Bioorganic & Medicinal Chemistry Letters 20 (2010) 2634–2638

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

# Identification of SD-0006, a potent diaryl pyrazole inhibitor of p38 MAP kinase

John K. Walker *, Shaun R. Selness, Rajesh V. Devraj, Michael E. Hepperle, Win Naing, Huey Shieh, Ravi Kurambail, Syaulan Yang, Daniel L. Flynn, Alan G. Benson, Dean M. Messing, Tom Dice, Tina Kim, R. J. Lindmark, Joseph B. Monahan, Joseph Portanova

*Pfizer Global Research and Development, Chesterfield Parkway West, St. Louis, MO 63017, USA*

ARTICLE INFO

*Article history:*
Received 12 January 2010
Revised 10 February 2010
Accepted 10 February 2010
Available online 14 February 2010

Dedicated to the memory of Joseph Portanova a gifted scientist and valued colleague.

*Keywords:*
p38 Kinase
Diaryl pyrazoles
Inhibitors
Rheumatoid arthritis
SD-0006
Tumor necrosis factor-a

ABSTRACT

Starting from an initial HTS screening lead, a novel series of C(5)-substituted diaryl pyrazoles were developed that showed potent inhibition of p38α kinase. Key to this outcome was the switch from a pyridyl to pyrimidine at the C(4)-position leading to analogs that were potent in human whole blood based cell assay as well as in a number of animal efficacy models for rheumatoid arthritis. Ultimately, we identified a clinical candidate from this substrate; SD-0006.



The advent of biologic agents such as Enbrel® and Remicade® represent a significant advance in the treatment of auto-immune disorders such as rheumatoid arthritis (RA).[1] These agents work via regulating levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1B (IL-1B) and their effectiveness validates targeting these pro-inflammatory cytokines for therapeutic benefit.[2] However, even with the introduction of the biological agents there remains an increasing need to develop orally available small molecule agents that target the pathways leading to pro-inflammatory cytokine production. The mitogen activated protein kinase (MAPK) p38 has been shown to play a critical role in cell signaling pathways which lead to the production of both TNF-α and IL-1B.[3,4] As a result, p38 represents an attractive candidate for intervention to block biosynthesis of these pro-inflammatory cytokines. Herein we describe the synthesis and medicinal chemistry efforts that led to the identification of our recently disclosed clinical candidate SD-0006,[5] (**1**), which is a potent inhibitor of p38 (Fig. 1).

Recently it was reported from these labs the identification of high-throughput screening lead, diaryl pyrazole SC-102, (**2**)[6] which was found to be a moderately potent inhibitor of p38α ($IC_{50}$ = 600 nM). The X-ray crystal structure of **2** bound in the p38 active site revealed several important features important in guiding our design of new analogs (Fig. 2).[7] The pyridine nitrogen forms a hydrogen bond with the backbone N–H of Met-109. The fluorophenyl group, at the C(2)-position, occupied a lipophilic pocket located past the gate keeper residue, Thr-106. The pyrazole ring nitrogen was engaged in a water mediated hydrogen bond with Asp-168. Further inspection of **2** bound in the ATP binding site suggested the potential to build off the C(5) position and possibly engage either the Asp-112 or Asp-113 which are located near solvent exposed space. Alternatively, we envisioned that building towards solvent space would also allow us to incorporate substituents that would provide a handle to improve physical chemical properties.

The earlier report dealt with attempts to optimize **2** via preparation of the N-linked piperazine scaffold **3**, where X = halogen, as a handle to build off of towards the Asp-112. While these compounds showed early promise we prosecuted several alternate scaffolds, in parallel, that could project the desired moieties towards the solvent exposed space. Of particular interest were the related C-linked piperidine scaffolds of **4** and **5** (see Fig. 3). The piperidines were considered to possess a number of desirable attributes including that they lacked one of the basic nitrogens and they possessed a flexible and efficient synthesis allowing for easy

* Corresponding author. Tel.: +1 636 247 8895.
*E-mail address:* jkwalker24@sbcglobal.net (J.K. Walker).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.02.047

