

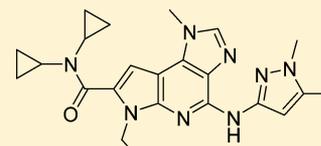
Discovery of a Highly Selective JAK2 Inhibitor, BMS-911543, for the Treatment of Myeloproliferative Neoplasms

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Supporting Information

ABSTRACT: JAK2 kinase inhibitors are a promising new class of agents for the treatment of myeloproliferative neoplasms and have potential for the treatment of other diseases possessing a deregulated JAK2-STAT pathway. X-ray structure and ADME guided refinement of C-4 heterocycles to address metabolic liability present in dialkylthiazole **1** led to the discovery of a clinical candidate, BMS-911543 (**11**), with excellent kinome selectivity, *in vivo* PD activity, and safety profile.



11 (BMS-911543)
JAK2 IC₅₀ = 1.1 nM
JAK1 / JAK3 / Tyk2 IC₅₀ (nM) = 360 / 75 / 66
SET-2 IC₅₀ = 60 nM

KEYWORDS: JAK2, selective inhibitor, myeloproliferative neoplasm, structure-guided design, BMS-911543

Myeloproliferative neoplasms (MPNs) are a subset of myeloid malignancies that are characterized by the expansion of a hematopoietic progenitor stem cell. MPNs encompass polycythemia vera (PV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF).¹ In the majority of cases, this cluster of diseases has been shown to be associated with the somatic mutation JAK2-V617F that constitutively activates the Janus kinase 2 (JAK2) enzyme, a member of the JAK family of nonreceptor tyrosine kinases.² In MPNs the acquisition of the JAK2-V617F and other JAK2-STAT pathway mutations result in cytokine-independent activation of the pathway and the uncontrolled growth of hematopoietic cells with erythrocytes, platelets, and granulocyte/monocytes being the predominant lineages expanded in ET, PV, and PMF, respectively.³ The uncontrolled growth of these cell lineages in MPNs results in severe patient complications including splenomegaly, hemorrhage, thrombosis, bone marrow fibrosis, and transformation to acute myeloid leukemia. The overall survival rate for patients afflicted with advanced myelofibrosis is estimated to be 3–5 years.⁴

The causal role of JAK2 in MPNs is supported by significant genetic and pharmacological data. Transgenic reconstitution of JAK2 mutations into rodent bone marrow stem cells results in a phenotype mirroring the main features of human MPNs including splenomegaly, bone marrow fibrosis, and elevated levels of certain hematopoietic lineages (e.g., erythrocytes, leukocytes).⁵ Administration of small molecule JAK2 kinase inhibitors reverses the pathophysiological features of the

transgenic phenotype.⁶ Moreover, clinical testing of two small molecule JAK2 inhibitors (e.g., ruxolitinib, fedratinib, pacritinib) showed effects on splenomegaly and normalization of blood counts (Figure 1).^{7–9} Based upon the late stage clinical efficacy and tolerability profile, ruxolitinib was approved to treat myelofibrosis (MF). Several other JAK2 inhibitors with varying degrees of JAK family as well as overall kinome selectivity profiles are in mid to late-stage clinical trials for MF.¹⁰ However, it is important to note that most of these compounds also inhibit other JAK family members that could be associated with immunosuppression, an undesired side effect for this indication. Additionally, other off-target kinome activities (e.g., FLT3) could further compromise the anticipated high safety window needed for long-term treatment in MPNs.

We have recently disclosed the identification of a potent and highly selective JAK2 inhibitor **1**.¹¹ X-ray crystallographic studies of **1** bound to the JAK2 kinase domain indicated that it engages the Tyr931 residue through hydrogen bonding with the thiazole nitrogen atom. In addition, unfavorable interactions of the 4,5-dimethylthiazole fragment with nonconserved residues in the extended hinge region of other JAK family members provided high selectivity. Further ADME profiling indicated that **1** was rapidly metabolized across species and was

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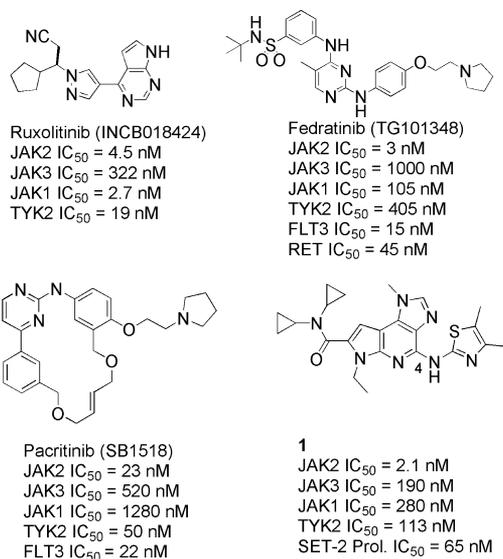


