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The design and synthesis of novel α-ketoamide-based p38 MAP kinase inhibitors

Antonio Garrido Montalban,* Erik Boman, Chau-Dung Chang, Susana Conde Ceide, Russell Dahl, David Dalesandro, Nancy G. J. Delaet, Eric Erb, Justin T. Ernst, Andrew Gibbs, Jeffrey Kahl, Linda Kessler, Jan Lundström, Stephen Miller, Hiroshi Nakanishi, Edward Roberts, Eddine Saiah, Robert Sullivan, Zhijun Wang and Christopher J. Larson

Drug Discovery, Kémia, Inc., 5871 Oberlin Drive, Suite 100, San Diego, CA 92121, USA

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Abstract—We have identified a novel series of potent p38 MAP kinase inhibitors through structure-based design which due to their extended molecular architecture bind, in addition to the ATP site, to an allosteric pocket. In vitro ADME and in vivo PK studies show these compounds to have drug-like characteristics which could result in the development of an oral treatment for inflammatory conditions.

Since the mitogen-activated protein (MAP) kinase p38 was first reported in 1993,[1] it has received an extraordinary level of attention by the pharmaceutical industry[2] and medicinal chemistry community.[3] This notion stems from the fact that p38 has been recognized as a highly attractive target for therapeutic intervention. It is well established that the proinflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), play an important role in the pathogenesis of various inflammatory diseases and that the stress-activated signal transduction pathway leading to these cytokines is in part regulated by p38. Blockade of TNF-α by the biologics etanercept (Enbrel) and infliximab (Remicade), for example, is clinically proven to be effective in the treatment of rheumatoid arthritis, Crohn's disease, and psoriasis.[4] In addition, clinical validation of the MAP kinase pathway in rheumatoid arthritis has been achieved with VX-745[5] and BIRB-796.[6] The different safety profiles reported[7] for these two distinct structural classes and others suggest that toxicity is probably more structure- than mechanism-based, but despite all efforts, a small-molecule therapeutic utilizing this mechanism of action still remains elusive.[7]

After the ground breaking work by SmithKline Beecham (initially followed by RWJ[8] and Merck[9]) that led to SB203580,[10] numerous other ATP-competitive or orthosteric p38 inhibitors have been described.[11] On the other hand, only a few p38 inhibitors that bind to an allosteric site (noncompetitive inhibitors) have been reported so far. In fact, at the time this work was initiated, the only known p38 inhibitors of this new class were related to BIRB-796.[12] More recently, AstraZeneca[13] and Astex[14] have also reported p38 inhibitors that bind to an allosteric site. In contrast to pure ATP mimics, these compounds interact, in addition to the active site, with a region on the kinase that is spatially distinct from the ATP pocket. Furthermore, they inhibit p38 MAP kinase via a conformation (DFG-out) that is incompatible with ATP binding. Thus, stabilization of the inactive conformation should, in principle, lead to improved selectivity across the kinome due to the inactive or 'off' state between kinases being conformationally more different than the activated or 'on' state.[15] In addition, selectivity for ATP-competitive binders under physiological conditions may be quite different from what is observed in vitro due to ATP having different affinities for kinases and being present at high concentrations.[16]

Keywords: p38 MAP kinase; Antiinflammatory; SAR; Ketoamides; Cytokines; Drug-like.
* Corresponding author. Tel.: +1 619 519 1787; fax: +1 858 538 0946; e-mail: catalaba@hotmail.com

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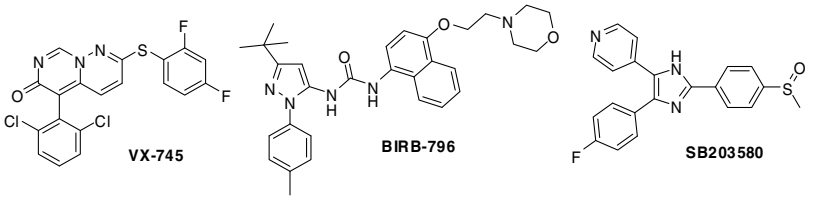
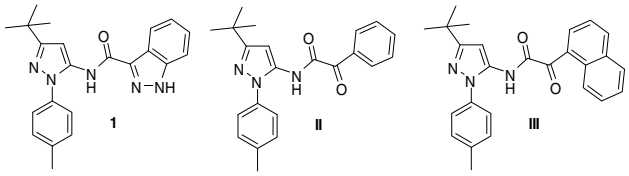


The above considerations, and the limited number of noncompetitive or allosteric, as compared to competitive or orthosteric, p38 inhibitors studied thus far, led us to believe that it could be an attractive strategy to deliver a small molecule p38 therapeutic. We chose the cellular TNF-α inhibitory assay to guide our SAR efforts since it has been previously used to successfully identify potent p38α inhibitors.[11b] During the screening of our compound collection, the indazol derivative **1** (TNF-α IC_{50} = 2.9 μM) was identified. We noticed the partial structural overlap to BIRB-796, and herein we report how **1** evolved to a potent new structural class of allosteric p38 inhibitors based on an α-ketoamide scaffold using BIRB-796 as a template.

