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Benzothiazole based inhibitors of p38α MAP kinase

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Abstract—Rational design, synthesis, and SAR studies of a novel class of benzothiazole based inhibitors of p38α MAP kinase are described. The issue of metabolic instability associated with vicinal phenyl, benzo[*d*]thiazol-6-yl oxazoles/imidazoles was addressed by the replacement of the central oxazole or imidazole ring with an aminopyrazole system. The proposed binding mode of this new class of p38α inhibitors was confirmed by X-ray crystallographic studies of a representative inhibitor (**6a**) bound to the p38α enzyme.
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The p38α mitogen-activated protein (MAP) kinase is an important mediator of inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β).[1] It has been demonstrated by numerous preclinical studies[2] that inhibition of p38α MAP kinase could effectively inhibit TNF-α production both in vitro and in vivo. Excessive production of TNF-α and IL-1β is believed to underlie many inflammatory diseases including rheumatoid arthritis (RA), Crohn's disease, inflammatory bowel disease, and psoriasis.[3] The blockage of TNF-α function by biological agents, such as etanercept (Enbrel®), a soluble TNF-α receptor, and infliximab (Remicade®), a TNF-α antibody, has clinically proven to be effective in the treatment of RA and Crohn's disease.[4] Therefore, it is expected that low molecular weight p38α MAP kinase inhibitors may become orally active therapeutic agents for the treatment of inflammatory conditions.

A large number of classes of p38α inhibitors have been identified.[5] One is the vicinal aryl, pyridin-4-yl heteroarenes, derived from SB-203580[6] that was identified at SmithKline Beecham (Fig. 1). Modifications to SB-203580, until recently, have been limited to changes of the central imidazole ring to other five membered bioisosteres. More recently, however, scientists at Roche

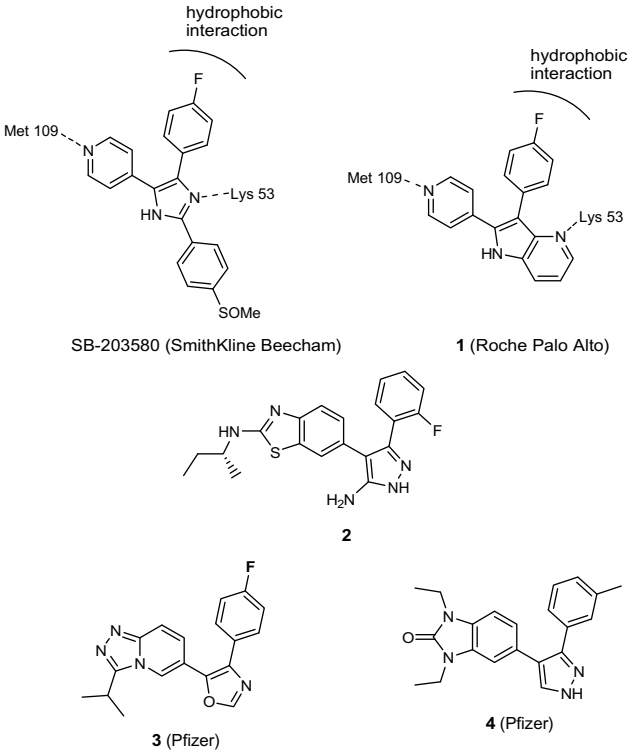

Figure 1. Novel p38α inhibitor **2** versus some of the known p38α inhibitors.

