5-(Piperidin-2-yl)- and 5-(Homopiperidin-2-yl)-1,4-benzodiazepines: High-Affinity, Basic Ligands for the Cholecystokinin-B Receptor

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The design, synthesis, and biological activity of a series of high-affinity, basic ligands for the cholecystokinin-B receptor are described. The compounds, which incorporate a piperidin-2-yl or a homopiperidin-2-yl group attached to C_5 of a benzodiazepine core structure, are substantially more basic (e.g., **9d**, pK_a = 9.48) than previously reported antagonists based on 5-amino-1,4-benzodiazepines (e.g., **5**, pK_a = 7.1) and have improved aqueous solubility. In view of their basicity, it would be tempting to speculate that the present series of compounds might be binding to the CCK-B receptor in their protonated form. Compounds such as **9d,e** and **10d** showed high affinity for this receptor (IC_{50} < 2.5 nM) and very good selectivity over CCK-A (CCK-A/CCK-B > 2000), even as the racemates. Additionally, a significantly improved *in vivo* half-life was observed for a selection of compounds compared to the clinical candidate L-365,-260 (**1**).

Introduction

Over the past decades the polypeptide hormone cholecystokinin (CCK) has been recognized as an important neurotransmitter/neuromodulator of central nervous system (CNS) function, which exerts its biological activities through the interaction with two distinct receptor subtypes, CCK-A and CCK-B. For example, central CCK-A receptors might play a significant role in neuropsychiatric disorders, while CCK-B receptors have been suggested as important mediators in anxiety, panic, depression, nociception, and satiety.[1,2] Both, CCK-A[3] and CCK-B,[4] human receptors have been cloned and shown to belong to the G-protein-coupled receptor (GPCR) superfamily. Although crystallographic structural data for these membrane-embedded proteins, with seven putative transmembrane-spanning domains, is lacking, a better understanding of their receptor architectures is now beginning to emerge through the combined utilization of site-directed mutagenesis[5] and molecular modeling.[6,7] In spite of these limitations, the creativity of medicinal chemists has resulted in the identification and development of distinct series of non-peptide receptor antagonists which should enable the physiological roles of both CCK-A and CCK-B receptors to be clarified.[1,8,9] Interestingly, non-peptide CCK-A receptor agonists based on a 1,5-benzodiazepine skeleton are also beginning to appear in the literature.[9e,i,j]

The isolation and characterization of the natural product asperlicin as a non-peptide CCK receptor antagonist marked the beginning of an extensive area of research in our laboratories, and several series of CCK-B receptor antagonists which incorporate a privileged benzodiazepine core structure have been reported by us and subsequently by others. The discovery of L-365,260 (**1**) and its refinement into both acidic and basic series of compounds in order to modulate its physicochemical and biological properties has now been well documented.[1,8] In this regard, while both the acidic and basic CCK-B receptor antagonists developed over the years showed impressive *in vitro* biological profiles, the intrinsic better brain penetration of the latter makes these compounds more suitable to understand the role of the neuromodulatory peptide CCK in several CNS disorders. In the present paper, we report on the design, synthesis, and biological evaluation of a novel series of CCK-B receptor antagonists (see structures **9** and **10**; Chart 1) which are substantially more basic than those previously documented.

Design Process

The conception of the idea for the present series of CCK-B ligands was based on the compounds shown in Chart 1. Thus, it was known at the time that the C_5-phenyl ring of **1** could be advantageously replaced by more lipophilic cycloalkyl groups (e.g. **2**, L-708,474; Table 1) although at the expense of an already low aqueous solubility.[10] This drawback could, however, be overcome with the development of a series of protonatable amidines such as **3**, **4**, and **5** (L-740,093).[11] Examination of the data for these compounds (Table 1) reinforces the importance of lipophilicity of the C_5-substituent for achieving high CCK-B receptor affinity. It was also known that the C_5-phenyl of **1** could be replaced by a 2-pyridyl ring as in **6**, with only an 8-fold reduction in receptor affinity.[12] This detrimental effect could, nevertheless, be balanced by modification of the benzodiazepine N_1-substituent to give, for example, the *N*,*N*-diethylacetamido derivative **7** which showed a 100-fold improvement in affinity compared to the *N*-methyl analogue **6**. The crucial piece of information, however, came from examination of the methiodide analogue of **7** (**8**). This compound, in spite of being permanently charged, was able to bind to the CCK-B receptor with low nanomolar affinity (IC_{50}, 18 nM). It could be speculated that the basic amidines described above (e.g.,

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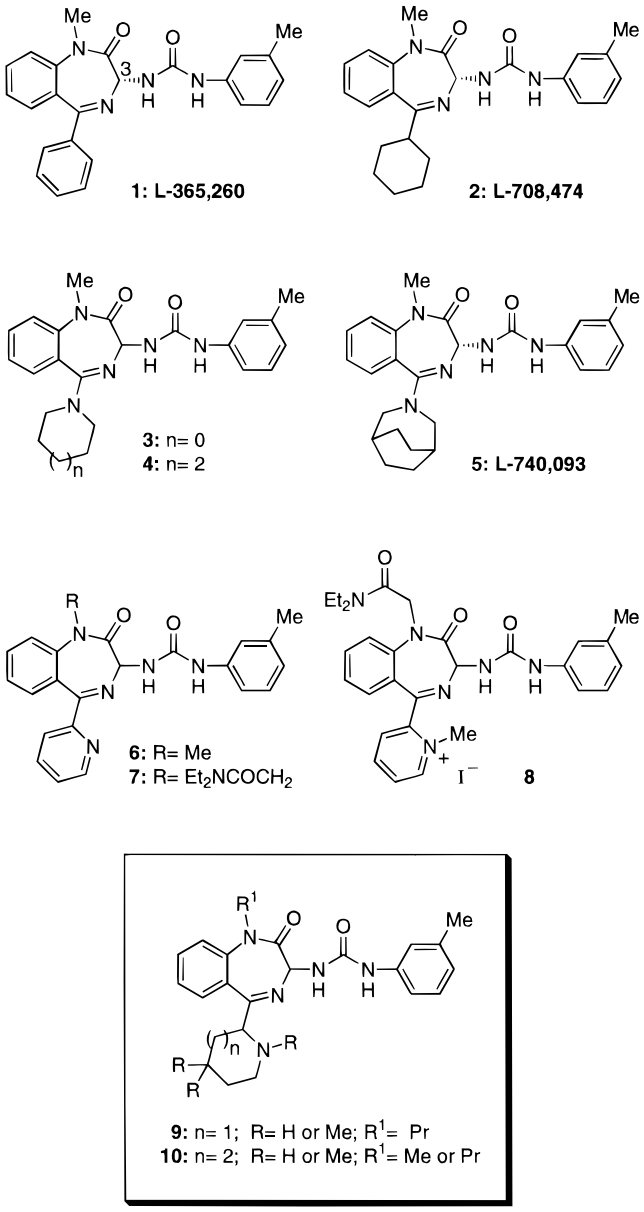
Chart 1



5, pK_a 7.1) could also be binding to this receptor in their protonated forms, although at the pH of the binding assay (pH = 6.5) a substantial proportion of uncharged species (*ca.* 20%) would be present. It was, therefore, envisaged that compounds with general structures such as **9** and **10** (Chart 1), which incorporate an overtly basic center in the same region of space of the positively charged pyridinium group in **8**, should bind to this receptor with respectable affinity, and show improved aqueous solubilities. Because **8** showed a 30-fold reduction in affinity compared to the uncharged **7**, it was decided to take advantage of the beneficial effects of large N_1-alkyl substituents (e.g., propyl) and to increment the lipophilicity of the C_5-cycloalkylamine by either substitution or ring enlargement in order to better mimic the aza-bicycle moiety of the optimized amidine **5**.

Synthetic Chemistry

Preparation of the compounds shown in Table 2 was carried out by reaction of the required isocyanates with the protected 3-aminobenzodiazepines **32**, **33**, **35**, and **36**, which in turn were synthesized from the appropriate (2-aminophenyl)(1-azacycloalk-2-yl) methanones **14**, **16**, and **18** following well-precedented benzodiazepine ring construction protocols. Reaction of 2-bromo-2′-nitroacetophenone (**11**) with hexamethylenetetraamine followed by acid hydrolysis and subsequent *N*-BOC protection afforded aminoacetophenone **12** in moderate yield (Scheme 1). Initial attempts to generate the required piperidine ring by double carbon/nitrogen alkylation of **12** with 1,4-dibromobutane in the presence of strong base (NaH, LDA) were, however, unsuccessful. Because this methodology had been previously reported to work satisfactorily with 2-[*N*-(*tert*-butyloxycarbonyl)-amino]acetophenone itself,[13] it was thought that the presence of the nitro group in **12** might interfere with the generation and alkylation of its corresponding enolate. The nitro group was, therefore, catalytically reduced to give aniline **13**. Treatment of **13** with 2 equiv of NaH in DMF at room temperature followed by reaction with 1,4-dibromobutane, indeed, afforded the expected piperidine **14** in 46% yield. Formation of a small quantity (10%) of a 1,1-disubstituted-cyclopentane **15** was also observed in this reaction. It is noteworthy that modification of the above reaction conditions (e.g., different base, solvent) resulted in reduced yields of **14**. Attempted alkylation of **13** with 1,4-dibromo-2,2-dimethylbutane failed to give significant amounts of the 4,4-dimethylpiperidine **16**, and 1,1-disubstituted-cyclopentane **17** was the only isolable product. Thus, the presence of a *gem*-dimethyl group in the electrophile significantly altered the reaction pathway, from a 6-*exo-tet* process to a more favored 5-*exo-tet* mode of cyclization. Preparation of the 5,5-dimethylhomopiperidine **18** was possible under the standard conditions, albeit in low (21%) yield and accompanied by formation of a similar quantity of the cyclohexyl derivative **19**. Alkylation of **13** with 1,5-dibromopentane failed to give either a homopiperidine or a 1,1-disubstituted cyclohexane and suggests the involvement of a *gem*-dimethyl (or reactive rotamer) effect in the previous case.[14]

