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Discovery of pyrrolo[2,1-*f*][1,2,4]triazine C6-ketones as potent, orally active p38α MAP kinase inhibitors

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ABSTRACT

Pyrrolo[2,1-*f*][1,2,4]triazine based inhibitors of p38α have been prepared exploring functional group modifications at the C6 position. Incorporation of aryl and heteroaryl ketones at this position led to potent inhibitors with efficacy in in vivo models of acute and chronic inflammation.

p38 MAP (mitogen-activated protein) kinase is a member of a serine-threonine kinase family involved in a stress response signal transduction pathway. It is widely expressed in many cell types, and while there are four known isoforms of p38 (α, β, γ, and δ), it is p38α that has been shown to be on the critical path to pro-inflammatory cytokine production.[1] Upon activation by a number of extracellular stimuli, p38α phosphorylates and activates intracellular substrates such as transcription factors, including ATF-2 and NF-κB, and MAPKAP-kinases, which in turn regulate the biosynthesis of pro-inflammatory mediators (notably TNFα and IL-1). Biotherapeutic treatments, including the soluble TNFα receptor (etanercept), the IL-1 receptor antagonist (anakinra), and anti-TNFα antibodies (infliximab, adalimumab) have provided clinical validation for anti-cytokine approaches to treating rheumatoid arthritis, Crohn's disease and psoriasis.[2] Additional preclinical studies suggest that anti-cytokine therapies have potential in the treatment of stroke and cardiovascular disease.[3] Small molecule based inhibition of p38α offers an alternative approach to block production of these cytokines with the potential benefits of reduced cost (production and patient costs) and ease of administration. These aspects, along with the ability to simultaneously affect multiple cytokines and inflammatory mediators,

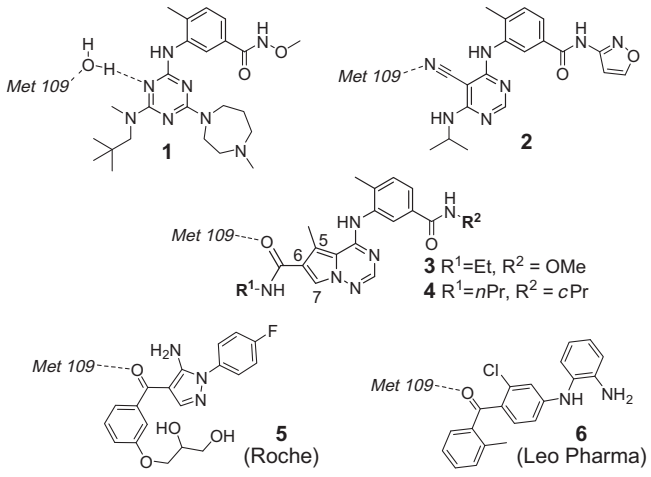

Figure 1. p38α inhibitors from BMS (**1**–**4**) Roche (**5**) and Leo (**6**) illustrating elements demonstrated or proposed to interact with Met109.

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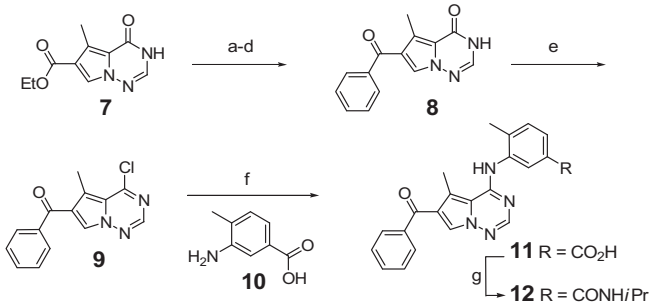
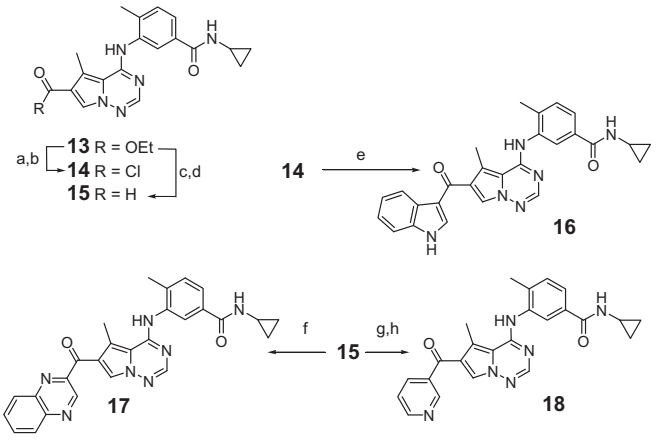


Scheme 1. Synthesis of pyrrolotriazine C6 ketones. Reagents and conditions: (a) $LiAlH_4$, THF; 0 °C; (b) Jones reagent, acetone; (c) PhMgBr, THF; (d) Jones reagent, acetone; (e) $POCl_3$ 100 °C; (f) aniline, DIPEA, DMF, 60–100 °C; (g) isopropyl amine, BOP, DMF.



