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A new series of 4-(4-methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepines **1a-k** has been synthesized from 4-bromo-2-methylthiophene **6** or ethyl 2-amino-4,5-dimethyl-3-thiophencarboxylate **10**. Preparation of the key intermediate thieno[2,3-*b*][1,5]benzoxazepine-4(5*H*)-ones **4a-i, 4k** were carried out by treatment of 2-bromo-*N*-(2-hydroxyphenyl)-3-thiophencarboxamides **5a-i, 5k** with potassium carbonate in DMSO. Compounds **1** are thienoanalogues of loxapine, a potent antipsychotic drug. Of these compounds, the neuroleptic activity of 2-methyl-4-(4-methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepine **1a** (R^1, R^3=H, R^2=CH_3) demonstrated potent antipsychotic activity.

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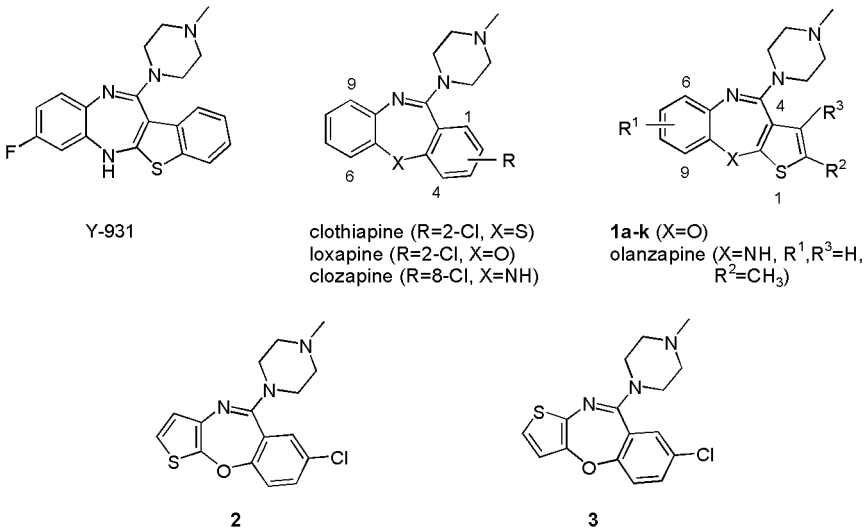
Benzothiazepine, benzoxazepine and benzodiazepine derivatives have desirable antipsychotic activities [1-4]. Investigations into the synthesis of these novel compounds and their biological activities may promote exciting progress in the medical field. We reported previously that Y-931 is an effective atypical antipsychotic [5] (Chart 1). It is well known that a number of 11-piperazinyl derivatives of dibenzo[*b*,*f*][1,4]thiazepines (X=S), dibenzo[*b*,*f*][1,4]oxazepines (X=O) and dibenzo[*b*,*f*][1,4]-diazepines (X=NH) have significant CNS activity. The most closely related compounds to this series are clothiapine, loxapine and clozapine.

Chart 1

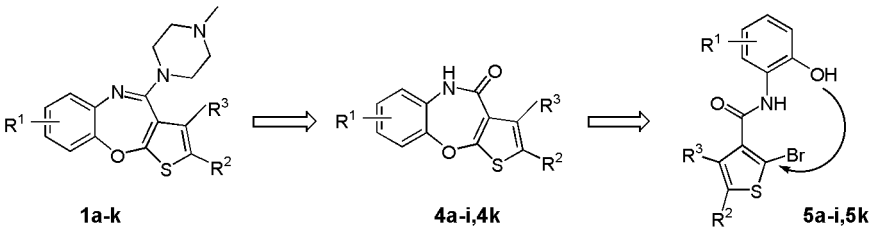


It is reported that the pharmacological activity is maintained even though a benzene ring is replaced by an isoster thiophene ring [6]. Indeed, olanzapine, which is a thienobenzodiazepine derivative structurally related to clozapine, has more an effective antipsychotic activity than clozapine [7]. On the other hand, Laimer and Erker reported that thienobenzoxazepines **2** and **3**, which are thienoanalogues of loxapine, did not have effective antipsychotic activity [8]. In the course of our approach to synthesizing novel antipsychotic agents, we designed a series of the title compounds **1** (X=O) in which the right side benzene ring of loxapine was replaced by a thiophene ring. In this report, we describe the synthesis of the thieno[2,3-*b*][1,5]benzoxazepine derivatives **1** which demonstrate potent neuroleptic activities.

We planned the synthesis of the series of compounds **1** from phenols **5** *via* oxazepines **4** as indicated in Scheme 1. To our knowledge, there are only a few reports on the synthesis of 2-aryloxythiophenes that are comprised in oxazepines **4** [8-10]. We applied an intramolecular cyclization of the phenols **5** to the synthesis of the oxazepine derivatives **4**.

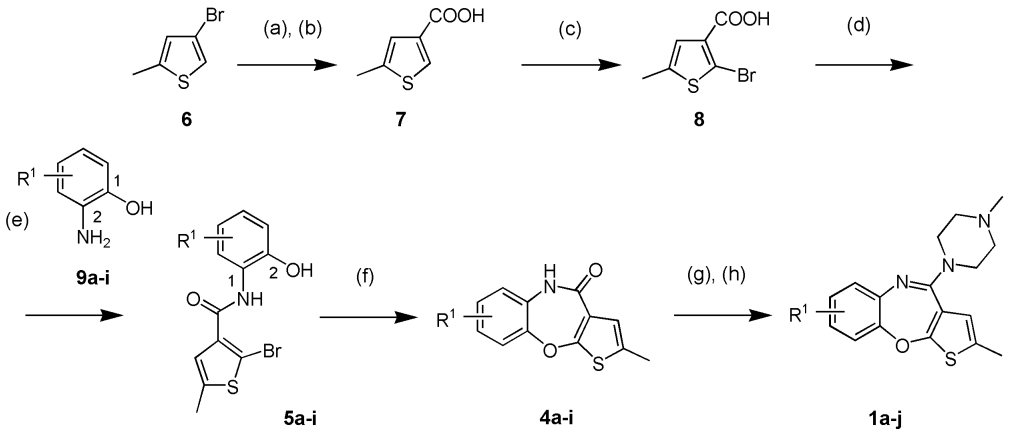
Compounds **1a-j** (X=O, R^2=CH_3, R^3=H) were synthesized from 4-bromo-2-methylthiophene **6** which was pre-

