Naphthamides as Novel and Potent Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors: Design, Synthesis, and Evaluation[¶]

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A series of naphthyl-based compounds were synthesized as potential inhibitors of vascular endothelial growth factor (VEGF) receptors. Investigations of structure–activity relationships led to the identification of a series of naphthamides that are potent inhibitors of the VEGF receptor tyrosine kinase family. Numerous analogues demonstrated low nanomolar inhibition of VEGF-dependent human umbilical vein endothelial cell (HUVEC) proliferation, and of these several compounds possessed favorable pharmacokinetic (PK) profiles. In particular, compound **48** demonstrated significant antitumor efficacy against established HT29 human colon adenocarcinoma xenografts implanted in athymic mice. A full account of the preparation, structure–activity relationships, pharmacokinetic properties, and pharmacology of analogues within this series is presented.

Angiogenesis, the formation of new blood vessels from existing vasculature, is an important pathway for normal embryogenesis, growth, and tissue repair.[1,2] It is also involved in a number of pathological processes, including inflammation,[3] rheumatoid arthritis,[4] ocular neovascularization,[5] psoriasis,[6] tumor growth,[7] and metastasis.[8] Vascular endothelial growth factor (VEGF[a]) and its receptor tyrosine kinases VEGFR-2 or kinase insert domain receptor (KDR) and VEGFR-1 are key regulators of angiogenesis.[9] The increased understanding of the molecular mechanisms involved in the VEGF signaling pathway has enabled the development of agents that can interfere with this process. Moreover, the concept of blocking the growth of a solid tumor by suppressing its blood supply via the inhibition of the VEGF pathway is now well established.[7,10] Several successful strategies for the inhibition of angiogenesis have been effectively demonstrated in preclinical and clinical settings. These approaches include VEGF soluble decoy receptors,[11] antibodies directed against VEGF,[12] and small molecules that inhibit KDR.[13,14] Bevacizumab, a recombinant humanized monoclonal antibody directed against VEGF, has now been approved for first or second line treatment of patients with metastatic carcinoma of the colon or rectum and for patients with advanced non-squamous non-small-cell lung cancer.[15,16] In addition, two small-molecule inhibitors of KDR, sunitinib (**1**)[17,18] and sorafenib (**2**),[19,20] have been approved for the treatment of advanced renal cell carcinoma (Figure 1). We previously reported the discovery of AMG 706 (*N*-(3,3-dimethyl-2,3-dihydro-1*H*-indol-6-yl)-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide, motesanib diphosphate, compound **3**), a potent inhibitor of VEGF receptors 1, 2, and 3 (VEGFR1–3).[21] This molecule is being evaluated in the clinic for its ability to inhibit angiogenesis and lymphangiogenesis and is also under investigation for its potential direct antitumor activity by targeting platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-Kit) signaling.

Recently, we reported the discovery of 2-aminobenzoxazoles (Figure 2, **4**) as a novel class of potent KDR inhibitors.[22] Separately, we also disclosed the discovery of a novel series of pyridylpyrimidine derivatives as Tie-2 kinase inhibitors (Figure 2, **5**).[23] Interestingly, in this latter series several compounds were identified that displayed potent inhibition of KDR (i.e., **5**, IC_{50} KDR = 2 nM). In an effort to utilize this scaffold as a starting point to discover a new series of KDR inhibitors, an X-ray cocrystal structure of **5** bound to KDR was obtained. As illustrated by the cocrystal structures of **4** and **5** complexed with KDR (Figure 2), the binding mode of these inhibitors to KDR is similar (PDB accession codes 2QU6 and 3BE2, respectively). Of particular interest was the observation that both of these inhibitors force the protein to adopt a "DFG-out" conformation. This conformational change in turn enables the inhibitors to

[¶] The PDB accession codes for cocrystals of compounds **4**, **5**, and **48** in the KDR ATP-binding pocket are 2QU6, 3BE2, and 3B8Q, respectively.

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[a] Abbreviations: VEGF, vascular endothelial growth factor; KDR, kinase domain region; HUVEC, human umbilical vein endothelial cells; PDGF, platelet-derived growth factor; HTRF, homogeneous time-resolved fluorescence; bFGF, basic fibroblast growth factor; FBS, fetal bovine serum; MRT, mean retention time; DIPEA, diisopropylethyl amine; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; EDCI, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride; NHDF, normal human dermal fibroblast; DPPP, 1,3-bis(diphenylphospino) propane; HOAt, 1-hydroxy-7-aza-benztriazole.

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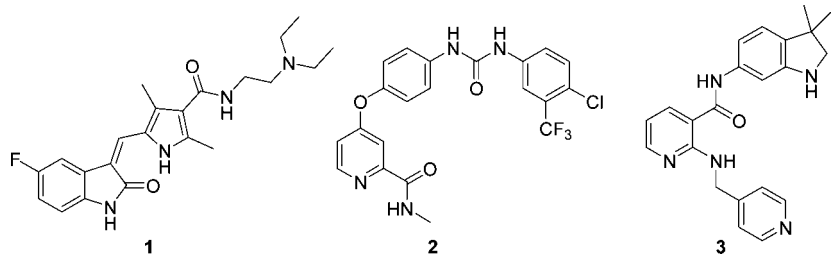
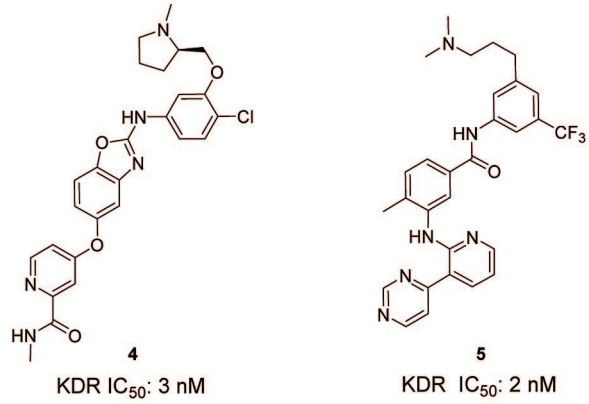


Figure 1. Examples of small-molecule KDR inhibitors undergoing clinical trials.



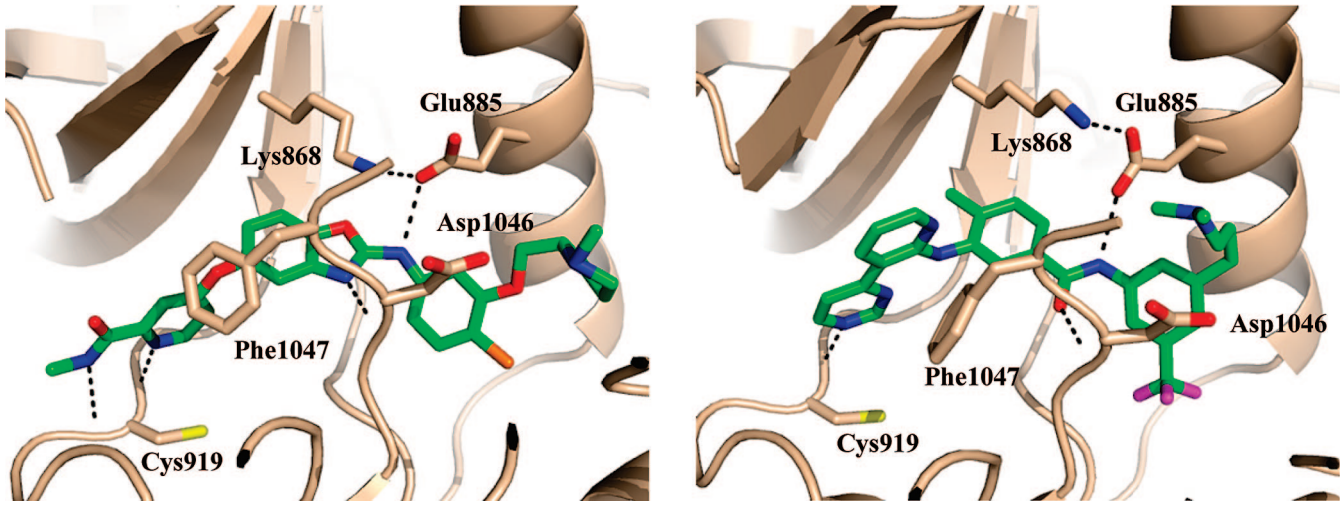


Figure 2. Crystallographic analysis of compounds **4** (left) and **5** (right) in the ATP-binding pocket of KDR. Hydrogen bonds are shown between the inhibitors and KDR (dotted lines).

project into the extended hydrophobic pocket, a lipophilic pocket that cannot be accessed when the enzyme is in the "DFG-in" conformation.

Examination of an overlay of **4** and **5** revealed a number of similarities that could potentially be exploited (Figure 3). Good overlap was observed between the pyridine of **4** and the pyrimidine of **5**, with both groups binding to the hinge region of KDR. The *p*-chloroaniline of **4** and the *m*-trifluoromethylaniline of **5** occupied similar areas in the extended lipophilic pocket. In addition, the overlay of the 2-aminobenzoxazole of **4** and the 3-aminobenzamide of **5**, both of which occupy the hydrophobic pocket, suggested that a naphthyl or structurally similar unit could serve as a scaffold from which to build a novel series of KDR inhibitors. In order to maintain the critical interactions with the protein, we hypothesized that the resulting hybrid structure should retain the pyridine moiety from **4** to bind to the hinge region of the kinase while also preserving the amide functionality from **5** which not only would serve to engage Glu 885 and Asp 1046 but could also project a lipophilic moiety into the extended hydrophobic pocket. It was anticipated that the resulting naphthamide (i.e., **6**) could afford a starting point for a novel series of potent and selective inhibitors of KDR with improved properties over those observed for the parent aminobenzoxazoles (**4**)[24] and pyridylpyrimidines (**5**).[25] Herein, we describe the synthesis, structure–activity relationships (SAR), and pharmacological characterization of naphthamides, a new series of potent KDR inhibitors.[26]

Chemistry

Our strategy for the construction of the naphthamides described in this paper is outlined in the retrosynthetic analysis shown in Scheme 1.[26] Naphthamides **7** and related compounds were prepared via activation of the carboxylic acid **8** and subsequent reaction with the desired amine R_1NH_2. Carboxylic acid **8** was in turn accessed via coupling of 6-hydroxynaphthoic acid (**10**) or a related derivative (i.e., **9**) with the desired

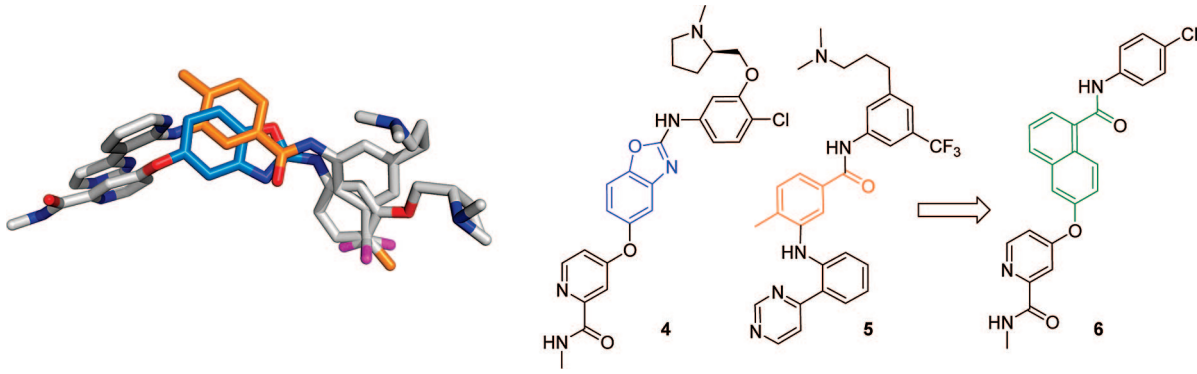
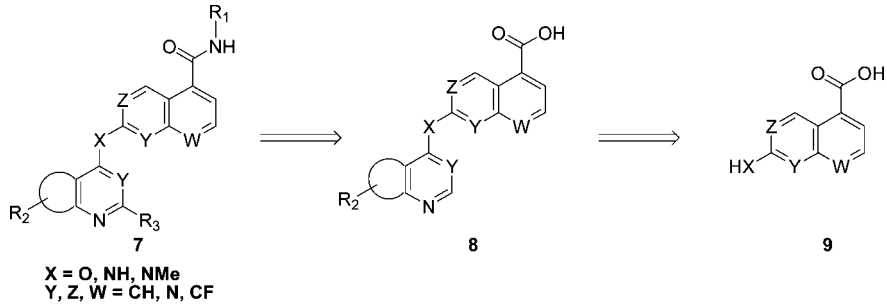
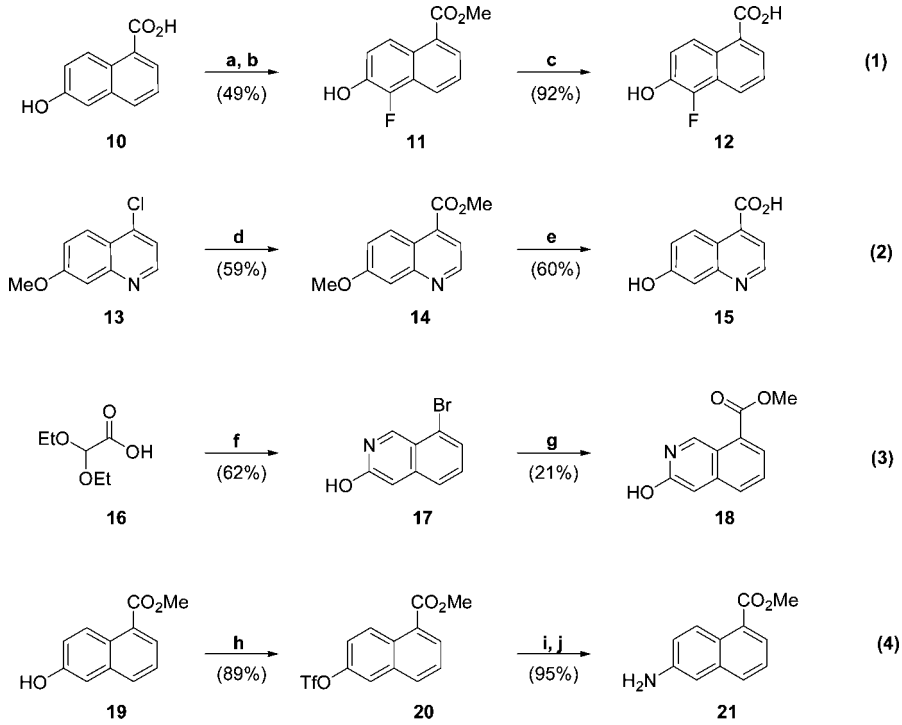


Figure 3. Overlay of 2-aminobenzoxazole **4** and pyridylpyrimidine **5** (left) and the emergence of a novel naphthamide-based scaffold (right).

Scheme 1. Retrosynthetic Analysis of Naphthamides



Scheme 2. Synthesis of Naphthoic Acid and Related Bicyclic Compounds[a]

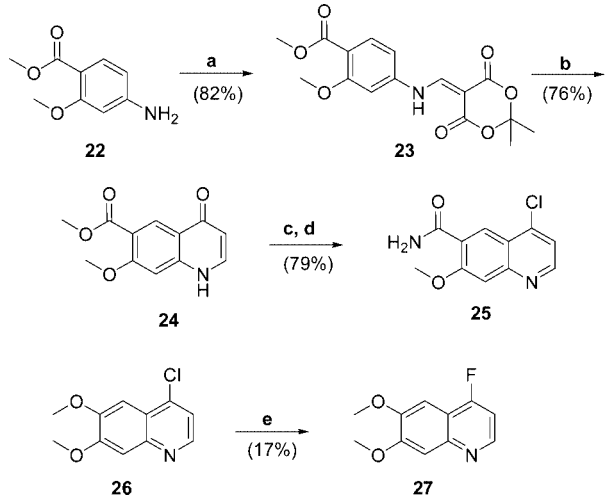


[a] Reagents: (a) $SOCl_2$, MeOH, room temp; (b) Selectfluor, MeCN, 85 °C; (c) NaOH, H_2O, MeOH, reflux; (d) CO, 50 psi, MeOH, $Pd(OAc)_2$, DPPP, Et_3N, DMF, 70 °C; (e) BBr_3, CH_2Cl_2, 0 °C to room temp; (f) $SOCl_2$; Et_3N, 2-bromobenzylamine; H_2SO_4; (g) $Pd(OAc)_2$, DPPP, Et_3N, CO, 30 psi, DMF, MeOH, 100 °C; (h) Tf_2O, DIPEA, CH_2Cl_2, −78 °C; (i) $Pd_2(dba)_3$, K_3PO_4, DME, 2-(dicyclohexylphosphino)biphenyl, benzophenone imine; (j) HCl.

heterocycle. This concise modular route allowed for the efficient construction of the desired naphthamides and rapid exploration of the SAR.

The 6-hydroxynaphthoic acid derivatives and related bicyclic units were either obtained from commercial sources (**10**) or prepared (**12**, **15**, **18**, and **21**) as outlined in Scheme 2. 5-Fluoro-6-hydroxynaphthoic acid (**12**) was synthesized in three steps from 6-hydroxynaphthoic acid (**10**) starting with the conversion of the carboxylic acid to the corresponding methyl ester.[27] Subsequent fluorination with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate proceeded in a regioselective fashion to afford **11** in modest yield. Hydrolysis of the methyl ester yielded the desired naphthoic acid **12** in nearly quantitative yield. 7-Hydroxyquinoline-4-carboxylic acid

Scheme 3. Synthesis of 4-Chloroquinolines[a]



[a] Reagents: (a) Meldrum's acid, *i*-PrOH, 80 °C; (b) Ph_2O, 240 °C; (c) $SOCl_2$, DMF, reflux; (d) NH_4OH, 110 °C; (e) *n*-Bu_4PHF_2, microwave heating, 120 °C.

(**15**) was accessed from 4-chloro-7-methoxyquinoline (**13**) in two steps. Palladium-mediated carbonylation of **13** yielded **14** which following exposure to BBr_3 gave rise to acid **15**. Isoquinoline **18** was prepared from diethylacetal glyoxalic acid (**16**) via coupling with 2-bromobenzylamine followed by in situ cyclization to afford 8-bromo-3-hydroxyisoquinoline (**17**) in good yield. Subsequent palladium-mediated carbonylation yielded the desired methyl ester **18**. Finally, aminonapthyl **21** was derived from methyl 6-hydroxynaphthoate (**19**) via triflate **20**, which underwent a palladium-mediated amination with benzophenone immine. Hydrolysis of the derived immine provided aniline **21**.

The heterocycles employed as linker binder elements in our naphthamides were obtained from commercial sources, prepared as previously described,[28] or prepared by the methods outlined in Scheme 3 (**25**, **27**). Quinoline **25** was synthesized in four steps starting with the condensation of methyl 4-amino-2-methoxybenzoate (**22**) with Meldrum's acid in isopropanol to afford enamide **23**. Subsequent heating of **23** at 240 °C triggered intramolecular cyclization to give quinolone **24**, which upon chlorination of the ketone and aminolysis of the methyl ester led to the desired chloroquinoline **25**. 4-Fluoro-6,7-dimethoxyquinoline (**27**) was prepared from commercially available 4-chloroquinoline (**26**) by nucleophilic aromatic substitution using tetrabutylphosphonium fluoride hydrofluoride under microwave (MW) irradiation.

