Studies on Disease-Modifying Antirheumatic Drugs. IV.[1] Synthesis of Novel Thieno[2,3-*b*:5,4-*c*′]dipyridine Derivatives and Their Anti-inflammatory Effect

Atsuo BABA,* Akira MORI, Tsuneo YASUMA, Satoko UNNO, Haruhiko MAKINO, and Takashi SOHDA

Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532–8686, Japan. Received March 2, 1999; accepted April 7, 1999

The syntheses and anti-inflammatory activities of novel thieno[2,3-*b*]pyridine and thieno[2,3-*b*:5,4-*c*′]dipyridine derivatives are described. These compounds were designed by modification of the quinoline template of a new type of disease-modifying antirheumatic drug (DMARD), TAK-603, and prepared by the Friedländer reaction as a key reaction. Their anti-inflammatory effects were evaluated using an adjuvant arthritis rat model. Most of the compounds which included a diethylamino moiety in the side chain had potent anti-inflammatory effect. In particular, ethyl 2-(diethylaminomethyl)-4-(3,4-dimethoxyphenyl)thieno[2,3-*b*:5,4-*c*′]dipyridine-3-carboxylate (21) exhibited more potent activity than TAK-603.

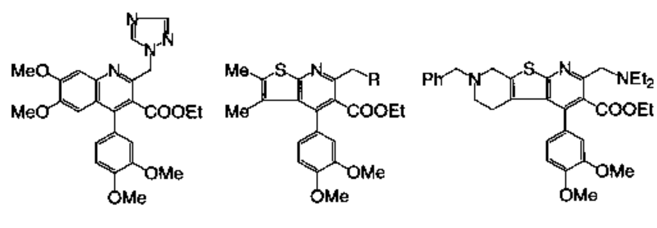
Key words thieno[2,3-*b*:5,4-*c*′]dipyridine; disease-modifying antirheumatic drug; TAK-603; adjuvant arthritis; anti-inflammatory effect

Rheumatoid arthritis (RA) is a disease of unknown etiology chracterized primarily by chronic synovitis and a broad spectrum of immune abnormalities.[2] Since RA is an autoimmune disease, disease-modifying antirheumatic drugs (DMARDs), which have selective and direct effects on the abnormal immune system, have attracted a great deal of attention as potentially effective treatments for RA.[3] In previous papers,[4—7] we reported the synthesis and biological profile of an immunomodulator of novel quinoline derivative, TAK-603 (**1**, Fig. 1), which is under clinical evaluation as a new type of DMARD.[8] In this context, our efforts were primarily directed toward the generation of new DMARDs with a diverse core structure and improved anti-inflammatory properties. As a part of these studies, thieno[2,3-*b*]pyridine derivatives **2a** and **2b** were prepared and their effects in an adjuvant arthritis (AA) rat model[9] were examined. Although compound **2a** had only decreased activity, **2b** was moderately active. Thus, **2b** was further modified by extension of its skeleton to the tricyclic thieno[2,3-*b*:5,4-*c*′]dipyridine, with generation of the much more potent **3a**. In this paper, the syntheses of a novel series of thieno[2,3-*b*]pyridine and thieno[2,3-*b*:5,4-*c*′]dipyridine derivatives and structure–activity relationships (SAR) with regard to their anti-inflammatory effects in an AA rat model are discussed.

Chemistry The thieno[2,3-*b*]pyridine derivatives **2**, the thienodipyridine derivatives **3**—**5** and the benzo[*b*]thieno[2,3-*b*]pyridine derivative **6** were generally synthesized by the method shown in Chart 1. The Friedländer reaction[10] of the aminobenzoylthiophene derivatives **7**—**11** with ethyl 4-chloroacetoacetate gave **12**—**16**. Incorporation of amines or azoles into the side chain afforded the desired compounds **2**—**6**.

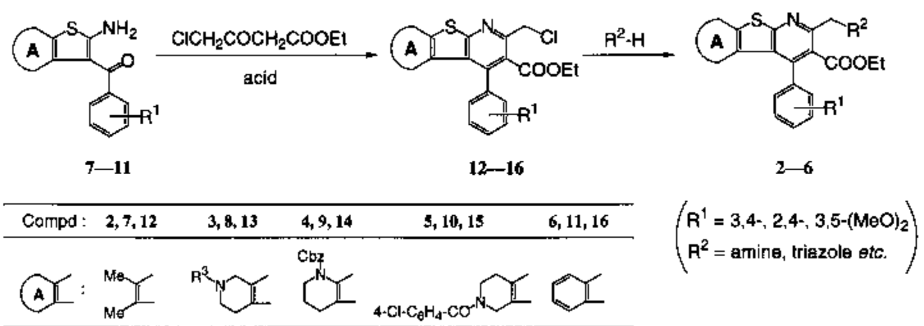
The *N*-unsubstituted derivative **17** was synthesized by the standard catalytic hydrogenation of **4**. Removal of the benzoyl groups on the nitrogen by hydrolysis yielded analogues **18** and **19**. Oxdative aromatization of **17**—**19** with MnO_2 produced **20**—**22** (Chart 2). The 7-substituted compounds **3f**, **g**, **i**, **j**, **k** (Table 2) were prepared from **18** by usual methods (see Experimental).

The aminobenzoylthiophene derivatives **7**—**11** were obtained from the benzoylacetonitriles **23** using Gewalt's procedure[11] (Chart 3). Since MnO_2 oxidation of the carba-ana-



1: TAK-603   **2a**: R= 1,2,4-triazol-1-yl **2b**: R= NEt$_2$ **3a**

Fig. 1

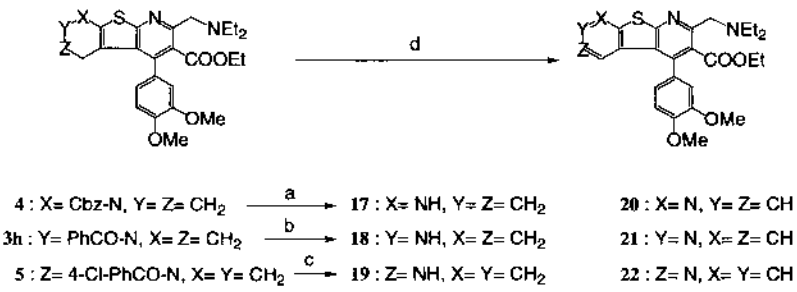


7—11 **12—16** **2—6**

Chart 1

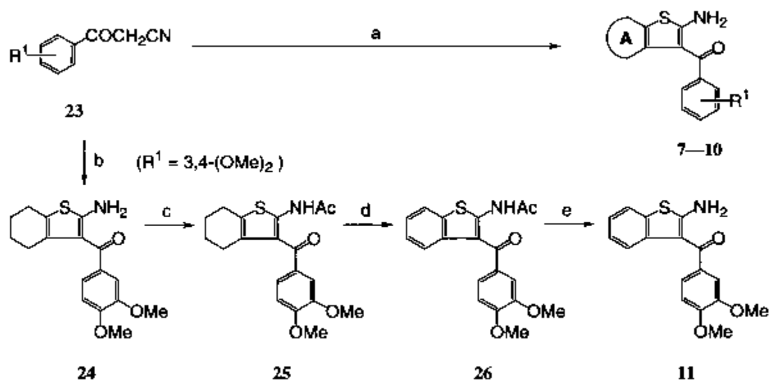
* To whom correspondence should be addressed.