Scheme 1



pared according to the method reported by Gronowitz [6] (Scheme 2). Lithiation of **6** with *n*-BuLi followed by treatment with dry ice gave thiophene carboxylic acid **7** in 54% yield. After bromination of **7** at the 2-position, the resulting 2-bromo-5-methyl-3-thiophene carboxylic acid **8** was converted to the acylchloride with thionyl chloride. The reaction of the acylchloride with 2-aminophenols **9a-i** afforded amides **5a-i** in 57-97% yields (Table 1 and 2). piperazine gave the target compounds **1a-i** in 25-91% yields (Table 5 and 6). Although demethylation of compound **1h** by BBr_3 [11], Me_3SiI [12], or NaI [13] was unsuccessful, the phenol derivative **1j** was obtained in 39% yield by treating with ethanedithiol in the presence of $AlCl_3$ [14,15]. The synthesis of the 2,3-dimethylanalogue **1k** (X=O, R^1=H, R^2, R^3=CH_3) was carried out as shown in Scheme 3. Ethyl 2-amino-4,5-dimethyl-3-thiophenecar-

Scheme 2



	R^1
9a:	H
9b:	3-Me
9c:	4-Me
9d:	4-Cl
9e:	5-OMe
9f:	5-Me
9g:	5-Cl
9h:	6-OMe
9i:	6-Me

	R^1
5a:	H
5b:	6-Me
5c:	5-Me
5d:	5-Cl
5e:	4-OMe
5f:	4-Me
5g:	4-Cl
5h:	3-OMe
5i:	3-Me

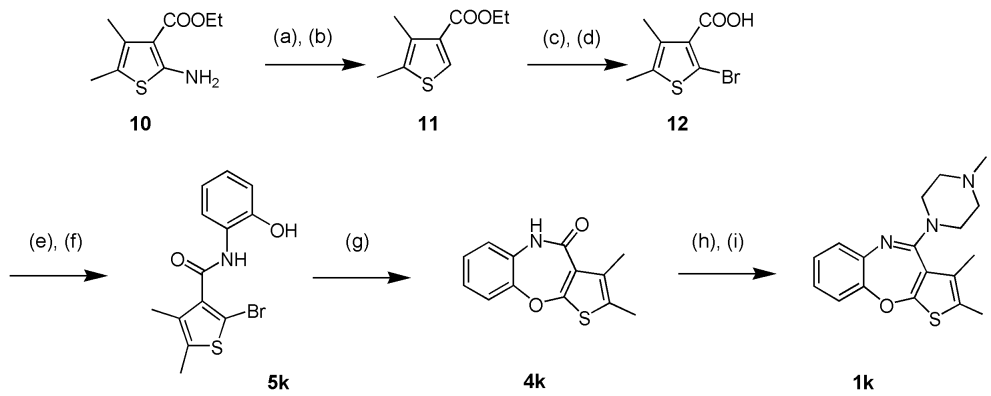
	R^1
4a:	H
4b:	6-Me
4c:	7-Me
4d:	7-Cl
4e:	8-OMe
4f:	8-Me
4g:	8-Cl
4h:	9-OMe
4i:	9-Me

	R^1
1a:	H
1b:	6-Me
1c:	7-Me
1d:	7-Cl
1e:	8-OMe
1f:	8-Me
1g:	8-Cl
1h:	9-OMe
1i:	9-Me
1j:	9-OH

Reagents: (a) *n*-BuLi, diethylether (b) dry ice (c) Br_2, AcOH (d) $SOCl_2$ (e) 2-aminophenol derivatives (**9a-i**), pyridine, toluene (f) K_2CO_3, DMSO (g) $POCl_3$ (h) 1-methylpiperazine (i) 1,2-ethanedithiol, $AlCl_3$, CH_2Cl_2

2-Amino-6-methoxyphenol **9h** and 2-amino-6-methylphenol **9i** were prepared from 3-methoxysalicylic acid and 3-methylsalicylic acid, respectively (Scheme 4 and 5). Intramolecular cyclizations of the amides **5** were achieved by potassium carbonate in DMSO (Table 3 and 4). After conversion of the oxazepinones **4** into the iminochloride by phosphoryl chloride, treatment with excess 1-methyl- boxylate **10** was prepared according to the method described by Gewald [16]. Reaction of **10** with sodium nitrite followed by treatment with sodium hypophosfite gave **11** in 27% yield. Hydrolysis of **11** with potassium hydroxide and treatment with bromine in acetic acid afforded compound **12** in 80% yield. 2-Bromothiophene **12** was converted to the acylchloride with thionyl chloride.

Scheme 3



Reagents: (a) $NaNO_2$, conc .HCl, EtOH (b) NaH_2PO_2 (c) KOH, EtOH-H_2O (d) Br_2, AcOH (e) $SOCl_2$ (f) 2-aminophenol, pyridine, toluene (g) K_2CO_3, DMSO (h) $POCl_3$ (i) 1-methylpiperazine

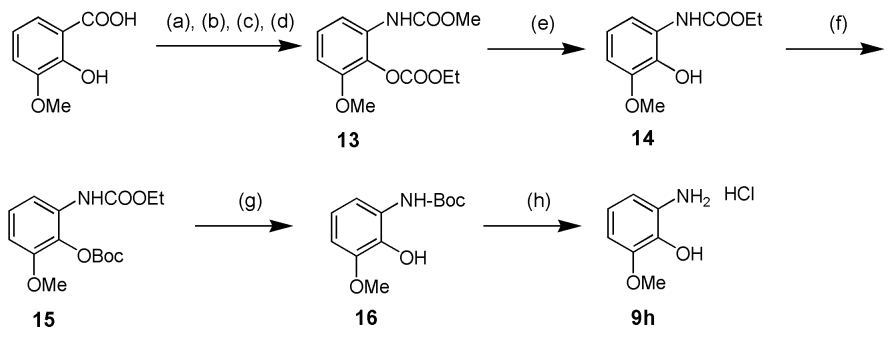
Table 1

Synthetical and Analytical Data of 2-Bromo-*N*-(2-hydroxyphenyl)-3-thiophenecarboxamides **5a-i**, **5k**