The various building blocks could be combined to form the desired naphthoic acid intermediates or related compounds as shown in Schemes 4 and 5. Scheme 4 illustrates the synthesis of inhibitors centered around an unmodified naphthyl core. Biaryl ethers **29a**−**e** were obtained by nucleophilic aromatic substitution (SNAr) of the corresponding heteroaryl chloride **28** with 6-hydroxynaphthoic acid (**10**) in the presence of cesium carbonate at 140 °C (Scheme 4, reaction 1). The construction of 3-fluoroquinoline derivative **29f** was achieved by the palladium-mediated coupling of 6-hydroxynaphthoic acid (**10**) and 6,7-dimethoxy-3-fluoro-4-chloroquinoline because coupling of these two partners under standard nucleophilic aromatic substitution conditions led to unselective addition at the 3 and 4 positions of the quinoline.[28] Pyridine and pyrimidine containing compounds **31a**−**d** and **34a**−**c** were obtained in a manner similar to that described above wherein formation of the aryl ether was achieved utilizing SNAr chemistry (Scheme 4, reactions 2 and 3). The latter compounds (**34a**−**c**), which encompass an aminopyridine or aminopyrimidine moiety, were accessed in two steps from the appropriate dichloropyridine or pyrimidine by treatment with cesium carbonate followed by reaction with methylamine.

The construction of inhibitors wherein the central naphthyl ring was modified is illustrated in Scheme 5. Preparation of the 5-fluoro-1-naphthoic acid derivative **36a** and the 7-quinoline-4-carboxylic acid **36c** were achieved using the SNAr conditions described above. The preparation of isoquinoline **36b** required the use of the more reactive 4-fluoro-6,7-dimethoxyquinoline (**27**) because low yields were obtained when the less reactive 4-chloro-6,7-dimethoxyquinoline (**35**) was employed. In the event, coupling of isoquinoline **18** and **27** in the presence of cesium carbonate with microwave irradiation afforded the corresponding biaryl ether which after in situ hydrolysis of the methyl ester provided acid **36c** (Scheme 5, reaction 1). Construction of the biarylamine core (**37a**,**b**) occurred most smoothly when acidic conditions were employed. Thus, 6-aminonaphthoyl derivative **21** was heated with 6,7-dimethoxyquinoline (**35**) and trifluoroacetic acid in isopropanol to afford the corresponding biarylamine (Scheme 5, reaction 2). The derived amine could be advanced to aniline **37a** by hydrolysis of the methyl ester. Alternatively, alkylation of the derived aniline by exposure to sodium hydride and methyl iodide followed by hydrolysis furnished **37b**.

Scheme 6 outlines the completion of the synthesis of the naphthamides and related compounds **39**. Amide bond construction was accomplished either by treatment of the appropriate acid (i.e., **38**) with the desired amine in the presence of an activating agent (i.e., HATU, TBTU, or EDCI) or by conversion of the acid to the corresponding acid chloride and subsequent reaction with the desired amine.

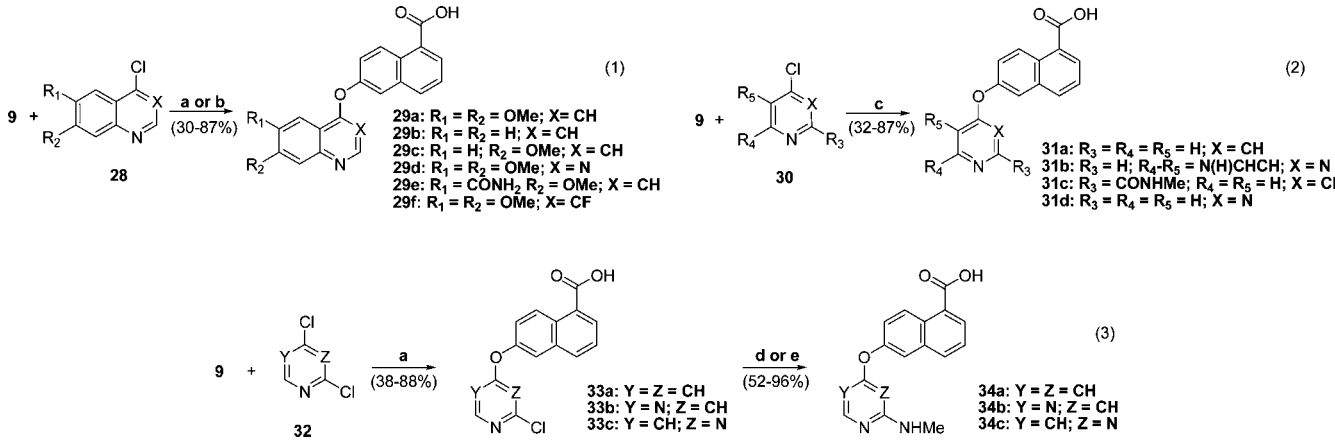
Results and Discussion

Structure–Activity Relationships (SAR). The in vitro enzymatic activity of all compounds was assessed using a homogeneous time-resolved fluorescence (HTRF) assay with the catalytic domain of KDR. Potency at the cellular level was evaluated by determining the inhibition of human umbilical vein endothelial cell (HUVEC) proliferation induced by VEGF, an assay that is carried out in the presence of 10% fetal bovine serum (FBS). As a cellular selectivity screen used to assess inhibition of basic fibroblast growth factor receptor (bFGFR) and downstream kinases that participate in the angiogenic signaling cascade, inhibition of HUVEC proliferation driven by basic fibroblast growth factor (bFGF) was also measured. While bFGF is known to be an important growth factor involved in angiogenesis, the use of a bFGF-driven HUVEC proliferation assay as a selectivity screen would allow for a more direct correlation between VEGFR-2 inhibition and the observed pharmacology.

To test our original hypothesis, compound **6** was evaluated for enzyme and cell activity. Naphthamide **6** inhibited KDR with an IC_{50} of 3 nM and the VEGF driven proliferation of HUVECs with an IC_{50} of 210 nM. This enzymatic and cellular potency was combined with an encouraging selectivity at the cellular level (bFGF-HUVEC IC_{50} > 1100 nM). This initial promising result led us to explore variations of the pyridyl moiety binding to the hinge region while maintaining the *N*-4-chlorophenylnaphthamide functionality. The enzyme potencies as well as cellular activities are summarized in Table 1.

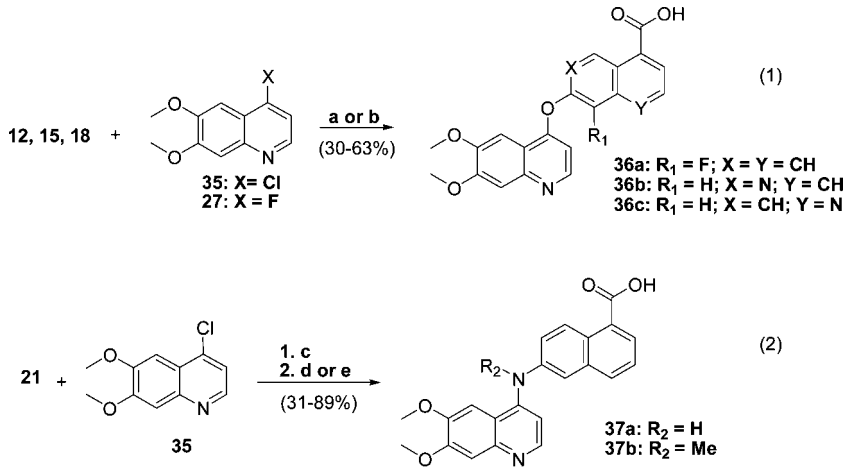
Within the *N*-4-chlorophenylnaphthamide series, the enzyme tolerated the incorporation of a variety of monocyclic (**6**, **40**–**44**)

Scheme 4. Preparation of Naphthoic Acid and Related Intermediates[a]



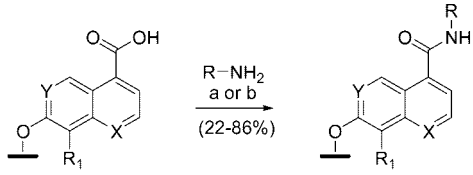
[a] Reagents: (a) Cs_2CO_3, DMSO, 140 °C; (b) 5 mol % $Pd(OAc)_2$, 10 mol % *t*-Bu-XPhos, K_3PO_4, DMF, 100 °C; (c) Cs_2CO_3, DMSO, 110 °C; (d) $MeNH_2$, 235 °C; (e) $MeNH_2$, THF, 0 °C to room temp.

Scheme 5. Preparation of Naphthoic Acid and Related Intermediates[a]



[a] Reagents: (a) Cs_2CO_3, DMSO, 140 °C; (b) Cs_2CO_3, DMF, microwave heating, 120 °C; (c) TFA, *i*-PrOH, 90 °C; (d) 6 N NaOH, MeOH, room temp; (e) NaH, MeI, DMF, 0 °C to room temp; 6 N NaOH, MeOH, room temp.

Scheme 6. Preparation of Naphthamides and Related Compounds[a]

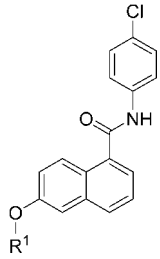


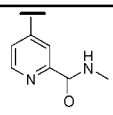
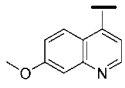
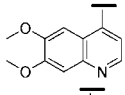
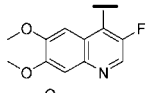
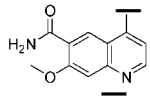
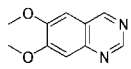
[a] Reagents: (a) amine, HATU, DIPEA, DMF; or amine, TBTU, DIPEA, DMF; or amine, HOAt, EDCI, DIPEA, DMF; (b) $(COCl)_2$, cat. DMF, CH_2Cl_2; amine; or thionyl chloride; amine.

and bicyclic (**45**–**51**) heterocycles (Table 1). Removal of the carboxamide group led to a 6-fold reduction in enzyme potency (**6** vs **40**), presumably because of the loss of the hydrogen-bond interaction between the NH of the carboxamide and the carbonyl of Cys919 in the hinge region of KDR. The inclusion of a heterocycle with a suitably placed hydrogen bond donor to interact with the hinge region of KDR provided improved potency. This trend is exemplified by **41** and **46**, wherein it is the C8 proton of the quinoline ring in **46** that is engaged with the carbonyl of Cys919.[29] Pyrimidine **42** was the only analogue examined that displayed substantially reduced enzymatic activity. While pyridine **40** and 2-substituted pyridines **6** and **41** displayed potent inhibition at the enzyme level, these compounds exhibited a 12- to 70-fold enzyme to cell shift. The 2-substituted and 5-substituted aminomethylpyrimidine derivatives **43** and **44** were slightly less potent at the enzymatic level but exhibited a smaller enzyme to cell shift than the corresponding pyridine (**41**). The fusion of a second ring obtained by closing the 6-aminomethylpyrimidine **44** to the corresponding 7*H*-pyrrolo[2,3-*d*]pyrimidine provided **45**. This modification led to an inhibitor with similar inhibition of KDR but improved cellular potency compared to the 6-aminomethylpyrimidine **44**, 37 nM vs 106 nM. Furthermore, 6,6-fused bicycles **46**–**48** and **50**, **51** afforded single digit nanomolar inhibitors of KDR. Quinoline derivatives bearing a 6 and/or 7 substituent (s) (**47**, **48**, and **50**) provided compounds that inhibited VEGF-induced proliferation of HUVEC with $IC_{50} < 10$ nM with a high degree of selectivity (100-fold) over bFGF-induced proliferation. Other modifications included the 3-F quinoline **49**, which resulted in a 40-fold loss in activity compared with **48**, and quinazoline **51**, which proved to be slightly more potent than **48** at the cellular level while maintaining selectivity.

Having established the 6,7-dimethoxyquinoline as one of the more favorable heterocycles to bind to the hinge region of KDR, we turned our attention toward modifications of the arylamide

Table 1. Structure–Activity Relationship (SAR): Variation of the Nitrogen Containing Heterocycle Binding the Hinge Region[a]

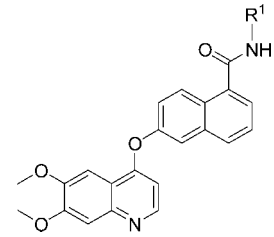


Compound	R^1	KDR IC_{50} (nM)	HUVEC IC_{50} (nM)[b]	
			VEGF	bFGF
6		3	210	>1100
40		18	220	>1100
41		7	140	>1100
42		310	ND	ND
43		46	296	>1100
44		20	106	>1100
45		28	37	>1140
46		4	34	>1100
47		1	8	>1100
48		0.5	8	>1100
49		20	69	>1100
50		0.2	3	380
51		2	2	>1100

[a] IC_{50} values were averaged values determined by at least two independent experiments. [b] Human umbilical vein endothelial cells. ND: not determined.

occupying the extended hydrophobic pocket of the enzyme. A number of alterations were made to explore the effects on enzyme inhibition, cellular activity, and selectivity; the results of these studies are detailed in Table 2. Removal of the *p*-Cl substituent from **48** provided phenylnaphthamide **52**, which retained its potency against KDR. The incorporation of substituents on the phenyl ring (**53**–**63**) did not significantly impact the enzyme–inhibitory activity (0.3–2 nM). In this regard,

Table 2. SAR: Variations of the Naphthamide Moiety[a]



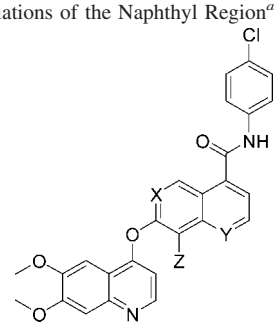
compd	R^1	KDR IC_{50} (nM)	HUVEC IC_{50} (nM)[b]	
			VEGF	bFGF
48	4-Cl-Ph	0.5	8	>1140
52	Ph	0.2	0.8	577
53	2-F-Ph	2	7	>1140
54	3-F-Ph	0.6	3	ND
55	4-F-Ph	1	2	305
56	3-Cl-Ph	0.3	5.1	ND
57	4-Me-Ph	0.5	2	548
58	3-CF_3-Ph	0.5	34	205
59	4-CF_3-Ph	0.5	16	228
60	4-t-Bu-Ph	0.7	63	944
61	2,4-Cl-Ph	2	14	>1140
62	3,5-Cl-Ph	0.3	28	742
63	3-CF_3-4-Cl-Ph	1	247	228
64	2-pyridyl	0.8	2	286
65	3-pyridyl	0.8	2	1100
66	4-pyridyl	2	2	>1140
67	2-thiazolyl	0.3	2	605
68	3-isoxazole	0.2	0.4	ND
69	5-methyl-3- isoxazolyl	0.6	6	250
70	3-methyl-5-isoxazolyl	1	7	>1140
71	5-*tert*-butyl-3-isoxazolyl	0.8	68	190
72	cyclopropyl	0.6	1	167
73	1-methylcyclopropyl	15	70	ND
74	cyclobutyl	3	7	>1140
75	cyclopentyl	9	7	>1140
76	propyl	1.3	7	>1140
77	isopropyl	5	4	>1140

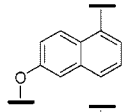
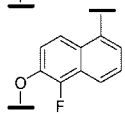
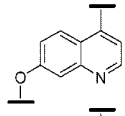
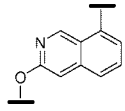
[a] See Experimental Section for the description of the assays. IC_{50} values were averaged values determined by at least two independent experiments. [b] Human umbilical vein endothelial cells. ND: not determined.

increasing the size and placement of substituents on the phenylnaphthamide had very little impact on enzyme inhibition. However, cellular potency was more sensitive to modifications in this region as is observed by the range of cellular activity displayed by **53**–**63** (2−247 nM). While small lipophilic groups such as chlorine (**48**, **56**) and methyl (**57**) did not significantly impact the enzyme to cell shift (2- to 16-fold), larger and/or more lipophilic groups, such as *tert*-butyl (**60**) and trifluoromethyl (**58**, **59**) led to decreased cell potency, despite promising enzyme activity. With the exception of **58**–**60** and **62**, all of the phenyl substituted naphthamides demonstrated >75 fold selectivity at the cellular level.

The preparation of a more diverse group of naphthamides was next pursued, and several heteroaromatic rings (**64**–**71**), cycloalkyl groups (**72**–**75**), and small alkyl groups (**76**, **77**) were incorporated into the inhibitors. The heteroaryl derivatives **64**–**70** exhibited enzyme and cellular activities comparable to the substituted phenyl compounds. It is noteworthy that pyridyl derivatives **64**–**66** were tolerated in the extended hydrophobic region of the enzyme. While isoxazole **69** exhibited favorable cellular activity, erosion of selectivity at the cellular level was observed; however, 3-methylisoxazolyl derivative **70** demonstrated potent and selective inhibition at the cellular level. Cycloalkylamides **72**–**75** were also well tolerated, though some loss of potency was observed with methylcyclopropyl **73**. Interestingly, the cyclopropyl derivative **72** achieved remarkable enzyme and cellular potency.[30] Small alkyl groups such as

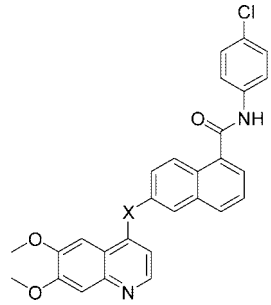
Table 3. SAR: Variations of the Naphthyl Region[a]



Compound	Ring	KDR IC_{50} (nM)	HUVEC IC_{50} (nM)[b]	
			VEGF	bFGF
48		0.5	8	>1140
78		0.3	2	280
79		22	10	88
80		23	175	>1140

[a] IC_{50} values were averaged values determined by at least two independent experiments. [b] Human umbilical vein endothelial cells.

Table 4. SAR: Variations of the Linker Atom[a]



compd	X	KDR IC_{50} (nM)	HUVEC IC_{50} (nM)[b]	
			VEGF	bFGF
48	O	0.5	8	>1100
81	NH	8	14	115
82	NMe	>1400	ND	ND

[a] IC_{50} values were averaged values determined by at least two independent experiments. [b] Human umbilical vein endothelial cells. ND: not determined.

n-propyl and isopropyl were also well tolerated, as demonstrated by the enzyme and cellular potency of compounds **76** and **77**.

Cognizant of the inherent metabolic activation liabilities potentially associated with the naphthyl residue, modifications of the central bicyclic aromatic core were explored (Table 3). Inclusion of a fluorine at the 5-position of the naphthoyl moiety afforded **78**, a potent KDR inhibitor with impressive cellular potency and selectivity. An alternative approach involved the incorporation of a heteroatom into the naphthyl ring and led to quinoline **79** and isoquinoline **80**. While quinoline **79** was 40-fold less potent than **48** at the enzymatic level, it exhibited no enzyme to cell shift and retained cellular potency. The selectivity of **79** at the cellular level was decreased in comparison with the corresponding naphthyl derivatives. Isoquinoline **80** displayed reduced enzymatic and cellular potency and yet did not inhibit bFGF-stimulated HUVEC proliferation. These findings suggest that the lipophilic pocket of KDR is more sensitive and less tolerant of variation when compared to the extended lipophilic pocket.

Table 5. Pharmacokinetic Parameters for Naphthamides **48**, **64–66**, **70**, and **78**

	48	**64**	**65**	**66**	**70**	**78**
RLM ((μL/min)/mg)[a]	50	90	90	80	40	30
HLM ((μL/min)/mg)[a]	30	80	90	30	40	30
Cyp 3A4 IC_{50} (μM)	>50	13	2	0.1	40	>50
Cyp 2D6 IC_{50} (μM)	>50	>50	17	0.7	>50	>50
Rat Pharmacokinetics						
Cl ((L/h)/kg)	0.2[b]	0.4[d]	0.9[d]	0.6[d]	1.3[g]	0.1[h]
V_{ss} (L/kg)	7.3[b]	3.1[d]	1.3[d]	1.4[d]	2.7[g]	2.4[h]
$t_{1/2}$ (h)	24[b]	6.1[d]	1.1[d]	1.8[d]	2.4[g]	17[h]
MRT (h)	31[b]	7.8[d]	1.4[d]	2.5[d]	2.1[g]	22[h]
C_{max} (ng/mL)	420[c]	200[e]	5710[f]	1690[f]	ND	610[i]
$AUC_{(0-24)}$ (ng·h/mL)	5250[c]	1240[e]	27100[f]	10980[f]	ND	6010[i]
F (%)	21[c]	45[e]	100[f]	62[f]	ND	50[i]

[a] Rat microsomal clearance (RLM). Human microsomal clearance (HLM). Compound concentration = 1 μM. Microsomal protein concentration = 1 mg/mL. [b] iv, 2 mpk, DMSO. [c] po, 5 mg/kg, OraPlus. [d] iv, 1 mg/kg, DMSO. [e] po, 2 mg/kg, OraPlus. [f] po, 10 mg/kg, OraPlus. [g] iv, 0.5 mg/kg, DMSO; [h] iv, 0.25 mg/kg, DMSO. [i] 2 mg/kg, 1% Tween-80, 2% HPMC, 97% water adjusted pH 2.