© 1999 Pharmaceutical Society of Japan



Reagents : a) H_2, Raney Ni / EtOH; b) 3 N HCl; c) KOH / EtOH; d) MnO_2 / toluene.

Chart 2



Reagents : a) ketone, S, morpholine / EtOH; b) cyclohexanone, S, morpholine / EtOH; c) Ac_2O / pyridine; d) Pd–C; e) 1 N NaOH / EtOH.

Chart 3

logue of **18** to obtain the benzo[*b*]thieno[2,3-*b*]pyridine derivative **6** was unsuccessful, the alternative route shown in Chart 3 was used. The key intermediate **11** was obtained by dehydrogenation[12] of **25** followed by saponification.

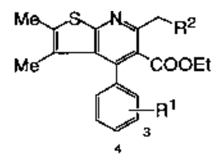
Results and Discussion

The structures and anti-inflammatory effects of the compounds prepared are shown in Tables 1 and 2. Anti-inflammatory activities are evaluated using the AA rat model, and are expressed in terms of percentage inhibition of plantar edema.

In our search for a compound with a more favorable pharmacological profile, especially improved anti-inflammatory properties, our interest was directed toward replacement of the quinoline ring of TAK-603 by a thieno[2,3-*b*]pyridine ring. Of these compounds, **2b**, having a diethylamino moiety at the side chain was found to be moderately active, whereas compound **2a** with the triazolyl moiety present in the structure of TAK-603 exhibited only decreased activity (Table 1). Replacement of the diethylamino moiety with a bulky *tert*-butyl ethyl amino moiety lowered activity, suggesting that the small dialkylamino moiety at this position favors anti-inflammatory activity (**2c** *vs.* **2b**).

Concerning the substituent effect on the pendent phenyl ring (R^1), the activity of the 3,4-dimethoxyphenyl derivative (**2b**) was better than that of the 2,4- (**2d**) and the 3,5-dimethoxy (**2e**) analogues. This SAR agrees with data published on a series of the quinoline derivatives.[4] We therefore proceeded to explore SAR around **2b**, and further ring extension of the thieno[2,3-*b*]pyridine of **2b** to the tricyclic thieno[2,3-*b* : 5,4-*c*′]dipyridine structure was performed. Good anti-inflammatory activity comparable to that of TAK-603 was observed for compound **3a** (Table 2). Subsequent investigation was therefore focused on the structure of **3a**. Conversion of the diethylamino moiety into the 3,5-dimethylpiperidine (**3b**), the 1,2,4-triazole (**3c**) and the isopropylthio (**3d**) moieties revealed that the diethylamino moiety is a superior side chain substituent in this series of compounds (**3a** *vs.* **3b**—**d**). With the above SAR in hand, study was continued with the compounds bearing the diethylamino moiety on the side chain at the 2-position and the 3,4-

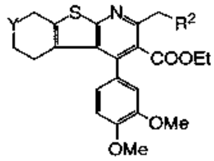
Table 1. Structures and Anti-inflammatory Effects in an AA Rat Model of the Thieno[2,3-*b*]pyridine Derivatives **2** (*p.o.*, 14 d)



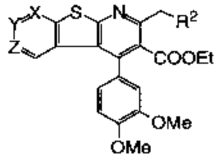
Compd.	R^1	R^2	Dose (mg/kg)	Paw volume (% inhibition)
2a	3,4-$(OMe)_2$	1,2,4-Triazol-1-yl	25	<30
2b	3,4-$(OMe)_2$	NEt_2	25	66*
2c	3,4-$(OMe)_2$	N(*tert*-Bu)Et	25	32
2d	2,4-$(OMe)_2$	NEt_2	12.5	3
2e	3,5-$(OMe)_2$	NEt_2	12.5	32

Statistically significant at $*p<0.01$ by Dunnet's test.

Table 2. Structures and Anti-inflammatory Effects in an AA Rat Model of the Thienodipyridine Derivatives **3**, **18**, **20**—**22** and the Benzo[*b*]thieno[2,3-*b*]pyridine Derivative **6** (*p.o.*, 14 d)



3, 18



6, 20, 21, 22

Compd.	X	Y	Z	R^2	Dose (mg/kg)	Paw volume (% inhibition)
3a		$PhCH_2N$		NEt_2	6.25	50*
3b		$PhCH_2N$		3,5-Dimethylpiperidin-1-yl	6.25	<30
3c		$PhCH_2N$		1,2,4-Triazol-1-yl	12.5	<30
3d		$PhCH_2N$		S-iso-Pr	6.25	<30
3e		EtN		NEt_2	6.25	49*
3f		iso-PrN		NEt_2	6.25	<30
3g		1-Naphthylmethyl-N		NEt_2	6.25	<30
3h		PhCON		NEt_2	6.25	49
3i		CH_3CON		NEt_2	6.25	60**
3j		$PhSO_2N$		NEt_2	6.25	<30
3k		PhNHCON		NEt_2	6.25	56*
6	CH	CH	CH	NEt_2	6.25	<30
18		HN		NEt_2	6.25	<30
20	N	CH	CH	NEt_2	3.13	<30
21	CH	N	CH	NEt_2	3.13	74**
22	CH	CH	N	NEt_2	3.13	44
1 (TAK-603)					12.5	65**

Statistically significant at $^*p<0.05$, $^{**}p<0.01$ by Dunnet's test.

dimethoxy moiety on the pendent phenyl ring.

Modification of the [5,4-*c*′]pyridine part was studied in compounds **3a**, **e**—**k**, **6**, **18** and **20**—**22**. Potent activity was observed for the 7-benzyl (**3a**) and the 7-ethyl derivatives (**3e**), while the 7-isopropyl (**3f**) and the 7-naphthylmethyl (**3g**) derivatives were less active. Since the alkyl group on nitrogen is a possible site of metabolism in animals, the 7-unsubstituted derivative **18** was examined. Contrary to our expectation, compound **18** did not retain activity. In addition to the derivatives with alkyl moieties, the 7-benzoyl (**3h**), the 7-acetyl (**3i**) and the 7-phenylcarbamoyl (**3k**) derivatives had favorable activities, but the 7-phenylsulfony derivative **3j** exhibited decreased activity (**3h**, **i**, **k** *vs.* **3j**). Aromatization of **18** caused abrupt enhancement of activity despite lack of the substituent on the 7-nitrogen (**21** *vs.* **18**). Shifting the nitrogen from the 7-position to the 6- (**22**) or the 8-position (**20**) and removal of the nitrogen from the 7-position (**6**) resulted in loss of activity (**21** *vs.* **6**, **20**, **22**). These findings suggest that a nitrogen atom at the 7-position is required for activity and that anti-inflammatory potency depends on the overall steric effect around the [5,4-*c*′]pyridine ring.

In conclusion, modification of the quinoline template of TAK-603 led to the finding of the potent thieno[2,3-*b* : 5,4-*c*′]dipyridine derivative **21** bearing a diethylamino moiety on the side chain at the 2-position. Since compound **21** has no effect on cyclooxygenase-2 inhibition *in vitro* (5 μM), its anti-inflammatory activity is expected to be based on its profile as an immunomodulator. Detailed biological investigation of **21** including its mechanism of action is now underway and will be reported elsewhere in the future.