Figure 1. JAK2 inhibitors.

susceptible to generation of reactive metabolites (*vide infra*), which prevented its further progression. Herein we report ADMET and structure-guided optimization of heterocycles at the C-4 position of the imidazopyrrolopyridine core leading to the discovery of a highly selective JAK2 inhibitor, BMS-911543 (11), as a clinical candidate for the treatment of MPNs. Earlier we have reported biological characterization of BMS-911543.¹²

In vitro biotransformation studies with compound 1 using human liver microsomes revealed the formation of a thiourea metabolite in significant amounts (15%). This metabolic process presumably involves cytochrome P450-mediated oxidation of the thiazole ring to an epoxide and subsequent opening to form a diol intermediate. Decomposition of the diol intermediate leads directly to a thiourea and diketone species (Figure 2). Thioureas have the potential to form an active metabolite *in vivo*, which could disrupt thyroid function and could also have adverse effects in lung, liver, and bone marrow.¹³

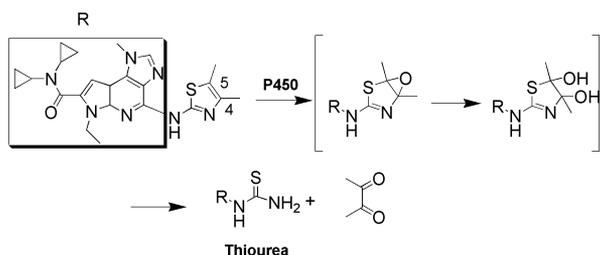
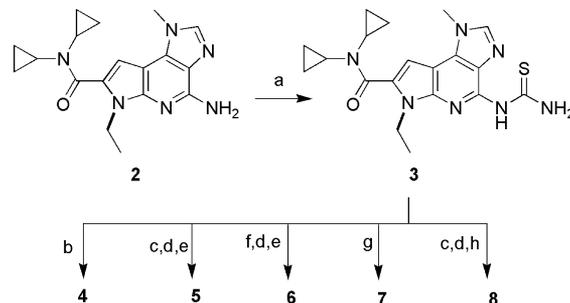


Figure 2. Metabolism of 1.

Literature reports indicated that the introduction of either electron withdrawing groups on the thiazole or increasing sterics may reduce initial complexation with CYP enzymes, which could suppress oxidative ring opening.^{13,14} Accordingly, analogues 4–8 were prepared using the approach outlined in Scheme 1, starting from aminopyridine 2.^{15,16}

As anticipated, adding substitution on the 4-methyl group (4) maintained the JAK family selectivity profile of the parent compound (Table 1). However, this change still resulted in formation of thiourea in significant amounts in *in vitro* biotransformation studies. Introduction of electron withdraw-

Scheme 1^a

^aReagents and conditions: (a) benzoylisothiocyanate, acetone; then 1 N NaOH, ethanol, 60 °C, 72%; (b) 3-bromopentan-2-one, 60 °C, 44%; (c) methyl 2-bromo-3-oxobutanoate, ethanol, 65 °C, 84%; (d) 1 N NaOH, methanol, 65 °C, 93%; (e) methylamine, HATU, 2,6-lutidine, DMF, 75%; (f) methyl 3-bromo-2-oxobutanoate, ethanol, 65 °C, 70%; (g) 1-bromo-1-(methylsulfonyl)propan-2-one ethanol, 65 °C, 62%; (h), 1,1-dioxo-1-thiomorpholine, HATU, 2,6-lutidine, DMF, 62%.

