Synthesis and Biological Activities of 4-Phenyl-5-pyridyl-1,3-thiazole Derivatives as Selective Adenosine A_3 Antagonists

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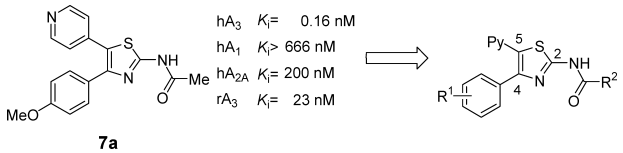
To investigate the potency of an adenosine A_3 receptor (A_3AR) antagonist as an anti-asthmatic drug, a novel series of 4-phenyl-5-pyridyl-1,3-thiazole derivatives was synthesized and evaluated in human adenosine A_1, A_{2A} and A_3 receptor and rat adenosine A_3 receptor binding assays. From investigation of the SAR study, compound 7af was identified as a highly potent human and rat A_3AR antagonist. This compound inhibited IB-MECA-induced plasma protein extravasation in the skin of rats and showed good oral absorption. Also, compound 7af significantly inhibited antigen-induced hyper-responsiveness to acetylcholine in actively sensitized Brown Norway rats. These results show that 4-phenyl-5-pyridyl-1,3-thiazole derivatives are potential candidates to enable the evaluation of A_3AR antagonists. Further evaluation of this class of compounds may afford a novel anti-inflammatory agent such as an anti-asthmatic drug.

Key words 5-pyridyl-1,3-thiazole; adenosine A_3 receptor antagonist; antiphlogistic; rat antigen-induced asthma model; Brown Norway rat

Adenosine, an endogenous purine nucleoside, modulates a variety of physiological functions in various organs and tissues, and interacts with four specific G-protein-coupled receptor subtypes (GPCRs), classified as A_1, A_{2A}, A_{2B}, and A_3.[1,2] All four receptors are coupled *via* G proteins to the adenylate cyclase—cAMP signal transduction pathway. Activation of A_1 and A_3 receptors inhibits adenylate cyclase through G_i coupling, while activation of A_{2A} and A_{2B} receptors stimulates adenylate cyclase through G_s coupling.[3] In particular, the adenosine A_3 receptor (A_3AR) is distributed in different organs (lung, liver, kidney, heart and brain),[4] and the potential therapeutic applications of antagonizing this receptor are proposed to be useful for the treatment of inflammation,[5] myocardial and brain ischemia,[6—8] and cancer.[9,10]

As human adenosine A_3 receptor (hA_3AR) antagonists, many potent and selective antagonists, such as xanthine derivatives,[11] 1,4-dihydropyridines,[12—15] triazoloquinazolines,[16,17] flavonoids,[18] triazolonaphthyridines,[19] thiazolopyrimidines,[19,20] isoquinolines,[21,22] quinazolines,[21] pyrazolotriazolopyrimidines,[23—25] thiazoles and thiadiazoles,[26] and triazolopurines[27,28] have been reported as new hA_3AR antagonists. Although these antagonists showed strong hA_3AR antagonistic activity and good selectivity against other adenosine receptor subtypes, they were found to be weak or ineffective against rat A_3AR (rA_3AR),[1,11,12,15,28,29] and could therefore not be evaluated in rat *in vivo* models. The homology of A_3AR among several species was reported and the only 72% homology between human and rat A_3AR was one reason for species differences.[28] As selective hA_3AR antagonists that showed moderate affinity to rA_3AR, only MRS 1191[14] and MRS 1523[15] (K_i=1.42, 0.113 μM, respectively) have been reported, but these activities seemed to be insufficient for evaluation in rat models. Thus, A_3AR antagonists which show equipotent affinity and selectivity in different species have been desired for pharmacological probes on animal models, and the evaluation and selection of new drugs in preclinical phase candidates is likely to be easier.

Our focus on an anti-asthmatic research program prompted us to evaluate the potential of A_3AR antagonist as a therapeutic target. From high throughput screening, 4-phenyl-5-pyridyl-1,3-thiazole derivative **7a** was identified as the preferable lead compound. We have already reported 1,3-thiazole derivatives as p38 MAP kinase inhibitors.[30,31] These compounds were bound at the ATP binding site of the kinase, and ATP is an adenosine-related compound. We therefore focused our attention on compound **7a** and investigated further. In the *in vitro* binding assay, compound **7a** showed strong hA_3AR antagonistic activity (K_i=0.16 nM) and good hA_3AR selectivity, as shown in Fig. 1. Moreover, the rA_3AR antagonistic activity of this compound was moderate (K_i=23 nM). To evaluate the efficacy of the rat asthma model, improvement of the rA_3AR antagonistic activity of **7a** was critical. In the present paper, we report the discovery of a series of 2-acylamino-4-phenyl-5-pyridyl-1,3-thiazole derivatives as novel and potent antagonists against human and rat A_3AR through structural modification based on screening hit **7a**.



7a

Fig. 1. Chemical Structure and Biological Profiles of Lead Compound **7a**

Chemistry

The general approach for the several 4,5-disubstituted 2-acylamino-1,3-thiazoles **7** is outlined in Chart 1, according to the previous report.[30]

The *N*-benzoyl-2-methylaziridines **2** were prepared from the corresponding acid chlorides and commercially available 2-methylaziridine, according to the Schotten–Baumann procedure. The *N*-benzoyl-2-methylaziridines **2** were condensed with the lithium anion of methylpyridine **3** to afford the corresponding ketones **4**.[30,32] In this reaction, the selective lithiation at methyl proton was occurred and no product from

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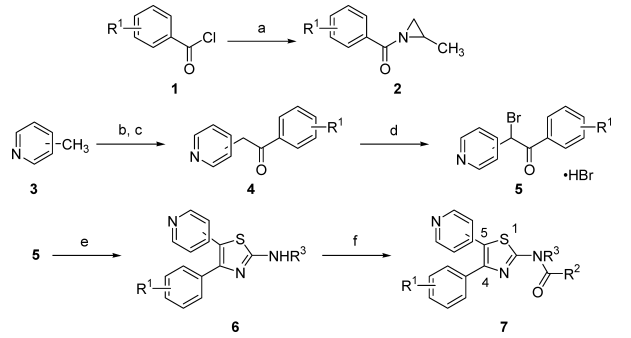
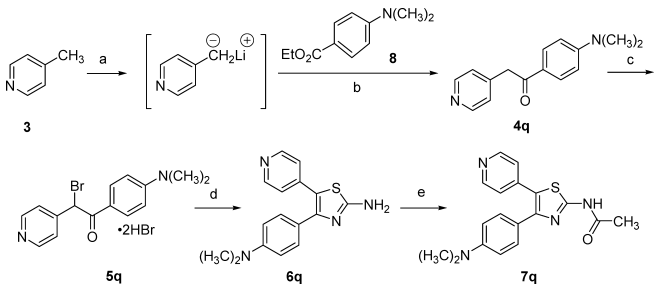


Reagents: (a) 2-methylaziridine, ether, 2 N NaOH, 0 °C; (b) LDA, hexane, THF, −78 °C then −20 °C; (c) **2**, −78 °C; (d) Br_2, AcOH, 70 °C; (e) $H_2NC(S)NHR^3$, Et_3N, CH_3CN, 80 °C; (f) R^2COCl, DMAP, DMA, 70 °C.

Chart 1. Synthesis of 2-Acylaminothiazole Derivatives (**7**)



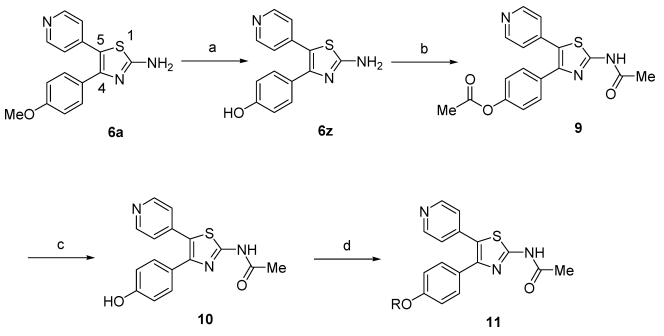
Reagents: (a) LDA, hexane, THF, −78 °C then −20 °C; (b) ethyl 4-(*N*,*N*-dimethylamino)benzoate **8**, −10 °C; (c) Br_2, 30% HBr (aq.), AcOH, 70 °C; (d) $H_2NC(S)NH_2$, Et_3N, CH_3CN, 80 °C; (h) CH_3COCl, DMAP, DMA, 70 °C.

Chart 2. Synthesis of 4-[4-(*N*,*N*-Dimethylamino)phenyl]thiazole Derivative (**7q**)

lithium anion of pyridine core was observed. Ketones **4** were brominated to give α-bromoketones **5**. Cyclization of bromoketones **5** and thioureas provided 2-amino-1,3-thiazoles **6**. Acylation of 2-amino-1,3-thiazoles **6** was carried out using various acid chlorides with a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) in *N*,*N*-dimethylacetamide (DMA) at 70 °C.

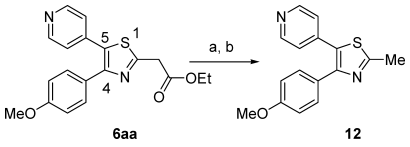
In order to obtain 4-[4-(*N*,*N*-dimethylamino)phenyl]thiazole derivative **7q**, we tried to take a slightly different approach as shown in Chart 2. 1-[4-(*N*,*N*-Dimethylamino)-phenyl]-2-(4-pyridyl)ethanone **4q** was obtained from ethyl 4-(*N*,*N*-dimethylamino)benzoate **8** and 4-pyridylmethyllithium, which was prepared from 4-methylpyridine **3a** and lithium diisopropylamide (LDA), because of a failure to obtain 4-(*N*,*N*-dimethylamino)benzoyl-2-methylaziridine. Although direct bromination of ketone **4q** was unsuccessful due to the *N*,*N*-dimethylamino moiety, we achieved bromination using the hydrobromide salt of **4q**, which was prepared with hydrobromic acid *in situ*. Cyclization reaction of **5q** and acylation of **6q** was carried out under the same condition.

The 4-methoxyphenyl derivative **6a** was converted to 4-alkoxyphenyl derivative **11**, as shown in Chart 3. Acid hydrolysis of the methoxy group of **6a** yielded 4-hydroxyphenyl derivative **6z** and acetylation of **6z** was performed using acetyl chloride and DMAP in DMA to give diacetyl derivative **9**. Saponification of compound **9** provided 4-hydroxyphenyl derivative **10** and the alkylation of intermediate **10** using the corresponding alkyl iodide (RI) gave the alkoxy derivative **11**.



Reagents: (a) 47% HBr (aq.), reflux; (b) MeCOCl (5 eq.), DMAP, DMA, 70 °C; (c) K_2CO_3, rt.; (d) ^{t}BuOK, DMA, 0 °C, then alkyl iodide.

Chart 3. Synthesis of 4-Alkoxyphenylthiazole Derivatives (**11**)



Reagents: (a) 2 N-NaOH (aq.), rt.; (b) EtOH, reflux.

Chart 4. Synthesis of 2-Methylthiazole Derivative (**12**)

Hydrolysis of ethyl 2-thiazoleacetate **6aa** and decarboxylation provided the desired 2-methyl compound **12**, as shown in Chart 4, according to the previous report.[31] All of the synthesized thiazole derivatives are listed in Table 1.

Results and Discussion

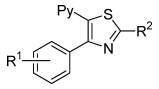
All compounds were tested in radioligand binding assays to determine their affinities for adenosine A_3, A_1, and A_{2A} receptors. K_i values are summarized in Tables 2, 3, 4, and 5.

