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# Dual CCK-A and CCK-B Receptor Antagonists (II). Preparation and Structure Activity Relationships of 5-Alkyl-9-methyl-1,4-benzodiazepines and Discovery of FR208419

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**In our continuing research for dual CCK-A and -B antagonists, according to our hypothesis that dual CCK-A and -B antagonists should be more efficacious than selective CCK-A antagonists for the treatment of pancreatitis, we have prepared various 5-alkyl-9-methyl-1,4-benzodiazepines. From the compounds prepared, 1-cyclohexyl-carbonylmethyl-5-ethyl-9-methyl-3-(*m*-tolylureido)-2-oxo-1,4-benzodiazepine, (40) was selected as a candidate for development due to its well-balanced high affinity for both receptors. The *R*-enantiomer of 40, (*R*)-40 (FR 208419), had 27-fold higher affinity for the CCK-A receptor and 8-fold more potent CCK-B receptor binding activity than (*S*)-40.**

**The biological activity after *p.o.* administration of (*R*)-40, estimated from the $\mathrm{ID}_{50}$ value (0.23 mg/kg *p.o.*) obtained by preliminary evaluation by gastric emptying effects, is considered to be high enough for further development. This compound is now undergoing further biological evaluations with a view to clinical development.**

**Key words** dual CCK-A and -B antagonist; pancreatitis; 5-alkyl-9-methyl-1,4-benzodiazepine; (3*R*)-1-cyclohexylcarbonylmethyl-5-ethyl-9-methyl-2-oxo-[3-(*m*-tolyl)ureido]-1,4-benzodiazepine

We reported earlier the discovery of **1** (FR 193108)[1,2] as a dual CCK-A and -B antagonist, according to our hypothesis that a dual CCK-A and CCK-B antagonist is more efficacious for the treatment of pancreatitis than a CCK-A selective antagonist.[3] Furthermore, we have shown that the most suitable substituent at the C-9 position of the 1,4-benzodiazepines is a methyl group from the relationship between dihedral angles calculated by AM1(MOPAC93) for N-1 and C-9 substituents and dual antagonistic activity.[2] However, **1** was found to be only poorly absorbed upon oral administration in rats in subsequent studies in spite of its well-balanced and high affinity for both receptors. Accordingly, we focused on improving the bioavailability by keeping the key substituent at the C-9 position to be a methyl group. We considered that the poor bioavailability of FR193108 might be due to the bulkiness of the molecule and to the presence of the hydrophilic tetrazolyl group, and thus planned to prepare compounds with lower molecular weight without the tetrazolyl group.

Initially, we changed the substituent in the 5 position of the ring system from 2-fluorophenyl to various alkyl groups. In this novel series of 5-alkyl-9-methyl-1,4-benzodiazepine derivatives, we found that the dual CCK-A and -B antagonistic activity was maintained even when the aryl substituent in the 5 position of the nucleus was converted to a small methyl group, and could discover more potent and well-balanced dual CCK-A and -B antagonists, for example **7**. However, the biological activity of *p.o.* administration was found to be only slightly improved.

Next, we speculated that the poor activity after *p.o.* administration of these compounds was due to the bulky, caged 3-azabicyclo[3.2.2]nonanyl amide moiety; however, this bulkiness also seemed to be necessary for their potent activities. Thus, we synthesized other types of amides and ketones possessing a degree of bulkiness, keeping the 3, 5- and 9-substituents as 3-tolylureido and 5,9-dimethyl as in compound **7**, to lead to **35** with high affinity for both CCK-A and -B receptors and relatively good biological activity after *p.o.* administration.

Although compound **35** showed very high affinity for both CCK-A and -B receptors with $\mathrm{IC}_{50}$ values of 1.1 and 3.7 nM, respectively, and a dose dependent gastric emptying effect ($\mathrm{ID}_{50}$ 0.4 mg/kg *p.o.*) that was affected by CCK-A antagonistic property and had good oral absorption, we attempted to modify the C-5 alkyl substituents for further optimization in order to obtain even more potent activity of inhibition of $^{125}$I-CCK-8 binding to the CCK-B receptor. As a result of our studies, we have now discovered **40**, which showed higher affinity than **35** for the CCK-B receptor and was almost equal for the CCK-A receptor as **35**.

The optically active enantiomers of **40** were prepared *via* an optical resolution of the 3-amino intermediate. The 3*R*-isomer, (*R*)-**40** (FR208419), is now undergoing further biological evaluation with a view to clinical development.

The design leading to (*R*)-**40**, has been outlined in a review.[4] In this paper we describe in full the synthesis and structure-activity relationships of (*R*)-**40** and its related compounds.

## Chemistry

A very convenient method for building the 1,4-benzodiazepine nucleus was reported by Sherrill[5] employing the reagent 2-(benzotriazol-1-yl)-*N*-protected glycine. This method was applied to the preparation of our key intermediate 3-benzyloxycarbonyl-5-alkyl-9-methyl-1,4-benzodiazepines (**4a**—**i**) and the target compounds (**7**—**14**) were synthesized as shown in Chart 1.

*o*-Toluidine (**2**) was regioselectively acylated by the Suga-

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sawa reaction;[6] 2-methyl-6-(4′-chlorobutanoyl)aniline was obtained in the case employing cyclopropylcyanide as the acylating reagent under the Sugasawa reaction. However, this was transformed to the desired 2-cyclopropanoyl-6-methylaniline (**3e**) by treatment with potassium *tert*-butoxide.[7] 2-Chloroacetyl-6-methylaniline (**3g**), obtained from *o*-toluidine (**2**) and chloroacetonitrile, was converted to 2-methoxyacetyl and 2-dimethylaminoacetyl aniline derivatives (**3h** and **3i**) by treatment with sodium methoxide and dimethylamine, respectively. These 2-acyl-6-methylaniline derivatives were easily acylated with the acid chloride, prepared from Sherrill's reagent, 2-(benzotriazol-1-yl)-*N*-benzyloxy-carbonyl glycine, and oxalyl chloride *in situ*, in the presence of *N*-methylmorpholine. The acylated compounds were treated, without isolation, with saturated methanolic ammonia followed by cyclization with ammonium acetate in acetic acid at ambient temperature to afford 5-alkyl-9-methyl-3-benzyloxycarbonylamino-1,4-benzodiazepine nuclei (**4a**—**i**) in moderate yields. The intermediates **6-1** (**a**—**i**) were prepared by alkylation at N-1 position of (**4a**—**i**) with ethyl bromoacetate in the presence of sodium hydride, followed by alkaline hydrolysis and amidation with 3-azabicyclo[3.2.2]nonane in a procedure similar to that reported in our previous paper.[1] The benzyloxycarbonyl group of **6-1** was removed by hydrogenolysis using ammonium formate and 10% palladium on carbon in ethanol at ambient temperature. The obtained 3-amino intermediates (**6-2**) were then acylated with *m*-tolyl isocyanate to give the initially targeted compounds **7**—**14**.

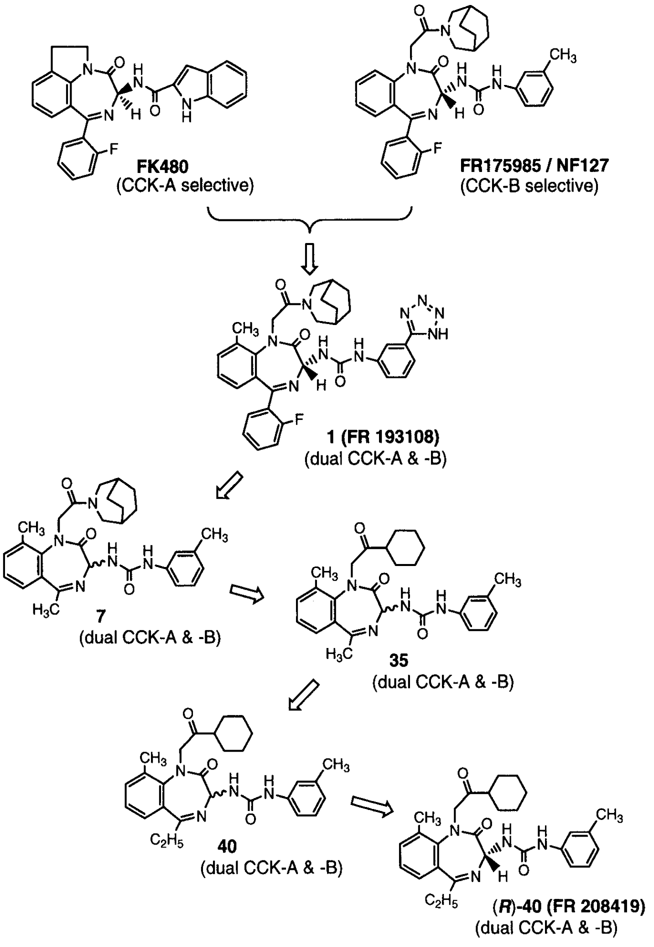
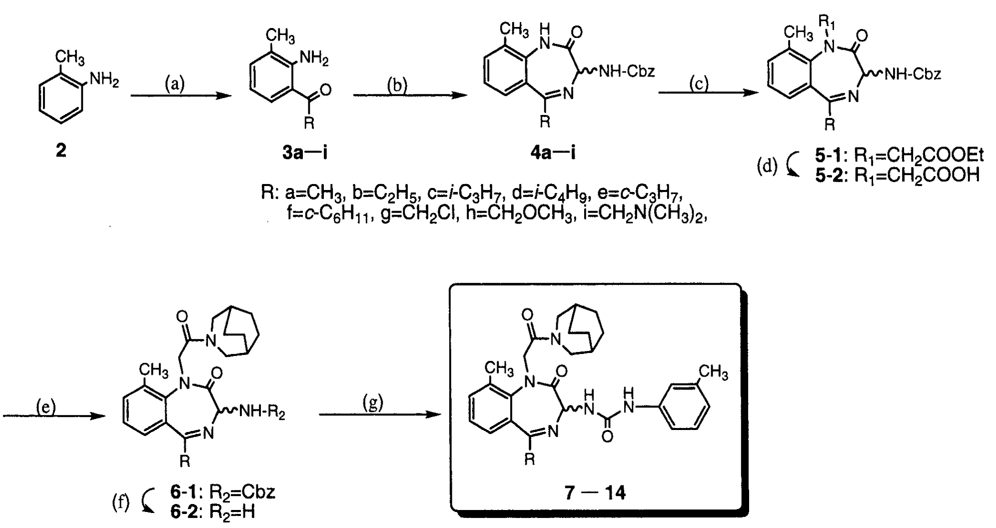


Fig. 1. Research Process Leading to FR208419, (*R*)-**40**

5-Acetoxymethyl-, 5-hydroxymethyl-, and 5-methylthiomethyl-1,4-benzodiazepines (**16**, **17** and **18**) were prepared as follows; treatment of **7** with *m*-chloroperbenzoic acid in methylene chloride afforded N-4 oxide (**15**), which could be transformed to **16** by treatment with acetic anhydride and was followed by alkaline hydrolysis to give **17**. Mesylation of **17** and displacement with sodium methylmercaptide afforded **18**, as shown in Chart 2. The yields and physical data of **7**—**18** are summarized in Table 1 and those of their intermediates are described in the Experimental.

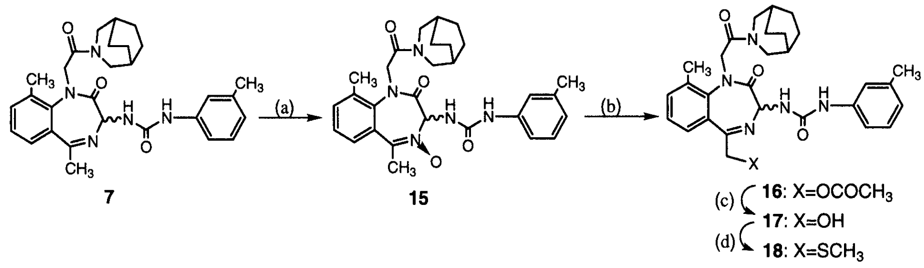
We also installed other types of amide and ketones as N-1 side chain to the 5,9-dimethyl-1,4-benzodiazepine ring system in order to avoid the bulky 3-azabicyclo[3.2.2]nonanyl amide as shown in Chart 3.

3-Benzyloxycarbonylamino-5,9-dimethyl-2-oxo-1,4-benzodiazepine (**4a**) was deprotected by hydrogenolysis to afford the 3-amino derivative (**19**), which was acylated with *m*-tolyl isocyanate to afford an N-1-unsubstituted urea (**20**). Acetic acid at N-1 (**22**) was prepared *via* its ethyl ester (**21**) in a sim-



Reagents: (a) i) R-CN, $BCl_3$, $AlCl_3$; 2*N*-HCl, ii) R=$CH_2Cl$ was reacted with $NaOCH_3$ and $HN(CH_3)_2$; (b) i) 2-(benzotriazol-1-yl)-*N*-Cbz-Gly-OH, $(COCl)_2$, *N*-Me-morpholine, ii) $NH_3$-MeOH; (c) NaH, $BrCH_2COOEt$; (d) 1N-NaOH/DME; (e) 3-azabicyclo[3,2,2]nonane, HOBT, WSCD·HCl, $Et_3N$; (f) $HCOONH_4$, 10% Pd-C; (g) *m*-Tolyl-NCO

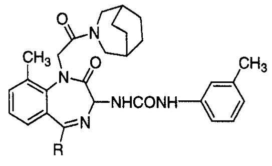
Chart 1. Preparation of Compounds **7**—**14**

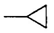
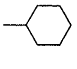


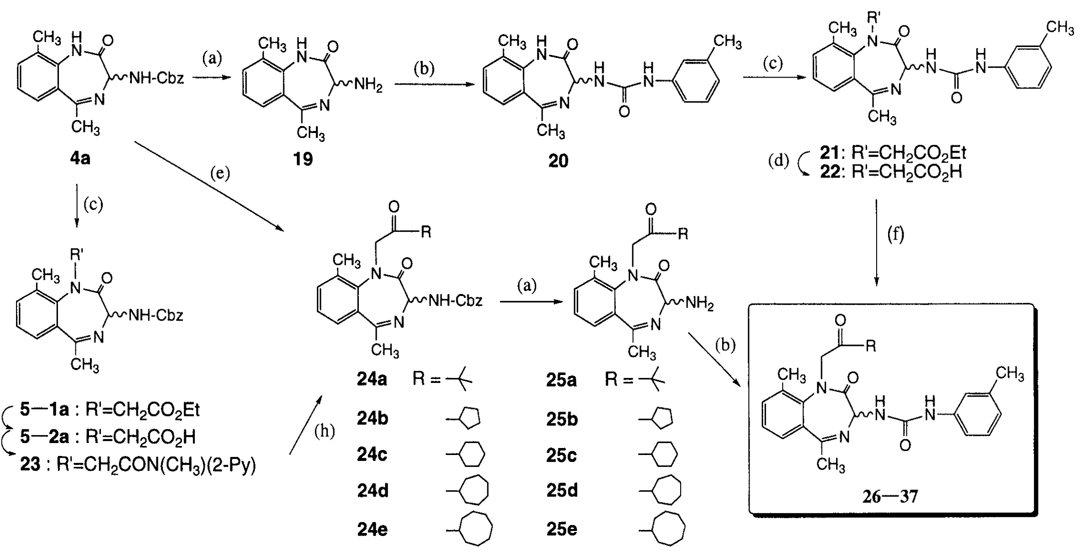
(a) *m*-CPBA; (b) $Ac_2O$; (c) 1N-NaOH/DME; (d) i ) MsCl, i-$Pr_2NEt$ ii ) $NaSCH_3$

