

Discovery of a New Series of Naphthamides as Potent VEGFR-2 Kinase Inhibitors

Yongcong Lv,^{†,∇} Mengyuan Li,^{‡,§,⊥,∇} Ting Liu,^{†,||,○} Linjiang Tong,[‡] Ting Peng,[‡] Lixin Wei,[§] Jian Ding,[‡] Hua Xie,^{*,‡} and Wenhui Duan^{*,†}

[†]Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China

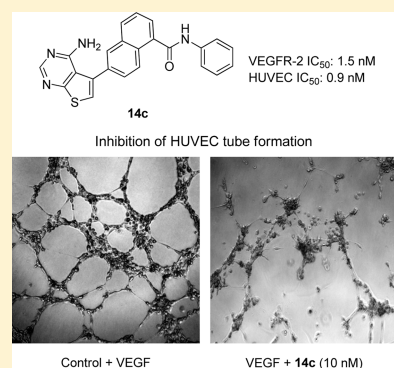
[‡]Division of Anti-Tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China

[§]Northwest Institute of Plateau Biology, Chinese Academy of Sciences, 23 Xinning Road, Qinghai 81008, China

^{||}Medical College of Nanchang University, 461 Bayi Road, Nanchang, Jiangxi 330066, China

Supporting Information

ABSTRACT: Inhibition of VEGFR-2 signaling pathway has already become one of the most promising approaches for the treatment of cancer. In this study, we describe the design, synthesis, and biological evaluation of a new series of naphthamides as potent inhibitors of VEGFR-2. Among these compounds, **14c** exhibited high VEGFR-2 inhibitory potency in both enzymatic and HUVEC cellular proliferation assays, with IC₅₀ values of 1.5 and 0.9 nM, respectively. Kinase selectivity profiling revealed that **14c** was a multitargeted inhibitor, and it also exhibited good potency against VEGFR-1, PDGFR-β, and RET. Furthermore, **14c** effectively blocked tube formation of HUVEC at nanomolar level. Overall, **14c** might be a promising candidate for the treatment of cancer.



KEYWORDS: Angiogenesis, HUVEC, inhibitor, naphthamide, VEGFR-2

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is essential for both embryonic growth and normal physiological processes, such as reproduction and wound healing.^{1,2} Aberrant angiogenesis has been observed in a wide range of diseases including atherosclerosis, retinopathies, endometriosis, arthritis, and cancer.³ As angiogenesis plays an important role in the process of tumor growth and metastasis, it has been proved in humans that restricting the blood supply could limit the growth of a solid tumor.⁴

Many factors are involved in tumor angiogenesis, among which the vascular endothelial growth factors (VEGFs) play a major role.⁵ Overactivation of vascular endothelial growth factor receptors (VEGFRs), especially VEGFR-2, is closely related to poor prognosis and metastasis in the majority of solid tumor patients.^{6,7} The VEGF-mediated VEGFR-2 signaling promotes several endothelial responses required for the formation of new blood vessels, such as cell proliferation, migration, and survival.⁸

As VEGFR-2 signaling is important in tumor angiogenesis, blocking VEGFR-2 signaling pathway has become an attractive approach for the treatment of cancers. Receptor tyrosine kinase (RTK) inhibitors that target VEGFR-2 have been demonstrated to possess substantial antitumor activity, and generally they are ATP-competitive small molecule inhibitors.^{9–11} In fact, six such inhibitors (sorafenib,¹² sunitinib,¹³ pazopanib,¹⁴

axitinib,¹⁵ vandetanib,¹⁶ and regorafenib¹⁷) targeting VEGFR-2 and/or other kinases have been approved for the treatment of cancers, such as advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC). In this communication, we report the design, synthesis, and biological evaluation of a new series of naphthamides as potent VEGFR-2 inhibitors (Figure 1).

Linifanib (**1**) (ABT869, Figure 1), a multitargeted RTK inhibitor bearing an *N,N'*-diaryl urea moiety, is a potent VEGFR-2 inhibitor (IC₅₀ = 4 nM). It also inhibits other kinases such as VEGFR-1 (Flt-1), Flt-3, Kit, and PDGFR-β with IC₅₀ values of 3, 4, 14, and 66 nM, respectively. It is currently in phase III clinical trials for the treatment of advanced HCC.¹⁸ In 2008, Amgen Inc. researchers reported a series of naphthamides¹⁹ and 2,3-dihydro-1,4-benzoxazines²⁰ as potent VEGFR inhibitors. Of naphthamides, representative compound **2** (Figure 1) showed IC₅₀ values of 0.5 and 8 nM for VEGFR-2 and VEGF-induced proliferation of human umbilical vein endothelial cells (HUVEC), respectively. In benzoxazine series,