Cmpd	Mp (°C)	Yield (%)[b]	IR(cm^{-1}; KBr disk)	MS (m/z)	Molecular Formula	Analysis % Calcd. / Found		
5a	183-186	82	1633(amide)	312	$C_{12}H_{10}$ Br NO_2S	46.17	3.23	4.49
						46.45	3.24	4.43
5b	164-167	84	1633(amide)	326	$C_{13}H_{12}$ Br NO_2S	47.86	3.71	4.29
						47.58	3.72	4.26
5c	173-175	97	1637(amide)	326	$C_{13}H_{12}$ Br NO_2S	47.86	3.71	4.29
						48.20	3.75	4.29
5d	232-235	76	1631(amide)	346	$C_{12}H_9$ BrCl NO_2S	41.58	2.62	4.04
						41.95	2.81	4.10
5e	183-184	57	1637(amide)	342	$C_{13}H_{12}$ Br NO_3S	45.63	3.53	4.09
						45.51	3.51	4.11
5f	210-212	77	1641(amide)	326	$C_{13}H_{12}$ Br NO_2S	47.86	3.71	4.29
						47.92	3.66	4.27
5g	225-228	65	1640(amide)	346	$C_{12}H_9$ BrCl NO_2S	41.58	2.62	4.04
						41.22	2.58	4.02
5h	169-172	89	1651(amide)	342	$C_{13}H_{12}$ Br NO_3S $1/2H_2O$	44.46	3.73	3.99
						44.74	3.44	4.12
5i	108-111	80	1628(amide)	326	$C_{13}H_{12}$ Br NO_2S	47.86	3.71	4.29
						47.54	3.66	4.23
5k [a]	185-188	82	1649(amide)	326	$C_{13}H_{12}$ Br NO_2S	47.86	3.71	4.29
						47.52	3.32	4.21

[a] See Scheme 3; [b] Isolated yield.

Scheme 4



Reagents: (a) ClCOOEt, Et_3N, acetone (b) NaN_3 (c) benzene (d) MeOH (e) LiOH, THF-MeOH-water (f) $(BOC)_2O$, DMAP, Et_3N, THF (g) LiOH, THF-MeOH-water (h) 4 *N* HCl-Dioxane

Table 2

^{1}H-NMR Data of 2-Bromo-*N*-(2-hydroxyphenyl)-3-thiophenecarboxamides **5a-i, 5k**

Cmpd	pmr(δ: dimethylsulfoxide-d_6)
5a	10.27 (s, 1H), 9.71 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.12 (s, 1H), 7.00 (ddd, J = 1.5, 7.8 and 7.8 Hz, 1H), 6.91 (dd, J = 1.5 and 7.8Hz, 1H), 6.81 (ddd, J = 1.5, 7.8 and 7.8Hz, 1H), 2.42 (s, 3H)
5b	9.24 (s, 1H), 9.22 (s, 1H), 7.11 (s, 1H), 7.00 (dd, J = 7.3 and 7.8 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 7.3 Hz, 1H), 2.43 (s, 3H), 2.14 (s, 3H)
5c	9.62 (s, 1H), 9.16 (s, 1H), 7.67 (s, 1H), 7.11 (s, 1H), 6.78 (m, 2H), 2.42 (s, 3H), 2.20 (s, 3H)
5d	10.31 (s, 1H), 9.22 (s, 1H), 7.99 (s, 1H), 7.12 (s, 1H), 7.03 (dd, J = 2.5 and 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 2.42 (s, 3H)
5e	9.84 (s, 1H), 9.17 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.11(s, 1H), 6.46 (s, 1H), 6.40 (d, J = 8.8 Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H)
5f	9.74 (s, 1H), 9.17 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.11 (s, 1H), 6.71 (s, 1H), 6.62 (d, J = 7.9 Hz, 1H), 2.42 (s, 3H), 2.21 (s, 3H)
5g	10.22 (s, 1H), 9.94 (s, 1H), 7.42 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 2.31 (s, 3H)
5h	8.62 (br.s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.09 (s, 1H), 6.86 (dd, J = 8.3 and 8.3 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.27 (s, 1H), 3.81 (s, 3H), 2.41 (s, 3H)
5i	9.71 (s, 1H), 8.95 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.14 (s, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.74 (dd, J = 7.8 and 7.8 Hz, 1H), 2.37 (s, 3H), 2.19 (s, 3H)
5k	9.77 (s, 1H), 9.43 (s, 1H). 7.77 (d, J = 8.3 Hz, 1H), 7.00 (dd, J=7.8 and 7.8 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 6.8 and
[a]	8.2 Hz, 1H), 2.29 (s, 3H), 2.11 (s, 3H)

[a] See Scheme 3.

Table 3

Synthetical and Analytical Data of Methylthieno[2,3-*b*][1,5]benzoxazepine-4(5*H*)-ones **4a-i**, **4k**

Cmpd	IR(cm^{-1}; KBr disk)	MS (m/z)	Molecular Formula	Analysis % Calcd.	Found
4a	1676(amide) 1201(ArOAr)	231	$C_{12}H_9NO_2S$	231.03540	231.03094
4b	1670(amide) 1203(ArOAr)	245	$C_{13}H_{11}NO_2S$	245.05105	245.05123
4c	1678(ArOAr) 1209(ArOAr)	245	$C_{13}H_{11}NO_2S$	245.05105	245.05018
4d	1670(amide) 1203(ArOAr)	265	$C_{12}H_8ClNO_2S$	264.99643	264.99528
4e	1672(amide) 1200(ArOAr)	261	$C_{13}H_{11}NO_3S$	261.04597	261.04145
4f	1676(amide) 1207(ArOAr)	245	$C_{13}H_{11}NO_2S$	245.05105	245.05131
4g	1677(amide) 1200(ArOAr)	265	$C_{12}H_8ClNO_2S$	264.99643	264.99522
4h	1676(amide) 1204(ArOAr)	261	$C_{13}H_{11}NO_3S$	261.04597	261.04295
4i	1678(amide) 1205(ArOAr)	245	$C_{13}H_{11}NO_2S$	245.05105	245.05076
4k	1672(amide)	245	$C_{13}H_{11}NO_2S$	245.05105	245.05052
[a]	1207(ArOAr)				

[a] See Scheme 3.

