Novel Inhibitor of p38 MAP Kinase as an Anti-TNF-α Drug: Discovery of *N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (TAK-715) as a Potent and Orally Active Anti-Rheumatoid Arthritis Agent

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The p38 mitogen-activated protein (MAP) kinase has been implicated in the proinflammatory cytokine signal pathway, and its inhibitors are potentially useful for the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease. To develop a new drug for RA, we synthesized a novel series of 4-phenyl-5-pyridyl-1,3-thiazoles and evaluated their inhibition of p38 MAP kinase, lipopolysaccharide (LPS)-stimulated release of tumor necrosis factor-α (TNF-α) from human monocytic THP-1 cells in vitro, and LPS-induced TNF-α production in vivo in mice. During the course of the study, we found that these compounds risk the inhibition of cytochrome P450 (CYP) isoforms by coordination of the 4-pyridyl nitrogen with heme iron. We therefore investigated the effects of substitution at the 2-position of the pyridyl ring on the inhibitory activity of p38 MAP kinase and CYPs in more detail. As a result, *N*-[4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (**8h**, TAK-715) exhibited potent inhibitory activity in these assays (inhibition of p38α, IC_{50} = 7.1 nM; LPS-stimulated release of TNF-α from THP-1, IC_{50} = 48 nM; LPS-induced TNF-α production in mice, 87.6% inhibition at 10 mg/kg, po) and no inhibitory activity for major CYPs, including CYP3A4. This compound also showed good bioavailability in mice and rats and significant efficacy in a rat adjuvant-induced arthritis model. Compound **8h** was selected as a clinical candidate and is now under clinical investigation for the treatment of RA.

Introduction

Rheumatoid arthritis (RA), which affects about 1% of the world's population, is a serious, chronic, and systemic inflammatory disease characterized by inflammation and progressive joint destruction. The drug treatment to date has primarily focused on the use of nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). More recently, novel biological products (the chimeric tumor necrosis factor-α (TNF-α) antibody infliximab,[1−3] the soluble TNF-α receptor etanercept,[4] and interleukin-1 (IL-1)-receptor antagonist anakinra[5]) that modify proinflammatory cytokines have gained clinical approval. These biological drugs have shown that lowering proinflammatory cytokine levels is a valid treatment for RA patients, but there are drawbacks related to patient cost, production efficiency, and administration by injection. Therefore, attention in inflammation research has focused on the development of orally active small molecular inhibitors of cytokine release. TNF-α and IL-1β are proinflammatory cytokines implicated as causal agents in the onset and progression of bone and joint destruction and are regulated by a mitogen-activated protein (MAP) kinase known as p38. Indeed, selective inhibitors of this kinase, such as the prototypical SB 203580, potently suppress the release of these proinflammatory cytokines and are presently under investigation in clinical trials.[6,7]

In a previous paper,[8] we reported the development of p38 MAP kinase inhibitors that contain a pyridyl thiazole core (Figure 1). Although compound **1** had desirable p38 MAP kinase and TNF-α inhibitory activity, it was also a potent inhibitor of cytochrome P450 (CYP) 3A4, CYP2C9 and CYP2C19, a property that would dramatically complicate its clinical use due to the potential for serious drug−drug interactions and hepatotoxicity.[9]

It was previously reported that nitrogen-containing heterocycles, such as imidazole and pyridine, are known to be good ligands for ferric ion, the heme iron of CYPs, and compounds with such a heterocyclic moiety are often potent inhibitors of CYPs.[10] The GSK group reported that the introduction of a methyl group adjacent to pyridyl nitrogen in pyridylimidazole derivatives reduced CYP2D6 affinity, but this modification lowered the oral activity.[11] The Aventis group reported that RPR 203494, a 2-cyclopropylamino-pyrimidine analogue, showed good potency and had no inhibitory effect on CYP2D6, CYP1A2, and CYP2C9 up to 50 μM.[12] Recently the Eberhard-Karls University Tübingen and Merckle GmbH group reported that the combination of substituents at the pyridine C2 and imidazole N1 positions resulted in almost no interference with CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[13]

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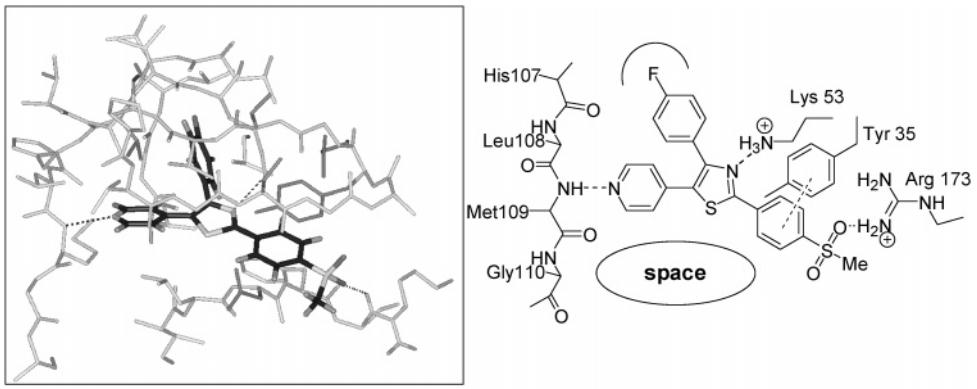
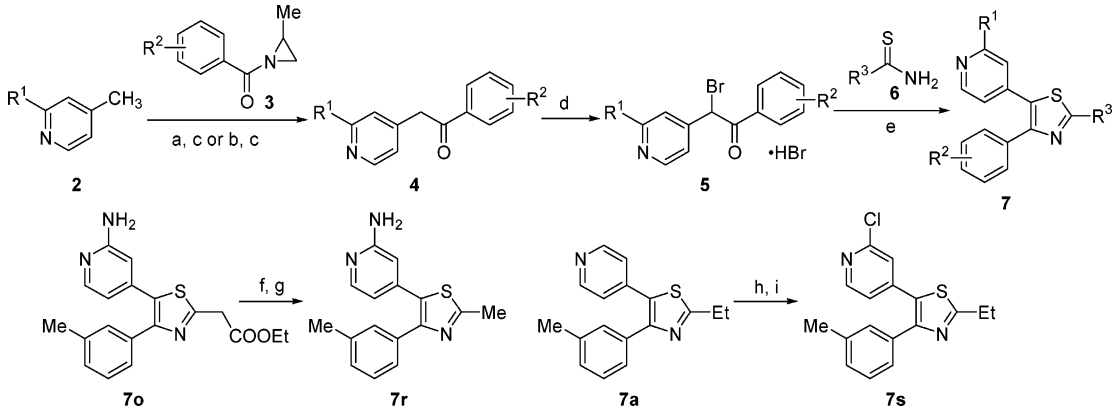


Figure 1. Docking model of compound **1** with p38 MAP kinase.

Scheme 1. Synthesis of 4-Phenyl-5-pyridyl-1,3-thiazoles **7**[a]



[a] Reagents: (a) LDA, hexane, THF, −78 °C and then −20 °C; (b) ^{n}BuLi (2 equiv), hexane, THF, −78 °C and then 0 °C; (c) **3**, −78 °C; (d) Br_2, AcOH, 70 °C; (e) **6**, DMF, 80 °C; (f) NaOH (aq), EtOH; (g) 150 °C; (h) *m*CPBA, DMF; (i) $POCl_3$, 100 °C.

We evaluated a docking experiment between compound **1** and p38 MAP kinase using crystal data of the complex of SB 203580 and p38 MAP kinase (Figure 1).[14] This suggested that the space near pyridine is sufficient to tolerate a substitution adjacent to the pyridyl nitrogen, and furthermore, hydrophobic substituents such as alkyl or phenyl were expected to interact in the groove between Leu108 and Gly110 of p38 MAP kinase. Therefore, the introduction of a substituent into the pyridyl ring seemed a good approach for reducing CYP3A4 inhibitory activity without reducing p38 MAP kinase inhibitory activity.

In this report, we describe further efforts to elucidate the in vitro potency, in vitro CYP3A4 inhibition profile, bioavailability, and in vivo efficacy.

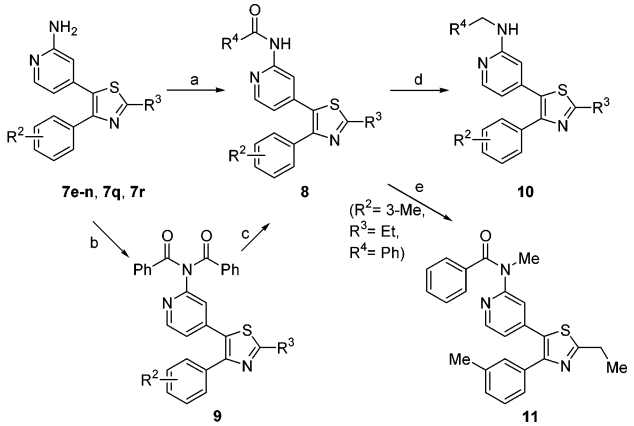
Chemistry

The preparation of 4-phenyl-5-pyridyl-1,3-thiazoles **7** from 4-methylpyridines **2**, the key intermediate of this work, is shown in Scheme 1.

The 4-methylpyridines **2** were treated with lithium diisopropyl amide (LDA) (method A) or 2 equiv of *n*-butyllithium (method B) and reacted with 1-benzoyl-2-methylaziridines **3**[8] to provide the ketones **4**. Bromination of **4** gave α-bromo ketones **5**, which were converted into 1,3-thiazoles **7** with various thioamides **6**, except thioacetamide (R^3 = Me). In the case of reacting **5g** (R^1 = NH_2, R^2 = 3-Me) with thioacetamide, only a trace of the cyclization product **7r** was generated, and debromination mainly occurred to give the corresponding ketone **4** (R^1 = NH_2, R^2 = 3-Me). Alternatively, treating α-bromo ketone **5g** with ethyl 3-amino-3-thioxopropanoate[8] followed by hydrolysis and decarboxylation provided the desired **7r** via **7o**. Oxidation of **7a** with *m*-chloroperbenzoic acid (*m*CPBA) gave the *N*-oxide, which was converted into the 2-chloropyridyl derivative **7s** using phosphorus oxychloride ($POCl_3$).

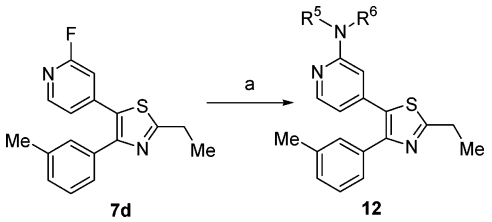
General modification of the amino group at the 2 position of the pyridyl ring is outlined in Schemes 2 and 3. Direct acylation of 2-aminopyridines **7** was performed with acyl chlorides with good yields, except for benzoyl chloride. The use of 1 equiv of benzoyl chloride proved

Scheme 2. Synthesis of Amides **8** and **11** and Secondary Amines **10**[a]



[a] Reagents: (a) R^4COCl, Et_3N, DMF or THF; (b) PhCOCl (2 equiv), Et_3N, THF; (c) HCl (aq), 40 °C; (d) $LiAlH_4$, $AlCl_3$, THF, reflux; (e) NaH, DMSO and then CH_3I.

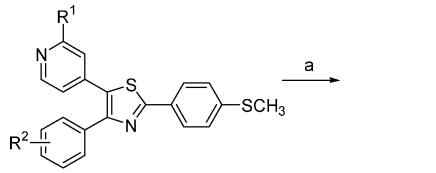
Scheme 3. Direct Amination of 2-Fluoropyridine **7d**[a]



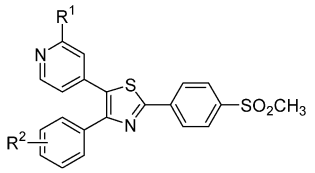
7d **12**

[a] Reagents: (a) R^5R^6NH, reflux.