Experimental

Chemistry Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out by the Analytical Department of Takeda Chemical Industries, Ltd. ^{1}H-NMR spectra of deuteriochloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6) solutions (internal standard tetramethylsilane (TMS), δ 0) were recorded on a Gemini-200 (FT-200 MHz) spectrometer. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer. All compounds exhibited ^{1}H-NMR, IR, and analytical data consistent with the proposed structures. Column chromatography was performed with E. Merck Silica gel 60 (0.063—0.200 mm).

Ethyl 6-Chloromethyl-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno-[2,3-*b*]pyridine-5-carboxylate (12a) A mixture of 2-amino-3-(3,4-dimethoxybenzoyl)-4,5-dimethylthiophene (**7a**) (5.0 g, 17 mmol), ethyl 4-chloroacetoacetate (3.1 g, 19 mmol), conc. H_2SO_4 (0.1 g, 1.0 mmol), and acetic acid (90 ml) was stirred at 100 °C for 3 h. After the solvent was evaporated off, the residue was made alkaline with 2 N aqueous NaOH solution and extracted with $CHCl_3$. The extract was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with $CHCl_3$–hexane (4 : 1) to give crystals. Recrystallization from EtOH afforded **12a** as colorless prisms (4.0 g, 56%), mp 162—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, $J=7.0$ Hz), 1.65 (3H, s), 2.43 (3H, s), 3.70 (3H, s), 3.87 (3H, s), 4.04 (2H, q, $J=7.0$ Hz), 4.84 (1H, d, $J=11.4$ Hz), 4.93 (1H, d, $J=11.4$ Hz), 6.38—6.64 (2H, m), 7.00 (1H, d, $J=9.2$ Hz). IR (KBr) cm^{-1}: 1722. *Anal.* Calcd for $C_{21}H_{22}ClNO_4S$: C, 60.00; H, 5.28; N, 3.34. Found: C, 60.01; H, 5.12; N, 3.50.

Compounds **12b** and **12c** were prepared by a similar procedure to that used for the preparation of **12a** and their physicochemical data are described in Table 3.

Ethyl 7-Benzyl-2-chloromethyl-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b* : 5,4-*c*′]dipyridine-3-carboxylate (13a) A mixture of 2-amino-6-benzyl-3-(3,4-dimethoxybenzoyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (**8a**) (6.0 g, 15 mmol), ethyl 4-chloroacetoacetate (2.7 g, 16 mmol), conc. H_2SO_4 (1.4 g, 15 mmol), and acetic acid (140 ml) was stirred at 100 °C for 3 h. After the solvent was evaporated off, the residue was made alkaline with 2 N aqueous NaOH solution and extracted with $CHCl_3$. The extract was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on

Table 3. Physicochemical Data of 6-Chloromethyl-2,3-dimethylthieno[2,3-*b*]pyridines **12**, 2-Chloromethylthienodipyridines **13**—**15** and 2-Chloromethylbenzo[*b*]thieno[2,3-*b*]pyridine **16**

Compd.	R^1	R^3	Formula	mp (°C)	Solvent[a]	^{1}H-NMR (ppm, in $CDCl_3$, J in Hz)	Yield[b] (%)
12b	2,4-$(MeO)_2$		$C_{21}H_{22}ClNO_4S$	108—109	EtOH	1.01 (3H, t, J=7.0), 1.65 (3H, s), 2.43 (3H, s), 3.70 (3H, s), 3.87 (3H, s), 4.04 (2H, q, J=7.0), 4.84 (1H, d, J=11.2), 4.93 (1H, d, J=11.2), 6.38—6.64 (2H, m), 7.00 (1H, d, J=9.2)	56
12c	3,5-$(MeO)_2$		$C_{21}H_{22}ClNO_4S$	124—125	EtOH	1.01 (3H, t, J=7.2), 1.71 (3H, s), 2.45 (3H, s), 3.79 (6H, s), 4.08 (2H, q, J=7.2), 4.88 (2H, s), 6.45 (2H, d, J=2.2), 6.53 (1H, t, J=2.2)	43
13b	3,4-$(MeO)_2$	Et	$C_{24}H_{27}ClN_2O_4S$	132—133	EtOH	1.01 (3H, t, J=7.2), 1.16 (3H, t, J=7.0), 2.06—2.17 (2H, m), 2.45—2.69 (4H, m), 3.73—3.77 (2H, m), 3.86 (3H, s), 3.95 (3H, s), 4.07 (2H, q, J=7.2), 4.85 (1H, d, J=11.2), 4.92 (1H, d, J=11.2), 6.81—6.92 (3H, m)	40
13c	3,4-$(MeO)_2$	PhCO	$C_{29}H_{26}ClN_2O_5S \cdot 0.5H_2O$	Amorphous		1.02 (3H, t, J=6.8), 2.03—2.18 (2H, m), 3.38—3.73 (2H, m), 3.87 (3H, s), 3.95 (3H, s), 4.07 (2H, q, J=6.8), 4.65—4.86 (2H, m), 4.87 (2H, s), 6.81—6.94 (3H, m), 7.43 (5H, s)	59
14	3,4-$(MeO)_2$		$C_{30}H_{29}ClN_2O_6S$	178—179	EA–H	1.02 (3H, t, J=7.0), 1.75—1.81 (2H, m), 1.96—2.02 (2H, m), 3.83—3.88 (5H, m), 3.94 (3H, s), 4.06 (2H, q, J=7.0), 4.88 (2H, d, J=1.8), 5.31 (2H, s), 6.81—6.92 (3H, m), 7.37—7.40 (5H, m)	79
15	3,4-$(MeO)_2$		$C_{29}H_{26}Cl_2N_2O_5S$	Amorphous		0.98 (3H, t, J=7.2), 2.90—3.20 (2H, m), 3.60—4.20 (12H, m), 4.85 (2H, s), 6.50—7.50 (7H, m)	57
16	3,4-$(MeO)_2$		$C_{23}H_{20}ClNO_4S$	180—181	EA–H	1.05 (3H, t, J=7.2), 3.85 (3H, s), 4.01 (3H, s), 4.12 (2H, q, J=7.2), 4.89 (1H, d, J=11.2), 4.98 (1H, d, J=11.2), 6.91—7.00 (3H, m), 7.05 (1H, d, J=8.4), 7.17 (1H, dt, J=7.2, 1.2), 7.44 (1H, dt, J=7.2, 1.2), 7.87 (1H, d, J=8.0)	57

a) Recrystallization solvent, EA=ethyl acetate, H=hexane. *b*) Yield from the corresponding 2-amino-3-benzoylthiophene derivatives **7**—**11**.

SiO_2 with $CHCl_3$–hexane (4 : 1) to give crystals. Recrystallization from EtOH afforded **13a** as colorless prisms (3.4 g, 43%), mp 120—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.2 Hz), 2.00—2.18 (2H, m), 2.50—2.69 (2H, m), 3.67 (2H, s), 3.74 (2H, s), 3.85 (3H, s), 3.93 (3H, s), 4.06 (2H, q, J=7.2 Hz), 4.84 (1H, d, J=11.4 Hz), 4.91 (1H, d, J=11.4 Hz), 6.78—7.15 (3H, m), 7.24—7.45 (5H, m). IR (KBr) cm^{-1}: 1719. *Anal.* Calcd for $C_{29}H_{29}ClN_2O_4S$: C, 64.85; H, 5.44; N, 5.22. Found: C, 64.75; H, 5.33; N, 5.08.