Table 6. Pharmacokinetic Parameters for **48** (Monomethansulfonic Salt) in Mouse, Dog, and Cyno

species	Cl ((L/h)/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	MRT (h)	*F* (%)
mouse	0.2[a]	4.8[a]	17[a]	23[a]	24[b]
dog	0.1[c]	6.7[c]	48[c]	66[c]	72[b]
cyno	0.2[c]	4.3[c]	56[c]	22[c]	62[b]

[a] iv, 3 mg/kg, propylene glycol. [b] po, 10 mg/kg, OraPlus. [c] iv, 1 mg/kg, propylene glycol.

As summarized in Table 4, a brief examination of modifications to the tether that serves to link the naphthyl ring and the heterocycle binding the hinge region revealed that alteration to this tether has a dramatic effect on KDR inhibition. Replacement of the ether linkage in **48** with the amine tether in **81** resulted in less than 2-fold decrease in cell potency but an almost 10-fold loss in selectivity. Furthermore, methylation of this amine provided **82**, which displayed a further 140-fold reduction of activity on KDR. The disparity between **81** and **82** may arise from the methyl group on the amine disrupting the coplanarity of the quinoline and naphthyl rings by generating a steric clash between the *N*-methyl group and the C5 hydrogen on the quinoline.

Pharmacokinetic Profiles. After the features necessary for potent and selective KDR inhibitors were established, the pharmacokinetic profiles of several compounds were evaluated (Table 5). Compounds **48**, **64–66**, **70**, and **78** all exhibited low to moderate intrinsic clearance in rat (RLM) and human (HLM) liver microsomes. Given the propensity of nitrogen containing heterocycles to bind to the heme of cytochrome P450, this set of compounds was screened against the 3A4 and 2D6 isoforms. With the exception of the pyridyl-containing compounds (**64–66**), no significant levels of Cyp inhibition were observed. However, the 4-pyridyl derivative **66** strongly inhibited both 3A4 and 2D6 Cyp isoenzymes with estimated IC_{50} values of 100 and 700 nM, respectively. The position of the nitrogen in the ring had a dramatic effect on the inhibitory activity at the 3A4 and 2D6 isoforms, and the 2-pyridyl derivative **64** had a favorable profile with IC_{50} values above 10 μM.

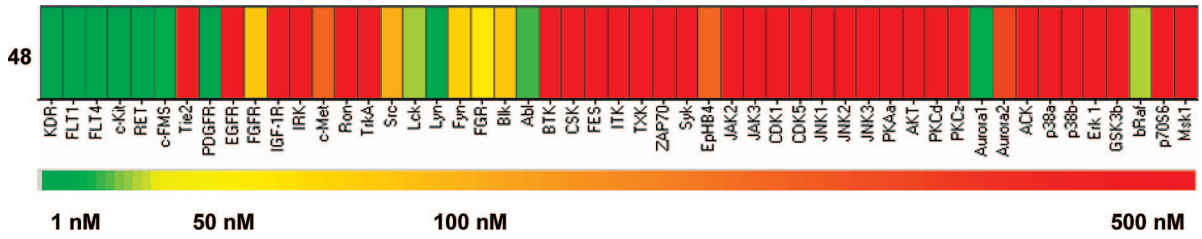


Figure 4. Selectivity profile of compound **48**.

Table 7. Enzyme and Cellular Selectivity Profile for Compound **48**

enzyme	IC_{50} (nM)	cell	functional readout[a]	IC_{50} (nM)
KDR	0.5	HUVEC	proliferation[b]	8
c-FMS	20	Balb/c3T3	proliferation[c]	25
PDGFR-β	<1	NHDF	proliferation[d]	25
FGFR-2	55	HUVEC	proliferation[e]	>1140
Lck	38	T cell	proliferation[f]	>20000
Aurora B	18	Hela cell	histone H3 phosphorylation	1100
b-Raf V600E	40	A375 (melanoma)	Erk phosphorylation	>1000

[a] Stimulation. [b] VEGF. [c] CSF-1. [d] PDGF. [e] FGF. [f] Anti-CD3.

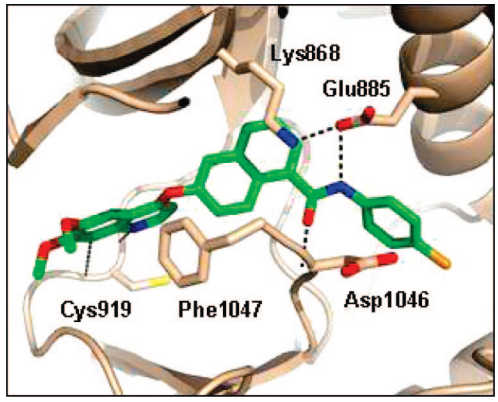


Figure 5. X-ray crystal structure of compound **48** bound to KDR.

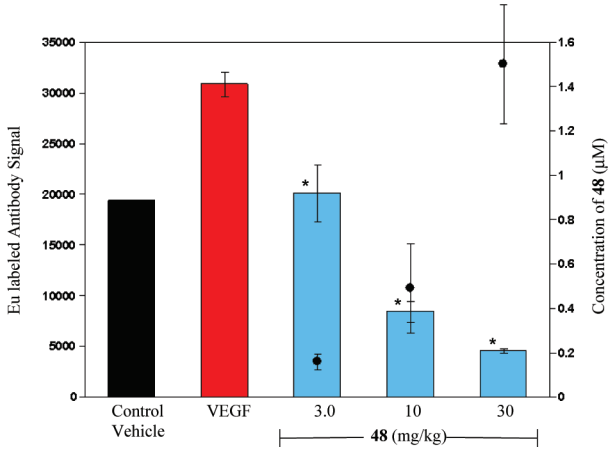


Figure 6. Inhibition of murine KDR (Flk-1) phosphorylation in lungs by compound **48** ($n = 3$ animals per group): (*) $P \leq 0.0001$.

Consistent with their low in vitro metabolic turnover in RLM, the naphthamides examined were cleared at low to moderate rates after dosing to male Sprague–Dawley rats. The highest rates of clearance were observed for 3-pyridyl **65** and 3-methyl-5-isoxazolyl **70** at 0.9 and 1.3 (L/h)/kg, respectively. All of the compounds examined demonstrated acceptable bioavailability and suitable half-lives.[31] The extended mean retention time (MRT) exhibited by compounds **48** and **78** (24 and 17 h) is a

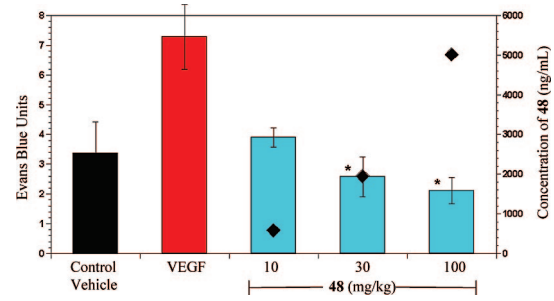


Figure 7. Effect of **48** on VEGF-induced vascular permeability in mice. HEK 293 cells transfected with murine VEGF or vector were mixed with Matrigel and injected subcutaneously into CD-1 nu/nu mice. A single dose of compound was given and vascular permeability in the skin overlying the Matrigel plug assessed 6 h later. Data represent the mean ± standard error ($n = 5$ animals per group): (*) $P \leq 0.0001$.

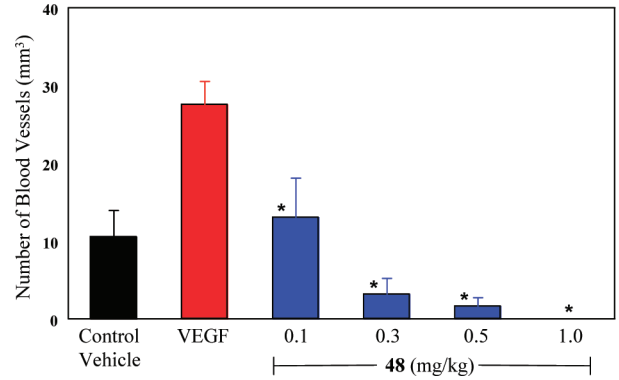


Figure 8. Inhibition of VEGF-induced angiogenesis in the rat corneal model by **48**. Angiogenesis was induced by implanting a VEGF-soaked or BSA-soaked (control) nylon disk into the corneal stroma. The number of blood vessels intersecting the midpoint between the disk and the limbus was measured. Data represent the mean ± standard error ($n =$ 8 animals per group): (*) $P \leq 0.001$.

reflection of the low clearance (0.1–0.2 (L/h)/kg) and moderate to high V_{ss} (2.4–7.3 L/kg) exhibited by these two compounds.

To assess the potential for metabolic activation of the naphthamide moiety of **48**, ^{14}C labeled **48** was synthesized and incubated with human liver microsomes.[32,33] No significant levels of covalent binding were observed (<100 (pM/mg)/h).

On the basis of its impressive in vitro profile and rat pharmacokinetics, an expanded PK profile of compound **48** across species was obtained. As illustrated in Table 6, compound **48** demonstrated low clearance and acceptable oral bioavailability in mouse, dog, and monkey (cynomolgous). Analogous to the pharmacokinetics that compound **48** exhibited in rats, the low clearance and high volume of distribution were observed across all species and in turn gave rise to extended MRTs (22–66 h). The measured plasma protein binding of compound **48** in rat, mouse, dog, and human was 98.0%, 98.6%, 97.4%, and 99.3%, respectively.

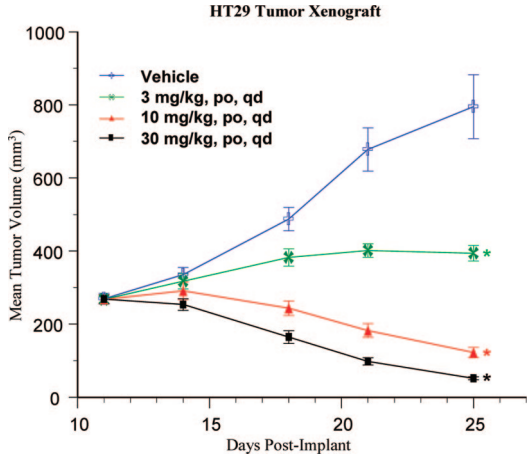


Figure 9. Antitumor activity upon treatment with **48** or vehicle in an HT29 colon cancer xenograft in CD-1 nu/nu mice ($n = 10$ animals per group): (*) $P \leq 0.0001$.

Table 8. In Vivo Antitumor Activity of **48** against Established Human HT29 Colon Cancer Xenografts Implanted Subcutaneously in CD-1 Nu/Nu Mice[a]

dose (mg/kg)[b]	effect	AUC_{0-24} (μM·h)	C_{max} (μM)
3	74% inhibition	6.2	0.5
10	regression	24.1	2.2
30	regression	48.4	3.9

[a] $n = 10$ animals per group. [b] The freebase was dosed po as a suspension in OraPlus.

Selectivity Profile. Prior to an in vivo pharmacological evaluation of compound **48**, the kinase selectivity profile was examined. As shown by the heat map in Figure 4, **48** was a pan VEGFR inhibitor displaying an IC_{50} value of 0.5 nM for VEGFR-1 (Flt-1) and 2.0 nM for VEGFR-3 (Flt-4). Compound **48** exhibited selectivity over a variety of tyrosine and serine/threonine kinases (~500-fold: IGF-1R, CDK1, CDK5, JNK, BTK, etc.).[34] More importantly, compound **48** was selective against numerous receptor tyrosine kinases implicated in angiogenic processes. Toward this end, compound **48** was highly selective against FGFR1, c-Met, and Tie-2 while it showed modest activity against PDGFR-β. Consistent with the kinome, **48** strongly inhibited the VEGF-related kinases PDGFR-β, c-Kit, and c-Fms. The implication of the potency of **48** against other kinases was further examined at the cellular level (Table 7). In addition to VEGF driven HUVEC proliferation, **48** inhibited the proliferation of Balb/c3T3 cells stimulated with CSF-1 and of NHDF cells stimulated with PDGF, in agreement with its inhibitory activity on c-FMS and PDGFR, respectively. However, inhibition of FGFR-2, Lck, Aurora B (Aurora 1), and b-Raf did not translate into any significant cellular activity.

X-Ray Structural Analysis. In an effort to confirm the binding elements responsible for the observed potency and to substantiate our original design hypothesis, an X-ray cocrystal structure of KDR with naphthamide **48** was obtained. As illustrated in Figure 5, **48** bound to the ATP binding site of KDR and forced the protein to adopt a "DFG-out" conformation, enabling the *p*-chlorophenyl ring to penetrate into the extended hydrophobic pocket (PDB accession code 3B8Q). A highly conserved hydrogen-bond interaction between the backbone amide-NH of Cys919 and the nitrogen of the quinoline ring anchors the inhibitor to the hinge region of the binding pocket and orients the naphthyl ring into the hydrophobic pocket. The carbonyl and NH groups of the amide form critical hydrogen bonds with the backbone NH of Asp1046 and the side chain of Glu885, respectively.

Pharmacodynamic Profile. The in vivo inhibitory activity of compound **48** for the VEGF RTK was assessed by measuring the inhibition of murine KDR (Flk-1) phosphorylation in mouse lungs. In addition, the in vivo pharmacological properties of compound **48** were evaluated in a VEGF-induced vascular permeability assay, a VEGF-induced rat corneal angiogenesis model, and a tumor xenograft disease model. Results of these in vivo studies are described below.

Murine KDR (Flk-1) Lung Phosphorylation Assay. Balb/c female mice were dosed orally with compound **48** at 3, 10, and 30 mpk. Two hours after dosing with **48**, 3 μg of murine VEGF was injected intravenously, and after 5 min the mice were sacrificed and the lungs were immediately dissected. Levels of phosphorylated Flk-1 were subsequently determined by Delphia assay. As shown in Figure 6, a dose dependent inhibition of Flk-1 phosphorylation was observed with significant inhibition seen at all doses tested ($P < 0.0001$). At the three doses examined, terminal plasma levels of compound **48** were measured to be 0.16, 0.49, and 1.5 μM.

Matrigel Plug Assay. Vascular permeability was induced in female CD-1 nu/nu mice by subcutaneous implantation of a Matrigel plug containing HEK293 cells overexpressing recombinant murine VEGF. After 22 h, a single dose of compound **48** was administered orally at 10, 30, and 100 mg/kg. After an additional 6 h, an iv injection of 0.1 mL 1% Evans blue dye was administered. Vascular permeability was quantified by the amount of extravasated dye in a 1 cm^2 piece of skin overlying the plug. A dose dependent inhibition of vascular permeability was observed with statistically significant effects being seen at doses of 30 and 100 mg/kg (Figure 7). At the active doses of 30 and 100 mg/kg, the plasma concentrations of **48** at $t = 6$ h were 4.0 and 10.3 μM, respectively.

Rat Corneal Assay. Compound **48** was also evaluated in the rat corneal angiogenesis model (Figure 8). Female Sprague–Dawley rats were implanted with a VEGF- or BSA-soaked disk into the corneal stroma. Compound **48** was administered once daily (QD) for 7 days, at which point the corneas were photographed and the number of blood vessels was measured. A dose dependent decrease in the number of blood vessels was observed with an estimated ED_{50} of 0.1 mg/kg. Pharmacokinetic analysis determined the corresponding AUC and C_{max} to be 1.3 μM·h and 0.2 μM, respectively.

Tumor Xenograft Model. The antitumor activity of **48** was measured in a human colon adenocarcinoma (HT29) xenograft model in female CD-1 nu/nu mice (Figure 9). Mice bearing tumors staged at approximately the same size (300 mm^3) were dosed orally with vehicle or **48** once a day for 14 days. The tumor volume was determined twice per week by caliper measurements and recorded along with body weights as an indicator of gross toxicity. Significant inhibition of tumor growth was observed at doses of 3, 10, and 30 mg/kg, and significant tumor regression was observed at doses of 10 and 30 mg/kg after 7 and 10 days, respectively (Table 8). These strong pharmacological effects were observed without any significant weight loss.

Conclusions

Guided by the X-ray structures of two inhibitors bound to the VEGF receptor tyrosine kinase, a novel series of potent inhibitors, naphthamides, were designed and evaluated. Through modification of the different units of this scaffold, we identified several potent and selective compounds. Among them, **48** demonstrated good pharmacokinetics across species and robust pharmacological activity that included in vivo inhibition of

angiogenesis and regression of established HT29 tumors in female CD-1 nu/nu mice. Further optimization of this series of KDR inhibitors toward the selection of a clinical candidate will be reported in due course.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were purchased from Aldrich packaged under nitrogen in Sure/Seal bottles. Purity of final compounds was measured using Agilent 1100 series high-performance liquid chromatography (HPLC) systems with UV detection at 254 nm (system A consisting of Agilent Zorbax Eclipse XDB-C8 4.6 mm × 150 mm, 5 μm, 5–100% CH_3CN in H_2O with 0.1% TFA for 15 min at 1.5 mL/min; system B consisting of Phenomenex Gemini, 3.0 mm × 50 mm, 5 μm, 5–95% CH_3CN in H_2O with 0.1% FA for 3 min at 1.5 mL/min); system C consisting of Waters Xterra 4.6 mm × 150 mm, 3.5 μm, 5–95% CH_3CN in H_2O with 0.1% TFA for 12 min at 1.0 mL/min. ^{1}H NMR spectra were recorded on a Bruker AV-4000 (400 MHz) spectrometer at ambient temperature. Chemical shifts are reported in ppm from the solvent resonance (DMSO-d_6, 2.50 ppm; $CDCl_3$, 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Low-resolution mass spectral (MS) data were determined on an Agilent 1100 series LCMS with UV detection at 254 nm and a low-resonance electrospray mode (ESI). High-resolution mass spectra were obtained on a high-resonance electrospray time-of-flight mass spectrometer. Combustion analysis was performed by Galbraith Laboratories, Inc., Knoxville, TN, and were within 0.4% of calculated mass unless otherwise noted.

Methyl 5-Fluoro-6-hydroxy-1-naphthoate (11). To a solution of 6-hydroxy-1-naphthoic acid (**10**, 10.00 g, 53.1 mmol) in 500 mL of methanol at 0 °C was added thionyl chloride (6.28 g, 53.1 mmol). The mixture was allowed to warm to ambient temperature and was stirred for 12 h before being concentrated to provide the corresponding methyl ester (10.53 g, 98%) as a colorless oil. To a solution of the derived ester (7.00 g, 34.6 mmol) in 60 mL of CH_3CN was added Selectfluor (12.3 g, 34.6 mmol). The mixture was heated at 85 °C for 24 h before being allowed to cool to room temperature. The mixture was diluted with ethyl acetate (500 mL) and sequentially washed with water (250 mL) and brine. Drying over sodium sulfate followed by filtration and concentration provided a residue that was purified by silica gel chromatography (100% CH_2Cl_2) to provide the title compound (3.81 g, 50%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.32 (s, 1 H), 8.40 (d, J = 8.88 Hz, 1 H), 8.14 (d, J = 8.44 Hz, 1 H), 7.96 (d, J = 8.43 Hz, 1 H), 7.59 (t, J = 8.43 Hz, 1 H), 7.37 (t, J = 9.88 Hz, 1 H), 3.90 (s, 3 H). MS, m/z ($C_{12}H_9FO_3$): calcd, 220.1; found, 221.0 (MH).

