety between rings B and C of **6d** forms two significant hydrogen bond interactions with the backbone NH of Asp594 (3.0 Å) and the side chain carboxylate of Glu501 in the C-helix (3.0 Å). These interactions may be important for stabilizing the DFG-out inactive conformation of BRAF. Furthermore, the 2-chloro-3-(1-cyanocyclopropyl)benzene ring is located in a back pocket that is twisted away from the carbonyl surface by 44.4° (Figure 5B). The bulky cyanocyclopropyl group occupies the hydrophobic back pocket formed by Val504, Thr508, Leu567, His574, and Ile592 (indicated by the green area in Figure 5B); this hydrophobic interaction plays an important role enhancing the BRAF(V600E) cellular activity.

Table 5. Kinase Selectivity of 6d

kinase	IC_{50} (nM)[a]	kinase	IC_{50} (nM)[a]
BRAF(wt)	12	PKA	>10000
C-RAF	1.5	PKCθ	>10000
FGFR3	22	CHK1	6300
PDGFRα	12	CK1δ	>10000
PDGFRβ	5.5	ERK1	>10000
EGFR	>10000	CDK1	2200
Her2	>10000	CDK2	2700
TIE2	>10000	Aurora B	240
c-Met	>10000	p38α	1100
c-Kit	>10000	JNK1	>10000
Src	420	GSK3β	2900
IR	>10000	MEK1	>10000
IKKβ	>10000	MEKK1	>10000

[a] $n = 2$.

The cocrystal structure of VEGFR2 (PDB code 3VNT) also revealed that **6d** occupies the ATP binding site of VEGFR2 and stabilizes the DFG-out conformation of VEGFR2 (Figure 5C). Since similar hydrogen bond interactions (depicted in the red dotted lines in Figure 5C), compared to those of BRAF, and occupation of the 3-(1-cyanocyclopropyl)benzene moiety in the back pocket region of VEGFR2 (Figure 5D) were observed, **6d** was proved to be a DFG-out type RAF/VEGFR2 inhibitor.

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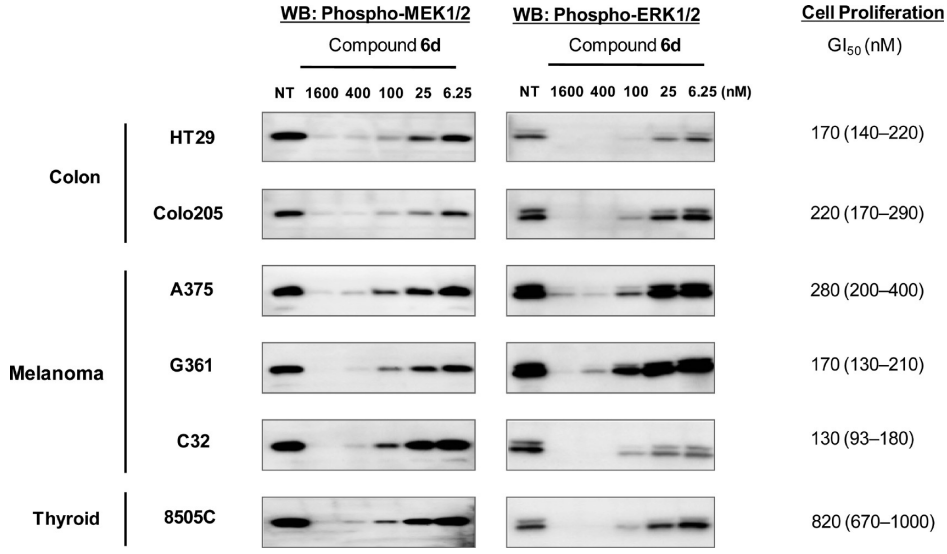

Figure 6. MAPK signal suppression effect by 2 h treatment of **6d** (Western blotting) and its antiproliferative activity (GI_{50}) in various cancer cell lines possessing the $BRAF^{V600E}$ mutated gene.

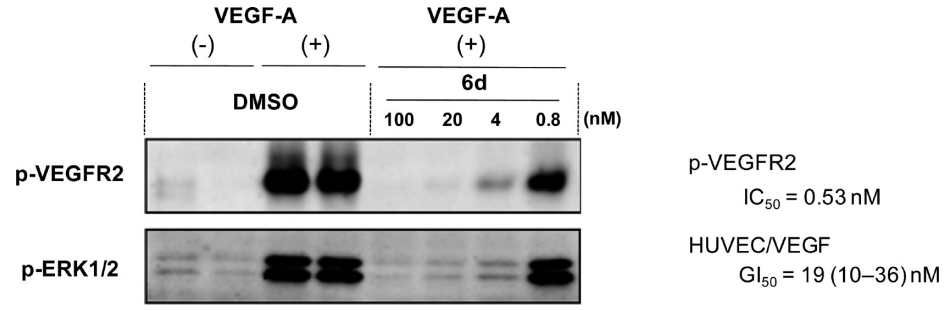

Figure 7. VEGF signal suppression effect by 2 h treatment of **6d** (Western blotting) in 293/KDR cell lines. The 293/KDR cells were untreated (−) or treated (+) with VEGF-A (final concentration of 50 ng/mL) for 10 min.

Table 6. Mean[a] Pharmacokinetic Parameters for 6d in Rats

dose (mg/kg)	route	CL_{total} (mL h^{-1} kg^{-1})	V_{dss} (mL/kg)	MRT (h)	AUC_{0-24h} (μg h/mL)	C_{max}, po (μg/mL)	F (%)
1[b]	iv	886 ± 203	1655 ± 493	1.86 ± 0.24	1.167 ± 0.25		
10[c]	oral			4.38 ± 0.43	8.23 ± 1.04	1.29 ± 0.07	70.5 ± 8.9

[a]Values shown are the mean ± SD of data from three rats. [b]Delivered in polyethylene glycol/DMA (1/1). [c]Solid dispersion (SD) powder, prepared by spray dry method using hydroxypropylmethylcellulose (HP-55) (**6d**/HP-55 (1:4)); delivered in distilled water.

The stabilized planar conformation of the 2-amide group with the [1,3]thiazolo[5,4-*b*]pyridine scaffold by the sulfur−carbonyl interaction was also observed in the VEGFR2 cocrystal structure. However, because of the replacement of the indole ring (Trp531) in BRAF with the phenyl ring (Phe918) in VEGFR2, the VEGFR2 pocket appears to be spacious and more accommodating to the various bicyclic fused rings with diversified and less planar amide conformations compared to BRAF in Table 3.

Kinase Inhibitory Profiles of 6d. The inhibitory profiles of **6d** against 26 different kinases are summarized in Table 5. Compound **6d** exhibited potent inhibitory activity against not only BRAF(V600E) (IC_{50} = 7.0 nM) but also wild-type BRAF (12 nM) and C-RAF (1.5 nM). Additionally, other kinases related to angiogenesis,[36] such as FGFR3, PDGFRα, PDGFRβ, were inhibited with IC_{50} values comparable to that of VEGFR2 inhibition. Several kinases, including Aurora B and Src, were moderately inhibited with IC_{50} values ranging from 240 to 420 nM, and no significant inhibition was observed against the remaining 19 kinases. Therefore, **6d** was considered to have a character as a pan-RAF and angiogenesis-related kinases inhibitor.

In Vitro Pharmacology of 6d. To determine the potency of **6d** as a BRAF(V600E) inhibitor, we investigated the in vitro MAPK signal suppression effect of **6d** in various cancer cells harboring the $BRAF^{V600E}$ mutation (Figure 6). In several types of colon, melanoma, and thyroid cancer cells, **6d** suppressed both phospho-MEK1/2 and phospho-ERK1/2 levels in a concentration-dependent manner. Reflecting the inhibition of the downstream molecules in MAPK signal transduction, **6d** demonstrated antiproliferative activities among these cell lines, with GI_{50} of 130−820 nM.

Next, the cellular VEGFR2 inhibitory activity of **6d** was evaluated in VEGFR2-overexpressing 293/KDR cells[37] (Figure 7). Compound **6d** significantly inhibited the VEGFR2 phosphorylation induced by treatment with vascular endothelial growth factor A (VEGF-A), with an IC_{50} of 0.53 nM. Furthermore, **6d** potently inhibited the VEGF-induced proliferation of HUVEC at a GI_{50} of 19 nM. These results indicated that the cellular

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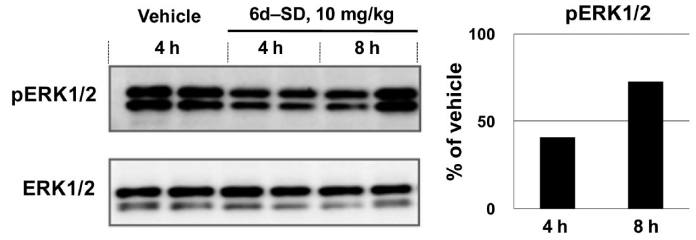
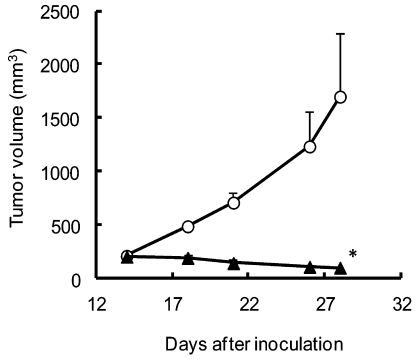


	Dose (mg/kg)	Time after administration (h)	pERK level[b] (% of vehicle)
Vehicle[c]	–	4	100
6d–SD[d]	10[e]	4	41
6d–SD[d]	10[e]	8	73

Figure 8. Mean (n = 2) phosphorylated ERK1/2 levels in F344 nude rats bearing A375 ($BRAF^{V600E}$ mutant) human melanoma xenograft tumors after treatment with single dose of **6d-SD**. Footnotes in the table portion indicate the following: (b) detected by Western blotting; (c) delivered in distilled water; (d) solid dispersion formulation was delivered in distilled water; (e) dose of **6d** is described.



		Dose (mg/kg)	T/C (%)
○	**Vehicle**[c]	–	100
▲	**6d–SD**[b,d]	10[e]	−7.0

Figure 9. Mean (n = 3) tumor volumes and body weights in F344 nude rats bearing A375 human melanoma xenograft tumors dosed with **6d-SD** or vehicle. Footnotes in the table portion indicate the following: (b) compound **6d-SD** was administered orally twice daily for 14 days; (c) delivered in distilled water; (d) dolid dispersion formulation was delivered in distilled water; (e) dose of **6d** is described. $P \leq 0.05$ vs control at day 14 (t-test).

antiangiogenesis activity of **6d** resulted in enhanced in vivo antitumor efficacy against various types of cancers.

Pharmacokinetic Profiles and in Vivo Studies of 6d in Rats. To maximize the oral bioavailability of **6d**, we applied a spray-dried solid dispersion (SD) formulation[38] to this compound using hydroxypropyl methylcellulose phthalate (HPMCP, HP-55). The obtained **6d-SD** showed sufficient oral bioavailability (F = 70.5%) at a dose of 10 mg/kg for **6d** in rats (Table 6).

Reflecting the sufficient oral bioavailability, **6d-SD** demonstrated significantly decreased phosphorylation levels of ERK1/2 4 h after oral administration in an A375 ($BRAF^{V600E}$ mutant) human melanoma xenograft model in rats (Figure 8).

Finally, we examined the antitumor efficacy of **6d-SD** administered orally twice daily in an A375 melanoma xenograft model in rats (Figure 9). Two weeks after administration at a dose of 10 mg/kg for **6d**, we observed tumor regression with T/C of −7.0% without severe toxicity. Since **6d** also shows potent VEGFR2 inhibitory activity (Table 5, Figure 7), this tumor regression should include the efficacy based on the antiangiogenesis potency and BRAF inhibitory activity.

CONCLUSION

We designed and developed RAF/VEGFR2 inhibitors bearing a novel [1,3]thiazolo[5,4-*b*]pyridine scaffold **6** on the basis of structure-based drug design using docking models of our lead imidazo[1,2-*b*]pyridazines **1a**,**b** with BRAF. Target compounds were designed as DFG-out type binders for binding the inactive conformation of BRAF. X-ray cocrystal structural analysis of the representative compound **6d** indicated that the two hydrogen bonds in benzamide between rings B and C with Asp594 and Glu501 play a key role in stabilizing the DFG-out conformation. Furthermore, the sulfur−carbonyl interactions were important for the planar conformation of the 2-amide, together with coordination of the $\pi-\pi$ interaction with the indole ring of Trp531, which was significant for enhancing BRAF inhibition. The optimal compound **6d** showed excellent in vitro potency as a BRAF(V600E) and VEGFR2 dual kinase inhibitor.

In vitro pharmacologycal evaluation of **6d** revealed potent MAPK cascade suppression in various $BRAF^{V600E}$ mutant tumor cell lines. Furthermore, **6d** showed antiangiogenesis by suppressing the VEGFR2 pathway in 293/KDR and VEGF-stimulated HUVEC cells. Compound **6d-SD**, prepared using a spray-dried SD formulation, demonstrated a mechanism-based in vivo PD effect as well as regressive antitumor efficacy in an A375 human melanoma xenograft model in rats. These results suggest that dual inhibition of BRAF(V600E) and VEGFR2 may provide strong antitumor efficacy and that **6d** is a promising candidate for the treatment of various human cancers harboring the $BRAF^{V600E}$ mutation.

EXPERIMENTAL SECTION

General Chemistry Information. The starting materials, reagents, and solvents for reactions were reagent-grade and were used as purchased. Thin-layer chromatography (TLC) was carried out using Merck Kieselgel 60, 63−200 mesh, F254 plates, or Fuji Silysia Chemical Ltd., 100−200 mesh, NH plates. Chromatographic purification was carried out using silica gel (Merck, 70−230 mesh) or basic silica gel (Fuji Silysia Chemical Ltd., DM1020, 100−200 mesh). Melting points were obtained using an OptiMelt melting point apparatus MPA100 and used uncorrected. Proton nuclear magnetic resonance ^{1}H NMR spectra

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were recorded using a Bruker AVANCE II (300 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. The NMR data are given as follows: chemical shift (δ) in ppm, multiplicity (where applicable), coupling constants (J) in Hz (where applicable), and integration (where applicable). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublets), dt, (double triplet), ddd (double double doublet), br s (broad singlet), or m (multiplet). MS spectra were collected with a Waters LC−MS system (ZMD-1) and were used to confirm ≥95% purity of each compound. The column used was an L-column 2 ODS (3.0 mm × 50 mm i.d., CERI, Japan) with a temperature of 40 °C and a flow rate of 1.2 mL/min. Mobile phase A was 0.05% TFA in ultrapure water. Mobile phase B was 0.05% TFA in acetonitrile which was increased linearly from 5% to 90% over 2 min, 90% over the next 1.5 min, after which the column was equilibrated to 5% for 0.5 min. Elemental analyses (Anal.) and high-resolution mass spectrometry (HRMS) were carried out at Takeda Analytical Laboratories, Ltd. Yields were not optimized.

