Bioorganic & Medicinal Chemistry Letters 19 (2009) 5547–5551

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

The discovery of thienopyridine analogues as potent IκB kinase β inhibitors. Part II

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ARTICLE INFO

Article history:
Received 21 July 2009
Revised 10 August 2009
Accepted 12 August 2009
Available online 15 August 2009

Keywords:
Thienopyridine
IkB Kinase b
IKKb
Inhibitors

ABSTRACT

An SAR study that identified a series of thienopyridine-based potent IκB Kinase β (IKKβ) inhibitors is described. With focuses on the structural optimization at C_4 and C_6 of structure **1** (Fig. 1), the study reveals that small alkyl and certain aromatic groups are preferred at C_4, whereas polar groups with proper orientation at C_6 efficiently enhance compound potency. The most potent analogues inhibit IKKβ with IC_{50}s as low as 40 nM, suppress LPS-induced TNF-α production in vitro and in vivo, display good kinase selectivity profiles, and are active in a HeLa cell NF-κB reporter gene assay, demonstrating that they directly interfere with the NF-κB signaling pathway.

The NF-κB family of transcription factors plays a major role in a broad range of biological processes, including immune responses and cell growth.[1] Activated NF-κB induces the expression of a large number of pro-inflammatory genes, including those encoding chemokines, cytokines, and cell adhesion molecules. NF-κB also activates genes whose protein products control growth responses and suppress apoptotic pathways.

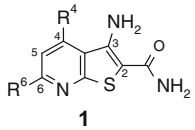
IκB kinase (IKK) is an enzyme complex critical for the activation of the NF-κB pathway.[2] IKKβ, one of the catalytic subunits in the IKK complex, has been identified as essential for the activation of the complex in response to inflammatory stimuli.[2] The potential for utilizing IKKβ inhibitors as treatment for cancer and immunological disorders has been widely recognized and actively pursued by the pharmaceutical industry, as evidenced by a plethora of publications and patent applications in recent years.[3,4]

In a previous paper, we reported a lead identification process that identified a class of IKKβ inhibitors characterized by a thienopyridine core (Fig. 1).[5] These compounds exhibited moderate activity in an IKKβ enzyme assay (IC_{50} = 2–20 μM) and showed marginal cellular activity in an NF-κB luciferase reporter gene assay.[12a] Preliminary SAR revealed that aliphatic substitutions of moderate sizes at C_4 and C_6 of structure **1** are tolerated, indicating the possibility for further improvement. This profile, coupled with a structure amenable to chemical modification, encouraged us to further pursue this class of IKKβ inhibitors in a lead optimization program. In this Letter, we report the SAR studies that led to the discovery of a series of potent IKKβ inhibitors based on structure **1**.

Early exploratory studies had revealed that substitutions of moderate sizes at C_4 and C_6 positions of structure **1** are tolerated, while modifications at C_5 and the 2,3-aminoamide moieties generally reduce compound potency.[5] We therefore decided to focus on C_4 and C_6 of structure **1**.

Compounds **21–24** in Table 1 were synthesized according to Scheme 1. Treatment of 2-chloro-3-cyano-4-methoxypyridine (**2**)[6] with HBr in acetic acid followed by alkylation gave a 2:1 mixture of 2-bromo and 2-chloro pyridyl ethers **3a** and **3b**. The mixture of **3a** and **3b** was then reacted with 2-mercaptoacetamide and NaH to give the thienopyridyl derivative **4**.

Compounds **25–33** in Table 1 were prepared according to Scheme 2. Reaction of compound **5**[7] with 2-cyanothioacetamide



1

Figure 1. Thienopyridine-based IKKβ inhibitors.

