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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,

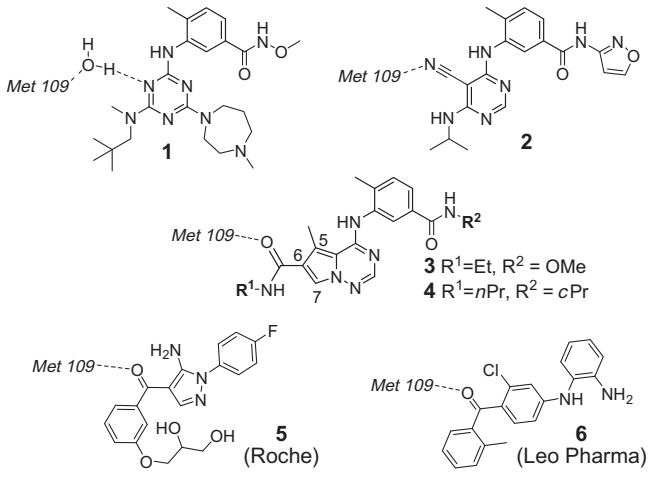

Figure 1. p38α inhibitors from BMS (**1**–**4**) Roche (**5**) and Leo (**6**) illustrating elements demonstrated or proposed to interact with Met109.

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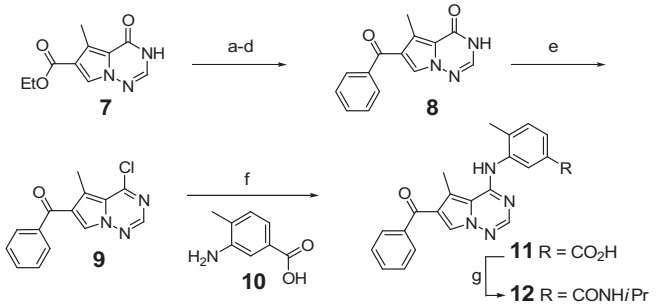
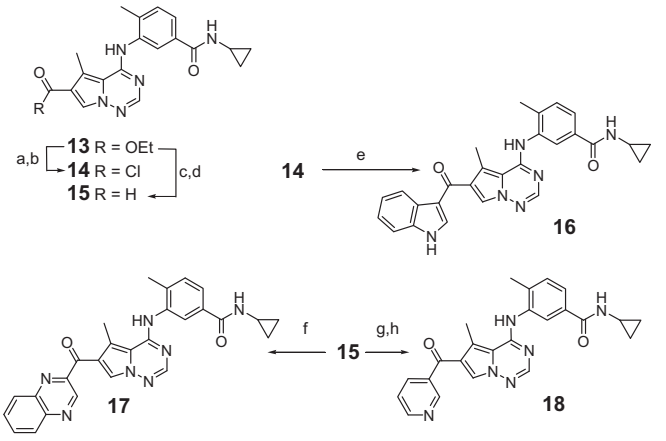


Scheme 1. Synthesis of pyrrolotriazine C6 ketones. Reagents and conditions: (a) $LiAlH_4$, THF; 0 °C; (b) Jones reagent, acetone; (c) PhMgBr, THF; (d) Jones reagent, acetone; (e) $POCl_3$ 100 °C; (f) aniline, DIPEA, DMF, 60–100 °C; (g) isopropyl amine, BOP, DMF.



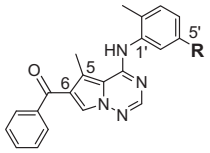
Scheme 2. Ketone synthesis from elaborated PTZ. Reagents and conditions: (a) NaOH, THF, H_2O, MeOH; (b) $SOCl_2$; (c) $LiAlH_4$, THF; 0 °C (d) Jones reagent, acetone; (e) indole, Et_2AlCl, DCM; (f) 2-chloroquinoxaline, 1,3-dimethylimidazolium iodide, 4-$MePhSO_2Na$, NaH, DMF, 55–70 °C; (g) 3-bromopyridine,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