Keywords: Inhibitors of p38α MAP kinase; Benzothiazoles; Vicinal phenyl, benzo[*d*]thiazol-6-yl oxazoles; Vicinal phenyl, benzo[*d*]thiazol-6-yl imidazoles; Vicinal phenyl, benzo[*d*]thiazol-6-yl pyrazoles; X-ray co-crystal structure; TNFα inhibition in hPBMC.
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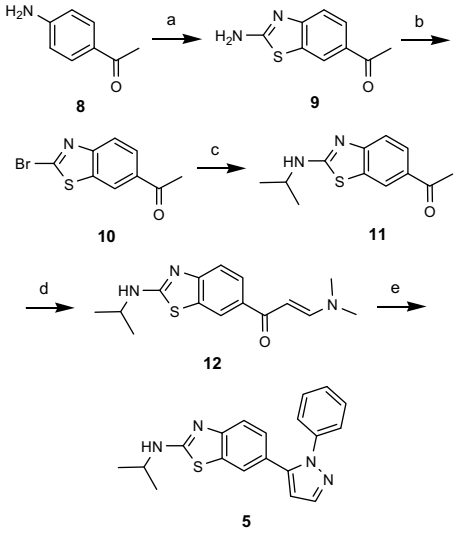
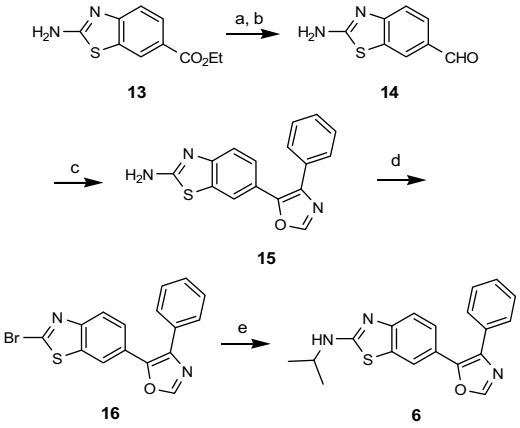
Palo Alto demonstrated with **1**[2f] that the central five membered ring could also be replaced with bicyclic heteroaryl rings. X-ray co-crystal structures of both SB-203580 and **1** with the p38α enzyme indicate that the binding modes for these two inhibitors are essentially the same. That is, as shown in Figure 1, the key interactions include: (1) a hydrogen-bonding interaction between the terminal pyridine nitrogen and the main chain NH of Met109 of p38α, (2) a hydrogen-bonding interaction between an imidazole nitrogen in SB-203580 or between the 4-azaindole nitrogen of **1** and Lys53 of p38α, and (3) a hydrophobic interaction of the phenyl with a hydrophobic pocket of p38α. In the modification of SB-203580 into **1**, the imidazole nitrogen is extended outward by a distance of one bond. With a similar consideration, we wondered if the pyridine ring in the vicinal aryl, pyridin-4-yl heteroarene series could be replaced with a bicyclic heteroaryl system wherein a hydrogen-bonding acceptor (for Met109) is present, but extended outward by a distance of one bond compared to the original pyridine nitrogen. Our investigation has resulted in the discovery of a novel class of benzothiazole based inhibitors of p38α MAP kinase. Among them, compound **2** represents a series that is not only highly potent against p38α and effective in inhibiting TNFα production in cells, but also possesses appropriate metabolic and pharmacokinetic profiles for further investigation. It should be mentioned that in the course of our studies, structurally similar p38α inhibitors such as **3** and **4** were disclosed by scientists at Pfizer.[7] Inhibitor **3** was reported to be metabolically unstable, while **4** was disclosed only with enzymatic activity and appeared to represent a series of moderately potent p38α inhibitors.

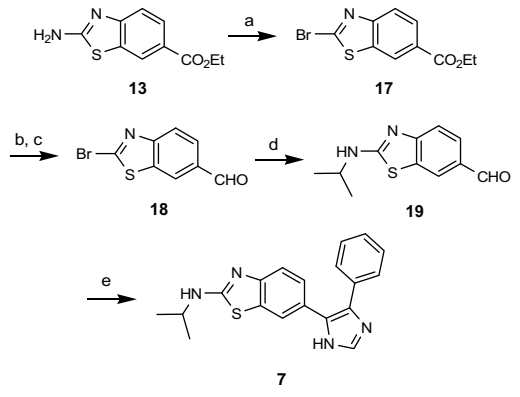
We envisioned that the bicyclic benzothiazole system might be a replacement for the original pyridine ring in SB-203580, prompting us to synthesize compounds **5** (Scheme 1), **6** (Scheme 2), and **7** (Scheme 3). It was expected that the benzothiazole nitrogen would form a hydrogen bond with the NH of Met109 of p38α. Based on our previous experience,[2d] 2-Isopropylamino was also installed with the expectation that the amino NH would make a secondary hydrogen bond to the carbonyl oxygen of Met109, and that the isopropyl would provide a hydrophobic interaction close to the binding site. The synthesis of **5** started with the treatment of 1-(4-aminophenyl)ethanone (**8**) with potassium thiocyanate and bromine in glacial acetic acid at room temperature (RT) to provide 2-aminobenzothiazole **9**. Reaction of **9** with *tert*-butyl nitrite and copper (II) bromide at RT supplied 2-bromobenzothiazole **10**. Mixing **10** with isopropyl amine in 1,4-dioxane at 100 °C resulted in the formation of **11**. The target **5** was then obtained by heating **11** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), followed by phenyl hydrazine.



