Design of Potent and Selective 2-Aminobenzimidazole-Based p38α MAP Kinase Inhibitors with Excellent in Vivo Efficacy

Alfonso de Dios,*,† Chuan Shih,‡
Beatriz López de Uralde,† Concepción Sánchez,†
Miriam del Prado,† Luisa M. Martín Cabrejas,†
Sehila Pleite,† Jaime Blanco-Urgoiti,†
María José Lorite,† C. Richard Nevill Jr.,‡
Rosanne Bonjouklian,‡ Jeremy York,‡ Michal Vieth,‡
Yong Wang,‡ Nicholas Magnus,‡
Robert M. Campbell,‡ Bryan D. Anderson,‡
Denis J. McCann,‡ Deborah D. Giera,‡ Paul A. Lee,‡
Richard M. Schultz,‡ Li C. Li,‡ Lea M. Johnson,‡ and
Jeffrey A. Wolos‡

Eli Lilly and Co., Lilly S.A., Avenida de la Industria, 30, 28108 Alcobendas, Madrid, Spain, and Lilly Research Laboratories, Eli Lilly and Co., Lilly Corporate Center, Indianapolis, Indiana 46285

Received December 17, 2004

Abstract: We report the design and discovery of a 2-aminobenzimidazole-based series of potent and highly selective p38α inhibitors. The lead compound **1** had low-nanomolar activity in both ATP competitive enzyme binding and inhibition of TNFα release in macrophages. Compound **18** showed excellent pharmacokinetics properties and oral activity in the rat collagen induced arthritis model compared with other p38 reference compounds. A SAR strategy to address CyP3A4 liability is also described.

Over the past decade, the pursuit of p38α MAP kinase inhibitors has received an extraordinary level of attention in the pharmaceutical industry[1] and in the medicinal chemistry community.[2] A unique combination of well-established pharmacology, clinical efficacy,[3−6] and the opportunity to utilize structure-based drug design[7] has made this a highly attractive target for therapeutic intervention.[8]

There is overwhelming evidence indicating that p38α plays a dominant role in the pathogenesis of acute and chronic inflammatory responses.[1,2] Activation of p38α occurs in monocytes and macrophages under different stress-related stimuli. Subsequent phosphorylation of downstream effectors and transcriptional factors leads to the biosynthesis of potentially deleterious proinflammatory cytokines such as TNFα and IL-1β.[9] The clinical proof of concept in rheumatoid arthritis achieved with VX-745[3] and BIRB-796[4] validates the MAP kinase pathway as a useful mechanism for intervention in inflammatory disease.

The seminal work by SmithKline Beecham[10] (initially followed by Merck[11] and RWJ[12]) with the aid of X-ray crystallography and mutagenesis studies[13] has revealed the structural basis for much of the observed SAR around the well-known pyridinylimidazole p38 pharmacophore.[14] The prototypical inhibitor, SB203580 (**3**, Figure 1), reduces IL-1β and TNFα levels in vitro and in vivo.[15] Several other lead molecules (e.g., SB242235 **4**,[5,16] RWJ67657 **5**,[6] and L-790070 **6**,[11,17] etc.) have been advanced to preclinical or clinical studies. In the past 3 years many disclosures present scaffolds with different structural features;[18] however, only Boehringer's BIRB796[19] seems to offer a distinct profile in terms of binding kinetics (slow binding using an allosteric domain). In this communication we show that a novel design combined with a strategy to address some well-known CyP450 liabilities[20] provides great advantage in terms of in vivo efficacy.