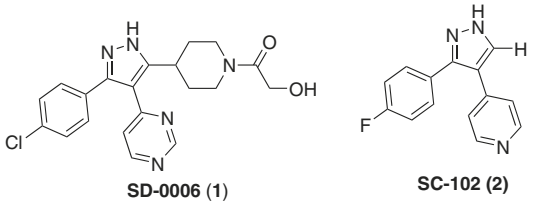



**Figure 1.** Previously disclosed diaryl pyrazole p38 inhibitors.

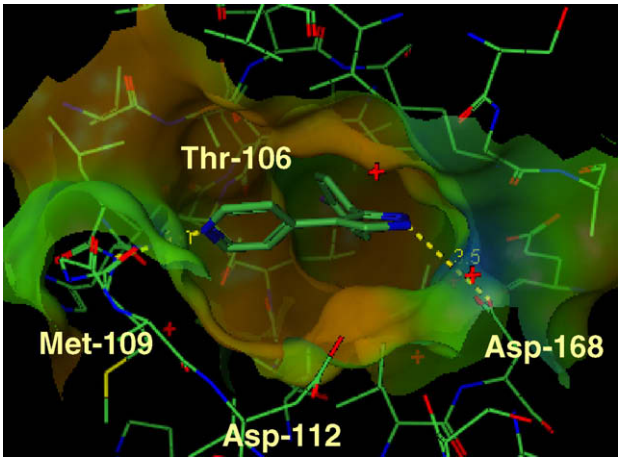



**Figure 2.** Overlay of the lipophilic surface area of **2** bound in the active site of p38.

preparation of analogs that could be modified at all three positions of the pyrazole.

At the outset of our effort we planned to focus on two major criteria in assessing compounds. The first of these was p38α potency and selectivity vs the β-isoform. While four p38 isoforms are known to exist, p38α, p38β, p38γ and p38δ, it was the α- and β-isoforms that we were concerned with. The major driver in the immune response was demonstrated to be p38α while the role of p38β was less well understood,[8] but because of it's closely related homology to p38α we considered it desirable to spare this isoform as much as possible for general safety considerations. Unfortunately at the time we undertook this work there was limited understanding of the differences between α and β and our strategy was driven largely by empirical means.[9]

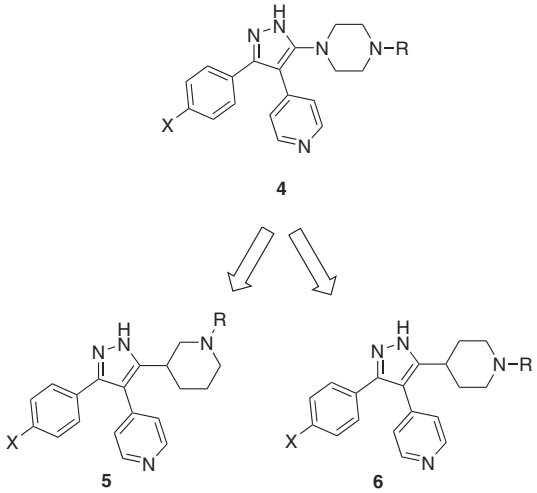
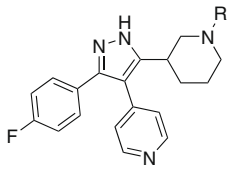
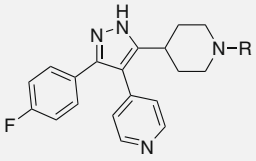



**Figure 3.** Switch from C(5)-piperazine to C(5)-piperidines

**Table 1**
p38 inhibition data for a set of nipecotate and isonipecotate derived pyrazoles



| # | R | p38α[a,b] | p38β[a,b] | rLPS % inh[a,c,d] |
|---|---|---|---|---|
| **6** | H | 48.3 | 404 | 53 |
| **7** | Me | 90.0 | 2520 | 63 |
| | |  | | |
| 8 | Ac | 281.0 | 1680 | ND |
| 9 | H | 25.3 | 510 | 2 |
| 10 | Me | 54.7 | 1960 | 77 |
| 11 | Ac | 82.0 | 2770 | 41 |

ND = not determined.
[a] For experimental conditions see Ref. 5.
[b] $IC_{50}$'s reported in nM.
[c] Dosed at 5 mpk, 4 h prior to administration of LPS.
[d] %reduction in TNFα levels measured 1.5 h after LPS stimulation.