Effects of Amide Group at C-2 Position and Pyridine Ring at C-5 Position First, the effect of the substituent on the 2-position (R^2) of thiazole ring was evaluated with **6a**, **12** and **7a**, as shown in Table 2. Although the acetamide **7a** showed strong affinity to hA_3AR, removal of the acetyl group or replacement with a methyl group led to weak affinity (**7a** *vs.* **6a** and **12**). Introduction of a methyl group into the 2-acetamide **7a** also reduced affinity (**7a** *vs.* **7e**). These results suggested that the carbonyl group and hydrogen atom of amide at the C-2 position were important to interact with the receptor. The structure–activity relationships (SAR) around the pyridine ring at the C-5 position of the thiazole nucleus were evaluated with **7a**—**d**. The 2-pyridyl derivative **7c** and 5-unsubstituted derivative **7d** were less active than 4- or 3-pyridyl derivatives **7a** and **7b**, indicating that nitrogen atoms of 3- and 4-pyridyl groups are important for hA_3AR affinity. The role of these substituents will be discussed in the Molecular Modeling Section.

The rA_3AR affinity of the 3-pyridyl derivative **7b**, 5-unsubstituted compound **7d** and *N*-methylacetamide compound **7e** was examined; however, these compounds showed less affinity than the lead compound **7a**.

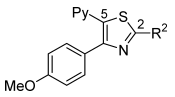
SAR of the Substituent on Benzene Ring at C-4 Position of 1,3-Thiazole Because of fairly good rA_3AR affinity, we selected the 4-pyridyl group at C-5 position of the thiazole ring, and the influence of substituents on the phenyl ring at C-4 position of thiazole was investigated, as shown in

Table 1. Physicochemical Properties of 5-Pyridyl-1,3-thiazole Derivatives



Compd.	Py	R^1	R^2	Formula	mp (°C)	Anal.
6a	4-Py	4-MeO	NH_2	$C_{15}H_{13}N_3OS$	282—284	C, H, N
6b	3-Py	4-MeO	NH_2	$C_{15}H_{13}N_3OS$	265—266	C, H, N
6c	2-Py	4-MeO	NH_2	$C_{15}H_{13}N_3OS$	217—218	C, H, N
6d	H	4-MeO	NH_2	$C_{10}H_{10}N_2OS$	203—204	C, H, N
6e	4-Py	4-MeO	NHMe	$C_{16}H_{15}N_3OS \cdot 0.5H_2O$	175—177	C, H, N
6f	4-Py	3-MeO	NH_2	$C_{15}H_{13}N_3OS$	232—234	C, H, N
6g	4-Py	2-MeO	NH_2	$C_{15}H_{13}N_3OS \cdot 0.2H_2O$	213—215	C, H, N
6h	4-Py	4-Me	NH_2	$C_{15}H_{13}N_3S$	296—298	C, H, N
6i	4-Py	3-Me	NH_2	$C_{15}H_{13}N_3S$	255—258	C, H, N
6j	4-Py	2-Me	NH_2	$C_{15}H_{13}N_3S \cdot 0.2H_2O$	235—238	C, H, N
6k	4-Py	4-Cl	NH_2	$C_{14}H_{10}ClN_3S$	>300	C, H, N
6l	4-Py	3-Cl	NH_2	$C_{14}H_{10}ClN_3S$	256—258	C, H, N
6m	4-Py	2-Cl	NH_2	$C_{14}H_{10}ClN_3S$	232—235	C, H, N
6n	4-Py	4-Et	NH_2	$C_{16}H_{15}N_3S$	285—288	C, H, N
6o	4-Py	4-^{n}Pr	NH_2	$C_{17}H_{17}N_3S$	240—242	C, H, N
6p	4-Py	4-^{n}Bu	NH_2	$C_{18}H_{19}N_3S \cdot 0.5H_2O$	204—206	C, H, N
6q	4-Py	4-^{i}Pr	NH_2	$C_{17}H_{17}N_3S$	267—269	C, H, N
6r		4-^{t}Bu	NH_2	$C_{18}H_{19}N_3S \cdot 0.5H_2O$	254—257	C, H, N
6s	4-Py	4-Me_2N	NH_2	$C_{16}H_{16}N_4S$	309—311	C, H, N
6t	4-Py	3,4-diMe	NH_2	$C_{16}H_{15}N_3S$	248—250	C, H, N
6u	4-Py	3,5-diMe	NH_2	$C_{16}H_{15}N_3S$	242—244	C, H, N
6v	4-Py	3,4-di(MeO)	NH_2	$C_{16}H_{15}N_3O_2S$	218—219	C, H, N
6w	4-Py	3,4-(OCH_2O)	NH_2	$C_{15}H_{11}N_3O_2S$	273—275	C, H, N
6x	3-Py	4-^{t}Bu	NH_2	$C_{18}H_{19}N_3S$	239—241	C, H, N
6y	3-Py	3,5-diMe	NH_2	$C_{16}H_{15}N_3S$	237—240	C, H, N
6z	4-Py	4-HO	NH_2	$C_{16}H_{15}N_3OS \cdot 3H_2O$	323—326	C, H, N
6aa	4-Py	4-MeO	CH_2CO_2Et	$C_{19}H_{18}N_2O_3S$	Oil	
7a	4-Py	4-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	282—284	C, H, N
7b	3-Py	4-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	119—120	C, H, N
7c	2-Py	4-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	230—232	C, H, N
7d	H	4-MeO	NHAc	$C_{12}H_{12}N_2O_2S$	192—193	C, H, N
7e	4-Py	4-MeO	NMeAc	$C_{18}H_{17}N_3O_2S$	180—181	C, H, N
7f	4-Py	3-MeO	NHAc	$C_{17}H_{15}N_3O_2S \cdot 0.3H_2O$	234—236	C, H, N
7g	4-Py	2-MeO	NHAc	$C_{17}H_{15}N_3O_2S$	259—261	C, H, N
7h	4-Py	4-Me	NHAc	$C_{17}H_{15}N_3OS$	308—309	C, H, N
7i	4-Py	3-Me	NHAc	$C_{17}H_{15}N_3OS$	287—289	C, H, N
7j	4-Py	2-Me	NHAc	$C_{17}H_{15}N_3OS$	272—274	C, H, N
7k	4-Py	4-Cl	NHAc	$C_{16}H_{12}ClN_3OS \cdot 0.2H_2O$	317—320	C, H, N
7l	4-Py	3-Cl	NHAc	$C_{16}H_{12}ClN_3OS$	290—293	C, H, N
7m	4-Py	2-Cl	NHAc	$C_{16}H_{12}ClN_3OS$	292—293	C, H, N
7n	4-Py	4-Et	NHAc	$C_{18}H_{17}N_3OS \cdot 0.1H_2O$	294—295	C, H, N
7o	4-Py	4-^{n}Pr	NHAc	$C_{19}H_{19}N_3OS \cdot 0.2H_2O$	256—258	C, H, N
7p	4-Py	4-^{n}Bu	NHAc	$C_{20}H_{21}N_3OS$	259—261	C, H, N
7q	4-Py	4-^{i}Pr	NHAc	$C_{19}H_{19}N_3OS$	295—297	C, H, N
7r	4-Py	4-^{t}Bu	NHAc	$C_{20}H_{21}N_3OS$	280—281	C, H, N
7s	4-Py	4-Me_2N	NHAc	$C_{18}H_{18}N_4OS \cdot 0.2H_2O$	289—291	C, H, N
7t	4-Py	3,4-diMe	NHAc	$C_{18}H_{17}N_3OS$	248—250	C, H, N
7u	4-Py	3,5-diMe	NHAc	$C_{18}H_{17}N_3OS \cdot 0.1H_2O$	284—286	C, H, N
7v	4-Py	3,4-di(MeO)	NHAc	$C_{18}H_{17}N_3O_3S$	265—267	C, H, N
7w	4-Py	3,4-(OCH_2O)	NHAc	$C_{17}H_{13}N_3O_3S$	295—296	C, H, N
7x	4-Py	4-^{t}Bu	NHCOEt	$C_{21}H_{23}N_3OS$	295—297	C, H, N
7y	4-Py	4-^{t}Bu	NHCO(^{c}Pen)	$C_{24}H_{27}N_3OS$	309—311	C, H, N
7z	4-Py	4-^{t}Bu	NHCOPh	$C_{25}H_{23}N_3OS$	292—294	C, H, N
7aa	4-Py	4-^{t}Bu	NHCO(3-Py)	$C_{24}H_{22}N_4OS$	326—328	C, H, N
7ab	4-Py	4-^{t}Bu	NHCO(4-Py)	$C_{24}H_{22}N_4OS$	326—329	C, H, N
7ac	4-Py	3,5-diMe	NHCOEt	$C_{19}H_{19}N_3OS$	291—293	C, H, N
7ad	4-Py	3,5-diMe	NHCO(^{c}Pen)	$C_{22}H_{23}N_3OS$	275—278	C, H, N
7ae	4-Py	3,5-diMe	NHCOPh	$C_{23}H_{19}N_3OS$	285—286	C, H, N
7af	4-Py	3,5-diMe	NHCO(3-Py)	$C_{22}H_{18}N_4OS$	267—270	C, H, N
7ag	4-Py	3,5-diMe	NHCO(4-Py)	$C_{22}H_{18}N_4OS \cdot 0.2H_2O$	302—304	C, H, N
7ah	3-Py	4-^{t}Bu	NHAc	$C_{20}H_{21}N_3OS \cdot 0.3H_2O$	228—230	C, H, N
7ai	3-Py	4-^{t}Bu	NHCO(3-Py)	$C_{24}H_{22}N_4OS$	251—253	C, H, N
7aj	3-Py	3,5-diMe	NHAc	$C_{18}H_{17}N_3O_2S$	288—289	C, H, N
7ak	3-Py	3,5-diMe	NHCO(3-Py)	$C_{22}H_{18}N_4OS$	277—278	C, H, N
9	4-Py	4-AcO	NHAc	$C_{18}H_{15}N_3O_3S \cdot 0.2H_2O$	254—257	C, H, N
10	4-Py	4-HO	NHAc	$C_{16}H_{13}N_3O_2S \cdot 0.7H_2O$	285—287	C, H, N
11a	4-Py	4-EtO	NHAc	$C_{18}H_{17}N_3O_2S$	206—209	C, H, N
11b	4-Py	4-^{n}BuO	NHAc	$C_{20}H_{21}N_3O_2S$	201—203	C, H, N
12	4-Py	4-MeO	Me	$C_{16}H_{14}N_2OS \cdot 0.1H_2O$	132—133	C, H, N

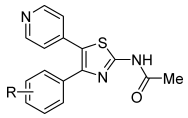
Table 2. Binding Affinity for Human A_3, A_1 and A_{2a}, and Rat A_3 Receptors



Compd.	Py	R^2	K_i (nM)			
			hA_3	hA_1	hA_{2A}	rA_3
6a	4-Py	NH_2	>285	NT[a]	NT[a]	NT[a]
12	4-Py	Me	>285	>666	>826	NT[a]
7a	4-Py	NHAc	0.16	>666	200	23
7b	3-Py	NHAc	0.08	>666	145	160
7c	2-Py	NHAc	9.0	>666	160	NT[a]
7d[b]	(H)	NHAc	5.8	>666	>826	>980
7e	4-Py	NMeAc	7.9	>666	>826	360

a) NT indicates 'not tested'. *b*) **7d** is 5-unsubstituted derivative.

