New 1,4-Benzodiazepin-2-one Derivatives as Gastrin/Cholecystokinin-B Antagonists

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A novel series of 1-aroylmethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives was prepared and evaluated for activity as gastrin/cholecystokinin (CCK)-B receptor antagonists. *In vitro* binding studies showed that some derivatives exhibited potent affinity for gastrin/CCK-B receptor and high selectivity over peripheral CCK (CCK-A) receptor. Furthermore, these compounds potently inhibited pentagastrin-induced gastric acid secretion upon intravenous administration in an *in vivo* model in rats. Structure–activity relationship studies of this series suggested that 1-[(*R*)-2,3-dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-(3-methylphenyl)urea (35b, YM022) was the optimal compound with IC_{50} values of 0.17, 0.11 and 150 nM for gastrin, CCK-B and CCK-A receptors, respectively, and an ED_{50} value of 9.5 nmol/kg (i.v.) in rats. The absolute configuration of the precursor of YM022, an (*R*)-3-amino-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivative ((*R*)-25), was determined by X-ray crystallographic analysis of its (*S*)-mandelate.

It would be expected that YM022, a potent and selective gastrin/CCK-B receptor antagonist, inhibits gastric acid secretion without inducing gastrin-mediated side-effects such as hypergastrinemia and hyperplasia of oxyntic mucosa.

Key words gastrin/CCK-B receptor antagonist; 1,4-benzodiazepine; YM022; structure–activity relationship; pentagastrin-induced gastric acid secretion

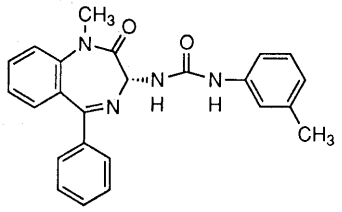
Since gastric acid secretion is activated by $(H^+ + K^+)$-ATPase (proton pump) in response to stimulation of muscarinic (M_3), histamine (H_2) or gastrin receptors on parietal cells, blockade of these receptors or inhibition of the enzyme can provide effective treatment for peptic ulcer. In fact, H_2 receptor antagonists and proton pump inhibitors[1-3] potently inhibit acid secretion and are widely used in the treatment of peptic ulcer. However, it has been reported that prolonged inhibition of acid secretion with these antagonists and inhibitors continuously stimulates G cells, resulting in hypergastrinemia and hyperplasia of oxyntic mucosa,[4,5] thereby leading to the acid rebound phenomenon.

Gastrin, a gastrointestinal polypeptide hormone which acts as a physiological mediator of acid secretion in response to meals, is closely related to cholecystokinin (CCK); they have identical C-terminal pentapeptide (–Gly–Trp–Met–Asp–Phe–NH_2) sequences. Cloning of the two subtypes of CCK receptor, namely the peripheral (CCK-A) and central type (CCK-B),[6,7] has indicated that the gastrin receptor is identical to the CCK-B receptor.[8] Research into the gastrin/CCK-B receptor has led to the discovery of potent antagonists such as L-365,260 (**1**)[9] and CI-988 (**2**)[10] (Fig. 1).

Recently, it was demonstrated that L-365,260, a selective gastrin/CCK-B receptor antagonist, inhibits pentagastrin-induced gastric acid secretion in mice.[11] Moreover, gastrin/CCK-B receptor antagonists have been shown to abolish almost completely[12] hypergastrinemia-induced increases in histamine and histidine decarboxylase (HDC) contents in enterochromaffin-like (ECL) cells and in oxyntic mucosal ECL cell density.[4,5] These results suggested that gastrin/CCK-B receptor antagonists might be valuable as new antiulcer agents and in the treatment of diseases caused by gastrin, such as Zollinger–Ellison syndrome and G cell hyperplasia.

The aim of our investigation was to discover potent and selective gastrin/CCK-B receptor antagonists which could be used clinically with reduced hypergastrinemia-related side-effects due to the gastrin receptor antagonistic mechanism.[12]

We noted that the 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one framework of L-365,260 can be readily synthesized. It was also reported that displacement of the methyl group with a 1-pyrrolidinylcarbonylmethyl group led to higher affinity for the gastrin/CCK-B receptor.[9] We considered that the β-carbonyl group at the N1-position might be important in increasing the affinity for gastrin/CCK-B receptors and focused our synthetic efforts on a series of



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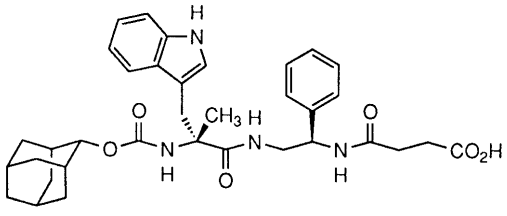

2

Fig. 1

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1-aroylmethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives.

Chemistry

The target compounds were prepared according to the methods of Bock *et al.*[13] (Chart 1). 1,3-Dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**)[14] obtained in two steps from 2-aminobenzophenone was treated with aroylmethyl bromides under phase-transfer conditions or with sodium hydride/DMF to give N1-alkylated compounds (**4**—**13**).