***N*-{6-[3-({[3-(Trifluoromethyl)phenyl]carbonyl}amino)-phenoxy]imidazo[1,2-*b*]pyridazin-2-yl}tetrahydro-2*H*-pyran-4-carboxamide (1a).** To a solution of *N*-{3-[(2-aminoimidazo[1,2-*b*]-pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide **10** (150 mg, 0.36 mmol) in *N*,*N*-dimethylformamide (5 mL) were successively added tetrahydro-2*H*-pyran-4-carboxylic acid (70.8 mg, 0.54 mmol), EDCI·HCl (104 mg, 0.54 mmol), HOBt (73.6 mg, 0.54 mmol), and triethylamine (76 μL, 0.54 mmol), and the reaction mixture was stirred at room temperature for 14 h. The mixture was partitioned between ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The oily residue was purified with silica gel column chromatography (50−100% ethyl acetate in *n*-hexane). Desired fractions were evaporated in vacuo and the oily residue was crystallized with ethyl acetate/*n*-hexane (1:4) to give **1a** (155 mg, 81%) as a pale yellow amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.52−1.81 (m, 4H), 2.56−2.83 (m, 1H), 3.25−3.40 (m, 2H), 3.80−3.97 (m, 2H), 7.03 (dd, J = 2.1, 7.7 Hz, 1H), 7.08 (d, J = 9.4 Hz, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.58−7.71 (m, 1H), 7.74 (t, J = 2.1 Hz, 1H), 7.75−7.86 (m, 1H), 7.98 (d, J = 8.1 Hz, 1H), 8.01−8.12 (m, 2H), 8.17−8.38 (m, 2H), 10.60 (s, 1H), 10.81 (s, 1H). HRMS (ESI) calcd for $C_{26}H_{22}F_3N_5O_4$ $[M + H]^+$ 526.1697. Found: 526.1659.

***N*-(3-{[2-(Propionylamino)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-phenyl)-3-(trifluoromethyl)benzamide (1c).** Compound **1c** (116 mg) was prepared in a similar manner to that described for **1a** from **10** (150 mg, 0.363 mmol), using propionic acid (40 μL, 0.544 mmol), EDCI·HCl (104 mg, 0.544 mmol), HOBt (73 mg, 0.544 mmol), triethylamine (76 μL, 0.544 mmol), and *N*,*N*-dimethylformamide (5 mL). Yield 68%, white crystals; mp 190−194 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.07 (t, J = 7.5 Hz, 3H), 2.37 (q, J = 7.5 Hz, 2H), 7.01−7.11 (m, 2H), 7.46 (t, J = 8.2 Hz, 1H), 7.65−7.83 (m, 3H), 7.94−8.00 (m, 1H), 8.02 (s, 1H), 8.05 (d, J = 9.6 Hz, 1H), 8.22−8.30 (m, 2H), 10.59 (s, 1H), 10.75 (s, 1H). HRMS (ESI): calcd for $C_{23}H_{18}F_3N_5O_3$ $[M + H]^+$ 470.1435. Found: 470.1457.

***N*-(3-{[2-(Isobutyrylamino)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-phenyl)-3-(trifluoromethyl)benzamide (1d).** Compound **1d** (74 mg) was prepared in a similar manner to **1a** from **10** (150 mg, 0.363 mmol), using 2-methylpropanoic acid (50 μL, 0.544 mmol), EDCI·HCl (104 mg, 0.544 mmol), HOBt (73 mg, 0.544 mmol), triethylamine (76 μL, 0.544 mmol), and *N*,*N*-dimethylformamide (5 mL). Yield 42%, pale green crystals; mp 193 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.08 (d, J = 7.0 Hz, 6H), 2.65−2.77 (m, 1H), 7.00−7.11 (m, 2H), 7.46 (t, J = 8.1 Hz, 1H), 7.63−7.83 (m, 3H), 7.94−8.09 (m, 3H), 8.22−8.30 (m, 2H), 10.59 (s, 1H), 10.75 (s, 1H). MS (ESI) m/z 484.15 $(M + H)^+$. Anal. Calcd for $C_{24}H_{20}F_3N_5O_3$: C, 59.63; H, 4.17; N, 14.49. Found: C, 59.53; H, 4.25; N, 14.55.

***N*-{3-[(2-Acetamidoimidazo[1,2-*b*]pyridazin-6-yl)oxy]-phenyl}-3-(trifluoromethyl)benzamide (1b).** To a solution of **10** (150 mg, 0.362 mmol) in pyridine (3 mL) was added acetyl chloride (31 μL, 0.435 mmol), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo. The resulting slurry was triturated with water (10 mL). The resulting precipitate was collected and recrystallized from ethanol to give compound **1b** (99 mg, 60%) as pale yellow crystals, mp 224−226 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.07 (s, 3H), 7.01−7.11 (m, 2H), 7.46 (t, J = 8.1 Hz, 1H), 7.63−7.83 (m, 3H), 7.95−8.01 (m, 2H), 8.06 (d, J = 9.6 Hz, 1H), 8.22−8.30 (m, 2H), 10.59 (s, 1H), 10.80 (s, 1H). HRMS (ESI): calcd for $C_{22}H_{16}F_3N_5O_3$ $[M + H]^+$ 456.1278. Found: 456.1283.

***N*-[3-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-*b*]-pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (1e).** Compound **1e** (132 mg) was prepared in a similar manner to **1b** from **10**, using cyclopropanecarbonyl chloride (45.5 mg, 0.44 mmol) and pyridine (3 mL). Yield 75%, colorless crystals; mp 203−204 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.61−1.04 (m, 4H), 1.67−2.04 (m, 1H), 7.03 (dd, J = 2.1, 7.6 Hz, 1H), 7.08 (d, J = 9.6 Hz, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.73 (t, J = 2.1 Hz, 1H), 7.75−7.86 (m, 1H), 7.87−8.02 (m, 2H), 8.06 (d, J = 9.6 Hz, 1H), 8.19−8.41 (m, 2H), 10.59 (s, 1H), 11.09 (s, 1H). MS (ESI): m/z 482.2 $(M + H)^+$. Anal. Calcd for $C_{24}H_{18}F_3N_5O_3$: C, 59.88; H, 3.77; N, 14.55. Found: C, 59.91; H, 3.88; N, 14.37.

***N*-[3-({2-[(Cyclobutylcarbonyl)amino]imidazo[1,2-*b*]-pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (1f).** Compound **1f** (98 mg) was prepared in a similar manner to **1b** from **10** (150 mg, 0.362 mmol), using cyclobutanecarbonyl chloride (50 μL, 0.435 mmol), triethylamine (75 μL, 0.544 mmol), and tetrahydrofuran (5 mL). Yield 54%, white amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.83−2.11 (m, 2H), 2.15−2.46 (m, 4H), 3.14−3.28 (m, 1H), 6.88 (d, J = 9.4 Hz, 1H), 7.00−7.06 (m, 1H), 7.42−7.48 (m, 2H), 7.60−7.68 (m, 1H), 7.69−7.85 (m, 4H), 7.91−7.98 (m, 1H), 8.04−8.09 (m, 1H), 8.13 (s, 1H), 8.19 (s, 1H). HRMS (ESI): calcd for $C_{25}H_{20}F_3N_5O_3$ $[M + H]^+$ 496.1591. Found: 496.1588.

***N*-[3-({2-[(Cyclopentylcarbonyl)amino]imidazo[1,2-*b*]-pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (1g).** Compound **1g** (105 mg) was prepared in a manner similar to **1b** from **10** (150 mg, 0.362 mmol), using cyclopentanecarbonyl chloride (53 μL, 0.435 mmol), triethylamine (75 μL, 0.544 mmol), and tetrahydrofuran (5 mL). Yield 57%, white crystals; mp 215−217 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.47−1.90 (m, 8H), 2.81−2.95 (m, 1H), 7.00−7.10 (m, 2H), 7.46 (t, J = 8.2 Hz, 1H), 7.63−7.83 (m, 3H), 7.94−8.09 (m, 3H), 8.21−8.30 (m, 2H), 10.59 (s, 1H), 10.77 (s, 1H). HRMS (ESI): calcd for $C_{26}H_{22}F_3N_5O_3$ $[M + H]^+$ 510.1748. Found: 510.1711.

***N*-[3-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-*b*]-pyridazin-6-yl}oxy)phenyl]-4-(trifluoromethyl)benzamide (1h).** Compound **1h** (110 mg) was prepared in a similar manner to **1a** from *N*-[6-(3-aminophenoxy)imidazo[1,2-*b*]pyridazin-2-yl]cyclopropanecarboxamide **14** (100 mg, 0.32 mmol), using, 4-(trifluoromethyl)-benzoic acid **15h** (63 mg, 0.33 mmol), EDCI·HCl (65 mg, 0.34 mmol), HOBt (46 mg, 0.34 mmol), and *N*,*N*-dimethylformamide (5 mL). Yield 68%, white crystals; mp 240−241 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.62−0.94 (m, 4H), 1.76−2.06 (m, 1H), 6.99−7.05 (m, 1H), 7.08 (d, J = 9.6 Hz, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.63−7.71 (m, 1H), 7.74 (t, J = 2.1 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.98 (s, 1H), 8.06 (d, J = 9.6 Hz, 1H), 8.13 (d, J = 8.2 Hz, 2H), 10.60 (s, 1H), 11.09 (s, 1H). MS (ESI): m/z 482.02 $(M + H)^+$. Anal. Calcd for $C_{24}H_{18}F_3N_5O_3$: C, 59.88; H, 3.77; N, 14.55. Found: C, 59.92; H, 3.88; N, 14.43.

***N*-[3-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-*b*]-pyridazin-6-yl}oxy)phenyl]-2-(trifluoromethyl)benzamide (1i).** To a solution of 2-(trifluoromethyl)benzoic acid **15i** (110 mg, 0.581 mmol) in tetrahydrofuran (5 mL) was added oxalyl chloride (84 μL, 0.969 mmol) followed by *N*,*N*-dimethylformamide (5 μL) at 4 °C. The reaction mixture was stirred at room temperature for 1.5 h and evaporated in vacuo. The residue was diluted with NMP (5 mL), and to the mixture was added **14** (150 mg, 0.484 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate (20 mL), washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL) successively, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (0−100% ethyl acetate in *n*-hexane) to give compound **1i** (176 mg, 75%) as a white amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.77−0.84 (m, 4H), 1.86−1.98 (m, 1H), 6.98−7.04 (m, 1H), 7.07 (d, J = 9.6 Hz, 1H), 7.43

(t, J = 8.1 Hz, 1H), 7.51−7.57 (m, 1H), 7.64 (t, J = 2.1 Hz, 1H), 7.67−7.76 (m, 2H), 7.76−7.88 (m, 2H), 7.98 (s, 1H), 8.05 (d, J = 9.6 Hz, 1H), 10.71 (s, 1H), 11.07 (s, 1H). HRMS (ESI): calcd for $C_{24}H_{18}F_3N_5O_3$ $[M + H]^+$ 482.1435. Found: 482.1432.

_N_-[3-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-_b_]pyridazin-6-yl}oxy)phenyl]-3-methoxybenzamide (1j). Compound **1j** (49 mg) was prepared in a similar manner to **1i** from **14** (80 mg, 0.26 mmol) using 3-methoxybenzoic acid **15j** (48 mg, 0.32 mmol), oxalyl chloride (32 μL, 0.37 mmol), *N*,*N*-dimethylformamide (5 μL), tetrahydrofuran (2 mL), and NMP (2 mL). Yield 43%, white crystals; mp 186−187 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.77−0.85 (m, 4H), 1.85−1.99 (m, 1H), 3.83 (s, 3H), 6.95−7.03 (m, 1H), 7.07 (d, J = 9.6 Hz, 1H), 7.12−7.21 (m, 1H), 7.37−7.49 (m, 3H), 7.48−7.56 (m, 1H), 7.61−7.70 (m, 1H), 7.73 (t, J = 2.1 Hz, 1H), 7.98 (s, 1H), 8.05 (d, J = 9.6 Hz, 1H), 10.34 (s, 1H), 11.09 (s, 1H). MS (ESI): m/z 444.02 $(M + H)^+$. Anal. Calcd for $C_{24}H_{21}N_5O_4$: C, 65.00; H, 4.77; N, 15.79. Found: C, 64.73; H, 4.87; N, 15.69.

3-_tert_-Butoxy-_N_-[3-({2-[(cyclopropylcarbonyl)amino]-imidazo[1,2-_b_]pyridazin-6-yl}oxy)phenyl]benzamide (1k). Compound **1k** (160 mg) was prepared in a similar manner to **1i** from **14** (150 mg, 0.49 mmol), using 3-*tert*-butoxybenzoic acid **15k** (110 mg, 0.58 mmol), oxalyl chloride (63 μL, 0.73 mmol), *N*,*N*-dimethylformamide (5 μL), tetrahydrofuran (4 mL), and NMP (4 mL). Yield 57%, white crystals; mp 206−207 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.74−0.87 (m, 4H), 1.33 (s, 9H), 1.85−1.98 (m, 1H), 6.90−7.03 (m, 1H), 7.07 (d, J = 9.6 Hz, 1H), 7.16−7.27 (m, 1H), 7.36−7.48 (m, 2H), 7.48−7.53 (m, 1H), 7.61−7.70 (m, 2H), 7.73 (t, J = 2.1 Hz, 1H), 7.98 (s, 1H), 8.05 (d, J = 9.6 Hz, 1H), 10.34 (s, 1H), 11.09 (s, 1H). MS (ESI): 486.25 $(M + H)^+$. Anal. Calcd for $C_{27}H_{27}N_5O_4$: C, 66.79; H, 5.61; N, 14.42. Found: C, 66.68; H, 5.56; N,14.41.

Methyl 3-({[3-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-_b_]pyridazin-6-yl}oxy)phenyl]amino}carbonyl)benzoate (1l). Compound **1l** (270 mg) was prepared by a similar manner to **1a** from **14** (250 mg, 0.81 mmol), using 3-(methoxycarbonyl)benzoic acid **15l** (150 mg, 0.83 mmol), EDCI·HCl (160 mg, 0.84 mmol), HOBt (110 mg, 0.81 mmol), and *N*,*N*-dimethylformamide (8 mL). Yield 72%, white crystals; mp 216−217 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.74−0.85 (m, 4H), 1.84−1.98 (m, 1H), 3.91 (s, 3H), 6.97−7.05 (m, 1H), 7.08 (d, J = 9.6 Hz, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.63−7.79 (m, 3H), 7.98 (s, 1H), 8.06 (d, J = 9.6 Hz, 1H), 8.12−8.19 (m, 1H), 8.19−8.26 (m, 1H), 8.52 (t, J = 1.5 Hz, 1H), 10.59 (s, 1H), 11.09 (s, 1H). Anal. Calcd for $C_{25}H_{21}N_5O_5$: C, 63.69; H, 4.49; N, 14.85. Found: C, 63.48; H, 4.51; N, 14.76.

_N_-[3-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-_b_]pyridazin-6-yl}oxy)phenyl]-3-(1-hydroxy-1-methylethyl)-benzamide (1m). To a solution of methyl 3-({[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-*b*]pyridazin-6-yl}oxy)phenyl]-amino}carbonyl)benzoate **1l** (100 mg, 0.212 mmol) in tetrahydrofuran (5 mL) was added dropwise a solution of 1.4 M methylmagnesium bromide in tetrahydrofuran/toluene (0.76 mL, 1.1 mmol) under ice-cooling. After addition, the reaction mixture was stirred at room temperature for 12 h. To the mixture was added water (10 mL), and the mixture was treated with 1 N HCl (5 mL). The mixture was extracted with ethyl acetate (30 mL), and the organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (40−100% ethyl acetate in *n*-hexane) to give compound **1m** (19 mg, 19%) as a white amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.75−0.85 (m, 4H), 1.46 (s, 6H), 1.85−1.97 (m, 1H), 5.14 (s, 1H), 6.96−7.03 (m, 1H), 7.07 (d, J = 9.6 Hz, 1H), 7.37−7.50 (m, 2H), 7.67 (m, 2H), 7.73 (t, J = 2.1 Hz, 1H), 7.75−7.81 (m, 1H), 7.98 (s, 1H), 8.01 (t, J = 1.5 Hz, 1H), 8.05 (d, J = 9.6 Hz, 1H), 10.35 (s, 1H), 11.09 (s, 1H). HRMS (ESI): calcd for $C_{26}H_{25}N_5O_4$ $[M + H]^+$ 472.1979. Found: 472.1941.