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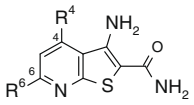
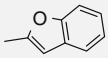
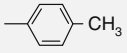
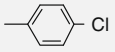
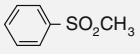
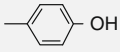
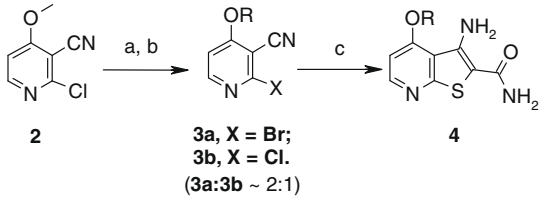
doi:10.1016/j.bmcl.2009.08.054

Table 1
Structure–activity-relationship at C_4 position



Compd	R^4	R^6	IKKβ IC_{50} (μM)
16[a]	H	Me	12.7[b]
17[a]	Me	Me	2.7 ± 0.4
18[a]	Pr	Me	1.3 ± 0.1
19[a]	^{i}Bu	Me	2.5 ± 0.2
20[a]	CH_2OH	Me	13.5 ± 0.7
21	OMe	H	4.7 ± 0.2
22	OEt	H	2.0 ± 0.2
23	OPr	H	2.2 ± 0.2
24		H	10.8 ± 0.2
25		Me	1.1 ± 0.2
26		Me	16.9 ± 1.1
27		Me	2.0 ± 0.7
28		Me	6.0 ± 1.0
29		Me	7.4 ± 0.5
30		Me	8.5 ± 2.3
31		Me	14.0[b]
32		Me	1.3 ± 0.2
33		Me	>20

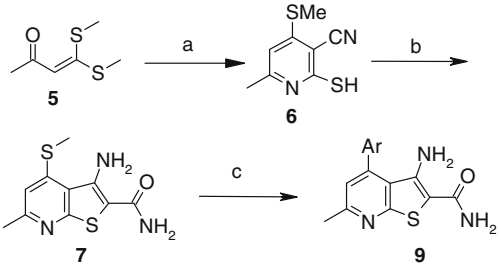
[a] For synthesis of compounds **16**–**20**, see Ref. 5.
[b] Result of single test.



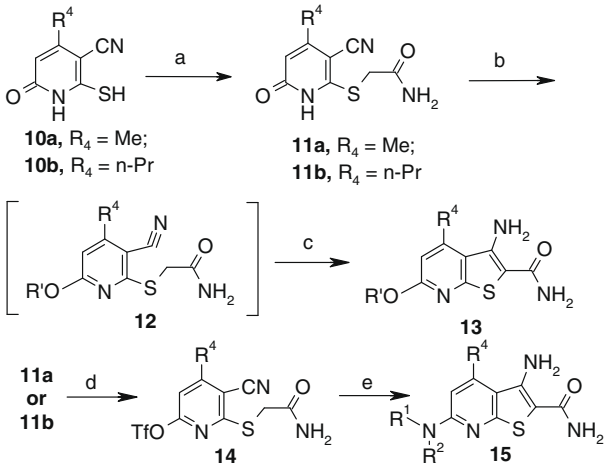
Scheme 1. (a) 30% HBr/AcOH, 100 °C, ~60%; (b) NaH, RBr, DMF, 60 °C, 20–60%; (c) $HSCH_2C(O)NH_2$, NaH, DMF, 60 °C, 40–60%.

produced thiopyridine derivative **6**. Compound **6** was then reacted with 2-bromoacetamide in the presence of sodium methoxide to give the thienopyridine derivative **7**. Cross coupling of thioether **7** with an arylboronic acid (**8**) using Pd–Cu catalyst[8] gave the 4-aryl derivative **9**.

Scheme 3 outlines the synthesis of the compounds in Tables 2 and 3. Compound **10a** or **10b**, prepared according to literature pro-

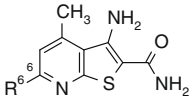


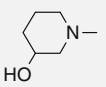
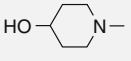
Scheme 2. (a) 2-Cyanothioacetamide, NaO^{i}Pr, HO^{i}Pr, reflux, 95%; (b) 2-bromoacetamide, NaOMe, MeOH, reflux, 41%; (c) Ar-B(OH)$_2$ (**8**), Pd_2dba_3/Cu(I)TC, (*o*-furyl)$_3$P, THF, 60 °C, 30–40%.