Chart 2. Preparation of Compounds **16**, **17** and **18**

Table 1. Yield, Physical, and Spectral Data of Compounds **7**—**18**



| Compd. | R | Yield (%) | mp (°C) | Anal. (Calcd/Found) | $^1$H-NMR | IR (Nujol $cm^{-1}$) | MS *m/z* |
|---|---|---|---|---|---|---|---|
| **7** | $CH_3$ | 97.9 | 176.9—179.1 | $C_{29}H_{35}N_5O_3 \cdot 1/3C_6H_{14}O$<br>C, 69.51/69.27<br>H, 7.47/7.38<br>N, 13.07/13.11 | (DMSO-$d_6$, $\delta$) 1.4—1.8 (8H, m), 1.9—2.1 (2H, m), 2.22 (3H, s), 2.36 (3H, s), 2.44 (3H, s), 3.0—3.4 (2H, m), 3.6—4.0 (2H, m), 3.96 (1H, d, $J$=16 Hz) 5.11 (1H, d, $J$=16 Hz), 5.0—5.1 (1H, m), 6.71 (1H, d, $J$=6.6 Hz), 7.0—7.6 (7H, m), 8.87 (1H, br) | 1670,<br>1640 | 502<br>(M+1) |
| **8** | $CH_2CH_3$ | 86.2 | 130.1—133.0 | $C_{30}H_{37}N_5O_3 \cdot 0.3C_6H_{14}O$<br>C, 69.91/69.99<br>H 7.60/7.59<br>N, 12.82/12.72 | (DMSO-$d_6$, $\delta$) 1.26 (3H, t, $J$=7.3 Hz), 1.4—1.9 (8H, m), 1.9—2.1 (2H, m), 2.22 (3H, s), 2.37 (3H, s), 2.7—3.4 (4H, m), 3.7—3.9 (2H, m), 3.98 (1H, d, $J$=16.2 Hz), 5.08 (1H, d, $J$=16.2 Hz), 5.14 (1H, d, $J$=7.7 Hz), 6.71 (1H, d, $J$=6.5 Hz), 7.0—7.6 (7H, m) 8.86 (1H, br) | 1650,<br>1610 | 516<br>(M+1) |
| **9** | $CH(CH_3)_2$ | 77.9 | 189.9—192.8 | $C_{31}H_{39}N_5O_3 \cdot 0.75H_2O$<br>C, 68.55/68.69<br>H, 7.51/7.53<br>N, 12.89/12.77 | (DMSO-$d_6$, $\delta$) 1.11 (3H, d, $J$=7.0 Hz), 1.21 (3H, t, $J$=6.5 Hz), 1.4—2.1 (10H, m), 2.22 (3H, s), 2.37 (3H, s), 3.0—3.4 (2H, m), 3.6—4.0 (2H, m), 4.04 (1H, d, $J$=16.1 Hz), 5.00 (1H, d, $J$=16.1 Hz), 5.09 (1H, d, $J$=8.4 Hz), 6.72 (1H, d, $J$=6.2 Hz), 7.0—7.7 (7H, m), 8.85 (1H, br) | 1700,<br>1650,<br>1610 | 530<br>(M+1) |
| **10** | $CH_2CH(CH_3)_2$ | 56.0 | 133.6—135.4 | $C_{32}H_{41}N_5O_3 \cdot 0.3C_6H_{14}O$<br>C, 70.68/70.98<br>H, 7.93/8.09<br>N, 12.19/12.06 | (DMSO-$d_6$, $\delta$) 0.94 (6H, d, $J$=6.6 Hz), 1.4—1.9 (8H, m), 1.9—2.1 (2H, m), 2.22 (3H, s), 2.37 (3H, s), 2.1—2.2 (1H, m), 2.6—2.8 (2H, m), 3.0—3.2 (1H, m), 3.5—4.0 (3H, m), 4.01 (1H, d, $J$=16 Hz), 5.00 (1H, d, $J$=16 Hz), 5.11 (1H, d, $J$=8.6 Hz), 6.73 (1H, m), 7.0—7.6 (7H, m), 8.85 (1H, br) | 1650,<br>1610 | 544<br>(M+1) |
| **11** |  | 72.6 | 172.0—174.4 | $C_{31}H_{37}N_5O_3$<br>C, 70.56/70.58<br>H, 7.07/7.01<br>N, 13.27/13.13 | (DMSO-$d_6$, $\delta$) 0.7—0.9 (2H, m), 0.9—1.3 (2H, m), 1.4—1.9 (8H, m), 1.9—2.2 (3H, m), 2.22 (3H, s), 2.38 3H, s), 3.1—3.4 (2H, m), 3.6—3.9 (2H, m), 4.00 (1H, d, $J$=16 Hz), 5.04 (1H, d, $J$=16 Hz), 5.06 (1H, d, $J$=8.5 Hz), 6.71 (1H, d, $J$=5.6 Hz), 7.0—7.8 (7H, m), 8.82 (1H, br) | 1680,<br>1650,<br>1610 | 528<br>(M+1) |
| **12** |  | 82.8 | — | Amorphous | (DMSO-$d_6$, $\delta$) 1.05—2.1 (20H, m), 2.22 (3H, s), 2.37 (3H, s), 2.29 (1H, m), 3.05—3.35 (2H, m), 3.65—3.87 (2H, m), 4.01 (1H, d, $J$=16.2 Hz), 5.05 (1H, d, $J$=16.2 Hz), 5.08 (1H, d, $J$=8.4 Hz), 6.7—7.6 (8H, m), 8.85 (1H, br) | 3390,<br>3275,<br>1705,<br>1688,<br>1634 | 570<br>(M+1) |
| **13** | $CH_2OCH_3$ | 28.0 | — | Amorphous | (DMSO-$d_6$, $\delta$) 1.4—1.9 (8H, m), 1.9—2.1 (2H, m), 2.22 (3H, s), 2.38 (3H, s), 3.35 (3H, s), 3.3—4.1 (4H, m), 4.00 (1H, d, $J$=16.9 Hz), 4.52 (2H, m), 5.0—5.3 (2H, m), 6.74 (1H, br), 7.0—7.7 (7H, m), 8.88 (1H, br) | 1640 | 532<br>(M+1) |
| **14** | $CH_2N(CH_3)_2$ | 30.3 | — | Amorphous | (DMSO-$d_6$, $\delta$) 1.4—1.8 (8H, m), 1.9—2.1 (2H, m), 2.22 (3H, s), 2.25 (6H, s), 2.37 (3H, s), 3.0—3.2 (1H, m), 3.4—3.9 (5H, m), 3.9—4.1 (1H, m), 4.9—5.1 (1H, m), 5.13 (1H, d, $J$=8.0 Hz), 6.73 (1H, m), 7.0—7.9 (7H, m), 8.88 (1H, br) | 1650,<br>1610 | 545<br>(M+1) |
| **16** | $CH_2OCOCH_3$ | 59.3 | — | Amorphous | ($CDCl_3$, $\delta$) 1.50—2.17 (10H, m), 2.10 (3H, s), 2.29 (3H, s), 2.38 (3H, s), 3.28—3.74 (4H, m), 4.62 (1H, d, $J$=15.6 Hz), 5.17 (1H, d, $J$=15.6 Hz), 5.59 (1H, d, $J$=7.8 Hz), 6.7—7.6 (9H, m) | 1720,<br>1675,<br>1620 | 560<br>(M+1) |
| **17** | $CH_2OH$ | 66.0 | — | Amorphous | (DMSO-$d_6$, $\delta$) 1.3—2.2 (10H, m), 2.22 (3H, s), 2.48 (3H, s), 2.9—3.4 (2H, m), 3.6—4.0 (2H, m), 4.01 (1H, d, $J$=16.3 Hz), 4.5—4.6 (2H, m), 5.11 (1H, d, $J$=16.3 Hz), 5.23 (1H, d, $J$=8.5 Hz), 6.75 (1H, d, $J$=6.5 Hz), 7.0—7.2 (3H, m), 7.2—7.7 (4H, m), 8.90 (1H, br) | 1640 | 518<br>(M+1) |
| **18** | $CH_2SCH_3$ | 46.2 | — | Amorphous | ($CDCl_3$, $\delta$) 1.45—2.1 (10H, m), 2.20 (3H, s), 2.29 (3H, s), 2.38 (3H, s), 3.25—3.55 (4H, m), 3.7—4.0 (3H, m), 5.03 (1H, d, $J$=15.8 Hz), 5.54 (1H, d, $J$=8.2 Hz), 6.7—7.8 (9H, m) | 1670,<br>1620 | 548<br>(M+1) |



Reagents: a) HCOONH$_4$, 10% Pd-C; b) (for **33**—**37**) *m*-Tolyl-NCO; c) NaH, BrCH$_2$CO$_2$Et; d) 1N-NaOH/DME; e) NaH, BrCH$_2$COR; f) (for **26**—**32**) Amine, HOBT, WSCD·HCl, Et$_3$N; g) HN(CH$_3$)(2-Py.), HOBT, WSCD·HCl, Et$_3$N; h) RMgX.

Chart 3. Preparation of Compounds **26**—**37**

ilar procedure to those carried out in the synthesis of **5-1** and **5-2**, described above. The target amides (**26**—**32**) were prepared from **22** by standard amidation using *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide (WSCD) in the presence of 1-hydroxybenzotriazole (HOBT). The target ketones (**35**, **37**) were synthesized by direct N-1 alkylation of **4a** with 1-bromo-3,3-dimethyl-2-oxobutane or bromoacetylcyclohexane in the presence of sodium hydride, followed by deprotection and acylation with *m*-tolyl isocyanate. The intermediates **24b**, **d**, **e** were prepared by amidation of N-1-acetic acid **5-2a** with *N*-methyl-*N*-(2-pyridyl)amine to give the activated amide **23**, which was easily reacted with the respective Grignard reagents. The deprotection and acylation were performed as described above to give the target ketones **34**, **36**, and **37**. The yields and physical data of **26**—**37** are summarized in Table 2 and those of their intermediates are described in the Experimental.

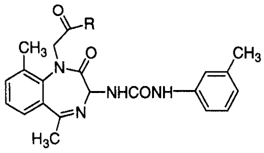
Finally, we introduced other lower alkyl groups excluding a methyl group into the 5 position of the 1-cyclohexylcarbonylmethyl-9-methyl-1,4-benzodiazepine nucleus. Alkylation of **4b**—**e** with bromomethylcyclohexylketone in the presence of sodium hydride afforded **38a**—**d** in a similar manner to that carried out in the preparation of **24c** from **4a**. Deprotection of **38a**—**d** by hydrogenolysis with ammonium formate and 10% palladium on carbon in ethanol gave **39a**—**d**. The target compounds (**40**—**43**) were prepared by a similar acylation with *m*-tolyl isocyanate as shown in Chart 4 and their yields and physical data are summarized in Table 3 and their intermediates are described in the Experimental.

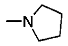
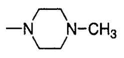
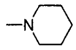
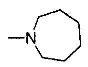
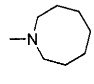
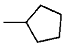
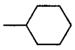
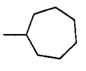
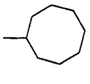
**Biological Evaluation** The biological evaluation was performed by means of the following tests[8]: i) inhibition of $^{125}$I-CCK-8 binding in the guinea-pig cerebral cortex, ii) inhibition of $^{125}$I-CCK-8 binding in the rat pancreas, iii) the ratio of the respective IC$_{50}$ values, and iv) gastric emptying effect in mice after *p.o.* administration *in vivo*,[9] for compounds showing high affinity for both CCK-A and CCK-B receptors. The results are summarized in Tables 4, 5, and 6 for compounds **7**—**18**, possessing various C-5 alkyl substituents in N-1-3-azabicyclo[3.2.2]nonanylcarbonylmethyl-9-methyl-1,4-benzodiazepines, for **26**—**37**, substituted by other types of amides and ketones as N-1 side chain in 5,9-dimethyl-1,4-benzodiazepines, and for **40**—**43**, containing other lower alkyl groups as C-5 substituents in 1-cyclohexylcarbonylmethyl-9-methyl-1,4-benzodiazepines, respectively along with respective reference compounds **1** in Table 4, **7** in Table 5, and **35** in Table 6.

In the N-1-3-azabicyclo[3.2.2]nonanylcarbonylmethyl-9-methyl-1,4-benzodiazepine ring system (Table 4), the introduction of lower alkyl groups (**7**—**10**) in the 5 position instead of the 2-fluorophenyl group increased the affinity for the CCK-A receptor by 3- to 6- fold, whereas the affinity for the CCK-B receptor was maintained or slightly reduced. Thus, the ratio of IC$_{50}$ values to the CCK-A to CCK-B receptors approached unity. A cyclohexyl group was not suitable for the 5 position substituent of this ring system. A methoxymethyl and a methylthiomethyl group were effective substituents, whereas a dimethylaminomethyl group was not suitable as shown by **13**, **14** and **18**. An acetoxymethyl group was also effective as shown by **16**, but a hydroxymethyl group reversed the affinity for the CCK-A and CCK-B receptors and the ratio of them for **17** was 0.2. When considering **7**, **13** and **17**, it seemed that the hydroxy group of **17** possibly had some contribution to binding affinity for the CCK-A receptor. Methylthio derivative **18** had high affinity for both CCK-A and CCK-B receptors, and the value of the two affinities was close. Potent compounds were evaluated by the gastric emptying test in mice after oral administration. However, their biological activity after *p.o.* administration was only slightly improved, as shown in Table 4. We selected a methyl group as the substituent in the 5 position of the 1,4-benzodiazepine nucleus for further optimization research on the N-1 side chain.

Other types of amides and ketones containing a certain degree of bulkiness, which is thought to be necessary to maintain the potent activities, as N-1 side chain in 5,9-dimethyl-1,4-benzodiazepines, are summarized in Table 5. Acyclic and 5- to 6-membered cyclic amides were found to have reduced affinity for the CCK-B receptor (**26**—**30**). However, com-

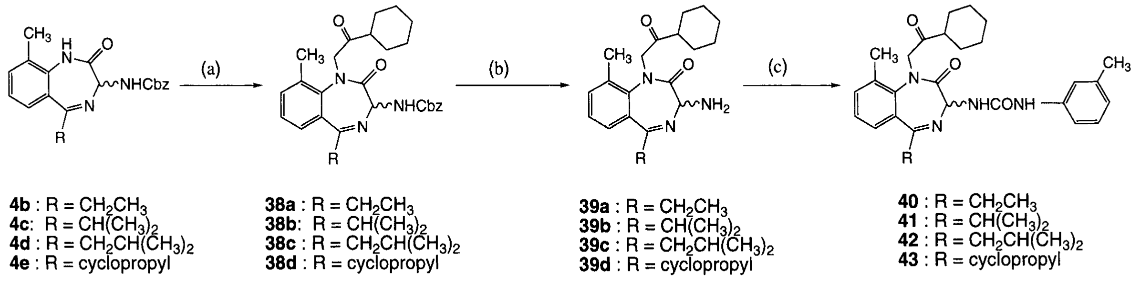
Table 2. Yield, Physical, and Spectral Data of Compounds **26**—**37**



