Synthesis and Biological Activities of 4-Phenyl-5-pyridyl-1,3-thiazole Derivatives as p38 MAP Kinase Inhibitors

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A novel series of 4-phenyl-5-pyridyl-1,3-thiazole analogues possessing potent *in vitro* inhibitory activity against p38 mitogen-activated protein kinase and the release of tumor necrosis factor-α (TNF-α) from human monocytic THP-1 cells stimulated by lipopolysaccharide has been identified. Subsequent structure–activity relationship (SAR) studies and optimization for absorption, distribution, metabolism, and elimination (ADME) profiles led to the identification of compounds 7g and 10b as orally active lead candidates that block the *in vivo* production of proinflammatory cytokine (TNF-α). In pharmacokinetic studies, compound 10b showed good oral administration in mice and demonstrated significant *in vivo* anti-inflammatory activity in an anti-collagen monoclonal antibody-induced arthritis mouse model (minimum effective dose (MED)=30 mg/kg). Further elucidation of this class of compounds may provide novel anti-inflammatory agents, such as anti-rheumatoid arthritis drugs.

Key words 5-pyridyl-1,3-thiazole; p38 mitogen-activated protein (MAP) kinase; rheumatism; tumor necrosis factor (TNF)-α; anti-collagen monoclonal antibody-induced arthritis

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine, mainly produced by activated monocytes and macrophages. Excessive production of TNF-α is believed to underlie the progression of many serious inflammatory diseases, such as rheumatoid arthritis (RA), Crohn's disease and psoriasis.[1,2] Recent clinical data, obtained using chimeric TNF-α antibodies[3,4] and soluble TNF-α receptor fusion proteins[5] in the treatment of RA, have confirmed the important role of TNF-α in these inflammatory conditions. These agents are generally well tolerated but have drawbacks relating to patient cost, efficiency of production, and administration by injection. Therefore, inflammation research has focused on the development of orally active small molecular inhibitors of cytokine release.

A serine/threonine kinase termed p38 mitogen-activated protein (MAP) kinase is a member of the stress-activated protein kinases and is considered as an attractive target. The prototypical p38 MAP kinase inhibitor SB 203580 (Fig. 1) showed inhibitory activity *in vivo* against pro-inflammatory cytokine production in both mice and rats,[6] and several novel structural classes of p38 MAP kinase inhibitors have been demonstrated to efficiently reduce cytokine levels.[7] Thus, the regulation of TNF-α *via* the inhibition of p38 MAP kinase is expected to have beneficial effects in the treatment of inflammatory diseases. Although the efforts to develop small molecule agents for p38 MAP kinase have not yet yielded an agent ready to market, several inhibitors are presently under investigation in human clinical trials.

We have previously reported that 4-phenyl-5-pyridyl-1,3-thiazole derivatives showed strong anti-inflammatory activities[8,9] but the anti-inflammatory mechanism of these compounds was not well-known. In a continuing effort to elucidate the mechanism, we found that 2-amino-4-phenyl-5-pyridyl-1,3-thiazole derivatives had potent adenosine receptor antagonistic activity and phosphodiesterase inhibitory activity.[10] These receptors and enzymes are related to adenosine or adenosine-3,5-triphosphate (ATP), suggesting that 4-phenyl-5-pyridyl-1,3-thiazole derivatives mimic adenosine and its related substrates. Taking these results into consideration, we explored the 4-phenyl-5-pyridyl-1,3-thiazole template, including rarely reported 2-acetylaminothiazole compounds. Herein, we report the synthesis and biological activities of a novel series of 4-phenyl-5-pyridyl-1,3-thiazole derivatives as p38 MAP kinase inhibitors.

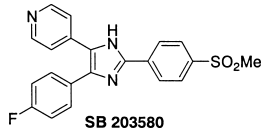
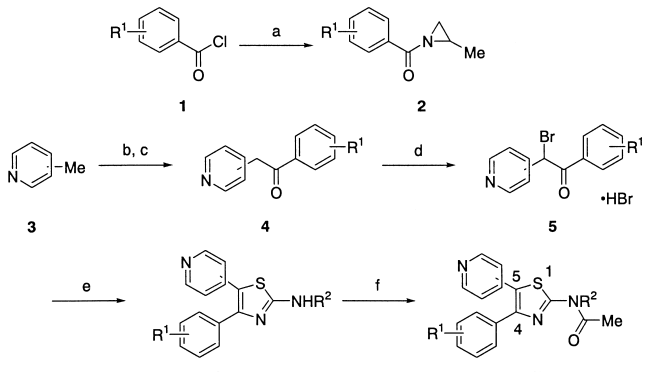


Fig. 1. Structure of SB 203580

Chemistry

The general approach for the synthesis of 4,5-disubstituted 2-acetylamino-1,3-thiazoles **7** is outlined in Chart 1. The 1-benzoyl-2-methylaziridines **2** were prepared from the corresponding acid chloride and commercially available 2-methylaziridine according to the Schotten–Baumann procedure. The lithium anion of methylpyridine **3** was condensed with 1-benzoyl-2-methylaziridines **2** and the resulting ketones **4**



Reagents: (a) 2-methylaziridine, ether, 2N-NaOH, 0 °C; (b) LDA, hexane, THF, —78 °C then —20 °C; (c) **2**, —78 °C; (d) Br_2, AcOH, 70°C; (e) $H_2NC(S)NHR^2$, MeCN, 80 °C; (f) MeCOCl, DMAP, DMA, 70 °C.

Chart 1. Synthesis of 2-Acetylaminothiazoles (**7**)

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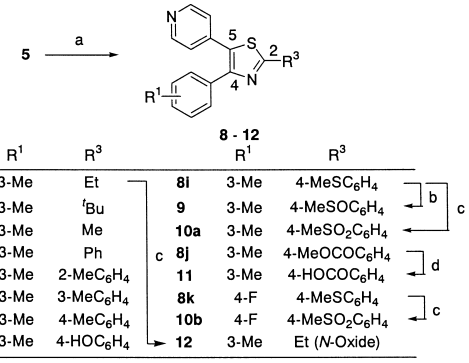
were brominated to give α-bromoketones **5**.[11] Condensation of **5** with thiourea afforded 1,3-thiazoles **6**. Since the subsequent acetylation of **6** under various standard conditions (acetic anhydride or acetyl chloride with triethylamine, or the Schotten–Baumann procedure) was unsuccessful due to the low reactivity of the amino moiety, we used *N*,*N*-dimethyl-4-aminopyridine (DMAP) as a catalyst in the reaction with acetyl chloride in *N*,*N*-dimethylacetamide (DMA).

The 4,5-disubstituted 2-alkyl(aryl)-1,3-thiazoles **8** were prepared from α-bromoketones **5** and thioamides **13** (Chart 2), which were prepared from the corresponding nitriles according to a process described in the previous report.[12] The cyclization reaction under previous condition using triethylamine as a base gave **8** in low to moderate yields, but an improvement in yield was achieved when no base was used. However, even under these conditions, the cyclization reaction of **5** and thioacetoamide **8c** proceeded with low yield (20%) and ketone **4** was the major product obtained. Sulfide **8i** was converted into the corresponding sulfoxide **9** on treatment with potassium peroxodisulfate in aqueous acetic acid.[13] The sulfonyl derivatives **10a** and **10b** were synthesized by oxidization of the corresponding sulfide **8i** or **8k** using 2 equivalents of *m*-chloroperbenzoic acid (*m*CPBA) in *N*,*N*-dimethylformamide (DMF). Saponification of **8j** provided the corresponding carboxylic acid **11**. Thiazole **8a** was oxidized with *m*CPBA in DMF to afford *N*-oxide **12**. All the synthesized thiazoles are listed in Table 1.



Reagents: (a) $R^3C(S)NH_2$ (13), DMF, r.t.; (b) $K_2S_2O_8$, AcOH, water, r.t.; (c) *m*CPBA, DMF, 0 °C then r.t.; (d) 2N-NaOH, EtOH, r.t.

Chart 2. Synthesis of 2-Alkyl(aryl)-thiazoles (**8**—**12**)

Results and Discussion

The p38 MAP kinase inhibitory activities of 1,3-thiazole derivatives are shown in Table 2. Firstly, the structure–activity relationship (SAR) around the pyridine ring at the 5-position of the thiazole nucleus was evaluated with **7a**—**c** and **12**. The 2- and 3-pyridyl derivatives **7c** and **7b** led to a drastic loss in activity, indicating that the 4-pyridyl group is essential for inhibitory activity. The diminished potency of *N*-oxide **12** indicated the importance of the nitrogen atom of the 4-pyridyl moiety as a hydrogen bond acceptor. According to the previous X-ray crystallographic data, the nitrogen atom seems to form a crucial hydrogen bond with the backbone NH of Met 109 in the enzyme.[14—16]

Next, we focused on the SAR around the phenyl ring at 4-position. The bulky substituents, for example 4-*tert*-butyl (**7m**), had weak activity but the small substituents, such as 4-methyl (**7f**) or 4-chloro (**7i**) were tolerated. The introduction of substituents at the 2-position of the phenyl ring led to considerably less active compounds (**7e**, **h**, **k**). In addition, 3-chloro (**7j**) showed superior activity to 3-methoxy (**7d**) or 3-fluoro (**7l**). These results suggested that the steric requirement is a more important factor than the electronic factor. The most interesting compound in these 2-acetylaminothiazoles was the 3-methyl derivative **7g**. Based on these results, we selected the 3-methyl group as a favorable substituent on the phenyl ring for the next SAR study around the 2-position of the thiazole.