Scheme 3. (a) $BrCH_2C(O)NH_2$, K_2CO_3, DMF, 70 °C, 80%; (b) R'Br, K_2CO_3, DMF, 70 °C; (c) Na_2CO_3, DMF, 100 °C; 50–70%, two steps; (d) Tf_2NPh, iPr_2NEt, dioxane, rt, 90%; (e) $R^1R^2NH_2$, DMF, 100 °C then Na_2CO_3, DMF, 100 °C, 50–80%.

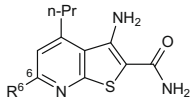
Table 2
Structure–activity-relationship at C_6



Compd	R^6	IKKβ IC_{50} (μM)
34	$HO(CH_2)_2O$	6.6 ± 0.4
35	$HO(CH_2)_3O$	5.1 ± 0.1
36	$HO(CH_2)_2N$	5.8 ± 0.3
37	$H_2N(CH_2)_2O$	2.9 ± 0.1
38	$H_2N(CH_2)_3O$	>50
39		2.4 ± 0.0
40		2.5 ± 0.1
41		2.4 ± 0.2
42		0.75 ± 0.02
43		0.68 ± 0.03

[a]Result from single test.

Table 3
Structure–activity-relationship at C_6



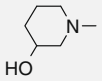
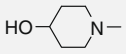
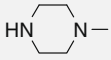
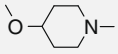
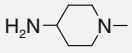
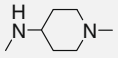
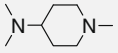
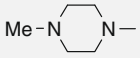
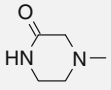
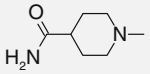
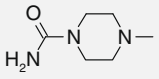
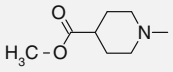
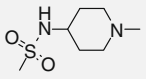
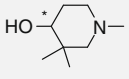
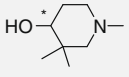
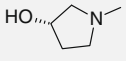
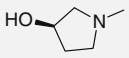
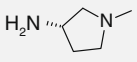
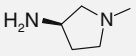
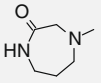
Compd	R^6	IKKβ IC_{50} (μM)
44		0.57 ± 0.08
45		0.28 ± 0.07
46		0.12 ± 0.00
47		0.68[a]
48		0.041 ± 0.002
49		0.12 ± 0.02
50		0.68 ± 0.14
51		0.52 ± 0.01
52		2.0 ± 0.4
53		1.3 ± 0.1
54		0.15 ± 0.01
55		7.8[a]
56		0.098 ± 0.011
57[b]		0.042[a]
58[b]		0.24[a]
59		1.45 ± 0.05
60		1.95 ± 0.05
61		0.59 ± 0.01

Table 3 (*continued*)

Compd	R^6	IKKβ IC_{50} (μM)
62		0.50 ± 0.07
63		0.072 ± 0.001
64		0.63[a]
65		0.14 ± 0.01

[a] Results of single test.
[b] The absolute stereochemistry of **57** and **58** was not determined.

cedures,[9] was reacted with 2-bromoacetamide to give the corresponding thioether **11a** or **11b**. Thioether **11a** or **11b** was then reacted with an alkyl bromide R′Br to provide the alkoxy intermediate **12**, which was directly treated with Na_2CO_3 to give compound **13**. Alternatively, **11a** or **11b** was converted into triflate **14** by reaction with bis(trifluoromethanesulfonyl)aniline. Triflate **14** was subsequently reacted with an amine followed by Na_2CO_3 to give the 6-aminothienopyridine derivatives **15**.

We started our SAR studies at the C_4 position. A series of compounds with various aliphatic and aromatic substitutions at C_4 position were prepared and tested in the IKKβ enzyme assay.[12a] As shown in Table 1, most of the compounds gave IC_{50}s of 1–15 μM in the enzyme assay, showing no clear SAR trends. Among the best analogues, C_4-propyl analogue **18** and C_4-furyl derivative **25** displayed IC_{50}'s of about 1 μM.