Methyl-5-fluoro-6-hydroxy-1-naphthoic Acid (12). To a solution of methyl 5-fluoro-6-hydroxy-1-naphthoate (**11**, 3.70 g, 16.8 mmol) in 100 mL of methanol was added a solution of NaOH (50.4 g, 1.26 mol) in 30 mL of water. After heating at 80 °C for 20 h, the mixture was allowed to cool to room temperature and was poured into 200 mL of 1 N HCl, resulting in the formation of a slightly yellow precipitate. HCl (6 N) was slowly added until the formation of no additional precipitate was observed. The solid was filtered and washed with water to provide the title compound (3.20 g, 92%) as a slightly yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.27 (s, 1 H), 8.51 (d, J = 9.63 Hz, 1 H), 8.10 (d, J = 7.63 Hz, 1 H), 7.96 (d, J = 7.18 Hz, 1 H), 7.57 (t, J = 8.03 Hz, 1 H), 7.35 (t, J = 9.18 Hz, 1 H). MS, m/z ($C_{12}H_7FO_3$): calcd, 206.1; found, 207.3 (MH).

Methyl 7-Methoxyquinoline-4-carboxylate (14). A 25 mL sealable tube was charged with 4-chloro-7-methoxyquinoline (**13**, 0.60 g, 3.10 mmol), $Pd(OAc)_2$ (67 mg, 0.30 mmol), 1,3-bis(diphenylphosphino)propane (185 mg, 0.45 mmol), triethylamine (0.87 mL, 6.20 mmol), MeOH (1 mL), and DMF (5 mL). The mixture was purged with carbon monoxide for 10 min and then placed under 50 psi of CO. The reaction vessel was sealed and heated at 70 °C. After heating for 6 h, additional $Pd(OAc)_2$ (134 mg, 0.60 mmol) and 1,3-bis(diphenylphosphino)propane (370 mg, 0.90 mmol) were added. The mixture was again purged with carbon monoxide for 10 min, placed under 50 psi of CO, then sealed and heated at 70 °C for 16 h. The mixture was allowed to cool to room temperature and was passed through a plug of Celite before being concentrated and purified by silica gel chromatography to provide the title compound (400 mg, 59%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (d, J = 4.44 Hz, 1 H), 8.52 (d, J = 9.60 Hz, 1 H), 7.77 (d, J = 4.45 Hz, 1 H), 7.50 (s, 1 H), 7.39 (t, J = 9.70 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). MS, m/z ($C_{12}H_{11}NO_3$): calcd, 217.1; found, 218.0 (MH).

7-Hydroxyquinoline-4-carboxylic Acid (15). To a solution of methyl 7-methoxyquinoline-4-carboxylate (**14**, 378 mg, 1.74 mmol) in 25 mL of CH_2Cl_2 at 0 °C was added boron tribromide (1.0 M in CH_2Cl_2, 9.0 mL). The mixture was allowed to warm to room temperature over 3 h and maintained at ambient temperature for an additional 48 h. The reaction was quenched with ice (50 g), which resulted in the formation of a yellow solid. The derived solid was filtered and washed with ether to provide the title compound (233 mg, 60%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.10 (d, J = 4.51 Hz, 1 H), 8.50 (d, J = 9.50 Hz, 1 H), 7.60 (d, J = 4.54 Hz, 1 H), 7.55 (s, 1 H), 7.37 (t, J = 9.72 Hz, 2 H). MS, m/z ($C_{10}H_7NO_3$): calcd, 189.1; found, 190.1 (MH).

8-Bromoisoquinolin-3-ol (17). To a solution of 2,2-diethoxyacetic acid (16.8 g, 113.5 mmol) in 90 mL of ether was added sulfuryl dichloride (8.259 mL, 113.5 mmol). After being stirred at 10 °C for 10 min, the mixture was heated to reflux for 30 min and then cooled to room temperature. The derived acid chloride was used immediately in the next step. To a solution of the derived acid chloride (18.91 g, 113.5 mmol) in Et_2O (90 mL) was added a solution of (2-bromophenyl)methanamine (21.11 g, 113.5 mmol) in 60 mL of toluene and 35 mL of pyridine. The mixture was heated to reflux for 30 min before being cooled to room temperature and partitioned between toluene (100 mL) and ice–water (250 mL). The layers were separated, and the aqueous layer was extracted with toluene (3 × 100 mL). The combined organic extracts were washed with 2% HCl and water and concentrated in vacuo. The resulting residue was purified by silica gel chromatography to provide *N*-(2-bromobenzyl)-2,2-diethoxyacetamide (22.8) as a light-yellow oil. MS, m/z ($C_{13}H_{18}BrNO_3$): calcd, 315.0; found, 316.2 (MH).

To concentrated sulfuric acid (100 g) at 10 °C was added the derived *N*-(2-bromobenzyl)-2,2-diethoxyacetamide (22.8 g, 72.1 mmol). The resulting solution was allowed to warm to room temperature and was stirred for 24 h. The mixture was poured into ice–water (250 mL) and filtered, and the filtrate was neutralized with 33% ammonium hydroxide. The resulting solid was filtered to provide the title compound (15.9 g, 62%) as a bright-yellow solid. MS, m/z (C_9H_6BrNO): calcd, 223.0; found, 224.1 (MH).

Methyl 3-Hydroxyisoquinoline-8-carboxylate (18). To a pressure vessel was added 8-bromoisoquinolin-3-ol (**17**, 5.00 g, 22.3 mmol), 1,3-bis(diphenylphosphino)propane (552 mg, 1.34 mmol), and $Pd(OAc)_2$ (200 mg, 0.893 mmol) followed by 15 mL of DMF, 25 mL of methanol, and triethylamine (7.76 mL, 55.8 mmol). The vessel was purged three times with carbon monoxide, pressurized to 30 psi, and heated to 100 °C for 12 h. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and washed successively with water and brine. Purification by silica gel chromatography provided the title compound (0.960 g, 21% yield) as a yellow solid. MS, m/z ($C_{11}H_9NO_3$): calcd, 203.1; found, 204.1 (MH).

Methyl 6-(Trifluoromethylsulfonyloxy)-1-naphthoate (20). To a solution of methyl 6-hydroxy-1-naphthoate (**19**, 1.50 g, 7.40 mmol) in 100 mL of CH_2Cl_2 at −78 °C was added DIPEA (3.80 mL, 22.0 mmol) and triflic anhydride (1.55 mL, 9.25 mmol). Stirring was continued at this temperature for 1 h at which point the mixture was poured into saturated NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2

(3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography provided the title compound (2.21 g, 89%) as a light-brown solid. MS, *m/z* ($C_{13}H_9F_3O_5S$): calcd, 334.0; found, 335.1 (MH).

Methyl 6-Amino-1-naphthoate (21). In a 250 mL sealable tube were added $Pd_2(dba)_3$ (55 mg, 0.06 mmol), (biphenyl)dicyclohexylphosphine (84 mg, 0.23 mmol), potassium phosphate (1.90 g, 8.90 mmol), and dimethoxyethane (10 mL). The mixture was degassed for 10 min at which point methyl 6-(trifluoromethylsulfonyloxy)-1-naphthoate (**20**, 2.00 g, 6.0 mmol) and benzophenone imine (1.25 mL, 7.5 mmol) were added. The flask was sealed and heated at 90 °C for 8 h. The mixture was allowed to cool to room temperature, and 4 mL of 2 N HCl was added. After the mixture was stirred for 30 min, 50 mL of ethyl acetate was added and the pH was adjusted to 10 with 6 N NaOH. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The derived residue was purified by silica gel chromatography (0–30% ethyl acetate in hexanes) to provide **21** (1.15 g, 95%) as a light-brown oil that was used immediately in the next step. MS, *m/z* ($C_{12}H_{11}N_2O_2$): calcd, 201.1; found, 202.1 (MH).

Methyl 4-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino)-2-methoxybenzoate (23). A suspension of methyl 4-amino-2-methoxybenzoate (**22**, 10.00 g, 55.19 mmol) in 200 mL of isopropanol was heated at 50 °C for 10 min at which point 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (9.64 g, 51.78 mmol) was added. The resulting suspension was heated at 80 °C for 1 h before being cooled to room temperature. The solid was filtered, washed well with ether, and dried in vacuo to provide the title compound (**23**, 15.25 g, 82%) as a brown solid that was immediately used in the next step.

Methyl 7-Methoxy-4-oxo-1,4-dihydroquinoline-6-carboxylate (24). A suspension of methyl 4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino)-2-methoxybenzoate (**23**, 15.00 g, 53.96 mmol) in 135 mL of diphenyl ether was heated at 240 °C for 8 h. The mixture was cooled to room temperature and filtered. The resulting brown solid was washed with ether and dried in vacuo to provide methyl 7-methoxy-4-oxo-1,4-dihydroquinoline-6-carboxylate (**24**, 9.60 g, 76%) as a brown solid that was used without further purification.

4-Chloro-7-methoxyquinoline-6-carboxamide (25). Methyl 7-methoxy-4-oxo-1,4-dihydroquinoline-6-carboxylate (**24**, 5.00 g, 21.46 mmol) was added to 20 mL of thionyl chloride. Three drops of DMF were added, and the mixture was heated at 125 °C for 3 h. The mixture was cooled to room temperature, and the solvent was removed in vacuo. The derived solid was taken up in CH_2Cl_2 (250 mL) and poured into saturated $NaHCO_3$ (500 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (250 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to provide a tan solid. Trituration of the solid with ether/hexanes provided methyl 4-chloro-7-methoxyquinoline-6-carboxylate (4.70 g, 87%) as a tan solid. The derived ester (1.00 g, 3.97 mmol) was added to ammonium hydroxide (20 mL), and the mixture was heated at 110 °C for 8 h before being cooled to room temperature. The mixture was filtered and the resulting solid was washed sequentially with water and ether to provide the title compound (852 mg, 91%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (d, J = 4.80 Hz, 1 H), 8.49 (s, 1 H), 7.90 (br s, 1 H), 7.80 (br s, 1 H), 7.65 (d, J = 4.80 Hz, 1 H), 7.59 (s, 1 H), 4.03 (s, 3 H). MS, *m/z* ($C_{11}H_9ClN_2O_2$): calcd, 236.0; found, 237.1 (MH).

4-Fluoro-6,7-dimethoxyquinoline (27). A mixture of 4-chloro-6,7-dimethoxyquinoline (**26**, 0.200 g, 0.89 mmol) and tetrabutylphosphonium fluoride hydrofluoride (1.9 g, 6.3 mmol) was heated to 120 °C in a resealable tube. After 1 h, additional tetrabutylphosphonium fluoride hydrofluoride (0.95 g, 3.1 mmol) was added and the solution was heated at 120 °C for an additional 48 h. The solution was cooled to room temperature, diluted with ethyl acetate, and washed with water and brine. The organic fraction was dried over Na_2SO_4, concentrated in vacuo, and purified by reverse-phase chromatography to provide the title compound (0.032 g, 17%) as a white solid. MS, *m/z* ($C_{11}H_{10}FNO_2$): calcd, 207.1; found, 208.1 (MH).

6-(2-(Methylcarbamoyl)pyridin-4-yloxy)-1-naphthoic Acid (31c). To a solution of 6-hydroxynaphthoic acid (**10**, 1.50 g, 7.98 mmol) in 20 mL of DMSO was added cesium carbonate (7.80 g, 24.0 mmol). After the mixture was stirred for 5 min, 4-chloro-*N*-methylpicolinamide (1.36 g, 7.98 mmol) was added and the resulting slurry was heated to 140 °C for 16 h. The mixture was allowed to cool to room temperature and was purified by silica gel chromatography (0–10% CH_3OH in CH_2Cl_2) to provide a pink oil. The derived oil was taken up in 400 mL of ethyl acetate and was washed with water (3 × 150 mL). The organics were washed with brine, dried over sodium sulfate, and filtered. Concentration to 10% of the original volume provided a purple mixture that was placed in the refrigerator overnight. The resulting precipitate was filtered and washed with ethyl acetate (2 × 50 mL) to provide the title compound (1.75 g, 68%) as a slightly pink solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.29 (s, 1 H), 9.03 (d, J = 9.35 Hz, 1 H), 8.80 (d, J = 4.93 Hz, 1 H), 8.56 (d, J = 5.56 Hz, 1 H), 8.14–8.22 (m, 2 H), 7.89 (d, J = 2.53 Hz, 1 H), 7.62–7.70 (m, 1 H), 7.55 (dd, J = 9.35, 2.53 Hz, 1 H), 7.48 (d, J = 2.65 Hz, 1 H), 7.26 (dd, J = 5.56, 2.53 Hz, 1 H), 2.79 (d, J = 4.80 Hz, 3 H). MS, *m/z* ($C_{18}H_{14}N_2O_4$): calcd, 322.1; found, 323.1 (MH).

6-(6,7-Dimethoxyquinolin-4-yloxy)-1-naphthoic Acid (29a). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 24.2 g, 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.29 (s, 1 H), 9.05 (d, J = 9.35 Hz, 1 H), 8.56 (d, J = 5.43 Hz, 1 H), 8.13–8.23 (m, 2 H), 7.95 (d, J = 2.53 Hz, 1 H), 7.62–7.70 (m, 2 H), 7.61 (s, 1 H), 7.48 (s, 1 H), 6.67 (d, J = 5.56 Hz, 1 H), 3.99 (s, 3 H), 3.97 (s, 3 H). MS, *m/z* ($C_{22}H_{17}NO_5$): calcd, 375.1; found, 376.3 (MH).

6-(Quinolin-4-yloxy)-1-naphthoic Acid (29b). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 10.4 g, 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.03 (d, J = 9.17 Hz, 1 H), 8.70 (d, J = 5.13 Hz, 1 H), 8.35 (d, J = 8.43 Hz, 1 H), 8.13–8.16 (m, 2 H), 8.05 (d, J = 8.04 Hz, 1 H), 7.91 (d, J = 2.19 Hz, 1 H), 7.84 (t, J = 7.33 Hz, 1 H), 7.60–7.69 (m, 3 H), 6.72 (d, J = 5.13 Hz, 1 H). MS, *m/z* ($C_{20}H_{13}NO_3$): calcd, 315.3; found, 316.3 (MH).

6-(7-Methoxyquinolin-4-yloxy)-1-naphthoic Acid (29c). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 807 mg, 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.00 (d, J = 8.72 Hz, 1 H), 8.61 (d, J = 4.13 Hz, 1 H), 8.22 (d, J = 9.10 Hz, 1 H), 8.15 (d, J = 4.85 Hz, 1 H), 7.88 (s, 1 H), 7.48–7.52 (m, 3 H), 7.42 (s, 1 H), 7.29 (d, J = 9.10 Hz, 1 H), 6.58 (d, J = 5.20 Hz, 1 H), 3.93 (s, 3 H). MS, *m/z* ($C_{21}H_{15}NO_4$): calcd, 345.1; found, 346.3 (MH).

6-(6,7-Dimethoxyquinazolin-4-yloxy)-1-naphthoic Acid (29d). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 900 mg, 68%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.06 (d, J = 9.17 Hz, 1 H), 8.51 (s, 1 H), 7.63–7.68 (m, 2 H), 7.68 (d, J = 7.29 Hz, 1 H), 7.41 (s, 1 H), 7.38–7.40 (m, 2 H), 7.33 (d, J = 9.18 Hz, 1 H), 3.98 (s, 6 H). MS, *m/z* ($C_{21}H_{16}N_2O_5$): calcd, 376.1; found, 377.3 (MH).

6-(6-Carbamoyl-7-methoxyquinolin-4-yloxy)-1-naphthoic Acid (29e). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 623 mg, 46%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.07 (d, J = 9.35 Hz, 1 H), 8.70–8.78 (m, 2 H), 8.20 (d, J = 7.58 Hz, 2 H), 7.99 (d, J = 2.40 Hz, 1 H), 7.93 (br s, 1 H), 7.80 (br s, 1 H), 7.63–7.71 (m, 2 H), 7.60 (s, 1 H), 6.71 (d, J = 5.43 Hz, 1 H), 4.07 (s, 3 H). MS, *m/z* ($C_{22}H_{16}N_2O_5$): calcd, 388.1; found, 389.1 (MH).

6-(3-Fluoro-6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic Acid (29f). A resealable tube was charged with 4-chloro-3-fluoro-6,7-dimethoxyquinoline (0.610 g, 2.52 mmol), 6-hydroxy-1-naphthoic acid (**10**, 0.474 g, 2.52 mmol), palladium acetate (0.023 g, 0.101 mmol), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl (0.086 g, 0.202 mmol), potassium phosphate (2.14 g, 10.08 mmol), and DMF (13 mL). The system was flushed with argon, and the tube was sealed. The mixture was stirred at 100 °C for 19 h and then cooled to room temperature. Water (13 mL) was added, and the pH was adjusted to 6–7 with aqueous 6 N HCl. The resulting precipitate was filtered, washed with water, and then purified by column chromatography on silica gel to afford the title compound (0.301 g, 30%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (d, J = 9.7 Hz, 1 H), 8.85 (s, 1 H), 7.89–8.08 (m, 2 H), 7.48–7.63 (m, 3 H), 7.41 (d, J = 3.2 Hz, 1 H), 7.26 (s, 1 H), 3.96 (s, 3 H), 3.81 (s, 3 H). MS, m/z ($C_{22}H_{16}FNO_5$): calcd, 393.1; found, 394.0 (MH).

6-(Pyridin-4-yloxy)-1-naphthoic Acid (31a). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 1.09 g, 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.26 (s, 1 H), 9.00 (d, J = 9.35 Hz, 1 H), 8.48–8.53 (m, 2 H), 8.14–8.20 (m, 2 H), 7.83 (d, J = 2.53 Hz, 1 H), 7.61–7.68 (m, 1 H), 7.52 (dd, J = 9.41, 2.59 Hz, 1 H), 7.04 (dd, J = 4.80, 1.52 Hz, 2 H). MS, m/z ($C_{16}H_{11}NO_3$): calcd, 265.1; found, 266.1 (MH).

6-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-1-naphthoic Acid (31b). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 3.32 g, 38%. MS, m/z ($C_{17}H_{11}N_3O_3$): calcd, 305.1; found, 306.1 (MH).

6-(Pyrimidin-4-yloxy)-1-naphthoic Acid (31d). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. Yield: 5.92 g, 87%. MS, m/z ($C_{15}H_{10}N_2O_3$): calcd, 266.1; found, 267.1 (MH).

6-(2-(Methylamino)pyridin-4-yloxy)-1-naphthoic Acid (34a). Carboxylic acid **33a** was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. This procedure furnished 6-(pyridin-4-yloxy)-1-naphthoic acid (**33a**, 2.55 g, 68%) as an off-white solid. Acid **33a** (6.60 g, 22.0 mmol) was added to a melt of *N*-methylamine hydrochloride (73.6 g, 109 mmol) at 235 °C in one portion. The mixture was maintained at this temperature for 3 min at which point it was removed from the oil bath and allowed to cool to room temperature. To the resulting brown oil were added water (100 mL) and ethyl acetate (100 mL). After the mixture was stirred for 30 min, the resulting white precipitate was filtered and washed with ethyl acetate. Purification of this residue by silica gel chromatography (5% CH_3OH in CH_2Cl_2) provided the title compound (4.90 g, 76%) as a white solid. MS, m/z ($C_{17}H_{14}N_2O_3$): calcd, 294.1; found, 295.3 (MH).

6-(6-(Methylamino)pyrimidin-4-yloxy)-1-naphthoic Acid (34b). Carboxylic acid **33b** was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. This procedure furnished 6-(6-chloropyrimidin-4-yloxy)-1-naphthoic acid (**33b**, 1.55 g, 38%) as an off-white solid. The title compound was prepared from **33b** using a method analogous to the preparation of **33a**. Yield: 1.50 g, 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.90 (d, J = 9.17 Hz, 1 H), 8.11–8.12 (m, 3 H), 7.76 (s, 1 H), 7.59 (t, J = 7.33 Hz, 1 H), 7.43 (d, J = 9.16 Hz, 1 H), 7.34 (s, 1 H), 5.84 (s, 1 H), 2.76 (s, 3 H). MS, m/z ($C_{16}H_{13}N_3O_3$): calcd, 295.1; found, 296.1 (MH).