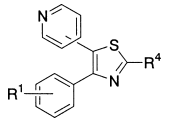
The 2-amino derivative **6g** can also provide good inhibitory affinity as seen with the acetyl amino compound **7g**. The lower alkyl substituents (**8a**—**c**) were tolerated and the ethyl derivative **8a** was the most potent in this series. The 2-phenyl analogue **8d** did not result in improved activity. However, the introduction of substituents on the phenyl ring (**8e**—**i**) enhanced the potency. The compound **8g** with a methyl group at the 4-position was more active than 2-methylphenyl (**8e**) or 3-methylphenyl (**8f**).

To evaluate the role of the substituent on the 2-phenyl ring, we examined a docking study between **10b** and p38 MAP kinase using the DOCK program based on the X-ray crystal structure of the complex between SB 203580 and p38 MAP kinase.[15] The result of this study, as shown in Fig. 2, suggested that the 4-methylsulfonylphenyl ring of **10b** could form π–π staking interaction with Tyr 35 of the enzyme and an appropriate substituent on the phenyl ring would have the potency to derive additional contact with Arg 173 of the enzyme. The potency of sulfoxide **9** and sulfone **10a** compared to sulfide **8i** strongly supported the validity of this further contribution to binding potency. The phenol analogue **8h** retained potent activity, while carboxylic acid analogue **11** resulted in decreased activity.

These compounds were further evaluated for their inhibitory activity by the lipopolysaccharide (LPS)-stimulated TNF-α release assay using the THP-1 cell for secondary screening (Table 2). There was no outstanding difference in p38 MAP kinase inhibitory activity between compounds bearing methoxy (**7a**, **d**) or chloro (**7i**, **j**) substituents. However, in this cell-based assay, compounds **7a** and **7i** with substituents at 4-position on the phenyl ring showed 5-fold and 22-fold more potency than **7d** and **7j** with substituents at 3-position, respectively. On the other hand, the 3-methyl analogue **7g** exhibited improved activity compared to the 4-methyl derivative **7f**, suggesting that methyl analogues produce a significantly different SAR.

To investigate the structural requirement of 4-(3-methylphenyl)thiazole derivatives in more detail, compounds with various substituents at 2 position of the thiazole ring were further profiled for their ability to inhibit TNF-α production. The amino (**6g**), which had strong inhibitory activity against p38 MAP kinase, showed less activity than 2-acetylamino (**7g**). Lower-alkyl substituents, such as methyl (**8c**) or ethyl (**8a**), were well tolerated, but *tert*-butyl (**8b**) and phenyl (**8d**) gave less activity. Little difference was observed in the series of 2-phenyl (**8e**—**g**). Although phenol (**8h**) was the most potent p38 MAP kinase inhibitor in this series, sulfoxide (**9**) and sulfone (**10a**) were much better tolerated than **8h** in the cellular assay. It seemed that the hydrophobic substituents at 2-positon, such as methyl or ethyl, or less polar

Table 1. Physicochemical Properties of 5-Pyridyl-1,3-thiazoles



Compd.	Py	R^1	R^4	Formula	Yield (%)[a)]	mp (°C)	*Anal.*
6a	4-Py	4-MeO	NH_2	$C_{15}H_{13}N_3OS$	68	282—284	C, H, N
6b	3-Py	4-MeO	NH_2	$C_{15}H_{13}N_3OS$	90	265—266	C, H, N
6c	2-Py	4-MeO	NH_2	$C_{15}H_{13}N_3OS$	55	217—218	C, H, N
6d	4-Py	3-MeO	NH_2	$C_{15}H_{13}N_3OS$	37	232—234	C, H, N
6e	4-Py	2-MeO	NH_2	$C_{15}H_{13}N_3OS \cdot 0.2H_2O$	61	213—215	C, H, N
6f	4-Py	4-Me	NH_2	$C_{15}H_{13}N_3S$	75	296—298	C, H, N
6g	4-Py	3-Me	NH_2	$C_{15}H_{13}N_3S$	72	255—258	C, H, N
6h	4-Py	2-Me	NH_2	$C_{15}H_{13}N_3S \cdot 0.2H_2O$	42	235—238	C, H, N
6i	4-Py	4-Cl	NH_2	$C_{14}H_{10}ClN_3S$	73	>300	C, H, N
6j	4-Py	3-Cl	NH_2	$C_{14}H_{10}ClN_3S$	60	256—258	C, H, N
6k	4-Py	2-Cl	NH_2	$C_{14}H_{10}ClN_3S$	24	232—235	C, H, N
6l	4-Py	3-F	NH_2	$C_{14}H_{10}FN_3S$	86	263—264	C, H, N
6m	4-Py	4-^{t}Bu	NH_2	$C_{18}H_{19}N_3S \cdot 0.5H_2O$	69	254—257	C, H, N
6n	4-Py	3-Me	NHMe	$C_{16}H_{15}N_3S$	67	199—202	C, H, N
7a	4-Py	4-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	92	282—284	C, H, N
7b	3-Py	4-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	82	119—120	C, H, N
7c	2-Py	4-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	29	230—232	C, H, N
7d	4-Py	3-MeO	NHAc	$C_{17}H_{15}N_3O_2S \cdot 0.3H_2O$	70	234—236	C, H, N
7e	4-Py	2-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	54	259—261	C, H, N
7f	4-Py	4-Me	NHAc	$C_{17}H_{15}N_3OS$	54	308—309	C, H, N
7g	4-Py	3-Me	NHAc	$C_{17}H_{15}N_3OS$	68	287—289	C, H, N
7h	4-Py	2-Me	NHAc	$C_{17}H_{15}N_3OS$	56	272—274	C, H, N
7i	4-Py	4-Cl	NHAc	$C_{16}H_{12}ClN_3OS \cdot 0.2H_2O$	73	317—320	C, H, N
7j	4-Py	3-Cl	NHAc	$C_{16}H_{12}ClN_3OS$	57	290—293	C, H, N
7k	4-Py	2-Cl	NHAc	$C_{16}H_{12}ClN_3OS$	47	292—293	C, H, N
7l	4-Py	3-F	NHAc	$C_{16}H_{12}FN_3OS$	82	326—328	C, H, N
7m	4-Py	4-^{t}Bu	NHAc	$C_{20}H_{21}N_3OS$	50	280—281	C, H, N
7n	4-Py	3-Me	NMeAc	$C_{18}H_{17}N_3OS$	64	169—170	C, H, N
8a	4-Py	3-Me	Et	$C_{17}H_{16}N_2S$	59	56—58	C, H, N
8b	4-Py	3-Me	^{t}Bu	$C_{19}H_{20}N_2S$	53	140—142	C, H, N
8c	4-Py	3-Me	Me	$C_{16}H_{14}N_2S$	20	74—75	C, H, N
8d	4-Py	3-Me	Ph	$C_{21}H_{16}N_2S$	74	118—120	C, H, N
8e	4-Py	3-Me	2-MeC_6H_4	$C_{22}H_{18}N_2S$	68	Paste	C, H, N
8f	4-Py	3-Me	3-MeC_6H_4	$C_{22}H_{18}N_2S$	76	86—87	C, H, N
8g	4-Py	3-Me	4-MeC_6H_4	$C_{22}H_{18}N_2S$	72	138—139	C, H, N
8h	4-Py	3-Me	4-HOC_6H_4	$C_{21}H_{16}N_2OS$	78	248—249	C, H, N
8i	4-Py	3-Me	4-$MeSC_6H_4$	$C_{22}H_{18}N_2S_2$	45	101—102	C, H, N
8j	4-Py	3-Me	4-$MeOCOC_6H_4$	$C_{23}H_{18}N_2O_2S$	58	152—153	C, H, N
8k	4-Py	4-F	4-$MeSC_6H_4$	$C_{21}H_{15}FN_2S_2$	84	115—118	C, H, N
9	4-Py	3-Me	4-$MeSOC_6H_4$	$C_{22}H_{18}N_2OS_2$	58	188—189	C, H, N
10a	4-Py	3-Me	4-$MeSO_2C_6H_4$	$C_{22}H_{18}N_2O_2S_2$	63	171—174	C, H, N
10b	4-Py	4-F	4-$MeSO_2C_6H_4$	$C_{21}H_{15}FN_2O_2S_2$	71	191—194	C, H, N
11	4-Py	3-Me	4-$HOCOC_6H_4$	$C_{22}H_{16}N_2O_2S$	74	335—336	C, H, N
12	4-Py oxide	3-Me	Et	$C_{17}H_{16}N_2OS$	74	143—144	C, H, N

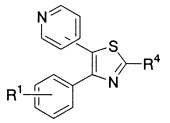
a) No attempt was made to optimize yields. Numbers respect the yield for the last step.

substituents, such as sulfinyl or sulfonyl, were superior to polar substituents, such as amino and phenol, in the cellular assay.

Based on p38 MAP kinase inhibition, TNF-α release assay results and the structural features, the three compounds, 2-acetamide (**7g**), 2-sulfonylphenyl derivatives **10a** and **10b**, were selected for the *in vivo* assay (Table 3). Compound **7g** inhibited TNF-α production by 43% while **10b** was still more effective with 67% inhibition. Compound **10a** showed no activity in this model at 10 mg/kg. These data suggest that the fluoro group has greater *in vivo* efficacy than the methyl group. We therefore examined the mouse plasma concentration after oral administration of **7g** and **10b** (Table 3). These two compounds demonstrated good results and compound **10b** in particular had a more favorable pharmacokinetic (PK) profile in mice. Although the Novartis group has reported that pyridylthiazole has no activity in *in vivo* LPS mice,[17] these compounds showed significant anti-TNF-α activity *in vivo* and good oral absorption. In our effort to obtain an orally active p38 MAP kinase inhibitor, compounds **7g** and **10b** provided evidence of the potency of thiazole nucleus.