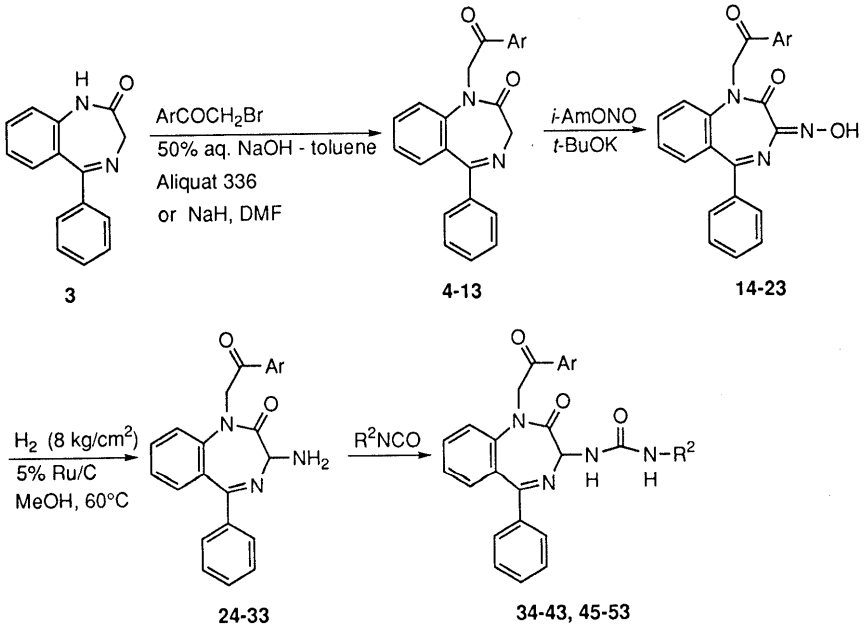


Chart 1

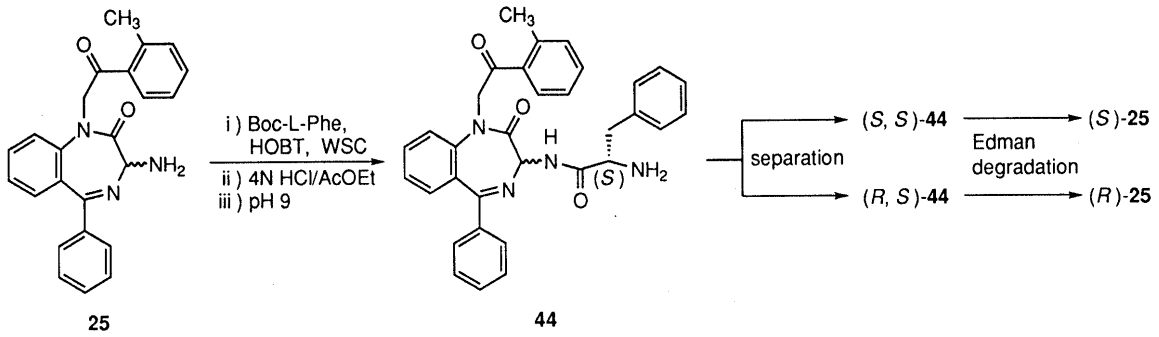


Chart 2

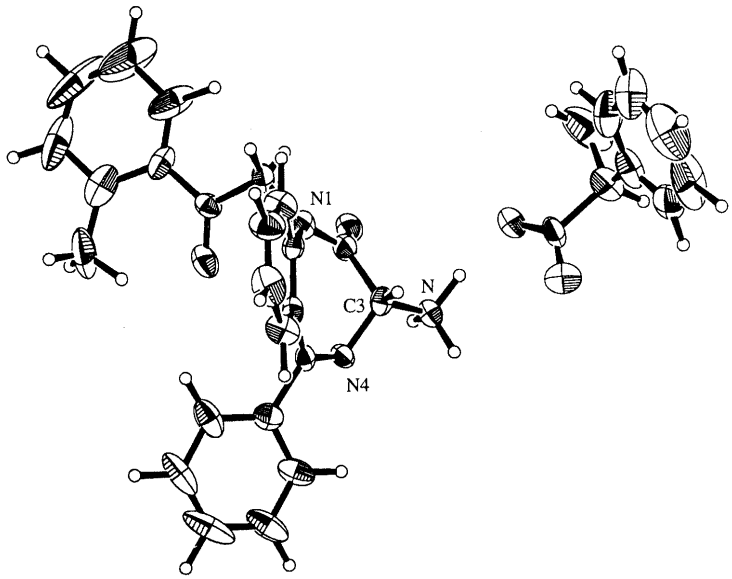
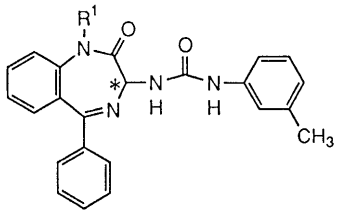
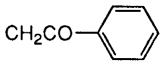
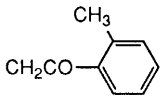
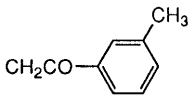
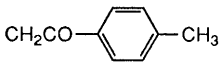
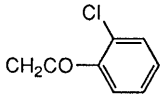
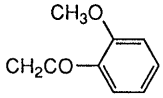
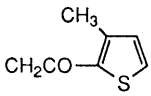
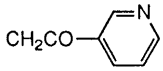
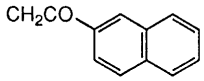
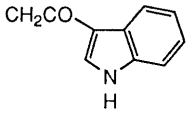


Fig. 2. An ORTEP Drawing of the Molecule of (*R*)-**25** (*S*)-Mandelate

Table 1. Structure–Activity Relationships of N1-Substituents



Compound	R^1	C3-stereo	Binding assay: IC_{50} (nM)			Inhibition (%) of acid secretion at 0.1 μmol/kg i.v. in SD rats
			CCK-A[a]	CCK-B[b]	Gastrin[c]	
1	CH_3	*R*	12000	29	10.03	15 (at 1 μmol/kg)
34		*RS*	660	1.18	0.69	53
35		*RS*	590	0.15	0.52	84
36		*RS*	2000	1.45	0.54	67
37		*RS*	430	0.22	0.48	93
38		*RS*	440	0.95	0.55	52
39		*RS*	780	0.52	NT	76
40		*RS*	54	0.16	0.34	87
41		*RS*	3300	4.23	NT	30
42		*RS*	> 1000	2.39	NT	40
43		*RS*	> 10000	7.46	NT	9

a) IC_{50} (nM) of [^{3}H]L-364,718 binding to rat pancreas membranes. *b*) IC_{50} (nM) of [^{125}I]CCK-8 binding to rat brain membranes. *c*) IC_{50} (nM) of [^{125}I]CCK-8 binding to guinea pig gastric glands. NT: not tested.

Compounds **4**—**13** were treated with potassium *tert*-butoxide and isoamyl nitrite in toluene to give the oximes (**14**—**23**). The 3-amino moiety in **24**—**33** was constructed by catalytic reduction of **14**—**23**, and subsequent reaction of **24**—**33** with 3-methylphenyl isocyanate gave racemic ureas (**34**—**43**).

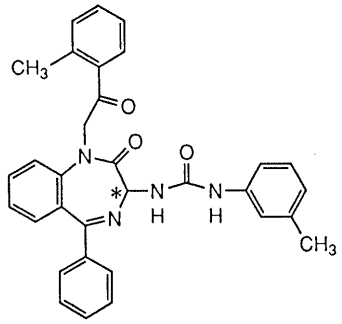
The racemic amine ((*RS*)-**25**) was optically resolved as the diastereomeric amides of L-phenylalanine (**44**) and subsequent Edman degradation retrieved both chiral amines in a small-scale synthesis, as described in the literature[13] (Chart 2). The racemic amine ((*RS*)-**25**) was also resolved by fractional crystallization of the (*R*)-amine as its (*S*)-mandelate without seeding in acetonitrile. Furthermore, the application of "resolution-racemization"[15] in a large-scale synthesis successfully produced (*R*)-**25** (*S*)-mandelate in an 85% yield. The enantiomeric integrity of (*R*)-**25** was assessed by high-performance liquid chromatography (HPLC) with a chiral stationary-phase column and found to be 99.6% ee. The absolute configuration of (*R*)-**25** was determined by X-ray crystallographic analysis of its (*S*)-mandelate[16] (Fig. 2).

The (*R*)-ureas (**35b**, **45**—**53**) were also prepared from (*R*)-**25** by treatment with isocyanates.