Received: January 29, 2014

Accepted: February 24, 2014

Published: February 24, 2014

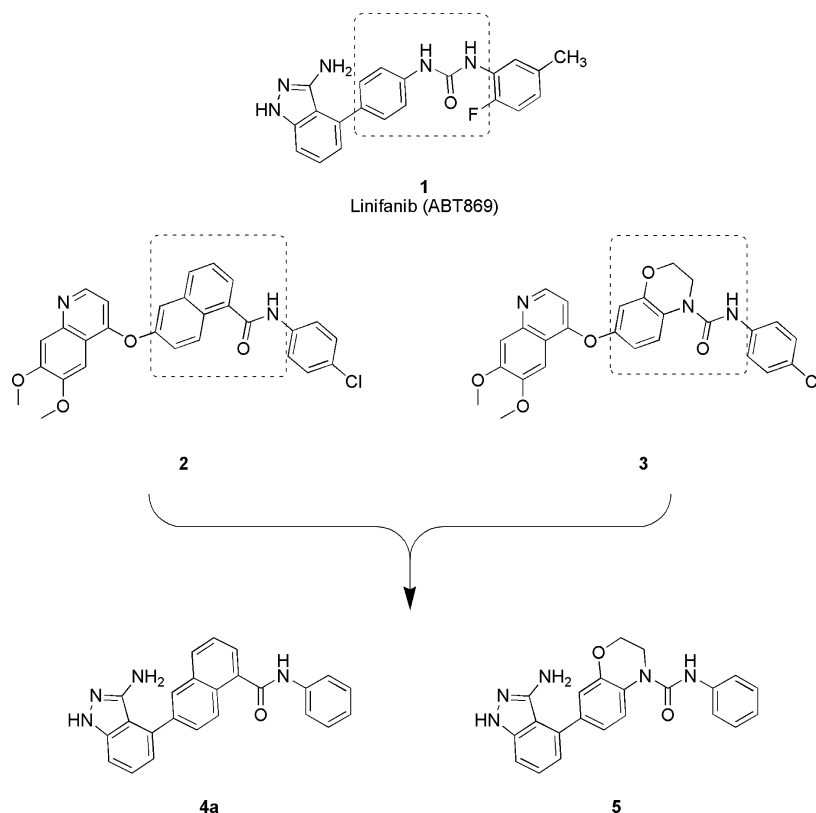
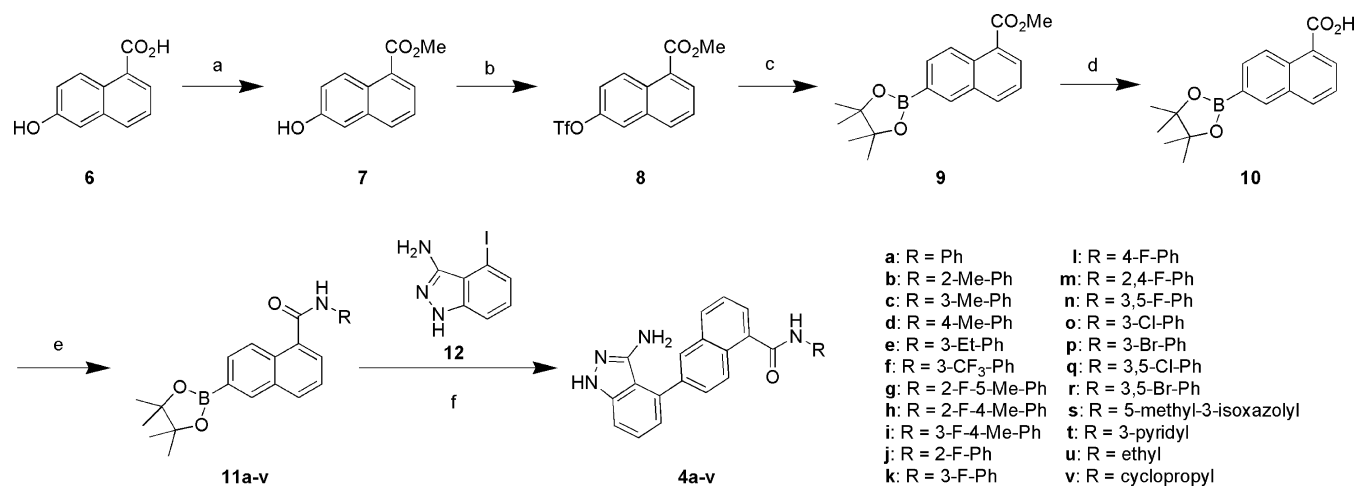


Figure 1. Design of hybrid compounds 4a and 5.

