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# Syntheses of N-(1-Methyl-2-piperazinoethyl)propionanilides and 2-Alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]benzothiazoles[1]

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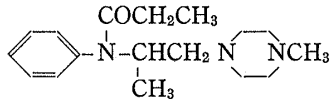
N-(1-Methyl-2-piperazinoethyl)anilines (**5a**—**e**) and 2-alkoxy-6-[1-methyl-2-(4-phenethylpiperazino)ethyl]-amino-benzothiazoles (**8a**—**d**) were prepared by the reduction of 1-(2-anilinopropionyl)piperazines (**4a**—**e**) and 1-[2-(2-alkoxy-benzothiazolyl-(6))-amino-propionyl]-4-phenethylpiperazines (**7a**—**d**). N-(1-Methyl-2-piperazinoethyl)propionanilides (**6a**—**e**) and 2-alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionamide]-benzothiazoles (**9a**—**d**) were prepared by N-propionylation of **5a**—**e** and **8a**—**d**.

Analgesic activity testing showed that (A) N-[1-methyl-2-(4-benzylpiperazino)ethyl]-propionanilide (**6d**) and N-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionanilide (**6e**) possessed *ca.* 1/3 of the analgesic effect of pentazocine; (B) N-propionylation of N-[1-methyl-2-(4-benzylpiperazino)ethyl]aniline (**5d**) and N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-aniline (**5e**) increased the analgesic activity, but N-propionylation of **8a**—**d** decreased the analgesic activity; (C) an aniline derivative (**6e**) was more potent than the 2-alkoxy-6-aminobenzothiazole derivatives (**9a**—**d**).

**Keywords**——syntheses of analgesics; piperazines; lithium aluminium hydride; 2-alkoxy-6-aminobenzothiazoles; N-propionylation

In a previous paper[3] we reported the synthesis and analgesic activity of N-[1-methyl-2-(4-methylpiperazino)ethyl]propionanilide (**1**).

The piperazine derivative (**1**) was examined for analgesic activity by subcutaneous administration to mice according to Haffner's method.[4] The piperazine derivative (**1**) possessed *ca.* 1/9 of the analgesic effect of morphine and exhibited more rapid onset and shorter duration of action than morphine. Nalorphine antagonized the analgesic effect of the piperazine derivative (**1**).



**1**

In this paper, the syntheses and analgesic activities of N-(1-methyl-2-piperazinoethyl)propionanilides (**6a**—**e**) are reported. In addition, 2-alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionamide]-benzothiazoles (**9a**—**d**) were prepared and examined for analgesic activities.

The piperazine derivatives (**6a**—**e**) were prepared as shown in Chart 1. Namely, 1-ethyl-(**2a**),[5a] 1-isopropyl- (**2b**),[5b] 1-*n*-butyl- (**2c**),[5c] 1-benzyl -(**2d**)[5d] and 1-phenethyl-piperazine (**2e**)[5d] were used as starting materials for the following syntheses. Acylation could be conducted by stirring a mixture of mono-substituted piperazines (**2a**—**e**) and α-bromopropionyl bromide (mole ratio 2: 1) in absolute $Et_2O$ to afford 1-(2-bromopropionyl)piperazine (**3a**—**e**). Crude **3a**—**e** and anilines were condensed by refluxing in ethanol in the presence of potassium carbonate to afford 1-(2-anilinopropionyl)piperazines (**4a**—**e**). The overall yields of **4a**—**e** based on **2a**—**e** were in the range of about 40% to 68%.

1) Reported at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1980.
2) Location: *Yoshida Shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan.*
3) J. Okada and M. Shimabayashi, *Yakugaku Zasshi*, **98**, 1619 (1978).
4) F. Haffner, *Dtsch. Med. Wschr.*, **55**, 731 (1929).
5) *a*) T.S. Moore, M. Boyle, and V.M. Thorn, *J. Chem. Soc.*, **1929**, 39; *b*) H.W. Stewart, R.J. Turner, and J.J. Denson, *J. Org. Chem.*, **13**, 134 (1948); *c*) Y. Ikeda, Y. Nitta, and K. Yamada, *Yakugaku Zasshi*, **89**, 669 (1969); *d*) R. Baltzly, J.S. Buck, E. Lorz, and W. Schon, *J. Am. Chem. Soc.*, **66**, 263 (1944).

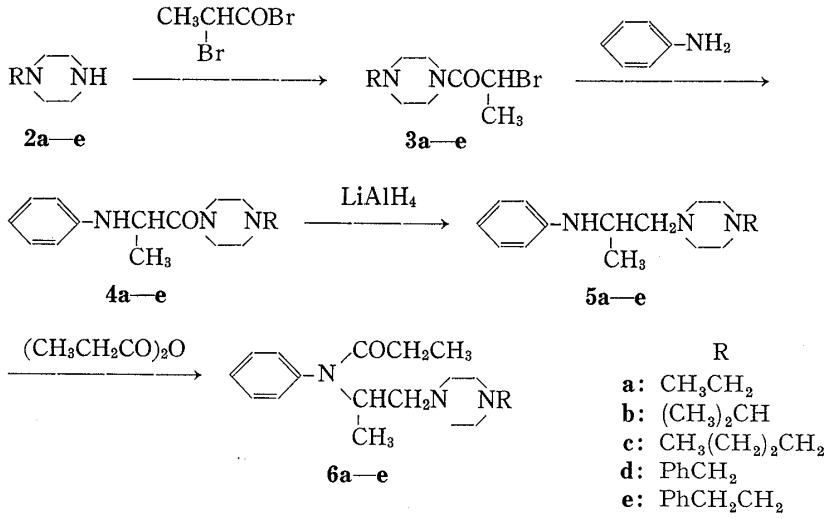



Chart 1

N-(1-Methyl-2-piperazinoethyl)anilines (**5a**—**e**) were prepared by lithium aluminium hydride reduction of **4a**—**e** in absolute $Et_2O$ or absolute $Et_2O$–THF. These free bases (**5a**—**e**) were all viscous oils and were transformed into oxalates in the usual manner.