To evaluate the *in vivo* potency of p38 MAP kinase inhibitor as an anti-RA drug, compound **10b** (10—50 mg/kg; *p.o.*) was tested in an anti-collagen (anti-CII) monoclonal antibody (mAb)-induced arthritis mouse model, as shown in Fig. 3. In this mouse model, severe arthritis occurs about 24 h after LPS injection and persists for more than 21 d.[18] Treat-

Table 2. Inhibitory Activities of Pyridylthiazoles on p38 MAP Kinase and LPS-Stimulated Release of TNF-α in THP-1 Cells



Compd.	Py	R^1	R^4	IC_{50} (nM)			
				p38α[a]		TNF-α[a]	
6g	4-Py	3-Me	NH_2	7.3	(5.7—9.4)	350	(140—880)
7a	4-Py	4-MeO	NHAc	74	(57—95)	240	(100—590)
7b	3-Py	4-MeO	NHAc	>1000		NT[b]	
7c	2-Py	4-MeO	NHAc	>1000		NT[b]	
7d	4-Py	3-MeO	NHAc	73	(48—110)	1200	(250—5800)
7e	4-Py	2-MeO	NHAc	1300	(910—1800)	NT[b]	
7f	4-Py	4-Me	NHAc	76	(67—86)	220	(48—980)
7g	4-Py	3-Me	NHAc	8.9	(6.9—11)	80	(32—200)
7h	4-Py	2-Me	NHAc	340	(210—330)	210	(64—690)
7i	4-Py	4-Cl	NHAc	45	(37—54)	170	(67—420)
7j	4-Py	3-Cl	NHAc	43	(36—51)	3700	(580—24000)
7k	4-Py	2-Cl	NHAc	260	(210—330)	850	(390—1900)
7l	4-Py	3-F	NHAc	140	(110—190)	4600	(570—38000)
7m	4-Py	4-^{t}Bu	NHAc	>1000		NT[b]	
7n	4-Py	3-Me	NMeAc	48	(34—67)	3100	(800—12000)
8a	4-Py	3-Me	Et	15	(12—19)	73	(36—150)
8b	4-Py	3-Me	^{t}Bu	31	(25—40)	820	(270—2500)
8c	4-Py	3-Me	Me	27	(23—32)	66	(34—130)
8d	4-Py	3-Me	Ph	200	(160—250)	1600	(960—2700)
8e	4-Py	3-Me	2-MeC_6H_4	69	(55—87)	340	(180—640)
8f	4-Py	3-Me	3-MeC_6H_4	74	(65—84)	380	(150—1000)
8g	4-Py	3-Me	4-MeC_6H_4	41	(33—53)	510	(190—1300)
8h	4-Py	3-Me	4-HOC_6H_4	5.3	(3.9—7.2)	130	(81—220)
8i	4-Py	3-Me	4-MeSC_6H_4	22	(19—26)	3800	(1200—12000)
9	4-Py	3-Me	4-MeSOC_6H_4	15	(11—19)	67	(32—140)
10a	4-Py	3-Me	4-MeS$O_2C_6H_4$	14	(12—16)	49	(29—84)
10b	4-Py	4-F	4-MeS$O_2C_6H_4$	51	(n=1)	380	(190—760)
11	4-Py	3-Me	4-HOCOC_6H_4	210	(170—280)	170	(54—550)
12	4-Py oxide	3-Me	Et	1700	(1100—2800)	NT[b]	

a) Numbers in parentheses represent 95% confidence intervals or remark; *b*) NT indicates 'not tested'.

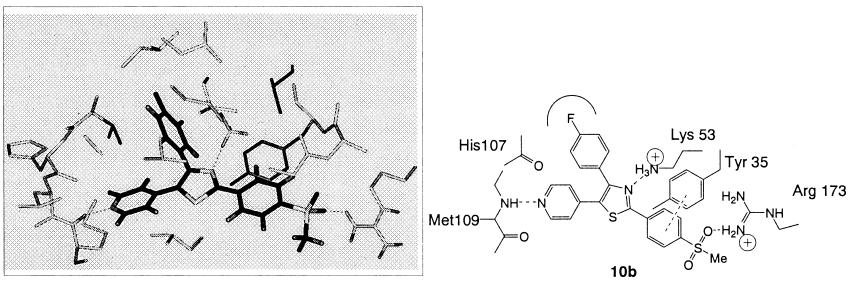


Fig. 2. Docking Model of Compound **10b** with p38 MAP Kinase

Table 3. Inhibitory Activities of Pyridylthiazoles on LPS-Induced TNF-α Production in Mice and Pharmacokinetic Parameters

Compd.	LPS mouse (10 mg/kg, *p.o.*)	Mouse PK[b] (10 mg/kg, *p.o.*)	
	% inh.[a]	C_{max} (μg/ml)	$AUC_{0—24\,h}$ (μg·h/ml)
7g	43.3*	1.078	0.874
10a	7.3	NT[c]	NT[c]
10b	67.4*	2.420	19.778

a) $*p<0.01$ *vs.* LPS-treated control (n=7); *b*) n=3; *c*) NT indicates 'not tested'.

ment with compound **10b** (30, 50 mg/kg; *p.o.*) demonstrated a significant ameliorative effect on the arthritis by preventing the development of footpad swelling (on day 11).

Conclusion

A series of novel thiazole analogues possessing potent *in vitro* inhibitory activity against p38 MAP kinase has been identified. The introduction of various substituents onto the phenyl ring and 2-position of the thiazole ring produced inhibitors with increased *in vitro* potency while maintaining excellent potency in the cellular assay. The potent analogue **10b** inhibited p38 MAP kinase with an IC_{50} of 51 nM and

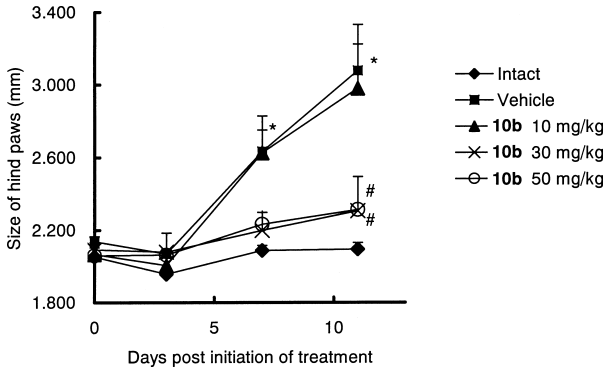


Fig. 3. Effect of Compound **10b** on the Size of Hind Paws in Anti-collagen Antibody-Induced Arthritis of Female BALB/c Mice

$*p<0.05$ *vs.* Intact; $\#p<0.05$ *vs.* vehicle; Dunnett type test ($n=6$).

TNF-α production by 67% in mice at 10 mg/kg. This compound also displayed a significant ameliorative effect on the mouse anti-CII mAb-induced arthritis model (MED: 30 mg/kg; *p.o.*). The excellent *in vitro* and *in vivo* potency of this series warrants further investigation in more advanced analogues for the treatment of inflammatory diseases.

Experimental

General Melting points were determined on Yanagimoto micro melting point apparatus or Büche B-545 and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer, with tetramethylsilane as the internal standard. TLC analyses were carried out on Merck Kieselgel 60 F_{254} plates. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd., and are within $\pm 0.4\%$ of the theoretical values unless otherwise noted. Tetrahydrofuran (THF) was distilled over calcium hydride before use and other solvents and reagents were used without purification. Extracted solutions were dried over anhydrous Na_2SO_4 unless otherwise noted and concentration of the organic solution was carried out under reduced pressure. Chromatographic purification was carried out on silica gel columns (Kieselgel 60, 0.063—0.22 mm, Merck) unless otherwise noted. The yields reported are not optimized.

1-(4-Methoxybenzoyl)-2-methylaziridine (2a) A solution of 2-methylaziridine (50.5 ml, 0.645 mol) in diethyl ether (325 ml) was added to a 2 N aqueous sodium hydroxide (325 ml). This mixture was cooled to 0 °C and 4-methoxybenzoyl chloride (100 g, 0.586 mol) was added dropwise to the mixture. After the addition, the mixture was further stirred for 1 h at 0 °C. The organic phase was separated and the aqueous phase was extracted with ethyl ether. The combined organic phase was dried, and concentrated to afford 112 g (yield quant.) of **2a** as an oil: ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, $J=5.9$ Hz), 2.11 (1H, d, $J=3.3$ Hz), 2.50—2.63 (2H, m), 3.87 (3H, s), 6.94 (2H, d, $J=9.2$ Hz), 8.00 (2H, d, $J=9.2$ Hz).

1-(3-Methoxybenzoyl)-2-methylaziridine (2b) This compound was prepared from 3-methoxybenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, $J=5.9$ Hz), 2.14 (1H, d, $J=2.9$ Hz), 2.52—2.65 (2H, m), 3.86 (3H, s), 7.10 (1H, ddd, $J=8.4$, 2.6, 1.1 Hz), 7.37 (1H, dd, $J=8.4$, 7.3 Hz), 7.55 (1H, dd, $J=2.6$, 1.5 Hz), 7.63 (1H, ddd, $J=7.3$, 1.5, 1.1 Hz).

1-(2-Methoxybenzoyl)-2-methylaziridine (2c) This compound was prepared from 2-methoxybenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, $J=5.5$ Hz), 2.10 (1H, d, $J=3.3$ Hz), 2.50 (1H, d, $J=5.9$ Hz), 2.53—2.65 (1H, m), 3.90 (3H, s), 6.95—7.05 (2H, m), 7.41—7.52 (1H, m), 7.81—7.88 (1H, m).

1-(4-Methylbenzoyl)-2-methylaziridine (2d) This compound was prepared from 4-methylbenzoyl chloride as described in the synthesis of **2a**, as an oil, yield 91%: ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, $J=5.5$ Hz), 2.12 (1H, d, $J=2.9$ Hz), 2.42 (3H, s), 2.50—2.62 (2H, m), 7.25 (2H, d, $J=8.1$ Hz), 7.92 (2H, d, $J=8.1$ Hz).