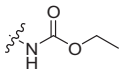
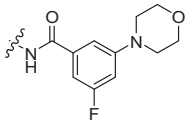
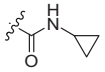
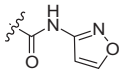
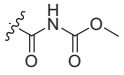
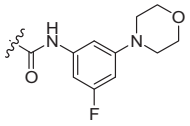
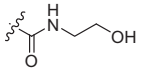
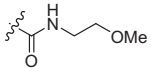
have stimulated continued efforts by numerous organizations to develop safe, potent and orally active p38α inhibitors.[4]

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

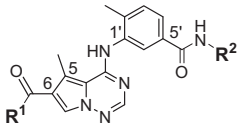


Compd	R	p38α[c] IC_{50}, nM	hPBMC[d] IC_{50}, nM
19[a]		6	27
20[a]		45	<4.1
11	CO_2H	>1000	–
21[b]	$CONH_2$	7	230
22[a]	CONHMe	14	170
23[b]	CONHEt	11	180
12	CONH*i*Pr	27	99
24[a]		4	<8.2
25[a]		3	<8.2
26[a]		3	<4.1
27[a]		88	–
28[b]		240	–
29[b]		230	–

[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

Table 2
Combined C6 and C5′ SAR



Compd	R^1	R^2	p38α [d] IC_{50}, nM	hPBMC[e] IC_{50}, nM
30	*(C6 = CH_2OH)[c]	*c*Pr	>1000	—
15	H	*c*Pr	55	>1000
31[a]	*n*Pr	*c*Pr	19	240
32[a]	Me—≡—	*c*Pr	12	300
33[a]	2-Methyl-phenyl	Me	12	110
34[a]	2-Methoxy-phenyl	Me	59	1700
35[a]	3-Methoxy-phenyl	Me	14	1100
36[a]	3-Fluoro-phenyl	Me	36	>2000
37[a]	4-Fluoro-phenyl	Me	140	—
38[a]	Benzo[*d*][1,3]dioxol-5-yl	Me	35	>2000
39[a]	(6-Methylpyridi*n*-2-yl)	Me	51	890
40[a]	(6-Methylpyridi*n*-2-yl)	*c*Pr	8	120
41[a]	2-Pyridyl	*c*Pr	40	290
18	3-Pyridyl	*c*Pr	19	170
17	(Quinoxalin-2-yl)	*c*Pr	15	1400
42[b]	(1*H*-pyrrol-2-yl)	*c*Pr	10	100
43[b]	(1*H*-pyrrol-3-yl)	*c*Pr	10	68
44[b]	(1-Methyl-1*H*-pyrrol-2-yl)	*c*Pr	44	670
45[b]	(1-Methyl-1*H*-pyrrol-3-yl)	*c*Pr	18	730
46[b]	(Furan-2-yl)	*c*Pr	5	270
16	(1*H*-Indol-3-yl)	*c*Pr	11	57
47[b]	(1-Methyl-1*H*-indol-2-yl)	*c*Pr	52	>2000
48[b]	(1-Methyl-1*H*-indol-3-yl)	*c*Pr	55	>2000

[a] Prepared in analogy to **11** and **18** utilizing appropriate organometallic reagents and substituted anilines.
[b] Prepared in analogy to **16**.
[c] Prepared as shown in Scheme 2, step (c).
[d] Assay variability measured using a standard control was <30% (n = 77).
[e] Assay variability measured using a standard control was <85% (n = 65).

in binding kinetics.[5g,6] Despite the impressive cellular activity, liabilities including CYP inhibition (IC_{50}:2C9 350 nM, 3A4 470 nM) deterred further evaluation of **20**. The remaining C5′ SAR efforts focused on carboxamide substitution. Carboxylic acid **11** showed very little activity in the biochemical assay, while the primary amide **21** was found to inhibit p38α with single digit nanomolar activity, highlighting the importance of the amide functionality. Simple alkyl amides (**12**, **22**, **23**) were also found to show good inhibition in enzyme and cell based assays. Activity was diminished with aryl amide **27** and 2-hydroxyethyl (**28**) or 2-methyoxyethyl (**29**) analogs.