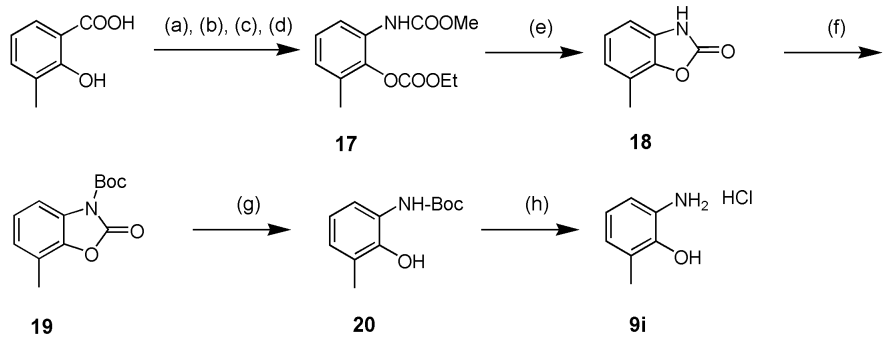
Table 4

^{1}H-NMR Data of Methylthieno[2,3-*b*][1,5]benzoxazepine-4(5*H*)-ones **4a-i, 4k**

Cmpd	pmr(δ:dimethylsulfoxide-d_6)
4a	10.12 (s, 1H), 7.09-7.23 (m, 4H), 6.72 (s, 1H), 2.31 (s, 3H)
4b	9.45 (s, 1H), 7.05-7.09 (m, 3H), 6.70 (s, 1H), 2.32 (s, 3H), 2.31 (s, 3H)
4c	10.05 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.94 (s, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.71 (s, 1H), 2.30 (s, 3H), 2.20 (s, 3H)
4d	10.28 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.13-7.21 (m, 2H), 6.73 (s, 1H), 2.32 (s, 3H)
4e	9.95 (s, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 2.9 Hz, 1H), 6.80 (dd, J = 2.9 and 8.3 Hz, 1H), 6.70 (s, 1H), 3.73 (s, 3H), 2.31 (s, 3H)
4f	10.02 (s, 1H), 7.01-7.04 (m, 3H), 6.71 (s, 1H), 2.31 (s, 3H), 2.24 (s, 3H)
4g	10.17 (s, 1H), 7.36 (s, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.67 (s, 1H), 2.26 (s, 3H)
4h	10.09 (s, 1H), 7.10 (dd, J = 8.3 and 8.3 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.71 (s, 1H), 3.81 (s, 3H), 2.31 (s, 3H)
4i	10.08 (s, 1H), 6.99-7.09 (m, 3H), 6.72 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H)
4k	10.17 (s, 1H), 7.11-7.22 (m, 4H), 2.21 (s, 3H), 2.13 (s, 3H)
[a]	

[a] See Scheme 3.

Scheme 5



Reagents: (a) ClCOOEt, Et_3N, acetone (b) NaN_3 (c) benzene (d) MeOH (e) LiOH, THF-MeOH-water (f) $(Boc)_2O$, DMAP, Et_3N, THF (g) $CsCO_3$, THF-MeOH (h) 4 *N* HCl-Dioxane

The reaction of the acylchloride with 2-aminophenol afforded smoothly amide **5k** in 82% yield (Table 1 and 2). Furthermore, the resulting **5k** was heated at 140° for 2 hours in the presence of potassium carbonate in DMSO to provide **4k** in 55% yield (Table 3 and 4). After the activation of **4k** to an iminochloride by phosphoryl chloride, the reaction of the iminochloride with 1-methylpiperazine gave the desired amine **1k** in good yield (Table 5 and 6).

high affinity for dopamine D_2 receptors (IC_{50}=36 nmol/L) and antagonized locomotor hyperactivity induced by apomorphine *in vivo* (ED_{50}=0.04 mg/kg, mice).

In conclusion, we have synthesized a new series of 4-(4-methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepines **1** from 4-bromo-2-methylthiophene **6** or ethyl 2-amino-4,5-dimethyl-3-thiophencarboxyate **10**. Of these compounds, **1a** showed potent antipsychotic activity. The detailed pharma-

Table 5

Synthetical and Analytical Data of 4-(4-Methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepines **1a-k**

Cmpd	Mp (°C)	Yield (%)[c]	IR(cm^{-1}; KBr disk)	MS (m/z)	Molecular Formula	Analysis % Calcd. / Found		
1a	132-133	52	1195(ArOAr)	313	$C_{17}H_{19}N_3OS$	65.15	6.11	13.41
						65.10	6.15	13.34
1b	114-117	43	1194(ArOAr)	327	$C_{18}H_{21}N_3OS$	66.02	6.46	12.83
						65.77	6.44	12.61
1c	146-148	25	1180(ArOAr)	327	$C_{18}H_{21}N_3OS$	66.02	6.46	12.83
						65.81	6.48	12.63
1d	227-228	55	1203(ArOAr)	347	$C_{17}H_{18}ClN_3OS$	54.37	4.78	9.06
					fumalate 1/4H_2O	54.16	4.70	9.00
1e	219-222	63	1197(ArOAr)	343	$C_{18}H_{21}N_3O_2S$	56.94	5.54	9.06
					fumalate 1/5H_2O	56.96	5.60	8.93
1f	149-150	65	1195(ArOAr)	327	$C_{18}H_{21}N_3OS$	66.02	6.46	12.83
						65.75	6.48	12.76
1g	96-100	49	1195(ArOAr)	347	$C_{17}H_{18}ClN_3OS$	58.70	5.22	12.08
						58.68	5.22	12.09
1h	239-241	91	1201(ArOAr)	343	$C_{18}H_{21}N_3O_2S$	57.06	5.53	9.07
					fumalate 1/5H_2O	57.06	5.51	9.08
1i	149-150	54	1197(ArOAr)	327	$C_{18}H_{21}N_3OS$	66.02	6.46	12.83
						65.97	6.40	12.71
1j	200-204	39	2837(OH)	329	$C_{17}H_{19}N_3O_2S$	61.98	5.81	12.76
[a]			1195(ArOAr)			61.81	5.89	12.52
1k	102-103	91	1198(ArOAr)	327	$C_{18}H_{21}N_3OS$ EtOH	61.09	6.99	9.91
[b]					1/2fumalate 1/4 H_2O	60.92	6.89	9.62

[a] See Scheme 2; [b] See Scheme 3; [c] Isolated yield.

All target compounds (**1a-k**) were screened for neuroleptic activity. Compound **1a** (R^1, R^3=H, R^2=CH_3) showed a cological activity of 4-(4-methylpiperazin-1-yl)thieno-[2,3-*b*][1,5]benzoxazepines will be reported in due course.