Scheme 4. Synthesis of Methyl Sulfones **13**[a]



7b, **7p**, **8g**, **8s**, **10b**, **10d**



13

[a] Reagents: (a) *m*CPBA, DMF.

inefficient, providing a mixture of **8** and **9**. Therefore, the amines **7** were converted to dibenzoyl intermediates **9** with 2 equiv of benzoyl chloride, which were subsequently cleaved by hydrolysis to give monobenzoyl derivates **8**. The resulting amides **8** were reduced to amines **10** using a complex of lithium aluminum hydride and aluminum chloride. The amide **8h** (R^2 = 3-Me, R^3 = Et, R^4 = Ph) was alkylated with methyl iodide to afford **11**. Secondary and tertiary amine derivatives **12** were obtained by direct amination of 2-fluoropyridyl derivative **7d** (Scheme 3). Sulfonyl derivatives **13** were synthesized by oxidization of the corresponding sulfide with 2 equiv of *m*CPBA in *N*,*N*-dimethylformamide (DMF) (Scheme 4). All synthesized compounds are listed in Table 1.

Results and Discussion

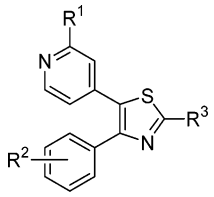
SAR data for the pyridine 2-substituent of the 4-phenyl-5-pyridyl-1,3-thiazole derivatives are shown in Table 2. Introduction of a methyl group adjacent to the pyridyl nitrogen gave slightly diminished activity against p38 MAP kinase (**7a** vs **7c**), while halogenopyridines **7d** and **7s** were also less potent inhibitors. This is presumably due to the reduced electron density at the pyridyl nitrogen atom, which interacts with the amide NH of Met109. These results indicate that substitution at the 2-position of the pyridyl ring appears crucial to p38 MAP kinase inhibitory activity. *N*-Monoalkylamines **10a**, **10c**, **10e**, and **12a** resulted in significant improvements in potency against p38 MAP kinase inhibitory activity, whereas the tertiary amine in **12b** reduced the activity. This suggested that the hydrogen atom of the amino group acts as a hydrogen donor for tight binding at the linker region of the enzyme. This result triggered a search for even more suitable substituents at the 2-position of the pyridyl ring.

We then focused on various amide derivatives in the hope of obtaining improved interactions with the enzyme. Some were identified as having superior activity compared to the *N*-monoalkyl analogues. In the series of alkyl amide derivatives, propionamide **8b** induced a substantial boost in activity compared to acetamide **8a** or butyramide **8c**. Compounds with bulky amide groups on the pyridyl ring, such as cyclohexanecarboxamide **8d**, phenylacetamide **8e**, 3-phenylpropionamide **8f**, and benzamide **8h**, proved to be as effective as the initial monoalkylamines (**10a**, **10c**, **10e**, **12a**). However, *N*-methylation of the amide group dramatically reduced the potency (**8h** vs **11**), as shown by the tertiary amine analogue **12b**. To evaluate the role of the 2-substituent on the pyridyl ring, we conducted a docking simulation between compound **8h** and p38 MAP kinase (Figure 2). The phenyl ring of the benzamide moiety interacted with the hydrophobic groove between Leu108 and Gly110, and there were two hydrogen bonds between the amino pyridyl moiety and the kinase backbone Met109 amide. This hydrophobic interaction with the enzyme seems to result in increased inhibitory activity.

For kinase inhibitors, it is well-known that the SAR for a cell-based assay does not parallel that for the corresponding kinase enzymatic assay. These compounds were therefore further evaluated for their inhibitory activity of TNF-α production in LPS-stimulated THP-1 cells as a secondary screen (Table 2). Compound **7s**, with chloro acting as an electron-withdrawing group, exhibited weak anti-TNF-α activity in parallel with its weak p38 MAP kinase inhibitory activity. The introduction of methyl (**7c**) adjacent to the pyridyl nitrogen resulted in diminished activity, as in the p38 MAP kinase assay. Changing the methyl group of **7c** to an amino group (**7h**, **10a**, **10c**, **10e**, **12a**) increased the activity, but the activity was sensitive to the length of the methylene spacer. Cyclopentylamino **12a** showed the most potent cellular activity among them. In contrast to these amino derivatives, amide derivatives did not vary considerably in activity with respect to the methylene spacer length. Benzamide **8h** gave slightly reduced cellular activity, but phenylacetamide **8e** and 3-phenylpropionamide **8f** showed strong inhibitory activity, suggesting that amide substituents were preferable to amines.

CYP3A4 is one of the most important enzymes in drug metabolic processes,[15] and the SAR trends for inhibition of other CYPs such as CYP2C9 and CYP2C19 are typically similar to that for CYP3A4. We therefore selected CYP3A4 as a representative CYP, and measured the percent inhibition as shown in Table 2. Although compound **7a**, which has no substituent on the pyridyl ring, exhibited moderate to high affinity for CYP3A4, substitution at the pyridine C2 position eliminated that interaction. In particular, the introduction of an electron-withdrawing substituent, such as fluoro (**7d**) or chloro (**7s**), into the pyridyl moiety dramatically reduced CYP3A4 inhibition. This decreased affinity is most likely due to reduced electron density at the pyridyl nitrogen, so that coordination to the heme iron of CYP3A4 is weak. However, this series of compounds showed poor p38 inhibitory potency, and this approach did not seem promising. Replacement of the chlorine atom of **7s** by methyl (**7c**) or amino (**7h**) (sterically

Table 1. Physicochemical Properties of 4-Phenyl-5-pyridyl-1,3-thiazoles



compd	R^1	R^2	R^3	formula	yield (%)[a]	mp (°C)	anal.[b]
7a	H	3-Me	Et	$C_{17}H_{16}N_2S$	59	56−58	C, H, N
7b	H	3-Me	4-MeSPh	$C_{22}H_{18}N_2S_2$	84	101−102	C, H, N
7c	Me	3-Me	Et	$C_{18}H_{18}N_2S{\cdot}H_2O$	60	oil	C, H, N
7d	F	3-Me	Et	$C_{17}H_{15}FN_2S$	38	oil	C, H, N
7e	NH_2	4-MeO	Et	$C_{17}H_{17}N_3OS$	75	153−154	C, H, N
7f	NH_2	3-MeO	Et	$C_{17}H_{17}N_3OS$	65	130−131	C, H, N
7g	NH_2	4-Me	Et	$C_{17}H_{17}N_3S$	73	126−127	C, H, N
7h	NH_2	3-Me	Et	$C_{17}H_{17}N_3S$	60	144−146	C, H, N
7i	NH_2	2-Me	Et	$C_{17}H_{17}N_3S$	59	107−108	C, H, N
7j	NH_2	3-Cl	Et	$C_{16}H_{14}ClN_3S$	81	131−132	C, H, N
7k	NH_2	H	Et	$C_{16}H_{15}N_3S$	84	158−159	C, H, N
7l	NH_2	4-F	Et	$C_{16}H_{14}FN_3S$	76	140−141	C, H, N
7m	NH_2	3-CF_3	Et	$C_{17}H_{14}F_3N_3S$	72	117−118	C, H, N
7n	NH_2	3-Me	Pr	$C_{18}H_{19}N_3S$	62	113−115	C, H, N
7o	NH_2	3-Me	CH_2CO_2Et	$C_{19}H_{19}N_3O_2S$	63	131−132	C, H, N
7p	Me	3-Me	4-MeSPh	$C_{23}H_{20}N_2S_2$	91	119−122	C, H, N
7q	NH_2	3-Me	4-MeSPh	$C_{22}H_{19}N_3S_2$	71	181−183	C, H, N
7r	NH_2	3-Me	Me	$C_{16}H_{15}N_3S$	72	152−153	C, H, N
7s	Cl	3-Me	Et	$C_{17}H_{15}ClN_2S$	81	oil	C, H, N
8a	AcNH	3-Me	Et	$C_{19}H_{19}N_3OS$	66	119−120	C, H, N
8b	EtCONH	3-Me	Et	$C_{20}H_{21}N_3OS$	64	103−104	C, H, N
8c	PrCONH	3-Me	Et	$C_{21}H_{23}N_3OS$	56	88−89	C, H, N
8d	[c]HexCONH	3-Me	Et	$C_{24}H_{27}N_3OS$	75	98−100	C, H, N
8e	$PhCH_2CONH$	3-Me	Et	$C_{25}H_{23}N_3OS$	88	107−108	C, H, N
8f	$Ph(CH_2)_2CONH$	3-Me	Et	$C_{26}H_{25}N_3OS$	75	126−127	C, H, N
8g	$PhCH_2CONH$	3-Me	4-MeSPh	$C_{30}H_{25}N_3OS_2{\cdot}0.25H_2O$	77	205−206	C, H, N
8h	PhCONH	3-Me	Et	$C_{24}H_{21}N_3OS$	88	113−114	C, H, N
8i	PhCONH	3-Cl	Et	$C_{23}H_{18}ClN_3OS$	52	128−129	C, H, N
8j	PhCONH	H	Et	$C_{23}H_{19}N_3OS$	77	95−97	C, H, N
8k	PhCONH	4-F	Et	$C_{23}H_{18}FN_3OS$	71	135−136	C, H, N
8l	PhCONH	3-CF_3	Et	$C_{24}H_{18}F_3N_3OS{\cdot}0.5H_2O$	88	94−95	C, H, N
8m	PhCONH	2-Me	Et	$C_{24}H_{21}N_3OS$	55	104−105	C, H, N
8n	PhCONH	4-Me	Et	$C_{24}H_{21}N_3OS$	69	116−117	C, H, N
8o	PhCONH	3-MeO	Et	$C_{24}H_{21}N_3O_2S$	75	97−98	C, H, N
8p	PhCONH	4-MeO	Et	$C_{24}H_{21}N_3O_2S$	74	112−113	C, H, N
8q	PhCONH	3-Me	Me	$C_{23}H_{19}N_3OS$	95	145−146	C, H, N
8r	PhCONH	3-Me	Pr	$C_{25}H_{23}N_3OS$	68	amorphous	C, H, N
8s	PhCONH	3-Me	4-MeSPh	$C_{29}H_{23}N_3OS_2$	83	180−182	C, H, N
10a	$PhCH_2NH$	3-Me	Et	$C_{24}H_{23}N_3S$	62	106−107	C, H, N
10b	$PhCH_2NH$	3-Me	4-MeSPh	$C_{29}H_{25}N_3S_2$	56	134−136	C, H, N
10c	$Ph(CH_2)_2NH$	3-Me	Et	$C_{25}H_{25}N_3S{\cdot}0.25H_2O$	48	97−98	C, H, N
10d	$Ph(CH_2)_2NH$	3-Me	4-MeSPh	$C_{30}H_{27}N_3S_2$	35	137−139	C, H, N
10e	$Ph(CH_2)_3NH$	3-Me	Et	$C_{26}H_{27}N_3S$	54	52−53	C, H, N
11	PhCONMe	3-Me	Et	$C_{25}H_{23}N_3OS$	65	94−96	C, H, N
12a	[c]PenNH	3-Me	Et	$C_{22}H_{25}N_3S$	33	117−118	C, H, N
12b	*N*-pyrrolidinyl	3-Me	Et	$C_{21}H_{23}N_3S$	75	108−109	C, H, N
13a	H	3-Me	4-$MeSO_2Ph$	$C_{22}H_{18}N_2O_2S_2$	62	171−174	C, H, N
13b	Me	3-Me	4-$MeSO_2Ph$	$C_{23}H_{20}N_2O_2S_2$	70	134−138	C, H, N
13c	PhCONH	3-Me	4-$MeSO_2Ph$	$C_{29}H_{23}N_3O_3S_2$	54	212−214	C, H, N
13d	$PhCH_2CONH$	3-Me	4-$MeSO_2Ph$	$C_{30}H_{25}N_3O_3S_2$	52	244−245	C, H, N
13e	$PhCH_2NH$	3-Me	4-$MeSO_2Ph$	$C_{29}H_{25}N_3O_2S_2$	52	148−150	C, H, N
13f	$Ph(CH_2)_2NH$	3-Me	4-$MeSO_2Ph$	$C_{30}H_{27}N_3O_2S_2$	70	174−176	C, H, N

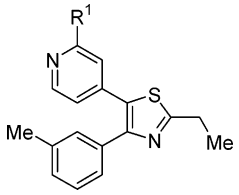
[a] No attempt was made to optimize yields. Numbers respect the yield for the last step. [b] Analytical results are within ±0.4% of the theoretical value.

similar, but electronically different) resulted in reduced CYP3A4 affinity.

We attempted to calculate the coordination energy of pyridine or 2-methylpyridine to heme using D-Mol, an ab initio method, to determine the energetic contribution of a having a substituent adjacent to the pyridyl nitrogen (Figure 3). In this calculation, the pyridine−heme complex is 15.8 kcal/mol more stable than the 2-methylpyridine−heme complex, and this stability may be crucial for the CYP interaction.