Biology

Binding Assay Rat brain membranes (for CCK-B

Table 2. Structure–Activity Relationships of Configuration at the C3-Position



Compd.	C3-stereo	Binding assay: IC_{50} (nM)			Inhibition (%) of acid secretion at 0.1 μmol/kg i.v. in SD rats
		CCK-A[a]	CCK-B[b]	Gastrin[c]	
35	*RS*	590	0.15	0.52	84
35a	*S*	1100	190	30	37 (at 1 μmol/kg)
35b (YM022)	*R*	150	0.11	0.17	81 (at 0.03 μmol/kg)

a) IC_{50} (nM) of [^{3}H]L-364,718 binding to rat pancreas membranes. *b*) IC_{50} (nM) of [^{125}I]CCK-8 binding to rat brain membranes. *c*) IC_{50} (nM) of [^{125}I]CCK-8 binding to guinea pig gastric glands.

binding)[17] and guinea pig gastric glands (for gastric binding)[18] were suspended in binding assay buffer with [^{125}I]CCK-8 and the appropriate concentration of unlabeled compounds. The suspensions were incubated at 25 °C for 2 h. Rat pancreas membranes (for CCK-A binding)[19] were suspended in binding assay buffer with [^{3}H]devazepide. The suspensions were incubated at 37 °C for 30 min. Incubation was terminated by filtration through glass fiber GF/B filters and washing four times with washing buffer. Specific binding was defined as the difference between total binding and nonspecific binding in the presence of 1 μM CCK-8 or 1 μM devazepide.

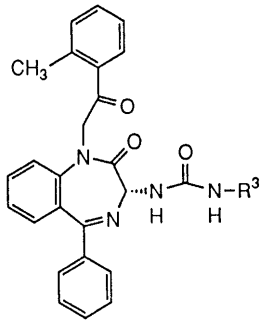
Determination of Gastric Acid Secretion in Anesthetized Rats Gastric acid secretion was measured in anesthetized rats using the pH-stat method.[20] The abdomen of the anesthetized rat was incised, and the stomach and duodenum were exposed. An acute gastric fistula was created in the forestomach using polyethylene tubing. Another portion of tubing was inserted into the stomach through a slit in the duodenum and held in place by a ligature around the pylorus. The stomach was perfused at a flow rate of 1.5 ml/min with saline adjusted to pH 7.0, gassed with 100% oxygen, heated to 37 °C and kept in a reservoir. Acid secretion was measured at pH 7.0 by the addition of 0.025 N NaOH to the reservoir. When basal acid secretion had stabilized, pentagastrin (20 nmol/kg/h) was infused *via* the femoral vein.

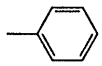
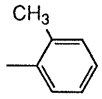
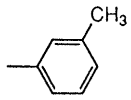
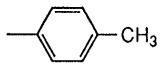
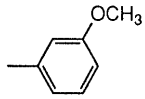
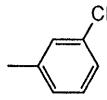
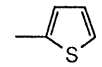
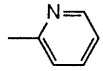
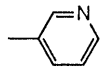
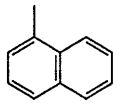
Test compounds were intravenously injected 1 h after the start of pentagastrin infusion. Data are expressed in the tables as maximal inhibition.

Results and Discussion

As the activity data in Table 1 show, all representative compounds (**34**—**43**) possessing N1-aroylmethyl groups proved to be more potent than L-365,260 in the blockade

Table 3. Structure–Activity Relationships at the C3-Urea Terminal



Compd.	R^3	Binding assay: IC_{50} (nM)		Inhibition (%) of acid secretion at 0.1 μmol/kg i.v. in SD rats
		CCK-B[a]	Gastrin[b]	
45		1.54	0.11	74
46		19.27	1.73	29
35b (YM022)		0.11	0.17	81 (at 0.03 μmol/kg)
47		1.67	0.15	58
48		1.10	0.11	79
49		2.81	NT	63
50		8.07	NT	26
51		18.78	NT	9
52		6.13	NT	33
53		7.64	NT	45

a) IC_{50} (nM) of [^{125}I]CCK-8 binding to rat brain membranes. *b*) IC_{50} (nM) of [^{125}I]CCK-8 binding to guinea pig gastric glands. NT: not tested.

of gastrin/CCK-B receptors in spite of their racemic forms. The results of radioligand ([^{125}I]CCK-8) binding studies for CCK-B receptors in rat brain membranes show that the affinity of N1-aroylmethyl derivatives was 4—193 times higher than that of L-365,260. The attachment of a phenacyl group to the N1-position increased CCK-B receptor binding affinity about 25-fold (*cf.* L-365,260 and **34**) while the introduction of a methyl substituent at the 2- or 4-position of the phenyl ring led to a greater than 100-fold improvement (*cf.* L-365,260, **35** and **37**). In addition, selectivity for the gastrin/CCK-B receptor was improved, with the CCK-A/CCK-B ratio increasing from

Table 4. Physical and Spectral Data for Compounds **4**—**13**

Compd.	Ar	Yield (%) (Method)	mp (°C)	^{1}H-NMR ($CDCl_3$) δ	MS m/z
4	Phenyl	90 (A)	131—133	3.95 (1H, d, J=11 Hz), 4.88 (1H, d, J=11 Hz), 5.14 (1H, d, J=18 Hz), 5.41 (1H, d, J=18 Hz), 7.10—8.10 (14H, m)	354 (M^+)
5	2-Methylphenyl	78 (A)	119—121	2.46 (3H, s), 3.93 (1H, d, J=11 Hz), 4.87 (1H, d, J=11 Hz), 5.01 (1H, d, J=20 Hz), 5.26 (1H, d, J=20 Hz), 7.05—7.75 (13H, m)	368 (M^+)
6	3-Methylphenyl	43 (A)	Amorphous	2.33 (3H, s), 3.94 (1H, d, J=11 Hz), 4.89 (1H, d, J=11 Hz), 5.17 (1H, d, J=18 Hz), 5.39 (1H, d, J=18 Hz), 7.05—7.85 (13H, m)	368 (M^+)
7	4-Methylphenyl	37 (A)	Amorphous	2.33 (3H, s), 3.93 (1H, d, J=11 Hz), 4.88 (1H, d, J=11 Hz), 5.04 (1H, d, J=19 Hz), 5.37 (1H, d, J=19 Hz), 7.06—7.85 (13H, m)	368 (M^+)
8	2-Chlorophenyl	Quant. (A)	Amorphous	3.90 (1H, d, J=11 Hz), 4.82 (1H, d, J=11 Hz), 5.00 (1H, d, J=18 Hz), 5.25 (1H, d, J=18 Hz), 7.10—7.70 (13H, m)	388 (M^+)
9	2-Methoxyphenyl	Quant. (A)	Amorphous	3.89 (3H, s), 3.94 (1H, d, J=11 Hz), 4.86 (1H, d, J=11 Hz), 5.02 (1H, d, J=18 Hz), 5.35 (1H, d, J=18 Hz), 6.87—7.92 (13H, m)	384 (M^+)
10	3-Methyl-2-thienyl	64 (B)	Amorphous	2.59 (3H, s), 3.95 (1H, d, J=11 Hz), 4.80 (1H, d, J=17 Hz), 4.88 (1H, d, J=11 Hz), 5.32 (1H, d, J=17 Hz), 6.97 (1H, d, J=5 Hz), 7.00—7.80 (10H, m)	374 (M^+)
11	3-Pyridyl	49 (B)	179—181	3.94 (1H, d, J=11 Hz), 4.88 (1H, d, J=11 Hz), 5.14 (1H, d, J=18 Hz), 5.39 (1H, d, J=18 Hz), 7.11—7.65 (10H, m), 8.20 (1H, dt, J=2, 8 Hz), 8.74 (1H, dd, J=2, 5 Hz), 9.15 (1H, d, J=2 Hz)	355 (M^+)
12	2-Naphthyl	51 (A)	153—155	(DMSO-d_6) 3.95 (1H, d, J=11 Hz), 4.80 (1H, d, J=11 Hz), 5.47 (2H, m), 7.20—8.53 (16H, m)	404 (M^+)
13	1-Benzyloxycarbonyl-3-indolyl	66 (B)	185—187	3.95 (1H, d, J=11 Hz), 4.90 (1H, d, J=11 Hz), 5.16 (2H, s), 5.37 (2H, s), 7.00—7.80 (16H, m), 8.00—8.40 (3H, m)	527 (M^+)