1-(3-Methylbenzoyl)-2-methylaziridine (2e) This compound was prepared from 3-methylbenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, $J=5.5$ Hz), 2.14 (1H, d, $J=3.3$ Hz), 2.41 (3H, s), 2.51—2.66 (2H, m), 7.32—7.39 (2H, m), 7.79—7.87 (2H, m).

1-(2-Methylbenzoyl)-2-methylaziridine (2f) This compound was prepared from 2-methylbenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, $J=5.5$ Hz), 2.08 (1H, d, $J=3.3$ Hz), 2.43—2.57 (5H, m), 7.20—7.31 (2H, m), 7.33—7.43 (1H, m), 7.89 (1H, d, $J=7.7$ Hz).

1-(4-Chlorobenzoyl)-2-methylaziridine (2g) This compound was prepared from 4-chlorobenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, $J=5.5$ Hz), 2.15 (1H, d, $J=2.9$ Hz), 2.51—2.66 (2H, m), 7.39—7.47 (2H, m), 7.93—8.01 (2H, m).

1-(3-Chlorobenzoyl)-2-methylaziridine (2h) This compound was prepared from 3-chlorobenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, $J=5.1$ Hz), 2.17 (1H, d, $J=3.3$ Hz), 2.53—2.68 (2H, m), 7.40 (1H, dd, $J=8.1$, 7.7 Hz), 7.53 (1H, ddd, $J=8.1$, 2.2, 1.5 Hz), 7.90 (1H, dt, $J=7.7$, 1.5 Hz), 8.00 (1H, dd, $J=2.2$, 1.5 Hz).

1-(2-Chlorobenzoyl)-2-methylaziridine (2i) This compound was prepared from 2-chlorobenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, $J=5.1$ Hz), 2.12 (1H, d, $J=3.3$ Hz), 2.53 (1H, d, $J=5.5$ Hz), 2.56—2.68 (1H, m), 7.28—7.48 (3H, m), 7.75—7.81 (1H, m).

1-(4-Fluorobenzoyl)-2-methylaziridine (2j) This compound was prepared from 4-fluorobenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, $J=5.2$ Hz), 2.14—2.15 (1H, m), 2.52—2.63 (2H, m), 7.08—7.19 (2H, m), 8.00—8.10 (2H, m).

1-(3-Fluorobenzoyl)-2-methylaziridine (2k) This compound was prepared from 3-fluorobenzoyl chloride as described in the synthesis of **2a**, as an oil, yield 77%: ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, $J=5.5$ Hz), 2.16 (1H, d, $J=3.3$ Hz), 2.52—2.68 (2H, m), 7.25 (1H, ddd, $J=8.4$, 2.6, 1.1 Hz), 7.43 (1H, ddd, $J=8.1$, 7.7, 5.5 Hz), 7.69 (1H, ddd, $J=8.1$, 2.6, 1.5 Hz), 7.81 (1H, ddd, $J=7.7$, 1.5, 1.1 Hz).

1-[4-(1,1-Dimethylethyl)benzoyl]-2-methylaziridine (2l) This compound was prepared from 4-*tert*-butylbenzoyl chloride as described in the synthesis of **2a**, as an oil, yield quant.: ^{1}H-NMR ($CDCl_3$) δ: 1.35 (9H, s), 1.41 (3H, d, $J=5.5$ Hz), 2.12 (1H, d, $J=2.9$ Hz), 2.51—2.64 (2H, m), 7.47 (2H, d, $J=8.8$ Hz), 7.96 (2H, d, $J=8.8$ Hz).

1-(4-Methoxyphenyl)-2-(4-pyridyl)ethanone (4a) Under argon atmosphere, a solution of diisopropylamine (46.3 ml) in THF (300 ml) was cooled to −78 °C and a solution of 1.6 M *n*-butyllithium in hexane (208 ml) was added dropwise to the solution. After addition, the solution was stirred for 10 min and a solution of 4-methylpyridine (**3**) (28.3 ml) in THF (30 ml) was added dropwise to the LDA solution. The reaction mixture was allowed to warm up to −10 °C and stirred for 20 min. The resulting mixture was cooled to −78 °C and a solution of **2a** (57.4 g) in THF (30 ml) was added dropwise to the mixture. After addition, the mixture was stirred for 1 h at −78 °C, and then the reaction mixture was allowed to warm to room temperature. Water (300 ml) was added to the mixture and the organic phase was separated. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried and concentrated to give a crude crystal. This was recrystallized from ethyl acetate to afford 36.5 g (yield 54%) of **4a** as a solid, mp 103—104 °C, ^{1}H-NMR ($CDCl_3$) δ: 3.88 (3H, s), 4.24 (2H, s), 6.96 (2H, d, $J=9.0$ Hz), 7.21 (2H, d, $J=6.0$ Hz), 7.98 (2H, d, $J=9.0$ Hz), 8.56 (2H, d, $J=6.2$ Hz).

1-(4-Methoxyphenyl)-2-(3-pyridyl)ethanone (4b) This compound was prepared from **2a** and 3-methylpyridine as described in the synthesis of **4a** as a solid, yield 85%, mp 71—72 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 3.88 (3H, s), 4.25 (2H, s), 6.96 (2H, d, $J=8.8$ Hz), 7.29 (1H, d, $J=4.8$ Hz), 7.59—7.63 (1H, m), 8.01 (2H, d, $J=8.8$ Hz), 8.50—8.52 (2H, m).

1-(4-Methoxyphenyl)-2-(2-pyridyl)ethanone (4c) This compound was prepared from **2a** and 2-methylpyridine as described in the synthesis of **4a** as a solid, yield 66%, mp 103—104 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s), 4.45 (2H, s), 6.93 (2H, d, $J=8.8$ Hz), 7.17 (1H, dd, $J=7.3$, 4.8 Hz), 7.31 (1H, d, $J=8.1$ Hz), 7.64 (1H, ddd, $J=8.1$, 7.3, 1.3 Hz), 8.06 (2H, d, $J=8.8$ Hz), 8.56 (1H, dd, $J=4.8$, 1.8 Hz).

1-(3-Methoxyphenyl)-2-(4-pyridyl)ethanone (4d) This compound was prepared from **2b** as described in the synthesis of **4a** as an oil, yield 44%, ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s), 4.28 (2H, s), 7.14 (1H, ddd, $J=8.1$, 2.6, 1.1 Hz), 7.20 (2H, d, $J=6.2$ Hz), 7.36 (1H, dd, $J=8.1$, 7.7 Hz), 7.51 (1H, dd, $J=2.6$, 1.5 Hz), 7.58 (1H, ddd, $J=7.7$, 1.5, 1.1 Hz), 8.57 (2H, d, $J=6.2$ Hz).

1-(2-Methoxyphenyl)-2-(4-pyridyl)ethanone (4e) This compound was prepared from **2c** as described in the synthesis of **4a** as an oil, yield 59%, ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 4.30 (2H, s), 6.95—7.07 (2H, m), 7.17 (2H, d, $J=5.9$ Hz), 7.50 (1H, ddd, $J=8.4$, 7.3, 1.8 Hz), 7.73 (1H, dd, $J=7.7$, 1.8 Hz), 8.53 (2H, d, $J=5.9$ Hz).

1-(4-Methylphenyl)-2-(4-pyridyl)ethanone (4f) This compound was

prepared from **2d** as described in the synthesis of **4a** as a solid, yield 70%, mp 110—111 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 4.26 (2H, s), 7.20 (2H, d, J=5.9 Hz), 7.29 (2H, d, J=8.1 Hz), 7.90 (2H, d, J=8.1 Hz), 8.56 (2H, d, J=5.9 Hz).

1-(3-Methylphenyl)-2-(4-pyridyl)ethanone (4g) This compound was prepared from **2e** as described in the synthesis of **4a** as a solid, yield 65%, mp 115—116 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 4.28 (2H, s), 7.20 (2H, dd, J=4.4, 1.8 Hz), 7.32—7.46 (2H, m), 7.76—7.83 (2H, m), 8.56 (2H, dd, J=4.4, 1.8 Hz).

1-(2-Methylphenyl)-2-(4-pyridyl)ethanone (4h) This compound was prepared from **2f** as described in the synthesis of **4a** as an oil, yield 58%, ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 4.23 (2H, s), 7.19 (2H, d, J=6.2 Hz), 7.24—7.47 (3H, m), 7.73 (1H, d, J=7.7 Hz), 8.56 (2H, d, J=6.2 Hz).

1-(4-Chlorophenyl)-2-(4-pyridyl)ethanone (4i) This compound was prepared from **2g** as described in the synthesis of **4a** as a solid, yield 56%, mp 93—94 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 4.26 (2H, s), 7.19 (2H, d, J=6.2 Hz), 7.47 (2H, d, J=8.6 Hz), 7.94 (2H, d, J=8.6 Hz), 8.58 (2H, d, J=6.2 Hz).

1-(3-Chlorophenyl)-2-(4-pyridyl)ethanone (4j) This compound was prepared from **2h** as described in the synthesis of **4a** as a solid, yield 75%, mp 79—80 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 4.27 (2H, s), 7.19 (2H, d, J=6.0 Hz), 7.44 (1H, dd, J=7.9, 7.7 Hz), 7.58 (1H, ddd, J=7.9, 1.8, 1.0 Hz), 7.87 (1H, ddd, J=7.7, 1.8, 1.0 Hz), 7.97 (1H, t, J=1.8 Hz), 8.58 (2H, d, J=6.0 Hz).