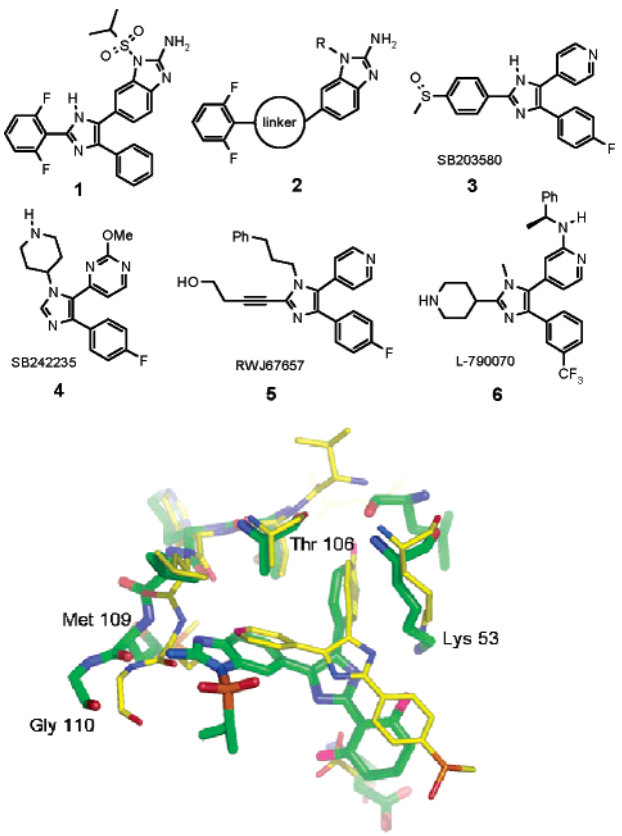


Figure 1. Hybrid design, known p38 inhibitors, and X-ray structure of **1** (green) bound to the ATP-binding site of p38α and superposed onto X-ray structure of SB203580 **3** (yellow).

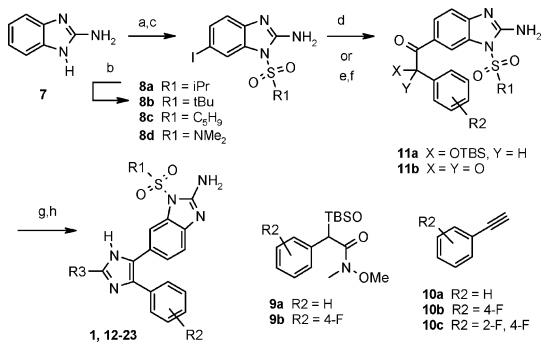
Kinase screening efforts at Lilly led to the identification of modestly potent hits with C-6 substituted 2-aminobenzimidazoles as the generic core structure (**2**, R = R_1SO_2 in some cases, Figure 1). Docking studies indicated the potential for the C-2 amino group and N-3 imine nitrogen in the benzimidazole core to interact with the kinase hinge region in the ATP binding cleft. On the basis of the known X-ray structures for triarylimidazoles such as **3** and the docking hypothesis of **2**, we envisioned that a hybrid molecule **1** (Figure 1) would have potent p38α activity. Because of the larger size of benzimidazole compared to the 4-pyridyl, it was expected that binding of **1** would require a rearrangement in the flexible p38α hinge (from His107 to Ala111) or a more probable rearrangement of the Lys53 side chain.

We were pleased to discover that the first molecule designed and synthesized in this series, **1**, turned out

* To whom correspondence should be addressed. Phone: +34-91-6633412. Fax: +34-916633411. E-mail: a.de_dios@lilly.com.
† Eli Lilly and Co., Spain.
‡ Eli Lilly and Co., Indiana.

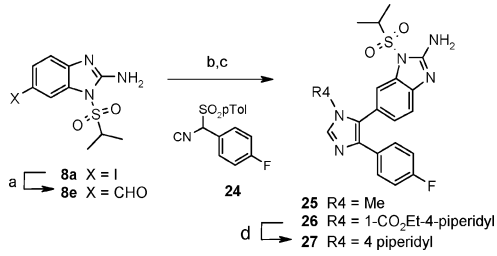
10.1021/jm048978k CCC: $30.25
Published on Web 02/19/2005

Scheme 1[a]