Compounds **13b**, **c**, **14**, **15** and **16** were prepared by a similar procedure to that used for the preparation of **13a**, and their physicochemical data are also listed in Table 3.

Ethyl 4-(3,4-Dimethoxyphenyl)-2,3-dimethyl-6-(1,2,4-triazol-1-ylmethyl)thieno[2,3-*b*]pyridine-5-carboxylate (2a) A stirred solution of 1*H*-1,2,4-triazole (271 mg, 3.9 mmol) in *N*,*N*-dimethylformamide (DMF) (15 ml) was treated with NaH (60% in oil, 171 mg, 4.3 mmol) at room temperature for 15 min, and then **12a** (1.5 g, 3.5 mmol) was added. The whole was stirred at 80 °C for 35 min, poured into H_2O and extracted with AcOEt. The extract was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with $CHCl_3$–MeOH (3 : 1) to give crystals. Recrystallization from AcOEt–hexane afforded **2a** as colorless prisms (1.0 g, 62%), mp 136—137 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.2 Hz), 1.65 (3H, s), 2.44 (3H, s), 3.50 (3H, s), 3.93 (2H, q, J=7.2 Hz), 3.94 (3H, s), 5.59 (1H, d, J=14.6 Hz), 5.67 (1H, d, J=14.6 Hz), 6.77—6.92 (3H, m), 7.92 (1H, s), 8.25 (1H, s). IR (KBr) cm^{-1}: 1705. *Anal.* Calcd for $C_{23}H_{24}N_4O_4S$: C, 61.05; H, 5.35; N, 12.38. Found: C, 60.91; H, 5.13; N, 12.30.

Ethyl 7-Benzyl-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-2-(1,2,4-triazol-1-ylmethyl)thieno[2,3-*b* : 5,4-*c′*]dipyridine-3-carboxylate (3c) The title compound was prepared by a similar procedure to that used for the preparation of **2a**: Colorless prisms (yield: 35%), mp 136—137 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.2 Hz), 2.00—2.17 (2H, m), 2.50—2.71 (2H, m), 3.67 (2H, s), 3.73 (2H, s), 3.84 (3H, s), 3.92 (3H, s), 3.95 (2H, q, J=7.2 Hz), 5.64 (2H, s), 6.70—6.95 (3H, m), 7.22—7.45 (5H, m), 7.93 (1H, s), 8.25 (1H, s). IR (KBr) cm^{-1}: 1718. *Anal.* Calcd for $C_{31}H_{31}N_5O_4S$: C, 65.36; H, 5.48; N, 12.29. Found: C, 65.76; H, 5.88; N, 12.29.

Ethyl 6-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-*b*]pyridine-5-carboxylate (2b) A mixture of **12a** (1.5 g, 3.6 mmol), diethylamine (1.4 g, 14.3 mmol) and CH_2Cl_2 (35 ml) was refluxed overnight. After cooling, the mixture was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with $CHCl_3$ to give crystals. Recrystallization from AcOEt–hexane afforded **2b** as colorless prisms (1.1 g, 68%), mp 100—101 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.2 Hz), 0.96 (6H, t, J=7.2 Hz), 1.64 (3H, s), 2.42 (3H, s), 2.54 (4H, q, J=7.2 Hz), 3.85 (3H, s), 3.90 (2H, s), 3.92 (2H, q, J=7.2 Hz), 3.94 (3H, s), 6.78—6.93 (3H, m). IR (KBr) cm^{-1}: 1719. *Anal.* Calcd for $C_{25}H_{32}N_2O_4S$: C, 65.47; H, 7.06; N, 6.14. Found: C, 65.59; H, 6.94; N, 6.19.

Compounds **2c**—**e**, **3a**, **b**, **e**, **h**, **4**, **5** and **6** were prepared by a similar procedure to that used for the preparation of **2b**, and their physicochemical data are listed in Table 4.

Ethyl 7-Benzyl-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-2-(isopropylthiomethyl)thieno[2,3-*b* : 5,4-*c′*]dipyridine-3-carboxylate (3d) A mixture of **13a** (1.2 g, 2.2 mmol), 2-propanethiol (255 mg, 3.3 mmol), K_2CO_3 (340 mg, 2.5 mmol) and DMF (20 ml) was stirred at room temperature for 3 h, poured into H_2O and extracted with AcOEt. The extract was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with AcOEt to give crystals. Recrystallization from AcOEt–hexane afforded **3d** as colorless prisms (850 mg, 66%), mp 115—116 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.0 Hz), 1.26 (3H, d, J=6.8 Hz), 1.27 (3H, d, J=6.8 Hz), 1.90—2.21 (2H, m), 2.40—2.71 (2H, m), 2.98 (1H, septet, J=6.8 Hz), 3.66 (2H, s), 3.72 (2H, s), 3.85 (3H, s), 3.93 (3H, s), 4.02 (2H, q, J=7.0 Hz), 4.08 (2H, s), 6.78—6.95 (3H, m), 7.20—7.50 (5H, m). IR (KBr) cm^{-1}: 1713. *Anal.* Calcd for $C_{32}H_{36}N_2O_4S$: C, 66.64; H, 6.29; N, 4.86. Found: C, 66.64; H, 6.22; N, 4.93.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-7-isopropylthieno[2,3-*b* : 5,4-*c′*]dipyridine-3-carboxylate (3f) A mixture of ethyl 2-(diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b* : 5,4-*c′*]dipyridine-3-carboxylate (**18**) (1.0 g, 2.1 mmol), 2-iodopropane (425 mg, 2.5 mmol), K_2CO_3 (370 mg, 2.7 mmol) and acetone (30 ml) was stirred at room temperature overnight, and then the solvent was evaporated off. The residue was dissolved in AcOEt, washed successively with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with AcOEt–MeOH (20 : 1) to

Table 4. Physicochemical Data of Thieno[2,3-*b*]pyridines **2**, Thienodipyridines **3**—**5** and Benzo[*b*]thieno[2,3-*b*]pyridine **6**