Scheme 1. Synthesis of Indazolynaphthamides 4a–v^a



^aReagents and conditions: (a) SOCl₂, MeOH, reflux, 99%; (b) Tf₂O, DIPEA, DCM, −78 °C, 93%; (c) Pd(dppf)Cl₂, dppf, AcOK, bis(pinacolato)-diboron, dioxane, 80 °C, 98%; (d) LiOH, H₂O, THF, rt, 78%; (e) RNH₂, EDCI, DMAP, DCM, 0 °C to rt, 21–68%; (f) Pd(PPh₃)₂Cl₂, Na₂CO₃, EtOH, toluene, H₂O, 85 °C, 38–80%.

compound 3 (Figure 1) showed IC₅₀ values of 0.5 and 4 nM for VEGFR-2 and HUVEC, respectively.

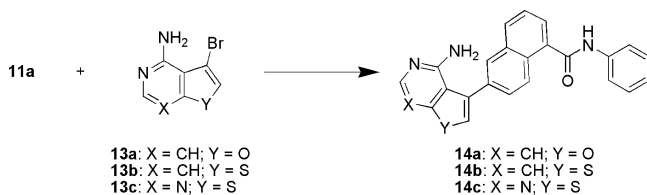
Linifanib binds to the ATP binding site of VEGFR-2 and forces the protein to adopt a DFG-out conformation.¹⁸ This conformation is incompatible with ATP binding, enabling an appropriately substituted inhibitor to penetrate into the extended hydrophobic pocket.²¹ Linifanib forms several hydrogen bonds with the amino acid residues in the catalytic site of VEGFR-2: in the hinge region, the 3-amino group on the indazole and the backbone carbonyl of Glu917, the ring N2 nitrogen, and the backbone amide NH of Cys919; the urea

carbonyl and the backbone amide NH of Asp1046; and finally the urea external NH and Glu885 carboxylate.¹⁸ Compounds 2 and 3 have similar interaction patterns with VEGFR-2: both bind to the ATP binding site in the DFG-out conformation, enabling the *p*-chlorophenyl to penetrate into the extended hydrophobic pocket; the nitrogen of the quinoline forms a hydrogen bond with the backbone amide NH of Cys919; the carbonyl oxygen and the amide NH in compound 2 or the urea NH in compound 3 form two hydrogen bonds with the backbone amide NH of Asp1046 and the side chain of Glu885, respectively.^{19,20} As the *N,N'*-diaryl urea moiety of 1, the

naphthamide moiety of **2**, and the urea moiety of **3** occupy similar areas of kinase region, forming two hydrogen bonds with Asp1046 and Glu885, we envisioned that cyclization of **1** to the corresponding naphthamide or 2,3-dihydro-1,4-benzoxazine may form new VEGFR-2 inhibitor scaffolds. To test the hypothesis, naphthamide **4a** and 2,3-dihydro-1,4-benzoxazine **5** (Figure 1) were prepared, and the enzymatic assay showed that both **4a** and **5** were potent VEGFR-2 inhibitors with IC_{50} values of 1.6 and 40.8 nM, respectively. Encouraged by the high potency of **4a**, we chose **4a** as the lead molecule for further structure–activity relationship (SAR) exploration.

The general synthetic strategy for indazolynaphthamides **4a–v** is outlined in Scheme 1. Triflate **8** was synthesized in two steps starting with the conversion of the 6-hydroxy-1-naphthoic acid **6** to the corresponding methyl ester **7** followed by triflation in the presence of DIPEA.¹⁹ Palladium-catalyzed coupling of the triflate **8** with bis(pinacolato)-diboron afforded the naphthylborate **9**, which was then hydrolyzed to the carboxylic acid **10**. Treatment of **10** with the corresponding amines in the presence of EDCI and DMAP gave naphthamides **11a–v**. Preparation of **4a–v** was achieved by Suzuki coupling between 4-iodo-1H-indazol-3-amine **12** and **11a–v**. Derivatives **14a–c** were similarly prepared by using a coupling reaction of **11a** with corresponding heteroaryl bromides **13a–c** (Scheme 2).