Table 5. Physical and Spectral Data for Compounds **14**—**23**

Compd.	Ar	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6) δ	MS m/z	*Anal.*[a]
14	Phenyl	55	209—213	5.51 (1H, d, J=20 Hz), 5.59 (1H, d, J=20 Hz), 7.29—8.01 (14H, m), 11.08 (1H, s)	383 (M^+)	$C_{23}H_{17}N_3O_3$ C, H, N
15	2-Methylphenyl	78	222—227	2.33 (3H, s), 5.35 (2H, s), 7.05—7.75 (13H, m), 11.08 (1H, s)	397 (M^+)	$C_{24}H_{19}N_3O_3$ C, H, N
16	3-Methylphenyl	28	195—198	2.36 (3H, s), 5.53 (2H, s), 7.20—7.90 (13H, m), 11.07 (1H, s)	397 (M^+)	$C_{24}H_{19}N_3O_3$ C, H, N
17	4-Methylphenyl	29	221—224	2.36 (3H, s), 5.48 (1H, d, J=10 Hz), 5.56 (1H, d, J=10 Hz), 7.24—7.94 (13H, m), 11.07 (1H, s)	397 (M^+)	$C_{24}H_{19}N_3O_3$ C, H, N
18	2-Chlorophenyl	64	216—219	5.30 (2H, s), 7.10—7.80 (13H, m), 11.04 (1H, s)	417 (M^+)	$C_{23}H_{16}ClN_3O_3$ C, H, Cl, N
19	2-Methoxyphenyl	80	Amorphous	($CDCl_3$) 3.87 (3H, s), 5.31 (2H, br), 6.78—7.90 (13H, m)	413 (M^+)	NT
20	3-Methyl-2-thienyl	72	193—198 (dec.)	2.49 (3H, s), 5.24 (2H, s), 7.00—8.00 (11H, m), 11.03 (1H, s)	403 (M^+)	$C_{22}H_{17}N_3O_3S$ C, S H (Calcd 4.25, Found 4.66), N (Calcd 10.41, Found 9.81)
21	3-Pyridyl	67	238—241	5.45 (2H, s), 7.10—8.00 (10H, m), 8.30 (1H, d, J=8 Hz), 8.81 (1H, br), 9.21 (1H, br), 10.98 (1H, br)	384 (M^+)	$C_{22}H_{16}N_4O_3$ C, H, N (Calcd 14.58, Found 13.81)
22	2-Naphthyl	57	Amorphous	5.55 (2H, br), 7.10—8.40 (16H, m)	433 (M^+)	NT
23	3-Indolyl	95	200—205 (dec.)	5.27 (1H, d, J=18 Hz), 5.51 (1H, d, J=18 Hz), 7.00—8.30 (13H, m), 8.48 (1H, d, J=3 Hz), 11.03 (1H, s), 12.09 (1H, s)	422 (M^+)	$C_{25}H_{18}N_4O_3$ C, H, N

a) Analytical results were within ±0.4% of the theoretical values unless otherwise noted. NT: not tested.

414 to over 1950. The effects of chloro and methoxy substituents were moderate (compounds **38** and **39**). Among the other aroylmethyl compounds (**40**—**43**), the (3-methyl-2-thenoyl)methyl derivative (compound **40**) showed strong affinity for the CCK-B receptors, comparable to that of compound **35**, although a lower CCK-A/CCK-B ratio was observed.

Compounds **35**, **37** and **40** also showed potent inhibition of acid secretion upon intravenous administration at a dose of 0.1 μmol/kg in rats, and the activities correlated with the IC_{50} values for the CCK-B receptors.

As shown in Table 2, the active enantiomer **35b** had the (*R*)-configuration at the C3-position, like L-365,260, and showed over 170 times greater affinity for the gastrin/CCK-B receptors than the (*S*)-enantiomer **35a**. It is noteworthy that the selectivity for gastrin/CCK-B receptors was retained in the case of **35a**, even though it was reported that the (*S*)-enantiomer of L-365,260 is highly selective for the CCK-A receptor.[9]