Scheme 1. Reagents and conditions: (a) KSCN, Br_2, AcOH, rt; (b) $CuBr_2$, *t*-BuONO, MeCN, RT, 31% yield over two steps; (c) *i*-$PrNH_2$, 1,4-dioxane, 100 °C; (d) DMFDMA, 100 °C; (e) PhNHNH2HCl, Na_2CO_3, AcOH, MeOH/H_2O, reflux, 50% yield over three steps.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 46% yield; (b) MnO_2, THF, RT, 87% yield; (c) (1-phenyl-1-tosyl)methyl isocyanide, K_2CO_3, EtOH, reflux, 52% yield; (d) $CuBr_2$, *t*-BuONO, MeCN, rt, 23% yield; (e) *i*-$PrNH_2$, THF, 50 °C, 43% yield.



Scheme 3. Reagents and conditions: (a) $CuBr_2$, *t*-BuONO, MeCN, RT, 84% yield; (b) Dibal-H, toluene, THF, −78 °C to RT, 90% yield; (c) MnO_2, THF, RT, 83% yield; (d) i. *i*-$PrNH_2$, 1,4-dioxane, pressure tube, 150 °C; ii. 1 N HCl, 1,4-dioxane, 65 °C, 81% yield; (e) i. aq NH_4OH, RT; ii. (1-phenyl-1-tosyl)methyl isocyanide, piperazine, 19% yield.

For the preparation of **6** (Scheme 2), benzothiazole-6-caboxylate **13** was reduced with $LiAlH_4$ at 0 °C, and the resultant alcohol was then oxidized with manganese (IV) oxide at RT to aldehyde **14**. Treatment of **14** with (1-phenyl-1-tosyl)methyl isocyanide in the presence of K_2CO_3 in refluxing ethanol afforded oxazole **15**. Conversion of **15** to **6** was realized in the same way as 2-aminobenzothiazole **9** was converted to 2-isopropylaminobenzothiazole **11** (Scheme 1).

To synthesize **7** (Scheme 3), 2-aminobenzothiazole **13** was converted to 2-bromobenzothiazole **17** with *tert*-butyl nitrite and copper (II) bromide at RT. Reduction of the ester functionality of **17** with diisobutylaluminum hydride (Dibal-H) at −78 °C and a subsequent oxidation with manganese (IV) oxide at RT gave rise to benzothiazole-6-carbaldehyde **18**. When **18** was treated with excess isopropyl amine in 1,4-dioxane at 150 °C in a pressure tube, the desired substitution reaction at the 2-position occurred smoothly. Meanwhile, the aldehyde formed the corresponding imine with isopropyl amine. The imine could readily be hydrolyzed back to aldehyde **19** with 1 N hydrochloride acid at 65 °C. Reacting **19** sequentially with aqueous ammonium hydroxide and (1-phenyl-1-tosyl)methyl isocyanide furnished imidazole **7**.

Compounds **5**, **6**, and **7** were then assayed against the p38α enzyme.[2d] To our encouragement, all three compounds proved to be potent p38α inhibitors. Inhibitors **5** and **6** both displayed an IC_{50} value of 21 nM, and the potency (IC_{50}) of **7** was determined to be 7.1 nM (Table 1). Moreover, all three compounds were active at inhibiting LPS-induced TNF-α production in human peripheral blood mononuclear cells (hPBMC)[2d] with IC_{50} values of 213 nM, 96 nM, and 107 nM, respectively.

With **5**, **6**, and **7** in hand, our lead optimization started with the exploration of substituents on the phenyl ring. This SAR study was efficiently conducted with analogues of pyrazole **5** since, according to Scheme 1, these analogues could be prepared by parallel synthesis at the very last step with a variety of commercially available substituted phenyl hydrazines. Compounds with p38α IC_{50} values below 100 nM were routinely tested for the inhibition of LPS-induced TNFα production in hPBMC. Selected results are summarized in Table 2. For traditional vicinal phenyl, pyridin-4-yl heteroarene p38 inhibitors, a *p*- or *m*-substituent on the phenyl was usually preferred.[6,8] However, this was not the case after replacement of the pyridine-4-yl with benzo[*d*]thiazol-6-yl. When a methyl group was present at the *p*-position, the corresponding analogue **5a** displayed an IC_{50} of greater than 1000 nM against p38α. This is a drop of greater than 50-fold in p38α activity compared to **5**. Methyl substitutions at the *m*-position and *o*-position also led to losses in p38α activity, though to a lesser extent as demonstrated by analogues **5b** (p38α IC_{50} = 33 nM) and **5c** (p38α IC_{50} = 146 nM). A very similar SAR was observed with chloro substitutions (**5d–f**). It was further found that even *p*-F (**5g**, p38α IC_{50} = 48 nM) and *m*-F (**5h**, p38α IC_{50} = 33 nM) seemed to decrease the p38 activity slightly. The only substituent that did not appear detrimental to p38α binding affinity was *o*-F, as **5i** was at least as potent as **5**. To assess further the SAR of *o*-F, thiazole analogue **6a** and imidazole **7a** were synthesized (Table 2). Analogue **6a** inhibited p38α and TNFα production in hPBMC with IC_{50} values of 6.4 nM and 40 nM, respectively, versus 21 nM and 96 nM, respectively, for **6**. Similarly, **7a** was more potent than **7** in both enzymatic (IC_{50} of 3.3 nM versus 7.1 nM) and cellular assays (IC_{50} of 35 nM vs 107 nM). This SAR was also confirmed with analogues where the isopropylamino was replaced with other alkylamino groups (data not shown). Thus, it could be concluded that the *o*-F substitution on the phenyl of **5, 6, 7**, and their analogues was at least tolerated and most likely preferred.