6-(2-(Methylamino)pyrimidin-4-yloxy)-1-naphthoic Acid (34c). The title compound was prepared from 6-hydroxy-1-naphthoic acid (**10**) using a method analogous to the preparation of compound **31c**. This procedure furnished 6-(2-chloropyrimidin-4-yloxy)-1-naphthoic acid (**33c**, 6.00 g, 88%) as a white solid. The derived acid **33c** (1.00 g, 3.33 mmol) was taken up in 20 mL of THF and cooled to 0 °C at which point *N*-methylamine (16.6 mL, 2 M in THF) was added. The reaction vessel was sealed, and the solution was allowed to warm to room temperature where it was maintained for 8 h. Concentration and purification by silica gel chromatography provided **34c** (517 mg, 52%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (d, J = 9.16 Hz, 1 H), 8.20 (m, 1 H), 8.12 (t, J = 8.06 Hz, 2 H), 7.82 (s, 1 H), 7.59 (t, J = 7.70 Hz, 1 H), 7.49 (s, 1 H), 6.95 (s, 1 H), 6.21 (s, 1 H), 3.32 (s, 3 H). MS, m/z ($C_{16}H_{13}N_3O_3$): calcd, 295.1; found, 296.1 (MH).

6-(6,7-Dimethoxyquinolin-4-yloxy)-5-fluoro-1-naphthoic Acid (36a). The title compound was prepared from 5-fluoro-6-hydroxy-1-naphthoic acid (**12**) using a method analogous to the preparation of compound **31c**. Yield: 2.06 g, 56%. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 8.83 (d, J = 6.63 Hz, 1 H), 8.44 (d, J = 5.13 Hz, 1 H), 8.30 (d, J = 8.43 Hz, 1 H), 8.23 (d, J = 6.96 Hz, 1 H), 7.63–7.70 (m, 2H), 7.59 (s, 1H), 7.42 (s, 1H), 6.51 (d, J = 5.15 Hz, 1 H), 3.95 (s, 6H). MS, m/z ($C_{22}H_{16}FNO_5$): calcd, 393.1; found, 394.2 (MH).

3-(6,7-Dimethoxyquinolin-4-yloxy)isoquinoline-8-carboxylic Acid (36b). A mixture of 4-fluoro-6,7-dimethoxyquinoline (**27**, 0.150 g, 0.724 mmol), methyl 3-hydroxyisoquinoline-8-carboxylate (**18**, 0.294 g, 1.45 mmol), and cesium carbonate (0.590 g, 1.81 mmol) in DMF (3.0 mL) was combined in a sealable tube. The mixture was exposed to microwave radiation at 120 °C for 3 h at which point additional cesium carbonate (0.295 g, 0.90 mmol) was added and the whole was exposed to microwave irradiation at 120 °C for an additional 4 h. The mixture was cooled to room temperature, diluted with water (4 mL), and acidified to pH 3 with 1 N HCl. The resulting brown precipitate was filtered and washed with water to give the title compound (0.172 g, 0.45 mmol, 63% yield) as a brown solid. MS, m/z ($C_{21}H_{16}N_2O_5$): calcd, 376.1; found, 377.0 (MH).

7-(6,7-Dimethoxyquinolin-4-yloxy)quinoline-4-carboxylic Acid (36c). The title compound was prepared from 7-hydroxyquinoline-4-carboxylic acid (**15**) using a method analogous to the preparation of compound **31c**. Yield: 138 mg, 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.86 (d, J = 4.43 Hz, 1 H), 8.82 (d, J = 9.23 Hz, 1 H), 8.48 (d, J = 4.83 Hz, 1 H), 7.70 (s, 1 H), 7.61 (d, J = 4.00 Hz, 1 H), 7.51–7.54 (m, 2H), 7.41 (s, 1H), 6.63 (d, J = 4.85 Hz, 1 H), 3.94 (s, 3H), 3.90 (s, 3H). MS, m/z ($C_{22}H_{16}FNO_5$): calcd, 393.1; found, 394.2 (MH). MS, m/z ($C_{21}H_{16}N_2O_5$): calcd, 376.1; found, 377.3 (MH).

6-(6,7-Dimethoxyquinolin-4-ylamino)-1-naphthoic Acid (37a). A solution of methyl 6-amino-1-naphthoate (**21**, 300 mg, 1.50 mmol) and 4-chloro-6,7-dimethoxyquinoline (**35**, 416 mg, 1.80 mmol) in 6 mL of isopropyl alcohol was treated with trifluoroacetic acid (287 μL, 3.70 mmol). After the mixture was heated at 90 °C for 15 min, another 6 mL of isopropyl alcohol was added and the mixture was heated at 90 °C for 8 h. The mixture was allowed to cool to room temperature and placed in the refrigerator overnight. The resulting precipitate was filtered and washed with methanol to provide methyl 6-(6,7-dimethoxyquinolin-4-ylamino)-1-naphthoate (550 mg, 95%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.91 (d, J = 9.22 Hz, 1 H), 8.38 (d, J = 6.95 Hz, 1 H), 8.26 (d, J = 8.21 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, J = 7.20 Hz, 1 H), 8.16 (d, J = 2.02 Hz, 1 H), 7.80 (dd, J = 9.16, 2.21 Hz, 1 H), 7.65–7.73 (m, 1 H), 7.49 (s, 1 H), 6.92 (d, J = 6.95 Hz, 1 H), 4.04 (s, 3 H), 4.00 (s, 3 H), 3.98 (s, 3 H). MS, m/z ($C_{23}H_{20}N_2O_4$): calcd, 388.1; found, 389.1 (MH). A solution of the derived ester (275 mg, 0.71 mmol) in 5 mL of methanol was treated with 1.5 mL of 6 N NaOH. After the mixture was stirred for 8 h, the organics were removed in vacuo, the white mixture was diluted with 5 mL of water, and the pH was adjusted to 3–4 with 1 N HCl. The resulting solid was filtered and washed with ether to provide the title compound (256 mg, 94%) as a slightly green solid that was used immediately in the next step. MS, m/z ($C_{22}H_{18}N_2O_4$): calcd, 374.1; found, 375.1 (MH).

6-((6,7-Dimethoxyquinolin-4-yl)(methyl)amino)-1-naphthoic Acid (37b). To a suspension of methyl 6-(6,7-dimethoxyquinolin-4-ylamino)-1-naphthoate (125 mg, 0.32 mmol) in 3 mL of DMF at 0 °C was added sodium hydride (20 mg, 0.48 mmol). The resulting mixture was allowed to warm to room temperature for 30 min before being cooled to 0 °C at which point methyl iodide (30 μL, 0.48 mmol) was introduced. After warming to room temperature

and being stirred for 30 min, the orange mixture was recooled to 0 °C and additional sodium hydride (20 mg, 0.48 mmol) was added. After the mixture was stirred at 0 °C for 10 min, additional methyl iodide (30 μL, 0.48 mmol) was added to the reaction mixture. The mixture was allowed to warm to room temperature and was stirred for 1 h before being quenched with 10 mL of saturated NH_4Cl. Ethyl acetate (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organics were washed sequentially with water and brine before being dried over sodium sulfate. The mixture was filtered and concentrated to provide an orange residue. Purification by silica gel chromatography (0–10% CH_3OH in CH_2Cl_2) provided methyl 6-((6,7-dimethoxyquinolin-4-yl)(methyl)amino)-1-naphthoate (40 mg, 31%, two steps) as a yellow solid that was used immediately in the next step. MS, *m*/*z* ($C_{24}H_{22}N_2O_4$): calcd, 402.2; found, 403.3 (MH).

4-(5-((4-Chlorophenyl)carbamoyl)naphthalen-2-yloxy)-*N*-methylpicolinamide (6). To a suspension of 6-(2-(methylcarbamoyl)pyridin-4-yloxy)-1-naphthoic acid **31c** (50 mg, 0.15 mmol) in 2 mL of CH_2Cl_2 was added oxalyl chloride (28 μL, 0.31 mmol) followed by 1 μL of DMF. After being stirred for 45 min, the resulting suspension was concentrated to provide the corresponding acid chloride as a yellow solid. The derived solid was taken up in 2 mL of CH_2Cl_2 at which point triethylamine (108 mL, 0.77 mmol) and 4-chloroaniline (20 mg, 0.15 mmol) were added. After being stirred for 1 h, the mixture was concentrated and purified by silica gel chromatography (50% acetone in hexanes) to provide 4-(5-((4-chlorophenyl)carbamoyl)naphthalen-2-yloxy)-*N*-methylpicolinamide (**6**) (42 mg, 63%) as an off-white solid. HPLC purity: 99% (system A); 96% (system C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.78 (s, 1 H), 8.81 (d, J = 4.93 Hz, 1 H), 8.57 (d, J = 5.56 Hz, 1 H), 8.32 (d, J = 9.22 Hz, 1 H), 8.12 (d, J = 8.46 Hz, 1 H), 7.91 (d, J = 2.53 Hz, 1 H), 7.83–7.88 (m, 2 H), 7.81 (d, J = 6.57 Hz, 1 H), 7.65–7.72 (m, 1 H), 7.51 (dd, J = 9.22, 2.53 Hz, 1 H), 7.43–7.48 (m, 3 H), 7.28 (dd, J = 5.62, 2.59 Hz, 1 H), 2.79 (d, J = 4.93 Hz, 3 H). HRMS $(C_{24}H_{19}ClN_3O_3)^+$: calcd, 432.110 95; found, 432.111 05.

***N*-(4-Chlorophenyl)-6-(pyridin-4-yloxy)-1-naphthamide (40).** The title compound was prepared from 6-(pyridin-4-yloxy)-1-naphthoic acid (**31a**) using a method analogous to the preparation of compound **6**. Yield: 55 mg, 56%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.75 (s, 1 H), 8.51 (d, J = 6.19 Hz, 2 H), 8.31 (d, J = 9.22 Hz, 1 H), 8.10 (d, J = 8.34 Hz, 1 H), 7.81–7.89 (m, 3 H), 7.79 (d, J = 6.82 Hz, 1 H), 7.63–7.70 (m, 1 H), 7.41–7.51 (m, 3 H), 7.03 (dd, J = 4.80, 1.52 Hz, 2 H). HRMS $(C_{22}H_{16}ClN_2O_2)^+$: calcd, 375.089 48; found, 375.089 33. Anal. ($C_{22}H_{15}ClN_2O_2$) C, H, N.

***N*-(4-Chlorophenyl)-6-(2-(methylamino)pyridin-4-yloxy)-1-naphthamide (41).** To a solution of 6-(2-(methylamino)pyridin-4-yloxy)-1-naphthoic acid (**34a**, 170 mg, 0.58 mmol) and DIPEA (201 μL, 1.5 mmol) in 3 mL of DMF were added 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (223 mg, 0.69 mmol) and 4-chloroaniline (110 mg, 0.86). After the mixture was stirred for 5 h, the reaction was quenched with 1 mL of 1 N HCl. The pH was adjusted to 7 with 1 N NaOH, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed sequentially with water and brine before being dried over sodium sulfate and filtered. Concentration provided a residue that was purified by silica gel chromatography (0–10% CH_3OH in CH_2Cl_2) to provide the title compound (125 mg, 54%) as a white solid. HPLC purity: 91% (system A); 94% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.76 (s, 1 H), 8.53 (s, 1 H), 8.22–8.29 (m, 1 H), 8.07 (d, J = 8.08 Hz, 1 H), 7.92 (d, J = 6.69 Hz, 1 H), 7.85 (d, J = 8.21 Hz, 2 H), 7.75 (s, 2 H), 7.60–7.67 (m, 1 H), 7.37–7.48 (m, 2 H), 6.44–6.54 (m, 1 H), 6.21 (d, J = 3.66 Hz, 1 H), 5.91 (s, 1 H), 2.71 (s, 3 H). HRMS $(C_{23}H_{19}ClN_3O_2)^+$: calcd, 404.116 03; found, 404.11796. Anal. Calcd for $C_{23}H_{18}ClN_3O_2$: C, 68.40; H, 4.49; N, 10.40. Found: C, 69.10; H, 4.51; N, 10.20.

***N*-(4-Chlorophenyl)-6-(pyrimidin-4-yloxy)-1-naphthamide (42).** To a solution of 6-(pyrimidin-4-yloxy)-1-naphthoic acid (**31d**, 100 mg, 0.37 mmol), diisopropylethylamine (102 μL, 0.75 mmol), 1-hydroxy-7-azabenztriazole (HOAt) (51 mg, 0.37 mmol), and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (108 mg, 0.56 mmol) in 0.5 mL of CH_2Cl_2 and 100 mL of DMF was added 4-chloroaniline. After being stirred for 4 h, the mixture was concentrated and purified by HPLC to provide the title compound (41 mg, 29%) as a white solid. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.76 (s, 1 H), 8.78 (s, 1 H), 8.74 (d, J = 5.81 Hz, 1 H), 8.27 (d, J = 9.09 Hz, 1 H), 8.10 (d, J = 7.83 Hz, 1 H), 7.91 (d, J = 2.15 Hz, 1 H), 7.87 (s, 1 H), 7.85 (s, 1 H), 7.80 (d, J = 6.95 Hz, 1 H), 7.67 (t, J = 7.71 Hz, 1 H), 7.43–7.53 (m, 3 H), 7.26 (d, J = 5.81 Hz, 1 H). HRMS $(C_{21}H_{15}ClN_3O_2)^+$: calcd, 376.084 73; found, 376.085 13. Anal. ($C_{21}H_{14}ClN_3O_2$) C, H, N.

***N*-(4-Chlorophenyl)-6-(2-(methylamino)pyrimidin-4-yloxy)-1-naphthamide (43).** The title compound was prepared from 6-(2-(methylamino)pyrimidin-4-yloxy)-1-naphthoic acid (**34c**) using a method analogous to the preparation of compound **6**. Yield: 30 mg, 22%. HPLC purity: 96% (system A); 97% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.74 (s, 1 H), 8.24 (s, 1 H), 8.22 (s, 1 H), 8.09 (d, J = 8.21 Hz, 1 H), 7.83–7.89 (m, 4 H), 7.77 (d, J = 6.82 Hz, 1 H), 7.61–7.68 (m, 1 H), 7.42–7.48 (m, 4 H), 3.33 (s, 3 H). HRMS $(C_{22}H_{18}ClN_4O_2)^+$: calcd, 405.111 28; found, 405.112 05.

***N*-(4-Chlorophenyl)-6-(6-(methylamino)pyrimidin-4-yloxy)-1-naphthamide (44).** The title compound was prepared from 6-(6-(methylamino)pyrimidin-4-yloxy)-1-naphthoic acid (**34b**) using a method analogous to the preparation of compound **42**. Yield: 53 mg, 68%. HPLC purity: 99% (system A); 100% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.75 (s, 1 H), 8.23 (d, J = 9.22 Hz, 1 H), 8.10–8.19 (m, 1 H), 8.08 (d, J = 8.21 Hz, 1 H), 7.87 (s, 1 H), 7.85 (s, 1 H), 7.79 (d, J = 2.40 Hz, 1 H), 7.76 (d, J = 6.82 Hz, 1 H), 7.61–7.67 (m, 1 H), 7.39–7.48 (m, 3 H), 7.31–7.39 (m, 1 H), 5.89 (s, 1 H), 2.79 (s, 3H). HRMS $(C_{22}H_{18}ClN_4O_2)^+$: calcd, 405.111 28; found, 405.111 78.

6-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-*N*-(4-chlorophenyl)-1-naphthamide (45). The title compound was prepared from (**31b**) using a method analogous to the preparation of compound **6**. Yield: 53 mg, 48%. HPLC purity: 99% (system A); 99% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.28 (s, 1 H), 10.79 (s, 1 H), 8.31 (s, 1 H), 8.26 (d, J = 9.29 Hz, 1 H), 8.10 (d, J = 8.02 Hz, 1 H), 7.94 (d, J = 2.45 Hz, 1 H), 7.87 (d, J = 8.80 Hz, 2 H), 7.79 (d, J = 6.16 Hz, 1 H), 7.63–7.69 (m, 1 H), 7.55 (dd, J = 9.24, 2.49 Hz, 1 H), 7.52 (d, J = 3.52 Hz, 1 H), 7.42–7.48 (m, 2 H), 6.56 (d, J = 3.42 Hz, 1 H). HRMS $(C_{23}H_{16}ClN_4O_2)^+$: calcd, 415.095 63; found, 415 095 93.

***N*-(4-Chlorophenyl)-6-(quinolin-4-yloxy)-1-naphthamide (46).** The title compound was prepared from 6-(quinolin-4-yloxy)-1-naphthoic acid (**29b**) using a method analogous to the preparation of compound **6**. Yield: 160 mg, 62%. HPLC purity: 99% (system A); 99% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.78 (s, 1 H), 8.74 (d, J = 5.05 Hz, 1 H), 8.34–8.39 (m, 2 H), 8.12 (d, J = 8.21 Hz, 1 H), 8.08 (d, J = 8.46 Hz, 1 H), 7.95 (d, J = 2.53 Hz, 1 H), 7.79−7.90 (m, 4 H), 7.66–7.73 (m, 2 H), 7.60 (dd, J = 9.09, 2.53 Hz, 1 H), 7.46 (d, J = 8.84 Hz, 2 H), 6.75 (d, J = 5.05 Hz, 1 H). HRMS $(C_{26}H_{18}ClN_2O_2)^+$: calcd, 425.105 13; found, 425.106 01. Anal. Calcd ($C_{26}H_{17}ClN_2O_3$) C, 73.50; H, 4.03; N, 6.59. Found: C, 70.91; H, 4.34; N, 6.21.

***N*-(4-Chlorophenyl)-6-(7-methoxyquinolin-4-yloxy)-1-naphthamide (47).** The title compound was prepared from 6-(7-methoxyquinolin-4-yloxy)-1-naphthoic acid (**29c**) using a method analogous to the preparation of compound **6** modified such that $NaHCO_3$ (5 equiv) was employed as the base. Yield: 69 mg, 55%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.77 (s, 1 H), 8.66 (d, J = 5.18 Hz, 1 H), 8.34 (d, J = 9.22 Hz, 1 H), 8.25 (d, J = 9.09 Hz, 1 H), 8.11 (d, J = 8.34 Hz, 1 H), 7.92 (d, J = 2.40 Hz, 1 H), 7.87 (d, J = 8.84 Hz, 2 H), 7.81 (d, J = 6.44 Hz, 1 H), 7.64–7.71 (m, 1 H), 7.58 (dd, J = 9.16, 2.46 Hz, 1 H), 7.42–7.48 (m, 3 H), 7.32 (dd, J = 9.16, 2.46 Hz, 1 H), 6.61

(d, J = 5.18 Hz, 1 H), 3.96 (s, 3 H). HRMS $(C_{27}H_{20}ClN_2O_3)^+$: calcd, 455.115 70; found, 455.118 57. Anal. ($C_{27}H_{19}ClN_2O_3$) C, H, N.