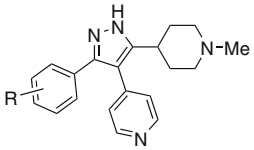
The second important distinguishing criteria for compound selection was efficacy in an acute rat model of inflammation. We chose to utilize a rat lipopolysaccharide (LPS) model[5,10] to give us a basic readout on in vivo efficacy. This model was relatively high-throughput and provided us flexibility with regard to dose and time course which provided an excellent tool to interrogate compounds.

Table 1 highlights a representative data set for analogs prepared in both the 3- and 4-piperidinyl scaffolds. The 3-piperidinyl analogs (**6**–**8**) all demonstrated good potency relative to **2** with only the acetamide, **8**, having an $IC_{50}$ >100 nM. Compounds **6** and **7** also showed moderate efficacy in the LPS model of inflammation (53% and 63%, respectively) with small to modest selectivities against the p38 β-isoforms ranging from only 6–28-fold. The 4-piperidinyl analogs were also potent against p38α being slightly better when compared directly to their 3-piperidinyl counterparts (**6** vs **9**, **7** vs **10**, **8** vs **11**). Additionally, their selectivities against p38β were also modestly superior ranging from 20- to 35-fold. While compound **9** showed little efficacy (~2%) in the rLPS model and acetamide **11** had modest inhibition (41%) the basic *N*-methyl analog **10** possessed good activity (77%). In addition to the good activity displayed by the basic analogs **7** and **10**, we were also encouraged to find that neutral analog **11** also possessed modest activity as well suggesting the SAR would tolerate both basic and neutral substituents.

Based on a slightly better α/β selectivity profile and because it lacks the chiral center associated with the 3-piperidyl ring we elected to focus primarily on the 4-piperidinyl scaffold. We next turned our attention to optimization of the C(3)-aryl ring. The crystal structure had indicated the 4-fluorophenyl group resided in a large lipophilic pocket. We prepared a number of analogs looking to optimize this lipophilic interaction. We surveyed this SAR by selecting single point variations of compound **10** focusing on small lipophilic R groups at either the para- and meta-positions with a representative set highlighted in Table 2.

In general, we found most small lipophilic groups at either the 3- or 4-position to be well tolerated, with p38α $IC_{50}$'s typically

**Table 2**
SAR for the C(3)-phenyl substituent



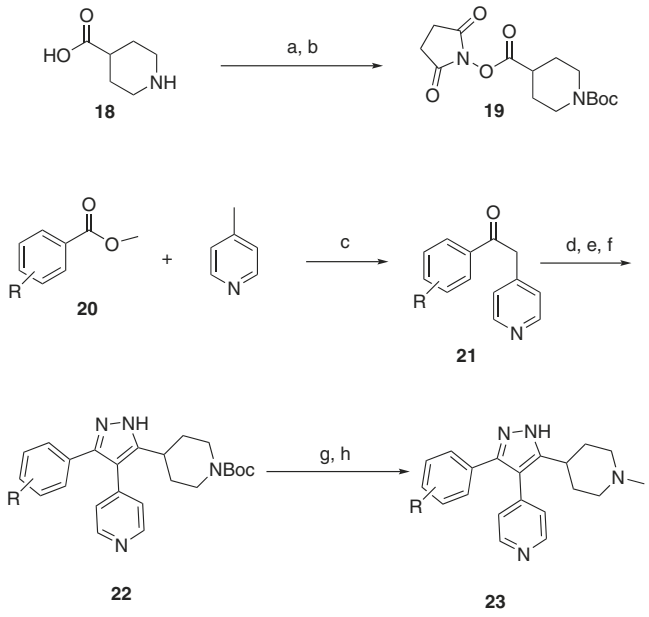
| # | R | p38α[a,b] | p38β[a,b] | % inh rLPS[a,c,d] |
|---|---|---|---|---|
| 10 | 4-F | 54.7 | 1960 | 41 |
| 12 | 4-Cl | 31.6 | 2680 | 71 |
| 13 | 3-Cl | 39.2 | 1050 | 27 |
| 14 | 4-$CF_3$ | 40.5 | 3770 | 22 |
| 15 | 3-$CF_3$ | 26.5 | 164 | 6 |
| 16 | 4-Me | 99.6 | 3070 | 44[e] |
| 17 | 3-Me | 67.3 | 2350 | 81[e] |

[a] For experimental conditions see Ref. 5
[b] $IC_{50}$'s reported in nM.
[c] Unless otherwise noted dosed at 5 mpk, 4 h prior to administration of LPS.
[d] %reduction in TNFa levels measured 1.5 h after LPS stimulation.
[e] Dosed at 20 mpk.