Benzamide **8h** also showed reduced CYP3A4 affinity, but phenylacetamide **8e** and 3-phenylpropionamide **8f** showed increased affinity in proportion to the increasing length of the methylene spacer. The benzyl derivative **10a** showed stronger affinity than the corresponding amide **8h**. Cyclopentylamine **12a** and tertiary amine **12b** gave higher affinity than benzylamine **10a**. It appears that the CYP3A4 affinity is related to lipophilicity as well as steric effects of the substituent.

Table 2. SAR of Pyridine-2-substitutient



compd	R^1	IC_{50} (nM)[a] p38α		TNF-α		CYP3A4 (% inhibn, at 1 μM)
7a	H	15	(12−19)	73	(36−150)	48.5
7c	Me	53	(41−69)	450	(170−1200)	24.0
7d	F	94	(68−130)	NT[b]		−5.1
7h	NH_2	20	(17−24)	130	(74−230)	10.2
7s	Cl	240	(150−390)	890	(370−2200)	1.2
8a	AcNH	26	(18−39)	NT[b]		17.2
8b	EtCONH	8.8	(5.9−13)	6.1	(4.1−13)	13.0
8c	PrCONH	13	(10−18)	NT[b]		16.9
8d	[c]HexCONH	7.9	(6.3−10)	77	(37−150)	−4.3
8e	$PhCH_2CONH$	5.6	(4.8−6.5)	13	(7.1−25)	7.2
8f	$Ph(CH_2)_2CONH$	8.1	(6.3−11)	19	(13−29)	12.9
8h	PhCONH	7.1	(6.4−7.7)	48	(35−71)	4.3
10a	$PhCH_2NH$	6.7	(4.3−10)	28	(22−35)	9.5
10c	$Ph(CH_2)_2NH$	5.1	(3.8−6.8)	42	(25−71)	17.3
10e	$Ph(CH_2)_3NH$	8.1	(6.2−11)	120	(61−240)	17.9
11	PhCONMe	>1000		NT[b]		NT[b]
12a	[c]PenNH	3.0	(2.1−4.1)	5.1	(3.2−8.2)	15.9
12b	*N*-pyrrolidinyl	160	(110−230)	NT[b]		21.9

[a] 95% Confidence intervals or remarks are in parentheses. [b] NT means not tested.

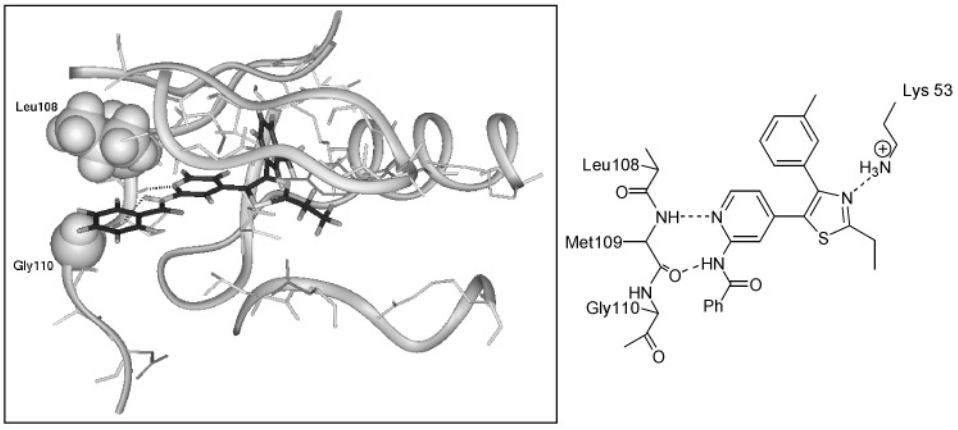


Figure 2. Docking model of compound **8h** with p38 MAP kinase.

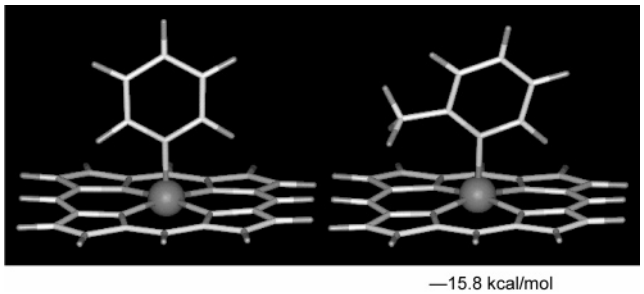


Figure 3. Computation of coordination energy between pyridine and 2-methylpyridine to heme.

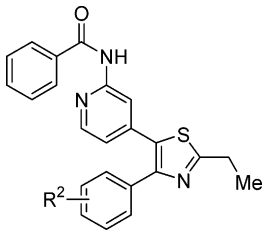
We chose the benzamide group as a representative substituent on the pyridyl ring for the next SAR study around the phenyl ring on the 4-position of the thiazole ring (Table 3). We introduced small substituents into the phenyl ring, such as fluorine, methyl, and methoxy, as in our previous studies.[8] By comparison, 3-chloro **8i**, unsubstituted **8j**, 4-fluoro **8k**, and 3-trifluoromethyl **8l** were nearly equipotent in the p38 MAP kinase inhibition assay, suggesting no significant electronic effect involved with substitution at this position and that the strong activity seen with 3-methyl **8h** is likely due to favorable steric interactions.

TNF-α inhibition was relatively insensitive to substitution on the 4-phenyl ring (**8h**−**8p**). Compounds 3-chloro **8i**, unsubstituted **8j**, 4-fluoro **8k**, 3-methoxy **8o**, and 4-methoxy **8p** retained relatively constant activity, except for 3-trifluoromethyl **8l**. A comparison of methyl-substituted derivatives (**8h**, **8m**, **8n**) revealed a trend toward increasing activity from para to ortho to meta.

Variation of the 4-phenyl substituent had little influence on CYP inhibitory potency. While overall these compounds showed little CYP3A4 inhibition, the compounds with large electronegative substituents, chloro **8i** and trifluoromethyl **8l**, did possess the highest inhibition of the series.

As the introduction of lower alkyl and 4-methylsulfonylphenyl substituents at the 2-position of

Table 3. SAR of Phenyl Ring Substitutution



compd	R^2	IC_{50} (nM)[a] p38α		TNF-α		CYP3A4 (% inhibn, at 1 μM)
8h	3-Me	7.1	(6.4−7.7)	48	(35−71)	4.3
8i	3-Cl	30	(23−40)	130	(78−210)	8.2
8j	H	31	(23−43)	110	(77−140)	−12.5
8k	4-F	31	(21−48)	93	(68−130)	2.4
8l	3-CF_3	91	(66−120)	690	($n = 1$)	10.3
8m	2-Me	110	(77−170)	220	(150−330)	NT[b]
8n	4-Me	210	(140−290)	450	(210−950)	NT[b]
8o	3-MeO	120	(93−160)	110	(66−200)	NT[b]
8p	4-MeO	130	(96−180)	130	(83−200)	NT[b]

[a] 95% Confidence intervals or remarks are in parentheses. [b] NT means not tested.

the thiazole ring was well-tolerated in our previous studies,[8] we examined the effect of substitution at the thiazole 2-position in this work as well (Table 4). The lower alkyl compounds, such as methyl **8q** and propyl **8r**, gave strong inhibition of p38 MAP kinase and TNF-α. 4-Methylsulfonylphenyl derivatives methyl **13b**, benzylamino **13e**, and phenethylamino **13f** exhibited p38 MAP kinase inhibitory activity as strong as the corresponding 2-ethyl thiazole derivatives (**7c**, **10a**, **10c**, respectively). These results are similar to the previously reported SAR trend found in a series of pyrimidinyl-imidazoles.[16]

In the series of 4-methylsulfonylphenyl derivatives (**13a**−**f**), substitution at the 2-position of the pyridyl ring had a significant impact on cell-based activity. Methyl compound **13b** and benzylamino compound **13e** showed less potency than unsubstituted **13a**. Although the activity was retained when amide groups (**13c**, **13d**) were introduced, they led to a decrease relative to the parent compounds **8h** and **8e**.

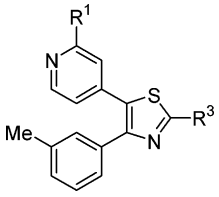
The substituent effects on CYP3A4 inhibition for these compounds were greater than for the 2-ethyl derivatives. Methyl derivative **13b** showed no affinity for CYP3A4, and amide derivatives **13c** and **13d** gave good results, suggesting that the introduction of a substituent adjacent to the pyridyl nitrogen was effective in reducing CYP3A4 interaction, and amide substituents gave the best results for 4-phenyl-5-pyridyl-1,3-thiazoles.

Some potent compounds were tested for their ability to inhibit LPS-induced TNF-α production in mice with 10 mg/kg oral administration; also examined was the plasma concentration after the oral administration of various compounds in mice (Table 5). Benzylamine **10a** and cyclopentylamine **12a** inhibited TNF-α levels by more than 50% at 10 mg/kg; however, they had very poor oral absorption. In contrast to these amine derivatives, the amide compounds showed significantly more potent activity. Among these compounds, acetyl **8a** and propionyl **8b** displayed excellent anti-TNF-α activities (85.5% and 89.5%, respectively) and good oral absorption. Cyclohexylcarbonyl **8d** also had strong activity, but lower plasma concentration. Among the benzoyl compounds, 3-methylphenyl **8h**, 3-chlorophenyl **8i**, phenyl **8j**, and 4-fluorophenyl **8k** inhibited TNF-α levels by more than 80%, but a slightly bulkier substituent such as trifluoromethylphenyl (**8l**) gave less activity. 3-Methylphenyl **8h** showed the best overall results in both the in vivo TNF-α assay and plasma concentration.

On the basis of their promising in vivo activity, compounds **8b** and **8h** were further evaluated in rat pharmacokinetic studies. Compound **8b** showed good bioavailability (BA) in mice (50.3%), but only 4.6% in rats (data not shown). In contrast, compound **8h** had a modest mouse BA (18.4%) and a slightly improved rat BA (21.1%) profile. The rat PK parameters for compound **8h** are shown in Table 6.

Compound **8h** was further tested to evaluate its selectivity for p38 MAP kinase over several other protein kinases (Table 7). Notably, it only significantly inhibited p38α (IC_{50} = 7.1 nM) and p38β (IC_{50} = 200 nM) in a concentration-dependent manner and was approximately 28 times more selective for p38α over p38β. Compound **8h** was also examined for its potential to inhibit 11 CYP isoforms and was found to have no significant inhibitory effect at 1−100 μM (Figure 4). To

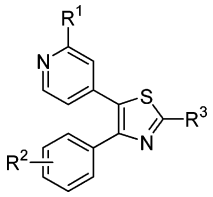
Table 4. SAR of Thiazole 2-Substituent



compd	R^1	R^3	IC_{50} (nM)[a] p38α		TNF-α		CYP3A4 (% inhibn, at 1 μM)
8q	PhCONH	Me	13	(10−17)	33	(19−60)	NT[b]
8r	PhCONH	Pr	13	(10−18)	37	(22−62)	NT[b]
13a	H	4-$MeSO_2C_6H_4$	14	(12−16)	49	(29−84)	25.0
13b	Me	4-$MeSO_2C_6H_4$	26	(22−31)	440	(310−630)	−1.7
13c	PhCONH	4-$MeSO_2C_6H_4$	37	(27−50)	70	(42−120)	5.7
13d	$PhCH_2CONH$	4-$MeSO_2C_6H_4$	34	(23−52)	61	(24−150)	6.8
13e	$PhCH_2NH$	4-$MeSO_2C_6H_4$	11	(8.7−15)	130	(120−150)	11.3
13f	$Ph(CH_2)_2NH$	4-$MeSO_2C_6H_4$	9.1	(6.9−12)	43	(32−57)	12.0

[a] 95% Confidence intervals or remarks are in parentheses. [b] NT means not tested.