***N*-(4-Chlorophenyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (48).** To a solution of 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**, 19.0 g, 50.6 mmol) in 127 mL of DMF were sequentially added triethylamine (35.3 mL, 253 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) (25.0 g, 65.8 mmol). After the mixture was stirred for 2 h, 4-chloroaniline (12.9 g, 101 mmol) was added and stirring was continued for 8 h. The mixture was diluted with 500 mL of ethyl acetate and washed sequentially with saturated $NaHCO_3$, water and brine before being dried over sodium sulfate. Filtration and concentration provided a solid that was passed through silica gel (10% CH_3OH in CH_2Cl_2) to provide a solid that was then recrystallized to provide the title compound (12.5 g, 51%) as a light-yellow solid. Yield: 12.5 g, 51%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.77 (s, 1 H), 8.50 (d, J = 5.18 Hz, 1 H), 8.33 (d, J = 9.35 Hz, 1 H), 8.10 (d, J = 7.96 Hz, 1 H), 7.92 (s, 1 H), 7.83–7.90 (m, 2 H), 7.79 (d, J = 6.06 Hz, 1 H), 7.63–7.71 (m, 1 H), 7.53–7.60 (m, 2 H), 7.40–7.50 (m, 3 H), 6.58 (d, J = 5.18 Hz, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H). HRMS $(C_{28}H_{22}ClN_2O_4)^+$: calcd, 485.126 26; found, 485.127 69. Anal. ($C_{28}H_{21}ClN_2O_4 \cdot CH_3OH$) C, H, N.

***N*-(4-Chlorophenyl)-6-(3-fluoro-6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (49).** The title compound was prepared from 6-(3-fluoro-6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29f**) using a method analogous to the preparation of compound **42**. Yield: 16 mg, 26%. HPLC purity: 90% (system A); 93% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.74 (s, 1 H), 8.86 (d, J = 2.2 Hz, 1 H), 8.25 (d, J = 9.5 Hz, 1 H), 7.97 (d, J = 8.1 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H), 7.70 (d, J = 6.2 Hz, 1 H), 7.55–7.61 (m, 2 H), 7.51 (s, 1 H), 7.44–7.47 (m, 1 H), 7.44 (d, J = 8.8 Hz, 2 H), 7.26 (s, 1 H), 3.96 (s, 3 H), 3.82 (s, 3 H). MS (ESI, positive ion) *m*/*z*: 503.0 (M + H). Mass calcd for $C_{28}H_{20}ClFN_2O_4$: 502.1. HRMS $(C_{28}H_{21}ClFN_2O_4)^+$: calcd, 503.116 84; found, 503.117 23.

4-(5-((4-Chlorophenyl)carbamoyl)naphthalen-2-yloxy)-7-methoxyquinoline-6-carboxamide (50). A 10 mL flask was charged with 6-(6-carbamoyl-7-methoxyquinolin-4-yloxy)-1-naphthoic acid (**29e**, 1.00 g, 2.58 mmol). Thionyl chloride (10 mL) was added, and the mixture was heated at 60 °C for 1 h before being cooled to room temperature. Concentration under reduced pressure provided the acid chloride as a brown solid that was used immediately in the next step. A solution of the derived acid chloride (200 mg, 0.49 mmol) was taken up in 3 mL of pyridine and treated with 4-chloroaniline (55 mg, 0.59 mmol). After being stirred for 8 h, the mixture was concentrated and purified by silica gel chromatography (10% CH_3OH in CH_2Cl_2) to provide the title compound (189 mg, 80%) as a white solid. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.78 (s, 1 H), 8.73 (s, 1 H), 8.71 (d, J = 5.18 Hz, 1 H), 8.35 (d, J = 9.09 Hz, 1 H), 8.10–8.15 (m, 1 H), 7.96 (d, J = 2.65 Hz, 1 H), 7.84–7.89 (m, 3 H), 7.82 (d, J = 5.94 Hz, 1 H), 7.76 (s, 1 H), 7.66–7.72 (m, 1 H), 7.60 (dd, J = 9.16, 2.59 Hz, 1 H), 7.57 (s, 1 H), 7.47 (s, 1 H), 7.45 (s, 1 H), 6.63 (d, J = 5.31 Hz, 1 H), 4.06 (s, 3 H). HRMS $(C_{28}H_{21}ClN_3O_4)^+$: calcd, 498.121 51; found, 498.123 35. Anal. ($C_{28}H_{20}ClN_3O_4 \cdot CH_3OH$) C, H, N.

***N*-(4-Chlorophenyl)-6-(6,7-dimethoxyquinazolin-4-yloxy)-1-naphthamide (51).** The title compound was prepared from 6-(6,7-dimethoxyquinazolin-4-yloxy)-1-naphthoic acid (**29d**) using a method analogous to the preparation of compound **42**. Yield: 38 mg, 49%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.78 (s, 1 H), 8.55 (s, 1 H), 8.29 (d, J = 9.35 Hz, 1 H), 8.12 (d, J = 8.21 Hz, 1 H), 8.00 (d, J = 2.27 Hz, 1 H), 7.87 (d, J = 8.97 Hz, 2 H), 7.81 (d, J = 6.82 Hz, 1 H), 7.63–7.71 (m, 2 H), 7.61 (dd, J = 9.16, 2.34 Hz, 1 H), 7.47 (s, 1 H), 7.45 (s, 1 H), 7.43 (s, 1 H), 4.01 (s, 6 H). HRMS $(C_{27}H_{21}ClN_3O_4)^+$: calcd, 486.121 51; found, 486.122 95. Anal. Calcd for $(C_{27}H_{20}ClN_3O_4)$: C, 66.74; H, 4.15; N, 8.65. Found: C, 66.11; H, 4.28; N, 8.66.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-phenyl-1-naphthamide (52). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **48**. Yield: 326 mg, 34%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.65 (s, 1 H), 8.51 (s, 1 H), 8.36 (d, J = 8.46 Hz, 1 H), 8.11 (d, J = 7.45 Hz, 1 H), 7.92 (s, 1 H), 7.74–7.86 (m, 3 H), 7.68 (t, J = 6.06 Hz, 1 H), 7.52–7.60 (m, 2 H), 7.44 (s, 1 H), 7.39 (t, J = 6.82 Hz, 2 H), 7.14 (t, J = 6.88 Hz, 1 H), 6.58 (s, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{28}H_{23}N_2O_4)^+$: calcd, 451.165 23; found, 451.166 44. Anal. ($C_{28}H_{22}N_2O_4 \cdot CH_3OH$) C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(2-fluorophenyl)-1-naphthamide (53). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 147 mg, 34%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.42 (s, 1 H), 8.51 (d, J = 5.18 Hz, 1 H), 8.42 (d, J = 9.22 Hz, 1 H), 8.11 (d, J = 8.08 Hz, 1 H), 7.92 (d, J = 2.40 Hz, 1 H), 7.74–7.86 (m, 2 H), 7.67 (t, J = 7.71 Hz, 1 H), 7.54−7.63 (m, 2 H), 7.44 (s, 1 H), 7.20–7.38 (m, 3 H), 6.59 (d, J = 5.18 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{28}H_{22}FN_2O_4)^+$: calcd, 469.155 81; found, 469.156 19. Anal. ($C_{28}H_{21}FN_2O_4$) C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(3-fluorophenyl)-1-naphthamide (54). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 236 mg, 56%. HPLC purity: 99% (system A); 99% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.87 (s, 1 H), 8.52 (d, J = 5.18 Hz, 1 H), 8.35 (d, J = 9.22 Hz, 1 H), 8.12 (d, J = 8.21 Hz, 1 H), 7.93 (d, J = 2.53 Hz, 1 H), 7.84 (s, 1 H), 7.81 (d, J = 6.19 Hz, 1 H), 7.68 (t, J = 7.64 Hz, 1 H), 7.54–7.61 (m, 3 H), 7.37–7.47 (m, 2 H), 6.93–7.02 (m, 1 H), 6.59 (d, J = 5.18 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{28}H_{22}FN_2O_4)^+$: calcd, 469.155 81; found, 469.156 91.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(4-fluorophenyl)-1-naphthamide (55). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 237 mg, 55%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.68 (s, 1 H), 8.51 (d, J = 5.18 Hz, 1 H), 8.35 (d, J = 9.22 Hz, 1 H), 8.10 (d, J = 8.08 Hz, 1 H), 7.91 (s, 1 H), 7.81–7.88 (m, 2 H), 7.79 (d, J = 7.20 Hz, 1 H), 7.67 (t, J = 7.58 Hz, 1 H), 7.53−7.60 (m, 2 H), 7.44 (s, 1 H), 7.26–7.22 (m, 2 H), 6.58 (d, J = 5.18 Hz, 1 H), 3.98 (s, 3 H), 3.94 (s, 3 H). HRMS $(C_{28}H_{22}FN_2O_4)^+$: calcd, 469.155 81; found, 469.155 30. Anal. ($C_{28}H_{21}FN_2O_4 \cdot CH_3OH$) C, H, N.

***N*-(3-Chlorophenyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (56).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **48**. Yield: 260 mg, 39%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.82 (s, 1 H), 8.52 (d, J = 5.18 Hz, 1 H), 8.36 (d, J = 9.22 Hz, 1 H), 8.12 (d, J = 8.08 Hz, 1 H), 8.05 (s, 1 H), 7.92 (d, J = 2.53 Hz, 1 H), 7.79–7.84 (m, 1 H), 7.65–7.73 (m, 2 H), 7.55–7.60 (m, 2 H), 7.39–7.46 (m, 2 H), 7.18–7.24 (m, 1 H), 6.60 (d, J = 5.18 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{28}H_{22}ClN_2O_4)^+$: calcd, 485.126 26; found, 485.126 99. Anal. ($C_{28}H_{22}ClN_2O_4 \cdot 1.6H_2O$) C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-*p*-tolyl-1-naphthamide (57). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **48**. Yield: 325 mg, 86%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.84 (s, 1 H), 8.53 (d, J = 5.16 Hz, 1 H), 8.32 (d, J = 9.22 Hz, 1 H), 8.09 (d, J = 8.30 Hz, 1 H), 7.90 (d, J = 2.62 Hz, 1 H), 7.74–7.89 (m, 2 H), 7.65 (t, J = 7.70 Hz, 1 H), 7.51–7.61 (m, 3 H), 7.31–7.44 (m, 2 H), 6.91–7.00 (m, 1 H), 6.63 (d, J = 5.21 Hz, 1 H), 3.98 (s, 3 H), 3.93 (s, 3 H), 2.40 (s, 3 H). HRMS $(C_{29}H_{25}N_2O_4)^+$: calcd, 465.180 88; found, 465.181 10. Anal. ($C_{29}H_{24}N_2O_4$) C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(3-(trifluoromethyl)phenyl)-1-naphthamide (58). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 36 mg, 60%. HPLC purity: 100% (system A); 100% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.97 (s, 1 H), 8.0 (d, J = 5.45 Hz, 1 H), 8.38 (d, J = 9.37 Hz, 1 H), 8.10 (d, J = 8.71 Hz, 1 H), 8.06–8.08 (m, 2 H), 7.97 (d, J = 2.30 Hz, 1 H), 7.81 (d, J = 6.30 Hz, 1 H), 7.78 (s, 1 H), 7.77 (s, 1 H), 7.66–7.69 (m, 1 H), 7.51–7.62 (m, 2 H), 7.44 (s, 1 H), 6.65 (d, J = 5.34 Hz, 1 H) 3.96 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{29}H_{22}F_3N_2O_4)^+$: calcd, 519.152 62; found, 519.153 73.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(4-(trifluoromethyl)phenyl)-1-naphthamide (59). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **48**. Yield: 39 mg, 66%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.00 (s, 1 H), 8.52 (d, J = 5.30 Hz, 1 H), 8.36 (d, J = 9.47 Hz, 1 H), 8.13 (d, J = 8.21 Hz, 1 H), 8.06 (s, 1 H) 8.04 (s, 1 H), 7.93 (d, J = 2.40 Hz, 1 H), 7.84 (d, J = 6.69 Hz, 1 H), 7.78 (s, 1 H), 7.76 (s, 1 H), 7.65–7.72 (m, 1 H), 7.53−7.62 (m, 2 H), 7.44 (s, 1 H), 6.60 (d, J = 5.18 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{29}H_{22}F_3N_2O_4)^+$: calcd, 519.152 62; found, 519.152 02 Anal. $(C_{29}H_{21}F_3N_2O_4 \cdot 0.5CH_3OH)$ C, H, N.

***N*-(4-*tert*-Butylphenyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (60).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 27 mg, 46%. HPLC purity: 100% (system A); 99% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.55 (s, 1 H), 8.52 (d, J = 5.18 Hz, 1 H), 8.35 (d, J = 9.47 Hz, 1 H), 8.10 (d, J = 7.83 Hz, 1 H), 7.91 (d, J = 2.40 Hz, 1 H), 7.72–7.79 (m, 3 H), 7.64–7.70 (m, 1 H), 7.54–7.59 (m, 2 H), 7.44 (s, 1 H), 7.41 (s, 1 H), 7.39 (s, 1 H), 6.59 (d, J = 5.31 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 1.30 (s, 9 H). HRMS $(C_{32}H_{31}N_2O_4)^+$: calcd, 507.227 83; found, 507.226 91.

***N*-(2,4-Dichlorophenyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (61).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **48**. Yield: 95 mg, 26%. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.42 (s, 1 H), 8.51 (d, J = 5.18 Hz, 1 H), 8.49 (d, J = 9.22 Hz, 1 H), 8.12 (d, J = 8.08 Hz, 1 H), 7.92 (d, J = 2.40 Hz, 1 H), 7.88 (d, J = 6.44 Hz, 1 H), 7.74–7.81 (m, 2 H), 7.69 (t, J = 7.58 Hz, 1 H), 7.60 (dd, J = 9.22, 2.53 Hz, 1 H), 7.57 (s, 1 H), 7.54 (dd, J = 8.59, 2.15 Hz, 1 H), 7.44 (s, 1 H), 6.60 (d, J = 5.31 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{28}H_{21}Cl_2N_2O_4)^+$: calcd, 519.087 29; found, 519.088 78. Anal. $(C_{28}H_{20}Cl_2N_2O_4 \cdot 1.5CH_3OH)$ C, H, N.

***N*-(3,5-Dichlorophenyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (62).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **48**. Yield: 160 mg, 39%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.96 (s, 1 H), 8.52 (d, J = 5.18 Hz, 1 H), 8.36 (d, J = 8.84 Hz, 1 H), 8.14 (d, J = 9.09 Hz, 1 H), 7.93 (t, J = 2.21 Hz, 3 H), 7.84 (d, J = 6.82 Hz, 1 H), 7.66–7.73 (m, 1 H), 7.55–7.61 (m, 2 H), 7.44 (s, 1 H), 7.39 (t, J = 1.89 Hz, 1 H), 6.60 (d, J = 5.05 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{28}H_{21}Cl_2N_2O_4)^+$: calcd, 519.087 29; found, 519. 090 80. Anal. $(C_{28}H_{20}Cl_2N_2O_4)$ C, H, N.

***N*-(4-Chloro-3-(trifluoromethyl)phenyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (63).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **48**. Yield: 39 mg, 61%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.96 (s, 1 H), 8.52 (d, J = 5.18 Hz, 1 H), 8.38 (d, J = 9.22 Hz, 1 H), 8.35 (s, 1 H), 8.13 (d, J = 8.21 Hz, 1 H), 8.04 (d, J = 8.08 Hz, 1 H), 7.93 (d, J = 2.53 Hz, 1 H), 7.85 (d, 1 H), 7.61–7.72 (m, 2 H), 7.55–7.60 (m, 2 H), 7.51 (d, J = 8.08 Hz, 1 H), 7.44 (s, 1 H), 6.60 (d, J = 5.18 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{29}H_{21}ClF_3N_2O_4)^+$: calcd, 553.113 65; found, 553.113 00. Anal. Calcd for $C_{29}H_{20}ClF_3N_2O_4$: C, 62.99; H, 3.65; N, 5.07. Found: C, 63.45; H, 3.75; N, 5.10.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(pyridin-2-yl)-1-naphthamide (64). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 113 mg, 31%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.10 (s, 1 H), 8.51 (d, J = 5.18 Hz, 1 H), 8.40 (d, J = 3.79 Hz, 1 H), 8.37 (d, J = 9.47 Hz, 1 H), 8.32 (d, J = 8.34 Hz, 1 H), 8.10 (d, J = 8.21 Hz, 1 H), 7.87–7.93 (m, 3 H), 7.81 (d, J = 6.69 Hz, 1 H), 7.62–7.68 (m, 1 H), 7.55–7.60 (m, 2 H), 7.44 (s, 1 H), 7.19–7.23 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{27}H_{22}N_3O_4)^+$: calcd, 452.160 48; found, 452.160 62. Anal. $(C_{27}H_{21}N_3O_4 \cdot 0.6H_2O)$ C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(pyridin-3-yl)-1-naphthamide (65). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 264 mg, 32%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.85 (s, 1 H), 8.97 (d, J = 2.40 Hz, 1 H), 8.52 (d, J = 5.18 Hz, 1 H), 8.39 (d, J = 9.22 Hz, 1 H), 8.36 (dd, J = 4.61, 1.20 Hz, 1 H), 8.28 (d, J = 9.35 Hz, 1 H), 8.13 (d, J = 8.34 Hz, 1 H), 7.93 (d, J = 2.53 Hz, 1 H), 7.85 (d, J = 6.95 Hz, 1 H), 7.65–7.73 (m, 1 H), 7.55–7.62 (m, 2 H), 7.40–7.48 (m, 2 H), 6.60 (d, J = 5.18 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{27}H_{22}N_3O_4)^+$: calcd, 452.160 48; found, 452.160 77. Anal. $(C_{27}H_{21}N_3O_4)$ C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(pyridin-4-yl)-1-naphthamide (66). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **49**. Yield: 225 mg, 53%. HPLC purity: 97% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.19 (s, 1 H), 8.51–8.62 (m, 3 H), 8.37 (d, J = 9.35 Hz, 1 H), 8.16 (d, J = 8.08 Hz, 1 H), 7.96 (d, J = 2.40 Hz, 1 H), 7.84–7.92 (m, 3 H), 7.71 (t, 1 H), 7.53–7.63 (m, 2 H), 7.46 (s, 1 H), 6.64 (d, J = 5.30 Hz, 1 H), 3.98 (s, 3 H), 3.96 (s, 3 H). HRMS $(C_{27}H_{22}N_3O_4)^+$: calcd, 452.160 48; found, 455.160 52. Anal. $(C_{27}H_{22}N_3O_4 \cdot 1.6H_2O)$ C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(thiazol-2-yl)-1-naphthamide (67). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 240 mg, 51%. HPLC purity: 97% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.85 (s, 1 H), 8.51 (d, J = 5.31 Hz, 1 H), 8.41 (d, J = 9.47 Hz, 1 H), 8.15 (d, J = 8.21 Hz, 1 H), 7.93 (d, J = 2.53 Hz, 1 H), 7.90 (d, J = 7.20 Hz, 1 H), 7.64–7.71 (m, 1 H), 7.58–7.63 (m, 2 H), 7.57 (s, 1 H), 7.44 (s, 1 H), 7.35 (d, J = 3.54 Hz, 1 H), 6.61 (d, J = 5.31 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{25}H_{20}N_3O_4S)^+$: calcd, 458.116 90; found, 458.119 48. Anal. $(C_{25}H_{19}N_3O_4S \cdot 0.6H_2O)$ C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(isoxazol-3-yl)-1-naphthamide (68). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 77 mg, 22%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.71 (s, 1 H), 8.87−8.94 (m, 1 H), 8.51 (d, J = 5.18 Hz, 1 H), 8.38 (d, J = 9.35 Hz, 1 H), 8.13 (d, J = 8.34 Hz, 1 H), 7.92 (d, J = 2.40 Hz, 1 H), 7.82–7.88 (m, 1 H), 7.63–7.70 (m, 1 H), 7.54–7.61 (m, 2 H), 7.44 (s, 1 H), 7.15 (s, 1 H), 6.60 (d, J = 5.18 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). HRMS $(C_{25}H_{20}N_3O_5)^+$: calcd, 442.139 75; found, 442.139 81. Anal. $(C_{25}H_{19}N_3O_5 \cdot 0.6CH_3OH)$ C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(5-methylisoxazol-3-yl)-1-naphthamide (69). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 50 mg, 30%. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.51 (s, 1 H), 8.46 (d, J = 5.18 Hz, 1 H), 8.31 (d, J = 9.22 Hz, 1 H), 8.07 (d, J = 8.46 Hz, 1 H), 7.86 (d, J = 2.40 Hz, 1 H), 7.77 (d, J = 6.82 Hz, 1 H), 7.60 (d, J = 15.41 Hz, 1 H), 7.48–7.55 (m, 2 H), 7.39 (s, 1 H), 6.80 (s, 1 H), 6.54 (d, J = 5.18 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 2.52 (s, 3 H). HRMS

$(C_{26}H_{22}N_3O_5)^+$: calcd, 456.155 40; found, 456.155 48. Anal. ($C_{26}H_{21}N_3O_5 \cdot 0.5CH_3OH$) C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-(3-methylisoxazol-5-yl)-1-naphthamide (70). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 28 mg, 45%. HPLC purity: 95% (system A); 97% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.49 (s, 1 H), 8.52 (d, J = 5.28 Hz, 1 H), 8.37 (d, J = 9.42 Hz, 1 H), 8.10 (d, J = 8.33 Hz, 1 H), 7.90 (d, J = 2.43 Hz, 1 H), 7.72 (d, J = 6.78 Hz, 1 H), 7.62 (d, J = 14.2 Hz, 1 H), 7.37–7.52 (m, 2 H), 7.41 (s, 1 H), 6.89 (s, 1 H), 6.58 (d, J = 5.11 Hz, 1 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 2.47 (s, 3 H). HRMS $(C_{26}H_{22}N_3O_5)^+$: calcd, 456.155 40; found, 456.155 52. Anal. Calcd for $C_{26}H_{21}N_3O_5$: C, 68.56; H, 4.65; N, 9.23. Found: C, 69.00; H, 4.71; N, 9.13.