Since it appeared that 2- and 4-methylphenacyl groups

Table 6. Physical and Spectral Data for Compounds **24**—**33**

Compd.	Ar	Yield (%)	^{1}H-NMR ($CDCl_3$) δ	MS *m/z*
24	Phenyl	94	2.46 (2H, br), 4.65 (1H, s), 5.33 (2H, s), 7.00—8.10 (14H, m)	369 (M^+)
25	2-Methylphenyl	70	2.10 (2H, br), 2.44 (3H, s), 4.62 (1H, s), 5.20 (2H, s), 7.00—7.80 (13H, m)	384 ($M^+ + 1$)
26	3-Methylphenyl	86	2.12 (2H, br), 2.31 (3H, s), 4.62 (1H, s), 5.30 (2H, s), 7.08—7.78 (13H, m)	384 ($M^+ + 1$)
27	4-Methylphenyl	74	2.00 (2H, br), 2.34 (3H, s), 4.66 (1H, s), 5.34 (2H, s), 7.16—7.88 (13H, m)	384 ($M^+ + 1$)
28	2-Chlorophenyl	79	2.33 (2H, br), 4.62 (1H, s), 5.08 (1H, d, J=18 Hz), 5.30 (1H, d, J=18 Hz), 7.10—7.70 (13H, m)	403 (M^+)
29	2-Methoxyphenyl	73	2.87 (2H, br), 3.90 (3H, s), 4.63 (1H, s), 5.10 (1H, d, J=18 Hz), 5.28 (1H, d, J=18 Hz), 6.80—7.95 (13H, m)	399 (M^+)
30	3-Methyl-2-thienyl	69	2.38 (2H, br), 2.57 (3H, s), 4.65 (1H, s), 4.90 (1H, d, J=18 Hz), 5.31 (1H, d, J=18 Hz), 6.85—7.75 (11H, m)	389 (M^+)
31	3-Pyridyl	39	2.56 (2H, br), 4.67 (1H, s), 5.32 (2H, s), 7.10—7.70 (10H, m), 8.18 (1H, dt, J=2, 8 Hz), 8.74 (1H, dd, J=2, 5 Hz), 9.14 (1H, d, J=2 Hz)	370 (M^+)
32	2-Naphthyl	78	2.78 (2H, br), 4.71 (1H, s), 5.37 (1H, d, J=18 Hz), 5.59 (1H, d, J=18 Hz), 7.05—8.42 (16H, m)	420 ($M^+ + 1$)
33	3-Indolyl	37	3.23 (2H, br), 4.48 (1H, s), 5.17 (1H, d, J=18 Hz), 5.46 (1H, d, J=18 Hz), 7.00—8.43 (13H, m), 12.00 (1H, br)	409 ($M^+ + 1$)

Table 7. Physical and Spectral Data for Compounds **34**—**43** (R^2 = 3-methylphenyl, C3-stereo = *RS*)

Compd.	Ar	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6) δ	MS *m/z*	*Anal.*[a]
34	Phenyl	77	212—214	($CDCl_3$) 2.24 (3H, s), 5.17 (1H, d, J=18 Hz), 5.44 (1H, d, J=18 Hz), 5.72 (1H, d, J=8 Hz), 6.70—7.95 (20H, m)	503 ($M^+ + 1$)	$C_{31}H_{26}N_4O_3$ C, H, N
35	2-Methylphenyl	91	141—143	($CDCl_3$) 2.25 (3H, s), 2.38 (3H, s), 5.09 (1H, d, J=17 Hz), 5.30 (1H, d, J=17 Hz), 5.72 (1H, d, J=7 Hz), 6.80—7.60 (19H, m)	517 ($M^+ + 1$)	$C_{32}H_{28}N_4O_3$ C, H, N
36	3-Methylphenyl	65	225—227	($CDCl_3$) 2.27 (3H, s), 2.32 (3H, s), 5.24 (1H, d, J=19 Hz), 5.42 (1H, d, J=19 Hz), 5.74 (1H, d, J=8 Hz), 6.80—7.70 (19H, m)	517 ($M^+ + 1$)	$C_{32}H_{28}N_4O_3$ C, H, N
37	4-Methylphenyl	62	193—196	($CDCl_3$) 2.28 (3H, s), 2.33 (3H, s), 5.21 (1H, d, J=17 Hz), 5.42 (1H, d, J=17 Hz), 5.71 (1H, d, J=7 Hz), 6.70—7.80 (19H, m)	517 ($M^+ + 1$)	$C_{32}H_{28}N_4O_3$ C, H, N
38	2-Chlorophenyl	92	191—193	2.25 (3H, s), 5.40 (3H, m), 6.75—7.90 (18H, m), 8.98 (1H, s)	537 ($M^+ + 1$)	$C_{31}H_{25}ClN_4O_3 \cdot 0.3H_2O$ C, H, Cl, N
39	2-Methoxyphenyl	69	160—163	2.26 (3H, s), 3.96 (3H, s), 5.34 (2H, s), 5.40 (1H, d, J=9 Hz), 6.77 (1H, d, J=6 Hz), 7.05—7.73 (17H, m), 9.01 (1H, s)	533 ($M^+ + 1$)	$C_{32}H_{28}N_4O_4 \cdot 0.5H_2O$ C, H, N
40	3-Methyl-2-thienyl	74	150—153	2.25 (3H, s), 2.53 (3H, s), 5.32 (2H, s), 5.42 (1H, d, J=10 Hz), 6.78 (1H, d, J=5 Hz), 7.00—7.80 (14H, m), 7.94 (1H, d, J=6 Hz), 9.01 (1H, s)	523 ($M^+ + 1$)	$C_{30}H_{26}N_4O_3S \cdot 0.35H_2O$ C, H, N, S
41	3-Pyridyl	76	239—241	2.25 (3H, s), 5.42 (1H, d, J=10 Hz), 5.58 (1H, d, J=18 Hz), 5.68 (1H, d, J=18 Hz), 6.77 (1H, d, J=8 Hz), 7.05—7.80 (14H, m), 8.34 (1H, d, J=10 Hz), 8.84 (1H, d, J=3 Hz), 8.99 (1H, s), 9.20 (1H, s)	504 ($M^+ + 1$)	$C_{30}H_{25}N_5O_3$ C, H, N
42	2-Naphthyl	75	204—206	2.25 (3H, s), 5.42 (1H, d, J=10 Hz), 5.69 (1H, d, J=16 Hz), 5.78 (1H, d, J=16 Hz), 6.76 (1H, d, J=6 Hz), 7.00—8.20 (19H, m), 8.80 (1H, s), 9.00 (1H, s)	553 ($M^+ + 1$)	$C_{35}H_{28}N_4O_3$ C, H, N
43	3-Indolyl	79	232—237	2.26 (3H, s), 5.34 (1H, d, J=17 Hz), 5.44 (1H, d, J=8 Hz), 5.50 (1H, d, J=17 Hz), 6.78 (1H, d, J=8 Hz), 7.10—7.75 (16H, m), 8.10 (1H, d, J=8 Hz), 8.52 (1H, d, J=2 Hz), 9.02 (1H, s), 12.08 (1H, br)	542 ($M^+ + 1$)	$C_{33}H_{27}N_5O_3 \cdot 0.1H_2O$ C, H, N

a) Analytical results were within ±0.4% of the theoretical values unless otherwise noted.

were the most effective substituents at the N1-position, our investigation focused on modification of the phenyl moiety at the C3-urea terminal in the (*R*)-enantiomers. The results of modification at the urea terminal are presented in Table 3. Although several replacements of the phenyl substituent and exchange of the phenyl for other aryl groups were attempted (compounds **45**—**53**), no remarkable improvement was observed.

