Facile Synthesis of Furobenzothiazepines

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The reaction of methyl 5-(2-isocyanatophenylthio)-2-furancarboxylate **2** with *N*-methylpiperazine gave 5-(2-*N*-piperazinocarbamoylphenylthio)-2-furancarboxylate **3a**. Furthermore, 4-*N*-methylpiperazinyl-2-methoxycarbonylfuro[2,3-*b*][1,5]benzothiazepine **4a** was obtained by the Bischler-Napieralski reaction of **3a** with phosphorus oxychloride in the present of phosphorus pentoxide. Three furobenzothiazepines could be obtained using the same method. Based on the pharmacological studies of these compounds, it was found that 4-morpholinyl-2-methoxycarbonylfuro[2,3-*b*][1,5]benzothiazepine **4b** had anti-inflammatory activity similar to flufenamic acid.

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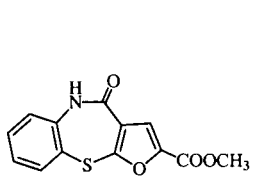
Many tricyclic compounds have biological activities and are used as drugs in various fields of clinical medicine. We have been studying the tricyclic compounds containing a furan ring in this laboratory [2]. In our previous work, the synthesis of the novel tricyclic compound, 5*H*-2-methoxycarbonyl-4-oxofuro[2,3-*b*][1,5]benzothiazepine **1**, was investigated [3]. In this study, we wish to report the synthesis of the 4-amino substituted compounds, and the examination of the pharmacological actions of these compounds. The anti-psychoneurotic drug, clothiapine, was used as the model compound (Figure 1).



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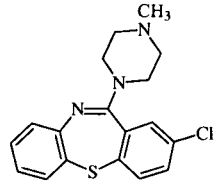
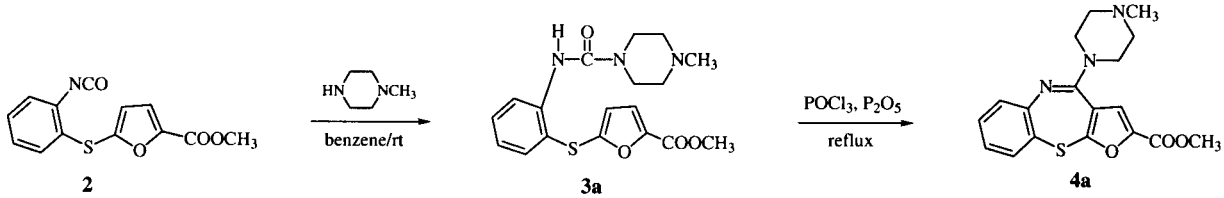


Clothiapine

Figure 1

Next, the synthesis of the 4-amino substituted compounds was attempted *via* another route. Schmutz *et al.* [4] synthesized 11-amino substituted dibenzo[*b,f*][1,4]thiazepines by the Bischler-Napieralski reaction, which is one of the most frequently employed methods for the synthesis of isoquinoline derivatives, of the corresponding urea with phosphorus oxychloride. Methyl 5-(2-isocyanatophenylthio)-2-furancarboxylate **2**, an intermediate product for the synthesis of **1**, was obtained in a high yield by a three-step reaction from methyl 5-(2-carboxy phenylthio)-2-furancarboxylate [3]. In this process, **2** was first allowed to react with various secondary amines, and the corresponding carbamoyl derivatives were synthesized. Methyl 5-(2-*N*-methylpiperazinocarbamoyl phenylthio)-2-furancarboxylate **3a** was obtained in nearly quantitative yield by adding droppwise a solution of 4-methylpiperazine in benzene into **2** dissolved in benzene (Scheme 1). Three carbamoyl derivatives were obtained using the same method (Scheme 2).