N-Propionylation could be conducted by warming **5a**—**e** with propionic anhydride without any solvent to afford N-(1-methyl-2-piperazinoethyl)propionanilides (**6a**—**e**). As it was difficult to purify **6a**—**e** by vacuum distillation because of thermal decomposition, the propionanilides (**6a**—**e**) were purified by extraction and alumina column chromatogrophy with $CHCl_3$. These free bases (**6a**—**e**) were all obtained as viscous oils in about 50%—98% yields and were transformed into oxalates in the usual manner.

From the pharmacological data for the oxalates described above, it became apparent that the N-benzylpiperazine derivative (**6d**) and the N-phenethylpiperazine derivative (**6e**) possessed

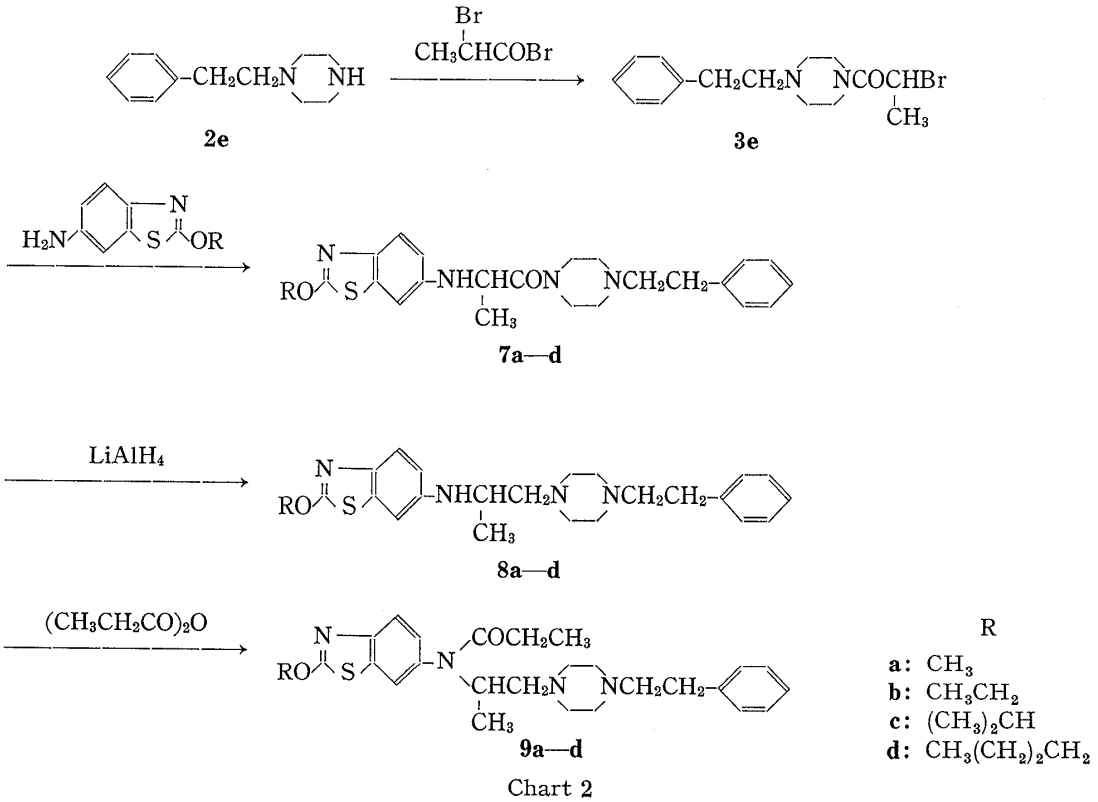



Chart 2

*ca.* 1/3 of the analgesic effect of pentazocine. It is also noteworthy that 2-amino-6-ethoxybenzothiazole[6] and 6-ethoxy-2-imino-3-methyl-2,3-dihydrobenzothiazole[7] have weak analgesic activity. Next, by using the similar compound, 2-alkoxy-6-aminobenzothiazole instead of aniline, 6-propionamide-benzothiazoles (**9a—d**) were prepared in a similar manner (Chart 2).

Namely, 1-(2-bromopropionyl)-4-phenethylpiperazine (**3e**) and 2-alkoxy-6-aminobenzothiazoles were condensed to afford **7a—d**. 2-Alkoxy-6-[1-methyl-2-(4-phenethylpiperazino)-ethyl]-amino-benzothiazoles (**8a—d**) were prepared by lithium aluminium hydride reduction of **7a—d**. These free bases (**8a—d**) were all obtained as viscous oils. They were purified by alumina column chromatogrophy with $CHCl_3$ and were transformed into oxalates in the usual manner. N-Propionylation could be conducted by warming **8a—d** with propionic anhydride without any solvent to afford **9a—d**. For the reason described above, **9a—d** were purified by extraction and column chromatography. These free bases **9a—d** were all pale yellow oils and were transformed into oxalates in the usual manner.

## Pharmacological Results

The eighteen oxalates described above were examined, by subcutaneous administration to mice, for analgesic activity in terms of the inhibition of writhing induced by acetic acid[8] in comparison with pentazocine. These compounds were also tested for acute toxicity in mice. The pharmacological results are listed in Table I.