Table 3. Effect of Substituent on 4-Phenyl Ring



Compd.	R	K_i (nM)			
		hA_3	hA_1	hA_{2A}	rA_3
7a	4-MeO	0.16	>666	200	23
7f	3-MeO	0.12	110	61	69
7g	2-MeO	1.1	46	350	1100
7h	4-Me	0.08	9.3	27	32
7i	3-Me	0.15	25	29	140
7j	2-Me	1.8	62	460	>1000
7k	4-Cl	0.10	20	56	480
7l	3-Cl	0.15	17	18	>1000
7m	2-Cl	0.73	59	110	2100
7n	4-Et	0.20	70	130	81
7o	4-^{n}Pr	0.28	180	>826	64
7p	4-^{n}Bu	0.26	>666	>826	56
7q	4-^{i}Pr	0.40	>666	>826	180
7r	4-^{t}Bu	0.21	>666	>826	45
11a	4-EtO	22	170	>826	>980
11b	4-^{n}BuO	130	>666	>826	230
7s	4-Me_2N	0.26	>666	>826	49
7t	3,4-diMe	0.20	34	49	9.7
7u	3,5-diMe	0.25	>666	>826	4.1
7v	3,4-di(MeO)	0.30	>666	>826	93
7w	3,4-(OCH_2O)	0.29	19	25	33

Introduction of methoxy (**7a**, **f**), methyl (**7h**, **i**) and chloro (**7k**, **l**) substituents into 4- and 3-positions of the phenyl ring showed potent activity for hA_3AR, and substitution (**7a**, **h**, **k**) at 4-position of the phenyl ring was more favored for rA_3AR than corresponding substitution (**7f**, **i**, **l**) at 3-position. The introduction of substituents (**7g**, **j**, **m**) into the 2-position of the phenyl ring led to significant reduction of hA_3AR activity. As for receptor sub-type selectivity, methyl (**7h**—**j**) and chloro (**7k**—**m**) derivatives exhibited somewhat potent activity for hA_1AR and $hA_{2A}AR$. In general, the 2- (**7g**, **j**, **m**) or 3-substituted (**7f**, **i**, **l**) compounds showed less hA_3AR selectivity than the corresponding 4-substituted compounds (**7a**, **f**, **g**).

Therefore, we focused the substituent at 4-position on the benzene ring, and examined further to identify the effect of activity and selectivity. Introduction of the bulky substituent at 4-position slightly diminished hA_3AR affinity but increased hA_3AR selectivity and rA_3AR affinity. The 4-ethyl **7n** and 4-propyl **7o** derivatives gave slightly less hA_3AR and rA_3AR affinity than 4-methyl **7h**, whereas the hA_3AR selectivity of these compounds increased. Although compounds **7p** and **7q** showed good hA_3AR affinity and poor rA_3AR affinity, the 4-*tert*-butyl derivative **7r** showed potent rA_3AR affinity as 4-methyl derivative **7h**. Although alkoxy derivatives **11a** and **11b** were synthesized and tested for their affinity, these compounds showed less affinity for hA_3AR than methoxy derivative **7a**. The 4-dimethylamino derivative **7s** showed good hA_3AR affinity and selectivity. These results suggested that the steric effect of the substituent would be a more important factor than the electronic effect for hA_3AR selectivity and rA_3AR affinity.

As for disubstitued derivatives, 3,4-dimethyl **7t** and 3,4-methylenedioxy derivatives **7w** showed good hA_3AR affinity, but the selectivity was insufficient. Dimethoxy **7v** and 3,4-methylenedioxy compounds **7w** gave potent hA_3AR affinity as well as good selectivity, but showed moderate rA_3AR affinity. Among these disubstituted derivatives, the 3,5-dimethyl derivative **7u** showed potent human and rat A_3AR affinity as well as good selectivity.

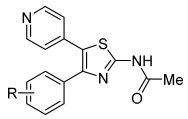
On the basis of these results, we chose 4-*tert*-butyl and 3,5-dimethyl groups as representative substituents on the benzene ring for the next SAR study around 2-position of the thiazole.

SAR of Acyl Group at 2-Position on 1,3-Thiazole The influence of substituents at 2-position of thiazole was evaluated, as shown in Table 4. Among 4-*tert*-buthyl derivatives, it was observed that propionyl **7x** and isonicotinoyl **7ab** retained activity, and cyclopentylcarbonyl **7y**, benzoyl **7z** and nicotinoyl **7aa** slightly reduced hA_3AR affinity. 3,5-Dimethylphenyl derivatives **7ac**—**ag** showed comparable hA_3AR activity to acetyl compound **7u**. For rA_3AR affinity, introduction of an aromatic acyl substituent such as benzoyl **7z**, **7ae**, nicotinoyl **7aa**, **7af**, or isonicotinoyl **7ag** led to a dramatic increase in rA_3AR affinity. Among these compounds, benzoyl derivative **7ae** and nicotinoyl derivatives **7aa**, **7af** showed the best results for receptor binding activity for both hA_3AR and rA_3AR as well as selectivity over hA_1AR and $hA_{2A}AR$.

Finally, we investigated the adenosine receptor affinity of compounds which have 3-pyridyl at 5-position on 1,3-thiazole, as shown in Table 4, because 3-pyridyl derivative **7b** (hA_3; K_i=0.08 nM) was stronger than the relative 4-pyridyl derivative **7a** (hA_3; K_i=0.16 nM). Among 4-*tert*-butylphenyl derivatives, replacement of 4-pyridyl with 3-pyridyl led to the reduction of both hA_3AR and rA_3AR affinity (**7r** *vs.* **7ah**, and **7u** *vs.* **7aj**). In 3,5-dimethylphenyl derivatives, 2-acetamide **7aj** showed strong hA_3AR activity; however, its rA_3AR activity was weak. Although 2-nicotinoyl derivative **7ak** showed stronger rA_3AR affinity than **7aj**, its affinity for both A_3AR was less than that of the corresponding 4-pyridyl derivative **7af**.

Molecular Modeling Study To explain the above SAR, we tried to perform a docking study using a homology model of the hA_3AR constructed from the crystal structure of bovine rhodopsin (PDBID: 1F88) as a template, based on

Table 4. Effect of Acyl Group at 2-Position on Thiazole



Compd.	Py	R^1	R^2	K_i (nM)			
				hA_3	hA_1	hA_{2A}	rA_3
7r	4-Py	4-^{t}Bu	NHCOMe	0.21	>666	>826	45
7x	4-Py	4-^{t}Bu	NHCOEt	0.32	>666	>826	30
7y	4-Py	4-^{t}Bu	NHCO(^{c}Pen)	0.88	>666	>826	11
7z	4-Py	4-^{t}Bu	NHCOPh	1.0	>666	>826	2.5
7aa	4-Py	4-^{t}Bu	NHCO(3-Py)	0.50	>666	>826	4.3
7ab	4-Py	4-^{t}Bu	NHCO(4-Py)	0.35	>666	>826	130
7ah	3-Py	4-^{t}Bu	NHCOMe	7.7	>666	>826	>1000
7ai	3-Py	4-^{t}Bu	NHCO(3-Py)	19	>666	>826	550
7u	4-Py	3,5-diMe	NHCOMe	0.25	>666	>826	4.1
7ac	4-Py	3,5-diMe	NHCOEt	0.24	>666	>826	7.0
7ad	4-Py	3,5-diMe	NHCO(^{c}Pen)	0.24	>666	76	3.5
7ae	4-Py	3,5-diMe	NHCOPh	0.42	>666	>826	1.2
7af	4-Py	3,5-diMe	NHCO(3-Py)	0.36	>666	>826	1.6
7ag	4-Py	3,5-diMe	NHCO(4-Py)	0.34	>666	>826	4.0
7aj	3-Py	3,5-diMe	NHCOMe	0.50	>666	63	>1000
7ak	3-Py	3,5-diMe	NHCO(3-Py)	2.1	>666	>826	120

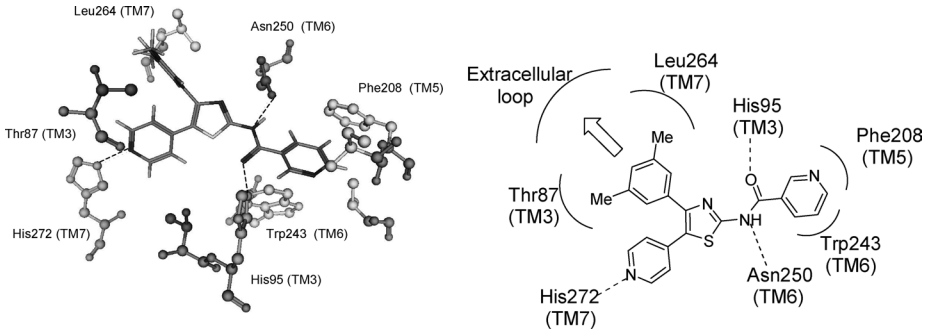


Fig. 2. Schematic Model for Binding hA_3AR with Compound **7af**

mutational studies, as previously reported.[33,34] The homology model of hA_3AR was constructed using the molecular operating environment (MOE 2005.06, Chemical Computing Group: Montreal, Canada), and docking was performed manually using GOLD v3.0.[35] Figure 2 shows the most reasonable binding mode between A_3AR and compound **7af**.

In this model, the amide moiety at 2-position of thiazole in **7af** interacted with Asn250 (TM6) and His95 (TM3), suggesting that the amine **6a** and methyl derivative **12** without an acyl group showed weak hA_3AR binding activity. The pyridyl group at 2-position of **7af** was placed in the hydrophobic pocket bordered by Phe208 (TM5) and Trp243 (TM6), and it was predicted that no residue of hA_3AR would interact with the nitrogen atom of the pyridyl group. The replacement of Phe208 with Leu in rA_3AR and π–π interaction between Trp243 and the aryl substituent of 2 position of thiazole could explain the increased affinity of rA_3AR. The third hydrogen bond between the nitrogen atom of the pyridine ring and His272 (TM7) was predicted and the 4-position of the phenyl ring of **7af** was surrounded by Leu264 (TM7) and Thr87 (TM3). This result also suggested that 2-pyridyl compound **7c** and hydrogen compound **7d** showed less activity than 3-pyridyl compound **7b** and 4-pyridyl compound **7a**. Although this model can explain some SAR of these compounds for hA_3AR, it was difficult to explain the SAR of the substituent at 4-position on the phenyl ring from the results of our study. In this model, the substituent of the 4-position of thiazole was directed toward the extracellular loop and subtype selectivity of the compound might be explained by interaction with the loop. In general, extracellular loops are so flexible that modeling studies of these areas are very difficult. As a species difference, Leu264 (TM7) replaced Ser and Thr87 (TM3) replaced Met in rA_3AR, with the model suggesting that the space for the ligand binding site in rA_3AR was wider than hA_3AR. Better accommodation might be one reason that 3,5-dimethyl and 4-*tert*-butyl phenyl moieties showed good rA_3AR affinity.

***In Vivo* Efficacy of Selected A_3AR Antagonists** On the basis of the adenosine receptor binding assay, the six compounds listed were selected and evaluated for inhibition activity on IB-MECA (N^6-(3-iodobenzyl)-9-[5-(methylcarbamoyl)-β-D-ribofuranosyl]adenine)-induced plasma protein extravasation in the skin of rats, as shown in Table 5. Although compounds **7z** and **ae** showed no significant activity

in this model at a dose of 10 mg/kg, *p.o.*, the other four compounds **7u**, **7aa**, **7af** and **7ag** showed significant inhibitory activity in this model. Compounds **7u** and **7af**, in particular completely inhibited dye leakage at 10 mg/kg, *p.o.* and PK data of compounds **7u** and **7af** in rats is shown in Table 5. Compound **7af** demonstrated a good oral absorption profile and bioavailability (62.5±19.0%), whereas compound **7u** showed a poor oral absorption profile and low bioavailability (9.9%).

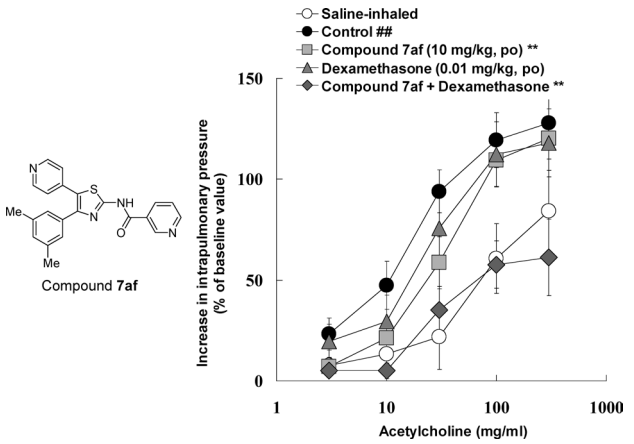


Fig. 3. Effect of Combined Administration of **7af** and Dexamethasone on Antigen-Induced Airway Hyper-Responsiveness to Acetylcholine in Actively Sensitized BN Rats

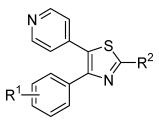
BN rats were actively sensitized and 3 weeks later were challenged with saline or 1% OVA. Airway responsiveness to acetylcholine was measured 23—30 h after antigen challenge. Compound **7af** (10 mg/kg) and dexamethasone (0.01 mg/kg) were orally administered 1 h before and 7 h after antigen challenge. Data are the mean±S.E. of 8 rats. ## $p<0.01$, *vs.* saline-inhaled group, ** $p<0.01$, *vs.* OVA-inhaled control group (two-way ANOVA).