Scheme 2. Synthesis of Naphthamides **14a–c**^a



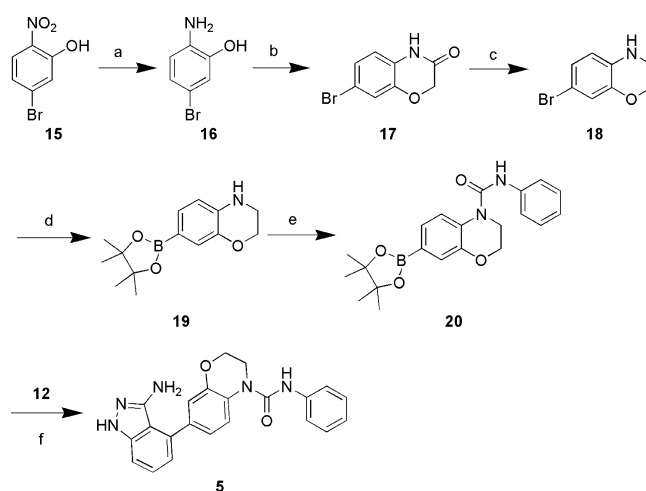
^aReagents and conditions: Pd(PPh₃)₂Cl₂, Na₂CO₃, EtOH, toluene, H₂O, 85 °C, 69–81%.

The synthesis of **5** is illustrated in Scheme 3. Reduction of 5-bromo-2-nitrophenol **15** followed by cyclization gave **17**, which was then reduced to benzoxazine **18**. The palladium-catalyzed coupling of **18** with bis(pinacolato)-diboron afforded the borate **19**, which was reacted with phenyl isocyanate to provide **20**. Finally, coupling **20** with iodide **12** afforded **5**.

All compounds depicted in Tables 1–3 were evaluated for their inhibitory activity against VEGFR-2 and VEGF-induced proliferation of HUVEC, using linifanib as reference. Starting with the first two compounds **4a** and **5**, the biological data revealed that naphthamide **4a** displayed more potent VEGFR-2 inhibition than that of 2,3-dihydro-1,4-benzoxazine **5** (IC_{50} : 1.6 nM for **4a** vs 40.8 nM for **5**, Table 1). The result was similar in the further HUVEC cellular assay: **4a** exhibited higher cellular potency than **5** (IC_{50} : 3.8 nM for **4a** vs 12.9 nM for **5**). Accordingly, **4a** was chosen as the lead molecule for further SAR exploration.

We first examined the impact of the amide variations on their biological activity. Table 2 contains derivatives differing in the substitution patterns of the benzene rings, the isosteres of the benzene ring, and the types of alkyl groups. Incorporation of a methyl at *ortho*-position of the phenyl moiety led to a significant loss in both enzymatic and cellular potency by 16.7-fold and 22.7-fold, respectively (**4b** vs **4a**). A methyl at the *meta*-position also reduced enzymatic potency but improved

Scheme 3. Synthesis of 2,3-Dihydro-1,4-benzoxazine **5**^a



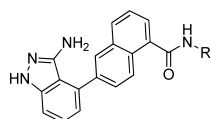
^aReagents and conditions: (a) Fe, NH₄Cl, EtOH, H₂O, 70 °C, 70%; (b) chloroacetyl chloride, Cs₂CO₃, MeCN, rt, 82%; (c) BH₃·THF, THF, reflux, 96%; (d) Pd(dppf)Cl₂, AcOK, bis(pinacolato)-diboron, dioxane, 110 °C, 55%; (e) PhNCO, Et₃N, DCM, rt, 95%; (f) Pd(PPh₃)₂Cl₂, Na₂CO₃, EtOH, toluene, H₂O, 85 °C, 30%.

Table 1. Biological Activity of Compounds **4a** and **5**^a

compd	Ring	VEGFR-2 IC_{50} (nM)	HUVEC ^b IC_{50} (nM)
4a		1.6 ± 0.5	3.8 ± 0.4
5		40.8 ± 9.3	12.9 ± 1.7
linifanib	-	6.2 ± 1.8	2.3 ± 0.3

^a IC_{50} values were the mean ± SD of two or more independent experiments. ^bInhibition of VEGF-induced proliferation of human umbilical vein endothelial cells.

cellular potency by 1.8-fold (**4c** vs **4a**). The *para*-methyl analogue **4d** showed similar inhibition of the enzyme (IC_{50} = 1.9 nM) but improved cellular potency (IC_{50} = 1.3 nM) compared to **4a**. *meta*-Ethyl substitution (**4e**) reduced enzymatic potency by 11.4-fold but improved cellular potency by 2.7-fold (**4e** vs **4a**). Besides, *meta*-trifluoromethyl analogue **4f** showed the same enzymatic potency (IC_{50} = 7.3 nM) but a drastically decreased cellular potency (IC_{50} > 100 nM) compared to **4c**. Incorporation of an additional fluorine atom at the *para*-position to the methyl on the phenyl in **4c** provided a 2-fold improvement in enzymatic potency accompanied by a 3-fold reduction in cellular potency (**4g** vs **4c**). However, placing an additional fluorine atom on the phenyl of **4d** made the molecule less active in both enzymatic and cellular assays (**4h** and **4i**). In halogen-containing analogues **4j–r**, no improvement was observed in the enzymatic assay compared to **4a**, while compounds **4k**, **4m**, **4n**, and **4o** showed a slightly improved cellular potency (IC_{50} = 2.3, 2.6, 1.6, and 3.1 nM, respectively). Isostere replacement of the amide benzene ring

