Discovery of Aryl Aminoquinazoline Pyridones as Potent, Selective, and Orally Efficacious Inhibitors of Receptor Tyrosine Kinase c-Kit†

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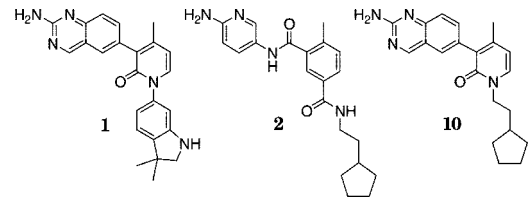
Abstract: Inhibition of c-Kit has the potential to treat mast cell associated fibrotic diseases. We report the discovery of several aminoquinazoline pyridones that are potent inhibitors of c-Kit with greater than 200-fold selectivity against KDR, p38, Lck, and Src. In vivo efficacy of pyridone **16** by dose-dependent inhibition of histamine release was demonstrated in a rodent pharmacodynamic model of mast cell activation.

Mast cells have been implicated in several fibrotic diseases such as scleroderma and idiopathic pulmonary fibrosis (IPF[a]).[1] These are grievous diseases with high mortality rates. Patients with IPF, for example, have a mean life span of 3−8 years from onset of disease. Mast cells are predominantly expressed beneath epithelia surfaces, in the mucosal and connective tissues of the skin, the airways, and the intestines. Considered as effector cells in allergy, inflammation, autoimmunity, and fibrosis, these cells are a major source of preformed TNF, pro-inflammatory, and profibrotic mediators.[2] In fibrosis, activated mast cells release mediators to promote fibroblast proliferation.[1] Reciprocally, fibroblasts secrete stem cell factor (SCF), also known as mast cell growth factor or Steel ligand, to induce further mast cell expansion and activation.[3] Excessive elevation of mast cell burden has been linked to various fibrotic diseases.[4] Furthermore, attenuation of fibrosis has been reported in mast cell deficient mice.[5] Therefore, regulation of mast cell proliferation and function may have therapeutic potential in fibrotic diseases.

Table 1. Comparison of Kinase Selectivity



kinase IC_{50}, (μM)[a]	1	2	10
c-Kit	0.0061	0.077	0.0010
KDR	0.048	>25	1.4
p38	0.20	0.99	5.8
Lck	0.019	1.9	0.58
Src	0.40	5.0	0.80

[a] Potency data is reported as an average of 2 runs.

Essential for mast cell survival, proliferation, activation, and chemotaxis is the activation of c-Kit receptors expressed on the surface of mast cells.[6] c-Kit is a member of the type III receptor tyrosine kinase family along with colony-stimulating factor-1 (cFMS) and platelet-derived growth factor receptor (PDGFR). c-Kit is activated upon binding of its cognate ligand, stem cell factor. Excessive levels of SCF or autoactivation of c-Kit, due to gain-of-function mutations, have been linked to mastocytosis.[6] The association between c-Kit, mast cells, and fibrosis is supported by several preclinical studies conducted with imatinib mesylate, a multikinase inhibitor that inhibited c-Kit.[7] In the clinic, imatinib treatment reduced bone marrow fibrosis in patients with chronic myelogenous leukemia.[8] Clinical evaluation of imatinib in IPF patients is currently underway.

We were interested in developing a potent and selective c-Kit inhibitor for the treatment of fibrotic diseases. To enhance the safety margin, we decided that a more selective c-Kit inhibitor that does not interfere with kinases associated with angiogenesis and immune cell signaling pathways, such as KDR, p38, Lck, and Src, was highly desired.

Our investigation began with novel pyridone **1**, which was identified by a screen of our proprietary kinase preferred library. Pyridone **1** was a nonselective inhibitor of c-Kit (IC_{50} = 6.1 nM, Table 1). This report describes the structure−activity relationship investigations that led to the discovery of potent c-Kit inhibitors that exhibited greater than 200-fold kinase selectivity against KDR, p38, Lck, and Src. Inhibition of c-Kit phosphorylation was measured by a homogeneous time-resolved fluorescent kinase assay and a SCF stimulated UT7 cell proliferation/survival assay. In vivo efficacy was assessed in a rodent pharmacodynamic model of mast cell activation to demonstrate proof-of-concept.