To determine the potency of A_3AR antagonist as an anti-asthmatic drug, the selected compound **7af** was evaluated in an antigen-induced asthma model using Brown Norway (BN) rats. Compound **7af** dose-dependently inhibited antigen-induced hyper-responsiveness to acetylcholine in actively sensitized BN rats and this effect was statistically significant at oral administration of 10 mg/kg (Fig. 3). Compound **7af** increased the anti-asthmatic effect of dexamethasone by combination therapy and these results suggested that the A_3AR antagonist could become a new type of anti-asthma drug as an enhancer of steroids.

Conclusion

In this study, we found a novel series of 4-phenyl-5-pyridyl-1,3-thiazole derivatives with human A_3AR affinity, which had received considerable attention for their structural similarity to p38 MAPK inhibitors.[30,31] The SAR of these compounds was summarized as 1) pyridyl moiety at 5-position of thiazole is important for affinity of hA_3AR and rA_3AR; 2) the substituent on the phenyl ring at 4-position of thiazole is related to adenosine receptor subtype selectivity; 3) the acyl moiety at 2-position of thiazole is important for affinity of rA_3AR, as shown in Fig. 4. As a result of the SAR study, the highly potent hA_3AR and rA_3AR antagonist **7af** has been identified. This compound inhibited IB-MECA-induced plasma protein extravasation in the skin of rats, and showed good oral absorption in rats. Compound **7af** significantly inhibited antigen-induced hyper-responsiveness to acetylcholine in actively sensitized BN rats. These results show that 4-phenyl-5-pyridyl-1,3-thiazole derivatives are po-

Table 5. Inhibition Activity on IB-MECA Induced Plasma Protein Extravasation in the Skin of Rats and Plasma Concentration after Oral Administration in Rats



Compd.	R^1	R^2	K_i (nM)		IB-NECA rat (%inh.) Dose (mg/kg, *p.o.*)		rat PK[a] Dose (10 mg/kg, *p.o.*)		
			hA_3AR	rA_3AR	1	10	C_{max} (μg/ml)	$AUC_{0—24\,h}$ (μg·h/ml)	BA (%)
7u	3,5-Me_2	NHCOMe	0.25	4.1	73**	107**	0.035±0.011	0.263±0.053	9.9±2.0
7z	4-^{t}Bu	NHCOPh	1.0	2.5	41	78	NT[b]	NT[b]	NT[b]
7aa	4-^{t}Bu	NHCO(3-Py)	0.50	4.3	43**	91**	NT[b]	NT[b]	NT[b]
7ae	3,5-Me_2	NHCOPh	0.42	1.2	48	77	NT[b]	NT[b]	NT[b]
7af	3,5-Me_2	NHCO(3-Py)	0.36	1.6	83**	102**	0.871±0.268	4.273±1.302	62.5±19.0
7ag	3,5-Me_2	NHCO(4-Py)	0.34	4.0	77**	80**	NT[b]	NT[b]	

** $p<0.01$ *vs.* IB-MECA injection control (Dunnett's test). $n=6$. *a*) $n=3$. *b*) NT indicates 'not tested'.

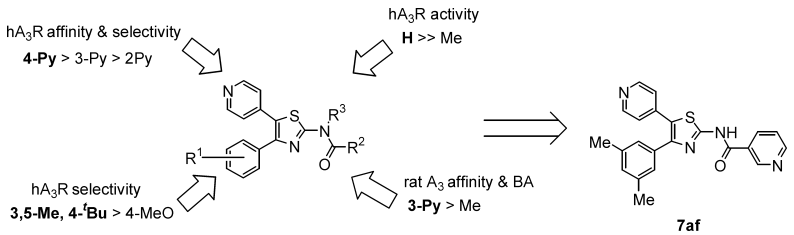


Fig. 4. Structural Factors of Thiazole Compounds Affected the Binding Profile

tential candidates to evaluate A_3AR antagonists as new drugs for the treatment of inflammatory diseases, such as asthma.

Experimental

General Melting points (mp) were determined on a Yanagimoto micro melting point apparatus or Büche B-545 and are uncorrected. Proton nuclear magnetic resonance (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 ±0.4% of the theoretical values unless otherwise noted. THF was distilled over calcium hydride prior to use and other solvents and reagents were used without purification. Extracted solutions were dried over anhydrous Na_2SO_4 unless otherwise noted and the 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 **2a**—**i**, 1-phenyl-2-pyridylethanones **4a**—**k** and **4p**, 2-bromo-1-phenyl-2-pyridylethanones **5a**—**k** and **5p**, 4-phenyl-5-pyridyl-1,3-thiazol-2-ylamines **6a**—**c**, **6f**—**m**, and **6r**, and *N*-(4-phenyl-5-pyridyl-1,3-thiazol-2-yl)acetamides **7a**—**c**, **7f**—**m** and **7r** were prepared according to a previous report.[30]

The 1-benzoylaziridine derivatives **2** were unstable under silica gel column chromatography or distillation, so these compounds were used for next reaction without purification as following typical condition.

1-(4-Ethylbenzoyl)-2-methylaziridine (2j) A solution of 2-methylaziridine (14.3 ml, 0.183 mol) in diethyl ether (170 ml) was added to 2 N aqueous sodium hydroxide solution (95 ml). This mixture was cooled to 0 °C and 4-ethylbenzoyl chloride (28.0 g, 0.166 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 diethyl ether. The combined organic phase was dried, and concentrated to afford 36.4 g (yield quant.) of **2j** as an oil, ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.6 Hz), 1.39 (3H, d, J=5.5 Hz), 2.12 (1H, d, J=2.9 Hz), 2.50—2.61 (2H, m), 2.71 (2H, q, J=7.6 Hz), 7.47 (2H, d, J=8.8 Hz), 7.96 (2H, d, J=8.8 Hz).

1-(4-Propylbenzoyl)-2-methylaziridine (2k) This compound was prepared from 4-propylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.3 Hz), 1.39 (3H, d, J=5.5 Hz), 1.57—1.75 (2H, m), 2.12 (1H, d, J=3.3 Hz), 2.50—2.59 (2H, m), 2.65 (2H, t, J=7.7 Hz), 7.26 (2H, d, J=8.1 Hz), 7.94 (2H, d, J=8.1 Hz).

1-(4-Butylbenzoyl)-2-methylaziridine (2l) This compound was prepared from 4-butylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.1 Hz), 1.26—1.47 (5H, m), 1.54—1.73 (2H, m), 2.12 (1H, d, J=2.9 Hz), 2.51—2.62 (2H, m), 2.67 (2H, t, J=7.7 Hz), 7.26 (2H, d, J=8.1 Hz), 7.94 (2H, d, J=8.1 Hz).

1-[4-(1-Methylethyl)benzoyl]-2-methylaziridine (2m) This compound was prepared from 4-(1-methylethyl)benzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=7.0 Hz), 1.40 (3H, d, J=5.4 Hz), 2.12 (1H, d, J=3.2 Hz), 2.51—2.63 (2H, m), 2.87—3.03 (1H, m), 7.31 (2H, d, J=8.4 Hz), 7.96 (2H, d, J=8.4 Hz).

1-(3,4-Dimethylbenzoyl)-2-methylaziridine (2o) This compound was prepared from 3,4-dimethylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J=5.5 Hz), 2.12 (1H, d, J=3.3 Hz), 2.32 (6H, s), 2.49—2.61 (2H, m), 7.21 (1H, d, J=7.7 Hz), 7.77 (1H, dd, J=7.7, 1.8 Hz), 7.80 (1H, d, J=1.8 Hz).

1-(3,5-Dimethylbenzoyl)-2-methylaziridine (2p) This compound was prepared from 3,5-dimethylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J=5.5 Hz), 2.13 (1H, d, J=3.7 Hz), 2.37 (6H, s), 2.47—2.62 (2H, m), 7.19 (1H, s), 7.64 (2H, s).

1-(3,4-Dimethoxybenzoyl)-2-methylaziridine (2q) This compound was prepared from 3,4-dimethoxybenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, J=5.5 Hz), 2.12 (1H, d, J=3.3 Hz), 2.51—2.63 (2H, m), 3.94 (3H, s), 3.95 (3H, s), 6.92 (1H, d, J=8.5 Hz), 7.56 (1H, d, J=2.2 Hz), 7.69 (1H, dd, J=8.5, 2.2 Hz).

1-(1,3-Benzodioxol-5-ylcarbonyl)-2-methylaziridine (2r) This compound was prepared from 1,3-benzodioxol-5-ylcarbonyl chloride as described in the synthesis of **2j**, as an oil, yield 92%, ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=4.9 Hz), 2.11 (1H, d, J=3.1 Hz), 2.48—2.64 (2H, m), 6.05 (2H, s), 6.86 (1H, d, J=8.2 Hz), 7.48 (1H, d, J=1.7 Hz), 7.65 (1H, dd, J=8.2, 1.7 Hz).

1-(4-Ethylphenyl)-2-(4-pyridyl)ethanone (4l) Under argon atmosphere, a solution of diisopropylamine (15.4 ml) in tetrahydrofuran (100 ml) was cooled to −78 °C and a solution of 1.6 M *n*-butyllithium in hexane (68.3 ml) was added dropwise to the solution. After addition, the solution was stirred for 10 min and a solution of 4-methylpyridine (**3a**) (9.31 g) in tetrahydrofuran (10 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 **2j** (18.9 g) in tetrahydrofuran (10 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 crude crystals, which were recrystallized from ethyl acetate–isopropyl ether to afford 9.78 g (yield 43%) of **4l** as a solid, mp 87—89 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.5 Hz), 2.72 (2H, q, J=7.5 Hz), 4.27 (2H, s), 7.21 (2H, d, J=6.2 Hz), 7.31 (2H, d, J=8.4 Hz), 7.93 (2H, d, J=8.4 Hz), 8.56 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.83; H, 6.72; N, 6.20.

1-(4-Propylphenyl)-2-(4-pyridyl)ethanone (4m) This compound was prepared from **2k** as described in the synthesis of **4l** as a solid, yield 32%, mp 71—72 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.57—1.76 (2H, m), 2.66 (2H, t, J=7.7 Hz), 4.27 (2H, s), 7.21 (2H, d, J=6.2 Hz), 7.29 (2H, d, J=8.6 Hz), 7.92 (2H, d, J=8.6 Hz), 8.56 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.33; H, 7.16; N, 5.79.

1-(4-Butylphenyl)-2-(4-pyridyl)ethanone (4n) This compound was prepared from **2l** as described in the synthesis of **4l** as a solid, yield 20%, mp 41—43 °C (isopropyl ether–hexane), ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz), 1.26—1.47 (2H, m), 1.54—1.72 (2H, m), 2.68 (2H, t, J=7.7 Hz), 4.27 (2H, s), 7.21 (2H, d, J=6.0 Hz), 7.29 (2H, d, J=8.6 Hz), 7.92 (2H, d, J=8.6 Hz), 8.56 (2H, d, J=6.0 Hz). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.55; H, 7.31; N, 5.47.