Table 5. Inhibitory Potencies of 4-Phenyl-5-pyridyl-1,3-thiazoles on LPS-induced TNF-α Production in Mice and Pharmacokinetic Parameters



				LPS mice (10 mg/kg, po)		mice (10 mg/kg, po)[d]	
compd	R^1	R^2	R^3	% inhibn[a]	SE	C_{max} (μg/mL)	AUC_{0-4h} (μg·h/mL)
8a	AcNH	3-Me	Et	85.5**	2.4	1.82	1.70
8b	EtCONH	3-Me	Et	89.5**	3.2	1.72	2.85
8d	[c]HexCONH	3-Me	Et	75.4**	7.0	0.06	0.06
8f	$Ph(CH_2)_2CONH$	3-Me	Et	60.7	4.5	0.03	0.07
8h	PhCONH	3-Me	Et	87.6*	6.2	0.59	1.16
8i	PhCONH	3-Cl	Et	90.9**	3.1	0.15	0.36
8j	PhCONH	H	Et	86.6**	3.6	0.10	0.16
8k	PhCONH	4-F	Et	98.2**	1.3	0.05	0.11
8l	PhCONH	3-CF_3	Et	59.6**	12.2	NT[b]	NT[b]
8q	PhCONH	3-Me	Me	64.2	8.7	0.10	0.25
10a	$PhCH_2NH$	3-Me	Et	64.6*	11.7	ND[c]	
12a	[c]PenNH	3-Me	Et	66.3	15.0	0.06	0.09
13b	Me	3-Me	4-$MeSO_2C_6H_4$	46.8	16.4	0.71	1.79
13c	PhCONH	3-Me	4-$MeSO_2C_6H_4$	58.6	15.7	0.05	0.10

[a] Dunnett-type test: $*p < 0.05$, $**p < 0.01$ vs control. [b] NT means not tested. [c] ND means not detected. (<0.01 μg/mL). [d] Parameters were calculated from the mean concentration (Balb/c mouse, female, 8 weeks, $n = 3$).

Table 6. Pharmacokinetic Parameters of Selected p38 MAP Kinase Inhibitor **8h** in Rat[a]

	1 mg/kg, iv		10 mg/kg, po		
compd	C_{5min} (μg/mL)	AUC_{0-24h} (μg·h/mL)	C_{max} (μg/mL)	AUC_{0-24h} (μg·h/mL)	BA (%)
8h	1.25 ± 0.03	0.55 ± 0.01	0.19 ± 0.05	1.16 ± 0.16	21.1 ± 2.9

[a] Results are shown as the mean ± SE.

Table 7. Selectivity Profile of **8h** for Representative Kinases

kinase	IC_{50} (μM)	kinase	IC_{50} (μM)
p38α	0.0071	ERK1	>10
p38β	0.20	IKKβ	>10
p38γ	>10	MEKK1	>10
p38δ	>10	TAK1	>10
JNK1	>10		

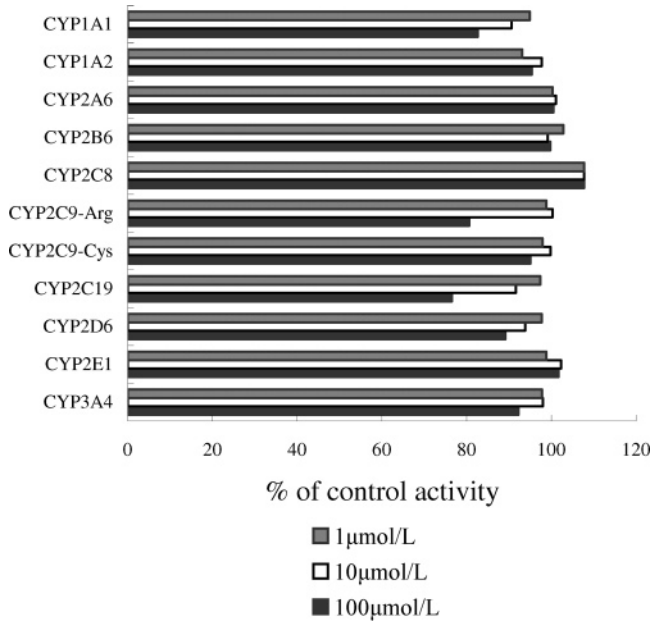


Figure 4. Inhibition of **8h** for representative CYP isoforms.

evaluate its potency as an anti-RA drug, **8h** was tested in a rat adjuvant-induced arthritis (AA) model (3, 10, and 30 mg/kg, po), as shown in Figure 5, and significantly reduced the secondary paw volume (25 ± 6% inhibition vs vehicle) with no influence on the animal body weight compared to control animals.

Conclusion

A novel structural class of 4-phenyl-5-pyridyl-1,3-thiazoles was optimized as inhibitors of p38 MAP kinase and the proinflammatory cytokine TNF-α. In this series of compounds, it was shown that the introduction of an electron-withdrawing substituent or bulky substituent at the pyridine C2 position was a very effective approach to reduce the inhibition activity of CYPs such as CYP3A4. The introduction of an electron-withdrawing group led to reduced p38 MAP kinase inhibitory activity, but this effect could be overcome by introducing an appropriate bulky substituent adjacent to the pyridyl nitrogen. Among various bulky substituents, good cellular activity and pharmacokinetic profiles were observed for several amide derivatives. The most promising compound in this series, **8h**,was a specific inhibitor of p38α MAP kinase with an IC_{50} value of 7.1 nM and exhibited inhibition of TNF-α production by 87.6% in mice with a 10 mg/kg single oral administration. Moreover, **8h** displayed a markedly reduced inhibition profile for CYP isoforms with reasonable mouse and rat pharmacokinetics. Compound **8h** was evaluated in a rat AA model (30 mg/kg, po), providing 25 ± 6% inhibition of the secondary paw volume, further validating this class of p38 MAP kinase inhibitors. On the basis of its overall profile, compound **8h** was chosen as a promising drug candidate for the treatment of inflammatory diseases mediated by TNF-α, such as rheumatoid arthritis, and is now under clinical evaluation.

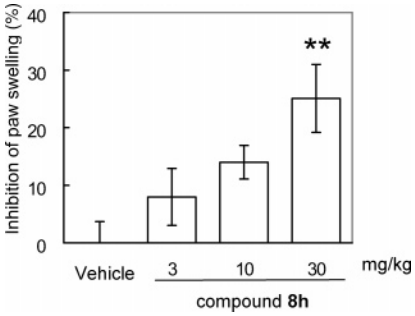


Figure 5. Antiinflammatory effects in the rat adjuvant-induced arthritis model of **8h** (po, 14 days). $^{**}p < 0.01$ vs vehicle (Dunnett-type test; $n = 12$).

Experimental Section

Chemistry. The melting points were determined on a Yanagimoto micro melting point apparatus or a Büche B-545 and are uncorrected. Proton nuclear magnetic resonance (^{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 were within ± 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.

The 1-benzoyl-2-methylaziridines **3** and thioamides **6** were prepared according to a previous report.[8] The 2-fluoro-4-methylpyridine **2c**[17,18] and 2-*tert*-butoxycarbonylamino-4-methylpyridine **2d**[19,20] were synthesized according to previous reports.

1-(3-Methylphenyl)-2-(2-methyl-4-pyridyl)ethanone (4a). Under an argon atmosphere, a solution of diisopropylamine (110 mL, 0.78 mol) in THF (760 mL) was cooled to −50 °C and a 1.6 M solution of *n*-butyllithium in hexane (500 mL, 0.80 mol) was added dropwise to the solution. After the addition, the solution was stirred for 10 min and a solution of 2,4-dimethylpyridine (**2a**) (88 mL, 0.76 mol) in THF (76 mL) was added dropwise at −30 °C. The reaction mixture was stirred for 1 h at −10 °C and then the resulting mixture was cooled to −78 °C. A solution of 1-(3-methylbenzoyl)-2-methylaziridine (140 g, 0.80 mol) in THF (76 mL) was added dropwise at −78 °C. After the addition, the mixture was stirred for 2 h at −78 °C and then the reaction mixture was allowed to warm to room temperature. Water (800 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extracts were washed with water, dried, and concentrated to give a residue. The residue was crystallized with isopropyl ether/hexane to afford 156 g (91%) of **4a** as a solid. Mp: 56−57 °C. ^{1}H NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.54 (3H, s), 4.23 (2H, s), 7.00 (1H, d, $J = 5.1$ Hz), 7.07 (1H, s), 7.33−7.45 (2H, m), 7.76−7.83 (2H, m), 8.44 (1H, d, $J = 5.1$ Hz).

1-(3-Methylphenyl)-2-(4-pyridyl)ethanone (4b). This compound was prepared from 4-methylpyridine (**2b**) as described in the synthesis of **4a** as a solid. Yield: 65%. Mp: 115−116 °C (ethyl acetate/hexane). ^{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).

2-(2-Fluoro-4-pyridyl)-1-(3-methylphenyl)ethanone (4c). This compound was prepared from 2-fluoro-4-methylpyridine (**2c**)[17,18] as described in the synthesis of **4a** as a solid. Yield: 53%. Mp: 66−67 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 2.43 (3H, s), 4.32 (2H, s), 6.85 (1H, s), 7.08−7.10 (1H, m), 7.32−7.81 (3H, m), 8.16−8.19 (2H, m).

***tert*-Butyl [4-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-pyridyl]carbamate (4d).** Under an argon atmosphere, a solution of 2-*tert*-butyl (4-methyl-2-pyridyl)carbamate (**2d**)[19,20] (20 g, 97 mmol) in THF (300 mL) was cooled to −78 °C and a 1.6 M solution of *n*-butyllithium in hexane (140 mL, 0.23 mol) was added dropwise to the solution. After the addition, the solution was stirred for 30 min at 0 °C and cooled to −78 °C. A solution of 1-(4-methoxybenzoyl)-2-methylaziridine (25 g, 0.13 mol) in THF (50 mL) was added dropwise to the mixture. The reaction mixture was allowed to warm to room temperature and stirred for 2 h at room temperature. Water (100 mL) and isopropyl ether (300 mL) were added to the reaction mixture, and the resulting crude crystal was collected by filtration to give crude crystalline. This crude crystal was recrystallized from THF/hexane to afford 23 g (yield 69%) of **4d** as a solid. Mp: 187−190 °C. ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 3.85 (3H, s), 4.37 (2H, s), 6.92 (1H, dd, $J = 5.2$, 1.1 Hz), 7.06 (2H, d, $J = 8.8$ Hz), 7.72 (1H, s), 8.02 (2H, d, $J = 8.8$ Hz), 8.15 (1H, d, $J = 5.2$ Hz), 9.70 (1H, brs).

***tert*-Butyl [4-[2-(3-Methoxyphenyl)-2-oxoethyl]-2-pyridyl]carbamate (4e).** This compound was prepared from 1-(3-methoxybenzoyl)-2-methylaziridine as described in the synthesis of **4d** as a solid. Yield: 53%. Mp: 99−100 °C (ethyl acetate/isopropyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.52 (9H, s), 3.86 (3H, s), 4.27 (2H, s), 6.87 (1H, dd, $J = 5.2$, 1.4 Hz), 7.10−7.16 (1H, m), 7.39 (1H, dd, $J = 8.3$, 7.7 Hz), 7.50−7.53 (1H, m), 7.55−7.59 (1H, m), 7.66 (1H, brs), 7.91 (1H, s), 8.19 (1H, d, $J = 5.2$ Hz).

***tert*-Butyl [4-[2-(4-Methylphenyl)-2-oxoethyl]-2-pyridyl]carbamate (4f).** This compound was prepared from 2-methyl-1-(4-methylbenzoyl)aziridine as described in the synthesis of **4d** as a solid. Yield: 68%. Mp: 137−138 °C (ethyl acetate/isopropyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.52 (9H, s), 2.42 (3H, s), 4.26 (2H, s), 6.87 (1H, dd, $J = 5.1$, 1.5 Hz), 7.28 (2H, d, $J = 8.1$ Hz), 7.66 (1H, brs), 7.89 (2H, d, $J = 8.1$ Hz), 7.90 (1H, d, $J = 0.7$ Hz), 8.18 (1H, dd, $J = 5.1$, 0.7 Hz).

***tert*-Butyl [4-[2-(3-Methylphenyl)-2-oxoethyl]-2-pyridyl]carbamate (4g).** This compound was prepared from 2-methyl-1-(3-methylbenzoyl)aziridine as described in the synthesis of **4d** as a solid. Yield: 81%. Mp: 144−146 °C (ethyl acetate/isopropyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.53 (9H, s), 2.42 (3H, s), 4.28 (2H, s), 6.87 (1H, d, $J = 5.1$ Hz), 7.32−7.43 (2H, m), 7.75−7.83 (2H, m), 7.92 (1H, s), 8.06 (1H, brs), 8.21 (1H, d, $J = 5.1$ Hz).