[a] Reagents and conditions (yields for **1**): (a) R_1SO_2Cl, NaOH, CH_3CN/H_2O, 90%; (b) PhLi, ^{t}BuLi, MeI, THF, −78 °C; (c) NIS, AcOH, 84%; (d) ^{i}PrMgCl, THF, −78 °C, then **9a**,**b,** 0 °C, 50%; (e) **10a**−**c**, $Pd(PPh_3)_2(AcO)_2$, CuI, DMSO, Et_3N, room temp, 86%; (f) $KMnO_4$, $MgSO_4/NaHCO_3$, acetone, 35 °C, 83%; (g) R_3CHO (or paraformaldehyde for R_3 = H), $Cu(OAc)_2$, NH_4OAc, AcOH, 90 °C, 62% from **11a** or R_3CHO, NH_4OAc, ^{n}BuOH, 55 °C, 78% from **11b**. (h) Some compounds were isolated as mesylate salts: MsOH, MeOH, 98% for **14** (see Supporting Information).

Scheme 2[a]



[a] Reagents and conditions: (yields for **27**): (a) PhLi, ^{t}BuLi, DMF, THF, from −78 °C to 0 °C, 76%; (b) R_4NH_2, DMF, room temp, 95%; (c) **24**, ^{t}BuNH$_2$, MeOH, reflux, 25%; (d) concentrated HCl, reflux, then aqueous NaOH to pH 7, 43%.

to be a potent inhibitor of p38α (K_i = 5 nM, ATP-competitive) and p38β. The binary complex of **1** bound to rat p38α was obtained (Figure 1) and confirmed the predicted binding,[21] showing a clear shift in the hinge. The N-3 imine nitrogen acted as the key hydrogen bond acceptor for Met109 amide N−H, and the ^{i}Pr sulfonyl group was exposed to the small lipophilic pocket in proximity to Gly110. Interestingly, it was not clear that a hydrogen bond existed between imidazole N-3 and terminal NH_2 in Lys53 because the shorter distance with Lys53Nϵ was with one of the fluorine atoms (2.83 Å). Broader kinase profiling with **1** showed that it had remarkable selectivity with the exception of JNK2 (vide infra). As hypothesized, **1** shifted the flexible hinge to accommodate the benzimidazole moiety but did not produce the Gly110 carbonyl flip described for other inhibitors.[17] This peptide flip seems to serve as a source of p38 selectivity vs JNKs because of the restriction in the Ramachandran space for the analogue Asp residue in JNKs.[17] The fact that p38 accommodated **1** without the Gly110 flip may very well explain the JNK2 activity.

The synthesis of our inhibitors is outlined in Schemes 1 and 2. Starting from commercially available 2-aminobenzimidazole, sulfonylation at N-1 followed by regioselective iodination with NIS afforded 6-iodobenzimidazoles **8a**−**d**.[22] The *tert*-butyl sulfone was synthesized by lithiation of the ^{i}Pr sulfone derivative of **7** followed by alkylation with MeI to afford **8b** after the iodination step.[23]

Metal−halogen exchange and addition to Weinreb amides **9a**,**b**[24] led to the silyloxy ketone intermediates **11a** that underwent copper(II)-catalyzed oxidative cyclization with the appropriate aldehyde to yield final products in just four steps. Alternatively, a more efficient route could be used. Palladium-catalyzed coupling of the corresponding iodide **8** with arylalkynes (**10a**−**c**) followed by oxidation using $KMnO_4$ led to diketones **11b**. In this case, no oxidating copper reagent was required to afford the final desired C-2 substituted imidazoles **1** and **12**−**23** (Table 1). For the synthesis of N-1 substituted imidazoles (Scheme 2), the key intermediate was found to be the C-6 carboxaldehyde **8e** that was prepared from **8a** via lithiation and DMF addition. Imine formation and van Leusen cyclization[25] using TosMIC reagent **24**[26] afforded the desired derivatives.

Inhibition of p38α was determined for compounds in Table 1 using recombinant human p38α in a standard filter binding protocol using ATP[γ-^{33}P] and EGFR 21-mer peptide as substrate. Almost all of the compounds showed potent p38α inhibition with IC_{50} values ranging from 1 to 30 nM. Only N-1 piperidyl substituted imidazole **27** showed decreased activity, indicating that our SAR did not parallel that of SB242235 (**4**)[16] and only smaller substitutions were well tolerated (**25**).

