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Piperidine-based heterocyclic oxalyl amides as potent p38α MAP kinase inhibitors

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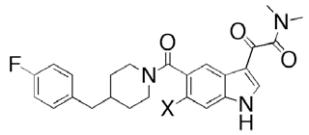
ABSTRACT

The design and synthesis of a new class of p38α MAP kinase inhibitors based on 4-fluorobenzylpiperidine heterocyclic oxalyl amides are described. Many of these compounds showed low-nanomolar activities in p38α enzymatic and cell-based cytokine TNFα production inhibition assays. The optimal linkers between the piperidine and the oxalyl amide were found to be [6,5] fused ring heterocycles. Substituted indoles and azaindoles were favored structural motifs in the cellular assay.

The pro-inflammatory cytokines, tumor necrosis factor alpha (TNFα), and interleukin 1 beta (IL-1β) are known to be involved in the pathogenesis of inflammatory disorders such as rheumatoid arthritis (RA), Crohn's disease, and psoriasis.[1–4] The FDA approval of biologics (Enbrel®, Remicade®, Humira®, and Kineret®) specifically targeting these cytokines by mimicking their receptors[5–8] have demonstrated the effectiveness of this treatment paradigm. However, like many biological agents, these drugs have disadvantages relating to high costs and inconvenient dosing regimens. Thus, there remain unmet needs for developing safe, effective, and orally active small molecule inhibitors that serve the same therapeutic functions.

p38 MAP kinase is a serine–threonine protein kinase and is identified initially as the molecular target of a pyridylimidazole class of compounds. These compounds are known to inhibit the biosynthesis of TNFα and IL-1β in lipopolysaccharide (LPS)-stimulated human monocytes.[9] Among the four known isoforms of p38 (α, β, γ, and δ), the α and β isoforms are the most widely expressed. While the function of the β isoform is not well understood, the α isoform has been shown to be a control point which, when activated, translates multiple stimuli to multiple responses and results in the release of a pro-inflammatory cassette of cytokines including IL-1β, IL-6, and TNFα.[10] As p38α activation is not involved in normal physiology, it is believed that inhibition of this kinase target could result in a reduction of the levels of these cytokines that are thought to play a pathophysiological role in many inflammatory diseases. Therefore, p38α MAP kinase is considered to be a potential therapeutic target for the treatment of inflammatory diseases such as RA[11,12] and has been the focus of many clinical candidates by various pharmaceutical companies in the past decades.[13,14]

We previously reported the discovery of a novel series of 4-fluorobenzylpiperidine indole-based p38α MAP kinase inhibitors represented by Figure 1.[15] The proposed binding mode of **1** in the ATP site of p38α MAP kinase (Fig. 2) shows this class of molecules



1, X = Cl, p38α IC_{50} 0.018 μM
2, X = OMe, p38α IC_{50} 0.01 μM

Figure 1. Structures and potencies of 4-fluorobenzylpiperidine indole analogs, **1** and **2**.

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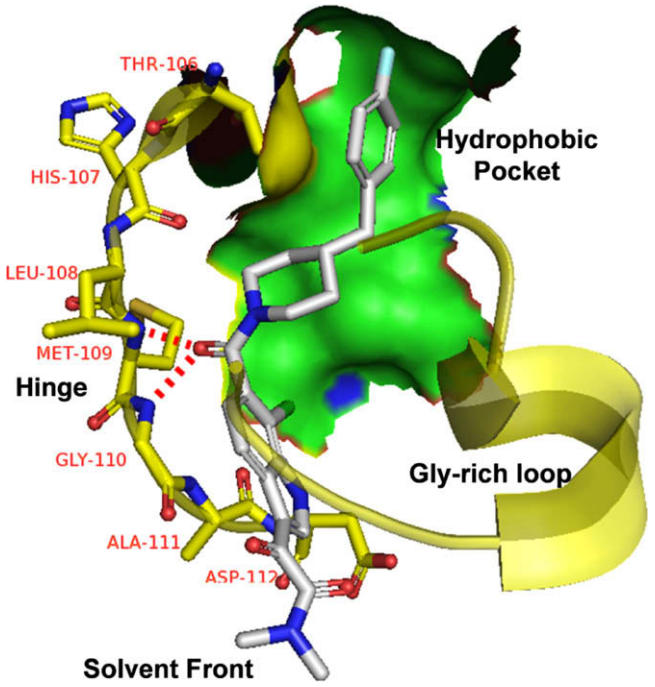


Figure 2. Proposed binding mode of piperidine indole analog **1** in the ATP site of p38α MAP kinase.