Table 1. Biotransformation and Thiazole Substitution SAR^{a,b,c}

Cmpd	R	%Thiourea observed ^c	JAK2 (IC ₅₀ , nM) ^{a,b}	JAK1 (IC ₅₀ , nM) ^{a,b}	JAK3 (IC ₅₀ , nM) ^{a,b}	SET-2 (IC ₅₀ , nM) ^{a,b}
1		13	2.1	190	280	65
4		23	1.4	250	460	92
5		MS ^d	0.9	19	19	120
6		MS ^d	3.1	22	49	100
7		MS ^d	1.4	40	52	51
8		ND ^e	0.7	48	31	330

^aAssay protocols are provided in the Supporting Information. ^bAssay results are the average of at least two replicates. ^cPercent thiourea determined in human liver microsomes. ^dOnly trace levels detected by mass spectrometry. ^eNo data was generated.

ing groups led to identification of potent JAK2 inhibitors (compounds 5–7), which were significantly less susceptible to generation of the thiourea metabolite. However, such substitutions caused considerable erosion of selectivity versus other JAK family kinases. With respect to the selectivity of the amide-containing thiazoles, differences in the JAK family members around JAK2 Gln 853 may provide a rationale for the loss in selectivity observed. The smaller serine present in JAK3 would likely be able to accommodate the larger polar amide-containing analogues. However, the arginine present in JAK1 could be positioned such that a favorable hydrogen bond to the amide at the 4- or 5-position on the thiazole may also contribute to loss of selectivity (Figure 3 for JAK1 model with compound 6). Further steric bulk on the amide (8) failed to

improve JAK family selectivity (compared to **1**) and reduced cellular potency.

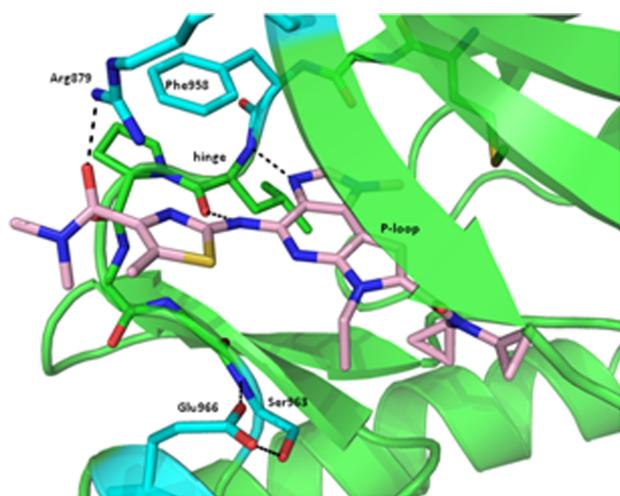
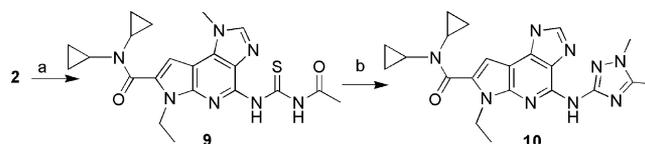


Figure 3. Model of **6** bound to the kinase catalytic domain of JAK1. The carbons of **6** are colored in pink, and the carbons for JAK1 are colored in green except for the residues near the C-4 group, which differ in the JAK family (carbons are colored cyan). Oxygen atoms are colored red, nitrogens blue, and sulfurs yellow. Hydrogen bonds are indicated with dashed lines.

We next turned our attention to explore other closely related five-membered isosteric dialkylthiazole ring isosteres that would dispose alkyl groups in the extended hinge region similar to **1** (Table 2). Accordingly, triazole analogue **10** was prepared (Scheme 2).¹⁷

Triazole **10** displayed modest JAK2 potency and high JAK family selectivity. We postulated the loss of potency may be due to a disfavored interaction of the triazole ring nitrogen with the pyridyl nitrogen forcing the rings to adopt a less planar conformation than compound **1**. Removal of a nitrogen from

Scheme 2.^a



^aReagents and conditions: (a) acetyl isocyanate, acetone, 35 °C, 44%; (b) methyl hydrazine, AcOH, 80 °C, 31%.

the triazole ring re-established the planarity (*vide infra*) and led to the discovery of 1,5-dimethyl pyrazole analogue **11**. Compound **11**, henceforth referred to as BMS-911543, displayed an IC₅₀ of 1.1 nM against JAK2 and was approximately 350-, 75-, and 65-fold selective vs JAK1, JAK3, and TYK2, respectively. Assessment of dissociation constants of BMS-911543 for JAK1, JAK2, and JAK3 indicated greater selectivity with K_i values of 110, 0.48, and 360 nM, respectively. BMS-911543 was also evaluated in the KinomeScan (formerly Ambit) panel (consisting of 451 kinases) as well as the internal kinase panel to assess overall kinome selectivity. It displayed a high level of selectivity across the kinome (see Supporting Information for complete data set).¹⁸