1-(2-Chlorophenyl)-2-(4-pyridyl)ethanone (4k) This compound was prepared from **2i** as described in the synthesis of **4a** as an oil, yield 79%, ^{1}H-NMR ($CDCl_3$) δ: 4.28 (2H, s), 7.20 (2H, d, J=6.2 Hz), 7.28—7.39 (1H, m), 7.41—7.48 (3H, m), 8.56 (2H, d, J=6.2 Hz).

1-(4-Fluorophenyl)-2-(4-pyridyl)ethanone (4l) This compound was prepared from **2j** as described in the synthesis of **4a** as a solid, yield 56%, mp 93—94 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 4.27 (2H, s), 7.12—7.21 (4H, m), 8.00—8.07 (2H, m), 8.56—8.59 (2H, m).

1-(3-Fluorophenyl)-2-(4-pyridyl)ethanone (4m) This compound was prepared from **2k** as described in the synthesis of **4a** as an amorphous solid, yield 80%, ^{1}H-NMR ($CDCl_3$) δ: 4.28 (2H, s), 7.20 (2H, d, J=6.2 Hz), 7.33 (1H, ddd, J=8.1, 2.6, 1.1 Hz), 7.49 (1H, ddd, J=8.1, 7.7, 5.5 Hz), 7.68 (1H, ddd, J=9.5, 2.6, 1.5 Hz), 7.79 (1H, ddd, J=7.7, 1.5, 1.1 Hz), 8.58 (2H, d, J=6.2 Hz).

1-[4-(1,1-Dimethylethyl)phenyl]-2-(4-pyridyl)ethanone (4n) This compound was prepared from **2l** as described in the synthesis of **4a** as a solid, yield 43%, mp 75—76 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 1.34 (9H, s), 4.27 (2H, s), 7.21 (2H, d, J=6.2 Hz), 7.50 (2H, d, J=8.6 Hz), 7.94 (2H, d, J=8.6 Hz), 8.56 (2H, d, J=6.2 Hz).

2-Bromo-1-(4-methoxyphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5a) Bromine (1.6 ml, 31 mmol) was added dropwise to a solution of **4a** (7.0 g, 31 mmol) in acetic acid (30 ml) and the mixture was stirred for 3 h at 80 °C. The solvent was removed *in vacuo* and ethyl acetate was added to the residue. The resulting crystal was collected by filtration and washed with ethyl acetate to afford 11 g (yield 93%) of **5a** as a solid, ^{1}H-NMR (DMSO-d_6) δ: 3.89 (3H, s), 6.02 (1H, br s), 7.13 (2H, d, J=9.2 Hz), 7.28 (1H, s), 8.13 (2H, d, J=9.2 Hz), 8.18 (2H, d, J=6.6 Hz), 8.95 (2H, d, J=6.6 Hz).

2-Bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone Hydrobromide (5b) This compound was prepared from **4b** as described in the synthesis of **5a** as a solid, yield 89%, ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, s), 4.60 (1H, br s), 7.11 (2H, d, J=9.0 Hz), 7.16 (1H, s), 7.61—7.69 (1H, m), 8.11 (2H, d, J=9.0 Hz), 8.20 (1H, d, J=8.1 Hz), 8.65 (1H, dd, J=6.6, 4.8 Hz), 8.86 (1H, d, J=2.2 Hz).

2-Bromo-1-(4-methoxyphenyl)-2-(2-pyridyl)ethanone Hydrobromide (5c) This compound was prepared from **4c** as described in the synthesis of **5a** as a solid, yield 44%, ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s), 7.01 (2H, d, J=9.2 Hz), 7.16 (1H, s), 7.37 (1H, dd, J=7.3, 4.9 Hz), 7.56 (1H, br s), 7.74 (1H, d, J=7.7 Hz), 7.91 (1H, dd, J=7.7, 7.3 Hz), 7.98 (2H, d, J=9.2 Hz), 8.51 (1H, d, J=4.8 Hz).

2-Bromo-1-(3-methoxyphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5d) This compound was prepared from **4d** as described in the synthesis of **5a** as a crude oil and this compound was used for the next reaction without further purification.

2-Bromo-1-(2-methoxyphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5e) This compound was prepared from **4e** as described in the synthesis of **5a** as a solid, yield 57%, ^{1}H-NMR (DMSO-d_6) δ: 3.90 (3H, s), 4.57 (1H, br s), 6.92 (1H, s), 7.09 (1H, dd, J=7.7, 7.3 Hz), 7.20 (1H, d, J=8.4 Hz), 7.63 (1H, ddd, J=8.4, 7.3, 1.5 Hz), 7.71 (1H, dd, J=7.7, 1.5 Hz), 8.00 (2H, d, J=6.0 Hz), 8.87 (2H, d, J=6.6 Hz).

2-Bromo-1-(4-methylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5f) This compound was prepared from **4f** as described in the synthesis of **5a** as a solid, yield quant., ^{1}H-NMR (DMSO-d_6) δ: 2.41 (3H, s), 4.52 (1H, br s), 7.22 (1H, s), 7.41 (2H, d, J=8.1 Hz), 7.99 (2H, d, J=6.0 Hz), 8.03 (2H, d, J=8.1 Hz), 8.85 (2H, d, J=6.0 Hz).

2-Bromo-1-(3-methylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5g) This compound was prepared from **4g** as described in the synthesis of **5a** as a crude oil and this compound was used for the next reaction without further purification.

2-Bromo-1-(2-methylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5h) This compound was prepared from **4h** as described in the synthesis of **5a** as a solid, yield 77%, ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s), 5.34 (1H, br s), 7.20 (1H, s), 7.34—7.58 (3H, m), 8.03—8.14 (3H, m), 8.92 (2H, d, J=6.6 Hz).

2-Bromo-1-(4-chlorophenyl)-2-(4-pyridyl)ethanone Hydrobromide (5i) This compound was prepared from **4i** as described in the synthesis of **5a** as a solid, yield 93%, ^{1}H-NMR (DMSO-d_6) δ: 4.78 (1H, br s), 7.26 (1H, s), 7.70 (2H, d, J=8.6 Hz), 8.08 (2H, d, J=6.6 Hz), 8.15 (2H, d, J=8.6 Hz), 8.91 (2H, d, J=6.6 Hz).

2-Bromo-1-(3-chlorophenyl)-2-(4-pyridyl)ethanone Hydrobromide (5j) This compound was prepared from **4j** as described in the synthesis of **5a** as a solid, ^{1}H-NMR (DMSO-d_6) δ: 5.75 (1H, br s), 7.32 (1H, s), 7.65 (1H, t, J=8.1 Hz), 7.77—7.85 (1H, m), 8.05—8.12 (1H, m), 8.13—8.21 (3H, m), 8.95 (2H, d, J=6.6 Hz).

2-Bromo-1-(2-chlorophenyl)-2-(4-pyridyl)ethanone Hydrobromide (5k) This compound was prepared from **4k** as described in the synthesis of **5a** as a solid, yield 65%, ^{1}H-NMR (DMSO-d_6) δ: 5.68 (1H, br s), 7.44 (1H, s), 7.50—7.66 (3H, m), 7.90—8.06 (3H, m), 8.90 (2H, d, J=6.6 Hz).

2-Bromo-1-(4-fluorophenyl)-2-(4-pyridyl)ethanone Hydrobromide (5l) This compound was prepared from **4l** as described in the synthesis of **5a** as a solid, yield 81%, ^{1}H-NMR (DMSO-d_6) δ: 4.65 (1H, br s), 7.19 (1H, s), 7.43 (2H, t, J=8.8 Hz), 7.81—7.90 (2H, m), 8.19 (2H, dd, J=8.8, 5.4 Hz), 8.74—8.80 (2H, m).

2-Bromo-1-(3-fluorophenyl)-2-(4-pyridyl)ethanone Hydrobromide (5m) This compound was prepared from **4m** as described in the synthesis of **5a** as a solid, yield 66%, ^{1}H-NMR (DMSO-d_6) δ: 5.19 (1H, br s), 7.05 (1H, s), 7.58—7.75 (2H, m), 7.95—8.07 (2H, m), 8.26 (2H, d, J=6.2 Hz), 9.02 (2H, d, J=6.2 Hz).

2-Bromo-1-[4-(1,1-dimethylethyl)phenyl]-2-(4-pyridyl)ethanone Hydrobromide (5n) This compound was prepared from **4n** as described in the synthesis of **5a** as an amorphous solid, yield 96%, ^{1}H-NMR (DMSO-d_6) δ: 1.33 (9H, s), 5.81 (1H, br s), 7.28 (1H, s), 7.62 (2H, d, J=8.4 Hz), 8.09 (2H, d, J=8.4 Hz), 8.14 (2H, d, J=6.6 Hz), 8.93 (2H, d, J=6.6 Hz).

[4-(4-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6a) Thiourea (2.2 g, 31 mmol) was added to a mixture of **5a** (11 g, 28 mmol) in acetonitrile (170 ml), and then triethylamine (4.1 ml, 30 mmol) was added to the mixture. The resulting solution was refluxed for 3 h. The solvent was removed *in vacuo* and aqueous sodium hydrogen carbonate was added to the residue. The precipitate was collected by filtration and the resulting solid was washed with water and then ether. The crude crystal was recrystallized from ethanol to afford 5.5 g (yield 68%) of **6a** as a solid, mp 282—284 °C, ^{1}H-NMR (DMSO-d_6) δ: 3.77 (3H, s), 6.90 (2H, d, J=8.8 Hz), 7.08 (2H, d, J=6.2 Hz), 7.34 (2H, d, J=8.8 Hz), 7.38 (2H, br s), 8.38 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.37; H, 4.71; N, 14.80.