Compd.	mp (°C)	Solvent[a]	^{1}H-NMR (ppm, in $CDCl_3$, *J* in Hz)	IR (KBr, cm^{-1})	Formula	*Anal.* Calcd (Found)			Yield[b] (%)
						C	H	N	
2c	87—88	EA–H	0.75 (3H, t, *J*=7.2), 0.90 (3H, t, *J*=7.0), 1.09 (9H, s), 1.63 (3H, s), 2.42 (3H, s), 2.61 (2H, q, *J*=7.0), 3.85 (3H, s), 3.93 (2H, q, *J*=7.2), 3.94 (3H, s), 4.07 (2H, s), 6.75—6.94 (3H, m)	1719	$C_{27}H_{36}N_2O_4S$	66.91 (66.88	7.49 7.26	5.78 5.73)	42
2d	88—90	EA–H	0.94 (9H, t, *J*=7.0), 1.64 (3H, s), 2.40 (3H, s), 2.53 (4H, q, *J*=7.0), 3.68 (3H, s), 3.76 (1H, d, *J*=13.6), 3.86 (3H, s), 3.90 (2H, q, *J*=7.0), 3.98 (1H, d, *J*=13.6), 6.41—6.56 (2H, m), 7.00 (1H, d, *J*=8.8)	1718	$C_{25}H_{32}N_2O_4S$	65.76 (65.61	7.06 6.88	6.14 5.97)	65
2e	87—88	EA–H	0.94 (3H, t, *J*=7.0), 0.95 (6H, t, *J*=7.0), 1.69 (3H, s), 2.42 (3H, s), 2.53 (4H, q, *J*=7.0), 3.78 (6H, s), 3.91 (2H, s), 3.94 (2H, q, *J*=7.0), 6.49 (2H, d, *J*=1.8), 6.50 (1H, t, *J*=1.8)	1710	$C_{25}H_{32}N_2O_4S$	65.76 (65.46	7.06 6.80	6.14 5.96)	55
3a	133—134	EA–H	0.93 (3H, t, *J*=7.0), 0.95 (6H, t, *J*=7.0), 2.00—2.15 (2H, m), 2.45—2.65 (6H, m), 3.66 (2H, s), 3.71 (2H, s), 3.85 (3H, s), 3.91 (2H, s), 3.92 (3H, s), 3.93 (2H, q, *J*=7.0), 6,78—6.90 (3H, m), 7.25—7.40 (5H, m)	1710	$C_{33}H_{39}N_3O_4S$	69.08 (69.10	6.85 6.76	7.32 7.18)	60
3b	177—178	EA–H	0.75 (3H, t, *J*=7.0), 1.27 (6H, d, *J*=7.0), 1.38—1.65 (6H, m), 1.70—2.21 (2H, m), 2.96 (1H, septet, *J*=7.0), 3.09—3.75 (6H, m), 3.97 (2H, q, *J*=7.0), 4.20—4.70 (6H, m), 6.91—7.38 (4H, m), 7.40—7.60 (3H, m), 7.62—7.85 (2H, m)	1718	$C_{36}H_{43}N_3O_4S$	70.44 (70.42	7.06 6.97	6.85 6.83)	70
3e	93—94	EA–H	0.94 (3H, t, *J*=7.6), 0.96 (6H, t, *J*=7.2), 1.15 (3H, t, *J*=7.0), 2.05—2.15 (2H, m), 2.49—2.56 (6H, m), 2.58 (2H, q, *J*=7.6), 3.73 (2H, s), 3.86 (3H, s), 3.90 (2H, s), 3.93 (2H, q, *J*=7.0), 3.94 (3H, s), 6.81—6.91 (3H, m)	1730	$C_{28}H_{37}N_3O_4S$	65.73 (65.57	7.29 7.25	8.21 8.24)	44
3h	86—87	EA–H	0.93 (3H, t, *J*=7.2), 0.95 (6H, t, *J*=7.0), 1.95—2.00 (2H, m), 2.02—2.18 (2H, m), 2.54 (4H, q, *J*=7.0), 3.36—3.70 (2H, m), 3.86 (3H, s), 3.91 (2H, s), 3.93 (2H, q, *J*=7.2), 4.62—4.73 (1H, m), 4.74—5.16 (1H, m), 6.81—6.92 (3H, m), 7.43 (5H, s)	1720 1639	$C_{33}H_{37}N_3O_5S$	67.44 (67.79	6.35 6.00	7.15 7.05)	70
4	138—139	EA–H	0.94 (3H, t, *J*=7.0), 0.95 (6H, t, *J*=7.0), 1.74—1.79 (2H, m), 1.96—1.99 (2H, m), 2.54 (4H, q, *J*=7.0), 3.86 (3H, s), 3.87—3.97 (9H, m), 5.30 (2H, s), 6.82—6.86 (3H, m), 7.36—7.39 (5H, m)	1704	$C_{34}H_{39}N_3O_6S$	66.10 (65.84	6.36 6.14	6.80 6.73)	70
5	91—97	EA–H	0.90 (3H, t, *J*=7.2), 2.51 (4H, q, *J*=7.2), 2.90—3.10 (2H, m), 3.66 (2H, s), 3,70—4.20 (10H, m), 7.06 (2H, d, *J*=8.2), 7.30 (2H, d, *J*=8.2)	1729 1643	$C_{33}H_{36}ClN_3O_5S$	63.71 (63.37	5.83 6.10	6.75 6.56)	85
6	133—134	EA	0.98 (3H, t, *J*=7.2), 0.99 (6H, t, *J*=7.2), 2.58 (4H, q, *J*=7.2), 3.85 (3H, s), 3.98 (2H, s), 3.99 (2H, q, *J*=7.2), 4.01 (3H, s), 6.90—6.97 (3H, m), 7.03 (1H, d, *J*=8.2), 7.13 (1H. dt, *J*=8.2, 1.0), 7.40 (1H, dt, *J*=8.2, 1.0), 7.84 (1H, dd, *J*=8.2, 1.0)	1722	$C_{27}H_{30}N_2O_4S$	67.76 (67.67	6.32 6.39	5.85 5.80)	68

a) Recrystallization solvent, EA=ethyl acetate, H=hexane. *b*) Yield from the corresponding chloromethyl derivatives **12**—**16**.

give crystals. Recrystallization from AcOEt–hexane afforded **3f** as colorless prisms (218 mg, 20%), mp 97—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, *J*=6.6 Hz), 0.96 (6H, t, *J*=7.2 Hz), 1.11 (6H, d, *J*=6.4 Hz), 2.04—2.13 (2H, m), 2.48—2.65 (6H, m), 2.88 (1H, septet, *J*=6.4 Hz), 3.83 (2H, s), 3.86 (3H, s), 3.91 (2H, s), 3.93 (2H, q, *J*=6.6 Hz), 3.95 (3H, s), 6.81—6.91 (3H, m). IR (KBr) cm^{-1}: 1722. *Anal.* Calcd for $C_{29}H_{39}N_3O_4S$: C, 66.26; H, 7.48; N, 7.99. Found: C, 66.02; H, 7.40; N, 8.09.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-7-(1-naphthylmethyl)thieno[2,3-*b*:5,4-*c′*]dipyridine-3-carboxylate (3g) A mixture of **18** (1.3 g, 2.9 mmol), 1-chloromethylnaphthalene (610 mg, 3.5 mmol), K_2CO_3 (590 mg, 4.3 mmol) and 2-butanone (20 ml) was stirred at room temperature overnight, poured into H_2O, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with $CHCl_3$–MeOH (40 : 1) to give crystals. Recrystallization from AcOEt–hexane afforded **3g** as colorless prisms (460 mg, 26%), mp 87—89 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, *J*=7.0 Hz), 0.94 (6H, t, *J*=7.0 Hz), 2.00—2.14 (2H, m), 2.53 (4H, q, *J*=7.0 Hz), 2.67 (2H, t, *J*=5.6 Hz), 3.79 (2H, s), 3.84 (3H, s), 3.90 (2H, s), 3.92 (3H, s), 3.93 (2H, q, *J*=7.0 Hz), 4.07 (2H, s), 6.79—6.89 (3H, m), 7.41—7.51 (4H, m), 7.79—7.92 (2H, m), 8.26—8.34 (1H, m). IR (KBr) cm^{-1}: 1722. *Anal.* Calcd for $C_{37}H_{41}N_3O_4S$: C, 71.42; H, 6.62; N, 6.74. Found: C, 70.78; H, 6.68; N, 6.73.

