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Design and synthesis of dihydroindazolo[5,4-*a*]pyrrolo[3,4-*c*]carbazole oximes as potent dual inhibitors of TIE-2 and VEGF-R2 receptor tyrosine kinases

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Abstract—Fused dihydroindazolopyrrolocarbazole oximes have been identified as low nanomolar, potent dual TIE-2 and VEGF-R2 receptor tyrosine kinase inhibitors with excellent cellular potency. Development of the structure–activity relationships (SAR) led to identification of compounds **35** and **40** as potent, selective dual TIE-2/VEGF-R2 inhibitors with favorable pharmacokinetic properties. Compound **35** was orally active in tumor models with no observed toxicity.

Antiangiogenic therapy—inhibition of the generation and growth of new blood vessels from the endothelium of an existing vascular, an essential process required to support solid tumor growth and metastasis—remains an area of focused drug discovery research.[1] Angiogenesis and vasculogenesis are dynamic and complex processes that are critical during early embryonic development as well as in a number of disease processes including cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, and age-related macular degeneration.[2–7] The exact mechanisms that regulate these processes have not been completely characterized, however, normal vasculature development is believed to be dependent on vascular endothelial growth factor (VEGF) and its receptor tyrosine kinases, mainly VEGF-R2 and the angiopoietins (Ang-1 and Ang-2) and their receptor tyrosine kinase, primarily TIE-2. VEGF and VEGF-Rs, principally VEGF-R2, play an important role by directing the differentiation of mesodermal cells into endothelial cells and the proliferation and migration of endothelial cells to form tubular cells.[8–10] The angiopoietins (Ang-1 and Ang-2) and their receptor tyrosine kinases mainly TIE-2 are believed to be involved in the later stages of modulating cell–cell and cell–matrix interactions required for vasculature remodeling and maturation.[11,12] Thus, optimal anti-angiogenic kinase therapy may require concurrently blocking both TIE-2 and VEGF-R2 receptor signaling to significantly inhibit tumor growth and metastasis.[9,13]

Dual TIE-2/VEGF-R2 receptor tyrosine kinase inhibitors have been reported by Pfizer (thiazole 1[14] TIE-2/VEGF-R2 IC_{50} = 18/11 nM), GlaxoSmithKline (furo[2,3-*d*]pyrimidine 2[15] TIE-2/VEGF-R2 IC_{50} = 2/3 nM), and Amgen (pyridinyl pyrimidine 3[16] TIE-2/VEGF-R2 IC_{50} = 4/4 nM) (Fig. 1).

Previously we reported on our first generation pan-VEGF-R anti-angiogenic clinical candidate **4** (CEP-7055)[17] that advanced into phase 1 clinical trials (Fig. 2). Our objective for a second generation compound superior to CEP-7055 (in terms of biochemical, pharmacokinetic (PK), pharmacodynamic, and anti-tumor efficacy profiles) was to build in TIE-2 activity

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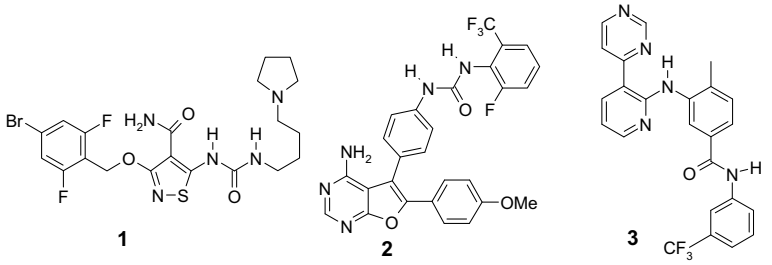


Figure 1. Structures of dual VEGF-R2/TIE-2 inhibitors.

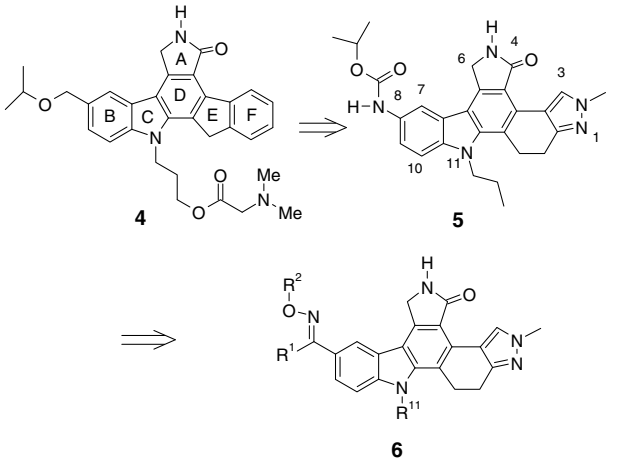
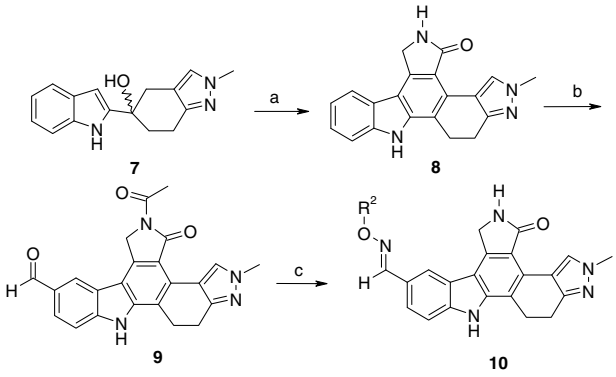