Table 2. Variations of the Naphthamide^a

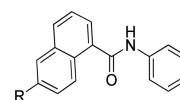
compd	R	VEGFR-2 IC ₅₀ (nM)	HUVEC ^b IC ₅₀ (nM)
4a	Ph	1.6 ± 0.5	3.8 ± 0.4
4b	2-Me-Ph	26.7 ± 1.4	86.4 ± 3.5
4c	3-Me-Ph	7.3 ± 0.1	2.1 ± 0.5
4d	4-Me-Ph	1.9 ± 0.4	1.3 ± 0.3
4e	3-Et-Ph	18.2 ± 2.8	1.4 ± 0.4
4f	3-CF ₃ -Ph	7.3 ± 0.4	>100
4g	2-F-5-Me-Ph	3.8 ± 1.0	6.1 ± 0.7
4h	2-F-4-Me-Ph	7.6 ± 0.2	3.3 ± 0.9
4i	3-F-4-Me-Ph	4.5 ± 0.7	4.5 ± 1.7
4j	2-F-Ph	18.7 ± 0.7	6.1 ± 0.9
4k	3-F-Ph	7.1 ± 0.3	2.3 ± 0.1
4l	4-F-Ph	9.2 ± 0.2	17.0 ± 2.4
4m	2,4-F-Ph	92.5 ± 5.9	2.6 ± 0.5
4n	3,5-F-Ph	10.8 ± 2.6	1.6 ± 0.4
4o	3-Cl-Ph	48.4 ± 4.2	3.1 ± 1.3
4p	3-Br-Ph	24.0 ± 4.2	3.9 ± 0.9
4q	3,5-Cl-Ph	1.4 ± 0.7	>100
4r	3,5-Br-Ph	2.5 ± 0.3	>100
4s	5-methyl-3-isoxazolyl	9.7 ± 0.2	5.7 ± 0.4
4t	3-pyridyl	20.2 ± 0.3	ND ^c
4u	ethyl	101.3 ± 29.0	7.0 ± 1.0
4v	cyclopropyl	95.2 ± 5.7	2.8 ± 0.7
linifanib		6.2 ± 1.8	2.3 ± 0.3

^aIC₅₀ values were the mean ± SD of two or more independent experiments. ^bInhibition of VEGF-induced proliferation of human umbilical vein endothelial cells. ^cND: not determined.

proved to be tolerable. In fact, isoxazole derivative **4s** exhibited high enzymatic and cellular activities (IC₅₀ = 9.7 and 5.7 nM, respectively), which was comparable to the phenyl derivatives. To further explore the variations of amide moiety, two derivatives in which phenyls were replaced with ethyl or cyclopropyl groups were prepared (**4u** and **4v**). These two compounds showed poor inhibitory activity in VEGFR-2 enzymatic assay (IC₅₀: 101.3 nM for **4u**; 95.2 nM for **4v**), while exhibiting low nanomolar inhibition in the cellular assay (IC₅₀: 7.0 nM for **4u**; 2.8 nM for **4v**). We speculated that, in addition to VEGFR-2, **4u** and **4v** might work on other anticancer targets in HUVEC; therefore, they performed better in a cellular system than in enzymatic system.

Next, we tested the influence of the replacement of indazole moiety with other heterobicycles on their activity. This modification led to derivatives **14a–c** as shown in Table 3. Compared with **4a**, 4-aminofuro[3,2-*c*]pyridine derivative **14a** and 4-aminothieno[3,2-*c*]pyridine **14b** displayed a 4.4-fold reduction in enzymatic potency (IC₅₀ = 1.6 vs 7.0 and 7.1 nM) and a 5.4-fold reduction in cellular potency (IC₅₀ = 3.8 vs 20.5 and 20.2 nM) while 4-aminothieno[2,3-*d*]pyrimidine derivative **14c** exhibited matched enzymatic potency (IC₅₀ = 1.5 nM) but improved cellular potency (IC₅₀ = 0.9 nM).