Molecular modeling[17] suggests that, similar to BIRB-796,[12] compound **1** binds to the allosteric site of p38 whereby the *tert*-butyl group occupies the exposed Phe169 hydrophobic pocket and the amide simultaneously hydrogen bonds via the carbonyl with the backbone amide hydrogen of Asp168 and through the N—H with the carboxylate of Glu71. The nitrogen at position two of the indazole, on the other hand, acts as a hydrogen-bond acceptor for the amide hydrogen of the conserved Lys53 residue which would otherwise form a salt-bridge with the carboxylate of Glu71, whereas the nitrogen at position one does not seem to form any contributing binding interactions. In contrast to BIRB-796,[12] the rigidity of the indazol system does not place the phenyl ring favorably within the kinase specificity pocket and, therefore, does not appear to form a good edge-to-face interaction with the phenyl of the displaced Phe169 side chain. By analogy with the BIRB-796 series[12] and the goal of increasing the flexibility of the phenyl ring while retaining the beneficial hydrogen-bond acceptor atom at position two, the bicyclic structure was replaced by a monocyclic system. Indeed, modeling of α-ketoamide **II** showed it to be a better fit, with the phenyl ring interacting with the specificity pocket similar to SB203580-type inhibitors.[18] This interaction was further accentuated in the naphthyl analogue **III** in which the second ring of the naphthyl moiety resides deep within the kinase specificity pocket while the first one maintains the ideal edge-to-face interaction with Phe169 in a similar manner to BIRB-796.[12] We then decided to attach the ethoxy morpholino group to the 4-position of the naphthalene in order to reach into the ATP binding region of p38. Again, docking results[19] showed that the extended molecular architecture of compound **2** binds to the DFG-out conformation of p38, allowing it to simultaneously interact with the active site and the allosteric pocket as is the case with BIRB-796.[12] Thus, in addition to all the above binding interactions, the morpholino group forms a conserved hydrogen bond with the backbone amide hydrogen of Met109 (Fig. 1). The prototype α-ketoamide **2** was prepared, tested in vitro and found to have a TNF-α IC_{50} of 440 nM. Table 1 summarizes the results of our subsequent SAR survey.



Ketoamides **2**–**10** were synthesized, as shown in Scheme 1, through reaction of the corresponding pyrazolamines **16** with the acid chloride (**20**) derived from naphthol ether **17**. The pyrazole precursors were prepared via condensation of the correspondingly substituted hydrazines and 4,4-dimethyl-3-oxopentanenitrile in refluxing toluene.[12] Acid chloride **20**, on the other hand, was synthesized through the acylation of naphthol ether **17**,[20] followed by the hydrolysis of the resulting ester **18** and the treatment of acid **19** with oxalyl chloride.

The synthesis of compound **11** started with the BOC-protection (**22**) of commercially available amino-naphthol **21** followed by alkylation with 2-chloroethylmorpholine to give **23**, deprotection (**24**), subsequent Sandmeyer reaction (**25**), and acylation to give ester **26**. The reaction of ester **26** with the anion derived from

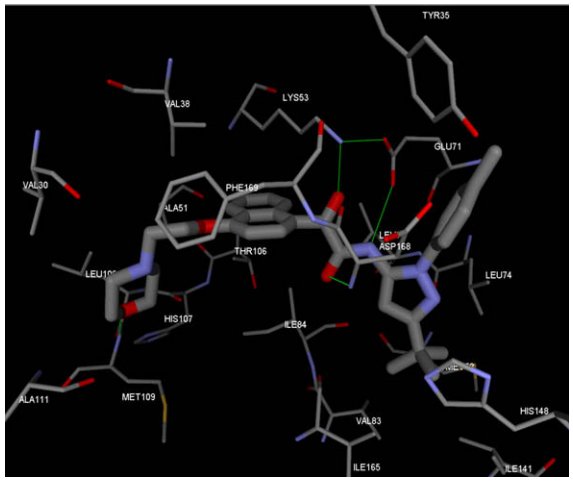
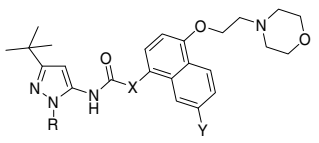


Figure 1. Docked structure of compound **2** in a thick tube drawing to p38α using the induced fit docking protocol based on the X-ray structure of p38α cocrystallized with BIRB-796 (pdb1kv2.ent). Only residues within 5 Å from compound **2** are shown for clarity. Hydrogen bonds between the inhibitor and residues Glu71, Lys53, and Met109 are shown in green line.