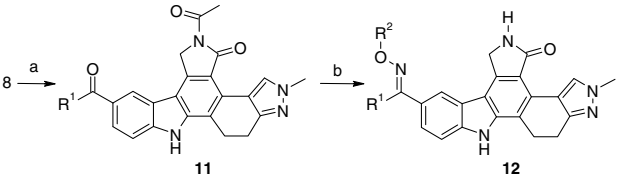
Figure 2. Design of dual VEGF-R2/TIE-2 inhibitors.

and improve upon the pharmacokinetic and in vivo profile of **4**. The project objective was to advance dual TIE-2/VEGF-R2 inhibitors with IC_{50} values less than 25 nM that demonstrated good cell potency and pharmacokinetic properties for in vivo evaluation. As a starting point to design in TIE-2 activity, structural modifications were made to the E- and F-rings ultimately identifying the N2-methyl dihydroindazole core (DHI) (see structure **8**; TIE-2 IC_{50} = 1.3 μM).[18] Early SAR development produced a series of carbamate (e.g., **5**) and urea dual TIE-2/VEGF-R2 inhibitors with good enzyme and cellular potency, but less than favorable pharmacokinetic properties. In addition, compound **5** displayed in vivo toxicity in tumor models.[18] In this paper we disclose the optimization and SAR for a series of C8 oxime dual inhibitors **6** with improved pharmacokinetic properties and significant oral in vivo anti-tumor efficacy.

The synthesis of DHI oximes **10**, **12**, and **16** commenced from common intermediate **7**.[19] Diels–Alder reaction of **7** with (*Z*)-3-cyanoacrylic acid ethyl ester, followed by DDQ oxidative aromatization and Raney-Ni reduction of the resulting cyano group led to lactam **8**[20] (Scheme 1). Lactam **8** was selectively protected with refluxing acetic anhydride to the *N*-acetyl, followed by a modified Duff reaction[21] with hexamethylenetetramine and trifluoroacetic acid to produce aldehyde **9**. Treatment of **9** with hydroxylamine hydrochloride or *O*-alkyl hydroxylamine hydrochloride, followed by hydrolysis of the *N*-acetyl with potassium carbonate in methanol produced the desired oximes **10**.



Scheme 1. Reagents and conditions: (a) i—(*Z*)-3-cyanoacrylic acid ethyl ester, $YbBr_3$, 80 °C, AcOH; ii—DDQ, CH_3CN; iii—Raney-Ni, DMF, MeOH, 50 psi, 27–30%; (b) i—Ac_2O, reflux; ii—hexamethylenetetramine, TFA, reflux, 79–88%; (c) i—$NH_2OH{\cdot}HCl$ or $R^2ONH_2{\cdot}HCl$, NMP, EtOH, reflux; ii—K_2CO_3, MeOH, reflux, 50–55%.



Scheme 2. Reagents and conditions: (a) i—acetyl chloride or isobutyryl chloride, $AlCl_3$, CH_2Cl_2, $MeNO_2$, rt; ii—Ac_2O, reflux, 71–80%; (b) i—$NH_2OH{\cdot}HCl$ or $R^2ONH_2{\cdot}HCl$, NMP, EtOH, reflux; ii—K_2CO_3, MeOH, reflux, 65–72%.

Scheme 2 illustrates the synthesis of the second class of oximes **12**, prepared in an analogous manner to **10**. Friedel–Crafts acylation of **8** with acid chlorides and $AlCl_3$ followed by selective lactam N-acylation proceeded smoothly to **11**. Treatment of **11** with hydroxylamine hydrochloride or *O*-alkylhydroxylamines generated oximes **12** after deprotection.

The third class of *N*-alkyl oximes **16** is delineated in Scheme 3. Alkylation of the cyano-ester intermediate **13** (10 N NaOH, alkyl halide, acetone reflux) and reductive cyclization produced **14**.[19] Friedel–Crafts acylation of **14** followed by *N*-acetyl protection produced **15**. Oxime formation and removal of the acetyl group gave oximes **16**.