To assess the selectivity of this class of derivatives, compound **14c** was profiled against a panel of tyrosine kinases. As shown in Table 4, **14c** exhibited strong potency against VEGFR-1, PDGFR-β, and RET, with IC₅₀ values of 35.1, 4.6, and 20.2 nM, respectively. It is worth mentioning that, in

Table 3. Investigation of the Heterocycle Binding to the Hinge Region^a

compd	R	VEGFR-2 IC ₅₀ (nM)	HUVEC ^b IC ₅₀ (nM)
4a		1.6 ± 0.5	3.8 ± 0.4
14a		7.0 ± 0.7	20.5 ± 0.4
14b		7.1 ± 0.4	20.2 ± 3.4
14c		1.5 ± 0.2	0.9 ± 0.1
linifanib		6.2 ± 1.8	2.3 ± 0.3

^aIC₅₀ values were the mean ± SD of two or more independent experiments. ^bInhibition of VEGF-induced proliferation of human umbilical vein endothelial cells.

Table 4. Enzyme Selectivity Profile of **14c**^a

enzyme	IC ₅₀ (nM)	enzyme	IC ₅₀ (nM)
VEGFR-1	35.1	ErbB2	>10000
VEGFR-2	1.5	ErbB4	>10000
Flt-3	>10000	EGFR (T790M/L858R)	>10000
PDGFR-α	548.6		
PDGFR-β	4.6	c-Src	>10000
RET	20.2	ABL	>10000
FGFR-1	643.7	EPH-A2	>10000
EGFR	>10000	IGF-1R	>10000

^aIC₅₀ values were means of two or more independent experiments.

addition to VEGFR-2, PDGFR-β is also an important anticancer target through antiangiogenic pathway.²² Therefore, inhibiting VEGFR-2 and PDGFR-β simultaneously may be beneficial for antiangiogenic tumor therapy. However, **14c** displayed high selectivity over PDGFR-α (365-fold, IC₅₀ = 548.6 nM) and FGFR-1 (429-fold, IC₅₀ = 643.7 nM) and excellent selectivity (>6666-fold) over Flt-3, EGFR, ErbB2, ErbB4, EGFR (T790M/L858R), c-Src, ABL, EPH-A2, and IGF-1R.

We finally investigated the in vitro antiangiogenic activity of compound **14c** in a tube formation assay. HUVEC were placed on growth factor reduced matrigel and cultured with different concentration of **14c** in the presence of VEGF. As shown in Figure 2, compound **14c** effectively inhibited endothelial cell tube formation induced by VEGF in a concentration-dependent manner, and tube formation was significantly inhibited by 10 nM of **14c**.

In conclusion, we report the design, synthesis, and biological evaluation of novel naphthamides as a new class of VEGFR-2 inhibitors. The hybrid compound **4a** served as a starting point for SAR exploration. SAR studies demonstrated that this new scaffold was tolerable to most of the modifications, such as isostere replacement of indazole and benzene and various

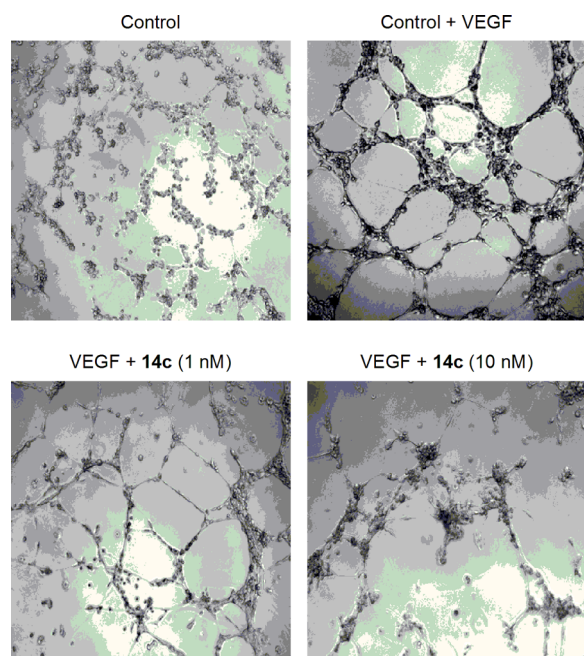


Figure 2. Effect of **14c** on VEGF-induced endothelial tube formation. HUVEC (20,000 cells/well on a 96-well plate) were treated with different concentration of **14c** in the presence of VEGF (100 ng/mL) after placed on matrigel. Tube formation was observed by electron microscope at 4 \times magnification after incubated at 37 $^{\circ}$ C for 6 h.

substitution patterns of benzene ring. Privileged compound **14c** exhibited high potency in both enzymatic and cellular assays. Kinase selectivity studies revealed that, in addition to VEGFR inhibition, **14c** also inhibited PDGFR and RET kinases but showed high selectivity over other kinases. Moreover, **14c** effectively inhibited angiogenesis in HUVEC tube formation assay. Therefore, our hybrid design of new VEGFR-2 inhibitor scaffolds and an understanding of their SARs offer promising opportunities to develop more effective anticancer agents.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General synthetic schemes and details of experimental procedures for the synthesis of all compounds, analytical data, and biological assay descriptions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

* (W.D.) E-mail: whduan@sim.ac.cn. Phone: +86 21 50806032.