***tert*-Butyl [4-[2-(2-Methylphenyl)-2-oxoethyl]-2-pyridyl]carbamate (4h).** This compound was prepared from 2-methyl-1-(2-methylbenzoyl)aziridine as described in the synthesis of **4d** as a solid. Yield: 61%. Mp: 131−132 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.52 (9H, s), 2.50 (3H, s), 4.22 (2H, s), 6.87 (1H, dd, $J = 5.1$, 1.5 Hz), 7.23−7.45 (3H, m), 7.65 (1H, brs), 7.73 (1H, d, $J = 7.7$ Hz), 7.87 (1H, s), 8.19 (1H, d, $J = 5.1$ Hz).

***tert*-Butyl [4-[2-(3-Chlorophenyl)-2-oxoethyl]-2-pyridyl]carbamate (4i).** This compound was prepared from 1-(3-chlorobenzoyl)-2-methylaziridine as described in the synthesis of **4d** as a solid. Yield: 78%. Mp: 152−153 °C (ethyl acetate/isopropyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.53 (9H, s), 4.26 (2H, s), 6.85 (1H, dd, $J = 5.2$, 1.8 Hz), 7.43 (1H, dd, $J = 8.0$, 7.7 Hz), 7.56 (1H, ddd, $J = 8.0$, 2.2, 1.1 Hz), 7.86 (1H, ddd, $J = 7.7$, 1.7, 1.1 Hz), 7.91 (1H, s), 7.95 (1H, brs), 7.97 (1H, dd, $J = 2.2$, 1.7 Hz), 8.22 (1H, dd, $J = 5.2$, 0.6 Hz).

***tert*-Butyl [4-(2-Oxo-2-phenylethyl)-2-pyridyl]carbamate (4j).** This compound was prepared from 1-benzoyl-2-methylaziridine as described in the synthesis of **4d** as a solid. Yield: 72%. Mp: 162−163 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.53 (9H, s), 4.29 (2H, s), 6.87 (1H, dd, $J = 5.2$, 1.4 Hz), 7.41−7.63 (3H, m), 7.92−8.05 (3H, m), 8.34 (1H, d, $J = 5.2$ Hz), 8.50 (1H, brs).

***tert*-Butyl [4-[2-(4-Fluorophenyl)-2-oxoethyl]-2-pyridyl]carbamate (4k).** This compound was prepared from 1-(4-fluorobenzoyl)-2-methylaziridine as described in the synthesis of **4d** as a solid. Yield: 76%. Mp: 139−141 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.53 (9H, s), 4.26 (2H, s), 6.86

(1H, dd, J = 5.3, 1.7 Hz), 7.16 (2H, t, J = 6.8 Hz), 7.92 (1H, s), 8.02 (2H, t, J = 6.8 Hz), 8.18 (1H, d, J = 5.3 Hz), 8.34 (1H, brs).

***tert*-Butyl [4-[2-Oxo-2-(3-trifluoromethylphenyl)ethyl]-2-pyridyl]carbamate (4l).** This compound was prepared from 2-methyl-1-(3-trifluoromethylbenzoyl)aziridine as described in the synthesis of **4d** as a solid. Yield: 70%. Mp: 149−150 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.53 (9H, s), 4.32 (2H, s), 6.87 (1H, dd, J = 5.2, 1.4 Hz), 7.64 (1H, t, J = 7.7 Hz), 7.85 (1H, d, J = 7.7 Hz), 7.93 (1H, s), 8.11−8.27 (4H, m).

2-Bromo-1-(3-methylphenyl)-2-(2-methyl-4-pyridyl)-ethanone Hydrobromide (5a). Bromine (24 mL, 0.46 mol) was added dropwise to a solution of **4a** (150 g, 0.46 mol) in acetic acid (450 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 crystalline material was collected by filtration and washed with ethyl acetate to afford 168 g (yield 66%) of **5a** as a solid. ^{1}H NMR (DMSO-d_6) δ: 2.42 (3H, s), 2.72 (3H, s), 3.39 (1H, brs), 7.26 (1H, s), 7.45−7.59 (2H, m), 7.90−8.01 (3H, m), 8.02 (1H, s), 8.81 (1H, d, J = 6.2 Hz).

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

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

2-(2-Amino-4-pyridyl)-2-bromo-1-(4-methoxyphenyl)-ethanone Hydrobromide (5d). This compound was prepared from **4d** as described in the synthesis of **5a** as a solid. Yield: 82%. ^{1}H NMR (DMSO-d_6) δ: 3.38 (2H, brs), 3.88 (3H, s), 6.97 (1H, dd, J = 6.8, 1.8 Hz), 7.09 (1H, s), 7.11 (2H, d, J = 9.0 Hz), 7.19 (1H, s), 7.95 (1H, d, J = 6.8 Hz), 8.09 (2H, d, J = 9.0 Hz), 8.15 (1H, brs).

2-(2-Amino-4-pyridyl)-2-bromo-1-(3-methoxyphenyl)-ethanone Hydrobromide (5e). This compound was prepared from **4e** as described in the synthesis of **5a** as a solid. Yield: 58%. ^{1}H NMR (DMSO-d_6) δ: 3.39 (2H, brs), 3.84 (3H, s), 6.97 (1H, dd, J = 6.7, 1.7 Hz), 7.15 (1H, s), 7.18 (1H, s), 7.30 (1H, dd, J = 8.0, 1.9 Hz), 7.52 (1H, dd, J = 8.3, 8.0 Hz), 7.59 (1H, t, J = 1.9 Hz), 7.69 (1H, d, J = 8.3 Hz), 7.96 (1H, d, J = 6.7 Hz), 8.14 (1H, brs).

2-(2-Amino-4-pyridyl)-2-bromo-1-(4-methylphenyl)-ethanone Hydrobromide (5f). This compound was prepared from **4f** as described in the synthesis of **5a** as a solid. Yield: 75%. ^{1}H NMR (DMSO-d_6) δ: 2.41 (3H, s), 3.41 (2H, brs), 6.97 (1H, dd, J = 6.9, 1.5 Hz), 7.10 (1H, s), 7.19 (1H, d, J = 1.5 Hz), 7.40 (2H, d, J = 8.1 Hz), 7.95 (1H, d, J = 6.9 Hz), 8.01 (2H, d, J = 8.1 Hz), 8.16 (1H, brs).

2-(2-Amino-4-pyridyl)-2-bromo-1-(3-methylphenyl)-ethanone Hydrobromide (5g). This compound was prepared from **4g** as described in the synthesis of **5a** as a solid. Yield: 86%. ^{1}H NMR (DMSO-d_6) δ: 2.41 (3H, s), 3.41 (1H, brs), 6.98 (1H, d, J = 6.8 Hz), 7.12 (1H, s), 7.20 (1H, s), 7.43−7.58 (2H, m), 7.87−8.00 (3H, m), 8.17 (2H, brs).

2-(2-Amino-4-pyridyl)-2-bromo-1-(2-methylphenyl)-ethanone Hydrobromide (5h). This compound was prepared from **4h** as described in the synthesis of **5a** as a solid. Yield: 82%. ^{1}H NMR (DMSO-d_6) δ: 2.40 (3H, s), 6.95 (1H, dd, J = 6.0, 1.7 Hz), 7.04 (1H, s), 7.18 (1H, s), 7.34−7.42 (2H, m), 7.47−7.55 (1H, m), 7.96 (1H, d, J = 6.6 Hz), 8.01 (2H, d, J = 7.2 Hz), 8.17 (1H, brs).

2-(2-Amino-4-pyridyl)-2-bromo-1-(3-chlorophenyl)ethanone Hydrobromide (5i). This compound was prepared from **4i** as described in the synthesis of **5a** as a solid. Yield: 64%. ^{1}H NMR (DMSO-d_6) δ: 3.42 (3H, s), 6.98 (1H, dd, J = 6.9, 1.7 Hz), 7.12 (1H, s), 7.20 (1H, s), 7.64 (1H, t, J = 8.0 Hz), 7.80 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 6.9 Hz), 8.05 (1H, d, J = 8.0 Hz), 8.15 (1H, s).

2-(2-Amino-4-pyridyl)-2-bromo-1-phenylethanone Hydrobromide (5j). This compound was prepared as described from **4j** in the synthesis of **5a** as a solid. Yield: 86%. ^{1}H NMR (DMSO-d_6) δ: 6.98 (1H, dd, J = 6.8, 1.6 Hz), 7.16 (1H, s), 7.22 (1H, s), 7.60 (2H, t, J = 7.9 Hz), 7.67−7.80 (1H, m), 7.97 (1H, d, J = 6.8 Hz), 8.06−8.28 (4H, m).

2-(2-Amino-4-pyridyl)-2-bromo-1-(4-fluorophenyl)ethanone Hydrobromide (5k). This compound was prepared from **4k** as described in the synthesis of **5a** as a solid. Yield: 82%. ^{1}H NMR (DMSO-d_6) δ: 6.98 (1H, dd, J = 6.8, 1.8 Hz), 7.14 (1H, s), 7.21 (1H, s), 7.45 (2H, t, J = 8.8 Hz), 7.97 (1H, d, J = 6.8 Hz), 8.06−8.28 (5H, m).

2-(2-Amino-4-pyridyl)-2-bromo-1-[3-(trifluoromethyl)-phenyl]ethanone Hydrobromide (5l). This compound was prepared from **4l** as described in the synthesis of **5a** as a solid. Yield: 93%. ^{1}H NMR (DMSO-d_6) δ: 6.95 (1H, dd, J = 6.8, 1.6 Hz), 7.23 (2H, s), 7.80−7.94 (2H, m), 7.96 (1H, d, J = 6.8 Hz), 8.10 (2H, d, J = 7.4 Hz), 8.21 (2H, brs), 8.32−8.44 (1H, m).

4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]pyridine (7a). Propanethioamide (0.53 g, 5.9 mmol) was added to a solution of **5b** (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 the mixture was extracted with ethyl acetate. The extracts were washed with brine, dried, and concentrated to give a solid. The crude crystalline was recrystallized from ethanol to afford 8.9 g (yield 59%) of **7a** 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. ($C_{17}H_{16}N_2S$) C, H, N.

4-[4-(3-Methylphenyl)-2-(4-methylthiophenyl)-1,3-thiazol-5-yl]pyridine (7b). This compound was prepared from **5b** and 4-(methylthio)benzenecarbothioamide as described in the synthesis of **7a** as a solid. Yield: 84%. 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. ($C_{22}H_{18}N_2S_2$) C, H, N.

4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-methylpyridine (7c). This compound was prepared from **5a** and propanethioamide as described in the synthesis of **7a** as an oil. Yield: 60%. ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.6 Hz), 2.33 (3H, s), 2.51 (3H, s), 3.09 (2H, q, J = 7.6 Hz), 6.99 (1H, dd, J = 5.2, 1.2 Hz), 7.13−7,30 (4H, m), 7.39 (1H, s), 8.38 (1H, d, J = 5.2 Hz). Anal. ($C_{18}H_{18}N_2S\cdot H_2O$) C, H, N.

4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-fluoropyridine (7d). This compound was prepared from **5c** and propanethioamide as described in the synthesis of **7a** as an oil. Yield: 38%. ^{1}H NMR ($CDCl_3$) δ: 1.64 (3H, t, J = 7.6 Hz), 2.34 (3H, s), 3.10 (2H, q, J = 7.6 Hz), 6.84−6.86 (1H, m), 7.05−7.09 (1H, m), 7.13−7.25 (3H, m), 7.37 (1H, s), 8.10 (1H, d, J = 5.6 Hz). Anal. ($C_{17}H_{15}FN_2S$) C, H, N.

4-[2-Ethyl-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]-2-pyridylamine (7e). This compound was prepared from **5d** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 75%. Mp: 153−154 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.6 Hz), 3.06 (2H, q, J = 7.6 Hz), 3.82 (3H, s), 4.41 (2H, brs), 6.45 (1H, d, J = 1.4 Hz), 6.57 (1H, dd, J = 5.4, 1.4 Hz), 6.84 (2H, d, J = 8.2 Hz), 7.47 (2H, d, J = 8.2 Hz), 7.98 (1H, d, J = 5.4 Hz). Anal. ($C_{17}H_{17}N_3OS$) C, H, N.

