(3*R*)-*N*-(1-(*tert*-Butylcarbonylmethyl)-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl)-*N*′-(3-(methylamino)phenyl)urea (YF476): A Potent and Orally Active Gastrin/CCK-B Antagonist

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Received September 25, 1996[⊗]

A number of new 1,4-benzodiazepin-2-one-based gastrin/CCK-B receptor antagonists related to the archetypal analogue L-365,260, and more closely to the recently reported compound YM022, have been synthesized and evaluated for biological activity. The compounds were screened for their ability to inhibit the binding of [^{125}I]CCK-8 to gastrin/CCK-B receptors prepared from rat brains and that of [^{3}H]L-364,718 to CCK-A receptors from rat pancreas, and were shown to be potent and selective ligands for the gastrin/CCK-B receptor. Functional studies *in vivo* demonstrated the compounds to be antagonists of the receptor as evidenced by their ability to inhibit pentagastrin-induced gastric acid secretion in anesthetized rats. More extensive evaluation *in vivo* included determination of ED_{50} values in the rat acid secretion model for selected compounds and an examination of the effect of these compounds on pentagastrin-induced gastric acid secretion in Heidenhain pouch dogs following oral and intravenous administration. Two compounds, i.e. (3*R*)-*N*-[1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-(methylamino)phenyl]urea, **15c** (YF476), and (3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-(dimethylamino)phenyl]urea hydrochloride, **15d**, showed potent dose-dependent effects in both models with the former showing excellent oral bioavailability and an ED_{50} of 21nmol/kg po in dogs. **15c** is currently under clinical investigation for the treatment of gastro-oesophagal reflux disease (GORD).

Introduction

Gastric acid secretion is controlled by the action of (H^+,K^+)-ATPase (the proton pump) in response to stimulation of muscarinic (M_3), histamine (H_2), or gastrin receptors by their respective agonists. H_2 receptor antagonists and proton pump inhibitors are highly effective in reducing acid secretion[1−3] and have been the treatments of choice for peptic ulcer disease for a number of years. However, prolonged inhibition of secretion with either of these agents causes continuous stimulation of G-cells, resulting in hypergastrinaemia which is believed to lead to hyperplasia of the oxyntic mucosa[4,5] and the so-called acid rebound phenomenon. In addition, long-term administration of omeprazole, the prototypical proton pump inhibitor, results in the growth of gastric carcinomas in rats,[6] although such an effect has not been observed in humans.[7]

With the discovery of evidence for the involvement of the pathogen *Helicobacter pylori* in the majority of peptic ulcer cases, clinical prescribing regimens have changed. The increasing use of combination therapies has meant that antisecretory drugs are given for much shorter periods of time and any rebound effect is less important. However, *Helicobacter pylori* is not implicated in the pathogenesis of gastro-oesophagal reflux disease (GORD), and with longer treatment courses required with existing antisecretory drugs for treatment of this disorder, hypergastrinaemia, acid rebound, and relapse again present a problem.

Gastrin-17 is a heptadecapeptide hormone which acts as a physiological mediator of acid secretion in response to meals. It is closely related to cholecystokinin (CCK), the C-terminal pentapeptide portion being identical. Cloning of the gastrin and CCK receptors, designated CCK-A (the peripheral receptor) and CCK-B (the central receptor), has shown the gastrin and CCK-B receptors to be identical.[8] More recently there has been convincing evidence for a second gastrin receptor, which can bind the glycine-extended form of gastrin-17 and which appears to be responsible for the mitogenic effects of gastrin.[9]

With the above in mind, we decided to investigate inhibitors of the gastrin/CCK-B receptor as an alternative method of reducing gastric acid secretion, or indeed as an adjunct to longer term treatment with known inhibitors of acid secretion, which would avoid gastrin-mediated side effects and hence provide a useful new treatment for GORD and other gastrointestinal disorders.

We have recently described the discovery of a potent series of 1,4-benzodiazepin-2-one gastrin/CCK-B receptor antagonists related to the archetypal analogue L-365,260 (**1**, Figure 1) with sub-nanomolar affinities for the receptor, the compound YM022 (**2**)[10] being the optimal structure in our series.[11] Further improvement of the *in vivo* activity and bioavailability of these derivatives by incorporation of 1-alkylcarbonylmethyl and 5-(2-pyridyl) substituents has been communicated in preliminary form.[12,13]

In this paper we would like to present the structure−activity relationship studies which led us to the discovery of (3*R*)-*N*-[*1*-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-

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⊗ Abstract published in *Advance ACS Abstracts,* January 1, 1997.

S0022-2623(96)00669-3 CCC: $14.00

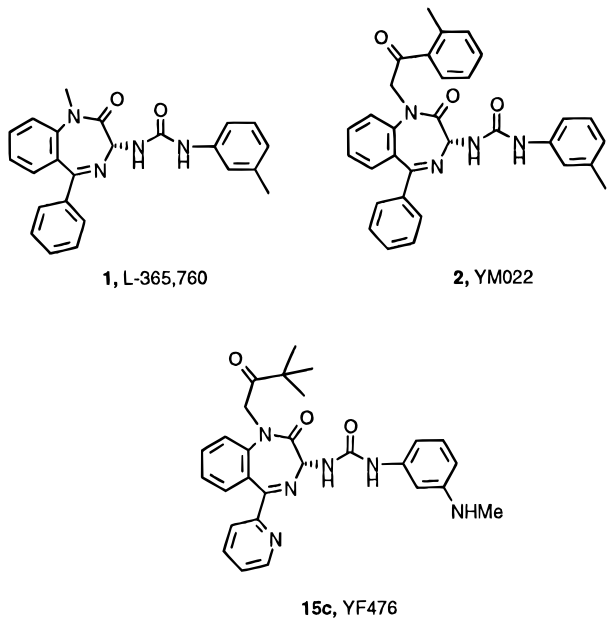

Figure 1. Structures of benzodiazepine-based gastrin/CCK-B ligands.

2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-(methylamino)phenyl]urea, (**15c**, YF476), a novel, potent gastrin/CCK-B antagonist incorporating a combination of these and other modifications and which is currently undergoing clinical trials.

Chemistry

Two approaches have previously been applied successfully to the synthesis of 3-substituted 1,4-benzodiazepines. The first involves construction of the parent heterocycle, followed by functionalization. In the case of 3-amino derivatives, this has been best achieved by formation of an oxime at the 3-position of the 1-alkylated 1,4-benzodiazepine, followed by catalytic hydrogenation.[14] As previously reported, YM022 was readily prepared using this procedure.[11] This method turned out not to be generally applicable, however, as attempts to adapt the chemistry for use in compounds with a 5-(2-pyridyl) substituent on the benzodiazepine scaffold failed at the final stage (Figure 2) when imine isomerization to give **8** was observed in addition to the desired oxime reduction.

The alternative strategy for the synthesis of 3-substituted 1,4-benzodiazepin-2-ones requires N-acylation of a 2-aminobenzoyl derivative with a carboxylic acid containing a suitable masked amine group X at the α-position (Figure 3). The amine functionality is eventually revealed and the intermediate cyclized to give the desired benzodiazepine.

This approach has been used to provide 3-amino-substituted benzodiazepines in good yield by coupling of 2-aminobenzophenone to α-(isopropylthio)-*N*-(benzyloxycarbonyl)glycine[15] (i.e. Figure 3, X = isopropylthio), followed by mercuric chloride-induced displacement of the thioether group with ammonia and finally acid-catalyzed cyclization to provide the desired benzodiazepine.[16] In our hands, this method proved very useful for the small-scale preparation of a wide range of protected 3-amino-5-arylbenzodiazepines and was highly amenable to producing series of analogues with 1-, 3-, and 5-position variations. Scale-up reactions, however,

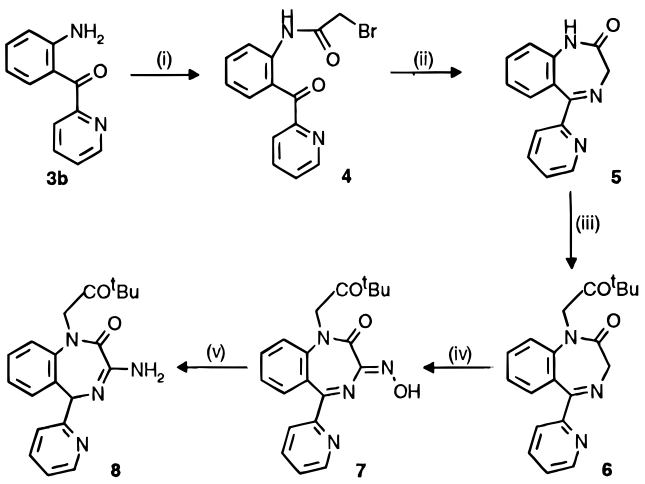

Figure 2. Synthesis of 3-amino-1-[(*tert*-butylcarbonyl)-methyl]-2,5-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one. Reagents and conditions: (i) $BrCH_2COBr$, AcOH; (ii) (a) NH_3, (b) AcOH; (iii) (a) NaH, DMF, (b) $^tBuCOCH_2Br$; (iv) (a) KO^tBu, (b) ^iAmONO; (v) H_2/5% Ru on C, 60 °C, 20 kg/cm^2.

