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Discovery of novel FMS kinase inhibitors as anti-inflammatory agents

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Abstract—The optimization of the arylamide lead **2** resulted in identification of a highly potent series of 2,4-disubstituted arylamides. Compound **8** (FMS kinase IC_{50} = 0.0008 μM) served as a proof-of-concept candidate in a collagen-induced model of arthritis in mice.

The colony stimulating factor-1 receptor (CSF-1R, also known as M-CSFR, or FMS) is the exclusive receptor for its ligand, colony stimulating factor-1 (CSF-1 or macrophage colony stimulating factor, M-CSF). The binding of CSF-1 to the extracellular domain of FMS induces the dimerization and trans-autophosphorylation of several cytoplasmic tyrosine residues. These phosphorylated sites function as binding sites for Src homology-2 (SH2) domain-containing signaling proteins which promote gene expression and proliferation. High expression of FMS is limited principally to monocyte/macrophages, oocytes, trophoblasts, mammary epithelium (during lactation), and to cells of the macrophage lineage, while CSF is the predominant growth factor for macrophage lineage cells including osteoclasts.[1,2] Recent studies have demonstrated a direct correlation between tumor-associated macrophage numbers and tumor progression[3] and between synovial macrophage numbers and disease severity in rheumatoid arthritis.[4] Further, osteoclasts mediate bone erosions leading to pain and fracture in metastatic bone disease and deformity in rheumatoid arthritis.

Hence the inhibition of FMS appears to be of therapeutic value in treating diseases such as rheumatoid arthritis and metastatic cancer to the bone where osteoclasts and macrophages are pathogenic. This hypothesis is also well-supported by the biological studies conducted with CSF-1 deficient mice.[5–7]

A recent publication[8] describes the identification of arylamides (**1** and **2**) as FMS inhibitors. Herein we describe the results of further investigation of the SAR of this chemotype and the identification of a potent FMS inhibitor suitable for in vivo studies (See Fig. 1).

In addition to the lead-like properties of the 5-hydroxymethyl compound **2**, it also stabilized an engineered form of the FMS kinase domain[9] and thereby provided X-ray crystallographic information to guide optimization efforts. It was immediately apparent from the

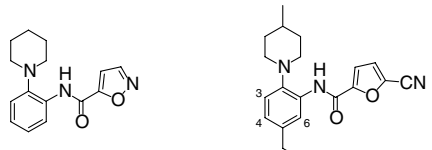

Figure 1. FMS high-throughput screening hit **1** and the lead compound **2**.

Keywords: FMS; CSF-1R; M-CSF; Colony stimulating factor-1; Macrophages; Anti-inflammatory activity.
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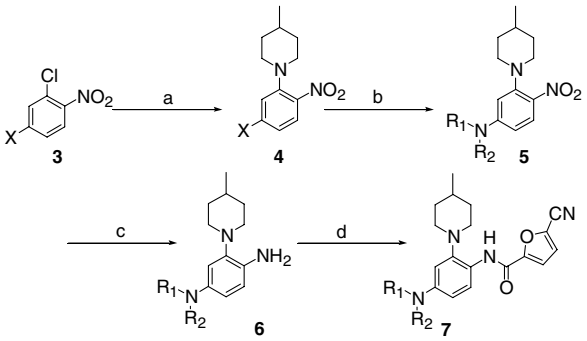


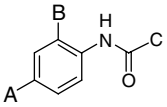
Scheme 1. Synthesis of 2,4-disubstituted arylamides. Reagents and conditions: (a) 4-methylpiperidine/ rt; (b) R_1R_2NH, THF, reflux 2 h; (c) H_2, Pd/C, EtOH, rt, 1 h; (d) 5-cyanofuran-2-carbonyl chloride, DCM, Et_3N, rt, 3 h.

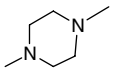
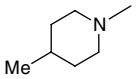
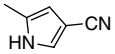
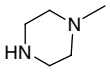
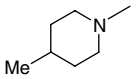
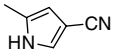
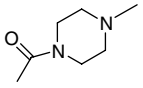
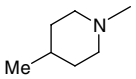
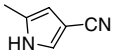
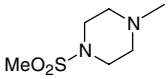
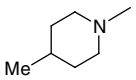
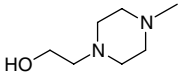
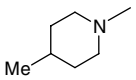
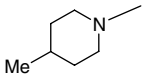
co-crystal structure of FMS and **2** that there was insufficient space at the 6-position of the benzene ring to allow substitution without significant disruption of key binding interactions. Initial efforts geared toward exploring the C-5 position did not lead to further improvement in potency of the lead compound (data not shown). The co-crystal structure of the kinase domain of FMS and **2**[8] revealed the C-4 position to be a promising site for further elaboration, and optimization efforts began at this site.

The synthesis of compound **7** in Scheme 1 illustrates the general chemistry involved in the synthesis of the 2,4-disubstituted arylamide chemotype. The initial focus was the introduction of amine substituents at the 2- and 4-positions as the ease of sequential S_NAr reactions on dihalonitrobenzenes permitted rapid analoging for SAR development. Two consecutive S_NAr reactions of 2,4-dichloronitrobenzene **3** (X = Cl) with 4-methylpiperidine and a primary or secondary amine in refluxing THF, respectively, installed the desired C-2 and C-4 substituents in high yields. The reduction of the nitro group to the aniline followed by standard amide bond formation with 5-cyanofuran-2-carbonyl chloride afforded the desired final product **7**. Compound **16** was prepared using thiomorpholine as the second nucleophile followed by oxidation prior to acid chloride coupling. Compounds **15** and **20** were prepared employing methylamine as the second nucleophile followed by acylation and sulfonylation prior to the amide bond formation. Compound **19** was made in the same fashion using NH_3 in place of methylamine. Compound **21** was made substituting amine R_1R_2NH with sodium ethoxide. Compound **22** was synthesized by the Sonogashira coupling of propargyl alcohol with intermediate **4** where X = Br, followed by Pd-catalyzed hydrogenation, mesylation and substitution of the mesylate with methylethylamine followed by acylation of the resulting aniline.

First, the SAR at the C-4 position (Table 1, A) was explored with a variety of N-substitutions, including both saturated and unsaturated N-containing heterocycles. As we have previously reported that both 5-cyanofuran

Table 1. FMS enzyme inhibitory activity[10] for **8**–**23**



Compound	A	B	C	FMS IC_{50}[a] (μM)
8				0.0008
9				0.0010
10				0.0007
11				0.0009
12				0.0006
13				0.0110

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