For lead compound **1**, the observed IC_{50} was equivalent to the K_i, which showed promise for good cell activity within this series. Deletion of C-2 imidazole substitution and introduction of small alkyl groups at that position and/or fluorine atoms in the phenyl ring also led to potent inhibitors (**12**−**18**), which is consistent with previous observations.[14]

Introduction of bulkier sulfonyl derivatives (**18**, **22**) or a sulfamoyl group (**23**) was not detrimental for binding relative to **1**, indicating that larger or polar groups could be accommodated in the small lipophilic pocket close to Gly110. In general, this series showed equally potent activity against p38β2, some cross-reactivity against JNKs (see Table 2), and high selectivity against the other kinases screened in the panel.[27]

Functional inhibition of TNFα in murine peritoneal macrophages was determined using LPS stimulation in the presence of test compounds (Table 1). Compounds **1**, **12**−**19**, and **21**−**23** were potent inhibitors of TNFα release in the cell-based assay (IC_{50} = 2−60 nM). N-1 substituted imidazoles **25** and **27** showed decreased cell activity that for **27** correlates with decreased enzyme activity. The C-2 piperidyl derivative **20** had a dramatic loss in cell-based potency presumably because of poor cell permeability. *N*-Isobutyl substitution at the piperidyl nitrogen, **21**, restored the cell activity.[28]

To assess potential drug−drug interaction for this series as early as possible,[20] in vitro CyP3A4 inhibition was determined. Increasing the steric hindrance around the C-2 imidazole carbon greatly reduced the CyP3A4 inhibition (compare compounds **12**−**16** in Table 1). C2-unsubstituted analogues (**12** and **13**) were found to be potent inhibitors, while ethyl and isopropyl analogues and especially the ^{t}Bu derivative **16** led to reduced activity at the 3A4 isoform.[29]

Plasma exposure was measured after oral administration in the rat. Besides the low exposure observed for C-2 unsubstituted **12** and **13**, it is interesting to compare the modest exposure and bioavailability for **1**

Table 1. Biochemical, in Vivo, and Rat Pharmacokinetics Data for Aminobenzimidazole-Based P38α Inhibitors (See Scheme 1 for Structure)

compd	R1	R2	R3	p38α IC_{50},[a] nM (*n*)	cell TNFα inh IC_{50},[a] nM, mouse macrophages (*n*)	CyP3A4 inh IC_{50},[b] μM	mice TNFα inh (iv LPS), oral[c] $TMED_{50}$,[d] mg/kg	rat oral AUC_{0-inf} (10 mg/kg),[c] μM h
1	^{i}Pr	H	2,6-F_2-C_6H_4	4.9 ± 0.4 (17)	10.3 ± 0.4 (202)	6.3	5.2	5.4
12	^{i}Pr	H	H	4.2 ± 0.5 (8)	31.8 ± 7.8 (4)	1.6	19.8	3.7
13[e]	^{i}Pr	4-F	H	4.3 ± 1.8 (5)	65.7 ± 3.1 (4)	0.8	9.6	1.4
14[f]	^{i}Pr	4-F	Et	4.7 ± 1.7 (3)	47.2 ± 12.8 (4)	4.4	6.5	NT[g]
15[f]	^{i}Pr	4-F	^{i}Pr	4.5 ± 1.7 (4)	28.6 ± 5.6 (4)	6.1	4.9	12.8
16[e]	^{i}Pr	4-F	^{t}Bu	15.9 ± 2.5 (7)	31.1 ± 5.6 (4)	31.8	3.9	13.5
17[f]	^{i}Pr	2-F, 4-F	^{t}Bu	4.4 ± 0.6 (5)	6.2 ± 1.8 (4)	NT[g]	2.2	14.6
18[f]	^{t}Bu	2-F, 4-F	^{t}Bu	4.8 ± 1.7 (3)	1.6 ± 0.2 (4)	NT[g]	5.3	28.3
19[f]	^{i}Pr	H	2,6-Cl_2-C_6H_4	15.3 ± 5.0 (3)	3.4 ± 1.2 (4)	NT[g]	2.5	17.0
20	^{i}Pr	H	4-piperidyl	2.7 ± 0.4 (3)	2885 (2)	NT[g]	NT[g]	NT[g]
21	^{i}Pr	H	1-^{i}Bu-4-piperidyl	5.5 ± 0.9 (3)	27.9 ± 7.6 (4)	5.3	7.3	NT[g]
22[e]	C_5H_9	H	2,6-F_2-C_6H_4	19.9 ± 5.2 (3)	6.0 (2)	13.0	5.1	0.9
23[e]	NMe_2	H	2,6-F_2-C_6H_4	22.8 ± 10.9 (3)	8.8 ± 3.3 (3)	NT[g]	12.5	9.8
25	see Scheme 2			20.7 ± 5.5 (3)	720 ± 154 (4)	NT[g]	NT[g]	NT[g]
27	see Scheme 2			125 ± 23.2 (4)	4457 ± 2083 (4)	NT[g]	NT[g]	NT[g]