4-[2-Ethyl-4-(3-methoxyphenyl)-1,3-thiazol-5-yl]-2-pyridylamine (7f). This compound was prepared from **5e** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 65%. Mp: 130−131 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.6 Hz), 3.08 (2H, q, J = 7.6 Hz), 3.75 (3H, s), 4.41 (2H, brs), 6.45 (1H, d, J = 0.6 Hz), 6.58 (1H, dd, J = 5.5, 1.7 Hz), 6.84−6.89 (1H, m), 7.06−7.11 (2H, m), 7.19−7.26 (1H, m), 7.99 (1H, d, J = 5.5 Hz). Anal. ($C_{17}H_{17}N_3$-OS) C, H, N.

4-[2-Ethyl-4-(4-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine (7g). This compound was prepared from **5f** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 73%. Mp: 126−127 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.6 Hz), 2.35 (3H, s), 3.06 (2H, q,

J = 7.6 Hz), 4.45 (2H, brs), 6.44 (1H, d, J = 0.8 Hz), 6.57 (1H, dd, J = 5.2, 1.7 Hz), 7.13 (2H, d, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.97 (1H, d, J = 5.2 Hz). Anal. ($C_{17}H_{17}N_3S$) C, H, N.

4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine (7h). This compound was prepared from **5g** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 60%. Mp: 144−146 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.6 Hz), 2.34 (3H, s), 3.08 (2H, q, J = 7.6 Hz), 4.42 (2H, brs), 6.44 (1H, dd, J = 1.4, 0.8 Hz), 6.56 (1H, dd, J = 5.2, 1.4 Hz), 7.10−7.28 (3H, m), 7.42 (1H, s), 7.97 (1H, dd, J = 5.2, 0.8 Hz). Anal. ($C_{17}H_{17}N_3S$) C, H, N.

4-[2-Ethyl-4-(2-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine (7i). This compound was prepared from **5h** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 59%. Mp: 107−108 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.6 Hz), 2.12 (3H, s), 3.08 (2H, q, J = 7.6 Hz), 4.31 (2H, brs), 6.25 (1H, dd, J = 0.8, 0.6 Hz), 6.40 (1H, dd, J = 5.5, 1.7 Hz), 7.13−7.32 (4H, m), 7.88 (1H, d, J = 5.5 Hz). Anal. ($C_{17}H_{17}N_3S$) C, H, N.

4-[4-(3-Chlorophenyl)-2-ethyl-1,3-thiazol-5-yl]-2-pyridylamine (7j). This compound was prepared from **5i** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 81%. Mp: 131−132 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.4 Hz), 3.07 (2H, q, J = 7.4 Hz), 4.46 (2H, brs), 6.45 (1H, s), 6.50 (1H, dd, J = 5.6, 1.6 Hz), 7.18−7.36 (3H, m), 7.62 (1H, m), 8.01 (1H, d, J = 5.6 Hz). Anal. ($C_{16}H_{14}ClN_3S$) C, H, N.

4-(2-Ethyl-4-phenyl-1,3-thiazol-5-yl)-2-pyridylamine (7k). This compound was prepared from **5j** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 84%. Mp: 158−159 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.5 Hz), 3.08 (2H, q, J = 7.5 Hz), 4.44 (2H, brs,), 6.43 (1H, s), 6.56 (1H, dd, J = 5.2, 1.8 Hz), 7.27−7.39 (3H, m), 7.49−7.57 (2H, m), 7.97 (1H, d, J = 5.2 Hz). Anal. ($C_{16}H_{15}N_3S$) C, H, N.

4-[2-Ethyl-4-(4-fluorophenyl)-1,3-thiazol-5-yl]-2-pyridylamine (7l). This compound was prepared from **5k** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 76%. Mp: 140−141 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.5 Hz), 3.07 (2H, q, J = 7.5 Hz), 4.46 (2H, brs), 6.42 (1H, s), 6.54 (1H, dd, J = 5.4, 1.4 Hz), 6.97−7.07 (2H, m), 7.47−7.54 (2H, m), 8.00 (1H, d, J = 5.4 Hz). Anal. ($C_{16}H_{14}FN_3S$) C, H, N.

4-[2-Ethyl-4-[3-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl]-2-pyridylamine (7m). This compound was prepared from **5l** and propanethioamide as described in the synthesis of **7a** as a solid. Yield: 72%. Mp: 117−118 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.8 Hz), 3.19 (2H, q, J = 7.8 Hz), 4.47 (2H, brs), 6.42 (1H, s), 6.54 (1H, dd, J = 5.2, 1.6 Hz), 7.41 (1H, dd, J = 7.8, 7.6 Hz), 7.57 (1H, d, J = 7.6 Hz), 7.54 (1H, d, J = 7.8 Hz), 7.91 (1H, s), 8.00 (1H, d, J = 5.2 Hz). Anal. ($C_{17}H_{14}F_3N_3S$) C, H, N.

4-[4-(3-Methylphenyl)-2-propyl-1,3-thiazol-5-yl]-2-pyridylamine (7n). This compound was prepared from butanethioamide and **5g** as described in the synthesis of **7a** as a solid. Yield: 62%. Mp: 113−115 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 0.98 (3H, t, J = 7.3 Hz), 1.76−1.92 (2H, m), 2.34 (3H, s), 3.04 (2H, t, J = 7.4 Hz), 4.14 (2H, brs), 6.44 (1H, s), 6.56 (1H, dd, J = 5.4, 1.5 Hz), 7.09−7.26 (3H, m), 7.41 (1H, s), 7.96 (1H, d, J = 5.4 Hz). Anal. ($C_{18}H_{19}N_3S$) C, H, N.

Ethyl [5-(2-Amino-4-pyridyl)-4-(3-methylphenyl)-1,3-thiazol-2-yl]acetate (7o). This compound was prepared from ethyl 3-amino-3-thioxopropanoate and **5g** as described in the synthesis of **7a** as a solid. Yield: 63% (ethanol). Mp: 131−132 °C. ^{1}H NMR ($CDCl_3$) δ: 1.33 (3H, t, J = 7.2 Hz), 2.34 (3H, s), 4.11 (2H, s), 4.27 (2H, q, J = 7.2 Hz), 4.43 (2H, brs), 6.47 (1H, s), 6.58 (1H, d, J = 5.3 Hz), 7.10−7.27 (3H, m), 7.41 (1H, s), 7.99 (1H, d, J = 5.3 Hz). Anal. ($C_{19}H_{19}N_3O_2S$) C, H, N.

2-Methyl-4-[4-(3-methylphenyl)-2-[4-(methylthio)-phenyl]-1,3-thiazol-5-yl]pyridine (7p). This compound was prepared from 4-(methylthio)benzenecarbothioamide and **5a** as described in the synthesis of **7a** as a solid. Yield: 91%. Mp: 119−122 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.52 (3H, s), 2.54 (3H, s), 7.04 (1H, d, J = 4.9 Hz), 7.15−7.23 (3H, m), 7.25−7.34 (3H, m), 7.47 (1H, s), 7.93 (2H, d, J = 8.8 Hz), 8.40 (1H, d, J = 4.9 Hz). Anal. ($C_{23}H_{20}N_2S_2$) C, H, N.

4-[4-(3-Methylphenyl)-2-[4-(methylthio)phenyl]-1,3-thiazol-5-yl]-2-pyridylamine (7q). This compound was prepared from 4-(methylthio)benzenecarbothioamide and **5g** as described in the synthesis of **7a** as a solid. Yield: 71%. Mp: 181−183 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.36 (3H, t, J = 7.2 Hz), 2.54 (3H, s), 4.44 (2H, s), 6.50 (1H, s), 6.61 (1H, dd, J = 5.3, 1.4 Hz), 7.14−7.34 (5H, m), 7.50 (1H, s), 7.99 (2H, d, J = 8.6 Hz), 8.00 (1H, d, J = 5.3 Hz). Anal. ($C_{22}H_{19}N_3S_2$) C, H, N.

4-[2-Methyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine (7r). A mixture of **7o** (7.0 g, 20 mmol) in ethanol (40 mL) and 1 N aqueous sodium hydroxide (40 mL, 40 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 crystalline was washed with water and ethanol. The crystalline material was dried to afford 6.1 g (yield 95%) of [5-(2-amino-4-pyridyl)-4-(3-methylphenyl)-1,3-thiazol-2-yl]acetic acid (**7t**) as a solid. Mp: 132−133 °C. ^{1}H NMR (DMSO-d_6) δ: 2.29 (3H, s), 4.14 (2H, s), 6.11 (2H, brs), 6.33 (1H, dd, J = 5.4, 1.8 Hz), 6.44 (1H, s), 7.12−7.29 (3H, m), 7.38 (1H, s), 7.86 (1H, d, J = 5.4 Hz). Anal. ($C_{17}H_{15}N_3O_2S\cdot 0.25H_2O$) C, H, N.

Solid **7t** (0.50 g, 1.5 mmol) was heated at 140 °C for 15 min. The oil was cooled to room temperature. The crude crystalline material was recrystallized from ethyl acetate/ether to afford 0.31 g (yield 72%) of **7r** as a solid. Mp: 152−153 °C. ^{1}H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.76 (3H, s), 4.40 (2H, brs), 6.44 (1H, s), 6.56 (1H, dd, J = 5.1, 1.5 Hz), 7.10−7.26 (3H, m), 7.42 (1H, s), 7.97 (1H, d, J = 5.1 Hz). Anal. ($C_{16}H_{15}N_3S$) C, H, N.

2-Chloro-4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-pyridine (7s). To a solution of **7a** (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 the mixture was extracted with ethyl acetate. The extracts were washed with brine, dried, and concentrated to give a solid. The crude crystalline was washed with hexane to afford 2.2 g (yield 74%) of 4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide (**7u**) 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. ($C_{17}H_{16}N_2OS$) C, H, N.