3-(1-Cyano-1-methylethyl)-_N_-[3-({2-[(cyclopropylcarbonyl)-amino]imidazo[1,2-_b_]pyridazin-6-yl}oxy)phenyl]benzamide (1n). Compound **1n** (120 mg) was prepared by a similar manner to **1a** from **14** (100 mg, 0.32 mmol), using 3-(1-cyano-1-methylethyl)benzoic acid **15n** (62 mg, 0.33 mmol), EDCI·HCl (65 mg, 0.34 mmol), HOBt (46 mg, 0.34 mmol), and *N*,*N*-dimethylformamide (5 mL). Yield 77%, white crystals; mp 225−226 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.73−0.86 (m, 4H), 1.74 (s, 6H), 1.83−1.98 (m, 1H), 6.99−7.04 (m, 1H), 7.08 (d, J = 9.6 Hz, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.54−7.69 (m, 2H), 7.69−7.80 (m, 2H), 7.92 (dt, J = 7.8, 1.2 Hz, 1H), 7.98 (s, 1H), 8.00−8.10 (m, 2H), 10.45 (s, 1H), 11.09 (s, 1H). HRMS (ESI): calcd for $C_{27}H_{24}N_6O_3$ $[M + H]^+$ 481.1983. Found: 481.1969.

3-(1-Cyano-1-methylethyl)-_N_-[3-({2-[(cyclopropylcarbonyl)-amino]imidazo[1,2-_a_]pyridin-6-yl}oxy)phenyl]benzamide (2). To a solution of 3-(1-cyano-1-methylethyl)-*N*-[3-({2-[(trifluoroacetyl)-amino]imidazo[1,2-*a*]pyridin-6-yl}oxy)phenyl]benzamide **25** (400 mg, 0.788 mmol) in ethanol (4.0 mL) was added 1 N NaOH (8.0 mL), and the reaction mixture was stirred at 45 °C for 12 h. To the reaction mixture was added water (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The organic layer was washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography (0−20% methanol in ethyl acetate), and the desired fractions were combined and concentrated under reduced pressure to give *N*-{3-[(2-aminoimidazo[1,2-*a*]pyridin-6-yl)oxy]phenyl}-3-(1-cyano-1-methylethyl)benzamide (0.35 g, quantitative yield) as colorless amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.73 (s, 6H), 5.08 (s, 2H), 6.78 (dd, J = 2.1, 8.1 Hz, 1H), 6.87 (dd, J = 2.1, 9.6 Hz, 1H), 7.01 (s, 1H), 7.22 (d, J = 9.6 Hz, 1H), 7.34 (t, J = 8.2 Hz, 1H), 7.44 (s, 1H), 7.50−7.62 (m, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.98 (s, 1H), 8.34 (d, J = 2.1 Hz, 1H), 10.34 (s, 1H). MS (ESI): m/z 412.05 $(M + H)^+$.

To a solution of *N*-{3-[(2-aminoimidazo[1,2-*a*]pyridin-6-yl)oxy]-phenyl}-3-(1-cyano-1-methylethyl)benzamide (200 mg, 0.486 mmol) in *N*,*N*-dimethylacetamide (2.0 mL) was added cyclopropanecarbonyl chloride (46 μL, 0.510 mmol), and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with 5% aqueous $NaHCO_3$ (50 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (50−100% ethyl acetate in *n*-hexane). The desired fractions were combined and concentrated under reduced pressure, and the residue was triturated with ethyl acetate and *i*-Pr_2O to give **2** (100 mg, 43%) as colorless crystals, mp 138−140 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.73−0.85 (m, 4H), 1.73 (s, 6H), 1.86−2.03 (m, 1H), 6.81 (dd, J = 2.4, 8.1 Hz, 1H), 7.10 (dd, J = 2.4, 9.6 Hz, 1H), 7.36 (t, J = 8.1 Hz, 1H), 7.44−7.52 (m, 2H), 7.57 (t, J = 7.8 Hz, 2H), 7.69−7.78 (m, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 1.5 Hz, 1H), 8.07 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 10.35 (s, 1H), 10.98 (s, 1H). MS (ESI): m/z 480.2 $(M + H)^+$. Anal. Calcd for $C_{28}H_{25}N_5O_3$: C, 70.13; H, 5.25; N, 14.60. Found: C, 70.26; H, 5.46; N, 14.56.

3-(1-Cyano-1-methylethyl)-_N_-[3-({2-[(cyclopropylcarbonyl)-amino]-1_H_-benzimidazol-6-yl}oxy)phenyl]benzamide (3a). A mixture of *tert*-butyl [3-({2-[(cyclopropylcarbonyl)amino]-1*H*-benzimidazol-6-yl}oxy)phenyl]carbamate **29a** (1.58 g, 3.88 mmol) and trifluoroacetic acid (50 mL) was refluxed at 80 °C for 1 h. The reaction mixture was cooled at room temperature and evaporated in vacuo. The residue was diluted with ethyl acetate (200 mL), washed with 0.1 N HCl (100 mL) and saturated $NaHCO_3$ (100 mL) successively, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo. The residue was crystallized from methanol to give *N*-[6-(3-aminophenoxy)-1*H*-benzimidazol-2-yl]cyclopropanecarboxamide (1.06 g, 88%) as pale brown crystals, mp 213-214 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.90−0.92 (m, 4H), 1.91−2.01 (m, 1H), 5.13 (br s, 2H), 6.07−6.10 (m, 2H), 6.22−6.26 (m, 1H), 6.79 (dd, J = 2.4, 8.7 Hz, 1H), 6.91−7.12 (m, 2H), 7.40 (br d, J = 8.4 Hz, 1H), 11.81 (br s, 1H), 11.99 (br s, 1H). HRMS (ESI): calcd for $C_{17}H_{16}N_4O_2$ $[M + H]^+$ 309.1346. Found: 309.1327.

Compound **3a** (168 mg) was prepared in a similar manner to **1a** from *N*-[6-(3-aminophenoxy)-1*H*-benzimidazol-2-yl]cyclopropanecarboxamide (156 mg, 0.506 mmol), using 3-(1-cyano-1-methylethyl)-benzoic acid **15n** (195 mg, 1.03 mmol), pyridine (5 mL), EDCI·HCl (407 mg, 2.12 mmol), DMAP (58.2 mg, 0.476 mmol). Yield 69%,

colorless crystals; mp 139−141 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.91−0.93 (m, 4H), 1.73 (s, 6H), 1.94−2.00 (m, 1H), 6.74 (dd, J = 1.8, 7.8 Hz, 1H), 8.85 (dd, J = 2.4, 8.4 Hz, 1H), 7.05−7.18 (m, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.41−7.59 (m, 4H), 7.72−7.75 (m, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.97−7.98 (m, 1H), 10.31 (br s, 1H), 11.84 (br s, 1H), 12.03 (br s, 1H). HRMS (ESI): calcd for $C_{28}H_{25}N_5O_3$ [M + H]$^+$ 480.2030. Found: 480.1995.

3-(1-Cyano-1-methylethyl)-*N*-[3-({2-[(cyclopropylcarbonyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}oxy)phenyl]benzamide (3b). *N*-[6-(3-Aminophenoxy)-1-methyl-1*H*-benzimidazol-2-yl]cyclopropanecarboxamide (1.02 g) was prepared in a similar manner to intermediate of **3a**, *N*-[6-(3-aminophenoxy)-1*H*-benzimidazol-2-yl]cyclopropanecarboxamide from using *tert*-butyl [3-({2-[(cyclopropylcarbonyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}oxy)-phenyl]carbamate **29b** (1.52 g, 3.60 mmol), using trifluoroacetic acid (50 mL). Yield 88%, pink amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93−0.98 (m, 2H), 1.11−1.13 (m, 2H), 1.94−1.99 (m, 1H), 3.68 (s, 3H), 6.34 (t, J = 2.1 Hz, 1H), 6.38−6.41 (m, 1H), 6.46−6.49 (m, 1H), 6.96 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 2.1, 8.4 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H), 7.28−7.37 (m, 1H). HRMS (ESI): calcd for $C_{18}H_{18}N_4O_2$ [M + H]$^+$ 323.1503. Found: 323.1487.

Compound **3b** (97.3 mg) was prepared in a similar manner to **1a** from *N*-[6-(3-aminophenoxy)-1-methyl-1*H*-benzimidazol-2-yl]cyclopropanecarboxamide (166 mg, 0.514 mmol), using 3-(1-cyano-1-methylethyl)benzoic acid **15n** (316 mg, 1.67 mmol), pyridine (5 mL), EDCI·HCl (456 mg, 2.38 mmol), and DMAP (38.9 mg, 0.318 mmol). Yield 38%, colorless crystals; mp 129−130 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.82−0.92 (m, 4H), 1.73 (s, 6H), 1.90−2.05 (m, 1H), 3.54 (s, 3H), 6.76 (dd, J = 1.8, 7.8 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 7.31−7.37 (m, 2H), 7.41−7.60 (m, 4H), 7.72−7.75 (m, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.98−8.00 (m, 1H), 10.35 (br s, 1H), 10.89 (br s, 1H). HRMS (ESI): calcd for $C_{29}H_{27}N_5O_3$ [M + H]$^+$ 494.2187. Found: 494.2171.

3-(1-Cyano-1-methylethyl)-*N*-[3-({2-[(cyclopropylcarbonyl)amino]-3*H*-imidazo[4,5-*b*]pyridin-5-yl}oxy)phenyl]benzamide (4a). A mixture of *N*-{3-[(2-amino-3-*tert*-butyl-3*H*-imidazo[4,5-*b*]-pyridin-5-yl)oxy]phenyl}-3-(1-cyano-1-methylethyl)benzamide **34a** (0.23 g, 0.5 mmol), cyclopropanecarbonyl chloride (0.21 g, 2.0 mmol), and DMAP (0.24 g, 2.0 mmol) in pyridine (2.0 mL) was stirred at room temperature for 18 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (0−100% ethyl acetate in *n*-hexane) to give *N*-[3-({3-*tert*-butyl-2-[(cyclopropylcarbonyl)amino]-3*H*-imidazo[4,5-*b*]pyridin-5-yl}oxy)-phenyl]-3-(1-cyano-1-methylethyl)benzamide (0.15 g, 0.28 mmol, 56%) as a colorless amorphous solid. The overreacted bis-(cyclopropylcarbonyl) derivative was treated by 1 N NaOH and methanol (5:1) to give additional *N*-[3-({3-*tert*-butyl-2-[(cyclopropylcarbonyl)amino]-3*H*-imidazo[4,5-*b*]pyridin-5-yl}oxy)phenyl]-3-(1-cyano-1-methylethyl)-benzamide (0.11 g, 40%) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.77−0.86 (m, 2H), 1.01−1.11 (m, 2H), 1.67−1.73 (m, 1H), 1.76 (s, 15H), 6.74 (d, J = 8.5 Hz, 1H), 6.94 (dt, J = 6.8, 1.1 Hz, 1H), 7.31−7.55 (m, 4H), 7.59 (t, J = 2.1 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.98 (t, J = 1.7 Hz, 1H), 8.11 (br s, 1H), 12.86 (br s, 1H). MS (ESI): m/z 537 (M + H)$^+$.

A solution of *N*-[3-({3-*tert*-butyl-2-[(cyclopropylcarbonyl)amino]-3*H*-imidazo[4,5-*b*]pyridin-5-yl}oxy)phenyl]-3-(1-cyano-1-methylethyl)-benzamide (0.23 g, 0.48 mmol) in trifluoroacetic acid (2 mL) was stirred at 80 °C for 2 h. The mixture was cooled at room temperature and evaporated in vacuo. The residue was partitioned between ethyl acetate (50 mL) and 0.1 N NaOH (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was crystallized with acetone to give compound **4a** (188 mg, 82%) as colorless crystals, mp 180−181 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.41−1.19 (m, 4H), 1.74 (s, 6H), 2.53−2.60 (m, 1H), 6.77 (d, J = 8.3 Hz, 2H), 7.22−7.35 (m, 1H), 7.42−7.54 (m, 2H), 7.56−7.79 (m, 3H), 7.91 (d, J = 7.9 Hz, 1H), 8.03 (t, J = 1.8 Hz, 1H), 9.60 (br s, 1H), 11.65 (br s, 1H), 13.23 (br s, 1H). HRMS (ESI): calcd for $C_{27}H_{24}N_6O_3$ [M + H]$^+$ 481.1983. Found: 481.1966.

3-(1-Cyano-1-methylethyl)-*N*-[3-({2-[(cyclopropylcarbonyl)amino]-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl}oxy)phenyl]benzamide (4b). To a solution of **34b** (170 mg, 0.40 mmol) in pyridine (2 mL) were added cyclopropanecarbonyl chloride (105 mg, 1.0 mmol) and DMAP (120 mg, 1.0 mmol) successively. The reaction mixture was stirred at room temperature for 18 h. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (0−100% ethyl acetate in *n*-hexane) to give compound **4b** (110 mg, 56%) as colorless crystals, mp 132−134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85−0.90 (m, 2H), 1.01−1.14 (m, 2H), 1.76 (s, 6H), 1.79−1.91 (m, 1H), 3.60 (s, 3H), 6.73 (d, J = 8.3 Hz, 1H), 6.96 (dt, J = 7.5, 1.9 Hz, 1H), 7.34−7.48 (m, 2H), 7.47−7.64 (m, 3H), 7.69 (ddd, J = 1.0, 2.0, 7.9 Hz, 1H), 7.77 (dt, J = 7.7, 1.2 Hz, 1H), 7.97 (t, J = 1.8 Hz, 2H), 12.13 (br s, 1H). HRMS (ESI): calcd for $C_{28}H_{26}N_6O_3$ [M + H]$^+$ 495.2139. Found: 495.2135.

3-(1-Cyano-1-methylethyl)-*N*-[3-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}oxy)phenyl]benzamide (5). Potassium thiocyanate (8.09 g, 83.2 mmol) was added to acetic acid (150 mL). To the solution was added a solution of *N*-[3-(4-aminophenoxy)phenyl]-3-(1-cyano-1-methylethyl)benzamide **38** (7.34 g, 19.8 mmol) in acetic acid (150 mL). The mixture was stirred at room temperature for 15 min. To the mixture was added a solution of bromine (4.0 g, 25.0 mmol) in acetic acid (100 mL) at room temperature over 30 min, and the reaction mixture was stirred at room temperature for 4 h. The resulting yellow precipitate was removed by filtration through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was diluted with tetrahydrofuran (100 mL) and ethyl acetate (200 mL), and the mixture was basified with 2 N NaOH (200 mL). The organic layer was washed with saturated NH_4Cl (200 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give *N*-{3-[(2-amino-1,3-benzothiazol-6-yl)oxy]phenyl}-3-(1-cyano-1-methylethyl)-benzamide (7.4 g, 87%) as a pale yellow amorphous solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.73 (s, 6H), 6.73−6.76 (m, 1H), 6.96 (dd, J = 2.7, 8.7 Hz, 1H), 7.31−7.36 (m, 2H), 7.42−7.60 (m, 6H), 7.72−7.75 (m, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.98 (t, J = 1.8 Hz, 1H), 10.33 (br s, 1H). MS (ESI): m/z 429.05 (M + H)$^+$.