<100 nM. Replacement of the fluorine atom with chlorine resulted in an analog, **12**, with similar p38α potency but possessing a two-fold improvement in the β/α selectivity ratio (84 vs 35) as compared to **10**. The trend of greater β/α selectivity for the compounds bearing a para-substituent relative to meta-substitution was consistent within this series and resulted from compounds with para-substituents having less affinity for the β-isoform. More importantly, however, was fact that this improvement in selectivity was achieved without any loss of in vivo efficacy as judged by the rLPS model (71% for **12** vs 77% for **10**). Compound **13**, where the chlorine substituent was in the 3-position was also potent against p38α but demonstrated poor efficacy in the rLPS model. The larger more lipophilic trifluoromethyl moiety in either the 3- or 4-position (compounds **14** and **15**) yielded analogs potent against p38α but with poor efficacy in the LPS model. The 3-methylphenyl compound **17** did show good efficacy (81%) in the LPS model, albeit at a higher dose of 20 milligrams per kilogram (mpk) but as noted above it also possessed reduced selectivity for p38α while the corresponding 4-methyl analog (**16**) possessed selectivity and rLPS efficacy comparable to compound **10**. Based on the in vivo efficacy and better selectivity against p38β, we elected to fix the 4-chlorophenyl group at the C(3)-position and turned our attention next to optimization of the N-substituent on the piperidine ring.

Scheme 1 depicts the general synthetic scheme we employed for the synthesis of our diaryl pyrazole analogs. Starting with isonipecotic acid (**18**) conversion to the protected *n*-succinimyl acid ester, **19**, was achieved in two steps. In parallel, the pyridyl phenyl ketones of type **21** were obtained via reaction of the anion of 4-methylpyridine and the appropriately substituted benzoates esters, **20**. Ketone **21** was subsequently deprotonated with potassium *tert*butoxide and allowed to react with **19** to give a 1,3-diketone intermediate which upon further exposure to hydrazine followed by acidic work-up yielded the desired pyrazole **22**. Finally, removal of the Boc group yields the free amine which can then be appropriately substituted to yield the desired compounds.

With the C(3)-position now fixed we set about optimization of the piperidine ring to probe the solvent exposed space and/or engage Asp-112. A number of alkyl and amide derived substitutions were examined. The simple hydroxy substituted alkyl groups (**24**–**26**) were potent and selective p38α inhibitors with roughly 100× selectivity over β. Compounds **24** and **25** were also very potent in the rLPS model (dosed @ 5 mpk) with **24** further distinguishing itself by maintaining efficacy at a lower dose (72% inh @ 1 mpk). Sulfonyl urea, **27** and sulfonamide **28** both showed good

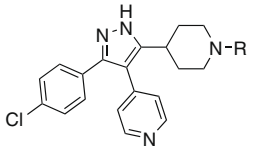



**Scheme 1.** General synthesis of the diarylpyrazole scaffold. Reagents and conditions: (a) NaOH, $(BOC)_2O$, dioxane, 85%; (b) *n*-hydroxysuccinimide, EDC, DMAP, $CH_2Cl_2$, 90%; (c) LiHMDS, 0 °C, 4-methylpyridine, 30 min then add benzoic ester, 90–95%; (d) $^tBuOK$, THF, 0 °C, 1 h then add **19**; (e) AcOH; (f) $H_2NNH_2$, 15–35%; (g) 4 N HCl-dioxane; (h) $H_2CO$, $HCO_2H$.

potency on p38α and good efficacy in the LPS model at the 5 mpk dose but displayed a significant loss in efficacy at the 1 mpk dose. Glycine derivative, **29**, failed to achieve efficacy in the LPS model (20% inh @ 5 mpk). Acetamide derivative **30** was moderately efficacious, at 5 mpk, in the rLPS model but also suffered a substantial loss in efficacy at the low dose. We also prepared a set of amides derivatives bearing additional polar functionality (**30**–**33**) including some to mimic compounds such as **24** and **25**. In general, these analogs displayed good potency for p38α and where highly efficacious in the LPS model at the 5 mpk dose. Compounds **31** and **32** were particular attractive as they did not suffer any drop off in efficacy at the 1 mpk dose (76% and 85% inh, respectively). Amide **33** however suffered a complete loss of activity at 1 mpk. In general, selectivities for the amide derivatives ranged 16–80X with only **31** showing a β/α ratio significantly <50 (16X). We also profiled these analogs in a cell-based human whole blood (HWB) assay. Following stimulation with LPS, compounds were evaluated for their ability to block TNF-α production. The analogs derived from alkyl substitution, where the piperidine nitrogen remains basic, generally gave potencies in the sub-micromolar range in the HWB assay. Analogs with neutral substitution, however, typically gave potencies in the low micromolar range.