1-[4-(1-Methylethyl)phenyl]-2-(4-pyridyl)ethanone (4o) This compound was prepared from **2m** as described in the synthesis of **4l** as a solid, yield 43%, mp 86—88 °C (isopropyl ether–hexane), ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, d, J=7.0 Hz), 2.87—3.06 (1H, m), 4.27 (2H, s), 7.21 (2H, d, J=6.2 Hz), 7.34 (2H, d, J=8.4 Hz), 7.94 (2H, d, J=8.4 Hz), 8.56 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.29; H, 7.18; N, 5.84.

1-[4-(*N*,*N*-Dimethylamino)phenyl]-2-(4-pyridyl)ethanone (4q) Under argon atmosphere, a solution of diisopropylamine (15.4 ml) in tetrahydrofuran (100 ml) was cooled to −78 °C and a solution of 1.6 M *n*-butyllithium in hexane (68.3 ml) was added dropwise to the solution. After addition, the solution was stirred for 10 min and a solution of 4-methylpyridine (**3a**) (9.31 g) in tetrahydrofuran (10 ml) was added dropwise to the LDA solution. The reaction mixture was allowed to warm up to −10 °C and stirred for 1 h. A solution of ethyl 4-(*N*,*N*-dimethylamino)benzoate (21.3 g) in tetrahydrofuran (10 ml) was added dropwise to the mixture. After addition, the mixture was stirred for 1 h at −10 °C and then the reaction mixture was allowed to warm to room temperature. Water (100 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 washed, dried and concentrated to give crude crystals, which were recrystallized from ether to afford 7.19 g (yield 30%) of **4q** as a solid, mp 189—192 °C, ^{1}H-NMR ($CDCl_3$) δ: 3.07 (6H, s), 4.19 (2H, s), 6.66 (2H, d, J=9.0 Hz), 7.22 (2H, d, J=5.9 Hz), 7.90 (2H, d, J=9.0 Hz), 8.53 (2H, d, J=5.9 Hz). *Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.98; H, 6.78; N, 11.65.

1-(3,4-Dimethylphenyl)-2-(4-pyridyl)ethanone (4r) This compound was prepared from **2o** as described in the synthesis of **4l** as a solid, yield 40%, mp 81—83 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 2.33 (6H, s), 4.26 (2H, s), 7.21 (2H, d, J=5.9 Hz), 7.24 (1H, d, J=7.9 Hz), 7.73 (1H, dd, J=7.9, 1.8 Hz), 7.77 (1H, d, J=1.8 Hz), 8.56 (2H, d, J=5.9 Hz). *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.89; H, 6.72; N, 6.15.

1-(3,5-Dimethylphenyl)-2-(4-pyridyl)ethanone (4s) This compound was prepared from **2p** as described in the synthesis of **4l** as a solid, yield 58%, mp 90—91 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 2.38 (6H, s), 4.26 (2H, s), 7.20 (2H, d, J=5.9 Hz), 7.24 (1H, s), 7.60 (2H, s), 8.56 (2H, d, J=5.9 Hz). *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.83; H, 6.73; N, 6.18.

1-(3,4-Dimethoxyphenyl)-2-(4-pyridyl)ethanone (4t) This compound was prepared from **2q** as described in the synthesis of **4l** as a solid, yield 29%, mp 110—111 °C (ethyl acetate–hexane), ^{1}H-NMR ($CDCl_3$) δ: 3.94 (3H, s), 3.97 (3H, s), 4.26 (2H, s), 6.91 (1H, d, J=8.4 Hz), 7.22 (2H, d, J=5.9 Hz), 7.55 (1H, d, J=2.0 Hz), 7.64 (1H, dd, J=8.4, 2.0 Hz), 8.56 (2H,

d, J=5.9 Hz). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.97; H, 5.81; N, 5.47.

1-(1,3-Benzodioxol-5-yl)-2-(4-pyridyl)ethanone (4u) This compound was prepared from **2r** as described in the synthesis of **4l** as a solid, yield 36%, mp 126—127 °C (ethyl acetate–isopropyl ether), ^{1}H-NMR ($CDCl_3$) δ: 4.21 (2H, s), 6.07 (2H, s), 6.87 (1H, d, J=8.2 Hz), 7.20 (2H, d, J=6.0 Hz), 7.46 (1H, d, J=1.7 Hz), 7.61 (1H, dd, J=8.2, 1.7 Hz), 8.56 (2H, d, J=6.0 Hz). *Anal.* Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.76; H, 4.53; N, 5.78.

1-[4-(1,1-Dimethylethyl)phenyl]-2-(3-pyridyl)ethanone (4v) This compound was prepared from **2n** and 3-methylpyridine as described in the synthesis of **4l** as an oil, yield 28%, ^{1}H-NMR ($CDCl_3$) δ: 1.34 (9H, s), 4.28 (2H, s), 7.22—7.31 (1H, m), 7.50 (2H, d, J=8.4 Hz), 7.56—7.65 (1H, m), 7.94 (2H, d, J=8.4 Hz), 8.48—8.55 (2H, m). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.45; N, 5.41.

1-(3,5-Dimethylphenyl)-2-(3-pyridyl)ethanone (4w) This compound was prepared from **2p** and 3-methylpyridine as described in the synthesis of **4l** as an oil, yield 11%, ^{1}H-NMR ($CDCl_3$) δ: 2.38 (6H, s), 4.27 (2H, s), 7.24—7.30 (2H, m), 7.58—7.63 (3H, m), 8.50—8.52 (2H, m). *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.89; H, 6.72; N, 6.13.

2-Bromo-1-(4-ethylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5l) Bromine (1.1 ml, 22 mmol) was added dropwise to a solution of **4l** (5.0 g, 22 mmol) in acetic acid (22 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 crystals were collected by filtration and washed with ethyl acetate to afford 6.1 g (yield 71%) of **5l** as a solid, ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7.6 Hz), 2.72 (2H, q, J=7.6 Hz), 6.38 (1H, br s), 7.29 (1H, s), 7.45 (2H, d, J=8.1 Hz), 8.07 (2H, d, J=8.1 Hz), 8.15 (2H, d, J=6.2 Hz), 8.94 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{14}BrNO\cdot HBr\cdot 0.5H_2O$: C, 45.71; H, 4.09; N, 3.55. Found: C, 45.86; H, 3.99; N, 3.48.

2-Bromo-1-(4-propylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5m) This compound was prepared from **4m** as described in the synthesis of **5l** as a solid, yield 90%, ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.1 Hz), 1.53—1.74 (2H, m), 2.67 (2H, t, J=7.3 Hz), 5.14 (1H, br s), 7.25 (1H, s), 7.42 (2H, t, J=7.1 Hz), 8.06 (2H, d, J=7.1 Hz), 8.10 (2H, d, J=5.3 Hz), 8.91 (2H, d, J=5.3 Hz). *Anal.* Calcd for $C_{16}H_{16}BrNO\cdot HBr$: C, 48.15; H, 4.29; N, 3.51. Found: C, 48.04; H, 4.19; N, 3.43.

2-Bromo-1-(4-butylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5n) This compound was prepared from **4n** as described in the synthesis of **5l** as a solid, yield 88%, ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.3 Hz), 1.22—1.43 (2H, m), 1.51—1.69 (2H, m), 2.69 (2H, t, J=7.5 Hz), 6.12 (1H, br s), 7.29 (1H, s), 7.43 (2H, t, J=8.1 Hz), 8.07 (2H, d, J=8.1 Hz), 8.18 (2H, d, J=5.9 Hz), 8.96 (2H, d, J=5.9 Hz). *Anal.* Calcd for $C_{17}H_{19}BrNO\cdot HBr\cdot 1.5H_2O$: C, 46.39; H, 5.04; N, 3.18. Found: C, 46.61; H, 5.26; N, 3.05.

2-Bromo-1-[4-(1-methylethyl)phenyl]-2-(4-pyridyl)ethanone Hydrobromide (5o) This compound was prepared from **4o** as described in the synthesis of **5l** as a solid, yield 93%, ^{1}H-NMR (DMSO-d_6) δ: 1.24 (6H, d, J=6.6 Hz), 2.92—3.09 (1H, m), 5.75 (1H, br s), 7.27 (1H, s), 7.48 (2H, d, J=8.2 Hz), 8.08 (2H, d, J=8.2 Hz), 8.13 (2H, d, J=6.7 Hz), 8.93 (2H, d, J=6.7 Hz). *Anal.* Calcd for $C_{16}H_{16}BrNO\cdot HBr$: C, 48.15; H, 4.29; N, 3.51. Found: C, 48.15; H, 4.23; N, 3.34.

2-Bromo-1-[4-(*N*,*N*-dimethylamino)phenyl]-2-(4-pyridyl)ethanone Dihydrobromide (5q) Bromine (0.20 ml, 4.2 mmol) was added dropwise to a solution of **4q** (1.0 g, 4.2 mmol) in acetic acid (5 ml) and 30% hydrogen bromide acetic acid solution (1.23 g, 4.6 mmol) and the mixture was stirred for 3 h at 80 °C. The precipitate was collected by filtration and washed with ethyl acetate to afford 1.0 g (yield 50%) of **5q** as a solid, ^{1}H-NMR (DMSO-d_6) δ: 3.07 (6H, s), 6.24 (2H, br s), 6.78 (2H, d, J=9.0 Hz), 7.20 (1H, s), 7.97 (2H, d, J=9.0 Hz), 8.22 (2H, d, J=6.6 Hz), 8.96 (2H, d, J=6.6 Hz). *Anal.* Calcd for $C_{15}H_{15}BrN_2O\cdot 2HBr\cdot 1.5H_2O$: C, 35.46; H, 3.97; N, 5.51. Found: C, 35.64; H, 4.03; N, 5.34.

2-Bromo-1-(3,4-dimethylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5r) This compound was prepared from **4r** as described in the synthesis of **5l** as a solid, yield 94%, ^{1}H-NMR (DMSO-d_6) δ: 2.33 (6H, s), 7.32 (1H, s), 7.37 (2H, d, J=7.7 Hz), 7.85—7.96 (2H, m), 8.20 (2H, d, J=6.8 Hz), 8.97 (2H, d, J=6.8 Hz), 1H hidden. *Anal.* Calcd for $C_{15}H_{14}BrNO\cdot Br$: C, 46.78; H, 3.93; N, 3.64. Found: C, 46.51; H, 3.94; N, 3.43.

2-Bromo-1-(3,5-dimethylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5s) This compound was prepared from **4s** as described in the synthesis of **5l** as a solid, yield 81%, ^{1}H-NMR (DMSO-d_6) δ: 2.38 (6H, s), 5.71 (1H, br s), 7.28 (1H, s), 7.38 (1H, s), 7.77 (2H, s), 8.16 (2H, d, J=5.5 Hz), 8.95 (2H, d, J=5.5 Hz). *Anal.* Calcd for $C_{15}H_{14}BrNO\cdot HBr$: C, 46.78; H, 3.93; N, 3.64. Found: C, 46.68; H, 4.22; N, 3.40.

2-Bromo-1-(3,4-dimethoxyphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5t) This compound was prepared from **4t** as described in the synthesis of **5l** as a solid, yield 79%, ^{1}H-NMR (DMSO-d_6) δ: 3.85 (3H, s), 3.89 (3H, s), 4.61 (1H, br s), 7.14 (1H, d, J=8.4 Hz), 7.28 (1H, s), 7.57 (1H, d, J=1.8 Hz), 7.86 (1H, dd, J=8.4, 1.8 Hz), 8.01 (2H, d, J=6.2 Hz), 8.85 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{14}BrNO_3\cdot HBr\cdot 0.2H_2O$: C, 42.82; H, 3.69; N, 3.33. Found: C, 42.81; H, 3.81; N, 3.24.