Table I. Analgesic Activity

| Compd. No. | Route[a] | mg/kg | Inhibition (%) of writhing | Toxicity mg/kg (*s.c.*) |
|---|---|---|---|---|
| **5a** | *s.c.* | 30 | 19 | 300 Sedation |
| **5b** | *s.c.* | 30 | 45 | 300 Loss of weight |
| **5c** | *s.c.* | 30 | 49 | 300 Sedation, mydriasis, catalepsy |
| **5d** | *s.c.* | 30 | 29 | 300 Sedation |
| **5e** | *s.c.* | 30 | 24 | 300 Sedation |
| **6a** | *s.c.* | 30 | 15 | 300 Sedation |
| **6b** | *s.c.* | 30 | 44 | 300 Sedation, mydriasis |
| **6c** | *s.c.* | 30 | 47 | 100 Convulsion, mydriasis |
| **6d** | *s.c.* | 10 | 51 | 100 Convulsion |
| | *s.c.* | 30 | 68 | |
| **6e** | *s.c.* | 10 | 39 | 100 Sedation, mydriasis |
| | *s.c.* | 30 | 78 | 30 Normality |
| **8a** | *s.c.* | 30 | 62 | 1000 Myasthenia, sedation, death with in 24 hr |
| **8b** | *s.c.* | 30 | 26 | 1000 Sedation, loss of weight |
| **8c** | *s.c.* | 30 | 33 | 1000 Convulsion, death within 48 hr |
| **8d** | *s.c.* | 30 | 29 | 1000 Convulsion, death within 48 hr |
| **9a** | *s.c.* | 30 | 7 | 1000 Myasthenia, death within 24 hr |
| **9b** | *s.c.* | 30 | 19 | 1000 Sedation |
| **9c** | *s.c.* | 30 | 0 | 1000 Sedation |
| **9d** | *s.c.* | 30 | 4 | 1000 Sedation |
| Pentazocine | *s.c.* | 5 | 32 | 150 Convulsion, mydriasis |
| | *s.c.* | 10 | 81 | Trembling |

a) subcutaneous administration

The conclusion can be summarized as follows.

1) Amoung the eighteen oxalates, seven oxalates (**5b, c, 6b, c, d, e, 8a**) exhibited over 44% inhibition at 30 mg/kg *s.c.*

6) Kaufmann, *Arch. Pharm.*, **273**, 31 (1935).
7) T. Takahashi and J. Okada, *Yakugaku Zasshi*, **71**, 423 (1951).
8) R. Kostar, M. Anderson, and E.J. Debbeer, *Fed. Proc.*, **22**, 248 (1963).

2) The N-benzylpiperazine derivative (**6d**) and the N-phenethylpiperazine derivative (**6e**) possessed *ca.* 1/3 of the analgesic effect of pentazocine.

3) The N-ethylpiperazine derivatives (**5a**) and (**6a**) were practically inactive,

4) It is noteworthy that N-propionylation of **5d** and **5e** increased the analgesic activity, while N-propionylation of **8a**—**d** decreased the analgesic activity.

5) The aniline derivative (**6e**) showed more potent analgesic activity than 2-alkoxy-6-aminobenzothiazole derivatives (**9a**—**d**).

## Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on a Hitachi 215 spectrometer or a Hitachi 260-10 spectrometer and $^1$H-NMR spectra on a Varian A-60 spectrometer or a JEOL JNM-PMX 60 spectrometer operating at 60 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. Mass spectra were determined with a JEOL JMS-01SG-2 mass spectrometer.

**1-(2-Anilinopropionyl)piperazines**——1-(2-Anilinopropionyl)-4-ethylpiperazine (**4a**): A solution of α-bromopropionyl bromide (10.4 g) in absolute $Et_2O$ (90 ml) was added dropwise to a solution of 1-ethylpiperazine (**2a**) (11 g) in absolute $Et_2O$ (80 ml) at 5° over a period of 2 hr with stirring. The mixture was stirred at 5° for 1 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The pale yellow oily residue (**3a**) (12 g) was dissolved in EtOH (100 ml). $K_2CO_3$ (6.8 g) and aniline (4.6 g) were added to the solution. The mixture was refluxed for 8 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from petroleum ether and the crystals were collected by filtration and washed with petroleum ether. Recrystallization from isopropyl alcohol (iso-PrOH) gave **4a** (7.1 g, 56.4% yield) as colorless fine prisms, mp 127—127.5°. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1630 (C=O). NMR ($CDCl_3$) $\delta$: 1.03 (3H, t, $J$=7 Hz, $NCH_2\underline{CH_3}$), 1.33 (3H, d, $J$=6 Hz, $CH\underline{CH_3}$), 4.57 (1H, broad s, NH). MS *m/e*: 261 ($M^+$). *Anal.* Calcd for $C_{15}H_{23}N_3O$: C, 68.97; H, 8.81; N, 16.09. Found: C, 69.22; H, 8.84; N, 16.10.

1-(2-Anilinopropionyl)-4-isopropylpiperazine (**4b**): A solution of α-bromopropionyl bromide (17 g) in absolute $Et_2O$ (150 ml) was added dropwise to a solution of 1-isopropylpiperazine (**2b**) (20 g) in absolute $Et_2O$ (100 ml) at 5° over a period of 3 hr with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford a pale yellow oily residue (**3b**) (15 g). A mixture of **3b** (15 g), $K_2CO_3$ (7.9 g), aniline (5.3 g) and EtOH (120 ml) was refluxed for 8 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4b**. Recrystallization from iso-PrOH-$H_2O$ gave **4b** (6.7 g, 42.8% yield) as colorless prisms, mp 110—111°. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1625 (C=O). NMR ($CDCl_3$) $\delta$: 1.03 (6H, d, $J$=6 Hz, $NCH(\underline{CH_3})_2$), 1.38 (3H, d, $J$=6 Hz, $CH\underline{CH_3}$), 4.57 (1H, broad s, NH). MS *m/e*: 275 ($M^+$). *Anal.* Calcd for $C_{16}H_{25}N_3O$: C, 69.82; H, 9.09; N, 15.27. Found: C, 69.76; H, 8.93; N, 15.04.