Compound **35b** (YM022), one of the most potent and selective gastrin/CCK-B receptor antagonists of this series, was selected for further evaluation of its antisecretory activity *in vivo* in comparison with that of other agents. The effects of YM022, L-365,260, CI-988, famotidine (H_2 receptor antagonist) and omeprazole (proton pump inhibitor) on pentagastrin-induced gastric acid secretion in anesthetized rats are shown in Fig. 3. YM022 given in an intravenous dose range of 0.003—0.03 μmol/kg inhibited gastric acid secretion induced by 20 nmol/kg/h

Table 8. Physical and Spectral Data for Compounds **35a**, **35b** and **45**—**53** (Ar = 2-methylphenyl, C3-stereo = *R*)

Compd.	R^2	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$) δ	MS *m/z*	$[\alpha]_D^{20}$	*Anal.*[a]
45	Phenyl	92	229—231	2.39 (3H, s), 5.11 (1H, d, J=20 Hz), 5.29 (1H, d, J=20 Hz), 5.71 (1H, d, J=10 Hz), 6.93—7.60 (20H, m)	503 (M^++1)	+128.7° (c=1.00, $CHCl_3$)	$C_{31}H_{26}N_4O_3$ C, H, N
46	2-Methylphenyl	79	178—181	2.31 (3H, s), 2.39 (3H, s), 5.11 (1H, d, J=15 Hz), 5.33 (1H, d, J=15 Hz), 5.73 (1H, d, J=5 Hz), 6.56 (1H, s), 6.80 (1H, br), 7.08—7.63 (17H, m)	517 (M^++1)	+151.8° (c=1.03, CH_2Cl_2)	$C_{32}H_{28}N_4O_3$ C, H, N
35a[b]	3-Methylphenyl	87	194—198	Identical with those of racemate **35**	517 (M^++1)	−136.9° (c=1.01, CH_2Cl_2)	$C_{32}H_{28}N_4O_3$ C, H, N
35b	3-Methylphenyl	89	197—199	Identical with those of racemate **35**	517 (M^++1)	+138.1° (c=0.99, CH_2Cl_2)	$C_{32}H_{28}N_4O_3$ C, H, N
47	4-Methylphenyl	91	256—259	2.28 (3H, s), 2.39 (3H, s), 5.11 (1H, d, J=20 Hz), 5.30 (1H, d, J=20 Hz), 5.73 (1H, br s), 6.88—7.60 (19H, m)	517 (M^++1)	+149.6° (c=0.39, DMF)	$C_{32}H_{28}N_4O_3$ C, H, N
48	3-Methoxyphenyl	63	192—195	2.40 (3H, s), 3.74 (3H, s), 5.12 (1H, d, J=18 Hz), 5.28 (1H, d, J=18 Hz), 5.72 (1H, br s), 6.57—7.61 (19H, m)	533 (M^++1)	+151.5° (c=0.31, CH_2Cl_2)	$C_{32}H_{28}N_4O_4$ C, H, N
49	3-Chlorophenyl	74	132—133	2.39 (3H, s), 5.13 (1H, d, J=18 Hz), 5.28 (1H, d, J=18 Hz), 5.71 (1H, d, J=8 Hz), 6.90—7.63 (19H, m)	537 (M^++1)	+115.8° (c=1.00, $CHCl_3$)	$C_{31}H_{25}ClN_4O_3 \cdot 0.2H_2O$ C, H, Cl, N
50	2-Thienyl	77	201—205	2.38 (3H, s), 5.09 (1H, d, J=18 Hz), 5.32 (1H, d, J=18 Hz), 5.70 (1H, d, J=8 Hz), 6.60—7.65 (18H, m)	509 (M^++1)	+132.0° (c=1.01, CH_2Cl_2)	$C_{29}H_{24}N_4O_3S \cdot 0.45H_2O$ C, H, N, S
51	2-Pyridyl	66	138—140	(DMSO-d_6) 2.33 (3H, s), 5.39 (2H, s), 5.47 (1H, d, J=8 Hz), 6.96—8.25 (18H, m), 9.60 (1H, s)	504 (M^++1)	+136.4° (C=0.56, CH_2Cl_2)	$C_{30}H_{25}N_5O_3 \cdot 0.6H_2O$ C, H, N
52	3-Pyridyl	59	243—245	(DMSO-d_6) 2.34 (3H, s), 5.37 (3H, m), 7.26—8.16 (17H, m), 8.55 (1H, s), 9.24 (1H, s)	504 (M^++1)	+109.5° (c=0.22, CH_2Cl_2)	$C_{30}H_{25}N_5O_3$ C, H, N
53	1-Naphthyl	86	135—137	(DMSO-d_6) 2.35 (3H, s), 5.40 (2H, s), 5.46 (1H, d, J=8 Hz), 7.27—8.24 (21H, m), 9.11 (1H, s)	553 (M^++1)	+156.9° (c=0.63, DMF)	$C_{35}H_{28}N_4O_3 \cdot 0.3H_2O$ C, H, N

a) Analytical results were within ±0.4% of the theoretical values unless otherwise noted. *b*) C3-stereo = *S*.

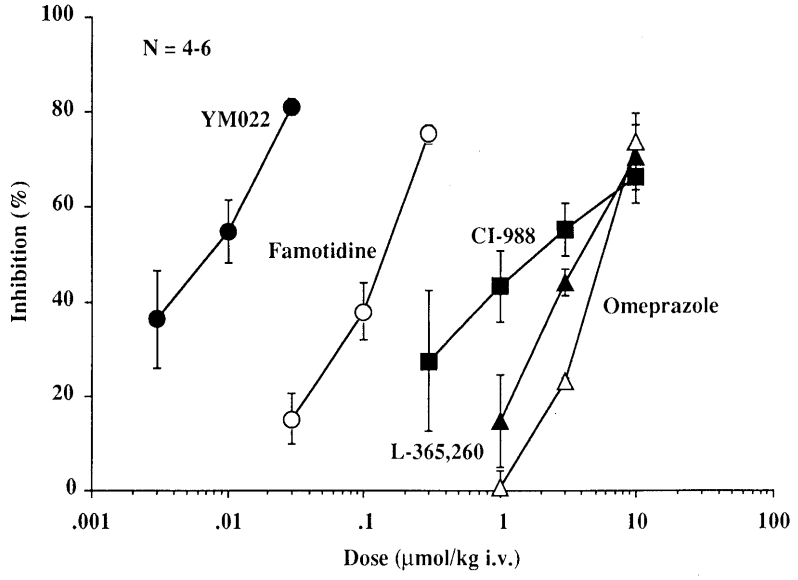


Fig. 3. Effects of YM022 and Reference Compounds on Pentagastrin-Induced Gastric Acid Secretion in Stomach-Perfused Anesthetized Rats

of pentagastrin in a dose-dependent manner. The degree of inhibition was 81% at 0.03 μmol/kg and the calculated ED_{50} was 9.5 nmol/kg. This effect was more potent than that of any of the other antisecretory agents.