The general synthetic strategy for these pyridone analogues is illustrated in Scheme 1. In a two-step, one-pot protocol developed by Hynes and Campbell, 5-bromo-2-fluorobenzaldehyde **3** was reacted with guanidine carbonate at 160 °C to form 2-amino-6-bromoquinazoline **4**.[9] Miyaura conditions converted the aryl bromide to boronic ester **5**.[10] Preparation of PMB protected pyridine **7** was accomplished by reacting 3-bromo-2-chloro-4-methylpyridine **6** with (4-methoxyphenyl)methanol. Suzuki coupling of aminoquinazoline boronic ester **5** with bromo pyridine **7** afforded aminoquinazoline pyridine **8**. Deprotection with trifluoroacetic acid produced pyridone **9**. Selective N-alkylation was achieved with sodium hydride to form alkyl pyridone **10**. Buchwald's copper-catalyzed aryl amidation provided aryl pyridones **11**−**19** in good yield.[11]

† Atomic coordinates and structure factors for cocrystal structures of compounds **1**, **2**, and **16** with V916T KDR can be accessed using PDB codes 3CP9, 3CPB, and 3CPC, respectively.

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[a] Abbreviations: IPF, idiopathic pulmonary fibrosis; cFMS, colony-stimulating factor; PDGFR, platelet-derived growth factor receptor; SCF, stem cell factor; PMB, *para*-methoxy benzyl; SAR, structure−activity relationship; PK, pharmacokinetic; CL, clearance.

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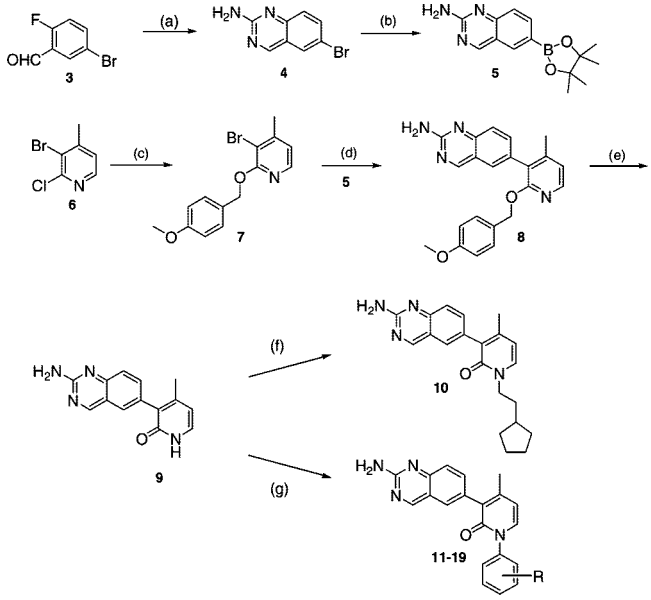
Scheme 1. General Preparation of Aryl Pyridones[a]



[a] Reaction conditions: (a) guanidine carbonate, DIPEA, NMP, 160°C, (48%); (b) bis(pinacolato)diboron, KOAc, $PdCl_2(dppf)\cdot CH_2Cl_2$, 85°C, (50%); (c) NaH, PMBOH, (96%); (d) $Pd(OAc)_2$, S-phos, K_3PO_4 (90%); (e) TFA; (f) NaH, 2-cyclopentylethyl 4-methylbenzenesulfonate, 70°C (20%); (g) CuI, K_3PO_4, DMEDA, ArI, NMP, 85°C (60−80% two steps).

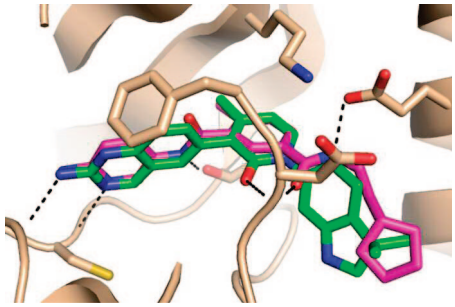


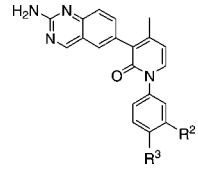
Figure 1. Overlap of co-crystal structures of pyridone **1** and bisamide **2** in V916T KDR mutant protein.