1-(2-Anilinopropionyl)-4-*n*-butylpiperazine (**4c**): A solution of α-bromopropionyl bromide (11.4 g) in absolute $Et_2O$ (100 ml) was added dropwise to a solution of 1-*n*-butylpiperazine (**2c**) (15 g) in absolute $Et_2O$ (80 ml) at 5° over a period of 2 hr with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford the pale yellow oily residue (**3c**) (12.3 g). A mixture of **3c** (12.3 g), $K_2CO_3$ (6.2 g), aniline (4.2 g) and EtOH (100 ml) was refluxed for 8 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4c**. Recrystallization from dioxane-$H_2O$ gave **4c** (6.0 g, 39.3% yield) as colorless prisms, mp 95—96°. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1625 (C=O). NMR ($CDCl_3$) $\delta$: Exact values could not be determined because of broadening or overlapping. MS *m/e*: 289 ($M^+$). *Anal.* Calcd for $C_{17}H_{27}N_3O$: C, 70.59; H, 9.34; N, 14.53. Found: C, 70.39; H, 9.40; N, 14.42.

1-(2-Anilinopropionyl)-4-benzylpiperazine (**4d**): A solution of α-bromopropionyl bromide (19 g) in absolute $Et_2O$ (200 ml) was added dropwise to a solution of 1-benzylpiperazine (**2d**) (30 g) in absolute $Et_2O$ (150 ml) at 5° over a period of 3 hr with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford a pale yellow oily residue (**3d**) (27.5 g). A mixture of **3d** (27.5 g), $K_2CO_3$ (13 g), aniline (8.3 g) and EtOH (200 ml) was refluxed for 7.5 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4d**. Recrystallization from iso-PrOH gave **4d** (13.7 g, 49.8% yield) as colorless prisms, mp 112—112.5°. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1635 (C=O). NMR ($CDCl_3$) $\delta$: 1.33 (3H, d, $J$=6 Hz, $CH\underline{CH_3}$), 4.53 (1H, broad s, NH), 7.23 (5H, s, $NCH_2\underline{Ph}$). MS *m/e*: 323 ($M^+$). *Anal.* Calcd for $C_{20}H_{25}N_3O$: C, 74.30; H, 7.74; N, 13.00. Found: C, 74.40; H, 7.80; N, 12.97.

1-(2-Anilinopropionyl)-4-phenethylpiperazine (**4e**): A solution of α-bromopropionyl bromide (11.9 g) in absolute benzene (50 ml) was added dropwise to a solution of 1-phenethylpiperazine (**2e**) (21 g) in absolute benzene (100 ml) at 5° over a period of 25 min with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford a pale yellow oily residue (**3e**) (16 g). A mixture of **3e** (16 g), $K_2CO_3$ (6.8 g), aniline (4.6 g) and EtOH (50 ml) was refluxed for 10 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4e**. Recrystallization from MeOH gave **4e** (12.7 g, 68.2% yield) as colorless prisms, mp 105—106°. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1630 (C=O). NMR ($CDCl_3$) $\delta$:

1.34 (3H, d, $J$=6 Hz, CH$\underline{CH_3}$), 4.40 (1H, broad s, NH), 7.23 (5H, s, NCH$_2$CH$_2\underline{Ph}$). MS *m/e*: 337 ($M^+$). *Anal.* Calcd for $C_{21}H_{27}N_3O$: C, 74.78; H, 8.01; N, 12.46. Found: C, 74.62; H, 7.93; N, 12.56.

**N-(1-Methyl-2-piperazinoethyl)anilines**——N-[1-Methyl-2-(4-ethylpiperazino)ethyl]aniline (**5a**): A solution of **4a** (2.5 g) in absolute THF (40 ml) was added dropwise to a solution of $LiAlH_4$ (0.74 g) in absolute THF (50 ml) at 2° over a period of 1.5 hr with stirring. The mixture was refluxed for 7 hr, then cooled, and $H_2O$ (0.9 ml), 15% aqueous NaOH solution (2.4 ml) and $H_2O$ (2.4 ml) were successively added to the reaction mixture at below 5° with vigorous stirring. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The oily residue was distilled under reduced pressure to give **5a** (1.0 g, 41.9% yield) as a pale yellow oil, bp 126° (1.0 mmHg). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1600 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 1.05 (3H, t, $J$=7 Hz, NCH$_2\underline{CH_3}$), 1.18 (3H, d, $J$=6 Hz, CH$\underline{CH_3}$), 4.20 (1H, broad s, NH). MS *m/e*: 247 ($M^+$). Oxalate: mp 213—214° (dioxane-$H_2O$). *Anal.* Calcd for $C_{15}H_{25}N_3\cdot 2C_2H_2O_4$: C, 53.39; H, 6.79; N, 9.84. Found: C, 53.34; H, 6.93; N, 9.95.

N-[1-Methyl-2-(4-isopropylpiperazino)ethyl]aniline (**5b**): A solution of **4b** (3 g) in absolute $Et_2O$ (20 ml) and THF (20 ml) was added dropwise to a solution of $LiAlH_4$ (0.83 g) in absolute THF (60 ml) at 2° over a period of 2 hr with stirring. The mixture was stirred at room temperature for 21 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5b** (1.64 g, 57.6% yield) as a pale yellow oil, bp 126° (0.4 mmHg). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1597 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 1.01 (6H, d, $J$=6 Hz, NCH($\underline{CH_3}$)$_2$), 1.17 (3H, d, $J$=6 Hz, CH$\underline{CH_3}$), 4.33 (1H, broad s, NH). MS *m/e*: 261 ($M^+$). Oxalate: mp 203—204° (dioxane-$H_2O$). *Anal.* Calcd for $C_{16}H_{27}N_3\cdot 2C_2H_2O_4$: C, 54.42; H, 7.03; N, 9.52. Found: C, 54.58; H, 6.96; N, 9.32.