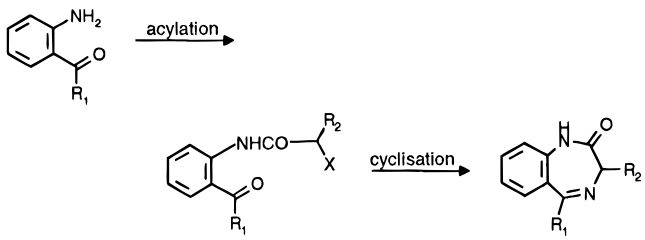

Figure 3. General strategy for benzodiazepine synthesis.

gave variable yields, and large-scale use of thioethers and highly toxic mercury salts is clearly undesirable. We were, however, able to make use of the same strategy for the construction of the benzodiazepine ring by using benzotriazole as the displaceable group (Figure 4) as reported recently by ourselves[17] and others.[18] The benzyl carbamate of α-(1-benzotriazolyl)glycine[19] (**9**) was coupled to the requisite (2-aminobenzoyl)aryl derivative in excellent yield, the benzotriazole moiety was then displaced with ammonia under mild conditions, and the ring synthesis was completed by brief acid treatment to form the benzodiazepine **11**. High yields of crystallizable products were obtained in this way under mild conditions and without the use of toxic reagents, and this route became our method of choice.

Conversion of **11** to the key intermediate **13** was accomplished by 1-alkylation with 1-bromopinacolone, followed by removal of the carbamate protecting group. In the 5-phenyl series the alkylated compound **12a** could be readily deprotected by hydrogenolysis of its benzyl carbamate (Z) protecting group. However, attempted removal of the Z-group from the 5-(2-pyridyl) analogue **12b** under the same conditions resulted in concomitant reduction and/or isomerization of the benzodiazepine imine function, depending on the hydrogenation conditions. The deprotection could, however, be effected in this case by treatment of **12b** with dry HBr in DCM. With carbamate protecting groups other than Z, a cleaner conversion to **13b** was achieved by treatment with TMSI.[17]

It is well documented that the opposite enantiomers of benzodiazepine-based gastrin/CCK-B ligands behave quite differently towards the receptor, with the (3*R*)-isomer being consistently the more active species.[11,20]

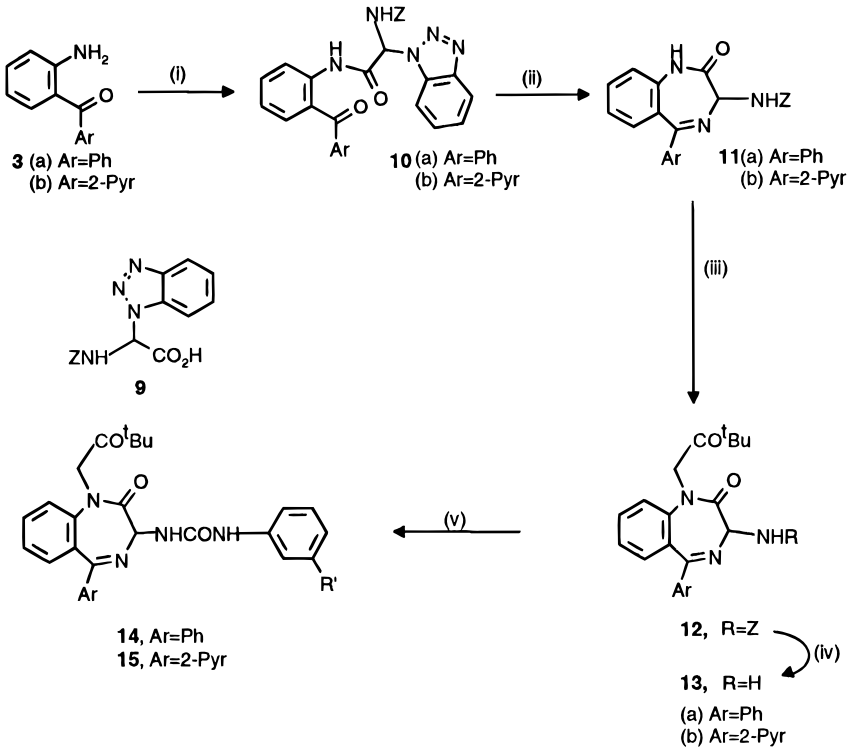

Figure 4. Benzotriazole-mediated synthesis of 5-phenyl- and 5-(2-pyridyl)-1,4-benzodiazepin-2-ones. Reagents and conditions: (i) EDC, **9**, 0 °C to room temperature; (ii) (a) NH_3/MeOH, (b) AcOH; (iii) (a) NaH, DMF, (b) $^tBuCOCH_2Br$; (iv) Ar=Ph, H_2/5% Pd on C; Ar=2-Pyr, HBr in DCM, 0 °C; (v) 3-R′-PhNCO.

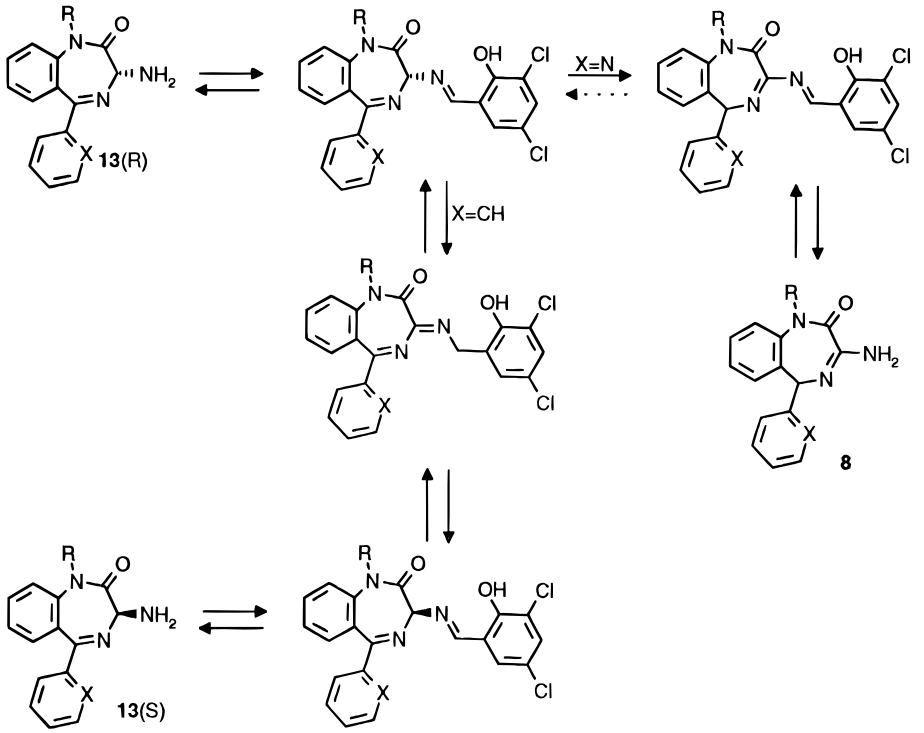

Figure 5. Interconversion of isomeric benzodiazepines *via* 3,5-dichlorosalicyl imines.

Where appropriate, we prepared the more active enantiomers of **14** and **15** by resolution of the 3-amino derivatives **13** followed by reaction of the resultant homochiral amine intermediate with the required isocyanate. The amine **13a** was readily resolved using a resolution−racemization method,[21] but under the same conditions, the analogue **13b** was converted to the isomeric 3-amino-2,5-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (**8**) obtained previously, and we were only able to resolve **13b** by classical fractional crystallization of its (*R*)- and (*S*)-mandelate salts.[17]

The resolution−racemization process operates through the interconversion of a series of imine intermediates which reversibly epimerize the 3-amino center (Figure 5, X = CH). However it appears that when the 5-substituent is a 2-pyridyl group (Figure 5, X = N) the favored isomerization is for the imino function within the benzodiazepine ring to move into conjugation with

the external imine and not *vice versa*. This process does not appear to be reversible when X = N, and so the eventual hydrolysis of the salicyl imine in this case gave the mandelic acid salt of **8** as the only isolable product. As with the differences in the hydrogenolysis products between the two series, the formation of this alternative product can only be ascribed to the differing electronic properties of the 5-phenyl and 5-(2-pyridyl) substituents adjacent to the benzodiazepine imine function.

Biology

The methods used for measuring binding of [^{125}I]CCK-8 to rat brains and that of [^{3}H]L-364,718 to rat pancreas were essentially identical to those described previously.[22] Specific binding was defined as the difference between total binding and nonspecific binding in the presence of 1 mM CCK-8 or L-364,718.

For *in vivo* screening studies, gastric acid secretion was measured in anesthetized rats as reported previously.[10] Acid secretion was measured at pH 7.0 using the pH-stat method with the addition of 0.025 N NaOH to the reservoir. Approximately 30 min after basal secretion had stabilized, pentagastrin at a rate of 20 nmol/kg/h was infused through the femoral vein. Test compounds were dissolved with polyethylene glycol 300 and injected iv 1 h after the start of pentagastrin infusion.

In the secondary *in vivo* test system, male beagle dogs with a Heidenhain pouch were used. One month after preparation of the pouch, secretory experiments were performed once a week in each animal throughout the experiments. Acidity of the gastric juice was measured by automatic titration of the gastric juice with 0.05 M NaOH to pH 7.0. Pentagastrin was infused at a rate of 8 μmol/kg/h through the femoral vein. Test compounds were administered po or iv at 3 h after the start of pentagastrin infusion.