Ethyl 7-Acetyl-2-(diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*:5,4-*c′*]dipyridine-3-carboxylate (3i) Acetyl chloride (208 mg, 2.7 mmol) was added to a stirred mixture of **18** (1.0 g, 2.1 mmol), Et_3N (268 mg, 2.6 mmol) and tetrahydrofuran (THF) (10 ml) with ice-water cooling. After stirring at room temperature for 3 h, the mixture was poured into H_2O and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with $CHCl_3$–MeOH (100 : 1) to afford **3i** as an amorphous solid (650 mg, 60%). ^{1}H-NMR ($CDCl_3$) δ: 0.85—1.10 (9H, m), 2.00—2.25 (5H, m), 2.45—2.70 (4H, m), 3.49 (2H, t, *J*=5.6 Hz), 3.80—4.10 (10H, m), 4.73, 4.86 (total 2H, each s), 6.75—7.00 (3H, m). IR (KBr) cm^{-1}: 1720, 1650. *Anal.* Calcd for $C_{28}H_{35}N_3O_5S$: C, 63.98; H, 6.71; N, 7.99. Found: C, 64.01; H, 6.77; N, 8.22.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-7-phenylsulfonylthieno[2,3-*b*:5,4-*c′*]dipyridine-3-carboxylate (3j) The title compound was prepared by a similar procedure to that used for the preparation of **3i**: Colorless needles (yield: 76%), mp 161—162 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, *J*=7.0 Hz), 0.96

Table 5. Physicochemical Data of 2-Amino-3-benzoyl-4,5-dimethylthiophenes **7a**, **c**, and 2-Amino-3-benzoylthienopyridines **8**—**10**

Compd.	R^1	R^3	Formula	mp (°C)	Solvent[a)]	^{1}H-NMR (ppm, in $CDCl_3$, J in Hz)	Yield[b)] (%)
7a	3,4-$(MeO)_2$		$C_{15}H_{17}NO_3S$	172—173	EA–H	1.58 (3H, s), 2.16 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 5.97 (2H, br s), 6.87 (1H, d, J=7.6), 7.16 (1H, dd, J=7.6, 1.8), 7.18 (1H, d, J=1.8)	41
7c	3,5-$(MeO)_2$		$C_{15}H_{17}NO_3S$	154—155	EA–H	1.62 (3H, s), 2.13 (3H, s), 3.81 (6H, s), 6.44 (2H, br s), 6.55 (1H, t, J=2.4), 6.65 (2H, d, J=2.4)	34
8b	3,4-$(MeO)_2$	Et	$C_{18}H_{22}N_2O_3S$	190—192	EtOH	1.14 (3H, t, J=7.2), 2.08—2.10 (2H, m), 2.46—2.54 (2H, m), 2.55 (2H, q, J=7.2), 3.45 (2H, s), 3.92 (3H, s), 3.93 (3H, s), 6.50 (2H, s), 6.84 (1H, d, J=8.8), 7.09—7.15 (2H, m)	57
8c	3,4-$(MeO)_2$	PhCO	$C_{23}H_{21}N_2O_4S$	143—145	EtOH	2.08—2.16 (2H, m), 3.36—3.46 (2H, m), 3.92 (3H, s), 3.95 (3H, s), 4.37—4.75 (2H, m), 6.50 (2H, br s), 6.88 (1H, d, J=8.6), 7.13 (2H, br s), 7.42 (5H, s)	71
9	3,4-$(MeO)_2$		$C_{24}H_{24}N_2O_5S$	177—178	EA	1.60—1.80 (2H, m), 2.00—2.20 (2H, m), 3.71—3.80 (2H, m), 3.91 (3H, s), 3.94 (3H, s), 5.24 (2H, s), 6.86 (1H, d, J=8.8), 7.10—7.20 (2H, m), 7.32—7.50 (5H, m)	16
10	3,4-$(MeO)_2$		$C_{23}H_{21}ClN_2O_4S \cdot 0.25H_2O$	Amorphous		2.60—2.80 (2H, m), 3.40—3.92 (4H, m), 3.93 (6H, s), 6.20—7.50 (9H, m)	16

a) Recrystallization solvent, EA=ethyl acetate, H=hexane. *b*) Yield from the corresponding benzoylacetonitriles **23**.

(6H, t, J=7.0 Hz), 2.05—2.30 (2H, m), 2.54 (4H, q, J=7.0 Hz), 3.03—3.34 (2H, m), 3.85 (3H, s), 3.91 (2H, s), 3.93 (2H, q, J=7.0 Hz), 3.95 (3H, s), 4.33 (1H, d, J=15.0 Hz), 4.46 (1H, d, J=15.0 Hz), 6.74—6.91 (3H, m). 7.48—7.65 (3H, m), 7.77—7.85 (2H, m). IR (KBr) cm^{-1}: 1722. *Anal.* Calcd for $C_{32}H_{37}N_3O_6S_2$: C, 61.62; H, 5.98; N, 6.74. Found: C, 61.29; H, 5.71; N, 6.90.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-7-phenylcarbamoylthieno[2,3-*b*:5,4-*c*′]dipyridine-3-carboxylate (3k) A mixture of **18** (1.0 g, 2.1 mmol), phenylisocyanate (0.3 g, 2.3 mmol) and THF (20 ml) was stirred at room temperature for 3 h, and then concentrated *in vacuo.* The residue was chromatographed on SiO_2 with AcOEt–hexane–MeOH (20 : 20 : 1) to give crystals. Recrystallization from AcOEt–hexane afforded **3k** as colorless prisms (1.1 g, 88%), mp 154—155 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.2 Hz), 0.96 (6H, t, J=7.2 Hz), 2.00—2.30 (2H, m), 2.54 (4H, q, J=7.2 Hz), 3.41—3.70 (2H, m), 3.86 (3H, s), 3.92 (2H, s), 3.94 (2H, q, J=7.2 Hz), 3.96 (3H, s), 4.81 (2H, s), 6.43 (1H, s), 6.82—6.94 (3H, m), 7.28—7.39 (5H, m). IR (KBr) cm^{-1}: 1718, 1539. *Anal.* Calcd for $C_{33}H_{38}N_4O_5S$: C, 65.76; H, 6.35; N, 9.30. Found: C, 65.55; H, 6.27; N, 9.30.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*:5,4-*b*′]dipyridine-3-carboxylate (17) A mixture of **4** (0.6 g, 0.9 mmol), Raney Ni (1.0 g), THF (24 ml) and EtOH (30 ml) was hydrogenated under balloon pressure for 2 h. The catalyst was filtered out and the filtrate was concentrated *in vacuo* to give **17** as a colorless oil (0.7 g, quant). ^{1}H-NMR ($CDCl_3$) δ: 0.90—0.99 (9H, m), 1.65—1.72 (2H, m), 1.86—1.89 (2H, m), 2.53 (4H, q, J=7.2 Hz), 3.27—3.30 (2H, m), 3.84 (2H, s), 3.87 (3H, s), 3.92 (2H, q, J=7.0 Hz), 3.93 (3H, s), 6.83—6.86 (3H, m). IR (neat) cm^{-1}: 1722.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*:5,4-*c*′]dipyridine-3-carboxylate (18) A mixture of **3h** (4.0 g, 6.8 mmol) and 3 N aqueous HCl (12 ml, 36 mmol) was stirred at 80 °C for 13 h. The reaction mixture was neutralized with 1 N aqueous NaOH with ice-cooling, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with $CHCl_3$–MeOH (30 : 1) to give crystals. Recrystallization from AcOEt–hexane afforded **18** as colorless prisms (2.3 g, 70%), mp 72—74 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.6 Hz), 0.96 (6H, t, J=7.2 Hz), 1.95—2.15 (2H, m), 2.54 (4H, q, J=7.2 Hz), 2.91 (2H, t, J=5.8 Hz), 3.86 (3H, s), 3.92 (2H, s), 3.94 (3H, s), 3.95 (2H, q, J=7.6 Hz), 4.11 (2H, s), 6.82—6.87 (3H, m). IR (KBr) cm^{-1}: 1720. *Anal.* Calcd for $C_{26}H_{33}N_3O_4S$: C, 64.57; H, 6.88; N, 8.69. Found: C, 64.60; H, 6.88; N, 8.66.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*:4,5-*c*′]dipyridine-3-carboxylate (19) A solution of KOH (0.6 g, 11 mmol) in H_2O (10 ml) was added to a solution of **5** (1.8 g, 3.1 mmol) in EtOH (20 ml) at room temperature. The mixture was refluxed for 5 h, poured into H_2O and extracted with AcOEt. The extract was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford **19** as a light brown oil (1.2 g, 83%). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 0.95 (6H, t, J=7.2 Hz), 2.54 (4H, q, J=7.2 Hz), 2.70—3.30 (6H, m), 3.85 (3H, s), 3.91 (2H, s), 3.92 (2H, q, J=7.2 Hz), 3.93 (3H, s), 6.70—7.00 (3H, m). IR (neat) cm^{-1}: 1719.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)thieno[2,3-*b*:4,5-*c*′]dipyridine-3-carboxylate (22) A mixture of **19** (1.1 g, 2.2 mmol), MnO_2 (5.0 g) and toluene (40 ml) was stirred at 100 °C for 30 min. The insoluble solid was filtered out, washed with hot THF–MeOH (1 : 1), and the filtrate was concentrated *in vacuo.* The residue was chromatographed on SiO_2 with AcOEt–hexane (1 : 1) to give crystals. Recrystallization from AcOEt–hexane afforded **22** as pale yelow needles (0.64 g, 59%), mp 141—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.2 Hz), 0.99 (6H, t, J=7.2 Hz), 2.59 (4H, q, J=7.2 Hz), 3.85 (3H, s), 3.99 (5H, s), 4.00 (2H, q, J=7.2 Hz), 6.90 (1H, d, J=1.8 Hz), 6.96 (1H, dd, J=8.2, 1.8 Hz), 7.04 (1H, d, J=8.2 Hz), 7.78 (1H, d, J=5.6 Hz), 8.18 (1H, s), 8.50 (1H, d, J=5.6 Hz). IR (KBr) cm^{-1}: 1727. *Anal.* Calcd for $C_{26}H_{29}N_3O_4S$: C, 65.11; H, 6.09; N, 8.76. Found: C, 65.03; H, 6.08; N, 8.73.