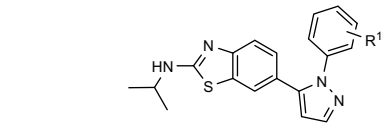
Based on the enzymatic and cellular data from **5i**, **6a**, and **7a**, we were then more focused on the series represented by **6a** and **7a**. Our next SAR study was to exam-

Table 1. In vitro activity of **5**, **6**, and **7**

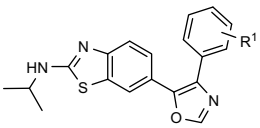
Compound	**5**	**6**	**7**
p38α IC_{50}[a] (nM)	21	21	7.1
hPBMC TNFα IC_{50}[b] (nM)	213	96	107

[a] $n = 4$, variation in individual values, <20%.
[b] $n = 3$, variation in individual values, <25%.

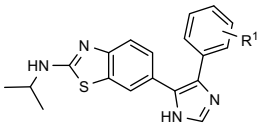
Table 2. In vitro activity of **5a–i** versus **5**, **6a** versus **6**, and **7a** versus **7**



5a-i



6, 6a



7, 7a

Compound	R^1	p38α IC_{50}[a] (nM)	hPBMC TNFα IC_{50}[b] (nM)
5	H	21	213
5a	*p*-Me	> 1000	
5b	*m*-Me	33	171
5c	*o*-Me	146	
5d	*p*-Cl	> 1000	
5e	*m*-Cl	72	232
5f	*o*-Cl	175	
5g	*p*-F	48	> 250
5h	*m*-F	33	171
5i	*o*-F	20	249
6	H	21	96
6a	*o*-F	6.4	40
7	H	7.1	107
7a	*o*-F	3.3	35

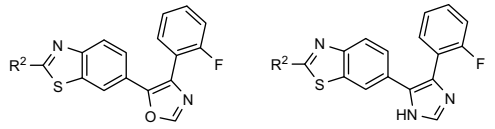
[a] $n = 4$, variation in individual values, <20%.
[b] $n = 3$, variation in individual values, <25%.

ine whether the isopropylamino group on **6a** and **7a** was optimal. This was accomplished primarily with analogues of oxazole **6a**, and the results are given in Table 3. As expected, removal of the isopropylamino group from **6a** resulted in a drop in p38α potency, as **6b** (p38α IC_{50} = 47 nM) was shown to be 8-fold less active than **6a**. Adding the NH_2 group to **6b** improved the p38 IC_{50} to 16 nM, but **6c** was still less potent than **6a**. The cellular activities (TNFα IC_{50}s) of **6b** and **6c** were determined to be greater than 250 nM and 247 nM, respectively. Replacement of the isopropylamino group with ethylamino (**6d**) also increased the p38α IC_{50} from 6.4 nM to 12 nM and TNFα IC_{50} from 40 nM to 167 nM. However, (*R*)-2-butylamino and (*S*)-2-butylamino were found to be appropriate replacements for the isopropylamino, as both **6e** (p38α IC_{50} = 6.5 nM, TNFα IC_{50} = 27 nM) and **6f** (p38α IC_{50} = 10 nM, TNFα IC_{50} = 30 nM) showed very comparable enzymatic and cellular potency to **6a**. The use of (*R*)-2-butylamino and (*S*)-2-butylamino in place of isopropylamino in imidazole **7a** led to **7b** and **7c**, the most potent benzothiazole based p38α inhibitors identified. Compounds **7b** and **7c** inhibited p38α with IC_{50} values of 1.6 nM and 2.7 nM, respectively. Both compounds were also very effective in inhibiting TNFα production in cells, displaying hPBMC TNFα IC_{50} of 13 nM and 20 nM, respectively. In summary, isopropylamino, (*R*)-2-butylamino, and (*S*)-2-butylamino were the most preferred groups identified for R_2.