To a solution of *N*-{3-[(2-amino-1,3-benzothiazol-6-yl)oxy]-phenyl}-3-(1-cyano-1-methylethyl)benzamide (5.13 g, 12.0 mmol) in pyridine (50 mL) were added cyclopropanecarbonyl chloride (2.5 mL, 27.6 mmol) and DMAP (89.3 mg, 0.731 mmol), successively, at 4 °C. The reaction mixture was stirred at room temperature for 6 h. To the mixture were added methanol (50 mL) and 2 N NaOH (10 mL) successively, and the mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate (300 mL). The mixture was washed with water (150 mL), 0.1 N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), successively. The organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (5−50% ethyl acetate in *n*-hexane). Desired fractions were combined and evaporated in vacuo and the residue was crystallized from ethyl acetate/*i*-Pr_2O to give compound **5** (4.40 g, 88%) as colorless crystals, mp 120−121 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.94−0.97 (m, 4H), 1.73 (s, 6H), 1.93−2.01 (m, 1H), 6.80 (dd, J = 1.8, 8.1 Hz, 1H), 7.17 (dd, J = 2.4, 8.7 Hz, 1H), 7.37 (t, J = 8.1 Hz, 1H), 7.48 (t, J = 2.1 Hz, 1H), 7.55−7.61 (m, 2H), 7.72−7.78 (m, 3H), 7.89 (d, J = 8.1 Hz, 1H), 7.98 (t, J = 1.8 Hz, 1H), 10.35 (br s, 1H), 12.63 (br s, 1H). HRMS (ESI): calcd for $C_{28}H_{24}N_4O_3S$ [M + H]$^+$ 497.1642. Found: 497.1647.

3-(1-Cyano-1-methylethyl)-*N*-[3-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-*b*]pyridin-5-yl}oxy)phenyl]benzamide (6a). Compound **6a** (111 mg) was prepared in a similar manner to **1i** from *N*-[5-(3-aminophenoxy)[1,3]thiazolo[5,4-*b*]pyridin-2-yl]cyclopropanecarboxamide **42** (126 mg, 0.387 mmol), using 3-(1-cyano-1-methylethyl)benzoic acid **15n** (147 mg, 0.778 mmol), thionyl chloride (100 μL, 1.37 mmol), toluene (5 mL), DMAP (10 mg, 0.0819 mmol), and pyridine (3 mL). Yield 58%, colorless crystals; mp 234 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.94−0.97 (m, 4H), 1.74 (s, 6H),

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1.95−2.04 (m, 1H), 6.93 (ddd, J = 0.9, 2.4, 8.1 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.57−7.65 (m, 3H), 7.75 (ddd, J = 0.9, 2.1, 7.8 Hz, 1H), 7.92 (dt, J = 7.2, 1.5 Hz, 1H), 8.02 (t, J = 1.8 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 10.41 (br s, 1H), 12.68 (br s, 1H). MS (ESI): m/z 498.15 (M + H)$^+$. HRMS (ESI): calcd for $C_{27}H_{23}N_5O_3S$ [M + H]$^+$ 498.1594. Found: 498.1580.

3-(1-Cyanocyclopropyl)-*N*-[3-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-*b*]pyridin-5-yl}oxy)phenyl]benzamide (6b). Compound **6b** (82 mg) was prepared in a similar manner to **1i** from *N*-[5-(3-aminophenoxy)[1,3]thiazolo[5,4-*b*]pyridin-2-yl]cyclopropanecarboxamide **42** (118 mg, 0.362 mmol), using 3-(1-cyano-1-methylethyl)benzoic acid **15o** (151 mg, 0.808 mmol), thionyl chloride (200 μL, 2.74 mmol), toluene (5 mL), DMAP (10 mg, 0.0819 mmol), and pyridine (2 mL). Yield 46%, colorless crystals; mp 208−215 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.94−0.97 (m, 4H), 1.61 (dd, J = 5.4, 8.4 Hz, 2H), 1.81 (dd, J = 5.4, 8.4 Hz, 2H), 1.97−2.01 (m, 1H), 6.91−6.95 (m, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.52−7.59 (m, 2H), 7.62−7.64 (m, 2H), 7.81 (br s, 1H), 7.86 (dt, J = 6.0, 2.4 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 10.40 (br s, 1H), 12.70 (br s, 1H). MS (ESI): m/z 495.46 (M + H)$^+$. HRMS (ESI): calcd for $C_{27}H_{21}N_5O_3S$ [M + H]$^+$ 496.1438. Found: 496.1406.

2-Chloro-3-(1-cyanocyclopropyl)-*N*-[3-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-*b*]pyridin-5-yl}oxy)phenyl]-benzamide (6c). Compound **6c** (169 mg) was prepared in a similar manner to **1a** from *N*-[5-(3-aminophenoxy)[1,3]thiazolo[5,4-*b*]-pyridin-2-yl]cyclopropanecarboxamide **42** (120 mg, 3.68 μmol), using 2-chloro-3-(1-cyclopropyl)benzoic acid **15p** (90 mg, 405 μmol), HATU (154 mg, 405 μmol), and pyridine (3 mL). Yield 87%, colorless crystals; mp 226−227 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.88−0.99 (m, 4H), 1.38−1.49 (m, 2H), 1.78−1.84 (m, 2H), 1.93−2.04 (m, 1H), 6.93 (ddd, J = 0.9, 2.3, 8.1 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.51−7.56 (m, 1H), 7.58−7.63 (m, 2H), 7.66 (dd, J = 1.7, 7.6 Hz, 1H), 8.17 (d, J = 8.7 Hz, 1H), 10.70 (br s, 1H), 12.70 (br s, 1H). HRMS (ESI): calcd for $C_{27}H_{20}ClN_5O_3S$ [M + H]$^+$ 530.1048. Found: 530.1033.

2-Chloro-3-(1-cyanocyclopropyl)-*N*-[5-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-*b*]pyridin-5-yl}oxy)-2-fluorophenyl]-benzamide (6d). To a mixture of *N*-{5-[(2-amino[1,3]thiazolo[5,4-*b*]pyridin-5-yl)oxy]-2-fluorophenyl}-2-chloro-3-(1-cyanocyclopropyl)-benzamide **45** (9.0 g, 18.8 mmol) and pyridine (2.3 mL, 28.1 mmol) in tetrahydrofuran (90 mL) was added dropwise cyclopropanecarbonyl chloride (1.89 mL, 20.8 mmol) at 4 °C. The reaction mixture was stirred at room temperature for 3 h. An additional amount of cyclopropanecarbonyl chloride (0.063 mL, 0.69 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for an additional 12 h. To the mixture were added water (100 mL) and saturated $NaHCO_3$ (100 mL), and the mixture was stirred at room temperature for 30 min. The resulting precipitate was collected by filtration, washed with water (200 mL), and dried under vacuum to give compound **6d** (9.85 g, 96%) as colorless crystals, mp 213 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.77−1.08 (m, 4H), 1.35−1.53 (m, 2H), 1.73−1.88 (m, 2H), 1.92−2.07 (m, 1H), 7.07 (dt, J = 8.7, 3.6 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.38 (dd, J = 9.1, 10.2 Hz, 1H), 7.43−7.50 (m, 1H), 7.55−7.69 (m, 2H), 7.78 (dd, J = 3.0, 6.4 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 10.57 (s, 1H), 12.70 (s, 1H). MS (ESI): m/z 548.0 (M + H)$^+$. Anal. Calcd for $C_{27}H_{19}ClFN_5O_3S$: C, 59.18; H, 3.49; N, 12.78. Found: C, 59.01; H, 3.53; N, 12.65.

2-Chloro-*N*-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]-[1,3]thiazolo[5,4-*b*]pyridin-5-yl}oxy)phenyl]-3-(1-cyanocyclopropyl)benzamide (6e). Under ice-cooling, to a suspension of sodium borohydride (5.63 g, 149 mmol) in methanol (66 mL) was added in small portions *N*-(5-{4-chloro-3-[(trifluoroacetyl)amino]phenoxy}-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)cyclopropanecarboxamide **48** (3.4 g, 7.44 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate (150 mL) and partitioned with water (200 mL). The organic layer was concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL), washed with brine (100 mL), and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent, ethyl acetate) and triturated with i-Pr_2O to give *N*-[5-(3-amino-4-chlorophenoxy)[1,3]thiazolo[5,4-*b*]-pyridin-2-yl]cyclopropanecarboxamide (2.00 g, 75%) as white crystals, mp 237−238 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.88−1.10 (m, 4H), 1.90−2.10 (m, 1H), 5.49 (br s, 2H), 6.32 (dd, J = 2.7, 8.6 Hz, 1H), 6.54 (d, J = 2.7 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 12.69 (br s, 1H). MS (ESI): m/z 361.0 (M + H)$^+$.

Compound **6e** (151 mg) was prepared in a similar manner to **1i** from *N*-[5-(3-amino-4-chlorophenoxy)[1,3]thiazolo[5,4-*b*]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.416 mmol), using 2-chloro-3-(1-cyanocyclopropyl)benzoic acid **15q** (184 mg, 0.830 mmol), oxalyl chloride (88 μL, 1.04 mmol), *N*,*N*-dimethylformamide (15 μL), tetrahydrofuran (4.6 mL), and *N*,*N*-dimethylacetamide (4.6 mL). Yield 64%, white crystals; mp 138−140 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.90−1.00 (m, 4H), 1.40−1.50 (m, 2H), 1.75−1.82 (m, 2H), 1.95−2.05 (m, 1H), 7.15 (dd, J = 3.0, 9.0 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 7.40−7.55 (m, 1H), 7.55−7.70 (m, 4H), 8.20 (d, J = 8.7 Hz, 1H), 10.38 (br s, 1H), 12.71 (br s, 1H). HRMS (ESI): calcd for $C_{27}H_{19}Cl_2N_5O_3S$ [M + H]$^+$ 564.0658. Found: 564.0660.

Ethyl 6-(3-Aminophenoxy)imidazo[1,2-*b*]pyridazine-2-carboxylate (8). A mixture of ethyl 6-iodoimidazo[1,2-*b*]pyridazine-2-carboxylate **7** (13.6 g, 42.8 mmol), 3-aminophenol (7.02 g, 64.3 mmol), potassium carbonate (10.2 g, 64.3 mmol), and *N*,*N*-dimethylformamide (100 mL) was stirred at 150 °C for 5 h. After the mixture was cooled at room temperature, ethyl acetate (300 mL) and water (300 mL) were added to the reaction mixture, and the resulting insoluble material was filtered through a pad of Celite. The aqueous layer was extracted with ethyl acetate (5 × 200 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (300 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by basic silica gel column chromatography (0−50% ethyl acetate/*n*-hexane) to give **8** (6.41 g, 50%) as colorless crystals, mp 138−139 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.30 (t, J = 7.2 Hz, 3H), 4.29 (q, J = 7.2 Hz, 2H), 5.33 (br s, 2H), 6.32−6.50 (m, 3H), 7.07 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 9.6 Hz, 1H), 8.20 (d, J = 9.6 Hz, 1H), 8.61 (s, 1H). MS (ESI): m/z 299.00 (M + H)$^+$. Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.28; H, 4.65; N, 18.63.

Ethyl 6-(3-{[3-(Trifluoromethyl)benzoyl]amino}phenoxy)-imidazo[1,2-*b*]pyridazine-2-carboxylate (9). A mixture of **8** (4.63 g, 15.5 mmol), 3-(trifluoromethyl)benzoic acid (4.42 g, 23.2 mmol), HOBt (3.13 g, 23.2 mmol), EDCI·HCl (4.44 g, 23.2 mmol) in *N*,*N*-dimethylformamide (90 mL) was stirred at room temperature for 3 h. Saturated aqueous ammonium chloride (90 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (300 mL). The separated organic layer was dried over anhydrous $MgSO_4$ and filtered through a pad of basic silica gel using ethyl acetate as eluting solvent. The filtrate was concentrated under reduced pressure. The resulting slurry was triturated with ethyl acetate/i-Pr_2O (1:1) and the resulting precipitate was collected by filtration to give **9** (6.31 g, 86%) as colorless crystals, mp 218−219 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.29 (t, J = 7.1 Hz, 3H), 4.29 (q, J = 7.1 Hz, 2H), 7.10 (dd, J = 2.0, 8.2 Hz, 1H), 7.30 (d, J = 9.8 Hz, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.66−7.73 (m, 1H), 7.76−7.84 (m, 2H), 7.95−8.01 (m, 1H), 8.23−8.31 (m, 3H), 8.62 (s, 1H), 10.63 (s, 1H). MS (ESI): m/z 471.10 (M + H)$^+$. Anal. Calcd for $C_{23}H_{17}F_3N_4O_4$: C, 58.73; H, 3.64; N, 11.91. Found: C, 58.63; H, 3.78; N, 11.85.

***N*-{3-[(2-Aminoimidazo[1,2-*b*]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (10).** A mixture of **9** (5.81 g, 12.3 mmol) and 8 N NaOH (20 mL) in methanol (100 mL) was stirred at room temperature for 4 h. The mixture was acidified with 5 N HCl to pH 5 and extracted with 25% tetrahydrofuran in ethyl acetate (3 × 300 mL). The combined organic layer was dried over anhydrous $MgSO_4$. The insoluble was filtered off, and the filtrate was evaporated under reduced pressure to give 6-(3-{[3-(trifluoromethyl)benzoyl]-amino}phenoxy)imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4.95 g, 91%) as a colorless solid, mp 229−231 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.10 (dd, J = 1.8, 8.2 Hz, 1H), 7.27 (d, J = 9.8 Hz, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.75−7.84 (m, 2H), 7.98

(d, J = 7.7 Hz, 1H), 8.21−8.32 (m, 3H), 8.52 (s, 1H), 10.62 (s, 1H), 12.87 (br s, 1H). MS (ESI): m/z 443.05 $(M + H)^+$. Anal. Calcd for $C_{21}H_{13}F_3N_4O_4$: C, 57.02; H, 2.96; N, 12.67. Found: C, 56.98; H, 3.02; N, 12.57.

To a suspension of 6-(3-{[3-(trifluoromethyl)benzoyl]amino}-phenoxy)imidazo[1,2-*b*]pyridazine-2-carboxylic acid (3.00 g, 6.78 mmol) in tetrahydrofuran (200 mL) and *tert*-butanol (200 mL) was added triethylamine (1.89 mL, 13.5 mmol) at room temperature, and the mixture was stirred at room temperature for 10 min. To the mixture was added diphenylphosphorylazide (2.17 mL, 10.1 mmol). The reaction mixture was stirred at room temperature for 10 min and then stirred at 100 °C for 14 h. After the mixture was cooled at room temperature, ethyl acetate (400 mL) was added to the mixture. The mixture was washed with saturated aqueous $NaHCO_3$ (200 mL), and the separated organic layer was washed with brine (200 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (0−95% ethyl acetate in *n*-hexane) to give *tert*-butyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-*b*]-pyridazin-2-yl]carbamate (3.10 g, 89%) as colorless crystals, mp 123−125 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.46 (s, 9H), 6.99−7.07 (m, 2H), 7.45 (t, J = 8.1 Hz, 1H), 7.64−7.83 (m, 4H), 7.94−8.05 (m, 2H), 8.22−8.30 (m, 2H), 10.05 (br s, 1H), 10.60 (br s, 1H). MS (ESI): m/z 514.15 $(M + H)^+$. Anal. Calcd for $C_{25}H_{22}F_3N_5O_4 \cdot 0.8H_2O$: C, 56.88; H, 4.51; N, 13.27. Found: C, 56.65; H, 4.55; N, 13.15.