N-[1-Methyl-2-(4-*n*-butylpiperazino)ethyl]aniline (**5c**): A solution of **4c** (3 g) in absolute $Et_2O$ (20 ml) and THF (20 ml) was added dropwise to a solution of $LiAlH_4$ (0.79 g) in absolute $Et_2O$ (60 ml) at 2° over a period of 2 hr with stirring. The mixture was stirred at room temperature for 22 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5c** (1.26 g, 44.1% yield) as a pale yellow oil, bp 136° (0.5 mmHg). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1600 (benzene nucleus). NMR ($CDCl_3$) $\delta$: Exact values could not be determined because of broadening or overlapping. MS *m/e*: 275 ($M^+$). Oxalate: mp 202.5—203° (dioxane-$H_2O$). *Anal.* Calcd for $C_{17}H_{29}N_3\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 54.31; H, 7.33; N, 9.05. Found: C, 54.45; H, 7.22; N, 9.05.

N-[1-Methyl-2-(4-benzylpiperazino)ethyl]aniline (**5d**): A solution of **4d** (3.2 g) in absolute $Et_2O$ (20 ml) and THF (20 ml) was added dropwise to a solution of $LiAlH_4$ (0.75 g) in absolute $Et_2O$ (60 ml) at 2° over a period of 2 hr with stirring. The mixture was stirred at room temperature for 4 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5d** (1.302 g, 42.5% yield) as a pale yellow oil, bp 165° (0.2 mmHg). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1598 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 1.18 (3H, d, $J$=6 Hz, CH$\underline{CH_3}$), 3.47 (2H, s, N$\underline{CH_2}$Ph), 4.43 (1H, broad s, NH), 7.23 (5H, s, NCH$_2\underline{Ph}$). MS *m/e*: 309 ($M^+$). Oxalate: mp 204—205° (dioxane-$H_2O$). *Anal.* Calcd for $C_{20}H_{27}N_3\cdot 2C_2H_2O_4$: C, 58.89; H, 6.34; N, 8.59. Found: C, 58.62; H, 6.43; N, 8.50.

N-[1-Methyl-2-(4-phenethylpiperazino)ethyl]aniline (**5e**): A solution of **4e** (6.7 g) in absolute $Et_2O$ (50 ml) and THF (50 ml) was added dropwise to a solution of $LiAlH_4$ (1.52 g) in absolute $Et_2O$ (100 ml) at 2° over a period of 40 min with stirring. The mixture was refluxed for 2 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5e** (2.6 g, 40.5% yield) as a pale yellow oil, bp 179° (0.5 mmHg). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1595 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 1.20 (3H, d, $J$=6 Hz, CH$\underline{CH_3}$), 4.06 (1H, broad s, NH), 7.18 (5H, s, NCH$_2$CH$_2\underline{Ph}$). MS *m/e*: 323 ($M^+$). Oxalate: mp 207—208° (dioxane-$H_2O$). *Anal.* Calcd for $C_{21}H_{29}N_3\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 58.60; H, 6.64; N, 8.20. Found: C, 58.73; H, 6.52; N, 8.35.

**N-(1-Methyl-2-piperazinoethyl)propionanilides**——N-[1-Methyl-2-(4-ethylpiperazino)ethyl]propionanilide (**6a**): A mixture of **5a** (1.0 g) and propionic anhydride (4.3 ml) was heated at 100° for 3 hr. The mixture was poured over ice in a beaker and neutralized with $NaHCO_3$. The solution was made acidic with 20% aqueous HCl solution and washed with $Et_2O$. The acidic aqueous solution was made alkaline with 15% aqueous NaOH solution and extracted with $Et_2O$. The $Et_2O$ extract was dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue was subjected to alumina column chromatography with $CHCl_3$ to afford a pale yellow viscous oil **6a** (1.2 g, 97.8% yield). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1645 (C=O). NMR ($CDCl_3$) $\delta$: 5.23 (1H, q, $J$= 7 Hz, $\underline{CH}CH_3$). Other values could not be determined exactly because of overlapping. MS *m/e*: 303 ($M^+$).

A solution saturated with oxalic acid (anhydrous) in absolute $Et_2O$ was added dropwise to the mixture of **6a** (1.2 g) and absolute $Et_2O$ (20 ml). The crystals were collected by filtration and recrystallized from dioxane-$H_2O$ to give the oxalate of **6a** (1.8 g, 92.1% yield) as a colorless powder, mp 203—203.5°. *Anal.* Calcd for $C_{18}H_{29}N_3O\cdot 2C_2H_2O_4$: C, 54.66; H, 6.83; N, 8.70. Found: C, 54.40; H. 6.81; N, 8.67.

N-[1-Methyl-2-(4-isopropylpiperazino)ethyl]propionanilide (**6b**): A mixture of **5b** (1.0 g) and propionic anhydride (4.5 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6b** (0.852 g, 70.1% yield). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1638 (C=O). NMR ($CDCl_3$) $\delta$: 5.20 (1H, q, $J$=7 Hz, $\underline{CH}CH_3$). Other values could not be determined exactly because of overlapping. MS *m/e*: 317 ($M^+$). Oxalate: 1.2 g, 61.9% yield. Colorless powder, mp 192—193° (dioxane-$H_2O$). *Anal.* Calcd for $C_{19}H_{31}N_3O\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 54.54; H, 7.12; N, 8.30. Found: C, 54.87; H, 7.12; N, 8.45.