Thus far, the vicinal phenyl, benzo[*d*]thiazol-6-yl oxazoles/imidazoles were identified as a novel class of highly potent p38 inhibitors. However, profiling these compounds indicated that they might be metabolically unstable, especially in mice. For example, the metabolic rates in microsomes[2d] for **7a** were 0.109 nmol/min mg-protein in humans, 0.081 nmol/min mg-protein in rats, and 0.255 nmol/min mg-protein in mice. As a result, the rest of the SAR study was focused on improving the metabolic stability of this class of p38α inhibitors. Since substitution on the phenyl ring in **5**, **6**, and **7** at different positions and replacement of the isopropyl with a variety of other alkyl or complete removal of the isopropylamino did not address the issue, we turned our attention to the central five membered ring. Considering that the 3-position of pyrazole **5** and the 2-position of oxazole **6** and imidazole **7** could be sites for metabolic oxidation, our interest was particularly drawn toward substituting the carbon at those positions in the five membered rings with a nitrogen atom. We also wanted to make the targets reasonably more hydrophilic, which should also favor improving metabolic stability and other properties, such as solubility. Thus, aminopyrazole **8** and its analogues were synthesized according to Scheme 4. (Benzo[*d*]thiazol-6-yl)acetonitrile **23** was synthesized from commercially available 2-(4-aminophenyl)acetonitrile (**20**) in the same way as 1-(benzo[*d*]thiazol-6-yl)ethanone (**11**) from 1-(4-aminophenyl)ethanone (**8**) (Scheme 1). Treatment of **23** with lithium bis(trimethylsilyl)amide, followed by methyl 2-flurobenzoate, provided oxopropanenitrile **24**. Heating **24** with hydrazine afforded **8**.

Table 4 lists the in vitro activities of aminopyrazole **8** and its analogues, **2** and **8a–c**. Analogue **8** inhibited p38α with an IC_{50} of 3.7 nM and TNFα production in hPBMC with an IC_{50} of 51 nM. Similarly, **2** and **8a** displayed p38α IC_{50} values of 3.2 nM and 5.5 nM, respectively. The cellular activities (TNFα IC_{50} values) of **2** and **8a** were 39 nM and 77 nM, respectively. More importantly, the metabolic stability of these compounds was significantly improved compared to their oxazole and imidazole counterparts. The metabolic rates in microsomes for **2**, for example, were 0.006 nmol/min mg-protein in humans, 0.052 nmol/min mg-protein in rats, and 0.056 nmol/min mg-protein in mice. Compounds **8b** and **8c** demonstrated that N-alkylation of the pyrazole at the position next to the amino group incurred a loss in p38α activity, as the N-methylation (**8b**)

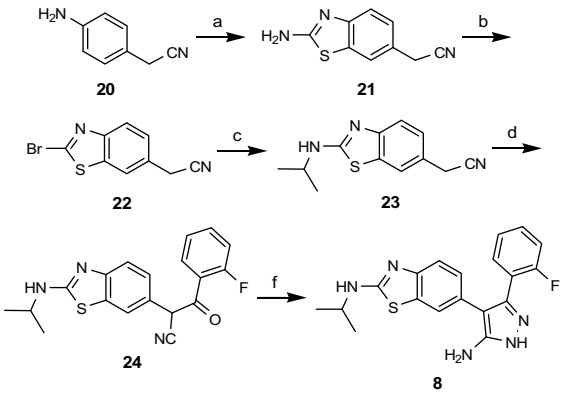
Table 3. In vitro activity of **6a–h** and **7a–c**



6a-f **7a-c**

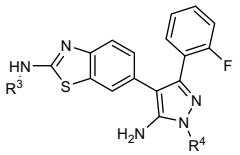
Compound	R^2	p38α IC_{50}[a] (nM)	hPBMC TNFα IC_{50}[b] (nM)
6a	*i*-PrNH	6.4	40
6b	H	47	>250
6c	NH_2	16	247
6d	EtNH	12	167
6e	(*R*)-2-BuNH	6.5	27
6f	(*S*)-2-BuNH	10	30
7a	*i*-PrNH	3.3	35
7b	(*R*)-2-BuNH	1.6	13
7c	(*S*)-2-BuNH	2.7	20

[a] n = 4, variation in individual values, <20%.
[b] n = 3, variation in individual values, <25%.