A mixture of *tert*-butyl [6-(3-{[3-(trifluoromethyl)benzoyl]-amino}phenoxy)imidazo[1,2-*b*]pyridazin-2-yl]carbamate (400 mg, 0.779 mmol), 4 N HCl in ethyl acetate (10 mL), and methanol (10 mL) was stirred at room temperature for 14 h. The solvent was neutralized with 8 N NaOH (5 mL). The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL), successively, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (50−100% ethyl acetate in *n*-hexane) to give **10** (215 mg, 67%) as pale green crystals, mp 158−160 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.29−5.35 (m, 2H), 6.80 (d, J = 9.4 Hz, 1H), 6.93−7.00 (m, 1H), 7.16 (s, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.62−7.68 (m, 2H), 7.70−7.82 (m, 2H), 7.97 (d, J = 7.9 Hz, 1H), 8.21−8.29 (m, 2H), 10.55 (s, 1H). MS (ESI): m/z 414.16 $(M + H)^+$. Anal. Calcd for $C_{20}H_{14}F_3N_5O_2 \cdot 0.3H_2O$: C, 57.36; H, 3.51; N, 16.72. Found: C, 57.36; H, 3.49; N, 16.62.

Ethyl (6-Iodoimidazo[1,2-*b*]pyridazin-2-yl)carbamate (12). To a solution of 6-iodopyridazine-3-amine **11** (20.0 g, 90.5 mmol) in *N*,*N*-dimethylacetamide (160 mL) were added ethyl (chloroacetyl)-carbamate (25.5 g, 153 mmol) and disodium hydrogenphosphate (32.1 g, 226 mmol), and the reaction mixture was stirred at 110 °C for 4 h. After the mixture was cooled at room temperature, water (700 mL) was added to the mixture, and the precipitated crystals were filtered and washed with water (200 mL), acetonitrile (100 mL), and *n*-hexane (200 mL), successively, to give compound **12** (22.8 g, 76%) as black crystals, mp 215−216 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.26 (t, J = 7.1 Hz, 3H), 4.17 (q, J = 7.1 Hz, 2H), 7.48 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 8.07 (s, 1H), 10.51 (s, 1H). MS (ESI): m/z 332.87 $(M + H)^+$.

***N*-(6-Iodoimidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide (13).** To a solution of barium hydroxide octahydrate (28.5 g, 90.3 mmol) in water (400 mL) was added a solution of ethyl (6-iodoimidazo[1,2-*b*]pyridazin-2-yl)carbamate **12** (20.0 g, 60.2 mmol) in NMP (200 mL). The reaction mixture was stirred at 120 °C for 12 h. After cooling to 80 °C, the mixture was diluted with water (200 mL), tetrahydrofuran (200 mL), and ethyl acetate (400 mL). The mixture was stirred at room temperature for 20 min. The insoluble was filtered off, and the filtrate was washed with water (200 mL) and brine (200 mL), successively, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residual slurry was triturated with water (200 mL), and the resulting crystals were collected by filtration to give 6-iodoimidazo[1,2-*b*]pyridazine-2-amine (11.0 g, 71%) as orange crystalline needles, mp 173−175 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.59 (s, 2H), 7.23 (d, J = 8.9 Hz, 1H), 7.34−7.42 (m, 2H). MS (ESI): m/z 260.95 $(M + H)^+$.

To a solution (10 mL) of 6-iodoimidazo[1,2-*b*]pyridazine-2-amine (10 g, 38.4 mmol) in *N*,*N*-dimethylacetamide (120 mL) was added cyclopropanecarbonyl chloride (4.20 mL, 46.1 mmol) at 4 °C. The reaction mixture was stirred at room temperature for 16 h. Water (240 mL) was added to the reaction mixture at 4 °C. The resulting precipitate was collected by filtration and washed with water (200 mL) to give compound **13** (12.3 g, 98%) as pale yellow crystals, mp 248−250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.79−0.87 (m, 4H), 1.89−2.00 (m, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 8.23 (s, 1H), 11.19 (s, 1H). MS (ESI): m/z 328.95 $(M + H)^+$. Anal. Calcd for $C_{10}H_9IN_4O$: C, 36.61; H, 2.76; N, 17.08. Found: C, 36.89; H, 2.84; N, 17.20.

***N*-[6-(3-Aminophenoxy)imidazo[1,2-*b*]pyridazine-2-yl]-cyclopropanecarboxamide (14).** A mixture of **13** (12.3 g, 37.4 mmol), 3-aminophenol (8.18 g, 74.9 mmol), and potassium carbonate (11.9 g, 74.9 mmol) in *N*,*N*-dimethylformamide (120 mL) was stirred at 150 °C for 24 h. The mixture was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (150 mL). The mixture was filtered through a pad of Celite. The filtrate was partitioned between ethyl acetate (150 mL) and saturated aqueous $NaHCO_3$ (150 mL). The aqueous layer was extracted with ethyl acetate (4 × 100 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (50−100% ethyl acetate in *n*-hexane) to give compound **14** (9.24 g, 80%) as pale brown crystals, mp 237−239 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.74−0.86 (m, 4H), 1.87−1.98 (m, 1H), 5.29 (s, 2H), 6.30 (dd, J = 1.7, 8.0 Hz, 1H), 6.35 (t, J = 1.7 Hz, 1H), 6.43 (dd, J = 1.7, 8.0 Hz, 1H), 6.95 (d, J = 9.8 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.92−8.04 (m, 2H), 11.06 (s, 1H). MS (ESI): m/z 328.94 $(M + H)^+$. Anal. Calcd for $C_{16}H_{15}N_5O_2 \cdot 0.1H_2O$: C, 61.77; H, 4.92; N, 22.51. Found: C, 61.68; H, 4.93; N, 22.50.

3-(1-Cyano-1-methylethyl)benzoic Acid (15n). To a solution of methyl 3-(cyanomethyl)benzoate **17** (7.0 g, 40 mmol) in dimethylsulfoxide (80 mL) was slowly added sodium hydride (60% in oil, 4.8 g, 120 mmol) under ice-cooling. The reaction mixture was stirred at room temperature for 20 min. To the mixture was added iodomethane (7.5 mL, 120 mmol), and the mixture was stirred at room temperature for 16 h. Under ice-cooling, the reaction mixture was diluted with water (80 mL). The mixture was extracted with ethyl acetate (200 mL), and the organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (5−50% ethyl acetate in *n*-hexane) to give methyl 3-(1-cyano-1-methylethyl)benzoate (6.4 g, 79%) as a colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.72 (s, 6H), 3.89 (s, 3H), 7.61 (t, J = 7.8 Hz, 1H), 7.84 (ddd, J = 1.2, 2.1, 7.8 Hz, 1H), 7.95 (dt, J = 7.8, 1.2 Hz, 1H), 8.08 (t, J = 1.5 Hz, 1H). MS (ESI): m/z 204.06 $(M + H)^+$.

To a solution of methyl 3-(1-cyano-1-methylethyl)benzoate (2.8 g, 14 mmol) in tetrahydrofuran (30 mL) were added lithium hydroxide monohydrate (0.98 g, 24 mmol), methanol (10 mL), and water (10 mL), and the mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure, and the residue was diluted with water (15 mL). The mixture was adjusted to pH 3 by adding 1 N HCl slowly. The resulting white precipitate was collected by filtration and washed with water (100 mL) to give the compound **15n** (2.5 g, 98%) as white crystals, mp 166−168 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.72 (s, 6H), 7.57 (t, J = 7.8 Hz, 1H), 7.78 (dt, J = 7.8, 1.5 Hz, 1H), 7.92 (dt, J = 7.8, 1.5 Hz, 1H), 8.08 (t, J = 1.5 Hz, 1H), 13.19 (s, 1H). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.64; H, 5.95; N, 7.34.

3-(1-Cyanocyclopropyl)benzoic Acid (15o). Methyl 3-(1-cyanocyclopropyl)benzoate (1.30 g) was prepared in a similar manner to the intermediate of **15n**, methyl 3-(1-cyano-1-methylethyl)benzoate from methyl 3-(cyanomethyl)benzoate **17** (1.5 g, 8.56 mmol), using sodium hydride (60% in oil, 1.03 g, 25.7 mmol), 1,2-dibromoethane (2.41 g, 12.84 mmol), and dimethylsulfoxide (30 mL). Yield 76%, colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38−1.56 (m, 2H),

1.74−1.82 (m, 2H), 3.93 (s, 3H), 7.40−7.49 (m, 1H), 7.55−7.62 (m, 1H), 7.88 (t, J = 1.5 Hz, 1H), 7.96 (dt, J = 7.8, 1.5 Hz, 1H).

Compound **15o** (0.73 g) was prepared in a similar manner to **15n** from methyl 3-(1-cyanocyclopropyl)benzoate (1.28 g, 6.36 mmol), using lithium hydroxide monohydrate (0.443 g, 10.8 mmol), tetrahydrofuran (12 mL), methanol (4 mL), and water (6 mL). Yield 61%, colorless crystals; mp 192−193 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43−1.53 (m, 2H), 1.73−1.84 (m, 2H), 4.26 (br s, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.66 (dt, J = 7.8, 1.5 Hz, 1H), 7.94 (t, J = 1.5 Hz, 1H), 8.04 (dt, J = 7.8, 1.5 Hz, 1H). Anal. Calcd for $C_{11}H_9NO_2 \cdot 0.3H_2O$: C, 68.60; H, 5.02; N, 7.27. Found: C, 68.64; H, 4.99; N, 7.34.

2-Chloro-3-(1-cyano-1-methylethyl)benzoic Acid (15p). Methyl 2-chloro-3-(1-cyanocyclopropyl)benzoate (1.99 g) was prepared in a similar manner to the intermediate of **15n**, methyl 3-(1-cyano-1-methylethyl)benzoate from methyl 2-chloro-3-(cyanomethyl)benzoate **20** (2.00 g, 9.54 mmol), using sodium hydride (60% in mineral oil, 1.14 g, 28.6 mmol), iodomethane (1.78 mL, 28.6 mmol), and dimethylsulfoxide (20 mL). Yield 88%, colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90 (s, 6H), 3.95 (s, 3H), 7.33−7.40 (m, 1H), 7.57−7.64 (m, 2H). MS (ESI): m/z 238.00 $(M + H)^+$.

Compound **15p** (1.43 g) was prepared in a similar manner to **15n** from methyl 2-chloro-3-(1-cyanocyclopropyl)benzoate (1.67 g, 7.02 mmol), using lithium hydroxide monohydrate (501 mg, 11.9 mmol), tetrahydrofuran (24 mL), methanol (8 mL), and water (8 mL). Yield 91%, white crystals; mp 124−125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92 (s, 6H), 7.41 (t, J = 7.8 Hz, 1H), 7.67 (dd, J = 1.6, 7.8 Hz, 1H), 7.85 (dd, J = 1.6, 7.8 Hz, 1H). Anal. Calcd for $C_{11}H_{10}ClNO_2 \cdot 0.1H_2O$: C, 58.60; H, 4.56; N, 6.21. Found: C, 58.56; H, 4.49; N, 6.14.

2-Chloro-3-(1-cyanocyclopropyl)benzoic Acid (15q). Methyl 2-chloro-3-(1-cyanocyclopropyl)benzoate (25.7 g) was prepared in a similar manner to the intermediate of **15n**, methyl 3-(1-cyano-1-methylethyl)benzoate from methyl 2-chloro-3-(cyanomethyl)benzoate **20** (40.0 g, 191 mmol), using sodium hydride (60% in mineral oil, 22.9 g, 573 mmol), 1,2-dibromoethane (34 mL, 395 mmol), and dimethylsulfoxide (400 mL). Yield 57%, colorless crystals; mp 63−64 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33−1.39 (m, 2H), 1.76−1.83 (m, 2H), 3.95 (s, 3H), 7.32 (t, J = 7.7 Hz, 1H), 7.50 (dd, J = 1.7, 7.7 Hz, 1H), 7.74 (dd, J = 1.7, 7.7 Hz, 1H). MS (ESI): m/z 236 $(M + H)^+$. Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.97; H, 4.32; N, 5.93.

Compound **15q** (22.1 g) was prepared in a similar manner to **15n** from methyl 2-chloro-3-(1-cyanocyclopropyl)benzoate (25.7 g, 109 mmol), using lithium hydroxide monohydrate (6.69 g, 159 mmol), tetrahydrofuran (210 mL), methanol (70 mL), and water (70 mL). Yield 91%, white crystals; mp 155−156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32−1.42 (m, 2H), 1.79−1.87 (m, 2H), 4.47 (br s, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.56 (dd, J = 1.7, 7.7 Hz, 1H), 7.95 (dd, J = 1.7, 7.7 Hz, 1H). Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.57; H, 3.66; N, 6.23.

Methyl 3-(Cyanomethyl)benzoate (17). To a solution of methyl 3-(bromomethyl)benzoate **16** (10.0 g, 44 mmol) in acetonitrile (100 mL) were added potassium cyanate (5.7 g, 87 mmol) and 18-crown-6 (1.0 g), and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (5−30% ethyl acetate in *n*-hexane). The combined desired fractions were concentrated under reduced pressure to give compound **17** (7.0 g, 91%) as a colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.88 (s, 3H), 4.17 (s, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.61−7.69 (m, 1H), 7.88−7.95 (m, 1H), 7.97 (br s, 1H). MS (ESI): m/z 176.03 $(M + H)^+$.

Methyl 3-(Bromomethyl)-2-chlorobenzoate (19). To a solution of methyl 2-chloro-3-methylbenzoate **18** (3.60 g, 19.4 mmol) in acetonitrile (60 mL) were added 1-bromopyrrolidine-2,5-dione (11.5 g, 64.3 mmol) and AIBN (960 mg, 5.84 mmol), and the reaction mixture was stirred at 90 °C for 26 h. The reaction mixture was concentrated under reduced pressure, and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0−5% ethyl acetate in *n*-hexane) to give compound **19** (3.42 g, 66%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H), 4.64 (s, 2H), 7.31 (t, J = 7.7 Hz, 1H), 7.58 (dd, J = 1.7, 7.7 Hz, 1H), 7.71 (dd, J = 1.7, 7.7 Hz, 1H). MS (ESI): m/z 264.90 $(M + H)^+$.

Methyl 2-Chloro-3-(cyanomethyl)benzoate (20). To a solution of **19** (748 mg, 2.84 mmol) in *N*,*N*-dimethylformamide (7 mL) was added sodium cyanate (412 mg, 8.41 mmol), and the reaction mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with a mixed solvent of ethyl acetate and *n*-hexane (1:1, 200 mL). The mixture was washed with water (200 mL) and brine (200 mL), successively, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (2−20% ethyl acetate in *n*-hexane) and recrystallized from ethyl acetate and *n*-hexane to give compound **20** (470 mg, 79%) as white crystals, mp 68−69 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 2H), 3.95 (s, 3H), 7.39 (t, J = 7.8 Hz, 1H), 7.66−7.72 (m, 1H), 7.76−7.81 (m, 1H). Anal. Calcd for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68. Found: C, 57.20; H, 3.80; N, 6.74.