At the C_6 position, previous SAR revealed that unfunctionalized alkyl groups were tolerated but resulted in flat SAR.[5] This steered us to explore the effects of polar functional groups. With a methyl group fixed at C_4 position, hydroxyalkyl and aminoalkyl substitutions were introduced at the C_6 position (Table 2). Compounds **34–38,** in which the polar groups were attached to flexible aliphatic chains, did not show improvement in potency over those with unfunctionalized C_6 substitutions. When certain polar groups were attached to six-membered rings, a modest improvement in potency was observed. Compound **42**, with a 4′-hydroxypiperidyl group at C_6, gave an IC_{50} of 0.75 μM, three times more potent than the C_6-piperidyl analogue **39**. Compound **43**, which contains C_6-piperazinyl group, also showed better potency (IC_{50} = 0.68 μM). Compound **41**, the C_6-(3′-hydroxypiperidyl) analogue, did not show any improvement compared to the C_6-piperidyl analogue **39**, revealing an orientation effect of the functional groups. It appears that the amino and hydroxyl groups in compounds **42** and **43** are engaged in polar interactions.

Having identified C_6 substitutions that improved the enzyme potency, we next incorporated the C_4-propyl group to determine if we could further increase the potency. As shown in Table 3, compounds **44–46** displayed better potency compared to their C_4-methyl analogues **41–43**. Therefore, an *n*-propyl group was maintained at the C_4 position for further C_6 SAR.

Subsequent SAR studies were directed toward understanding and further optimizing the polar interaction(s) around C_6 (Table 3). Methylation of the OH group in **45** reduced compound potency

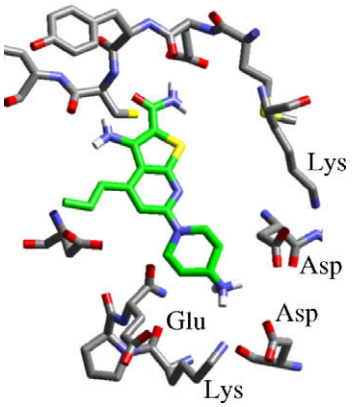


Figure 2. Homology model of the IKKβ/ATP binding site. Compound **48** is shown.

(**47**, IC_{50} = 0.68 μM), suggesting that the OH in **45** might be a H-bond donor. The 4′-aminopiperidyl analogue **48** (IC_{50} = 0.041 μM) was sevenfold more potent than compound **45**, indicating a possible acid–base interaction. Mono-methylation of the NH_2 group in **48** decreased potency (**49**, IC_{50} = 0.12 μM), and di-methylation further lowered activity (**50**, IC_{50} = 0.68 μM). Similarly, methylation of the NH group in the pyrazinyl analogue **46** also reduced potency (compare **46**, and **51**). It appears that in addition to possible acid–base interactions, the presence of H-bond donors in **48** and **46** contribute to compound activities.

Other modifications involved substituting the OH group in **45** with other functional groups. The amide/urea/ester analogues **53–55** are less potent, whereas the sulfonamide analogue **56** (IC_{50} = 0.098 μM) has similar potency compared to the amino analogue **48**. The piperazonyl anologue **52**, in which the nitrogen atom is non-basic, is less potent (IC_{50} = 2.0 μM).

The stereoselective nature of the interactions around C_6 was revealed by two enantiomers **57** and **58**. Compound **57** gave an IC_{50} of 0.042 μM, whereas its enantiomer **58** was five times less potent (IC_{50} = 0.24 μM).[10]

Analogues with different ring sizes were also examined (**59–65**). While some seven-membered ring analogues are comparable to their six-membered counterparts (**63**), five-membered ring derivatives are less active (compounds **59–62**).

An IKKβ homology model[11] provided structural insight into the interactions around the C_6 region. As shown in Figure 2, this region is lined with polar amino acid residues, providing opportunities for polar–polar interactions. The presence of the acidic residues aspartate and glutamate suggest the possibility of acid–base interactions.

Selected compounds were further evaluated for their ability to inhibit TNF-α production in cells and in mice. Some of the results are shown in Table 4. In a human whole blood assay,[12b] compounds **44–46** and **48** reduced LPS-stimulated TNF-α production, with IC_{50}'s between 1 and 10 μM. In a mouse model of LPS-stimulated TNF-α production,[12c] compounds **44–46** showed inhibitory effects at 30 mg/kg (oral dosing). Compound **48**, the most potent compound in the enzyme and cellular assay, was active at 100 mg/kg but not at 30 mg/kg. The lower in vivo efficacy of compound **48** was attributed to its poor pharmacokinetic properties as indicated by a low plasma level (0.02 μM at 30 mg/kg, 120 min post-dosing).[13] Efforts aimed at improving PK properties will be reported in subsequent publications.