Results and Discussion

A major drawback associated with the early benzodiazepine-based gastrin/CCK-B receptor antagonists was their lack of oral efficacy. This is exemplified by L-365,260, which is only sparingly soluble in water and has very limited oral bioavailability unless dosed as a solution in PEG 600.[23] We have previously shown that incorporation of a (*tert*-butylcarbonyl)methyl group at the 1-position[12] or a 2-pyridyl group at the 5-position[13] of the parent benzodiazepine structure provides a significant increase in absorption. Similar results have been achieved by incorporation of either a cyclohexyl group[24] or a cyclic amine to form an amidino functionality in the 5-position.[25] Other attempts to improve aqueous solubility have included introducing acidic groups,[26] or lipophilic surrogates thereof,[27] into the 3-position of the aryl urea portion of either the 1,4-benzodiazepin-2-one parent system or closely related structures.[28] We have recently shown that the opposite strategy, introducing basic amino substituents into the same region of the YM022 series, can provide an improvement in selectivity for the gastrin/CCK-B receptor over the CCK-A receptor. More significantly perhaps, increased inhibition of pentagastrin-induced gastric acid secretion in rats following intraduodenal administration was also observed for these compounds when compared to either the (3-methylphenyl)- or (3-carboxyphenyl)urea derivatives.[29] We can now report that when combinations of the above modifications are incorporated into the same molecule, the improvements in the *in vivo* effects are essentially additive, resulting eventually in the identification of **15c** which has potent oral antisecretory activity in Heidenhain pouch dogs.

We initially examined the effect of incorporating neutral, acidic, or basic groups in the 3-position of the phenylurea substituent of the 1-[(*tert*-butylcarbonyl)-methyl]-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one core structure as shown in Table 1. We observed that the incorporation of a 3-carboxy substituent, to give **14b**, did not improve binding to the rat gastrin/CCK-B receptor, although some *in vivo* antisecretory activity was still observed at 0.1 μmol/kg iv in our rat screening model. It is important to note that basal levels of acid secretion in this model are typically around 25−30% of the pentagastrin-induced peak; hence a figure of 75−80% inhibition represents the return of acid secretion to basal levels or below.

The (3-aminophenyl)urea derivative **14f** was essentially equipotent with the parent 3-tolylurea derivative **14a** both *in vitro* and *in vivo* in rats. However, when alkylated amino groups were incorporated into the same position (**14g**−**j**), there was a significant improvement in the compounds' affinities for the gastrin/CCK-B receptor, which was accompanied in most cases by improved receptor selectivity. In addition, all of the [3-(alkylamino)phenyl]urea analogues showed significant inhibition of pentagastrin-induced gastric acid secretion *in vivo* in rats at the screening dose of 0.1 μmol/kg iv.

We next examined the effect of introducing the 5-(2-pyridyl) substituent, which we had previously shown conferred improved bioavailability when incorporated as a single change to the parent structure,[13] into the [3-(alkylamino)phenyl]urea series. As can be seen in Table 1, all of the resulting compounds with the exception of the 3-(1-piperidyl)phenyl urea analogue **15h** showed comparable or improved affinity and selectivity for the gastrin/CCK-B receptor when compared to the parent 3-tolylurea derivative **15a**. In addition, the active compounds in this second [3-(alkylamino)phenyl]-urea series again showed potent inhibition of pentagastrin-induced gastric acid secretion *in vivo* in rats at the screening dose of 0.1 μmol/kg iv. No significant advantage was observed by either increasing the size of the alkyl groups on the amino nitrogen or incorporating them into a ring.

Several compounds from the two series were selected for more extensive evaluation *in vivo* (Table 2) according to the methods previously described.[30] ED_{50} values were determined for the inhibition of pentagastrin-induced gastric acid secretion in rats following iv administration of the test compound, and as expected, all of the analogues tested showed potency comparable to that of the original parent compound YM022 in this model.

We next examined the effect of the compounds on pentagastrin-induced gastric acid secretion in Heidenhain pouch dogs. As we were searching for compounds with significant oral activity, for our first screening point we selected an oral dose of 3 μmol/kg and all of the compounds tested showed a significant effect at this dose. There was already an indication that the incor-

Table 1. Structure−Activity Relationships of 3-Substituted Phenylurea Derivatives of 2,3-Dihydro-1*H*-1,4-benzodiazepin-2-ones **14** and **15**

compd no.	config	R′	CCK-B[a] (nM)	CCK-A[b] (nM)	ratio (CCK-A/CCK-B)	*in vivo* screening (% inhibition of H^+ secretion in rats at 0.1 μmol/kg iv)[c]
2			0.11 (0.10−0.11)	146 (120−170)	1327	ED_{50} = 8.3 nmol/kg (6.1−10.9)
14a	*R*	Me	0.52 (0.43−0.63)	111 (85−146)	213	77[d]
14b	*RS*	CO_2H	3.29 (2.41−4.50)	2059 (1594−2659)	626	56
14c	*RS*	NO_2	0.16 (0.10−0.28)	589 (527−658)	3681	76
14d	*RS*	CN	1.29 (0.25−6.70)	700 (631−776)	542	65
14e	*RS*	NHCHO	0.59 (0.28−1.21)	561 (521−605)	951	74
14f	*R*	NH_2	0.50 (0.38−0.67)	953 (807−1125)	1906	75
14g	*R*	NHMe	0.11 (0.08−0.15)	120 (88−164)	1091	80
14h	*R*	NMe_2	0.21 (0.18−0.29)	89 (73−108)	423	65
14i	*R*	NEt_2	0.14 (0.11−0.18)	558 (421−741)	3986	82
14j	*R*	1-pyrrolidyl	0.17 (0.13−0.22)	157 (145−171)	923	79
15a	*R*	Me	0.44 (0.33−0.59)	470 (361−611)	1068	78
15b	*R*	NH_2	0.43 (0.35−0.54)	1820 (1699−1949)	4233	62
15c	*R*	NHMe	0.10 (0.08−0.13)	502 (434−581)	5020	87
15d	*R*	NMe_2	0.20 (0.15−0.26)	113 (82−156)	565	65[d]
15e	*S*	NMe_2	1.26 (0.83−1.91)	572 (486−674)	454	nd
15f	*R*	NEt_2	0.11 (0.07−0.19)	301 (230−395)	2736	74
15g	*R*	1-pyrrolidyl	0.11 (0.10−0.12)	253 (188−342)	2300	75
15h	*R*	1-piperidyl	0.84 (0.79−0.88)	944 (759−1173)	1124	55

[a] IC_{50} value for displacement of [^{125}I]CCK-8 from gastrin/CCK-B receptors from rat brain (95% confidence limits). [b] IC_{50} value for displacement of [^{3}H]L-364,718 from CCK-A receptors from rat pancreas (95% confidence limits). [c] Inhibition of pentagastrin-induced gastric acid secretion in anethsetized rats (0.1 μmol/kg iv). [d] Percent inhibition at a dose of 0.03 μmol/kg.

Table 2. Further *in Vivo* Evaluation of New Gastrin/CCK-B Antagonists. Inhibition of Pentagastrin-Induced Gastric Acid Secretion in Rats and Heidenhain Pouch Dogs

compd	SD rat (iv) ED_{50} (μmol/kg)	inhibition of pentagastrin-induced gastric acid secretion in Heidenhain pouch dogs (po)	inhibition of pentagastrin-induced gastric acid secretion in Heidenhain pouch dogs (iv)
YM022 (**2**)	0.0078	72% at 3 μmol/kg 26% at 1 μmol/kg ED_{50} = 1.9 μmol/kg (1.0−2.9)[a]	ED_{50} = 0.026 μmol/kg (0.008−0.051)
14a	0.0057	53% at 3 μmol/kg	nd
14h	0.012	99% at 3 μmol/kg	nd
15a	0.016	97% at 3 μmol/kg 7% at 0.3 μmol/kg	nd
15c	0.008	100% at 0.1 μmol/kg 65% at 0.03 μmol/kg ED_{50} = 0.021 μmol/kg (0.013−0.029)	ED_{50} = 0.018 μmol/kg (0.013−0.027)
15d	0.011	98% at 0.1 μmol/kg 77% at 0.03 μmol/kg	ED_{50} = 0.014 μmol/kg (0.009−0.033)

[a] Figures in parentheses represent 95% confidence limits. nd = not determined.

poration of an alkylated amino group conferred beneficial effects on oral absorption, as **14h** was considerably more potent than **14a** at this preliminary oral dose level.

All three analogues which incorporated a 5-(2-pyridyl) substituent showed complete inhibition of acid secretion at the first screening dose. Lowering the dose allowed us to show that the combination of a 5-(2-pyridyl) group and a 3-(alkylamino) substituent on the urea portion provided highly potent orally active compounds. **15c** and **15d** were essentially equipotent in this dog model, and an ED_{50} value of 21 nmol/kg (∼0.01 mg/kg) was determined for **15c**,[30] thus showing this compound to be about 90 times more potent than YM022 after oral administration. In addition, the inhibiton curves (Figure 6) showed that both compounds had an excellent duration of action, maintaining complete inhibiton of acid secretion for more than 6 h following oral administration at the 100 nmol/kg dose level.