The X-ray structure of BMS-911543 bound to the JAK2 kinase domain displayed a similar binding mode as **1**. One of the nitrogens of the pyrazole ring formed a hydrogen bond with Tyr931 while maintaining coplanarity with the pyrrolopyridine scaffold. The 1,5-dimethyl pyrazole occupied the extended hinge region where key residue differences such as JAK2-Gln853, JAK3-Ser826, JAK1-Arg868, and TYK2-Arg901 resulted in high selectivity within the JAK family (see Figure 4 for location of other nonconserved residues that may affect selectivity).¹⁹

As expected the introduction of bulkier substitution on the pyrazole nitrogen resulted in further enhancement of selectivity within the JAK family (>140-fold) as observed for the analogue **12** while retaining the positive attributes found in BMS-911543.

Table 2. C-4 Heterocycle SAR^{a,b}

Cmpd	R	JAK2 (IC ₅₀ , nM) ^{a,b}	JAK1 (IC ₅₀ , nM) ^{a,b}	JAK3 (IC ₅₀ , nM) ^{a,b}	TYK2 (IC ₅₀ , nM) ^{a,b}	SET-2 (IC ₅₀ , nM) ^{a,b}
1		2.1	190	280	280	65
10		33	6000	3800	ND	1300
11		1.1	75	360	66	60
12		1.5	330	210	220	55
13		230	540	5000	2300	>2000
14		1.2	16	87	1.9	53

^aAssay protocols are provided in the Supporting Information. ^bAssay results are the average of at least two replicates.

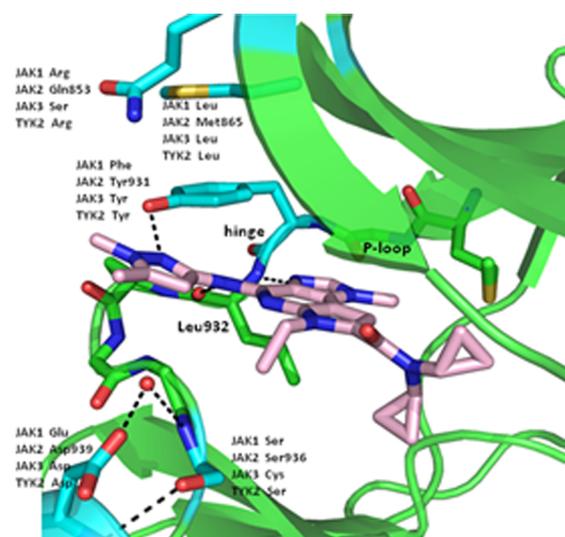
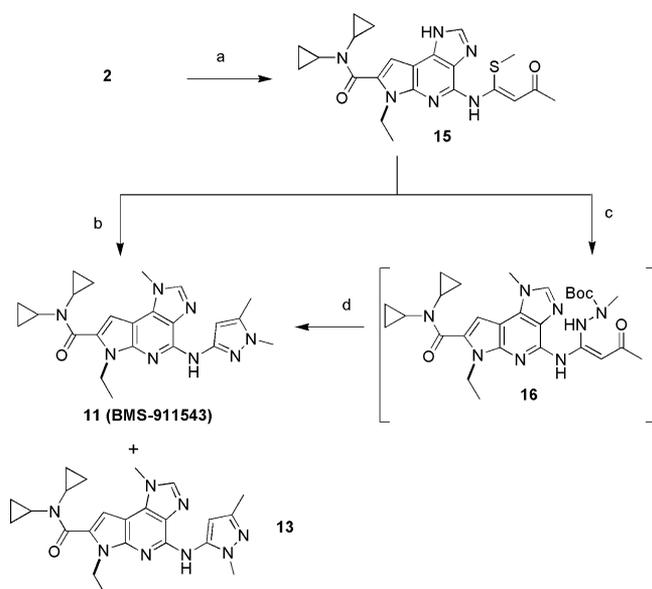


Figure 4. Crystal structure of BMS-911543 bound to the kinase catalytic domain of JAK2. The carbons of BMS-911543 are colored in pink and the carbons for JAK2 are colored in green except for the residues near the C-4 group, which differ in the JAK family (carbons are colored cyan). Oxygens are colored red, nitrogens blue, and sulfurs yellow. Hydrogen bonds are indicated with dashed lines.