5-(3-Aminophenoxy)pyridine-2-amine Dihydrochloride (22). To a mixture of 5-bromo-2-nitropyridine **21** (20.5 g, 101 mmol) and cesium carbonate (50 g, 153 mmol) in *N*,*N*-dimethylformamide (200 mL) was added dropwise a solution of 3-nitrophenol (15.5 g, 111 mmol) in *N*,*N*-dimethylformamide (100 mL) over 1 h, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water (300 mL) and extracted with ethyl acetate (600 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (300 mL) and brine (300 mL) and dried over anhydrous Na_2SO_4. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (10−40% ethyl acetate in *n*-hexane), and the desired fractions were concentrated under reduced pressure to give 2-nitro-5-(3-nitrophenoxy)pyridine (14.28 g, 54%) as colorless crystals, mp 113−114 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.69−7.87 (m, 3H), 8.10 (t, J = 2.1 Hz, 1H), 8.17 (dt, J = 7.7, 1.8 Hz, 1H), 8.38 (d, J = 9.0 Hz, 1H), 8.53 (d, J = 2.7 Hz, 1H). MS (ESI): m/z 262.07 $(M + H)^+$. Anal. Calcd for $C_{11}H_7N_3O_5$: C, 50.58; H, 2.70; N, 16.09. Found: C, 50.51; H, 2.69; N, 16.06.

To a solution of 2-nitro-5-(3-nitrophenoxy)pyridine (14.0 g, 53.6 mmol) in methanol/tetrahydrofuran/ethyl acetate (5:1:1, 1.4 L) was added 10% palladium/carbon (1.4 g), and the reaction mixture was stirred at room temperature under hydrogen atmosphere (1.0 atm) for 20 h. The insoluble material was filtered off, and the filtrate was concentrated in vacuo. The residue was diluted with ethyl acetate (300 mL), and to the mixture was added dropwise slowly 4 N HCl in ethyl acetate (30 mL). The resulting colorless precipitate was collected by filtration, washed with *i*-Pr_2O (100 mL) and *n*-hexane (100 mL), and dried under vacuum to give the compound **22** (15.2 g, quantitative yield) as colorless solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.69−6.83 (m, 2H), 6.85−6.95 (m, 1H), 7.09 (d, J = 9.6 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.86 (dd, J = 2.7, 9.6 Hz, 1H), 7.98 (d, J = 2.7 Hz, 1H), 8.15 (br s, 3H), 10.02 (br s, 3H).

***N*-{3-[(6-Aminopyridin-3-yl)oxy]phenyl}-3-(1-cyano-1-methylethyl)benzamide (23).** Compound **23** (3.44 g) was prepared in a similar manner to **1i** from 5-(3-aminophenoxy)pyridine-2-amine dihydrochloride **22** (3.5 g, 12.7 mmol), using 3-(1-cyano-1-methylethyl)benzoic acid **15n** (2.66 g, 14.0 mmol), oxalyl chloride (1.63 mL, 19.1 mmol), *N*,*N*-dimethylformamide (20 μL), tetrahydrofuran (28 mL), and *N*,*N*-dimethylacetamide (50 mL). Yield 66%, colorless crystals; mp 143−144 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.74 (s, 6H), 5.91 (s, 2H), 6.51 (d, J = 8.9 Hz, 1H), 6.66−6.77 (m, 1H), 7.23 (dd, J = 2.7, 8.9 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 7.38 (t, J = 2.1 Hz, 1H), 7.43−7.52 (m, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.68−7.82 (m, 2H), 7.84−7.94 (m, 1H), 7.99 (t, J = 1.8 Hz, 1H), 10.33 (s, 1H). MS (ESI): m/z 373.10 $(M + H)^+$. Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.93; H, 5.46; N, 15.01.

***N*-{3-[(1-(2-Amino-2-oxoethyl)-6-{[(4-methylphenyl)-sulfonyl]imino}-1,6-dihydropyridin-3-yl)oxy]phenyl}-3-(1-cyano-1-methylethyl)benzamide (24).** To a solution of **23** (2.5 g,

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6.71 mmol) in pyridine (60 mL) was added 4-methylbenzenesulfonyl chloride (1.34 g, 7.05 mmol) under ice-cooling, and the reaction mixture was stirred at 80 °C for 2 days. After the mixture was cooled at room temperature, water (200 mL) was added to the mixture. The mixture was extracted with ethyl acetate (300 mL). The organic layer was washed with brine (300 mL) and dried over anhydrous Na_2SO_4. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure to give 3-(1-cyano-1-methylethyl)-*N*-{3-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]-phenyl}benzamide (3.48 g, 99%) as colorless crystals, mp 156−157 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.74 (s, 6H), 2.34 (s, 3H), 6.75 (dd, J = 2.4, 8.1 Hz, 1H), 7.15 (d, J = 9.0 Hz, 1H), 7.27−7.45 (m, 4H), 7.46−7.68 (m, 3H), 7.71−7.83 (m, 3H), 7.89 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 8.02 (d, J = 3.0 Hz, 1H), 10.37 (s, 1H), 11.07 (br s, 1H). MS (ESI): m/z 527.2 $(M + H)^+$. Anal. Calcd for $C_{29}H_{26}N_4O_4S$: C, 66.14; H, 4.98; N, 10.64. Found: C, 66.17; H, 5.01; N, 10.45.

To a solution of 3-(1-cyano-1-methylethyl)-*N*-{3-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}benzamide (3.2 g, 6.08 mmol) in *N*,*N*-dimethylformamide (20 mL) was added *N*-ethyl-*N*-isopropylpropan-2-amine (1.11 mL, 6.38 mmol), and the reaction mixture was stirred at room temperature for 15 min. 2-Iodoacetamide (1.18 g, 6.38 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated under reduced pressure, and to the residue was added 5% aqueous $NaHCO_3$ (150 mL). The mixture was extracted with ethyl acetate (300 mL). The organic layer was washed with brine (150 mL) and dried over anhydrous Na_2SO_4. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50−100% ethyl acetate in *n*-hexane) and triturated with a mixed solvent of ethyl acetate, *i*-Pr_2O, and *n*-hexane (1:1:1, 20 mL) to give compound **24** (2.23 g, 63%) as colorless crystals, mp 128−130 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.74 (s, 6H), 2.34 (s, 3H), 4.83 (s, 2H), 6.76 (dd, J = 2.4, 7.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.32−7.46 (m, 3H), 7.48 (t, J = 2.1 Hz, 1H), 7.59 (t, J = 7.8 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.71−7.82 (m, 3H), 7.86−7.94 (m, 1H), 8.01 (t, J = 1.8 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 10.41 (s, 1H). MS (ESI): m/z 584.15 $(M + H)^+$. Anal. Calcd for $C_{31}H_{29}N_5O_5S$: C, 63.79; H, 5.01; N, 12.00. Found: C, 63.64; H, 5.24; N, 11.79.

***N*-{3-[(2-Aminoimidazo[1,2-*a*]pyridin-6-yl)oxy]phenyl}-3-(1-cyano-1-methylethyl)benzamide (25).** To a solution of **24** (1.00 g, 1.72 mmol) in dichloromethane (8 mL) was added trifluoroacetic acid anhydride (6 mL), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, and to the mixture was added 5% aqueous $NaHCO_3$ (150 mL), and the mixture was extracted with ethyl acetate (150 mL). The organic layer was washed with brine (150 mL) and dried over anhydrous Na_2SO_4. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30−60% ethyl acetate in *n*-hexane) and triturated with *i*-Pr_2O and *n*-hexane to give compound **25** (450 mg, 52%) as colorless crystals, mp 130−132 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.73 (s, 6H), 6.84 (dd, J = 2.4, 7.5 Hz, 1H), 7.22 (dd, J = 2.4, 9.6 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.51 (t, J = 2.4 Hz, 1H), 7.54−7.68 (m, 3H), 7.70−7.79 (m, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.99 (t, J = 1.8 Hz, 1H), 8.27 (s, 1H), 8.66 (d, J = 2.4 Hz, 1H), 10.36 (s, 1H), 12.48 (s, 1H). MS (ESI): m/z 508.10 $(M + H)^+$.

5-Fluoro-*N*-methyl-2-nitroaniline (27b). Methylamine solution (40%, 38.4 g) was added dropwise to 2,4-difluoro-1-nitrobenzene **26** (25.0 g, 157 mmol) at 0 °C over 15 min. After completion of the addition, the reaction mixture was stirred at 0 °C for 1.5 h. To the mixture was added water (500 mL) and the resulting crystals were collected by filtration to give compound **27b** (26.4 g, 99%) as a yellow crystalline solid, mp 105−106 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.94 (d, J = 4.8 Hz, 3H), 6.53 (ddd, J = 2.7, 7.8, 10.2 Hz, 1H), 6.78 (dd, J = 2.7, 12.3 Hz, 1H), 8.17 (dd, J = 6.3, 9.6 Hz, 1H), 8.32 (br s, 1H). Anal. Calcd for $C_7H_7FN_2O_2$: C, 49.41; H, 4.15; N, 16.46. Found: C, 49.15; H, 4.20; N, 16.45.

***tert*-Butyl [3-(3-Amino-4-nitrophenoxy)phenyl]carbamate (28a).** To a solution of *tert*-butyl (3-hydroxyphenyl)carbamate (6.89 g, 32.9 mmol) and 5-fluoro-2-nitroaniline **27a** (5.09 g, 32.6 mmol) in *N*,*N*-dimethylformamide (100 mL) was added potassium carbonate (11.2 g, 80.9 mmol), and the reaction mixture was stirred at 100 °C for 14 h. The mixture was cooled at room temperature and diluted with ethyl acetate/*n*-hexane (1:1, 250 mL). The mixture was washed with water (2 × 150 mL) and brine (100 mL), successively, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified with silica gel column chromatography (2−30% ethyl acetate in *n*-hexane) to give compound **28a** (7.7 g, 69%) as yellow crystals, mp 130−131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.54 (s, 9H), 6.13 (br s, 2H), 6.19 (d, J = 2.7 Hz, 1H), 6.35 (dd, J = 2.4, 6.3 Hz, 1H), 6.57 (br s, 1H), 6.74−6.78 (m, 1H), 7.11−7.16 (m, 1H), 7.28−7.35 (m, 2H), 8.12 (d, J = 9.6 Hz, 1H).

***tert*-Butyl {3-[3-(Methylamino)-4-nitrophenoxy]phenyl}-carbamate (28b).** Compound **28b** (21.8 g) was prepared in a similar manner to **28a** from **27b** (8.58 g, 50.4 mmol), using *tert*-butyl (3-hydroxyphenyl)carbamate (11.0 g, 52.3 mmol), *N*,*N*-dimethylformamide (200 mL), and potassium carbonate (28.6 g, 207 mmol). Yield, quantitative; orange amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.51 (s, 9H), 2.92 (d, J = 5.1 Hz, 3H), 6.22 (dd, J = 2.7, 9.6 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 6.64 (br s, 1H), 6.75 (ddd, J = 0.9, 2.4, 8.1 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.27−7.33 (m, 2H), 8.14 (d, J = 9.6 Hz, 1H), 8.19 (br d, J = 4.8 Hz, 1H).

***tert*-Butyl [3-({2-[(Cyclopropylcarbonyl)amino]-1*H*-benzimidazol-6-yl}oxy)phenyl]carbamate (29a).** A mixture of **28a** (5.51 g, 15.6 mmol), 10% palladium/carbon (875 mg), tetrahydrofuran (20 mL), and methanol (100 mL) was stirred at room temperature under hydrogen atmosphere for 18 h. The insoluble was filtered off and the filtrate was evaporated in vacuo to give *tert*-butyl [3-(3,4-diaminophenoxy)phenyl]carbamate (5.17 g, quant) as a purple amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.49 (s, 9H), 3.24 (br s, 2H), 3.49 (br s, 2H), 6.37−6.43 (m, 3H), 6.61 (ddd, J = 0.9, 2.4, 8.1 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.90 (t, J = 2.1 Hz, 1H), 7.07−7.11 (m, 1H), 7.17 (t, J = 8.1 Hz, 1H).

To a solution of *tert*-butyl [3-(3,4-diaminophenoxy)phenyl]-carbamate (3.00 g, 9.51 mmol) in tetrahydrofuran (150 mL) was added cyanogen bromide (2.93 g, 27.7 mmol). The reaction mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with ethyl acetate (300 mL). The mixture was washed with saturated $NaHCO_3$ (2 × 100 mL) and brine (100 mL), successively, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give *tert*-butyl {3-[(2-amino-1*H*-benzimidazol-6-yl)oxy]-phenyl}carbamate (4.37 g, quant) as brown crystals, mp 117−119 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44 (s, 9H), 4.16 (br s, 2H), 6.59−6.69 (m, 2H), 6.77−6.90 (m, 2H), 6.96−6.98 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H). MS (ESI): m/z 341.05 $(M + H)^+$.

To a solution of *tert*-butyl {3-[(2-amino-1*H*-benzimidazol-6-yl)oxy]-phenyl}carbamate (1.30 g, 3.82 mmol) in pyridine (50 mL) were added cyclopropanecarbonyl chloride (1 mL, 11.0 mmol) and DMAP (21.3 mg, 0.174 mmol). The reaction mixture was stirred at room temperature for 16 h. To the reaction mixture were added methanol (30 mL) and 8 N NaOH (3 mL), successively, and the mixture was stirred at room temperature for 2.5 h. The mixture was evaporated in vacuo, and the residue was dissolved in methanol (5 mL) and ethyl acetate (50 mL). The mixture was washed with 0.1 N HCl (50 mL) and saturated $NaHCO_3$ (50 mL), successively, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo. The residue was crystallized from ethyl acetate and *i*-Pr_2O to give the compound **29a** (1.53 g, 98%) as a colorless crystalline solid, mp 144−145 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.90−0.92 (m, 4H), 1.42 (s, 9H), 1.92−1.99 (m, 1H), 6.51−6.55 (m, 1H), 6.80 (dd, J = 2.1, 8.4 Hz, 1H), 7.02−7.21 (m, 3H), 7.36−7.41 (m, 2H), 9.36 (br s, 1H), 11.83 (br s, 1H), 12.01 (br s, 1H). MS (ESI): m/z 409.15 $(M + H)^+$.

***tert*-Butyl [3-({2-[(Cyclopropylcarbonyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}oxy)phenyl]carbamate (29b).** *tert*-Butyl {3-[4-amino-3-(methylamino)phenoxy]phenyl}carbamate (10.1 g) was prepared in a similar manner to the intermediate of **29a**, *tert*-butyl [3-(3,

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4-diaminophenoxy)phenyl]carbamate from **28b** (10.9 g, 30.4 mmol), using 10% palladium/carbon (1.8 g), tetrahydrofuran (150 mL), ethanol (100 mL), and hydrogen (3 atm). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.49 (s, 9H), 2.81 (s, 4H), 2.88 (s, 1H), 2.95 (s, 1H), 6.31 (dd, J = 2.7, 8.1 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.47 (br s, 1H), 6.60−6.67 (m, 2H), 6.89 (t, J = 2.1 Hz, 1H), 7.11−7.20 (m, 2H). MS (ESI): m/z 330.05 $(M + H)^+$.

tert-Butyl {3-[(2-amino-1-methyl-1*H*-benzimidazol-6-yl)oxy]-phenyl}carbamate (7.46 g) was prepared in a similar manner to the intermediate of **29a**, *tert*-butyl {3-[(2-amino-1*H*-benzimidazol-6-yl)-oxy]phenyl}carbamate from *tert*-butyl {3-[4-amino-3-(methylamino)-phenoxy]phenyl}carbamate (10.1 g, 30.4 mmol), using tetrahydrofuran (200 mL) and cyanogen bromide (4.33 g, 40.9 mmol). Yield, 69% in two steps; black amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.43 (s, 9H), 3.33 (br s, 2H), 3.46 (s, 3H), 6.47−6.50 (m, 2H), 6.65 (dd, J = 2.4, 8.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 7.10−7.19 (m, 3H), 9.34 (br s, 1H). MS (ESI): m/z 355.05 $(M + H)^+$.