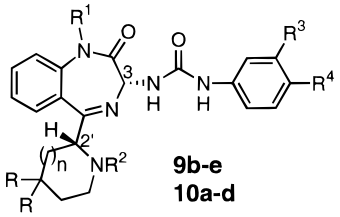
Having failed to prepare methanone **16** by construction of the piperidine ring, a different approach was sought where a preformed and suitably protected piperidine-2-carboxaldehyde (or piperidine-2-carboxamide) could be appended to the ortho position of aniline. *N*-BOC-4,4-dimethylpipecolic acid (**23**) was synthesized from 4,4-dimethyl-2-cyclohexenone following a literature procedure (Scheme 2)[15] and then converted to the

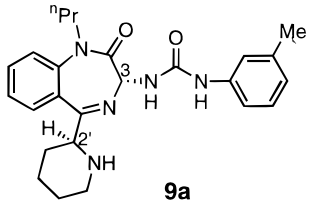
Table 1. CCK Receptor Binding Affinities for Compounds in Chart 1

compd	C_3 stereo	IC_{50} (nM)[a] CCK-B	CCK-A
1	*R*	8.5	736
2	*R*	0.28	1800
3	*R,S*	137	480
4	*R,S*	1.3	10
5	*R*	0.1	1600
6	*R,S*	66	65
7	*R,S*	0.56	435
8	*R,S*	18	1750

[a] Receptor binding is expressed as IC_{50}, the concentration of compound required for half-maximal inhibition of the binding of [^{125}I]BH CCK-8s to receptors in pancreatic tissue (CCK-A) or guinea pig cortical membranes (CCK-B). The results represent the geometric mean of two to four separate experiments. The variation in the measured IC_{50} values between each experiment was less than 2-fold of the mean quoted.

Table 2. CCK Receptor Binding Affinities of 5-(Piperidin-2′-yl)-1,4-benzodiazepines and 5-(homopiperidin-2′-yl)-1,4-benzodiazepines

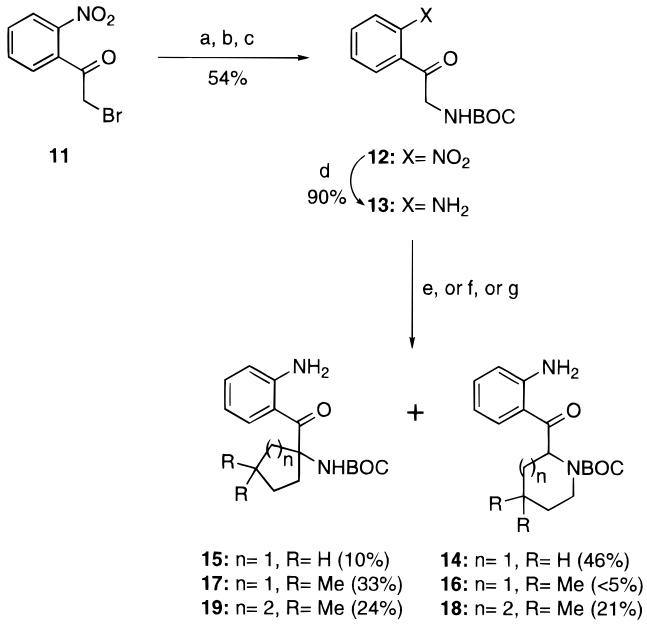




								IC$_{50}$ (nM)[b]	
compd	*n*	stereo[a]	R	R^1	R^2	R^3	R^4	CCK-B	CCK-A[c]
9a	1	3*RS*,2′*SR*						41	3000 (27
9b	1	3*RS*,2′*RS*	H	*n*-Pr	H	Me	H	36	3000 (16)
9c	1	3*RS*,2′*RS*	H	*n*-Pr	Me	Me	H	54	2090
9d	1	3*RS*,2′*RS*	Me	*n*-Pr	H	Me	H	1.5	3090
9e	1	3*RS*,2′*RS*	Me	*n*-Pr	H	−CH$_2$CH$_2$CH$_2$−		1.2	4020
10a	2	3*RS*,2′*RS*	Me	*n*-Pr	H	Me	H	15	1510
10b	2	3*RS*,2′*RS*	Me	*n*-Pr	Me	Me	H	26	3540
10c	2	3*RS*,2′*RS*	Me	Me	H	Me	H	12	1390
10d	2	3*RS*,2′*RS*	Me	Me	H	−CH$_2$CH$_2$CH$_2$−		2.4	6490

[a] All compounds are racemic. [b] See footnote *a* under Table 1. [c] Where full IC$_{50}$ not obtained, percentage of inhibition at a concentration of 3000 nM is given in parentheses.

Scheme 1[a]



[a] Reagents: (a) hexamethylenetetraamine, PhCl, 55 °C; (b) concentrated HCl, EtOH, 25 °C; (c) (BOC)$_2$O, Et$_3$N, CH$_2$Cl$_2$, 25 °C; (d) H$_2$, Pd−C, EtOH; (e) NaH, 1,4-dibromobutane, DMF, 0 °C; (f) NaH, 1,4-dibromo-2,2-dimethylbutane, DMF, 0 °C; (g) NaH, 1,5-dibromo-3,3-dimethylpentane, DMF, 0 °C.

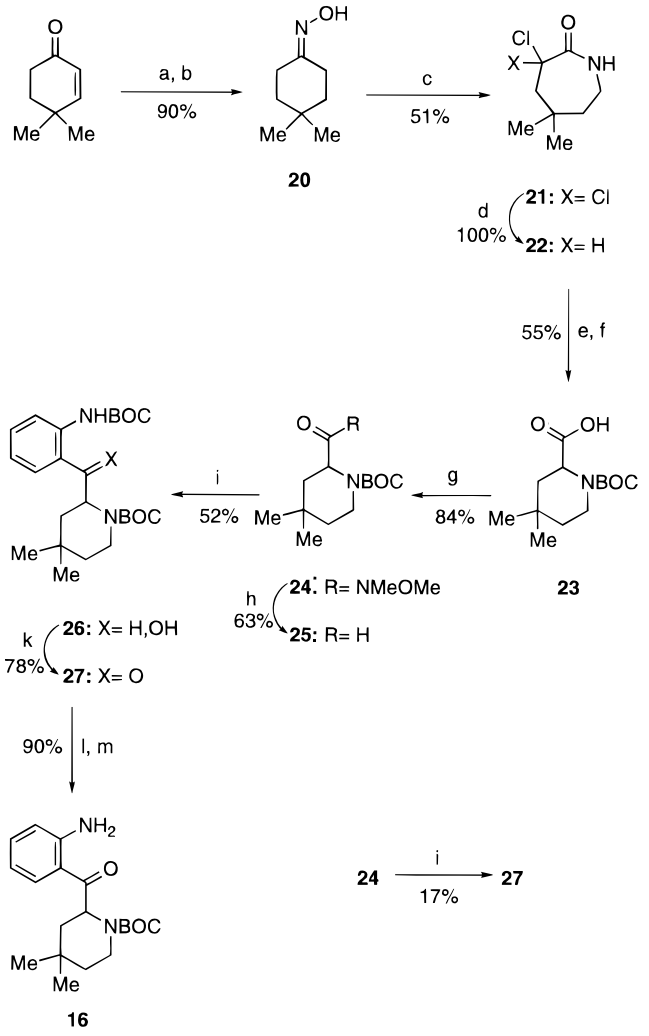
Weinreb amide **24**. Reaction of this material with the dilithium anion of *N*-BOC-aniline afforded ketone **27** in a disappointing 17% yield. This process could be somewhat improved, however, by DIBAL-H reduction of amide **24** to aldehyde **25**, followed by reaction with dilithiated *N*-BOC-aniline to give mainly a single diastereomer of alcohol **26** in 33% overall yield. Oxidation of **26** to ketone **27** proceeded smoothly (78%) using Ley's TPAP/NMO procedure.[16] Removal of the BOC protecting groups of **27** and selective reprotection of the piperidine nitrogen finally afforded methanone **16**.

Synthesis of 3-[(benzyloxycarbonyl)amino]benzodiazepines from amino ketones **14**, **16**, and **18** was carried out using a three-step procedure[10] which involved (i) BOP-Cl-promoted coupling of the anilines with α-isopropylthio-*N*$^{\alpha}$-Z-glycine, (ii) treatment with ammonia in the presence of HgCl$_2$, and finally (iii) acid cyclization of the intermediate acylaminal (Schemes 3 and 4). Under these conditions a mixture of diastereomers was obtained in all cases. Thus, from **14** a 2:1 mixture of **28** (more polar) and **29** (less polar) was obtained in 65% yield, while in the case of **16** the more polar diastereomer **30** was formed in a more selective manner (**30**:**31**, 10:1). The different diastereomeric ratios can be easily rationalized if one invokes their isomerization under the reaction conditions employed. In this regard, it was demonstrated that **31** could be completely converted into **30** by warming (50 °C) in AcOH for several hours. Similar results were obtained with homopiperidine **18**, which gave the more polar compound **34** in 60% yield together with 34% of the other diastereomer. Although at this stage it was not possible to ascertain the relative stereochemistry of these compounds, **28** and **29** were independently converted into the final molecules **9b** and **9a** by (i) N$_1$-alkylation with propyl iodide, (ii) removal of the CBZ protecting group (HCOOH/MeOH, Pd−C), (iii) reaction with *m*-tolyl isocyanate, and (iv) removal of the BOC group. Fortunately, suitable crystals of **9b** were obtained for an X-ray crystallographic determination which both proved the structure itself and its relative stereochemistry (3*RS*,2′*RS*), as well as that of its precursor **28**. On the basis of the similar behavior of diastereomers **28**, **30**, and **34**, they have been assumed to have the same 3*RS*,2′*RS* relative stereochemistry. Because **9a** did not appear to offer any advantage over **9b** in the binding assay (*vide infra*), and due to the tendency of **29** and **31** to isomerize to the more polar **28** and **30**, only the latter two intermediates (and **34**) were subsequently converted into final target compounds. Preparation of **9d,e** and **10a,c,d** was carried out following analogous sequences to that described for **9b**, while **9c** and **10c** were synthesized from **9b** and **10a** using a standard N-methylation procedure.