In contrast, 1,3-dimethylpyrazole substitution (**13**) was found to be detrimental to JAK2 potency and selectivity, probably due to lack of the hydrogen bonding interaction with Tyr931 and suboptimal hydrophobic interaction with the extended hinge region. Consistent with our model, removal of the methyl group from the pyrazole nitrogen (**14**) led to significant loss of JAK family selectivity.

Although compound **12** displayed superior JAK family selectivity, it demonstrated higher potential for QT prolongation in the patch clamp hERG channel assay (75% and 20% inhibition for **12** and BMS-911543 at 30 μM , respectively). In addition, **12** also showed an inferior pharmacokinetic profile compared to BMS-911543 and hence was not progressed further for additional studies.

BMS-911543 and related pyrazoles were synthesized using the reaction sequence depicted in Scheme 3. Condensation of **2**

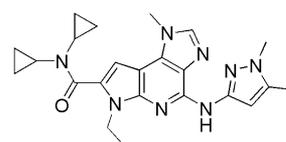
Scheme 3^a

^aReagents and conditions: (a) NaH, 4,4-bis(methylthio)but-3-en-2-one, DMF, RT, 75%; (b) methyl hydrazine, EtOH, 85 °C, 30%; (c) *tert*-butyl 1-methylhydrazinecarboxylate, AcOH, 50 °C; (d) formic acid, 60 °C, 65%.

with 4,4-bis(methylthio)but-3-en-2-one gave intermediate **15**. Initially, **14** was directly combined with methyl hydrazine furnishing a 1:9 mixture of desired 1,5- and undesired 1,3-dimethylpyrazole regioisomers (BMS-911543 and **13**, respectively).²⁰ By subjecting **15** to condensation with *tert*-butyl 1-methylhydrazinecarboxylate followed by subsequent treatment with formic acid, BMS-911543 was formed exclusively.²¹ The reaction sequence proceeds through the kinetically formed intermediate **16**, which undergoes cyclization after Boc-deprotection to yield the desired regioisomer. Pyrazoles **12** and **14** were prepared from **15** in analogous manner as BMS-911543.

In cellular assays, BMS-911543 showed potent antiproliferative activity in the SET-2 as well as BaF3-V617F engineered cell lines (both dependent upon JAK2 pathway), with IC₅₀ values of 60 and 70 nM, respectively. The antiproliferative activity of BMS-911543 in SET-2 and BaF3-V617F cells correlated with similar activity on constitutively active pSTAT5 (IC₅₀ 80 and 65 nM, respectively). In contrast, non-JAK2-

dependent cell lines (A549, MDA-MB-231, MiaPaCa-2) were significantly less sensitive to the inhibitor treatment. The excellent biochemical selectivity versus JAK1/3 translated to good cellular and functional selectivity in an IL-2 mediated T-cell proliferation assay (IC₅₀ 990 nM).¹² Also, cell lines that rely on other JAK family members, including CTLL2 and parental BaF3 cells stimulated with IL-3, showed weak antiproliferative activity for BMS-911543 (IC₅₀ 2.9 and 3.5 μM , respectively) (Figure 5).¹²



BMS-911543

JAK Family Selectivity:

JAK2 IC₅₀ = 1.1 nM (K_i = 0.48 nM)
 JAK3 IC₅₀ = 75 nM (K_i = 360 nM)
 JAK1 IC₅₀ = 360 nM (K_i = 110 nM)
 TYK2 IC₅₀ = 66 nM

Cellular and Functional Activity:

Cellular:
 SET2 IC₅₀ = 60 nM
 BaF3-V617F IC₅₀ = 61 nM
 A549 IC₅₀ = 2400 nM
 Ba/F3 + IL-3 IC₅₀ = 3500 nM
 CTLL2 IC₅₀ = 2900 nM

Functional:

IL-2 mediated T Cell Prol IC₅₀ = 990 nM
 (JAK1/3)

Mechanistic:

SET2 pSTAT5 IC₅₀ = 80 nM
 BaF3-V617F pSTAT5 IC₅₀ = 70 nM

Figure 5. Biochemical and cellular data summary of BMS-911543.