Kinase selectivity is a general concern with any kinase inhibitor. For IKKβ inhibitors, a specific issue concerns the selectivity against IKKα.[14] To assess the selectivity of the current series of IKKβ inhibitors, selected compounds were tested against IKKα and 29 serine/threonine kinases and 14 tyrosine kinases.[15] In the IKKα assay, compound **48** gave an IC_{50} of 0.090 μM, merely twofold less potent than its activity against IKKβ, while **44–46** displayed better selectivity (>28-fold). In the serine/threonine screen, at concentration of 10 μM, none of the compounds in Table 5 inhibited any of the

Table 4
Cellular and in vivo profiles (selected compounds)

Compd	*hu.* wh. blood IC_{50}[a] (μM)	% Inhib. LPS-induced TNF-α in mice and plasma levels[b] (μM, in parentheses)		
		100 mg/kg	30 mg/kg	10 mg/kg
44	13.0	93 (22.5 ± 1.4) p = 0.001	67 (3.1 ± 0.3) p <0.05	14[c] (0.17)
45	9.8	98 (42.3 ± 5.2) p = 0.0007	94 (15.5 ± 1.3) p <0.05	42 (1.6) p <0.05
46	3.2	74 (3.5 ± 1.5) p <0.05	35 (<0.01) p <0.05	12[c] (<0.01)
48	1.6	81 (2.8 ± 0.2) p = 0.0006	14[c] (0.02) —	17[c] (<0.01) —

[a] Values are means of at least two experiments. Standard deviations are typically within 50% of reported value.
[b] 120 min post-dosing.
[c] Not significant.

Table 5
Kinase selectivity and action mechanism

Compd	IKKβ IC_{50} (μM)	IKKα IC_{50} (μM)	Hit against Ser/Tyr kinases[a]	Hit against Tyr kinases[b]	Hela NFκB (μM)
44	0.57 ± 0.08	13.3 ± 0.7	0	0	6.1 ± 0.6
45	0.28 ± 0.07	11.2[f]	0	2[c]	5.3 ± 1.9
46	0.12 ± 0.00	3.4 ± 0.3	0	1[d]	7.5 ± 0.7
48	0.041 ± 0.002	0.090 ± 0.008	0	1[e]	1.5 ± 0.2

[a] Number of serine/threonine kinases inhibited at 50% POC or less at 10 μM. 29 Serine/threonine kinases were screened.
[b] Number of tyrosine kinases inhibited at IC_{50} <10 μM. 14 Tyrosine kinases were screened.
[c] Compound 45 hit HEK at 9 μM, TrkA at 8 μM.
[d] Compound 46 hit HEK at 8 μM, PDGFRa at 0.3 μM.
[e] Compound 52 hit HEK at 7 μM.
[f] Result from single test.

kinases at 50% POC (percent of control) or less. For the tyrosine kinase panel, with the exception that compound **46** inhibits PDGFRα at 0.3 μM (IC_{50}), no other kinases were inhibited at IC_{50}'s below 7 μM. Overall, these compounds demonstrated excellent kinase selectivity profiles (Table 5, columns 3–5).

Another issue relates to the mechanism by which these compounds inhibit TNFα production, which could be due to mechanisms other than interference with the NF-κB pathway. As a mechanistic verification, compounds **44–46** and **48** were tested in a HeLa cell NF-κB reporter gene assay, a cellular assay specific for the NF-κB pathway.[12a] In this assay, compounds **44–46** and **48** gave IC_{50}'s in the low micromolar range, indicating that they indeed interfere with the NF-κB pathway (Table 5, column 6).

To summarize, we have identified a series of potent IKKβ inhibitors from the thienopyridine structural class. These compounds inhibit IKKβ in the low nanomolar range, suppress LPS-induced TNF-α production in human whole blood and in mice (oral dosing), and have good selectivity profiles against IKKα and a range of serine/threonine and tyrosine kinases. In addition, they demonstrate activity in a cell based reporter gene assay dependent upon signaling through NF-κB, showing that these compounds directly interfere with the target pathway.