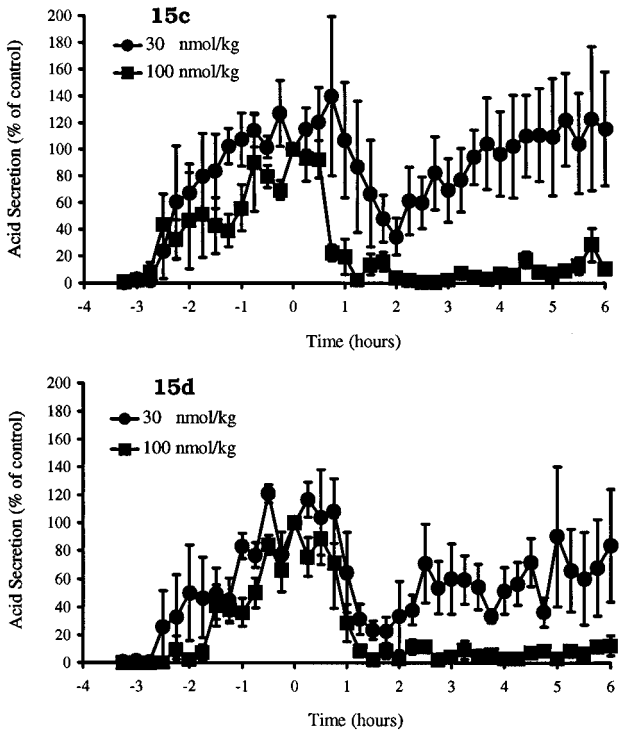

Figure 6. Inhibition of pentagastrin-induced gastric acid secretion in Heidenhain pouch dogs by oral administration of **15c** and **15d**. Pentagastrin 8 μmol/kg/h was infused from 3 h before, until 6 h after drug administration ($t = 0$), and acid secretion was measured by automatic titration. Each point is represented as a percentage of values observed immediately before drug administration and is the mean ± SEM (five animals per group).

To obtain an indication of the magnitude of the advantage provided by our new analogues in terms of oral bioavailability, we determined the ability of YM022, **15c**, and **15d** to inhibit pentagastrin-induced gastric acid secretion in Heidenhain pouch dogs following iv administration, and as expected all three compounds showed potent effects *via* this route (Table 2). When compared to their effects following oral dosing, we observed that compounds **15c** and **15d** showed only a modest difference in activity between oral and iv administration, whereas YM022 was around 70 times less potent following oral administration than by the iv route. These data indicated that both **15c** and **15d**, but not YM022, have excellent oral bioavailibility in dogs, and this together with their long duration of action *in vivo* suggested that we had identified two possible clinical candidates for the treatment of GORD and other gastrointestinal disorders.

Finally we conducted physicochemical studies on the two potential clinical candidates to determine their stability in the crystalline form. Gratifyingly, **15c** was obtained in a single-crystal form when isolated as its free base and remained stable even after 3 months at 40 °C and 75% relative humidity (no imine bond tautomerization was observed under these conditions). This compound, given the code number YF476, was selected for further development and is currently under clinical investigation for the treatment of GORD.

Experimental Section

Analytical and spectroscopic data for test compounds are included in the Supporting Information. Melting points were determined using a Yanaco MP-500D instrument and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter and are uncorrected. ^{1}H NMR spectra were obtained using either a JEOL FX-90Q, a JEOL EX-270, or a JEOL JNN-EX-400 spectrometer. ^{13}C NMR spectra were obtained using a JEOL EX-270 spectrometer. Carbon atom types were determined by 90- and 135-DEPT experiments. Chemical shifts are reported in ppm (δ) downfield of tetramethylsilane as an internal reference (δ 0.0). Positive FAB mass spectra were recorded in glycerol or thioglycerol matrix either at the Michael Barber Centre for Mass Spectrometry, UMIST, Manchester, U.K., or by the Analytical Department of Yamanouchi Pharmaceutical Co. Elemental analyses were determined either by Elemental Microanalysis Ltd., Okehampton, Devon, U.K. or by the Analytical Department of Yamanouchi Pharmaceutical Co. and are within ±0.4% of calculated values. All reagents were obtained from commercial sources and used without further purification unless otherwise noted.

2-[2-[2-Bromoacetyl)amino]benzoyl]pyridine (4)[31]. **3b**[17,32] (2.5 g, 12.63 mmol) was taken up in acetic acid (25 mL) and the mixture stirred at 4 °C. Bromoacetyl bromide (1.1 mL, 12.8 mmol) was added dropwise over 20 min, and stirring continued for a further 15 min at 4 °C. The mixture was then evaporated, and the residue was partitioned between EtOAc (50 mL) and 0.5 M NaOH (50 mL). The organic portion was washed with water and brine, dried over Mg_2SO_4, and evaporated. The title compound was crystallized from EtOAc/hexane as a pale brown solid (3.25 g, 81%): mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (br s, 1H), 8.73 (d, 1H, J = 5Hz), 8.64 (d, 1H, J = 8Hz), 7.96−7.90 (m, 2H), 7.82 (dd, 1H, J_1 = 8 Hz, J_2 = 2 Hz), 7.61 (m, 1H), 7.51 (ddd, 1H, J_1 = 7 Hz, J_2 = 5 Hz, J_3 = 2 Hz), 7.17 (t, 1H, J = 8 Hz), 4.03 (s, 2H) ppm. Anal. ($C_{14}H_{11}N_2O_2Br$) C, H, N, Br.

2,3-Dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (5). The title compound was prepared directly from **3b** without purification of the bromoacetylated intermediate **4** as described:[31] mp 245−246 °C (lit.[31] mp 232−234 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (br s, 1H), 8.64 (dd, 1H, J_1 = 5 Hz, J_2 = 1 Hz), 7.95 (d, 1H, J = 8 Hz), 7.81 (dt, 1H, J_t = 8 Hz, J_d = 2Hz), 7.37 (dd, 1H, J_1 = 7 Hz, J_2 = 5 Hz), 7.33 (dd, 1H, J_1 = 8 Hz, J_2 = 1 Hz), 7.15 (t, 1H, J = 8 Hz), 7.08 (d, 1H, J = 8 Hz), 4.37 (s, 2H) ppm. Anal. ($C_{14}H_{11}N_3O$) C, H, N.

1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (6). **5** (8.3 g, 35 mmol) was azeotroped with DMF and the residue dissolved in dry DMF (300 mL) at 4 °C under nitrogen. Sodium hydride (1.4 g, 80% dispersion in oil, 46.6 mmol) was added portionwise with stirring, and the mixture was stirred for 40 min at 4 °C. 1-Bromopinacolone (6.0 mL, 46 mmol) was added, and the mixture was stirred at 4 °C to room temperature over 2 h. The mixture was evaporated to dryness and partitioned between EtOAc and water. The organic portion was washed with brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from EtOAc/hexane to provide a colorless solid (8.65 g, 74%): mp 180−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, 1H, J_1 = 5 Hz, J_2 = 1 Hz), 8.08 (d, 1H, J = 8 Hz), 7.81 (dt, 1H, J_t = 8 Hz, J_d = 2 Hz), 7.48 (dt, 1H, J_t = 8 Hz, J_d = 2 Hz), 7.38−7.33 (m, 2H), 7.21 (m, 1H), 7.08 (d, 1H, J = 8Hz), 5.09 (d, 1H, J = 18 Hz), 4.86 (d, 1H, J = 10 Hz), 4.36 (d, 1H, J = 18 Hz), 3.98 (d, 1H, J = 10 Hz), 1.28 (s, 9H) ppm; FAB-MS $(M + H)^+$ = 336. Anal. ($C_{20}H_{21}N_3O_2$) C, H, N.

1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-3-oximido-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (7). The title compound was prepared using a modified version of the previously described procedure.[14,11] **6** (2.00 g, 6.0 mmol) was suspended in dry toluene (72 mL) at −20 °C under nitrogen. KO^{t}Bu (2.68 g, 23.9 mmol) was added portionwise to the stirring mixture so that the internal temperature did not rise above −10 °C, and stirring continued for a further 30 min at −20 °C. Isoamyl nitrite (2.10 g, 3equiv) was added, and the mixture was stirred at −20 to −5 °C over 3 h and then poured into a mixture of ice (100 g), AcOH (5 mL), and EtOAc (100 mL). The aqueous portion was basified and extracted with EtOAc (50 mL), and the combined organic portions were washed with brine, dried (Mg_2SO_4), and evaporated. The residue was crystallized from hot EtOAc (70 mL) as a pale

yellow solid (1.10 g, 51%): mp 262−264 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (1H, s), 8.65 (d, 1H, J = 8 Hz), 8.22 (d, 1H, J = 8 Hz), 8.05 (dt, 1H, J_t = 8 Hz, J_d = 2 Hz), 7.63−7.58 (m, 2H); 7.40 (d, 1H, J = 6 Hz), 7.30−7.24 (m, 2H), 5.03 (d, 1H, J = 18 Hz), 4.91 (d, 1H, J = 18 Hz), 1.17 (s, 9H) ppm; FAB-MS $(M + H)^+$ = 365. Anal. ($C_{20}H_{20}N_4O_3$) C, H, N.