***N*-(5-*tert*-Butylisoxazol-3-yl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (71).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 200 mg, 43%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.62 (s, 1 H), 8.52 (d, J = 5.18 Hz, 1 H), 8.37 (d, J = 9.35 Hz, 1 H), 8.12 (d, J = 8.46 Hz, 1 H), 7.92 (d, J = 2.53 Hz, 1 H), 7.82 (d, J = 6.44 Hz, 1 H), 7.62–7.69 (m, 1 H), 7.55−7.61 (m, 2 H), 7.45 (s, 1 H), 6.83 (s, 1 H), 6.61 (d, J = 5.43 Hz, 1 H), 3.98 (s, 3 H), 3.95 (s, 3 H), 1.45 (s, 9 H). HRMS $(C_{29}H_{27}N_3O_5Na)^+$: calcd, 520.184 29; found, 520.186 63. Anal. ($C_{29}H_{27}N_3O_5$) C, H, N.

***N*-Cyclopropyl-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (72).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. The derived amine was taken up in ethanol and treated with 1 equiv of HCl (1 M in ether) to provide the hydrochloride salt as a white solid. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.79 (d, J = 6.57 Hz, 1 H), 8.68 (d, J = 4.29 Hz, 1 H), 8.45 (d, J = 9.22 Hz, 1 H), 8.07 (d, 2 H), 7.82 (s, 1 H), 7.55–7.71 (m, 4 H), 6.90 (d, J = 6.44 Hz, 1 H), 4.06 (s, 6 H), 2.88–3.02 (m, 1 H), 0.69–0.81 (m, 2 H), 0.55–0.65 (m, 2 H). HRMS $(C_{25}H_{23}N_2O_4)^+$: calcd, 415.165 23; found, 415.164 66. Anal. ($C_{25}H_{22}N_2O_4 \cdot HCl$) C, H, N.

***N*-(Cyclopropylmethyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (73).** To a solution of the acid chloride derived from acid **29a** (120 mg, 0.305 mmol) and $NaHCO_3$ (76.8 mg, 0.914 mmol) in 5 mL of CH_2Cl_2 was added cyclopropylmethylamine (0.048 μL, 0.549 mmol). Upon complete consumption of starting material the reaction was quenched with saturated $NaHCO_3$ (25 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and filtered. Concentration in vacuo and purification by silica gel chromatography (CH_3OH in CH_2Cl_2) provided the title compound (66 mg, 51% yield) as an off-white solid. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.63–8.75 (m, 1 H), 8.49 (d, J = 5.18 Hz, 1 H), 8.37 (d, J = 9.22 Hz, 1 H), 7.95–8.10 (m, 1 H), 7.86 (d, J = 2.40 Hz, 1 H), 7.49–7.65 (m, 4 H), 7.43 (s, 1 H), 6.55 (d, J = 5.18 Hz, 1 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.24 (t, J = 6.19 Hz, 2 H), 1.03–1.17 (m, 1 H), 0.41–0.53 (m, 2 H), 0.23–0.35 (m, 2 H). HRMS $(C_{26}H_{25}N_2O_4)^+$: calcd, 429.180 88; found, 429.181 22. Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 73.37; H, 5.91; N, 6.40.

***N*-Cyclobutyl-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (74).** Thionyl chloride (10 mL) was added to acid **29a** (1.00 mg, 2.67 mmol), and the whole was heated at reflux for 1 h at which point the mixture was concentrated. The derived solid was azeotroped with benzene (20 mL) to provide the hydrochloride salt of the corresponding acid chloride (1.14 g, 100%) as a tan solid that was used without further purification. To a portion of the derived acid chloride (400 mg, 0.930 mmol) in 2.5 mL of CH_2Cl_2 were added DIPEA (810 μL, 4.65 mmol), cyclobutylamine (159 μL, 1.86 mmol), and a crystal of 4-dimethylaminopyridine. Stirring was continued for 24 h at which point the mixture was diluted with 10 mL of dichloromethane and poured into 1 N NaOH. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (CH_3OH in CH_2Cl_2) or reverse-phase HPLC provided the title compound (175 mg, 40%) as a white solid. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J = 7.83 Hz, 1 H), 8.51 (d, J = 5.18 Hz, 1 H), 8.33 (d, J = 9.22 Hz, 1 H), 8.03 (dd, J = 6.76, 2.84 Hz, 1 H), 7.87 (d, J = 2.65 Hz, 1 H), 7.56–7.64 (m, 3 H), 7.54 (dd, J = 9.16, 2.46 Hz, 1 H), 7.44 (s, 1 H), 6.56 (d, J = 5.18 Hz, 1 H), 4.41–4.61 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 2.22–2.36 (m, 2 H), 2.08 (t, J = 9.28 Hz, 2 H), 1.60−1.78 (m, 2 H). HRMS $(C_{26}H_{25}N_2O_4)^+$: calcd, 429.180 88; found, 429.180 33. Anal. ($C_{26}H_{24}N_2O_4 \cdot H_2O$) C, H, N.

***N*-Cyclopentyl-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide (75).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 113 mg, 24%. HPLC purity: 95% (system A); 99% (system C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.57 (d, J = 6.95 Hz, 1 H), 8.51 (d, J = 4.93 Hz, 1 H), 8.33 (d, J = 9.09 Hz, 1 H), 7.98–8.05 (m, 1 H), 7.86 (s, 1 H), 7.50–7.65 (m, 4 H), 7.44 (s, 1 H), 6.56 (d, J = 4.80 Hz, 1 H), 4.26–4.40 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 1.90–2.03 (m, 2 H), 1.50−1.77 (m, 6 H). HRMS $(C_{27}H_{27}N_2O_4)^+$: calcd, 443.196 53; found, 443.196 10.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-propyl-1-naphthamide (76). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 190 mg, 43%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (d, J = 6.44 Hz, 1 H), 8.63 (t, J = 5.62 Hz, 1 H), 8.44 (d, J = 9.22 Hz, 1 H), 8.08 (d, J = 6.06 Hz, 1 H), 8.05 (d, J = 2.27 Hz, 1 H), 7.81 (s, 1 H), 7.59–7.71 (m, 4 H), 6.90 (d, J = 6.44 Hz, 1 H), 4.05 (s, 3 H), 4.05 (s, 3 H), 3.31 (q, J = 6.61 Hz, 2 H), 1.52–1.66 (m, 2 H), 0.96 (t, J = 7.39 Hz, 3 H). HRMS $(C_{25}H_{25}N_2O_4)^+$: calcd, 417.180 88; found, 417.181 36. Anal. ($C_{25}H_{24}N_2O_4 \cdot 3.5H_2O$) C, H, N.

6-(6,7-Dimethoxyquinolin-4-yloxy)-*N*-isopropyl-1-naphthamide (77). The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthoic acid (**29a**) using a method analogous to the preparation of compound **6**. Yield: 287 mg, 54%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (d, J = 5.18 Hz, 1 H), 8.46 (d, J = 7.58 Hz, 1 H), 8.33 (d, J = 9.22 Hz, 1 H), 8.01 (dd, J = 6.44, 3.16 Hz, 1 H), 7.86 (d, J = 2.53 Hz, 1 H), 7.55–7.62 (m, 3 H), 7.53 (dd, J = 9.28, 2.59 Hz, 1 H), 7.43 (s, 1 H), 6.54 (d, J = 5.31 Hz, 1 H), 4.10–4.24 (m, 1 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 1.23 (s, 3 H), 1.21 (s, 3 H). HRMS $(C_{25}H_{25}N_2O_4)^+$: calcd, 417.180 88; found, 417.181 32. Anal. ($C_{25}H_{24}N_2O_4$) C, H, N.

***N*-(4-Chlorophenyl)-6-(6,7-dimethoxyquinolin-4-yloxy)-5-fluoro-1-naphthamide (78).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-yloxy)-5-fluoro-1-naphthoic acid (**36a**) using a method analogous to the preparation of compound **42**. Yield: 14 mg, 27%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.83 (s, 1 H), 8.48 (d, J = 5.18 Hz, 1 H), 8.28 (d, J = 8.21 Hz, 1 H), 8.17 (d, J = 8.97 Hz, 1 H), 7.93 (d, J = 6.82 Hz, 1 H), 7.78–7.88 (m, 3 H), 7.65–7.73 (m, 1 H), 7.61 (s, 1 H), 7.47 (s, 1 H), 7.44 (s, 2 H), 6.52 (d, J = 5.31 Hz, 1 H), 3.97 (d, J = 1.26 Hz, 6 H). HRMS $(C_{28}H_{21}ClFN_2O_4)^+$: calcd, 503.116 84; found, 503.117 04. Anal. ($C_{28}H_{20}ClFN_2O_4 \cdot 0.6CH_3OH$) C, H, N.

***N*-(4-Chlorophenyl)-7-(6,7-dimethoxyquinolin-4-yloxy)quinoline-4-carboxamide (79).** The title compound was prepared from 7-(6,7-dimethoxyquinolin-4-yloxy)quinoline-4-carboxylic acid (**36c**) using a method analogous to the preparation of compound **42**. Yield: 15 mg, 28%. HPLC purity: 98% (system A); 99% (system B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.95 (s, 1 H), 9.05 (d, J = 3.85 Hz, 1 H), 8.52 (d, J = 5.05 Hz, 1 H), 8.27 (d, J = 9.05 Hz, 1 H), 7.77–7.82 (m, 4 H), 7.75 (d, J = 3.92 Hz, 1 H), 7.62 (d, J = 9.10 Hz, 1 H), 7.48 (d, J = 8.99 Hz, 1 H), 7.43 (s, 2 H), 6.68 (d, J = 4.96 Hz, 1 H), 3.94 (s, 3H), 3.90 (s, 3H). HRMS $(C_{27}H_{21}ClN_3O_4)^+$: calcd, 486.121 51; found, 486.121 61.

***N*-(4-Chlorophenyl)-3-(6,7-dimethoxyquinolin-4-yloxy)isoquinoline-8-carboxamide (80).** The title compound was prepared from 3-(6,7-dimethoxyquinolin-4-yloxy)isoquinoline-8-carboxylic acid (**36b**) using a method analogous to the preparation of compound **42**. Yield: 14 mg, 27%. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.70 (s, 1 H), 9.28 (s, 1 H), 8.39 (d, J = 5.05 Hz, 1 H), 7.97–8.05 (m, 1 H), 7.72–7.80 (m, 2 H), 7.65–7.72 (m, 3 H), 7.31 (d, J = 5.56 Hz, 2 H), 7.28 (d, J = 1.39 Hz, 2 H), 6.63 (d, J = 5.18 Hz, 1 H), 3.80 (s, 3 H), 3.74 (s, 3 H). HRMS $(C_{27}H_{21}ClN_3O_4)^+$: calcd, 486.121 51; found, 486.121 54. Anal. ($C_{27}H_{20}ClN_3O_4 \cdot 2H_2O$) C, H, N.

***N*-(4-Chlorophenyl)-6-(6,7-dimethoxyquinolin-4-ylamino)-1-naphthamide (81).** The title compound was prepared from 6-(6,7-dimethoxyquinolin-4-ylamino)-1-naphthoic acid (**37a**) using a method analogous to the preparation of compound **42**. Yield: 94 mg, 49%. HPLC purity: 97% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.72 (s, 1 H), 8.98 (s, 1 H), 8.34 (d, J = 5.35 Hz, 1 H), 8.19 (d, J = 8.50 Hz, 1 H), 8.01 (d, J = 8.15 Hz, 1 H), 7.82–8.88 (m, 3 H), 7.70 (s, 1 H), 7.52–7.65 (m, 3 H), 7.40–7.45 (m, 2 H), 7.28 (s, 1 H), 7.01 (d, J = 5.48 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H). HRMS $(C_{28}H_{23}ClN_3O_3)^+$: calcd, 484.142 25; found, 484.142 97. Anal. ($C_{28}H_{22}ClN_3O_3 \cdot H_2O$) C, H, N.

***N*-(4-Chlorophenyl)-6-((6,7-dimethoxyquinolin-4-yl)(methyl)amino)-1-naphthamide (82).** The title compound was prepared from 6-((6,7-dimethoxyquinolin-4-yl)(methyl)amino)-1-naphthoic acid (**37b**) using a method analogous to the preparation of compound **6**. Yield: 37 mg, 47%. HPLC purity: 96% (system A). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.62 (s, 1 H), 8.22 (d, J = 5.45 Hz, 1 H), 7.81 (s, 1 H), 7.77 (d, J = 5.70 Hz, 1 H), 7.58–7.62 (m, 2 H), 7.43 (s, 1 H), 7.41 (t, J = 4.15 Hz, 1 H), 7.37 (s, 1 H), 7.35 (s, 1 H), 7.29 (s, 1 H), 7.20 (s, 1 H), 7.15–7.19 (m, 2 H), 6.99 (s, 1 H), 4.01 (s, 3 H), 3.64 (s, 3 H), 3.57 (s, 3 H). HRMS $(C_{29}H_{25}ClN_3O_3)^+$: calcd, 498.157 90; found, 498.160 01. Anal. ($C_{29}H_{24}ClN_3O_3 \cdot H_2O$) C, H, N.

VEGFR-2 Kinase Assay.[21] In a 96-well plate, 5 nM/L of either the phosphorylated or nonphosphorylated form of the VEGFR-2 kinase domain was incubated with compound (10-point titration ranging from 3 μM to 0.15 nM), 1 μM/L gastrin substrate, 20 mM/L Tris-HCl, pH 7.5, 10 mM/L $MgCl_2$, 100 mM/L NaCl, 1.5 mM/L EGTA, 1 mM/L DTT, 0.2 mM/L sodium orthovanadate, and 20 μg/mL BSA for 30 min at 25 °C. ATP was added at a final concentration of 11.8 μM and incubated for 60 min at room temperature. Eu-labeled antiphosphotyrosine pT66 antibody (Perkin-Elmer) was then used for detection.

HUVEC Proliferation Assay.[21] Cells were cultured in endothelial growth medium-2 (Cambrex). HUVECs were seeded into flat-bottom, 96-well plates (BD Falcon) at 3000 cells per well in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS), penicillin, and streptomycin. After culture for 22 h, media were removed and cells were preincubated for 2 h with serial dilutions of compound diluted 1:400 in DMEM with 10% FBS plus penicillin/streptomycin. HUVECs were then challenged with 50 ng/mL VEGF or 20 ng/ml bFGF and incubated for 72 h at 37 °C, 5% CO_2. Cells were washed twice with Dulbecco's phosphate buffered saline (DPBS), and plates were frozen at −70 °C for 24 h. Plates were thawed, incubated with CyQuant dye (Molecular Probes), and read on a Victor 1420 workstation (Perkin-Elmer Corporation). IC_{50} data were calculated using the Levenburg−Marquardt algorithm in a four-parameter logistic equation (ID Business Solutions Ltd., Alameda, CA).

In Vitro Metabolism and CL_{int} Calculations. The in vitro intrinsic clearances, CL_{int}, of the test compounds were determined by incubations with human and rat liver microsomes purchased from BD Biosciences (San Jose, CA). The 400 μL incubations contained 0.25 mg of microsomal protein/mL, 1 mM NADPH, 2 mM $MgCl_2$ in 50 mM potassium phosphate buffer, pH 7.4. Test compounds were added to the prewarmed (37 °C) incubation mixtures at the final concentration of 1 μM. At 0, 10, 20, 30, and 40 min following addition of test compound, aliquots of the incubation mixture (35 μL) were collected into an equal volume of acetonitrile + internal standard (1 μM tolbutamide). The samples were centrifuged at 3500*g* for 15 min and analyzed on a liquid chromatography tandem mass spectrometry system consisting of 2 Shimadzu LC-10AD HPLC pumps and a DGU-14A degasser (Shimadzu, Columbia, MD), CTC PAL autoinjector (Leap Technologies, Carrboro, NC) and a API3000 LC−MSMS system. Chromatography was conducted on a Sprite Armor C18 (20 mm × 2.1 mm, 10μm) analytical column (Analytical Sales and Products, Pompton Plains, NJ) with a 0.5 μm PEEK guard filter, using the following mobile phase gradient program: MPA = H_2O with 0.1% formic acid; MPB = acetonitrile with 0.1% formic acid; 0 min = 98% MPA, 2% MPB; 0.3 min = 98% MPA, 2% MPB; 0.7 min = 5% MPA, 95% MPB; 1.3 min = 5% MPA, 95% MPB; 1.4 min = 98% MPA, 2% MPB; 1.7 min = end of run; approximately 2 min between sample injections. For each compound, peak areas at each time point were converted to the natural log of the percentage remaining relative to the 0 min samples.[35] The resulting slope of these values relative to time (k) was converted to in vitro $T_{1/2}$ where $T_{1/2} = -0.693/k$. CL_{int} was calculated using the following relationship: $CL_{int} = (0.693/T_{1/2})(1/0.25 \text{ mg/mL})$.

Murine KDR (Flk-1) Lung Phosphorylation Assay. Balb/c female mice were dosed orally with compound **48** at the indicated doses. Two hours after dosing with **48**, 3 μg of murine VEGF was injected intravenously, and after 5 min the mice were sacrificed and the lungs were immediately dissected. Blood samples were collected to determine plasma drug concentrations. Levels of phosphorylated Flk-1 were subsequently determined by Delphia assay. Data represent the mean ± standard error. Statistical analysis was performed by analysis of variance (ANOVA) followed by Bonferroni−Dunn post hoc test.

In Vivo Vascular Permeability Assay. Vascular permeability was induced using a modified Miles assay[36] and was conducted as previously described.[21]

Rat Corneal Angiogenesis Model. Corneal angiogenesis was evaluated in adult female Sprague–Dawley rats as previously described.[37]

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

Tumor Xenograft Model. The HT29 cell line was originally obtained from ATCC. The cells were maintained at 37 °C in DMEM high glucose/5% FBS, 1× NEAA, 2 mM L-glutamine (Gibco/BRL, Grand Island, NY) under standard tissue culture conditions. CD1 nu/nu mice within approximately 4–8 weeks of age were challenged with subcutaneous implants of cultured HT29 human colon cancer cells (1×10^7 cells per mouse). Eleven days later when tumors had reached approximately 300 mm^3, animals began continuous daily treatment with compound **48** administered po, qd at the indicated dose levels. Tumor volumes as established by caliper measurements were recorded twice per week, along with body weights as an index of toxicity. Data are expressed as mean values ± standard errors as a function of time. Statistical significance of observed differences was evaluated by repeated measures analysis of variance (RMANOVA) followed by Scheffé post hoc testing for multiple comparisons.