* (H.X.) E-mail: hxie@sim.ac.cn. Phone: +86 21 50805897.

Present Addresses

[†](M.L.) Division of Anti-Tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China.

[○](T.L.) Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China.

Author Contributions

[▽](Y.L. and M.L.) These authors contributed equally to this work. All authors have given approval to the final version of the manuscript.

Funding

We thank the National Natural Science Foundation of China (No. 81273365, 81173080), Major Projects in National Science and Technology "Creation of Major New Drugs" (no. 2012ZX09103101-024), and the Shanghai Science and Technology Commission (no. 11431921100 and 12DZ1930802) for their financial support.

Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; RTK, receptor tyrosine kinase; ATP, adenosine triphosphate; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; Flt, fms-like tyrosine kinase receptor; KIT, stem cell factor receptor; PDGFR, platelet-derived growth factor receptor; HUVEC, human umbilical vein endothelial cells; DFG, highly conserved triad Asp-Phe-Gly; SAR, structure-activity relationship; DIPEA, ethyldiisopropylamine; EDCl, 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride; DMAP, 4-dimethylaminopyridine; RET, rearranged during transfection; FGFR-1, fibroblast growth factor receptor 1; EGFR, epidermal growth factor receptor; ErbB2, human epidermal growth factor receptor 2; ErbB4, human epidermal growth factor receptor 4; EGFR (T790M/L858R), EGFR with T790M/L858R mutations; c-Src, tyrosine kinase encoded by the CSK gene; ABL, Abelson tyrosine kinase; EPH-A2, ephrin receptor A2; IGF-1R, insulin-like growth factor 1 receptor

■ REFERENCES

- (1) Carmeliet, P. Angiogenesis in health and disease. *Nat. Med.* **2003**, *9*, 653–660.
- (2) Siemann, D. W.; Chaplin, D. J.; Horsman, M. R. Vascular-targeting therapies for treatment of malignant disease. *Cancer* **2004**, *100*, 2491–2499.
- (3) Potente, M.; Gerhardt, H.; Carmeliet, P. Basic and therapeutic aspects of angiogenesis. *Cell* **2011**, *146*, 873–887.
- (4) Gasparini, G.; Longo, R.; Toi, M.; Ferrara, N. Angiogenic inhibitors: a new therapeutic strategy in oncology. *Nat. Clin. Pract. Oncol.* **2005**, *2*, 562–577.
- (5) Olsson, A. K.; Dimberg, A.; Kreuger, J.; Claesson-Welsh, L. VEGF receptor signaling: in control of vascular function. *Nat. Rev. Mol. Cell Biol.* **2006**, *7*, 359–371.
- (6) Poon, R. T.; Fan, S. T.; Wong, J. Clinical implications of circulating angiogenic factors in cancer patients. *J. Clin. Oncol.* **2001**, *19*, 1207–1225.
- (7) Takahashi, Y.; Kitadai, Y.; Bucana, C. D.; Cleary, K. R.; Ellis, L. M. Expression of vascular endothelial growth factor and its receptor, KDR, correlates with vascularity, metastasis, and proliferation of human colon cancer. *Cancer Res.* **1995**, *55*, 3964–3968.
- (8) Holmes, K.; Roberts, O. L.; Thomas, A. M.; Cross, M. J. Vascular endothelial growth factor receptor-2: structure, function, intracellular signalling and therapeutic inhibition. *Cell Signaling* **2007**, *19*, 2003–2012.
- (9) Schenone, S.; Bondavalli, F.; Botta, M. Antiangiogenic agents: an update on small molecule VEGFR inhibitors. *Curr. Med. Chem.* **2007**, *14*, 2495–2516.
- (10) Zhong, H.; Bowen, J. P. Recent advances in small molecule inhibitors of VEGFR and EGFR signaling pathways. *Curr. Top. Med. Chem.* **2011**, *11*, 1571–1590.

(11) Musumeci, F.; Radi, M.; Brullo, C.; Schenone, S. Vascular endothelial growth factor (VEGF) receptors: drugs and new inhibitors. *J. Med. Chem.* **2012**, *55*, 10797–10822.

(12) Wilhelm, S.; Carter, C.; Lynch, M.; Lowinger, T.; Dumas, J.; Smith, R. A.; Schwartz, B.; Simantov, R.; Kelley, S. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat. Rev. Drug Discovery* **2006**, *5*, 835–844.

