Core Replacements in a Potent Series of VEGFR-2 Inhibitors and Their Impact on Potency, Solubility, and hERG

Nello Mainolfi,^{*,†,§} James Powers,^{*,†} Erik Meredith,[†] Jason Elliott,[†] Karl G. Gunderson,[†] Stephen Poor,[‡] Fang Liu,[‡] and Karen Anderson[‡][†]Global Discovery Chemistry, Novartis Institutes for Biomedical Research, 100 Technology Square, Cambridge, Massachusetts 02139, United States[‡]Ophthalmology, Novartis Institutes for Biomedical Research, 500 Technology Square, Cambridge, Massachusetts 02139, United States

S Supporting Information

ABSTRACT: Anti-VEGF therapy has been a clinically validated treatment of age-related macular degeneration (AMD). We have recently reported the discovery of indole based oral VEGFR-2 inhibitors that provide sustained ocular retention and efficacy in models of wet-AMD. We disclose herein the synthesis and the biological evaluation of a series of novel core replacements as an expansion of the reported indole based VEGFR-2 inhibitor series. Addition of heteroatoms to the existing core and/or rearranging the heteroatoms around the 6–5 bicyclic ring structure produced a series of compounds that generally retained good on-target potency and an improved solubility profile. The hERG affinity was proven not be dependent on the change in lipophilicity through alteration of the core structure. A serendipitous discovery led to the identification of a new indole-pyrimidine connectivity: from 5-hydroxy to 6-hydroxy-indole with potentially vast implication on the *in vitro/in vivo* properties of this class of compounds.

KEYWORDS: Vascular endothelial growth factor receptor 2, VEGF, KDR, bicyclic core, scaffold morphing, AMD

The current approved therapies for the treatment of wet or neovascular AMD are the anti-VEGF-A antibody ranibizumab, the anti-VEGF-A aptamer pegaptanib, and the anti-VEGF-A trap fusion protein aflibercept. Each of these wet-AMD treatments must be delivered by intravitreal injections, and 60 percent of patients do not experience a clinically

significant gain of visual acuity (≥ 15 letters).¹ Based on this we have envisioned an opportunity for orally available inhibitor of the receptor tyrosine kinase (RTK) VEGFR-2 (KDR, Flt-1) to provide an alternative wet-AMD treatment paradigm. The role of VEGF-A in the regulation of angiogenesis is well established, and although, new vessel growth and maturation are highly complex processes, requiring the sequential activation of a series of receptors by numerous ligands, VEGF-A signaling often represents a critical rate-limiting step.² VEGF-A promotes growth of vascular endothelial cells and is also known to induce vascular leakage. Ocular VEGF-A levels are increased in neovascular diseases of the retina such as neovascular AMD.^{3,4}

We have recently disclosed the medicinal chemistry efforts around the indole-pyrimidine series of VEGFR-2 inhibitors⁵ where several approaches were taken toward modulation of on-target potency, solubility, pk, and *in vivo* efficacy. This was accomplished by focusing on the optimization of the two extremities of the molecules: the urea and the pyrimidine.⁵ Herein, we focus on the modification/replacement of the

Figure 1. Representative example (1) of previously reported indole pyrimidine scaffold.⁵

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Scheme 1. Retrosynthetic Scheme to Access Compounds 1^{5,a}

^aReplacements of hydroxy indole 4 will be discussed herein.

Scheme 2. Synthesis of Imidazopyridine 8 and Its Use in the Synthesis of VEGFR-2 Inhibitor 13^a

^aReagents and conditions: (a) 7 (3 equiv), EtOH, 72 °C, 3 h; (b) 9 (1.5 equiv), PyBOP (1.3 equiv), DBU (4 equiv), CH₃CN, 60 °C, 3 h; (c) LiOH (40 equiv), THF/H₂O (1:1), rt; (d) oxalyl chloride (1.5 equiv), DMF (cat.), DCM, 0 °C then 12 (8 equiv), pyridine (20 equiv), rt, overnight; (e) DCM/TFA (1:1), 1 h.

indole core and discuss how those changes modulate *in vitro* potency, solubility, and hERG activity (Figure 1).

Introducing heteroatoms in flat aromatic rings is often used to reduce lipophilicity and hence improve aqueous solubility, reduce hERG activity,^{6–16} and generally enhance the overall developability profile of drug candidates.^{17,18}

We decided to investigate how the introduction of heteroatoms (especially nitrogens) in the 6–5 bicyclic aromatic system would impact its potency against VEGFR-2, aqueous solubility at pH 6.8, and hERG channel activity. In order to facilitate interpretation of the data the pyrimidine and the urea moieties were mostly kept constant in the selection of compounds presented herein (Figure 1).