3-Amino-1-[(*tert*-butylcarbonyl)methyl]-2,5-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (8). **7** (500 mg, 1.36 mmol) was taken up in MeOH (25 mL). The solution was degassed and treated with 5% Ru/C (Lancaster Synthesis, 150 mg). The mixture was hydrogenated in a Parr apparatus (20 kg/cm^2 H_2, 60 °C, 24 h) and then filtered and the catalyst well washed with methanol. The solvent was removed by evaporation, and the title compound was obtained by chromatography on silica (eluant 5% MeOH in $CHCl_3$) as a colorless solid (446 mg, 93%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.65 (d, 1H, J = 4 Hz), 7.97 (d, 1H, J = 8 Hz), 7.81 (m, 1H), 7.26 (m, 1H), 7.19 (m, 1H), 7.01 (m, 2H), 6.44 (d, 1H, J = 8 Hz), 5.98 (s, 1H), 5.15 (d, 1H, J = 18 Hz), 4.89 (br s, 2H), 4.70 (d, 1H, J = 18 Hz), 1.31 (s, 9H) ppm; FAB-MS $(M + 1)^+$ = 351.

Preparation of 3-Substituted Carboxylic Acids and Isocyanates. 3-(Formylamino)benzoic Acid. Acetic anhydride (76 mL) was added to 98% formic acid (130 mL), and the mixture was stirred at room temperature for 30 min. 3-Aminobenzoic acid (15 g, 109.5 mmol) was then added. The mixture was stirred at room temperature for 1 h and then treated with water (1.3 L) and stirring continued overnight. The resultant white precipitate was collected, washed with water, and dried *in vacuo* over P_2O_5 (15.4 g, 85%): ^{1}H NMR (270 MHz, MeOH-d_4) δ 8.45−8.3 (m, 2H), 8.0−7.5 (m, 4H) ppm.

3-(*N*-Formylmethylamino)benzoic Acid. A solution of 3-(formylamino)benzoic acid (2.28 g, 13.8 mmol) in DMF (25 mL) was added dropwise to a suspension of sodium hydride (1.05 g, 80% dispersion in oil) in DMF (15 mL) at 0 °C. The mixture was allowed to warm to room temperature over 1 h, and then iodomethane (0.95 ml) was added. A second portion of iodomethane (0.95 mL) was added after 1 h, and the mixture was stirred at room temperature overnight. The solvent was removed by evaporation, and the residue was partitioned between ethyl acetate and 1 M HCl. The organic layer was washed with brine, filtered (Whatman 1 PS phase separator), and evaporated. The residue was chromatographed on silica (eluant 60% EtOAc in hexane) to provide the methyl ester of the title compound as a colorless solid (2.30 g, 86%). A portion of this ester (900 mg, 4.66 mmol) was taken up in dioxane/water (2/1, v/v, 30 mL) and treated with LiOH·H_2O (378 mg, 9 mmol) at room temperature with stirring overnight. The mixture was acidified with 1 M HCl and extracted twice with EtOAc. The combined extracts were washed with brine, filtered (Whatman 1 PS phase separator), and evaporated. The title compound (420 mg, 50%) was used in the next step without further purification: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.0−7.85 (m, 2H), 7.5−7.35 (m, 2H), 3.36 (s, 3H) ppm.

3-(1-Pyrrolidyl)benzoic Acid. *m*-Aminobenzoic acid (13.7 g, 0.1 mol) was taken up in methanol (150 mL) and cooled to 0 °C. Acetyl chloride (10 mL) was added dropwise, and then the mixture was heated at reflux under nitrogen for 1 h. The mixture was cooled, evaporated, and partitioned between EtOAc and 5% $KHCO_3$. The organic portion was washed with brine, filtered (Whatman 1PS phase separator) and evaporated to provide methyl *m*-aminobenzoate as a brown oil which crystallized on standing (13.2 g, 88%). A portion of this amino ester (5.45 g, 36.1 mmol) was taken up in dry DMF (70mL) and treated with sodium hydride (3.78 g, 80% dispersion in oil, 126 mmol) at 0 °C under nitrogen for 14 h. 1,4-Dibromobutane (14.05 g, 65 mmol) and potassium iodide (0.6 g, 3.7 mmol) were added, and the mixture was heated at 80 °C for 72 h. The mixture was cooled, evaporated, and partitioned between EtOAc and 5% $KHCO_3$. The organic portion was washed with brine, filtered (Whatman 1PS phase separator), and evaporated. The residue was chromatographed on silica (eluant 8% EtOAc in hexane) to provide methyl 3-(1-pyrrolidyl)benzoate as a pale yellow solid (1.70 g, 23%). The solid was taken up in dioxane/water (40 mL) and treated with LiOH·H_2O (1.75 g, 5 equiv) at room temperature for 10 min, then at 40 °C for 30 min. Acetic acid (10 mL) was added, and the mixture was evaporated, azeotroped with toluene, and crystallized from AcOH/water/dioxane to provide a pale brown solid (1.26 g, 80%) which was dried *in vacuo* over P_2O_5: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.4−7.2 (m, 3H), 6.78 (m, 1H), 3.35 (m, 4H), 2.02 (m, 4H) ppm.

Methyl 3-(4-Pentenoylamino)benzoate. Methyl 3-aminobenzoate (4.5 g, 29.8 mmol) was taken up in DCM (10 mL) and pyridine (1 mL) at 0 °C. 4-Pentenoyl chloride (freshly prepared from 4-pentenoic acid (3.0 g, 29.97 mmol) and thionyl chloride (6.6 mL) at room temperature for 1 h, evaporated and azeotroped with DCM) was added dropwise in DCM (3 mL). The mixture was allowed to warm to room temperature, stirred overnight, and then evaporated. The residue was partitioned between EtOAc and 1 M HCl. The organic portion was washed with 5% $KHCO_3$ and brine, filtered (Whatman 1PS phase separator), and evaporated. The residue was chromatographed (eluant 30% EtOAc in hexanes) to provide a colorless oil (2.20 g, 32%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.05 (t, 1H, J = 1.5 Hz), 7.93 (d, 1H, J = 8 Hz), 7.79 (d, 1H, J = 8 Hz), 7.56 (br s, 1H), 7.42 (t, 1H, J = 8 Hz), 5.92 (m, 1H), 5.2−5.0 (m, 2H), 3.93 (s, 3H), 2.51 (m, 4H) ppm.

Methyl 3-[(5-Bromopentanoyl)amino]benzoate. Methyl 3-(4-pentenoylamino)benzoate (1.7 g, 7.3 mmol) was taken up in dry THF (25 mL) at room temperature under nitrogen. 9-BBN (20 mL, 0.5M solution) was added, and the mixture was stirred at room temperature for 3 h. NaOH 1 M, (8 mL) was then added followed by 27% hydrogen peroxide (2.5 mL, dropwise). Stirring was continued at 40 °C for 1 h, and then the mixture was evaporated, taken up in EtOAc, and washed with 5% $KHCO_3$ and brine. The organic portion was filtered (Whatman 1PS phase separator), evaporated, and chromatographed (eluant 95% EtOAc in hexanes) to provide methyl 3-[(5-hydroxypentanoyl)amino]benzoate as a mixture with borates. The crude product was taken up in DCM (120 mL) and treated with triphenylphosphine (5 g) and carbon tetrabromide (6.2 g) at room temperature for 2 h with stirring. The mixture was then evaporated and chromatographed (eluant 40% EtOAc in hexanes) to provide the title compound as a colorless oil which solidified to a wax on standing (1.54 g, 67%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.62 (br s, 1H), 8.26 (t, 1H, J = 1.5 Hz), 7.95−7.8 (m, 2H), 7.4 (m, 1H), 3.96 (s, 3H), 3.44 (m, 2H), 2.66 (m, 2H), 1.98 (m, 4H) ppm.

Methyl 3-(2-Oxo-1-piperidinyl)benzoate. Methyl 3-[(5-bromopentanoyl)amino]benzoate (1.50 g, 4.88 mmol) was taken up in dry DMF (40 mL) and treated with NaH (160 mg, 80% dispersion in oil, 5.33 mmol) at 0 °C. The mixture was stirred at room temperature under nitrogen for 10 min, KI (80 mg) was added, and the mixture was heated at 70 °C for 4 h. The mixture was evaporated and partitioned between EtOAc and 1 M HCl. The organic portion was washed with 5% $KHCO_3$ and brine, filtered (Whatman 1 PS phase separator), and evaporated. The residue was chromatographed (eluant 2% MeOH in EtOAc) to provide the title compound as a colorless oil (640 mg, 56%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.1−7.95 (m, 2H), 7.60−7.50 (m, 2H), 3.98 (s, 3H), 3.75 (m, 2H), 2.64 (m, 2H), 2.03 (m, 4H) ppm.

3-(1-Piperidinyl)benzoic Acid. Methyl 3-(2-oxo-1-piperidinyl)benzoate (640 mg, 2.75 mmol) was dissolved in dry THF (30 mL), and borane−tetrahydrofuran complex (5 mL, 1 M solution in THF) was added. The mixture was stirred under nitrogen at reflux for 1 h, then cooled, and evaporated. The residue was taken up in MeOH/acetic acid (6/1, v/v, 70 mL) and heated at reflux for 3 h, then evaporated, and chromatographed (eluant 10% EtOAc in hexane) to provide the methyl ester of the title compound as a colorless oil (540 mg, 90%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.59 (t, 1H, J = 1.5 Hz), 7.46 (dd, 1H, J_1 = 8 Hz, J_2 = 1.5 Hz), 7.28 (t, 1H, J = 8 Hz), 7.11 (m, 1H), 3.89 (s, 3H), 3.18 (m, 4H), 1.75−1.62 (m, 4H), 1.61−1.55 (m, 2H) ppm. The oil was dissolved in dioxane (12 mL) and water (8 mL). LiOH·H_2O (300 mg, 7.143 mmol) was added, and the mixture was stirred at 40 °C for 1 h, then acidified with acetic acid, evaporated, and azeotroped with toluene. The residue was chromatographed on silica (eluant 60:40:2, EtOAc/hexanes/AcOH, v/v/v) to provide the title compound as a colorless solid (450 mg, 90%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.54 (d, 1H, J = 8 Hz), 7.32 (t,

1H, J = 8 Hz), 7.17 (dd, 1H, J_1 = 8 Hz, J_2 = 1.5 Hz), 3.22 (m, 4H), 1.72 (m, 4H), 1.61 (m, 2H) ppm.