Table 6

^{1}H-NMR Data of 4-(4-Methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepines **1a-k**

Cmpd	solvent	pmr(δ)
1a	deuteriochloroform	6.95-6.99 (m, 4H), 6.29 (s, 1H), 3.58 (br.t, 4H), 2.48 (t, J = 4.0 Hz, 4H), 2.33 (s, 3H), 2.32 (s, 3H)
1b	deuteriochloroform	6.95-7.01 (m, 1H), 6.83-6.88 (m, 2H), 6.30 (s, 1H), 3.59 (t, J = 4.9 Hz, 4H), 2.49 (t, J = 4.9 Hz, 4H), 2.34 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H)
1c	deuteriochloroform	6.91 (d, J = 1.9 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 1.9 and 8.3 Hz, 1H), 6.28 (s, 1H), 3.57 (t, J = 4.9 Hz, 4H), 2.48 (t, J = 4.9 Hz, 4H), 2.32 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H)
1d	dimethylsulfoxide-d_6	6.99 (m, 3H), 6.60 (s, 2H), 6.54 (s, 1H), 3.53 (br.t, 4H), 2.43 (br.t, 4H), 2.34 (s, 3H), 2.24 (s, 3H)
1e	dimethylsulfoxide-d_6	6.95 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.60 (s, 2H), 6.49 (s, 1H), 3.70 (s, 3H), 3.47 (br.t, 4H), 2.62 (br.t, 4H), 2.33 (s, 3H), 2.26 (s, 3H)
1f	deuteriochloroform	6.98 (d, J = 7.8 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.80 (s, 1H), 6.28 (s, 1H), 3.56 (br.t, 4H), 2.43 (t, J = 4.9 Hz, 4H), 2.33 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H)
1g	deuteriochloroform	7.02-7.04 (m, 3H), 6.31 (s, 1H), 3.60 (br.t, 4H), 2.50 (t, J = 4.0Hz, 4H), 2.36 (s, 3H), 2.35 (s, 3H)
1h	dimethylsulfoxide-d_6	6.98 (dd, J = 7.8 and 8.3 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.60 (s, 2H), 6.58 (d, J = 7.8 Hz, 1H), 6.51 (s, 1H), 3.78 (s, 3H), 2.50-4.50 (br.s, 8H), 2.33 (s, 3H), 2.28 (s, 3H)
1i	dimethylsulfoxide-d_6	6.96 (dd, J = 7.4 and 7.8 Hz, 1H), 6.88 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 7.4 Hz, 1H), 6.51 (s, 1H), 3.47 (br.t, 4H), 2.38 (br.t, 4H), 2.33 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H)
1j [a]	deuteriochloroform	6.91 (dd, J = 7.8 and 8.3 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.30 (s, 1H), 5.60 (br.s, 1H), 3.59 (br.t, 4H), 2.50 (t, J = 4.9 Hz, 4H), 2.33 (s, 6H)
1k [b]	dimethylsulfoxide-d_6	7.09-6.98 (m, 4H), 6.60 (br.s, 1H), 7.00-4.50 (br.s, 1H), 4.00-2.10 (m, 8H), 3.45 (q, 2H), 2.28 (s, 3H), 2.21 (s, 3H), 2.03 (s, 3H), 1.06 (t, 3H)

[a] See Scheme 2; [b] See Scheme 3.

EXPERIMENTAL

Silica gel chromatography was performed on a Merck Kieselgel 60. Melting points were obtained on a Büchi 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL α400 spectrometer (400 MHz) or a HITACHI R-90H spectrometer (90 MHz) using tetramethylsilane (TMS) as an internal standard. Mass spectra were measured on a JEOL-JMS-DX300 instrument. Infrared spectra were recorded on a JASCO FT/IR-5300 spectrometer. Element analyses were performed on a Yanako CHN coder MT-5, and the results indicated by element symbols are within ±0.4% of the calculated values.

General Procedure for the Preparation of 4-(4-Methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepines **1a-i, 1k**.

2-Methylthieno[2,3-*b*][1,5]benzoxazepine-4(5*H*)-one derivative **4a-i, 4k** (4.3 mmoles) was suspended in phosphorus oxychloride (6.4 ml) and *N*,*N*-dimethylaniline (240 mg) was added. The mixture was stirred under reflux for 1 hour. The solvent was completely evaporated azeotropically with toluene under reduced pressure, and 1-methylpiperazine (25 ml) was added to the residue. The mixture was stirred under reflux for 40 minutes. The reaction system was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was extracted twice with chloroform and washed with water and brine. The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol 100:1). The obtained compound was recrystallized from diisopropyl ether to give the 2-methyl-4-(4-methylpiperazin-1-yl)thieno[2,3-*b*][1,5] benzoxazepines **1a-i, 1k**. The products are shown in Table 5 and 6.

9-Hydroxy-2-methyl-4-(4-methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepine (**1j**).

To a solution of 9-methoxy-2-methyl-4-(4-methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepine **1h** (0.51 g, 1.49 mmoles) and 1,2-ethanedithiol (2.4 ml, 28.6 mmoles) in dichloromethane (30 ml) was added aluminum chloride (3.0 g, 22.0 mmoles). The mixture was stirred at room temperature for 2 hours followed by addition of 1 *N* NaOH (100 ml), and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography (chloroform-methanol 10:1) to give 9-hydroxy-2-methyl-4-(4-methylpiperazin-1-yl)thieno[2,3-*b*][1,5]benzoxazepine **1j** (0.19 g, 39%) as colorless crystals (Table 5 and 6).

General Procedure for the Preparation of Thieno[2,3-*b*][1,5]benzoxazepin-4(5*H*)-ones **4a-i, 4k**.

To a solution of 2-bromo-*N*-(2-hydroxyphenyl)-5-methyl-3-thiophene carboxamide derivative **5a-i, 5k** (48 mmoles) in dimethylsulfoxide (100 ml) was added potassium carbonate (13 g) and the mixture was stirred at 140° for 2 hours. The reaction system was cooled to room temperature and the mixture was poured into water (800 ml). After neutralization with hydrochloric acid (37 wt. % in water), the mixture was extracted twice with chloroform and washed with aqueous sodium hydrogencarbonate. The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. To the residue was added chloroform and the crystals were collected by filtration to give the thieno[2,3-*b*][1,5]benzoxazepine-4(5*H*)-ones **4a-i, 4k**. The products are shown in Table 3 and 4.

General Procedure for the Preparation of 2-Bromo-*N*-(2-hydroxyphenyl) -5-methyl-3-thiophenecarboxamides **5a-i, 5k**.

2-Bromo-5-methyl-3-thiophenecarboxylic acid **8** or 2-bromo-4,5-dimethyl-3-thiophenecarboxylic acid 12 (22.6 mmoles) was suspended in thionyl chloride (20 ml) and the mixture was stirred under reflux for 75 minutes. Thionyl chloride was evaporated under reduced pressure and the residue was dissolved in toluene (5 ml). This toluene solution was added dropwise to a solution of 2-

aminophenol derivatives **9a-i** (33 mmoles) in pyridine (30 ml) at 0°. The mixture was stirred at room temperature for 6 hours and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate. It was washed with diluted hydrochloric acid and saturated aqueous sodium hydrogencarbonate, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and diisopropyl ether was added. The precipitated crystals were collected by filtration and washed with hexane to give 2-bromo-*N*-(2-hydroxyphenyl)-5-methyl-3-thiophene carboxamides **5a-i, 5k**. The products are shown in Table 1 and 2.