Compound **29b** (1.89 g) was prepared in a similar manner to **29a** from *tert*-butyl {3-[(2-amino-1-methyl-1*H*-benzimidazol-6-yl)oxy]-phenyl}carbamate (2.45 g, 6.91 mmol), using pyridine (100 mL), cyclopropanecarbonyl chloride (3.0 mL, 33.1 mmol), and DMAP (258 mg, 2.11 mmol). Yield 65%, pale brown amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85−0.90 (m, 2H), 1.06−1.11 (m, 2H), 1.50 (s, 9H), 1.80−1.90 (m, 1H), 3.60 (m, 3H), 6.56 (br s, 1H), 6.64−6.68 (m, 1H), 6.90−6.94 (m, 2H), 7.08−7.11 (m, 2H), 7.20−7.33 (m, 2H), 8.63−8.65 (m, 1H). MS (ESI): m/z 423.15 $(M + H)^+$.

3-(1-Cyano-1-methylethyl)-*N*-(3-hydroxyphenyl)benzamide (30). Compound **30** (13.0 g) was prepared in a similar manner to **1i** from 3-(1-cyano-1-methylethyl)benzoic acid **15n** (10.0 g, 52.8 mmol), using tetrahydrofuran (200 mL), *N*,*N*-dimethylformamide (80 μL), oxalyl chloride (6.28 mL, 72.0 mmol), 3-aminophenol (5.24 g, 48.0 mmol), $NaHCO_3$ (6.05 g, 72.0 mmol), and water (60 mL). Yield 96%, white crystals; mp 172 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75 (s, 6H), 6.49−6.55 (m, 1H), 7.08−7.18 (m, 2H), 7.30−7.34 (m, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.72−7.77 (m, 1H), 7.88−7.93 (m, 1H), 8.01 (t, J = 1.7 Hz, 1H), 9.43 (s, 1H), 10.18 (s, 1H). MS (ESI): m/z 281 $(M + H)^+$.

***N*-*tert*-Butyl-6-chloro-3-nitropyridin-2-amine (32a).** To a solution of 2,6-dichloro-3-nitropyridine **31** (25.2 g, 131 mmol) in toluene (150 mL) was added dropwise a solution of *tert*-butylamine (9.63 g) in toluene (100 mL) at 0 °C over 30 min. The reaction mixture was stirred at room temperature for 6 h. To the reaction mixture was added an additional amount of *tert*-butylamine (10.0 g), and the mixture was stirred at room temperature for an additional 8 h. To the reaction mixture was added water (300 mL). The organic layer was washed with saturated ammonium chloride (200 mL) and brine (200 mL), successively, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give compound **32a** (29.6 g, 99%) as an orange crystalline solid, mp 87 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.50 (s, 9H), 6.81 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H), 8.44 (d, J = 8.7 Hz, 1H). Anal. Calcd for $C_9H_{12}ClN_3O_2$: C, 47.07; H, 5.27; N, 18.30. Found: C, 46.97; H, 5.22; N, 18.26.

6-Chloro-*N*-methyl-3-nitropyridin-2-amine (32b). To a solution of 2,6-dichloro-3-nitropyridine **31** (3.86 g, 20 mmol) was added dropwise 2 M methylamine solution in tetrahydrofuran (15 mL, 30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The mixture was partitioned between ethyl acetate (300 mL) and water (300 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (0−100% ethyl acetate in *n*-hexane) to give compound **32b** (2.94 g, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.18 (d, J = 4.9 Hz, 3H), 6.62 (d, J = 8.5 Hz, 1H), 8.25−8.40 (m, 2H). MS (ESI): m/z 187.95 $(M + H)^+$.

***N*-(3-{[6-(*tert*-Butylamino)-5-nitropyridin-2-yl]oxy}phenyl)-3-(1-cyano-1-methylethyl)benzamide (33a).** A mixture of 2-*tert*-butylamino-3-nitro-6-chloropyridine **32a** (1.15 g, 5.0 mmol), 3-(1-cyano-1-methylethyl)-*N*-(3-hydroxyphenyl)benzamide **30** (1.40 g, 5.0 mmol), and potassium carbonate (0.69 g, 5.0 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 18 h. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (0−100% ethyl acetate in *n*-hexane) to give compound **33a** (1.70 g, 3.59 mmol, 72%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.19 (s, 9H), 1.78 (s, 6H), 6.26 (d, J = 9.0 Hz, 1H), 6.77−7.04 (m, 1H), 7.34−7.50 (m, 2H), 7.50−7.59 (m, 1H), 7.65 (t, J = 2.1 Hz, 1H), 7.70 (ddd, J = 1.0, 2.0, 7.9 Hz, 1H), 7.77 (dt, J = 7.7, 1.4 Hz, 1H), 7.90 (s, 1H), 7.98 (t, J = 1.7 Hz, 1H), 8.43 (d, J = 9.0 Hz, 1H), 8.63 (s, 1H). MS (ESI): m/z 474 $(M + H)^+$.

3-(1-Cyano-1-methylethyl)-*N*-(3-{[6-(methylamino)-5-nitropyridin-2-yl]oxy}phenyl)benzamide (33b). Compound **33b** (3.96 g) was prepared in a similar manner to **33a** from **32b** (1.88 g, 10 mmol), using **30** (2.80 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and *N*,*N*-dimethylformamide (80 mL). Yield 88%, yellow amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.78 (s, 6H), 2.92 (d, J = 4.9 Hz, 3H), 6.21 (d, J = 9.0 Hz, 1H), 6.90−7.10 (m, 1H), 7.38−7.47 (m, 2H), 7.48−7.60 (m, 1H), 7.66−7.75 (m, 2H), 7.79 (dt, J = 7.7, 1.3 Hz, 1H), 7.93 (s, 1H), 7.99 (t, J = 1.7 Hz, 1H), 8.32−8.54 (m, 2H). MS (ESI): m/z 432.15 $(M + H)^+$.

***N*-{3-[(2-Amino-3-*tert*-butyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)-oxy]phenyl}-3-(1-cyano-1-methylethyl)benzamide (34a).** A mixture of *N*-(3-{[6-(*tert*-butylamino)-5-nitropyridin-2-yl]oxy}-phenyl)-3-(1-cyano-1-methylethyl)benzamide **33a** (1.42 g, 3.0 mmol) and 10% palladium/carbon (0.50 g) in methanol (10 mL) and tetrahydrofuran (5 mL) was stirred at room temperature under hydrogen atmosphere for 2 h. The catalyst was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to give *N*-(3-{[5-amino-6-(*tert*-butylamino)pyridin-2-yl]oxy}phenyl)-3-(1-cyano-1-methylethyl)-benzamide (1.33 g, quant) as a purple amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 9H), 1.77 (s, 6H), 2.85 (br s, 2H), 4.30 (br s, 1H), 6.07 (d, J = 7.9 Hz, 1H), 6.89 (d, J = 7.9 Hz, 2H), 7.28−7.40 (m, 2H), 7.40−7.57 (m, 2H), 7.65−7.81 (m, 3H), 7.95 (t, J = 1.8 Hz, 1H). MS (ESI): m/z 444.30 $(M + H)^+$.

The obtained solid (1.33 g) was dissolved in tetrahydrofuran (10 mL). To the solution was added cyanogen bromide (0.74 g, 7.00 mmol), and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched by the addition of saturated $NaHCO_3$ (50 mL). The mixture was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (0−100% ethyl acetate in *n*-hexane) to give compound **34a** (1.15 g, 2.45 mmol, 82% in two steps) as a pale black amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.76 (s, 15H), 4.78 (br s, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.92 (ddd, J = 1.0, 2.2, 8.1 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.40−7.54 (m, 3H), 7.56 (d, J = 8.3 Hz, 1H), 7.70 (ddd, J = 1.1, 2.1, 7.9 Hz, 1H), 7.76 (dt, J = 7.6, 1.4 Hz, 1H), 7.91 (s, 1H), 7.96 (t, J = 1.7 Hz, 1H). MS (ESI): m/z 469 $(M + H)^+$.

***N*-{3-[(2-Amino-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)-oxy]phenyl}-3-(1-cyano-1-methylethyl)benzamide (34b).** *N*-(3-{[5-Amino-6-(methylamino)pyridin-2-yl]oxy}phenyl)-3-(1-cyano-1-methylethyl)benzamide (3.54 g) was prepared in a similar manner to the intermediate of **34a**, *N*-(3-{[5-amino-6-(*tert*-butylamino)pyridin-2-yl]oxy}phenyl)-3-(1-cyano-1-methylethyl)benzamide from compound **33b** (3.96 g, 8.83 mmol), using 10% palladium/carbon (1.0 g), tetrahydrofuran (5 mL), and methanol (10 mL) to give a purple amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.73 (s, 6H), 2.63−3.27 (m, 5H), 4.42 (br s, 1H), 5.95 (d, J = 7.9 Hz, 1H), 6.80−6.95 (m, 2H), 7.27−7.33 (m, 1H), 7.36 (t, J = 2.1 Hz, 1H), 7.40−7.51 (m, 2H), 7.62−7.71 (m, 1H), 7.75 (dd, J = 7.7, 1.7 Hz, 1H), 7.95 (t, J = 1.8 Hz, 1H), 8.12 (s, 1H). MS (ESI): m/z 402.15 $(M + H)^+$.

Compound **34b** (0.34 g) was prepared in a similar manner to **34a** from *N*-(3-{[5-amino-6-(methylamino)pyridin-2-yl]oxy}phenyl)-3-(1-cyano-1-methylethyl)benzamide (0.40 g), using cyanogen bromide (0.53 g, 5.0 mmol) and tetrahydrofuran (10 mL). Yield, 80% in two steps; pale brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.73 (s, 6H), 3.53 (s, 3H), 4.82 (s, 2H), 6.64 (d, J = 8.3 Hz, 1H), 6.90

(dd, J = 2.1, 7.9 Hz, 1H), 7.29−7.38 (m, 1H), 7.38−7.44 (m, 1H), 7.48 (t, J = 7.2 Hz, 2H), 7.56 (d, J = 8.3 Hz, 1H), 7.67 (dd, J = 1.0, 7.8 Hz, 1H), 7.72−7.80 (m, 1H), 7.95 (t, J = 1.7 Hz, 1H), 8.21 (br s, 1H). MS (ESI): m/z 427.20 $(M + H)^+$.

3-(4-Nitrophenoxy)aniline (36). Compound **36** (21.8 g) was prepared in a similar manner to **8** from 1-fluoro-4-nitrobenzene **35** (14.1 g, 100 mmol), using 3-aminophenol (11.2 g, 102 mmol), potassium carbonate (26.5 g, 191 mmol), and *N*,*N*-dimethylformamide (150 mL). Yield 95%, yellow crystalline solid; mp 79 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.39 (br s, 2H), 6.26 (ddd, J = 0.9, 2.4, 7.8 Hz, 1H), 6.31 (t, J = 2.1 Hz, 1H), 6.48 (ddd, J = 0.9, 2.1, 8.1 Hz, 1H), 7.07−7.14 (m, 3H), 8.24 (dt, J = 7.2, 3.6 Hz, 2H). MS (ESI): m/z 271.95 $(M + H)^+$. Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.63; H, 4.39; N, 12.19.

3-(1-Cyano-1-methylethyl)-*N*-[3-(4-nitrophenoxy)phenyl]-benzamide (37). Compound **37** (8.10 g) was prepared in a similar manner to **1i** from **36** (4.69 g, 20.4 mmol), using **15h** (3.98 g, 21.0 mmol), EDCI·HCl (4.69 g, 24.5 mmol), DMAP (151 mg, 1.24 mmol), and pyridine (100 mL). Yield 99%, yellow amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.75 (s, 6H), 6.97 (dd, J = 1.8, 8.4 Hz, 1H), 7.20 (dt, J = 10.5, 3.3 Hz, 2H), 7.49 (t, J = 7.8 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.67−7.71 (m, 2H), 7.76 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 8.02 (t, J = 1.5 Hz, 1H), 8.29 (dt, J = 10.5, 3.3 Hz, 2H), 10.49 (br s, 1H). MS (ESI): m/z 402.05 $(M + H)^+$.

***N*-[3-(4-Aminophenoxy)phenyl]-3-(1-cyano-1-methylethyl)-benzamide (38).** To a solution of **37** (8.10 g, 20.2 mmol) in tetrahydrofuran (50 mL) and methanol (50 mL) was added 10% palladium/carbon (555 mg), and the reaction mixture was stirred at room temperature under hydrogen atmosphere (2.5 atm) for 14 h. The insoluble was filtered off and the filtrate was concentrated in vacuo to give compound **38** (7.34 g, 98%) as a pale gray amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.74 (s, 6H), 5.00 (br s, 2H), 6.58−6.67 (m, 3H), 6.77−6.81 (m, 2H), 7.27 (t, J = 8.1 Hz, 1H), 7.37 (t, J = 2.1 Hz, 1H), 7.43−7.46 (m, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.74 (ddd, J = 0.9, 2.1, 7.8 Hz, 1H), 7.90 (dt, J = 8.1, 1.2 Hz, 1H), 7.99 (t, J = 1.5 Hz, 1H), 10.30 (br s, 1H). MS (ESI): m/z 372.10 $(M + H)^+$.

***tert*-Butyl {3-[(5-Aminopyridin-2-yl)oxy]phenyl}carbamate (40).** To a suspension of *tert*-butyl (3-hydroxyphenyl)carbamate (3.02 g, 14.4 mmol) and potassium carbonate (2.99 g, 21.7 mmol) in *N*,*N*-dimethylformamide (35 mL) was added 2-chloro-5-nitropyridine **39** (2.52 g, 15.9 mmol), and the reaction mixture was stirred at 70 °C for 2 h. To the reaction mixture was added water (100 mL), and the mixture was extracted with ethyl acetate (100 mL, 50 mL). The combined extracts were washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure to give *tert*-butyl {3-[(5-nitropyridin-2-yl)oxy]phenyl}carbamate as a yellow solid. To a solution of *tert*-butyl {3-[(5-nitropyridin-2-yl)oxy]phenyl}carbamate in ethanol/tetrahydrofuran (4:1, 100 mL) was added 10% palladium/carbon (1.54 g), and the reaction mixture was stirred at room temperature for 7 h under hydrogen atmosphere (1.0 atm). The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from methanol to give compound **40** (3.35 g, 77% in two steps from **39**) as brown crystalline solid, mp 166−167 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.45 (s, 9H), 5.11 (br s, 2H), 6.52 (dd, J = 1.5, 7.4 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 7.07 (dd, J = 2.2, 8.7 Hz, 1H), 7.10−7.23 (m, 3H), 7.55 (d, J = 2.2 Hz, 1H), 9.36 (br s, 1H).

***tert*-Butyl {3-[(2-Amino[1,3]thiazolo[5,4-*b*]pyridin-5-yl)oxy]-phenyl}carbamate (41).** Compound **41** (3.51 g) was prepared in a similar manner to **5** from **40** (3.33 g, 11.1 mmol), using potassium thiocyanate (4.30 g, 44.2 mmol), AcOH (60 mL), and bromine (1.85 g, 11.6 mmol). Yield 88%, pale yellow crystals; mp 181−182 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.45 (s, 9H), 6.62−6.70 (m, 1H), 6.88 (d, J = 8.9 Hz, 1H), 7.18−7.29 (m, 3H), 7.62 (br s, 2H), 7.71 (d, J = 8.9 Hz, 1H), 9.43 (br s, 1H). MS (ESI): m/z 359.1 $(M + H)^+$.