[4-(4-Methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine (6b) This compound was prepared from **5b** as described in the synthesis of **6a** as a solid, yield 90%, mp 265—266 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 3.75 (3H, s), 6.86 (2H, d, J=8.8 Hz), 7.20—7.36 (5H, m), 7.55—7.63 (1H, m), 8.35—8.43 (2H, m). *Anal.* Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.40; H, 4.86; N, 14.81.

[4-(4-Methoxyphenyl)-5-(2-pyridyl)-1,3-thiazol-2-yl]amine (6c) This compound was prepared from **5c** as described in the synthesis of **6a** as a solid, yield 55%, mp 217—218 °C (pyridine), ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 6.95 (2H, d, J=8.8 Hz), 7.00—7.09 (2H, m), 7.09 (2H, br s), 7.39 (2H, d, J=8.8 Hz), 7.45—7.53 (1H, m), 8.35—8.43 (1H, d, J=4.8 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.35; H, 4.59; N, 14.73.

[4-(3-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6d) This compound was prepared from **5d** as described in the synthesis of **6a** as a solid, yield 37%, mp 232—234 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 3.69 (3H, s), 6.87—6.97 (3H, m), 7.09 (2H, d, J=6.2 Hz), 7.24 (1H, dd, J=8.4, 7.3 Hz), 7.43 (2H, br s), 8.40 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.33; H, 4.70; N, 14.78.

[4-(2-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6e) This compound was prepared from **5e** as described in the synthesis of **6a** as a solid, yield 61%, mp 213—215 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 3.51 (3H, s), 6.88 (2H, d, J=6.2 Hz), 6.95—7.08 (2H, m), 7.26 (1H, dd, J=7.3, 1.8 Hz), 7.34—7.45 (3H, m), 8.28 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3OS \cdot 0.2H_2O$: C, 62.78; H, 4.71; N, 14.64. Found: C, 62.73; H, 4.82; N, 14.61.

[4-(4-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6f) This compound was prepared from **5f** as described in the synthesis of **6a** as a solid, yield 75%, mp 296—298 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s), 7.07 (2H, d, J=6.0 Hz), 7.15 (2H, d, J=8.1 Hz), 7.35 (2H, d, J=8.1 Hz), 7.39 (2H, br s), 8.37 (2H, d, J=6.0 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.13; H, 4.76; N, 15.63.

[4-(3-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6g) This compound was prepared from **5g** as described in the synthesis of **6a** as a solid, yield 72%, mp 255—258 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 2.27 (3H, s), 7.07 (2H, d, J=6.2 Hz), 7.10—7.29 (5H, m), 7.40 (1H, s), 8.37 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.26; H, 4.83; N, 15.60.

[4-(2-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6h) This compound was prepared from **5h** as described in the synthesis of **6a** as a solid, yield 42%, mp 235—238 °C (ethyl acetate), ^{1}H-NMR (DMSO-d_6) δ: 2.08 (3H, s), 6.80 (2H, d, J=6.2 Hz), 7.12—7.34 (4H, m), 7.47 (2H, br s), 8.26 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{13}N_3S \cdot 0.2H_2O$: C, 66.49; H, 4.98; N, 15.51. Found: C, 66.82; H, 5.04; N, 15.20.

[4-(4-Chlorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6i) This compound was prepared from **5i** as described in the synthesis of **6a** as a solid, yield 73%, mp >300 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 7.10 (2H, d, J=6.2 Hz), 7.40 (4H, s), 7.46 (2H, br s), 8.42 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{14}H_{10}ClN_3S$: C, 58.43; H, 3.50; N, 14.60. Found: C, 58.41; H, 3.57; N, 14.60.

[4-(3-Chlorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6j) This compound was prepared from **5j** as described in the synthesis of **6a** as a solid, yield 60%, mp 256—258 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 7.12 (2H, d, J=6.2 Hz), 7.27—7.42 (3H, m), 7.44—7.51 (3H, m), 8.43 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{14}H_{10}ClN_3S$: C, 58.43; H, 3.50; N, 14.60. Found: C, 58.35; H, 3.58; N, 14.51.

[4-(2-Chlorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6k) This compound was prepared from **5k** as described in the synthesis of **6a** as a solid, yield 24%, mp 232—235 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 7.14 (2H, d, J=5.7 Hz), 7.43—7.68 (4H, m), 8.15 (2H, br s), 8.46 (2H, d, J=5.7 Hz). *Anal.* Calcd for $C_{14}H_{10}ClN_3S$: C, 58.43; H, 3.50; N, 14.60. Found: C, 58.23; H, 3.72; N, 14.38.

4-(3-Fluorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-ylamine (6l) This compound was prepared from **5m** as described in the synthesis of **6a** as a solid, yield 86%, mp 263—264 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 7.11 (2H, d, J=6.3 Hz), 7.16—7.46 (6H, m), 8.43 (2H, d, J=6.3 Hz). *Anal.* Calcd for $C_{14}H_{10}FN_3S$: C, 61.98; H, 3.72; N, 15.49. Found: C, 61.78; H, 3.60; N, 15.20.

4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-ylamine (6m) This compound was prepared from **5n** as described in the synthesis of **6a** as a solid, yield 69%, mp 254—257 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.29 (9H, s), 7.10 (2H, d, J=6.2 Hz), 7.34 (6H, s), 8.38 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{18}H_{19}N_3S \cdot 0.5H_2O$: C, 67.89; H, 6.33; N, 13.20. Found: C, 67.77; H, 6.29; N, 12.86.

***N*-Methyl-[4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6n)** This compound was prepared from **5g** and *N*-methylthiourea as described in the synthesis of **6a** as a solid, yield 67%, mp 199—202 °C (ethanol), ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.81 (3H, d, J=4.4 Hz), 6.79 (1H, br s), 7.07 (2H, d, J=6.2 Hz), 7.16—7.25 (3H, m), 7.33 (1H, s), 8.39 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.23; H, 5.32; N, 15.06.

***N*-[4-(4-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7a)** Acetyl chloride (1.7 g, 21 mmol) was added to a solution of **6a** (4.0 g, 14 mmol) and DMAP (0.52 g, 4.2 mmol) in DMA (40 ml), and the resulting mixture was stirred at 80 °C for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and extracted with ethyl acetate. The extracts were washed with brine, dried and concentrated to give a solid. This was recrystallized from ethanol to afford 4.2 g (yield 92%) of **7a** as a solid, mp 282—284 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.78 (3H, s), 6.93 (2H, d, J=8.8 Hz), 7.26 (2H, d, J=6.2 Hz), 7.37 (2H, d, J=8.8 Hz), 8.50 (2H, d, J=6.2 Hz), 12.42 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.71; H, 4.77; N, 13.18.

***N*-[4-(4-Methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide (7b)** This compound was prepared from **6b** as described in the synthesis of **7a** as a solid, yield 82%, mp 119—120 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.66 (3H, s), 3.82 (3H, s), 6.86 (2H, d, J=8.8 Hz), 7.26 (1H, dd, J=8.2, 5.2 Hz), 7.40 (2H, d, J=8.8 Hz), 7.66 (1H, dt, J=8.2, 3.9 Hz), 8.54 (1H, dd, J=5.2, 1.6 Hz), 8.62 (1H, d, J=1.6 Hz), 11.51 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.38; H, 4.32; N, 12.67.

***N*-[4-(4-Methoxyphenyl)-5-(2-pyridyl)-1,3-thiazol-2-yl]acetamide (7c)** This compound was prepared from **6c** as described in the synthesis of **7a** as a solid, yield 29%, mp 230—232 °C (ethanol), ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, s), 3.85 (3H, s), 6.90—6.95 (2H, m), 7.08—7.14 (1H, m), 7.20—7.25 (1H, m), 7.44—7.51 (3H, m), 8.58—8.61 (1H, m), 10.78 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.57; H, 4.60; N, 12.99.

***N*-[4-(3-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7d)** This compound was prepared from **6d** as described in the synthesis of **7a** as a solid, yield 70%, mp 234—236 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.68 (3H, s), 6.89—7.02 (3H, m), 7.22—7.33 (3H, m), 8.52 (2H, d, J=6.2 Hz), 12.46 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3O_2S \cdot 0.3H_2O$: C, 61.73; H, 4.75; N, 12.70. Found: C, 61.99; H, 5.10; N, 12.38.

***N*-[4-(2-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7e)** This compound was prepared from **6e** as described in the synthesis of **7a** as a solid, yield 54%, mp 259—261 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.45 (3H, s), 6.97—7.12 (4H, m), 7.28—7.47 (2H, m), 8.41 (2H, d, J=6.2 Hz), 12.40 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.60; H, 4.65; N, 12.90.

***N*-[4-(4-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7f)** This compound was prepared from **6f** as described in the synthesis of **7a** as a solid, yield 54%, mp 308—309 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 2.33 (3H, s), 7.18 (2H, d, J=7.9 Hz), 7.26 (2H, d, J=6.0 Hz), 7.33 (2H, d, J=7.9 Hz), 8.50 (2H, d, J=6.0 Hz), 12.44 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 65.96; H, 4.76; N, 13.42.

***N*-[4-(3-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7g)** This compound was prepared from **6g** as described in the synthesis of **7a** as a solid, yield 68%, mp 287—289 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 2.28 (3H, s), 7.14—7.35 (6H, m), 8.50 (2H, d, J=6.2 Hz), 12.45 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 66.06; H, 4.78; N, 13.68.

***N*-[4-(2-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7h)** This compound was prepared from **6h** as described in the synthesis of **7a** as a solid, yield 56%, mp 272—274 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.06 (3H, s), 2.20 (3H, s), 7.03 (2H, d, J=6.0 Hz), 7.15—7.42 (4H, m), 8.39 (2H, d, J=6.0 Hz), 12.39 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 65.87; H, 4.84; N, 13.63.