Additionally, it is noteworthy that YM022 is a pure gastrin/CCK-B receptor antagonist. It is well known that H_2 receptor antagonists and L-365,260 inhibit gastric acid secretion induced not only by histamine but also by bethanechol and pentagastrin,[21] but that YM022 is only effective against the secretion induced by pentagastrin.[22] We therefore expected that such a pure gastrin/CCK-B receptor antagonist would inhibit gastric acid secretion

without gastrin-mediated side-effects such as hypergastrinemia and hyperplasia of oxyntic mucosa, representing a novel antiulcer agent.

Conclusions

Among the novel class of 1-aroylmethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives described here, compound **35b** (YM022) is the optimal compound. It is a potent and selective gastrin/CCK-B receptor antagonist, and was also found to be a pure gastrin/CCK-B receptor antagonist which inhibits only pentagastrin-induced gastric acid secretion.

We therefore consider that YM022 is a promising candidate for development as a novel antiulcer agent, with reduced side-effects associated with hypergastrinemia, an unavoidable characteristic of long-acting H_2 receptor antagonists and proton pump inhibitors.

Experimental

Melting points were determined on a Yanaco MP-500D and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL FX-90, a JEOL FX-100 and a JEOL FX-270 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 (EI) or a JEOL JMS DX-300 (FAB) mass spectrometer. Elemental analysis was performed with a Yanaco MT-5. X-Ray diffraction measurements were made with a Rigaku AFC5R diffractometer using Cu K_α radiation. Column chromatography was performed on silica gel (Merck Kieselgel 60, 70—230 mesh).

1,3-Dihydro-1-phenacyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (4). Method A A 50% aqueous NaOH solution (18 ml) was added dropwise to a solution of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**)[14] (3.54 g, 15.0 mmol), Aliquat 336 (0.13 g, 0.3 mmol) and 2-bromoacetophenone (10.45 g, 52.5 mmol) in toluene (60 ml) at 5 °C, and the mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with water (150 ml) and extracted with toluene (2 × 100 ml). The combined organic extracts were washed with water (2 × 100 ml) and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1) to give **4** (4.80 g, 90%): mp 131—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (1H, d, J = 11 Hz, one of C3-H), 4.88 (1H, d, J = 11 Hz, one of C3-H), 5.14 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COPh), 5.41 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COPh), 7.10—8.10 (14H, m, aromatic). EI-MS m/z: 354 (M^+). With this method, compounds **5**—**9** and **12** in Table 4 were synthesized.

1,3-Dihydro-1-nicotinoylmethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (11). Method B Sodium hydride (60% in mineral oil, 0.88 g, 22.0 mmol) was added to a solution of **3**[14] (1.89 g, 8.0 mmol) in *N*,*N*-dimethylformamide (DMF, 40 ml) at room temperature, and the mixture was stirred for 15 min. 3-Bromoacetylpyridine hydrobromide (3.37 g, 16.8 mmol) was added portionwise at 5 °C and the stirring was continued at room temperature for 4 h. The reaction was stopped with water (100 ml) and the mixture was extracted with toluene–AcOEt (1 : 1, 2 × 50 ml). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 4) to give **11** (1.34 g, 49%) after crystallization from ether: mp 179—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.94 (1H, d, J = 11 Hz, one of C3-H), 4.88 (1H, d, J = 11 Hz, one of C3-H), 5.14 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COAr), 5.39 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COAr), 7.11—7.65 (10H, m, aromatic), 8.20 (1H, dt, J = 2, 8 Hz, C4-H of pyridine), 8.74 (1H, dd, J = 2, 5 Hz, C6-H of pyridine), 9.15 (1H, d, J = 2 Hz, C2-H of pyridine). EI-MS m/z: 355 (M^+). With this method, compounds **10** and **13** in Table 4 were synthesized.

1,3-Dihydro-3-hydroxyimino-1-phenacyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (14). Method C Compound **4** (4.61 g, 13.0 mmol) and potassium *tert*-butoxide (3.65 g, 32.5 mmol) were stirred in toluene (65 ml) at −20 °C. After 45 min, isoamyl nitrite (1.83 g, 15.6 mmol) was added dropwise and stirring was continued for 2 h below −15 °C. The reaction mixture was poured into a mixture of ice (130 g), AcOH (6.5 ml) and AcOEt (130 ml) with vigorous stirring. After 1 h, the aqueous phase was extracted with AcOEt (130 ml). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was crystallized from toluene (20 ml) to give **14** (2.74 g, 55%): mp 209—213 °C. ^{1}H-NMR (DMSO-d_6) δ: 5.51 (1H, d, J = 20 Hz, one of C$\underline{H}_2$COPh), 5.59 (1H, d, J = 20 Hz, one of C$\underline{H}_2$COPh), 7.29—8.01 (14H, m, aromatic), 11.08 (1H, s, NOH): EI-MS m/z: 383 (M^+). *Anal.* Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.26; H, 4.63; N, 10.79. With this method, compounds **15**—**23** in Table 5 were synthesized.

3-Amino-1,3-dihydro-1-phenacyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (24). Method D A mixture of **14** (0.84 g, 2.2 mmol) and 5% ruthenium on activated charcoal (0.21 g) in MeOH (20 ml) was stirred overnight at 60 °C under hydrogen (8 kg/cm^2). The cooled solution was filtered and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 30 : 1) to give **24** (0.76 g, 94%) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (2H, br, NH_2), 4.65 (1H, s, C3-H), 5.33 (2H, s, C$\underline{H}_2$COPh), 7.00—8.10 (14H, m, aromatic). EI-MS m/z: 369 (M^+). With this method, compounds **25**—**33** in Table 6 were synthesized.

Optical Resolution of 3-Amino-1,3-dihydro-1-(2-methylphenacyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (25). (*S*)-2-Amino-*N*-[(*S*)-2,3-dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]benzenepropanamide [(*S*,*S*)-44] and Its (*S*,*R*)-Diastereomer A solution of racemic **25** (500 mg, 1.30 mmol) in dry DMF (3.5 ml) was successively treated with Boc-L-phenylalanine (363 mg, 1.37 mmol), 1-hydroxybenzotriazole (185 mg, 1.37 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (262 mg, 1.37 mmol) and Et_3N (139 mg, 1.37 mmol). The mixture was stirred at room temperature for 1 h and partitioned between AcOEt and 10% aqueous citric acid solution. The aqueous phase was extracted with AcOEt and the combined organic extracts were washed with 1 N NaOH, water and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2 : AcOEt = 9 : 1) to give a mixture of diastereomeric amide (739 mg, 90%).

The above diastereomeric amide mixture (700 mg, 1.11 mmol) was treated with 4 N HCl in AcOEt (2.75 ml) at 5 °C for 1.5 h and diluted with AcOEt. The mixture was basified (pH 9) with 1 N NaOH and the aqueous phase was extracted with AcOEt. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was separated by silica gel column chromatography (AcOEt) to give (*S*,*S*)-**44** (298 mg, quant.) and (*S*,*R*)-**44** (218 mg, 37%).