[a] Mean values ± SEM of at least three independent determinations. [b] $n = 1$. [c] Vehicle: 1% NaCMC/0.25% Tween-80 in water. [d] Threshold minimal effective doses (mg/kg). [e] Bismesylate salt. [f] Monomesylate salt. [g] Not tested.

Table 2. Selectivity Profile of **1**

kinase[a]	kinase assay IC_{50} (nM)[b]	kinase	kinase assay IC_{50} (nM)
p38β2	11.9 ± 0.1	rCAMKII	>20000
p38γ	>20000	PKAα	>20000
JNK1α1	4422 ± 1653	E/CDK2	>20000
JNK2α2	141.7 ± 38.2	PKCβII	>20000
MAPKAPK2	>20000	PI3K	>20000
TGFβ RI	>20000	VEGFR2	>20000

[a] Human kinases unless otherwise indicated. [b] Mean values ± SEM of at least three determinations.

Table 3. Rat in Vivo Data for Selected p38 Inhibitors[a]

compd	TNFα inh,[b] rat joint, %	CIA, paw swelling $TMED_{50}$, mg/kg[c]	CIA, histology, $TMED_{50}$, mg/kg[c]
17	81	1.5	8.1
18	82	1.5	4.2
BIRB796	55	15	30
SB242235	ND[d]	5.0	7.0
RWJ67657	<50	>30	>30

[a] Vehicle: see Table 1. [b] 3 mg/kg oral dose. [c] Oral bid dosing for 14 days, therapeutic, $p < 0.05$ for all cases. [d] Not determined.

($F = 39\%$) with the excellent data for the 2,6-dichloro analogue **19** (3-fold higher AUC, $F = 55\%$). Additionally, ^{t}Bu substitution (**16**−**18**) led to readily absorbed and highly bioavailable compounds.

Analysis of plasma from a rat bioavailability study of **12** resulted in the identification of major oxidative metabolites derived from imidazole ring opening (data not shown). This exposure data suggest that both *tert*-butyl and 2,6-dichlorophenyl substitutions might act as protecting groups of the C-2 imidazole carbon. This position seems to be prone to extensive oxidation and ring opening,[29] leading to reduced oral exposure.

To evaluate how the observed cell activity could translate to in vivo acute TNFα inhibition, compounds were orally dosed to Balb/c mice followed by iv LPS administration for 2 h (Table 1). From these dose−response studies, a $TMED_{50}$ dose[30] (threshold minimum 50% effective dose) was determined. $TMED_{50}$ values ranged from 2 to 20 mg/kg. Unsubstituted imidazoles **12** and **13** were some of the less potent derivatives, which correlates with more extensive oxidative metabolism and lower plasma exposure (vide supra).