Our first approach to improve the kinase selectivity was to compare pyridone **1** to bisamide **2**, a more selective c-Kit inhibitor we recently reported (Table 1).[12] The aliphatic group on **2** was necessary for kinase selectivity, but the reason for the selectivity was not evident based on the co-crystal structure. Nevertheless, overlay of co-crystal structures of **1** and **2** in the V916T mutant KDR protein (a close analog of c-Kit) showed that the aliphatic section of **2** was also the region where the molecules most differed (Figure 1). We hypothesized that attaching a similar alkyl group to the pyridone scaffold could improve its kinase selectivity. Indeed, alkyl pyridones such as cyclopentylethyl **10** did obtain greater than 500-fold kinase selectivity. However, these pyridones also exhibited high in vivo clearance in rats. Attempts to enhance metabolic stability by adding heteroatoms to the alkyl groups decreased c-Kit activity.

Based on the overlapped structures, we then speculated that an investigation of substitutions on the 3- and 4- positions of the aryl pyridones could improve kinase selectivity. Furthermore, pharmacokinetic profiles of these pyridones might be more desirable. Thus, a systematic examination of the aryl pyridones was undertaken (Table 2). Devoid of any substitution on the lower aromatic ring, **11** exhibited decreased c-Kit activity (IC_{50} = 0.21 μM). Mimicking the *gem*-dimethyl group on **1** with a *tert*-butyl group at the 4-position, **12** regained c-Kit potency (IC_{50} = 2.1 nM) but exhibited poor selectivity. Further decreasing the steric bulk from trifluoromethyl group (**13**) to methoxy group (**14**) or chlorine (**15**) notably reduced inhibitory activity against KDR and p38 to the micromolar range. Regioisomer **16** exhibited comparable c-Kit potency and kinase selectivity. However, a nearly 4-fold decrease in c-Kit activity was observed with **17**. Whereas 3-fluoro-4-chloro substitution (**18**) reduced c-Kit potency, 3-fluoro-4-methyl substitution (**19**) afforded a potent c-Kit inhibitor with at least 125-fold selectivity and greater than 5 μM activity against KDR, p38, Lck, and Src.[13] Switching the positions of the methyl and fluoro groups (**20**) decreased kinase selectivity against Lck and Src.

Unfortunately, pyridone **19** also exhibited high clearance in rats (CL = 1.95 L/h/kg). With its 4-substituted methyl group a likely metabolic liability by oxidation, we examined alternative substituents at the 4-position to improve clearance. A representative subset of the analogs examined is shown in Table 3. Acetyl (**21**) and ethyl ester (**22**) replacements decreased selectivity against Lck and Src. While morpholine (**23**) restored Lck and Src activity to the micromolar range, N-linked pyrazole (**24**) reduced selectivity against Lck and Src. Fortunately, oxazole **25** resulted in both excellent c-Kit potency (enzyme IC_{50} = 22 nM, cell IC_{50} = 16 nM) and greater than 200-fold

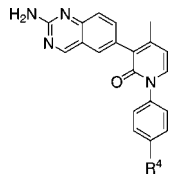
Table 2. SAR of Phenyl Ring Substitutions



cmpd	R^2	R^3	c-Kit Enzyme IC_{50}(μM)[a]	c-Kit cell IC_{50} (μM)[a]	KDR IC_{50} (μM)[a]	p38 IC_{50} (μM)[a]	Lck IC_{50} (μM)[a]	Src IC_{50} (μM)[a]
11	H	H	0.21		>1.0		1.7	0.99
12	H	^{t}Bu	0.0021	0.016	0.011	0.028	0.0072	0.036
13	H	CF_3	0.0079	0.018	1.8	3.9	1.2	0.75
14	H	OMe	0.017	0.018	>5.0	6.5	0.15	0.15
15	H	Cl	0.020	0.014	>5.0	4.9	0.34	0.26
16	CF_3	H	0.014	0.028	>5.0	6.1	1.7	0.86
17	OMe	H	0.065	0.028	>5.0	8.0	0.41	0.27
18	F	Cl	0.060	0.022	>5.0	9.2	0.48	0.39
19	F	Me	0.040	0.012	>5.0	40	25	25
20	Me	F	0.014	0.018	4.3	4.5	0.74	0.043

[a] Potency data is reported as an average of 2 runs.