***N*-[4-(4-Chlorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7i)** This compound was prepared from **6i** as described in the synthesis of **7a** as a solid, yield 73%, mp 317—320 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 7.28 (2H, d, J=6.0 Hz), 7.45 (4H, s), 8.53 (2H, d, J=6.0 Hz), 12.49 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}ClN_3OS \cdot 0.2H_2O$: C, 57.64; H, 3.75; N, 12.60. Found: C, 57.87; H, 3.80; N, 12.41.

***N*-[4-(3-Chlorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7j)** This compound was prepared from **6j** as described in the synthesis of **7a** as a solid, yield 57%, mp 290—293 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 7.30 (2H, d, J=6.2 Hz), 7.32—7.46 (3H, m), 7.50 (1H, s), 8.55 (2H, d, J=6.2 Hz), 12.49 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.10; H, 3.72; N, 12.75.

***N*-[4-(2-Chlorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7k)** This compound was prepared from **6k** as described in the synthesis of **7a** as a solid, yield 47%, mp 292—293 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 7.06 (2H, d, J=6.2 Hz), 7.40—7.62 (4H, m), 8.38 (2H, d, J=6.2 Hz), 12.47 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.27; H, 3.53; N, 12.75.

***N*-[4-(3-Fluorophenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7l)** This compound was prepared from **6l** as described in the synthesis of **7a** as a solid, yield 82%, mp 326—328 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 7.16—7.46 (6H, m), 8.54 (2H, d, J=5.8 Hz), 12.46 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}FN_3OS$: C, 61.33; H, 3.86; N, 13.41. Found: C, 61.24; H, 3.91; N, 13.14.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7m)** This compound was prepared from **6m** as described in the synthesis of **7a** as a solid, yield 50%, mp 280—281 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.29 (9H, s), 2.20 (3H, s), 7.28 (2H, d, J=6.0 Hz), 7.38 (4H, s), 8.51 (2H, d, J=6.0 Hz), 12.41 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}N_3OS$: C,

68.35; H, 6.02; N, 11.96. Found: C, 68.34; H, 5.99; N, 11.95.

***N*-Methyl-*N*-[4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7n)** This compound was prepared from **6n** as described in the synthesis of **7a** as a solid, yield 64%, mp 169—170 °C (ethanol), ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.46 (3H, s), 3.79 (3H, s), 7.12—7.29 (5H, m), 7.37 (1H, s), 8.50 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.88; H, 5.26; N, 12.98.

4-(Methylthio)benzenecarbothioamide (13a) *O*,*O*-Diethyl hydrogen dithiophosphate (15 ml, 88 mmol) was added to a solution of 4-methylthiobenzonitrile (12 g, 80 mmol) in a solution of 4 N hydrogen chloride in ethyl acetate (130 ml) and the mixture was stirred for 22 h at room temperature. The reaction mixture was washed with brine (100 ml) twice and aqueous sodium hydrogen carbonate. The organic phase was dried and concentrated to give a residue. This was recrystallized from ethyl acetate to afford 10 g (yield 67%) of **13a** as a solid, mp 176—178 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.51 (3H, s), 7.27 (2H, d, J=8.4 Hz), 7.88 (2H, d, J=8.4 Hz), 9.42 (1H, br s), 9.77 (1H, br s).

Methyl 4-(Aminothioxomethyl)benzoate (13b) This compound was prepared from methyl 4-cyanobenzoate as described in the synthesis of **13a** as a solid, yield 85%, mp 191—192 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 7.21 (1H, br s), 7.67 (1H, br s), 7.91 (2H, d, J=8.6 Hz), 8.07 (2H, d, J=8.6 Hz).

2-Methylbenzenecarbothioamide (13c) This compound was prepared from 2-methylbenzonitrile as described in the synthesis of **13a** as an oil, yield 54%, ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 6.88 (1H, br s), 7.06—7.23 (3H, m), 7.24—7.31 (1H, m), 7.88 (1H, br s).

3-Methylbenzenecarbothioamide (13d) This compound was prepared from 3-methylbenzonitrile as described in the synthesis of **13a** as a solid, yield 72%, mp 88—89 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 7.18 (1H, br s), 7.24—7.36 (2H, m), 7.62 (1H, dt, J=6.2, 1.8 Hz), 7.70 (1H, br s), 7.88 (1H, br s).

4-Methylbenzenecarbothioamide (13e) This compound was prepared from 4-methylbenzonitrile as described in the synthesis of **13a** as a solid, yield 62%, mp 172—174 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 7.15 (1H, br s), 7.21 (2H, d, J=8.1 Hz), 7.57 (1H, br s), 7.79 (2H, d, J=8.1 Hz).

4-Hydroxybenzenecarbothioamide (13f) This compound was prepared from 4-hydroxybenzonitrile as described in the synthesis of **13a** as a solid, yield 39%, mp 206—207 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 6.75 (2H, d, J=8.8 Hz), 7.86 (2H, d, J=8.8 Hz), 9.21 (1H, br s), 9.52 (1H, br s), 10.09 (1H, br s).

2,2-Dimethylpropanethioamide (13g) This compound was prepared from 2,2-dimethylpropionitrile as described in the synthesis of **13a** as a solid, yield 19%, mp 117—119 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 1.38 (9H, s), 7.04 (1H, br s), 7.86 (1H, br s).

2-Ethyl-4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazole (8a) Thiopropionamide (0.53 g, 5.9 mmol) was added to a suspension of **5g** (2.0 g, 5.4 mmol) in DMF (6.0 ml) and the resulting mixture was stirred at room temperature for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and extracted with ethyl acetate. The extracts were washed with brine, dried, and concentrated to give a solid. This was recrystallized from ethanol to afford 8.9 g (yield 59%) of **8a** as a solid, mp 56—58 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7.6 Hz), 2.33 (3H, s), 3.09 (2H, q, J=7.6 Hz), 7.11—7.24 (5H, m), 7.37 (1H, s), 8.51 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.63; H, 5.94; N, 9.90.

2-(1,1-Dimethylethyl)-4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazole (8b) This compound was prepared from **5g** and **13g** as described in the synthesis of **8a** as a solid, yield 53%, mp 140—142 °C (ethyl acetate), ^{1}H-NMR ($CDCl_3$) δ: 1.51 (9H, s), 2.33 (3H, s), 7.14—7.22 (5H, m), 7.38 (1H, s), 8.49—8.52 (2H, m). *Anal.* Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found; C, 73.65; H, 6.44; N, 9.09.

2-Methyl-4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazole (8c) This compound was prepared from **5g** and thioacetamide as described in the synthesis of **8a** as a solid, yield 20%, mp 74—75 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.78 (3H, s), 7.11—7.23 (5H, m), 7.37 (1H, s), 8.51 (2H, d, J=5.9 Hz). *Anal.* Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52. Found: C, 72.05; H, 5.18; N, 10.34.

4-(3-Methylphenyl)-2-phenyl-5-(4-pyridyl)-1,3-thiazole (8d) This compound was prepared from **5g** and thiobenzamide as described in the synthesis of **8a** as a solid, yield 74%, mp 118—120 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s), 7.14—7.38 (5H, m), 7.43—7.50 (3H, m), 7.46 (1H, s), 7.99—8.09 (2H, m), 8.54 (2H, d, J=4.6 Hz). *Anal.* Calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 77.01; H, 5.14; N, 8.34.

2-(2-Methylphenyl)-4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazole (8e) This compound was prepared from **5g** and **13c** as described in the synthesis of **8a** as a paste, yield 68%, ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.70 (3H, s), 7.14—7.38 (8H, m), 7.46 (1H, s), 7.81 (1H, ddd, J=6.6, 1.8, 1.1 Hz), 8.56 (2H, d, J=6.0 Hz). *Anal.* Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 76.95; H, 5.07; N, 8.05.

2-(3-Methylphenyl)-4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazole (8f) This compound was prepared from **5g** and **13d** as described in the synthesis of **8a** as a solid, yield 76%, mp 86—87 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.44 (3H, s), 7.17—7.31 (6H, m), 7.36 (1H, dd, J=7.7, 7.3 Hz), 7.46 (1H, s), 7.80 (1H, d, J=7.3 Hz), 7.87 (1H, s), 8.54 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.19; H, 5.37; N, 8.21.

2-(4-Methylphenyl)-4-(3-methylphenyl)-5-(4-pyridyl)-1,3-thiazole (8g) This compound was prepared from **5g** and **13e** as described in the synthesis of **8a** as a solid, yield 72%, mp 138—139 °C (ethyl acetate), ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.42 (3H, s), 7.14—7.32 (7H, m), 7.46 (1H, s), 7.91 (2H, d, J=8.1 Hz), 8.54 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 76.96; H, 5.38; N, 8.13.

4-[4-(3-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]phenol (8h) This compound was prepared from **5g** and **13f** as described in the synthesis of **8a** as a solid, yield 78%, mp 248—249 °C (THF), ^{1}H-NMR (DMSO-d_6) δ: 2.30 (3H, s), 7.00 (2H, d, J=8.6 Hz), 7.17—7.28 (3H, m), 7.30 (2H, d, J=5.7 Hz), 7.39 (1H, s), 7.84 (2H, d, J=8.6 Hz), 8.54 (2H, d, J=5.7 Hz), 10.13 (1H, s). *Anal.* Calcd for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13. Found: C, 73.34; H, 4.61; N, 7.90.

4-(3-Methylphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1,3-thiazole (8i) This compound was prepared from **5g** and **13a** as described in the synthesis of **8a** as a solid, yield 45%, mp 101—102 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.54 (3H, s), 7.16—7.34 (7H, m), 7.45 (1H, s), 7.94 (2H, d, J=8.8 Hz), 8.54 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{22}H_{18}N_2S_2$: C, 70.55; H, 4.84; N, 7.48. Found: C, 70.55; H, 4.96; N, 7.74.