A solution of **7u** (1.00 g, 3.37 mmol) in $POCl_3$ (6.5 mL) was stirred at 100 °C for 2 h. The reaction solution was cooled, and a saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate and washed with brine. The combined organic phase was dried and concentrated to give a residue. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (2:1) to afford 0.90 g (yield 81%) of **7s** as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.42 (3H, t, J = 7.7 Hz), 2.35 (3H, s), 3.10 (2H, q, J = 7.7 Hz), 7.09 (1H, dd, J = 5.2, 1.4 Hz), 7.12−7.30 (4H, m), 7.37 (1H, s), 8.22−8.27 (1H, m). Anal. ($C_{17}H_{15}ClN_2S$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]acetamide (8a).** Acetyl chloride (0.33 mL, 4.6 mmol) was added to a solution of **7h** (1.3 g, 4.4 mmol) in THF (13 mL), and triethylamine (0.64 mL, 4.6 mmol) was added to the mixture. The resulting mixture was stirred for 1 h at room temperature and aqueous sodium hydrogen carbonate was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The extracts were washed with aqueous sodium hydrogen carbonate, dried, and concentrated to give a residue. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (2:1), and recrystallized from ethyl acetate/hexane to afford 0.99 g (yield 66%) of **8a** as a solid. Mp: 119−120 °C. ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.7 Hz), 2.21 (3H, s), 2.33 (3H, s), 3.09 (2H, q, J = 7.7 Hz), 6.86 (1H, dd, J = 5.1, 1.5 Hz), 7.13−7.24 (3H, m), 7.39 (1H, s), 8.02 (1H, brs), 8.08 (1H, d, J = 5.1 Hz), 8.27 (1H, s). Anal. ($C_{19}H_{19}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]propionamide (8b).** This compound was prepared from **7h** and propionyl chloride as described in the synthesis of **8a** as a solid. Yield: 64%. Mp: 103−104 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7.7 Hz), 1.42 (3H, t, J = 7.7 Hz), 2.33 (3H, s), 2.44 (2H, q, J = 7.7 Hz), 3.09 (2H, q, J = 7.7 Hz), 6.83 (1H, dd, J = 5.1, 1.5 Hz), 7.11−7.23 (3H, m), 7.39 (1H, s), 8.06 (1H, dd, J = 5.1, 0.7 Hz), 8.08 (1H, brs), 8.34 (1H, s). Anal. ($C_{20}H_{21}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]butyramide (8c).** This compound was prepared from **7h** and butyryl chloride as described in the synthesis of **8a** as a solid. Yield: 56%. Mp: 88−89 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.01 (3H, t, J = 7.3 Hz), 1.45 (3H, t, J = 7.6 Hz), 1.65−1.87 (2H, m), 2.33 (3H, s), 2.38 (2H, t, J = 7.3 Hz), 3.08 (2H, q, J = 7.6 Hz), 6.83 (1H, dd, J = 5.4, 1.7 Hz), 7.10−7.23 (3H, m), 7.39 (1H, s), 7.98 (1H, brs), 8.06 (1H, d, J = 5.4 Hz), 8.34 (1H, s). Anal. ($C_{21}H_{23}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]cyclohexanecarboxamide (8d).** This compound was prepared from **7h** and cyclohexanecarbonyl chloride as described in the synthesis of **8a** as a solid. Yield: 75%. Mp: 98−100 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.21−2.08 (13H, m), 2.20−2.31 (1H, m), 2.33 (3H, s), 3.08 (2H, q, J = 7.5 Hz), 6.82 (1H, dd, J = 5.3, 1.7 Hz), 7.10−7.35 (3H, m), 7.39 (1H, s), 8.00 (1H, brs), 8.07 (1H, d, J = 5.3 Hz), 8.37 (1H, s). Anal. ($C_{24}H_{27}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]-2-phenylacetamide (8e).** This compound was prepared from **7h** and phenylacetyl chloride as described in the synthesis of **8a** as a solid. Yield: 88%. Mp: 107−108 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.5 Hz), 2.31 (3H, s), 3.08 (2H, q, J = 7.5 Hz), 3.76 (2H, s), 6.81 (1H, dd, J = 5.2, 1.4 Hz), 7.10−7.47 (9H, m), 7.90 (1H, s), 8.02 (1H, d, J = 5.2 Hz), 8.33 (1H, s). Anal. ($C_{25}H_{23}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]-3-phenylpropionamide (8f).** This compound was prepared from **7h** and 3-phenylpropionyl chloride as described in the synthesis of **8a** as a solid. Yield: 75%. Mp: 126−127 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.5 Hz), 2.31 (3H, s), 2.70 (2H, t, J = 7.7 Hz), 3.06 (2H, t, J = 7.7 Hz), 3.09 (2H, q, J = 7.5 Hz), 6.83 (1H, dd, J = 5.4, 1.4 Hz), 7.10−7.47 (9H, m), 7.97 (1H, s), 8.04 (1H, d, J = 5.4 Hz), 8.32 (1H, s). Anal. ($C_{26}H_{25}N_3OS$) C, H, N.

***N*-[4-[4-(3-Methylphenyl)-2-(4-methylthiophenyl)-1,3-thiazol-5-yl]-2-pyridyl]-2-phenylacetamide (8g).** This compound was prepared from **7q** and phenylacetyl chloride as described in the synthesis of **8a** as a solid. Yield: 77%. Mp: 205−206 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.54 (3H, s), 3.77 (2H, s), 6.86 (1H, dd, J = 5.3, 1.7 Hz), 7.18−7.45 (11H, m), 7,84 (1H, s), 7.93 (2H, d, J = 7.0 Hz), 8.04 (1H, d, J = 5.3 Hz), 8.39 (1H, s). Anal. ($C_{30}H_{25}N_3OS_2 \cdot 0.25H_2O$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8h).** Benzoyl chloride (21.6 mL, 186 mmol) was added to a solution of **7h** (50.0 g, 169 mmol) in THF (500 mL), and triethylamine (28.3 mL, 203 mmol) was added to the mixture. The resulting mixture was stirred for 3 h at room temperature and aqueous sodium hydrogen carbonate was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The extracts were washed with aqueous sodium hydrogen carbonate, dried, and concentrated to give a residue. Concentrated hydrochloric acid (100 mL) was added to the residue and the mixture was stirred at 40 °C for 14 h. The mixture was basified with 8 N aqueous sodium hydroxide and extracted with ethyl acetate. The extracts were dried and concentrated to give a residue. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (2:1), and recrystallized from ethyl acetate/hexane to afford 59.8 g (yield 88%) of **8h** as a solid. Mp: 113−114 °C. ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, J = 7.6 Hz), 2.34 (3H, s), 3.10 (2H, q, J = 7.6 Hz), 6.87 (1H, dd, J = 5.2, 1.4 Hz), 7.13−7.30 (3H, m), 7.45−7.63 (4H, m), 7.94 (2H, d, J = 7.5 Hz), 8.06 (1H, d, J = 5.2 Hz), 8.52 (1H, s), 8.74 (1H, brs). Anal. ($C_{24}H_{21}N_3OS$) C, H, N.

***N*-[4-[4-(3-Chlorophenyl)-2-ethyl-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8i).** This compound was prepared from **7j** as described in the synthesis of **8h** as a solid. Yield: 52%. Mp: 128−129 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.47 (3H, t, J = 7.6 Hz), 3.10 (2H, q, J = 7.6 Hz), 7.09 (1H, dd, J = 5.2, 1.4 Hz), 7.10−7.39 (3H, m), 7.45−7.63 (4H, m), 7.90−7.97 (2H, m), 8.16 (1H, dd, J = 5.2, 0.8 Hz), 8.50 (1H, d, J = 0.8 Hz), 8.67 (1H, brs). Anal. ($C_{23}H_{18}ClN_3OS$) C, H, N.

***N*-[4-(2-Ethyl-4-phenyl-1,3-thiazol-5-yl)-2-pyridyl]benzamide (8j).** This compound was prepared from **7k** as described in the synthesis of **8h** as a solid. Yield: 77%. Mp: 95−97 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.47 (3H, t, J = 7.6 Hz), 3.11 (2H, q, J = 7.6 Hz), 6.88 (1H, dd, J = 5.2, 1.2 Hz), 7.29−7.39 (3H, m), 7.45−7.63 (5H, m), 7.90−7.96 (2H, m), 8.11 (1H, d, J = 5.2 Hz), 8.50 (1H, d, J = 1.2 Hz), 8.65 (1H, brs). Anal. ($C_{23}H_{19}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(4-fluorophenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8k).** This compound was prepared from **7l** as described in the synthesis of **8h** as a solid. Yield: 71%. Mp: 135−136 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, J = 7.7 Hz), 3.10 (2H, q, J = 7.7 Hz), 6.88 (1H, dd, J = 5.2, 1.6 Hz), 7.03 (2H, t, J = 8.8 Hz), 7.45−7.63 (5H, m), 7.88−7.95 (2H, m), 8.14 (1H, d, J = 5.2 Hz), 8.49 (1H, d, J = 1.6 Hz), 8.67 (1H, brs). Anal. ($C_{23}H_{18}FN_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-[3-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8l).** This compound was prepared from **7m** as described in the synthesis of **8h** as a solid. Yield: 88%. Mp: 94−95 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.47 (3H, t, J = 7.5 Hz), 3.11 (2H, q, J = 7.5 Hz), 6.87 (1H, dd, J = 5.2, 1.6 Hz), 7.39−7.73 (6H, m), 7.86−7.96 (3H, m), 8.15 (1H, d, J = 5.2 Hz), 8.51 (1H, s), 8.71 (1H, brs). Anal. ($C_{24}H_{18}F_3N_3OS \cdot 0.5H_2O$) C, H, N.

***N*-[4-[2-Ethyl-4-(2-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8m).** This compound was prepared from **7i** as described in the synthesis of **8h** as a solid. Yield: 55%. Mp: 104−105 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.47 (3H, t, J = 7.7 Hz), 2.14 (3H, s), 3.10 (2H, q, J = 7.7 Hz), 6.62 (1H, dd, J = 5.5, 1.8 Hz), 7.18−7.37 (4H, m), 7.45−7.63 (3H, m), 7.88−7.95 (2H, m), 8.01 (1H, dd, J = 5.5, 0.9 Hz), 8.46 (1H, d, J = 0.9 Hz), 8.54 (1H, brs). Anal. ($C_{24}H_{21}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(4-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8n).** This compound was prepared from **7g** as described in the synthesis of **8h** as a solid. Yield: 69%. Mp: 116−117 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, J = 7.5 Hz), 2.36 (3H, s), 3.09 (2H, q, J = 7.5 Hz), 6.89 (1H, dd, J = 5.1, 1.5 Hz), 7.14 (2H, d, J = 8.1 Hz), 7.45 (2H, d, J = 8.1 Hz), 7.46−7.62 (3H, m), 7.89−7.96 (2H, m), 8.11 (1H, d, J = 5.1 Hz), 8.50 (1H, d, J = 1.5 Hz), 8.65 (1H, brs). Anal. ($C_{24}H_{21}N_3OS$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methoxyphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8o).** This compound was prepared from **7f** as described in the synthesis of **8h** as a solid. Yield: 75%. Mp: 97−98 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, J = 7.6 Hz), 3.10 (2H, q, J = 7.6 Hz), 3.76 (3H, s), 6.86−6.92 (2H, m), 7.06−7.11 (2H, m), 7.23 (1H, d, J = 8.3 Hz), 7.47−7.62 (3H, m), 7.93 (2H, d, J = 6.9 Hz), 8.10 (1H, d, J = 5.5 Hz), 8.52 (1H, dd, J = 1.7, 0.8 Hz), 8.71 (1H, brs). Anal. ($C_{24}H_{21}N_3O_2S$) C, H, N.

***N*-[4-[2-Ethyl-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8p).** This compound was prepared from **7e** as described in the synthesis of **8h** as a solid. Yield: 74%. Mp: 112−113 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, J = 7.7 Hz), 3.09 (2H, q, J = 7.7 Hz), 3.82 (3H, s), 6.87 (2H, d, J = 9.1 Hz), 6.91 (1H, dd, J = 5.2, 1.4 Hz), 7.43−7.63 (5H, m), 7.93 (2H, d, J = 6.9 Hz), 8.13 (1H, dd, J = 5.2, 0.6 Hz), 8.50 (1H, dd, J = 1.4, 0.6 Hz), 8.63 (1H, brs). Anal. ($C_{24}H_{21}N_3O_2S$) C, H, N.

***N*-[4-[2-Methyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8q).** This compound was prepared from **7r** as described in the synthesis of **8h** as a solid. Yield: 95%. Mp: 145−146 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.78 (3H, s), 6.86−6.89 (1H, m), 7.16−7.22 (3H, m), 7.41 (1H, s), 7.46−7.59 (3H, m), 7.90−7.91 (2H, m), 8.09 (1H, d, J = 5.2 Hz), 8.50 (1H, s), 8.69 (1H, brs). Anal. ($C_{23}H_{19}N_3OS$) C, H, N.

***N*-[4-[4-(3-Methylphenyl)-2-propyl-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8r).** This compound was prepared from **7n** as described in the synthesis of **8h** as an amorphous powder. Yield: 68%. ^{1}H NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7.1 Hz), 1.80−1.99 (2H, m), 2.34 (3H, s), 3.04 (2H, t, J = 7.7 Hz), 6.88 (1H, dd, J = 5.2, 1.7 Hz), 7.15−7.63 (7H, m), 7.90−7.95 (2H, m), 8.11 (1H, d, J = 5.2 Hz), 8.51 (1H, s), 8.61 (1H, brs). Anal. ($C_{25}H_{23}N_3OS$) C, H, N.

***N*-[4-[4-(3-Methylphenyl)-2-(4-methylthiophenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (8s).** This compound was prepared from **7q** as described in the synthesis of **8h** as a solid. Yield: 83%. Mp: 180−182 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.54 (3H, s), 5.92 (1H, dd, J = 5.3, 1.4 Hz), 7.16−7.40 (5H, m), 7.45−7.64 (4H, m), 7.92−7.97 (4H, m), 8.12 (1H, d, J = 5.3 Hz), 8.59 (1H, s), 8.70 (1H, brs). Anal. ($C_{29}H_{23}N_3OS_2$) C, H, N.

