Bioorganic & Medicinal Chemistry Letters 20 (2010) 2560–2563

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Amide-based inhibitors of p38α MAP kinase. Part 2: Design, synthesis and SAR of potent *N*-pyrimidyl amides

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ARTICLE INFO

Article history:
Received 8 January 2010
Revised 23 February 2010
Accepted 24 February 2010
Available online 2 March 2010

Keywords:
p38
MAP
Kinase
Antiinflammatory

ABSTRACT

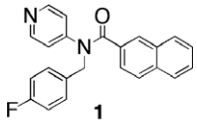
Optimization of a tri-substituted *N*-pyridyl amide led to the discovery of a new class of potent *N*-pyrimidyl amide based p38α MAP kinase inhibitors. Initial SAR studies led to the identification of 5-dihydrofuran as an optimal hydrophobic group. Additional side chain modifications resulted in the introduction of hydrogen bond interactions. Through extensive SAR studies, analogs bearing free amino groups and alternatives to the parent (*S*)-α-methyl benzyl moiety were identified. These compounds exhibited improved cellular activities and maintained balance between p38α and CYP3A4 inhibition.

p38 Mitogen-activated protein kinase (MAPK) is a serine–threonine protein kinase and one of the best characterized enzymes involved in the inflammatory process.[1,2] Of the four isoforms (α, β, γ, and δ), p38α is the most studied and perhaps the most physiologically relevant kinase involved in inflammatory responses.

p38α MAP kinase is activated in response to cellular stress, growth factors and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). Once activated, p38α stimulates cytokine production through activation of additional kinases leading to phosphorylation of heat shock proteins and transcription factors. Since modulation of cytokines has shown clinical efficacy in treating inflammatory disorders such as rheumatoid arthritis,[3–5] inflammatory bowel disease,[6] congestive heart failure[7] and psoriasis,[8] the ability of p38α to modulate cytokine production has led to its implication in inflammation-based pathologies.[2,9–13]

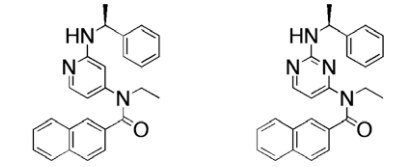
Driven by the central role of p38α in settings of inflammation, this enzyme has been an active target for drug discovery efforts over the past decade.[14–18] Contributing to these efforts, we previously described initial studies focusing on a novel class of *N*-pyridyl amides (Fig. 1).[19]

Subsequent SAR studies involving incorporation of a (*S*)-α-methyl benzyl moiety at the 2-position of the pyridine accompanied by additional structural modifications led to the discovery of compound **2**.[19] Later conversion of the pyridine to a pyrimidine resulted in identification of compound **3** (Fig. 2) possessing



1
p38α IC_{50} 1.26 μM

Figure 1. Structure and potency of *N*-pyridyl amide lead **1**.



2
p38α IC_{50} 0.313 μM
dWBA >1 μM

3
p38α IC_{50} 0.064 μM
dWBA 0.187 μM

Figure 2. Structure and potency comparison between *N*-pyridyl amide **2** and *N*-pyrimidyl amide **3**.

significant improvements in potency against p38α in both enzymatic and cell-based assays. Herein we describe our subsequent SAR activities focused on the pyrimidine scaffold.

As illustrated in Figure 3, the proposed binding mode of the *cis*-conformer of **3** in the ATP binding site of p38α MAP kinase involves a hydrogen bond between a pyrimidine nitrogen and the amide NH of Met-109. An additional hydrogen bond is noted between the

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doi:10.1016/j.bmcl.2010.02.090

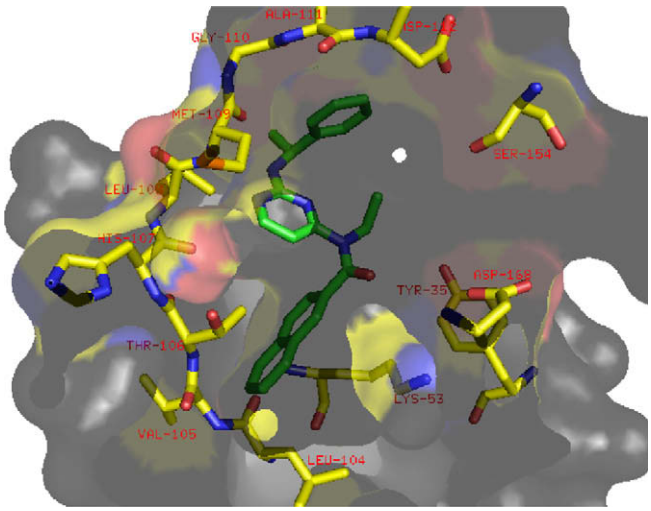
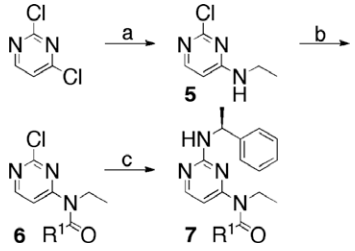