References and notes

1. (a) Barnes, P.; Karin, M. N. *Engl. J. Med.* **1997**, *336*, 1066; (b) Karin, M.; Cao, Y.; Greten, F. R.; Li, Z. W. *Nat. Rev. Cancer* **2002**, *2*, 301; (c) Barkett, M.; Gilmore, T. D. *Oncogene* **1999**, *18*, 6910; (d) Baeuerle, P. A.; Baltimore, D. *Cell* **1996**, *87*, 13.
2. Karin, M. *Oncogene* **1999**, *18*, 6867.
3. A selection of patents and patent applications claiming IKK inhibitors is listed below: WO0158890(A1); US20020107252; WO03010163; WO03010158; WO04063185; WO04063186; WO0130774(A1); WO0100610; WO0168648; WO04022553; WO04022057; US2004116494; WO03039545; WO2004022553; US2005049265; WO0224679(A1); US6562811; WO0244153(A1); WO03076447 (A1); WO03076447; US6869956; WO05011609; WO02094813; WO0246170; WO0246171; WO0230353; WO0230423(A1); WO030866309(A2); WO0241843 (A2); WO03040131(A1); WO03048152(A2).
4. (a) Murata, T.; Shimada, M.; Sakakibara, S.; Yoshino, T.; Kadono, H.; Masuda, T.; Shimazaki, M.; Shintani, T.; Fuchikami, K.; Sakai, K.; Inbe, H.; Takeshita, K.; Niki, T.; Umeda, M.; Bacon, K. B.; Ziegelbauer, K. B.; Lowingera, T. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 913; (b) Murata, T.; Shimada, M.; Kadono, H.; Sakakibara, S.; Yoshino, T.; Masuda, T.; Shimazaki, M.; Shintani, T.; Fuchikami, K.; Bacon, K. B.; Ziegelbauer, K. B.; Lowinger, T. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4013; (c) Murata, T.; Shimada, M.; Sakakibara, S.; Yoshino, T.; Masuda, T.; Shintani, T.; Sato, H.; Koriyama, Y.; Fukushima, K.; Nunami, N.; Yamauchi, M.; Fuchikami, K.; Komura, H.; Watanabe, A.; Ziegelbauer, K. B.; Bacon, K. B.; Lowinger, T. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4019; (d) Burke, J. R.; Pattol, M. A.; Gregor, K. R.; Brassil, P. J.; MacMaster, J. F.; McIntyre, K. W.; Yang, X.; Iotzova, V. S.; Clarke, W.; Strnad, J.; Qiu, Y.; Zusi, F. C. *J. Biol. Chem.* **2003**, *278*, 1450; (e) McIntyre, K. W.; Shuster, D. J.; Gillooly, K. M.; Dambach, D. M.; Pattoli, M. A.; Lu, P.; Zhou, X.-D.; Qiu, Y.; Zusi, F. C.; Burke, J. R. *Arthritis Rheum.* **2003**, *48*, 2652; (f) Baxter, A.; Brough, S.; Cooper, A.; Floettmann, E.; Foster, S.; Harding, C.; Kettle, J.; McInally, T.; Martin, C.; Mobbs, M.; Needham, M.; Newham, P.; Paine, S.; St-Gallay, S.; Salter, S.; Unitt, J.; Xue, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2817; (g) Castro, A. C.; Dang, L. C.; Soucy, F.; Grenier, L.; Mazdiyasni, H.; Hottelet, M.; Parent, L.; Pien, C.; Palombella, V.; Adams, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2419; (h) Bonafoux, D.; Bonar, S.; Christine, L.; Clare, M.; Donnelly, A.; Guzova, J.; Nandini Kishore, N.; Lennon, P.; Libby, A.; Mathialagan, S.; McGhee, W.; Rouw, S.; Sommers, C.; Tollefson, M.; Tripp, C.; Richard Weier, R.; Wolfsona, S.; Min, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2870; (i) Christopher, J. A.; Avitabile, B. G.; Bamborough, P.; Champigny, A. C.; Cutler, G. J.; Dyos, S. L.; Grace, K. G.; Kerns, J. K.; Kitson, J. D.; Mellor, G. W.; Morey, J. V.; Morse, M. A.; O'Malley, C. F.; Patel, C. B.; Probst, N.; Rumsey, W.; Smith, C.; Wilson, M. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3972; (j) Belema, M.; Bunker, A.; Nguyen, V. N.; Beaulieu, F.; Ouellet, C.; Qiu, Y.; Zhang, Y.; Martel, A.; Burke, J.; McIntyre, K. W.; Pattoli, M. A.; Daloisio, C.; Gillooly, K. M.; Clarke, W. J.; Brassil, P. J.; Zusi, F. C.; Vyas, D. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4284.