Compounds **20** and **21** were prepared by a similar procedure to that used for the preparation of **22**, and their physicochemical data are described below.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)thieno[2,3-*b*:5,4-*b*′]dipyridine-3-carboxylate (**20**): Light brown prisms (yield: 18%), mp 156—157 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (9H, t, J=6.8 Hz), 2.58 (4H, q, J=6.8 Hz), 3.85 (3H, s), 3.99 (2H, s), 4.00 (2H, q, J=6.8 Hz), 4.01 (3H, s), 6.88—6.96 (2H, m), 7.04 (1H, d, J=8.2 Hz), 7.08—7.12 (2H, m), 8.54—8.57 (1H, m). IR (KBr) cm^{-1}: 1722. *Anal.* Calcd for $C_{26}H_{29}N_3O_4S$: C, 65.11; H, 6.09; N, 8.76. Found: C, 64.78; H, 6.16; N, 8.79.

Ethyl 2-(Diethylaminomethyl)-4-(3,4-dimethoxyphenyl)thieno[2,3-*b*:5,4-*c*′]dipyridine-3-carboxylate (**21**): Colorless prisms (yield: 24%), mp 163—165 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (9H, t, J=7.4 Hz), 2.59 (4H, q, J=7.4 Hz), 3.86 (3H, s), 3.99 (2H, q, J=7.4 Hz), 4.02 (3H, s), 6.79 (1H, d, J=5.6 Hz), 6.89—7.08 (3H, m), 8.34 (1H, d, J=5.6 Hz), 9.14 (1H, s). IR (KBr) cm^{-1}: 1722. *Anal.* Calcd for $C_{26}H_{29}N_3O_4S$: C, 65.11; H, 6.09; N, 8.76. Found: C, 64.98; H, 6.15; N ,8.72.

2-Amino-3-(2,4-dimethoxybenzoyl)-4,5-dimethylthiophene (7b) A mixture of 2,4-dimethoxybenzoylacetonitrile (**23b**) (25 g, 0.12 mol), 2-butanone (9.7 g, 0.13 mol), S (4.3 g, 0.13 mol), morpholine (11.6 g, 0.13 mol) and EtOH (190 ml) was refluxed for 3 h, poured into H_2O, and extracted with $CHCl_3$. The extract was washed successively with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with $CHCl_3$–hexane (4 : 1) to give crystals. Recrystallization from AcOEt–hexane afforded **7b** as colorless prisms (18%), mp 181—182 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3H, s), 2.10 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 6.44—6.54 (2H, m), 6.84 (2H, br s), 7.11 (1H, d, J=9.2 Hz). IR (KBr) cm^{-1}: 3400, 3280, 1581. *Anal.* Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.54; H, 6.00; N, 4.67.

Compounds **7a** and **7c** were prepared by a similar procedure to that used for the preparation of **7b**, and their physicochemical data are described in Table 5.

2-Amino-6-benzyl-3-(3,4-dimethoxybenzoyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (8a) A mixture of 3,4-dimethoxybenzoylacetonitrile (**23a**) (10.0 g, 48 mmol), 1-benzyl-4-piperidone (10.0 g, 54 mmol), S (1.7 g, 54 mmol), morpholine (4.7 g, 54 mmol) and EtOH (150 ml) was refluxed for

3 h, poured into H_2O, and extracted with $CHCl_3$. The extract was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with $CHCl_3$–AcOEt (20 : 1) to give crystals. Recrystallization from EtOH afforded **8a** as yellow prisms (8.4 g, 42%), mp 149—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.04—2.16 (2H, m), 2.52 (2H, t, J=5.6 Hz), 3.44 (2H, s), 3.64 (2H, s), 3.91 (3H, s), 3.93 (3H, s), 6.43 (2H, br s), 6.85 (1H, d, J=8.4 Hz), 7.08—7.19 (2H, m), 7.20—7.40 (5H, m). IR (KBr) cm^{-1}: 3410, 3385, 1582. *Anal.* Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.98; N, 6.86. Found: C, 67.41; H, 5.81; N, 6.65.

Compounds **8b**, **c**, **9**, **10** were prepared by a similar procedure to that used for the preparation of **8a**, and their physicochemical data are also listed in Table 5.

