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7-[1*H*-Indol-2-yl]-2,3-dihydro-isoindol-1-ones as dual Aurora-A/VEGF-R2 kinase inhibitors: Design, synthesis, and biological activity

Terry V. Hughes *, Stuart L. Emanuel, Harold R. O'Grady, Peter J. Connolly, Catherine Rugg, Angel R. Fuentes-Pesquera, Prabha Karnachi, Richard Alexander, Steven A. Middleton

Johnson & Johnson Pharmaceutical Research and Development, L.L.C, PO Box 300, 1000 Route 202, Raritan, NJ 08869, USA

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ABSTRACT

A novel series of 7-[1*H*-indol-2-yl]-2,3-dihydro-isoindol-1-ones designed to be inhibitors of VEGF-R2 kinase was synthesized and found to potently inhibit VEGF-R2 and Aurora-A kinases. The structure-based design, synthesis, and initial SAR of the series are discussed.

Vascular endothelial growth factor (VEGF) is an important regulator of vascular growth and permeability. Overexpression of VEGF in solid tumors has been shown to promote angiogenesis, thereby facilitating tumor growth. VEGF acts on VEGF-R2, a receptor tyrosine kinase present on the surface of endothelial cells. The inhibition of VEGF-R2 by small molecules is a validated therapeutic approach for treating cancer and has received much attention in the literature.[1] We have concentrated our efforts to find novel inhibitors of the VEGF receptor kinases. By coupling the computer modeling of virtual compounds with traditional medicinal chemistry principles, we designed a new kinase inhibitor scaffold **1** based on known kinase inhibitors (Fig. 1).[2] Initial modeling of our scaffold using a homology structure of VEGF-R2 overlaid with known VEGF-R2 inhibitors showed that key binding interactions were maintained. Kinase screening of early examples of this series revealed that the scaffold displayed inhibition of VEGF-R2 kinase and unexpected inhibition of Aurora-A kinase.

The Aurora kinases (Aurora-A, Aurora-B, and Aurora-C) are serine/threonine kinases that are essential for mitotic progression. Aurora-A kinase plays a role in spindle formation and organization

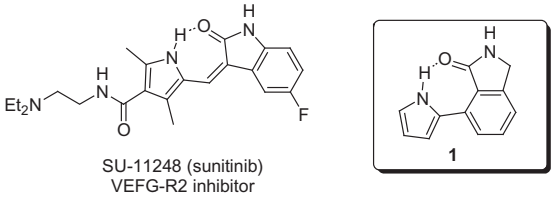

Figure 1. Pharmacophore **1** and known VEGF-R2 inhibitor SU-11248 (sunitinib). The dashed lines depict intramolecular hydrogen bonds.

of the centrosome and Aurora-B regulates chromosomal movement and cytokinesis. The biological function of Aurora-C is still not understood. The inhibition of Aurora kinases by a small molecule has been reported to induce apoptosis in a variety of cancer cell lines and suppress tumor growth in vivo.[3,4] The dual inhibition of VEGF-R2 and Aurora-A kinases is an attractive compound profile and may provide for enhanced antitumor activity toward a wide range of cancers.

In this letter, scaffold design, synthesis, and preliminary structure–activity relationships for the series are presented. Modeling of our scaffold using a homology structure of Aurora-A, and an X-ray structure of an analog in Aurora-A, have added to the understanding of the unexpected activity against Aurora-A, thereby helping to direct our future synthetic efforts.

* Corresponding author. Tel.: +1 610 270 6561; fax: +610 270 6609.
E-mail address: hughe007@hotmail.com (T.V. Hughes).