Table 3. SAR of 4-Substituted Pyridones[a]



cmpd	R^4	c-Kit enzyme IC_{50} (μM)[a]	c-Kit cell IC_{50} (μM)[a]	KDR IC_{50} (μM)[a]	p38 IC_{50} (μM)[a]	LCK IC_{50} (μM)[a]	Src IC_{50} (μM)[a]
21	Ac	0.020	0.031	>5.0	18	0.57	0.39
22		0.017	0.068	>5.0	7.5	0.23	0.17
23		0.013	0.072	4.4	21	1.8	1.4
24		0.010	0.018	3.4	3.8	0.11	0.077
25		0.022	0.016	>5.0	40	7.8	>5.0

[a] Potency data is reported as an average of 2 runs.

Table 4. Comparison of Rat Pharmacokinetic Profiles[a]

cmpd	CL[b] (L/h/kg)	V_{dss}[b] (L/kg)	AUC_{0-t}[c] (ng*h/mL)	C_{max}[c] (ng/mL)	$T_{1/2}$[c] (h)	F[c] (%)
16	2.46	4.12	1036	253	1.83	25
19	1.95	2.39	1309[d]	280[d]	2.9[d]	100[d]
25	0.46	1.59	9860	1230	2.6	39

[a] Male Sprague−Dawley rats (n = 3). [b] iv, 1.0 mg/kg (DMSO). [c] po, 10.0 mg/kg (2% HPMC, 1% Tween 80, pH 2.0 with HCl). [d] po, 2.0 mg/kg (2% HPMC, 1% Tween 80, pH 2.0 with HCl).

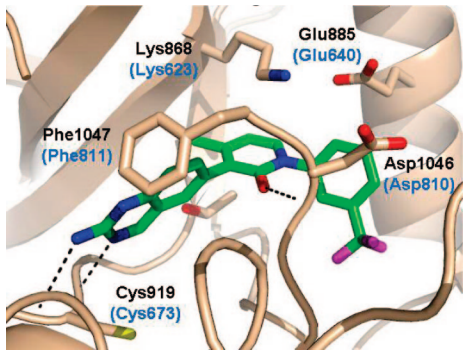


Figure 2. Co-crystal structure of **16** in mutant KDR (V916T), a close analog of c-Kit. mKDR residue numbers in black, and c-Kit residue numbers in blue.

selectivity against KDR, p38, Lck, and Src. Furthermore, clearance in rats also improved (CL = 0.46 L/h/kg, Table 4).

Although obtaining co-crystals of these pyridones in the c-Kit protein has been challenging, we succeeded in crystallizing **16** in mutant KDR (V916T). By changing the gatekeeper residue from valine to threonine, this mutant shares the majority of residues with c-Kit in the ATP binding pocket. On the basis of the co-crystal structure, we were able to infer the key interactions the compound would make in c-Kit (Figure 2). Occupying the ATP binding site, the inhibitor binds in the "DFG-out" conformation. Two nitrogens from the aminoquinazoline portion of the molecule form hydrogen bonding interactions with linker region of the enzyme at Cys673. The pyridone scaffold is further anchored by the hydrogen bond contacts between its carbonyl group and Asp810.