Table 1. TNF-α inhibition data for pyrazole α-ketoamide derivatives



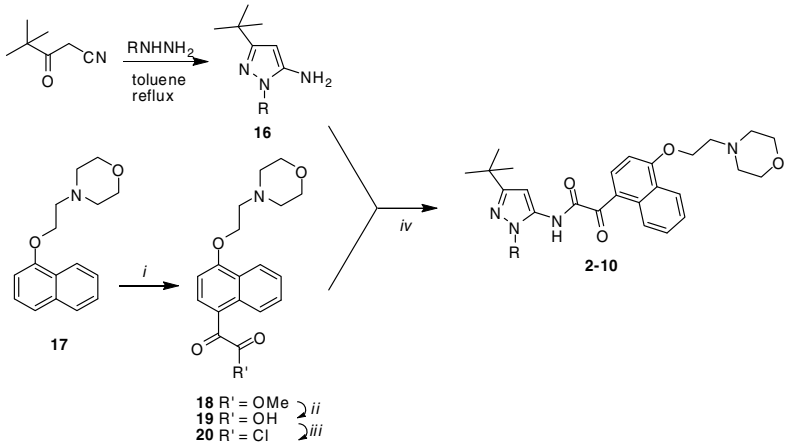
Compound	R	X	Y	TNF-α IC_{50}[a] (μM)
BIRB-796	*p*-Tolyl	NH	H	0.013
2	*p*-Tolyl	CO	H	0.44
3	H	CO	H	1.5
4	Phenyl	CO	H	2.1
5	*m*-Tolyl	CO	H	0.34
6	3-Fluorophenyl	CO	H	0.44
7	3,4-Dimethylphenyl	CO	H	0.45
8	*o*-Tolyl	CO	H	1.5
9	3-F-4-Methylphenyl	CO	H	0.22
10	Me	CO	H	0.44
11	*p*-Tolyl	CO	Cl	2.6
12	*p*-Tolyl	CNOH	H	0.023
13	*p*-Tolyl	CNOMe	H	1.5
14	*p*-Tolyl	CH_2	H	1.4
15	*p*-Tolyl	CHOH	H	0.97

[a] IC_{50} of LPS-stimulated TNF-α production in the immortalized human cells of a monocytic lineage (THP-1). IC_{50}'s given represent the means of a minimum of two, and generally three or more, independent experiments. Standard deviation for assays typically ±30% of the mean or less.

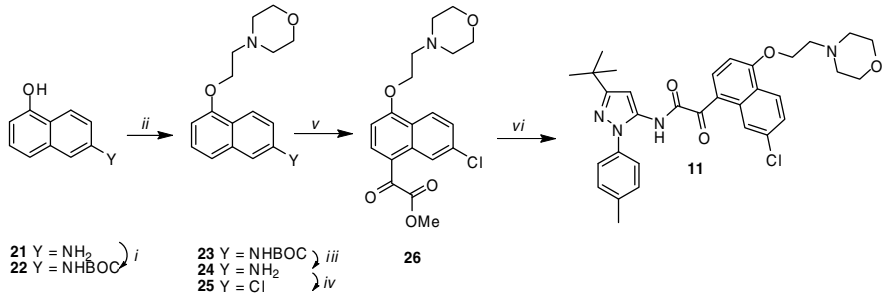
3-amino-5-*tert*-butyl-2-tolyl-*2H*-pyrazole under microwave irradiation gave the above final compound (Scheme 2).

Oxime **12** (X = C═NOH) and methyloxime **13** (X = C═NOMe) were readily prepared as a mixture of geometrical isomers by treating **2** with hydroxylamine and *O*-methylhydroxylamine, respectively. The reduction of **2**, on the other hand, gave alcohol **15** (X = CHOH) whereas **14** was prepared from acid chloride **30** (X = CH_2), which was in turn synthesized from α-ketoester **18** as shown in Scheme 3.