1-(1,3-Benzodioxol-5-yl)-2-bromo-2-(4-pyridyl)ethanone Hydrobromide (5u) This compound was prepared from **4u** as described in the synthesis of **5l** as a solid, yield 91%, ^{1}H-NMR (DMSO-d_6) δ: 5.02 (1H, br s), 6.19 (2H, s), 7.13 (1H, d, J=8.3 Hz), 7.24 (1H, s), 7.60 (1H, d, J=1.5 Hz), 7.82 (1H, dd, J=8.3, 1.5 Hz), 8.18 (2H, d, J=7.5 Hz), 8.92 (2H, d, J=7.5 Hz). *Anal.* Calcd for $C_{14}H_{10}BrNO_3\cdot HBr\cdot 0.2H_2O$: C, 41.55; H, 2.84; N, 3.46. Found: C, 41.60; H, 2.92; N, 3.37.

2-Bromo-[4-(1,1-dimethylethyl)phenyl]-2-(3-pyridyl)ethanone Hydrobromide (5v) This compound was prepared from **4v** as described in the synthesis of **5l** as a solid, yield 66%, ^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 4.53 (1H, br s), 7.25 (1H, s), 7.63 (2H, d, J=8.5 Hz), 7.94—8.08 (1H, m), 8.09 (2H, d, J=8.5 Hz), 8.57—8.71 (1H, m), 8.84—8.93 (1H, m), 9.04—9.13 (1H, m). *Anal.* Calcd for $C_{16}H_{16}BrNO\cdot HBr\cdot H_2O$: C, 46.07; H, 4.59; N, 3.36. Found: C, 46.19; H, 4.22; N, 2.99.

2-Bromo-1-(3,5-dimethylphenyl)-2-(3-pyridyl)ethanone Hydrobromide (5w) This compound was prepared from **4w** as described in the synthesis of **5l** as a solid, yield 92%, ^{1}H-NMR (DMSO-d_6) δ: 2.38 (6H, s), 6.45 (1H, br s), 7.28 (1H, s), 7.37 (1H, s), 7.78 (2H, s), 8.01—8.08 (1H, m), 8.65—8.69 (1H, m), 8.89—8.92 (1H, m), 9.10—9.11 (1H, m). *Anal.* Calcd for $C_{15}H_{14}BrNO\cdot HBr\cdot 0.5H_2O$: C, 45.71; H, 4.09; N, 3.55. Found: C, 45.67; H, 3.95; N, 3.49.

[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]amine (6d) Thiourea (3.3 g, 46 mmol) was added to a mixture of 4′-methoxyphenacyl bromide (10 g, 44 mmol) in acetonitrile (260 ml). 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 ether successively. The crude crystals were recrystallized from ethanol to afford 6.5 g (yield 73%) of **6d** as a solid, mp 203—204 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 3.77 (3H, s), 6.80 (1H, s), 6.91 (2H, d, J=8.8 Hz), 6.98 (2H, br s), 7.72 (2H, d, J=8.8 Hz). *Anal.* Calcd for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.08; H, 4.86; N, 13.91.

***N*-[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]methylamine (6e)** *N*-Methylthiourea (3.8 g, 43 mmol) was added to a mixture of **5a** (15 g, 39 mmol) in acetonitrile (200 ml) and then triethylamine (5.7 ml, 41 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 ether successively. The crude crystals were recrystallized from ethanol to afford 11 g (yield 88%) of **6e** as a solid, mp 175—177 °C (ethyl acetate), ^{1}H-NMR (DMSO-d_6) δ: 2.88 (3H, d, J=4.8 Hz), 3.78 (3H, s), 6.92 (2H, d, J=8.4 Hz), 7.08 (2H, d, J=6.0 Hz), 7.36 (2H, d, J=8.4 Hz), 7.91 (1H, q, J=4.8 Hz), 8.38 (2H, d, J=6.0 Hz). *Anal.* Calcd for $C_{16}H_{15}N_3OS\cdot 0.5H_2O$: C, 62.72; H, 5.26; N, 13.71. Found: C, 62.66; H, 5.05; N, 14.07.

[4-(4-Ethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6n) This compound was prepared from **5l** as described in the synthesis of **6e** as a solid, yield 71%, mp 285—288 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7.5 Hz), 2.62 (2H, q, J=7.5 Hz), 7.08 (2H, d, J=6.2 Hz), 7.17 (2H, d, J=8.1 Hz), 7.32 (2H, d, J=8.1 Hz), 7.40 (2H, br s), 8.37 (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, 68.14; H, 5.40; N, 15.09.

[4-(4-Propylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6o) This compound was prepared from **5m** as described in the synthesis of **6e** as a solid, yield 94%, mp 240—242 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.3 Hz), 1.50—1.72 (2H, m), 2.57 (2H, t, J=7.9 Hz), 7.08 (2H, d, J=4.9 Hz), 7.16 (2H, d, J=7.9 Hz), 7.31 (2H, d, J=7.9 Hz), 7.42 (2H, br s), 8.38 (2H, d, J=4.9 Hz). *Anal.* Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.86; H, 5.82; N, 14.25.

[4-(4-Butylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6p) This compound was prepared from **5n** as described in the synthesis of **6e** as a solid, yield 63%, mp 204—206 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.1 Hz), 1.24—1.43 (2H, m), 1.49—1.66 (2H, m), 2.59 (2H, t, J=7.7 Hz), 7.07 (2H, d, J=6.0 Hz), 7.15 (2H, d, J=7.9 Hz), 7.31 (2H, d, J=7.9 Hz), 7.36 (2H, br s), 8.37 (2H, d, J=6.0 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, 67.98; H, 6.13; N, 13.23.

[4-[4-(1-Methylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6q)

This compound was prepared from **5o** as described in the synthesis of **6e** as a solid, yield 77%, mp 267—269 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6.9 Hz), 2.82—2.98 (1H, m), 7.10 (2H, d, J=6.1 Hz), 7.21 (2H, d, J=8.3 Hz), 7.34 (2H, d, J=8.3 Hz), 7.40 (2H, br s), 8.39 (2H, d, J=6.1 Hz). *Anal.* Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.08; H, 5.52; N, 14.25.

[4-(*N*,*N*-Dimethylamino)phenyl-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6s) This compound was prepared from **5q** as described in the synthesis of **6e** as a solid, yield 54%, mp 309—311 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 2.93 (6H, s), 6.65 (2H, d, J=9.0 Hz), 7.10 (2H, d, J=6.2 Hz), 7.25 (2H, d, J=9.0 Hz), 7.32 (2H, br s), 8.36 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90. Found: C, 64.49; H, 5.40; N, 18.82.

[4-(3,4-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6t) This compound was prepared from **5r** as described in the synthesis of **6e** as a solid, yield 96%, mp 248—250 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 2.23 (3H, s), 7.05—7.11 (4H, m), 7.24 (1H, s), 7.37 (2H, br s), 8.36 (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, 68.62; H, 5.39; N, 15.13.

[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6u) This compound was prepared from **5s** as described in the synthesis of **6e** as a solid, yield 55%, mp 242—244 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.22 (6H, s), 6.97 (1H, s), 7.01 (2H, s), 7.07 (2H, d, J=6.2 Hz), 7.39 (2H, br s), 8.37 (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, 68.17; H, 5.34; N, 14.70.

[4-(3,4-Dimethoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6v) This compound was prepared from **5t** as described in the synthesis of **6e** as a solid, yield 70%, mp 218—219 °C (pyridine), ^{1}H-NMR (DMSO-d_6) δ: 3.68 (3H, s), 3.81 (3H, s), 6.90—6.99 (2H, m), 7.02 (1H, s), 7.27 (2H, d, J=6.8 Hz), 7.74 (2H, br s), 8.43 (2H, d, J=6.8 Hz). *Anal.* Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.45; H, 4.40; N, 13.02.

[4-(1,3-Benzodioxol-5-yl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6w) This compound was prepared from **5u** as described in the synthesis of **6e** as a solid, yield 79%, mp 273—275 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 6.04 (2H, s), 6.83—6.92 (3H, m), 7.09 (2H, d, J=6.2 Hz), 7.37 (2H, br s), 8.39 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.67; H, 3.81; N, 14.24.

[4-[4-(1,1-Dimethylethyl)phenyl]-5-(3-pyridyl)-1,3-thiazol-2-yl]amine (6x) This compound was prepared from **5v** as described in the synthesis of **6e** as a solid, yield 82%, mp 239—241 °C (ethanol–ethyl acetate), ^{1}H-NMR (DMSO-d_6) δ: 1.27 (9H, s), 7.21 (2H, br s), 7.30 (4H, s), 7.34 (1H, dd, J=8.2, 4.9 Hz), 7.62 (1H, ddd, J=8.2, 2.2, 1.8 Hz), 8.38 (1H, d, J=2.2 Hz), 8.41 (1H, dd, J=4.9, 1.8 Hz). *Anal.* Calcd for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58. Found: C, 69.75; H, 6.17; N, 13.43.

[4-(3,5-Dimethylphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine (6y) This compound was prepared from **5w** as described in the synthesis of **6e** as a solid, yield 52%, mp 237—240 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.17 (6H, s), 6.91 (1H, s), 6.97 (2H, s), 7.22 (2H, br s), 7.27—7.33 (1H, m), 7.55—7.59 (1H, m), 8.36—8.42 (2H, m). *Anal.* Calcd for $C_{16}H_{15}N_3OS$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.03; H, 5.25; N, 14.87.

[4-(4-Hydroxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6z) A solution of **6a** (7.3 g) in 47% hydrobromic acid (60 ml) was refluxed for 5 h. The resulting mixture was cooled with an ice bath and neutralized with 8 N aqueous sodium hydroxide. The precipitate was collected by filtration and washed with water. The crude crystals were washed with ethanol and dried to afford 7.09 g (28 mmol, yield quant.) of **6z** as a solid, mp 323—326 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 6.76 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=6.6 Hz), 7.26 (2H, d, J=8.8 Hz), 7.69 (2H, br s), 8.41 (2H, d, J=6.6 Hz), 9.74 (1H, br s). *Anal.* Calcd for $C_{14}H_{11}N_3OS \cdot 3H_2O$: C, 52.00; H, 5.30; N, 12.99. Found: C, 51.64; H, 4.99; N, 12.96.

Ethyl [4-(4-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetate (6aa) This compound was prepared from ethyl thiocarbamoylacetate[31] as described in the synthesis of **6a** as an oil, yield 77%, ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7.0 Hz), 3.82 (3H, s), 4.12 (2H, s), 4.27 (2H, q, J=7.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=6.2 Hz), 7.41 (2H, d, J=9.0 Hz), 8.54 (2H, d, J=6.2 Hz).

***N*-[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]acetamide (7d)** A solution of ethyl cyanoacetate (1.2 g, 10 mmol) and **6d** (2.1 g, 10 mmol) in acetic acid (10 ml) was refluxed for 38 h. The solvent was removed *in vacuo* and the reside was treated with aqueous sodium hydrogen carbonate. The crude crystals were collected by filtration and washed, and then recrystallized from ethanol to afford 4.2 g (yield 47%) of **7d** as a solid, mp 192—193 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.16 (3H, s), 3.79 (3H, s), 6.98 (2H, d, J=8.8 Hz), 7.41 (1H, s), 7.82 (2H, d, J=8.8 Hz), 12.19 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.06; H, 4.69; N, 11.28.

***N*-[4-(4-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]-*N*-methylacetamide (7e)** Acetyl chloride (3.8 g, 48 mmol) was added to a solution of **6e** (10 g, 32 mmol) and 4-dimethylaminopyridine (1.2 g, 9.6 mmol) in *N*,*N*-dimethylacetamide (50 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. Extracts were washed with brine, dried and concentrated to give a solid. The crude crystals were recrystallized from ethanol to afford 7.0 g (yield 65%) of **7e** as a solid, mp 180—181 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s), 3.71 (3H, s), 3.78 (3H, s), 6.94 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=5.9Hz), 7.40 (2H, d, J=8.4 Hz), 8.52 (2H, d, J=5.9 Hz). *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.40; H, 5.01; N, 12.18.