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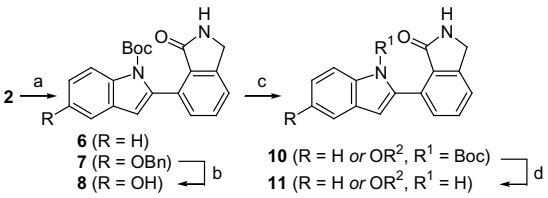
We observed that the VEGF-R2 kinase inhibitor SU-11248 (sunitinib) as well as other potent kinase inhibitors were capable of forming a pseudocycle via an intramolecular hydrogen bond (Fig. 1).[2,5,6] We felt that the intramolecular hydrogen bonding in these compounds held them in a flat, planar conformation that would facilitate binding to the hinge region in the active site of protein kinases. With this hypothesis in mind we proposed the novel pharmacophore **1** as a scaffold for the inhibition of protein kinases. Molecular modeling confirmed that in the minimum energy conformation, the pyrrole NH of pharmacophore **1** is well situated to participate in an intramolecular hydrogen bond with the isoindolinone carbonyl oxygen (Fig. 1).

The synthesis of compound **1** is shown in Scheme 1. Suzuki coupling of the known[7] 7-bromo-2,3-dihydro-isoindol-1-one (**2**) with commercially available 1-(*tert*-butoxycarbonyl)pyrrole-2-boronic acid afforded the Boc-protected core **3**. Thermolytic cleavage of the Boc-protecting group[8] cleanly afforded the proposed pharmacophore **1**. Additionally, the isoindolinone **3** was N-methylated with methyl iodide to give compound **4**. Subsequent thermal deprotection of **4** afforded the N-methylated analog **5**. Kinase data for these analogs are shown in Table 1.

Gratifyingly, our proposed core **1** displayed promising activity against VEGF-R2 kinase (IC_{50} = 1.10 μM), and good activity against Aurora-A kinase (IC_{50} = 0.338 μM). It was established that the NH of the isoindolinone ring was important for kinase inhibition since the N-methylated analog **5** displayed very weak kinase activity. Additionally, the NH of the pyrrole ring was also found to be important for kinase activity since the *N*-Boc analog **3** was also only weakly active. At this point we considered **1** to be a solid hit for VEGF-R2 and Aurora-A kinase inhibition with surprisingly good potency, low molecular weight (198), and a straightforward synthesis. We then explored the SAR for the left hand pyrrole side of the pharmacophore **1**. The synthesis of a representative set of analogs is shown in Scheme 2.

The Suzuki coupling of **2** with 1-Boc-indole-2-boronic acid afforded **6** in good yield when Pd(dppf)Cl_2 was used as the catalyst. Similarly, coupling of **2** with 5-benzyloxy-1-Boc-indole-2-boronic acid afforded **7**. Removal of the benzyl group of **7** proceeded smoothly under mild hydrogenolysis conditions to yield the phenol **8**. Alkylation of the phenol with alkyl chlorides and Cs_2CO_3 in DMF at 50 °C occurred to give protected intermediates **10**. Final removal

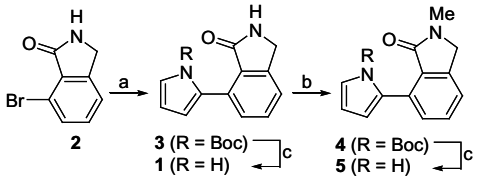


Scheme 2. Reagents and conditions: (a) 1-Boc-indole-2-boronic acid or 5-benzyloxy-1-Boc-indole-2-boronic acid, Pd(dppf)Cl_2, 2 N Na_2CO_3, THF (70–80%); (b) H_2 (balloon), 10% Pd/C, THF/MeOH, (100%); (c) Cs_2CO_3, DMF, 50 °C, R^2Cl, (65–83%); (d) TFA, DCM (95%) or 185 °C, neat (85–100%).

of the Boc group was achieved by either thermolytic cleavage or under acidic conditions using TFA in DCM at 25 °C to give the analogs **11**. Various indolyl analogs (**12c**, **12d**, **12f**–**12j**) were prepared using this general route (Scheme 2). Analogs **12a**, **12b**, and **12e** were synthesized from **12c** via an oxidation/reductive-amination sequence. The kinase data for representative analogs are summarized in Table 2.