| Compd. | R | Yield (%) | mp (°C) | Anal. (Calcd/Found) | $^1$H-NMR (DMSO-$d_6$, $\delta$) | IR (Nujol cm$^{-1}$) | MS *m/z* |
|---|---|---|---|---|---|---|---|
| **26** | $NHC(CH_3)_3$ | 80.3 | 243.4—244.4 | $C_{25}H_{31}N_5O_3 \cdot 0.2H_2O$<br>C, 66.26/66.17<br>H, 6.98/7.19<br>N, 15.45/15.38 | 1.13 (9H, s), 2.22 (3H, s), 2.32 (3H, s), 2.43 (3H, s), 3.68 (1H, d, *J*=15.7 Hz), 4.62 (1H, d, *J*=15.7 Hz), 5.07 (1H, d, *J*=8.6 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.87 (1H, s) | 3310,<br>1645 | 450<br>(M+1) |
| **27** | $N[CH_2CH(CH_3)_2]_2$ | 89.7 | 226.9—229.1 | $C_{29}H_{39}N_5O_3 \cdot 0.6H_2O$<br>C, 67.44/67.26<br>H, 7.85/7.83<br>N, 13.56/13.76 | 0.7—0.8 (6H, m), 0.8—1.0 (6H, m), 2.22 (3H, s), 2.36 (3H, s), 2.43 (3H, s), 2.9—3.2 (4H, m), 3.89 (1H, d, *J*=16.0 Hz), 4.99 (1H, d, *J*=16.0 Hz), 5.07 (1H, d, *J*=7.1 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.85 (1H, s) | 1680,<br>1660 | 506<br>(M+1) |
| **28** |  | 52.3 | 208.7—209.3 | $C_{25}H_{29}N_5O_3 \cdot 1.0H_2O$<br>C, 64.50/64.53<br>H, 6.71/6.53<br>N, 15.04/14.83 | 1.6—2.0 (2H, m), 2.22 (3H, s), 2.35 (3H, s), 2.43 (3H, s), 2.1—3.3 (2H, m), 3.88 (1H, d, *J*=16.4 Hz), 4.86 (1H, d, *J*=16.4 Hz), 5.10 (1H, d, *J*=7.2 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.92 (1H, s) | 1650 | 448<br>(M+1) |
| **29** |  | 78.4 | — | Amorphous | 2.15 (3H, s), 2.22 (3H, s), 2.35 (3H, s), 2.43 (3H, s), 3.3—3.5 (4H, m), 3.91 (1H, d, *J*=16 Hz), 5.04 (1H, d, *J*=16 Hz), 5.11—5.12 (1H, m), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.92 (1H, s) | 1675,<br>1640,<br>1610 | 477<br>(M+1) |
| **30** |  | 60.2 | 132.8—135.0 | $C_{28}H_{31}N_5O_3 \cdot 0.6H_2O$<br>C, 66.11/66.34<br>H, 6.87/6.94<br>N, 14.83/14.46 | 1.2—1.6 (6H, m), 2.22 (3H, s), 2.36 (3H, s), 2.44 (3H, s), 3.2—3.4 (4H, m), 3.89 (1H, d, *J*=16 Hz), 5.04 (1H, d, *J*=16 Hz), 5.10 (1H, d, *J*=8 Hz), 6.72 (1H, d, *J*=6.6 Hz), 7.0—7.6 (7H, m), 8.94 (1H, s) | 3338,<br>2935,<br>1677,<br>1652,<br>1614,<br>1594 | 462<br>(M+1) |
| **31** |  | 83.0 | 203.6—204.2 | $C_{27}H_{33}N_5O_3 \cdot 0.5H_2O$<br>C, 66.92/67.08<br>H, 7.07/7.24<br>N, 14.45/14.56 | 1.3—1.9 (8H, m), 2.22 (3H, s), 2.36 (3H, s), 2.44 (3H, s), 3.0—3.2 (1H, m), 3.2—3.4 (1H, m), 3.4—3.7 (2H, m), 3.92 (1H, d, *J*=16.2 Hz), 4.96 (1H, d, *J*=16.2 Hz), 5.09 (1H, d, *J*=7.4 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.87 (1H, s) | 1670,<br>1630 | 476<br>(M+1) |
| **32** |  | 60.3 | — | Amorphous | 1.2—1.8 (10H, m), 2.22 (3H, s), 2.36 (3H, s), 2.44 (3H, s), 2.9—3.3 (2H, m), 3.3—3.6 (2H, m), 3.88 (1H, d, *J*=16.1 Hz), 4.95 (1H, d, *J*=16.1 Hz), 5.09 (1H, d, *J*=7.1 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.86 (1H, s) | 1650,<br>1610 | 490<br>(M+1) |
| **33** | $C(CH_3)_3$ | 62.4 | 179.6—181.2 | $C_{25}H_{30}N_4O_3 \cdot 0.2H_2O$<br>C, 68.53/68.51<br>H, 6.99/7.18<br>N, 12.79/12.63 | 1.08 (9H, s), 2.22 (3H, s), 2.34 (3H, s), 2.47 (3H, s), 4.01 (1H, d, *J*=17.4 Hz), 5.08 (1H, d, *J*=8.5 Hz), 5.22 (1H, d, *J*=17.4 Hz), 6.7—6.8 (1H, m), 7.0—7.7 (7H, m), 8.84 (1H, s) | 1720,<br>1670,<br>1645 | 435<br>(M+1) |
| **34** |  | 100 | 150.1—155.5 | $C_{26}H_{30}N_4O_3 \cdot 0.2H_2O$<br>C, 69.38/69.78<br>H, 6.81/7.14<br>N, 12.45/12.15 | 1.4—1.9 (8H, m), 2.22 (3H, s), 2.33 (3H, s), 2.47 (3H, s), 2.8—3.1 (1H, m), 4.10 (1H, d, *J*=17.6 Hz), 4.97(1H, d, *J*=17.6 Hz), Hz), 5.08 (1H, d, *J*=7.0 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.86 (1H, s) | 3280,<br>1720,<br>1670,<br>1645 | 447<br>(M+1) |
| **35** |  | 21.7 | 179.2—180.9 | $C_{27}H_{32}N_4O_3 \cdot 0.4H_2O$<br>C, 69.33/69.71<br>H, 7.07/7.24<br>N, 11.98/11.76 | 1.0—1.8 (10H, m), 2.22 (3H, s), 2.33 (3H, s), 2.47 (3H, s), 2.8—3.1 (1H, m), 4.06 (1H, d, *J*=17.6 Hz), 5.02 (1H, d, *J*=17.6 Hz), 5.08 (1H, d, *J*=7.0 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.84 (1H, s) | 1710,<br>1655,<br>1638 | 461<br>(M+1) |
| **36** |  | 77.1 | — | Amorphous | 1.2—2.0 (12H, m), 2.22 (3H, s), 2.33 (3H, s), 2.47 (3H, s), 2.4—2.7 (1H, m), 4.09 (1H, d, *J*=18 Hz), 5.00 (1H, d, *J*=18 Hz), 5.06 (1H, d, *J*=8.3 Hz), 6.7—6.8 (1H, m), 7.0—7.7 (7H, m), 8.86 (1H, s) | 3360,<br>1720,<br>1660,<br>1640 | 475<br>(M+1) |
| **37** |  | 73.5 | — | Amorphous | 1.3—2.0 (14H, m), 2.22 (3H, s), 2.33 (3H, s), 2.47 (3H, s), 2.5—2.7 (1H, m), 4.09 (1H, d, *J*=18 Hz), 5.00 (1H, d, *J*=18 Hz), 5.07 (1H, d, *J*=9.4 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.85 (1H, s) | 3350,<br>1720,<br>1680,<br>1640,<br>1605 | 489<br>(M+1) |

pounds **31** and **32**, which have 7- and 8-membered cyclic amides, showed high affinity for both receptors. The affinity for the CCK-B receptor is higher for the larger ring size (**28**, **30**, **31** and **32**), but the affinity for the CCK-A receptor is reversed in the 7- and 8-membered rings. Therefore, the ratio of $IC_{50}$ values for **31** and **32** were 0.53 and 1.62, respectively. When compared with compound **7**, selected as a reference for further optimization, **31** and **32** were as potent for CCK-A receptor binding but decreased in the affinity for the CCK-B receptor by 3- to 5-fold. It was an additional disadvantage that they had poor activities in the gastric emptying after *p.o.* administration.

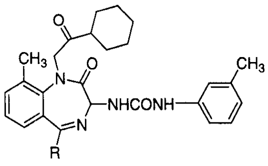
On the other hand, compounds **33**—**37**, which contain certain bulky ketones as the N-1 side chain, showed 5- to 20-fold more potent effects than compound **7** on gastric emptying, although their affinities for the CCK-B receptor dimin-

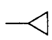


(a) NaH, bromomethylcyclohexylketone ; (b) $HCOONH_4$, 10% Pd-C; (c) *m*-Tolyl-NCO

Chart 4. Preparation of Compounds **40**—**43**

Table 3. Yield, Physical, and Spectral Data of Compounds **40**—**43**



| Compd. | R | Yield (%) | mp (°C) | Anal. (Calcd/Found) | $^1$H-NMR (DMSO-$d_6$, $\delta$) | IR (Nujol cm$^{-1}$) | MS *m/z* |
|---|---|---|---|---|---|---|---|
| **40** | $CH_2CH_3$ | 67.1 | — | Amorphous | 1.0—1.4 (8H, m), 1.5—2.0 (5H, m), 2.22 (3H, s), 2.35 (3H, s), 2.2—2.5 (1H, m), 2.8—3.1 (2H, m), 4.11 (1H, d, *J*=17.6 Hz), 5.04 (1H, d, *J*=17.6 Hz), 5.21 (1H, d, *J*=7.4 Hz), 6.72 (1H, d, *J*=6.6 Hz), 7.0—7.7 (7H, m), 8.99 (1H, s) | 3350,<br>1730,<br>1680,<br>1650 | 475<br>(M+1) |
| **41** | $CH(CH_3)_2$ | 62.6 | 142.4—146.1 | $C_{29}H_{36}N_4O_3\cdot 0.6H_2O$<br>C, 67.44/67.26<br>H, 7.85/7.83<br>N, 13.56/13.76 | 1.09 (3H, d, *J*=7.0 Hz), 1.22 (3H, d, *J*=6.5 Hz), 1.5—2.0 (5H, m), 2.22 (3H, s), 2.34 (3H, s), 2.3—2.5 (1H, m), 3.2—3.5 (1H, m), 4.11 (1H, d, *J*=17.4 Hz), 4.94 (1H, d, *J*=17.4 Hz), 5.08 (1H, d, *J*=7.8 Hz), 6.6—6.8 (1H, m), 7.0—7.6 (7H, m), 8.84 (1H, s) | 3320,<br>1730,<br>1680,<br>1650 | 489<br>(M+1) |
| **42** | $CH_2CH(CH_3)_2$ | 50.1 | 152.3—154.8 | $C_{25}H_{29}N_5O_3\cdot 1.0H_2O$<br>C, 64.50/64.53<br>H, 6.71/6.53<br>N, 15.04/14.83 | 0.94 (6H, d, *J*=6.6 Hz), 1.1—1.4 (5H, m), 1.5—2.0 (5H, m), 2.0—2.2 (1H, m), 2.22 (3H, s), 2.32 (3H, s), 3.3—3.6 (1H, m), 3.6—3.8 (2H, m), 4.72 (1H, d, *J*=17.6 Hz), 4.89 (1H, d, *J*=17.6 Hz), 5.09 (1H, d, *J*=8.5 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.83 (1H, s) | 3410,<br>3250,<br>1730,<br>1680,<br>1650 | 503<br>(M+1) |
| **43** |  | 86.5 | — | Amorphous | 0.8—1.4 (9H, m), 1.5—2.0 (5H, m), 2.22 (3H, s), 2.34 (3H, s), 2.8—3.0 (1H, m), 4.09 (1H, d, *J*=17 Hz), 4.94 (1H, d, *J*=17 Hz), 5.06 (1H, d, *J*=8.3 Hz), 6.7—6.8 (1H, m), 7.0—7.6 (7H, m), 8.8—9.0 (1H, m) | 3370,<br>1720,<br>1680,<br>1650 | 487<br>(M+1) |

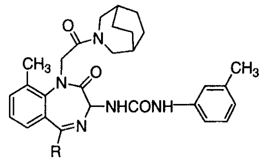
ished by 5- to 15-fold, when compared with **7**. The compounds with a 6- or 7-membered cycloalkyl methyl ketone were found to be the most suitable for the N-1 side chain. Compounds **35** and **36** showed almost equal high affinity for both receptors, but **35** showed more potent activity in gastric emptying than **36**. We selected **35** as a lead compound for further chemical modification in searching for a suitable alkyl group for the 5-substutuent on the 5-alkyl-1-cyclohexylcarbonylmethyl-9-methyl-1,4-benzodiazepine.

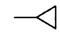
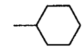
Ethyl, isopropyl, isobutyl and cyclopropyl groups were introduced at the 5 position, respectively (Table 6), however a cyclohexyl group was excluded because of its poor activity in our ring system as shown in Table 4. When compared with **35**, the affinities of compounds **40**, **42**, and **43** for the CCK-B receptor were increased 2- to 3-fold except for **41**, whereas the affinity for the CCK-A receptor was nearly equal or only slightly reduced. Furthermore, the ratio of $IC_{50}$ values for CCK-A to CCK-B receptors was $<1.0$ for **40** and **41** and $>1.0$ for **42** and **43**. It was found that compound **40** was as potent as **35** in the gastric emptying effect after *p.o.* administration, while those of compounds **41**, **42**, and **43** decreased by 4- to 14-fold.

From all compounds prepared, we selected **40** due to its high and well-balanced affinity for both CCK-A and CCK-B receptors and its good activity after *p.o.* administration.

**Optical Resolution of 40 and Biological Evaluation of the Enantiomers** Initially, optical resolution of (3*RS*)-3-amino-1-cyclohexyl-carbonylmethyl-5-ethyl-9-methyl-1,4-benzodiazepine-2-one (**39a**) was attempted by classical diastereomeric salt formation with a suitable optically active acid. Unfortunately, crystalline salt formation was unsuccessful, despite many trials with a variety of optically active acids, solvents and their combinations. However we did succeed in the optical resolution by the method[10] of diastereoisomers formation with L-phenylalanine, followed by their separation by column chromatography and Edman

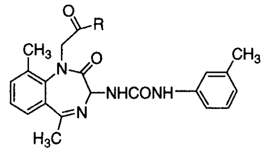
Table 4. Results of Biological Activities of 5-Substituted 9-methyl-1,4-benzodiazepine Derivatives

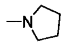
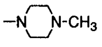
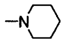
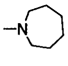
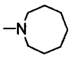
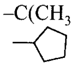
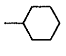
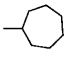
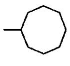


| Compound No. | R | $IC_{50}$ (nM)[a] for CCK-B | $IC_{50}$ (nM)[b] for CCK-A | Selectivity[c] A/B | Gastric emptying[d] (% at 10 mg/kg *p.o.*) |
|---|---|---|---|---|---|
| **1** | | 0.38 | 9.2 | 24.2 | 0 |
| **7** | $CH_3$ | 0.68 | 2.2 | 3.2 | 90 ($ID_{50}$=5.7 mg/kg) |
| **8** | $CH_2CH_3$ | 0.72 | 1.4 | 1.9 | 70 |
| **9** | $CH(CH_3)_2$ | 1.3 | 3.0 | 2.3 | 70 |
| **10** | $CH_2CH(CH_3)_2$ | 0.48 | 2.1 | 4.4 | 30 |
| **11** |  | 0.89 | 1.5 | 1.7 | 20 |
| **12** |  | 68.6% ($10^{-8}$ M) | 49.5% ($10^{-8}$ M) | — | N.T. |
| **13** | $CH_2OCH_3$ | 0.96 | 2.4 | 2.5 | 30 |
| **14** | $CH_2N(CH_3)_2$ | 31.5% ($10^{-8}$ M) | N.T. | — | N.T. |
| **16** | $CH_2OCOCH_3$ | 0.88 | 9.7 | 11.0 | N.T. |
| **17** | $CH_2OH$ | 7.0 | 1.4 | 0.2 | 100 ($ID_{50}$=1.3 mg/kg) |
| **18** | $CH_2SCH_3$ | 1.2 | 2.0 | 1.7 | 0 |

*a*) Inhibition of $^{125}$I-CCK-8 binding to guinea-pig cerebral cortical membranes. *b*) Inhibition of $^{125}$I-CCK-8 binding to rat pancreatic membranes. *c*) Ratio of $IC_{50}$ values obtained by CCK-A and CCK-B receptor binding assays. *d*) Inhibitory effect of compounds on CCK-8 induced inhibition of charcoal meal gastric empting in mice.

Table 5. Results of Biological Activities of 5,9-Dimethyl-1-substituted 1,4-benzodiazepine Derivatives



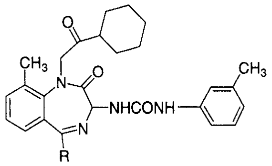
| Compound No. | R | $IC_{50}$ (nM)[a] for CCK-B | $IC_{50}$ (nM)[b] for CCK-A | Selectivity[c] A/B | Gastric emptying[d] $ID_{50}$ (mg/kg *p.o.*) |
|---|---|---|---|---|---|
| **7** | FR 196979 | 0.68 | 2.2 | 3.24 | 5.7 |
| **26** | $-NHC(CH_3)_3$ | 25.3% ($10^{-8}$ M) | 6.3% ($10^{-8}$ M) | — | N.T. |
| **27** | $-N[CH_2CH(CH_3)_2]_2$ | 56.6% ($10^{-8}$ M) | N.T. | — | N.T. |
| **28** |  | 25.8% ($10^{-8}$ M) | N.T. | — | N.T. |
| **29** |  | 9.2% ($10^{-8}$ M) | N.T. | — | N.T. |
| **30** |  | 44.7% ($10^{-8}$ M) | N.T. | — | N.T. |
| **31** |  | 3.0 | 1.6 | 0.53 | 50% (10 mg/kg) |
| **32** |  | 2.1 | 3.4 | 1.62 | 10% (10 mg/kg) |
| **33** | $-C(CH_3)_3$ | 9.4 | 7.6 | 0.81 | 0.9 |
| **34** |  | 8.7 | 1.3 | 0.15 | 0.28 |
| **35** |  | 3.7 | 1.1 | 0.30 | 0.4 |
| **36** |  | 3.7 | 1.4 | 0.38 | 1.2 |
| **37** |  | 7.1 | 5.1 | 0.32 | 4.2 |

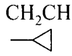
*a—d*) See footnotes in Table 4.

degradation of each diastereoisomer respectively as shown in Chart 5.