Structure−Affinity Relationships

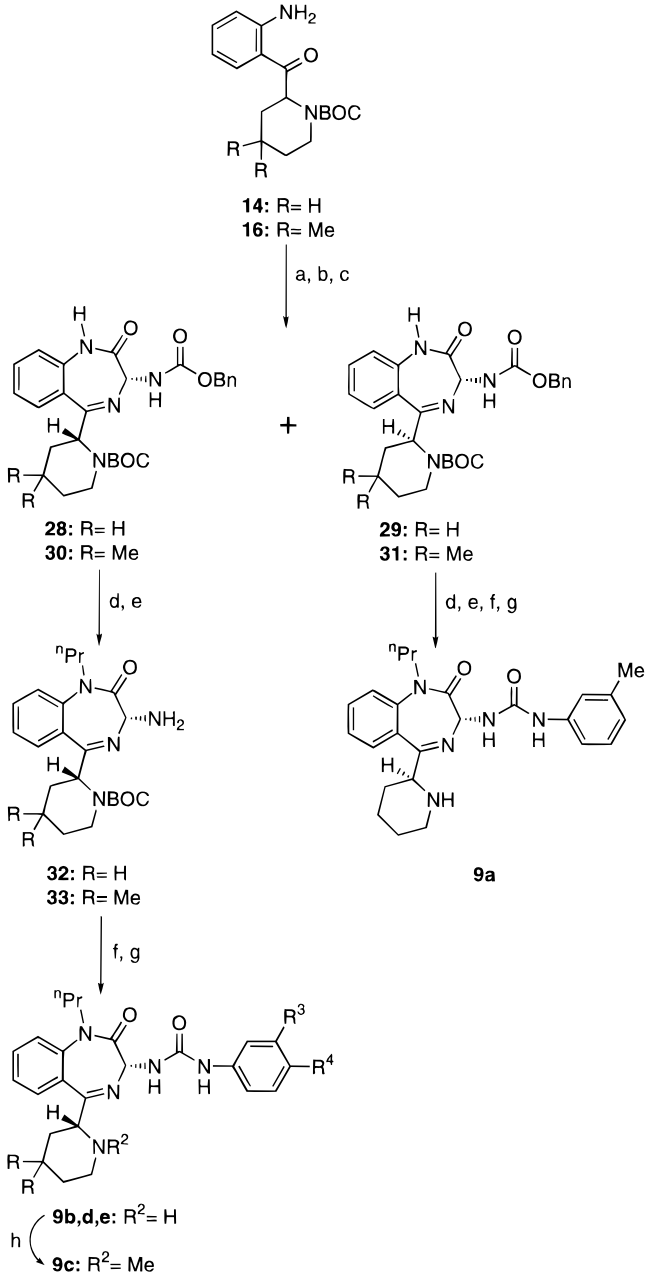
The CCK receptor affinity of the compounds shown in Table 2 was assessed by radioligand binding techniques in rat pancreatic tissue (CCK-A) or guinea pig cortical membranes (CCK-B), as previously reported.[1,17]

Scheme 2[a]



[a] Reagents: (a) H_2, Pd−C, EtOAc; (b) $H_2NOH{\cdot}HCl$, $NaHCO_3$, Et_2O-H_2O; (c) PCl_5, CH_2Cl_2, 7 °C, 0.5 h; then Cl_2(g), 16 h; (d) H_2, Pd−C, AcOH, 40 psi, 20 min; (e) $Ba(OH)_2$, H_2O, reflux; (f) $(BOC)_2O$, NaOH, dioxane−H_2O; (g) HNMeOMe·HCl, 1-HOBT, Et_3N, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, DMF; (h) DIBAL-H, toluene, −78 °C; (i) *N*-BOC-aniline, t-BuLi, THF, −78 °C to −22 °C, 2 h; then add **25** or **24**, −70 °C to −30 °C, 3 h; (k) TPAP, NMO, 4 Å sieves, CH_2Cl_2; (l) TFA−CH_2Cl_2; (m) $(BOC)_2O$, Et_3N, CH_2Cl_2.

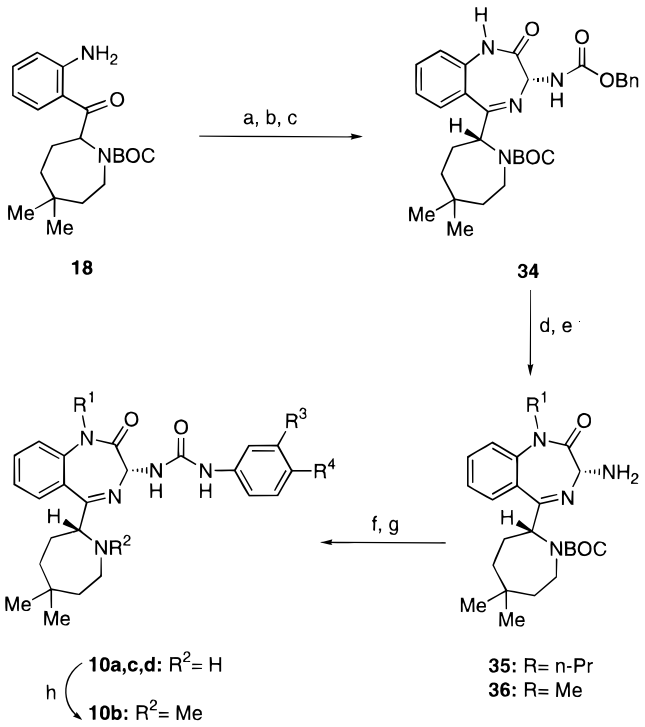
Scheme 3[a]



[a] Reagents: (a) α-(isoprophylthio)-N^{α}-Z-glycine, BOP-Cl, Et_3N, CH_2Cl_2; (b) $HgCl_2$, NH_3, THF, −5 °C; (c) AcOH, NH_4OAc, 25−50 °C; (d) Cs_2CO_3, ^nPrI, DMF; (e) HCO_2H, Pd−C, MeOH; (f) ArNCO, THF; (g) TFA−CH_2Cl_2; (h) CH_2O, $NaCNBH_3$, AcOH, MeOH.

The compounds were tested as the racemates except for **9d**, which was resolved into its individual enantiomers by preparative HPLC using a chiral DNBL column. Examination of the data in Table 2 shows that both diastereomers **9a** and **9b** bind to CCK-B receptors with the same and respectable affinity (IC_{50}, 40 nM), although this is substantially reduced compared to the cyclohexyl analogue **2** (IC_{50}, 0.28 nM).[18] As previously mentioned, because of the similar binding profiles of **9a** and **9b** only (3*RS*,2′*RS*)-diastereomers were subsequently prepared and evaluated. On the basis of available data for previously described compounds such as **3** and **4** (Table 1), incorporation of a *gem*-dimethyl group into a homopiperidine ring was initially pursued, with the expectation that an increase in lipophilicity/size of the benzodiazepine C_5 substituent would result in improved CCK-B receptor affinity. Disappointingly, the increase in affinity for **10a** was only 2-fold compared to the piperidinyl analogue **9b**, a result which was in marked contrast to the previously decribed SAR for the amidine series (e.g., **3** *vs* **4**, Table 1). It was thought, however, that perhaps the large increase in size of the C_5 substituent might not be well accommodated by the receptor at the same time as a large N_1-alkyl, in this case propyl, group. The N_1-methyl derivative **10c** was therefore prepared, although it is known that for closely related benzodiazepine compounds replacement of the N_1-methyl group by an N_1-propyl group improves CCK-B receptor afffinity by 10-fold,[8c] and not surprisingly had the same affinity as **10a**. Thus, it would appear that the *gem*-dimethylhomopiperidine moiety present in **10a** was indeed too large to optimally bind to this receptor. Examination of Dreiding molecular models suggested that the azabicyclo[3.2.2]nonane present in the optimized amidine **5** would be better mimicked by positioning a *gem*-dimethyl substituent at C_4 of a piperidine ring, rather than at C_5 of a homopiperazine as in the case of **10a**. This was supported by semiempirical SCF-

Scheme 4[a]



[a] Reagents: (a) α-(isopropylthio)-*N*α-Z-glycine, BOP-Cl, Et_3N, CH_2Cl_2; (b) $HgCl_2$, NH_3, THF, −5 °C; (c) AcOH, NH_4OAc, 25−50 °C; (d) Cs_2CO_3, ^nPrI or MeI, DMF; (e) HCO_2H, Pd−C, MeOH; (f) ArNCO, THF; (g) TFA−CH_2Cl_2; (h) CH_2O, $NaCNBH_3$, AcOH, MeOH.

MO molecular modeling studies carried out on the benzodiazepine core structures (**37**, **38**, and **39**) present in **5**, **10a**, and **9d** (Chart 2 and Figure 1). It can be clearly seen in panel a that the total volume occupied by the three lowest-energy conformations (AM1 heats of formation within 3 kcal/mol) of the *gem*-dimethylhomopiperidine is significantly larger than that for the azabicyclo[3.2.2]nonane. In the case of the less flexible *gem*-dimethylpiperidine, no other conformations could be found within 3 kcal/mol (AM1) of the best minimum found by a stochastic search/minimization method, and the volume occupied is significantly smaller and in an area of space not explored by the *gem*-dimethylhomopiperidine (panels c and d). Gratifyingly, **9d** showed a much improved receptor binding affinity (IC_{50}, 1.5 nM) compared to both **10a** (10-fold) and to the unsubstituted piperidine **9b** (24-fold). The relatively poor affinity of **10a** might, therefore, be explained by the presence of unfavorable steric interactions between the receptor and the *gem*-dimethylhomopiperidine ring, in areas of space not occupied by either the azabicyclo[3.2.2]nonane or the *gem*-dimethylpiperidine, effectively ruling out low-energy binding. Modification of the *m*-tolylurea of **9d** by incorporation of an indanyl group to give **9e** (IC_{50}, 1.2 nM) had no effect on CCK-B receptor affinity. In the case of the homopiperidine **10c**, however, this increase in lipophilicity provided a 5-fold improvement in receptor affinity, and **10d** (IC_{50}, 2.4 nM) was almost equipotent with **9e**. N-Methylation of the piperidine or homopiperidine rings present in **9b** and **10a** to give **9c** and **10c**, respectively, had a marginal (2-fold) deleterious effect on CCK-B affinity.