Scheme 1

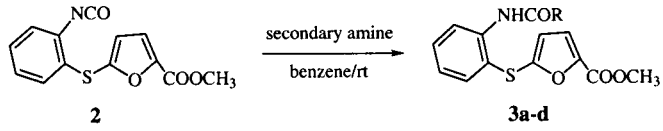


Schmutz *et al.* [4] synthesized 11-amino substituted dibenzo[*b,f*][1,4]thiazepine by the aminolysis of the iminochloride, 11-chlorodibenzo[*b,f*][1,4]thiazepine. First, the synthesis of 5*H*-2-methoxycarbonyl-4-chlorofuro-[2,3-*b*][1,5]benzothiazepine was attempted. Compound **1** was treated with phosphorus oxychloride and *N,N*-dimethylaniline, but the corresponding iminochloride was not obtained. Only a small amount of **1** was recovered. Moreover, the chlorination of **1** was tried under various conditions, but the expected compound was not obtained.

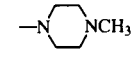
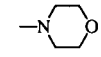
Compound **3a** was then treated with phosphorus oxychloride, but the required compound was not obtained. On the other hand, Howell *et al.* [5] synthesized 11-amino substituted dibenzo[*b,f*][1,4]thiazepine with phosphorus oxychloride in the presence of phosphorus pentoxide. In this reaction, 4-(4-methylpiperazinyl)-2-methoxycarbonyl-

Scheme 2

Methyl 5-(2-Aminocarbamoylphenylthio)-2-furancarboxylates **3a-d**



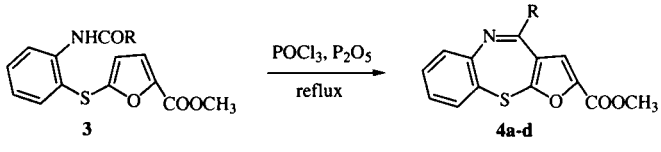
2 **3a-d**

Compound	R	mp (°C)	Yield (%)
3a		100-101	96
3b		147-148	73
3c		97-98	62
3d		118-120	88

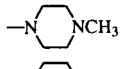
furo[2,3-*b*][1,5]benzothiazepine (**4a**) was obtained in 40% yield (Scheme 1). The structure of **4a** was supported by the ^{1}H-nmr, ir, and ms data and the elemental analysis result. Three furobenzothiazepines could be obtained using the same method (Scheme 3).

Scheme 3

4-Amino-2-methoxycarbonylfuro[2,3-*b*][1,5]bezothiazepines **4a-d**



3 **4a-d**

Compound	R	mp (°C)	Yield (%)
4a		153-154	40
4b		168-169	84
4c		136-138	84
4d		173-174	75

Next, the pharmacological studies of **4b** and **4d** were carried out. First, their effects on carbon dioxide induced amnesia were evaluated in male Std:ddy mice. Neither **4b** nor **4d** had an anti-amnesia effect at 100 mg/kg x 2, p. o. (Table 1). The brain acetylcholine esterase inhibitor activity was also examined using the method of Ellman *et al.* [6], but no activity was noted. The effects on the general symptoms were then evaluated by Irwin's observation and recording method, but no changes in the general symptoms were noted by the oral administration of **4b** or **4d** at 100 mg/kg. With intraperitoneal administration, **4b** and **4d** caused stretching at 30 and 100 mg/kg and a reduction in spontaneous movements accompanied by pronation at 30 mg/kg or above and 10 mg/kg or above, respectively. Finally, the effects on an increase in the vascular permeability were evaluated by Whittle's method. Compound **4b** inhibited the increase in the vascular permeability to that of the anti-inflammatory agent, flufenamic acid, at 100 mg/kg, p. o. (Table 2).

In summary, we synthesized four furobenzothiazepines in which a secondary amine was introduced to position 4 of **1**. Compounds **4b** and **4d** showed no anti-amnesia effect by a cholinergic mechanism contrary to our expectation, but **4b** exhibited anti-inflammatory activity similar to that of flufenamic acid.

EXPERIMENTAL

All melting points (open capillaries) were determined using a Yamato MP-21 and are uncorrected. The ^{1}H-nmr spectra were

Table 1

Effect of **4b** and **4d** on Carbon Dioxide Induced Disruption of the Memory of a Passive Avoidance Response in Mice

Compound	Dose (mg/kg x 2, p.o.)	n	Latency (seconds)	Criteria (seconds) 60	100	200	300	Percent improvement
Non carbon dioxide		10	227.8 ±14.9 [a]	10	10	9	7	
Carbon dioxide		10	97.9 ±33.6	4	4	2	1	
4b	100	10	115.3 ±35.2	6	4	2	2	9.7
4d	100	10	85.3 ±29.6	4	3	1	1	-7.0

[a] $p<0.05$ *vs* the CO2 group (Dunnett's test).