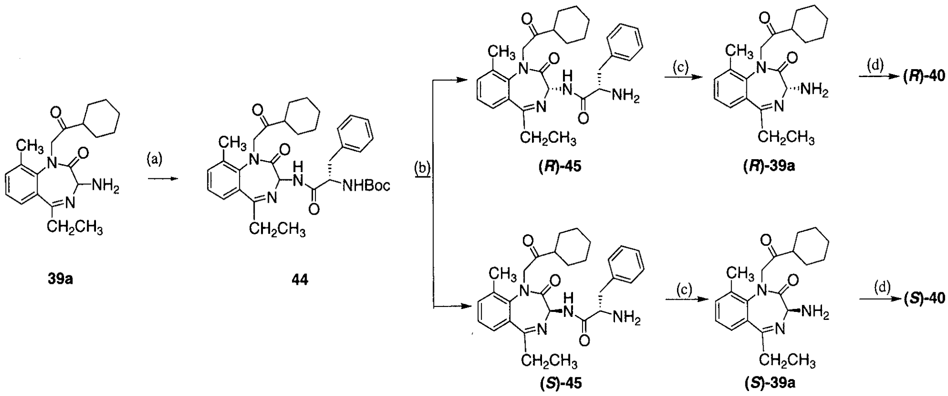
The amine, **39a**, was acylated with *N-tert*-butoxycarbonyl-L-phenylalanine in the presence of WSCD and HOBT in *N*,*N*-dimethylformamide (DMF) followed by de-*tert*-butoxycarbonylation with 4 N hydrogen chloride in ethyl acetate to afford a diastereomeric mixture (**45**) of (3*S*)-[3-(*S*)-phenylalanylamino]- and (3*R*)-[3-(*S*)-phenylalanylamino]-derivatives, which were separated by medium pressure liquid column chromatography on silica gel eluting with a mixture of

Table 6. Results of Biological Activities of 5-Alkyl-9-methyl-1-cyclohexylcarbonylmethyl-1,4-benzodiazepines



| Compound No. | R | Stereochemistry at $C_3$ | IC$_{50}$ (nM)[a] for CCK-B | IC$_{50}$ (nM)[b] for CCK-A | Selectivity[c] A/B | Gastric emptying[d] ID$_{50}$ (mg/kg *p.o.*) |
|---|---|---|---|---|---|---|
| **35** | $CH_3$ | *RS* | 3.7 | 1.1 | 0.30 | 0.4 |
| **40** | $CH_2CH_3$ | *RS* | 1.6 | 0.9 | 0.38 | 0.4 |
| **41** | $CH(CH_3)_2$ | *RS* | 3.4 | 1.7 | 0.50 | 2.1 |
| **42** | $CH_2CH(CH_3)_2$ | *RS* | 1.4 | 2.5 | 1.79 | 5.7 |
| **43** |  | *RS* | 1.1 | 2.0 | 1.82 | 1.8 |

*a—d*) See footnotes in Table 4.



Reagents: (a) WSCD·HCl, HOBT, (*L*)-*N*-Boc-Phe; (b) i) 4*N*-HCl in AcOEt. ii) separation by column chromatography on $SiO_2$ ($CHCl_3$: MeOH=20 : 1); (c) i) phenyl isothiocyanate, ii) TFA; (d) *m*-tolyl isocyanate.

Chart 5. Optical Resolution of **40**

chloroform and methanol (20 : 1). Each diastereoisomer (*S*)-**45** and (*R*)-**45** was then degraded under Edman reaction conditions to afford the 3-amino enantiomers (*S*)-**39a** and (*R*)-**39a**. This method was not practical for large scale preparation since it contains a separation process *via* column chromatography, but it does afford sufficient quantities and purities for full assignment of stereostructure and assessment of biological activities. The purities and absolute configuration of these enantiomers (*S*)-**39a** and (*R*)-**39a** were determined by $^1$H-NMR spectra and X-ray crystallographical analysis of their ureido derivatives formed with (*S*)-(−)-$\alpha$-methylbenzyl isocyanate, respectively. The more polar diastereoisomer of the L-phenylalanylamide separated by column chromatography was degraded to the amine followed by reaction with (*S*)-(−)-$\alpha$-methylbenzyl isocyanate and recrystallization to afford colorless prisms from a mixture of diisopropyl ether and methanol. An X-ray crystallographical analysis confirmed that the afforded prismatic crystals were (3*S*)-1-cyclohexylcarbonylmethyl-5-ethyl-3-[(*S*)-$\alpha$-methylbenzylureido]-9-methyl-1,4-benzodiazepin-2-one (**46**) (Fig. 2).

Thus, the optically active 3-amino intermediate obtained by Edman degradation from the more polar diastereoisomer was determined to be the (3*S*)-isomer, (*S*)-**39a**, and from the less polar diastereomer to be the (3*R*)-isomer, (*R*)-**39a**.

The target *m*-tolyl ureas (*S*)-**40** and (*R*)-**40** were prepared from these optically active amines by reaction with *m*-tolyl isocyanate without stereoinversion. The enantiomer excesses of the target compounds were determined to be 97.0% and 98.7%, respectively, by high-performance liquid chromatography (HPLC) with a chiral stationary-phase column (CHIRALCEL OD). Their biological activities are shown in Table 7 along with those of the parent racemate.

The *R*-enantiomer, (*R*)-**40**, was found to have higher affinity for both CCK-A and -B receptors and to be 27-fold higher for CCK-A receptor affinity and 8-fold more potent in CCK-B receptor binding activity than (*S*)-**40**. The selectivity (A/B) of (*R*)-**40** was found to be 0.30.

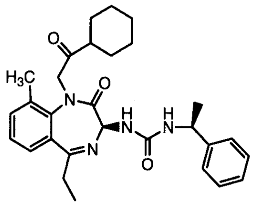
The activity after *p.o.* administration of (*R*)-**40** is considered to be high enough for further development, which was estimated from the ID$_{50}$ value obtained by preliminary evaluation of gastric emptying effects.

This final compound, (*R*)-**40** (FR208419), is now undergoing further research for a practical method of optical resolution and further pharmaceutical evaluations with a view to clinical development.

## Conclusion

In our continuing research for dual CCK-A and -B antagonists according to our hypothesis that dual CCK-A and -B antagonists should be more efficacious than selective CCK-A antagonists for the treatment of pancreatitis, we have prepared various 5-alkyl-9-methyl-1,4-benzodiazepines. Of all compounds prepared, 1-cyclohexylcarbonyl-methyl-5-ethyl-9-methyl-3-(*m*-tolylureido)-2-oxo-1,4-benzodiazepine, **40**, was selected as a candidate compound due to its well-balanced high affinity for both receptors. The *R*-enantiomer, (*R*)-**40**, was found to have higher affinities for both CCK-A and -B receptors than (*S*)-**40**. The selectivity (A/B) of (*R*)-**40** was found to be 0.30.

The activity after *p.o.* administration of (*R*)-**40**, estimated from the $ID_{50}$ value (0.23 mg/kg *p.o.*) obtained by preliminary evaluation by gastric emptying effects, is considered to be high enough for further development. This compound is now undergoing further biological evaluations with a view to clinical development.



**46**

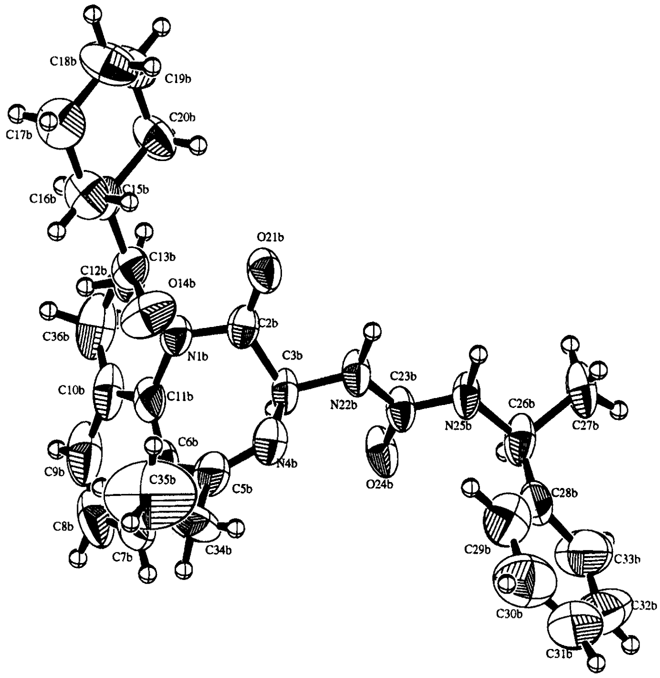


Fig. 2. ORTEP Drawing of *N*-[(3*S*)-1-Cyclohexylcarboxymethyl-2,3-dihydro-5-ethyl-9-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[(*S*)-α-methylbenzyl]urea (**46**)

## Experimental

Melting points were determined on a BÜCHI 535 meltemp apparatus and are uncorrected. IR spectra were recorded on a Shimazu IR-408 spectrometer. $^1$H-NMR (200 MHz) spectra were performed on a Bruker AC 200 P instrument, using tetramethylsilane (TMS) as an internal standard. Mass spectra were measured on an atmospheric pressure ionization HITACHI M-1000 mass instrument. Optical rotations were determined with a JASCO DIP-360. Elemental analyses were within ±0.4% of the theoretical values for elements indicated unless otherwise noted. The yields reported are not optimized.

**2-Acetyl-6-methylaniline (3a)** To a solution of *o*-toluidine (**2**) (32.8 g, 0.3 mol) and acetonitrile (6.22 g, 0.15 mol) in toluene (200 ml) was added dropwise 1 M-borontrichloride toluene solution (150 ml) with stirring and cooling in an ice bath below 5 °C. After the addition was completed, the mixture was stirred at ambient temperature for 1 h. The mixture was cooled again and aluminum chloride (20.0 g, 0.15 mol) was added portionwise. The resultant mixture was gradually warmed and refluxed for 5 h. The reaction mixture was cooled in an ice bath and 2 N aqueous hydrochloric acid (200 ml) was added dropwise under stirring. The mixture was refluxed for 2.5 h. The reaction mixture was cooled to ambient temperature and extracted with ethyl acetate. The organic extract was washed with water twice and brine, successively, and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave crystals, which were washed with hexane and collected by filtration to give **3a** (8.91 g, 39.8%) as light yellow crystals, mp 51.1—52.9 °C. $^1$H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.59 (3H, s), 6.4 (1H, br), 6.59 (1H, t, $J$=7.9 Hz), 7.19 (1H, d, $J$=7.9 Hz), 7.63 (1H, d, $J$=7.9 Hz). IR (Nujol): 3410, 3300, 1630, 1610, 960, 740 $cm^{-1}$. MS *m/z*: 150 ($M^+$+1).

Compounds **3b**—**i** were obtained in a similar manner to that carried out in the preparation of **3a**.

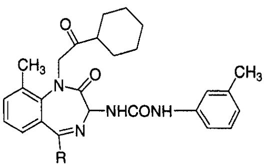
**2-Propanoyl-6-methylaniline (3b)** Yield 64.5%. mp 40.5—41.3 °C. $^1$H-NMR ($CDCl_3$) δ: 1.21 (3H, t, $J$=7.3 Hz), 2.16 (3H, s), 2.98 (2H, q, $J$=7.3 Hz), 6.40 (2H, m), 6.5—6.6 (1H, m), 7.18 (1H, d, $J$=7.1 Hz), 7.66 (1H, d, $J$=8.1 Hz). IR (Nujol): 3463, 3336, 1646, 1610 $cm^{-1}$. MS *m/z*: 164 ($M^+$+1).

**2-Isobutyloyl-6-methylaniline (3c)** Yield 85.9%. mp 47—49 °C. $^1$H-NMR ($CDCl_3$) δ: 1.21 (6H, d, $J$=6.8 Hz), 2.16 (3H, s), 3.62 (1H, heptet, $J$=6.8 Hz), 6.4 (1H, br), 6.60 (1H, t, $J$=7.3 Hz), 7.19 (1H, d, $J$=7.3 Hz), 7.69 (1H, d, $J$=7.3 Hz). IR (Nujol): 3470, 3320, 1638, 1607, 1580, 1550, 1422, 1380, 1230, 1094, 1011, 984, 745 $cm^{-1}$. MS *m/z*: 178 ($M^+$+1).

**2-Isopentanoyl-6-methylaniline (3d)** Yield 100%. mp 46.6—47.5 °C. $^1$H-NMR ($CDCl_3$) δ: 0.99 (6H, d, $J$=6.6 Hz), 2.17 (3H, s), 2.27 (1H, m), 2.81 (2H, d, $J$=6.9 Hz), 6.4 (1H, br), 6.59 (1H, dd, $J$=7.3, 8.0 Hz), 7.16—7.3 (2H, m), 7.66 (1H, d, $J$=8.0 Hz). IR (Nujol): 3475, 3330, 1638, 1610, 1580, 1555 $cm^{-1}$. MS *m/z*: 192 ($M^+$+1).

**2-Cyclopropylcarbonyl-6-methylaniline (3e)** A mixture of 2-(4-chlorobutanoyl)-6-methylaniline (538 mg, 2.54 mmol), obtained in a similar procedue to that carried out in the preparation of **3a** with cyclopropyl cyanide instead of acetonitrile, and potassium *tert*-butoxide (285 mg, 2.54 mmol) in tetrahydrofuran (8 ml) was stirred at ambient temperature for 1.5 h. Ethyl acetate and 0.1 N aqueous hydrochloric acid were added to the reaction mixture. The separated organic layer was washed with water, saturated aqueous sodium bicarbonate and brine, successively, and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded **3e** as an amorphous powder (445 mg, 100%). $^1$H-NMR ($CDCl_3$) δ: 0.90—1.00 (2H, m), 1.14—1.21 (2H, m), 2.17 (3H, s), 2.5—2.8 (1H, m), 6.25 (2H, m), 6.64 (1H, t, $J$=7.2 Hz), 7.22 (1H, d, $J$=7.2 Hz), 7.88 (1H, d, $J$=8.2 Hz). IR (Nujol):

Table 7. Results of Biological Activities of (*S*)-**40** and (*R*)-**40** Isomers



| Compound No. | R | Stereochemistry at $C_3$ | $IC_{50}$ (nM)[a] for CCK-B | $IC_{50}$ (nM)[b] for CCK-A | Selectivity[c] A/B | Gastric emptying[d] $ID_{50}$ (mg/kg) |
|---|---|---|---|---|---|---|
| **40** | $CH_2CH_3$ | *RS* | 1.6 | 0.9 | 0.38 | 0.4 |
| (*S*)-**40** | $CH_2CH_3$ | *S* (97.0% ee) | 7.8 | 8.2 | 1.05 | 6.8 |
| (*R*)-**40** | $CH_2CH_3$ | *R* (98.7% ee) | 1.0 | 0.3 | 0.30 | 0.23 |

*a*—*d*) See footnotes in Table 4.

3450, 3300, 1610 $cm^{-1}$. MS *m/z*: 176 ($M^+$+1)

**2-Cyclohexylcarbonyl-6-methylaniline (3f)** Yield 98.4%. $^1$H-NMR ($CDCl_3$) $\delta$: 1.2—1.95 (8H, m), 2.16 (3H, s), 3.23—3.36 (1H, m), 6.4 (1H, br), 6.60 (1H, t, *J*=7.3 Hz), 7.18 (1H, d, *J*=7.3 Hz), 7.68 (1H, d, *J*=7.3 Hz). IR (Nujol): 3470, 3320, 1638, 1608, 1580, 1550, 1424, 1380, 1310 $cm^{-1}$. MS *m/z*: 218 ($M^+$+1).

**2-Chloroacetyl-6-methylaniline (3g)** Yield 60.4%. $^1$H-NMR ($CDCl_3$) $\delta$: 2.17 (3H, s), 4.70 (2H, s), 6.2 (1H, br), 6.60 (1H, t, *J*=7.2 Hz), 7.22 (1H, d, *J*=7.2 Hz), 7.53 (1H, d, *J*=7.2 Hz). IR (Nujol): 3400, 3340, 1655, 1610, 1587, 1560, 1380 $cm^{-1}$. MS *m/z*: 184 ($M^+$+1), 186 ($M^+$+3).