***N*-[4-(4-Ethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7n)** This compound was prepared from **6n** as described in the synthesis of **7e** as a solid, yield 47%, mp 294—295 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7.5 Hz), 2.19 (3H, s), 2.63 (2H, q, J=7.5 Hz), 7.21 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=6.0 Hz), 7.36 (2H, d, J=8.1 Hz), 8.50 (2H, d, J=6.0 Hz), 12.45 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3OS \cdot 0.1H_2O$: C, 66.48; H, 5.33; N, 12.92. Found: C, 66.41; H, 5.03; N, 12.88.

***N*-[4-(4-Propylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7o)** This compound was prepared from **6o** as described in the synthesis of **7e** as a solid, yield 57%, mp 256—258 °C (ethyl acetate), ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.3 Hz), 1.50—1.72 (2H, m), 2.19 (3H, s), 2.57 (2H, t, J=7.3 Hz), 7.18 (2H, d, J=8.1 Hz), 7.26 (2H, d, J=6.2 Hz), 7.35 (2H, d, J=8.1 Hz), 8.50 (2H, d, J=6.2 Hz), 12.42 (1H, br s). *Anal.* Calcd for $C_{19}H_{19}N_3OS \cdot 0.2H_2O$: C, 66.91; H, 5.73; N, 12.32. Found: C, 66.82; H, 5.70; N, 12.26.

***N*-[4-(4-Butylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7p)** This compound was prepared from **6p** as described in the synthesis of **7e** as a solid, yield 57%, mp 259—261 °C (ethyl acetate), ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.1 Hz), 1.25—1.43 (2H, m), 1.46—1.66 (2H, m), 2.19 (3H, s), 2.59 (2H, t, J=7.5 Hz), 7.18 (2H, d, J=8.1 Hz), 7.25 (2H, d, J=6.2 Hz), 7.35 (2H, d, J=8.1 Hz), 8.49 (2H, d, J=6.2 Hz), 12.42 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}N_3OS$: C, 68.35; H, 6.02; N, 11.96. Found: C, 68.10; H, 5.81; N, 11.82.

***N*-[4-[4-(1-Methylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7q)** This compound was prepared from **6q** as described in the synthesis of **7e** as a solid, yield 62%, mp 295—297 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=7.0 Hz), 2.19 (3H, s), 2.82—2.99 (1H, m), 7.19—7.30 (4H, m), 7.37 (2H, d, J=8.1 Hz), 8.51 (2H, d, J=5.9 Hz), 12.42 (1H, br s). *Anal.* Calcd for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.68; N, 12.45. Found: C, 67.66; H, 5.66; N, 12.55.

***N*-[4-[4-(*N*,*N*-Dimethylamino)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]-acetamide (7s)** A 4 N hydrogen chloride in ethyl acetate (0.37 ml) was added to a solution of **6s** (0.40 g, 1.4 mmol) in *N*,*N*-dimethylacetamide (4.0 ml) and acetyl chloride (0.16 g, 2.0 mmol) was added to the mixture. The resulting mixture was stirred at 80 °C for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was washed with water and dried. The crude crystals were recrystallized from ethanol to afford 0.26 g (yield 56%) of **7s** as a solid, mp 289—291 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.18 (3H, s), 2.93 (6H, s), 6.67 (2H, d, J=8.8 Hz), 7.24—7.32 (4H, m), 8.48 (2H, d, J=6.3 Hz), 12.34 (1H, br s). *Anal.* Calcd for $C_{18}H_{18}N_4OS \cdot 0.2H_2O$: C, 63.21; H, 5.42; N, 16.38. Found: C, 63.08; H, 5.40; N, 16.42.

***N*-[4-(3,4-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7t)** This compound was prepared from **6t** as described in the synthesis of **7e** as a solid, yield 29%, mp 248—250 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (6H, s), 2.24 (3H, s), 7.10 (2H, s), 7.22—7.30 (3H, m), 8.49 (2H, d, J=5.9 Hz), 12.43 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.66; H, 5.28; N, 13.08.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7u)** This compound was prepared from **6u** as described in the synthesis of **7e** as a solid, yield 29%, mp 284—286 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 2.22 (6H, s), 7.00 (1H, s), 7.04 (2H, s), 7.26 (2H, d, J=6.2 Hz), 8.50 (2H, d, J=6.2 Hz), 12.43 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3OS \cdot 0.1H_2O$: C, 66.48; H, 5.33; N, 12.92. Found: C, 66.35; H, 5.21; N, 13.07.

***N*-[4-(3,4-Dimethoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7v)** This compound was prepared from **6v** as described in the synthesis of **7e** as a solid, yield 62%, mp 265—267 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.62 (3H, s), 3.77 (3H, s), 6.94 (2H, s), 7.02 (1H, s), 7.29 (2H, d, J=5.7 Hz), 8.52 (2H, d, J=5.7 Hz), 12.45 (1H, br s). *Anal.* Calcd for

$C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82. Found: C, 60.70; H, 4.73; N, 11.83.

***N*-[4-(1,3-Benzodioxol-5-yl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7w)** This compound was prepared from **6w** as described in the synthesis of **7e** as a solid, yield 68%, mp 295—296 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 6.05 (2H, s), 6.86—6.96 (3H, m), 7.27 (2H, d, J=6.0 Hz), 8.51 (2H, d, J=6.0 Hz), 12.40 (1H, br s). *Anal.* Calcd for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found: C, 60.04; H, 3.88; N, 12.44.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide (7x)** This compound was prepared from **6r** and propionyl chloride as described in the synthesis of **7a** as a solid, yield 74%, mp 295—297 °C (ethyl acetate–ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.13 (3H, t, J=7.5 Hz), 1.29 (9H, s), 2.49 (2H, q, J=7.5 Hz), 7.28 (2H, d, J=6.2 Hz), 7.38 (4H, s), 8.51 (2H, d, J=6.2 Hz), 12.41 (1H, br s). *Anal.* Calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 68.88; H, 6.36; N, 11.50.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]cyclopentanecarboxamide (7y)** This compound was prepared from **6r** and cyclopentanecarbonyl chloride as described in the synthesis of **7e** as a solid, yield 74%, mp 309—311 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.29 (9H, s), 1.53—2.01 (8H, m), 2.91—3.05 (1H, m), 7.27 (2H, d, J=6.2 Hz), 7.38 (4H, s), 8.52 (2H, d, J=6.2 Hz), 12.40 (1H, br s). *Anal.* Calcd for $C_{24}H_{27}N_3OS$: C, 71.08; H, 6.71; N, 10.36. Found: C, 71.00; H, 6.76; N, 10.26.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]benzamide (7z)** This compound was prepared from **6r** and benzoyl chloride as described in the synthesis of **7e** as a solid, yield 74%, mp 292—294 °C (ethyl acetate–ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.31 (9H, s), 7.33 (2H, d, J=6.1 Hz), 7.40 (2H, d, J=8.9 Hz), 7.48 (2H, d, J=8.9 Hz), 7.52—7.72 (3H, m), 8.16 (2H, d, J=7.0 Hz), 8.55 (2H, d, J=6.1 Hz), 12.39 (1H, br s). *Anal.* Calcd for $C_{25}H_{23}N_3OS$: C, 72.61; H, 5.61; N, 10.16. Found: C, 72.53; H, 5.45; N, 10.28.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]-nicotinamide (7aa)** This compound was prepared from **6r** and nicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 73%, mp 326—328 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.31 (9H, s), 7.32 (2H, d, J=5.9 Hz), 7.42 (4H, s), 7.59 (1H, dd, J=8.1, 4.8 Hz), 8.47 (1H, dd, J=8.1, 2.2 Hz), 8.54 (2H, d, J=5.9 Hz), 8.81 (1H, d, J=4.8 Hz), 9.26 (1H, d, J=2.2 Hz), 12.39 (1H, br s). *Anal.* Calcd for $C_{24}H_{22}N_4OS$: C, 69.54; H, 5.35; N, 13.52. Found: C, 69.51; H, 5.30; N, 13.82.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]isonicotinamide (7ab)** This compound was prepared from **6r** and isonicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 74%, mp 326—329 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.31 (9H, s), 7.32 (2H, d, J=6.2 Hz), 7.42 (4H, s), 8.03 (2H, d, J=6.2 Hz), 8.55 (2H, d, J=6.2 Hz), 8.83 (2H, d, J=6.2 Hz), 12.40 (1H, br s). *Anal.* Calcd for $C_{24}H_{22}N_4OS$: C, 69.54; H, 5.35; N, 13.52. Found: C, 69.53; H, 5.32; N, 13.66.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide (7ac)** This compound was prepared from **6u** and propionyl chloride as described in the synthesis of **7e** as a solid, yield 67%, mp 291—293 °C (ethanol), ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.6 Hz), 2.01 (2H, q, J=7.6 Hz), 2.27 (6H, s), 7.01 (1H, s), 7.08 (2H, s), 7.22—7.25 (2H, m), 8.50—8.53 (2H, m), 10.60 (1H, br s). *Anal.* Calcd for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.68; N, 12.45. Found: C, 67.57; H, 5.52; N, 12.48.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]cyclopentanecarboxamide (7ad)** This compound was prepared from **6u** and cyclopentanecarbonyl chloride as described in the synthesis of **7e** as a solid, yield 59%, mp 275—278 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.52—1.98 (8H, m), 2.21 (6H, s), 2.92—3.00 (1H, m), 7.00 (1H, s), 7.05 (2H, s), 7.25—7.28 (2H, m), 8.49—8.52 (2H, m), 12.43 (1H, br s). *Anal.* Calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.76; H, 6.05; N, 11.13.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]benzamide (7ae)** This compound was prepared from **6u** and benzoyl chloride as described in the synthesis of **7e** as a solid, yield 26%, mp 285—286 °C (ethanol), ^{1}H-NMR ($CDCl_3$) δ: 2.23 (6H, s), 6.93 (1H, s), 7.03 (2H, s), 7.26—7.29 (2H, m), 7.43—7.63 (3H, m), 7.87—7.91 (2H, m), 8.50—8.54 (2H, m), 10.37 (1H, br s). *Anal.* Calcd for $C_{23}H_{19}N_3OS$: C, 71.66; H, 4.97; N, 10.90. Found: C, 71.39; H, 4.91; N, 11.14.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide (7af)** This compound was prepared from **6u** and nicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 61%, mp 267—270 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.23 (6H, s), 7.03 (1H, s), 7.10 (2H, s), 7.32 (2H, d, J=6.0 Hz), 7.58—7.65 (1H, m), 8.45—8.56 (3H, m), 8.81—8.84 (1H, m), 9.26—9.27 (1H, m), 13.21 (1H, br s). *Anal.* Calcd for $C_{22}H_{18}N_4OS$: C, 68.37; H, 4.69; N, 14.50. Found: C, 68.25; H, 4.57; N, 14.50.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]isonicotinamide (7ag)** This compound was prepared from **6u** and isonicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 32%, mp 302—304 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.23 (6H, s), 7.02 (1H, s), 7.09 (2H, s), 7.31 (2H, d, J=6.2 Hz), 8.03 (2H, d, J=6.2 Hz), 8.53 (2H, d, J=5.9 Hz), 8.83 (2H, d, J=5.9 Hz), 13.29 (1H, br s). *Anal.* Calcd for $C_{22}H_{18}N_4OS \cdot 0.2H_2O$: C, 67.74; H, 4.75; N, 14.36. Found: C, 67.81; H, 4.72; N, 14.35.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide (7ah)** This compound was prepared from **6x** as described in the synthesis of **7e** as a solid, yield 67%, mp 228—230 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.28 (9H, s), 2.19 (3H, s), 7.35 (4H, s), 7.41 (1H, dd, J=7.7, 4.8 Hz), 7.76 (1H, ddd, J=7.7, 2.2, 1.5 Hz), 8.48 (1H, d, J=2.2 Hz), 8.52 (1H, dd, J=4.8, 1.5 Hz), 12.36 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}N_3OS \cdot 0.3H_2O$: C, 67.31; H, 6.10; N, 11.77. Found: C, 67.31; H, 6.11; N, 11.53.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(3-pyridyl)-1,3-thiazol-2-yl]-nicotinamide (7ai)** This compound was prepared from **6x** and nicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 63%, mp 251—253 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 1.29 (9H, s), 7.37 (2H, d, J=8.9 Hz), 7.42 (2H, d, J=8.9 Hz), 7.43 (1H, dd, J=7.7, 4.8 Hz), 7.60 (1H, dd, J=8.0, 4.8 Hz), 7.81 (1H, ddd, J=7.7, 2.2, 1.7 Hz), 8.48 (1H, ddd, J=8.0, 2.1, 1.7 Hz), 8.54 (1H, d, J=2.2 Hz), 8.55 (1H, dd, J=4.8, 1.7 Hz), 8.82 (1H, dd, J=4.8, 1.7 Hz), 9.27 (1H, d, J=2.1 Hz), 12.37 (1H, br s). *Anal.* Calcd for $C_{24}H_{22}N_4OS$: C, 69.54; H, 5.35; N, 13.52. Found: C, 69.47; H, 5.39; N, 13.46.