On the basis of a combination of in vitro, in vivo activity, and rat oral exposure, **17** and **18** were considered for further evaluation. Both compounds showed potent inhibition of acute LPS-induced TNFα production in rat joints as measured in the rat synovial lavage fluid ($p < 0.05$). In a 14-day rat collagen induced arthritis model (CIA, therapeutic dosing), both compounds showed excellent dose-dependent inhibition after oral administration (Table 3).[31] Our data show that activity obtained for these aminobenzimidazoles in inflammation (rat ankle size) and histopathology scores (bone erosion and cartilage destruction) compares favorably with that of other advanced molecules in clinical development. Compound **18** showed remarkable efficacy in this model with a $TMED_{50}$ of 1.5 mg/kg for inflammation and 4.2 mg/kg for histology (10- and 7-fold better than BIRB796, respectively). Similar half-life (6−8 h) and increased exposure in **18** with respect to **17** may explain the 2-fold increase in histology efficacy within the aminobenzimidazoles.

In summary, we have developed a potent series of 2-aminobenzimidazole based p38α MAP kinase inhibitors. The binding mode based on X-ray data and preliminary SAR trends have been outlined, as well as the molecular basis for in vitro activity, reduced CyP3A4 liability, enhanced rat oral exposure, and improved in vivo efficacy compared with other advanced triaryl imidazoles.

Acknowledgment. The authors thank Harold Brooks and Scott Watkins for K_i determination, Alfonso Espada for HPLC data, and James Wikel, Andrea Zaliani, Luis Casarrubios, and Chafiq Hamdouchi for useful suggestions.

Supporting Information Available: Crystallographic information for **1**, experimental procedures for compound preparation, and biological assay protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Kumar, S.; Boehm, J.; Lee, J. C. p38 MAP kinases: key signaling molecules as therapeutic targets for inflammatory diseases. *Nat. Rev. Drug Discovery* **2003**, *2*, 717−726. (b) Pargellis, C.; Reagan, J. Inhibitor of p38 mitogen-activated protein kinase for the treatment of rheumatoid arthritis. *Curr. Opin. Invest. Drugs* **2003**, *4*, 566−571. (c) Foster, M. L.; Halley, F.; Souness, J. E. Potential of p38 inhibitors in the treatment of rheumatoid arthritis. *Drug News Perspect.* **2000**, *13*, 488−497.