**2-Methoxyacetyl-6-methylaniline (3h)** To a solution of **3g** (1.84 g, 10 mmol) in methanol (50 ml) was added 28% methanolic sodium methoxide (5.79 g, 10.0 mmol) with stirring and cooling in an ice-bath. The mixture was stirred for 0.5 h, and then at ambient temperature overnight. Methanol was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with water and brine successively. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give an oil, which was subjected to column chromatography on silica gel eluting with chloroform. The fractions containing the desired product were combined and evaporated to give **3h** as an oil (1.07 g, 59.7%). $^1$H-NMR ($CDCl_3$) $\delta$: 2.17 (3H, s), 3.51 (3H, s), 4.70 (2H, s), 6.41 (1H, br), 6.58 (1H, t, *J*=7.3 Hz), 7.19 (1H, d, *J*=7.3 Hz), 7.49 (1H, d, *J*=7.3 Hz). IR (Nujol): 3410, 3340, 1655, 1620, 1610, 1585, 1560, 1460, 1429, 1380 $cm^{-1}$. MS *m/z*: 180 ($M^+$+1).

**2-Dimethylaminoacetyl-6-methylaniline (3i)** The title compound was obtained by a similar procedure to that carried out for the preparation of **3h** using dimethylamine instead of sodium methoxide as a light yellow amorphous powder (yield 52.8%). $^1$H-NMR ($CDCl_3$) $\delta$: 2.16 (3H, s), 2.37 (6H, s), 3.71 (2H, s), 6.41 (1H, br), 6.58 (1H, dd, *J*=7.2, 8.1 Hz), 7.18 (1H, d, *J*=7.2 Hz), 7.71 (1H, d, *J*=7.2 Hz). IR (Nujol): 3410, 3300, 1640, 1612, 1585, 1552, 1378 $cm^{-1}$. MS *m/z*: 193 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (4a)** To a solution of *N*-benzyloxycarbonyl-2-(benzotriazol-1-yl)glycine (14.11 g, 43 mmol) in dry tetrahydrofuran (100 ml) was added oxalyl chloride (3.77 ml, 43 mmol) and dimethylformamide (3 drops) with stirring at 0 °C in an ice-salt bath under a nitrogen stream. After the mixture was stirred at the same temperature for 2 h, a mixture of **3a** (4.30 g, 29 mmol) and *N*-methylmorpholine (8.74 g, 86 mmol) in tetrahydrofuran (20 ml) was added dropwise over a period of 20 min. After the addition was completed, the mixture was allowed to warm to ambient temperature with stirring. Tetrahydrofuran was removed *in vacuo* and the residue was dissolved in ethyl acetate. The mixture was washed with water twice and dried over magnesium sulfate. Removal of the solvent gave an intermediate product as an oil, to which was added 20% methanolic ammonia (75 ml) and stirred at ambient temperature overnight. The resultant precipitate was collected by filtration and washed with cold methanol and diisopropyl ether successively and dried to give **4a** as a white crystalline powder (6.17 g, 63.5%), mp 238.0—239.5 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 2.36 (3H, s), 2.46 (3H, s), 5.11 (2H, s), 5.14 (1H, d, *J*=8.3 Hz), 6.50 (1H, d, *J*=8.3 Hz), 7.13—7.47 (8H, m), 8.48 (1H, s). IR (Nujol): 3210, 1718, 1690, 1678, 1628 $cm^{-1}$. MS *m/z*: 338 ($M^+$+1).

Compounds **4b**—**i** were obtained by a similar manner to that carried out in the preparation of **4a**.

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5-ethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (4b)** Yield 50.5%. mp >250 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.99 (3H, t, *J*=7.4 Hz), 2.34 (3H, s), 2.65—2.9 (2H, m), 4.86 (1H, d, *J*=8.6 Hz), 5.03 (2H, s), 7.1—7.5 (7H, m), 7.58 (1H, d, *J*=7.9 Hz), 8.09 (1H, d, *J*=8.6 Hz), 9.95 (1H, s). IR (Nujol): 1705, 1675, 1610 $cm^{-1}$. MS *m/z*: 352 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5-isopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (4c)** Yield 38.9%. mp 205.7—207.1 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 0.91 (3H, d, *J*=7.0 Hz), 1.27 (3H, d, *J*=7.0 Hz), 2.36 (3H, s), 3.13 (1H, heptet, *J*=7.0 Hz), 5.11 (2H, s), 5.15 (1H, d, *J*=8.4 Hz), 6.46 (1H, d, *J*=8.4 Hz), 7.1—7.45 (8H, m), 8.59 (1H, s). IR (Nujol): 3300, 3200, 1710, 1690, 1614 $cm^{-1}$. MS *m/z*: 366 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5-isobutyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (4d)** Yield 84.2%. mp 208.0—209.4 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 0.75 (3H, d, *J*=6.6 Hz), 0.89 (3H, d, *J*=6.6 Hz), 1.79 (1H, m), 2.36 (3H, s), 2.46 (1H, dd, *J*=9.4, 13.9 Hz), 2.87 (1H, dd, *J*=3.9, 13.9 Hz), 5.10 (2H, s), 5.15 (1H, d, *J*=8.4 Hz), 6.48 (1H, d, *J*=8.4 Hz), 7.12—7.45 (8H, m), 8.24 (1H, s). IR (Nujol): 3250, 3200, 1718, 1690, 1680, 1526 $cm^{-1}$. MS *m/z*: 380 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-5-cyclopropyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (4e)** Yield 29.7%. mp 244.5—246.0 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.7—1.2 (4H, m), 2.03 (1H, m), 2.34 (3H, s), 4.79 (1H, d, *J*=8.6 Hz), 5.02 (2H, br), 7.1—7.5 (6H, m), 7.6—7.8 (1H, m), 7.9—8.2 (1H, m), 9.96 (1H, br). IR (Nujol): 1715, 1675, 1620 $cm^{-1}$. MS *m/z*: 364 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-5-cyclohexyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (4f)** Yield 58.3%. $^1$H-NMR ($CDCl_3$) $\delta$: 0.8—2.0 (8H, m), 2.33 (3H, s), 2.91 (1H, br), 4.86 (1H, d, *J*=8.7 Hz), 5.03 (2H, s), 7.16—7.60 (8H, m), 8.11 (1H, d, *J*=8.7 Hz). IR (Nujol): 3390, 3300, 3200, 1710, 1685, 1620 $cm^{-1}$. MS *m/z*: 406 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5-methoxy-methyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (4h)** Yield 6.5%. $^1$H-NMR ($CDCl_3$) $\delta$: 2.23 (3H, s), 3.31 (3H, s), 4.50 (2H, m), 5.11 (2H, s), 5.18 (1H, br), 6.58 (1H, br), 7.15—7.6 (8H, m), 8.30 (1H, s). IR (Nujol): 3250, 3210, 1719, 1696, 1685, 1530 $cm^{-1}$. MS *m/z*: 368 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5-dimethylaminomethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (4i)** Yield 9.3%. $^1$H-NMR ($CDCl_3$) $\delta$: 2.18 (6H, s), 2.34 (3H, s), 3.52 (2H, m), 5.11 (2H, s), 5.19 (1H, d, *J*=8.4 Hz), 6.53 (1H, d, *J*=8.4 Hz), 7.18—7.4 (7H, m), 7.59 (1H, d, *J*=7.8 Hz), 8.07 (1H, s). IR (Nujol): 3250, 3200, 1718, 1695, 1685, 1685, 1615 $cm^{-1}$. MS *m/z*: 381 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5,9-dimethyl-1-ethoxycarbonylmethyl-1*H*-1,4-benzodiazepin-2-one (5-1a)** A mixture of **4a** (1.0 g, 2.96 mmol) and 60% sodium hydride (120 mg, 3 mmol) in dimethylformamide (10 ml) was stirred at 0 °C for 1 h and at ambient temperature for 3 h. To the resultant mixture was added dropwise ethyl bromoacetate (476 mg, 2.96 mmol) under cooling at 5 °C in an ice bath. The mixture was stirred at ambient temperature for 5.5 h. The reaction mixture was poured into 0.1 N aqueous hydrochloric acid and extracted with ethyl acetate. The extract was washed with water twice, saturated aqueous sodium bicarbonate and brine, successively, and dried over magnesium sulfate. The solvent was removed *in vacuo* to afford **5-1a** as an oil (1.25 g, 100%). $^1$H-NMR ($CDCl_3$) $\delta$: 1.19 (3H, t, *J*=7.1 Hz), 2.33 (3H, s), 2.56 (3H, s), 3.78 (1H, d, *J*=16.9 Hz), 4.08 (2H, q, *J*=7.1 Hz), 4.92 (1H, d, *J*=16.9 Hz), 5.0—5.2 (2H, m), 5.2—5.3 (1H, m), 6.50 (1H, d, *J*=8.6 Hz), 7.2—7.5 (8H, m). MS *m/z*: 424 (M+1).

Compounds **5-1b**—**5-1i** were obtained by a similar procedue to that carried out in the preparation of **5-1a**.

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-1-ethoxy-carbonylmethyl-5-ethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-1b)** Yield 100%. $^1$H-NMR ($CDCl_3$) $\delta$: 1.0—1.35 (6H, m), 2.33 (3H, s), 2.75—2.98 (2H, m), 3.78 (1H, d, *J*=16.8 Hz), 4.10 (2H, q, *J*=7.1 Hz), 4.85 (1H, d, *J*=16.8 Hz), 5.06 (1H, d, *J*=12.3 Hz), 5.13 (1H, d, *J*=12.3 Hz), 5.27 (1H, d, *J*=8.6 Hz), 6.49 (1H, d, *J*=8.6 Hz), 7.2—7.4 (8H, m). IR (neat): 1747, 1714, 1698, 1670 $cm^{-1}$. MS *m/z*: 438 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-1-ethoxy-carbonylmethyl-5-isopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-1c)** Yield 100%. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—1.4 (9H, m), 2.34 (3H, s), 3.1—3.4 (1H, m), 3.82 (1H, d, *J*=16.7 Hz), 4.12 (2H, q, *J*=7.1 Hz), 4.72 (1H, d, *J*=16.7 Hz), 5.0—5.2 (2H, m), 5.2—5.3 (1H, m), 6.49 (1H, d, *J*=8.6 Hz), 7.2—7.5 (8H, m). IR (neat): 1747, 1714, 1698, 1670, 1622 $cm^{-1}$. MS *m/z*: 452 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-1-ethoxy-carbonylmethyl-5-isobutyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-1d)** Yield 100%. $^1$H-NMR ($CDCl_3$) $\delta$: 0.96 (6H, d, *J*=6.6 Hz), 1.21 (3H, t, *J*=7.1 Hz), 2.13—2.28 (1H, m), 2.35 (3H, s), 2.57—2.88 (2H, m), 3.89 (1H, d, *J*=16.9 Hz), 4.12 (2H, q, *J*=7.1 Hz), 4.64 (1H, d, *J*=16.9 Hz), 5.06 (1H, d, *J*=12.4 Hz), 5.13 (1H, d, *J*=12.4 Hz), 5.25 (1H, d, *J*=8.6 Hz), 6.50 (1H, d, *J*=8.6 Hz), 7.2—7.4 (8H, m). IR (Nujol): 1750, 1720, 1620 $cm^{-1}$. MS *m/z*: 466 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-5-cyclopropyl-2,3-dihydro-1-ethoxycarbonylmethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-1e)** Yield 100%. $^1$H-NMR ($CDCl_3$) $\delta$: 0.83—0.94 (2H, m), 0.98—1.10 (2H, m), 1.19 (3H, t, *J*=7.1 Hz), 1.9—2.4 (1H, m), 2.33 (3H, s), 3.80 (1H, d, *J*=16.8 Hz), 4.10 (2H, q, *J*=7.1 Hz), 4.85 (1H, d, *J*=16.8 Hz), 5.01—5.14 (2H, m), 5.18 (1H, d, *J*=8.7 Hz), 6.36 (1H, d, *J*=8.6 Hz), 7.2—7.4 (7H, m), 7.63—7.68 (1H, m). IR (Nujol): 1750, 1700, 1630 $cm^{-1}$. MS *m/z*: 450 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-5-cyclohexyl-2,3-dihydro-1-ethoxycarbonylmethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-1f)** Yield 86.5%. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—2.2 (10H, m), 1.21 (3H, t, *J* =7.1 Hz), 2.33 (3H, s), 2.7—2.9 (1H, m), 3.82 (1H, d, *J*=16.7 Hz), 4.12 (2H, q, *J*=7.1 Hz), 4.68 (1H, d, *J*=16.7 Hz), 5.0—5.2 (2H, br), 5.22 (1H, d, *J*=8.6 Hz), 6.47 (1H, d, *J*=8.6 Hz), 7.1—7.5 (8H, m). IR (Nujol): 1750, 1720, 1670 $cm^{-1}$. MS *m/z*: 492 ($M^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-1-ethoxy-carbonyl-**

**methyl-5-methoxymethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-1h)** Yield 100%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.22 (3H, t, *J*=7.1 Hz), 2.34 (3H, s), 3.46—3.48 (3H, m), 3.6—4.0 (2H, m), 4.12 (2H, q, *J*=7.1 Hz), 4.0—4.3 (1H, br), 4.8—5.1 (1H, br), 5.1—5.3 (2H, m), 5.3—5.7 (1H, m), 6.5—6.8 (1H, m), 7.2—7.6 (8H, m). MS *m/z*: 454 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5-dimethylaminomethyl-1-ethoxycarbonylmethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-1i)** Yield 100%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.20 (3H, t, *J*=7.1 Hz), 2.34 (3H, s), 2.35 (6H, s), 3.59 (2H, s), 3.82 (1H, d, *J*=16.9 Hz), 4.09 (2H, q, *J*=7.1 Hz), 4.76 (1H, d, *J*=16.9 Hz), 5.29 (1H, d, *J*=8.7 Hz), 6.54 (1H, d, *J*=8.6 Hz), 7.2—7.5 (8H, m). IR (Nujol): 1750, 1720, 1675, 1620 cm$^{-1}$. MS *m/z*: 467 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (5-2a)** A mixture of **5**-1a (1.25 g, 2.96 mmol) and 1 N aqueous sodium hydroxide (7.0 ml) in dimethoxyethane (DME, 10 ml) was stirred at ambient temperature overnight. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in a mixture of ethyl acetate and 1 N aqueous hydrochloric acid. The separated organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated *in vacuo*, and the residue was triturated with diisopropyl ether and collected by filtration to give **5-2a** (985 mg, 84.2%) as a white crystalline powder, mp 188.7—190.2 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 2.29 (3H, s), 2.46 (3H, s), 3.72 (1H, d, *J*=17.1 Hz), 4.91 (1H, d, *J*=17.1 Hz), 5.0—5.1 (2H, m), 5.25 (1H, d, *J*=8 Hz), 6.73 (1H, d, *J*=8 Hz), 7.2—7.5 (8H, m), 7.90 (1H, m). IR (Nujol): 1720, 1690, 1618 cm$^{-1}$. MS *m/z*: 396 (M$^+$+1).

Compounds **5-2b**—**5-2i** were obtained in a similar procedue to that carried out in the preparation of **5-2a**.