5. Morwick, T.; Berry, A.; Brickwood, J.; Cardozo, M.; Katrina Catron, K.; DeTuri, M.; Hrapchak, M.; Jacober, S.; Jakes, S.; Kaplita, P.; Ksiazek, J.; Liuzzi, M.; Magolda, R.; Marshall, D.; McNeil, A.; Prokopowicz, A., III; Sarko, C.; Scouten, E.; Sledziona, C.; Watrous, J.; Wu, J.-P.; Cywin, C. *J. Med. Chem.* **2006**, *49*, 2898.
6. Mittelbach, M. et al *Arch. Pharm. (Weinheim Ger.)* **1985**, *318*, 481.
7. Dimethylthiovinylketone **5** was prepared according to a literature procedure. See Spitzner, R.; Menzel, M.; Schroth, W. *Synthesis* **1982**, *3*, 206–210.
8. Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.
9. (a) Ratemi, E. S.; Namdev, N.; Gibson, M. S. *J. Heterocycl. Chem.* **1993**, *30*, 1513; (b) Sharaf, S. M.; El-Sadany, S. K.; Hamed, E. A.; Youssef, A.-H. A. *Can J. Chem.* **1991**, *69*, 1445.
10. The two enantiomers **57** and **58** were obtained by chiral HPLC resolution of the racemic material, each >98% ee. The absolute stereochemistry for each compound was not determined.
11. An IKKβ homology model was generated using the MODELLER program with five kinase X-ray structures as templates, including the structures of CDK2, PHK, LCK, JNK, and CPK (cAMP dependent protein kinase).
12. (a) The protocols for IKKβ inhibition and the HeLa NF-κB reporter gene assay are described in reference 5.; The procedure for human whole blood LPS–TNFα assay has been described, see (b) Regan, J. et al *J. Med. Chem.* **2003**, *46*, 4676; The mouse LPS/TNF-α assay was performed according to a procedure previously described, except that mice were pre-dosed with test compounds 60 min prior to LPS challenge, see (c) Regan, J. et al *J. Med. Chem.* **2002**, *45*, 2994.
13. The possibility that the compound decomposed in plasma was ruled out by a plasma stability study.
14. IKKα is one of the catalytic subunits in the IKK complex with roles in development of lymphoid organs and inflammatory resolution. It is generally considered desirable to avoid inhibiting IKKα in developing IKKβ inhibitors. See: (a) Hayden, M. S.; Ghosh, S. *Genes Dev.* **2004**, *18*, 2195; (b) Lawrence, T.; Bebien, M.; Liu, G. Y.; Nizet, V.; Karin, M. *Nature* **2005**, *434*, 1138.
15. (a) Serine/threonine kinase panel: MKK1, MAPK2/ERK2, JNK/SAPK1c, SAPK2a/p38, SAPK2b/p38b2, SAPK3/p38g, SAPK4/p38δ, MAPKAP-K1a, MAPKAP-K2, MSK1, PRAK, PKA, PKCα, PDK1, PKBDPH, SGK, S6K1, GSK3b, ROCK-II, AMPK, CHK1, CK2, PHOS.KINASE, Lck, CSK, CDK2/cyclin A, CK1, DYRK1a, PP2a.; (b) Tyrosine kinase panel: Btk, Eck, EGFR, FGFR3, Hek, HGFR, IGF1R, IR, Itk, Lyn, PDGFRα, Syk, TrkA, VEGFR1.