Table 2
Effect of Flufenamic Acid and **4b** on Increased Vascular Permebility Induced by Acetic Acid in Mice

Compound	Dose (mg/kg, p.o.)	n	Evans Blue [1] (μg/ml)	Inhibition (%)
Control	-	10	37.05 ±2.45	
Flufenamic acid	100	10	26.64 ±3.28	28.1
4b	100	10	28.34 ±1.97	23.5

[1] Each value represents the mean ± SE.
* Significantly different from the control at $p < 0.05$.

determined at 60 MHz using a Nippon Denshi JNM PMX60 SI spectrometer with tetramethylsilane as an internal reference. The ^{1}H-nmr of **4d** was also determined at 270 MHz using a Nippon Denshi JEOL GX270FT NMR spectrometer. The ir spectra were measured using a JASCO IR-810 spectrometer. The ms were obtained on a Nippon Denshi DX-300 spectrometer at 70ev.

General Production Method of Methyl 5-(2-Aminocarbamoylphenylthio)-2-furancarboxylate **3a-d**.

A 5 ml benzene solution of **2** (1.0 g, 3.6 mmoles) was added dropwise at room temperature to 5 ml of a benzene solution of the secondary amines (10.0 mmoles). After agitation at room temperature for 1 hour, the benzene was evaporated under reduced pressure. The resulting product was purified by recrystallization from benzene-hexane.

Methyl 5-(2-*N*-Methylpiperazinocarbamoylphenylthio)-2-furancaboxylate **3a**.

The product was colorless needles; ir (potassium bromide): 1740 ($COOCH_3$), 1675 (CONH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.15 (1H, dd, J = 2,8 Hz, Ph), 7.81 (1H, bs, NH, exchangeable proton), 7.53 (1H, dd, J = 2,8 Hz, Ph), 7.37-6.80 (2H, m, Ph), 7.07 (1H, d, J = 4 Hz, F-3), 6.41 (1H, d, J = 4 Hz, F-4), 3.85 (3H, s, $COOCH_3$), 3.61 (4H, t, J = 6 Hz, piperazine), 2.47 (4H, t, J = 6 Hz, piperazine), 2.33 (3H, s, NCH_3); ms: m/z 375 (M^+).

Anal. Calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.47; H, 5.63; N, 11.20.

Methyl 5-(2-Morpholinocarbamoylphenylthio)-2-furancaboxylate **3b**.

The product was colorless needles; ir (potassium bromide): 1735 ($COOCH_3$), 1680 (CONH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.17 (1H, dd, J = 2,8 Hz, Ph), 7.86 (1H, bs, NH, exchangeable proton), 7.55 (1H, dd, J = 2,8 Hz, Ph), 7.37-6.80 (2H, m, Ph), 7.05 (1H, d, J = 4 Hz, F-3), 6.45 (1H, d, J = 4 Hz, F-4), 3.91-3.47 (8H, m, morpholine), 3.83 (3H, s, $COOCH_3$); ms: m/z 362 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.54; H, 5.00; N, 7.73.

Methyl 5-(2-Piperidinocarbamoylphenylthio)-2-furancaboxylate **3c**.

The product was colorless needles; ir (potassium bromide): 1675 ($COOCH_3$), 1680 (CONH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.08 (1H, dd, J = 2,8 Hz, Ph), 7.68 (1H, bs, NH, exchangeable proton), 7.33 (1H, dd, J = 2,8 Hz, Ph), 6.98 (1H, d, J = 4 Hz, F-3), 6.80-7.28 (2H, m, Ph), 6.30 (1H, d, J = 4 Hz, F-4), 3.80 (3H, s, $COOCH_3$), 3.47 (4H, bs, piperidine), 1.62 (6H, bs, piperidine); ms: m/z 360 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 60.11; H, 5.61; N, 7.53.