3-[(*tert*-Butyloxycarbonyl)amino]benzoic Acid. 3-Aminobenzoic acid (24.69 g, 180 mmol) was taken up in 2 M KOH (180 mL) and dioxane (180 mL) and treated with di-*tert*-butyl dicarbonate (53.03 g, 243 mmol) at room temperature overnight. Dioxane was removed by evaporation, and the solution was diluted with 1 M KOH (300 mL). The aqueous portion was washed with ether (200 and 300 mL) and acidified to pH 4 with concentrated HCl. The resultant white precipitate was collected by filtration, washed with water, and dried *in vacuo* (P_2O_5) to give the title compound (38.97 g, 91%): ^{1}H NMR (90 MHz, DMSO-d_6) δ 9.52 (br s, 1H), 8.13 (m, 1H), 7.7−7.3 (m, 3H), 1.49 (s, 9H) ppm.

3-[N-(*tert*-Butyloxycarbonyl)methylamino]benzoic Acid. Sodium hydride (18.33 g, 60% dispersion in oil, 458.3 mmol) was added portionwise to a solution of 3-[(*tert*-butyloxycarbonyl)amino]benzoic acid (43.48 g, 183.3 mmol) in DMF (600 mL) below 10 °C, and the mixture was allowed to warm to room temperature with stirring over 1 h. MeI (84.54 g, 595.6 mmol) was added dropwise to the solution over 30 min at 5 °C, and the mixture was stirred at room temperature for 2 h. The mixture was evaporated, and the residue was partitioned between EtOAc (1.2 L) and water (600 mL). The organic portion was washed with saturated $NaHCO_3$ (100 mL) and water (5 × 200 mL), dried (Mg_2SO_4), and evaporated. The residual oil was taken up in methanol (1 L), 1 M LiOH (185 mL) was added to the solution at 5 °C, and the mixture was stirred at room temperature for 12 h. A further portion of 1 M LiOH (90 mL) was added, and the mixture was stirred for 1 h. The solution was concentrated to remove methanol, diluted with water and washed with EtOAc/hexane (1:2, v/v, 300 and 150 mL). The aqueous portion was acidified to pH 4 with concentrated HCl and extracted with EtOAc (400 and 200 mL). The combined organic portions were washed with brine, dried ($MgSO_4$), and evaporated. The residue was recrystallized from EtOAc/hexane (1:20 v/v, 420 mL) to give the title compound (36.08 g, 78%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.0−7.9 (m, 2H), 7.5−7.4 (m, 2H), 3.31 (s, 3H), 1.47 (s, 9H) ppm.

3-[*N*-(*tert*-Butyloxycarbonyl)methylamino]phenyl Isocyanate. Et_3N (3.71 g, 36.7 mmol) and a solution of ethyl chloroformate (4.31 g, 39.7 mmol) in acetone (10 mL) were successively added dropwise to a solution of 3-[*N*-(*tert*-butyloxycarbonyl)methylamino]benzoic acid (8.0 g, 31.8 mmol) in acetone (64 mL) below 5 °C. After the solution was stirred for 30 min, a solution of NaN_3 (3.1 g, 47.7 mmol) in water (10 mL) was added below 5 °C. The mixture was stirred at the same temperature for a further 1 h and then poured into toluene (80 mL) and water (160 mL). The organic portion was washed with brine, refluxed for 2 h, and evaporated. The residue was distilled (100−105 °C/0.9−1.0 mmHg) to afford the title compound (6.2 g, 78%) as a yellow oil.

3-(Dimethylamino)phenyl Isocyanate. 3-(Dimethylamino)benzoic acid (350 g, 2.12 mol) was dissolved in acetone (2.8 L). Et_3N (249 g, 2.46 mol) was added dropwise to the solution below 10 °C, followed by the addition of a solution of ethyl chloroformate (287 g, 2.65 mol) in acetone (875 mL) below 5 °C. After the mixture was stirred for 30 min, a solution of NaN_3 (201 g, 3.18 mol) in water (570 mL) was added dropwise below 5 °C. The reaction mixture was stirred at 0−5 °C for a further 1 h and then poured into toluene−ice water (2:3, 11 L). The aqueous portion was extracted with a small amount of toluene, and the combined organic portions were washed with water and brine and dried ($MgSO_4$). After $MgSO_4$ was removed by filtration, the filtrate was added dropwise to hot toluene (1.5 L). The mixture was refluxed for 1 h and then evaporated, and the residue was distilled (0.6−0.8 mmHg, 74−77 °C) to afford the isocyanate (252 g, 74%) as a pale yellow oil.

(*RS*)-3-[(Benzyloxycarbonyl)amino]-2,3-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (11b). 3b[17] (660 mg, 3.33 mmol) and **9**[19] (1.63 g, 5 mmol) were mixed together in DCM (30 mL) at 0 °C under nitrogen. Water soluble carbodiimide (EDC, 1 g, 5 mmol) and DMAP (30 mg) were added, and the mixture was stirred at 0 °C for 10 min and at room temperature for 10 min. The resulting pale brown solution was poured into a mixture of 5% $KHCO_3$ (100 mL) and EtOAc (150 mL). The organic portion was washed with 5% $KHCO_3$, water, and brine, dried, and evaporated. (The intermediate **10b** could be isolated at this stage by chromatography on silica (eluant 55% EtOAc in hexanes) to provide the pure compound as a yellow oil in 93% yield: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 11.65 (br s, 1H), 8.54 (d, 1H, J = 5.5 Hz), 8.50 (d, 1H, J = 8 Hz), 8.03 (d, 1H, J = 8 Hz), 7.75 (m, 3H), 7.5−7.08 (m, 12H), 6.98 (br m, 1H),; 5.05 (m, 2H) ppm.) The resultant crude product was treated with an ice-cold saturated solution of ammonia in methanol (30 mL), and the mixture was stoppered and stirred at room temperature for 1 h, then cooled, and evaporated. The residue was treated with a solution of ammonium acetate in acetic acid (0.1 g/mL, 30 mL) at room temperature for 1 h. The mixture was evaporated and partitioned between $CHCl_3$ and 1 M NaOH. The organic portion was washed with brine, dried, and evaporated, and the product was crystallized from EtOAc/hexane. The product was recrystallized from EtOAc/hexane to afford the title compound as a colorless solid (1.01 g, 79%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.0 (br s, 1H), 8.60 (d, 1H, J = 6 Hz), 8.07 (d, 1H, J = 8 Hz), 7.82 (dt, 1H, J_t = 8 Hz, J_d = 1 Hz), 7.4−7.2 (m, 9H), 6.98 (d, 1H, J = 8 Hz), 6.65 (d, 1H, J = 8 Hz), 5.37 (d, 1H, J = 8 Hz), 5.16 (m, 2H) ppm.

(*RS*)-3-[(Benzyloxycarbonyl)amino]-1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (12b). 11b (7.3 g, 18.9 mmol) was taken up in dry DMF (73 mL) at 0 °C. Sodium hydride (740 mg, 80% dispersion in oil, 1.3 equiv) was added portionwise keeping the internal temperature below 5 °C, and the mixture was stirred at room temperature 1 h. The mixture was recooled to 0 °C, and 1-bromopinacolone (10.21 g, 57 mmol) was added dropwise keeping the internal temperature below 10 °C, and stirring was continued at room temperature for a further 1 h. The mixture was evaporated, taken up in DCM (73 mL), and washed with 5% $NaHCO_3$ and brine. The organic portion was evaporated and recrystallized from EtOAc/hexane (1:1 v/v, ca. 150 mL) to provide the title compound as a white solid (7.31 g, 80%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.60 (d, 1H, J = 4 Hz), 8.14 (d, 1H, J = 8 Hz), 7.80 (dt, 1H, J_t = 7.5 Hz, J_d = 1.5 Hz), 7.50 (dt, 1H, J_t = 8.5 Hz, J_d = 1.5 Hz), 7.4−7.2 (m, 8H), 7.11 (d, 1H, J = 8 Hz), 6.72 (d, 1H, J = 8 Hz), 5.51 (d, 1H, J = 8 Hz), 5.12 (m, 2H), 5.0 (d, 1H, J = 17.8 Hz), 4.48 (d, 1H, J = 17.8 Hz), 1.25 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 208.2 (q), 166.7 (q), 166.2 (q), 155.7 (q), 148.6 (CH), 142.1 (q), 136.7 (CH), 136.2 (q), 132.0 (CH), 130.9 (CH), 128.4 (CH), 128.0 (CH), 124.8 (CH), 124.7 (CH), 124.3 (CH), 124.2 (q), 121.6 (CH), 68.8 (CH), 66.8 (CH_2), 54.2 (CH_2), 43.4 (q), 26.3 (CH_3) ppm.