The synthetic strategy to access most of the compounds in this class of VEGFR-2 inhibitors entails a condensation

Scheme 3. Synthesis of Pyrrolopyridine 18 and Its Use in the Synthesis of VEGFR-2 Inhibitor 20^a

^aReagents and conditions: (a) *t*BuMe₂SiCl (1 equiv), imidazole (2 equiv), DCM, 0 °C to rt, 2 h; (b) LDA (4 equiv), dimethyl carbonate (4.1 equiv), –78 °C, 1 h, then 1 N HCl in ether (1 equiv), MeOH, rt; (c) same as (b) in Scheme 2; (d) 2-chloroacetaldehyde (10 equiv), NaHCO₃ (6 equiv), acetone, 70 °C, overnight; (e) 19 (20 equiv), Me₃Al (20 equiv), toluene, 100 °C, 8 h; (f) DCM/TFA (1:1), 0 °C, 2 h.

Scheme 4. Synthesis of Azaindoles 23 and 24 and Their Use in the Synthesis of VEGFR-2 Inhibitors 25 and 26, Respectively^a

^aReagents and conditions: (a) *m*-CPBA (2 equiv), DCM, rt, overnight; (b) Ac₂O (32 equiv), reflux, overnight, then K₂CO₃ (1.4 equiv), MeOH, 1 h; (c) TFAA (5 equiv), DCM, 0 °C to rt, overnight, then NH₄OH.

Table 1. "Core Replacement" SAR: VEGFR-2 Potency, Solubility, and hERG

Entry	Inhibitor/Structure	KDR IC ₅₀ (μM) ^a	Baf3-KDR IC ₅₀ (μM) ^a	pH 6.8 Sol (μM)	hERG IC ₅₀ (μM) ^{a,b}
1		0.008	0.003	18	28
2		2.3	4.4	9	7.7
3		0.077	0.036	25	5.7
4		0.09	0.078	456	9.2
5		0.055	0.051	280	> 30
6		0.160	0.033	260	26
7		0.45	0.055	240	> 30

^aValues are means of at least two experiments. ^bRadioligand binding assay.

between hydroxy indole core 4 and chloropyrimidine 5 (Scheme 1) in addition to a urea formation reaction between the indole NH and an activated carbamate like 2. A conceptually similar overall synthetic plan was used for the synthesis of the new core structures presented below.

The imidazopyridine core, present in 13 (Scheme 2), was formed by simple condensation of aminopyridine 6 and chloroaldehyde 7 to give the desired core 8.¹⁹ Hydroxy-imidazo pyridine 8 was coupled with pyrimidinone 9 using modified peptide coupling conditions (PyBOP, DBU)²⁰ to give

intermediate 10. After basic hydrolysis of the ethyl ester, the isoxazole amide was formed using standard conditions. The desired novel compound 13 was obtained after final Boc removal using a mixture of DCM and TFA.

The more unique core structure present in the VEGFR-2 inhibitor 20 (Scheme 3) was prepared starting from the hydroxy pyridine 14. Transient protection of the phenolic OH was used to facilitate the deprotonation and subsequent functionalization of the pyridyl 2-methyl group to afford ester 16. After PyBOP mediated coupling²⁰ with pyrimidine 9,

Table 2. 6-Hydroxyindole SAR and Comparison with 5-Hydroxyindole Analogues

Entry	Inhibitor/Structure	KDR IC ₅₀ (μM) ^a	Baf3-KDR IC ₅₀ (μM) ^a	pH 6.8 Sol (μM)	hERG IC ₅₀ (μM) ^{a,b}
1	29	0.048	0.003	81	21
2	5-hydroxyindole analogue of 29 (1)	0.008	0.003	18	28
3	30	0.16	0.134	3	8.6
4	5-hydroxyindole analogue of 30 (ref 5b)	0.040	0.001	34	7.4

^aValues are means of at least two experiments. ^bRadioligand binding assay.

intermediate **17** was condensed with 2-chloroacetaldehyde in the presence of a weak base (NaHCO₃) to give pyrrolopyridine **18**.²¹ Trimethylaluminum mediated amidation with pyrazole **19** followed by deprotection afforded the wanted final compound **20**. Unfortunately, amide formation did not proceed well when amino-isoxazole **12** was used in place of amino-pyrazole **19**.

Azaindole core **23** (Scheme 4) was accessed using the well-established nucleophilic addition to pyridine *N*-oxides.^{22–27} Interestingly, it was found that if pyridine *N*-oxide **22** was heated to reflux in acetic anhydride, a meta addition of the acetate group was observed leading, after deprotection, to the initially undesired azaindole **24**. In order to access the desired azaindole **23**, treatment with TFAA at rt was found to be the optimal reaction condition. Transformation of **23** and **24** to their respective final compounds **25** and **26** was achieved following the same protocols as reported in ref **5** for compound **1**.

Indazole **27** and azaindole **28** (in Table 1) were accessed starting, respectively, from commercially available 1*H*-indazole-5-ol (CAS: 15579-15-4) and 1*H*-pyrrolo-[2,3-*b*]pyridin-5-ol (CAS: 98549-88-3) following the same protocols as reported in ref **5** for compound **1**. Indoles **29** and **30** (in Table 2) were accessed starting from commercially available 1*H*-indol-6-ol (CAS: 2380-86-1) following the same protocols as reported in ref **5** for their 5-hydroxyindole analogues.