It has been well established that in CCK-B receptor antagonists which are based on a benzodiazepine scaffold, the 3*R*-enantiomer usually confers CCK-B over CCK-A receptor selectivity, and in most cases this resolution is essential in order to achieve a high degree of discrimination between these two receptors.[1] It is noteworthy, therefore, that some of the racemic compounds described herein such as **9d**,**e** and **10d** are very selective (CCK-A/CCK-B, >2000) ligands for the CCK-B receptor. In the former two cases this selectivity profile might perhaps reflect the large size of the benzodiazepine N_1-substituent which has been shown to be advantageous for this purpose in other series.[8c] The selectivity of **10d** was somewhat more surprising. Both the affinity and selectivity of **9d** were improved by resolution into its enantiomers (+)-**9d** (L-751,892; IC_{50}, 0.93 nM; CCK-A/CCK-B, >3000) and (−)-**9d** (IC_{50}, 71 nM; CCK-A/CCK-B, 50).

The basicity of **9d** (L-747,238) was assessed by potentiometric titration,[19] and it had a measured pK_a of 9.48, which is substantially greater than that for the amidine **5** (pK_a, 7.1). Thus, at the pH of the binding assay (pH, 6.5) a significant (20%) proportion of unprotonated **5** would exist, but for **9d** the uncharged species would be present in only 0.1%. Taking into account the fact that methiodide **8** (Table 1) is a reasonably potent CCK-B receptor ligand, it is likely that the present series of basic 5-(piperidin-2-yl)- and 5-(homopiperidin-2-yl)benzodiazepine compounds might be binding to this receptor in their protonated form. The increased basicity of **9d** was also reflected in its improved aqueous solubility (0.76 mg/mL, pH = 5.0) compared to **5** (0.15 mg/mL, pH = 5.0) and to **1** (<0.002 mg/mL, pH = 3−7.4).

Evidence to support the antagonist properties of the present series of compounds was gained from an *in vitro* electrophysiological model of CCK-B receptor activation. Thus, compound **9d** inhibited the pentagastrin-induced excitation of single neurons in a slice preparation of the rat ventromedial hypothalamic nucleus (VMH slice)[20] with a K_b < 1 nM, indicating that it is a potent and selective CCK-B antagonist.

The metabolic stability of some compounds in this series such as **10a** and **10b** was evaluated in an *in vitro* rat liver microsome preparation at 37 °C, and they were found to be unusually resistant to degradation (>70% remaining after 24 h). Gratifyingly, these compounds proved to have a significantly improved half-life after iv administration to rats (3 mg/kg) compared to **1**. Interestingly, however, the improvement in half-life for **10a** and **10b** was apparently more the product of an increase in their volume of distribution rather than a reduction in their clearance (**10a**, Cl_p 31 mL/min/kg, $t_{1/2}$ 2.3 h, V_{dis} 4.9 L/kg; **10b**, Cl_p 33 mL/min/kg, $t_{1/2}$ 3.4 h, V_{dis} 8.4 L/kg; **1**, Cl_p 57 mL/min/kg, $t_{1/2}$ 0.6 h, V_{dis} 1.8 L/kg).[21] The increased volume of distribution for **10a**,**b** compared to **1** might perhaps arise from a higher degree of specific ionic interactions between the protonated amine functionality present in the former compounds and charged phosphate head groups in phospholipid membranes.[22] Similar pharmacokinetic parameters were measured for (+)-**9d** (Cl_p 83 mL/min/kg, $t_{1/2}$ 1.9 h, V_{dis} 8.2 L/kg).

In conclusion, a novel series of high-affinity, basic ligands for the CCK-B receptor which incorporate a piperidin-2-yl or a homopiperidin-2-yl group attached to C_5 of a benzodiazepine core structure was designed, and several compounds were synthesized. Compounds

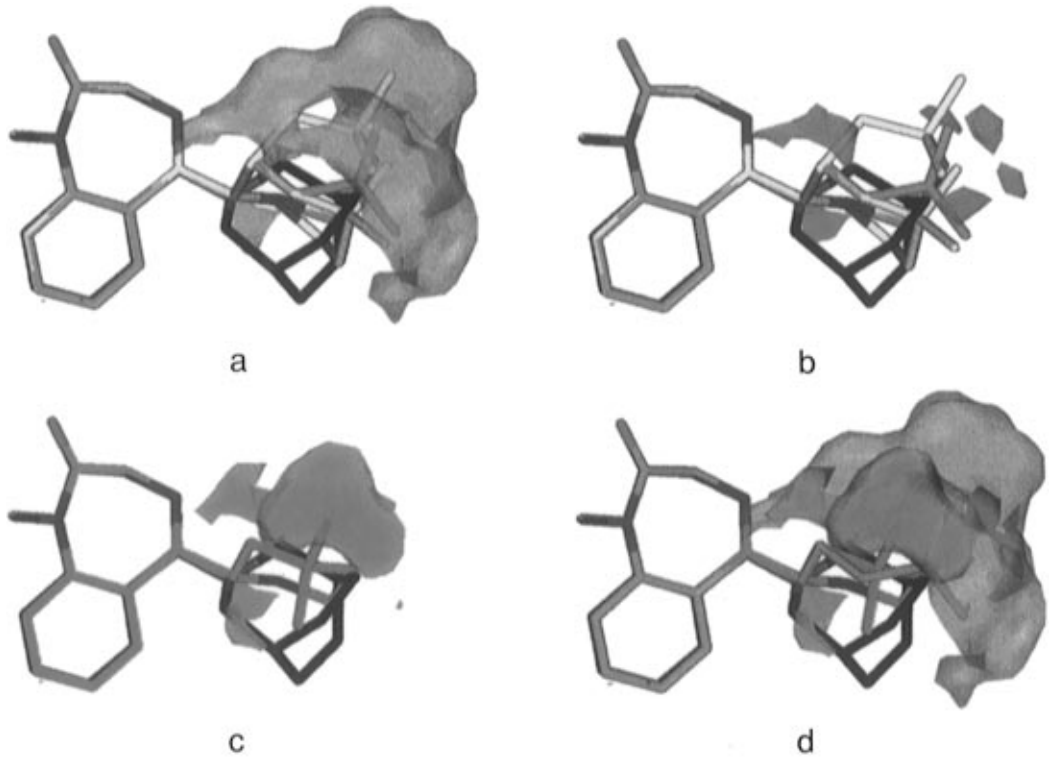
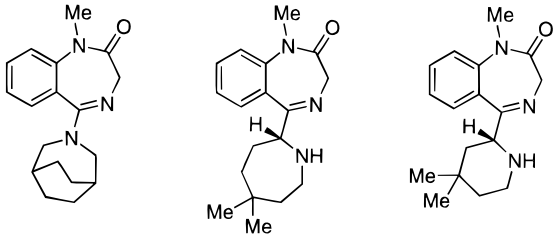


Figure 1. Comparison of the volumes occupied by the low-energy conformations of the benzodiazepine core structures **37**, **38**, and **39**. (a) Excess volume occupied by the lowest-energy conformation (orange) and two other conformations within 3 kcal/mol (yellow) for *gem*-dimethylhomopiperidine **38** compared to azabicyclo[3.2.2]nonane **37** (black). (b) Volume *necessarily* occupied (red) by *all* of the low-energy conformations of **38** but not by **37**. (c) Excess volume occupied by *gem*-dimethylpiperidine **39** (green) compared to **37**. (d) Volume occupied by **39** (green) is largely in an area of space not explored by **38** (orange); in particular, this volume (green) does not overlap with two areas identified as being obligatorily occupied by **38** (red).

Chart 2



37 **38** **39**

to emerge from the present study such as **9d,e** and **10d** showed high affinity for the CCK-B receptor (IC_{50} < 2.5 nM) and very good selectivity over CCK-A (CCK-A/CCK-B > 2000), even as the racemates. Additionally, **10a,b** were shown to be unusually resistent to rat microsomal degradation and to have substantially increased half-lives compared to that of the clinical compound **1**.

Experimental Section

Biological Methods. Detailed procedures for the assessment of antagonist properties of CCK-B ligands using *in vitro* pentagastrin-induced excitation of VMH neuron have been previously reported.[20] Radioligand binding to guinea pig cortical membranes was performed using 50 pM [^{125}I]-labeled Bolton Hunter CCK-8s in 20 mM HEPES buffer, pH 6.5, containing 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EGTA, and 0.025% bacitracin. For rat pancreatic membranes, assay buffer was supplemented with 0.01% trypsin inhibitor and 0.2% BSA. Guinea pig cortical membranes were prepared by homogenization in 0.32 M sucrose, centrifugation, and resuspension of the P2 pellet in assay buffer at 1 g wet weight in 120 mL. Rat pancreatic membranes were prepared in 10 mM HEPES/0.01% trypsin inhibitor, pH 7.4, and centrifuged, and the pellet was resuspended in assay buffer at a 1:2000 dilution. Specific binding in all cases was defined using 1 μM CCK-8s, and the reaction was terminated by filtration through Whatman GF/C filters, using a Brandel cell harvester with 3 × 3 mL washes in ice-cold 100 mM saline wash buffer. Filters were counted on a LKB γ counter.

pK_a Determinations. Potentiometric determination of the pK_a of **9d** was performed using a Sirius PCA-101 titrator (Sirius Analytical Instruments Ltd, East Sussex, England) equipped with a Ross type combination glass electrode calibrated for mixed solvent titrations. The mixed solvent approach was employed because of the limited aqueous solubility of the compounds across the pH range. A cosolvent of 1,4-dioxane/water (60:40, v/v), ionic strength adjusted with 0.15 M KCl, was used. Three separate titrations were performed for each compound with different water/cosolvent ratios to obtain pK_as in the presence of cosolvent (psK_a values). Aqueous pK_a values were calculated by extrapolation to 0% cosolvent using the Yasuda−Shedlovsky relationship:[19] a linear plot of psK_a + log [H_2O] versus $1/\epsilon$, where ϵ is the dielectric constant of the water cosolvent mixture.