(*RS*)-3-Amino-1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (13b). 12b (2.45 g, 5.12 mmol) was taken up in DCM (100 mL) at 0 °C, and the solution was saturated with dry HBr gas. The mixture was then stoppered and stirred at 0 °C for 4 h. EtOAc (100 mL) was then added, and the ice-cold mixture was filtered. The resultant hygroscopic pale yellow solid was washed well with EtOAc and then taken up in water (200 mL) and washed with ether (50 mL). The aqueous portion was basified with 5% $KHCO_3$ to pH 8 and extracted with chloroform (3 × 100 mL). The combined chloroform extracts were washed with brine, dried, and evaporated to give a near colorless foam (1.68 g, 93%): TLC (E. Merck; Kieselgel silica plates) single spot, R_f = 0.25 (eluant $CHCl_3$/MeOH/AcOH, 20:2:1, v/v/v); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.62 (d, 1H, J = 5 Hz), 8.18 (d, 1H, J = 8 Hz), 7.80 (dt, 1H, J_t = 8 Hz, J_d = 1 Hz), 7.48 (dt, 1H, J_t = 8 Hz, J_d = 1 Hz), 7.37 (m, 2H), 7.20 (t, 1H, J = 8 Hz), 7.09 (d, 1H, J = 8 Hz), 5.07 (d, 1H, J = 18 Hz), 4.66 (s, 1H), 4.45 (d, 1H, J = 18 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 208.9 (q), 169.9 (q), 155.9 (q), 148.8 (CH), 142.5 (q), 136.7 (CH), 131.8 (CH), 130.5 (CH), 128.7 (q), 124.5 (CH), 124.3 (CH), 124.1 (CH), 124.4 (CH), 70.4 (CH), 54.1 (CH_2), 44.0 (q), 26.4 (CH_3) ppm.

Attempted Racemization−Resolution of 13b. Crude **13b** (380 mg, 1.056 mmol) was taken up in MeCN (4 mL) and treated with (*S*)-mandelic acid (170 mg, 1.2 mmol). 3,5-Dichlorosalicaldehyde (10 mg) was added to the stirring mixture, and the mixture was cooled to 0 °C. Precipitation was observed, and stirring was continued at 0 °C overnight.

The resultant white solid was collected by filtration and washed with small portions of cold MeCN to provide the mandelate salt of **8** (304 mg, 58%). A portion of the salt (156 mg, 0.311 mmol) was partitioned between 5% $KHCO_3$ and $CHCl_3$ and the organic portion was washed with brine, filtered (Whatman 1 PS phase separator), and evaporated to give the free amine of **8** (110 mg, 98%). The analytical data for the free amine was identical to that described above for **8**.

Optical Resolution of 3-Amino-1-[(*tert*-butylcarbonyl)-methyl]-2,3-dihydro-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2-one (13b) by Fractional Crystallization. Crude **13b** (14 g, 40 mmol) was taken up in acetonitrile (50 mL) at −5 °C. (*R*)-Mandelic acid (3.2 g, 21 mmol) was added, and the mixture was stirred at −5 °C. A thick precipitate was formed, and acetonitrile (20 mL) was added dropwise to enable easier filtration. After 1 h at −5 °C the mixture was filtered and washed with small portions of cold MeCN. The resultant white precipitate was recrystallized from MeCN. (Anal. for mandelate salt ($C_{28}H_{30}N_4O_5 \cdot 0.5H_2O$) C, H, N.) The salt was partitioned between 5% $KHCO_3$ and $CHCl_3$, and the organic portion was washed with brine and filtered (Whatman 1 PS phase separator) to give the free (*R*)-amine (4.42 g, 32%): $[\alpha]_D = +212.6°$ ($c = 0.715$, $CHCl_3$); ^1H NMR and ^{13}C NMR data were identical to those for the racemic compound.

The filtrate from above was washed with base and taken up in MeCN (30 mL). Addition of (*S*)-mandelic acid afforded the (*S*)-amine salt in a similar manner. This was recrystallized from MeCN and washed with base to provide the free (*S*)-amine (3.87 g, 28%): $[\alpha]_D = -213.4°$ ($c = 0.671$, $CHCl_3$).

(*RS*)-3-[(Benzyloxycarbonyl)amino]-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-2-one (11a). The title compound was prepared from 2-aminobenzophenone and (benzyloxycarbonyl)(1-benzotriazolyl)glycine as described above for **11b** in 79% yield. Analytical data were identical to literature values.[14]

Preparation of (*RS*)-3-[(Benzyloxycarbonyl)amino]-1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-2-one (12a). The title compound was prepared by alkylation of **11a** with 1-bromopinacolone as described above for **12b** in 86% yield: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.8−7.2 (m, 14H), 6.74 (d, 1H, $J = 8$ Hz), 5.53 (d, 1H, $J = 8$ Hz), 5.23 (s, 2H), 5.05 (d, 1H, $J = 18$ Hz), 4.77 (d, 1H, $J = 18$ Hz), 1.33 (s, 9H) ppm.

Preparation of (*RS*)-3-Amino-1-[(*tert*-butylcarbonyl)-methyl]-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-2-one (8a). The title compound was prepared from **12a** by hydrogenolysis of the benzyl carbamate group in essentially quantitative yield as previously described:[16] ^1H NMR ($CDCl_3$, 270 MHz) δ 7.60 (d, 2H, $J = 8$ Hz), 7.5−7.0 (m, 7H), 4.96 (d, 1H, $J = 17$ Hz), 4.55 (m, 3H), 2.82 (br s, 2H), 1.18 (s, 9H) ppm.

Resolution of 3-Amino-1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-2-one (13a) by Resolution−Racemization Procedure. 13a was resolved using minor modifications to the resolution−racemization procedure previously described.[11,21] Racemic **13a** (7.7 g, 22.95 mmol) was taken up in acetonitrile (20 mL) at −5 °C, and (*S*)-mandelic acid (3.44 g, 22.63 mmol) was added to the stirred solution, followed 30 min later by 3,5-dichlorosalicaldehyde (65 mg). After the mixture was stirred overnight at −5 °C, the resultant precipitate was collected by suction filtration, washed with small portions of cold acetonitrile and ether, and recrystallized from acetonitrile to give the (*S*)-mandelate salt of the (*R*)-isomer title compound as a white solid (6.70 g, 59%). A portion of this solid (460 mg, 0.897 mmol) was partitioned between $CHCl_3$ and 0.5 M NaOH. The organic portion was washed with brine, filtered (Whatman 1PS phase separator), and evaporated to provide the title compound as a colorless foam (^1H NMR identical to racemate). The chiral integrity of the amine was examined by coupling to Boc-Phe-OH using water soluble carbodiimide/HOBT in DMF. Analytical HPLC (Spherisorb C-18, 4.6 × 100 mm, 5 μm column, linear gradient of 40−90% 0.1%TFA/acetonitrile in 0.1%TFA/water, flow rate 0.8 mL/min) of the crude product showed only a single diasteromer peak at 17.7 min, whereas the racemic amine produced a 1:1 mixture of diastereomers under the same conditions (retention times 17.4 and 17.7 min).

General Procedures for the Preparation of 3-Amino-1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one Urea Derivatives (14 or 15). Procedure A. Reaction of the Amine and the Pure Isocyanate. The required 3-amino-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (1 mmol) was taken up in DCM (25 mL) at 0 °C. To this solution was added the pure isocyanate (1.02 mmol, either from commercial sources or prepared as described above), and stirring was continued at room temperature for 2 h. The solvent was evaporated *in vacuo*, and the crude product was purified by flash chromatography on silica. Compounds **14a**, **14c**, **14d**, **14h**, **15a**, **15d**, and **15e** were prepared using this general method.

Procedure B. Reaction of the Amine and the Isocyanate Prepared *in Situ* from the Benzoic Acid. To a solution of the requisite benzoic acid (3 mmol, either from commercial sources or prepared as described above) in toluene (5 mL) was added diphenyl phosphoazidate (825 mg, 3 mmol) and Et_3N (303 mg, 3 mmol). The mixture was stirred at room temperature for 2 h, heated at reflux for 3 h, and cooled to 0 °C. A solution of the required 3-amino-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (1 mmol) in toluene (5 mL) was added, and the mixture was stirred at room temperature overnight, then evaporated, taken up in EtOAc, washed with 5% $KHCO_3$, H_2O, and brine, filtered (Whatman 1PS phase separator), and evaporated, and the crude product was purified by flash chromatography on silica. Compounds **14e**, **14i**, **14j**, **15f**, **15g**, and **15h** were prepared using this general method.

Specific Procedures for the Preparation of Urea Derivatives (14 or 15). *N*-[(3*RS*)-1-[(*tert*-butylcarbonyl)-methyl]-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin3-yl]-*N*′-(3-carboxyphenyl)urea (14b). (*RS*)-**13a** (600 mg, 1.72 mmol) was taken up in dry THF (8 mL) and Et_3N (0.26 mL, 1.9 mmol) and the solution cooled to 0 °C. The mixture was treated with a solution of *p*-nitrophenyl chloroformate (0.38 g, 1.9 mmol) in THF (4 mL), stirred at room temperature for 1 h, evaporated, and chromatographed (eluant EtOAc/hexane, 60:40, v/v) to provide an off-white solid (670 mg, 76%). The solid was taken up in DMF (10 mL) and *m*-aminobenzoic acid (245 mg, 1.75 mmol) added. The mixture was stirred at 45 °C for 18 h, cooled, and evaporated, and the residue was chromatographed (eluant EtOAc/hexane/AcOH, 60:40:2 v/v/v). The title compound was isolated as a colorless solid by recrystallization from acetonitrile (328 mg, 49%).