(13) Motzer, R. J.; Michaelson, M. D.; Redman, B. G.; Hudes, G. R.; Wilding, G.; Figlin, R. A.; Ginsberg, M. S.; Kim, S. T.; Baum, C. M.; DePrimo, S. E.; Li, J. Z.; Bello, C. L.; Theuer, C. P.; George, D. J.; Rini, B. I. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* **2006**, *24*, 16–24.

(14) Harris, P. A.; Bloor, A.; Cheung, M.; Kumar, R.; Crosby, R. M.; Davis-Ward, R. G.; Epperly, A. H.; Hinkle, K. W.; Hunter, R. N., III; Johnson, J. H.; Knick, V. B.; Laudeman, C. P.; Luttrell, D. K.; Mook, R. A.; Nolte, R. T.; Rudolph, S. K.; Szweczyk, J. R.; Truesdale, A. T.; Veal, J. M.; Wang, L.; Stafford, J. A. Discovery of 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-benzene-sulfonamide (pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. *J. Med. Chem.* **2008**, *51*, 4632–4640.

(15) Ho, T. H.; Jonasch, E. Axitinib in the treatment of metastatic renal cell carcinoma. *Future Oncol.* **2011**, *7*, 1247–1253.

(16) Commander, H.; Whiteside, G.; Perry, C. Vandetanib: first global approval. *Drugs* **2011**, *71*, 1355–1365.

(17) Strumberg, D.; Scheulen, M. E.; Schultheis, B.; Richly, H.; Frost, A.; Büchert, M.; Christensen, O.; Jeffers, M.; Heinig, R.; Boix, O.; Mross, K. Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. *Br. J. Cancer* **2012**, *106*, 1722–1727.

(18) Dai, Y.; Hartandi, K.; Ji, Z.; Ahmed, A. A.; Albert, D. H.; Bauch, J. L.; Bouska, J. J.; Bousquet, P. F.; Cunha, G. A.; Glaser, K. B.; Harris, C. M.; Hickman, D.; Guo, J.; Li, J.; Marcotte, P. A.; Marsh, K. C.; Moskey, M. D.; Martin, R. L.; Olson, A. M.; Osterling, D. J.; Pease, L. J.; Soni, N. B.; Stewart, K. D.; Stoll, V. S.; Tapang, P.; Reuter, D. R.; Davidsen, S. K.; Michaelides, M. R. Discovery of *N*-(4-(3-amino-1H-indazol-4-yl)phenyl)-*N'*-(2-fluoro-5-methylphenyl)urea (ABT-869), a 3-aminoindazole-based orally active multitargeted receptor tyrosine kinase inhibitor. *J. Med. Chem.* **2007**, *50*, 1584–1597.

(19) Harmange, J. C.; Weiss, M. M.; Germain, J.; Polverino, A. J.; Borg, G.; Bready, J.; Chen, D.; Choquette, D.; Coxon, A.; DeMelfi, T.; DiPietro, L.; Doerr, N.; Estrada, J.; Flynn, J.; Graceffa, R. F.; Harriman, S. P.; Kaufman, S.; La, D. S.; Long, A.; Martin, M. W.; Neervannan, S.; Patel, V. F.; Potashman, M.; Regal, K.; Roveto, P. M.; Schrag, M. L.; Starnes, C.; Tasker, A.; Teffera, Y.; Wang, L.; White, R. D.; Whittington, D. A.; Zanon, R. Naphthamides as novel and potent vascular endothelial growth factor receptor tyrosine kinase inhibitors: design, synthesis, and evaluation. *J. Med. Chem.* **2008**, *51*, 1649–1667.

(20) La, D. S.; Belzile, J.; Bready, J. V.; Coxon, A.; DeMelfi, T.; Doerr, N.; Estrada, J.; Flynn, J. C.; Flynn, S. R.; Graceffa, R. F.; Harriman, S. P.; Larrow, J. F.; Long, A. M.; Martin, M. W.; Morrison, M. J.; Patel, V. F.; Roveto, P. M.; Wang, L.; Weiss, M. M.; Whittington, D. A.; Teffera, Y.; Zhao, Z.; Polverino, A. J.; Harmange, J. C. Novel 2,3-dihydro-1,4-benzoxazines as potent and orally bioavailable inhibitors of tumor-driven angiogenesis. *J. Med. Chem.* **2008**, *51*, 1695–1705.

(21) Huang, L.; Huang, Z.; Bai, Z.; Xie, R.; Sun, L.; Lin, K. Development and strategies of VEGFR-2/KDR inhibitors. *Future Med. Chem.* **2012**, *4*, 1839–1852.

(22) Abramsson, A.; Lindblom, P.; Betsholtz, C. Endothelial and nonendothelial sources of PDGF-B regulate pericyte recruitment and influence vascular pattern formation in tumors. *J. Clin. Invest.* **2003**, *112*, 1142–1151.