Chemical Methods. General Directions. Unless otherwise stated, all ^{1}H NMR spectra were recorded at 360 MHz on a Bruker AM 360 spectrometer or at 250 MHz on a Bruker AC250 instrument. Mass spectra were obtained with a VG70-250 spectrometer. Melting points are uncorrected. Anhydrous THF, DMF, Et_2O, MeOH, and toluene were purchased from the Aldrich Chemical Co., Sureseal. Et_3N was distilled from CaH_2. All solutions were dried over Na_2SO_4 or $MgSO_4$ and concentrated on a Buchi rotary evaporator. Flash chromatography was performed on silica gel (Fluka Art. No. 60738).

2-[*N*-(*tert*-Butyloxycarbonyl)amino]-2′-nitroacetophenone (12). To a stirred mixture of finely powdered hexamethylenetetraamine (12.7 g) in anhydrous chlorobenzene (80 mL) was added *via* cannula a solution of 2-bromo-2′-nitroacetophenone (20 g) in anhydrous chlorobenzene (80 mL) over 5 min, under a nitrogen atmosphere. The resulting mixture was heated to 50−57 °C for 4 h before it was allowed to cool to

room temperature overnight. The precipitated solid was collected by filtration and washed with absolute EtOH (1 × 70 and 1 × 25 mL) and with Et_2O (1 × 200 mL). This pale yellow powder was added portionwise to a mixture of 95% EtOH (75 mL) and concentrated HCl (35 mL) over 2 min, and the resulting suspension was stirred at room temperature for 22 h. After being cooled to 5 °C, the solid was collected, washed with Et_2O (2 × 50 mL), and dried under high vacuum for 45 min. This material was suspended in anhydrous CH_2Cl_2 (500 mL) and treated with anhydrous Et_3N (6 mL) before di-*tert*-butyl dicarbonate (25.5 g) was added in one portion. Additional Et_3N (10 mL) was then added, and the mixture was stirred for 45 min, under nitrogen. The organic phase was washed with 10% aqueous citric acid (1 × 100 and 1 × 70 mL), water (1 × 100 mL), and brine (1 × 100 mL), dried, and concentrated. Flash chromatography of the residue (hexane/EtOAc, 60:40) gave 12.25 g (54%) of **12** as a yellow oil which solidified on standing: ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, dd, J = 8.2 and 0.9 Hz), 7.76 (1H, dt, J = 7.4 and 1.1 Hz), 7.64 (1H, dt, J = 8.2 and 1.6 Hz), 7.51 (1H, br d, J = 7.4 Hz), 5.25 (1H, br s), 4.33 (2H, d, J = 5.6 Hz), 1.40 (9H, s); MS (CI) m/z 280 (M^-).

2-[*N*-(*tert*-Butyloxycarbonyl)amino]-2′-aminoacetophenone (13). A solution of **12** (10.5 g) in a mixture of absolute EtOH (200 mL), EtOAc (60 mL), and water (20 mL) was hydrogenated at 26 psi over 10% Pd−C (2.06 g) for 7 min. The catalyst was removed by filtration and washed with absolute EtOH (50 mL), and solvents were removed under vacuum. The remaining residue was triturated with a mixture of hexane and Et_2O (1:1; 80 mL) to give 7.5 g (90%) of **13** as a pale yellow solid. The mother liquors were concentrated and purified by flash chromatography (hexane/EtOAc, 60:40) to give a further 0.95 g of **13**: ^{1}H NMR ($CDCl_3$) δ 7.63 (1H, d, J = 8.3 Hz), 7.29 (1H, dt, J = 8.0 and 1.5 Hz), 6.70−6.63 (2H, m), 5.57 (1H, br s), 4.61 (2H, d, J = 4.4 Hz), 1.48 (9H, s); MS (CI) m/z 251 ($M^+ + 1$). Anal. ($C_{13}H_{18}N_2O_3 \cdot 0.15H_2O$) C, H, N.

General Procedure for the Preparation of Aminoacetophenones 14 and 18. (2-Aminophenyl)[(2*R,S*)-1-(*tert*-butyloxycarbonyl)piperidin-2-yl]methanone (14) and (2-Aminophenyl)[1-[(*tert*-butyloxycarbonyl)amino]cyclopent-1-yl]methanone (15). To a cooled (−3 °C) and stirred solution of **13** (7.97 g) in anhydrous DMF (95 mL) was added sodium hydride (60% dispersion in oil; 2.67 g) in one portion, under nitrogen. After 20 min, 1,4-dibromobutane (4.18 mL) was added dropwise over 2 min, and stirring was continued at −3 °C for 1.5 h. The reaction was quenched by addition of EtOAc (150 mL), saturated aqueous NH_4Cl (280 mL), and water (100 mL), and the organic phase was decanted off. The aqueous layer was extracted with EtOAc (2 × 250 mL), and the combined organic solutions were washed with brine (2 × 100 mL), dried, and concentrated. Flash chromatography of the residue (hexane/Et_2O, 60:40) afforded 3.96 g (41%) of **14** as a pale yellow solid, together with 900 mg (9%) of **15** as pale yellow crystals.

14: mp 142−145 °C; ^{1}H NMR (DMSO-d_6) δ 7.74 (1H, d, J = 7.8 Hz), 7.27−7.20 (1H, m), 7.09 (2H, br s), 6.78 (1H, dd, J = 8.4 and 1.1 Hz), 6.56−6.49 (1H, m), 5.52 (1H, br s), 3.88−3.76 (1H, m), 3.31−3.16 (1H, m), 2.04−1.06 (1H, m); MS (CI) m/z 305 ($M^+ + 1$). Anal. ($C_{17}H_{24}N_2O_3$) C, H, N.

15: mp 185−192 °C (hexane/Et_2O); ^{1}H NMR (DMSO-d_6; two rotamers) δ 7.89 and 7.83 (1H, d, J = 5.6 Hz), 7.72 and 7.42 (1H, s), 7.18−7.08 (1H,m), 6.89 (0.64H, s), 6.76−6.64 (2.36H, m), 6.46−6.40 (1H, m), 2.32−2.16 (2H, m), 1.98−1.86 (2H, m), 1.74−1.52 (4H, m), 1.13 and 1.07 (9H, s); MS (CI) m/z 305 ($M^+ + 1$). Anal. ($C_{17}H_{24}N_2O_3$) C, H, N.

(2-Aminophenyl)[(2*R,S*)-1-(*tert*-butyloxycarbonyl)-5,5-dimethyl-2,3,4,5,6,7-hexahydro-1*H*-azepin-2-yl]methanone (18). The title compound was prepared in 21% isolated yield from **13** and 1,5-dibromo-3,3-dimethylpentane, following a similar procedure to that described above for **14**: ^{1}H NMR ($CDCl_3$) δ 7.88 and 7.74 (1H, two d, J = 8.1 Hz), 7.26 (1H, m), 6.65 (2H, t, J = 8.0 Hz), 6.18 (2H, s), 5.53 and 5.30 (1H, two dd, J = 12.2 and 5.7 Hz), 4.08 and 3.85 (1H, two m), 3.23 (1H, m), 2.05−1.92 (1H, m), 1.85−1.69 (1H, m), 1.56−1.43 (4H, m), 1.46 and 1.27 (9H, two s), 0.96−0.92 (6H, four s); MS (CI) m/z 347 ($M^+ + 1$); HRMS found m/z 346.2251, $C_{20}H_{30}N_2O_3$ requires m/z 346.2256.

1-(*tert*-Butyloxycarbonyl)-4,4-dimethylpipecolic Acid (23). To a stirred solution of 4,4-dimethylpipecolic acid[15] (24 g, 152 mmol) in a mixture of dioxane (380 mL) and 2 N NaOH (112 mL) was added di-*tert*-butyl dicarbonate (45 g, 206 mmol), and the resulting mixture was stirred at room temperature for 23 h. The organic solvent was removed under vacuum, and the aqueous residue was diluted with water (50 mL) and extracted with Et_2O (2 × 60 mL). The ethereal phases were washed once with water (50 mL), and the combined aqueous solutions were acidified to pH 2 with 5 N HCl, extracted with EtOAc (3 × 200 mL), dried, and concentrated to give 20 g (51%) of **23** as a white solid: mp 127−132 °C; ^{1}H NMR ($CDCl_3$) δ 4.86−4.55 (1H, m), 3.96−3.78 (1H, m), 3.24−3.05 (1H, m), 2.10−1.96 (1H, m), 1.64 (1H, dd, J = 14.0 and 7.4 Hz), 1.54−1.25 (10H, m and s), 0.95 (3H, s), 0.90 (3H, s). Anal. ($C_{13}H_{23}NO_4$) C, H, N.

1-(*tert*-Butyloxycarbonyl)-2(*R,S*)-[(*N,O*-dimethylhydroxylamino)carbonyl]-4,4-dimethylpiperidine (24). To a stirred solution of **23** (24.6 g, 95.6 mmol), *N,O*-dimethylhydroxylamine hydrochloride (12.12 g, 124.3 mmol), and 1-hydroxybenzotriazole (18.09 g, 133.8 mmol) in anhydrous DMF (400 mL) was added anhydrous Et_3N (30.7 mL, 219.9 mmol), followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (21.08 g, 109.9 mmol). The resulting mixture was stirred at room temperature, under nitrogen, for 23 h before it was diluted with Et_2O (1 L), washed with 1 N HCl (2 × 250 mL), 1 N NaOH (1 × 250 mL), and brine (1 × 200 mL), dried, and concentrated. Flash chromatography of the residue (hexane/Et_2O, 40:60) gave 24.1 g (84%) of **24** as a white solid: mp 66−68 °C; ^{1}H NMR ($CDCl_3$) δ 4.76 (1H, br s), 3.92−3.74 (1H, m), 3.75 (3H, s), 3.58−3.42 (1H, m), 3.19 (3H, s), 1.84 (1H, dd, J = 14.0 and 3.3 Hz), 1.64 (1H, dd, J = 14.0 and 7.6 Hz), 1.52−1.34 (11H, m and s), 0.94 (3H, s), 0.92 (3H, s); MS (CI) m/z 301 ($M^+ + 1$). Anal. ($C_{15}H_{28}N_2O_4$) C, H, N.