We have previously observed enhanced inhibition of p38α through incorporation of cyclopropyl or heterocyclyl amide substituents at C5′, rationalized through improved hydrogen bond donor ability of the benzamide NH.[5f] Consistent with those earlier findings, optimal enzymatic and cellular activity in the phenyl ketones was found with cyclopropyl-amide **24**, isoxazol-3-yl-amide **25**, and acyl carbamate **26**. However, in vitro metabolic stability of **26** (hLM 0.16 nmol/min/mg) was lower than cyclopropyl amide **24** (hLM 0.08 nmol/min/mg) and poor solubility was noted with in vivo formulations of **25**. As a result we chose to focus on methyl and cyclopropyl amides for SAR evaluation at C6.

Modifications to the C6 position were initiated with *N*-methyl and *N*-cyclopropyl amides at C5′ (Table 2). The C6-hydroxymethyl intermediate **30** was found to possess little activity against p38α but activity was restored to a moderate level after oxidation to aldehyde **15**. Further improvements were observed with alkyl and alkynyl ketones **31** and **32**, with activity approaching that observed with phenyl ketone **24**. In the series of substituted phenyl ketones (**33**–**38**) 2-methyl substitution was well tolerated, however other substituents led to a decrease in enzyme and/or cellular potency. Heteroaryl ketone substituents were also investigated. The 6-methylpyridin-2-yl ketone analogs were prepared with *N*-Me and *N*-cyclopropyl C5′ amides and in each case the in vitro activity was reduced as compared to the corresponding phenyl ketones (**39** vs **22**, **40** vs **24**). A deleterious effect on in vitro potency was noted upon N-methylation of the pyrrole and indole derivatives (**42** vs **44**, **43** vs **45**, **16** vs **48**). Furanyl ketone **46**, isosteric to **42** but lacking a hydrogen bond donor, showed favorable enzyme activity. This suggests that the unsubstituted pyrroles are not picking up significant hydrogen bonding interactions and that the negative N-methyl effect is steric in nature, with the substituent possibly interfering with the interaction between Met109 and the ketone carbonyl. Translation of biochemical to cellular activity was variable among the compounds examined, ranging from 10-fold or less (**16**, **18**, **33**, **39**, **41**–**43**) to greater than 90-fold for quinoxalinyl derivative **17**.[12]

Direct comparison between the C6-ketone and C6-amide PTZs can be made by examining p38α IC_{50} values for **31** (19 nM) **24** (4 nM) and **4**[5f] (13 nM). Propyl ketone **31**, sterically similar to the *N*-propyl amide of **4**, provided comparable level of p38α inhibition indicating that the C6 ketone was an effective amide surrogate. The enzyme activity of phenyl ketone **24** was improved slightly, possibly a result of enhanced hydrophobic interactions suggested by X-ray crystallography.

Examination of the X-ray structure of **24** co-crystallized with unphosphorylated p38α (Fig. 2) confirmed the proposed binding mode, including interaction of the ketone carbonyl with Met109, as expected by analogy to **3** and **4**.[5e,f,13] The phenyl ring of the C6 ketone is oriented along a hydrophobic surface created by residues

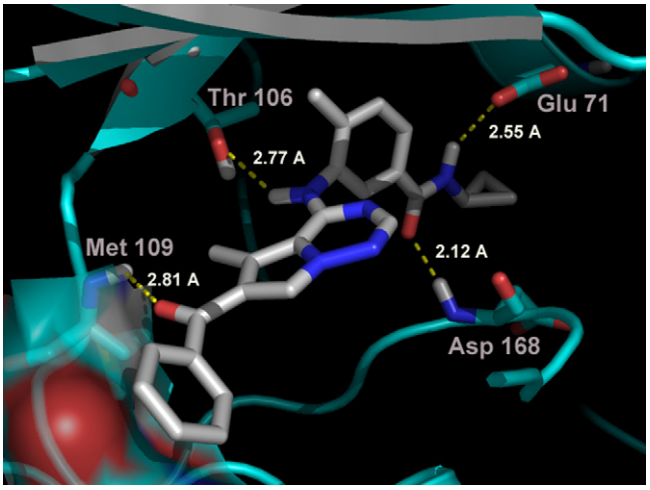


Figure 2. [13]X-ray co-crystal structure of **24** and unphosphorylated p38α with the foreground residues removed for clarity.