(3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-*N*′-(3-aminophenyl)urea (14f). 14e (700 mg, 1.37 mmol) was taken up in acetone (10 mL) and treated with 4 M HCl at room temperature for 62 h. The mixture was partially evaporated to remove the acetone and partitioned between DCM and 5% $KHCO_3$. The organic portion was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (eluant $CHCl_3$/MeOH/AcOH, 100:2:1, v/v/v), and the title compound was recrystallized from acetonitrile to provide a colorless solid (320 mg, 48%).

(3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-(methylamino)phenyl]urea (14g). (3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)-methyl]-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-(*N*-formylmethylamino)phenyl]urea was prepared from (*R*)-**13a** and 3-(*N*-formylmethylamino)benzoic acid using general procedure B, and the product was partially purified by chromatography (eluant 75% EtOAc in hexane; 960 mg, 65%). The residue was taken up in acetone (15 mL) and the stirring solution treated with 4 M HCl at room temperature for 3 days. The mixture was partially evaporated to remove acetone, and the residue was partitioned between 5% $KHCO_3$ and DCM. The organic portion was washed with brine, filtered (Whatman 1PS phase separator), and evaporated, and the crude product was purified by flash chromatography on silica (eluant $CHCl_3$/MeOH/AcOH, 120:2:1, v/v/v). The title compound was isolated as a colorless solid by recrystallization from MeCN (400 mg, 45%).

(3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*′-(3-aminophenyl)urea (15b). (3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)methyl]-

2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-[(*tert*-butyloxycarbonyl)amino]phenyl]urea was prepared from (*R*)-**13b** (850 mg, 2.43 mmol) and 3-[(*tert*-butyloxycarbonyl)amino]benzoic acid (1.19 g, 5 mmol) using general procedure B. The crude urea was taken up in DCM (10 mL) and treated with TFA (30 mL) at room temperature for 30 min under nitrogen. The mixture was evaporated and azeotroped with $CHCl_3$. The residue was partitioned between DCM and 5% $KHCO_3$, and the organic portion was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (eluant 6% MeOH in EtOAc). The residue was taken up in 1:1 EtOAc/ether (40 mL) at −10 °C and treated dropwise with 4 M HCl in dioxane (0.5 mL). The mixture was stirred at −10 °C for 30 min, and the resultant precipitate was collected by filtration, washed with ether, and dried over NaOH to provide the hydrochloride salt of the title compound as a colorless solid (845 mg, 67%).

(3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-(methylamino)phenyl]urea (15c). 3-[*N*-[(*tert*-Butyloxycarbonyl)-methyl]amino]phenyl isocyanate (19.30 g, 77.7 mmol) was added dropwise to a solution of (*R*)-**13b** (27.19 g, 77.6 mmol) in DCM (200 mL) below 20 °C, and the mixture was stirred at room temperature for 30 min and then evaporated. The residue was taken up in EtOAc (200 mL) and water (100 mL), concentrated HCl (120 mL) was then added dropwise to the mixture below 20 °C, and the mixture was stirred for 3 h. The aqueous phase was separated, added to DCM (500 mL), and then basified to pH 10 with 20% NaOH while the temperature was maintained below 20 °C. The resultant organic portion was washed with brine (300 mL), and evaporated, and the residue was crystallized from ethanol. The resultant solid was recrystallized from ethanol (1.8 L) to provide the title compound as a white crystalline solid (27.30 g, 72%), mp 243−246 °C.

(3*R*)-*N*-[1-[(*tert*-Butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*′-[3-(dimethylamino)phenyl]urea Hydrochloride (15d·HCl). 15d (70 g, 136.6 mmol, prepared as described in general method A but not chromatographed) was taken up in ethanol (1 L), and 2.26 M HCl/ethanol (63.5 mL, 143.4 mmol) was added dropwise. The mixture was warmed to 50 °C to afford a clear solution, which was seeded, cooled to 0 °C, and stirred at the same temperature overnight. The resultant precipitate was collected by filtration to provide the title compound as a white crystalline solid (62.4 g, 82%), mp 181−184 °C.

Measurement of Binding Affinity for CCK-B/Gastrin Receptors. About 100 Sprague−Dawley (SD) rats were decapitated without anesthesia, the whole brain was immediately excised from each of the rats and homogenized in a 10-fold volume of 0.32 M aqueous solution of sucrose by the use of a Teflon-coated homogenizer, the homogenate thus obtained was centrifuged for 10 min at 900*g* by the use of a cooled centrifuge, and the supernatant was further centrifuged for 15 min at 11500g. The pellet thus obtained was dispersed in 50 mM Tris-HCl buffer (pH 7.4) containing 0.08% Triton X-100. This suspension was allowed to stand for 30 min and again centrifuged for 15 min at 11500*g*. The precipitate thus obtained was washed twice with 5 mM Tris-HCl buffer and twice with 50 mM Tris-HCl buffer in that order with centrifugal separation. The washed precipitate was suspended in 50 mM Tris-HCl buffer, and the suspension thus obtained was stored at −80 °C until the membrane preparation was required. For the assay the membrane preparations were warmed to room temperature, diluted with 10 mM HEPES buffer (containing 130 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, and 0.25 mg/mL bacitracin; pH 6.5), incubated at 25 °C for 120 min in the presence of [^{125}I]BH-CCK-8 and the test compound (dissolved in DMSO), and then separated by suction filtration. Nonspecific binding was determined in the presence of 1 mM CCK-8. The amount of labeled ligand bound to the receptor was measured by the use of a γ-counter. IC_{50} values were determined, being that concentration of test compound required to inhibit specific binding by 50%.

Measurement of Binding Affinity for CCK-A Receptors. The pancreas of an SD rat was homogenized in a 20-fold volume of 50 mM Tris-HCl buffer (pH 7.7) by the use of a Polytrone-type homogeniser, the homogenate was twice centrifuged for 10 min at 50000*g* by the use of an ultracentrifuge, the pellet thus obtained was suspended in a 40-fold volume of 50 mM Tris-HCl buffer (containing 0.2% BSA, 5 mM $MgCl_2$, 0.1 mg/mL bacitracin and 5 mM DTT; pH 7.7), and the suspension was stored at −80 °C until the membrane preparations were required. The membrane preparations were then warmed to room temperature, diluted 1:10 with the buffer, and incubated at 37 °C for 30 min in the presence of [^{3}H]L-364, 718, and the test compound was then separated by suction filtration. Nonspecific binding was determined in the presence of 1 mM L-364,718. Test compounds were dissolved in DMSO. The amount of labeled ligand bound to the receptor was measured by the use of a liquid scintillation counter; IC_{50} values were determined, being that concentration of test compound required to inhibit specific binding by 50%.

Measurement of Inhibition of Pentagastrin-Stimulated Gastric Acid Secretion in Rats. A cannula was inserted into the trachea of a rat anesthetized with urethane (intraperitoneally administered, 1.25 g/kg), the abdominal wall was incised to expose the gastric and duodenal portions, and a polyethylene cannula was set in the anterior stomach after ligation of the cardia. The duodenum was then subjected to slight section, a polyethylene cannula was inserted from the incised portion toward the stomach, and the pylorus was ligated to fix the cannula. Physiological saline (with pH adjusted to 7.0) was perfused from the anterior stomach toward the pylorus at a rate of 3 mL/min, and the gastric acid secretion was measured by continuous titration of the perfusate by the use of a pH-stat (AUT-201; Toa Electronics, Ltd.). The continuous titration was carried out by using 25 mM NaOH solution until the pH reached 7.0, and the result was expressed as the amount of gastric acid secreted for every 10 min (mequiv/10 min). Pentagastrin was intravenously administered at a rate of 15 mg/kg/h. The secretion of gastric acid increased upon administration of pentagastrin, reaching the maximum level after 60 min, after which time the level was stably maintained. A test drug was then intravenously administered, and the secretion of gastric acid was measured. ED_{50} values were determined for some examples, this being the amount of the drug required to reduce the amount of secreted gastric acid down to 50% of the maximum level.

Measurement of Inhibition of Gastric Acid Secretion in Heidenhain Pouch Dogs. Male beagle dogs with Heidenhain pouch were used.[33] One month after preparation of the pouch, secretory experiments were performed once a week in each animal throughout the course of the investigation. Dogs were deprived of food for 18 h prior to experiments but allowed free access to water. A polyethylene tube was intubated through the femoral vein to infuse pentagastrin at a rate of 8 μmol/kg/h. Test compounds were administered po or iv at 3 h after the start of pentagastrin infusion. Gastric juice was collected every 15 min and the volume measured. The acidity of the gastric juice was measured by automatic titration with 0.05 N NaOH to pH 7.0. In the case of iv injection, test compounds were dissolved in DMF.

Supporting Information Available: Spectroscopic data for test substances (1 page). Ordering information is given on any current masthead page.

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JM960669+