1-(*tert*-Butyloxycarbonyl)-4,4-dimethylpiperidine-2(*R,S*)-carboxaldehyde (25). To a cooled (−75 °C) and stirred solution of **24** (4.0 g, 13.3 mmol) in anhydrous toluene (200 mL) was added dropwise, *via* cannula, DIBAL-H (1 M in toluene; 21.3 mmol) over 45 min, under nitrogen. The mixture was stirred at −75 °C for 3.5 h and at −30 °C for 3.5 h before more DIBAL-H was added (4 mL). After a further 1 h at −30 °C, excess DIBAL-H was destroyed by addition of MeOH (14 mL) followed by aqueous citric acid (10%; 140 mL). Products were extracted with Et_2O (3 × 125 mL), and the combined organic solutions were washed with brine (2 × 50 mL), dried, and concentrated. Flash chromatography of the residue (hexane/Et_2O, 60:40) afforded 2.0 g (63%) of **25** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.55 (1H, s), 4.26 (1H, t, J = 5.7 Hz), 3.80−3.51 (1H, m), 3.30−3.14 (1H, m), 1.80 (1H, dd, J = 13.8 and 5.1 Hz), 1.57 (1H, dd, J = 13.8 and 6.5 Hz), 1.52−1.30 (11H, m and s), 0.98 (3H, s), 0.85 (3H, s); MS (CI) m/z 242 ($M^+ + 1$).

[2-[*N*-(*tert*-Butyloxycarbonyl)amino]phenyl][1-(*tert*-butyloxycarbonyl)-4,4-dimethylpiperidin-2-yl]methanol (26). To a cooled (−75 °C) and stirred solution of *N*-(*tert*-butyloxycarbonyl)aniline (3.62 g, 18.74 mmol) in anhydrous THF (30 mL) was added dropwise, *via* cannula, *tert*-butyllithium (1.7 M in pentane; 21.5 mL) over 27 min, under nitrogen. After a further 10 min, the mixture was allowed to warm to −22 °C, and it was stirred for 2 h before being recooled to −70 °C. A solution of **25** (1.95 g, 9.14 mmol) in anhydrous THF (15 mL) was added over 9 min, and the resulting solution was stirred at this temperature for 1 h 50 min and at −30 °C for 50 min. Water (60 mL) was added, and products were extracted with EtOAc (2 × 80 mL), dried, and concentrated. Flash chromatography of the residue (hexane/Et_2O, 60:40) gave 2.06 g (52%) of **26** as a single diastereomer: ^{1}H NMR ($CDCl_3$) δ 8.19 (1H, s), 7.95 (1H, d, J = 7.8 Hz), 7.32−7.24 (1H, m), 7.14−7.06 (1H, m), 7.04−6.94 (1H, m), 4.84 (1H, d, J = 9.1 Hz), 4.40−4.28 (1H, br q), 3.80−3.62 (1H, m), 3.25−3.06 (1H, m), 1.51 (9H, s), 1.50−0.98 (4H, m), 0.91 (3H, s), 0.83 (3H, s); MS (CI) m/z 435 ($M^+ + 1$).

[2-[*N*-(*tert*-Butyloxycarbonyl)amino]phenyl][(2*R,S*)-1-(*tert*-butyloxycarbonyl)-4,4-dimethylpiperidin-2-yl]methanone (27). Method A. To a cooled (−38 °C) and stirred suspension of *N*-(*tert*-butyloxycarbonyl)aniline (5.27 g, 27.3 mmol) in anhydrous Et_2O (60 mL) was added dropwise, *via* cannula, *tert*-butyllithium (1.7 M in pentane; 31.3 mL) over 20 min, under nitrogen. The resulting clear yellow solution was stirred at −5 °C for 3 h before it was cooled to −60 °C, and a solution of **24** (4.0 g, 13.3 mmol) in anhydrous Et_2O (15 mL) was added dropwise over 4 min. After 20 min, the mixture was allowed to warm to −25 °C and stirred for 1 h 50 min. Saturated aqueous NH_4Cl (100 mL) was added, and the organic phase was decanted off. The aqueous layer was extracted with Et_2O (120 mL), and the combined ethereal phases were washed with 1 N HCl (50 mL) and brine (50 mL), dried, and concentrated. The residual oil was triturated with a mixture of hexane and Et_2O (80:20; 40 mL), and the precipitated *N*-(*tert*-butyloxycarbonyl)aniline was removed by filtration. The filtrate was concentrated under vacuum and the residue purified by flash chromatography (hexane/CH_2Cl_2, 50:50 to 30:70) to give 1.0 g (17%) of **27** as a thick colorless oil: ^{1}H NMR ($CDCl_3$) δ 10.18 (1H, br s), 8.38 (1H, d, J = 8.4 Hz), 7.75 (1H, d, J = 7.9 Hz), 7.50 (1H, t, J = 8.2 Hz), 7.03 (1H, t, J = 8.0 Hz), 5.46−5.30 (1H, m), 3.94- 3.82 (1H, m), 2.54−2.40 (1H, m), 1.79 (1H, d, J = 6.4 Hz), 1.60−1.22 (20H, m), 0.92 (3H, s), 0.78 (3H, s); MS (CI) m/z 432 (M^-).

Method B. To a stirred solution of **26** (1.50 g, 3.45 mmol) and 4-methylmorpholine *N*-oxide monohydrate (850 mg, 6.20 mmol) in anhydrous CH_2Cl_2 (35 mL) were added 4 Å sieves (1.6 g), and the mixture was stirred for 15 min before tetrapropylammonium perruthenate (60 mg, 0.20 mmol) was added. After being stirred at room temperature for 19 h, the mixture was diluted with CH_2Cl_2 (200 mL) and washed with aqueous $NaHCO_3$ (10%; 60 mL), brine (60 mL), and saturated aqueous $CuSO_4$ (60 mL). The organic solution was then filtered through a plug of silica gel and eluted with Et_2O (3 × 40 mL). The filtrate was concentrated under vacuum, and the residue purified by flash chromatography (hexane/Et_2O, 80:20) to give 1.16 g (78%) of **27** as a thick colorless oil.

(2-Aminophenyl)[(2*R,S*)-1-(*tert*-butyloxycarbonyl)-4,4-dimethylpiperidin-2-yl]methanone (16). A solution of **27** (2.49 g, 5.75 mmol) in a mixture of anhydrous CH_2Cl_2 (40 mL) and TFA (12 mL) was stirred at room temperature for 30 min, under nitrogen. Solvents were removed under vacuum, and the residue was azeotroped with MeOH (50 mL). The residue was dissolved in a mixture of CH_2Cl_2 and EtOAc (1:1; 100 mL) and washed with saturated aqueous K_2CO_3 (40 mL). The aqueous layer was extracted with the same solvent system (100 mL), and the combined organic solutions were washed with brine (40 mL), dried, and concentrated. The remaining yellow oil was dissolved in a mixture of anhydrous THF (20 mL), anhydrous CH_2Cl_2 (20 mL), and anhydrous Et_3N (800 μL, 5.75 mmol), and di-*tert*-butyl dicarbonate (1.5 g, 6.90 mmol) was added. After 15 h at room temperature, the reaction mixture was partitioned between 1 N HCl (40 mL) and Et_2O (2 × 150 mL), and the combined organic solutions were washed with brine (2 × 30 mL), dried, and concentrated. Flash chromatography of the residue (hexane/Et_2O, 60:40) gave 1.72 g (90%) of **16** as a white solid: mp 128−130 °C (hexane/Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, d, J = 8.0 Hz), 7.29−7.24 (1H, m), 6.72 (1H, d, J = 7.6 Hz), 6.67 (1H, t, J = 8.0 Hz), 5.48−5.23 (1H, m), 3.92−3.82 (1H, m), 3.56−3.44 (1H, m), 1.92−1.78 (2H, m), 0.93 (3H, s), 0.80 (3H, s); MS (CI) m/z 333 (M^+ + 1). Anal. ($C_{19}H_{28}N_2O_3$) C, H, N.

General Procedure for the Preparation of Benzodiazepines 28, 29, 30, 31, and 34. 3-[(Benzyloxycarbonyl)amino]-5-[1-(*tert*-butyloxycarbonyl)piperidin-2-yl]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one: Diastereomers 28 and 29. To a cooled (5 °C) and stirred solution of **14** (3.25 g, 10.7 mmol) and α-(isopropylthio)-*N*-(benzyloxycarbonyl)glycine (4.23 g, 14.9 mmol) in anhydrous CH_2Cl_2 (50 mL) was added anhydrous Et_3N (4.16 mL, 29.9 mmol) followed by BOP-Cl (3.80 g, 14.9 mmol) in one portion. The mixture was stirred at 5 °C for 5 min and at room temperature for 55 min before it was diluted with Et_2O (200 mL). The organic solution was washed with aqueous citric acid (10%; 2 × 40 mL), saturated aqueous $NaHCO_3$ (40 mL), water (40 mL) and brine (40 mL), dried, and concentrated. Flash chromatography of the residue (hexane/Et_2O, 60:40) gave the intermediate α-(isopropylthio)-glycinamide derivative (2.78 g) as a pale yellow oil: ^{1}H NMR (DMSO-d_6) δ 11.44−11.18 (1H, m), 8.52−8.26 (2H, m), 8.08−7.98 (1H, br d), 7.70−7.58 (1H, br t), 7.44−7.20 (6H, m), 5.62−5.55 (1H, m), 5.50−5.38 (1H, m), 5.10 (2H, s), 3.88−3.70 (1H, m), 3.28−3.02 (2H, m), 2.00−1.10 (21H, m); MS (CI) m/z 569 (M^-).

Ammonia gas was bubbled for 1.5 h through a cooled (−5 °C) and stirred solution of the above α-(isopropylthio)glycinamide (2.77 g, 4.9 mmol) in anhydrous THF (100 mL). $HgCl_2$ (2.64 g, 9.7 mmol) was then added, and ammonia bubbling was continued for a further 3 h at the same temperature. The reaction mixture was filtered through hyflo filter aid, and the filtrate was concentrated under vacuum. The remaining residue was suspended in glacial AcOH (40 mL), NH_4OAc (1.5 g) was added, and the mixture was stirred at room temperature for 19 h and at 50 °C for 1.5 h, under nitrogen. Solvents were removed under vacuum, the residue was partitioned between 2 N NaOH (80 mL) and Et_2O (2 × 200 mL), and the combined ethereal phases were washed with brine (2 × 50 mL), dried, and concentrated. Flash chromatography of the crude product (hexane/Et_2O, 20:80) afforded 577 mg (25%) of diastereomer **29** (3*RS*,2′*SR*; less polar) and 940 mg (40%) of diastereomer **28** (3*RS*,2′*RS*, more polar) as white solids. Both diastereomers had MS (CI) m/z 493 (M^+ + 1).