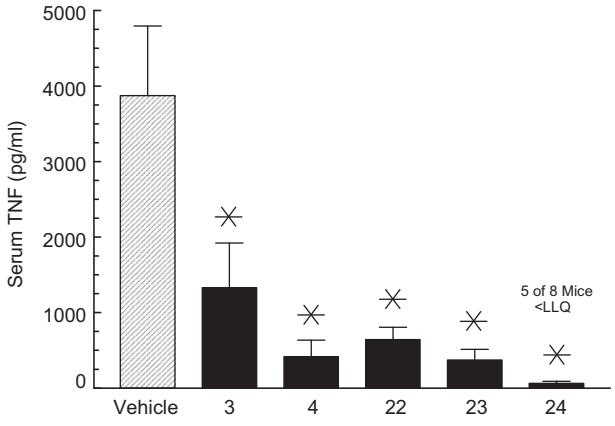


Figure 3. Inhibition of LPS-induced TNFα release by **3**, **4**, **22**, **23**, and **24** in mouse. BALB/c female mice (Harlan, 6–8 weeks of age, $n = 8$/treatment) were dosed with compounds (5 mg/kg) in PEG 300 by oral gavage in a volume of 0.1 ml. Control mice received PEG300 alone ('vehicle'). Two hours later, mice were injected intraperitoneally with 50 μg/kg lipopolysaccharide (LPS; *Escherishia coli* O111:B4; Sigma). Blood samples were collected 90 min after LPS injection. Serum was separated and analyzed for the level of TNFα by commercial ELISA assay (BioSource) according to the manufacturer's instructions. Data shown are mean standard deviation. $^{*}p$ <0.005 versus vehicle by Student's t test.

in the hinge region which seems to readily accommodate this structural feature. This is depicted as the transparent surface in Figure 2. PTZ based p38α inhibitors have previously been found to bind with the DFG loop in both the '-out' and '-in' conformations.[5d–g,6b] In the case of **24** the structure revealed a conventional DFG-in orientation of the protein, with the C5′ amide being involved in a hydrogen bonding network with Glu71 and Asp168. The phenyl ring of the aniline benzamide sits in a hydrophobic pocket just beyond the Thr106 'gatekeeper residue', the hydroxyl of which makes a potential contact with the aniline NH.

In addition to TNFα, compound **24** was found to potently antagonize the production of several additional cytokines from hPBMC cells stimulated with LPS (IC_{50}:IL-1α <8 nM, IL-1β 41 nM, IL-6 173 nM, IL-10 21 nM). The cytokine suppressive activity was maintained in a whole blood assay, with **24** inhibiting the LPS induced production of IL-6 from monkey whole blood (IC_{50} 382 nM).

C6 ketone derivatives with demonstrated potency in the hPBMC cellular assay (IC_{50} <300 nM) and acceptable in vitro metabolic stability (data not shown) were examined in a mouse model of acute