(*S*,*S*)-**44**: ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, CH_3), 2.83 (1H, dd, J = 10, 14 Hz, one of C$\underline{H}_2$Ph), 3.36 (1H, dd, J = 3, 14 Hz, one of C$\underline{H}_2$Ph), 3.72 (1H, dd, J = 4, 10 Hz, C$\underline{H}$CH$_2$Ph), 5.14 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COPh), 5.27 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COPh), 5.69 (1H, d, J = 8 Hz, C3-H), 7.14—7.63 (19H, m, aromatic), 8.99 (1H, d, J = 8 Hz, NHCO). EI-MS m/z: 530 (M^+).

(*S*,*R*)-**44**: ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, CH_3), 2.70 (1H, dd, J = 10, 14 Hz, one of C$\underline{H}_2$Ph), 3.37 (1H, dd, J = 4, 14 Hz, one of C$\underline{H}_2$Ph), 3.74 (1H, dd, J = 4, 10 Hz, C$\underline{H}$CH$_2$Ph), 5.14 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COPh), 5.31 (1H, d, J = 18 Hz, one of C$\underline{H}_2$COPh), 5.67 (1H, d, J = 8 Hz, C3-H), 7.14—7.63 (19H, m, aromatic), 8.98 (1H, d, J = 8 Hz, NHCO). EI-MS m/z: 530 (M^+).

Edman Degradation of (*S*,*S*)-44 and (*S*,*R*)-44 Phenylisothiocyanate (1.08 g, 8.0 mmol) was added to a solution of (*S*,*S*)-**44** (3.87 g, 7.3 mmol) in CH_2Cl_2 (9 ml). The mixture was refluxed for 10 min and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2 : AcOEt = 93 : 7) to give the intermediate thiourea (4.69 g, 97%). The thiourea was dissolved in trifluoroacetic acid (TFA, 7 ml) and warmed to 50 °C for 30 min. The mixture was evaporated *in vacuo* and purified by silica gel column chromatography (CH_2Cl_2 : MeOH : AcOH : H_2O = 93 : 7 : 0.7 : 0.7) to give (*S*)-**25** trifluoroacetate, which was converted to the free base with 1 N NaOH in CH_2Cl_2. The dried ($MgSO_4$) organic phase was evaporated *in vacuo* to give (*S*)-**25** (2.14 g, 80%) as a foam: $[\alpha]_D^{20}$ −190.4° (c = 1.00, CH_2Cl_2).

(*R*)-**25** was prepared similarly from (*S*,*R*)-**44**: $[\alpha]_D^{20}$ +188.2° (c = 0.99, CH_2Cl_2).

Resolution-racemization[15] of 3-Amino-1,3-dihydro-1-(2-methylphenacyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (25) (*S*)-(+)-Mandelic acid (0.98 g, 6.4 mmol) was added to a solution of racemic **25** (2.75 g, 7.2 mmol) in acetonitrile (55 ml), and the mixture was stirred for 30 min at room temperature. The resulting slurry was treated with 3,5-dichlorosalicylaldehyde (41 mg, 0.21 mmol) and stirred for an additional 18 h. The crystalline product was collected by filtration and washed with acetonitrile (15 ml) to give the optically pure (*R*)-**25** (*S*)-mandelate (2.94 g, 85%): mp 157—160 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s, CH_3), 4.62 (1H, s, C3-H), 4.87 (1H, s, C2-H of (*S*)-mandelic acid), 5.34 (2H, s,

$C\underline{H}_2COAr$), 7.22—7.85 (18H, m, aromatic); 99.6% ee. $[\alpha]_D^{20}$ +152.5° (c=1.00, MeOH). *Anal.* Calcd for $C_{24}H_{21}N_3O_2 \cdot C_8H_8O_3$: C, 71.76; H, 5.46; N, 7.85. Found: C, 71.64; H, 5.49; N, 7.79. The optical purity of (*R*)-**25** was measured by HPLC under the following conditions; column, α-AGP (4 mm × 100 mm); column temperature, 30 °C; eluent, 0.02 M phosphate buffer (adjusted to pH 4.5)–2-propanol (93 : 7); flow rate, 1.0 ml/min; detector, Hitachi L-4000 UV Detector; detector wavelength, 240 nm. With this method, the optically pure (*S*)-amine **25** (*R*)-mandelate was synthesized in 88% yield. The melting point and ^{1}H-NMR data were identical with those of (*R*)-amine **25** (*S*)-mandelate; 99.6% ee. $[\alpha]_D^{20}$ −151.2° (c=1.00, MeOH). *Anal.* Calcd for $C_{24}H_{21}N_3O_2 \cdot C_8H_8O_3$: C, 71.76; H, 5.46; N, 7.85. Found: C, 71.74; H, 5.56; N, 7.86.

1-(2,3-Dihydro-2-oxo-1-phenacyl-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-3-(3-methylphenyl)urea (34). Method E A solution of 3-methylphenyl isocyanate (0.27 g, 2.0 mmol) in tetrahydrofuran (THF, 3 ml) was added to a solution of 3-amino-1,3-dihydro-1-phenacyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one **24**, (0.74 g, 2.0 mmol) in THF (5 ml), and the mixture was stirred for 4 h at room temperature. The solvent was evaporated *in vacuo* and the residue was recrystallized from toluene–*n*-hexane to give **34** (0.78 g, 77%): mp 212—214 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s, CH_3), 5.17 (1H, d, J=18 Hz, one of $C\underline{H}_2COPh$), 5.44 (1H, d, J=18 Hz, one of $C\underline{H}_2COPh$), 5.72 (1H, d, J=8 Hz, C3-H), 6.70—7.95 (20H, m, NHCONH and aromatic). FAB-MS (Pos.) m/z: 503 $(M+1)^+$. *Anal.* Calcd for $C_{31}H_{26}N_4O_3$: C, 74.09; H, 5.21; N, 11.15. Found: C, 74.21; H, 5.26; N, 11.08. With this method, compounds **35**—**43**, **35a**, **35b** and **45**—**53** in Tables 7 and 8 were synthesized.

X-Ray Crystallographic Analysis of (*R*)-25 (*S*)-Mandelate[16] Suitable crystals ($C_{24}H_{21}N_3O_2 \cdot C_8H_8O_3$) for X-ray diffraction studies were formed from 2-propanol. Crystal data: crystal system, hexagonal; space group, $P6_1$ (#169); lattice parameters, a=16.210(2) Å, c=18.581(2) Å, V=4228(1) Å^3; $D_{calc.}$, 1.262 g/cm^3; Z value, 6; F_{000}, 1692.00; final R value, R=0.055, R_W=0.036.

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