Figure 3. Proposed binding mode of **3** in the p38α ATP binding site.[20]

bridging NH and the Met-109 carbonyl. The naphthyl group occupies the Thr-106 hydrophobic pocket known to be responsible for p38α kinase specificity.[23–25] The α-methyl benzyl moiety occupies an additional hydrophobic pocket. The model also identifies a distal hydrogen bonding formed between the amide carbonyl of **3** and the Lys-53 side chain. Based on this binding mode, we hypothesize that potency enhancements may be achieved through incorporation of additional hydrogen bonds with neighboring amino acids, such as Asp-112, Ser-154, Asp-168 and Tyr-35.

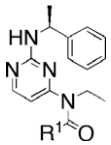
The compounds of the present study were prepared as illustrated in Scheme 1. As shown, reaction of 2,4-dichlo-pyrimidine with ethylamine gave 2-chloro-4-ethylaminopyrimidine, **5**. Deprotonation with NaH followed by quenching with various acid chlorides allowed development of the R^1 SAR. Final treatment with (*S*)-α-methyl benzyl amine via palladium catalysis gave the desired final products, compounds **7**.[26] The p38 activities for this series are summarized in Table 1.

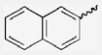
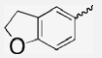
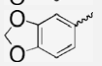
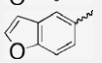
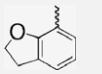
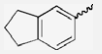
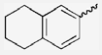
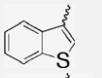
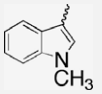
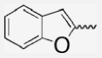
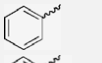
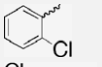
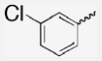
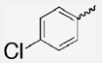
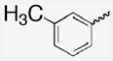
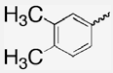
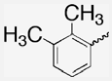
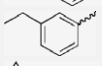
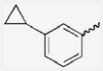
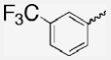
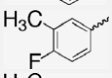
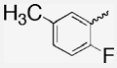
As shown in Table 1, compared to the 2-naphthyl analog, **3**, compounds bearing bicyclic groups such as 5-dihydrobenzofuryl, **7a,** and 5-indanyl, **7e,** showed improved enzyme activity. In contrast, analogs incorporating groups such as 3,4-(methylenedioxy)phenyl, **7b**, 7-dihydrobenzofuryl, **7d**, 3-benzo-thienyl, **7g**, *N*-methyl-3-indolyl, **7h,** and 2-benzofuryl, **7i,** were several fold less active. Regarding compound **7f**, the fourfold loss in potency compared to **7e** may be caused by steric effects due to a six-membered ring versus a five-membered ring. Due to this hypothesis, a series of analogs bearing monocyclic groups at R^1 was prepared. This hypothesis was validated through the observation that substituted phenyl groups were compatible with potent p38α inhibition. Of particular interest were *meta*-substituted compounds **7l**, **7o**, **7r**, and **7t**—all showing activity in the enzyme assay at approximately 80 nM or better. The two most



Scheme 1. General synthesis of *N*-pyrimidyl amides **7**. Reagents and conditions: (a) ethyl amine, K_2CO_3, DMF, 45%; (b) NaH, DMF then acid chloride, 70–95%; (c) (*S*)-α-benzyl amine, $Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane, 110 °C, 30–80%.

Table 1
p38α enzyme and cellular activity for compounds **7a–v**



Compd	R^1	p38α IC_{50} (μM, $n = 3$)[21]	dWBA (μM, $n = 3$)[22]
3		0.064	0.187
7a		0.017	0.387
7b		0.164	>1
7c		0.071	0.313
7d		0.09	0.829
7e		0.045	0.3
7f		0.180	>1
7g		0.188	>1
7h		0.154	>10
7i		0.179	>10
7j		0.193	>10
7k		0.267	>1
7l		0.081	0.533
7m		0.313	>10
7o		0.013	0.14
7p		0.091	0.143
7q		0.081	0.4
7r		0.065	0.152
7s		0.104	0.349
7t		0.064	>1
7u		0.039	0.178
7v		0.026	0.058

potent compounds (**7u** and **7v**) were identified as the more metabolically stable analogs of **7o**. In reconciling the enzyme inhibitory activity with the proposed binding mode in Figure 3, it appears that the hydrophobic pocket formed by Thr-106, Val-105, and Leu-104 can tolerate both polar and non-polar substituents. However, when polar groups reside in this pocket, activity is dependent upon the orientation of the group.