General Procedure for the N_1-Alkylation and Removal of the CBZ Group of Benzodiazepines 28, 29, 30, and 34. 3(*R,S*)-Amino-5-[(2*R,S*)-1-(*tert*-butyloxycarbonyl)-4,4-dimethylpiperidin-2-yl]-1,3-dihydro-1-(1-propyl)-2*H*-1,4-benzodiazepin-2-one (33). A mixture of **30** (200 mg, 0.38 mmol), Cs_2CO_3 (132 mg, 0.40 mmol), and 1-iodopropane (56 μL, 0.58 mmol) in anhydrous DMF (6 mL) was stirred at room temperature, under nitrogen for 1 h 40 min. Water (25 mL) was added, and the product was extracted with EtOAc (2 × 50 mL), washed with brine (20 mL), dried, and concentrated. Flash chromatography of the residue (hexane/EtOAc, 70:30) gave 200 mg (92%) of the intermediate N_1-propyl derivative as a thick colorless oil: ^{1}H NMR (DMSO-d_6) δ 8.19 (1H, br d, J = 6.3 Hz), 7.76−7.56 (3H, m), 7.42−7.29 (6H, m), 5.40−5.30 (1H, m), 5.02−4.92 (3H, m), 3.80−3.68 (2H, m), 3.64−3.54 (1H, m), 3.28−3.10 (1H, m), 1.80−1.54 (3H, m), 1.40−1.20 (12H, m), 0.88 (3H, t, J = 7.3 Hz), 0.78 (3H, s), 0.56 (3H, s); MS (CI) m/z 563 (M^+ + 1).

To a stirred suspension of 10% Pd−C (350 mg) in a mixture of MeOH and 90% HCOOH (95.5:4.5; 80 mL) was added dropwise, *via* cannula, a solution of the product from the preceding step (790 mg, 1.40 mmol) in the same solvent mixture (22 mL), over 15 min. After being stirred for a further 25 min at room temperature, under nitrogen, the catalyst was removed by filtration and washed with MeOH/CH_2Cl_2 (1:1; 3 × 50 mL). The filtrate was basified with 10% aqueous Na_2CO_3, and the organic solvents were removed under vacuum. The residue was diluted with water (20 mL) and saturated aqueous K_2CO_3, and the product was extracted with EtOAc (2 × 150 mL). The combined organic solutions were dried and concentrated to give 577 mg (96%) of **33** as a thick colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.64−7.46 (2H, m), 7.36 (1H, d, J = 7.7 Hz), 7.24 (1H, t, J = 7.4 Hz), 5.44−5.32 (1H, m), 4.34 (1H, s), 3.96−3.80 (2H, m), 3.52−3.24 (2H, m), 2.36−1.90 (3H, m), 1.80−1.24 (14H, m), 0.97 (3H, t, J = 7.4 Hz), 0.80 (3H, s), 0.59 (3H, s); MS (CI) m/z 429 (M^+ + 1).

32: ^{1}H NMR ($CDCl_3$) δ 7.84−7.60 (1H, br s), 7.50 (1H, t, J = 8.1 Hz), 7.34 (1H, d, J = 8.1 Hz), 7.25 (1H, t, J = 7.4 Hz), 5.52−5.30 (1H, br s), 4.30−4.18 (2H, m), 3.96−3.83 (1H, m), 3.64−3.40 (2H, m), 1.93 (2H, br s), 1.76−1.10 (17H, m); MS (CI) m/z 401 (M^+ + 1).

35: ^{1}H NMR ($CDCl_3$) δ 8.02 and 7.67 (1H, two d, J = 6.4 Hz), 7.56−7.45 (1H, m), 7.37−7.24 (2H, m), 5.18−5.00 (1H, m), 4.35−4.24 (2H, m), 3.97 and 3.75 (1H, two m), 3.58 (1H, m), 3.22−3.00 (1H, m), 1.91−1.21 (10H, m), 1.50 and 1.47 (9H, s), 0.90−0.82 (9H, m); MS (CI) m/z 443 (M^+ + 1).

36: ^{1}H NMR ($CDCl_3$) δ 8.06 and 7.68 (1H, two d), 7.53−7.47 (1H, m), 7.32−7.24 (2H, m), 5.14−4.96 (1H, m), 4.30 (1H, m), 3.95−3.76 (1H, two m), 3.43 and 3.42 (3H, two s), 3.28−

3.05 (1H, m), 2.19 (2H, br s), 1.50 and 1.47 (9H, two s), 1.42−1.24 (6H, m), 0.94−0.87 (6H, m); MS (CI) m/z 415 ($M^+ + 1$).

General Procedure for the Preparation of 3-Ureidobenzodiazepines 9a−g and 10a−d. *N*-[2,3-Dihydro-2-oxo-5-[piperidin-2(*R,S*)-yl]-1-(1-propyl)-1*H*-1,4-benzodiazepin-3(*R,S*)-yl]-*N*′-(3-methylphenyl)urea Hydrochloride Salt (9b). To a stirred solution of **32** (370 mg, 0.92 mmol) in anhydrous THF (10 mL) was added dropwise *m*-tolyl isocyanate (130 μL, 1.0 mmol) over 2 min, under nitrogen. After the mixture was stirred at room temperature for 4.5 h, MeOH (8 mL) was added and solvents were removed under vacuum. The remaining residue was triturated with a mixture of hexane (15 mL) and Et_2O (10 mL) to give 432 mg (88%) of *N*-[5-[1-(*tert*-butyloxycarbonyl)piperidin-2(*R,S*)-yl]-2,3-dihydro-2-oxo-1-(1-propyl)-1*H*-1,4-benzodiazepin-3(*R,S*)-yl]-*N*′-(3-methylphenyl)urea as a white solid: mp 206−213 °C; ^{1}H NMR ($CDCl_3$) δ 7.76−7.60 (7H, m), 6.86 (1H, br d, J = 7.8 Hz), 6.62 (1H, br s), 6.35 (1H, br d, J = 8.0 Hz), 5.50−5.38 (2H, m), 4.30−4.20 (1H, m), 3.98−3.84 (1H, m), 3.66−3.52 (1H, m), 3.44−3.22 (1H, br s), 2.31 (3H, s), 1.80−1.04 (17H, m), 0.86 (3H, t, J = 7.3 Hz); MS (CI) m/z 533 (M^-). Anal. ($C_{30}H_{39}N_5O_4$) C, H, N.

A solution of the above product (80 mg) in a mixture of CH_2Cl_2 (4 mL) and TFA (2 mL) was allowed to stand at room temperature for 20 min. Solvents were removed under vacuum and the residue azeotroped with MeOH (2 × 15 mL) before it was partitioned between 10% aqueous K_2CO_3 (5 mL) and EtOAc (50 mL). The combined organic solutions were dried and concentrated, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 90:10) to give 46 mg (71%) of **9b** free base. The hydrochloride salt was prepared and recrystallized from MeOH/Et_2O: mp 191−195 °C; ^{1}H NMR ($CDCl_3$) δ 10.65 (1H, s), 9.27 (1H, br d), 9.02 (1H, d, J = 8.6 Hz), 8.89 (1H, br q), 7.83 (1H, d, J = 6.8 Hz), 7.54 (1H, t, J = 7.2 Hz), 7.40−7.24 (4H, m), 6.98 (1H, t, J = 7.7 Hz), 6.67 (1H, d, J = 7.5 Hz), 5.39 (1H, d, J = 8.6 Hz), 4.32−4.23 (1H, m), 3.96 (1H, br t), 3.54−3.42 (1H, m), 3.11 (1H, br d, J = 12.6 Hz), 2.87 (1H, br q, J = 11 Hz), 2.23 (3H, s), 1.92−1.76 (1H, m), 1.70−1.44 (2H, m), 1.30−1.02 (4H, m), 0.77 (3H, t, J = 7.3 Hz), 0.46−0.30 (1H, m); MS (CI) m/z 433 (M^-). Anal. ($C_{25}H_{31}N_5O_2$·1.0HCl·0.7H_2O) C, H, N.

9a hydrochloride: ^{1}H NMR (DMSO-d_6) δ 9.34−9.22 (2H, m), 7.76−7.46 (1H, br s), 7.80 (1H, d, J = 7.9 Hz), 7.73 (1H, dt, J = 7.8 and 1.2 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.49 (1H, d, J = 8.2 Hz), 7.44 (1H, t, J = 7.9 Hz), 7.19 (1H, s), 7.15−7.06 (2H, m), 6.73 (1H, d, J = 7.3 Hz), 5.13 (1H, d, J = 8.2 Hz), 4.50−4.38 (1H, br s), 3.88−3.74 (2H, m), 3.17 (1H, br d, J = 12.9 Hz), 3.04−2.90 (1H, br s), 2.41 (1H, br d, J = 11 Hz), 2.22 (3H, s), 1.90−1.52 (6H, m), 0.86 (3H, t, J = 7.3 Hz); MS (CI) m/z 433 (M^-). Anal. ($C_{25}H_{31}N_5O_2$·1.0HCl) C, H, N.

9d hydrochloride: mp 181−183 °C (MeOH/Et_2O); ^{1}H NMR ($CDCl_3$) δ 10.63 (1H, s), 9.10 (1H, br d), 9.02 (1H, d, J = 8.6 Hz), 8.62 (1H, br q), 7.83 (1H, dd, J = 7.9 and 1.2 Hz), 7.55 (1H, dt, J = 7.1 and 1.3 Hz), 7.38−7.24 (4H, m), 6.99 (1H, t, J = 7.7 Hz), 6.69 (1H, d, J = 7.5 Hz), 5.42 (1H, d, J = 8.6 Hz), 4.35−4.21 (2H, m), 3.54−3.43 (1H, m), 3.15−2.93 (2H, m), 2.25 (3H, s), 1.62−1.50 (1H, m), 1.32−1.04 (3H, m), 0.95−0.86 (4H, m and s), 0.73 (3H, t, J = 7.3 Hz), 0.64 (3H, s), 0.44 (1H, t, J = 13.3 Hz); MS (CI) m/z 461 (M^-). Anal. ($C_{27}H_{35}N_5O_2$·1.0HCl·0.2H_2O) C, H, N.