***N*-[5-(3-Aminophenoxy)[1,3]thiazolo[5,4-*b*]pyridin-2-yl]-cyclopropanecarboxamide (42).** The intermediate *tert*-butyl [3-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-*b*]pyridin-5-yl}oxy)phenyl]carbamate (1.02 g) was prepared in a similar manner to **5** from *tert*-butyl {3-[(2-amino[1,3]thiazolo[5,4-*b*]pyridin-5-yl)-oxy]phenyl}carbamate **41** (1.00 g, 2.79 mmol), using cyclopropanecarbonyl chloride (327 μL, 3.63 mmol) and pyridine (30 mL). Yield 86%, pale yellow crystals; mp 199 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86−1.03 (m, 4H), 1.45 (s, 9H), 1.92−2.05 (m, 1H), 6.68−6.79 (m, 1H), 7.08 (d, J = 8.7 Hz, 1H), 7.20−7.38 (m, 3H), 8.15 (d, J = 8.7 Hz, 1H), 9.48 (br s, 1H), 12.66 (br s, 1H).

A solution of *tert*-butyl [3-({2-[(cyclopropylcarbonyl)amino][1,3]-thiazolo[5,4-*b*]pyridin-5-yl}oxy)phenyl]carbamate (900 mg, 2.11 mmol) and anisole (1 mL) in trifluoroacetic acid (10 mL) was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and to the residue was added saturated aqueous $NaHCO_3$ (50 mL), and the mixture was extracted with tetrahydrofuran/ethyl acetate (1:1, 50 mL and then 15 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran/ethyl acetate to give compound **42** (542 mg, 79%) as pale yellow crystals, mp 261−263 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.87−1.03 (m, 4H), 1.92−2.05 (m, 1H), 5.25 (br s, 2H), 6.23 (ddd, J = 0.8, 2.4, 7.9 Hz, 1H), 6.28 (t, J = 2.4 Hz, 1H), 6.40 (ddd, J = 0.8, 2.4, 7.9 Hz, 1H), 6.97−7.08 (m, 2H), 8.11 (d, J = 8.7 Hz, 1H), 12.67 (br s, 1H). MS (ESI): m/z 327.1 $(M + H)^+$. Anal. Calcd for $C_{16}H_{14}N_4O_2S{\cdot}0.1H_2O$: C, 58.56; H, 4.36; N, 17.07. Found: C, 58.55; H, 4.40; N, 17.03.

2-Chloro-3-(1-cyanocyclopropyl)-*N*-(2-fluoro-5-hydroxyphenyl)-benzamide (43). Compound **43** (23.4 g) was prepared in a similar manner to **1i** from 2-chloro-3-(1-cyanocyclopropyl)benzoic acid **15q** (16.0 g, 72.2 mmol), using oxalyl chloride (7.2 mL, 84.0 mmol), *N*,*N*-dimethylformamide (0.1 mL), tetrahydrofuran (150 mL), 3-amino-4-fluorophenol (9.00 g, 70.8 mmol), $NaHCO_3$ (13.9 g, 166 mmol), water (100 mL), and tetrahydrofuran (50 mL). Yield 100%, brown crystals; mp 188−189 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.40−1.49 (m, 2H), 1.76−1.85 (m, 2H), 6.52−6.63 (m, 1H), 7.07 (dd, J = 9.0, 10.5 Hz, 1H), 7.39 (dd, J = 2.9, 6.5 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.53−7.60 (m, 1H), 7.64 (dd, J = 1.7, 7.6 Hz, 1H), 9.48 (s, 1H), 10.30 (s, 1H). MS (ESI): m/z 331.1 $(M + H)^+$. Anal. Calcd for $C_{17}H_{12}ClFN_2O_2$: C, 61.73; H, 3.66; N, 8.47. Found: C, 61.68; H, 3.93; N, 8.15.

***N*-{5-[(5-Aminopyridine-2-yl)oxy]-2-fluorophenyl}-2-chloro-3-(1-cyanocyclopropyl)benzamide (44).** A mixture of **43** (23.0 g, 69.6 mmol), 2-chloro-5-nitropyridine **39** (12.2 g, 77.1 mmol), and potassium carbonate (11.5 g, 83.1 mmol) in *N*,*N*-dimethylformamide (70 mL) was stirred at room temperature for 4 h. The mixture was diluted with *N*,*N*-dimethylformamide (130 mL). Water (250 mL) was added to the mixture. The mixture was stirred at room temperature for 1 h. The resulting precipitate was collected by filtration and washed with water (250 mL) to give 2-chloro-3-(1-cyanocycropropyl)-*N*-{2-fluoro-5-[(5-nitropyridin-2-yl)oxy]phenyl}benzamide (29.3 g, 93%) as gray crystals, mp 201−202 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.38−1.51 (m, 2H), 1.74−1.86 (m, 2H), 7.08−7.19 (m, 1H), 7.32 (d, J = 9.1 Hz, 1H), 7.42 (dd, J = 9.0, 10.3 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.56−7.62 (m, 1H), 7.65 (dd, J = 1.7, 7.6 Hz, 1H), 7.85 (dd, J = 2.8, 6.4 Hz, 1H), 8.65 (dd, J = 2.6, 9.1 Hz, 1H), 9.06 (d, J = 2.6 Hz, 1H), 10.62 (s, 1H). MS (ESI): m/z 453.1 $(M + H)^+$. Anal. Calcd for $C_{22}H_{14}ClFN_4O_4$: C, 58.35; H, 3.12; N, 12.37. Found: C, 58.34; H, 3.32; N, 12.57.

A mixture of 2-chloro-3-(1-cyanocycropropyl)-*N*-{2-fluoro-5-[(5-nitropyridin-2-yl)oxy]phenyl}benzamide (6.60 g, 14.6 mmol), reduced iron (1.68 g, 30.0 mmol), calcium chloride (3.33 g, 30.0 mmol), water (80 mL), and ethanol (20 mL) was stirred at 80 °C for 18 h. The reaction mixture was cooled at room temperature. To the mixture were added water (250 mL), 1 N NaOH (250 mL), ethyl acetate (300 mL), and Celite (33 g), successively, and the mixture was stirred for 15 min. The mixture was filtered through a pad of Celite. The insoluble was washed with ethyl acetate (100 mL). The filtrate and washings were combined, and the separated organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo. The resulting slurry was triturated with diethyl ether to give compound **44** (4.23 g, 69%) as pale yellow crystals, mp 186−187 °C. ^{1}H NMR

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($CDCl_3$, 300 MHz): δ 1.35−1.42 (m, 2H), 1.80−1.85 (m, 2H), 3.45−3.57 (br s, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.82−6.88 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.12 (dd, J = 7.5, 8.4 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.50 (dd, J = 1.5, 7.5 Hz, 1H), 7.66 (dd, J = 1.8, 7.8 Hz, 1H), 7.70 (d, J = 3.0 Hz, 1H), 7.97−8.03 (br s, 1H), 8.28 (dd, J = 3.0, 6.6 Hz, 1H). MS (ESI): m/z 423.1 $(M + H)^+$. Anal. Calcd for $C_{22}H_{16}ClFN_4O_2 \cdot 0.25H_2O$: C, 61.83; H, 3.89; N, 13.11. Found: C, 61.94; H, 3.84; N, 12.83.

***N*-{5-[(2-Amino[1,3]thiazolo[5,4-*b*]pyridin-5-yl)oxy]-2-fluorophenyl}-2-chloro-3-(1-cyanocyclopropyl)benzamide (45).** The mixture of potassium thiocyanate (3.89 g, 40 mmol) in acetic acid (50 mL) was stirred at room temperature for 10 min. To the mixture was added **44** (4.23 g, 10 mmol), and the mixture was stirred at room temperature for an additional 5 min. To the mixture was added a solution of bromine (2.40 g, 15 mmol) in acetic acid (50 mL) at 15 °C. The resulting mixture was stirred at room temperature for 6 h. The resulting yellow precipitate was removed by filtration through a pad of Celite and washed with acetic acid (50 mL). The filtrate and washings were combined and concentrated under reduced pressure. The residue was diluted with 0.1 N NaOH (100 mL), and the mixture was extracted with ethyl acetate (100 mL). The organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo. The residue was purified with silica gel column chromatography (0−100% ethyl acetate in *n*-hexane). Desired fractions were combined and evaporated in vacuo. And the resulting slurry was triturated with diethyl ether to give the compound **45** (3.32 g, 69%) as pale yellow crystals, mp 215−216 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.41−1.49 (m, 2H), 1.75−1.85 (m, 2H), 6.95 (d, J = 8.5 Hz, 1H), 6.97−7.03 (m, 1H), 7.33 (dd, J = 9.3, 10.2 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.56−7.67 (m, 4H), 7.69 (dd, J = 2.9, 6.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 10.53 (s, 1H). HRMS (ESI): calcd for $C_{23}H_{15}ClFN_5O_2S$ $[M + H]^+$ 480.0692. Found: 480.0692.

2-Chloro-5-[(5-nitropyridin-2-yl)oxy]aniline (46). To a solution of 2-chloro-5-nitropyridine **39** (4.76 g, 30 mmol) and 3-amino-4-chlorophenol (4.31 g, 30 mmol) in *N*,*N*-dimethylformamide (15 mL) was added potassium carbonate (4.15 g, 30 mmol), and the reaction mixture was stirred at room temperature for 16 h. To the reaction mixture was added ethyl acetate (80 mL), and the mixture was washed successively with water (50 mL) and saturated brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual solid was recrystallized from ethyl acetate/*n*-hexane (1:1) (30 mL), and the crystals were collected by filtration, washed with *i*-Pr_2O (20 mL), and dried under vacuum to give compound **46** (6.74 g, 85%) as brown crystals, mp 123−124 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.19 (br s, 2H), 6.48 (dd, J = 2.7, 8.6 Hz, 1H), 6.58 (d, J = 2.7 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 8.47 (dd, J = 2.7, 9.0 Hz, 1H), 9.05 (d, J = 2.7 Hz, 1H). MS (ESI): m/z 266.0 $(M + H)^+$. Anal. Calcd for $C_{11}H_8ClN_3O_3$: C, 49.73; H, 3.04; N, 15.82. Found: C, 49.73; H, 3.13; N, 15.64.

***N*-{5-[(5-Aminopyridin-2-yl)oxy]-2-chlorophenyl}-2,2,2-trifluoroacetamide (47).** A solution of **46** (6.5 g, 24.5 mmol) in tetrahydrofuran (50 mL) and trifluoroacetic anhydride (3.73 mL, 26.9 mmol) was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (80 mL). The solution was washed with saturated $NaHCO_3$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residual solid was collected by filtration using *i*-Pr_2O (30 mL) and dried under vacuum to give *N*-{2-chloro-5-[(5-nitropyridin-2-yl)oxy]phenyl}-2,2,2-trifluoroacetamide (7.73 g, 87%) as white crystals, mp 117−118 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.95−7.19 (m, 2H), 7.52 (dd, J = 1.5, 9.0 Hz, 1H), 8.20−8.30 (m, 1H), 8.40−8.60 (m, 2H), 9.00−9.10 (m, 1H). MS (ESI): m/z 362.0 $(M + H)^+$. Anal. Calcd for $C_{13}H_7ClF_3N_3O_4$: C, 43.17; H, 1.95; N, 11.62. Found: C, 43.17; H, 2.06; N, 11.54. To a solution of *N*-{2-chloro-5-[(5-nitropyridin-2-yl)oxy]phenyl}-2,2,2-trifluoroacetamide (13 g, 35.9 mmol) in acetic acid (200 mL) was added reduced iron (10 g, 179 mmol). The mixture was stirred at 60 °C for 3 h. After cooling at room temperature, the reaction mixture was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate (150 mL), and to the mixture was slowly added saturated $NaHCO_3$ (200 mL). The mixture was filtered through Celite. The organic layer of the filtrate was collected and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was dissolved in toluene, and the solution was purified by silica gel column chromatography (20−80% ethyl acetate in *n*-hexane) to give compound **47** (10.9 g, 91%) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.57 (br s, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.93 (dd, J = 2.8, 8.7 Hz, 1H), 7.11 (dd, J = 2.8, 8.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 3.0 Hz, 1H), 8.11 (d, J = 3.0 Hz, 1H), 8.41 (br s, 1H). MS (ESI): m/z 332.0 $(M + H)^+$.

***N*-(5-{4-Chloro-3-[(trifluoroacetyl)amino]phenoxy}[1,3]-thiazolo[5,4-*b*]pyridin-2-yl)cyclopropanecarboxamide (48).** To a mixture of **47** (12 g, 36.2 mmol) and potassium thiocyanate (14.1 g, 145 mmol) in acetic acid (145 mL) was added dropwise bromine (8.67 g, 54.3 mmol) under ice-cooling. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in ethyl acetate (100 mL), and to the mixture was slowly added saturated $NaHCO_3$ (150 mL), and the mixture was partitioned. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residual solid was collected by filtration using *i*-Pr_2O (100 mL) and dried under vacuum to give *N*-{5-[(2-amino[1,3]-thiazolo[5,4-*b*]pyridin-5-yl)oxy]-2-chlorophenyl}-2,2,2-trifluoroacetamide (10.1 g, 72%) as pale yellow crystals, mp 164−165 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.98 (d, J = 8.5 Hz, 1H), 7.16 (dd, J = 2.8, 8.8 Hz, 1H), 7.27 (d, J = 2.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.66 (br s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 11.30 (br s, 1H). MS (ESI): m/z 389.0 $(M + H)^+$. Anal. Calcd for $C_{14}H_8ClF_3N_4O_2S$: C, 43.25; H, 2.07; N, 14.41. Found: C, 43.01; H, 2.17; N, 14.28.

To a solution of *N*-{5-[(2-amino[1,3]thiazolo[5,4-*b*]pyridin-5-yl)oxy]-2-chlorophenyl}-2,2,2-trifluoroacetamide (5.0 g, 12.86 mmol) in pyridine (25 mL) was added dropwise cyclopropanecarbonyl chloride (1.28 mL, 14.2 mmol) under ice-cooling, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was treated with saturated $NaHCO_3$ (100 mL) and diluted with ethyl acetate (100 mL), and the organic layer was collected. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residual solid was crystallized from ethyl acetate (30 mL), collected by filtration, and dried under vacuum to give compound **48** (3.46 g, 59%) as white crystals, mp 235−236 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86−1.07 (m, 4H), 1.90−2.10 (m, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.26 (dd, J = 2.7, 8.9 Hz, 1H), 7.38 (d, J = 2.7 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H), 11.34 (br s, 1H), 12.72 (br s, 1H). MS (ESI): m/z 457.0 $(M + H)^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Information methods used in kinase enzyme assays, cellular assays, in vivo studies, computational studies, structural biology studies, solubility study, microsomal study, and pharmacokinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

†PDB accession codes are 4DBN for the BRAF cocrystal structure and 3VNT for the VEGFR2 cocrystal structure.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

^{1}H NMR, proton nuclear magnetic resonance; AUC, area under the blood concentration time curve; CL_{total}, clearance; ERK, extracellular signal-regulated kinase; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; HPLC, high-performance liquid chromatography; HUVEC, human umbilical vein endothelial cell; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; MS, mass spectrometry; PD, pharmacodynamic; PDB, Protein Data Bank; PDGFR, platelet-derived growth factor receptor; PK, pharmacokinetic; RTK, receptor tyrosine kinase; SAR, structure−activity relationship; SD, solid dispersion; SD, standard deviation; VD_{ss}, steady state volume of distribution; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2

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