2-Amino-3-(3,4-dimethoxybenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (24) A mixture of 3,4-dimethoxybenzoylacetonitrile (**23a**) (1.0 g, 5.0 mmol), cyclohexanone (540 mg, 5.5 mmol), S (180 mg, 5.5 mmol), morpholine (520 mg, 6.0 mmol) and EtOH (10 ml) was refluxed for 3 h, and then concentrated *in vacuo.* The residue was dissolved in AcOEt, washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with AcOEt–hexane (1 : 2) to give crystals. Recrystallization from AcOEt–hexane afforded **24** as yellow prisms (1.1 g, 66%), mp 162—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.49—1.55 (2H, m), 1.74—1.79 (2H, m), 1.95—2.01 (2H, m), 2.51—2.58 (2H, m), 3.92 (3H, s), 3.94 (3H, s), 6.30 (2H, br s), 6.86 (1H, d, J=9.0 Hz), 7.14 (1H, d, J=2.0 Hz), 7.15 (1H, dd, J=9.0, 2.0 Hz). IR (KBr) cm^{-1}: 3410, 3280, 1585. *Anal.* Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.20; H, 6.06; N, 4.23.

2-Acetylamino-3-(3,4-dimethoxybenzoyl)-4,5,6,7-tetrahydrobenzo-[*b*]thiophene (25) Pyridine (15 drops) was added to a stirred solution of **24** (2.6 g, 8.2 mmol) in Ac_2O (17 ml) at room temperature. The whole was refluxed for 2 h, poured into H_2O, and extracted with AcOEt. The extract was washed successively with saturated aqueous $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crystals. Recrystallization from AcOEt–hexane afforded **25** as light yellow prisms (2.7 g, 91%), mp 131—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.67 (2H, m), 1.74—1.88 (2H, m), 2.08 (2H, t, J=5.8 Hz), 2.24 (3H, s), 2.70 (2H, t, J=5.8 Hz), 3.93 (3H, s), 3.96 (3H, s), 6.89 (1H, d, J=8.8 Hz), 7.19 (1H, d, J=1.6 Hz), 7.22 (2H, dd, J=8.8, 1.6 Hz). IR (KBr) cm^{-1}: 1724, 1693. *Anal.* Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.26; H, 5.82; N, 3.85.

2-Acetylamino-3-(3,4-dimethoxybenzoyl)benzo[*b*]thiophene (26) A mixture of **25** (1.0 g, 2.6 mmol), 10% Pd–C (50% wet, 2.0 g) and $CHCl_3$ (30 ml) was stirred at room temperature for 10 min, and then the solvent was evaporated off. The resulting powder was heated at 130 °C for 20 h, cooled to room temperature, and extracted with AcOEt. The insoluble solids were filtered out, and the filtrate was concentrated *in vacuo* to give crystals. Recrystallization from AcOEt–hexane yielded **26** as colorless prisms (350 mg, 35%), mp 150—151 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.87 (3H, s), 3.99 (3H, s), 6.90 (1H, d, J=8.4 Hz), 7.16—7.37 (5H, m), 7.78 (1H, dt, J=7.6, 2.0 Hz). IR (KBr) cm^{-1}: 1691, 1598. *Anal.* Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.21; H, 4.70; N, 4.06.

2-Amino-3-(3,4-dimethoxybenzoyl)benzo[*b*]thiophene (11) A mixture of **26** (2.0 g, 5.7 mmol), 1 N aqueous NaOH (6.0 ml, 6.0 mmol) and EtOH (18 ml) was refluxed for 5 h, and then concentrated *in vacuo.* The residue was diluted with AcOEt, washed successively with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was chromatographed on SiO_2 with AcOEt–hexane (1 : 2) to give crystals. Recrystallization from AcOEt–hexane afforded **11** as light yellow prisms (1.7 g, 89%), mp 124—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s), 3.97 (3H, s), 6.84—6.97 (1H, m), 7.00—7.12 (2H, m), 7.20—7.32 (3H, m), 7.45—7.56 (1H, m). IR (KBr) cm^{-1}: 3363, 3259, 1594. *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 64.96; H, 5.00; N, 4.78.

Biological Procedure. Anti-inflammatory Effect in AA Rat Model[13)] Male Lewis rats (7 weeks old; Charles River Japan Inc.) (n=6—7) were sensitized by injecting Freund's complete adjuvant (a 0.5% suspension of killed *Mycobacterium tuberculosis* (H37 RA, Difco) in liquid paraffin) (0.05 ml) intradermally at a plantar site on the right hind leg. A suspension of a test compound in 0.5% methylcellulose was orally administered once a day for 14 d. The administration was started just before sensitization (day 0). The left hind paw volume was measured before sensitization (day 0) and on day 14, and the plantar edema inhibitory rate was determined by comparison with a nonsensitized group.

References and Notes

1) Part III: Baba A., Oda T., Taketomi S., Notoya K., Nishimura A., Makino H., Sohda T., *Chem. Pharm. Bull.*, **47**, 369—374 (1999).
2) Harris E. D., *N. Engl. J. Med.*, **322**, 1277—1289 (1990).
3) *a*) McCulloch J., Lydyard P. M., Rook G. A. W., *Clin. Exp. Immunol.*, **92**, 1—6 (1993); *b*) Wick I., McColl G., Harrison L., *Immunol. Today*, **15**, 553—556 (1994).
4) Baba A., Kawamura N., Makino H., Ohta Y., Taketomi S., Sohda T., *J. Med. Chem.*, **39**, 5176—5182 (1996).
5) Ohta Y., Fukuda S., Baba A., Nagai H., Tsukuda R., Sohda T., Makino H., *Immunopharmacology*, **34**, 17—26 (1996).
6) Ohta Y., Yamane M., Sohda T., Makino H., *Immunology*, **92**, 75—83 (1997).
7) Ohta Y., Fukuda S., Makino H., *Immunopharmacology*, **37**, 167—174 (1997).
8) Makino H., Ohta Y., Baba A., Sohda T., *Rheumatoid Arthritis ID Research Alert*, **1**, 573—582 (1997).
9) Jaffee B. D., Kerr J. S., Jones E. A., Giannarans J. V., McGowan M., Ackerman N. R., *Agents Actions*, **27**, 344—346 (1989).
10) *a*) Cheng C.-C., Yan S.-J., *Org. React.*, **28**, 37—201 (1982); *b*) Corral C., Madronero R., Ulecia N., *Afinidad*, **35**, 129—133 (1978).
11) *a*) Gewalt K., Schike E., Böttcher H., *Chem. Ber.*, **99**, 94—100 (1966); *b*) Nakanishi M., Tahara T., Araki K., Shiroki M., Tsumagari T., Takigawa Y., *J. Med. Chem.*, **16**, 214—219 (1973); *c*) Tinney F. J., Sachez J. P., Noga J. A., *ibid.*, **17**, 624—630 (1974).
12) *a*) Phillips D. D., Johnson A. W., *J. Am. Chem. Soc.*, **77**, 5977—5982 (1955); *b*) Harvey R. G., Arzadon L., Grant J., Urberg K., *ibid*, **91**, 4535—4541 (1969); *c*) Pickering R. E., Wysocki M. A., Eisenbraun E. J., Pell R. J., Gearhart H. L., Hamming M. C., *J. Labelled Compd. Rad.*, **24**, 919—924 (1987).
13) Pearson C. M., *Proc. Soc. Exp. Biol. Med.*, **91**, 95—101 (1956).