A set of potentially promising compounds from Tables 2 and 3 were further profiled further in a series of assays to better assess their overall drugability (Table 4). The compounds were evaluated an in vitro human liver microsome assay (HLM) to assess potential metabolism issues, a dofetilide competition binding assay for assessing potential CV safety risks and the mouse collagen induced arthritis (CIA) model to assess efficacy in a chronic inflammation model.[10] The more basic alkyl substituted analogs such as **11**, **24** and **25** were found to have high intrinsic clearances in the HLM assay and >50% inhibition in the dofetilide assay. Following this result analog **11** was further examined in a hERG patch clamp assay and found to be reasonably potent ($IC_{50}$ = 790 nM) on the hERG channel. Compounds **11** and **25** did, however, exhibit efficacy in the chronic CIA model. After 21 days of dosing only a 22%

**Table 3**
SAR for the piperidine substituent



| # | R | p38α[a,b] | p38β[a,b] | HWB[a,c] | % inh rLPS[a,c,d] (mpk) |
|---|---|---|---|---|---|
| 24 | $-CH_2CH_2OH$ | 41 | 3390 | 120 | 88(5); 72(1) |
| 25 | $-CH_2CH_2OMe$ | 70 | 6720 | 520 | 84(5); 56(1) |
| 26 | $-CH_2(CH_2)_2OMe$ | 106 | 6550 | ND | ND |
| 27 | $-SO_2NH_2$ | 14 | 1650 | ND | 68(5); 21(1) |
| 28 | $-SO_2Me$ | 70 | 3530 | 820 | 75(5); 45(1) |
| 29 | $-CH_2CO_2H$ | 126 | 4340 | ND | 20(5) |
| 30 | $-C(O)CH_3$ | 68 | 3130 | 3600 | 66(5); 32(1) |
| 31 | $-C(O)CH_2OH$ | 111 | 1790 | 1500 | 85(5); 76(1) |
| 32 | $-C(O)CH_2OMe$ | 71 | 3450 | 3500 | 90(5);85(1) |
| 33 | $-C(O)CH_2NMe_2$ | 80 | 6720 | 10,100 | 85(5); 0(1) |

ND = not determined.
[a] For experimental conditions see Ref. 5.
[b] $IC_{50}$'s reported in nM.
[c] Specified dose given 4 h prior to administration of LPS.
[d] %reduction in TNFα levels measured 1.5 h after LPS stimulation.

**Table 4**
Additional data for select C(4)-pyridyl compounds

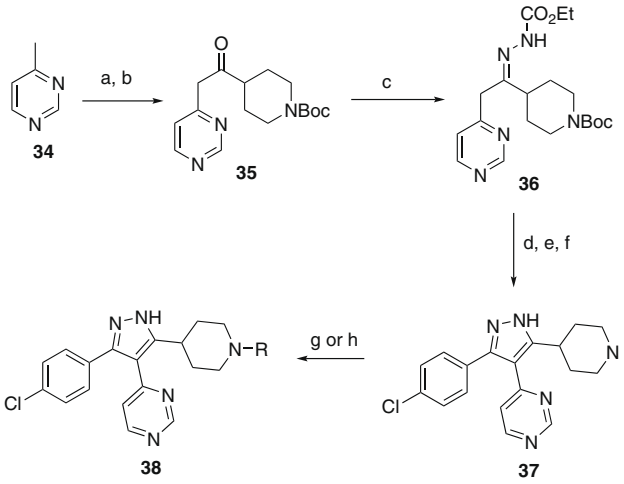
| Compd # | $Cl_{int}$[a] ($T_{1/2}$) | Dof[b] (% inh) | mCIA[c] (% inc) |
|---|---|---|---|
| **11** | 62.3(16.6 min) | 64 | 38 |
| **24** | 32.0 (30.5 min) | 61 | 70 |
| **25** | 47.7(21.5 min) | 74 | 22 |
| **30** | 22.5 (43.3 min) | ND | 50 |
| **31** | 15.8 (62 min) | 24 | 60 |