Scheme 4. Reagents and conditions: (a) KSCN, Br_2, AcOH, rt, 86% yield; (b) $CuBr_2$, *t*-BuONO, MeCN, RT, 83% yield; (c) *i*-$PrNH_2$, 1,4-dioxane, pressure tube, 130 °C, 72% yield; (d) lithium bis(trimethylsilyl)amide, methyl 2-fluorobenzoate, −78 °C to RT; (f) anhydrous NH_2NH_2, AcOH/EtOH, 90 °C, 6 h, 17% yield over two steps.

Table 4. In vitro activity of **8**, **2**, and **8a–c**



8, 2, 8a-c

Compound	R^3	R^4	p38α IC_{50}[a] (nM)	hPBMC TNFα IC_{50}[b] (nM)
8	*i*-Pr	H	3.7	51
2	(*R*)-2-Bu	H	3.2	39
8a	(*S*)-2-Bu	H	5.5	77
8b	(*R*)-2-Bu	Me	11	118
8c	(*R*)-2-Bu	Et	17	> 250

[a] $n = 4$, variation in individual values, <20%.
[b] $n = 3$, variation in individual values, <25%.

and N-ethylation (**8c**) increased the p38α IC_{50} from 3.2 nM (**2**) to 11 nM and 17 nM, respectively. The cellular activities (TNFα IC_{50} values) of **8b** and **8c** were determined to be 118 nM and greater than 250 nM, respectively.

A pharmacokinetic study of **2** in rats was undertaken,[9] and the results showed that **2** had a half life ($t_{1/2}$) of 1.7 h and a clearance of 1.4 L/h kg after intravenous dosing at 2 mg/kg. The oral AUC and bioavailability of **2** were 2266 nM h and 24% after administration of a solution dosed (5 mg/kg) in PEG400.

Further profiling of **2** indicates that it is selective to p38α over a number of other kinases. When tested at 10 μM, **2** showed negligible activity (20% inhibition or less) against the following kinases: Atk1, Atk2, Atk3, Blk, Bmx, Brk, Btk, CaMKIIα, CHK1, CHK2, CK2α1, c-MET, Csk, EGFR, EphA3, EphB4, ERK1, ERK2, FES, FGFR1, FGFR2, FGFR3, FGFR4, Fyn, GSK3α, GSK3β, Hck, Hyl, IGF1R, IRAK4, Lck, Lyn A, Lyn B, MAPKAP-K2, MAPKAP-K3, MAPKAP-K5, NEK2, PDGFRβ, PHKG2, PKA, PKCα, PKCβ1, PKCβ2, PKCγ, PKCδ, RSK2, Src, Yes. However, **2** did show activity against Abl1 (65% inhibition), Fgr (54% inhibition), and Flt3 (68% inhibition). JNK family members were not included in the kinase panel at the time when **2** was studied. Interestingly, **2** was found to be 10-fold more selective for p38α versus p38β. This noticeable p38α selectivity over p38β is generally true for the benzothiazole based inhibitors of p38α MAP kinase.

The anticipated binding mode of this class of p38α inhibitors was confirmed by an X-ray crystallographic study of **6a** bound to the p38α enzyme.[10] Figure 2 illustrates the X-ray structure of the complex of **6a** with p38α. The ligand engages two H-bonds with p38α at the hinge region: between the benzothiazole nitrogen and the Met109 NH (2.09 Å), and the isopropylamine NH and the Met109 carbonyl oxygen (1.84 Å). Another H-bond occurs between the oxazole nitrogen and the

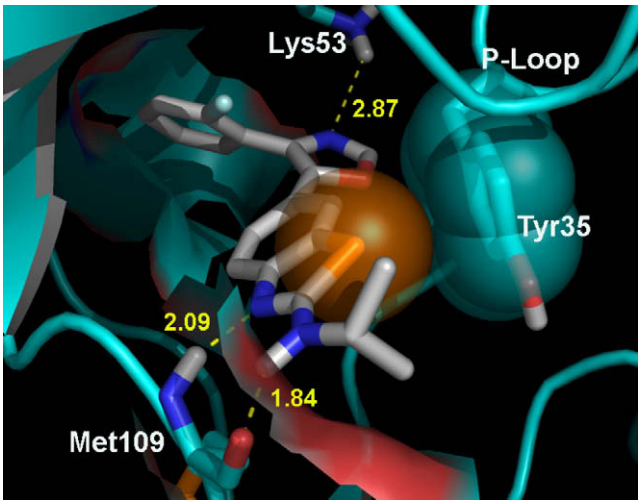


Figure 2. The X-ray co-structure of **6a** with p38α.