***N*-Benzyl-*N*-[4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]amine (10a).** Aluminum lithium hydride (0.18 g, 4.7 mmol) was added to a suspension of aluminum chloride (0.59 g, 4.4 mmol) in THF (40 mL), and the mixture was stirred at room temperature for 15 min. A solution of **8h** (0.50 g, 1.3 mmol) in THF (10 mL) was added to the mixture, and the resulting mixture was heated to reflux for 2 h. After the reaction mixture was cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. The extracts were washed with brine, dried, and concentrated to give a residue. The residue was recrystallized from ethyl acetate/hexane to afford 0.31 g (yield 62%) of **10a** as a solid. Mp: 106−107 °C. ^{1}H NMR ($CDCl_3$) δ: 1.43 (3H, t, J = 7.5 Hz), 2.34 (3H, s), 3.06 (2H, q, J = 7.5 Hz), 4.38 (2H, d, J = 5.8 Hz), 4.75−4.95 (1H, m), 6.32 (1H, s), 6.53 (1H, dd, J = 5.5, 1.4 Hz), 7.12−7.38 (8H, m), 7.40 (1H, s), 8.01 (1H, d, J = 5.5 Hz). Anal. ($C_{24}H_{23}N_3S$) C, H, N.

***N*-Benzyl-*N*-[4-[4-(3-methylphenyl)-2-(4-methylthiophenyl)-1,3-thiazol-5-yl]-2-pyridyl]amine (10b).** This compound was prepared from **8s** as described in the synthesis of **10a** as a solid. Yield: 56%. Mp: 134−136 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.53 (3H, s), 4.39 (2H, d. J = 5.8 Hz), 4.86 (1H, d, J = 5.8 Hz), 6.37 (1H, s), 6.58 (1H, dd, J = 5.5, 1.5 Hz), 7.13−7.30 (11H, m), 7.48 (1H, s), 7.91 (1H, d, J = 8.6 Hz), 8.38 (1H, d, J = 5.5 Hz). Anal. ($C_{29}H_{25}N_3S_2$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]-*N*-(2-phenylethyl)amine (10c).** This compound was prepared from **8e** as described in the synthesis of **10a** as a solid. Yield: 48%. Mp: 97−98 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.5 Hz), 2.32 (3H, s), 2.81 (2H, t, J = 7.0 Hz), 3.08 (2H, q, J = 7.5 Hz), 3.36−3.46 (2H, m), 4.50−4.65 (1H, m), 6.30 (1H, s), 6.51 (1H, dd, J = 5.2, 1.4 Hz), 7.05−7.35 (8H, m), 7.43 (1H, s), 8.00 (1H, d, J = 5.2 Hz). Anal. ($C_{25}H_{25}N_3S\cdot0.25H_2O$) C, H, N.

***N*-[4-[4-(3-Methylphenyl)-2-(4-methylthiophenyl)-1,3-thiazol-5-yl]-2-pyridyl]-*N*-(2-phenylethyl)amine (10d).** This compound was prepared from **8g** as described in the synthesis of **10a** as a solid. Yield: 35%. Mp: 137−139 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.54 (3H, s), 2.82 (2H, t, J = 7.0 Hz), 3.43 (2H, dt, J = 6.0, 7.0 Hz), 4.57 (1H, t, J = 6.0 Hz), 6.34 (1H, s), 6.56 (1H, dd, J = 5.3, 1.3 Hz), 7.11−7.35 (10H, m), 7.51 (1H, s), 7.92 (2H, d, J = 8.4 Hz), 8.02 (1H, d, J = 5.3 Hz). Anal. ($C_{30}H_{27}N_3S_2$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]-*N*-(3-phenylpropyl)amine (10e).** This compound was prepared from **8f** as described in the synthesis of **10a** as a solid. Yield: 54% (ethyl acetate/hexane). Mp: 52−53 °C. ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.5 Hz), 1.77−1.95 (2H, m), 2.32 (3H, s), 2.69 (2H, t, J = 7.7 Hz), 3.00−3.22 (4H, m), 4.47−4.60 (1H, m), 6.26 (1H, s), 6.49 (1H, dd, J = 5.2, 1.4 Hz), 7.05−7.35 (8H, m), 7.42 (1H, s), 7.98 (1H, d, J = 5.2 Hz). Anal. ($C_{26}H_{27}N_3S$) C, H, N.

***N*-[4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]-*N*-methylbenzamide (11).** Sodium hydride (60% paraffin dispersion, 0.12 g, 3.0 mmol) was added to a solution of **8h** (1.1 g, 2.7 mmol) in dimethyl sulfoxide (20 mL), and the mixture was stirred at room temperature for 1 h. Methyl iodide (0.17 mL, 2.7 mmol) was added to the reaction mixture, and the resulting mixture was stirred at room temperature for 1 h. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated to give a residue. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (2:1), and the crude crystalline was washed with hexane to afford 0.71 g (yield 65%) of **11** as a solid. Mp: 94−96 °C. ^{1}H NMR ($CDCl_3$) δ: 1.43 (3H, t, J = 7.6 Hz), 2.36 (3H, s), 3.07 (2H, q, J = 7.6 Hz), 3.83 (3H, s), 6.19−6.23 (1H, m), 7.18−7.32 (4H, m), 7.39−7.48 (4H, m), 8.29−8.34 (2H, m), 8.54 (1H, d, J = 2.2 Hz). Anal. ($C_{25}H_{23}N_3OS$) C, H, N.

***N*-Cyclopentyl-4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine (12a).** A mixture of **7d** and cyclopentylamine (1.6 mL, 16 mmol) was heated at 110 °C for 14 h. The mixture was cooled to room temperature, and aqueous sodium hydrogen carbonate was added to the mixture. The mixture was extracted with ethyl acetate, and the extracts were washed with brine. The combined organic phase was dried and concentrated to give a residue. The residue was recrystallized from ethyl acetate to afford 0.19 g (yield 33%) of **12a** as a solid. Mp: 117−118 °C. ^{1}H NMR ($CDCl_3$) δ: 1.22−1.93 (11H, m), 2.33 (3H, s), 3.08 (2H, q, J = 7.4 Hz), 3.65−3.81 (1H, m), 4.56 (1H, d, J = 6.6 Hz), 6.28 (1H, s), 6.48−6.51 (1H, m), 7.10−7.18 (3H, m), 7.41 (1H, s), 7.97 (1H, d, J = 5.6 Hz). Anal. ($C_{22}H_{25}N_3S$) C, H, N.

4-[2-Ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-(1-pyrrolidinyl)pyridine (12b). This compound was prepared from **7d** and pyrrolidine as described in the synthesis of **12a** as a solid. Yield: 75%. Mp: 108−109 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.5 Hz), 1.94−2.01 (4H, m), 2.34 (3H, s), 3.08 (2H, q, J = 7.5 Hz), 3.32−3.39 (4H, m), 6.30 (1H, s), 6.40−6.44 (1H, m), 7.09−7.28 (3H, m), 7.45 (1H, s), 8.04 (1H, d, J = 5.2 Hz). Anal. ($C_{21}H_{23}N_3S$) C, H, N.

4-[4-(3-Methylphenyl)-2-[4-(methylsulfonyl)phenyl]-1,3-thiazol-5-yl]pyridine (13a). To a solution of **7b** (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 solution was added to the reaction mixture, and the resulting mixture was 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 crude crystalline material, which was recrystallized from ethyl acetate/isopropyl ether to afford 0.54 g (yield 62%) of **13a** 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. ($C_{22}H_{18}N_2O_2S_2$) C, H, N.

2-Methyl-4-[4-(3-methylphenyl)-2-[4-(methylsulfonyl)-phenyl]-1,3-thiazol-5-yl]pyridine (13b). This compound was prepared from **7p** as described in the synthesis of **13a** as a solid. Yield: 70%. Mp: 134−138 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.55 (3H, s), 3.11 (3H, s), 7.07 (1H, d, J = 5.2 Hz), 7.16−7.31 (4H, m), 7.47 (1H, s), 8.05 (2H, d, J = 8.5 Hz), 8.22 (2H, d, J = 8.5 Hz), 8.45 (1H, d, J = 5.2 Hz). Anal. ($C_{23}H_{20}N_2O_2S_2$) C, H, N.

***N*-[4-[4-(3-Methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (13c).** This compound was prepared from **8s** as described in the synthesis of **13a** as a solid. Yield: 54%. Mp: 212−214 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.12 (3H, s), 6.95 (1H, dd, J = 5.4, 1.6 Hz), 7.26−7.36 (3H, m), 7.50−7.58 (4H, m), 7.92−7.97 (2H, m), 8.05 (2H, d, J = 8.6 Hz), 8.18 (1H, d, J = 5.4 Hz), 8.24 (2H, d, J = 8.6 Hz), 8.62 (1H, s), 8.67 (1H, s). Anal. ($C_{29}H_{23}N_3O_3S_2$) C, H, N.

***N*-[4-[4-(3-Methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]-2-phenylacetamide (13d).** This compound was prepared from **8g** as described in the synthesis of **13a** as a solid. Yield: 52%. Mp: 244−245 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.36 (3H, s), 3.11 (3H, s), 3.78 (2H, s), 6.95 (1H, dd, J = 5.0, 1.6 Hz), 7.20−7.45 (9H, m), 7.87 (1H, s), 8.04 (2H, d, J = 8.4 Hz), 8.05 (1H, d, J = 5.0 Hz), 8.21 (2H, d, J = 8.4 Hz), 8.43 (1H, s). Anal. ($C_{30}H_{25}N_3O_3S_2$) C, H, N.

***N*-Benzyl-*N*-[4-[4-(3-methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]amine (13e).** This compound was prepared from **10b** as described in the synthesis of **13a** as a solid. Yield: 52%. Mp: 148−150 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.10 (3H, s), 4.41 (2H, d, J = 6.0 Hz), 4.91 (1H, t, J = 6.0 Hz), 6.38 (1H, s), 6.59 (1H, dd, J = 5.2, 1.4 Hz), 7.20−7.33 (8H, m), 7.48 (1H, s), 8.00−8.10 (3H, m), 8.20 (2H, d, J = 8.8 Hz). Anal. ($C_{29}H_{25}N_3O_2S_2$) C, H, N.

***N*-[4-[4-(3-Methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]-*N*-(2-phenylethyl)amine (13f).** This compound was prepared from **10d** as described in the synthesis of **13a** as a solid. Yield: 70%. Mp: 174−176 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.84 (2H, t, J = 7.1 Hz), 3.11 (3H, s), 3.33−3.50 (2H, m), 4.43−4.67 (1H, m), 6.36 (1H, s), 6.58 (1H, dd, J = 5.4, 1.4 Hz), 7.15−7.36 (8H, m), 7.52 (1H, s), 8.02−8.07 (3H, m), 8.22 (2H, d, J = 8.8 Hz). Anal. ($C_{30}H_{27}N_3O_2S_2$) C, H, N.

Biological Methods. p38 MAP Kinase Assay, THP-1 TNF-α Release Assay and Mouse TNF-α Release Assay. These assays were performed according to the protocols described previously.[8]

Measurement of CYP Inhibition Activity. The inhibition activity of the thiazole derivatives on CYP3A4 was evaluated by incubating 40 μM 7-benzyloxyquinoline with the microsomes derived from CYP3A4-expressing insect cell (BD Biosciences) in the presence of 1 μM compounds. The concentration of 7-benzyloxyquinoline metabolite was measured with a spectrofluorometer.

The inhibition activity of compound **8h** on CYP isoforms was also evaluated by using specific CYP-expressing human B-limphoblastoid cells (BD Biosciences). The concentrations of **8h** were 1, 10, and 100 μM. The substrates of each CYPs were 4 μM ethoxyresorufin for CYP1A1 and CYP1A2, 400 μM coumarin for CYP2A6, 400 μM 7-ethoxycoumarin for CYP2B6, 400 μM tolbutamide for CYP2C8 and CYP2C9, 80 μM *S*-(±)-mephenytoin for CYP2C19, 200 μM (±)-bufuralol for CYP2D6, 500 μM 4-nitrophenol for CYP2E1, and 80 μM testosterone for CYP3A4. The concentration of the marker metabolite for CYP1A1, CYP1A2, and CYP2A6 was measured with a spectrofluorometer, and for the other CYPs it was measured by HPLC.

Adjuvant-Induced Arthritis Assay. Arthritis was induced in 7-week-old male Lewis rats (n = 6) by an intradermal injection of 0.25 mg of *Mycobacterium tuberculosis* in 0.05 mL of liquid paraffin at a site on the right hind paw on day 0. The paw volume of the untreated (left) hind paw was determined on day 14. Drugs (3, 10, and 30 mg/kg, po) and the vehicle (saline) were administered from day 0 to day 13.

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Supporting Information Available: Elemental analyses for compounds **7**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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