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-2,3-dihydro-5-ethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-2b)** Yield 100%. mp 80.2—87.0 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.14 (3H, t, *J*=7.4 Hz), 2.31 (3H, s), 2.74—2.95 (2H, m), 2.79 (1H, d, *J*=17.1 Hz), 4.86 (1H, d, *J*=17.1 Hz), 5.01 (1H, d, *J*=12.4 Hz), 5.03 (1H, d, *J*=12.4 Hz), 5.26 (1H, d, *J*=8.7 Hz), 6.62 (1H, d, *J*=8.7 Hz), 7.2—7.4 (8H, m), 7.87 (1H, br). IR (Nujol): 1720, 1670, 1615 cm$^{-1}$. MS *m/z*: 410 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-2,3-dihydro-5-isopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-2c)** Yield 100%. mp 163.5—165.9 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.0—1.4 (6H, m), 2.32 (3H, s), 3.1—3.3 (1H, m), 3.84 (1H, d, *J*=17.0 Hz), 4.76 (1H, d, *J*=17.0 Hz), 5.0—5.2 (2H, m), 5.22 (1H, d, *J*=8.1 Hz), 6.54 (1H, d, *J*=8.7 Hz), 7.2—7.5 (8H, m). IR (Nujol): 1722, 1691, 1644 cm$^{-1}$. MS *m/z*: 424 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-2,3-dihydro-5-isobutyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-2d)** Yield 89.5%. $^1$H-NMR (CDCl$_3$) $\delta$: 0.91 (3H, d, *J*=6.6 Hz), 0.93 (3H, d, *J*=6.6 Hz), 2.1—2.2 (1H, m), 2.34 (3H, s), 2.55—2.73 (2H, m), 3.91 (1H, d, *J*=17.2 Hz), 4.68 (1H, d, *J*=17.2 Hz), 5.04 (1H, d, *J*=12.4 Hz), 5.12 (1H, d, *J*=12.4 Hz), 5.24 (1H, d, *J*=8.6 Hz), 6.56 (1H, d, *J*=8.6 Hz), 7.2—7.4 (8H, m). IR (Nujol): 1715, 1680, 1610 cm$^{-1}$. MS *m/z*: 438 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-5-cyclopropyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-2e)** Yield 91.6%. mp 85.2—89.1 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.82—0.90 (2H, m), 0.96—1.07 (2H, m), 1.26 (3H, t, *J*=7.1 Hz), 1.90—2.04 (1H, m), 2.31 (3H, s), 3.80 (1H, d, *J*=17.3 Hz), 4.89 (1H, d, *J*=17.3 Hz), 4.93—5.12 (2H,m), 5.18 (1H, d, *J*=8.7 Hz), 6.40 (1H, d, *J*=8.7 Hz,) 7.2—7.4 (7H, m), 7.5—7.6 (1H, m). IR (Nujol): 1730, 1680, 1610 cm$^{-1}$. MS *m/z*: 422 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-5-cyclohexyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-2f)** Yield 96.2%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.1—2.2 (10H, m), 2.32 (3H, s), 2.81 (1H, m), 3.84 (1H, d, *J*=17.1 Hz), 4.72 (1H, d, *J*=17.1 Hz), 4.9—5.2 (2H, m), 5.21 (1H, d, *J*=8.6 Hz), 6.52 (1H, d, *J*=8.7 Hz), 7.2—7.5 (8H, m). IR (Nujol): 1720, 1680 cm$^{-1}$. MS *m/z*: 464 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-2,3-dihydro-5-methoxymethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-2h)** Yield 82.7%. $^1$H-NMR (CDCl$_3$) $\delta$: 2.34 (3H, s), 3.4—3.9 (6H, m), 5.0—5.3 (2H, m), 5.4—5.7 (1H, m), 6.6—6.8 (1H, m), 7.2—7.6 (8H, m). IR (Nujol): 1720, 1680 cm$^{-1}$. MS *m/z*: 426 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-carboxymethyl-2,3-dihydro-5-dimethylaminomethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (5-2i)** Yield 100%. $^1$H-NMR (CDCl$_3$) $\delta$: 2.27 (3H, s), 2.31 (3H, s), 2.46 (3H, s), 3.5—3.8 (3H, m), 3.42 (1H, d, *J*=16.5 Hz), 4.98 (1H, d, *J*=9.6 Hz), 5.01 (2H, s), 7.1—7.4 (5H, m), 7.45 (1H, d, *J*=7.1 Hz), 7.76 (1H, d, *J*=7.3 Hz), 8.07 (1H, d, *J*=8.6 Hz), 8.31 (1H, s). IR (Nujol): 1715, 1685, 1600 cm$^{-1}$. MS *m/z*: 439 (M$^+$+1).

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (6-1a)** A mixture of **5-2a** (985 mg, 2.49 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (642 mg, 3.35 mmol), HOBT (453 mg, 3.35 mmol), 3-azabicyclo[3.2.2]nonane (419 mg, 3.35 mmol) and triethylamine (0.455 ml, 3.3 mmol) in DMF (30 ml) was stirred at ambient temperature overnight. Ethyl acetate and 0.1 N aqueous hydrochloric acid were added to the reaction mixture, which was stirred for several min. The separated organic layer was washed with 1 N aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate and brine successively, and then dried over magnesium sulfate. The solvent was evaporated *in vacuo*, triturated with diisopropyl ether and collected by filtration to afford **6-1a** (999 mg, 79.9%) as a crystalline powder, mp 202.2—203.8 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.26 (3H, t, *J*=7.4 Hz), 1.5—1.8 (10H, m), 2.34 (3H, s), 2.90 (2H, q, *J*=7.4 Hz), 3.29—3.36 (2H, m), 3.55—3.64 (1H, m), 3.79 (1H, d, *J*=15.6 Hz), 3.7—3.86 (1H, m), 5.05 (1H, d, *J*=12.4 Hz), 5.12 (1H, d, *J*=12.4 Hz), 5.14 (1H, d, *J*=15.6 Hz), 5.28 (1H, d, *J*=8.7 Hz), 6.50 (1H, d, *J*=8.7 Hz), 7.2—7.4 (8H, m). IR (Nujol): 1718, 1675, 1650 cm$^{-1}$. MS *m/z*: 517 (M$^+$+1).

Compounds **6-1b**—**6-1i** were obtained in a similar procedue to that carried out in the preparation of **6-1a**.

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-2,3-dihydro-5-ethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-1b)** Yield 90.0%. mp 135.2—137.3 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.5—1.9 (8H, m), 1.9—2.1 (2H, m), 2.35 (3H, s), 2.60 (3H, s), 3.2—3.4 (2H, m), 3.60 (1H, dd, *J*=5, 13.7 Hz), 3.77 (1H, d, *J*=15.8 Hz), 3.87 (1H, dd, *J*=5, 13.7 Hz), 5.0—5.1 (2H, m), 5.19 (1H, d, *J*=15.8 Hz), 5.2—5.4 (1H, m), 6.52 (1H, d, *J*=8.7 Hz), 7.2—7.5 (8H, m). IR (Nujol): 1720, 1675, 1650 cm$^{-1}$. MS *m/z*: 503 (M$^+$+1).

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-2,3-dihydro-5-isopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-1c)** Yield 90.0%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.22 (3H, d, *J*=7.1 Hz), 1.33 (3H, d, *J*=6.6 Hz), 1.4—1.9 (8H, m), 1.9—2.1 (2H, m), 2.36 (3H, s), 3.1—3.9 (5H, m), 3.86 (1H, d, *J*=15.5 Hz), 5.0—5.2 (2H, m), 5.24 (1H, d, *J*=8.2 Hz), 6.50 (1H, d, *J*=8.7 Hz), 7.2—7.5 (8H, m). IR (Nujol): 1720, 1650 cm$^{-1}$. MS *m/z*: 531(M$^+$+1).

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-2,3-dihydro-5-isobutyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-1d)** Yield 88.2%. mp 192.7—194.0 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.15 (6H, d, *J*=6.6 Hz), 1.5—1.8 (8H, m), 1.9—2.2 (2H, m), 2.2—2.3 (1H, m), 2.36 (3H, s), 2.58—2.95 (2H, m), 3.31—3.40 (2H, m), 3.53—3.82 (2H, m), 3.91 (1H, d, *J*=15.7 Hz), 4.95 (1H, d, *J*=15.7 Hz), 5.05 (1H, d, *J*=12.4 Hz), 5.12 (1H, d, *J*=12.4 Hz), 5.27 (1H, d, *J*=8.6 Hz), 6.51 (1H, d, *J*=8.6 Hz), 7.1—7.5 (7H, m), 7.6—7.7 (1H, m). IR (Nujol): 1710, 1675, 1650 cm$^{-1}$. MS *m/z*: 545(M$^+$+1).

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-5-cyclopropyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-1e)** Yield 91.6%. mp 166.7—169.0 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.87—1.09 (4H, m), 1.25—1.73 (8H, m), 2.03—2.15 (3H, m), 2.36 (3H, s), 3.31—3.80 (4H, m), 3.84 (1H, d, *J*=15.5 Hz), 5.1 (2H, m), 5.14 (1H, d, *J*=15.5 Hz), 5.19 (1H, d, *J*=8.7 Hz), 6.38 (1H, d, *J*=8.7 Hz), 7.2—7.5 (7H, m), 7.6—7.7 (1H, m). IR (Nujol): 1725, 1675, 1650, 1615 cm$^{-1}$. MS *m/z*: 529 (M$^+$+1).

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-5-cyclohexyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-1f)** Yield 100%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.1—2.2 (20H, m), 2.35 (3H, s), 2.7—3.0 (1H, m), 3.3—3.9 (4H, m), 3.88 (1H, d, *J*=15.5 Hz), 4.96 (1H, d, *J*=15.5 Hz), 4.9—5.2 (2H, m), 5.23 (1H, d, *J*=8.6 Hz), 6.50 (1H, d, *J*=8.6 Hz), 7.2—7.6 (8H, m). IR (Nujol): 1720, 1660 cm$^{-1}$. MS *m/z*: 571 (M$^+$+1).

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-2,3-dihydro-5-methoxymethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-1h)** Yield 82.5%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.4—1.9 (8H, m), 1.9—2.2 (2H, m), 2.36 (3H, s), 3.2—3.4 (2H, m), 3.49 (3H, s), 3.5—3.7 (2H, br), 3.7—3.9 (2H, m), 4.6—4.8 (1H, m), 5.1—5.3 (3H, m), 5.3—5.4 (1H, m), 6.5—6.6 (1H, m), 7.2—7.6 (8H, m). IR (Nujol): 1720, 1680 cm$^{-1}$. MS *m/z*: 533 (M$^+$+1).

**(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-3-benzyloxycarbonylamino-2,3-dihydro-5-dimethylaminomethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-1i)** Yield 80.8%. mp 201.3—204.5 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.5—1.9 (8H, m), 1.9—2.2 (2H, m), 2.22 (3H, s), 2.34 (6H, s), 3.1—3.5 (4H, m), 3.6—3.8 (2H, m), 3.82 (1H, d, *J*=15.5 Hz), 4.97—5.31 (4H, m), 7.1—7.5 (7H, m), 7.7—7.9 (1H, m). IR (Nujol): 1735, 1655, 1625 cm$^{-1}$. MS *m/z*: 546 (M$^+$+1).

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-**

**dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (6-2a)** A mixture of **6-1a** (999 mg, 1.93 mmol), 10% palladium on carbon (50% wet, 250 mg) and ammonium formate (600 mg, 9.5 mmol) in ethanol (15 ml) was stirred at ambient temperature for 1 h. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, and brine successively. After drying over sodium sulfate, the solvent was evaporated *in vacuo*, and the residue was triturated in diisopropyl ether and collected by filtration to give **6-2a** (644 mg, 87.0%) as an amorphous mass. $^1$H-NMR (CDCl$_3$) $\delta$: 1.27 (3H, t, $J$=7.3 Hz), 1.5—1.8 (8H, m), 1.8—2.1 (2H, m), 2.35 (3H, s), 2.89 (2H, q, $J$=7.3 Hz), 3.3—3.4 (2H, m), 3.5—3.6 (2H, m), 3.79 (1H, d, $J$=15.5 Hz), 4.41 (1H, m), 5.17 (1H, d, $J$=15.5 Hz), 7.1—7.4 (3H, m). IR (Nujol): 3370, 3360, 1680, 1655 cm$^{-1}$. MS $m/z$: 383 (M$^+$+1).

Compounds **6-2b**—**6-2i** were obtained in a similar procedue to that carried out in the preparation of **6-2a**.

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5-ethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-2b)** Yield 69.8%. mp 168.0—170.1 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.4—1.9 (8H, m), 1.9—2.1 (2H, m), 2.35 (3H, s), 2.58 (3H, s), 3.2—3.5 (2H, m), 3.5—3.9 (2H, m), 4.42 (1H, s), 5.23 (1H, d, $J$=15.6 Hz), 7.2—7.5 (3H, m). IR (Nujol): 3350, 3270, 1665, 1620 cm$^{-1}$. MS $m/z$: 369 (M$^+$+1).

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5-isopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-2c)** Yield 69.8%. mp 169.1—163.5 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.2—1.3 (3H, m), 1.34 (3H, d, $J$=6.6 Hz), 1.5—2.3 (10H, m), 2.36 (3H, s), 3.21 (1H, m), 3.4—3.9 (4H, m), 3.87 (1H, d, $J$=15.5 Hz), 4.38 (1H, s), 5.02 (1H, d, $J$=15.5 Hz), 7.1—7.5 (3H, m). IR (Nujol): 3330, 3250, 1660, 1630 cm$^{-1}$. MS $m/z$: 397 (M$^+$+1).

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5-isobutyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-2d)** Yield 73.1%. mp 171.3—173.0 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.98 (3H, d, $J$=6.5 Hz), 0.99 (3H, d, $J$=6.5 Hz), 1.5—1.8 (8H, m), 1.9—2.1 (2H, m), 2.2—2.3 (1H, m), 2.36 (3H, s), 2.56—2.68 (1H, m), 2.77 (1H, m), 3.35—3.44 (2H, m), 3.53—3.63 (1H, m), 3.77—3.85 (1H, m), 3.82 (1H, d, $J$=15.7 Hz), 4.41 (1H, s), 4.97 (1H, d, $J$=15.7 Hz), 7.1—7.4 (3H, m). IR (Nujol): 3380, 1680, 1650 cm$^{-1}$. MS $m/z$: 411 (M$^+$+1).

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-5-cyclopropyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-2e)** Yield 87.6%. mp 186.6—187.3 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.85—1.06 (4H, m), 1.4—1.8 (8H, m), 1.9—2.2 (2H, m), 2.23 (1H, br), 2.37 (3H, s), 3.35—3.67 (4H, m), 3.86 (1H, d, $J$=15.5 Hz), 4.37 (1H, s), 5.17 (1H, d, $J$=15.5 Hz), 7.1—7.5 (2H, m), 7.6—7.7 (1H, m). IR (Nujol): 3330, 3250, 1675, 1645, 1600 cm$^{-1}$. MS $m/z$: 395 (M$^+$+1).

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-5-cyclohexyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-2f)** Yield 50.1%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.1—2.2 (18H, m), 2.41 (3H, s), 2.7—3.0 (2H, m), 3.3—3.8 (5H, m), 3.91 (1H, d, $J$=15.8 Hz), 5.09 (1H, d, $J$=5.2 Hz), 5.14 (1H, d, $J$=15.8 Hz), 7.2—7.5 (3H, m). MS $m/z$: 437 (M$^+$+1).

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5-methoxymethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-2h)** Yield 80.2%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.4—2.1 (10H, m), 2.35 (3H, s), 3.2—3.5 (2H, m), 3.61 (3H, s), 3.6—3.9 (4H, m), 4.5—4.8 (2H, m), 5.21 (1H, d, $J$=15.6 Hz), 7.1—7.6 (3H, m). MS $m/z$: 399 (M$^+$+1).

**(3*RS*)-3-Amino-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5-dimethylaminomethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (6-2i)** Yield 53.0%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.2—2.6 (19H, m), 3.2—4.0 (6H, m), 4.13 (1H, m), 4.47 (1H, m), 5.10 (1H, m), 7.2—7.7 (3H, m). IR (Nujol): 3320, 1645 cm$^{-1}$. MS $m/z$: 412 (M$^+$+1).

***N*-[(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5,9-dimethyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]-*N*′-(3-methylphenyl)urea (7)** To a solution of **6-2a** (310 mg, 0.84 mmol) in tetrahydrofuran (5 ml) was added dropwise 3-tolyl isocyanate (113 mg, 0.99 mmol) at ambient temperature under stirring. The reaction mixture was stirred for 1 h under the same conditions and the solvent was removed *in vacuo*. The residue was pulverized in diisopropyl ether to give **7** (410 mg, 97.9%) as a white powder.

Other target compounds **8**—**14** were obtained in a similar procedure to that carried out in the preparation of **7**. Physical and spectral data of these compounds (**7**—**14**) are summarized in Table 1.

***N*-[(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one-4-oxido-3-yl]-*N*′-(3-methylphenyl)urea (15)** To a suspension of **7** (140.5 mg, 0.28 mmol) in methylene chloride (5 ml) was added 80% *m*-chloroperbenzoic acid (*m*-CPBA, 72.5 mg, 0.42 mmol) portionwise under stirring at ambient temperature. After stirring for 5.5 h, additional *m*-CPBA (48 mg) was added and the stirring was continued for a further 3.5 h. Methylene chloride was removed *in vacuo* to give a residue, which was dissolved in ethyl acetate and washed with an aqueous solution of sodium bicarbonate, water and brine successively. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to afford a reddish oil, which was subjected to preparative thin layer chromatography on silica gel developed with a mixture of chloroform and methanol (10 : 1) to give **15** as a white crystalline powder (65.5 mg, 48.0%), mp 242.4—244.6 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.53—1.73 (8H, m), 1.94 (1H, br), 2.05 (1H, br), 2.25 (3H, s), 2.41 (3H, s), 3.20—3.36 (2H, m), 3.54—3.81 (2H, m), 4.5—5.5 (2H, m), 5.97 (1H, s), 6.76—7.45 (9H, m). MS $m/z$: 518 (M$^+$+1).