(2) (a) Chakravarty, S.; Dugar, S. Inhibitors of p38a MAP Kinase. *Annu. Rep. Med. Chem.* **2002**, *37*, 177−186. (b) Adams, J. L.; Badger, A. M.; Kumar, S.; Lee, J. C. p38 kinase: molecular target for the inhibition of proinflammatory cytokines. *Prog. Med. Chem.* **2001**, *38*, 1−60.
(3) (a) Ferracioli, G. F. VX-745 Vertex Pharmaceutical. *Curr. Opin. Anti-Inflammatory Immunomodulatory Invest. Drugs* **2000**, *2*, 74−77. (b) Salituro, F. G. VX-745. Presented at the 11th RSC-SCI Medicinal Chemistry Symposium, Churchill College, Cambridge, U.K., September 9−12, 2001.
(4) Gupta, A. Safety, pharmacokinetics and pharmacodynamics of single doses of an oral p38 MAP kinase inhbitior (BIRB 796) in healthy human males, a placebo controlled, randomized study, double blinded at each dose level. *Annu. Meet. Am. Acad. Allergy, Asthma, Immunol.* **2002**, *109*, S66, A167.
(5) Fullerton, T.; Sharma, A.; Prabhakar, U.; Tucci, M.; Boike, S.; Davis, H.; Jorkasky, D.; Williams, W. Suppression of ex vivo cytokine production by SB-242235, a selective inhibitor of (p38) map kinase. *Clin. Pharmacol. Ther.* **2000**, *67*, 114 (Abstract OI-B-4).
(6) Wadsworth, S. A.; Cavender, D. E.; Beers, S. A.; Lalan, P.; Schafer, P. H.; Malloy, E. A.; Wu, W.; Fahmy, B.; Olini, G. C.; Davis, J. E.; Pellegrino-Gensey, J. L. RWJ67657, a potent, orally active inhibitor of p38 mitogen-activated protein kinase. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 680−687.
(7) (a) Wang, Z. L.; Canaragajah, B. J.; Boehm, J. C.; Kassis, S.; Cobb, M. H.; Young, P. R.; Abdel-Meguid, S.; Adams, J. L.; Goldsmith, E. J. Structural basis for in vitro selectivity in MAP kinases. *Structure* **1998**, *6*, 1117−1128. (b) Wilson, K. P.; McCaffrey, P. G.; Hsiao, K.; Pazhanisamy, S.; Galullo, V.; Bemis, G. W.; Fitzgibbon, M. J.; Caro, P. R.; Murcko, M. A.; Su, M. S. The structural basis for the specificity of pyridinylimidazole inhibitors of p38 MAP kinase. *Chem. Biol.* **1997**, *4*, 423−431.
(8) (a) Boehm, J. C.; Adams J. L. New inhibitors of p38 kinase. *Expert Opin. Ther. Pat.* **2000**, *10*, 25−37. (b) Hanson, G. J. Inhibitors of p38 kinase. *Expert Opin. Ther. Pat.* **1997**, *7*, 729−733.
(9) Feldmann, M.; Brennan, F. M.; Maini, R. Role of cytokines in rheumatoid arthritis. *Annu. Rev. Immunol.* **1996**, *14*, 397−440.
(10) Boehm, J. C.; Smietana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, L. M.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. 1-Substituted 4-aryl-5-pyridinyl imidazoles: a new class of cytokine suppressive drugs with low 5-lipoxigenase and cyclooxygenase inhibitory potency. *J. Med. Chem.* **1996**, *39*, 3929−3937.
(11) Liverton, N. J.; Butcher, J. W.; Claiborne, C. F.; Claremon, D. A.; Libby, D. B.; Nguyen, K. T.; Pitzenberger, S. M.; Selnick, H. G.; Smith, G. R.; Tebben, A.; Vacca, J. P.; Varga, S. L.; Agarwal, L.; Dancheck, K.; Forsyth, A. J.; Fletcher, D. S.; Frantz, B.; Hanlon, W. A.; Harper, C. F.; Hofsess, S. J.; Kostura, M.; Linn, J.; Luell, S.; O'Neill, E. A.; Orevillo, C. J.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Visco, D. M.; O'Keefe, S. J. Design and synthesis of potent, selective, and orally bioavailable tetrasubstituted imidazole inhibitors of p38 mitogen-activated protein kinase. *J. Med. Chem.* **1999**, *42*, 2180−2190.
(12) Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, S. A.; Cavender, D. E.; Fahmy, B.; Olini, G. C.; Davis, J. E.; Pellegrino-Gensey, J. L. 6-Amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridyl)-1*H*-pyrrolo[2,3-*b*]pyridine (RWJ 68354): a potent and selective p38 kinase inhibitor. *J. Med. Chem.* **1998**, *41*, 4196−4198.
(13) Gum, R.; McLaughlin, M. M.; Kumar, S.; Wang, Z. L.; Bower, M. J.; Lee, J. C.; Adams, J. L.; Livi, G. P.; Goldsmith, E. J.; Young, P. R. Acquisition of sensitivity of stress-activated protein kinases to the p38 inhibitor, SB 203580, by alteration of one or more amino acids within the ATP binding pocket. *J. Biol. Chem.* **1998**, *273*, 15605−15610.