5-Methyl-3-thiophencarboxylic Acid (**7**).

To a solution of 4-bromo-2-methylthiophene **6** (35.9 g, 202 mmoles) in dimethyl ether at -70° was added 1.6 *M* *n*-BuLi hexane solution (133 ml, 212 mmoles). After stirring at -70° for 1 hour, crushed dry ice (24 g, 545 mmoles) was added and the reaction mixture was stirred for 30 minutes. Water (200 ml) and hydrochloric acid (37 wt. % in water, 30 ml) were added and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure. Silica gel column chromatography, eluting with chloroform-methanol (20:1), gave 5-methyl-3-thiophencarboxylic acid **7** (15.49 g, 54%) as yellow crystals, mp 126-128°; ir (potassium bromide): 2860, 1680, 1271 cm^{-1}; ms: m/z 142 (M^+); ^1H nmr (deuteriochloroform): δ 7.98 (s, 1H), 7.19 (s, 1H), 2.48 (s, 3H).

Anal. Calcd. for $C_6H_6O_2S$: C, 50.69; H, 4.25. Found: C, 50.31; H, 4.19.

2-Bromo-5-methyl-3-thiophencarboxylic Acid (**8**).

To a suspension of 5-methyl-3-thiophencarboxylic acid **7** (13.7 g, 96.5 mmoles) in acetic acid (120 ml) was added bromine (5.5 ml, 106 mmoles). The mixture was stirred at room temperature for 3 hours and poured into water. The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine. After it was dried over sodium sulfate, the solvent was removed to give a residue. Recrystallization from ethyl acetate/*n*-hexane gave 2-bromo-5-methyl-3-thiophene carboxylic acid **8** (15.4 g, 72%) as colorless crystals, mp 191-195°; ir (potassium bromide): 2864, 1676, 1475, 1269, 729 cm^{-1}; ms: m/z 221 (M^+); ^1H nmr (deuteriochloroform): δ 6.82 (s, 1H), 2.40 (s, 3H).

Anal. Calcd. for $C_6H_5BrO_2S$: C, 32.60; H, 2.28. Found: C, 32.97; H, 2.26.

2-Methoxy-6-aminophenol Hydrochloride (**9h**).

A suspension of 3-*t*-butyloxycarbonylamino-2-hydroxyanisole **16** (3.1 g, 12.9 mmoles) in 4 *N* HCl (in dioxane, 35 ml) was stirred at room temperature for 1 hour. The reaction mixture was filtrated, washing with diisopropyl ether gave 2-methoxy-6-aminophenol hydrochloride **9h** (1.85 g, 81%) as colorless crystals, mp 180°; ir (potassium bromide): 2849, 1504, 1485, 1282, 1221 cm^{-1}; ms: m/z 139 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ 9.83 (br.s, 4H), 6.99 (d, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.83 (dd, J = 8.3 and 8.3 Hz, 1H), 3.83 (s, 3H).

Anal. Calcd. for $C_7H_9NO_2$•HCl: C, 47.88; H, 5.74; N, 7.98. Found: C, 47.59; H, 5.81; N, 7.90.

2-Methyl-6-aminophenol Hydrochloride (**9i**).

A suspension of 3-*t*-butyloxycarbonylamino-2-hydroxytoluene **20** (8.78 g, 39.3 mmoles) in 4 *N* HCl (in dioxane, 80 ml) was stirred at room temperature for 1 hour. The reaction mixture was filtrated, washing with diisopropyl ether gave the 2-methyl-6-aminophenol hydrochloride **9i** (4.85 g, 81%) as colorless crystals, mp 250°; ir (potassium bromide): 3314, 2937, 1453, 1479, 1203 cm^{-1}; ms: m/z 123 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ 9.86 (br.s, 3H), 9.58 (br.s, 1H), 7.12-7.17 (m, 2H), 6.82 (dd, J = 7.8 and 7.9 Hz, 1H), 2.23 (s, 3H).

Anal. Calcd. for C_7H_9NO•HCl•H_2O: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.71; H, 6.66; N, 8.02.

Ethyl 4,5-Dimethyl-3-thiophencarboxylate (**11**).

To a solution of ethyl 2-amino-4,5-dimethyl-3-thiophenecarboxylate **10** (11.5 g, 58.6 mmoles) and hydrochloric acid (30%, 60 ml) in ethanol (60 ml) a solution of sodium nitrate (22 wt. % in water, 15 ml) was added dropwise at -2°. After stirring at -2° for 1 hour, sodium hypophosphite (38 wt. % in water, 50 ml) was added. The reaction mixture was partitioned between ethyl acetate and water. The combined organic layers were washed with brine. After it was dried over sodium sulfate, the solvent was removed to give a residue. Silica gel column chromatography, eluting with hexane-ethyl acetate (95:5), gave the ethyl 4,5-dimethyl-3-thiophencarboxylate **11** (2.9 g, 27%) as a colorless oil, ir (potassium bromide): 1732, 1452, 1269 cm^{-1}; ms: m/z 184 (M^+); ^1H nmr (deuteriochloroform): δ 7.19 (s, 1H), 4.16 (q, J = 7.3 Hz, 2H), 2.29 (s, 3H), 2.25 (s, 3H), 1.30 (t, J = 7.3 Hz, 3H).

2-Bromo-4,5-dimethyl-3-thiophencarboxylic Acid (**12**).

To a solution of ethyl 4,5-dimethyl-3-thiophencarboxylate **11** (2.9 g, 17.2 mmoles) in ethanol (100 ml) and water (14 ml) potassium hydroxide (1.44 g, 25.7 mmoles) was added at room temperature. After stirring at 40° for 5 hours, hydrochloric acid (35 wt. % in water) was added dropwise. The precipitate was collected and washed with *n*-hexane to give 4,5-dimethyl-3-thiophencarboxylic acid. To a solution of 4,5-dimethyl-3-thiophenecarboxylic acid (2.4 g, 15.4 mmoles) in acetic acid (10 ml) bromine (2.7 g, 17.1 mmoles) was added at room temperature. After stirring at room temperature for 3 hours, the precipitated solids were collected by filtration and washed with water to give 2-bromo-4,5-dimethyl-3-thiophenecarboxylic acid **12** (2.9 g, 80%) as a colorless solid, mp 178-180°; ir (potassium bromide): 2926, 2600, 1674, 1452, 1269, 729 cm^{-1}; ms: m/z 234, 236 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ 13.14 (br. s, 1H), 2.29 (s, 3H), 2.24 (s, 3H).