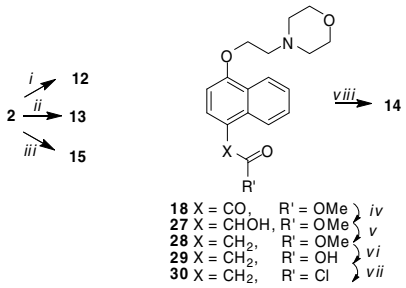
By analogy with BIRB-796[12] and as our modeling suggested, the group at position one of the pyrazole ring is hypothesized to be in close proximity and could, therefore, favorably interact with the hydrophobic portion of the side chain of the conserved residue of Glu71. While the lack of substitution (**3**) or a plain phenyl (**4**) resulted in a decreased potency, the *m*-substituted phenyl derivatives **5** and **6** and the 3,4-disubstituted phenyl derivative **7** showed similar activities to **2**. The *o*-tolyl derivative **8**, on the other hand, appeared again to be less potent, suggesting that lack of either rotational freedom or steric bulk around the ketoamide NH decreased the binding energy. The combination of both a 3-fluoro- and a 4-methyl-group as in **9** resulted in a favorable potency trend and perhaps hinting to a preferred phenyl substitution pattern. Interestingly, the methyl analogue **10** was as potent as the parent compound **2**. Next, we turned our attention to the naphthyl ring-system. Our modeling suggested that, in addition to the favorable π—π edge-to-face interaction with the phenyl ring of Phe169, substitution at the 6- and/or 7-positions of the naphthalene could further strengthen the lipophilic interaction with the kinase specificity pocket. The 6-chloro analogue **11** was prepared but led only to a decrease in potency, suggesting a tight fit of the second naphthyl ring to the specificity pocket, as did the replacement of the naphthyl- by a phenyl-ring (data not shown) that is consistent with the calculated binding energies of **II**, **III**, and related BIRB-796 analogues.[12] Other changes and combinations (data not shown) investigated that also trended to less TNF-α inhibitory activity include modifications of the *tert*-butyl group, substitution at the 4-position of the pyrazole ring, alkylation of the amide nitrogen, removal or changing the position of the ethoxymorpholino group, homologation of the ethyl linker, substitution at the 3- and/or 5-positions, and the replacement of the morpholino group for other heterocyclic- and ring-open-analogues. These data are generally consistent with the related BIRB-796 series[12] and suggest that (a) the *tert*-butyl group has about the optimal size for the Phe169 hydrophobic pocket; (b) a substituent adjacent (4-position of pyrazole) to it is not well tolerated, probably for conformational or steric reasons; (c) the hydrogen bond interaction between the amide N—H



Scheme 1. Reagents and conditions: (i) CH_2Cl_2, $AlCl_3$, rt then methyl oxalyl chloride, 16 h, 97%; (ii) 6 N HCl, 80 °C, 16 h, 59%; (iii) CH_2Cl_2, DMF (cat), oxalyl chloride, rt, 2 h; (iv) EtOAc, 0.5 N $NaHCO_3$, 60 °C, 16 h.



Scheme 2. Reagents and conditions: (i) EtOAc, 0.5 N $NaHCO_3$, BOC_2O, 60 °C, 16 h, quantitative; (ii) MeCN, K_2CO_3, *N*-(2-chloroethyl)-morpholine hydrochloride, 75 °C, 16 h, 4.4%; (iii) CH_2Cl_2, TFA, Et_3SiH, rt, 60 h, quantitative; (iv) 6 N HCl, $NaNO_2$, 0 °C, 1 h then CuCl, 100 °C, 1 h, 11%; (v) CH_2Cl_2, $AlCl_3$, rt then methyl oxalyl chloride, 16 h, 83%; (vi) 3-amino-5-*tert*-butyl-2-tolyl-2*H*-pyrazole, dioxane/DMF, BuLi, 150 °C, microwave, 5 min, 12%.



Scheme 3. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, EtOH, pyridine, 45 °C, 12 h, 58%; (ii) $NH_2OMe{\cdot}HCl$, EtOH, pyridine, 45 °C, 12 h, 76%; (iii) MeOH, $NaBH_4$, rt, 1 h, 12%; (iv) MeOH, Pd/C (10% wt), H_2, rt, 16 h; (v) CH_2Cl_2, TFA, Et_3SiH, rt, 16 h; (vi) MeOH/THF, 2 N NaOH, rt, 4 h; (vii) CH_2Cl_2, DMF (cat), oxalyl chloride, rt, 4 h; (viii) 3-amino-5-*tert*-butyl-2-tolyl-2*H*-pyrazole, EtOAc, 0.5 N $NaHCO_3$, 60 °C, 16 h.