BMS-911543 suppressed the pSTAT5 levels (mediated by wild type JAK2) relative to vehicle control when stimulated with thrombopoietin (TPO) in a mouse pharmacodynamic model.¹² The responses were dose dependent and resulted in nearly complete normalization of pSTAT5 levels for 18 h at the highest oral dose of 30 mg/kg. At an intermediate 10 mg/kg oral dose, ~65% reduction was observed up to 18 h, whereas at the 5 mg/kg dose, approximately 50% reduction in pSTAT5 for 8 h was achieved. Observed pSTAT5 reductions correlated with exposures of BMS-911543, with AUC_{0-8h} values of 23, 41, and 109 $\mu\text{M}\cdot\text{h}$, respectively, for dose levels of 5, 10, and 30 mg/kg. In addition, BMS-911543 demonstrated a potent and sustained (2 mg/kg up to 7 h) PD effect in blocking pSTAT5 formation in mice grafted with human SET-2 cells harboring JAK2-V617F mutation.

In *in vitro* ADMET profiling assays, BMS-911543 showed good metabolic stability, excellent intrinsic permeability, and moderate drug–drug interaction potential based upon CYP inhibition of the CYP3A4 and CYP1A2 isoforms. In an *in vitro* safety panel consisting of 45 targets, BMS-911543 showed IC₅₀ > 25 μM for all targets except PDE4 (IC₅₀ 5.6 μM). BMS-911543 was not mutagenic or clastogenic in exploratory Ames and *in vitro* micronucleus assays, respectively. In addition to weak activity in the patch clamp hERG assay, BMS-911543 also showed similar trends in *in vitro* Na⁺ and Ca²⁺ binding assays, indicating a low potential to cause cardiovascular effects (Table 3). In *in vitro* biotransformation studies with human liver microsomes, BMS-911543 formed small amounts (~4%) of 1-demethylated metabolite (compound **14**) as the major metabolite.

The pharmacokinetics of BMS-911543 was investigated in mice, rats, dogs, and monkeys (Table 4 and Supporting Information). The absolute oral bioavailability in solution was

Table 3. In Vitro ADMET Profile of BMS-911543

metabolic stability ($T_{1/2}$ min)	49 (H), 108 (M), 69 (R), 70 (D)
PAMPA (pH 7.4)	698 nm/sec
HLM CYP IC_{50}	all >40 μ M; except CYP3A4 (3 μ M) and 1A2 (1 μ M)
hERG patch clamp	20% inh at 30 μ M
Na ⁺ patch clamp	<10% inh at 10 μ M (1 Hz and 4 Hz)
Ca ²⁺ patch clamp IC_{50}	>80 μ M
PXR EC_{50}	>50 μ M
HEPG2 IC_{50}	>50 μ M

Table 4. Pharmacokinetic Profile of BMS-911543

PK	mouse ^a	rat ^b	dog ^c	cyno ^d
CL (mL/min/kg)	0.55	0.7	6.5	5.3
V _{ss} (L/kg)	0.26	0.3	1.6	1.1
$T_{1/2}$ (h)	5.1	5	2.2	2.4
F (%)	100	100	82	53

^aMice were dosed 2.0 mg/kg IV and 10.0 mg/kg PO. ^bRats were dosed 1.0 mg/kg IV and 1.0 mg/kg PO. ^cDogs were dosed 0.2 mg/kg IV and 0.2 mg/kg PO. ^dCyno were dosed 1.0 mg/kg IV and 1.0 mg/kg PO.

>50% in all the species tested. In addition, the absorption of BMS-911543 was not significantly impacted by particle dissolution (suspension formulation), with a relative bioavailability (vs solution) of ~60% in rats and ~100% in dogs.

In single-dose toxicological studies, BMS-911543 was well tolerated up to 100 mg/kg in rats (mean AUC_{0-72h} 11300 μ M·h) and dogs (AUC_{0-24} 610 μ M·h). In two-week repeat dose studies in rats, a 15 mg/kg/day dose (Day 14 AUC_{0-24} 3200 μ M·h) was well tolerated. The most sensitive effects observed were decreases in reticulocytes and subsequent reductions in red blood cell mass. These effects, and observed decreases in platelets, are consistent with JAK2 inhibition.

In summary, ADMET and X-ray structure-guided refinement of the C-4 heterocycle to address metabolic liability present in 4,5-dimethylthiazole **1** led to the discovery of BMS-911543 (**11**), with excellent kinome selectivity, *in vivo* pharmacodynamic activity, and safety profile. BMS-911543 is currently in clinical trials for the treatment of MF.²²

■ ASSOCIATED CONTENT

📄 Supporting Information

Full experimental details for key compounds and biological protocols. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.5b00226.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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