ND = not determined.
[a] Human liver microsomes with clearance measured in ml/min/kg.
[b] Test concentration was 10 μM.
[c] Mice were dosed at 30 mpk and disease measured after 21 days.

incidence of disease was observed with **25**, as measured by amount of paw swelling relative to control animals. The neutral amide analogs **30** and **31** were also evaluated. The compounds showed moderate intrinsic clearance in the HLM assay and markedly reduced effect in the dofetilide assay. In their respective mCIA studies both **30** and **31** gave only modest responses (50% and 60% incidence).

Despite identifying several promising compounds in terms of potency, selectivity and in vivo efficacy within this series some issues were also identified which needed to be addressed going forward. While it was readily apparent that piperidine analogs derived from alkyl substituents were potent in the cell and efficacious in vivo they also tended to have higher clearance in our HLM model and also posed a potential CV safety risk. Replacing the alkyl groups with amide substituents tended to mitigate both the clearance and safety risks but these analogs also tended to be less potent in both the cell and in vivo relative to the basic compounds. Previously, work done by researchers at Smithkline Beecham had demonstrated that for a related chemical template replacement of a pyridine group with pyrimidine had resulted in a boost in potency.[11] We envisioned that such a replacement of the C(4)-pyridyl moiety with a pyrimidine ring as a potential approach to improving efficacy for the neutral analogs. Additionally, this switch would reduce the lipophilicity of the scaffold and thus might also help address issues around clearance and/or safety for the basic analogs. With this in mind, we turned our attention to preparing a series of pyrazole analogs with a C(4)-pyrimidyl ring.

Scheme 2 depicts the synthesis devised for the pyrimidine scaffold which in turn proved more efficient and higher yielding than

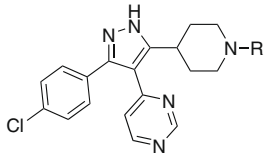


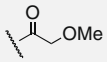

**Scheme 2.** Synthesis of C(4)-pyrimidine analogs. Reagents and conditions: (a) LiHMDS, THF, 0 °C; (b) add ethyl *N*-Boc-piperidine-4-carboxylate, 70%; (c) $EtCO_2NHNH_2$; EtOH, ACOH; (d) LiHMDS, 0 °C, 30 min, add 4-chloro benzoylchloride, 1 h; (e) Add 4 N HCl-dioxane; (f) 2 N NaOH; (g) R-CHO, $Na(OAc)_3BH$, $CH_2Cl_2$ or; (h) $R-CO_2H$, EDC, DMAP, Hunig's base, $CH_2Cl_2$.

that for the pyridine scaffold. Starting with 4-methyl pyrimidine, (**34**), ketone **35** already incorporating the C(5)-piperidine ring was prepared via acylation of the anion of **34** with the Boc-protected ethyl isonipecotate in two steps in a 70% overall yield. Next, ketone **35** was condensed with ethyl carbazate to give hydrazone **36**. Conversion of **36** to pyrazole **37** was achieved in three steps via (1) dianion formation of **36** followed by acylation with 4-chloro benzoylchloride to give a α-acyl hydrazide, (2) formation of the pyrazole ring via exposure to 4 N HCl-dioxane, (3) base catalyzed removal of the carboethoxy group which gave rise to the desired pyrazole scaffold, **37**. The desired *N*-alkyl substituted analogs were then prepared through a standard reductive amination protocol while the amide compounds were prepared using a standard amide coupling procedures or via addition and subsequent ring opening of the appropriate epoxides.