Changing the pyrrole ring of pharmacophore **1** to an indole ring as in **12i** provided 10-fold better VEGF-R2 potency (IC_{50} = 144 nM) and a 3-fold increase in Aurora-A potency (IC_{50} = 100 nM). Molecular modeling suggested that substitution at the 5-position of the indole ring should be allowed as that position is solvent-exposed. Extension of the series through alkylation of the phenol **12h** afforded very potent inhibitors (**12a**–**12f**) of VEGF-R2 and Aurora-A. Generally, the VEGF-R2 potency tracked with the Aurora-A potency, with the most potent analogs having a pendant amine tethered to the indole ring by an alkyloxy linker. The length of the linker, either 2-carbon (**12d**) or 3-carbon (**12e**), did not have a significant effect on potency. All analogs of **12** were inactive against cyclin-dependent kinase—1 (CDK1, IC_{50} > 100 μM).

To continue variations of the left side of pharmacophore **1** we synthesized the carboxylic acid intermediate **18** (Scheme 3). Reaction of the commercially available 3-methyl phthalic anhydride (**13**) with MeOH and H_2SO_4 afforded an isomeric mixture of phthalic acid mono-esters. The isomeric mixture was converted to the bis methyl ester **14** with TMS diazomethane in toluene/MeOH. Treatment of **14** with NBS in CCl_4 using AIBN as a catalyst afforded the benzyl bromide **15**. Direct conversion of **15** to the isoindoli-



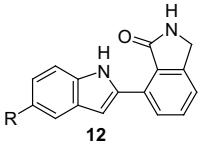
Scheme 1. Reagents and conditions: (a) Pd(OAc)$_2$, 2 N Na_2CO_3, P(*o*-tolyl)$_3$, 1-(*tert*-Butoxycarbonyl)pyrrole-2-boronic acid, DMF, (17%); (b) THF, NaH, MeI, (23%), (c) N_2, 185 °C, (73%).

Table 1
VEGF-R2, Aurora-A, and CDK1 kinase activity for **1**, **3**–**5**

Compound	VEGF-R2 IC_{50}[a] (μM)	Aurora-A IC_{50}[a] (μM)	CDK1 IC_{50}[a] (μM)
1	1.10	0.338	(63%)[b]
3	(46%)[b]	(25%)[b]	(<10%)[b]
4	>100	>100	>100
5	(<10%)[b]	(37%)[b]	(24%)[b]

[a] IC_{50} data are the average of at least two separate experiments. IC_{50} values listed as >100 indicate no observed 50% inhibition at the highest dose tested, nor was an inhibition maximum observed.
[b] Values in parentheses indicate % inhibition at 100 μM.

Table 2
VEGF-R2, Aurora-A, and CDK1 kinase activity for **12**



Compound	R	VEGF-R2 IC_{50}[a] (μM)	Aurora-A IC_{50}[a] (μM)	CDK1 IC_{50}[a] (μM)
12a	$O(CH_2)_3$4-ethyl-piperazin-1-yl	0.014	0.044	>100
12b	$O(CH_2)_3$4-hydroxy-piperidin-1-yl	0.018	0.061	>100
12c	$O(CH_2)_3OH$	0.030	0.100	>100
12d	$O(CH_2)_2$piperidin-1-yl	0.056	0.200	>100
12e	$O(CH_2)_3$piperidin-1-yl	0.065	0.179	>100
12f	$O(CH_2)_2$morpholin-4-yl	0.074	0.135	>100
12g	OMe	0.111	0.070	>100
12h	OH	0.119	0.090	13.3
12i	H	0.144	0.100	>100
12j	$OCH_2C_6H_5$	11.26	21.23	>100

[a] IC_{50} data are the average of at least two separate experiments. IC_{50} values listed as >10 or >100 indicate no observed 50% inhibition at the highest dose tested, nor was an inhibition maximum observed.