***N*-[(3*RS*)-5-Acetoxymethyl-1-(3-azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one-3-yl]-*N*′-(3-methylphenyl)urea (16)** A mixture of **15** (45.3 mg, 0.088 mmol) and acetic anhydride (1.8 ml) was stirred at 50 °C for 5 h. After the reaction was completed, acetic anhydride was removed under reduced pressure. The residue was subjected to preparative thin layer chromatography on silica gel developed with a mixture of chloroform, ethyl acetate and methanol (14 : 1 : 0.4) to give **16** as an amorphous powder, which was triturated in diisopropyl ether and collected by filtration (26.5 mg, 59.3%). Physical and spectral data of this compound are summarized in Table 1.

***N*-[(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-5-hydroxylmethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one-3-yl]-*N*′-(3-methylphenyl)urea (17)** To a solution of **16** (208 mg, 0.37 mmol) in ethanol (4 ml) was added 1 N aqueous sodium hydroxide (1 ml) under stirring at ambient temperature. The mixture was stirred for 20 min under the same conditions. After removal of the solvent, water was added to the mixture, which was adjusted to pH 4 with diluted hydrochloric acid and extracted with ethyl acetate twice. The combined extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave an amorphous powder, which was triturated in diisopropyl ether to afford **17** (127 mg, 66.0%) as an amorphous powder. Physical and spectral data of this compound are summarized in Table 1.

***N*-[(3*RS*)-1-(3-Azabicyclo[3.2.2]nonan-3-yl)carbonylmethyl-2,3-dihydro-9-methyl-5-methylthiomethyl-1*H*-1,4-benzodiazepin-2-one-3-yl]-*N*′-(3-methylphenyl)urea (18)** To a mixture of **17** (147 mg, 0.28 mmol) and diisopropylethylamine (55.1 mg, 0.43 mmol) in methylene chloride (2 ml) was added dropwise a solution of methanesulfonyl chloride (48.7 mg, 0.43 mmol) in methylene chloride (1 ml) under stirring and cooling at 5 °C in an ice-bath. The mixture was stirred for 1.5 h under the same conditions. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in tetrahydrofuran (2 ml) and cooled in an ice-bath. To the solution obtained above was added 15% aqueous solution of sodium methanethiolate (0.5 g). The mixture was stirred under cooling for 0.5 h and at ambient temperature for 2 h. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and washed with water twice. The separated organic layer was dried over magnesium sulfate and evaporated *in vacuo* to afford an amorphous mass, which was subjected to preparative thin layer chromatography on silica gel developing with a mixture of chloroform and methanol (10 : 1) to give **18** as an amorphous mass. This was triturated in diisopropyl ether and collected by filtration to give a crystalline powder (71.9 mg, 46.2%). Physical and spectral data of this compound are summarized in Table 1.

**(3*RS*)-3-Amino-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (19)** The title compound was obtained in a similar procedure to that carried out in the preparation of **6-2a** as a white crystalline powder (yield 59.3%), mp 166.6—168.0 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 2.1—2.3 (2H, br), 2.33 (3H, s), 2.54 (3H, s), 4.40 (1H, br), 7.1—7.6 (3H, m). IR (Nujol): 3380, 1680, 1620 cm$^{-1}$. MS $m/z$: 204 (M$^+$+1).

***N*-[(3*RS*)-2,3-Dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one-3-yl]-*N*′-(3-methylphenyl)urea (20)** The title compound was obtained in a similar procedure to that carried out in the preparation of **7** (yield 80.2%), mp 240.4—241.1 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.24 (3H, s), 2.35 (3H, s), 2.45 (3H, s), 5.09 (1H, dd, $J$=8.6, 1.4 Hz), 6.72 (1H, d, $J$=6.4 Hz), 7.0—7.6 (7H, m), 8.9 (1H, s). IR (Nujol): 3300, 1690, 1685, 1645, 1615 cm$^{-1}$. MS $m/z$: 337 (M$^+$+1).

***N*-[(3*RS*)-2,3-Dihydro-5,9-dimethyl-1-ethoxycarbonylmethyl-1*H*-1,4-benzodiazepin-2-one-3-yl]-*N*′-(3-methylphenyl)urea (21)** The title compound was obtained in a similar procedure to that carried out in the preparation of **5-1a** (yield 85.0%), mp 223.1—226.6 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.12 (3H, t, $J$=7.1 Hz), 2.22 (3H, s), 2.33 (3H, s), 2.45 (3H, s), 4.05 (2H, q, $J$=7.1 Hz), 4.09 (1H, d, $J$=17 Hz), 4.68 (1H, d, $J$=17 Hz), 5.11 (1H, dd, $J$=8.6, 1.4 Hz), 6.72 (1H, d, $J$=6.4 Hz), 7.0—7.64 (7H, m), 8.87 (1H, s). IR

(Nujol): 3300, 1750, 1685, 1645, 1615 cm$^{-1}$. MS *m/z*: 423 (M$^+$+1).

***N*-[(3*RS*)-1-Carboxymethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one-3-yl]-*N*′-(3-methylphenyl)urea (22)** The title compound was obtained in a similar procedure to that carried out in the preparation of **5-2a** as a white crystalline powder (yield 86.2%), mp 192.3—196.5 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.22 (3H, s), 2.33 (3H, s), 2.41 (3H, s), 3.94 (1H, d, $J$=17.0 Hz), 4.65 (1H, d, $J$=17.0 Hz), 5.10 (1H, d, $J$=7.2 Hz), 6.72 (1H, d, $J$=6.4 Hz), 7.0—7.6 (7H, m), 8.91 (1H, s). IR (Nujol): 1690, 1658, 1620 cm$^{-1}$. MS *m/z*: 395 (M$^+$+1).

***N*-(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5,9-dimethyl-1-[*N*-methyl-*N*-(2-pyridyl)amino]carbonylmethyl-1*H*-1,4-benzodiazepin-2-one (23)** A mixture of **5-2a** (3.26 g), *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.62 g, 8.24 mmol), 1-hydroxybenzotriazole (1.14 g, 8.44 mmol), 2-(methylamino)pyridine (913 mg, 8.44 mmol) and triethylamine (854 mg) in DMF (20 ml) was stirred at ambient temperature overnight. Ethyl acetate and 0.1 N aqueous hydrochloric acid were added to the reaction mixture with stirring. The separated organic layer was washed with water, saturated aqueous sodium bicarbonate and brine successively, and then dried over sodium sulfate. The solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (2 : 1) to give **23** as a powder (1.60 g, 41.1%), mp 148.1—151.0 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 2.25 (3H, s), 2.62 (3H, s), 3.30 (3H, s), 4.06 (1H, d, $J$=16 Hz), 4.75 (1H, d, $J$=16 Hz), 5.0—5.3 (3H, m), 6.45 (1H, d, $J$=8 Hz), 7.1—7.5 (7H, m), 8.4—8.5 (1H, br). IR (Nujol): 1710, 1670, 1620 cm$^{-1}$. MS *m/z*: 486 (M$^+$+1).

***N*-(3*RS*)-3-Benzyloxycarbonylamino-2,3-dihydro-5,9-dimethyl-1-(1,1-dimethylethyl)carbonylmethyl-1*H*-1,4-benzodiazepin-2-one (24a)** The title compound was obtained in a similar procedure to that carried out in the preparation of **5-1a** using 1-bromo-3,3-dimethyl-2-butanone instead of ethyl bromoacetate (yield 100%), mp 126.8—129.1 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.12 (9H, s), 2.32 (3H, s), 2.62 (3H, s), 3.80 (1H, d, $J$=17.2 Hz), 5.0—5.3 (3H, m), 6.45 (1H, d, $J$=8.7 Hz), 7.1—7.5 (8H, m). IR (Nujol): 1710, 1670, 1620 cm$^{-1}$. MS *m/z*: 436 (M$^+$+1).

***N*-(3*RS*)-3-Benzyloxycarbonylamino-1-cyclopentylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (24b)** To a solution of **23** (400 mg, 0.82 mmol) in tetrahydrofuran (4 ml) was added cyclopentyl magnesium chloride diethylether solution (2.0 mol/l, 1.08 ml) dropwise with stirring at 0 °C. The mixture was stirred for 20 min under the same conditions and at ambient temperature overnight. Ethyl acetate and saturated aqueous ammonium chloride were added to the reaction mixture. The separated organic layer was washed with 0.1 N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, successively, and dried over magnesium sulfate. The solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (20 : 1) to give **24b** as a powder (140 mg, 36.6%). $^1$H-NMR (CDCl$_3$) $\delta$: 1.1—2.0 (8H, m), 2.2—2.2 (1H, m), 2.31 (3H, s), 2.4—2.8 (3H, br), 3.81 (1H, d, $J$=17.0 Hz), 4.88 (1H, d, $J$=17.0 Hz), 5.07—5.08 (2H, m), 5.19 (1H, d, $J$=9 Hz), 6.42 (1H, d, $J$=9 Hz), 7.1—7.5 (8H, m). MS *m/z*: 448 (M$^+$+1).

***N*-(3*RS*)-3-Benzyloxycarbonylamino-1-cyclohexylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (24c)** The title compound was obtained in a similar procedure to that carried out in the preparation of **5-1a** using bromoacetylcyclohexane instead of ethyl bromoacetate (yield 80.4%), mp 149.1—153.0 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.3—2.0 (10H, m), 2.32 (3H, s), 2.4—2.6 (1H, m), 3.75 (1H, d, $J$=17 Hz), 5.10 (1H, d, $J$=17 Hz), 5.0—5.2 (2H, m), 5.24 (1H, d, $J$=8.7 Hz), 6.48 (1H, d, $J$=8.7 Hz), 7.1—7.5 (8H, m). IR (Nujol): 3400, 1720, 1670, 1620 cm$^{-1}$. MS *m/z*: 462 (M$^+$+1).

***N*-(3*RS*)-3-Benzyloxycarbonylamino-1-cycloheptylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (24d)** The title compound was obtained in a similar procedure to that carried out in the preparation of **24b** using cycloheptyl magnesium bromide instead of cyclopentyl magnesium chloride (yield 80.4%). $^1$H-NMR (CDCl$_3$) $\delta$: 1.3—2.0 (12H, m), 2.32 (3H, s), 2.4—2.6 (1H, m), 2.61 (3H, s), 3.75 (1H, d, $J$=17 Hz), 5.10 (1H, d, $J$=17 Hz), 5.0—5.2 (2H, m), 5.24 (1H, m), 6.48 (1H, d, $J$=8.7 Hz), 7.1—7.5 (8H, m). IR (Nujol): 3400, 1730, 1690, 1670 cm$^{-1}$. MS *m/z*: 476 (M$^+$+1).

***N*-(3*RS*)-3-Benzyloxycarbonylamino-1-cyclooctylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (24e)** The title compound was obtained in a similar procedure to that carried out in the preparation of **24b** using cyclooctyl magnesium bromide instead of cyclopentyl magnesium chloride (yield 67.4%). $^1$H-NMR (CDCl$_3$) $\delta$: 1.3—2.0 (14H, m), 2.33 (3H, s), 2.61 (3H, s), 2.4—2.6 (1H, m), 3.75 (1H, d, $J$=17 Hz), 5.10 (1H, d, $J$=17 Hz), 5.0—5.2 (2H, m), 5.24 (1H, m), 6.48 (1H, d, $J$=8.7 Hz), 7.1—7.5 (8H, m). IR (Nujol): 3400, 1730, 1690, 1670 cm$^{-1}$. MS *m/z*: 490 (M$^+$+1).

***N*-(3*RS*)-3-Amino-1-(1,1-dimethylethyl)carbonylmethyl-2,3-dihydro-5,9-dimethyl-1H-1,4-benzodiazepin-2-one (25a)** The title compound was obtained in a similar procedure to that carried out in the preparation of **6-2a** as a white amorphous powder (yield 80.3%). $^1$H-NMR (CDCl$_3$) $\delta$: 1.13 (9H, s), 2.32 (3H, s), 2.61 (3H, s), 3.79 (1H, d, $J$=17.2 Hz), 4.4 (1H, m), 5.29 (1H, d, $J$=17.2 Hz), 7.1—7.5 (3H, m). IR (Nujol): 1710, 1670, 1615 cm$^{-1}$. MS *m/z*: 302 (M++1).

Compounds **25b—e** were obtained in a similar procedue to that carried out in the preparation of **25a**.

**(3*RS*)-3-Amino-1-cyclopentylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (25b)** Yield 14.6%. mp 80.2—86.1 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.1—2.0 (8H, m), 2.0—2.2 (1H, m), 2.3 (3H, s), 2.60 (3H, s), 3.72 (1H, d, $J$=17.2 Hz), 4.4 (1H, m), 5.13 (1H, d, $J$=17.2 Hz), 7.1—7.5 (3H, m). IR (Nujol): 1715, 1670 cm$^{-1}$. MS *m/z*: 314 (M$^+$+1).

**(3*RS*)-3-Amino-1-cyclohexylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (25c)** Yield 100%. mp 124.3—125.1 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.1—2.0 (10H, m), 2.0—2.2 (1H, m), 2.32 (3H, s), 2.60 (3H, s), 3.72 (1H, d, $J$=17.2 Hz), 4.4 (1H, m), 5.13 (1H, d, $J$=17.2 Hz), 7.1—7.5 (3H, m). IR (Nujol): 1715, 1670 cm$^{-1}$. MS *m/z*: 328 (M$^+$+1).

**(3*RS*)-3-Amino-1-cycloheptylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (25d)** Yield 75.2%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.3—2.3 (12H, m), 2.32 (3H, s), 2.4—2.6 (1H, m), 2.60 (3H, s), 3.74 (1H, d, $J$=17 Hz), 4.39 (1H, s), 5.12 (1H, d, $J$=17 Hz), 7.1—7.5 (3H, m). IR (Nujol): 3360, 3320, 1720, 1670, 1620 cm$^{-1}$. MS *m/z*: 342 (M$^+$+1).

**(3*RS*)-3-Amino-1-cyclooctylcarbonylmethyl-2,3-dihydro-5,9-dimethyl-1*H*-1,4-benzodiazepin-2-one (25e)** Yield 91.2%. $^1$H-NMR (CDCl$_3$) $\delta$: 1.3—2.0 (14H, m), 2.33 (3H, s), 2.4—2.6 (1H, m), 2.60 (3H, s), 3.74 (1H, d, $J$=17 Hz), 4.39 (1H, m), 5.12 (1H, d, $J$=17 Hz), 7.1—7.5 (3H, m). IR (Nujol): 3400, 3300, 1725, 1690, 1660 cm$^{-1}$. MS *m/z*: 356 (M$^+$+1).

The target compounds **26—32** were obtained in a similar procedure to that carried out in the preparation of **6-1a**. The target compounds **33—37** were obtained in a similar procedure to that carried out in the preparation of **7**. Physical and spectral data of **26—37** are summarized in Table 2.

**(3*RS*)-3-Benzyloxycarbonylamino-1-cyclohexyl-carbonylmethyl-2,3-dihydro-5-ethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (38a)** The title compound was obtained in a similar procedure to that carried out in the preparation of **24c** as a white crystalline powder (yield 41.2%), mp 74.1—76.8 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.27 (3H, t, $J$=7.4 Hz), 1.1—2.0 (10H, m), 2.2—2.4 (1H, m), 2.32 (3H, s), 2.92 (2H, q, $J$=7.4 Hz), 3.75 (1H, d, $J$=17 Hz), 5.05 (1H, d, $J$=17 Hz), 5.0—5.2 (2H, m), 5.25 (1H, d, $J$=8.7 Hz), 6.45 (1H, d, $J$=8.6 Hz), 7.1—7.5 (8H, m). IR (Nujol): 3350, 1710, 1670, 1620 cm$^{-1}$. MS *m/z*: 476 (M$^+$+1).

Compounds **38b—d** were obtained in a similar procedue to that carried out in the preparation of **38a**.

**(3*RS*)-3-Benzyloxycarbonylamino-1-cyclohexyl-carbonylmethyl-2,3-dihydro-5-isopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (38b)** Yield 66.4%. mp 128.0—130.7 °C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.19 (3H, d, $J$=7.1 Hz), 1.33 (3H, d, $J$=6.6 Hz), 1.1—2.0 (10H, m), 2.2—2.4 (1H, m), 2.32 (3H, s), 3.1—3.3 (1H, m), 3.79 (1H, d, $J$=17 Hz), 4.93 (1H, d, $J$=17 Hz), 5.05 (1H, d, $J$=12.6 Hz), 5.12 (1H, d, $J$=12.6 Hz), 5.20 (1H, d, $J$=8.7 Hz), 6.42 (1H, d, $J$=8.6 Hz), 7.1—7.5 (8H, m). IR (Nujol): 3350, 1720, 1670, 1610 cm$^{-1}$. MS *m/z*: 490 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-cyclohexyl-carbonylmethyl-2,3-dihydro-5-isobutyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (38c)** Yield 77.8%. $^1$H-NMR (CDCl$_3$) $\delta$: 0.97 (6H, d, $J$=6.6 Hz), 1.1—2.0 (10H, m), 2.1—2.3 (2H, m), 2.31 (3H, s), 2.5—3.0 (2H, m), 3.90 (1H, d, $J$=17.3 Hz), 4.83 (1H, d, $J$=17.3 Hz), 5.0—5.2 (2H, m), 5.23 (1H, d, $J$=8.7 Hz), 6.46 (1H, d, $J$=8.5 Hz), 7.1—7.5 (8H, m). IR (Nujol): 3300, 1710, 1665 cm$^{-1}$. MS *m/z*: 504 (M$^+$+1).