Table 5 highlights enzyme binding, HWB and LPS data for a representative set of pyrimidine analogs. As seen previously in the C(4)-pyridine series the methyl piperidine, **39**, was potent on p38α but only moderately effective in the rLPS model. As before, we prepared a number of alkyl substituted piperidines bearing a heteroatom in the alkyl chain (**40**–**45**). Simple aminoalcohol **40** was potent on p38α and in the HWB assay as well as being efficacious at both 5 and 1 mpk in the rLPS model. Adding methyl groups to the alkyl chain of **40** proved ineffective as we saw greatly diminished efficacy in the rLPS model with these compounds (**41** and **42**). The furanyl analog, **43**, was potent on p38α and in the HWB assay. Similar to **40** it also maintained efficacy in the rLPS model at the 1 mpk dose. Pyranyl compound, **44**, however was less potent on p38α ($IC_{50}$ = 205 nM) and had only modest efficacy at 5 mpk in the rLPS model. Cyclopentyl alcohol, **45**, was one of the most potent compounds measured in the p38 activity assay but was unable to maintain efficacy (40%) in the rLPS model at a 1 mpk dose. Pyridine derivative, **46**, failed to achieve good rLPS efficacy at even the 5 mpk dose. In general, the neutral analogs were still less potent on p38α than the corresponding basic analogs, but still worked well in the LPS model. Acetamide **47** was only moderately potent on p38α ($IC_{50}$ = 152 nM) but was still efficacious in the rLPS model at both the 1 and 5 mpk doses (90% and 72%). The glycolate derived amides (**1** and **48**) behaved similarly to **47** in both models with **1** having the best efficacy in the LPS model at 1 mpk (81%). Urea **49** and sulfonamide **50** were both potent analogs that also showed a drop in efficacy in rLPS when dosed at 1 mpk. As seen previously in the

**Table 5**
Data for pyrimidine analogs



| # | R | p38α[a,b] | p38β[a,b] | HWB[a,b] | rLPS % inh dose[a,c,d] (mpk) |
|---|---|---|---|---|---|
| **39** | $-CH_3$ | 48 | 2320 | 800 | 63(5); 36(1) |
| **40** |  | 35 | 2540 | 490 | 88(5); 80(1) |
| **41** |  | 184 | 2780 | ND | 0(5); ND(1) |
| **42** |  | 88 | 9780 | 1000 | 34(5); 3(1) |
| **43** |  | 31 | 7410 | 520 | 70(5); 80(1)[b] |
| **44** |  | 205 | 9500 | >5000 | 46(5); ND(1) |
| **45** |  | 19 | 3380 | ND | 70(5); 40(1) |
| **46** |  | 47 | 3290 | ND | 27(5); ND(1) |
| **47** |  | 152 | 3710 | ND | 90(5); 72(1) |
| **1** |  | 110 | 3450 | 1500 | 87(5); 81(1) |
| **48** |  | 94 | 3250 | ND | 88(5); 71(1) |
| **49** |  | 88 | 3480 | ND | 88(5); 53(1) |
| **50** |  | 198 | 4100 | >5000 | 89(5); 26(1) |

ND = not determined.
[a] For experimental conditions see Ref. 5
[b] $IC_{50}$'s reported in nM.
[c] Specified dose given 4 h prior to administration of LPS.
[d] %reduction in TNFα levels measured 1.5 h after LPS stimulation.

**Table 6**
Additional data for select C(4)-pyrimidyl compounds

| Compd # | $Cl_{int}$[a] ($T_{1/2}$) | Dof[b] (%inh) | mCIA[c] (%inc) |
|---|---|---|---|
| **39** | 31.5 (31.2 min) | 51 | 20 |
| **40** | 21.4 (47.6 min) | 46 | 61 |
| **43** | 16.3 (61.3 min) | 35 | 50 |
| **47** | 9.5 (102 min) | ND | 50 |
| **1** | <8 (>120 min) | 16 | 16 |
| **50** | 18.1 (53.9 min) | ND | 44 |

ND = not determined.
[a] Human liver microsomes with clearance measured in ml/min/kg.
[b] Test concentration was 10 μM.
[c] Mice were dosed at 30 mpk and disease measured after 21 days.

pyridine scaffold the basic analogs performed well in the HWB assay while the neutral analogs were typically in the low micromolar range.

**Table 7**
Selected pharmacokinetic parameters for compound **1**

| Species[a] | Cl (ml/min/kg) | $V_d$ (L/kg) | $T_{1/2}$ (h) |
|---|---|---|---|
| Rat[b] | 4.96 | 1.74 | 4.05 |
| Dog[c] | 2.92 | 1.07 | 4.48 |

[a] Compounds were dosed intraveniously (IV) at the specified doses.
[b] 5 mg/kg dose.
[c] 2.5 mg/kg dose.

