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Design and synthesis of 3,7-diarylimidazopyridines as inhibitors of the VEGF-receptor KDR

Zhicai Wu,* Mark E. Fraley, Mark T. Bilodeau, Mildred L. Kaufman, Edward S. Tasber, Adrienne E. Balitza, George D. Hartman, Kathleen E. Coll, Keith Rickert, Jennifer Shipman, Bin Shi, Laura Sepp-Lorenzino and Kenneth A. Thomas

Departments of Medicinal Chemistry and Cancer Research, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA

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Abstract—3,7-Diarylsubstituted imidazopyridines were designed and developed as a new class of KDR kinase inhibitors. A variety of imidazopyridines were synthesized and potent inhibitors of KDR kinase activity were identified with good aqueous solubility.

Vascular endothelial growth factor (VEGF) is a regulator of vascular permeability and an inducer of endothelial cell proliferation, migration, and survival. Activation of the VEGF pathway is a fundamental regulation of angiogenesis, the formation of new capillaries from established blood vessels. In principle, anti-VEGF drugs have potential as new therapy for neovascularization-related diseases such as diabetic retinopathy,[1] rheumatoid arthritis,[2] psoriasis,[3] and cancer.[4] As elucidated in molecular mechanisms, the mitogenic signal of VEGF is mediated through the receptor tyrosine kinase KDR (VEGFR-2).[5] Accordingly, the signaling pathway can be terminated by inhibitors against VEGF or its receptor KDR. Indeed, antibodies against VEGF[6] and KDR,[7] soluble VEGF decoy-receptors,[8] and small molecule inhibitors of KDR kinase[9] have been shown to be efficacious in in vivo tumor xenograft models. These results have attracted much attention to develop therapeutic reagents from anti-VEGF molecules, especially, the small molecule KDR kinase inhibitors. Several classes of KDR kinase inhibitors including indolin-2-ones, phthalazines, and quinazolines have entered clinical trials. Most recently, bevacizumab, an antibody against VEGF was shown to significantly prolong the time to progression of disease in patients with metastatic renal-cell cancer.[10]

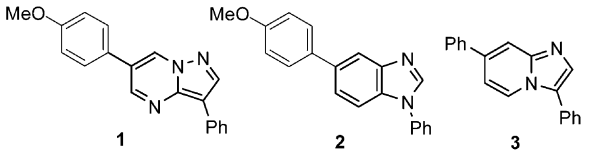

Chart 1.

As part of an effort to develop inhibitors of KDR, 3,6-diarylpyrazolo[1,5-*a*]pyrimidines (**1**, Chart 1) have been found to be potent inhibitors of KDR kinase activity.[11,12] Compounds of this series had been hindered by poor physical properties, including low solubility, high logP and high protein binding. To address these limitations, an effort was initiated to explore other templates including benzimidazoles **2** and imidazopyridines **3**. These cores are likely replacements for the pyrazolo[1,5-*a*]pyrimidine core since they share the same key pharmacophore as **1**: N-1 is an important hydrogen bond acceptor and the two aryl substituents form crucial hydrophobic interactions. [11] Indeed, 1,5-diarylbenzimidazoles have been identified as potent inhibitors of KDR kinase.[13] In this communication, we report the development of 3,7-diarylimidazopyridines as a new class of KDR inhibitors.

Shown in Scheme 1 is the synthesis of the simple diphenyl imidazopyridine **3**. The protected aminopyridine **5** was obtained through the Curtius rearrangement of

* Corresponding author. Tel.: +1-215-652-6331; fax: +1-215-652-7310; e-mail: zhicai_wu@merck.com

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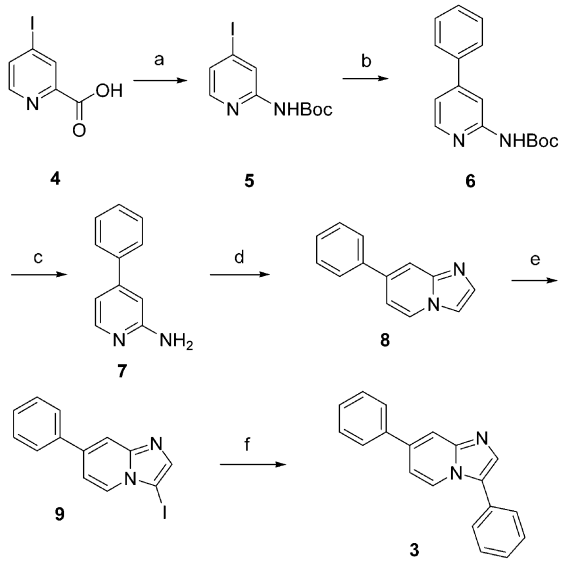
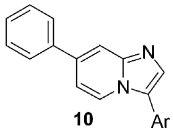


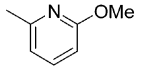
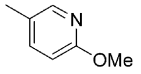
Scheme 1. (a) Diphenylphosphoryl azide, Et_3N, *t*-BuOH, reflux, 82%; (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, reflux, 59%; (c) HCl, EtOAc, 70%; (d) $BrCH_2CHO$, $NaHCO_3/H_2O$, 80 °C, 19%; (e) ICl, AcOH, 72%; (f) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, reflux, 26%.