Methyl 4-[4-(3-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]benzoate (8j) This compound was prepared from **5g** and **13b** as described in the synthesis of **8a** as a solid, yield 58%, mp 152—153 °C (ethanol), ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 3.96 (3H, s), 7.19—7.27 (3H, m), 7.28 (2H, d, J=6.2 Hz), 7.46 (1H, s), 8.09 (2H, d, J=8.8 Hz), 8.15 (2H, d, J=8.8 Hz), 8.57 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{23}H_{18}N_2O_2S$: C, 71.48; H, 4.69; N, 7.25. Found: C, 71.39; H, 4.60; N, 6.99.

4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1,3-thiazole (8k) This compound was prepared from **5l** and **13a** as described in the synthesis of **8a** as a solid, yield 84%, mp 115—118 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s), 7.06 (2H, t, J=8.8 Hz), 7.25 (2H, d, J=6.2 Hz), 7.30 (2H, d, J=8.2 Hz), 7.55 (2H, dd, J=8.8, 5.5 Hz), 7.92 (2H, d, J=8.2 Hz), 8.57 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{21}H_{15}FN_2S_2$: C, 66.64; H, 3.99; N, 7.40. Found: C, 66.56; H, 4.05; N, 7.33.

4-(3-Methylphenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1,3-thiazole (9) A solution of potassium persulfate (0.64 g, 2.4 mmol) in water (20 ml) was added to a solution of **8i** (0.80 g, 2.1 mmol) in acetic acid (30 ml) and the mixture was stirred for 14 h at room temperature. The solvent was removed *in vacuo*. Aqueous sodium hydrogen carbonate was added to the reaction mixture and extracted with ethyl acetate. The extracts were washed with water, dried, and concentrated to give a crude crystal. This was recrystallized from ethyl acetate to afford 0.48 g (1.2 mmol, yield 58%) of **9** as a solid, mp 188—189 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.37 (3H, s), 2.79 (3H, s), 7.20—7.32 (5H, m), 7.46 (1H, s), 7.76 (2H, d, J=8.6 Hz), 8.19 (2H, d, J=8.6 Hz), 8.57 (2H, d, J=8.6 Hz). *Anal.* Calcd for $C_{22}H_{18}N_2OS_2$: C, 67.66; H, 4.65; N, 7.17. Found: C, 67.36; H, 4.73; N, 7.11.

4-(3-Methylphenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)-1,3-thiazole (10a) To a solution of **8i** (0.80 g, 2.1 mmol) in DMF (8.0 ml) was added *m*CPBA (0.90 g, 3.7 mmol) at 0 °C and the mixture was stirred at room temperature for 3 h. An 8 N aqueous sodium hydroxide was added to the reaction mixture and extracted with ethyl acetate. The extracts were washed with brine, dried, and concentrated to give a residue. The residue was chromatographed on silica gel eluting with hexane–ethyl acetate (3 : 7) to give a crude crystal. This was recrystallized from ethyl acetate–isopropyl ether to afford 0.54 g (1.3 mmol, yield 63%) of **10a** as a solid, mp 171—174 °C, ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 3.11 (3H, s), 7.18—7.32 (5H, m), 7.45 (1H, s), 8.05 (2H, d, J=8.4 Hz), 8.22 (2H, d, J=8.4 Hz), 8.58 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{22}H_{18}N_2O_2S_2$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.96; H, 4.41; N, 7.02.

4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)-1,3-thia-

zole (10b) This compound was prepared from **8k** as described in the synthesis of **10a** as a solid, yield 71%, mp 191—194 °C (ethyl acetate), ^{1}H-NMR ($CDCl_3$) δ: 3.12 (3H, s), 7.08 (2H, t, J=8.8 Hz), 7.28 (2H, d, J=6.0 Hz), 7.57 (2H, dd, J=8.8, 5.5 Hz), 8.06 (2H, d, J=8.8 Hz), 8.22 (2H, d, J=8.8 Hz), 8.62 (2H, d, J=6.0 Hz). *Anal.* Calcd for $C_{21}H_{15}FN_2O_2S_2$: C, 61.45; H, 3.68; N, 6.82. Found: C, 61.25; H, 3.69; N, 6.64.

4-[4-(3-Methylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]benzoic Acid (11) A mixture of **8j** (1.0 g, 2.6 mmol) in ethanol (5.2 ml) and 1 N aqueous sodium hydroxide (5.2 ml, 5.2 mmol) was stirred at room temperature for 2 h. The reaction solution was acidified with 2 N hydrochloric acid and the precipitate was collected by filtration. The crude crystal was washed with water and ethanol. The crystal was dried to afford 0.72 g (yield 74%) of **11** as a solid, mp 335—336 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s), 7.22—7.30 (3H, m), 7.37 (2H, d, J=5.5 Hz), 7.44 (1H, s), 8.09 (2H, d, J=8.6 Hz), 8.16 (2H, d, J=8.6 Hz), 8.60 (2H, d, J=5.5 Hz). *Anal.* Calcd for $C_{22}H_{16}N_2O_2S$: C, 70.95; H, 4.33; N, 7.52. Found: C, 70.91; H, 4.31; N, 7.45.

4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]pyridine 1-Oxide (12) To a solution of **8a** (2.8 g, 10 mmol) in DMF (50 ml) was added *m*CPBA (3.0 g, 12 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and extracted with ethyl acetate. The extracts were washed with brine, dried, and concentrated to give a solid. The crude crystal was washed with hexane to afford 2.2 g (yield 74%) of **12** as a solid, mp 143—144 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.6 Hz), 2.35 (3H, s), 3.09 (2H, q, J=7.6 Hz), 7.13—7.26 (5H, m), 7.36 (1H, s), 8.06—8.10 (2H, m). *Anal.* Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.90; H, 5.41; N, 9.62.

Biological Methods. p38 MAP Kinase Assays. Preparation of Recombinant p38 cDNAs encoding human p38α[19] were isolated by polymerase chain reaction (PCR) with primers containing sequences encoding a FLAG-tag (DYKDDDDK) in the amino-terminal region and subcloned into pFASTBAC1 (Life Technologies, U.S.A.). cDNAs encoding human MKK3[20] and MKK6[21] were isolated by PCR and subcloned into pT7Blue-T vector (Novagen, Germany). Ser^{189} and Thr^{193} of MKK3 and Ser^{151} and Thr^{155} of MKK6 were substituted with Glu using a QuickChange Site-Directed Mutagenesis Kit (Stratagene, U.S.A.) and subcloned into pFASTBAC1 (Life Technologies, U.S.A.). Recombinant baculoviruses were prepared according to the procedure of the Bac-to-Bac baculovirus expression system (Life Technologies, U.S.A.). For the preparation of active-type p38α, Sf21 cells were infected with both p38α and constitutive active MKK3 recombinant baculoviruses. Infected Sf21 cells were cultured at 28 °C for 72 h, and then harvested by centrifugation. Cells were lysed and FLAG-tagged p38 proteins were purified by affinity chromatography using anti-FLAG M2 affinity gel (Sigma, U.S.A.).

***In Vitro* Phosphorylation Assay** Kinase reactions of purified human p38 MAP kinase α were performed at 30 °C for 1 h in kinase reaction buffer (25 mmol/l HEPES, pH 7.5, 10 mmol/l magnesium acetate, 1 mmol/l dithiothreitol) containing 0.1 μCi [γ-^{32}P]ATP, 500 nmol/l ATP, and myelin basic protein (MBP) (Upstate Biotechnology, U.S.A.). The kinase reactions were terminated by the addition of 10% trichloroacetic acid (Wako, Japan). Phosphorylated proteins were filtrated through GF/C filter plates (Packard, U.S.A.) with a Cell harvester (Packard, U.S.A.), washing out free [γ-^{32}P]-ATP with 250 mmol/l phosphoric acid. The plates were then incubated for 60 min at 45 °C, followed by the addition of 40 μl of MicroScint-O (Packard, U.S.A.). Radioactivity was counted using a Top-count scintillation counter (Packard, U.S.A.).

THP-1 TNF-α Release Assay THP-1 cells were suspended in RPMI1640 medium (Nikken Bio Medical Lab., Japan) containing 1% fetal bovine serum and 50 μg/ml gentamicin. Aliquots of 1×10^5 cells were seeded in 96-well plates (Corning Coster, U.S.A.), incubated with test compounds for 1 h, and subsequently stimulated with 5 μg/ml LPS (Wako, Japan) for 4 h. After centrifugation, the quantity of TNF-α in the medium was measured using a human TNF-α ELISA kit (Diaclone, France). A cell viability assay was performed using an oxidation-reduction indicator, AlamarBlue (Trec Diagnostic Systems, U.S.A.).

Mouse TNF-α Release Assay BALB/c mice (female, 7 weeks old, Charles River, Japan) were orally administered the tested compound at 30 min before intraperitoneal challenge with LPS (Sigma, U.S.A.). Ninety minutes later, blood samples were collected from the eye ground into heparinized tubes. Plasma was obtained by centrifugation and assayed for TNF-α by ELISA using a mouse TNF-α ELISA Kit (Amersham Pharmacia Biotech, U.K.).

Anti-collagen Antibody-Induced Arthritis Assay Anti-collagen antibody-induced arthritis was induced in 7-week-old female BALB/c mice (n=6). Monoclonal anti-collagen antibody was injected (2 mg/mouse, i.v.) on day 0, and then each mouse was injected with LPS (0.025 mg/mouse, i.p.) on day 3. Hind paw thickness was determined on day 0, 3, 7 and 11. Drugs (10, 30 or 50 mg/kg/day *p.o.*) and a vehicle (0.5% methyl cellulose solution in distilled water) were administered from day 0 to day 10.

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