N-[1-Methyl-2-(4-*n*-butylpiperazino)ethyl]propionanilide (**6c**): A mixture of **5c** (0.8 g) and propionic anhydride (4 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6c** (0.929 g, 96.5% yield). IR $\nu_{max}^{Film}$ cm$^{-1}$: 1640 (C=O). NMR ($CDCl_3$) $\delta$: 5.17 (1H, q, $J$=7 Hz, $\underline{CH}CH_3$). Other values could not be determined exactly because of overlapping.

MS *m/e*: 331 ($M^+$). Oxalate: 1.356 g, 91.2% yield. Colorless powder, mp 211—211.5° (dioxane-$H_2O$). *Anal.* Calcd for $C_{20}H_{33}N_3O \cdot 2C_2H_2O_4$: C, 56.36; H, 7.24; N, 8.22. Found: C, 56.28; H, 7.36; N, 7.93.

N-[1-Methyl-2-(4-benzylpiperazino)ethyl]propionanilide (**6d**): A mixture of **5d** (0.8 g) and propionic anhydride (3 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6d** (0.47 g, 49.8% yield). IR $\nu_{max}^{Film}$ $cm^{-1}$: 1640 (C=O). NMR ($CDCl_3$) $\delta$: 1.00 (3H, t, $J=7$ Hz, $NCOCH_2\underline{CH_3}$), 1.02 (3H, d, $J=7$ Hz, $CH\underline{CH_3}$), 5.20 (1H, q, $J=7$ Hz, $\underline{CH}CH_3$), 7.23 (5H, s, $NCH_2\underline{Ph}$). MS *m/e*: 365 ($M^+$). Oxalate: 0.573 g, 40.6% yield. Colorless powder, mp 184—185° (dioxane-$H_2O$). *Anal.* Calcd for $C_{23}H_{31}N_3O \cdot 2C_2H_2O_4$: C, 59.45; H, 6.42; N, 7.71. Found: C, 59.22; H, 6.67; N, 7.62.

N-[1-Methyl-2-(4-phenethylpiperazino)ethyl]propionanilide (**6e**): A mixture of **5e** (1.0 g) and propionic anhydride (3 ml) was heated at 100° for 2.5 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6e** (0.605 g, 51.6% yield). IR $\nu_{max}^{Film}$ $cm^{-1}$: 1643 (C=O). NMR ($CDCl_3$) $\delta$: 1.00 (3H, t, $J=7$ Hz, $NCOCH_2\underline{CH_3}$), 1.03 (3H, d, $J=7$ Hz, $CH\underline{CH_3}$), 5.20 (1H, q, $J=7$ Hz, $\underline{CH}CH_3$), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 379 ($M^+$). Oxalate: 0.716 g, 41.4% yield. Colorless powder, mp 196—197° (dioxane-$H_2O$). *Anal.* Calcd for $C_{24}H_{33}N_3O \cdot 2C_2H_2O_4$: C, 60.11; H, 6.62; N, 7.51. Found: C, 60.33; H, 6.77; N, 7.42.

**2-Alkoxy-6-aminobenzothiazoles**——6-Amino-2-methoxy-benzothiazole,[9c] 6-amino-2-ethoxy-benzothiazole[9c] and 6-amino-2-*n*-butoxy-benzothiazole[9c] were used as starting materials for the syntheses. The method of Takahashi *et al.*[9a-c] could be applied to prepare the novel compounds 2-isopropoxy-6-nitro-benzothiazole and 6-amino-2-isopropoxy-benzothiazole.

2-Isopropoxy-6-nitro-benzothiazole: 2-Chloro-6-nitro-benzothiazole[10] (22 g) was added to a solution of sodium (2.3 g) in absolute iso-PrOH (150 ml). The mixture was refluxed for 5 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The crystalline residue was recrystallized from 50% aqueous MeOH solution to give 2-isopropoxy-6-nitro-benzothiazole (12.5 g, 51.2% yield) as yellow needles, mp 96—97°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 760 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 1.50 (6H, d, $J=6$ Hz, $CH(\underline{CH_3})_2$), 5.47 (1H, m, $J=6$ Hz, $\underline{CH}(CH_3)_2$), 7.66—8.70 (3H, m, aromatic protons). MS *m/e*: 238 ($M^+$). *Anal.* Calcd for $C_{10}H_{10}N_2O_3S$: N, 11.76; S, 13.45. Found: N, 12.02; S, 13.55.

6-Amino-2-isopropoxy-benzothiazole: Iron (15 g) was added to a solution of 2-isopropoxy-6-nitro-benzothiazole (12.5 g) in 50% aqueous acetic acid (120 ml) and EtOH (100 ml) at room temperature over a period of 30 min with stirring. The mixture was refluxed for 2 hr, then cooled, made alkaline with 25% aqueous NaOH solution and extracted with $Et_2O$. The $Et_2O$ extract was dried over $MgSO_4$ and concentrated. The oily residue was distilled under reduced pressure to afford 6-amino-2-isopropoxy-benzothiazole (3.7 g, 33.9% yield) as a pale yellow oil, bp 166° (5 mmHg), mp *ca.* 78°. IR $\nu_{max}^{Film}$ $cm^{-1}$: 3300 ($NH_2$), 1600 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 1.40 (6H, d, $J=6$ Hz, $CH(\underline{CH_3})_2$), 3.62 (2H, s, $NH_2$), 5.28 (1H, m, $J=6$ Hz, $\underline{CH}(CH_3)_2$), 6.53—7.70 (3H, m, aromatic protons). MS *m/e*: 208 ($M^+$). *Anal.* Calcd for $C_{10}H_{12}N_2OS$: H, 5.77; N, 13.46; S, 15.39. Found: H, 5.39; N, 13.78; S, 15.40.