4-iodopicolinic acid. Subsequent Suzuki coupling with phenylboronic acid produced the diaryl compound **6**. Deprotection followed by cyclization with bromoacetaldehyde afforded the imidazopyridine **8**. Treatment with iodine, and then reaction with phenylboronic acid generated **3**.[14] The KDR kinase inhibitory activity of **3** ($IC_{50} = 98$ nM)[15] was similar to that of pyrazolopyrimidine **1** and benzimidazole **2**. Encouraged by the initial result, we decided to examine this new imidazopyridine class thoroughly.

First, we simply extended the chemistry illustrated in Scheme 1 to replace the 3-phenyl with different aryl groups via palladium catalyzed cross-coupling reactions of compound **9**. The KDR inhibitory potencies of these compounds are shown in Table 1. It is worth noting that 4-pyridyl (**10a**) maintained similar potency while 3-pyridyl group (**10b**) displayed decreased potency. This result was in contrast to 3,6-diarylpyrazolo[1,5-*a*]-pyrimidines[11,12] in which both 3-pyridyl and 4-pyridyl gave similar activity when compared to the phenyl substituent. Moreover, substituted 3-pyridyls (**10d**) showed significantly reduced potency. In the 3,6-diarylpyrazolo[1,5-*a*]pyrimidines series, the 3-thienyl analogue gave the best intrinsic potency.[11] Thus, imidazopyridines with 5-membered heterocycles at position C-3 were examined. We were pleased to find that the 2-(1,3-thiazolyl) and 3-isothiazolyl substituents[16] increased KDR activity 2-fold. These results were consistent with docking studies using a KDR homology model that depicted the bicyclic core bound in the adenine region of the ATP binding site.[17] In this model the 3-aryl substituent occupies the sterically confined hydrophobic region I. Thus, small steric or electronic modifications led to very different results (**10a** vs **10b**; **10b** vs **10d**; **10e**, **10g** vs **10f**). The 2-(1,3-thiazolyl) (**10e**) and 3-isothiazolyl (**10g**) substituents met presumably the electronic and steric requirements of region I and gave the best potency.

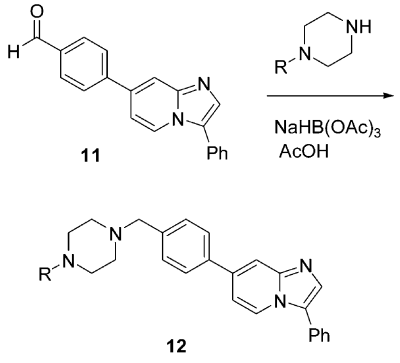
Table 1. SAR of imidazopyridine 3-substituent



Compd	Ar	KDR IC_{50} (nM)
10a		145±37
10b		930
10c		242
10d		2840
10e		42±0.5
10f		99±15
10g		50±6

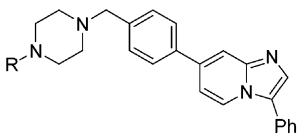
Having explored 3-substituents, we turned to position C-7 of the imidazopyridines. Guided by synthetic accessibility, we focused on 3-phenylimidazopyridines while modifying 7-substituents. First, various substituents were attached to the 7-phenyl group through the same sequence as in Scheme 1. Instead of using phenyl boronic acid, 4-formylphenylboronic acid was employed for the preparation of intermediate **11**. The formyl functionality in **11** was then utilized to append various amines through reductive amination (Scheme 2).

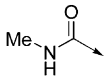
The KDR kinase inhibitory activity of **12a–d** is presented in Table 2. We were pleased to find that the intrinsic potency of these compounds was improved to



Scheme 2. Synthesis of compounds **12a–d**.

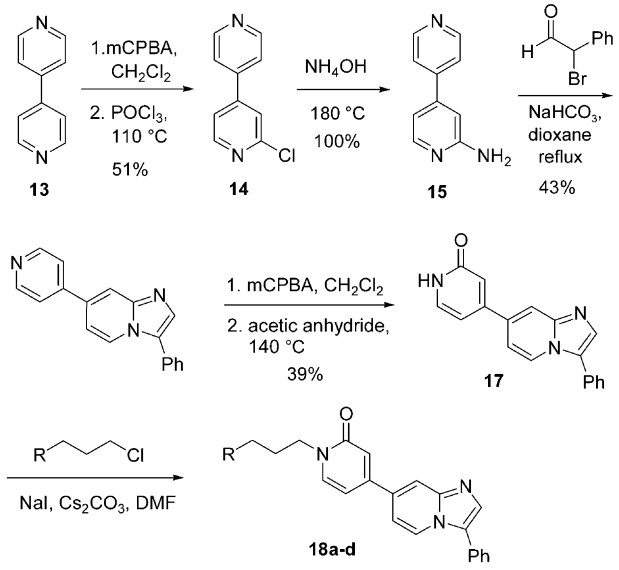
Table 2. SAR of 7-phenyl imidazopyridines