Methyl 5-(2-Pyrrolidinocarbamoylphenylthio)-2-furancaboxylate **3d**.

The product was colorless needles; ir (nujol) 1735 ($COOCH_3$), 1670 (CONH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.30 (1H, dd, J = 2,8 Hz, Ph), 7.60 (1H, bs, NH, exchangeable proton), 7.53 (1H, dd, J = 2,8 Hz, Ph), 7.35-6.75 (2H, m, Ph), 7.30 (1H, d, J = 4 Hz, F-3), 6.37 (1H, d, J = 4 Hz, F-4), 3.83 (3H, s, $COOCH_3$), 3.66-3.43 (4H, m, pyrrolidine), 2.10-1.87 (4H, m, pyrrolidine); ms: m/z 346 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09. Found: C, 59.17; H, 5.29; N, 8.14.

General Production Method of 4-Amino Substituted 2-Methoxycarbonylfuro[2,3-*b*][1,5]benzothiazepine **4a-d**.

Two mmole of **3a-d** was added to a suspension of 0.8 g of phosphorus pentoxide and 7 ml of phosphorus oxychloride, and then the reactants were refluxed with stirring for 2 hours. After the reaction mixture was poured into ice-cold water and made neutral with sodium bicarbonate, the solution was extracted with ethyl acetate. The organic layer was isolated and extracted with 10% hydrochloric acid. The aqueous layer was isolated and made neutral with sodium bicarbonate. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, then dried over anhydrous sodium sulfate, and evaporated. The residue was purified by recrystallization from methanol.

4-*N*-Methylpiperazinyl-2-methoxycarbonylfuro[2,3-*b*][1,5]benzothiazepine **4a**.

The product was colorless prisms; ir (nujol): 1730($COOCH_3$) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.33-6.74 (4H, m, Ph), 6.98 (1H, s, F-3), 3.99-3.39 (4H, m, piperazine), 3.83 (3H, s, $COOCH_3$), 2.71-1.94 (4H, m, piperazine), 2.33 (3H, s, NCH_3); ms: m/z 357 (M^+).

Anal. Calcd. for $C_{18}H_{19}N_3O_3S$: C, 60.49; H, 5.36; N, 11.76. Found: C, 60.74; H, 5.40; N, 11.64.

4-Morpholinyl-2-methoxycarbonylfuro[2,3-*b*][1,5]benzothiazepine **4b**.

The product was colorless needles; ir (nujol): 1720 ($COOCH_3$) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.36-6.95 (4H, m, Ph), 7.02 (1H, s, F-3), 3.85 (3H, s, $COOCH_3$), 3.82-3.43 (8H, m, morpholine); ms: m/z 344 (M^+), 313(M^+-OMe).

Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.28; H, 4.68; N, 8.05.

4-Piperidinyl-2-methoxycarbonylfuro[2,3-*b*][1,5]benzothiazepine **4c**.

The product was colorless prisms; ir (nujol): 1730 ($COOCH_3$) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.30-6.72 (4H, m, Ph), 6.97 (1H, s, F-3), 3.82 (3H, s, $COOCH_3$), 3.53 (4H, bs, piperidine), 1.68 (6H, bs, piperidine); ms: m/z 342 (M^+).

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.10; H, 5.44; N, 8.10.

4-Pyrrolidinyl-2-methoxycarbonylfuro[2,3-*b*][1,5]benzothiazepine **4d**.

The product was colorless needles; ir (nujol): 1720 ($COOCH_3$) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.30 (1H, dd, J = 7.70, 1.46 Hz, Ph), 7.72 (1H, dt, J = 7.70, 1.46 Hz, Ph), 7.17 (1H, s, F-3), 7.11 (1H, dd, J = 7.70, 1.46 Hz, Ph), 6.95 (1H, dt, J = 7.70,

1.46 Hz, Ph), 3.88 (3H, s, $COOCH_3$), 3.60 (4H, bs, CH_2 x 2), 2.00 (4H, bs, CH_2 x 2); ms: m/z 328 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.15; H, 5.07; N, 8.29.

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