Lys53 NH (2.87 Å). In addition to these H-bonding interactions, the 2-fluorophenyl group occupies the hydrophobic selectivity pocket. The pendant isopropyl group interacts with the second hydrophobic site characteristically found at the outer rim of the hinge region. The relatively lipophilic P-Loop is closed upon the ligand, forming a tight hydrophobic interaction between the sulfur of the benzothiazole ring system and Tyr35 (shown by van der Waals spheres).

In summary, a novel class of benzothiazole based inhibitors of p38α MAP kinase was proposed, synthesized, and evaluated. Vicinal phenyl, benzo[*d*]thiazol-6-yl oxazoles/imidazoles were found to be highly potent p38α inhibitors in vitro, but were metabolically unstable. The issue of metabolic instability was addressed by the replacement of the oxazole or imidazole ring with an aminopyrazole system. The proposed binding mode of this new class of p38α inhibitors was confirmed by X-ray co-crystal structure of **6a** with the p38α enzyme.

References and notes

1. (a) Schieven, G. L. *Curr. Top. Med. Chem.* **2005**, *5*, 921; (b) Saklatvala, J. *Curr. Opin. Pharm.* **2004**, *4*, 372; (c) Kumar, S.; Boehm, J.; Lee, J. C. *Nat. Rev. Drug Discov.* **2003**, *2*, 717; (d) Adams, J. L.; Badge, A. M.; Kumar, S.; Lee, J. C. *Prog. Med. Chem.* **2001**, *38*, 1; (e) Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kimar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heys, J. R.; Landvatter, S. W.; Strickler, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature* **1994**, *372*, 739.
2. For example (a) Hynes, J., Jr.; Dyckman, A. J.; Lin, S.; Wrobleski, S.; Wu, H.; Gillooly, K. M.; Kanner, S. B.; Lonial, H.; Loo, D.; McIntyre, K. W.; Pitt, S.; Shen, D. R.; Shuster, D. J.; Yang, X.; Zhang, R.; Behnia, K.; Zhang, H.; Marathe, P. H.; Doweyko, A. M.; Tokarski, J. S.; Sack, J. S.; Pokross, M.; Kiefer, S. E.; Newitt, J. A.; Barrish, J. C.; Dodd, J. H.; Schieven, G. L.; Leftheris, K. *J. Med. Chem.* **2008**, *51*, 4; (b) Goldberg, D. R.; Hao, M.; Qian, K. C.; Swinamer, A. D.; Gao, D. A.; Xiong, Z.; Sarko, C.; Berry, A.; Lord, J.; Magolda, R. L.; Fadra, T.;

Kroe, R. R.; Kukulka, A.; Madwed, J. B.; Martin, L.; Pargellis, C.; Skow, D.; Song, J. J.; Tan, Z.; Torcellini, C. A.; Zimmitti, C. S.; Yee, N. K.; Moss, N. *J. Med. Chem.* **2007**, *50*, 4016; (c) Natarajan, S. R.; Liu, L.; Levorse, M.; Thompson, J. E.; O'Neill, E. A.; O'Keefe, S. J.; Vora, K. A.; Cvetovich, R.; Chung, J. Y.; Carballo-Jane, E.; Visco, D. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5468; (d) Liu, C.; Wrobleski, S. T.; Lin, J.; Gillooly, K. M.; Mcintyre, K.; Pitt, S.; Shen, D. R.; Shuster, D. J.; Zhang, H.; Doweyko, A. M.; Sack, J. S.; Barrish, J. C.; Dodd, J. H.; Schieven, G. L.; Leftheris, K. *J. Med. Chem.* **2005**, *48*, 6261; (e) Revesz, L.; Blum, E.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Rucklin, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3595; (f) Trejo, A.; Arzeno, H.; Browner, M.; Chanda, S.; Cheng, S.; Comer, D. D.; Dalrymple, S. A.; Dunten, P.; Lafargue, J.; Lovejoy, B.; Freire-Moar, J.; Lim, J.; Mcintosh, J.; Miller, J.; Papp, E.; Reuter, D.; Roberts, R.; Saunders, J.; Song, K.; Villasenor, A.; Warren, S. D.; Welch, M.; Weller, P.; Whiteley, P. E.; Zeng, Lu; Goldstein, D. M. *J. Med. Chem.* **2003**, *46*, 4702; (g) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347; (h) Branger, J.; van den Blink, B.; Weijer, S.; Madwed, J.; Bos, C. L.; Gupta, A.; Polmar, S. H.; Olszyna, D. P.; Hack, C. E.; van Deventer, S. J. H.; Peppelenbosch, M. P.; van der Poll, T. *J. Immunol.* **2002**, *168*, 4070.