In vitro activity against the target VEGFR-2 receptor tyrosine kinase was assessed with two primary assays: a KDR receptor tyrosine kinase biochemical assay and a cellular assay with BaF3-Tel-KDR cells (an immortalized murine bone marrow-derived pro-B-cell line) that are engineered to constitutively require VEGFR-2 kinase domain activity for survival and proliferation. The addition of an extra nitrogen to the 2-position of the indole core of **1**, to give indazole **27** (Entry 2, Table 1), resulted in a marked loss of potency (>1000-fold). While aqueous solubility was similar for compound **1** and **27**, counterintuitively (usually addition of polarity reduces affinity for hERG channel) the hERG affinity was enhanced. 7-Azaindole **28** (Entry 3, Table 1) exhibited a slight drop in potency (~10-fold). The solubility profile was not altered, however in this case the affinity for the hERG channel was

reduced (5.7 vs 28 μM in **1**). To our delight, the imidazopyridine (**13**, Entry 4, Table 1), which was a major departure from the usual indole-type core (note that the urea was now replaced with an amide), was found to be a potent VEGFR-2 inhibitor (90 and 78 nM, respectively, in the biochemical and cell assay). Additionally, **13** provided a large improvement in solubility (456 vs 18 μM in **1**). Again, it was disappointing to find that the polarity increase did not affect its ability to block the hERG channel (9.2 μM). The novel pyrrolopyridine core containing compound **20** (Entry 5, Table 1) was also found to be a potent VEGFR-2 inhibitor (55 and 51 nM, respectively, in the biochemical and cell assay). Although direct comparison of the changes in solubility and hERG in this compound are confounded by the different heterocycles in the amide region, **20** shows good solubility and minimal hERG affinity. It has been shown previously that amino pyrazoles are in general more efficient in improving both solubility and hERG profile of compounds of this type.⁵ 4-Azaindole **25** (Entry 6, Table 1) was pleasantly still potent against the target (160 and 33 nM, respectively, in the biochemical and cell assay) and also provided increased aqueous solubility (260 vs 18 μM in **1**). The 6-hydroxy-4-azaindole **26** (Entry 7, Table 1), serendipitously synthesized as a result of an unexpected reversed selectivity in the formation of its core structure (Scheme 4), was surprisingly still a potent VEGFR-2 inhibitor (450 and 55 nM, respectively, in the biochemical and cell assay). This finding highlighted the conformational flexibility of the connectivity between the core and hinge binding region. Solubility and hERG activity were similar to its 5-hydroxy analogue **25**.

Further investigation in this new series of 1–6 connected indole-pyrimidines showed that the nitrogen in the 4-position of the indole core in **26** was actually not needed for potency, and in fact, a simple and commercially available 6-hydroxyindole core as in **29** (Entry 1, Table 2) was able to give rise to an exquisitely potent compound with comparable potency to the well optimized 5-hydroxyindole analogue. Further investigation into the potential binding mode showed that, while in the 5-hydroxyindole series the pyrimidine substitution allows for a very diverse SAR,⁵ this is not the

case for the 6-hydroxyindole series. Initial exploration seems to point to the importance of the 6,5-bicyclic pyrimidine present in 29. In fact, when a 6,6-substituted pyrimidine was coupled onto the 6-hydroxyindole core, compound 30 (Entry 3, Table 2), a >100-fold loss in potency against VEGFR-2 was observed compared to its 5-hydroxyindole analogue (Entry 4, Table 2).

The synthesis of a series of indole-core replacement within an optimized series of VEGFR-2 inhibitors and their impact on on-target potency, solubility and hERG affinity was reported herein. Generally, introducing additional nitrogens in the core structure was reasonably well tolerated, including cases where the connectivity of the core with the aminoheterocycle was changed from urea to amide. The most noticeable positive effect of such changes was observed on aqueous solubility, while the hERG affinity did not seem to be broadly reduced. The serendipitous synthesis of a 6-hydroxyindole analogue led to the uncovering of a novel connectivity for such series of compounds with potential vast implication on off-target profile, *in vivo* activity, and pk.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00018.

Experimental details and ¹H NMR of compounds in Tables 1 and 2 (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*Phone: 1-857-201-2763. E-mail: nello@razetx.com.

*Phone: 1-617-871-7876. E-mail: james.powers@novartis.com.

Present Address

§N.M.: Raze Therapeutics, 400 Technology Square, Cambridge, Massachusetts 02139, United States.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

VEGFR-2, vascular endothelial growth factor receptor 2; hERG, human Ether-à-go-go-related gene; PyBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; SAR, structure–activity relationship; FCC, flash column chromatography; LCMS, liquid chromatography mass spectrometry

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