Additional profiling data of select pyrimidyl compounds from above are shown in Table 6. A consistent trend we observed was that the intrinsic clearance ($Cl_{int}$) was lower for the pyrimidyl series versus the pyridyl series. Most notable was the 50% reduction in $Cl_{int}$ observed with **39** (31.5 vs 62.3 ml/min/kg) compared to C(4) pyridyl analog **11**. The other basic analogs **40** and **43** also saw reductions in intrinsic clearance when compared to their respective pyridine versions. This trend also was observed with the neutral analogs such as **1** and **50**. The switch to pyrimidine also diminished the potential for crossover on the hERG channel as measured by the dofetilide binding assay. Reductions in competitive binding were observed with all pyrimidine analogs as compared to their pyridyl versions. Neutral compounds such as **1** and **50** were significantly less active than the basic analogs. Finally, compounds **39** and **1** showed a significant reduction in incidence in the mCIA model. Compound **1** showed the greatest efficacy in the model with only 16% incidence of disease at a 30 mpk dose (administered 15 mpk bid). Additionally, **1** showed excellent metabolic stability as measured by the HLM assay with a $T_{1/2}$ of >2 h.

Finally, pharmacokinetic experiments (Table 7.) in both the dog and rat indicated compound **1** possessed desirable properties in terms of half-life (rat and dog $t_{1/2}$ = 5–6 h) with bioavailabilities >80% in both species. On the basis of the data presented here as well as previously disclosed data,[5] compound **1** was selected for advancement to clinical trials.

## References and notes


1. Vaz, A.; Lisse, J.; Rizzo, W.; Albani, S. *Expert Rev. Clin. Immunol.* **2009**, *5*, 291.
2. Taylor, P. C.; Feldman, M. *Nat. Rev. Rheumatol.* **2009**, *5*, 578.
3. Westra, J.; Limburg, P. C.; de Boer, P.; van Rijswijk, M. H. *Ann. Rheum. Dis.* **2004**, *63*, 1453.
4. Schett, G.; Zwerina, J.; Firestein, G. *Ann. Rheum. Dis.* **2008**, *67*, 909.
5. Burnette, B. L.; Selness, S. R.; Devraj, R.; Jungblath, G.; Kurambail, R.; Stilwell, L.; Anderson, G.; Mnich, S.; Hirsch, J.; Compton, R.; De Ciechi, P.; Hope, H.; Hepperle, M.; Keith, R. H.; Naing, W.; Shieh, H.; Portanova, J.; Zhang, Y.; Zhang, J.; Leimgruber, R. M.; Monahan, J. *Pharmacology* **2009**, *84*, 42.
6. Graneto, M. J.; Kurambail, R. G.; Vazquez, M. L.; Shieh, H.; Pawlitz, J. L.; Williams, J. M.; Stallings, W. C.; Geng, L.; Naraian, A. S.; Koszyk, F. J.; Stealey, M. A.; Xu, X. D.; Weier, R. M.; Hanson, G. J.; Mourey, R. J.; Compton, R. P.; Mnich, S. J.; Anderson, G. D.; Monahan, J. B.; Devraj, R. *J. Med. Chem.* **2007**, *50*, 5712.
7. The coordinates have been deposited in the PDB under accession code 1BL7.
8. (a) Hale, K. K.; Trollinger, D.; Rihanek, M.; Manthey, C. L. *J. Immunol.* **1999**, *162*, 4252; (b) O'Keefe, S. J.; Mudgett, J. S.; Cupo, S.; Parsons, J. N.; Chartrain, N. A.; Fitzgerald, C.; Chen, S.-L.; Lowitz, K.; Rosa, C.; Visco, D.; Luell, S.; Carballo-Jane, E.; Owens, K.; Zaller, D. M. *J. Biol. Chem.* **2007**, *282*, 34663.
9. (a) For a recent review on p38 selectivity see, Goldstein, D. M.; Kuglstatter, A.; Lou, Y.; Soth, M. J. *J. Med. Chem.* **2010**, ASAP.; (b) For recent work on defining the active site of p38β see Patel, S. B.; Cameron, P. M.; O'Keefe, S. J.; Frantz-Wattley, B.; Thompson, J.; O'Neill, E. A.; Tennis, T.; Liu, L.; Becker, J. W.; Scapin, G. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2009**, *D65*, 777.
10. (a) The Pfizer Institutional Animal Care and Use Committee reviewed and approved the animal use in these studies. The animal care and use program is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. (b) For experimental conditions around this model please refer to Ref. 5
11. Adams, J. L.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111.