3. (a) Foster, M. L.; Halley, F.; Souness, J. E. *Drug News Perspect.* **2000**, *13*, 488; (b) Feldmann, M.; Brennan, F. M.; Maini, R. N. *Annu. Rev. Immunol.* **1996**, *14*, 397; (c) Tracey, K. J.; Cerami, A. *Annu. Rev. Cell Biol.* **1993**, *9*, 317.
4. (a) Seymour, H. E.; Worsley, A.; Smith, J. M.; Thomas, S. H. L. *Br. J. Clin. Pharmacol.* **2001**, *51*, 201; (b) Jarvis, B.; Faulds, D. *Drugs* **1999**, *57*, 945; (c) Rutgeerts, P. J. *Aliment. Pharmacol. Ther.* **1999**, *13*, 9.
5. Selected reviews (a) Diller, D. J.; Lin, T. H.; Metzger, A. *Curr. Top. Med. Chem.* **2005**, *5*, 967; (b) Hynes, J.; Leftheris, K. *Curr. Top. Med. Chem.* **2005**, *5*, 967; (c) Natarajan, S. R.; Doherty, J. B. *Curr. Top. Med. Chem.* **2005**, *5*, 987; (d) Wrobleski, S. T.; Doweyko, A. M. *Curr. Top. Med. Chem.* **2005**, *5*, 1005; (e) Goldstein, D. M.; Gabriel, T. *Curr. Top. Med. Chem.* **2005**, *5*, 1017; (f) Bolós, J. *Mini-Rev. Med. Chem* **2005**, *5*, 857; (g) Boehm, J. C.; Adams, J. L. *Exp. Opin. Ther. Patents* **2000**, *10*, 25; (h) Hanson, G. J. *Exp. Opin. Ther. Patents* **1997**, *7*, 729.
6. 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. *J. Med. Chem.* **1996**, *39*, 3929.
7. (a) McClure, K. F.; Letavic, M. A.; Kalgutkar, A. S.; Gabel, C. A.; Audoly, L.; Barberia, J. T.; Braganza, J. F.; Carter, D.; Carty, T. J.; Cortina, S. R.; Dombroski, M. A.; Donahue, K. M.; Elliott, N. C.; Gibbons, C. P.; Jordan, C. K.; Kuperman, A. V.; Labasi, J. M.; LaLiberte, R. E.; McCoy, J. M.; Naiman, B. M.; Nelson, K. L.; Nyuyen, H. T.; Peese, K. M.; Sweeney, F. J.; Taylor, T. J.; Trebino, C. E.; Abramov, Y. A.; Laird, E. R.; Volberg, W. A.; Zhou, J.; Bach, J.; Lombardo, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4339; (b) Dombroski, M. A.; Letavic, M. A.; McClure, K. F.; Barberia, J. T.; Carty, T. J.; Cortina, S. R.; Csiki, C.; Dipesa, A. J.; Elliott, N. C.; Gabel, C. A.; Jordan, C. K.; Labasi, J. M.; Martin, W. H.; Peese, K. M.; Stock, I. A.; Svensson, L.; Sweeney, F. J.; Yu, C. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 919.
8. Fitzgerald, C. E.; Patel, S. B.; Becker, J. W.; Cameron, P. M.; Zaller, D.; Pikounis, V. B.; O'Keefe, S. J.; Scapin, G. *Nat. Struct. Biol.* **2003**, *10*, 764.
9. Pharmacokinetic study of **2**: Male Sprague–Dawley rats (250–300 g) were fasted overnight prior to PO dosing and fed 4 h post dose. Blood samples (0.3 mL) were collected from the jugular vein into K_2EDTA-containing tubes and then centrifuged at 4 °C (1500–2000*g*) to obtain plasma. Two groups of animals ($N = 3$ per group) received the compound either as an intravenous infusion (2 mg/kg over 10 min) via the jugular vein or by oral gavage (5 mg/kg). Serial blood samples were obtained at 0.17 (for IV only), 0.25, 0.5, 0.75, 1, 2, 4, 6, and 8 h post dose. Plasma samples, obtained by centrifugation at 4 °C (1500–2000*g*), were stored at −20 °C until analysis by LC/MS/MS.
10. PDB deposition number: 3C5U.