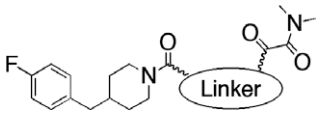
forming a critical hydrogen bond with the kinase backbone at hinge amino acid Met-109.[16] Additionally, the 4-fluorobenzyl group occupies an adjacent hydrophobic pocket that is both critical for activity and, as shown in the literature,[17–19] is a crucial region relating to kinase specificity. Substitutions such as chlorine, methoxy and methyl ortho to the amide moiety at indole position 6 were found to improve p38α enzymatic potency presumably due to the restricted conformation along the carbonyl aryl C–C bond. An oxalyl amide modification at C-3 of the indole was found to further improve enzyme activity. While findings in several of these areas will be the focus of future publications, this Letter describes structure–activity data relating to the heterocyclic core only.

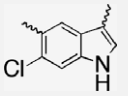
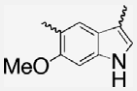
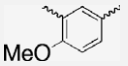
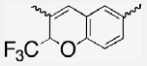
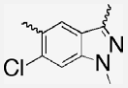
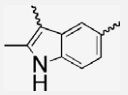
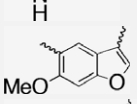
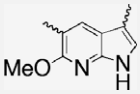
Due to a lack of X-ray crystallographic data at the time of our studies, the exact role of the oxalyl amide was unknown and attention was focused on whether an indole was the optimal linker joining the piperidine amide to the oxalyl amide. Thus, a number of heterocyclic analogs with either different lengths or different electronic properties relative to indole were proposed. Representative analogs, compounds **4–9**, are illustrated in Table 1.

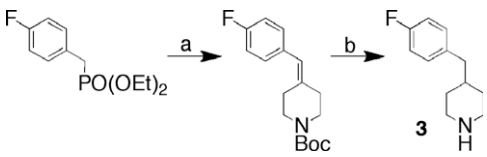
4-Fluorobenzylpiperidine **3** was a common intermediate used in the synthesis of each analog, and was prepared by reacting diethyl 4-fluorobenzylphosphonate with BOC-protected piperidone via a Horner–Emmons reaction, followed by catalytic hydrogenation of the double bond and Boc-deprotection (Scheme 1). Where direct acylation of heteroaromatics with oxalyl chloride could be utilized, the preparation of target compounds was straightforward as illustrated in Scheme 2 for compounds **1**, **2**, and **9**.

For heterocycles inert to treatment with oxalyl chloride, an aldehyde was chosen as a precursor for the oxalyl moiety and one of two coupling protocols were utilized. In the first set of conditions, reaction of an aldehyde with TMSCN followed by treatment with acid and subsequent base hydrolysis provided an α-hydroxy aryl acetic acid. After first forming a methyl ester, PCC oxidation of the hydroxyl group provided the α-keto ester. Hydrolysis with NaOH and coupling with dimethyl amine then gave the desired α-keto amide. Both compounds **4** and **5** were prepared using this route (Scheme 3).

Table 1
p38α enzyme and cellular activity for compounds **1**, **2**, and **4-9**



Compd	Linker	p38α IC_{50}[25] (μM, $n = 3$)	dWBA IC_{50}[26] (μM, $n = 3$)
1		0.018	0.10
2		0.010	0.03
4		0.945	17%@1 μM
5		>10	ND
6		0.10	26%@0.3 μM
7		0.090	ND
8		0.60	10%@1 μM
9		0.06	0.048



Scheme 1. Preparation of 4-fluorobenzylpiperidine. Reagents and conditions: (a) NaH, DMF then 4-oxopiperidine-1-*tert*-butyl carbamate, 48%; (b) H_2, Pd/C, then HCl/ether, 98%.

For the second set of conditions, a mild basic transformation was developed for the preparation of compound **6** (Scheme 4). As shown, the indazole 3-aldehyde intermediate was prepared in a one step process from its corresponding indole derivative via double nitrosation followed by ring rearrangement.[24] The aldehyde group was then protected as a dithiane prior to introduction of the methyl group at N-1 of the indazole. Treatment with butyl lithium followed by quenching with dimethylcarbamyl chloride gave the protected oxalyl amide. Upon deprotection, compound **6** was obtained.

Flipped indole analog **7** was prepared according to Scheme 5 by first reacting 4-nitrophenylglyoxylic acid with dimethyl amine followed by $SnCl_2$ reduction to give corresponding aniline. Reductive amination with 1,1-dimethoxyacetone followed by treatment with $AlCl_3$ resulted in cyclization forming the desired indole core. Subsequent reaction with phosgene followed by quenching with 4-fluorobenzylpiperidine gave the desired oxalyl amide.

Finally, regarding heterocyclic systems such as benzofuran that could not be incorporated utilizing an aldehyde route, synthesis was achieved through oxidation of a methylene group to an oxalyl moiety (Scheme 6). Beginning with methyl 2,4-dihydroxybenzoate,