**(3*RS*)-3-Benzyloxycarbonylamino-1-cyclohexyl-carbonylmethyl-2,3-dihydro-5-cyclopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (38d)** Yield 70.8%. $^1$H-NMR (CDCl$_3$) $\delta$: 0.8—1.5 (10H, m), 1.5—1.9 (4H, m), 2.0—2.2 (1H, m), 2.2—2.4 (1H, m), 2.32 (3H, s), 3.78 (1H, d, $J$=17 Hz), 5.01 (1H, d, $J$=17 Hz), 5.0—5.2 (2H, m), 5.17 (1H, d, $J$=9 Hz), 6.33 (1H, d, $J$=9 Hz), 7.1—7.4 (7H, m), 7.6—7.7 (1H, m). IR (Nujol): 3300, 1715, 1665, 1605 cm$^{-1}$. MS *m/z*: 488 (M$^+$+1).

**(3*RS*)-3-Amino-1-cyclohexylcarbonylmethyl-2,3-dihydro-5-ethyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (39a)** The title compound was obtained in a similar procedure to that carried out in the preparation of **25c** as a white crystalline powder (yield 100%), mp 140.6—143.1 °C. $^1$H-NMR

($CDCl_3$) $\delta$: 1.29 (3H, t, $J$=7.1 Hz), 1.1—1.4 (5H, m), 1.5—2.0 (5H, m), 2.0—2.2 (2H, m), 2.2—2.4 (1H, m), 2.32 (3H, s), 2.8—3.0 (2H, m), 3.74 (1H, d, $J$=17.0 Hz), 4.39 (1H, m), 5.06 (1H, d, $J$=17.0 Hz), 7.1—7.4 (3H, m). IR (Nujol): 3380, 3320, 1720, 1680 cm$^{-1}$. MS *m/z*: 342 ($M^+$+1).

Compounds **39b—d** were obtained in a similar procedue to that carried out in the preparation of **39a**.

**(3*RS*)-3-Amino-1-cyclohexylcarbonylmethyl-2,3-dihydro-5-isopropyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (39b)** Yield 100%. mp 101.9—103.2 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.21 (3H, d, $J$=7.0 Hz), 1.35 (3H, d, $J$=6.6 Hz), 1.1—1.5 (5H, m), 1.5—2.2 (5H, m), 2.2—2.4 (1H, m), 2.35 (3H, s), 3.1—3.3 (1H, m), 3.80 (1H, d, $J$=17.0 Hz), 4.34 (1H, s), 4.92 (1H, d, $J$=17.0 Hz), 7.1—7.4 (3H, m). IR (Nujol): 3380, 3320, 1725, 1680, 1620 cm$^{-1}$. MS *m/z*: 356 ($M^+$+1).

**(3*RS*)-3-Amino-1-cyclohexylcarbonylmethyl-2,3-dihydro-5-isobutyl-9-methyl-1*H*-1,4-benzodiazepin-2-one (39c)** Yield 94.2 %. $^1$H-NMR ($CDCl_3$) $\delta$: 0.98 (6H, d, $J$=6.6 Hz), 1.1—2.0 (10H, m), 2.0—2.4 (4H, m), 2.31 (3H, s), 2.5—2.9 (2H, m), 3.90 (1H, d, $J$=17 Hz), 3.38 (1H, m), 4.83 (1H, d, $J$=17 Hz), 7.1—7.4 (3H, m). IR (Nujol): 3380, 3320, 1720, 1680, 1620 cm$^{-1}$. MS *m/z*: 370 ($M^+$+1).

**(3*RS*)-3-Amino-1-cyclohexylcarbonylmethyl-5-cyclopropyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (39d)** Yield 87.9%. $^1$H-NMR ($CDCl_3$) $\delta$: 0.8—2.4 (16H, m), 2.32 (3H, s), 2.2—2.4 (1H, m), 2.7—2.9 (1H, m), 3.88 (1H, d, $J$=17 Hz), 4.32 (1H, s), 5.01 (1H, d, $J$=17 Hz), 7.1—7.4 (3H, m). IR (Nujol): 3400, 3310, 1720, 1680, 1610 cm$^{-1}$. MS *m/z*: 356 ($M^+$+1).

The target compounds **40—43** were obtained in a similar procedure to that carried out in the preparation of **7**. Physical and spectral data of **40—43** are summarized in Table 3.

**(3*RS*)-1-Cyclohexylcarbonylmethyl-3-[*N-tert*-butoxycarbonyl-(*S*)-phenylalanyl]amino-5-ethyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one (44)** A mixture of **39a** (24.7 g, 75.4 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (15.3 g, 80 mmol), 1-hydroxybenzotriazole (10.8 g, 80 mmol), and *N-tert*-butoxycarbonyl-(*S*)-phenylalanine (20.0 g, 75.4 mmol) in DMF (268 ml) was stirred at ambient temperature overnight. Ethyl acetate and water were added to the reaction mixture with stirring. The separated organic layer was washed with water, saturated aqueous sodium bicarbonate and brine successively, and then dried over magnesium sulfate. The solvent was evaporated *in vacuo* to afford **44** (43.2 g, 100%) as an amorphous mass. $^1$H-NMR ($CDCl_3$) $\delta$: 1.15—1.35 (9H, m), 1.37 (9H, s), 1.6—1.85 (4H, m), 1.85—2.0 (1H, m), 2.2—2.4 (1H, m), 2.34 (3H, s), 2.85—3.1 (2H, m), 3.14—2.39 (1H, m), 3.75 (1H, d, $J$=17.2 Hz), 4.50 (1H, br), 4.94 (1H, br), 5.06 (1H, d, $J$=17.2 Hz), 5.39—5.46 (1H, m), 7.19—7.5 (8H, m), 7.61 (1H, br). MS *m/z*: 589 ($M^+$+1).

**(3*S*)-1-Cyclohexylcarbonylmethyl-3-[(*S*)-phenylalanyl]amino-5-ethyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one ((S)-45)** A mixture of **44** (43.2 g, 75.4 mmol) and 4 N hydrogen chloride in ethyl acetate (800 ml) was stirred for 0.5 h under cooling in an ice-bath and for 3 h at ambient temperature. After babbling with nitrogen gas, the solution was washed with dilute aqueous sodium bicarbonate twice and with water. After drying over magnesium sulfate, the solvent was evaporated *in vacuo* to give an oil (35.5 g) as a mixture of diastereoisomers, which were separated by medium pressure liquid chromatography on silica gel eluting with a mixture of chloroform and methanol (20 : 1). The respective fractions containing (*S*)-**45** and (*R*)-**45** were combined and evaporated *in vacuo* to afford pure (*S*)-**45** (11.8 g) and (*R*)-**45** (14.3 g).

(*S*)-**45**: $^1$H-NMR ($CDCl_3$) $\delta$: 1.05—1.45 (5H, m), 1.28 (3H, t, $J$=7.4 Hz), 1.60 (2H, s), 1.6—2.0 (5H, m), 2.25—2.43 (1H, m), 2.35 (3H, s), 2.60 (1H, dd, $J$=10.5, 13.7 Hz), 2.92 (2H, q, $J$=7.4 Hz), 3.34 (1H, dd, $J$=3.5, 13.7 Hz), 3.66 (1H, dd, $J$=3.5, 10.5 Hz), 3.75 (1H, d, $J$=17.1 Hz), 5.08 (1H, d, $J$=17.1 Hz), 5.48 (1H, d, $J$=8.5 Hz), 7.15—7.45 (8H, m), 8.77 (1H, d, $J$=8.5 Hz). MS *m/z*: 489 ($M^+$+1).

**(3*R*)-1-Cyclohexylcarbonylmethyl-3-[(*S*)-phenylalanyl]amino-5-ethyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one ((*R*)-45)** $^1$H-NMR ($CDCl_3$) $\delta$: 1.05—1.45 (5H, m), 1.28 (3H, t, $J$=7.4 Hz), 1.63 (2H, s), 1.6—2.0 (5H, m), 2.25—2.43 (1H, m), 2.34 (3H, s), 2.70 (1H, dd, $J$=10.1, 13.7 Hz), 2.94 (2H, q, $J$=7.4 Hz), 3.31 (1H, dd, $J$=3.8, 13.7 Hz), 3.64 (1H, dd, $J$=3.8, 10.1 Hz), 3.74 (1H, d, $J$=17.1 Hz), 5.06 (1H, d, $J$=17.1 Hz), 5.46 (1H, d, $J$=8.5 Hz), 7.15—7.45 (8H, m), 8.73 (1H, d, $J$=8.5 Hz). MS *m/z*: 489 ($M^+$+1).

**(3*S*)-3-Amino-1-cyclohexylcarbonylmethyl-5-ethyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one ((*S*)-39a)** A mixture of (*S*)-**45** (14.3 g) and phenyl isothiocyanate (4.35 g) in methylene chloride (250 ml) was heated with stirring. This procedure was repeated three times. The resultant reaction mixture was evaporated *in vacuo* to remove methylene chloride completely. To the obtained oil was added trifluoroacetic acid (200 ml) and the mixture was heated with stirring at 50 °C for 20 min. The trifluoroacetic acid was removed *in vacuo* completely. The residue was subjected to column chromatography on silica gel eluting with a mixture of chloroform and methanol (20 : 1). The fractions containing the desired product were combined and evaporated *in vacuo* to give an oily product, which was dissolved in ethyl acetate and washed with diluted aqueous sodium bicarbonate. After drying over magnesium sulfate, the solvent was removed *in vacuo* to afford (*S*)-**39a** (6.30 g, 63.1%) as an amorphous solid. $^1$H-NMR ($CDCl_3$) $\delta$: 1.05—1.4 (5H, m), 1.26 (3H, t, $J$=7.1 Hz), 1.55—1.95 (5H, m), 2.25—2.43 (1H, m), 2.32 (3H, s), 2.90 (2H, q, $J$=7.1 Hz), 2.96 (2H, br), 3.75 (1H, d, $J$=17.1 Hz), 4.46 (1H, s), 5.07 (1H, d, $J$=17.1 Hz), 7.15—7.4 (3H, m). MS *m/z*: 342 ($M^+$+1). $[\alpha]_D^{29.2}$ −6.59° ($c$=1.41, $CHCl_3$).

**(3*R*)-3-Amino-1-cyclohexylcarbonylmethyl-5-ethyl-2,3-dihydro-9-methyl-1*H*-1,4-benzodiazepin-2-one ((R)-39a)** The target compound was obtained by the same procedure as that carried out for the preparation of (*S*)-**39a**. $^1$H-NMR ($CDCl_3$) $\delta$: 1.05—1.4 (5H, m), 1.26 (3H, t, $J$=7.1 Hz), 1.55—1.95 (5H, m), 2.25—2.45 (1H, m), 2.32 (3H, s), 2.90 (2H, q, $J$=7.1 Hz), 3.47 (2H, br), 3.75 (1H, d, $J$=17.1 Hz), 4.48 (1H, s), 5.07 (1H, d, $J$=17.1 Hz), 7.15—7.4 (3H, m). MS *m/z*: 342 ($M^+$+1). $[\alpha]_D^{29.2}$ + 5.78° ($c$=1.41, $CHCl_3$).

***N*-[(3*S*)-1-Cyclohexylcarboxymethyl-2,3-dihydro-5-ethyl-9-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]-*N*′-(3-methylphenyl)urea ((S)-40)** The title compound was obtained from (*S*)-**39a** in a similar procedure to that carried out for the preparation of **7** from **6-2a** as a white amorphous powder (yield 72.4%). $^1$H-NMR ($CDCl_3$) $\delta$: 1.05—1.4 (5H, m), 1.26 (3H, t, $J$=7.4 Hz), 1.55—1.9 (5H, m), 2.02 (1H, br), 2.2—2.35 (1H, m), 2.29 (3H, s), 2.33 (3H, s), 2.92 (2H, q, $J$=7.4 Hz), 3.77 (1H, d, $J$=17.2 Hz), 5.06 (1H, d, $J$=17.2 Hz), 5.48 (1H, d, $J$=8.3 Hz), 6.7—7.4 (8H, m). MS *m/z*: 475 ($M^+$+1). $[\alpha]_D^{30}$ −53.36° ($c$=1.16, $CHCl_3$).

***N*-[(3*R*)-1-Cyclohexylcarboxymethyl-2,3-dihydro-5-ethyl-9-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]-*N*′-(3-methylphenyl)urea ((R)-40)** The title compound was obtained from (*R*)-**39a** in a similar procedure to that carried out for the preparation of **7** from **6-2a** as a white amorphous powder (yield 64.1%). $^1$H-NMR ($CDCl_3$) $\delta$: 1.05—1.4 (5H, m), 1.26 (3H, t, $J$=7.4 Hz), 1.55—1.9 (5H, m), 1.95—2.35 (2H, m), 2.29 (3H, s), 2.32 (3H, s), 2.92 (2H, q, $J$=7.4 Hz), 3.77 (1H, d, $J$=17.2 Hz), 5.06 (1H, d, $J$=17.2 Hz), 5.48 (1H, d, $J$=8.3 Hz), 6.7—7.4 (8H, m). MS *m/z*: 475 ($M^+$+1). $[\alpha]_D^{30}$ +50.92° ($c$=1.08, $CHCl_3$).

***N*-[(3*S*)-1-Cyclohexylcarboxymethyl-2,3-dihydro-5-ethyl-9-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[(*S*)-*α*-methylbenzyl] urea (46)** A mixture of (*S*)-**45** (341 mg, 1.04 mmol) and (*S*)-(−)-$\alpha$-methylbenzyl isocyanate (150 mg, 0.93 mmol) in tetrahydrofuran (5 ml) was stirred for 1 h. The solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with dilute hydrochloric acid, dilute aqueous sodium bicarbonate, water, and brine successively. After drying over magnesium sulfate, the solvent was removed *in vacuo* to give an amorphous solid, which was subjected to column chromatography on silica gel eluting with chloroform. The fractions containing the desired product were combined and evaporated to give an amorphous solid, which crystallized by standing in diisopropyl ether. The collected crystals were recrystallized from a mixture of diisopropyl ether and methanol to afford the title compound as colorless prisms (343 mg, 70.2%), mp 169—171 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.05—1.4 (4H, m), 1.25 (3H, t, $J$=7.4 Hz), 1.43 (3H, d, $J$=6.8 Hz), 1.53—2.0 (6H, m), 2.2—2.4 (1H, m), 2.30 (3H, s), 2.90 (2H, q, $J$=7.4 Hz), 3.74 (1H, d, $J$=17.1 Hz), 4.87 (1H, quintet, $J$=7.0 Hz), 5.00 (1H, d, $J$=17.1 Hz), 5.06 (1H, d, $J$=7.0 Hz), 5.39 (1H, d, $J$=8.5 Hz), 6.12 (1H, d, $J$=8.5 Hz), 7.16—7.4 (8H, m). IR (Nujol): 3350, 3280, 1685, 1630, 1570, 1550, 1375, 1200, 689 cm$^{-1}$. MS *m/z*: 489 ($M^+$+1)

**Single-Crystal X-Ray Analysis of 46** Colorless prismatic crystals were grown from a mixture of diisopropylether and methanol. Crystal data: $C_{29}H_{37}N_4O_{3.50}$, $Mr$=497.64, triclinic, lattice parameters ($a$=12.228 (9) Å, $b$=14.174 (9) Å, $c$=9.28 (1) Å, $\alpha$=109.20 (7)°, $\beta$=112.04 (6)°, $\gamma$=89.05 (7)°, $V$=1397 (2) Å$^3$, $Z$=2, $D_{calc.}$=1.182 g/cm$^3$, $F_{000}$=534.00, $\mu$ ($CuK_\alpha$)=6.29 cm$^{-1}$, space group P1, R-factor=0.079).

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