To evaluate the efficacy of these c-Kit inhibitors in vivo, pyridone **16** was tested in a clinically relevant rodent pharmacodynamic model of mast cell activation. Functional activation of

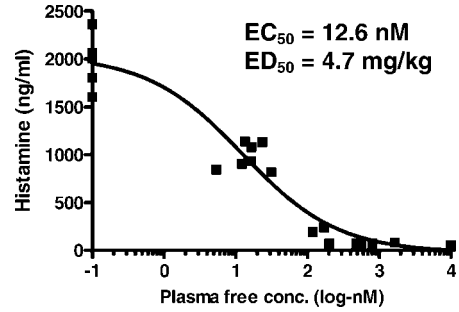
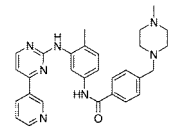
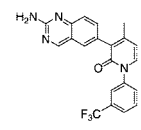
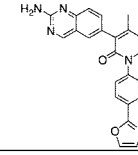


Figure 3. Pyridone **16** decreased SCF-induced release of histamine in a dose-dependent manner.

Table 5. Comparison of Imatinib and Pyridones **16** and **25**

IC_{50} (μM)[a]	imatinib 	16 	25 
c-Kit enzyme	0.052	0.014	0.022
c-Kit cell	0.046	0.028	0.016
KDR	>25	>25	>5.0
p38	14	6.1	>40
Lck	0.32	1.7	7.8
Src	>25	0.86	>5.0
Abl	0.098	1.4	>25
PDGFRα	0.018	0.009	
BE[b] (kcal/atom)	0.16	0.23	0.21

[a] Potency data is reported as an average of 2 runs. [b] BE = binding efficiency.

mast cells in vivo following systemic administration of recombinant human stem cell factor has been reported in the clinic. Moreover, SCF administration to nonhuman primate results in mast cell hyperplasia.[14] Thus, we used recombinant rodent SCF to promote mast cell activation in mice and assessed the extent of activation by measuring histamine release in the blood stream. The study began with a single oral administration of pyridone **16** to female C57BL/6 mice at 100, 20, and 5 mg/kg. One hour postdosing, 80 μg/kg of SCF was administered by intravenous injection. Fifteen minutes after SCF treatment, the mice were euthanized and blood was collected by cardiac puncture for histamine measurement and PK analysis. As shown in Figure 3, a dose-dependent decrease in SCF-induced histamine release was observed with ED_{50} of 4.7 mg/kg. With mouse protein binding of 87.85% by ultracentrifugation, free fraction EC_{50} was 12.6 nM, comparable to cell IC_{50} of 28 nM for **16**.[15]

Compared to imatinib, pyridones **16** and **25** exhibited comparable or better potency against c-Kit with approximately two-thirds of the molecular weight of imatinib (Table 5). Besides higher binding efficiency,[16] these two compounds also achieved improved selectivity against off-target kinases such as p38 and Lck. Both pyridones also exhibited better selectivity against Abl, while **16** showed comparable selectivity against PDGFR compared to imatinib. Better selectivity against Abl may be desirable given a reported link between cardiotoxicity and inhibition of Abl.[17] Because the residues comprising the ATP binding pocket of c-Kit and PDGFR are over 98% homologous, selectivity against PDGFR will likely be difficult to achieve.[18] To date, a c-Kit inhibitor with significant PDGFR selectivity has not been reported. Meanwhile, several studies have suggested that inhibition of PDGFR may be beneficial for treatment of certain fibrotic conditions.[19] Thus, a c-Kit

inhibitor with PDGFR activity but lacking KDR, p38, Lck, and Src activity may be desired. Further internal kinase screens showed that **16** and **25** were also selective against 36 and 41 other kinases, respectively.[20]

In conclusion, starting with a novel pyridone **1**, our SAR efforts resulted in the identification of potent, selective, and orally efficacious c-Kit inhibitors. Improvements in kinase selectivity were achieved with alkyl pyridone **10** and aryl pyridones **16**, **19**, and **25**. Pyridone **25** exhibited potent inhibition of c-Kit, greater than 200-fold selectivity against KDR, p38, Lck, and Src, and desirable pharmacokinetic properties. Oral efficacy in vivo was demonstrated in a clinically relevant rodent pharmacodynamic model of mast cell activation. Efficacy of c-Kit inhibition in a wound fibrogenesis model of mast cell activation and expansion will be reported in a separate publication.[21] These findings suggest that the pyridones are promising therapeutic compounds for the treatment of fibrotic diseases.

Supporting Information Available: Experimental details and characterization of all compounds, biological methods as well as X-ray crystal data for **1**, **2**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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