Anal. Calcd. For $C_7H_7BrO_2S$: C, 35.76; H, 3.00. Found: C, 35.81; H, 3.10.

2-Ethoxycarbonyloxy-3-methoxycarbonylaminoanisole (**13**).

To a solution of 3-methoxysalicylic acid (25 g, 148 mmoles) and triethylamine (30 g, 297 mmoles) in acetone (50 ml) ethyl chloroformate (28 ml, 297 mmoles) was added at 0°. The mixture was stirred for 1 hour at 0° and a solution of sodium azide (12 wt. % in water, 75 ml) was added. The mixture was stirred for 2 hours at 0°, poured into water and extracted with chloroform. After it was dried over sodium sulfate, the solvent was removed to give a residue. The residue in benzene (200 ml) was heated for 1 hour at 70°. After cooling, methanol (120 ml) was added and the mixture was heated for 1 hour at 55°. The solvent was removed to give a residue and it was washed by *n*-hexane to give 2-ethoxycarbonyloxy-3-methoxycarbonylaminoanisole **13** (32.83 g, 82%) as colorless crystals, mp 85-87°; ir (potassium bromide): 3319, 1761, 1712, 1234 cm^{-1}; ms: m/z 269 (M^+); ^1H nmr (deuteriochloroform): δ 7.72 (br.d, 1H), 7.17 (dd, J = 8.3 and 8.3 Hz, 1H), 6.87 (br.s, 1H), 6.67 (d, J = 8.3 Hz, 1H), 4.34 (q, J = 7.3 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 1.40 (t, J = 7.3 Hz, 3H).

Anal. Calcd. For $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.50; H, 5.57; N, 5.26.

2-Hydroxy-3-methoxycarbonylaminoanisole (**14**).

To a solution of 2-ethoxycarbonyloxy-3-methoxycarbonylaminoanisole **13** (32.8 g, 122.0 mmoles) in methanol (150 ml), tetrahydrofuran (300 ml) and water (225 ml) lithium hydroxyde monohydrate (20.5g, 487.0 mmol) was added. After stirring at 60° for 4 hours, the reaction mixture was concentrated, and partitioned between ethyl acetate and water. The organic layer was separated, and washed with brine. The solution was dried over sodium sulfate, and evaporated. Silica gel column chromatography, eluting with hexane-ethyl acetate (2:1), gave the 2-hydroxy-3-methoxycarbonylaminoanisole **14** (8.1 g, 31%) as colorless crystals, mp 84-86°; ir (potassium bromide): 3530, 3383, 1734, 1248 cm^{-1}; ms: m/z 211 (M^+); ^1H nmr (deuteriochloroform): δ 7.56 (br.d, 1H), 6.96 (br.s, 1H), 6.77 (dd, J = 8.3 and 8.3 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 5.77 (s, 1H), 4.16(q, J = 7.3 Hz, 2H), 3.81 (s, 3H), 1.23 (t, J = 7.3 Hz, 3H).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.55; H, 6.15; N, 6.64.

2-*t*-Butyloxycarbonyl-3-ethoxycarbonylaminoanisole (**15**).

To a solution of 2-hydroxy-3-methoxycarbonylaminoanisole **14** (5.6 g, 26.5 mmoles), triethylamine (3.22 g, 31.8 mmoles), and 4-dimethylaminopyridine (1.3 g, 10.6 mmoles) in tetrahydrofuran (190 ml) di-*tert*-butyl dicarbonate (6.94 g, 31.8 mmoles) was added. After stirring at room temperature for 2 hours, the reaction mixture was concentrated. Silica gel column chromatography, eluting with hexane-ethyl acetate (3:1), gave the 2-*t*-butyloxycarbonyl-3-ethoxycarbonylaminoanisole **15** (5.0 g, 61%) as a colorless oil, ms: m/z 311 (M^+); ^1H nmr (deuteriochloroform): δ 7.71 (br.d, 1H), 7.12 (dd, J = 8.3 and 8.3 Hz, 1H), 6.82 (br.s, 1H), 6.64 (d, J = 8.3 Hz, 1H), 4.19 (q, J = 7.3 Hz, 2H), 3.82 (s, 3H), 1.38 (s, 9H), 1.30 (t, J = 7.3 Hz, 3H).

3-*t*-Butyloxycarbonylamino-2-hydroxyanisole (**16**).

To a solution of 2-*t*-butyloxycarbonyl-3-ethoxycarbonylaminoanisole **15** (5.0 g, 16.0 mmoles) in methanol (20 ml), tetrahydrofuran (40 ml) was added lithium hydroxide monohydrate (2.7 g, 64.2 mmoles). The mixture was stirred at 45° for 1 hour and concentrated under reduced pressure. The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine. After the solution was dried over sodium sulfate, the solvent was removed to give a residue. Silica gel column chromatography, eluting with hexane-ethyl acetate (2:1), gave 3-*t*-butyloxycarbonylamino-2-hydroxyanisole **16** (3.1 g, 80%) as a red oil, ir (neat): 3433, 2978, 1730, 1533, 1467, 1249, 1157 cm^{-1}; ms: m/z 239 (M^+); ^1H nmr (deuteriochloroform): δ 7.58 (br.d, 1H), 6.87 (br.s, 1H), 6.82 (dd, J = 8.3 and 8.3 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 5.81 (s, 1H), 3.88 (s, 3H), 1.52 (s, 9H).

2-Ethoxycarbonyloxy-3-methoxycarbonylaminotoluene (**17**).

To a solution of 3-methylsalicylic acid (30.0 g, 197.2 mmoles) and triethylamine (39.9 g, 394.4 mmoles) in acetone (700 ml) was added ethyl chloroformate (37 ml, 394.4 mmoles) at 0°. The mixture was stirred at 0° for 1 hour and a solution of sodium azide (12 wt. % in water, 100 ml) was added. The mixture was stirred for 2 hours at 0°, poured into water, and extracted with chloroform. The extract was washed with brine, dried over sodium sulfate, and evaporated. The residue in benzene (300 ml) was heated for 1 hour at 70°. After cooling, methanol (150 ml) was added and the mixture was heated for 1 hour at 55°. The solvent was removed to give a residue and it was washed by *n*-hexane to give 2-ethoxycarbonyloxy-3-methoxycarbonylaminotoluene **17** (42.1 g, 97%), mp 67-71°; ir (potassium bromide): 3354, 1739, 1622, 1483, 1273, 1224, 1178 cm^{-1}; ms: m/z 253 (M^+); ^1H nmr (deuteriochloroform): δ 7.88 (br.s, 1H), 7.13 (dd, J = 7.8 and 7.8 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.77 (br.d, 1H), 4.32 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 2.18 (s, 3H), 1.38 (q, J = 7.3 Hz, 3H).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.05; H, 5.88; N, 5.64.