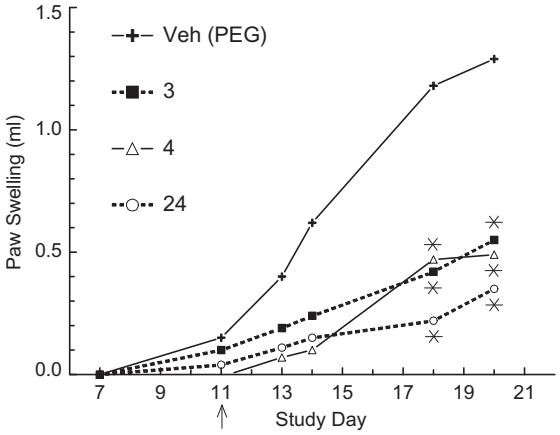


Figure 4. Rat adjuvant arthritis study using **3** (squares), **4** (triangles), **24** (circles). Lewis rats ($n = 8$/group) were immunized with complete Freund's adjuvant on day 0. On day 11, twice-daily oral treatment was initiated with vehicle (PEG300) or compound (10 mg/kg/dose). Hind paw volume increases were determined by plethysmometry on the days indicated. $^{*}p$ <0.05 versus vehicle, Student's t test.

inflammation for their ability to inhibit TNFα production in response to an LPS challenge in vivo. Select examples are shown in Figure 3, along with the vehicle control and C6-amide analogs (**3** and **4**) for comparison. The compounds in the study were dosed at 5 mg/kg 2 h prior to LPS challenge and all showed significant inhibition of the TNFα response. Aryl ketone **24** was particularly efficacious, with 5 of 8 mice studied showing no detectable levels of serum TNFα (LLQ 200 pg/ml). The level of inhibition demonstrated by **24** was also statistically superior to C6-amide compound **3** ($p < 0.05$). Furthermore, **24** displayed an extended duration of action, with a 5 mg/kg dose giving 95% inhibition of TNFα response even when administered 6 h prior to LPS challenge, with 2 of 8 mice showing no detectable levels of TNFα in that particular study (data not shown).

Preliminary evaluation of selectivity in this series was obtained against a panel of 26 additional enzymes. Aside from p38 β (IC_{50} 19 nM), compound **24** did not show significant off-target activity.[14] An oral pharmacokinetic study in rats (10 mg/kg in PEG400) showed acceptable exposure for compound **24** (C_{max} 752 ng/ml, C_{4h} 550 ng/ml, AUC_{0-4h} 2300 ng h/ml). As a result of its superior in vitro profile, results in the murine LPS-TNFα model and rat pharmacokinetic properties, compound **24** was examined for efficacy in a rodent model of arthritis (rat adjuvant arthritis). The study (Fig. 4) was run with the compounds (10 mg/kg, b.i.d, po) first administered near the time of disease onset (day 11) and continuing through the end of the study on day 20. Compounds **3** and **4** were included in this study enabling a direct comparison of the C6 amide and C6 ketone pyrrolotriazine compounds. All three compounds were highly efficacious in this study, showing statistically significant inhibition of paw swelling. Although aryl ketone **24** appeared to provide the greatest activity with a 73% reduction in paw swelling, statistical differentiation between the three treatment groups was not possible.

In conclusion, structural analysis of the p38α co-crystal structure of pyrrolo[2,1-*f*][1,2,4]triazine compounds from our labs, along with additional reports of aryl ketone derived inhibitors led to the rational design of the PTZ-C6-ketone p38α inhibitors. Members of this series were found to be selective and highly potent in vitro as well as being orally efficacious in rodent models of acute and chronic inflammation.

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13. Binding interactions between **24** and unphosphorylated p38α based on X-ray crystallographic analysis (2.2 Å resolution). Hydrogen bond distances are given in angstroms with key protein residues labeled. The X-ray coordinates have been deposited with the RCSB Protein Data Bank (RCSB ID Code: rcsb065758 and PDB ID Code: 3S4Q).
14. Selectivity: (IC_{50} > 25 μM for p38δ p38γ, Akt, cdk2, Emt, FGFR1, HER1, HER2, IGF1R, JAK3, Jnk1, LCK, MEK/ERK, MET. MK2, PKA, PKCα, PKCδ, PKCθ, PKCζ, Syk, VEGF_R2) (IC_{50} >10 μM for IKK2) (IC_{50} >5 μM for PDE-3, -4, -7).