Covalent Binding Studies. Human and rat liver microsomes (20 mg/mL) were purchased from Xenotech, LLC (Lenexa, KS). NADPH and glutathione were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). $H_2{}^{18}O$ was ordered from Cambridge

Isotope Laboratories Inc. (Andover, MA), and SOLVABLE was purchased from Perkin-Elmer Life Sciences (Boston, MA).

Microsomal Incubations. ^{14}C compound (10 μM) and liver microsomes (1 mg/mL) were mixed with 0.1 M potassium phosphate buffer (pH 7.4) for a final volume of 0.5 mL. The samples were preincubated at 37 °C for 3 min, and then 1 mM NADPH was added. The incubations were quenched with 1.0 mL of ice-cold acetonitrile after 60 min followed by vortex mixing and centrifugation. The supernatant was dried under a steady stream of N_2 and reconstituted in the initial mobile phase described below. A 50 μL injection was made using the LCMS method described below.

In Vitro Covalent Binding Assay. ^{14}C compound (10 μM) was again incubated with liver microsomes (1 mg/mL), (±)-glutathione (1 mM), 0.1 M potassium phosphate buffer (pH 7.4), and NADPH (1 mM) in a final volume of 0.2 mL. The incubations were quenched with 0.4 mL of ice-cold acetonitrile after 60 min followed by vortex mixing, centrifugation, and removal of the supernatant. The pellet was washed three times with 80% methanol, twice with 3:1 ethanol/ether, and twice with 80% methanol. The total radioactivity in the final supernatant was determined by liquid scintillation counting and was not more than background. The pellet was dried overnight and then solubilized in 0.5 mL of 60% SOLVABLE. The protein concentration was determined using a standard BCA protein assay, and 0.375 mL of the solubilized protein was used for liquid scintillation counting.

LCMS Assay. HPLC analyses were carried out on an Agilent 1100 gradient system (Palo Alto, CA). Separation was achieved on a Waters YMC ODS-AQ 4.6 mm × 150 mm column with a flow rate of 1 mL/min. The mobile phase consisted of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). The gradient started at 95% A and linearly ramped to 50% A over 30 min. The flow was split so that 0.8 mL/min flowed through an INUS β-RAM (Rivera Beach, FL; scintillation cocktail flow rate of 2.4 mL/min) and 0.2 mL/min flowed into a Thermo Electron ion trap mass spectrometer (LCQ-Deca XP plus or LTQ; San Jose, CA).

Protein Binding Assay. Plasma filtrate was used for the calibration curve and QC samples. To generate plasma filtrate, an aliquot of plasma was filtered through Millipore Centriplus (a filter) by spinning at 3000*g* (4980 rpm) at 4 °C for 24 h with a Beckman Avanti J-251 ultracentrifuge. An aliquot of 10 μL of test compound (1 mg/mL in DMSO) was added to 1990 μL of human, rat, dog, and mouse plasma to give a final concentration of 5 mg/mL (12.9 μM). Separate QC samples were prepared by adding 10 μL of the test compound spiked plasma sample (5 μg/mL) to 490 μL of plasma filtrate, in duplicate. The plasma samples including the QC samples were then incubated at 37 °C for 15 min. Following incubation, 800 μL was transferred to the centrifuge tube (in duplicate) and spun at 120 000 rpm for 3 h at 37 °C with a TLA-120.2 rotor (Optima TLX ultracentrifuge, Beckman Coulter). The top portion below the lipid layer of the centrifuged plasma sample was aspirated (100 μL in triplicate) for LCMS analysis. The QC samples (100 μL in duplicate) were also aspirated for LCMS analysis. The concentrations of the samples ($n = 6$) and QCs ($n = 2$) were determined from a linear regression of peak area ratios (analyte peak area/IS peak area) versus the theoretical concentrations of the calibration standards. The percent of binding was calculated as

$$\%\ \text{protein binding} = 1 - (\text{concentration of the centrifuged plasma sample})/(\text{mean concentration of the QC}) \times 100$$

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Supporting Information Available: Tables of elemental analysis, HPLC anlysis, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Ferrara, N. VEGF and the quest for tumour angiogenesis factors. *Nat. Rev. Cancer* **2002**, *2*, 795–803. (b) Carmeliet, P. Angiogenesis in health and disease. *Nat. Med.* **2003**, *9*, 653–660.

(2) (a) Cherrington, J. M.; Strawn, L. M.; Shawver, L. K. New paradigms for the treatment of cancer: the role of anti-angiogenesis agents. *Adv. Cancer Res.* **2000**, *79*, 1–38. (b) Siemann, D. W.; Chaplin, D. J.; Horsman, M. R. Vascular-targeting therapies for treatment of malignant disease. *Cancer* **2004**, *100*, 2491–2499.

(3) Fava, G. A. Affective disorders and endocrine disease. New insights from psychosomatic studies. *Psychosomatics* **1994**, *35*, 341–353.

(4) Walsh, D. A.; Haywood, L. Angiogenesis: a therapeutic target in arthritis. *Curr. Opin. Invest. Drugs* **2001**, *2*, 1054–1063.

(5) Aiello, L. P.; Avery, R. L.; Arrigg, P. G.; Keyt, B. A.; Jampel, H. D.; Shah, S. T.; Pasquale, L. R.; Thieme, H.; Iwamoto, M. A.; Park, J. E.; et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N. Engl. J. Med.* **1994**, *331*, 1480–1487.

(6) Detmar, M. The role of VEGF and thrombospondins in skin angiogenesis. *J. Dermatol. Sci.* **2000**, *24* (Suppl. 1), S78–S84.

(7) Folkman, J. Anti-angiogenesis: new concept for therapy of solid tumors. *Ann. Surg.* **1972**, *175*, 409–416.

(8) Liotta, L. A.; Steeg, P. S.; Stetler-Stevenson, W. G. Cancer metastasis and angiogenesis: an imbalance of positive and negative regulation. *Cell* **1991**, *64*, 327–336.

(9) (a) Terman, B. I.; Dougher-Vermazen, M.; Carrion, M. E.; Dimitrov, D.; Armellino, D. C.; Gospodarowicz, D.; Bohlen, P. Identification of the KDR tyrosine kinase as a receptor for vascular endothelial cell growth factor. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 1579–1586. (b) Veikkola, T.; Karkkainen, M.; Claesson-Welsh, L.; Alitalo, K. Regulation of angiogenesis via vascular endothelial growth factor receptors. *Cancer Res.* **2000**, *60*, 203–212. (c) Shinkaruk, S.; Bayle, M.; Lain, G.; Deleris, G. Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy. *Curr. Med. Chem.: Anti-Cancer Agents* **2003**, *3*, 95–117.

(10) Kim, K. J.; Li, B.; Winer, J.; Armanini, M.; Gillett, N.; Phillips, H. S.; Ferrara, N. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* **1993**, *362*, 841–844.

(11) Cardones, A. R.; Banez, L. L. VEGF inhibitors in cancer therapy. *Curr. Pharm. Des.* **2006**, *12*, 387–394.

(12) D'Adamo, D. R.; Anderson, S. E.; Albritton, K.; Yamada, J.; Riedel, E.; Scheu, K.; Schwartz, G. K.; Chen, H.; Maki, R. G. Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. *J. Clin. Oncol.* **2005**, *23*, 7135–7142.

(13) Adjei, A. A. Novel small-molecule inhibitors of the vascular endothelial growth factor receptor. *Clin. Lung Cancer* **2007**, *8* (Suppl. 2), S74–S78.

(14) (a) Thomas, A. L.; Morgan, B.; Dreves, J.; Unger, C.; Wiedenmann, B.; Vanhoefer, U.; Laurent, D.; Dugan, M.; Steward, W. P. Vascular endothelial growth factor receptor tyrosine kinase inhibitors: PTK787/ZK 222584. *Semin. Oncol.* **2003**, *30* (Suppl. 6), 32–38. (b) Ryan, A. J.; Wedge, S. R. ZD6474-A novel inhibitor of VEGFR and EGFR tyrosine kinase activity. *Br. J. Cancer* **2005**, *92* (Suppl. 1), S6–S13. (c) Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J.-Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. *J. Med. Chem.* **2003**, *46*, 1116–1119. (d) Gingrich, D. E.; Reddy, D. R.; Iqbal, M. A.; Singh, J.; Aimone, L. D.; Angeles, T. S.; Albom, M.; Yang, S.; Ator, M. A.; Meyer, S. L.; Robinson, C.; Ruggeri, B. A.; Dionne, C. A.; Vaught, J. L.; Mallamo, J. P.; Hudkins, R. L. A new class of potent vascular endothelial growth factor receptor tyrosine kinase inhibitors: structure activity relationships for a series of 9-alkoxymethyl-12-(3-hydroxypropyl) indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazole-5-ones and the identification of CEP-5214 and its dimethylglycine ester prodrug clinical candidate CEP-7055. *J. Med. Chem.* **2003**, *46*, 5375–5388. (e) Hennequin, L. F.; Stokes, E. S. E.; Thomas, A. P.; Johnstone, C.; Ple, P. A.; Ogilvie, D. J.; Dukes, M.; Wedge, S. R.; Kendrew, J.; Curwen, J. O. Novel 4-anilinoquinazolines with C-7 basic side chains: design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors. *J. Med. Chem.* **2002**, *45*, 1300–1312. (f) Ruggeri, B.; Singh, J.; Gingrich, D.; Angeles, T.; Albom, M.; Chang, H.; Robinson, C.; Hunter, K.; Dobrzanski, P.; Jones-Bolin, S.; Aimone, L.; Klein-Szanto, A.; Herbet, J.-M.; Bono, F.; Schaeffer, P.; Casellas, P.; Bourie, B.; Pili, R.; Isaacs, J.; Ator, M.; Hudkins, R.; Vaught, J.; Mallamo, J.; Dionne, C. CEP-7055: a novel, orally active pan inhibitor of vascular endothelial growth factor

receptor tyrosine kinases with potent antiangiogenic activity and antitumor efficacy in preclinical models. *Cancer Res.* **2003**, *63*, 5978–5991. (g) Beebe, J. S.; Jani, J. P.; Knauth, E.; Goodwin, P.; Higdon, C.; Rossi, A. M.; Emerson, E.; Finkelstein, M.; Floyd, E.; Harriman, S.; Atherton, J.; Hillerman, S.; Soderstrom, C.; Kou, K.; Gant, T.; Noe, M. C.; Foster, B.; Rastinejad, F.; Marx, M. A.; Schaeffer, T.; Whalen, P. M.; Roberts, W. G. Pharmacological characterization of CP-547,632, a novel vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for cancer therapy. *Cancer Res.* **2003**, *63*, 7301–7309.

(15) (a) Cohen, M. H.; Gootenberg, J.; Keegan, P.; Pazdur, R. FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer. *Oncologist* **2007**, *12*, 356–361. (b) Culy, C. Bevacizumab: antiangiogenic cancer therapy. *Drugs Today* **2005**, *41*, 23–36. (c) Sandler, A.; Gray, R.; Perry, M. C.; Brahmer, J.; Schiller, J. H.; Dowlati, A.; Lilenbaum, R.; Johnson, D. H. Paclitaxel−carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* **2006**, *355*, 2542–2550.

(16) Giaccone, G. The potential of antiangiogenic therapy in non-small cell lung cancer. *Clin. Cancer Res.* **2007**, *13*, 1961–1970.

(17) (a) Atkins, M.; Jones, C. A.; Kirkpatrick, P. Sunitinib maleate. *Nat. Rev. Drug Discovery* **2006**, *5*, 279–280. (b) Fiedler, W.; Serve, H.; Doehner, H.; Schwittay, M.; Ottmann, O. G.; O'Farrell, A. M.; Bello, C. L.; Allred, R.; Manning, W. C.; Cherrington, J. M.; Louie, S. G.; Hong, W.; Brega, N. M.; Massimini, G.; Scigalla, P.; Berdel, W. E.; Hossfeld, D. K. A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. *Blood* **2005**, *105* (3), 986–993.

(18) Goodman, V. L.; Rock, E. P.; Dagher, R.; Ramchandani, R. P.; Abraham, S.; Gobburu, J. V. S.; Booth, B. P.; Verbois, S. L.; Morse, D. E.; Liang, C. Y.; Chidambaram, N.; Jiang, J. X.; Tang, S.; Mahjoob, K.; Justice, R.; Pazdur, R. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin. Cancer Res.* **2007**, *13*, 1367–1373.

(19) (a) Bukowski, R.; Cella, D.; Gondek, K.; Escudier, B. Effects of sorafenib on symptoms and quality of life: results from a large randomized placebo-controlled study in renal cancer. *Am. J. Clin. Oncol.* **2007**, *30*, 220–227. (b) Flaherty, K. T. Sorafenib in renal cell carcinoma. *Clin. Cancer Res.* **2007**, *13*, 747s–752s.

(20) Strumberg, D.; Clark, J. W.; Awada, A.; Moore, M. J.; Richly, H.; Hendlisz, A.; Hirte, H. W.; Eder, J. P.; Lenz, H.-J.; Schwartz, B. Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. *Oncologist* **2007**, *12*, 426–437.

(21) Polverino, A.; Coxon, A.; Starnes, C.; Diaz, Z.; DeMelfi, T.; Wang, L.; Bready, J.; Estrada, J.; Cattley, R.; Kaufman, S.; Chen, D.; Gan, Y.; Kumar, G.; Meyer, J.; Neervannan, S.; Alva, G.; Talvenheimo, J.; Montestruque, S.; Tasker, A.; Patel, V.; Radinsky, R.; Kendall, R. AMG 706, an oral, multikinase inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and kit receptors, potently inhibits angiogenesis and induces regression in tumor xenografts. *Cancer Res.* **2006**, *66*, 8715–8721.

(22) Potashman, M. H.; Bready, J.; Coxon, A.; DeMelfi, T. M., Jr.; DiPietro, L.; Doerr, N.; Elbaum, D.; Estrada, J.; Gallant, P.; Germain, J.; Gu, Y.; Harmange, J.-C.; Kaufman, S. A.; Kendall, R.; Kim, J. L.; Kumar, G. N.; Long, A. M.; Neervannan, S.; Patel, V. F.; Polverino, A.; Rose, P.; vander Plas, S.; Whittington, D.; Zanon, R.; Zhao, H. Design, synthesis, and evaluation of orally active benzimidazoles and benzoxazoles as vascular endothelial growth factor-2 receptor tyrosine kinase inhibitors. *J. Med. Chem.* **2007**, *50*, 4351–4373.

(23) Hodous, B. L.; Geuns-Meyer, S. D.; Hughes, P. E.; Albrecht, B. K.; Bellon, S.; Caenepeel, S.; Cee, V. J.; Chaffee, S. C.; Emery, M.; Fretland, J.; Gallant, P.; Gu, Y.; Johnson, R. E.; Kim, J. L.; Long, A. M.; Morrison, M.; Olivieri, P. R.; Patel, V. F.; Polverino, A.; Rose, P.; Wang, L.; Zhao, H. Synthesis, structural analysis, and SAR studies of triazine derivatives as potent, selective Tie-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2886–2889.

(24) Aminobenzoxazoles exhibited potent inhibition of KDR in our enzyme assay; however, the 2-aminobenzoxazoles were considerably less potent when tested in our human umbilical vein endothelial cell assay (60-fold enzyme to cell shift). While incorporation of a basic solubilizing group afforded improved cellular potency, it also resulted in compounds with inferior pharmacokinetic properties, such as large volumes of distribution and high plasma clearance levels.

(25) Pyridylpyrimidine **5** lacks selectivity and is equipotent against KDR and Tie-2.

(26) (a) He, M.; Kania, R. S.; Lou, J.; Zhou, R. Preparation of Naphthalenecarboxamides and Their Derivatives as New Antiangiogenic Agents. WO 2005/021553 A1, 2005. (b) Potashman, M.; Kim, T.; Bellon, S.; Booker, S.; Cheng, Y.; Kim, J. L.; Tasker, A.; Xi, N.; Xu, S.; Harmange, J.-C.; Borg, G.; Weiss, M.; Hodous, B. L.; Graceffa, R.; Buckner, W. H.; Masse, C. E.; Choquette, D.; Martin, M. W.; Germain, J.; Dipietro, L. V.; Chaffee, S. C.; Nunes, J. J.; Buchanan, J. L.; Habgood, G. J.; McGowan, D. C.; Whittington, D. A. Preparation of Heteroaryl Substituted Naphthalenes as Inhibitors of Lck, VEGFR and/or HGF Related Activity. WO 2005/070891 A2, 2005.

(27) Protection of the carboxylic acid was necessary to achieve fluorination of the naphthyl ring in moderate yield.

(28) Thomas, A. P.; Hennequin, L. F. A.; Ple, P. A. Quinoline Derivatives Inhibiting the Effect of Growth Factors Such as VEGF. WO 1998/13350 A1, 1998.

(29) Pierce, A. C.; Sandrettio, K. L.; Bemis, G. W. Kinase inhibitors and the case for CH−O hydrogen bonds in protein−ligand binding. *Proteins: Struct., Funct., Genet.* **2002**, *49*, 567–576.

(30) Weiss, M. M.; Harmange, J.-C.; Polverino, A. J.; Bauer, D.; Berry, L.; Berry, V.; Borg, B.; Bready, J.; Chen, D.; Choquette, D.; Coxon, A.; DeMelfi, T.; Doerr, N.; Estrada, J.; Flynn, J.; Graceffa, R. F.; Harriman, S. P.; Kaufman, S.; La, D. S.; Long, A.; Neervannan, S.; Patel, V. F.; Potashman, M.; Regal, K.; Roveto, P. M.; Schrag, M. L.; Starnes, C.; Tasker, A.; Teffera, Y.; Whittington, D.; Zanon, R. Evaluation of a series of naphthamides as potent, orally active vascular endothelial growth factor receptor-2 tyrosine kinase inhibitors. *J. Med. Chem.* **2008**, *51*, 1668–1680.

(31) Compounds formulated in OraPlus were administered as solutions; however, when formulated in Tween/HPMC, compounds were administered as suspensions.

(32) Compound **48** was labeled at the C1 position of the naphthamide moiety. The ^{14}C labeled 6-hydroxynaphthoic acid was prepared from the 6-hydroxyiodonaphthalene by the Rosenmund−von Braun reaction using ^{14}C copper cyanide.

(33) (a) Lanza, D. L.; Code, E.; Crespi, C. L.; Gonzalez, F. J.; Yost, G. S. Specific dehydrogenation of 3-methylindole and epoxidation of naphthalene by recombinant human Cyp2F1 expressed in lymphoblastoid cells. *Drug Metab. Dispos.* **1999**, *27*, 798–803. (b) Gram, T. E. Chemically reactive intermediates and pulmonary xenobiotic toxicity. *Pharmacol. Rev.* **1997**, *49*, 298–341.

(34) All kinases were tested at their apparent K_m of ATP with respect to 1 μM peptide substrate.

(35) Obach, R. S. Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: an examination of in vitro half-life approach and nonspecific binding to microsomes. *Drug Metab. Dispos.* **1999**, *27*, 1350–1359.

(36) Miles, A. A.; Miles, E. M. Vascular reactions to histamine, histamine-liberator, and leukotaxine in the skin of guinea pigs. *J. Physiol.* **1952**, *118*, 228–257.

(37) Coxon, A.; Bolon, B.; Estrada, J.; Kaufman, S.; Scully, S.; Rattan, A.; Duryea, D.; Hu, Y. L.; Rex, K.; Pacheco, E.; Van, G.; Zack, D.; Feige, U. Inhibition of interleukin-1 but not tumor necrosis factor suppresses neovascularization in rat models of corneal angiogenesis and adjuvant arthritis. *Arthritis Rheum.* **2002**, *46*, 2604–2612.

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