(14) For a review, see: Jackson, P. F.; Bullington, J. L. Pyridinyl imidazole based p38 MAP kinase inhibitors. *Curr. Top. Med. Chem.* **2002**, *2*, 1021−1035. For a recent disclosure, see: Revesz, L.; Blum, E.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Rucklin, G. Novel p38 inhibitors with potent oral efficacy in several models of rheumatoid arthritis. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3595−3599.
(15) Badger, A. M., Bradbeer, J. N.; Votta, B.; Lee, J. C.; Adams, J. L.; Griswold, D. E. Pharmacological profile of SB203580, a selective inhibitor of cytokine suppressive binding protein p38 kinase, in animal models of arthritis, bone resorption, endotoxin shock and immune function. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 1453−1461.
(16) Adams, J. L.; Boehm, J. C.; Gallagher, T. F.; Kassis, S.; Webb, E.; Hall, R.; Sorenson, M.; Garigipati, R. S.; Griswold, D. E.; Lee, J. C. Pyridinylimidazole inhibitors of p38: cyclic N-1 imidazole substituent enhance p38 kinase inhibition and oral activity. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2867−2870.
(17) Fitzgerald, C. E.; Patel, S. B.; Becker, J. W.; Cameron, P. M.; Zaller, D.; Pikounis, V. B.; O'Keefe, S. J.; Scapin, G. Structural basis for p38 MAP kinase quinazoline and pyridol-pyrimidine inhibitor specificity. *Nat. Struct. Biol.* **2003**, *10*, 764−769 and references therein.
(18) Cirillo, P. F.; Pargellis, C.; Regan, J. The non-diaryl heterocycle classess of p38 MAP kinase inhibitors. *Curr. Top. Med. Chem.* **2002**, *2*, 1021−1035.
(19) Pargellis, C. A.; Tong, L.; Churchill, L.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Grob, P. M.; Hickey, E. R.; Moss, N.; Pav, S.; Regan, J. Inhibition of p38 MAP kinase by utilizing a novel allosteric binding site. *Nat. Struct. Biol.* **2002**, *9*, 268−272.
(20) 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*, 3111−3116 and references therein.
(21) Wu, G.; Robertson, D. H.; Brooks, C. L., III; Vieth, M. A detailed analysis of grid-based molecular docking. A case study of CDOCKER—a CHARMm based MD docking algorithm. *J. Comput. Chem.* **2003**, *24*, 1549−1562.
(22) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. Palladium-catalyzed hydroarylation of propiolamides. A regio- and stereocontrolled method for preparing 3,3-diarylacrylamides. *J. Org. Chem.* **1998**, *63*, 5050−5058.
(23) Some other linear acyclic sulfonyl groups were introduced in this building block, but in all cases, chemical instability and extensive desulfonylation were observed later in the synthetic route.
(24) Barrow, R. A.; Moore, R. E.; Li, L.-H.; Tius, M. A. Synthesis of 1-aza-cryptophycin 1, an unstable cryptophycin. An unusual skeletal rearrangement. *Tetrahedron* **2000**, *56*, 3339−3351.
(25) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. An investigation of imidazole and oxazole syntheses using aryl-substituted TosMIC reagents. *J. Org. Chem.* **2000**, *65*, 1516−1524.
(26) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. An efficient method for the synthesis of substituted Tosmic precursors. *Tetrahedron Lett.* **1996**, *37*, 8113−8116.
(27) Additionally, **1** showed no significant activity against other 30 different kinases (data not shown) when tested at 1 μM in duplicate.
(28) Measured log *D* values (pH 7) for both derivatives were found to be 0.09 and 1.74, indicating that a cell permeability problem for the polar piperidyl was overcome by increasing lipophilicity with the *N*-isobutyl residue.
(29) This steric effect may prevent the coordination of the heme iron to imidazole N1 or N3, and therefore, it might be a tentative explanation of this effect. See: Dalvie, D. K.; Kalgutkar, A. S.; Khojasteh-Bakht, S. C.; Obach, R. S.; O'Donnell, J. P. Invited review: Biotransformation reactions of five-membered aromatic heterocyclic rings. *Chem. Res. Toxicol.* **2002**, *15*, 269−299.
(30) $TMED_{50}$ is defined as the lowest dose where statistically significant efficacy was achieved, and there was at least 50% inhibition compared to vehicle control.
(31) $TMED_{50}$ was calculated from the AUC (paw swelling) or composite histology score using JMP5.1.1.

JM048978K