**1-[2-(2-Alkoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazines**——1-[2-(2-Ethoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7b**): A solution of α-bromopropionyl bromide (6.2 g) in absolute $Et_2O$ (70 ml) was added dropwise to a solution of 1-phenethylpiperazine (**2e**) (10.8 g) in absolute $Et_2O$ (70 ml) at 5° over a period of 1 hr with stirring. The mixture was stirred at 5° for 1.5 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The pale yellow oily residue (**3e**) (9.1 g, 98.5% yield) was dissolved in EtOH (70 ml). $K_2CO_3$ (4.0 g) and 6-amino-2-ethoxy-benzothiazole (5.5 g) were added to the solution. The mixture was refluxed for 6 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7b** (6.9 g, 55.4% yield) as colorless fine prisms, mp 127—128°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3270 (NH), 1623 (C=O). NMR ($CDCl_3$) $\delta$: 1.42 (3H, t, $J=7$ Hz, $OCH_2\underline{CH_3}$), 4.50 (1H, broad s, NH), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 438 ($M^+$). *Anal.* Calcd for $C_{24}H_{30}N_4O_2S$: C, 65.75; H, 6.85; N, 12.78; S, 7.31. Found: C, 65.69; H, 6.94; N, 12.64; S, 7.29.

1-[2-(2-Methoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7a**): A solution of **3e** (9.8 g) [prepared from **2e** (11 g) and α-bromopropionyl bromide (6.3 g) by the method described above (c.f. **7b**)], $K_2CO_3$ (4.0 g) and 6-amino-2-methoxy-benzothiazole (5.2 g) in EtOH (70 ml) was refluxed for 6 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7a** (5.0 g, 40.7% yield) as colorless fine prisms, mp 159—160°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3320 (NH), 1643 (C=O). NMR ($CDCl_3$) $\delta$: 1.40 (3H, d, $J=6$ Hz, $CH\underline{CH_3}$), 4.11 (3H, s, $OCH_3$), 4.53 (1H, broad s, NH), 7.21 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 424 ($M^+$). *Anal.* Calcd for $C_{23}H_{28}N_4O_2S$: C, 65.09; H, 6.60; N, 13.21; S, 7.55. Found: C, 65.37; H, 6.69; N, 13.06; S, 7.68.

1-[2-(2-Isopropoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7c**): A solution of **3e** (6.5 g) [prepared from **2e** (6.4 g) and α-bromopropionyl bromide (3.6 g) by the method described above

9) *a*) T. Takahashi and H. Taniyama, *Yakugaku Zasshi*, **66**, 37 (1946); *b*) *Idem, ibid.*, **67**, 42 (1947); *c*) *Idem, ibid.*, **67**, 123 (1948).
10) T. Takahashi and H. Taniyama, *Yakugaku Zasshi*, **66**, 25 (1946).

(c.f. **7b**)], $K_2CO_3$ (2.3 g) and 6-amino-2-isopropoxy-benzothiazole (3.5 g) in EtOH (40 ml) was refluxed for 5 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7c** (4.0 g, 52.5% yield) as colorless fine prisms, mp 138—139°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3340 (NH), 1630 (C=O). NMR ($CDCl_3$) $\delta$: 1.55 (6H, d, $J$=6 Hz, $OCH(\underline{CH_3})_2$), 4.56 (1H, broad s, NH), 7.32 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 452 ($M^+$). *Anal.* Calcd for $C_{25}H_{32}N_4O_2S$: C, 66.37; H, 7.08; N, 12.39; S, 7.08. Found: C, 66.61; H, 7.36; N, 12.14; S, 7.03.

1-[2-(2-*n*-Butoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7d**): A solution of **3e** (7.3 g) [prepared from **2e** (8.6 g) and α-bromopropionyl bromide (4.9 g) by the method described above (c.f. **7b**)], $K_2CO_3$ (3.2 g) and 6-amino-2-*n*-butoxy-benzothiazole (5.0 g) in EtOH (60 ml) was refluxed for 5.5 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7d** (5.9 g, 55.9% yield) as colorless fine prisms, mp 89—90°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3350 (NH), 1630 (C=O). NMR ($CDCl_3$) $\delta$: 4.27 (1H, broad s, NH), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 466 ($M^+$). *Anal.* Calcd for $C_{26}H_{34}N_4O_2S$: C, 66.95; H, 7.30; N, 12.01; S, 6.87. Found: C, 66.89; H, 7.31; N, 11.85; S, 7.05.

**2-Alkoxy-6-[1-methyl-2-(4-phenethylpiperazino)ethyl]-amino-benzothiazoles**——6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-ethoxy-benzothiazole (**8b**): A solution of **7b** (4.5 g) in absolute $Et_2O$ (70 ml) and THF (80 ml) was added dropwise to a solution of $LiAlH_4$ (0.8 g) in absolute $Et_2O$ (100 ml) at 0° over a period of 2 hr with stirring. The mixture was refluxed for 5 hr, then cooled and the post-treatment described above (c.f. **5a**) was carried out to afford a dark reddish-purple oily residue. The oily residue was subjected to alumina column chromatography with $CHCl_3$ to afford a dark purple viscous oil **8b** (4.1 g, 94.1% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 3325 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 1.18 (3H, d, $J$=6 Hz, $CH\underline{CH_3}$), 1.25 (3H, t, $J$=7 Hz, $OCH_2\underline{CH_3}$), 4.23 (1H, broad s, NH), 7.17 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 424 ($M^+$). Oxalate: mp 197—198° (MeOH). *Anal.* Calcd for $C_{24}H_{32}N_4OS\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 54.81; H, 6.04; N, 9.13; S, 5.22. Found: C, 54.91; H, 5.91; N, 9.18; S, 5.03.