Compd	R	KDR IC_{50} (nM)	Cell IC_{50} (nM)
12a		77	300
12b		52	410
12c		69	nd
12d		13	110

IC_{50} = 13 nM (**12d**). However, the compounds were still quite lipophilic with low aqueous solubility even though a basic amine was present. Also, the cell potency of these compounds (representing the inhibition of VEGF-stimulated phosphorylation of KDR on tyrosine residues as determined in human embryonic kidney cells expressing full length human KDR) was modest.

To increase the hydrophilicity of these imidazopyridines, we decided to introduce more polarity into the core. In the benzimidazole class, incorporation of pyridone functionality enhanced cell potency and significantly improved polarity and aqueous solubility. Thus, imidazopyridines with a pyridone group were prepared (Scheme 3). Starting with bipyridine **13**, oxidation and chlorination gave the chloropyridine **14**. Treatment of **14** with ammonium hydroxide at 180 °C afforded aminopyridine **15**, which reacted with phenylbromoacetaldehyde to produce imidazopyridine **16**.



Scheme 3. Synthesis of imidazopyridines **18a–d**.

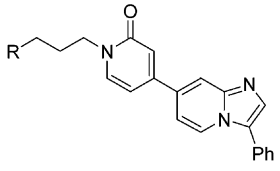
Following a standard pyridine N-oxidation, rearrangement sequence the pyridone **17** was obtained. Alkylation of **17** provided various imidazopyridines.

The activity of a selected set of compounds **18a–d** is shown in Table 3. Indeed, the incorporation of a pyridone substituent with a piperidine basic terminal group resulted in a compound (**18a**) that exhibits good intrinsic activity as well as cell potency. More importantly, **18a** demonstrated increased hydrophilic character with an aqueous solubility of 3.4 mg/mL at pH 7.4. Other substituents on the pyridone, such as acyclic amine **18c**, alcohol **18b** or substituted piperidine **18d** led to decreased KDR activity.

The selectivity of these imidazopyridines for KDR versus other closely related receptor tyrosine kinases and a non-receptor tyrosine kinase is shown for compounds **10e** and **18a** in Table 4. In general, these compounds show modest levels of selectivity against the most KDR-homologous kinases: Flt-1, Flt-4, and PDGF-receptor β, and high level of selectivity against FGF receptor-1, FGF receptor-2, and c-Src. This selectivity profile is similar to that of the benzimidazole and pyrazolopyrimidine analogues.

In summary, we have developed imidazopyrimidines as a new class of potent KDR inhibitors with good aqueous solubility. A variety of 3,7-disubstituted imidazopyrimidines were synthesized and their KDR inhibitory activity tested. It was found that the introduction of pyridone functionality at position C-7 significantly improved potency and physical properties. The potency and polarity of this class of compounds may be further enhanced by a 3-thiazolyl or isothiazolyl substituent.

Table 3. SAR of imidazopyridines with 7-pyridone functionality



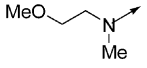
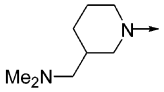
Compd	R	KDR IC_{50} (nM)	Cell IC_{50} (nM)
18a		28 ± 4	51
18b	OH	120	nd
18c		96	nd
18d		67 ± 0	280

Table 4. Fold-selectivity versus a series of kinases

Compd	Flt-1	Flt-4	PDGFRβ	FGFR-1	FGFR-2	c-Src
10e	7.0	1.7	1.4	47	23	165
18a	3.1	2.8	1	60	35	68

Further efforts along this line will be reported in due course.

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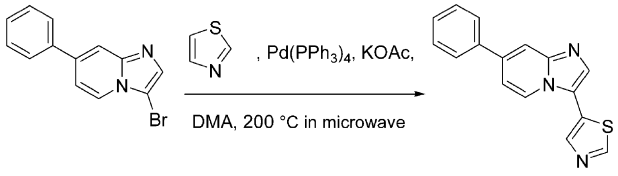
14. All target compounds were fully characterized by ^{1}H NMR and mass spectroscopy.
15. The KDR IC_{50} value represents biochemical inhibition of phosphorylation of a poly-Glu/Tyr (4:1) peptide substrate by isolated KDR kinase (cloned and expressed as a GST-fusion protein), see: Kendall, R. L.; Rutledge, R. Z.; Mao, X.; Tebben, A. L.; Hungate, R. W.; Thomas, K. A. *J. Biol. Chem.* **1999**, *274*, 6453. Values are reported as single determinations or as the average of at least two determinations ± standard deviation.
16. Compounds **10f** and **10g** were prepared similarly according to the following Scheme:



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