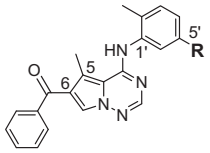
Scheme 2. Ketone synthesis from elaborated PTZ. Reagents and conditions: (a) NaOH, THF, H_2O, MeOH; (b) $SOCl_2$; (c) $LiAlH_4$, THF; 0 °C (d) Jones reagent, acetone; (e) indole, Et_2AlCl, DCM; (f) 2-chloroquinoxaline, 1,3-dimethylimidazolium iodide, 4-$MePhSO_2Na$, NaH, DMF, 55–70 °C; (g) 3-bromopyridine, Mg(s), THF; (h) MnO_2, THF.

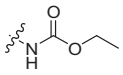
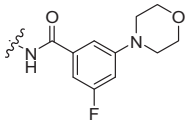
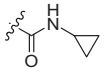
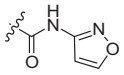
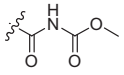
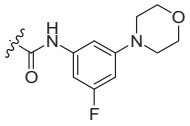
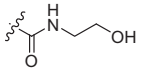
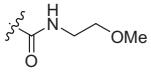
have stimulated continued efforts by numerous organizations to develop safe, potent and orally active p38α inhibitors.[4]

We, along with our collaborators, have previously reported on a variety of novel, selective and potent p38α inhibitors (Fig. 1 and **1**–**4**).[5] X-ray co-crystallography studies indicated several common binding features of these inhibitors, including a key interaction with the backbone NH of Met109. This contact has been noted in the majority of p38α inhibitors for which structural information has been disclosed.[6] In the case of triaminotriazine **1**,[5a] this hydrogen bond interaction is indirect via the intermediacy of a water molecule whereas direct interactions were observed with the nitrile of cyanopyrimidine **2**[5b] and an amide carbonyl of pyrrolo[2,1-*f*][1,2,4]triazine (PTZ) **3**[5d] and **4**.[5f] We were intrigued by the reports that this interaction was observed or proposed with aryl ketones in **5**[7] or **6**,[8] respectively, and set out to investigate whether a ketone would be a suitable replacement for the C6-amide in the PTZ chemotype.[9]

The preparation of PTZ C6-ketones was accomplished following several routes. As shown in Scheme 1, the C6-ketone could be introduced early in the sequence by modification of known pyrrolotriazine ester **7**[5d] through conversion to the corresponding aldehyde, addition of phenylmagnesium bromide and oxidation to ketone **8**. Chlorination of **8** with $POCl_3$ followed by displacement with an appropriately substituted aniline afforded either the final products directly, or intermediate carboxylic acid **11** which could in turn be utilized to prepare a range of C5′ amides. Alternative synthetic approaches (Scheme 2) relied on the availability of advanced PTZ-C6-ester intermediate **13**.[5f] Conversion of **13** to acid chloride **14** allowed for ketones to be prepared via Friedel–Crafts acylation,[10] while conversion to aldehyde **15** allowed the target molecules to be obtained by treatment with organometallic reagents and subsequent oxidation or, in the case of example **17**, reaction with 2-chloroquinoxaline under umpolung catalysis conditions.[11]

Table 1
C5′ SAR with C6-phenyl ketone



Compd	R	p38α[c] IC_{50}, nM	hPBMC[d] IC_{50}, nM
19[a]		6	27
20[a]		45	<4.1
11	CO_2H	>1000	–
21[b]	$CONH_2$	7	230
22[a]	CONHMe	14	170
23[b]	CONHEt	11	180
12	CONH*i*Pr	27	99
24[a]		4	<8.2
25[a]		3	<8.2
26[a]		3	<4.1
27[a]		88	–
28[b]		240	–
29[b]		230	–

[a] Prepared in analogy to **11** utilizing the appropriately substituted aniline in place of **10**.
[b] Prepared in analogy to **12** using the appropriate amine.
[c] Assay variability measured using a standard control was <30% (n = 77).
[d] Assay variability measured using a standard control was <85% (n = 65).

Table 1 displays the C5′ SAR with a series of compounds bearing a phenyl ketone at C6. Compounds were evaluated for activity in biochemical (p38α) and cellular assays (inhibition of LPS stimulated TNFα response in hPBMCs).[5a] Examples of both aniline and carboxamide functionalities at C5′ were examined, following SAR points from our earlier series.[5g] C5′-anilino derivative **20** showed greater activity in the cellular based assay than predicted by the corresponding level of p38α enzyme inhibition. While this could be related to unidentified off target activity, another consideration is that the morpholino-benzamide moiety of **20** has been described in earlier reports as binding to the pocket revealed by the DFG-out conformation of p38α, a binding mode that can lead to differences