6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-methoxy-benzothiazole (**8a**): A solution of **7a** (4.0 g) in absolute $Et_2O$ (25 ml) and THF (240 ml) was added dropwise to a solution of $LiAlH_4$ (0.8 g) in absolute $Et_2O$ (90 ml) at 0° over a period of 2 hr with stirring. The mixture was refluxed for 5 hr. The post-treatment described above (c.f. **8b**) was carried out to afford a dark purple viscous oil **8a** (3.7 g, 95.7% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 3320 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 4.23 (3H, s, $OCH_3$), 7.33 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 410 ($M^+$). Oxalate: mp 201—202° (MeOH). *Anal.* Calcd for $C_{23}H_{30}N_4OS\cdot 2C_2H_2O_4$: C, 54.92; H, 5.76; N, 9.49; S, 5.42. Found: C, 54.78; H, 5.83; N, 9.04; S, 4.81.

6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-isopropoxy-benzothiazole (**8c**): A solution of **7c** (3.5 g) in absolute $Et_2O$ (50 ml) and THF (60 ml) was added dropwise to a solution of $LiAlH_4$ (0.6 g) in absolute $Et_2O$ (86 ml) at 0° over a period of 1 hr with stirring. The mixture was refluxed for 5 hr. The post-treatment described above (c.f. **8b**) was carried out to afford a dark reddish-purple viscous oil **8c** (3.2 g, 94.4% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 3310 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 4.33 (1H, broad s, NH), 7.30 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 438 ($M^+$). Oxalate: mp 194° (MeOH). *Anal.* Calcd for $C_{25}H_{34}N_4OS\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 55.50; H, 6.22; N, 8.93; S, 5.11. Found: C, 55.19; H, 6.20; N, 8.79; S, 5.22.

6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-*n*-butoxy-benzothiazole (**8d**): A solution of **7d** (4.0 g) in absolute $Et_2O$ (50 ml) and THF (70 ml) was added dropwise to a solution of $LiAlH_4$ (0.7 g) in absolute $Et_2O$ (100 ml) at 0° over a period of 1.5 hr with stirring. The mixture was refluxed for 5 hr. The post-treatment described above (c.f. **8b**) was carried out to afford a dark reddish-purple viscous oil **8d** (3.7 g, 95.4% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 3325 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) $\delta$: 4.30 (1H, broad s, NH), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 452 ($M^+$). Oxalate: mp 199—200° (MeOH). *Anal.* Calcd for $C_{26}H_{36}N_4OS\cdot 2C_2H_2O_4\cdot H_2O$: C, 55.38; H, 6.46; N, 8.62; S, 4.92. Found: C, 55.68; H, 6.29; N, 8.46; S, 4.53.

**2-Alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazoles**——2-Methoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9a**): A mixture of **8a** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **9a** (1.0 g, 44.0% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 1640 (C=O). NMR ($CDCl_3$) $\delta$: 1.13 (3H, t, $J$=7 Hz, $COCH_2\underline{CH_3}$), 1.25 (3H, d, $J$=7 Hz, $CH\underline{CH_3}$), 3.52 (3H, s, $OCH_3$), 7.18 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 466 ($M^+$). Oxalate: mp 186° (MeOH). *Anal.* Calcd for $C_{26}H_{34}N_4O_2S\cdot 2C_2H_2O_4$: C, 55.73; H, 5.88; N, 8.67; S, 4.95. Found: C, 55.45; H, 6.10; N, 8.61; S, 4.74.

2-Ethoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9b**): A mixture of **8b** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford an orange-colored viscous oil **9b** (1.5 g, 66.3% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 1645 (C=O). NMR ($CDCl_3$) $\delta$: 1.08 (3H, d, $J$=7 Hz, $CH\underline{CH_3}$), 1.50 (3H, t, $J$=7 Hz, $OCH_2\underline{CH_3}$), 4.62 (2H, q, $J$=7 Hz, $O\underline{CH_2}CH_3$), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 480 ($M^+$). Oxalate: mp 199° (MeOH). *Anal.* Calcd for $C_{27}H_{36}N_4O_2S\cdot 2C_2H_2O_4$: C, 56.36; H, 6.06; N, 8.49; S, 4.85. Found: C, 56.33; H, 5.99; N, 8.54; S, 4.84.

2-Isopropoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9c**): A mixture of **8c** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **9c** (1.0 g, 44.3% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 1640 (C=O). NMR ($CDCl_3$) $\delta$: 3.43 (2H, q, $J$=7 Hz, $CO\underline{CH_2}CH_3$), 7.17 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 494 ($M^+$). Oxalate: mp 183° (MeOH). *Anal.* Calcd for $C_{28}H_{38}N_4O_2S\cdot 2C_2H_2O_4$: C, 56.97; H, 6.23; N, 8.31; S,

4.75. Found: C, 56.64; H, 6.30; N, 8.13; S, 4.62.

2-*n*-Butoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9d**): A mixture of **8d** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **9d** (1.3 g, 57.8% yield): IR $\nu_{max}^{Film}$ $cm^{-1}$: 1645 (C=O). NMR ($CDCl_3$) $\delta$: 1.25 (3H, d, $J$=7 Hz, $CH\underline{CH_3}$), 3.57 (2H, q, $J$=7 Hz, $CO\underline{CH_2}CH_3$), 7.30 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 508 ($M^+$). Oxalate: mp 189—189.5° (MeOH). *Anal.* Calcd for $C_{29}H_{40}N_4O_2S \cdot 2C_2H_2O_4$: C, 57.56; H, 6.40; N, 8.14; S, 4.65. Found: C, 57.81; H, 6.48; N, 8.20; S, 4.44.

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