***N*-[4-(3,5-Dimethylphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide (7aj)** This compound was prepared from **6y** and acetyl chloride as described in the synthesis of **7e** as a solid, yield 71%, mp 288—289 °C (ethanol–ethyl acetate), ^{1}H-NMR ($CDCl_3$) δ: 1.88 (3H, s), 2.23 (6H, s), 6.95 (1H, s), 7.04 (2H, s), 7.20—7.26 (1H, m), 7.61—7.67 (1H, m), 8.51—8.55 (1H, m), 8.60—8.61 (1H, m), 10.47 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.64; H, 5.29; N, 12.84.

***N*-[4-(3,5-Dimethylphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]isonicotinamide (7ak)** This compound was prepared from **6y** and isonicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 64%, mp 277—278 °C (ethanol), ^{1}H-NMR (DMSO-d_6) δ: 2.20 (6H, s), 6.98 (1H, s), 7.07 (2H, s), 7.40—7.46 (1H, m), 7.55—7.64 (1H, m), 7.76—7.80 (1H, m), 8.45—8.53 (3H, m), 8.81 (1H, d, J=3.0 Hz), 9.26 (1H, s), 13.15 (1H, br s). *Anal.* Calcd for $C_{22}H_{18}N_4OS$: C, 68.37; H, 4.69; N, 14.50. Found: C, 68.14; H, 4.53; N, 14.51.

4-[2-(Acetylamino)-5-(4-pyridyl)-1,3-thiazol-4-yl]phenyl Acetate (9) Acetyl chloride (10.0 g, 127 mmol) was added to a solution of **6z** (6.5 g, 25 mmol) and 4-dimethylaminopyridine (0.93 g, 7.6 mmol) in *N*,*N*-dimethylacetamide (50 ml), and the resulting mixture was stirred at 80 °C for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was washed with water and dried. The crude crystals were recrystallized from ethanol to afford 5.33 g (yield 59%) of **9** as a solid, mp 254—257 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 2.28 (3H, s), 7.14 (2H, d, J=8.8 Hz), 7.28 (2H, d, J=6.0 Hz), 7.47 (2H, d, J=8.8 Hz), 8.52 (2H, d, J=6.0 Hz), 12.47 (1H, br s). *Anal.* Calcd for $C_{18}H_{15}N_3O_3S \cdot 0.2H_2O$: C, 60.56; H, 4.35; N, 11.77. Found: C, 60.61; H, 4.23; N, 11.80.

***N*-[4-(4-Hydroxyphenyl)-5-(4-pyridinyl)-1,3-thiazol-2-yl]acetamide (10)** A mixture of **9** (5.0 g, 14 mmol) and potassium carbonate (2.2 g, 16 mmol) in methanol (500 ml) was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was treated with water. The mixture was acidified with 3 N hydrochloric acid and extracted with tetrahydrofuran and ethyl acetate. Extracts were washed with brine, dried and concentrated *in vacuo* to give a solid. The crude crystals were recrystallized from ethanol to afford 4.02 g (yield 91%) of **10** as a solid, mp 285—287 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.18 (3H, s), 6.74 (2H, d, J=8.8 Hz), 7.25 (2H, d, J=8.8 Hz), 7.26 (2H, d, J=5.9 Hz), 8.49 (2H, d, J=5.9 Hz), 9.68 (1H, br s), 12.47 (1H, br s). *Anal.* Calcd for $C_{16}H_{13}N_3O_2S \cdot 0.7H_2O$: C, 59.32; H, 4.48; N, 12.97. Found: C, 59.34; H, 4.75; N, 13.12.

***N*-[4-(4-Ethoxyphenyl)-5-(4-pyridinyl)-1,3-thiazol-2-yl]acetamide (11a)** A mixture of **10** (0.40 g, 1.3 mmol) and potassium butoxide (0.15 g, 1.4 mmol) in *N*,*N*-dimethylacetamide (4.0 ml) was stirred at 0 °C for 0.5 h. Ethyl iodide (0.22 g, 1.4 mmol) was added to the mixture at 0 °C and allowed to warm up to room temperature. The mixture was stirred at room tempera-

ture for 16 h and 3 N hydrochloric acid was added to the mixture. Aqueous sodium hydrogen carbonate was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was washed with water and dried. The solid was chromatographed on silica gel eluting with hexane–ethyl acetate (1 : 2) to give crude crystals, which were recrystallized from ethyl acetate to afford 0.08 g (yield 19%) of **11a** as a solid, mp 206—209 °C, ^{1}H-NMR (DMSO-d_6) δ: 1.34 (3H, t, J=7.0 Hz), 2.45 (3H, s), 4.24 (2H, q, J=7.0 Hz), 6.75 (2H, d, J=6.2 Hz), 7.24—7.32 (4H, m), 8.50 (2H, d, J=6.2 Hz), 9.66 (1H, br s), 12.37 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.25; H, 4.99; N, 12.21.

***N*-[4-(4-Butoxyphenyl)-5-(4-pyridinyl)-1,3-thiazol-2-yl]acetamide (11b)** This compound was prepared from butyl iodide as described in the synthesis of **11a** as a solid, yield 20%, mp 201—203 °C (ethyl acetate), ^{1}H-NMR (DMSO-d_6) δ: 0.96 (3H, t, J=7.1 Hz), 1.29—1.50 (2H, m), 1.66—1.84 (2H, m), 2.45 (3H, s), 4.20 (2H, t, J=7.5 Hz), 6.75 (2H, d, J=8.8 Hz), 7.27 (2H, d, J=5.9 Hz), 7.28 (2H, d, J=8.8 Hz), 8.51 (2H, d, J=5.9 Hz), 9.68 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.05; H, 5.81; N, 11.50.

4-(4-Methoxyphenyl)-2-methyl-5-(4-pyridyl)-1,3-thiazole (12) A 2 N sodium hydroxide solution (8.5 ml, 17 mmol) was added to a solution of **6aa** (3.0 g, 8.5 mmol) in ethanol (8.5 ml) at room temperature and the resulting mixture was stirred for 2 h. The solvent was removed *in vacuo* and the residue was acidified with 3 N hydrochloric acid. The precipitate was collected by filtration and dried. The crystal was added to ethanol (100 ml) and the mixture was refluxed for 3 h. The solvent was removed *in vacuo* and the crude crystals were recrystallized from ethanol to afford 1.5 g (yield 56%) of **11** as a solid, mp 132—133 °C, ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s), 3.83 (3H, s), 6.86 (2H, d, J=9.0 Hz), 7.21 (2H, d, J=6.2 Hz), 7.41 (2H, d, J=9.0 Hz), 8.52 (2H, d, J=6.2 Hz). *Anal.* Calcd for $C_{16}H_{14}N_2OS \cdot 0.1H_2O$: C, 67.63; H, 5.04; N, 9.86. Found: C, 67.60; H, 4.99; N, 9.75.

Human A_1, A_{2A}, and A_3 Receptor and Rat A_3 Binding Assay Binding assay for A_3AR was performed in 100 μl binding assay buffer (50 mM Tris–HCl (pH 7.5), 1 mM EDTA, 10 mM $MgCl_2$, 0.25 mM PMSF, 1 mg/ml pepstatin, 20 mg/ml leupeptin) containing 10 μg of membrane protein and 20 nM [^{3}H]-NECA (Amersham Life Sciences, Inc., Tokyo) in the presence of various concentrations of compounds. Following incubation at room temperature for 1 h, the binding reaction was filtrated through the GF/C unifilter (Packard Instrument Company, Tokyo) and washed three times with ice-cold 50 mM Tris–HCl (pH 7.5), using a Cell Harvester (Packard Instrument Company, Tokyo). The filter was dried and MicroScint-O was placed on the filter. Radioactivity retained on the filter was determined by Top-Count (Packard Instrument Company, Tokyo).

IB-MECA Induced Plasma Protein Extravasation Assay Male Sprague-Dawley rats (8 weeks old, CLEA Japan, Inc.) were used under light ether anesthesia. The back of the animal was shaved and intravenously injected with 1.0 ml of 0.5% Evans blue (Tokyo Chemical Industry Co., Ltd.) in saline. Immediately, each animal was injected intradermally with 50 μl of IB-MECA (10 μM) and 50 μl of vehicle (PBS), respectively. Thirty minutes after intradermal injections, rats were sacrificed and the dorsal skin was carefully removed, and the injection sites were excised with a cork borer (15 mm diameter). For dye recovery, the skin samples were placed in test tubes containing 2 ml of a mixture of 0.3% Na_2SO_4 and acetone (3 : 7) at room temperature overnight. Plasma protein extravasation was quantitated by measuring the absorbance of Evans blue at 610 nm with a spectrophotometer (TR-1000T, CORONA ELECTRIC). The compounds were orally administered 1 h before IB-MECA intradermal injection.

Antigen-Induced Rat Asthma Model. Animals, Sensitization and Antigen Challenge Male Brown Norway rats (8 weeks old, Charles River Japan Inc., Yokohama, Japan) were sensitized by an intramuscular injection of 1 mg ovalbumin (OVA, Grade III, Sigma Chemical Co.) and 200 mg of aluminium hydroxide (Wako Pure Chemical Industries, Ltd.) in 1 ml of saline. At the same time, 1 ml of Bordetella pertussis vaccine (Wako Pure Chemical Industries, Ltd.) containing 1×10^{10} heat-killed bacilli in saline was administered intraperitoneally as an adjuvant. Three weeks after sensitization, animals were placed in a box (20×21×13 cm) and exposed to aerosolized 1% OVA or saline for 5 min. The aerosol was generated with an ultrasonic nebulizer (Atom Medical Systems).

Assessment of Airway Responsiveness Airway responsiveness to acetylcholine was measured 23—30 h after antigen challenge. The rats were anesthetized with an intraperitoneal injection of pentobarbital sodium (50 mg/kg, Abbott Laboratories). A tracheal cannula, through which the rat was mechanically ventilated, was inserted *via* a tracheotomy. A cannula was also inserted into the external jugular vein. The rat was mechanically ventilated (2—3 ml/breath, 90 breaths/min, 10 cm H_2O) (rodent ventilator MODEL683, Harvard Apparatus). Pancuronium bromide (1 mg/kg, Sigma Chemicals Co.) was then administered intravenously and 1 min later, propranol (1 mg/kg) was given intravenously. One minute after propranol administration, the rat was given aerosolized saline for 15 s and baseline was decided. After 1.5 min, the rat was given aerosolized acetylcholine at an initial dose of 3 mg/ml and then 10, 30, 100 and 300 mg/ml for 15 s at 2-min intervals. The aerosol was generated with an ultrasonic nebulizer (Aerosonic MODEL5000D; Devilbiss). Intrapulmonary pressure was measured with a transducer and the response was measured as the peak increase above the baseline. Compound **7af** (10 mg/kg) and dexamethasone (0.01 mg/kg) were orally administered 1 h before and 7 h after antigen challenge.

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