2,3-Dihydro-7-methyl-3*H*-benzoxazole-2-one (**18**).

To a solution of 2-ethoxycarbonyloxy-3-methoxycarbonylaminotoluene **17** (20.0 g, 79.0 mmoles) in methanol (100 ml), tetrahydrofuran (200 ml) and water (150 ml) lithium hydroxide monohydrate (13.3 g, 315.9 mmoles) was added. After stirring at 60° for 3 hours, the reaction mixture was concentrated, and partitioned between ethyl acetate and water. The organic layer was separated, and washed with brine. The solution was dried over sodium sulfate, and evaporated. Silica gel column chromatography, eluting with hexane-ethyl acetate (3:1), gave 2,3-dihydro-7-methyl-3*H*-benzoxazole-2-one **18** (6.2 g, 53%) as brown crystals, mp 155-159°; ir (potassium bromide): 3244, 1765, 1645, 1585, 1466 cm^{-1}; ms: m/z 149 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ 8.54 (br.s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.67 (dd, J = 8.3 and 8.3 Hz, 1H), 2.16 (s, 3H).

Anal. Calcd. for $C_8H_7NO_2 \cdot 1/2H_2O$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.53; H, 4.70; N, 8.83.

3-*t*-Butyloxycarbonyl-2,3-dihydro-7-methyl-3*H*-benzoxazole-2-one (**19**).

To a solution of 2,3-dihydro-7-methyl-3*H*-benzoxazole-2-one **18** (6.2 g, 41.5 mmoles), triethylamine (5.04 g, 49.8 mmoles), and 4-dimethylaminopyridine (1.0 g, 8.3 mmoles) in tetrahydrofuran (300 ml) di-*tert*-butyl dicarbonate (11.8 g, 54.0 mmoles) was added. After stirring at room temperature for 2 hours, the reaction mixture was concentrated. Silica gel column chromatography, eluting with hexane-ethyl acetate (5:1), gave 3-*t*-butyloxycarbonyl-2,3-dihydro-7-methyl-3*H*-benzoxazole-2-one **19** (10.5 g, 99%) as colorless crystals, mp 118-119°; ir (potassium bromide): 1828, 1319, 1290, 1257, 1157 cm^{-1}; ms: m/z 249 (M^+); ^1H nmr (deuteriochloroform): δ 7.49 (d, J = 7.8 Hz, 1H), 7.09 (dd, J = 7.8 and 8.3 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 2.35 (s, 3H), 1.65 (s, 9H).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.55; H, 6.20; N, 5.45.

3-*t*-Butyloxycarbonylamino-2-hydroxytoluene (**20**).

To a solution of 3-*t*-butyloxycarbonyl-2,3-dihydro-7-methyl-3*H*-benzoxazole-2-one **19** (9.54 g, 38.3 mmoles) in methanol (400 ml) and tetrahydrofuran (50 ml) cesium carbonate (12.5 g, 38.3 mmoles) was added at room temperature. After stirring at 60° for 2 hours, citric acid (8.04 g, 38.3 mmoles) was added and the solvents removed *in vacuo*. Silica gel column chromatography, eluting with hexane-ethyl acetate (3:1), gave 3-*t*-butyloxycarbonylamino-2-hydroxytoluene **20** (8.78 g, 99%) as a colorless oil, ir (neat): 3324, 2980, 1682, 1531, 1485, 1369, 1249, 1159 cm^{-1}; ms: m/z 223 (M^+); ^1H nmr (deuteriochloroform): δ 8.10 (br.s, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.83 (d, J = 7.3 Hz, 1H), 6.73 (dd, J = 7.3 and 7.8 Hz, 1H), 6.55 (br.s, 1H), 2.26 (s, 3H), 1.45 (s, 9H).

REFERENCES AND NOTES

[1] J. K. Chakrabarti, T. M. Hotten, I. A. Pullar and D. J. Steggles, *J. Med. Chem*., **32**, 2375 (1989).

[2] J. B. Press, C. M. Hofmann, N. H. Eudy, I. P. Day, E. N. Greenblatt and S. R. Safir, *J. Med. Chem*., **24**, 154 (1981).

[3] Y. Lieo, B. J. Venhuis, N. Rodenhuis, W. Timmerman and H. Wikström, *J. Med. Chem*., **42**, 2235 (1999).

[4] J-F. F. Liégeois, F. A. Rogister, J. Bruhwyler, J. Damas, T. P. Nguyen, M-O. Inarejos, E. M. G. Chleide, M. G. A. Mercier and J. E. Delarge, *J. Med. Chem*., **37**, 519 (1994).

[5] H. Tanaka, K. Kimura, H. Horiuchi, T. Kohara, M. Fujimura, K. Hashimoto, H. Yasumatsu, T. Morimoto, K. Yamagami, and M. Arita, "16th International Symposium on Medicinal Chemistry", Bologna, Italy, September 18-22, 2000, pp 404.

[6] S. Gronowitz, Thiophene and Its Derivatives, Part IV, John Wiely and Sons. (1985).

[7] C. M. Beasley, G. Tollefson, P. Tran, W. Satterlee, T. Sanger and S. Hamilton, *Neuropsychopharmacology*, **14**, 111 (1996).

[8] I. Laimer and T. Erker, *J. Heterocyclic. Chem*., **31**, 1053 (1994).

[9] J. Sice, *J. Am. Chem. Soc*., **75**, 3697 (1953).

[10] S. Katou, M. Ishizaki (Tokuyama Soda KK), Jpn. Kokai Tokkyo Koho JP 62106029 (1987); *Chem. Abstr.*, **108**, 93811b (1987).

[11] M. Demuynck, P. D. Clercq and M. Vandewalle, *J. Org. Chem*., **44**, 4863 (1979).

[12] M. E. Jung and M. A. Lyster, *J. Org. Chem*., **42**, 3761 (1977).

[13] T. Tsunoda, M. Amaike, U. S. F. Tambunan, Y. Fujise, S. Ito and M. Kodama, *Tetrahedron Lett*., **28**, 2537 (1987).

[14] G. Vidari, S. Ferrino and P. A. Grieco, *J. Am. Chem. Soc*., **106**, 3539 (1984).

[15] M. Node, H. Hori and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 2237 (1976).

[16] K. Gewald, *Z. Chem*., **2**, 305 (1962).