The enantiomers of this compound were separated by HPLC using a DNBL column (250 × 20 mm i.d.; 5 μm particle size) and eluting with hexane/EtOH (70:30; flow 20 mL/min; detection at 230 nm) to afford (+)-**9d** (retention time 16.1 min) and (−)-**9d** (retention time 23.5 min). The enantiomeric purity of these compounds was shown to be >99% ee for (+)-**9d** and 97.7% ee for (−)-**9d**, using an analytical DNBL column (250 × 4.6 mm i.d.; 5 μm particle size) and eluting with a mixture of MeOH, 1-chlorobutane, and AcOH (10:89:1) (retention times 4.9 and 6.8 min, respectively). (−)-**9d**: $[\alpha]_D$ −6.0 (c = 0.55, MeOH).

9e hydrochloride: mp 170 °C (dec; CH_2Cl_2/Et_2O); ^{1}H NMR ($CDCl_3$) δ 10.51 (1H, s), 9.14−9.02 (2H, m), 8.76−8.60 (1H, m), 7.84 (1H, dd, J = 7.9 and 1.2 Hz), 7.54 (1H, dt, J = 7.2 and 1.4 Hz), 7.35 (1H, d, J = 8.2 Hz), 7.32−7.22 (3H, m), 6.94 (1H, d, J = 8.0 Hz), 5.42 (1H, d, J = 8.6 Hz), 4.36−4.20 (2H, m), 3.54−3.44 (1H, m), 3.12−2.90 (2H, m), 2.82−2.68 (4H, m), 2.00−1.87 (2H, m), 1.60−1.45 (1H, m), 1.34−1.10 (3H, m), 0.95−0.86 (4H, m and s), 0.73 (3H, t, J = 7.4 Hz), 0.59 (3H, s), 0.48 (1H, t, J = 13.5 Hz); MS (CI) m/z 400 ($M^+ + 1$). Anal. ($C_{29}H_{37}N_5O_2$·1.0HCl·0.5H_2O) C, H, N.

10a hydrochloride: mp 174−184 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.33 (1H, br s), 9.27 (1H, s), 8.52 (1H, br s), 7.92 (1H, d, J = 7.6 Hz), 7.76−7.74 (2H, m), 7.52−7.46 (2H, m), 7.20−7.15 (2H, m), 7.09 (1H, t, J = 7.7 Hz), 6.73 (1H, d, J = 7.5 Hz), 5.21 (1H, d, J = 8.3 Hz), 4.95 (1H, m), 4.22 (1H, m), 3.73 (1H, m), 3.18 (2H, m), 2.22 (3H, s), 1.73−1.23 (8H, m), 0.92 (3H, s), 0.76 (3H, t, J = 7.3 Hz); MS (CI) m/z 476 ($M^+ + 1$). Anal. ($C_{28}H_{37}N_5O_2$·1.0HCl·0.7H_2O) C, H, N.

10c hydrochloride: mp 193−203 °C; ^{1}H NMR (DMSO-d_6) δ 9.40 (1H, br m), 9.27 (1H, s), 8.49 (1H, br m), 7.92 (1H, dd), 7.77 (1H, dt), 7.65 (1H, dd), 7.48 (2H, m), 7.19−7.15 (2H, m), 7.09 (1H, t, J = 7.6 Hz), 6.73 (1H, dd), 5.24 (1H, d, J = 8.2 Hz), 4.94 (1H, m), 3.37 (3H, s), 3.18 (2H, m), 2.22 (3H, s), 1.74−1.24 (6H, m), 0.91 (3H, s), 0.83 (3H, s); MS (CI) m/z 448 ($M^+ + 1$). Anal. ($C_{26}H_{33}N_5O_2$·1.0HCl·0.4H_2O) C, H, N.

10d hydrochloride: mp 171−175 °C; ^{1}H NMR (DMSO-d_6) δ 9.41 (1H, m), 9.17 (1H, s), 8.47 (1H, m), 7.91 (1H, d, J = 7.9 Hz), 7.76 (1H, t, J = 7.8 Hz), 7.65 (1H, d, J = 8.1 Hz), 7.48 (1H, t, J = 7.6 Hz), 7.43 (1H, d, J = 8.5 Hz), 7.26 (1H, s), 7.07 (2H, m), 5.25 (1H, d, J = 8.4 Hz), 4.93 (1H, m), 3.37 (3H, s), 3.18 (2H, m), 2.76 (4H, q, J = 6.9 Hz), 1.96 (2H, qn, J = 7.3 Hz), 1.70−1.24 (6H, m), 0.91 (3H, s), 0.83 (3H, s); MS (CI) m/z 473 (M^-). Anal. ($C_{28}H_{35}N_5O_2$·1.0HCl·0.6H_2O) C, H, N.

General Procedure for the N-Methylation of 9b and 10a. *N*-[2,3-Dihydro-5-[1-methylpiperidin-2(*R,S*)-yl]-2-oxo-1-(1-propyl)-1*H*-1,4-benzodiazepin-3(*R,S*)-yl]-*N*′-(3-methylphenyl)urea Hydrochloride (9c). To a stirred solution of **9b** (100 mg, 0.23 mmol) in a mixture of MeOH (5 mL) and glacial AcOH (53 μL, 0.92 mmol) was added $NaCNBH_3$ (15 mg, 0.23 mmol) followed by a solution of CH_2O (38% w/v aqueous solution; 23 μL) in MeOH (1 mL). After 40 min, saturated aqueous K_2CO_3 (2 mL) was added, and the MeOH was removed under vacuum. The residue was diluted with water (15 mL), and the product was extracted with CH_2Cl_2 (2 × 40 mL), washed with brine (20 mL), dried, and concentrated. Flash chromatography of the residue (CH_2Cl_2/MeOH, 90:10) gave 96 mg of **9c** as a white solid. The hydrochloride salt was prepared from MeOH/Et_2O; mp 180−187 °C; ^{1}H NMR (DMSO-d_6) δ 9.62 (1H, br s), 9.30 (1H, s), 8.01 (1H, d, J = 7.8 Hz), 7.82−7.72 (2H, m), 7.59 (1H, d, J = 7.2 Hz), 7.51 (1H, br t, J = 8.0 Hz), 7.22−7.06 (3H, m), 6.74 (1H, d, J = 7.4 Hz), 5.08 (1H, d, J = 7.2 Hz), 4.90−4.80 (1H, m), 4.30−4.21 (1H, m), 3.80−3.69 (1H, m), 3.48−3.38 (1H, m), 3.28−3.10 (1H, m), 2.97 (3H, br s), 2.22 (3H, s), 1.86−1.66 (4H, m), 1.56−1.18 (4H, m), 0.75 (3H, t, J = 7.3 Hz); MS (CI) m/z 447 (M^-). Anal. ($C_{26}H_{33}N_5O_2$·1.0HCl·1.0H_2O) C, H, N.

10b hydrochloride: mp 160−167 °C; ^{1}H NMR (DMSO-d_6) δ 9.33 (1H, s), 9.15 (1H, br m), 7.97 (1H, d, J = 7.6 Hz), 7.82−7.73 (2H, m), 7.56−7.49 (2H, m), 7.19−7.15 (1H, m), 7.09 (1H, t, J = 7.7 Hz), 6.73 (1H, d, J = 7.2 Hz), 5.13 (1H, d, J = 7.5 Hz), 5.03 (1H, m), 4.18 (1H, m), 3.75 (1H, m), 3.40 (2H, m), 2.98 and 2.97 (3H, two s), 2.22 (3H, s), 1.76−1.24 (8H, m), 0.92 (3H, s), 0.83 (3H, s), 0.78 (3H, t, J = 7.3 Hz); MS (CI) m/z 490 ($M^+ + 1$). Anal. ($C_{29}H_{39}N_5O_2$·1.0 HCl·1.8H_2O) C, H, N.

Molecular Modeling. Structures were built for the simplified analogues of **5**, **10a**, and **9d** (**37**, **38**, and **39**, respectively) from the fragments in the Sybyl[23] fragment library and/or, where available, based on X-ray crystal structures of analogous compounds. The conformation of **37** was chosen based on comparison with X-ray crystallographic data while conformations for the other two models were generated using Sybyl randomsearch method,[24] using 1000 attempts and energy cutoffs of 30 kcal/mol higher than the energy of the initial structure. Chirality was checked on carbons only. This process produced 58 conformations of **39** and 84 conformations of **38**. All of those structures generated with molecular mechanics energy (Tripos forcefield) within 3.2 kcal/mol of the best minimum found (11 for **39**, and 15 for **38**) were submitted to further optimization by eigenvector following using the AM1 Hamiltonian with PRECISE convergence criteria in the semiempirical SCF-MO package MOPAC.[25] The lowest-energy con-

formation found for **39** (heat of formation 2.79 kcal/mol) was predicted to be more than 3 kcal/mol more stable than the next-most-stable conformer found, while three conformers were found for **38** within 3 kcal/mol of the lowest-energy conformer of that species (heat of formation −0.26 kcal/mol); for the purpose of this study, this was considered a reasonable definition of the term "low-energy conformer". The models thus generated were not in conflict with any experimental data. The compounds were aligned using the Sybyl "MATCH" command, with the atoms of the benzodiazepine system identified as the match points. Molecular volumes of the various structures were then combined logically (as described in the main text) using the Sybyl "MVOLUME" command. Contours of the pseudo-electron density maps generated by the command were drawn at the level of 66 units to reduce the noise in the picture and illustrate the most strongly occupied areas.

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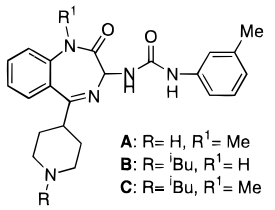

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