and Glu71 is essential for binding; (d) the naphthalene 1,4 substitution pattern is ideal for orienting the groups interacting with the Phe-out pocket and ATP binding region; and (e) with the ethoxy linker providing optimally spaced binding moieties. Molecular modelling, on the other hand, suggests that the alpha-keto group forms a hydrogen bond interaction with the amide hydrogen of the conserved Lys53 residue (vide supra). We reasoned, therefore, that chemical modifications of the α-ketoamide scaffold could probe this hypothesis and also result in additional binding interactions not seeing with the urea moiety of the BIRB-796 series.[12] The conversion of **2** to its corresponding oxime **12**, for example, resulted in a TNF-α inhibitory activity of 23 nM. This improvement in potency may be due to the hydrogen bond interaction observed in the docked structure for the oxime O—H with one of the amide carbonyl groups of the conserve residue of Glu71. In contrast, the urea hydrogen of BIRB-796 in the same region forms a hydrogen bond to the carboxylate oxygen of Glu71.[12] Consequently, oxime ether **13** and deoxygenated analogue **14**, lacking either one or both of these important hydrogen-bond donor/acceptor moieties (e.g. carbonyl or oxime), were much less potent. Reduction to alcohol **15** also resulted in decreased potency.

Activity in the THP-1 whole cell assay was confirmed for compounds **2**, **10**, and **12** in a human p38α kinase assay (Table 2). The results from the p38α kinase assay

Table 2. Comparison of IC_{50} data of selected compounds for the biochemical-, cell-based-, and phospho-p38 assay

Compound	p38α IC_{50} (μM)	TNF-α IC_{50} (μM)	PP38-α IC_{50} (μM)
BIRB-796	0.044	0.013	0.017
SB203580	0.039	0.16	6.0
VX-745	0.029	0.039	5.3
2	0.32	0.44	0.31
10	0.15	0.22	0.30
12	0.023	0.023	0.15

IC_{50}'s given represent the means of a minimum of two, and generally three or more, independent experiments. Standard deviation for assays typically ±30% of the mean or less.

was indistinguishable from the cell-based data when taking the different assay conditions and intra-assay variability into account.

The conformational change (DFG-in → DFG-out) prevents the activating upstream kinase (MKK3/MKK6)[21] from phosphorylating p38. This conformational change can be indirectly measured by a phosphorylation inhibition assay. The same set of compounds (Table 2) was tested in this assay and the results suggest that they caused the necessary conformational change to inhibit p38 phosphorylation similar to BIRB-796. In contrast, the orthosteric/competitive p38 inhibitors SB203580, and VX-745 did not prevent p38α from being phosphorylated by its upstream kinase. BIRB-796, SB203580, and VX-745 were measured under the same conditions as our compounds in all three assays and the data are included in Table 2 for comparison. Thus, these results support that our p38 inhibitors are likely to bind to the DFG-out conformation of the protein. Kinetic studies have not been conducted to confirm a formal noncompetitive versus competitive mechanism of enzyme inhibition for compounds of this class, but based on the reasoning from molecular modeling data, similarity of the pharmacophore to that in the structurally characterized BIRB796-p38 cocrystal structure, and the above results for inhibition of the flexible DFG activation loop, we propose that these compounds inhibit at least partially via an allosteric/noncompetitive mode rather than an orthosteric/competitive mode of binding.

Table 3. Single dose plasma pharmacokinetic parameters of **12** following dosing in rats

	iv	po
Dose (mg/kg)	10	30
T_{max} (h)		1.0
C_{max} (μg/mL)		4.5
$T_{1/2}$ (h)		1.4
AUC (μg h/mL)		36
po F%		100
Cl (L/h/kg)	0.90	
V_{dss} (L/kg)	1.9	

In vitro ADME evaluation of our α-ketoamide series was consistent with drug-like characteristics. This was further confirmed by in vivo rat snapshot PK studies of compound **12** for which the parameters are summarized in Table 3.

In summary, we have developed a novel series of potent p38 inhibitors using an α-ketoamide scaffold. Despite limited enzyme inhibition data, we established SAR trends that are consistent with the related BIRB-796 series and achieved potencies in the double digit nanomolar range. We further believe, based on computational modeling and a phospho-p38α inhibition assay, that these compounds are novel allosteric p38 inhibitors. This series of inhibitors shows potential for the development of an oral treatment for inflammatory conditions and further optimization of this novel scaffold will be reported in due course.

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